Neurobiology- Lectures

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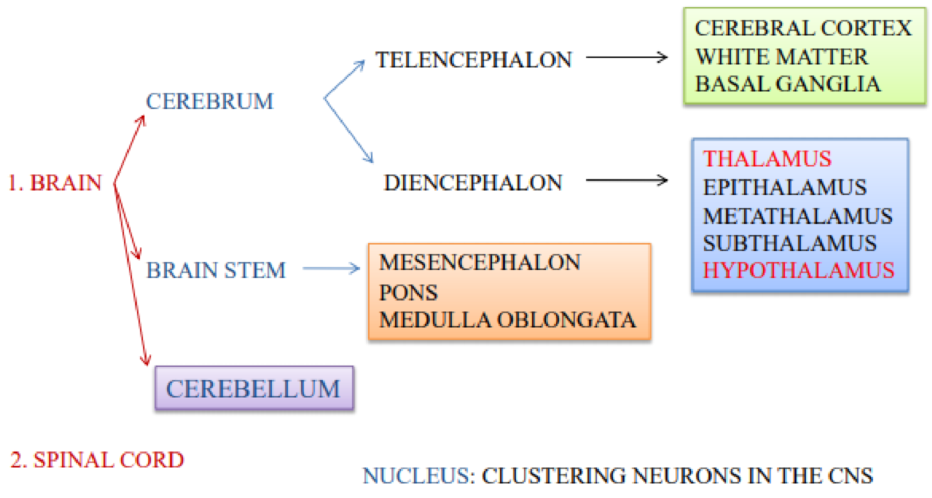
<u>The organ systems in our body</u>:

- skeletal system
  - bones, joints, ligaments, movements
- muscular system
  - skeletal, smooth, cardiac muscle
- circulatory system
  - systemic, pulmonary circulation; microcirculation
  - the lymphatic system
- visceral system
  - digestive system
    - breakdown of food
  - respiratory system
    - gas exchange
  - urinary system
    - production and excretion of urine
  - reproductive system
    - production of gamete cells, sex hormones
- nervous system
- endocrine system
  - regulation of homeostasis, adaptation, reproduction, mood
- organs of special senses
  - visual system
    - detection of light
  - auditory system
    - sense of sound perception
  - vestibular system
    - sensing body movement, direction and acceleration
  - olfactory system
    - sense of smell
  - taste system
    - triggers ingestion and prepares the gi-tract for food intake
- lymphatic and immune system

Development of the nervous system

- 3 germ layers → neural tube formation

CENTRAL NERVOUS SYSTEM (CNS)



Peripheral nervous system (PNS)

Structural units:

- cranial nerves (12)
- spinal nerves (31)
- sensory ganglia
- autonomic (vegetative) ganglia

Ganglion: clustering neurons in the PNS

Common features of the *brain* and the *spinal cord*

- protected by bones: skull & vertebral column
- investing membranes: meninges (dura mater, arachnoid, pia mater), subarachnoid space
- surrounded by a liquid compartment: cerebrospinal fluid (CSF)
- special shape and surface anatomy
- composed by grey and white matters
- contain cavities inside: brain vesicles, cerebral aqueduct, central canal
- establish multiple connections with each other
- communicate with the external and internal environments

Characteristics of the brain

- cerebral cortex
  - 4 lobes: frontal, temporal, parietal, occipital
  - convoluted gyri on its surface
  - hemispheric dominance
- basal ganglia
  - contributes to the control of the motor system

- thalamus
    - relays motor, sensory and limbic information to the cortex
- hypothalamus
    - neurosecretory capacity
    - controls the pituitary-endocrine axes and autonomic functions
- brain stem
    - control over the cranial part of the parasympathetic system
    - exerts monoaminergic and peptidergic cell groups of the arousal system
    - contains vital circulatory and respiratory centers
- cerebellum
    - coordinates duration, extent and force of muscle contraction

<u>Characteristics of the spinal cord</u>

- segments: cervical (8), thoracic (12), lumbar (5), sacral (5), coccyx
- grey matter organized in column, white matter divided into funiculi → butterfly shape
- structure of the spinal segment:
    - ventral root fibers (motor functions)
    - dorsal root fibers + dorsal root ganglion (sensory functions)
    - spinal nerve
    - dorsal ramus
    - ventral ramus
- spinal reflexes & injuries

<u>Peripheral Nervous System</u>

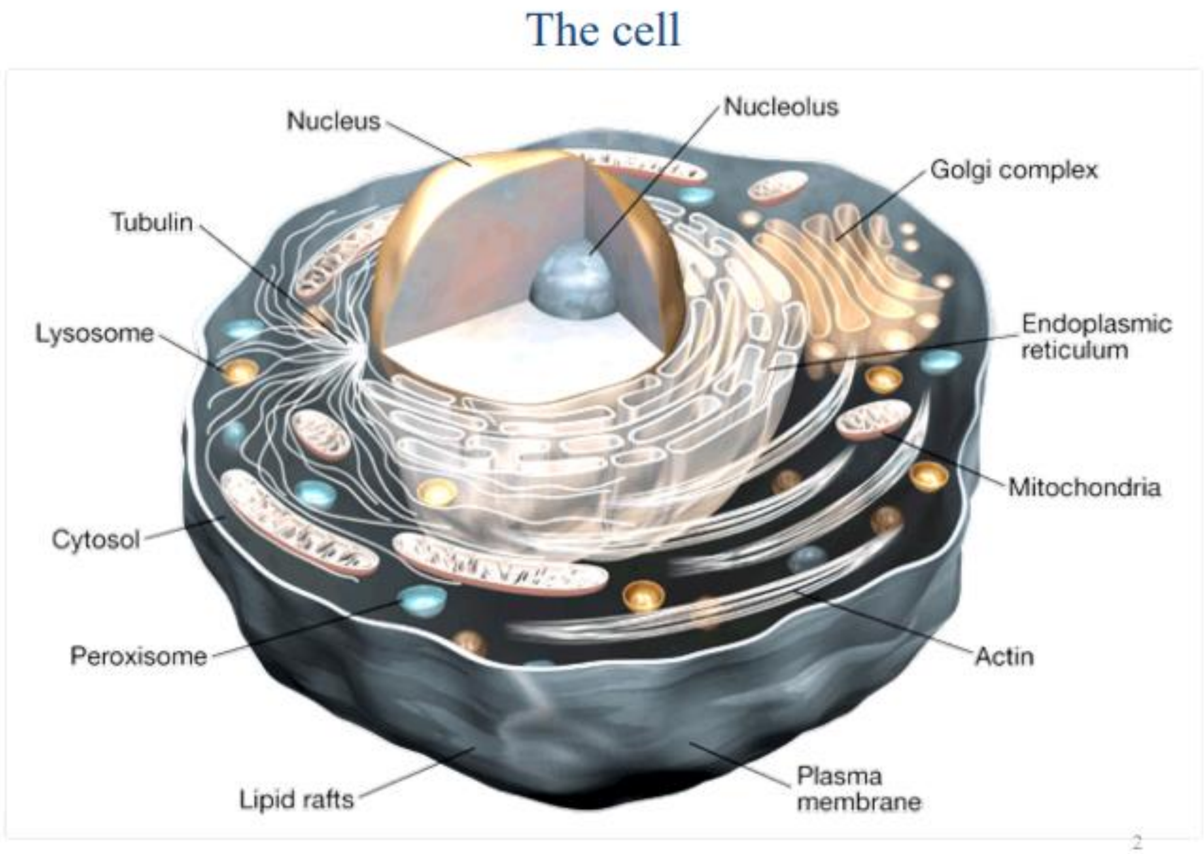
- The Somatic Part
    - somatomotor nerves innervate skeletal muscles
    - the lower motorneurons and the innervated striated muscle fibers form motor units that execute the active movements
    - the complex upper motorneuron system controls the lower motorneurons
    - the peripheral process of ganglion cells communicates with special receptors that pick up stimuli from the internal and external environments
- The Visceral Part
    - organ systems are controlled by the autonomic nervous system
    - two wings:
        - sympathetic part: utilizes stored energy for emergency
            - centers: in thoraco-lumbar segments of the spinal cord
        - parasympathetic part: conserves energy for the body
            - centers: in the brain stem and the sacral part of the spinal cord
    - do not innervate directly the target organs

<u>Basic tissue types</u>

- Epithelia
    - covering, glandular, sensory, pigmented
    - eg. gut and vessel lining
    - functions: barrier, absorption, secretion
    - its cells are tightly bound together by cell junctions

- Connective tissue
    - embryonic, dense, loose, elastic, loose, reticular, adipose, cartilage, bone
    - function: organize and maintain body structure
    - its cells produce and interact with extracellular matrix material
- Muscle tissue
    - smooth, skeletal, cardiac
    - function: movement
    - filamentous proteins make them contract
- Nervous tissue
    - neurons, glia
    - function: direct cell communication
    - release chemical messengers onto surface of other cells

<u>Cell organelles</u>



Cell membrane

- fluid mosaic model of membrane structure
- phospholipid bilayer
- inner membrane proteins, surface proteins, transmembrane proteins
- transport across plasma membranes:
    - passive diffusion (concentration gradient dependent)
    - facilitated diffusion (requires transporters)
    - active transport (requires energy, against conc. gradient)

Cytoplasm

- hosts the cell organelles
- 70% of the cell volume, contains water, inorganic salts and organic molecules
- the cytoskeleton is embedded, the organelles are suspended in it
- site of metabolic actions, signal transduction and cell division

Nucleus

- nuclear envelope: double membrane layer, continuous with RER
- nuclear pores: regulates trafficking between the nucleus and cytoplasm
- nuclear matrix: DNA, RNA, nucleoproteins, barr body
- storage of genetic information, the human genome
- transcription

Nucleolus

- produces ribosomal RNAs, that are conjugated with riboproteins in order to make ribosomal subunits

Rough Endoplasmic Reticulum (RER)

- composed by tubules, vesicles and flattened sacs
- ribosomes are attached to its surface
- in neurons: RER patches = Nissl-bodies
- newly synthesized proteins get into the lumen of the membrane sacs

Smooth Endoplasmic Reticulum (SER)

- it does not carry ribosomes
- continuous with the RER system and linked to the Golgi system
- takes part in lipid synthesis, glycogen metabolism, breakdown of metabolites and detoxification
- stores and releases Calcium in excitable tissues

Golgi complex

- consists of stacked saucer-shaped flattened cisternae
- between the nucleus and the ER system
- cis or forming face: faces the ER system
- trans or maturing face: the concave surface
- communicates via membrane bound vesicles with the rest of the cell organelles
- transfer vesicles budding off the ER fuse with the cis face and transport macromolecules for further processing
- the tagging of macromolecules enables their sorting for domestic use, secretion for external utilization or local degradation
- liposomal vesicles, proteoglycans originate from the Golgi complex

Transport vesicles

- secretory vesicles
    - store proteins for extracellular use, triggered by release signals they move to and fuse with the plasma membrane
- exocytic vesicles
    - constitutive secretion maintaining a continuous supply of proteins to the extracellular space by exocytosis
- lysosomal vesicles
    - contain proteins, degrading enzymes; they get incorporated into the lysosomal digestive machinery

Lysosome

- Golgi hydrolase vesicles contain several kinds of digesting enzymes (lipase, nuclease, protease, amylase)
- they fuse with endosomes resulting in endolysosomes whose internal milieu is acidic which is maintained by pumping H^+ ions from the cytoplasm via Cl^- ion channels and proton pumps
- from endolysosomes lysosomes are formed
- after digestion, residual bodies are formed from lysosomes, some enzymes get recycled

Mitochondrion

- covered by the outer membrane, the inner membrane is folded and sends projecting cristae into the organelles, the two membranes surround intermembranous space
- the cavity of the mitochondrion is filled with the matrix substance
- contains circular DNA, RNA, ribosomes and a wide array of enzymes
- the power plants of the cell, providing ATP as a source of chemical energy

Cytoskeleton

- microfilaments
    - made of actin; in muscle tissue, they interact with myosin →contraction
- microtubules
    - compose of alpha and beta tubulins, MAPs stabilize the structure; dynein & kinesin act as motors in delivery along the microtubules; anterograde and retrograde transport mechanisms in neurons; vital in cell division
- intermediate filaments
    - form a relatively stable, fibrous network in cells; the protein composition of the intermediate filaments seems to be tissue specific

Cilium

- membrane covered, finger like projection of the cytoplasm
- they swipe mucous on the surface of epithelial cells

Centriole

- they organize the growth of microtubules

<u>The main characteristics of the nervous tissue:</u>

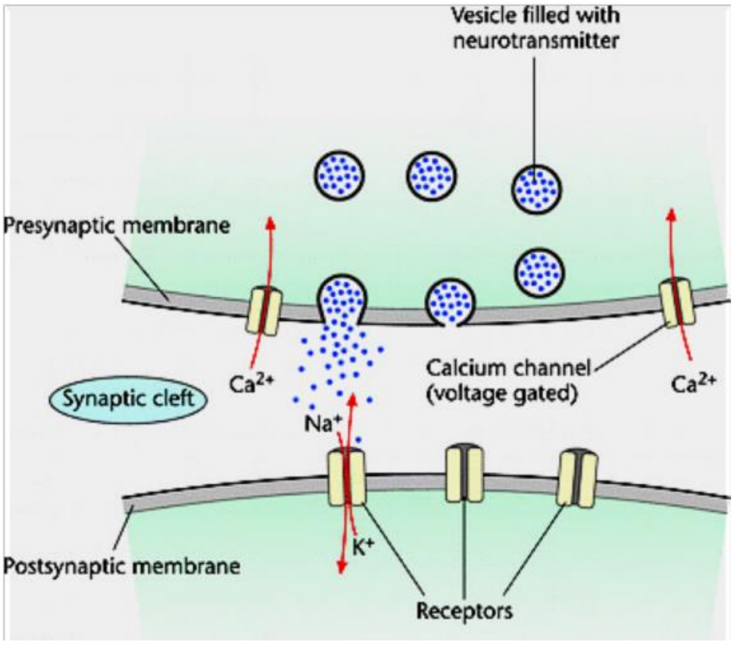
- based on the incoming data, it dispatches commands that regulate the basic functions of the body and adjust them to the changing internal and external conditions
- two major cell types: neurons & glial cells
- neurons have processes (dendrites, axons) that are used for networking and communication
- neurons are excitable cells that maintain a -70 mV resting potential due to the uneven distribution of K^+ , Na^+ and Cl^- ions across the plasma membrane
- increase in the K^+ and Na^+ conductances → action potential → electric or chemical signalling affecting the membrane properties of the synaptically coupled neurons
- glial cells are in structural and functional symbiosis with neurons

Basic neuron types:

- multipolar neurons
  - the most common type, extended and branching dendritic tree
  - motorneurons of the spinal cord
- bipolar neurons
  - a dendritic process & an axon, originating from the opposite poles of the cell
  - sensory neurons of the vestibular ganglion
- pseudo-unipolar neurons
  - the dendrite and the axon arise from a common stem of the neuron
  - sensory neurons of the spinal ganglion

The structure of a neuron

- dendritic tree
  - collection of dendrites, has dendritic spines, receives afferent axon terminals from other neurons
- cell body
  - rich in cell organelles, ensures protein production
- axon hillock
  - the site for axon origin, high density of voltage-dependent Na^+ channels, action potential initiation
- axon collateral
  - branch of the axon process, takes part in neuronal networks
- axon
  - efferent process of the neuron, propagates action potential, ensures transport mechanisms
- axon terminal
  - the branching processes of the axon, communicating with other elements releases neuro-messengers



Main cellular functions of neurons

- generate internal activity
- receive external, synaptic inputs
- integrate internal and external signals
- encode the pattern of output
- distribute information via synapses

The cell body

- 10-100 μm wide
- central nucleus with 1-2 nucleoli
- the cytoplasm contains well-developed RER system (Nissl-bodies), many mitochondria and has a high RNA content
- free ribosomes, RER and Golgi complexes take part in the production and sorting of proteins

The cell body-free region of the neural tissue is called *neuropil*.

Dendrites

- continuous with the cytoplasm
- primary, secondary and tertiary units
- they establish thin cytoplasmic projections called dendritic spines
- dendritic shafts and spines receive most of the incoming information, therefore synapsing axon terminals can be found on their surfaces
- the dendritic tree takes part in neuronal plasticity and remodelling
- they contain microtubules, RER, polysomes and specific mRNAs
- rich in specific peptide and transmitter receptors
- primary role: integration of the incoming information from thousands of axons

Axons

- initial segment: axon hillock, has a high density of ion channels, the generation of action potential begins here
- they carry specialized pre-synaptic machineries for communication
- they branch at their final destination, pre-terminal arborization
- the axon terminal:
    - contains microtubules, neurofilament bundles, mitochondria and pools of synaptic vesicles
    - its terminal enlargement is called bouton

Histological classification of nerve fibers

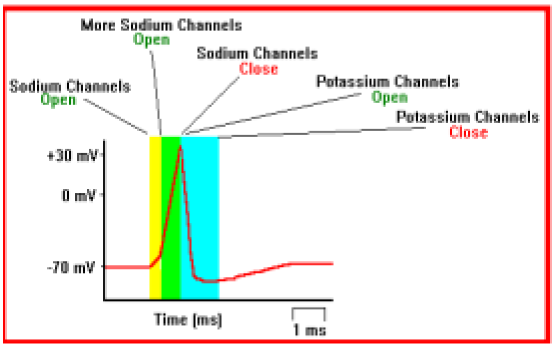
- naked axons
    - the thinnest axons in the nervous system
    - diameter: 0.1-0.3 μm
    - no insulating sheath → direct contact with the extracellular space and fluid
    - occur in axon bundles within the CNS
    - their conduction velocity is low (0.5-2 m/sec)
    - the initial and the terminal segments of neurons are naked as well
- non-myelinated axons
    - individual Schwann cells enclose 150-200 μm segments of the axon
    - a single Schwann cell hosts several axons in its cell body
    - also called remak-fibers
    - fibers belonging to this category are
        - post ganglionic fibers of the autonomic nervous system
        - sensory fibers carrying crude touch, temperature and pain sensations
- axons myelinated by Schwann cells
    - appear in the PNS
    - Schwann cells rotate around the axons → the formation of a concentric, multi-laminar membrane structure called myelin (lipids + proteins)
    - outside the myelin sheath, the compressed Schwann cell bodies occur
    - the myelin insulation is not continuous → Ranvier nodes → ion movements between the intra- and the extracellular compartments take place
    - the myelin sheath speeds up the propagation of the information in the axon
- axons myelinated by oligodendrocytes
    - appear in the CNS
    - a single oligodendrocyte can insulate about 50 axons
    - Ranvier nodes also exist between the adjacent myelin insulations
    - myelinated axons propagate action potential in a saltatory manner from one Ranvier node to the other
    - demyelination → severe and diffuse neural diseases

Peripheral nerves

- neural fiber bundles, wrapped by connective tissue → endo-, peri- and epineurium
- sensory, motor or mixed phenotypes
- establish connections with receptor and effector structures

Action potential

- transmits signals from the cell body toward the axon terminal
- due to the sudden change in the distribution and concentration of ions in the intra- and extracellular fluid compartments separated by the axon membrane
- 3 successive stages:
    - resting stage, membrane is polarised, -70 mV membrane potential
    - depolarisation stage, Na^+ ion inflow, +50 mV membrane potential
    - repolarisation stage, Na^+ channels close, opening K^+ channels allow the outflow of K^+ from inside
- afterhyperpolarisation
- refractory period
- saltatory and wave like conductions of AP



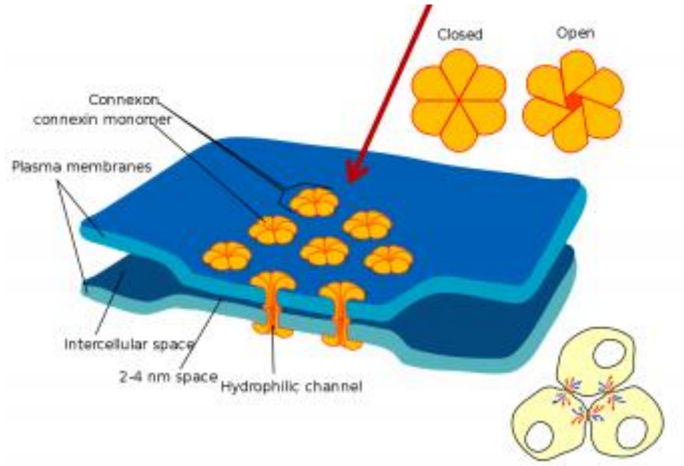
Classification of neuroglia

- astroglia
    - protoplasmic astrocyte (in the grey matter)
    - fibrous astrocyte (in the white matter)
    - astrocytes have several, thin processes, contain glial fibrillary acidic protein (GFAP) made filaments and glycogen
    - their processes fill the gaps among neurons, project to blood vessels to form the blood-brain-barrier, surround and isolate synapsing neuronal elements and form the internal and external glial laminae
    - astrocytes are coupled by gap junctions, they generate spreading Ca waves
    - they express glutamine-synthetase, a key enzyme participating in ammonia detoxification and GABA, glutamate transmitter inactivation
    - regulation of extracellular K^+
    - control of Ca^{2+} homeostasis
    - regulation of pH and extracellular space volume
- oligodendroglia
    - intrafascicular oligodendrocytes occur in axon bundles of the CNS where they interact with axons and form the myelin sheath for them
    - satellite oligodendrocytes are juxtaposed to neurons and support them
    - oligodendrocytes are small-sized cells with numerous branching processes
    - a single oligodendrocyte may work together with dozens of axons

- microglia
    - resting microglia has several ramifying processes that move constantly and survey the neighbouring area
    - they operate as resident immune cells of the CNS
    - they are capable of phagocytosis and removal of damaged neurons, degenerative plaques, and infectious agents
    - together with astrocytes, they form a powerful defence system for the protection of the CNS
    - activated microglia
        - has a larger cell body and thicker processes, in case of a severe pathological insult the reactive microglia can transform into macrophages
        - the triggers of activation: glutamate receptor activation, changes in extracellular K^+ level, lipopolysaccharides, pro-inflammatory cytokines and necrosis factors
        - special functions:
            - cleaning up debris
            - engulfing cellular elements
            - releasing proteases, cytokines, glutamate
            - antigen presentation
            - extracellular signaling
- ependyma
    - ependymocytes
    - neural tissue facing the cavities of the brain and spinal cord
    - they are cuboidal or columnar in nature carrying microvilli and kinocilia on their ventricular, apical surfaces
    - the kinocilila support the flow of CSF, the microvilli are used for absorption
    - situated at the border of the CSF and the extracellular space liquid compartments
    - tight and gap junctions occur between ependymal cells
    - tanycytes
        - cover the floor region of the third cerebral ventricle
        - transport substances from the CSF to the circulation
        - contain type 2 deiodinase enzyme that generates the active thyroid hormone, triiodothyronine from its pro-hormone
- Schwann cells

<u>Functions of neuroglia</u>

- guidance of neuron migration in early development
- establishment of the blood brain barrier
- formation of myelin
- participation in brain energy metabolism
- production of extracellular matrix
- neurotransmitter uptake, the glutamate-glutamine shuttle
- synthesis of growth factors and cytokines
- phagocytosis, neuroprotection, aging

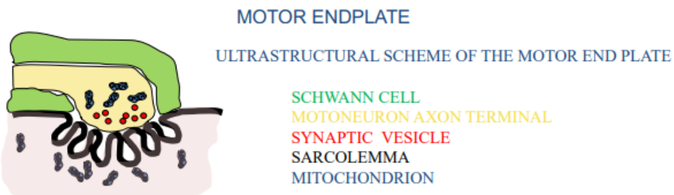


BLOOD-BRAIN BARRIER

<u>Nerve endings</u>

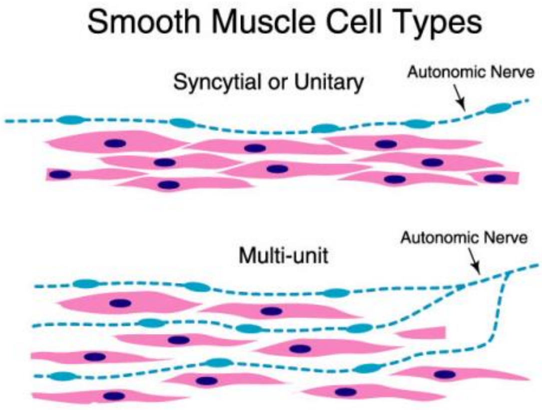
Neurons communicate with *non-neuronal* elements via specialzed nerve endings belonging to effector and receptor categories.

- effectors
    - motor end plate
        - axons of somatic motor neurons innervate skeletal muscle fibers
        - the terminal axon loses its myelin sheath and the terminal boutons juxtapose to the sarcolemma, the membrane of the muscle fiber
        - the axon terminal contains synaptic vesicles filled with the neurotransmitter acetylcholine
        - activation of the nerve terminal leads to the release of the transmitter that binds to its receptors embedded into the muscle membrane the receptor activation evokes cascade events resulting in the contraction of the muscle fibers



    - autonomic fiber plexus
        - postganglionic nerve fibers of the sympathetic and parasympathetic branches of autonomic nervous system innervate the cardiac muscle, smooth muscle bundles of visceral organs and glands
        - these axons do not establish synapses with the target cells

        - they release the transmitter into the extracellular space from their axon varicosities
        - specific receptors of the target cells pick up the transmitters and initiate the cellular responses



- receptors
    - muscle receptors
        - muscle spindle is a capsulated receptor composed of special, striated muscle fibers, the structure is embedded among extrafusal muscle fibers
        - the stretching of the extrafusal muscle fibers activates the receptor that informs the CNS and evokes the contraction
    - sensory epithelial cells
        - capable of sensing special stimuli
        - related to the special sense organ system
        - primary sensory cells convey the information to the CNS by their own processes
        - secondary sensory cells forward the information by the peripheral processes of sensory ganglion neurons
    - mechanoreceptors
        - respond to pressure and distortion
        - numerous in the superficial and deep layers of the skin
        - either free or encapsulated nerve endings
    - thermoreceptors
        - code absolute and relative changes in temperature
        - free nerve endings of unmyelinated and thin myelinated fibers
        - cold and warm sensitive types
    - pain receptors
        - respond to tissue damaging noxious stimuli
        - crucial role in avoiding the harmful insults of the environment and help to preserve the integrity of the body
        - fast and slow conducting systems
        - integrated within the nociceptor reflex arc
    - chemoreceptors
        - monitor changes in the chemical composition of the circulating blood
        - sense O_2, CO_2 saturation and pH
        - contribute to the regulation of respiration and circulation

Neurons communicate with other neuronal elements via specialized structural and functional units.

- synapses
    - chemical synapse
        - axo-dendritic
        - axo-spinous
        - axo-somatic
        - axo-axonic
        - dendro-dendritic
    - electrical synapse

Cellular events of synaptic information transfer

1. thousands of axon boutons terminate on the dendritic tree and somata of target neurons carrying excitatory and inhibitory signals
2. the integrated membrane potential reaching the threshold evokes an action potential in the presynaptic cell which is propagated toward its axon terminal
3. the action potential opens the voltage-gated Ca channels in the terminal allowing the influx of Ca
4. Ca activates the protein machineries of synaptic vesicle docking resulting in the exocytosis of vesicles
5. the neurotransmitter is released into the synaptic cleft
6. the neurotransmitter acts on the postsynaptic membrane activating ion channels and receptor-coupled intracellular messenger systems
7. after the action, the neurotransmitter gets inactivated in the synaptic cleft by breakdown or undergoes re-uptake

Excitatory synapses	**Inhibitory synapses**
neurotransmitters: acetylcholine, serotonin, dopamine, noradrenaline and histamine	neurotransmitters like GABA and glycine in certain systems and developmental periods, some neurotransmitters can also act in an opposite manner
they increase the membrane permeability to Na^+ → increase of the resting membrane potential: excitatory postsynaptic potential (EPSP)	inhibitory transmitters open K^+ and/or Cl^- channels → decrease of the resting membrane potential (hyperpolarisation): inhibitory postsynaptic potential (IPSP)
they generally carry spherical synaptic vesicles with 30-40 nm diameter	they generally carry flattened synaptic vesicles
the formed synaptic specializations are asymmetric in nature with prominent thickening of the postsynaptic membrane	the formed synaptic specializations are symmetric in nature, the pre- and postsynaptic membrane regions are equal in thickness

Special features of synaptic communication

- synaptic delay (about 0.5 millisecond)
- synaptic strength: defined by the change in transmembrane potential resulting from activation of the postsynaptic neurotransmitter receptors
- fatigue of synaptic transmission: gradual decline of discharges of the postsynaptic neuron
- post-tetanic facilitation: in the rest period after a repetitive, tetanic stimulation the synapse might become even more responsive to subsequent stimulation than normally

Synaptic types in some special networks of the CNS

- bouton-type synapse
- en passant synapse
- basket-like synapse
- parallel contacts
- glomerular synapse

FEATURE	ELECTRICAL SYNAPSES	CHEMICAL SYNAPSES
➢ Distance between pre- and postsynaptic cell membranes	3.5 nm	30-50 nm
➢ Cytoplasmic continuity between pre- and postsynaptic cells	Yes	No
➢ Ultrastructural components	Gap junction channels	Presynaptic active zones and vesicles; postsynaptic receptors
➢ Agent of transmission	Ionic current	Chemical transmitter
➢ Synaptic delay	Virtually absent	Significant: at least 0.3 ms, usually 1-5 ms or longer
➢ Direction of transmission	Usually bidirectional	Unidirectional

Neurotransmitters

- the synthesis of the chemical transmitter takes place in the presynaptic neuron
- it is stored in the release compartment of the cell, usually in axon terminals
- they are released to the synaptic cleft upon the excitation of the presynaptic element
- they bind to receptor(s) that belong to ionotropic and metabotropic classes

Classification of neurotransmitters

	AMINE	PEPTIDE
cell body	production of • synthesizing enzymes • storage vesicles	production of • peptide precursors • converting enzymes • storage vesicles
axon	axonal transport of • synthesizing enzymes • storage vesicles	axonal transport of • storage vesicles
terminal	supply of constituents • from cell body • local synthesis • re-uptake	supply of constituents • from cell body
example	acetylcholine GABA glutamate serotonin noradrenaline	enkephalin dynorphin vasopressin somatostatin cholecystokinin

<u>Amine neurotransmitters</u>

- dopamine
  - derivative of: L-dopa
  - synthesizing enzymes: tyrosine hydrolase, dopa decarboxylase
  - inactivation: monoamine oxydase (MAO), dopamine transporter (DAT)
  - receptor: D1, D2, D3, D4, D5 receptors, G protein-coupled
  - packed into synaptic vesicles by: vesicular monoamine-transporter-2
- noradrenaline
  - derivative of: dopamine
  - synthesizing enzyme: dopamine beta-hydroxylase
  - inactivation: MAO, re-uptake by norepinephrine transporter (NET)
  - receptors: G protein-coupled, alpha and beta types
  - packed into synaptic vesicles by: vesicular monoamine-transporter-2
- serotonin
  - derivative of: tryptophan
  - synthesizing enzymes: tryptophan hydrolase, aromatic L-amino acid decarboxylase
  - inactivation: MAO, re-uptake by serotonin transporter
  - receptors: ligand-gated ion channel, G protein-coupled
  - packed into synaptic vesicles by: vesicular monoamine-transporter-2
- histamine
  - derivative of: histidine
  - synthesizing enzymes: L-histidine decarboxylase
  - inactivation: histamin-N-methyl transferase, MAO-B
  - receptors: histamine receptors 1-4
  - packed into synaptic vesicles by: vesicular monoamine-transporter-2

- acetylcholine
  - derivative of: ester of acetic acid and choline
  - synthesizing enzymes: choline acetyltransferase
  - inactivation: acetylcholinesterase, choline transporter
  - receptors: nicotinic, ionotropic, ligand-gated ion channel,
    muscarinic, G protein-coupled, M1-M4
  - packed into synaptic vesicles by: vesicular Ach transporter
- glutamate
  - derivative of: alpha-ketoglutarate and glutamine
  - synthesizing enzymes: aminotransferase, glutaminase
  - inactivation: neuronal and glial uptake by plasme membrane glutamate transporters
  - receptors: ionotropic, AMPA, kainite, NMDA
    metabotropic, G protein-coupled
  - packed into synaptic vesicles by: vesicular glutamate transporter
- GABA
  - derivative of: L-glutamate
  - synthesizing enzymes: glutamate decarboxylase
  - inactivation: GABA aminotransferase
  - receptors: GABA A, chloride channels with various binding sites, GABA B
  - packed into synaptic vesicles by: vesicular GABA transporter (VGAT)
- glycine
  - derivative of: serine
  - synthesizing enzymes: serine hydroxymethyltransferase
  - inactivation: converted to glutathione, glycine transporters
  - receptors: chloride channels
  - packed into synaptic vesicles by: VGAT, VIAAT

<u>Characteristics of neuropeptides</u>

- composed of short chains of amino acids and synthesized by nerve cells
- used as signal molecules in interneural communication
- classified into neuropeptide hormone families based on similarities in origin, structure and function
- the hypothalamus is rich in neuropeptides
- neuropeptide precursor proteins are synthesized at the RER, then they are directed to the Golgi complex where modification occurs
- maturing proteins are packed in secretory vesicles that are released from the trans Golgi face
- neuropeptides are stored within neurosecretory granules of axon terminals, their diameter in in the range of 80-200 nm
- in the synaptic cleft, neuropeptides bind to their receptors that are coupled to G proteins
- in peptidergic synapses, recycling of neuropeptides does not occur, they rather diffuse and get cleaved by endopeptidases

Neuropeptide families:

- tachykinins: substance P, neurokinin A, neurokinin B
- opiod peptides: enkephalin, dynorphin, endorphin
- pancreatic polypeptide-releated: neuropeptide Y, peptide YY, pancreatic polypeptide
- insulin family: insulin, insulin-like growth factor
- gastrins: gastrin, cholecystokinin
- secretins: vasoactive intestinal peptide (VIP), secretin, glucagon
- neurohypophyseal hormones: oxytocin, vasopressin, neurophysin I-II
- release- and release-inhibiting: LHRH, TRH, CRH, somatostatin
- feeding peptides: neuropeptide Y, agouti releated peptide, alpha-melanocyte stimulating hormone, nesfatin, orexin

Hypothalamic hormones and their functions

SECRETED HORMONE	ABBREVIATION	PRODUCED BY	EFFECT
CORTICOTROPIN-RELEASING HORMONE	CRH or CRF	Parvocellular neurosecretory neurons	Stimulate adrenocorticotropic hormone (ACTH) release from anterior pituitary
THYROTROPIN-RELEASING HORMONE	TRH, TRF	Parvocellular neurosecretory neurons	Stimulate thyroid-stimulating hormone (TSH) release from anterior pituitary Stimulate prolactin release from anterior pituitary
GONADOTROPIN RELEASING HORMONE	GnRH or LHRH	Parvocellular neurosecretory neurons	Stimulate follicle-stimulating hormone (FSH) release from anterior pituitary Stimulate luteinizing hormone (LH) release from anterior pituitary
DOPAMINE (PROLACTIN-INHIBITING HORMONE)	DA or PIH	Dopamine neurons of the arcuate nucleus	Inhibit prolactin release from anterior pituitary
GROWTH HORMONE-RELEASING HORMONE	GHRH	Parvocellular neurosecretory neurons	Stimulate growth hormone (GH) release from anterior pituitary
SOMATOSTATIN (GROWTH HORMONE-INHIBITING HORMONE)	SS, GHIH, or SRIF	Parvocellular neurosecretory neurons	Inhibit Growth hormone (GH) release from anterior pituitary Inhibit thyroid-stimulating hormone (TSH) release from anterior pituitary
OXYTOCIN		Magnocellular neurosecretory cells	Uterine contraction Lactation (letdown reflex)
VASOPRESSIN (ANTIDIURETIC HORMONE)	ADH or AVP	Magnocellular neurosecretory neurons	Increases water permeability in the distal convoluted tubule and collecting duct of nephrons, thus promoting water reabsorption and increasing blood volume
DOPAMINE (PROLACTIN-INHIBITING HORMONE)	DA or PIH	Dopamine neurons of the arcuate nucleus	Inhibit prolactin release from anterior pituitary

The synaptic vesicle

- classic neurotransmitters are packed into small (40-50 nm), electron lucent vesicles possessing either round or flattened shape
- important protein structures built in the synaptic membrane:
  - vesicular transmitter transporters: uptake and accumulation of transmitters
  - proton pump: generation of electrochemical gradient
  - synaptobrevin: vesicular fusion
  - synaptotagmin: binding of Ca^{2+} ions
  - synapsin: binding to actin
  - RAB3: regulation of vesicle targeting
  - cysteine string protein: Regulation of Ca channels
  - synaptophysin
  - SV2

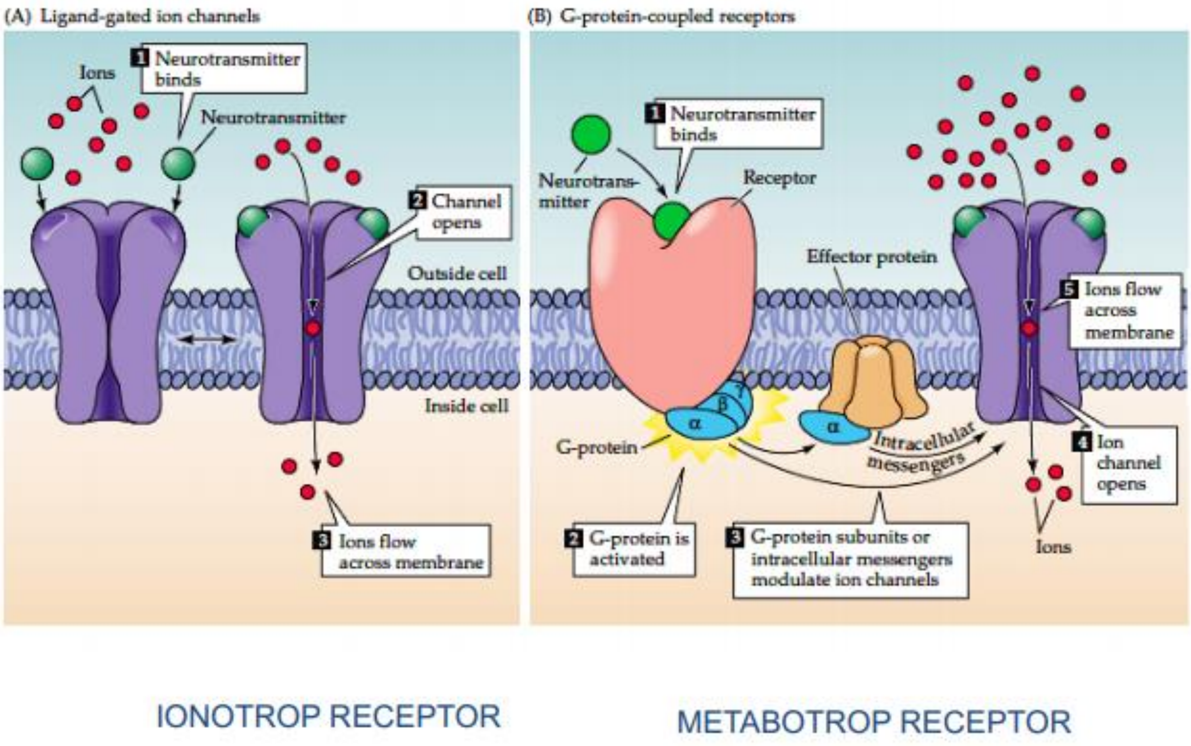
- the uptake of transmitters into the synaptic vesicles:
  - proton pumps help the translocation of protons from the cytoplasm to the organelle
  - electrochemical gradient is also used for the uptake
  - the process results in an extreme accumulation of the transmitter in the vesicles in comparison with its original cytoplasmic concentration
- the presynaptic active zone, docking of vesicles
  - Ca rushed in the terminal liberates the synaptic vesicles from actin filaments of the cytoskeleton
  - vesicles get inserted in the pre-synaptic grid which is a hexagonal array of electron dense particles attached to the cytoplasmic face of the presynaptic membrane
  - the presynaptic grid consists of 50 nm pyramid-shaped particles being interconnected by 100 nm spaced fibrils
  - the process of insertion and establishing contact with the presynaptic membrane is called docking
- excitation-coupled secretion of vesicles
  - action potential opens voltage gated Ca channels in the terminals that allow the influx of Ca
  - the Ca channels are situated in the membrane facing the active zone of the synapse where the docked and primed vesicles are waiting for release
  - elevation of Ca concentration → acceleration of the quantal release
  - decreasing Ca concentration → reduced response
  - high Ca concentration and functional Ca channels can evoke transmitter release under blocked Na action potential and K channels
- membrane fusion
  - the SNARE protein superfamily is composed of dozens of peptides, their role is to assist the docking, fusing and emptying of synaptic vesicles
  - in addition to synaptobrevin, syntaxin ans SNAP-25 contribute to the formation of the SNARE or pore complex
    syntaxin and SNAP-25 are primarily associated with cell membrane
  - the vesicular components of the complex are referred to as V-SNARE, while membrane-associated unit is called T-SNARE
  - the tight SNARE brings together the two membranes
  - the Ca influx triggers the formation of an initial membrane pore similar to a gap junction that gradually enlarges and leads to the collapse of the exocytotic vesicle
    synaptotagmin serves as Ca sensor in the process
- recycling of synaptic vesicles
  - the synaptic membrane is retrieved by endocytosis, the clathrin-coated recovered membrane appears in endosomes that are used for the production of new vesicles
  - the presynaptic membrane of the axon terminal contains transmitter transporters that allow the uptake of the transmitter or its breakdown product from the synaptic cleft for recycling

Quantal release of neurotransmitters

- spontaneous release of transmitters from synaptic vesicles occurs in packets in the absence of action potential
- the action potential increases, accelerates and synchronizes the release of quanta in order to evoke a postsynaptic potential
- the size of the quantum is independent of the action potential and the cytoplasmic concentration of the transmitter

Transmitter receptors

- receptors are complex proteins that show high-affinity binding for transmitter ligands
- ligand binding alters the conformation of the receptor that evokes postsynaptic responses
- transmitter receptors belong to two categories
    - ionotropic receptors: they form pores, specific ion channels in the membrane that allow the passage of ions upon activation, they perform as ligand-gated ion channels
    - metabotropic receptors: they are coupled to GTP-binding proteins via their intracellular domains, G protein activation evokes secondary responses in the cell that alter their metabolism



Ionotropic receptors:

- they contribute to fast post-synaptic responses
- they are excitatory or inhibitory in nature

Types of ion channels

- resting K^+ channel (always open)
- voltage-gated channel (opens in response to change in the membrane potential)
- ligand-gated channel (opens in response to a specific extracellular neurotransmitter)
- signal-gated channel (opens in response to a specific intracellular molecule)

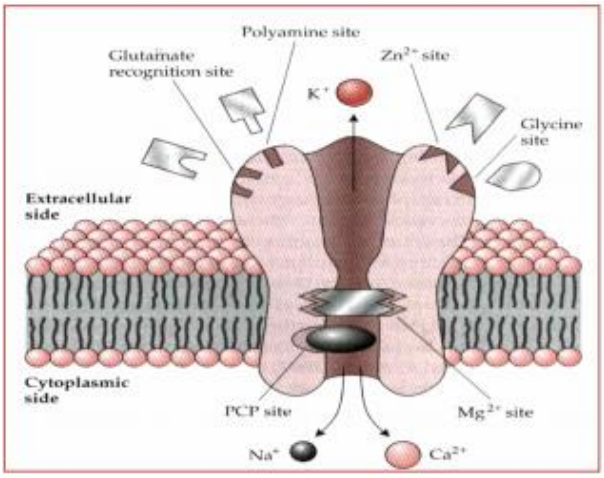
Nicotinic acetylcholine receptor

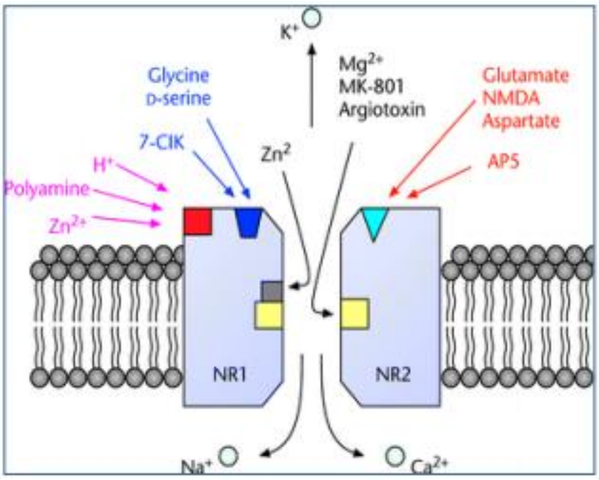
- basic role: opens pores for Na^+ ion inflow and K^+ ion outflow, muscle contraction, EPSP
- agonists: nicotine, choline, epibatidine
- antagonists: hexamethonium, atracurium, succinylcholine, 18-methoxycoronaridine
- functional roles: execution of movement and autonomic functions, modulation of CNS networks via pre- and postsynaptic regulation

Serotonin receptor

- basic role: opens pores for Na^+ ion inflow and K^+ ion outflow, EPSP
- agonists: benzylpiperazine
- antagonists: carbazole, indazoles, indoles
- functional roles: role in addiction, anxiety, vomiting, gi motility, nausea

NMDA receptor





Glutamate receptor-NMDA type

- basic role: non specific cation channel allowing Ca^{2+}, Na^+ and K^+ passage
- agonists: glutamate, aspartate, glycine, D-serine
- antagonists: amantadine, ketamine, phencyclidine
- functional roles: long term potentiation, synaptic plasticity

AMPA receptor

- basic role: mediate most excitatory actions in the CNS, fast kinetics, low Ca permeability, EPSP

- agonists: AMPA, domoic acid
- antagonists: GYKI53655, kynurenic acid
- functional roles: synaptic transmission, synaptic plasticity

Kainate receptor

- basic role: excitatory at postsynaptic sites, inhibitory at presynaptic sites
  pores are permeable for Na^+ and K^+
- agonists: SYM 2081, kainic acid, domoic acid
- antagonists: NS102, kynurenic acid
- functional roles: function-dependent synaptic plasticity

GABA-A

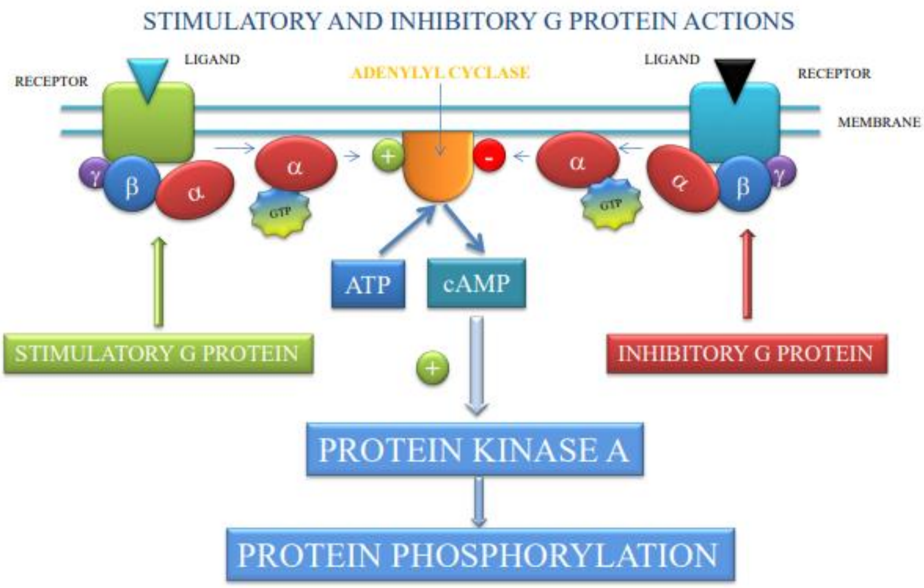
- basic role: regulation of chloride channels, IPSP
- agonists: muscimol, baclofen, ethanol, barbiturates, benzodiazepines
- antagonists: bicuculine
- functional roles: agonists exert anxiolytic, anticonvulsant, amnesic, sedative, hypnotic and muscle relaxant effects

Glycine receptor

- basic role: regulation of chloride channels, IPSP
- agonists: serine, taurine
- antagonists: strychinine, caffeine
- functional roles: dominant inhibitors neurotransmitter in the spinal cord and brainstem

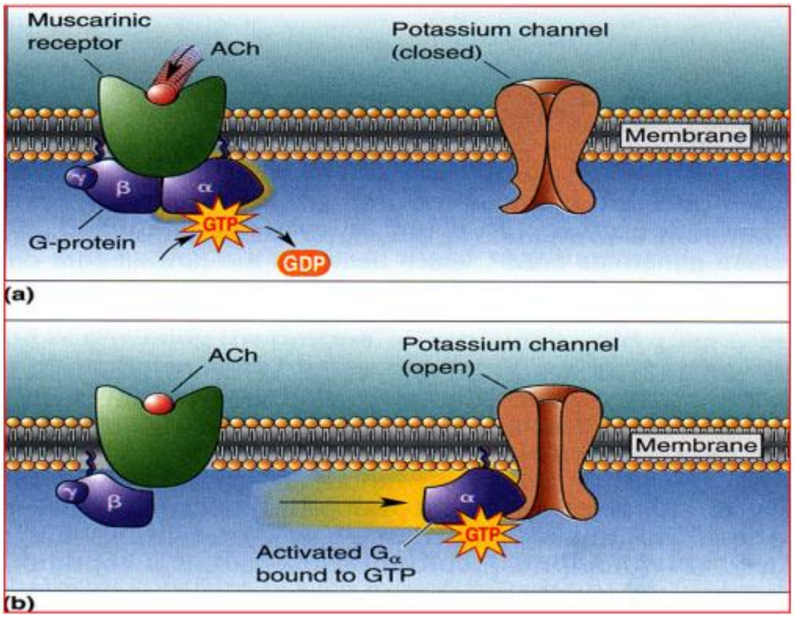
<u>Metabotropic receptors</u>

- the response evoked via metabotropic receptors has a slower onset and longer duration
- certain classic transmitters utilize both the fast ionotropic and the slower metabotropic receptors for communication
- peptides use G protein-coupled receptors exclusively
- the receptor possesses 7 transmembrane domains
- the activated GPCR can turn on an associated G-protein by exchanging its bound GDP for a GTP
- the G protein has alpha, beta and gamma subunits
  the alpha subunit together with the bound GTP dissociates and affects second messengers



Muscarinic acetylcholine receptor

- basic role: M1, M3, M5 couple to G proteins that stimulate phopholypase C
  M2, M4: couple to G proteins that regulate potassium and Ca channels
- agonists: muscarine, pilocarpine, betanechol
- antagonists: atropine, scopolamine, pirenzepine
- functional roles: regulation of CNS networks and autonomic nervous system



Metabotropic glutamate receptor

- basic role:
  - group I: stimulation of phospholipase C
  - group II - III: inhibition of adenylyl cyclase
- agonists: 2-chloro-5-hydroxyphenylglycine, 3.5-dihydroxyphenylglycine
- antagonists: 4-carboxyphenylglycine, 1-aminoindan-1,5-dicarboxylic acid
- functional roles: regulation of CNS networks

Metabotropic GABA receptor (GABA B receptor)

- basic role: activation of GABA B receptor → increase in K^+ conductance, decrease in Ca^{2+} conductance, changes in the levels of second messengers
- agonists: baclofen
- antagonists: saclofen
- functional roles: regulation of CNS networks

Metabotropic serotonin receptor

- basic role:
  - increasing cellular levels of cAMP: subtypes 4, 6, 7;
    IP3 and DAG: subtype 2
  - decreasing cellular levels of cAMP: subtypes 1, 5
- agonists: large scale of subtype specific agonists are known
- antagonists: large scale of subtype specific antagonists are known
- functional roles: regulation of CNS networks

Dopamine receptor

- basic role:
  - D1-like family activates adenyl cyclase
  - D2-like family inhibits adenyl cyclase
- agonists: ropinirole, pramipexole
- antagonists: clozapine, risperidone, olanzapine, quetiapine
- functional roles: regulation of CNS networks, controlling movement, mood, addiction

Adrenergic receptor

- basic role: alpha-2 adrenergic receptors decrease cyclic AMP, beta adrenergic receptors increase cyclic AMP
- agonists: isoproterenol
- antagonists: propranolol, phentolamine
- functional roles: regulation of CNS and PNS functions

<u>Causes of neural tissue damage</u>

- genetic mutations: trinucleotide repeat expansion disorders
- traumatic brain injury: haemorrhagic contusions
- tumour: malignant and benignant cell proliferations
- infection: inflammation caused by bacteria and viruses
- oxidative stress: superoxide radical, hydrogen peroxide
- chemical damage: alcohol, drug abuse, organic solvents
- ischemia: restriction in blood supply (arteriosclerosis)
- hypoxia: shortage in oxygen supply
- aging: structural and neurochemical properties of neurons change

Apoptotic death of neurons

- cell shrinkage and rounding due to the breakdown of the cytoskeleton by caspases
- the cytoplasm appears dense, the organelles appear tightly packed
- chromatin undergoes condensation into compact patches against the nuclear envelope
- the nuclear envelope becomes discontinuous and the DNA fragmented
- the cell membrane shows irregular buds known as blebs
- the cell breaks apart into several vesicles called apoptotic bodies which become phagocytosed

Necrosis of neurons

- major darkening and shrinkage of the nucleus and cytoplasm
- plasma membrane and the nuclear membrane become irregular
- the cytoplasm generally contains many large vacuoles
- swollen mitochondria with disrupted cristae
- the neurons fall apart and get phagocytosed

Wallerian degeneration of neurons after axon transection

- excentric nucleus
- enlarged perikaryon
- chromatolysis
- distal axon stump death
- breakdown of myelin
- microglia infiltration
- occurs in CNS and PNS

Neuropathology of Alzheimer disease

- gradual decline of cognitive functions
- causes: acetylcholine, beta-amylod, tau and prion hypotheses
- the formation of amylod plaques in the nervous tissue and the presence of neurofibrillary tangles in degenerating neurons are characteristic neuropathological features

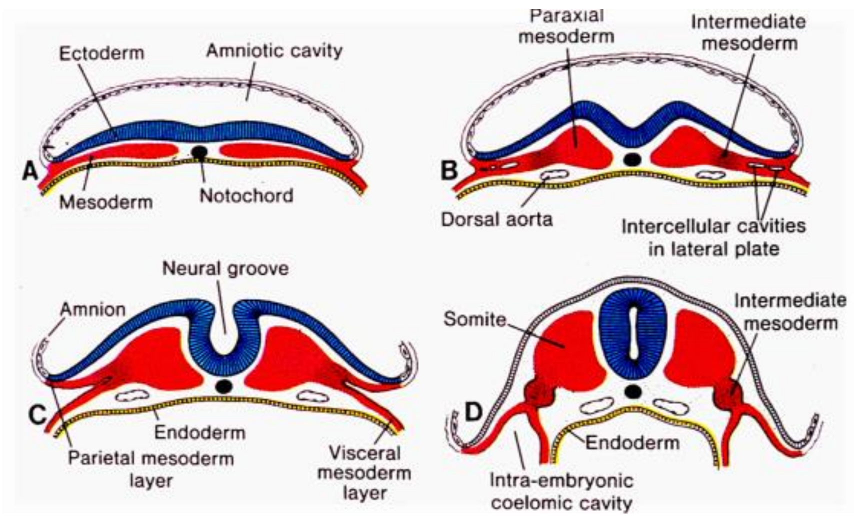
Features of the human development

- formation of germ layers during embryonic development: ectoderm, endoderm, mesoderm
- simultaneous development of the organ systems

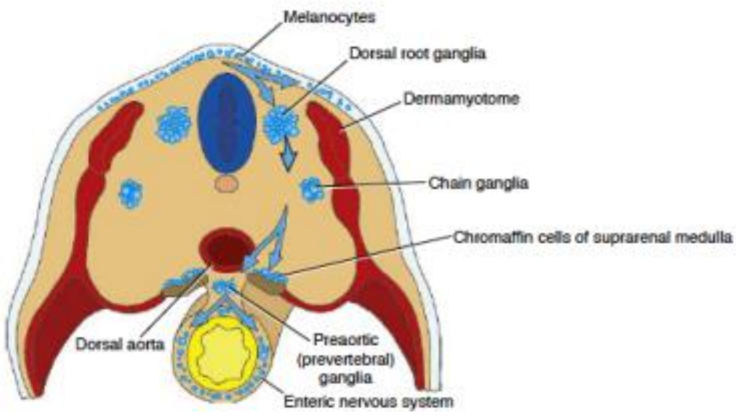
Early events of the neural development

- formation of the neural tube from the ectoderm
  the inductive role of the notochord
- the sonic hedgehog morphogen signalling
- anterior and posterior neuropores and their closing
- development of the neural crest and its derivatives
- formation of sensory and autonomic ganglia, connections with the central nervous system and target structures
- the placode plate and its derivatives
- the nonproportional development of the neural tube
- the early formation of the spinal cord
- the early appearance of the brain primordium

Neurulation



Derivatives of the neural crest

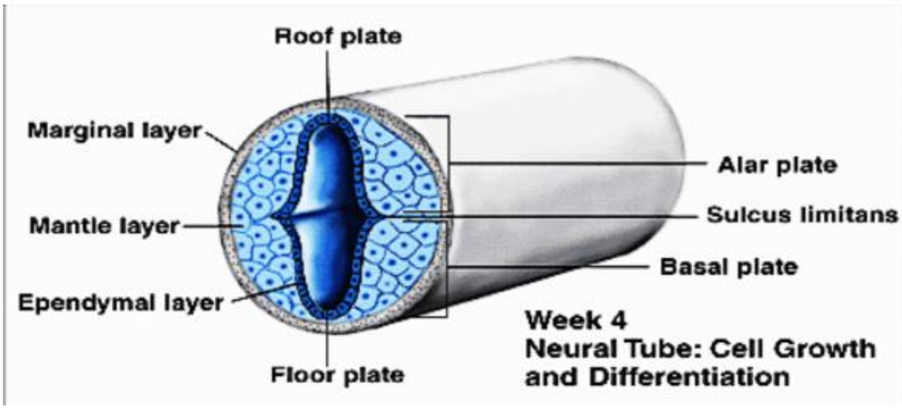


Cellular differentiation of the neural tube

- parallel to the growth of the embryo the neural tube gets thicker and elongates
- the cranial end of the neural tube develops more intensively resulting in the primary brain vesicles
- from the less intensely proliferating caudal part of the neural tube the spinal cord derives
- the epithelial cells lining the neural tube divide heavily and give rise to the cellular constituents of the brain and spinal cord
- at first glioblast and neuroblast cells develop
- glioblasts differentiate into glial cells that maintain the self-renewal capability and accordingly divide frequently
- in addition to providing astrocytes, oligodendrocytes and ependymal cells, glioblast also form radial glia cells

Cellular differentiation of the neural tube

- the processes of radial glia cells stretch through the entire thickness of the developing neural tube in a perpendicular orientation relative to the ependymal lining of the neural tube
- radial glia cell processes provide pathways and guidance for neurons migrating from the ependymal to the mantle layer
- the migrating neurons are postmitotic cells incapable of dividing
- this migratory process is called: radial migration
- layers growing around the neural canal include
    - ependymal layer
    - mantle layer forms the grey matter
    - marginal layer forms the white matter

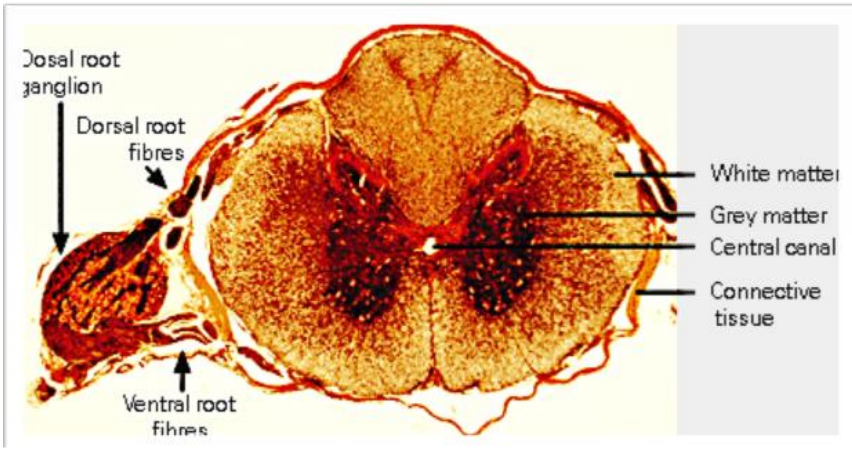


Development of the spinal cord

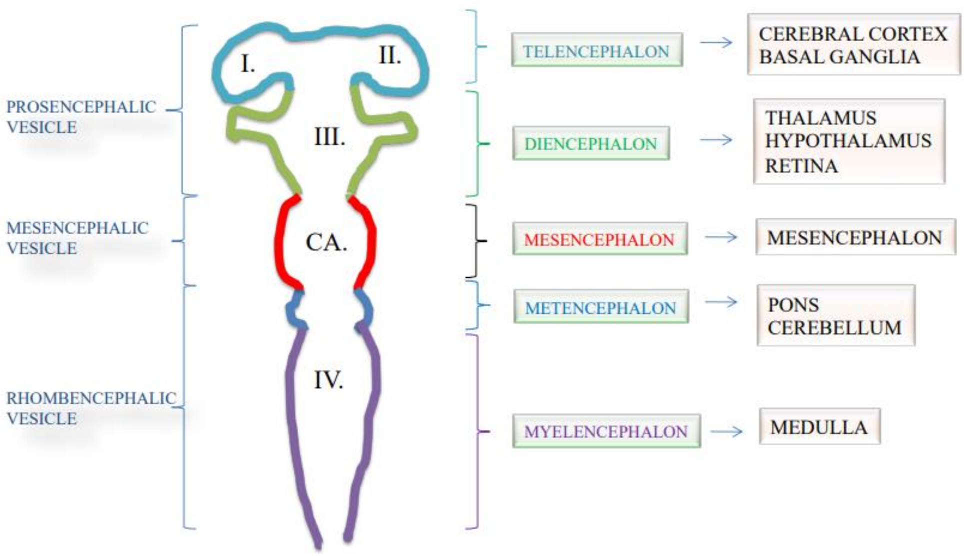
- within the fourth embryonic week, the mantle layer differentiates into ventrally located basal and dorsally positioned alar plates on both sides
- in the median sagittal plane, the mantle layer remains thin forming the flop plate ventrally and the roof plate dorsally
- from the basal plate the ventral horn of spinal cord develops
- the dorsal, sensory horn derives from the alar plate

- somatomotor neurons developing in the basal plate grow axons that leave the spinal primordium and establish connections with striated muscles developing in the same segment
  this is the early formation of the neuromuscular junctions
- vegetative motor neurons developing at the level of the sulcus limitans provide axons that communicate with autonomic ganglion cells outside the spinal primordium
- neurons of the alar plate differentiate further and establish complex nuclei that are functionally coupled to the processing of sensory information
- the sensory stimuli are carried to the alar plate by the central processes of external pseudo-unipolar neurons
  these cells differentiate from the neural crest and establish the sensory dorsal root ganglia in the segments of the body
  the peripheral processes of these sensory neurons are linked with receptors
- in the marginal layer, axon bundles can be found
  they either belong to short intersegmental connections or to major ascending and descending fiber tracts interconnecting the spinal segments with other regulatory parts of the neuroaxis

The spinal segment



Schematic illustration of brain vesicles and their derivatives



Development of the brain, formation of primary and secondary brain vesicles

- from the rostral part of the neural tube three brain vesicles derive:
    - prosencephalon → lateral and third cavities develop
        - telencephalon
        - diencephalon
    - mesencephalon → cerebral aqueduct develops
      (maintains its original integrity)
    - rhombencephalon → fourth cerebral ventricle develops
        - metencephalon
        - myelencephalon
- at the level of the fourth ventricle, three apertures develop that allow the outflow of the CSF into the subarachnoid space

Folding of the brain, compartmentalization of the brain stem

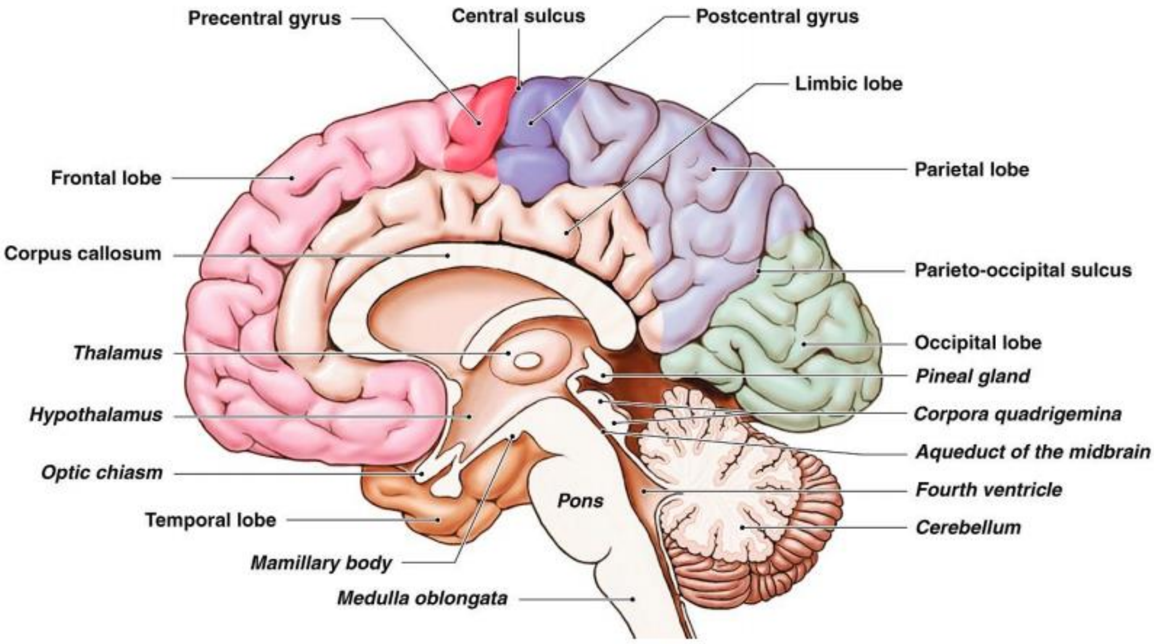
- the embryo displays a characteristic rostro-caudal, c-shaped flexure
- at the end of the first month, two flexures of the brain are obvious:
    - cervical flexure between the spinal cord and the medulla
    - mesencephalic flexure at the level of the midbrain

  the concavity of both flexures points toward the ventral part of the body
- later, the third flexure develops at the level of the rhombencephalon, called the pontine flexure
  it folds the metencephalon back to the myelencephalon, the rhombic lips
- the lateral out-pocketings of the telencephalic vesicles are also characteristic features, together with the development of the optic cup which provides the primordium of the retina
- the brain stem shows an organisation resembling the pattern of the spinal cord
  from the basal and alar plates centers of the certain cranial nerves develop

Development of the telencephalon

- the telencephalon vesicles grow laterally as bubbles on both sides, in a spiral manner similar to the shape of the RAM's horn, the developing vesicle provides the frontal, parietal, temporal and occipital lobes, as well as, the insula, these parts gradually cover and hide the diencephalon, the cavity of the telencephalic vesicle is the lateral ventricle
- from the dorsal part of the wall of the growing telencephalic vesicle the cerebral cortex develops
- from the thicker, ventral part of the vesicle the corpus striatum develops
- the ventral surface of the telencephalic vesicle gets juxtaposed to the diencephalic structure, the thalamus
- this border zone is crossed by an extremely massive and functionally crucial fiber bundle system, the internal capsule
  it contains fibers establishing communication between the thalamus and the cerebral cortex, and also multiple connections among the cortex the brain stem and the spinal cord
  both ascending and descending fiber tracts are represented in it

Derivatives of the cerebral cortex



<u>The spinal cord</u>

Main features

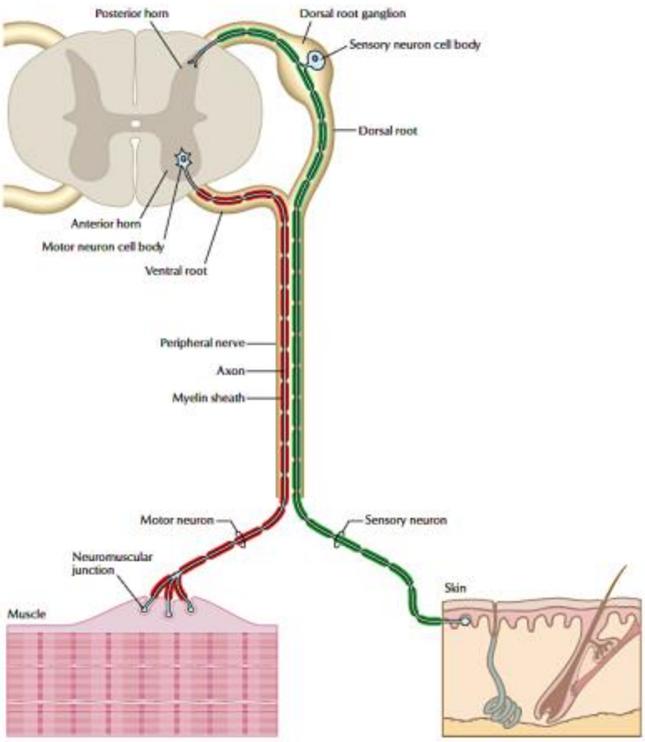
- cylindrical structure slightly flattened dorso-ventrally
- it is in continuity with the brain and developmentally it derives from the caudal part of the neural tube
- located in the vertebral canal → high-level physical protection
- enclosed by the meninges
  both the pachymeninx and the leptomeninx take part in its ensheating
- the CSF circulating in the subarachnoid space also surrounds the spinal cord and contributes to its protection
- shorter than the vertebral canal → the cord ends at the level of upper lumbar vertebrae
- fracture of the vertebral column might severely damage the spinal cord

Spinal meninges

- the pachymeninx is formed by the dura mater
  the dural sac has two layers that define the epidural space
- injection to the epidural space → blockade of neural transmission → analgesia
- the arachnoid and the pia mater form the inner envelopes → subarachnoid space
- the innermost pia mater smoothly and tightly covers the entire surface of the spinal cord
  arising from this membrane one can find serrated ligaments on both sides of the spinal cord that attach the cord to the dura mater
  actually, the spinal cord is suspended and floats in the CSF
- caudal to the termination of the pinal cord, the meninges surround the bundles of the dorsal and ventral roots of lumbo-sacral segments (locus of lumbar puncture)

Spinal segments

- the grey matter is located centrally within the spinal cord
  it is butterfly-shaped and composed of neurons and glial cells
- the white matter has a peripheral location surrounding the grey matter
  it consists of fiber bundles, so-called tracts and glial cells
- the grey and white matter constituents of the spinal cord are not segmented, both establish columnar, continuous organisations
- the incoming sensory fibers and the outgoing motor axons define particular regions of the spinal cord called segments
  these are 1-3 cm high divisions of the cord
- 31 segments: 8 cervical, 12 thoracic, 5 lumbar, 5 sacral, 1 coccygeal
- the dorsal root and its ganglion convey sensory information
- the fibers of the ventral root execute motor commands
- the dorsal and ventral roots join and form spinal nerve that after a short journey splits into ventral and dorsal rami



Segmental innervation of the skin

- the sensory components of a given pair of spinal nerves innervate well-defined and shaped segmented regions of the skin called dermatomes
- the innervation of the skin follows the segmental motor nerve supply to underlying muscles
- the dermatomes seem to overlap

Innervation of muscles

- skeletal muscles of the body develop predominantly from myotomes that are derivatives of the mesoderm layer
  myotomes provide myogenic cells that generate the muscles
- the myotomes are segmented structures
  accordingly, muscles developing from given segments are innervated by somatic motorneurons developing in the ventral horn of the spinal cord of the same segments
  these neuromuscular connections are established early
  as muscles migrate to their final destination they pull the motorneuron axons with themselves

Segmental differences within the spinal cord

- the ratio of white/grey matter volume changes according to the cranio-caudal position of the segment
  cranially, the cervical segments are larger with much more white matter in them in comparison with caudal, sacral segments
- the spinal cord shows two enlargements
    - cervical: C5-T1, give rise to the brachial nerve plexus that supplies the upper extremities
    - lumbo-sacral: L1-S3, take their origin and project to the lower extremities to supply them

Internal structure of the spinal cord

Organization of the white and grey matters

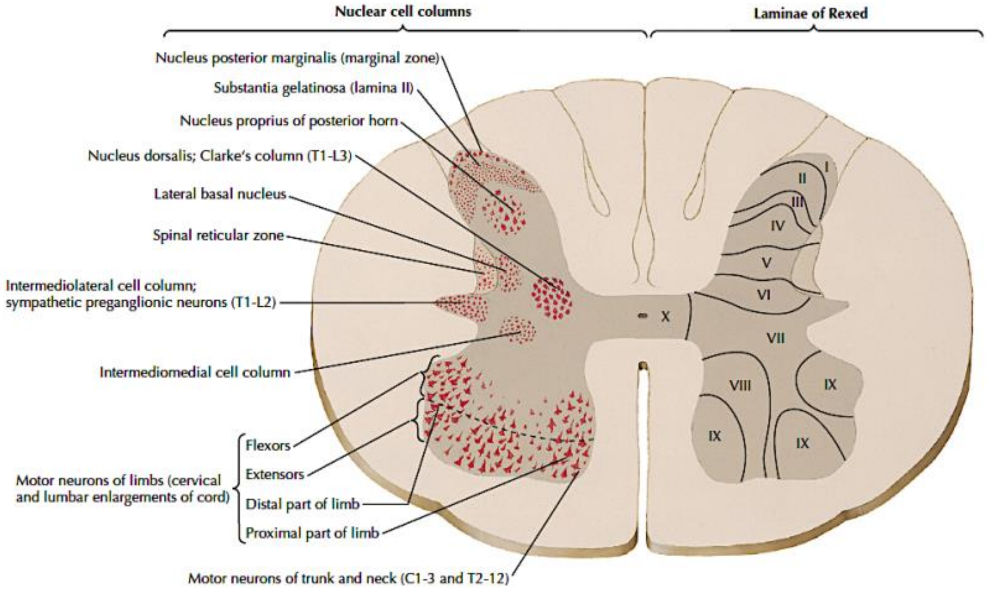
- the grey matter is organized into 3 horns:
    - dorsal horn: associated with sensory information processing
    - lateral horn: it is explicit at certain thoraco-lumbar and sacral segments from where the sympathetic and parasympathetic outflows occur
      it is packed by autonomic, preganglionic cells
      their axons leave the spinal cord and enter the ventral root
    - ventral horn: consists of large, somatic motorneurons and interneurons
      the axonal projection of motorneurons uses the ventral root and the spinal nerve for exiting
- in the center of the grey matter, the original cavity of the neural tube, the *canalis centralis* is located
  cranially it is continuous with the 4th cerebral ventricle

Cytoarchitecture of the grey matter

- lamina I: thin layer that caps the posterior surface of the dorsal horn
    - consists of small and medium sized cells that form the *postero-marginal nucleus*
    - it mainly receives primary afferents and axons of lamina II cells
    - responds to noxious stimuli
- lamina II: contains tightly packed round cells
    - the layer corresponds to the *substantia gelatinosa*

- it receives innocuous mechanoreceptor stimuli
- the axon projections of this layer target neighbouring laminae
- substance P and opiod receptors are expressed in this layer

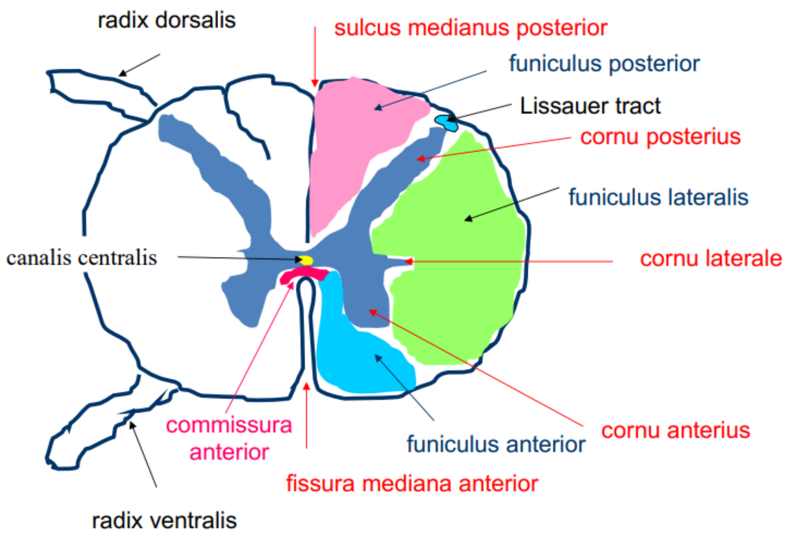
- lamina III: the cells show a wide phenotypic variety
  - they seem to establish local connections and act as interneurons
- lamina IV: thickest layer in the region
  - the cells respond to light touch stimuli
  - the cells form the *proper sensory nucleus*
  - it projects in the contralateral side to the thalamus
- lamina V: broad zone at the origin of the posterior horn
  - some cells project to lamina II
- lamina VI: obvious in the enlargements of the spinal cord
  - receives group I muscle afferents
  - projects contralaterally to the cerebellum via the ventral spinocerebellar pathway
- lamina VII: intermediate zone
  - some of its cells establish columns, the most notable is the *dorsal nucleus of Clarke*
  - receives mechano-information from muscles and tendons and relay them ipsilaterally via the dorsal spinocerebellar tract
  - other columnar organisation corresponds to the *intermediolateral nucleus*, receives visceral sensory information
  - contains the preganglionic vegetative neurons
- lamina VIII: locus of heterogeneous cell populations receiving several descending tracts
- lamina IX: contains large, multipolar somatic motor neurons and smaller motorneurons
  - gamma neurons innervate the muscle spindle fibers
  - the cells are organized into medial and lateral groups

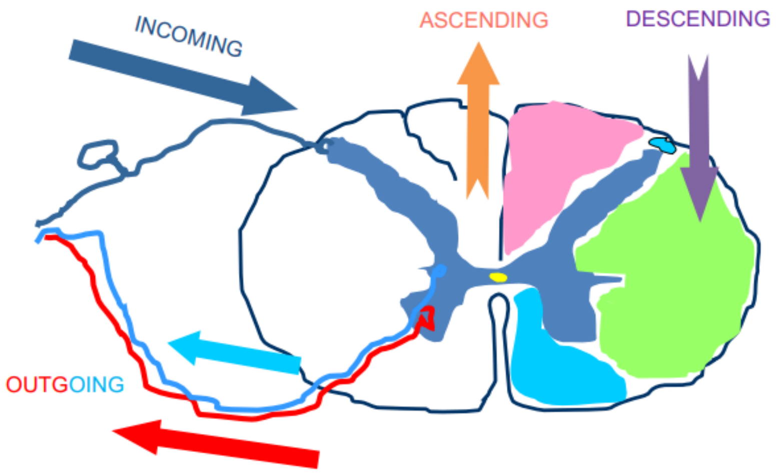


Behaviour of dorsal root afferents

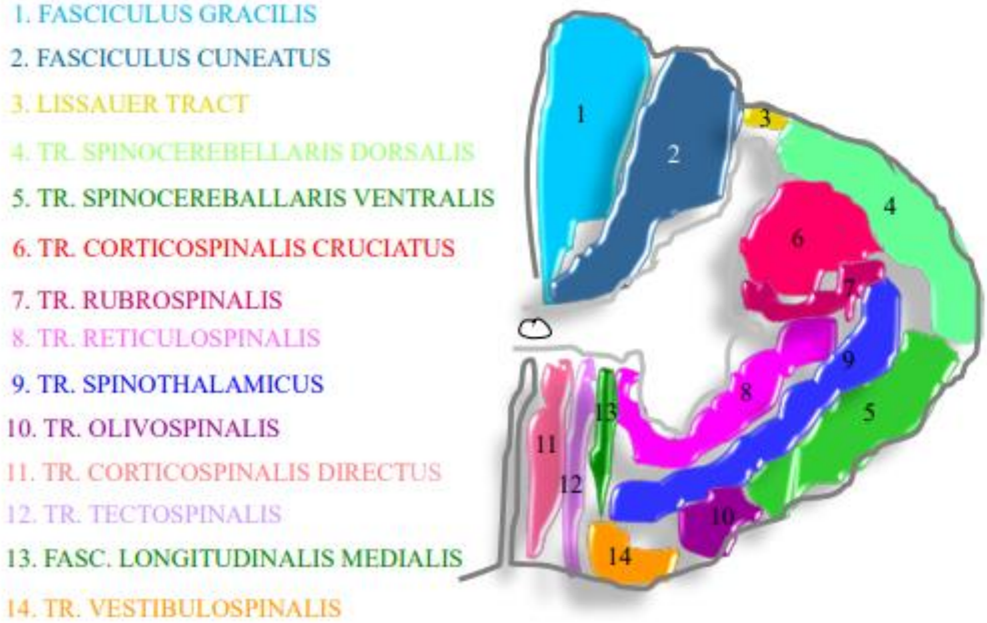
1. approach the dorsolateral surface of the spinal cord, they belong to two categories:
   - thick myelinated axon group
     - they divide into descending and ascending nerve tracts
     - the ascending branches enter the dorsal funiculus and project to the medulla
     - they carry information from encapsulated receptors
   - thin, myelinated or non-myelinated axon group
     - they carry information associated with light touch, pain and thermal stimuli
     - they enter a thin fiber compartment, called the Lissauer zone that covers the surface of the posterior horn
     - fibers entering the grey matter most frequently terminate in layers I&II
     - this kind of sensory information is relayed further to the thalamus via crossed spinothalamic tract

Organisation of the white matter



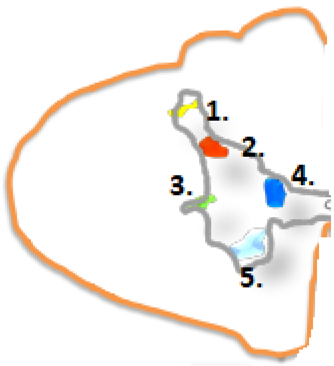


Tracts of the spinal cord



Spinal nuclei:

1. substantia gelatinosa
2. nucleus proporius
3. nucleus intermedio-lateralis
4. nucleus dorsalis
5. nucleus motorius

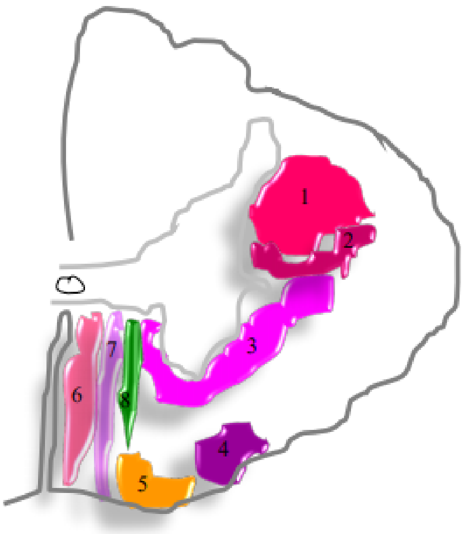


The ascending tracts

	Fasciculus gracilis	**Fasciculus cuneatus**	**Spinothalamic tract**	**Dorsal spinocerebel-lar tract**	**Ventral spinocerebel-lar tract**
	thick myelinated fibers from S, L, T6-12 segments	thick myelinated fibers from T1-6, C segments			
origin	spinal ganglia	spinal ganglia	contralateral grey matter, laminae I, IV and V	ipsilateral clarke column	laminae V, VI and VII contralaterally
termination	nucleus gracilis in medulla	nucleus cuneatus	thalamus	cerebellar cortex	cerebellar cortex
function	sensory, fine touch, vibration, 2-point discrimination, position sense	sensory, fine touch, vibration, 2-point discrimination, position sense	sensory, harmful (noxious) pain and thermal stimuli, crude touch	coordination of movements and posture	coordination of movements

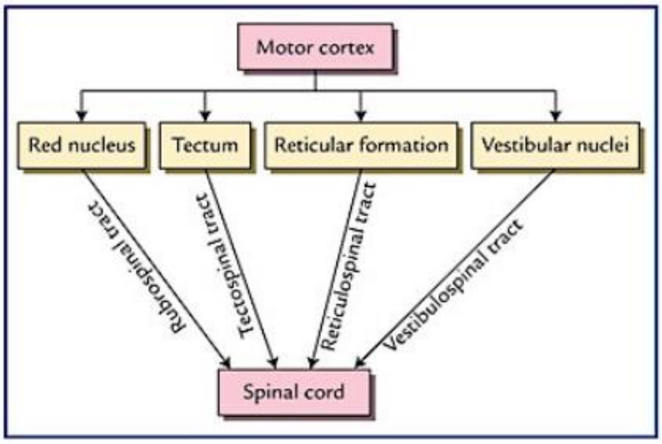
Main descending tracts of the spinal cord

1. TR. CORTICOSPINALIS CRUCIATUS
2. TR. RUBROSPINALIS
3. TR. RETICULOSPINALIS
4. TR. OLIVOSPINALIS
5. TR. VESTIBULOSPINALIS
6. TR. CORTICOSPINALIS DIRECTUS
7. TR. TECTOSPINALIS
8. FASCICULUS LONGITUDINALIS MEDIALIS



- Corticospinalis cruciatus:
  - the main regulatory tract of lower motorneurons
  - originates from the cerebral cortex
  - runs through the internal capsule
  - intersects (decussates) the medulla oblongata (in an x shape)
  - terminates the interneurons of the ventral horn that are associated with motorneurons

- Rubrospinalis
  - originates from the red nucleus of the brain stem
  - terminates on ventral horn interneurons
  - conveys information from the cortex and cerebellum mainly to motor neurons innervating flexor and extensor muscles
- Reticulospinalis
  - carries information from pontine and medullary units of the reticular formation to the dorsal and ventral horns
  - controls voluntary movements, muscle tone, central sensory transmission
  - regulates respiratory and circulatory activities
- Olivospinalis
  - pathway originating from the inferior olive structure of the medulla
  - innervates cervical segments
- Vestibulospinalis
  - arises from the lateral vestibular nucleus
  - shows somatotopic projections
  - mediates cerebellar and vestibular information toward the spinal cord
  - exerts facilitatory influence on spinal reflexes
  - controls muscle tone
- Corticospinalis directus
  - originates from the cerebral cortex
  - carries motor commands to neurons
  - it does not decussate in the medulla
  - terminates in the intermediate zone of the grey matter
- Tectospinalis
  - neurons residing in the colliculus superior of the midbrain tectum project to the spinal cord
  - controls the movements of the head
- Fasciculus longitudinalis medialis
  - originates from the caudal part of the brainstem
  - carries information from secondary vestibular neurons to cervical segments
  - controls the movements of the head



The stretch reflex

Features of reflexes

- rapid, involuntary neuronal regulatory actions, executed in response to sensory stimuli
- associated with neuronal assemblies of spinal segments and cranial nerve nuclei
- ensure the adaptation of the body to external and internal environments and the continuously changing challenges
- used in the regulation of both somatic and visceral functions
- some are innate (inborn), others are learned ones
- reflex arc: the structural organization of reflexes

The reflex arc

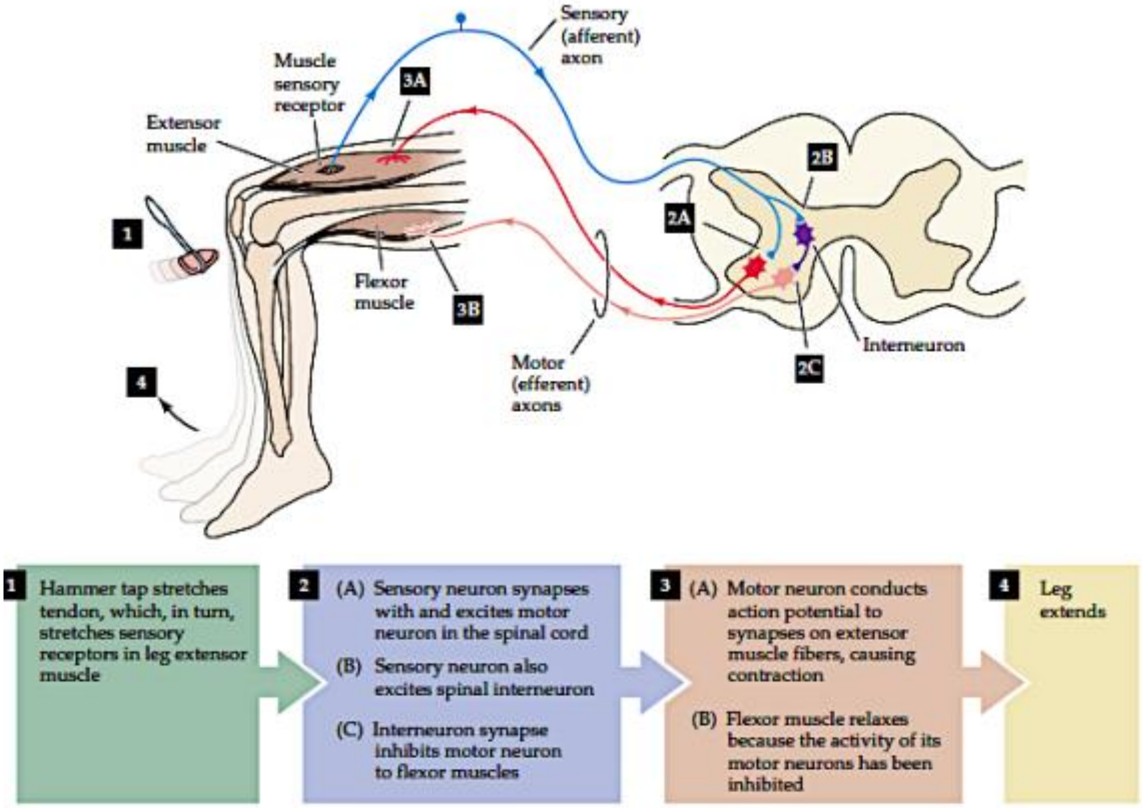
- structural constituents
    - receptor
        - picking up the information
    - afferents
        - sensory nerves
        - carrying the stimulus-evoked information to the centre
    - centre
        - handling, processing the incoming sensory information
    - efferents
        - somatomotor or visceromotor nerves
        - conveying the response to the site of the compensatory actions
    - effector
        - executing the regulatory commands

The stretch reflex

- muscle length and muscle tone are important features of muscle function and their regulation is a key factor in movements
- they are controlled by the stretch reflex
- it is a monosynaptic, postural reflex that among others works against the gravity force

- Characteristics of the reflex:
    1. stimulus: stretching of the muscle
    2. receptor: muscle spindle, intrafusal muscle fibers, nuclear bag and nuclear chain receptors
    3. afferent path: I. and II. type nerve fibers of sensory ganglion cells
    4. centre: spinal cord, ventral horn, somatomotor neurons
    5. efferent path: axons of alpha motorneurons
    6. effector: extrafusal muscle fibers of the muscle
    7. compensatory action: shortening of the muscle

The knee jerk reflex:



The gamma reflex loop

- gamma motoneurons: smaller cells, stored in the anterior horn
- they innervate intrafusal muscle fibers of the muscle spindle receptor
- descending tracts excite gamma motoneurons causing contraction of the intrafusal fibers
- as a result, the increased firing from sensory endings informs the alpha motoneurons that will make an adjustment of the muscle length
- gamma motoneurons can adjust the level of sensitivity of muscle spindle receptor fibers, initiate contraction according to higher motoneuron commands and set muscle tone

<u>The flexor reflex</u>:

- associated with the operation of the limbs
- a protective reflex: in response to a painful stimuli the limb is withdrawn
- the shortening of the limb on one side generally evokes a compensatory mechanism that extends the limb on the other side, therefore the reflex is also referred to as a flexor-crossed extensor reflex
- it is a polysynaptic reflex arc that modifies both the ipsi- and the contralateral limbs

Specific features of the flexor crossed extensor reflex

- stimulus: crude and dangerous stimuli that can destroy the integrity of the affected tissues of the limb, harmful pain and thermal stimuli are the triggerers
- receptor: heat and pain receptors
- afferent path: thin, myelinated and unmyelinated axons of pseudo-unipolar cells of spinal ganglia
- centre: spinal cord, dorsal and ventral horns, involvement of interneurons
- efferent path: axons of alpha motoneurons innervating flexor muscles of the limb ipsilaterally and axon projections from contralaterally located motoneurons innervating extensors of the limb on the opposite side to the stimulus
- effector: extrafusal muscle fibers of the involved muscles
- actions: ipsilateral flexion and contralateral extension

example: The hand withdrawal reflex

> The receptor is the heat receptor in the skin, which being exposed to the candle flame senses heat and converts it to a sensory impulse. The sensory/afferent pathway is the transmission of the sensory impulse from the receptor to the centre. The sensory neuron is located in the dorsal root ganglion and its long projections form the *sensory fibers of the spinal nerve* that carry the sensory impulse from the receptor to the spinal cord via dorsal root. The controlling centre is represented by an interneurone in the spinal cord that connects the sensory neurone to the motor neurone of the ventral horn. The motor/efferent pathway is the transmission of the motor impulses generated in the motor neurone to the effectors along its axon. In the hand-jerk reflex this pathway is formed by the *motor fibers of the spinal nerve* that leave the spinal cord via ventral root. The effectors are the muscles of the hand and lower arm that by contracting move the hand away from the flame.

The autonomic reflex

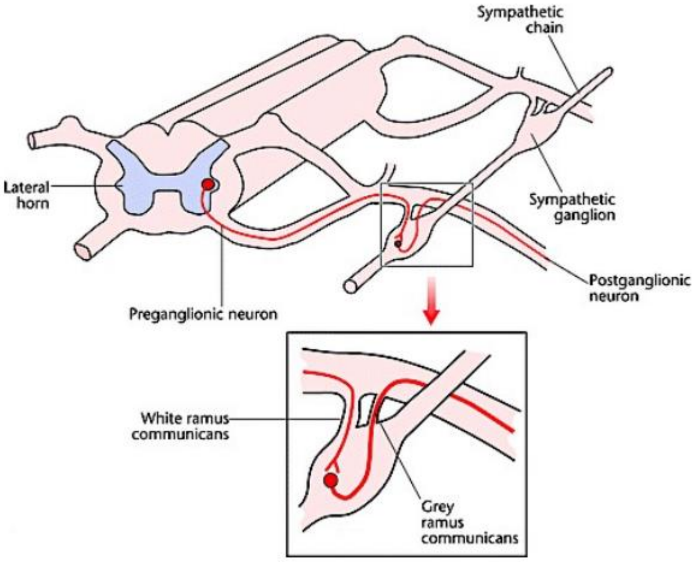
- the operation of the visceral organs is modulated by the autonomic nervous system
- sensory visceral afferents convey information to the centres of the CNS from receptors distributed in the organs
- the brain stem and the spinal cord regulate the motor activity of the organs via viscero-motor efferents
- the visceromotor innervation is indirect and consists of two units:
  - preganglionic motor neurons residing in the CNS
  - ganglionic motor neurons distributed at the periphery
    they transmit central information to the target organs
- the organs receive a dual visceromotor innervation by getting supply from both sympathetic and parasympathetic sources
- the CNS utilizes the autonomic reflex arc for executing modulatory actions in response to incoming visceral stimuli

Specific features of the autonomic reflex

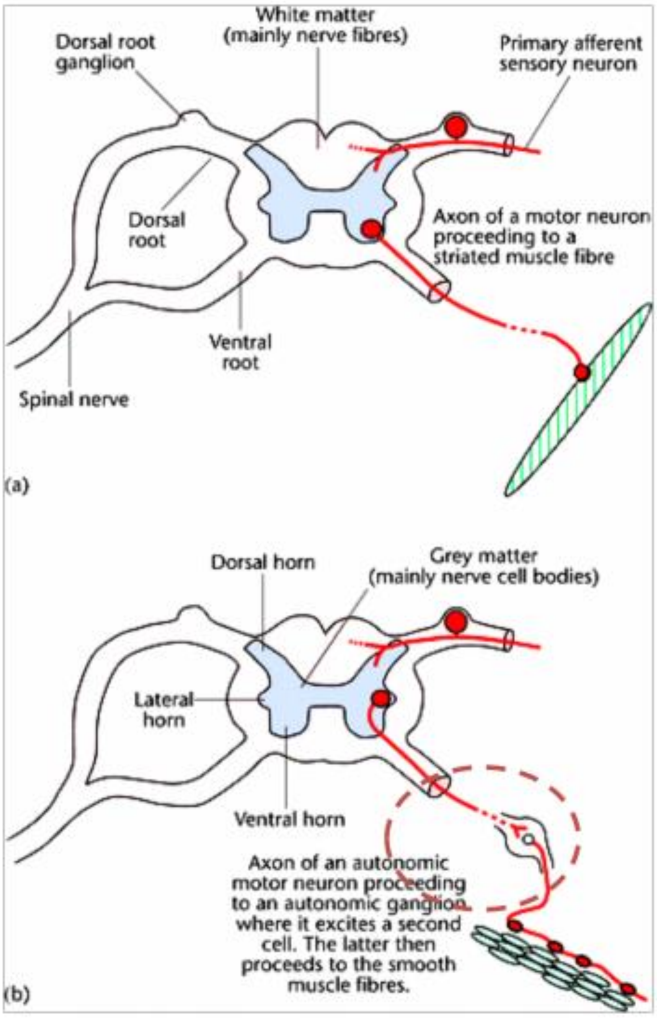
- stimulus: change in pressure, alternation of chemical milieu, inflammation related pain and heat, distension of luminal viscera
- receptor: baroreceptors, chemoreceptors, mechanoreceptors, heat receptors
- afferent path: processes of pseudo-unipolar cells of the spinal ganglia
- centre: spinal cord, brain stem
- efferent path:
    1. preganglionic neurons projecting from the intermedilateral nucleus to the peripheral autonomic ganglia
    2. processes of visceral ganglion cells projecting to the organs
- effector: cardiac and smooth muscle
- actions: modulation of the visceral functions
  (eg.: pacemaker activity, lumen of blood vessels, smooth muscles in bronchi)

Comparison of sympathetic and parasympathetic functions

Structure	**Sympathetic function**	**Parasympathetic function**
Eye	Dilatation of pupil	Constriction of pupil
Lacrimal gland and Salivary glands	Viscous secretion	Watery secretion
Bronchial smooth muscle	Relaxation	Contraction
Heart	Increases heart rate	Decreases heart rate
GIT	Decreases peristalsis and constricts the sphincters	Increases peristalsis and relaxes sphincters
Genitourinary tract		
• Bladder wall and sphincter	Relaxes bladder wall and constricts the sphincter	Contracts the bladder wall and relaxes the sphincter
• Penis	Ejaculation	Erection
Skin		
• Sweat glands	Produce sweating	No effect
• Arrector pili	Contraction of arrector pili leading erection of hair	No effect



Comparison of somatomotor (a) and visceromotor (b) innervation patterns



<u>Information flow in visceral and parietal sympathetic reflex arcs</u>

	Visceral	**Parietal**
sensory stimulus	generated in the organ	to the skin
primary afferents	carry the info to the dorsal horn	in the dorsal root ganglion, convey info to the posterior horn
information transfer	to interneurons	to interneurons
transfer of input	to visceral somatomotor neurons	to preganglionic neurons of the lateral horn
preganglionic efferents	to the prevertebral ganglion	to cells of the paravertebral ganglion
	innervation of ganglionic cells	information transfer to paravertebral neurons
postganglionic afferents	to executive structure (smooth muscle)	to blood vessels, hair and sweat glands of the skin
	change in contraction state of smooth muscles	

The brain stem:

1. medulla oblongata
2. pons
3. mesencephalon
4. cerebellum

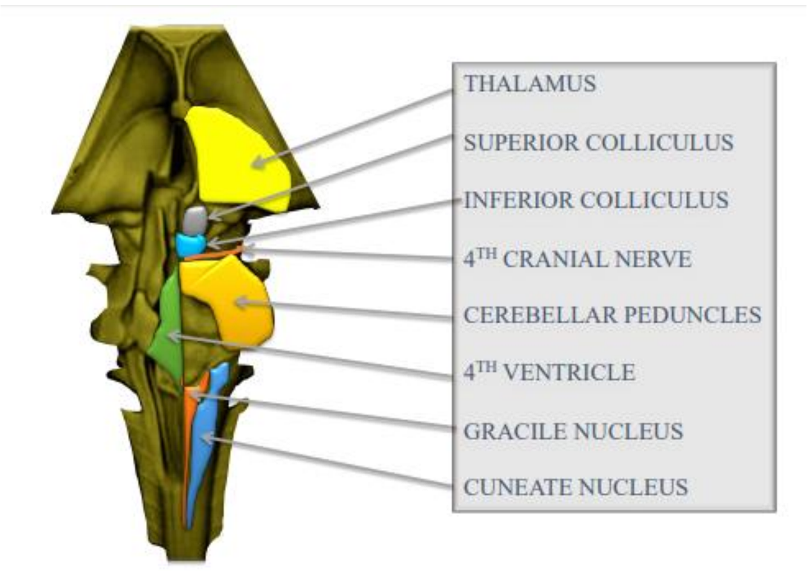
Main characteristics:

- its constituents develop from the hindbrain
  the cerebellum derives from the rhombencephalon
- its inner cavity is the 4^{th} cerebral ventricle
- important somatic and autonomic centers are located in it
- the processing centers of most cranial nerves are within the brain stem
- the reticular formation system is part of the brain stem
  it controls vital respiratory and circulatory mechanisms and arousal
- the main source of monoamine transmitters
- major motor and sensory projections pass through the brain stem
- subcortical acoustic and vestibular centers are represented in the brain stem

The arterial supply of the base of the brain

- the vertebral and internal carotid arteries supply the brain
- the main branches are associated with the ventral surface of the brain
- the systems are interconnected via the posterior communicating arteries
- the anterior cerebral arteries are also interconnected by the anterior communicating artery
- the established loop is called the *arterial circle of willis*

Dorsal landmarks of the brain stem



The cerebellum

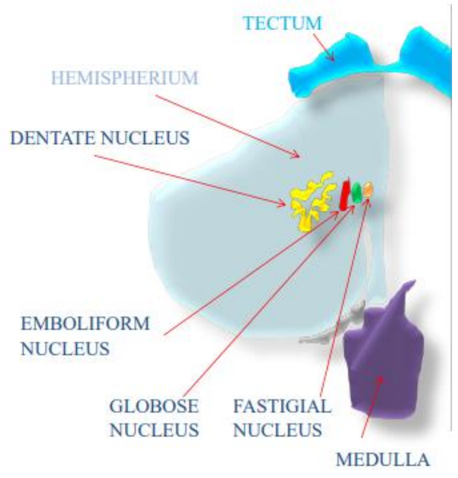
- basic constituents:
    - cerebellar cortex
    - medullary substance
    - deep, intrinsic nuclei
- built up of two symmetrical hemispheres, between which the vermis is found
- cerebellar fissures divide the cerebellum into lobes (anterior, posterior and flocculo-nodular) thar contain further subunits (lobes I- X)
  the division applies to both hemispheres
- phylogenetically it also has three parts:
    - archicerebellum: contains the flocculo-nodular system
      related to the vestibular system
      concerned with equilibrium
      functionally, it is the vestibulo-cerebellum
    - paleocerebellum: consists of the anterior portions of the hemispheres and most of the vermis
      linked to the spinal cord
      also called spinocerebellum
    - neocerebellum: the rest of the cerebellum, linked to the cerebral cortex
      also called cerebro-cerebellum

Characteristics of the cerebellum

- highly interconnected with the rest of the neuro-axis
- the incoming and outgoing projections are organized into three cerebellar peduncules connecting the cerebellum to the medulla, the pons and the mesencephalon
- receives a large quantity of sensory information
  but it’s not concerned with conscious perception
- the stimuli from receptors are important regulators of cerebellar mechanisms controlling the automatic coordination of somatic movement, muscle tone and maintenance of equilibrium
- the processed information from the cerebellar cortex is transmitted to the deep cerebellar nuclei, the main relay structures that project to distinct brains stem and diencephalic nuclei
- the cerebellum develops from the rhombic lip
- main functions of the cerebellum:
    - coordination of skilled voluntary movements
    - the regulation of the muscle tone
    - the control of the equilibrium

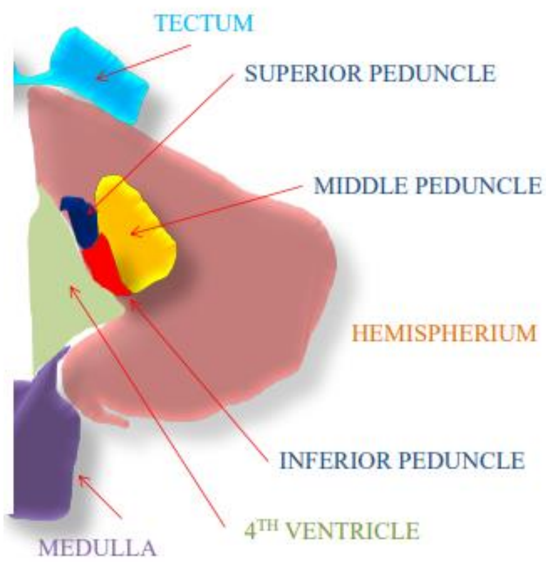
Deep nuclei of the cerebellum

- the incoming afferent axons give excitatory collaterals to the deep nuclei
- they receive the heaviest innervation from the purkinje cells
- the cortical input to the deep nuclei is inhibitory, utilizing gaba for neurotransmission

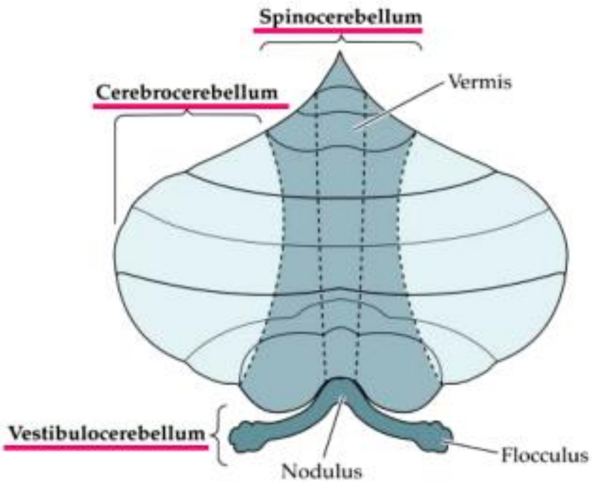


Peduncles of the cerebellum

- the cerebellum is tightly bound to the brain stem via cerebellar penducles
- there are three pairs of them:
  - superior peduncle:
    - composed of efferent fibers projecting to the thalamus and red nucleus of the midbrain
  - middle peduncle:
    - the thickest
    - connects the cerebellum to the pons
    - carries axons from the contralateral pontine nuclei that mainly receive cerebral cortical afferents
  - inferior peduncle:
    - establishes communication with the spinal cord and structures located in the caudal part of the brainstem



Functional parcellation:



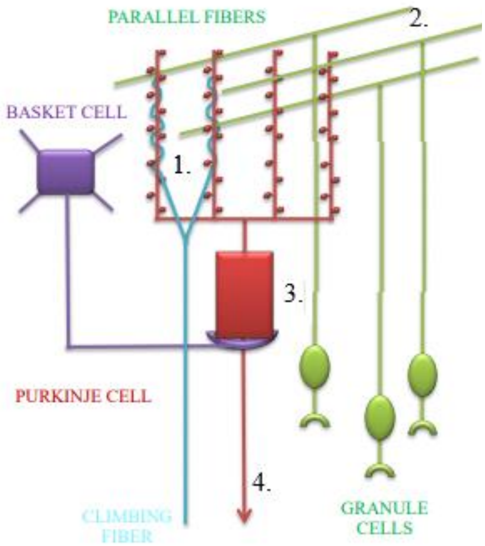
Networking of the cerebellum

Extrinsic and intrinsic network connections

- afferent fibers carry information to the cerebellum via *mossy fibers* and *climbing fibers*
- mossy fibers terminate on *granule cells* in the cerebellar cortex
- climbing fibers wind around the dendrites of *purkinje cells*
- the excitatory afferents also give *collaterals* to the deep cerebellar nuclei
- the cerebellar machinery is composed of
  - purkinje and granule cells, as principal neurons
  - inhibitory interneurons like *basket cells*, *Golgi neurons* and *stellate cells*
  - glia cells
  - *climbing fibers*
- during development of the cerebellar cortex, the radial, *Bergmann glia* has a fundamental role
- the cerebellar cortex converts the excitatory information into inhibitory signals transmitted by the axons of purkinje cells mainly to deep cerebellar nuclei
- the deep nuclei and the purkinje cells are coupled to the neuronal pacemaker activity of the inferior olive neurons whose axons transmit synchronous and rhythmic excitatory synaptic inputs

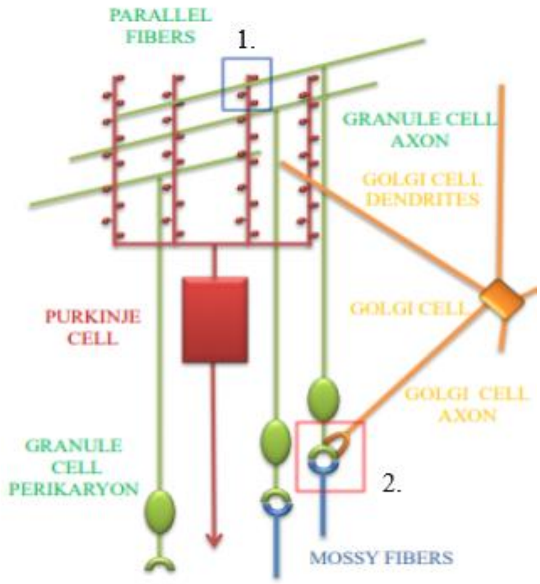
Neuronal inputs to purkinje cells

1. climbing fibers arising from the inferior olive of the medulla wrap around the dendrites of the purkinje cell establishing multiple synaptic contacts
2. parallel fibers are axons of granule cells that synapse with the spines of purkinje cell dendrites
   a single purkinje neuron communicates with about seventy thousand parallel fibers
3. basket cells located in the molecular layer innervate purkinje cells by forming a dense terminal field at the axon hillock
4. the axons of purkinje cells leave the cerebellar cortex

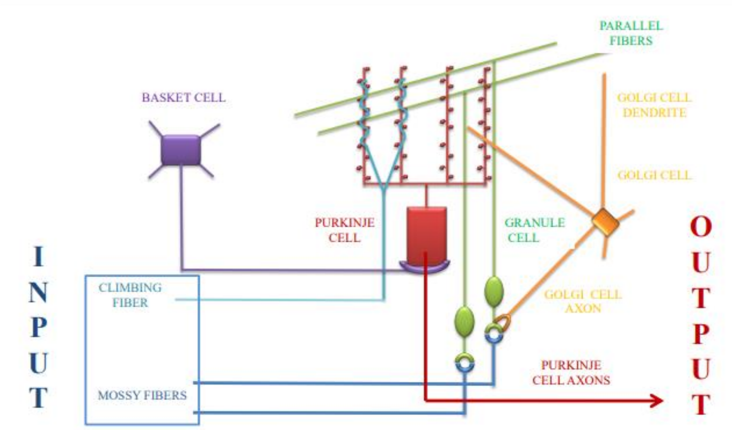


Neuronal inputs to granule cells

1. parallel fibers form en passant type synapses with dendritic spines of purkinje cells (cross over synapse)
2. mossy fibers communicate with dendrites of granule cells
   the axo-dendritic synapses are controlled by axons of Golgi neurons
   the complex synaptic structure is called cerebellar glomerulus



The neuronal circuit of the cerebellum:



Collateral inhibition

- activated cerebellar regions are surrounded by inhibited zones the basket cells generate the collateral inhibition

Types of synapses in the cerebellar cortex

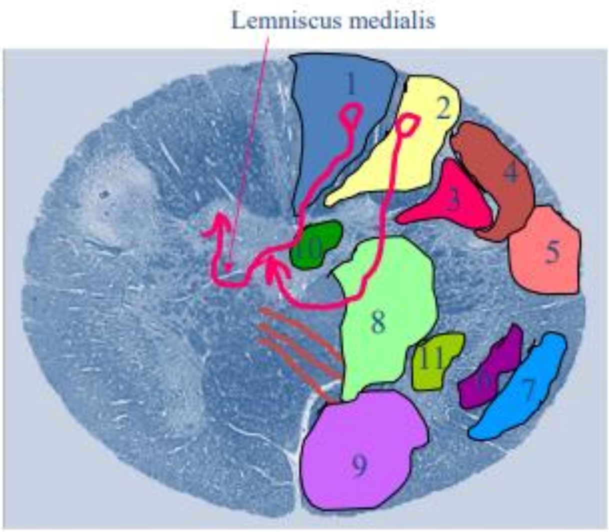
- parallel contact
  - climbing fiber-purkinje cell dendrite
- cross over synapse
  - parallel fiber- purkinje cell dendrite
- glomerular synapse
  - mossy fiber- granule dell dendrite- Golgi cell axon
- basket cell synapse
  - basket cell axon- purkinje cell body

Extrinsic connections of the cerebellum

- efferent pathway
  - cerebello-rubro-thalamo-cortical tract
- afferent pathway
  - tr. reticulocerebellaris
  - tr. pontocerebellaris
  - tr. vestibulocerebellaris
  - tr. olivocerebellaris
  - tr. spinocerebellaris posterior
  - tr. spinocerebellaris anterior

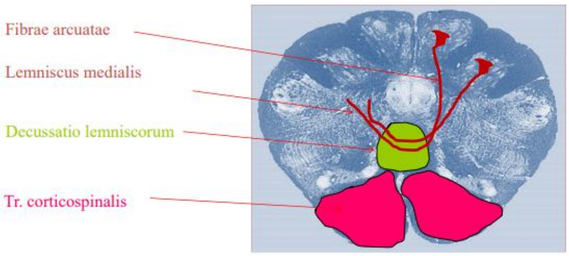
<u>Organisation of the brain stem</u>

Spino-medullary junction, pyramidal decussation



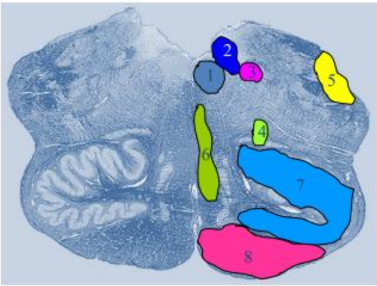
1. Tractus and nucleus gracilis
2. Tractus and nucleus cuneatus
3. N. spinalis n.V
4. Tr. spinalis n.V
5. Tr. spinocerebellaris d.
6. Tr. spinothalamicus
7. Tr. spinocerebellaris v.
8. Decussatio pyramidum
9. Pyramid
10. Nucleus n. XII
11. Nucleus ambiguus. N. motorius IX, X, XI

Medulla oblongata, at the level of decussation of the medial lemniscus



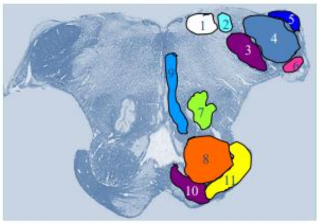
Medulla, at the level of inferior olive

1. N. nervi XII
2. N. dorsalis. n. X
3. N. et tractus solitarius
4. N. ambiguus
5. Ped. cerebellaris inf.
6. Lemniscus medialis
7. Oliva inferior
8. Tr. corticospinalis



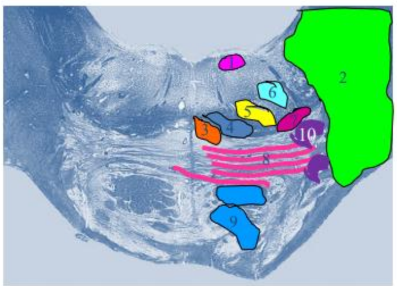
The open part of the medulla

1. N. vestibularis medialis
2. N. vestibularis inferior
3. N. et tr. spinalis n. V
4. Ped. cerebellaris inf.
5. N. cochlearis dorsalis
6. N. cochlearis ventralis
7. Oliva inferior
8. Pyramidal tract
9. Lemniscus medialis
10. Basis pontis
11. Pedunculus cerebellaris medius



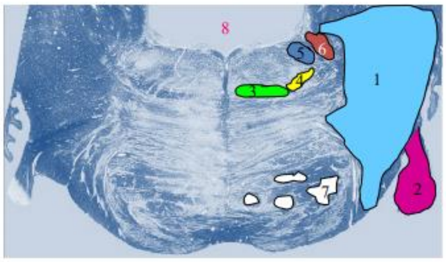
Pons at the level of the facial colliculus

1. Colliculus facialis
2. Brachium pontis
3. Corpus trapezoideum
4. Lemniscus medialis
5. Oliva superior
6. N. motorius n. VII
7. Lemniscus lateralis
8. Pontocerebellar fibers
9. Pyramid tract
10. Nuclei pontis



Pons at the level of trigeminal nuclei

1. BRACHIUM PONTIS
2. N. TRIGEMINUS
3. LM+ EDINGER TRACT (E)
4. LEMN. LATERALIS
5. N. MOT. N. V
6. N. SEN. PRINC. N. V.
7. PYRAMID TRACT
8. 4TH VENTRICLE

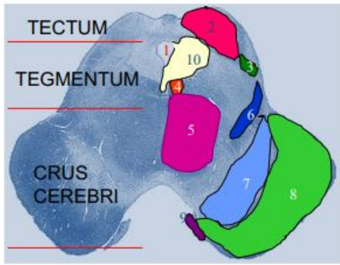


Rostral part of the pons

1. 4TH VENTRICLE
2. UPPER CEREBELLAR PEDUNCLE
3. CEREBELLUM
4. BRACHIUM PONTIS
5. FASC. LONG. MED.
6. LM+E
7. LEMNISCUS LATERALIS
8. PYRAMID TRACT

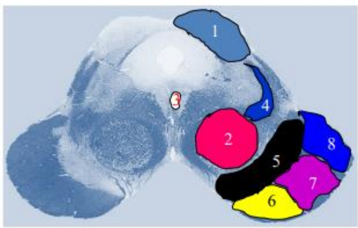
Mesencephalon at the level of inferior colliculi

1. AQUEDUCTUS CEREBRI
2. COLLICULUS INFERIOR
3. LEMNISCUS LATERALIS
4. NUCL. NERVI IV.
5. DECUSSATION OF SUP. CEREBEL. PED.
6. LM+E
7. SUBSTANTIA NIGRA
8. PEDUNCULUS CEREBRI
9. N. OCULOMOTORIUS
10. CENTRAL GRAY MATTER



Mesencephalon at the level of superior colliculi

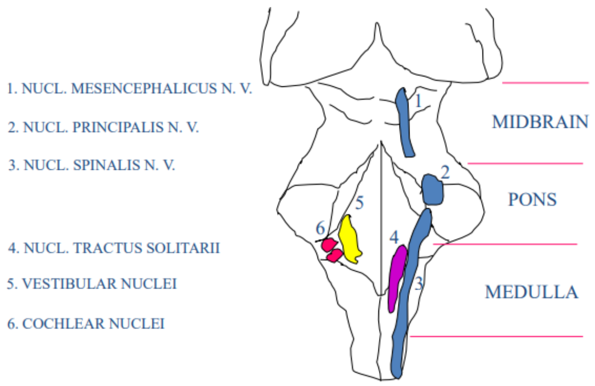
1. COLLICULUS SUPERIOR
2. NUCLEUS RUBER
3. NUCLEUS N. III.
4. LM+E
5. SUBSTANTIA NIGRA
6. TR. FRONTOPONTINUS
7. TR. CORTICOSPINALIS
8. TR. OCCIPITO-TEMPOROPONTINUS



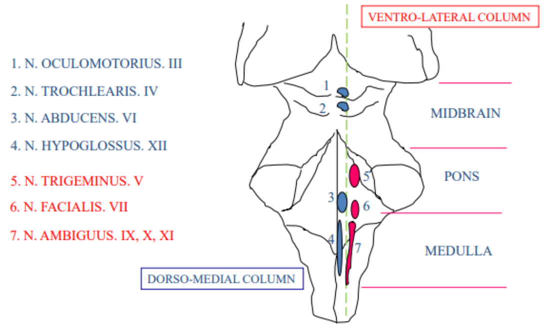
Networking of brain stem

- the somatic and visceral nuclei of cranial nerves (III-XII) are located in the brain stem, therefore via these connections it is in communication with many units of the body
- the reticular formation and the cranial parasympathetic regulatory centre provide powerful control over visceral functions
- it has particular role in controlling the sensory and motor functions of the head
- it relays information from the cerebral cortex toward the cerebellum and form the cerebellum to the thalamus
- its centers control the muscle tone and orchestrate movements
- vulnerable, long ascending sensory (medial lemniscus, spinothalamic) and descending motor (corticospinal) pathways pass through it
- neuronal centers of crucial reflex mechanisms (pupillary, accommodation, vestibulo-ocular, jaw reflex) are in the brainstem
- it is the main source of serotonergic, dopaminergic and adrenergic projections to the entire neuroaxis

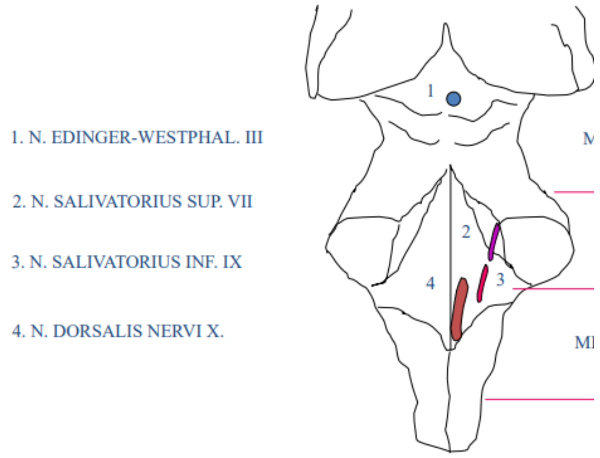
Sensory cranial nerve nuclei



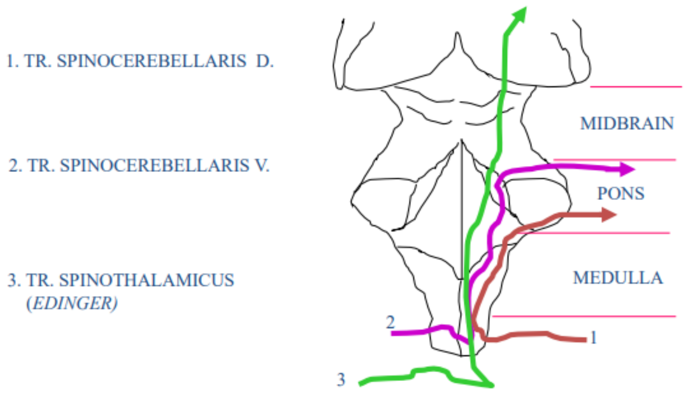
Somatomotor cranial nerve nuclei



Visceromotor cranial nerve nuclei

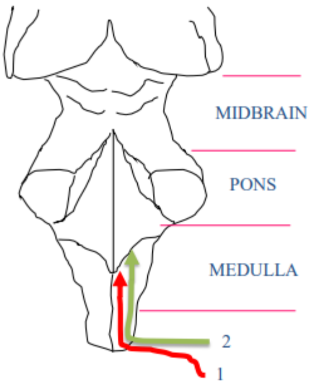


Ascending pathways passing through the brain stem



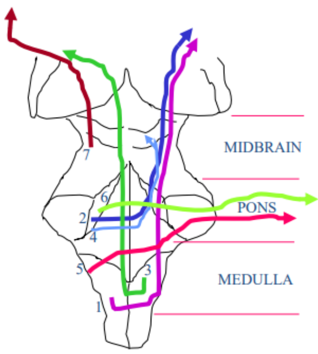
Ascending tracts terminating in brain stem

1. FASCICULUS GRACILIS
2. FASCICULUS CUNEATUS



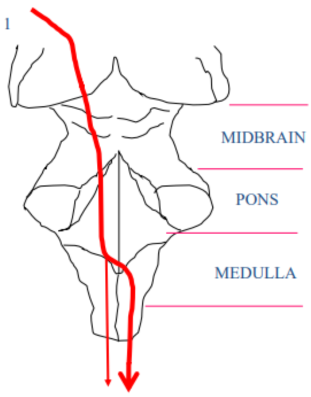
Ascending tracts originating from brain stem

1. LEMNISCUS TRIGEMINALIS
2. LEMN. TRIGEM. DORSALIS
3. LEMNISCUS MEDIALIS
4. LEMNISCUS LATERALIS
5. TR. OLIVOCEREBELLARIS
6. TR. PONTOCEREBELLARIS
7. NIGROSTRIATAL PATHWAY



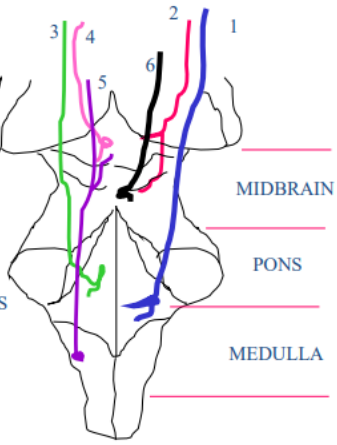
Descending tract passing through the brain stem

1. TRACTUS CORTICOSPINALIS



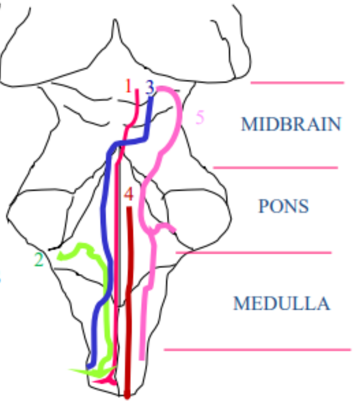
Descending pathways terminating in brain stem

1. TR. CORTICOBULBARIS
2. TR. CORTICOMESENCEPHALICUS
3. TR. CORTICOPONTINUS
4. TR. CORTICORUBRALIS
5. FASC. TEGMENTALIS CENTRALIS
6. FASC. LONGITUDINALIS DORSALIS



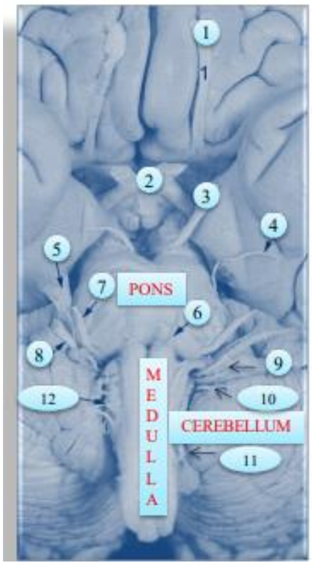
Descending pathways originating from brain stem

1. TR. TECTOSPINALIS
2. TR. VESTIBULOSPINALIS
3. TR. RUBROSPINALIS
4. TR. RETICULOSPINALIS
5. FASC. LONGITUDINALIS MEDIALIS



Cranial nerves

- 12 pairs of cranial nerves with widespread sensory, motor and autonomic functions
- the *olfactory* and *optic* nerves are associated with prosencephalic derivatives, the rest of the cranial nerves belongs to the brainstem



1. OLFACTORY BULB+TRACT
2. OPTIC NERVE (+OPTIC CHIASM)
3. OCULOMOTOR NERVE
4. TROCHLEAR NERVE
5. TRIGEMINAL NERVE
6. ABDUCENT NERVE
7. FACIAL NERVE
8. VESTIBULOCOCHLEAR NERVE
9. GLOSSOPHARYNGEAL NERVE
10. VAGUS NERVE
11. ACCESSORY NERVE
12. HYPOGLOSSAL NERVE

CRANIAL NERVE	NAME	FUNCTION	TESTING
I	olfactory nerve	olfaction	with smelly substance
II	optic nerve	vision	vision chart
III	oculomotor nerve	most eye muscles	“follow the moving finger”
IV	trochlear nerve	superior oblique (muscle neither parallel nor perpendicular to the long axis of the body or a limb)	look down at the nose
V	trigeminal nerve	facial sensation	touch the face
		muscles of mastication	clench the teeth
VI	abducent nerve	lateral rectus	look to the side
VII	facial nerve	facial expression	smile, raise the eyebrows
		taste	sugar or salt
VIII	vestibulocochlear nerve	hearing	a tuning fork
		balance	look for vertigo
IX	glossopharyngeal nerve	pharynx sensation	gag reflex
X	vagus nerve	muscles of larynx and pharynx, parasymp.	check for hoarseness, open wide and say ‘AH’
XI	accessory nerve	trapezius and sternocleidomastoid	test shoulder raise or turning the head
XII	hypoglossal nerve	tongue muscles	stick out the tongue

Functional classification of cranial nerves

SENSORY	MOTOR	MIXED SENSORY AND MOTOR	PARASYMPATHETIC
olfactory	oculomotor	trigeminal	oculomotor
optic	trochlear	facial	facial
vestibulocochlear	abducens	glossopharyngeal	glossopharyngeal
	accessory	vagus	vagus
	hypoglossal		

Sensory ganglia of cranial nerves

- fibers carrying sensory information to the brain stem arise from sensory ganglia
- the *vestibular* and *cochlear* ganglia are composed of bipolar neurons, the rest of the ganglia contains pseudo-unipolar cells
- the pattern is similar to that of the sensory system of the spinal cord

Functions of parasympathetic ganglia belonging to cranial nerves

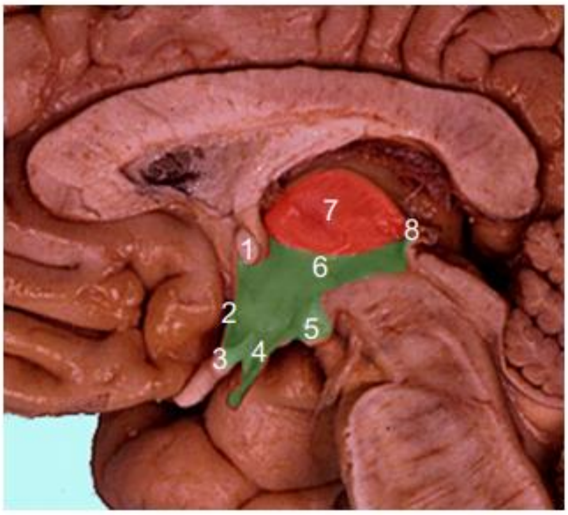
AUTONOMIC GANGLIA	CRANIAL NERVE	FUNCTION
ciliary	oculomotor	constricts pupil, lens accommodation
pterygopalatine	facial	lacrimation (tearing) nasal gland secretion
submandibular	facial	salivation of submandibular and sublingual glands
otic	glossopharyngeal	salivation of parotid gland
intramural	vagus	gland secretion peristalasis

<u>Diencephalon</u>

- the rostral continuation of the brain stem
- with the exception of its ventral part, it is covered by telencephalic structures
- develops from the prosencephalic vesicle, its cavity is the third cerebral ventricle
- the major constituents of the diencephalon include the thalamus, hypothalamus, metathalamus, epithalamus and subthalamus
- the thalamus and the basal telencephalic nuclear complex form a clinically important passageway for projecting fibers, the internal capsule
- thalamic structures are in reciprocal connection with the cerebral cortex
  they communicate with major motor and sensory systems and they are linked with the limbic system
- the hypothalamus controls autonomic centers and via the pituitary it orchestrates the performance of the endocrine system
  it secrets a wide scale of hormones into the systemic and portal circulations

The major components:

- thalamus
- hypothalamus
- epithalamus
- metathalamus
- subthalamus



1. COMMISSURA ANTERIOR
2. LAMINA TERMINALIS
3. CHIASMA OPTICUM
4. INFUNDIBULUM
5. CORPUS MAMILLARE
6. SULCUS HYPOTHALAMICUS
7. THALAMUS
8. EPITHALAMUS

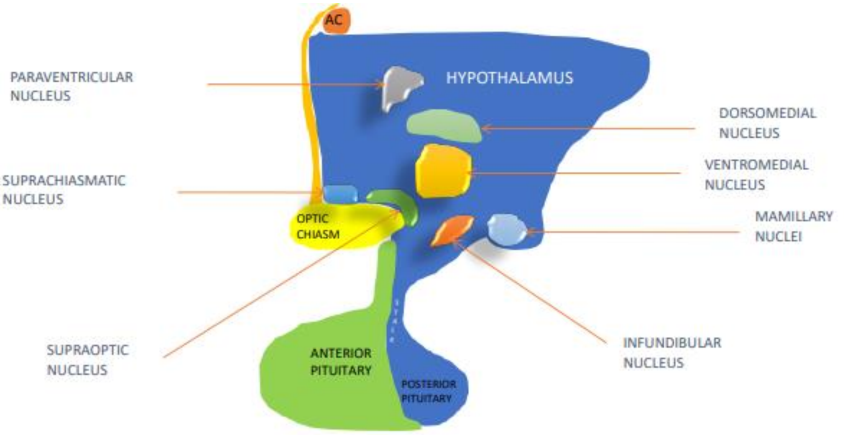
Thalamic nuclear groups:

- medial group: anterior nucleus; dorsomedial nucleus
- lateral group
    - dorsal tier: lateral dorsal & posterior nucleus; pulvinar
    - ventral tier: ventral anterior, lateral & posterior nucleus; lateral geniculate nucleus, medial geniculate nucleus
- intralaminar group: paracentral nucleus, central lateral nucleus, centromedian nucleus, parafascicular nucleus
- midline group: paraventricular nucleus, nucleus reuniens (hypothalamic and hippocampal connections)
- other: thalamic reticular nucleus (intrinsic thalamic connections)

Thalamic fiber tracts:

- external & internal medullary lamina
- anterior, superior, inferior & posterior thalamic peduncle
- mammillothalamic tract of thalamus
- stratum zonale of thalamus

Scheme of hypothalamic nuclei in mid-sagittal section



The magnocellular neurosecretory system

- magnocellular neurons located in the supraoptic and paraventricular nuclei synthesize: oxytocin, vasopressin and neurophysins
- these hormones are transported down to the posterior pituitary
- upon specific stimuli, the hormones are released to the systemic circulation
- they control smooth muscle functions and absorption of water in kidney

The parvicellular neurosecretory system

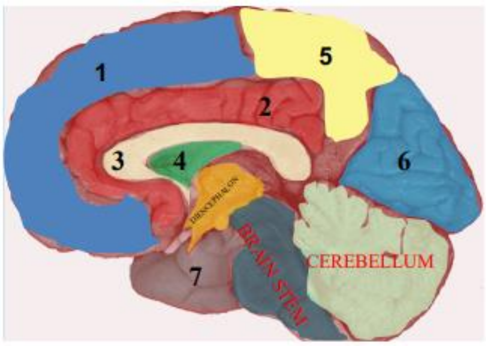
- parvicellular neurons secret releasing and release-inhibiting hormones into the portal circulation
- the hormones control the troph hormone output of different pituitary gland cells
- the system regulates reproduction, stress, adaptation, body growth and metabolism

<u>Divisions of the telencephalon</u>

Development of the telencephalon

- the telencephalon and the diencephalon derive from the prosencephalic vesicle
- the telencephalic vesicles grow laterally and rostro-caudally
- gradually they cover and hide most of the diencephalon and the rostral part of the brain stem
- the cerebral cortex, the basal ganglia and constituents of the limbic system derive from them

Scheme of the median sagittal brain surface



1. FRONTAL LOBE
2. GYRUS CINGULI
3. CORPUS CALLOSUM
4. SEPTUM PELLUCIDUM
5. PARIETAL LOBE
6. OCCIPITAL LOBE
7. TEMPORAL LOBE

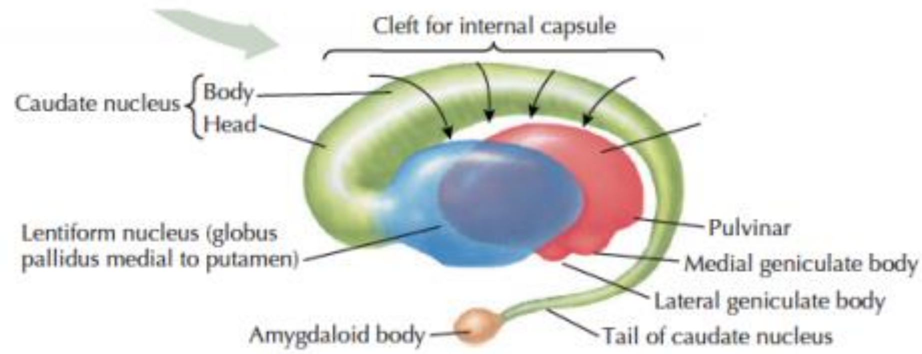
Association of specific functions with cortical areas

- frontal lobe: primary motor center
- parietal lobe: primary somatosensory center
- temporal lobe: hearing center
- occipital lobe: visual center

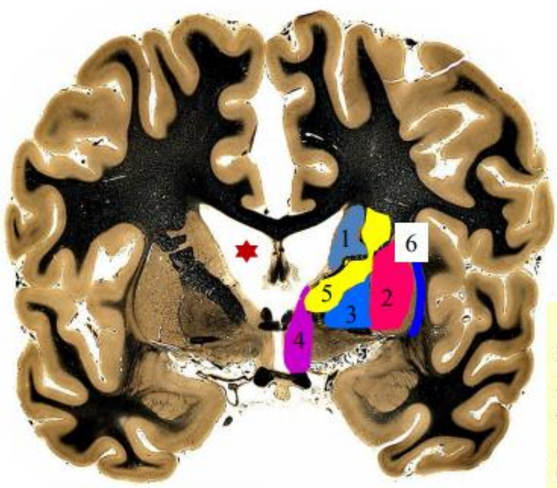
Functions related to the frontal cortex

Attention	Coordinated movements
Behavior	Generalized, mass movements
Abstract thought	Some eye movements
Problem solving	Muscle movements
Creative thought	Skilled movements
Emotion	Sense of smell
Intellect	Supplementary motor skills
Judgment	Physical reaction
Initiative	Sexual urges

Caudate nucleus and lentiform nucleus



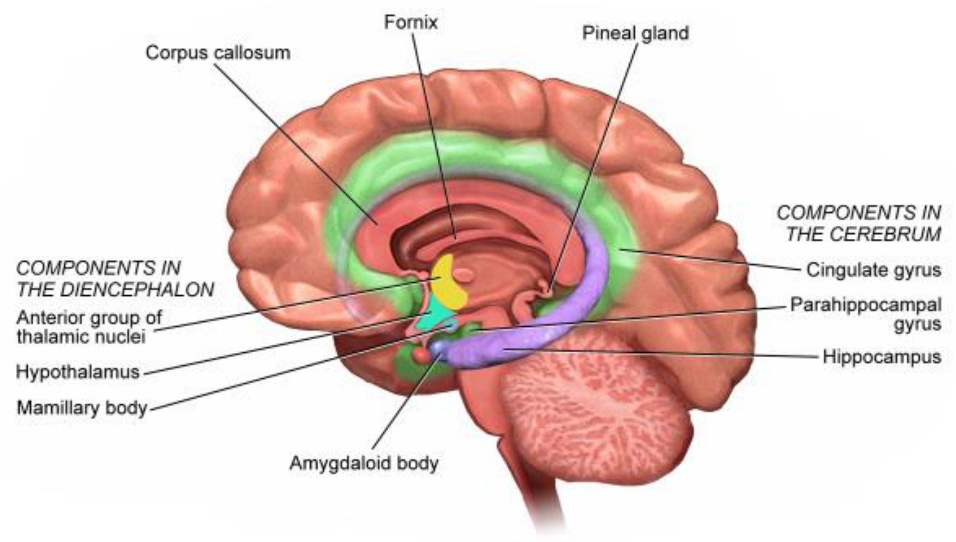
Basal ganglia and the internal capsule:



1. N. CAUDATUS
2. PUTAMEN
3. GLOBUS PALLIDUS
4. DIENCEPHALON
5. CAPSULA INTERNA
6. CLAUSTRUM

The limbic system

- contains the limbic lobe, hippocampal formation, amygdaloid body and their widespread connections
- associated with processes of learning, memory, emotions and regulation of homeostasis
- developmentally, it arises from the transition zone between the diencephalic and telencephalic vesicles



AREAS	FUNCTIONS
Cingulate gyrus	autonomic functions regulating heart rate and blood pressure as well as cognitive, attentional and emotional processing
Parahippocampal gyrus	spatial memory
Hippocampus	long-term memory
Amygdala	anxiety, aggression, fear conditioning emotional memory and social cognition
Hypothalamus	regulates the autonomic nervous system via hormone production and release secondarily affects and regulates blood pressure, heart rate, hunger, thirst, sexual arousal and the circadian rhythm sleep/wake cycle
Mammillary body	memory
Nucleus accumbens	reward, addiction

Cytoarchitecture of cerebral cortex

Cellular composition of the cerebral cortex

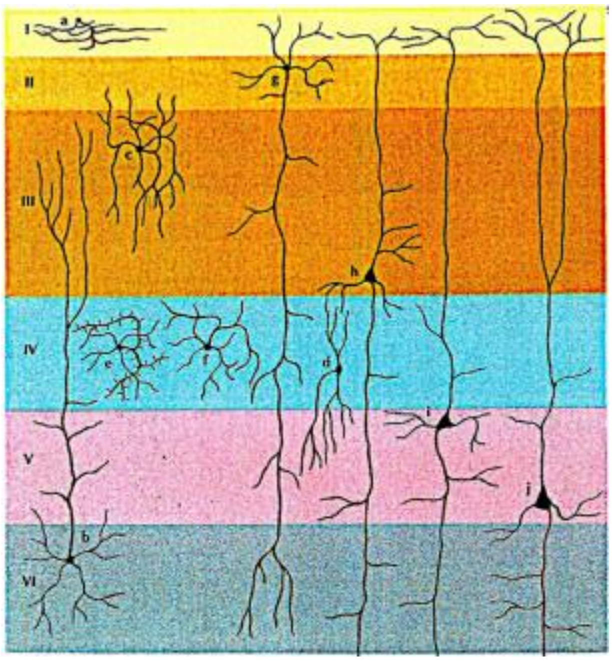
- the cerebral cortex consists of
    - the archicortex (hippocampal formation
    - paleocortex (olfactory areas)
    - neocortex (comprised of six superimposed layers)
- there are about 10^{10} neurons in the cerebral cortex
- the cortex is built up by
    - principal, pyramidal neurons
    - inhibitory interneurons
    - glia cells
- there are variations in the cytoarchitecture of the cortex:
  the *primary sensory cortex* is granular
  the *primary motor cortex* is rather agranular in nature
- the incoming subcortical afferents have special termination patterns
  they transfer the information to interneurons, that relay it further to principal cells
- neurons interacting locally are organized in columns called cortical modules

Organization of neurons in cortical layers

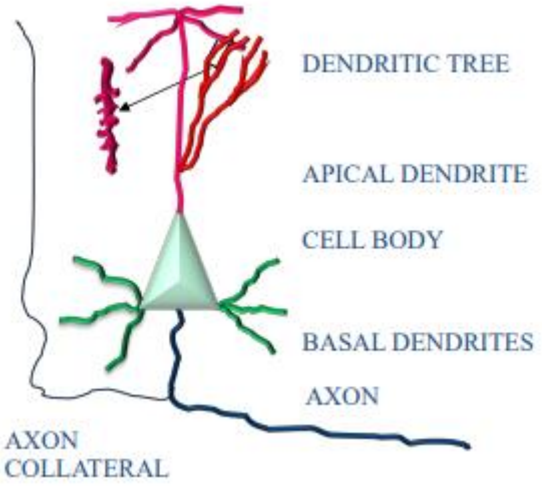
1. molecular layer
2. external granular layer
3. external pyramidal layer
4. internal granule layer
5. internal pyramidal layer
6. multiform layer

Cell types of the cerebral cortex

- horizontal cell
- cell of Martinotti
- chandelier cell
- aspiny granule cell
- spiny granule cell
- stellate (granule) cell
- small pyramidal cell of layers II, III
- small pyramidal association and projection cells of layer V
- large pyramidal projection cell (Betz cell)



The pyramidal neuron



Features of interneurons

- they are classified based on their structural, electrophysiological and chamical properties
- the most known representatives of interneurons are the basket, chandelier, stellate, Retzius-Cajal and Martinotti cells
- interneurons establish sophisticated circuits with principal neurons and relay the information brought in by specific and non-specific afferents to pyramidal cells

Properties of cortical interneurons

Morphological features
• Soma: shape; size; orientation; other
• Dendrite: arborization polarity; branch metrics; fine structure; postsynaptic element; other
• Axon: initial segment; arbor trajectory; terminal shape; branch metrics; boutons; synaptic targets;
other
• Connections: chemical and electrical; source; location and distribution; other

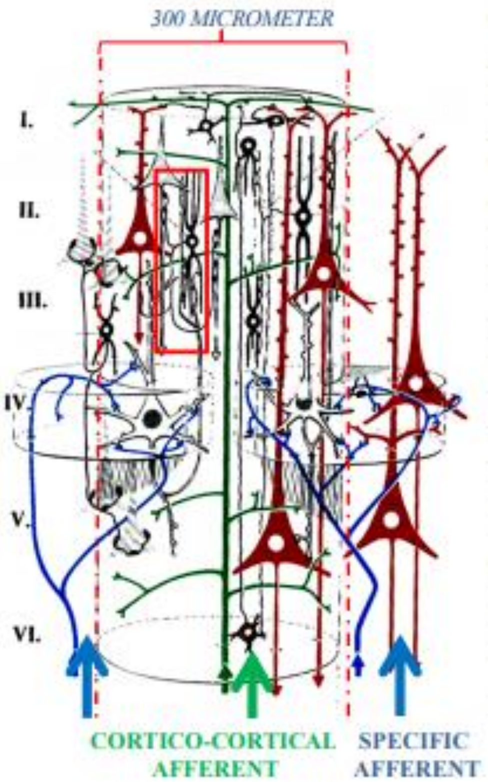
Molecular features
•Transcription factors
• Neurotransmitters or their synthesizing enzymes
• Neuropeptides
• Calcium-binding proteins
• Receptors: ionotropic; metabotropic
• Structural proteins
• Cell-surface markers
• Ion-channels
• Connexins
• Transporters: plasma membrane; vesicular
• Others

Physiological features
• Passive or subthreshold parameters: resting membrane potential; membrane time constants; input
resistance; oscillation and resonance; rheobase and chronaxie; rectification
• Action potential (AP) measurements: amplitude; threshold; half-width; afterhyperpolarization;
afterdepolarization; changes in AP waveform during train.
• Dendritic back-propagation
• Depolarizing plateaus
• Firing pattern: oscillatory and resonant behaviour; onset response to depolarizing step; steadystate
response to depolarizing step
• Response to hyperpolarizing step: rectification; rebound
• Spiking recorded extracellularly: phase relationship to oscillations; functional response specificity;
cross-correlation and other dynamics
• Postsynaptic responses: spontaneous and evoked; ratio of receptor subtypes; spatial and temporal
summation; short- and long-term plasticity; gap junctions

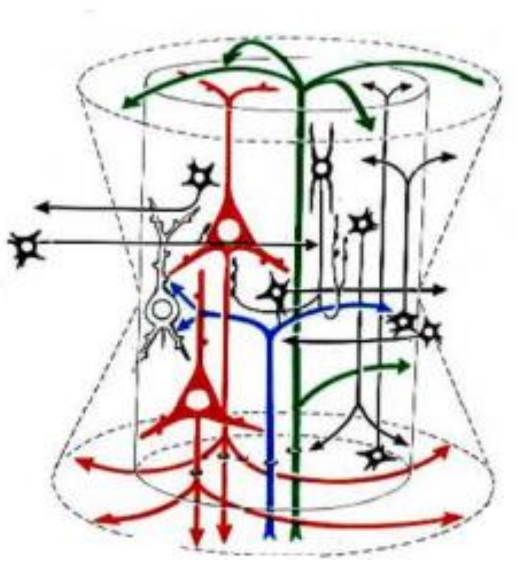
Neuronal assembly of a cortical module

- the cortical column is about 300 µm wide and has the height of the cortex
- each hosts about five thousand neurons
- there are approximately $2x10^6$ cortical modules in humans
- the system specific afferents and the cortio-cortical afferents feed the cortical columns

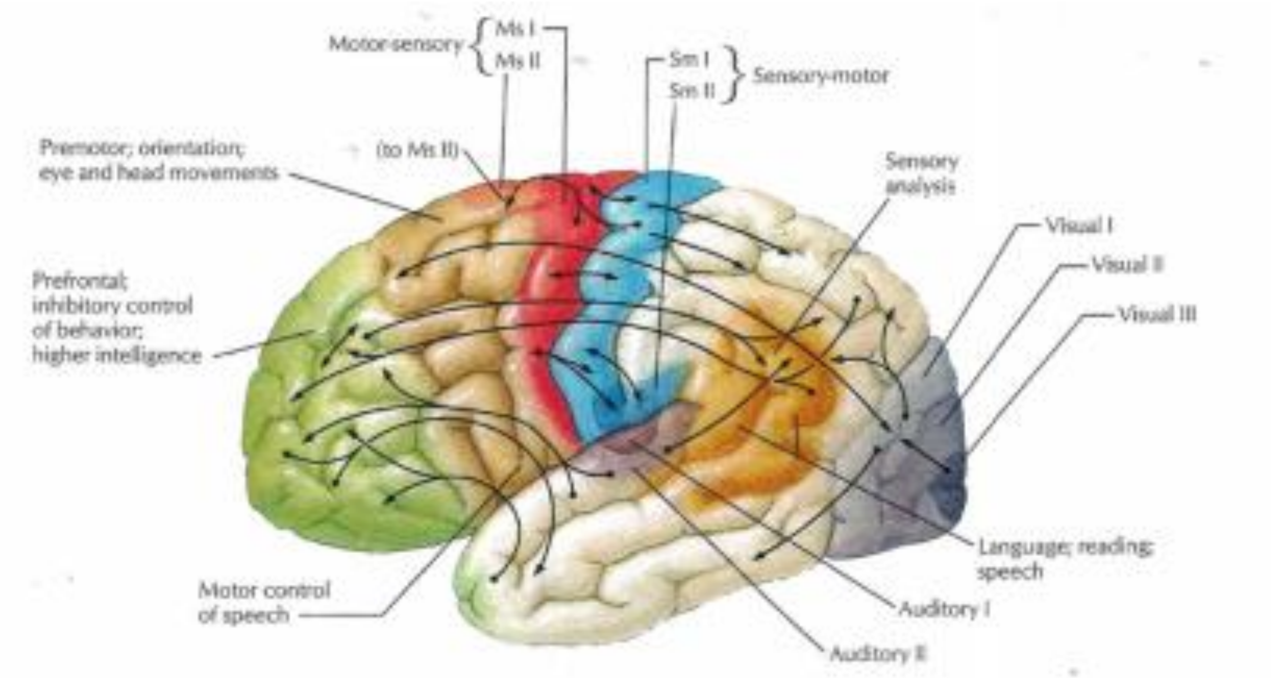
- the system specific afferents terminate in the middle area, while the cortico-cortical afferents terminate in the superficial zone of the column
- axons of chandelier cells form axo-axonic connections with pyramidal neurons
- at the top and the base of the column the excitation spreads laterally, while in the middle part the lateral information flow is limited
- the outflow from the column is executed by axons of pyramid cells
- layer III cells project to cortical regions as associative and commissural fibers, while the large Betz pyramidal neurons of layer V establish the descending connections



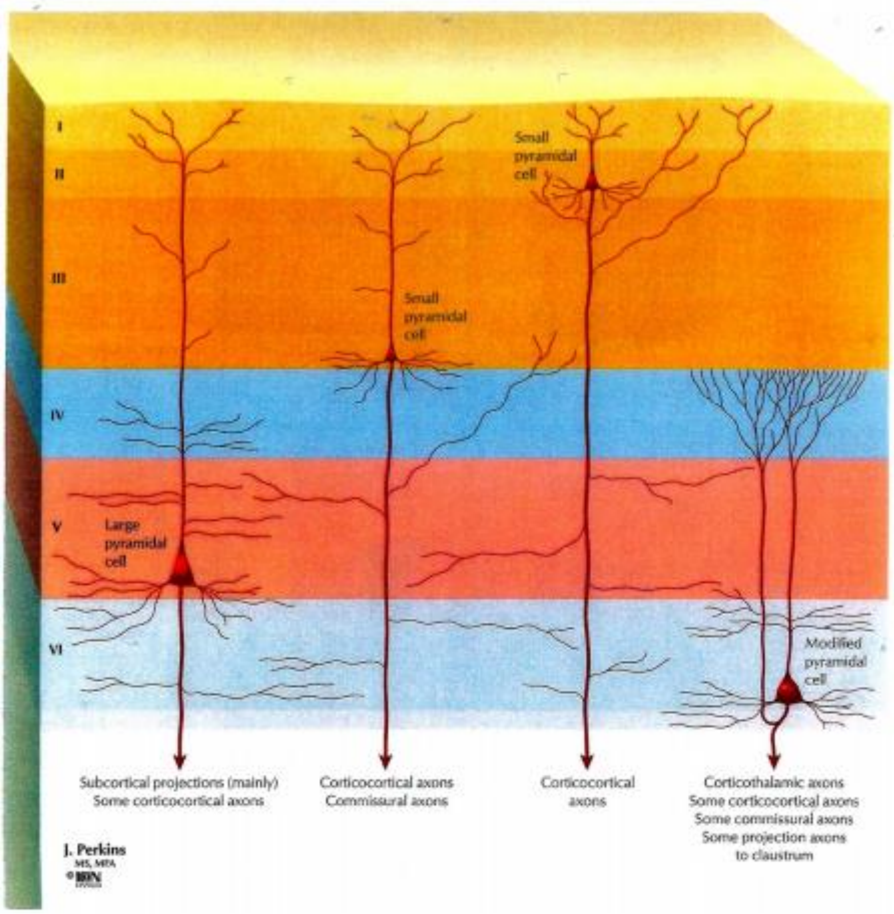
Communication among cortical modules



Cortical association pathways



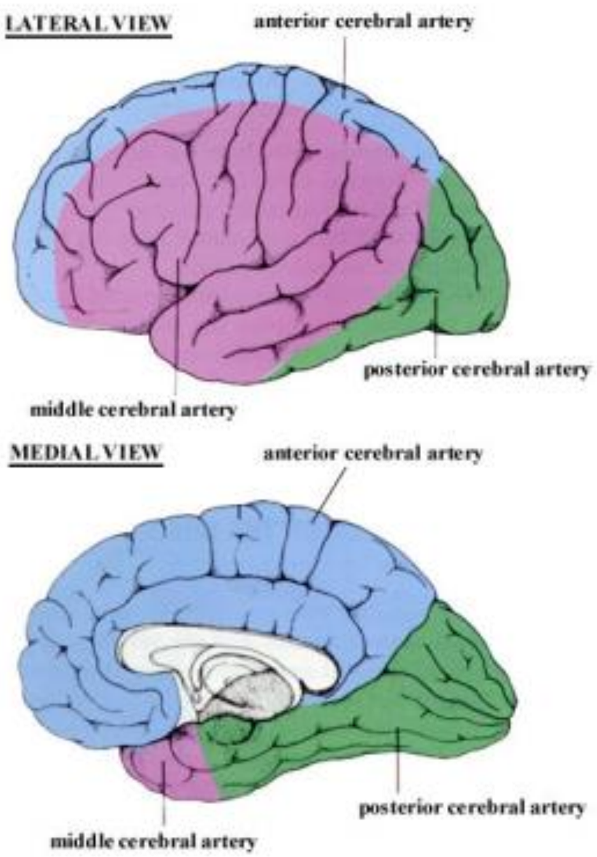
Efferent neurons of the cortex



Different functional outputs of cortical modules of different brain regions

CORTICAL AREA	FUNCTION
PREFRONTAL CORTEX	PROBLEM SOLVING, EMOTION, COMPLEX THOUGHT
MOTOR ASSOCIATION CORTEX	COORDINATION OF COMPLEX MOVEMENT
PRIMARY MOTOR CORTEX	INITIATION OF VOLUNTARY MOVEMENT
PRIMARY SOMATOSENSORY CORTEX	RECEIVES TACTILE INFORMATION FROM THE BODY
SENSORY ASSOCIATION AREA	PROCESSING OF MULTISENSORY INFORMATION
VISUAL ASSOCIATION AREA	COMPLEX PROCESSING OF VISUAL INFORMATION
VISUAL CORTEX	DETECTION OF SIMPLE VISUAL STIMULI
WERNICKE'S AREA	LANGUAGE COMPREHENSION
AUDITORY ASSOCIATION AREA	COMPLEX PROCESSING OF AUDITORY INFORMATION
AUDITORY CORTEX	DETECTION OF SOUND QUALITY (LOUDNESS, TONE)
MOTOR SPEECH CENTER (BROCA'S AREA)	SPEECH PRODUCTION AND ARTICULATION

Blood supply of the cerebral cortex



Sensory systems

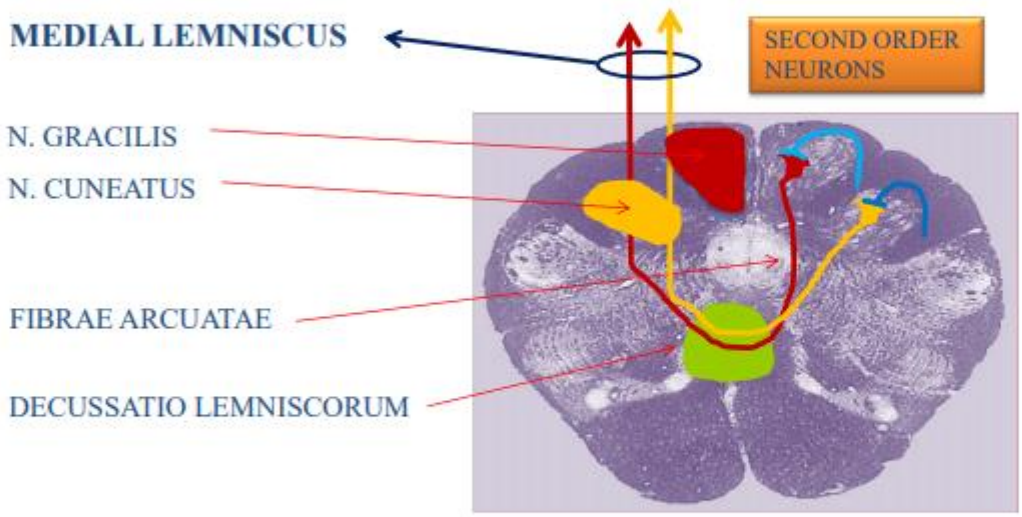
Features of the general sensory system

- touch, pain, temperature and conscious proprioceptive stimuli provide useful information about objects in the environment and the actual state of body parts
- from most parts of the body, two general sensory systems carry the information from receptors to higher processing centers, the spinothalamic system and the medial lemniscus system
- from the head region, the trigeminal and dorsal trigeminal tracts forward the sensory information to the thalamus
- the systems are crossed and multisynaptic in nature
- they are linked to the sensory nuclei of the thalamus, especially the ventral postero-medial and ventral postero-lateral nuclei
- the major processing site of general sensory information is in the primary somatosensory cortex located in the postcentral gyrus of the parietal lobe

Origin and initial course of the medial lemniscus system

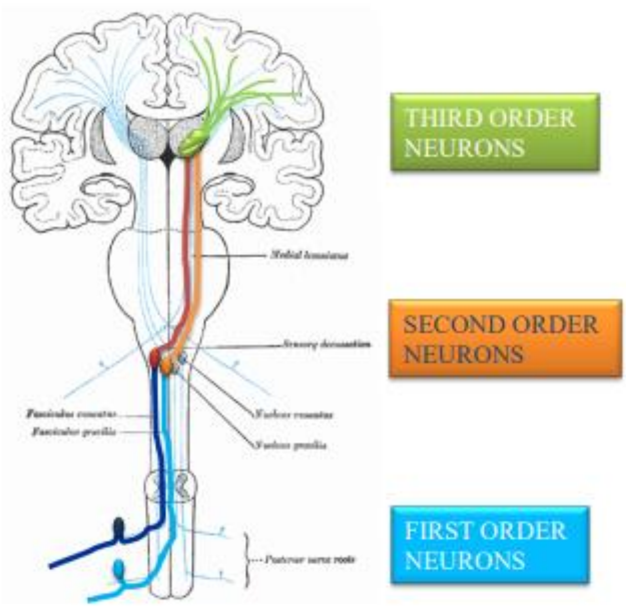
- *fasciculus gracilis:* thick myelinated fibers from S, L, T6-12 segments
    - origin: spinal ganglia
    - termination: nucleus gracilis in medulla
    - function: sensory, light touch, vibration, 2-point discrimination, position sense
- *fasciculus cuneatus:* thick myelinated fibers from T1-6, and all C segments
    - origin: spinal ganglia
    - termination: nucleus cuneatus
    - function: sensory, light touch, vibration, 2-point discrimination, position sense

The medial lemniscus system at the level of its decussation



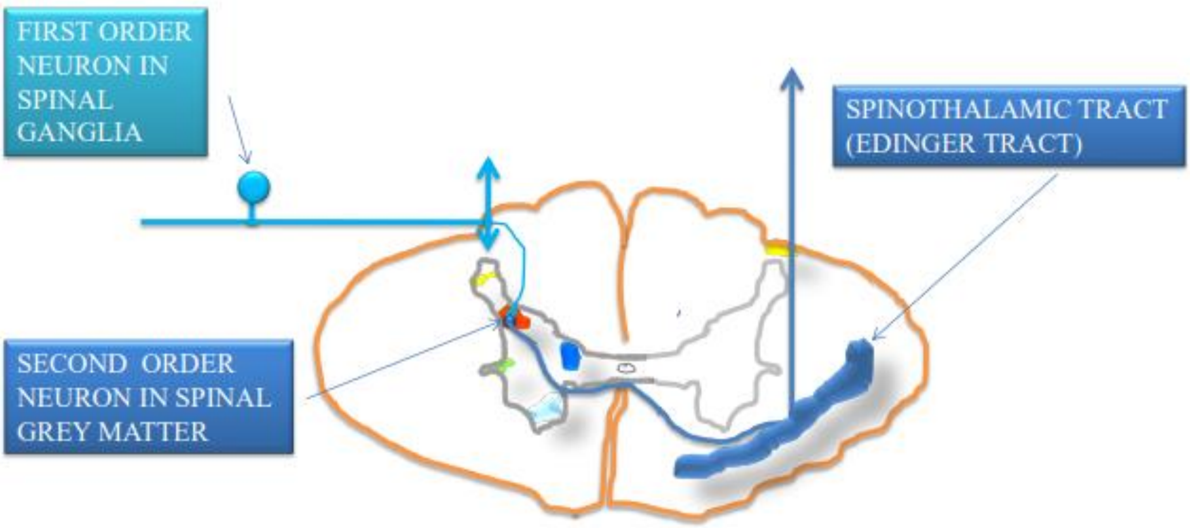
- the axons of first order neurons terminate on second order neurons residing in n. gracilis and n. cuneatus
- the ascending, crossed tract originating from them is the medial lemniscus, projecting to the thalamus

Projections of the medial lemniscus system to the thalamus and the somatosensory cortex



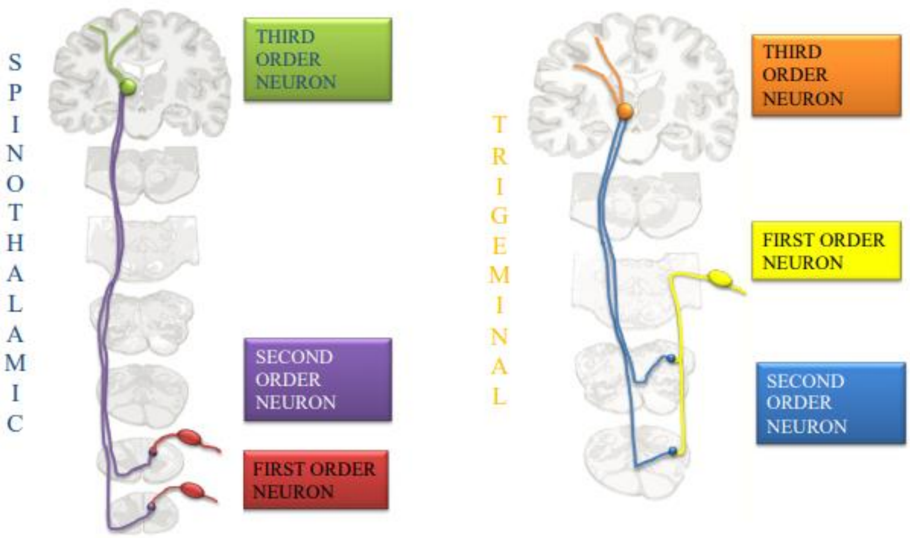
- the ascending medial lemniscus terminates in the ventral postero-lateral nucleus of the thalamus
- cells of this nucleus serve as third order neurons and project to the primary somatosensory cortex in the parietal lobe
- from the head region, light touch, vibration, 2-point discrimination senses are processed by the principle sensory nucleus of the trigeminal nerve located in the pons
- the projection from this nucleus terminates in the ventral postero-medial nucelues of the thalamus

Origin and initial course of the spinothalamic tract

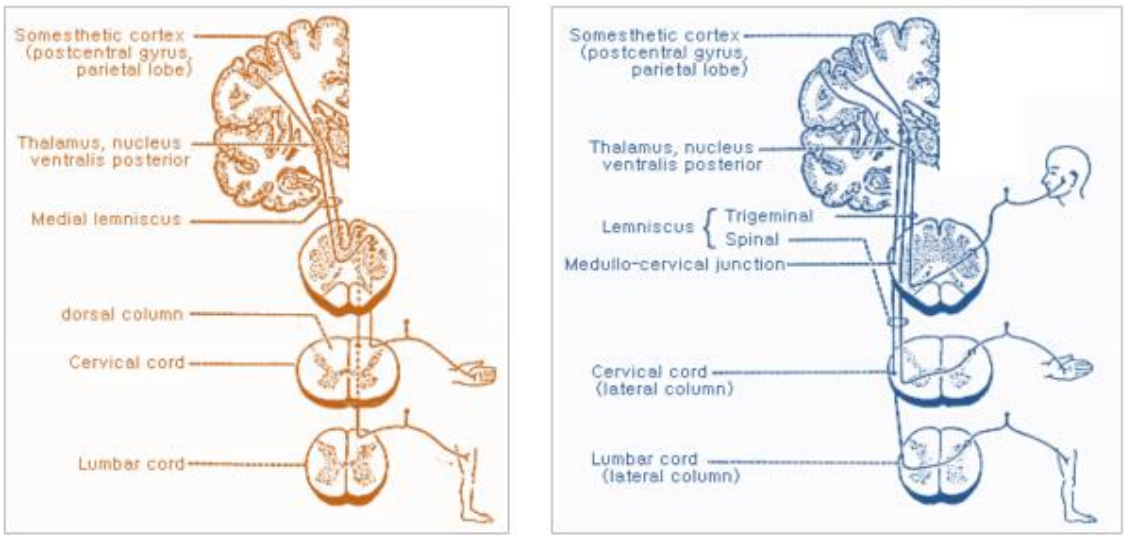


- *spinothalamic tract:*
    - origin: contralateral grey matter, laminae I, IV and V
    - termination: thalamus
    - function: sensory, noxious (harmful) pain and thermal stimuli, crude touch

Course of the spinothalamic and trigeminal tracts



Comparison of the two sensory systems



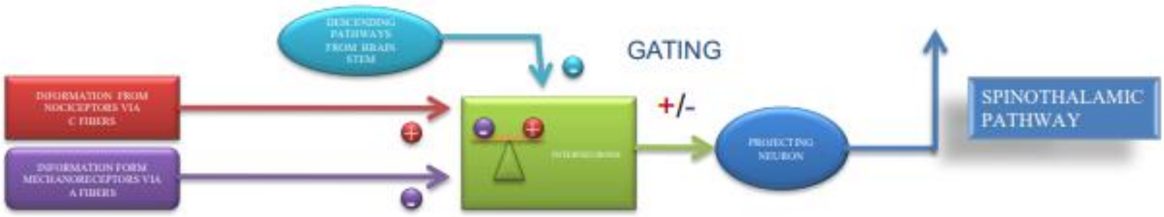
THE MEDIAL LEMNISCUS SYSTEM THE SPINOTHALAMIC SYSTEM

Somatic sensations transmitted by the two sensory systems

MEDIAL LEMNISCUS	SPINOTHALAMIC
touch sensations with high degree of localisation of the stimulus	pain
touch sensations requiring transmission of fine gradients of intensity	crude touch and pressure sensations
sensations that signal movement occurs against the skin	thermal sensations (cold, warm)
phasic sensation (vibration)	sexual sensations
position sensations	tickle sensations
pressure sensations, fine degrees of judgement of pressure intensity	itch sensation

Pain sensation

- tissue damage evokes acute or chronic pain which is an unpleasant sensory and emotional experience
- it negatively influences the quality of life
- pain killing is a primary obligation of medical practice
- painful events are categorized according to duration, severity, anatomical location, body system involved, cause, temporal features and the neurochemical mechanisms involved
- *pain gate theory*: the projecting neurons carrying tissue damage/pain-related information to higher processing sensory centers are controlled locally in the grey matter by incoming information of non-noxious stimuli
  these arrive from the segmental level via thick, myelinated fibers of mechanoreceptors and also tracts descending from the brain stem
  opening of the pain gate and pain threshold level seem to depend on the actual balance of information supplied by these, multiple systems



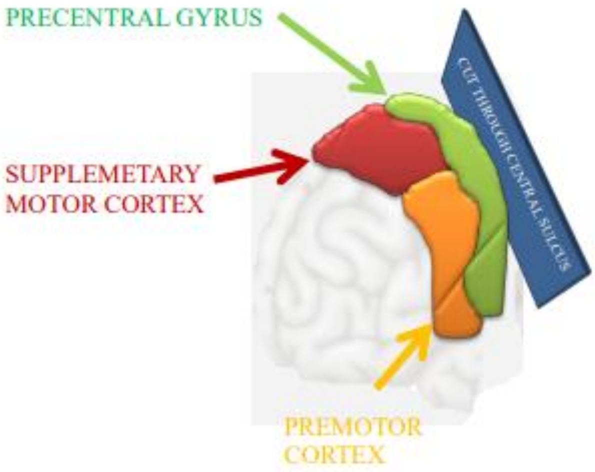
<u>Motor systems</u>

Characteristics of the motor systems

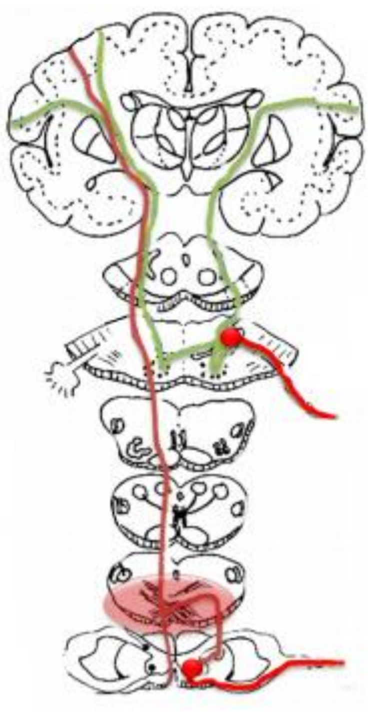
- extrafusal striated muscle fibers and alpha motoneurons that innervate them form the motor unit
- the somato-motoneurons are disturbed in the brain stem and the spinal cord collectively, they are called as lower motoneurons
- lower motoneurons are controlled by upper motoneurons
- the term refers to descending pathways (corticospinal, rubrospinal, tectospinal, vestibulospinal, reticulospinal tracts) that regulate the lower motoneurons either by a direct or an interneuron-mediated manner
- the main motor systems include the motor cortex, the cerebellar machinery and the basal ganglia
- the cerebellar machinery and the basal ganglia are channelled to the frontal motor cortex via the ventral lateral nucleus of the thalamus
- the main cortical motor system uses the corticobulbar and cortico-spinal tracts for execution of voluntary movements
- lesion of the upper motor neuron pathways results in spastic paralysis, exaggerated stretch reflex and some abnormal reflexes
- cerebellar disorders change the rate, direction, range and force of movements
- lesions of the basal ganglia are manifested in dyskinesia

The motor cortex

- the motor cortex is comprised of
    - the precentral gyrus, as the primary motor center
    - the supplementary motor cortex
    - the prefrontal motor cortex
    - certain parietal lobe regions
- the muscle groups of the body are represented in a somatotopic fashion in the primary motor cortex (motor homunculus)

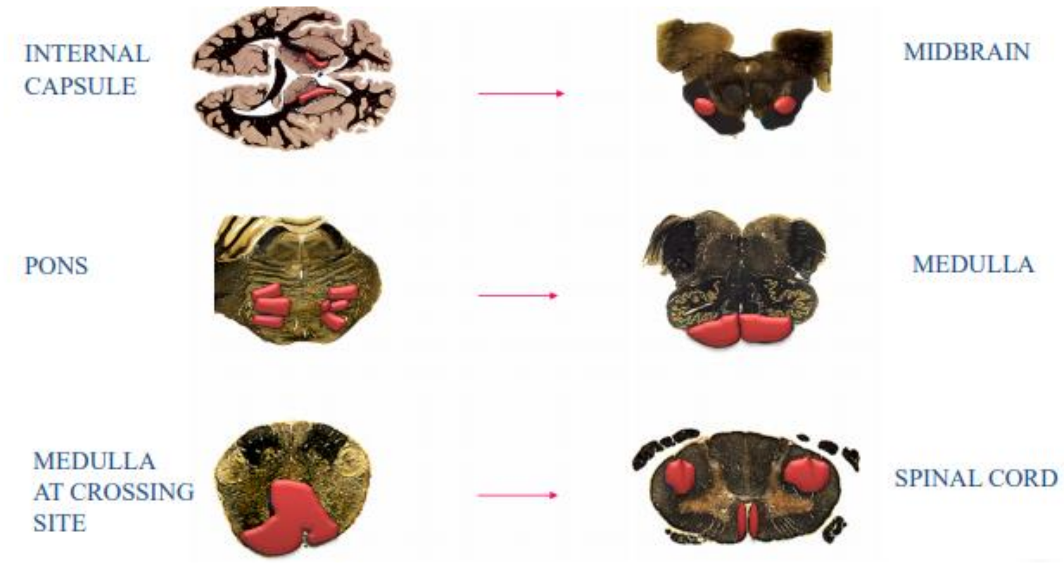


The corticobulbar and corticospinal projections

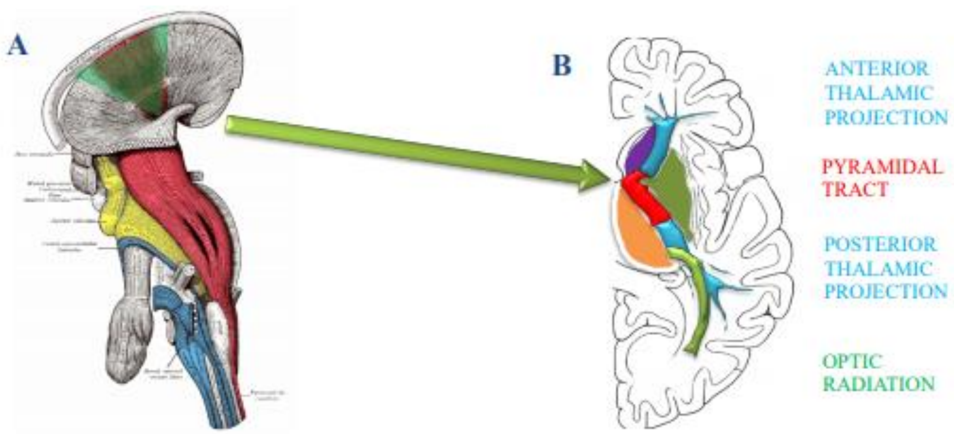


- the descending corticobulbar motor fibers supply motoneurons of the brain stem
- while the corticospinal projection that splits at the level of the medulla feeds the lower motoneurons of the spinal cord via the lateral and anterior corticospinal tracts
- bilateral innervation of the trigeminal motor nucleus in the pons
- the crossing of the majority of the corticospinal axons in the medulla is highlighted by pink shadow

Course of the descending pyramidal pathway

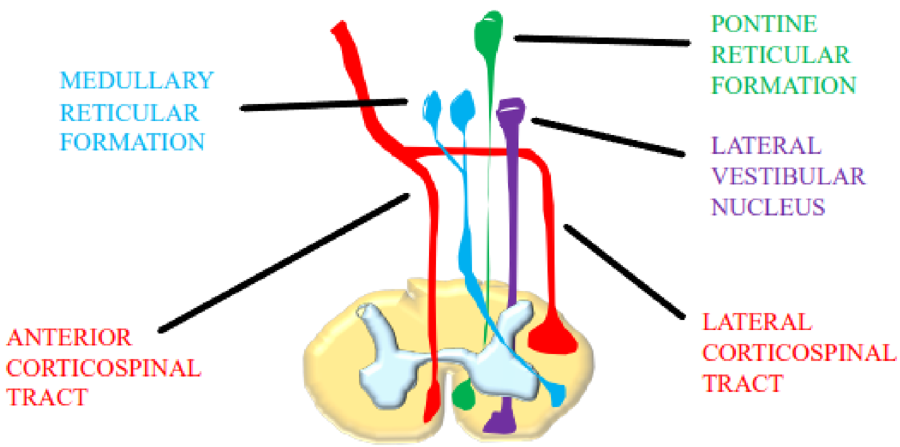


Corticospinal projection within the internal capsule

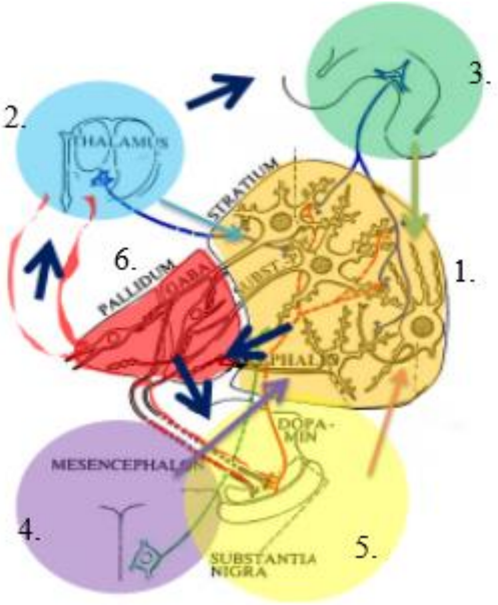


- A: the downstream course of corticospinal fibers
- B: the pyramidal tract in the genu of the capsule wedged between the anterior and posterior thalamic projections

Illustration of some descending upper motoneuron systems

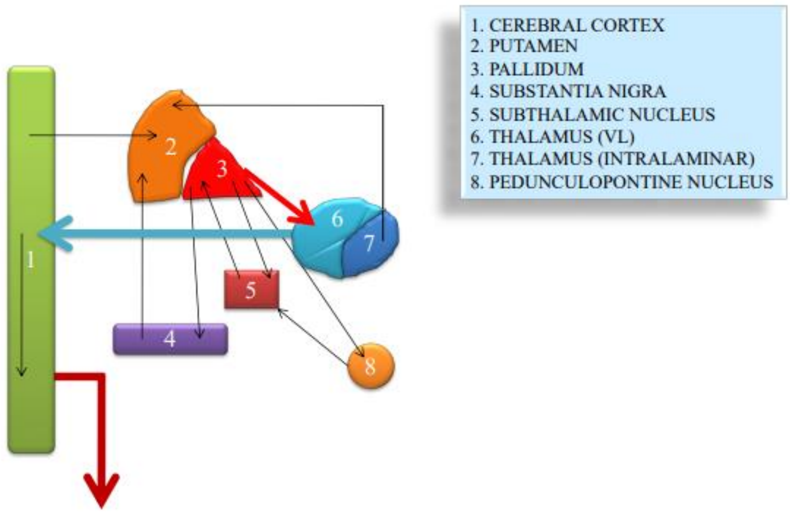


Neuronal links and local circuits of the striatum



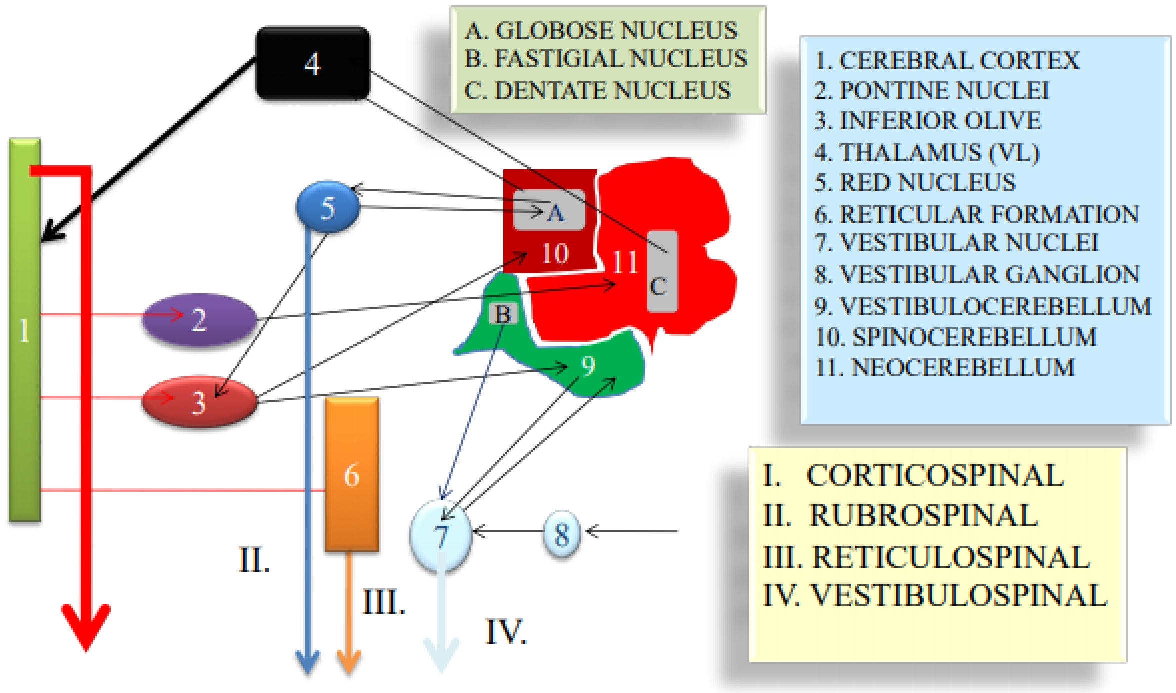
- the *putamen* (1) part of the caudate nucleus receives information from the *thalamus* (2), *cerebral cortex* (3), *mesencephalon* (4) and *substantia nigra* (5)
- glutamate inputs from the thalamus and cortex are excitatory, the dopamine innervation from the substantia nigra is supposed to be inhibitory
- the inputs are received by spiny enkephalin- and substance P-ergic neurons
- they transmit the processed information to the *globus pallidus* (pallidum (6)) that is the main efferent structure of the system
- it sends projections to the substantia nigra and different nuclei of the thalamus
- the thalamus feeds the information back to the cortex

Role of the striatum in the motor system

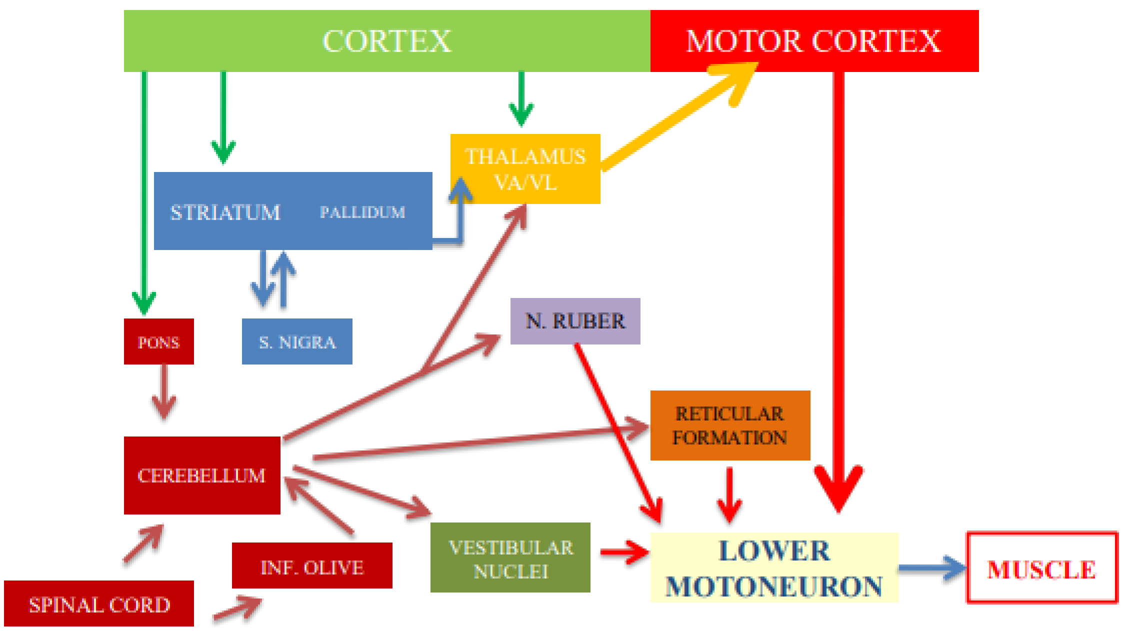


- the information processed in the striatum is transmitted to the cerebral cortex
- the cortex incorporates the striatal message and conveys the outgoing motor information via the corticospinal tract

Role of cerebellum in control of movement



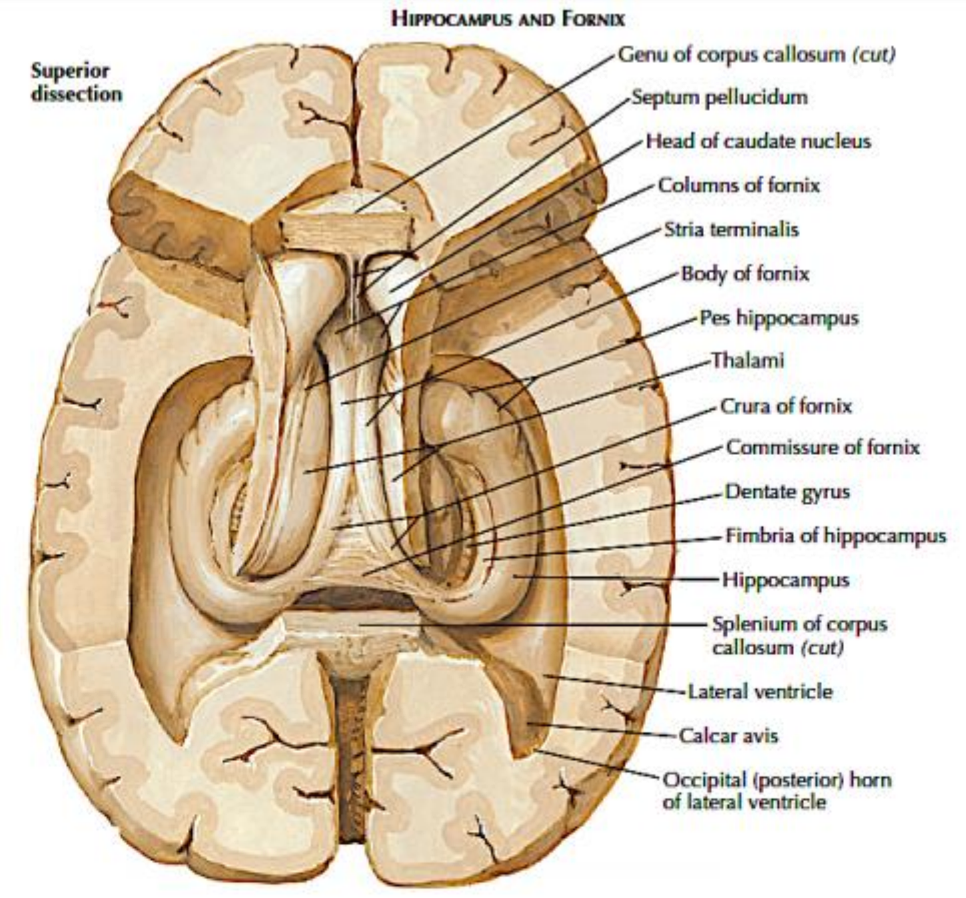
Integration of the different motor systems

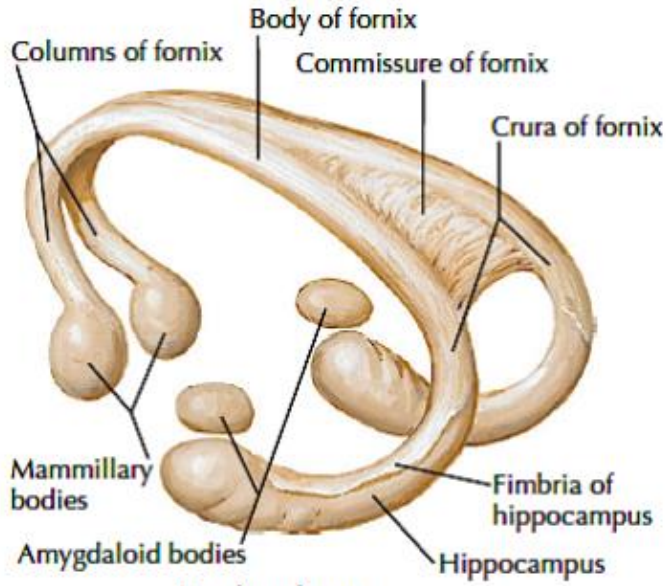


Hippocampal formation

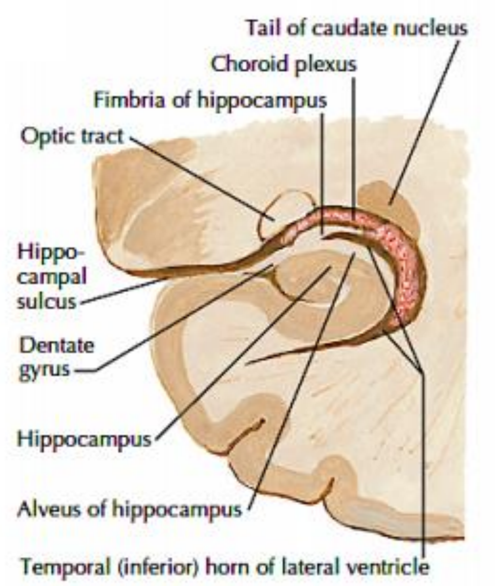
Characteristics:

- part of the limbic system of the brain
- composed of the *dentate gyrus* and the *hippocampus* (cornu ammonis)
- the complex structure belongs to the allocortex
- the hippocampus is divided into 3 sectors: CA1 (Sommer's sector), CA2 and CA3
- there are 3 cytoarchitectural layers in the hippocampus: *molecular*, *pyramidal* and the *polymorphic* (oriens) layers
- the dentate gyrus comprises the molecular layer, the granule cell layer and the hilus
- in its subgranular zone adult neurogenesis occurs
- afferents arrive via the performant and alvear paths
  efferent fiber projections leave the temporal lobe via the fornix system
- it gives rise to both associative and commissural efferents
- the hippocampus is linked with multiple brain networks via the limbic connections
- information conveyed by the performant path is processed in a trisynaptic intrinsic circuit within the hippocampal formation
- the hippocampus has a pivotal role in long term memory and spatial navigation
- it is vulnerable to hypoxia, excitotoxins and amyloid



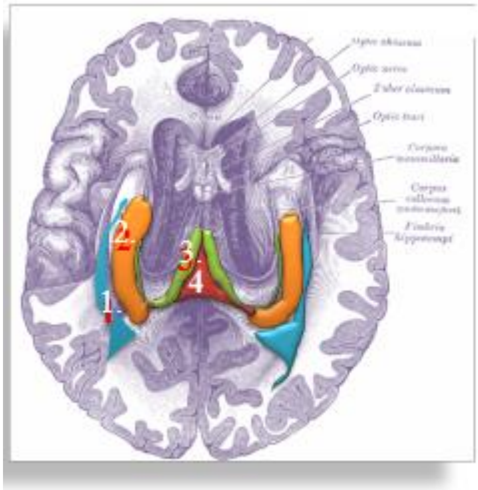


Fornix: schema



Coronal section: posterior view

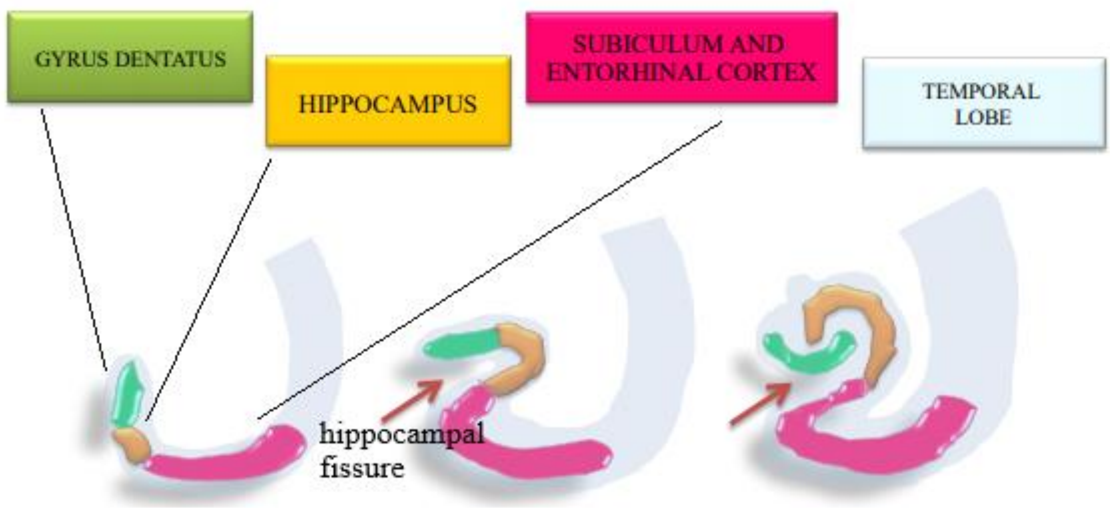
Macroscopic properties of the hippocampus



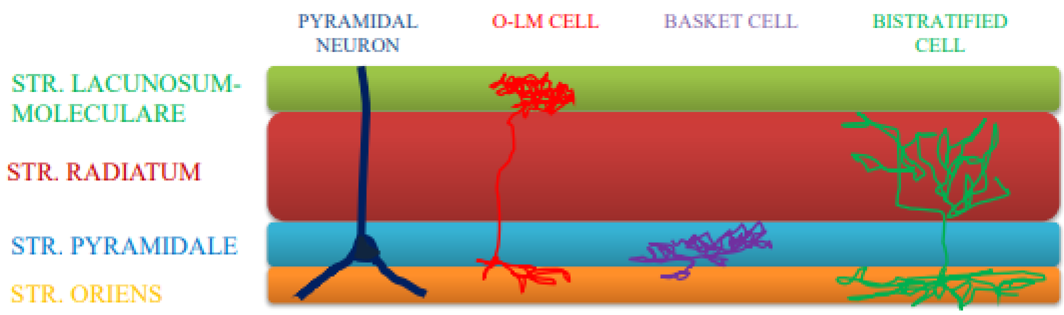
1. LATERAL VENTRICLE
2. HIPPOCAMPUS
3. FORNIX
4. COMMISSURA FORNICIS

- the *hippocampus* is a C-shaped, paired structure located in the temporal lobe
- anterior to it is the *amygdala*, in dorsal direction the *lentiform nucleus* is a close neighbour
- the structure protrudes into the *inferior horn of the lateral ventricle*
- its efferent and afferent paths form the *fornix*
- it begins as a thin crus, continues as corpus and terminates as column splitting into *pre- and post-commissural components* that terminate in the *septum* and *hypothalamus*
- fibers interconnecting the two hippocampal structures form *Dave's lyre*

Development of the hippocampal formation

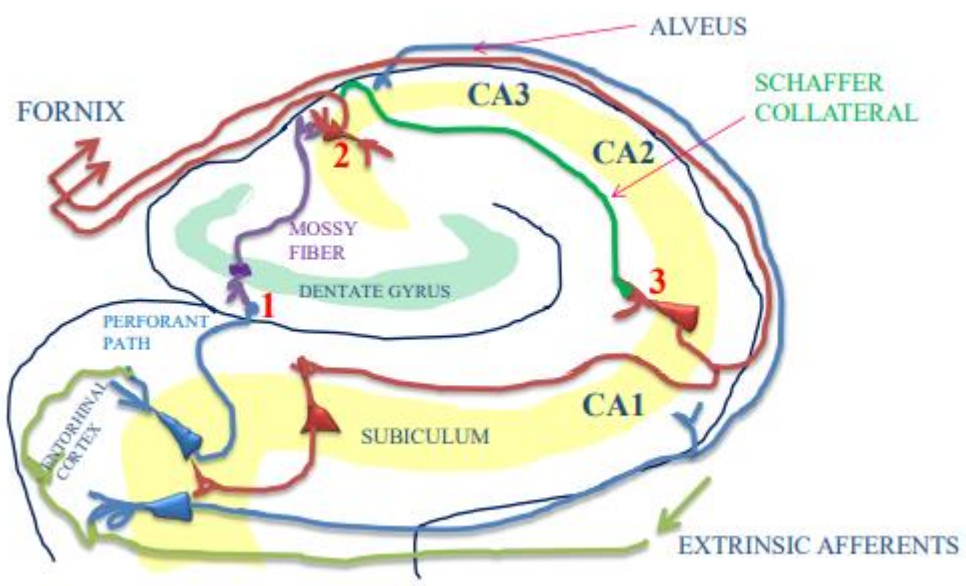


Layers and cell types of the hippocampus

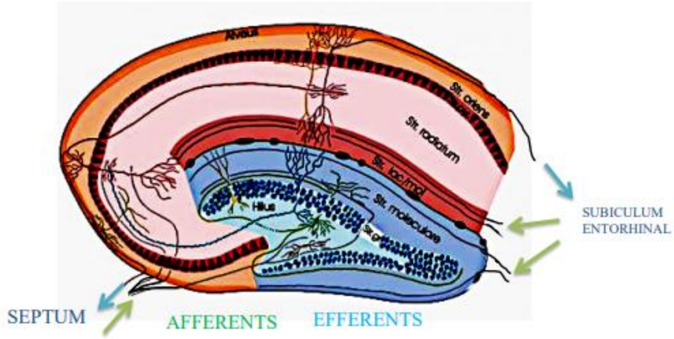


- principal, pyramidal neurons and inhibitory interneurons such as O-LM cells, basket cells and bistratified cells occupy the main layers of the hippocampus

The intrinsic circuits and connections of the hippocampal formation



Afferent and efferent connections of the hippocampus

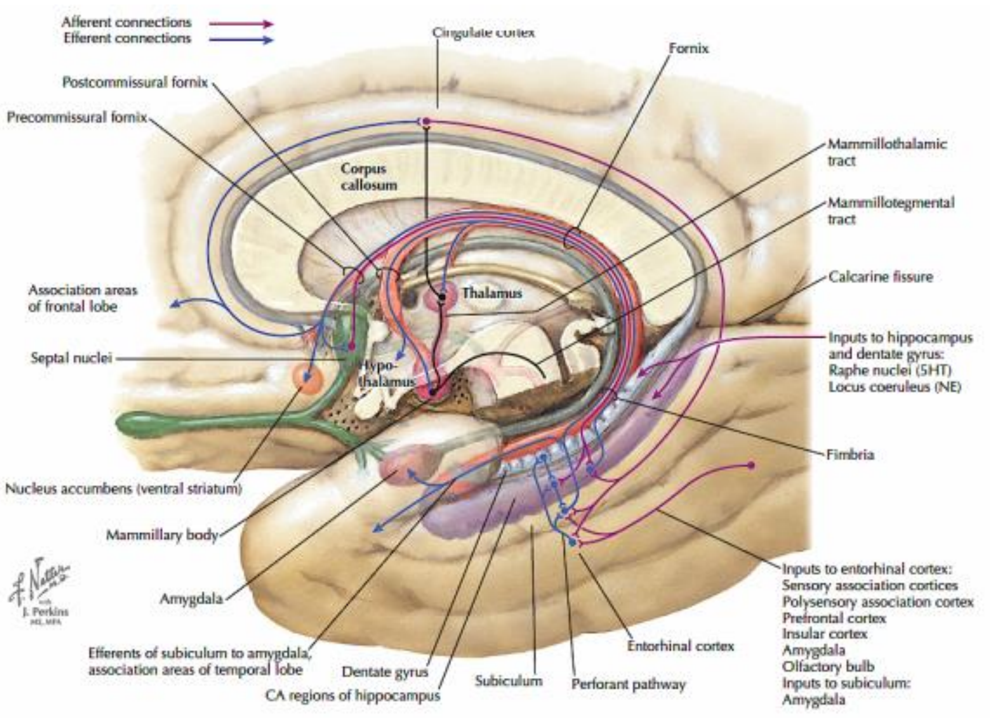


- main afferent inputs arrive from entorhinal cortex via the performant and alvear paths, the septum, the contralateral hippocampus and the reticular formation
- efferents are sent to the sources of afferent inputs
- the fornix is the main projecting efferent system to the septum, subtantia innominate, anterior hypothalamus and the mammillary body

Integration of the hippocampus within the limbic system

- the main limbic structures are highly integrated with each other
- a prominent formation is the *circuit of papez*
  it involves the connections and projections of the hippocampal formation with emphasis on the link with the mammillary body
- this nucleus projects via the thalamus to the *cingulate cortex* that is known to feed back to entorhinal cortex
- a descending unit is called the *mamillotegmental fasciculus* oriented mainly to the *raphe nuclei* and the reticular formation

Major afferent and efferent connections of the hippocampal formation



Functional correlates of the limbic system

Physiological correlates

1. place cells
2. theta rhythm
3. sharp waves
4. long term potentiation
5. short term potentiation
6. learning
7. spatial memory
8. Morris water maze
9. emotions
10. behaviour

Pathological correlates

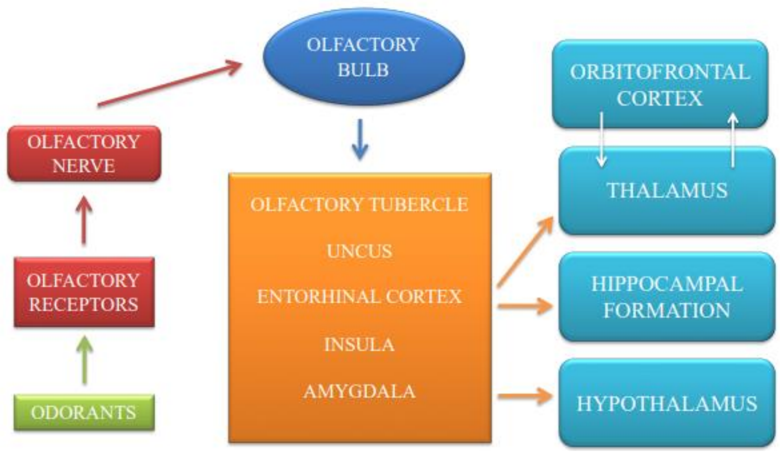
1. anxiety
2. depression
3. epilepsy
4. schizophrenia
5. amnesia
6. Korsakoff's psychosis
7. abnormal sexual activity
8. abnormal appetite
9. aging
10. Alzheimer disease

<u>Olfactory system</u>

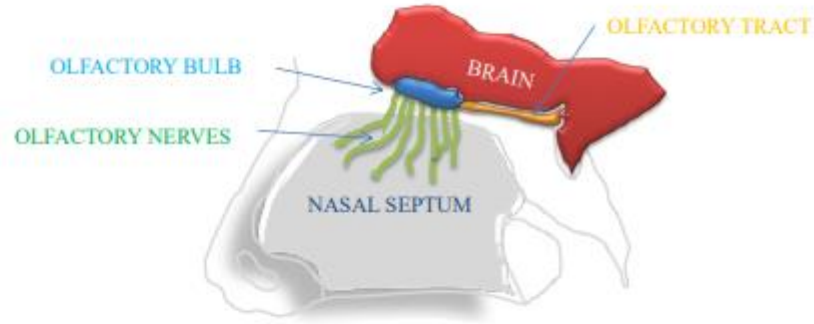
Features of the olfactory system

- odorants are chemical substances of the environment that are sensed by the olfactory system
- they provide information about members of the biological community and potential hazards threatening the individuals
- species specific odorants, called pheromones, are linked with reproduction
- the human being is microsmatic and depends less in this particular chemical sense in comparison with different animal species
- odorants trigger specific G protein-coupled receptors of the olfactory epithelium cells
- the information of smell is conveyed by the olfactory nerve to the olfactory bolb for initial processing
- the olfactory bulb projects via the olfactory tract to higher processing centers like the pyriform cortex and the amygdala
- these areas relay the information further to the orbitofrontal cortex, hypothalamus and the hippocampus
- these connections allow the conscious perception of smell and processing its emotion, motivation and memory-related components

General design of the system processing olfactory information

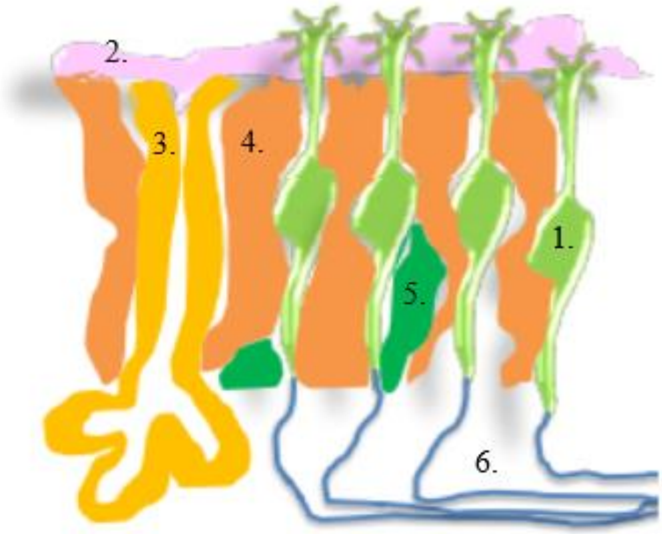


The olfactory apparatus



- primary sensory epithelial cells are embedded in the olfactory mucosa situated at the top of the nasal cavity
- the cells possess cilia that contain odorant receptors
- water soluble odorant substances are taken through the nasal cavity during a sniff or breathing where they bind to their receptors

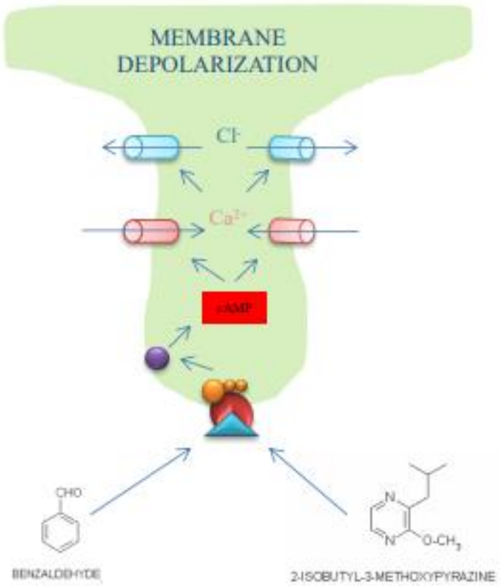
Structure of the olfactory epithelium



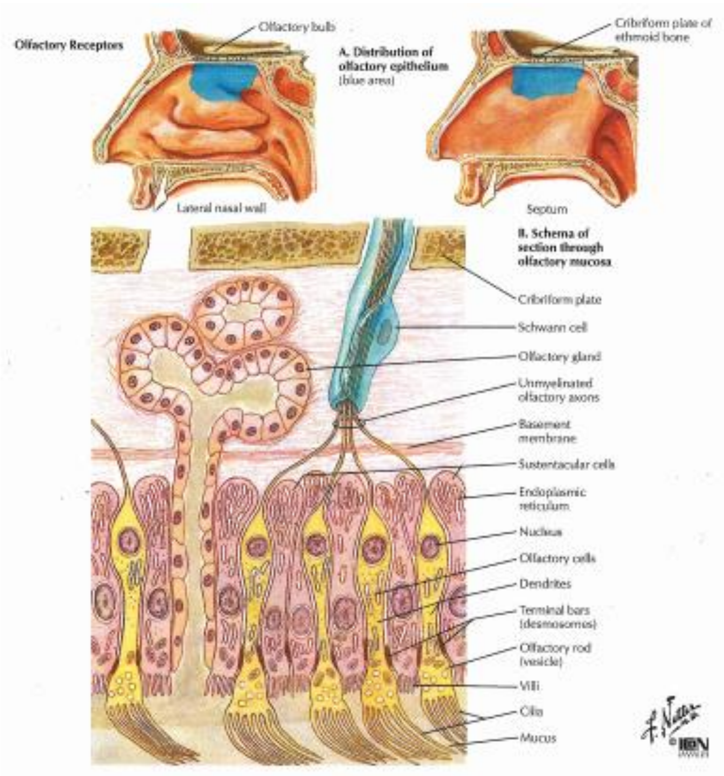
- the *sensory epithel cells* (1) are bipolar
- their peripheral poles form olfactory vesicles that are decorated with cilia
- the vesicles with the cilia are embedded in a *mucous fluid* (2) produced by special *glands* (3)
- the sensory cells are surrounded by *supporting epithel cells* (4)
- the olfactory epithelium has a remarkable regenerative capacity
- there are about 25 million cells on each side and survive for two months
- the renewal originates from the *basal cells* (5) that show high mitotic activity
- the *axon processes* (6) of the bipolar cells gather into 20 bundles on each side and enter the anterior cerebral fossa of the skull through the cribriform plate
- they terminate in the olfactory bulb
- the bulb has to adapt to the continuously ingrowing axons

The olfactory receptor and signal transduction

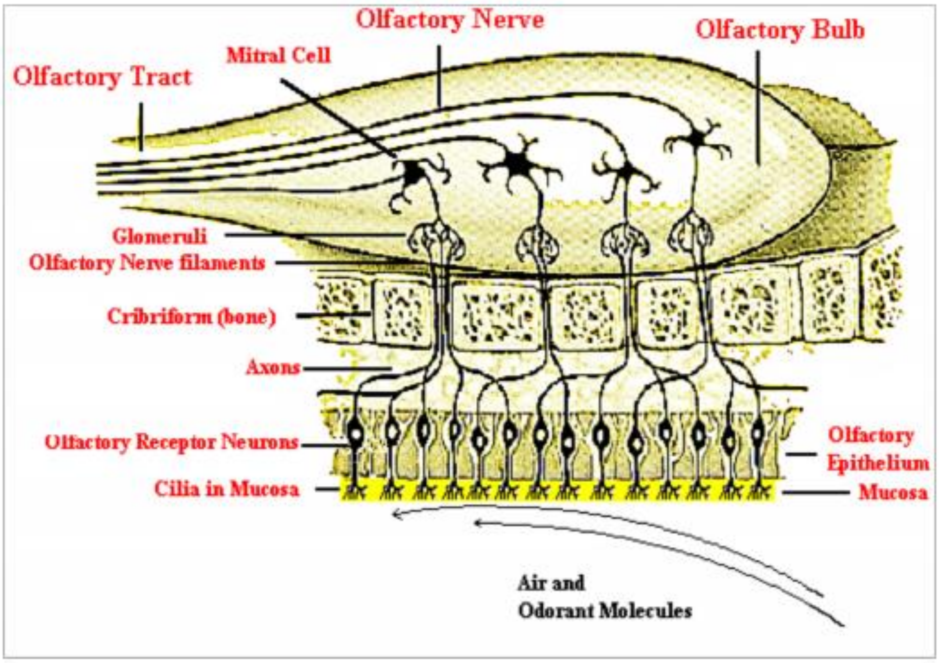
- seven transmembrane domain odorant receptor proteins
- binding of the ligand activates G proteins that in turn activate adenyl cyclase III generating cAMP
- it is followed by the opening of sodium/calcium channels
- the inflow of calcium opens calcium-gated chloride channels leading to depolarization of the membrane of cilia



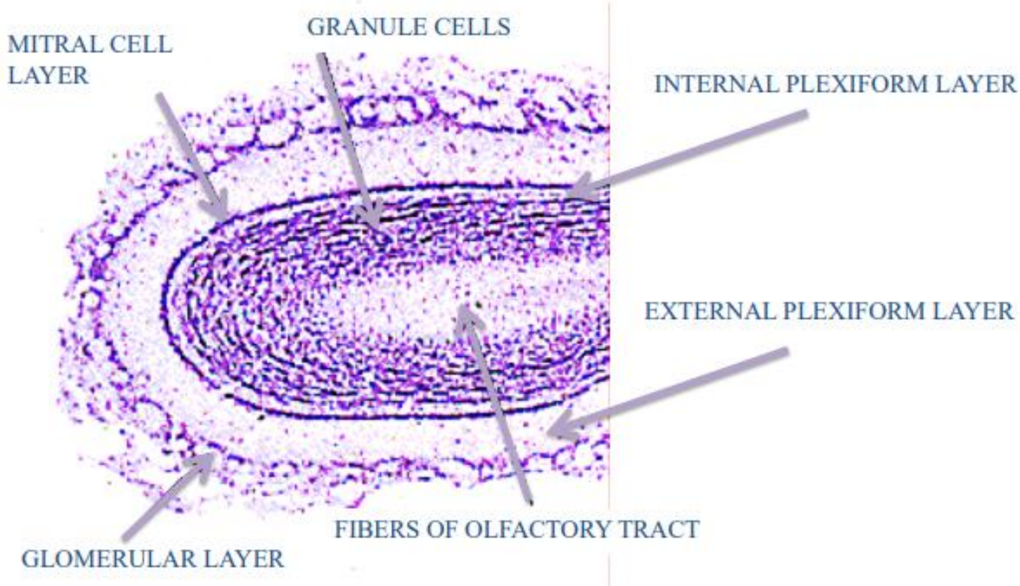
The structure of the olfactory epithelium



Bulbus olfactorius



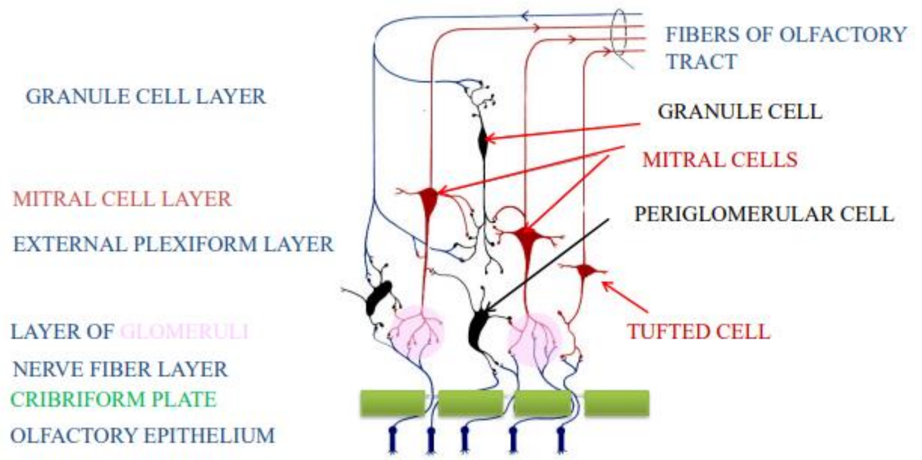
Histology of the olfactory bulb



Main layers of the olfactory bulb

- glomerular layer
- external plexiform and mitral cell layers
- internal plexiform and granule cell layers

Neuronal networks of the olfactory bulb



Characteristics of olfactory bulb networks

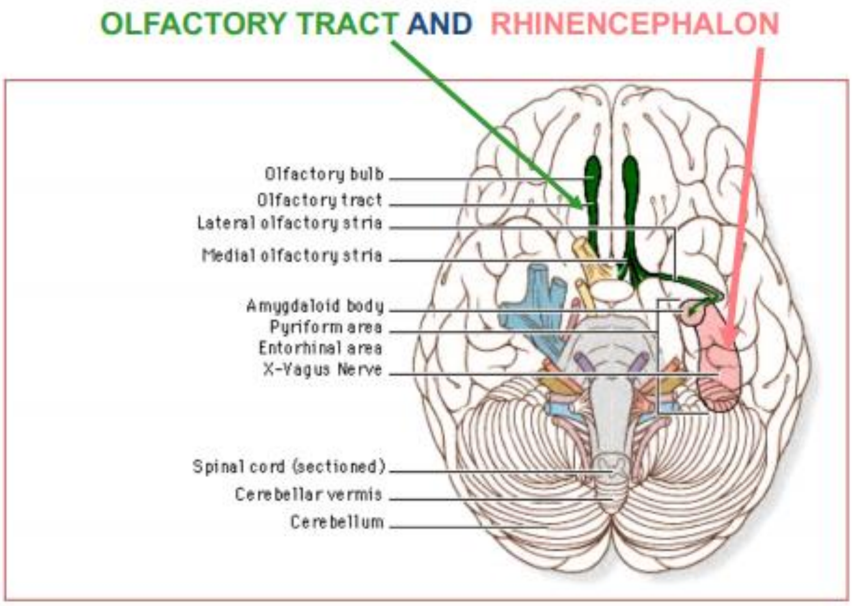
- the bulb receives two kinds of afferent inputs
  - the *olfactory nerves* from olfactory epithelium
  - *centrifugal fibers* from the olfactory tubercle
  - *diagonal band* convey information

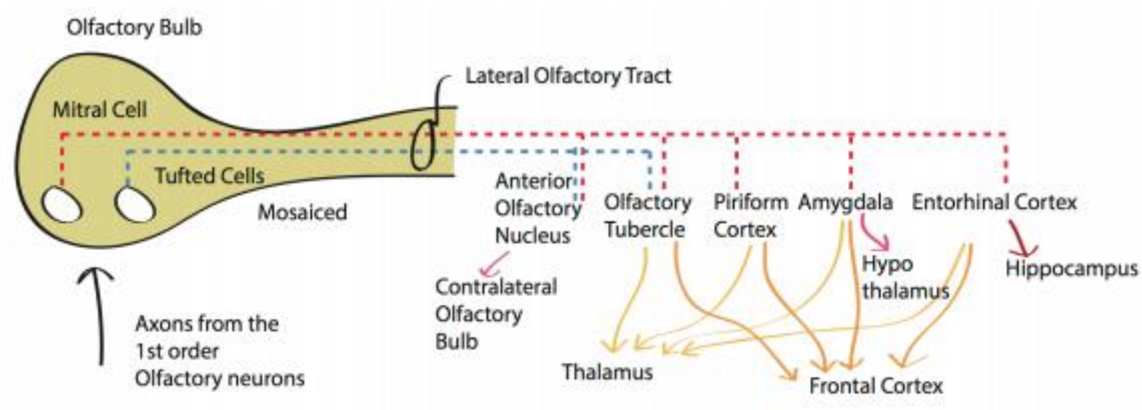
    these signals are excitatory
- within the bulb, olfactory fibers establish connections with dendrites of *mitral, tufted and periglomerular cells*
- these structures together form the characteristic compositions of the olfactory bulb, the *glomeruli*
- the centrifugal fibers communicate mainly with the *inhibitory periglomerular and the granule cells*
- granule cells have no definitive axons
- their dendrites pick up the information from the centrifugal fibers and establish connections with mitral cell dendrites
- they contribute to lateral inhibition

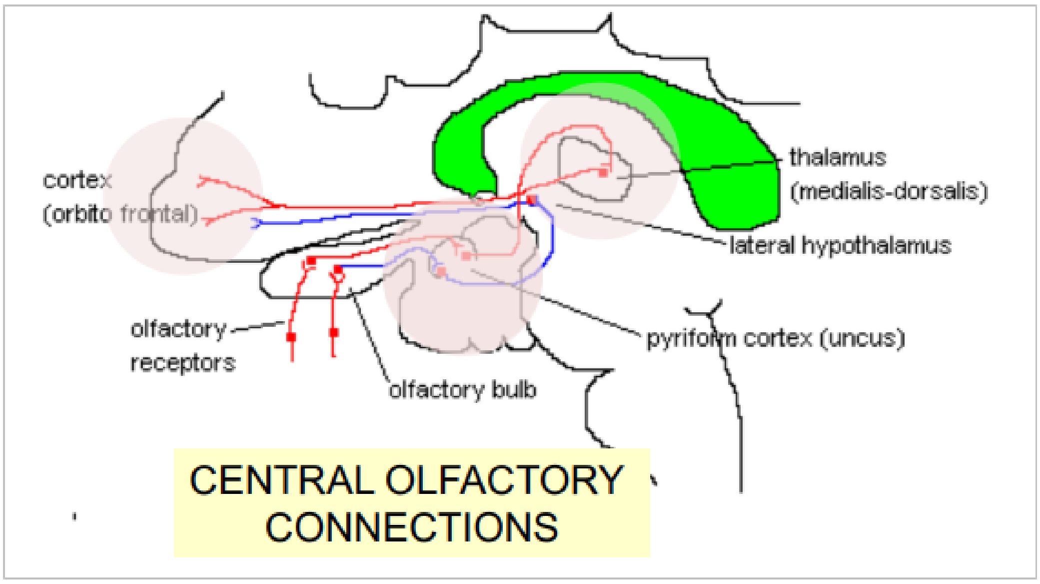
  the inhibitory cells are replaced throughout life
- the efferent projections are sent by axons of mitral and tufted cells via the olfactory tract

Projections of the olfactory bulb, primary olfactory area

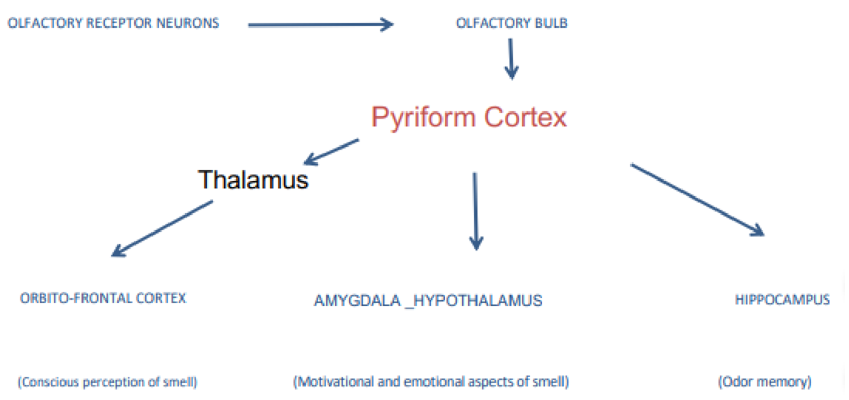
- from the olfactory bulb, the information is taken via the olfactory tract and olfactory striae to higher level processing centers
- the lateral stria is interconnected with the *uncus, the entorhinal cortex* and the *limen insulae*
- these structures form the primary olfactory area which is pear-shaped in rodents
- the system is linked to the amygdala as well
- the conscious perception of odor takes place in the *orbitofrontal and cingulate cortex*


OLFACTORY TRACT AND RHINENCEPHALON
Olfactory bulb
Olfactory tract
Lateral olfactory stria
Medial olfactory stria
Amygdaloid body
Pyriform area
Entorhinal area
X-Vagus Nerve
Spinal cord (sectioned)
Cerebellar vermis
Cerebellum


Olfactory Bulb
Mitral Cell
Tufted Cells
Mosaiced
Lateral Olfactory Tract
Anterior Olfactory Nucleus
Olfactory Tubercle
Piriform Cortex
Amygdala
Entorhinal Cortex
Hypo thalamus
Hippocampus
Contralateral Olfactory Bulb
Thalamus
Frontal Cortex
Axons from the 1st order Olfactory neurons


cortex (orbito frontal)
thalamus (medialis-dorsalis)
lateral hypothalamus
olfactory receptors
pyriform cortex (uncus)
olfactory bulb
CENTRAL OLFACTORY CONNECTIONS

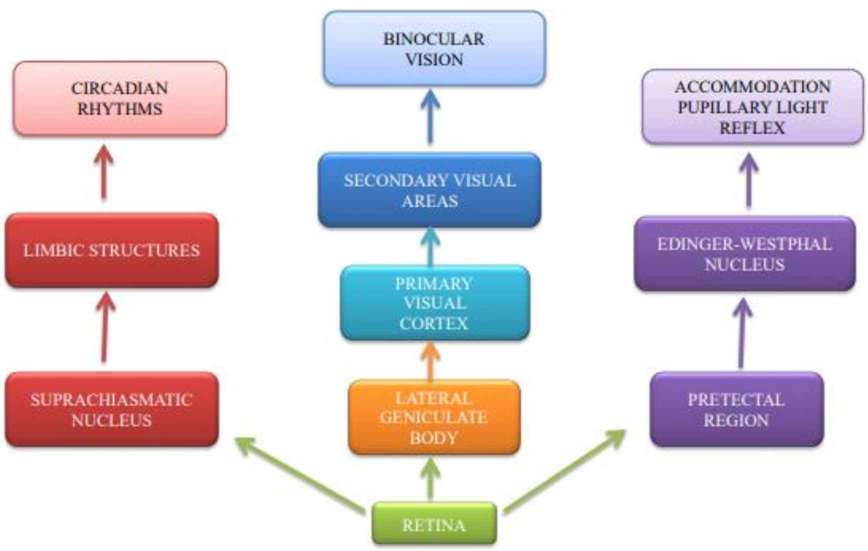
Processing olfactory information



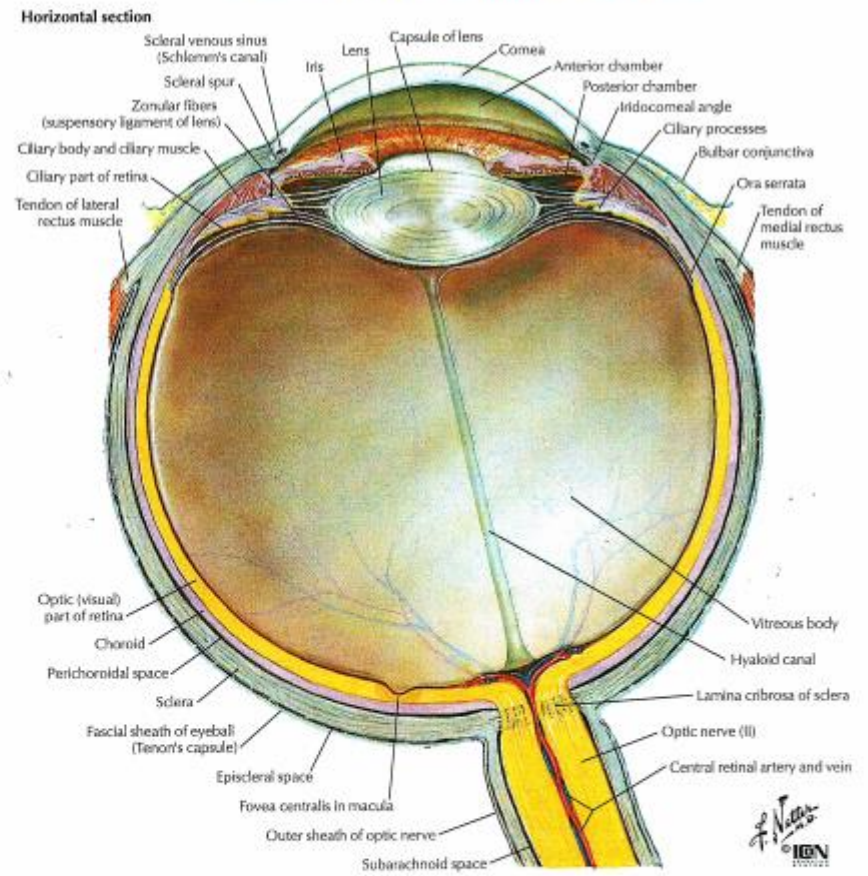
<u>Visual system</u>

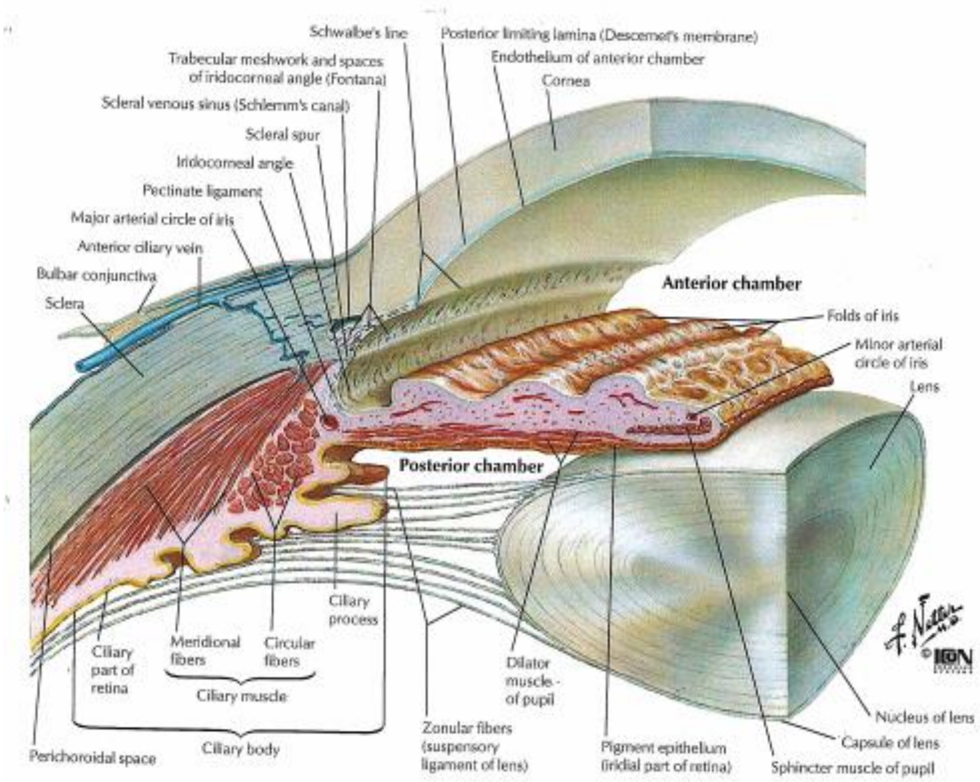
- the visual system is part of the CNS
- it consists of the *retina* and its projections, *the lateral geniculate body*, *the optic radiation*, *the primary and secondary cortical processing centers*
- in association with the system, *the oculomotor reflex* and *accommodation* are functionally important mechanisms
- the main task of the visual system is the conscious perception of the visual scene
- the information about the light/dark periods of the day is directed to the *suprachiasmatic nucleus* of the hypothalamus that orchestrates the diurnal (circadian) rhythm of several neuronal, endocrine and metabolic functions
- although the visual field is represented in all key units of the visual system from the retina to the cortical visual areas, the proper binocular vision (shape, size, sharpness, depth, colour of objects) requires a delicate cooperation of processing structures performing at different levels in the hierarchy of the neuronal organization
- the image and special attributes of the objects seen in the binocular visual field are gradually build up from simplex (retina) to complex (visual cortex) processing levels

Scheme of the organization of the visual system



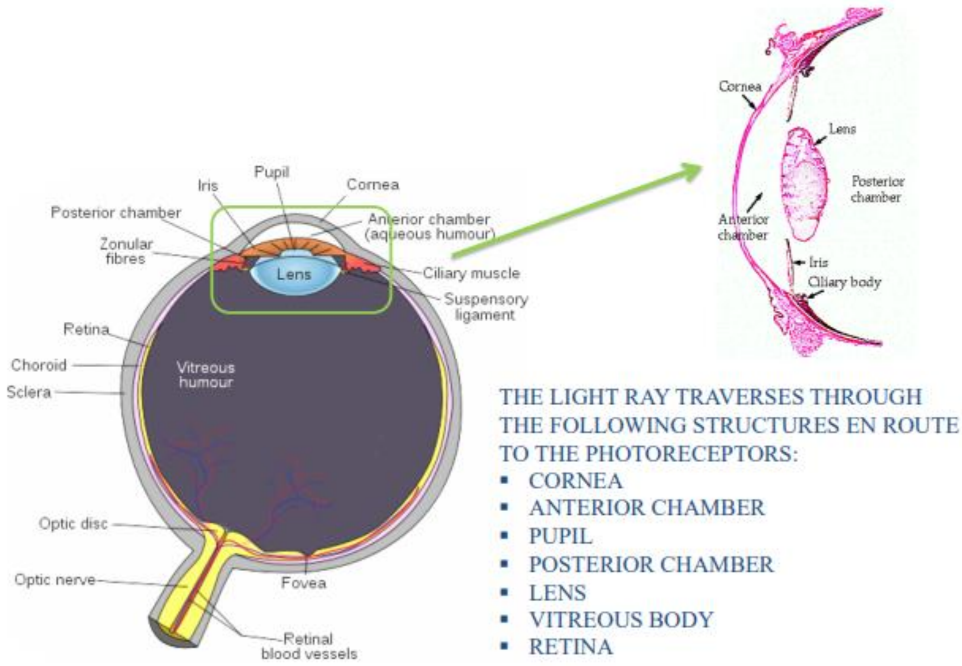
ANATOMY OF THE EYEBALL

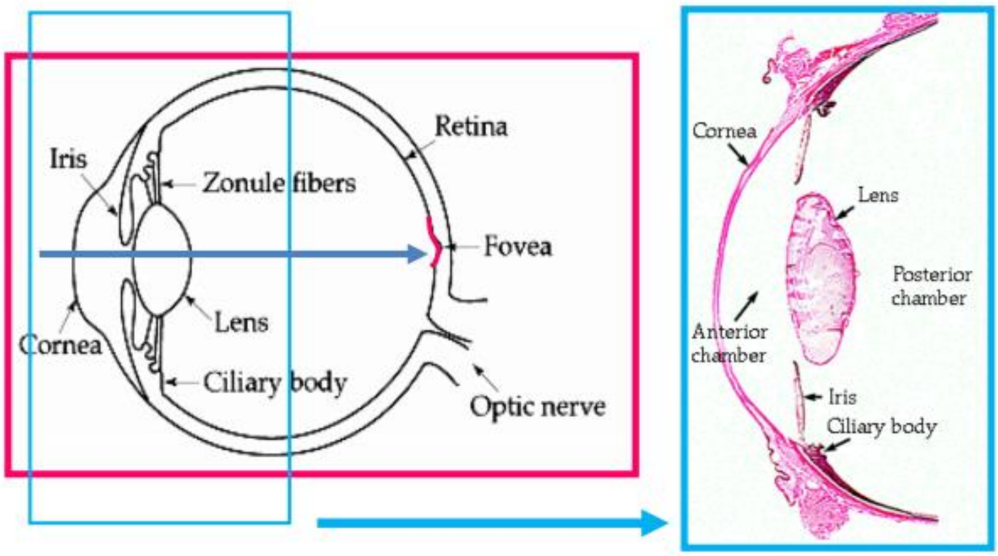




Note: For clarity, only single plane of zonular fibers shown; actually, fibers surround entire circumference of lens

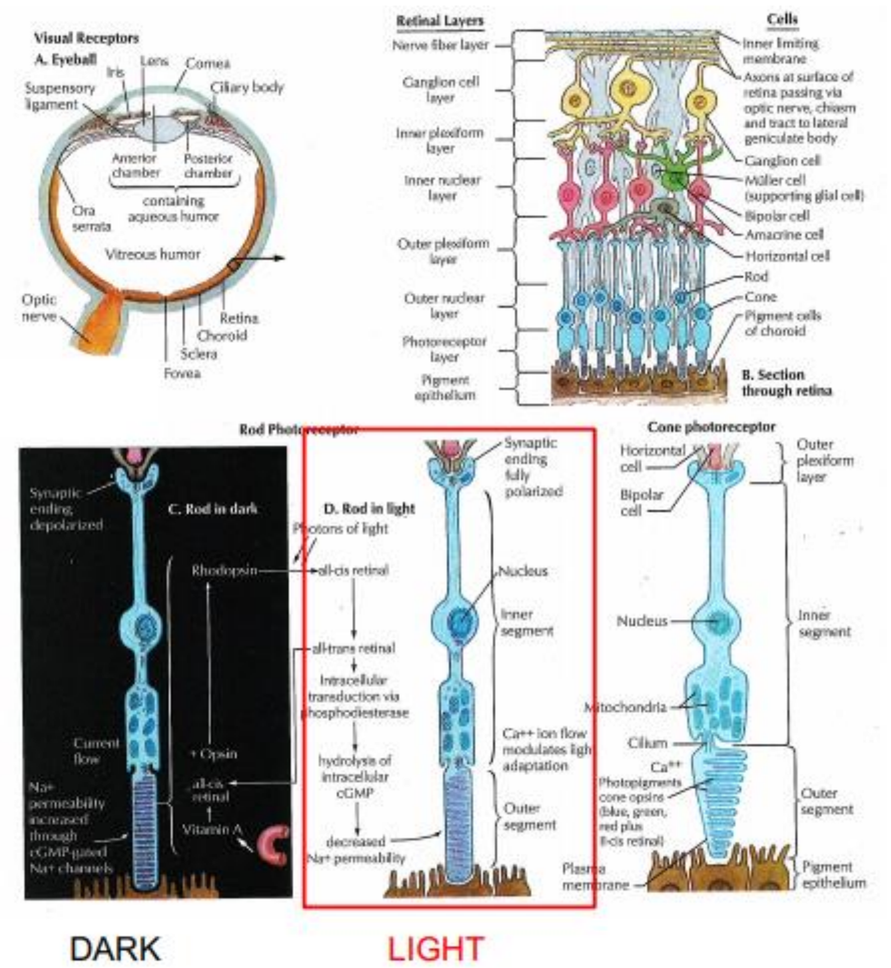
The refractive structures of the eye





The structure of the retina

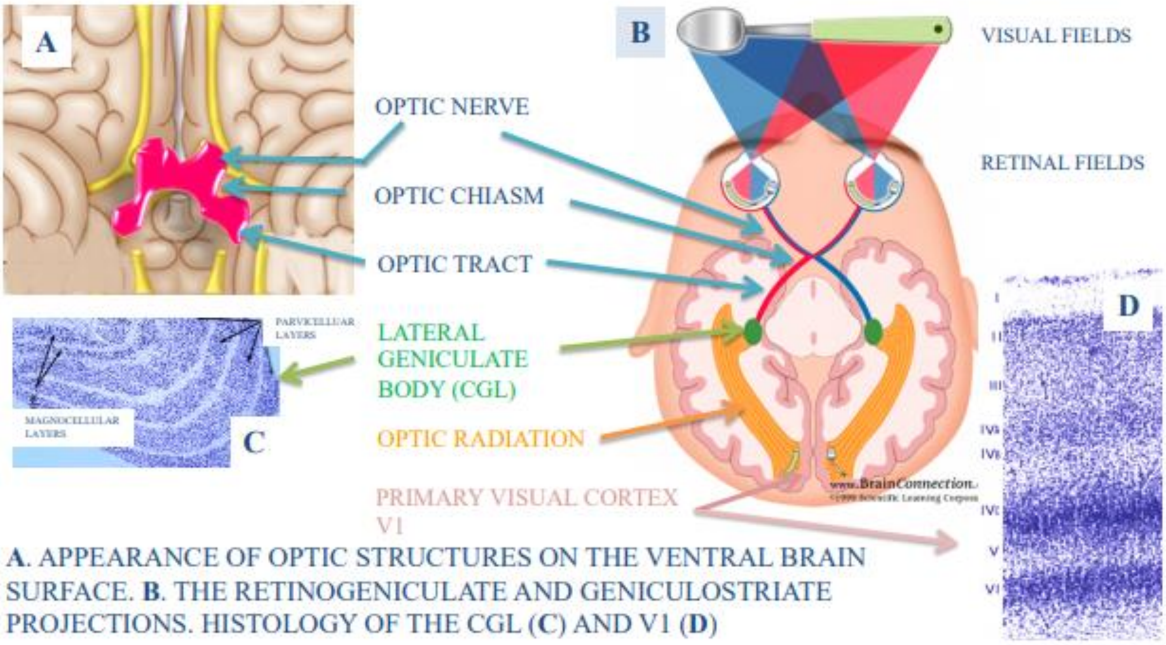
1. pigment cell layer
2. layer of rods and cones
3. outer limiting membrane
4. outer nuclear layer
5. outer plexiform layer
6. inner nuclear layer
7. inner plexiform layer
8. ganglion cell layer
9. optic nerve fiber layer
10. inner limiting membrane



Signal transduction in the retina

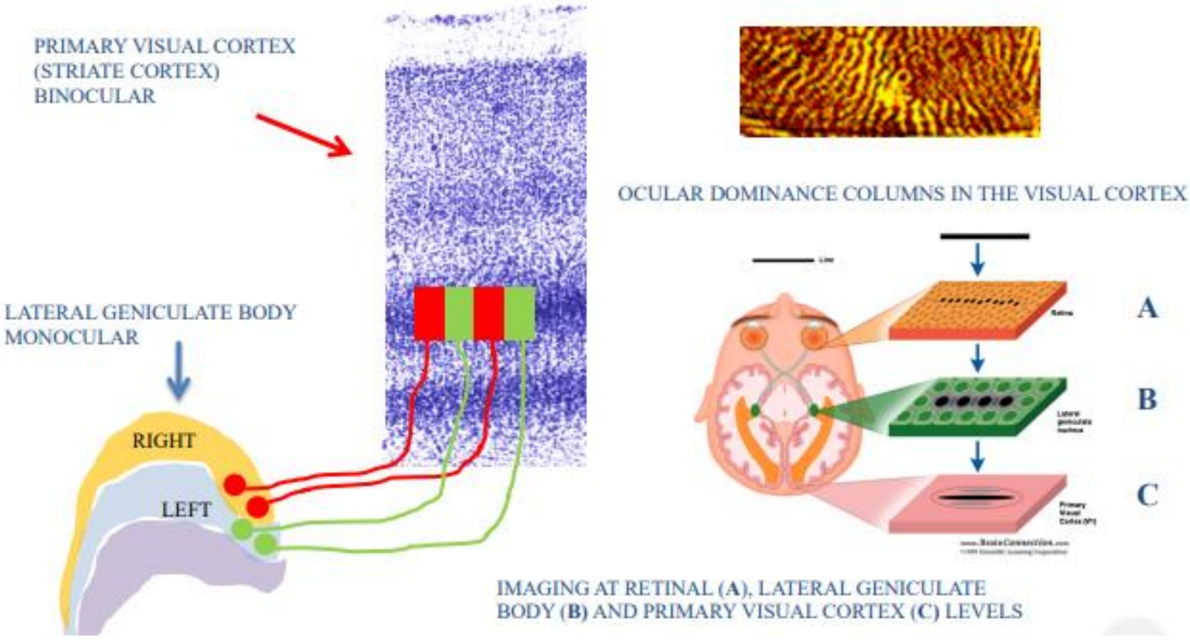
- the light ray passes through the inner layers of the retina and reaches the outer segments of photoreceptor cells, the rods and cones
- shining light on photoreceptors leads to hyperpolarization of the receptor cells
- in dark, the receptor cells are depolarized resulting in sodium and calcium influx through cyclic guanosine monophosphate (cGMP)-gated channels
  this inward current at the outer segment is opposed by an outward current of potassium
  the net balance of cations results in a membrane potential of -40 mV
- the absorption of light reduces the cGMP content in the photoreceptor leading to the closure of outer segment cation channels
  accordingly, the efflux of potassium ions becomes dominant, the positive charge decreases, and hyperpolarization develops

MAIN COMPONENTS AND PROJECTIONS OF THE VISUAL SYSTEM



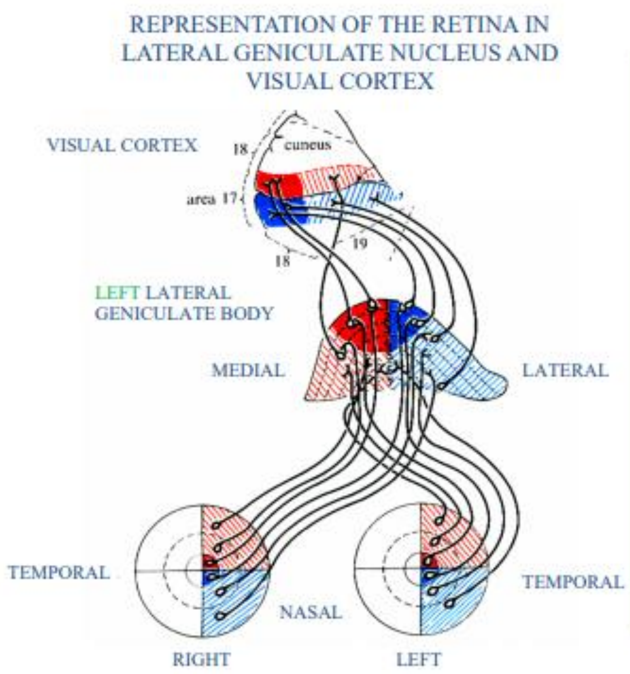
A. APPEARANCE OF OPTIC STRUCTURES ON THE VENTRAL BRAIN SURFACE. **B**. THE RETINOGENICULATE AND GENICULOSTRIATE PROJECTIONS. HISTOLOGY OF THE CGL (**C**) AND V1 (**D**)

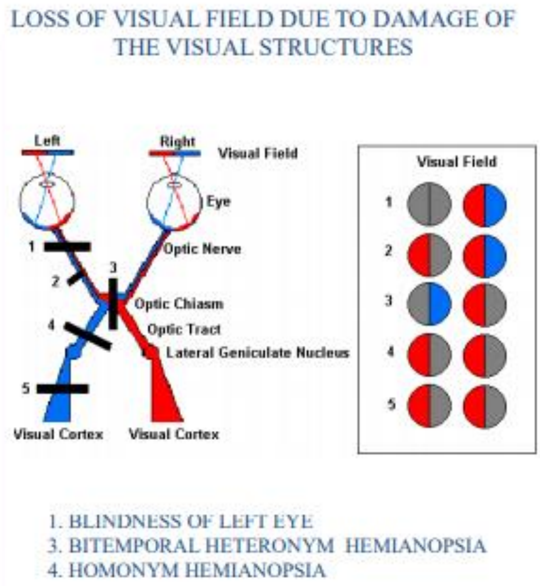
THE GENICULO-STRIATE PROJECTION. OCULAR DOMINANCE COLUMNS

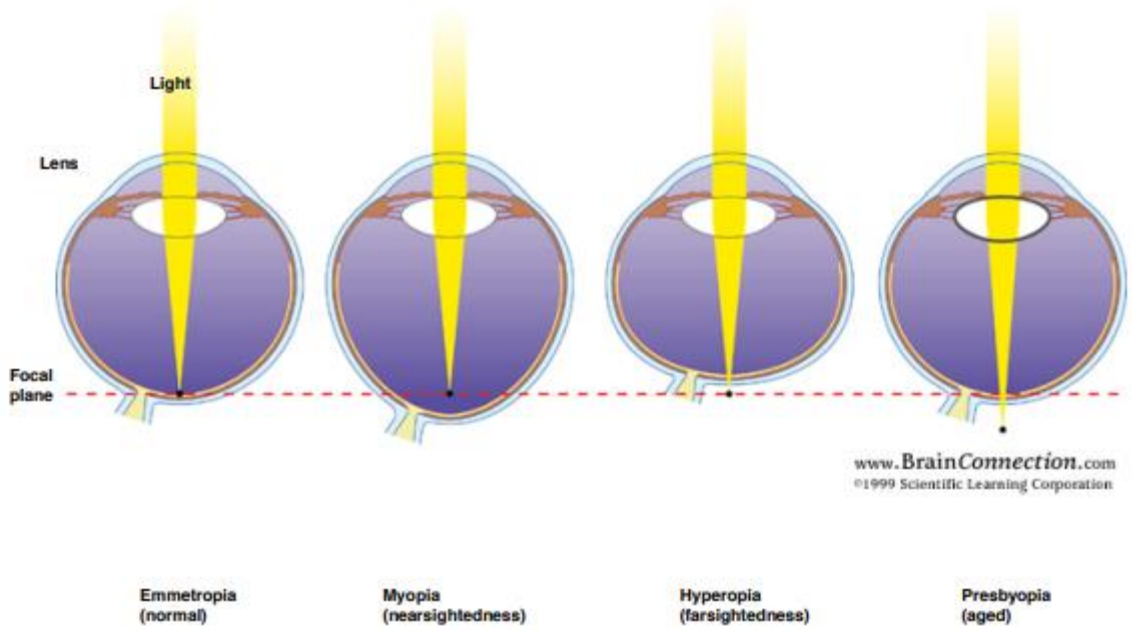


OCULAR DOMINANCE COLUMNS IN THE VISUAL CORTEX

IMAGING AT RETINAL (**A**), LATERAL GENICULATE BODY (**B**) AND PRIMARY VISUAL CORTEX (**C**) LEVELS


REPRESENTATION OF THE RETINA IN LATERAL GENICULATE NUCLEUS AND VISUAL CORTEX
VISUAL CORTEX
18
cuneus
area 17
19
18
LEFT LATERAL GENICULATE BODY
MEDIAL
LATERAL
TEMPORAL
NASAL
TEMPORAL
RIGHT
LEFT


LOSS OF VISUAL FIELD DUE TO DAMAGE OF THE VISUAL STRUCTURES
Left
Right
Visual Field
Eye
Optic Nerve
Optic Chiasm
Optic Tract
Lateral Geniculate Nucleus
Visual Cortex
Visual Cortex
Visual Field
1
2
3
4
5
1. BLINDNESS OF LEFT EYE
3. BITEMPORAL HETERONYM HEMIANOPSIA
4. HOMONYM HEMIANOPSIA

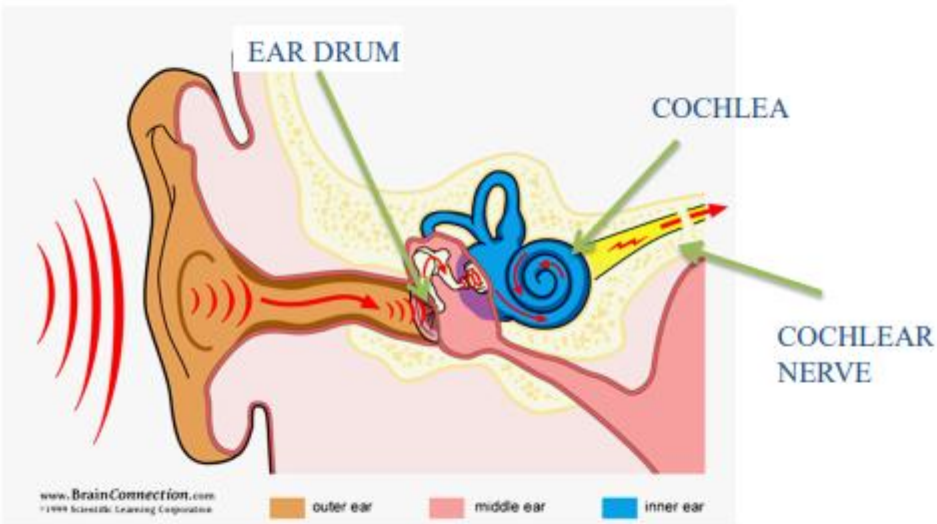

Light
Lens
Focal plane
www.BrainConnection.com
©1999 Scientific Learning Corporation
Emmetropia (normal)
Myopia (nearsightedness)
Hyperopia (farsightedness)
Presbyopia (aged)

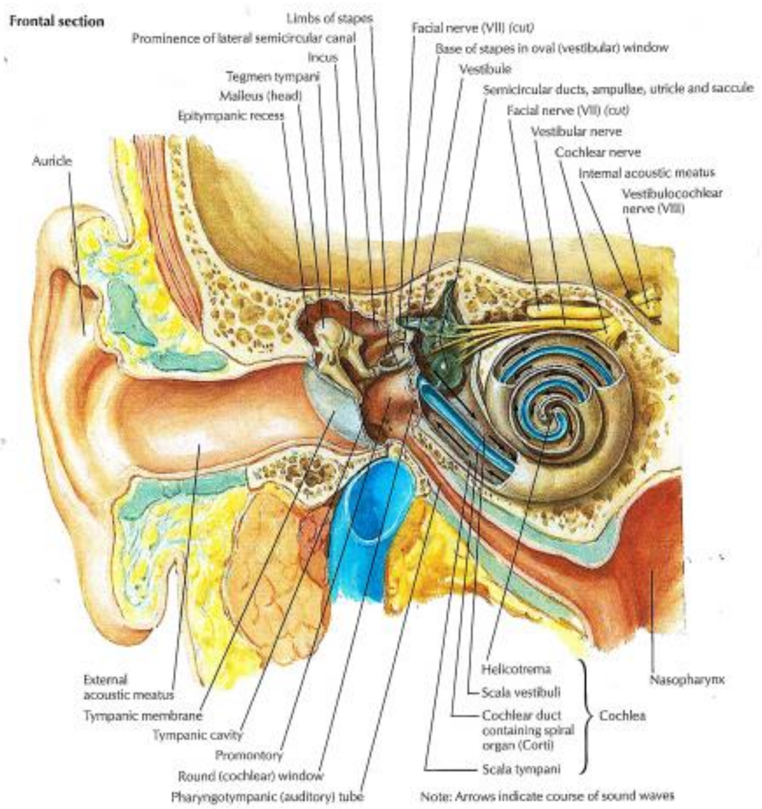
Cochlear and vestibular systems

Characteristics:

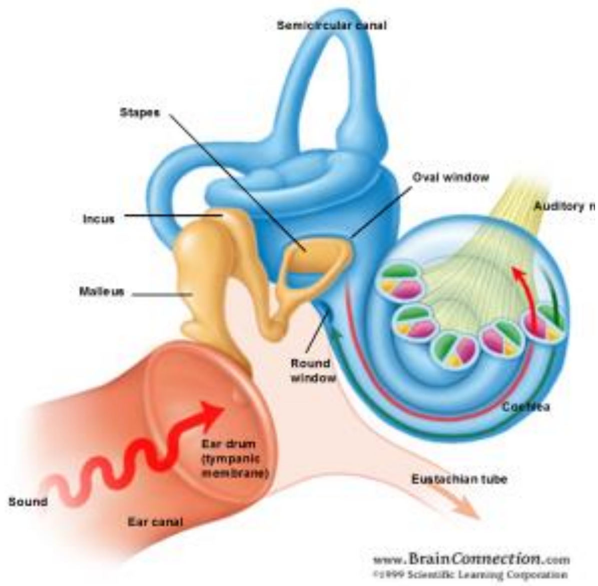
- the auditory system ensures the sense of hearing
- the system has two major constituents: the ear with the *cochlear apparatus* and the *auditory neuronal system*
- sound causes vibration of the *tympanic membrane* that is transmitted via the *otic ossicles* to the *perilymphatic fluid*
- it generates a spreading wave in the *cochlear duct* filled with *endolymph*
- the result of these events is the activation of *hair cells* in the *organ of corti*
- this signal is transmitted by *the cochlear nerve* to *cochlear nuclei* of the brainstem
- the cochlear nuclei project upstream and send the information via brain stem and metathalamic structures to the primary auditory cortex located in the superior temporal gyrus
- the vestibular system senses linear acceleration, deceleration and angular rotation of the head
- receptors are in the *utricle*, *saccule* and the *semi-circular canals*
- the generated signals are carried by the vestibular nerve to its nuclei for processing
- the system is interconnected with motor nuclei of muscles regulating the movements of eye
- the vestibular information is also forwarded to the cerebellum and the spinal cord

Organisation of the ear



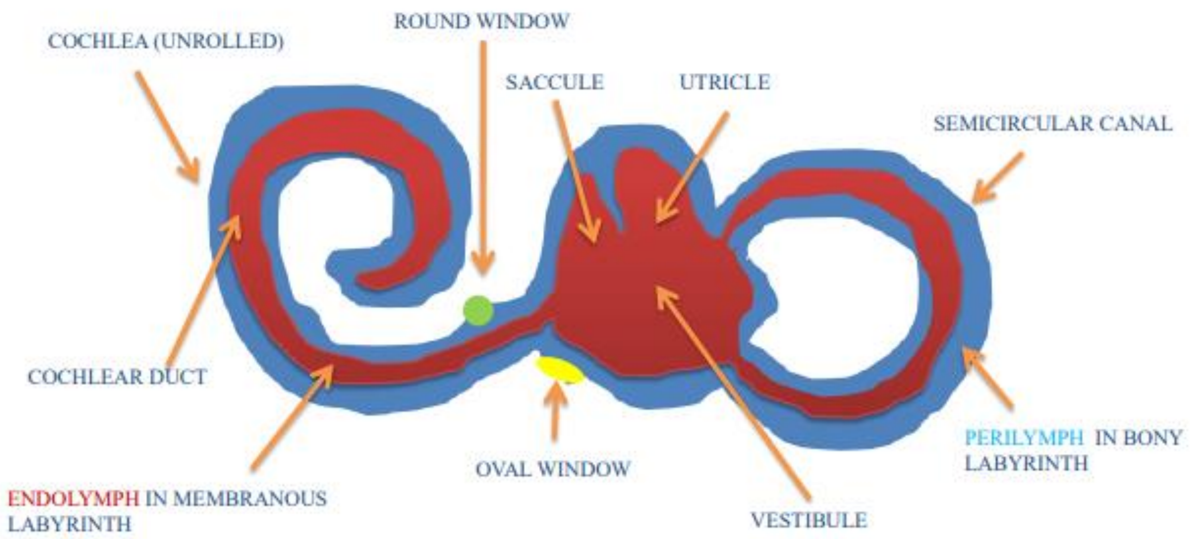


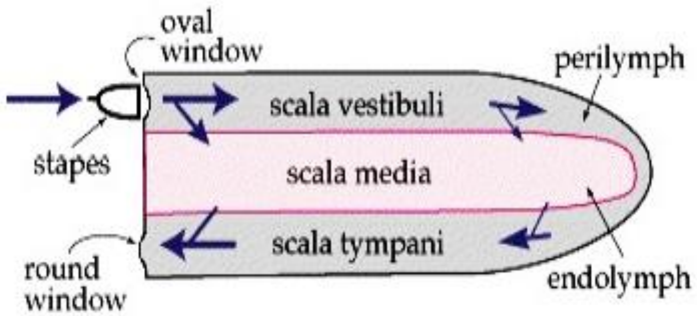
Details of signal propagation in the ear



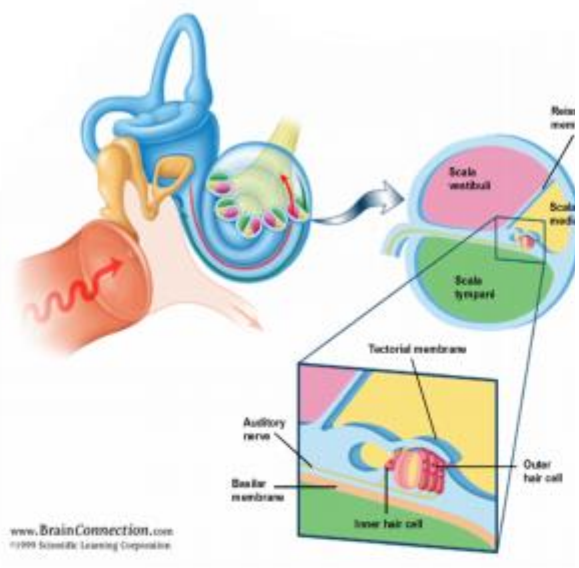
- sound causes vibration of the tympanic membrane which is transmitted by a chain of tiny bones: the *malleus*, *incus* and *stapes* to the oval window of the cochlea
- the basis of the stapes transmits the signal to the perilymph, a fluid filling the *scala vestibuli* and *scala tympani* compartments of the cochlea
- the scala vestibuli starts at the oval window and the fluid filled membranous tube winds around the vertical axis of the cochlea, then it turns downhill and continues as scala tympani which ends at the membrane covering the round window
- scala tympani and scala vestibuli surround the membranous tube *cochlear duct* which is filled with endolymph

Fluid compartments of the bony and membranous labyrinths



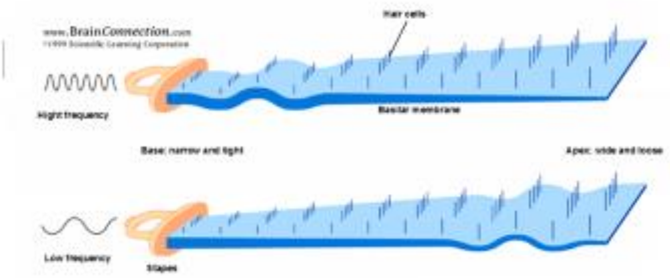


The structure of the corti organ

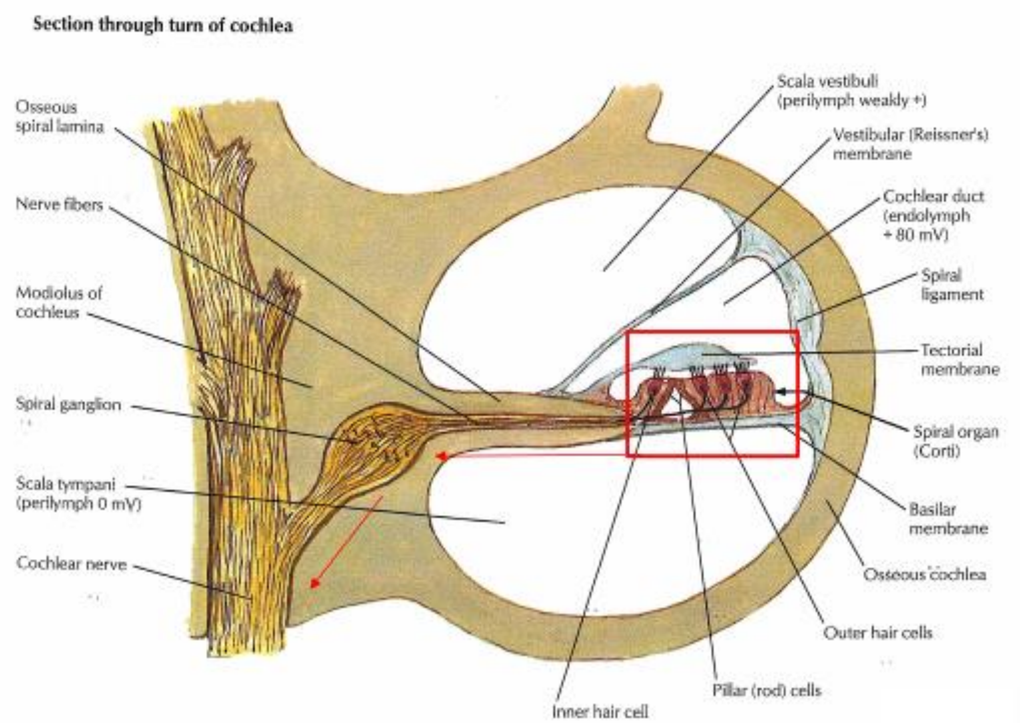


- the organ of corti is situated within the cochlear duct
- it is built up by sensory epithel hair cells and supportive epithel cells
- the sensory cells pick up the signal of spreading endolymphatic fluid wave
- neurons of the cochlear ganglion convey the information to auditory centers of the brain stem

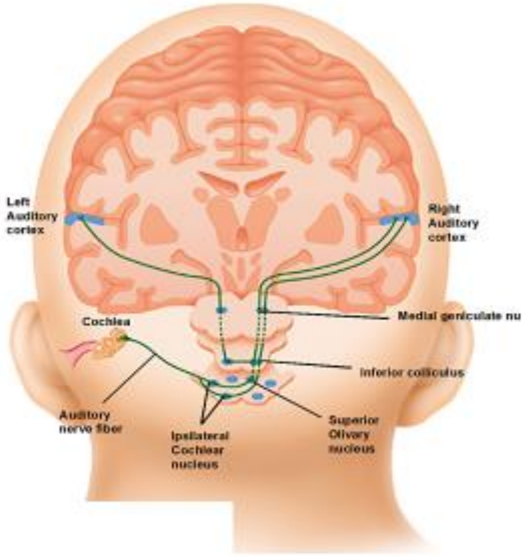
Vibration of the basilar membrane, hair cell activation



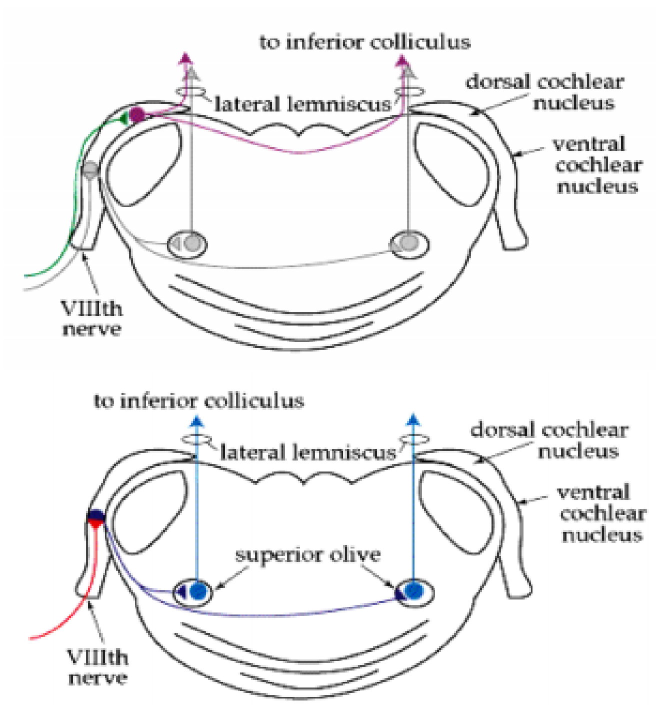
- depending on the pitch of the sound, a particular region of the basilar membrane vibrates with a maximal intensity
- signals at high frequency generate vibrations at high frequency generate vibrations at the base of the membrane, while sounds at low frequency initiate movement at the wider and looser apical part of the basilar membrane
- the evoked movement results in bending of the hairs of sensory epithel cells toward the stereocilium which, in turn, causes depolarization and increases the release of transmitters from hair cells
- this event activates the peripheral processes of cochlear ganglion neurons

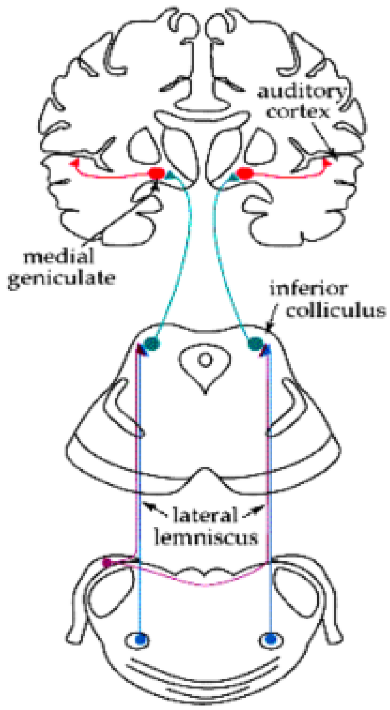


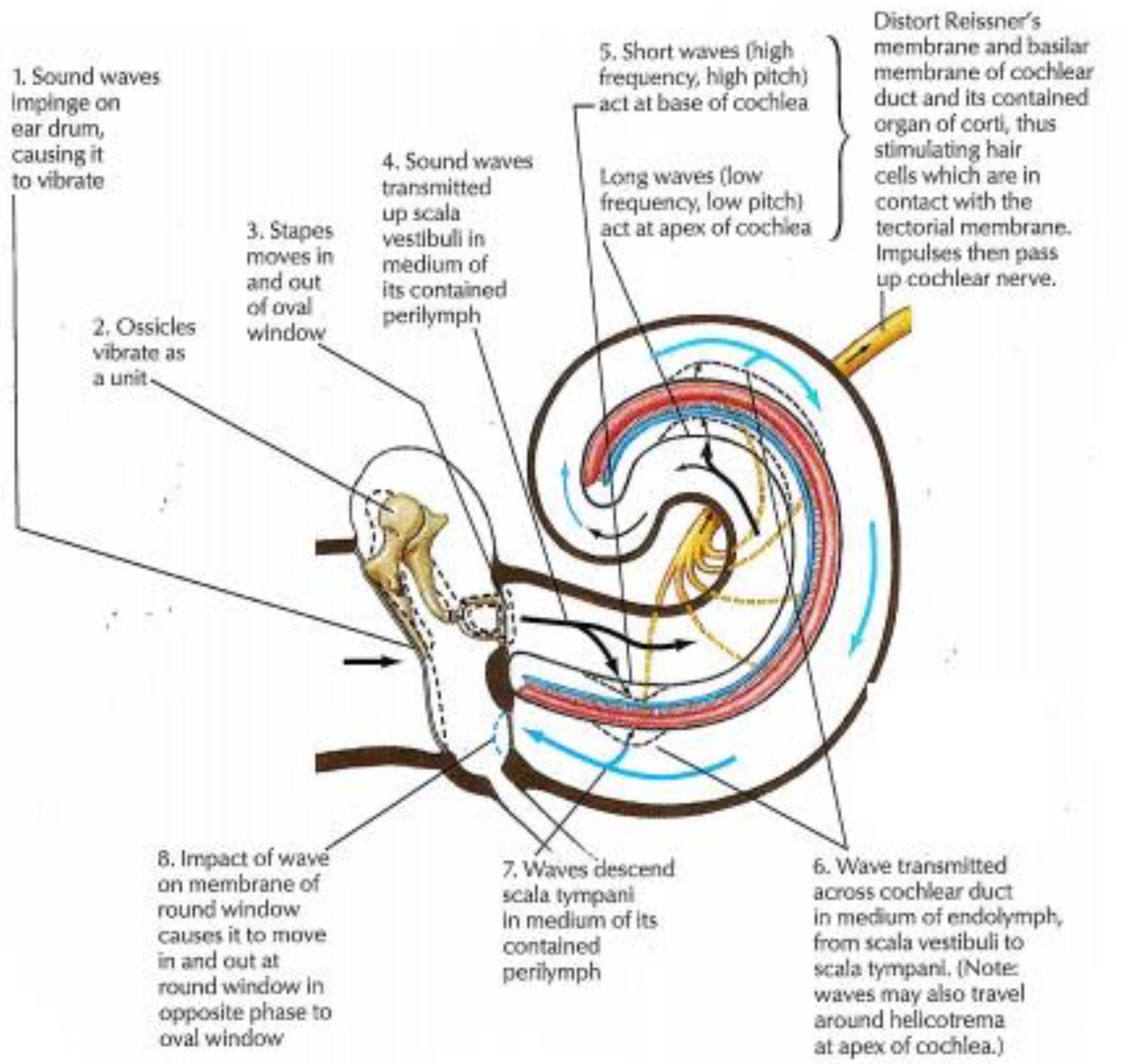
The auditory pathway



- the central processes of cochlear ganglion cells terminate in the dorsal and ventral cochlear nuclei of the brain stem
- the cochlear nuclei communicate with the superior olive from where the auditory fibers ascend to the inferior colliculus forming the lateral lemniscus
- this nucleus relays the information to the thalamus
- the final acoustic radiation reaches the primary auditory field of the superior temporal gyrus
- the auditory center has a tonotopic organization the apex of the cochlea projects to the anterior part of the field, high frequency sounds are represented at the posterior pole
- behind this region is the sensory speech area of Wernicke

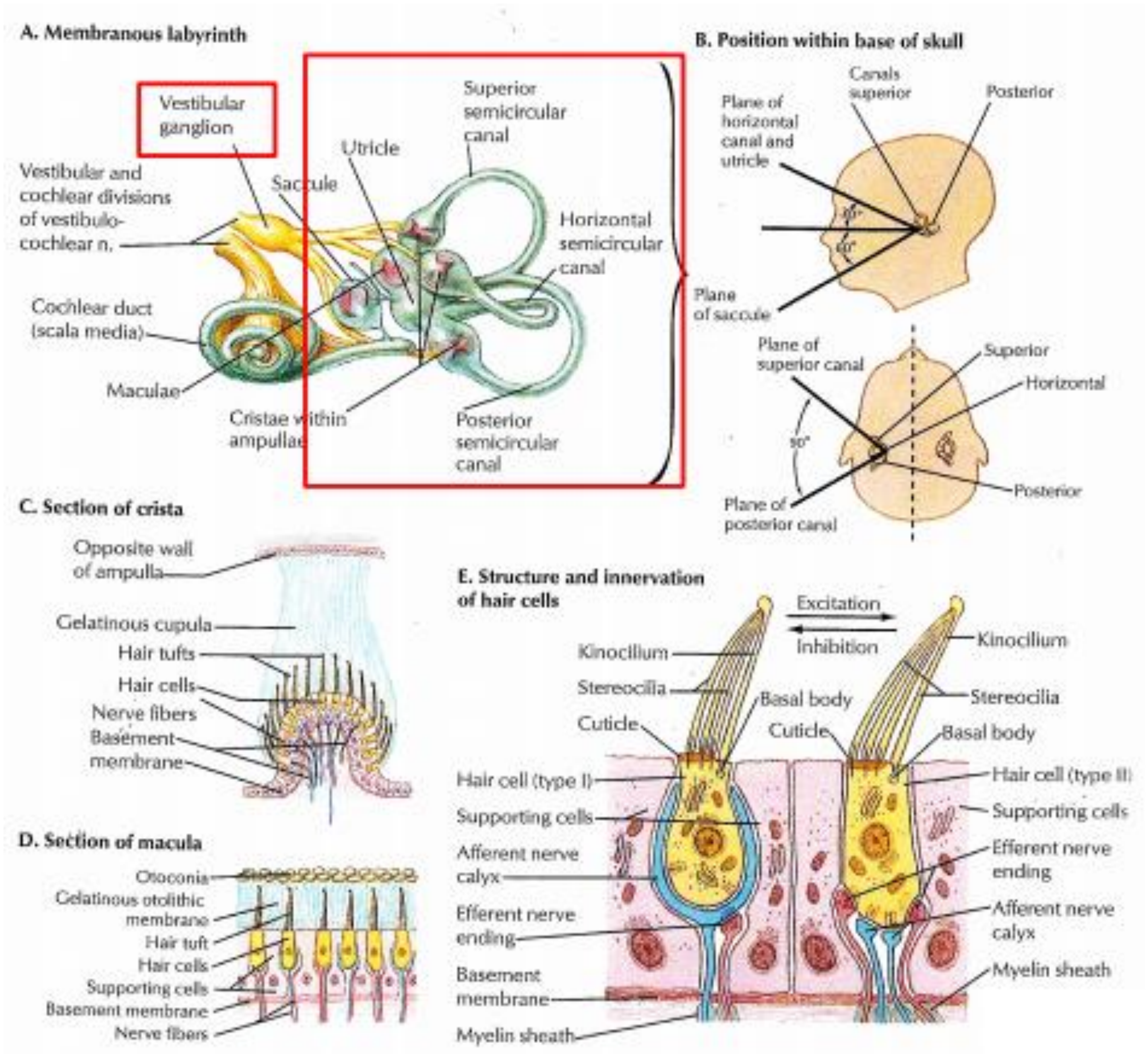




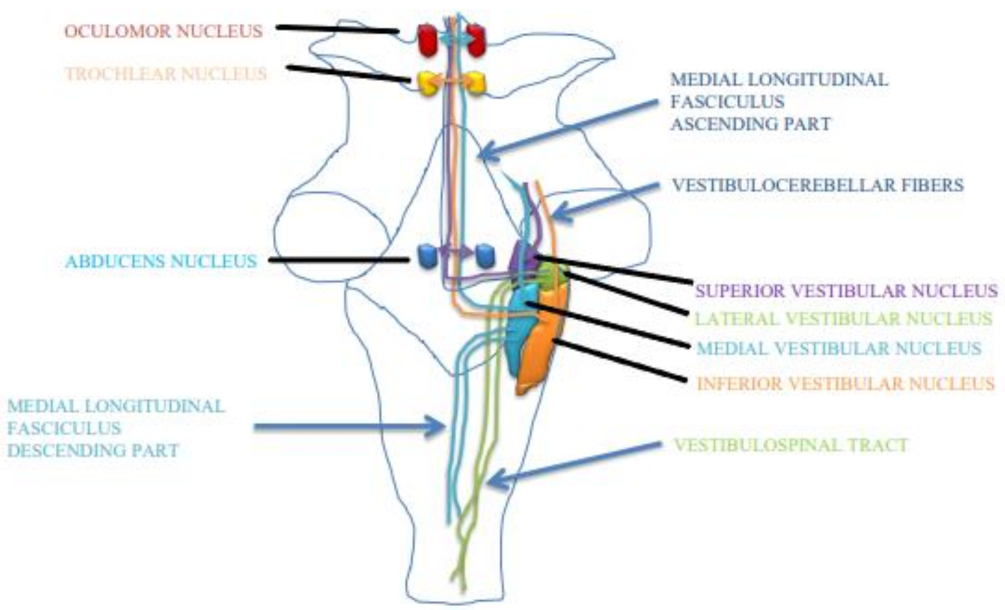


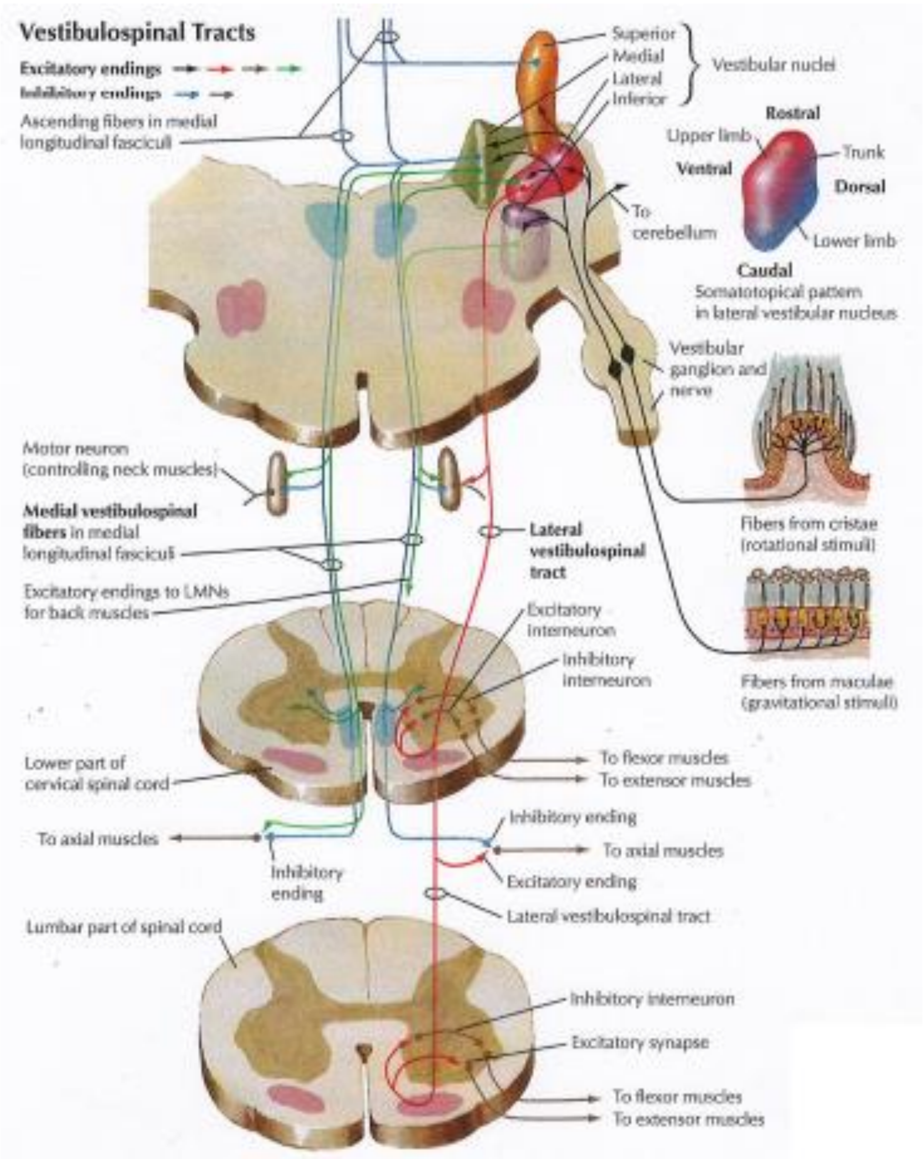
The vestibular system

- the receptor structures of the vestibular system are located in the bony vestibule and semi-circular canals of the inner ear
- the linear acceleration and deceleration are sensed by receptors built into the endolymph-filled saccule and utricle
- the angular rotation is monitored by hair cells of the crista ampullaris, a receptor structure present in each of the membranous semi-circular canals
- the spatial arrangement of the semi-circular canals enables the detection of angular rotation of the head in all directions
- the hair cells of the utricle and saccule possess hairs embedded in the otolith membrane a higher specific gravity than the endolymph and by bending the hairs it can stimulate the hair cells
- in the semi-circular canals, the movement of endolymph triggers the hair cells and changes their activity depending on the direction of the flow
- the altered receptor status is reported by the vestibular nerve

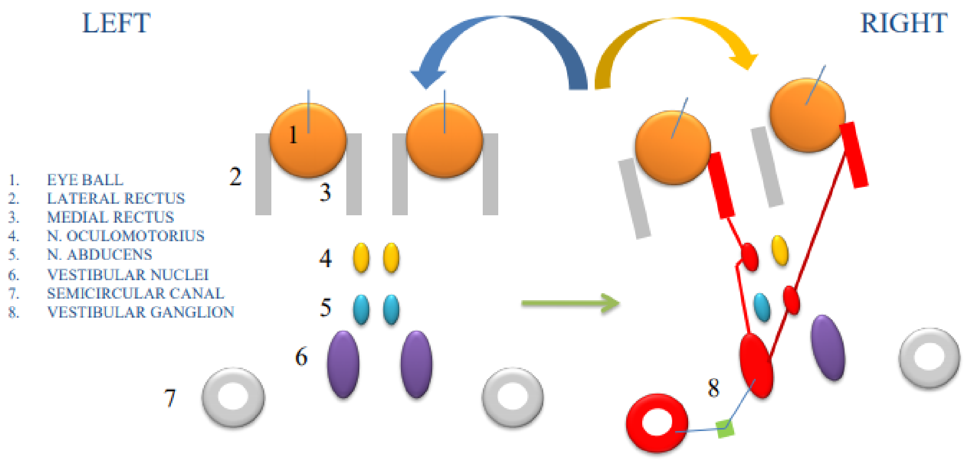


THE VESTIBULAR PATHWAYS





The vestibulo-ocular reflex



MOVING THE HEAD TO THE LEFT SIDE IN THE HORIZONTAL PLANE EVOKES THE CONJUGATED MOVEMENT OF THE EYEBALLS TOWARD THE RIGHT SIDE