Integrative neurophysiology
A 43-year-old woman is brought to her primary care physician by her family because of concerns about her forgetfulness. The patient has a history of Down syndrome but no other medical problems. Over the last year, she has become more forgetful. Once-easy-tasks are becoming increasingly difficult such as placing a telephone call, following directions, and housekeeping. She has difficulty naming objects and telling time. She often does not recognize old friends and forgets previous conversations. Physical examination confirms many of the memory and cognitive deficits. After a thorough workup, no specific etiology can be found, and the patient is diagnosed with Alzheimer disease.

◆ What type of memory is available for conscious retrieval?
◆ Which part of the brain stores semantic (factual) memories?
Alzheimer's disease is characterized by progressive loss of short-term memory followed by general loss of cognitive and other brain functions, the need for constant care, and, eventually, death.

It was originally characterized in middle-aged people, and similar deterioration in elderly individuals is technically senile dementia of the Alzheimer type, though it is frequently just called Alzheimer's disease as well. Most cases are sporadic, but some are familial. Senile dementia can be caused by vascular disease and other disorders, but Alzheimer's disease is the most common cause, accounting for 50–60% of the cases.
Objectives

1. Know the types of memory and their general anatomic locations.

2. Know about basic mechanisms of learning and memory.
The cerebral cortex:
Intellectual function of the brain;
learning and memory

Chapter 57
Physiological Anatomy of the cerebral cortex

Cytoarchitecture of cortical layer

Major neuron types:
- Granular (stellate)
- Fusiform
- Pyramidal
Cortex

Inputs and outputs
Anatomical and functional relations of the cerebral cortex to the thalamus
Specific cortical area
Function of specific cortical area

- **Frontal lobe**: motor behavior, planning and execution voluntary motor acts
  - Prefrontal cortex: personality & emotional behavior
  - Lesion: deficit in attention, problem solving, inappropriate social behavior. reduced aggressive behavior

- **Parietal lobe**: processing and perception of somatosensory information, spatial analysis

- **Occipital lobe**: visual processing and perception.

- **Temporal lobe**: hearing, processing of vestibular information, IT cortex (prospagnosia), *Wernicke's area*
  - Lesion: language disorder
Association areas

Parieto-occipitotemporal Association area

Prefrontal Association area

Limbic Association area
Parieto-occipitotemporal Association area

- Analysis of the spatial coordinates of the body
- Area for language comprehension
- Area for initial processing of visual language (reading)
- Area for naming object

Dr. Z akbari
Prefrontal Association area

✓ Broca's area
✓ Working memory
✓ Prefrontal lobotomy:
  • Aggressiveness & inappropriate social responses
  • Inability to progress toward goals
Area for recognition of faces:
Medial occipitotemporal lobe

Prospagnosia
General interpretative area *(Wernicke's area)*

Angular gyrus: interpretation of visual information
Language

Sensory aspect: Wernicke’s Aphasia; Global aphasia
(Comprehension, recognition, and construction of words and language)

Motor aspect: Broca's; motor Aphasia
(Mechanical production of speech)

Articulation
SPEAKING A HEARD WORD

Motor cortex
Arcuate fasciculus

Broca's area
Primary auditory area
Wernicke's area
### TABLE 27.1
Characteristics of Broca’s and Wernicke’s Aphasias

<table>
<thead>
<tr>
<th><strong>Broca’s aphasia</strong>&lt;sup&gt;a&lt;/sup&gt;</th>
<th><strong>Wernicke’s aphasia</strong>&lt;sup&gt;b&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>Halting speech</td>
<td>Fluent speech</td>
</tr>
<tr>
<td>Repetitive (perseveration)</td>
<td>Little repetition</td>
</tr>
<tr>
<td>Disordered syntax</td>
<td>Syntax adequate</td>
</tr>
<tr>
<td>Disordered grammar</td>
<td>Grammar adequate</td>
</tr>
<tr>
<td>Disordered structure of</td>
<td>Contrived or inappropriate words</td>
</tr>
<tr>
<td>individual words</td>
<td></td>
</tr>
</tbody>
</table>

<sup>a</sup> Also called motor, expressive, or production aphasia

<sup>b</sup> Also called sensory or receptive aphasia
**Limbic system:** limbic lobe and deep lying structures (hippocampus and amygdala)

(Ant pole of temporal lobe, Ventral of frontal lobe, Cingulate gyrus)

- Perception of feeling and emotion.
- Behavior, Motivation, Emotional experience (amygdala)

![Brain Diagram](image)
Brain Laterality

Concept of dominant hemisphere

- **Lt hemisphere**: language & speech, major problem solving, voluntary facial expression, recognition of familiar faces, represent local information

- **Rt hemisphere**: visuospatial task, voluntary facial expression, recognition of unfamiliar faces, represent global information

- **Corpus callosum**: Interhemispheric transfer of information
**Memory**

**Learning**: process by which new information is acquired

**Memory**: mechanism of storage and/or retrieval of information

**Temporal categories of memory:**

- **Short-term memory** (seconds-minutes)
  - **Working memory**: The ability to hold information in mind long enough to carry out sequential actions
- **Intermediate-term memory** (minutes-hours)
- **Long-term memory** (days-years)

Dr. Z akbari
Qualitative categories of human memory

- Explicit (Declarative): associated with consciousness/awareness
- Implicit (nondeclarative)
Explicit knowledge involves four distinct processes

1- **Encoding**: Processes by which new information is attended and processed when first encountered (role of motivation).

2- **Consolidation**: Processes that alter newly stored and labile information to more stable for long-term storage (*gene expression* and *protein synthesis*).

3- **Storage**: Mechanism and sites by which memory is retained over time

4- **Retrieval**: Processes that permit recall and use of stored information

Dr. Z akbari
Memory

✔ Short term storage of memory results from changes in the effectiveness of synaptic transmission

✔ Sensitization involve presynaptic facilitation of synaptic transmission

✔ Habituation involves presynaptic depression of synaptic transmission
B. Three molecular targets involved in presynaptic facilitation

**Figure 57-9**
Memory system that has been discovered in the snail *Aplysia*.
Structural changes in long term memory

- Increase in number of release site
- Increase in number of transmitter vesicle
- Increase in number of presynaptic terminal
- Structural changes in dendritic spines
Hippocampus promotes storage of memories
Processing information for explicit memory storage

Dr. Z akbari
Amnesia: memory deficit

✓ **Anterograde amnesia:**
Capable of new learning and retain old prelesion memories, but they cannot form new long-term memories.

✓ **Retrograde amnesia:** The inability to recall previous memories

Amygdala stores emotional components of memory
Limbic system
&
Hypothalamus

Chapter 58
Implementation of integrative functions:

1. The **hypothalamus**: major controller of the endocrine and ANS. It is a key site for the control of homeostatic functions and motivated behaviors, including eating, circadian rhythms, and the sex drive.

2. The **reticular formation**: several well-defined nuclei. Give origin to monoaminergic neurons; the widespread connections of these neurons form the **diffuse modulatory systems of the brain**. Is essential for determining the level of consciousness and general arousal.

3. The **limbic system** is the seat of emotions. Formed from a series of cortical and subcortical structures that have reciprocal connections with the reticular formation and hypothalamus.

*Dysfunction of the limbic system and diffuse modulatory systems underlie psychiatric diseases such as major depression, bipolar disorder, and schizophrenia.*

Dr. Z akbari
Hypothalamus

Key output pathway for the limbic system, playing a role in the expression of emotions
Hypothalamus

Afferent inputs:
■ Collaterals from the **visceral & somatic sensory pathways** (e.g., via the medial lemniscus and RF) serve the hypothalamus in its role as an integrator of homeostatic & visceral function.

■ Afferent fibers from **frontal lobe & parts of the limbic system** link the hypothalamus with the higher centers for mood and emotion.

Output fibers:
➢ **Descending pathways via RF control the peripheral ANS.**
   The hypothalamus sends efferents to the BS nuclei for parasympathetic outflow and to the lateral horn of the SC for sympathetic outflow.

➢ **Output to the endocrine sys. via connections with the pituitary gland**
   Via the hypothalamohypophyseal tract, to the post pituitary and hypophyseal portal blood supply to the anterior pituitary.

➢ **Output is conveyed to the limbic system**
   Through several pathways (e.g., the mammillothalamic tract).

Dr. Z akbari
<table>
<thead>
<tr>
<th>Function of the Hypothalamus</th>
<th>Area of the Hypothalamus</th>
</tr>
</thead>
<tbody>
<tr>
<td>Secretion of hormonal release factors controlling the pituitary gland</td>
<td>Arcuate and paraventricular nuclei; periventricular area</td>
</tr>
<tr>
<td>Activation of sympathetic nervous system</td>
<td>Dorsal and posterior areas</td>
</tr>
<tr>
<td>Eating behavior</td>
<td>Ventromedial and arcuate nuclei; lateral area</td>
</tr>
<tr>
<td>Drinking behavior and thirst</td>
<td>Lateral area</td>
</tr>
<tr>
<td>Water and electrolyte balance</td>
<td>Supraoptic and paraventricular nuclei</td>
</tr>
<tr>
<td>Body temperature regulation</td>
<td>Preoptic area</td>
</tr>
<tr>
<td>Sexual behavior</td>
<td>Preoptic and anterior area</td>
</tr>
<tr>
<td>Circadian rhythms</td>
<td>Suprachiasmatic nucleus</td>
</tr>
</tbody>
</table>
Vegetative and endocrine functions of hypothalamus

**Anterior**: Preoptic area (BP, Blood composition, Temp, Cycles of activity, Endocrine and reproductive activity)

**Middle**: DM, VM, PV, SO, Arc (Regulating ANS, Neuroendocrine, Integrative function: Control growth, maturation, feeding, reproduction)

**Posterior**: MB (Histaminergic cell: Wakefulness and arousal)

Dr. Z akbari
Behavioral function of hypothalamus and limbic system

**Stimulation:**
- Lat hypothalamus: ↑ general activity, thirst & eating
- VMn: satiety, eating, tranquility
- PVn: fear & punishment reaction
- Most ant or post area: sexual drive

**Inhibition**
- Lat: passivity
- VMn: hyperactivity

**Reward and punishment function of limbic system**
- Reward center: Lat & VMn
  - Weaker stimuli: Sense of reward
  - Stronger stimuli: sense of punishment
- Punishment center: PAG, PVn (inhibits reward center)
Consciousness
Consciousness requires proper functioning of the reticular activating system and both cerebral hemispheres.

Therefore, the principal causes of unconsciousness or coma are:

1. Lesions that damage the reticular activating system.

2. Diffuse damage to both cerebral hemispheres.

3. Global suppression of the cerebrum and/or RAS by drugs (e.g., sedative-hypnotics or alcohol) or metabolic derangements (e.g., anoxia, hypercapnia, hypoglycemia, or hepatic encephalopathy).
Ascending Reticular Activating System

**ARAS**

Reticular formation

↓

Thalamus (intralaminar, n)

nonspecific

↓

Thalamocortical fiber

↓

Diffuse activation of cortex

Dr. Z akbari
Activating driving systems of the brain

✓ Ascending projection from brain stem modulate arousal and consciousness (Ascending arousal system)

✓ Reticular excitatory area located in the upper brain stem

✓ Reticular inhibitory area located in the lower brain stem

✓ Excitation of BS excitatory area by nonspecific peripheral sensory signals

↑ activity of RAS by feedback signal return from cerebrum

✓ Thalamus (Distribution system) controls activity of cortex
Neurohormonal control of brain activity

Four major diffuse modulatory systems:

- Substantia nigra (dopamine)
- Gigantocellular neurons of reticular formation (acetylcholine)
- Locus ceruleus (norepinephrine)
- Nuclei of the raphe (serotonin)

Dr. Zakbari
Acetylcholine system

- In midbrain (Giant cell in RAS) … to the BS and thalamus: cortical arousal
- In basal forebrain: enhance cortical response to incoming sensory stimulus
  - cognition
Locus coeruleus - Norepinephrin system

Functions as an “alarm center” that becomes most active when new environmental stimuli appear.

Regulation of

Attention
Arousal
Sleep-wake cycle
Mood
Brain metabolism
Raphe nuclei – Serotonin system

- To forebrain and BS.....

  regulate:
  - Sleep-wake cycle
  - Mood and emotion: fluoxetine
  - Food intake
  - Thermoregulation
  - Sexual behavior
  - Pain
**Substantia nigra - Dopamine system**

- From SN to striatum (**nigrostriatal sys**): facilitate initiation of voluntary movement

- From VTA to the forebrain (**prefrontal & limbic system** (**mesocorticolimbic sys**)): mediate reward and drug addiction

**Antipsychotic drugs (neuroleptics): DR antagonist**
The Limbic System

Phylogenetically the oldest part of the cerebral cortex.

The limbic system comprises specific areas of the cortex and subcortical structures interconnected via circuitous pathways that link the cerebrum with the diencephalon and brainstem:

- **Cingulate gyrus**
- **Parahippocampal gyrus** (ant and inf continuation of the cingulate gyrus)
- **Hippocampal formation** (lies deep in the parahippocampal gyrus)
  (hippocampus proper, the dentate gyrus, and the subiculum)

Prefrontal cortex and other association area provide information based on previous learning and currently perceived needs.

All ascending sensory systems in the BS send axon collaterals to RF, which, in turn, innervates the limbic system, (particularly via monoaminergic pathways)...... to impart an emotional tone to the sensory information.

Dr. Z. Akbari
**Function of Limbic system**

- Experience and Control emotion
- Coordination of response to emotional stimuli
- Learning and memory

**Malfunctions in the limbic system:**

major psychiatric disorders (bipolar disorder, major depression, schizophrenia, and dementia)
Function of amygdala:
mediating both the unconscious emotional state and conscious feeling

Central nucleus:
- Lat hypothalamus…. sympathetic activation
- Paraventricular hypothalamus…… ACTH release
- DMV (ambiguous)…… parasympathetic activation
- VTA, locus ceruleus…… dopamine and norepinephrin system activation
- Trigeminal, facial mn…… facial expression of fear

fear and anxiety

Klüver-Bucy syndrome
- Hypersexuality (lack of social sexual restraint)
- Hyperorality (strong compulsion to place objects in the mouth)
- Visual agnosia (able to see objects, but unable to identify them)
- Flat affect, and placidity (able to approach danger without anger or fear)
State of brain activity

Sleep

Brain wave

Chapter 59
Electroencephalogram

- EEG records electrical activity of the cerebral cortex via electrodes placed on the skull.
- EEG waves are not action potentials. Electrodes on the surface of the skull are not sufficiently sensitive to detect the small voltage changes of single action potentials.
Different type of brain wave:

**Alpha:** 8 - 13 HZ. Relaxed wakefulness. Moderate amplitude. Occipital lobe,

**Beta:** 13 - 30 HZ. Intense mental activity. Lower amplitude. Parietal & frontal

**Theta:** 4 - 7 HZ. Drowsiness. Parietal & temporal in children,

**Delta:** 0.5 - 4 HZ. Drowsiness, Deep sleep, independent of thalamic input.
Sleep

• Behavioral definition of sleep
  ➢ Reduced motor activity
  ➢ Decreased response to stimulation
  ➢ Stereotypic postures
  ➢ Relatively easy reversibility (different from coma…)

Dr. Z akbari
Two types of sleep

- **Non-REM**: Slow – wave sleep
  
  EEG spindle and slow-wave produced by synchronized synaptic potential in cortex (Rhythmic firing of thalamocortical neurons and these type of firing occludes transmission of sensory information through thalamus and cortex)

- **REM sleep**: Paradoxical, desynchronized sleep
  
  Cholinergic cells of midbrain are active in waking and REM sleep (These fiber inhibits thalamic relay neuron … they fire asynchronously … Low-voltage EEG in REM and waking

Dr. Z akbari
Non-REM Sleep

- Neuronal activity is low
- Brain temp and metabolic rate of brain at their lowest
- Sympathetic outflow decreased
- HR & TPR decreased
- Parasympathetic outflow increased (pupil constriction)
- Muscle tone and reflexes are intact

REM Sleep (Active form of sleep)

- Overall increase in neuronal activity
- Brain temp and metabolic rate of brain
- Muscle tone decreased (atonia) except in eyes, middle ear, diaphragm
- High ratio of parasympathetic to sympathetic outflow
- Haemostatic mechanism attenuated (RT, Temp)
EEG at different stage of wakefulness & sleep
Human are easier to awake in REM than Non-REM sleep

Most dream are thought to occur in REM sleep

REM and Non-REM sleep alternate cyclically:

Stage 1 → stage 4 (Non-REM) → Stage 2 / 3 → 1\textsuperscript{st} REM phase → awake

→ stage 1 / 2 Non-REM

Sleep period changes over the life span:

Daily sleep decline

Decline in time spent in REM sleep (50% to 20%)
Different neural system promote arousal and sleep

- **Areas that promote waking state:**
  - Midbrain reticular formation (Cholinergic cells)
  - Posterior hypothalamus (Role of Histaminergic neurons)
  - Raphe nucleus

- **Areas that promote Non-REM sleep:**
  - Ant hypothalamus & Basal Forebrain

- **Areas that promote REM sleep:**
  - Nucleus Reticularis Pontin Oralis/Cudalis (RPO/RPC)
    - PGO-on cells

Dr. Z akbari
Major regions of the BS and forebrain in sleep control

Dr. Z akbari
These substances have hypogenic properties

- Muramyl peptides
- IL-1
- Adenosine
- PGD2

Physiological effect of sleep

- Effect in nervous system (Cognition, neural maturation and mental health)
- Effect on other functional systems (Thermoregulation, conservation of metabolic energy)
Epilepsy and seizure

**Epilepsy**: chronic condition of repetitive seizure

**Classification**:

I. Partial (focal) seizure

II. Generalized seizure:
   - Petit mal
   - Tonic-clonic (grand mal)

*The end*