

## Limbic System Disorders: Wernicke-Korsakoff Syndrome, Klüver-Bucy Syndrome, Alzheimer's Disease

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The limbic system is a cluster of brain structures located on both sides of the thalamus immediately below the cerebrum, mainly responsible for the emotion, behavior, memory, and arousal response. It is thought to be an outcome of the evolutionary response that occurred in all mammals including human beings. It is not a different system, but a group of organs derived from the telencephalon, diencephalon, and mesencephalon. However, the development of this system is far greater in human beings compared to other mammals.



### Components of the Limbic System

**Hypothalamus**, located in the middlemost is often considered a separate structure by some anatomists. However, because of its major physiological role, it is often considered an important constituent of the system.

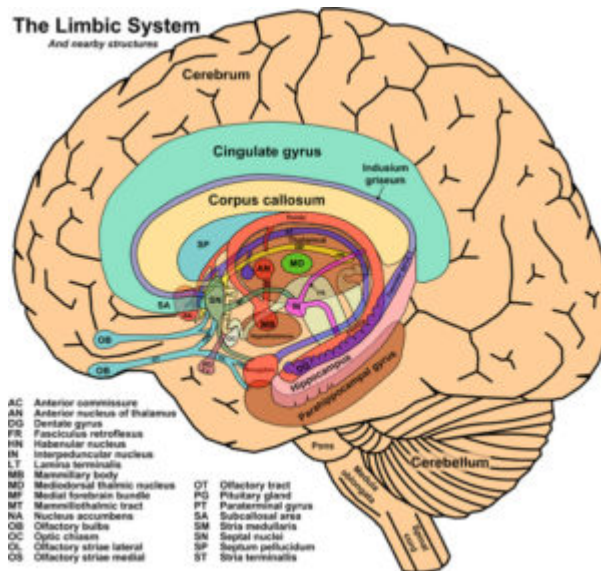


Image: "Cutout anatomy diagram of the human limbic system and some nearby structures." by John Taylor - Taylor, John. General Science. Taylor Electronics. Archived from the original on 9 June 2013. Retrieved on 27 March 2014. License: Public Domain

Other subcortical areas included are the **septum**, the **para-olfactory area**, the **anterior nucleus of the thalamus**, the **basal ganglia**, the **hippocampus**, and the **amygdala**.

The **orbitofrontal cortex**, **subcallosal gyrus**, **cingulate gyrus**, and **para-hippocampal gyrus** surround these areas. A ring of **cerebral cortex** surrounding the subcortical areas forms the **limbic cortex**.

## Functions of the hypothalamus

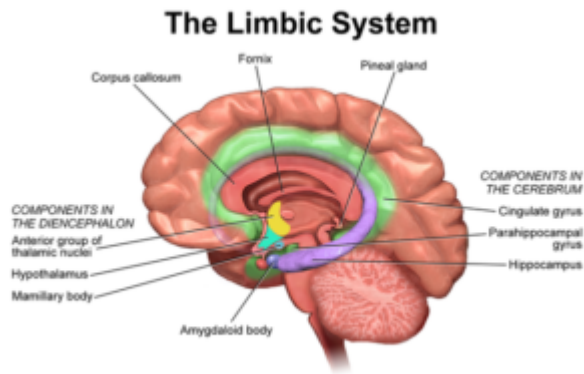
The hypothalamus is an important brain structure that plays its role in the maintenance of **homeostasis**. It controls several internal conditions, such as control of body weight, drives to eat and drink, temperature regulation and maintenance of body fluids volume.

Stimulation of the **lateral hypothalamus** not only causes thirst and eating but also rage and fighting. Any lesions in this area will lead to decreased drinking and eating causing lethal starvation.

Similarly, the stimulation of the **ventromedial nucleus** provokes a sense of satiety and tranquility. If this area of the hypothalamus is damaged, it will result in excessive eating, drinking, and hyperactivity.

The stimulation of the thin zone of the **periventricular nucleus** leads to fear and punishment reactions.

The major reward centers are located in the **lateral and ventromedial nucleus** of the hypothalamus. Milder stimulation of these areas gives a sense of reward, while stronger stimulation provokes rage and a sense of punishment. The **thalamus** produces a similar response to that of the hypothalamus.



[Image:](#) "Limbic System." by Blausen.com staff. "Blausen Gallery 2014". Wikiversity Journal of Medicine. DOI:10.15347/wjm/2014.010. ISSN 20018762. - Own Work. License: [CC BY 3.0](#)

## Functions of the amygdala

The amygdala has an enormous **bidirectional connection with the hypothalamus**. It receives neuronal signals from all portions of the limbic cortex, as well as from the auditory and visual association areas. It is therefore referred to as the '**window**' through which the limbic system sees the place of a person in the world.

It sends outward signals to the hypothalamus, thalamus, hippocampus, septum and the same cortical areas through which it has received the sensory signals. The amygdala works in **collaboration with the hypothalamus**. Its stimulation can also provoke feelings of rage, punishment, fear, and escape.

Different types of **involuntary movements**, such as tonic movements, clonic rhythmic movements, and movements associated with eating and olfaction are controlled by the amygdala. Certain portions of the amygdala once stimulated, are involved in **sexual activities** such as erection and ejaculation in males and ovulation and uterine contractility in females and may also cause abortion.

Like the hippocampus, the amygdala seems to have processes that impact the episodic autobiographic memory networks.

## Functions of the hippocampus

The hippocampus also receives incoming signals from other structures of the brain and sends outgoing signals to other parts of the limbic system. Its stimulation causes similar responses to that of the amygdala, such as rage, passivity, excess sex drive and so forth.

A weak electrical stimulation of the hippocampus may cause **local epileptic seizures** that last for a few seconds, even after the stimulation is over. During hippocampal seizures, a patient may experience various **psychomotor effects** and **hallucinations**. Even if the person is conscious and knows them to be unreal, these effects cannot be suppressed.

The hippocampus also plays an important role in the formation of **long-term memory**. This is evident by the fact that patients who had undergone bilateral hippocampus removal for the treatment of **epilepsy** were unable to remember the names of the persons they met after the surgery. The pre-operative memories, however, remain unaffected. This showed that it was responsible for making new memories.

As mentioned earlier, the feelings of reward and punishment are the 'immediate memory' which needs to be converted into 'a secondary memory.' When the same stimulus is given over and over again, a permanent perception is made in the brain regarding that particular stimulus as either 'a reward' or 'a punishment.' This is the **transmission of immediate memory into secondary memory** and is also performed by the hippocampus.

## Functions of the limbic cortex

The **cingulate gyrus** is responsible for linking the **olfactory and visual signals** to the previous memories and **emotions**. It also plays a role in **aggression**. If the posterior portion of the **orbital frontal gyrus** is ablated bilaterally, it results in severe **anosmia** and **motor restlessness**. Ablation of the cingulate gyri and the subcallosal gyri release the inhibitory signals on the septum and the hypothalamus and results in extreme rage and aggressive behavior.

## Functions of the basal ganglia

It includes the caudate nucleus, the putamen, Globus pallidus, and substantia nigra. It lies over the sides of the limbic system and is tightly connected to the cortex above. It is involved in **rule-based learning**. It also controls the **initiation of desired movements** while inhibiting the undesired movements at the same time. The **working memory** and **attention span** are also under the influence of the basal ganglia.

## Clinical Correlations: Wernicke-Korsakoff Syndrome

Wernicke-Korsakoff-Syndrome is a combination of two different medical conditions; namely, **Wernicke's encephalopathy** and **Korsakoff syndrome**. Both of them result in **brain damage** due to a **deficiency of Vitamin B1** (Thiamine). In Wernicke's encephalopathy, the thalamus and the hypothalamus are damaged, while in Korsakoff syndrome, the area of the brain involved in memory is permanently impaired.

## Causes of Wernicke-Korsakoff syndrome

Wernicke-Korsakoff syndrome arises from thiamine deficiency that is very common in :

- **Chronic alcohol abusers who have altered thiamine absorption and storage capacity as well as disordered activation of thiamine pyrophosphate.**
- Individuals suffering from **malabsorption** syndromes such as post-**bariatric surgery patients**.
- Starvation.
- Clinical conditions that result in low levels of thiamine, such as **AIDS, cancer, hyperemesis gravidarum, long-term dialysis, cardiac failure, thyrotoxicosis** and **total parenteral nutrition** (TPN) for a long time with no thiamine replacement.

## Symptoms of Wernicke-Korsakoff syndrome

In Wernicke's encephalopathy, the patient presents with the classic triad of **confusion**, ataxia, and nystagmus. However, other variants are also possible such as **loss of muscle activity** and **visual disturbances**, such as abnormal eye movements, diplopia, and

drooping of eyelids.

In Korsakoff syndrome, **loss of memory, hallucinations, and confabulation** are the presenting complaints for which the patient is brought for the medical check-up.

## Examination and investigation of Wernicke-Korsakoff syndrome

The examination of the **ocular movements, muscle power, reflexes, gait, and coordination** give clues to the appropriate diagnosis.

The classical laboratory findings are **low levels of Vitamin B1 and albumin** in serum. The **transketolase activity** is also reduced in the red blood cells. In addition, **liver enzymes** are often deranged in chronic alcohol abusers.

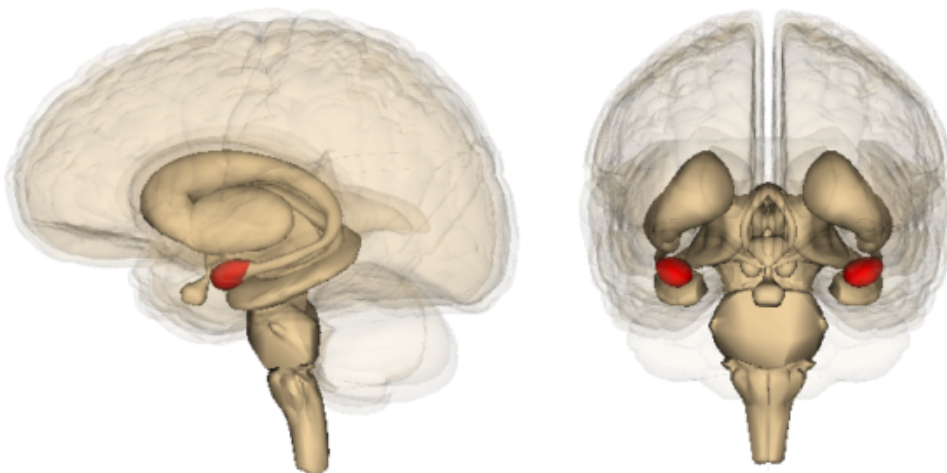
## Treatment of Wernicke-Korsakoff syndrome

The patient is **hospitalized** if unconscious or in delirium. An **Intravenous or intramuscular dose of thiamine** is given which may improve the symptoms of confusion, ocular movements and muscle power; however, the loss of memory cannot be reverted. **Improvement of nutrition and thiamine supplements and stopping alcohol intake** may prevent further damage to the brain.

In alcoholics, thiamine should be administered before glucose since the administration of glucose takes up the remaining thiamine and tips of the patient to the most severe form of Korsakoff psychosis.

## Clinical Correlations: Klüver-Bucy Syndrome

Klüver-Bucy syndrome is a **rare neuro-behavioral syndrome** that results from **bilateral lesions in the amygdaloid body**, located in the temporal lobe. The figure below shows the site of lesion in the brain.



## Causes of Klüver-Bucy syndrome

The lesions may result because of **tuberculous meningitis, meningoencephalitis, primary cerebral [Whipple's disease](#), trauma or head injury, post-epilepsy, [stroke](#), inadequate oxygen in brain tissues, Niemann-Pick disease of the brain, hypoglycemia and cerebrovascular diseases.**

## Symptoms of Klüver-Bucy syndrome

- **Visual agnosia:** inability to recognize familiar faces and people
- **Hyperorality:** putting or taking everything to the mouth
- **Hypersexuality:** uncontrollable sexual desire
- **Hyperphagia:** excessive eating and swallowing of non-food particles (pica)
- **Amnesia:** loss of memory
- **Docility or emotional blunting:** low aggression and diminished responses

## Examination and investigation of Klüver-Bucy syndrome

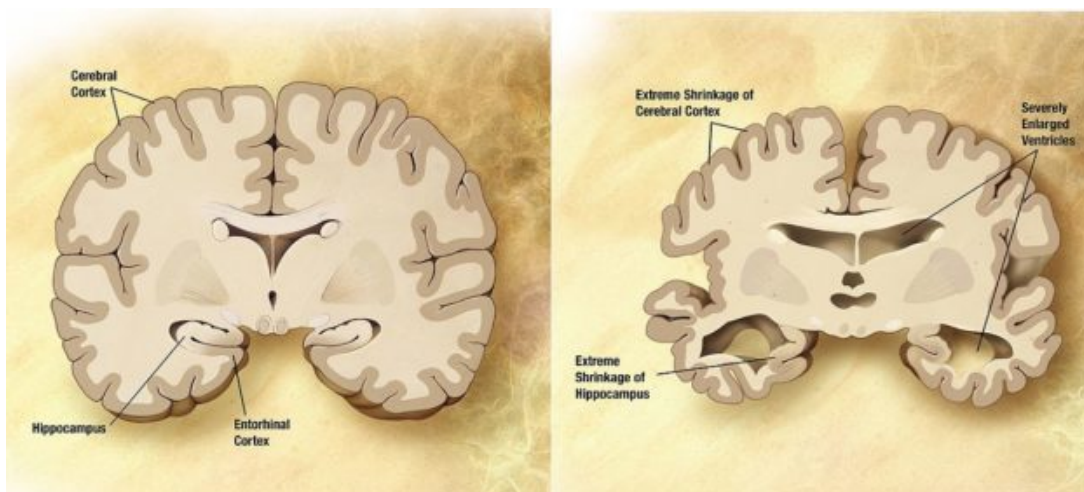
The diagnosis is based upon the **clinical signs and symptoms**. **Brain imaging** is helpful in locating the site of lesions.

## Treatment of Klüver-Bucy syndrome

No definite treatment is available; only **supportive and symptomatic treatment** is given. Patients undergo **psychotherapy** sessions and are also being assisted in their daily activities. **Carbamazepine**, an antipsychotic drug, has shown clinical improvement in the symptoms.

## Clinical Correlations: Alzheimer's Disease

Alzheimer's disease is a **chronic neurodegenerative disease** affecting individuals in their 40's. According to the **cholinergic hypothesis**, it results due to a **deficiency of a neurotransmitter, acetylcholine**. There is **loss of neurons** in the cerebral cortex and certain subcortical regions, resulting in **gross atrophy and degenerative changes** of the affected regions as shown in the figure below.



**Image:** "Diagram of a healthy brain compared to one with Alzheimer's disease." by derivative work: Garrondo (talk) SEVERESLICE\_HIGH.JPG; ADEAR: "Alzheimer's Disease Education and Referral Center, a service of the National

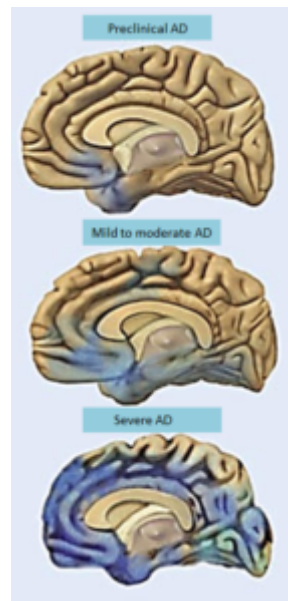
## Causes of Alzheimer’s disease

The exact cause of Alzheimer’s is unknown; however, **genetics** is thought to play a vital role. Several genes may be involved. There are other risk factors such as **trauma** and **head injuries, depressive disorders** and **hypertension**.

### Genetic Factors linked to Alzheimer’s disease

Genetic factor	Chromosome	Onset age (years)	% of early-onset cases	% of all cases
Down’s syndrome	21	> 35	NA	NA
APP mutation	21	45-66	< 1	< 0.1
PS1 mutation	14	28-62	50	1-2
PS2 mutation	1	40-85	< 1	< 0.1
APOE e4	19	> 60	NA	40

## Symptoms of Alzheimer’s disease



**Image:** "Progression of brain degeneration in Alzheimer's disease." by National Institute on Aging - <http://www.nia.nih.gov/alzheimers/topics/alzheimers-basics>. License: Public Domain

As mentioned earlier, the onset of the disease begins with **mild symptoms**. Patients often complain of **short-term memory loss, disorientation, mood swings** and **loss of motivation**.

As the disease progresses, their **language is reduced** from simple phrases to complete loss of speech. They become **completely bed-bound** and **dependent upon caregivers**. Further worsening symptoms are **extreme apathy, lack of mobility, dementia, and exhaustion**, eventually leading to death. The progression of the disease is shown in the image below.

# Examination and investigation of Alzheimer's Disease

**History** of the patient and **clinical examination** are the major clues to the diagnosis of Alzheimer's disease. **Brain imaging**, such as **CT** and **MRI** scans, are used to exclude other brain lesions and causes of dementia.

## Treatment of Alzheimer's disease

**Four acetylcholinesterase inhibitors** namely **rivastigmine**, **donepezil**, **galantamine** and **tacrine** and **memantine**, which is an NMDA receptor antagonist, are currently in use to improve the cognitive functions.

These medications, however, do not halt the progression of the disease. **Psychosocial interventions**, such as **supportive psychotherapy** and **simulated presence therapy**, are often done as an adjunct therapy. **Antipsychotic drugs** may be used modestly because of their adverse effects.

## References

[Alzheimer's Disease](#) via medlineplus.gov

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[Wernicke-Korsakoff syndrome](#) via medlineplus.gov

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