Neuroscience

① Types of axoplasmatic transports according to direction and speed, their functions in the intact neuron and during axon regeneration, examples of transported molecules.

Axoplasmic transport:
- active (ATP dependent) process
- responsible for movement of mitochondria, lipids, synaptic vesicles, proteins and other cell parts (organelles)
  ↳ to and from neuron - intraneural transport of molecules.

- Axonal proteins are synthesized in neuron cell body and transported through microtubules along axon and provide cytoskeletal track for transportation.
- The motor proteins kinesin and dynein are enzymes that move cargoes in the anterograde (towards axon tip) and retrograde (towards cell body) directions.
  ↳ they carry organelles (mitochondria), cytoskeletal polymers and vesicles containing neurotransmitters or enzymes to synthesize them.

1. Anterograde - towards synapse → KINESIN
2. Retrograde - towards cell body → DYNEIN

Anterograde transport

* Slow (1-12 mm/day)
  - cytoskeletal molecules (subunits of microtubules, neurofilaments, microfilaments)
* Fast (410 mm/day)
  - molecules for creation, maintenance and functions of synapses

Retrograde transport ③

* 150-200 mm/day
  - transport of used or damaged organelles (mitochondria, ER, membrane components)
  - transport of trophic and signalling molecules - involved in development/regeneration of axons
  - transport of viral particles, toxins and proteins

② Glial cells and their role in the ontogenic development of the CNS

Astrocytes ← fibrous, protoplasmic
Oligodendrocytes
Ependymal
Microglia

Glial cells

- surround neurons and hold them in place
- provide nutrition (nutrients/O_2)
- help maintain homeostasis
- provide electrical insulation
- destroy pathogens
- regulate neuronal repair, removal of dead neurons
- participate in signal transmission.

Includes

- **Astrocytes** - can be protoplasmic or fibrous, they function similarly but differ in morphology/distribution.
  - Protoplasmic astrocytes have short, thick, highly branched processes and are typically found in the gray matter
  - Fibrous astrocytes have long, thinner, less branched processes and are most commonly found in white matter

  Functions: provide "scaffolding" for developing nerve cells. They contribute to the BBB by having end feet between neurons and capillaries → isolate and perform exchanges between capillaries + neurons.
- **Oligodendrocytes** - myelinate the axons of the CNS. During development, oligodendrocytes wrap around axons to form the myelin sheath → Provides insulation, allows AP to jump to Nodes of Ranvier. This allows for much faster conduction of signal over an axon.
- **Ependymal cells** - line the ventricles and canalis centralis of spinal cord. They secrete CSF and beat their cilia to help circulate the CSF. Also makes CSF-blood barrier.
- **Microglia** - are the macrophages of the CNS. Act as main form of active immune defense in CNS.
  ↳ of mesenchymal origin.

- Most glia are derived from ectodermal tissue of the developing embryo, from neural tube + crest, except microglia.

) Glial cells and their role in the ontogenic development of the PNS

There are 2 types of glial cells in PNS: Schwann + satellite cells

* Satellite cells - surround neurons in ganglia (sensory ganglia, sympathetic ganglia, parasympathetic ganglia). Supply nutrients to the neurons and separate them from the connective tissue.

* Schwann cells - There are 2 types: myelinating Schwann cells and unmyelinating Schwann cells. They myelinate axons in PNS.
  - In a myelin sheath, 1 Schwann cell wraps around only one axon several times.
  - In nonmyelinated (which are involved in maintenance of axons) axons, one schwann cell covers many axons.

- Myelin sheath begins to form during fetal development.
  → The cell body of the Schwann cell forms a groove into which the axon embeds. The groove deepens, its margins approach and meet until the mesaxons form which wraps around the axon like a spiral.

  → Schwann cells also have phagocytic activity and clear cellular debris in support of the regrowth of PNS neurons.

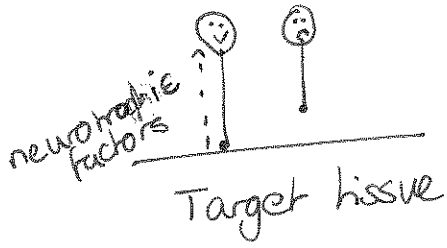
- In the PNS, glia derive from the neural crest (ectoderm) forming the Schwann and satellite cells.

Glial cells in PNS
- Terminal Schwann cells in NMJ
- Satellite cells
- Myelinating Schwann cells
- Non-myelinating Schwann cells
- Specialized cells of SNF

④. Trophic interactions amongst the neurons and target tissue, neurotrophic factors and their characteristic feature.

- During development, both neurons and connections are produced in excess. This means that some must be degenerated during development to get rid of the excess.
  → Neurotrophic factors ensure that adequate number of neurons survive - induce survival, development and function of neurons.

- The number of cells that survive into adulthood depends on the amount of target tissue with which these neurons interact during development.
  → This is due to the limited quantities of neurotrophic factors produced by the target tissue, which are taken up by peripheral nerve endings and transported retrogradely to the cell body.
  → Neurons compete for these factors during development and those that acquire them survive
  → They work by preventing activation of apoptosis in cells.



Thoracic tissues secrete less neurotrophic factors

e.g. thoracic segments innervate less than cervical, therefore they receive a smaller supply of trophic factors.

· Trophism: ability of trophic molecules to stimulate cell survival, by stimulating growth/regeneration

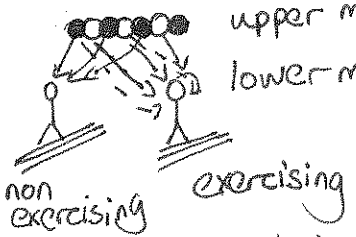
Examples of neurotrophic factors: (4)
- Nerve growth factor (NGF)
- Brain derived neurotrophic factor (BDNF)
- Neurotrophic factor-3
- Neurotrophic factor-4/5

(5). Molecular mechanisms for axon navigation to the target tissue during development and regeneration of the nervous system.

Growth conus – important terminal component of growing axon.
– it has finger-like processes which it uses to examine the surface of the target
– looks for permissive / non-permissive molecules to know where to grow.

There are 2 types of plasticity:
- Adaptable plasticity = provide structural or functional conditions for adapting the NS to external changes.
- Reparable plasticity = correct errors or small interruptions in NS, during normal activity or after injury = Wallerian degeneration.

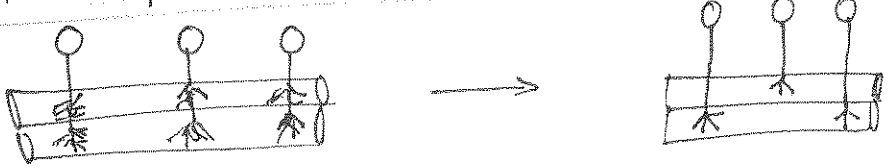
- Rebuilding synapses at adaptable changes of NS
For example, during increased intake of signals such as longterm exercise. Muscle exercised produces more neutrophins. → more motor neurons innervate the muscle.
Motor neurons in cortex send axons to exercising muscle's lower muscles instead of non-exercising muscle which undergoes atrophy.



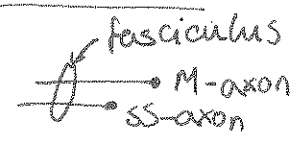
- Experience-dependent plasticity
The cortical map of sensory function will be increased or decreased e.g. loss of an arm. Some neurons in cortex loose their afferentation. Instead, some other neurons in cortex (next to them free of afferentation) will start to send axons to them. This will result in a cortical differentiation.

- Axon navigation to target tissue during development (neurons, synapses)
During development, a lot of neurons are produced. They send axons to tissues, but only those who reach the tissue can receive neutrophins to survive.
Each tissue produces its own attractive molecules called neutrophins which stimulate the growth of the axons. Neurons will only send off axons to tissues which secrete neutrophins.

Same happens with synapses, the axons that send synapses fast enough will survive, as they receive the neutrophins. → Many terminal synapses are formed on muscles then a reduction occurs and synapses from a specific neuron will focus on fewer fibres.



- How do motor axons reach and SS axons reach target tissue?
  - Motor axons navigate the SS-axons by fasciculization
  - Motor axons grow first or SS-axon will follow and they will form the peripheral nerve.



- Axon navigation has 4 molecular mechanisms:
  1) Fasciculation
  2) Attractive molecules = neutrophins
  3) Permissive surface
  4) Non-permissive surface.

  ] motor axons will attach to surfaces with high concentrations of permissive molecules and not to surfaces with non-permissive molecules.

⑥ The CNS liquid compartments and their barriers

- The brain contains 4 ventricles.
  - → Paired lateral ventricles communicate with the third ventricle of the diencephalon through the interventricular foramina.
  - → The third ventricle in turn communicates with the fourth ventricle through the cerebral aqueduct.
  - → The fourth ventricle then continues caudally as the canalis centralis of the spinal cord.
    - ↳ There are 3 openings in the fourth ventricle through which ventricular system communicates with subarachnoid space.
      - → Unpaired median aperture (of Magendie)
      - → 2 lateral apertures (of Luschka)

- CSF is formed by the choroid plexus within the ventricles, fills them and travels through foramina in 4th ventricle to fill the subarachnoid space.
- It is responsible for suspension and absorbing physical shocks to the brain but it also regulates composition of fluid bathing the neurons and glial cells of CNS and distributes nutritive materials to and removes waste from nervous tissue.

- The choroid plexus is a network which projects into each ventricle.
- Ependymal cells line these capillaries
  - ↳ the ependymal cells maintain a blood-CSF barrier controlling the composition of the CSF. On the surface of the CNS the space with CSF (subarachnoid space) is enclosed by the arachnoid matter and dura mater. CSF is absorbed into the venous blood through arachnoid villi.

⑦ Formation and absorption of CSF. Function of CSF.

Cerebrospinal fluid:
- clear, colourless liquid containing a low amount of cells, mainly lymphocytes
- produced by the choroid plexus of the ventricles
  ↳ formed by an invagination of the pia mater (tela choroidea)
- formation of CSF is continuously active and involves the enzyme carbonic anhydrase
- Total volume in ventricles and subarachnoid space: 80-150mL
  Ventricles alone: 15-40mL

- 500ml/day produced
- Movement assisted by pulsation of arteries in subarachnoid space → it is pulsatile

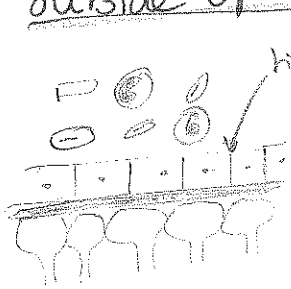
Movement:
lateral ventricles → interventricular foramina → 3rd ventricle → cerebral aqueduct → 4th ventricle → median aperture (of Magendie) + foramina (of Luschka) → subarachnoid space → venous circulation (via arachnoid granulations) /arachnoid villi

Functions:
- buoyant effect of CSF to reduce friction exerted upon the brain, nerves and blood vessels /cushioning effect/.
- removes metabolites from CNS
- immunological protection → contains lymphocytes

Composition:
Na^+, Cl^-, HCO_3^-, less proteins than plasma (main difference). Glucose and K^+ are lower in CSF than in serum.

(8). Structural basis for the hematoencephalic barrier and its significance. Transport mechanisms through the hematoencephalic barrier.

- The **blood-brain barrier** or hematoencephalic barrier is a functional barrier that prevents certain substances such as antibiotics or chemical/bacterial toxic matter from entering the nerve tissue.
- The barrier results from the reduced permeability that is characteristic of blood capillaries of nerve tissue.
- **Tight junctions**, which provide continuity between the endothelial cells of these capillaries represent the main structural component of the barrier.
  - ↳ such junctions not found elsewhere in body, they allow less ionic/molecular traffic.
  - ↳ cells do not have the fenestrations found in other locations.
- **Astrocyte "end feet"** (terminal regions of astrocytes) surround the outside of capillary endothelial cells.



The barrier results from tight junctions between the endothelial cells, basal lamina and end feet processes from astrocytes which envelop the capillaries.

- However, the brain actually needs some substances from the blood, such as nutrients, oxygen and ions. As well as it needs to excrete waste products.
  - → Therefore there are several transport mechanisms through the barrier.
    - Oxygen, carbon dioxide and small lipophilic substances such as barbiturates, nicotine, heroin and diazepam pass through by **diffusion**.
    - Glucose, some amino acids and nucleosides are transported by **facilitated diffusion** (no energy but has specific carriers).
    - Substances which are transported **actively** are some amino acids and potassium ions and other compounds, for example, Fe ions are transported by transcytosis (in vesicles)

⑨. Structures free of total hematoencephalic barrier, funchional effects.

-The BBB is a funchional barrier that prevents the passage of substances from the blood to the nerve tissue. The barrier results from tight junchions between the endothelial cells, basal lamina and end feet processes from astrocytes which envelope the capillaries.

-However, the BBB is not complete and it is interrupted in some specific points. The capillaries of the choroid plexus are fenestrated and substances can leave them only to be stopped by the tight junchions between adjacent chorioid epithelial cells.

-There are several other locations where the cerebral capillaries are fenestrated and allow free communication between the blood and the brain's extracellular fluid. These additional sites are in contact with the walls of the 3rd + 4th ventricles are collectively called circumventricular organs. These include: the pineal body, neurohypophysis, median eminence, subformical organ, subcommissural organ, area postrema (under 4th ventricle) and vascular organ of the lamina terminalis (ant. wall of 3rd ventricle).

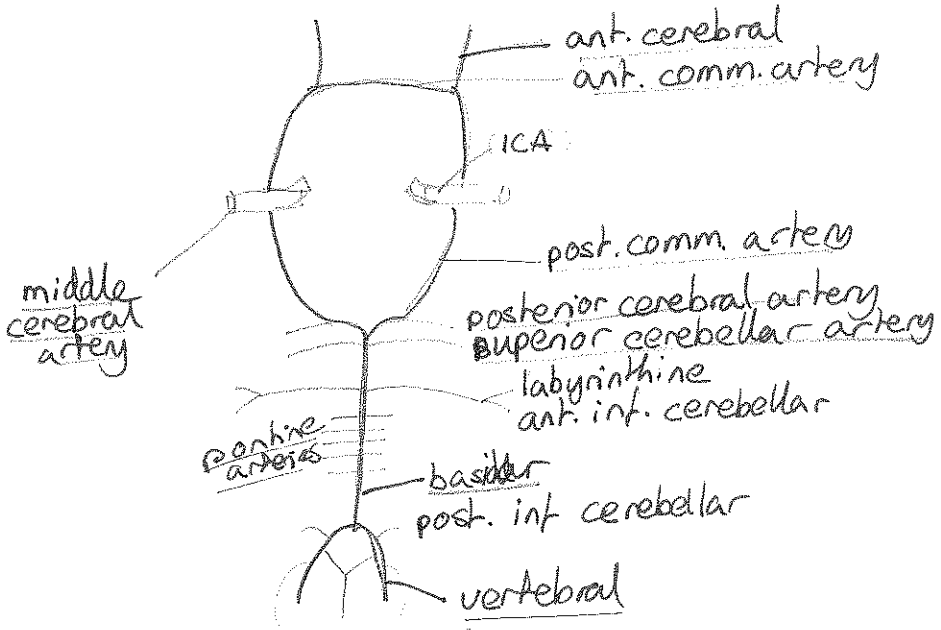
(same pic q. 8)

Circumventricular organs - positioned at different sites around the margin of ventricular system of brain

- Pineal gland - secretes melatonin (circadian rhythms)
- Neurohypophysis - stores + secretes ADH and oxytocin
- Median eminence - regulates the anterior pituitary through release of neurohormones
- Subformical organ - fluid regulation
- Subcommissural organ - secretes certain proteins into CSF
- Area postrema - vomiting centre of brain
- Vascular organ of lamina terminalis - fluid regulation

(10). Cerebral blood flow and its regulation. Factors affecting cerebral blood flow. Brain metabolism and oxygen requirements. Regional blood flow changes - autoregulation.

- Normal blood flow through brain is 750-900 ml/min (15% of CO)
- Blood flow is supplied by 4 large arteries → 2 vertebral, 2 carotid, which merge to form the circle of Willis at the base of the brain.
- The arteries from the circle of Willis travel along the surface of the brain and give rise to pial arteries which branch out into smaller penetrating arteries + arterioles.



- The brain is very active and has no oxygen or glc store therefore a stable blood supply is needed.

Factors contributing to cerebral blood flow regulation:
- → CO_2 conc. ↑CO_2 → ↑ flow
- → $[H^+]$ ↑H^+ → ↑ flow
- → $[O_2]$ ↓O_2 → ↑ flow
- → Substances released from astrocytes - cells which couple neuronal activity with local blood flow regulation

- Cerebral blood vessels are able to change their flow of blood through them by altering their diameters (autoregulation). They constrict when BP increases and dilate when it is low → physiologic control systems.
- A large majority of CNS synapses use glutamate as neurotransmitter, so increased synaptic activity causes increase release of glutamate.
  → Some spills to nearby astrocytes which also have glut receptors. This causes release of vasodilating factors from end-feet to nearby blood vessels causing increase in blood flow.

(11). Resting potential of the neuron. Equilibrium potential for sodium, potassium and chloride.

- Resting potential is the difference in electrical charges across a cells plasma membrane.
- The membrane potential changes when signals travel along it, transmitting information.
- The membrane potential of a resting neuron (not sending signals) is known as the resting potential and is between -60 to -80 mV.

Formation of resting potential

- K^+ and Na^+ play most important role in maintaining resting potential by forming a concentration gradient

	ICF	ECF
$[Na^+]$	50	150
$[K^+]$	150	5.6
$[Cl^-]$	9	125

- The gradient is maintained by Na^+/K^+ pumps
- The conc. gradient represents a chemical form of potential
- The conc. gradient which is converted into an electrical potential using energy which is converted into an electrical potential using ion channels
- A resting neuron has many open K^+ channels and only few Na^+. This means that K^+ can flow down its conc. gradient.

2 factors influence the movement of K^+ ions:
→ Diffusion force - down conc. gradient into the exterior of the cell. But since Cl^- ions can't move, they are left inside the cell the increasing negative charge will cause K^+ to enter back into the cell (electrical force)
→ Electrical force - occurs until diffusion force is in balance with electric force. This is when there is no net movement of K^+ in + out of the cell.

→ Resulting electrical potential is called the equilibrium potential for K^+ (EK)
→ Value of EK can be calculated using Nerst equation.
→ Determined using conc. of ion inside and outside of cell
↳ can only be used for 1 ion:

$$E = \frac{RT}{zF} \cdot \ln \frac{[ion]\ out}{[ion]\ in}$$

→ If we wish to calculate the potential of a cell we must take into account all 3 ions using Goldman equation: (relative permeability)

$$E = 6.1 \cdot \log \left[\frac{(P_K \times C_K + P_{Na} \times C_{Na})\ out + (P_{Cl} \times C_{Cl})\ in}{(P_K \times C_K + P_{Na} \times C_{Na})\ in + (P_{Cl} \times C_{Cl})\ out} \right]$$

(12) Receptor, synaptic and action potential - description.

- Electrical signals are produced by neurons are caused by responses to stimuli, which then changes the resting membrane potential.
- Receptor potentials are due to activation of sensory neurons by external stimuli, such as light, sound or heat.

- Another type of electrical signal is associated with communication between neurons at synaptic contacts. Activation of these synapses generates synaptic potentials (can be excitatory or inhibitory), which allow transmission of information from one neuron to another.
- The action potential (AP) is a response generated by the neuron consisting of a brief change from negative to positive in the transmembrane potential.
- The AP fully occurs or not at all. If the amplitude or duration of the stimulus is increased enough, multiple AP occur. Therefore, the intensity of a stimulus is encoded in the frequency of action potentials rather than in amplitude. → This differs from receptor potentials whose amplitude are proportional to the magnitude of the sensory stimulus, whose amplitude varies according to number of synapses activated.

(13). Ion channels in neurons - their distribution

There are different types of ion channels:
→ voltage gated
→ ligand gated
→ stretch- and heat-activated

- The latter is important in sensory receptors to generate receptor potentials for example. In neurons, however, the ligand and voltage gated channels are the most important.

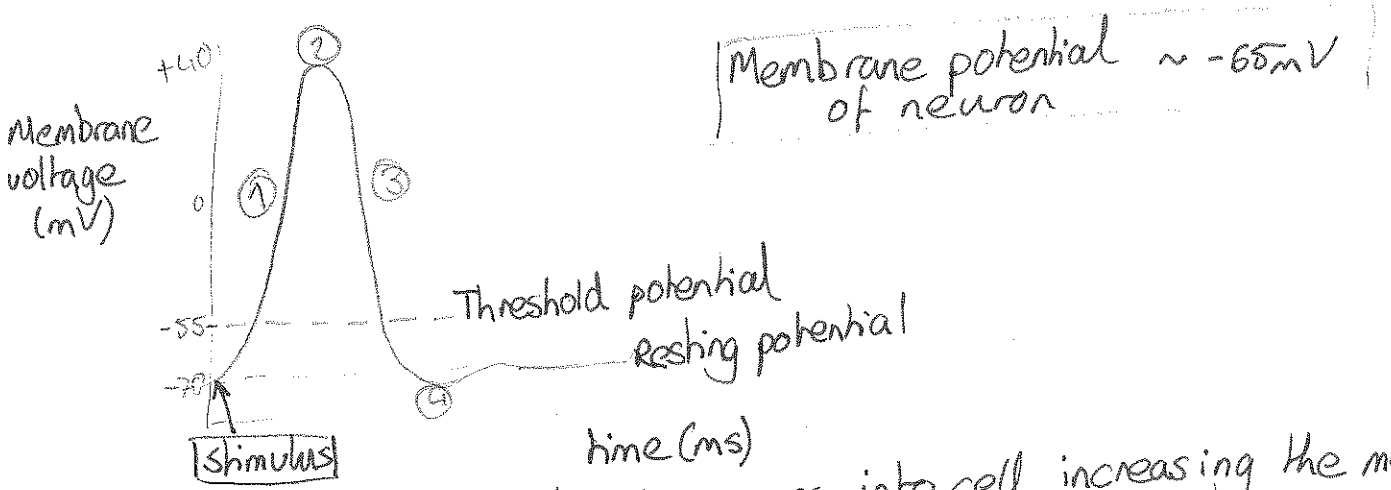
- At synaptic junctions, the cell membrane contains ligand-gated channels which bind neurotransmitters. And towards the synaptic terminals, voltage-gated calcium channels are present to mediate the release of vesicles with neurotransmitters.

- Voltage-gated sodium channels are highly concentrated in the nodes of Ranvier, and the initial segment in myelinated neurons.
↳ the nodes are the sites where impulses are normally generated and other nodes are the sites to which the impulses jump during saltatory conduction ∴ number of Na^+ channels is high.
→ Na^+ is actively transported out and K^+ in:
$[Na^+]$ high outside / $[K^+]$ high inside.

- Conc. gradients are maintained by a combination of selective permeability characteristics and active pumping mechanisms.

(14). Action potential - description, ionic fluxes, places of generation. Refractory period. Conduction velocity of the action potential, its determinants.

Action potential:
- short-lasting event in which the membrane potential of a cell rises + falls by movement of ions
- in neurons, play central role in cell-cell communication.
- generated by voltage-gated ion channels embedded in the membrane
- is an all-or-none response because it either fully occurs or not at all. If membrane potential reaches a certain threshold value, the AP occurs.



Membrane potential ~ -65mV of neuron

① - Opening of Na^+ channels, Na^+ moves into cell increasing the membrane voltage. (depolarization)
② - Na^+ channels are all open → sodium maximized.
③ - Opening of K^+ channels to move K^+ out of the cell and closing of Na^+ channels. This lowers the permeability to Na^+ and increases to K → repolarization.
④ - The raised voltage resulted in many opened K^+ channels that do not close right away when the membrane returns to its normal resting voltage and open due to increase influx of Ca^{2+} during AP → hyperpolarization

- In neurons, the types of ion channels in the membrane vary across different parts of the cell, giving dendrites, axons and cell body different electrical properties
- Some parts may be excitable (capable of generating AP) and others not.
- Most excitable part - axon hillock (point where axon leaves cell body).

Refractory period - each AP is followed by this period which means the impossibility to evoke another AP, or during which a stronger than usual stimulus is required.
(absolute) (relative)

Absolute - after an AP Na^+ channels enter an "inactivated state" in which they cannot open regardless of potential.

Relative - Na^+ channels back to normal but some K^+ channels remain open making it difficult to depolarize

factors affecting conduction velocity:
→ diameter of axon → myelin sheath → temperature → internal axon resistance

(15). Nerve fibre classification - fibre diameter and conduction velocity

Nerve fibre: thread-like extension of a nerve cell that consists of an axon and myelin sheath (if present) < CNS oligodendrocytes / PNS Schwann cells

→ Present in CNS + PNS
→ Can be myelinated or unmyelinated

Central nerve fibres

- Differ in size, conduction velocity and presence or lack of myelin
  e.g. olfactory nerve fibres are short and without myelin

Descending nerve fibres - have long nerve fibres that descend from brain to spinal cord (corticospinal tract). Have important role in motor control

Ascending nerve fibres - carry sensory information from periphery to different areas of brain (cortex/cerebellum/brain stem) e.g. spinothalamic tr.

Peripheral nerve fibres
- sensory nerve fibres (aff)
- Motor nerve fibres (eff)
- Autonomic nerve fibres

Classification of peripheral nerve fibres: (based on diameter)

Large diameter + myelin → increased conduction velocity

A group
- large diameter
- high conduction velocity
- myelinated fibres

4 types:
- A alpha (aff. or eff.) - muscle contraction
- A beta (aff. or eff.)
- A gamma (eff)
- A delta (aff)

B group (proportional to)
- small diameter
- myelinated
- preganglionic fibres of ANS
- low conduction

C group
- unmyelinated
- small diameter
- low conduction velocity
- postganglionic fibres of ANS
- dorsal root fibres

(16). Types of the neuronal synapses and their characteristics by localization and transmitters. Electrical and chemical transmission at synapses. structural and functional differences

(17). Chemical synapses - mechanisms of neurotransmitter release and its inactivation

(18). Chemical synapses - receptors, their structure, localization and function

- Axons end with knob-like swellings that are known as botons. Together with the membrane of the next neuron they form the synapse where signals are transmitted from one neuron to another.
  - → synapse consists of presynaphic membrane, synaptic cleft and the postsynaphic membrane.
  - → inside the presynaptic knob are mitochondria as well as membrane-enclosed vesicles with neurotransmitters.

There are 2 major types of synapses:

- Electrical synapses / adjacent cells communicate through pores called gap junctions. Cells linked by gap junctions are electrically coupled. The synaptic cleft space is reduced (2 nm). The information is transferred by ion flow. Electrical synapses are frequently present between rods + cones, in retina and among nuclei of the thalamos. Part of the electrical synapse is the connexon which consists of 6 connexins.
- Chemical synapse - found in almost all synapses used for signals in the CNS. Transmission of signal is mediated by neurotransmitters, mostly by acetylcholine, glutamate, GABA and glycine). → ther. Ach
  Glutamate is the most common excitatory transmitter, GABA is a transmitter of inhibitory synapses in the brain and glycine an inhibitory transmitter in the SC. The catecholamines epinephrine and norepinephrine and dopamine also act as transmitters. They are produced in the perikaryon and stored in vesicles at the axon terminals. Most of the vesicles are located near the presynaphic membrane, they empty their content (upon stimulation) into the synaptic cleft by fusing with the presynaphic membrane.

→ The synapses can be located on different parts of postsynaphic neuron:
- axodendritic synapse
- axosomatic synapse
- axo axonal synapse

there are:

- Excitatory synapses: found at dendrites, often at the heads of spines
- Inhibitory synapses: found at perikaryon or at the axon hillock.

-Electrical transmission

→ 2mm cleft
→ 2 way information flow
→ current is generated by an impulse in one neuron, spreads to another through a pathway of low electrical resistance.
→ synapses found at gap junctions called connexins (regulated by Ca^{2+} ions)
→ ion channels connect the cytoplasm of pre and post synaptic cells.
→ found where neurons have to be highly synchronized (e.g. hypothalamus) so they fire almost simultaneously and secrete a burst of the hormone in the circulation.
→ Voltage-gated channels in the presynaptic neuron - post-synaptic neuron (rapid transmission - less than 0.1ms).

-Chemical transmission

→ no continuity of cytoplasm
→ cleft 20-30 nm
→ one way information flow because receptors only on postsynaptic neuron.
→ can amplify signals
→ Mechanism:
1) AP arrives and depolarizes presynaptic terminal
2) Voltage-gated Ca^{2+} channels open
3) Ca^{2+} enters the cell → activation of synapsin-1.
4) Vesicles move and fuse with membrane at the active zone and release neurotransmitters into cleft.
5) Neurotransmitters diffuse across the cleft to the postsynaptic mem.
6) Bind to receptors, which are connected to channels.
7) They open and ions enter/leave the neuron.

→ Nature of response depends on the type of receptor being activated and increases/decreases the permeability to that ion species.

Chemical receptors

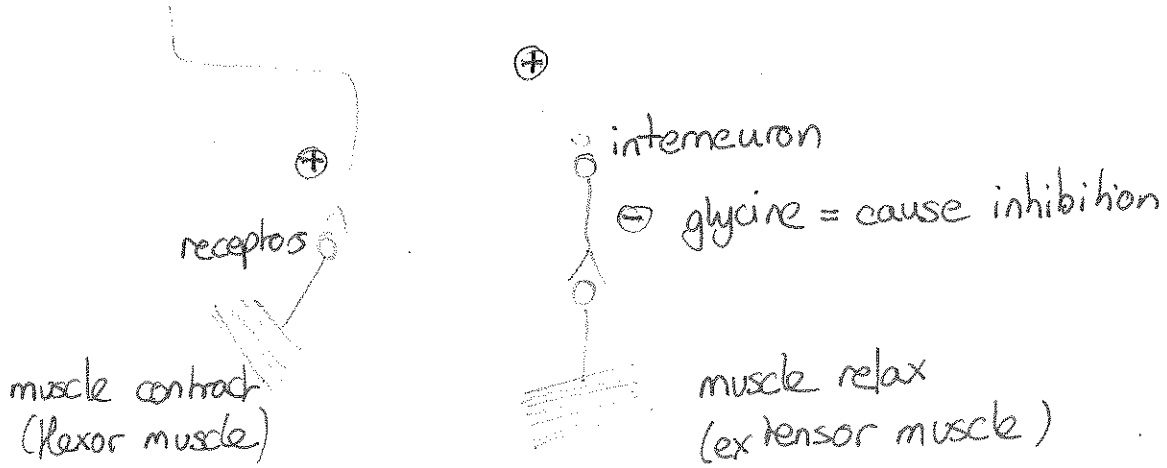
(19). Excitatory and inhibitory neurotransmitters.

The sense in which the synapse will act is determined by the chemical nature of the neurotransmitter and its interaction with the postsynaptic membrane.

- Excitation/mediators = glutamate (in CNS) or acetylcholine (in NMJ/CNS)
  - → Both substances act as ligands. They bind to the protein of sodium channels. The channel will open and Na^+ will go into cell. The membrane potential will change in the so called excitation post-synaptic potential. This is not an AP, only a change in membrane potential.
  - → When multiple EPSPs occur on a single point of the postsynaptic mem. they will fuse to one large EPSPs and when it reaches a threshold the postsynaptic neuron will fire an AP.

- Inhibitory mediators = GABA or glycine
  - → It acts as a ligand to chloride channels. Cl^- will go into cell and this will make a drop in membrane potential, the so called inhibition postsynaptic potential (IPSP).
  - → This potential will decrease the change of an AP and be formed.

Function of antagonist muscles:



(20). Neuromuscular junction - structure and function. Mechanisms of signal transmission, end plate potential.

- Skeletal muscle fibres are innervated by nerve fibres that originate from large motor neurons in the anterior horns of the spinal cord. Each nerve fibre after entering the muscle belly, branches and stimulates 3-100 skeletal muscle fibres (motor unit).

- Each nerve ending joins with the muscle fibre - neuromuscular junction.
  - → The end feet invaginate into the surface of muscle fibre but lie outside of the plasma membrane. The invaginated membrane (of the muscle fibre) is called the synaptic gutter.
  - → The space between the terminal and the muscle fibre is called the synaptic cleft.
  - → At the bottom of the gutter are numerous smaller folds of the muscle membrane called subneural clefts, which greatly increase the surface area at which the synaptic transmission can occ. In the axon terminal are many mitochondria that supply ATP used for synthesis of acetylcholine. The Ach in turn excites the muscle fibre membrane. Ach is synthesized in cytoplasm of terminal but is absorbed into many small synaptic vesicles. In the synapse are large quantities of acetylcholinesterase which destroys Ach after it is released.

- When a nerve impulse reaches the NMJ, about 125 vesicles of Ach are released from the terminals into the synaptic cleft. On the neural mem. are voltage gated Ca^{2+} channels. When an AP spreads over the terminal, these channels open and allow Ca^{2+} to diffuse to the interior.
  - → This triggers the fusion of the vesicles with the membrane and empty their Ach into the synaptic space by exocytosis. Many Ach receptors are present in the gutter. These are Ach-gated ion channels and are located in the subneural clefts. The principle effect of opening the Ach gated channels is to allow large number of Na ions to pour inside of the fibre carrying with them a large number of +ve charges. This creates a local positive potential charge inside the muscle fibre - end-plate potential. This initiates an AP that spreads along the muscle membrane → muscle contraction.

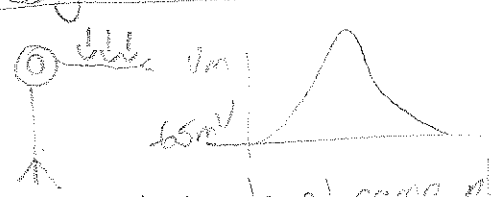
↓ when enough EPSPs

(21). Synaptic (postsynaptic) potentials - mechanisms of generation. Length and time constant of the neuronal membrane and its relation to temporal and spatial summation of membrane potentials.

- Post-synaptic potentials (PSPs) actually decrease the probability that the postsynaptic cell will generate an action potential. PSPs are called excitatory (EPSPs) if they increase the likelihood of a postsynaptic AP to occur and inhibitory (IPSPs) if they decrease this likelihood.
- The principles of excitation are those described for the NMJ. The principles of postsynaptic inhibition are much the same as for excitation. In both cases, neurotransmitters binding to receptors open or close ion channels in the postsynaptic cell. Whether a postsynaptic response is an EPSP or an IPSP depends on the type of channel that is coupled to the receptor and on the concentration of ions inside and outside the cell. influx of Na^+ → EPSP, Cl^- → IPSP
- Stimuli from dendrites are gathered at the hillock, when it reaches a certain level, an AP will be formed. Na^+ channels open if the value of resting membrane potential changes by at least 15 mV in the positive sense, this is called local response.
- When the channels are opened, they allow inward flow of Na^+ which results in a further rise in membrane potential. This cause more channels to open and more local responses or rise in membrane potential. This process continues until all channels are opened. The magnitude of local responses depends on the magnitude of stimuli.
- The AP always travel in one direction. This is due to the hyperpolarization at places through which the AP has already passed. Hyperpolarization causes a drop in the sensitivity of the membrane to another electric impulse.

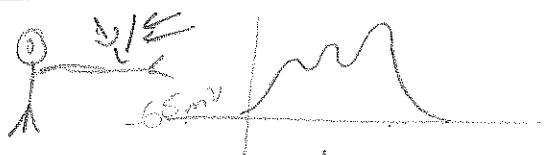
Temporospatial summation: the postsynaptic neuron will fire an AP when the threshold potential has been reached. One individual synapse does not have the power through a single synaptically evoked potential to bring a postsynaptic neuron closer to threshold. Only the cumulative effect of thousands of synapses on any given postsynaptic neuron will elicit an AP. The synapses receiving input must be close together (A) and receive input in the same timeframe (B). This is temporospatial summation

A. Length summation



all inputs at same place

B. Time summation



inputs added at same time

figures show how synaptically evoked potentials received at the same time and in the same area can bring the neuron close to threshold, which results in AP generation.

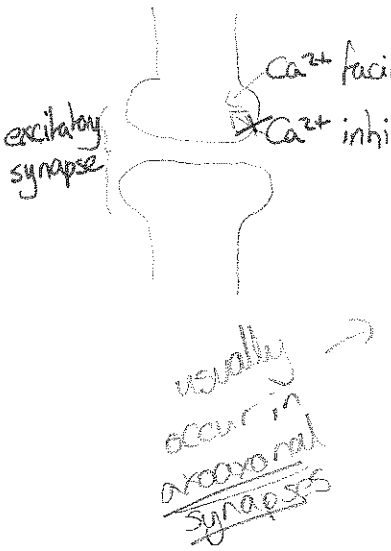
Length constant - constant used to quantify the distance electrical impulse will travel along a cell body. The higher the λ the higher the length summation

Time constant (τ) - the rise time characterizing the response to a time varying input

(22). Short-term modulation at synapses - presynaptic inhibition and facilitation, potentiation and posttetanic potentiation.

GABA glu/Ach

Presynaptic inhibition + facilitation:



usually occur in axoaxonal synapses

- Presynaptic inhibition, the transmitter is GABA
  - → opens Cl^- channels on presynaptic neuron. Cl^- makes AP↓
  - → because Cl^- go into cell, less Ca^{2+} channels are opened and Ca^{2+} don't go into terminal
  - → less transmitter in excitatory synaptic cleft released.
- The opposite happens (with Ach/glutamate) and is presynaptic facilitation.
  - → enhances + prolongs neurotransmitter release by keeping the presence of serotonin causing Ca^{2+} channels to remain open longer

Potentiation

The increase in strength of nerve impulses along pathways that have been used previously either long term or short term

- Long term potentiation - a persistent increase in synaptic strength following high frequency stimulation of a chemical synapse (enhancement of synaptic transmission). LTP is widely considered one of major cellular mechanisms that underlies learning + memory.

Post-tetanic potentiation - type of short term potentiation

- An incrementary response without change of AP, amplitude, occurring with repetitive nerve stimulation
- Generally thought to be presynaptic
- Similar mechanism to paired pulse facilitation in that after a tetanic (high frequency train of stimuli) there's a high level of residual Ca^{2+} in the presynaptic cell, temporarily increasing the release probability.

(23). Receptor (generator) potential - mechanisms of generation. Coding of sensory information - intensity, duration and modality. Adaptation of sensory receptors.
↓ proportional to magnitude/frequency

- Sensory receptor cells are those specialized to respond to a specific environmental stimulus.

→ the receptor cell is connected to an afferent neuron then relays the information to a sense organ composed of receptor cells that transform the stimulus.

- Receptor cells respond specifically to certain stimuli, there are 4 major types:
  a) thermoreceptors b) chemoreceptors
  c) photoreceptors d) mechanoreceptors.

Coding

- A stimulus is characterized by its modality, intensity, duration and location. Sensation evoked by a stimulus depends on the part of the brain that has been stimulated. e.g. touch centre evokes touch sensation
- Sensory information is processed by the thalamus and is transmitted to the cerebral cortex, where the nerve pathways from a particular sense organ are stimulated, the sensation evoked is that for which the receptor is specialized, no matter how long the pathway or where along the pathway the activity has been initiated.

Law of projection: no matter where a particular sensory pathway is stimulated along its course to the cortex, the conscious adaptation produced is referred to the place of the receptor (e.g. phantom limb sensation in amputees).

- The magnitude of the sensation is proportional to the logarithm of the intensity of the stimulus

$$\frac{\Delta I}{I} = K$$

ΔI = difference threshold
I = initial stimulus intensity
K = constant

→ the intensity also involves the variation of frequency of AP and varies with the number of receptors activated.

- The receptor field of a sensory unit is the area from which a stimulus produces a response in that unit. As strength of stimulus increases, it spreads and covers a large area and activates sense organs + neurons in surrounding area.
- The sensory receptor converts a stimulus into neural activity → stimulus transduction. A stimulus induces a generator (or receptor) potential in the receptor membrane. This propagates electrically. The stimulus, depolarizes the membrane by influx of Na^+ and efflux of K^+. Characteristics such as intensity and duration are converted into patterns of action potentials, that are called neural codes. e.g. ↑duration of stimulus causes ↓amplitude of receptor potential → adaptation of response. This response may be fast or slow (Pacinian corpuscle vs. Merkel's receptor).

(24.) Temperature sense - stimuli, receptors and their characteristics. Temperature regulation.

Thermal gradations are discriminated by at least 3 types of sensory receptors:
- cold receptors
- warmth receptors
- pain receptors → these are stimulated only by extreme degrees of heat and cold, causing sensation of burning hot and freezing cold.

- Cold + warmth receptors are located immediately under the skin.
- There are 4-5 times more cold-sensitive as heat-sensitive spots and the number in different areas of the body varies.

• Cold receptors - respond from 10-38 degrees. It is a specialized, small type myelinated nerve ending that branches several times. The afferents for cold are Aδ fibres (and also C fibres). Cold → Aδ → C Warm → C

• Warmth receptors - are assumed to be free nerve endings. They respond to temperatures from 30-45 degrees. Afferents for heat are C fibres.

- It is believed that the cold and warmth receptors are stimulated by changes in metabolic rate and that these changes result from the fact that temperature alters the rate of intracellular chemical reaction.
- In general, thermal signals are transmitted in pathways parallel to those for pain signals.

PATHWAY: on entering the spinal cord, these signals travel for a few segments upward or downward in the tract of Lissauer and then terminate mainly in laminae 1, 2 + 3 of the dorsal horns. After a small amount of processing by neurons, the signals enter long, ascending thermal fibres that cross to the opposite anterolateral sensory tract and terminate on both the reticular areas of the brain stem and the ventrobasal complex of the thalamus

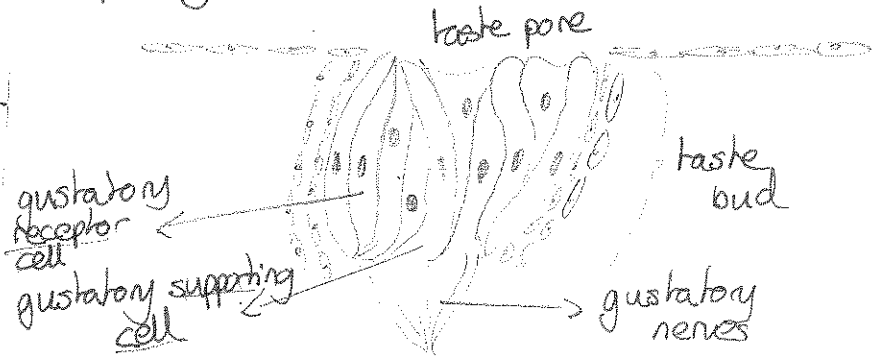
- Thermoregulation is mainly controlled by the preoptic area of the anterior hypothalamus.

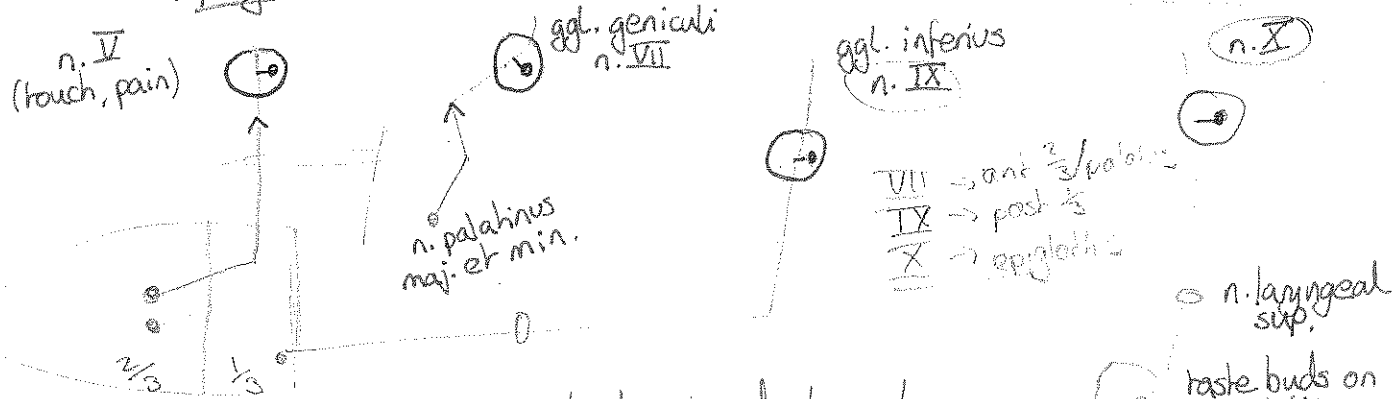
Heat loss
- → convection
- → conduction
- → radiation
- → evaporation

- Skin assists in homeostasis ↗ vasoconstriction ↘ vasodilation + sweating

(25). Taste - stimuli, modalities. Receptor cells - localization, innervation. Transduction mechanisms in taste buds.

- Taste buds contain 50-150 receptor cells, supporting cells and afferent axons.
- Chemical constituents of food interact with receptors on taste cells located in taste buds in tongue. → found in tongue papillae
  ↳ outer tips of taste cells are located near taste pores
- Taste cells in individual taste buds synapse with primary afferent axons from branches of (3 CN): facial VII
  glossopharyngeal IX
  vagus X
- The chemosensory transduction occurs in the taste cells, which have receptors in the microvilli in the taste pores. The major perceptual categories of taste are: salt, bitter, sweet, umami and sour and they are represented by 5 distinct classes of taste receptors.
  → Salty and sour tastes are primarily elicited by ionic stimuli such as Na^+ or H^+ ions. These ions initiate sensory transduction via specific ion channels. The receptor potential generated by the positive inward current carried either by sodium or hydrogen ion depolarize the taste cell. This initial depolarization leads to the activation of voltage gated calcium channels, leading to release of neurotransmitter from the basal aspect of the taste cell and the activation of APs in the nerve fibre.
  Salt Sour (ions) Na^+ depolarize
  → The receptors for sweet and bitter taste are G-protein coupled. Upon binding on the receptor, a G-protein-mediated signal transduction cascade occurs which leads to the activation of phospholipase C which increases concentration of IP_3 and to the opening of Ca^{2+} channels → depolarization.
  Sweet Bitter (G) PLC ↑IP_3 → ↑Ca^{2+}
- → Taste cells in individual taste buds synapse with primary afferent axons from branches of 3 cranial nerves: facial/IX/X
  Located in 3 types of papillae: circumvalatae, foliate, fungiform



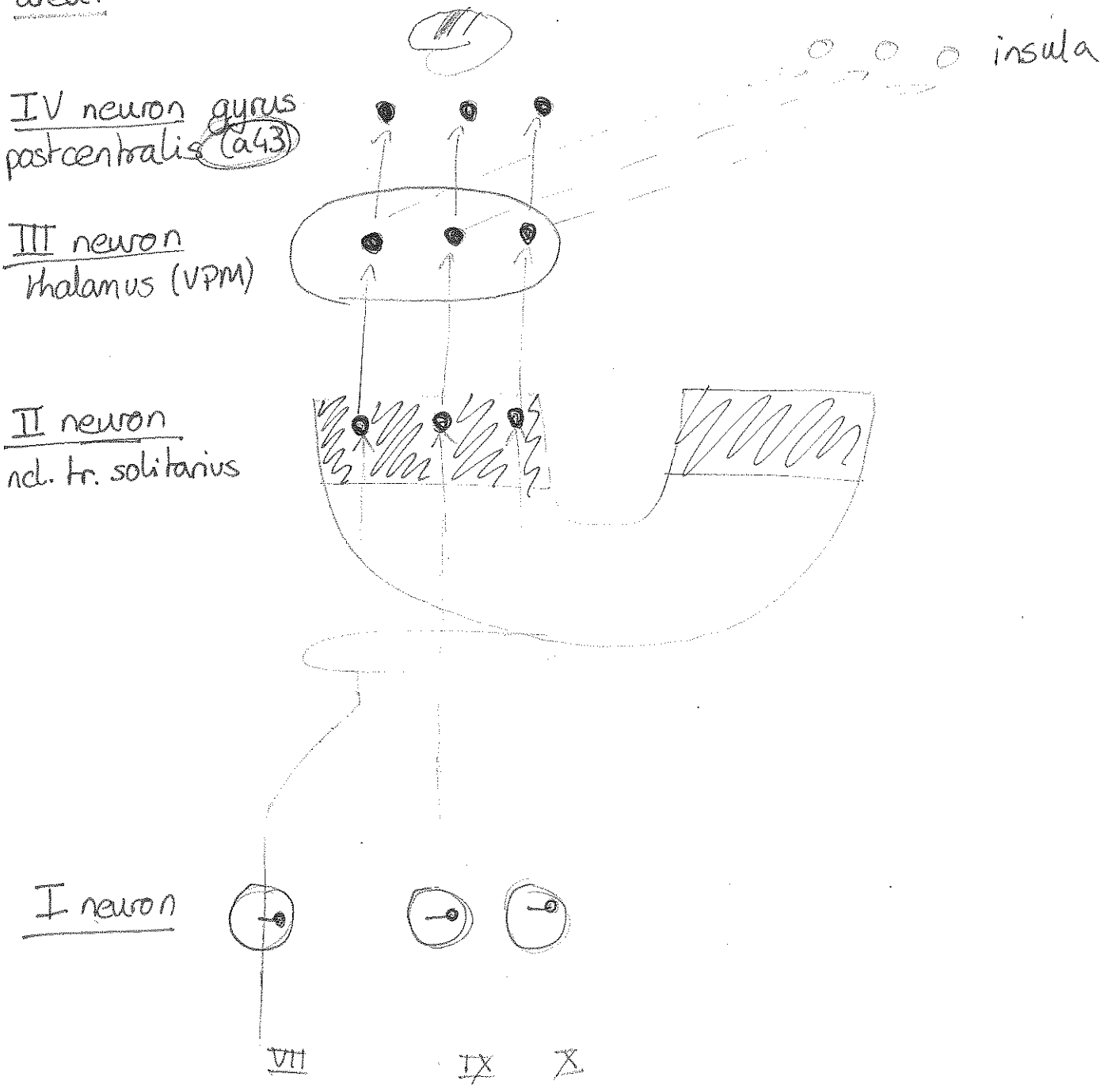


→ N. palatinus major et minores convey taste signals to ggl. geniculi from taste buds on palatus.

(26) Pathway that convey taste information to the upper structures of CNS.

- Taste impulses from the anterior $\frac{2}{3}$ of the tongue pass first into the lingual nerve, then through the chorda tympani into the facial nerve and finally into the trachus solitarius in the brain stem. ant $\frac{2}{3}$ → lingual → facial
- Taste shimuli from the posterior $\frac{1}{3}$ of the tongue is transmitted through glossopharyngeal nerve also into the trachus solitarius. post $\frac{1}{3}$ → glossopharyngeal → sol. tr.
- Taste signals are also transmitted into the trachus solitarius from the epiglottis by the vagus nerve. epiglottis
  → The nuclei of trachus solitarius (2nd order) send axons to the ventral posterior nucleus of the thalamus. VPM

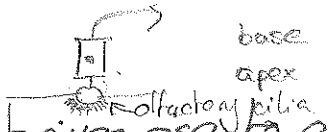
From the thalamus (3rd order neurons), axons run to the lower tip of the postcentral gyrus in the parietal cerebral cortex (4th order), where it curls deep into the Sylvian fissure and to the adjacent opercular insular area.



(27). Smell -stimuli, receptor cells and their localization, transduction mechanism of smell stimuli in bipolar cells

-Olfactory receptor cells (neurons) fire in response to stimulation by chemical compounds called odorants.

-The transduction of olfactory information occurs in the olfactory epithelium which is located superiorly in the nasal cavity. This epithelium includes several cell types: olfactory receptor neurons, basal cells, stem cells and supporting cells. A thick layer of mucus covers the olfactory epithelium and is secreted by Bowman's glands.



-The olfactory receptor neuron is a bipolar cell that gives rise to a small-diameter unmyelinated axon at its basal surface that transmits olfactory information centrally. At its apical surface, it gives rise to a single dendritic process that expands into a knob-like protrusion from which several microvilli, called olfactory cilia extend into the mucous layer.

-Odorants in mucous bind directly or via odorant binding proteins to receptors located in the membranes of cilia. This receptor is coupled to a G-protein which is activated upon the binding of the odorant. Activated G-protein in turn activates adenylate cyclase resulting in increased [cAMP], cAMP binds to cation selective channels that when open permits the influx of (Na^+ and Ca^{2+}) into the cilia, resulting in depolarization and generation of AP travelling into the CNS by way of olfactory nerve (I).

Odorant in mucus → receptor in cilia → G-protein activated by odorant binding → activates AC → ↑cAMP → binds + opens cation channels (Na^+ Ca^{2+}) → depolarization → AP travelling through olfactory nerve (I)

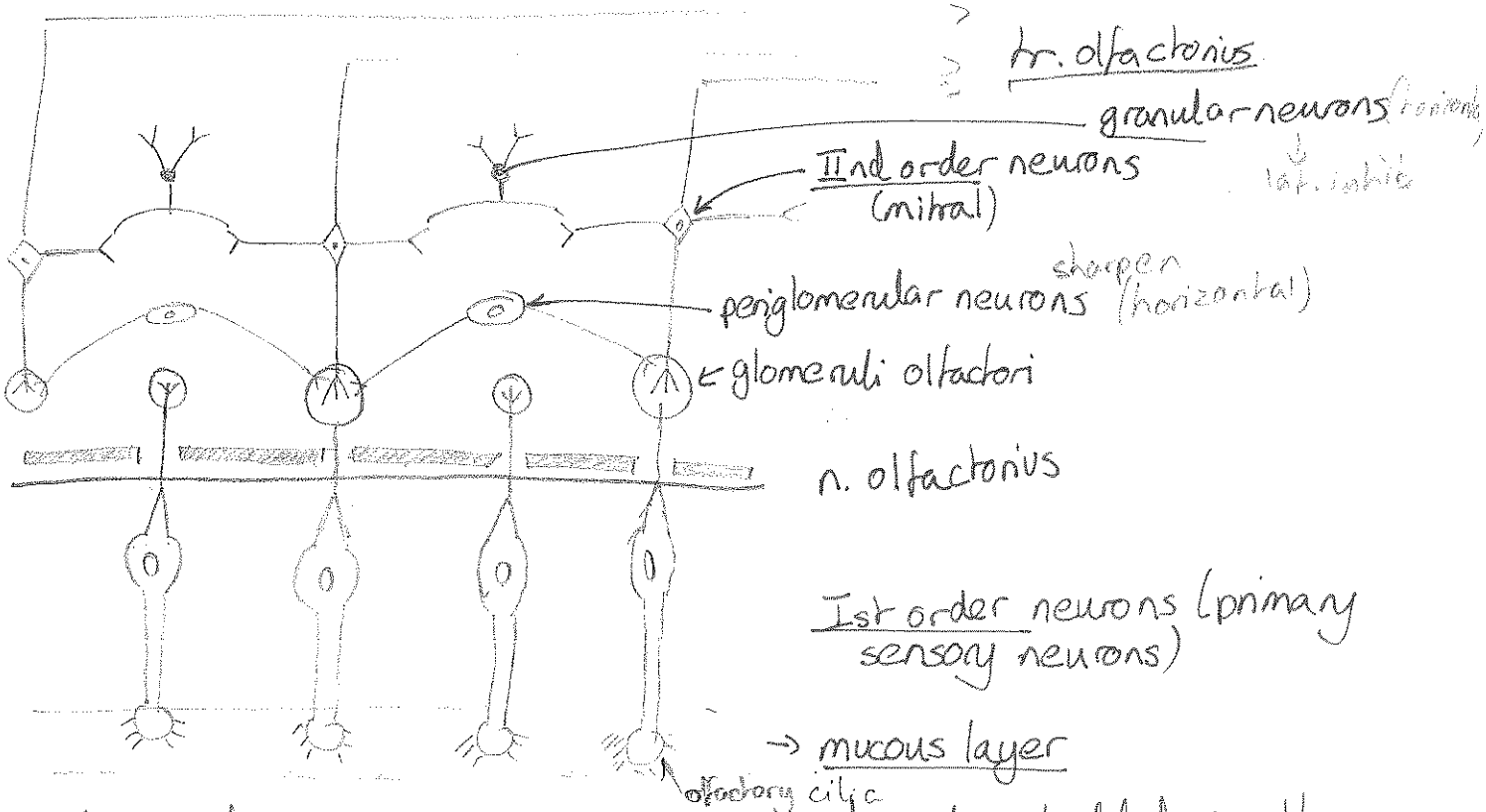
(28). Description of neurons and their horizontal and vertical connections in the olfactory bulb.

-As the olfactory receptor axons leave the olfactory epithelium, they coalesce to form a large number of bundles that together make up the olfactory nerve. They travel through the holes of the cribiform plate of the ethmoid bone and enter the olfactory bulb.

→ Here, they terminate on the dendrites of the so-called mitral cells in multiple globular structures called glomeruli. Each glomerulus also contains dendritic processes from the periglomerular cells (it is generally assumed that these neurons sharpen the sensitivity of individual glomeruli)

-Granule cells synapse primarily on dendrites of mitral cells and are thought to establish local lateral inhibitory circuits as well as participating in synaptic plasticity in the olfactory bulb.

-The mitral cells send their axons through the olfactory tract to transmit olfactory signals to higher levels in CNS.



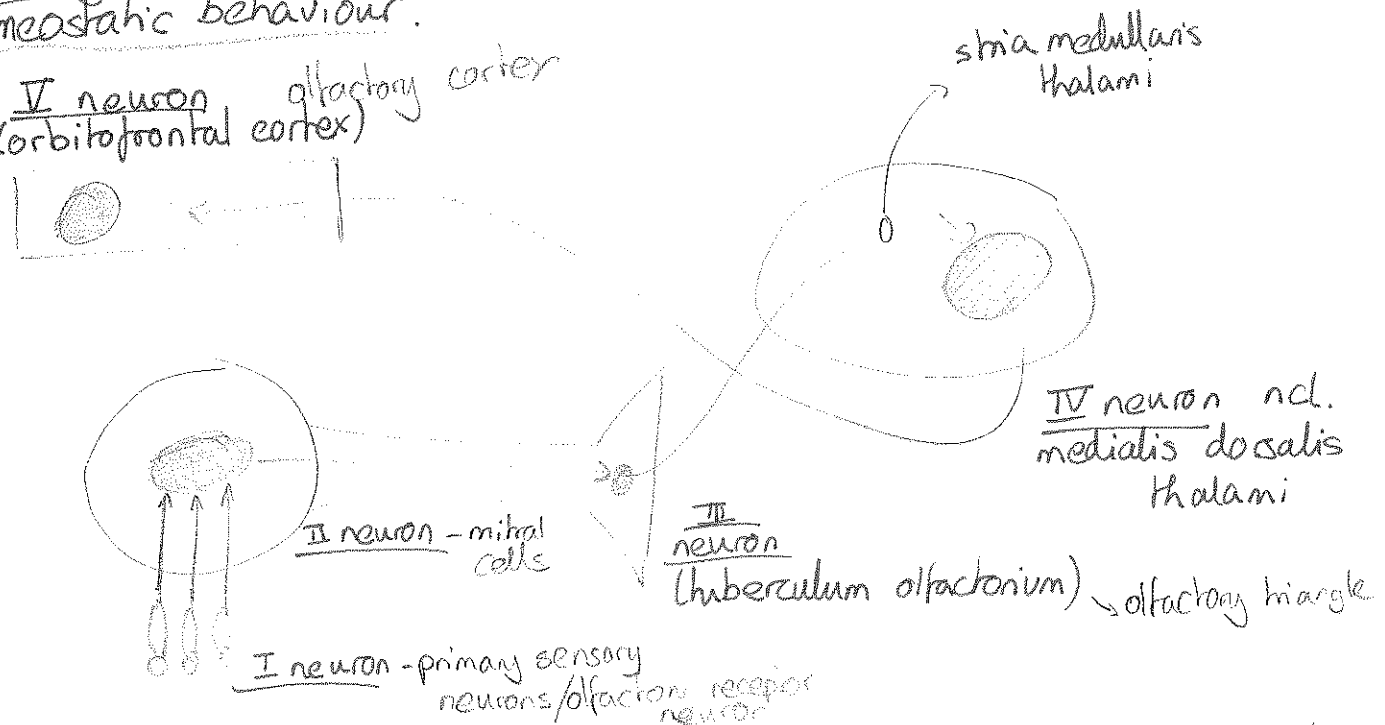
→ Dendrites of sensory neurons are enlarged and embedded in the mucosa of the regio olfactoria nasi. Axons run through cribiform plate and constitute n. olfactorius

→ Axons terminate on IInd order neurons (mitral). The synapse between Ist + IInd are enlarged and called glomeruli olfactori

→ Axons of IInd order neurons constitute tr. olfactorius

(29). Pathway for conscious sense of smell.

- The mitral cell axons form a bundle called the olfactory tract that projects to the accessory olfactory nuclei, olfactory tubercle, the entorhinal cortex and portions of amygdala.
- The major target of the olfactory tract is the 3 layered pyriform cortex in the ventromedial aspect of the temporal lobe near the optic chiasma. Neurons in the pyriform cortex respond to odors and mitral cell inputs from glomeruli receiving odorant receptor specific projections remain partially segregated.
- The axons of pyramidal cells in the pyriform cortex project in turn to several thalamic and hypothalamic nuclei and to the hippocampus and amygdala. Some neurons from pyriform cortex also innervate a region in the orbitofrontal cortex comprising multimodal neurons that respond to olfactory and gustatory stimuli.
- Information about odors thus reaches a variety of forebrain regions allowing olfactory cues to influence cognitive, visual, emotional and homeostatic behaviour.



Axons in tractus olfactorius go to IIIrd order neurons in olfactory triangle which constitute a small hillock called tuberculum olfactorium. Their axons continue to thalamus through stria medullaris thalami into nucleus medialis dorsalis thalami. There we have IVth order neurons. Their axons project into olfactory cortex which is the orbitofrontal cortex. In this cortex lies the Vth order neurons which analyse the smell.

There is also an additional pathway: the signals from tr. olfactorius will go into pyriform and entorhinal cortex. These cortexes are parts of limbic forebrain and therefore important in our behaviour when we smell. Ex. when we smell smth bad we want to move away from it.

(30). Transduction of light signal in photoreceptors

- Each rod and cone in the retina contains visual pigment that consists of a light-absorbing molecule called retinal (aldehyde of vit A-retinal) bound to a membrane protein called opsin.

→ when combined with retinal, opsin becomes rhodopsin

- Absorption of light causes retinal to change from a cis to trans configuration. Following absorption, signal transduction in photoreceptor cells closes sodium channels. In the dark, binding of cGMP to Na channels causes them to stay open
  → Breakdown of cGMP in response to light allows Na channels to close, hyperpolarizing the photoreceptor cell

1. Light isomerizes (cis → trans) retinal, activating rhodopsin
2. Active rhodopsin in turn activates a G protein - transducin.
3. Transducin activates phosphodiesterase
4. Phosphodiesterase detaches cGMP from Na^+ channels in plasma membrane by hydrolysing the cGMP to GMP.
5. The Na^+ channels close when cGMP detaches. Membrane's permeability to Na^+ decreases causing the rod to hyperpolarize.
   → Rhodopsin returns to its inactive state when enzymes convert retinal back to cis form.

Light → retinal cis → trans → active rhodopsin → activates G-protein transducin → activates phosphodiesterase → detaches cGMP from Na^+ channels (cGMP → GMP) → Na^+ channel closes → hyperpolarization

In dark: binding of cGMP to Na channels keeps them open (no hyperpolarization)

(31). Perception of depth - monocular and binocular cues, cortical areas concerned with depth analysis

-Ganglion cell axons mostly terminate on the lateral geniculate nucleus. Due to the crossing of some fibres in the optic chiasm the geniculate nucleus receives fibres from both left and right eye. These fibres, however, terminate in separate layers so that individual neurons are monocular. Inputs from right and left eyes remain segregated even beyond the geniculate because the axons of geniculate neurons terminate in eye synaptic columns within cortical layer 4.

Brodmann's area 17, 18, 19 (striate cortex) (occipital lobe)

→ Layer 4 neurons send their axons to other cortical layers where the information from the 2 eyes converges onto individual neurons.

→ Bringing together the inputs from the 2 eyes in the visual cortex provides a basis for the sensation of depth that arises from viewing nearby objects with 2 eyes instead of 1.

-Because the eyes look at different angles, objects that lie in front or behind the plane of fixation project to noncorresponding points on the 2 retinas. For a small distance on either side of the plane of fixation, where the disparity between the 2 views of the world remains small, a single image is perceived, the disparity between the 2 eye views of objects nearer or farther than the point of fixation is interpreted as depth.

. Monocular vision: vision in which each eye is used separately. By using the eyes in this way, as opposed by binocular vision, the field of view is increased while depth perception is limited. The eyes are usually positioned on opposite sides of animal's heads giving them the ability to see 2 objects at once. e.g. birds/rabbits

. Binocular vision: having 2 eyes confers at least 4 advantages over 1.

1. It gives a "spare" eye in case one is damaged.
2. It gives a wider field of view → 200° with 2 eyes, 160° with 1 eye. (horizontal field)
3. It gives binocular summation in which the ability to detect faint objects is enhanced.
4. It can give stereopsis in which parallax provided by the 2 eyes different position on the head give precise depth perception.

Monocular: (2)
eyes used separately
→ larger vision field
→ less depth perception

Binocular: (4)
with eyes close
→ "spare eye"
→ wider (horizontal) vision field
→ binocular summation to see faint objects
→ precise depth perception

(32) Visual acuity - definition, testing. Visual field - definition, perimetry, visual field deficits.

• Visual acuity - acuteness or clearness of vision, which is dependent on the sharpness of the retinal focus within the eye and the sensitivity of the interpretative faculty of the brain.
→ measure of the spatial resolution of the visual processing system. Is tested by requiring the person to identify characters (letters or numbers) on a chart from a set distance. Chart characters are represented as black symbols against a white background (for maximum contrast)

• Visual field - total area in which object can be seen in the side (periphery) while the eyes focus a central point. Physical objects and light sources in the external world that impinge the retina.
→ the visual field is measured by perimetry.

- Perimetry = systematic measurement of differential light sensitivity in the visual field by detection of the presence of test targets on a defined background.
It can be performed by keeping the subject's gaze fixed, while presenting objects at various places in their visual field. This is generally used to explore the extreme boundaries of the visual field.

- Blind spot = obscuration of the visual field. Place that corresponds to the lack of light-detecting photoreceptor cells in the retina where the optic nerve passes through it.

- Visual field deficits = may occur due to disease or disorders of the eye, optic nerve or brain. Several types:
→ Altitudinal field defects - loss of vision above or below the horizontal - associated with ocular abnormalities
→ Bitemporal hemianopia - loss of vision at the sides
→ Central scotoma - loss of central vision
→ Homonymous hemianopsia - loss at one side in both eyes.

Bitemporal hemianopia
Central scotoma
Homonymous hemianopia

(33). Projection of the visual information to subcortical structures, description and functional significance.

- The optic tract branches in to a lateral and a medial arm.
- Lateral arm carries most of the information from the retina to the lateral geniculate nucleus (thalamus) and primary visual cortex. (Brodmann's)
- Medial arm connects ganglion cells with subcortical structures. These include the tectum of mesencephalon: to the pretectal nucleus- serves for the pupillary light reflex, and to the colliculus superior- serves for coordination of head and eye movements.

Fibres also project through the tr. retinohypothalamicus to the suprachiasmatic nucleus of the hypothalamus. This nucleus control the circadian rhythmus.

And finally to pulvinar thalami which coordinates visual and somatosensory perception. For example if you have extreme pain, you might have visualizations.

Optic tract

Lateral arm → info from retina to lat. gen. ncl. + primary visual cortex

Medial arm → connects ganglion cells from retina to subcortical structures

↓

→ tectum of mesencephalon

pretectal ncl → pupillary light reflex

colliculus sup → coordinate head + eye.

tr. retinohypothalamicus → suprachiasmatic ncl.

↓

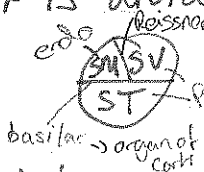
circadian rhythms

do pulvinar → coordinates visual and SS perception

- e.g. if you have extreme pain you might have visualizations

(34). Capturing sound - functions of the external ear, tympanic membrane and middle ear ossicles. Traveling wave in the cochlea. aulla ext. ear

- The 3 auditory ossicles and tympanic membrane form the sound conducting apparatus. The sound is conducted from the tympanic membrane through the middle ear to the cochlea (inner ear).
- Attached to the tympanic membrane is the manubrium (handle) of the malleus. The malleus is bound to the incus by ligaments. The opposite end of the incus articulates with the stem of the stapes and the foot plate of the stapes lies against the membranous labyrinth of the cochlea in the opening of the oval window.
- The ossicles of the middle ear are suspended by ligaments in such way that the malleus and incus act as a lever. The articulation of the incus with the stapes causes the stapes to push forward on the oval window and on the cochlear fluid on the other side of the window every time the tympanic membrane moves inward. 2 tiny muscles attached to the middle ear bones modulate the transmission of vibrations to the inner ear. The tensor tympani is attached to the handle of the malleus, when it contracts it increases the tension on the tympanic membrane and decreases the transmission of vibrations through the ossicular chain. The stapedius is attached to the stapes; it too decreases the vibrations transmission when it contracts. The tensor tympani receive motor innervation from n. trigeminus and the stapedius from the facial nerve. They provide a protective function. tensor tympani → V, stapedius → VII
- The external ear gathers sound energy and focuses it on the tympanic mem. The ossicular system provides "impedance matching" between sound waves in the air and the sound vibrations in the cochlea. The lever system increases the force of movement of the stapes against the oval window. In addition, the surface area of the tympanic membrane is much bigger than the SA of the stapes. This difference in area also causes a higher force of movement. Because fluid has greater inertia than air does, it is easily understood that increased amounts of force are needed to cause vibration in the fluid.
- The cochlea is a spiral shaped canal located in the innear ear. It is involved in hearing. It is divided into 3 canals:
  - → scala vestibuli
  - → scala media
  - → scala tympani



tymp rest

→ scala vestibuli + tympani are filled with perilymph, scala media with endolymph

- Scala media is separated from scala vestibuli by Reissners membrane and from scala tympani by the basilar membrane. The basilar membrane bears the organ of Corti, which contains the mechanoreceptors of the ear, hair cells with hairs projecting into the endolymph. Many of the hairs are attached to the tectorial membrane which hangs over the organ of Corti.
- Vibrations of the stapes against the oval window produce pressure waves in the fluid of the cochlea. The waves travel to the apex of the cochlea through scala vestibuli, turn around the helicotrema and travels back towards the base through scala tympani. The energy in the waves causes the basilar membrane to vibrate, stimulating hair cells.
- The basilar membrane is stiffer and narrower at the base and more flexible and wide at the apex. As a result different frequencies of pressure waves in the cochlea cause different portions of the basilar membrane to vibrate, stimulating particular hair cells and sensory neurons. Stimulation is perceived in the brain as a sound at a certain pitch.

(35.) Auditory signal - physical characteristic, mechanisms of transduction in the hair cells of Corti organ. Endocochlear potential.

- There are 2 kinds of hair cells in the cochlea. One inner row of about 3500 cells and the outer rows of about 12000 cells.
- The inner cells are the actual sensory receptors and 95% of the fibres of the auditory nerve that project to the brain arise from these cells.
- The terminations on the outer hair cells are almost all from efferent axons that arise from cells in the superior olivary complex. It is thought that the outer hair cells sharpen the frequency by actively contracting and relaxing thus changing the stiffness of the tectorial membrane at different locations.

• Endocochlear potential - the positive voltage of 80-100mV seen in the cochlear endolymphatic spaces. Within the cochlea, the EP varies in the magnitude all along its length. When a sound is present, the endocochlear potential changes either +ve or -ve in the endolymph, depending on stimulus. (+80-100mV)

→ 3500 inner hair cells (95% of afferent fibres), perception of sound
→ 12000 outer hair cells (efferent fibres), olivo-cochlear tract = turning of tectorial membrane.

- The movement of fluid in cochlea produce vibrations in the basilar membrane. These vibrations bend the stereocilia inserted into the tectorial membrane. Depending on the direction of bend, ion channels in the hair cell either stretch open or close. Ultimately a change of ion conductance in hair cells will either increase or decrease the firing rate of auditory nerve fibres.
- The stereocilia are stiff structures protruding from the apical surface of the hair cells. Each hair cell has about 100 stereocilia which become progressively longer on the side of the hair cell away from the modiolus. The tops of the shorter stereocilia are attached to periphery by thin filaments called tip-links to their adjacent longer stereocilia. Therefore, when the hair bundle is reflected towards the tallest stereocilium, cation selective channels open near the tips of the stereocilia. Opening of the channels causes an influx of K^+ ions and a rapid depolarization of the entire hair cell. The depolarization, in turn, leads to an influx of Ca^{2+} ions through voltage-gated Ca channels at the base of the hair cell. This causes vesicles (excitatory glutamate) to release neurotransmitter into the synaptic cleft. This stimulates the afferent nerve fibres - which form part of the auditory nerve - and the signal is thus passed along to the brain.

(36) Otoacoustic emissions. Audiometry.

An otoacoustic emission (OAE) is a sound which is generated within the inner ear. Was first demonstrated experimentally by David Kemp and have since been shown to arise by a number of different cellular mechanism within the inner ear.

→ Studies have shown that OAEs disappear after the inner ear has been damaged, so OAEs are often used in laboratory and the clinic as a measure of inner ear health.

2 types:

- Spontaneous otoacoustic emissions can occur without external stimulation
- Evoked otoacoustic emissions which require an evoking stimuli

→ Are considered to be related to the amplification function of the cochlea. In the absence of external stimuli, the activity of the cochlear amplifier increases leading to the production of sound (outer hair cells).

Audiometry - science of measuring hearing acuity for variations in sound intensity and pitch and for tonal purity, involving thresholds and different frequencies.

→ Determines a subject's hearing levels with the help of an audiometer but may also measure ability to discriminate between different sound intensities.

(37). Localisation of sound in space

- Humans use at least 2 different strategies to localize the position of sound sources depending on the frequencies in the shimulus.
- For frequencies below 3 KHz interaural time differences are used. Sound of lower frequency reaches one ear slightly before the other ear. Action potential begins travelling toward MSO (medial superior olivary). Sound reaches the second ear a little later. AP from the 1st ear begins travelling toward MSO. Then, both APs converge on a MSO neuron that responds most strongly if the arrival is coincident.

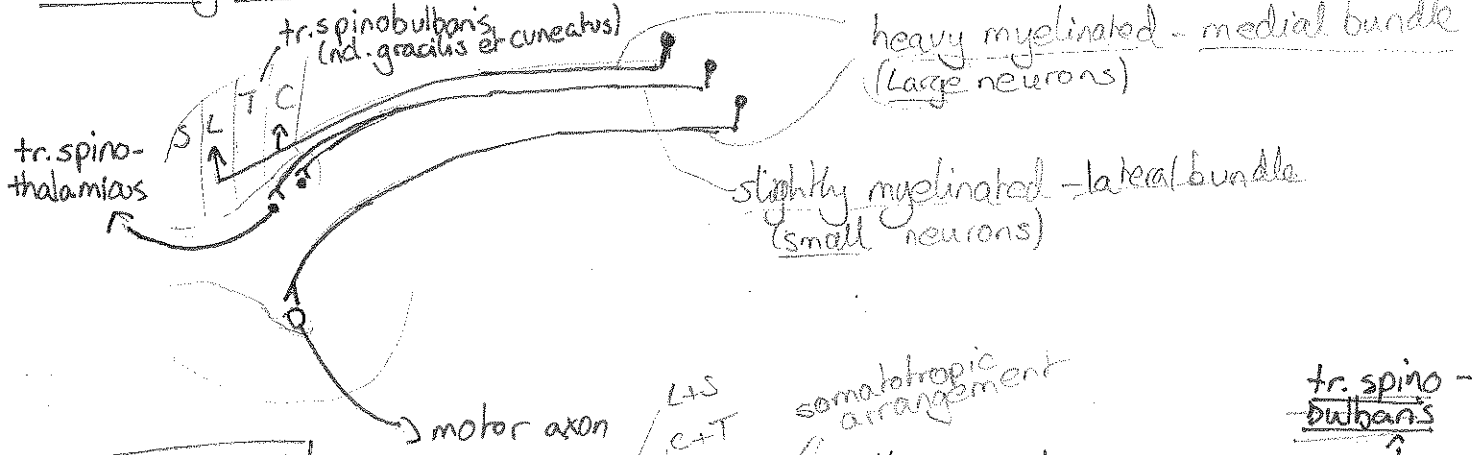
- The neural circuitry that computes such tiny interaural differences consists of bineural input to the medial superior olive that arise from the right and left anterior cochlear nuclei. The medial superior olive contains cells with bipolar dendrites that extend both medially and laterally. The lateral dendrites receive input from the ipsilateral anterior nucleus and the medial dendrites receive input from the contralateral anterior cochlear nucleus. Medial superior olive cells work as coincidence detectors responding when both excitatory shimuli receive at the same time. Different neurons are maximally sensitive to different interaural time delays.
- For sound of higher frequency, the interaural intensity differences are used for localization. The shimulus is stronger to one ear than to the other. The circuits that compute the position of a sound source on this basis are found in the lateral superior olive and the medial nucleus of the trapezoid body. Excitatory axons project directly from the ipsilateral anterior nucleus to the lateral superior olive. The LSO also receives inhibitory input from the contralateral ear via an inhibitory neuron in the medial nucleus of the trapezoid body. This excitatory/inhibitory interaction results in a net excitation of the LSO on the same side of the body as the source sound.

low freq

high freq

MSO vs. LSO
+ trapezoid body

(38) Somatosensory afferents in the spinal cord - describe type of axons, their organization and connection to spinal cord neurons.



L+S
C+T
somatotropic arrangement

tr. spino-bulbaris

Medial bundle (heavy myelin, large neurons) - all sensations except pain/temperature
- axons from lower part of body → more medially (gracilis)
- axons from upper part of body → more laterally (cuneatus)

] lemniscal system

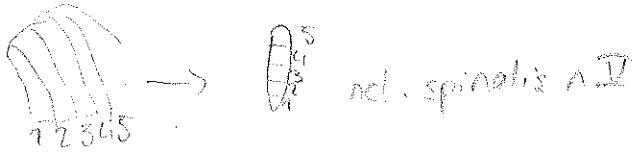
Lateral bundle (slightly myelin, small neurons) - pain/temperature + "light touch"
- axons travel in tr. spinothalamicus
- → tr. spinothalamicus lateral = pain/temperature
- → tr. spinothalamicus anterior = "light touch"

] anterolateral system

somatotropic arr.

→ Some of axons of medial bundle however, terminate on motor neurons, forming the reflex arch

Other somatotropically arranged areas in SS pathway:
- Thalamus - VPM nucleus receives axons from face + tongue
  - VPL nucleus receives from rest of body.
- trigeminal system - the IInd neurons in ncl. spinalis n. V are arranged according to areas of face



(39.) Muscle spindles and Golgi tendon organs, structure, innervation and function

Both of these are proprioceptors so they detect the position of our body in space and relay it to the CNS.
Muscles and tendons have receptors that detect muscle length (muscle spindles) and muscle strength (Golgi tendon organs)
They also contain free nerve endings that are thought to detect muscle pain

Muscle spindle - detect changes in muscle length and are spread in skeletal muscle
- are composed of a few muscle fibres and nerve endings surrounded by a capsule

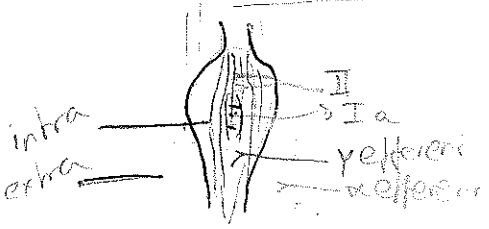
a) Intrafusal fibres are the muscle fibres inside the spindle while the extrafusal ones are outside it.
All these fibres are parallel and when the muscle is stretched, the intrafusal fibres are passively stretched

Intrafusal < Larger - has all of its nuclei in middle - nuclear bag fiber
Others - have nuclei arranged in a line - nuclear chain fibres

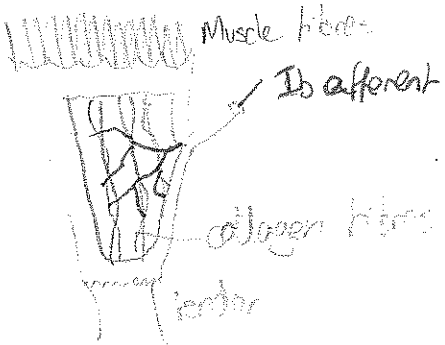
2 types of sensory endings in muscle spindle
↳ (Ia) - innervate middle portion of all intrafusal fibres.
↳ (II) - innervate nuclear chain fibres

Motor innervation comes via γ motor neurons → contraction (remain responsive)

b) Muscle spindle density - varies among muscles
Muscles that require precise movement (extraocular/fingers) - ↑ density
gross movements (leg) - ↓ density



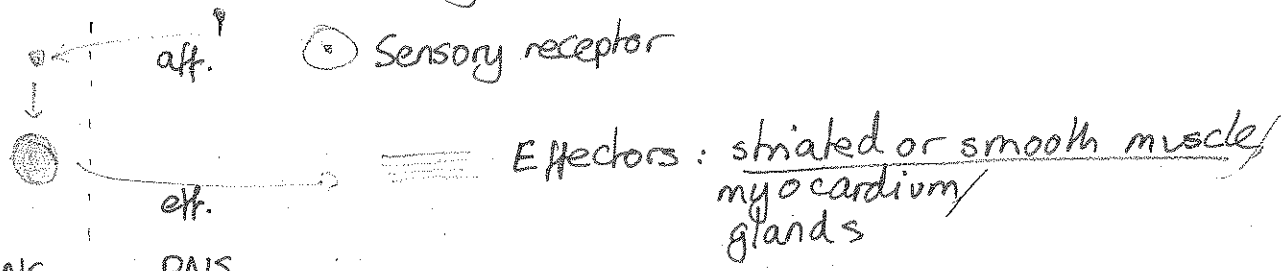
Golgi tendon organs - are found in the tendon-muscle junction. Are slowly adapting mechanoreceptors stimulated by tension in tendon
- consist of a mesh-like weave of collagenous bundles with a thin capsule
- They are innervated by Ib sensory endings that enter the capsule (detect tension among collagen fibres)



(40) Reflexes in motor control - monosynaptic, polysynaptic reflexes. Reflex arc. Muscle tone. Alpha and gamma motorneurons, their function.

- Sensory information is integrated at all levels of the NS and causes immediate motor response in spinal cord with simple muscle reflexes whilst more complex responses travel to BS/cortex for more complicated muscle skills.
  - → grey matter of SC is integrative area for cord reflexes
  - 2 separate destinations of signals:
    - local cord reflex in gray matter terminating immediately → local reflex
    - signal to BS/cortex for fine motor skill.

Reflexes are elicited by reflex arches/loops:



- Sensory receptor - responds to environmental stimuli e.g. in skin for temperature
- Afferent fibre - conveys signal through peripheral nerves to the gray matter of CNS.

→ In the simple arch, the afferent root enters the spinal cord and synapses directly on lower motor neurons - monosynaptic

→ In more complicated arches, afferent root synapses with interneurons which synapse with lower motor neurons - polysynaptic

↳ lower motor neurons transmit impulse to effectors.

Muscle tone: continuous and passive partial contraction of the muscles or the muscle's resistance to passive stretch during resting state

→ If a sudden pull or stretch occurs, the body responds by automatically increasing muscle tension.

Alpha and gamma motorneurons, their function

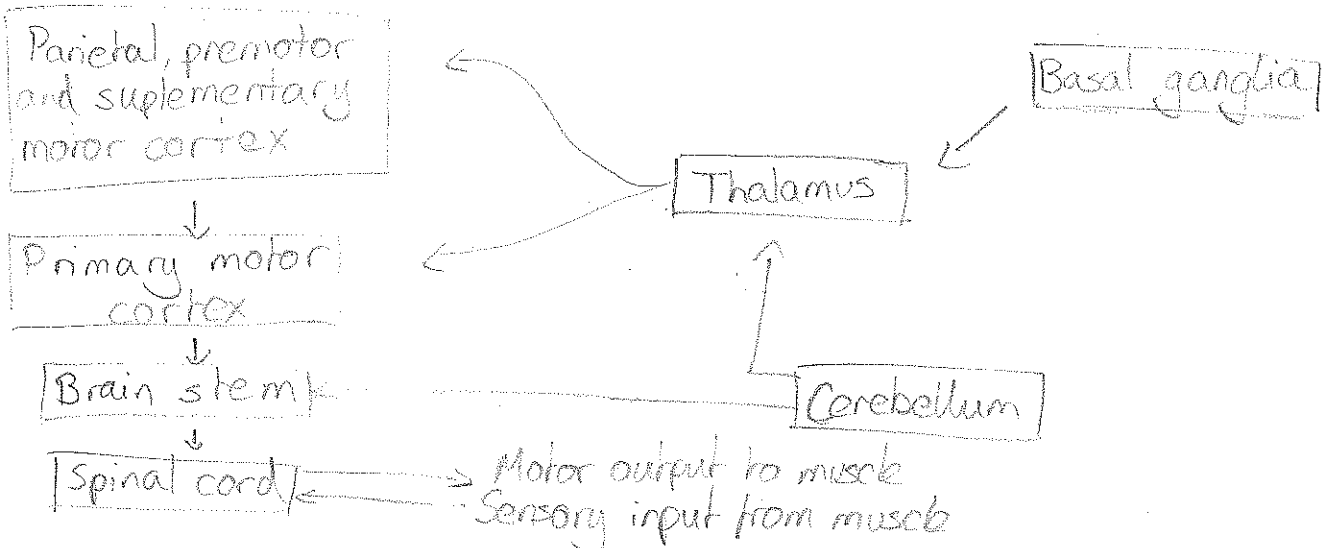
ALPHA

- large, lower motorneurons of BS + SC
- innervate extrafusal muscle fibres of skeletal muscle and directly responsible for initiating their contraction.
- cell bodies found in CNS in nuclei - motor nuclei.
- ipsilateral innervation (except trochlear ncl. in BS which goes to sup. oblique muscle of other side)
- in spinal cord, found in ventral horn (gray matter)
- receive input from uppermost neurons, sensory neurons + interneurons

GAMMA

- system by which CNS controls muscle spindle sensitivity.
- located in BS and SC and are smaller than alpha-motor neurons
- myelinated and slow conduction velocity
- regulate the gain of stretch reflex by adjusting the level of tension in the intrafusal muscle fibres of the muscle spindle
- 2 types: dynamic + static

(41) Hierarchic organizaĥon of motor system, classes of movements. General categorization of motor pathways.



In this scheme, lower motor neurons and their interneurons are influenced by: (1) sensory feedback from periphery, (2) descending brainstem-spinal system modulated by the cerebral cortex and (3) the corticospinal systems.

Furthermore the motor areas in the cortex are hierarchically organized such that the output of the corticospinal system is regulated and modulated by higher order motor cortices. When a voluntary movement is desired, a plan for the movement is organized by the (combined efforts) of the highest order motor areas and then transmitted to primary motor cortex which then executes the plan by communicating with the spinal motor apparatus either directly or indirectly via brainstem-spinal systems.

There are different classificaĥons of movements. In one of the classificaĥon we have:

- Voluntary movements are complex, targeted and purposeful movements stimulated by our own will.
  It can be a reaĉion to an external stimuli. It can be improved by learning.
- Reflex movements are simple movement reaĉion to external stimuli. They are minimally influenced by our will. This is a stereotypical and fast movement.
- Rhythmic motor patterns begin and finish by our own will. The movements are stereotypical.

In other classificaĥons we have:

- Supporting movements → maintain posture + position of body
- Target motor movements are related to human work. Serve to obtain food and for communicaĥon (motor control of speech).
- Emotion motor control express our emoĥons and serve for communicaĥon.

(42) Organization of spinal motorneurons in vertebral horn. Motor unit, types.

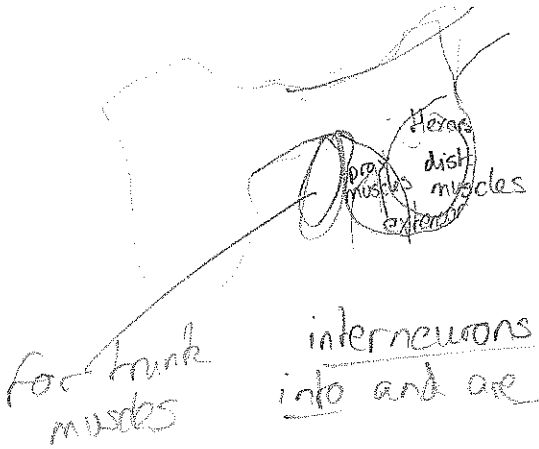
Motor unit: a connection of one motorneuron (SC or BS) by its axon with a number of muscle fibres.

Size of motor units:

- **Small motor unit**: 1 motorneuron innervates a few muscle fibres (oculomotor muscles, distal muscles of upper limb) → more specific/controlled movements
- **Large motor unit**: 1 motorneuron innervates about 500-1000 muscle fibres (e.g. back muscles/leg muscles) → less specific, broad movements

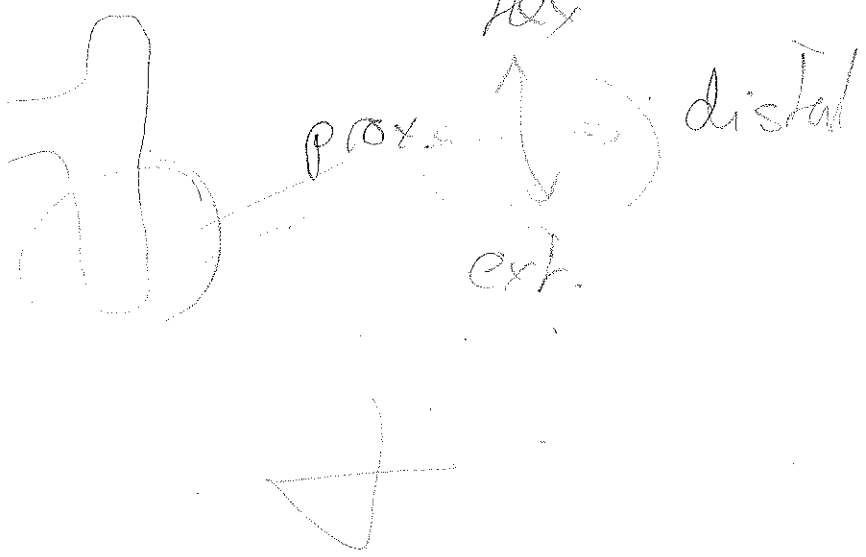
Anterior horn - motorneurons in anterior horn project to the muscles supplied by the spinal cord level from which they exit.

- α motorneurons are regulated by Renshaw cells
- Cervical + lumbar ant. horns are very large because they supply the limbs while thoracic is narrower - supplies axial muscles only



← somatotopically arranged

interneurons in ant. horn filter descending motor into and are part of localized reflex circuits.



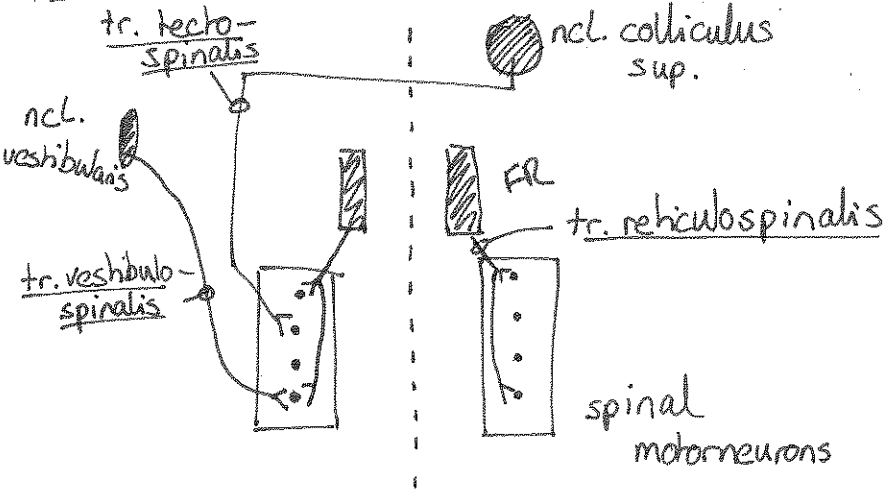
(43) System of the medial and lateral pathways from the brainstem that influence the spinal motoneurons, their functions.

Motor systems for control of movement

Medial system < brainstem pathways / cortical pathways

Lateral system < brainstem pathways / cortical pathways.

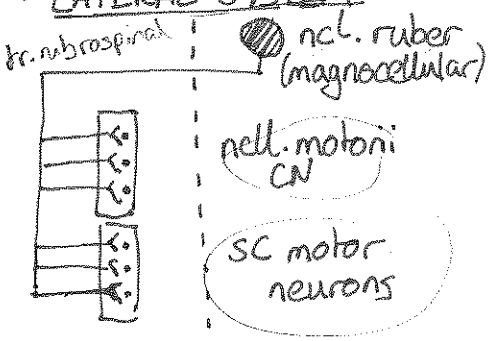
• MEDIAL SYSTEM



- The medial pathways from the BS which influence lower motor neurons includes the:
  - vestibulospinal tract
  - reticulospinal tract
  - fibres from sup. colliculus through tr. tectospinalis

- The vestibulospinal system has a medial and lateral vestibulospinal tracts.
  → Medial tract is made mainly from medial vestibular nucleus, descends bilaterally into spinal cord as medial longitudinal fasciculus. (FLM)
    ↳ projects as long as cervical/upper thoracic levels influencing motor neurons of neck musculature.
  → Lateral tract formed from axons from lateral vestibular nucleus, descends ipsilaterally through anterior portion of brainstem to cause in anterior funiculus of spinal cord.
    ↳ extends throughout spinal cord and excites motoneurons that innervate paravertebral extensors + proximal limb extensors → "antigravity" muscles.
- The reticular system consists of:
  → pontine reticular nuclei (exciting antigravitational muscles)
  → medullary reticular nuclei (relaxing antigravitational muscles)

• LATERAL SYSTEM



- The red nucleus is located in mesencephalon
- It functions in close association to corticospinal tract from who it receives collaterals to form the corticorubrospinal tract passing through mesencephalon. This tract and axons from tr. corticoruber synapse in ncl. ruber to give rise to rubrospinal tract.
  ↳ rubrospinal tract crosses to opposite side and courses just anterior to corticospinal tract into the lateral columns of spinal cord

- Rubrospinal fibres terminate mostly on interneurons of intermediate areas of cord grey matter along with corticospinal fibres but some of rubrospinal fibres terminate on anterior motor neurons and on cranial nuclei.

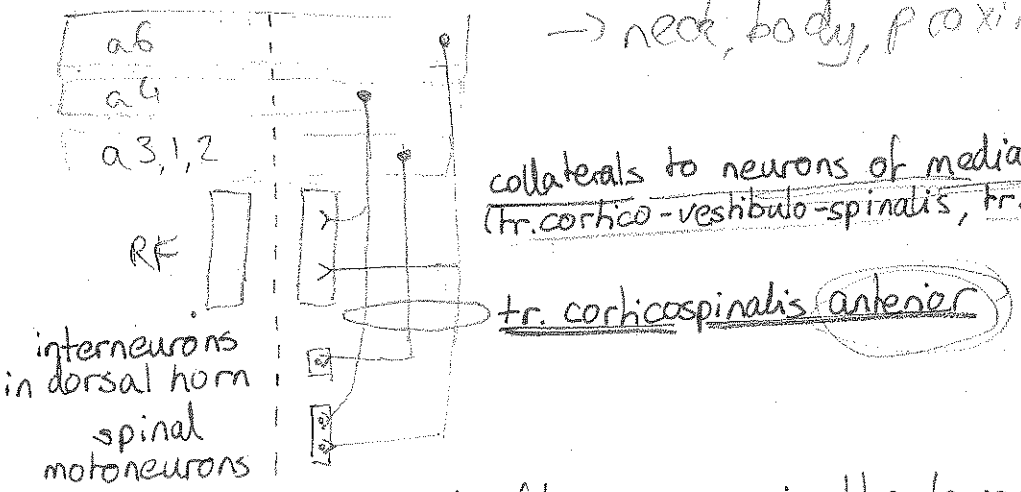
↳ rubrospinal tract controls distal muscles of limbs and links lateral columns of SC to the brainstem

(44) System of motor cortical pathways that influence the motorneurons in spinal cord and brainstem, their functions

- The most important output pathway from the motor cortex is the corticospinal tract. → also called pyramidal tract. Originates about:
  - ~ 30% from primary motor cortex (area 4 - gyrus precentralis)
  - ~ 30% from premotor and supplementary motor areas (area 6)
  - ~ 40% from somatosensory areas (a 3, 2, 1)

→ leaves cortex and passes through posterior limb of internal capsule and then through brainstem forming pyramids of medulla. The majority of the pyramidal fibres then cross in lower medulla to oppasite side.

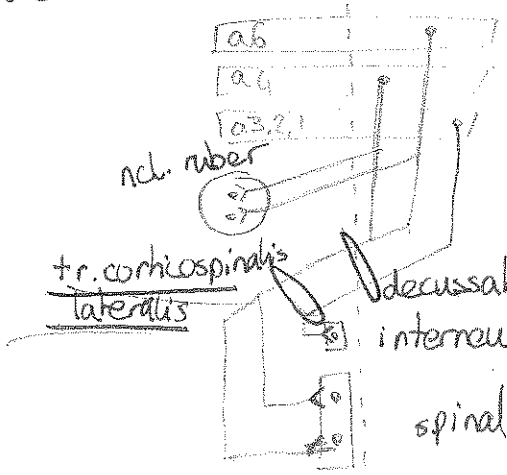
→ a few of the fibres do not cross but pass ipsilaterally down the cord in the anterior corticospinal tracts. These fibres may be concerned with control of bilateral postural movements, voluntary innervation of the neck, body and proximal muscles of extremities.



→ neck, body, proximal muscles

→ The majority of the fibres cross in the lower medulla to the opposite side and descend into the lateral corticospinal tract of the cord, finally terminating in the interneurons in the intermediate region of gray matter, a few on sensory relay neurons in dorsal horn and very few directly on the anterior motor neurons that cause contraction.

→ The lateral corticospinal tracts control the activity of contralateral lower motorneurons innervating distal muscles of extremities (voluntary movements). Since the lateral corticospinal tract lies in the lateral columns of BS and controls the more distal muscles of the limbs, this is called lateral cortical motor system.



Lateral

→ distal muscles

(45). Structure of enteric nervous system - localization, connection and function of different neurons

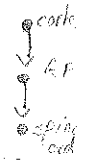
- CNS influence over activities of digestive system is conveyed by sympa or parasympa pathways. However, the digestive tract is able to perform its basic reflexive functions of secretion, absorption, mixing and movement of luminal contents independently from regulation by CNS.
  → high degree of autonomy is possible because wall of gut (oesophagus → anus) has an intrinsic network of neurons termed the enteric nervous system. → sometimes seen as 3rd division of ANS.
  → majority of enteric neurons are in myenteric and submucosal plexuses

- Many functional types of intrinsic neurons can be identified such as several kinds of sensory neurons (mechanoreceptors, chemoreceptors, nociceptors), interneurons and motor neurons (secretomotor, excitatory + inhibitory muscle motor)
- The gut wall also has smooth muscle-like cells called interstitial cells of Cajal, that spontaneously initiate rhythmic activity. → they are responsible for generation and propagation of slow waves of depolarization in the smooth muscle layers of the gut wall, but input from the enteric NS is still necessary for peristaltic movements.
- A specific function of the enteric NS is the peristaltic reflex where the presence of ingested material in ~~intestine~~ gut evokes waves of contraction and relaxation that slowly propel material towards anus.
  → can be initiated either when presence of food bolus distends initial wall and activates intrinsic mechanoreceptive sensory neurons or when enteroendocrine cells in the epithelium responds to contents in the lumen by signalling chemoreceptive neurons
  → propulsion of bolus towards anus done by combination of constriction of intestine above bolus (excitatory interneurons activate excitatory motor neurons and inhibitory motor neurons downstream of bolus) and relaxation below bolus.

(46). Central nervous structures that control the ANS, their description + connect

- The major locus of central control in the visceral motor system is the hypothalamus (chief structure for endocrine and autonomic systems) and the tegmentum of mesencephalon.

- Structures influencing preganglionic parasympathetic and sympathetic neurons are:



→ Cortex and reticular formation: fibres descend from cerebral cortex to reticular formation by the way of corticoreticular tract and then by tr. reticulospinalis to preganglionic neurons of ANS.
→ Area septalis contain neuronal structures important for modulation of control of behaviour. Fibres run in medial forebrain bundle through hypothalamus where fibres then become the hypothalamo-tegmental tract and control the sympathetic neurons.
→ From the hypothalamus and limbic forebrain, fibres descend through fasciculus longitudinalis dorsalis and dorsal tegmentum. This control the parasympathetic neurons.
→ Amygdalar nuclei and periaqueductal gray also contributes to the control of autonomic neurons.

- The hypothalamus is an important structure in control of ANS:
  - Nuclei of anterior hypothalamus (ncl. preopticus + supraopticus) influence parasympathetic NS. Stimulation of anterior hypothalamus results in constriction of pupil, decrease in BP/heart rate, vasodilation, increase in peristalsis, mobility + secretion in G-I-T.
  - Nuclei of posterior hypothalamus (ncl. mamillaris + post. hypothalamicus) influence sympathetic NS. Stimulation of posterior hypothalamus results in dilation of pupil, increase of BP + HR, vasoconstriction, decrease in peristalsis + mobility + secretion in G-I-T and hair erection.

- The preganglionic parasympathetic NS originate from neurons in the brainstem and sacral spinal cord. They travel in sacral spinal nerves and in cranial nerves (III, VII, IX, X) to ganglia. C/S
- The preganglionic sympathetic fibres originate from neurons in the thoracic and lumbar segments. They travel in spinal nerves to ganglia T/L

ncl. ant hypo → parasympa
post hypo → sympa

(47). Control of feeding behaviour (motivation and its determinants, central structures, corresponding behaviour.)

- The chief structure for regulation of food intake and energy balance is the hypothalamus. Multiple feedback signals about nutrient levels and stores enters the hypothalamus which results in coordinate endocrine, autonomic, behavioural responses.

Ventromedial part - center for satiety
Lateral part - feeding center

VM - satiety
Lat - feeding

- Neurons in arcuate nucleus of hypothalamus combine signals relevant for feeding behaviour. Arcuate neurons receive projections from the nucleus of the solitary tract dealing with stomach distension, and the contents ~~of the stomach distension, and the~~ contents of the stomach and intestine, they are directly sensitive to glucose and other nutrients and have receptors for several peptide hormones, whose levels fluctuate in proportion to nutrient levels. 2 important examples of the latter are ghrelin + leptin.
  - Ghrelin is secreted by the stomach at rates that increase with time since the last meal; it binds to arcuate neuron receptors and stimulates feeding behaviour.
  - Leptin is produced by adipocytes and has the opposite effect. → also binds to arcuate receptors

- Body weight seems to be regulated by a set point → can be modulated by stress, palatability of food, exercise, environmental + genetic factors
  - → Short-term cues consist primarily of chemical properties of the food that act in the mouth and in the gastrointestinal system - visceral afferentation, communicating with the lateral hypothalamic regions.
  - → It is also modulated by long-term signals that reflect body weight e.g. leptin → leptin receptors in ncl. arcuatus → release of neuropeptide Y
    ↓
    growth of fat tissue

Stomach + intestine + contents distension → solitary nucleus → arcuate nucleus

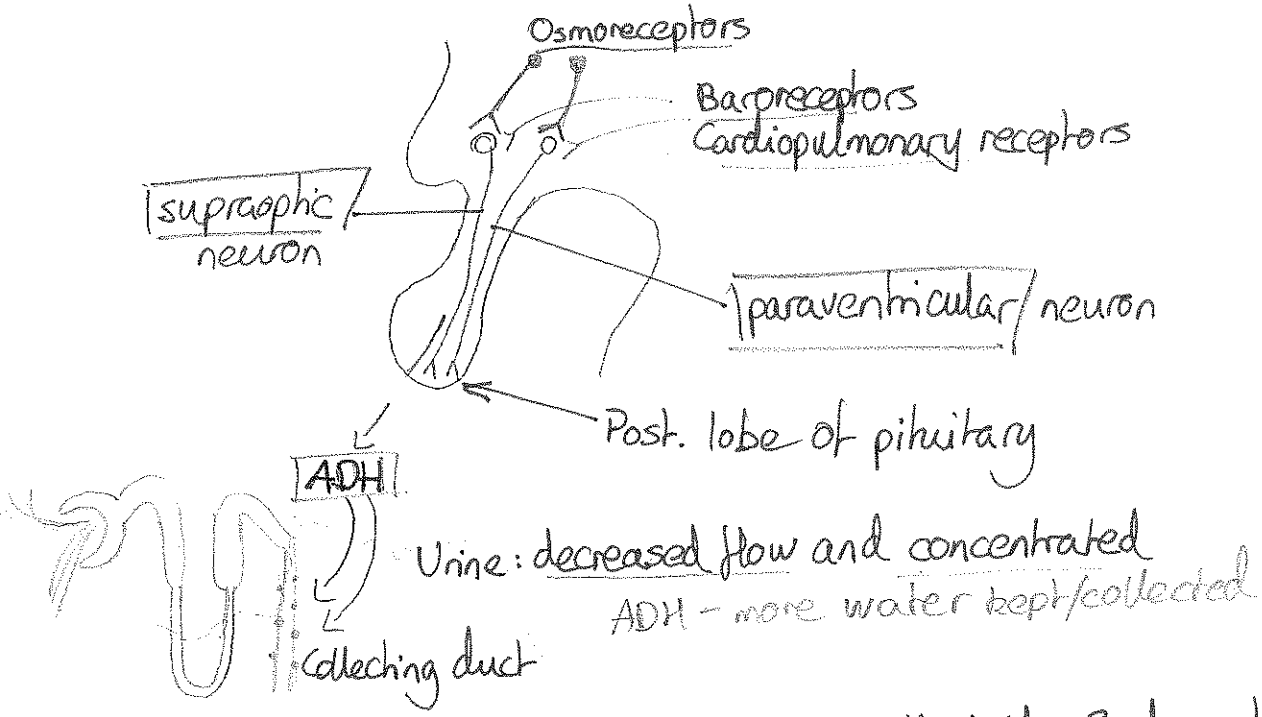
- Stom + intestine directly sensitive to glc + ... receptors)

Ghrelin (feeding) vs. Leptin (adipocytes)
→ binds to arcuate neuron receptors
→ ...

(48). Control of fluid intake (motivation and its determinants, central structures, corresponding behaviour)

Fluids intake is regulated by the thirst mechanism, which, together with the osmoreceptor-ADH mechanism, maintains precise control of extracellular fluid osmolarity and sodium concentration. Water is important to maintain electrolyte or other solute concentrations constant. Many of the same factors that stimulate ADH secretion also increase thirst, which is defined as the conscious desire for water.

CENTRAL NS CENTERS FOR THIRST



The same area along the anterolateral wall of the 3rd ventricle that promotes ADH release also stimulates thirst. Located anterolaterally in the preoptic nucleus is another small area, that when stimulated, causes immediate drinking that continues as long as the stimulation lasts. All these areas together are called the ~~thirst center~~.

The neurons of the thirst center function as osmoreceptors to activate the thirst mechanism (↑osmolarity of ECF → osmoreceptor shrink → ↑firing → thirst feeling; ↓osmolarity of ECF → osmoreceptors swell → ↓firing).

Increased osmolarity of the CSF in the 3rd ventricle has essentially the same effect to promote drinking.

- Stimuli for thirst

1. Increased extracellular fluid osmolarity - causes intracellular dehydration in the thirst centers, thereby stimulating sensation of thirst.
2. Decreases in ECF volume and arterial pressure.
3. Angiotensin II - because angiotensin II is stimulated by factors associated with hypovolemia and low blood pressure, its effect on thirst helps to restore blood volume and blood pressure toward normal.

(49) Control of sexual behaviour - Sexual differentiation of the brain

Many parts of the nervous system are involved in mating. Copulation itself is made up of a series of reflexes integrated in spinal and lower brain stem centers but the urge to copulate and the behavioural components that accompany it are regulated to a large degree in the limbic forebrain and the hypothalamus.

A variety of reproductive behaviour, including desire, priming and parenting behaviours are governed by the hypothalamus. In Rhesus monkeys it has been showed that neurons in the medial preoptic area of the male hypothalamus fire rapidly before sexual behaviour, but decrease their activity upon mating. In contrast, neurons in the dorsal anterior hypothalamus begin firing at the onset of mating.

Paralimbic association cortical area is involved in the control of sexual behaviour.

In nonprimate mammals, removal of gonads leads eventually to decreased or absent sexual activity in both female and male. Injections of gonadal hormones in castrated animals revive sexual activity.

While the sexual activity of the male is constant, it is cyclic in females. Sexual activity occurs throughout the menstrual cycle, but there is more spontaneous female initiated sexual activity at about the time of ovulation.

Most experiments regarding structural sex differences in the brain between male and female have been done in rats. In them, there are several structures which clearly differ in number, size, and connectivity of their neurons between male and females. In humans, structural differences are less obvious but still present.

Sex-related differences in the phenotypic expression of genotype are called sexual dismorphisms. They are present in the anterior hypothalamus and cerebral cortical structures. The development of these structural differences depends primarily on the early effect of gonadal steroid hormones on maturing brain circuits, an influence that apparently continues to some extent throughout life.

The presence of either 2 X chromosomes or an X and a Y chromosome in the cells of an embryo sets in motion events that establish phenotypical sex, including the sexual dimorphic development of the brain. The effects are determined by the production of hormones, which depends in turn on the presence of either female or male gonads. The primary genetic influence on the development of the typical male phenotype is the sex-determining region on the Y chromosome. When this region of the chromosome is activated during development, it turns on the production of a protein called testis-determining factor (TDF). It is TDF that instructs the testes to begin

developing. If Y chromosome is absent, the fetus will get ovaries.

The gonads, in turn, are responsible for producing most of the circulating sex hormones. Differences in circulating hormones leads to a variety of differential effects on the individual's development, including their physical appearance and brain development.

Much studies have been done on rodents which show that different hormone levels at critical times organizes and activates circuits generating female or male typical behaviour. Males have an early surge of testosterone which masculinizes the genitalia and nervous system and ultimately behaviour.

Gonadal steroids - whether estrogens or androgens - stimulate sexually dimorphic patterns of development by binding to estrogen or androgen receptors. These receptors, which are transcription factors activated by hormone binding influence gene transcription and ultimately the development of an array of targets, including sexually dimorphic neural circuits.

(51). Specialization of the hemispheres

The brain is divided into 2 hemispheres (right + left). They are linked by corpus callosum. Both hemispheres resemble each other and have structures that are mirrored by the other.

→ The left hemisphere analyzes the right visual field, serves for stereogenesis of the right hand, lexical (words) and syntahic (grammar) languge, writing and speech.

→ The right hemisphere analyzes the left visual field, serves for stereogenesis of left hand, emotional coloring of language and rudimentary speech.

· The proof for this is the split brain pahients in which the corpus callosum is cut. The Wada test is used to establish cerebral language and memory representation of each hemisphere. The test is conducted with the patient awake. A barbiturate is introduced into one of the internal carotid arteries. The effect is to shut down any language and/or memory function in that hemisphere. They do it in one hemisphere at the time and in that one where it causes paralysis of speech is the "dominant" hemispheres for language.

Left	Right
Analysis of R visual field	Analysis of L visual field
Stereognosis of R hand	Stereogenesis of L hand
Understanding + speech	Emotional colouring of language
Writing	Spatial abilities
Grammar	Rudimentary speech

Broca: frontal lobe - speech

Wernicke's: temporal lobe - understanding of spoken language.

(52) Gnostic functions - examples, impairments. Function of polynodal association cortices.

Polynodal association cortices function to produce a meaningful perceptive experience of the world enabling us to interact effectively and support abstract thinking and language.

The parietal, temporal and occipital lobes: all located in the posterior part of cortex - organize sensory information into a coherent perceptual model of our environment centered on our body image.

The frontal lobe or prefrontal association complex is involved in planning of actions and movement as well as abstract thought

Agnosia - loss of ability to recognize objects/people/sounds/shapes or smells → but there is no defect in senses or memory loss
→ usually associated with brain injury/neurological illnesses.

There are several types of agnosia such as visual agnosia which is a deficiency in the ability to recognize visual objects. Thus not even being able to name them.

Another type of agnosia is prosopagnosia which is the inability to recognize faces → difficulty recognizing family or friends.

(Agnosia may frequently appear to people recovering from blindness)

(53). Sleep-waking periodicity / Reticular formation involvement.

Sleep follows a circadian rhythm. This term comes from latin "circa" means around and "dian" meaning day. It is influenced by both the time of the day and recent sleep history.

Adult humans sleep at night for 7-8 hours, but we sleep both sooner and longer after losing sleep the night before. The basic periodicity comes from a biological clock in the hypothalamus - the suprachiasmatic nucleus. It receives information about light from photosensitive ganglion cells in the retina via the retinohypothalamic tract. These cells represent approximately 2% of the retinal ganglion cells in humans and express the photopigment melanopsin.

Ncl. suprachiasmaticus → ncl. paraventricularis → spinal cord → g. cerv. sup. → (pineal gland:) secretion of melatonin (during darkness).

This night-time rise in pineal melatonin secretion is thought to provide a signal that helps "set" the circadian clock.

Reticular formation ⟹ has projections to the thalamus and cerebral cortex that allow it to exert some control over which sensory signals reach the cerebrum and come to our conscious attention. Plays a central role in states of consciousness.

AFAS → sends warning signal before sending sensory info

(54) Modulatory brain systems

- In brain modulation, several classes of transmitters regulate diverse populations of central nervous system neurons. One neuron uses different neurotransmitters to connect to several neurons.
- A neuromodulator is a neurotransmitter that is not reabsorbed by the presynaptic neuron or broken down into a metabolite. Such neuromodulators spend a significant amount of time in the CNS, affecting the overall activity of certain areas of the brain.
- Work through G-protein coupled receptors

Neuromodulatory systems

① Noradrenaline systems
- origin: locus ceruleus (pigmented with melanin) in 4th ventricle
- targets: adrenergic receptors in thalamus, spinal cord, hypothalamus, striatum and limbic system.
- effects: arousal (physiological state of being awake + reactive)

② Dopamine system
- origin: dopamine pathways; mesocortical, mesolimbic, nigrostriatal pathways.
- targets: dopamine receptors at pathway terminations
- effect: reward system, motor system, cognition

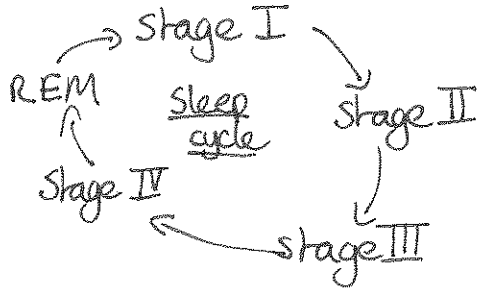
③ Serotonin system
- origin: rostral and caudal dorsal raphe nuclei
- target: limbic system structures, cortex, spinal cord
- effect: increase mood, safety, sleep + decreases nociception

④ Cholinergic system
- origin: pedunculopontine nucleus, dorsolateral tegmental nuclei, septal nuclei, basal nucleus of meynert?
- target: M_1 receptors in brainstem, deep cerebellar nuclei, basal ganglia, hypocampus
- functions: learning, short-term memory, reward

noradren
dopamine
serotonin
cholinergic

(55). Sleep cycles (non REM, REM phases, EEG and vegetative correlates). Examples of sleep disorders.

Sleep is defined by an unconsciousness from which the person can be aroused by sensory or other stimuli. It is to be distinguished from coma, which is unconsciousness from which the person can't be aroused.
Sleep is actively induced and it's a highly organized brain state.



- During sleep: 4-6 cycles
- Deeper sleep stages can be achieved only during 1st, 2nd cycles.

- Criteria of sleep: reduced motor activity, decreased response to stimulation; stereotypic posture; relatively easy reversibility.
- 1st type (non REM) → includes several stages (1,2,3,4) in which the EEG gets progressively slower and more synchronized.

Non-REM sleep
- ↓ neuronal activity · ↓ metabolic rate and brain temperature
- ↓ sympathetic outflow, ↓ HR, ↓ BP · ↑ parasympathetic activity
- skeletal muscle relaxed, muscle tone and reflexes are intact.

- Approximately every 90-120 mins, we shift to the second type, REM sleep also called paradoxal sleep.

REM sleep
- ↑ neuronal activity · ↑ metabolic rate and brain temperature
- atonia - ↓ skeletal tone (except eye muscle and diaphragm)
- homeostatic mechanisms are attenuated

→ Destruction of ncl. reticularis pontis oralis inhibits REM sleep.

- Regulation of sleep
Ventrolateral preoptic nucleus (hypothalamus) produce **orexin**; orexin stimulate cholinergic, noradrenergic, serotoninergic, histaminergic nuclei → induce awakeness (cholinergic ncl, raphe ncl, locus ceruleus, tuberomammilary ncl.)
GABA inhibits these nuclei → induce sleep.

- Dreams
→ In both REM and non-REM stages.
→ Reports of non-REM dreams tend to be shorter, less vivid, less emotional and more coherent than REM dreams.

Sleep disorders
- **Insomnia** - inability to sleep for a sufficient length at a time to produce a subjective sense of refreshment
  - stress, jet lag, coffee, working night shift / associated with depression.
- **Sleep apnea** - pattern of interrupted breathing during sleep causing waking up dozens or more times with the results - no slow wave sleep and less time in REM sleep. Frequent in males and obese people.
- **Narcolepsia** - REM sleep attacks during the day without going through non REM. 30s-30min
  The onset of sleep can be abrupt - cataplexy.

(56). Electroencephalogram - description of electrical activity, basic rhythms, clinical meaning. Evoked potentials. Event related potentials.

Electroencephalography is a method of detection and recording the bioelectrical activity of the brain. This method records the potential differences between two electrodes representing an EEG's lead.

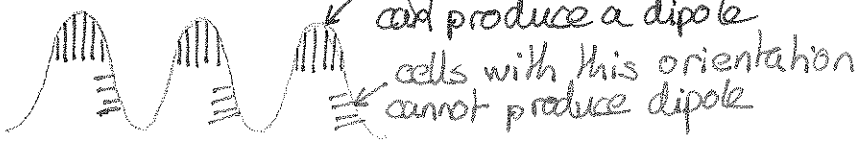
→ Both bipolar and unipolar leads are used
→ When using unipolar leads, the indifferent electrode is usually placed on the earlobe or on mastoid process.

EEG reflect the synchronous activity of a high number of neurons. This is based on the potential difference on dendrites and neuron bodies resulting from the sum of postsynaptic potentials, both excitatory and inhibitory.

The electrodes localized on the surface of the head are called scalp EEG. The method where the electrodes are in direct contact with the brain tissue is called electrocorticography. When the electrodes are located deep in the brain is called stereo electroencephalography.

In non-invasive scalp EEG we use 21 leads.

Pyramidal cells give the major contribution to EEG because of their long dendrites. The synaptic potential in these dendrites creates a dipole.

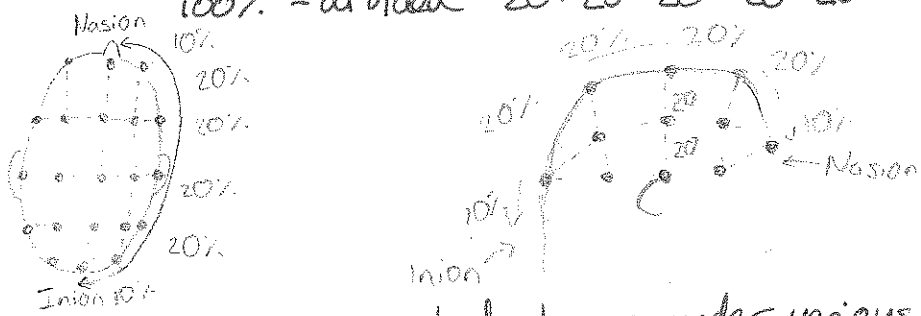


Electrodes: Nasion - Inion

40cm = 100% - divided 10-20-20-20-20-10

Biauricular

100% - divided 20-20-20-20-20



EEG activity undergoes marked changes under various physiological+pathological conditions. EEG curve is composed of waves of characteristic frequency and amplitude. The 4 standard waves are:

Alpha
Beta
Theta
Delta

Alpha: 8-13 Hz - wakeful, healthy, relaxed adults (maximum above occipital lobe when eyes are closed)
Beta: 13-30 Hz healthy, wakeful adult
Theta: 4-8 Hz - in general a pathological feature, physiologically only during sleep.
Delta: 1-3Hz - physiologically only during non-REM sleep

- Evoked potential - electrical potential recorded from nervous system following presentation of a stimulus, as distinct from spontaneous potentials
  - VEP - visual evoked potential
  - BAEP - brainstem auditory evoked potential
  - SSEP - somatosensory evoked potential
- Event-related potential - measured brain response that is the direct result of a specific sensory, cognitive or motor event.

57. Measuring of the cerebral blood flow changes - functional magnetic resonance imaging (FMRI) and positron emission tomography (PET). Principles of measurement, examples of clinical + experimental use.

The brain doesn't store glucose, when neurons go active getting them back to their original state requires actively pumping back ions through the membrane, this requires ATP which in turn requires glucose. More blood flows in to transport more glucose also bringing in more O_2.

Usually the brought in O_2 is more than the oxygen consumed in burning glucose and this causes a net decrease in that brain area's blood vessels. This damages the magnetic property of blood making it interfere less with the magnetization and it's decay induced by MRI process

The dHb molecule is more attracted to magnetic field than an oHb, therefore it distorts the surrounding magnetic field induced by an MRI scanner causing the nuclei to lose magnetization faster via T_2 decay. Therefore there is more MR signal when blood is highly oxygenated than when it's not.

fMRI - MRI procedure that measures brain activity by detecting associated changes in blood flow. Primary form of fMRI uses the blood-oxygen-level-dependent contrast

Clinical uses: clinicians use fMRI to anatomically map the brain and detect the effects of tumors, strokes, head injury + diseases such as Alzheimer's

PET - positron emission tomography is a nuclear medicine imaging technique that produces a 3D image or picture of functional processes in the body. The system detects pairs of γ-rays emitted by a positron emitting radionuclide which is introduced to the body or a biologically active molecule, often combined with CT
- If the biologically active molecule chosen for PET is fluorodeoxyglucose (FDG), an analogue of glucose, the concentrations of tracer imaged then give tissue metabolic activity.

INTEGRATED TOPICS

(58) Skin sensation from the body: 1) crude sensation and temperature sense, 2) discriminative and vibration sensation. Stimuli, receptors and their distribution. Draw and describe a simple scheme illustrating position, localization and connections of neurons that convey 1) crude and 2) discriminative skin sensation from the body to cortex, describe their somatotopic arrangement including cortex. Dermatomes.

1) CRUDE SENSATION (light touch) - Aβ information about localization and implement of contact (① Meissner corpuscle and organs ② Pacinian corpuscles ③ hair follicles receptors ④ free nerve endings)

TEMPERATURE SENSE - information about temperature through thermoreceptors which analyze how cold something is (Aδ - cold receptors, C fibres warmth receptors)

2) DISCRIMINATIVE tachile sensation - differentiation of 2 points, quality of the surface, stereognosia - fine movements

- Vibration - ① Meissners and ② Pacinian corpuscles (Aβ)

- Stimuli, receptors and their distribution

Touch: Aβ fibres

Stimuli

We can detect the sense of touch, pressure or vibration by means of mechanoreceptors:

1. Pacini corpuscle: located in subcutaneous tissue, has a capsule with 20-70 layers of c.t. and a nerve terminal in the middle. When the capsule is compressed, energy is transferred to mechanoreceptor and channels open.

Receptors discrimination

2) Meissner's corpuscle: located in hairless skin
3) Ruffini's corpuscle: both hairy/hairless skin
4) Meckel's receptor: hairless skin
5. Krause's end bulb: around lips + external genitalia.

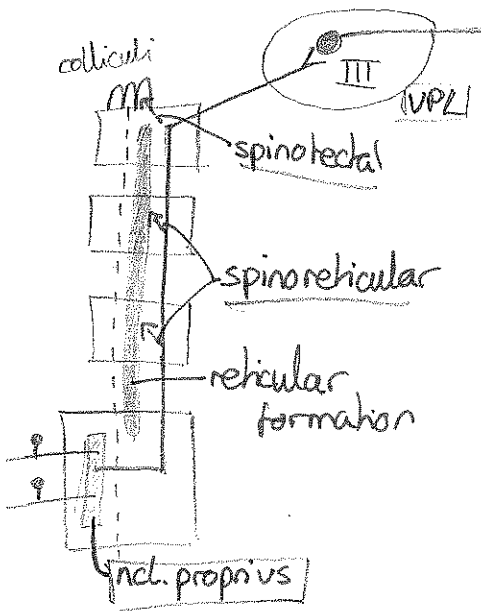
- Two things determine the sensitivity of spatial discrimination in an area of skin:
  - → size of receptor field of receptor
  - → density of receptors
- Pacinis have broad receptive field, but Meissner's and Meckel's have small. Small receptor field is important for high spatial discrimination (e.g. fingertips)

6. Free nerve endings
7. Hair follicle receptors

Temperature

Cutaneous receptors are free nerve endings
1) warmth receptors - increase firing with ↑heat
2) cold receptors - increase firing with ↓heat

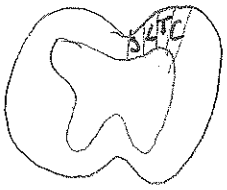
CRUDE SENSATION



- I neuron - originates from the receptors, either Aδ or C.
- II neuron - I fibres ascend in tract of Lissauer and synapse in ncl. propriis. II fibres cross midline
- III neuron - from ventroposterolateral nuclei in thalamus to cortex
- IV neuron - cortex areas 3, 1, 2 postcentral gyrus

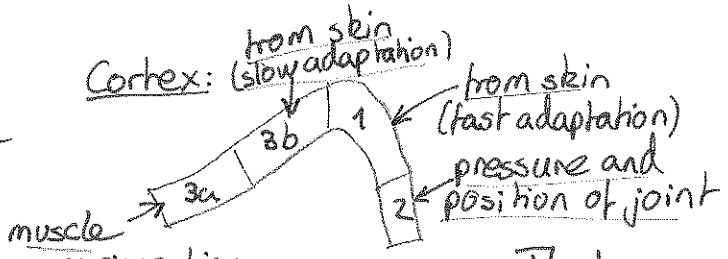
Somatotropic arrangement:

SC:



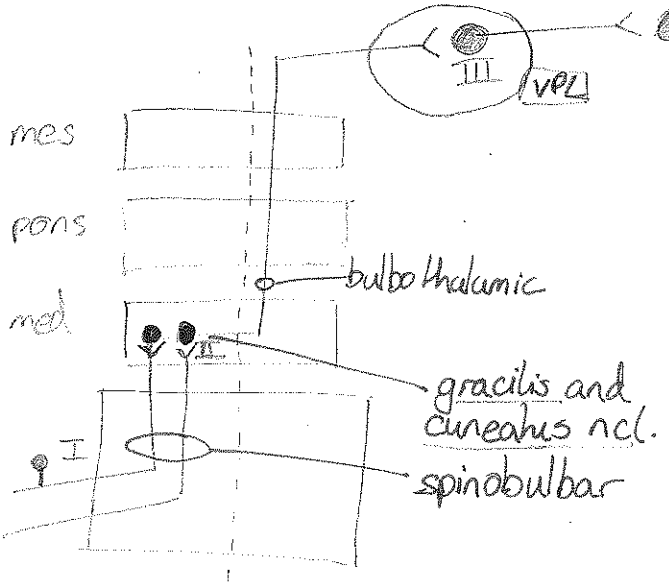
Upper: lateral
Lower: medial

Cortex:



Thalamus:
VPM: face/tongue
VPL: rest of body

DISCRIMINATIVE SENSATION



- I neuron - originates from the skin receptor (Aδ)
- II neuron - originates from ncl. gracilis and cuneatus (gracilis - medial - lower limb; cuneatus - lateral - upper limb)
- III neuron - from VPL nucleus
- IV neuron - post central gyrus

Dermatome: area of skin that is mainly supplied by a single nerve. Each nerve conveys sensation from a particular region of skin to the cortex.