DFM3 MODULE 2
THE NERVOUS SYSTEM – FROM ION CHANNEL TO BEHAVIOUR

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VT 2020

Structure and development of the nervous system: *5*

Describe the nervous system's macroscopic anatomy including identifying major core areas and pathways (S2) **5**

Describe blood supply to the brain and fluid circulation (S2) **12**

Describe the development of the nervous system from ectoderm to mature nervous system (S2, S3) **0**

Describe the principles that control axon growth and the synapse formation (S2, S3) **4**

Cellular neurobiology: *7*

describe the function and importance of glial cells (S2) **7**

describe and explain the passive properties of nerve cells and understand how they affect incoming signals (S3, S4) **8**

describe the active properties of nerve cells and the most important function of ion channels (S3, S4) **10**

describe the presynaptic mechanism for transmitter release at the molecular level and the main classes of transmitters (S3, S4) **15**

describe different types of postsynaptic receptors and signal transduction mechanisms (S3, S4) **20**

describe and explain the properties of the synapses and their importance for information processing in the CNS (S3) **24**

Have knowledge about the mechanisms of action of toxins and diseases affecting synaptic transmission, including botulism, tetanus, myasthenia gravis, excitotoxicity and nerve gas poisoning (S1, S2) **33**

Have knowledge of methods used to register activity in individual nerve cells and groups of nerve cells (S1) **35**

Sensory functions: *37*

describe the different types of specialized sensory cells / receptors for the different sensory modalities (touch, proprioception, pain, vision, hearing, balance/spatial orientation, taste and smell), and describe their anatomical and histological organization (S2, S3) **37**

explain, for the different sensory modalities, how specialized sensory cells / receptors transduce a stimulus into electrical signals (S2, S3) **63**

define the central pathways conveying sensory information from the different parts of the body (S2, S3) **72**

explain, for the different sensory modalities, how sensory information is processed in specific brain regions (S2, S3, S4) **80**

explain how we perceive different sensory stimuli and how they can be modulated (S2, S3, S4) **97**

Have knowledge of the most common methods utilised to examine vision, hearing and balance (M2) **99**

Motor functions: *103*

describe and explain basic motor functions at the spinal level, and the concept of the central motor programme (S3) **103**

describe the nervous system's control of locomotion (S3) **110**

describe the different descending motor pathways (S2) and relate their organisation to the control of different movements (S3)..... 114

describe the functional principles behind the balance control system (S2-S3)..... 120

describe the location and main function of different cortical motor areas (S2) and describe and analyse the areas' respective roles with different types of cortical controlled movements (S3-S4) 123

describe the basal ganglia´s structure and internal connections as well as their connections to other parts of the CNS (S2). Be able to relate this knowledge to and describe the role of the basal ganglia in motor control (S3-S4). 126

describe the different types of eye movement and their general functions (S2)..... 129

describe the cerebellum's macroscopic and microscopic structure and its connections to other parts of the CNS and general role in motor control (S2). Be able to explain synaptic connections in the cerebellum cortex and relate these to the function of the cerebellum (S3-S4). 131

describe motor defects caused by damage to or degeneration of different parts of the CNS, including stroke, Parkinson´s disease, Huntington´s disease and spinal cord trauma (S2, S3). .. 134

Neuropsychology: The brain and behaviour: 137

explain central theories and models in cognitive neuroscience (S2). 137

describe how specific brain regions together contribute to cognitive processes and behaviour (such as emotions and memories) (S2-S4). For example, this includes how subcortical and cortical systems interact. 137

explain how common brain disorders (such as stroke, cancer and ADHD) and everyday life (such as stress and sleep) affect cognitive processes and behaviour (S2-S3). 149

Be able to describe common methods used for diagnosis and to study healthy brains (S2)..... 149

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Oral Exam 1 - Cellular neurobiology 154

1.Describe the different types of glial cells and their functional roles 154

1.Describe the different types of glial cells and their functional roles V2 155

2.Describe the basis of the resting membrane potential and the function of the Na/K pump .. 156

3.Describe the basis of the action potential –which are its different phases and which are the underlying ionic mechanisms 157

4.Compare excitatory and inhibitory synapses –what are the effects on the postsynaptic neuron and how do the two types of synapse interact 159

5.Compare the process of release of "small" neurotransmitters (such as glutamate and GABA) with that of "large"neurotransmitters (such as neuropeptide Y and substance P) –similarities and differences 160

6.Describe the molecular machinery that mediates fusion of synaptic vesicles with the plasma membrane 162

7.Poisoning by Botulinum toxins and Tetanus toxin giverise to different symptoms. How do these toxins act? How do the symptoms produced by the two toxins differ and why?..... 163

8.Describe the mechanisms underlying the inactivation of neurotransmitters..... 165

9.Describe the main structural and functional differences between ionotropic and metabotropic receptors..... 166

10.Which are the main types of postsynaptic glutamate receptor and how do they differ? 168

11.Describe the mechanisms underlying synaptic short-term plasticity 170

12.Describe the mechanisms underlyingsynaptic long-term plasticity 172

ORAL EXAM 2 173

Oral Exam 2 - Sensory functions 173

1.Describe the different types of mechanoreceptors in the skin and explain what two-point discrimination is. 173

2.Describe the central pathways conveying tactile information (touch, vibration, proprioception). 177

3.Describe the central pathways conveying pain and temperature. 183

4.Discuss pain modulation from descending pathways and its physiological relevance. 185

5.Describe the anatomy of the eye. 187

6.Describe the histology of the retina with its different cell types and explain how rods and cones are distributed in different parts of the retina. 188

7.Explain the process of phototransduction in a rod. 192

8.Explain the functions of the projections from the retina to different parts of the brain (except the primary visual cortex). 196

9.Describe the anatomy and histology of the ear and explain the concept of "frequency tuning" in the inner ear. 197

10.Explain the mechanisms responsible forcircular and linear accelerations. 203

11.Explain the functions and the distribution of the different taste receptor cells. 206

12.Describe how an odor activates olfactory receptor cells. 208

ORAL EXAM 3 210

Oral exam 3 – Motor functions 210

1. Describe the different types of motor units and their properties. Explain how the CNS grades muscle force on the basis of motor units. 210

2. Two types of afferent fibers carry information from a limb, the Ia and Ib afferents. Which types of stimuli does each one respond to and what are their roles in motor control? 211

3. What are central motor programs? – give a definition and examples of both innate and learned/acquired motor programs. 213

4. Describe the flexion reflex (=flexion crossed extension reflex) – which neurons are involved and how are they connected. What is the role of this reflex? 214

5. Describe the control system for locomotion. 214

6. Describe the functional organization of the descending tracts: Where are they located in the spinal cord and what are their roles in motor control. 216

7. Describe briefly the roles of the following three cortical areas in motor control: primary motor cortex (M1), dorsal premotor cortex, and supplementary motor cortex (=medial premotor cortex). 219

8. The basal ganglia: What is their general role in motor control and what are the functions of the direct and indirect pathways. 220

9. Give an explanation of the hypokinesia symptoms seen in patients with Parkinson´s disease. 222

10. The roles of cerebellum are to correct motor errors during ongoing movements and to participate in motor learning. Which types of signal are important for correction of motor errors? Describe also the cellular mechanisms in the cerebellar cortex that underlie motor learning. 223

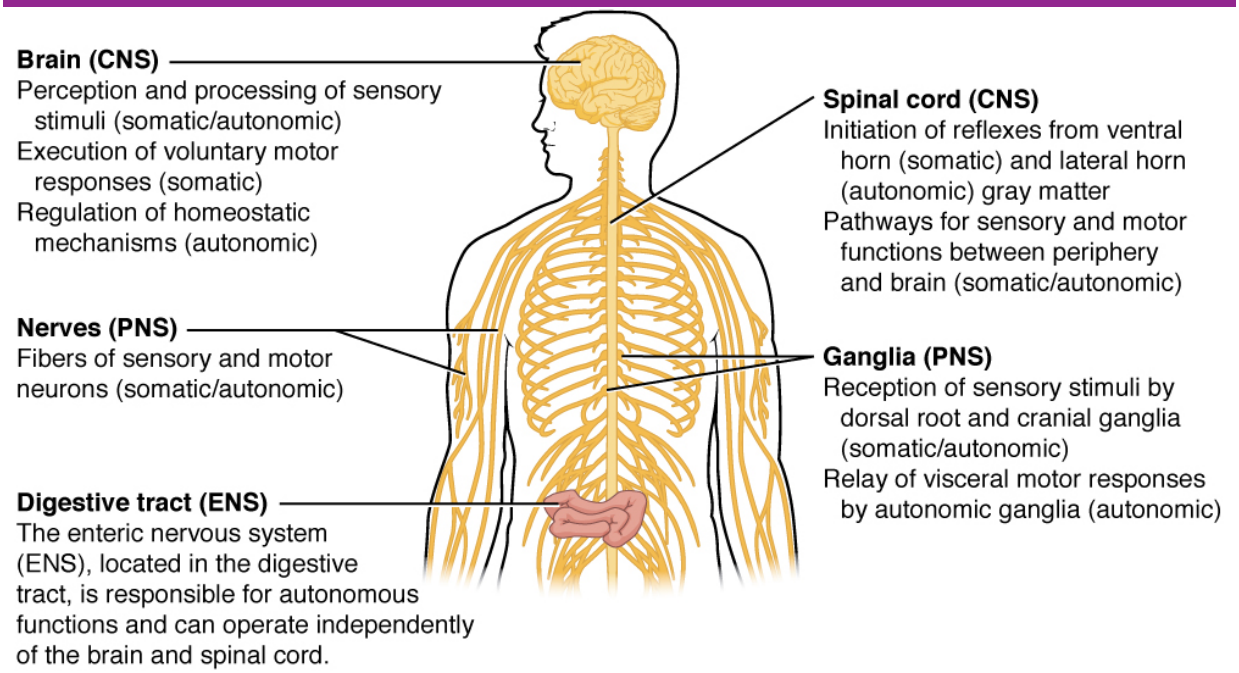
11. Which are the three functional parts of cerebellum (based on their inputs) and what are their respective roles? Which symptoms occur after lesion to each of these parts? 225

12. Describe the different types of eye movements and their respective roles. 226

True/false 227

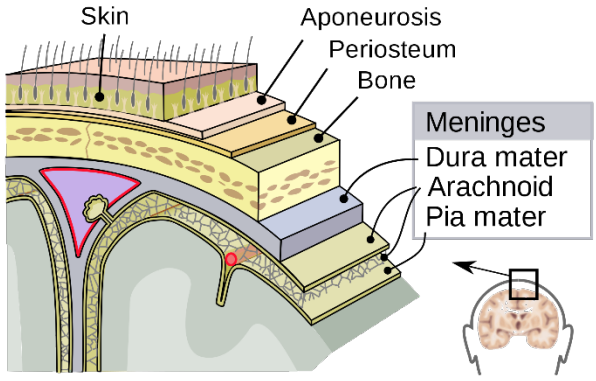
STRUCTURE AND DEVELOPMENT OF THE NERVOUS SYSTEM:

DESCRIBE THE NERVOUS SYSTEM'S MACROSCOPIC ANATOMY INCLUDING IDENTIFYING MAJOR CORE AREAS AND PATHWAYS (S2)



The nervous system is divided into a central nervous system (CNS) and a peripheral nervous system (PNS). The PNS consist of peripheral nerves and ganglia while the CNS consist of the brain and spinal cord.

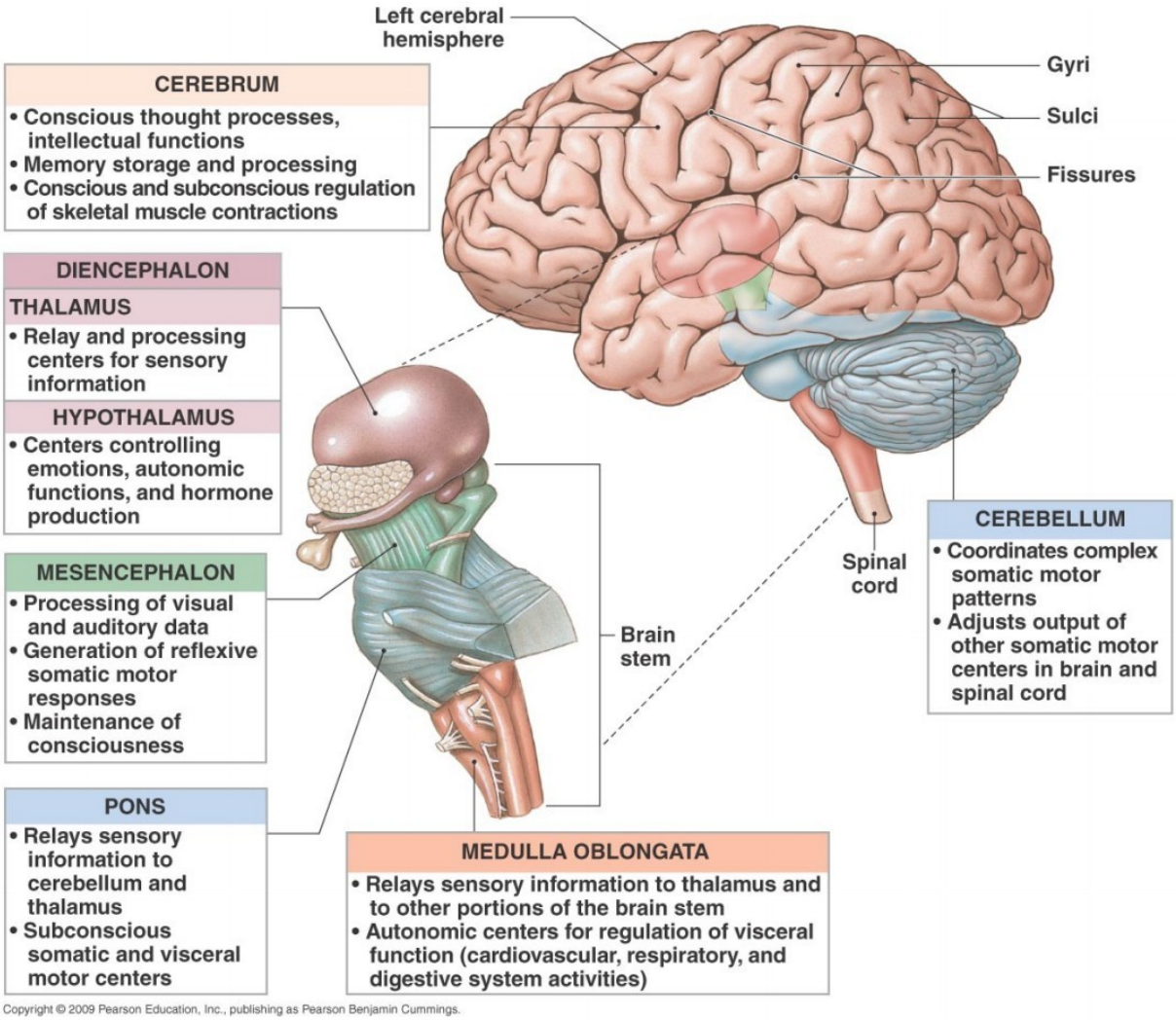
The CNS is surrounded by three barriers: the dura mater, arachnoid mater and pia mater.



THE BRAIN

The brain is the bodies third largest organ and for an adult weigh approximately 1.2 -1.4 kg. It is a complex organ that acts as the control centre of the body by sending, receiving, processing and directing sensory information. The brain is split into left and right hemispheres by a band of fibers called the corpus callosum.

The brain is also divided into divisions depending on their function:

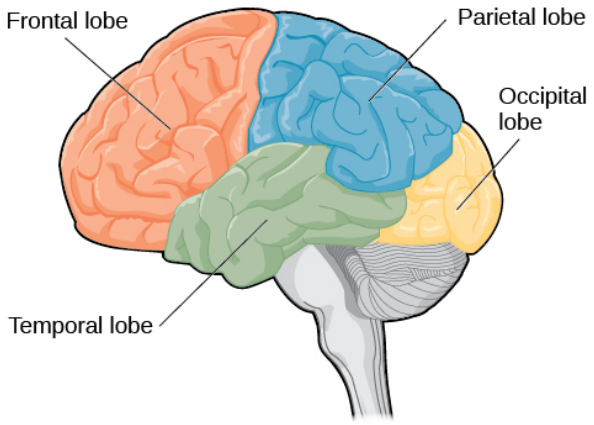


CEREBRUM OR TELENCEPHALON

The cerebrum or telencephalon is a large part of the brain that contain the cerebral cortex as well as several subcortical structures (including the hippocampus, basal ganglia and olfactory bulb). It functions as a centre for sensory perception, memory, thoughts and judgement as well as a centre for all ones' voluntary actions. Cranial nerve I originate in the cerebrum.

Due to its large size the cortex is heavily folded to be able to fit inside the cranium. These folds give rise to sulci and gyri.

The cortex can be further divided into four lobes: frontal (lobus frontalis), parietal (lobus parietalis), Occipital (lobus occipitalis) and temporal (lobus temporalis).



LOBUS FRONTALIS

Located at the forward part of the brain extending back to a fissure known as the central sulcus the frontal lobe is involved in reasoning, motor control, emotion and language. It contains the motor cortex which is involved in planning and coordinating movement; it also contains the prefrontal cortex which is responsible for higher level cognitive functioning as well as Broca's area which is essential for language production.

LOBUS PARIETALIS

The brains parietal lobe is located immediately behind the frontal lobe and is involved in processing information from the body's senses. It contains the somatosensory cortex which is essential for processing sensory information from across the body such as touch, temperature and pain.

LOBUS TEMPORALIS

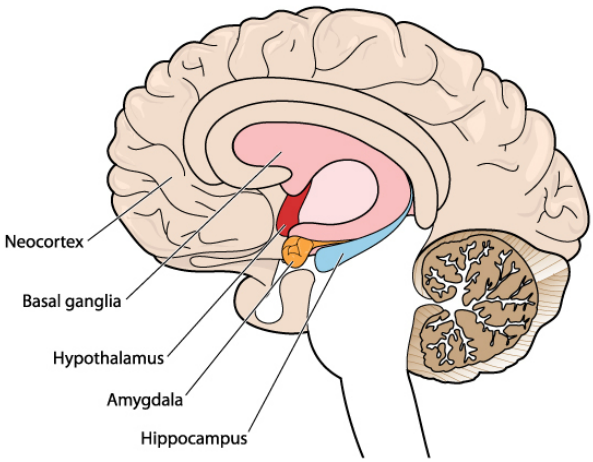
The temporal lobe is located on the side of the head and is associated with hearing, memory, emotion and some aspects of language. The auditory cortex, the main area responsible for processing auditory information is located within the temporal lobe. Wernicke's area which is important for speech comprehension is also located here.

LOBUS OCCIPITALIS

The occipital lobe is located at the very back of the brain and contains the primary visual cortex which is responsible for interpreting incoming visual information.

HIPPOCAMPUS

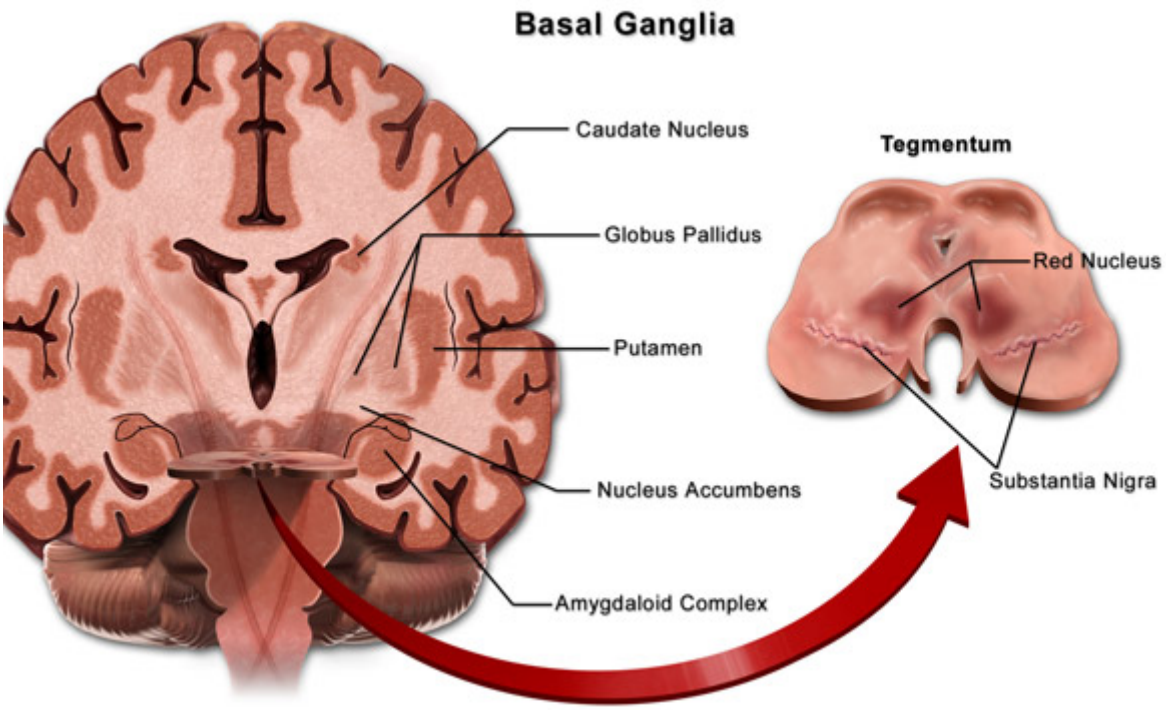
The hippocampus is a major component of the brain with one on each side for a total of two hippocampi per brain. It is part of the limbic system and plays important roles of consolidation of information from short term memory into long term memory. As well as in spatial memory that enables navigation.



AMYGDALA

Also considered a part of the limbic system the amygdala is located in the temporal lobes of the brain. The amygdala has a primary role in processing of memory, decision making and emotional responses (including fear, anxiety and aggression.

BASAL GANGLIA



The basal ganglia are a group of subcortical nuclei of varied origin that are situated at the base of the cerebrum and top of diencephalon. Basal ganglia are strongly interconnected with the cerebral cortex, thalamus, brainstem and several other areas. They are associated with a variety of functions including control of voluntary movements, procedural learning, habit learning, eye movements, cognition and emotion.

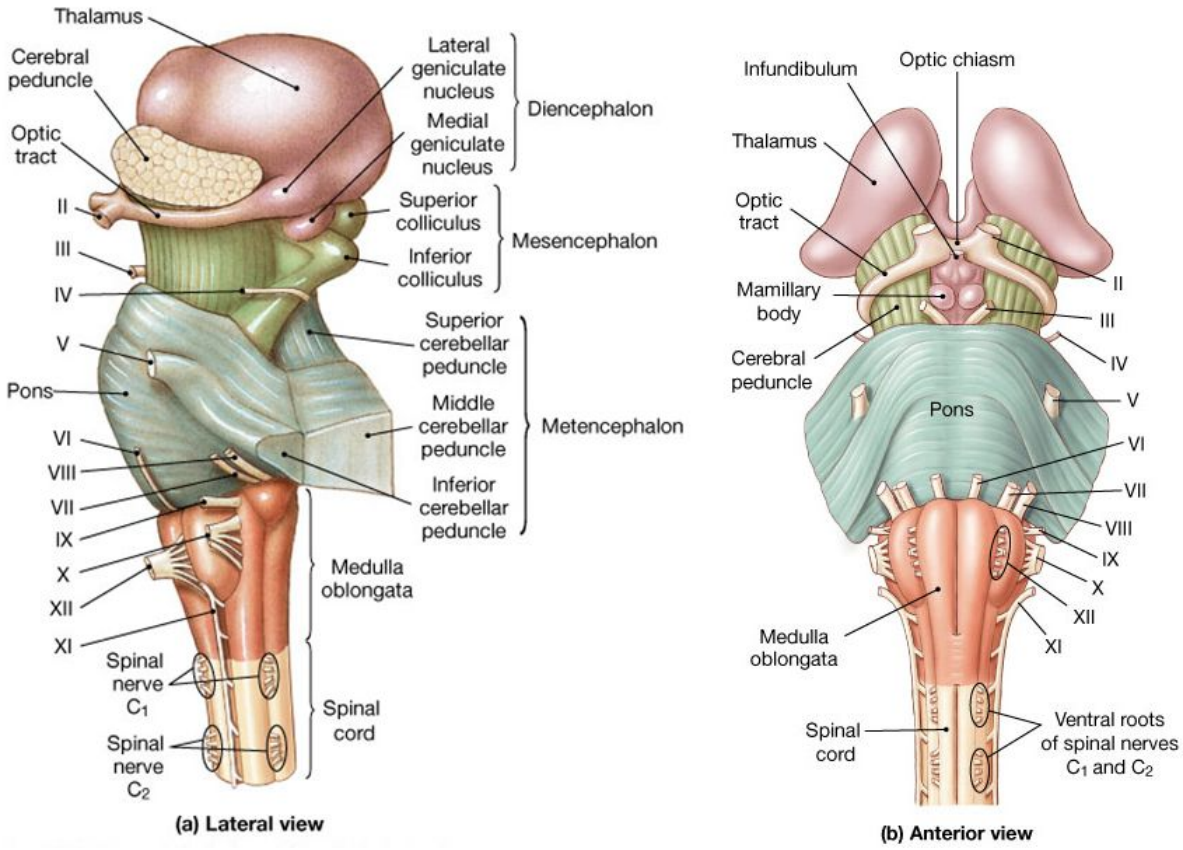
DIENCEPHALON

The diencephalon is situated between the telencephalon and the mesencephalon. It consists of structures that are on either side of the third ventricle which are the thalamus, hypothalamus, epithalamus and subthalamus. The diencephalon serves as a relay and processing centre for sensory and motor impulses between the spinal cord and medulla oblongata and the cerebrum. The hypothalamus also links the nervous system to the endocrine system via the pituitary gland. Cranial nerve II originates in the diencephalon.

MESENCEPHALON

The mesencephalon (also called midbrain) is the forward most portion of the brainstem (makes up the brainstem with the pons and medulla oblongata) and is associated with vision, hearing, motor control, sleep and wakefulness, arousal and temperature regulation. Cranial nerves III and IV originate in the mesencephalon.

BRAINSTEM



PONS

The pons is part of the brainstem and lies inferior to the mesencephalon and superior to the medulla oblongata and anterior to the cerebellum. This region of the brainstem has neural pathways and tracts that conduct signals from the brain down to the cerebellum and medulla as well as tracts that carry sensory signals up into the thalamus. The pons also has four cranial nerves (V-VIII) that include regulation for respiration, involuntary actions, sensory roles in hearing, equilibrium, taste and facial sensations such as touch and pain as well as motor roles in eye movement, facial expressions, chewing, swallowing and the secretion of saliva and tears.

MEDULLA OBLONGATA

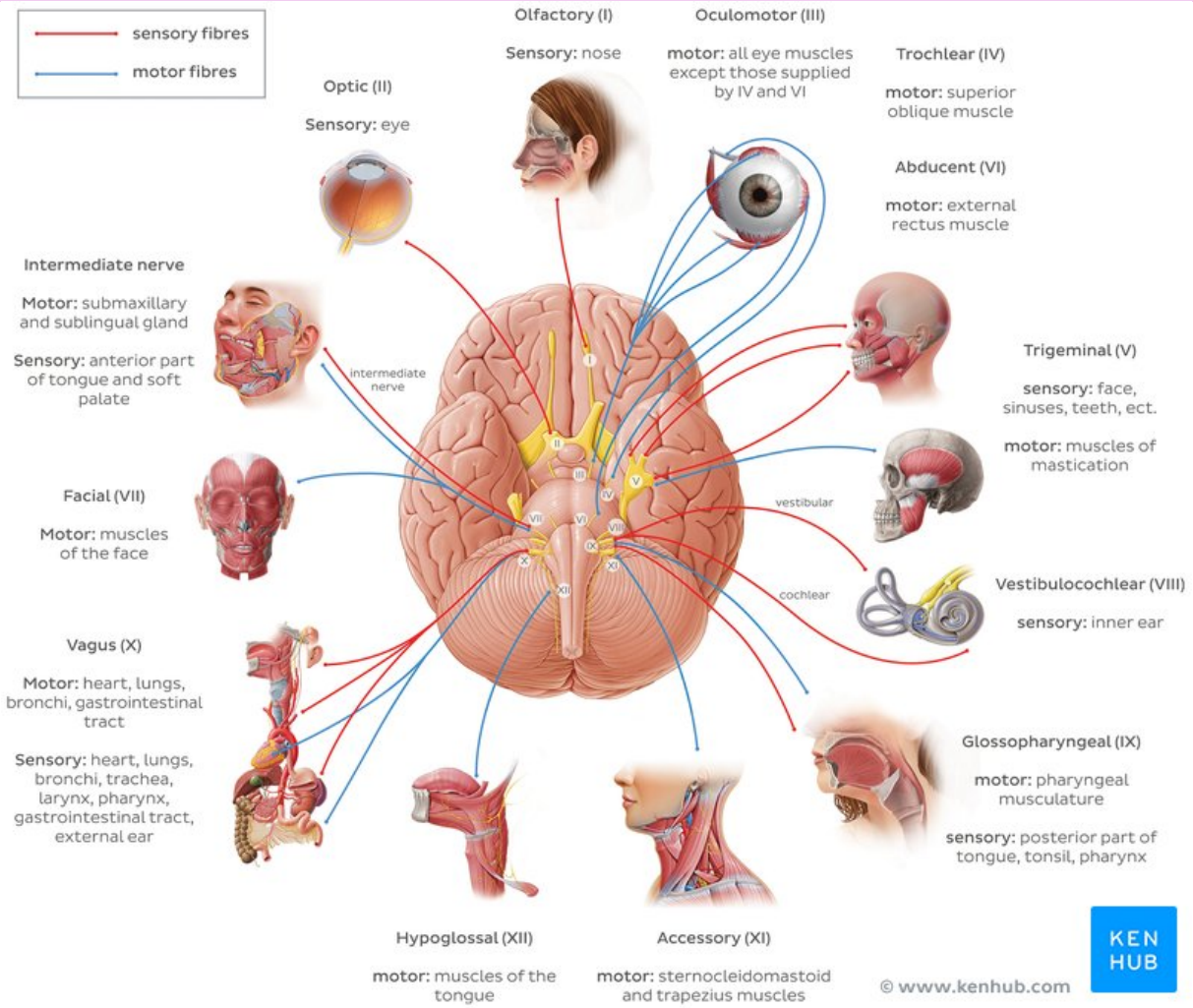
The medulla oblongata (or medulla) is inferior to the pons (last part of brainstem) and is responsible for autonomic (involuntary) actions and contains the cardiac, respiratory, vomiting and vasomotor centers and therefore deals with the autonomic functions of breathing, heart rate and blood pressure as well as the sleep wake cycle. Cranial nerves IX-XII originate in the medulla oblongata.

CEREBELLUM

The cerebellum is a major feature of the hindbrain and plays an important role in motor control, it doesn't initiate movement but instead contribute to coordination, precision and

accurate timing: it receives input from sensory systems of the spinal cord and from other parts of the brain and integrates these inputs to finetune motor activity.

CRANIAL NERVES

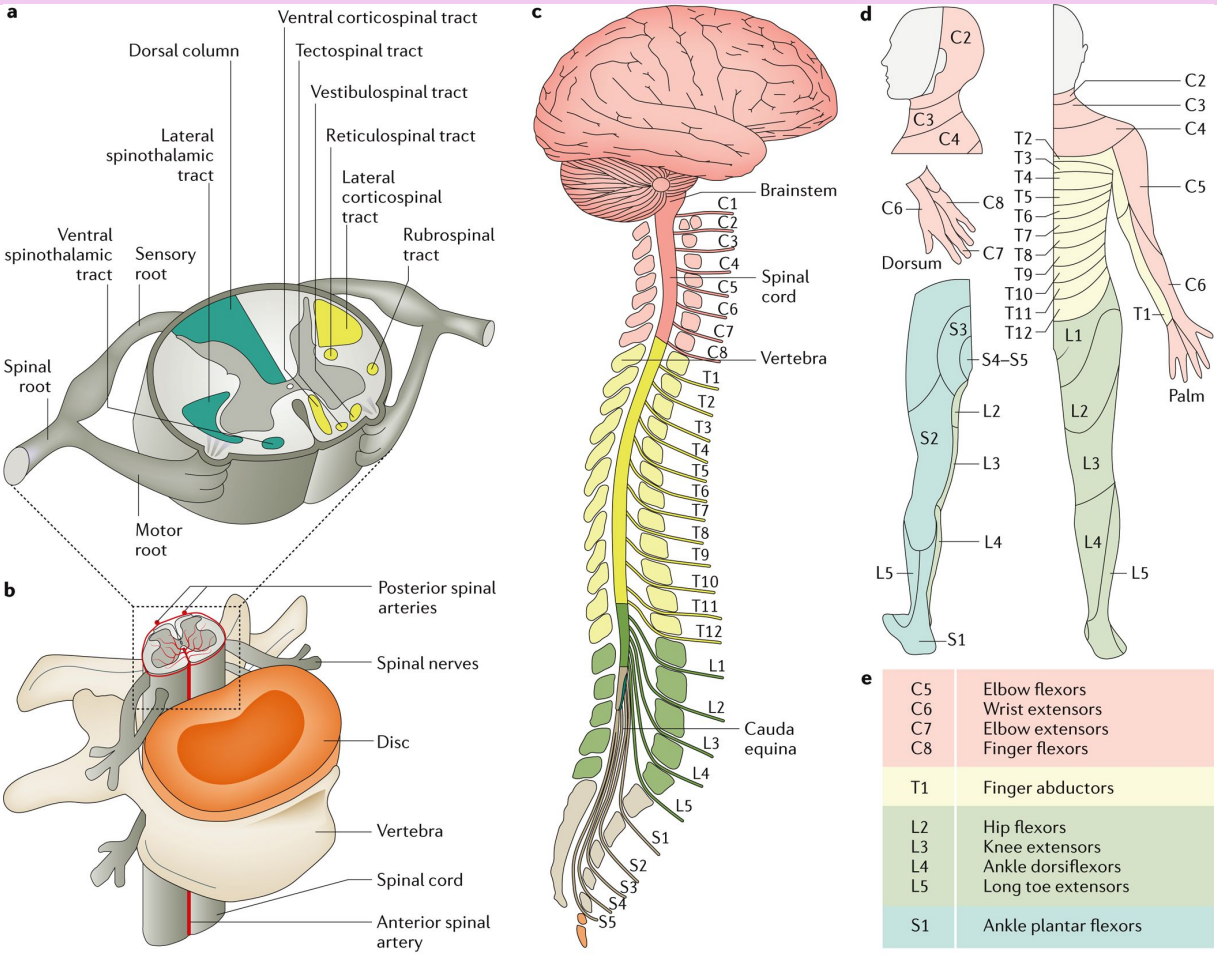


The twelve cranial nerves are:

1. **N. Olfactorius:** Sense of smell
2. **N. Opticus:** Vision
3. **N. Oculomotorius:** All eye muscle movements part from those supplied by CN IV and VI
4. **N. Trochlearis:** Superior oblique muscle
5. **N. Trigeminus:** Sensory fibres for face
6. **N. Abducens:** External rectus muscle
7. **N. Facialis:** Motor fibres for face muscles
8. **N. Vestibulocochlearis:** Inner ear sensory fibres
9. **N. Glossopharyngeus:** Motor fibres for pharyngeal musculature, sensory fibres for posterior part of tongue, tonsil and pharynx
10. **N. Vagus:** Motor fibres for heart, lungs, bronchi and GI tract. Sensory fibres for heart, lungs, bronchi, trachea, larynx, pharynx, GI tract and external ear.

11. **N. Accesorius:** Motor fibres for sternocleidomastoid and trapezius muscles.
12. **N. Hypoglossus:** Motor fibres for tongue muscles.

SPINAL CORD | MEDULLA SPINALIS



Nature Reviews | Disease Primers

The spinal cord is a long, thin, tubular structure made up of nervous tissue which extends from the medulla oblongata to the lumbar region of the vertebral column. It is divided into 31 segments which are defined by the 31 pairs of nerves that exit the cord. These nerves are divided into 8 cervical, 12 thoracic, 5 lumbar, 5 sacral and 1 coccygeal nerve. Dorsal and ventral roots enter and leave the vertebral column respectively through intervertebral foramen at the vertebral segments corresponding to the spinal segment. The cervical nerves leave over the vertebra with the same name (C2 leaves the spine between vertebra C1 and C2) and C8 leaves under C7. After the cervical nerves all the nerves leave underneath their corresponding vertebra (Th1 leaves under vertebra Th1).

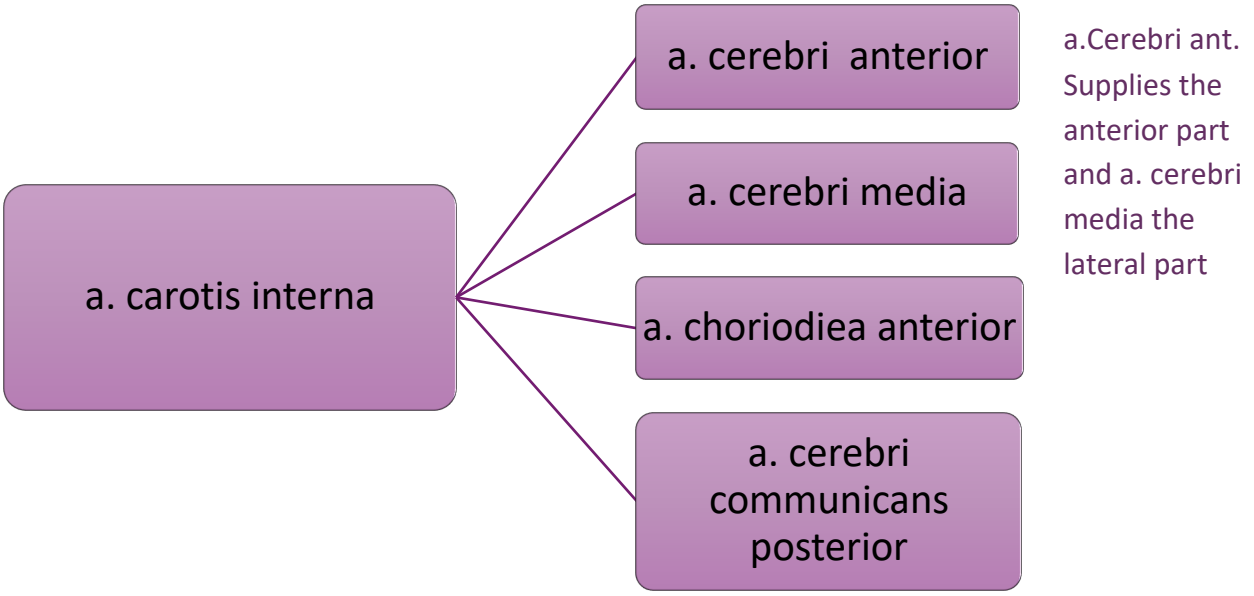
The cord is sheathed in the same three meninges as the brain: the pia, arachnoid and dura. The spinal cord ends at L1-L2 and is thereafter called the cauda equina, the nerves still

leaves under their respective vertebra, however. There is no pia mater around the cauda equina.

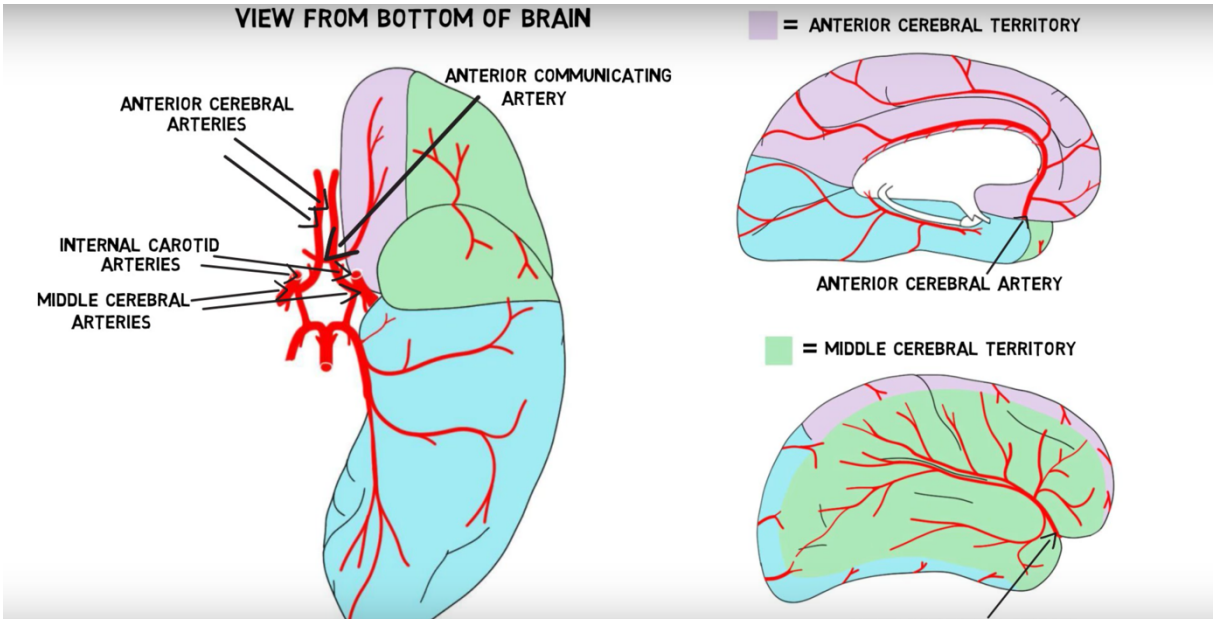
DESCRIBE BLOOD SUPPLY TO THE BRAIN AND FLUID CIRCULATION (S2)

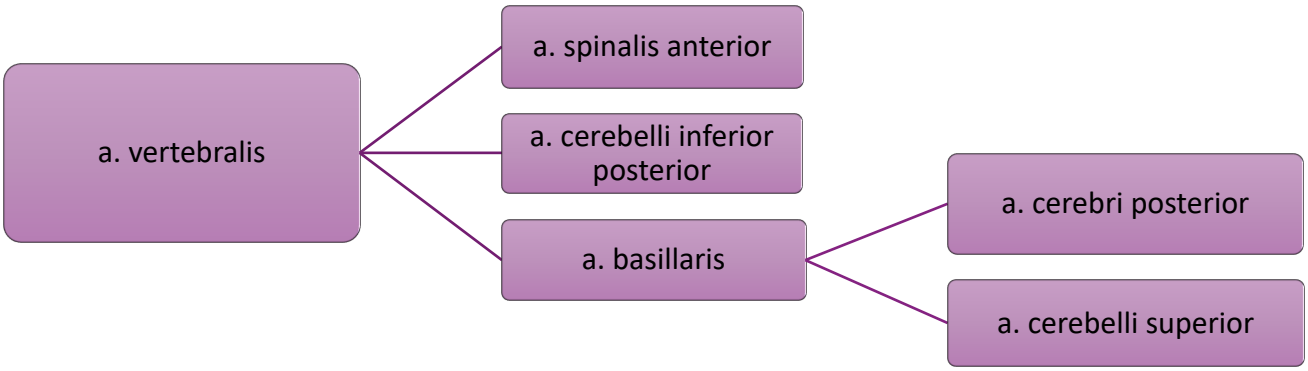
BLOOD SUPPLY – ARTERIES

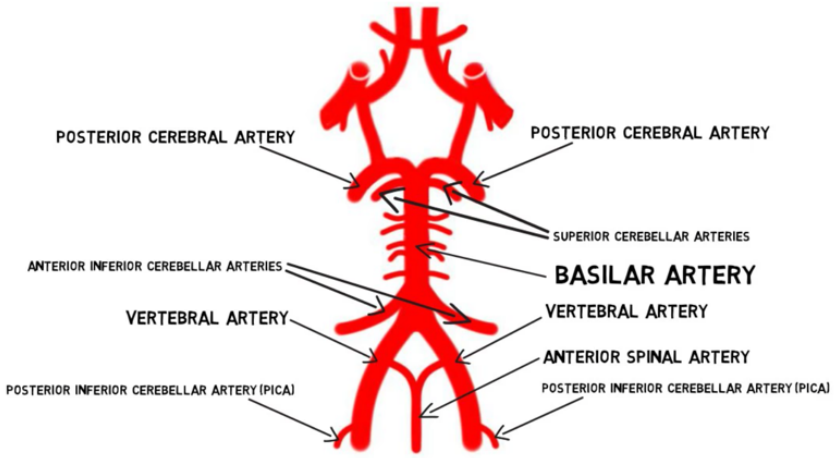
The brain receives 80 % of its blood supply from the internal carotid arteries (aa. Carotis interna) and 20 % from the vertebral artery (a. vertebralis).



a.Cerebri ant. Supplies the anterior part and a. cerebri media the lateral part







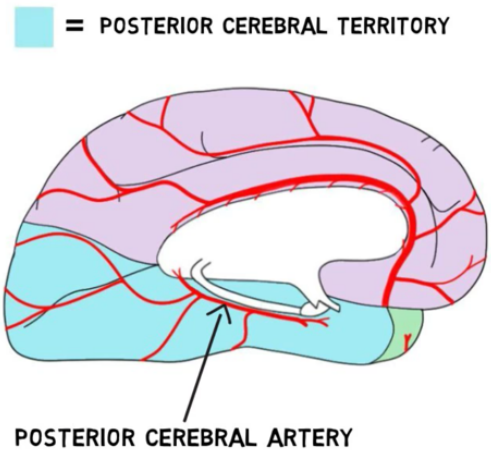
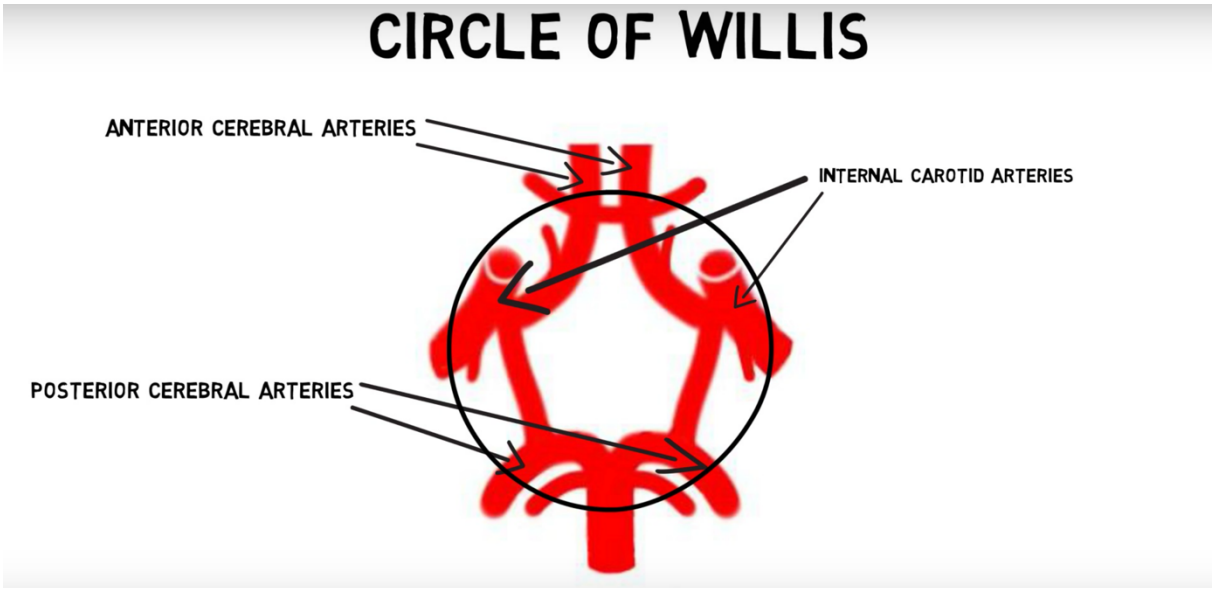


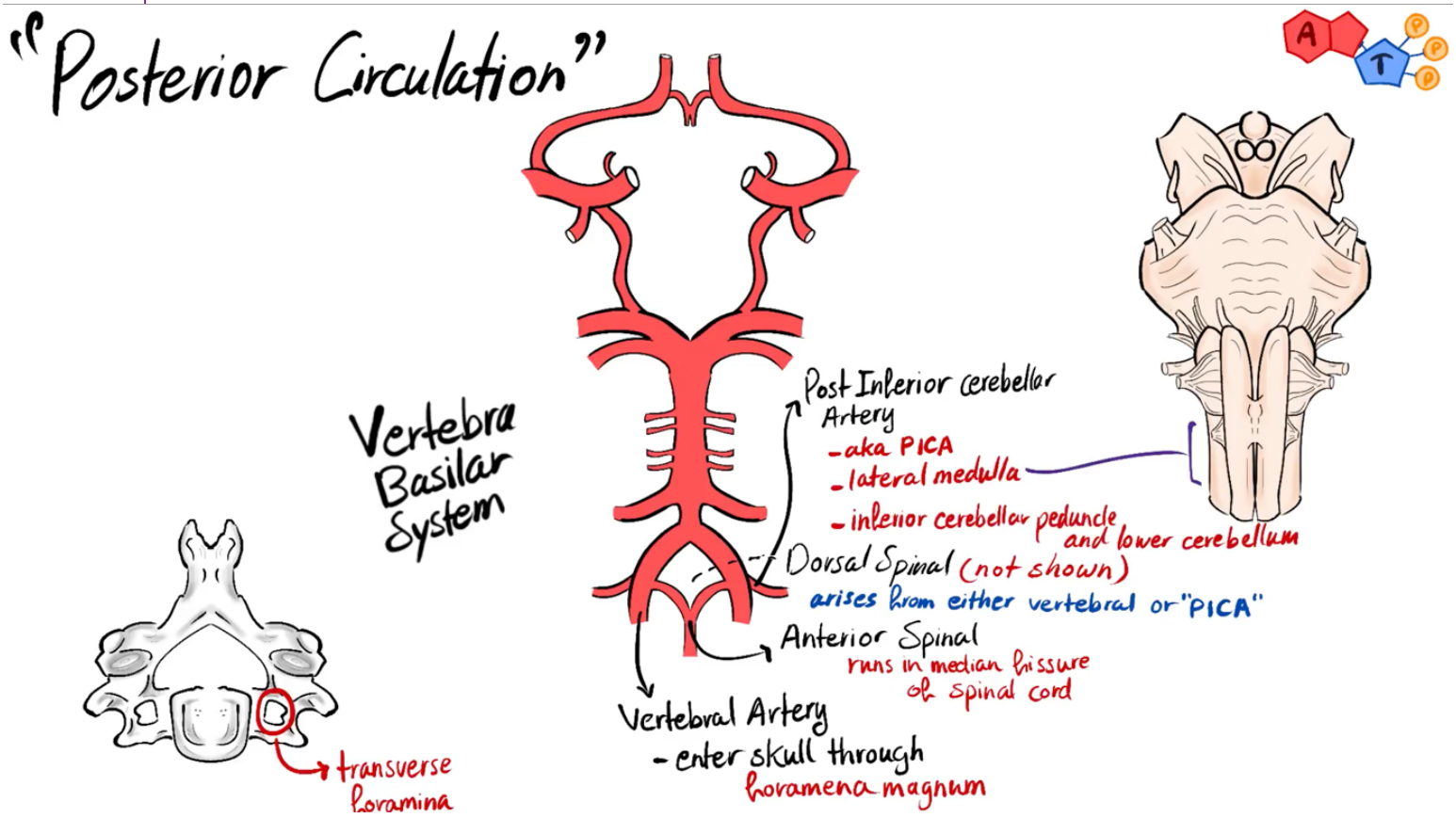
Figure 1 picture of the arteries and samt a. cerebri posteriors area that it supplies

CIRCLE OF WILLIS

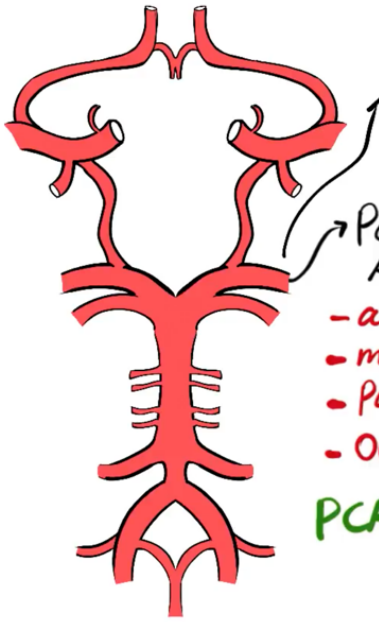
a. cerebri posterior, a. carotis interna and a. cerebri anterior together form the circle of Willis. This anastomose is important if for the bloodflow of the brain I case of an occlusion.

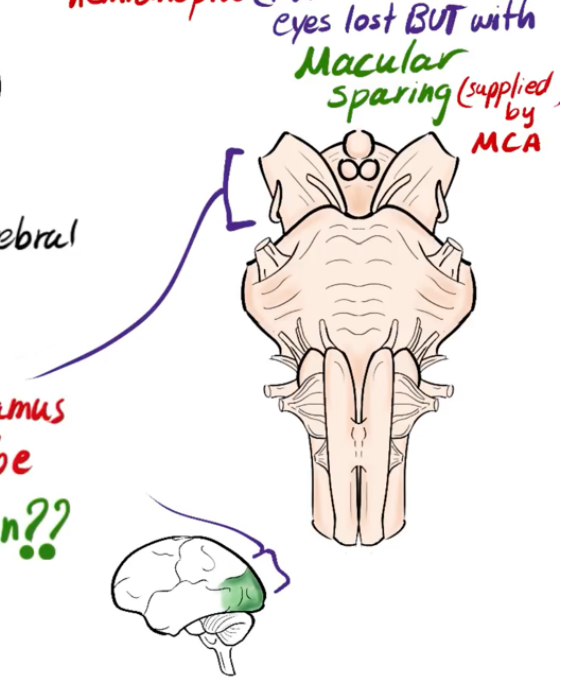


SUMMARISING PICTURES OF THE BLOOD SUPPLY OF THE BRAIN



"Posterior Circulation"





Right PCA occlusion
→ left contralateral homonymous hemianopia (left vision of both eyes lost BUT with Macular Sparing (supplied by MCA

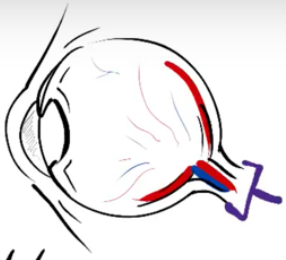
Posterior Cerebral Artery (PCA)
- above CN3
- midbrain
- Part of thalamus
- occipital lobe

PCA Occlusion??

Anterior Circulation

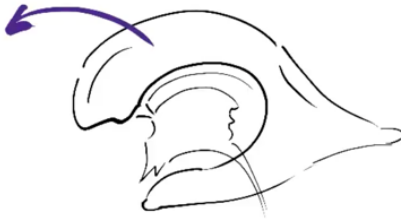
Internal Carotid Artery

Ophthalmic Artery
- Central retina



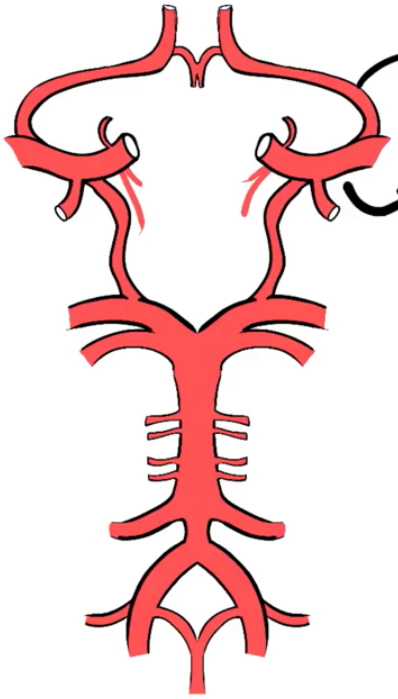
Ophthalmic artery

Anterior Choroidal Artery
- Choroid plexus of lateral ventricle and cerebrum



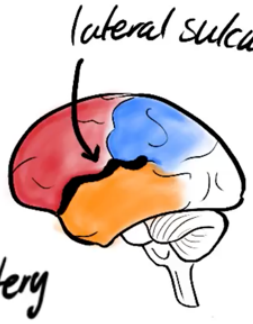
Hypophyseal Artery
- Arterial network of pituitary gland

Anterior Circulation



Anterior Cerebral Artery (ACA)

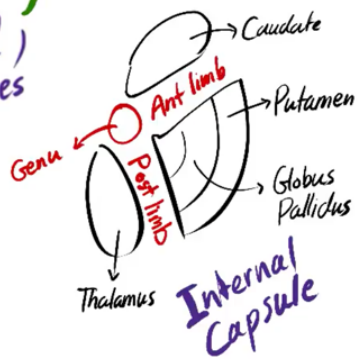
Middle Cerebral Artery (MCA)



- runs in lateral sulcus
- lateral hemispheres (except superior 1 inch of) frontal and parietal lobes

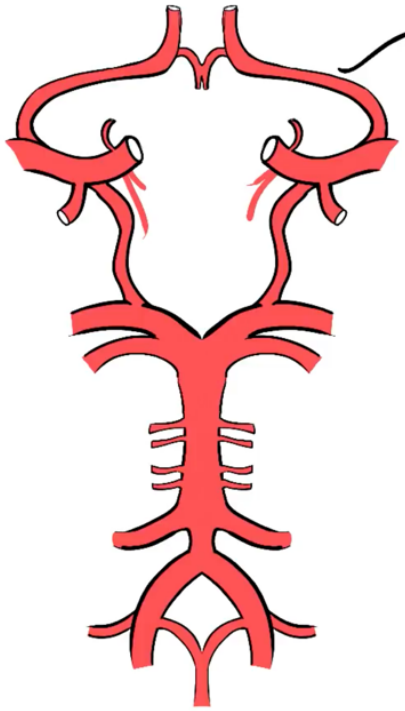
→ supplied by ACA

- Internal capsule
  - Post limb + Genu



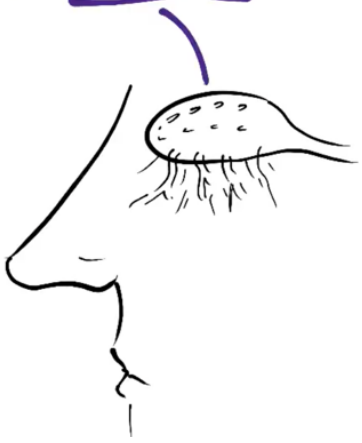
Corticospinal + Corticobulbar tracts run in them!

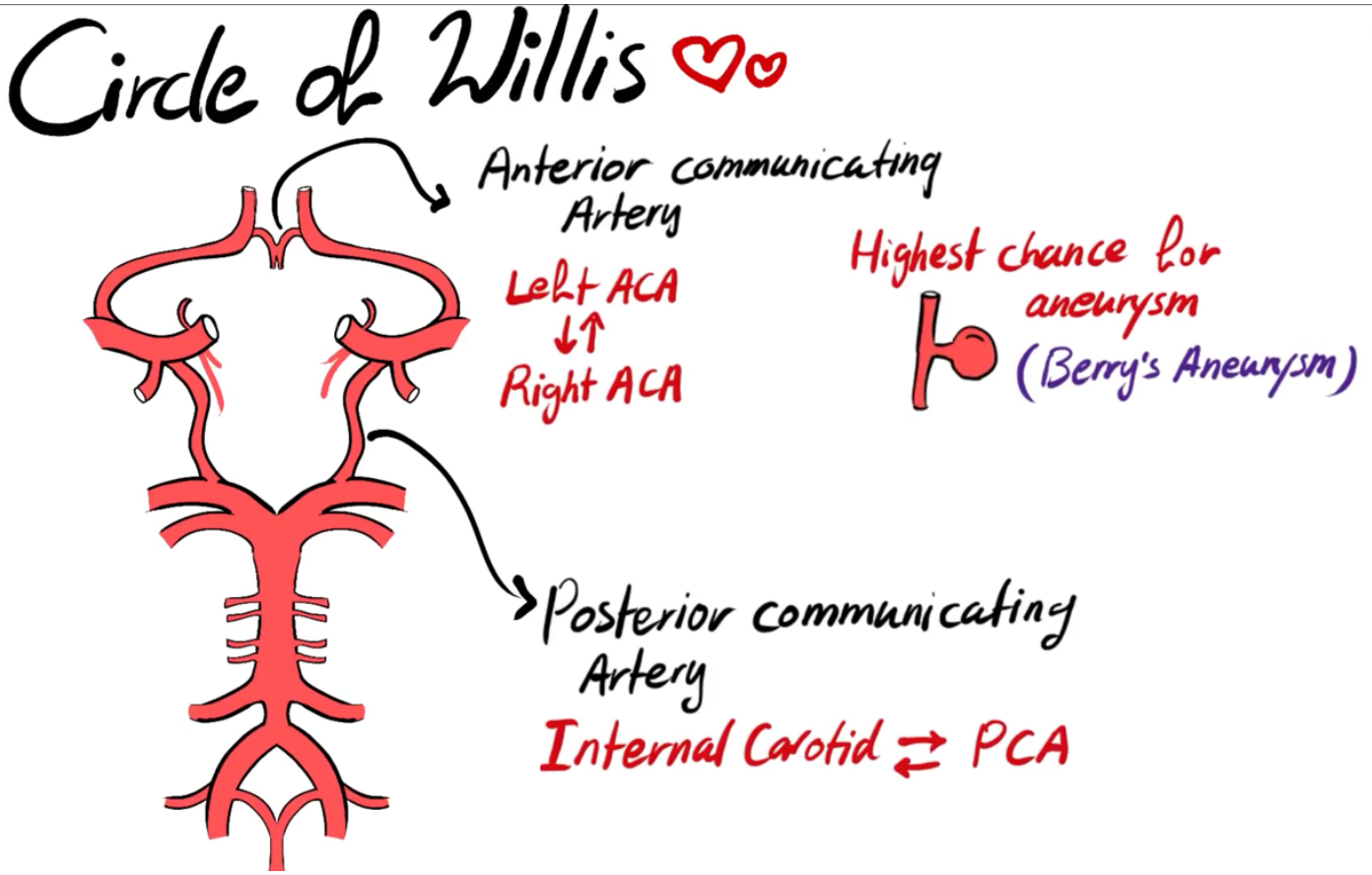
Anterior Circulation



Anterior Cerebral Artery

- Medial aspect of cerebral hemispheres
- Lower limb
- Olfactory bulb + tract





WHAT PART OF THE BRAIN/WHAT BRAIN STRUCTURES ARE SUPPLIED BY WHICH ARTERY? *(NOT ENTIRELY IMPORTANT BUT BEEN SOME EXAM QUESTIONS ON LIKE THE FIRST BULLETIN)*

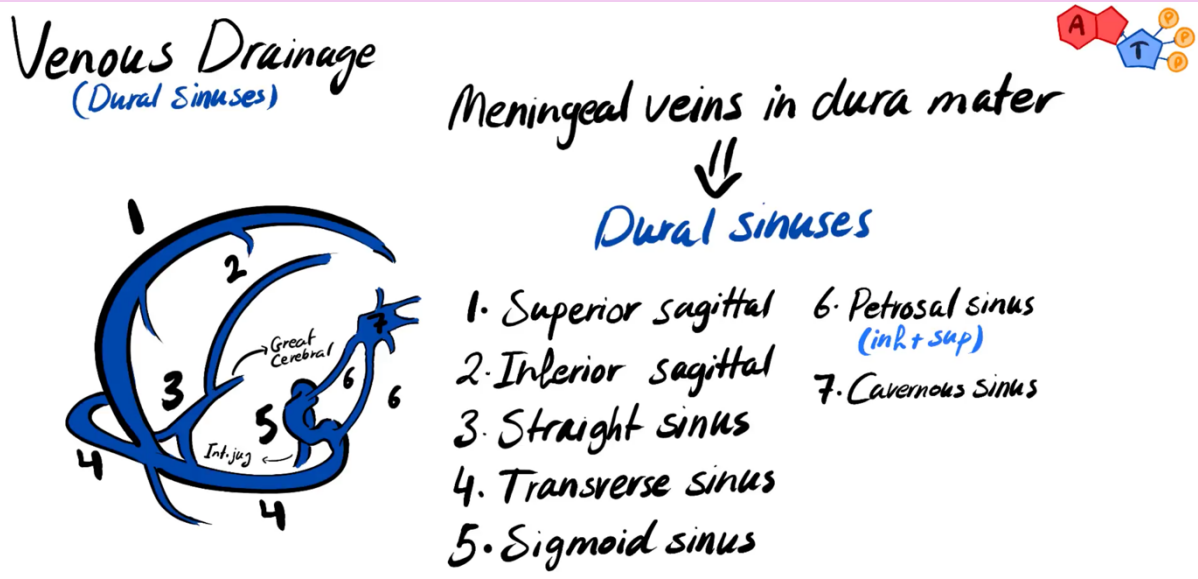
- **a. cerebri anterior** supplies the medial aspects of the frontal and parietal lobes of the cerebral hemispheres. However, branches of **a. cerebri media** provide most of the arterial blood supply for the primary motor cortex. a. cerebri anterior does however supply the medial aspects (legs) of the primary motor cortex

- **a. cerebelli posterior inferior –** supplies medial part of the cerebellar hemisphere, inferior vermis and inferior cerebellar surface. It also supplies medulla oblongata, the choroid plexus of the fourth ventricle and the dentate nucleus. Anastomoses with anterior inferior and superior cerebellar arteries.
- **a. cerebelli anterior inferior –** supplies the anterior inferior surface of cerebellum, the flocculus, the middle cerebellar peduncle, the inferior portion of the pons and the inner ear.
- **A. cerebelli superior** – supplies the superior surface of the cerebellum and parts of the midbrain. It also gives of branches to the pineal body, anterior medullary velum and to the tela choroidea of the third ventricle.
- **A. cerebri anterior –** supplies medial aspects of frontal and parietal lobes of cerebral hemispheres. Some of it branches supplies areas of the motor and somatosensory

cortices, orbital gyrus, gyrus rectus, cingulate gyrus, fornix, corpus callosum, septum pellucidum, the putamen, head of the caudate nucleus and internal capsule.

- **A. cerebri media** - supplies blood to the the motor and somatosensory cortex, auditory area of the cerebral cortex and insula and the subcortical structures. More exactly inferior frontal gyrus and the lateral orbital surface of the frontal lobe, precentral, middle and inferior frontal gyri. It also supplies supply the postcentral gyrus, inferior parietal lobule, and lower part of the superior parietal lobule as well as the lentiform complex, internal capsule, and caudate nucleus.
- **A. cerebri posterior –** supplies the occipital, temporal lobes and visual areas of the cerebral cortex, and also several subcortical structures. To be more exact it supply the uncus, parahippocampal, medial and lateral occipitotemporal gyri. the cuneus, lingual gyrus, and posterolateral surface of the occipital lobe. It also supplies the cuneus and precuneus, the anterior thalamus, subthalamus, lateral wall of the third ventricle, and globus pallidus, lateral geniculate body, choroid plexuses of the third, lateral ventricles, and the fornix. As well as the peduncle and the posterior thalamus, superior and inferior colliculi of the midbrain, pineal gland, and medial geniculate body.

VENOUS DRAINAGE



The meningeal veins in the dura mater drain to the dural sinuses. There are 10 different dural sinuses.

1. **Sinus sagittalis superior**
2. **Sinus sagittalis inferior**
3. **Sinus rectus** – the sinus sagittalis inferior meets with the great cerebral vein (cisterna quadrigeminalis/cisterna venae cerebri magnae) to form sinus rectus

4. **Sinus transversus** (sinister and dexter) – sinus transversus sin. gets blood from sinus rectus. Sinus transversus dx. gets blood from sinus sagittalis superior.
5. **Sinus sigmoideus (sinister et dexter)** – goes through foramen jugulare and form v. jugularis interna
6. **Sinus petrosal inferior et superior**
7. **Sinus cavernosum**

VENTRICLES, FLUID CIRCULATION

The ventricles are a network of cavities distributed throughout the brain. They are lined with a specialised membrane called **choroid plexus** that are composed of glial cells called **ependymal cells**. The ependymal cells are specialised cells that secrete cerebrospinal fluid, a clear liquid that forms a protective layer around the brain to reduce strain forces from gravity, remove toxins, regulate the extracellular environment of neurons. CSF flows through the ventricles and the brain. The main role of the ventricles is production and distribution of cerebrospinal fluid.

THERE ARE FOUR VENTRICLES:

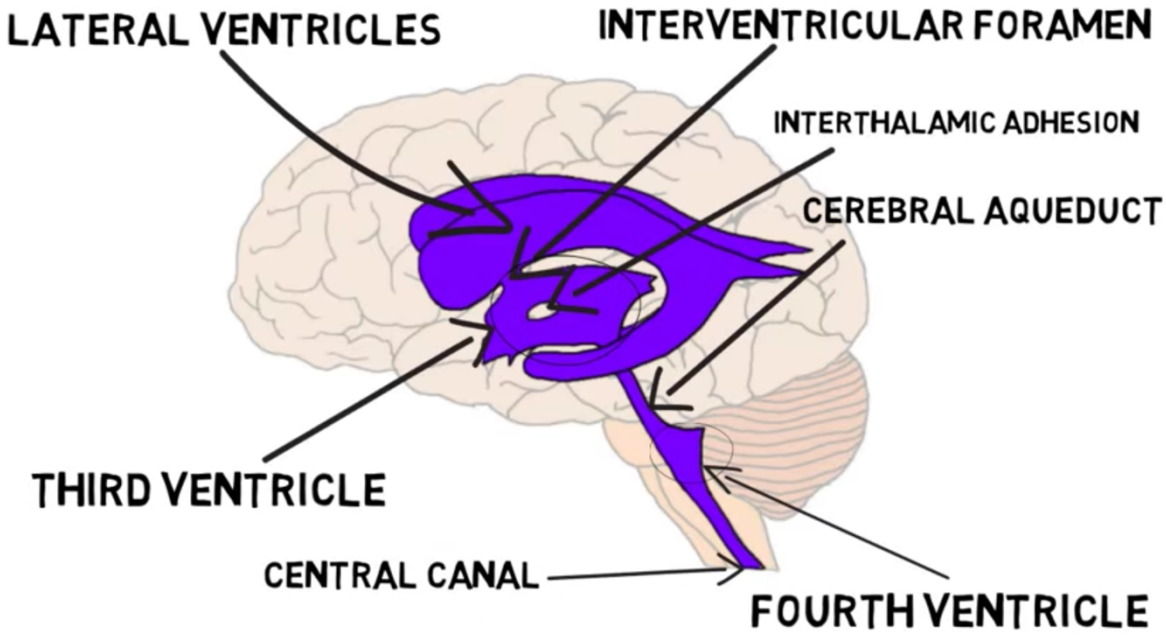
- 2 c-shaped called the **lateral ventricles**, one in each cerebral hemisphere

- **3rd ventricle**, a narrow cavity that runs along the midline of the diencephalon. It looks a bit like a misshaped donut and the hole is the **interthalamic adhesion** where the thalamus makes up the wall.

- The **4th ventricle** are wedged between the cerebellum and the brainstem and it looks like a tent with its peak to the cerebellum. The 4th ventricle has 3 openings to allow CSF to enter the **subarachnoid space** (a CSF containing cavity that surrounds the brain). The 4th ventricle also extends to and is continuous with the **central canal** (a CSF filled cavity that runs the length of the spinal cord).

- The **lateral ventricles** are connected to the **3rd ventricle** via the **interventricular foramen.**

- The 3rd ventricle are connected to the 4th ventricle via the **cerebral aqueduct**.



As mentioned above is the CSF produced in choroid plexus that covers the floor of the lateral ventricle and the roof of the 3rd ventricle. The flow of the CSF is as follows:

The choroid plexus → body and tail of the lateral ventricle → 3rd ventricle via the interventriculare foramen → 4th ventricle via the cerebral aqueduct

Exiting the 4th ventricle via the medial and lateral apertures

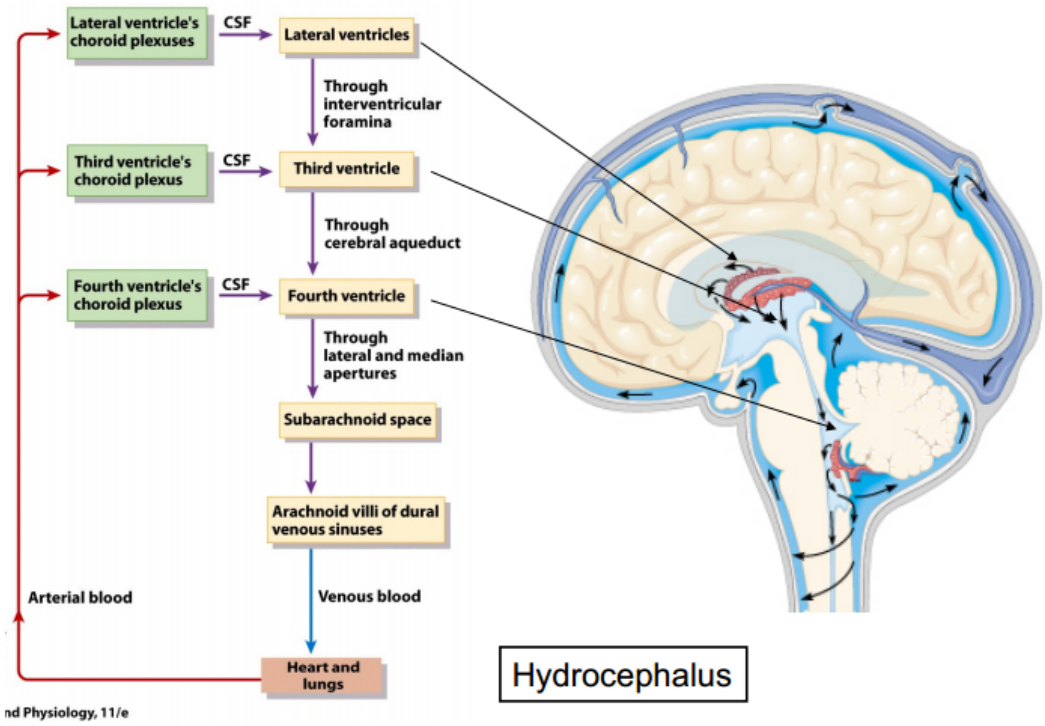
Lateral apertures: CSF that exist via the lateral apertures flows to the **pontine cistern** (the ventral surface of the brainstem).

Medial aperture: CSF that exist via the medial apertures enters the **cerebello-medullary cistern** where it can follow one of the following two paths.

1. Flow around the cerebellum draining into the **superior cistern** → then it flows to the **interpeduncular cistern**.
2. Flow down the **subdural space** around the spinal cord to the **lumbar cistern** (this is where fluid is taken from in a lumbar puncture) → flows back up the spinal cord and joins the flows from the 4th ventricle and **superior cistern**.

From the ventral cisterns CSF flows across the cortical surfaces in the subarachnoid space draining into the **superior sagittal sinus** via the **arachnoid granulations**. It then flows down the posterior surface towards the **confluence of sinuses** where it joins the venous blood flow from the subcortical regions via the **straight sinus**.

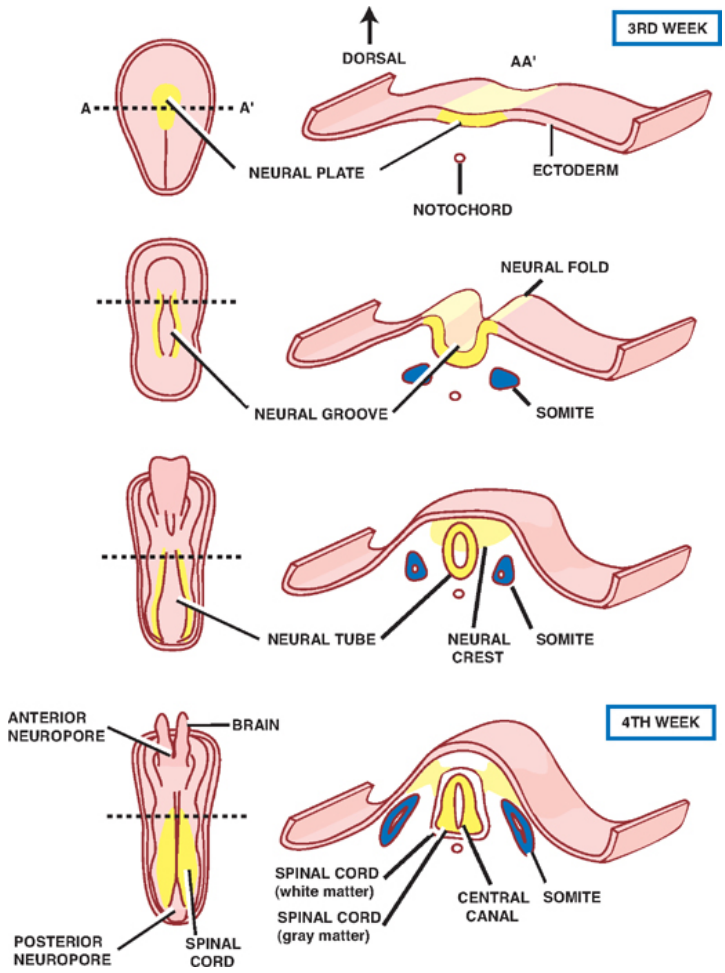
Pathway of CSF flow



Hydrocephalus

DESCRIBE THE DEVELOPMENT OF THE NERVOUS SYSTEM FROM ECTODERM TO MATURE NERVOUS SYSTEM (S2, S3)

The development of the nervous system mainly consists of gastrulation and neurulation. During gastrulation three layers consisting of endoderm (lungs and GI tract), mesoderm (muscles, skeleton and urogenital organs) and ectoderm (nervous system and skin) are formed. The mesoderm is also responsible for forming the notochord which will secrete signal substances to the overlying ectoderm. These signal substances induce the formation of the nervous system by making the cells in the ectoderm affected by these signal substances become a neuroectoderm also called a neural plate which contain precursors to nerve cells and glial cells.



At day 18 neurulation begins, which means that the neural plate begins to fold to form a neural groove. The cells that exist most dorsally in this groove (at the neural fold) are called neural crest cells which will later migrate away around day 20 to form the peripheral nervous system with sensory and autonomic ganglia, adrenal gland and other nonneural cells such as melanocytes.

The groove closes from the middle and out to both ends to form the neural tube which finishes around day 24. The neural tube then forms the CNS, the anterior part forms the brain and the caudal part the spinal cord. The formation of the neural tube also leads to the formation of a floor and roof plate, these both have the same function as the notochord which is to secrete signal substances. When the neural tube has finished closing somites have formed the mesoderm which will later form vertebrae and axial musculature. Inability to close the neural tube leads to spina bifida if it occurs caudally or anencephaly if rostrally.

The structures responsible for forming the signal substances that induce cell and tissue differentiation: primitive knot, notochord, floor plate, roof plate, neuroectoderm and somites.

Some substances used by these are:

RESINOIC ACID

A vitamin A derivate which is a steroid hormone that binds to transcription factors intracellularly. Ensures the formation of the neural tube and creates the ventrodorsal body axis. Can at too high doses result in deformations.

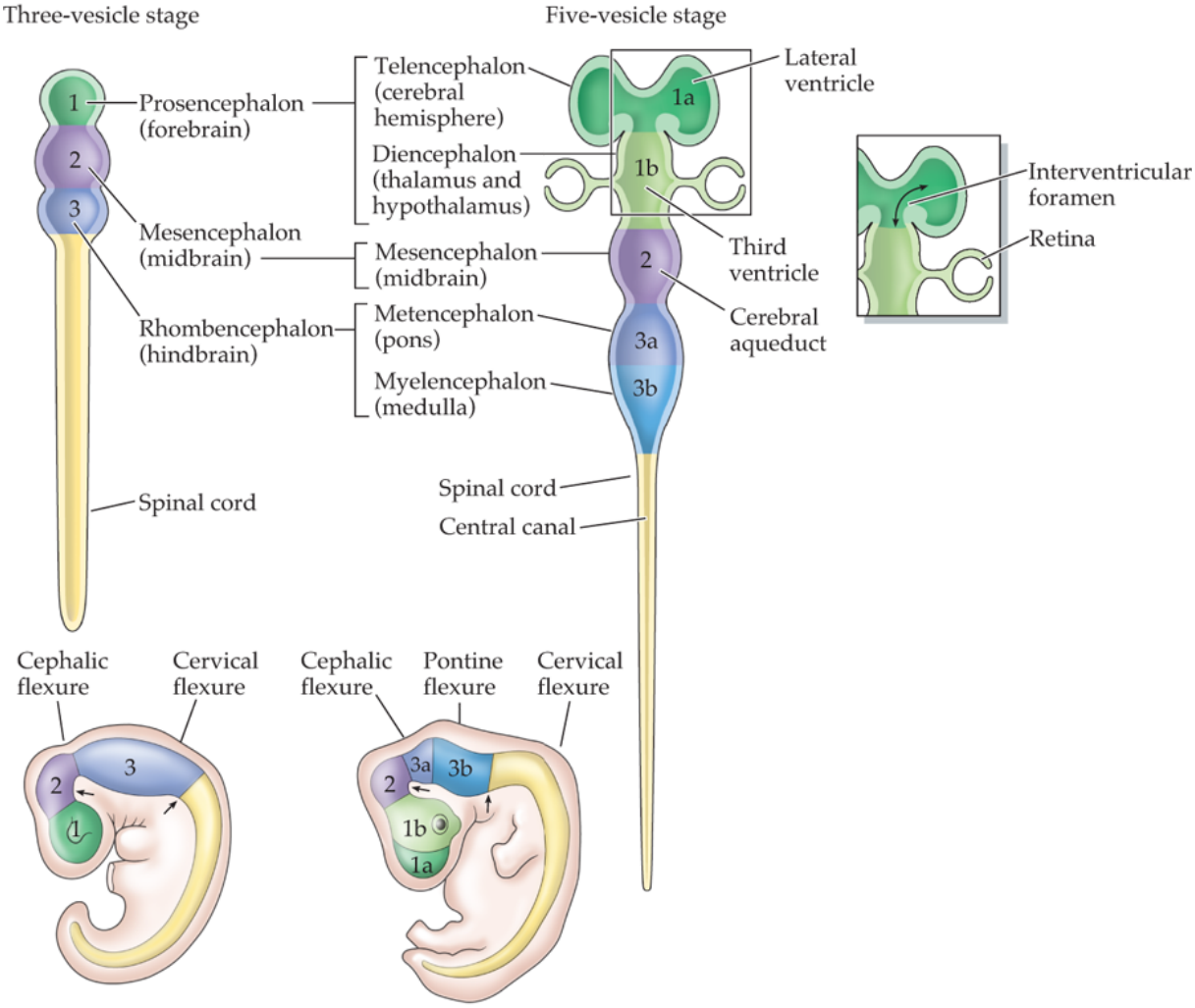
FIBROBLAST GROWTH FACTOR AND BONE MORPHOGENETIC PROTEIN

These are peptide hormones that bind to membrane receptors which regulate gene expression through phosphorylation. BMP is responsible for creating epidermal cells where needed. Other cells are also exposed to BMP but there are antagonists to BMP (called noggin and chordin) which are released to cells that shouldn't form neuroectodermal cells and therefor remain as precursors for the nervous system.

SONIC HEDGEHOG AND WNT

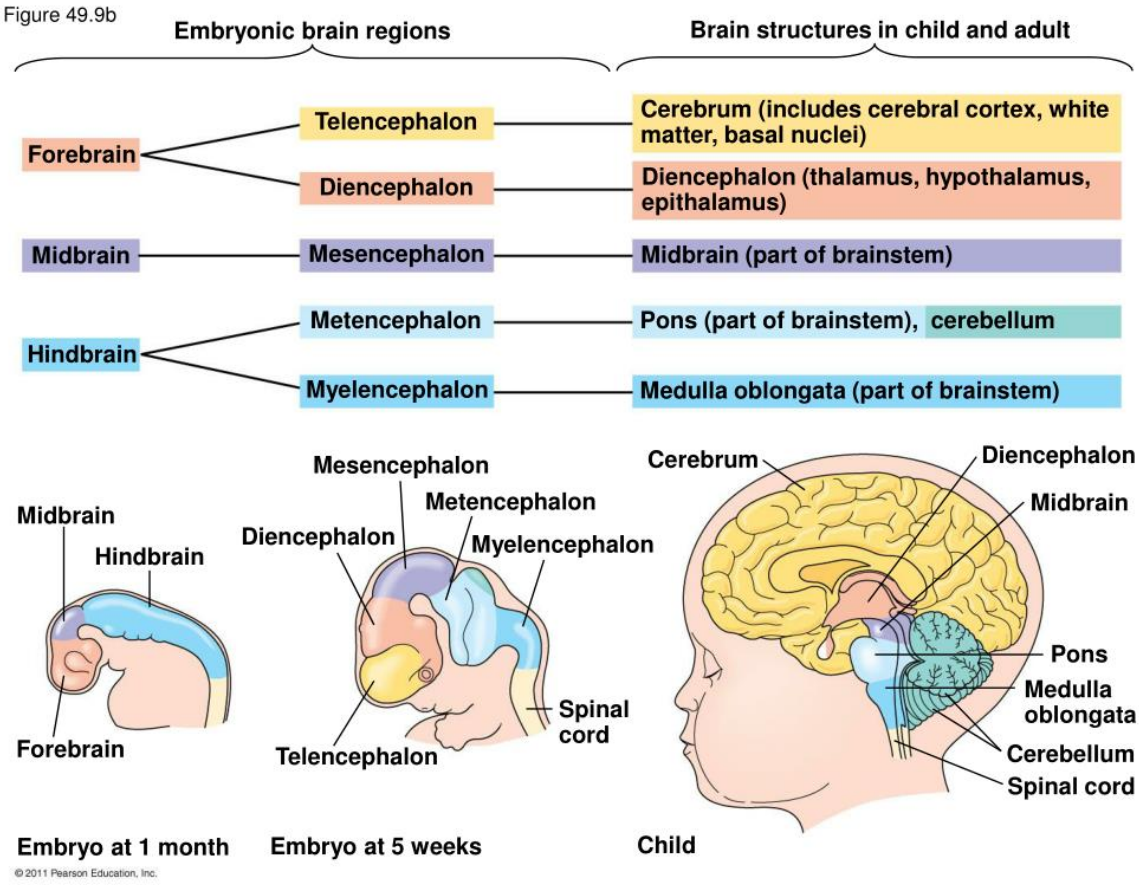
Peptides that bind to membrane receptors. Sonic hedgehog amongst other things differentiate motor neurons and are released from the floor plate and notochord.

VESICLE STAGE



Four weeks after conception three vesicles are formed rostrally on the neural tube and starts bending ventrally: prosencephalon, mesencephalon and rhombencephalon.

At week five the prosencephalon will then divide into the telencephalon and diencephalon while the rhombencephalon will divide into the metencephalon and myelencephalon (medulla oblongata). Meaning there is a total of five vesicles. When the vesicles are formed a major folding occurs and this makes the lumen of the neural tube enlarge to form the brains four ventricles. At the end of the second trimester the brain is basically fully formed.



Through segmental division of the neural tube (neuromeres and rhombomeres) and hox genes complicated structures like the brain can form. Different hox genes are expressed at different sites to form the different part of the brain and spinal cord.

Once the neural tube has developed into a rudimentary brain and spinal cord the differentiation of neuron and glial cells can begin. The adult brain has about 100 billion neuron and up to ten times as many glial cells which all are generated during a few months from a small population of precursor cells. Precursor cells are located in the ventricular zone which is the innermost layer that surrounds the lumen of the neural tube. Around 250 000 new neurons are generated every minute during the fastest development time. The precursor cells can divide symmetrically to form new stemcells or asymmetrically to form specialized cells. Signal cells then decide whether or not they form neurons or glial cells.

NEURAL MIGRATION IN THE CNS

Cells that are meant to migrate to outer part of the CNS are thought to have to move past the inner layers. It is believed that this occurs by the neurons “hitching” a ride on the radial glia which are cells that create pathways for the traveling cells to adhere to so that they can reach their destination.

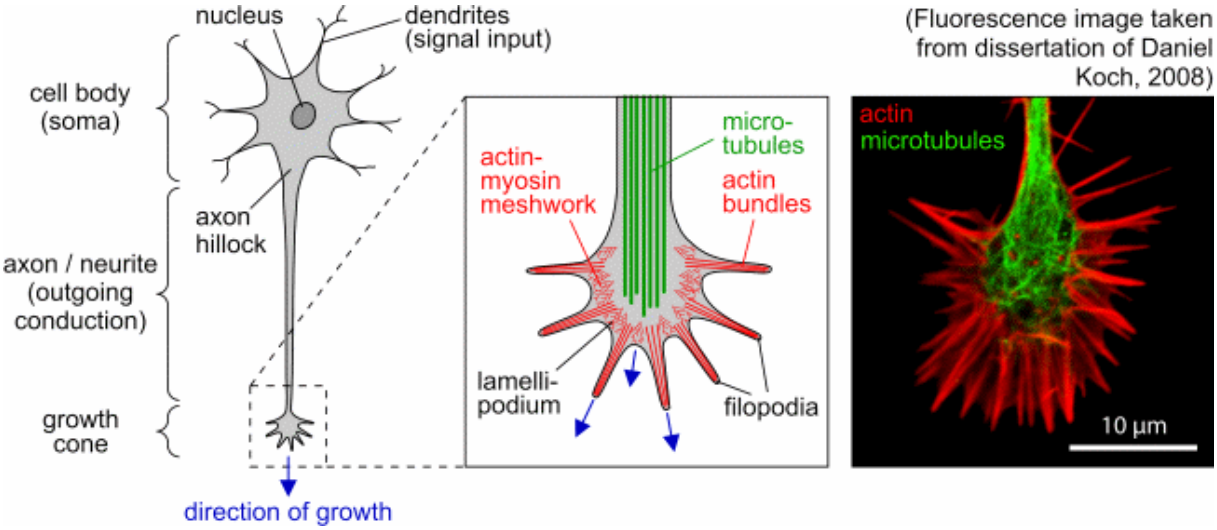
NEURAL MIGRATION IN THE PNS

Neural crest cells are guided through clear migration pathways by signal substances. During their travel they become more differentiated and mesenchymal due to the action of nearby cells and the substances they form.

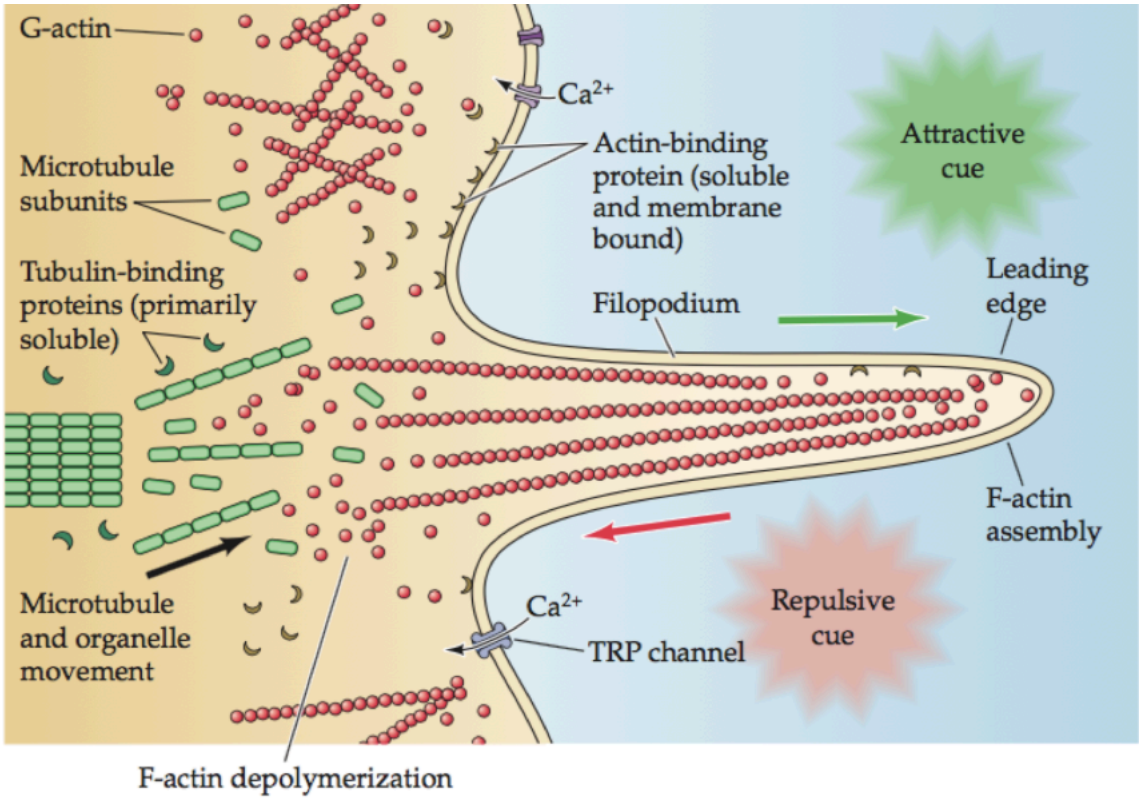
DESCRIBE THE PRINCIPLES THAT CONTROL AXON GROWTH AND THE SYNAPSE FORMATION (S2, S3)

Once the migration and aggregation of the premature neurons are done the axons and dendrites begin to grow. For the nervous system to work properly they must grow to appropriate targets. There’s a hypothesis called the **chemo affinity hypothesis** that states that postsynaptic targets release a chemical that guides the axonal growth, this means that the **growth cones** (more about them below) aren’t attracted by their target. They are instead influenced by a series of **chemical signals** along the route.

Growth cones are the tip of of each projection (axon or dendrite) that are growing. The Growth cone consists of both actin and microtubule. The growth cone’s protruding part are called filopodia, they consist of actin. The base between the filopodia that contains the actin-myosin meshwork is called lamellipodium.



The movement of the growth cone is dependent on the polymerisation and depolymerisation of actin. the filopodia sticks out with and can move because of the actin, the microtubules stabilise the movement by stabilising the axon shaft. The process is regulated by , levels stimulates the polymerisation.



Cue's – An axon can change its direction because of different cue's, some that repel and some that attract the axon.

Pioneer growth cones – the first to travel a route, interact with guidance molecules

Fasciculation – the tendency of developing axons to grow along the paths established by preceding axons.

NGF – nerve growth factor increases the growth/development of neurons. Growth factors (neutrophin factors) helps with maturation and attraction of axons.

CNS – axons can't regrow in the CNS because it lacks ECM (extra cellular matric) and glia cells release factors that inhibit axon growth. Damaged neurons in CNS release glutamate causing neuron cells to die.

PNS – in the PNS there are Schwann cells that synthesises ECM, the ECM in turn created trophic molecules that enables axon growth. (the trophic molecules guide axons to the right place by acting as cue's)

Once axons have reached their intended sites, they establish an appropriate pattern of synapses, the creation of synapses in contrast to the creation of axons has to be done by a coordinated activity in at least two neurons. The formation of new synapses is called **synaptogenesis** and depends on the presence of glial cells especially astrocytes and a chemical signal exchange between pre- and postsynaptic neurons.

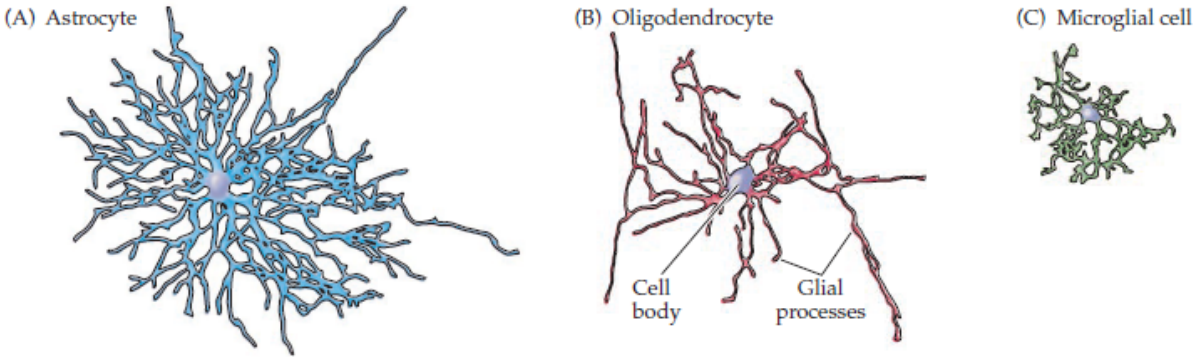
Synapses can be formed between:
Axon and soma → **axosomatic**

Axon and dendrite → **axodendritic**, there are different types; excitatory synapse = axon sends out an outgrowth to a dendrite or a dendrite sends out an outgrowth to a dendrite and inhibitory synapse = axon and dendrite can have direct contact
Axon and axon → **axoaxonic**
Axon and muscle → **neuromuscular**

About 50% more neurons than are needed are produced during development. Motoneuron's "fight" about who is to keep living, the one that reaches a muscle first wins the rest dies since their supply of growth factor is lower than the ones that bind. So, neurons that fail to establish correct connections are particularly likely to go in to apoptosis, the space that they leave is filled by sprouting axon terminals of surviving neurons. This leads to increased selectivity of transmission and improves efficiency.

CELLULAR NEUROBIOLOGY:

DESCRIBE THE FUNCTION AND IMPORTANCE OF GLIAL CELLS (S2)



Glial cells, which consist of microglia, astrocytes, ependymal cells and oligodendrocytes, constitute a large fraction of the brain. Being non-neuronal cells, they were originally considered to be a non-functional glue for neurons (hence the name glial cells, glia being the Greek word for glue), but research has since discovered the importance as well as several functions of glial cells.

ASTROCYTES

Astrocytes are restricted to the central nervous system (brain and spinal cord) and have elaborate local processes that give these cells a star like (”astral”) appearance. A major function for astrocytes is to maintain an appropriate chemical environment for neuronal signaling including the formation of the blood-brain barrier. Recent observations also suggest that astrocytes secrete substances that influence the formation of new synaptic connections and that a subset of astrocytes in the adult brain retain the characteristics of stem cells.

OLIGODENDROCYTES

Oligodendrocytes, which are also restricted to the CNS, lays down a myelin sheath (laminated, lipid-rich wrapping) around some, but not all, axons. Myelin has important effects on the transmission speeds of electrical signals. In the PNS (peripheral nervous system) the cells that provide myelin are called Schwann cells. Both oligodendrocytes and Schwann cells can retain neural stem cell properties in the mature nervous system.

MICROGLIAL CELLS

Microglial cells are primarily derived from hematopoietic precursor cells. They share many properties with macrophages found in other tissues in that they’re primarily scavenger cells that remove cellular debris from sites of injury and normal cell turnover. Like macrophages they also secrete signalling molecules, especially a wide range of cytokines that can modulate local inflammation and influence whether other cells live or die. Following brain damage the number of microglia increases dramatically.

EPENDYMAL CELLS

The ependyma is a thin neuroepithelial lining of the ventricular system of the brain and the central canal of the spinal cord. It is involved in the production of cerebrospinal fluid and is shown to serve as a reservoir for neuroregeneration.

DESCRIBE AND EXPLAIN THE PASSIVE PROPERTIES OF NERVE CELLS AND UNDERSTAND HOW THEY AFFECT INCOMING SIGNALS (S3, S4)

Nerve cells generate a variety of electrical signals that transmit and store information. However, they are not good conductors of electricity but have elaborate mechanism that help to generate electrical signals based on the flow of ions across their plasma membrane.

Nerve cells have in their status quo a negative potential that a generated due to the differences between the outside (ECM) and the inside of the cell (ICM), this is called resting potential. Electrical signals produced by neurons are caused by responses to stimuli, which then change the resting membrane potential. There are different types of potentials:

- **Receptor potentials** – sensory neuron reacts to external stimuli
- **Synaptic potentials** – communication between neurons at a synaptic contact
- **Action potentials** – electrical signal sent along the axon that creates “spikes” or “impulses”. A type of long-range transmission of information within the nervous system.

Action potential is generated when the potential makes the transmembrane potential positive. The potential is propagated along the axon, there is another type of electrical signal that are produced by activation of activation of synaptic contacts. All signals arise from ion fluxes brought about selective permeability of nerve cells membrane to different ion and the distribution of these ions across the membrane.

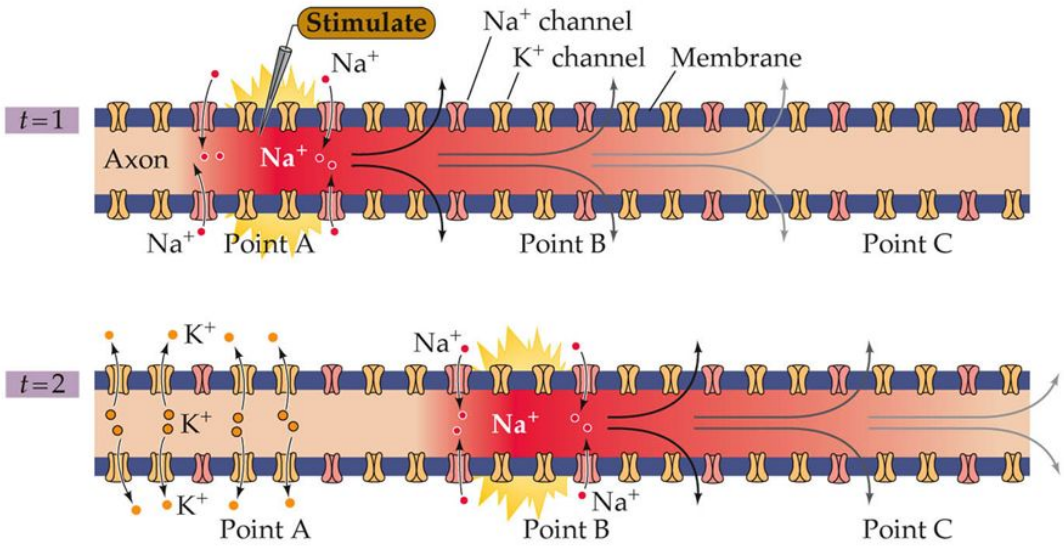
Axons are long and as said before bad conductors. However, they can passively conduct electricity. The signal gets weaker with the distant of the axon (difference is seen with just a couple of mM) due to that ions that leaks out across the axonal membrane. Ju further along the lower the current. The leakiness prevents effective passive conduction of electrical signals in all but the shortest axons.

If a subthreshold current is generated (injected in case of an experiment) it will spread along the axon until the current is gone due to the leakage out across the axonal membrane. As a result of the leakage if the potential is measured along the length of the axon it will get smaller with the distance from the point of generation. Depending on how leaky an axonal membrane is the passive current will go a shorter or longer length.

The passive flow of electrical current is important in the propagation of action potential, synaptic transmission and all other form of electrical signalling in nerve cells. A passive response is a response that are below threshold or more negative than the resting membrane potential. If it goes under the resting membrane protentional it's referred to as hyperpolarisation (passive electrical response).

But what are the difference between passive and active potentials?
ACTIVE POTENTIAL: If a stimulation is generated along the axon channels will open locally as a response to the stimuli and an action potential will be generated and flow upstream. Along the upstream part of the axon the potential will be large enough to open channels and more will flow in and keep the potential strong.

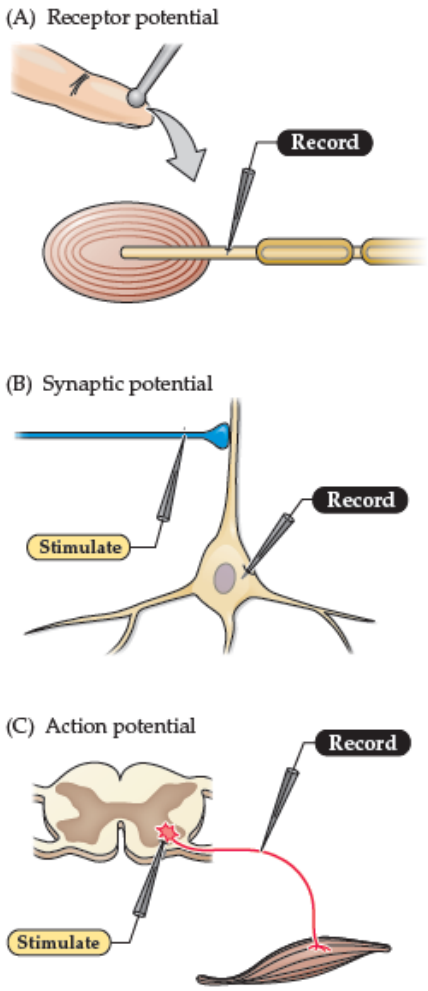
PASSIVE POTENTIAL: Downstream however, some depolarising current will flow passively, so there will be some of the potential going downstream but it won't be strong enough to generate the opening of channels. Therefore the potential will passively flow down and get lower and lower until it disappears due to the leakiness of the axonal membrane.



NEUROSCIENCE, Third Edition, Figure 3.12 (Part 1) © 2004 Sinauer Associates, Inc.

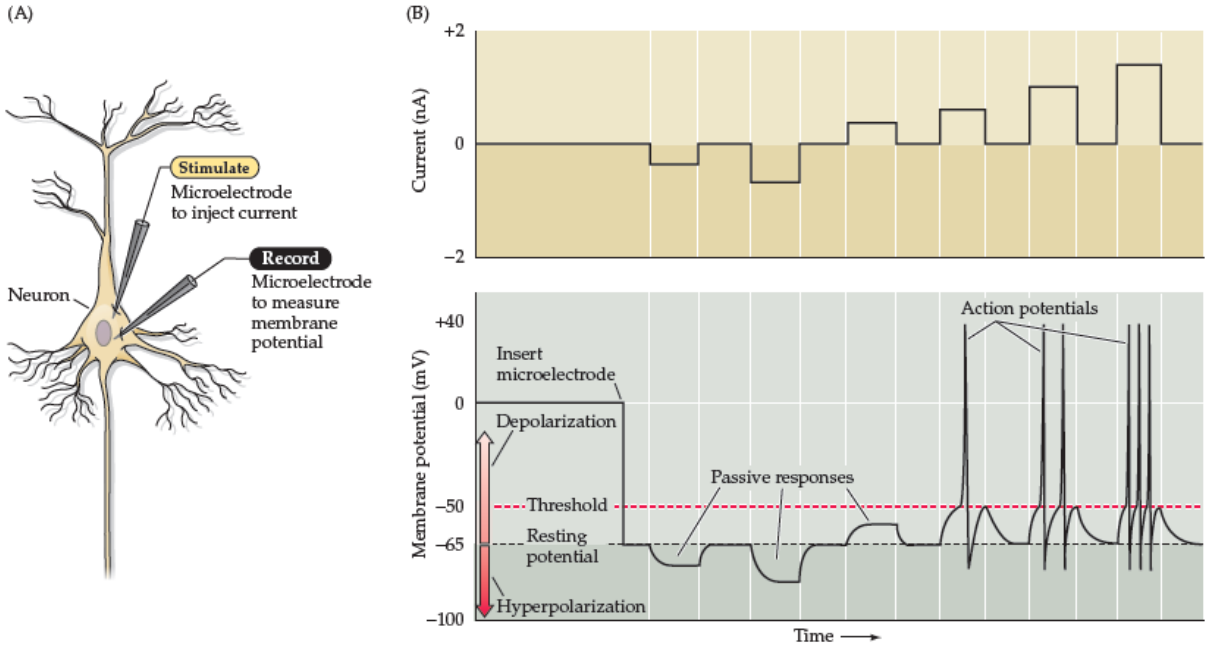
DESCRIBE THE ACTIVE PROPERTIES OF NERVE CELLS AND THE MOST IMPORTANT FUNCTION OF ION CHANNELS (S3, S4)

Nerve cells generate a variety of electrical signals that transmit and store information. Although neurons are not good conductors of electricity, they have elaborate mechanisms that generate electrical signals based on the flow of ions across their plasma membrane. Ordinarily neurons generate a negative potential called the resting membrane potential (depends on the neuron but is typically -40 to -90 mV). The action potential is a fundamental electrical signal that transiently abolishes the negative resting potential and makes the transmembrane potential positive.



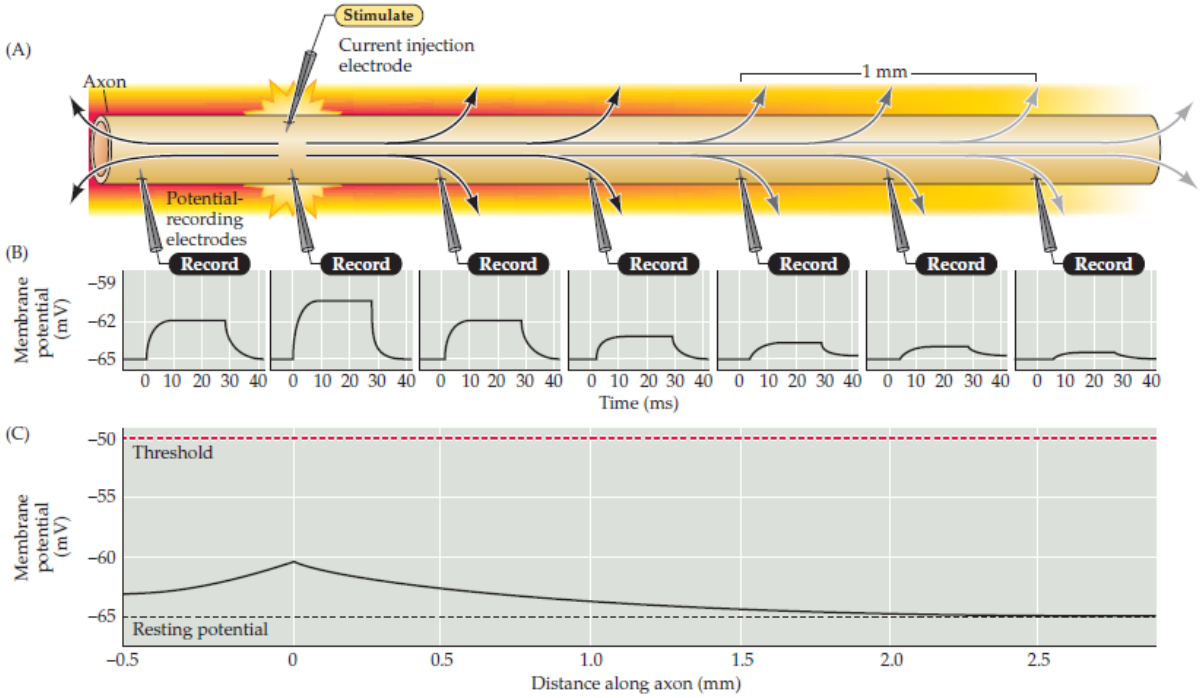
Neuronal electrical signals can be due to receptor potentials (sensory neurons activated by external stimuli such as light, sound, touch or heat for example), synaptic potentials (allows for transmission from one neuron to another) and action potentials (electrical signal that travel along the neurons long axons).

Depolarization occurs when the membrane potential is more positive than its resting membrane potential, if the depolarization is high enough to reach the threshold potential of the neuron this will in turn trigger an action potential. The action potential is an active response generated by the neuron and is typically brief (about 1 ms) change from negative to positive in the transmembrane potential. Action potentials are considered active responses because they are generated by selective changes in the permeability of the neuronal membrane. Important to note is that the amplitude of the action is independent of the magnitude of the current used to evoke it; that is, larger currents do not elicit larger action potentials. The action potential of a given neuron are therefore said to be all-or-none, that is they occur fully or not at all. If the amplitude or duration of the stimulus current is increased sufficiently, multiple action potentials occur (as can be seen on the imagine on the next page). It follows, then, that the intensity of a stimulus is encoded in the frequency of action potentials rather than in their amplitude. This differs from receptor potentials whose amplitude are graded in proportion to the magnitude of the sensory stimulus; and from that of synaptic potentials, whose amplitude vary according to the synapses activated, the strength of each synapse and the previous amount of synaptic activity.

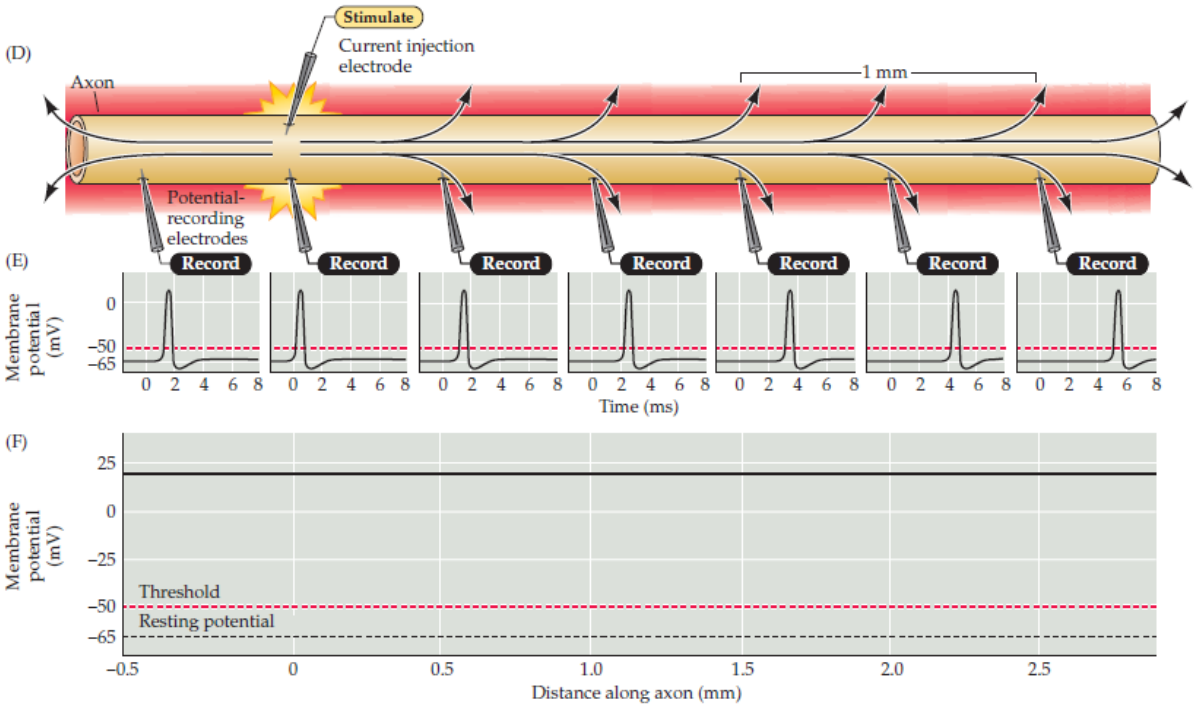


As mentioned in the beginning is that the neurons axons, which can be quite long, are not good electrical conductors. This can be seen when measuring the passive electrical properties of a nerve cell axon, if the current is below the threshold for generating an action potential, then the magnitude of the resulting potential change will decay with increasing distance of no more than a few millimetres away from the site of injection. Typically, the potential falls to a small fraction of its initial value at a distance of no more than a few millimetres away from the site of injection. For comparison, a wire would typically allow passive current flow over distances many thousands of times longer. The progressive decrease in the amplitude of the induced potential change occurs because the injected current leaks out across the axonal membrane. This leakiness of the axonal membrane prevents effective passive conduction of electrical signals along the length of all but the shortest axons (those 1mm or less).

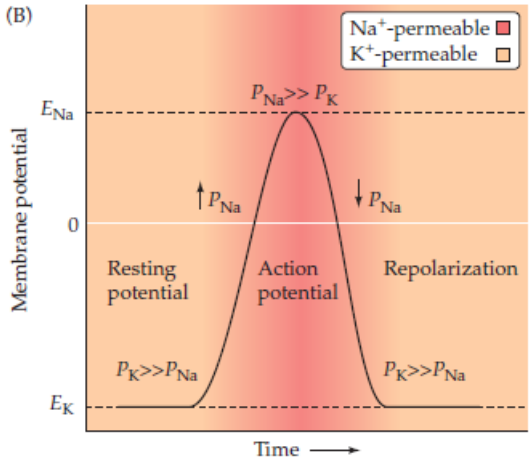
PASSIVE CONDUCTION DECAYS OVER DISTANCE



ACTIVE CONDUCTION IS CONSTANT OVER DISTANCE



To compensate for this deficiency, action potentials serve as a “booster system” that allows neurons to conduct electrical signals over great distances despite the poor passive electrical properties of axons. If a depolarizing current pulse is large enough to produce an action potential a constant amplitude is observed along the entire length of the axon. The fact that electric signals now occur without any decrement indicates that active conduction via action potentials is a very effective way to circumvent the inherent leakiness of neurons.



All type of neuronal electrical signalling is produced by similar mechanisms that rely on the movement of ions across the neuronal membrane. An ion concentration gradient is established by active transporters that transport ions in or out of the cell against their concentration gradient (the selective permeability of the membranes is largely due to ion channels). These ion transporters lead to there being more K^+ inside the neuron than out, and much more Na^+ outside than in which results in a resting membrane potential of about -70mV. There are also voltage gated ion channels embedded in the neuron’s plasma membrane. If the neuron reaches threshold value voltage gated sodium channels will open which allows Na^+ to flow into the cell, the local depolarization will cause neighbouring sodium channels to open and the action potential will travel down the axon. The rapid influx of Na^+ causes the polarity of the plasma membrane to reverse which causes the voltage gated sodium channels to become inactivated. Potassium channels are then activated which causes and outward current of which returns the electrochemical gradient to its resting state. Since sodium can no longer enter the neuron, they are actively transported back out of the plasma membrane.

After an action potential has occurred there is a transient negative shift, called the afterhyperpolarization, which is due to the potassium channels being slow to open and slow to close.

The importance of ion channels, therefore, is to create and maintain an ion concentration gradient between the neuron and extracellular space, allow for an action potentials to be able to occur and travel along the entire axon as well as restoring the ion concentration after so that action potentials can occur again.

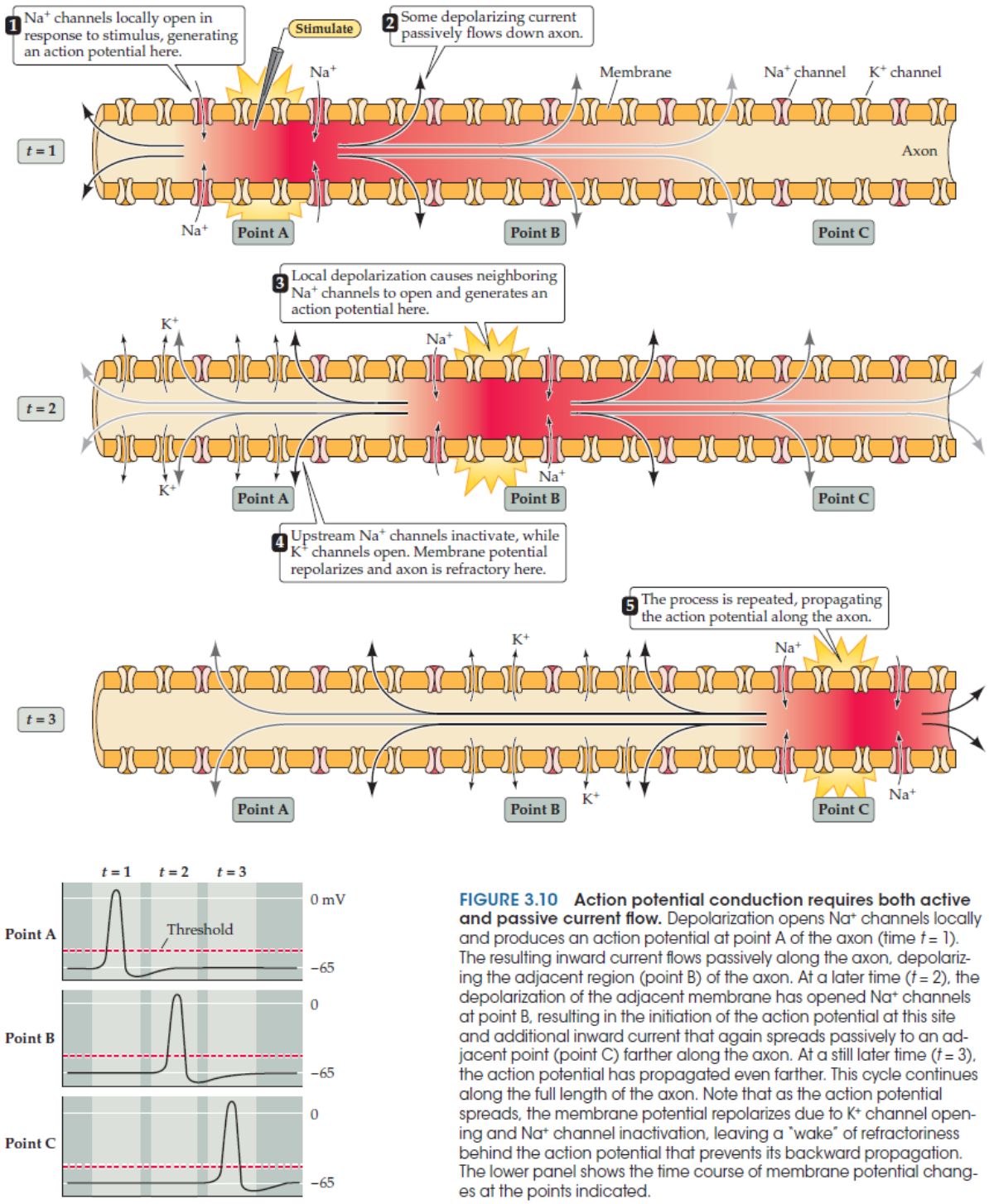


FIGURE 3.10 Action potential conduction requires both active and passive current flow. Depolarization opens Na^+ channels locally and produces an action potential at point A of the axon (time $t = 1$). The resulting inward current flows passively along the axon, depolarizing the adjacent region (point B) of the axon. At a later time ($t = 2$), the depolarization of the adjacent membrane has opened Na^+ channels at point B, resulting in the initiation of the action potential at this site and additional inward current that again spreads passively to an adjacent point (point C) farther along the axon. At a still later time ($t = 3$), the action potential has propagated even farther. This cycle continues along the full length of the axon. Note that as the action potential spreads, the membrane potential repolarizes due to K^+ channel opening and Na^+ channel inactivation, leaving a "wake" of refractoriness behind the action potential that prevents its backward propagation. The lower panel shows the time course of membrane potential changes at the points indicated.

DESCRIBE THE PRESYNAPTIC MECHANISM FOR TRANSMITTER RELEASE AT THE MOLECULAR LEVEL AND THE MAIN CLASSES OF TRANSMITTERS (S3, S4)

There are three criteria for neurotransmitters:

- They need to be accumulated in vesicles in the presynaptic terminal
- The substance needs to be released as a response to Ca^{2+} - influx
- When released the substance needs to affect the postsynaptic receptors and trigger a biological response.

There are about 100 identified neurotransmitters at this point. They can be divided in to two main groups:

- Classical neurotransmitters – these are small molecules like acetyl choline, catecholamines, glutamate and GABA
- Neuropeptides – larger molecules, amino chains/protein chains

CLASSICAL NEUROTRANSMITTERS

The classical neurotransmitters are created in the soma and are sent to the pre synapse where they are packed into vesicles. The vesicles already exist and the neurotransmitters trades places with H^+ (neurotransmitter moves into the vesicle, H^+ into the cytoplasm), this is done when H^+ goes with its concentration gradient. The concentration gradient is established by a pump that pumps H^+ into the vesicle from the cytoplasm, this pump uses ATP. Studies show that there are specific exchangers for the different classic neurotransmitters.

A signal caused by Ca^{2+} results in the release of neurotransmitters in the presynaptic cleft by exocytosis. When in the presynaptic cleft the neurotransmitters bind to channels on the post synapse. This reaction is fast, the effect of the neurotransmitter depends on:

- How fast the enzymatic inactivation is when the neurotransmitter is released into the synaptic cleft.
- How fast the neurotransmitter releases from the channel/protein it binds to and are transported back to the pre synapse.

The neurotransmitters are, as mentioned above, transported back to the pre synapse and then used again.

NEUROPEPTIDES

Are synthesised by mRNA, translated in the ER and put into vesicles in the Golgi apparatus. The vesicles are transported down the axon to the presynaptic terminal. These vesicles are bigger than the classical neurotransmitters. They are released by signals caused by Ca^{2+}, when used in the synaptic cleft they are degraded.

The classical neurotransmitters are often sent “alone” when there’s a low stimulation, at a stronger stimulation both classical neurotransmitters and neuropeptides are sent.

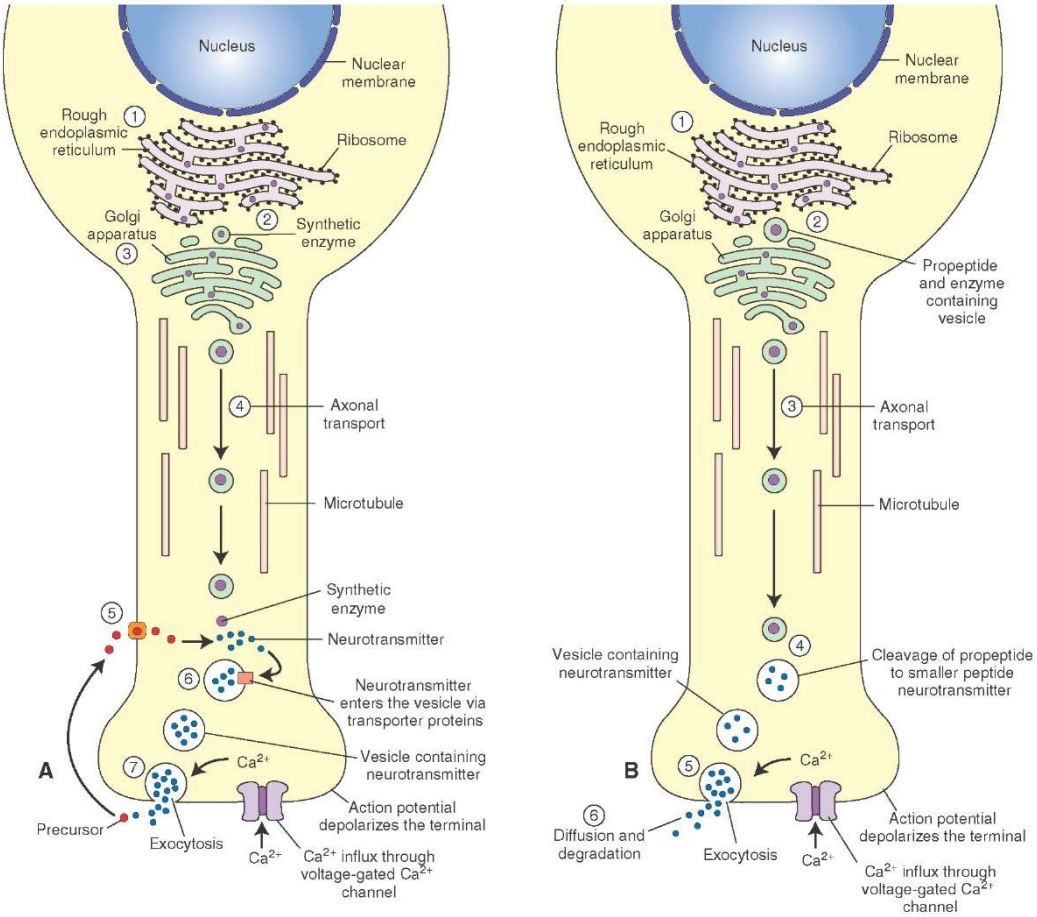
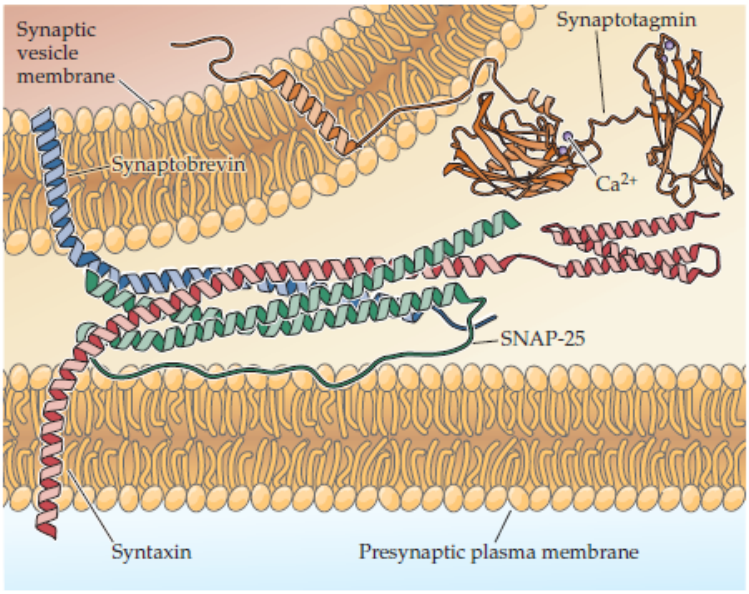
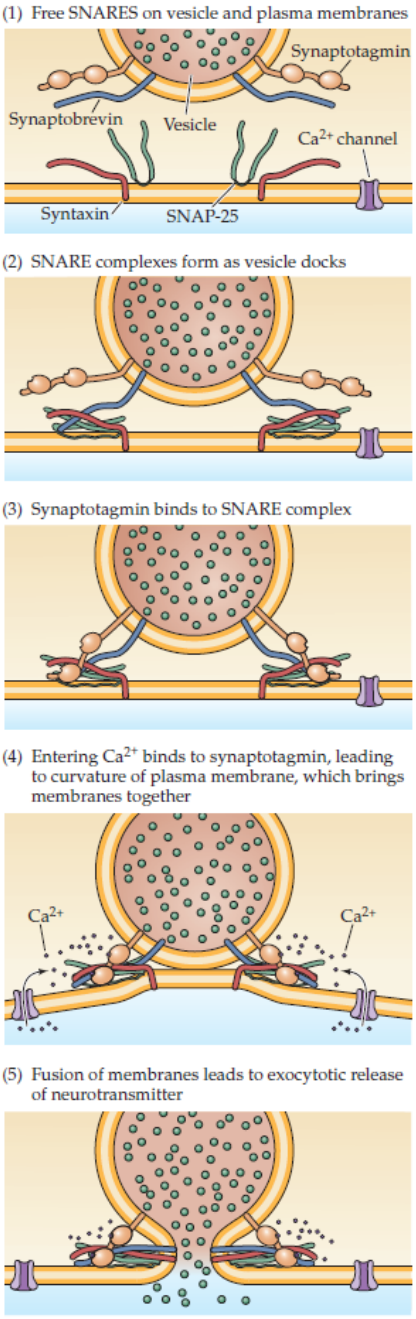


Figure 2: picture to the left shows a small classical neurotransmitters (transported individual). The picture on the right shows a neuropeptide.

THE MOLECULAR MACHINERY THAT MEDIATES FUSION OF SYNAPTIC VESICLES WITH THE PLASMA MEMBRANE

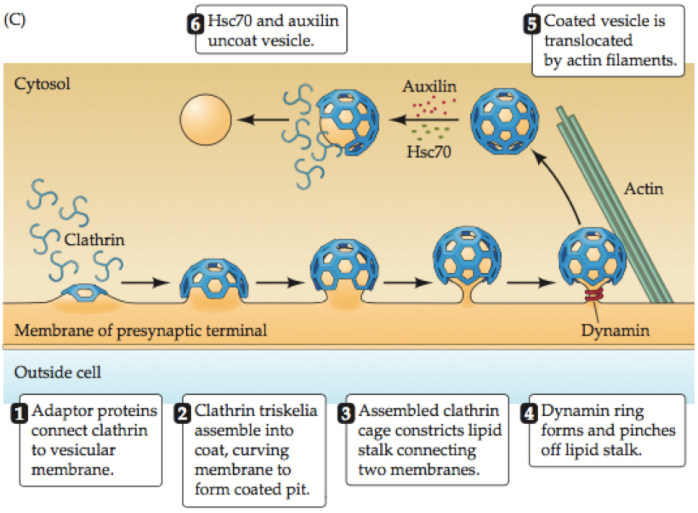




On the synaptic vesicles there are SNARE proteins called synaptobrevin that can form a macromolecular complex with the SNARE proteins syntaxin and SNAP-25 that are primarily found on the plasma membrane. This complex brings the membranes closer together to promote fusion of the membranes.

The SNARE proteins do not bind Ca^{2+} which is used to regulate neurotransmitter release, instead it appears that synaptotagmins on the synaptic vesicles acts as a Ca^{2+} sensor to trigger vesicle fusion. It is thought that Ca^{2+} binding to synaptotagmin leads to exocytosis by changing the chemical properties of synaptotagmin which allows it to insert into the plasma membrane. This causes the plasma membrane to locally curve and leads to fusion of the two membranes.

So, to summarize, SNARE proteins bring the two membranes close together while Ca^{2+} induced changes in synaptotagmin then produces the final curvature that enables rapid fusion of the two membranes.



To endocytose the fused vesicles a protein called clathrin is used to form a cage like coating around the vesicle membrane until it forms a coated vesicle like structure that is connected to the plasma membrane via a narrow lipid stalk (other adaptor proteins are also involved). This stalk is then pinched off with a protein called dynamin.

INACTIVATION OF NEUROTRANSMITTERS

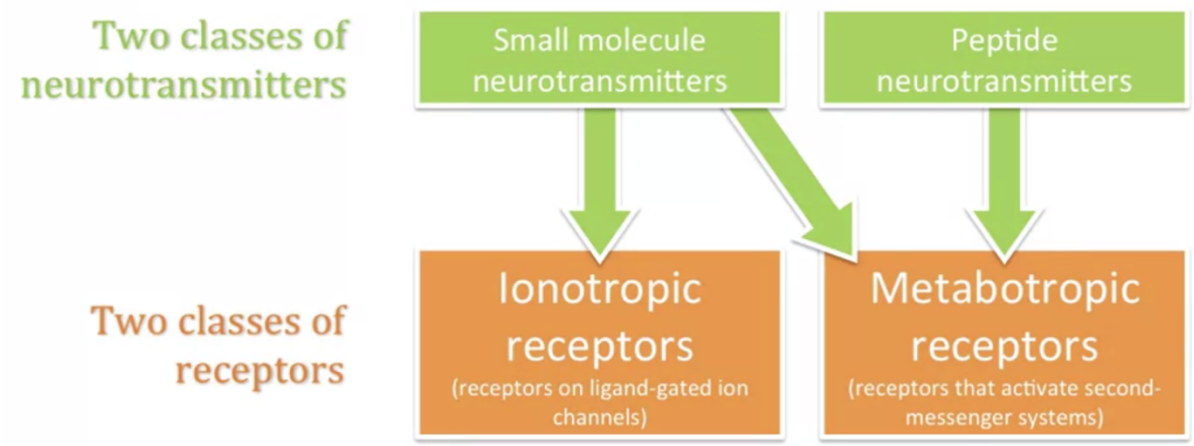
When neurotransmitters have "done it's work" in the postsynaptic cleft it's released back into the synaptic cleft, but they can't just stay there since that would cause constant stimulation of the post-synaptic cell and an excessive firing of action potentials.

There are four different ways of getting rid of the neurotransmitters:

1. **Enzymes:** There are neurotransmitters that can be inactivated by enzymes, this is mainly for acetylcholine which is inactivated by acetylcholinesterase.
2. **Passive diffusion:** Most neuropeptides just defuse away from the cleft to the surroundings and can there be degraded.
3. **Re-uptake pumps:** There are pumps in the presynaptic terminal that pumps neurotransmitters back into the terminal where there are used again.
4. **Astrocytes:** The astrocytes end feet can actively pump neurotransmitters out of the synapse. In the astrocyte it can be broken down, reused in the astrocyte or the astrocyte can transfer it back to the presynaptic terminal where it can be reused.

Example with glutamate:
Glutamate can either be pumped back to the presynaptic terminal via transporters or glutamate can be taken up by astrocytes (glia cells) and there converted to glutamine that is then transported to the presynaptic terminal where glutamine is converted to glutamate via the enzyme glutaminase. Called glutamate cycle.

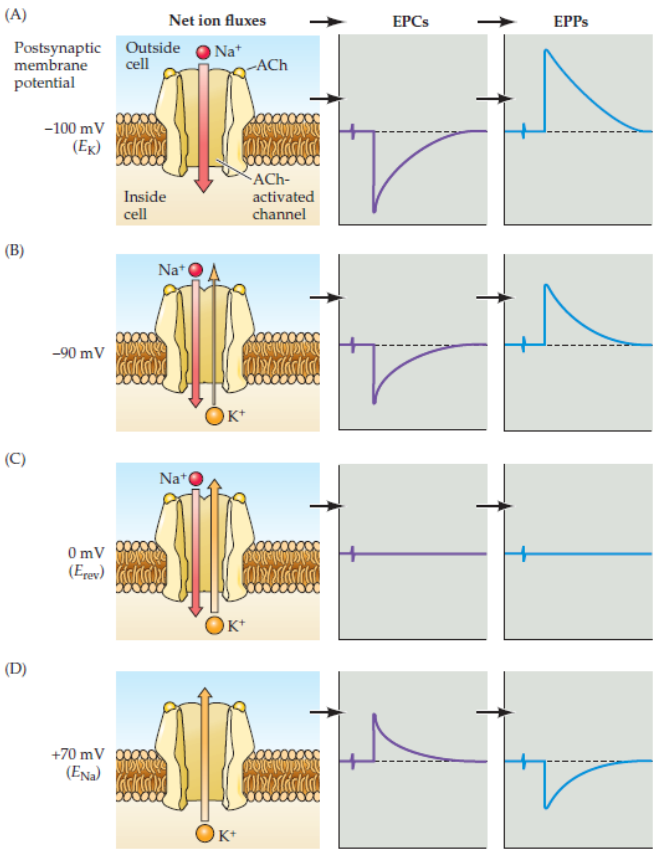
DESCRIBE DIFFERENT TYPES OF POSTSYNAPTIC RECEPTORS AND SIGNAL TRANSDUCTION MECHANISMS (S3, S4)



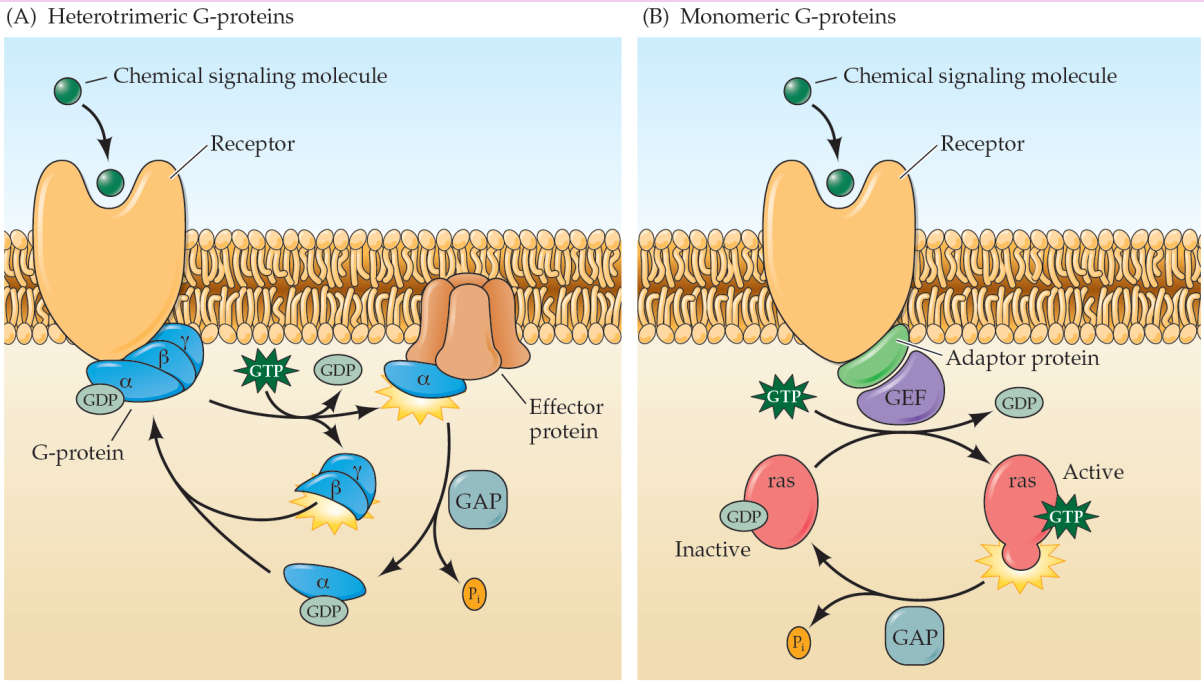
IONOTROPIC RECEPTORS

Ionotropic receptors are ligand gated ion channels, they can only be activated by small molecule neurotransmitters. They are formed by 4-5 subunits that form a pore through the membrane. They can be divided into positive and negative, examples on positive are nicotinacetylcholine receptors and glutamate receptors. Negative are GABA and glycine receptors.

The channels are gated by binding if neurotransmitter to the receptor site. There are a net current that flows through the channel, it depends on the membrane potential and are true for Vm-Erev ≠ 0 (either positive or negative driving force). Depending on the driving force there will be different ions that flow through.



METABOLIC RECEPTORS



Metabotropic receptors are G-protein coupled receptors that can be activated via small molecule neurotransmitters and neuropeptides. There are heteromeric G-proteins as well as monomeric G-proteins. The intercellular second messenger system related to the G-proteins can be quite diverse. The Heterotrimeric G-protein system when activated result in an activation of alfa subunit as well as betagamma subunit. These subunits can mediate a variety of postsynaptic effects by integrating with effector proteins, that could produce second messengers, activate enzymes and phosphorylate target proteins.

The Monomeric G-protein system activate the RAS system that can mediate a variety of postsynaptic effects.

G-protein system can lead to amplification of signals.

THE MAIN TYPES OF POSTSYNAPTIC GLUTAMATE RECEPTOR

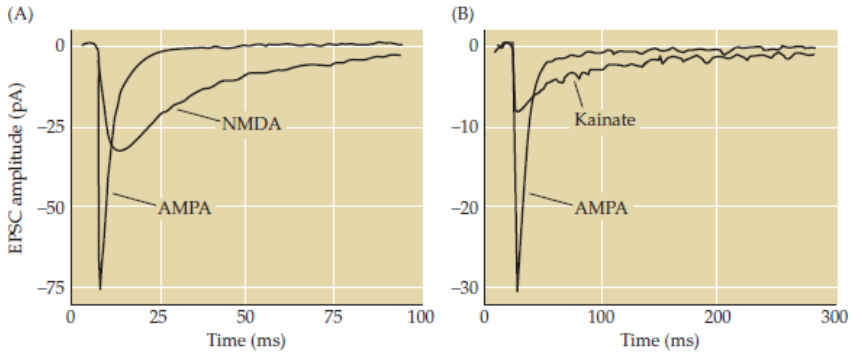
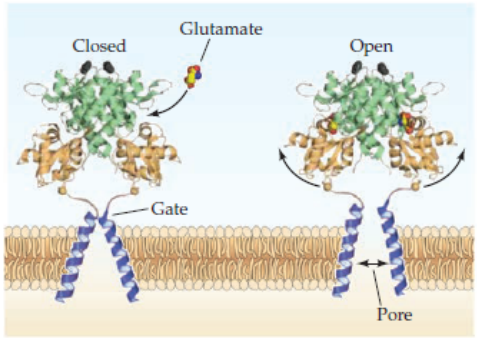


FIGURE 6.6 Postsynaptic responses mediated by ionotropic glutamate receptors. (A) Contributions of AMPA and NMDA receptors to EPSCs at a synapse between a presynaptic pyramidal cell and a postsynaptic interneuron in the visual cortex. Blocking NMDA receptors reveals a large and fast EPSC mediated by AMPA receptors, while blocking AMPA receptors reveals a slower EPSC component mediated by NMDA receptors. (B) Contributions of AMPA and kainate receptors to miniature EPSCs at the excitatory synapse formed between mossy fibers and CA3 pyramidal cells in the hippocampus. Pharmacological antagonists reveal that the component of EPSCs mediated by AMPA receptors is larger and decays faster than that mediated by kainate receptors. (A after Watanabe et al., 2005; B from Mott et al., 2008.)

The main types of postsynaptic glutamate receptors are ligand gated ion channels that are activated by the neurotransmitter glutamate. Glutamate is the most important transmitter for normal brain function. Nearly all excitatory neurons in the CNS are glutamatergic, and it is estimated that more than half of all brain synapses release this neurotransmitter.

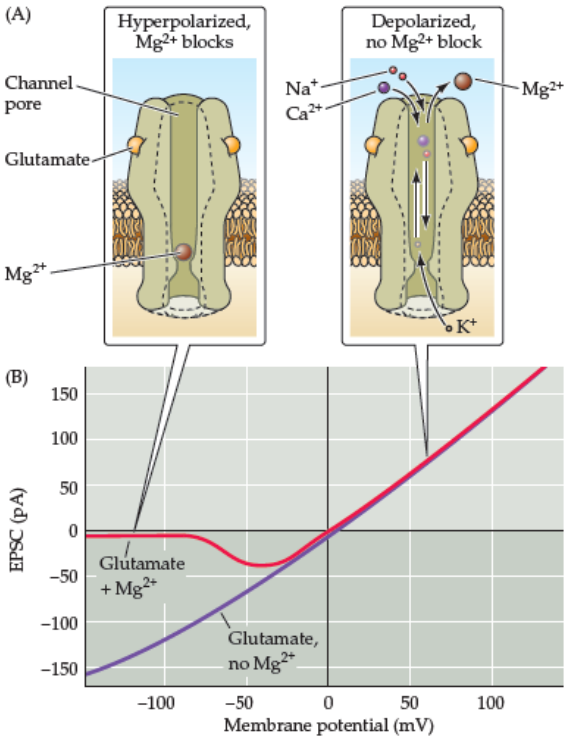
The main types of ionotropic glutamate receptors are AMPA receptors, NMDA receptors and kainate receptors (named after their antagonist). All of these receptors are glutamate-gated cation channels that allow the passage of Na^+ and K^+ which means that activation of these receptors always produce an excitatory postsynaptic response. Most central excitatory synapses possess both AMPA and NMDA receptors.

Experiments use antagonistic drugs that selectively block either AMPA or NMDA receptors to identify responses mediated by each receptor type. These experiments for example reveal that excitatory postsynaptic currents (EPSCs) produced by NMDA receptors are slower and last longer than those produced by AMPA receptors. EPSCs generated by AMPA receptors are usually much larger than the other ionotropic glutamate receptors which makes AMPA receptors the primary mediators of excitatory transmission in the brain. The physiological role of kainate receptors are less well defined, when found on postsynaptic cells kainate receptors generate EPSCs that rise quickly but decay more slowly than those mediated by AMPA receptors.



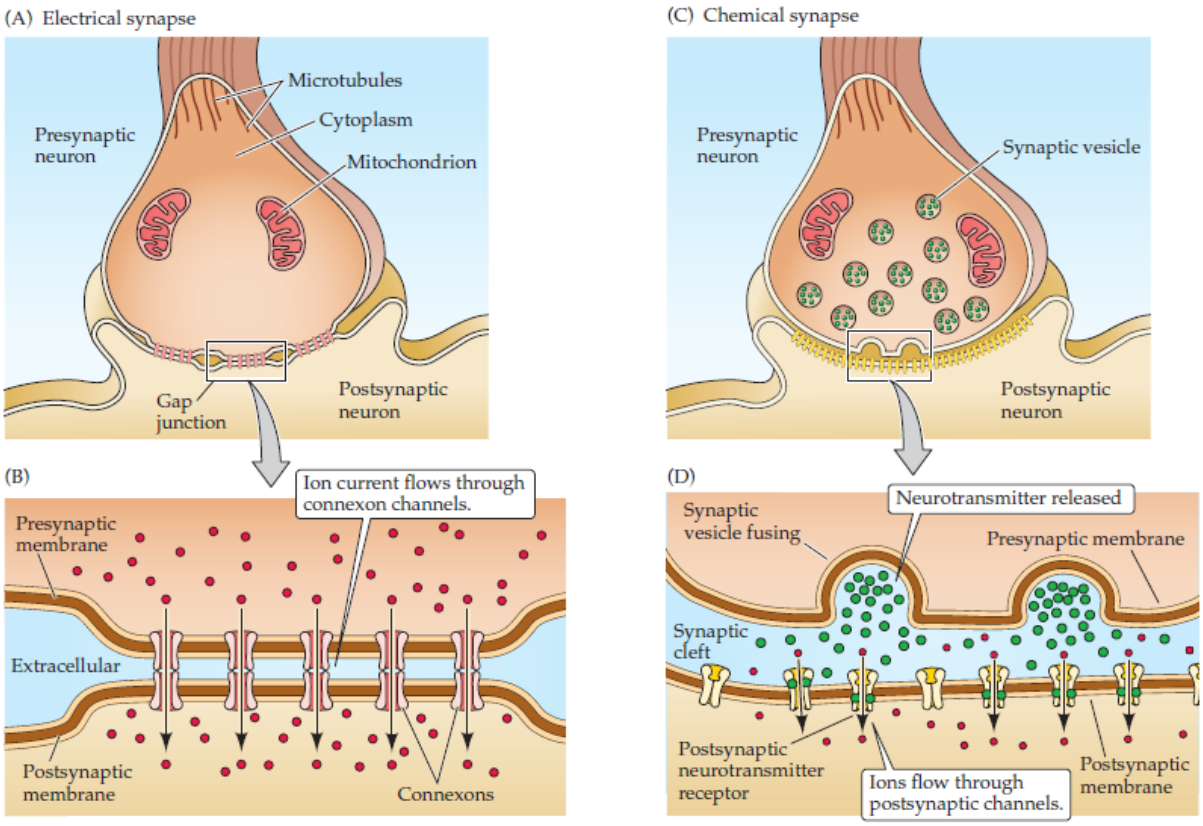
Like all ionotropic receptors, AMPA receptors are composed of multiple subunits. There are four different subunits, designated GluA1 to GluA4, with each subunit providing unique functional properties to AMPA receptors. The receptor subunits have several different domains, including an extracellular ligand binding domain that binds glutamate and a

transmembrane domain that forms the ion channel. Binding of glutamate to the AMPA receptor opens the channel pore.



NMDA receptors have physiological properties that set them apart from the other ionotropic glutamate receptors. The most significant being that its pore allows Ca^{2+} to pass through in addition to Na^+ and K^+. As a result, EPSPs produced by NMDA receptors increase the concentration of Ca^{2+} in the postsynaptic neuron which acts as a second messenger to activate intracellular signalling processes. Another important property of the NMDA receptor is that Mg^{2+} blocks the pore of this channel at hyperpolarized membrane potentials while depolarization pushes the Mg^{2+} out of the pore (removing extracellular Mg^{2+} eliminates this behaviour). Because of this behaviour NMDA receptors only pass cations when postsynaptic membrane potential is depolarized which is thought to underlie some forms of synaptic information storage, such as long-term synaptic plasticity. Another unusual feature of the NMDA receptor is that their gating requires a co-agonist in the form of the amino acid glycine.

DESCRIBE AND EXPLAIN THE PROPERTIES OF THE SYNAPSES AND THEIR IMPORTANCE FOR INFORMATION PROCESSING IN THE CNS (S3)



The human brain contains 86 billion neurons, each with the ability to influence many other cells. To communicate with each other the neurons uses synapses which are the functional contacts between them. Two different types of synapses – electrical and chemical – can be distinguished on the basis of their mechanism of transmission. Electrical synapses use current that flows through connexons (specialised membrane channels that connect two cells at gap junctions) to communicate while chemical synapses uses cell-to-cell communication via the secretion of neurotransmitters (chemical agents released by the presynaptic neuron which produce secondary current flow in postsynaptic neurons by activating specific neurotransmitter receptors).

There are well over 100 neurotransmitters but they all virtually undergo a similar cycle of use: synthesis and packaging into synaptic vesicles; release from the presynaptic cell; binding to postsynaptic receptors; and finally, rapid removal or degradation. The influx of Ca^{2+} through voltage-gated channels triggers the secretion of neurotransmitters; this, in turn, gives rise to a transient increase in Ca^{2+} concentration in the presynaptic terminal. The rise in Ca^{2+} concentration causes synaptic vesicles to fuse with the presynaptic plasma membrane and release their contents into the space between the pre- and postsynaptic cell. Neurotransmitters evoke postsynaptic electrical responses by binding to members of a diverse group of neurotransmitter receptors. There are two major classes of receptors: those in which the receptor molecule is also an ion channel, and those in which the receptor and ion channel are separate entities. Whether the postsynaptic actions of a particular neurotransmitter are excitatory or inhibitory is determined by the ion permeability of the

ion channel affected by the transmitter and by the electrochemical gradient of the transmitter.

Synaptic connections between neurons provide the basic “wiring” of the brain’s circuitry. However, unlike the wiring of an electronic device such as a computer, the strength of synaptic connections between neurons is a dynamic entity that is constantly changing in response to neural activity and other influences. Such changes in synaptic transmission arise from several forms of plasticity that vary in timescale from milliseconds to years.

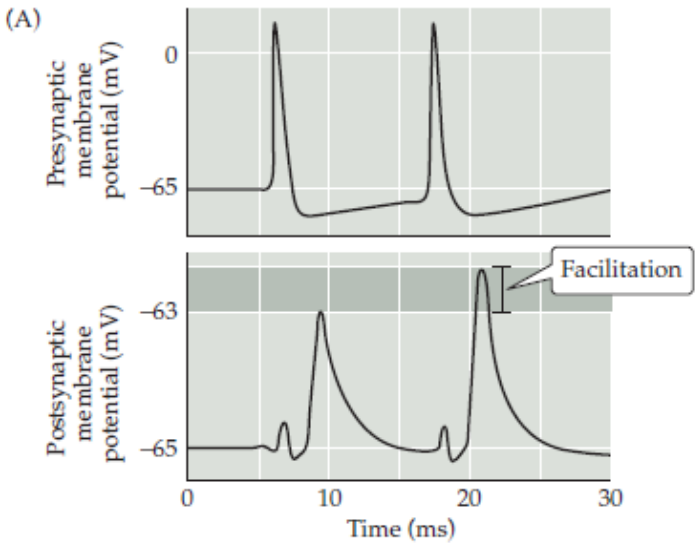
Most short-term forms of plasticity affect the amount of neurotransmitter released from the presynaptic terminals in response to a presynaptic action potential. Several forms of short-term plasticity – including facilitation, augmentation, and potentiation – enhance neurotransmitter release and are caused by persistent actions of calcium ions within the presynaptic terminal. Another form of short-term plasticity, synaptic depression, decreases the amount of neurotransmitter released and appears to be due to an activity-dependent depletion of synaptic vesicles that are ready to undergo exocytosis.

Long-term forms of synaptic plasticity alter synaptic transmission over timescales of 30 minutes or longer. Examples of such long-lasting plasticity include long-term potentiation and long-term depression. These long-lasting forms of synaptic plasticity arise from molecular mechanisms that vary over time: the initial changes in synaptic transmission arise from post-translational modifications of existing proteins, most notably changes in the trafficking of glutamate receptors, while later phases of synaptic modification result from changes in gene expression and synthesis of new proteins. These changes produce enduring changes in synaptic transmission including synapse growth, that can yield essentially permanent modifications of brain function.

FORMS OF SHORT-TERM PLASTICITY

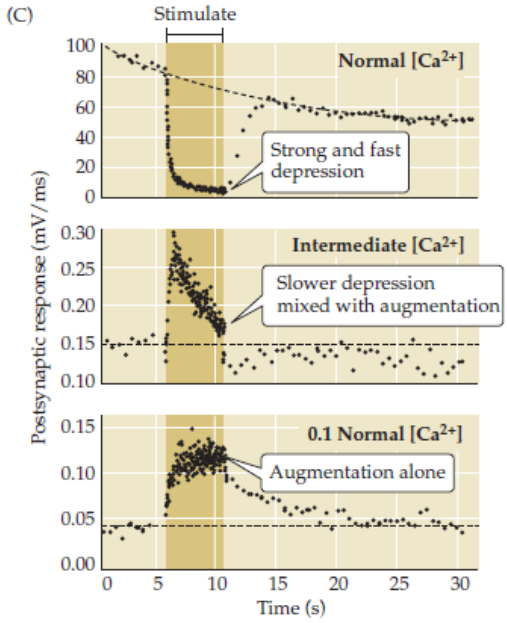
FACILITATION

Synaptic facilitation is a rapid increase in synaptic strength that occurs when two or more action potentials invade the presynaptic terminal within a few milliseconds of each other. By varying the time interval between presynaptic action potentials, it can be seen that facilitation produced by the first action potential lasts for tens of milliseconds. Many lines of evidence indicate that facilitation is the result of prolonged elevation of presynaptic calcium levels follow synaptic activity. Although the entry of calcium into the presynaptic terminal occurs within 1 to 2 milliseconds after an action potential invades, the mechanisms that return calcium to resting levels are much slower. Thus, when action potentials arrive close together in time, calcium builds up in the terminal and allows more neurotransmitter to be released by a subsequent presynaptic action potential.



POTENTIATION AND AUGMENTATION

Synaptic potentiation and augmentation are also elicited by repeated synaptic activity and serve to increase the amount of neurotransmitter released from presynaptic terminals. Both enhance the ability of incoming calcium to trigger fusion of synaptic vesicles with the plasma membrane, but the two processes work over different timescales. While augmentation rises and falls over a few seconds, potentiation acts over a timescale of tens of seconds to minutes. The mechanisms for these two processes are poorly understood.



DEPRESSION

Synaptic depression causes neurotransmitter release to decline during sustained activity. It is believed that depression is caused by progressive depletion of a pool of synaptic vesicles that are available for release: when rates of release are high, these vesicles deplete rapidly and cause a lot of depression; depletion slows as the rate of release is reduced, yielding less depression.

FORMS OF LONG-TERM PLASTICITY

HABITUATION

Habituation is the process that causes the individual to become less responsive to repeated occurrences of a stimulus. Habituation is found in many species, including humans. For example, when dressing we initially experience tactile sensations due to clothes stimulating our skin, but habituation quickly causes these sensations to fade.

SENSITIZATION

Sensitization is a process that allows an individual to generate an aversive response – elicited by a noxious stimulus – to a variety of other, non-noxious stimuli.

Both habituation and sensitization appear to rise from plastic changes in synaptic transmissions of the involved neurons. During habituation, transmission at the glutamatergic synapse between the sensory and motor neurons is depressed. Much like the short-term form of depression this depression is presynaptic and due to a reduction in the number of synaptic vesicles available for release. In contrast, sensitization modifies the function of this circuit by recruiting additional neurons. The stimuli that evokes sensitization activate sensory neurons that in turn excite modulatory interneurons that release serotonin onto the presynaptic terminals of the sensory neurons. Serotonin enhances transmitter release from the siphon sensory neuron terminals, leading to increased synaptic excitation of the motor neurons. This modulation of sensory neuron-motor neuron lasts approximately 1 hour.

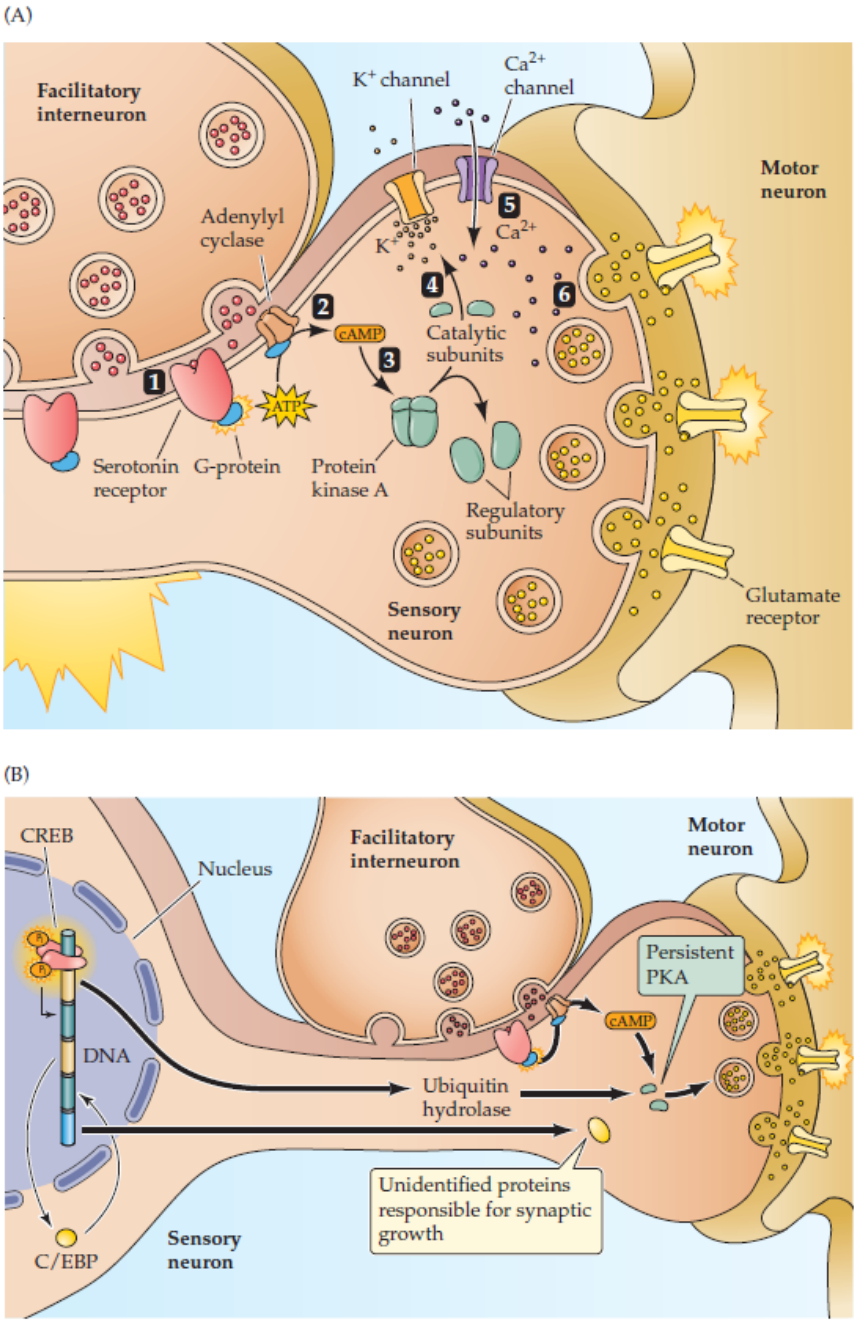


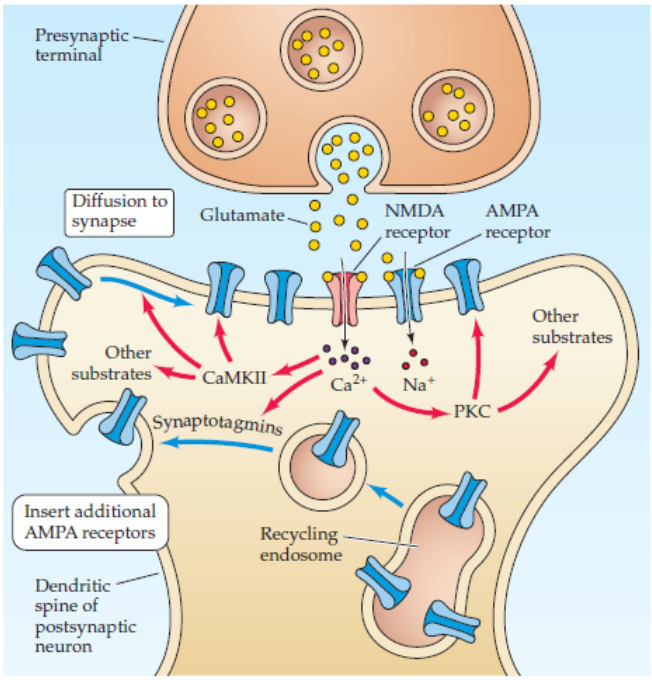
FIGURE 8.5 Mechanisms of presynaptic enhancement underlying behavioral sensitization. (A) Short-term sensitization is due to an acute, PKA-dependent enhancement of glutamate release from the presynaptic terminals of sensory neurons. See text for explanation. (B) Long-term sensitization is due to changes in gene expression, resulting in the synthesis of proteins that change PKA activity and lead to changes in synapse growth. (After Squire and Kandel, 1999.)

The same serotonin-induced enhancement of glutamate release that mediates short-term sensitization is also thought to underlie long-term sensitization. However, during long-term sensitization this circuitry is

affected up to several weeks. The prolonged duration of this form of plasticity is due to changes in gene expression and thus protein synthesis.

LONG-TERM POTENTIATION

Long-term potentiation (LTP) and long-term depression (LTD) are broad terms that describe only the direction of change in synaptic efficacy; in fact, different cellular and molecular mechanisms can be involved in producing LTP or LTD at different synapses throughout the brain. In general, LTP and LTD are produced by different histories of activity and are mediated by different complements of intracellular signal transduction pathways in the nerve cells involved. Long-term synaptic plasticity has been most thoroughly studied at excitatory synapses in the mammalian hippocampus.



The mechanism for inducing LTP in the Schaffer collateral- CA1 synapse is now well understood and relies on NMDA receptors. During normal depolarization the glutamate released by the presynaptic terminal bind to both AMPA and NMDA receptors; however, a Mg^{2+} blockade prevents the flow of Ca^{2+} through the NMDA receptors which means that the EPSP is mediated entirely by the AMPA receptors (which only allows Na^+ through its channel). The blockade of the NMDA receptors by Mg^{2+} is voltage dependent, which means that if a high-frequency stimulation leads to a prolonged depolarization then Mg^{2+} will be expelled from the NMDA channel pore. Removal of Mg^{2+} then allows Ca^{2+} to enter the dendritic spines of postsynaptic CA1 neurons.

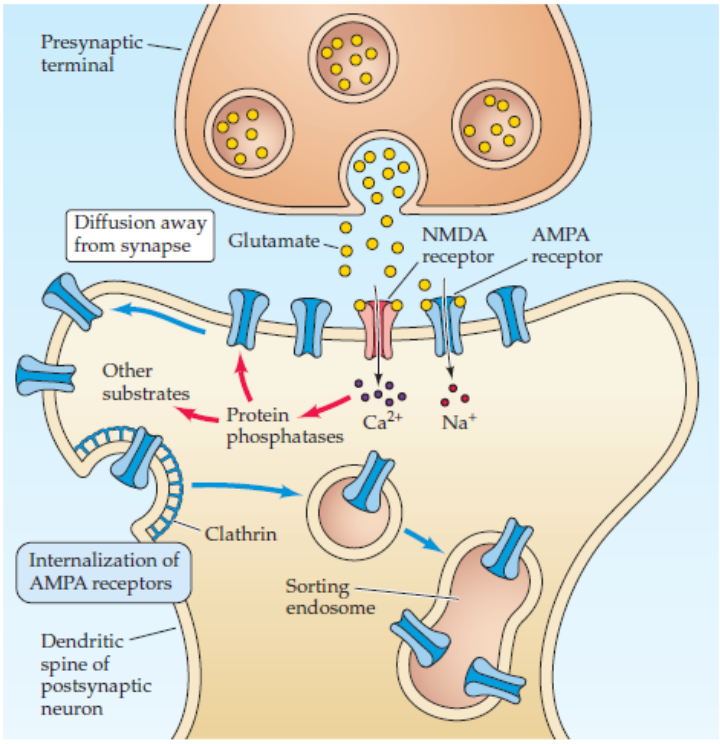
NMDA receptors are the cause for the induction of LTP, however, the expression of said LTP relies on dynamic changes in AMPA receptors. Excitatory synapses can dynamically regulate their postsynaptic AMPA receptors via the same some sorts of membrane trafficking processes that occur in presynaptic neurons during neurotransmitter release. LTP is apparently due to synaptotagmin-mediated insertion of AMPA receptors into the postsynaptic membrane. The resulting increase in the number of AMPA receptors increases the response of the postsynaptic cell to released glutamate, yielding a strengthening of synaptic transmission that can last for as long as LTP is maintained. LTP does not affect the number of postsynaptic NMDA receptors; thus, while these receptors are crucial for induction of LTP, they do not play a major role in LTP expression.

The scheme depicted in the image can account for the changes in synaptic transmission that occur over the first 1 to 2 hours after LTP is induced. However, there is also a later phase of LTP that depends on changes in gene expression and the synthesis of new proteins. This late phase appears to be initiated by protein kinase A, which goes on to activate transcription factors such as CREB, which stimulate the expression of other proteins. Most of the these newly synthesized proteins have not yet been identified and how they contribute to the later phase of LTP is not yet known.

LONG-TERM DEPRESSION

If synapses simply continued to increase in strength as a result of long-term potentiation, eventually they would reach some level of maximum efficacy, making it difficult to encode new information. Thus, to make synaptic strengthening useful, other processes must selectively weaken specific sets of synapses, and LTD is such a process.

In the 1970s, LTD was found to occur at the synapses between the Schaffer collaterals and the CA1 pyramidal cells in the hippocampus. Whereas LTP at these synapses required brief, high frequency stimulation, LTD occurs when the Schaffer collaterals are stimulated at a low rate – about 1 Hz – for long periods (10-15 minutes). This pattern of activity depresses the EPSP for several hours and, like LTP, is specific to the activated synapses. Moreover, LTD can erase the increase in EPSP size to due LTP, and conversely, LTP can erase the decrease in EPSP size due to LTP. This complementarity suggests that LTD and LTP reversibly affect synaptic efficiency by acting at a common site.



LTP and LTD at the Schaffer collateral-CA1 synapses share several key elements. Both require activation of NMDA-type glutamate receptors and the resulting entry of Ca^{2+} into the postsynaptic cell. The major determination of whether LTP or LTD arises appear to be due to the nature of the Ca^{2+} signal in the postsynaptic cell: small and slow rises in Ca^{2+} lead to depression, whereas large and fast increases in Ca^{2+} trigger potentiation. LTD appear to lead to activation of phosphatases (LTP, on the other hand, are partially caused by

activation of protein kinases due to increased Ca^{2+}) which seem to result in a loss of AMPA receptors; this loss probably arises from internalization of AMPA receptors into sorting endosomes into the postsynaptic cell, due to the same clathrin-dependent endocytosis mechanisms important for synaptic vesicle recycling. As is also the case for LTP, there is a late phase of LTD that requires synthesis of new proteins.

A quite different form of LTD has been observed in the cerebellum, it won't be explained but it is good to be reminded of what was said in the beginning; that LTP and LTD are broad terms that only explain the direction of change in synaptic efficacy.

HAVE KNOWLEDGE ABOUT THE MECHANISMS OF ACTION OF TOXINS AND DISEASES AFFECTING SYNAPTIC TRANSMISSION, INCLUDING BOTULISM, TETANUS, MYASTHENIA GRAVIS, EXCITOTOXICITY AND NERVE GAS POISONING (S1, S2)

BOTULISM

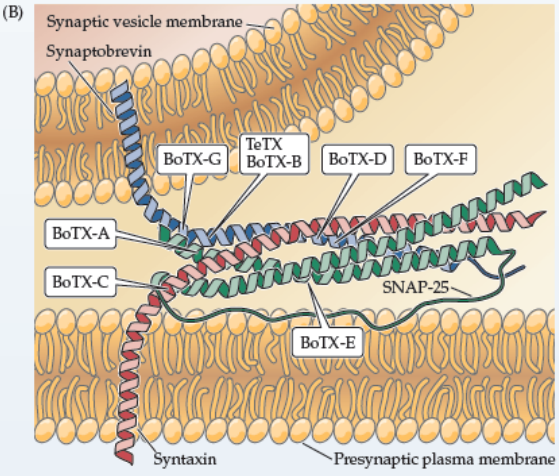
Botulism can occur by consuming food containing *Clostridium* bacteria or through infection of wounds with the spores from these organisms. The presence of the toxin can cause paralysis of peripheral neuromuscular synapses due to impaired neurotransmitter release. This causes skeletal muscle weakness or in the worst-case scenario respiratory failure due to paralysis of the diaphragm and other muscles required for breathing. Botulism toxin can also block synapses innervating smooth muscle of several organs giving rise to visceral motor disfunction. The paralysis/relaxation of muscle contraction also serves as a basis for clinical use in the toxin in cosmetic surgery and other applications.

TETANUS

Tetanus typically result from the contamination of puncture wounds by *Clostridium* bacteria that produce tetanus toxin. In contrast to botulism, tetanus poisoning blocks the release of inhibitory transmitters from interneurons in the spinal cord. This causes a loss of synaptic inhibition on spinal motor neurons which produces a hyper excitation of skeletal muscle and tetanic contractions in affected muscles.

MECHANISM FOR TETANUS AND BOTULISM

Although the symptoms from tetanus toxin differ dramatically to that of the botulism toxin studies have shown that these toxins have a common mechanism of action: they are highly specific proteases that inhibit neurotransmitter release by cleaving the SNARE proteins involved in fusion of the synaptic vesicles with the presynaptic plasma membrane.



(B) Cleavage of SNARE proteins by clostridial toxins. Indicated are the sites of proteolysis by tetanus toxin (TeTX) and various types of botulinum toxin (BoTX). (From Sutton et al., 1998.)

Tetanus toxin and botulism toxin types B, D, F and G specifically cleave the vesicle SNARE protein synaptobrevin. Other botulism toxins cleave syntaxin (type C) and SNAP-25 (types A and E) which are SNARE proteins found on the presynaptic plasma membrane. Destruction of these presynaptic proteins is the basis for the inhibitory actions of clostridium toxin on neurotransmitter disease.

The different actions of these toxins on synaptic transmission at excitatory motor versus inhibitory synapses apparently results from the fact that these toxins are taken up by different types of neurons: whereas botulism toxins are taken up by motor neurons, tetanus toxins are preferentially targeted to interneurons. The differential uptake of toxins is believed to arise from the presence of different types of toxin receptors on the two types of neurons.

MYASTHENIA GRAVIS

Is an autoimmune disease where antibodies target the nACh receptors and leads to a lower transmission between motor neurons and skeletal muscles. This often leads to drooping eyelids or ptosis and problems with eye movements causing double vision or diplopia due to its affect on the muscles controlling the eye and eyelid. Muscles controlling the facial expression, chewing, swallowing and speaking are also often affected.

It's unclear what triggers the autoimmune response against nACh receptors. The treatment for myasthenia gravis is neostigmine which are an AChesterase inhibitor which leads to more Ach (since it doesn't get broken down) and that Ach can bind more effectively to the nACh receptors.

EXCITOTOXICITY

Excitotoxicity is the ability of glutamate and related compounds to damage or kill neurons due to excessive stimulation. This occurs when the glumtamate receptors NMDA and AMPA are overactivated by a glutamatergic storm. The high levels of glutamate give rice to high levels if intra cellular which in turn generate free radicals and activates different enzymes. These enzymes damage the cell structure, for example the cytoskeleton, membrane and DNA which leads to death of the neuron.

Excitotoxic mechanism can happen after acute forms of neural insults such as; hypoglycaemia, trauma and status epilepticus (repeated intense seizures). Understanding how excitotoxicity works can have important implications for treating a variety of neurological disorders. For instance, blocking glutamate receptors can save neurons from damage during for example stroke and trauma. However clinical trials have not yet been able to show that the blockage of glutamate receptors does much of a difference in the outcome of a stroke.

NERVE GAS POISONING

Normally motor neurons releases ACh that bind to receptors on muscles and organs, then ACh-esterase immediately breaks down ACh so that the muscle or organ can relax. When exposed to nerve gas there is an inhibition of ACh-esterase due to the formation of a

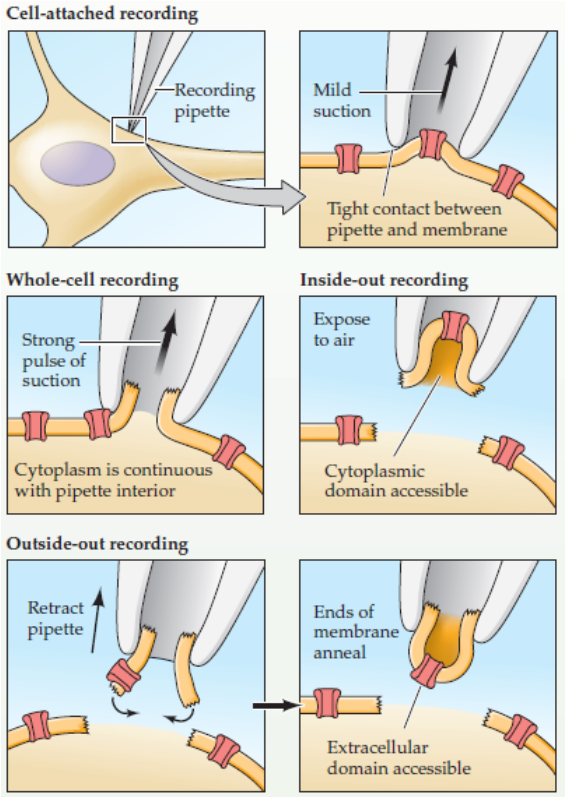
covalent bond at the active site. Therefore ACh can't be broken down and the impulse will be transmitted continuously. This leads to continues muscle contraction, uncontrolled drooling, lacrimation and excess production of mucus from the nose.

HAVE KNOWLEDGE OF METHODS USED TO REGISTER ACTIVITY IN INDIVIDUAL NERVE CELLS AND GROUPS OF NERVE CELLS (S1)

There are a number of methods available to measure the activity in individual- and groups of neurons; here three will be mentioned:

PATCH CLAMP METHOD

A glass pipette with a very small opening is used to make tight contact with a tiny area, or patch, of a neuronal membrane. After the application of a small amount of suction to the back of the pipette, the seal between the pipette and membrane becomes so tight that no ions can flow between the pipette and membrane. Thus, all the current that flows when a single ion channel opens must flow into the pipette. This minute electrical current can be measured with an ultrasensitive electronic amplifier connected to the pipette. This arrangement is the cell-attached patch clamp recording method. As with the conventional voltage clamp method, the patch clamp allows experimental control of the membrane potential to characterize the voltage dependence of membrane currents.



ELECTROENCEPHALOGRAPHY (EEG)

EEG is an electrophysiological monitoring method to record electrical activity of the brain. It's typically non-invasive, with electrodes placed along the scalp, and measures voltage fluctuations resulting from ionic current within the neurons of the brain. EEG is mainly used to measure the activity of the cortex as measurable results decrease with increased radius.

FUNCTIONAL MAGNETIC RESONANCE IMAGING (FMRI)

fMRI measures brain activity by detected changes associated with blood flow. This technique relies on the fact that cerebral blood flow and neuronal activation are coupled. When an area of the brain is in use, blood flow to that region increases. Haemoglobin and deoxyhemoglobin have different densities and therefor look different on fMRI scans, this is called the blood-oxygen-level dependent (BOLD) contrast and is what is used to detect changes in brain activity.

SENSORY FUNCTIONS:

DESCRIBE THE DIFFERENT TYPES OF SPECIALIZED SENSORY CELLS / RECEPTORS FOR THE DIFFERENT SENSORY MODALITIES (TOUCH, PROPRIOCEPTION, PAIN, VISION, HEARING, BALANCE/SPATIAL ORIENTATION, TASTE AND SMELL), AND DESCRIBE THEIR ANATOMICAL AND HISTOLOGICAL ORGANIZATION (S2, S3)

TOUCH

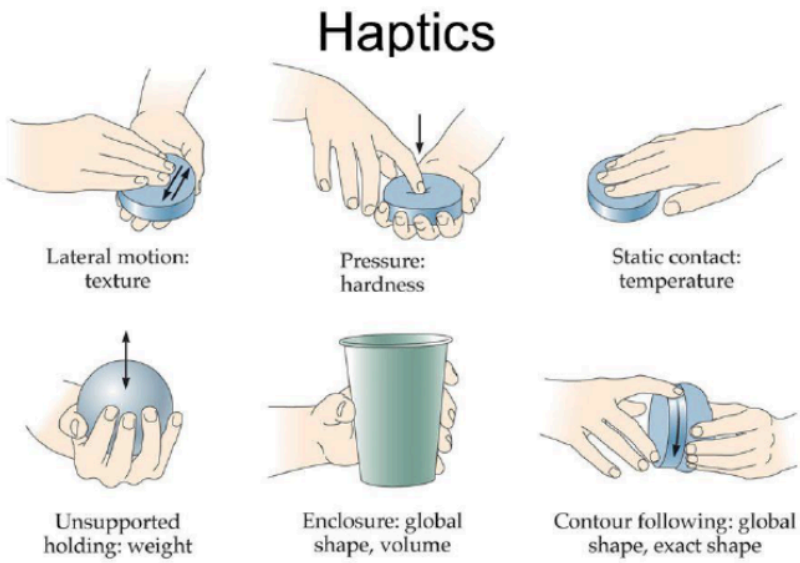
We are constantly subjects to different kinds of stimuli from our environment as well as internally. Our brain needs to sort through and prioritize among these stimuli's. The information from ex touch and vibration are transformed to electrical signals and are sent via the spinal cord to the cortex where the brain decides how we should act on a different stimulus. The transformation to an electrical signal is called transduction.

Touch are in the skin taken up by the type of sensory receptors that are called encapsulated endings and are mechanoreceptors.

There are different types of touch:

THE PASSIVE TACTILE PERCEPTION – when an object is pressed against the skin

THE ACTIVE TOUCHING OR HAPTICS – when one investigates something with their fingers or press your fingers against something. The different types are shown in the picture.



When an encapsulated afferent fibre in for example our finger register touch the channels for open and leads to a receptor potential (the response that the receptor gives, the cell responds to the receptors response by depolarisation or hyper repolarisation) and if the stimulus is strong enough an action potential is generated.

THE ADAPTATION OF THE MECHANORECEPTORS

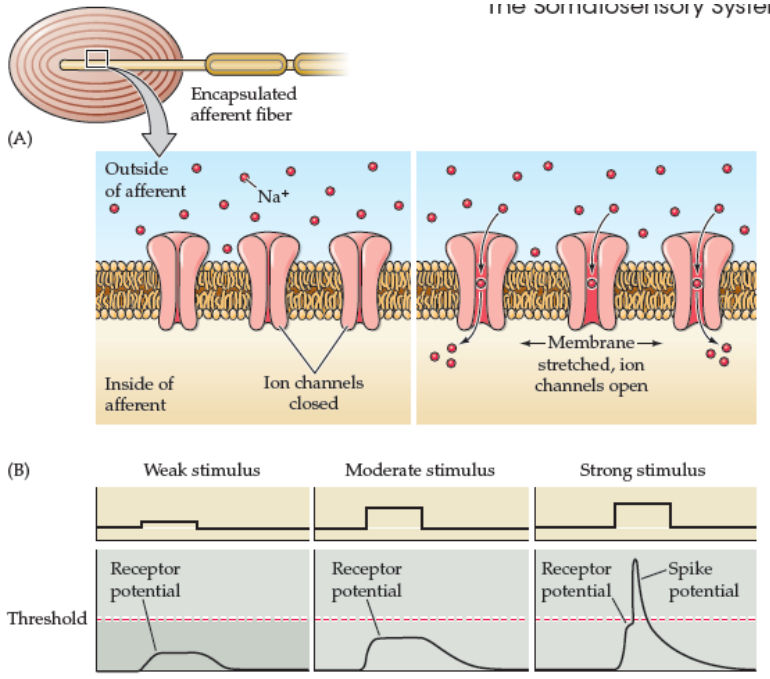
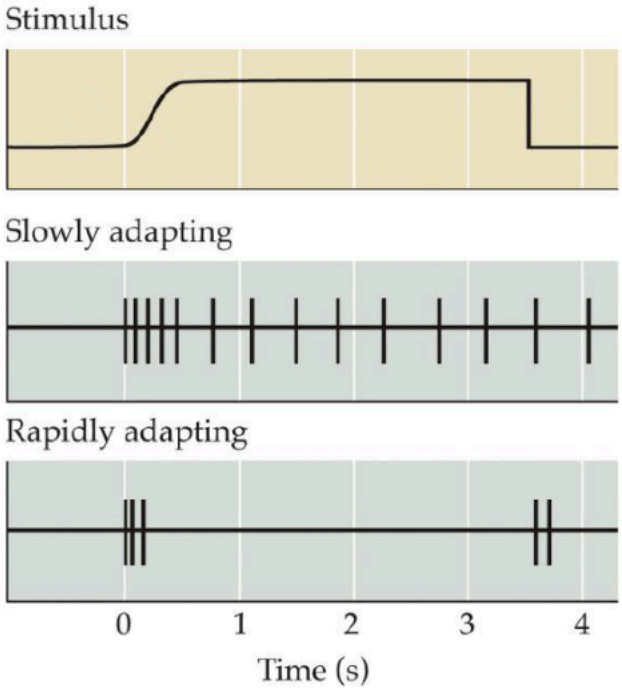


FIGURE 9.2 Transduction in a mechanosensory afferent. The process is illustrated here for a Pacinian corpuscle. (A) Deformation of the capsule leads to a stretching of the membrane of the afferent fiber, increasing the probability of opening mechanotransduction channels in the membrane. (B) Opening of these cation channels leads to depolarization of the afferent fiber (receptor potential). If the afferent is sufficiently depolarized, an action potential is generated and propagates to central targets.

When a neuron/cell with a mechanoreceptor is exposed to a stimulus over a period of time it can adapt. There are two types of adaptation; slow adaption (SA) and rapid adaption (RA).



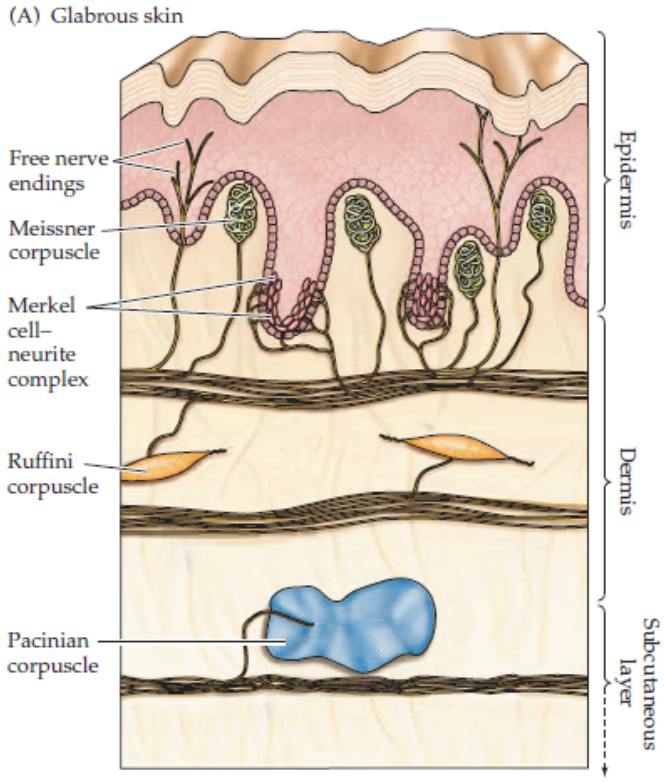
SLOW ADAPTION - The cell is constantly firing whilst the stimuli is present. It provides information to the CNS about spatial features ex size and shape, this is continuous during the whole stimuli. Called tonic receptors.

FAST ADAPTION - at the beginning of the stimuli a burst of signals are sent, then it stops firing if the stimuli is constant, allows to ignore irrelevant information and to inform about changes in the stimuli.

The receptors have a receptive field, this field can differ from receptor to receptor and depends on the branching of the receptor. This means that a receptor only registers the touch of an area and not the surrounding area.

Convergence – when several neuron (ex 1:st order) are connected to the same neuron (2:nd order neuron). This makes the receptor field becomes bigger then the secondary neuron.

THE DIFFERENT KINDS OF MECHANORECEPTORS



MERKEL CELL AFFERENTS

Merkel cell afferents are slowly adapting fibers that account for about 25% of the mechanosensory afferents in the hand. They are especially enriched in the fingertips and are the only afferents that sample information from receptor cells located in the epidermis.

Merkel cell afferents have the highest spatial resolution of all the sensory afferents (they can resolve spatial details of 0.5 mm). They are also sensitive to points, edges and curvature which makes them ideally suited for processing information about shape or texture.

MEISSNER AFFERENTS

Meissner afferents are rapidly adapting fibers that innervate the skin even more densely than Merkel afferents, accounting for about 40% of the mechanosensory innervation of the human hand. Meissner corpuscles lie in the tips of the dermal papillae adjacent to the primary ridges and closest to the skin surface. They are formed by a connective tissue capsule that contains a set of flattened lamellar cells derived from Schwann cells and nerve terminals that are suspended by collagen fibers. The capsule contains two to six afferent nerve fibers that terminate between and around the lamellar cells which contribute to the transient response to somatic stimulation.

With indentation of the skin, the dynamic tension transduced by the collagen fibers provide the transient mechanical force that deforms the corpuscle and triggers generator potentials that may induce a volley of action potentials in the afferent fibers. When the stimulus is removed, the indented skin relaxes, and the corpuscle returns to its resting configuration which generates another burst of action potentials. Meissner afferents therefore display characteristic rapidly adapting on-off responses.

Meissner afferents are more than four times as sensitive to skin deformation as Merkel afferents; however, their receptive fields are larger than those of Merkel afferents and therefor they transmit signals with reduced spatial resolution. Meissner corpuscles are particularly efficient in transducing information about the relatively low-frequency vibrations (3-40 Hz) that occur when textured objects are moved across the skin. Several lines of evidence suggest that information conveyed by Meissner afferents is responsible for detecting slippage between the skin and an object held in the hand. Essential feedback information for the efficient control of grip.

PACINIAN AFFERENTS

Pacinian afferents are rapidly adapting fibers that make up 10-15% of the mechanosensory innervation of the hand. Pacinian corpuscles are located deep in the dermis or in the subcutaneous tissue; their appearance resembles that of a small onion with concentric layers surrounding a single afferent fiber. The laminar capsule acts as a filter which only allows transient disturbances at high frequencies (250-350 Hz) to activate the nerve endings.

Pacinian corpuscles adapt more rapidly than Meissner corpuscles and have a lower response threshold. The most sensitive Pacinian afferents generate action potentials for displacements of the skin as small as 10 nanometers. Because they are so sensitive the receptive fields of Pacinian afferents are often large, and their boundaries are hard to define. The properties of Pacinian afferents make them well suited to detect vibrations transmitted through objects that contact the hand or are being grasped in the hand, especially when making or breaking contact. These properties are important for the skilled used of tools (e.g., writing or using a wrench).

RUFFINI AFFERENTS

Ruffini afferents are slowly adapting fibers that make up about 20% of the mechanoreceptors in the human hand, they are the least understood of the cutaneous mechanoreceptors. Ruffini endings are elongated, spindle-shaped, capsular specializations located deep in the skin, as well as in ligaments and tendons. The long axis of the corpuscle is usually oriented parallel to the stretch lines in skin which makes Ruffini corpuscles particularly sensitive to the cutaneous stretching produced by digit or limb movements.

While there are still some questions as to what their function is, they are thought to be especially responsive to skin stretches, such as those that occur during the movement of the fingers. It is therefor believed that information supplied by the Ruffini afferents contribute, along with the muscle receptors, to provide an accurate representation of finger position and the conformation of the hand.

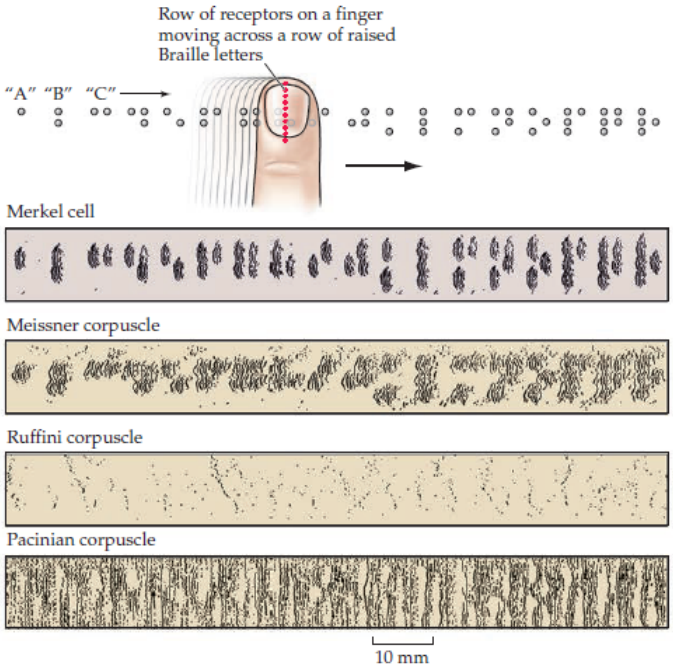


FIGURE 9.6 Simulation of activity patterns in different mechanosensory afferents in the fingertip. Each dot in the response records represents an action potential recorded from a single mechanosensory afferent fiber innervating the human finger as it moves across a row of Braille type. A horizontal line of dots in the raster plot represents the pattern of activity in the afferent as a result of moving the pattern from left to right across the finger. The position of the pattern (relative to the tip of the finger) was then displaced by a small distance, and the pattern was once again moved across the finger. Repeating this pattern multiple times produces a record that simulates the pattern of activity that would arise in a population of afferents whose receptive fields lie along a line in the fingertip (red dots). Only slowly adapting Merkel cell afferents (top panel) provide a high-fidelity representation of the Braille pattern—that is, the individual Braille dots can be distinguished only in the pattern of Merkel afferent neural activity. (After Phillips et al., 1990.)

SUMMARY MECHANORECEPTORS

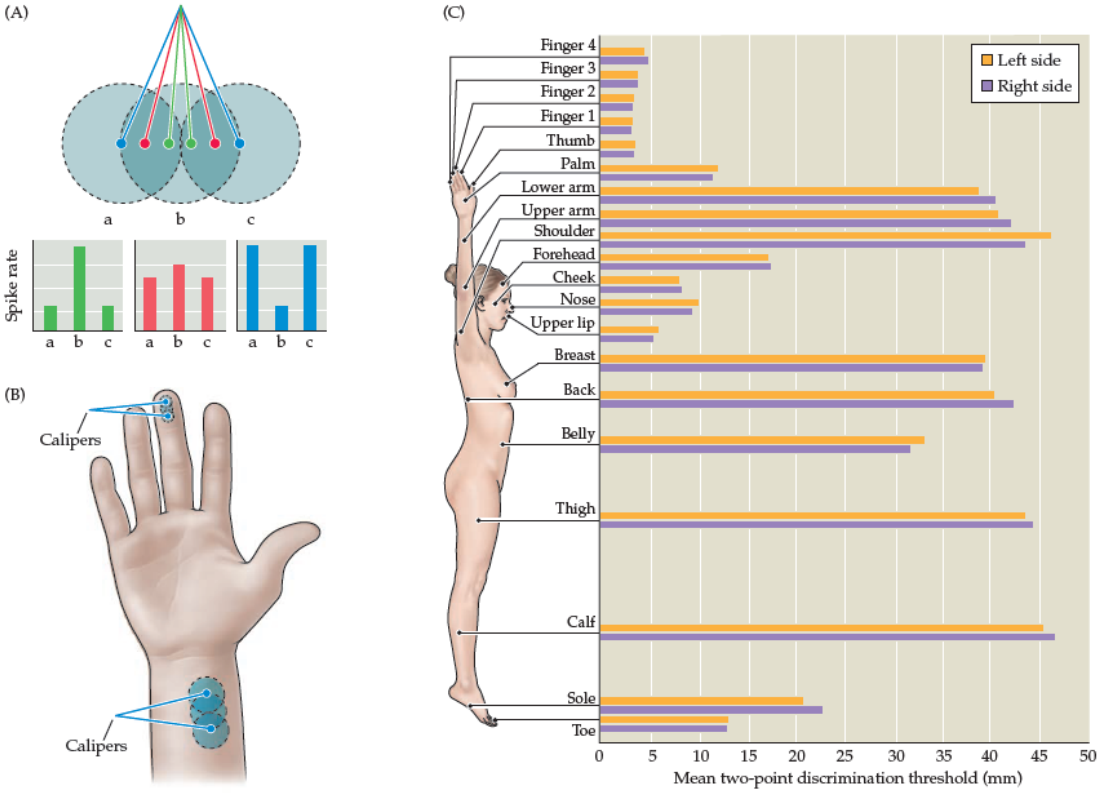
TABLE 9.2 ■ Afferent Systems and Their Properties

	Small receptive field		Large receptive field	
	Merkel	**Meissner**	**Pacinian**	**Ruffini**
Location	Tip of epidermal sweat ridges	Dermal papillae (close to skin surface)	Dermis and deeper tissues	Dermis
Axon diameter	7–11 μm	6–12 μm	6–12 μm	6–12 μm
Conduction velocity	40–65 m/s	35–70 m/s	35–70 m/s	35–70 m/s
Sensory function	Shape and texture perception	Motion detection; grip control	Perception of distant events through transmitted vibrations; tool use	Tangential force; hand shape; motion direction
Effective stimuli	Edges, points, corners, curvature	Skin motion	Vibration	Skin stretch
Receptive field area[a]	9 mm^2	22 mm^2	Entire finger or hand	60 mm^2
Innervation density (finger pad)	100/cm^2	150/cm^2	20/cm^2	10/cm^2
Spatial acuity	0.5 mm	3 mm	10+ mm	7+ mm
Response to sustained indentation	Sustained (slow adaptation)	None (rapid adaptation)	None (rapid adaptation)	Sustained (slow adaptation)
Frequency range	0–100 Hz	1–300 Hz	5–1000 Hz	0–? Hz
Peak sensitivity	5 Hz	50 Hz	200 Hz	0.5 Hz
Threshold for rapid indentation or vibration:				
Best	8 μm	2 μm	0.01μm	40 μm
Mean	30 μm	6 μm	0.08 μm	300 μm

[a]Receptive field areas as measured with rapid 0.5-mm indentation.

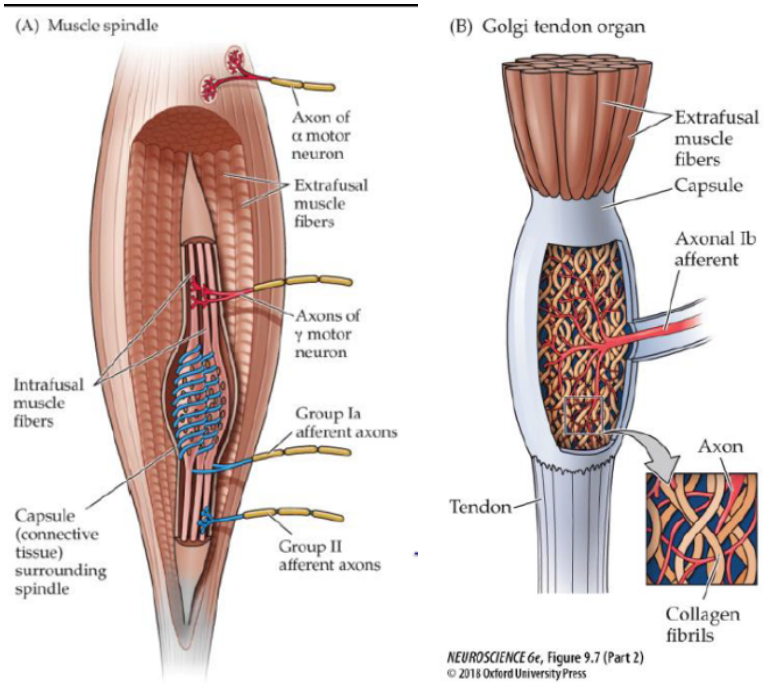
(After K. O. Johnson, 2002.)

TWO-POINT DISCRIMINATION



Two-point discrimination is the ability to discern that two nearby objects touching the skin are truly two distinct points and not one. 2PD is assumed to reflect how finely innervated an area of skin is, normally a person should recognize two points separated by 2-8 mm on fingertips and 8-12 cm on the palms for example.

PROPRIOCEPTION



Proprioception is the perception/awareness of motion and sense of static position. There are three types of proprioceptors: muscle spindle, Golgi tendon organ and joint receptor.

Muscle spindle exist in skeletal muscle and inform about the differences in the length of the muscle. There are about 4-8 intrafusal fibres with a capsule of connective tissue, around the intrafusal fibres there are nerve fibres (type Ia) wrapped around them, these are rapid adapting response to limb dynamics ie they send signals when you move. A bit further down the type II afferent fibres send slow adapting response, they send information about limb static position ie they send information about the position of the limb.

The Golgi tendon organ are present in the tendon and informs about the changes in the muscle tension and has primary (1b) nerve endings.

PAIN

Pain is the unpleasant sensory and emotional experience associated with stimuli that cause tissue damage. The perception of injurious stimuli, called nociception, depends on specifically dedicated receptors and pathways and not excessive stimuli of the same receptors that generate somatic sensations. The central distribution of nociceptive information is correspondingly complex, involving multiple areas in the brainstem, thalamus and forebrain.

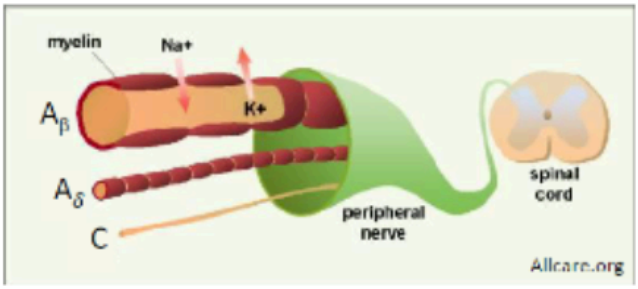
The relatively unspecialized nerve cell endings that initiate the sensation of pain are called nociceptors. Like other cutaneous and subcutaneous receptors, they transduce a variety of stimulus into receptor potentials which in turn trigger afferent action potentials. They arise, like other somatosensory receptors, from cell bodies in dorsal root ganglia that sends one axonal process to the periphery and the other into the spinal cord or brainstem.

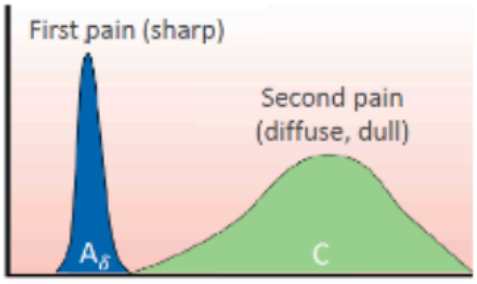
Because peripheral nociceptive axons terminate in morphologically unspecialized “free nerve endings” it’s conventional to categorize nociceptors according to the properties of the axons associated with them. Somatosensory receptors responsible for the perception of innocuous mechanical stimuli are associated with myelinated axons that have relatively rapid conduction velocities. The axons associated with nociceptors, in contrast, conduct relatively slowly; being only slightly myelinated or more commonly unmyelinated. Axons conveying information about pain fall into either the Aδ group of myelinated axons (with speeds of 5 to 30 m/s) or the C fiber group of unmyelinated axons (with speeds of less than 2 m/s).

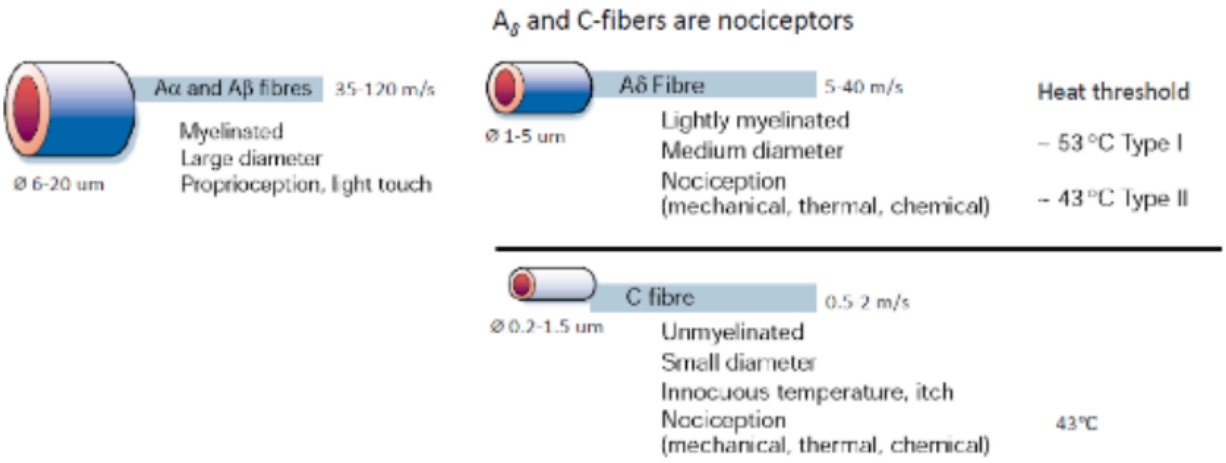
TWO CATEGORIES OF PAIN PERCEPTION HAVE BEEN DESCRIBED: a sharp **first pain** and a more delayed, diffuse and longer lasting **second pain**. Aδ fibers are responsible for the first pain and C fibers for second pain.

Aδ nociceptors fall into two main classes: type I Aδ fibers respond to dangerously intense mechanical and chemical stimuli but have a relatively high heat threshold, while type II Aδ fibers have complementary sensitivities – that is, much lower threshold for heat but very high threshold for mechanical stimulation.

The Aδ system therefore has specialized pathways for the transmission of heat and mechanical nociceptive stimulation. Most of the C fiber nociceptors respond to all forms of nociceptive stimuli – thermal, mechanical, and chemical – and are therefor said to be polymodal. There are subtypes however that respond better to certain stimuli, like heat for example.







Pain can be divided into different groups. Different pain needs different treatment.

- **Nociceptive**: pain in an intact nervous system – caused by for ex. inflammation
- **Neurogen**: pain in an impaired nervous system – caused by spinal cord herniatation
- **Idiopathic**: pain without a known reason or known neurological cause – diseases such as fibromyology
- **Psycogenic**: pain in psychological illness – for example due to anxiety or stress

Pain experience is subjective and depend on genetic predisposition, gender, personality, culture, psychological condition and the psychological state in which pain is experienced. The psychological state in which pain is experienced is the basis for placebo effect and nocebo effect.

VISION

ANATOMY

The eye is a fluid filled sphere enclosed by three layers of tissue. The innermost layer of the eye, the **retina**, contains neurons that are sensitive to light and transmit visual signals to central targets. The immediately adjacent layer of tissue includes three distinct, but continuous structures collectively referred to as the **uveal tract**. The largest component of the uveal tract is the choroid; which is composed of a rich capillary bed that nourishes the retinal photoreceptors. Extending from the choroid near the front of the eye is the **ciliary body**, a ring of tissue that encircles the lens and consists of two parts: a muscular that adjusts refractive power of the lens and a vascular component that produces the liquid that fills the front of the eye. The most anterior component of the uveal tract is the iris, the coloured portion of the eye that can be seen through the cornea. It contains two set of muscles that allow the size of the pupil to be adjusted under neural control. The sclera forms the outermost tissue layer of the eye and is composed of a tough, white, fibrous tissue. At the front of the eye however this opaque outer layer is transformed into the **cornea**, a highly specialized transparent tissue that permits light rays to enter the eye.

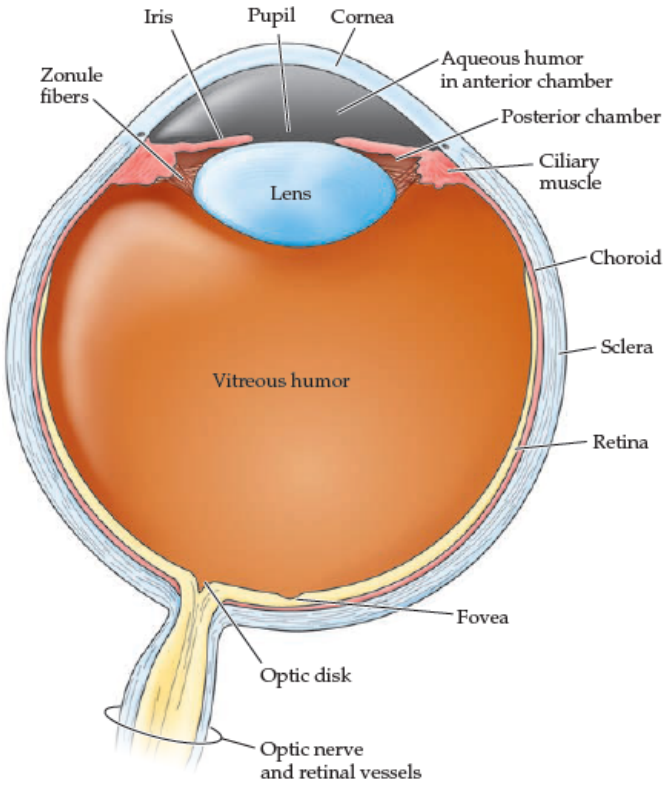


FIGURE 11.1 Anatomy of the human eye.

Once beyond the cornea, light rays pass through two distinct fluid environments before striking the retina. A clear, watery liquid that supplies nutrients to these structured are produced by the ciliary processes in the **posterior chamber** (the region between the lens and iris) and flows into the **anterior chamber** through the pupil. The amount of fluid produced is substantial, the entire volume of fluid in the anterior chamber is replaced about 12 times a day. Insufficient drainage causes glaucoma which is a disorder in which high levels of intraocular pressure reduce the blood supply to the eye and eventually damage the retinal neurons.

The space between the back of the lens and the surface of the retina is filled with a thick, gelatinous substance called the **vitreous humor**, which accounts for about 80% of the volume of the eye. In addition to maintaining the shape of the eye, the vitreous humor contains phagocytic cells that remove blood and other debris that might otherwise interfere with light transmission. The housekeeping abilities of the vitreous humor are limited,

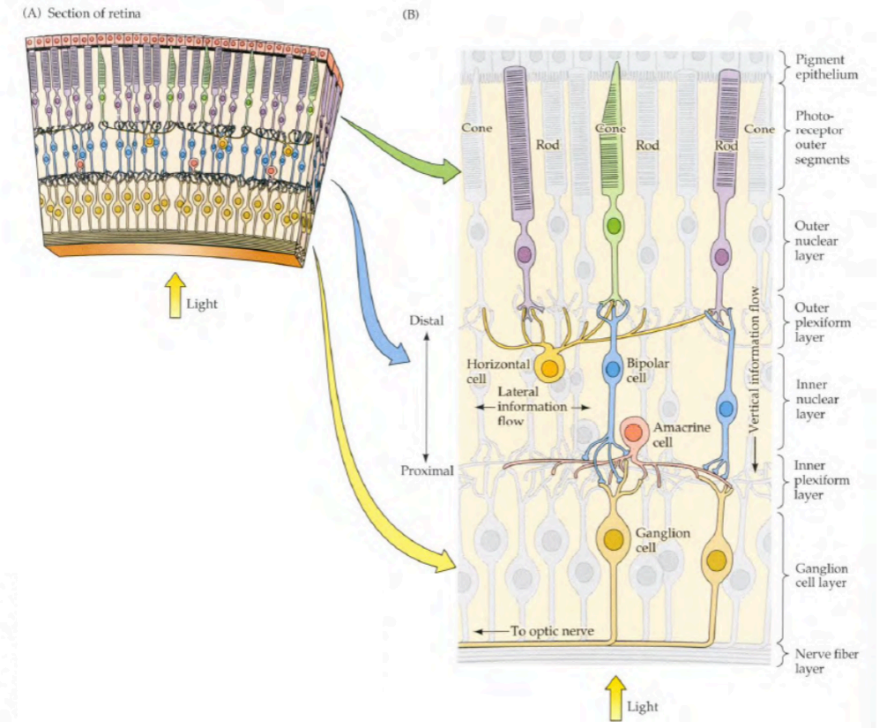
however, as many middle aged and elderly individuals with vitreal “floaters” will attest. Floaters are collections of debris too large for phagocytic consumption that therefore remain, casting annoying shadows on the retina.

HISTOLOGY OF THE RETINA

In the retina there are 5 types of neurons (cells); ganglion cells, bipolar cells, horizontal cells, amacrine cells, photoreceptors (rods and cones) behind that the retina also have pigment epithelial cells (most posterior/distal).

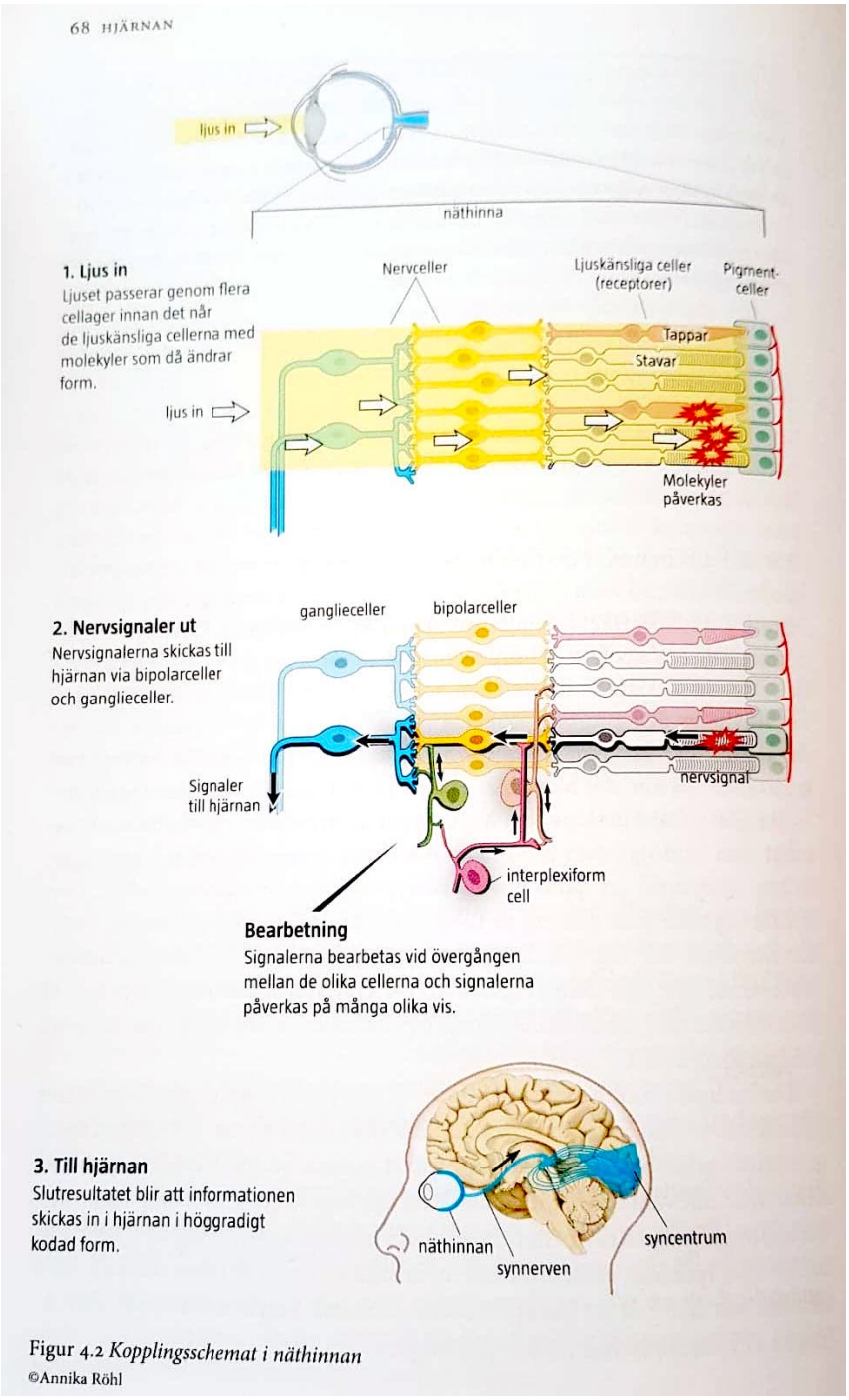
Light comes into the eye in the following order: Cornea → aqueous humor → lens → vitreous humor → retina

In the retina the light goes through the cells in the following order; ganglion cells → bipolar cells → horizontal cells → photoreceptors → pigment epithelial cells



The signal is generated from the rods and cones. From the cones the signal is sent via the bipolar cells to the ganglion cells and the to the brain, this is the simpler signalling way and the signal is processed in every step.

The rods signalling way is longer, they send their signal to a special type of bipolar cell that sends the information to the amacrine cells that sends it to the ganglion cell and then to the brain.



Figur 4.2 *Kopplingsschemat i näthinnan*
©Annika Röhl

GANGLION CELLS

Each ganglion cell responds to stimulation of a small circular patch of the retina, the receptor fields are circular. They have an organisation where the centre can be off or on and also a surrounding part. When the centre is activated (+) is the surrounding inactivated (-) and vice versa, the surrounding and centre is antagonists to each other. The ganglion cells notice contrasts and the difference in contrast.

The ganglion cells have axons to the optic nerve as well as synapses with the bipolar cells and amacrine cells. The ganglion cells take input from the bipolar cells and the action

potential travels through the axons to the optic nerve. The ganglion cells axon will bundle together on its way to the optic nerve and form the optic disk.

AMACRINE CELLS

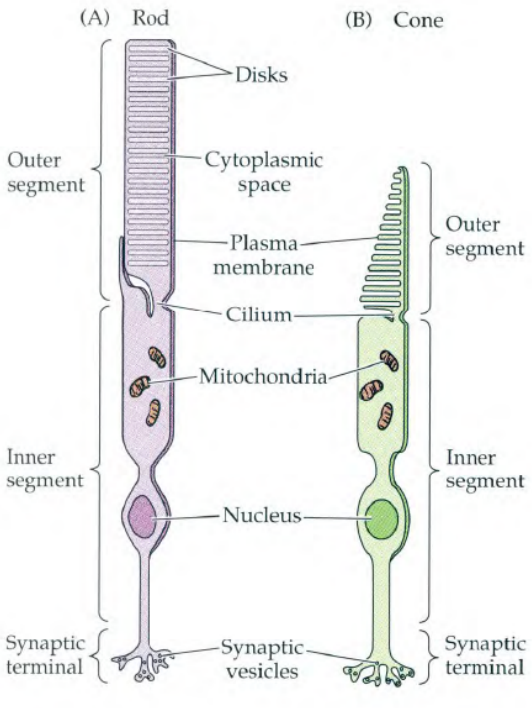
There are different classes of amacrine cells, the most "common" or the one we know most about transmission information from the special bipolar cells that the rods signal to and through to the ganglion cells.

BIPOLAR CELLS

The bipolar cells can both hyperpolarize and depolarize depending on the input they get from the rods and cones. They send the signal to amacrine cells (rods) and ganglion cells (cones).

HORIZONTAL CELLS

In the mammals the photoreceptors have little to non-contact with each other, but via the horizontal cells they can affect each other. Generally, this contact is inhibitory, they go laterally. This is important to give acuity to the signal, so it enables us to be sensitive to contrast.



PHOTORECEPTORS

The photoreceptors are nerve cells with a fine strand of hair a so-called cilium. The cilium has been transformed so that it has an outer surrounded with plasma membrane. The rod and cones have three regions; an outer segment, inner segment and synaptic region.

The outer segment is as mentioned above the old cilium, the outer segments differ from rods and cones. In the rods there are discs separated by cytoplasmic space, they don't touch each other or the outer membrane. The discs are important for the transduction of light and nerve impulses in the rods. For the cones there are one membrane with spaces in between that the same function as in the rods. They do differ in how they do to start a nerve impulse.

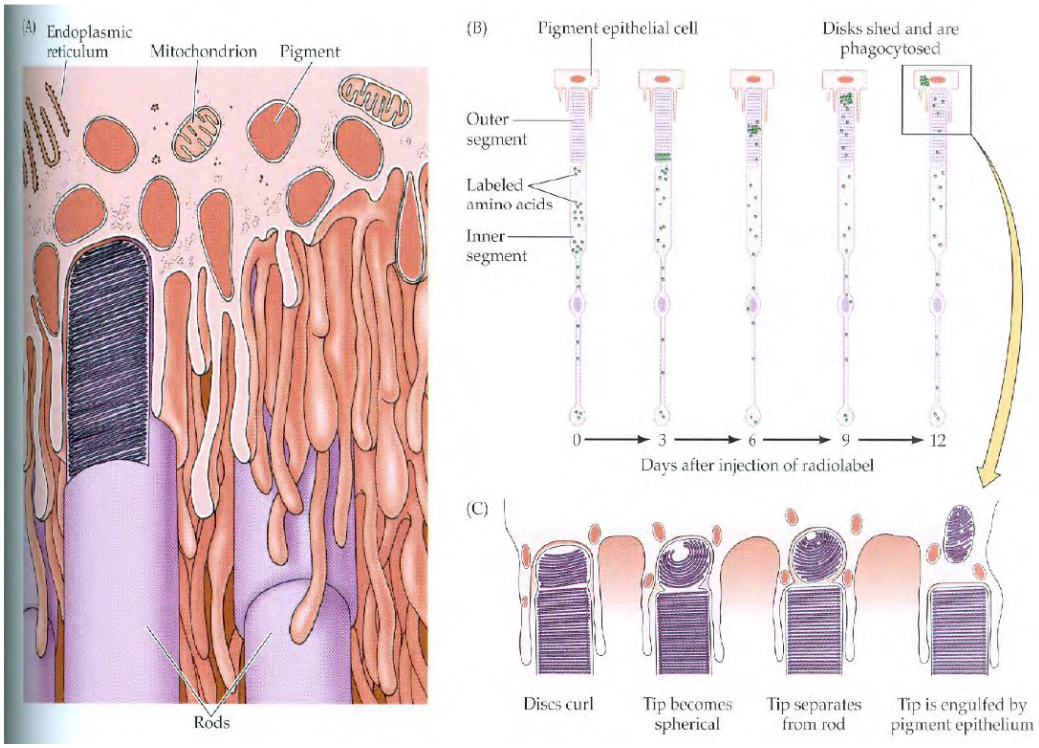
The inner segment is the same for both rods and cones, it has mitochondria's and nucleus.

The cones is important for the colour vision (during the day, we don't see colours during the night) and register the colours red, blue and green that can be combined to other colours. There are around 4 million cones and they have a low amplification and a high acuity. The cones have a fast adaptation in the dark.

Rods are important for the night vison and have a high amplification in the dark (see footnote), it has a low acuity. There are around 120 million. Rods have a slow adaptation in the dark so that they can notice all the photons.

We have a higher density of rods than to cones. In some parts of the eye the density of cones is higher than rods, in the fovea there are no rods and close to the optic disc there are only codes. in the optic disc neither cones nor rods are present. In the nasal side of the eye there are only rods.
The fovea has the best sharpness of vision due to that it's a groove so the light hits it more optimally and it only consists of cones that only innervate one nerve fibre. There's a 1:1 relation between a cone and a nerve fibre, whilst there are several nerves on one rod.

PIGMENT EPITHELIAL CELLS



Pigment epithelial cells that are located behind the photoreceptors are the Pac-man's/macrophages of the eye. They eat the discs in the rods, the discs constantly needs to be broken down, they are made proximally in the outer segment and gets pushed out distally where the pigment epithelial cells phagocytes them.

HEARING

ANATOMY OF THE EAR

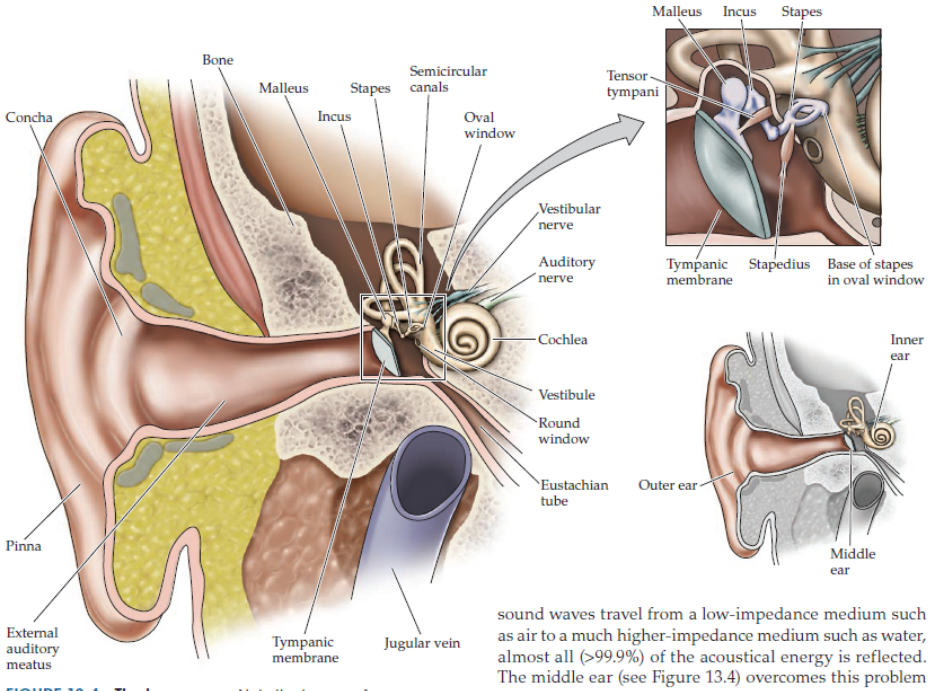


FIGURE 13.4 The human ear. Note the large surface area of the tympanic membrane (eardrum) relative to the oval window. This feature, along with the lever action of the malleus, incus, and stapes, facilitates transmission of airborne sounds to the fluid-filled cochlea.

sound waves travel from a low-impedance medium such as air to a much higher-impedance medium such as water, almost all (>99.9%) of the acoustical energy is reflected. The middle ear (see Figure 13.4) overcomes this problem and ensures transmission of the sound energy across the air–fluid boundary by boosting the pressure measured at the tympanic membrane almost 200-fold by the time it reaches the inner ear.

Two mechanical processes occur within the middle ear

EXTERNAL EAR

The external ear consists of the **pinna**, **concha** and **auditory meatus**, which gathers sound energy and focuses it on the eardrum (tympanic membrane). The structure of the auditory meatus boosts sound pressure 30- to 100- fold for frequencies around 3 kHz via passive resonance effects (which appears to be the range of human speech). A second function of the pinna and concha is to provide cues about the elevation of the sound source. The vertically asymmetrical convolutions of the pinna are shaped so that external ear transmits more high frequency components from an elevated source than from the same source at ear level.

THE MIDDLE EAR

The environment in the inner ear, where the sound induced vibrations are converted to neural impulses, is aqueous unlike that of the external and middle ear. The major function of the middle ear is to match relatively low impedance airborne sounds to the higher impedance fluid of the inner ear. The pressure measured at the tympanic membrane is boosted almost 200-fold by the time it reaches the inner ear.

Two mechanical processes occur within the middle ear to achieve this large pressure gain. The first major boost is achieved by focusing the force impinging on the relatively large diameter tympanic membrane onto a much smaller **oval window**, the site where the bones of the middle ear contact the inner ear. A second and related process relies on the mechanical advantages gained by the lever action of the small, interconnected middle ear

bones, or **ossicles** (i.e., the malleus, incus, and stapes), which connect the tympanic membrane to the oval window. In normal hearing the efficiency of sound transmission to the inner ear also is regulated by two small muscles in the middle ear, the tensor tympani, and the stapedius.

Contraction of these muscles, which is triggered automatically by loud noises or during self-generated vocalization, counteracts the movement of the ossicles and reduces the amount of sound energy transmitted to the cochlea, serving to protect the inner ear.

THE INNER EAR

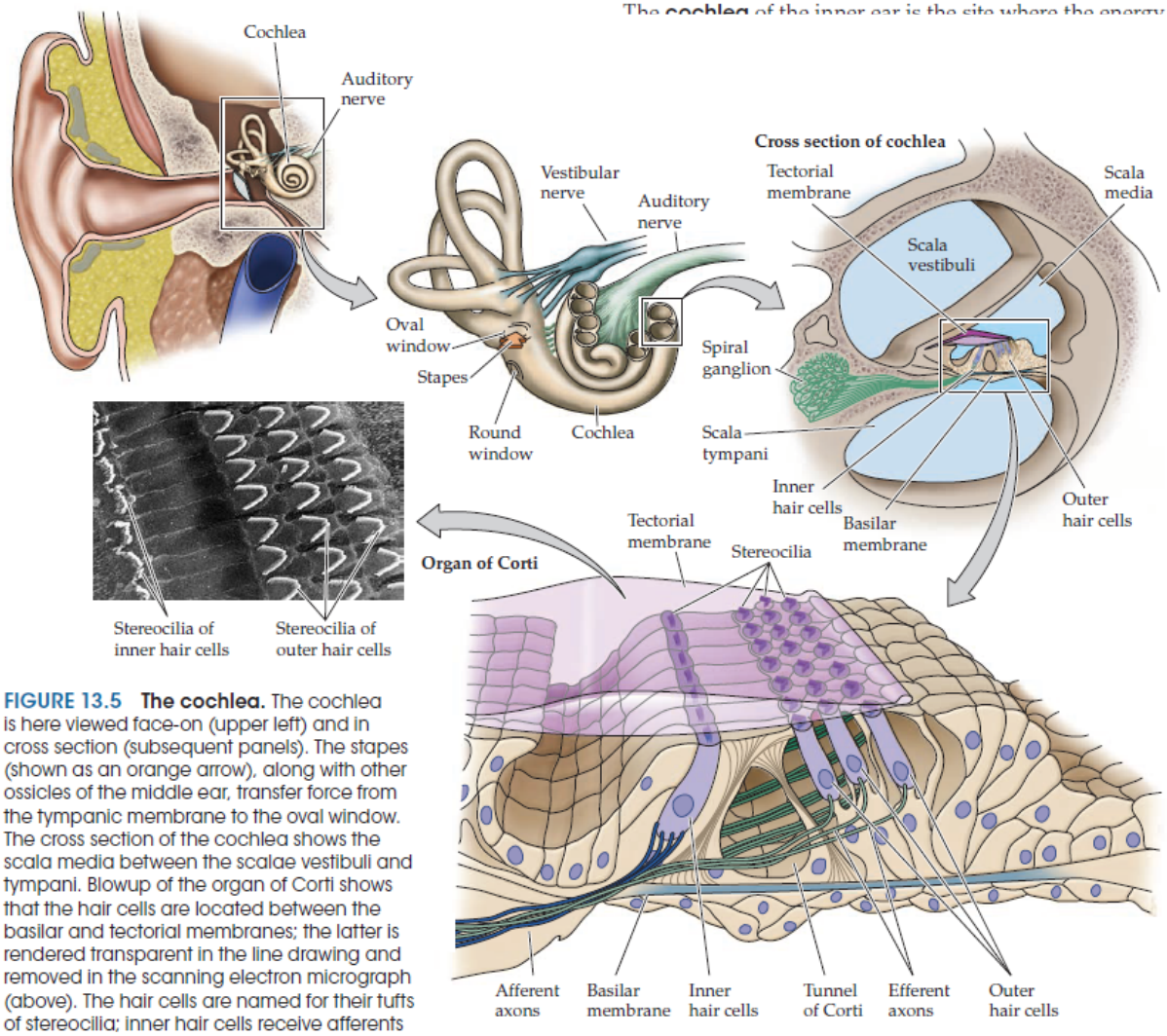
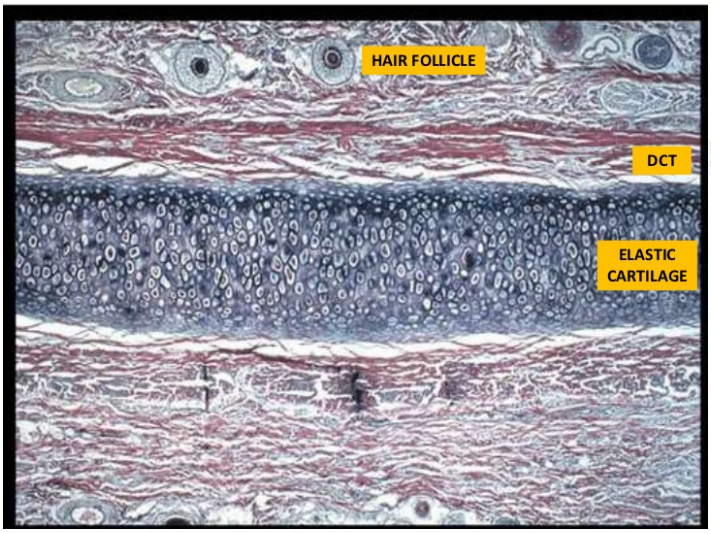


FIGURE 13.5 The cochlea. The cochlea is here viewed face-on (upper left) and in cross section (subsequent panels). The stapes (shown as an orange arrow), along with other ossicles of the middle ear, transfer force from the tympanic membrane to the oval window. The cross section of the cochlea shows the scala media between the scalae vestibuli and tympani. Blowup of the organ of Corti shows that the hair cells are located between the basilar and tectorial membranes; the latter is rendered transparent in the line drawing and removed in the scanning electron micrograph (above). The hair cells are named for their tufts of stereocilia; inner hair cells receive afferents from cranial nerve VIII, whereas outer hair cells receive mostly efferent innervation. (Micrograph from Counter et al., 1991.)

The **cochlea** of the inner ear is the site where the energy from sonically generated pressure waves is transformed into neural impulses. The cochlea not only amplifies sound waves and converts them into neural signals, but it also acts as a mechanical frequency analyser, decomposing complex acoustical waveforms into simpler elements.

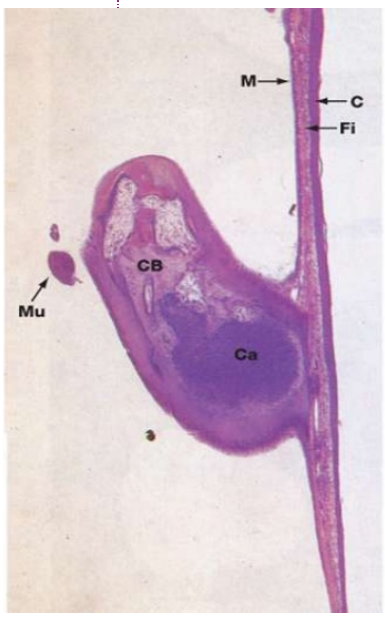
HISTOLOGY

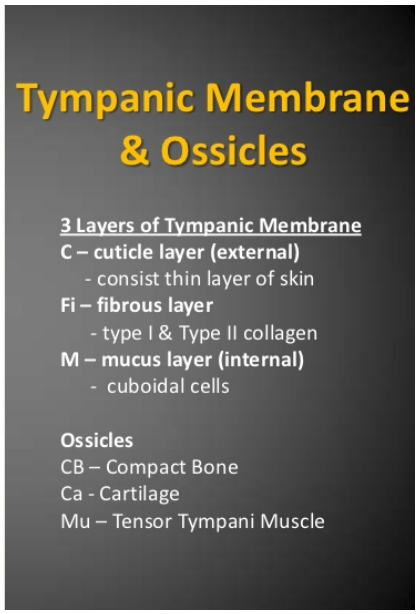
EXTERNAL EAR



In the external ear there are elastic cartilage which makes the ear flexible and a lot of hair to protect the middle ear. Therefore, in a histological view there are a lot of hair follicles to be seen.

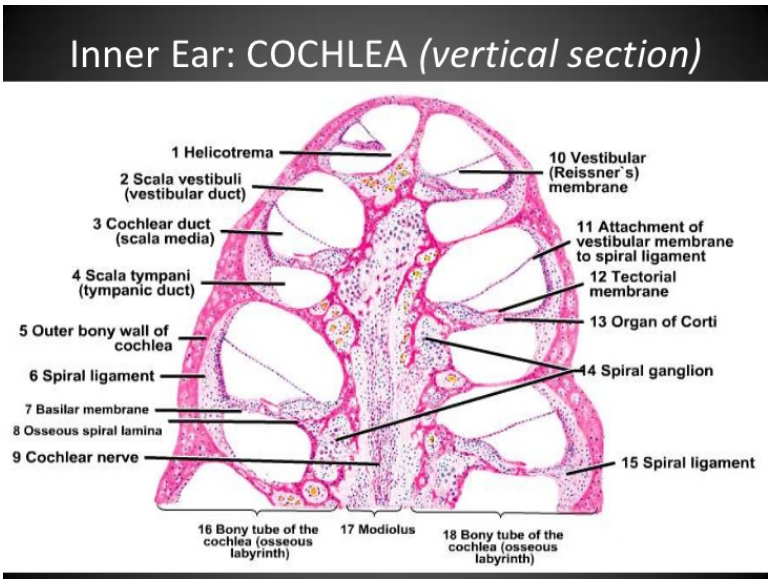
THE MIDDLE EAR





The middle ear contains the tympanic membrane, bones and the oval window.

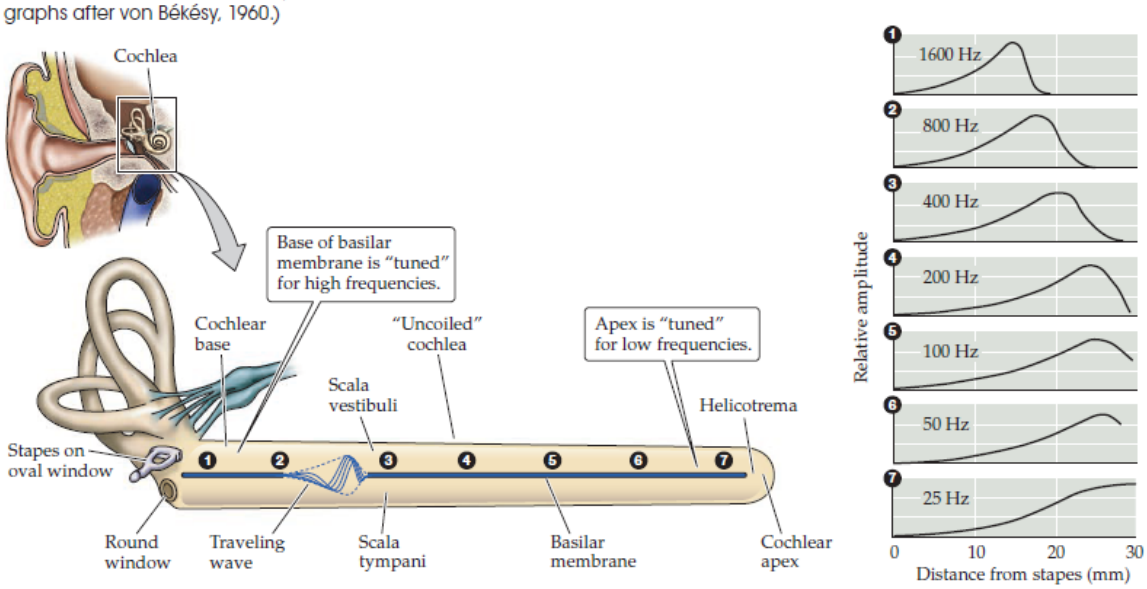
INNER EAR



The inner ear contains the cochlea, in the cochlea there are several hair cells that are important for generating signal that the axons take forth to the brain so that we can decode the signals into what we hear.

FREQUENCY TUNING

FIGURE 13.6 Traveling waves along the cochlea. A traveling wave is shown at a given instant along the cochlea, which has been uncoiled for clarity. The graphs on the right profile the amplitude of the traveling wave along the basilar membrane for different frequencies. The position (labeled 1–7 in the figure) at which the traveling wave reaches its maximum amplitude varies directly with the frequency of stimulation: Higher frequencies map to the base, and lower frequencies map to the apex. (Drawing after Dallos, 1992; graphs after von Békésy, 1960.)



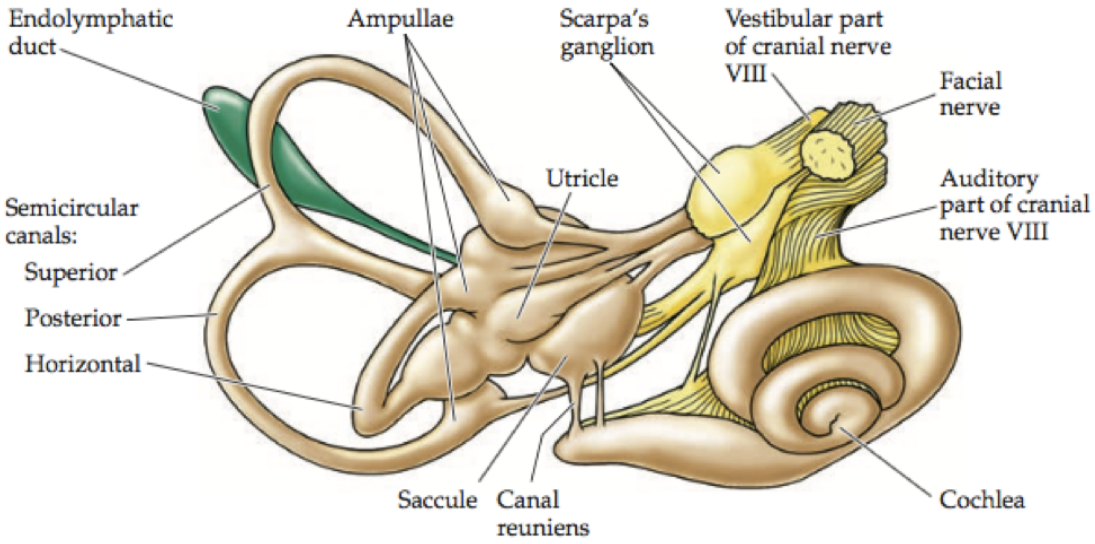
The auditory system is tonotopically organized where the basilar membrane is made up of fibers, where the base is stiffer and narrower than the apex. The base for the basilar membrane is tuned for higher frequencies, while the apex is tuned for lower frequencies. There are also outer hair cells that are frequency specific which move up and down in

response to specific frequencies.

A single auditory nerve fiber innervates only a single inner hair cell (although several or more auditory nerve fibers synapse on a single hair cell) meaning that each auditory nerve fiber transmits information about only a small part of the audible frequency spectrum. As a result, auditory nerve fibers related to the apical end of the cochlea respond to low frequencies, and fibers that are related to the basal end respond to high frequencies. These threshold functions are called **tuning curves**.

BALANCE/SPATIAL ORIENTATION

The vestibular system is important for balance, position and spatial orientation. The inner ear transforms mechanical information to action potentials that are sent to the brain. Apart from the cochlea that are a part of the auditory system, there are the vestibule that has the semi-circular and otolith organs that feel linear and circular accelerations.



CELLS IN VESTIBULE

The compositions of cells are the same in the utricle and the saccule only the position is different. There are hair cells in the apical part and reach up in the potassium rich endolymph whilst basal part in sodium rich perilymph.
The apical and basal part are separated by tight junctions allowing the different ion compositions.

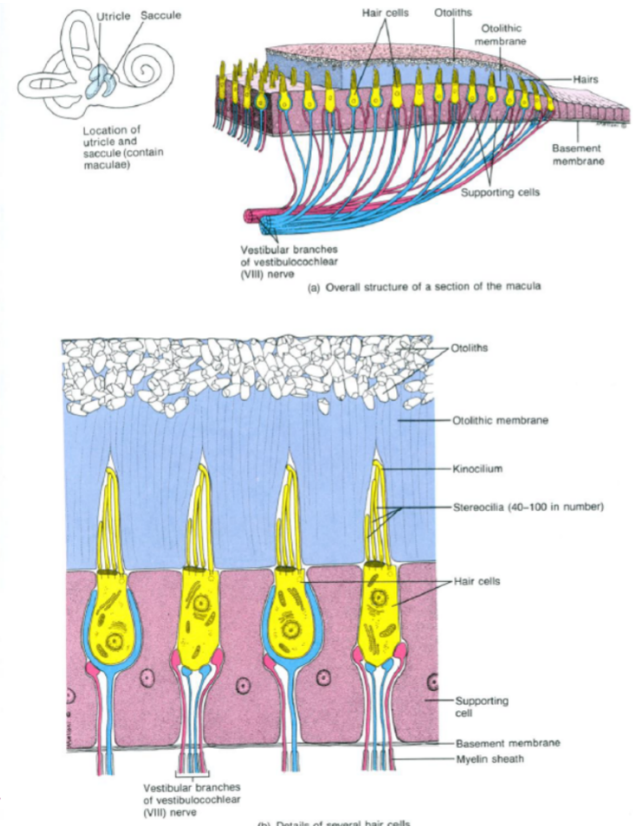
There are supporting cells, vestibule dark cells that secrete K+ to endolymph and hair cells of type I (bulgy) and type II (thin) that synapses with afferent axons from vestibular branch of CN 8

The otolithic membrane is a mucus rich membrane that are covering the hair cells, it has otoconia's on it. The otoconia's are calcium carbonate crystals.

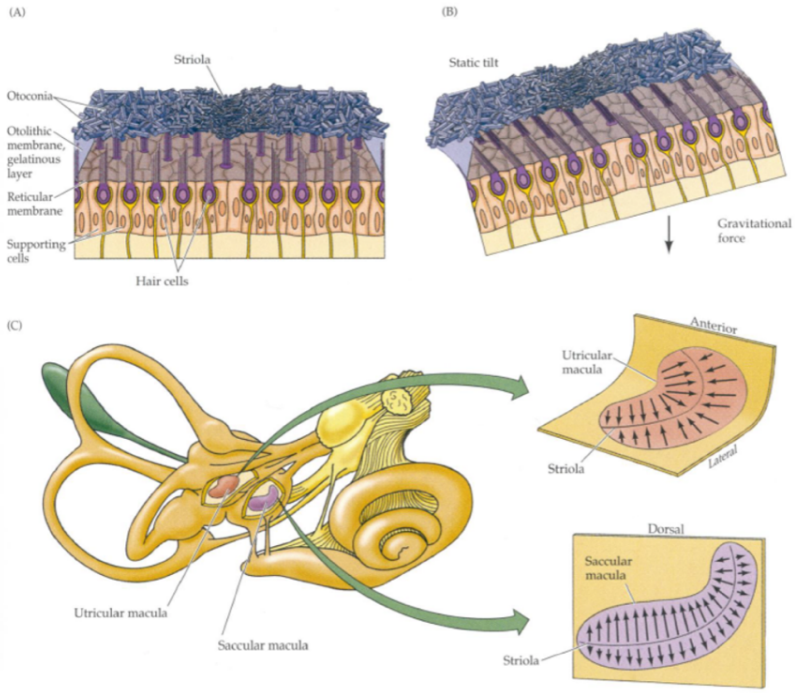
LINEAR ACCELERATION

In the inner ear there are areas that are answering to linear acceleration in both the horizontal and the vertical direction. These are called the otolith organs. The sacculus answer to the vertical and utricle to the horizontal movement. They have a similar morphology and mechanism.

They have a sensory epithelium called macula which has hair cells where stereocilium's grows. the stereocilium's are longer than the once in cochlea, above and around the stereocilium's there's a gelatinous membrane called otolithic membrane and above that there's otoconia. Otoconia is calcium carbonate crystals.



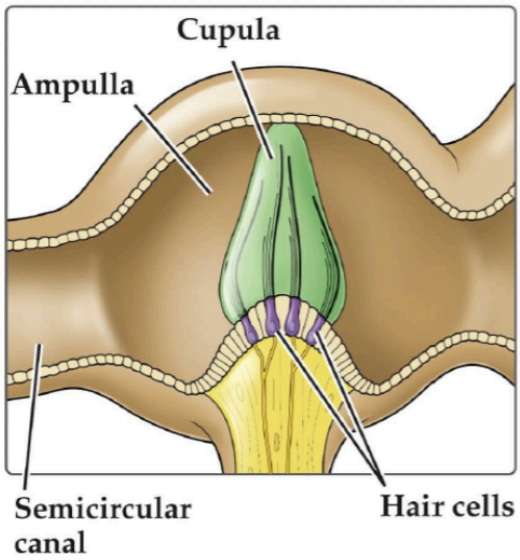
In a movement the hair cells get polarized and they bend, if they bend in the direction of the longer stereocilium it's an **excitation** and if it is bent in the direction of the shorter stereocilium it's an inhibition. When the stereocilium bends the otolithic membrane move and so does the otoconia. There's a groove called the striola and on one side of the striola the stereocilium's are arranged in one direction and on the other side they are arranged in a different direction. The striola creates a mirror of symmetry, so for example when we tilt our head forward hair cells of one side of the striola will be excited, while hair cells on the other side will be inhibited.

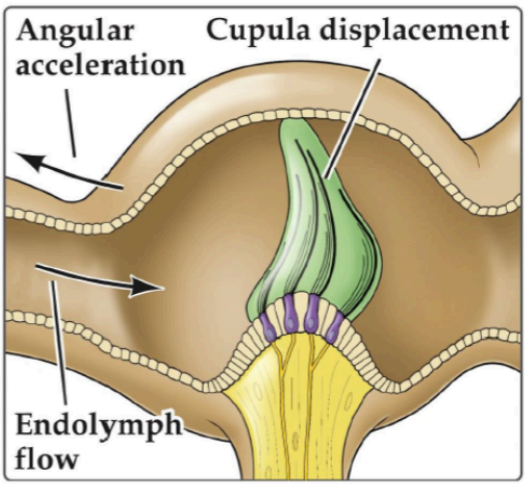


When the head is moved in a translational way there's a shearing force created between the stereocilium and because of the inertia of the otolithic membrane is greater than the macula there will be a delay in its movement compared to the macula.

There is always a spontaneous activity in the n. vetibulocochlearis and therefore there's always a small activity in the linear acceleration but not as much as in a movement.

CIRCULAR ACCELERATION





Rotation of the head are sensed by the semi-circular canals. They have an ampulla which is in the base of the semi-circular canals, here there are a cupula that have stereocilium's in it and the hair cells sits within the sensory epithelium that are called crista, this is a gelatinous mass. The hairs are arranged in one direction. In the canal there are a liquid called

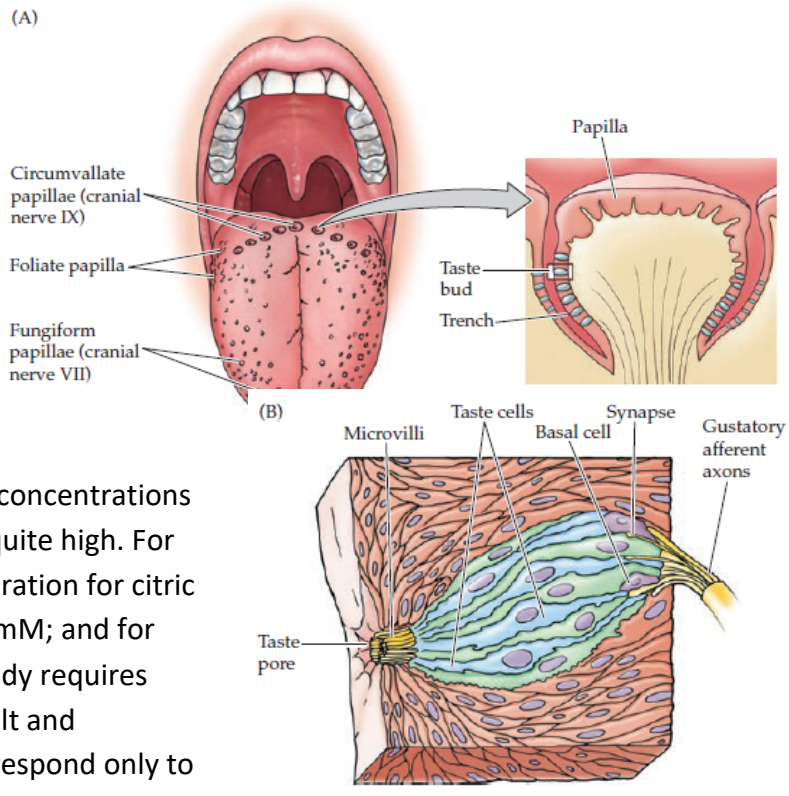
endolymph. If the liquid goes in one direction there's excitation and in the other inhibition. However, there are no striola so there are no axes for depolarisation instead the cupola creates a barrier in the flow of the endolymph.
When the head turns in the plane of one of the semi-circular canals, the inertial force causes endolymph to flow in the opposite direction. This will lead to displacements of the cupula; this will cause a deflection of the hair cells in the cupula. This results in that when we accelerate, we get a response, but if we keep rotating, the endolymph will move along the fixed structures and when we decelerate, we will get a response again.

The semi-circular canals are paired so when we rotate our head the endolymph will be set in motion on both sides; however, it will have a hyperpolarising effect on the hair cells of one side and a depolarisation of the other side. The semi-circular canals are mirror images of each other

For example, if the head is rotated to the left, endolymph in both horizontal canals will rotate to the right. This will lead to displacement of the cupula on both sides. On the left side, hair cells are displaced toward their kino- cilia, which causes the opening of cation channels and increased signal transduction. The opposite will happen on the other side.

TASTE

The taste system encodes information about the quantity as well as the identity of stimuli. Most taste stimuli are non-volatile, hydrophobic molecules that are soluble in saliva. In general, the perceived intensity of taste is directly proportional to the concentration of the taste stimulus. In humans, threshold concentrations for most ingested tastants are quite high. For example, the threshold concentration for citric acid is 2 mM; for salt (NaCl) 10 mM; and for sucrose 20 mM. Because the body requires substantial concentrations of salt and carbohydrates, taste cells may respond only to



relatively high concentrations of these essential substances in order to promote an adequate intake. The threshold for potentially dangerous substances, however, is much lower (0.008 mM for quinine and 0.0001 mM for the deadly substance strychnine).

Tastants are detected over the full surface of the tongue in receptive specializations called taste papillae. Papillae are defined by multicellular protuberances surrounded by local invaginations in the tongue epithelium. These invaginations for a trench to concentrate solubilized tastants. Taste buds are distributed along the lateral surfaces of the papillar protuberance as well as in the trench walls. They consist of specialized neuroepithelial receptor cells called taste cells, some supporting cells and occasional basal cells. In humans approximately 4000 taste buds are distributed throughout the surface of the tongue as well as the palate, epiglottis and oesophagus. Taste cells are clustered around a 1-mm opening called taste pore in the taste bud near the surface of the tongue. Solubilized tastants are further concentrated and are presented directly to the exposed taste receptor cells of the taste pore. Taste cells have a lifespan of about two weeks (presumably because they are exposed to infectious agents and environmental toxins) and are regenerated from basal cells.

There are three types of papillae: **fungiform** (which contain about 25% of the total number of taste buds), **circumvallate** (50%) and **foliate** (the remaining 25%). The three classes are distributed discontinuously on the surface of the tongue. Fungiform papillae are only found on the anterior two-thirds of the tongue; the highest density is at the tip. Fungiform papillae have a mushroom like structure and typically have three taste buds at their apical surface. There are nine circumvallate papillae that form a chevron (V-shape) at the back of the tongue. Each consists of a circular trench that contains about 250 taste bunds along the trench walls. Two foliate papillae are present on the posterolateral tongue, each having about 20 parallel ridges with about 600 taste buds in their walls. Thus, chemical stimuli on the tongue first stimulate receptors on fungiform receptors and then in the foliate and circumvallate papillae. Tastants subsequently stimulate scattered taste buds in the pharynx, larynx and upper oesophagus.

Based on general agreement across cultures, the taste system detects five perceptually distinct categories of tastants: **salt**, **sour**, **sweet**, **bitter** and **umami** (From the Japanese word for delicious and refers to the savory tastes, including monosodium glutamate and other amino acids) (though there are obvious limitations to this classification). Salt tastes include NaCl which is needed for electrolyte balance; sour tastes are associated with acidity and thus protons (H+) indicate palatability of various foods.; sweet tastes include sugars and other carbohydrates are needed for energy; bitter tasting molecules include plant alkaloids such as atropine, quinine and strychnine, indicate foods that might be poisonous; and umami tastes are associated with essential amino acids.

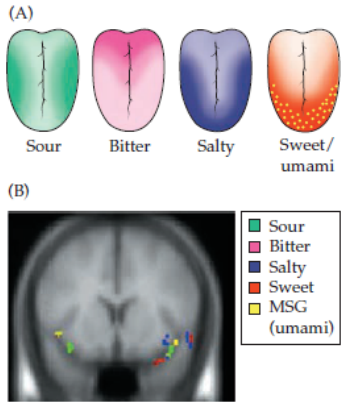
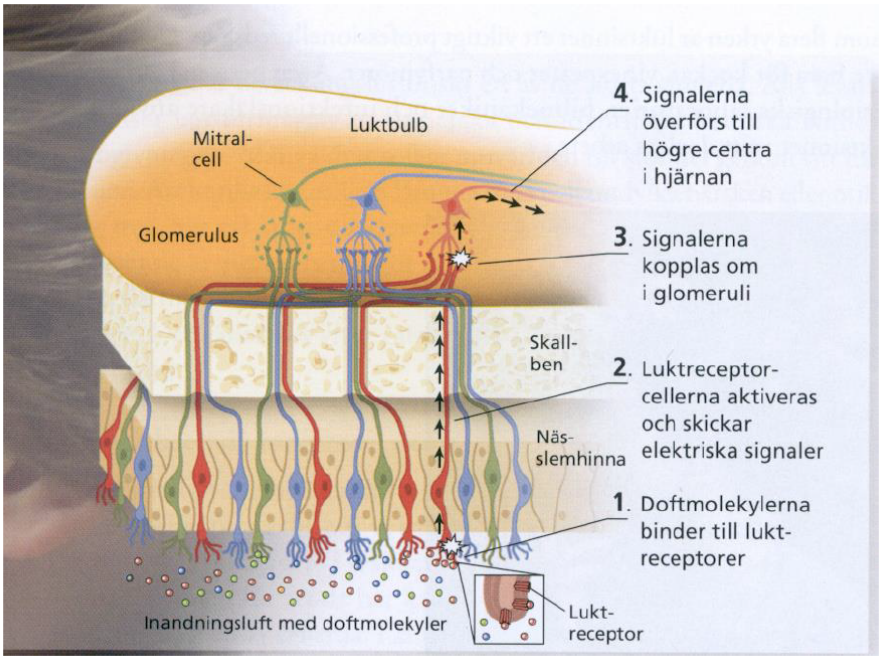


FIGURE 15.22 Peripheral innervation of the tongue. (A) Responses to sweet/umami, salty, sour, and bitter tastants recorded in the three cranial nerves that innervate the tongue and epiglottis. (B) Composite fMRI showing the different locations of focal activation in the insular cortex in response to each of the tastes encoded by taste receptors. (B from Schoenfeld et al., 2004.)

Although all tastes can be detected over the entire surface of the tongue, different regions of the tongue have different thresholds for various tastes. These discontinuities in taste sensitivity may be related to aesthetic, metabolic, and potentially toxic qualities detected by the taste receptors in the tongue. The tips of the tongue is most responsive to sweet, umami and salty compounds, all of which produce pleasurable sensations at somewhat higher concentrations. Tastes encountered by this region – the initial point of contact for most ingested foods – activate feeding behaviours such as mouth movements, salivary secretions, insulin release and swallowing. The acquisition of foods high in carbohydrates and amino acids is beneficial (in moderation), and thus it is not surprising that the most exposed region of the tongue is especially sensitive to these tastes.

Sour and bitter taste sensitivity is lowest towards the tip and greatest on the sides and back of the tongue. It seems reasonable that after it has analysed the food for nutrient content that they follow with evaluating the acidity and bitterness to indicate a lack of palatability (excessive sourness) or even toxicity (bitterness). Sour tasting compounds elicit grimaces, puckering, and massive salivary secretions to dilute the tastant. Activation of the rear of the tongue by bitter tasting substances elicit its protrusion of the tongue and other protective reactions (expectoration and gagging) that prevent ingestion.

SMELL

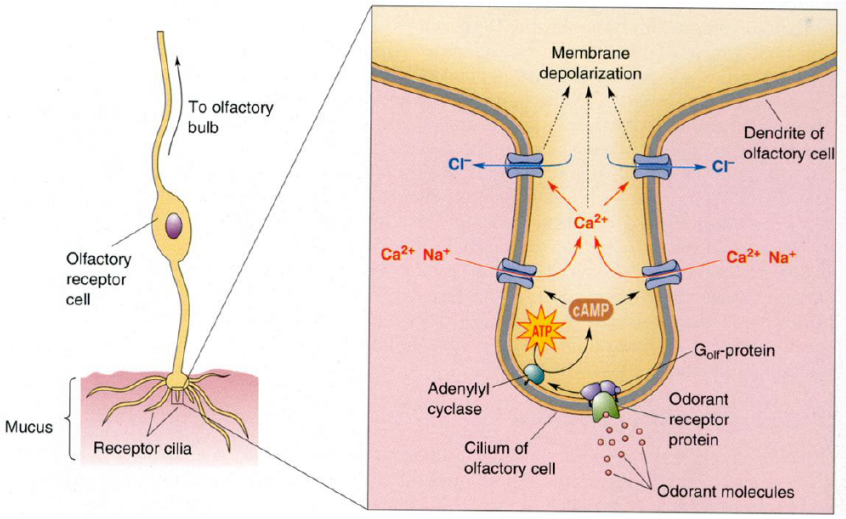


SUMMARY/OVERVIEW

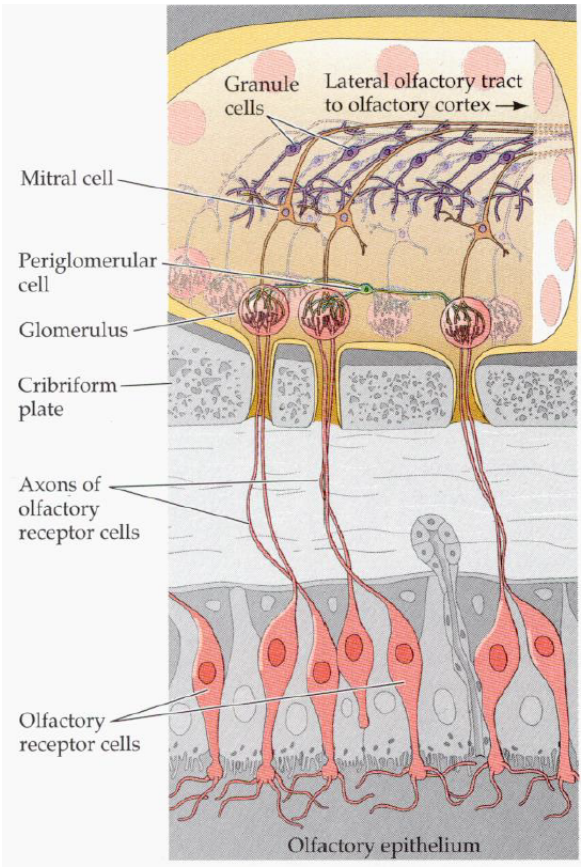
Odour molecules binds to receptors on cilium of the receptor cell of the olfactorius. That activates them and a signal is sent through the lamina cribrosa and are cutover in the glomerulus and transferred to the centre in the brain. There is a sorting of the odour molecules, they can only bind to specific receptors.

LONG VERSION

In the nose there are olfactory cells with an olfactory bulb and cilium's as well as bowman's glands that secrets a type of mucus. The odour molecules enter the nose and ends up in the mucus, then it binds to a receptor on the cilium. The receptor is coupled with a G-protein that activates adenylate cyclase that transforms ATP → cAMP. cAMP binds to cation channels and activate them, this results in that and can come into the cell and give rise to a transduction.



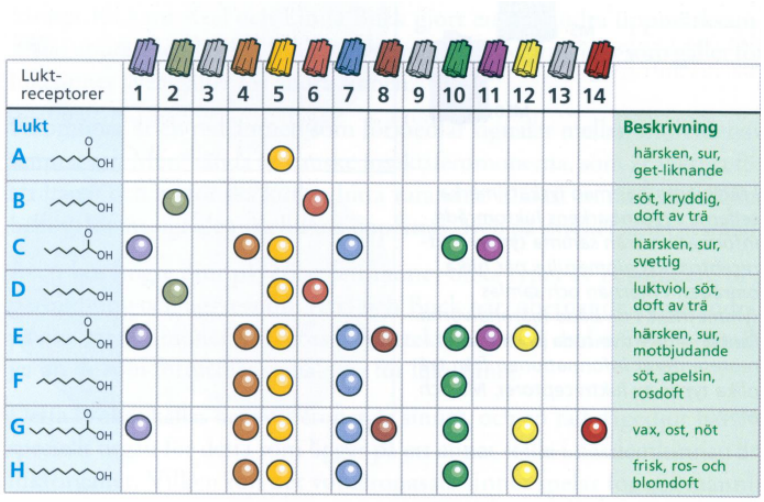
The membrane depolarisation leads to a signal being sent via the axons that run through the lamina cribrosa to the glomerulus. The glomeruli are bundles of axons (synapses) and dendrites (from the mitral cells). The mitral cells, that are the principal neuron in the olfactory bulb take the signal through the lateral olfactory tract to the olfactory cortex. By the glomerulus there are periglomerular cells that help with lateral inhibition, this is important in environments with a lot of odours where we need to sort out the most important odour. After the mitral cells there are granule cells that also is inhibitory (inhibitory interneurons) they are also important for the sorting.



Each olfactory receptor cell possesses only one type of odorant receptor (the G-receptor) and each of these can detect a limited number of odorant substances. So, one olfactory receptor cell expresses only one of the odorant receptor genes (there are several, about 3 % of our genome code for the different odour receptors), each one of these cells can react to several odour molecules that are related. So,

for example, to receptor 10 five different types of odour molecules can bind, they all have different types of odours and they vary from sweet, orange and rose sent to sour, sweat and rancid.
Each molecule can activate several receptors and the combination gives rise to a code or odour pattern. Most odours are composed of multiple odorant molecules and this is why we can distinguish and smell so many odours.

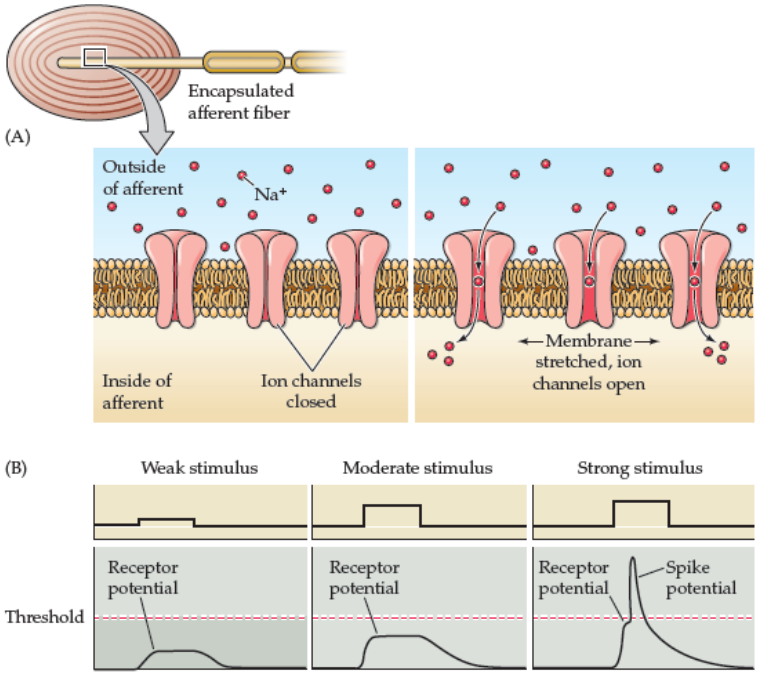
Combinatorial Code for Odors



EXPLAIN, FOR THE DIFFERENT SENSORY MODALITIES, HOW SPECIALIZED SENSORY CELLS / RECEPTORS TRANSDUCE A STIMULUS INTO ELECTRICAL SIGNALS (S2, S3)

TOUCH, VIBRATION, PRESSURE AND PAIN

The fundamental mechanism of sensory transduction – the process o
of a stimulus into an electrical signal – is similar in all somatosensory afferents: A stimulus alters the permeability of cation channels in the afferent nerve endings, generating a depolarizing current known as receptor (or generator) potential. If sufficient in magnitude, the receptor potential reaches threshold for the generation of action potentials in the afferent fiber; the resulting rate of action potential firing is roughly proportional to the magnitude of the depolarization.



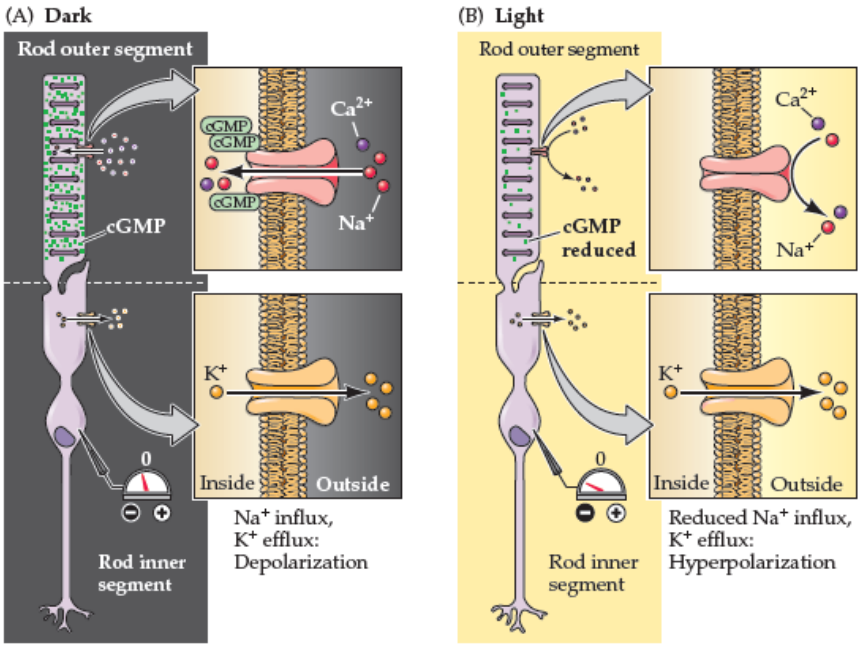
Afferent terminals that detect and transmit touch sensory stimuli (mechanoreceptors) are often encapsulated by specialized receptor cells that help tune the afferent fiber to particular features of somatic stimulation. Afferent fibers that lack specialized receptor cells are referred to as free nerve endings (nociceptors) and are especially important in the sensation of pain. Afferents that have encapsulated endings generally have lower thresholds for action potential generation and are thus more sensitive to sensory stimulation than free nerve endings.

TEMPERATURE

Thermoreceptors work by generating action potentials; the frequency of these action potentials, however, are affected by the environment temperature as well as changes in temperature. Cold receptors for example respond to sudden cooling with an increase in discharge frequency (dynamic response) that is directly related to the prior temperature and the magnitude and rate of the temperature decrease. If the cooler temperature is maintained, the discharge frequency adapts to a frequency of static discharge directly related to the cooler temperature. If the temperature increases, the discharge frequency decreases and later adapts to a new static value. Warm receptors show a similar response except that they increase discharge frequency to warming and decrease discharge frequency to cooling.

LIGHT

In most sensory systems, activation of a receptor by the appropriate stimulus causes the cell membrane to depolarize, ultimately stimulating an action potential and transmitter release onto the neurons it contacts. In the retina, however, photoreceptors do not exhibit action potentials; rather, light activation causes a graded change in membrane potential and a corresponding change in the rate of transmitter release onto postsynaptic neurons.



More surprising is that shining light on a photoreceptor, either a rod or a cone, leads to membrane hyperpolarization rather than depolarization. In the dark the receptor is in a depolarized state, with a membrane potential of about -40 mV (including those portions of the cell that release transmitters). Progressive increases in the intensity of illumination cause the potential across the receptor to become more negative, a response that saturates the when the membrane potential reaches about -65 mV. While it might seem odd the only logical requirement is a consistent relationship between luminance and rate of transmitter release from the photoreceptor terminals. As in other nerve cells, transmitter release is dependent on voltage sensitive Ca^{2+} channels in the terminal membrane. This in the dark, when photoreceptors are relatively depolarized, the number of open Ca2+ channels in the synaptic terminal is high, and the rate of transmitter release is correspondingly great; in the light when receptors are hyperpolarized the number of open Ca^{2+} channels is reduced and the rate of transmitter release is also reduced.

The reason for this unusual arrangement compared with that of other sensory receptor cells is not known but it may have to do with the challenge of responding to both increases and decreases in luminance. In the dark, cations (both Na^+ and Ca^{2+}) flow into the outer segment through membrane channels that are gated by cGMP. This inward current is opposed by an

outward current that is mediated by potassium selective channels in the inner segment. Thus, the depolarized state reflects the net contribution of Na^+ and Ca^{2+} influx, which acts to depolarize the cell, and K^+ efflux, which acts to hyperpolarize the cell. Absorption of light by the photoreceptor reduces the concentration of cGMP in the outer segment which in turn leads to a closure of cGMP-gated channels in the outer segment membrane and, consequently, a reduction in the inward flow of Na^+ and Ca^{2+}. As a result, positive charge (carried by K^+) flows out of the cell more rapidly than positive charge flows in and the cell becomes hyperpolarized.

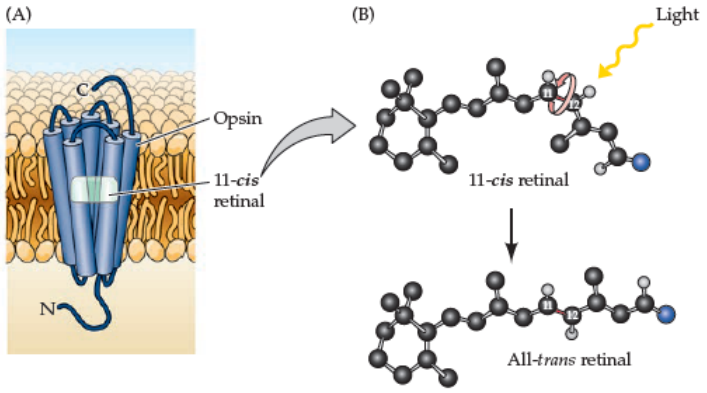
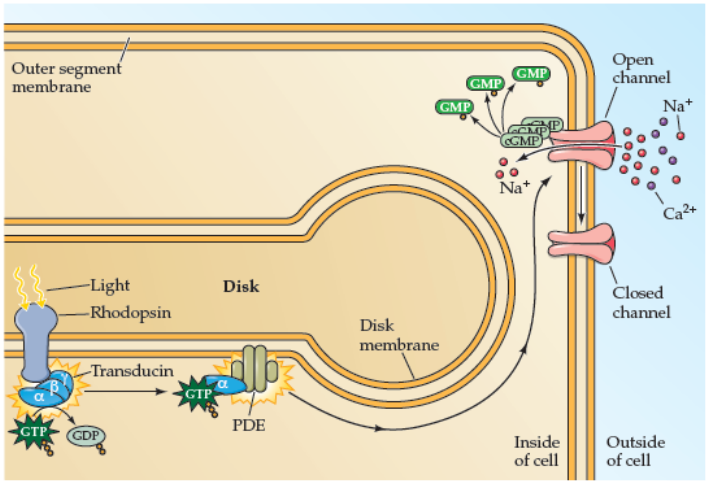


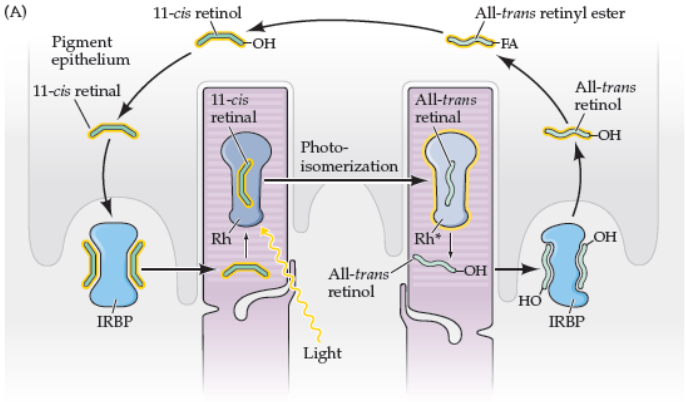
FIGURE 11.9 Phototransduction in rod photoreceptors. (A) Rhodopsin resides in the disk membrane of the photoreceptor outer segment. The seven transmembrane domains of the opsin molecule enclose the light-sensitive retinal molecule. (B) Absorption of a photon of light by retinal leads to a change in configuration from the 11-*cis* to the all-*trans* isomer. (C) The second messenger cascade of phototransduction. The change in the retinal isomer activates transducin, which in turn activates a phosphodiesterase (PDE). The PDE then hydrolyzes cGMP, reducing its concentration in the outer segment and leading to the closure of channels in the outer segment membrane. (A,B after Oyster, 1999; A after Stryer, 1986; B after Stryer, 1987.)

The series of biochemical changes that ultimately leads to a reduction in cGMP levels begin when a photon is absorbed by the photopigment in the receptor disks. The photopigment contains the light-absorbing chromophore retinal (an aldehyde of vitamin A) coupled to one of several possible proteins called opsins. The different opsins tune the molecule's absorption of light to a particular region of the light spectrum; this is the differing protein components of the photopigments in rods and cones that allow the functional specialization of these two receptor types.

In rods the photopigment is rhodopsin; the seven transmembrane domains of the opsin molecule traverse the membrane of the disks in the outer segment, forming a pocket in which the retinal molecule resides. When retinal absorbs a photon of light, one of the double bonds between the carbon atoms in the retinal molecule breaks and its configuration changes from the 11-cis isomer to all-trans retinal; this change triggers a series of alterations in the opsin component of the molecule. The changes in opsin lead, in turn, to the activation of an intracellular messenger called transducing, which activates a phosphodiesterase (PDE) that hydrolyses cGMP. The hydrolysis of PDE at the disk membrane lowers



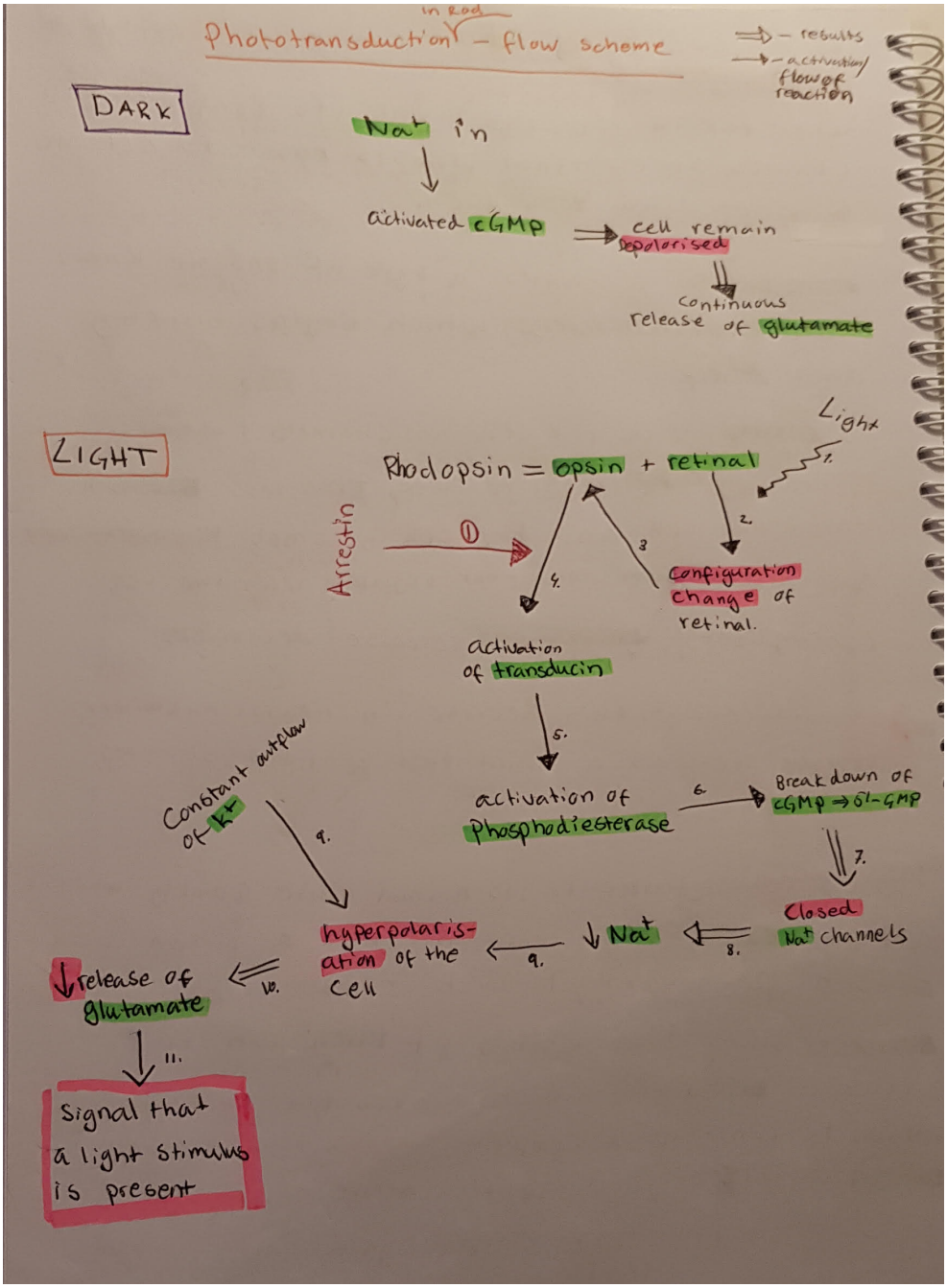
cGMP concentration throughout the outer segment which reduces the amount of cGMP molecules available to bind to the channels in the surface of the outer segment membrane and in turn leading to channel closure.



One of the important features of this complex is biochemical cascade initiated by photon capture is that it provides enormous signal amplification. A single light activated rhodopsin molecule can activate as many as 800 transducin molecules on the disk surface. Although each transducing molecule activates only one PDE molecule, each PDE is capable of catalysing the breakdown of as many as 6 cGMP molecules. As a result, the absorption of a single photon by a rhodopsin molecule results in the closure of approximately 200 ion channels, or about 2% of the number of channels in each rod that are open in the dark. This number of channel closures causes a net change in the membrane potential of about 1 mV.

Once initiated additional mechanisms limit the duration of this amplifying cascade and restore the various molecules of their inactivated states. Activated rhodopsin is rapidly phosphorylated by rhodopsin kinase, which permits the protein arrestin to bind to rhodopsin. Bound arrestin blocks the ability of activated rhodopsin to activate transducin which effectively truncate the phototransduction cascade.

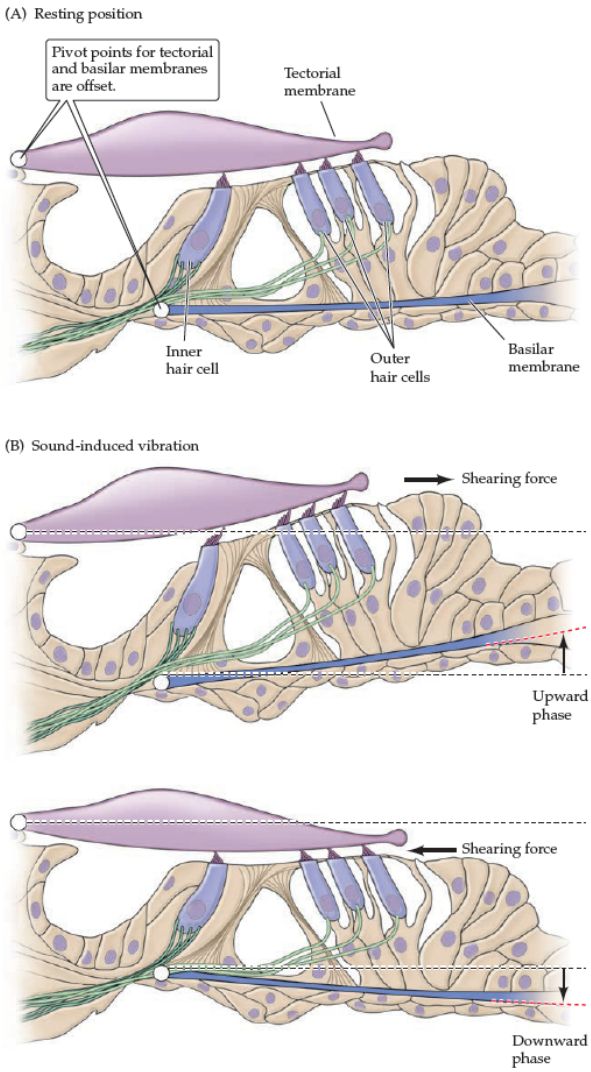
Restoration of retinal to a form capable of signalling photon capture is a complex process known as the retinoid cycle. The all-trans retinal dissociates from opsin and diffuses into the cytosol of the outer segment; there it is converted to all-trans retinol and transported into the pigment epithelium via a chaperone protein, inter-photoreceptor retinoid binding protein (IRBP) where appropriate enzymes ultimately convert it to 11-cis retinal. After being transported back into the outer segment via IRBP, 11-cis retinal recombines with opsin in the receptor disks.


Phototransduction in Rod – flow scheme
⇒ – results
→ – activation/ flow of reaction
DARK
Na+ in
activated cGMP
cell remain depolarised
continuous release of glutamate
LIGHT
Light
Rhodopsin = opsin + retinal
Arrestin
1.
2.
3
4.
configuration change of retinal.
activation of transducin
5.
activation of Phosphodiesterase
6
Break down of cGMP ⇒ 5'-GMP
7.
Closed Na+ channels
8.
↓ Na+
9.
hyperpolarisation of the cell
Constant outflow of K+
9.
10.
↓release of glutamate
11.
signal that a light stimulus is present

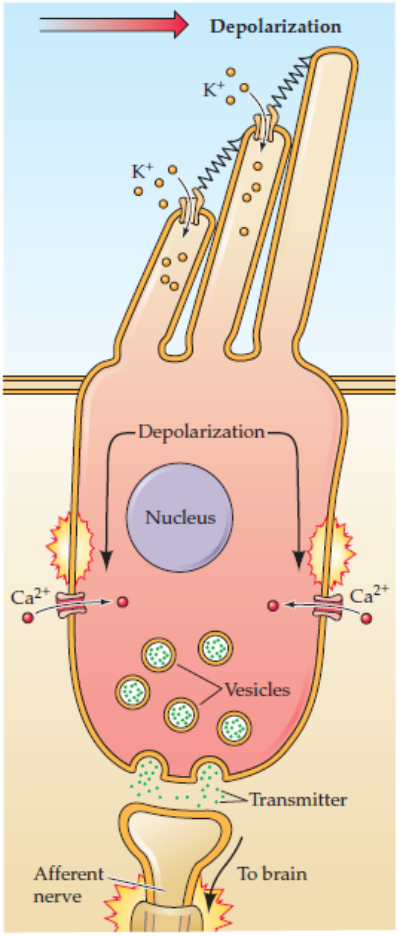
SOUND

The auditory system is an array of miniature acoustical detectors which can transduce vibrations as small as the diameter of an atom, and they respond 1000 times faster than visual photoreceptors.

Sound waves are transmitted via the external and middle ear to the cochlea of the inner ear, which exhibits a traveling wave when stimulated. The traveling wave initiates sensory transduction by displacing the sensory hair cells that sit atop the basilar membrane. Because the basilar membrane and the overlying tectorial membrane are anchored at different positions, the vertical component of the traveling wave is translated into a shearing motion between these two membranes. This motion bends the tiny processes, called stereocilia, that protrude from the apical ends of the hair cells, leading to voltage changes across the hair cell membrane.



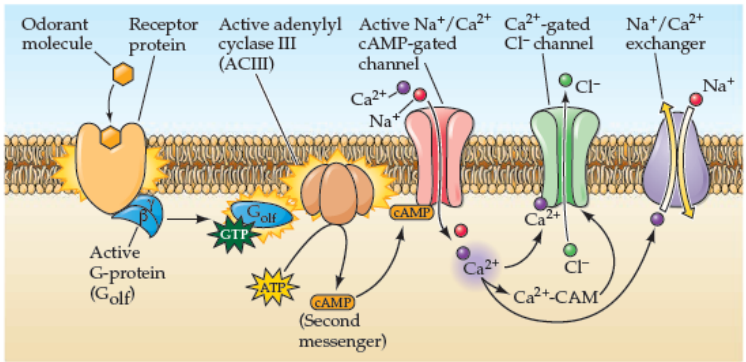
The cochlear hair cells in humans consist of one row of inner hair cells (sensory receptors) and three rows of outer hair cells. The hair cell is a flask-shaped epithelial cell named for the bundle of hairlike processes that protrude from its apical end into the scala media. Each hair bundle contains anywhere from 30 to a few hundred stereocilia, with one taller kinocilium (disappears shortly after birth in mammalian cochlear hair cells). The stereocilia are graded in height and are arranged in a bilaterally symmetrical fashion; in vestibular hair cells, this plane runs through the kinocilium. Fine filamentous structures, known as tip links, run in parallel to the plane of bilateral symmetry, connecting the tips of adjacent stereocilia.



The tip links, which consist of the cell adhesion molecules cadherin 23 and protocadherin 15, provide the means for rapidly translating hair bundle movement into a receptor potential. Displacement of the hair bundle parallel to the plane of bilateral symmetry in the direction of the tallest stereocilia stretches the tip links, directly opening cation-selective mechanoelectrical transduction (hair cell MET or hcMET) channels located at the end of the link and depolarizing the hair cell. Movement in the opposite direction compresses the tip links, closing the hcMET channels and hyperpolarizing the hair cell. As the linked stereocilia pivot back and forth, the tension on the tip link varies, modulating the ionic flow and resulting in a graded receptor potential that follows the movements of the stereocilia. This receptor potential in turn leads to transmitter release from the basal end of the hair cell, which triggers action potentials in cranial nerve VIII fibers that follow the up-and-down vibration of the basilar membrane at relatively low frequencies.

SMELL

The olfactory system—the most thoroughly studied component of the chemosensory triad—processes information about the identity, concentration, and quality of a wide range of airborne, volatile chemical stimuli called odorants.

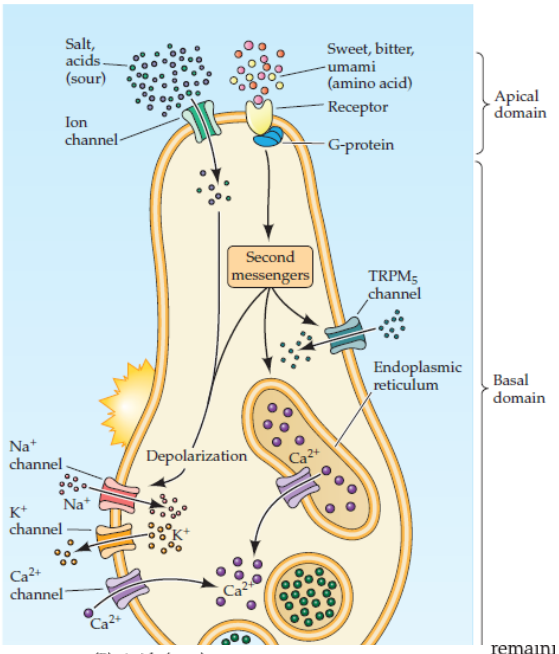


Odorants in the mucus bind directly (or are shuttled via odorant binding proteins) to one of

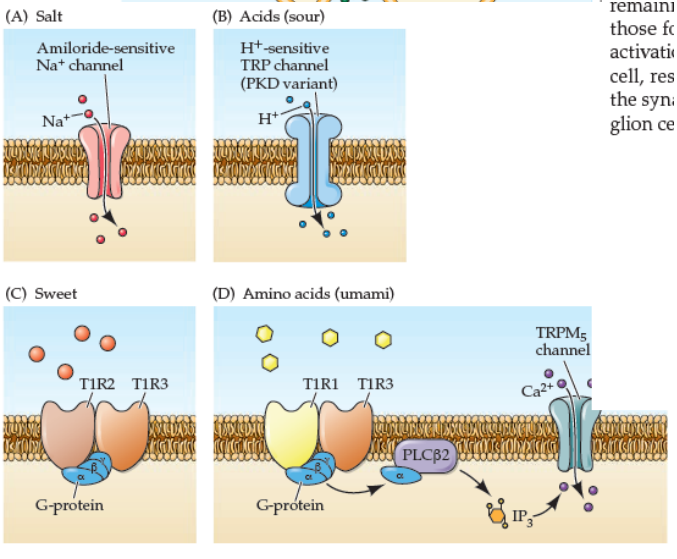
many receptor molecules located in the membranes of the cilia. This association activates an odorant-specific G-protein (Golf) that, in turn, activates an adenylate cyclase (ACIII), resulting in the generation of cyclic AMP (cAMP). One target of cAMP is a cation-selective channel that, when open, permits the influx of Na^+ and Ca^{2+} into the cilia, resulting in depolarization and action potentials. The ensuing increase in intracellular Ca^{2+} opens Ca^{2+}-gated Cl^- channels that provide most of the depolarization of the olfactory receptor potential.

TASTE

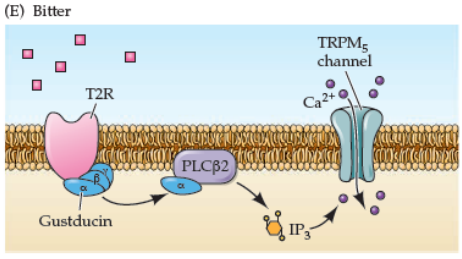
Based on general agreement across cultures, the taste system detects five perceptually distinct categories of tastants: **salt**, **sour**, **sweet**, **bitter** and **umami** (From the Japanese word for delicious and refers to the savory tastes, including monosodium glutamate and other amino acids) (though there are obvious limitations to this classification).



Taste cells arebpolarized epithelial cells with an apical and a basal domain separated by tight junctions. Tastant-transducing channels (salt and sour) and G-protein-coupled receptors (sweet, amino acid, and bitter) are limited to the apical domain. Intracellular signaling components that are coupled to taste receptor molecules (G-proteins and various second-messenger-related molecules) are also enriched in the apical domain. Voltage-regulated Na^+, K^+, and Ca^{2+} channels mediate release of neurotransmitter from presynaptic specializations at the base of the cell onto terminals of peripheral sensory afferents.



(A) Cation selectivity of the amiloride-sensitive Na+ channel versus the H+-sensitive proton channel provides the basis for specificity of salty tastes.



(B) Sour tastants are transduced by a proton-permeant, nonselective cation

channel that is a member of the transient receptor potential (TRP) channel family. In both cases, positive current via the cation channel leads to depolarization of the cell.

(C–E) For sweet, amino acid (umami), and bitter tastants, different classes of G-protein-coupled receptors mediate transduction.

DEFINE THE CENTRAL PATHWAYS CONVEYING SENSORY INFORMATION FROM THE DIFFERENT PARTS OF THE BODY (S2, S3)

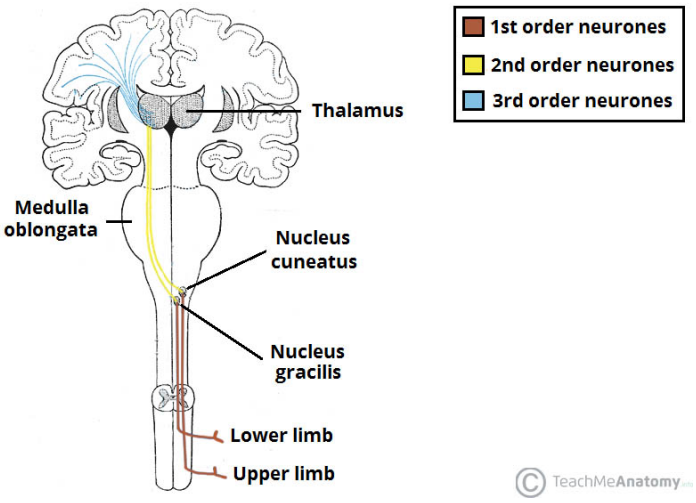
CENTRAL PATHWAY – POSTERIOR PART OF THE HEAD AND THE REST OF THE BODY

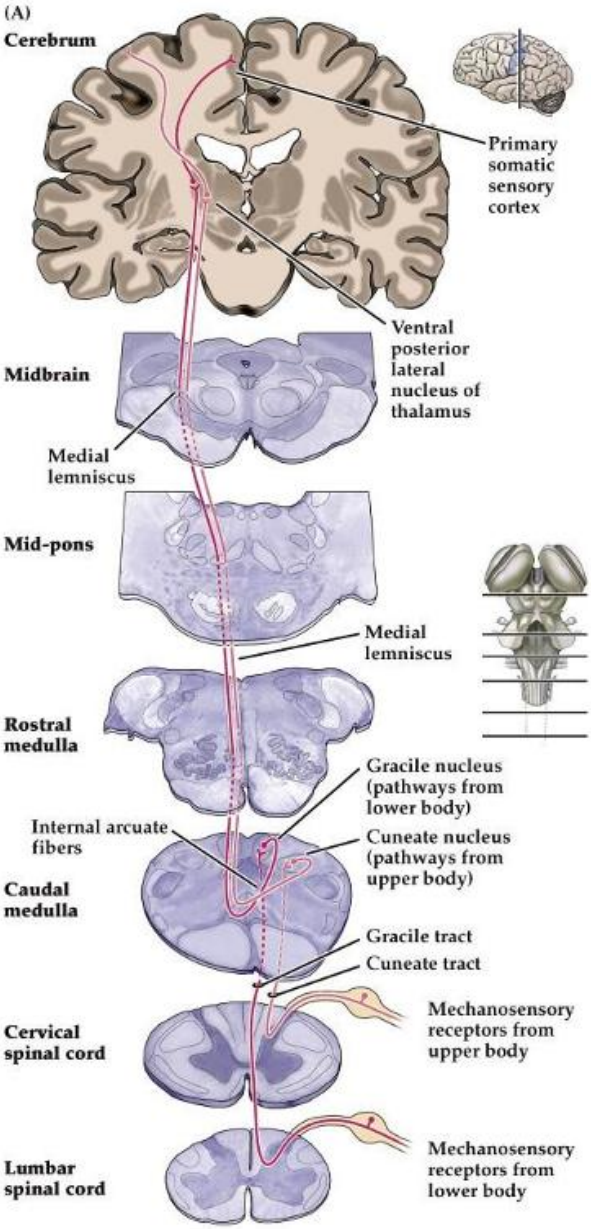
A signal from touch and a signal from temperature and pain is not travelling the same way from the visceral parts of the body to the brain. There's also a difference in the pathways depending on from where the signal comes from; for the posterior part of the head and the rest of the body there's one way and from the anterior part of the head (face) there's another pathway.

The central pathway for the posterior part of the head and the rest of the body below the head are called **DORSAL COLUMN – MEDIAL LEMNISCAL PATHWAY.** Here the signal goes through the axon to the **dorsal horn to the medulla** in the spinal cord. Here a cutover from the first order neuron to the second order neuron is made, this cutover takes place in a nucleus. For the **lower body** it takes place in the **gracile nucleus** and for the **upper body** in the **cuneate nucleus**.

The second order neurons axon is now crossing the midline, this is called **DECUSSATE**. It then travels up to the thalamus and the VPL (venteral posterior lateral thalamus) where a cutover to a third order neuron is made. The third order neuron axon goes to the somatosensory cortex (S1) where the signal is encoded.

Summary: 1:st order axon to dorsal horn → gracile nucleus/cuteate nucleus → 2:nd order axon decussate → VPL thalamus → 3:rd order axon to somatosensory cortex



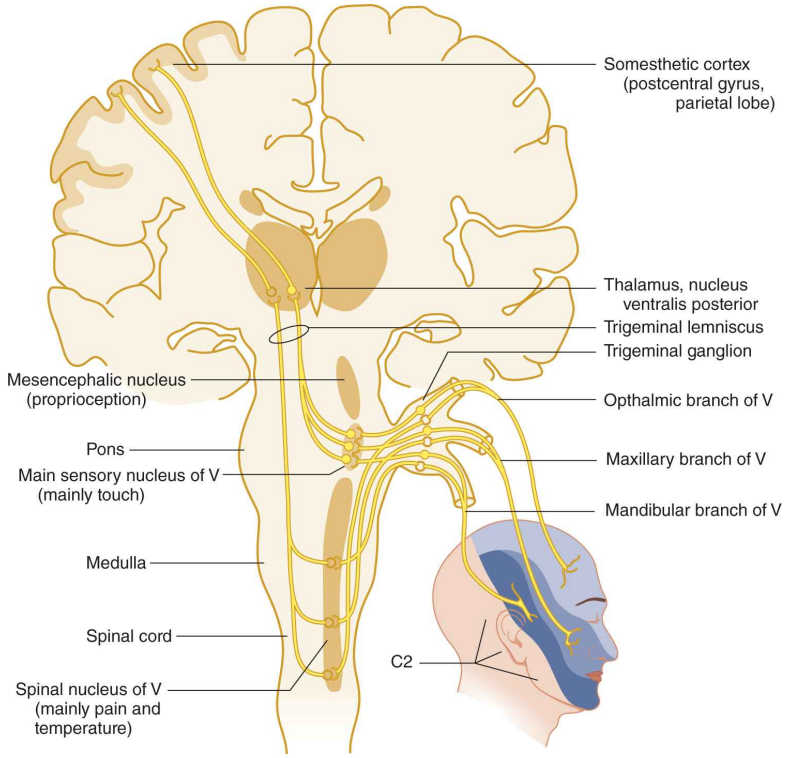


***NEUROSCIENCE 5e*, Figure 9.8 (Part 1)**

CENTRAL PATHWAY – ANTERIOR PART OF THE HEAD (FACE)

The sensory signal for the face is mainly sent from the n. trigeminus. It goes to the ganglion trigeminus to the principal nucleus of trigeminal complex where the cutover to the 2:nd

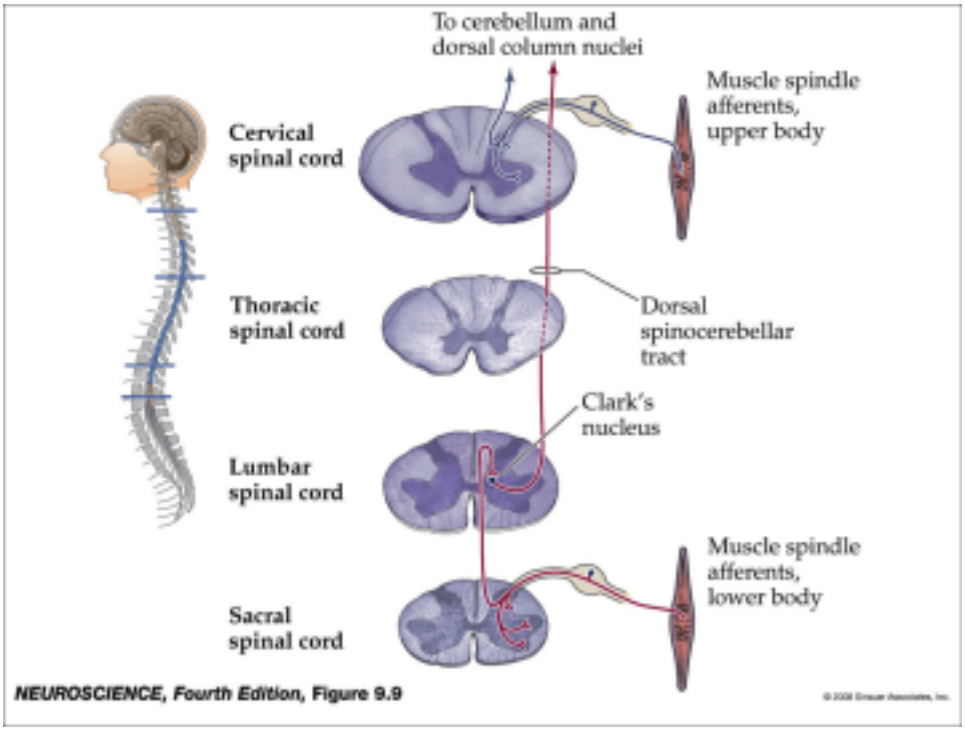
order neuron. Then the decussate (crossing) is made before the axon goes to medial lemniscus and up to the thalamus and more exactly the VPM thalamus (ventral posterior medial thalamus) where the cutover to the 3:rd neuron to the somatosensory cortex.



PROPRIOCEPTION PATHWAY

The first order neuron goes through the ganglion to the dorsal horn, here it splits up. The first order neurons have more than one synapses for reflexes and some parts goes upwards through the brain. In the thoracic region (for the lower body) and in the clarke's nucleus a cutover to the second order neuron and the axon goes via the tractus spinocerebellum dorsalis in the white matter to the cerebellum and some to the somatosensory cortex (it does not do a crossing). The afferents from the upper body goes to the dorsal horn in the cervical spinal cord, there it splits to both synapses for reflexes and some goes to the external cuneate nucleus.

The proprioceptive information from the face goes to the mesencephalic nucleus of the trigeminal nerve.



CENTRAL PAIN PATHWAY

The pathways responsible for pain originate with other sensory neurons in dorsal root ganglia, and like other sensory nerve cells, the central axons of nociceptive nerve cells enter the spinal cord via dorsal roots. When these centrally projecting axons reach the dorsal horn of the spinal cord, they branch into ascending and descending collaterals, forming the **dorsolateral tract of Lissauer**.

Axons in Lissauer's tract typically run up and down for one or two spinal cord segments before they penetrate the grey matter of the dorsal horn. Once within the dorsal horn, the axons give off branches that contact second-order neurons located in Rexed's laminae I, II, and V (Rexed's laminae are the descriptive divisions of the spinal gray matter in cross section). Laminae I and V contains projection neurons whose axons travel to the brainstem and thalamic targets. While there are interneurons in all laminae of the spinal cord, they are especially abundant in lamina II.

These afferent terminations are organized in a lamina specific fashion; C fibers terminate exclusively in laminae I and V and Aδ fibers in laminae I and V. Lamina V receives input from nociceptive and non-nociceptive afferents and are called wide-dynamic range neurons. Some of them receive visceral input making them a likely substrate for referred pain (i.e. pain that arises from damage to visceral organ but is misperceived as coming from a somatic location).

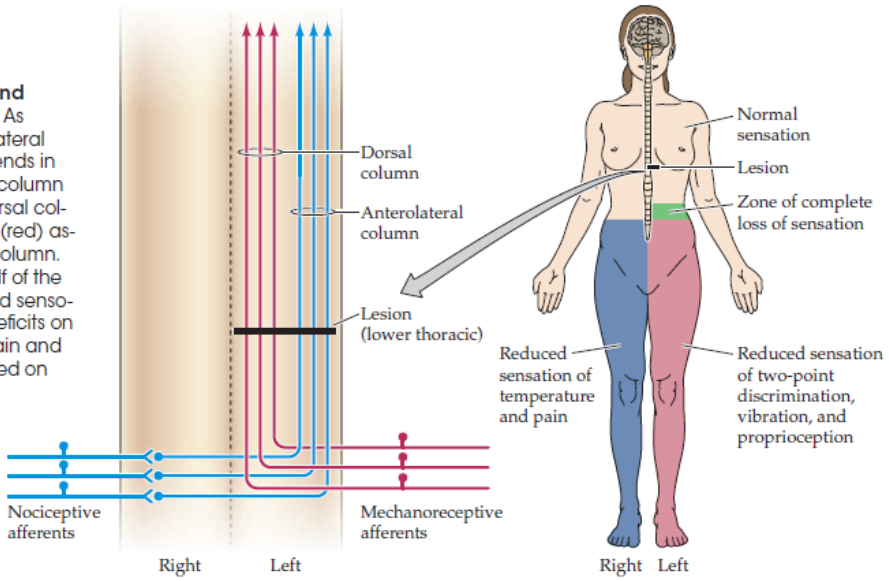
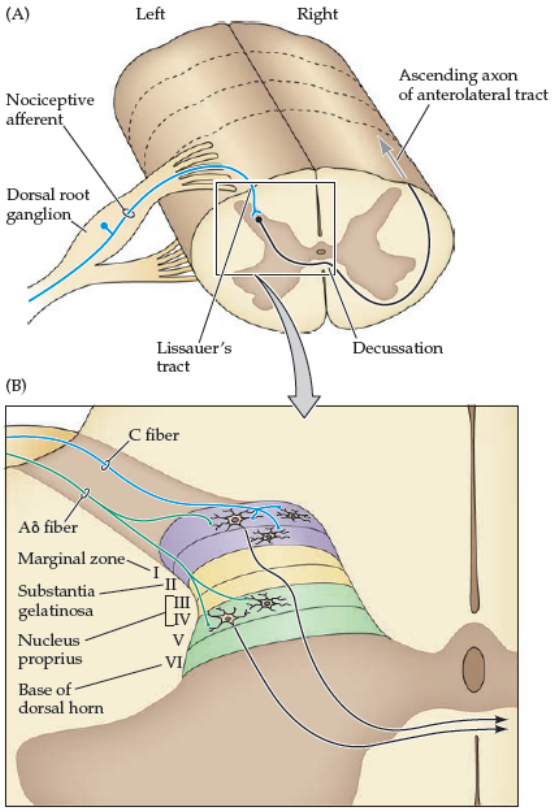


FIGURE 10.4 Nociceptive and mechanosensory pathways. As diagrammed here, the anterolateral system (blue) crosses and ascends in the contralateral anterolateral column of the spinal cord, while the dorsal column–medial leminiscal system (red) ascends in the ipsilateral dorsal column. A lesion restricted to the left half of the spinal cord results in dissociated sensory loss and mechanosensory deficits on the left half of the body, with pain and temperature deficits experienced on the right.

The axons of the second order neurons in laminae I and V of the dorsal horn of the spinal cord cross the midline and ascend to the brainstem and thalamus in the anterolateral (also called ventrolateral) quadrant of the contralateral half of the spinal cord. For this reason, the neural pathway that conveys pain and temperature information to higher centers is often referred to as the **anterolateral system**, to distinguish it from the dorsal column-medial lemniscal system that conveys mechanosensory information.



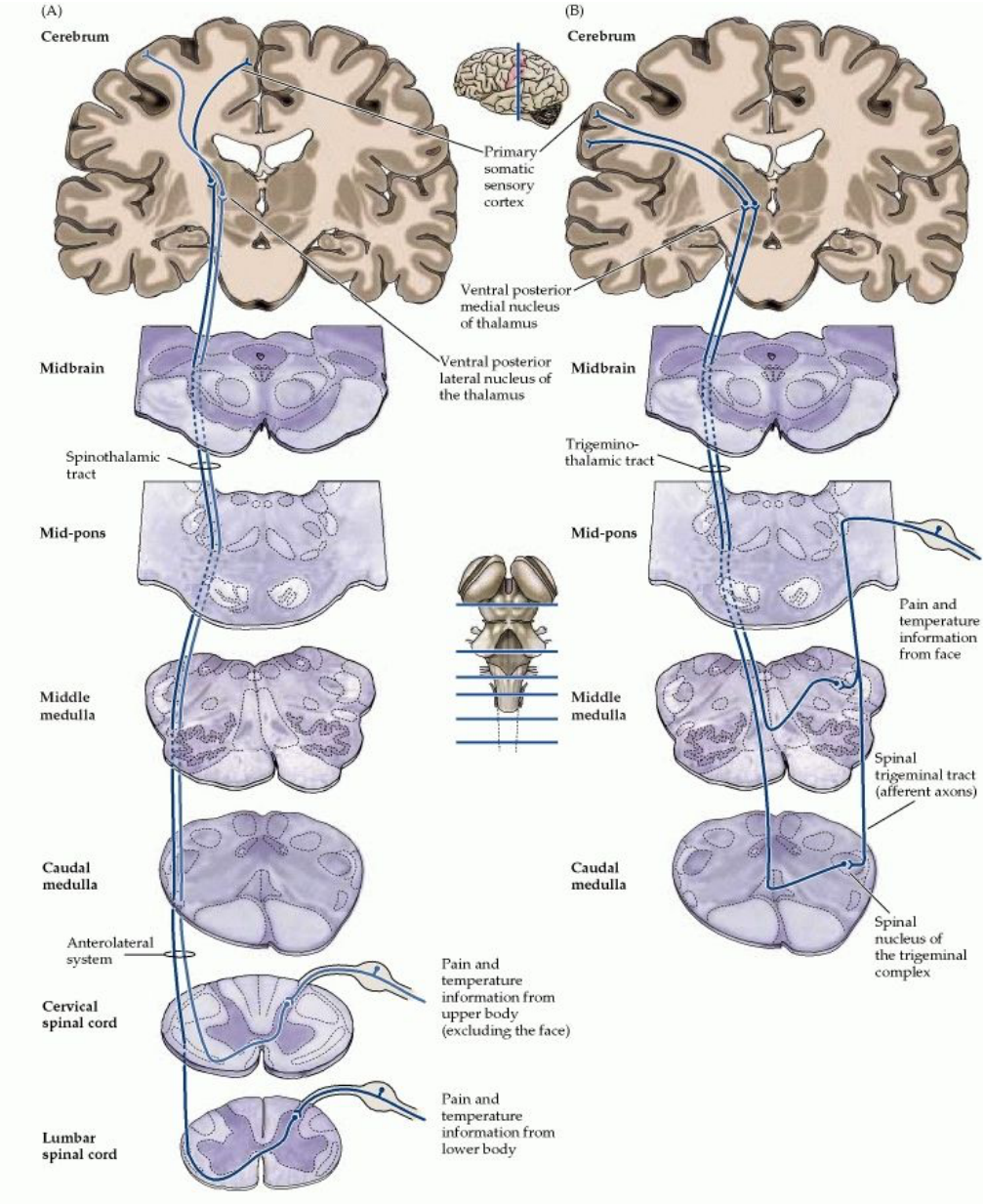
Axons conveying information for the anterolateral system and the dorsal column-medial lemniscal system travel in different parts of the spinal cord white matter which provides a clinically relevant sign that is useful for defining the locus of a spinal cord lesion.

The anterolateral system will travel up to the ventral posterior nuclei of the thalamus where it synapses with third order neurons that goes to the somatosensory cortex where the neuron is translated and perceived as pain.

SUMMARY:

- Depending on stimuli c-fibre or Aδ-fibre will be activated.
- Channels for and open and will trigger a transduction → transmission

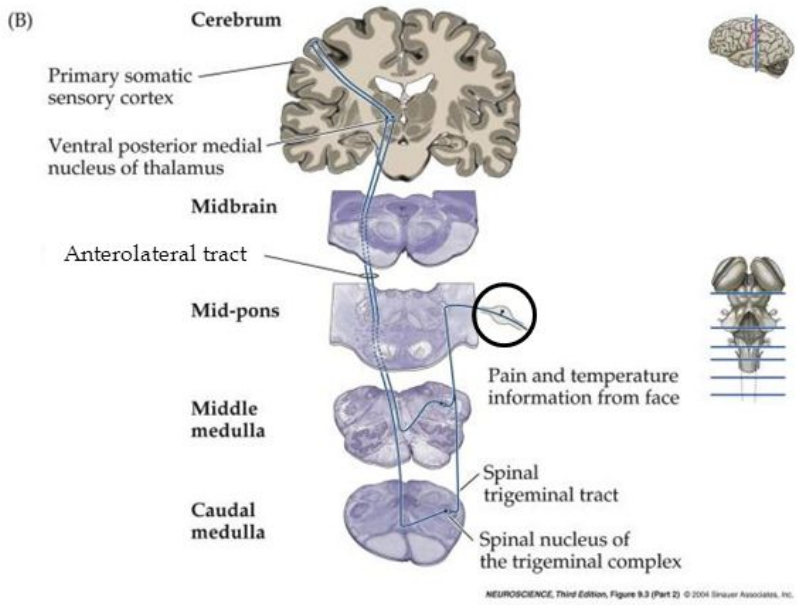
- Primary neuron enters the dorsal horn and makes a cutover to the second order neuron. The c-fibres makes this connection in lamina I or II and Aδ-fibres in lamina I and V.
- In lamina II there's mainly interneurons that send the signal to other lamina, these can be excitatory (glutamate) or inhibitory (GABA and/or Glycine). Lamina I and V have mainly second order neurons that send the signals forward through the pathway.
- When the first order neuron cutover to the second order neuron in lamina I and V they **decussate immediately** and keeps going on the contralateral side.
- First order neurons can also when entering the dorsal horn instead of immediately cutover to a second order neuron move up or down 1-2 segments and then cutover and decussate.
- Neurons from lamina I and V will mainly go through the **anterolateral system**. There are three tracts within the anterolateral system:
    - **Spinothalmic tract** – destined for thalamus and important for the localisation of pain and thermal stimuli. There are one anterior and one posterior; anterior – crude touch and pressure, posterior – pain and temperature.
    - **Spinoreticular tract** – destined for reticular formation (connections with the limbic system) causes alertness and arousal in response to painful stimuli.
    - **Spinotectal tract** – destined for tectum, orient eyes and head towards the stimuli.
- In the thalamus (VPL – ventral posyerolateral nucleus) the cutover to the third order neuron is made and their axons ascend ipsilateral and terminate in the sensory cortex.



CENTRAL PAIN PATHWAY - FACE

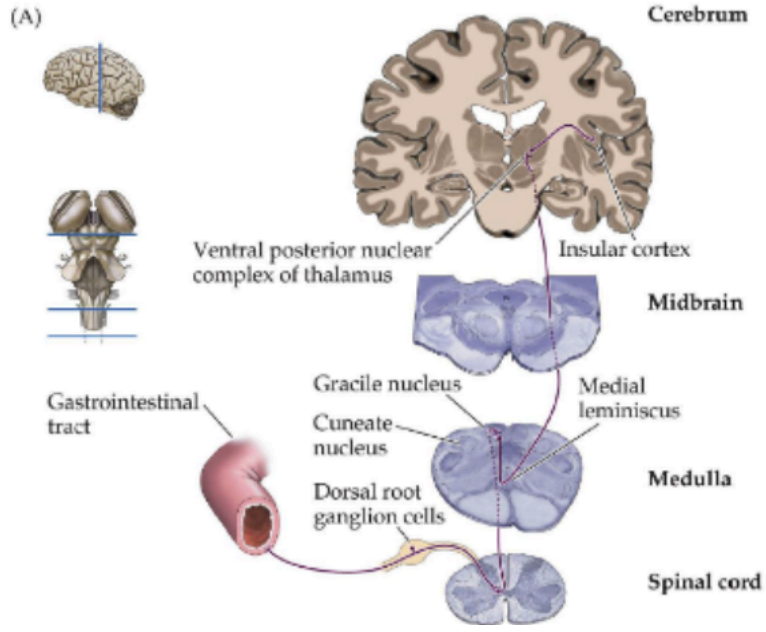
The information regarding pain and temperature from the face goes via first order neurons that are located in the trigeminal ganglion and ganglia associated with cranial nerves 7, 9 and 10.

They enter pons and descend to the medulla, this forms the spinal trigeminal tract. In the spinal trigeminal nucleus the neuron terminate in two subdivisions of the nucleus and do a cut over to a second order neuron. The second order neurons axon will cross and go to the brainstem and the thalamus. In the thalamus the second order neurons will synapse with a third order neuron in the ventral posterior nucleus. The third order axon will go forth and terminate in the primary somatosensory cortex.



NOCICEPTIVE SIGNALS FROM VISCERAL ORGANS PATHWAY

First order nucleus enters the dorsal horn and goes to laminae X that are close to the central canal. Here the cutover to the second order neuron happens and it travels up to the dorsal column nuclei (close to the gracile nucleus) where it synapses and then travels up via the medial lemniscus to the ventral posterior nucleus of thalamus there the cutover to the third order neuron is made. The third order neuron travels to the insular cortex.

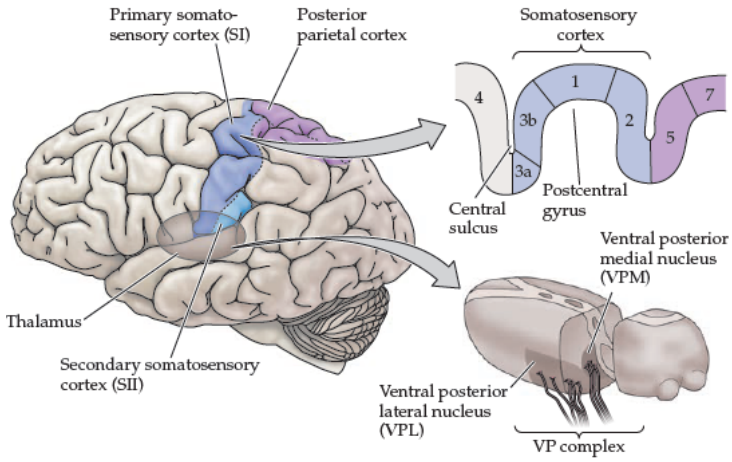


DIFFERENCE BETWEEN THE PATHWAYS – WHEN DO THEY CROSS

Central pain pathway crosses immediately in the spinal cord. Central sensory pathway crosses in the caudal medulla. The proprioceptic pathway never crosses and goes on the ipsilateral side.

EXPLAIN, FOR THE DIFFERENT SENSORY MODALITIES, HOW SENSORY INFORMATION IS PROCESSED IN SPECIFIC BRAIN REGIONS (S2, S3, S4)

TOUCH



Each of the several ascending somatosensory pathways originating in the spinal cord and brainstem converges on the ventral posterior complex of the thalamus and terminates in an organized fashion. This organized fashion gives an orderly somatotopic representation of the body and head; the more laterally located posterior lateral nucleus (VPL) receives projections from the medial lemniscus carrying somatosensory information from the body and posterior head, whereas the more medially located ventral posterior medial nucleus (VPM) receives axons from the trigeminal lemniscus conveying somatosensory information from the face. In addition, inputs carrying different types of somatosensory information—for example, those that respond to different types of mechanoreceptors, to muscle spindle afferents, or to Golgi tendon organs—terminate on separate populations of relay cells within the ventral posterior complex. Thus, the information supplied by different somatosensory receptors remains segregated in its passage to cortical circuits.

The majority of the axons arising from neurons in the ventral posterior complex of the thalamus project to cortical neurons located in layer 4 of the primary somatosensory cortex. The primary somatosensory cortex in humans is located in the postcentral gyrus of the parietal lobe and comprises four distinct regions, or fields, known as Brodmann's areas 3a, 3b, 1, and 2. Mapping studies in humans and other primates show further that each of these four cortical areas contains a separate and complete representation of the body. In these somatotopic maps, the foot, leg, trunk, forelimbs, and face are represented in a medial to lateral arrangement. More cortical representation occurs to areas with higher innervation (such as hands for example).

Although the topographic organization of the several somatosensory areas is similar, the functional properties of the neurons in each region are distinct. Experiments carried out in non-human primates indicate that neurons in areas 3b and 1 respond primarily to cutaneous stimuli, whereas neurons in 3a respond mainly to stimulation of proprioceptors; area 2 neurons process both tactile and proprioceptive stimuli.
These differences in response properties reflect, at least in part, parallel sets of inputs from functionally distinct classes of neurons in the ventral posterior complex. In addition, a rich pattern of corticocortical connections between SI areas contributes significantly to the elaboration of SI response properties. Area 3b receives the bulk of the input from the ventral posterior complex and provides a particularly dense projection to areas 1 and 2. This arrangement of connections establishes a functional hierarchy in which area 3b serves as an obligatory first step in cortical processing of somatosensory information. Studies where lesions of area 3b in non-human primates were made resulted in profound deficits in all forms of tactile sensations mediated by cutaneous mechanoreceptors, while lesions limited to areas 1 or 2 result in partial deficits and an inability to use tactile information to discriminate either the texture of objects (area 1 deficit) or the size and shape of objects (area 2 deficit).

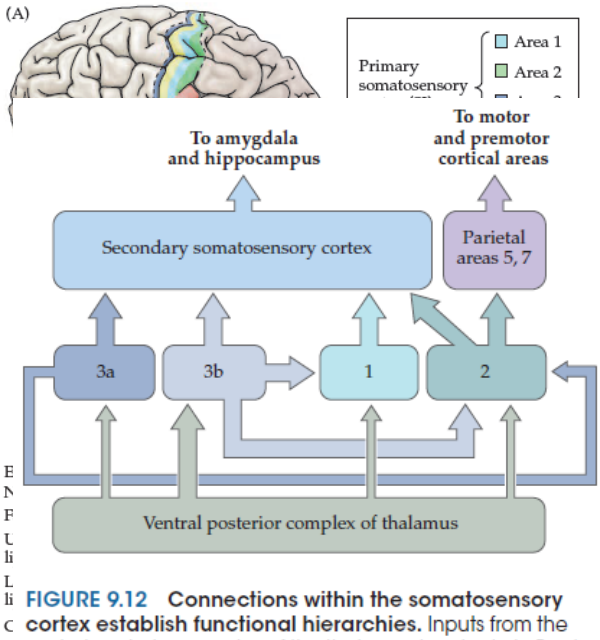


FIGURE 9.12 Connections within the somatosensory cortex establish functional hierarchies. Inputs from the ventral posterior complex of the thalamus terminate in Brodmann's areas 3a, 3b, 1, and 2, with the greatest density of projections in area 3b. Area 3b in turn projects heavily to areas 1 and 2, and the functions of these areas are dependent on the activity of area 3b. All subdivisions of primary somatosensory cortex project to secondary somatosensory cortex; the functions of SII are dependent on the activity of SI.

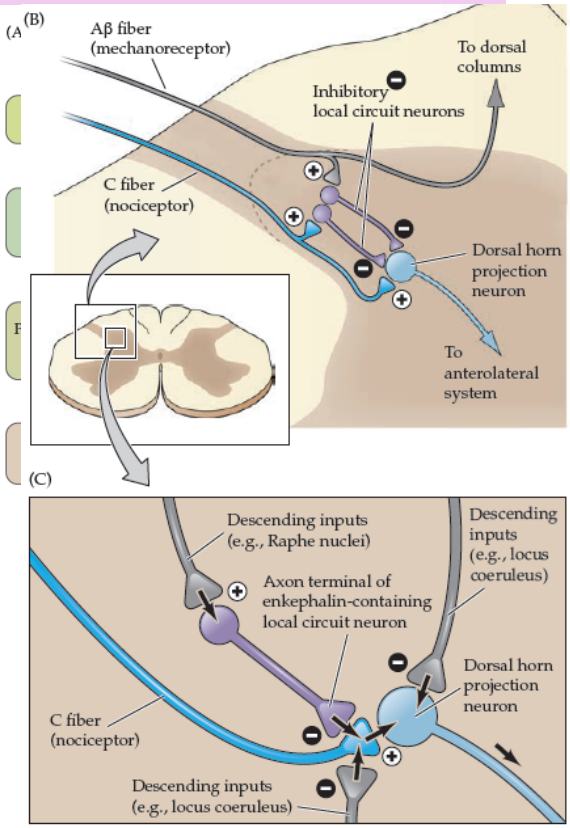
Somatosensory information is distributed from the primary somatosensory cortex to "higher-order" cortical fields. One of these higher-order cortical centers, the secondary somatosensory cortex, lies in the upper bank of the lateral sulcus. SII receives convergent projections from all subdivisions of SI, and these inputs are necessary for the function of SII; lesions of SI eliminate the somatosensory responses of SII neurons. SII sends projections in turn to limbic structures such as the amygdala and hippocampus. This latter pathway is believed to play an important role in tactile learning and memory.

Neurons in SI also project to parietal areas posterior to area 2, especially areas 5a and 7b. These areas receive direct projections from area 2 and, in turn, supply inputs to neurons in motor and premotor areas of the frontal lobe. This is a major route by which information derived from proprioceptive afferents signalling the current state of muscle contraction gains access to circuits that initiate voluntary movements. More generally, the projections from parietal cortex to motor cortex are critical for the integration of sensory and motor information.

Finally, a fundamental but often neglected feature of the somatosensory system is the presence of massive descending projections. These pathways originate in sensory cortical fields and run to the thalamus, brainstem, and spinal cord. Indeed, descending projections from the somatosensory cortex outnumber ascending somatosensory pathways. Although their physiological role is not well understood, it is generally thought that descending projections modulate the ascending flow of sensory information at the level of the thalamus and brainstem.

PAIN

Studies of descending pathways to the spinal cord have shown that several brainstem sites regulate the transmission of nociceptive information; including the parabrachial nucleus, dorsal raphe, locus coeruleus, and medullary reticular formation.



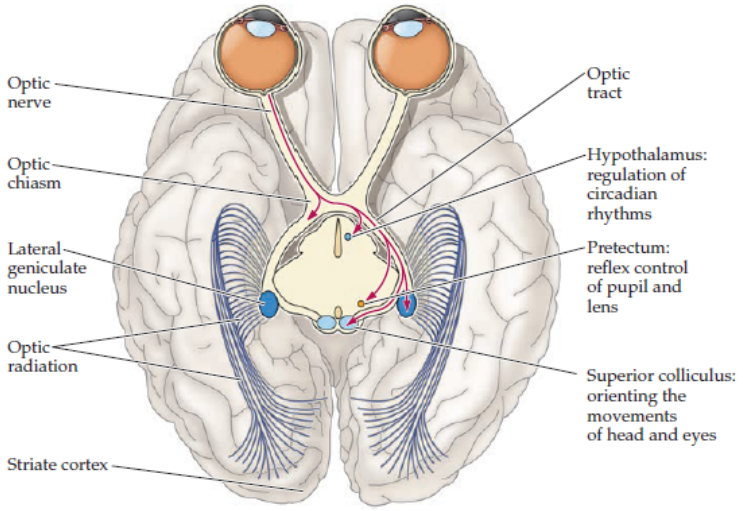
These centers employ a wealth of different neurotransmitters (e.g., noradrenaline, serotonin, dopamine, histamine, acetylcholine) and can exert both facilitatory and inhibitory effects on the activity of neurons in the dorsal horn. The complexity of these interactions is made even greater by the fact that descending projections can exert their effects on a variety of sites within the dorsal horn, including the synaptic terminals of nociceptive afferents, excitatory and inhibitory interneurons, and the synaptic terminals of the other descending pathways, as well as by contacting the projection neurons themselves. Although these descending projections were originally viewed as a mechanism that served primarily to inhibit the transmission of nociceptive signals, it is now evident that these projections provide a balance of facilitatory and inhibitory influences that ultimately determines the efficacy of nociceptive transmission.

In addition to descending projections, local interactions between mechanoreceptive afferents and neural circuits within the dorsal horn can modulate the transmission of nociceptive information to higher centers. These interactions are thought to explain the ability to reduce the sensation of sharp pain by activating low-threshold mechanoreceptors—for example, if you crack your shin or stub a toe, a natural (and effective) reaction is to vigorously rub the site of injury for a minute or two. Several categories of endogenous opioids have been isolated from the brain and intensively studied. These agents are found in the same regions involved in the modulation of nociceptive

afferents, although each of the families of endogenous opioid peptides has a somewhat different distribution. All three of the major groups—enkephalins, endorphins, and dynorphins —are present in the periaqueductal gray matter. Enkephalins and dynorphins have also been found in the rostral ventral medulla and in those spinal cord regions involved in pain modulation. They work by providing a powerful mechanism by which higher centers can decrease the activity relayed by nociceptive afferents.

VISION

Information supplied by the retina initiates interactions among multiple subdivisions of the brain; these interactions eventually lead to perception of the visual scene, whether consciously or not. The pathways and structures mediating this range of functions are necessarily diverse; of these, the primary visual pathway from the retina to the dorsolateral geniculate nucleus in the thalamus and on to the primary visual cortex is the most important and certainly the most thoroughly studied component of the visual system.



Ganglion cell axons exit the retina through a circular region in its nasal part called the optic disk, where they bundle together to form the optic nerve. Axons in the optic nerve run a straight course to the optic chiasm at the base of the diencephalon. In humans about 60% of these fibers cross in the chiasm; the other 40% continue towards the thalamus and midbrain targets on the same side. Once part the optic chiasm, the ganglion cell axons on each side form the optic tract. The optic tract, then, unlike the optic nerve, contains fibers from both eyes. The partial crossing (decussation) of ganglion cell axons at the optic chiasm allows information from corresponding points on the two retinas to be processed by approximately the same cortical site in each hemisphere.

The ganglion cell axons in the optic tract reach a number of structures in the diencephalon and midbrain. The major target being the dorsolateral geniculate nucleus of the thalamus. Neurons in the lateral geniculate nucleus, like their counterparts in the thalamic relays of

other sensory systems, send their axons to the cerebral cortex via the internal capsule. These axons pass through a portion of the internal capsule called the optic radiation and terminate in the primary visual cortex (V1), or striate cortex (also referred to as Brodmann's area 17), which lies largely along and within the calcarine fissure in the occipital lobe. The primary visual pathway (retinogeniculostriate pathway) conveys information that is essential for most of what is though of as seeing; damage anywhere along this route results in serious visual impairment. A second major target of ganglion cell axons is a collection of neurons that lies between the thalamus and the midbrain in a region known as the pretectum. Although small in size compared to the lateral geniculate nucleus, the pretectum is particularly important as the coordinating centre for the pupillary light reflex.

Pretectal neurons, in turn, project to the Edinger-Westphal nucleus, a small group of nerve cells that lie close to the nucleus of the oculomotor nerve in the midbrain. The Edinger-Westphal nucleus contains the preganglionic parasympathetic neurons that send their axons via the oculomotor nerve to terminate on neurons in the ciliary ganglion which innervate the constrictor muscle in the iris.

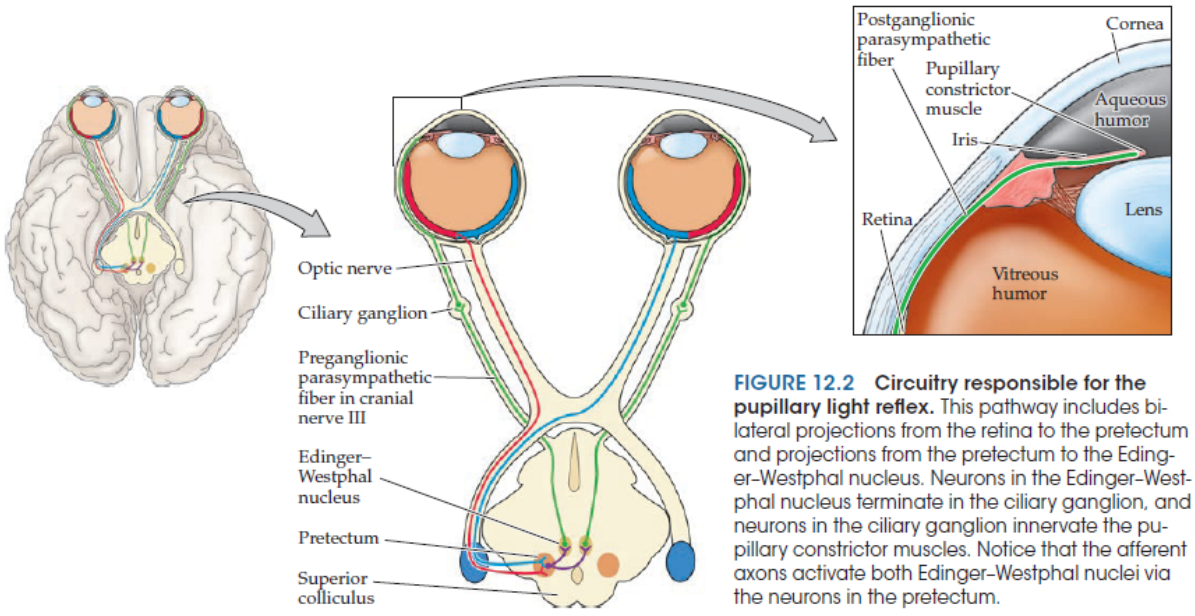
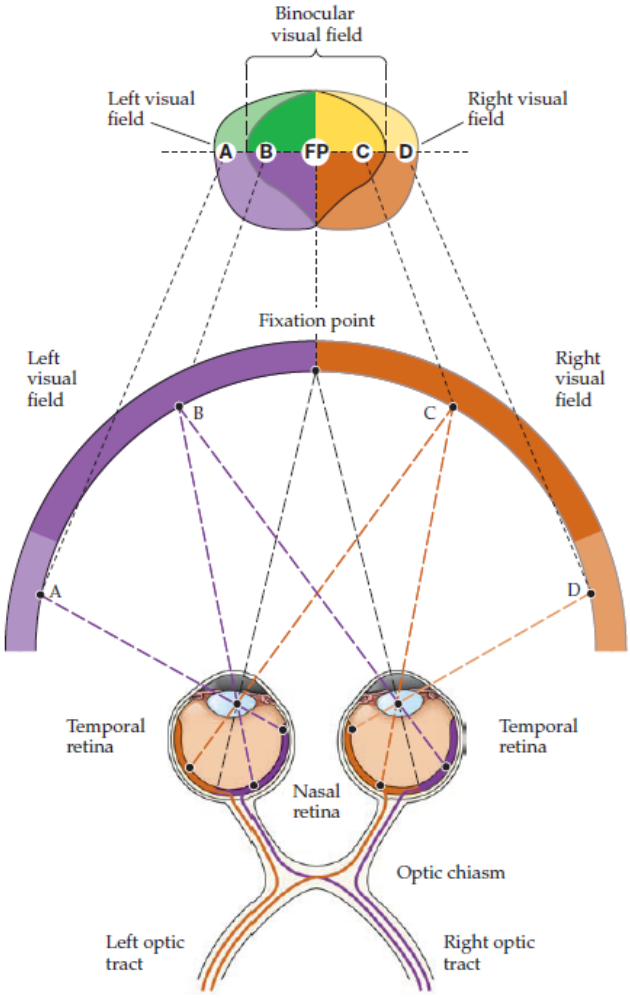
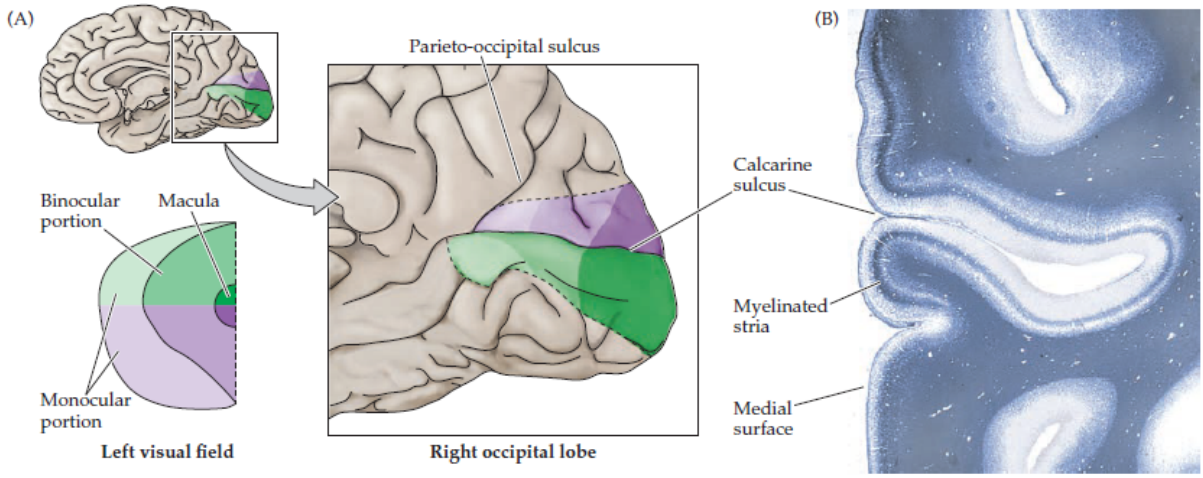


FIGURE 12.2 Circuitry responsible for the pupillary light reflex. This pathway includes bilateral projections from the retina to the pretectum and projections from the pretectum to the Edinger-Westphal nucleus. Neurons in the Edinger–Westphal nucleus terminate in the ciliary ganglion, and neurons in the ciliary ganglion innervate the pupillary constrictor muscles. Notice that the afferent axons activate both Edinger–Westphal nuclei via the neurons in the pretectum.

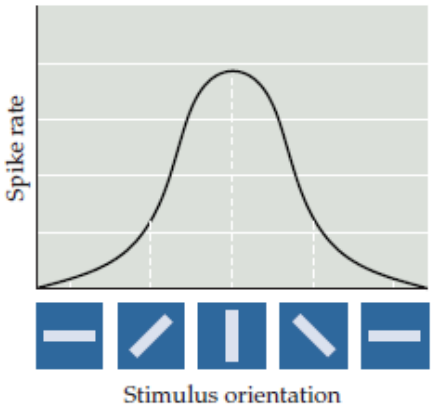
Retinal ganglion cell axons have several other important targets. One is the suprachiasmatic nucleus of the hypothalamus, the retinohypothalamic pathway is the route by which variation in light levels influences a spectrum of visceral functions that are entrained to the day and night cycle. Another target is the superior colliculus which coordinates head and eye movements to visual targets.



Each eye sees a part of a visual space that defines its visual field, which for descriptive purposes are usually divided into quadrants where the vertical line divides the retina into nasal and temporal divisions and the horizontal line divides the retina into superior and inferior divisions. With both eyes open, the two foveas normally align on a single target in visual space, causing the visual fields of both eyes to overlap extensively. This binocular field consists of two symmetrical visual hemifields (left and right). Ganglion cells that lie in the nasal division of each retina give rise to axons that cross in the optic chiasm, while those that lie in the temporal retina give rise to axons that remain on the same side. As a result, the right optic tract carries information from the left visual field and the left optic tract carries information from the right visual field. The boundary between contralaterally and ipsilaterally projecting ganglion cells run through the center of the fovea and defines the border between nasal and temporal hemiretinas.



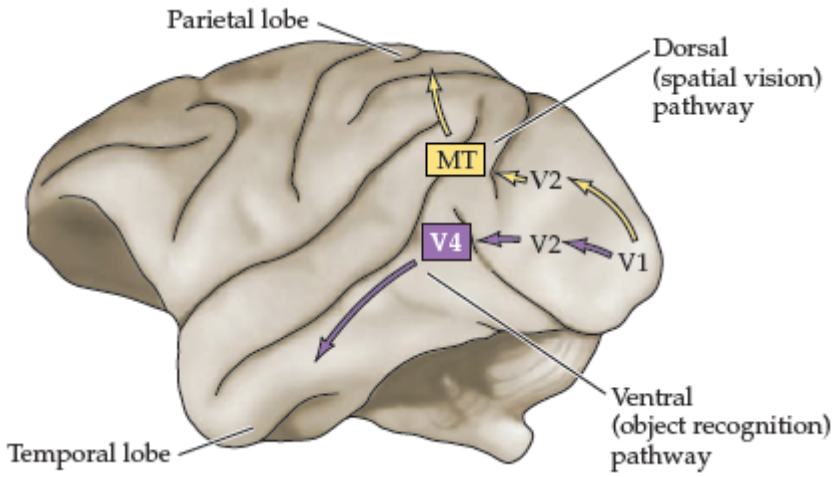
Optic tracts terminate in an orderly fashion within their target structures, thus generating well-ordered maps of the contralateral hemifield. For the primary visual pathway, the map of the contralateral hemifield established in the lateral geniculate nucleus is maintained in the projections of the lateral geniculate nucleus to the striate cortex. Thus, the fovea is represented in the posterior part of the striate cortex, whereas the more peripheral regions of the retina are represented in progressively more anterior parts of the striate cortex. The upper visual field is mapped below the calcarine sulcus, and the lower visual field above it. As in the somatosensory system, the amount of cortical area devoted to each unit of area of the sensory surface is not uniform but reflects the density of receptors and sensory axons that supply the peripheral region.



Like all neocortex, the visual cortex is a sheet approximately 2 mm thick and composed of two broad classes of neurons: spiny neurons (pyramidal and stellate) that exhibit dendritic spines, and aspinous or smooth dendritic neurons. They appear to be structured in a laminar fashion into six cellular layers. Neurons in the primary visual cortex appear to only respond to selectively ordered edges when presented with stimuli during experiments. By having neurons tuned to different orientations the information gathered from them would contain all the spatial information necessary to generate a faithful representation of the original image. Orientation preference is only of the qualities that define the filter properties of neurons in the primary visual cortex. A substantial fraction of cortical neurons are also tuned to the direction of stimulus movement. Neurons can also be characterized by their preference for spatial frequency (the coarseness or fineness of the variations in contrast that fall within their receptive fields) as well as temporal frequency (rate of change in contrast).

Unlike neurons at earlier stages in the primary visual pathway, most neurons in striate cortex are binocular, responding to stimulation of both the left and right eyes. Inputs from both eyes are present at the level of the lateral geniculate nucleus, but contralateral and ipsilateral retinal axons terminate in separate layers, so that individual geniculate neurons are strictly monocular, driven by either the left or right eye, but not by both.

Bringing together the inputs from the two eyes at the level of the striate cortex provides a basis for stereopsis, the sensation of depth that arises from viewing nearby objects with two eyes instead of one. Because the two eyes look at the world from slightly different angles, objects that lie in front of or behind the plane of fixation project to non-corresponding points on the two retinas.

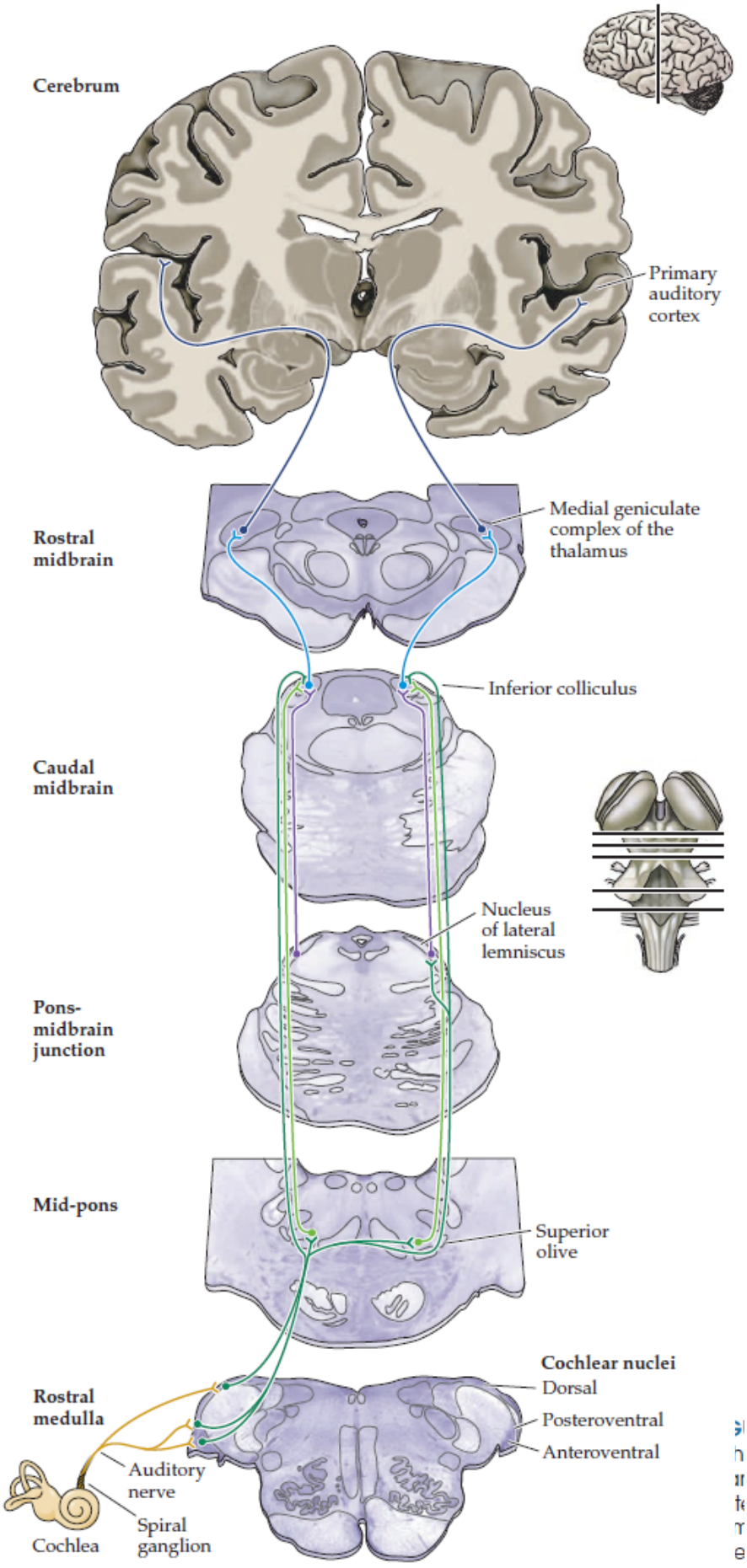


The primary visual pathway is composed of separate functional pathways that convey information from different types of retinal ganglion cells to the initial stages of cortical processing. The magnocellular pathway conveys information that is critical for the detection of rapidly changing stimuli; the parvocellular pathway mediates high-acuity vision and appears to share responsibility for color vision with the koniocellular pathway. Finally, beyond striate cortex, parcellation of function continues in the ventral and dorsal streams that lead to the extrastriate and association areas in the temporal and parietal lobes, respectively. Areas in the inferotemporal cortex are especially important in object recognition, whereas areas in the parietal lobe are critical for understanding the spatial relationships among objects in the visual field.

HEARING

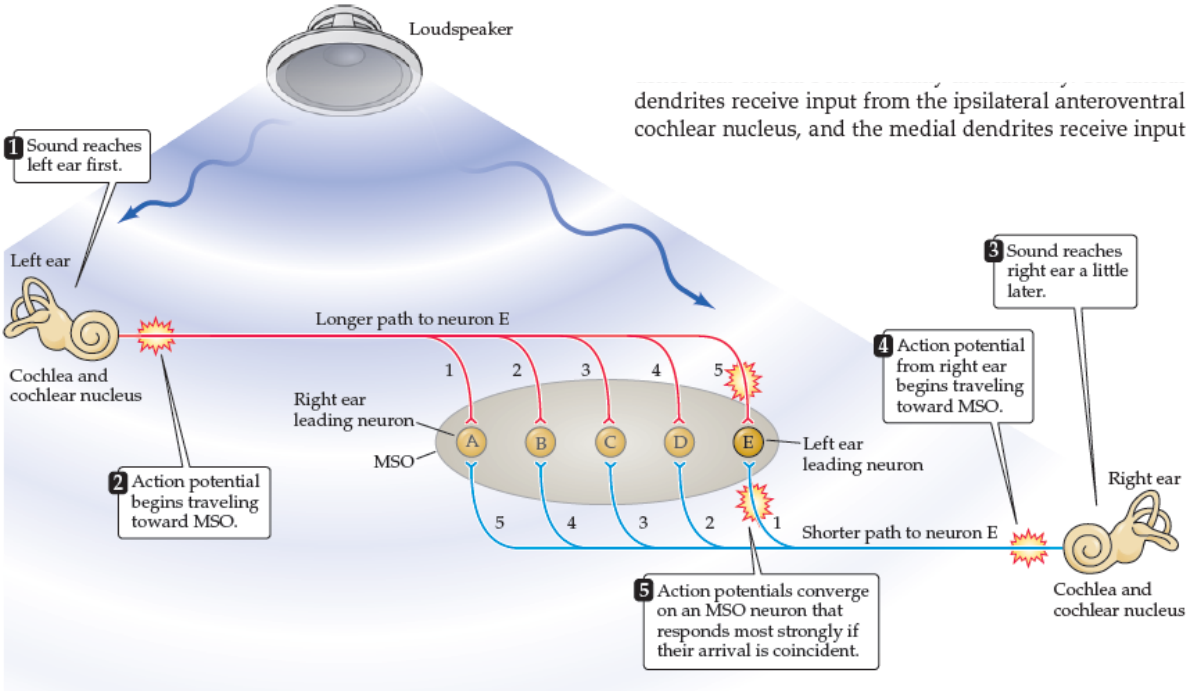
As in the visual system, the ascending auditory system is organized in parallel. This arrangement becomes evident as soon as the auditory nerve enters the brainstem, where it branches to innervate the three divisions of the cochlear nucleus. The auditory nerve (which, along with the vestibular nerve, constitutes cranial nerve VIII) comprises the central processes of the bipolar spiral ganglion cells in the cochlea; each of these cells sends a peripheral process to contact one or a few inner hair cells and a central process to innervate the cochlear nucleus. Within the cochlear nucleus, each auditory nerve fiber branches, sending an ascending branch to the anteroventral cochlear nucleus and a descending branch to the posteroventral cochlear nucleus and the dorsal cochlear nucleus.

The tonotopic organization of the cochlea is maintained in the three parts of the cochlear nucleus, each of which contains different populations of cells with quite different properties. In addition, the patterns of termination of the auditory nerve axons differ in density and type; thus, there are several opportunities at this level for transformation of the information from the hair cells.


Cerebrum
Primary auditory cortex
Rostral midbrain
Medial geniculate complex of the thalamus
Inferior colliculus
Caudal midbrain
Nucleus of lateral lemniscus
Pons-midbrain junction
Mid-pons
Superior olive
Cochlear nuclei
Dorsal
Posteroventral
Anteroventral
Rostral medulla
Auditory nerve
Spiral ganglion
Cochlea

Just as the auditory nerve branches to innervate several different targets in the cochlear nuclei, the neurons in these nuclei give rise to several different pathways. One clinically relevant feature of the ascending projections of the auditory brainstem is a high degree of bilateral connectivity, which means that damage to central auditory structures is almost never manifested as a monaural hearing loss.

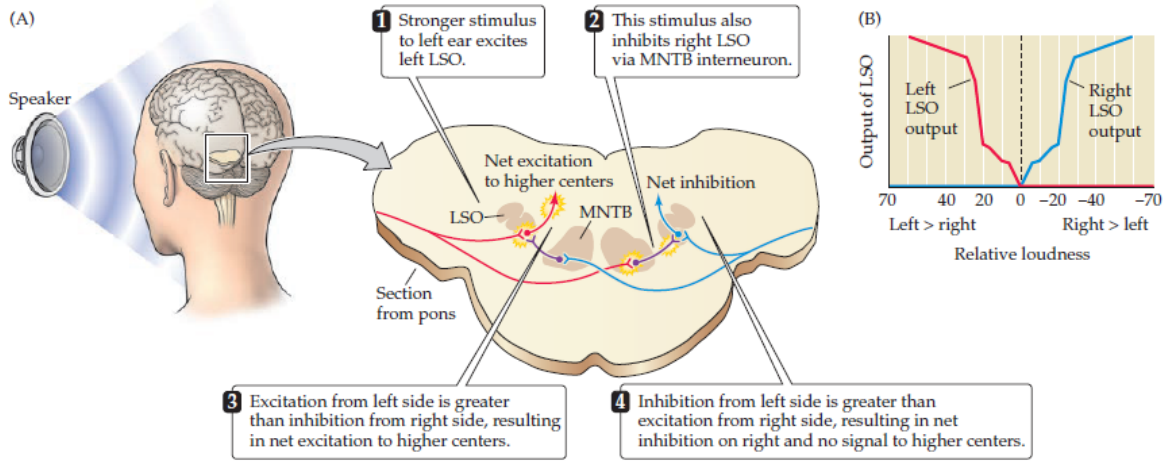
The best-understood function mediated by the auditory brainstem nuclei, and certainly the one most intensively studied, is sound localization. Humans use at least two different strategies to localize the horizontal position of sound sources, depending on the frequencies in the stimulus. For frequencies below 3 kHz (which auditory nerve fibers can follow in a phase-locked manner), interaural time differences are used to localize the source; above these frequencies, interaural intensity differences are used as cues. Parallel pathways originating from the cochlear nucleus serve each of these strategies for sound localization. The neural circuitry that computes these tiny interaural time differences consists of binaural inputs to the medial superior olive (MSO) that ar
cochlear nuclei.



The MSO contains cells with bipolar dendrites that extend both medially and laterally. The lateral dendrites receive input from the ipsilateral anteroventral cochlear nucleus, and the medial dendrites receive input from the contralateral anteroventral cochlear nucleus (both inputs are excitatory). The neurons of the MSO work as coincidence detectors, responding when both excitatory signals arrive at the same time. For a coincidence mechanism to be useful in localizing sound, different neurons must be maximally sensitive to different interaural time delays. The axons that project from the anteroventral cochlear nucleus evidently vary systematically in length to create delay lines. These anatomical differences compensate for sounds arriving at slightly different times at the two ears, so that the

resultant neural impulses arrive at a particular MSO neuron simultaneously, making each cell especially sensitive to sound sources in a particular place.

Sound localization perceived on the basis of interaural time differences requires phase-locked information from the periphery, which, as already emphasized, is available to humans only for frequencies below 3 kHz. Therefore, a second mechanism must come into play at higher frequencies. One clue to the solution is that at frequencies higher than about 2 kHz, the human head begins to act as an acoustical obstacle, because the wavelengths of the sounds are too short to bend around it. As a result, when high-frequency sounds are directed toward one side of the head, an acoustical "shadow" of lower intensity is created at the far ear. These intensity differences provide a second cue about the location of a sound. The circuits that compute the position of a sound source on this basis are found in the lateral superior olive (LSO) and the medial nucleus of the trapezoid body (MNTB).

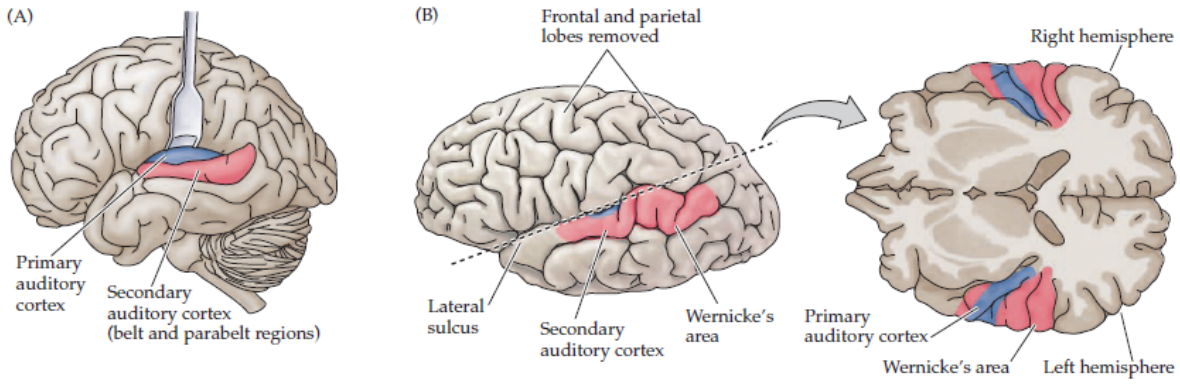


Excitatory axons project directly from the ipsilateral anteroventral cochlear nucleus to the LSO (as well as to the MSO. Note that the LSO also receives inhibitory input from the contralateral ear via an inhibitory neuron in the MNTB. This excitatory–inhibitory interaction results in a net excitation of the LSO on the same side of the head as the sound source. For sounds arising directly lateral to the listener's head, firing rates will be highest in the LSO on that side; in this circumstance, the excitation via the ipsilateral anteroventral cochlear nucleus will be maximal, and inhibition from the contralateral MNTB minimal. In contrast, sounds arising closer to the listener's midline will elicit lower firing rates in the ipsilateral LSO because of increased inhibition arising from the contralateral MNTB. For sounds arising at the midline, or from the other side, the increased inhibition arising from the MNTB is powerful enough to completely silence LSO activity. Note that each LSO encodes only sounds arising in the ipsilateral hemifield; therefore, it takes both LSOs to represent the full range of horizontal positions. The MSO and LSO pathways eventually merge in the midbrain auditory centers.

The binaural pathways for sound localization are only part of the output of the cochlear nucleus. A second major set of pathways from the cochlear nucleus bypasses the superior olive and terminates in the nuclei of the lateral lemniscus on the contralateral side of the brainstem. These pathways respond to sound arriving at one ear only and are thus referred to as monaural. Some cells in the lateral lemniscus nuclei signal the onset of sound,

regardless of its intensity or frequency. Other cells in the lateral lemniscus nuclei process other temporal aspects of sound, such as duration. The role of these pathways in processing temporal features of sound is not yet known. As with the outputs of the superior olivary nuclei, the pathways from the nuclei of the lateral lemniscus converge at the midbrain. Auditory pathways ascending via the olivary and lemniscal complexes, as well as other projections that arise directly from the cochlear nucleus, project to the midbrain auditory center, also known as the inferior colliculus. Neurons within this auditory space map in the colliculus respond best to sounds originating in a specific region of space; thus giving humans a clear perception of both the elevational and azimuthal (the vector from an observer to a point of interest) components of a sound's location. Another important property of the inferior colliculus is its ability to process sounds with complex temporal patterns. Many neurons in the inferior colliculus respond only to frequency-modulated sounds, while others respond only to sounds of specific durations or in specific temporal sequences. Such sounds are typical components of biologically relevant sounds, such as those made by predators, or intraspecific communication sounds, which in humans include speech. In summary, the high degree of convergence in the inferior colliculus of inputs conveying information about simpler cues, such as timing, intensity, and frequency, results in more integrative and complex response properties that are likely to be important to the representation of auditory objects.

Despite the parallel pathways in the auditory stations of the brainstem and midbrain, the medial geniculate complex (MGC) in the thalamus is an obligatory relay for all ascending auditory information destined for the cortex. Most input to the MGC arises from the inferior colliculus, although a few auditory axons from the lower brainstem bypass the inferior colliculus to reach the auditory thalamus directly. The MGC has several divisions, including the ventral division, which projects to the core region of the auditory cortex, and the medial and dorsal divisions, which are organized like a belt around the ventral division and project to the belt regions that surround the core region of the auditory cortex.



The auditory cortex is the major target of the ascending fibers from the MGC, and it plays an essential role in our conscious perception of sound, including recognition of speech and music. Although the auditory cortex has several subdivisions, as in the visual and

somatosensory systems a broad distinction can be made between primary (i.e., core) and secondary (i.e., belt and parabelt) regions. The core region in macaque monkeys comprises three divisions, including auditory area 1 (A1), rostral (R), and rostrotemporal (RT), all of which are located on the lower bank of the lateral sulcus in the medial and posterior part of the superior temporal gyrus (STG) in the temporal lobe. Imaging studies in humans indicate that the core region is located in the transverse temporal gyri (Heschl's gyri, or Brodmann's areas 41 and 42), buried in the lateral sulcus. The belt and parabelt regions of the auditory cortex receive more diffuse input from the belt division of the MGC, as well as input from the primary auditory cortex, and are less precise in their tonotopic organization.

Just as the visual and somatosensory systems represent their peripheral receptor surfaces in central maps, so the organization of the cochlea is laid out in a central map. Since frequencies are arrayed tonotopically along the length of the basilar membrane, this organization as reflected in A1 is said to comprise a tonotopic map, as do most of the ascending auditory structures between the cochlea and the cortex. Orthogonal to the frequency axis of the tonotopic map are irregular patches of neurons that are excited by both ears (and are therefore called EE cells) interspersed with patches of cells that are excited by one ear and inhibited by the other ear (EI cells). The EE and EI stripes alternate, an arrangement that is reminiscent of the ocular dominance columns in V1.

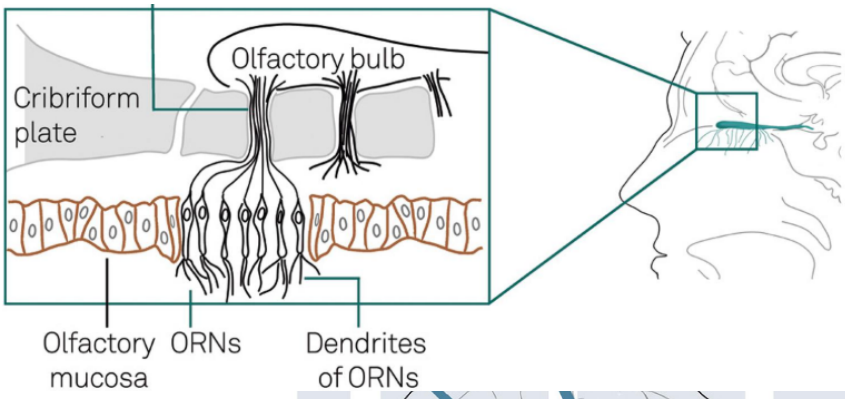
The auditory cortex obviously does much more than provide a tonotopic map and respond differentially to ipsilateral and contralateral stimulation. The sorts of sensory processing that occur in the auditory cortex are not fully understood, but they are likely to be important to higher-order processing of natural sounds, especially those used for communication.

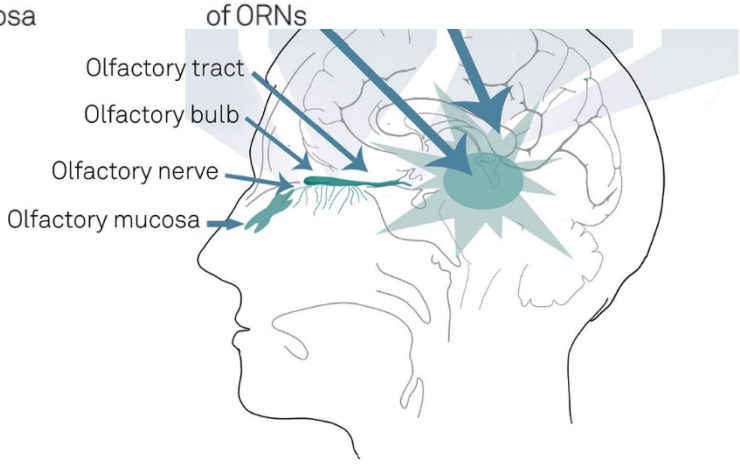
So, to summarize: Projections from the cochlea travel via the auditory nerve to the three main divisions of the cochlear nucleus. The targets of the cochlear nucleus neurons include the superior olivary complex and nuclei of the lateral lemniscus, where the binaural cues for sound localization are processed. The inferior colliculus, the target of nearly all of the auditory pathways in the lower brainstem, carries out important integrative functions, such as processing of sound frequencies and integration of the cues for localizing sound in space. The primary auditory cortex, which is also organized tonotopically, supports basic auditory functions, such as frequency discrimination and sound localization, and also plays an important role in processing of intraspecific communication sounds. Populations of neurons in belt areas of the auditory cortex, which have a less strict tonotopic organization, display activity patterns that correlate with speech intelligibility and that are strongly modulated by linguistic features and cognitive context. In the human brain, the major speech comprehension areas reside in the zone immediately adjacent to the auditory cortex, and motor-related activity can strongly modulate auditory cortical responses to vocalization-related auditory feedback, suggestive of a predictive sensorimotor mechanism.

The transduction of odorants in the olfactory cilia and the subsequent changes in electrical activity in the ORN are only the first steps in olfactory information processing. Unlike other primary sensory receptor cells (e.g., photoreceptors in the retina or hair cells in the cochlea), ORNs have axons, and these axons relay odorant information directly to the rest of the brain via action potentials. As the axons leave the olfactory epithelium, they coalesce to form a large number of bundles that together make up the olfactory nerve (cranial nerve I). Each olfactory nerve projects ipsilaterally to the olfactory bulb, which in humans lies on the ventral anterior aspect of the ipsilateral cerebral hemisphere. The most distinctive feature of the olfactory bulb is the array of glomeruli—more or less spherical accumulations of neuropil 100 to 200 µm in diameter. Glomeruli lie just beneath the surface of the bulb and are the synaptic target of the primary olfactory axons. In mammals, including humans, within each glomerulus the axons of the receptor neurons contact apical dendrites of mitral cells, which are the principal projection neurons of the olfactory bulb. The cell bodies of the mitral cells are located in a distinct layer of the olfactory bulb deep within the glomeruli. A mitral cell extends its primary dendrite into a single glomerulus, where the dendrite gives rise to an elaborate tuft of branches onto which the axons of ORNs synapse.

Mitral cell axons, as well as those from tufted cells (a less frequent class of olfactory bulb projection neurons), provide the only relay for olfactory information to the rest of the brain. The mitral cell axons from each olfactory bulb form a bundle—the lateral olfactory tract—that projects to the accessory olfactory nuclei, the olfactory tubercle, the pyriform and entorhinal cortices, as well as to portions of the amygdala.

In humans, the major target of the lateral olfactory tract is the three-layered pyriform cortex in the ventromedial aspect of the temporal lobe, near the optic chiasm. Mitral cell inputs from glomeruli that receive odorant receptor-specific projections are distributed across the pyriform cortex. Accordingly, neurons in pyriform cortex respond to odors based upon the relay of odorant information from ORNs through the olfactory bulb via mitral cell projections.

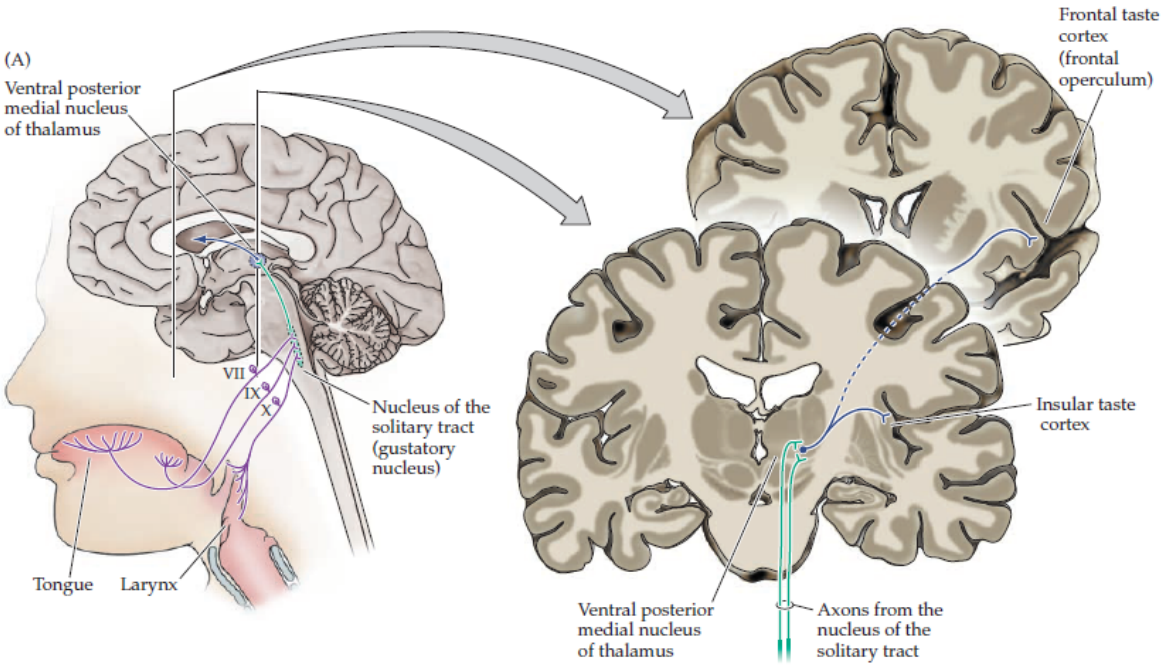




The pyriform cortex has pyramidal neurons that project to a variety of forebrain targets. Thus, olfactory information is distributed broadly to forebrain regions, where it can influence a wide range of behaviors. Significant numbers of neurons in the pyriform cortex innervate directly a variety of areas in the neocortex, including the orbitofrontal cortex in humans and other primates, where multimodal responses to complex stimuli—particularly food—include an olfactory component. Pyriform cortical neurons also project to the thalamus, hippocampus, hypothalamic nuclei, and amygdala. The connections between the pyriform cortex and the mediodorsal nucleus of the thalamus, which is implicated in human memory (see Chapter 30), are thought to influence olfactory-guided "declarative" memory via mediodorsal connections with the frontal cortex. Projections to the hippocampus are similarly thought to play a role in olfactory-guided memory, but there is very little indication of how olfaction and declarative, or conscious mnemonic information are integrated. Finally, connections between the pyriform cortex, hypothalamus, and amygdala are thought to influence visceral, appetitive, and sexual behaviors.

TASTE

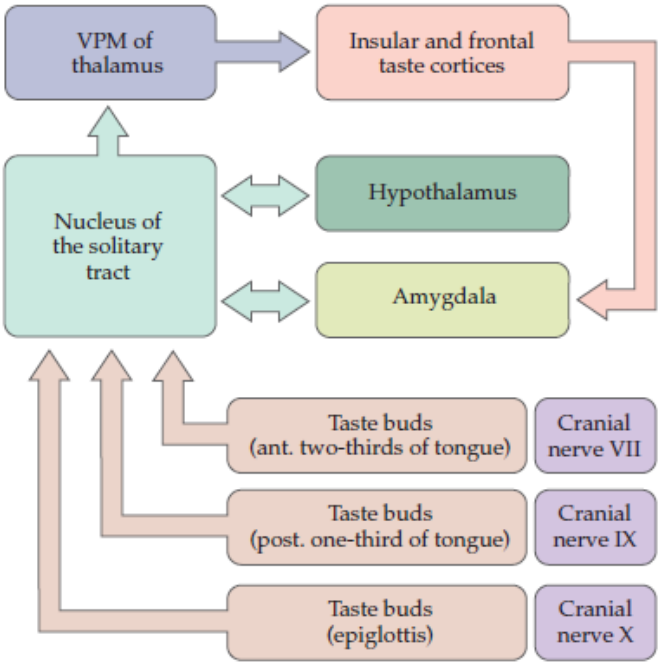
In concert with the olfactory and trigeminal systems, taste reflects the aesthetic and nutritive qualities of food as well as indicating whether or not a food item is safe to be ingested. Once in the mouth, the chemical constituents of food interact with receptor proteins on taste cells, which are located in epithelial specializations called taste buds in the tongue. Taste cells transduce chemical stimuli to encode information about the identity, concentration, and qualities (pleasant, unpleasant, or potentially harmful) of the substance. This information also prepares the gastrointestinal system to receive and digest food by causing salivation and swallowing—or if the substance is noxious, gagging and regurgitation. Information about the temperature and texture of food (including viscosity and fat content) is transduced and relayed from the tongue and mouth via somatosensory receptors from the trigeminal and other sensory cranial nerves to the thalamus and somatosensory cortices.



Like the olfactory system, the taste system is defined by its specialized peripheral receptors as well as by several central pathways that relay and process taste information. Taste cells synapse with primary sensory axons that run in the chorda tympani and greater superior petrosal branches of the facial nerve (cranial nerve VII), the lingual branch of the glossopharyngeal nerve (cranial nerve IX), and the superior laryngeal branch of the vagus nerve (cranial nerve X) to innervate the taste buds in the tongue, palate, epiglottis, and esophagus, respectively. The central axons of these primary sensory neurons in the respective cranial nerve ganglia project to rostral and lateral regions of the nucleus of the solitary tract in the medulla, also known as the gustatory nucleus of the solitary tract complex. Interneurons connecting the rostral and caudal regions of the nucleus represent the first interaction between visceral and gustatory stimuli, and these connections can be thought of as the sensory limb of a gustatory–visceral reflex arc.

Axons from the rostral (gustatory) part of the solitary nucleus project to the ventral posterior complex of the thalamus, where they terminate in the medial half of the ventral posterior medial nucleus. This nucleus projects in turn to several regions of the neocortex, including the anterior insula in the temporal lobe (the insular taste cortex) and the operculum of the frontal lobe.

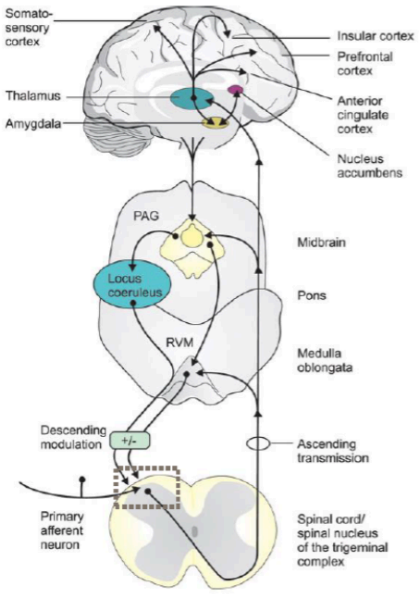
There is also a secondary neocortical taste area in the caudolateral orbitofrontal cortex; here neurons respond to combinations of visual, somatosensory, olfactory, and gustatory stimuli. Finally, reciprocal projections connect the nucleus of the solitary tract via nuclei in the pons to the hypothalamus and amygdala. These projections presumably influence affective aspects (e.g., pleasurable versus aversive experience of food; food-seeking behavior) of appetite, satiety, and other homeostatic responses associated with eating.

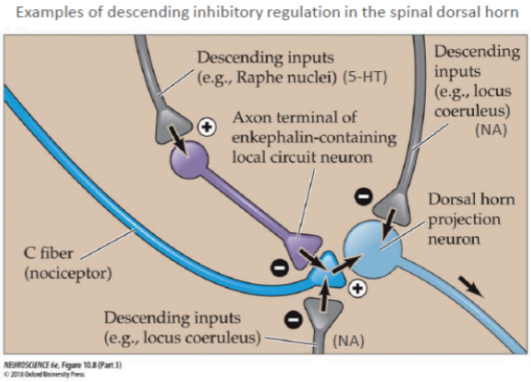


In the taste system, neural coding refers to the way that the identity, concentration, and "hedonic" (pleasurable or aversive) value of tastants is represented in the pattern of action potentials relayed to the brain from the taste buds. Neurons in the taste system might be specifically "tuned" to respond with a maximum change in electrical activity to a single taste stimulus. Such tuning might rely on specificity at the level of the receptor cells, as well as on the maintenance of separate channels for the relay of this information from the periphery to the brain. This sort of coding scheme is often referred to as a labeled line code, since responses in specific cells at multiple points in the pathway presumably correspond to distinct stimuli. The segregated expression of sour, sweet, amino acid, and bitter receptors in different taste cells and the maintenance of focal activation for each class of taste in the insular taste cortex are consistent with labeled line coding.

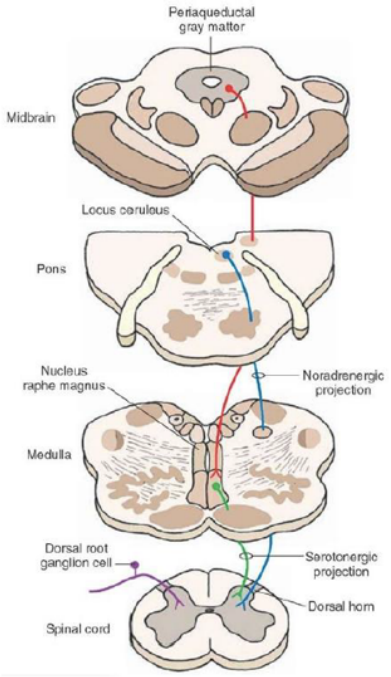
EXPLAIN HOW WE PERCEIVE DIFFERENT SENSORY STIMULI AND HOW THEY CAN BE MODULATED (S2, S3, S4)

When pain signal reaches cortical structures, the signals are sent to PAG, RVM, Locus coeruleus and nucleus raphe magnus. These structures are involved and important for the modulation of signals, they modulate the sensory input from the primary afferent fibres and projection neurons in the dorsal horn of the spinal cord. There are both an inhibitory and a facilizing modulation pathways, when it comes to the inhibitory pathways there are several. Example on these are the serotonergic-noradrenergic and opioidergic pathways.





THE DIFFERENT CORTICAL STRUCTURES AND PATHWAYS



SEROTONERGIC PROJECTION

The neurons located in PAG (periaqueductal grey matter) project to the serotonergic neurons in the nucleus raphe magnus which is the main origin of the serotonergic system. The serotonergic neuron project from nucleus raphe magnus to the dorsal horn. The serotonergic axons descend to all levels of the spinal cord.

NORADRENERGIC PATHWAY

The noradrenergic pathway originates from the locus coeruleus and projects to the dorsal horn. The noradrenergic axons descend to all levels of the spinal cord.

OPIOIDS

The body has their own opioids, these are strongly connected to GABA since they can inactivate GABA. In RVM there are GABAergic interneurons that inhibits descending signals from PAG to RVM, these are called off-cells. The opioids inhibit these off-cells in RVM. These opioids can also inhibit the facilitating “on-cells” that increase the nociception signalling. Example on these opioids are endorphins, enkephalins, morphine.

Example: if we have an interneuron that contains enkephalin it will make it harder for the neuron to release neurotransmitters. The enkephalin can also exist in postsynaptic and make it harder for the signal to continue.

HAVE KNOWLEDGE OF THE MOST COMMON METHODS UTILISED TO EXAMINE VISION, HEARING AND BALANCE (M2)

VISUAL ACUITY TEST

A visual acuity test is an eye exam that checks how well you see the details of a letter or symbol from a specific distance.

Visual acuity refers to your ability to discern the shapes and details of the things you see. It's just one factor in your overall vision. Others include colour vision, peripheral vision, and depth perception.

Two commonly used visual acuity tests are:

SNELLEN

The Snellen test uses a chart of letters or symbols. You've probably seen the chart in a school nurse's office or eye doctor's office. The letters are different sizes and arranged in rows and columns. Viewed from 14 to 20 feet away, this chart helps determine how well you can see letters and shapes.

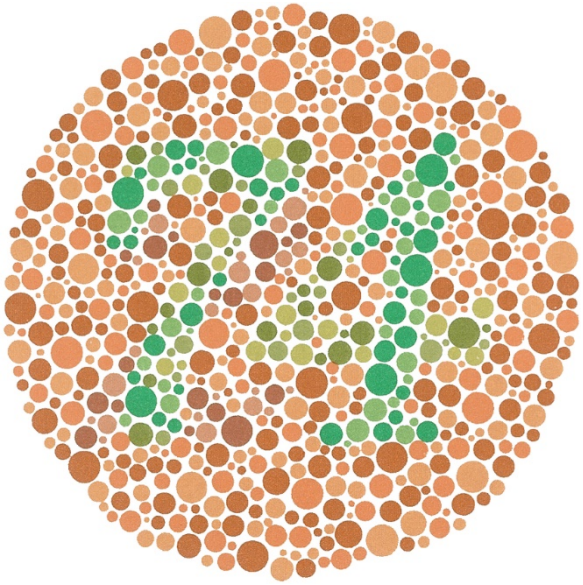
During the test, you'll sit or stand a specific distance away from the chart and cover one eye. You'll read out loud the letters you see with your uncovered eye. You'll repeat this process with your other eye. Typically, your doctor will ask you to read smaller and smaller letters until you can no longer accurately distinguish letters.

RANDOM E

In the random E test, you'll identify the direction the letter "E" is facing. Looking at the letter on a chart or projection, you'll point in the direction the letter is facing: up, down, left, or right.

ISHIHARA COLOUR TEST

The Ishihara test is a colour perception test for red-green colour deficiencies, the first in a class of successful colour vision tests called pseudo-isochromatic plates ("PIP").



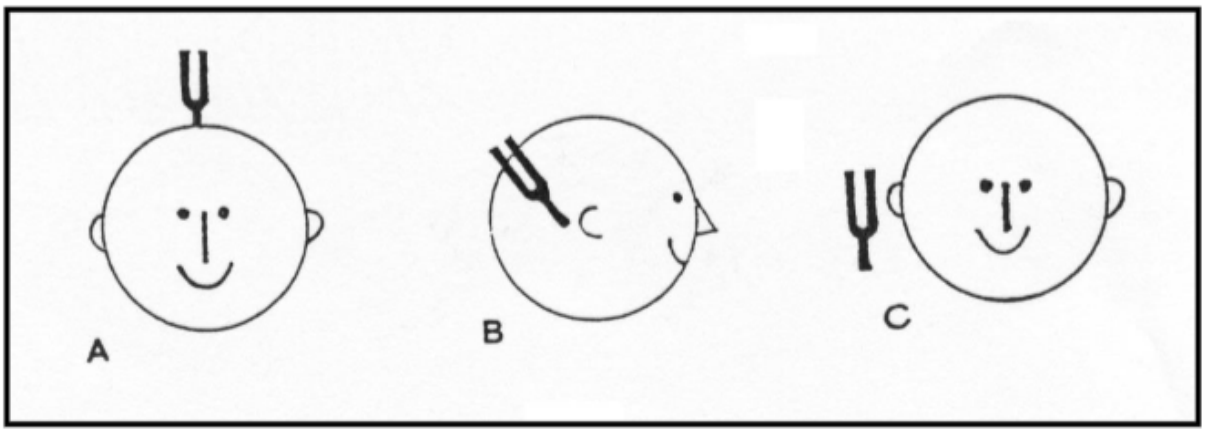
The test consists of a number of coloured plates, called Ishihara plates, each of which contains a circle of dots appearing randomized in colour and size.[2] Within the pattern are dots which form a number or shape clearly visible to those with normal colour vision, and invisible, or difficult to see, to those with a red-green colour vision defect. Other plates are intentionally designed to reveal numbers only to those with a red-green colour vision deficiency, and be invisible to those with normal red-green colour vision.

OPHTHALMOSCOPY

Ophthalmoscopy, also called funduscopy, is a test that allows a health professional to see inside the fundus of the eye and other structures using an ophthalmoscope (or funduscope). It is done as part of an eye examination and may be done as part of a routine physical examination. It is crucial in determining the health of the retina, optic disc, and vitreous humor.

The pupil is a hole through which the eye's interior will be viewed. Opening the pupil wider (dilating it) is a simple and effective way to better see the structures behind it. Therefore, dilation of the pupil (mydriasis) is often accomplished with medicated eye drops before funduscopy.

TUNING FORK



Hearing loss is typically classified into “conductive” or “sensorineural”. Conductive hearing loss involves a problem in the transmission of sounds to the cochlea via the middle ear and can involve for instance the tympanic membrane (perforation), the middle ear bone (otosclerosis), infection (middle ear fluids). Sensorineural hearing loss involves any altered function of the cochlea (most often the sensorial cells or the auditory neurons). To evaluate whether hearing loss is conductive or sensorineural, various tuning fork tests are performed.

WEBER’S TEST (FIGURE A)

In this test, the base of the vibrating tuning fork is placed on the vertex (the center of the skull). The subject indicates whether the tone is heard equally strong in both ears or if he / she is experiencing a side difference in tone volume (= lateralization). See Figure 1 A.

RESULT:

No lateralization suggests bilateral normal hearing or an equilateral hearing
Lateralization to: The "worse" ear indicates a conducting injury The "better" ear suggests a sensorineural loss

RINNE'S TEST

This method allows comparing the ability to perceive air- and bone-transmitted sound. In the test, the base of a vibrating tuning fork is placed on a mastoid process. When the subject does not perceive the tone longer, the legs of the tuning fork are placed just outside the outer ear canal of the same side. Normally, the test subject is again able to hear the tone (air-led sounds are easier than bone-led). See Figure 1, B and C. Opposite results are obtained if the test is performed in the other direction.

POSSIBLE RESULTS:

-Positive Rinne: the air-led sound is strongest. Might be observed in normal hearing, and for a sensorineural loss.

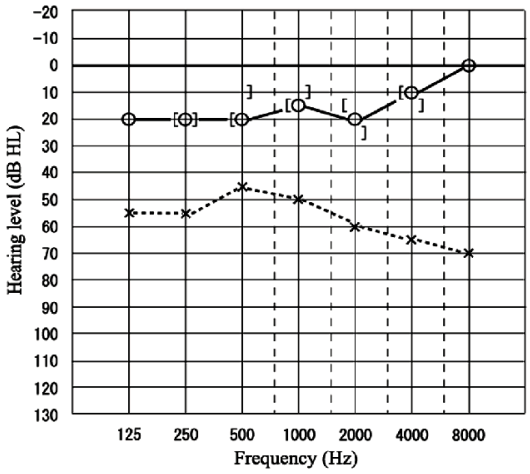
-Negative Rinne: the bone-led tone is strongest. Found in people with conductive injury. A simultaneous sensorineural hearing loss cannot be excluded.

It is preferred to perform Weber's and Rinne's tests at the same time. These tuning fork tests should always be complemented with precise hearing measurements in case of any damage.

Summary	Rinne's test	Weber's test
Normal hearing bilaterally	positive bilateral	no lateralization
Conductive injury	negative for injured (conductive) ear	lateralization to "worse" ear
Sensorineural damage	positive for the damaged ear	lateralization to "better" ear

PURE TONE AUDIOMETRY (PTA)

Pure-tone audiometry is a behavioural test used to measure hearing sensitivity. This measure involves the peripheral and central auditory systems. Pure-tone thresholds (PTTs) indicate the softest sound audible to an individual at least 50% of the time. Hearing sensitivity is plotted on an audiogram, which is a graph displaying intensity as a function of frequency.



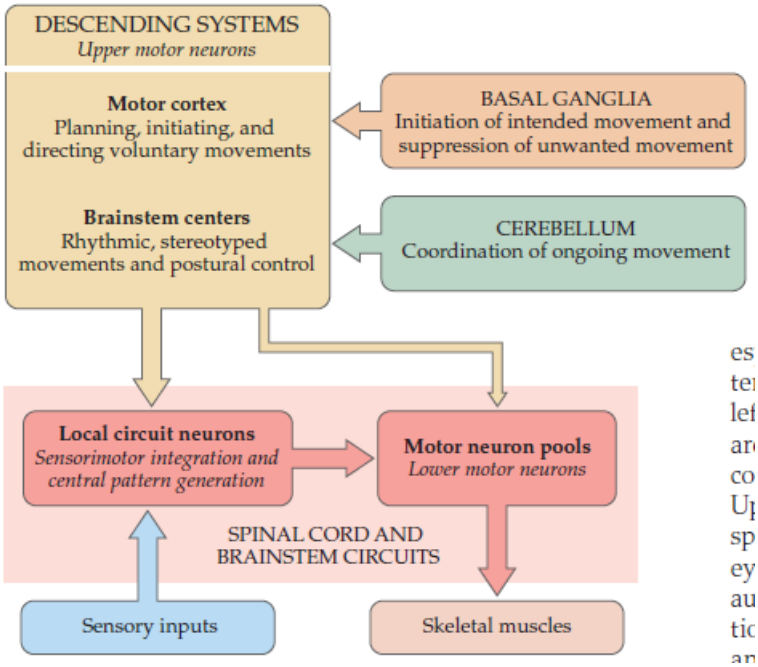
ROTATION CHAIR

A few experiments can be done in a rotation chair to check balance.

MOTOR FUNCTIONS:

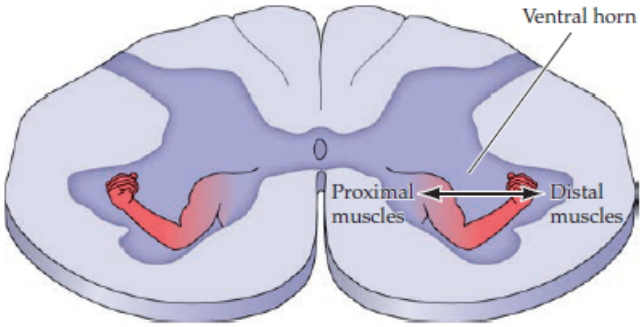
DESCRIBE AND EXPLAIN BASIC MOTOR FUNCTIONS AT THE SPINAL LEVEL, AND THE CONCEPT OF THE CENTRAL MOTOR PROGRAMME (S3)

Skeletal muscle contraction is initiated by "lower" motor neurons in the spinal cord and brainstem. The cell bodies of the lower neurons are located in the ventral horn of the spinal cord gray matter and in the motor nuclei of the cranial nerves in the brainstem. These neurons (also called α motor neurons) send axons directly to skeletal muscles via the ventral roots and spinal peripheral nerves or, in the case of brainstem motor nuclei, via cranial nerves. The local circuit neurons receive direct input from sensory neurons and mediate sensorimotor reflexes; they also maintain precise interconnections that enable the coordination of a rich repertoire of rhythmical and stereotyped behaviours. The local circuit neurons also receive input from descending pathways from higher centers. These descending pathways comprise the axons of "upper" motor neurons that modulate the activity of lower motor neurons by influencing the local circuitry. The cell bodies of the upper motor neurons are located in brainstem centers, such as the vestibular nuclei, superior colliculus, and reticular formation, as well as in the cerebral cortex.

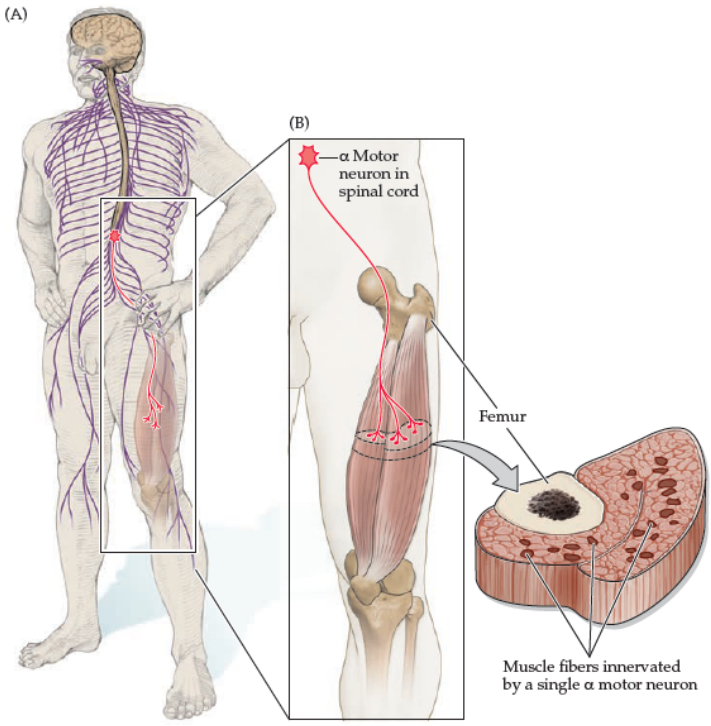


The neural centers responsible for the control of movement can be divided into four distinct but highly interactive subsystems, each of which makes a unique contribution to motor control. The first of these subsystems is located within the gray matter of the spinal cord and the tegmentum of the brainstem. The relevant cells include the lower motor neurons, which send their axons out of the brainstem and spinal cord to innervate the skeletal muscles of the head and body, respectively, and the local circuit neurons, which are the major source of synaptic input to all lower motor neurons. Commands for movement, whether reflexive or voluntary, are ultimately conveyed to the muscles by the activity of the lower motor neurons making them

the “final common path” for initiating movement. The local circuit neurons that innervate the lower motor neurons receive sensory inputs as well as descending projections from higher centers. The circuits they form provide much of the coordination between different muscle groups that is essential for organized movement. Even after the spinal cord is disconnected from the brain in an experimental animal, appropriate stimulation of local circuits in the isolated spinal cord can elicit involuntary but highly coordinated limb movements that resemble walking. The other three subsystems: the descending systems (upper motor neurons), the basal ganglia and cerebellum will be brought up in another question.



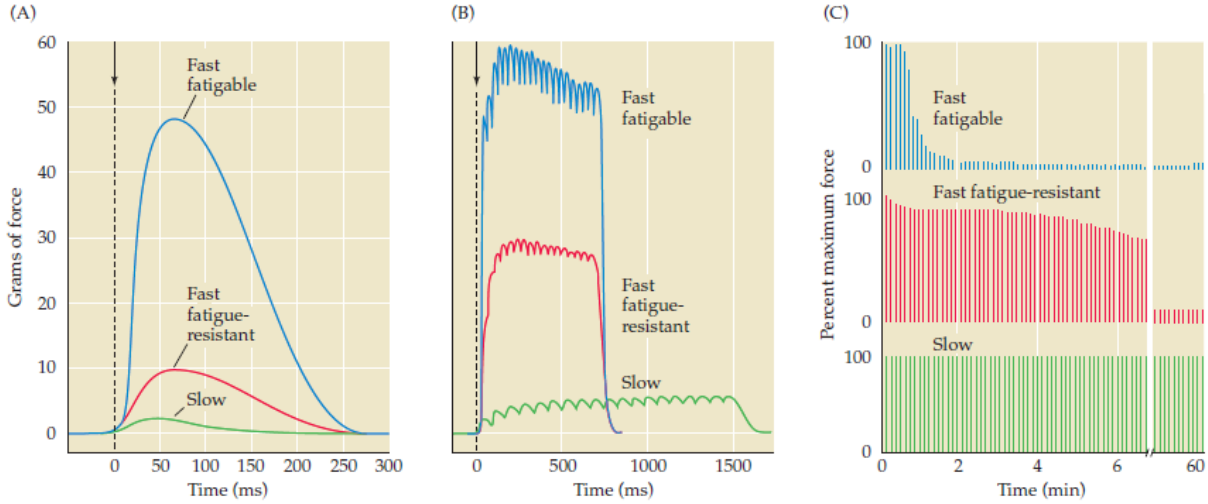
Lower motor neurons reside in the ventral horn of the spinal cord and show an orderly relationship between the location of motor neuron pools and the muscles they innervate. Neurons that innervate proximal muscles are located medially in the ventral horn while those that innervate distal musculature is located more laterally. The medial motor neurons govern postural control and the maintenance of balance while the more lateral motor neurons are more involved in the execution of skilled behaviour (use of hands for example).



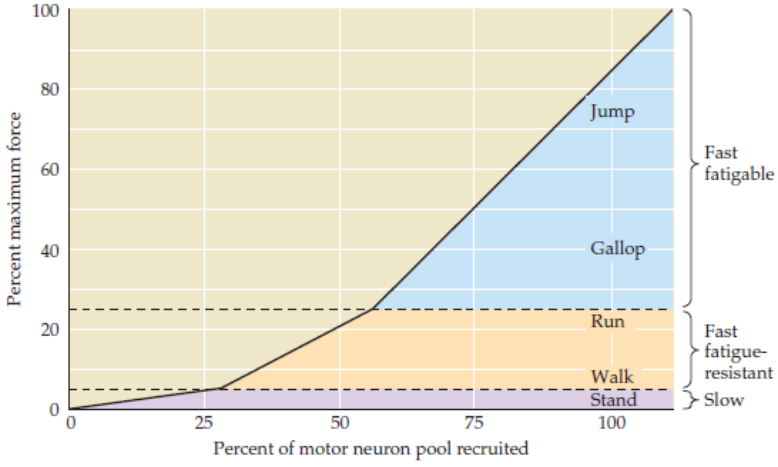
Two types of lower motor neurons are found in the motor neuron pools of the ventral horn. Large motor neurons are called α motor neurons; they innervate the striated muscle fibers that actually generate the forces needed for posture and movement. Interspersed among the α-motor neurons are smaller γ motor neurons, which are actually sensory receptors arranged in parallel with the force-generating striated muscle fibers. These specialized muscle fibers, called muscle spindles, are embedded within connective tissue capsules in the muscle and are thus referred to as intrafusal muscle fibers. The intrafusal muscle fibers are innervated by sensory axons that send information to the spinal cord and brainstem about the length of the muscle. The function of the γ motor

neurons is to regulate this sensory input by setting the intrafusal muscle fibers to an appropriate length. The output of both types of lower motor neurons is coordinated to optimize movement, particularly when the lengths of active muscles change and the forces acting on the body are dynamic.

Most extrafusal skeletal muscle fibers in mature mammals are innervated by only a single α motor neuron. Since there are, by far, more muscle fibers than motor neurons, individual motor axons branch within muscles to synapse on multiple extrafusal fibers. These fibers are typically distributed over a relatively wide area within the muscle, presumably to ensure that the contractile force is spread evenly. Because an action potential generated by a motor neuron typically brings to contraction threshold all of the muscle fibers the neuron contacts, the single α motor neuron and its associated muscle fibers constitute the smallest unit of force that can be activated by the muscle. Sherrington was again the first to recognize this fundamental relationship between an α motor neuron and the muscle fibers it innervates, for which he coined the term motor unit.



Both motor units and the α motor neurons themselves vary in size. Small α motor neurons innervate relatively few muscle fibers to form motor units that generate small forces, whereas large motor neurons innervate larger, more powerful motor units. Motor units also differ in the types of muscle fibers they innervate. In most skeletal muscles, the smaller motor units comprise small “red” muscle fibers that contract slowly and generate relatively small forces; but because of their rich myoglobin content, plentiful mitochondria, and rich capillary beds, these small red fibers are resistant to fatigue. These small units are called slow (S) motor units and are especially important



for activities that require sustained muscular contraction, such as maintaining an upright posture. Larger α motor neurons innervate larger, pale muscle fibers that generate more force; however, these fibers have sparse mitochondria and are therefore easily fatigued. These units are called fast fatigable (FF) motor units and are especially important for brief exertions that require large forces, such as running or jumping. A third class of motor unit has properties in between those of the other two. These fast fatigue resistant (FR) motor units are of intermediate size and are not quite as fast as FF motor units. They generate about twice the force of a slow motor unit and, as the name implies, are resistant to fatigue. These distinctions among different types of motor units explain how the nervous system produces movements appropriate for different circumstances.

Increasing or decreasing the number of motor units active at any one time changes the amount of force produced by a muscle. When synaptic input to the motor pool increases, progressively larger motor units that generate larger forces are recruited. Thus, as the synaptic activity driving a motor neuron pool increases, low-threshold S motor units are recruited first, then FR motor units, and finally, at the highest levels of activity, the FF motor units. This systematic relationship has come to be known as the size principle. (Picture shows motor recruitment in a cat)

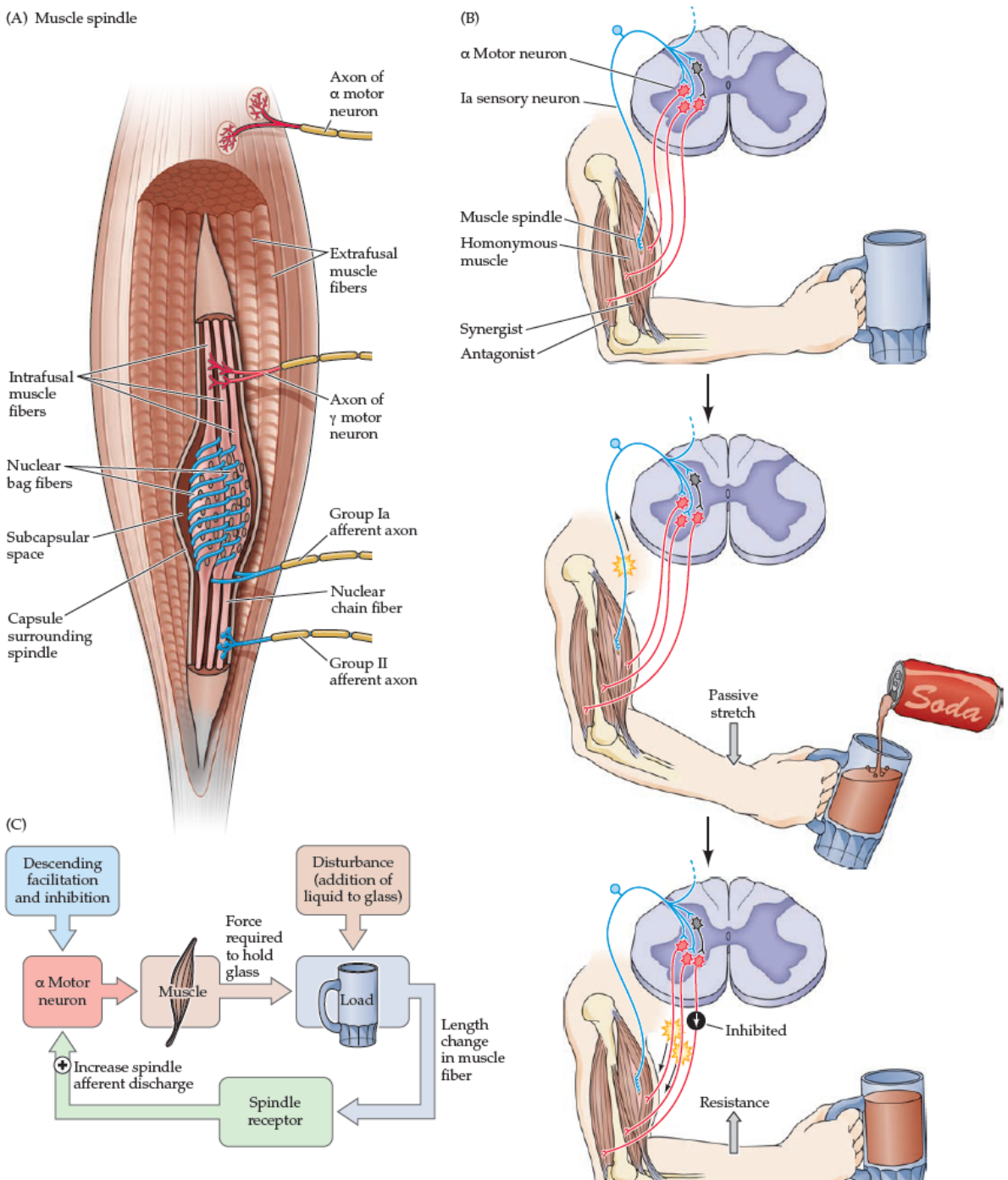


FIGURE 16.10 **Stretch reflex circuitry.** (A) Diagram of a muscle spindle, the sensory receptor that initiates the stretch reflex. (B) Stretching a muscle spindle leads to increased activity in group Ia afferents and an increase in the activity of α motor neurons that innervate the same muscle. Group Ia afferents also excite the motor neurons that innervate synergistic muscles, and they indirectly inhibit the motor neurons that innervate antagonists via intervening reciprocal-Ia-inhibitory interneurons (gray neurons; see also Figures 1.7–1.9). (C) The stretch reflex operates as a negative feedback loop to regulate muscle length.

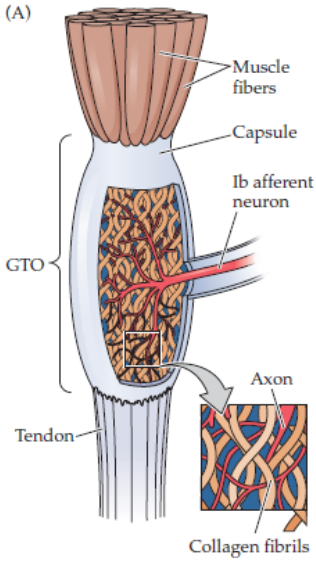
Local circuitry within the spinal cord mediates several sensorimotor reflexes. The simplest of these reflex arcs entails a sensory response to muscle stretch, which provides direct excitatory feedback to the motor neurons innervating the muscle that has been stretched. Two classes of intrafusal fibers can be distinguished by differences in their structure and function: nuclear bag fibers and nuclear chain fiber. The two classes differ in the

arrangement of their nuclei, the intrinsic architecture of their myofibrils, and their dynamic sensitivity to stretch.

Large-diameter sensory axons (group Ia afferents) are coiled around the middle region of each class of intrafusal fiber, forming so-called annulospiral primary endings. Nearly as large in diameter are the group II afferents, which form secondary endings, mainly on nuclear chain fibers; these are referred to as “flower-spray” endings because of their short, petal-like contacts just outside the middle region of the fiber. When the muscle is stretched the muscle deforms the intrafusal muscle fibers which in turn initiates action potentials by activating mechanotransduction channels in the group I and II axon endings. Group Ia tend to respond to small stretches while group II afferents signal the level of sustained fiber stretch by firing tonically at a frequency proportional to the degree of stretch.

The centrally projecting branch of the sensory neuron forms monosynaptic excitatory connections with those α motor neurons in the ventral horn of the spinal cord that innervate the same (homonymous) muscle and, via intervening GABAergic local circuit neurons (called reciprocal-Ia-inhibitory interneurons), forms inhibitory connections with those α motor neurons that innervate antagonistic (heteronymous) muscles. This arrangement is an example of reciprocal innervation and results in rapid contraction of the stretched muscle and simultaneous relaxation of the antagonist muscle. The excitatory pathway from a spindle to the α motor neurons innervating the same muscle is unusual in that it is a monosynaptic reflex; in most cases, sensory neurons from the periphery do not contact lower motor neurons directly but instead exert their effects through local circuit neurons. This monosynaptic reflex arc is variously referred to as the “stretch,” “deep tendon,” or “myotatic” reflex, and it is the basis of the knee, ankle, jaw, biceps, or triceps response tested in a routine physical examination.

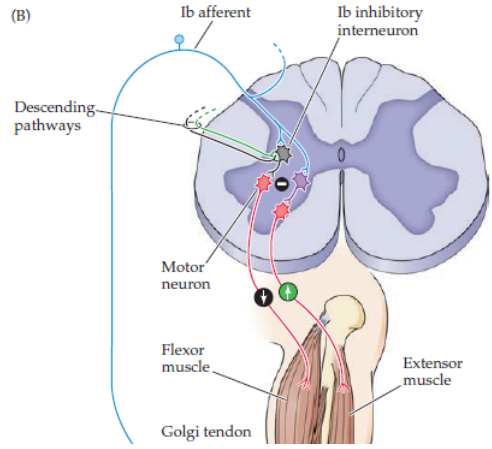
In terms of engineering principles, the stretch reflex arc is a negative feedback loop used to maintain muscle length at a desired value. In the context of motor control, the appropriate muscle length is specified by the activity of descending upper motor neuron pathways that influence the lower motor neuron pool. Deviations from the desired length are detected by the muscle spindles, since increases or decreases in the stretch of the intrafusal fibers alter the level of activity in the sensory axons that innervate the spindles. These changes lead, in turn, to adjustments in the activity of the α motor neurons, returning the muscle to the desired length by contracting the stretched muscle and relaxing the opposing muscle group, and by restoring the level of spindle activity and sensitivity.

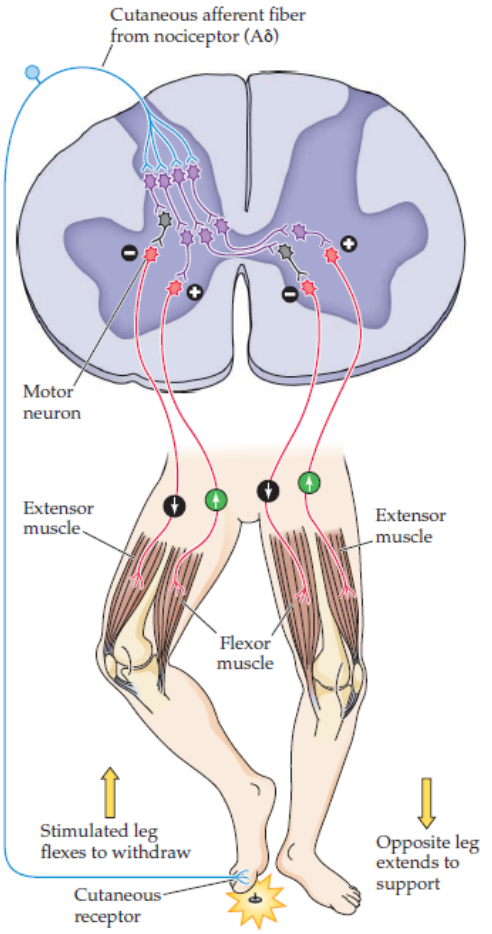


Another sensory receptor that is important in the reflexive

regulation of motor unit activity is the Golgi tendon organ. Golgi tendon organs are encapsulated afferent nerve endings located at the junction of a muscle and a tendon. Each tendon organ is innervated by a single group Ib sensory axon. In contrast to the parallel arrangement of extrafusal muscle fibers and spindles, Golgi tendon organs are in series with the extrafusal muscle fibers. When a muscle actively contracts, the force acts directly on the tendon, leading to an increase in the tension of the collagen fibrils in the tendon organ and consequent compression of the intertwined sensory nerve endings. Activation of the non-selective, cationic mechanosensitive ion channels in the nerve endings of the Golgi tendon organ results in a generator potential that, if suprathreshold, triggers generation of action potentials that are propagated along the group Ib axon to the spinal cord.

The Ib axons from Golgi tendon organs contact GABAergic inhibitory local circuit neurons in the spinal cord (called Ib inhibitory interneurons) that synapse, in turn, with the α motor neurons that innervate the same muscle. The Golgi tendon circuit is thus a negative feedback system that regulates muscle tension; it decreases the activation of a muscle when exceptionally large forces are generated and, in this way, protects the muscle. This reflex circuit also operates at lower levels of muscle force, counteracting small changes in muscle tension by increasing or decreasing the inhibition of α motor neurons. The same Ib afferents also make synaptic connections with excitatory interneurons that increase the excitability of α motor neurons that innervate the antagonistic muscle.





There is also the flexion reflex pathway which withdraws the limb from painful stimuli. This flexion reflex involves slowly conducting afferent axons and several synaptic links. As a result of activity in this circuitry, stimulation of nociceptive sensory fibers leads to withdrawal of the limb from the source of pain by excitation of ipsilateral flexor muscles and reciprocal inhibition of ipsilateral extensor muscles. Flexion of the stimulated limb is also accompanied by an opposite reaction in the contralateral limb (i.e., the contralateral extensor muscles are excited while flexor muscles are inhibited). This crossed

extension reflex provides postural support during withdrawal of the affected limb from the painful stimulus. As in the other reflex pathways, local circuit neurons in the flexion reflex pathway receive converging inputs from several different sources, including other spinal cord interneurons and upper motor neuron pathways.

The contribution of local circuitry to motor control is not limited to reflexive responses to sensory inputs. Studies of rhythmic movements, such as locomotion and swimming in animal models, have demonstrated that local circuits in the spinal cord, called central pattern generators, are fully capable of controlling the timing and coordination of such complex patterns of movements, and adjusting them in response to altered circumstances. Central pattern generators are likened to motor programmes as they are an abstract representation of movement that centrally organizes and controls the many degrees of freedom involved in performing an action.

DESCRIBE THE NERVOUS SYSTEM'S CONTROL OF LOCOMOTION (S3)

The movement of walking differs from other motion patterns that the nervous system regulate like; the patella reflex that is produced due to sensory stimuli or the precise movement of the complex learnt movements like playing tennis that involves several muscles. Locomotion is a repetitive and automatic pattern of movements where several groups of muscles are activated in a rhythmic and exact sequence. Locomotion is different types of patterns of movements that are used for motion like running, walking, flying, jumping and swimming.

The locomotion movements are organised and controlled at several levels of the central nervous system. The control system for the basic motion of walking has the following components:

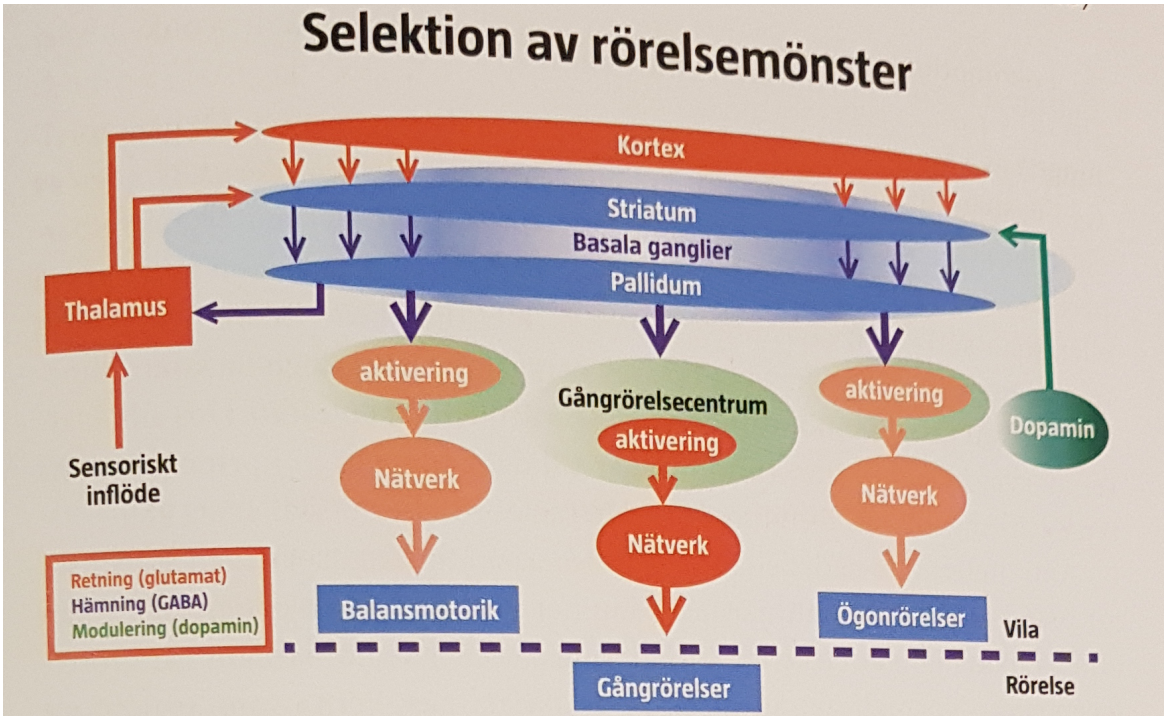
1. The basal ganglia in the forebrain is responsible for the main/superior control of the movements like when locomotion set on.
2. The basal ganglia affect the midbrains "command centre" which regulate the activity among the spinal cords nerve cells.
3. The network of nerve cells in the spinal cord control the motion and give rise to a rhythmic pattern of motion.
4. There's an influx of feedback signals from the organs of perception that sends signals to the spinal cord and higher centres in the medulla and cerebellum, this contribute to the smoothness of the motion.
5. Balance and body posture are controlled throughout the movement.
6. The central cortex gives an adjustment from the visual input it receives during the movement.

THE BASAL GANGLIA

The basal ganglia are important in the decision of what movement that are to be executed. There are two main parts of cells, efferent part called the pallidum and the afferent/receiving part called the striatum. The Pallidum have an inhibitory effect on its

target cells in the different motor cortexes and are very active during rest or nonemotion. When a locomotion motion is about to be performed the cortex will activate the cells in the striatum and which in turn leads to the pallidum not inhibiting the locomotion centre. The locomotion centre then gets activated and sends signals through the network of nerve cells in the spinal cord and the motion is initiated.

The basal ganglia are divided into different parts and they all affect the movements. These structures are in turn regulated by other parts of the brain and systems in the brain for example the thalamus and the dopamine system. In the system glutamate works as an executory stimuli, GABA as an inhibitory and dopamine as a modulating signal.



Figur 6.4 *Basala ganglierna väljer rörelsemönster*
Basala gangliernas utåtledande del (Pallidum) hämmar under vila konstant olika rörelsecentra (blå pilar; GABA). När ett rörelsemönster, till exempel gången, ska selekteras för att aktiveras minskar basala gangliernas hämning av motsvarande rörelsecentrum, här gångrörelsecentrum. Detta blir då aktivt och sätter igång de nervbanesystem som går ned till ryggmärgen och aktiverar nätverket för gångrörelser där, vilket sedan startar gångrörelserna. Basala gangliernas mottagande del (Striatum) mottar retande inflöde (röda pilar, glutamat) från både storhjärnebarken (Kortex) och från Thalamus, men även modulerande inflöde (grön pil, dopamin).

CENTRAL PATTERN GENERATORS – CPG

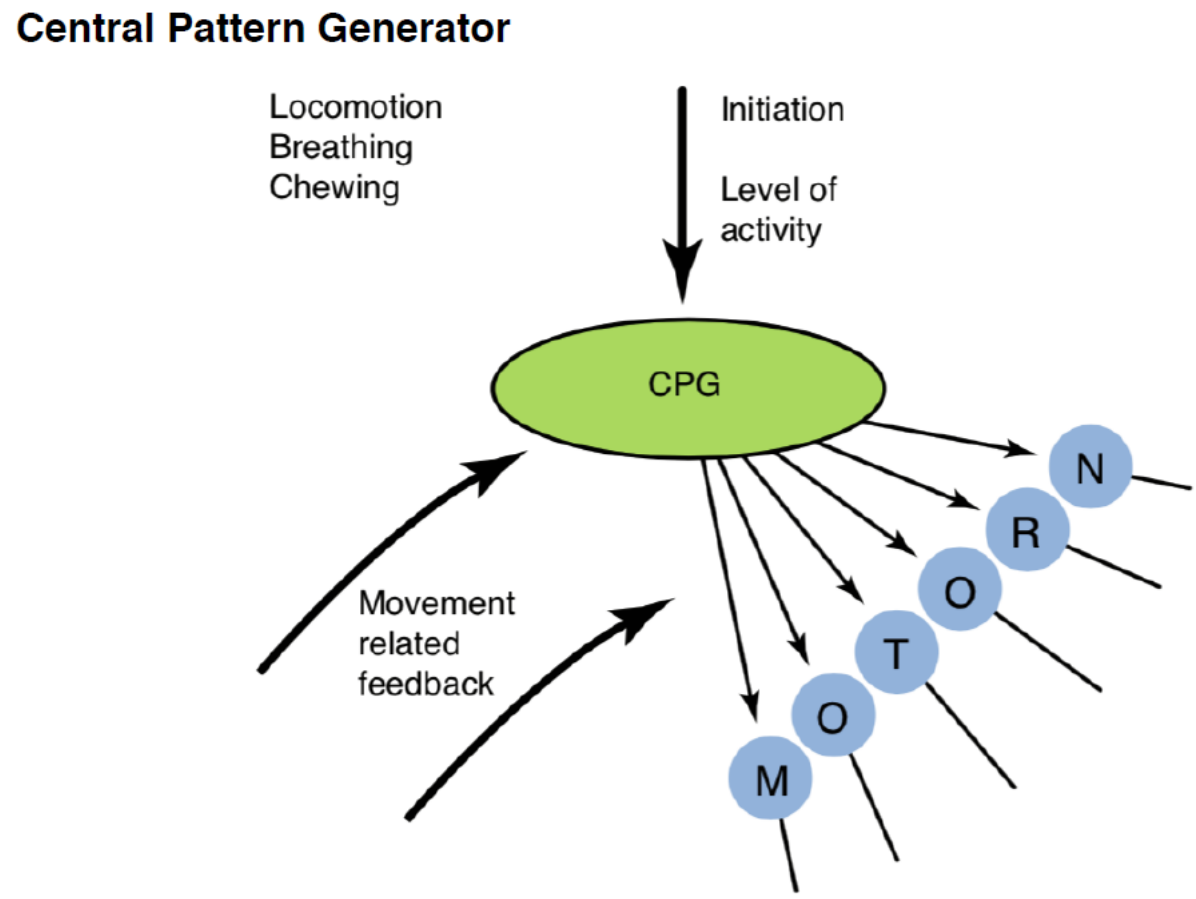
Locomotion control in humans and other mammals are regulated by higher brain functions and local circuitry as mentioned above. The local circuitry in the spinal cord give rise to central pattern generators (GPG) to every limb. In the CPG there are several neurons that

control the interaction between motions on the left end right side of the body. CPG is involved in both the recruitment and coordination of motor units.

CPG is crucial for the rhythmical movements such as chewing and walking. To explain why CPG is important we will use a fish model:
The fish wants to move forward, in order to do this, it need to contract the muscles on the left side of the body. At the same time the muscles on the right side of the body is inhibited so that there can be a flexation, this allows the body to arc one way, the same movement happens in the opposite direction and the fish moves forward.

Initiation of movement → recruitment of motor units → coordinated activity

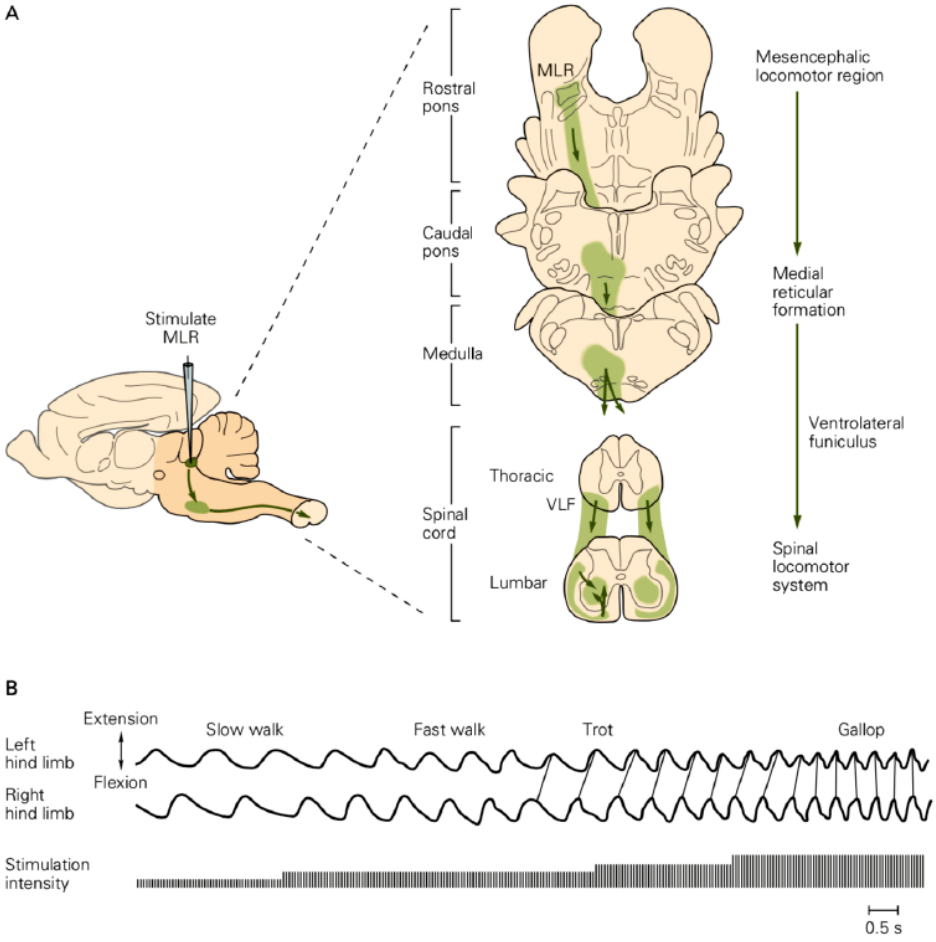
CPG is important to be able to coordinate the movement, the initiation of the locomotion comes from the brainstem but CPG takes care of the movement and does also receive sensory feedback. The descending tract called the Reticulospinal is important for the activation and inhibition of the CPG.



When it comes to CPG, it does not nessecarly need the brain to work, one example of this is refelxes.

MESENCEPHALIC LOCOMOTOR REGION - MLR

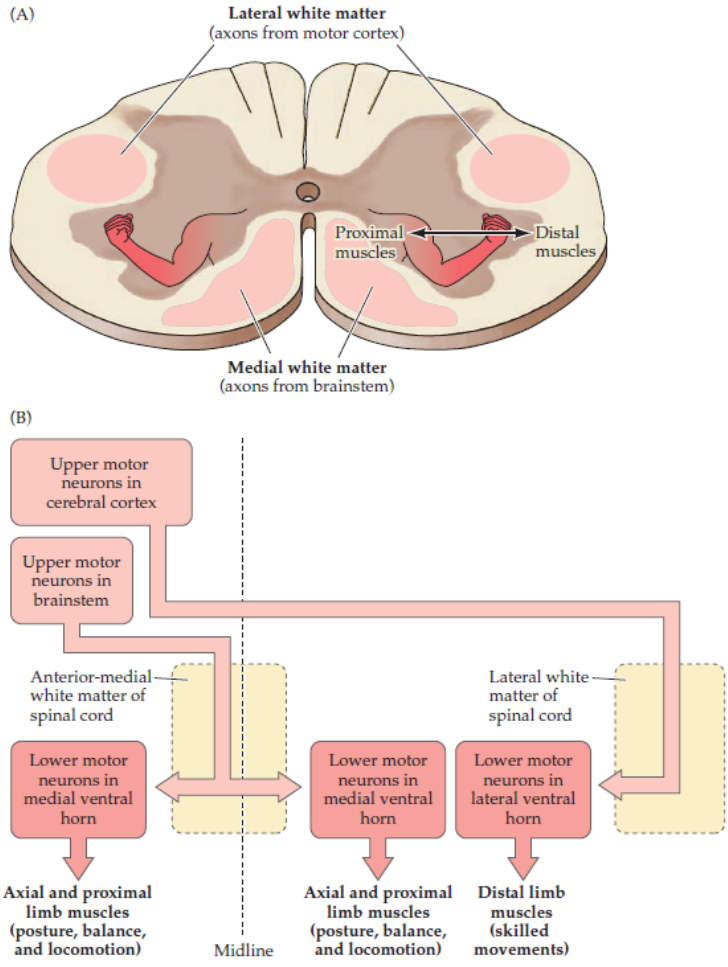
Even though the brainstem initiate the locomotion are there places above the brainstem that are activated. Mesencephalic locomotor region (MLR) is located in the brain, it's not entirely known exactly where but it seems to between the cortex and cerebellum. MLR can activate CPG, i.e it can initiate locomotion and are important in changing speed and pattern of locomotion through the alteration of the signals delivered to the spinal cord. The signal goes from the MLR → formation reticularis → via reticulospinal tract → spinal locomotor system



The CPG and the MLR are the Control systems of locomotion.

DESCRIBE THE DIFFERENT DESCENDING MOTOR PATHWAYS (S2) AND RELATE THEIR ORGANISATION TO THE CONTROL OF DIFFERENT MOVEMENTS (S3)

The axons of upper motor neurons arise from cell bodies in higher centers and descend to influence the local circuits in the brainstem and spinal cord. These local circuits organize movements by coordinating the activity of the lower motor neurons that innervate different muscles. The sources of these upper motor neuron pathways include several brainstem centers and multiple cortical areas in the frontal lobe. The motor control centers in the brainstem are especially important in postural control, orientation toward sensory stimuli, locomotion, and orofacial behaviour, with each centre having a distinct influence.



Just as with the lower motor neurons, the location in the spinal cord to where the upper motor neurons terminate conform to the functional distinction between axial and distal muscle groups. Axons from the upper motor neurons that originate in the brainstem terminate in the medial white matter and are responsible for governing the motor neurons responsible for posture, balance and locomotion while the axons that originate in the motor cortex terminate in the lateral white matter and govern the lower motor neurons in the lateral ventral horn responsible for skilled movement.

THE CORTICOSPINAL AND CORTICOBULBAR TRACTS

The upper motor neurons in the cerebral cortex reside in several adjacent and highly interconnected areas in the posterior frontal lobe, which together mediate the planning and initiation of complex temporal sequences of voluntary movements. These cortical areas all receive regulatory input from the basal ganglia and cerebellum via relays in the ventrolateral thalamus, as well as inputs from sensory regions of the parietal lobe. Although the label "motor cortex" is sometimes used to refer to these frontal areas collectively, the term is more commonly restricted to the primary motor cortex located in the precentral gyrus and the paracentral lobule. The pyramidal cells of cortical layer 5 are the upper motor neurons of the primary motor cortex. Among these neurons are the conspicuous Betz cells, which are the largest neurons (by soma size) in the human CNS.

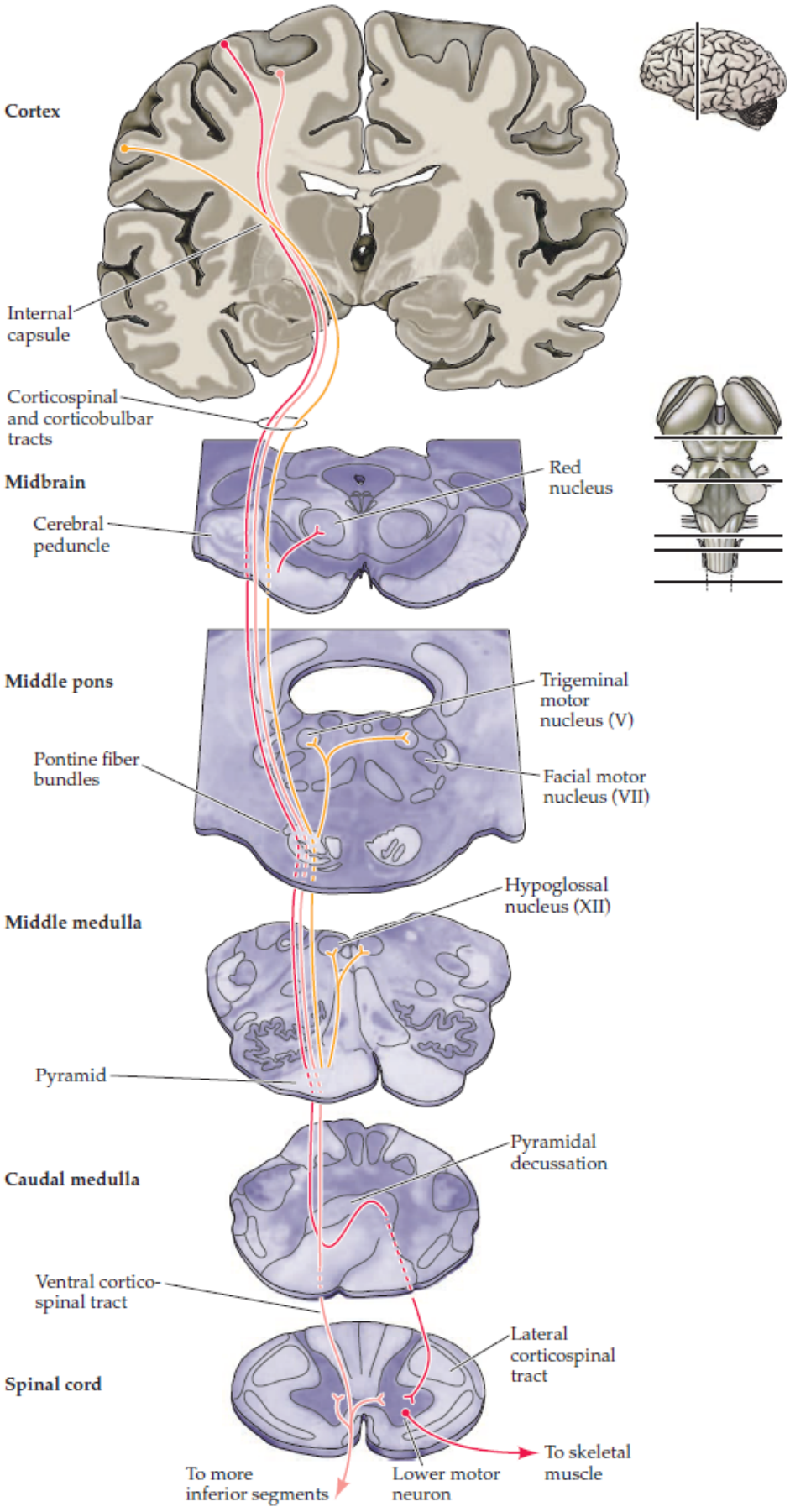


FIGURE 17.4 The corticospinal and corticobulbar tracts. Neurons in the motor cortex give rise to axons that travel through the internal capsule and coalesce on the ventral surface of the midbrain, within the cerebral peduncle. These axons continue through the pons and come to lie on the ventral surface of the medulla, giving rise to the medullary pyramids. As they course through the brainstem, corticobulbar axons (gold) give rise to bilateral collaterals that innervate brainstem nuclei (only collaterals to the trigeminal motor nuclei and the hypoglossal nuclei are shown). Most of the corticospinal fibers (dark red) cross in the caudal part of the medulla to form the lateral corticospinal tract in the spinal cord. Those axons that do not cross (light red) form the ventral corticospinal tract, which terminates bilaterally.

Although it is often assumed that Betz cells are the principal upper motor neurons of the motor cortex, there are far too few of them to account for the number of axons that project from the motor cortex to the brainstem and spinal cord (in the human CNS they account for no more than 5% of the axons that project from the motor cortex to the spinal cord). Despite their small numbers, Betz cells play an important role in the activation of lower motor neurons that control muscle activities in the distal extremities. The remaining upper motor neurons are the smaller, non-Betz pyramidal neurons of layer 5 that are found in the primary motor cortex and in each division of the premotor cortex. The axons of these upper motor neurons descend in the corticobulbar and corticospinal tracts, terms that are used to distinguish axons that terminate in the brainstem ("bulbar" refers to the brainstem) or spinal cord. Along their course, these axons pass through the posterior limb of the internal capsule in the forebrain to enter the cerebral peduncle at the base of the midbrain. They then pass through the base of the pons, where they are scattered among the transverse pontine fibers and nuclei of the basal pontine gray matter. They coalesce again on the ventral surface of the medulla, where they form the medullary pyramids. The components of this upper motor neuron pathway that innervate cranial nerve nuclei, the reticular formation, and the red nucleus (that is, the corticobulbar tract) leave the pathway at the appropriate levels of the brainstem. There is also a massive corticobulbar projection that terminates among nuclei in the base of the pons that project in turn to the cerebellum; this projection is often called the corticopontine tract.

Most corticobulbar axons that govern the cranial nerve motor nuclei (see the Appendix) terminate bilaterally on local circuit neurons embedded in the brainstem reticular formation, rather than directly on the lower motor neurons in the motor nuclei. These local circuit neurons, in turn, coordinate the output of different groups of lower motor neurons in the cranial nerve motor nuclei.

Near the caudal end of the medulla, nearly all of the fibers in the medullary pyramids are corticospinal axons. Just before entering the spinal cord, about 90% of these axons cross the midline—decussate—to enter the lateral columns of the spinal cord on the opposite side, where they form the lateral corticospinal tract. The remaining 10% of the pyramidal tract fibers enter the spinal cord without crossing; these axons, which constitute the ventral (anterior) corticospinal tract, terminate bilaterally. Collateral branches of these axons cross the midline via the ventral white commissure of the spinal cord to reach the opposite ventral horn. The ventral corticospinal pathway arises primarily from dorsal and medial regions of the motor cortex that serve trunk and proximal limb muscles.

The lateral corticospinal tract forms a direct pathway from the cortex to the spinal cord and terminates primarily in the lateral portions of the ventral horn and intermediate gray matter. Some of these axons (including those derived from Betz cells) synapse directly on α motor neurons that govern the distal extremities. However, this privileged synaptic contact on

lower motor neurons is restricted to a subset of α motor neurons that supply the muscles of the forearm and hand; most axons of the lateral corticospinal tract, in contrast, terminate among pools of local circuit neurons that coordinate the activities of the lower motor neurons in the lateral cell columns of the ventral horn that innervate different muscles. This difference in terminal distribution implies a special role for the lateral corticospinal tract in the control of the hands.

Some components of the corticobulbar and corticospinal projections do not participate directly in upper motor control of lower motor neurons. These components are derived from layer 5 neurons in somatosensory regions of the anterior parietal lobe and terminate among local circuit neurons near the sensory trigeminal nuclei and dorsal column nuclei of the brainstem, and in the dorsal horn of the spinal cord. They are likely involved in modulating the transmission of proprioceptive signals and other mechanosensory inputs relevant to sensory perception and the monitoring of body movements.

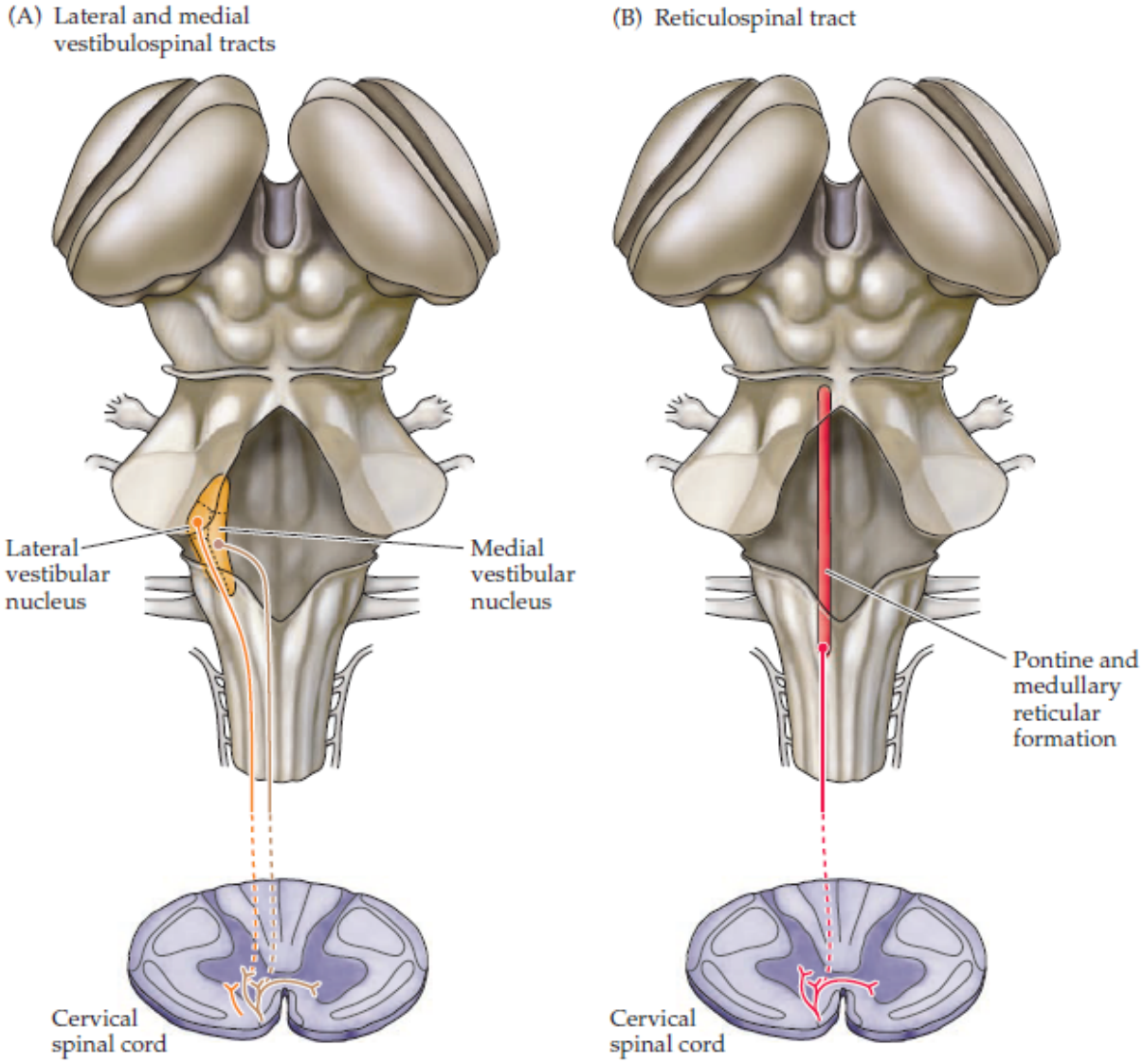
MEDIAL AND LATERAL VESTIBULOSPINAL TRACT

Several structures in the brainstem contain circuits of upper motor neurons whose activities serve to organize a variety of somatic movements involving the axial musculature of the trunk and the proximal musculature of the limbs. These movements include the maintenance of balance, the regulation of posture, the initiation and regulation of locomotion, and the orientation of visual gaze. They are governed by upper motor neurons in the nuclei of the vestibular complex, the reticular formation, and the superior colliculus.

The vestibular nuclei are the major destination of the axons that form the vestibular division of the eighth cranial nerve; as such, they receive sensory information from the semicircular canals and the otolith organs that specifies the position of the head and its rotational and translational movements. Many of the cells in the vestibular nuclei that receive this information are upper motor neurons with descending axons that terminate in the medial region of the spinal cord gray matter, although some extend more laterally to contact the neurons that control the proximal muscles of the limbs. The projections from the vestibular nuclei that control axial muscles and those that influence proximal limb muscles originate from different cells and take somewhat different routes to the spinal cord.

Neurons in the medial vestibular nucleus give rise to a medial vestibulospinal tract that terminates bilaterally in the medial ventral horn of the cervical cord. There, the medial vestibulospinal tract regulates head position by reflex activation of neck muscles in response to the stimulation of the anterior semi-circular canals resulting from unexpected rapid, downward rotation of the head. For example, when an individual falls forward, the medial vestibulospinal tract mediates reflexive dorsiflexion of the neck as well as extension of the arms in an attempt to protect the upper body from injury. Neurons in the lateral vestibular nucleus are the source of the lateral vestibulospinal tract, which courses through the

anterior white matter of the spinal cord in a slightly more lateral position relative to the medial vestibulospinal tract. Despite the modifier in its name, the lateral vestibulospinal tract terminates ipsilaterally among medial lower motor neuron pools that govern proximal muscles of the limbs. This tract facilitates the activation of limb extensor (antigravity) muscles when the otolith organs signal deviations from stable balance and upright posture. Other upper motor neurons in the vestibular nuclei project to local circuit neurons and lower motor neurons in the cranial nerve nuclei that control eye movements (the third, fourth, and sixth cranial nerve nuclei). This pathway produces the eye movements that maintain fixation while the head is moving.



RETICULOSPINAL TRACT

The reticular formation is a complicated network of circuits in the core of the brainstem that extends from the rostral midbrain to the caudal medulla; it is similar in structure and function to the local circuitry in the intermediate gray matter of the spinal cord. Unlike the

well-defined sensory and motor nuclei of the cranial nerves, the reticular formation comprises numerous clusters of neurons scattered among a welter of interdigitating axon bundles; it is therefore difficult to subdivide anatomically. The neurons within the reticular formation serve a disparate variety of functions, including cardiovascular and respiratory control, governance of myriad sensorimotor reflexes, coordination of eye movements, regulation of sleep and wakefulness, and most important for the topic at hand, the temporal and spatial coordination of limb and trunk movements, particularly those that control rhythmic, stereotypical behaviours such as locomotion.

The descending motor control pathways from the reticular formation to the spinal cord are similar to those of the vestibular nuclei; they terminate primarily in the medial parts of the gray matter, where they influence the local circuit neurons that coordinate axial and proximal limb muscles. With few exceptions, reticulospinal projections are distributed bilaterally to the medial ventral horns.

Both the vestibular nuclei and the reticular formation provide information to the spinal cord that maintains posture in response to environmental (or self-induced) disturbances of body position and stability. Direct projections from the vestibular nuclei to the spinal cord ensure a rapid compensatory feedback response to any postural instability detected by the vestibular labyrinth. In contrast, the motor centers in the reticular formation are controlled largely by motor centers in the cerebral cortex, hypothalamus, or brainstem. The relevant neurons in the reticular formation initiate feedforward adjustments that stabilize posture during ongoing movements.

DESCRIBE THE FUNCTIONAL PRINCIPLES BEHIND THE BALANCE CONTROL SYSTEM (S2-S3)

Brainstem have different structures and some of them contains circuits of upper motor neurons, they organise a variety of somatic movements including balance, posture and orientation visual gaze. These three are crucial in the balance control system. They are Govern/regulated/controlled by upper motor neurons in nucleus vestibularis, reticular formation and superior colliculus.

Nucleus vestibularis is major destination of axons form vestibular division of n. vestibulocochlearis i.e they get info from semi-circular canals and otolith organs that specify position and linear and angular acceleration of head. Many of the cells in the nuclei are upper motor neurons. Neurons in the medial part of the nucleus give rise to medial vestibulospinal tract that terminated in medial ventral horn in cervical cord it regulates head position by reflex activation of neck muscles due to stimulation of the semi-circular canals.

Neuron in lateral part give rise to the lateral vestibulospinal tract that goes more lateral than the medial in the anterior white matter. It terminates among lower motor neuronal pools that regulates proximal muscles in the limb. These facilitate the activation of limb extensor when otolith organs signal deviates from stable balance and upright posture.

There are other upper motor neurons along with some cranial nerves that are in charge for eye movement, so it maintains fixated while the head is moving called vestibulo-ocular reflex.

Reticular formation is a complicated network of circuits in the brainstem core goes from rostral midbrain to medulla caudatus. The reticular formation consists of clusters of neurons among a welter/clutter of axons. The neurons in the reticular formation have a variety of different functions such as cardiovascular and respiratory control. Regulation of sleep and wakefulness but also coordination of eye movements and the temporal and spatial coordination of limb and trunk movements.

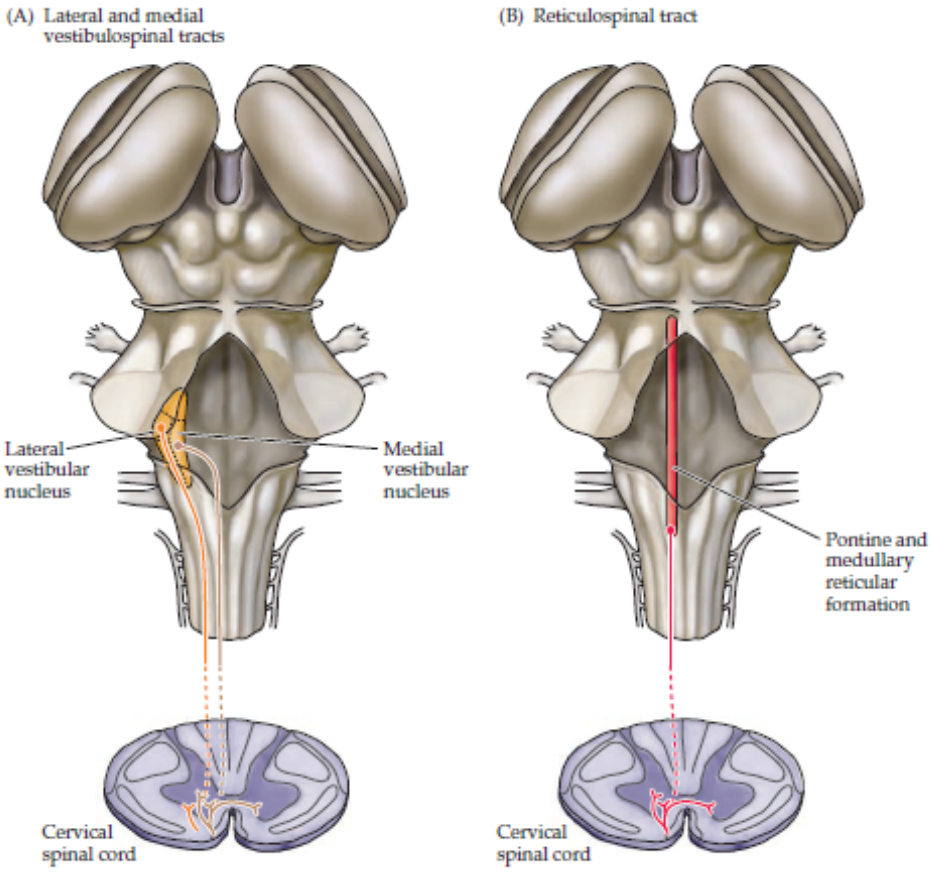
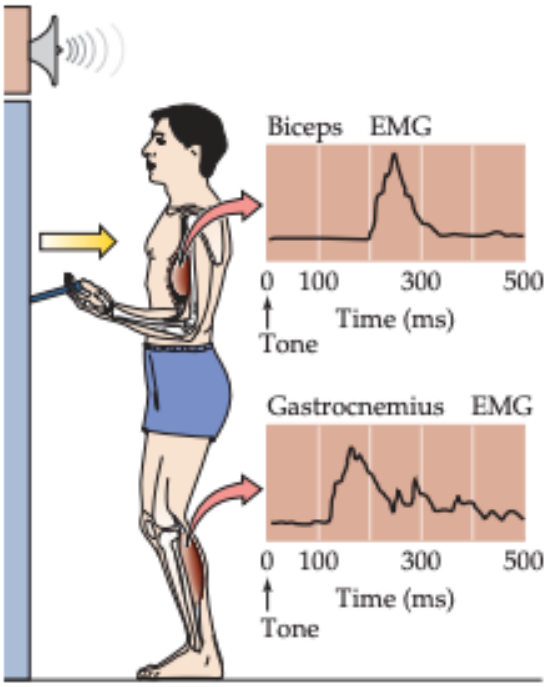


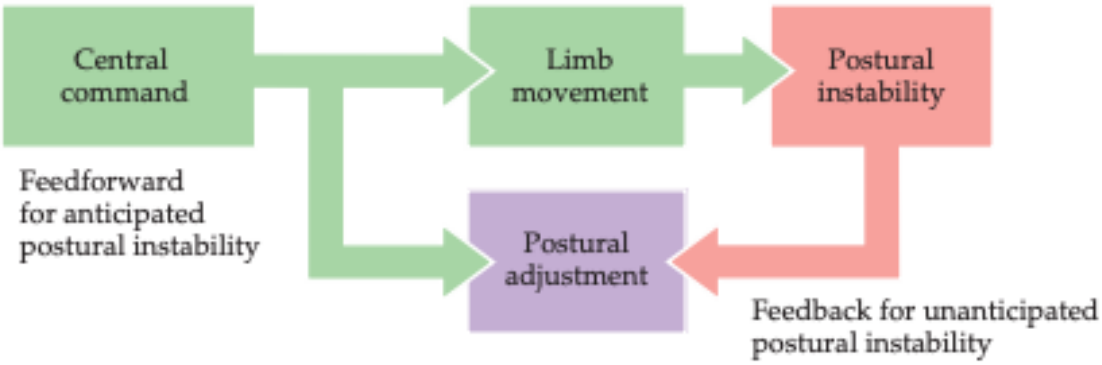
FIGURE 17.12 Descending projections from the brainstem to the spinal cord. Pathways that influence motor neurons in the medial part of the ventral horn originate in the vestibular nuclei (A) and the reticular formation (B).

The vestibular nuclei and reticular formation provide the spinal cord with information about posture in response to the environmental and self-induced disturbance of posture and stability. There are direct projections from the vestibular nuclei to the spinal cord that sends feedback about any postural instability that the vestibular system detects. The motor centre's in the reticular formation are mainly controlled by the motor centre's in the cerebral cortex, hypothalamus and brainstem, so the neurons in the reticular formation initiate feedforward adjustments that stabilize posture during movements.

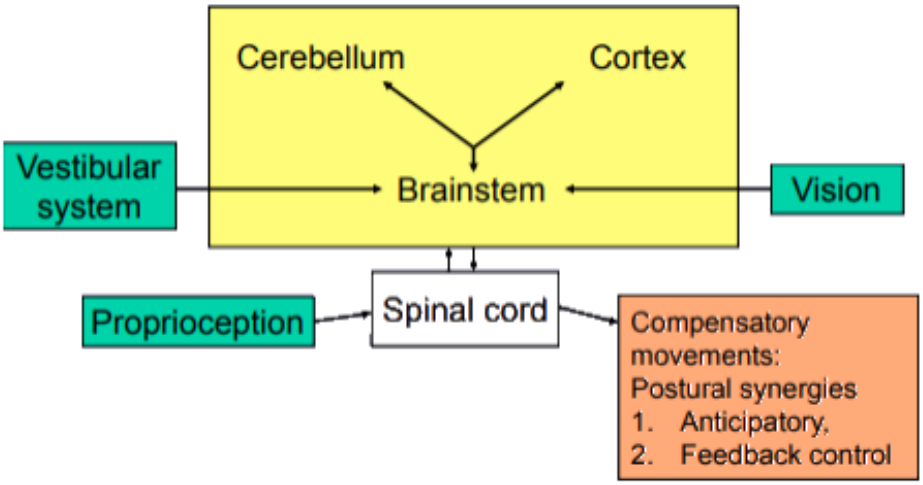


Let us illustrate what happens with the neurons of the reticular formation during a test where the subject pulls on a handle when he hears a tone.

The tone is heard when looking at the diagrams one can see that the gastrocnemius muscle tenses long before the actual tension of the biceps (that leads to the pulling of the handle). In order to pull the handle, the subject has to support the movement and stabilise his body, otherwise (in this case) the activation of the bicep would pull the entire body forward. So the reticular formation anticipate what is going to happen and stabilise the posture before the actual movement, i.e there is a feedforward (anticipatory) signal/mechanism that predicts the disturbance in the body's stability and generates an appropriate stabilising response.

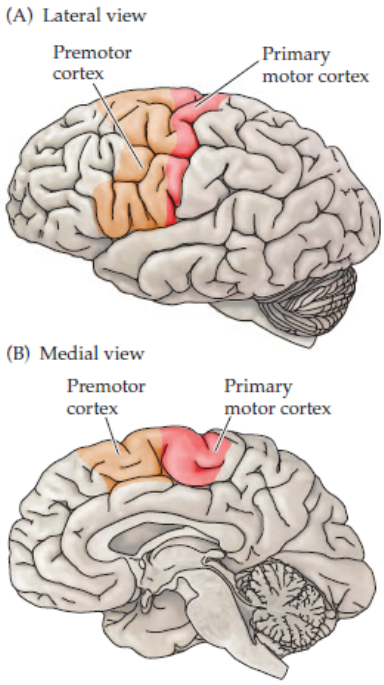


This picture summarises the balance control systems parts:



DESCRIBE THE LOCATION AND MAIN FUNCTION OF DIFFERENT CORTICAL MOTOR AREAS (S2) AND DESCRIBE AND ANALYSE THE AREAS' RESPECTIVE ROLES WITH DIFFERENT TYPES OF CORTICAL CONTROLLED MOVEMENTS (S3-S4)

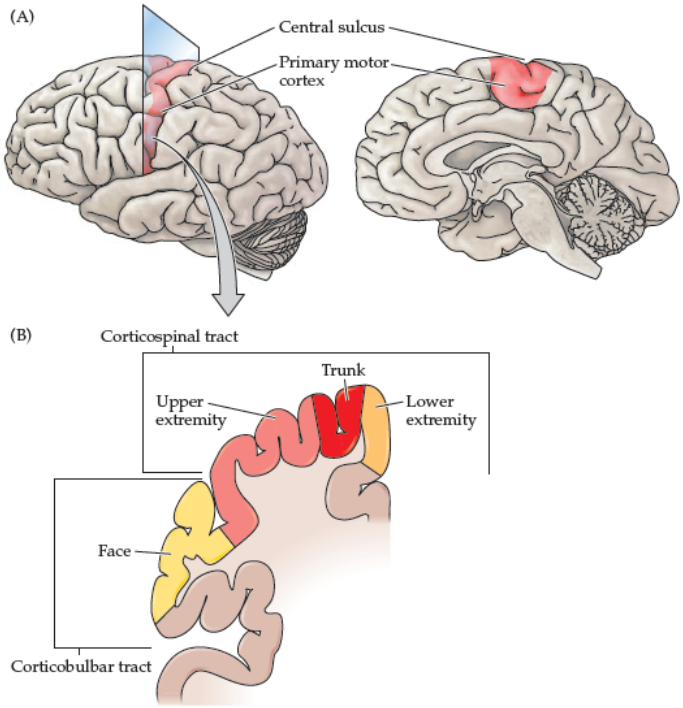
The cortical motor areas, or motor cortex, are involved in the planning, initiation and control of voluntary movements. It is usually split into a primary motor cortex (M1) and premotor cortex. The motor cortex receives regulatory signals from the cerebellum and basal ganglia via the thalamus as well as sensory information from the somatosensory cortex in the parietal lobe. The motor cortex is located posteriorly in the frontal lob and directly anterior of the central sulcus.



PRIMARY MOTOR CORTEX

Located directly anterior of the central sulcus the primary motor cortex has as mentioned consists of Betz cells and non-Betz pyramidal cells in layer 5.

Just like the primary somatosensory cortex the primary motor cortex is divided somatotopically into different areas that represent different parts of the body. This gives a contralateral map over the body with the same disproportionate size that could be seen in the somatosensory cortex. Parts of the body that requires fine motor abilities, such as the hands and face, are disproportionately large while areas in control of the legs and trunk are relatively small. Parts of the body that does require fine motor abilities (upper arms and hands) also have some direct connections between axons from the motor cortex to the α-motor neurons, instead of using the intermediary local circuit neurons that is the norm.



Studies using electrostimulation seem to suggest organized movement is represented in the map rather than individual muscles (because even the smallest current elicited a response that initiated the excitation of several muscles). They reach the conclusion that movements—or action goals—rather than the contractions of individual muscles are encoded in the cortex.

PREMOTOR CORTEX

A complex mosaic of interconnected frontal lobe areas that lie rostral to the primary motor cortex also contributes to motor functions. This functional division of the motor cortex includes Brodmann's areas 6, 8, and 44/45 on the lateral surface of the frontal lobe and parts of areas 23 and 24 on the medial surface of the hemisphere.

The upper motor neurons in this premotor cortex influence motor behaviour both indirectly, through extensive reciprocal connections with the primary motor cortex, and directly, via axons that project through the corticobulbar and corticospinal pathways to influence the local circuits that organize the output of lower motor neurons in the brainstem and spinal cord. Over 30% of the axons in the corticospinal tracts arise from neurons in the premotor cortex which, through experiments, indicate that the premotor cortex uses information from other cortical regions to select movements appropriate to the context of the goal of the action. The principal difference between the premotor cortex and primary motor cortex lies

in the strength of their connections to lower motor neurons, with more upper motor neurons in the primary motor cortex making monosynaptic connections to α motor neurons, especially those in the ventral horn of the cervical spinal cord that control precise movements of the distal upper extremities. Recent evidence suggests that other differences may reflect the mapping of purposeful movements relative to personal and extra-personal space and the nature of the signals that lead to the initiation of motor commands in the context of action goals. The action goals encoded by the primary motor cortex tend to be localized to personal space (within arm's length), while the action goals encoded by premotor cortex are more typically oriented toward extra-personal space (beyond arm's length).

LATERAL PREMOTOR CORTEX

The functions of the premotor cortex may be understood in terms of differences between the lateral and medial components of this region. As many as 65% of the neurons in the lateral premotor cortex have responses that are linked in time to the occurrence of movements; as in the primary motor area, many of these cells fire most strongly before and during movements made in a specific direction. That is rather than directly commanding the initiation of a movement, these neurons appear to encode the intention to perform a particular movement; thus, they seem to be particularly involved in the selection of movements based on external events.

A ventrolateral subdivision exists where a subset of its neurons responds not just in preparation for the execution of particular movements but also when the same action is observed, being performed by another individual. This subdivision gives rise to the mirror motor system which is involved in encoding the intention to make a specific movement based on the observation of the behaviourally relevant actions of others. Evidently, this system participates in an extended network of parietal and frontal regions that subserve action understanding and imitation learning, whether or not observed behaviour is "mirrored" in one's own actions.

Further evidence that the lateral premotor area is concerned with movement selection comes from the effects of cortical damage on motor behaviour. Lesions in this region severely impair the ability of monkeys to perform visually cued conditional tasks, even though they can still respond to the visual stimulus and can perform the same movement in a different setting. Similarly, patients with frontal lobe damage have difficulty learning to select a particular movement to be performed in response to a visual cue, even though they understand the instructions and can perform the movements. Individuals with lesions in the premotor cortex may also have difficulty performing movements in response to verbal commands.

Finally, a rostral division of the lateral premotor cortex in the human brain, especially in the

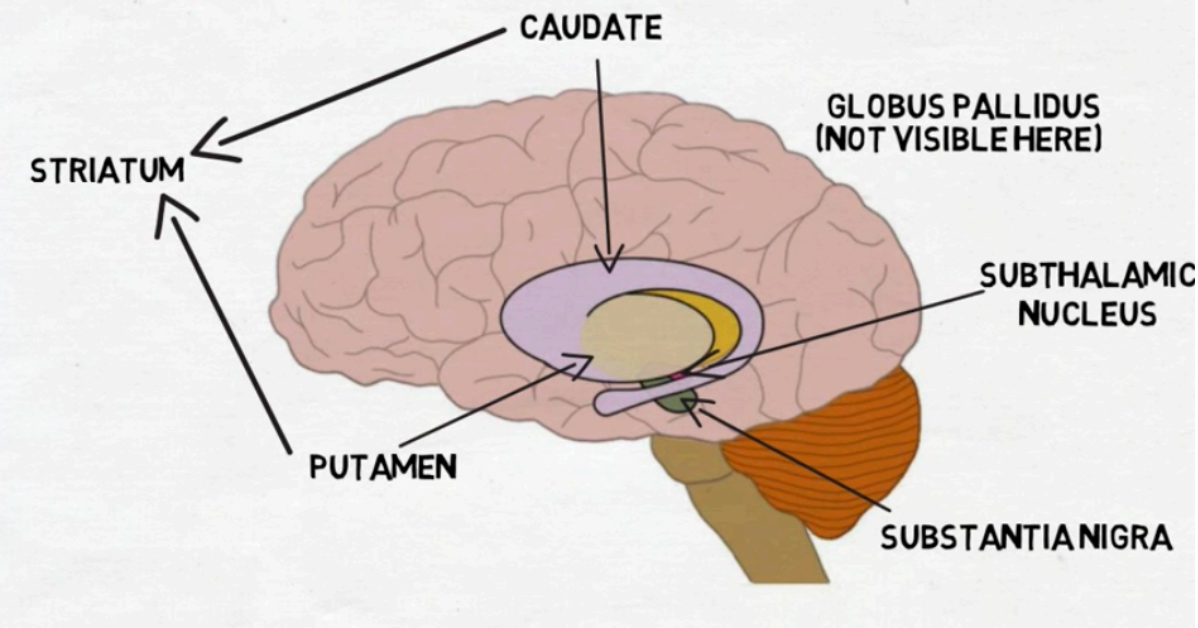
left hemisphere, has evolved to play a special role in the production of speech sounds. This region, called Broca's area (which typically corresponds to Brodmann's areas 44 and 45, but may be localized to adjacent area 6 in some individuals), is critical for the production of speech.

MEDIAL PREMOTOR CORTEX

The medial division of the premotor cortex extends onto the medial aspect of the frontal lobe (including a division that has been referred to as the "supplementary motor area"). Like the lateral area, the medial premotor cortex mediates the selection of movements. However, this region appears to be specialized for initiating movements specified by internal rather than external cues ("open-loop" conditions).

DESCRIBE THE BASAL GANGLIA´S STRUCTURE AND INTERNAL CONNECTIONS AS WELL AS THEIR CONNECTIONS TO OTHER PARTS OF THE CNS (S2). BE ABLE TO RELATE THIS KNOWLEDGE TO AND DESCRIBE THE ROLE OF THE BASAL GANGLIA IN MOTOR CONTROL (S3-S4).

THE STRUCTURE OF THE BASAL GANGLIA



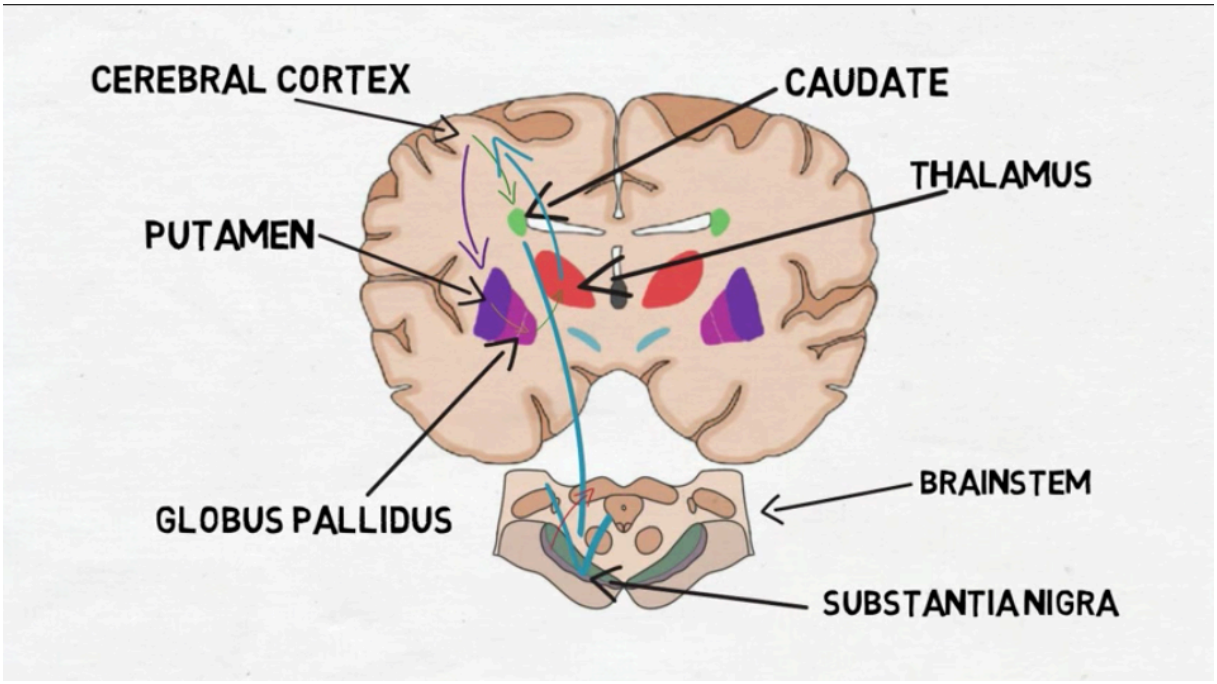
The basal ganglia are a group of structures that are found deep within the cerebral hemispheres and the brainstem. It include:

- Nucleus caudatus
- Putamen
- Globus Pallidus *(made up of several nuclei)*
- Substantia Nigra *(made up of several nuclei)*
- Nucleus subthalamicus

Nucleus caudatus and putamen can collectively be referred to as the striatum.

The basal ganglia are involved with a variety of functions, some of them nonmotor such as emotions, they are best known for their role in initiating movement and the controlling of movement amplitude.

THE INTERNAL CONNECTIONS OF THE BASAL GANGLIA

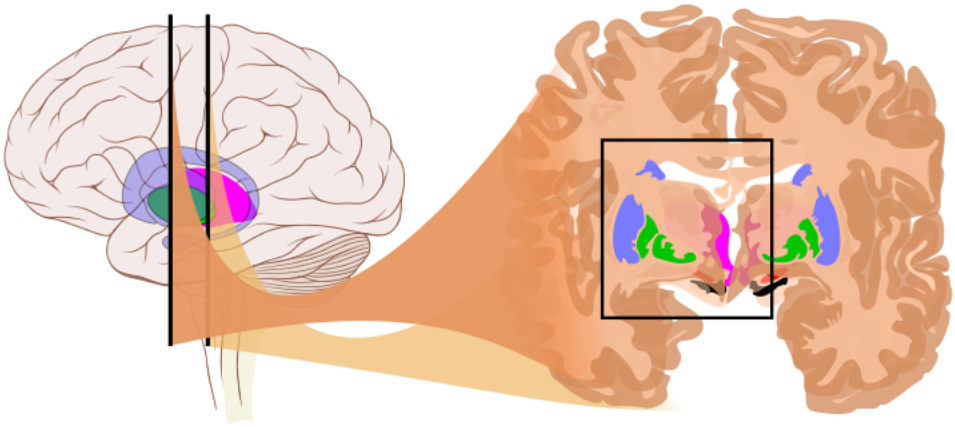


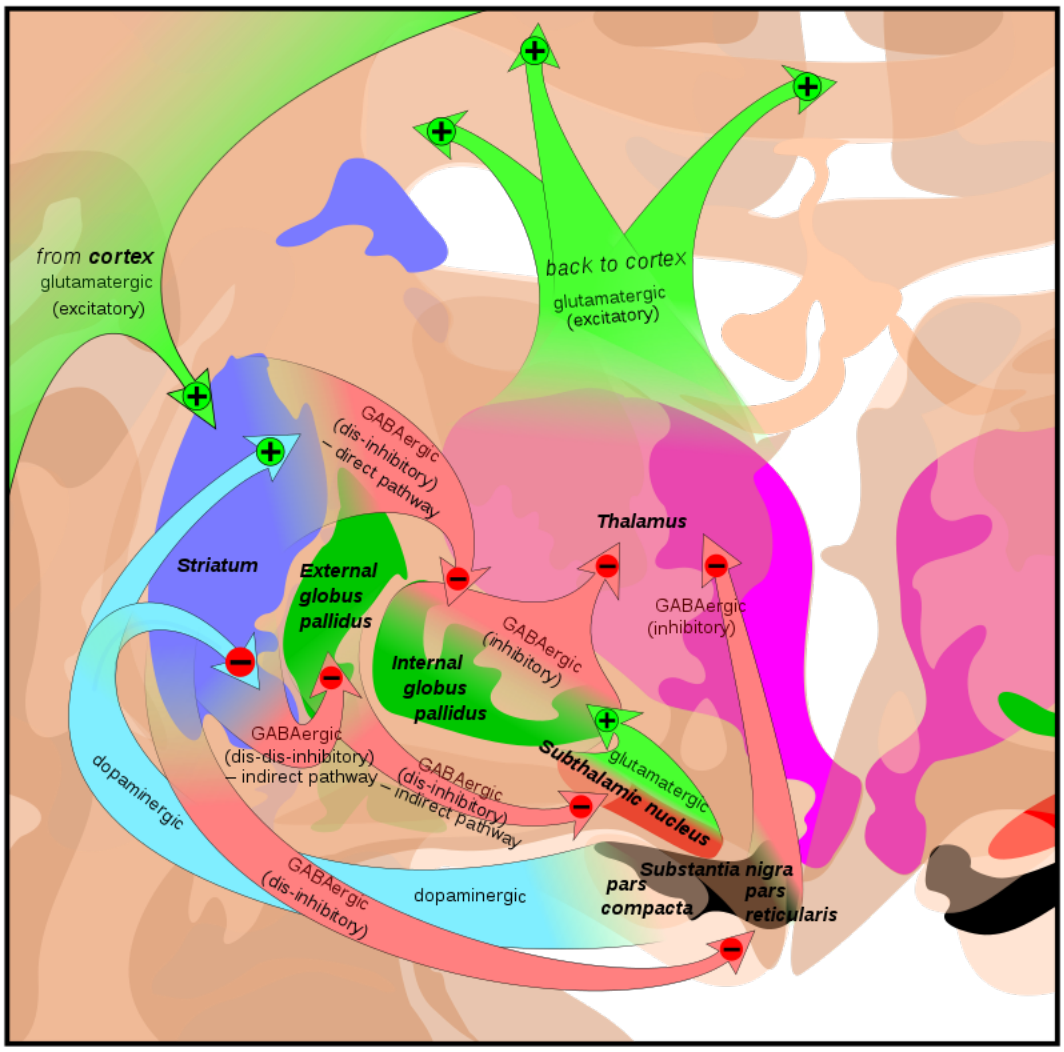
1. A lot of the information that the basal ganglia receives comes from the cerebral cortex. The information then travels to the nucleus caudatus or putamen, these are the main input nuclei of the basal ganglia.

2. The information from the nucleus caudatus or putamen are then sent forward to the main output nuclei, the globus pallidus and substanstantia nigra.

3. The globus pallidus and substantia nigra then send projections out from the basal ganglia to the cerebral cortex. But the signals mostly goes via the thalamus or the nuclei (colliculus superior?) in the brainstem.

The picture below shows a more complex view of circuits of the basal ganglia. There are excitatory pathways that are shown in green, these are glutamatergic pathways. These include the pathway to and from the cortex and from the subthalmic nucleus to the globus pallidus (nucleus internus). The red arrows shoe inhibitory pathways, so called GABAergic pathways. They run between the different nucleus mainly in the direction main input nucleus → main output nucleus → thalamus. The turquoise arrows are dopaminergic pathways and comes from substantia nigra (that produces dopamine). Dopamine act excitatory on the direct pathway for striatum → globus pallidus nucleus internus → thalamus → cortex and inhibitory. On the indirect pathway striatum → globus pallidus nucleus externus→ subthalmic nucleus → globus pallidus nucleus internus→ thalamus → cortex.





THE ROLE OF THE BASAL GANGLIA IN MOTOR CONTROL

The general role for the basal ganglia is being responsible for activation of the right motor program when initiating a movement and stopping unwanted movements. The basal ganglia

form circuits that can modulate movements, these circuits have to main pathways, the direct and the indirect.

DIRECT PATHWAY

The direct pathway leads to a movement, in this pathway the thalamus is disinhibited which means that it can forward information to other parts of the brain. In the case of movement to the motor cortex that sends information to the muscles via neurons. In the direct pathway as well as the indirect the dopaminergic neurons in the substatia nigra pars compacta play a role, in the direct pathway the dopamine released from the dopaminergic neurons bind to receptors called D1 that are G-protein coupled and activate Adenylate cyclase which leads to less cAMP. This has an excitory effect.

INDIRECT PATHWAY

The indirect pathway leads to the inhibition of the thalamus and no movement. Here dopamine from the dopaminergic neurons bind to D2 receptors that also are g-protein coupled, but in this case Adenylate cyclase is inhibited which leads to an increase in cAMP. This leads to an inhibitory effect.

These pathways are anagonists and work together to initiate and teminate movement. They are having a balance between them. It's thought that they fnction as an on/centre and off/surround. Where the direct pathway is the on/centre and stands for concreate movements and execution of specific movements whilst the indirect is the off /surround and stands for the diffuse movements and the silencing of several movements.

DESCRIBE THE DIFFERENT TYPES OF EYE MOVEMENT AND THEIR GENERAL FUNCTIONS (S2)

There are four basic types of eye movement:

- Saccades
- Smooth pursuit movements
- Vergence movements
- Vestibulo-ocular movements

Type of eye movement	Function	Stimulus	Clinical tests
Vestibular	Maintain steady fixation during head rotation	Head rotation	Fixate on object while moving head; calorics
Saccades	Rapid refixation to eccentric stimuli	Eccentric retinal image	Voluntary movement between two objects; fast phases of OKN or of vestibular nystagmus
Smooth pursuit	Keep moving object on fovea	Retinal image slip	Voluntarily follow a moving target; OKN slow phases
Vergence	Disconjugate, slow movement to maintain binocular vision	Binasal or bitemporal disparity; retinal blur motion	Fusional amplitudes; near point of convergence

OKN = optokinetic nystagmus.

SACCADES

Saccades are rapid, ballistic movements of the eyes that abruptly change the point of fixation. They range in the amplitude from the small movements made while reading, for example, to the much larger movements made while gazing around a room.

Saccades can be elicited voluntarily but occur reflexively whenever the eyes are open.

SMOOTH PURSUIT MOVEMENTS

Smooth pursuit movements are much slower tracking movements of the eyes designed to keep a moving stimulus on the fovea. Such movements are under voluntary control in the sense that the observer can choose whether or not to track a moving stimulus. Most people who try to move their eyes in a smooth fashion without a moving target simply make a saccade (highly trained observers can, however, make smooth pursuit movements in the absence of a moving target).

VERGENCE MOVEMENTS

Vergence movements align the fovea of each eye with targets located at different distances from the observer. Unlike other type of eye movements in which the two eyes move in the same direction (conjugate eye movements), vergence movements are disconjugate (or disjunctive); they involve either a convergence or divergence of the lines of sight of each eye to see an object that is nearer or farther away. Convergence is one of the three reflexive visual responses elicited by interest in a near object. The other components of the so-called near reflex triad are accommodation of the lens, which brings the object into focus, and pupillary constriction, which increases the depth of field and sharpens the image on the retina.

VESTIBULO-OCULAR MOVEMENTS

Vestibulo-ocular movements stabilize the eyes relative to the external world, thus compensating for head movements. These reflex responses prevent visual images from "slipping" on the surface of the retina as head position varies. The action of vestibulo-ocular movements can be appreciated by fixating an object and moving the head from side to side; the eyes automatically compensate for the head movement by moving the same distance but in the opposite direction, thus keeping the image of the object at more or less the same place on the retina.

While the vestibular system operates effectively to counteract rapid movements of the head, it is relatively insensitive to slow movements or to persistent rotation of the head. Compensation in this case would be due to activation of the smooth pursuit system if the eyes are open.

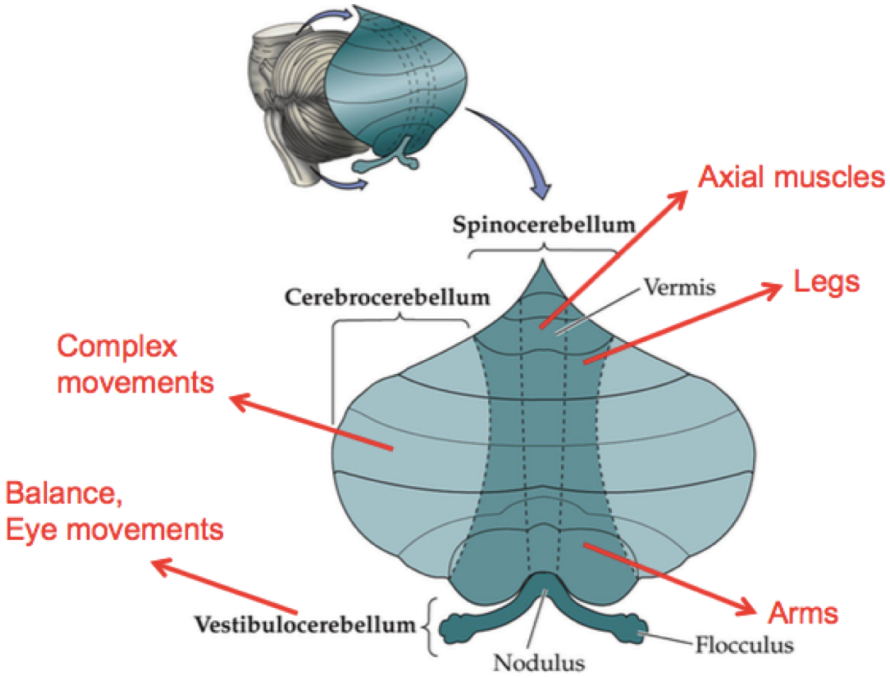
DESCRIBE THE CEREBELLUM'S MACROSCOPIC AND MICROSCOPIC STRUCTURE AND ITS CONNECTIONS TO OTHER PARTS OF THE CNS AND GENERAL ROLE IN MOTOR CONTROL (S2). BE ABLE TO EXPLAIN SYNAPTIC CONNECTIONS IN THE CEREBELLUM CORTEX AND RELATE THESE TO THE FUNCTION OF THE CEREBELLUM (S3-S4).

ANATOMY AND FUNCTIONAL PARTS OF THE CEREBELLUM

The cerebellum is divided into two hemispheres with folds that here are called folia (not gyrus). Between the two hemispheres there are a protruding structure that runs vertically that are called the vermis.

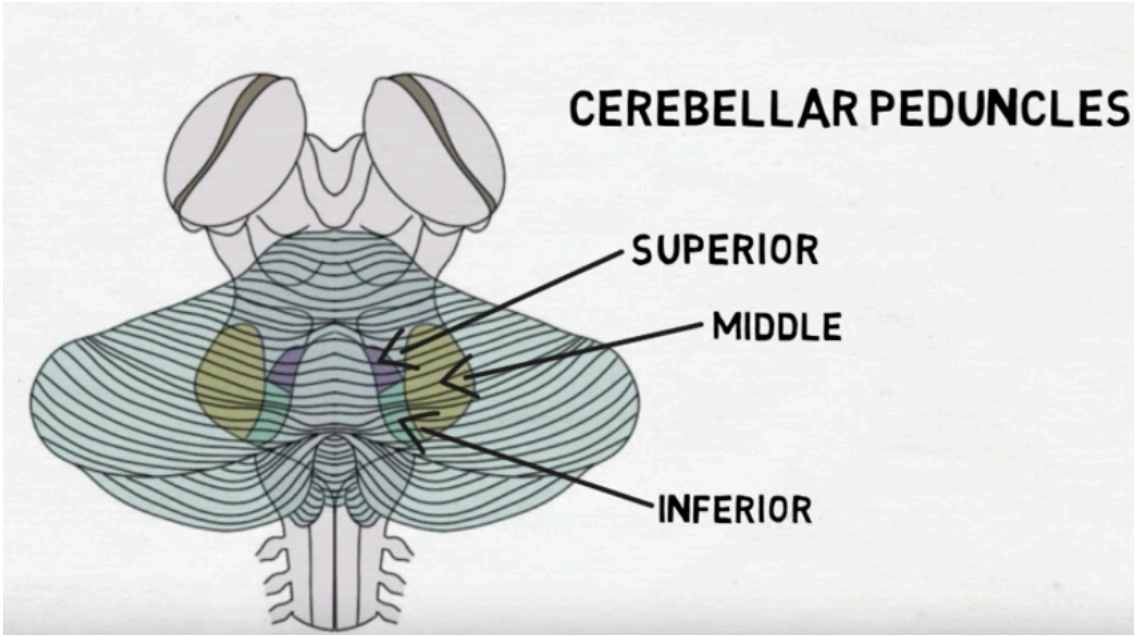
The cerebellum can be divided into 3 parts;

- **Cerebrocerebellum** – receives input from cerebral cortex and is involved with planning and initiating movements. It helps with complex movements i.e movements where one need to combine/synchronise a lot of muscles for example talking or fast pronation/supination of the underarms.
- **Spinocerebellum** – recives information about limb position, touch and pressure sensations from the spinal cord. It uses this information to compare where a limb is in space with where it should be if the movement were going as planned. If it's not the spinocerebellum can modify the motor signals to correct the errors.
    - **Vermis** – the vermis is the area of the spinocerebellum that runs along the midline and is involved with posture, limb and eye movements.
- **Vestibulocerebellum** – can also be called flocculonodular lobe since the structure it self are called flocculonodularis. It is important in maintaining equilibrium, balance and posture. It's also involced in eye movements.



COMMUNICATION WITH CNS AND SYNAPTIC CONNECTIONS IN CEREBELLUM

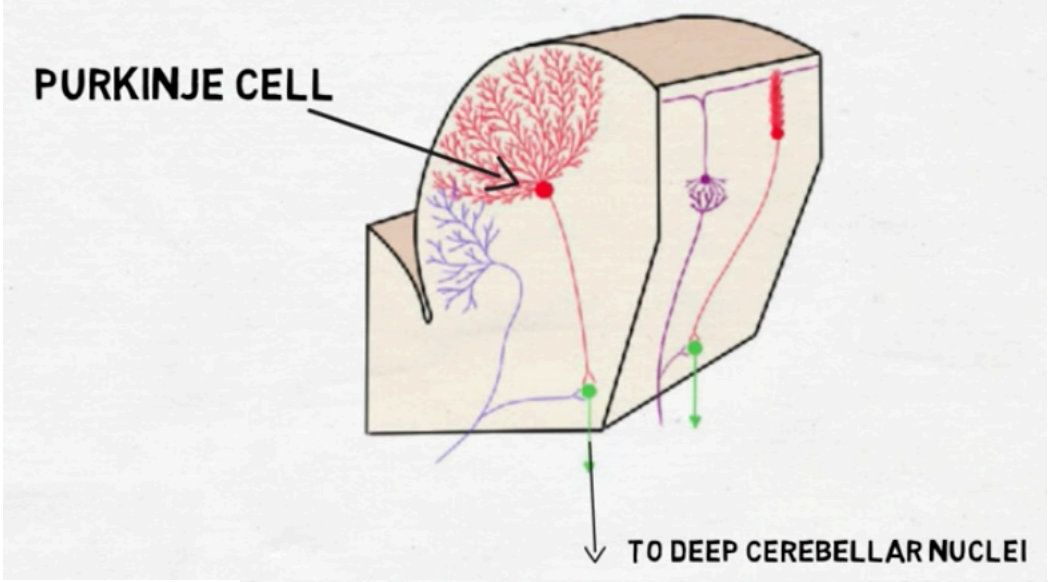
The cerebellum communicates with the rest of the nervous system through three large pathways called pedunculus cerebellaris (cerebellar peduncle).

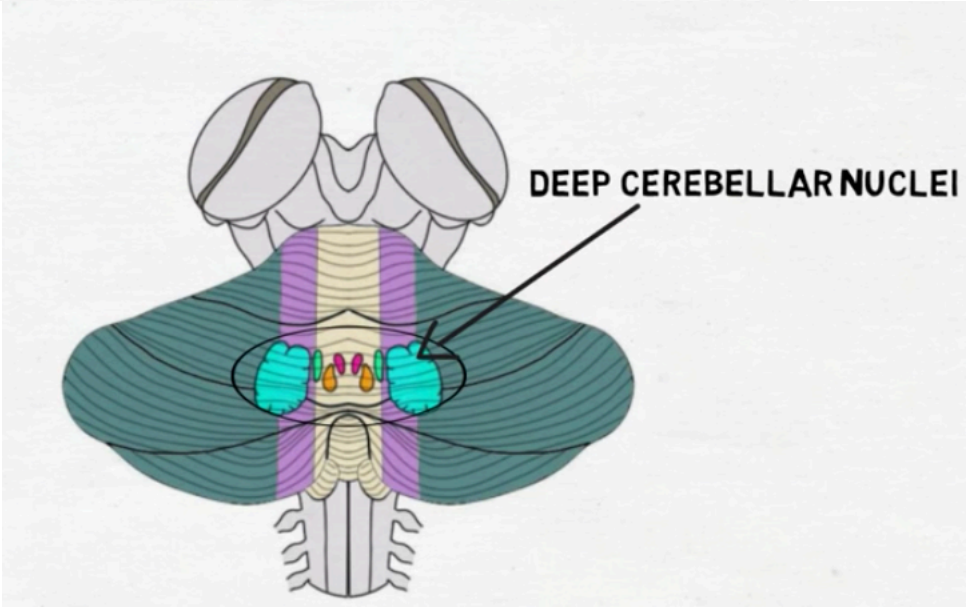


The pedunculus connects with the brain via axons (white matter).

When information is sent to the cerebellum it takes an indirect path to reach purkinje cells that project their axons to a group of nuclei in the centre of the cerebellum called the deep cerebellar nuclei. The deep cerebellar nuclei sends the information to various areas in the

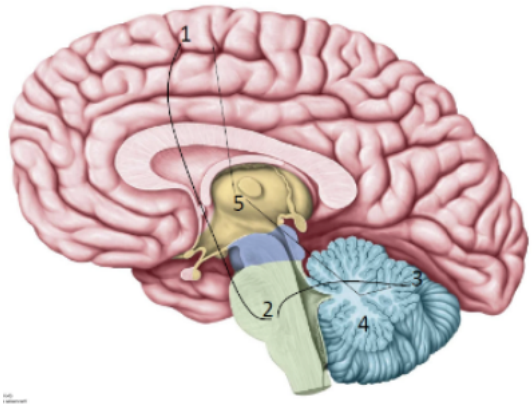
brainstem and thalamus that can influence motor areas of the cortex or descending motor tracts and modify movements. So this is how the cerebellum can be a part of planning complex movements, correcting errors and help with posture for example.





The cerebrum can send signals to the cerebellum:

1. Decision to move (from the cerebrum)
2. Signal travels to pons where decussate.
3. Goes to cerebellum cortex where it's processed
4. Signal goes to the deep nuclei in the cerebellum
5. Then from the deep nuclei to thalamus
6. Thalamus it goes back to the cerebrum cortex.



DESCRIBE MOTOR DEFECTS CAUSED BY DAMAGE TO OR DEGENERATION OF DIFFERENT PARTS OF THE CNS, INCLUDING STROKE, PARKINSON´S DISEASE, HUNTINGTON´S DISEASE AND SPINAL CORD TRAUMA (S2, S3).

STROKE

Stroke occurs when blood flow to a part of the brain is disrupted. There are two categories of stroke:

- **Ischemic** – the blood flow is reduced to a part of the brain due to a blockage or restriction usually caused by a blood clot. This blood clot can be formed in the area → thrombus or it can be formed somewhere else and travelled to the brain → embolus.
- **Haemorrhagic** – is a bleed into the brain caused by for example an aneurysm that burst or an artery that ruptures in the brain (can be caused of high blood pressure). The haemorrhagic stroke can lead to ischemia if the blood supply is restricted due to the haemorrhage. A haemorrhagic stroke can also result in tissue damage due to the collection of blood outside the vessels.

When cells are subjects to anaerobic environment for a longer period they go into necrosis. The necrotic area is called an infarct (only when an area is necrotic due to the lack of circulation).

THE SYMPTOMS

The symptoms of a stroke vary depending on what area of the brain that is affected. By knowing what area that are involved in different functions in and what arteries that supply that area one can figure out approximately in what area the stroke is located. Som common symptoms are weakness and loss of sensation on the contralateral side of the body especially face (face paresis) and arm are common. Symptom as visual impairment, speech difficulties, confusion, loss of balance and/or coordination and severe headache are also common.

PARKINSSON'S

The basal ganglia are important for our movements, it takes decisions connected to which type of movement that are to be executed. The basal gangliga are divided into parts that all affect how movements are preformed, these parts are affected both in a inhibitory, excitatory and modulating way from other structures and pathways. If this regulation isn't working as it should be it can give rise to different diseases.

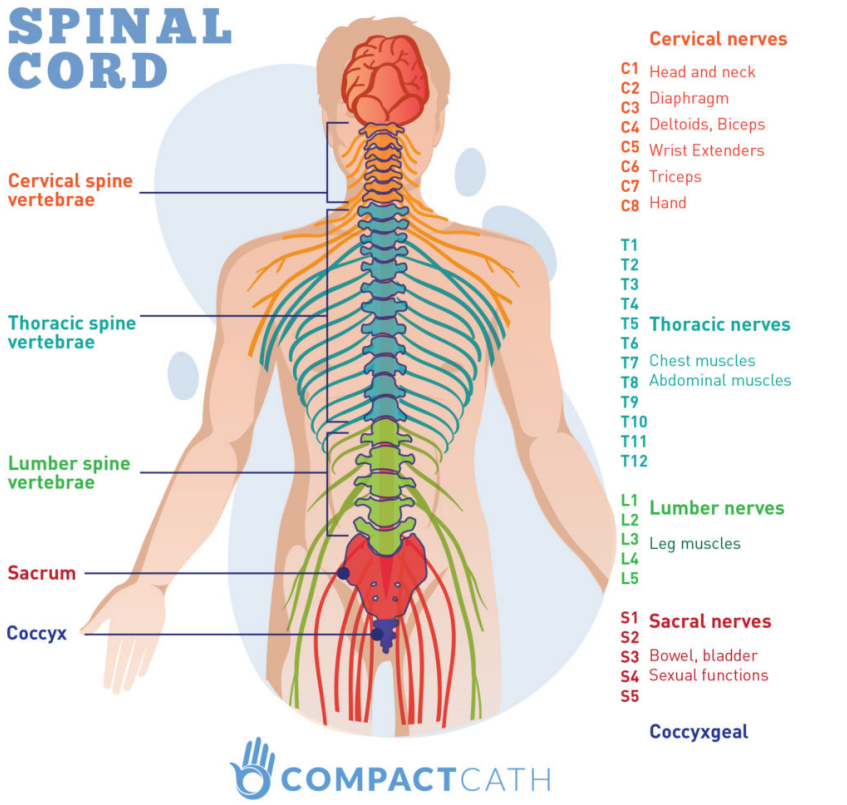
If the dopamine system isn't working or only partially working the modulating effect that it has on the striatum of the basal ganglia lost. The dopaminergic neurons in the substantia niagra dies. The striatum cells will activate when a motion is about to be initiated and in turn it leads to the pallidum not inhibiting the locomotion centre. If the dopamine system can't control the striatum as it should the inhibitory signals from the pallidum just keeps going. This leads to an inhibition of movement and a lack of ending this inhibition when a movement is to be executed. This leads to shaking while moving, making it harder to move and can present as slower movements, harder to initiate movements, the voice becomes lower. Patients also present with rigidness.

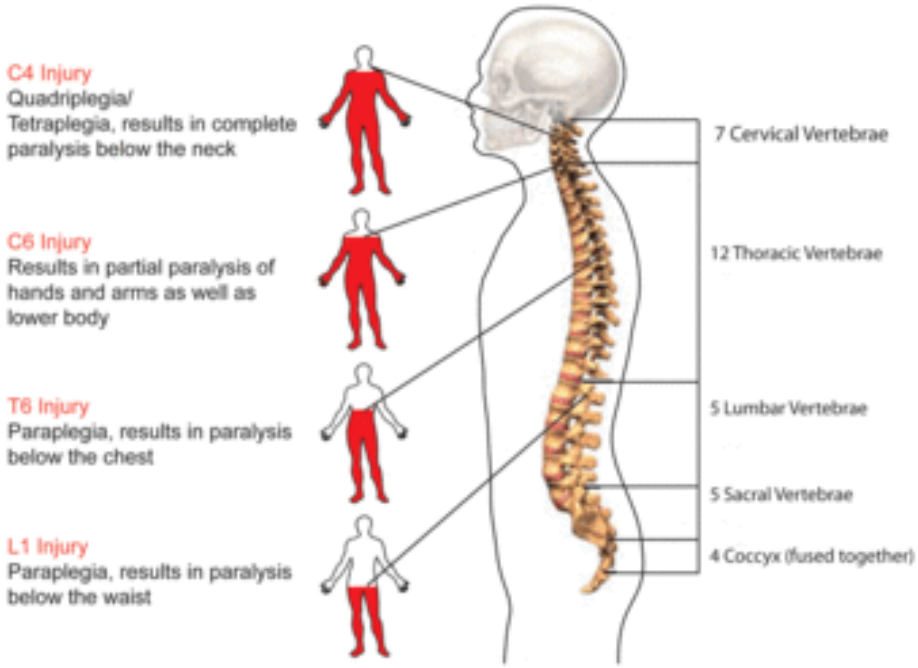
HUNTINGTON'S

With Huntington's disease (sometimes called the dancing sickness) is the efferent cells in the palladium subjects to inhibition. In such a way that the motor cortex doesn't get any inhibitory factors and are not controlled by anything. This will give rise to uncontrollable, lively or involuntary movements. In Huntington's it's the GABA system that are affected.

SPINAL CORD TRAUMA

The spinal cord is divided into 5 segments; cervical, thoracic, lumbar, sacrum and coccyx. Mainly in the first 4 vertebrae have important nerves and nerve plexus the pictures below shows the nerves and the functions corresponding. The chart underneath shows the different levels, if there's an injury above C4 the diaphragm will be affected and it's impossible to breath and therefore injuries above C4 is not consistent with life. Depending on the level of the injury patients can be divided into different groups such as tetraplegia or paraplegia.


SPINAL CORD
Cervical spine vertebrae
Thoracic spine vertebrae
Lumber spine vertebrae
Sacrum
Coccyx
Cervical nerves
C1 Head and neck
C2
C3 Diaphragm
C4 Deltoids, Biceps
C5 Wrist Extenders
C6
C7 Triceps
C8 Hand
T1
T2
T3
T4
T5 Thoracic nerves
T6
T7 Chest muscles
T8 Abdominal muscles
T9
T10
T11
T12
L1
L2 Lumber nerves
L3 Leg muscles
L4
L5
S1
S2 Sacral nerves
S3 Bowel, bladder
S4 Sexual functions
S5
Coccyxgeal
COMPACTCATH


C4 Injury
Quadriplegia/ Tetraplegia, results in complete paralysis below the neck
C6 Injury
Results in partial paralysis of hands and arms as well as lower body
T6 Injury
Paraplegia, results in paralysis below the chest
L1 Injury
Paraplegia, results in paralysis below the waist
7 Cervical Vertebrae
12 Thoracic Vertebrae
5 Lumbar Vertebrae
5 Sacral Vertebrae
4 Coccyx (fused together)

NEUROPSYCHOLOGY: THE BRAIN AND BEHAVIOUR:

EXPLAIN CENTRAL THEORIES AND MODELS IN COGNITIVE NEUROSCIENCE (S2).

”Cognitive neuroscience explores the neural basis of cognition, including perception, attention, language understanding, memory, problem solving, and decision-making. The field draws on findings on how neurons process and represent information, and on ideas about how learning may occur through the modification of properties of neurons and their connections. It is clear that there is specialization of function in the brain, yet brain areas appear to work together, interactively, to support emergent cognitive functions.”[1]

Read more about this in the question below → there is an overview of all the different cognitive processes.

DESCRIBE HOW SPECIFIC BRAIN REGIONS TOGETHER CONTRIBUTE TO COGNITIVE PROCESSES AND BEHAVIOUR (SUCH AS EMOTIONS AND MEMORIES) (S2-S4). FOR EXAMPLE, THIS INCLUDES HOW SUBCORTICAL AND CORTICAL SYSTEMS INTERACT.

In order to understand this question and how the information integration in the brain works it’s good to know more about the different parts of cognitive neuroscience. Therefore, will this question first cover this and end with the information integration.

COGNITION

The brain needs to generate behaviours in the right situation, to generate movement, to create complex behaviours and to understand language. If we can understand the environment (external) and the internal needs we can prepare actions and generate relevant behaviour. Cognition is the knowledge to take these external events and our internal memories and use them to simulate different outcomes in a situation.

All the information that we collect are used to predict the consequences of our actions, these processes can help us calculate what will happen next. For example we meet a lion, our cognitive process will take in the sight of the lion, maybe the sound of if and process it with our knowledge and memory about it. Then we will act, more or less conscious. The cognitive processes can be voluntary i.e. we get to decide what action we think has the best outcome and sometimes it won’t.

Thinking, planning, reasoning and deciding are all different types of cognitive processes. The human cognition are depended upon the prefrontal lobes, however there are also other parts in the brain that contribute. There are different types of cortexes in the brain, the association cortex is about 80 % of all the cortex, and that is everything that is not the

[1] https://www.sciencedirect.com/topics/psychology/cognitive-neuroscience

primary cortex. The primary cortex is motor cortex, somatosensory cortex, vision and auditory cortex.

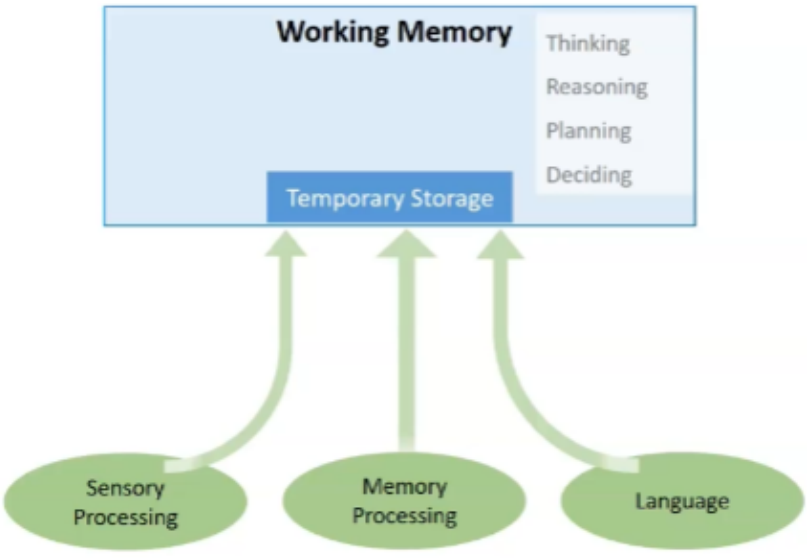
CORTEX ORGANISATION

Cortex is made of neocortex that has 6 layers. Each layer has primary source of input and output. Layers make up a certain functional area. Areas are interconnected with vertical and horizontal axons. Cells with common functional properties are grouped together and form specialized modules in particular brain regions. The connections between cells in specialized modules are short, use less energy and are often highly plastic.

Functional integration is supported by longer connections that go through" hub regions". The hub regions are mainly found along a central-axis, and hub regions tend to be characterized by their involvement in many different cortical functions. The brains functioning is dependent on both functioning of specialized modules but also on intact long-range connections between hub regions.

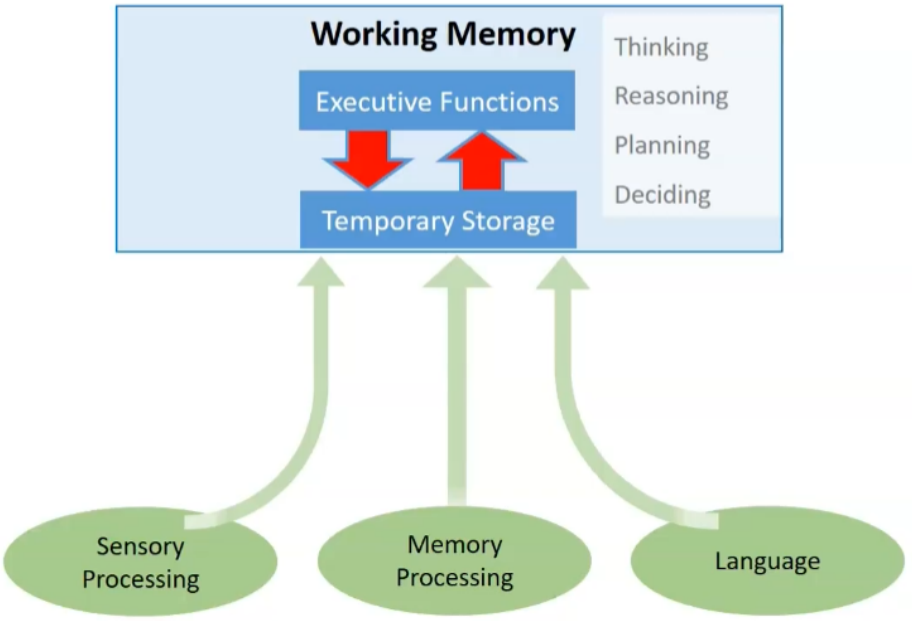
FUNCTION OF COGNITION AND THE WORKING MEMORY

The processes mentioned before; thinking, reasoning, planning and deciding are dependent on our ability to think. But how does the cognitive process work?

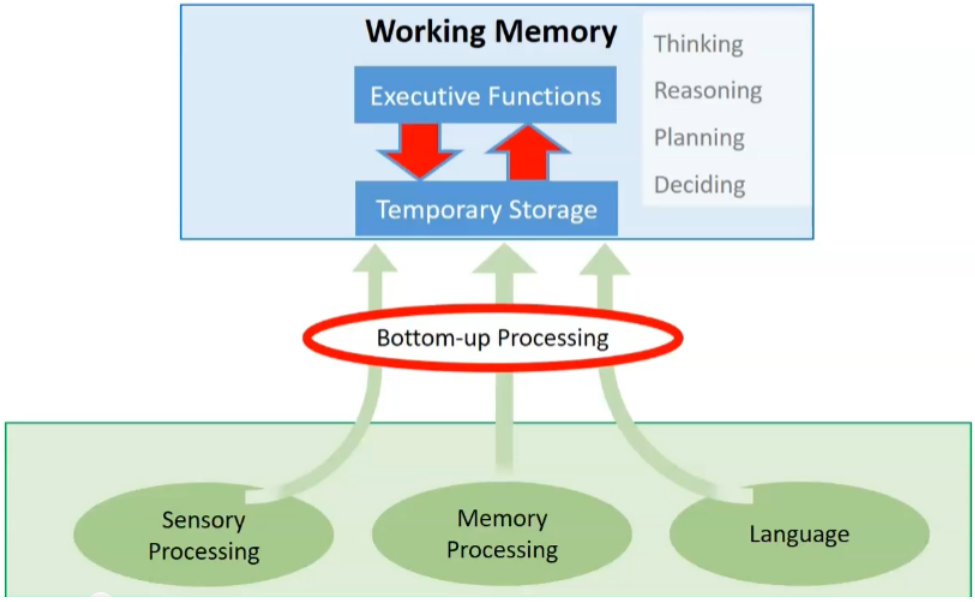


1: It starts with our working memory that can hold relevant information close by, it's a memory that last for a couple of seconds to a couple of minutes. This memory increases up to 25 years old. The structure in the brain involved are the frontal lobe. Working memory is typically studied in the context of declarative memory (information that can be used in the future to make decision or communicate), the short term memory also operates in the acquirement and storage of non-declarative memory (non-declarative or implicit memory is a long term memory that stands in contrast to explicit memory in that

it doesn't require consciousness. It's involved in skills like riding a bike or walking.). The working memory even though it's a ¢short-term memory it has important connections to how we do stuff in the future.

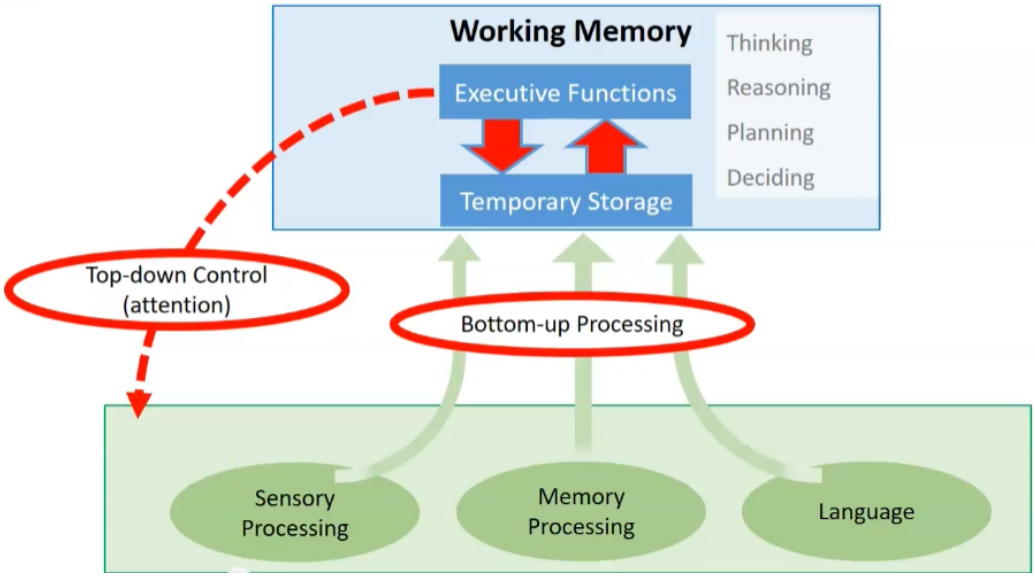


2: The executive functions get inputs from the working memory (temporary storage), the temporary storage in turn gets input from the sensory (external), memory (internal) and language parts.



3: This information is then used to create different predictions about what is going to happen whilst they try to attain a certain goal. This is a bottom-up processing (also called exogenous or stimuli driven processing), this is a type of attention that will be further discussed under attention. But bottom-up processing is being under control of a stimulus,

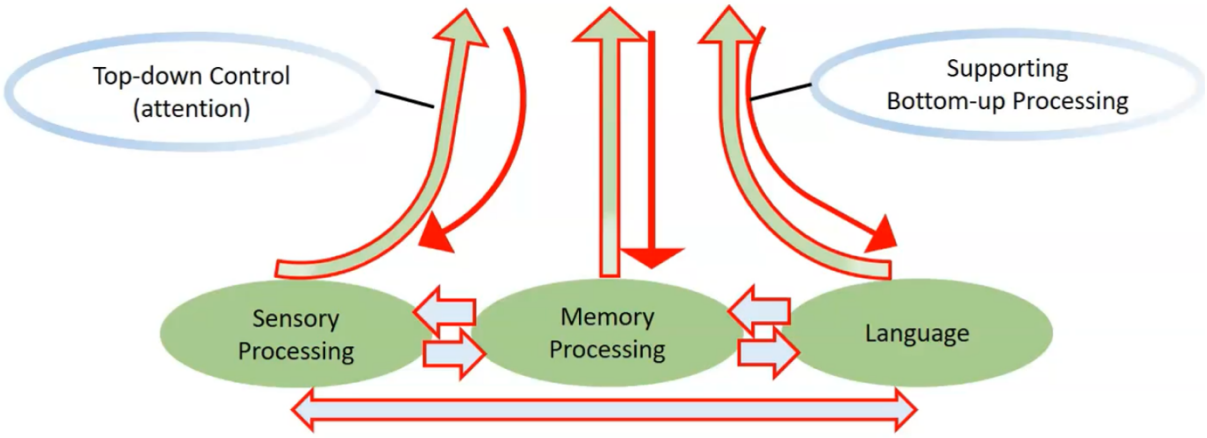
it's considered to be reflexive and automatic and caused by a sudden change in the periphery. However, it is fast, has near to unlimited capacity, needs little effort and is hard to change.



4: The input from the processing and the temporary storage leads to the executive functions that give rise to the way we act physically, ex we see something in the periphery that is round, in a certain thickness and black/grey/brown colour on the trail while we are out walking. This is a sensory input, our memory processing leads to snakes and our impulse to flight so that we don't get bitten by something that could harm us. This leads to us jumping and maybe backing away to get to a safer distance. We then get another sensory input or maybe a language input from whom ever that is with us that the thing on the ground only is a stick, this information will update the process.

so the executive functions will when the initial more reflexive act has started get updates and can then make changes by top-down control. Top-down control (or endogenous or goal-driven attention will be further discussed under attention) is more intentional and due to resources, that makes the observers goals and desire. The input needs to be processed and then acted upon purposefully.

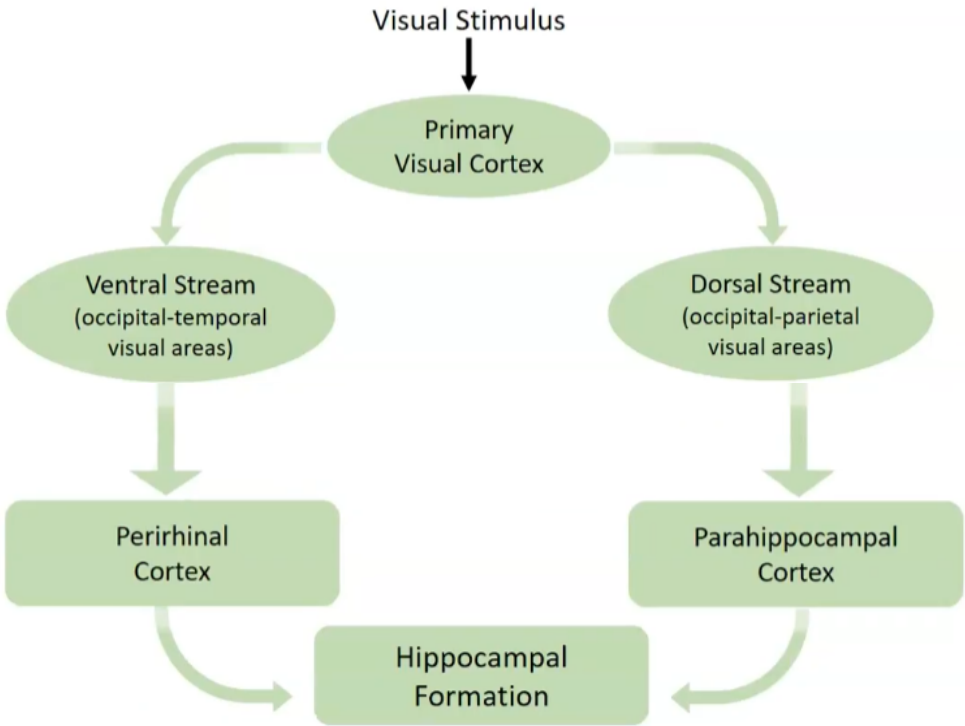
THE WORKING MEMORY COALITION HYPOTHESIS



The prefrontal executive functions are about coordination and control of the cortical cooperation. These processes make sure to enforce the goal and the meaning of the goal during for example when we are working towards a long-term goal that requires planning.

The executive processes can also engage abstract conceptual representations to create expectations about what is going on and further enhance and support lower-level areas. It can also complete missing information or ignore what is irrelevant.

VISUAL STIMULUS AND COGNITION



Upon receiving a visual stimulus it is sent to the primary visual cortex where it then is sent forward via the ventral or dorsal stream. The ventral stream ends in the occipital-temporal visual areas, the temporal lobe takes the new input and add it to old templates of what we already know.

Memories are important in translating what it is we are looking at. The temporal lobe help to form semantic memories whilst the parietal lobe help to form the episodic memory (when and where an object has been presented). The temporal lobe, the superior temporal sulcus, the parietal temporal junction and the prefrontal cortex have an ability to form abstract conceptual memories. This is done by intergrading and fusing accumulated experiences from across multiple modalities including language.

ATTENTION

The orientation of the attention can be controlled via external (exogenous) and internal (endogenous) processes. There seems to be some differences in what researchers say about these types of attentions from what I could find. The following has been said;

THEORY/EXPLANATION 1:

Exogenous is being under control of a stimuli, it's considered to be a reflexive and automatic and caused by a sudden change in periphery.
Endogenous orientation is internal and due to resources to a predetermined location or space, i.e. occurs according to the observers goals and desire these endogenous cues must be processed by the observer and then get acted upon purposefully.

It's suggested that there are four differences between the two kinds of cues:

- Exogenous orientating is less affected by cognitive load than endogenous orienting.
- Observers are able to ignore endogenous cues but not exogenous cues.
- Exogenous cues have bigger effects than endogenous cues.
- Expectancies about cue validity and predictive value affects endogenous orientation more than exogenous orientation.

THEORY/EXPLANATION 2:

Exogenous can also be called bottom-up processing or stimulus driven attention. It is a attentional processing which is driven by the properties of the objects themselves. Some processes, sudden motions or sudden loud noises can attract our attention in a preconscious way. We attend to them whether we want to or not. These aspects of attention are thought to involve parietal and temporal cortices as well as the brainstem.

Endogenous can also be called top-down processing or goal-driven attention.

MEMORY

DIFFERENT MEMORY SYSTEM

There are different ways to categorise the human memory but the most common is the following:

PROCEDURAL/IMPLICIT MEMORY – this type of memory is considered to be non-declarative. It's the ability to use previously learnt skills like riding a bicycle, typing on your computer, use a pencil or drive a car. It's presumed to be stored in the striatum and other parts of the basal ganglia. This is a type of long-term memory and the implicit memory seems to be associated with the activation of parietal and occipital regions of the brain.

PERCEPTUAL MEMORY – this memory is our ability to fast identify object and individuals in our surroundings, it's the long-term memory for visual, auditory and other perceptual information. The perceptual as well as the implicit memory can be used without any conscious cognitive processes and can be called priming.

SHOT TERM MEMORY – short term memory store the information that is relevant at the moment in our consciousness. It's usually divided into **primary and working memory**. The **primary memory** is when we passively hold information in our consciousness. Whilst, working memory is when we hold information in the consciousness at the same time as one process the information. The working memory is crucial for most of the cognitive activities that we preform like reading.

SEMANTIC MEMORY – has to do with our knowledge about the world, like that Wien is the capital of Austria or that the association between table and chair are stronger than the association between couch and gun. This is information we can access without being aware on when or where we acquired it.

EPISODIC MEMORY – this memory is based on experiences. With the episodic memory it's possible to recall a specific memory from a specific day and time.

There are also another way to divided memory into:

- Working memory
- Long-term memory

Where the long-term memory can further be divided into;

- Declarative memory (involving diencephalon and hippocampus)
    - Semantic (fast)
    - Episodic (personal)
- Non-declarative memory (involving cerebellum, basal ganglia and premotor cortex)
    - Procedural (form of motoric memory involving basal ganglia, cerebellum and prefrontal cortex)
    - Non-associative
    - Associative
    - Priming (unconscious memory involving the sensory association cortex)

WORKING MEMORY

Involves the frontal lobe. Is a memory that works for a couple of seconds to a couple of minutes. Although it is typically studied in the context of declarative memory, short-term memory also operates in the acquisition and ultimate storage of nondeclarative information.

LONG TERM MEMORY

When a short-term memory is consolidating, the change in synaptic strength → LTP, it converts to a long-term memory.

LEARNING

EMOTIONS

REWARD SYSTEM

LANGUAGE

Language is a way to express ideas, feelings, desires, emotions and more through thought, gestures, speech and writing. The parts of the brain, then, that are responsible for language are both the areas in the sensory part of the brain which processes the visual, auditory and sensory ques as well as the motor cortex that then plans and control the larynx, pharynx, mouth and tongue to produce sound or the face, hands and arms for gestures and sign language.

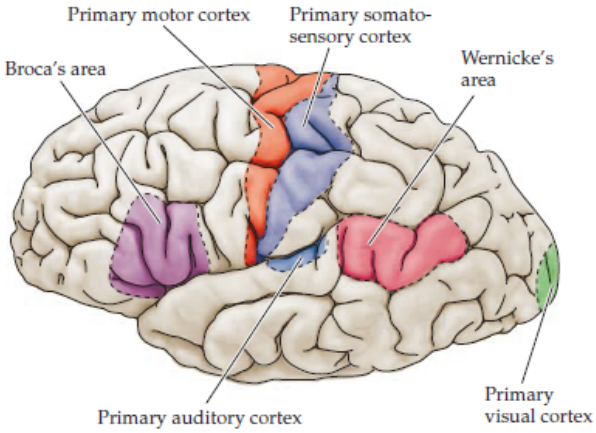


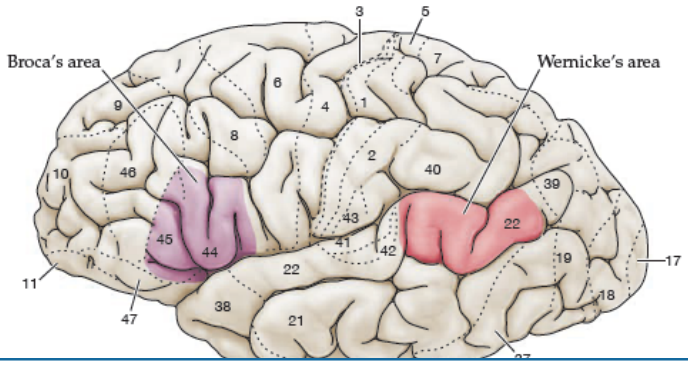
FIGURE 33.1 Diagram of the major brain areas involved in the comprehension and production of language. The primary sensory, auditory, visual, and motor cortices are indicated to show the relation of Broca's and Wernicke's language areas to these other areas that are involved in the comprehension and production of speech, albeit in a less specialized way.

APHASIAS

Aphasias is a term used to refer to syndromes that diminish or abolish the ability to comprehend and/or to produce language as a way to communicate meaningful statements while sparing the ability to perceive the relevant stimuli and produce intelligible words. Aphasia occurs due to damage to specific parts of the brain that comprise essential language functions while leaving the sensory and motor infrastructures of verbal communications intact. Patients suffering from aphasia are incapable of recognizing and employing the meaning of words correctly.

BROCA'S AND WERNICKE'S AREAS

The first evidence for the localization of language function to a specific region (and to a hemisphere) of the cerebrum is usually attributed to the French neurologist Paul Broca and the German neurologist Carl Wernicke, who made seminal observations in the late 1800s. Both Broca and Wernicke examined the brains of individuals who had become aphasic and later died. Based on correlations of the clinical picture and the location of the brain damage seen in autopsy, Broca suggested that language abilities were localized in the ventroposterior region of the frontal lobe. More important, he observed that the loss of the ability to produce meaningful language—as opposed to the ability to move the mouth and produce words—was usually associated with damage to the left hemisphere.



Broca's aphasia[a]	Wernicke's aphasia[b]
Halting speech	Fluent speech
Tendency to repeat phrases or words (perseveration)	Little spontaneous repetition
Disordered syntax	Syntax adequate
Disordered grammar	Grammar adequate
Disordered structure of individual words	Contrived or inappropriate words
Comprehension intact	Comprehension not intact

Although Broca was basically correct, he failed to grasp the limitations of thinking about language as a unitary function localized in a single cortical region. This issue was better appreciated by Wernicke, who distinguished between patients with impaired ability to comprehend language and those with impaired ability to produce language. Wernicke recognized that some aphasic patients who hear normally have great difficulty understanding speech. These patients retain the ability to produce utterances with reasonable grammatical and syntactic fluency, but often without meaningful content. He concluded that lesions of the posterior and superior temporal lobe on the left side tend to result in deficits of this sort. In contrast, other patients continue to comprehend language but lack the ability to produce syntactically complete utterances, even though it is clear that they know what they are trying to say. Thus, they repeat syllables and words and utter agrammatical phrases, even though the meaning eventually gets through.

As a consequence of these early observations, two rules about the localization of language have been taught ever since. The first is that lesions of the left frontal lobe in a region referred to as Broca's area affect the ability to produce language efficiently. This deficiency is called motor or expressive aphasia and is also known as Broca's aphasia. The second rule is that damage to the left temporal lobe causes difficulty understanding spoken language, a deficiency referred to as sensory or receptive aphasia, also known as Wernicke's aphasia.

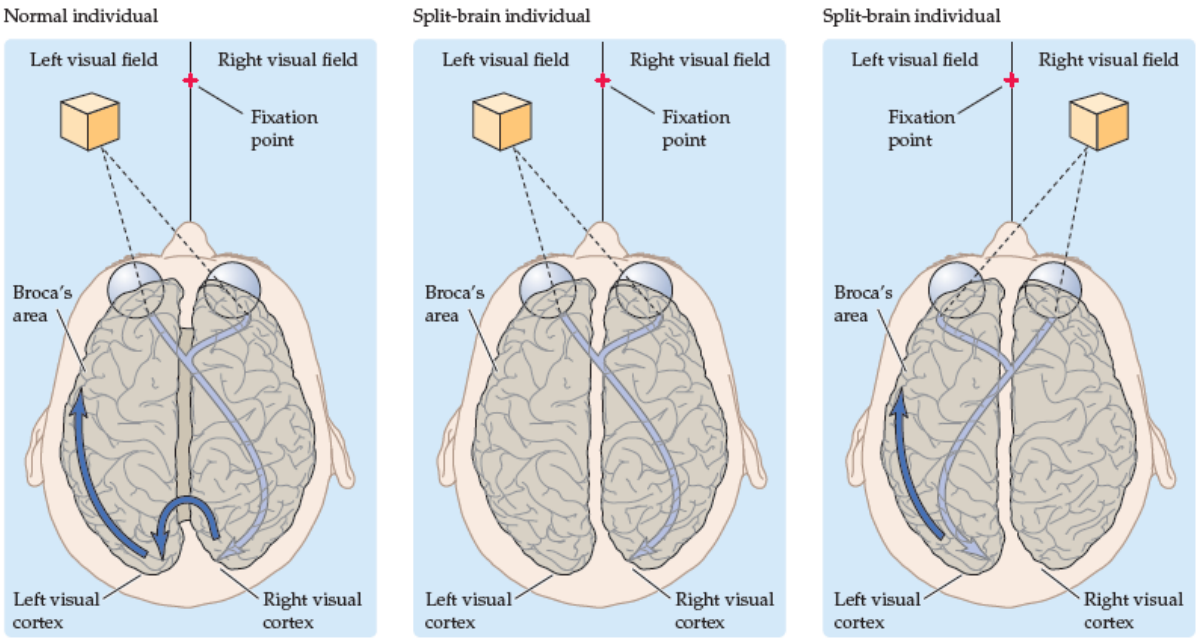
Receptive aphasia generally reflects damage to the auditory association cortices in the posterior temporal lobe, a region referred to as Wernicke's area.

A final broad category of language deficiency syndromes is conduction aphasia. These disorders arise from lesions to the pathways connecting the relevant temporal and frontal regions, such as the arcuate fasciculus that links Broca's and Wernicke's areas. Interruption of these pathways may result in an inability to produce appropriate responses to heard communication, even though the communication is understood.

LANGUAGE LATERALIZATION

Until the 1960s, observations about language localization and lateralization were based primarily on patients with brain lesions of varying severity, location, and etiology. Up until that time, the inevitable uncertainties of clinical findings had allowed some skeptics to argue that language and other complex cognitive functions might not be localized or even lateralized in the brain. Definitive evidence supporting the inferences from neurological observations came from studies of patients whose corpus callosum and anterior commissure were severed as a treatment for medically intractable epileptic seizures. In such patients, investigators could assess the function of the two cerebral hemispheres independently because the major axon tracts that connect them had been interrupted. The first studies of these so-called split-brain patients were carried out by Roger Sperry and his colleagues at the California Institute of Technology in the 1960s and 1970s and established the hemispheric lateralization of language beyond any doubt. To evaluate the functional capacity of each hemisphere in split-brain patients, they asked the subjects to use each hand independently to identify objects without any visual assistance to provide information to only one side of the brain.

Somatosensory information from the right hand is processed by the left hemisphere, and vice versa. Therefore, by asking the subject to describe an item being manipulated by one hand or the other, the researchers could test the language capacity of the relevant hemisphere. Using the left hemisphere, split-brain patients were able to name objects held in the right hand without difficulty. In contrast, and quite remarkably, an object held in the left hand could not be named. Using the right hemisphere, most split-brain patients could produce only an indirect description of the object that relied on rudimentary words and phrases rather than the precise lexical symbol for the object (for instance, "a round thing" instead of "a ball"); some could not provide any verbal account of what they held in their left hand.

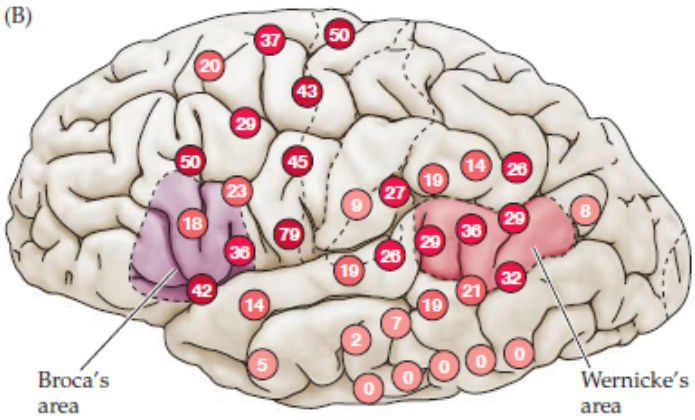


Observations using techniques to present visual information to the hemispheres independently (a method called tachistoscopic presentation) showed further that the left hemisphere responds to written commands, whereas the right hemisphere typically responds only to nonverbal stimuli (e.g., pictorial instructions or, in some cases, rudimentary written commands). These distinctions reflect broader hemispheric differences summarized by the statement that the left hemisphere in most humans is specialized for (among other things) the verbal and symbolic processing important in communication, whereas the right hemisphere is specialized for (among other things) visuospatial and emotional processing.

The ingenious work of Sperry and his colleagues on split-brain patients put an end to the century-long controversy about language lateralization. In most individuals, the left hemisphere is unequivocally the seat of the explicitly verbal language functions. There is significant variation in the degree of lateralization among individuals, however, and it would be wrong to suppose that the right hemisphere has no language capacity. As noted, in some individuals the right hemisphere can produce rudimentary words and phrases, a few individuals have fully right-sided verbal functions, and even for the majority with strongly left-lateralized language semantic abilities, the right hemisphere is normally the source of our emotional coloring of language.

VARIABILITY OF LANGUAGE REPRESENTATION

Observations and studies have since shown that there is a variability in language localization from patient to patient. The picture to the right summarizes data from 117 patients whose language areas were mapped by electrical recording at the time of surgery. The number in each red circle indicates the percentage of patients who showed interference with language in response to stimulation at that site. Note that many of the sites that elicited interference fall outside the classic language areas (Broca's area, shown in purple; Wernicke's area, shown in blue).



THE ROLE OF THE RIGHT HEMISPHERE

The right hemisphere has the same gross anatomical and cytoarchitectonic areas in the cortex as the left hemisphere, but these areas seem more involved in the emotional and tonal components of language, or prosody. Prosodic aspects of speech include stress, intonation, and rhythm, which informs the listeners about the aspects of communication not necessarily encoded in grammar, such as whether an utterance is a question, statement or command.

Deficiencies in speech prosody, referred to as aprosodias, are associated with right-hemisphere damage to the cortical regions that correspond to Broca's and Wernicke's areas and related regions in the left hemisphere. Aprosodias emphasize that although the left hemisphere (or better put, specialized cortical regions in that hemisphere) figures prominently in the comprehension and production of language for most humans, other regions, including corresponding areas in the right hemisphere, are needed to generate the full richness of everyday speech.

SIGN LANGUAGE

Studies were performed in America that looked into the signing deficits in congenitally deaf individuals who learned sign language from birth and later suffered lesions of the language areas in the left and right hemisphere.

Left-hemisphere damage produced signing problems in these patients analogous to the aphasias seen after comparable lesions in hearing, speaking patients. The patients with left-hemisphere lesions, which in each case involved the language areas of the frontal and/or temporal lobes, had measurable deficits in sign production and comprehension when compared with normal signers of similar age.

Patients with right-hemisphere damage on the other hand showed similar damage as from those in hearing patients

INFORMATION INTEGRATION IN THE BRAIN

EXPLAIN HOW COMMON BRAIN DISORDERS (SUCH AS STROKE, CANCER AND ADHD) AND EVERYDAY LIFE (SUCH AS STRESS AND SLEEP) AFFECT COGNITIVE PROCESSES AND BEHAVIOUR (S2-S3).

BE ABLE TO DESCRIBE COMMON METHODS USED FOR DIAGNOSIS AND TO STUDY HEALTHY BRAINS (S2).

There are several ways to study the brain and also for diagnosing neurological problems. When it comes to the diagnosing it's always good to use a complete neurological examination that consists of several parts including examination of the motor and sensory system, cranial nerve function, reflex evaluation as well as higher mental functions.

Cranial nerve	**Function/innervation**	**how**
I – n. olfactorius	Smell. Usually only tested when an injury is suspected.	In the examination each nostril will be tested separately. The patient will smell different familiar smells from small flasks. The sense of smell can be reduced (hyposmi) or can be completely abolished (anosmi). Damage can be seen in for example trauma or frontal lobe tumors.
II – n. opticus	Vision	Can be diveided into central vision (cone) and peripheral vision (rod). Pupil reactions are tested (tests for other nerves as well). Damage to visual pathways between retina and occipital lob → visual field defect. Damage to n. opticus → a bild eye Damage chiasma → shadow parch vision Damage tractus opticus → left or tight hemianopsia **How to test:** Visual field is assessed by having the test-person sitting in front of the examiner at a distance of app. 60 cm. The test-person covers the left or right eye, with the other eye looking straight into the examiners opposite eye. The examiner moves his hand from outside at half the distance to the test-person into the visual field of the test-person and the test-person has to indicate when he sees the hand or how

		many fingers the examiner moves. This is repeated for all four quadrants for both eyes. Normally there are big variations in the borders of the visual fields, but strong deficits can be demonstrated. A more precise measurement is done with a visual field examination.
III – n. oculomotorius	Movement of eye and eyelid	Tested with nerve IV and VI. Ask the test-person to focus on the examiner's finger and move the finger to the left and right and up and down. Note if both eyes are following normally. Does the test-person see double in some position? 4 In case of paralysis of one or several eye muscles the axes of the eyes do not correspond in certain sight directions which causes the double-sightedness. Check the upper eyelids. Drooping upper eyelids (ptosis) occurs when there is damage to the musculus levator palpebrae which is innervated by the oculomotor nerve. Also check pupil size and reaction to light. Should be contracted quick and also a reflexory contaction in the eye not examined
IV – n. Trochlearis	Innervates m. obliquus superior. It moves the eye laterally and down	
V – n. Trigeminus	Sensation face and mouth; chewing muscle	The sensibility is tested by lightly touching the different areas with the fingertips. This should be done simultaneously on both sides. Note if the touch feels the same on both sides. Is there any paresthesia or pain when touched? Check also the pain sensitivity by pricking with a toothpick. Temperature sensitivity is also tested clinically. Can use cotton stick and let the patient descide if it's the soft or hard side. Motor part This innervates the chewing-musculature. Palpate m. masseter bilaterally and let the test-person bite. Note if the muscles contract with normal force and bilaterally equal. Check also if both sides are equal when chewing or opening the mouth wide

VI – n. Absucens	Innervates m. rectus lateralis. Moves eye laterally	
VII – n. Facialis	Movement of facial muscles, secretion of tears and saliva and the taste bud on the tounge.	**Motor part** This nerve innervates the facial muscles and platysma (muscle of the head, face and neck). Note in rest any possible asymmetry, smoothed out nasal groove, drooping corner of the mouth or smoothed out convolutions in the forehead. Often a functional deficit emerges only with certain movements. Let the test-person frown, twitch the eyes, show the teeth, smile and whistle. **Sensory part** The taste on the tongue's front 2/3 passes through n. intermedius which follows the facialis-stem through chorda tympani. Leveldiagnostics for facialis-damage are therefore tested on the front part of the tongue. in practice a sweet, salty, sour and bitter substance is dropped on one half of the tongue each time while the patients keeps sticking out the tongue between each taste.
VII – n. Vestibulocohlearis	Hearing and balance	Test hearing with air born and bone led sounds. Balance can be tested in different ways.
IX – n. Glossopharyngeus	Taste, sensation in parts of the pharynx and the swallowing reflex.	Examined together with CN X. The functions of these nerves are tested by examinations of certain functions in the throat and larynx. Note the uvula's and the palate's positions in rest and when the test-person says 'aaa'. Is there a deviation towards one side? Check that the larynx lifts during swallowing and that test-person can make a cough. Note any hoarseness which can be a sign of recurrence paralysis. The swallowing reflex is clinically tested by touching the tonsils or the throat wall with a stick of cotton wool while holding the tongue down with a spatula. It is then checked if the palate is lifted symmetrically.
X – n. Vagus	Innervates pharynx, larynx, viscera and heart.	
XI – n. accessorious	Innervates m. trapezius and m.	This nerve innervates m. sternocleidomastoideus and the upper part of m. trapezius. Examine the force of m.

	stemocleidomastoideus. Swallowing reflexes	sternocleidomastoideus by letting the test-person turn the head towards each side while the examiner presses against the head with his hands (tests contralateral side). The force in m. trapezius is tested by letting the test-person lift the shoulders against the examiners resistance
XII – n. hypoglossus	Movements of the tongue.	This nerve innervates the muscles of the tongue. Ask the test-person to stick out the tongue and then draw it back again. Observe if the tongue deviates to one side. Note any possible atrophy or fasciculations, spontaneous, irregular, and reoccurring twitches in certain muscle groups.

Observation

- Assess for muscle size, symmetry, and posture.
- Are any involuntary movements apparent? If so, of what type? Myotonia? Fasciculation? Adventitious movements (e.g. tremors, myoclonic jerks)?

Palpation

- Examine for any tenderness? Palpable mass? Consistency?
- Assess muscle tone (i.e resistance with passive movements).

Strength

- Assess proximal and distal muscle groups in both upper and lower extremities. For example, this can be done as follows: The patient sits right in front of the examiner. The strength is examined joint by joint and the examiner fixes the joint proximally and flexes or extends against a resistance.

-The following joints are examined:

Wrist: Palm and dorsal flexion, radial and ulnar deviation, pro- and supination
Elbow: Flexion and extension
Shoulder: Ab- adduction, outward and inward rotation
Hip: Flexion, extension, ab- and adduction
Knee: Flexion, extension

Coordination

Fine-tuned voluntary movements are partly governed by sight, partly by muscle feeling. The part of the coordination that is governed without visual help is examined with the finger-nose and knee-heel test.

Implementation: The test-person is requested to slowly bring the right or left index-finger to the tip of the nose with closed eyes. This is repeated, but at the same time as test-person brings the finger to the nose the examiner applies a vibrator to the triceps-tendon. Note the effect.

Knee-heel is performed when lying down on the back with straight legs. The test-person is asked to slowly put the right or 1eft heel onto the opposing knee.

For a full neurological status additional examination are required: The sensibility of the skin is tested with respect to touch, pain and temperature. Proprioceptive sensibility is tested with a vibrating tuning fork and passive movements. A summary of mental functions is also necessary for a complete neurological status. As well as muscle reflexes.

VISUAL PICTURES OF BRAIN

CT (computer tomography) – take several 2D pictures that can be placed upon each other to create a 3D image, gives a good view of the brain.
MRI (magnetic resonance imaging) – gives a good contrast in tissue and therefore it's good to use to see differences in the brain like white and gray matter. Good to see for ex tumours.
Functional MRI – Uses MRI technics but can illustrate blood supply in the brain. Good to see cloths.
PET – Uses the decay of radioactive isotopes which gives 3D pictures of different substances movement in the body. In the brain glucose is used to see which parts that are more active i.e. uses more glucose.

APPENDIX

ORAL EXAM 1

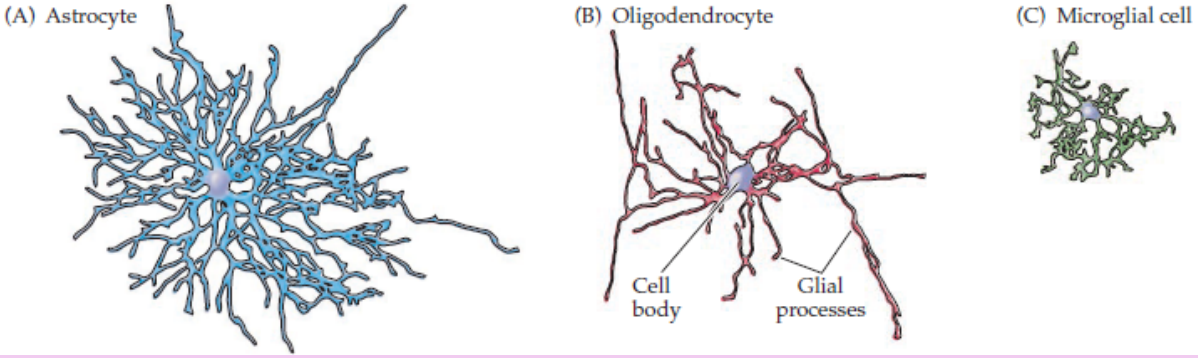
ORAL EXAM 1 - CELLULAR NEUROBIOLOGY

1.DESCRIBE THE DIFFERENT TYPES OF GLIAL CELLS AND THEIR FUNCTIONAL ROLES

In the 19th century there was a presumption that the glial cells held the nervous system together (*glia* being the Greek word for glue) and while there is a lack of evidence to suggest that is actually the case the name stuck around.

Glial cells differ from neurons but are at least as abundant and while they don't participate directly in synaptic transmission or electrical signalling their supportive functions help define synaptic contacts and maintain the signalling abilities of neurons.

There are three types of differentiated glial cells in the mature nervous system:



ASTROCYTES

Astrocytes are restricted to the central nervous system (brain and spinal cord) and have elaborate local processes that give these cells a starlike ("astral") appearance. A major function for astrocytes is to maintain an appropriate chemical environment for neuronal signalling including the formation of the blood-brain barrier. Recent observations also suggest that astrocytes secrete substances that influence the formation of new synaptic connections and that a subset of astrocytes in the adult brain retain the characteristics of stem cells.

OLIGODENDROCYTES

Oligodendrocytes, which are also restricted to the CNS, lays down a myelin sheath (laminated, lipid-rich wrapping) around some, but not all, axons. Myelin has important effects on the transmission speeds of electrical signals. In the PNS (peripheral nervous system) the cells that provide myelin are called Schwann cells. Both oligodendrocytes and Schwann cells can retain neural stem cell properties in the mature nervous system.

MICROGLIAL CELLS

Microglial cells are primarily derived from hematopoietic precursor cells. They share many properties with macrophages found in other tissues in that they're primarily scavenger cells that remove cellular debris from sites of injury and normal cell turnover. Like macrophages

they also secrete signalling molecules, especially a wide range of cytokines that can modulate local inflammation and influence whether other cells live or die. Following brain damage the number of microglia increases dramatically.

1.DESCRIBE THE DIFFERENT TYPES OF GLIAL CELLS AND THEIR FUNCTIONAL ROLES V2

Glia means glue in Greek, however they don't glue the nervous system together that scientists once thought. They maintain the ionic milieu of the nerve cells, they modulate the rate of the nerve signal as well as modulating the synaptic action. That is done by control of the uptake and metabolism of neurotransmitters. Glia are involved in providing scaffolds for the neural development and recovery from neural injury.

ASTROCYTES

Only in CNS. Looks like a star. Helps maintaining an appropriate chemical environment for neural signalling. (Regulate synapse formation. Metabolic support of neurons. Have control over the flow and what is transported in the CNS vascular system.)

OLIGODENDROCYTES

Only in CNS. Creates myelin around some axons. Myelin is important for the speed of the transmission of the electrical signals. In the PNS this is done by Schwann cells.

Most proliferative cell of the CNS. There's a dynamic regulation in the production of myelin, to finetune the neural circuit function. Organise the axonal domains and nodes of ranvier. Metaolic support to axons. Facilitate ion homeostasis – action potential conductance.

Oligodendrocytes are produced throughout life, the production doesn't stop. The myelin production can be regulated by the neurons.

MICROGLIAL CELLS

Are derived from hematopoietic precursor cells (mainly). Scavenger cells, remove cellular debris, secrete cytokines as a response to inflammation and influence cell death and survival.

GLIAL STEM CELLS:

Glial stem cells can generate glia and in some cases neurons when proliferating. Can be divided into two categories; astrocytes that are found in the ventricles and the subventricular zone. Oligodendroglia precursors are scattered through the white matter and can be referred to as polydendrocytes.

2.DESCRIBE THE BASIS OF THE RESTING MEMBRANE POTENTIAL AND THE FUNCTION OF THE NA/K PUMP

The negative resting membrane potential inside the neuron arises due to:

- The membrane of the resting neuron is more permeable to K^+ than any other ion present.
- There is more K^+ inside the neuron than outside.

The selective permeability to K^+ is caused by K^+-permeable membrane channels that are open in resting neurons while the large K^+ concentration gradient is produced by membrane transporters that selectively accumulate K^+ within neurons. If potassium channels in the membrane open then K^+ will move down its concentration gradient and out of the cell. Every time a K^+ ion leaves the cell, the cell's interior loses a positive charge. Because of this a slight excess of positive charge builds up on the outside of the cell membrane, and a slight excess of negative charge builds up on the inside, i.e. the inside of the cell becomes negative relative to the outside which sets up a difference in electrical potential across the membrane.

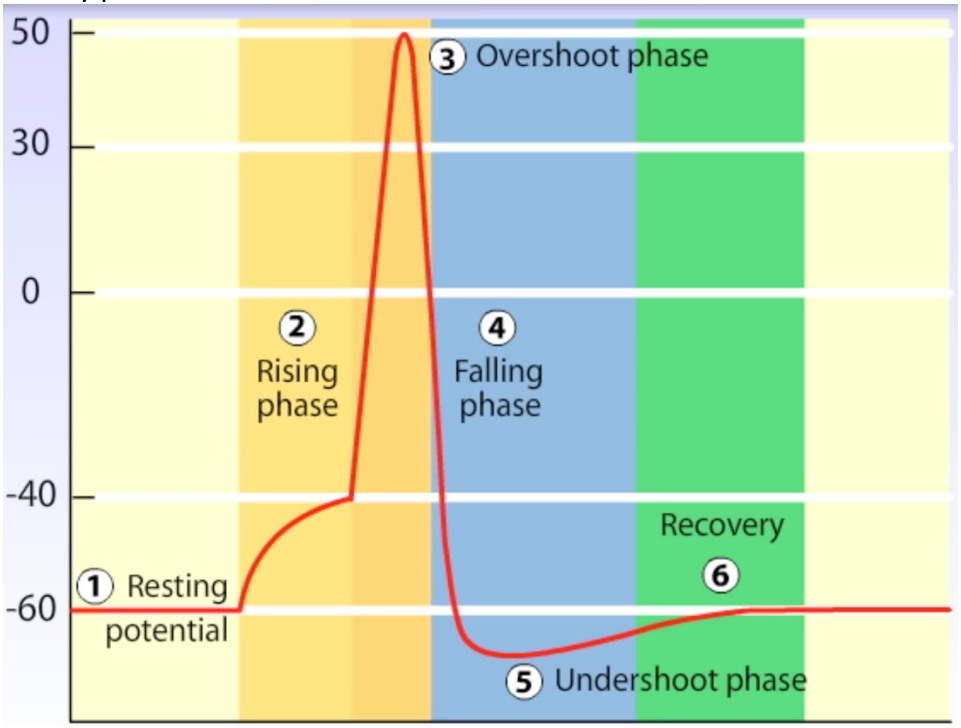
The opposite happens with sodium since that is in a higher concentration outside of the cell, when it flows into the cell through channels it creates a positive charge on the inside of the cell and a negative one on the outside.

In a neuron the resting membrane potential is closer to the potassium equilibrium potential than the sodium due to the resting membrane being more permeable to K^+ than to Na^+. Changing the number of open ion channels provides a way for the neuron to control its membrane potential and produce electrical signals.

The Na^+/K^+ ATPase pump is responsible for maintaining the transmembrane concentration gradients for both sodium and potassium (if they weren't there the concentration gradients would dissipate). Since they transport the ions against their concentration gradient, they require energy which comes from ATP hydrolysis. For every ATP that is broken down, 3 Na^+ ions are moved from the inside to the outside of the cell and 2 K^+ are moved from the outside to the inside.

3.DESCRIBE THE BASIS OF THE ACTION POTENTIAL –WHICH ARE ITS DIFFERENT PHASES AND WHICH ARE THE UNDERLYING IONIC MECHANISMS

The action potential can be divided in to six different phases: the resting phase (at resting potential), the rising phase, the overshoot phase, the falling phase, the undershoot phase and the recovery phase.



At the resting potential leaky potassium channels are open and allow potassium to get into the cell, this results in a successive opening of voltage gated sodium channels and allow more sodium to flow in. This depolarises the neuron giving it a positive charge, it is overshooting 0 mV and therefore this state is called the overshoot phase. In the overshooting phase the sodium channels start to close at the same time as voltage gated potassium channels starts to open and potassium flows out of the neuron. This is the start of the repolarising phase, as the mV gets closer to the resting membrane potential more sodium channels close and potassium channels open. At resting potential, the potassium channels start to close, they don't close all at once and therefore the neuron will be hyperpolarised, that phase is called the undershoot phase. The last phase is the recovery phase, in this phase are only the leaky potassium channels are open and the inflow of potassium from these channels makes the neuron go reach resting potential again and are ready to create a new action potential.

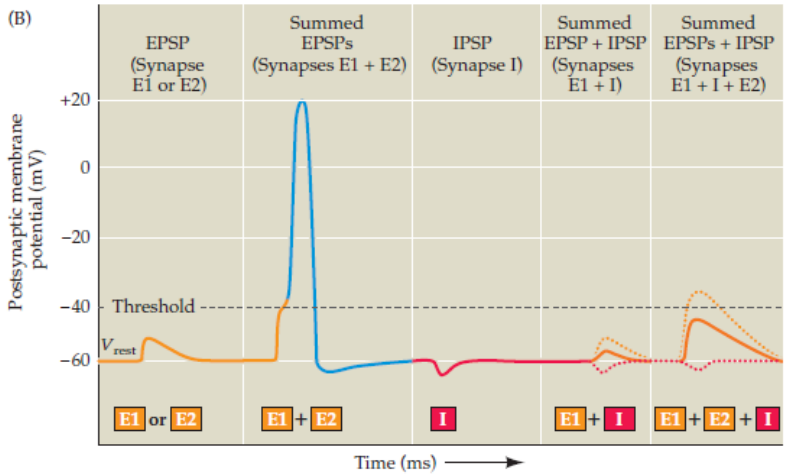
The falling phase can also be called refraction period, when the sodium channels has been inactivated and no action potential can be generated. The undershoot phase can be called relative refraction period, when both potassium and sodium channels are closed, a large enough stimulus can give rise to an action potential.

Throughout the axon there are Ranvier's nodes, where there are voltage gated potassium and sodium channels. When an action potential goes through out the axon it will activate sodium channels in the nodes of Ranvier and that will generate/feed the action potential so that it moves along the axon. When the action potential has passed the potassium channels

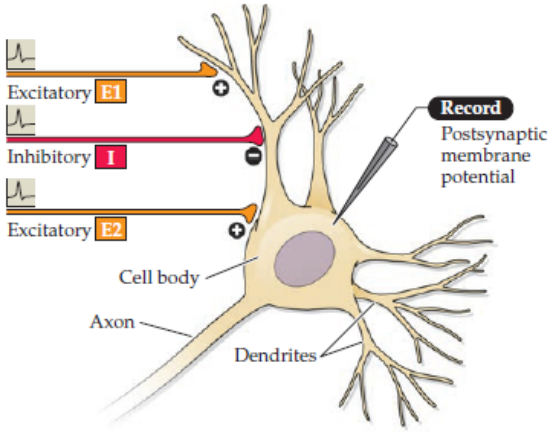
open. This is done so that an action potential can travel the great distant that some axons are, even though they are bad conductors and leaky.

4.COMPARE EXCITATORY AND INHIBITORY SYNAPSES –WHAT ARE THE EFFECTS ON THE POSTSYNAPTIC NEURON AND HOW DO THE TWO TYPES OF SYNAPSE INTERACT

Opening and closing of ion channels can be done to change the conductance of the postsynaptic cell. If opening or closing a channel increases the chance of an action potential taking place then it is considered excitatory, if it lowers the chance of an action potential taking place then it is considered inhibitory.



One individual excitatory synapse may only produce a fraction of a millivolt which is well below the threshold for generating a postsynaptic action potential. But since the neurons in the CNS are typically innervated by thousands of synapses the PSPs (postsynaptic potentials) produced by each active synapse can sum together to determine the behaviour of the postsynaptic neuron.



In the picture above one can see the effect where two excitatory synapses together can cause the postsynaptic neuron to depolarize enough to reach threshold potential while the addition of an inhibitory synapse prevents it from reaching that threshold. This leads to the neuron being able to integrate electrical information provided by all the inhibitory and excitatory synapses acting on it at any moment. Whether the sum of active synaptic inputs results in an action potential depends on the balance between excitation and inhibition.

To summarize, at chemical synapses neurotransmitter release from presynaptic terminals initiate a series of postsynaptic events that results in a change of the probability of a postsynaptic action potential occurring. This type of synaptic signalling allows neurons to form the intricate synaptic circuits that play a fundamental role in the brain's information processing. Recent studies also suggest that glial cells contribute to synaptic signalling which adds another dimension to information processing in the brain.

5.COMPARE THE PROCESS OF RELEASE OF ”SMALL” NEUROTRANSMITTERS (SUCH AS GLUTAMATE AND GABA) WITH THAT OF ”LARGE”NEUROTRANSMITTERS (SUCH AS NEUROPEPTIDE Y AND SUBSTANCE P) –SIMILARITIES AND DIFFERENCES

There are three criteria for neurotransmitters:

- They need to be accumulated in vesicles in the presynaptic terminal
- The substance needs to be released as a response to Ca^{2+} - influx
- When released the substance needs to affect the postsynaptic receptors and trigger a biological response.

There are about 100 identified neurotransmitters at this point. They can be divided in to two main groups:

- Classical neurotransmitters – these are small molecules like acetyl choline, catecholamines, glutamate and GABA
- Neuropeptides – larger molecules, amino chains/protein chains

CLASSICAL NEUROTRANSMITTERS

The classical neurotransmitters are created in the soma and are sent to the pre synapse where they are packed into vesicles. The vesicles already exist and the neurotransmitters trades places with H^+ (neurotransmitter moves into the vesicle, H^+ into the cytoplasm), this is done when H^+ goes with its concentration gradient. The concentration gradient is established by a pump that pumps H^+ into the vesicle from the cytoplasm, this pump uses ATP. Studies show that there are specific exchangers for the different classic neurotransmitters.

A signal caused by Ca^{2+} results in the release of neurotransmitters in the presynaptic cleft by exocytosis. When in the presynaptic cleft the neurotransmitters bind to channels on the post synapse. This reaction is fast, the effect of the neurotransmitter depends on:

- How fast the enzymatic inactivation is when the neurotransmitter is released into the synaptic cleft.
- How fast the neurotransmitter releases from the channel/protein it binds to and are transported back to the pre synapse.

The neurotransmitters are, as mentioned above, transported back to the pre synapse and then used again.

NEUROPEPTIDES

Are synthesised by mRNA, translated in the ER and put into vesicles in the Golgi apparatus. The vesicles are transported down the axon to the presynaptic terminal. These vesicles are bigger than the classical neurotransmitters. They are released by signals caused by Ca^{2+}, when used in the synaptic cleft they are degraded.

The classical neurotransmitters are often sent “alone” when there’s a low stimulation, at a stronger stimulation both classical neurotransmitters and neuropeptides are sent.

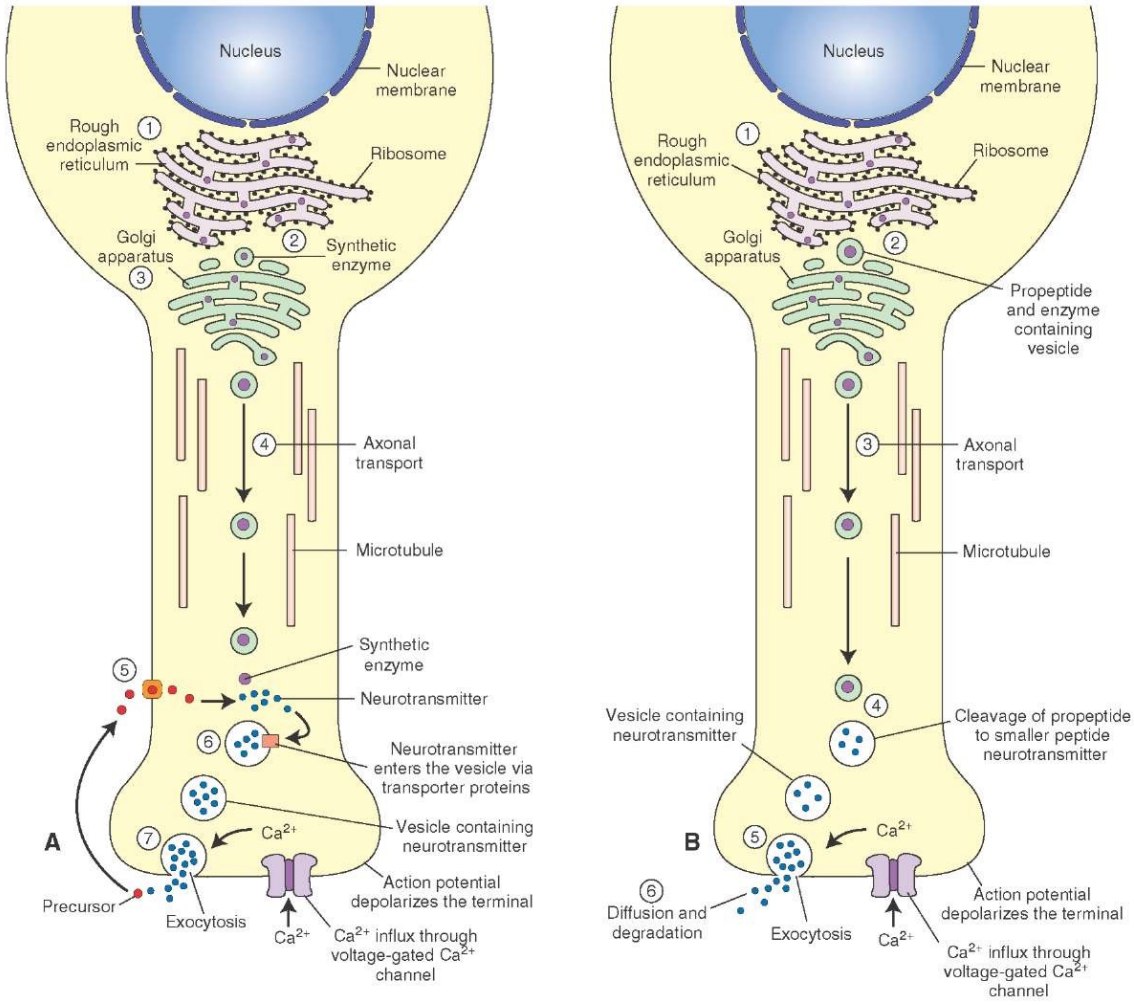
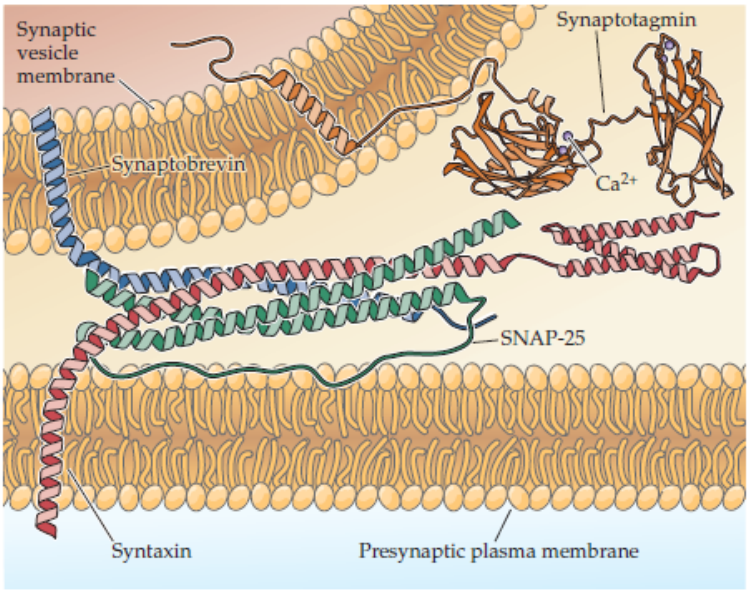
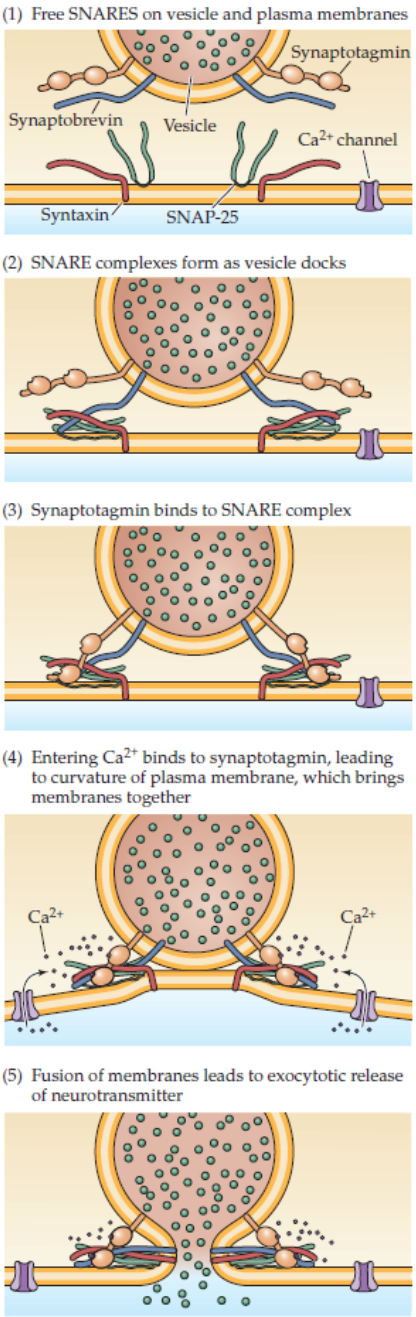


Figure 3: picture to the left shows a small classical neurotransmitters (transported individual). The picture on the right shows a neuropeptide.

6.DESCRIBE THE MOLECULAR MACHINERY THAT MEDIATES FUSION OF SYNAPTIC VESICLES WITH THE PLASMA MEMBRANE





On the synaptic vesicles there are SNARE proteins called synaptobrevin that can form a macromolecular complex with the SNARE proteins syntaxin and SNAP-25 that are primarily found on the plasma membrane. This complex brings the membranes closer together to promote fusion of the membranes.

The SNARE proteins do not bind Ca^{2+} which is used to regulate neurotransmitter release, instead it appears that synaptotagmins on the synaptic vesicles acts as a Ca^{2+} sensor to trigger vesicle fusion. It is thought that Ca^{2+} binding to synaptotagmin leads to exocytosis by changing the chemical properties of synaptotagmin which allows it to insert into the plasma membrane. This causes the plasma membrane to locally curve and leads to fusion of the two membranes.

So, to summarize, SNARE proteins bring the two membranes close together while Ca^{2+} induced changes in synaptotagmin then produces the final curvature that enables rapid fusion of the two membranes.

Not part of question but can be good to know:
To endocytose the fused vesicles a protein called clathrin is used to form a cagelike coating

around the vesicle membrane until it forms a coated vesicle like structure that is connected to the plasma membrane via a narrow lipid stalk (other adaptor proteins are also involved). This stalk is then pinched off with a protein called dynamin.

7.POISONING BY BOTULINUM TOXINS AND TETANUS TOXIN GIVERISE TO DIFFERENT SYMPTOMS. HOW DO THESE TOXINS ACT? HOW DO THE SYMPTOMS PRODUCED BY THE TWO TOXINS DIFFER AND WHY?

BOTULISM

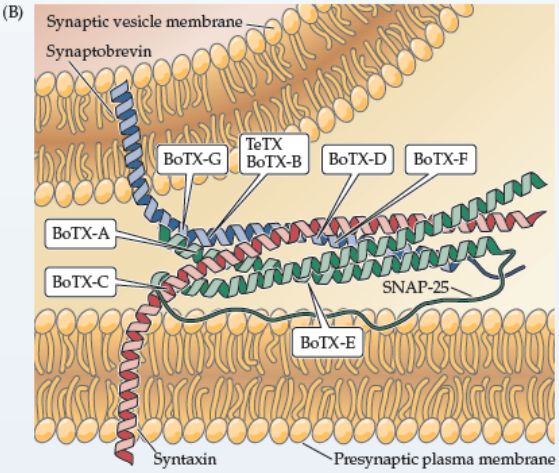
Botulism can occur by consuming food containing *Clostridium* bacteria or through infection of wounds with the spores from these organisms. The presence of the toxin can cause paralysis of peripheral neuromuscular synapses due to impaired neurotransmitter release. This causes skeletal muscle weakness or in the worst-case scenario respiratory failure due to paralysis of the diaphragm and other muscles required for breathing. Botulism toxin can also block synapses innervating smooth muscle of several organs giving rise to visceral motor disfunction. The paralysis/relaxation of muscle contraction also serves as a basis for clinical use in the toxin in cosmetic surgery and other applications.

TETANUS

Tetanus typically result from the contamination of puncture wounds by *Clostridium* bacteria that produce tetanus toxin. In contrast to botulism, tetanus poisoning blocks the release of inhibitory transmitters from interneurons in the spinal cord. This causes a loss of synaptic inhibition on spinal motor neurons which produces a hyper excitation of skeletal muscle and tetanic contractions in affected muscles.

MECHANISM

Although the symptoms from tetanus toxin differ dramatically to that of the botulism toxin studies have shown that these toxins have a common mechanism of action: they are highly specific proteases that inhibit neurotransmitter release by cleaving the SNARE proteins involved in fusion of the synaptic vesicles with the presynaptic plasma membrane.



(B) Cleavage of SNARE proteins by clostridial toxins. Indicated are the sites of proteolysis by tetanus toxin (TeTX) and various types of botulinum toxin (BoTX). (From Sutton et al., 1998.)

Tetanus toxin and botulism toxin types B, D, F and G specifically cleave the vesicle SNARE protein synaptobrevin. Other botulism toxins cleave syntaxin (type C) and SNAP-25 (types A and E) which are SNARE proteins found on the presynaptic plasma membrane. Destruction of these presynaptic proteins is the basis for the inhibitory actions of clostridium toxin on neurotransmitter disease.

The different actions of these toxins on synaptic transmission at excitatory motor versus inhibitory synapses apparently results from the fact that these toxins are taken up by different types of neurons: whereas botulism toxins are taken up by motor neurons, tetanus toxins are preferentially targeted to interneurons. The differential uptake of toxins is

believed to arise from the presence of different types of toxin receptors on the two types of neurons.

8.DESCRIBE THE MECHANISMS UNDERLYING THE INACTIVATION OF NEUROTRANSMITTERS

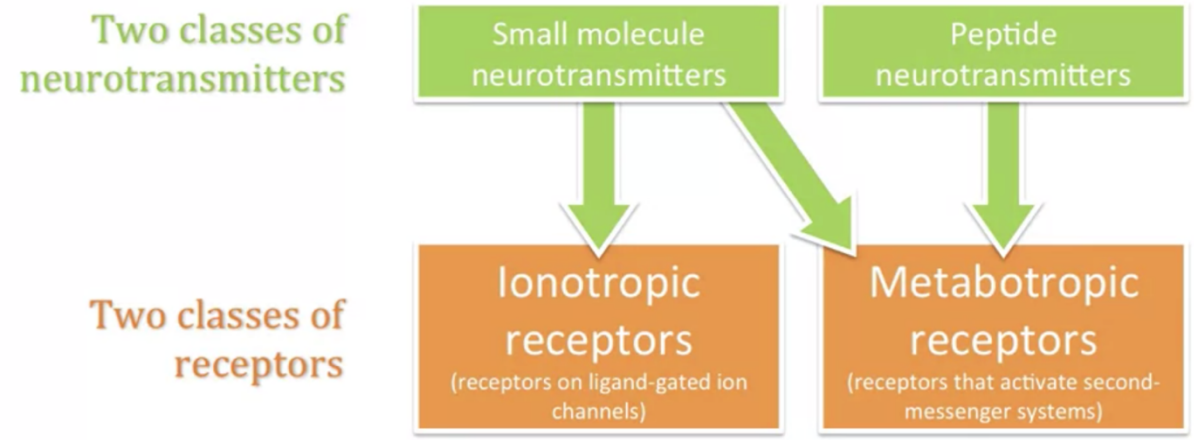
When neurotransmitters have “done it’s work” in the postsynaptic cleft it’s released back into the synaptic cleft, but they can’t just stay there since that would cause constant stimulation of the post-synaptic cell and an excessive firing of action potentials.

There are four different ways of getting rid of the neurotransmitters:

5. **Enzymes:** There are neurotransmitters that can be inactivated by enzymes, this is mainly for acetylcholine which is inactivated by acetylcholinesterase.
6. **Passive diffusion:** Most neuropeptides just defuse away from the cleft to the surroundings and can there be degraded.
7. **Re-uptake pumps:** There are pumps in the presynaptic terminal that pumps neurotransmitters back into the terminal where there are used again.
8. **Astrocytes:** The astrocytes end feet can actively pump neurotransmitters out of the synapse. In the astrocyte it can be broken down, reused in the astrocyte or the astrocyte can transfer it back to the presynaptic terminal where it can be reused.

Example with glutamate:
Glutamate can either be pumped back to the presynaptic terminal via transporters or glutamate can be taken up by astrocytes (glia cells) and there converted to glutamine that is then transported to the presynaptic terminal where glutamine is converted to glutamate via the enzyme glutaminase. Called glutamate cycle.

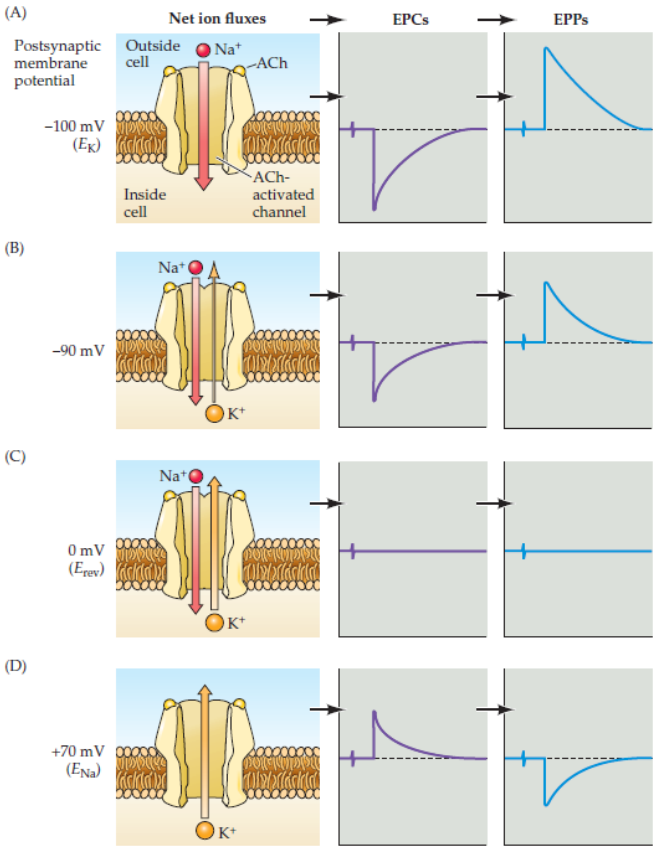
9.DESCRIBE THE MAIN STRUCTURAL AND FUNCTIONAL DIFFERENCES BETWEEN IONOTROPIC AND METABOTROPIC RECEPTORS



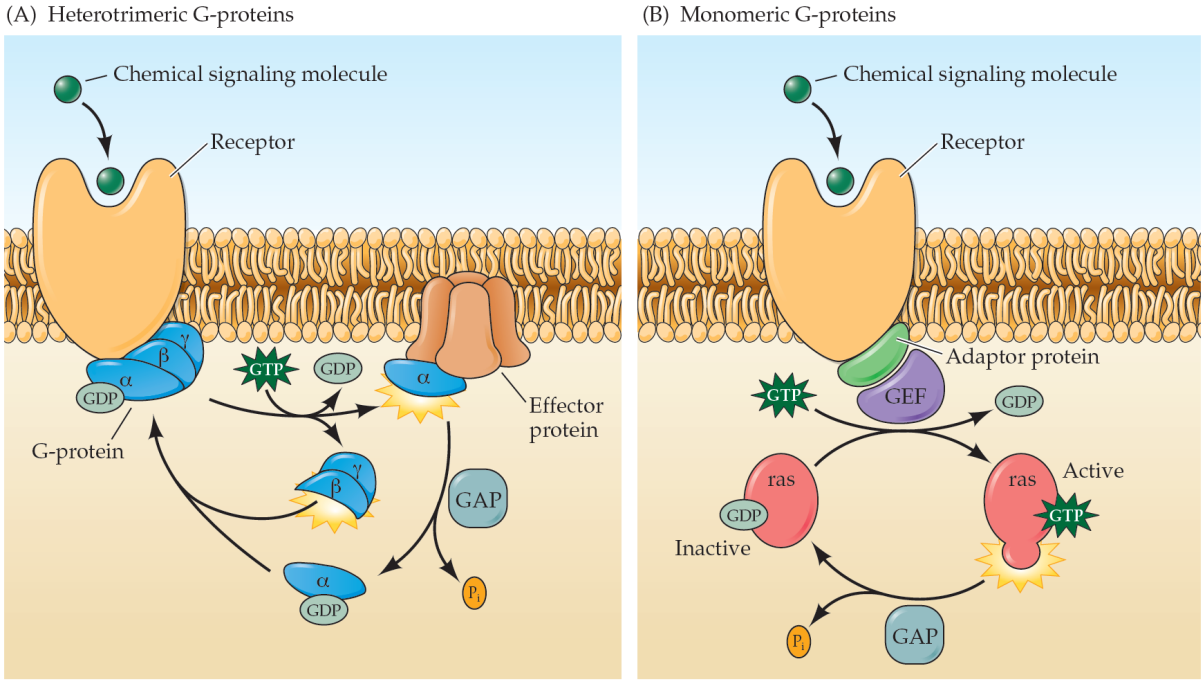
IONOTROPIC RECEPTORS

Ionotropic receptors are ligand gated ion channels, they can only be activated by small molecule neurotransmitters. They are formed by 4-5 subunits that form a pore through the membrane. They can be divided into positive and negative, examples on positive are nicotinacetylcholine receptors and glutamate receptors. Negative are GABA and glycine receptors.

The channels are gated by binding if neurotransmitter to the receptor site. There are a net current that flows through the channel, it depends on the membrane potential and are true for Vm-Erev ≠ 0 (either positive or negative driving force). Depending on the driving force there will be different ions that flow through.



METABOLIC RECEPTORS



Metabotropic receptors are G-protein coupled receptors that can be activated via small molecule neurotransmitters and neuropeptides. There are heteromeric G-proteins as well as monomeric G-proteins. The intercellular second messenger system related to the G-proteins can be quite diverse. The Heterotrimeric G-protein system when activated result in an activation of alfa subunit as well as betagamma subunit. These subunits can mediate a variety of postsynaptic effects by integrating with effector proteins, that could produce second messengers, activate enzymes and phosphorylate target proteins.

The Monomeric G-protein system activate the RAS system that can mediate a variety of postsynaptic effects.

G-protein system can lead to amplification of signals.

10.WHICH ARE THE MAIN TYPES OF POSTSYNAPTIC GLUTAMATE RECEPTOR AND HOW DO THEY DIFFER?

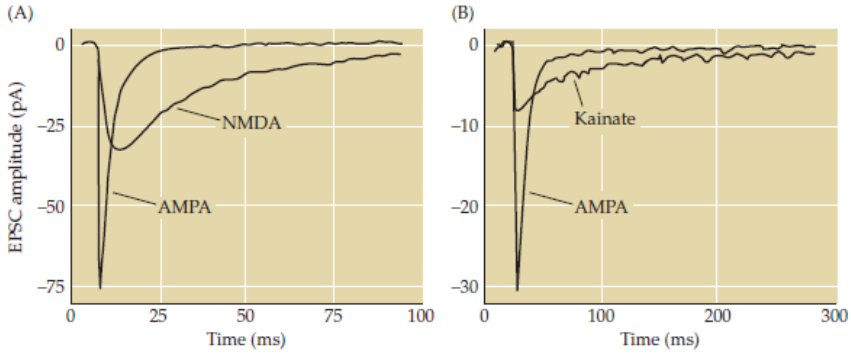
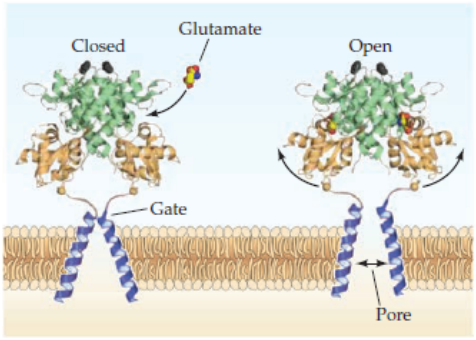


FIGURE 6.6 Postsynaptic responses mediated by ionotropic glutamate receptors. (A) Contributions of AMPA and NMDA receptors to EPSCs at a synapse between a presynaptic pyramidal cell and a postsynaptic interneuron in the visual cortex. Blocking NMDA receptors reveals a large and fast EPSC mediated by AMPA receptors, while blocking AMPA receptors reveals a slower EPSC component mediated by NMDA receptors. (B) Contributions of AMPA and kainate receptors to miniature EPSCs at the excitatory synapse formed between mossy fibers and CA3 pyramidal cells in the hippocampus. Pharmacological antagonists reveal that the component of EPSCs mediated by AMPA receptors is larger and decays faster than that mediated by kainate receptors. (A after Watanabe et al., 2005; B from Mott et al., 2008.)

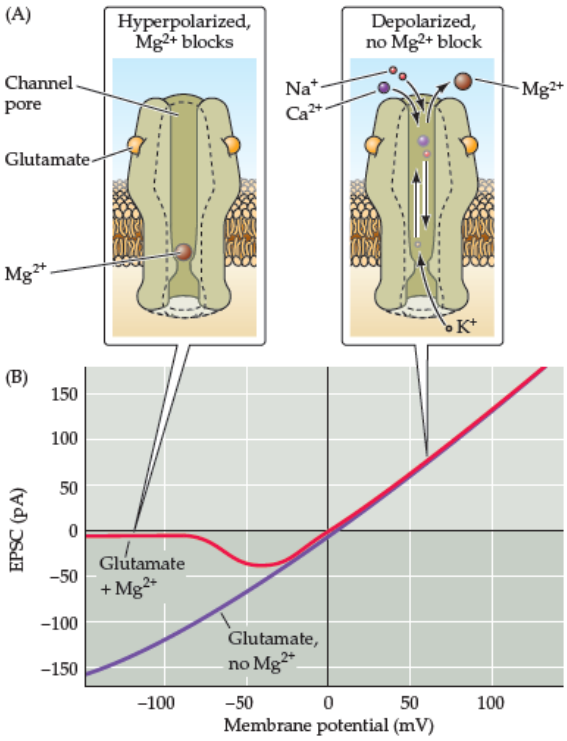
The main types of postsynaptic glutamate receptors are ligand gated ion channels that are activated by the neurotransmitter glutamate. Glutamate is the most important transmitter for normal brain function. Nearly all excitatory neurons in the CNS are glutamatergic, and it is estimated that more than half of all brain synapses release this neurotransmitter.

The main types of ionotropic glutamate receptors are AMPA receptors, NMDA receptors and kainate receptors (named after their antagonist). All of these receptors are glutamate-gated cation channels that allow the passage of Na^+ and K^+ which means that activation of these receptors always produce an excitatory postsynaptic response. Most central excitatory synapses possess both AMPA and NMDA receptors.

Experiments use antagonistic drugs that selectively block either AMPA or NMDA receptors to identify responses mediated by each receptor type. These experiments for example reveal that excitatory postsynaptic currents (EPSCs) produced by NMDA receptors are slower and last longer than those produced by AMPA receptors. EPSCs generated by AMPA receptors are usually much larger than the other ionotropic glutamate receptors which makes AMPA receptors the primary mediators of excitatory transmission in the brain. The physiological role of kainate receptors are less well defined, when found on postsynaptic cells kainate receptors generate EPSCs that rise quickly but decay more slowly than those mediated by AMPA receptors.



Like all ionotropic receptors, AMPA receptors are composed of multiple subunits. There are four different subunits, designated GluA1 to GluA4, with each subunit providing unique functional properties to AMPA receptors. The receptor subunits have several different domains, including an extracellular ligand binding domain that binds glutamate and a transmembrane domain that forms the ion channel. Binding of glutamate to the AMPA receptor opens the channel pore.



NMDA receptors have physiological properties that set them apart from the other ionotropic glutamate receptors. The most significant being that its pore allows Ca^{2+} to pass through in addition to Na^{+} and K^{+}. As a result, EPSPs produced by NMDA receptors increase the concentration of Ca^{2+} in the postsynaptic neuron which acts as a second messenger to activate intracellular signalling processes. Another important property of the NMDA receptor is that Mg^{2+} blocks the pore of this channel at hyperpolarized membrane potentials while depolarization pushes the Mg^{2+} out of the pore (removing extracellular Mg^{2+} eliminates this behaviour). Because of this behaviour NMDA receptors only pass cations when postsynaptic membrane potential is depolarized which is thought to underlie some forms of synaptic information storage, such as long-term synaptic plasticity. Another unusual feature of the NMDA receptor is that their gating requires a co-agonist in the form of the amino acid glycine.

11.DESCRIBE THE MECHANISMS UNDERLYING SYNAPTIC SHORT-TERM PLASTICITY

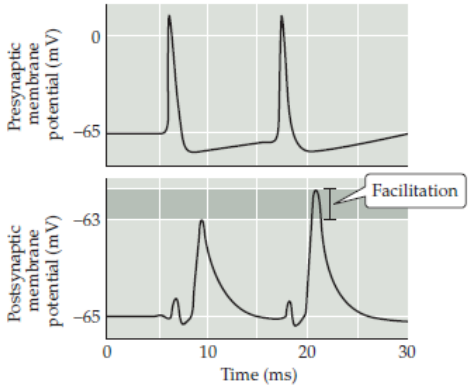
Plasticity is the ability of the brain to change and adapt to new information, synaptic plasticity controls how effectively two neurons can communicate with each other. The strength of communication between them is often likened to the volume of a conversation – some whisper while others shout. The volume setting of the synapse, or the synaptic strength, is not static and can change in both the short- and long-term. Synaptic plasticity refers to these changes in synaptic strength.

Only chemical synapses have plasticity, there are two types; short-term that last milliseconds or at most a few minutes and long-term that take anywhere from 30 minutes, to hours, days or years. Good thing to remember is that "cells that fire together, wire together" the brain automatically makes connections and that is what plasticity is.

Short term plasticity that facilitate signals result in an increased probability that the presynaptic terminals release transmitters in response to action potentials, this is done by an accumulation of Ca^{2+}. Basically, when a signal is transmitted it's easier to transmit the same signal again since the synapses "remember" the signal.
Short term plasticity that depress signals have a decreased probability of the presynaptic terminals releasing transmitters as a response to action potentials. The mechanism behind this is the depletion of vesicles and feedback.

SYNAPTIC FACILITATION

Synaptic facilitation is a rapid increase in synaptic strength that occurs when two or more action potentials invade the presynaptic terminal within a few milliseconds of each other. It is believed that synaptic facilitation occurs due to prolonged elevation of presynaptic calcium levels following synaptic activity. This is because although the entry of Ca^{2+} occurs within 1 to 2 milliseconds after an action potential invades the mechanism that returns Ca^{2+} to resting levels are much slower. Thus, when an action potential arrives close together in time, calcium builds up in the terminal and allows for more neurotransmitters to be released by a subsequent presynaptic action potential.

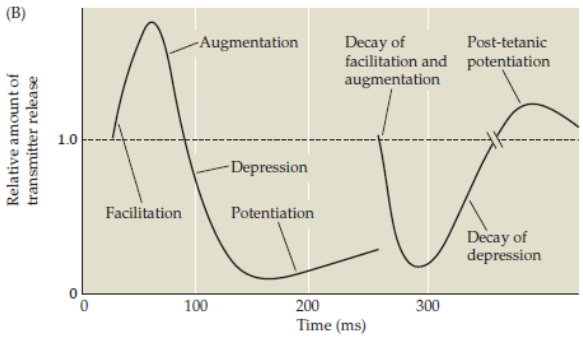


SYNAPTIC DEPRESSION

Synaptic depression causes neurotransmitter release to decline during sustained synaptic activity. The cause is believed to be a progressive depletion of a pool of synaptic vesicles that are available for release. With high sustained synaptic activity these pools decrease rapidly leading to a depression.

POTENTIATION AND AUGMENTATION

Potentiation and augmentation are elicited by repeated synaptic activity and serve to increase the amount of transmitter released from presynaptic vesicles. Both augmentation and potentiation enhance the ability of incoming Ca^{2+} to trigger fusion of synaptic vesicles with the plasma membrane, but the two processes work over different timescales.



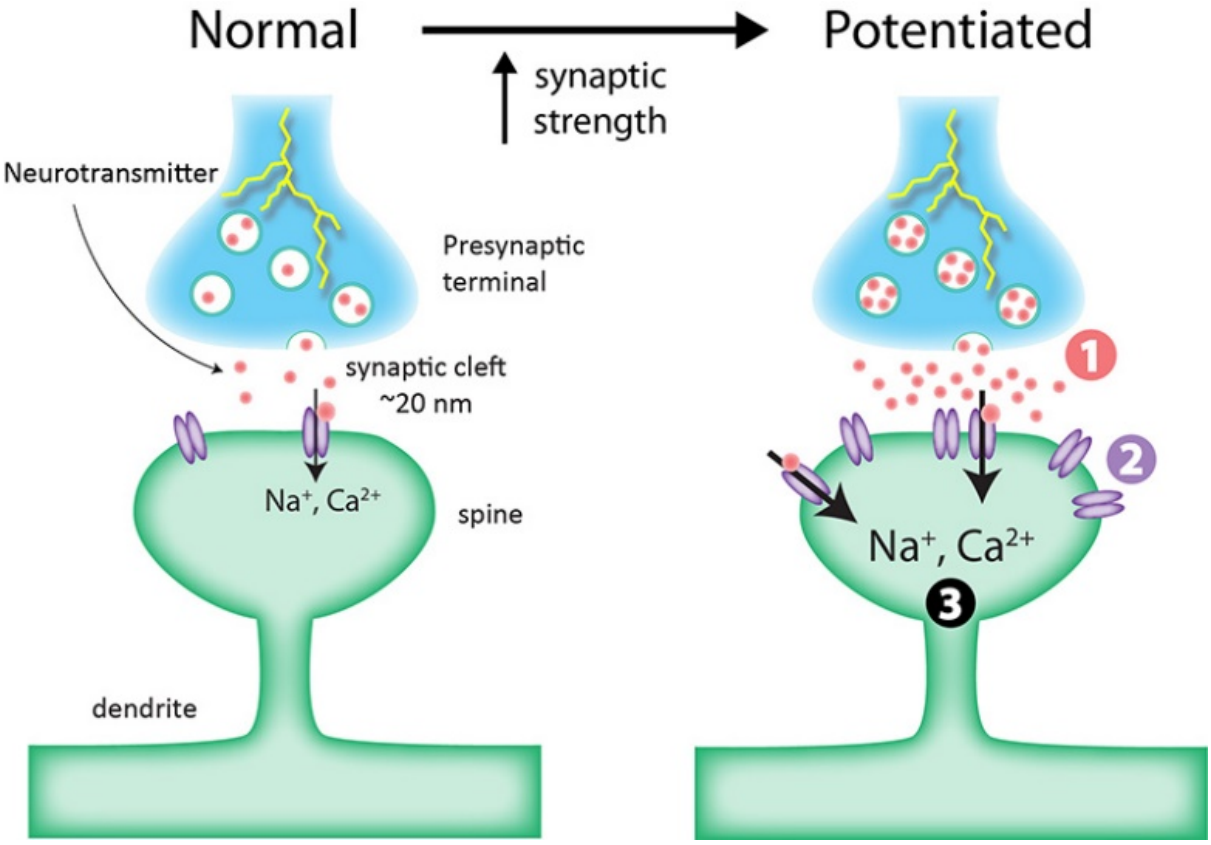
12.DESCRIBE THE MECHANISMS UNDERLYINGSYNAPTIC LONG-TERM PLASTICITY

Long-term plasticity the changes can last for hours, to days and months. There are changes in gene expression and in phosphorylation that yield changes in the synaptic strength for a long period of time. The genetic mechanism of long-term plasticity is made by the change in the synthesis of AMPA-receptors.

There are two types of long-term plasticity; depression and potentiation. The depression means that depress signals have a decreased probability of the presynaptic terminals releasing transmitters as a response to action potentials. The potentiation that facilitate signals result in an increased probability that the presynaptic terminals release transmitters in response to action potentials.

Long-term synaptic plasticity was first reported in 1973. Studying a pathway in the rabbit hippocampus, researchers discovered that rapidly and repeatedly activating the synapses made them stronger; the volume control was turned up and stayed that way. They called this long-lasting increase in synaptic strength **long-term potentiation**, or LTP. The reverse phenomenon, in which synapses become weaker for extended periods, also exists, and is called **long-term depression**, or LTD.

The strength of synapses can be increased or decreased, and whether or not and in which direction they change depends on their activity patterns. Very active synapses are likely to



become stronger (LTP), and those that are less active, or less effective at causing an action potential, tend to become weaker (LTD). Long-term synaptic plasticity forms the model for memory storage.

ORAL EXAM 2 - SENSORY FUNCTIONS

1.DESCRIBE THE DIFFERENT TYPES OF MECHANORECEPTORS IN THE SKIN AND EXPLAIN WHAT TWO-POINT DISCRIMINATION IS.

TABLE 9.2 ■ Afferent Systems and Their Properties

	Small receptive field		Large receptive field	
	Merkel	**Meissner**	**Pacinian**	**Ruffini**
Location	Tip of epidermal sweat ridges	Dermal papillae (close to skin surface)	Dermis and deeper tissues	Dermis
Axon diameter	7–11 μm	6–12 μm	6–12 μm	6–12 μm
Conduction velocity	40–65 m/s	35–70 m/s	35–70 m/s	35–70 m/s
Sensory function	Shape and texture perception	Motion detection; grip control	Perception of distant events through transmitted vibrations; tool use	Tangential force; hand shape; motion direction
Effective stimuli	Edges, points, corners, curvature	Skin motion	Vibration	Skin stretch
Receptive field area[a]	9 mm^2	22 mm^2	Entire finger or hand	60 mm^2
Innervation density (finger pad)	100/cm^2	150/cm^2	20/cm^2	10/cm^2
Spatial acuity	0.5 mm	3 mm	10+ mm	7+ mm
Response to sustained indentation	Sustained (slow adaptation)	None (rapid adaptation)	None (rapid adaptation)	Sustained (slow adaptation)
Frequency range	0–100 Hz	1–300 Hz	5–1000 Hz	0–? Hz
Peak sensitivity	5 Hz	50 Hz	200 Hz	0.5 Hz
Threshold for rapid indentation or vibration:				
Best	8 μm	2 μm	0.01μm	40 μm
Mean	30 μm	6 μm	0.08 μm	300 μm

[a]Receptive field areas as measured with rapid 0.5-mm indentation.

(After K. O. Johnson, 2002.)

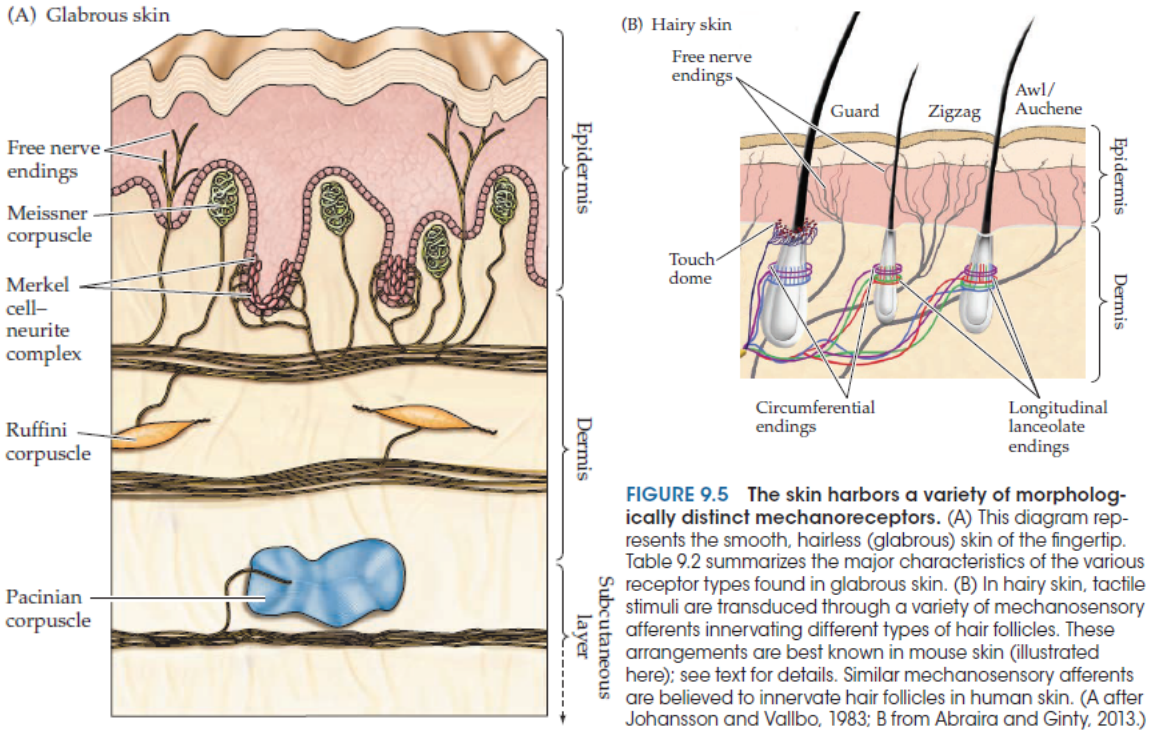
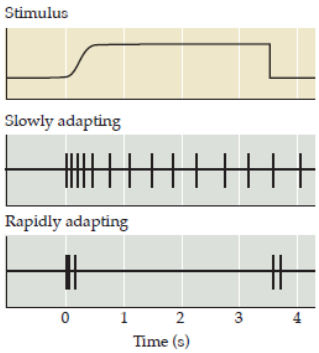


FIGURE 9.5 The skin harbors a variety of morphologically distinct mechanoreceptors. (A) This diagram represents the smooth, hairless (glabrous) skin of the fingertip. Table 9.2 summarizes the major characteristics of the various receptor types found in glabrous skin. (B) In hairy skin, tactile stimuli are transduced through a variety of mechanosensory afferents innervating different types of hair follicles. These arrangements are best known in mouse skin (illustrated here); see text for details. Similar mechanosensory afferents are believed to innervate hair follicles in human skin. (A after Johansson and Vallbo, 1983; B from Abraira and Ginty, 2013.)

SLOWLY AND RAPIDLY ADAPTING MECHANORECEPTORS PROVIDE DIFFERENT INFORMATION

Slowly adapting fibers mean that they continue to respond to stimulus whereas rapidly adapting receptors respond only at the onset and often the offset of stimulation.



Slowly adapting fibers are suited to provide information about spatial attributes of the stimulus, such as shape or size, while rapidly adapting receptors are effective in conveying information about changes in ongoing stimulus such as those produced by stimulus movement (the dynamic qualities of a stimulus).

MERKEL CELL AFFERENTS

Merkel cell afferents are slowly adapting fibers that account for about 25% of the mechanosensory afferents in the hand. They are especially enriched in the fingertips and are the only afferents that sample information from receptor cells located in the epidermis.

Merkel cell afferents have the highest spatial resolution of all the sensory afferents (they can resolve spatial details of 0.5 mm). They are also sensitive to points, edges and curvature which makes them ideally suited for processing information about shape or texture.

MEISSNER AFFERENTS

Meissner afferents are rapidly adapting fibers that innervate the skin even more densely than Merkel afferents, accounting for about 40% of the mechanosensory innervation of the human hand. Meissner corpuscles lie in the tips of the dermal papillae adjacent to the primary ridges and closest to the skin surface. They are formed by a connective tissue capsule that contains a set of flattened lamellar cells derived from Schwann cells and nerve terminals that are suspended by collagen fibers. The capsule contains two to six afferent nerve fibers that terminate between and around the lamellar cells which contribute to the transient response to somatic stimulation.

With indentation of the skin, the dynamic tension transduced by the collagen fibers provide the transient mechanical force that deforms the corpuscle and triggers generator potentials that may induce a volley of action potentials in the afferent fibers. When the stimulus is removed, the indented skin relaxes, and the corpuscle returns to its resting configuration which generates another burst of action potentials. Meissner afferents therefore display characteristic rapidly adapting on-off responses.

Meissner afferents are more than four times as sensitive to skin deformation as Merkel afferents; however, their receptive fields are larger than those of Merkel afferents and therefor they transmit signals with reduced spatial resolution. Meissner corpuscles are particularly efficient in transducing information about the relatively low-frequency vibrations (3-40 Hz) that occur when textured objects are moved across the skin. Several lines of evidence suggest that information conveyed by Meissner afferents is responsible for detecting slippage between the skin and an object held in the hand. Essential feedback information for the efficient control of grip.

PACINIAN AFFERENTS

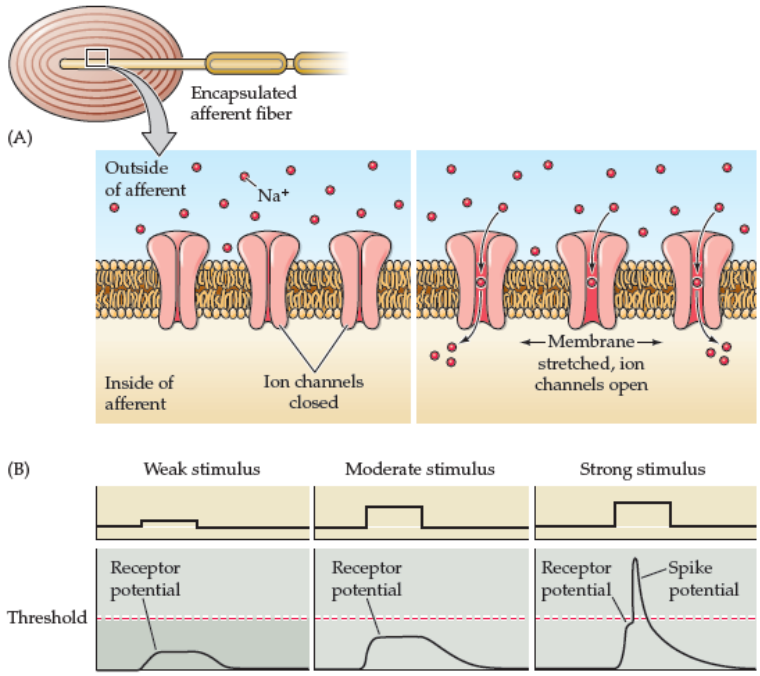


FIGURE 9.2 Transduction in a mechanosensory afferent. The process is illustrated here for a Pacinian corpuscle. (A) Deformation of the capsule leads to a stretching of the membrane of the afferent fiber, increasing the probability of opening mechanotransduction channels in the membrane. (B) Opening of these cation channels leads to depolarization of the afferent fiber (receptor potential). If the afferent is sufficiently depolarized, an action potential is generated and propagates to central targets.

Pacinian afferents are rapidly adapting fibers that make up 10-15% of the mechanosensory innervation of the hand. Pacinian corpuscles are located deep in the dermis or in the subcutaneous tissue; their appearance resembles that of a small onion with concentric layers surrounding a single afferent fiber. The laminar capsule acts as a filter which only allows transient disturbances at high frequencies (250-350 Hz) to activate the nerve endings.

Pacinian corpuscles adapt more rapidly than Meissner corpuscles and have a lower response threshold. The most sensitive Pacinian afferents generate action potentials for displacements of the skin as small as 10 nanometers. Because they are so sensitive the receptive fields of Pacinian afferents are often large, and their boundaries are hard to define. The properties of Pacinian afferents make them well suited to detect vibrations transmitted through objects that contact the hand or are being grasped in the hand, especially when making or breaking contact. These properties are important for the skilled used of tools (e.g., writing or using a wrench).

RUFFINI AFFERENTS

Ruffini afferents are slowly adapting fibers that make up about 20% of the mechanoreceptors in the human hand, they are the least understood of the cutaneous mechanoreceptors. Ruffini endings are elongated, spindle-shaped, capsular specializations located deep in the skin, as well as in ligaments and tendons. The long axis of the corpuscle is usually oriented parallel to the stretch lines in skin which makes Ruffini corpuscles particularly sensitive to the cutaneous stretching produced by digit or limb movements.

While there are still some questions as to what their function is, they are thought to be especially responsive to skin stretches, such as those that occur during the movement of the fingers. It is therefor believed that information supplied by the Ruffini afferents contribute, along with the muscle receptors, to provide an accurate representation of finger position and the conformation of the hand,

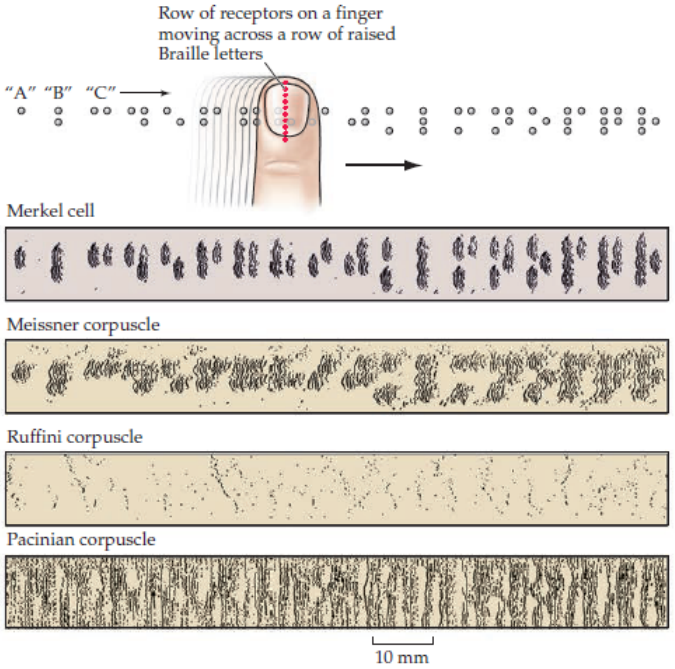
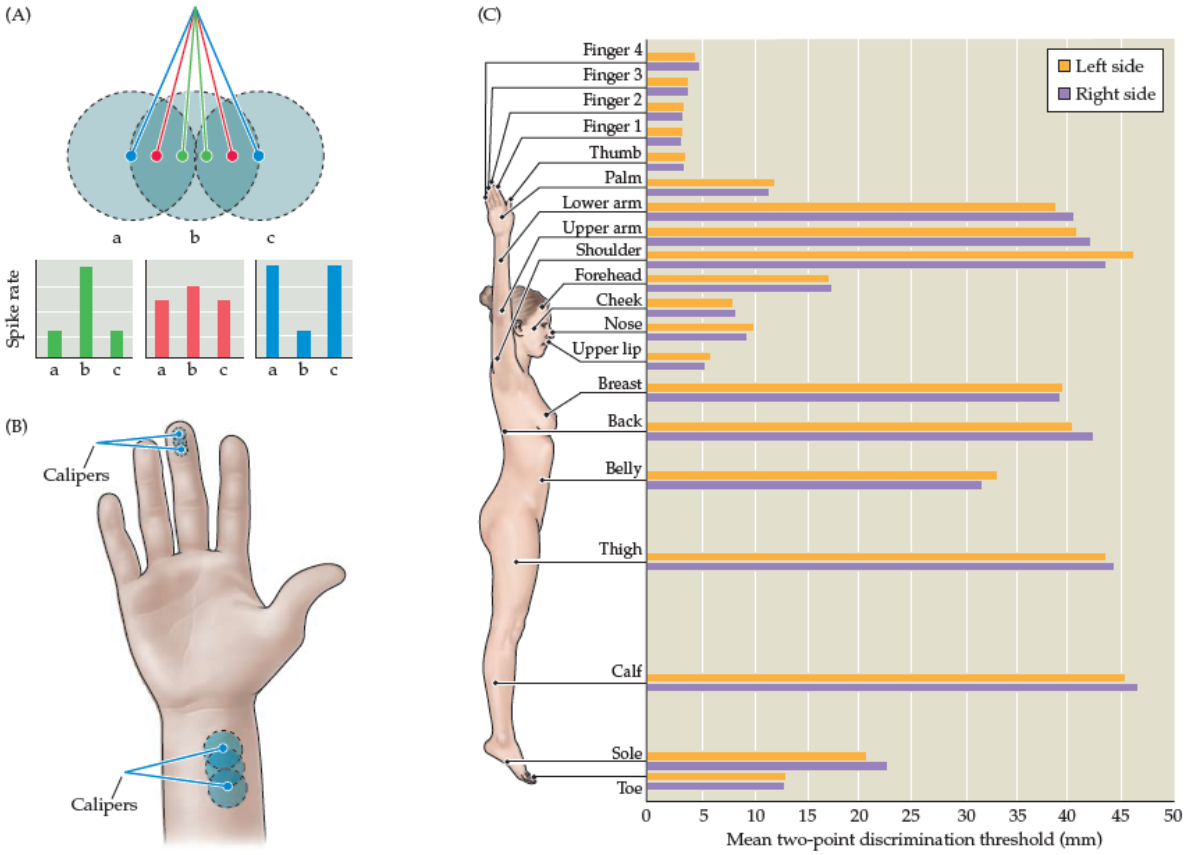


FIGURE 9.6 Simulation of activity patterns in different mechanosensory afferents in the fingertip. Each dot in the response records represents an action potential recorded from a single mechanosensory afferent fiber innervating the human finger as it moves across a row of Braille type. A horizontal line of dots in the raster plot represents the pattern of activity in the afferent as a result of moving the pattern from left to right across the finger. The position of the pattern (relative to the tip of the finger) was then displaced by a small distance, and the pattern was once again moved across the finger. Repeating this pattern multiple times produces a record that simulates the pattern of activity that would arise in a population of afferents whose receptive fields lie along a line in the fingertip (red dots). Only slowly adapting Merkel cell afferents (top panel) provide a high-fidelity representation of the Braille pattern—that is, the individual Braille dots can be distinguished only in the pattern of Merkel afferent neural activity. (After Phillips et al., 1990.)

TWO-POINT DISCRIMINATION



Two-point discrimination is the ability to discern that two nearby objects touching the skin are truly two distinct points and not one. 2PD is assumed to reflect how finely innervated an area of skin is, normally a person should recognize two points separated by 2-8 mm on fingertips and 8-12 cm on the palms for example.

2.DESCRIBE THE CENTRAL PATHWAYS CONVEYING TACTILE INFORMATION (TOUCH, VIBRATION, PROPRIOCEPTION).

We are constantly subjects to different kinds of stimuli from our environment as well as internally. Our brain needs to sort through and prioritize among these stimuli's. The information from ex touch and vibration are transformed to electrical signals and are sent via the spinal cord to the cortex where the brain decides how we should act on a different stimulus. The transformation to an electrical signal is called transduction.

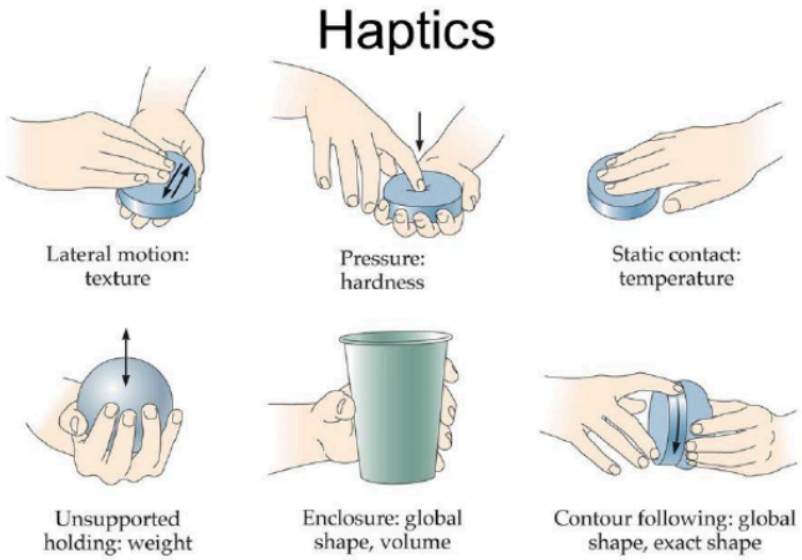
TOUCH AND VIBRATION

Touch are in the skin taken up by the type of sensory receptors that are called encapsulated endings and are mechanoreceptors.

There are different types of touch:

THE PASSIVE TACTILE PERCEPTION – when an object is pressed against the skin

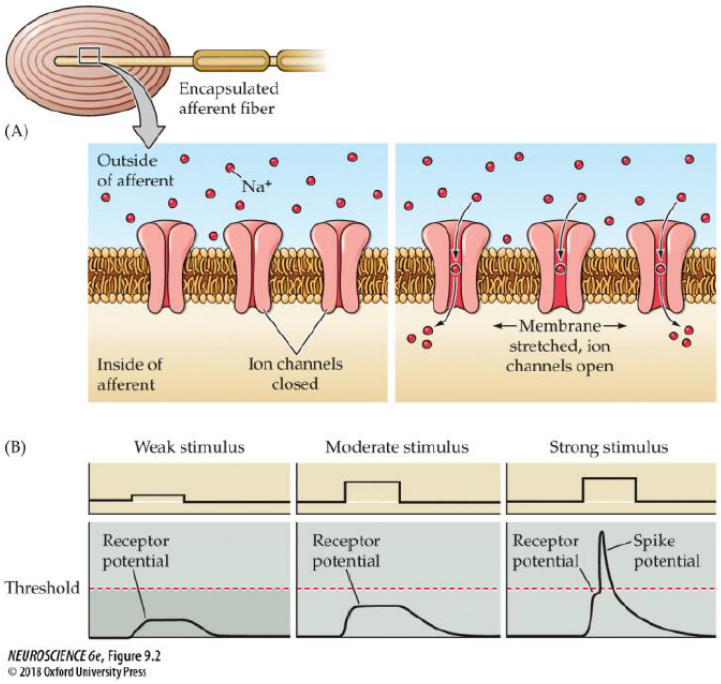
THE ACTIVE TOUCHING OR HAPTICS – when one investigates something with their fingers or press your fingers against something. The different types are shown in the picture.



When an encapsulated afferent fibre in for example our finger register touch the channels for Na^+ open and leads to a receptor potential[2] and if the stimulus is strong enough a action potential is generated.

[2] Receptor potential – the respons that the receptor gives, the cell responds to the receptors respons by depolarisation or hyperrepolarisation

FIGURE 9.2 Transduction in a mechanosensory afferent

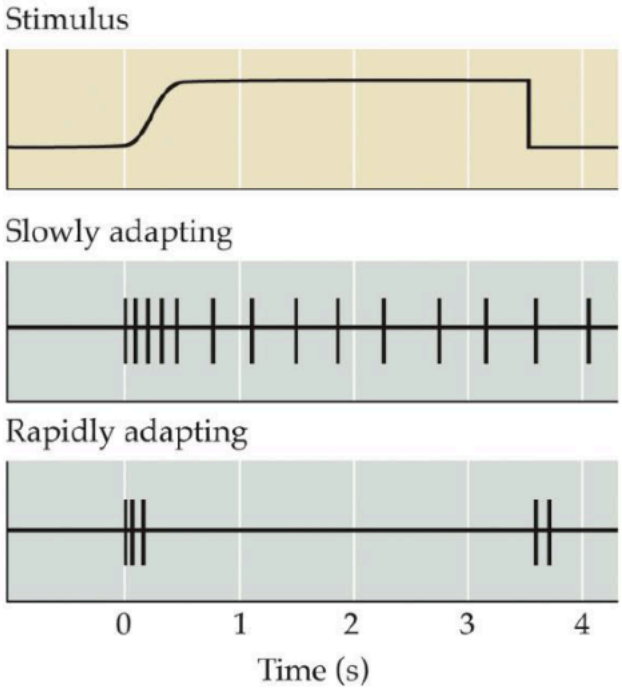


When a neuron/cell with a mechanoreceptor is exposed to a stimulus over a period of time it can adapt. There are two types of adaptation; slow adaption (SA) and rapid adaption (RA).

SLOW ADAPTION - The cell is constantly firing whilst the stimuli is present. It provides information to the CNS about spatial features ex size and shape, this is continuous during the whole stimuli. Called tonic receptors.

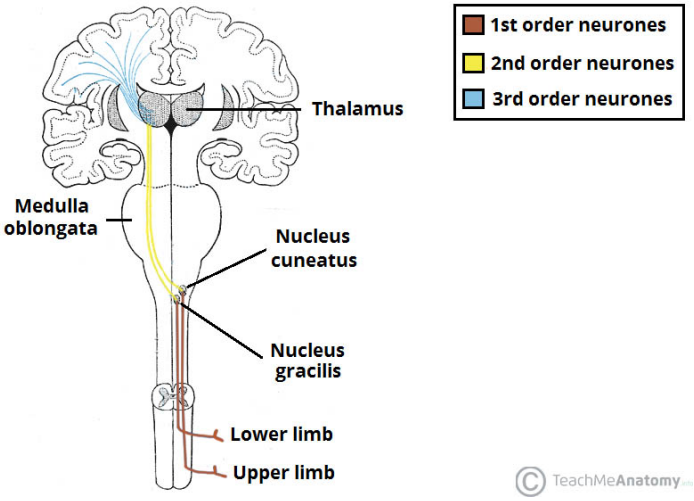
FAST ADAPTION - at the beginning of the stimuli a burst of signals are sent, then it stops firing if the stimuli is constant, allows to ignore irrelevant information and to inform about changes in the stimuli.

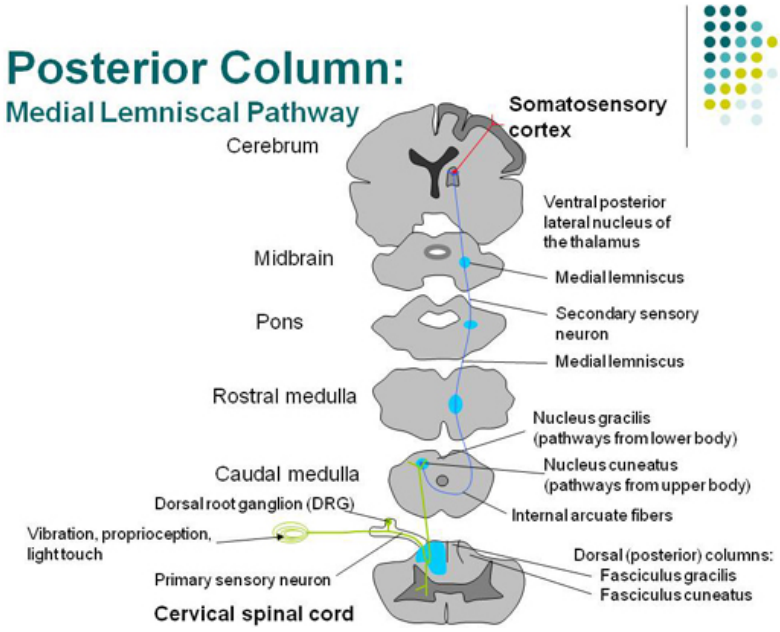
Note: (this might not be relevant to the question but is good to know) The receptors have a receptive field, this field can differ from receptor to receptor and depends on the branching of the receptor. This means that a receptor only registers the touch of an area and not the surrounding area.



Note: (this might not be relevant to the question but is good to know) convergence – when several neuron (ex 1:st order) are connected to the same neuron (2:nd order neuron). This makes the receptor field becomes bigger then the secondary neuron.

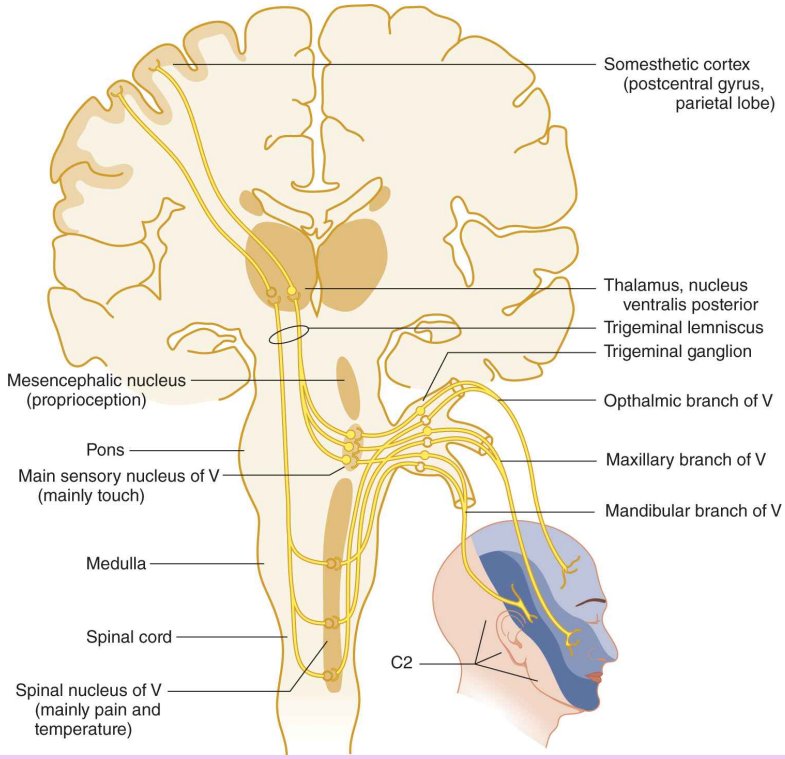
A signal from touch and a signal from temperature and pain is not travelling the same way from the visceral parts of the body to the brain. There's also a difference in the pathways depending on from where the signal comes from; for the posterior part of the head and the rest of the body there's one way and from the anterior part of the head (face) there's another pathway.
The central pathway for the posterior part of the head and the rest of the body below the head are called **DORSAL COLUMN – MEDIAL LEMNISCAL PATHWAY.** Here the signal goes through the axon to the dorsal horn to the medulla in the spinal cord. Here a cutover from the first order neuron to the second order neuron is made, this cutover takes place in a nucleus. For the **lower body** it takes place in the **gracile nucleus** and for the **upper body** in the **cuneate nucleus**.
The second order neurons axon is now crossing the midline, this is called **DECUSSATE**. It then travels up to the thalamus and the VPL (venteral posterior lateral thalamus) where a cutover to a third order neuron is made. The third order neuron axon goes to the somatosensory cortex (S1) where the signal is encoded.
Summary: 1:st order axon to dorsal horn → gracile nucleus/cuteate nucleus → 2:nd order axon decussate → VPL thalamus → 3:rd order axon to somatosensory cortex





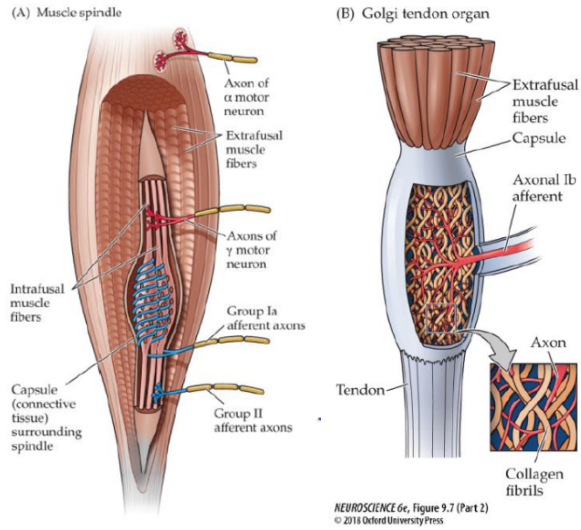
CENTRAL PATHWAY – ANTERIOR PART OF THE HEAD (FACE)

The sensory signal for the face is mainly sent from the n. trigeminus. It goes to the ganglion trigeminus to the principal nucleus of trigeminal complex where the cutover to the 2:nd order neuron. Then the decussate (crossing) is made before the axon goes to medial lemniscus and up to the thalamus and more exactly the VPM thalamus (ventral posterior medial thalamus) where the cutover to the 3:rd neuron to the somatosensory cortex.



PROPRIOCEPTION

Proprioception is the perception/awareness of motion and sense of static position. There are three types of proprioceptors: muscle spindle, Golgi tendon organ and joint receptor.



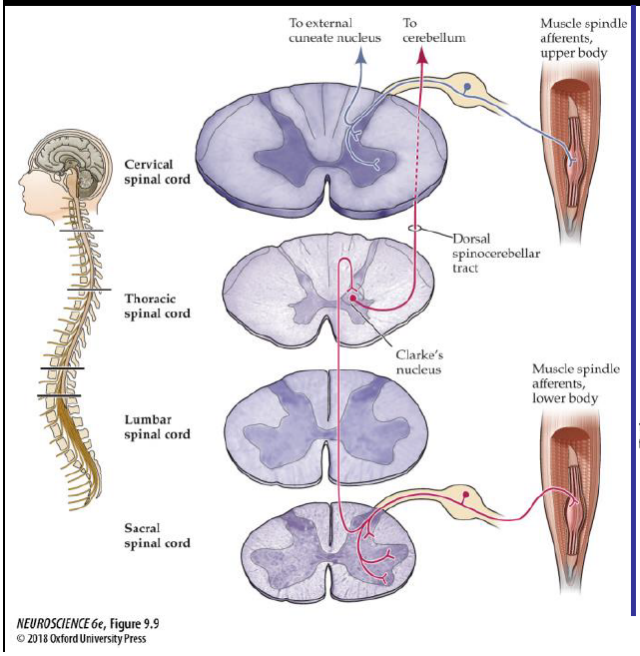
Muscle spindle exist in skeletal muscle and inform about the differences in the length of the muscle. There are about 4-8 intrafusal fibres with a capsule of connective tissue, around the intrafusal fibres there are nerve fibres (type Ia) wrapped around them, these are rapid adapting response to limb dynamics ie they send signals when you move. A bit further down the type II afferent fibres send slow adapting response, they send information about limb static position ie they send information about the position of the limb.

The Golgi tendon organ are present in the tendon and informs about the changes in the muscle tension and has primary (1b) nerve endings.

The first order neuron goes through the ganglion to the dorsal horn, here it splits up. The first order neurons have more than one synapses for reflexes and some parts goes upwards through the brain. In the thoracic region (for the lower body) and in the clarke's nucleus a cutover to the second order neuron and the axon goes via the tractus spinocerebellum dorsalis in the white matter to the cerebellum and some to the somatosensory cortex (it does not do a crossing). The afferents from the upper body goes to the dorsal horn in the cervical spinal cord, there it splits to both synapses for reflexes and some goes to the external cuneate nucleus.

The proprioceptive information from the face goes to the mesencephalic nucleus of the trigeminal nerve.

FIGURE 9.9 Proprioceptive pathways for the upper and lower body



NEUROSCIENCE 6e, Figure 9.9
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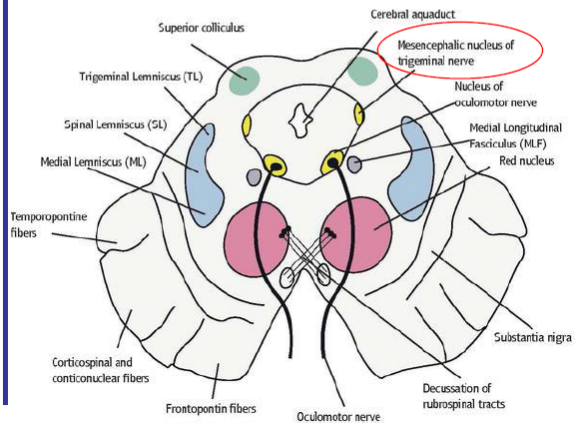
Proprioceptive information from the face: the mesencephalic trigeminal nucleus in the midbrain



3.DESCRIBE THE CENTRAL PATHWAYS CONVEYING PAIN AND TEMPERATURE.

PAIN AND NOCICEPTORS

Pain is the unpleasant sensory and emotional experience associated with stimuli that cause tissue damage. The perception of injurious stimuli, called nociception, depends on specifically dedicated receptors and pathways and not excessive stimuli of the same receptors that generate somatic sensations. The central distribution of nociceptive information is correspondingly complex, involving multiple areas in the brainstem, thalamus and forebrain.

The relatively unspecialized nerve cell endings that initiate the sensation of pain are called nociceptors. Like other cutaneous and subcutaneous receptors, they transduce a variety of stimulus into receptor potentials which in turn trigger afferent action potentials. They arise, like other somatosensory receptors, from cell bodies in dorsal root ganglia that sends one axonal process to the periphery and the other into the spinal cord or brainstem.

Because peripheral nociceptive axons terminate in morphologically unspecialized “free nerve endings” it’s conventional to categorize nociceptors according to the properties of the axons associated with them. Somatosensory receptors responsible for the perception of innocuous mechanical stimuli are associated with myelinated axons that have relatively rapid conduction velocities. The axons associated with nociceptors, in contrast, conduct relatively slowly; being only slightly myelinated or more commonly unmyelinated. Axons conveying information about pain fall into either the Aδ group of myelinated axons (with speeds of 5 to 30 m/s) or the C fiber group of unmyelinated axons (with speeds of less than 2 m/s).

Two categories of pain perception have been described: a sharp **first pain** and a more delayed, diffuse and longer lasting **second pain**. Aδ fibers are responsible for the first pain and C fibers for second pain. Aδ nociceptors fall into two main classes: type I Aδ fibers respond to dangerously intense mechanical and chemical stimuli but have a relatively high heat threshold, while type II Aδ fibers have complementary sensitivities – that is, much lower threshold for heat but very high threshold for mechanical stimulation. The Aδ system therefore has specialized pathways for the transmission of heat and mechanical nociceptive stimulation. Most of the C fiber nociceptors respond to all forms of nociceptive stimuli – thermal, mechanical, and chemical – and are therefor said to be polymodal. There are subtypes however that respond better to certain stimuli, like heat for example.

CENTRAL PAIN PATHWAY

The pathways responsible for pain originate with other sensory neurons in dorsal root ganglia, and like other sensory nerve cells, the central axons of nociceptive nerve cells enter the spinal cord via dorsal roots. When these centrally projecting axons reach the dorsal horn of the spinal cord, they branch into ascending and descending collaterals, forming the **dorsolateral tract of Lissauer**.

Axons in Lissauer’s tract typically run up and down for one or two spinal cord segments before they penetrate the gray matter of the dorsal horn. Once within the dorsal horn, the axons give off branches that contact second-order neurons located in Rexed’s laminae I, II,

and V (Rexed's laminae are the descriptive divisions of the spinal gray matter in cross section). Laminae I and V contains projection neurons whose axons travel to the brainstem and thalamic targets. While there are interneurons in all laminae of the spinal cord, they are especially abundant in lamina II. These afferent terminations are organized in a lamina specific fashion; C fibers terminate exclusively in laminae I and V and Aδ fibers in laminae I and V. Lamina V receives input from nociceptive and non-nociceptive afferents and are called wide-dynamic range neurons. Some of them receive visceral input making them a likely substrate for referred pain (i.e. pain that arises from damage to visceral organ but is misperceived as coming from a somatic location).

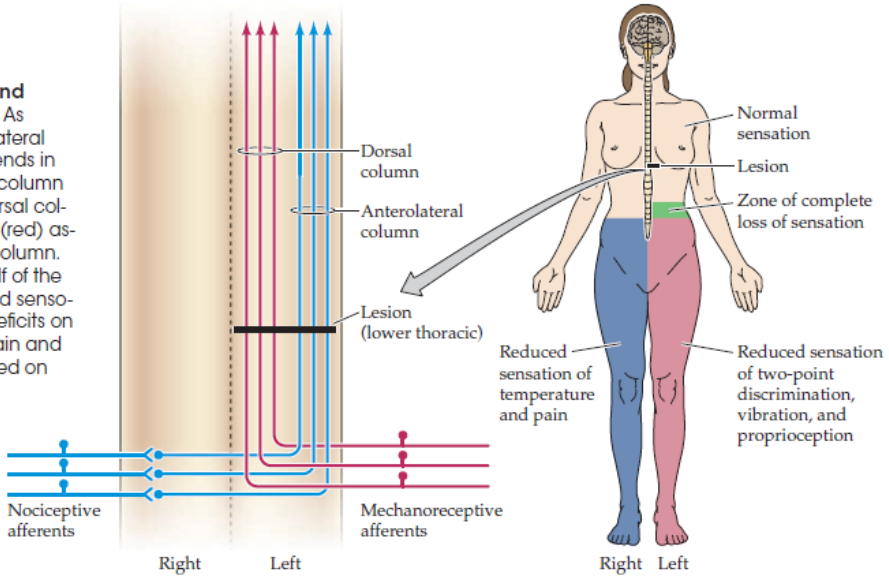
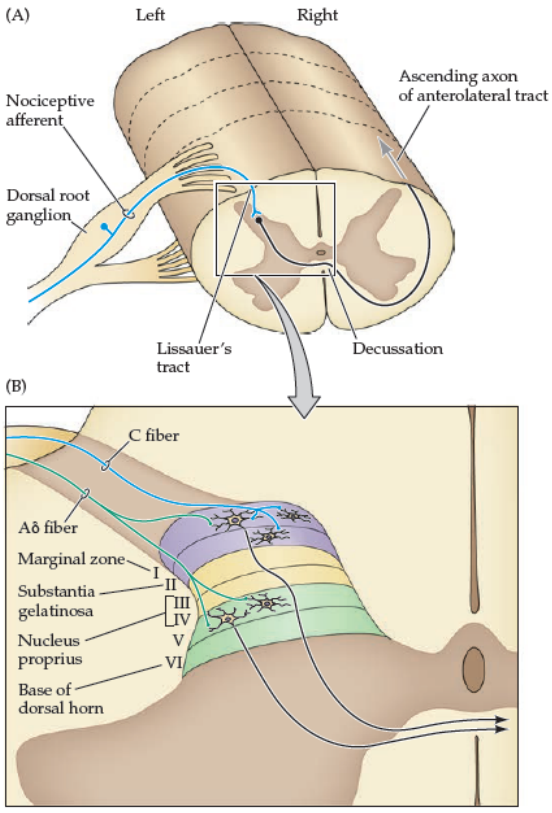


FIGURE 10.4 Nociceptive and mechanosensory pathways. As diagrammed here, the anterolateral system (blue) crosses and ascends in the contralateral anterolateral column of the spinal cord, while the dorsal column–medial leminiscal system (red) ascends in the ipsilateral dorsal column. A lesion restricted to the left half of the spinal cord results in dissociated sensory loss and mechanosensory deficits on the left half of the body, with pain and temperature deficits experienced on the right.

The axons of the second order neurons in laminae I and V of the dorsal horn of the spinal cord cross the midline and ascend to the brainstem and thalamus in the anterolateral (also called ventrolateral) quadrant of the contralateral half of the spinal cord. For this reason, the neural pathway that conveys pain and temperature information to higher centers is often referred to as the **anterolateral system**, to distinguish it from the dorsal column-medial lemniscal system that conveys mechanosensory information.



Axons conveying information for the anterolateral system and the dorsal column-medial lemniscal system travel in different parts of the spinal cord white matter which provides a clinically relevant sign that is useful for defining the locus of a spinal cord lesion.

The anterolateral system will travel up to the ventral posterior nuclei of the thalamus where it synapses with third order neurons that goes to the somatosensory cortex where the

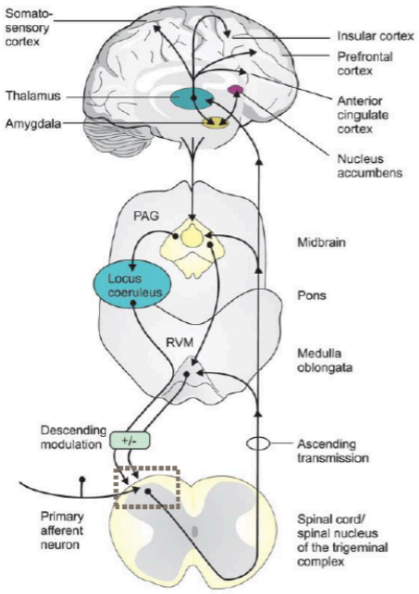
neuron is translated and perceived as

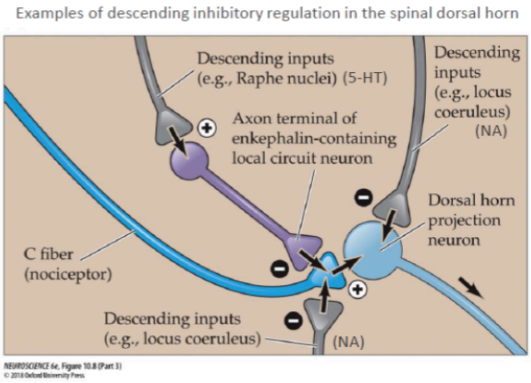
Face (kopierad från facit)
The information of pain and temperature from the face comes from first order neurons, which are located in the trigeminal ganglion and ganglia associated with cranial nerves 7,9 and 10.

1. The first order neurons enter the pons and they descend to the medulla, so forming the spinal trigeminal tract
2. They terminate in two subdivision of the spinal trigeminal nucleus.
3. Axons from the second order neurons from the spinal trigeminal nucleus cross the midline and terminate in the brainstem and thalamus.
4. In the thalamus they will do synapses with third order neurons in the ventral posterior nucleus.
5. The axons front he third order neurons send their axons to the primary somatosensory cortex.pain.

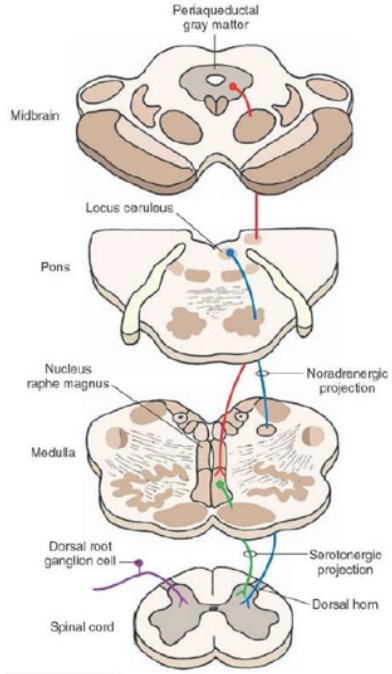
4.DISCUSS PAIN MODULATION FROM DESCENDING PATHWAYS AND ITS PHYSIOLOGICAL RELEVANCE.

When pain signal reaches cortical structures, the signals are sent to PAG, RVM, Locus coeruleus and nucleus raphe magnus. These structures are involved and important for the modulation of signals, they modulate the sensory input from the primary afferent fibres and projection neurons in the dorsal horn of the spinal cord. There are both an inhibitory and a facilizing modulation pathways, when it comes to the inhibitory pathways there are several. Example on these are the serotonergic-noradrenergic and opioidergic pathways.





THE DIFFERENT CORTICAL STRUCTURES AND PATHWAYS



SEROTONERGIC PROJECTION

The neurons located in PAG (periaqueductal grey matter) project to the serotonergic neurons in the nucleus raphe magnus which is the main origin of the serotonergic system. The serotonergic neuron project from nucleus raphe magnus to the dorsal horn. The serotonergic axons descend to all levels of the spinal cord.

NORADRENERGIC PATHWAY

The noradrenergic pathway originates from the locus coeruleus and projects to the dorsal horn. The noradrenergic axons descend to all levels of the spinal cord.

OPIOIDS

The body has their own opioids, these are strongly connected to GABA since they can inactivate GABA. In RVM there are GABAergic interneurons that inhibits descending signals from PAG to RVM, these are called off-cells. The opioids inhibit these off-cells in RVM. These opioids can also inhibit the facilitating “on-cells” that increase the nociception signalling. Example on these opioids are endorphins, enkephalins, morphine.

Example: if we have an interneuron that contains enkephalin it will make it harder for the neuron to release neurotransmitters. The enkephalin can also exist in postsynaptic and make it harder for the signal to continue.

5.DESCRIBE THE ANATOMY OF THE EYE.

The eye is a fluid filled sphere enclosed by three layers of tissue. The innermost layer of the eye, the **retina**, contains neurons that are sensitive to light and transmit visual signals to central targets. The immediately adjacent layer of tissue includes three distinct, but continuous structures collectively referred to as the **uveal tract**. The largest component of the uveal tract is the choroid; which is composed of a rich capillary bed that nourishes the retinal photoreceptors. Extending from the choroid near the front of the eye is the **ciliary body**, a ring of tissue that encircles the lens and consists of two parts: a muscular that adjusts refractive power of the lens and a vascular component that produces the liquid that fills the front of the eye. The most anterior component of the uveal tract is the iris, the coloured portion of the eye that can be seen through the cornea. It contains two set of muscles that allow the size of the pupil to be adjusted under neural control. The sclera forms the outermost tissue layer of the eye and is composed of a tough, white, fibrous tissue. At the front of the eye however this opaque outer layer is transformed into the **cornea**, a highly specialized transparent tissue that permits light rays to enter the eye.

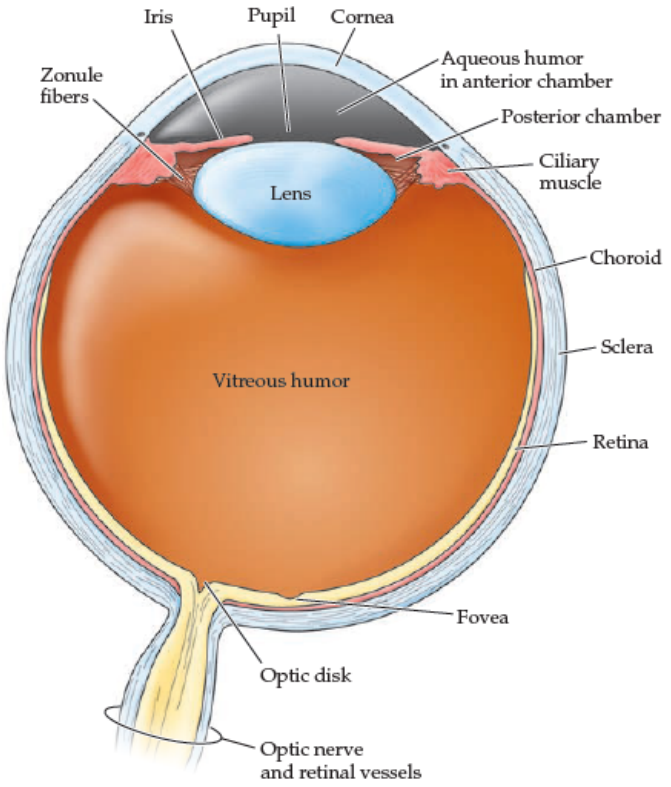


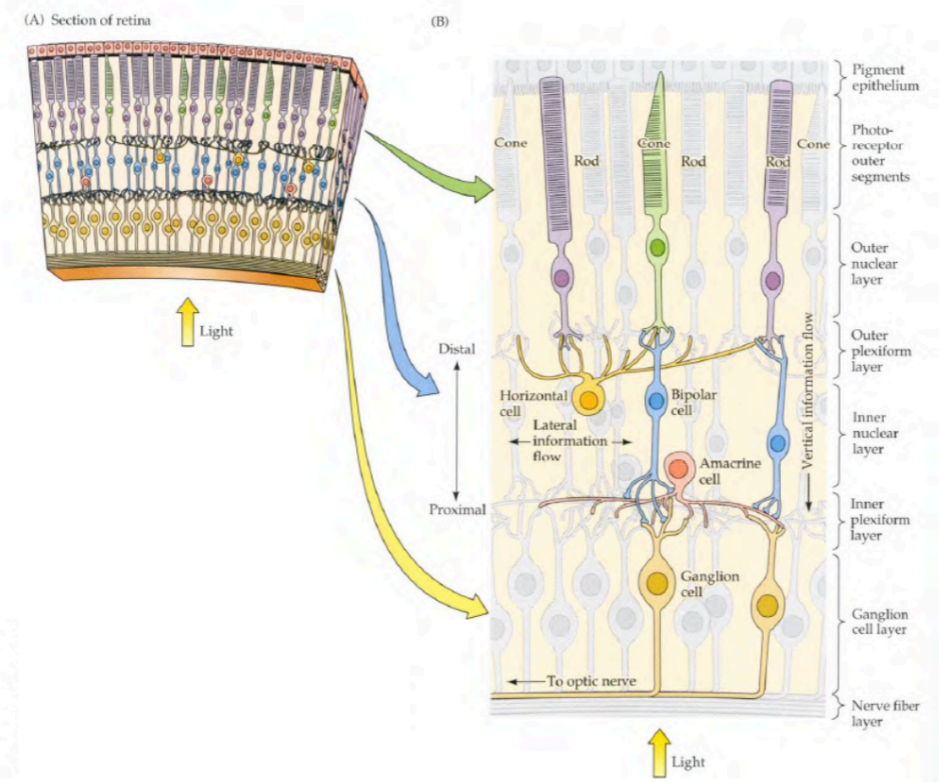
FIGURE 11.1 Anatomy of the human eye.

Once beyond the cornea, light rays pass through two distinct fluid environments before striking the retina. A clear, watery liquid that supplies nutrients to these structured are produced by the ciliary processes in the **posterior chamber** (the region between the lens and iris) and flows into the **anterior chamber** through the pupil. The amount of fluid produced is substantial, the entire volume of fluid in the anterior chamber is replaced about 12 times a day. Insufficient drainage causes glaucoma which is a disorder in which high levels of intraocular pressure reduce the blood supply to the eye and eventually damage the retinal neurons.

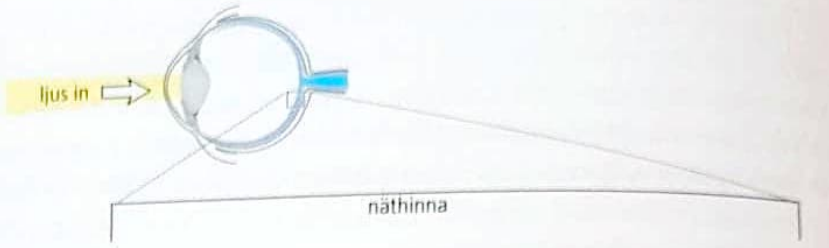
The space between the back of the lens and the surface of the retina is filled with a thick, gelatinous substance called the **vitreous humor**, which accounts for about 80% of the volume of the eye. In addition to maintaining the shape of the eye, the vitreous humor contains phagocytic cells that remove blood and other debris that might otherwise interfere with light transmission. The housekeeping abilities of the vitreous humor are limited, however, as many middle aged and elderly individuals with vitreal “floaters” will attest. Floaters are collections of debris too large for phagocytic consumption that therefore remain, casting annoying shadows on the retina.

6.DESCRIBE THE HISTOLOGY OF THE RETINA WITH ITS DIFFERENT CELL TYPES AND EXPLAIN HOW RODS AND CONES ARE DISTRIBUTED IN DIFFERENT PARTS OF THE RETINA.

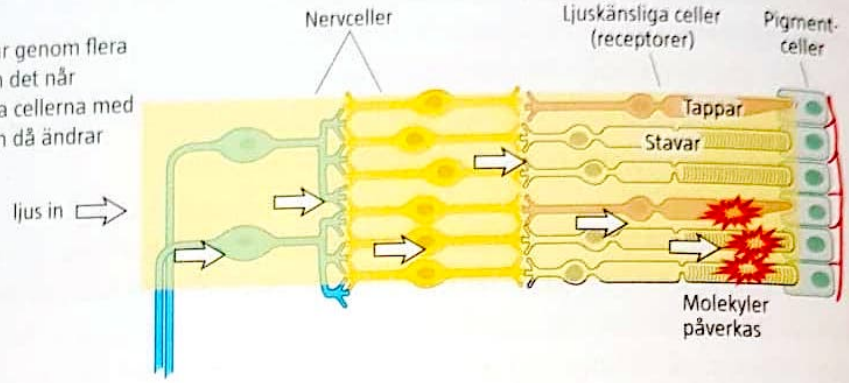
In the retina there are 5 types of neurons (cells); ganglion cells, bipolar cells, horizontal cells, amacrine cells, photoreceptors (rods and cones) behind that the retina also have pigment epithelial cells (most posterior/distal).
Light comes into the eye in the following order: Cornea → aqueous humor → lens → vitreous humor → retina
In the retina the light goes through the cells in the following order; ganglion cells → bipolar cells → horizontal cells → photoreceptors → pigment epithelial cells



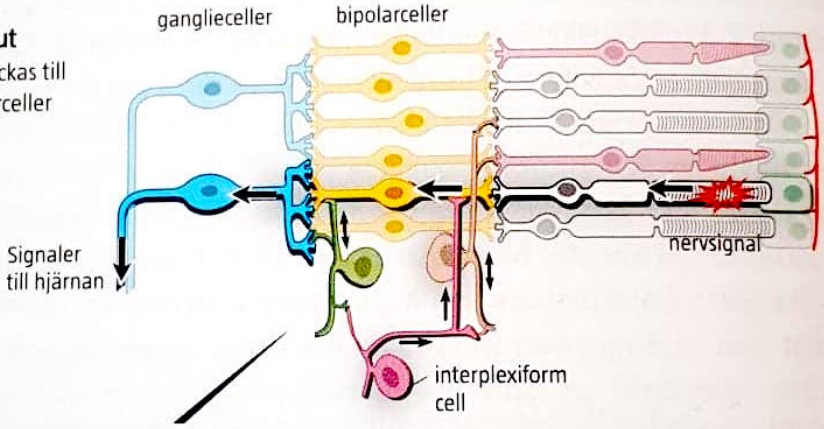
The signal is generated from the rods and cones. From the cones the signal is sent via the bipolar cells to the ganglion cells and the to the brain, this is the simpler signalling way and the signal is processed in every step.
The rods signalling way is longer, they send their signal to a special type of bipolar cell that sends the information to the amacrine cells that sends it to the ganglion cell and then to the brain.



1. Ljus in
Ljuset passerar genom flera cellager innan det når de ljuskänsliga cellerna med molekyler som då ändrar form.

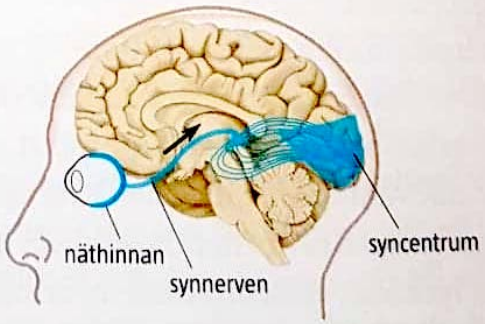


2. Nervsignaler ut
Nervsignalerna skickas till hjärnan via bipolarceller och ganglieceller.



Bearbetning
Signalerna bearbetas vid övergången mellan de olika cellerna och signalerna påverkas på många olika vis.

3. Till hjärnan
Slutresultatet blir att informationen skickas in i hjärnan i höggradigt kodad form.



Figur 4.2 *Kopplingsschemat i näthinnan*

GANGLION CELLS

Each ganglion cell responds to stimulation of a small circular patch of the retina, the receptor fields are circular. They have an organisation where the centre can be off or on and also a surrounding part. When the centre is activated (+) is the surrounding inactivated (-) and vice versa, the surrounding and centre is antagonists to each other. The ganglion cells notice contrasts and the difference in contrast.
The ganglion cells have axons to the optic nerve as well as synapses with the bipolar cells and amacrine cells. The ganglion cells take input from the bipolar cells and the action potential travels through the axons to the optic nerve. The ganglion cells axon will bundle together on its way to the optic nerve and form the optic disk.

AMACRINE CELLS

There are different classes of amacrine cells, the most “common” or the one we know most about transmission information from the special bipolar cells that the rods signal to and through to the ganglion cells.

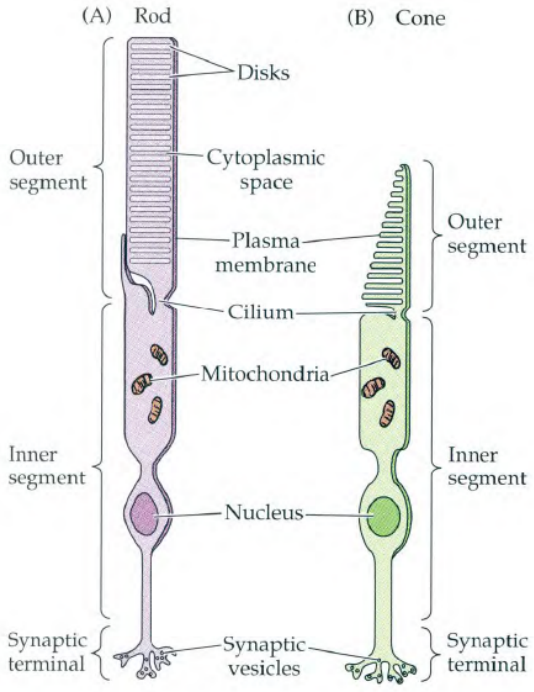
BIPOLAR CELLS

The bipolar cells can both hyperpolarize and depolarize depending on the input they get from the rods and cones. They send the signal to amacrine cells (rods) and ganglion cells (cones).

HORIZONTAL CELLS

In the mammals the photoreceptors have little to non-contact with each other, but via the horizontal cells they can affect each other. Generally, this contact is inhibitory, they go laterally. This is important to give acuity to the signal, so it enables us to be sensitive to contrast.

PHOTORECEPTORS



The photoreceptors are nerve cells with a fine strand of hair a so-called cilium. The cilium has been transformed so that it has an outer surrounded with plasma membrane. The rod and cones have three regions; an outer segment, inner segment and synaptic region.

The outer segment is as mentioned above the old cilium, the outer segments differ from rods and cones. In the rods there are discs separated by cytoplasmic space, they don't touch each other or the outer membrane. The discs are important for the transduction of light and nerve impulses in the rods. For the cones there are one membrane with spaces in between that the same function as in the rods. They do differ in how they do to start a nerve impulse. The inner segment is the same for both rods and cones, it has mitochondria's and nucleus.

The cones is important for the colour vision (during the day, we don't see colours during the night) and register the colours red, blue and green that can be combined to other colours. There are around 4 million cones and they have a low amplification[3] and a high acuity. The cones have a fast adaptation in the dark.

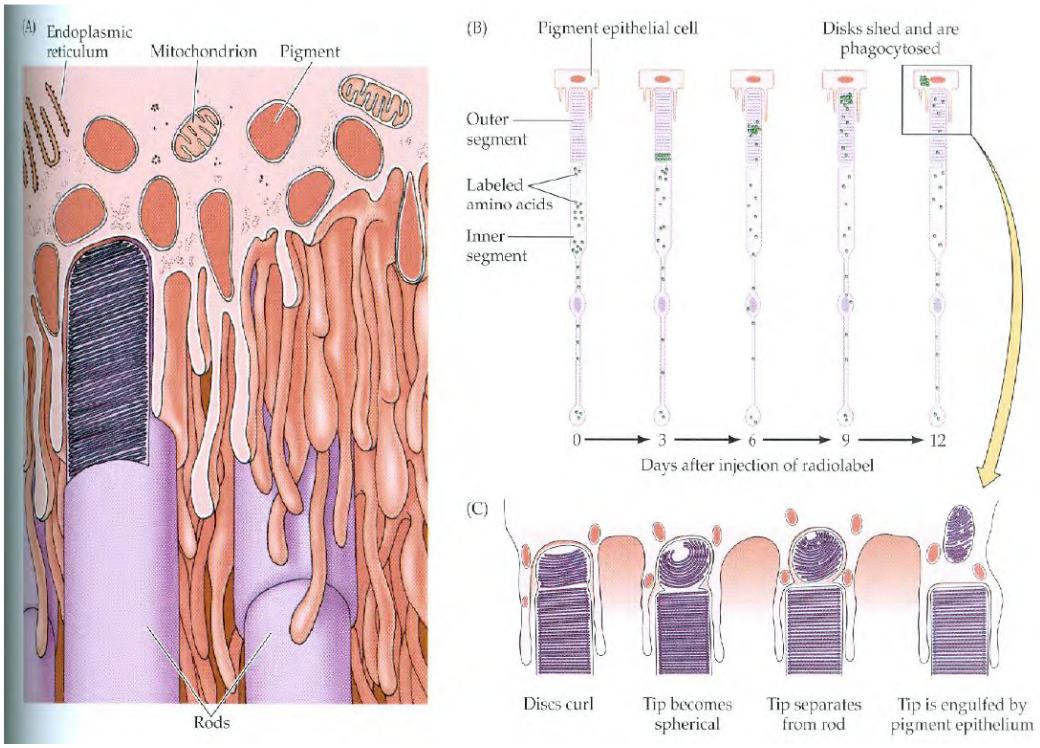
Rods are important for the night vison and have a high amplification in the dark (see footnote), it has a low acuity. There are around 120 million. Rods have a slow adaptation in the dark so that they can notice all the photons.

We have a higher density of rods than to cones. In some parts of the eye the density of cones is higher than rods, in the fovea there are no rods and close to the optic disc there are only codes. in the optic disc neither cones nor rods are present. In the nasal side of the eye there are only rods.

The fovea has the best sharpness of vision due to that it's a groove so the light hits it more optimally and it only consists of cones that only innervate one nerve fibre. There's a 1:1 relation between a cone and a nerve fibre, whilst there are several nerves on one rod.

PIGMENT EPITHELIAL CELLS

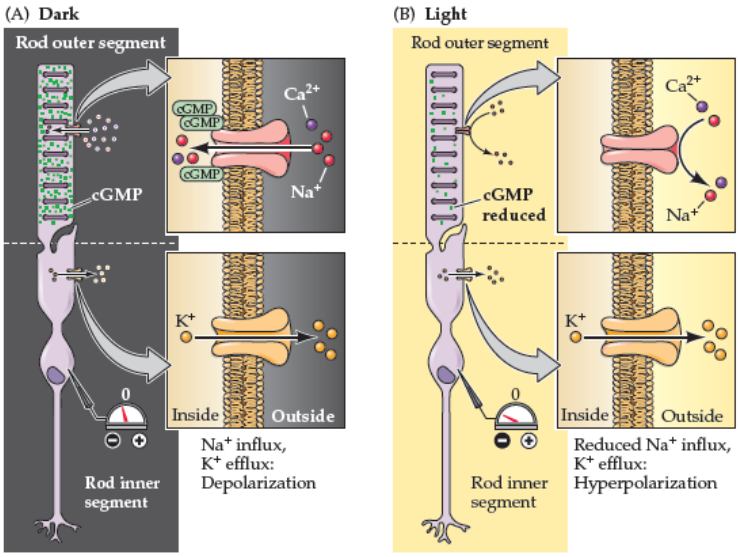
[3] en disk inne i en rod (stav). Rhodopsin (retinol + opsin) finns inne i disken. Till rhodopsin finns ett G-protein kopplat (den kallas transducin, men det behöver vi inte kunna). När disken får ljus aktiveras rhodopsins retinol som går från cis till trans och då aktiveras ett G-protein som i sin tur aktiverar PDE som bryter ned cGMP till GMP, den förändringen stänger natriumkanalerna till höger på bilden och leder till att cellen hyperpolariseras. Detta ger high amplication, dvs att den kan avge många transmittorer som gör att man kan se i mörker.



Pigment epithelial cells that are located behind the photoreceptors are the Pac-man's/macrophages of the eye. They eat the discs in the rods, the discs constantly needs to be broken down, they are made proximally in the outer segment and gets pushed out distally where the pigment epithelial cells phagocytes them.

7.EXPLAIN THE PROCESS OF PHOTOTRANSDUCTION IN A ROD.

In most sensory systems, activation of a receptor by the appropriate stimulus causes the cell membrane to depolarize, ultimately stimulating an action potential and transmitter release onto the neurons it contacts. In the retina, however, photoreceptors do not exhibit action potentials; rather, light activation causes a graded change in membrane potential and a corresponding change in the rate of transmitter release onto postsynaptic neurons.



More surprising is that shining light on a photoreceptor, either a rod or a cone, leads to membrane hyperpolarization rather than depolarization. In the dark the receptor is in a depolarized state, with a membrane potential of about -40 mV (including those portions of the cell that release transmitters). Progressive increases in the intensity of illumination cause the potential across the receptor to become more negative, a response that saturates the when the membrane potential reaches about -65 mV. While it might seem odd

the only logical requirement is a consistent relationship between luminance and rate of transmitter release from the photoreceptor terminals. As in other nerve cells, transmitter release is dependent on voltage sensitive Ca^{2+} channels in the terminal membrane. This in the dark, when photoreceptors are relatively depolarized, the number of open Ca2+ channels in the synaptic terminal is high, and the rate of transmitter release is correspondingly great; in the light when receptors are hyperpolarized the number of open Ca^{2+} channels is reduced and the rate of transmitter release is also reduced.

The reason for this unusual arrangement compared with that of other sensory receptor cells is not known but it may have to do with the challenge of responding to both increases and decreases in luminance. In the dark, cations (both Na^{+} and Ca^{2+}) flow into the outer segment through membrane channels that are gated by cGMP. This inward current is opposed by an outward current that is mediated by potassium selective channels in the inner segment. Thus, the depolarized state reflects the net contribution of Na^{+} and Ca^{2+} influx, which acts to depolarize the cell, and K^{+} efflux, which acts to hyperpolarize the cell. Absorption of light by the photoreceptor reduces the concentration of cGMP in the outer segment which in turn leads to a closure of cGMP-gated channels in the outer segment membrane and, consequently, a reduction in the inward flow of Na^{+} and Ca^{2+}. As a result, positive charge (carried by K^{+}) flows out of the cell more rapidly than positive charge flows in and the cell becomes hyperpolarized.

The series of biochemical changes that ultimately leads to a reduction in cGMP levels begin when a photon is absorbed by the photopigment in the receptor disks. The photopigment contains the light-absorbing chromophore retinal (an aldehyde of vitamin A) coupled to one of several possible proteins called opsins. The different opsins tune the molecule's absorption of light to a particular region of the light spectrum; this is the differing protein components of the photopigments in rods and cones that allow the functional specialization of these two receptor types.

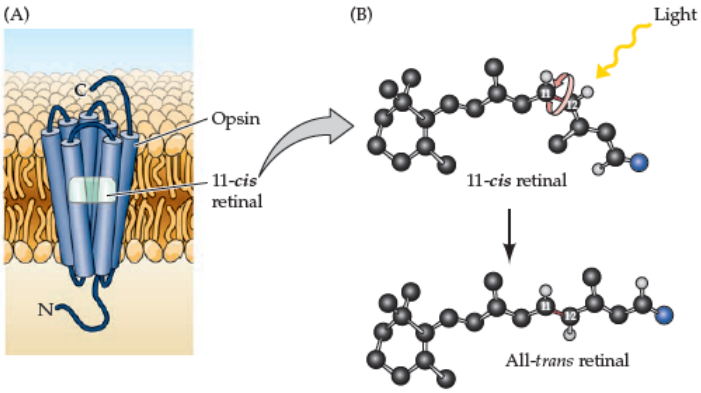
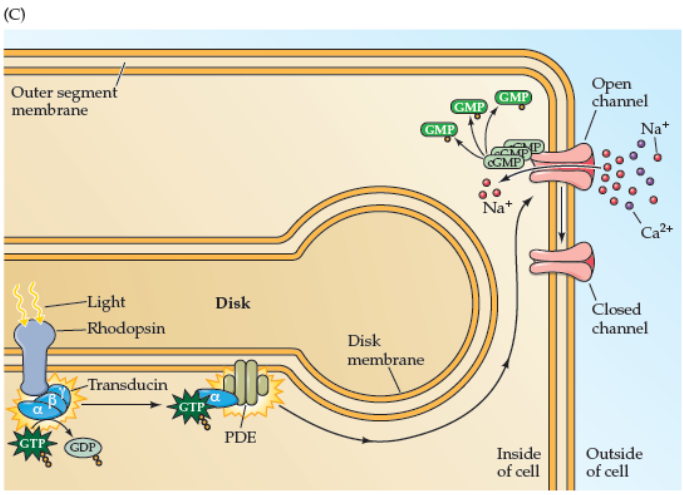


FIGURE 11.9 Phototransduction in rod photoreceptors. (A) Rhodopsin resides in the disk membrane of the photoreceptor outer segment. The seven transmembrane domains of the opsin molecule enclose the light-sensitive retinal molecule. (B) Absorption of a photon of light by retinal leads to a change in configuration from the 11-*cis* to the all-*trans* isomer. (C) The second messenger cascade of phototransduction. The change in the retinal isomer activates transducin, which in turn activates a phosphodiesterase (PDE). The PDE then hydrolyzes cGMP, reducing its concentration in the outer segment and leading to the closure of channels in the outer segment membrane. (A,B after Oyster, 1999; A after Stryer, 1986; B after Stryer, 1987.)



In rods the photopigment is rhodopsin; the seven transmembrane domains of the opsin molecule traverse the membrane of the disks in the outer segment, forming a pocket in which the retinal molecule resides. When retinal absorbs a photon of light, one of the double bonds between the carbon atoms in the retinal molecule breaks and its configuration changes from the 11-cis isomer to all-trans retinal; this change triggers a series of alterations in the opsin component of the molecule. The changes in opsin lead, in turn, to the activation of an intracellular messenger called transducing, which activates a phosphodiesterase (PDE) that hydrolyses cGMP. The hydrolysis of PDE at the disk membrane lowers cGMP concentration throughout the outer segment which reduces the amount of cGMP molecules available to bind to the channels in the surface of the outer segment membrane and in turn leading to channel closure.

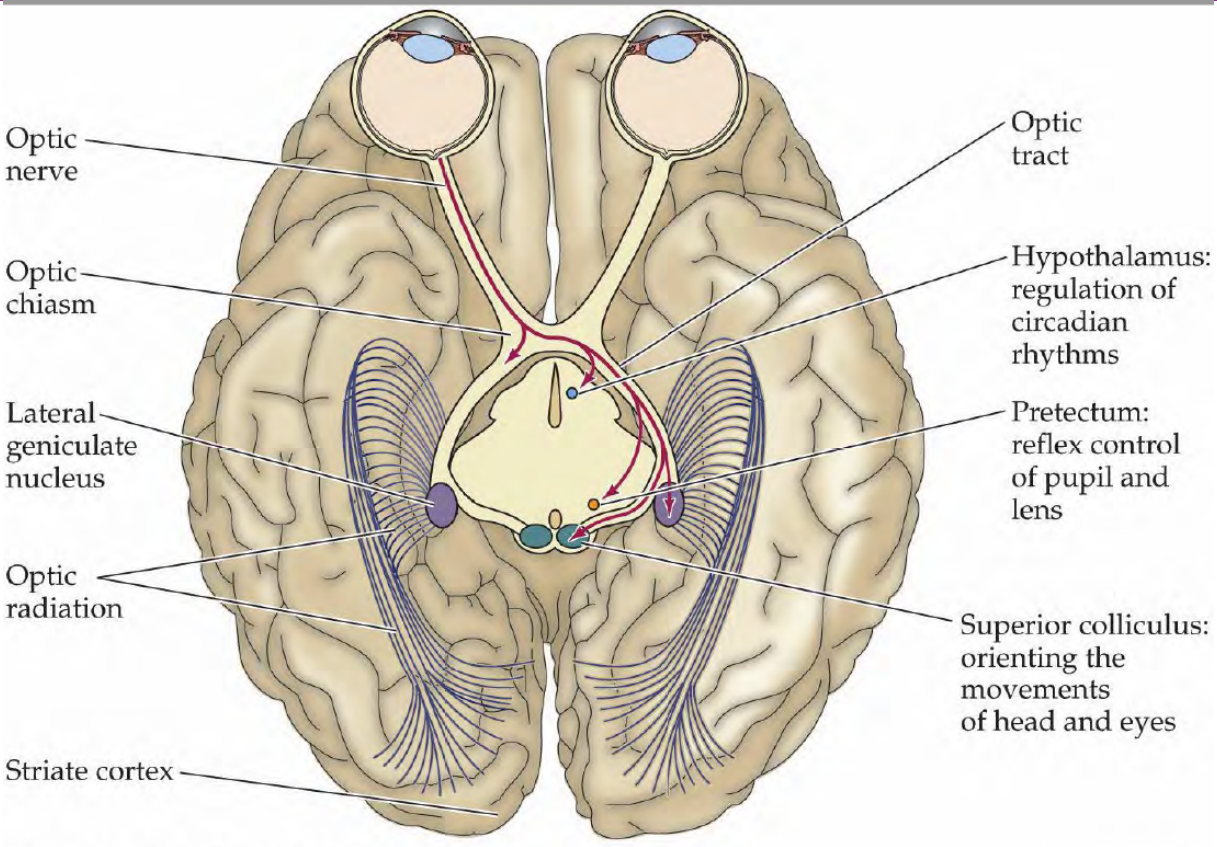
One of the important features of this complex is biochemical cascade initiated by photon capture is that it provides enormous signal amplification. A single light activated rhodopsin molecule can activate as many as 800 transducin molecules on the disk surface. Although each transducing molecule activates only one PDE molecule, each PDE is capable of catalysing the breakdown of as many as 6 cGMP molecules. As a result, the absorption of a single photon by a rhodopsin molecule results in the closure of approximately 200 ion channels, or about 2% of the number of channels in each rod that are open in the dark. This number of channel closures causes a net change in the membrane potential of about 1 mV.

Once initiated additional mechanisms limit the duration of this amplifying cascade and restore the various molecules of their inactivated states. Activated rhodopsin is rapidly phosphorylated by rhodopsin kinase, which permits the protein arrestin to bind to rhodopsin. Bound arrestin blocks the ability of activated rhodopsin to activate transducin which effectively truncate the phototransduction cascade.

Restoration of retinal to a form capable of signalling photon capture is a complex process

known as the retinoid cycle. The all-trans retinal dissociates from opsin and diffuses into the cytosol of the outer segment; there it is converted to all-trans retinol and transported into the pigment epithelium via a chaperone protein, inter-photoreceptor retinoid binding protein (IRBP) where appropriate enzymes ultimately convert it to 11-cis retinal. After being transported back into the outer segment via IRBP, 11-cis retinal recombines with opsin in the receptor disks.

8.EXPLAIN THE FUNCTIONS OF THE PROJECTIONS FROM THE RETINA TO DIFFERENT PARTS OF THE BRAIN (EXCEPT THE PRIMARY VISUAL CORTEX).



There are many areas in the brain that are affected by light, the primary visual pathway is via n. opticus → nucleus geniculate lateralis → cortex striate (visual cortex). But the light also effect other areas, for example goes signals to the hypothalamus for regulation of the circadian rhythm, here are the hormones that are deciding our diurnal rhythm (night and day) affected.

We also have pretectum that controls the pupillary reflex and the superior colliculus that helps orienting the movement of the head and eyes.

9.DESCRIBE THE ANATOMY AND HISTOLOGY OF THE EAR AND EXPLAIN THE CONCEPT OF "FREQUENCY TUNING" IN THE INNER EAR.

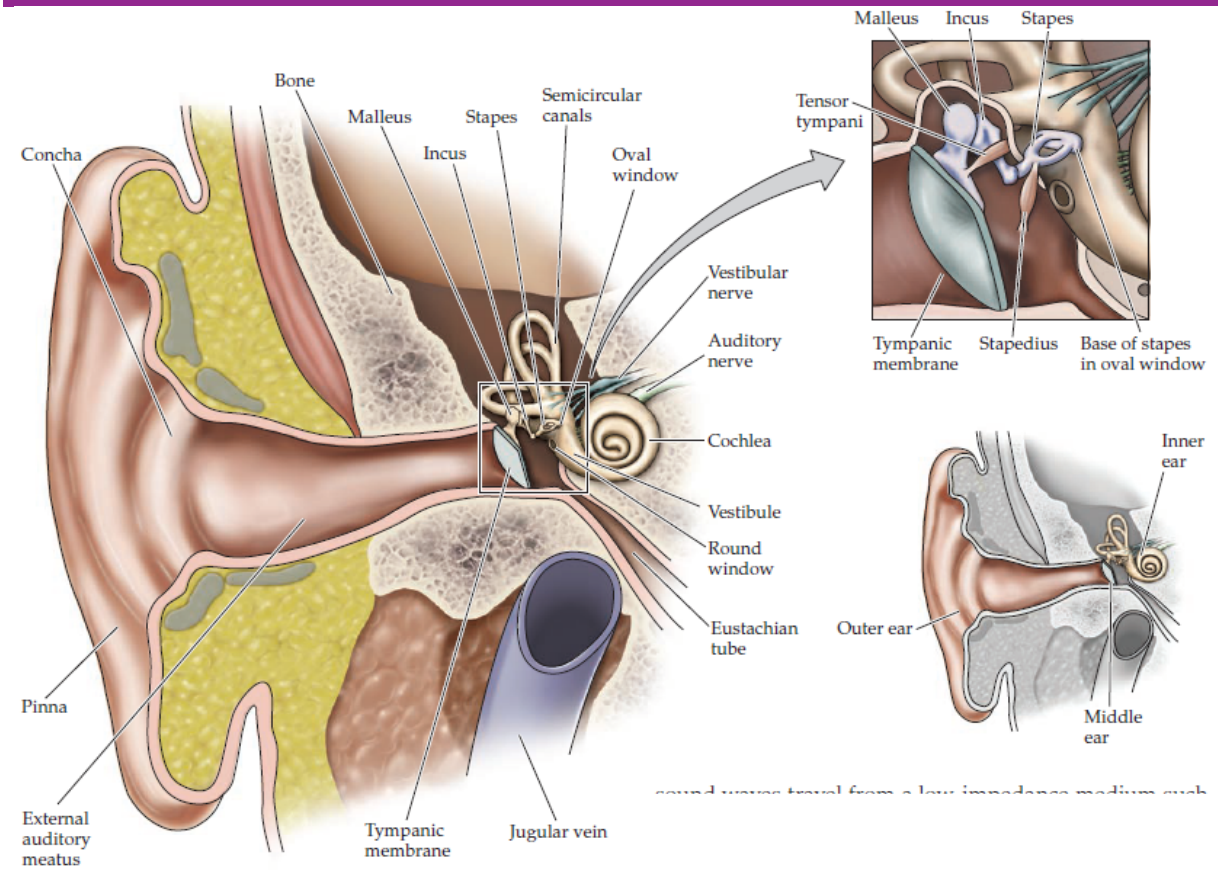


FIGURE 13.4 **The human ear.** Note the large surface area of the tympanic membrane (eardrum) relative to the oval window. This feature, along with the lever action of the malleus, incus, and stapes, facilitates transmission of airborne sounds to the fluid-filled cochlea.

ANATOMI

EXTERNAL EAR

The external ear consists of the **pinna**, **concha** and **auditory meatus**, which gathers sound energy and focuses it on the eardrum (tympanic membrane). The structure of the auditory meatus boosts sound pressure 30- to 100- fold for frequencies around 3 kHz via passive resonance effects (which appears to be the range of human speech). A second function of the pinna and concha is to provide cues about the elevation of the sound source. The vertically asymmetrical convolutions of the pinna are shaped so that external ear transmits more high frequency components from an elevated source than from the same source at ear level.

THE MIDDLE EAR

The environment in the inner ear, where the sound induced vibrations are converted to neural impulses, is aqueous unlike that of the external and middle ear. The major function of the middle ear is to match relatively low impedance airborne sounds to the higher impedance fluid of the inner ear. The pressure measured at the tympanic membrane is boosted almost 200-fold by the time it reaches the inner ear.

Two mechanical processes occur within the middle ear to achieve this large pressure gain. The first major boost is achieved by focusing the force impinging on the relatively large diameter tympanic membrane onto a much smaller **oval window**, the site where the bones of the middle ear contact the inner ear. A second and related process relies on the mechanical advantages gained by the lever action of the small, interconnected middle ear bones, or **ossicles** (i.e., the malleus, incus, and stapes), which connect the tympanic membrane to the oval window. In normal hearing the efficiency of sound transmission to the inner ear also is regulated by two small muscles in the middle ear, the tensor tympani, and the stapedius. Contraction of these muscles, which is triggered automatically by loud noises or during self-generated vocalization, counteracts the movement of the ossicles and reduces the amount of sound energy transmitted to the cochlea, serving to protect the inner ear.

THE INNER EAR

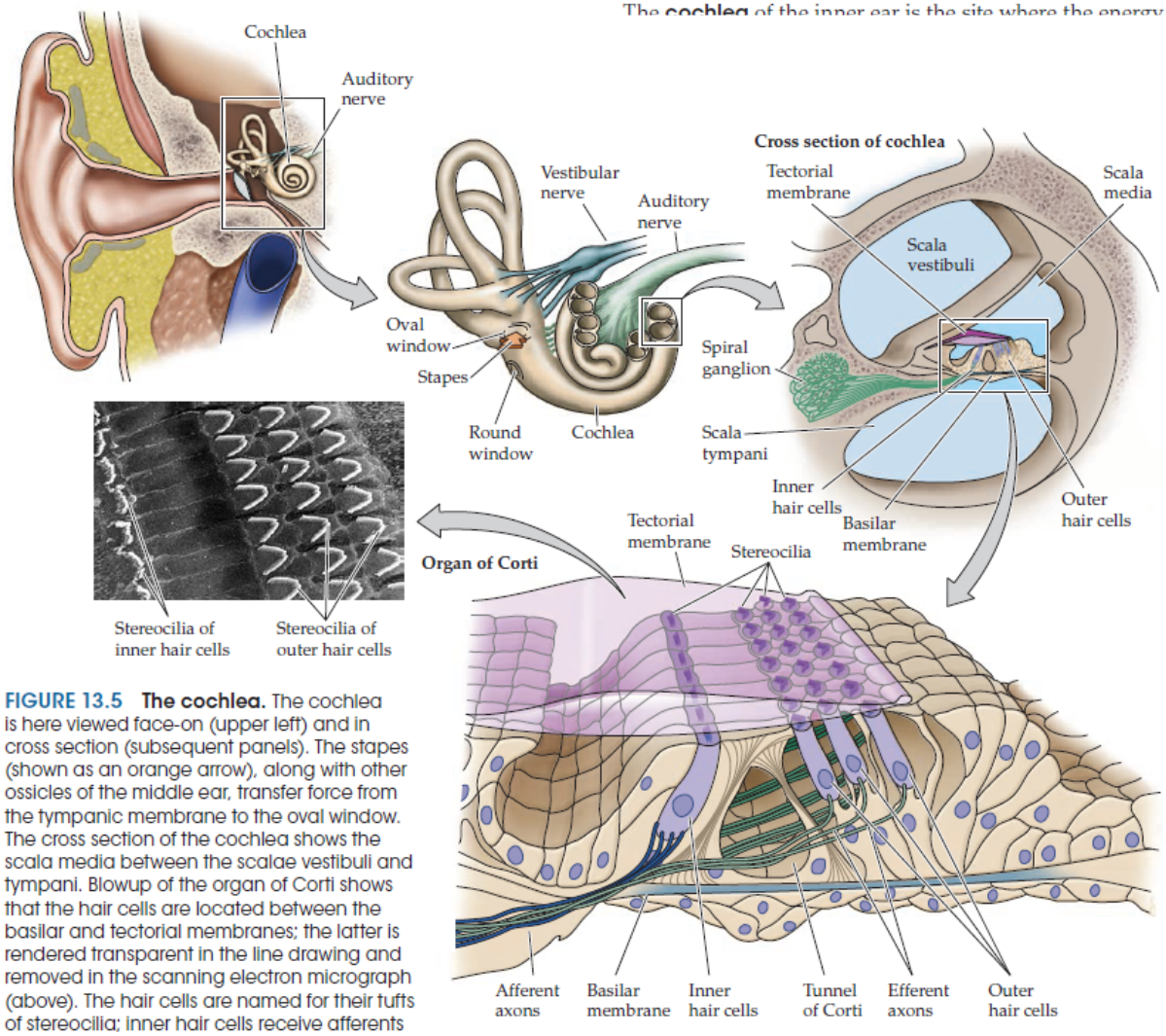
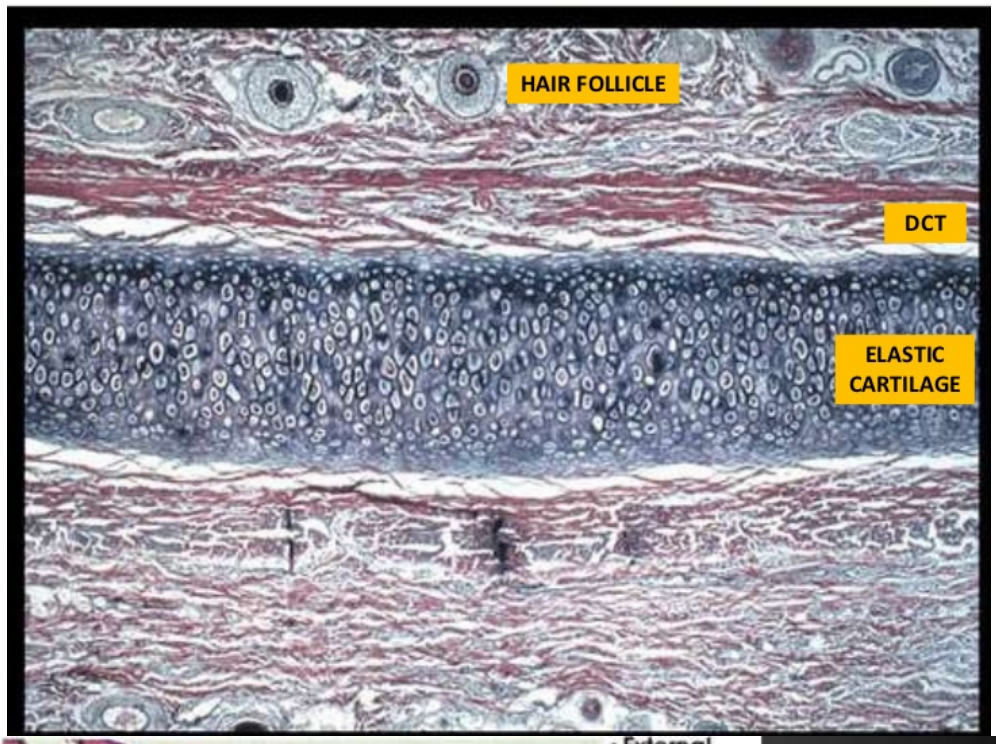


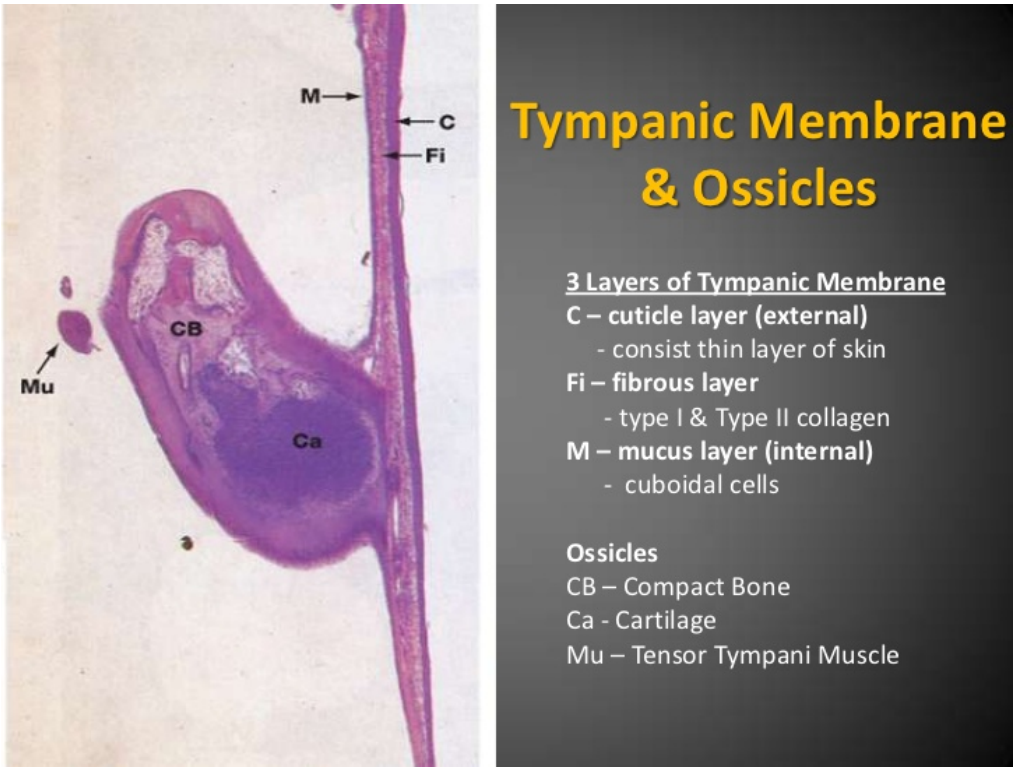
FIGURE 13.5 The cochlea. The cochlea is here viewed face-on (upper left) and in cross section (subsequent panels). The stapes (shown as an orange arrow), along with other ossicles of the middle ear, transfer force from the tympanic membrane to the oval window. The cross section of the cochlea shows the scala media between the scalae vestibuli and tympani. Blowup of the organ of Corti shows that the hair cells are located between the basilar and tectorial membranes; the latter is rendered transparent in the line drawing and removed in the scanning electron micrograph (above). The hair cells are named for their tufts of stereocilia; inner hair cells receive afferents from cranial nerve VIII, whereas outer hair cells receive mostly efferent innervation. (Micrograph from Counter et al., 1991.)

The **cochlea** of the inner ear is the site where the energy from sonically generated pressure waves is transformed into neural impulses. The cochlea not only amplifies sound waves and converts them into neural signals, but it also acts as a mechanical frequency analyser, decomposing complex acoustical waveforms into simpler elements.

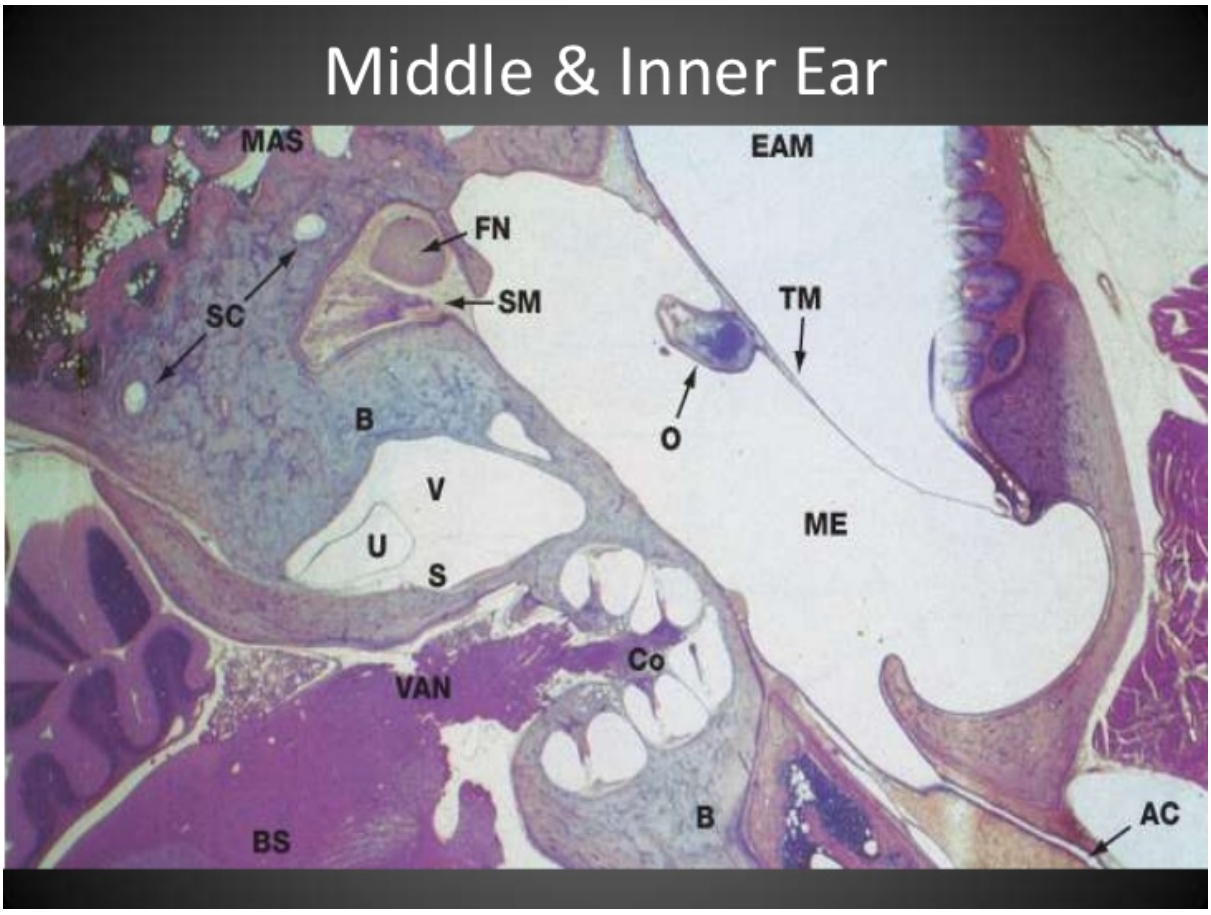
EXTERNAL EAR



THE MIDDLE EAR

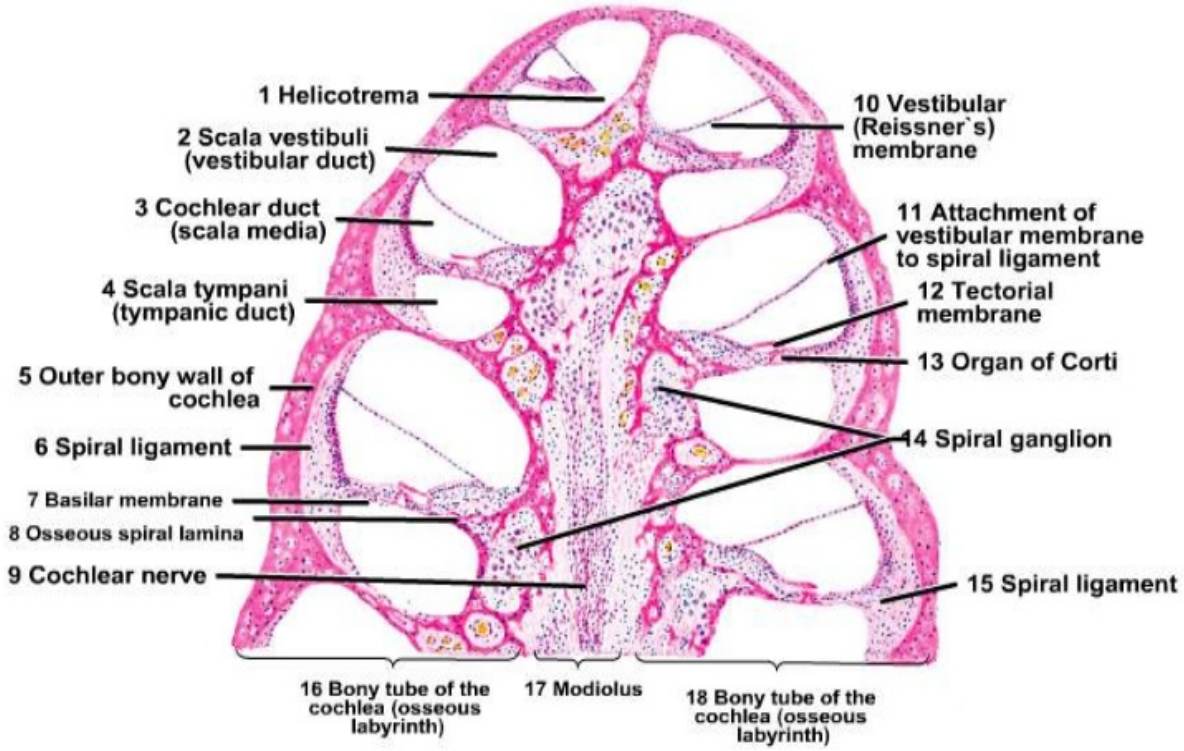


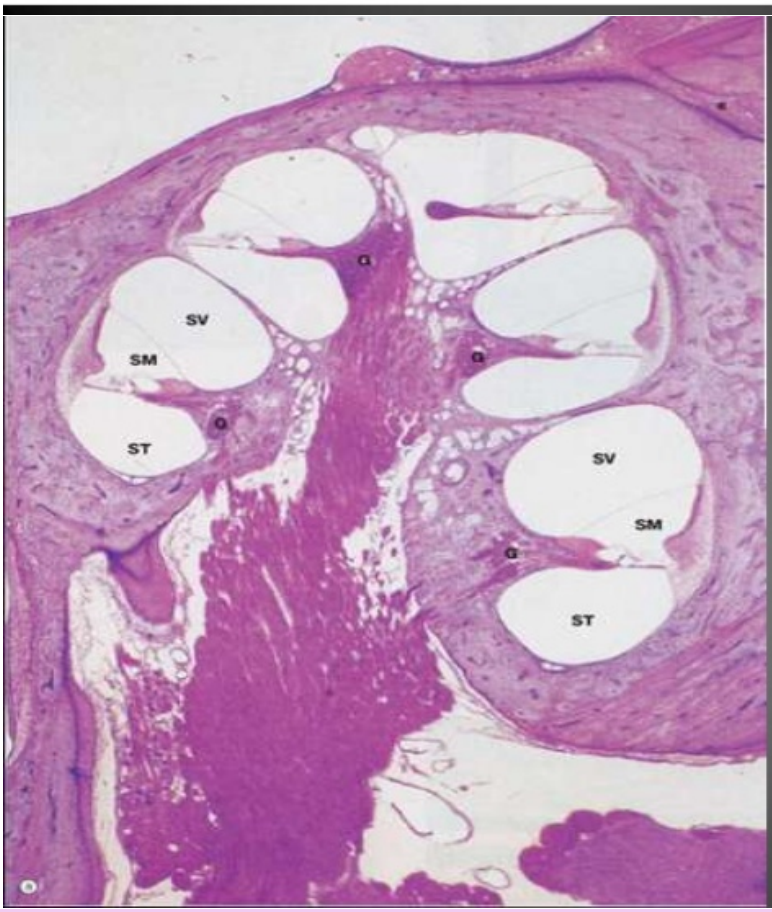
THE MIDDLE AND INNER EAR



INNER EAR

Inner Ear: COCHLEA *(vertical section)*



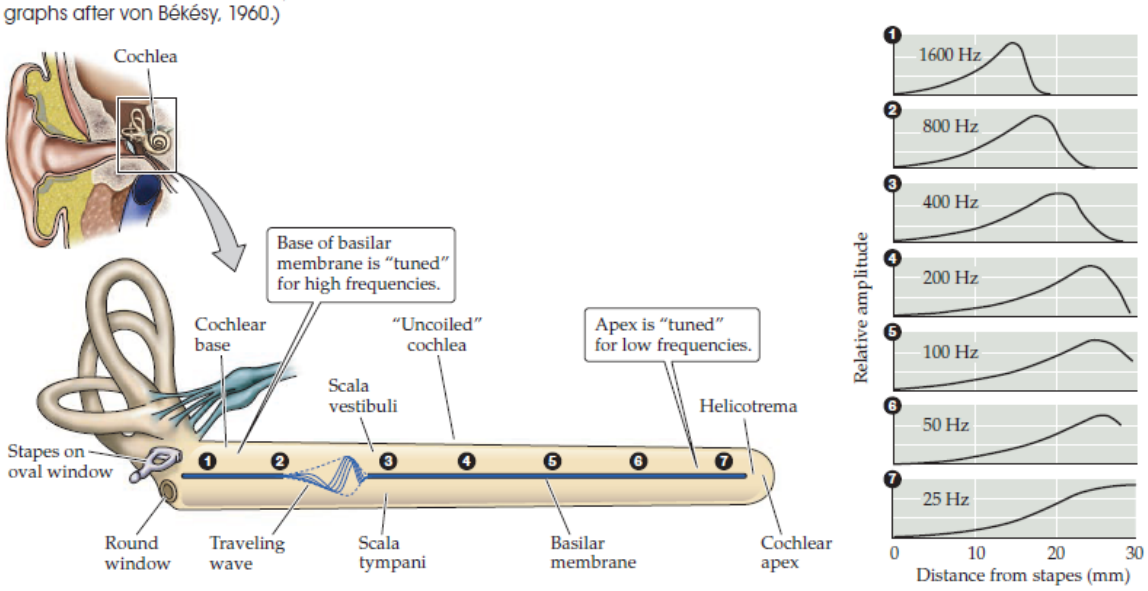


COCHLEA

O – Organ of Corti
SV – Scala Vestibuli
SM – Scala Media
ST – Scala Tympani

FREQUENCY TUNING

FIGURE 13.6 Traveling waves along the cochlea. A traveling wave is shown at a given instant along the cochlea, which has been uncoiled for clarity. The graphs on the right profile the amplitude of the traveling wave along the basilar membrane for different frequencies. The position (labeled 1–7 in the figure) at which the traveling wave reaches its maximum amplitude varies directly with the frequency of stimulation: Higher frequencies map to the base, and lower frequencies map to the apex. (Drawing after Dallos, 1992; graphs after von Békésy, 1960.)



The auditory system is tonotopically organized where the basilar membrane is made up of fibers, where the base is stiffer and narrower than the apex. The base for the basilar membrane is tuned for higher frequencies, while the apex is tuned for lower frequencies. There are also outer hair cells that are frequency specific which move up and down in response to specific frequencies.

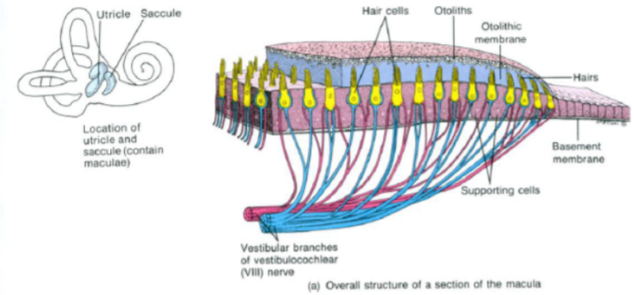
A single auditory nerve fiber innervates only a single inner hair cell (although several or more auditory nerve fibers synapse on a single hair cell) meaning that each auditory nerve fiber transmits information about only a small part of the audible frequency spectrum. As a result, auditory nerve fibers related to the apical end of the cochlea respond to low frequencies, and fibers that are related to the basal end respond to high frequencies. These threshold functions are called **tuning curves**.

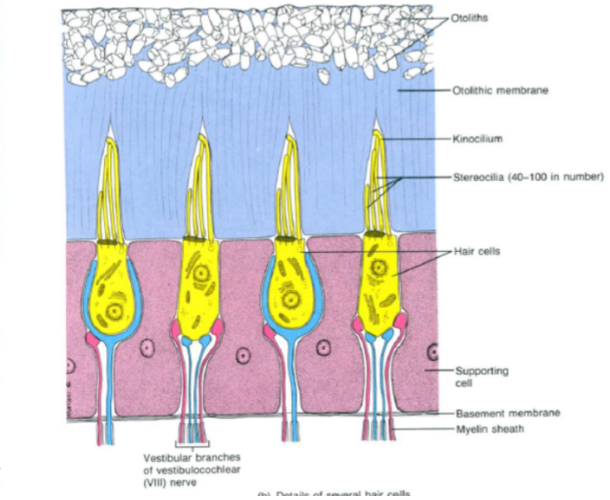
10.EXPLAIN THE MECHANISMS RESPONSIBLE FORCIRCULAR AND LINEAR ACCELERATIONS.

LINEAR ACCELERATION

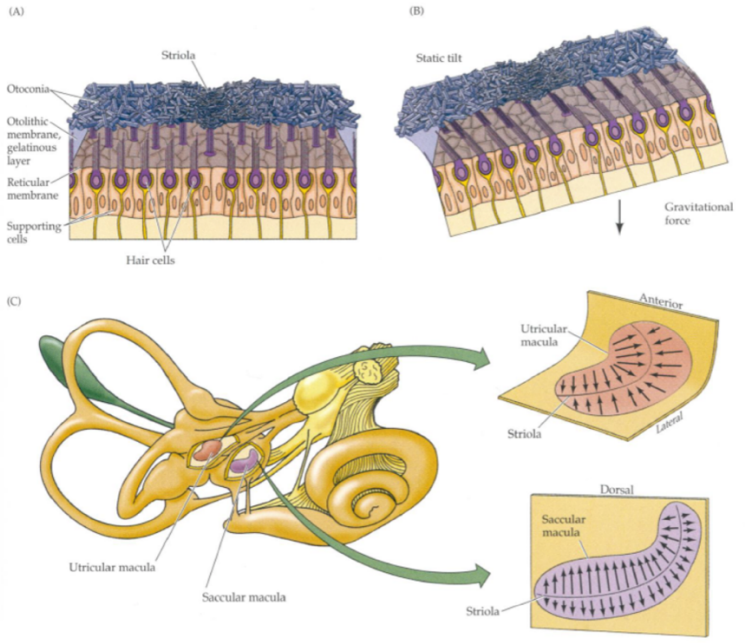
In the inner ear there are areas that are answering to linear acceleration in both the horizontal and the vertical direction. These are called the otolith organs. The sacculus answer to the vertical and utricle to the horizontal movement. They have a similar morphology and mechanism.

They have a sensory epithelium called macula which has hair cells where stereocilium's grows. the stereocilium's are longer than the once in cochlea, above and around the stereocilium's there's a gelatinous membrane called otolithic membrane and above that there's otoconia. Otoconia is calcium carbonate crystals .





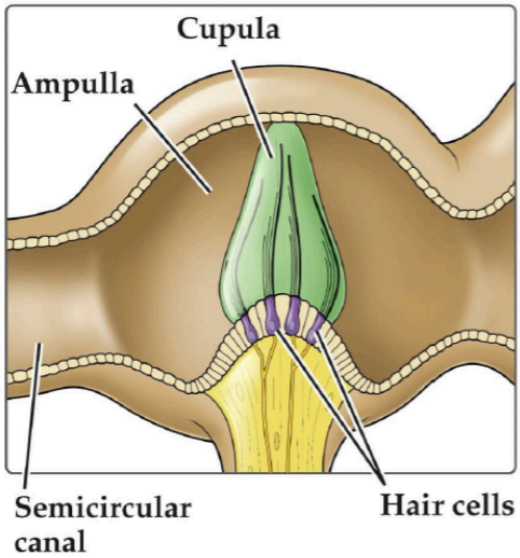
In a movement the hair cells get polarized and they bend, if they bend in the direction of the longer stereocilium it's an **excitation** and if it is bent in the direction of the shorter stereocilium it's an inhibition. When the stereocilium bends the otolithic membrane move and so does the otoconia. There's a groove called the striola and on one side of the striola the stereocilium's are arranged in one direction and on the other side they are arranged in a different direction. The striola creates a mirror of symmetry, so for example when we tilt our head forward hair cells of one side of the striola will be excited, while hair cells on the other side will be inhibited.

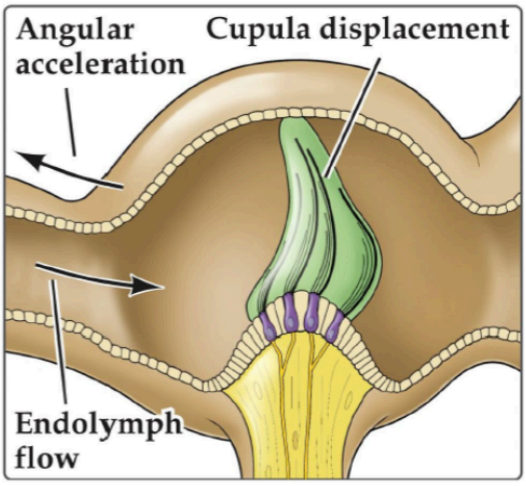


When the head is moved in a translational way there's a shearing force created between the stereocilium and because of the inertia of the otolithic membrane is greater than the macula there will be a delay in its movement compared to the macula.

There is always a spontaneous activity in the n. vetibulocochlearis and therefore there's always a small activity in the linear acceleration but not as much as in a movement.

CIRCULAR ACCELERATION





Rotation of the head are sensed by the semi-circular canals. They have an ampulla which is in the base of the semi-circular canals, here there are a cupula that have stereocilium's in it and the hair cells sits within the sensory epithelium that are called crista, this is a gelatinous mass. The hairs are arranged in one direction. In the canal there are a liquid called endolymph. If the liquid goes in one direction there's excitation and in the other inhibition. However, there are no striola so there are no axes for depolarisation instead the cupola creates a barrier in the flow of the endolymph.

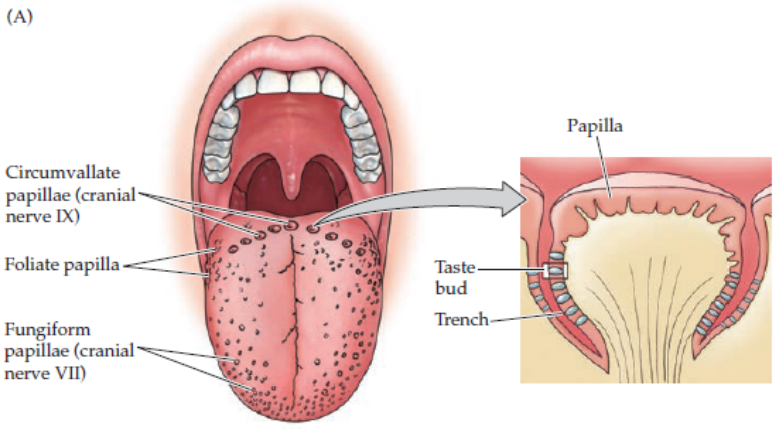
When the head turns in the plane of one of the semi-circular canals, the inertial force causes endolymph to flow in the opposite direction. This will lead to displacements of the cupula; this will cause a deflection of the hair cells in the cupula. This results in that when we accelerate, we get a response, but if we keep rotating, the endolymph will move along the fixed structures and when we decelerate, we will get a response again.

The semi-circular canals are paired so when we rotate our head the endolymph will be set in motion on both sides; however, it will have a hyperpolarising effect on the hair cells of one side and a depolarisation of the other side. The semi-circular canals are mirror images of each other

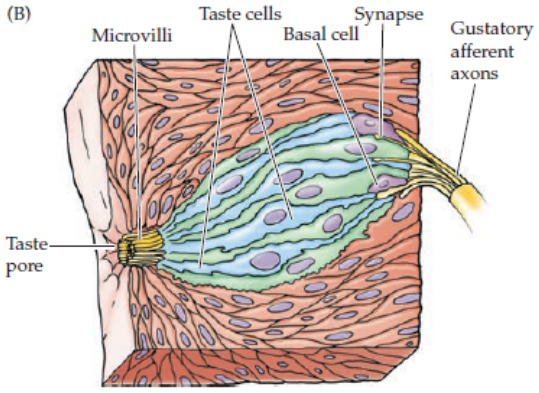
For example, if the head is rotated to the left, endolymph in both horizontal canals will rotate to the right. This will lead to displacement of the cupula on both sides. On the left side, hair cells are displaced toward their kino- cilia, which causes the opening of cation channels and increased signal transduction. The opposite will happen on the other side.

11.EXPLAIN THE FUNCTIONS AND THE DISTRIBUTION OF THE DIFFERENT TASTE RECEPTOR CELLS.

The taste system encodes information about the quantity as well as the identity of stimuli. Most taste stimuli are non-volatile, hydrophobic molecules that are soluble in saliva. In general, the perceived intensity of taste is directly proportional to the concentration of the taste stimulus. In humans,



threshold concentrations for most ingested tastants are quite high. For example, the threshold concentration for citric acid is 2 mM; for salt (NaCl) 10 mM; and for sucrose 20 mM. Because the body requires substantial concentrations of salt and carbohydrates, taste cells may respond only to relatively high concentrations of these essential substances in order to promote an adequate intake. The threshold for potentially dangerous substances, however, is much lower (0.008 mM for quinine and 0.0001 mM for the deadly substance strychnine).



Tastants are detected over the full surface of the tongue in receptive specializations called taste papillae. Papillae are defined by multicellular protuberances surrounded by local invaginations in the tongue epithelium. These invaginations for a trench to concentrate solubilized tastants. Taste buds are distributed along the lateral surfaces of the papillar protuberance as well as in the trench walls. They consist of specialized neuroepithelial receptor cells called taste cells, some supporting cells and occasional basal cells. In humans approximately 4000 taste buds are distributed throughout the surface of the tongue as well as the palate, epiglottis and oesophagus. Taste cells are clustered around a 1-mm opening called taste pore in the taste bud near the surface of the tongue. Solubilized tastants are further concentrated and are presented directly to the exposed taste receptor cells of the taste pore. Taste cells have a lifespan of about two weeks (presumably because they are exposed to infectious agents and environmental toxins) and are regenerated from basal cells.

There are three types of papillae: **fungiform** (which contain about 25% of the total number of taste buds), **circumvallate** (50%) and **foliate** (the remaining 25%). The three classes are distributed discontinuously on the surface of the tongue. Fungiform papillae are only found on the anterior two-thirds of the tongue; the highest density is at the tip. Fungiform papillae have a mushroom like structure and typically have three taste buds at their apical surface. There are nine circumvallate papillae that form a chevron (V-shape) at the back of the tongue. Each consists of a circular trench that contains about 250 taste bunds along the

trench walls. Two foliate papillae are present on the posterolateral tongue, each having about 20 parallel ridges with about 600 taste buds in their walls. Thus, chemical stimuli on the tongue first stimulate receptors on fungiform receptors and then in the foliate and circumvallate papillae. Tastants subsequently stimulate scattered taste buds in the pharynx, larynx and upper oesophagus.

Based on general agreement across cultures, the taste system detects five perceptually distinct categories of tastants: **salt**, **sour**, **sweet**, **bitter** and **umami** (From the Japanese word for delicious and refers to the savory tastes, including monosodium glutamate and other amino acids) (though there are obvious limitations to this classification). Salt tastes include NaCl which is needed for electrolyte balance; sour tastes are associated with acidity and thus protons (H+) indicate palatability of various foods.; sweet tastes include sugars and other carbohydrates are needed for energy; bitter tasting molecules include plant alkaloids such as atropine, quinine and strychnine, indicate foods that might be poisonous; and umami tastes are associated with essential amino acids.

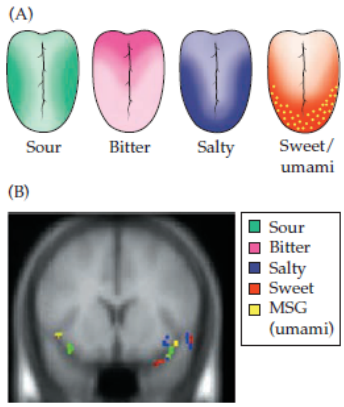
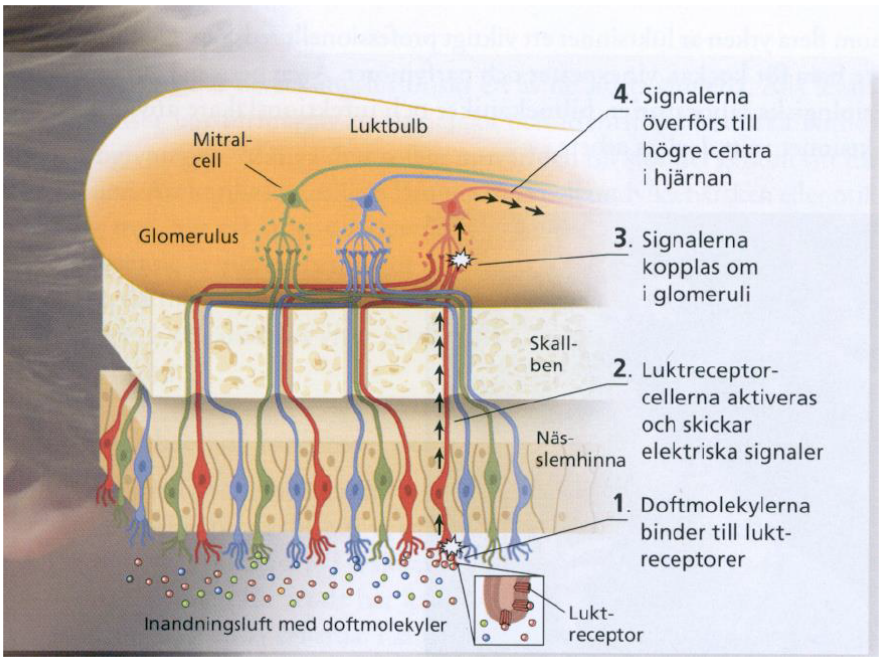


FIGURE 15.22 Peripheral innervation of the tongue. (A) Responses to sweet/umami, salty, sour, and bitter tastants recorded in the three cranial nerves that innervate the tongue and epiglottis. (B) Composite fMRI showing the different locations of focal activation in the insular cortex in response to each of the tastes encoded by taste receptors. (B from Schoenfeld et al., 2004.)

Although all tastes can be detected over the entire surface of the tongue, different regions of the tongue have different thresholds for various tastes. These discontinuities in taste sensitivity may be related to aesthetic, metabolic, and potentially toxic qualities detected by the taste receptors in the tongue. The tips of the tongue is most responsive to sweet, umami and salty compounds, all of which produce pleasurable sensations at somewhat higher concentrations. Tastes encountered by this region – the initial point of contact for most ingested foods – activate feeding behaviours such as mouth movements, salivary secretions, insulin release and swallowing. The acquisition of foods high in carbohydrates and amino acids is beneficial (in moderation), and thus it is not surprising that the most exposed region of the tongue is especially sensitive to these tastes.

Sour and bitter taste sensitivity is lowest towards the tip and greatest on the sides and back of the tongue. It seems reasonable that after it has analysed the food for nutrient content that they follow with evaluating the acidity and bitterness to indicate a lack of palatability (excessive sourness) or even toxicity (bitterness). Sour tasting compounds elicit grimaces, puckering, and massive salivary secretions to dilute the tastant. Activation of the rear of the tongue by bitter tasting substances elicit its protrusion of the tongue and other protective reactions (expectoration and gagging) that prevent ingestion.

12.DESCRIBE HOW AN ODOR ACTIVATES OLFACTORY RECEPTOR CELLS.

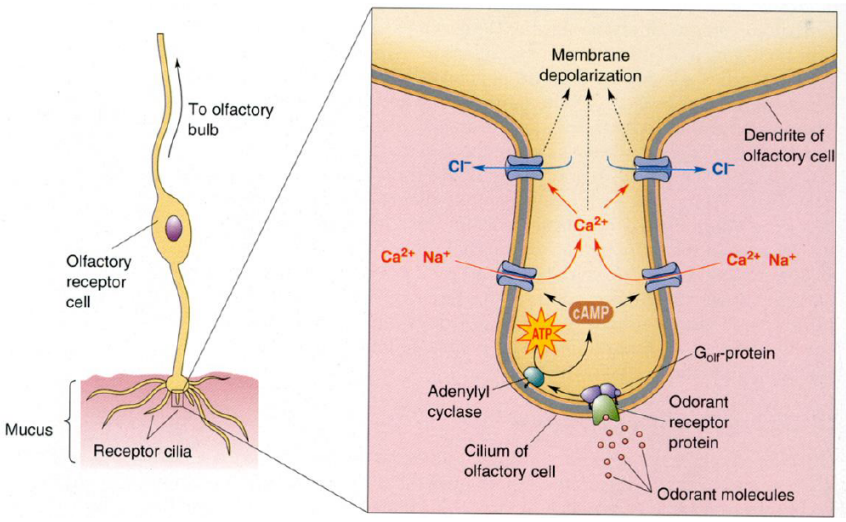


SUMMARY/OVERVIEW

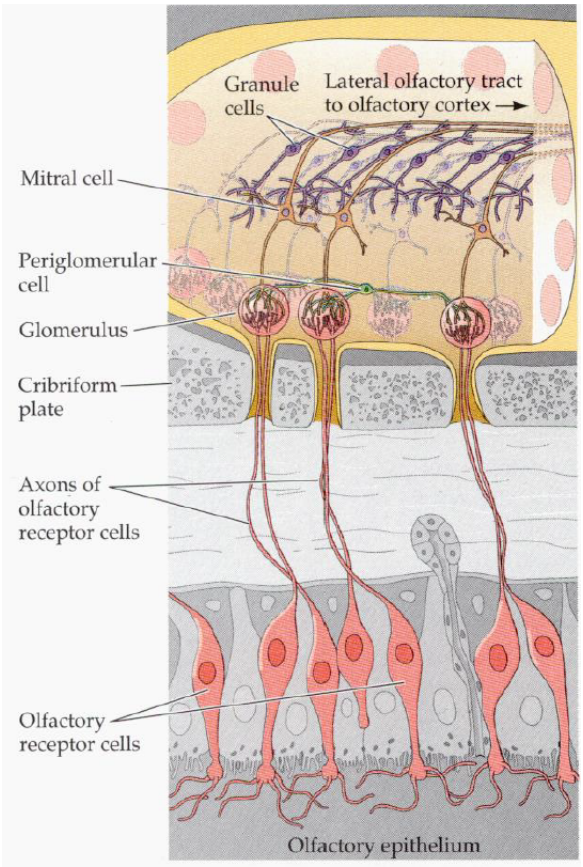
Odour molecules binds to receptors on cilium of the receptor cell of the olfactorius. That activates them and a signal is sent through the lamina cribrosa and are cutover in the glomerulus and transferred to the centre in the brain. There is a sorting of the odour molecules, they can only bind to specific receptors.

LONG VERSION

In the nose there are olfactory cells with an olfactory bulb and cilium's as well as bowman's glands that secrets a type of mucus. The odour molecules enter the nose and ends up in the mucus, then it binds to a receptor on the cilium. The receptor is coupled with a G-protein that activates adenylate cyclase that transforms ATP → cAMP. cAMP binds to cation channels and activate them, this results in that Na^+ and Ca^{2+} can come into the cell and give rise to a transduction.

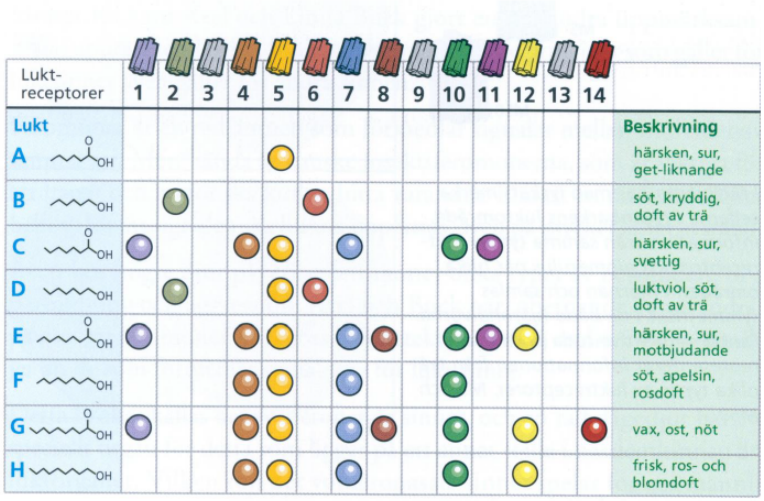


The membrane depolarisation leads to a signal being sent via the axons that run through the lamina cribrosa to the glomerulus. The glomeruli are bundles of axons (synapses) and dendrites (from the mitral cells). The mitral cells, that are the principal neuron in the olfactory bulb take the signal through the lateral olfactory tract to the olfactory cortex. By the glomerulus there are periglomerular cells that help with lateral inhibition, this is important in environments with a lot of odours where we need to sort out the most important odour. After the mitral cells there are granule cells that also is inhibitory (inhibitory interneurons) they are also important for the sorting.



Each olfactory receptor cell possesses only one type of odorant receptor (the G-receptor) and each of these can detect a limited number of odorant substances. So, one olfactory receptor cell expresses only one of the odorant receptor genes (there are several, about 3 % of our genome code for the different odour receptors), each one of these cells can react to several odour molecules that are related. So, for example, to receptor 10 five different types of odour molecules can bind, they all have different types of odours and they vary from sweet, orange and rose sent to sour, sweat and rancid.
Each molecule can activate several receptors and the combination gives rise to a code or odour pattern. Most odours are composed of multiple odorant molecules and this is why we can distinguish and smell so many odours.

Combinatorial Code for Odors



ORAL EXAM 3 – MOTOR FUNCTIONS

1. DESCRIBE THE DIFFERENT TYPES OF MOTOR UNITS AND THEIR PROPERTIES. EXPLAIN HOW THE CNS GRADES MUSCLE FORCE ON THE BASIS OF MOTOR UNITS.

The motor neurons of the body can be divided into lower motor neurons and higher motor neurons. The higher motor neurons are located in our brain and in our spinal cord. The lower motor neurons are located in the brainstem and spinal cord, they get a signal from the higher motor neurons and send the signal to our muscles to make them contract.

So, the higher motor neurons get their information from the primary motor cortex or premotor cortex, some projection neurons can receive information from the cerebellum and basal ganglia. They send their information to interneurons, that take the information to the lower motor neurons that then innervate the muscle. The lower motor neurons also get information from sensory afferents to interneurons and the lower motor neuron. With that said, muscle contractions are initiated by lower motor neuron also known as α motor neurons. The α motor neurons are located in the ventral horn of the spinal cord.

The lower motor neurons innervate one or several muscles in the periphery, a lower motor unit and a muscle that it innervates is called a motor unit. There are three types of motor units; slow, fast fatigable and fast fatigue resistant motor units.

SLOW MOTOR UNITS

The different motor units differ in size, the smaller ones innervate few muscle fibres and generate small forces. In the skeletal muscle that are called type I, they are also called “red” muscle fibres. These are characterised by their slow contraction, generating relatively small forces but they are very fatigue resistance due to their rich content of myoglobin, mitochondria’s and capillary beds. They are called slow motor units and are important for activities that requires a sustained muscular contraction like maintain posture. The threshold for recruiting the slow motor units are very low.

FAST FATIGABLE MOTOR UNITS

The fast fatigable motor units has a larger α motor neurons and a larger “paler” muscle fibre known as an type IIx. These fibres generate a larger force but have a fever amount of mitochondria, hence the paler colour, and therefore they easily tire. They are important for more explosive type of movement like running fast and jumping. They have a high threshold for activation and a large force.

FAST FATIGUE-RESISTANT MOTOR UNITS

The fast fatigue-resistant motor units lie between the two units mentioned above, they are more intermediate when it comes to activation threshold, force (about twice compared to slow motor units) and fairly fatigue resistant. They are a type IIa muscle fibre and are important in for example long distant running.

MOTOR NEURONS FORM 4 CIRCUITS *(MIGHT NOT BE IMPORTANT TO THE QUESTION)*

There are 4 types of circuits that motor neurons form:

LOCAL CIRCUIT NEURON that in exist in the grey mass of the spinal cord and tegmentum and are important for reflexes. It takes information from sensory/descending neurons and activate lower motor neurons.
UPPER MOTOR NEURON that are present in the brainstem and cortex and descends to the local circuit neurons.
CEREBELLUM coordinates the ongoing movements, its efferents connects with the upper motor neurons (→ local circuit → lower motor neurons)
BASAL GANGLIA Initiation of interpreted movement as well as suppression of unwanted movements efferents goes to upper motor neurons (→ local circuit → lower motor neurons)

2. TWO TYPES OF AFFERENT FIBERS CARRY INFORMATION FROM A LIMB, THE IA AND IB AFFERENTS. WHICH TYPES OF STIMULI DOES EACH ONE RESPOND TO AND WHAT ARE THEIR ROLES IN MOTOR CONTROL?

Ia afferents respond phasically to small stretches. This means they respond quickly when there is a change in length of the muscle = a stretch of the muscle. Type Ia afferents innervate both the nuclear bag and nuclear chain, which are a part of the muscle spindle. They have a low threshold and a fast ability to adapt movements, meaning that they fire a lot in the beginning of a movement, and then adapts to the new length and stops firing.

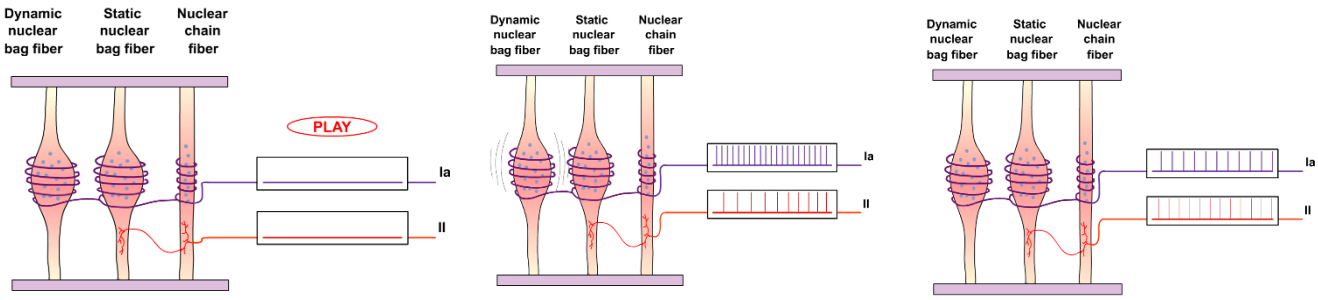
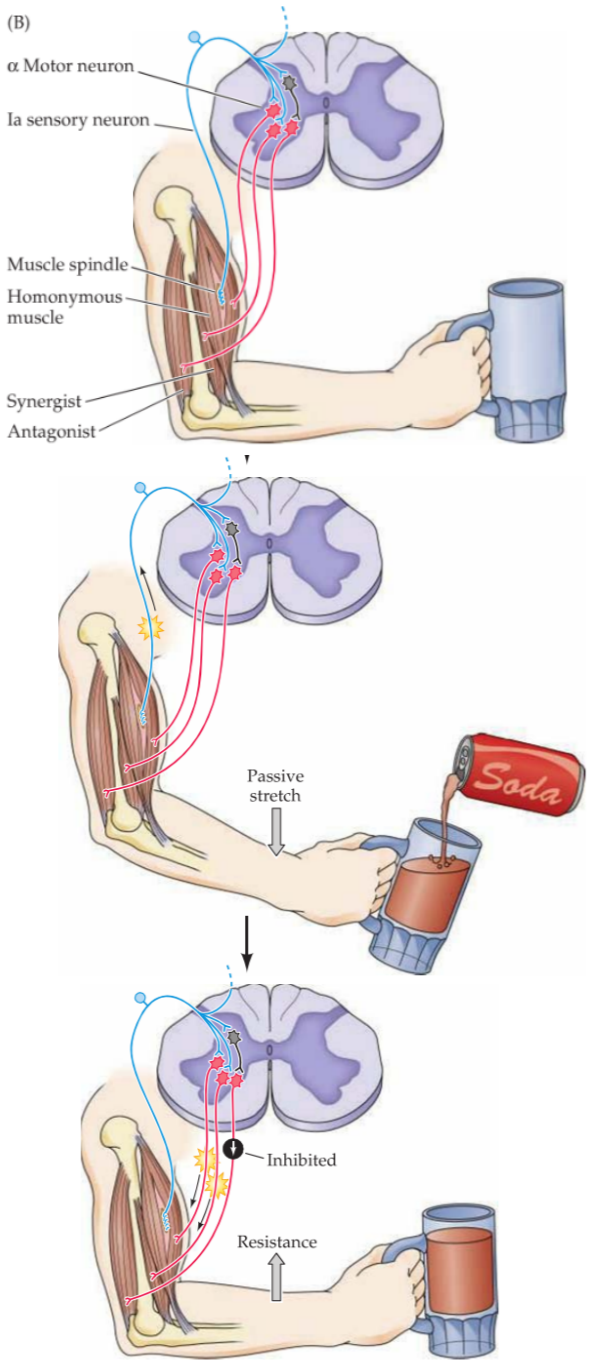


Figure 1.9
Responses of muscle spindles. The Group Ia afferent responds at a highest rate when the muscle is actively stretching, but also signals the static length of the muscle because of its innervation of the static nuclear bag fiber and the nuclear chain fiber. The Group II afferent signals only the static length of the muscle, increasing its firing rate linearly as a function of muscle length.
https://nba.uth.tmc.edu/neuroscience/s3/chapter01.html

Ia afferents also excite the motor neurons that innervate synergistic muscles, and they indirectly inhibit the motor neurons that innervate antagonists via intervening GABAergic local circuit neurons (reciprocal-Ia-inhibitory interneurons). This reciprocal innervation results in rapid contraction of the stretched muscle and simultaneous relaxation of the antagonist muscle. The stretch reflex operates as a negative feedback loop to regulate muscle length.

FIGURE 16.10 Stretch reflex circuitry.
Purves - Neuroscience 5th Edition c2012 txtbk.pdf



1b afferents are found in the golgi tendon organs that are sensitive to the change in tension, which happens when a muscle for example contracts. The Ib afferents will contact GABAergic inhibitory local circuit neurons in the spinal cord (Ib inhibitory interneurons). These inhibitory interneurons will then synapse with α motor neurons that innervate the same muscle → decreases their activity. So the GTO is a negative feedback system that regulates muscle tension. The activation of a muscle is decreased when exceptionally large forces are generated. In this way the muscle is protected from generating excessive tension.

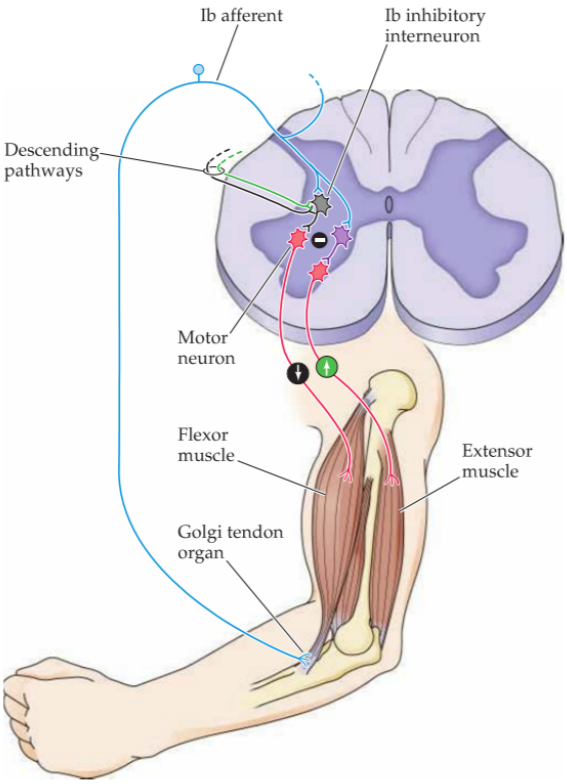


FIGURE 16.13 Negative feedback regulation of muscle tension by Golgi tendon organs. The Ib afferents from tendon organs contact inhibitory interneurons that decrease the activity of α motor neurons innervating the same muscle. The Ib inhibitory interneurons also receive input from other sensory fibers (not illustrated), as well as from descending pathways. This arrangement prevents muscles from generating excessive tension and helps maintain a steady level of tone.

3. WHAT ARE CENTRAL MOTOR PROGRAMS? – GIVE A DEFINITION AND EXAMPLES OF BOTH INNATE AND LEARNED/ACQUIRED MOTOR PROGRAMS.

The term motor programs is a topic of debate; in its most general sense it can be defined as "a central representation of a sequence of motor actions". Keele, Cohen, and Ivry (1990), for example, defined the motor program as ''...the representation of the orders of actions rather than their elementary movements... a plan" (p. 78). Others on the other hand mean that the term has such a loose definition that it is in danger of loosing its meaning.
https://www.krigolsonteaching.com/uploads/4/3/8/4/43848243/1-s2.0-s0167945709000189-main.pdf

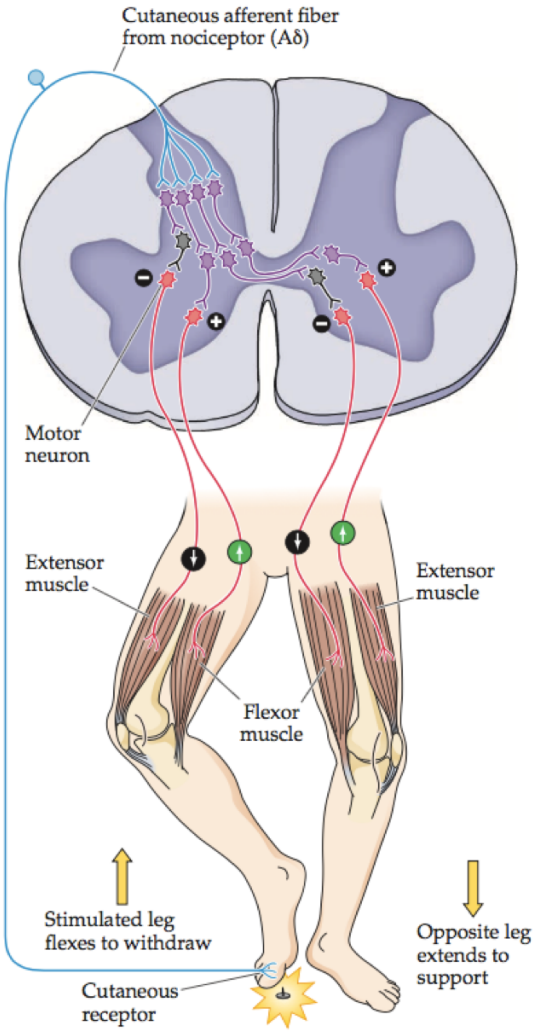
Kopierat från annan text:
A central motor program is a network of neurons, interconnected so that when the network is activated, a specific output pattern is generated that drives the proper motoneurons to produce a certain motor pattern.

Examples of innate motor programs are: the CPG for respiration, and the CPG for swallowing.

Learned motor programs, are for example those for precision grip.

(Väldigt lite info om motor programs, texten som är kopierad liknar det till central pattern generators iallafall)

4. DESCRIBE THE FLEXION REFLEX (=FLEXION CROSSED EXTENSION REFLEX) – WHICH NEURONS ARE INVOLVED AND HOW ARE THEY CONNECTED. WHAT IS THE ROLE OF THIS REFLEX?



If we step on something sharp like a needle, a nociceptor signal will be sent through an axon to the dorsal horn of the spinal cord. Here it will synapse with an interneuron that in turn will synapse with motor neurons. This signal will both be sent out on the ipsilateral side and the contralateral side.

IPSILATERAL SIDE

On the ipsilateral side the interneurons will send an inhibitory and a stimulating signal, the inhibitory goes to the extensor muscle to make it relax. Whilst the stimulating signal goes to the flexor muscle, this results in the leg flexing and us withdrawing our foot from the needle.

CONTRALATERAL SIDE

When we lift our foot away from the sharp object, we will automatically put all our weight on the contralateral leg. So, when the signal comes in the interneurons will send an inhibitory and stimulating signal to the contralateral side as well resulting in a tension in that leg so that we can lift the other foot. The inhibitory signal will go to the flexor muscle and the stimulating to the extensor muscle.

(a good animation from the book https://www.youtube.com/watch?v=vkyLnYnyZL4)

5. DESCRIBE THE CONTROL SYSTEM FOR LOCOMOTION.

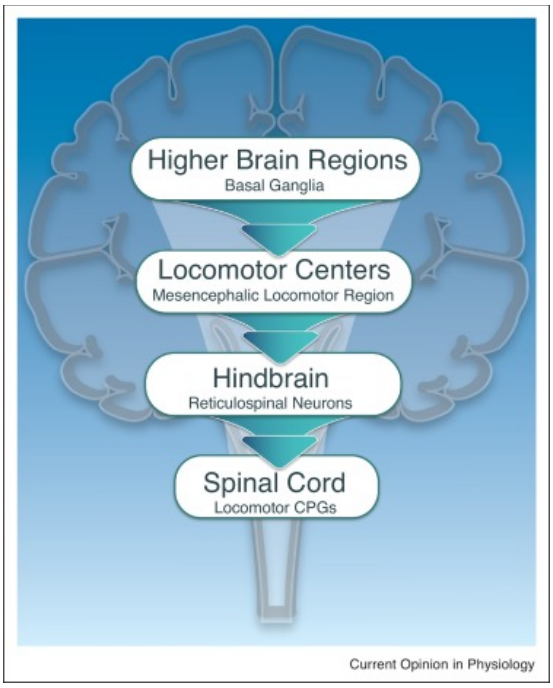
The central motor program for locomotion is located in the spinal cord, here we have central pattern generator (CPG) for each limb that is responsible for extension and flexion of the limbs.

The CPG is composed of local circuit neurons, which includes the glutamatergic neurons that are coupled to each other, inhibitory GABAergic and glycinergic neurons. But it is not well understood how different rhythms are generated, but some studies have shown that it

depends on the intrinsic membrane properties of excitatory local circuit neurons and the distribution of connections within the circuit.

The CPGs for the limbs are coupled with each other by modular circuits that coordinate left-right and forelimb-hindlimb activities, to get different sequences of movement in different speeds,

The CPG receives input from reticulospinal neurons from the brainstem, which are controlled by the mesencephalic locomotor region (MLR) and the subthalamic locomotor region (SLR), the MLRs are activated by disinhibition from the Basal Ganglia output nuclei (SNr).



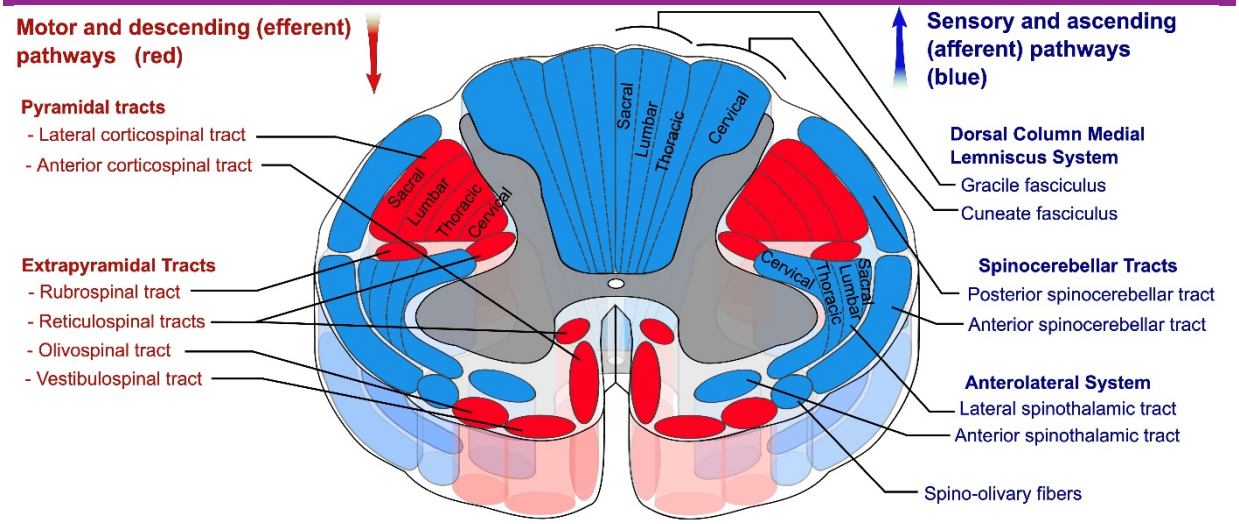
MLR and SLR are used for eliciting locomotion in different behavioral contexts. When MLR is stimulated it initiates locomotion to walk forward, in order not to change the direction. But when the SLR is activated searching locomotor behavior is induced. The MLR and SLR is found in the brainstem. The neurons of MLR are controlled by the basal ganglia, the neurons of BG project to the MLR and are inhibitory neurons, so this is used when we want to stand. But when we want to move the neurons of basal ganglia get inhibited.

The spinal locomotor CPGs are subjected to sensory influences. An afferent input from the limb assists in switching from one phase of the locomotor to another. For example it assists the limb to go from stance to swing by activation of afferent signals from the hip flexor afferent (from muscle spindles) and the signal from group Ia afferents from the extensor muscles disappear.

The cerebellum modifies the locomotion movements, without it the walking process becomes uncoordinated. It receives two inputs: one from the limb about the ongoing movement and one from the locomotor CPGs about the intended movement.

Commands for visually induced modifications of the locomotor pattern come to the spinal locomotor CPG from the motor cortex. Example: when we see an obstacle the swing phase become higher.

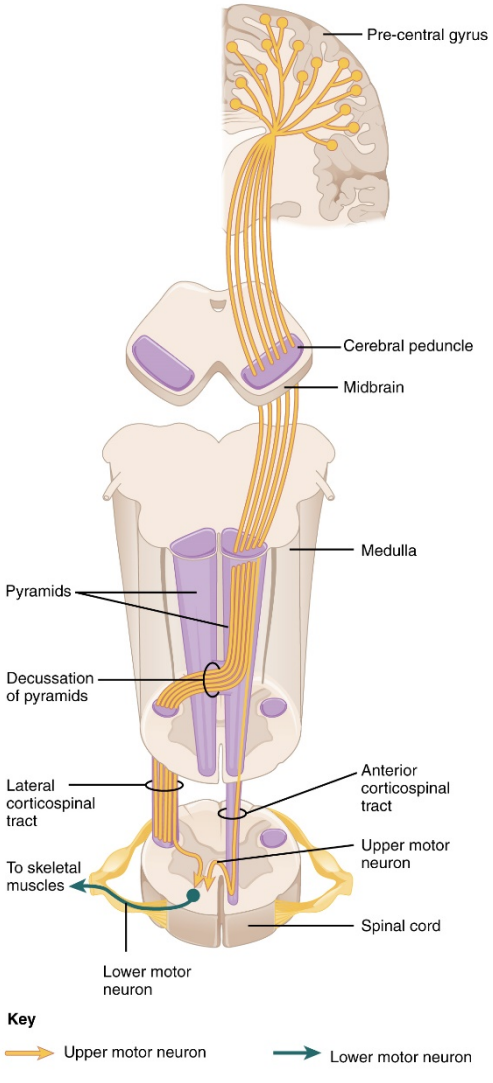
6. DESCRIBE THE FUNCTIONAL ORGANIZATION OF THE DESCENDING TRACTS: WHERE ARE THEY LOCATED IN THE SPINAL CORD AND WHAT ARE THEIR ROLES IN MOTOR CONTROL.



Descending tracts carry motor information in efferent nerves from upper motor neurons of cortical structures (like the cerebellum and cerebrum) to lower motor neurons, allowing it to reach muscles.

There are several motor tracts in the spinal cord; some of these are under conscious control and others under unconscious, reflexive or responsive control. These motor tracts can be grouped functionally into pyramidal and extrapyramidal tracts:

- **Pyramidal:** conscious control of muscles from the cerebral cortex to the muscles of the body and face; and
- **Extrapyramidal:** unconscious, reflexive or responsive control of muscles from various brainstem structures to postural or anti-gravity muscles



PYRAMIDAL TRACTS

The pyramidal tracts are so named because they run through the pyramids of the medulla oblongata and are responsible for the conscious, voluntary control of the body and face muscles.

They can be divided into two tracts that supply each of these areas:

- **Corticospinal tract (CST):** cortex to spine (body)
- **Corticobulbar tracts (CBT):** cortex to 'bulb'

CORTICOSPINAL TRACT

The CST communicates with three major cortical areas:

1. Primary motor cortex: located in the precentral gyrus; execution of movements
2. Premotor cortex: responsible for the control of behaviour, particularly of the trunk muscles
3. Supplementary motor cortex: stabilisation and coordination of the body during bimanual movements

As the CST passes through the caudal medulla, it divides into the lateral and anterior corticospinal tracts:

- **Lateral CST:** decussate in the pyramid of the medulla
- **Anterior CST:** stay ipsilateral

These tracts then descend into the spinal cord, terminating in the ventral horn of the spinal cord where they synapse onto lower motor neurons to supply the peripheral musculature.

CORTICOBULBAR TRACTS

Arising from the lateral aspect of the primary motor cortex (the cephalic region of the motor homunculus), the CBTs receive mostly the same inputs as the CSTs.

They follow a similar path but terminate in the brainstem at the motor nuclei rather than continuing down to the spinal cord. In the brainstem, they synapse on the cranial nerve motor nuclei, which are lower motor neuron structures that supply the head and neck muscles.

EXTRAPYRAMIDAL TRACTS

The extrapyramidal tracts all originate in the brainstem and do not pass through the pyramids.

These tracts all carry motor fibres to the spinal cord that allow for unconscious, reflexive or responsive movement of muscles to control balance, locomotion, posture and tone. There are four tracts:

- Reticulospinal
- Vestibulospinal
- Rubrospinal
- Tectospinal

RETICULOSPINAL TRACTS

The reticulospinal tracts do not decussate (decussation refers to a crossing within the central nervous system).

There are two reticulospinal tracts:

- **Medial reticulospinal tract:** originates in the pons and contributes to voluntary movements and increases in muscle tone in response to alerting or activating stimuli that stimulate the reticular activating system;
- **Lateral reticulospinal tract:** originates in the medulla and contributes to inhibition of voluntary movements, and also reduces muscle tone.

VESTIBULOSPINAL TRACTS

The vestibulospinal tracts do not decussate.

There are two vestibulospinal tracts that control anti-gravity muscles (a muscle that acts, often through the stretch reflex, to counterbalance the pull of gravity and to maintain an upright posture) via lower motor neurons:

- **Medial vestibulospinal tract:** originates in the medial vestibular nucleus, to control ipsilateral postural and tone adjustments in response to the vestibular apparatus.
- **Lateral vestibulospinal tract:** originates in the lateral, superior and inferior vestibular nuclei, to control ipsilateral postural and tone adjustments in response to the vestibular apparatus.

RUBROSPINAL TRACT

The rubrospinal tract decussates.

The rubrospinal tract begins in the red nucleus, where fibres immediately decussate and descend through the pons and medulla and into the spinal cord.

It is thought that the rubrospinal tracts supply upper limb flexors as well as trunk flexors. Disinhibition of the rubrospinal tract leads to upper limb flexion. Inhibition of the rubrospinal tract leads to upper limb extension.

TECTOSPINAL TRACT

The tectospinal tract decussates.

The tectospinal tract begins in the tectum, or roof of the midbrain, where the superior and inferior colliculi are located. Collectively, the two superior and two inferior colliculi are referred to as corpora quadrigemina.

The superior colliculus is involved in reflexive responses to visual stimuli.

The inferior colliculus is involved in reflexive responses to auditory stimuli.

Together, the colliculi send information about sights and sounds to the tectospinal tract, which decussates soon after leaving these structures, to supply muscles of the head and neck for reflexive localisation of these stimuli.

7. DESCRIBE BRIEFLY THE ROLES OF THE FOLLOWING THREE CORTICAL AREAS IN MOTOR CONTROL: PRIMARY MOTOR CORTEX (M1), DORSAL PREMOTOR CORTEX, AND SUPPLEMENTARY MOTOR CORTEX (=MEDIAL PREMOTOR CORTEX).

The motor cortex is a region in the frontal lobe, it's involved with voluntary movement and is located anteriorly to the central sulcus. The motor cortex can be divided into regions in different ways. Either as the primary motor cortex and the nonprimary motor cortex or further divided into the primary motor cortex, dorsal premotor cortex and supplementary motor cortex (or medial premotor cortex).
The motor cortex receives regulatory signals from the cerebellum and basal ganglia via the ventral thalamus as well as sensory information from the primary somatosensory cortex.

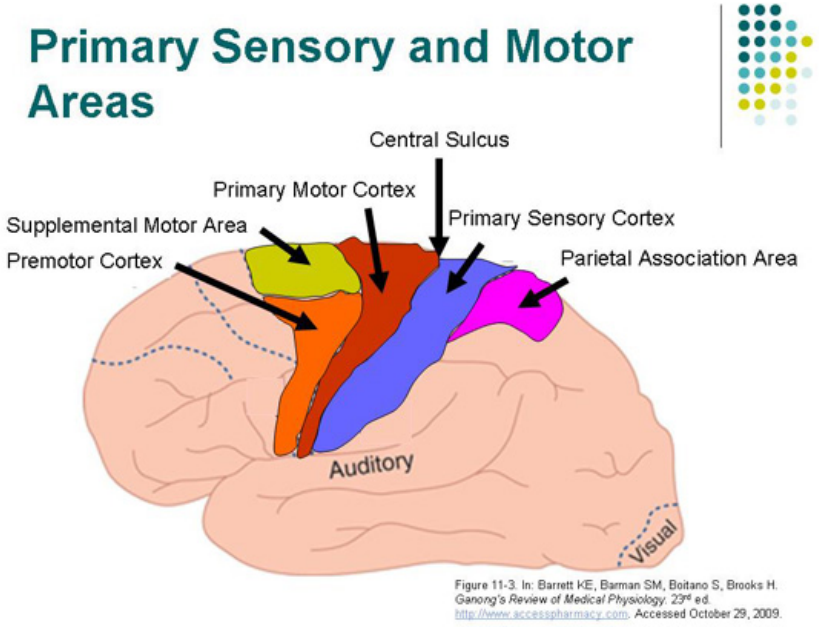


Figure 11-3. In: Barrett KE, Barman SM, Boitano S, Brooks H. *Ganong's Review of Medical Physiology*. 23rd ed. http://www.accesspharmacy.com. Accessed October 29, 2009.

PRIMARY MOTOR CORTEX

Primary precentral gyrus motor has a control motor/topographic map that indicates the division of movements. The primary motor cortex initiate movements. Most of neurons that travel from the primary motor cortex carrying signals about movement will enter either the corticospinal or the corticobulbar tract. Cortical spinal carries signal to spinal cord to cause movement of the body. Corticobulbar tract signals to the brainstem to cause movement of head neck and face

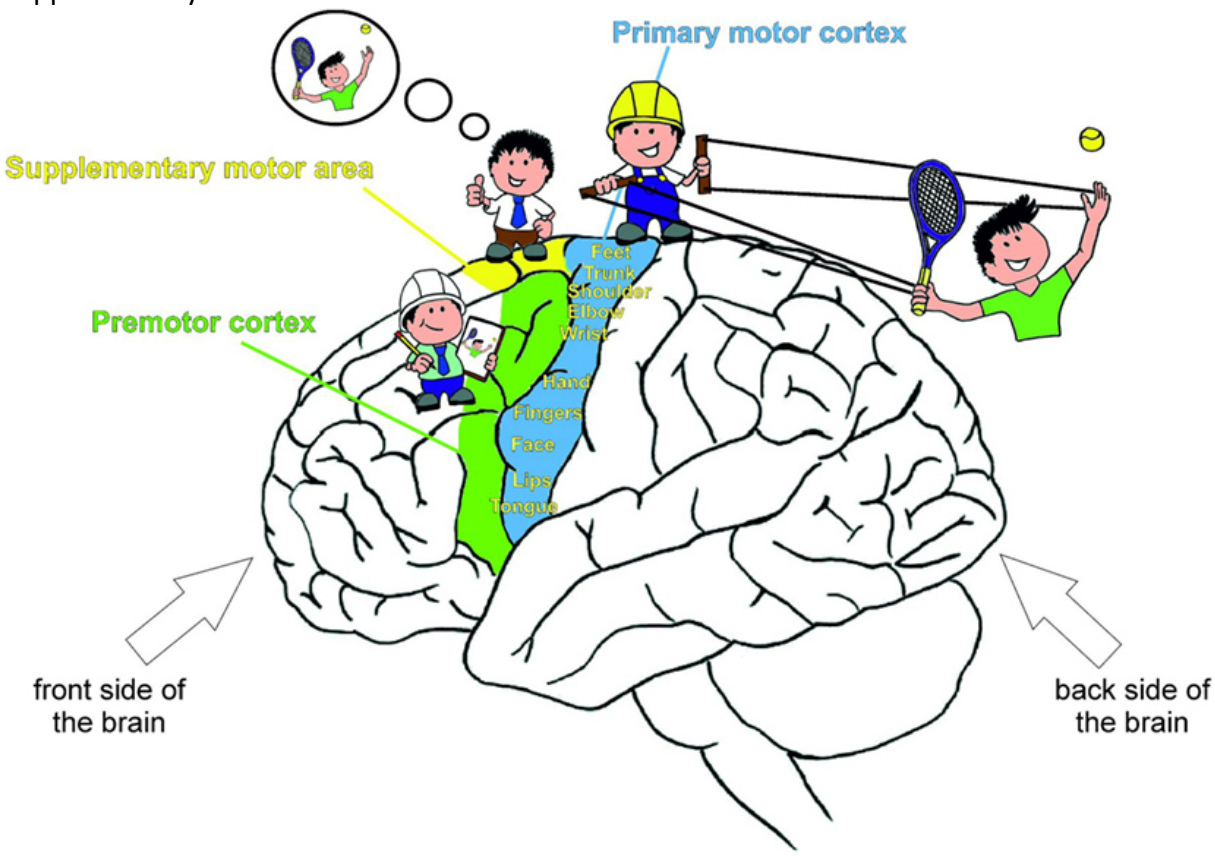
PREMOTOR CORTEX

The premotor cortex is not as well understood as the primary motor but makes up about 30 % of the neurons that enter the corticospinal spinal tract. However, it seems its more active during planning and preparing of movements i.e. It's important for selection of movements after a sensory input. The selection of which movement that is going to be planned depends

on the sensory input, when it's a planned movement it's thought to be trough the mirror neurons and when it's a situation related movement it seems to be situation related neurons.

SUPPLEMENTARY MOTOR CORTEX (MEDIAL PREMOTOR CORTEX)

Is not as well understood as the primary motor cortex but is believed to be involved in the execution of sequences of movement, the attainment of motor skills and he selection of movements based in incoming sensory information. It programs movements that are memorised, the neurons activate when a complex learned movement are executed or that one think of how movements are executed. Sends information to the primary motor cortex. The premotor cortex is mostly activated when a movement is not memorised and the supplementary motor cortex when an movement is memorised.



8. THE BASAL GANGLIA: WHAT IS THEIR GENERAL ROLE IN MOTOR CONTROL AND WHAT ARE THE FUNCTIONS OF THE DIRECT AND INDIRECT PATHWAYS.

The general role of the basal ganglia is gating proper initiation of movement, meaning that they are responsible for activating the right motor program and to stop unwanted movement input to pass forward to the thalamus etc.

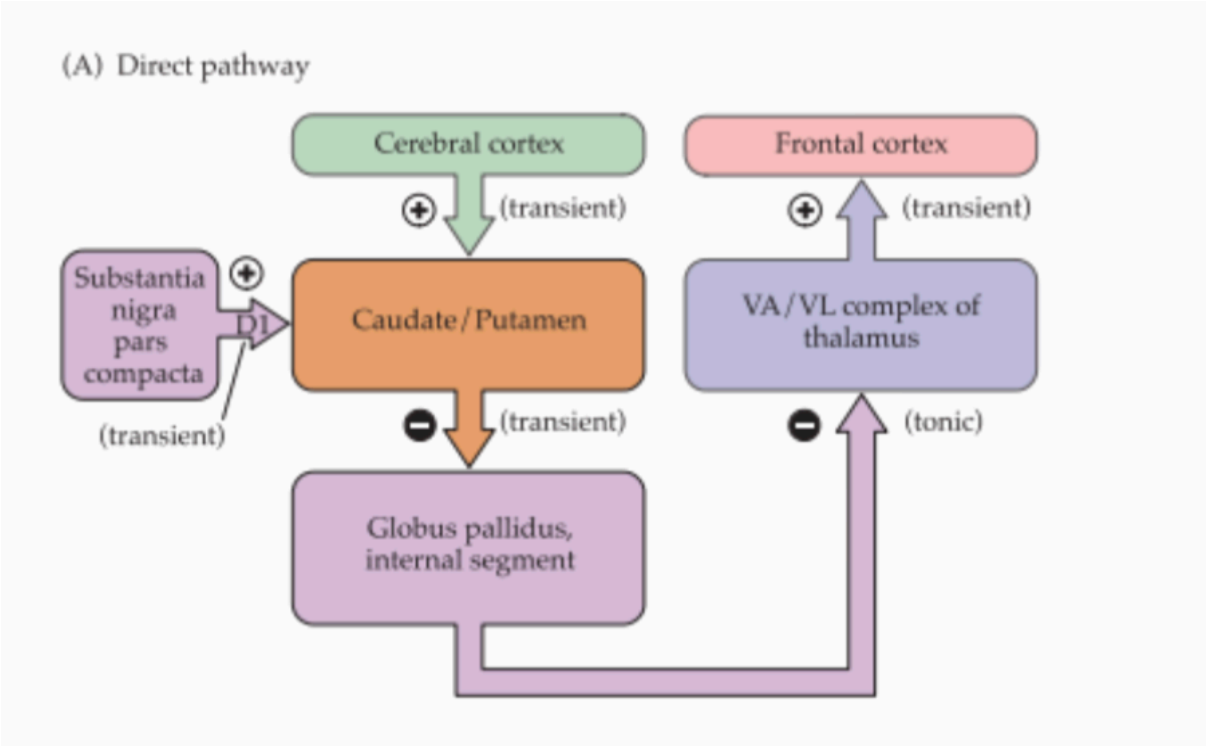
Direct pathway: lead to a movement.
Indirect pathway: suppression of unwanted movement.

The general function of basal ganglia is to stop unwanted movements and to activate wanted movements.

The output of the basal ganglia is GABAergic which leads to tonical inhibition of its efferent targets. Activation of the ganglia by the cerebral cortex will lead to disinhibition of these regions and selection of certain motor programs. The projection neurons within the basal ganglia are also dopaminergic, meaning that dopamine release from the substantia nigra pars compacta will modify the activity of the ganglia. The output neurons from the striatum are called medium spiny neurons.

Once activated by for example the cerebral cortex, the basal ganglia contain a direct and an indirect pathway for efference to motor regions such as the VA/VL-complex. Activation of the direct pathway leads to disinhibition of the VA/VL-complex which gives excitatory output to motor areas. In other words, activation of the direct pathway leads to selection of movement. The direct pathway also contains neurons with excitatory D1-dopamine receptors meaning that dopamine release will further disinhibit the VA/VL-complex.

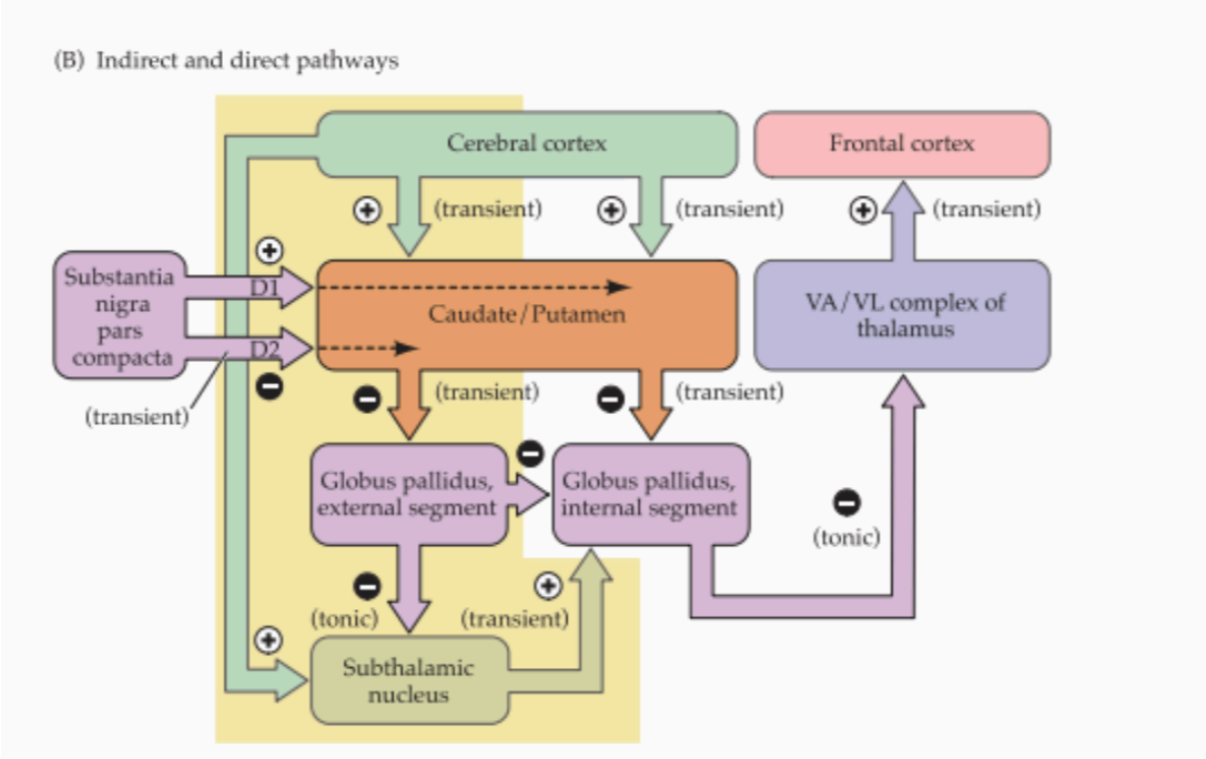
The pathways itself consists of excitatory input to the striatum which in turn gives inhibitory input to the internal globus pallidus. This lowers the inhibitory output of the ganglia, leading to disinhibition of for example the VA/VL-complex.



The indirect pathway involves the external globus pallidus as well as the subthalamic nucleus. Activation will give effects opposite to activation of the direct pathway, thus leading to increased inhibition of motor areas. The neurons of the indirect pathway contain inhibitory D2-receptors meaning that dopamine release will inhibit activation. Dopamine release will in other words always promote movement by inhibiting the indirect pathway and by activating the direct pathway.

Activation of the indirect pathway (marked by yellow in the image below) leads to inhibition of the external globus pallidus. This in turn lessens the inhibitory output to the excitatory

subthalamic nucleus. Disinhibition of the subthalamic nucleus (in combination with direct activation by the cortex) will lead to excitation of the internal globus pallidus. This activation of the internal segment will counteract the inhibition of the direct pathway, leading to increased tonical inhibition of the VA/VL-complex.



9. GIVE AN EXPLANATION OF THE HYPOKINESIA SYMPTOMS SEEN IN PATIENTS WITH PARKINSON´S DISEASE.

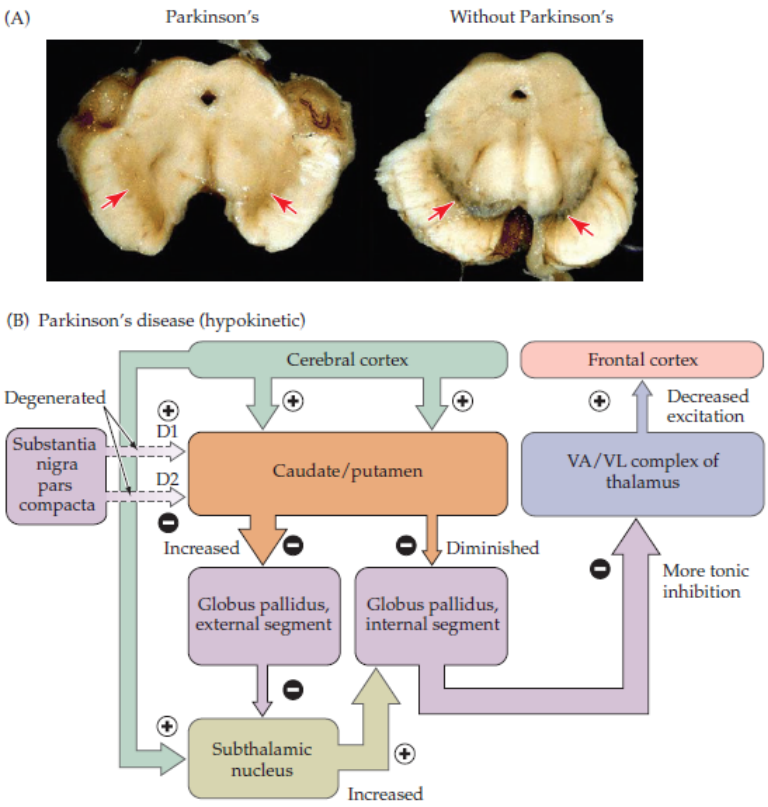


FIGURE 18.9 Degeneration of dopaminergic neurons reduces voluntary movement in Parkinson's disease. (A) In the midbrain of an individual with Parkinson's disease, the substantia nigra (pigmented area) is largely absent in the region above the cerebral peduncles. The midbrain from an individual without Parkinson's disease shows intact substantia nigra (cf. regions indicated with red arrows). (B) In Parkinson's disease, the dopaminergic inputs provided by the substantia nigra pars compacta are diminished (dashed arrows), making it more difficult to generate the transient inhibition from the caudate and putamen. The result of this change in the direct pathway is to sustain or increase the tonic inhibition from the internal segment of the globus pallidus to the thalamus (thicker arrow than corresponding arrow in Figure 18.7B), making thalamic excitation of the motor cortex less likely (thinner arrow from thalamus to frontal cortex). (© 2010, European Association for Predictive, Preventive and Personalised Medicine; B after DeLong, 1990.)

Hypokinesia is a decrease of voluntary movements due to a disruption in the basal ganglia. Parkinson's disease was described by James Parkinson in 1817 as a disorder characterized by tremor at rest, slowness of movement (bradykinesia), rigidity of the extremities and neck, and minimal facial expressions. Unlike other neurodegenerative diseases, Parkinson's disease has a spatial distribution of degenerating neurons that are largely restricted to the substantia nigra pars compacta.

Normally the release of dopamine in the striatum increases responsiveness of the direct pathway to corticostriatal input (a D1 effect) while decreasing the responsiveness of the indirect pathway (a D2 effect). Typically, both of these dopaminergic effects serve to decrease the inhibitory outflow of the basal ganglia and thus increase the excitability of upper motor neurons. In Parkinson's disease, however, when the dopaminergic cells of the pars compacta are destroyed the inhibitory outflow of the basal ganglia is abnormally high and timely thalamic activation of upper motor neurons are therefor less likely.

10. THE ROLES OF CEREBELLUM ARE TO CORRECT MOTOR ERRORS DURING ONGOING MOVEMENTS AND TO PARTICIPATE IN MOTOR LEARNING. WHICH TYPES OF SIGNAL ARE IMPORTANT FOR CORRECTION OF MOTOR ERRORS? DESCRIBE ALSO THE CELLULAR MECHANISMS IN THE CEREBELLAR CORTEX THAT UNDERLIE MOTOR LEARNING.

Cerebellum receives afferent info from the vestibular apparatus and the motor cortex as well as receiving proprioception info and sends efferent info to the motor cortex. The cerebellum has several functions such as balance, equilibrium, muscle tone, coordination of movements and motor learning. . It has many different functions it's primarily associated with movement and specifically facilitating movement by detecting errors that occur in the

course of a movement and correcting them. It's also involved in motor learning to reduce the likelihood of errors in the movement will occur again in the future.

When it comes to movement the cerebellum has an important role, it compares sensory information of the movement currently executed with efferent information about the planned movement. It can modify an activity in the motor program so that it resembles the planned movement and then sends a signal to cortex. The coordination happens both during and after movements. This is important for the correction of motor errors.

The cerebellum consist of two cerebellar hemispheres and can be divided into 3 parts, the cerebrocerebellum receives input from the cerebral cortex and is involved with planning and initiating movements. The spinocerebellum receives information about the limb position, touch and pressure sensations from the spinal cord. It uses this information to compare where a limb is in space with where it should be if the movement were going as planned. If there's a discrepancy the spinocerebellum can modify motor signals to correct any errors. The vermis runs along the midline of the cerebellum and is involved with posture, limb movement and eye movement. Vestibulocerebellum or the flocculonodular lobe is important for maintaining equilibrium, balance and posture.

The cerebellum communicates with the rest of the nervous system through three large pathways called the cerebellar peduncles which include the superior, middle and inferior. When information is sent to the cerebellum it takes an indirect path to reach branched cells that are called purkinje cells. The purkinje cells project to a group nuclei in the centre of the cerebellum called the pbellar nuclei. The purkinjebellar nuclei sends information to various areas in the brainstem and thalamus that then can influence motor areas of the cortex or the descending motor tracts to modify movements.

MOTOR LEARNING

The cerebellum receives input from two main sources, the mossy fibres and climbing fibres. The mossy fibres arise from a variety of brain fibres such as the spinal cord and motor cortex. The mossy fibres synapses to the cerebellum cortex and deep cerebellum nuclei and these provide input to the granual cells and are thought to encode information of voluntary limb movements.

The climbing fibres comes from the inferior olivary nucleus that are in the medulla oblongata and gets information from the ascending fibres spinal cord and areas of cortex. The climbing fibres tightly wraps around the purkinje cells, there are many synapses created between them, every purkinje cell gets information from just on climbing fibre however, on climbing fibre can connect to up to 10 purkinje cells.

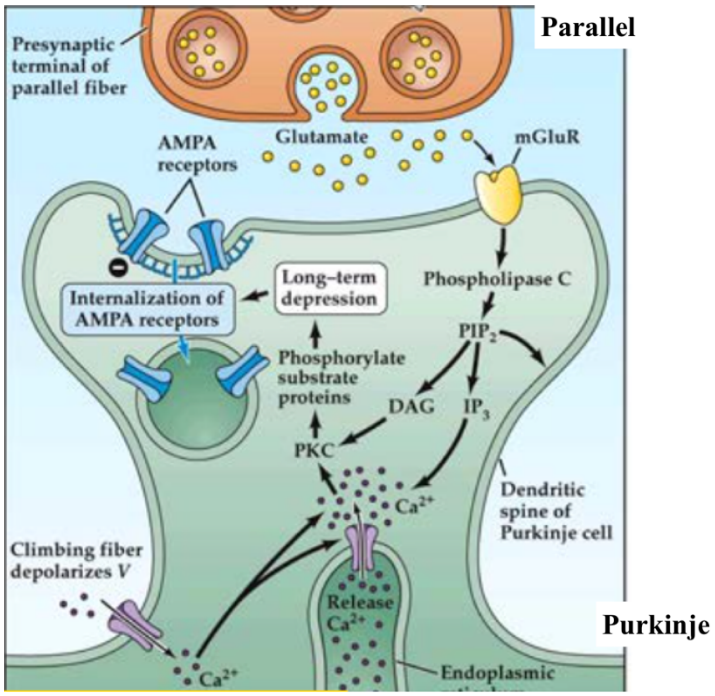
Motor learning in the cerebellum is believed to depend on the modulation of efferent signals from the cerebellum cortex. If a motor error is detected climbing fibres send signals to Purkinjean cells that can; activate a parallel fibre which leads to action potential in the purkinje cell or activation of a climbing fibre. The climbing fibre creates complex spikes in the purkinje cell, these spikes differ depending on the movement. If it's a simple movement the olive nuclei are inactive and there are no complex spikes activated, if it instead is a complex movement the olive nuclei are very active and there will be several spikes since a lot of the

climbing fibres are activated. When a complex movement is repeated and becomes more effective there will be fewer complex spikes.

The connection between purkinje cells and climbing fibres is one of the strongest excitatory synapses in the brain, this leads to the creation of plasticity in the purkinje cells. This plasticity is an important part of motor learning. The climbing fibres create a long-term depression (LTD) in the synapses between the parallel fibres and the purkinje cells. LTD is when climbing fibres and parallel fibres are activated at the same time which leads to a random detector mechanism. This happens in the following way;

1. Parallel fibres release glutamate in the synapses between the purkinje cells and themselves.
2. The release of glutamate activates AMPA-R and metabotropic-R. The AMPA-R leads to depolarisation whilst the Metabotropic-R activate PLC that in turn activates PIP_2 to IP_3 and DAG. IP_3binds to Ca^{2+} Channels that give an influx if Ca^{2+}
3. At the same time climbing fibres activate voltage gated channels in synapses between the climbing fibres and the purkinje cells that give rise to an influx if Ca^{2+}
4. This combined leads to activation of PKC through DAG. PKC mediates internalisation of AMPA-R in synapses between parallel fibres and purkinje cells.

This means that glutamate leads to the reduction of AMPA receptors and this is LTD. This through the activation of PKC.



11. WHICH ARE THE THREE FUNCTIONAL PARTS OF CEREBELLUM (BASED ON THEIR INPUTS) AND WHAT ARE THEIR RESPECTIVE ROLES? WHICH SYMPTOMS OCCUR AFTER LESION TO EACH OF THESE PARTS?

Cerebrocerebellum: is the largest subdivision in humans. It occupies most of the lateral part of the cerebellar hemisphere and receives input indirectly from many areas of the cerebral cortex. This region of the cerebellum is especially well developed in primates and is particularly prominent in humans. This subdivision is concerned with the regulation of highly

skilled movements, especially the planning and execution of complex spatial and temporal sequences of movement (including speech).

Lesions here can lead to problems with highly skilled learned movements such as playing a musical instrument.

Spinocerebellum: is medial to the cerebrocerebellum. This part occupies the median and paramedian zones of the cerebellar hemispheres and is the only part that receives input directly from the spinal cord. The more lateral part of the spinocerebellum is concerened primarly with movements of distal muscles. The most median strip of cerebellar hemisphere lies along the midline and is called the vermis.

Difficulty of walking can be a result of a lesion in this area.

Vestibulocerebellum: is the third major subdivision. This portion comprises the caudal-inferior lobes of the cerebellum and includes the flocculus and nodulus. Vestibulocerebellum receives input from the vestibular nuclei in the brainstem and is concerned primarily with the vestibulo-ocular reflex and with the regulation of movements that maintain posture and equilibrium.

Lesions here may result in problems in maintaining posture and maintaining the gaze.

12. DESCRIBE THE DIFFERENT TYPES OF EYE MOVEMENTS AND THEIR RESPECTIVE ROLES.

There are four basic types of eye movement:

- Saccades
- Smooth pursuit movements
- Vergence movements
- Vestibulo-ocular movements

Type of eye movement	Function	Stimulus	Clinical tests
Vestibular	Maintain steady fixation during head rotation	Head rotation	Fixate on object while moving head; calorics
Saccades	Rapid refixation to eccentric stimuli	Eccentric retinal image	Voluntary movement between two objects; fast phases of OKN or of vestibular nystagmus
Smooth pursuit	Keep moving object on fovea	Retinal image slip	Voluntarily follow a moving target; OKN slow phases
Vergence	Disconjugate, slow movement to maintain binocular vision	Binasal or bitemporal disparity; retinal blur motion	Fusional amplitudes; near point of convergence

OKN = optokinetic nystagmus.

SACCADES

Saccades are rapid, ballistic movements of the eyes that abruptly change the point of fixation. They range in the amplitude from the small movements made while reading, for example, to the much larger movements made while gazing around a room.

Saccades can be elicited voluntarily but occur reflexively whenever the eyes are open.

SMOOTH PURSUIT MOVEMENTS

Smooth pursuit movements are much slower tracking movements of the eyes designed to keep a moving stimulus on the fovea. Such movements are under voluntary control in the sense that the observer can choose whether or not to track a moving stimulus. Most people who try to move their eyes in a smooth fashion without a moving target simply make a

saccade (highly trained observers can, however, make smooth pursuit movements in the absence of a moving target).

VERGENCE MOVEMENTS

Vergence movements align the fovea of each eye with targets located at different distances from the observer. Unlike other type of eye movements in which the two eyes move in the same direction (conjugate eye movements), vergence movements are disconjugate (or disjunctive); they involve either a convergence or divergence of the lines of sight of each eye to see an object that is nearer or farther away. Convergence is one of the three reflexive visual responses elicited by interest in a near object. The other components of the so-called near reflex triad are accommodation of the lens, which brings the object into focus, and pupillary constriction, which increases the depth of field and sharpens the image on the retina.

VESTIBULO-OCULAR MOVEMENTS

Vestibulo-ocular movements stabilize the eyes relative to the external world, thus compensating for head movements. These reflex responses prevent visual images from "slipping" on the surface of the retina as head position varies. The action of vestibulo-ocular movements can be appreciated by fixating an object and moving the head from side to side; the eyes automatically compensate for the head movement by moving the same distance but in the opposite direction, thus keeping the image of the object at more or less the same place on the retina.

While the vestibular system operates effectively to counteract rapid movements of the head, it is relatively insensitive to slow movements or to persistent rotation of the head. Compensation in this case would be due to activation of the smooth pursuit system if the eyes are open.

TRUE/FALSE AND OTHER GOD THINGS COLLECTED FROM OLD EXAMS

ELECTRICAL PROPERTIES OF NEURONAL CELLS

THE FIRING FREQUENCY OF ACTION POTENTIALS

- The frequency at which a neuron elicits action potentials is often referred to as a firing rate or neural firing rate. Aa action potential is said to be all or none, if it goes above threshold there will be an action potential. The amplitude doesn't change no matter how strong the A.P is. However, it will encode the stimulus in frequency of action potentials instead. Since there are different thresholds on different neurons all the firing frequencies won't be the same.

- During the afterhyperpolarization there is a refraction period (falling phase= and relative refraction period (undershoot) period. During the refraction period the Na^{+}-channels are inactivated and no A.P can be generated, during the relative refraction period a strong enough stimulus can generate a A.P

- Ca^{2+} influx can indirectly affect the firing frequency of neuron since a neurotransmitter is released as a response to Ca^{2+} influx. If there is an high Ca^{2+} concentration in for ex. Presynaptic terminal it will result in more vesicles fusing with the membrane and release their neurotransmitters. This can lead to a higher firing frequency.

TIME AND SPACE CONSTANT + SUMMATION

- The space constant depends on how "easy" it is for ions to leak out. If it's a low membrane resistance i.e. many leaky channels $\Rightarrow\downarrow$ space constant
  $\uparrow$ resistant $\Rightarrow \downarrow$ leaky channels $\Rightarrow \uparrow$ space constant

- When an a.p is generated it's all or nothing. The time and space constants play no role in when an a.p is generated. However, they are important in the subthreshold phase in whether or not there will be an a.p (if it is going to go over the threshold).

- The summation of EPSP(=excitatory postsynaptic potential) depends on the decay of the first EPSP. So, if the EPSP hasn't gone down yet and another A.P comes the first EPSP will be summated with the new one. the time it takes for the EPSP to decay depends on the membrane size and the number of ions. The bigger membrane and the fewer ion channel the slower the decay. Time constant = resisters (number of channels) * capacitance (membrane size)

- $\uparrow$ membrane resistance = harder for ions to leak $\Rightarrow \uparrow$ space constant
  if $\uparrow$ space constant and $\uparrow$ time constant = the more efficient summations.

- Time and space constants don't determine the amplitude however they affect the propagation as well as the summation and thereby affect the frequency.

- An amplitude of an action potential is an all or nothing signal. A higher stimuli (if the compared threshold also reaches threshold) won't be larger, it can however give rise to several spikes.

- If we want neurons that will react fast we need to give them a low threshold and a high time constant. A high space constant = less leakiness of ions.

ACTION POTENTIAL AND DIFFERENT ION CHANNELS AND THEIR PROPERTIES.

- Propagation[4] is the transmission of action potential in the axon in a direction. This is done by active properties i.e. Na^{+}-channels that open along the axon to keep the a.p going. It also affects the amplitude. Blocked. Na^{+}-channels leads to $\downarrow$ amplitude of depolarisation and $\downarrow$ signalling between neurons/signals through the axon.

- The fast activation of Na^{+}-channels makes depolarisation and the a.p. their fast inactivation make so that it doesn't keep firing. So, the fast activation is essential for

[4] Propagation – fortplantning. Transmittion of motion in a particular direction through a medium

generating action potentials.

- All channels don't undergo inactivation. There are several types of channels and some are always open like the leaky ones.

- The structure of a channel determine the selectivity i.e. what type of ions that can go through the channel. But the flux of ions is not determined by the channel it's determined by the electric-chemical driving force.

- Gated ion channels can be activated from stimuli acting from both the inside and outside.

- Non-gated channels are always open. They don't pump ions through they only let them leak through and doesn't use energy doing that.

- Ionotropic(or also called ligand gated ion channels) are a type of gated ion channel.

- There are only non-gated (leaky) ion channels that actively contribute to the resting membrane potential.

- Some ion channels can become inactivated due to prolonged activation, an example of this is the sodium channels.

- Electrical synapses are fast synchronized, low in energy cost, but can't be modified and sent via complex signals. Electrical synapses pre and post synapses bind via GAP junctions and thereby can the action potential flow into the cell directly (can flow in both directions) and is very fast.

- The proporgation of an action potential is unidirectional (unlike graded potential) A.P propagation is facilitated by myelination because voltage gated sodium channels are concentrated at the rods of ranvier and the myelin insultates the axon and prevent ions from leaking out.

- The hyperpolarisation of a neuron is due to both voltage and ligand gated K+ channels.

ACETYL CHOLINE

- Acetyl choline is used as a neurotransmitter in motor neurons, postganglionic parasympathetic neurons, striatal cholinergic interneurons and cholinergic basal forebrain neurons.

- Acetyl choline is a classic neurotransmitter (also called small neurotransmitter) it's packed into vesicles in the presynaptic terminal into synaptic vesicles (also called

small synaptic vesicles). (neuropeptides are stored in large dense-cored vesicles)

- Acetyl choline receptors are:
    - Nicotinic receptors (nAChR) that are a ligand-gated ion channels also known as ionotropic receptors.
    - Muscarin receptors (mAChR) that are G-protein coupled receptors (second messenger system) also known as metabotropic.

- Acetyl choline is inactivated after the release into the synaptic cleft via acetyl cholinesterase that cleaves it to acetyl-CoA and choline. Choline is taken up by the presynaptic terminal via Na^+/choline symporter and reused.

- Pathology
    - There are different acetyl cholinesterase inhibitors (like neostigmine, rivastigmine and donezepil) that can be used to treat myasthenia gravis (more info higher up in document) , alzheimer's and glaucoma.
    - Nerve gas (sarin neurotoxin) inhibit the acetyl cholinesterase which leads to acetyl choline not being broken down and the impulses will be transmitted continuously. This results in muscle contractions, uncontrolled drooling, lacrimation and excess production of mucus from the nose.

PAIN PHYSIOLOGY

TYPES OF NOCICEPTORS:

- **Unimodal:**
    - Mechanosensitive – respond to intense mechanical stimulation that threaten to damage the tissue.
    - Thermosensitive – respond to temperatures >42 °C or <17 °C.
    - Chemosensitive – respond to the H +, K +, serotonin, bradykinin etc.

- **Polymodal** – respond to all types of nociceptive stimuli

- **Silent** – nerve endings that are normally not responsive to mechanical or thermal stimuli, but that are chemically activated during inflammation and then respond to mechanical and thermal stimuli.

DIFFERENT TYPES OF NEURONS IN THE DORSAL HORN THAT ARE ACTIVATED BY NOCICEPTIVE STIMULATION:

- Nociceptive specific (NS) neurons – are located in lamina I and have small receptive fields – receive input mostly from A-delta fibers – convey well localized (rapid) pain.

- Polymodal nociceptive neurons – are also located in lamina I but have large receptive fields – receive afference mostly from C-fibers – convey more diffuse (slow) pain.

- "Wide Dynamic Range" (WDR) neurons – receive input from both nociceptive and non-nociceptive afferents – lies in lamina 5 and has large receptor fields – convey more diffusely localized pain – some of them from visceral organs – possible substrate for referred pain.

PAIN AND PAIN FIBRE

first pain - A-delta fibre → first pain is brief, pricking and well localized

second pain - C-fibre → second pain is longer-lasting, burning and less well localized

SENSITIZATION

Sensitization is defined as increased responsiveness of nociceptive neurons to their normal input, and/or recruitment of a response to normally subthreshold inputs. It is also pointed out that spontaneous discharges and increases in receptive field size may occur.

hyperalgesia – increased response of nociceptive neurons to their normal input
allodynia – recruitment of a response to normally subthreshold inputs (=lowered threshold)
ongoing pain – spontaneous discharges

ACENDING PATHWAYS

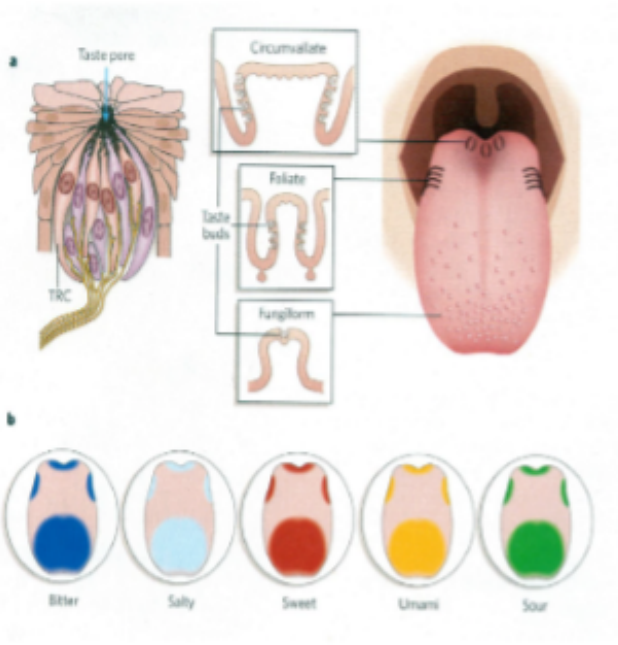
There are two major ascending nociceptive ("pain") pathways within the spinothalamic tract (anterolateral system);
- sensory-discriminative (neospinothalamic)
- affective- motivational (paleospinothalamic).

The sensory-discriminative (neospinothalamic) pathway:
Neospinothalmic --> VPL och VPI --> VPI to Primary sensory cortex, VPL to somatosensory cortex.

affective-motivational (paleospinothalamic) tract:
Paelospinothalamic --> intralaminar thalamus (where medial thalmic nuclei is included) --> anterior cingulate cortex and insula cortex.

TASTE

- Discrimination of bitter and umami (amino acids) both relies on the same mechanism $PLC\beta_2/IP_3/TRPM_5$. To the distinguishing occurs at the receptor level and separate channels for the relay of this information to the brain. Bitter uses T2R receptor and umami uses T1R1 and T1R3 receptors.



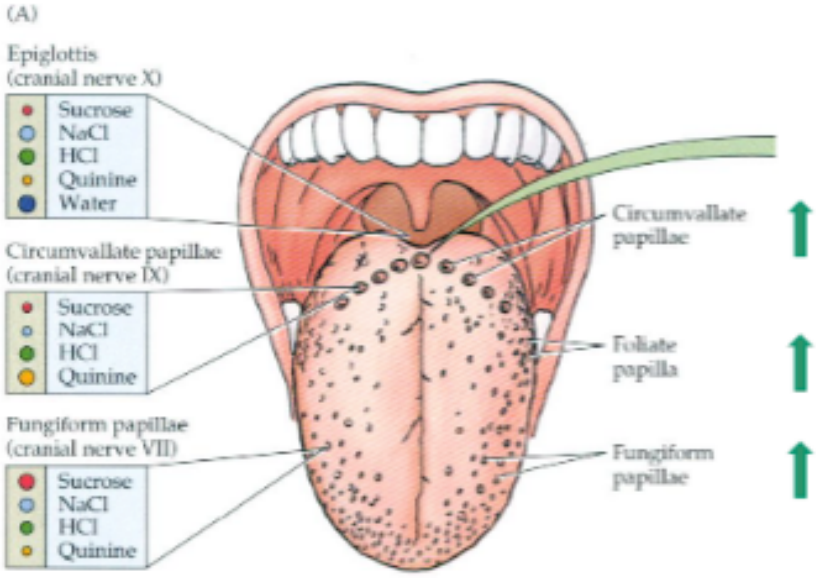
3 types of papillae:

Circumvallate, bitter, 48%, glossopharyngeal (IX)

Foliate, sour, 28%, glossopharyngeal(IX)

Fungiform, sweet and salty, 24%, facial nerve (VII) Red spots (rich in blood vessels)

Filiform *non-gustatory, texture sensors*



Chemical stimuli on the tongue first stimulate receptors in the fungiform papillae and then the foliate and circumvallate papillae.

MOTOR FUNCTIONS

- **Corticospinal tract from cortex cerebri via medulla spinalis to the hand:** cortex cerebri → centrum semiovale → corona radiata →capsula interna → ventral mesencephalon forming crus cerebri →ventral pons → forming pyramis medullae oblongatae (here the ,ajprity of the fibers decussate) → dorsal lateral spinal cord → cervical region → ventral horn → muscles of the hand

- The axons of the corticospinal tract receive their blood from: The axons begin by getting their blood from the carotis interna (mainly from a. cerebri media). s at the

level of crus cerbri the blood supply changes to the a. vertebralis and a. basilaris system.

- the primary motor cortex contains large neurons known as betz cells. Betz cells along with other cortical neurons send long axons down the spinal cord to synapse onto the interneuron circuitry of the spinal cord and also directly onto the alpha motor neurons in the spinal cord.

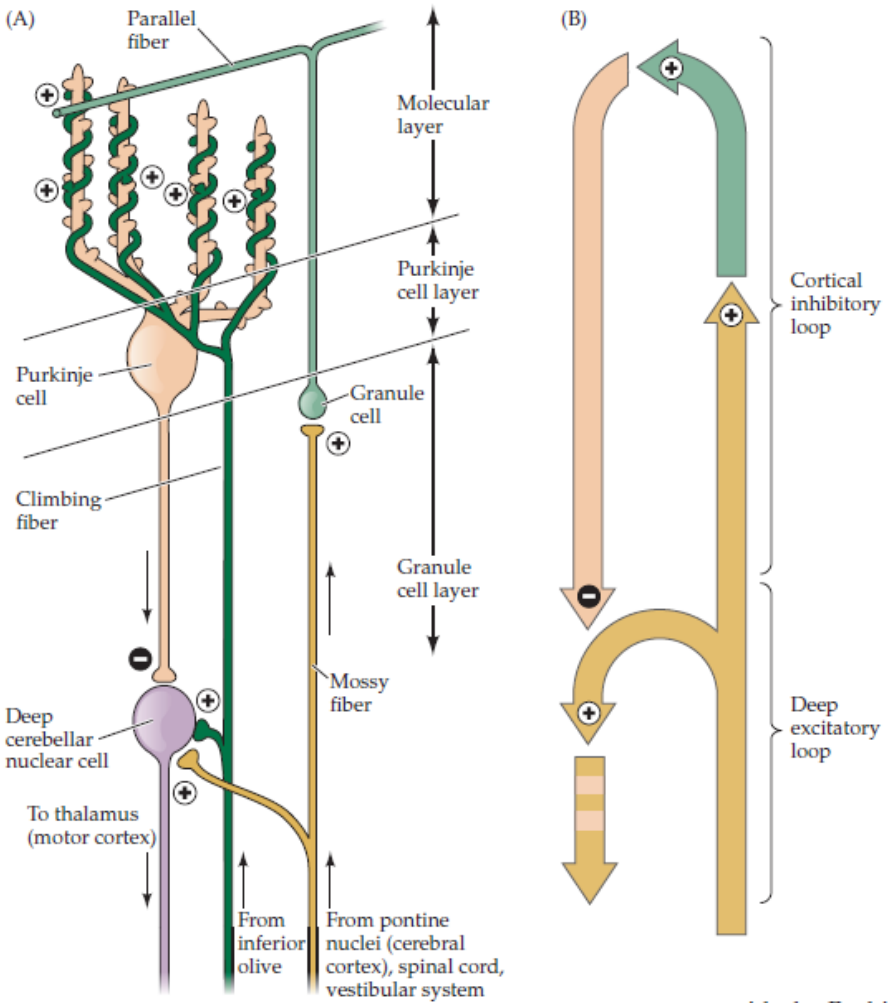
- surgical removal of M1 --> initial impairment but good recover of many general motor behaviours (walking, jumping, climbing, etc). However, a permanent inability to form precision grip.

- M1 =primary motor cortex, in gyrus precentralis. a. cerebri anterior supplies the medial aspects of the frontal and parietal lobes of the cerebral hemispheres. However, branches of **a. cerebri media** provide most of the arterial blood supply for the primary motor cortex. a. cerebri anterior does however supply the medial aspects (legs) of the M1

- the alpha motor neurons are lower motor neurons whose cell bodies are found in the anterior horn of the spinal cord (Anterior horn = ventral horn) and whose axons travel down to the body to innervate skeletal muscles to cause muscle contractions.

- superior colliculus is important in behavioural response to an environmental stimulus. Eye and head movement are a part of this as well as other responsive movements

CEREBELLUM MOTOR FUNCTIONS



- The cerebellar cortex recive info from the motor cortex and spinal cord via mossy fibers and climbing fibre. these send information directly to the deep cerebellar nucleus (DCN) that are excitatory. They also send information to the purkinje cell that sends the information to DCN but as an inhibitory input. The picture above shows this.

- The purkinje neurons (purkinje cell or fiber, have no clue what the difference is) receive inputs from different cells. They receive axodendric input from granule cells that are called parallel fibre connections. They also receive axosomatic input from the inferior olive, this are called climbing fibre input. They also receive local interneurons from basket input, golgi input and stellate input. All these inputs are a part of shaping the purkinje activity.

- **According to a model proposed by Ito and colleagues, inferior olive input to the cerebellum takes the form of a learning signal associated with motor learning?**
  One way to achieve weakening of Purkinje (P) activity is to induce long-term synaptic depression. This occurs when parallel fibre input is concurrent with climbing fibre input, thus, triggering AMPA internalization because of heightened levels of intracellular calcium hence activating second messenger systems, i.e. Phospho-Kinase C (PKC) pathways that will internalize AMPA receptors causing LTD on Purkinje neurons and reducing their excitability for as long as 20-30 minutes. During this

period, DCN activity may increase because of reduced inhibition. Without climbing fibre input, DCN are inhibited by P cells, hence low 'motor learning' output coming out of the cerebellum to affect cortical activity.

CIRCADIAN SYSTEM

- The function of the circadian rhythm is **synchronization** of biological processes in the body so that they are aligned with each other and the environment. This is an **adaptation** to changes of light/darkness in the environment. The system allows us to not only react but also **anticipate** and prepare the body for the changes in light/darkness

- Light in the morning shortens the circadian rhythm making a person more of a morning type. Since people with a shorter circadian rhythm is more of a morning person. We are very dependent upon light in the circadian rhythm the fact Is that humans actually have a system to wake up right before the sun goes up so that it won't startle us. Light in the evening or night will lead to less melatonin being released and thereby delaying the rhythm so we become more of night person.

- Light during the middle day is still supportive of health, but does not cause a delay or shortening of the rhythm. Not being exposed to light increases the risk of depression, obesity and diabetes for ex.

- **Regulation of circadian rhythm**

    1. Retinagagnlion cells in the eyes→melanopsin
        a. Retina ganglion cells register light →depolarize
    2. Send signal via n. opticus to anterior hypothalamus
    3. Synapse with Nucleus suprachiasmaticus (SCN) in hypothalamus
    4. SCN axons synapse with preganglionic sympathetic neuron
    5. Preganglionic sympathetic neuron project to Superior cervical ganglion
    6. Superior cervical ganglion sends postsynaptic sympathetic neuron
    7. Synapse with epiphysis
    8. Action potential inhibits production of melatonin
        a. Tryptophan→Melatonin
        b. Melatonin regulates the sleep/awake cycle
            i. Melatonin→at night →sleepy

- **SCN** is thought to be master regulator of circadian rhythm. Removal of SCN in animal studies showed abolished circadian sleep-wake cycle. SCN highest activity early in the morning/early afternoon & lowest after midnight. SCN can regulate some release of melatonin even without light that is why it is hard to fall asleep with closed eyes in a room with lights on.

- SCN also results in rhythms in the rest of the body.
  - Hormone secretion cycles
  - Body temperature
  - Blood pressure
  - Urine diures

- **To become more of a morning person**: As much daylight as possible in the morning, in combination with darkness/low light levels in the evening. Other factors include that melatonin can be used (in the early evening), and that one should avoid caffeine late in the evening (causing both a delay as well as potentially disturbing sleep).

STRESS

- **Seyle's "General Adaptation Syndrome"** – a stressor occurs and after a short while the body starts to cope with it by releasing more energy. More memory and attention is focused on the stressor. But after a while we have to pay it back i.e. the energy used during the cope time. This leads to exhausting phase (when reserves are depleted.)

- major neural pathways involved in the stress response is a very fast response of the Autonomic nervous system (ANS, both the involvement of the parasympathetic nervous system and the sympathetic nervous system). The ANS reacts to acute stress and the changes occur in seconds, the first response being an inhibition of the parasympathetic nervous system, directly followed by an activation of the sympathetic nervous system. This has large effects on our physiology, cognitive functioning and behaviour. For example, the fast ANS affects pupil size, heart rate, blood pressure, hand sweating, gives focus.

- Major neuroendocrinological pathways involved in the stress response is the Hypothalamic-pituatiry-adrenal (HPA) axis. The HPA-axis takes longer time to react, normally 20-30 minutes, and regulates many body processes including metabolic, digestion, immune functioning, For example, cortisol assures availability of glucose so that the person has energy to deal with a stressful situation.

SYNAPTIC TRANSMISSION

TYPE OF STRENGTHENING THAT LASTS FOR MILLISECONDS

Facilitation. It is due to successive accumulation of calcium in the presynaptic terminal during repetitive action potential stimulation.

TYPE OF STRENGTHENING THAT LASTS FOR UP TO A FEW HOURS

The early phase of long-term potentiation (LTP). It is triggered by brief high-frequency trains of action potentials that leads to opening of voltage-sensitive NMDA channels giving rise to calcium influx. This results in activation of kinases that eventually give rise to insertion of more AMPA receptors in the postsynaptic membrane (by exocytosis)

TYPE OF STRENGTHENING THAT LASTS FOR DAYS, WEEKS OR EVEN LONGER

The late phase of long-term potentiation (LTP). It is also triggered by brief high- frequency trains of action potentials that leads to opening of voltage-sensitive NMDA channels giving rise to calcium influx. This results in activation of kinases that eventually cause activation of transcription factors (such as CREB) resulting in increased expression of different genes encoding synaptic proteins. Thereby synapses can be enlarged and/or new synapses can form.

BRAIN FUNCTIONS THAT ARE LATERALIZED

- Language is lateralized so that about 90% of right handed people have their language centers, Broca's and Wernicke's area, in the left hemisphere. Only about 50% of left handed people have this laterialization, both symmetric and right-hemsphere representation is more common in this group.

- Somatosensory and motor processing is lateralized, so that information from the right side of the body is processed in the left hemisphere and vice versa. This is also roughly true for other sensory functions, but a bit more complex, for example, for the eyes, this lateralization is related to the visual field rather than the eyes.

- There is some support for the brain hemispheres to have different perceptual processing styles so that left hemisphere processing is more focused on details (local processing) while right hemisphere processing is disposed to be more holistic (global processing).

- The right parietal lobe is in most individuals more involved in spatial attention than the left hemispehere.

LESION

From a lesion in the right parietal lobe a attention problem called left hemispatial neglect syndrome can occur.

THE ROLE THE MESOLIMBIC DOPAMINE SYSTEM PLAY IN ADDICTION

It is important for learning which stimuli that gives reward, i.e. it is central for associating the drug with pleasure. Additionally, the activity of this system increases when a drug dependent person sees something that he / she associates with drug intake, eg cues that are correlated to drug craving. This is also called "wanting" and differs from "liking" that corresponds "to the well-being"/"rush you get from the drug."

In addition, addiction(andabuse)over time often leads to a down regulation of the dopaminergic system, which results in the need to increase the dose to get the same effect.

THE ROLE THE MESOLIMBIC DOPAMINE SYSTEM PLAY IN REWARD SYSTEM

Ventral Tegmental Area (VTA) and nucleus accumbens/ventrala striatum.

Evidence: In principle, all addictive agents increase dopamine levels in this system.
- Also natural rewards (like sex) activate this system.

- Dopamine neurons that originate from these areas and that project to nucleus accumbens regulate "salience" (motivation and desire), which is important input for choosing between different behaviors.
- Rats learning self-administration of drugs stop taking them if you block dopamine receptors at the nucleus accumbens with a D2-receptor antagonist.

PYRAMIDAL TRACTS

The pyramidal tracts include both corticospinal and corticobulbar tract.
They originate in cerebral ccortex carrying motor fibres to spinal cord and brainstem.
Are responsible for the voluntary control of the musculatur of the body and face.

Corticospinal tract divideds into two in the caudal part of the medulla.
the Lateral corticospinal tract decussate in the caudal medulla.
The anteriro corticospinal tract decussate in the ventral horn of the cervical and upper thoracic segmental regions.

The corticobulbar tract give of fibers in the brainstem (medulla, Pons and midbrain) and these synapses with other nerves. The corticobulbar tract travels trough the capsula interna.