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- Neuroanatomy
- Neuropathophysiology
- Neurology
- Neuropharmacology
- Neuro-ophthalmology
- Neuroanesthesia
- Neurosurgery
- Neuroradiology
- Psychiatry
- MCQs
- A to Z in Neurology

Highlights

- High yield topics, 5th edition updated with all chapters with more emphasis on Psychiatry
- List of signs and syndromes
- Last-minute revision

Pramod KS
K Gayathri

5th Edition

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CHAPTER

2

Neuropathophysiology

NEURONS

- The major function of neurons is to receive, integrate, and transmit information to other cells. Neurons consist of three parts: dendrites, which are elongated processes that receive information from the environment or from other neurons; the cell body, which contains the nucleus; and the axon, which may be up to 1 m long and conducts impulses to muscles, glands, or other neurons.
- Most neurons are multipolar, containing one axon and several dendrites. Bipolar neurons have one dendrite and one axon and are found in the cochlear and vestibular ganglia, retina, and olfactory mucosa.
- Spinal sensory ganglia contain pseudounipolar neurons that have a single process that emanates from the cell body and divides into two branches, one extending to the spinal cord and the other extending to the periphery.
- Axons and dendrites usually branch extensively at their ends. Dendritic branching can be very complex, with the result that a single neuron may receive thousands of inputs. Axon branching allows several target cells to simultaneously receive a message from one neuron. Each branch of the axon terminates on the next cell at a synapse, which is a structure specialized for information transfer from the axon to muscle, to glands, or to another neuron.

Synapses between neurons most often occur between axons and dendrites but may occur between an axon and a cell body, between two axons, or between two dendrites.

TRANSMISSION IN NEURONS

- Signals are propagated electrically along axons. Like other cells, neurons maintain cell size and osmolarity primarily through the action of Na^+–K^+ ATPase, which actively pumps Na^+ out of cells in exchange for K^+. This results in the formation of concentration gradients for Na^+ and K^+ across the cell membrane. The membrane is practically impermeable to Na^+, but the presence of K^+ leak channels permits the flow of K^+ out of cells. This produces a difference in electrical charge across the membrane that counters transport of K^+ from the cell. The flow of ions continues until the opposing electrical force reaches a value that balances the diffusional force and the membrane reaches the equilibrium potential for K^+ which is calculated by the Nernst equation.
- The membrane potential may be altered by increasing the permeability of the membrane to another ion, which drives the resting membrane potential toward the equilibrium potential for that ion. Neurons are highly specialized to use rapid changes in membrane potential to generate electrical signals. This is accomplished by ligand-gated and voltage-gated ion channels that allow the passage of Na^+, K^+, Ca^{2+}, or Cl^- ions in response to electrical or chemical stimuli. These channels are composed of protein complexes embedded in the lipid membrane to form aqueous pores to the inside of the cell. In general, channels are selective for a particular species of ion. An array of charged amino acids within voltage-dependent channels detects changes in voltage and induces a conformational change in the channel to alter ion permeability. Binding sites for neurotransmitters such as glutamate, Gamma-aminobutyric acid (GABA), glycine, and acetylcholine exist on ligand-gated channels and, when occupied, induce a conformational change to open the channel.
- Electrical signals are propagated in neurons because a voltage change across the membrane in one part of a neuron is propagated to other parts. Passive spread of a voltage disturbance weakens with increasing distance from the source unless energy-dependent processes amplify the signal. Passive spread of electrical signals works well over short distances and is a major mechanism of signal propagation in dendrites. However, long-distance communication down axons to nerve terminals requires amplification which is accomplished through the generation of self-propagating waves of excitation known as action potentials.

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- An action potential arises primarily from voltage-dependent changes in membrane permeability to Na^+ and K^+. If a depolarizing stimulus raises the membrane potential, allowing influx of Na^+, areas of membrane are depolarized to the threshold for Na^+ channel activation, propagating a wave of depolarization from the initial site.
- The resting potential is restored quickly by a combination of events. First, Na^+ channels close rapidly and remain in an inactive state until the membrane potential returns to negative levels for several milliseconds. Voltage-dependent K^+ channels open as the membrane potential peaks, speeding the efflux of K^+ from cells and driving the membrane potential back to E_K. K^+ channels are also inactivated, but more slowly than Na^+ channels, and this may transiently hyperpolarize cells. Plasma membrane ion exchangers and ion pumps then counteract the ion fluxes and eventually restore the resting state.
- Neurons transmit signals chemically to other cells at synapses. Presynaptic and postsynaptic cells are electrically isolated from each other and separated by a narrow synaptic cleft. Signaling across the cleft occurs through the release of neurotransmitters from the terminal of the presynaptic neuron. Most neurotransmitters are stored in membrane-bound synaptic vesicles and are released into the synaptic cleft by Ca^{2+}-dependent exocytosis. Depolarization of the nerve terminal opens voltage-gated Ca^{2+} channels, stimulating Ca^{2+} influx and neurotransmitter release.
- In general, excitatory neurotransmitters such as glutamate open cation channels that allow influx of Na^+ or Ca^{2+} and generate a depolarizing excitatory postsynaptic potential. Inhibitory neurotransmitters such as GABA and glycine open Cl^- channels and generate an inhibitory postsynaptic potential. Termination of the signal is achieved by removal of the neurotransmitter from the synaptic cleft. Acetylcholine is hydrolyzed by acetylcholinesterase at the postsynaptic membrane. Other neurotransmitters such as glutamate are removed by specific membrane transporters on nerve terminals or glial cells.
- Temporal summation occurs if repeated afferent stimuli cause new EPSPs before previous EPSPs have decayed. A longer time constant for the EPSP allows for a greater opportunity for summation. When activity is present in more than one synaptic knob at the same time, spatial summation occurs and activity in one synaptic knob summates with activity in another to approach the firing level.

EXCITATORY NEUROTRANSMITTERS

- Glutamate is a major excitatory neurotransmitter in the central nervous system (CNS). Its activation depolarizes neurons, increasing the number of action potentials generated.
  - There are three major ionotropic glutamate receptors – AMPA, Kainate and NMDA. The AMPA and kainate receptors are attached to ion channels that allow Na and K to pass through them; a small number of AMPA receptors are also permeable to Ca. The NMDA channels activated when neurons are already depolarized are permeable to Na, K, and Ca. Activation of NMDA channels has been associated with long-term changes in neuronal activity that may be cellular correlates of learning and memory.
  - Metabotropic receptors are also activated by glutamate. These receptors act via GTP – second messenger pathway [cAMP /IP3] which in turn can alter ionic conductance, cell Ca levels, and a host of other biochemical changes.

INHIBITORY NEUROTRANSMITTERS

- Gamma-aminobutyric acid (GABA) and glycine are major inhibitory neurotransmitters in the CNS. Their activation hyperpolarizes neurons, decreasing the number of action potentials generated. Inhibition is important for the brain and spinal cord to function.
  - GABA is a major inhibitory transmitter in the brain and spinal cord. The $GABA_A$ receptor contains a chloride channel that is opened when GABA binds. This activity is augmented by benzodiazepines, volatile anesthetics, and barbiturates. The $GABA_B$ receptor acts via a second messenger to open K channels.
  - Glycine is a major inhibitory transmitter in the spinal cord. Strychnine blocks the action of glycine.

ASTROCYTES

- Astrocytes serve a variety of metabolic, immunologic, structural, and nutritional support functions required for normal function of neurons. They possess numerous processes that radiate from the cell body, surrounding blood vessels and covering the surfaces of the brain and spinal cord. Foot processes form part of the blood-brain barrier. Astrocytes express voltage- and ligand-gated ion channels and regulates K^+ and Ca^{2+} concentrations within the interstitial space. Many synapses are invested with astrocytic processes, and this allows astrocytes to modulate neurotransmission by regulating extracellular concentrations of these cations.
- Astrocytes provide structural and trophic support for neurons through the production of extracellular matrix molecules such as laminin and through release of growth factors such as nerve growth factor, fibroblast growth factors, and brain-derived neurotrophic factor. End-feet of astrocytic processes at blood vessels provide sites for release of cytokines and chemoattractants during CNS injury.

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- Astrocytes respond to brain injury by increasing in size and in some cases in number through a process called reactive astrocytosis. This phenotypic change is characterized by an increase in cells expressing glial-fibrillary acidic protein and by synthesis and release of cytokines that regulate inflammatory responses and entry of hematogenous cells into the CNS.
- Astrocytes play an important role also in terminating neuronal responses to glutamate, the most abundant excitatory neurotransmitter in the brain. In cell cultures, neurons die in the presence of high levels of glutamate unless astrocytes are present. Glutamate transporters present on astrocyte cell membranes remove glutamate from the synapse. Astrocytes also contain glutamine synthase, which converts glutamate to glutamine, detoxifying the CNS of both glutamate and ammonia.

OLIGODENDROCYTES AND SCHWANN CELLS

- Plasma membranes of oligodendrocytes in the CNS and Schwann cells in the peripheral nervous system envelop axons. For many axons, the membranes of these glial cells are wrapped layer on layer around the axon, forming a myelin sheath.
- Gaps form between myelin sheaths from neighboring glia and produce nodes of Ranvier where a small portion of the axon is exposed to the interstitial space and where voltage-dependent Na^+ channels are clustered in the axonal membrane. Between the nodes, myelin insulates the axon from the extracellular space, allowing efficient spread of depolarization from one node to another. This allows action potentials to propagate rapidly by jumping from node to node in a process called saltatory conduction.

MICROGLIA

- Microglia which reside in the CNS, function as the main immune effector cells.
- They appear to be derived from bone marrow precursors of macrophage-monocyte lineage and invade the CNS during the perinatal period. Microglia cells are activated by brain injury, infection, or neuronal degeneration. Activation is characterized by proliferation, migration into damaged tissue, increased or de novo expression of surface receptors, including CD45 (leukocyte common antigen), MHC class I and class II and immunoglobulin Fc receptors, and secretion of several cytokines, reactive oxygen intermediates, and proteinases. This response functions to remove dead tissue and destroy invading organisms but may contribute to CNS damage, particularly in certain CNS inflammatory and degenerative diseases.

LOWER MOTOR NEURONS AND SKELETAL MUSCLES

- Each alpha motor neuron axon contacts up to about 200 muscle fibers, and together they constitute the motor unit. Axons of the motor neurons intermingle to form spinal ventral roots, plexuses, and peripheral nerves. Muscles are innervated from specific segments of the spinal cord, and each muscle is supplied by at least two roots. Motor fibers are rearranged in the plexuses so that most muscles are supplied by one peripheral nerve. Thus, the distribution of muscle weakness differs in spinal root and peripheral nerve lesions.
- The lower motor neurons are the final common pathway for all voluntary movement. Therefore, damage to lower motor neurons or their axons causes flaccid weakness of innervated muscles. In addition, muscle tone or resistance to passive movement is reduced, and deep tendon reflexes are impaired or lost.
- Each point of contact between nerve terminal and skeletal muscle forms a specialized synapse known as a neuromuscular junction composed of the presynaptic motor nerve terminal and a postsynaptic motor end plate. Presynaptic terminals store synaptic vesicles that contain the neurotransmitter acetylcholine. The amount of neurotransmitter within a vesicle constitutes a quantum of neurotransmitter. Action potentials depolarize the motor nerve terminal, opening voltage-gated calcium channels and stimulating calcium-dependent release of neurotransmitter from the terminal. Released acetylcholine traverses the synaptic cleft to the postsynaptic (end plate) membrane, where it binds to nicotinic cholinergic receptors. These receptors are ligand-gated cation channels, and, on binding to acetylcholine, they allow entry of extracellular sodium into the motor end plate. This depolarizes the motor end plate, which in turn depolarizes the muscle fiber. After activation, cholinergic receptors are rapidly inactivated, reducing sodium entry. They remain inactive until acetylcholine dissociates from the receptor. This is facilitated by the enzyme acetylcholinesterase, which hydrolizes acetylcholine and is present in the postsynaptic zone.

UPPER MOTOR NEURONS

- The motor cortex is the region from which movements can be elicited by electrical stimuli. This includes the primary motor area (Brodmann area 4), premotor cortex (area 6), supplementary motor cortex (medial portions of 6), and primary sensory cortex (areas 3, 1, and 2). In the motor cortex, groups of neurons are organized in vertical columns, and discrete groups control contraction of individual muscles.
- Planned movements and those guided by sensory, visual, or auditory stimuli are preceded by discharges from prefrontal, somatosensory, visual, or auditory cortices, which are then followed by motor cortex pyramidal cell discharges that occur several milliseconds before the onset of movement.

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- Cortical motor neurons contribute axons that converge in the corona radiata and descend in the posterior limb of the internal capsule, cerebral peduncles, ventral pons, and medulla. These fibers constitute the corticospinal and corticobulbar tracts and together are known as upper motor neuron fibers. As they descend through the diencephalon and brainstem, fibers separate to innervate extrapyramidal and cranial nerve motor nuclei. The lower brainstem motor neurons receive input from crossed and uncrossed corticobulbar fibers, although neurons that innervate lower facial muscles receive primarily crossed fibers.
- In the ventral medulla, the remaining corticospinal fibers course in a tract that on cross section is pyramidal in shape thus the name pyramidal tract. At the lower end of the medulla, most fibers decussate, although the proportion of crossed and uncrossed fibers varies somewhat between individuals. The bulk of these fibers descend as the lateral corticospinal tract of the spinal cord.
- Upper motor neurons are the final common pathway between cortical and subcortical structures, such as the basal ganglia, in the planning, initiation, sequencing, and modulation of all voluntary movement. Upper motor neuron lesions cause a characteristic pattern of limb weakness and change in tone. Antigravity muscles of the limbs become more active relative to other muscles. The arms tend to assume a flexed, pronated posture, and the legs become extended. In contrast, muscles that move the limbs out of this posture (extensors of the arms and flexors of the legs) are preferentially weakened. Tone is increased in antigravity muscles (flexors of the arms and extensors of the legs), and if these muscles are stretched rapidly, they respond with an abrupt catch, followed by a rapid increase and then a decline in resistance as passive movement continues. This sequence constitutes the clasp knife phenomenon. Clonus, a series of involuntary muscle contractions in response to passive stretch may be present.

The distribution of paralysis resulting from upper motor neuron lesions varies with the location of the lesion. Lesions above the pons impair movements of the contralateral lower face, arm, and leg. Lesions below the pons spare the face. Lesions of the internal capsule often impair movements of the contralateral face, arm, and leg equally, because motor fibers are packed closely together in this region. In contrast, lesions of the cortex or subcortical white matter tend to differentially affect the limbs and face, because the motor fibers are spread over a larger area of brain. Bilateral cerebral lesions cause weakness and spasticity of cranial and trunk muscles in addition to limb muscles and lead to dysarthria, dysphonia, dysphagia, bifacial paresis, and sometimes reflexive crying and laughing (pseudobulbar paralysis).

Tracts and Homunculus

Ascending tracts

Dorsal column:

a Fasciculus Gracilis (Tract of Goll): Lower half of the body

b Fasciculus Cuneatus (Tract of Burdach): Upper half of the body

- *Sensations:* Proprioception, fine touch, tactile localization, 2 point discrimination, stereognosis, position of joints and kinesthetic
- Anterior spinothalamic tract—crude touch
- Lateral spinothalamic tract—pain and temperature.
- Dorsal column CROSS to the opposite side in the thalamus whereas the anterolateral column CROSS to the opposite side in the spinal cord
- Therefore in lesion of spinal cord ipsilateral dorsal column and contralateral spinothalamic tract is involved.
- Second order neuron of dorsal column—thalamus.
- Second order neuron of spinothalamic tract—spinal cord
- First relay station of pain and temperature is—spinal cord
- First relay station of touch, proprioception and vibration—thalamus

Descending system is classified as medial and lateral descending system.

Medial: Lateral corticospinal tract, rubrospinal tract; they are involved in skilled voluntary movements of distal muscles

Medial pathways: Anterior white column of spinal cord; postural control (muscles of the trunk and proximal muscles of limb)

Ventral (anterior) corticospinal tract, vestibulospinal, reticulospinal, tectospinal tracts;

Lateral pathways: Lateral white column of spinal cord; fine skilled movements (distal muscles of limbs).

Lateral corticospinal tract and rubrospinal tract.

Body representation is vertical—upside down with face at the foot and legs and feet at the top.

Sensory homunculus: Lips, face tongue large representation.

- In the sensory cortex the part of the body represented is proportionate to the number of sensory receptors (innervations density)
- Fibres carrying tactile and proprioceptive information ascend through the thalamic radiation to the area 3 of primary somatic sensory cortex. If the somatosensory area is removed, tactile and proprioceptive sensations are lost, but pain and temperature persists, since they are appreciated primarily by the thalamus.

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- The sensations that are most affected by cortical lesions are: proprioception and tactile sensation (fine touch, two point discrimination, and astereognosis).

Motor Cortex

a. Primary motor area (4)
b. Premotor area (6, 44, 45, 8)
c. Supplementary motor area
   - Body representation is vertical,each PMA controls contralateral side of the body
   - Face is presented B/L, rest all U/L
   - Cortical presentation is proportional to skilled movements

MOTOR HOMUNCULUS

Maximum representation: Muscles for vocalization and mastication.

Motor System

- Area of leg presentation is on the medial surface of cerebral hemisphere in the central sulcus (paracentral lobule)
- Regulation of voluntary movement:

Cortical association area: Ideas (commands) for voluntary movement originate.
Basal ganglia, lateral portion of cerebellum and cerebral cortex:

Planning and Programming

- **Supplementary motor area:** Programming the motor sequences (not visually/sensory guided)
- **Premotor cortex:** Setting a posture (sensory inputs)
- **Somatosensory area:** Aiming hands toward an object (5), hand-eye coordination (7)
- **Spinocerebellum:** Smoothens and coordinates the movement
- **Corticospinal and corticobulbar tracts:** Final pathway for skillful movements
- **Extrapyramidal tract:** Back ground posture

Cerebral Dominance and Handedness

91% of population is right handed, 95% dominant hemisphere is left
In left handed also, 60–70% of population hemisphere is left, only 15% right hemisphere is dominant.
15% no lateralization

Right/nondominant/Representational

- Left-handed control
- Spatial relationship between person and surrounding (visuospatial relation).
- Insight/imagination
- Music/art
- Recognition of faces
- Identification of object by forms and shapes.

Lesions of Right Lobe

- Agnosia
- Agraphia
- Asterognosis
- Anosognosia
- Visuo-spatial defects

Left/Dominant/Categorial

- Right-handed control
- Language function
- Mathematical and scientific skill
- Reasoning

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Lesions

- Dyslexia
- Dyscalculia
- Fluent aphasia
- Loss of ability to think logically

Cerebellum

The cerebellum is responsible for the coordination of muscle groups, control of stance and gait, and regulation of muscle tone. Rather than causing paralysis, damage to the cerebellum interferes with the performance of motor tasks.

Basal Ganglia

Basal ganglia circuits regulate the initiation, amplitude, and speed of movements. Diseases of the basal ganglia cause abnormalities of movement and are collectively known as movement disorders.

Several neurotransmitters are found within the basal ganglia. Acetylcholine is present in high concentrations within the corpus striatum, where it is synthesized and released by large Golgi type 2 neurons. Acetylcholine acts as an excitatory transmitter at medium-sized spiny striatal neurons that synthesize and release the inhibitory neurotransmitter GABA and project to the globus pallidus. Dopamine is synthesized by neurons of the substantia nigra, whose axons form the nigrostriatal pathway that terminates in the corpus striatum. Dopamine released by these fibers inhibits striatal GABAergic neurons.

Somatosensory pathways confer information about touch, pressure, temperature, pain, vibration, and the position and movement of body parts. This information is relayed to thalamic nuclei and integrated in the sensory cortex of the parietal lobes to provide conscious awareness of sensation. Information is also relayed to cortical motor neurons to adjust fine movements and maintain posture. Some ascending sensory fibers, particularly pain fibers, enter the midbrain and project to the amygdala and limbic cortex, where they contribute to emotional responses to pain. In the spinal cord, painful stimuli activate local pathways that induce the firing of lower motor neurons and cause a reflex withdrawal. Thus, somatosensory pathways provide tactile information, guide movement, and serve protective functions.

Sensory receptors can be specialized dendritic endings of afferent nerve fibers, and they are often associated with non-neural cells that surround it, forming a sense organ**.** Touch and pressure are sensed by four types of mechanoreceptors.

- *Meissner corpuscles* are dendrites encapsulated in connective tissue and respond to changes in texture and slow vibrations.
- *Merkel cells* are expanded dendritic endings, and they respond to sustained pressure and touch.
- *Ruffini corpuscles* are enlarged dendritic endings with elongated capsules, and they respond to sustained pressure.
- *Pacinian corpuscles* consist of unmyelinated dendritic endings of a sensory nerve fiber, encapsulated by concentric lamellae of connective tissue. These receptors respond to deep pressure and fast vibration.

LAWS OF SENSORY SYSTEM

- *Weber–Fechner law:* The intensity of sensation is determined by the amplitude of the stimulus applied to the receptor. The magnitude of the sensation felt is proportional to the log of the intensity of the stimulus.
- *Law of specific nerve energies:* When the nerve pathways from a particular sense organ are stimulated, the sensation evoked is that for which the receptor is specialized no matter how or where along the pathway the activity is initiated.
- *Law of projection:* No matter where a particular sensory pathway is stimulated along its course to the cortex, the conscious sensation produced is referred to the location of the receptor.
- *Bell–Magendie law:* In the spinal cord the dorsal roots are sensory and the ventral roots are motor.

SENSORY MODALITIES

Pain

- Free nerve endings of unmyelinated C fibers and small-diameter myelinated fibers in the skin convey sensory information in response to chemical, thermal, and mechanical stimuli. Intense stimulation of these nerve endings evokes the sensation of pain. In contrast to skin, most deep tissues are relatively insensitive to chemical or noxious stimuli. Information from primary afferent fibers is relayed via sensory ganglia to the dorsal horn of the spinal cord and then to the contralateral spinothalamic tract, which connects to thalamic neurons that project to the somatosensory cortex.

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- Neuropeptides released by injured nerves may recruit an inflammatory reaction that stimulates pain. In the dorsal horn, denervated spinal neurons may become spontaneously active. In the brain and spinal cord, synaptic reorganization occurs in response to injury and may lower the threshold for pain. In addition, inhibition of pathways that modulate transmission of sensory information in the spinal cord and brainstem may promote neuropathic pain.
- Pain-modulating circuits exert a major influence on the perceived intensity of pain. One such pathway is composed of cells in the periaqueductal gray matter of the midbrain that receive afferents from frontal cortex and hypothalamus and project to rostroventral medullary neurons. These in turn project in the dorsolateral white matter of the spinal cord and terminate on dorsal horn neurons. Additional descending pathways arise from other brainstem nuclei (locus ceruleus, dorsal raphe nucleus, and nucleus reticularis gigantocellularis).

Mechanisms of Pain and Nociception

- *Nociception* is the mechanism whereby noxious peripheral stimuli are transmitted to the central nervous system. *Pain* is a subjective experience not always associated with nociception. Allodynia is a sensation of pain in response to innocuous stimuli. It is due to sensitivity of nociceptive afferent fibres due to chemicals released during injury.
- Polymodal nociceptors (PMNs) are the main type of peripheral sensory neuron that responds to noxious stimuli. The majority are non-myelinated C fibres whose endings respond to thermal, mechanical and chemical stimuli.
- Chemical stimuli acting on PMNs to cause pain include bradykinin, protons, ATP and vanilloids (e.g. capsaicin). PMNs are sensitised by prostaglandins, which explains the analgesic effect of aspirin-like drugs, particularly in the presence of inflammation.
- The vanilloid receptor TRPV1 (transient receptor potential vanilloid receptor 1) responds to noxious heat as well as capsaicin-like agonists. The lipid mediator anandamide is an agonist at vanilloid receptors, as well as being an endogenous cannabinoid receptor agonist; other TRP channels: TRPM8 (M – menthol) cooling effect given by mint; activated by moderate cold; TRPV4 (V – vanilloid) activated by warm temperature 34°C; TRPV 3 – activated by slightly higher temperature (35–39°C); V – activated also by intense heat, acids, chemicals such as capsaicin (hot pepper)
- Nociceptive fibres terminate in the superficial layers of the dorsal horn, forming synaptic connections with transmission neurons running to the thalamus.
- PMN neurons release glutamate (fast transmitter) and various peptides (especially substance P) that act as slow transmitters. Peptides are also released peripherally and contribute to neurogenic inflammation.
- Neuropathic pain, associated with damage to neurons of the nociceptive pathway rather than an excessive peripheral stimulus, is frequently a component of chronic pain states and may respond poorly to opioid analgesics.
- *Causalgia:* Spontaneous burning pain sensation in injured area, due to release of NA from sympathetic nerve fibres, (alpha blockers relieve pain).
- *Hyperalgesia:* Exaggerated response to painful stimuli, is of two types:
  1. *Primary:* Directly due to noxious stimuli (hypersensitization of nociceptors)
  2. *Secondary:* Noxious stimuli also activating the silent receptors, (increase sensitization of spinothalamic tract due to continuous discharge of type C fibre (sensory facilitation).
- *Analgesic system:*
  - Endogenous analgesic system
  - Dorsal horn gating
  - Dorsal horn gating/segmental suppression: Rubbing/massage/application of cold, counter irritants/acupuncture/TENS activation of AB presynaptic inhibition of pain carrying fibres, (blocking Ca^{++} channels) of AB
- *Endogenous analgesic system:*
  - Raphe magnus nucleus (RMN)
  - Periaquaductal gray matter (PAG)
- *RMN:* They contain neurons serotonin and substance P serotoninergic neurons exert post synaptic inhibition on nociceptive afferents in the dorsal horn.
- *PAG:* It inhibits pain by stimulating the RMN, they have OPIOID receptors.
- *Opioid receptors:*
  1. Present in the spinal cord (substantia gelatinosa)
  2. PAG MORPHINE can act on both the (spinal and supraspinal receptors.

PROPRIOCEPTION AND VIBRATORY SENSE

Receptors in the muscles, tendons, and joints provide information about deep pressure and the position and movement of body parts. This allows one to determine an object's size, weight, shape, and texture. Information is relayed to the spinal cord via large myelinated fibers and to the thalamus by the dorsal column-lemniscal system. Detecting vibration requires sensing touch

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and rapid changes in deep pressure. This depends on multiple cutaneous and deep sensory fibers and is impaired by lesions of multiple peripheral nerves, the dorsal columns, medial lemniscus, or thalamus but rarely by lesions of single nerves. Vibratory sense is often impaired together with proprioception.

DISCRIMINATIVE SENSATION

- Primary sensory cortex provides awareness of somatosensory information and the ability to make sensory discriminations. Touch, pain, temperature, and vibration sense are considered the primary modalities of sensation and are relatively preserved in patients with damage to sensory cortex or its projections from the thalamus.
- In contrast, complex tasks that require integration of multiple somatosensory stimuli and of somatosensory stimuli with auditory or visual information are impaired. These include the ability to distinguish two points from one when touched on the skin (two-point discrimination), localize tactile stimuli, perceive the position of body parts in space, recognize letters or numbers drawn on the skin (graphesthesia), and identify objects by their shape, size, and texture (stereognosis).

HEARING AND BALANCE

- **There are three types of hearing loss:**
  1. Conductive deafness, which is due to diseases of the external or middle ear that impair conduction and amplification of sound from the air to the cochlea;
  2. Sensorineural deafness, resulting from diseases of the cochlea or eighth cranial nerve; and
  3. Central deafness, resulting from diseases affecting the cochlear nuclei or auditory pathways in the CNS. Because of the redundancy of central pathways, almost all cases of hearing loss are due to conductive or sensorineural deafness.
- Conductive and sensorineural deafness may be distinguished by examining hearing with a vibrating 512Hz tuning fork. In the Rinne test, the tuning fork is held on the mastoid process behind the ear and then is placed at the auditory meatus. If the sound is louder at the meatus, the test is positive. Normally the test is positive, because sound transmitted through air is amplified by middle-ear structures. In sensorineural deafness, although sound perception is reduced, the Rinne test is still positive because middle-ear structures are intact. In conductive deafness, sounds are heard less well through air and the test is negative. In the Weber test, the tuning fork is applied to the forehead at the midline. In conductive deafness, the sound is heard best in the abnormal ear, whereas with sensorineural deafness the sound is heard best in the normal ear. Audiometry can distinguish types of hearing loss. In general, sensorineural deafness causes greater loss of high-pitched sounds, whereas conductive deafness causes more loss of low-pitched sounds.

In contrast to hearing, vestibular function is commonly disturbed by small brainstem lesions. The vestibular nuclei occupy a large portion of the lateral brainstem, extending from medulla to midbrain. Although there are extensive bilateral connections between vestibular nuclei and other motor pathways, these connections are not redundant but are highly lateralized and act in concert to control posture, balance, and conjugate eye movement.

CONSCIOUSNESS AND AROUSAL

- Consciousness is awareness of self and the environment. It has two aspects: arousal, which is the state of wakefulness, and cognition, which is the sum of mental activities. This distinction is useful because neurologic disorders can affect arousal and cognition differently.
- Arousal is generated by activity of the ascending reticular activating system, which is composed of neurons within the central mesencephalic brainstem, the lateral hypothalamus, and the medial, intralaminar, and reticular nuclei of the thalamus. Widespread projections from these nuclei synapse on distal dendritic fields of large pyramidal neurons in the cerebral cortex and generate an arousal response. Cognition is the chief function of the cerebral cortex, particularly of prefrontal cortex and cortical association areas of the occipital, temporal, and parietal lobes. Some specialized mental functions are localized to specific cortical regions. Several subcortical nuclei in the basal ganglia and thalamus are intimately linked with cortical association areas, and damage to these nuclei or their interconnections with cortex may give rise to cognitive deficits similar to those observed with cortical lesions.
- The reticular activating system is excited by a wide variety of stimuli, especially somatosensory stimuli. It is most compact in the midbrain and can be damaged by central midbrain lesions, resulting in failure of arousal, or coma. Higher nuclei and projections are less localized, and lesions rostral to the midbrain, therefore, must be bilateral to cause coma.

COGNITION

- The prefrontal cortex generally refers to areas 9, 10, 11, 12, 45, 46, and 47 of Brodmann on the superior and lateral surfaces of the frontal lobes and the anterior cingulate, parolfactory, and orbitofrontal cortex inferiorly and mesially. These regions are

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essential for orderly planning and sequencing of complex behaviors, attending to several stimuli or ideas simultaneously, concentrating and flexibly altering the focus of concentration, grasping the context and meaning of information, and controlling impulses, emotions, and thought sequences.

- The parietal association cortex is the region principally involved in visuomotor integration of constructional tasks. The visual cortex is required for observation, whereas the auditory cortex and the temporal language cortex are necessary for drawing objects on command. The inferior parietal cortex (areas 39 and 40) integrates visual and auditory information, and the output from this region is translated into motor patterns by motor cortex.

Calculation ability, abstract reasoning, problem solving, and several other aspects of intelligence are difficult to localize because they require integration of several cortical regions. They are frequently disturbed by diseases that cause widespread cortical dysfunction, such as those that cause dementia.

Hypothalamus and its Functions

The hypothalamus forms an integral part in maintaining the internal environment of the body.

Function	Corresponding areas
Temperature regulation	Anterior hypothalamus, response to heat; posterior hypothalamus, response to cold
Catecholamines	Dorsal and posterior hypothalamus
Vasopressin	Supraoptic and paraventricular nuclei
Oxytocin	Supraoptic and paraventricular nuclei
Thyroid-stimulating hormone (thyrotropin, TSH)	Paraventricular nuclei and neighboring areas
Adrenocorticotropic hormone (ACTH) and lipotropin (LPH)	Paraventricular nuclei
Follicle-stimulating hormone (FSH) and luteinizing hormone (LH)	Preoptic area; other areas
Prolactin	Arcuate nucleus
Growth hormone	Periventricular nucleus, arcuate nucleus
Thirst	Lateral superior hypothalamus
Hunger	Ventromedial, arcuate, and paraventricular nuclei; lateral hypothalamus
Sexual behavior	Anterior ventral hypothalamus plus, in the male, piriform cortex
Defensive reactions (fear, rage)	Diffuse, in limbic system and hypothalamus
Control of body rhythms	Suprachiasmatic nuclei
Hypothalamic functions	

TEMPERATURE REGULATION

Physiological changes to cold:(decrease heat loss)

- Cutaneous vasoconstriction: skin acts as a cold shell around a warm core and keeps the core warm, by reducing heat loss. (earliest response)
- Curling up posture
- Piloerection (animals)

Increase heat production:

- Shivering (major heat production)
- Hyperphagia and exercise
- Nonshivering thermogenesis
- *Hormones:* CA, Thyroxine

Nonshivering thermogenesis:

- *Organs:* Liver, abdominal viscera, skeletal muscle and brown fat.
- Activation of sympathetic nervous system (NE).
- *Human beings:* Very important in infants and neonates.
- Uncoupling of oxidative phosphorylation, UCP-1
- Mitochondria, B3 receptors.
- *Chemical thermogenesis:* Thyroxine.

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Heat loss from the body, when the environmental temperature falls below the body temperature;

- Radiation and conduction: 70%
- Vaporization of sweat: 27%
- Respiration: 2%
- Urination and defecation: 1%

When the environmental temperature is > body temperature (heat stress), then the major route of heat loss is sweating.
Physiological changes to heat:

- Cutaneous vasodilatation (earliest response)
- Sweating (sympathetic cholinergic (most important)
- Panting (animals).

Learning and Memory

- Learning is acquisition of the information that gives humans the ability to alter behavior on the basis of experience. Memory is the retention and storage of that information.
- Explicit or declarative memory is associated with consciousness and is dependent on the hippocampus and other parts of the medial temporal lobes of the brain for its retention. Explicit memory is divided into episodic memory for events and semantic memory for facts.
- Implicit or nondeclarative memory does not involve awareness, and its retention does not usually involve processing in the hippocampus.
- Explicit memory and many forms of implicit memory involve (1) short-term memory, which lasts seconds to hours, during which processing in the hippocampus and elsewhere lays down long-term changes in synaptic strength; and (2) long-term memory, which stores memories for years and sometimes for life. Working memory is a form of short-term memory that keeps information available, usually for very short periods, while the individual plans action based on it.

Mechanisms

- Memory requires that information be registered by the primary somatosensory, auditory, or visual cortex. Posterior cortical areas involved in comprehension of language are needed for immediate processing of spoken or written events and recalling them immediately. The hippocampi and their connections to the dorsal medial nuclei of the thalamus and the mamillary nuclei of the hypothalamus constitute a limbic system network crucial for learning and processing of events for long-term storage. Memories that remain with a person for years are considered remote memories and are stored in corresponding association cortex areas.
- Short- and long-term changes in synaptic function can occur due to discharge at a synapse. They can be presynaptic or postsynaptic in location. One form of plastic change is post-tetanic potentiation, the production of enhanced postsynaptic potentials in response to stimulation. Habituation is a simple form of learning in which a neutral stimulus is repeated many times. The subject becomes habituated to the stimulus and ignores it after a period of time. This is associated with decreased release of neurotransmitter from the presynaptic terminal because of decreased intracellular Ca^{2+}. Sensitization is the prolonged occurrence of augmented postsynaptic responses after a stimulus to which one has become habituated is paired once or several times with a noxious stimulus. Sensitization is due to presynaptic facilitation.
- Long-term potentiation (LTP) is a rapidly developing persistent enhancement of the postsynaptic potential response to presynaptic stimulation after a brief period of rapidly repeated stimulation of the presynaptic neuron. It is initiated by an increase in intracellular Ca^{2+} in the postsynaptic neuron.
- A classic example of associative learning is a conditioned reflex. A conditioned reflex is a reflex response to a stimulus that previously elicited little or no response, acquired by repeatedly pairing the stimulus with another stimulus that normally does produce the response. The salivation normally induced by placing meat in the mouth of a dog was studied in the Pavlov's classic experiments. A bell was rung just before the meat was placed in the dog's mouth (the unconditioned stimulus (US) and this was repeated a number of times until the animal would salivate when the bell was rung (conditioned stimulus (CS). After the CS and US had been paired a sufficient number of times, the CS produced the response originally evoked only by the US.
- The encoding process for short-term explicit memory involves the hippocampus. Information from the senses is temporarily stored in various areas of the prefrontal cortex as working memory. From there, it enters the hippocampus. The hippocampus is closely associated with the overlying parahippocampal cortex in the medial frontal lobe. The connections of the hippocampus to the diencephalon are involved in memory. Some cases of memory loss correlate well with the presence of pathologic changes in the mamillary bodies, which have extensive efferent connections to the hippocampus via the fornix. The amygdala is closely associated with the hippocampus and is concerned with encoding and recalling emotionally charged memories.

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- Output from the hippocampus leaves via the subiculum and the entorhinal cortex and somehow binds together and strengthens circuits in many different neocortical areas, forming over time the stable remote memories. Long-term memories are stored in various parts of the neocortex. Once long-term memories have been established, they can be recalled or accessed by a large number of different associations.
- The Wechsler Memory Scale-Revised (WMS-R) is the most widely used memory test battery for adults. The Benton Visual Retention Test is sensitive to short-term memory loss.

Language and Speech

- One group of functions localized to the neocortex in humans consists of those related to language, that is, understanding the spoken and printed word and expressing ideas in speech and writing.
- The hemisphere concerned with categorization and symbolization has been called the dominant hemisphere. The other hemisphere is not "nondominant;" but, is specialized in the area of spatiotemporal relations. It plays a primary role in the recognition of faces. The concept of "cerebral dominance" and a dominant and nondominant hemisphere has been replaced by a concept of complementary specialization of the hemispheres, one for sequential-analytic processes (the categorical hemisphere) and one for visuospatial relations (the representational hemisphere). The categorical hemisphere is concerned with language functions.
- In most of right-handed individuals, the left hemisphere is the dominant or categorical hemisphere, and in the remaining, the right hemisphere is dominant. However, in the majority of left-handers, the left hemisphere is the categorical hemisphere.
- The dominant cerebral hemisphere in right-handed individuals is highly developed in language function, understanding of spoken and written words and expressing speech; lesions of the left lobe is associated with aphasia; the nondominant or right hemisphere is representational hemisphere associated with music, art and spaciotemporal relationship; lesion of the nondominant hemisphere – agnosia, astereognosis.
- Language is one of the fundamental bases of human intelligence. The cortical regions most critical for language include Broca's area (area 44), Wernicke's area (area 22), the primary auditory cortex (areas 41 and 42), and neighboring frontal and temporoparietal association areas. Wernicke's area is concerned with comprehension of auditory and visual information. It projects via the arcuate fasciculus to Broca's area (area 44) in the frontal lobe.
- Broca's area processes the information received from Wernicke's area into a detailed and coordinated pattern for vocalization and then projects the pattern via a speech articulation area in the insula to the motor cortex, which initiates the appropriate movements of the lips, tongue, and larynx to produce speech. The angular gyrus behind Wernicke's area processes information from words that are read in such a way that they can be converted into the auditory forms of the words in Wernicke's area.

Wernicke's area(22): Posterior end of superior temporal gyrus (inferior branch of MCA)

- Area of comprehension (words are planned)
- Lesion: Sensory/fluent/receptive/Wernicke's aphasia.
- Comprehension" naming,* insight-Impaired
- Fluency, neologism* Present

Brocas area(44): Inferior frontal gyrus (superior branch of MCA)

- Motor centre for speech
- Lesion: Affluent/motor/expressive aphasia
- Insight, comprehension (except grammar)—Preserved fluency, naming-impaired
- Neologism-absent; motor writing centre—Middle frontal gyrus, Exner's area.
- Motor cortex for speech (area 4).
- **Conduction aphasia:** Understanding present, mistakes in framing a sentence; Lesion—arcuate fasciculus.
- **Anomic aphasia:** Difficulty in understanding written language and pictures; Lesion: Angular gyrus (Dejerine area, 38)
- **Causes:** Metabolic encephalopathy, head trauma and Alzheimer's

Nerve fibers have been divided into three types according to their diameters, conduction velocities, and physiologic characteristics.

1. A fibers are large and myelinated, conduct rapidly, and carry various motor or sensory impulses. They are most susceptible to injury by mechanical pressure or lack of oxygen.
2. B fibers are smaller myelinated axons that conduct less rapidly than A fibers. These fibers serve autonomic functions.
3. C fibers are the smallest and are nonmyelinated; they conduct impulses the slowest and serve pain conduction and autonomic functions.

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Classification of nerve fibres			
Fiber type	*Function*	*Fiber diameter (microm)*	*Conduction velocity (m/s)*
A–alpha	Proprioception; somatic motor	12–20	70–120
Beta	Touch, pressure	5–12	30–70
Gamma	Motor to muscle spindles	3–6	15–30
Delta	Pain, temperature, touch	2–5	12–30
B	Preganglionic autonomic	< 3	3–15
C–dorsal root sympathetic	Pain, reflex responses	0.4–1.2	0.5–2
	Postganglionic sympathetics	0.3–1.3	0.7–2.3

Number	Origin	Fiber type
Ia	Muscle spindle, annulospiral ending	A alpha
Ib	Golgi tendon organ	A alpha
II	Muscle spindle, flower-spray ending; touch, pressure	A beta
III	Pain and temperature receptors; some touch receptors	A delta
IV	Pain and other receptors	C

Muscle Spindles

- Each muscle spindle has three essential elements:
  1. A group of specialized intrafusal muscle fibers with contractile polar ends and a noncontractile center,
  2. Large diameter myelinated afferent nerves (types Ia and II) originating in the central portion of the intrafusal fibers, and
  3. Small diameter myelinated efferent nerves supplying the polar contractile regions of the intrafusal fibers
- Changes in muscle length are associated with changes in joint angle; thus muscle spindles provide information on position. The intrafusal fibers are positioned in parallel to the extrafusal fibers (the regular contractile units of the muscle) with the ends of the spindle capsule attached to the tendons at either end of the muscle. Intrafusal fibers do not contribute to the overall contractile force of the muscle, but rather serve a pure sensory function. There are two types of intrafusal fibers in mammalian muscle spindles. The first type contains many nuclei in a dilated central area and is called a nuclear bag fiber. The second intrafusal fiber type, the nuclear chain fiber, is thinner and shorter and lacks a definite bag.
- When the muscle spindle is stretched, its sensory endings are distorted and receptor potentials are generated. These in turn set up action potentials in the sensory fibers at a frequency proportional to the degree of stretching. Because the spindle is in parallel with the extrafusal fibers, when the muscle is passively stretched, the spindles are also stretched. This initiates reflex contraction of the extrafusal fibers in the muscle.
- When a stretch reflex occurs, the muscles that antagonize the action of the muscle involved (antagonists) relax. This phenomenon is said to be due to *reciprocal innervation.* Up to a point, the harder a muscle is stretched, the stronger is the reflex contraction. However, when the tension becomes great enough, contraction suddenly ceases and the muscle relaxes. This relaxation in response to strong stretch is called the *inverse stretch reflex.* The receptor for the inverse stretch reflex is in the Golgi tendon organ and it senses muscle tension.

ELECTROENCEPHALOGRAPHY (EEG)

- Summation of the excitatory postsynaptic potential generated by the pyramidal cells of the cerebral cortex gives rise to the electrical activity of the brain, which can be recorded as an electroencephalogram (EEG). The EEG comprises many underlying components with different frequencies and harmonics. The component waves are typically classified according to the respective frequencies. This electrical activity is volume conducted and can be recorded from the scalp and forehead, using surface or needle electrodes.
- Because the scalp has no electrically neutral area, EEG is typically recorded using a montage (electrode arrangement) with bipolar recording. Thus, both electrodes are active, and the polarity of the signal recorded depends on the arbitrary designation of recording versus referential electrode.
- The gold standard for raw EEG recording is 16-channel recording (eight channels for each hemisphere) with electrodes placed according to the International System. The EEG is a random activity reflecting the state of arousal and metabolic activity. The generation of electrical activity is an energy-requiring process that depends on an adequate supply of substrates including oxygen and glucose.

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ISBN 978-93-90020-03-4

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