Introduction to Functional Neurobiology

Lectures

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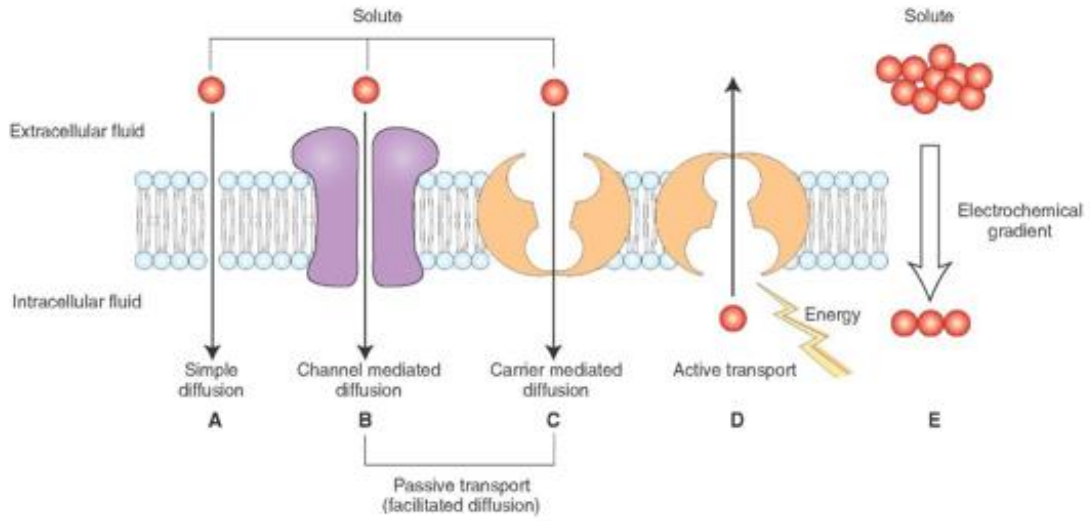
Contents

Electrophysiology I.

Lecture I.

Ionic composition of nerve cells



There are a lot of ions outside the membrane, but only a few inside in the cell → electrochemical gradient. This acts as a driving force that moves ions across the membrane to equilibrate the concentration.

	Outside the nerve cell	Inside the nerve cell
Na^+	150 mM	15 mM
K^+	5 mM	140 mM
Cl^-	120 mM	10 mM
A^-		100 mM

The Nernst Equation

The equilibrium potential for an ion can be calculated using the Nernst equation:

$$E_{ion} = 2.303 \frac{RT}{zF} \log \frac{[ion]_o}{[ion]_i}$$

where

E_{ion} = ionic equilibrium potential
R = gas constant
T = absolute temperature
z = charge of the ion
F = Faraday's constant
log = base 10 logarithm
$[ion]_o$ = ionic concentration outside the cell
$[ion]_i$ = ionic concentration inside the cell

$$E_K = 61.54\ mV \log \frac{[K^+]_o}{[K^+]_i}$$
$$E_{Na} = 61.54\ mV \log \frac{[Na^+]_o}{[Na^+]_i}$$
$$E_{Cl} = -61.54\ mV \log \frac{[Cl^-]_o}{[Cl^-]_i}$$

For K^+ ~ -80 mV

For Na^+ ~ +80 mV

For Cl^{--} ~ -65 mV

Resting membrane potential

$$E_m = \frac{P_{K+}}{P_{tot}} E_{K+} + \frac{P_{Na+}}{P_{tot}} E_{Na+} + \frac{P_{Cl-}}{P_{tot}} E_{Cl-}$$

where:

- E_m is the membrane potential, measured in volts.
- E_X is the equilibrium potential for ion X, measured in volts.
- P_X is the relative permeability of ion X in arbitrary units.
- P_{tot} is the total permeability of all permanent ions, in this case $P_{K+} + P_{Na+} + P_{Cl-}$

Maintaining the ion concentration through the nerve cell membrane

The Na-K pump in nerve cells use ATP and active transport to pump out two ions:

- pumps 3 sodium ions out of the cell
- 2 potassium ions into the cells by means of active transport.

As a result, the inside of the cell contains more K^+ ions and fewer Na^+ ions than the outside.

Action potential generation

Determining of ion movements during AP:

(Sir J. C. Eccles, A. L. Hodgkin, A. F. Huxley)

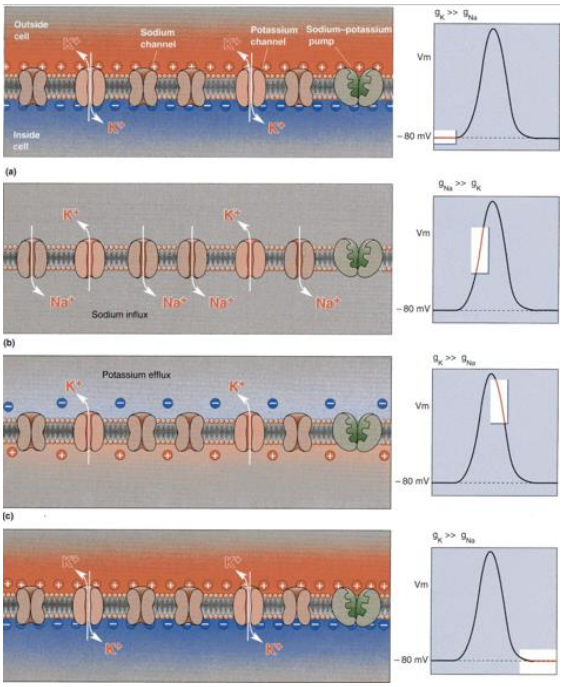
The AP is generated by the ionic movements, inflow of sodium ions, followed by the outflow of potassium ions.

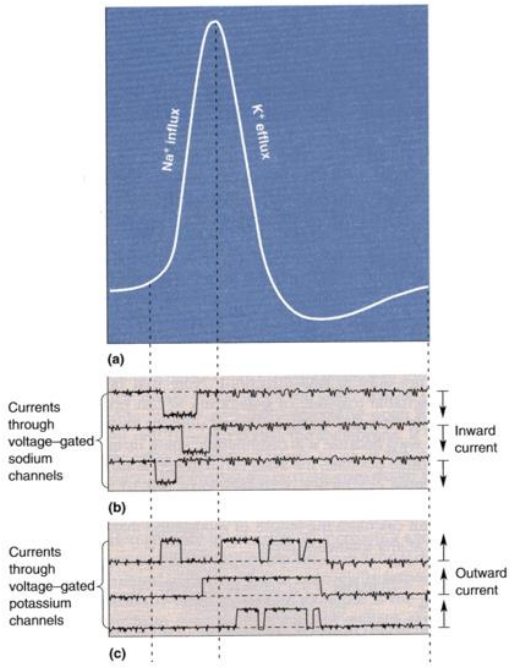
Patch-clamp recordings:

(Erwin Neher, Bert Sakmann)

They pushed a glass pipe to the membrane, and they generated a suction via the pipe → very tight seal with the membrane. There was an ion channel in the patch, the ion movement through that was measured.

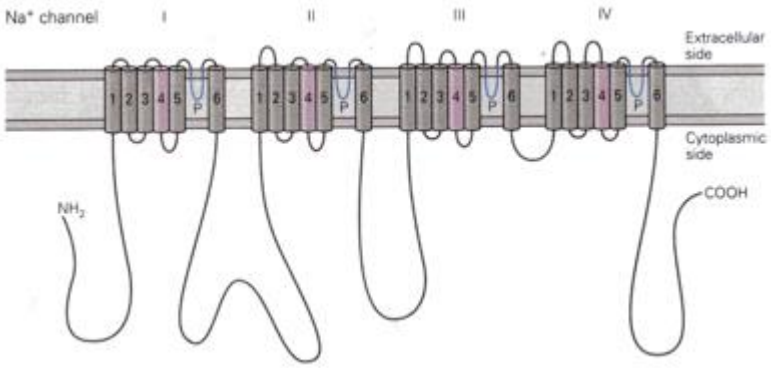
Current within the synapses is due to the fact that we have protein complexes in the membrane, and they can open and close and this opening/closing allows passing the membrane in a controlled manner. → ionic movements through the membrane (like sodium and potassium during AP)



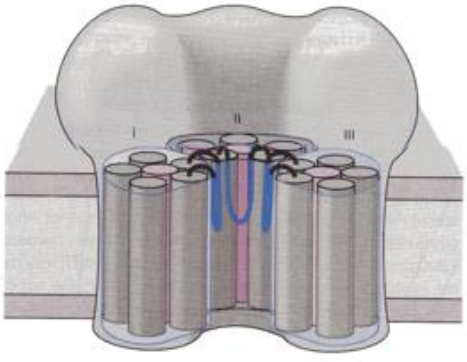


Structure and function of voltage-gated ion channels

4 units → single channel

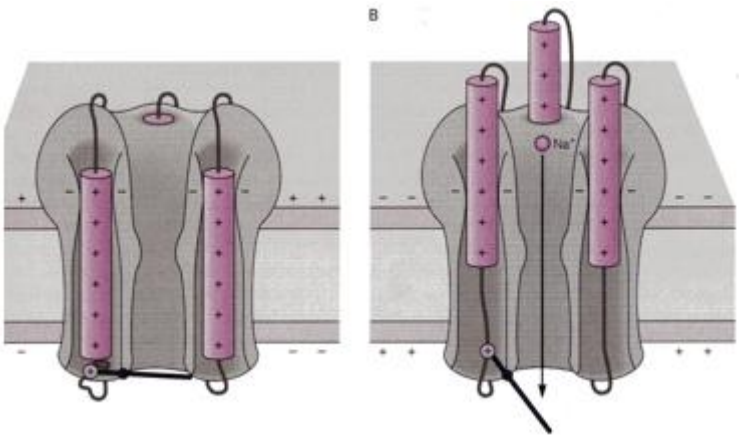


one unit:



<u>the channel</u>:

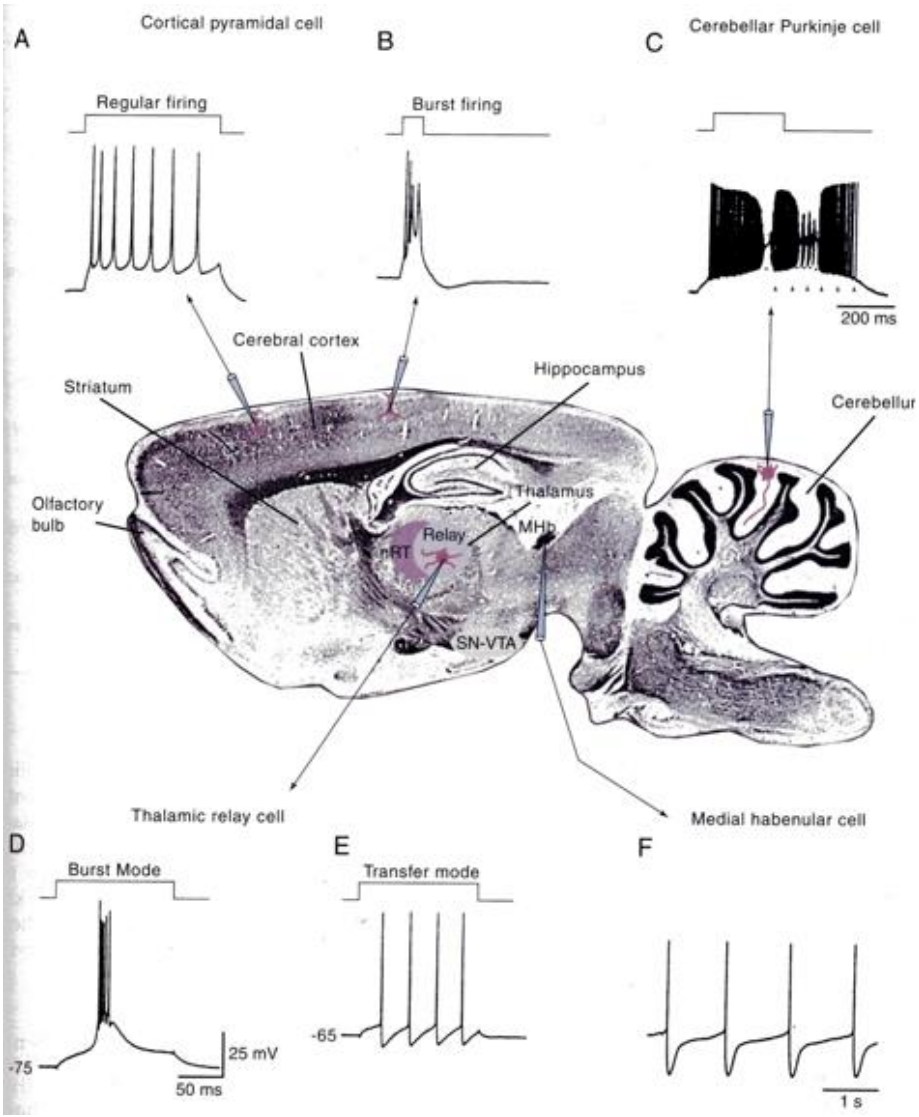
Each unit has six transmembrane helixes, they are arranged in a way that in the middle (the fourth transmembrane helix) is the voltage sensor. Charges and amino acids change the conformation according to the voltage changes of the membrane. If there is a depolarization the transmembrane helix physically moves, this allows the channel to open, so the ion can pass it. As the transmembrane helixes move due to the voltage changes, a gate opens as well.



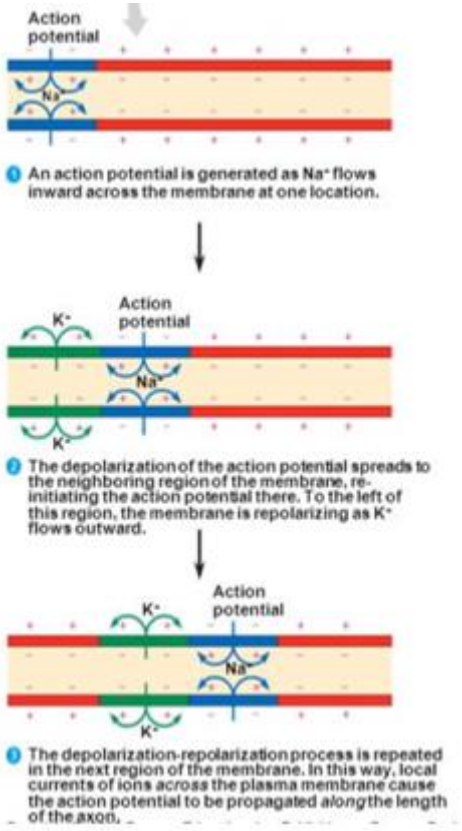
How is it determined, which ion can move through the channel?

Ion selectivity is determined by pi loops, its composition decides whether a sodium, a calcium or a potassium ion can pass the channel.

Diverse types of action potentials in the nervous system



AP propagation



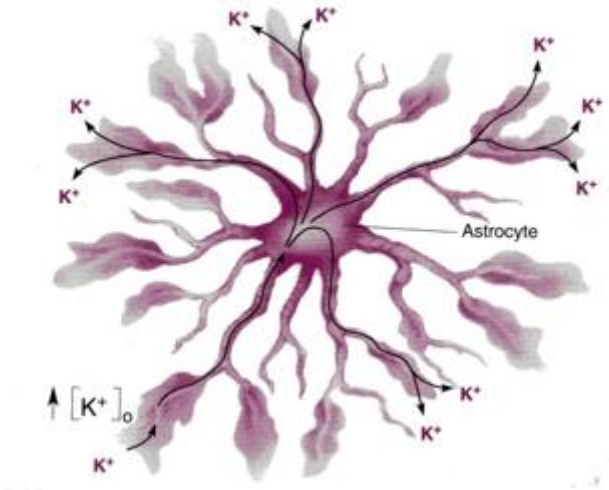
The AP originates from the axon hillock because it contains the highest density of voltage-gated Na channels. Depolarization travels along the axon. With a bit of relay, K channels open as well, and repolarization happens.

Backpropagation: When the action potential is generated, there is also a chance that it travels from the soma to the direction of the dendrites. That is because, at the very beginning, when voltage-gated channels open, the depolarization can travel in both directions. We can find voltage-gated channels on the dendrites as well.

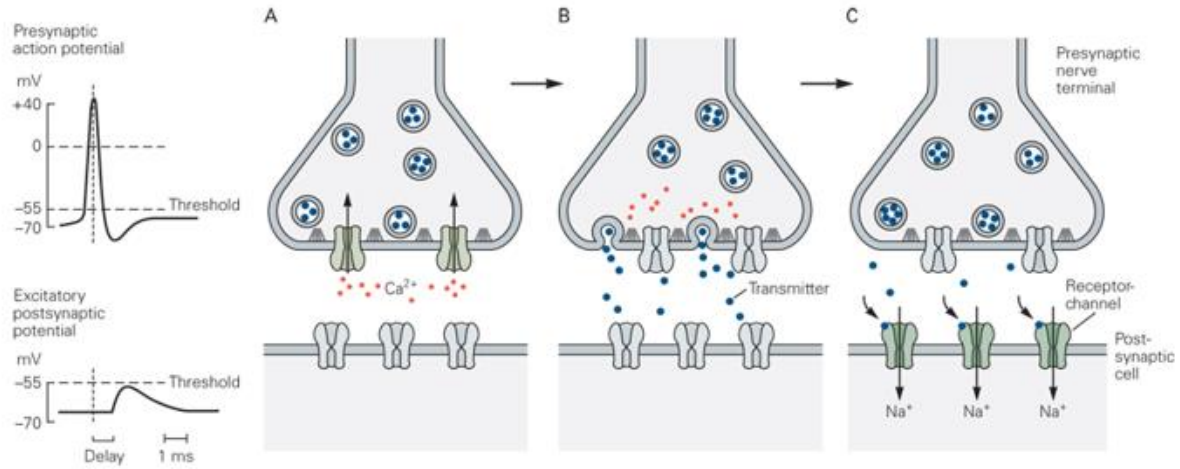
Remove of K^+ from the extracellular space

A sodium-potassium pump restores the ionic concentrations along the membrane (brings K^+ in, moves Na^+ out).

Astrocytes also help. They are a type of glial cells, which cannot be depolarized They participate in the homeostatic regulation of the nerve function, as well as contributing to nerve cell communication. They pick up K with the help of their endplates where they are in a high concentration, then they distribute it in the neighbouring milieu.

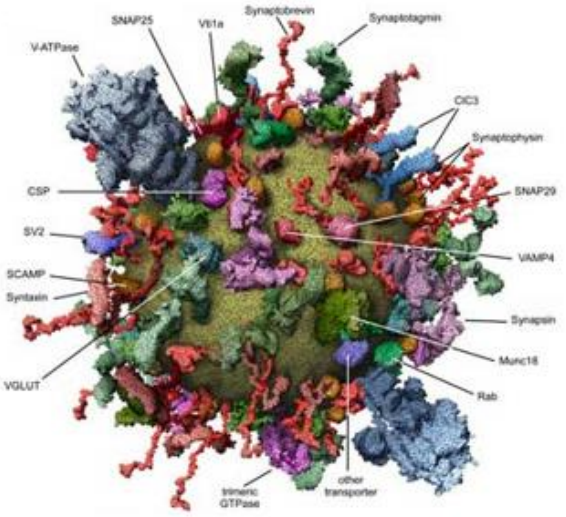


Presynaptic site of neurotransmission



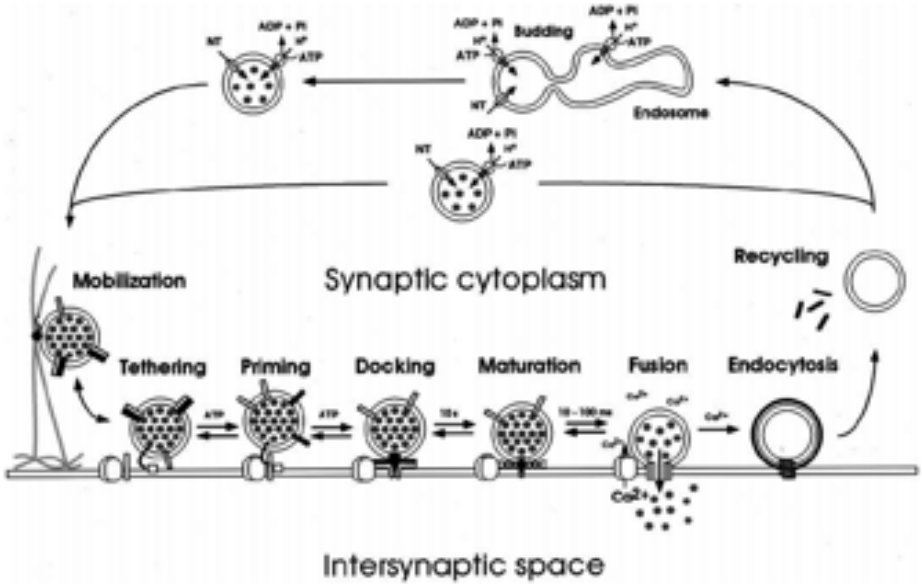
The action potential invasion opens the voltage-gated Ca^{2+} channels on the axon terminal → Ca^{2+} inflow → vesicle fusion → neurotransmitter molecules are released to the synaptic cleft → they bind to the receptors at the postsynaptic site, thus activating it → change in ionic conductance in the postsynaptic cell (postsynaptic response).

In the presynaptic site, the voltage change is ~110 mV, the postsynaptic potential is a lot lower ~10-15 mV.



There are many proteins inserted into the vesicle's membrane. Many of them are Ca^{2+} sensors, others help the docking of vesicles (e.g., SNARE complex). Some of them help the packing of neurotransmitters to the vesicle.

Vesicle fusion at the axon terminals



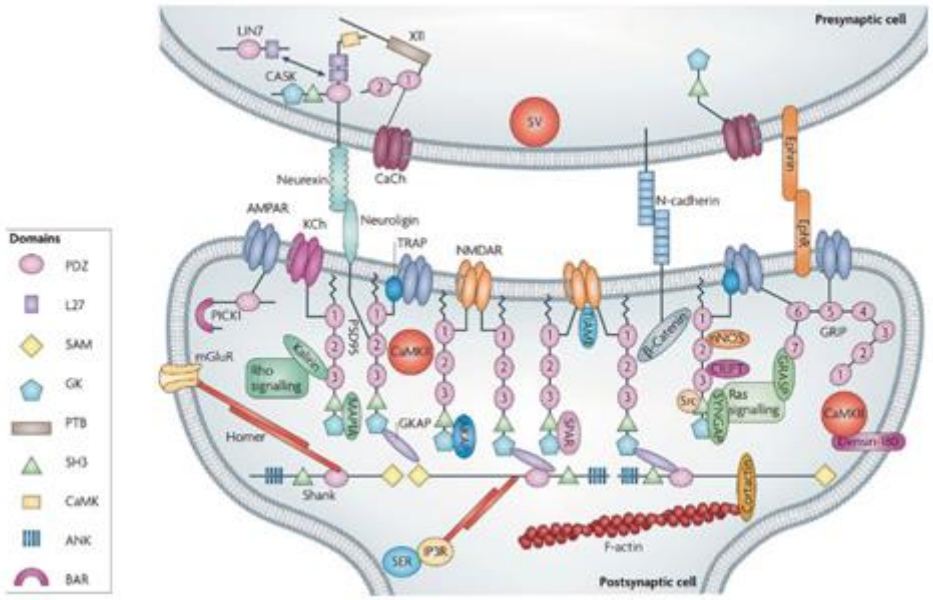
Neurotransmitter molecules are packed to the vesicle by a pump → with the help of actin filaments the vesicles get closer to the presynaptic site, where they dock to the membrane → because of the Ca^{2+} influx, the neurotransmitters are released to the synaptic cleft → after fusion the vesicles are recycled.

Molecule complexes that are needed for the fusion:

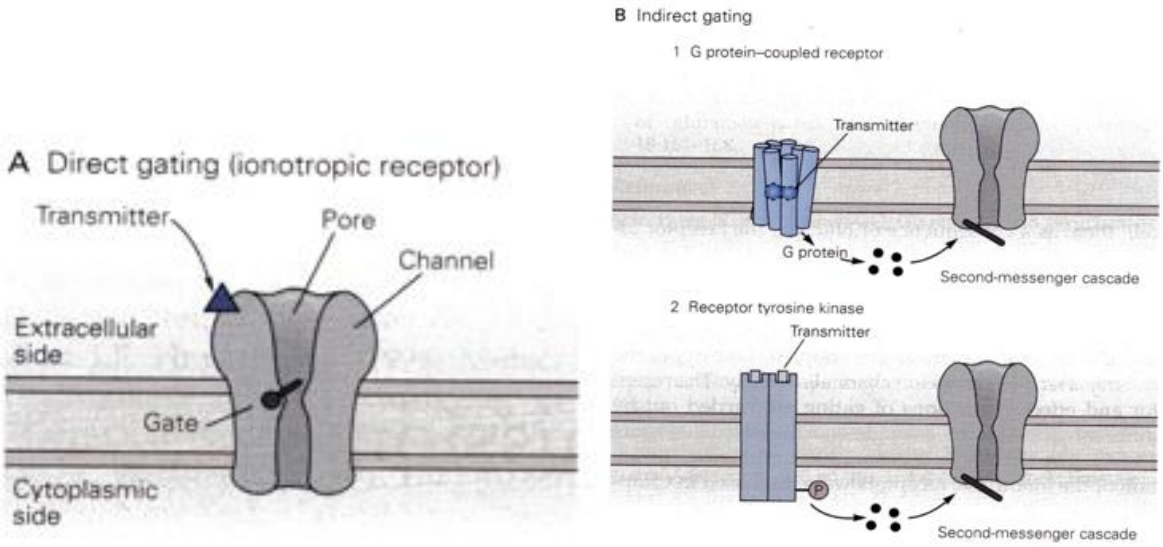
- SNARE complex (necessary for docking the vesicles)
- Ca^{2+} sensors

Postsynaptic site of neurotransmission

Structure of the postsynaptic site



The structure of ionotropic and metabotropic receptors



Fast transmission (10 ms) – ionotropic

Excitatory:
(membrane potential would be shifted towards the AP generation)

- glutamate receptors:
  - AMPA r. (Na^+ and K^+)
  - kainate r. (Na^+ and K^+)
  - NMDA r. (Na^+, K^+ and Ca^{2+})
- acetylcholine receptors
  - nicotinic r. (Na^+, K^+ and Ca^{2+})
- serotonergic receptors
  - 5HT3 r. (Na^+, K^+ and Ca^{2+})

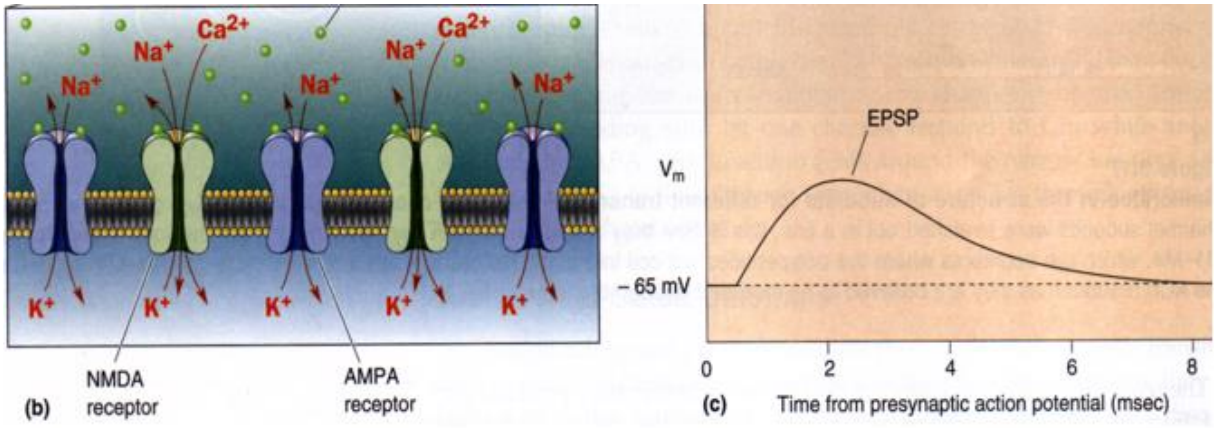
Inhibitory:
(membrane potential is shifted from the threshold value, trying to avoid AP)

- GABA receptors
  - GABAa r. (Cl^-)
- glycine receptors (Cl^-)

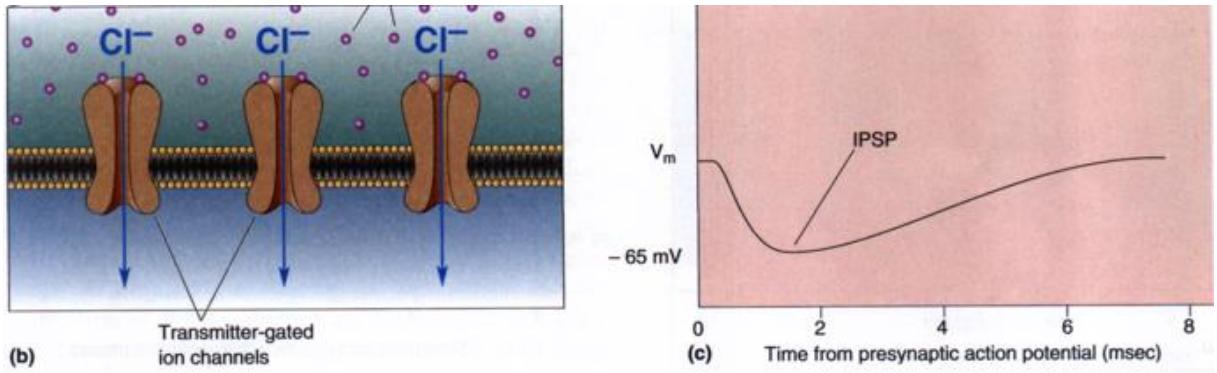
Slow transmission (100 ms) – metabotropic

- glutamate receptors (mGluR r.)
- GABA receptors (GABAb r.)
- acetylcholine receptor (muscarinic r.)
- serotonergic receptors (5HT1-8)
- dopaminergic receptors (D1-D6)
- adrenergic receptors (alpha1,2; beta1,2)
- Histamine receptors (H1-3)

Excitatory neurotransmission



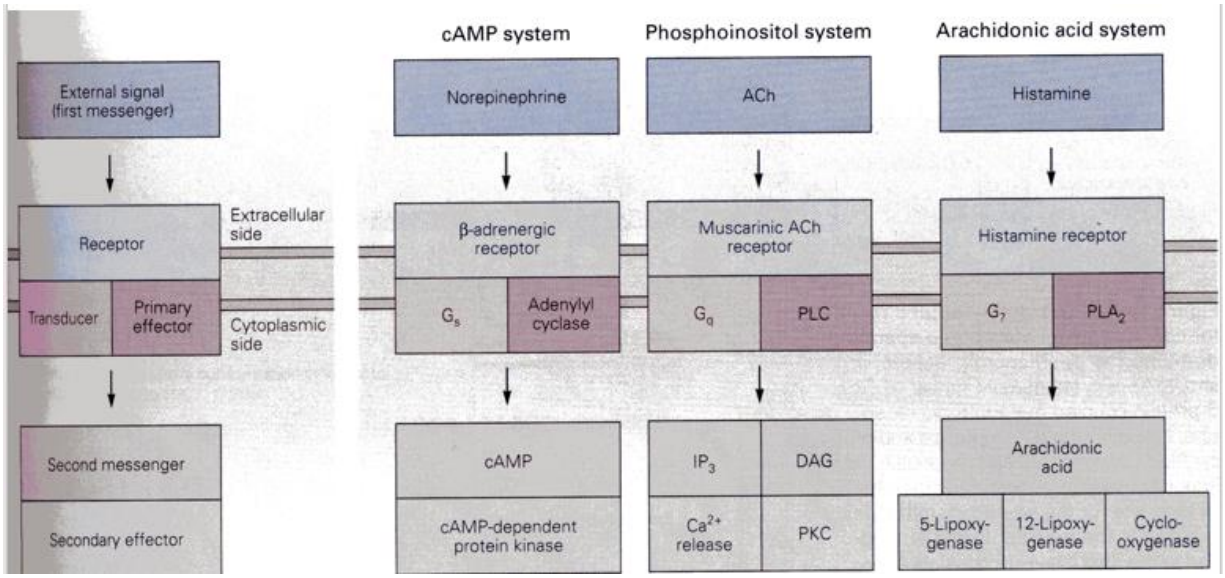
Inhibitory neurotransmission



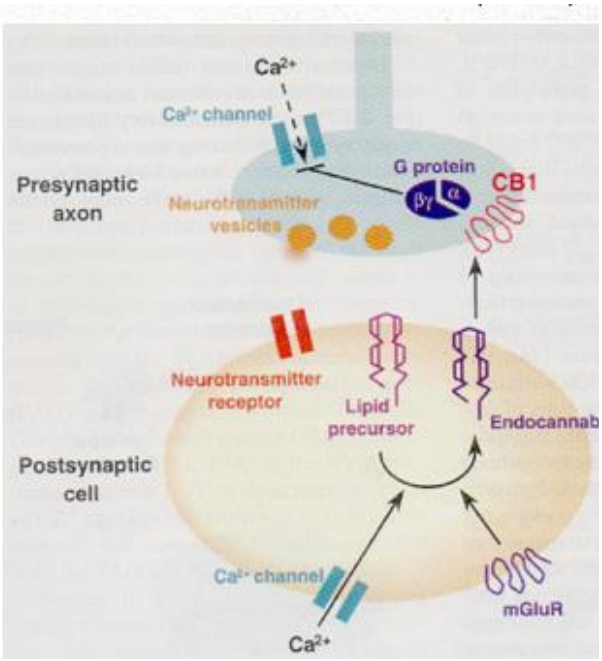
Systems working via slow neurotransmission

- Midbrain cholinergic system (acetylcholine)
- Raphe nuclei (serotonin)
- Locus coeruleus (norepinephrine)
- Ventral tegmental area (dopamine)

Molecular logic of second messengers



Retrograde signalling



The postsynaptic cell signals back to the presynaptic nerve terminal, usually reduces the neurotransmitter release. It is initiated within the postsynaptic cell; the effector is in the presynaptic terminal.

Molecules:

- gaseous molecules: nitrogen monoxide (NO), carbon monoxide (CO)
- peptides: BDNF, dynorphin
- lipids: endocannabinoids, arachidonoyl acid
- classical neurotransmitters: GABA, glutamate

Short- and long -term synaptic plasticity

plasticity: at the synapse, the communication between two cells can be changed, either enhanced or reduced

short term: the duration of the synapse can change in 10s or 100s of ms

long term: time scale of days

Short-term plasticity

Target-selectivity!

Depressing, facilitating, steady in time

Reasons for depression:

- large release probability
- de-sensitisation of postsynaptic receptors
- intracellular factors

Reasons for facilitation: accumulation of Ca^{2+} in the presynaptic boutons

Controlled by presynaptic receptors!

Helps to route the information flow.

Long-term plasticity

Target selectivity!

LTP- long-term potentiation

LTD- long-term depression

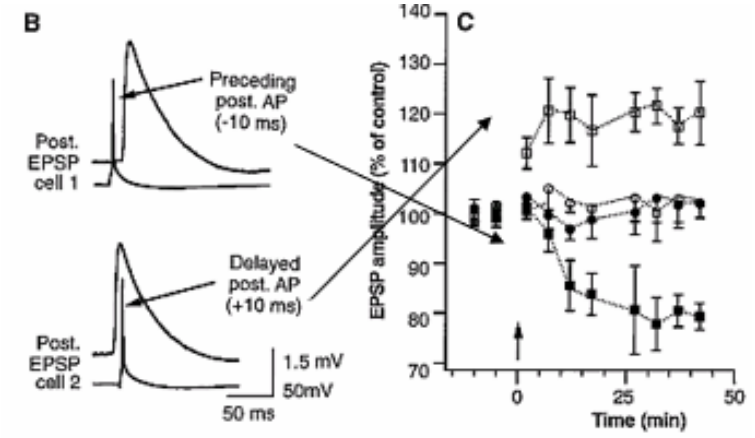
Induction protocols:

- high frequency stimulation of fibres
- spike timing-dependent plasticity

Mechanisms: NMDA-dependent, non-NMDA dependent, receptor insertion, replacing receptor subunits, retrograde signalling

Spike time-dependent plasticity -STDP

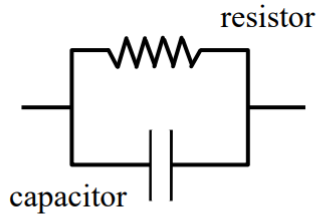
The timing of the pre- and postsynaptic activity determines whether the synapse could change into LTP or LTD. By timing the activity of the postsynaptic cell either before or after the postsynaptic response, we can enhance or reduce the strength of the synaptic transmission.



Electrophysiology II.

Lecture 2.

The description of the excitable membranes can be simplified to a parallelly coupled resistor and a capacitor. The resistor corresponds to the ionic channels, the capacitor represents the biological membranes. The membrane can separate charges between the inside and the outside, it can also discharge. The discharge of the capacitor depends on the distance of the two sides of the membrane.



$$Q = CV \qquad R = \frac{V}{I}$$

$$I = C\frac{dV}{dt} \qquad \tau = R \cdot C$$

The patch-clamp technique

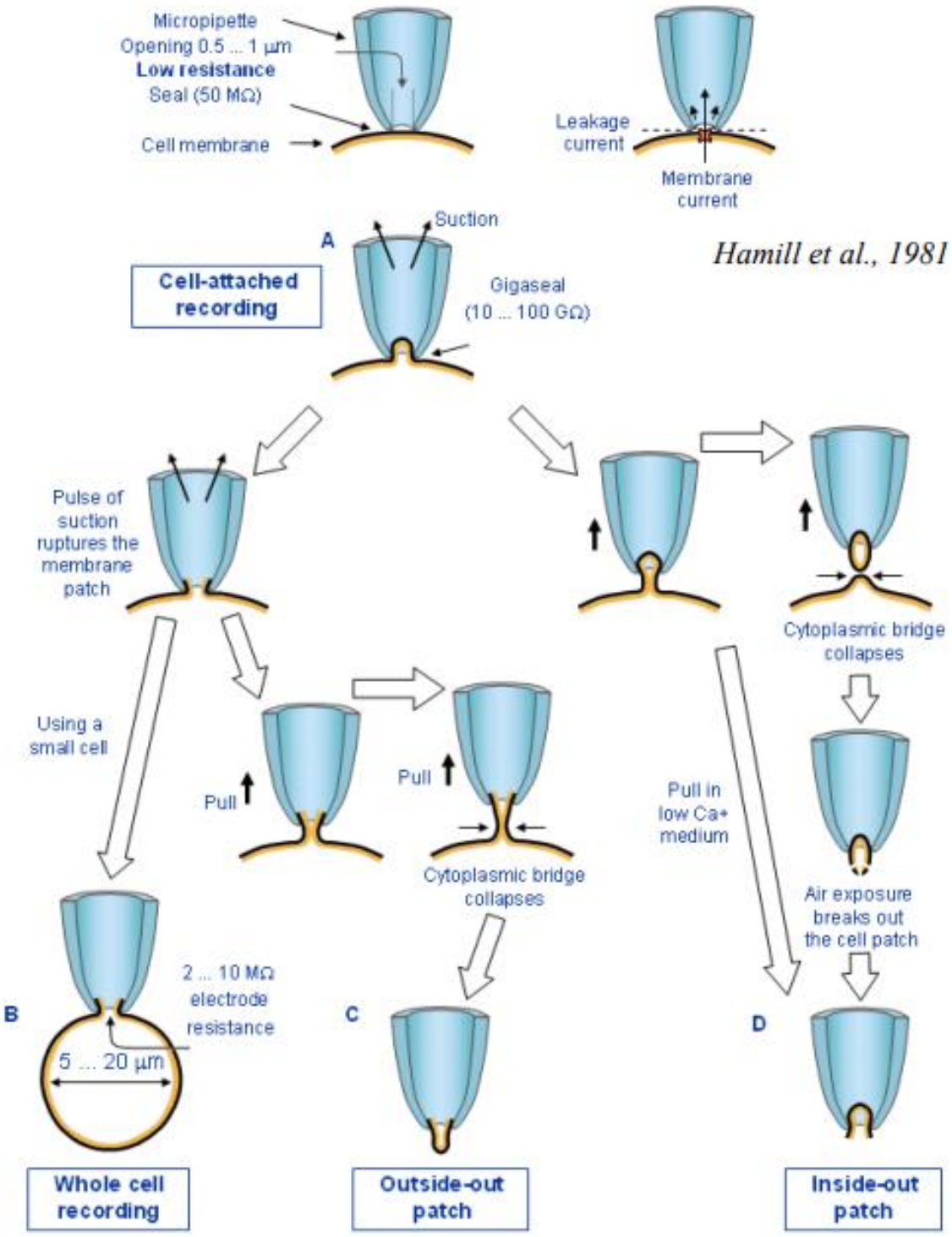
Voltage clamp: it enables us to measure the ionic currents of the membrane, it is a method to isolate the ionic component of the current from the capacity component.

$$I_M = I_{ion} + I_{cap}$$

$$I_{cap} = c_m \cdot \frac{dV}{dt}$$

If there is no change in the voltage, (c_m is the capacity constant) then the capacity current will be zero → all the current that we can measure from the cell membrane will be equal to the ionic current.

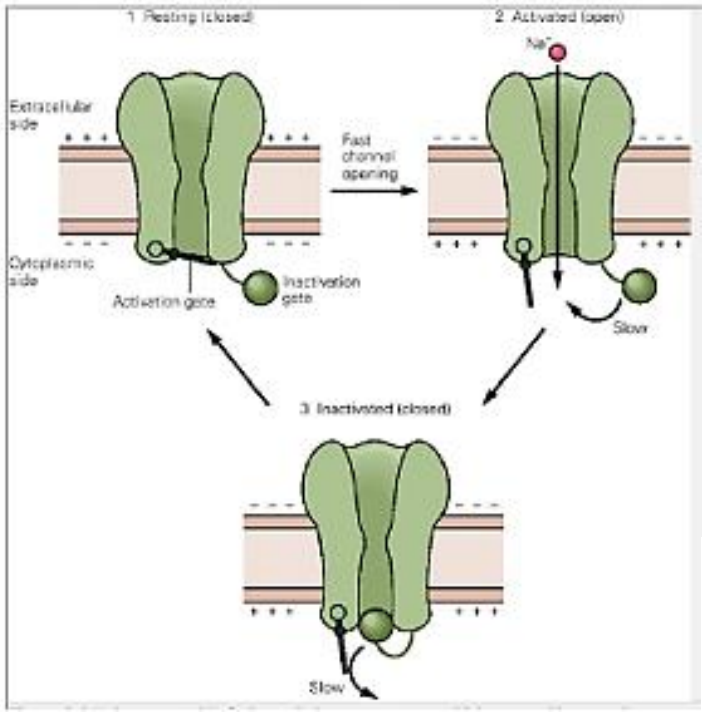
Single channel path clamp



There is a glass pipette, that is put on the membrane of the cell, because of the surface charges of the membrane and the pipette, they form a very strong resistance. The membrane goes into the tip of the pipette (gigaseal). Because of the high resistance we can isolate the currents, which are going through the very small membrane patch. → We can measure the current from a single ion channel.

Process of propagating electronic potential

Ionic channels, action potential



- Na^+ channels: fast activation, inactivation
- K^+ channels: delayed activation (deactivation vs. inactivation)

Axon initial segment

- higher density of sodium channels
- sodium channels can be activated at a slightly lower membrane potential (left shifted V-dependence)
- smaller membrane compared to the soma.

The quantal release of neurotransmitters

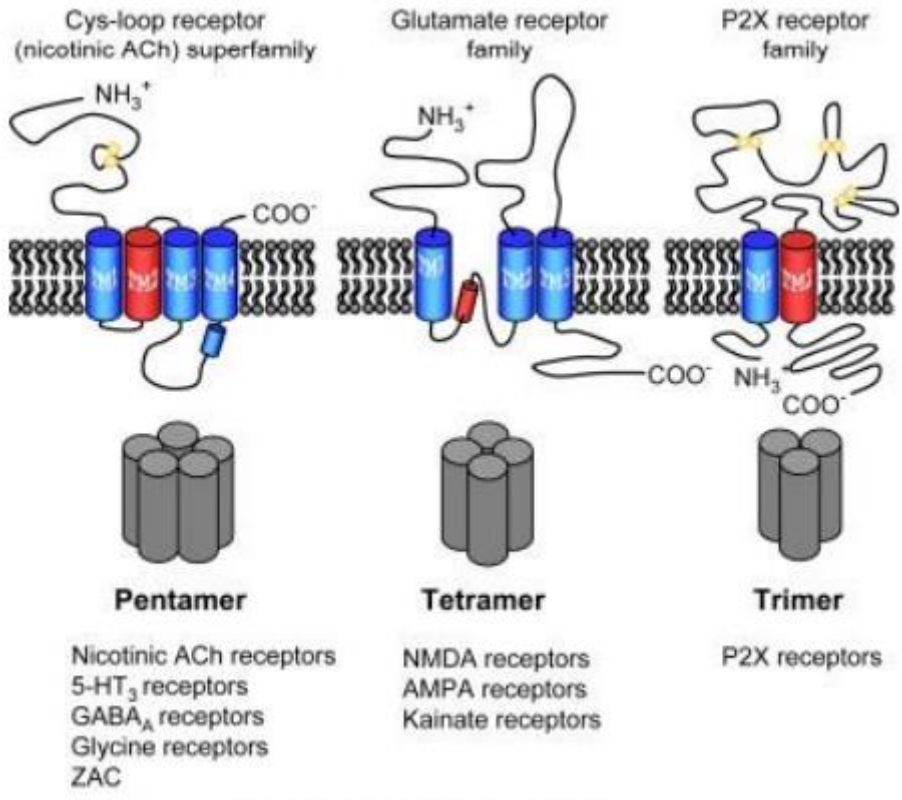
- the size of synaptic vesicles is constant.
- the specific membrane capacitance is constant, but if you increase the total surface of the membrane, it changes the capacitance
- release by exocytosis, then the vesicles are recycled.
- the release of the vesicles has to be triggered by action potentials (voltage-gated Ca^{2+} channels)
- SNARE complex

Operation of voltage- and ligand-gated ion channels

- receptor: transmitter, ion selectivity
- ionotropic-metabotropic receptors
- conductance change

Ligand activated ionic channels:

- trimer, tetramer or pentamer
- 4 transmembrane domains, one of them forms the pore, it opens by binding e.g., GABA



Dendritic morphology and spines

Each kind of neurons have a different dendritic tree shape, which also affects how signals can propagate.

Spine types: thin, mushroom, stubby. If the spine is very thin, the synapse will become much more isolated, because of the high resistance, voltage changes will be much larger.

Modern optical methods

Advantages:

- simultaneous measurements of multiple neurons and/or compartment
- cell type specific recording/stimulation
- multiple aspects: voltage, Ca^{2+}, release
- non-invasive

Current limitations:

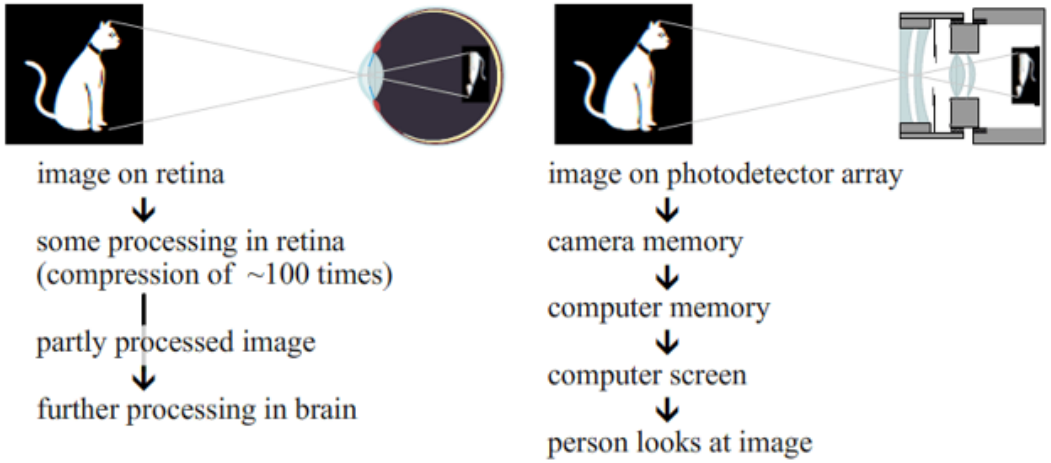
- low signal-to-noise ratio
- equipment: sensitivity, speed
- indirect values

Retina

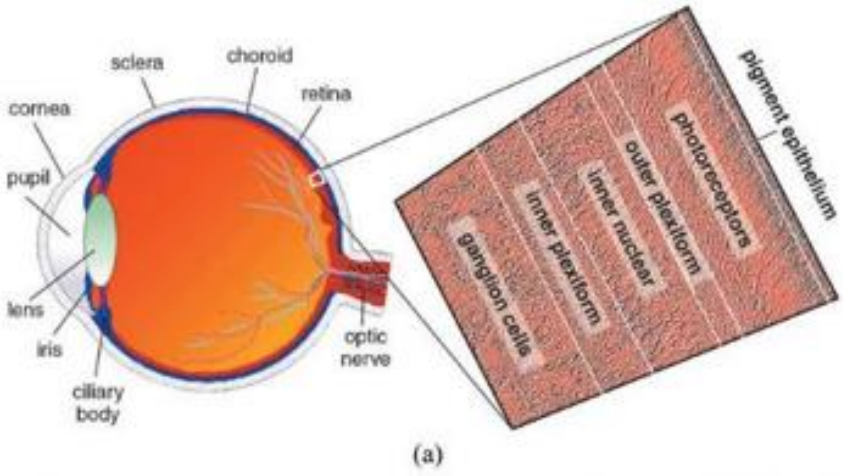
Lecture 3

The function of the human eye

- it has a lens system: *the lens + the cornea* in front of it → it makes sure that the image is focused on the retina.
- *iris, pupil* → an aperture by which we can modulate the level of the light that enters the eye.
- *retina* → photosensitive layer (it has a neuronal network which carries out the first steps of information processing)
- *pigment epithelium* → avoiding internal reflection of the light.

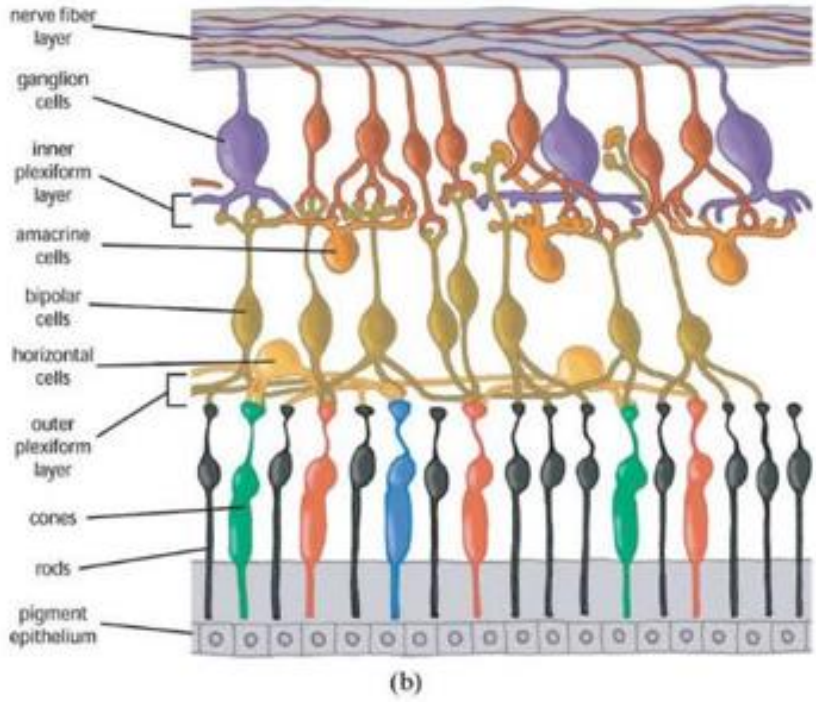


Retinal histology layers



- <u>Outer retina</u>:
  - *photoreceptor layer* maintains the neurons which are sensitive to the light, the layer that captures the photons, it transforms the information to electrical and chemical signals.
  - *outer plexiform layer*

- Inner retina
    - *inner nuclear layer*
    - *inner plexiform layer*
    - *ganglion cell layer*



Cell types of the retina:

- *light sensitive photoreceptors*
- interneurons of the retina
    - *bipolar cells*: they connect the photoreceptors directly to the ganglion cells and transmit information between them.
    - *horizontal cells*: they have laterally running dendritic fibres connecting the photoreceptors, they are inhibitory interneurons (they connect to retinal cells in one half of the retina) connecting to cells of the outer retina.
    - *amacrine cells*: inhibitory interneurons with laterally running dendrites, connecting to cells of the inner retina.
- *ganglion cells* ("output neurons")

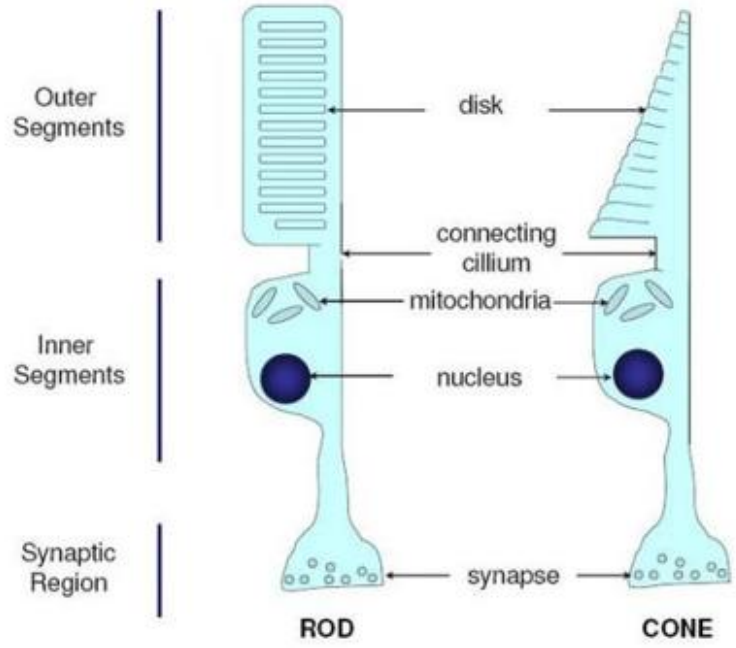
Photoreceptors

Rods

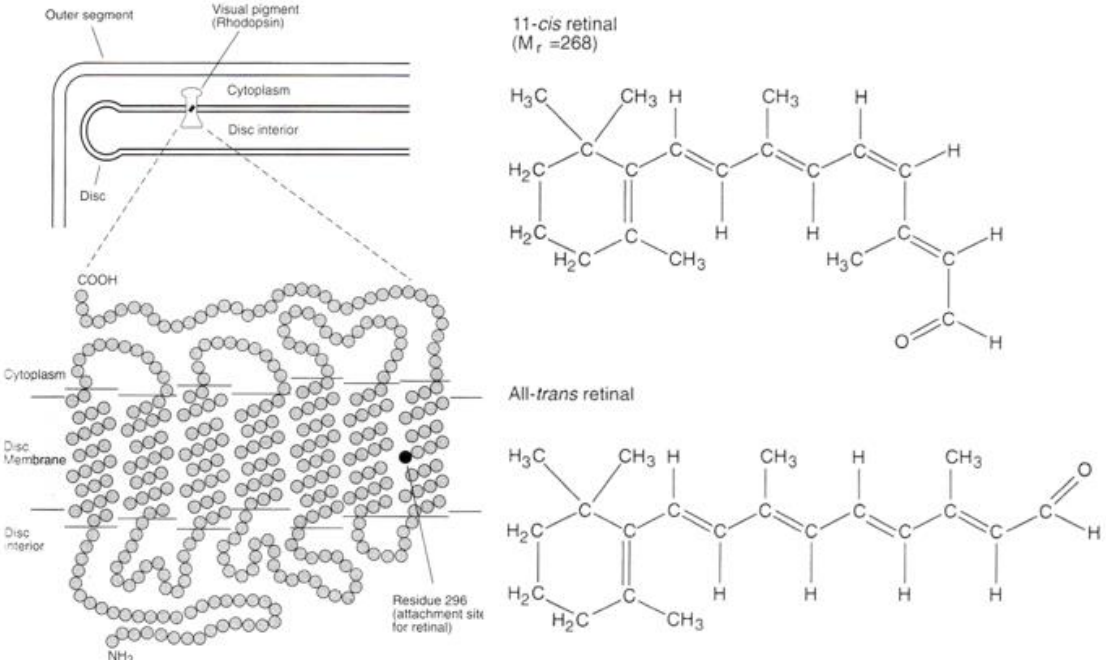
- one type
- longer outer segment (cylinder shape)
- closed endomembrane system (disks increase the membrane surface)
- ~100x sensitive than cones

Cones

- 3-4 types with various spectral sensitivity
- outer segment is cone shaped.
- one membrane system (foldings: they are similar to disks)
- they can differentiate between colours.

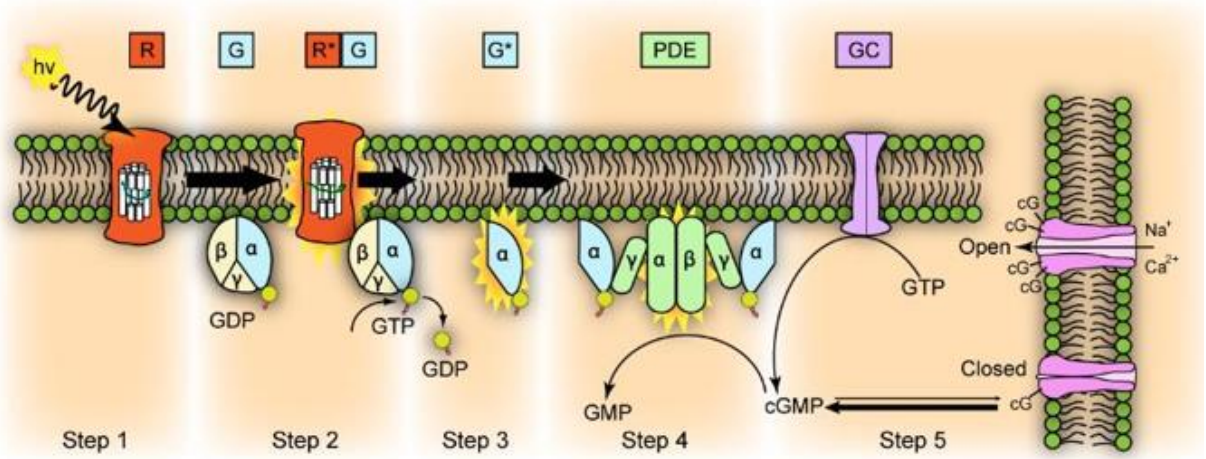


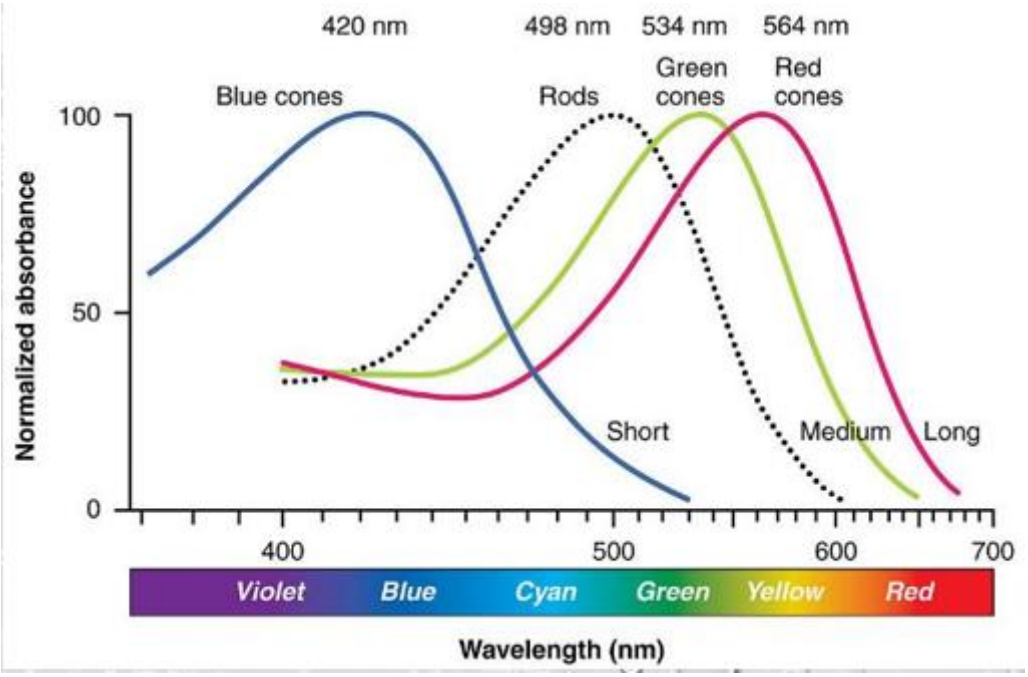
The structure of disks

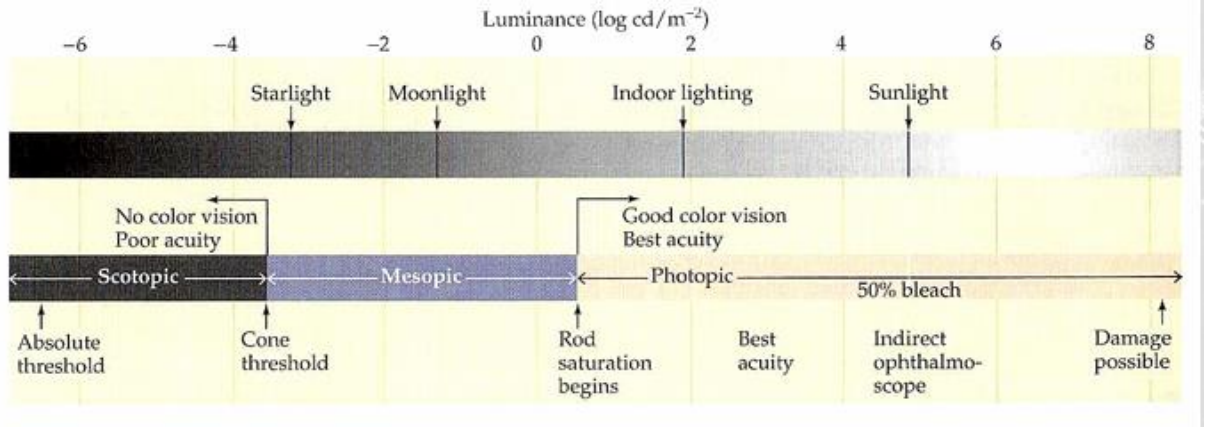


- *rhodopsin*
  - 7 transmembrane regions
  - 2 components:
    - opsin (protein)
    - retinal (2 conformations, the cis conformation is more favourable)
      - the cis conformation uses the energy of the photon to change its conformation to trans.

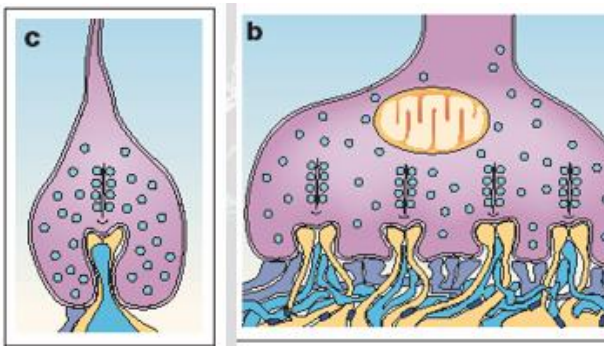
Phototransduction Activation







The photoreceptor synapses



c: rod axon terminal

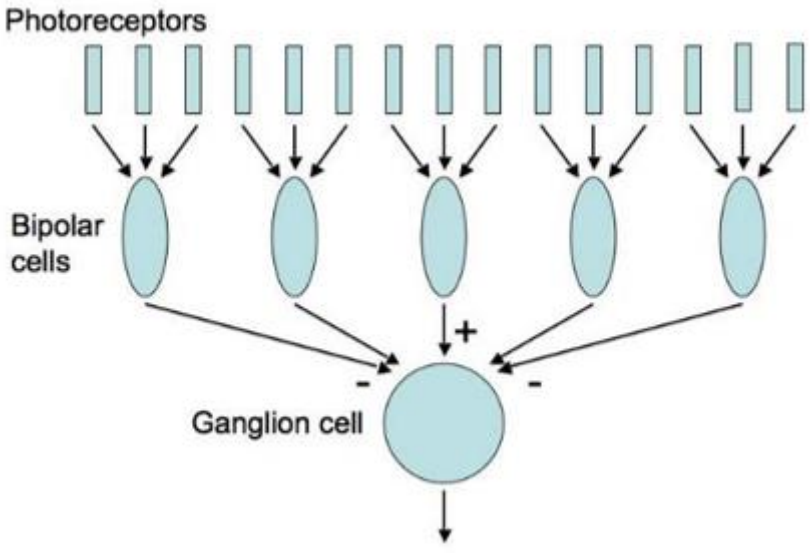
d: cone axon terminal

- some of the vesicles (blue) surround a thin, rod-like structure, called ribbon (→ *ribbon synapse*), the rest of the vesicles are floating freely in the axon terminal.
- the dynamic of the release of the two types of vesicles is different (fast- ribbon vesicles, slow: other vesicles)
- membrane infolding (invagination) → this synapse is also called *invaginating synapse*
- flat contacts with those post-synaptic sites that do not enter the invagination
- blue and purple colours: bipolar cells
- yellow colour: processes of the horizontal cells
- grey colour: other bipolar cells
- triad synapses (three synaptic partners)

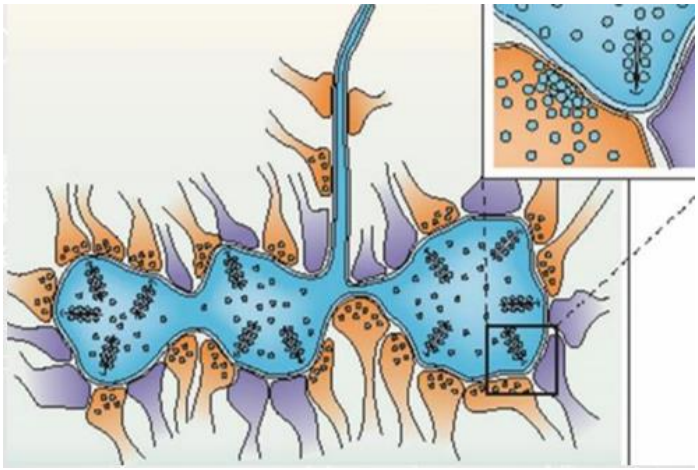
Retinal interneurons

<u>Bipolar cells</u>

- their dendritic processes receive the information from the photoreceptors (synapses at the outer plexiform layer)
- their common dendrite brings it to the soma
- axonal process: it brings the information to the axon terminal in the inner retina (synapses at the inner plexiform layer)
- they connect the two plexiform layers

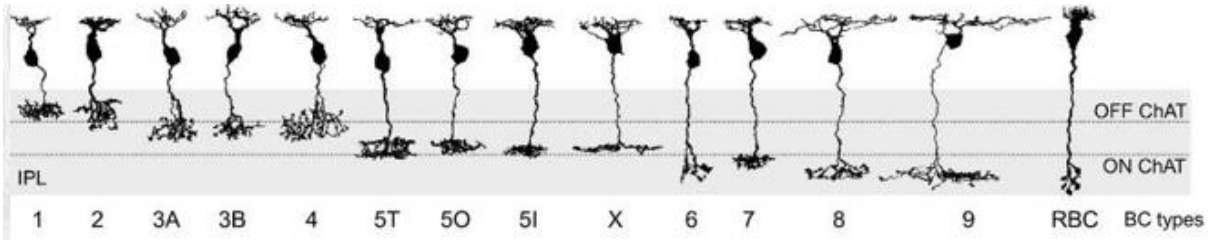


Bipolar cell synaptic outputs



- the axon terminal of the bipolar cell also has ribbons (→ ribbon synapses)
- post synaptic surface with vesicles (coloured with orange): amacrine cells, the inhibitory interneurons of the retina, they are not just receiving information from the bipolar cells, but they give negative feedback, or they provide feed forward inhibition from somewhere else, towards the axon terminals.
- processes that do not have any vesicles (coloured with purple): ganglion cell dendrites they just receive information, they do not give any information back to the bipolar cells.
- there are no invaginations in the axonal processes.
- diad synapses (there are only two synaptic partners)

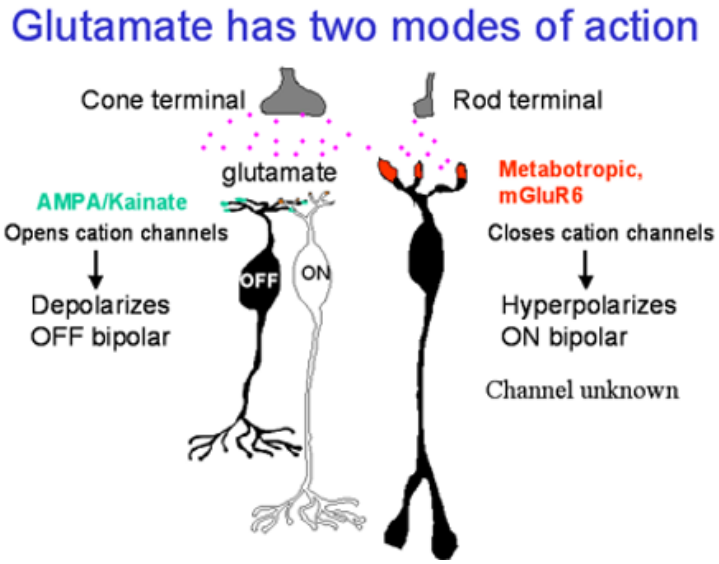
Bipolar cell types



- IPL (inner plexiform layer): divided into two parts
  - off layer (outer part) → off bipolar cells (they are depolarized in the dark)
  - on layer (the one closer to the ganglion cells) → on bipolar cells (they are activated when we turn the light on)
- cone-bipolar cells: they receive information mostly from the cones (there are on- and off-types of them)
- RBC: rod-bipolar cell (there is only on-type of RBCs)
- common properties:
  - they are all excitatory interneurons
  - they secrete glutamate as a transmitter
- chromatic/achromatic
- fast/slow

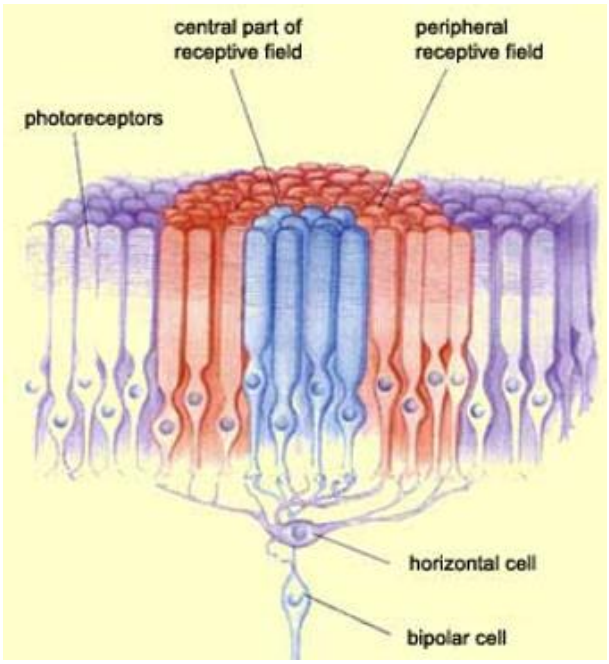
On-Off segregation

- in dark, the glutamate release is continuous, it binds to the glutamate receptors on the bipolar cells
- *off BCs* hyperpolarize to light; sign conserving (AMPA/KA)
- *on BCs* depolarize to light; sign inverting (mGluR6)



Receptive field

- they provide direct input between the photoreceptors and the ganglion cells
- they are the primary contrast detectors
- centre- and surround receptive field
    - bipolar cells are only connected to the central part
    - cells of the surround receptive field only give information to the bipolar cells through horizontal cells

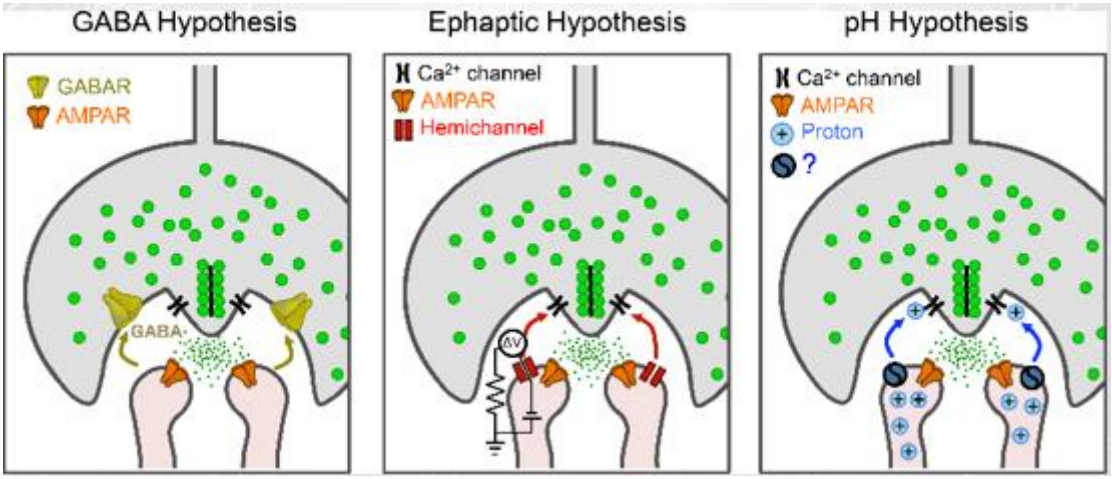


Horizontal cells

- two types:
    - A-type: soma + thick dendritic processes (axonless)
    - B-type: soma + thick dendrites + long, thin axon + dense axon terminal
- they bring cone information from the surround receptive field to the bipolar cells indirectly
- they provide negative feedback to cones to generate the surround RF
- triad synapses: 2 horizontal cells + 1 bipolar cell
- horizontal cells provide negative feedback to cones to generate the surround RF

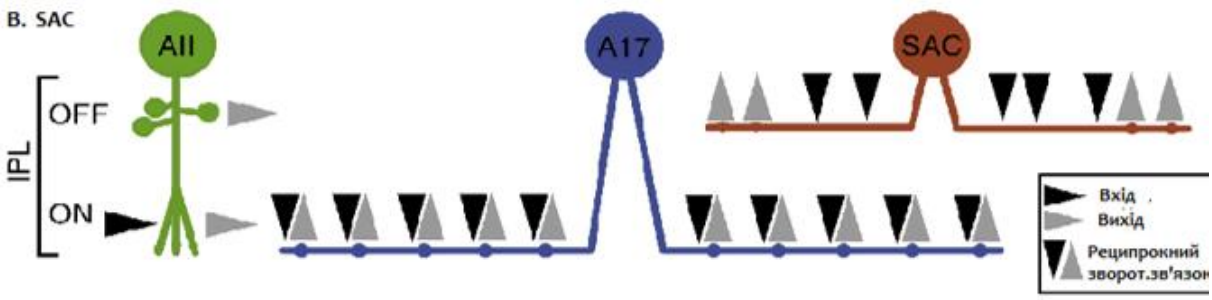
Horizontal cell physiology and neurochemistry

- they have ionotropic AMPA and kainite receptors on their dendrites
- in darkness, they are depolarized, they hyperpolarize to light
- their transmitter is GABA



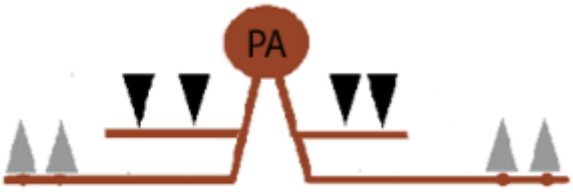
Amacrine cells

- they are in the inner retina
- they provide feedback or feed forward inhibitory signals to inner retinal neurons (bipolar cell axon terminals and ganglion cell dendrites
- diverse for morphology
- diverse for transmitters they release (glycine, GABA, neuromodulators)
- some of them have dendritic arbours which cover the entire cross section of the inner plexiform layer, so they are dealing with both on- and off-types of information (uni-, bi-, tri-, and multistratified ACS)
- they give inhibition to certain neuronal cells in the inner retina, the way they do that can vary from time to time.
    - cross-over inhibition (1)
    - local feed-back and feed-forward inhibition (2)
    - receiving bipolar cell info near the soma, but they give output at the end of the dendrites (3)



Amacrine cell types

- AII amacrine cells:
  - they express glycine
  - bistratified
  - rod BC input; GJ input to on cone bipolars, inhibition to off bipolars
- A17 or S1/S2 cells
  - they express GABA
  - rod BC input; negative GABA feedback to RBC
- Starburs cells
  - GABA- medium field GABA expressing AC
  - coexpress GABA and Ach
  - asymmetric I/O system
- Wide-field amacrine cells
  - GABA (some express modulators)
  - mostly unknown function
- Polyaxonal amacrine cells
  - GABA and often modulators
  - separate DF and AF (separation of in- and outputs)
  - distinction of background and object movement



- Dopamine expressing cells
  - they express DA and GABA
  - tristratified
  - they release DA when retina is exposed to bright background light (light adaptation)

Retinal ganglion cells

- diverse for morphology
- they collect direct information from bipolar cells and bring it towards the brain
- they are able to generate action potentials (spikes), these will be sent out as an information
- they release glutamate (so they are excitatory neurons)

Some GC types are not participating in image formation

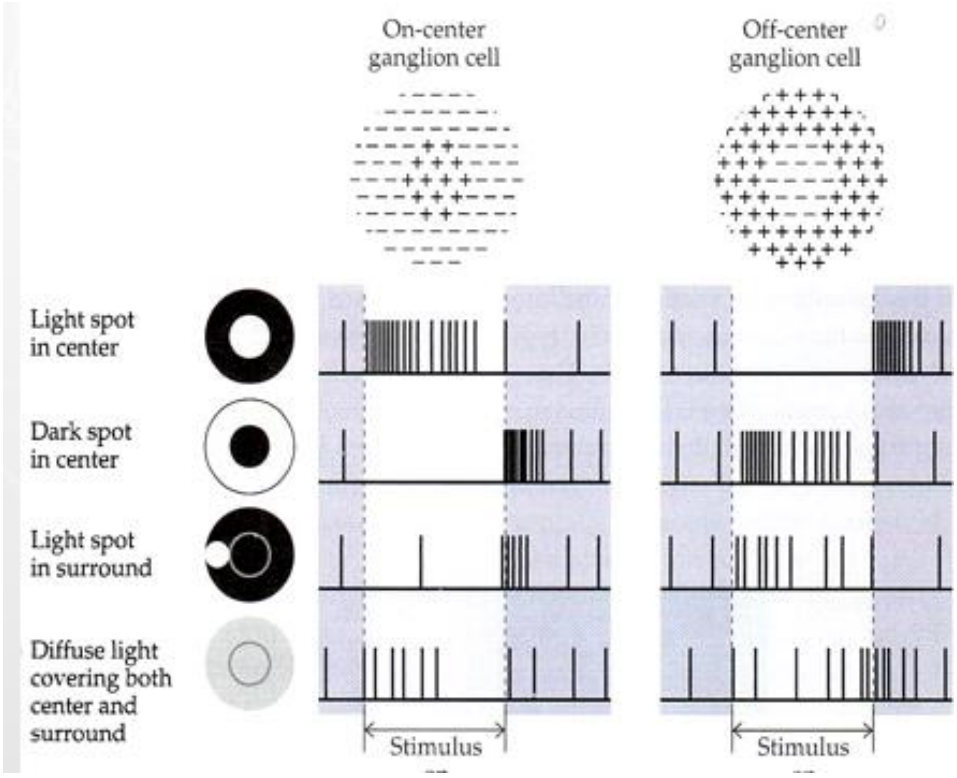
- Most of the nuclei do not take part in the image formation. They are responsible for e.g., pupil reflex.
- Some of the ganglion cell types are feeding those nuclei.

GC-s participating in IF encode various features of the visual field?

- The visual scene has many different features that has to be encoded separately and sent separately to the brain through parallel retinocortical channels.

Encoded features

- ganglion cells inherit the receptive field from the direct connection to bipolar cells
- on-centre ganglion cells
    - if light stimulation occurs in the centre receptive field, it will activate the ganglion cell
- off-centre ganglion cells
    - when there is light in the centre, we expect inactivation
- the contrast detection, which is created by the bipolar cells is inherited by certain ganglion cells



Visual features:

- achromatic they do not select from the input, they get both green and blue responses (e.g., local edge detector), luminosity contrast detectors.
- chromatic: blue-on / yellow-off chromatic ganglion cell, it can differentiate between the different chromatic aspects
- direction of lateral movement – they can differentiate between the direction of movements (not the movement itself)
- approaching movement – off alpha ganglion cells
- constant illumination sensitive cells – supressed by contrast gc, they get silent when the illumination is persisting
- orientation – orientation selective gc

Ganglion cells cover the retina, this tiling is economical, the do not overlap much, but their dendrites cover the entire retinal surface.

Neural stem cells

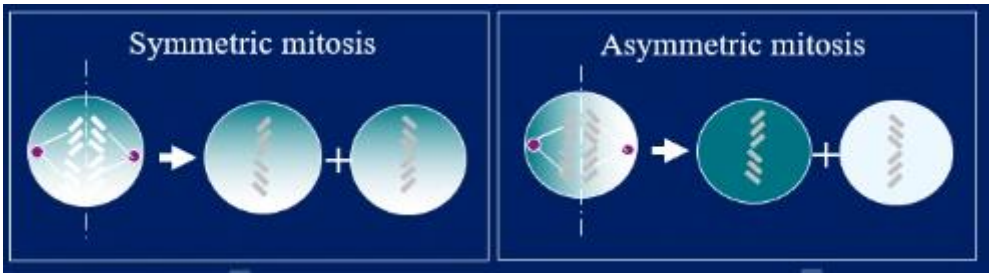
Lecture 4.

Terminally differentiated cells (neurons) cannot divide anymore.

In the body, most of the tissue cells are renewed from time to time. These cells divide through cell cycle.

Symmetric mitosis: produces two identical daughter cells, their phenotype will be the same.

Asymmetric mitosis: their DNA content is equal, but some regulatory materials in the cytoplasm are distributed unevenly, the gene expression pattern is different, the two cells' phenotype will be different (it is a characteristic of stem cells)



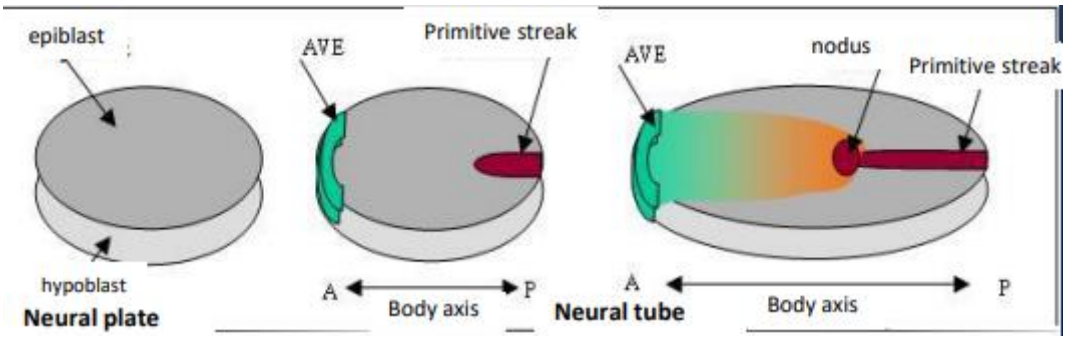
Embryonic development: by the early *blastocyst stage* (day 5), the dividing cells have to go through both symmetric and asymmetric mitosis, because not all the cells are equivalent. The inner cell mass gives rise to the whole embryonic body.

Inner cell mass → we can produce almost all tissues of the mammalian body. They are called (almost) omnipotent cells. They cannot be embedded into the uterus wall. These are called embryonic stem cells.

The blastocyst is embedded into the uterus wall with the help of the *trophoblast*.

The foetus is polarized very early in the development along the anterior-posterior axis. (head + tail part)

- posterior part: *primitive streak*: an organizer, which produces morphogens, proteins that can induce the fate of neighbouring cells.
- anterior part: *antero-ventral ectoderm*: it instructs the neighbouring cells to accept the neural ectodermal fate.
    - neuro ectodermal cells → nervous systems (first huge developmental stage)



Neural plate:

- epiblast: faces the womb wall
- hypoblast: faces the yolk sac

AVE: anteroventral epiderm → produces morphogens along a concentration gradient (conc. decreasing from the AVE)

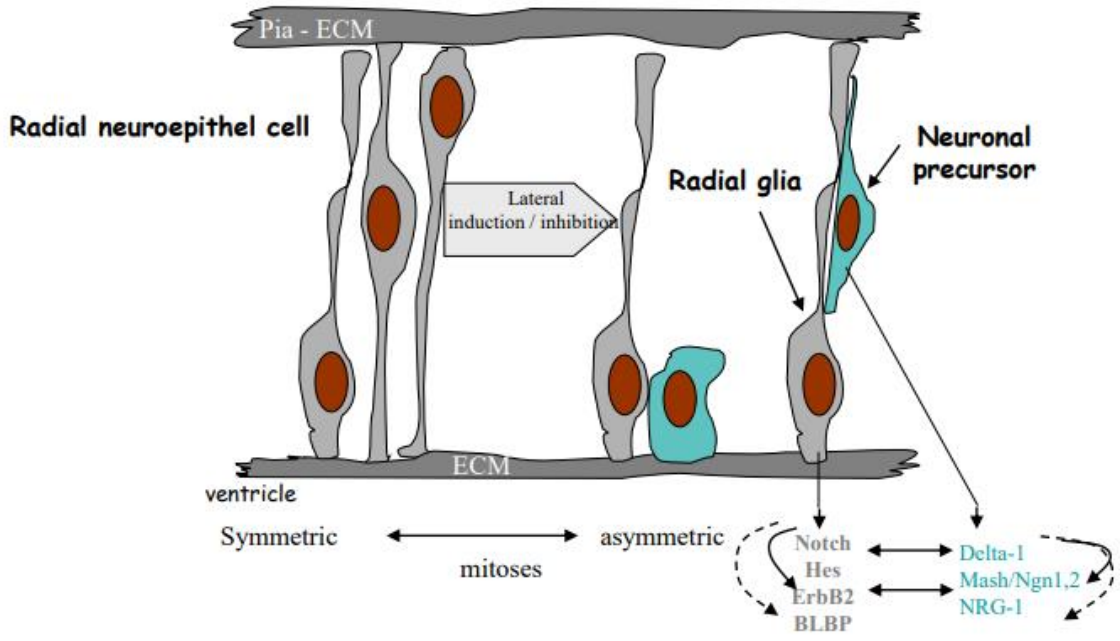
nodus: front part of the primitive streak, releases morphogens that decreases in space

The morphogens will distribute in regions on the neural plate. → Then this plate curls up, and a tube will be formed. The morphogens instruct the gene expression and gene repression in a way that in a specific region of the body, a specific gene will work.

Differential gene expression determines:

- the boundaries of brain regions
- the neurotransmitter-phenotype of neurons
- the position of the fibre tracks

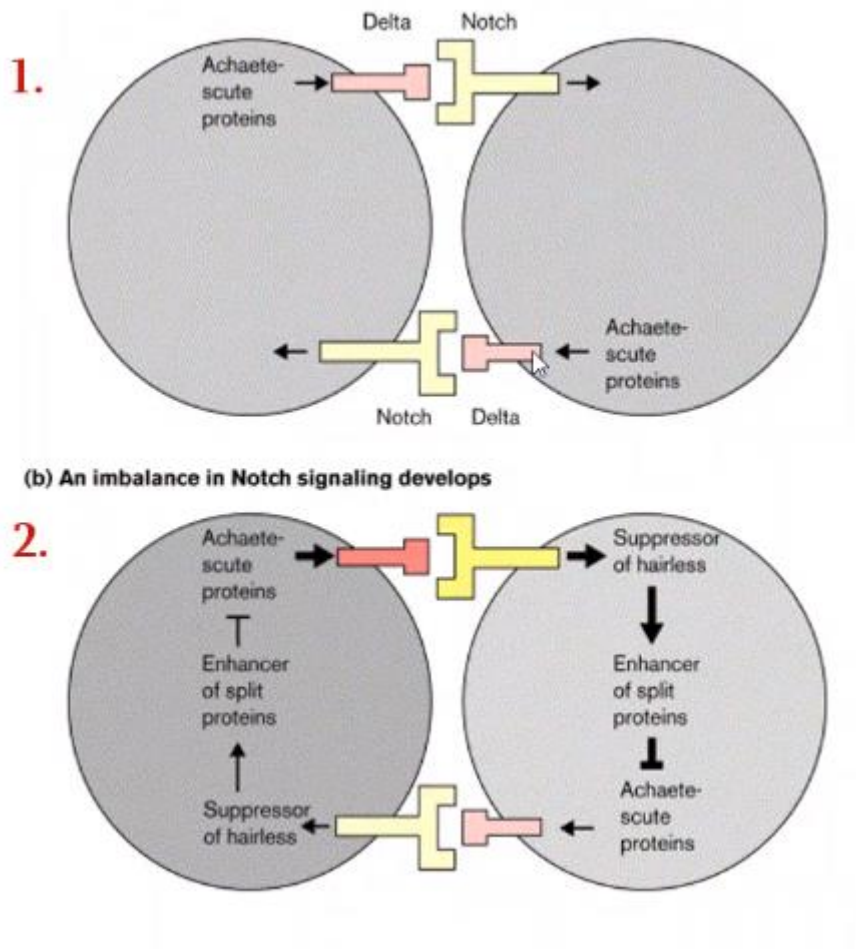
At the border of the gene expression regions, a very poor cell attachment structure is developing, so at these borders, very cells can settle. →there will be a border morphologically as well



Primary germinative zone

The neural plate is composed of radial cells, they produce a huge amount of stem cells, one of those start dividing asymmetrically.

Notch/delta system



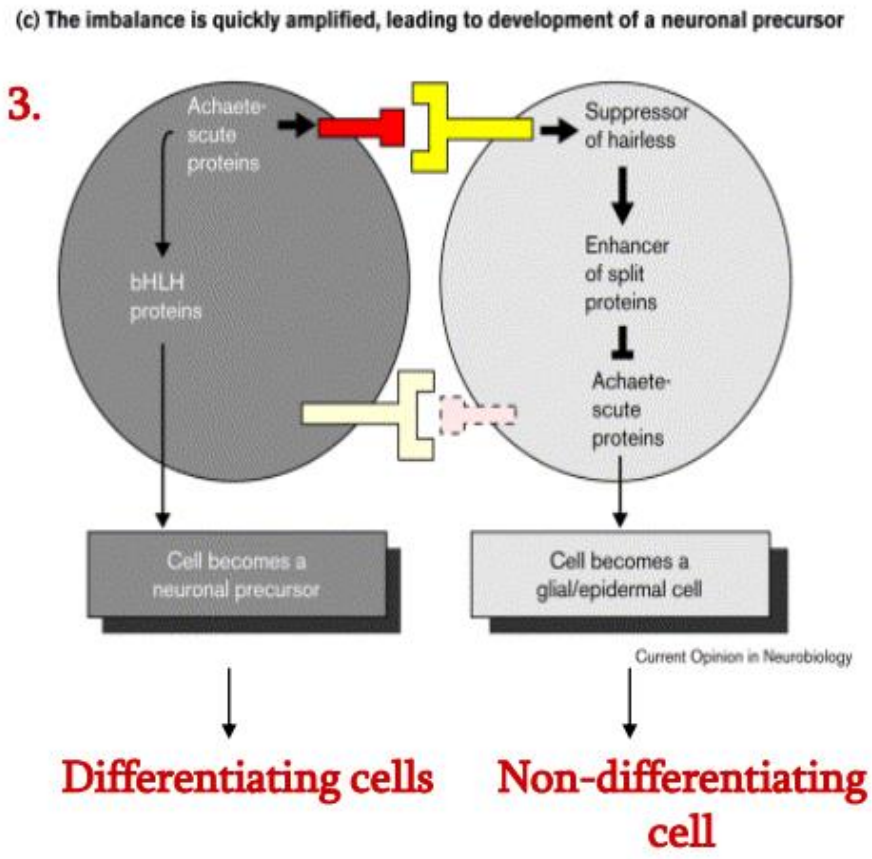
In a system, where equal cells are dividing symmetrically, there is a balance between two receptors: delta and notch. Both of them are located on the cell surfaces and they can connect to each other. After connection, both can signalize into its own inner cell.

notch signalling: a fragment of notch will be cleaved and will go to the cell nuclei and will instruct the genes which would promote differentiation to get silenced, it is an anti-differentiation gene which helps to maintain the proliferative state and the non-differentiated state of the cell.

delta signalling: The notch expression decreases, if the delta gets a notch signal, it will also produce an intracellular fragment, but it will not go to the nuclei. If delta is stimulated, the notch cannot affect, and the cells are not prevented from differentiation.

Differences between neighbouring cells are caused by stochastic events.

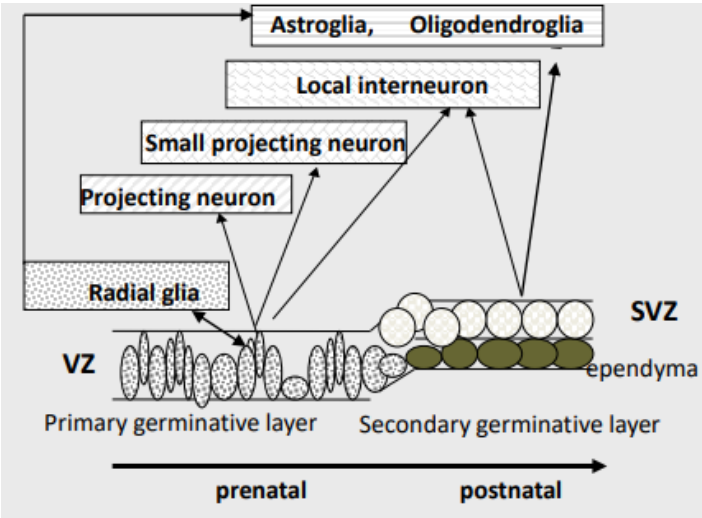
The notch-delta signalling is very important because it preserves a cell population which is not differentiated but can always differentiate, so it is a background pool of cell replacement in all parts of our body.



Embryonic cell migration from the primary germinative zone

At different time points, different types of cells are born, and they are migrating to different parts of the neural tube. In the cerebral isocortex, the first neural precursors develop first, and this are the very first *Cajal-Retzius cells*. (They are leading cells during development.) Secondarily, the six-layer cells will develop form the primary germinative zone in the isocortex. They will settle next to the Cajal-Retzius cells because they do not let them further. Then the fifth layer cells will be produced, and they migrate to the Cajal-Retzius cells as well.

From *the primary germinative zone*, only three layers of the isocortex were derived (6^{th}, 5^{th}, 4^{th})



The majority of local interneurons, which gives rise to really large part of our brain, is produced from the *secondary germinative layer* (also called sub-ventricular zone). The primary germinative layer will give the cover of ventricles but after the prenatal phase, they cannot divide asymmetrically anymore. Some of the radial glia cells migrate to the top of the ependymal cells, these will maintain their proliferation capacity. (→ sub-ventricular zone)

The forebrain cortex is composed by neurons derived from both, the primary and secondary germinative zones.

The neocortex produced from the 6^{th} -4^{th} layers mainly consist of glutaminergic neurons. The 2^{nd}, 3^{rd} layer neurons are GABAergic, and they develop from the secondary germinative layer.

Embryonic neuroectodermal stem cells

- neuroepithelial stem cells

Embryonic/foetal neural tissue stem cells

- radial glia cells in the ventricular zone
- neural stem cells in the subventricular zone

Adult-hood stem cells

- subventricular zone
- subgranular zone

In case of injury, the subependymal zone can produce cells along the entire neuroaxis.

Why there is no recovery in neural tissue injuries?

The brain environment does not let to develop the neuronal features and the region-specific neuronal features.

The axon growth cone follows extracellular instructions

Growth cones attach preferably to neighbouring processes: the neurites compose asciles

- they are attached to a surface or to each other
- they grow on each other
- when they meet, they mutually lead each other to the right place

Timed receptor-ligand interactions disable/enable defined process-elongation routes.

Synapses can be formed and maintained between synchronously active partners “synaptic plasticity”.

Giant depolarizing potentials (GDP)

- generated in diverse spots of the developing brain
- spread along fasciculated processes
- help to generate synapses of synchronously active axons
- play fundamental role in the formation of large projecting fibre tracks

ES cells, embryonic tissue stem cells and IPSCs are not to be used for direct cell therapy

The adult brain cannot support neuronal differentiation anymore. Stem cells have to be implanted during development.

The formation and maintenance of the functional nervous tissue resulted by continuous selection mechanisms.

Cell genesis: surviving cells are selected from an excess of generated cells

Cell migration: permissive, attractive, and repulsive signals select further the surviving progenitors and ingrowing axons.

Signals of the functioning tissue (secreted molecules and cell to cell connections) keep alive the cells
Only defined regions (Hippocampus g. dentatus granule cell layer, bulbus olfactorius, SVZ) of the adult CNS provides conditions for survival and development of stem cells and novel neuronal circuits. The environmental conditions for survival and proper development of neural stem cells are far from known, yet.

<u>Stem cells can be used for:</u>

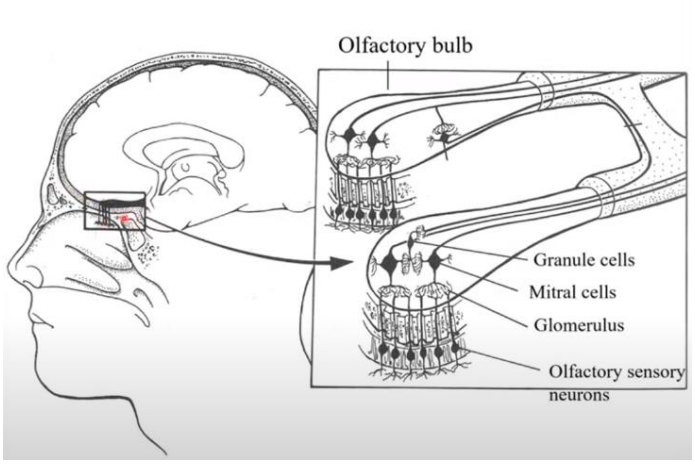
- in vitro
    - drug testing
    - assessing individual drug reaction of patient-derived iPSC generated neurons
    - basic studies of neuronal development and circuit formation
    - investigation of conditions for neurite regeneration
    - surface optimalization of intracerebral prostheses
- in vivo
    - dampening of local inflammatory processes
    - stimulating inherent regenerative processes

Olfaction

Lecture 5

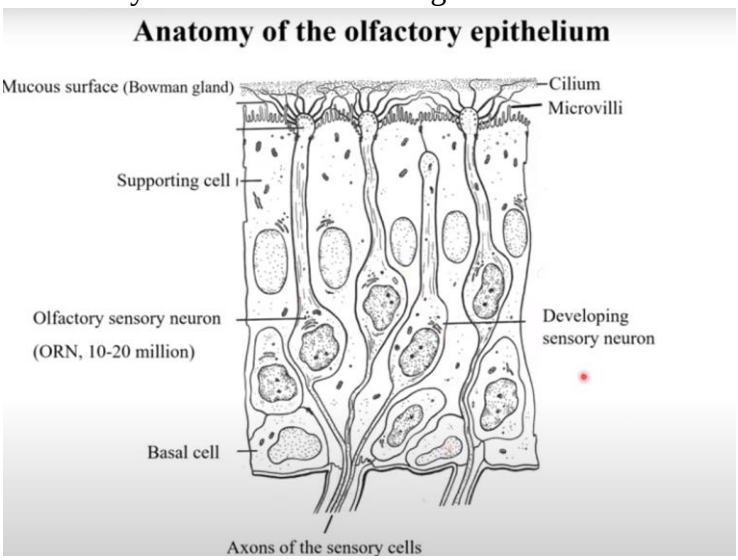
Location of the olfactory system

- the *olfactory epithelium* lies in the frontal basal part of the brain
- *OMP (olfactory marker protein)* is expressed by olfactory sensory neurons in the olfactory epithelium
- *MOE (main olfactory epithelium)*



Anatomy of olfactory epithelium

- olfactory sensory neurons: 10-20 mill in humans
  - central process (axon), which goes to the olfactory bulb
  - peripheral process, which goes to the surface of the epithelium
  - cilium: surface of the peripheral axons; contains the olfactory receptor proteins
  - generated from precursor basal cells
  - they recognize volatile chemical substances with special receptors
- supporting cells
- basal cells: all the time dividing, generating the olfactory sensory neurons, every 60 days the neurons are changed



Jacobson organ (vomeronasal organ)

- specialized sensory organ, to detect pheromones
- not present in humans
- located between the nasal cavity
- contains epithelium, they project to the accessory olfactory bulb
- pheromones are air born molecules
    - very species specific

Superfamily of the olfactory genes

- one OSN expresses only a single type of OR gene, indicating high specificity
- 3% of the human genome code olfactory receptors

Olfactory (OR) and vomeronasal (VR1, VR2) receptors

- 7 transmembrane G-protein coupled receptors
- end terminal in the extracellular space and a C terminal in the intracellular space
- in humans there are silenced vomeronasal receptors, in animals they are expressed

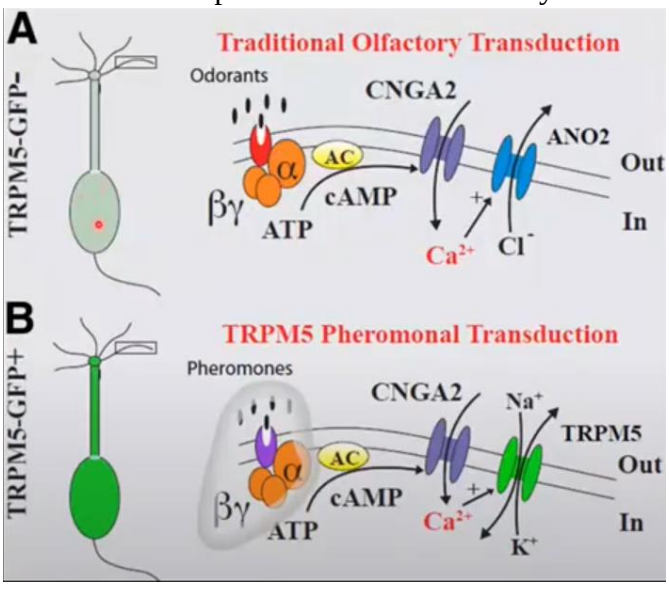
Activation of olfactory receptors and the signal transduction pathway

<u>Olfactory:</u>

- G-protein coupled receptors bind certain chemicals →hydrolyses of the alpha and beta and gamma subunits → activates the adenylyl cyclase → ATP → cAMP
- cAMP concentration rises → binds to nucleotide-gated ion channels → Ca^{2+} flows in →activates nonselective cation or Cl^- channels
- Cl concentration is high intracellular → Cl flows out through ANO2 → inside becomes + → depolarization of the neuron → propagates to the olfactory bulb

<u>Pheromonal:</u>

- same until Ca influx
- Ca bind to the TRPM5 channels → influx of Na, outflux of K → more permeable for Na → depolarization of the sensory neurons



The olfactory epithelium is a special part of the nasal mucosa that lies in the postero-dorsal part in human.

OSN-s are generated throughout life from precursor basal cells. They recognize volatile chemical substances with specialized receptors.

OR: seven transmembrane, G-protein coupled receptors that activate adenyl cyclase and increase the intracellular concentration of cAMP. cAMP in turn, activates cyclic nucleotide-gated ion channels. The fluxed Ca^{2+} ions further activate either nonselective cation or Cl^- channels.

One OSN expresses only a single type of PR gene, indicating high specificity. One OR, however, binds and gets activated by many different odours/chemical molecules.

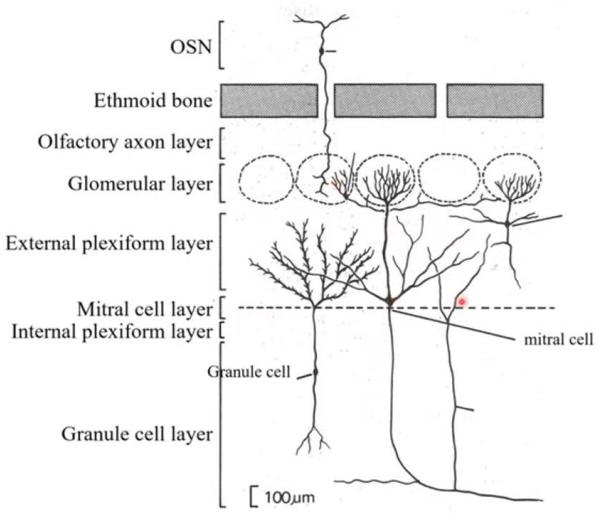
Activation of the olfactory receptors

- olfactory receptor genes are expressed only in individual neurons
- Olfactory receptors are not specific to only one chemical, they can be activated by many odours/chemicals
- single chemical can activate many neurons as well
- ORs and OSNs show low specificity

Adaptation of the OSN responses

- Each odour evokes specific spatio-temporal activity of the OSN population. The OSN ensembles can be partially overlapping.
- The electrical response of OSNs show adaptation. This adaptation is already evident in the amplitude of the OR-evoked current and in the number of action potentials.
- A given concentration of conditioning pulse reduces the response amplitude to the test pulse. The higher the concentration of the conditioning pulse, the larger its effect is on the test pulse.
- We can interpret the adaptation as a rightward shift in the dose-response curve.

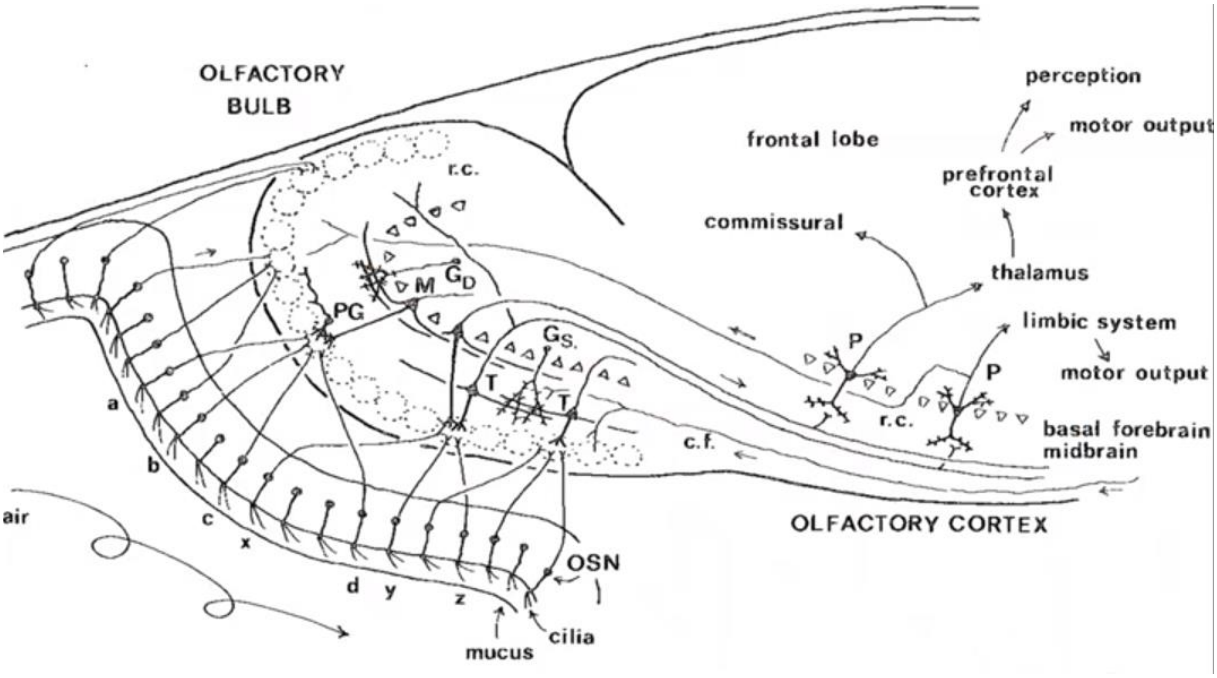
Cellular elements and synaptic connections of the main olfactory bulb (MOB)
Layers of the MOB



Nerve cells of the MOB

- Mitral cells:
  - in the mitral cell layer
  - principal cells of the MOB, providing the main output of the bulb
  - cell bodies are 15-30um
  - one primary dendrite that arborizes in a single glomerulus
  - many secondary dendrites in the external plexiform layer, where they receive dendro-dendritic inhibition from granule cells
  - excitatory cells
  - glutamatergic neurons
- Tufted cells:
  - in the glomerular layer
  - principal, glutamatergic cells of the MOB
  - synaptic connections are similar to mitral cells, but provide a more extensive local collateral system in the internal plexiform layer
  - located round the glomeruli or in the external plexiform layer
  - dense dendritic arborization
  - its axon innervated in the mitral cell and the internal plexiform layer
  - they also project to the medial part and innervate with the granule cells
  - excitatory cells
- Granule cells:
  - in the granule cell layer
  - axonless interneurons, only have dendrites
  - only can form dendro-dendritic synapses
  - inhibitory cells
  - GABAergic neurons
  - cell bodies are 6-8 um
  - they receive all their inputs (excitatory from mitral/tufted, inhibitory from dSACs) and provide their outputs (mainly to mitral/tufted cell dendrites) through their dendrites
- Periglomerular cells:
  - GABAergic inhibitory interneurons
  - small cell bodies located around the glomeruli
  - one short dendrite arborizes in one glomerulus
  - excitatory inputs from OSN axons and from mitral/tufted cell dendrites
  - GABAergic inputs from deep short-axon cells
  - GABAergic outputs to mitral/tufted cell dendrites and other PGCs (Periglomerular cells)
- Deep short-axon cells:
  - in the granule cell layer
  - 3 subtypes
    - axon can go to the glomerular layer
    - axon arborizes the granule layer
    - axon arborizes the external plexiform layer
  - GABAergic inhibitory (disinhibitory) interneurons

Synaptic connections of the MOB

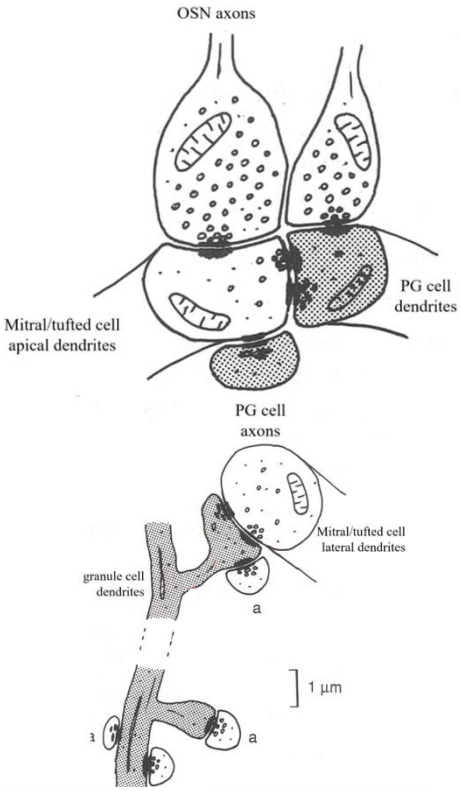


- sensory input:
  - glutamatergic inputs/synapses from OSNs in the glomeruli
- centrifugal inputs
  - glutamatergic input:
    - from the pyramidal cells of the piriform cortex and anterior olfactory nucleus
  - noradrenergic input:
    - from the locus coeruleus
  - cholinergic input:
    - from the diagonal band
  - serotoninergic input:
    - from the raphe nucleus
  - most of these fibers innervate the granule cells

Output of the MOB:

- mitral/tufted cells project to the anterior olfactory nucleus and to the piriform cortex (primary olfactory cortex)

Intrabulbar synaptic connections



- glomerular layer
    - PG = periglomerular cells and some short-axon cells provide inhibitory input to mitral/tufted cell primary dendrites
    - the primary dendrites of mitral/tufted cells also establish excitatory dendro-dendritic synapse on periglomerular cell
    - electrical synapses are present between the primary dendrites of mitral/tufted cells in the glomerulus
- external plexiform layer
    - local axon collaterals of mitral/tufted cells provide excitatory inputs to granule and dSACs

Electrical and chemical synapses are both present

- electrical synapse among mitral cells
- dendro-dendritic electrical synapses (gap junctions) are responsible for the synchronized activity of mitral cells that project to the same glomerulus

Distribution of connexin36 molecules in the MOB

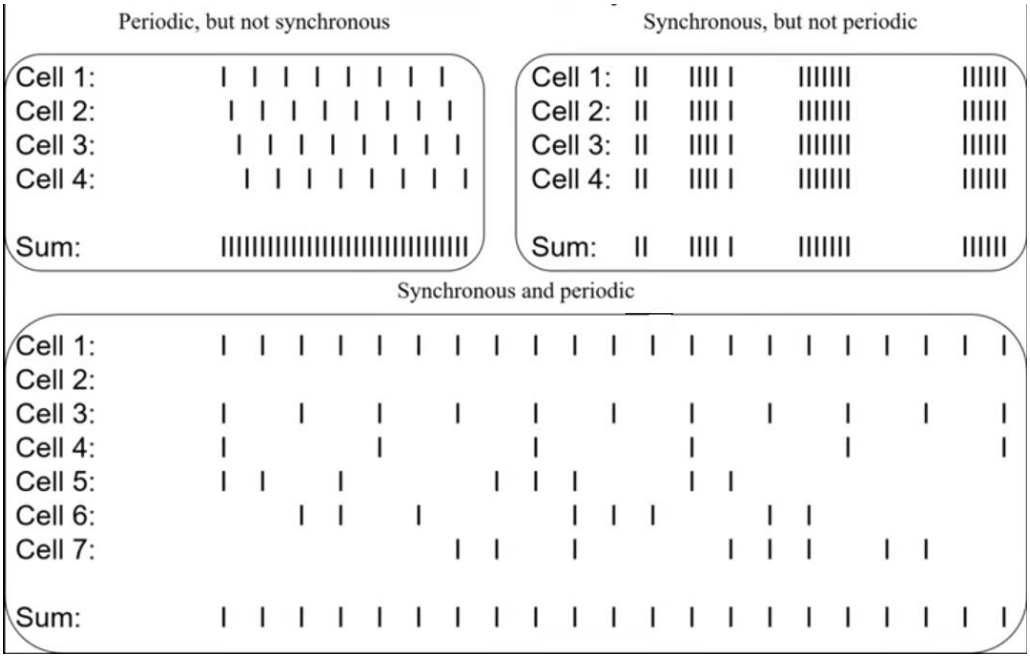
- in the glomeruli
- between mitral cell dendrites

Rhythmic network oscillations and information coding
Local field potentials

- from the surface of the skull (EEG) / the surface of the cortex / inside of the brain
- LFPs are consequence of the spatio-temporal summation of synaptic (ligand-gated) and voltage-gated conductances/currents
- as a consequence, it reflects the population activity in that given brain region

Oscillation:

- rhythmic changes in the LFP
- the emergence of rhythmic oscillations requires periodic and synchronous nerval activity
- there could be silenced cells, stochastically firing cells, but the only important thing is, if they fire, they fire at the same time!!



- The LFP oscillation on its own does not carry any information, but indicate that the activity of a population of nerve cells in a given grain region is periodic and synchronous
- however, as an outside examiner, oscillations can be used as temporal references to relate the activity of individual cells to that of the population

Brain maps and coding information

- brain (sensory) map:
  - is a region of nervous tissue, where the physical arrangement of neurons is correlated with some features of the environment, usually in an orderly fashion
- topographic map:
  - is a map in which the physical arrangement of neuron respects the neighbourhood relationships of the input (e.g.: frequency of sound)
- code:
  - is a symbolic language, a set of signals and rules, by which information can be transmitted
- an example where the physical map is an intrinsic part of the code:
  - mRNA → an mRNA molecule compromises a linear sequence of nitrogenous bases, and its physical arrangement encodes the amino-acids
- an example where the physical map is not part of the code:
  - rat hippocampus → here, PCs (place cells) represent the external space of the animal, such that most PCs have place related firing (place fields). The physical arrangement of place cells (e.g. CA1 PCs) bears no topological relation to the physical arrangement of their place fields
- Equating the olfactory receptor projection map and an olfactory code implies that the brain decodes the olfactory signals by using knowledge about physical origin of the cell. With other words, it implies that the computation underlying the encoding or decoding of olfactory signals by the brain makes obligatory use of neural positions. Nothing indicates that this is the case.

Dynamic evolution of neural activity in a cell population

- assume we have oscillation and we have nerve cell, that fire cyclical
- "population", "temporal" and "identity" code (theory)

Discrimination of odours:

- odours evoke stimulus-specific temporally changing responses
- the same odour evokes similar activity pattern in one neuron from time to time
- the same odour evokes different activity patterns in distinct neurons
- different odours evoke different activity patterns in a neuron
- thus, the odour-evoked activity pattern in the brain is stimulus and cell-specific
- the identity of the participating cells, the temporal structure of their activity and synchronicity among them are important
- thus, the brain uses "population", "temporal" and "identity" code for olfactory information

Optogenetics

Lecture 6

How does the brain work?

- a key issue: huge diversity of cell types

Observation of behaviour

- after observation we try to find the brain region and after that the specific neurons

Optogenetics:

- manipulation of behaviour-related neurons

Traditional ways of manipulating neural networks

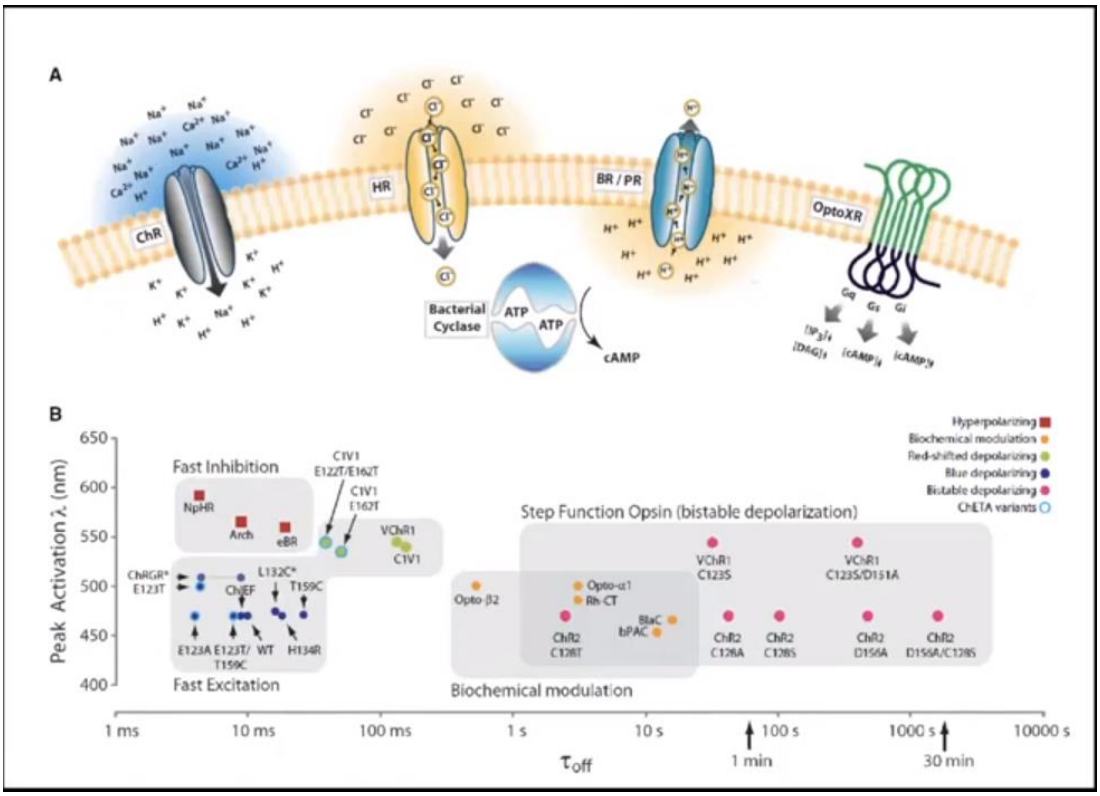
- electrical stimulation
    - non-specific
    - noisy (introduced by the non-specificity of the stimulation)
    - generates complex pattern of activated/inactivated regions
- pharmacology
    - little bit better because you can find the neuron
    - poor temporal resolution, because you have to inject your compound and it has to be washed out
    - moderate specificity
    - cumbersome, because you have to implant relatively large probes to implant water

Why do we have to selectively manipulate neurons at high temporal resolution?

- genetic tagging of target neurons
- in order to manipulate them using easily manageable physical phenomena (it is light)

Leading characters in optogenetics:

- microbial opsins
- G-protein coupled receptors belongs to the opsin superfamily



- channel rhodopsin:
  - ion channel
  - blue light -> inflow of pos. charged neurons
  - activating opsin because they depolarize the cell
  - rapidly activating
- Halo rhodopsin:
  - activated by yellow light
  - Cl^- inflow
  - inactivating opsin because they hyperpolarize the cell
- bacteria rhodopsin:
  - pumping proton out of the cell
  - inactivating opsin because they hyperpolarize the cell
- OptoXR:
  - they do not bind ligand
  - light indicates a change in conformation
  - the response generated are them is slower

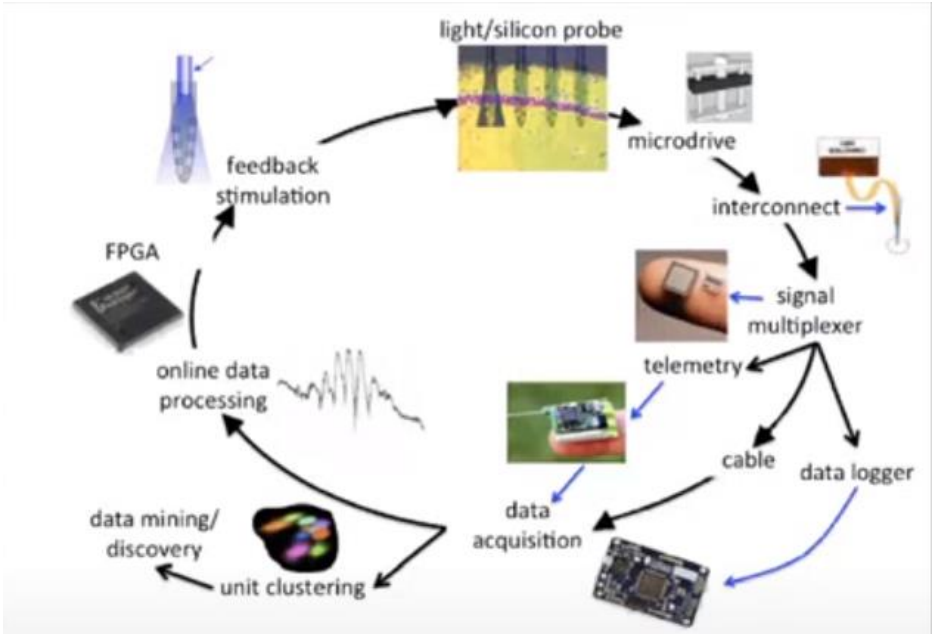
Delivery of opsins into target cells:

- viral gene transfer → vector: adeno-associated virus (AAV)
- endogenous promoters are usually weak
- we need strong, ubiquitous promoters, and we need to make them selective
  - recombinase make the promoters specific
  - shortcoming: requires drive line (transgenic mouse)
- substitute the mouse to another mouse → driver line + reporter line → double transgenic

Light delivery and electrophysiological readout

- light source: state laser or LED
- we use optic fibers to deliver the laser light
- recording: multisite electrode, juxtacellular optrode
- NOW: miniaturization of light delivery and recording

High density silicone probe recording and optical stimulation



- we can reconstruct the connections between the neurons

All optical manipulation and recording of neural activity

- system for simultaneous excitation and imaging: modifying a 2-photon laser microscope

Increasing the spatial resolution of light stimulation

- temporal focus
  - problem: the smaller the stimulated spot, the fewer activable channels are present: lower ability of activation
  - solution: increase the spot size while maintaining intensity (with one-photon laser scanning)

Wireless electromagnetic stimulation:

- problem: light delivery requires either an optic fibre (tethering) or an implantable light emitting device
- solution: delivery of heat dissipating magnetic nanoparticles along with a genetically encoded temperature sensor (TRPV1 cation channel)

Combinatorial optogenetics

- simultaneous manipulation of multiple neural population: biological implementation of logical operations
- selective activation of neurons targeting a single postsynaptic cell

Manipulation of intracellular signalling

- Chimaeric GPCRs: on opsin's light-sensitive domain + target receptor's intracellular G-protein-binding domain
- effect on neural activity and behaviour as well

Manipulation of cell shape:

- light-sensitive domain (LOV) sterically inhibits the binding of the GTPase Rac1 to its effector

Manipulate gene transcription

- light-induces recruitment of the transcription initiation complex: TALE: Transcription Activator-like Effector (targeting) + Cryptochrome-2; CIB2: Cry2-interacting partner

Advantages of optogenetics:

- selective manipulation of distinct cell types
- millisecond precision
- high spatial resolution by beam shaping
- simultaneous bidirectional manipulation of multiple cell types
- possibility of interrogating various biological processes at multiple timescales

Examples:

- optical deconstruction of Parkinson neural circuity

Motor control

Lecture 7

I. Development of active movement

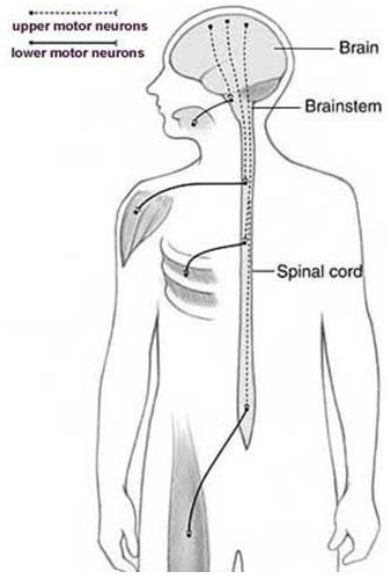
- movement serves preservation of higher „life" forms on Earth and survival for an individual by enabling
  - biodiversity – propagation
  - biodiversity – protection
  - species-propagation – reproduction
  - species-protection (communities, societies)
  - self-propagation – feeding, drinking
  - self-protection („flight or fight")
- Humans bring survival of the individual in front of the preservation of higher „life" forms on Earth by changing the priority order
  - self-propagation – feeding, drinking
  - self-protection („flight or fight")
  - species-propagation – reproduction
  - species-protection (communities, societies)
  - biodiversity – propagation
  - biodiversity – protection
- Movement is carried out by the co-operative work of the contractile tissue and the actuator (nervous system)
- some of the movements are involuntary (reflexes, fixes action patterns), some rhythmic movements are automatically carried out under continuous voluntary control (rhythmic motor patterns – locomotion) and some movements are voluntary (directed movements)
- we are born with the capability to carry out involuntary movements, and some of the rhythmic movements. Babies can do only a limited number of voluntary movements (e.g., crying)

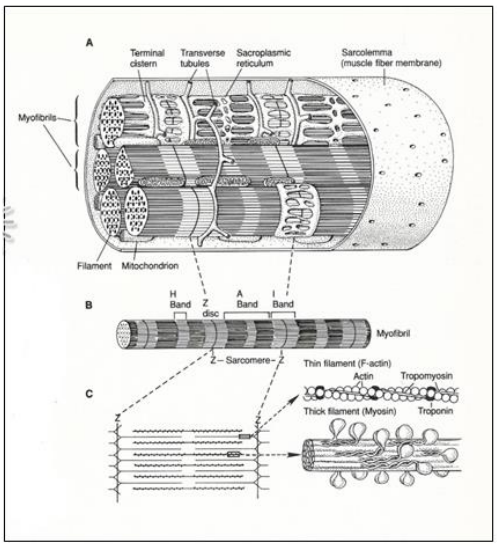
Speed, force, dimension, and **complexity** of movement are determined by

1. <u>state of the development of nervous system (phylogenetically and ontogenetically)</u>
   - more advanced nervous system means higher complexity of movements
   - maturation of the CNS shows species variation
   - The need to achieve **more complex movements** induces the appearance of a **more complex nervous tissue** and *vice versa* a more complex nervous tissue enables more complex movements for a living creature.
   - **Learning (gaining information through sensors and storing it**) is important in the process of building more complex structures and functions.
   - At a certain stage (based on the stored information) **planning of movement** emerges. Planning means using a **movement strategy** proved to be most effective in achieving a goal.
   - **Thoughts** can be considered as **planned movements**, which are either realised soon after or sometime in the future, or not realised at all.
2. <u>biomechanical properties of the skeleto-muscular system</u>

- units:
    - muscle + tendon
    - muscle fibre
        - extrafusal
        - intrafusal
    - myofibril
        - actin
        - myosin
        - troponin
        - tropomyosin
    - sarcomere (2µm)

How does the firing of **lower motoneurons** lead to muscle fibre contraction?





Muscle fibers contract in response to excitation.

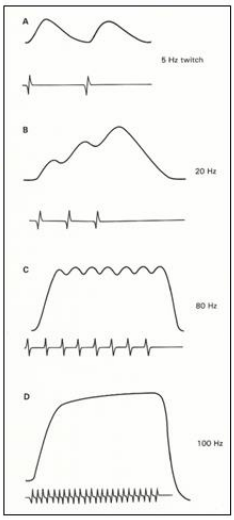
- muscle tension is regulated by motor neuron firing rate

Single MUs - **Twitch**

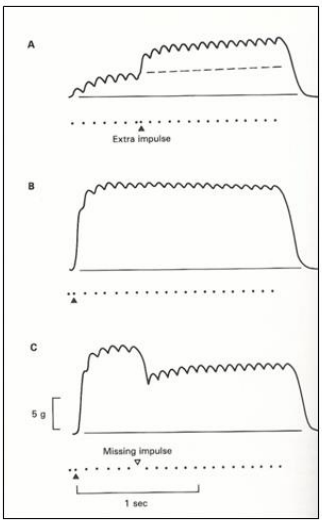
Contractile force is maintained by **Summation**

Incomplete tetanus

Tetanus

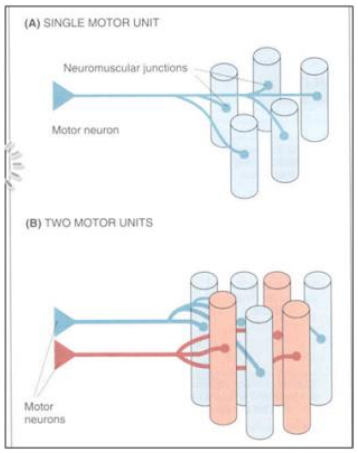


Effect of **extra** and **missing** impulses



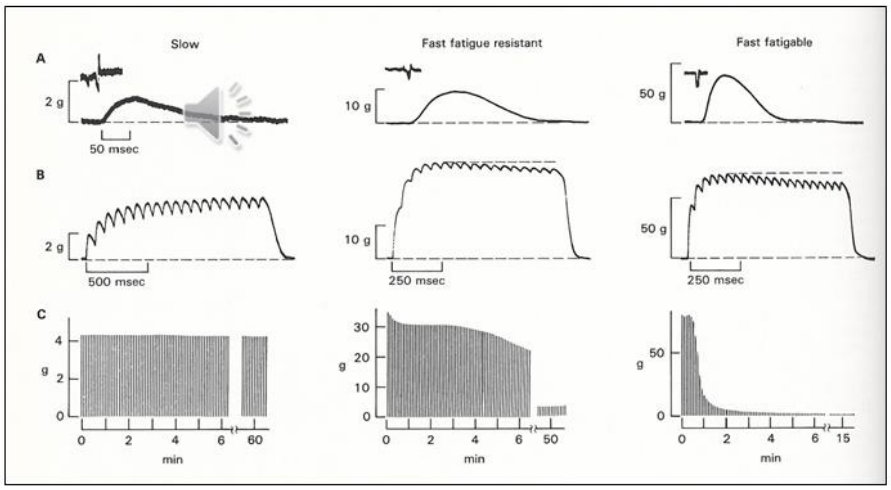
Fibers belonging to different motor units are intermingled. Hierarchical and asynchronous activation of motor units!

- *motor unit*: single motoneuron + all innervated muscle fibers



Speed and force of contraction depend on the motor units involved.

- **three basic types** of motor units

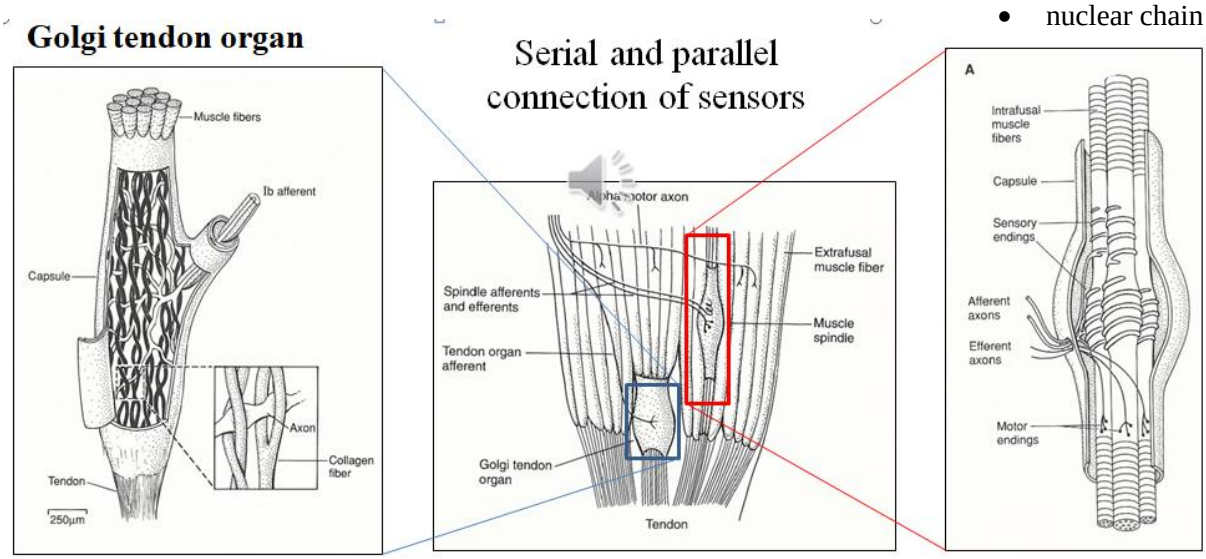


Muscle tension is modulated by receptors sensing active and passive tension, as well as static and dynamic changes during muscle contraction.

- Gain adjustment is possible in the muscle spindle.

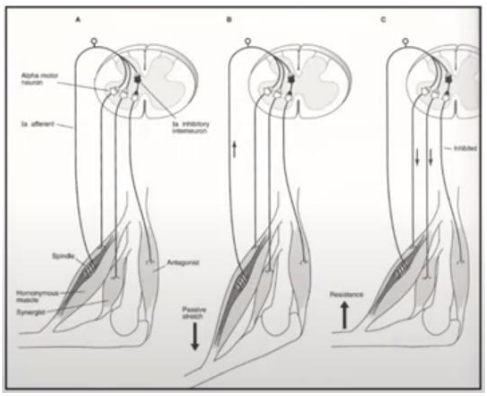
Muscle spindle:

- nuclear bag (static and dynamic)
- nuclear chain



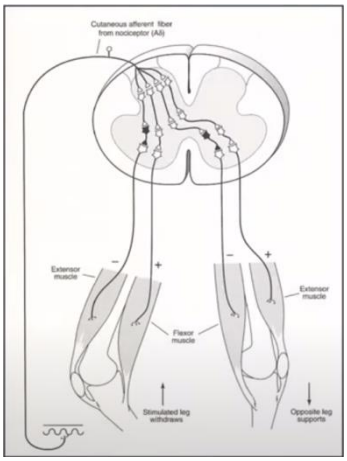
The proprioceptive reflex arch

- proprioception means the unconscious sense of self position and movement
- changes in the physical constant of the body with the support surface trigger unconscious compensatory actions through **(stretch reflex)**
- e.g., *patellar reflex, Achilles reflex*
- this reflex:
    - has phasic and tonic components
    - involves reciprocal innervation of the antagonistic muscle
    - is characterised by motor output to all homonym and ~60% of synergistic muscles
    - is characterised by adjustable sensitivity through setting fuzimotor fibre activity
    - can be modified by presynaptic inhibition of the afferent fibers
    - it is characterised by direst synaptic input to MNs; the delay is 0.5-0.9 ms
    - monosynaptic reflex arch



The nociceptive reflex arch

- multisensory convergence
- loss of specificity of sensory processing
- contralateral inhibition of flexor MNs
- multisynaptic reflex arch (many inhibitory and excitatory interneurons)
- e.g., *hand withdrawal reflex*



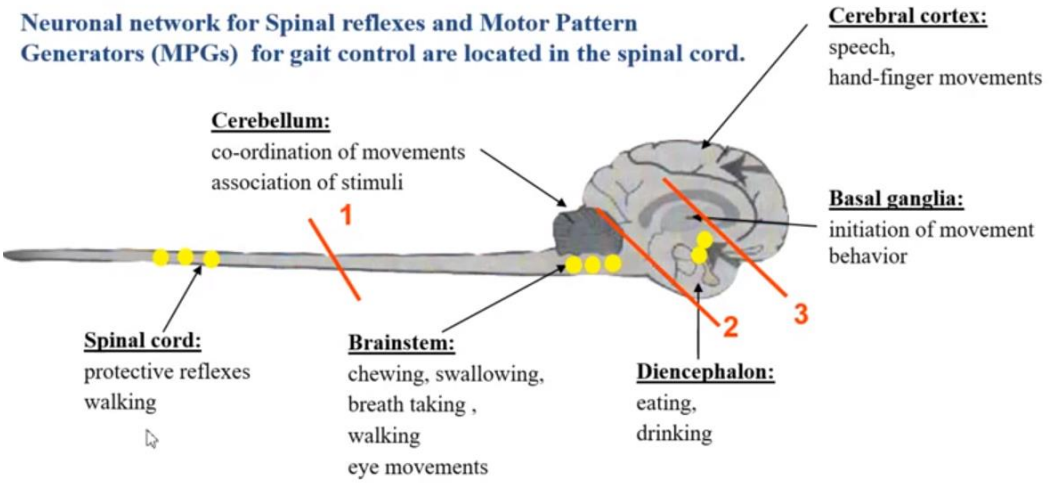
I-II. Summary:

- Speed, force, dimension, and complexity of movement are determined by state of the development of nervous system and the biomechanical properties of the skeleto-muscular system
- Motor units are recruited in the muscle contraction in a hierarchical and asynchronous manner!
- Reflex contractions and relaxations are triggered by muscle and skin receptors

III. Regulation of movement at spinal cord level

CNS lesions

1. spinal cord injury
2. decerebration
3. decortication



Human gait is composed of *phasic and tonic components*

- **the phasic component** means the rhythmic alternating contractions of limb and trunk muscles, produced mainly by central pattern generators – CPGs are functional at birth
- **the tonic component** is associated with postural muscles and quite immature at birth – it becomes functional by the maturation of
    - the musculoskeletal system
    - the sensorimotor networks
    - higher brain centres
    - descending motor pathways
    - ascending sensory pathways

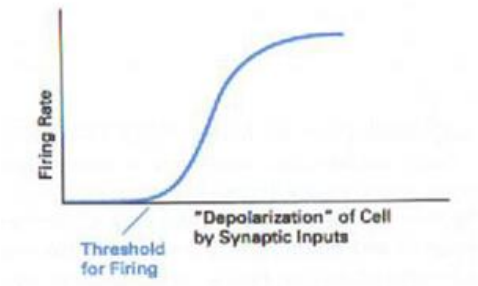
A network of spinal neurons (composed of interneurons and motoneurons) generates a rhythmic motor pattern. Due to its complexity in vertebrates, it is difficult to investigate the regulating neuronal network, which is therefore largely unknown.
The major observations about the function of cellular components and the operational rules of the neuronal network generating the rhythmic motor pattern derive from studies on **organisms with relatively simple neuronal systems i.e.**

- clione
- lobster
- leech
- lamprey

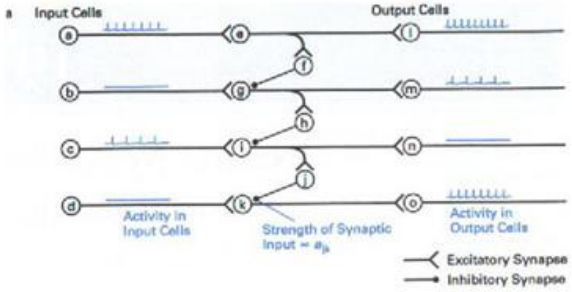
Central (motor) pattern generator (CPG, MPG): Neuronal network, which is capable of maintaining a rhythmic output without rhythmic sensory or central input.
Rhythms are generated:

- by endogenously oscillating neurons (currents) or
- by network activity of non-oscillating neurons

Cellular (neurons) response



Network (model) response



Formation of network oscillators

- **clione – two-neuron system**
- **Half-centre oscillator:** Two neurons connected in reciprocal manner generate rhythms – alternating muscular contraction and relaxation
- Post inhibitory rebound lead to generation of action potentials! „anode break spike"
- **<u>Common phenomenon</u>**: voltage-dependent Na channels or T-type calcium channels are partially inactivated at the resting potential. Transient hyperpolarization releases the channels from the inactivated state. Threshold of the action potential will be lower.
- Electrical properties of the participating neurons determine
    - oscillation in network output
    - activity of neurons
    - period rhythms

Significance of input on network activity

- lobster – multi-neuron system
- Rhythm generation is dependent on the activity of other cells – network input is essential!
- The released neurotransmitter alters the membrane characteristics of the neurons within the network!
- AB cell shows conditional **burst activity**! When it is active, a short depolarization induces a **driver (plateau) potential in** LP neuron!

Lobster - neuromodulators alter network activity and output

- *<u>Experiment:</u> Removing neuronal input (GABA, serotonin, dopamine, FMRFamide-like peptide etc.), adding neuromodulators*
- Alteration of excitability of neurons and synaptic strength within the network results in **different outputs!**

The role of "command" neurons in network activity

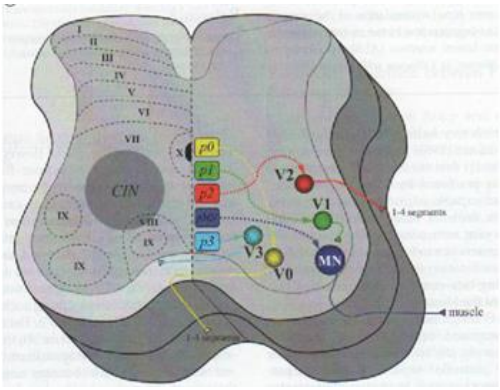
- leech – command neurons in the network activity
- **Trigger neurons** receive input from sensory neurons and initiate rhythmic activity of MPGs
- **Gaiting neurons** determine the duration of the MPGs activity – the duration of the swim
- Short activation of the **„trigger"** neuron induces a long-lasting activation of the **„gating"** neuron, which in turn leads to a long-lasting burst activation of **CPGs** and **the motoneurons**.

Development of the reticulospinal system to control CPGs

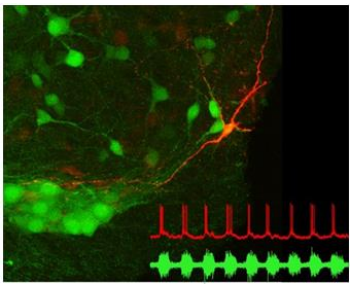
- lamprey – command system of vertebrates
- CPGs are composed of excitatory (E) and inhibitory interneurons (L&C). "C" interneurons are in reciprocal inhibition with its pair in the other half-centre. Stretch receptors (SR) send excitatory and inhibitory feed-back to CPGs. Excitatory reticulospinal neurons (R) induce plateau potentials in the pattern-generating neurons. Role of NMDA receptors is to increase calcium levels, which in turn activate calcium-dependent potassium channels.

The network responsible for controlling walking develops during the embryonic life. A dorsoventral gradient of brain morphogens trigger the expression of transcription factors, which in turn determine differentiation of neural stem cells to interneurons (V0-V3) and motoneurons (MN).

- V0 - coordination of left-right alternation (contralateral)
- V1 - speed of MNs output (ipsilateral inhibition)
- V2 - burst robustness
- left-right alternation
- V3 - burst robustness



HB9 expressing spinal motoneurons and interneurons in the neonatal mouse spinal cord shown in green by the reporter fluorescein protein.
An excitatory interneuron is recorded and filled with biocytin.
The Hb9 interneuron activity is characterized by rhythmic membrane depolarization underlying action potentials. The activity is in phase with the activity recorded from motor neurons (ventral root recording).



Interneurons on the ipsilateral side transfer stimulus from the skin, which **modify the motor program** and consequently the firing activity of motoneurons.

- region-specific
- modality of the stimulus determines the response

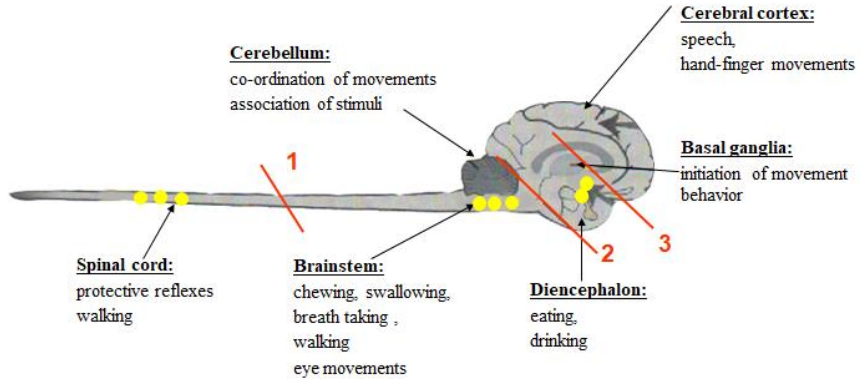
III. summary – what can be predicted for the operation of the MPGs in mammals (humans):

- similar membrane events (post inhibitory rebound, driver potential etc)
- similar reciprocal connection of half-centres
- neuromodulators influencing electrical properties of network elements
- cellular components brought in action determine the output signal of the network
- the existence of higher command system
- peripheral signals exert also strong influence on the MPGs

IV. Supraspinal motor control: the medial system controls posture and reflex behaviours

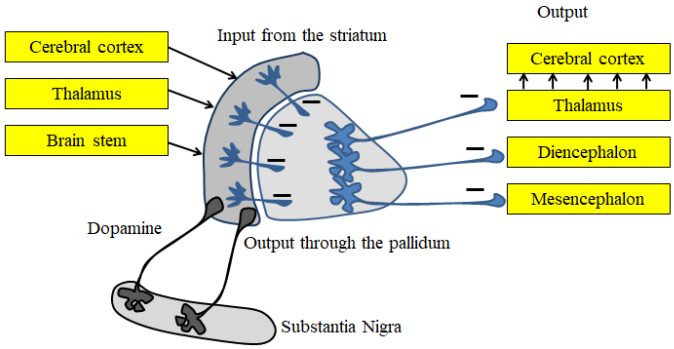
Supraspinal movement regulation is a result of activation of neuronal populations distributed in several discrete regions of the brain.

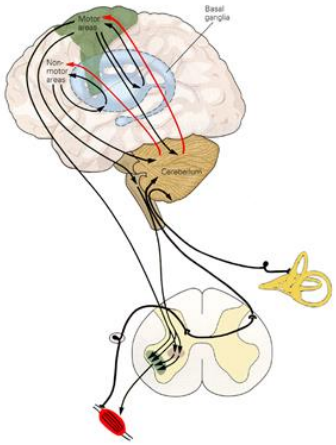
- Principal sites are in the brain stem, cerebellum, basal ganglia, and cerebral cortex.



Initiation of movement from the basal ganglia.

- Role of disinhibition



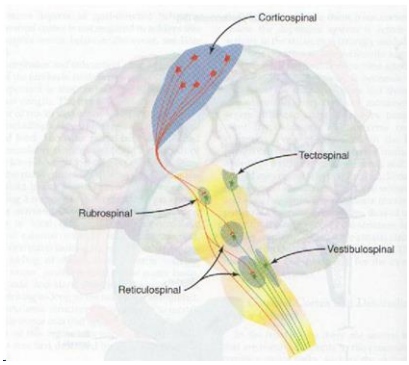


Cerebellum stores motor patterns that can be activated upon initiating a movement

- The motor patterns are continuously renewed to incorporate learned skills and physiological/pathological changes in the musculoskeletal system.

Five major pathways descend to control movement at the level of the spinal cord.

1. <u>corticospinal</u>
    - responsible for transmission of commands of skilled movements
    - correction of motor patterns generated by the spinal cord
2. <u>rubrospinal</u>
    - responsible for transmission of commands of skilled movements
    - correction of motor patterns generated by the spinal cord

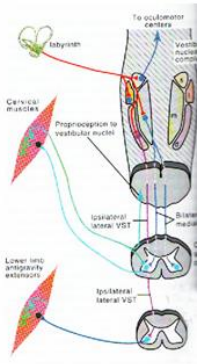


3. tectospinal
    - responsible for tracing the movements of other moving objects in our environment
    - and we can adjust our movements accordingly
    - tecto-reflex: frog uses to catch insects
4. vestibulospinal
    - responsible for generation of tonic activity in the anti-gravity muscles
5. reticulospinal
    - responsible for the activation of the spinal motor programs for stepping and other stereotypic movements
    - controlling the upright body posture

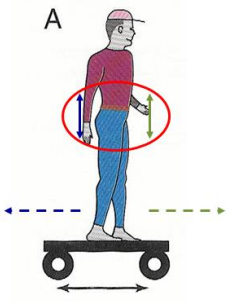
Supraspinal motor control: the medial system controls posture and reflex behaviours

- Posture and balance are maintained by continuous processing of sensory, vestibular, and visual inputs and generation of compensatory muscular contraction.
    - Sensory - proprioceptive inputs
    - Vestibular input
    - Visual input

The medial postural system processes proprioceptive, vestibular, and visual information and conveys motor responses to the spinal cord. It innervates the axial musculature and the proximal parts of the limbs.

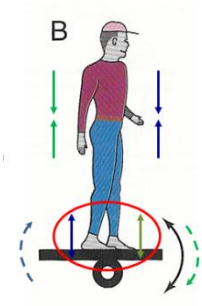


- The vestibular nuclei are in connection with the cerebellum, which receive sensory information from the body.
- The medial longitudinal fascicle contains fibers of superior vestibular nucleus projecting to the motor nuclei of the eye.
- The lateral vestibular nucleus project to the spinal cord to activate the extensor muscles of the ipsilateral limbs.

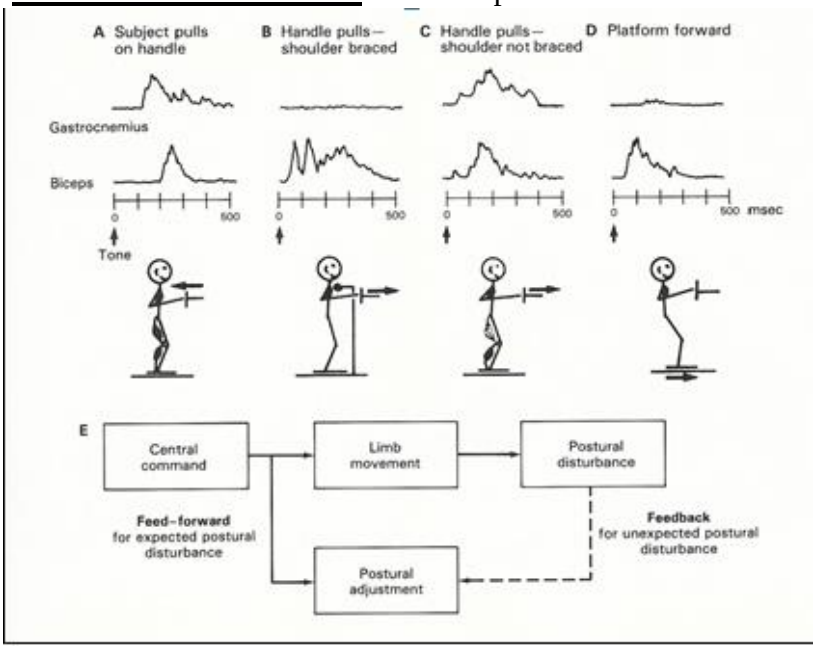


- Different mechanisms are adapted to the various positional changes of the support surface
- **Exp: _ Moving platform triggers the ankle strategy - feed-back mechanism**
- Activation of the muscles distal to proximal direction
- e.g.: forward movement of platform – backward sway: activation of TA-quadriceps muscles-abdominal muscles

- Different mechanisms are adapted to the various positional changes of the support surface
- **Exp: _ Tilting platform triggers the hip strategy - feed-back mechanism**
- Activation of the muscles proximal to distal direction
- e.g.: forward tilting – forward sway: activation of paraspinalis (erector spinae) – ham string muscles – triceps surae muscle
- Similar action, when the movement of the platform is LARGER and FASTER or when the surface is COMPLIANT (soft) or NARROW

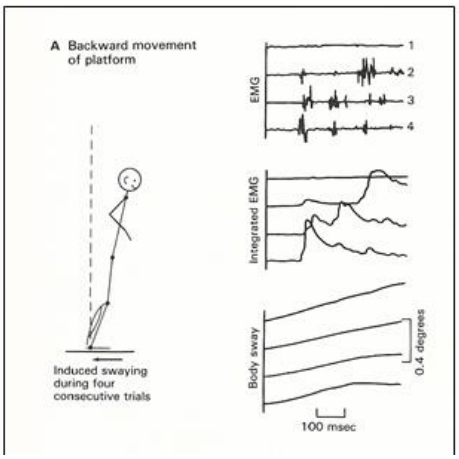


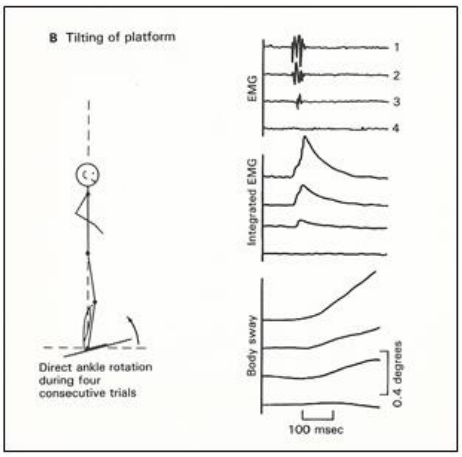
Feed-back corrections when the postural disturbance is unexpected.
Feed-forward corrections when the postural disturbance is expected.



The extent of muscle contraction depends on previous experience and expectations

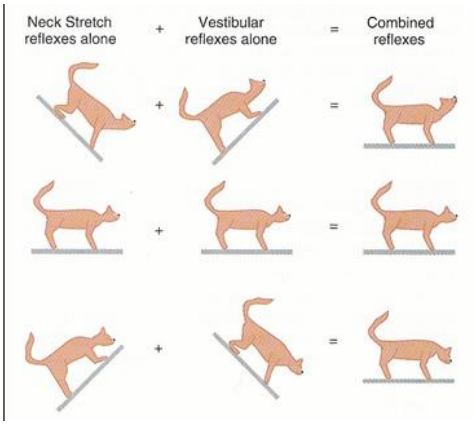
- Feedforward or preventing mechanisms are triggered



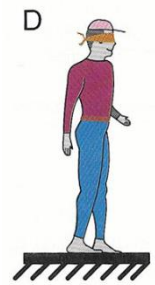


Exp: Vestibulocervical and vestibulospinal reflexes stabilize head and body posture

- Stretch in the neck muscles and stimuli of the vestibular organ excite pathways that contract neck and limb muscles to oppose an undesired movement of the body.



Removal of the visual input



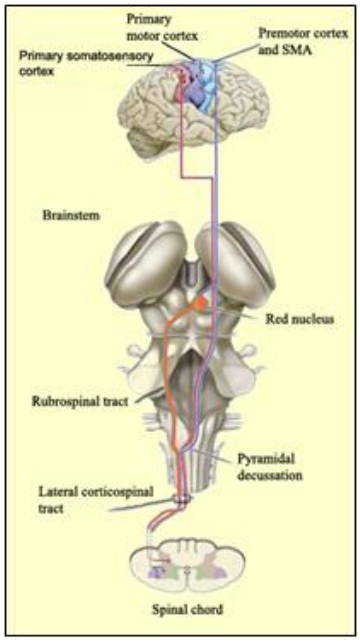
- only the proprioceptive and vestibular sensors are in action - **<u>Romberg test</u>**
- if the Romberg test is positive, it means that there is a damage in the cerebellum or in the proprioceptive or the vestibular system in the spinal cord and in the brain stem
- It is positive in the case of cerebellar, proprioceptive, and vestibular damage.

IV. Summary

- Stability of the body is provided by feed-forward control and rapid feedback compensatory corrections
- Vestibular and neck reflexes stabilize the head and sight (they act together and compensate each other)
- Brainstem and spinal cord mechanisms participate also in the postural control

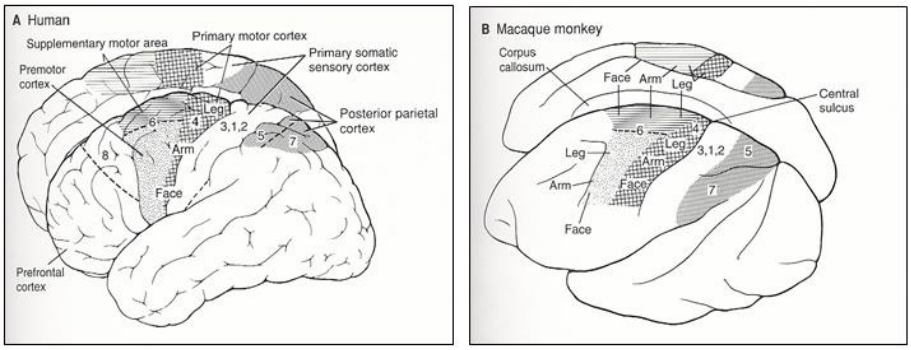
V. Supraspinal motor control: the lateral system controls voluntary movements.

- The corticospinal pathway
- The (cortico-) rubrospinal pathway

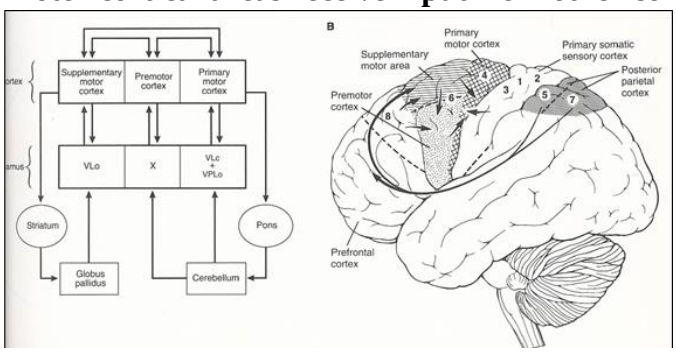


Cortical areas involved in motor control

- Their ablation results in deficits in movements, their stimulation induces or alters movements
- Cytoarchitectonic areas 4 and 6 Brodman (and areas 1, 2, 3, 5, 7 and 24)
- They communicate with other motor structures and receive area-specific subcortical (thalamic and basal ganglia) and cortical afferents.

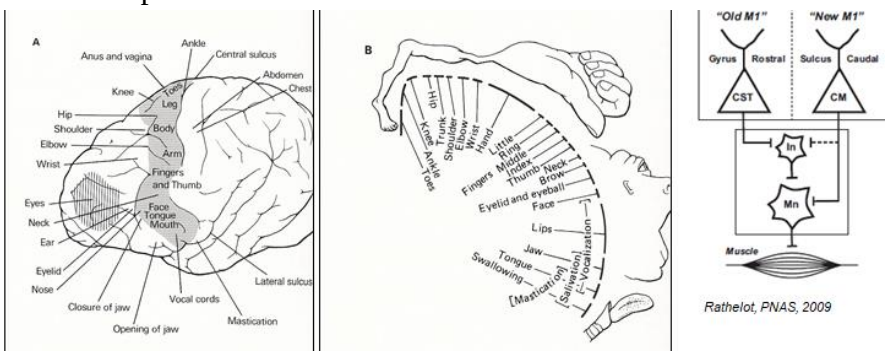


Motor cortical areas receive input from other cortical areas, as well as subcortical areas



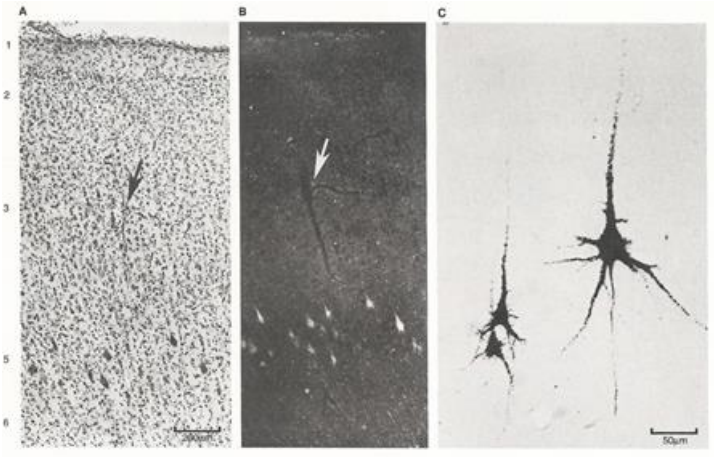
Somatotopic representation in monkeys and humans

- A large overlap in the representation fields of body parts, muscles, or movements!
- ″New ″ M1 bypasses spinal cord mechanisms and enables novel patterns of motor output



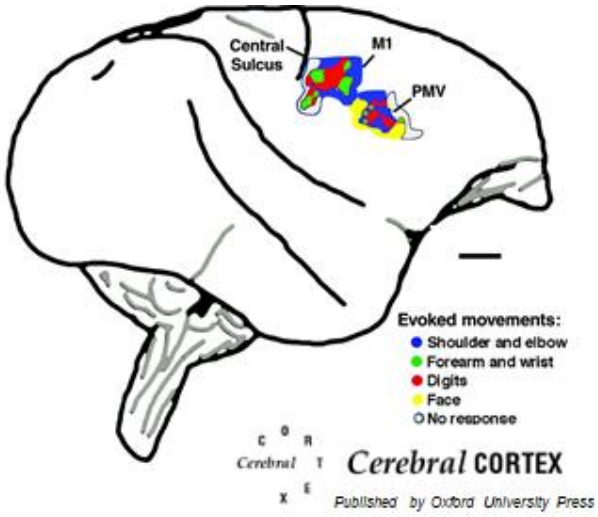
The primary motor cortex is agranular – predominantly there are <u>pyramidal cells</u> at this site

- Layer 4 is reduced or absent, no internal granular layer!
- in layer 5 there are the large pyramidal cells which establish the corticospinal pathway and the cortical corticobulbar pathway

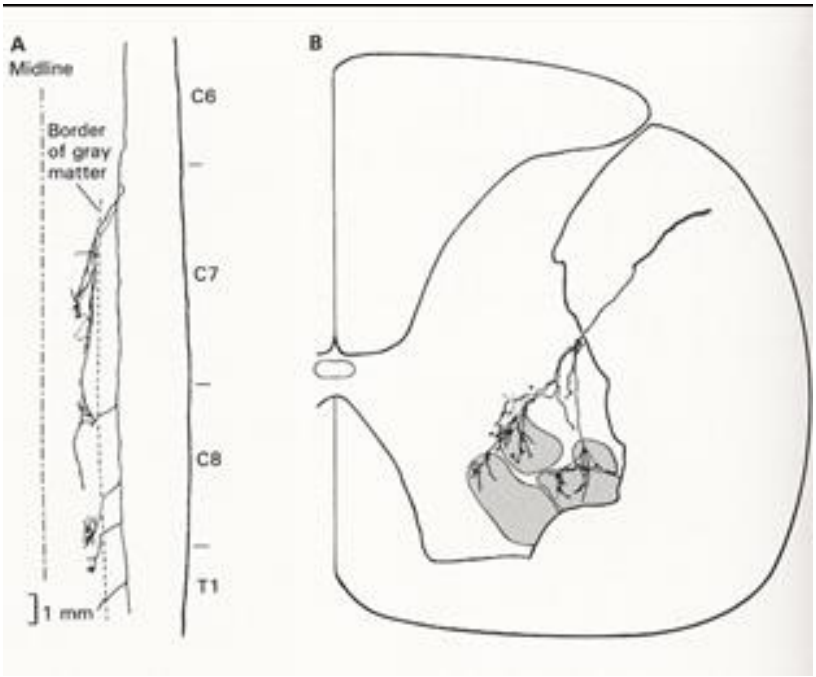


Convergence and divergence characterize the M1 neurons

- Convergence – they are distributed in complex mosaic arrangement

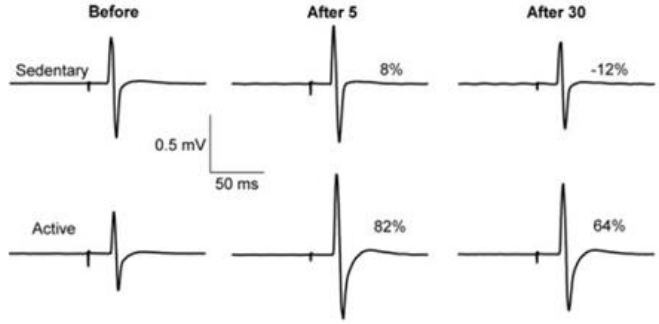


- Divergence – they ramify in multiple spinal segments



Plasticity of the motor cortex

- It occurs:
  - after denervation of one part of the body
  - when a muscle is stretched passively – rehabilitation after stroke
  - when muscles are used intensively for prolonged period
- Paired associative stimulus (electric stimuli of Median Nerve followed by TMS)
- Motor-evoked potential (MEP) amplitudes are substantially larger in active subjects!



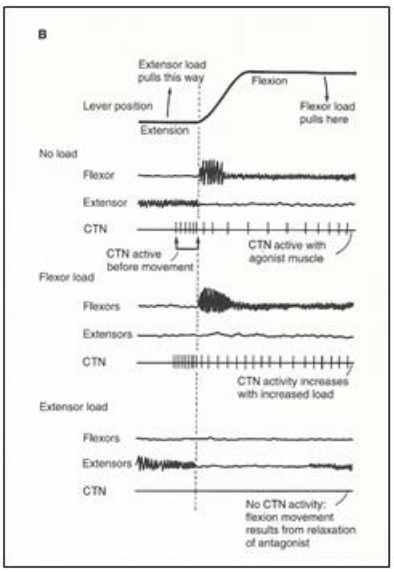
Several cortical areas are activated during planning and execution of voluntary movements.

- By complex hand movements bilateral activation of the:
  - Sensorimotor areas
  - Supplementer motor area
  - Ventrolateral premotor area
- contralateral activation of the:
  - Dorsolateral premotor area
  - Medial cortical areas rostral to the SMA
- Cortical electrical potentials 1s prior to movement!

Do cortical neurons fire during movement?

- there will be an increased activity of the muscles of the hand or the fingers or the arm in response to the increased load
- but also, there is an increased activity in the cerebral cortex
- so, the reflex to an increased load is not just affecting locally in the motor neurons in the spinal cord but through ascending pathways will influence the activity of the motor neurons in the cerebral cortex and they will increase their activity in response to the load

M1 neurons regulate kinematics and dynamics of movement



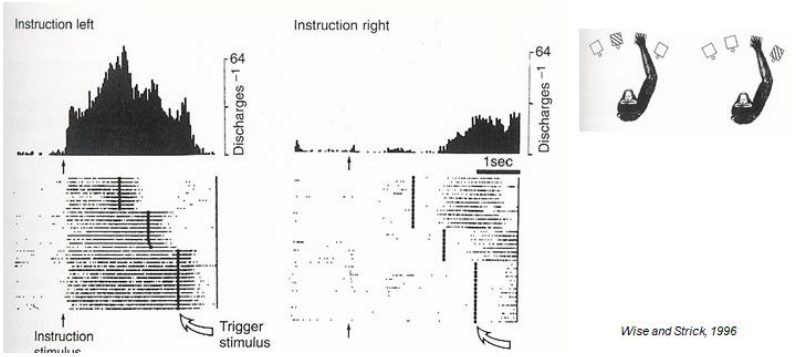
- Discharge of neurons is correlated with the force exerted. This was a single cell recording.
- if the flexor load was put on that rode, then it increased the activity of that cortical neuron and the flexors showed an increased activity
- but if the load was put on the extensor side, then the cortical neuron did not respond to that and the flexors were not activated in this case
- so cortical neurons respond to increased load of the wrist movement

Discharge of neurons is correlated with the **direction of movement**.

- Ensemble activity of a large population of cortical neurons is tuned for a particular direction of movement.

Cells in the premotor area respond to external cues (e.g., visual cues)**.**

- Delayed-reaction paradigm.

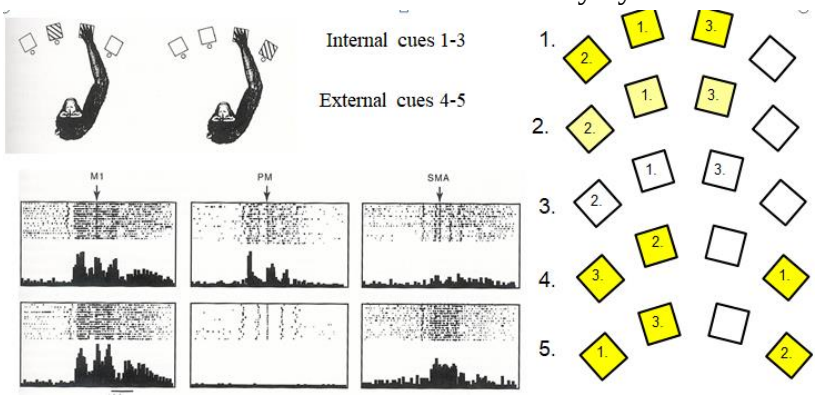


Processing of visual information –external cues - PM

- it is delayed; the input has to reach the cortical area responding to the stimulus and it lasts for a time
- *Simple reaction time* ~160 ms
- adults have shorter, children have long reaction time
- the choice reaction time is increasing in the adults, but in children it increases in larger steps
- it means that people can pay attention to only a single external cue
- *Choice reaction time* is increasing with the number of alternative responses and with age!

Internal cues activate cells in the SMA, whereas cells in the premotor area are active in response to visual cues

- the neurons in the primary somatomotor cortical area (M1) in the premotor cortical area (PM) and in the supplemental motor cortical area (SMA)
- the neurons in the M1 are involved in the execution of the movement in both cases (internal and external cues) the neurons are activated
- in the PM neurons are activated only by the external cues
- in the SMA neurons are activated only by the internal cu es



Local increase in blood flow shows also the role played by the supplementer motor area during mental rehearsal of motor tasks

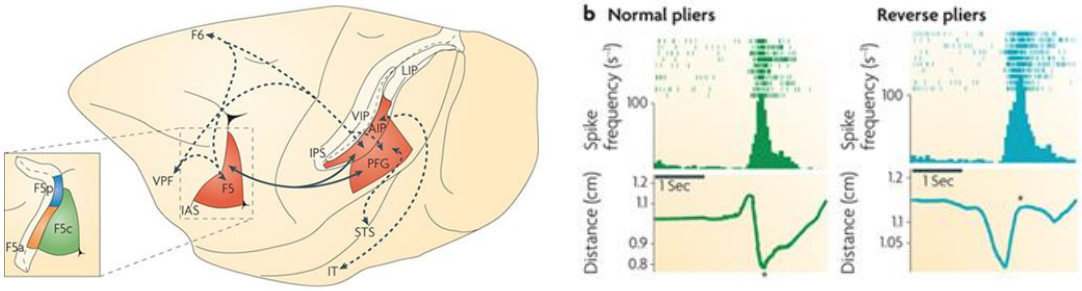
- the neurons are activated even if we think about the movement
- A – perform the movement → activation of somatic sensory cortex and motor cortex
- B – think abound the order of movements and execute it → activation of the supplementary motor area as well
- C – just think about the movement → only the supplementary motor area was activated

Lesion of the supplementer motor area results in a deficit in the bimanual coordination.

- 5 months after the lesion the animal was not able to perform the same movement
- to stop the mirror action of the hands a healthy supplemental motor area is required
- babies have this mirror movements, but as the brain develops it stops

Neurons in the F5 and IPL regions respond to interaction with objects: **the parieto-frontal mirror neuronal circuit**

- The mirror neurons encode the goal of the movement
- they are activated when not when performing the movement, but when you reach the goal of the movement (e.g., grabbing something)
- There are selective mirror neurons for the **extra personal** and **peripersonal space** operating in an observer-centred spatial framework.



V. Summary

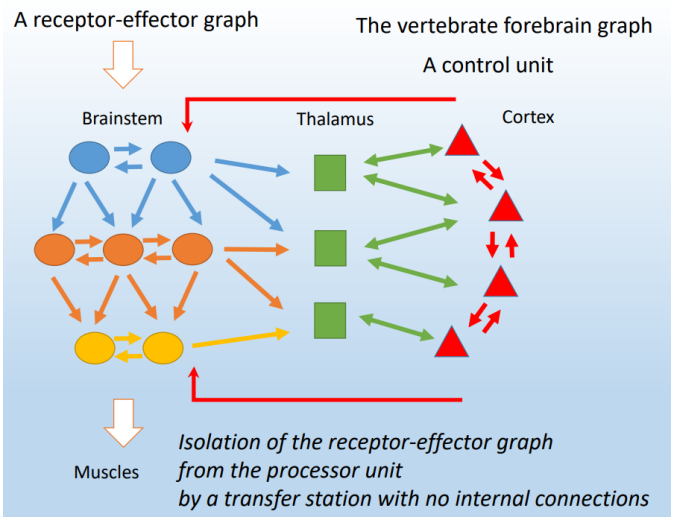
- Motor areas are characterized by somatotopic organization (the position of the neurons determine the activated muscles in the body)
- Neurons in the primary motor cortex encode the direction of the force, rate of change of force, and velocity of movement (these neurons respond with increased or decreased firing rate)
- The premotor (external cues) and supplementer (internal cues) cortical areas prepare the motor system for the movement
- The posterior parietal lobe provides the visual information for the targeted movements

Thalamus

Lecture 8

The thalamus collects a lot of information and transmits it to the cortex.

All cortical areas project to the thalamus, all thalamic neurons project to the cortex. All cortical areas are in reciprocal connection with the thalamus.



The *brainstem* receives almost all the inputs, it has a complex internal connectivity. It has the premotor neurons; it dictates the muscles and is responsible for the majority of our behaviour.

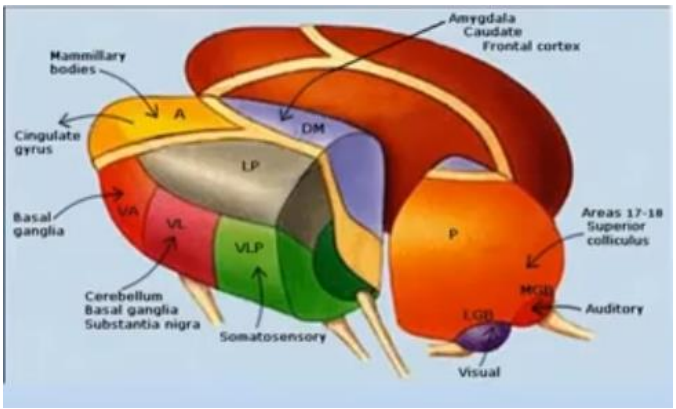
During evolution, the *thalamus* and the *cortex* were 'added' to the brain to increase its complexity. (Thus, we are capable of more complex responses.)

The cortex is isolated from the rest of the brain. The thalamus acts as a gate: collects all the glutamergic information from the brainstem and projects it to the cortex. (*Indirect connection* between the brainstem and the cortex.)

The cortex continuously discusses what is going on in the rest of the brain, with the thalamus. Once the decision is made, the cortex projects the information back to the brainstem.

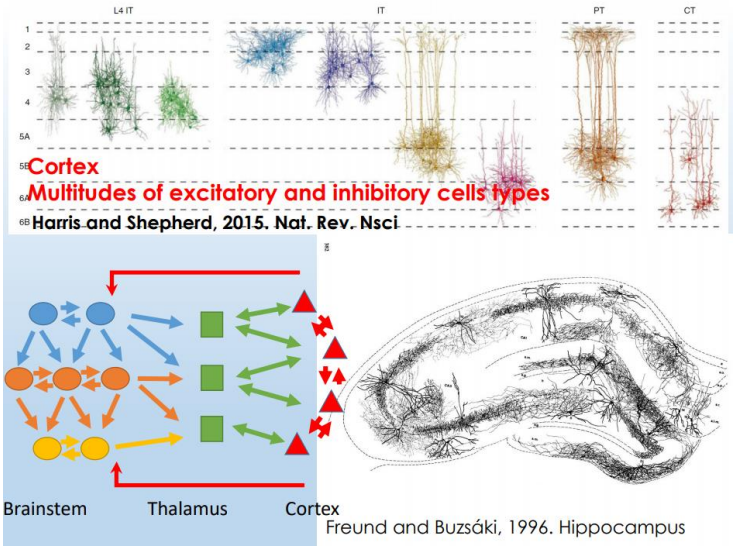
Comparison of thalamic and cortical networks

<u>Cell types</u>



The various parts of the brain are innervating different parts of the thalamus. The right and left parts of the thalamus are separated. The parts of white matter in separates the different nuclei in the thalamus.

The thalamus processes primary sensory information.



Most cortical layers have 6 layers (laminae), in every layer there are different cell types. Cell types can be classified by the structure of their soma-dendritic domains. The other major features are the inputs and outputs they receive.

The thalamus is a lot simpler than the cortex. (less cells, less connections)

Origin of cortical inputs

The entire thalamus is an input region of the cortex. In the olfactory bulb, the mitral cells project directly to the prefrontal cortex. Besides that, we have a handful of small nuclei in the brainstem, which have direct projection to the cortex, which does not go through the thalamus. These do not contain glutamate. Neurons in these pathways can innervate almost half of the collateral.

Origin of thalamic inputs

Almost the entire brain projects to the thalamus (including the entire cortex). The number of projecting areas is much more than in case of the cortex. (Considering number of projections, the thalamus is more complex than the cortex.)

Types of inputs

Thalamus: axon terminals are highly variable in size and complexity

All the synapses established by the axon terminals (in case of excitatory terminals it can be up to 50) are submerging on a single post synaptic target. If we have such a complex connection between two neurons, the response will be powerful.

Cortex: little variability in terminal types

Almost in the entire brain, the axon terminals contain one or two release sites (synapses). In the cortex only the granule cells have giant terminals with many synapses, all the other cells establish a single synapse.

Cortical vs. Subcortical regions

In the VPM:

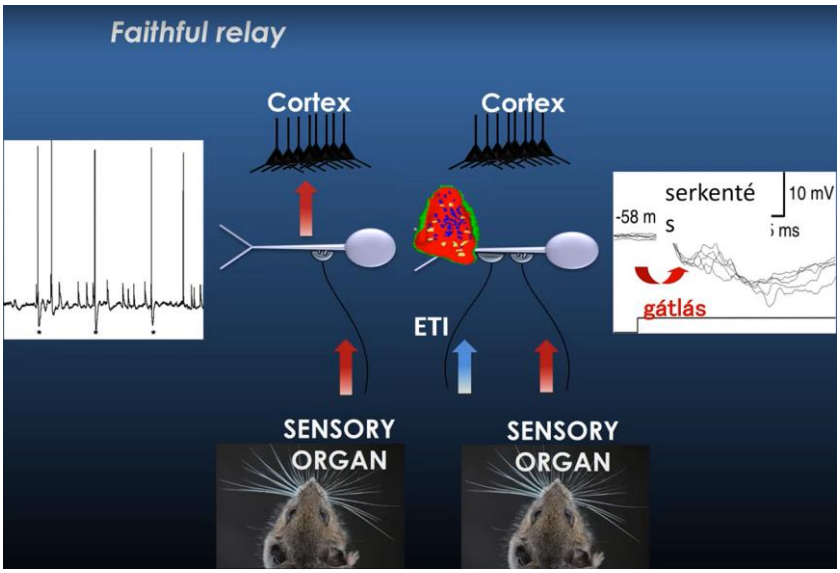
Subcortical terminals are giant, these are carrying sensory information. On the other hand, the cortical terminals are small and numerous.

In the pulvinar:

Besides the small cortical terminals, there are many huge ones as well. The huge, very important input to these structures is coming from the cortex. This region has no glutaminergic input from the subcortical area.

The actual structure, the size of the terminals, the complexity of the terminals does matter, how the information is handled in the thalamus.

How the thalamus handles the information

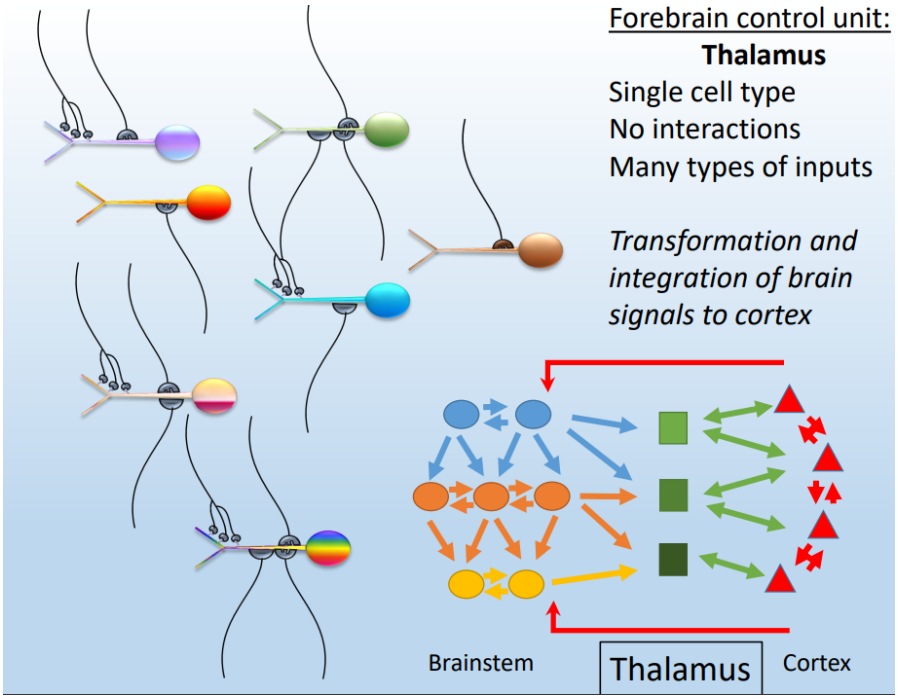


The inhibitory input can block the synaptic transmission. The second neuron is combining the information from two different pathways.

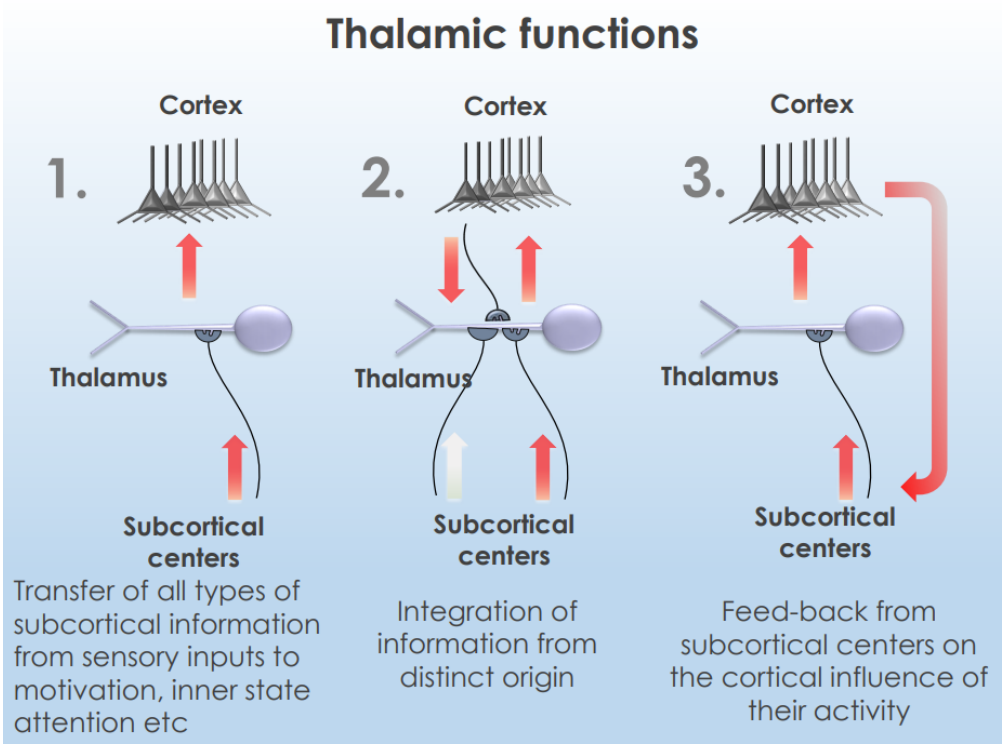
The thalamus receives:

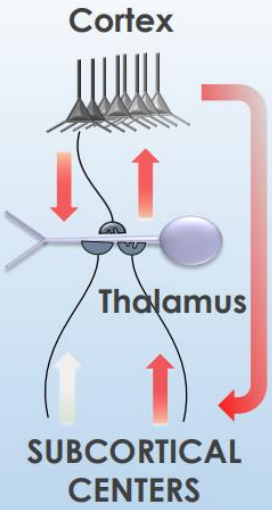
- a multitude of terminal types
- from many brain regions
- and integrate them in highly variable ways

The computational power of thalamus lies in integrating variable inputs rather complex interaction among the neurons.



The vertebrate forebrain graph is not a receptor-effector graph, but a complex internal "state generator" graph.





Instantenious control of cortical activity by integrating various cortical and subcortical activity via multiple mechanisms

Why many types of inputs?

The activity of different brain centers is highly heterogeneous these need to be integrated in a highly variable manner

Why a single type of neuron?

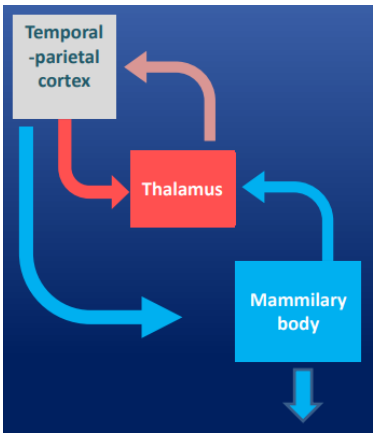
- The transformation of many differenc code into a single (cortical) language
- Easily switch global cortical states.

Cortex and thalamus: continuous interdependce

Memory

Lecture 9

Multiple embedded loops:

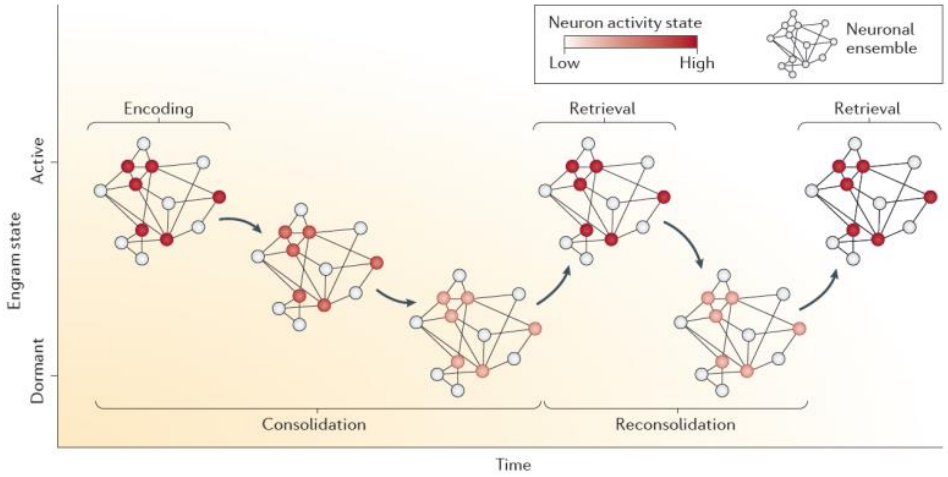


The temporal-parietal cortical areas project to the thalamus (+ there is back-projection). It also projects to the mammillary body (in a longer loop), that projects to many other places. Then, the loop closes back to the anterior thalamus.

Richard Semon and the concept of engram (memory trace):

- Engram is a *persistent alteration in the brain as a result of a specific event*. (Something needs to be permanently changed in our brain.)
- The content of the engram is linked to the information perceived during *encoding* and *predict what can be recalled later*. (We will remember those events which are important to us.)
- A major feature of engram is *ecphory*, the ability to change behaviour when reactivated with the appropriate keys. (The memory trace is able to change our behaviour.)
- The engram is in a *dormant state* between encoding and retrieval. (It is there, but "sleeping")

The life cycle of the engram:



During encoding, a subset of a neuronal ensemble gets activated, the connectivity between them is strengthened. After a certain amount of time, the neurons and their joint activity will diminish. This process is called *consolidation*. The neuronal ensemble must be reactivated many times in order to have a permanent engram. Consolidation takes place during sleep.

After retrieval, there is *reconsolidation* if we block it, the memory trace may be gone.

Based on experiments:

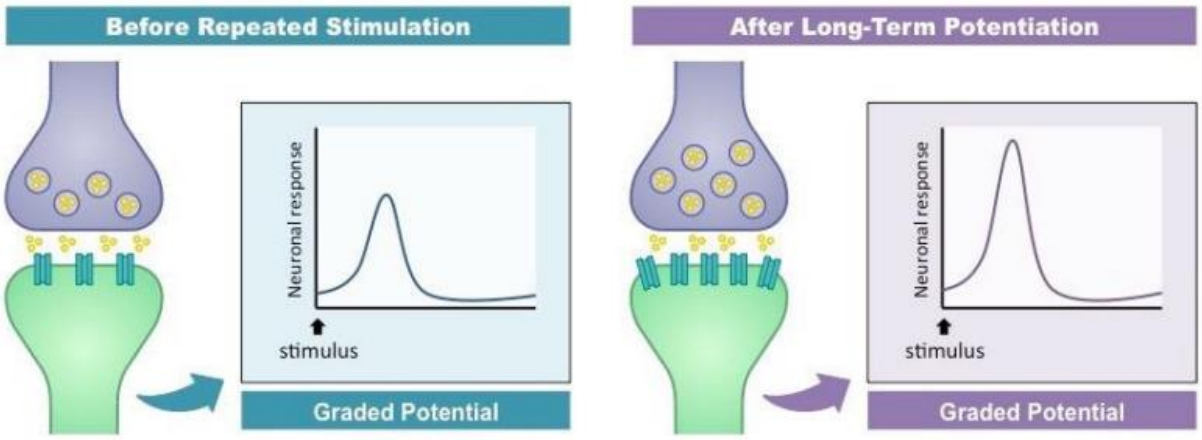
- The new memory trace is persistent, and it is linked to a special event, the linear track.
- It is also linked to the perceived information since it is possible to show that certain key features of the surrounding (the lab) are important for the animal to learn the task.
- Memory trace is able to change the behaviour.
- It gets into a dormant state (sleep replay only for 24 hours)

Formation of memory traces

Synaptic plasticity

Donald O. Hebb:

> When an axon of cell A is near enough to excite cell B and repeatedly or persistently takes part in firing it, some growth process or metabolic change takes place in one or both cells such that A's efficiency, as one of the cells firing B, is increased.
>
> (Originally, A is not able to fire B, but then comes a certain situation, when A starts to fire before B, and is able to take part in firing. The influence is so strong that A is able to fire B. If it happens repeatedly and persistently, then there will be an unknown growth process or metabolic change, the connectivity (the synaptic strength between them) between the two neurons will change.)
>
> "Neurons that fire together wire together."
>
> Long-term potentiation



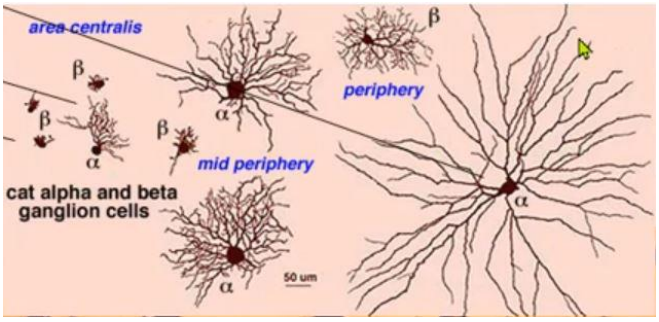
Summary:

- Memory encoding results in persistent structural and functional changes in the synapses of neurons participating in the engram.
- The engram is encoded and maintained in large scale neuronal networks consisting of different brain regions.
- The memory traces in first encoded, followed by a consolidation period and a dormant stage. Appropriate stimuli reactivate them.
- An engram has the capacity to alter behaviour similar to sensory stimuli.
- Engram can now be studied with high spatial and temporal resolutions.

Visual Processing

Lecture 10

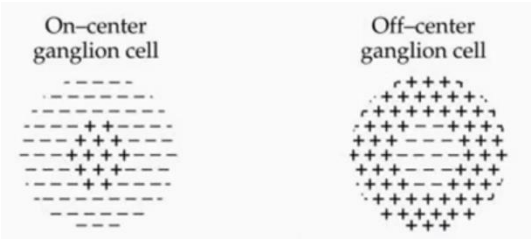
Types of retinal ganglion cells



- <u>cat alpha ganglion cells</u>
  - bigger
  - detect luminous changes
  - aka *magno cells*
- <u>cat beta ganglion cells</u>
  - smallest
  - their AP are continuously maintained, as long as the stimulus is overlapping with the receptor field
  - aka *parvo-cells*

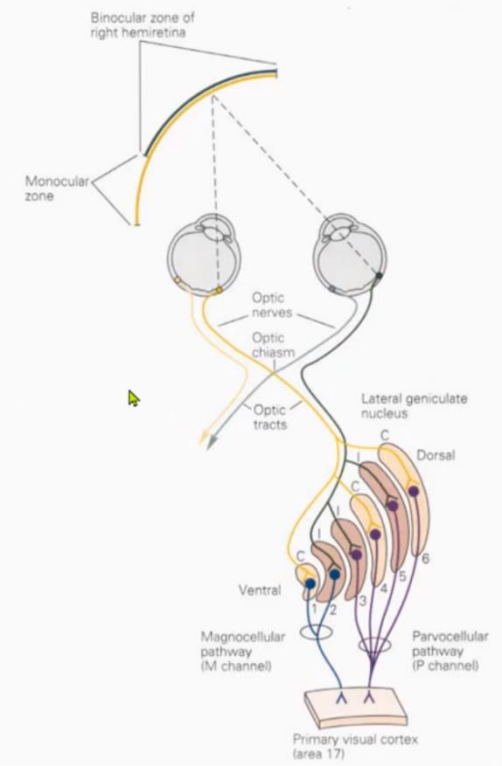
cell body and axon length get bigger as we move toward the periphery

Receptive field



- ganglion cell receptive field is circular
- centre surround arrangement
- each ganglion cell has this type of arrangement
- *on-centre ganglion cell*: centre responding to the amount of light
- *off-centre ganglion cell*: decrease of light → cell becomes more and more excited
- both of the area is surrounded with an *antagonist area*
- *centre part is dominating* over the surround area
- the information is transmitted to the thalamus, and in the thalamus similar receptive fields conveyed up to the visual cortex

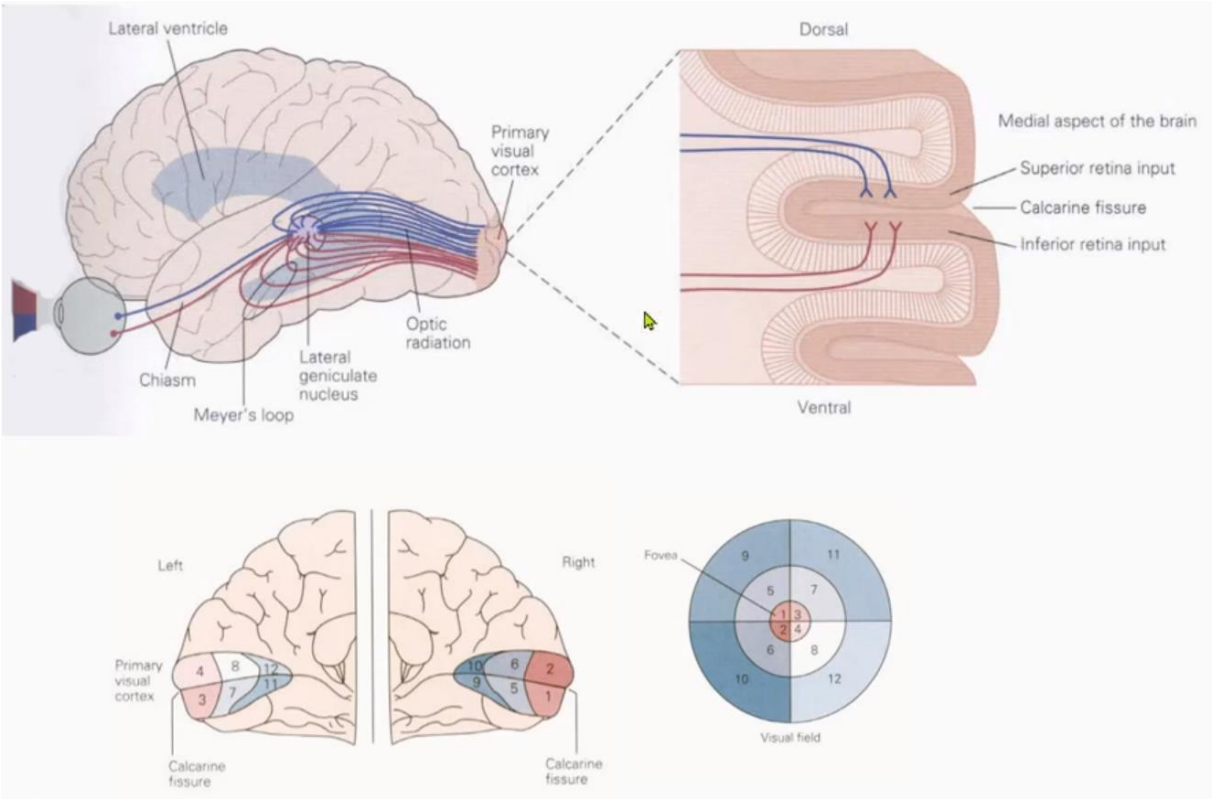
Magno- and Parvo-fibres



- from the nasal half of the retina the optic nerves cross each other (optic chiasm)
- behind the optic chiasm we can find the optic nerve
- Lateral geniculate nucleus:
    - 6 layers
        - consists of laminae and optic fibres
    - receive alternatively magno and parvo cellular inputs from both eyes
    - retinal fibres from the temporal retinal side, from the same side
    - opposite eyeball contributes from the nasal side of the retina
    - C1: magnocellular layer, input from opposite eyeball
    - C2: magnocellular layer, input from large alpha ganglion cells from the eyeball on the same side
    - C3-C6: parvocellular layer, input from parvo cells/beta cells
        - C3: input from ipsilateral eye (same)
        - C4: opposite eyeball
        - C5: same eyeball
        - C6: opposite eyeball
- these fibres arrive and ascend together up into the primary visual cortex (area 17)
- magno cell and parvo cell fibres are running together and innervate the primary visual cortex
- retinaltropy is detectable within each thalamic layer

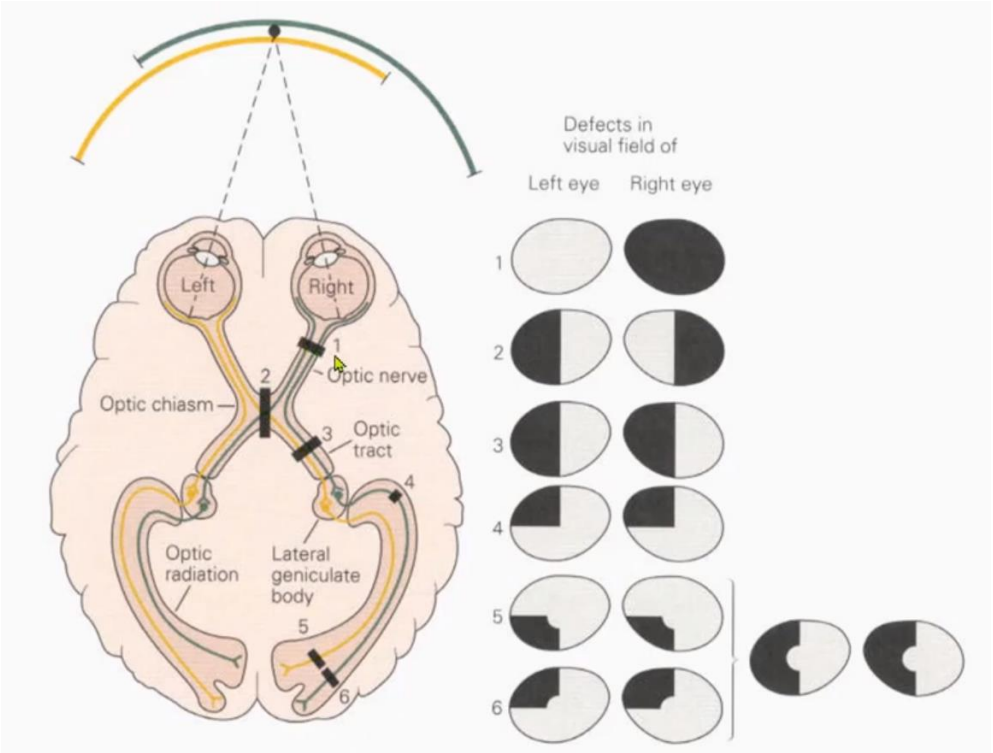
Visual information gets retinotopically to the cortex: (area 17)

- topology:
    - upper visual field, which is detected by the lower retinal ganglia cells, they project into the lower half of the visual cortex
    - upper visual filed represented in the lower half, and vice-versa
    - left visual hemisphere represented in the right hemisphere of the primary visual cortex, and vice-versa
    - vertical meridium: splits the visual hemisphere to left and right side



Visual pathway damages:

- 1: same eye's sight is lost
- 2: scotoma: loss of hemisphere
- 3: hemieropsia, losing the opposite hemisphere in both eyes
- 4: quadretonomia: quarter of the sight is lost

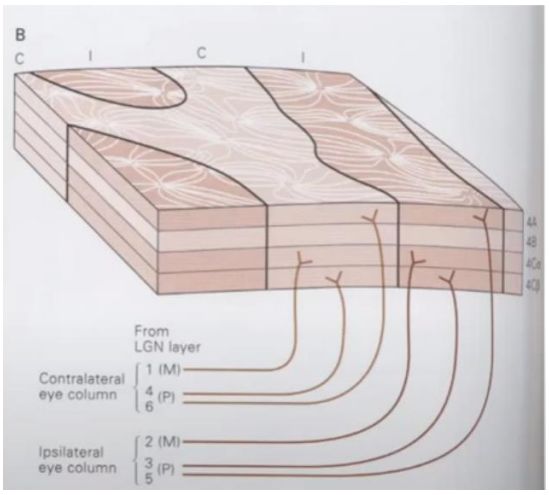


Several subregions of the visual cortex

- V1:
  - main visual cortex
- area 18:
  - ventral and dorsal domains
- complex network

Columnal structure of the cortex

- principal cells: pyramidal cells
- structural columnarity:
  - pyramidal cell dendrites emerge toward the surface
  - they are organised columnarly
  - incoming fibres, and local fibres are also perpendicular to the surface of the cortex
- functional properties are also following the columnal structure
  - stimulus orientation is organised in a columnar fashion



How the input arrives to the cortex from the thalamus

- visual thalamus has 6 layers
- each layer represents magno or parvocellular inputs
- information travelling transsynaptically
- larger layer 4 represents alternatively the inputs from the eyes
- ocular dominance pattern / ocular dominance columns
- ocular dominance is a mapped feature

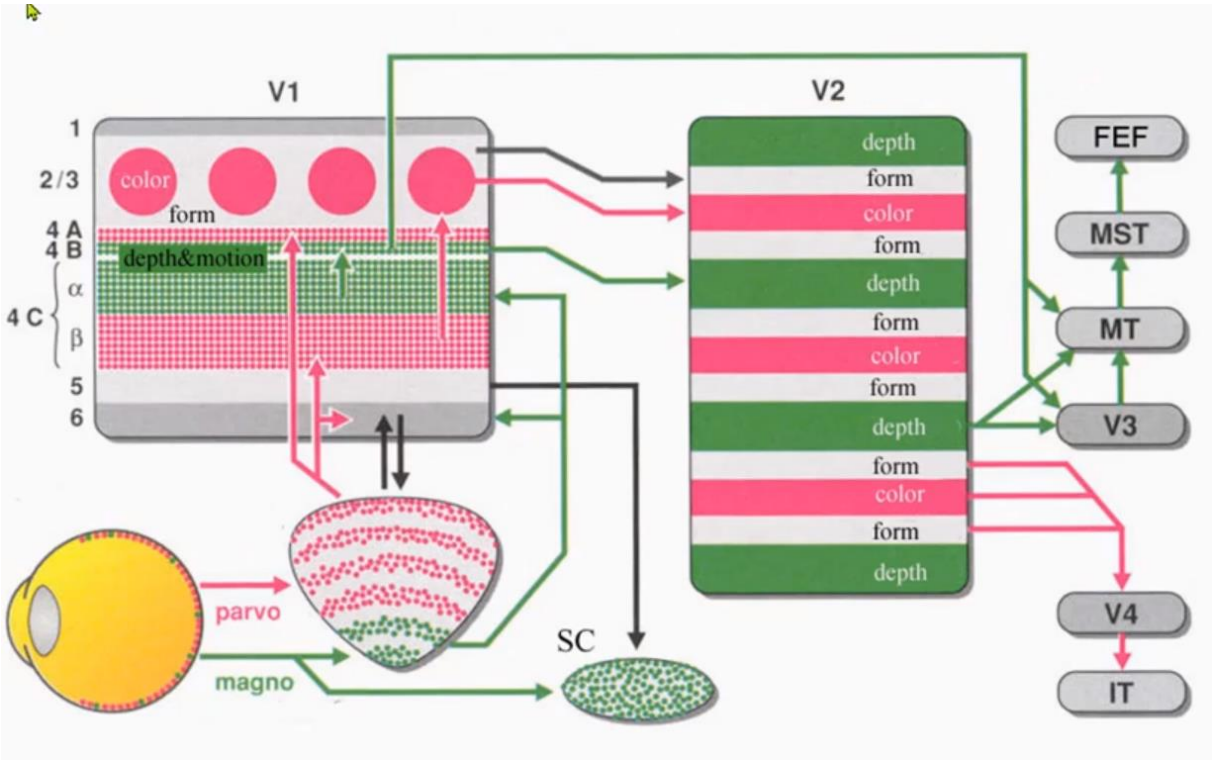
Colour engaged cortical cells

- cytocrome-oxidaze columns (blobs)
- in layer 2-3
- blob areas are containing cells which more sensitive to colour
- it is not a strict separation
- retinotopy is strictly present in the primary visual cortex

Magno-and Parvo pathways and their connection in the cortex

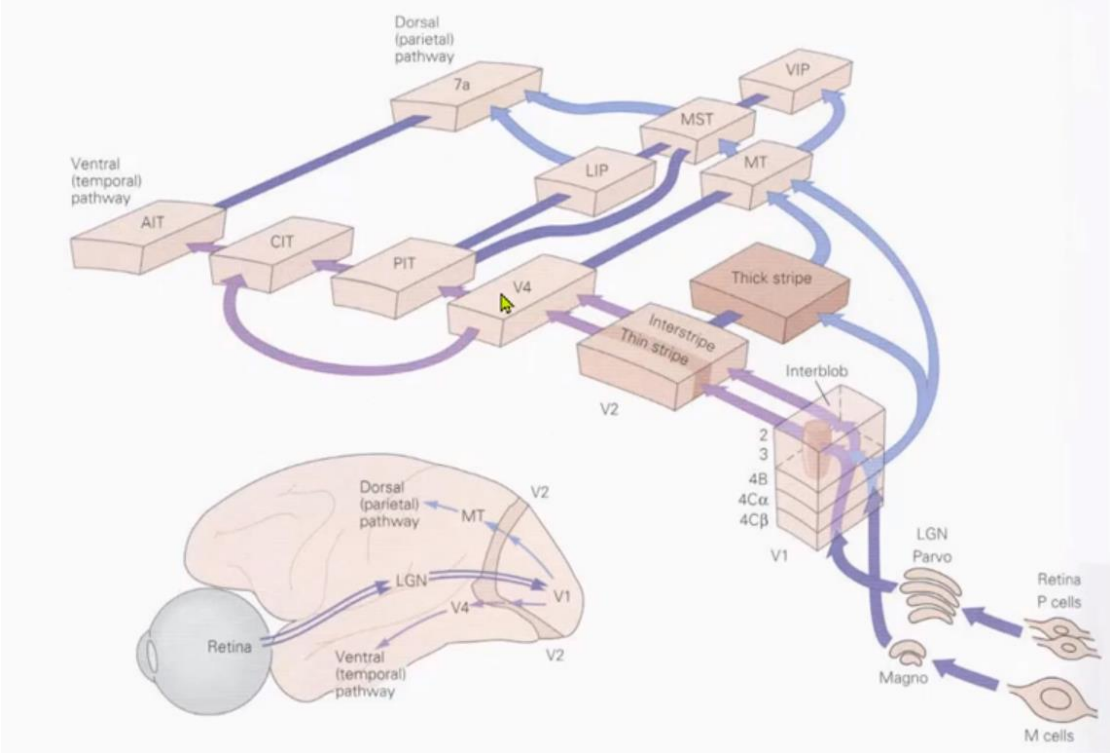
- V1: primary visual cortex
  - laminar fashion
- V1 to V2:
  - modularity distribution is detected
- this type of distribution is not detected at further places

- Ventral stream:
  - form and colour information are carried by *parvocellular pathways* toward the temporal lobe (V4, IT)
  - „what pathway”
- Dorsal stream:
  - motion signals, carried by *magnocellular pathways* are leave towards the dorsally located visual located areas (V3, MT, MST, FEF (in the heart of the frontal lobe))
  - „where pathway”



Interconnectivity between dorsal and ventral streams

- the strict hierarchy is not present
- motion and colour (V4) excite different cortical regions (experience)



In MT (V5) motion direction preferences

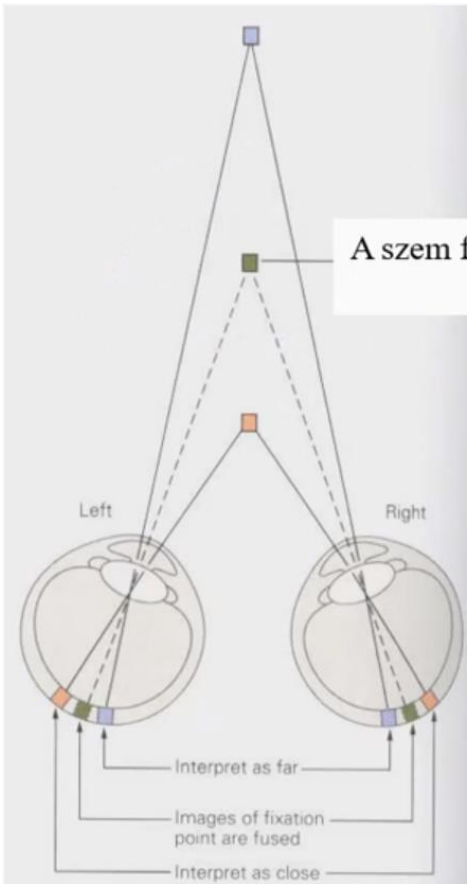
- motion sensitive cells show direction preference.
- MT lesion creates loss of correlation in motion detection
- MT receives information from area 17

Aperture problem:

- receptive field size is smaller in V1, compared to in V5
- V5 cells inherit their properties from V1
- problem: V1: grating movement (?)
- due to the small size of V1 cells receptive field → aperture problem
- MT cells are solving the aperture problem
- MT cells represent a higher order of visual cortex, which is not present in V1

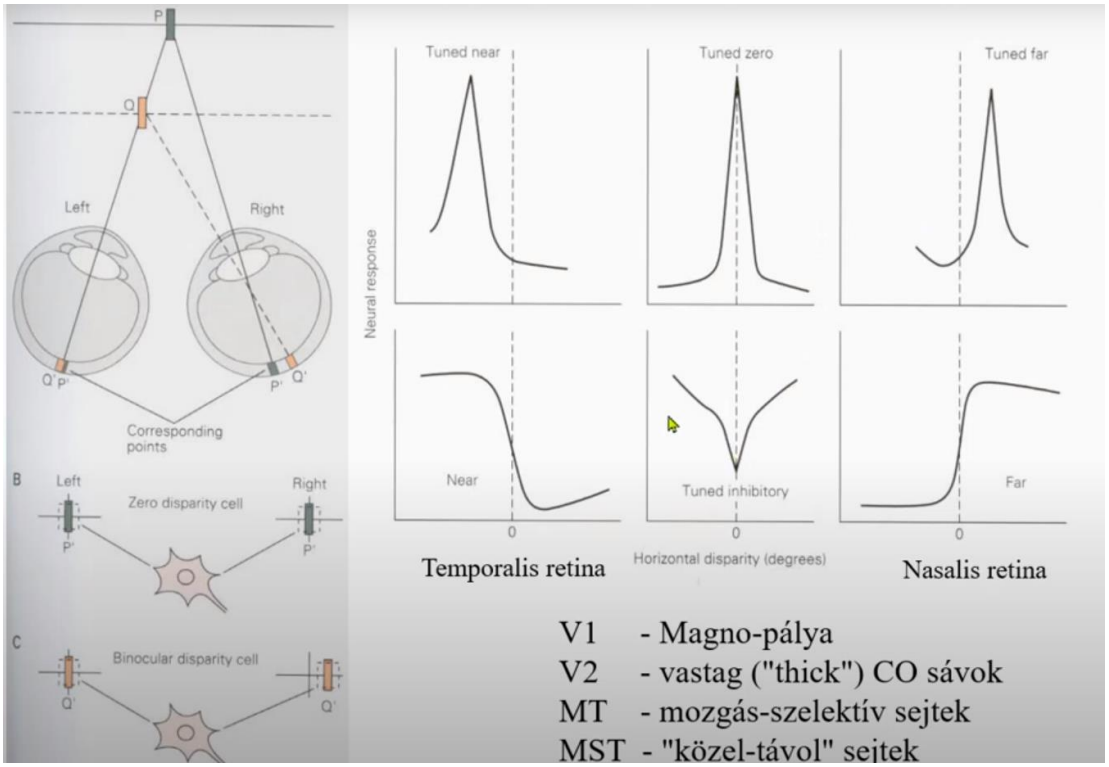
Monocular stereopsis (> 30 m)

- due to the position of the eyeball, which has a conjugate movement and a common focusing point
- also implement some learned features:
    - something is similar size -> difference of hight is considerable
    - perspective
    - occlusion
    - hue (lighter object is closer)
    - motion parallaxes:
        - near objects move opposite direction fast
        - behind focal point: move slower and follow the same direction
- determining features:
    - begins at the eyeball
    - if we take the fixation point, we consider the objects related to the fixation point
    - stereopsis is already detected in V1
    - stereopsis is largely carried by the magnocellular pathways



Disparity sensitive cells

- mainly in MST



V2 (V1) cells illusinic contour detection

- there are cells in V1, which are able to detect illusinic contour
- a fraction of the cells is able to detect illusinic contour

IT (Inferior Temporal Area) cells

- processing shape, form, and colour together
- neurons are sensitive to more complex shapes
- large receptive field
- common binocular representation
- bilateral lesion of IT indicates prosopagnosia

Binding problem

- how we perceive contours and identify the objects
- clue of the solution: temporal aspects of the signals and responses
- we know that neurons show synchronic and oscillating firing pattern
- solution: timing and synchronicity is key to the binding problem

Why do we need may visual cortex?

- many visual modalities must be processed at the same time

Types of cortical areas

- neocortex
    - heterogenous
    - laminated
        - 6 layers with sublayers (3, 4, 5, 6)

Cortical area differentiation

- cytoarchitectural, mieloarchitecture (fibers), chemoarchitecture (density of certain markers)
- connectivity features
- function maps
- receptive fields presence or absence
- modality types

Nomenclature of cortical areas

- Brodemann scheme are 17, 18, 19
- simpler/practical ways:
    - V1 (area17), V2 (18), V3 (19), etc.
    - MT, IT, etc

Neural population of the cerebral cortex

- Pyramidal cells or principal cells
    - Epical dendrites
    - axon from the cell body towards the white matter
    - 70% of all neurons
    - excitatory cells and use glutamate as neurotransmitter.
    - spiney cells:
        - pyramidal cells are present from layer 2 to layer 4.
        - star shape cells in layer 4
        - star-pyramidal cells in layer 4
    - their axon established asymmetric synapsis (Gray I. type)
    - circular vesicles
- small dendritic cells
    - they use inhibitory NT: GABA.
    - inhibitory neurons
    - establish symmetric synapses (Gray II. type)
    - pleomorf vesicles
    - 20 % of all neurons
    - present in all layers

Axon types

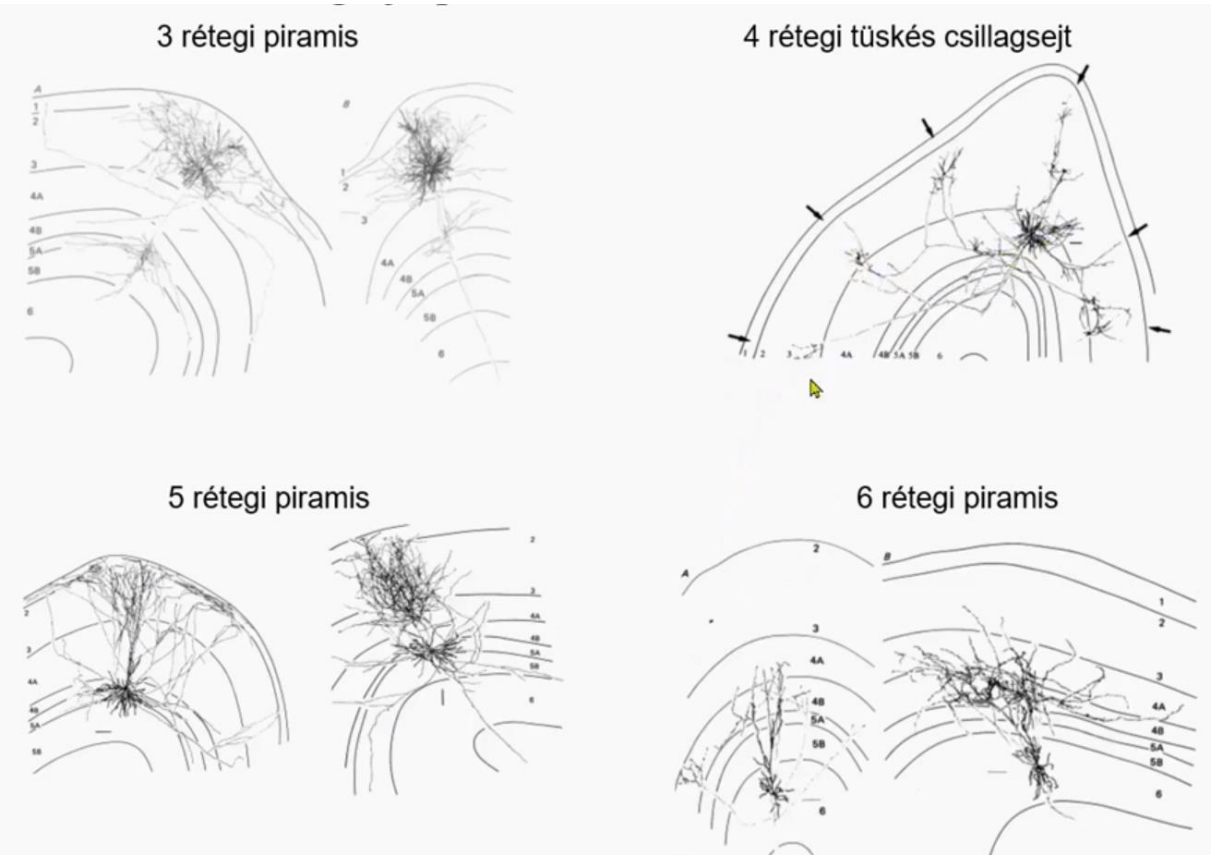
- great complexity

Synapse types

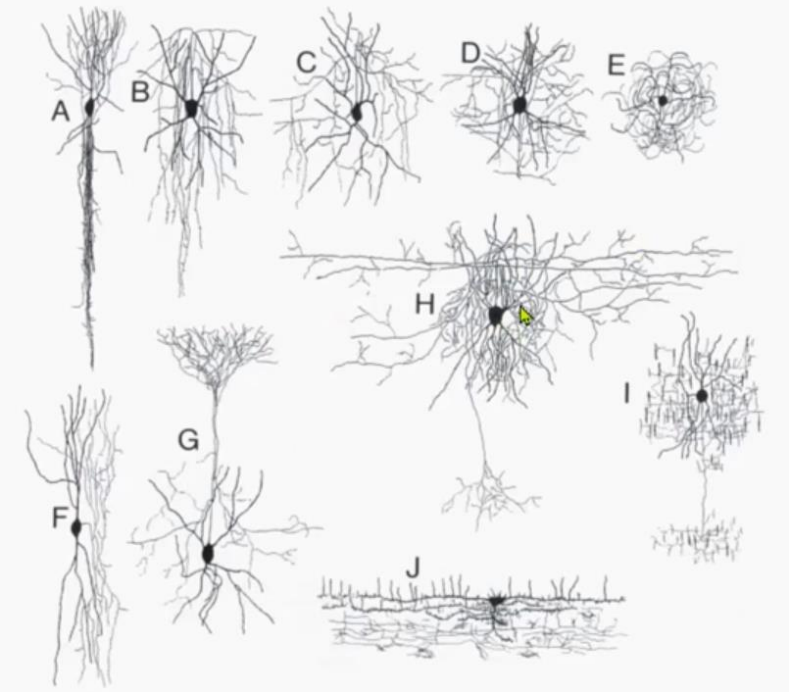
- asymmetric or symmetric

Main excitatory cell types

- targets:
    - other pyramidal cells



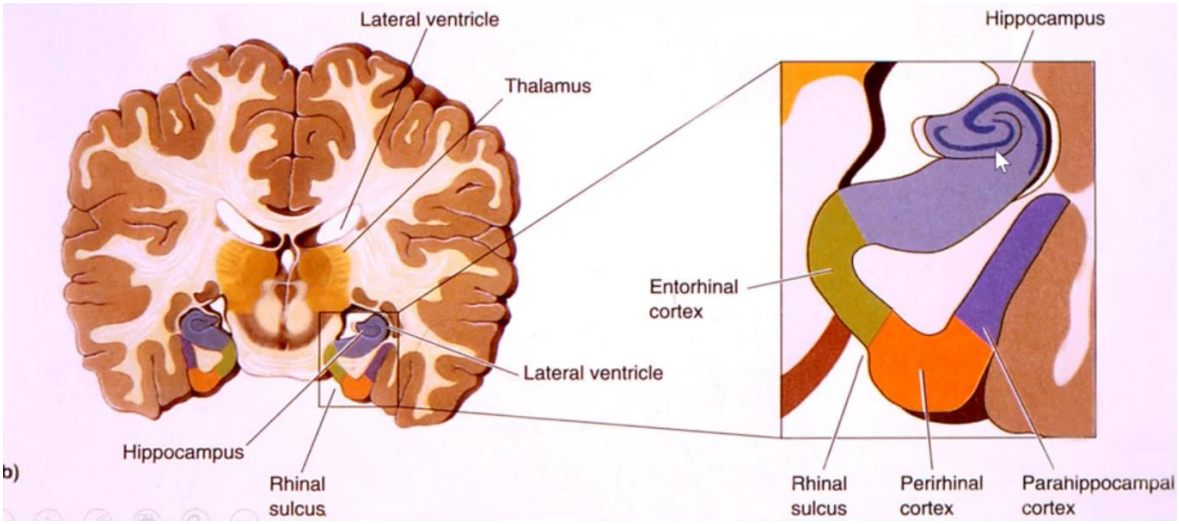
Inhibitory cell population



The Hippocampus I.

Lecture 11.

- archicortical structure
- reciprocal connection with all of the sensory and assocional cortical areas via the *entorhinal cortex*
- entorhinal cortex and perirhinal cortex: serve something like a funnel, which funnel all sensory cortical and assocional cortical inputs into the hippocampus.
- major output area: entorhinal cortex
- memory structure
- necessary for *burning in new memory traces*, but it *does not store memory*.



The hippocampus as a cognitive map

- every single neuron has a placefield: it gets selectively activated.
- they called *place cells*.
- with the help of the place cells the hippocampus can build a cognitive map of the surrounding area

Grid cells in MEC

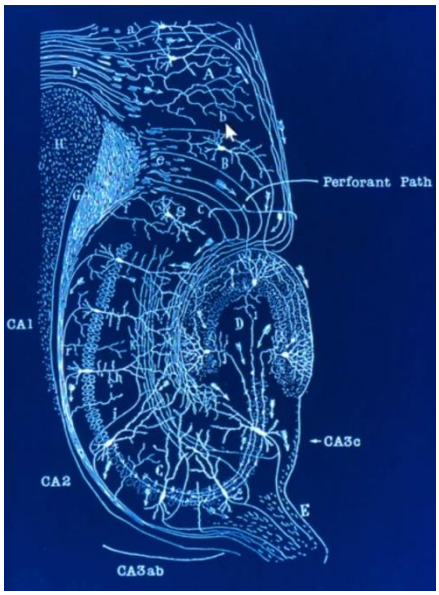
- grid pattern is generated by the cortex.
- the spacing and size varies between layers, grid orientation varies between neighbouring cells.
- cells maintain grid size and relative orientation, when moved to a new environment.
- there are exceptions when environment changes radically.
- grid cell field formation requires no visual input.
- the deep layers also contain head-direction cells.

Electro dependent activity

- theta activity
  - 4-8 Hz
  - oscillation EEG
  - during exploration and paradox sleeping
- sharp waves
  - quick, irregular EEG
  - during standing still, slow wave sleep and eating

The main regions, local projections of the hippocampus

- major subfields
  - dentate gyrus (D)
  - ammons horn (CA1, CA2, CA3)
- major cell types
  - principal cells in D
    - glutamate as NT
    - excitatory
    - the principal cells in the hippocampus: granule cells
    - granule cells' cell body forms a so-called stratum granulosum
    - granule cells' dendrites are radiating into the molecular layer.
  - principal cells in CA
    - pyramidal cells
    - basal dendrites form the stratum ories.
    - epical dendrites form the statum radiatum.
    - end tufts of the dendrites form the stratum loculosum moleculare.

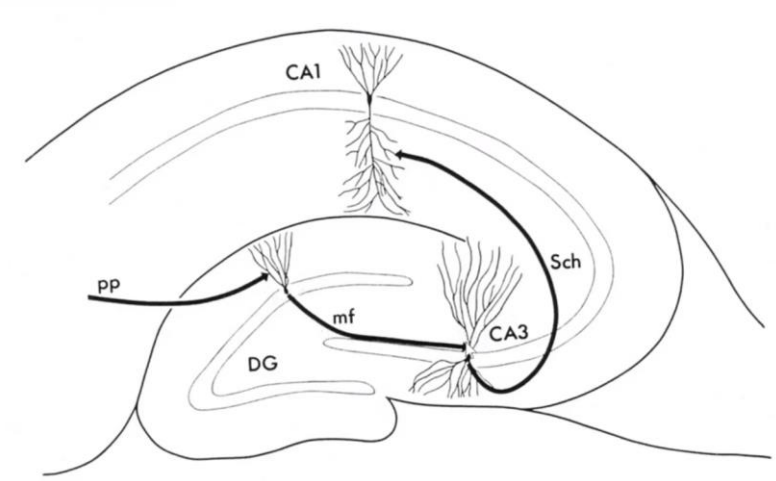


How is the hippocampus receiving inputs?

- perforant pathway:
  - major input coming from the entorhinal cortex.
  - it is penetrating through the subicular region to enter the hippocampus.
- the information terminates mainly in the dentate gyrus of the granule cells.
- granule cells have their axons, so called mossy fibres going to CA3.
- in CA3 the innervate the proximal dendrites of the pyramidal cells
- CA3 pyramidal cells project their axon to CA1, where they innervate mostly the mid-distal epical and basal dendrites, and the pyramidal cells then project back to the entorhinal cortex

The hippocampal trisynaptic loop

- mossy fibres innervate the CA3 pyramidal cells, their axons (*Shaffer collaterals*) innervate the CA1 pyramidal cells (in str. radiatum and ories regions), then back to the entorhinal cortex.



Local current connections in the hippocampus

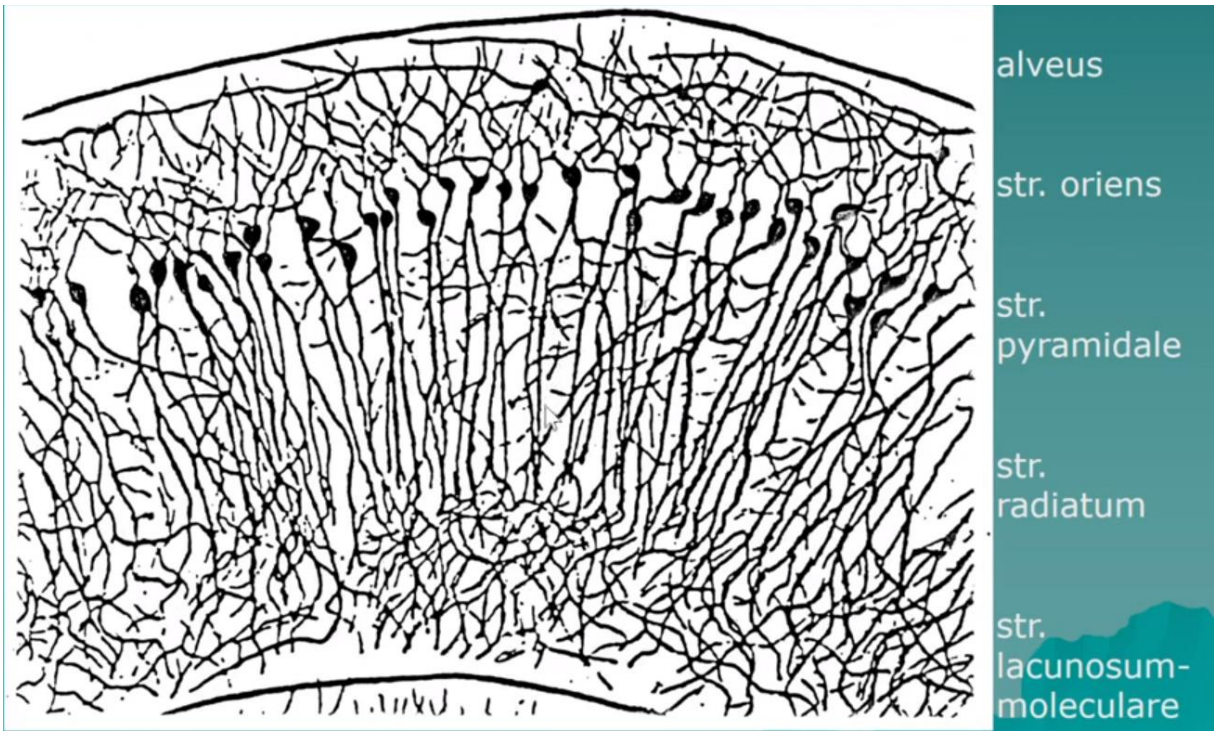
- granule cells receiving the perforant path input project into mossy fibers in CA3, they have local axon collaterals that arborize in the hilus of the dentate gyrus.
- in the hilus there are large number of different cell types
    - main type: mossy cells (mossy fibre collaterals innervate them, and they send their axons to the molecular layer innervating large number of granule cells)
- dendritic granule cells never innervate each other, their local collaterals and their dendrites are segregated into two different layers.
- however, these collaterals innervate the mossy fibers in the hilus
- CA3 receive their major input from mossy fibers, and they project as Shaffel collaterals in CA1
- in addition, they have local collaterals, by which they innervate each other, this enables the CA3 pyramidal cells to rapidly recruit a large number of neighbouring pyramidal cells into a population discharge pattern, that incorporates a large proportion of local CA3 pyramidal cells (this never happens in the dentate gyrus) → this is the so called sharp waves
- CA1 pyramidal cells have hardly any monosynaptic excitatory interaction between each other
- they have local collaterals that arborize the strictum ories of CA1, but they mostly innervate inhibitory interneurons.
- the major axon goes back to the entorhinal cortex and also the fimbria-fornix to subcortical regions.
- neither the granule cells of the dentate gyrus, nor the CA1 pyramidal cells are able to produce synchronous discharged pattern, because they innervate each other monosynapticly.

Major cell types of the hippocampus

- principal cells
  - excitatory, glutamatergic
  - 90% of neurons
  - pyramidal cells of the Ammon horn
  - granule cells of the dentate gyrus
  - mossy cells in the Hilus (associational cells of the dentate gyrus)
- inhibitory interneurons
  - 10% of neurons
  - transmitter: GABA
  - morphologically heterogeneous neurons

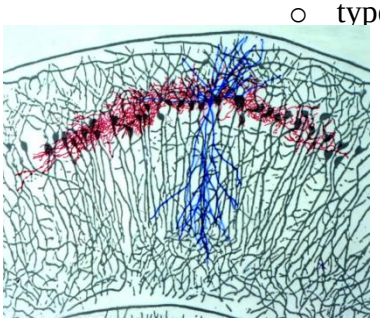
Principal cells

- excitatory
- transmitter: glutamate
- their dendritic tree receives 15-20 000 excitatory synapses mostly from other pyramidal cells.
- CA3 pyramidal cell axons can excite 40-60 000 other pyramidal cells in CA1 and in CA3.
- huge divergence and convergence → randomly connected network
- CA1 pyramidal cell local collaterals are sparse, arborize only the str. oriens, innervate mostly inhibitory interneurons.

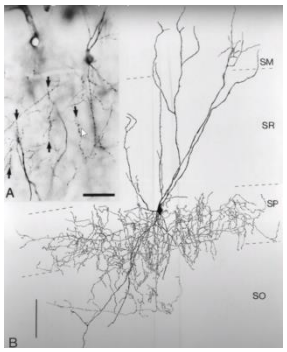


Inhibitory interneurons

- their morphological heterogeneity is associated with very precise functional specialisation.
- perisomatic inhibitory neurons
  - their axon is limited to the pyramidal cell body layer.
  - the axon is surrounding the pyramidal cell bodies, proximal dendrites, and axon initial segments.
  - function: *silencing* and *synchronising* pyramidal cell groups
  - types:



    - basket cells
      - their axon forms a basked around the pyramidal cell body → also named the basket cells.
      - one basket cell innervates more than 1000 pyramidal cell body and proximal dendrites.
      - dendrites have the same kind of distribution as the pyramidal cells.



    - axo-axonic (chandelier) cells
      - have bouton rows that are running in parallel with the epical dendrites of the pyramidal cells.
      - axo-axonic because, their axons innervate selectively the pyramidal cell axon initial segment.
      - why is the initial segment important? sodium gated ion channels are located here in the highest concentration → so we want inhibition, the most effective way if it near the AP generation space.
      - regulate the firing of principal cells.

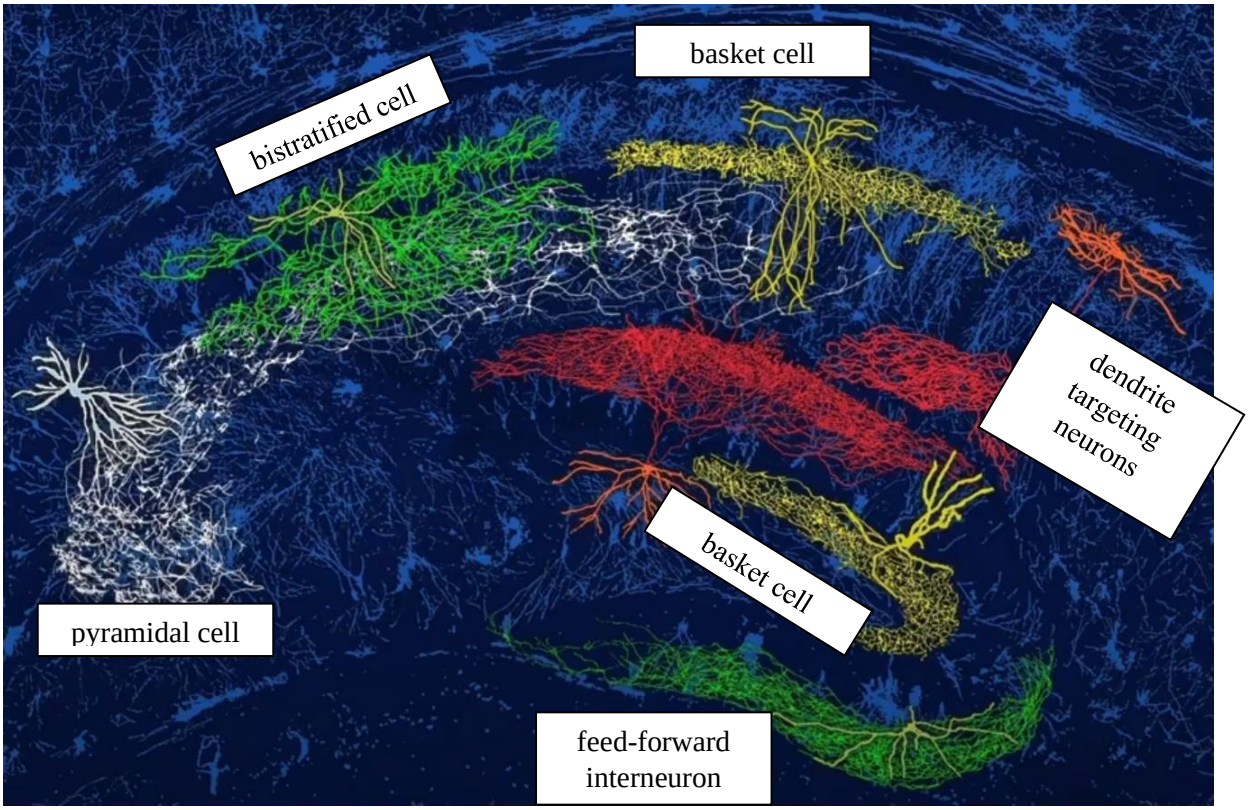
- dendritic inhibitory cells
  - their axon arborizes in the str. lacunosum-moleculare.
  - innervating the pyramidal cells distal dendrites
  - specialised to control the entorhinal input.
  - other dendritic inhibitory cell axons terminate in the str. radiatum and ories, where they regulate Schaffer collateral inputs.
  - function: *control the input to the pyramidal cells* that is coming from the entorhinal cortex.

Dendritic cell feed-forward inhibition

- the dendritic tree and the axon arborize in the outer two thirds of the str. moleculare, where the entorhinal input arrives.
- the cell regulates the entorhinal pathway efficiency, from where they receive their own input as well.
- so, this type of inhibitory neurons regulate their own efficiency via entorhinal afferents in function of their activity
- if there is too much excitation coming from the entorhinal cortex → these cells will be inactivated and reduce the efficiency of the entorhinal pathway.

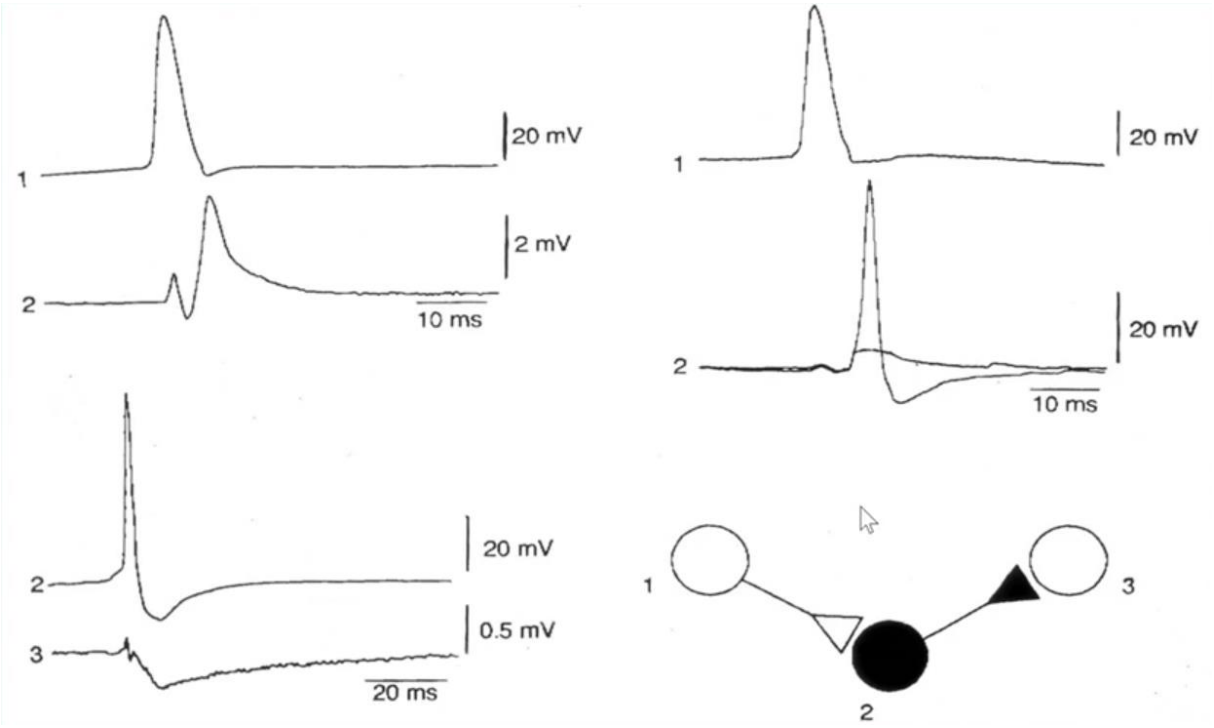
Dendritic cell feed-back inhibition

- the axon arborizes in the outer two third of the str. moleculare, where the entorhinal input arrives.
- the dendritic tree comes down to the hilus, where it receives its input from granule cell axon collaterals.
- this interneuron is inhibiting the perforant path / entorhinal input of granule cells as a function of granule cell output because they fire only if the granule cells fire.
- the cell regulates the entorhinal pathway efficiency as well, as a function of excitability of the dentate granule cells



Excitatory and inhibitory cell interactions

- can be measured intracellularly.
- cell no. 1 – excitatory because cell no. 2 fires excitatory postsynaptic potential
- cell no. 2 – inhibitory because cell no. 3 fires inhibitory postsynaptic potential
- basket cells induce big amplitude (2-3 mV) inhibitory postsynaptic potential (IPSP) in target pyramidal cells, via 2-8 axon terminals, which terminate in the cell body and in the most proximal dendrites.
- one basket cell AP can abort the pyramidal cells repetitive firing through 3 synapses.
- pyramidal cells are firing with no synchrony, but only until they receive an input from the basket cell, they hyperpolarize the principal cells, and when it releases them from hyperpolarization, they will fire AP in synchrony.

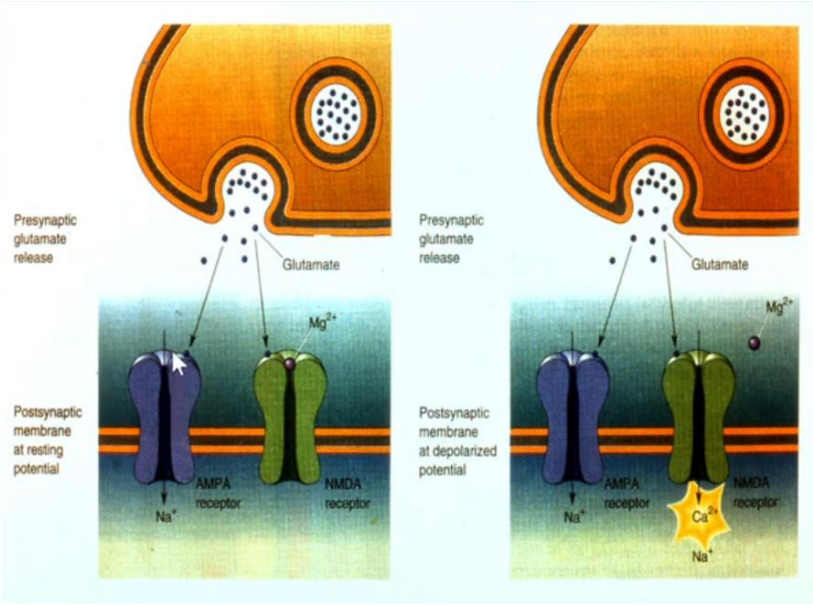


Synchronization of pyramidal cell population

- important because of synaptic potentiation / plasticity
- if the presynaptic axon and the postsynaptic neuron are discharged simultaneously → it can indicate increase in the EPSP:
- Long Term Potentiation (LTP) is the neuronal basis of learning a memory.

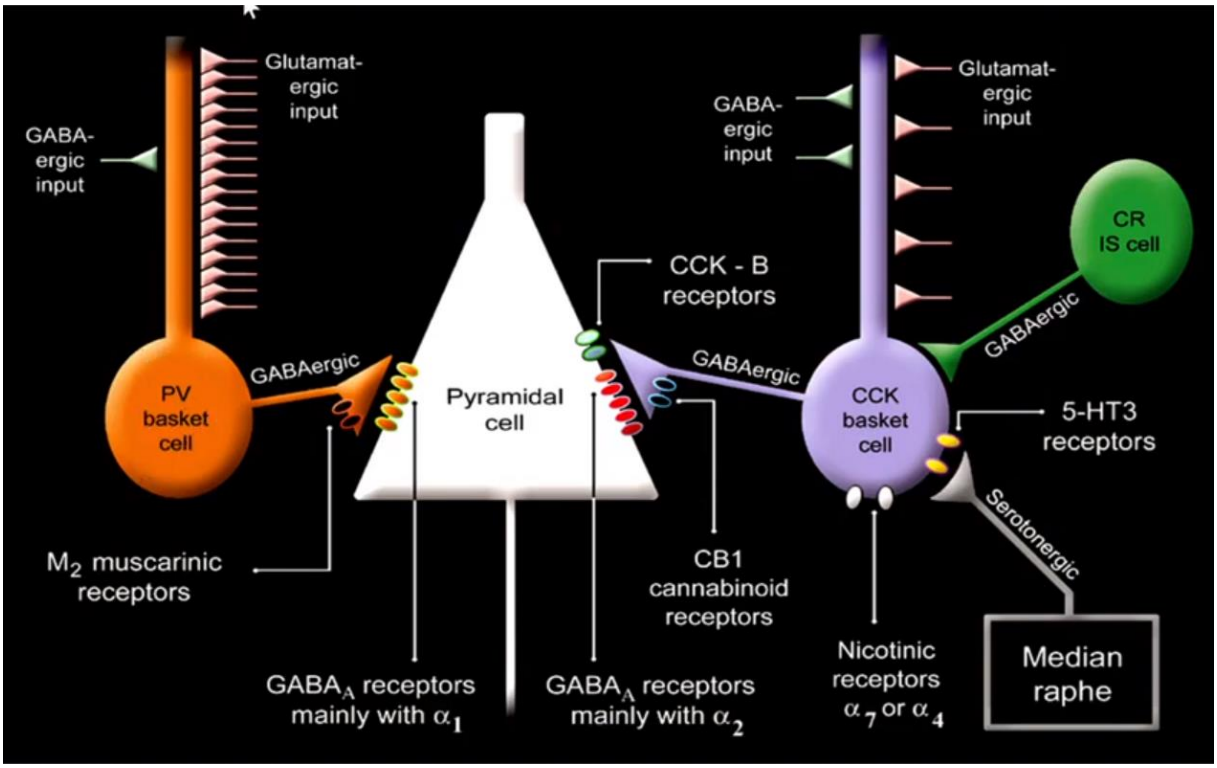
NMDA type glutamatergic receptors

- ligand and voltage gated receptors as well
- they are permeable for Na^+ and Ca^{2+} ions when they are open.
- when closed, it is blocked by Mg^{2+}
- backpropagating AP gets rid of the Mg in the NMDA channels at the same time, when glutamate is released



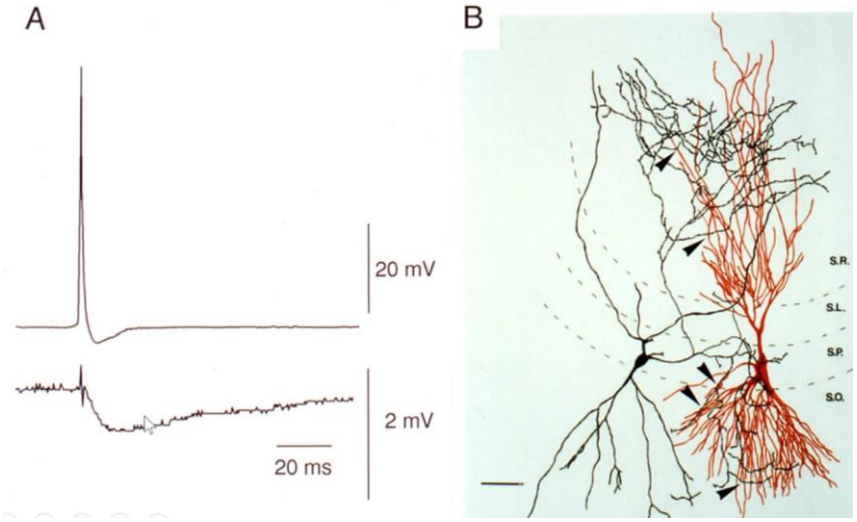
Basket cells

- they are heterogeneous.
- 2 types:
    - contains PV.
        - considered the rigid, non-plastic clockwork for oscillation, because of its input.
    - contains CCK
        - fine tuning device, that is responsible for the oscillations, the synchronous population discharges of principal cells as a function of their emotion and motivation state.



Dendritic inhibitory cells

- induce 0.5 – 2 mV IPSP in the pyramidal cells, through 3-18 synapses, which are located in the distalis dendritic tree.



Dendritic inhibition

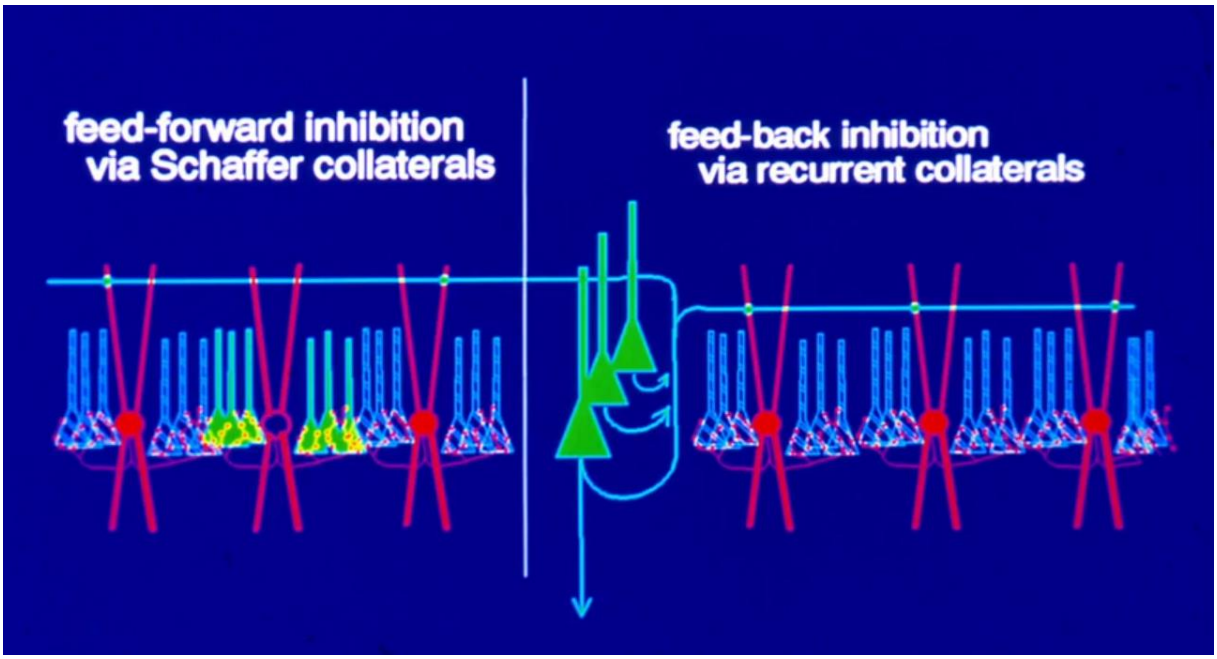
- regulates the excitatory input efficacy and plasticity.
- inhibits the voltage gated Ca-channels opening and the activation of NMDA receptors.

Perisomatic vs dendritic inhibition

- perisomatic inhibition is responsible for controlling the output of principal cells, synchronizing the output of large groups of principal cells, synchronizing them rhythmically at certain frequencies generating oscillation.
- dendritic inhibitory cells have nothing to do with the direct control of output, they are controlling the input of principal cells, but not only the efficiency of the excitatory input, but also the plasticity, because they are able to prevent Ca skip generation, which is one way of Ca entering the postsynaptic cell and the enter of Ca is necessary for any kind of synaptic plasticity, but also it is able to prevent NMDA receptor activation, because it is producing hyperpolarization out in the dendrites and (?) in the excitatory synaptic inputs, and if the membrane is hyperpolarized there and even if there is a backpropagating AP, the it cannot depolarize sufficiently the dendritic membrane, to get rid of the Mg block in the NMDA receptors

Hippocampal inhibition

- very efficient
- inhibition is dominating the activity of the hippocampal network.
- inhibition is powerful and the drive of inhibition is also very powerful.
- must be synchronized and timed precisely.
- this is the generation of oscillations of brain waves.


feed-forward inhibition
via Schaffer collaterals
feed-back inhibition
via recurrent collaterals

The Hippocampus II.

Lecture 12

The efficiency of inhibition in controlling pyramidal cell firing, as well as the excitatory drive of inhibitory cells is extremely powerful in the hippocampus.

The strength of pyramidal cell mediated activation of these inhibitory cells is also tremendously affected. Therefore, inhibition is so massive in the hippocampus, that there could be hardly any plasticity, hardly any neurons would be able to fire. What is the solution for this paradox?

Inhibition has to be synchronized and precisely timed. The result is the emergence of oscillations.

There are several different frequency oscillations in the hippocampus, the dominant ones are the *theta activity*, that characterizes exploratory behaviour, free moving and paradoxical sleep. The other one is *gamma oscillation*, that accompanies theta waves. Theta oscillation is the most characteristic activity pattern of the hippocampus.

What does "synchronization of inhibition" mean?

Basket cells are synchronising pyramidal cell firing in the hippocampus. Each pyramidal cell is firing in a wave in no synchrony, only until they get a massive barrage of inhibitory post-synaptic potential from a basket cell, then, when the basket cell mediated inhibition disappears, the action potential become synchronous.

How can we achieve synchronisation among the basket cells?

There is a cell assembly in the medial septum. The medial septum is a subcortical region, it contains GABAergic inhibitory neurons, and also cholinergic cells (most of those are excitatory). The GABAergic cells selectively innervate basket cells in the hippocampus. They inhibit inhibitory cells, thereby disinhibit the pyramidal cells. → rhythmic inhibition of inhibitory cells → rhythmic disinhibition of pyramidal cells.

Medial septum as the pacemaker of hippocampal theta activity

- MS units fire phase-locked to hippocampal theta. Following lesions of the MS-DBB, theta disappears from the hippocampus.
- Transection of fimbria/fornix: theta disappears in hippocampus, but MS neurons keep firing at theta frequency.

How can a few thousand pacemaker neurons synchronize membrane potential oscillation of millions of neurons in the hippocampus?

- Medial septal co-stimulation increases population spike amplitude evoked by perforant path stimulation.
- The slope and amplitude of the field EPSP does not change.
- The effect is non-cholinergic.

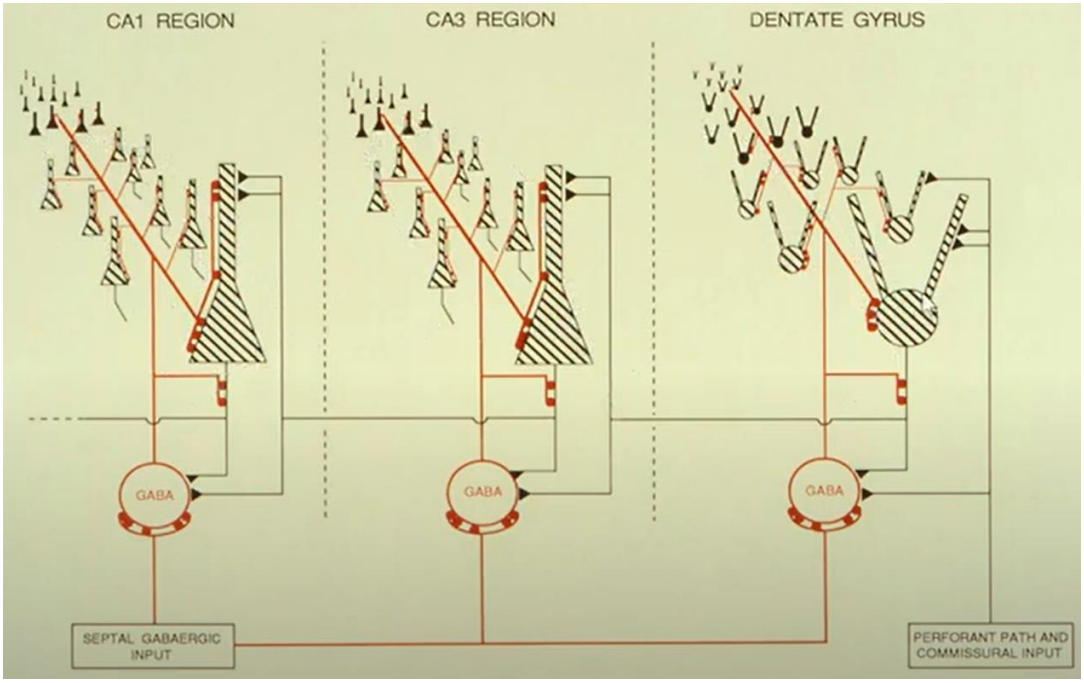
Two types of PhAL-labelled fibres in the hippocampus originating in the medial septum.

- Type 1 fibres were GABAergic, and selectively innervated GABAergic neurons. (large boutons)
- all interneuron types receive input from GABAergic sepptohippocampal.

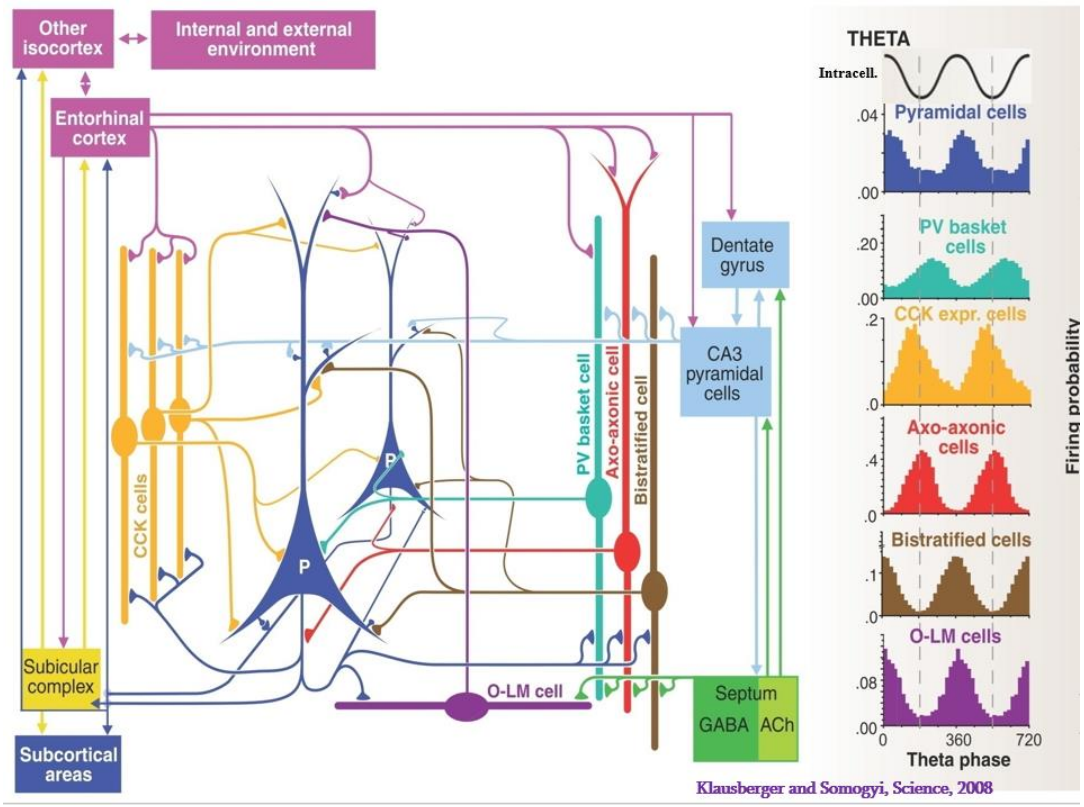
How theta activity can be generated by the septal pacemakers in the hippocampus and how numerically sparse projections can induce synchrony of millions of principle cells in another region:

The septal GABAergic pacemaker neurons selectively innervate local interneurons in the hippocampus. Each of these interneurons control a large population of principle cells.

Synchronization of hippocampal principal cells via GABA-GABAergic disinhibition

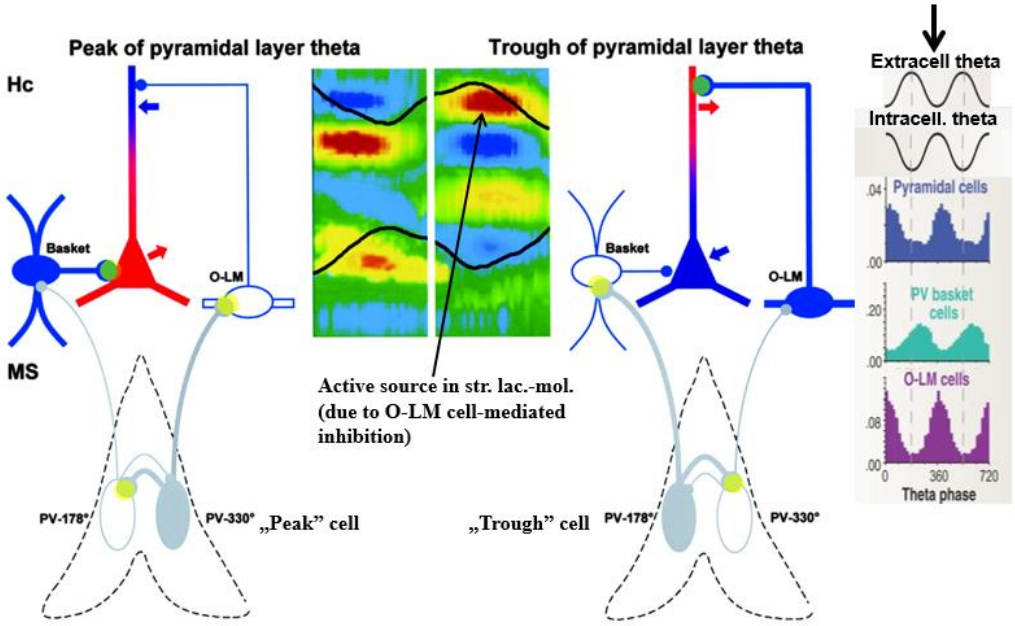


Basket cell firing is responsible for inducing the membrane potential oscillation, the synchronous membrane potential oscillation of principle cells.



Pyramidal cells are firing in the positive field of intracellular theta. Basket cells fire counterphase with the pyramidal cells. (That is because pyramidal cell firing is inhibited by basket cell firing.) This is the same in case of CCK expr. cells and axo-axonic cells. Bistratified and O-LM cells are dendritic inhibitory cells, they produce inhibition in the mid-distal or in the distal dendrites, influencing and controlling the efficacy and plasticity of incoming excitation. They fire in phase with pyramidal cells.

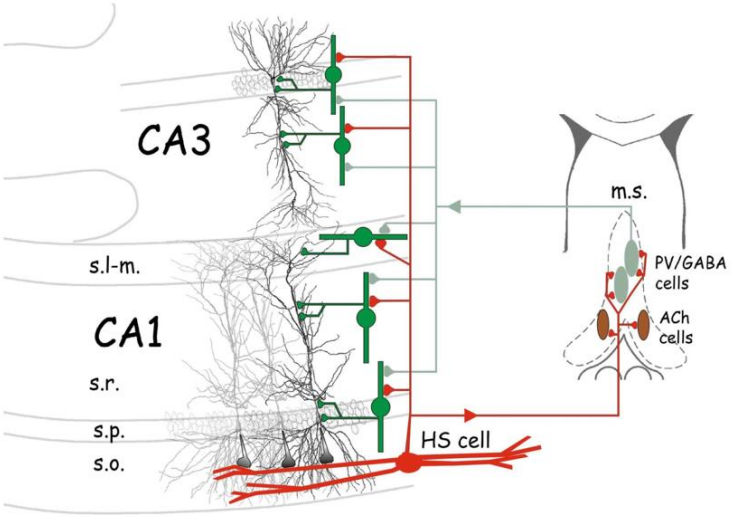
In the medial septum, we have two types of pacemaker cells, one of them is called peak cell, which fires at the peak of extracellular theta. The other one is the pyramidal cell, which is innervated by the basket cells (→ cell body) and the O-LM cells (→ dendrites).



Rhythmic activity of MS cells is generated by intrinsic pacemaker currents (I_{Na} and a low threshold outward I_K, de-inactivated at -80mV).

Individual pacemakers have to get synchronized in phase to dedicate a coherent rhythm to the hippocampus:

- recurrent collateral interactions among MS units
- hippocampal-septal feedback

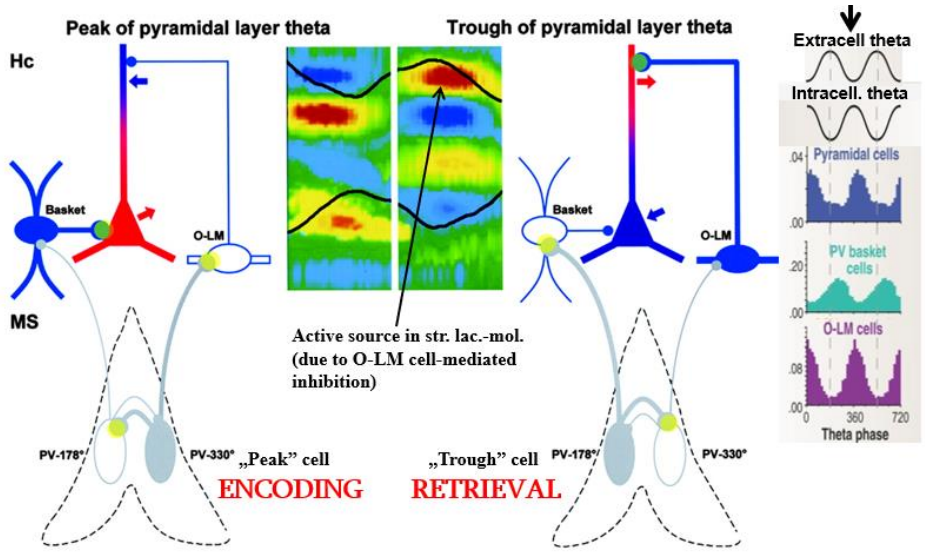


Hippocampal GABAergic cells project back to the medial septum. There they almost exclusively innervate the PV containing GABAergic pacemaker cells, and thereby they can synchronize them in phase. A GABAergic input is not there to simply inhibit, but it is there to synchronize. Each individual cell pacemaker cell in the medial septum will generate its own pacemaker rhythmic activity, but they have to be aligned in phase and this can be achieved by GABAergic back projection from the hippocampal special inhibitory cell type at the border of stratum oriens and the alveus. The major drive of this hippocampal-septal GABAergic cells are local collaterals of pyramidal neurons both in CA1 and CA3.

<u>Emergence of theta oscillations as a result of reciprocal sepptohippocampal network interactions</u>:

1. Enhanced cholinergic tone increases excitability in HIPP and absorbs SPWs.
2. Septal pacemakers induce rhythmic basket cell activity and pyramidal cell synchrony in focal hot spots in HIPP.
3. HS cells may get activated in these spots where large enough numbers of pyramids get synchronized.
4. These HS cells feed back into the MS and align firing of pacemaker cells in phase.
5. Emergence of theta activity coherent throughout the HIPP.

The out-of-phase activity of basket and O-LM cells predicts the role of these interneurons, *as well as the possible function of theta oscillation*.



During the encoding phase, the peak pacemaker cells silence the O-LM cells, thereby generating ideal conditions for entorhinal to get potentiated. Basket cells are also active, ensuring rhythmic synchronization of pyramidal cell activity.

During the retrieval phase, O-LM cells are active, so it is preventing any kind of information from the entorhinal cortex to come in and interfere with the retrieval process. The retrieval process can go on undisturbed because basket cells are inhibited, so pyramidal cells can fire.

O-LM cells in CA1 and HIPP cells in the dentate gyrus:

- mediate feed-back dendrite inhibition
- selectively control entorhinal input
- are active in the peak phase of intracellular theta.

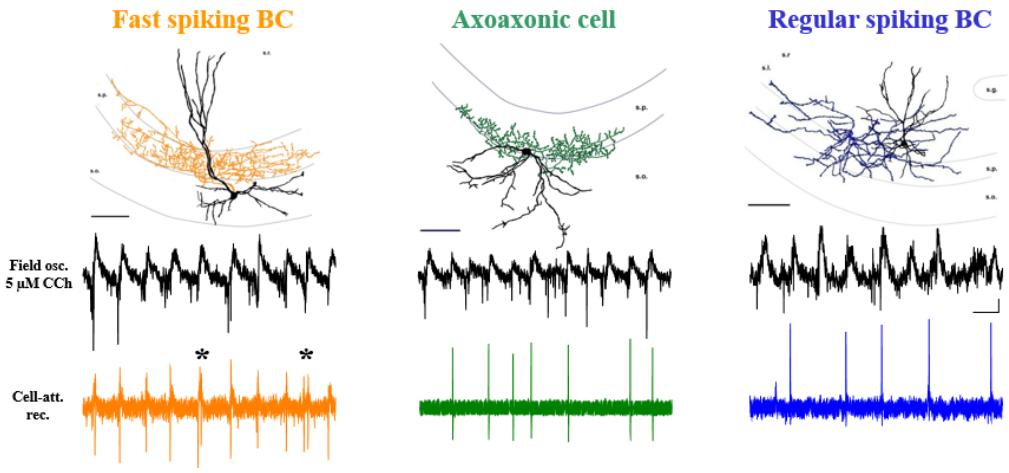
Associative LTP of entorhinal synapses prevented in the retrieval phase, blocking interference of sensory encoding with retrieval. In the peak phase only place cells can fire, when in phase-procession mode. These few pyramids cannot recruit O-LM cells, LTP of entorhinal synapses allowed.

Cholinergic activation of O-LM cells by aversive stimuli can prevent potentiation of those entorhinal inputs on pyramidal cells that carry the particular aversive sensory information.

Gamma oscillation

Gamma frequency oscillation is riding on theta waves.

Firing properties of perisomatic inhibitory cells during cholinergically-induced fast oscillations in CA3 hippocampal region



Basket cell firing always follows the pyramidal cell firing by 3 ms. This means that there is a monosynaptic drive of pyramidal cells, this supports a synaptic feedback model for the generation of gamma oscillations in the CA3 region.

Sharp waves

Shar wave activity happens only non-theta behaviour.

A high proportion of CA3 pyramidal cells fire together in synchronous bursts. The individual cells that participate, will join the burst at different timepoints thus speeding different periods in the burst. The longer they keep firing in the burst, the more they strengthen their connections with the rest of the pyramidal cells participating in the potentiated mini network.

Functional Imaging

Lecture 13

MR methods

- Their aim is to visualize the different structure and functional properties of the human brain.
- Structural imaging:
    - *T1 or T2 weighted imaging* provides an excellent resolution and highly detailed high-resolution anatomical image of the human brain. It nicely differentiates the different tissue types within the brain. It also outlines the different ventricles and structures in the brain.
    - *DTI*: Another method has been developed based on the diffusion imaging with the goal to be able to map and track the fibers that connect different brain regions within the brain. This technique is sensitive to the diffusion of the water molecule within the myelinated axons, that connect the different parts of the brain, especially the long-range wide accents. It allows us to measure the external tracts and visualize the connections the structural connections within the human brain.
- Functional imaging:
    - *bold fMRI:* A blood oxygen level dependent technique.
    - *ASL: (arterial spin labelling)* perfusion imaging using fMRI, that is used for measuring or quantifying the blood flow within a specific region of the brain. With this we can measure how neural activation changes the metabolic demand of the blood flow in the region, where the activation is increased.
- Spectroscopy:
    - It has been developed to be able to measure chemical components in the human brain in vivo. By this, it is possible to map the transmitter concentration within a given region of the brain.

fMRI

- Its main application fields:
    - cognitive neuroscience research
    - clinical research
    - pharmacological/translational research
- Advantages of fMRI:
    - non-invasive (no negative side effects to the tissue)
        - it can be used several times on the same participant (for longitudinal approaches)
        - it can be used on children.
    - relatively high spatiotemporal resolution, SR: 2-3 mm, TR: 1-3 sec (the temporal is not that good)
    - its capacity to investigate the entire network of brain areas during a particular task or during rest.

The Blood Oxygenation Level Dependent (BOLD) method

- The BOLD signal is measured on T2*-weighted images and its strength depends on the local magnetic field homogeneity.
- The BOLD signal is determined by the balance of deoxygenated (paramagnetic) to oxygenated (diamagnetic) haemoglobin in blood within a voxel. Within a voxel, if the balance is changing there will be a modulation of the broad sigma.
- If in a region of the brain, the neural activity is increasing or is changing, then there will be an effect on the relative concentration of the oxygenated and deoxygenated haemoglobin.
- BOLD signal is only an indirect measure of neural activity.
- Its magnitude is affected by:
    - oxygen consumption
    - blood flow volume
    - local microvascular architecture
- Thus, it is a complex function of resting haemodynamic state and activation-induced adjustments in metabolism and haemodynamics.

The neural basis of the bold signal

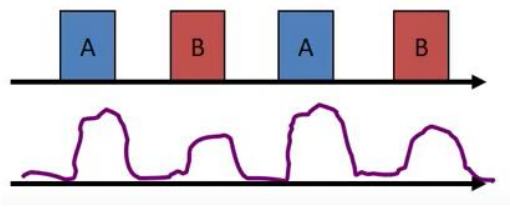
- BOLD signal strongly correlates with the local field potential (LFP) within the voxel.
- LFP is a mass neural signal reflecting multitude of neural processes, including:
    - synaptic potentials
    - afterpotentials of somatodendritic spikes
    - voltage-gated membrane oscillations
- Thus, BOLD reflects:
    - the input of a given cortical area.
    - its local intracortical processing, including the activity of excitatory and inhibitory interneurons.
    - the effect of neuromodulatory pathways (large neurotransmitter systems, such as dopamine, serotonin that will evoke a sustained neuromodality process, a modulation of the signals that the BOLD is most sensitive to)

BOLD is more sensitive to Neuromodulatory than to Driving activity.

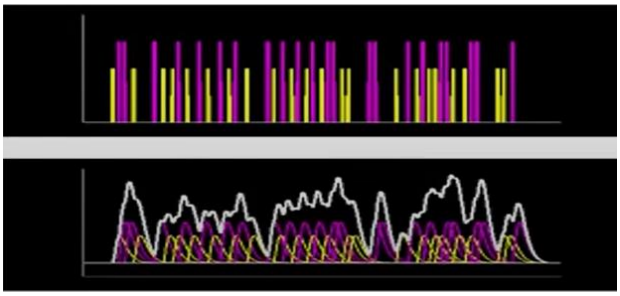
Neural activity associated with neuromodulatory, feedback (attentional, predictive, or anticipatory) processes induce larger changes in the fMRI signal than those, associated with driving, bottom-up (sensory) processes.

Task-related fMRI: Experimental design

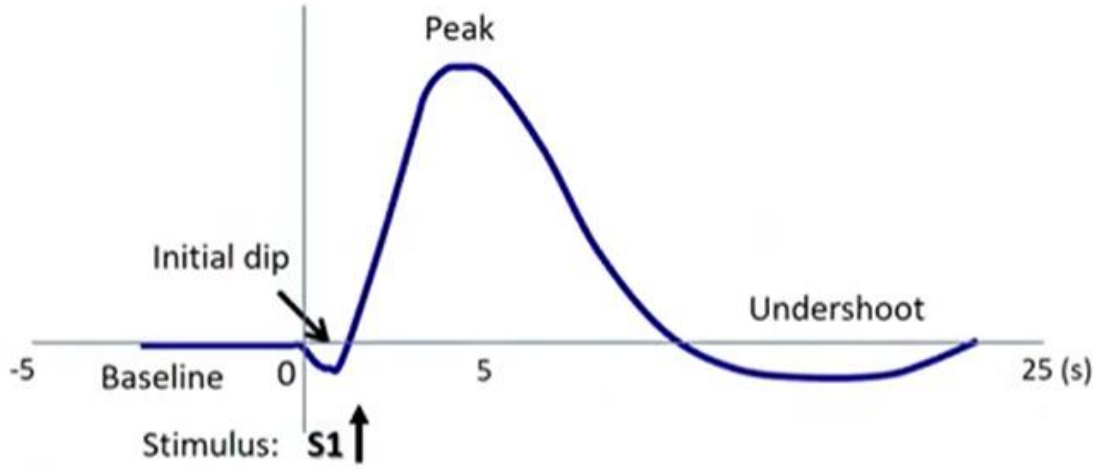
- <u>Block design</u>
    - long (10-20 s) stimulus and rest intervals
    - simple
    - robust, large SNR & statistical power
    - unnatural, rigid experimental design, long signal decay
    - difficult to adapt to different tasks.



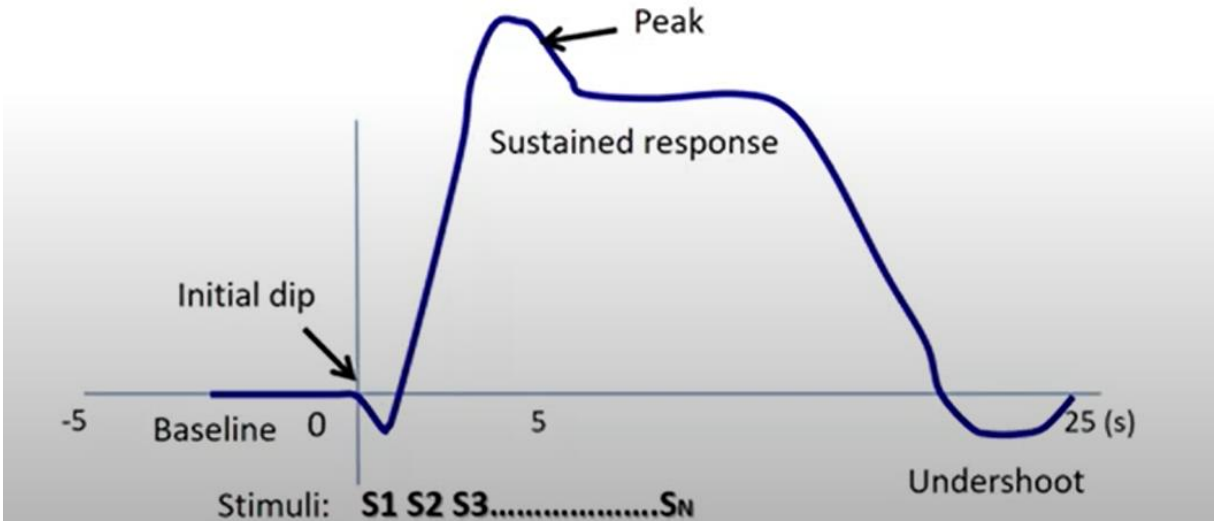
- Event-related design
  - more complex model
  - lower SNR
  - more repetitions required.
  - flexible



BOLD response



This is a BOLD response to a single stimulus. There is an initial dip in the response, there is no clear explanation why it is there. After a while, there is a rise in the signal, until it reaches a peak at around 4-5 seconds after stimulus presentation. That is because fMRI measures the evoked haemodynamic response, the remote change in the relative haemoglobin concentration, the increase in blood flow. After the peak, there is a small decay of the signal, and there is an undershoot.



When there is more than one stimulus, the initial response looks very similar. Then, after the peak, there is a sustained response, that will be maintained long after you stop your presentation. Then it will decay again, and there will be an undershoot as well.

Analysis of the fMRI data - Pre-processing

Whenever you do an fMRI experiment, in addition to the fMRI scans, you also collect structural imaging.

Multivariate analysis of the fMRI data – Decoding

In this case, voxels are not treated independently. The assumption here is that during fMRI, the stimulation evokes a specific pattern of activations in the voxels, that can be treated as activation patterns, and can be classified using machine vision algorithms such as the linear discriminant analysis or linear vector support machine and classify different stimuli based on the evoked cortical activation patterns so you can classify these activation patterns according to stimulus' orientation. By this, you can map the orientation selectivity in the early visual cortical areas.

Besides decoding the stimulus based on the brain activation, using this method we can test if we have a decoder that has been trained to decode different orientations of the grating.

Resting-state fMRI functional connectivity

functional connectivity- statistical interdependence of signals between brain regions

resting state fMRI functional connectivity- studying FC by measuring the correlation of spontaneous slow fluctuations in the BOLD signal across various brain regions during wakeful rest, with no explicit task.

major networks revealed:

- visual
- sensorimotor
- auditory
- default mode network
- dorsal attention
- executive control

The resting-state functional networks are closely corresponding and are determined to the known structural connectivities and functional networks in the brain. It has been also shown that functional networks that are identified using resting state functional connectivity, are very similar and correspond nicely to the functional networks that are revealed using different specific tasks dedicated to engaging a specific network.

The neural underpinnings and functional roles of spontaneous fluctuations and correlations are in the focus of intense research and the results suggest a close association between FC and neural activity.

Neural basis of resting state fMRI

BOLD signal correlates preferentially with specific frequency bands of the LFP:

- BOLD and gamma → correlate positively
- BOLD and alpha/beta → correlate negatively

Functional networks found in rs-fMRI research studies are characterized by alpha/beta and high-gamma-band coherence at infra-slow frequencies.

Static rs-fMRI FC

- is based on the assumption that the statistical interdependence of signals between distinct brain regions is constant over time.
- FC is represented as a single correlation coefficient that is calculated from the time series of the entire scan.
- highly constrained by structural connectivity

Analysis approaches

- *univariate* (e.g., seed-based correlation): measures the average statistical dependencies between two nodes over the measured period
- *multivariate* (e.g., independent component analysis): decomposing the fMRI data into a pre-specified number of components with maximal spatial independence reveals clusters of nodes fluctuating synchronously

Dynamic rs-fMRI FC

- given the known dynamic, condition-dependent nature of brain activity it is assumed that FC metrics computed on fMRI data will exhibit variation over time.
- revealed temporally independent functional modes, which ma more precisely to task-evoked modules than conventional ICNs, some of which contain submodules overlapping with other modes.

Analysis approaches

- sliding window analysis
- time-frequency analysis
- temporal independent component analysis

Application of functional MRI in cognitive neuroscience

Visual cortical areas: Those regions within the visual cortex that have a common site architecture and have a specific connectivity pattern.

Functional definitions:

- an area has a specific pattern of response (e.g., electrophysiology, fMRI response) to different stimulation (visual properties here)
- disruption of that area (by lesioning, cooling, transcranial magnetic stimulation) affects processing of a particular type of stimuli.
- stimulation of the area (e.g., electrode stimulation) evokes a particular percept or response.

Visual cortical areas are organized in a hierarchical way:

- low level
    - local feature detection (V1-V3) (most posterior part of the visual cortex)
        - spatial frequency contrast orientation motion direction
        - each point of the visual field, when it is projected into the visual cortex via the boundary on the cells of the retina, it preserves the relative position in the visual cortex → localizing the visual input, coding the spatial relationship between different objects in the scene.
- intermediate level
    - grouping and segmentation (V4, MT/MST)
    - the input to the brain is highly segmented, the ganglion and the coding is based on neurons that have very small receptive field, they perceive the environment through a very small angle.
- high level
    - object recognition / biological motion (IT, STS, PC)
    - we see global coherent motion of the different objects.

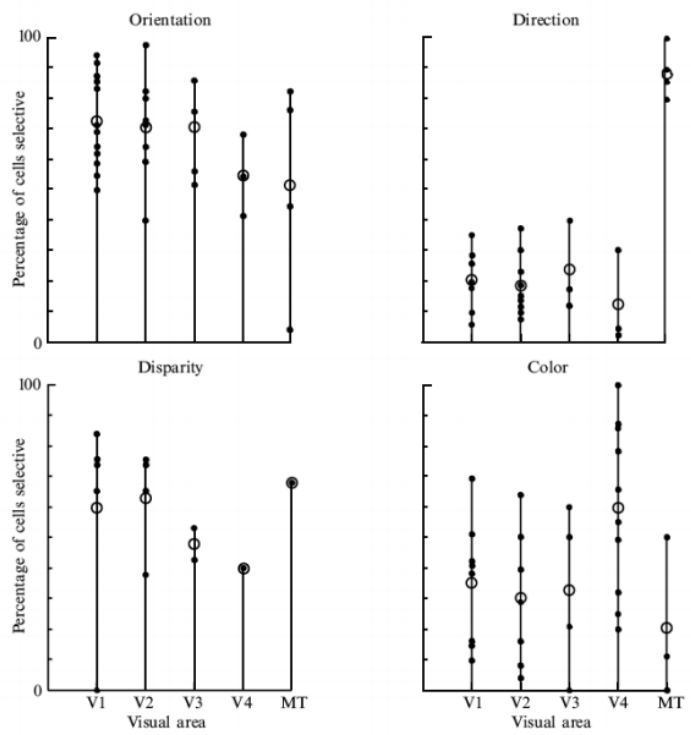
The different regions code different complexity of the visual information

- orientation
- direction
- disparity
- colour

In the different regions, it is not yes or no coding, instead it is a weighted code. E.g., V4 is more for colour, MT is more for visual motion direction. That gives a specific representation in the different visual cortical areas, that can be investigated using fMRI.

Two visual pathways:

- "what" (ventral stream) – object recognition
    - main input from "slow and detailed" parvo system
- "where" (dorsal stream) – spatial perception
    - main input from "quick and dirty" magno system



In humans: "what" vs. "how"

- dichotomy should be "what" vs "how".
- dorsal stream has string input to motor systems and is essential for using visual information to guide actions.

Perception vs. Action

Vision for Perception – Ventral Stream	Vision for Action – Dorsal Stream
inferotemporal cortex	posterior parietal cortex
object-based	viewer-based
object identification	movements/ visually guided actions
'conscious'	'automatic'

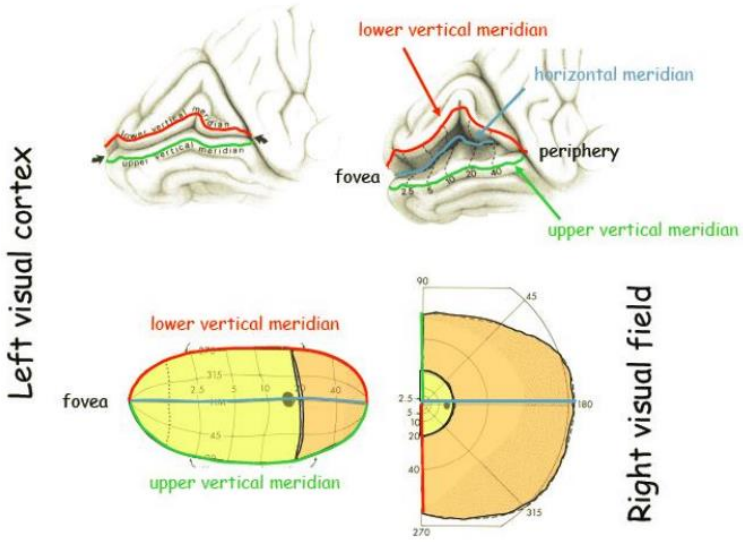
Human visual cortex

Using fMRI, we can map all the specific regions with dedicated functions:

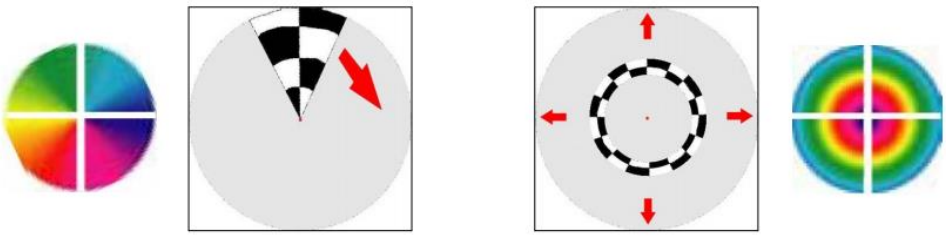
- mapping early and mid-level areas
  - retinotopic mapping
  - feature specificity (e.g., motion, colour)

Retinotopic Mapping

- The aim is to separate early and mid-level visual areas based on *topographical representation of the visual field.*
- visual field representation in human primary visual cortex (V1)



- protocol for retinotopy
  - phase reversing checkerboard stimulus for strong excitation.
  - aim is to probe the entire visual field:
    - rotating wedge to get information about visual field quadrants.
    - contracting-expanding ring to get information about eccentricity.



  - retinotopic map:
    - there is a contrast reversal on the border of each visual cortical areas → we can map the borders of the different areas.

Feature specific visual cortical areas.

- motion-specific area MT+/V5
- moving vs static stimuli

Category-specific areas

- identifying other different areas that might specialize for different attributes, object categories (e.g., faces, body parts)

Functional specialization within the visual cortical network

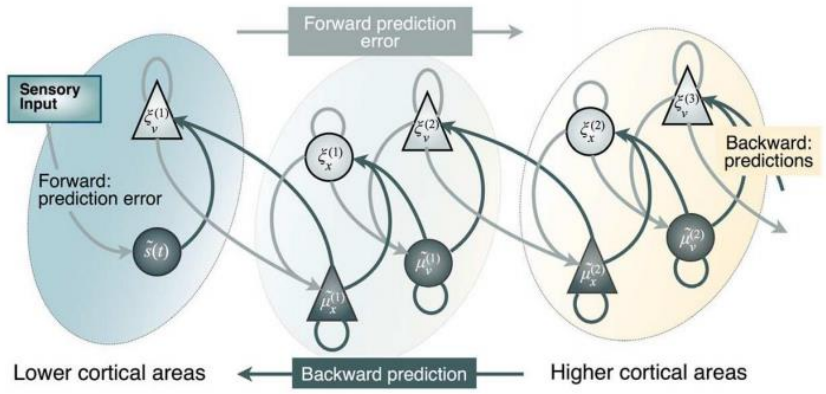
Object recognition is very fast and efficient when viewing conditions are good.

- object identification < 150 ms
- object discrimination < 200 ms
- in addition to very fast feed forward processing that will extract the most important, most robust information from visual objects you can have additional steps re-entrant feedback processes that will realize these objects if more in-depth information is needed.

However, under low visibility conditions the visual system must recruit additional processing resources to handle the noisy and deteriorated visual image, thus object recognition becomes slower and more effortful.

Predictive coding theory

- the brain has a probabilistic generative model of incoming sensory input.
- brain networks make top-down predictions about ascending input and then refine these predictions by minimising prediction errors.
- backward connections deliver predictions to lower levels, whereas forward connections convey prediction errors to upper levels.



Face processing in the human brain

- occipital face area
- fusiform face area
- superior temporal sulcus

Phase noise has a strong disruptive effect: the phases in an image carry location information, which in turn specifies object shape in terms of the spatial locations of features.

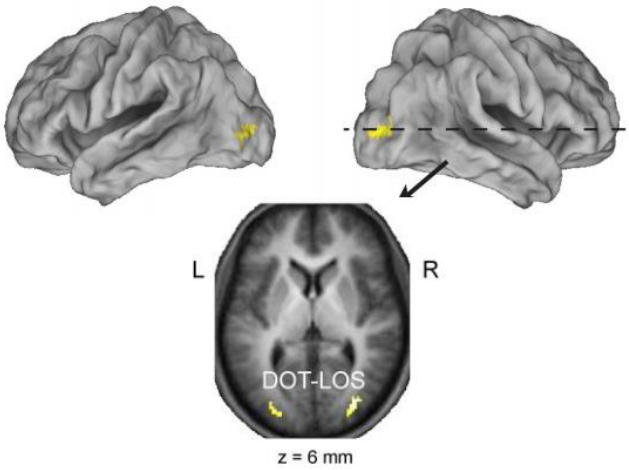
Combined use of fMRI and EEG

Task difficulty manipulations:

- decreasing gender difference (morph)
- decreasing phase coherence (noise)

(EEG is needed because fMRI gives a very poor temporal resolution.)

fMRI results: DOT-LOS corresponds to the shape selective, retinotopically organized LO2 region, which represents shape information with a spatial coordinate system.



Processing of deteriorated face images involves neural processes within the shape selective, retinotopically organized lateral occipital cortical region 200-250 ms after stimulus onset.

rs-fMRI functional connectivity in the visual cortex

Resting state functional connectivity within the visual cortex between the different visual cortical areas is actually organized in a way that follows the basic principles of the information processing within the cortex. It corresponds to the retinotopic and topographical organization of the visual cortex. It also corresponds to the feature specialized processing in the visual cortex. The functional connectivity during rest between the different visual cortical areas can actually predict the perceptual abilities in the specific task of the individuals who have been participating in the experiment.

Resting-state fMRI functional connectivity predicts face perception.

Strength of the intrinsic functional connectivity within the visual cortical network composed of bilateral FFA and bilateral object-selective lateral occipital cortex (LOC) predicted the participants' ability to discriminate the identity of noisy face images.

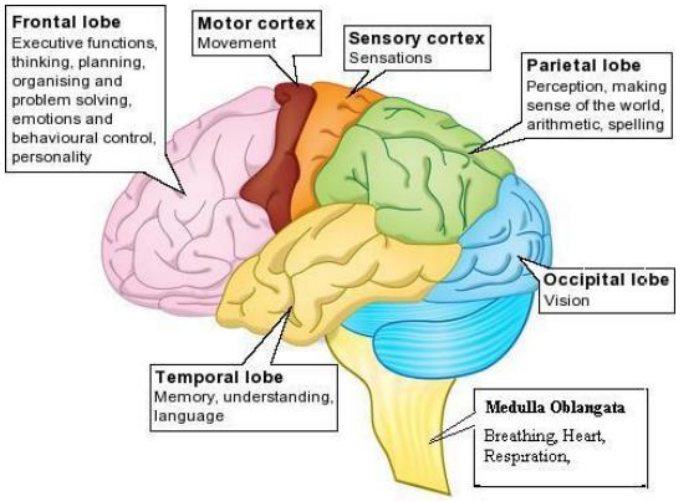
Perception of facial identity in the case of noisy, deteriorated face images is subserved by neural computations within a re-entrant processing loop involving bilateral FFA and LOC.

Studying brain disorders using fMRI

The human brain underwent a major change during evolution if we consider its size and weight, the number of neurons as well as the number of connections. This is not the case for all human organs (e.g., heart). The knowledge that is collected from animal model studies will have a restricted impact, because there are many specialized functions in the brain that cannot be studied, or the study of the functions is very limited in animal models.

Cognitive functions

- language
- reasoning, problem solving.
- logic
- social and emotional cognition
- consciousness

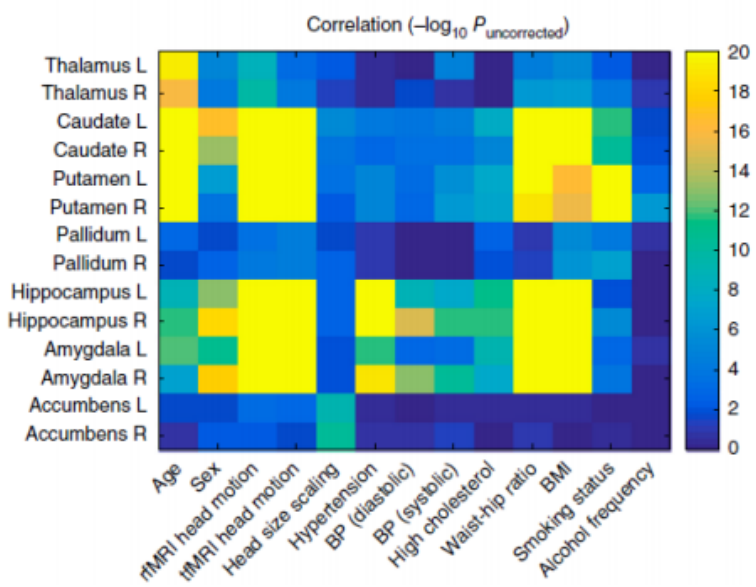


Using fMRI, it was possible to localize the regions in the prefrontal cortex that play a very important role and all of these functions including social commission, reasoning, working memory and so on.

The development of the brain is also very special. The development of the brain in humans is much longer than in animal models. fMRI has been used intensively to study the developmental processes in the brain and it has shown that up to 20 years, there are significant changes. The application of animal models is very limited.

The risk of neurodegenerative disease and cognitive decline increases with chronological age.

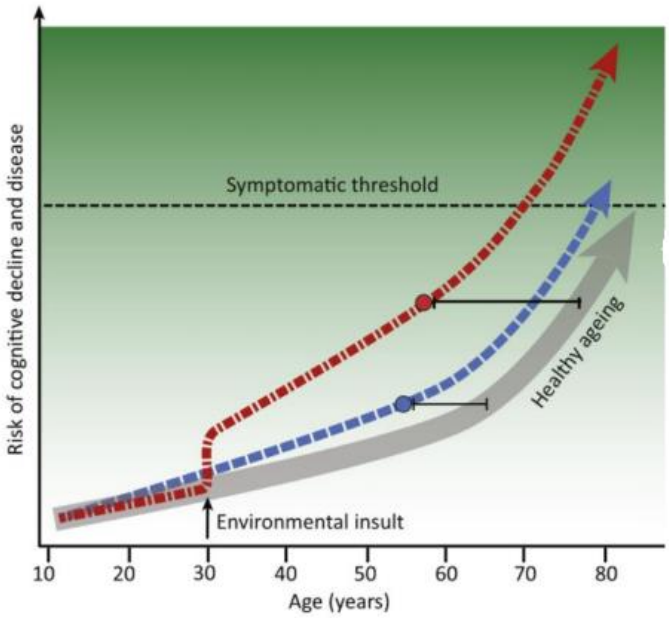
We can associate different functions to different structural alterations in the brain with aging, and there are many studies now that were successfully associating age or body mass index or different habits to different brain processes.



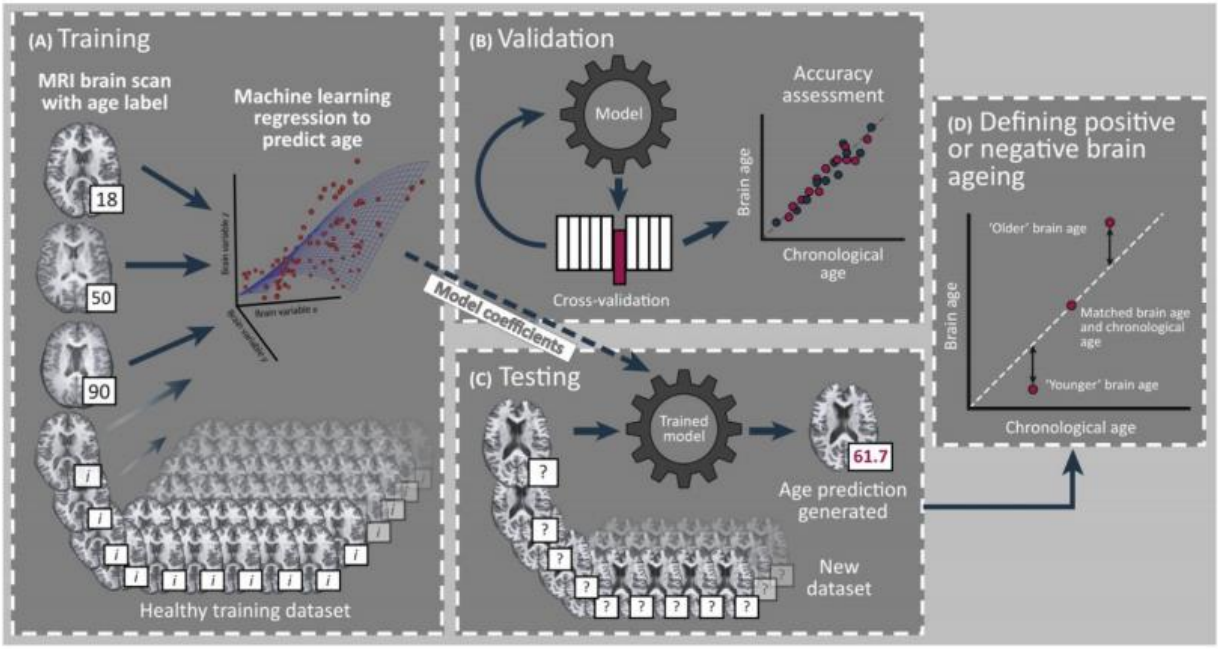
We have similar association of these subcortical regions to such factors that has motion within the scan. Participants with e.g., high BMI have more difficulties to maintain motionless during the scan. Large datasets and studies on these datasets are very promising and provide very important results about the changes, brain function and their association with different diseases, factors.

Trajectories of biological aging

- There is considerable individual variability in the rate of biological brain aging.
- With the use of brain imaging and machine learning, deviation from the general pattern can be quantified.



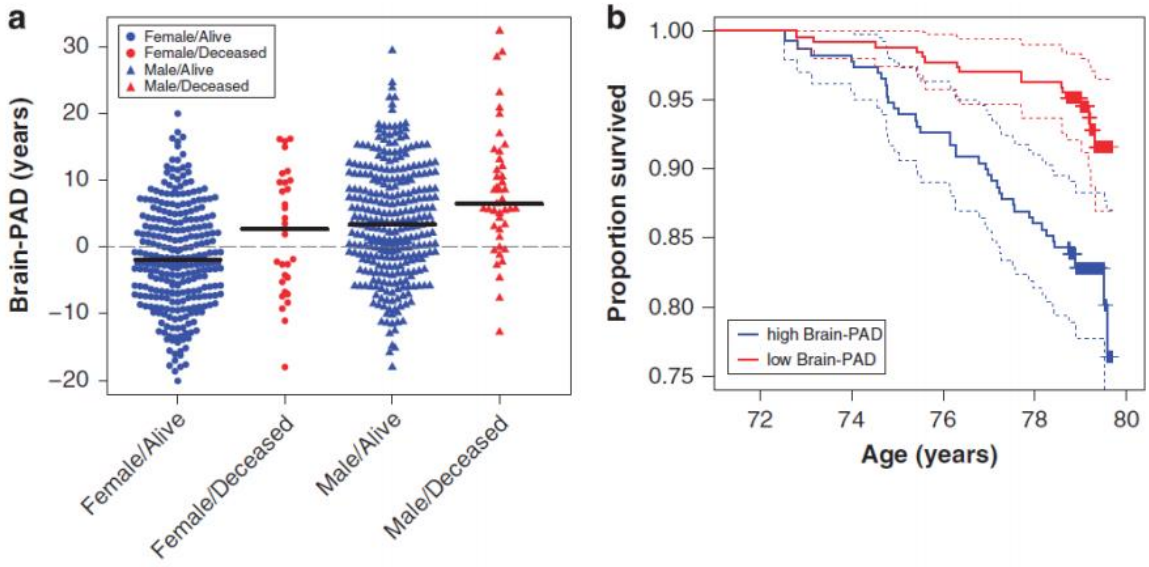
Predicting brain age via machine learning



The state of art in brain age prediction

- Convolutional neural networks (CNN)
- T1-weighted structural MRI scans
- Mean absolute error below 5 years.

Brain age predicts the risk of mortality.



Measuring brain age based on resting-state fMRI connectivity:

- Anatomically or functionally connected brain regions' intrinsic neural activity displays (some sort of) synchrony.
- Seed based connectivity map: one voxel's (ROI's) signal is correlated with the other region's time-series.
- Whole-brain connectivity matrix: Correlation coefficient is calculated between every brain voxel (ROI) pair.

We can use transfer learning to overcome the challenge of data security.

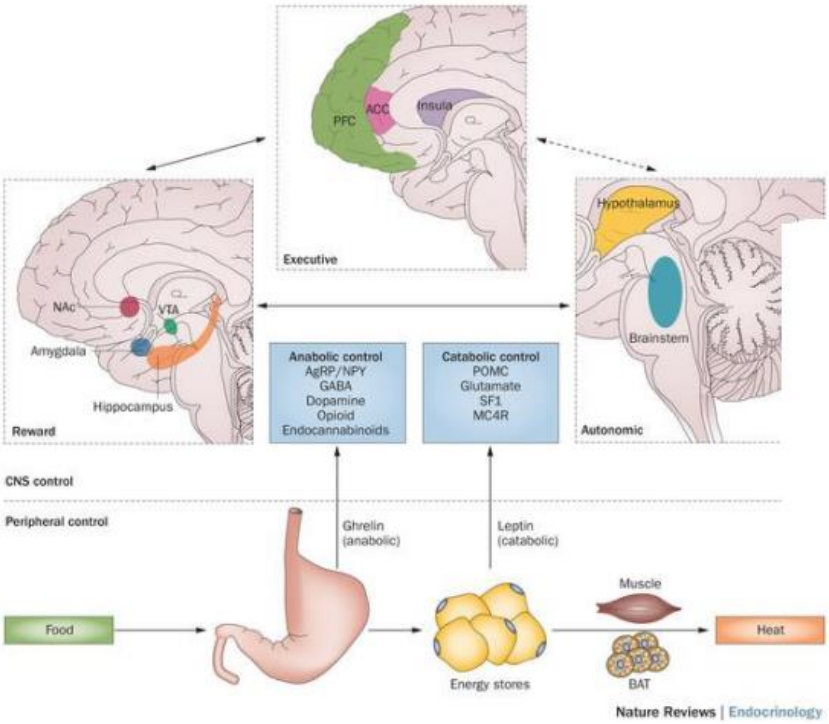
Conclusions

- Rs-fMRI is promising for brain age prediction.
- Transfer learning improves fMRI connectivity pattern analysis – a potential solution for data scarcity in neuroimaging.

Obesity

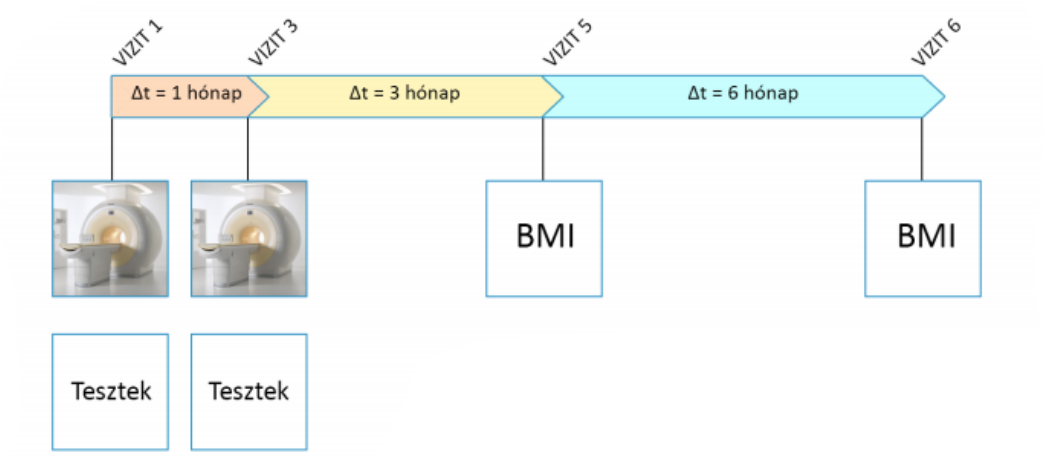
Neural basis

- *Cortical executive circuits* – response for the self-control of eating and engaging or adhering to physical activity.
- *Reward circuits*- interconnected nuclei and neurons capable of encoding the pleasurable and motivational aspects and food-related cues.
- *Autonomic energy balance regulation circuits* – composed of hypothalamic and brainstem nuclei, which modulate the activity of the cortical executive and reward circuitries and govern expenditure components such as thermogenesis.



Dynamic vulnerability model

Experimental protocol



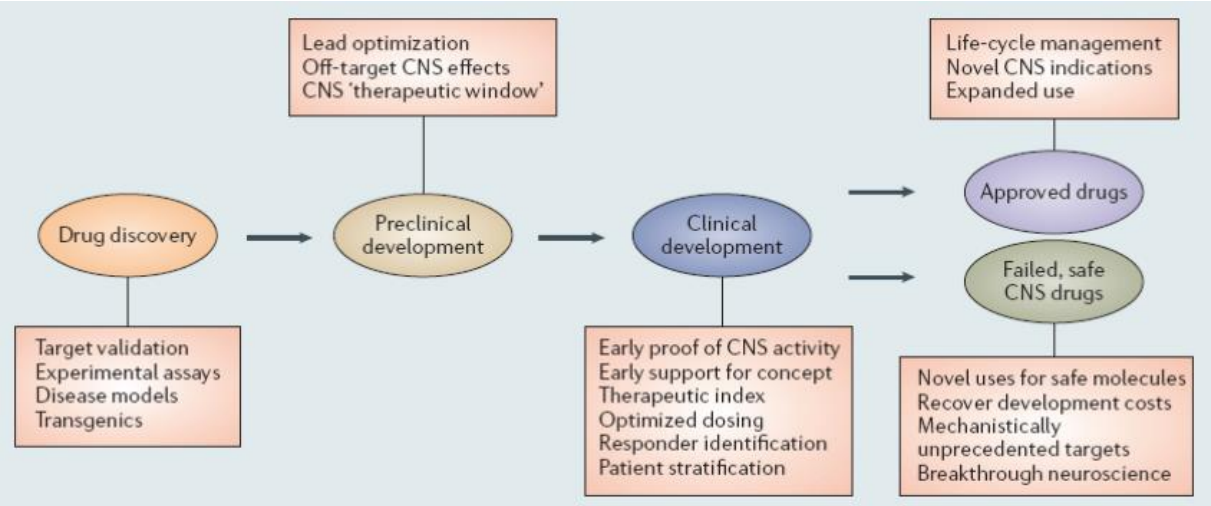
MRI measures:

- structural MRI
- resting-state fMRI
- task-related fMRI

Food cue reactivity alterations in the striatum during the first month predict BMI changes at the end of the intervention.

Translational neuroimaging

Translational research: Reciprocal partnership between preclinical and clinical research to further new molecular entities or compounds identified through the application of basic scientific discoveries, optimized into potential drug candidates, and eventually developed into clinically effective medications.



Alzheimer's Disease: Structural MRI biomarker

Prediction of the progression of the disease. We can use the structural MRI to segment the hippocampus. From the volume of the hippocampus, we can predict how the progression of the disease is going to take place in the patients.

Improving the efficacy of animal to human translation: *Default Mode network*

Translational neuroimaging – Pain

Perceived pain intensity depends on:

- context
  - pain beliefs
  - expectation
  - placebo
- mood
  - depression
  - catastrophising
  - anxiety
- cognitive set
  - hypervigilance
  - attention
  - distraction
  - catastrophising
- chemical structure
  - neurodegradation
  - metabolic (e.g., opidoergic, dopaminergic)
  - maladaptive plasticity
- injury
  - peripheral & central
  - sensitisation

Determining the peripheral and central influences on pain perception, ascertaining which are due to pathological versus emotional or cognitive influences will clearly aid decisions regarding the targeting of treatments (i.e., pharmacological, surgical, cognitive behavioural or physical rehabilitation).

Neuroanatomy of pain processing

The hard core:

- thalamus
- S1/S2
- insula
- ACC
- prefrontal

In many different areas the fMRI responses to pain stimulation show a correlation with the perceived pain intensity.

Conclusions

Translational MRI neuroimaging improves the efficacy of decision making in drug development by:

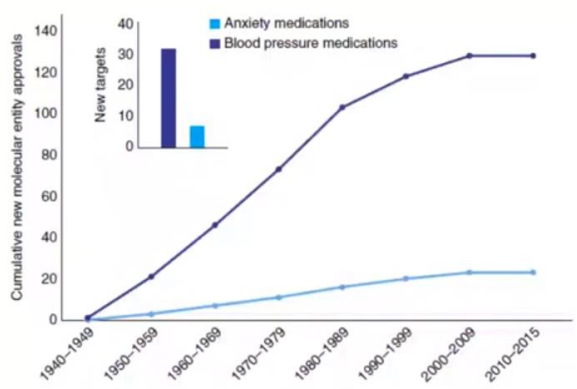
- providing a common methodological approach for investigation of animal and human pre-clinical disease models and improving the efficacy of animal to human translation
- fostering the understanding of healthy and pathological system-level brain functions and thus contributing to the development of better pre-clinical disease models and disease/drug profiles
- improving the patient stratification and enrolment for clinical investigations.

Behavioural studies

Lecture 14

In 2030, depression will be the leading cause of health burden and disability worldwide.
ROI of stress-related mental disorders: 2-6x

Development and efficacy of anxiolytic drugs



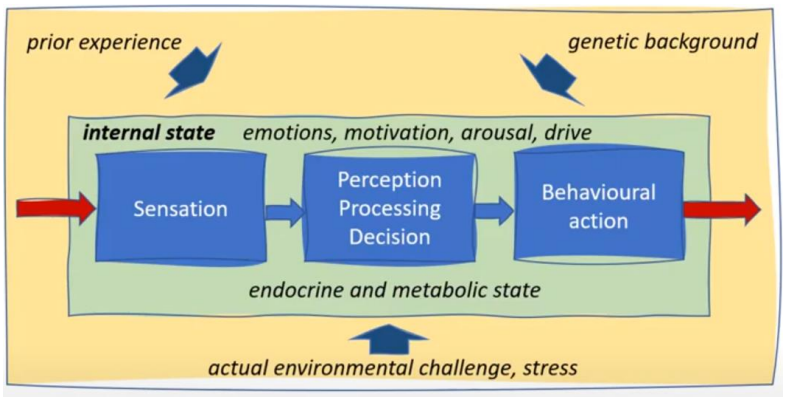
DSM (now 5th edition)

- collection of symptoms, that all psychiatrists use to diagnose uniformly different mental disorders.

Definition criteria for animal model validation

- Phenomenon – **Face validity**
  - defined as how well a model replicates the disease phenotype in humans (similarity of disease/symptoms/signs between humans and the animal model)
- Treatment – **Predictive validity**
  - defined as the measure of how well a model can be used to predict currently unknown aspects of the disease in humans (e.g., human-animal correlation of therapeutic outcomes)
- Mechanism – **Construct validity**
  - how well the mechanism used to induce the disease phenotype in animals reflects the currently understood disease aetiology in humans (similarity in the (neuro)biological dysfunctions between the human and animal model)

Organization of behaviour



Adequate behavioural responses to the actual challenge

- freezing
- escape
- attack

Inadequate behavioural response to the actual challenge ~ psychiatric disease
Models of disease
Model - phenotype – therapeutical target/mechanisms

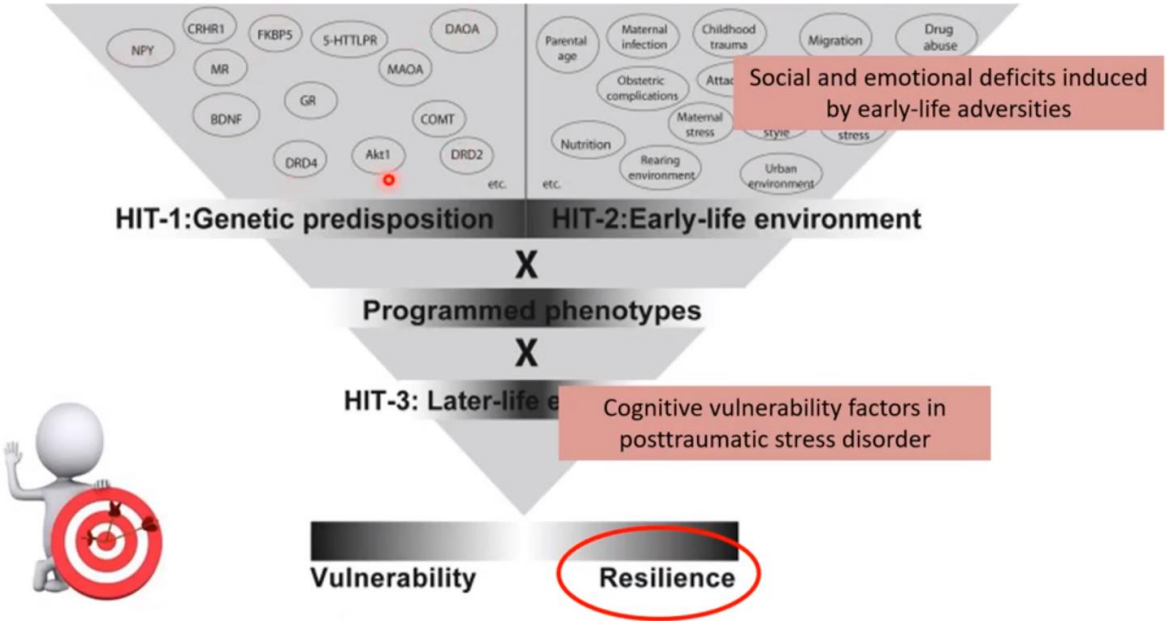
Psychiatric disorders are feeling or behaviours:

- that are inadequate/inappropriate to the situation.
- are persistent.
- result in suffering and/or dysfunctions in major areas of life (are debilitating)
- there are no better explanations to them.

Psychiatric disorders in their full complexity cannot be modelled, it is theoretically and practically impossible to create valid animal models for these, BUT some characteristics and symptoms of psychiatric disorders can be well modelled and from this a valid conclusion can be drawn.

Mental disorder – the three-hit hypothesis

- many factors contribute to the vulnerability and resilience to mental disorders.



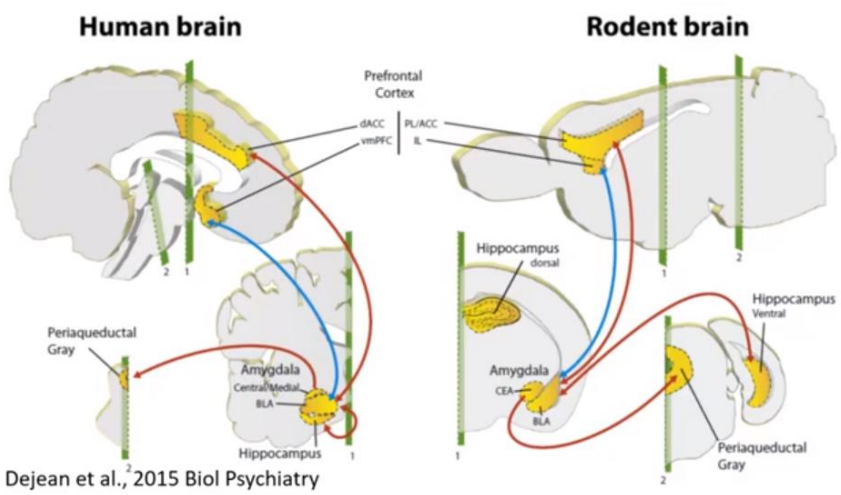
Posttraumatic stress disorder (PTSD) - vulnerability

- 10-30 % of people undergo traumatic life events go on and develop PTSD.
- no one understands what is the basic of vulnerability of this disorder.
- severe psychiatric disorder that develops following traumatic events
- treated by pharmacotherapy or psychotherapy.

- there are different types of animal models for PTSD
    - inescapable shocks: foot shock to mouse
    - predator stress: unprotected/protected exposure, predator scent
    - single prolongated stress
    - immobilization (IMO) or restraint stress
    - unpredictable variable stress (UVS)
    - social defeat stress (SDS)
- also, a cognitive disorder
- core symptoms:
    - contextual fear generalization
    - fear extinction deficits

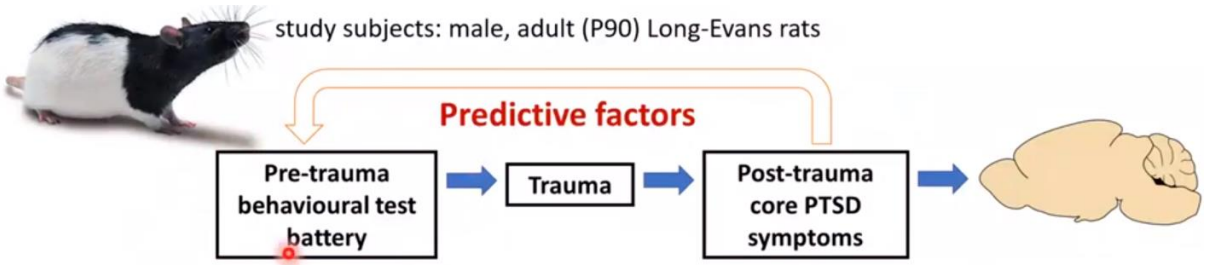
Neurobiological correlates of PTSD vulnerability

- in PTSD:
    - structural and functional alterations: prefrontal cortex, hippocampus, amygdala
    - pre-existing vulnerability or consequence of trauma?
    - PTSD vulnerability was associated with reduced hippocampal volume.



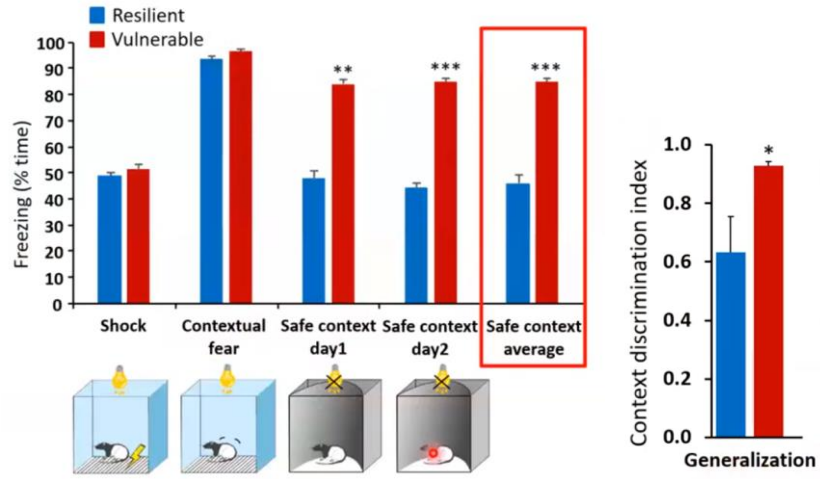
Aims

- identification of pre-trauma cognitive factors that predict core symptoms of PTSD (contextual generalization and fear extinction deficit)
- identification of neural mechanisms that underlie such vulnerabilities.
- animal model:



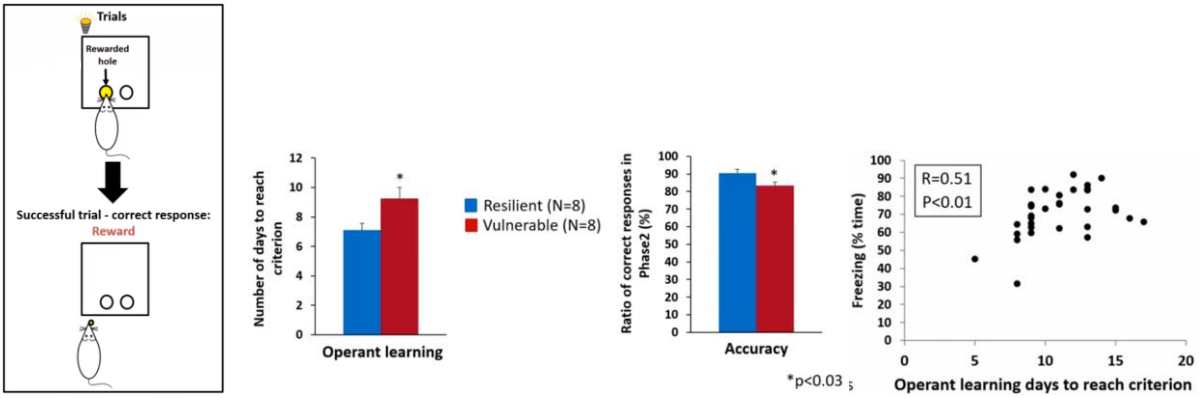
- pre-trauma behavioural test battery:
  - cognitive function
  - emotional function

Cognitive function	Emotional function
• Operant learning	• Elevated plus-maze
• Attention	• Open-field
• Spatial learning and memory	• Light-dark box
• Habitual learning	• Acoustic startle
• Cognitive flexibility	• Predator odor avoidance
• Inhibitory function	
• Working memory	
• Short-term contextual memory	
• Social recognition	



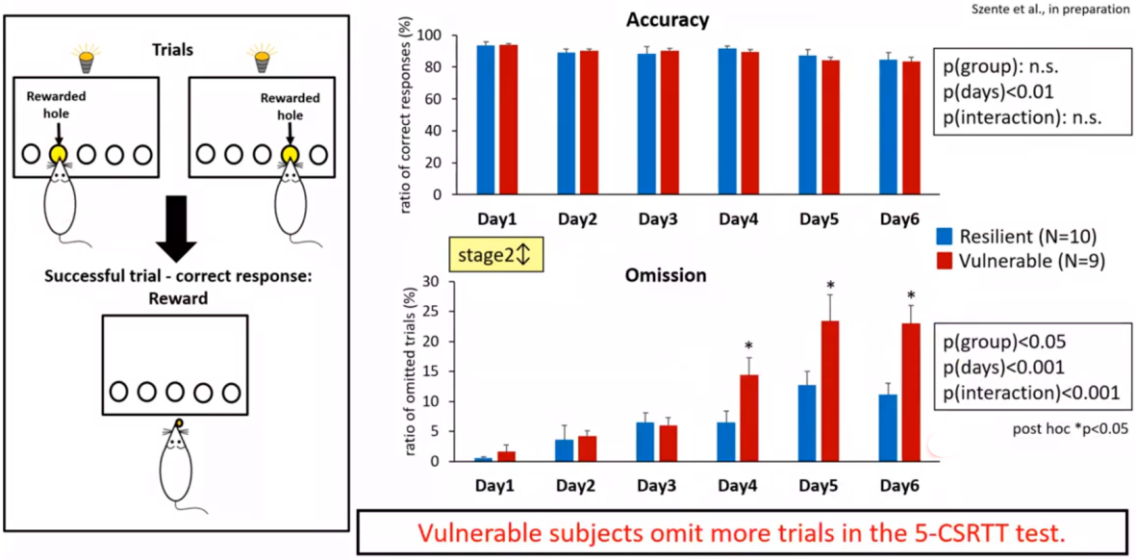
Major outcome indicating PTSD symptoms: generalization and impaired fear extinction.

Operant learning



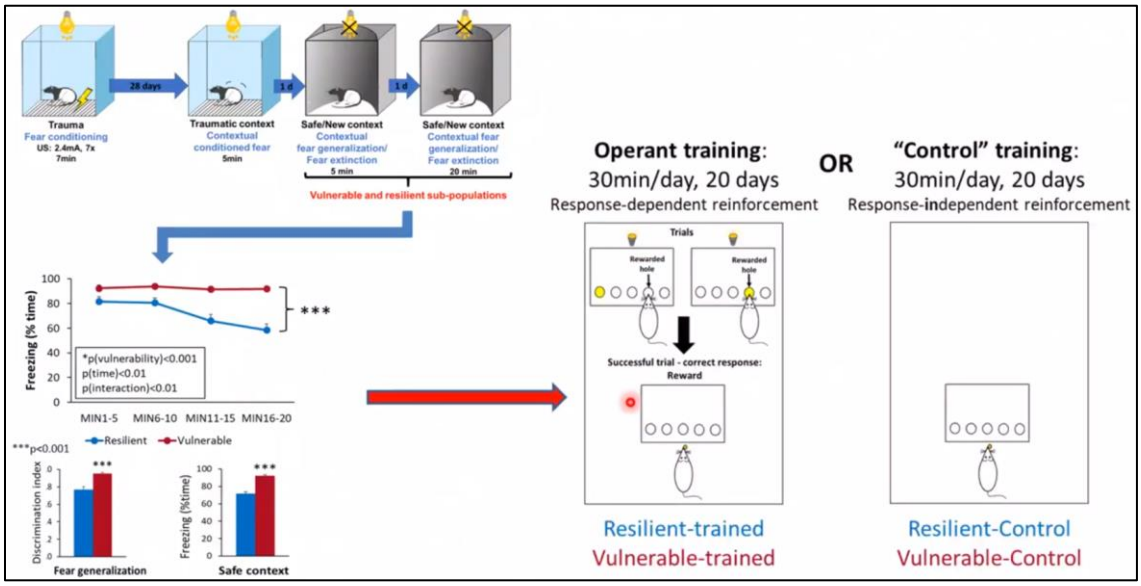
Pre-trauma operant learning is slower and less accurate in vulnerable subjects and correlates with extinction impairment.

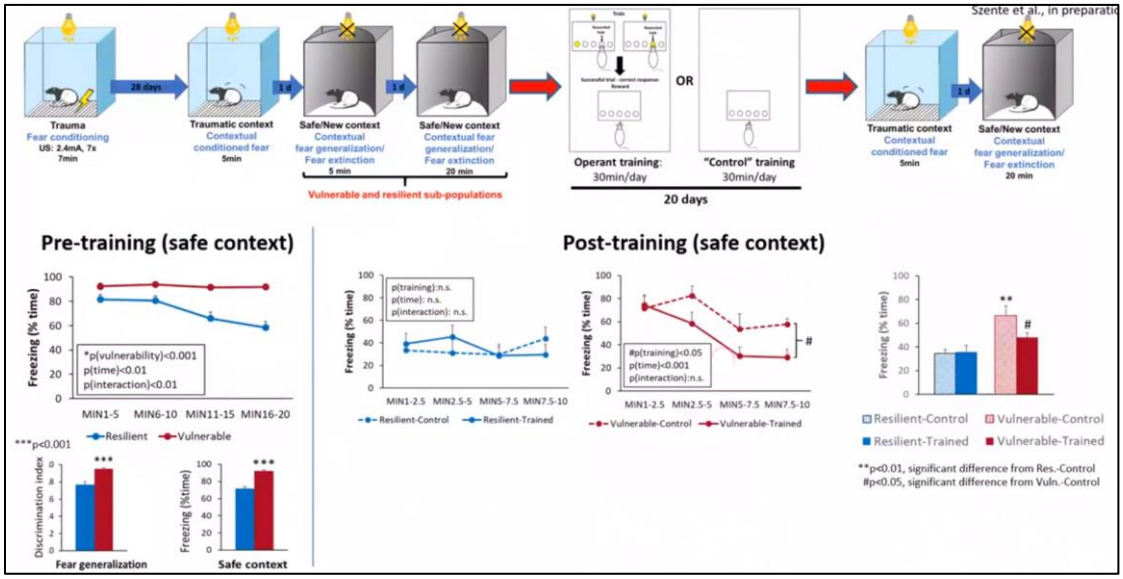
Attention: 5-choice serial reaction time task



Vulnerable subjects omit more trials in the 5-CSRTT test.

Effects of neurocognitive training





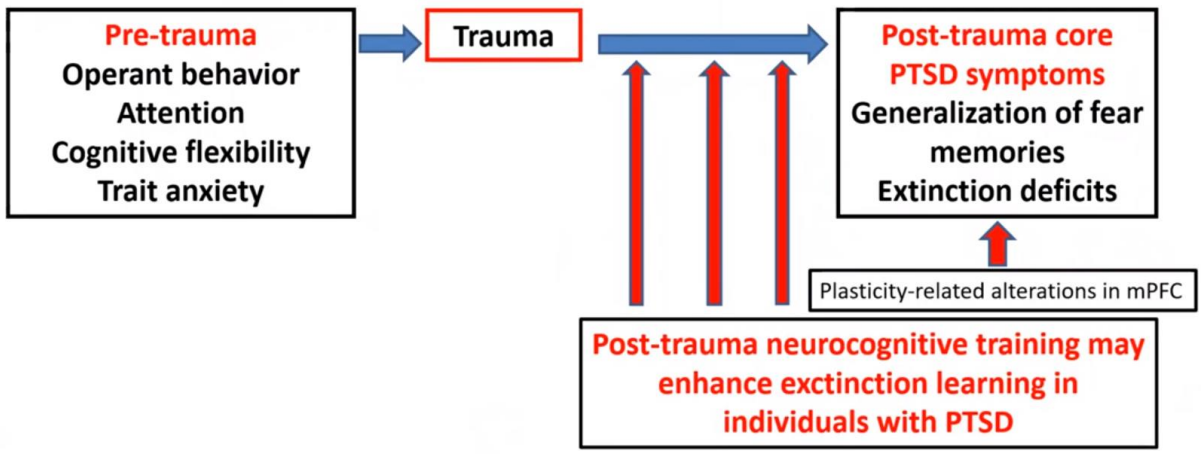
Post-traumatic neurocognitive training successfully enhanced extinction learning of vulnerable subjects.

Activity and plasticity in mPFC

- mPFC of vulnerable individuals:
  - altered neuronal activation during extinction that correlates with pre-trauma cognitive function.
  - reduced MAOA expression
  - enhanced CRH expression
  - diminished plasticity-related changes compared to resilient individuals (NGF, NoGoR, Neurocan)

Summary

- certain pre-trauma cognitive factors predict the appearance of major PTSD symptoms.



Understanding brain mechanisms underlying pre-trauma cognitive vulnerability factors will help to identify individuals at risk of developing PTSD, enabling preventive measures and to design individually tailored treatment strategies.

Do distinct brain circuits medicate emotions/behaviours?

- Yes and No, sometimes it is localized but mostly:
- The same brain region may participate in different emotions, so there is no simple, one-to-one relation between an emotion/behavioural response and a specific brain region, but certain brain regions definitely have control functions in certain emotional/cognitive processes.
- Brain activation during sadness, happiness, anger, and fear show several brain regions involved (complexity).

The **vulnerability to mental illness** is determined by complex combined effects of genetic effects, early life events, and the adult environment.

Efficacy of **current available treatments** of mental disorders if often **limited** (and these treatments often focus on symptoms rather than mechanisms). There are few novel molecular candidates, partly because of **lack of appropriate preclinical models**.

Mental illnesses cannot be modelled in animals in their full complexity, but we can draw valid conclusions based in **animal models reflecting certain characteristics and symptoms of psychiatric disorders**.

Recent advances in neuroscience reveal with an unprecedented accuracy the **mechanisms underlying psychopathologies** and holt the promise of developing **specific, novel treatment strategies** that focus on eliminating the causes of disorders rather than on ameliorating their symptoms, and as such, may be **more efficacious** than current medications.

Alzheimer's disease

Lecture 14

- women have the prevalence about twice as men.
- above the age of 80 about every second living population member suffering from dementia

Dementia

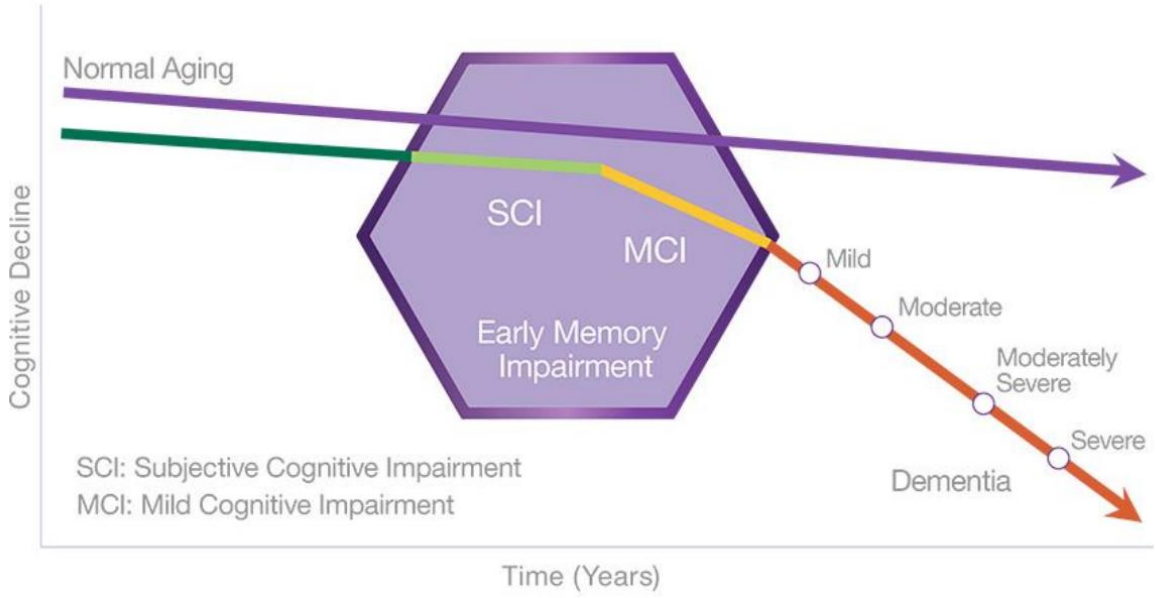
- collection of conditions
- DSM 5: Major and minor neurocognitive impairment
- Definition in DSM 4: „The development of multiple cognitive deficits that include memory impairment and at least one of the following cognitive disturbances: aphasia, apraxia, agnosia or a disturbance in executive functioning. The cognitive deficits must be sufficiently severe to cause impairment in the occupational or social functioning and must represent a decline from a previously higher level of functioning."

Mild cognitive impairment (MCI)

- Memory and/or other domains affected.
- Everyday activity/functions PRESERVED (no problem with them)

The spectrum of cognitive dysfunction

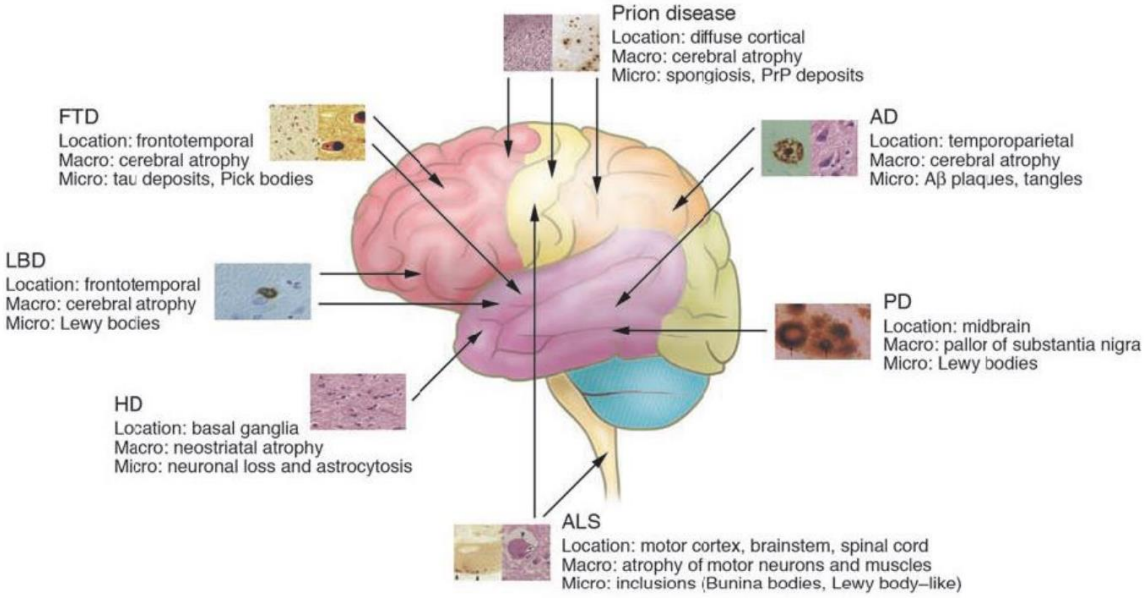
- problem: there is an obvious decay in the cognitive functions in normal aging and in some people parallel to this process the pathology begins, and the patient starts to complain about cognitive symptoms, but no cognitive symptoms are measured by sensitive neuropsychological tests. This stage is called Subjective Cognitive Impairment (SCI).
- The next stage is Mild Cognitive Impairment (MCI), when you can measure cognitive dysfunction but there are no problems in every activity and from there develop the symptoms of dementia in which the patient has everyday activity problem.



Causes of dementia:

- Primary degenerative dementia
    - Alzheimer's disease
    - Frontotemporal dementia
    - Lewy-body dementia
- Vascular dementia
- Trauma
- Tumours
- Hydrocephalus, NPH
- Infectious and inflammatory disorders
- Metabolic (exogenic and endogenic)/Toxic

Degenerative dementia



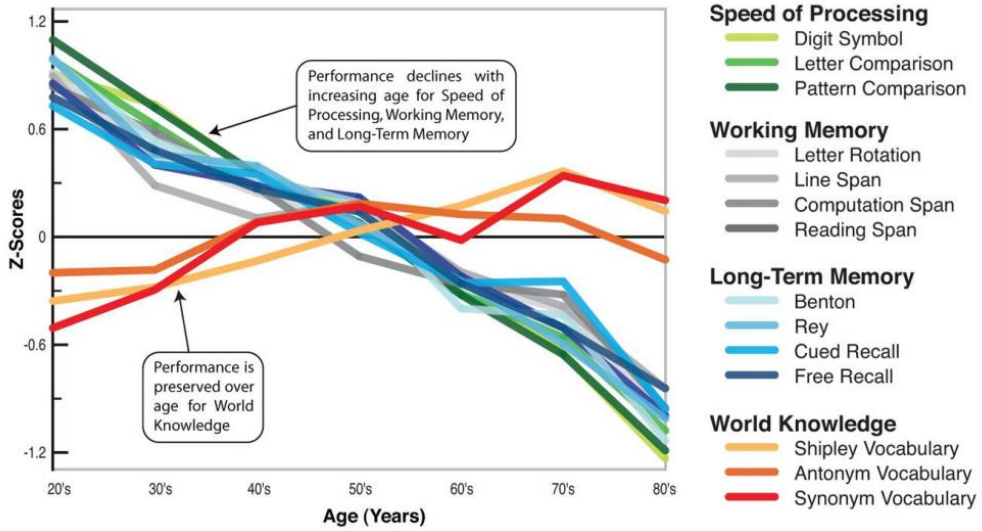
The commonest cause of dementia

- 70% Alzheimer disease
- 17% vascular dementia

In Hungary not many people are diagnosed with AD, so they think that mostly vascular dementia is causes Alzheimer disease

Cognitive functions and aging

- performance declines with increasing aging for Speed of Processing, Working Memory, and Long-Term Memory
- Performance is preserved over age for World Knowledge.



Brain volume with aging

- the lateral prefrontal cortex which is coding these executive functions steeply deteriorating with the age
- the volume of the lateral prefrontal function is decreasing with advancing age.
- in contrast the primary visual cortex, which function is quite preserved independently from the aging has a relatively stable volume.
- the hippocampal formation as the main memory storage structure is having a slight increase in size and then steeply deteriorating in elderly ages.

Healthy and pathological cognitive aging differences

- in vascularis dementia is the stepwise deterioration because repeated strokes are causing decreasing cognitive functions
- degenerative condition becomes more and more severe after any other type of brain lesion.

Alzheimer's disease

- histopathological changes
    - senile plaques are extracellular deposition of proteins.
        - formed by a peptide called beta amyloid.
    - neurofibrillary tangles are intra-neural inclusions.
        - main protein: hyper phosphorylated tau
        - initial formation in the locus coeruleus
- leads to neuronal and synaptic loss.
- these morphological changes are led to symptoms on the neuropsychological test.
- several ideas on what is causing the neuronal loss in AD.
- some believe that beta amyloids are the key players (they called Baptists), other believe that tau is the important one (they are the Taoist people)

The metabolism of amyloid precursor protein

- amyloid precursor gene
- large transmembrane protein with a water soluble alpha helical domain which protein contains a small fragment, which in normal conditions is cleaved off.
- two soluble isoforms of this APP are coming out from this procedure under normal conditions.
- in AD there are two other proteases which are splicing the protein and gamma and beta secretases are cutting out a peptide, which is called amyloid beta (37-42 amino acids), which is forming a beta sheet pattern.
- so, it will aggregate spontaneously forming dimers, oligomers, fibrillary aggregations, and these are aggregating into protein depositions int he ES, called senile plaques.
- the endogenous proteins cannot degrade this peptide which is aggregated.

Senile plaques

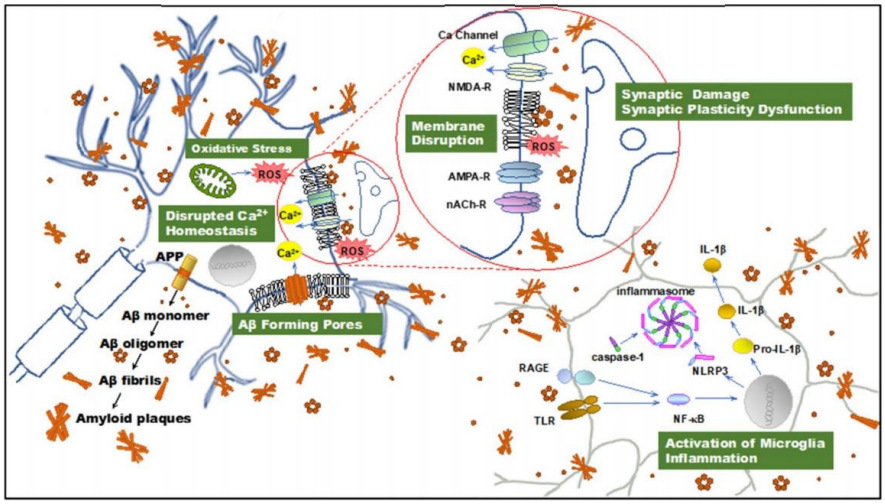
- Beta amyloid plaques
    - Subpial, Vascular, „Dysphoric", Granular, Diffuse (primitive), Laminar, Stellar, Ring-with-core (classical), Compact (burnt-out)
- „cotton wool" plaques in PSEN1 mutation

Thala's phase of amyloid deposition

1. starts in neocortical structures.
2. moves down to the limbic system, which is called allocortical stage.
3. subcortical nuclei
4. brainstem
5. latest stage: cerebellum

Neurotoxicity of beta amyloid

- forming amyloid beta pores in the membrane disrupting the calcium haemostasis, disrupting mitochondria functions, cdk mechanisms involved, microglial activation happens.



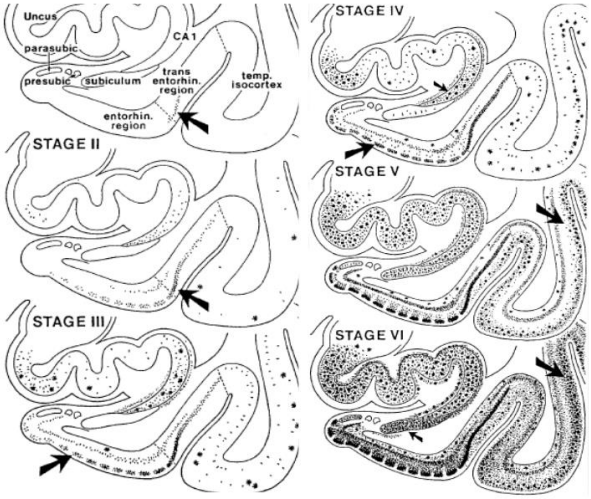
Tau

- In neurofibrillary tangles
- Hyperphosphorylation (MAPK, GSK-3?) probably happens with the MAPK or a glycogen synthesis kinase free enzyme.

Tau gene

- 17. chromosome
- 11 biallelic polymorphism, 5 AA change
- 15 exon, 11 coding; 2,3,10 alternative splicing ⇒ 3 or 4 microtubule binding domains

Braaks' stages of neurofibrillary degeneration



- Braak realized that those people who are in transcentrinal stage they are having no symptoms at all.
- those who are in the limbic stage, might have some symptoms; this stage probably corresponds to MCI.
- in neocortical stage people are usually affected with AD dementia

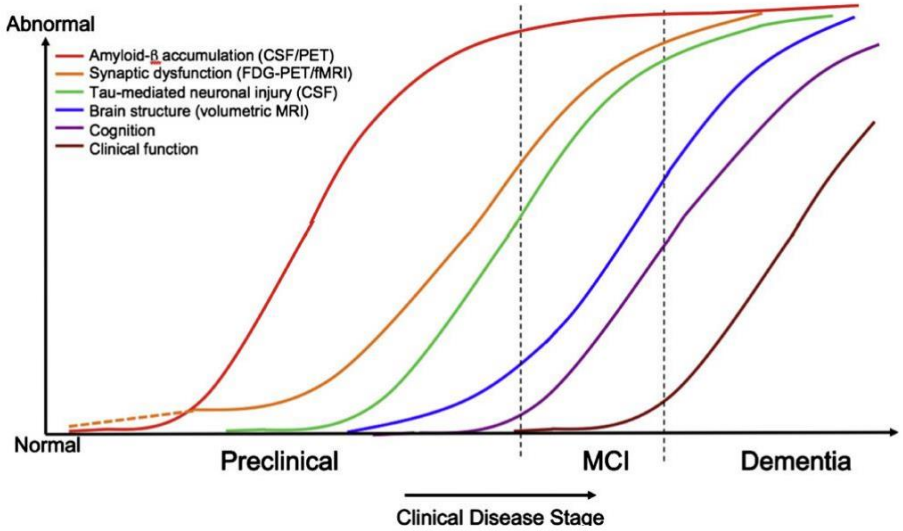
NIA-AA criteria of AD (ABC criteria)

		B NFT Stage (Braak)[1]			
A Aβ deposits (Thal Phases)[2]	C Neuritic Plaque Score (CERAD)[3]	0 (none)	1 (I/II)	2 (III/IV)	3 (V/VI)
0	0 (none)	Not AD	Not AD[4]	Not AD[4]	Not AD[4]
1, 2, or 3	0 (none)	Low	Low	Low	Low to Intermediate[5]
1, 2, or 3	1 (sparse)	Low	Low	Low	Intermediate[5]
1, 2, or 3	2 or 3 (moderate or frequent)	Low[6]	Low[6]	Intermediate	High

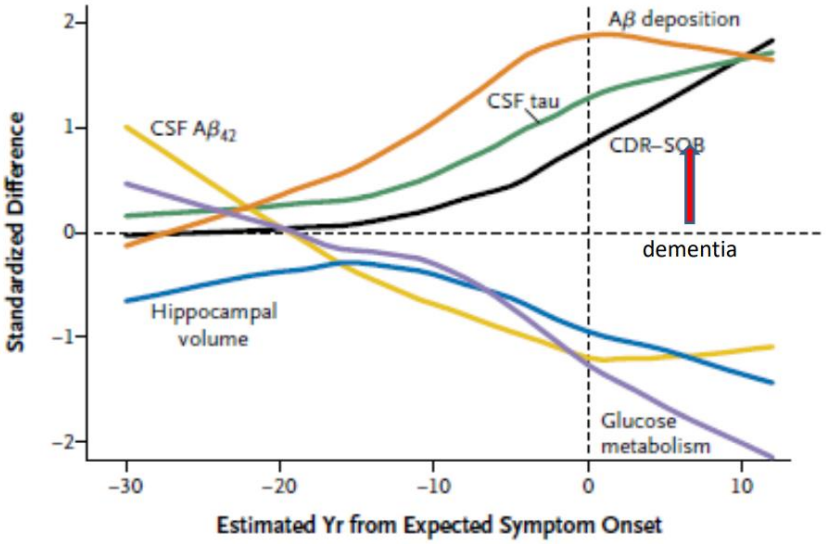
- without amyloid deposition it is not possible to call the disease Alzheimer's disease

Biomarkers during the course of AD

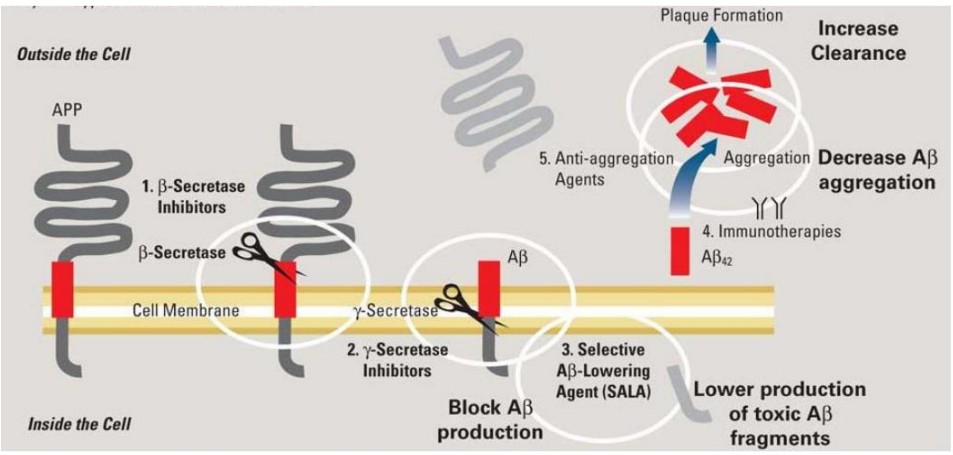
- this is the amyloid hypothesis.



Clinical and Biomarker Changes in Dominantly Inherited Alzheimer's Disease



Amyloid-based therapeutic options in AD



Active immunisation

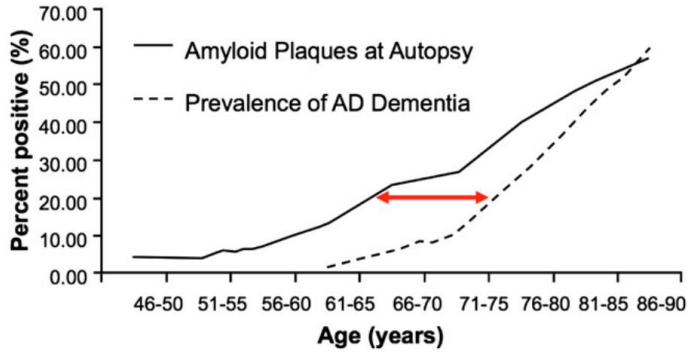
- Removal of brain amyloid
- Synaptic loss: no change
- No change in clinical condition

Passive immunisation against beta amyloid

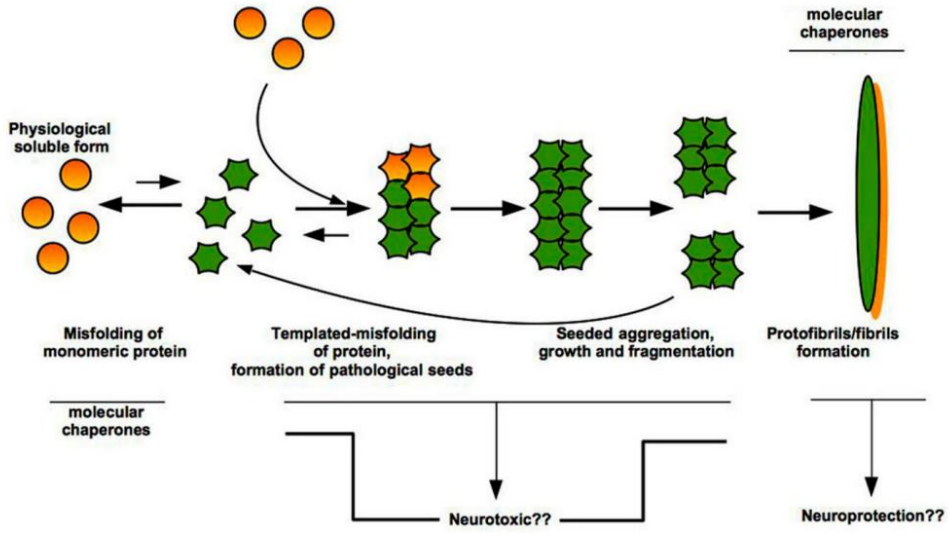
- microglia mediated.
- direct resolution
- peripheral sink
- blockade of toxic oligomers

Appearance of plaques vs. dementia

- 20 years difference



„spreading" → Prion diseases.



Spreading hypothesis

- Olfactory spreading of agents in degenerative diseases
- gastrointestinal system diseases spreading through the vagus nerve towards the brain, especially in Parkinson's disease.

Cerebellum

Lecture 15

Movement control

- *striatum/pallidum*: initiation of movements
  - sends info the thalamus.
  - persistent inhibition on the brain centres capable to initiate the movement.
  - movement initiation takes place by disinhibition.
- *thalamus*: integration of information deriving from the basal ganglia and cerebellum.
  - sends info the primary motor cortex.
- *cerebellum*: modification and coordination of movement
  - sends info the thalamus.
  - makes movements highly efficient and adaptive for the muscular system.
  - generates motor output patterns.
  - participates in learning new conditions and adapts the system to carry out movements.

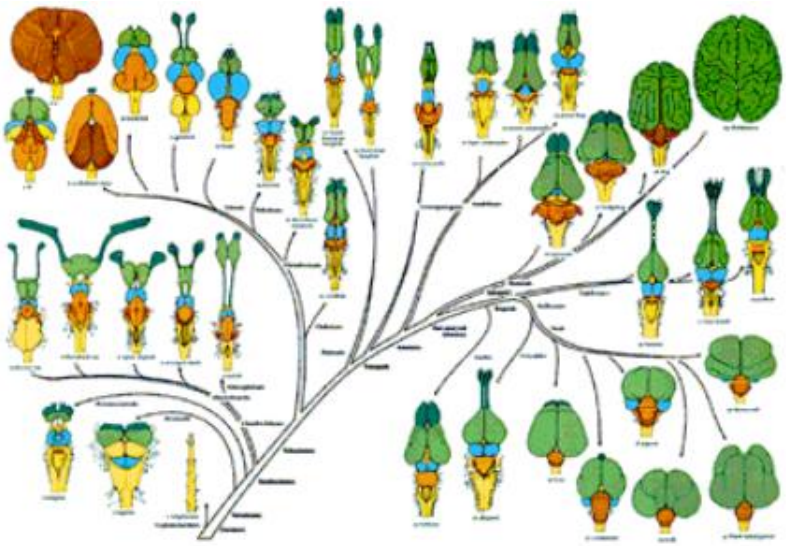
Cerebellum is a record and playback device!

> The cerebellum is capable of recording the motor pattern generated by the cerebral cortex (e.g., how to play the piano) Learns how to sit, hold the arms, hit the keys – and makes these movements automatic.

The **cerebellum** occupies approx. 10% of the brain volume but **contains over 50% of all the neurons**. **Over half of the neurons** in our brain are **dedicated to watch** what the other half of our neurons are doing. They monitor the changing conditions in the brain and can adapt our movement regulation to these conditions.

Phylogenetics and ontogenesis

The development of the CNS has many different ways of controlling movement and body functions. According to the phylogenetic branch, the cerebellum develops dramatically and surpasses the development of the cerebrum.



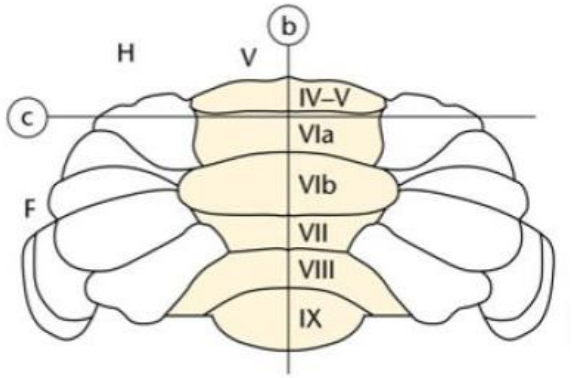
Macroscopic and microscopic structure

Major subdivisions of mammalian cerebellum

This phylogenetic development is reflected in the different parts of the cerebellum, which has three major parts:

- Vestibulocerebellum (archicerebellum)
  - developed first in the fish.
  - controls posture, balance, eye movements
  - the flocculo-nodular lobe belongs to this ancient part of the cerebellum.
  - also present in higher-order animals
- Spinocerebellum (paleocerebellum)
  - controls involuntary movements linked to e.g., body position, movement of the legs and the arms and regulates the muscle tone
  - medial (vermis) + intermediate cortex
- Cerebrocerebellum (neocerebellum)
  - planning and controlling of voluntary movements
  - lateral cortex

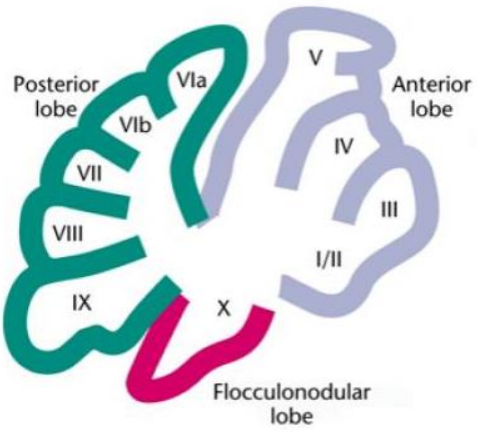
Antero-posterior (b) and medio-lateral (c) organisation of the cerebellum



Cerebellar tonsils: they have clinical significance, because they are on the side of the brainstem and when there is an intracranial pressure increased, then these tonsils can squeeze the brainstem into the foramen magnum of the skull and that can kill a person by preventing a good blood circulation in the brainstem, which is the centre of the respiration and circulation.

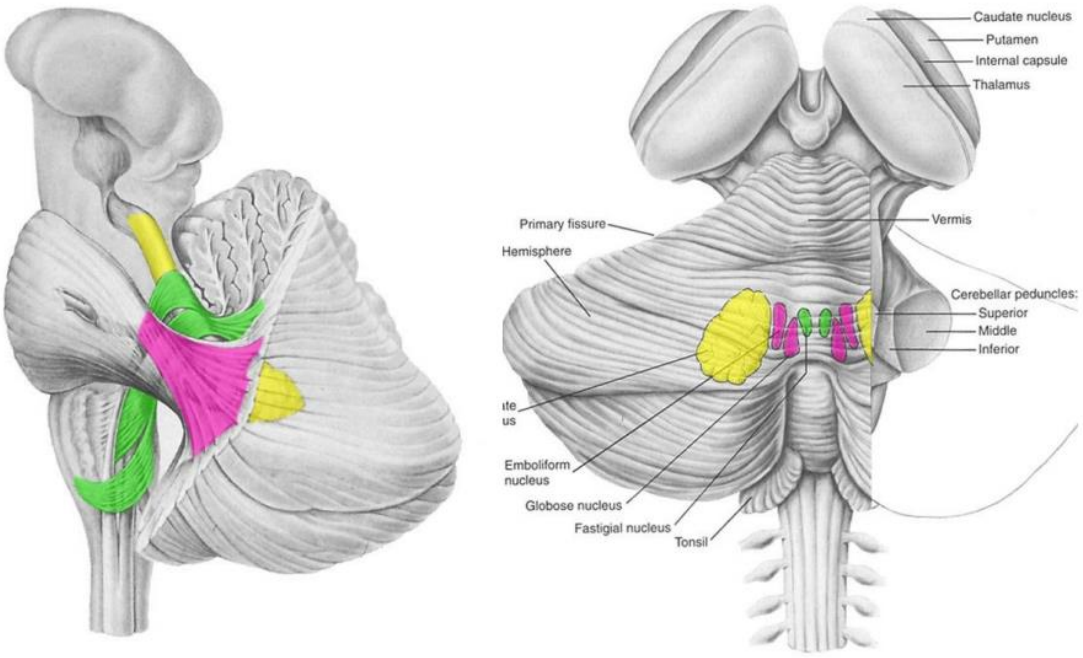
The cerebellar hemispheres are on the side of the vermis.

In the centre bit we can find the *vermis*, which consists of 10 different lobules:



These lobules belong to 3 major lobes: the *anterior lobe*, the *posterior lobe*, and the *flocculo-nodular lobe*. These lobules have continuations in the lateral direction.

Input and output



The cerebellum is connected to the brainstem, the pathways that connect these 2 are the cerebellar peduncles:

- *inferior peduncle*: communicates primarily with the medulla oblongata.
- *middle peduncle*: communicates with the pons.
- *superior peduncle*: communicates with the midbrain.

Each of these peduncles carry pathways and target primarily the cerebellar nuclei which are grey matter, so a group of neurons inside the white matter of the cerebellum.

These nuclei are:

- dentate nucleus: the biggest one, it is located in the cerebellar hemisphere and it communicates with the cerebrum.
- nucleus interpositous: communicates with the spinal cord.
  - emboliform nucleus
  - globose nucleus
- fastigial nucleus: communicates with the vestibular pathways.

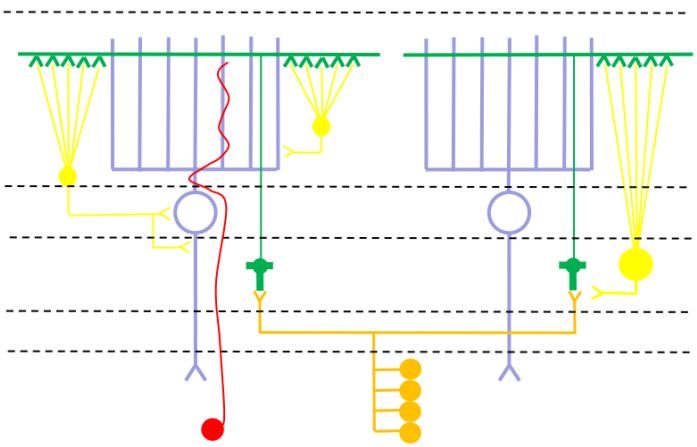
Histology

A mammalian cerebellar cortex is composed of three layers. A thin layer if white matter separates the cortical parts from each other.

- *molecular layer* (low density)- here we can also find the processes of Purkinje cells and incoming fibers.
- *Purkinje cell layer* (thin layer)- Purkinje cells are about 5 times bigger than the granule cells.
- *granule cell layer* (high density)

Similar to the cerebral cortex, the cerebellar cortex is highly folded (→ cerebellar folia). This increases the surface the possibilities for neurons to establish connections.

Basic neuron types



- Purkinje cells (purple colour)
  - the cell bodies occupy the Purkinje cell layer.
  - the dendritic tree of them extend to the molecular layer.
  - the axons pass through the granule cell layer to enter the white matter.
- granule cells (green colour)
  - they occupy the granule cell layer.
  - they have larger 3-4 dendritic processes there.
  - their axon ascends into the molecular layer and divide into two processes (→ parallel fibers) and establish connections with Purkinje cells and other cell types located in the molecular layer.
- mossy fibers (dark yellow colour)
  - they give input to the granule cells.
  - they derive from the vestibular nuclei.
- Golgi cells (light yellow colour- right)
  - they are inhibitory.
  - their cell body is located in the granule cell layer.
  - their dendrites extend into the molecular layer and receive information from the parallel fibers.
  - they send their axons to the place where the mossy fibers terminate on the dendrites of the granule cells, together they form a complex synapse, which is called the glomerulus of the cerebellum.
- basket cells (light yellow colour- left)
  - inhibitory cell types, that controls the output of the Purkinje cells with high efficiency.
  - receive information from the parallel fibers.
  - they project to the cell body and the axon initial segment of the Purkinje cells.
- stellate cells (light yellow- middle)
  - receive information from the parallel fibers.
  - they send their axons to the dendritic tree of the Purkinje cells.
  - they are capable to control the input of the Purkinje cells.

- climbing fibers (red colour)
    - their cell bodies are found in the brainstem (in the *inferior olive*)
    - they enter the cerebellar cortex and wind around the dendritic tree of the Purkinje cells.
    - they stimulate the Purkinje cells highly effectively.

The ultrastructure of a synapse:

- inhibitory:
    - the vesicles gather together at the presynaptic membrane.
    - they have different shape and size (typical of inhibitory synapses)
    - inhibitory cells (like basket cells) use GABA to inhibit the Purkinje cells.
- excitatory:
    - the post synaptic membrane has a very thick, electron dense layer.
    - synaptic gap: widened, there are adhesion molecules.
    - asymmetric
    - round vesicles
    - e.g., mossy fibers bring excitation to the granule cells, the parallel fibers bring excitation to the Purkinje cells

Operation of the cerebellum

- the cerebellum generates *neuronal activity pattern* to most movements.
- this is independent of whether it is carried out consciously or unconsciously.
- the cerebellum learns all cerebral activity pattern which are related to moving our musculoskeletal system.
- it stores the corresponding motor output patterns.
- when the cerebellum recognises a cerebral activity pattern, which brings the skeletal muscles in operation, it projects the learned motor output pattern immediately to the primary motor cortex (M1) via the thalamus.
- the motor output pattern of the cerebellum is used by the M1 to innervate the lower motor neurons unless this program is overwritten on purpose or by sudden change in the prevailing conditions.
- *the cerebellum is our autopilot*, we do not have to control movements consciously.

Motor symptoms of cerebellar dysfunctions

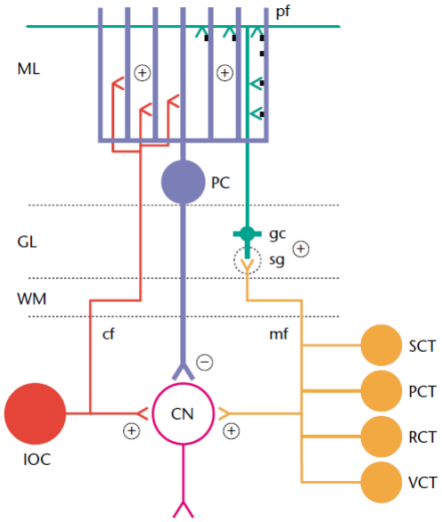
- people are unable to coordinate different body parts during movement.
- they are unable to adjust the proper extent of movement.
- they are unable to carry out fast, altering movements.
- they are unable to produce coordinated, multisegmental movement combination.
- muscle tone is lost.
- involuntary eye movements
- involuntary oscillating movements in the limbs

Pathways terminating in mossy fibers:

- pontocerebellar tract
  - brings information from all parts of the cerebral cortex.
  - there are corticopontine pathways descending to the pons where we can find nuclei and these nuclei will project to the cerebellum.
  - reading what we are willing to do.
- spinocerebellar tract
  - reading what is the position of our limbs.
- reticulocerebellar tract
  - brings information whether we move or not what are the conditions during walking.
- vestibulocerebellar tract
  - informs us about the position of our body before we start the movement.

<u>Neuronal connections – Electrophysiology</u>

Basic inputs: mossy fibers and climbing fibers.



- inferior olive cells (red) and granule cells (green) establish morphological and functional units in the cerebellum.
- a set of Purkinje cells are innervated by the inferior olive cells → *olivocerebellar module.*
  - climbing fibres innervate 10 Purkinje cells in the sagittal plane.
  - 300-1000 parallel contact-type synapse on each Purkinje cell- highly efficient!
- parallel fibers also innervate Purkinje cells in 2-4 mm distance→ *granulocerebellar module.*
  - there are about 200 000 crossover synapses on each Purkinje cell.
  - the efficiency of a single synapse established by a parallel fibre on a single dendritic spine is very low, we need many parallel fibers to get the Purkinje cell activated.
- most of the inputs target the deep cerebellar nuclei (pink), which generates the output.
- Purkinje cells are inhibitory, when they are in action, they inhibit the deep cerebellar nuclei, so the output is generated when the Purkinje cells are not in action.

- when the output is stopped, learning is running in the molecular layer.

Olivocerebellar module

- In each module a particular subnucleus of the inferior olive (IO) provides climbing fibres (CFs) to a particular, sagittally oriented zone of Purkinje cells (PCs), which in turn inhibit neurons in particular vestibular and/or cerebellar nuclei (CNs) that project back to the same olivary subnucleus.
- Olivary neurons are coupled by gap junctions within glomeruli, where the inhibitory terminals from the CN interact with excitatory terminals derived from brainstem areas such as the meso-diencephalic junction (MDJ).

Inhibition and excitation in the OC module

- In the cerebellar cortex, the dendrites, and axons of the molecular layer interneurons (MLIs) and Golgi cells stay within the boundaries of the sagittal PC zones.
- MLIs and Golgi cells are innervated directly by parallel fibres (PFs) and, via spill over, by CFs. MLIs and Golgi cells inhibit PCs and granule cells (GCs), respectively.
- The mossy-fibre (MF) axons of the local excitatory interneurons — the so-called unipolar brush cells (UBCs) — are relatively short and they forward signals to GCs.

Granule cell axons span multiple OC models.

- Thus, most cells involved in feedforward and feedback inhibition, as well as those involved in feedforward excitation, operate within the same sagittal PC zone as the CFs that provide the dominant drive of that particular PC zone.
- By contrast, the GCs, which are innervated by extracerebellar MFs and the MFs derived from UBCs, show ambiguous possibilities in that the ascending parts of their axons stay within zones, whereas their PFs span multiple sagittal zones.

Activity pattern in the OC module

- Inferior olive neuron in vivo has an oscillatory membrane potential and shows *occasional spiking*.
- Inferior olive spikes are mediated by calcium channels (mostly T-and P/Q-type channels), voltage-gated sodium channels and calcium-dependent potassium channels.
- *Oscillation*: generated at the low threshold T-type Ca channels → soma depolarization → high threshold P/Q channels → dendrite depolarization → potassium channels → hyperpolarization → low threshold T channels

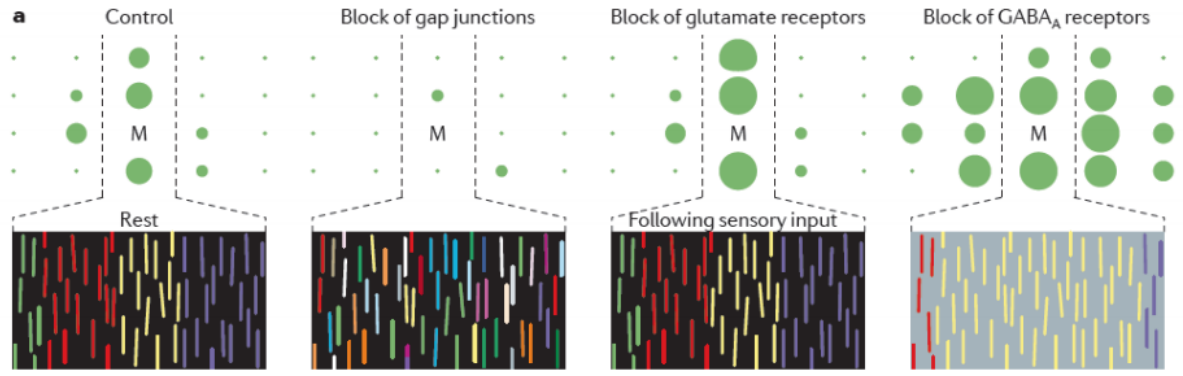
Activity of the Purkinje cells

- Purkinje cell activity in an alert mouse shows *simple spikes* and a *complex spike*.
- The complex spike is followed by a pause in simple-spike activity.
- Complex spikes are mediated by voltage-gated sodium channels and calcium channels, whereas the subsequent afterhyperpolarization is mediated by calcium-dependent potassium channels.

Activity pattern of CN cells

- An electrical stimulus to the cerebellar cortex can elicit a *burst of rebound action potentials* in a mouse cerebellar nucleus neuron.
- The right panel shows the averaged action potential of cerebellar-nucleus neurons, indicating the roles of sodium channels and low- and high-voltage activated calcium channels (mostly T-and N-type calcium channels, respectively).
- The slow-spike afterhyperpolarization is controlled by SK calcium-dependent K+ currents.
- The membrane potential of these neurons is continuously depolarized by calcium channel activation.

Synchronization of complex-spikes is influenced by events in the OI glomeruli.



- The coloured images represent the zones of Purkinje cells within the cerebellar module, there are about 3-19 lines of Purkinje cells in a microzone in the cerebellar cortex during activation.
- Within the microzones, there is a master Purkinje cell which is targeted primarily, the neighbouring Purkinje cells are about 250 µm away.
- The green dots represent the level of synchronization of the Purkinje cells with the master Purkinje cell.
- At normal conditions, we can see that further away from the master cell, there is less synchronization.
- When we block the gap junctions in the inferior olive, they are unable to synchronize there, so it will result in the disappearance of the synchronization of the Purkinje cells as well. We cannot see the separated microzones.
- When we block the glutamate receptors, the size of the microzones does not change. (Following e.g., sensory input.) In the microzones, the synchronization between the Purkinje cells is increased.
- When the inhibition is blocked in the inferior olive, the synchronization between the neighbouring Purkinje cells will be increased and the microzones will be enlarged.

How do we learn to respond to a new stimulus?

Some of the synapses, which will not be used anymore, will be inhibited. To learn new things, some of them will be potentiated and become stronger and will carry the new information to control the movement.

Oliva Inferior (OI)'s role in learning

- major input from nucleus ruber parvocellular
- reading the output of motor cortex

Summary

- The cerebellar cortex is *continuously involved* in controlling our muscular output behaviour.
- The afferent signal manifests as excitation on the Purkinje cells. The parallel fibers transmit *contextual sensory information* from the rest of the brain, while the climbing fibers ascend from the inferior olive and deliver a powerful, complex spike when an *error is noticed during a novel task.*
- An active climbing fibre input causes the cerebellar circuit to stop output and causes *the Purkinje neuron to learn (every second) the current dendritic pattern*. The Purkinje neuron firing causes its dendritic synapses that are active to be *strengthened* (LTP) and those that become inactive to be weakened (*LTD*).

Basal ganglia

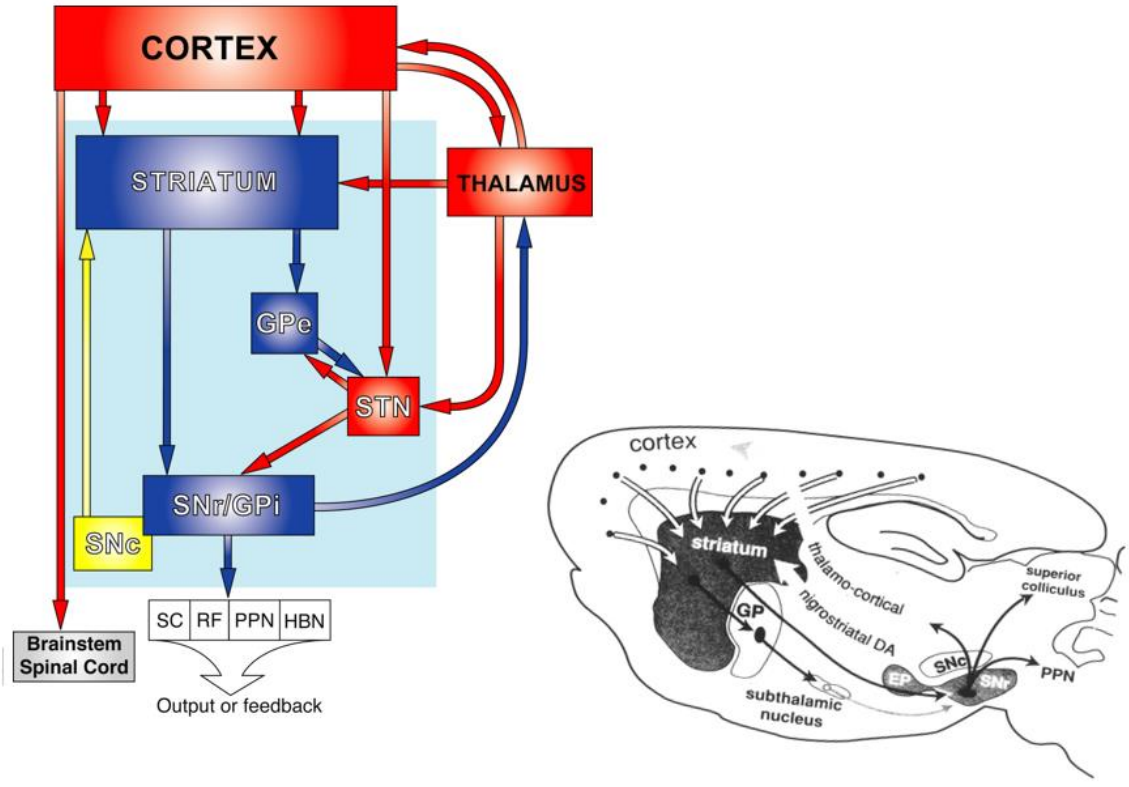
Lecture 15

The basal ganglia provide a major neural system through which the cortex effects behaviour:

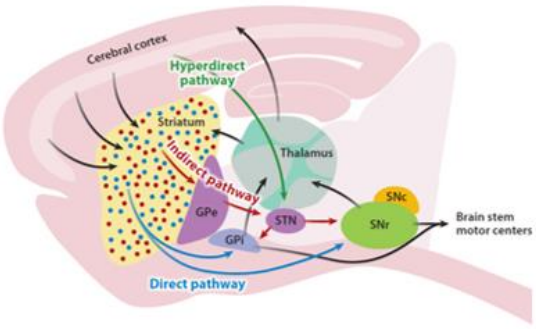
- voluntary control of movement (compromised by neurodegenerative diseases that involve the basal ganglia, e.g., Parkinson's disease and Huntington's chorea)
- broad role in the most subtle components of voluntary movements: e.g., action selection, memory, motivational, and emotional
- procedural learning, habits, addictive behaviour

<u>The basal ganglia consist of 4 major brain regions</u>:

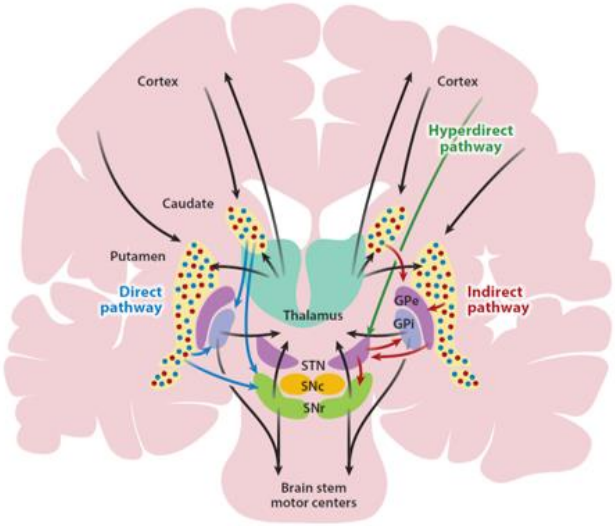
- striatum
- globus pallidus (GPe)
- substantia nigra
    - pars compacta (SNc)
    - pars reticulata (SNr) – major site of output
- subthalamic nucleus (STN)



Rat brain



Human brain



In the human brain the cortex's size is considerably relative to any other brain region. The *striatum* in the human brain is proportionately much smaller than the rat's (left image), but the same nuclei can be easily found. The *caudate nucleus* and the *putamen* together represent the *striatum*. The globus pallidus has two functionally distinct parts, the globus *pallidus externa* (dark purple), and the globus *pallidus interna* (light purple).

Three main transmitters:

- GABA (blue on the previous picture)
- glutamate (red on the previous picture)
- dopamine (yellow on the previous picture)

Additional co-transmitters:

- acetylcholine
- somatostatin
- enkephalin (GPe)
- substance P
- dynorphin

The direct/indirect pathway model of basal ganglia

Anatomical data that gave rise to the model initiated the surgical and the deep brain stimulation treatments of Parkinson's disease!

direct pathways:

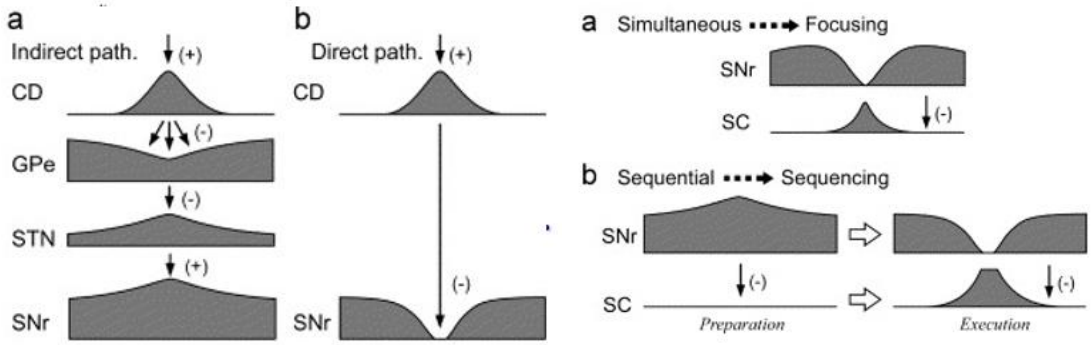
- cortex → striatum → substantia nigra: disinhibition of the targets of the basal ganglia
- when the striatum is silent, the substantia nigra will inhibit the output structures of the basal ganglia.
- when the striatum gets activated, it will inhibit the substantia nigra, this way, it will disinhibit the output structures of the basal ganglia.

indirect pathway:

- those neurons, that innervate the globus pallidus.
- the striatum will inhibit the globus pallidum GABAergic neurons, so they disinhibit the subthalamic nucleus' glutaminergic neurons → it will enhance the activity of the substantia nigra → enhancing inhibition of the output structures.

Output signal of the basal ganglia:

- resting conditions: basal ganglia *tonically inhibit* their targets.
  - (thalamus, superior colliculus, reticular formation, pedunculopontine nucleus, habenula)
- activating the *direct pathway*: disinhibition of basal ganglia targets
- activating the *indirect pathway*: inhibition of basal ganglia targets



Principle cell types of the striatum: the medium-size spiny neurons

- Projection neurons of the direct and indirect pathways are morphologically similar, both are GABAergic, but differ neurochemically.
- MSN neurons are the major targets of both corticostriatal and nigrostriatal afferents.

Functional organization of the basal ganglia

- The synaptic organization provides direct evidence for the existence of the *direct pathway*, and for *disinhibition* of basal ganglia targets.
- The synaptic organization provides direct evidence for the existence of the *indirect pathway*, and for *inhibition* of basal ganglia targets.
- Direct pathway:
  - basal ganglia behaviour
  - downregulated
- Indirect pathways:
  - inhibition, attenuation of basal ganglia behaviour
  - upregulated
- Imbalance between activity in the direct and indirect pathways →various disorders
- Attempt to restore the balance! →Surgical interventions in Parkinson's disease:
  - pallidotomy (akinesia): destroys the output of the basal ganglia.
  - subthalamotomy (akinesia)
  - deep brain stimulation of STN: seems to be the most successful treatment.
- Intralaminar thalamic nuclei also provide glutamatergic innervation of the striatum.

Convergence of the direct and indirect pathways

- they converge to the same projection neurons.
- innervation of the same neurons

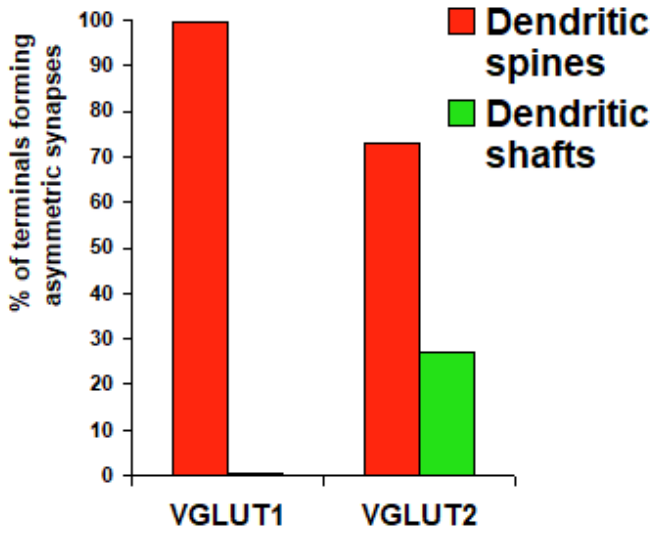
Neurons of the globus pallidus and their interactions with GABA interneurons in the striatum

- GP neurons innervate all caudal structures via collaterals.
- about one third of GP neurons also innervate the striatum
- neurons of the globus pallidus (GPe)
    - number of neurons in GPe = $4.6x10^4$
    - proportion projecting to striatum = 25%
    - mean number of boutons in striatum = $7.9x10^2$
    - total number of pallidal boutons in action → $9.08x10^6$
    - total number of neurons in the striatum: $2.79x10^6$
    - → therefore 3.25 pallidal boutons per striatal neuron
- GPe neurons innervate PV-positive GABA interneurons.
- GABAergic interneurons in striatum
    - GABA interneurons receive input from cortex.
    - may provide a feed-forward inhibition of output neurons.
    - may synchronise the activity of 'selected' groups of output neurons.
    - spatio-temporal selection of spiny neurons
- individual GABA interneurons innervate large numbers of spiny neurons.

Vesicular glutamate transporters are selectively expressed by corticostriatal (VGluT1) and thalamostriatal (VGluT2) neurons.

VGluT1 in corticostriatal terminals and VGluT2 in thalamostriatal terminals.

Thalamostriatal projections are of similar magnitude to the corticostriatal projections.

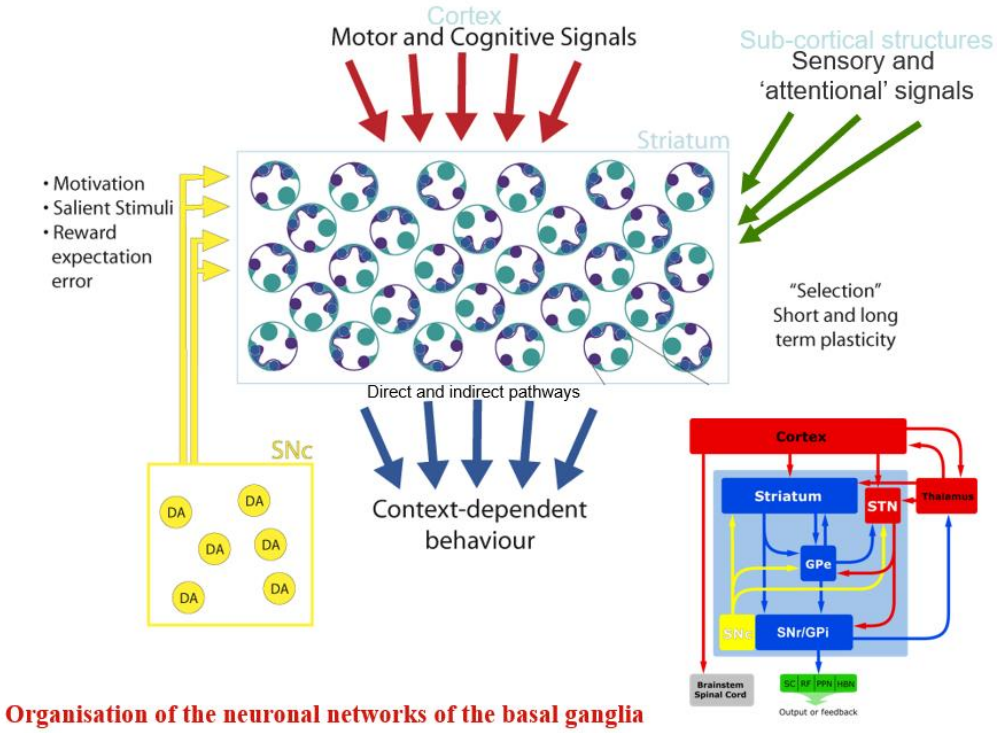


The thalamostriatal projection is complex, exhibiting a rich and diverse complexity of function.

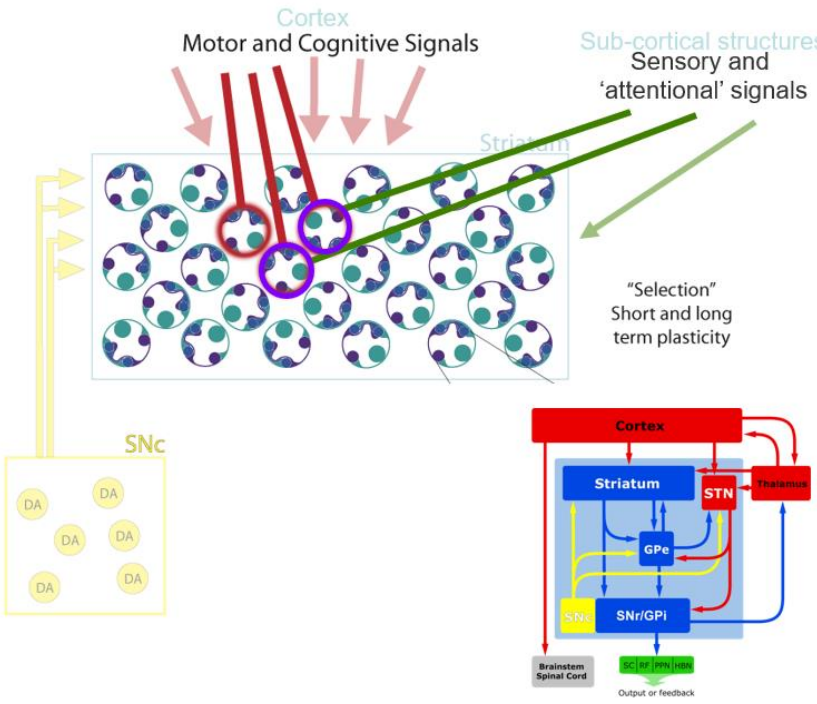
Cortical and thalamic afferents have a similar synaptic arrangement in the striatum.

A high proportion of thalamic terminals, like cortical terminals, form convergent inputs with dopamine terminals on spines of MSN neurons.

The interaction between glutamate and dopamine applies equally to the cortical and thalamic inputs.



Organisation of the neuronal networks of the basal ganglia



Neural modelling

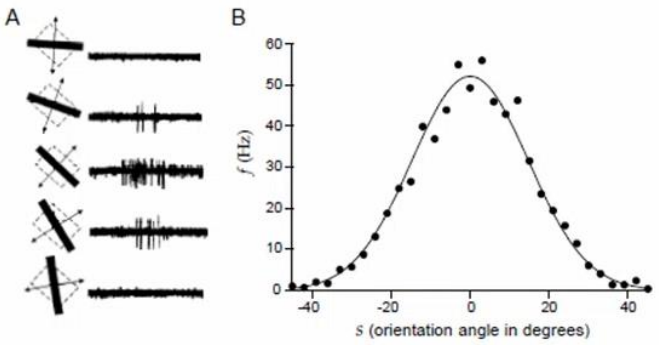
Lecture 16

Types of models:

- descriptive
  - connection between quantities and we describe it with mathematical equations.
  - tries to answer this question: What is it like?
  - e.g., neuron receiving synaptic input and we want to describe the time course of this input
- mechanistic
  - most usual meaning of model types
  - tries to answer this question: How does it function?
  - e.g., already have a descriptive model of single neurons, and we want to understand how networks function
- explanatory
  - not that common, but very important
  - tries to answer this question: Why is it like that?
  - general answer: because of surviving

How is information encoded by action potential trains?

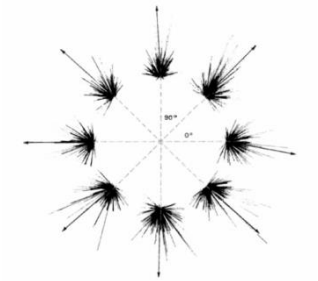
- neurons respond to input typically by producing complex spike sequences that reflect both the intrinsic dynamics of the neuron and the temporal characteristics of the stimulus.
- simple way: count the APs fired during stimulus, repeat the stimulus, and average the results:



- Picture: recordings from the visual cortex of a monkey. A bar of light was moved through the receptive field of the cell at different angles (fig. A). The highest firing rate was observed for input oriented at 0 degrees (fig. B).

How to decode information encoded by AP trains?

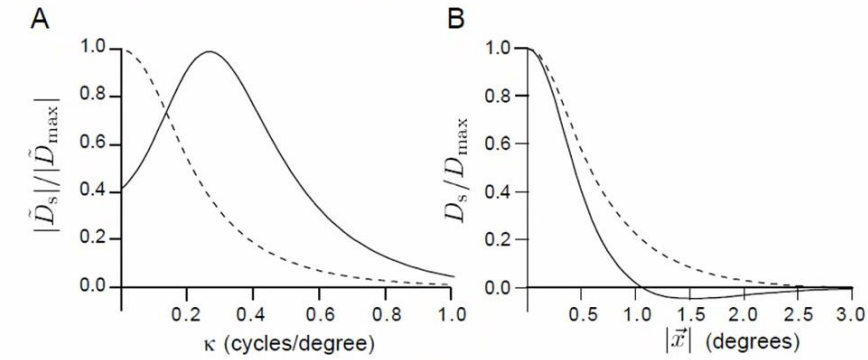
- Example: arm movement position decoding: If we take the average of the preferred directions of the neurons weighted by their firing rates, we get the arm movement direction vector.



- Picture: Comparison of arm position and arm position-sensitive neurons. The population activity was recorded in 8 directions. Arrows indicate vector sum of preferred directions, which is approximately the arm movement direction.

Why does a given part of the brain use a specific type of coding?

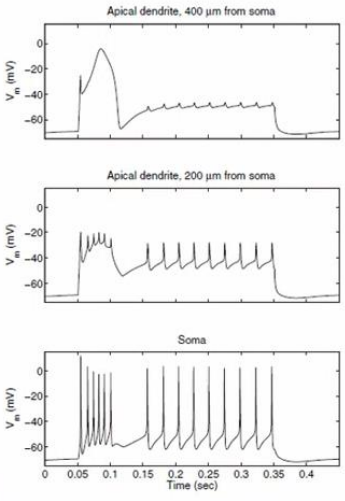
- Example: Visual input noise filtering in ganglion cells: The structure of the receptive field changes according to the input signal-to-noise ratio



- Solid curves are for low noise input (bright image), dashed lines are high noise input.
- Left image: The amplitude of the predicted Fourier-transformed linear filters
- Right image: The linear kernel as a function of the distance from the centre of the receptive field.

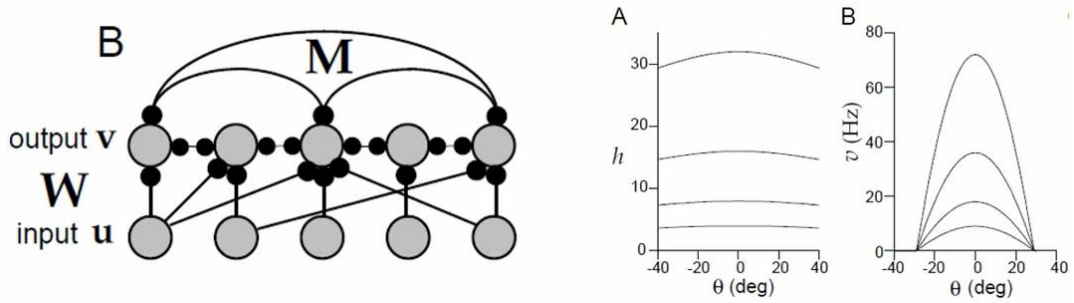
How do neurons as information processing units' function?

- Specifically, what is the relation between the temporal and spatial pattern of the input and the spatial and temporal pattern of the output?
- Picture: the effects of constant sustained dendritic current injection in a detailed model of a hippocampal pyramidal neuron. The cell responds with a burst of spikes, then sustained spiking. In distal regions only a slow, large-amplitude initial response is visible, corresponding to a dendritic calcium spike.



How do neurons communicate, and what collective behaviours emerge in networks?

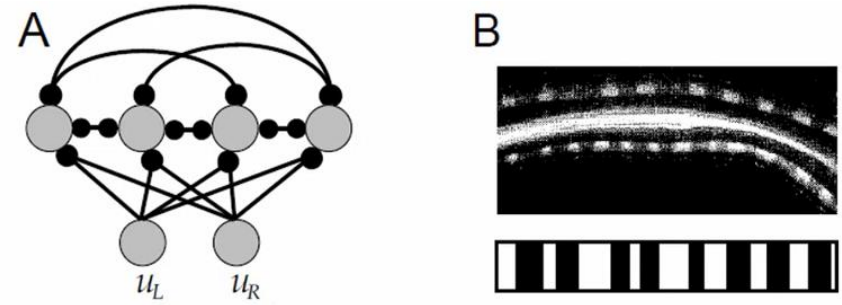
- Example: Orientation selectivity and contrast invariance in the primary visual cortex



- Left image: schematics of a recurrent network with feedforward inputs.
- Middle image: The effect of contrast on orientation tuning.
- Fig. A: orientation-tuned feedforward input curves for 80%, 40%, 20%, 10% contrast ratios.
- Right image: The output firing rates for response to input in fig. A.
- Due to network amplification, the response of the network is much more strongly tuned to orientation as a result of selective amplification by the recurrent network, and tuning width is sensitive to contrast.

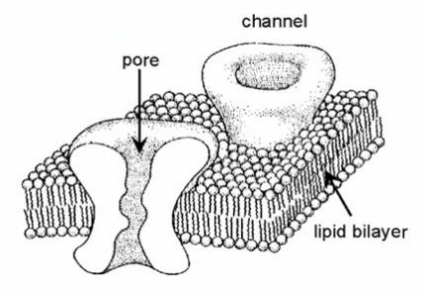
How does cellular-level (synaptic) plasticity function? How can we understand behavioural-level learning? What is the connection between the two?

- Example: The development of ocular dominance stripes in the primary visual cortex.



- Left image: schematics of the model network where right – and left-eye inputs from single retinal location drive an array of cortical neurons.
- Right image: Ocular dominance maps, the light and dark areas along the cortical regions at the top and bottom indicate alternating right- and left-eye innervation.
- Top: In vitro measurement
- Bottom: The pattern of innervation for the model after Hebbian development.

How neurons function and how can we model the function of neurons?



Neuronal membrane:

- lipid bilayer (insulator)
- ion channels
    - selectivity
    - modulation:
        - membrane potential
        - intracellular messengers (e.g., Ca^{2+})
        - neurotransmitters and –modulators
- ion pumps
- receptors not bound to ion channels.
- others

Ohm's law for drift

$$J_{drift} = -\mu z\,[C]\,\frac{\partial V}{\partial x}$$

J_{drift}	: Drift flux $(molecules/sec \cdot cm^2)$
μ	: Mobility $(cm^2/V \cdot sec)$
z	: Valence of the ion
$[C]$	: Concentration of ions $(molecules/cm^3)$

- Charged particles (e.g., ions) in a fluid (e.g., cell plasma or extracellular fluid) experience a force resulting from the interaction of their electric charges and the electric field in the environment.
- The equations states that drift of positively charged particles take place down the electric potential gradient and is everywhere directly proportional to the magnitude of that gradient.

Fick's law, diffusion of particles caused by concentration differences.

$$J_{diff} = -D\frac{\partial\,[C]}{\partial x}$$

J_{diff}	: Diffusion flux $(molecules/sec \cdot cm^2)$
D	: Diffusion coefficient (cm^2/sec)
$[C]$	: Concentration of ions $(molecules/cm^3)$

- Fick's law states that diffusion takes place down the concentration gradient and is everywhere directly proportional to the magnitude of that gradient, with proportionality constant D.

The Einstein relation between diffusion and mobility

$$D = \frac{kT}{q}\mu$$

μ	: Mobility $(cm^2/V \cdot sec)$
D	: Diffusion coefficient (cm^2/sec)
k	: Boltzmann constant
T	: Temperature (Kelvin)
q	: Charge of the molecule

- The relationship states that diffusion and drift processes in the same medium are related because the resistance presented by the medium to the two processes are the same.
- This equation enables us to convert diffusion coefficient to mobility.

Nernst-Planck equation

- From Ohm's law, Fick's law and the Einstein relation, the total current density is:

$$J = J_{drift} + J_{diff} = -\left(uz[C]\frac{\partial V}{\partial x} + u\frac{RT}{F}\frac{\partial [C]}{\partial x}\right)$$

- Which is the Nernst-Planck equation (in molar form, J is in $mol/sec{\cdot}cm^2$, and $u = \mu/N_A$, where N_A us Avogadro's number (6x1023/mol))
- The current density form of the equation can be obtained by multiplying the molar flux (J) by the molar charge (zF):

$$I = J \cdot zF = -\left(uz^2F[C]\frac{\partial V}{\partial x} + uzRT\frac{\partial [C]}{\partial x}\right)$$

- where I am A/cm^2.
- The Nernst-Planck equation describes the ionic current flow driven by electrochemical potentials (concentration gradient and electric field).
- This equation describes the passive behaviour of ions in biological systems.
- If the total electric current across the membrane is zero ($I = 0$),

$$\frac{\partial V}{\partial x} = -\frac{RT}{zF}\frac{1}{[C]}\frac{\partial [C]}{\partial x}$$

- If we integrate both sides across the membrane and define the membrane potential of a cell as

$$V_m = V_{in} - V_{out}$$

- the reversal potential of ion i, defined as the membrane potential where the membrane current carries by ion i is zero, can be expressed as:

$$E_i = V_m(I_i = 0) = \frac{RT}{zF} ln \frac{[C]_{out}}{[C]_{in}}$$

- This is called the **Nernst equation**.

- The Nernst equation also implies that when the membrane is at the reversal potential of an ion species, the cross-membrane voltage (drift force) and concentration gradient (diffusion force) exert equal and opposite forces.

Goldman-Hodgkin-Katz equation

- In typical neuron $[K^+]_{in} > [K^+]_{out}$ but $[Na^+]_{in} < [Na^+]_{out}$, $[Ca^{2+}]_{in} < [Ca^{2+}]_{out}$ and $[Cl^-]_{in} < [Cl^-]_{out}$
- The anions inside the cell, which cannot pass through the membrane, must be considered in the calculation too.
- Most of the ions are not in equilibrium:
- E_{Na}: 50 mV
- E_{Ca}: 150 mV
- E_K: -90 mV
- E_{Cl}: -70 mV
- Thus, ionic currents start to flow as soon as ion channels open, and ion concentration must be maintained by active transport (ion pumps).
- The equilibrium membrane potential is determined by the ion permeabilities of the membrane (Goldman-Hodgkin-Katz equation):

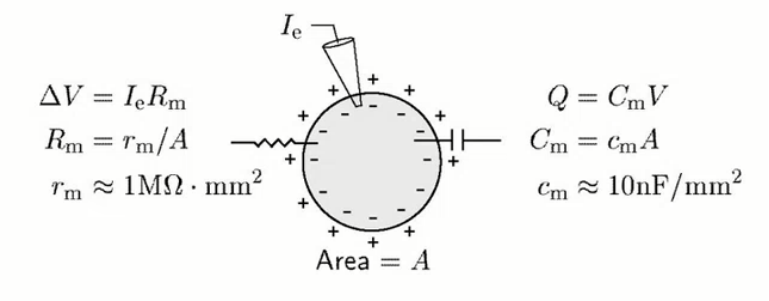
$$V = \frac{RT}{F} \ln \frac{P_K[K^+]_{out} + P_{Na}[Na^+]_{out} + P_{Cl}[Cl^-]_{in} + \dots}{P_K[K^+]_{in} + P_{Na}[Na^+]_{in} + P_{Cl}[Cl^-]_{out} + \dots}$$

- Where:
  - P_{ion} is the permeability for that ion (in meters per second)
  - V is the membrane potential.
  - [ion] is the concentration of that ion (in moles per cubic meter)
- The Goldman-Hodgkin-Katz equation is used in cell membrane physiology to determine the equilibrium potential of the cell's membrane considering all of the ions that are permeant through that membrane.

Resting potential

- The resting potential (V_{rest}) is between -80 and -50 mV, and with the change of the permeabilities the membrane potential can take up values between -90 mV and +50 mV.
- The following processes influence the membrane potential:
  - Depolarizing and hyperpolarizing voltage-gated conductances
  - Excitatory and inhibitory synapses
  - Shunting effect:
    - Conductances with reversal potentials near the resting potential (e.g. Cl^-), may pass little net current. Instead, their primary impact is to change the membrane resistance of the cell. Such conductances are called shunting because they increase the total conductance of a neuron.

Passive, isopotential (single compartment) neuron model



- *V*: Membrane potential [*V*].
- I_e: Current injected into the cell, with an electrode for example [*A*]
- *Q*: Excess internal charge [*C*].
- R_m: Membrane resistance, treated as a constant in the equations (proportional to the specific membrane resistance, r_m) [*Ohm*].
- C_m: Membrane capacitance, treated as a constant in the equations (proportional to the specific membrane capacitance, c_m) [*F*].
- The cell membrane is represented by a resistor and a battery in parallel with a capacitor.

Calculating the membrane current

- From definition of capacitance, the amount of current (charge per unit time) need to change the membrane potential of a neuron with a total capacitance C_m at a rate *dV/dt* is:

$$\frac{dQ}{dt} = C_m \frac{dV}{dt}$$

- Because of the principle of conservation of charge, the time derivative of the charge *dQ/dt* is equal to the current passing into the cell, so

$$\frac{dQ}{dt} = -\frac{V - E_r}{R_m} + I_e$$

- Where Er is the resting potential of the cell. In most equations membrane conductance (g_m) is used instead of resistance ($g_m = 1/R_m$), because it is directly related to biophysical properties of the neurons

$$C_m \frac{dV}{dt} = -g_m(V - E_r) + I_e$$

Calculating the membrane current: The membrane time constant

- The product of the membrane capacitance and the membrane resistance is a quantity in units of time, called the membrane time constant, denoted by *tau*:

$$\tau = R_m C_m$$

- The membrane time constant sets the basic time scale for changes in the membrane potential and typically falls in the range between 10 and 100 milliseconds.

$$\tau \frac{dV}{dt} = -V(t) + E_r + R_m I_e$$

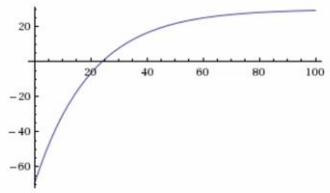
- The total membrane conductance can change dynamically, causing the membrane time constant to change too.

Response to current step at t = 0

$(\Delta V = R_m I_e,\ V_0 = E_r,\ V_\infty = R_m I_e + E_r)$

$$V(t) = \Delta V(1 - e^{-t/\tau}) + V_0 = V_\infty(1 - e^{-t/\tau}) + V_0 e^{-t/\tau}$$

Example:



(ΔV = 100 mV, *tau* = 20msec, V_0 = -70 mV)

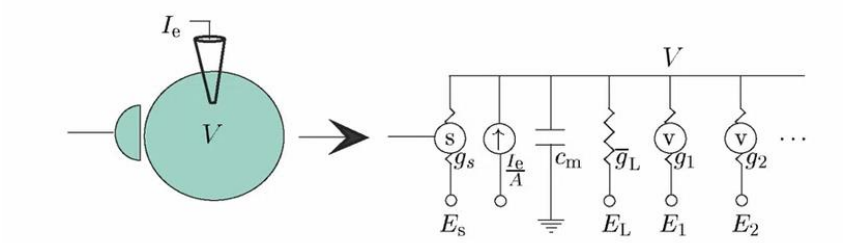
- The passive membrane behaves as a low pass filter

Total current flowing through the membrane

- If there are multiple conductances (ion channels):

$$I_\mathrm{m} = C_m \frac{dV}{dt} + \sum_i g_i(V - E_i) = I_e$$

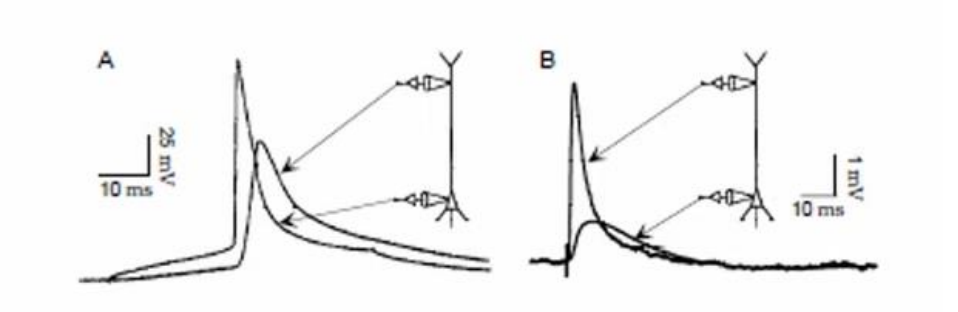
- Where $g_i(V\text{-}E_i)$ is the current flowing through ion channel i.
- Equivalent electric circuit:



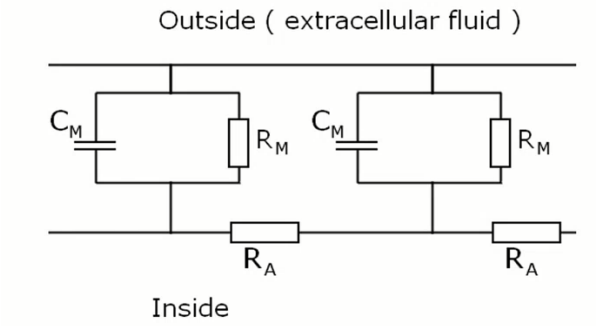
- Ion channels and synaptic channels can be represented as variable conductances.

Describing extended neurons, I: the cable equation

- The membrane potential can vary considerably over the surface of the cell membrane:

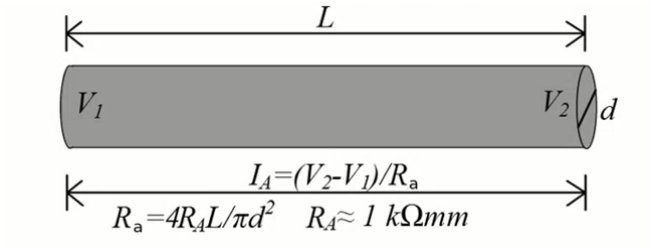


- Fig A: The delay and attenuation of an action potential as it propagates from the soma out to the dendrites of a cortical pyramidal neuron
- Fig. B: The delay and attenuation of an excitatory postsynaptic potential (EPSP) initiated in the dendrite by synaptic input as it spreads to the soma. Dendritic and axonal cables are usually narrow enough that variations of the potential in the radial direction (at a given axial location) are negligible compared to longitudinal variations, thus we only need a single longitudinal coordinate, denoted by *x*.
- Cable theory uses mathematical models to calculate the flow of electric current (and accompanying voltage) along passive neuronal fibers (neurites), particularly dendrites.



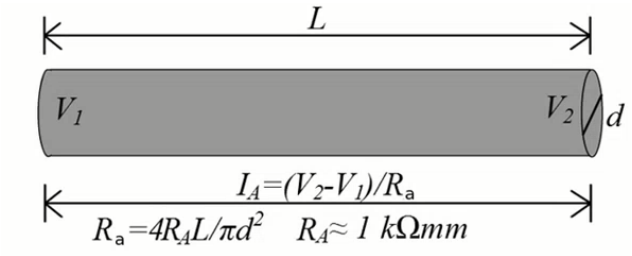
- Simplification: Represent the dendrite as a finite length cable
- Subdivide the dendrite into little pieces, small enough that the voltage is approximately constant everywhere within each such piece.
- C_M: membrane capacitance
- R_M: Membrane resistance
- R_A: Longitudinal (axial) resistance

Axial resistance (R_A)



- L: Cable length (cm)
- d: Cable diameter (cm)
- V_1, V_2: Membrane potential at the ends of the cable (mV)
- R_a: Axial (or longitudinal) resistance (Ohm)
- R_A: Specific axial resistance
- I_A: Longitudinal current (A)
- Axial resistance is proportional to the length of the segment (long segments have higher axial resistance than short ones). It is inversely proportional to the cross-section area of the segment (thin segments have higher resistance than thick ones).

Longitudinal current (I_A)



- For the cylindrical segment of the dendrite shown in the fig, the longitudinal current flowing from right to left satisfies V_2-V_1 = $I_A R_A$ (Ohm's law). This can be rewritten as:

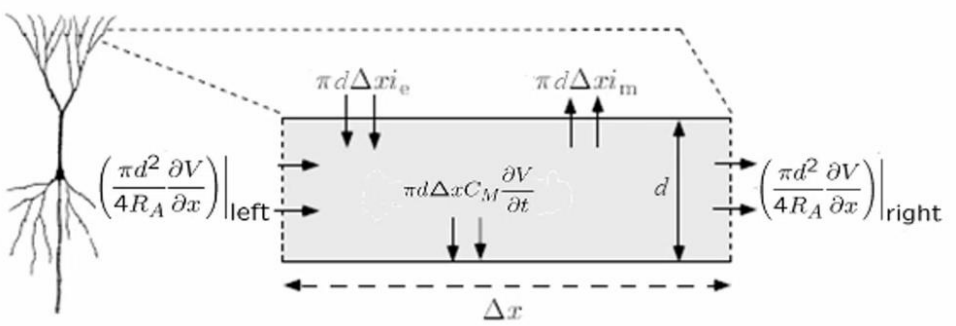
$$\Delta V = -R_a I_a = -\frac{4R_A \Delta x}{\pi d^2} I_a,$$

- If we take the limit of the expression for infinitesimally short cable segments, the equation becomes a partial differential equation:

$$I_a = -\frac{\pi d^2}{4R_A}\frac{\partial V}{\partial x}$$

The cable equation

- The segment of neuron used in the derivation of the cable equation (c_m is the membrane capacitance):



- We divide the membrane into small cylindrical parts. One cylinder of the membrane has a surface area of $\pi d\Delta x$ and hence a capacitance of $\pi d\Delta x c_m$.
- The total longitudinal current entering the cylinder is the difference between the current flowing in on the left and that flowing out on the right, so the current balance equation becomes:

$$\pi d\Delta x C_M \frac{\partial V}{\partial t} = -\left(\frac{\pi d^2}{4R_A}\frac{\partial V}{\partial x}\right)\Big|_{\text{left}} + \left(\frac{\pi d^2}{4R_A}\frac{\partial V}{\partial x}\right)\Big|_{\text{right}} - \pi d\Delta x(i_m - i_e),$$

If $\Delta x \to 0$

$$C_M \frac{\partial V}{\partial t} = \frac{1}{4dR_A}\frac{\partial}{\partial x}\left(d^2\frac{\partial V}{\partial x}\right) - i_m + i_e$$

- Which is called the **cable equation**.

Linear cable equation

- To solve the cable equation, we need to know the membrane current, the simplest (linear) case, which can be solved analytically, is the following:
  - Synaptic currents are ignored.
  - Membrane current is a linear function of the membrane potential.
- In real neurons, a linear approximation for the membrane current is valid only if the membrane potential stays within a limited range, Then the membrane current per unit area is:

$$i_m = (V_m - V_{\text{rest}})/R_M$$

- Now solving the cable equation means that we are looking for the values of V_m (x, t) given i_e (x, t).
- With the approximations the cable equation becomes:

$$\tau_m \frac{\partial V_m}{\partial t} = \lambda^2 \frac{\partial^2 V_m}{\partial x^2} - (V_m - V_{\text{rest}}) + R_M i_e$$

$\tau_{\text{m}} = R_M C_M$ Membrane time constant

$\lambda = \sqrt{\frac{dR_M}{4R_A}}$ Steady-state space constant

- (This form of the cable equation assumes that the radii of the cable segments used to model a neuron are constant except at branches and abrupt junctions.)
- In a canonical form:

$$T = t/\tau_{\text{m}} \quad X = x/\lambda \quad V(x,t) = V_m(x,t) - V_{\text{rest}}$$

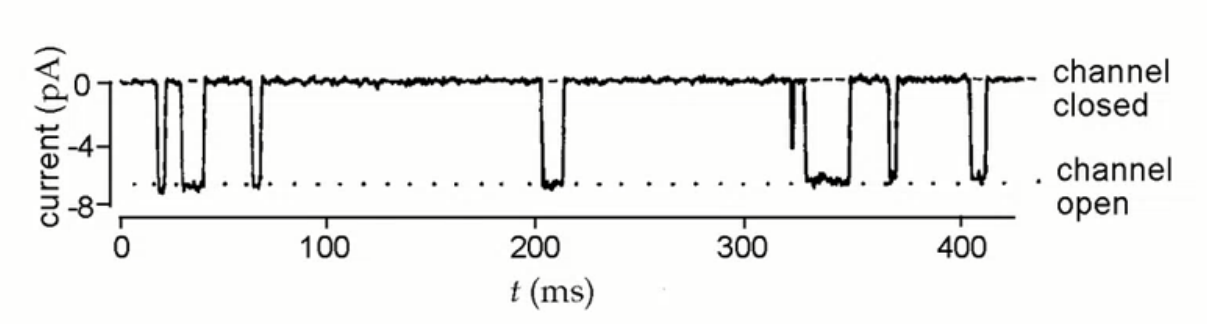
$$\frac{\partial V(X,T)}{\partial T} = \frac{\partial^2 V(X,T)}{\partial X^2} - V(X,T) + \frac{i_e(X,T)}{\lambda C_M}$$

Examples:

- infinite cable:
  - the current is injected into the cable is held constant, the membrane potential settles to steady-state solution that is independent of time.
  - there is a time dependent case as well.

Voltage dependent conductances

- Single ion channels are either in an open or a closed state.
- The probability of the states can depend on the membrane potential and on the binding of various substances (e.g., neurotransmitters) to the cell membrane



- Fig.: The currents passing through a single ion channel. In the open state, the channel passes -6.6pA at the holding potential of -140mV. This is equivalent to more than 10^7 charges per second passing through the channel.

The Hodgkin-Huxley equation

- Conductance per unit area of membrane for channel type i:

$$g_i = \overline{g}_{1,i}\rho_i P_i = \overline{g}_i P_i$$

- Where
  - P_i is the probability of a single channel being in the open state. This is approximately equal to the fraction of open channels (if the number of channels is large)
  - g_i is the maximal conductance per unit area of membrane.
- Structurally, ion channel pores have several gates, which all need to be open for current to flow through the channel.
- Example: In the case of the „delays rectifier' K^+ current:

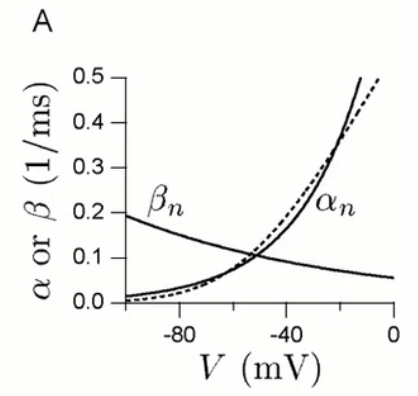
$$P_K = n^k, k = 4$$

- This means for the K^+ ions to pass, 4 gates need to be open.

Gating equation

$$\frac{dn}{dt} = \alpha_n(V)(1-n) - \beta_n(V)n$$

- the transition of each gate described by a kinetic scheme in which the gating transition closed-to-open occurs at voltage-dependent rate $\alpha_n(V)$ and the reverse transition occurs at rate $\beta_n(V)$
- n is the probability that we find a gate open.
- example transition function plotted as a function of the membrane potential:



- The same equation in a different, useful form:

$$\tau_n(V)\frac{dn}{dt} = n_\infty(V) - n$$

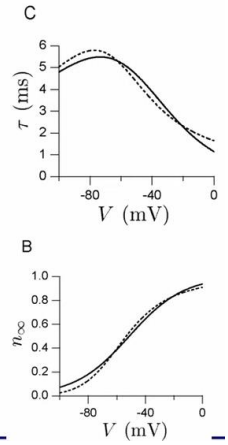
where

$$\tau_n(V) = \frac{1}{\alpha_n(V) + \beta_n(V)}$$

is called the time constant and

$$n_\infty(V) = \frac{\alpha_n(V)}{\alpha_n(V) + \beta_n(V)}$$

is the steady-state activation function.

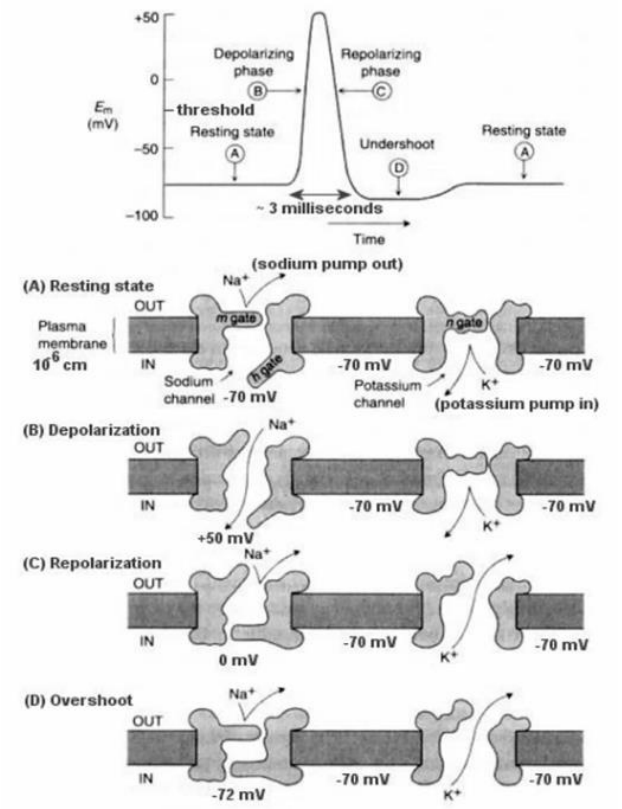


Transient current

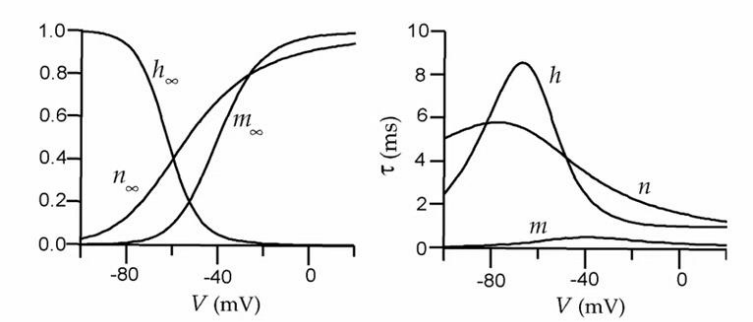
- Simplified description: activation and inactivation gate(s)
- Example: transient Na^+ current: The channel has *k=3* activation and 1 inactivation gates:

$$P_{\mathrm{Na}} = m^k h\,, k = 3$$

- activation-deactivation
- deinactivation-inactivation



Na and K channel examples



- Left: steady-state activation *(n, m)* and inactivation *(h)* curves plotted for the Na and delayed rectified K channels. It describes the fraction of channel gates that will be open if the membrane potential is clamped to *V* for a long time. For example, the m gate will be ~50% open at -40mV.
- Right: time constant functions for the gates. This function describes how fast the channel gate will reach its steady-state activation.

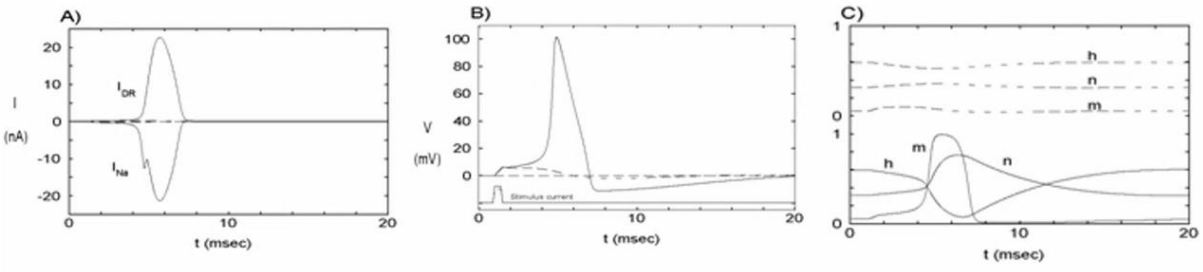
Action potential

- The full model of the giant squid axon with perfect „space clamp”:

$$C_m \frac{dV_m}{dt} = \overline{g}_{Na} m^3 h (E_{Na} - V_m) + \overline{g}_K n^4 (E_K - V_m) + g_l (E_l - V_m) + I_e$$

- The model includes:
  - *Na* conductance with 3 activation gates and 1 inactivation gate,
  - *K* conductance with 4 activation gates
  - a passive *leak* conductance (the current flowing through the conductance is in linear relation with the membrane potential)

Squid axon HH model



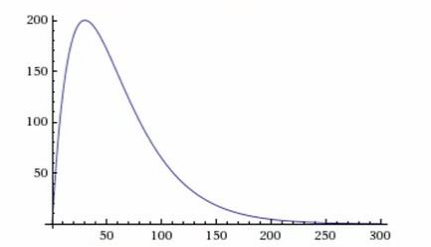
- Fig A: Currents flowing through the Na and K channels during an AP.
- Fig B: Membrane potential during an AP
- Fig C: Activation and inactivation values during the spike.

Phenomenological models of synaptic conductances

- Exponential (for example AMPA type glutamate receptor)
- difference of exponentials (e.g., $GABA_A$). This method uses two-time constants; thus, both rise and decay can be described
- Alpha functions

$$(P_S = \frac{P_{max} t}{\tau_S} \exp(1 - t/\tau_S))$$

  - This equation describes an isolated presynaptic release that occurs at t=0, reaches its maximum at the time constant, and decays with the same time constant.



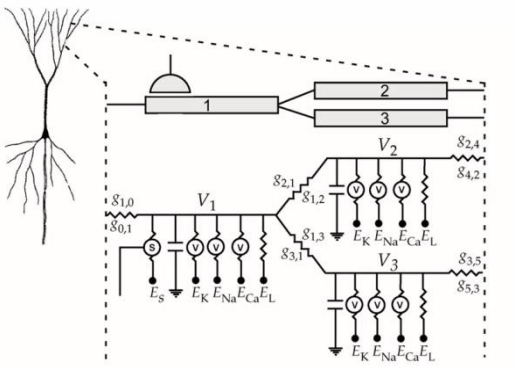
  - Fig: Example of alpha function with P_{max}=200 and tau=30.

Causes of more complex behaviour in real neurons

- many different types of ion channel
- complicated and cell-type dependent morphology
- the temporal and spatial pattern of synaptic input
- neuromodulators, intracellular messenger molecules

Biophysically detailed multicompartmental models

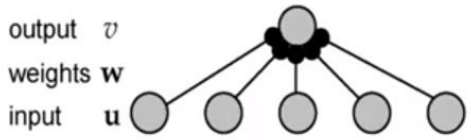
- Fig: the electrical circuit representation of three compartments in a multicompartmental model. Circles with V represent voltage-gated conductances.



Neural network modelling

Lecture 17

Fire-rate-based models



- picture: synaptic inputs to a single neuron
- *u*: input rate vector. Denote firing rate, not the membrane potential.
- *w*: synaptic (input) weight vector. For excitatory synapses w(i) > 0, for inhibition *w(i) < 0*
- *v*: output rate vector. In case of a single neuron, it has only one element.
- these rate-based models are also in many ways similar to artificial neural networks.

Synaptic kernel

- $K_s(t)$ is the synaptic kernel function, which describes the time course of the synaptic current in response to a presynaptic spike arriving at time *t=0*.
- properties:

$$\int_0^\infty K_s(t) = 1$$

$$K_s(t) \geq 0$$

- example: If an AP arrives at *t=0* at input b, the synaptic current generated at the postsynaptic neuron at time *t* is $w_b K_s(t)$, where $K_s(t)$ is the synaptic kernel.

1. Calculating the total (somatically measured) synaptic current

- The total synaptic current at time t:

$$I_S = \sum_{b=1}^{N_u} w_b \sum_{t_{b,i}<t} K_S(t - t_{b,i}) = \sum_{b=1}^{N_u} w_b \int_{-\infty}^{t} d\tau\, K_S(t-\tau)\rho_b(\tau)$$

- where:

$\rho_b(\tau) = \sum_i \delta(\tau - t_i)$ is the neural response function, which describes the sequence of spikes fired by presynaptic neuron *b*.
δ is the Dirac-delta function.

N_u is the number of input neurons.

$t_{b,i}$ is the time when a presynaptic spike occurs at input *b*.

- If the neuron response function is replaced by the firing rate of neuron *b*, denoted by $u_b(\tau)$

$$I_s = \sum_{b=1}^{N_u} w_b \int_{-\infty}^{t} d\tau\, K_S(t-\tau)u_b(\tau) \qquad (1)$$

- If the synaptic kernel is exponential

$$K_S(t) = \frac{1}{\tau_s} e^{-t/\tau_s}$$

- Then differentiating (1) gives:

$$\tau_S \frac{dI_S}{dt} = -I_S + \sum_{b=1}^{N_u} w_b u_b = -I_S + \mathbf{w} \cdot \mathbf{u}\,.$$

2. Calculating the firing rate: activation function

- To calculate the firing rate model, we must determine the postsynaptic firing rate v from I_S.
- For a constant input $v=F(I_S)$, where F is the **activation function**. It can be a sigmoid function, or – most frequently – linear function with a threshold:
- $F(IS) = [I_S - \gamma]_+$, where
  - γ is the threshold (measured in Hz), and
  - $[x]_+$ is the half wave rectification operator: For any x

$$[x]_+ = \begin{cases} x & if\ x \geq 0 \\ 0 & otherwise \end{cases}$$

- For convenience we assume that I_S, is multiplied by a constant which converts nA to Hz.
- advantage: this function is already a non-linear function which will allow non-linear operations, but it is a very simple function because it is a piecewise linear function.

Steady-state output fire rate

- If all the inputs are time-independent (or in steady-state), the total current is:

$$I_s = \boldsymbol{wu}$$

- As a consequence, the steady-state output firing rate is:

$$v_\infty = F(\mathbf{w} \cdot \mathbf{u})$$

- Where w is the synaptic weight vector and u is the synaptic input vector.
- This equation describes how the neuron responds to constant (time-independent) current.

Firing-rate model with time-dependent dynamics

- If $I_S(t)$ is time-dependent:

$$\tau_S \frac{dI_S}{dt} = -I_S + \sum_{b=1}^{N_u} w_b u_b = -I_S + \mathbf{w} \cdot \mathbf{u} \quad \text{and} \quad v = F(I_S)$$

- In this case it is assumed that the firing rates follow the time-varying currents instantaneously.
- Other model: The time-dependent firing rate is modelled as a low-pass filtered version of the steady-state firing rate:

$$\tau_r \frac{dv}{dt} = -v + F(I_S(t))$$

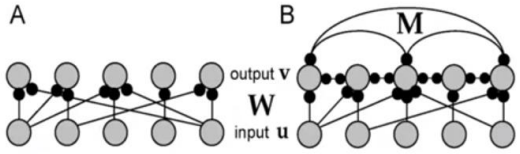
- where:
  - τ_r is a time constant that determines how rapidly the firing rate approaches its steady-state value for constant I_S.

- If $\tau_r \gg \tau_S$, meaning that the firing rate time constant is much larger than the synaptic rate time constant, then we can replace the time-dependent synaptic current function (IS*(t)*) with the total steady-state current (***wu***):

$$\tau_r \frac{dv}{dt} = -v + F(\mathbf{w} \cdot \mathbf{u})$$

- In other words, it is assumed that the firing rate is a low pass filtered version of the input current.

Feedforward and recurrent networks



- Pic A: Feedforward network
- Pic B: Recurrent network with feedforward inputs
- ***W***: Feedforward synaptic weight matrix, where W_{ab} is the strength of the synapse from input unit *b* to output into *a*
- ***M***: synaptic weight matrix for the recurrent layer
- Output firing rate in feedforward networks (fig. A):

$$\tau_r \frac{dv_a}{dt} = -v_a + F\left(\sum_{b=1}^{N_u} W_{ab} u_b\right), \quad \text{or} \quad \tau_r \frac{d\mathbf{v}}{dt} = -\mathbf{v} + \mathbf{F}(\mathbf{W} \cdot \mathbf{u})$$

- Adding the recurrent connections (fig. B):

$$\tau_r \frac{d\mathbf{v}}{dt} = -\mathbf{v} + \mathbf{F}(\mathbf{W} \cdot \mathbf{u} + \mathbf{M} \cdot \mathbf{v}) = -\mathbf{v} + \mathbf{F}(\mathbf{h} + \mathbf{M} \cdot \mathbf{v})$$

If we distinguish excitatory and inhibitory populations:

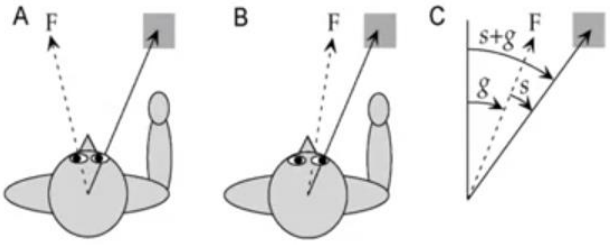
$$\tau_E \frac{d\mathbf{v}_E}{dt} = -\mathbf{v}_E + \mathbf{F}_E(\mathbf{h}_E + \mathbf{M}_{EE} \cdot \mathbf{v}_E + \mathbf{M}_{EI} \cdot \mathbf{v}_I)$$

$$\tau_I \frac{d\mathbf{v}_I}{dt} = -\mathbf{v}_I + \mathbf{F}_I(\mathbf{h}_I + \mathbf{M}_{IE} \cdot \mathbf{v}_E + \mathbf{M}_{II} \cdot \mathbf{v}_I)$$

- ***(h=Wu)***
- another frequent abstraction:
- $M_{aa'} = M_{a'a}$ (symmetric recurrent connections) → simpler dynamics
- These two assumptions are seemingly contradictory but can be reconciled if we assume that inhibition is much faster than excitation.
- Then steady-state inhibitory activation can be substituted into the first equation, and the effective interaction between excitatory neurons can be symmetric with appropriate weight matrices.

Coordinate transformation I feedforward networks.

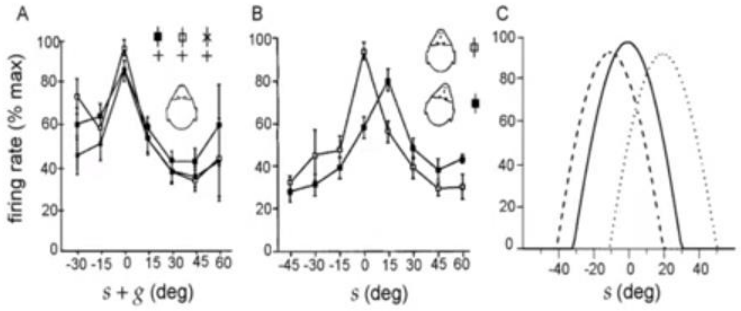
- Reaching for a visible object requires a transformation from (retinal) sensory coordinates to body-centred motor coordinates.



- *s* is the location of the target in retinal coordinates.
- *g* is the gaze angle, indicating the direction of gaze relative from the axis of the body.
- *s* + *g* is the direction of the target relative to the body.

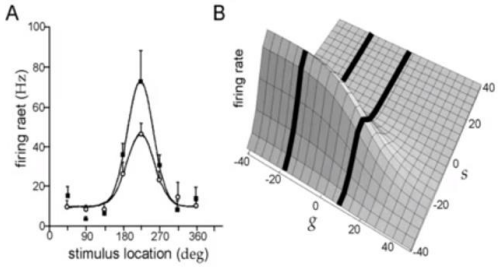
Neural coordinate transformation

- In the premotor area of the frontal lobes



- Picture:
  - Firing rates of a visual responsive neuron in the premotor cortex of a monkey. Visual stimuli were incoming objects at various angles.
  - A: The response tuning curve does not change with eye position
  - B: If monkey's head is turned 15 degrees to the right, the tuning curves shift by 15 degrees too.
  - C: Model turning curves at -20, 0, 10 degrees. (dotted, solid, heavy dotes)

Possible intermediate representation (in area 7a of the parietal lobe)



- Can be modelled by the product of a Gaussian function of s and a sigmoid function of g; the activity of various neurons of the population is:

$$u = f_u(s-\xi, g-\gamma)$$

- where ξ is the mean of the Gaussian and γ is the centre of the sigmoid
- We can combine the activity of such neurons in a feedforward network to create output neurons firing in body-centred coordinates.

Linear recurrent networks

$$\tau_r \frac{d\mathbf{v}}{dt} = -\mathbf{v} + \mathbf{h} + \mathbf{M} \cdot \mathbf{v} \qquad (1)$$

- Let assume that ***M*** is symmetric → real eigenvalues ($\lambda\mu$) and orthogonal eigenvectors(e_μ) forming a basis, so we may write:

$$\mathbf{v}(t) = \sum_{\mu=1}^{N_v} c_\mu(t)\mathbf{e}_\mu ,$$

- and substituting into (1),

$$\tau_r \sum_{\mu=1}^{N_v} \frac{dc_\mu}{dt}\mathbf{e}_\mu = -\sum_{\mu=1}^{N_v} (1-\lambda_\mu)c_\mu(t)\mathbf{e}_\mu + \mathbf{h}$$

- Multiplying by the eigenvector e_v

$$\tau_r \frac{dc_\nu}{dt} = -(1-\lambda_\nu)c_\nu(t) + \mathbf{e}_\nu \cdot \mathbf{h}$$

- For time-independent inputs the solution is:

$$c_\nu(t) = \frac{\mathbf{e}_\nu \cdot \mathbf{h}}{1-\lambda_\nu}\left(1 - \exp\left(-\frac{t(1-\lambda_\nu)}{\tau_r}\right)\right) + c_\nu(0)\exp\left(-\frac{t(1-\lambda_\nu)}{\tau_r}\right)$$

- If $\lambda > 1$ for any v, the network is unstable.
- If $\lambda < 1$ c_v exponentially approaches the stationary value $e_v \cdot h / (1 - \lambda_v)$ with the time constant $\tau_r / (1 - \lambda_v)$
- The steady-state value for v(t) is:

$$\mathbf{v}_\infty = \sum_{\nu=1}^{N_v} \frac{(\mathbf{e}_\nu \cdot \mathbf{h})}{1-\lambda_\nu}\mathbf{e}_\nu$$

- This transformation could also be implemented by a purely feedforward network!

Applications of linear recurrent networks

1. Selective amplification

- Assume that λ_1 is very close to 1, and all other eigenvalues are significantly smaller. Then the steady state is:

$$\mathbf{v}_\infty \approx \frac{(\mathbf{e}_1 \cdot \mathbf{h})\mathbf{e}_1}{1-\lambda_1}$$

- The response of the network is dominated by the projection of the input vector along the axis defined by e_1, in other words it encodes an amplified version of the input onto e_1.
- Strength of amplification:

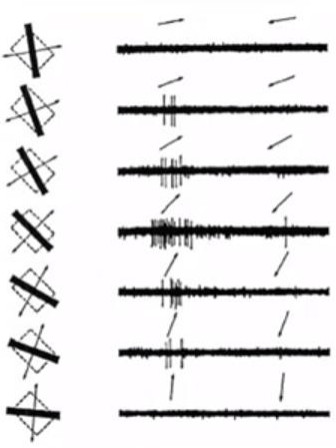
$$\frac{1}{1-\lambda_1}$$

Continuously parametrized neuronal populations

- Picture: In primary visual cortex, a neuron may be characterized by the orientation of its preferred stimulus (θ). These neurons tend to fire at the highest frequencies if the stimulus is at a specified angle in their receptive field.
- To model such networks, it is more efficient to index neurons by their (continuously varying) preferred parameters.
- We can replace the discrete population with a continuous population:

  $u(\theta)$, $v(\theta)$ firing rates, $W(\theta,\theta')$, $M(\theta,\theta')$ synaptic weights.

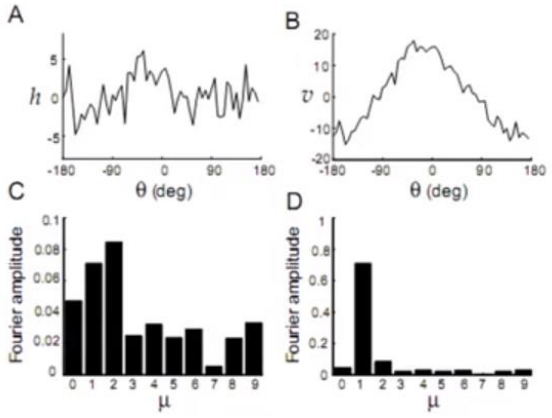
- Then the equation describing the dynamics becomes:



$$\tau_r \frac{dv(\theta)}{dt} = -v(\theta) + F\left(\rho_\theta \int_{-\pi}^{\pi} d\theta' \left[W(\theta,\theta')u(\theta') + M(\theta,\theta')v(\theta')\right]\right)$$

Application of linear recurrent networks: *Selective amplification*

- If the neurons are described by a preferred value of a periodic variable (θ), and *M (θ, θ') ~cos (θ - θ')*, the network selectively amplifies the first Fourier component of the input:



- Pic A: The input as a function of the preferred angle
- B: The activity of the network as a function of the preferred angle. Input stimulus was the same as in picture A.
- C: The Fourier transformation amplitudes of the input.
- D: The Fourier transformation amplitudes of the output.

2. Input integration

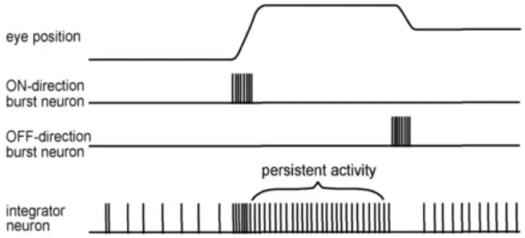
- If $\lambda_1 = 1$ and $\lambda_v < 1$ for $v > 1$, then

$$c_1(t) = c_1(0) + \frac{1}{\tau_r}\int_0^t dt'\, \mathbf{e}_1 \cdot \mathbf{h}(t')$$

- Since $c_v \rightarrow 0$ for $v > 1$, then if $c_1(0) = 0$,

$$\mathbf{v}(t) \approx \frac{\mathbf{e}_1}{\tau_r}\int_0^t dt'\, \mathbf{e}_1 \cdot \mathbf{h}(t')\,.$$

- ***(h=Wu)***
- For h=0, the network sustains its activity, which acts as a memory of the integral of previous inputs. In other words, the network "remembers" the previous state.
- Example: network for storing eye position, which integrates the output of brainstem ocular motor neurons



- Pic: Integrator neuron activity that is involved in horizontal eye positioning
- Problem: the eigenvalues most be really close to 1

<u>Nonlinear recurrent networks</u>

- In biological neural networks firing rates must be positive. Taking this into account:

$$\mathbf{F}(\mathbf{h} + \mathbf{M}\cdot\mathbf{r}) = [\mathbf{h} + \mathbf{M}\cdot\mathbf{r} - \boldsymbol{\gamma}]_+$$

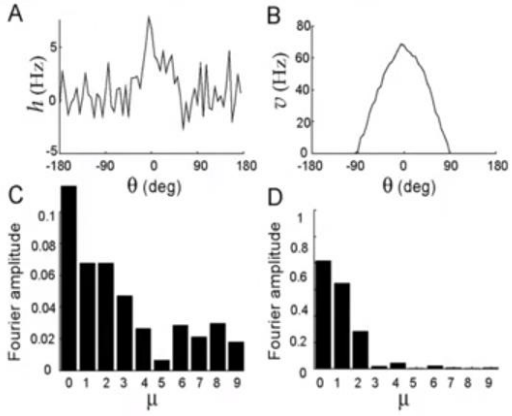
- where

$$[x]_+ = \begin{cases} x & if\ x \geq 0 \\ 0 & otherwise \end{cases}$$

- is the half wave rectification operator.
- The previous continuous model now becomes:

$$\tau_r \frac{dv(\theta)}{dt} = -v(\theta) + \left[h(\theta) + \frac{\lambda_1}{\pi}\int_{-\pi}^{\pi} d\theta'\, \cos(\theta - \theta')v(\theta')\right]_+$$

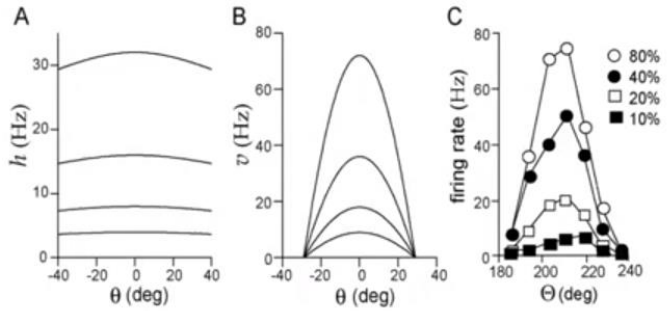
Selective amplification in the nonlinear case:



- Picture: Selective amplification in a linear network with $\lambda_1 = 1.9$
- A: The noisy input as a function of the preferred angle
- B: The steady-state output as a function of the preferred angle. Input stimulus was the same as in picture A.
- C: The Fourier transformation amplitudes of the input.
- D: The Fourier transformation amplitudes of the output.

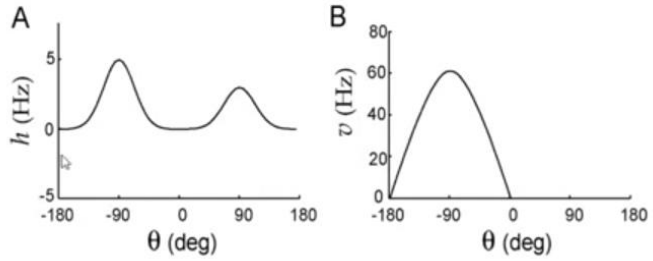
Selective amplification in the nonlinear case:
Recurrent model of simple cells in the primary visual cortex.

- Orientation selectivity and contrast invariance in V1



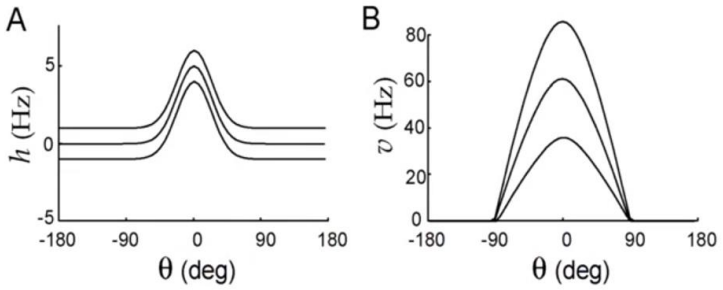
- Picture: The effect of contrast on orientation tuning
- A: The feedforward input as a function of preferred orientation. Contrast ratios are (from top to bottom): 80%, 40%, 20%, 10%
- B: The output firing rates in response to the inputs in fig. A
- C: Tuning curves measured experimentally.

Input selection in nonlinear networks: *Winner-takes-all input selection*



- Fig A: The input to the network consisting of two peaks.
- Fig B: Network response. The output has a single peak at the location of the higher of the two peaks of the input.

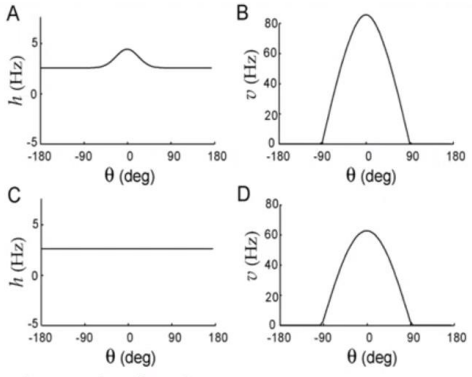
Input selection in nonlinear networks: *Gain modulation*



- (as see earlier in area 7a of the parietal lobe):
- Pic: Effect of adding a constant to the input.
- Fig A: The input to the network with one peak, with different amounts of added gain inputs
- Fig B: Network response. The higher gain yields a higher output.

Input selection in nonlinear networks

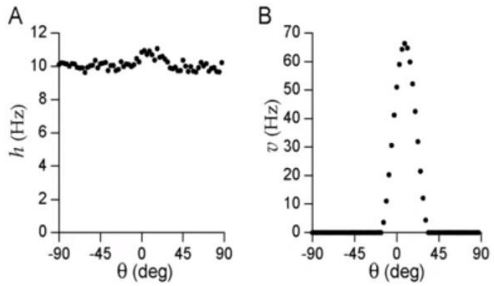
- Application: short-term (working) memory; the network "remembers" the preceding stimulus even in the absence of external input.



- Picture: Response to carrying input
- A, B: Input and output, with constant background and localized excitation
- C, D: After switching to a constant input, the response characteristics are the same.

Maximum likelihood estimation

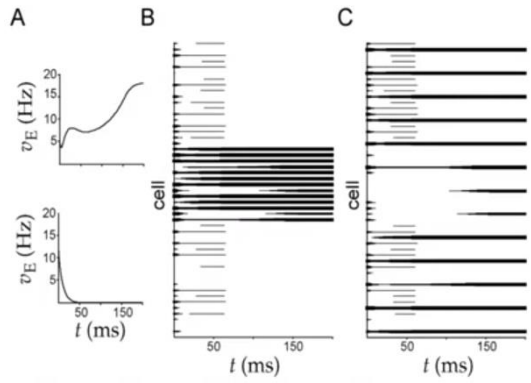
- The above computations can also be interpreted as (nonlinear) regression and may be used to approximate the "maximum likelihood" estimate of the value encoded by a noisy input.



- The standard deviation of the estimate is:
  - 4.5° for a simple "vector decoder"
  - 1.7° for recurrent network "clean-up" followed by vector decoding.
  - 0.88° for the optimal (real maximum likelihood decoder (Cramer-Rao lower bound)

Associative (long-term) memory

- As we have seen, recurrent networks often have activity patterns which behave as fixed-point attractors.
- These may also be considered as stored memory traces, provided that we can specify the fixed points (preferably via a plausible activity-based learning rule)
- Auto associative function: the dynamics of the network reconstructs the original pattern based on a fragment or a noisy version.



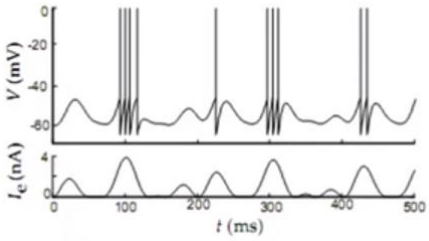
Integrate-and-fire model

- If the membrane potential reaches a threshold, the cell fires an aAP, and the membrane potential is set to a "reset potential".
- Simplest firing model: passive "integrate-and-fire".

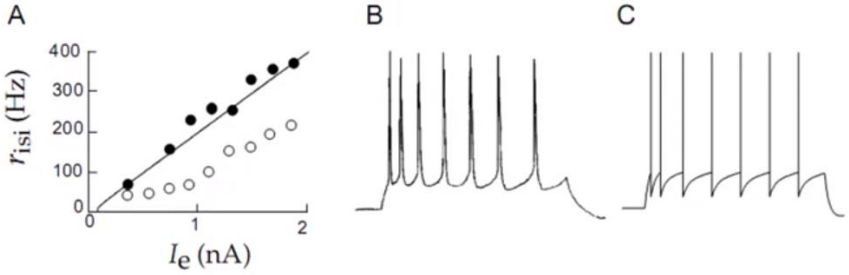
$$c_{\mathrm{m}}\frac{dV}{dt} = -\overline{g}_{\mathrm{L}}(V - E_{\mathrm{L}}) + \frac{I_{\mathrm{e}}}{A}$$

- or

$$\tau_{\mathrm{m}}\frac{dV}{dt} = E_{\mathrm{L}} - V + R_{\mathrm{m}}I_{\mathrm{e}}$$

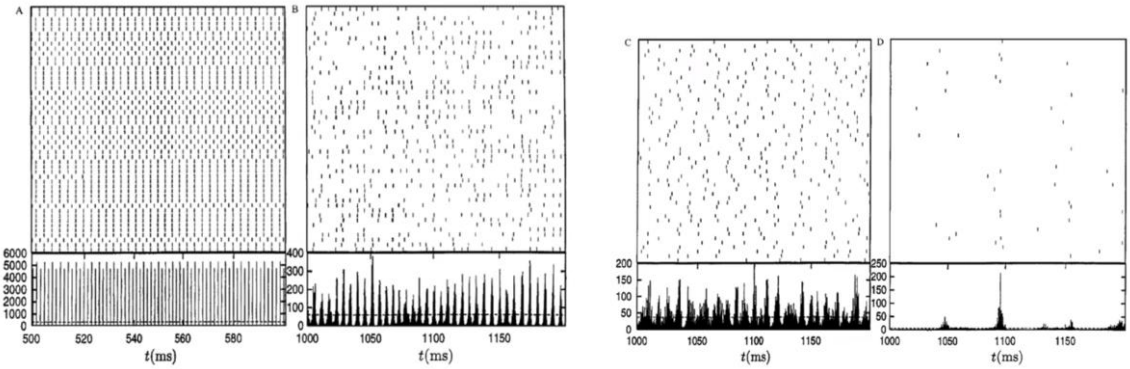


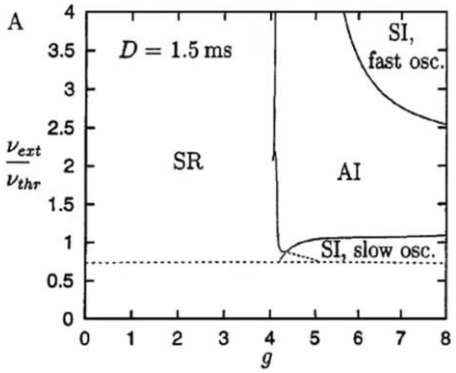
- Picture: Membrane potential trace of an integrate-and-fire model (I_e is the injected current)
- In the case of constant current injection, the analytic solution:



- Picture: integrate-and-fire models compared to in vitro recordings
- Left: Firing rate as a function of the injected current.
  - Continuous line: model results,
  - Filled circles: Results for the first two spikes fired in vivo recordings,
  - Open circles: steady-state firing frequency, in vivo recordings
- Middle: In vivo recording from pyramidal cell
- Right: voltage trace of the adaptive integrate-and-fire model
- The adaptation of the firing rate and refractory states are relatively easy to implement.

Population activity in networks of integrate-and-fire neurons





Motor disorders

Lecture 17

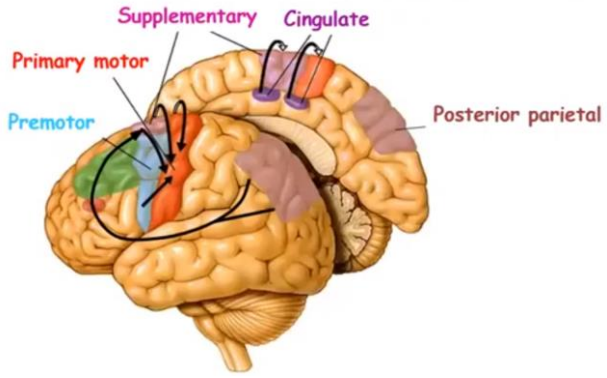
Events of voluntary movements

- decision of movement
- activation of the adequate motor pattern
- planning of movement
- starting of movement
- execution of movement
    - continuous adaptation of the muscle tone to the movement
    - continuous sensory control of the movement
- termination of movement

Structures of the nervous system controlling movement

- organization of movement
    - motor cortex
    - system of the basal ganglia
    - cerebellum
- execution of movement
    - "upper" motoneurons in the primary motor cortex
    - cortico-spinal pathway
    - "lower" motoneurons in the spinal cord
    - peripheral nerves
    - neuro-muscular transmission of the impulse

Major cortical areas participating in motor control

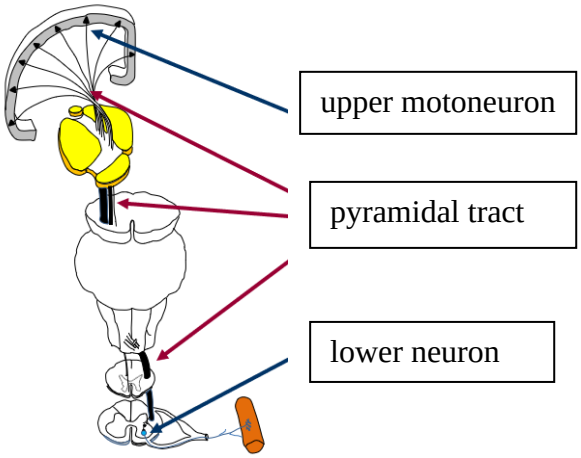


Functions of the various cortical areas

- Primary motor cortex
    - It coordinates muscle contractions.
    - It determines the temporal process of muscular activation.
    - Downstream information of motor centres about the planned movement
- Premotor cortex
    - It controls movements triggered by visual and auditory stimuli.
    - Postural settings necessary to carry out movements.
    - It facilitates the subsequent motor response.
    - Lesions in this brain region results in akinetic mutism.

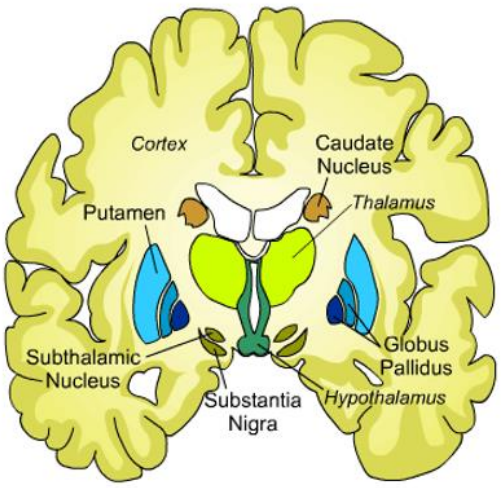
- Supplementary motor cortex
    - It transfers sensory information triggered by movements to the primary motor cortex.
    - It ensures coordinated muscle actions during complex movements.
    - It prevents mirror movements.
    - It influences motor control of the spinal cord.
- Cingular motor cortex
    - It plays role in the planning and initiation of movements.
    - It integrates motor actions related to emotions.
- Posterior parietal cortex
    - It provides important environmental information to carry out movements.
    - It collects visual, auditory, and somatosensory information about
        - the position of different body parts
        - the position of external objects
    - It transfers information to the dorsolateral prefrontal cortex and frontal eye field.

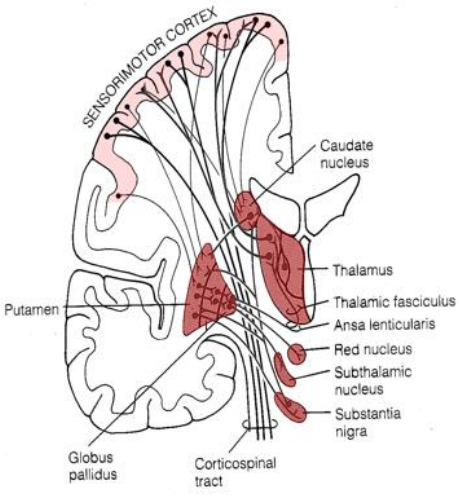
The most important executive motor system is the pyramidal tract



- Its lesion results in reduction (paresis) or complete loss (paralysis) of muscle power

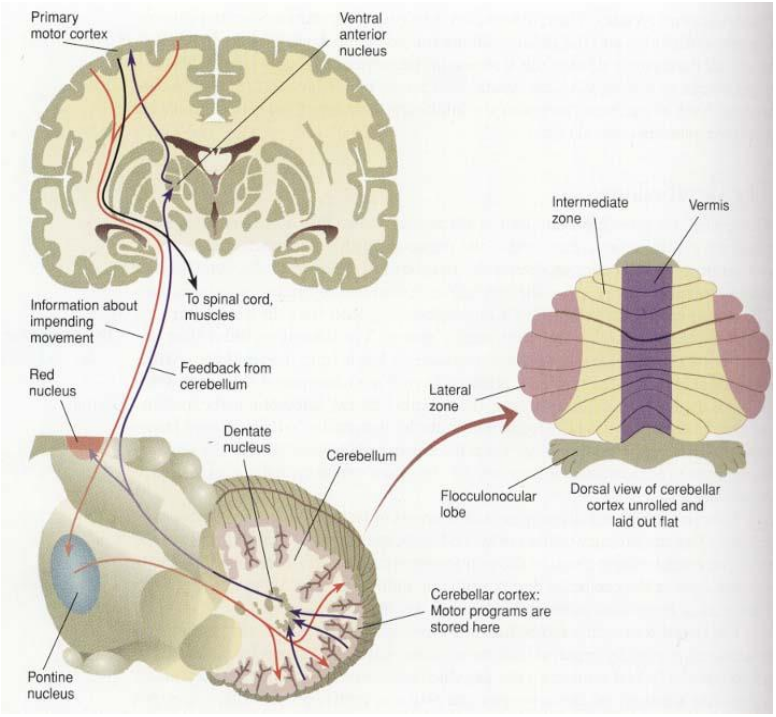
Subcortical structures of movement control: the basal ganglia





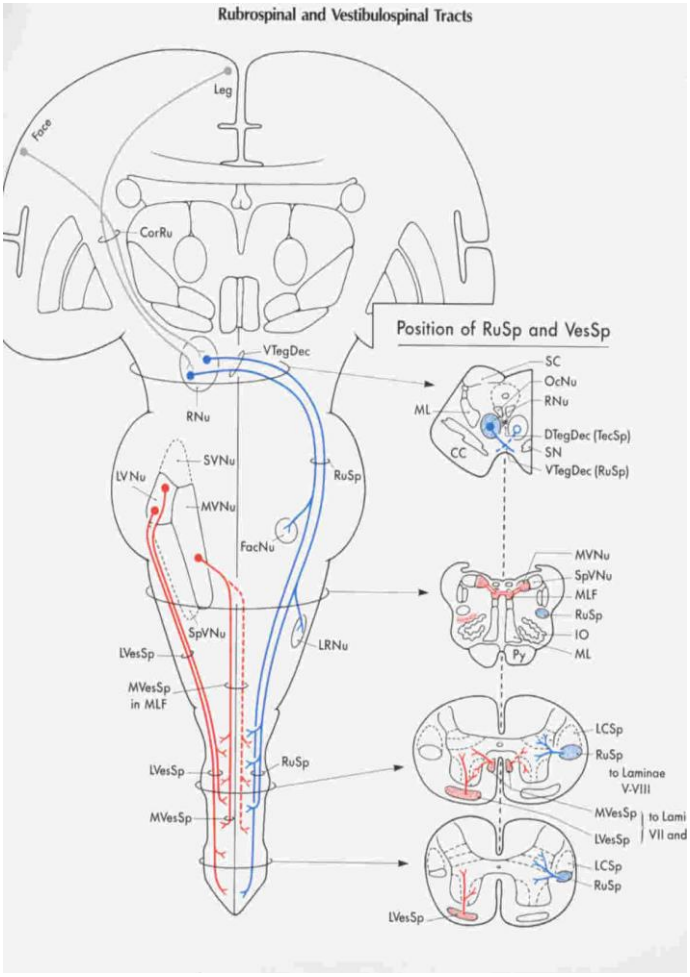
Cerebellar system of the movement control

- **Spinocerebellum** (vermis, intermedier zone): balance, gait
- **Cerebrocerebellum** (cerebellar hemispheres): accuracy of goal-directed fast movement
- **Vestibulocerebellum** (flocculonodular): spatial organization of movement



Descending motor pathways in the brainstem

- **Vestibulo-spinal tract**: It originates from brainstem vestibular nuclei, affects lower motoneurons via interneurons in the spinal cord. It mediates postural reactions; activates extensor and inhibits flexor motoneurons.
- **Cortico-reticular and reticulospinal pathways**: They regulate muscle tone (supplementary motor cortex - reticular system – spinal cord α and γ motoneurons).
- **Tecto-spinal and rubro-spinal pathways**: They regulate muscle tone via spinal cord interneurons and maintain head position and balance when fixing gaze.



Neuronal circuits regulating movement

- Striatal circuit
  - cerebral cortex (motor, sensory) - striatum - thalamus (VA, VL) - supplementary, premotor, and primary motor cortex
  - It regulates the direction and extent of movement.
- Cerebellar circuit
  - motor cortex - pons – cerebellar cortex - deep cerebellar nuclei - thalamus VL – motor cortical areas
  - It regulates initiation of movement and coordination of co-acting muscles.
- **CORTEX → …….. → THALAMUS → CORTEX**

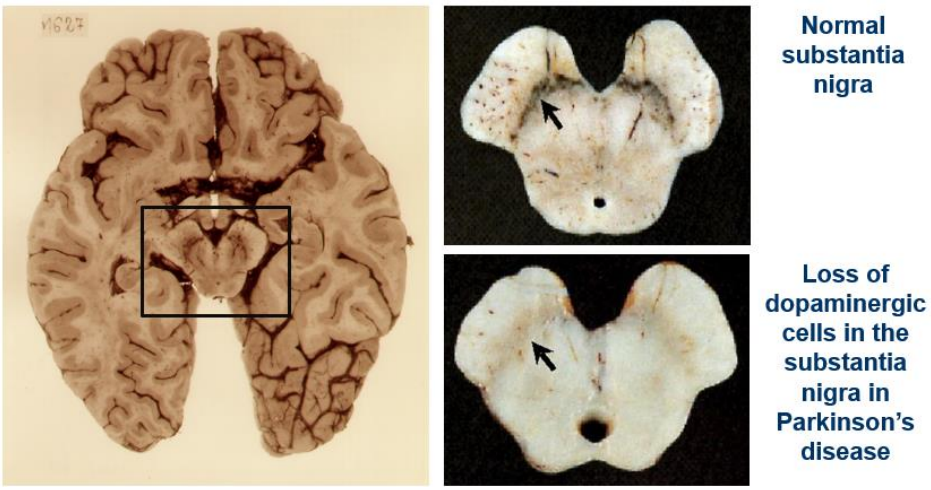
Examination of the motor system

- **Muscle tone:** the normal state of balanced tension in the relaxed muscle. The appropriate muscle tone is the prerequisite of precise motor control.
- **Muscle volume (trophy):** it is influenced by several undetermined factors, any disturbance in the neuro-muscular transmission results in a reduction of muscle mass.
- **Muscle power (strength):** the extent of work that can be carried out by a given muscle.
- **Stretch reflexes:** muscles contract in response to stretch. The stretch reflex may exaggerate or vanish under pathological conditions.
- **Symptoms of pyramidal tract injury:** various pathological reflexes, such as Babinski's sign, indicating a lesion of the pyramidal tract.
- **Coordination of movement:** capability to carry out goal-directed movements, which is ensured by the collaboration of motor, sensory and association systems.

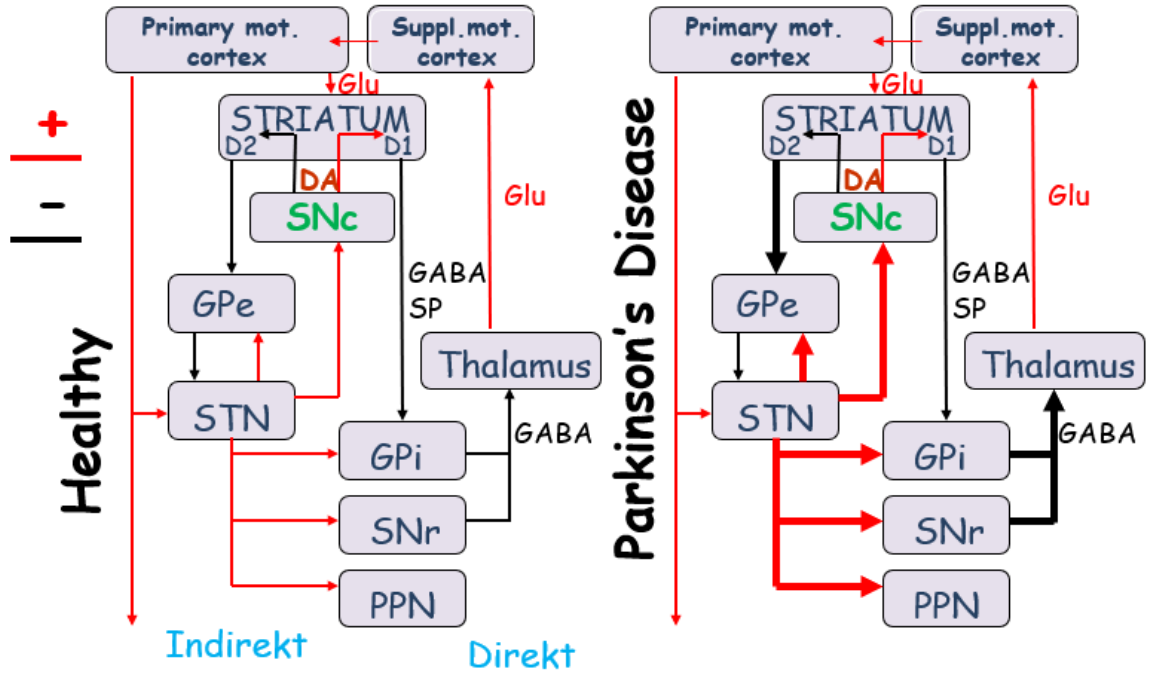
Disorders of the basal ganglia: Parkinson's disease

- A neurodegenerative disease with unknown aetiology.
- Main pathological characteristic is the loss of *dopaminergic neurons* in the substantia nigra.
- The *dopaminergic*, noradrenergic, serotoninergic, and cholinergic neurotransmission is disturbed.
- Serious motor and non-motor symptoms emerge.

Pathological changes in the brain



Changes in excitatory and inhibitory inputs in PD



- PD:
    - loss of inhibition and increased excitation
    - the whole system is dysfunctioning.
    - the GABAergic input to the thalamus is heavier, therefore the information from the thalamus to the supplementary motor cortex will be changed.
    - the glutamatergic information will be less and therefore the supplementary motor cortex information sent to the primary motor cortex will be different from normal.

Motor symptoms

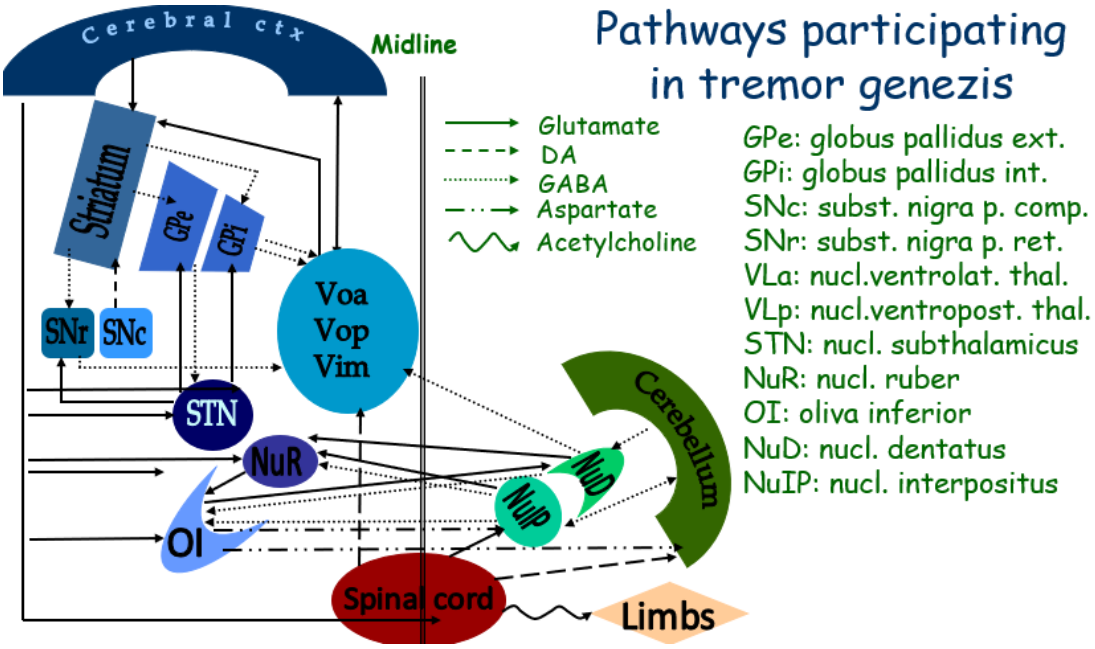
- *Tremor (resting)* (bent position)
- *Muscle rigidity* (muscle tone is not normal)
- Disturbance of posture
- Disturbance of movement initiation (akinesia)
- Slowing of movement (bradykinesia)
- Freezing: cannot start the movement after stopping

Non-motor symptoms (cognitive disturbances)

- working memory
- problem solving
- planning
- execution
- attention
- emotional life
- speech
- *Rey-complex test:* try to draw the same image.

Disorder of the cerebellar motor system

- Spinocerebellar ataxia
    - It is genetically determined group of diseases (9^{th} chromosome).
    - Degeneration of the posterior bundle of the spinal cord, the spinocerebellar and the cortico-spinal pathways.
    - Symptoms: limb- and trunk ataxia, ataxic gait, paraesthesia, ocular movement disorder etc.
- Essential tremor
    - Its aetiology is not known. Very likely that it is caused by the functional disturbance of both the brainstem and cerebellar motor control systems.
    - Symptoms: postural and intention tremor, tremor of the head and vocal cords.



The "cognitive" movement disorder: Apraxia

- The goal-directed motor acts are the result of the synthesis of elementary movement patterns.
- Execution of complex movements requires sufficient muscle force, muscle tone, intact coordination, and sensory systems.
- Preceding the motor actions, it is necessary to design a motor plan.
- Apraxia is the result of a brain injury, which makes patients incapable to carry out goal-directed movements, to execute learned complex movements, to coordinate the movements of the limbs, while they do not exhibit any muscle weakness, functional disturbance of coordination or the sensory system, and they do understand the task.

Types of apraxia

- **Ideomotor**: the patient is unable to imitate the action without the presence of the corresponding objects.
- **Ideator:** the patient is unable to plan complex movements, consequently the execution is often interrupted.
- **Kinetic:** the patient is unable to carry out fine movements
- **Constructive:** the patient is unable to execute tasks requiring spatial recognition even using eye control
- **Dressing apraxia**: the patient is unable to properly dress up.

Precise voluntary movements are the result of complex neuronal processes.

Neurosurgery

Lecture 18

Neurosurgery: the treatment of patients with neurological disorders, which are drug resistant; improving the quality of life; modern imaging techniques are used (e.g., fMRI)

Used devices:

- microsurgical techniques
- endoscopic techniques
- neuromodulation:
- endovascular: changing the bloodflow in vessels.
- stereotactic frame: navigating within the brain with the precision of 1 mm or less.
- reconstruction of the spine: the mobility and the biomechanical problems of the spine

Minimally invasive surgical techniques

- from the brain's viewpoint: we open up the skull, but the brain is not touched.
- according to the patient's clinical state: we use only a tiny hole in the skull.
- according to the patient's psychosomatic state: the patient does not feel that he had a big operation.

Endoscopic neurosurgery

- helps us to go into the ventricles through a little hole on the skull and remove tumours.
- we are able to connect compartments within the ventricles.

Stereotactic neurosurgery

- uses a coordination frame which is attached to the patient's head, with the help of this, we are able to make images of the patients head

Neuronavigation & robots

- making surgeries by programming robots

Endovascular neurosurgery

- we can block or close the weakened wall, the aneurysm of the vessels.
- we can put a wire into the little bubble of the weakened vessel's wall.
- the patient will not get a severe haemorrhage within the brain.

Radiosurgery

- Gamma radiosurgery
  - with a stereotactic frame we can localize exactly the target of the patient's head and within the gamma radiation we can focus the radiation to a certain point where we would like to irradiate
- Linac
  - uses beta radiation.
- Cyberknife
  - whole body stereotactic radiosurgical tool, the whole instrument is moving.

Spine surgery

- we can reconstruct spine biomechanical disorders, the degenerative disorders.

Intraoperative imaging

- X-ray, CT, MR
- the role of intraoperative diagnostics:
  - localize the boarders of the removable lesion.
  - map eloquent regions
  - localise epileptic zone.
  - localise deep brain structures.
  - preserve healthy tissues surrounding lesions.
  - preserve healthy fibers in the white matter.
- intraoperative diagnostic methods:
  - intraoperative neurological examination
  - anatomical orientation
  - preoperative imaging
  - neuronavigation, intraoperative imaging
  - electrophysiology

Functional MR imaging

- we are able to detect.
  - speech
  - sensory area
  - memory area
  - vision
  - hearing
- diffusion based tractography
  - we can see those white matter tracts which are coming from the cortex going down to the subcortical area or the spine (or vice versa)

Aim of epilepsy surgery

- localize the seizure onset zone.
- remove the seizure onset zone and preserve healthy structures.

Multimodal approach

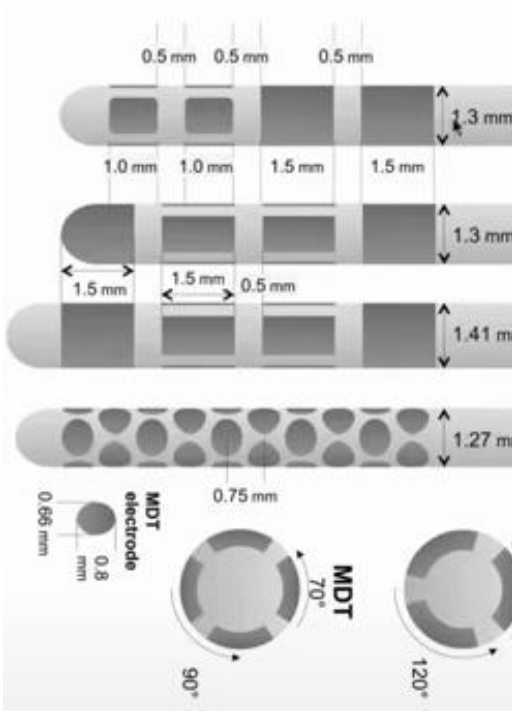
Semi-invasive and invasive electrodes

- FO electrode
- PEG electrode
- subdural strip and grid electrode
- intracerebral SEEG electrode

Medial thalamotomy

- in old times, instead of stimulation people made lesions in the head of the patients; either in the thalamus or in the cingulum → pain reduction
- nociceptive >neuropathic
- mesencephalotomy > MT
- low risk procedure (9%)
- 70% initial pain relief
  best response for: pain attacks, tactile allodynia, pins and needles and electric pain
- 30% response in continuous tearing, compressive deep pain, proprioceptive allodynia

Technical advancements in DBS



The electrodes are segmented, so we can stimulate selectively to different areas, directions. If on the other side of the electrode is a functioning area, we can simply just switch off those contacts and we stimulate a little bit further away from our electrodes. We can have the same result without side effects.

Motor cortex stimulation is also a good idea for neuropathic pain reduction. As the development of the surgical tools came since 1991 to 2005, the result of the visual analogue scale of pain reduction increased from 12% to 70%, because we were able to introduce fMRI and navigation systems.

Spinal cord stimulation helps for chronic pain patients who were operated several times with degenerative spine disorders, and they still have pain in the low back, in the lower extremity or cervical area and the upper extremity. If we stimulate the spinal cord within the spinal canal, then we can reduce the patient's pain.

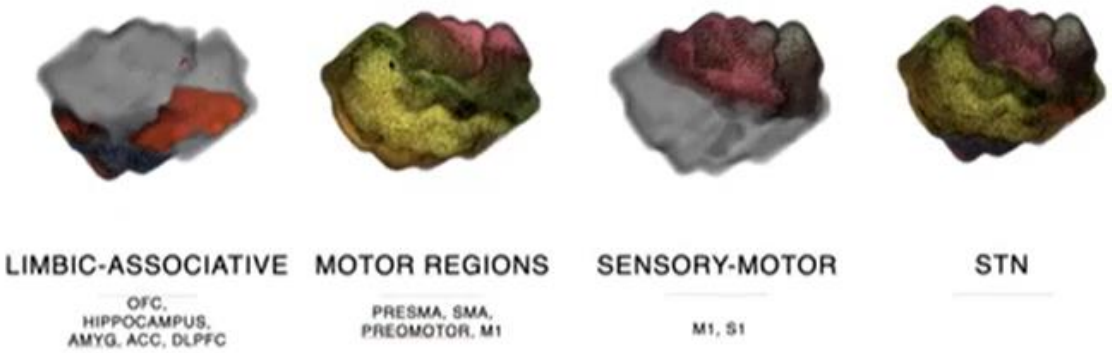
Atlas based planning

- we use stereotactic frame.

Optogenetic reconstruction of the STN

- we use functional connectivity maps.
- the 3x6 mm little brain area, deep seated in the middle of the brain is connected to different cortical areas.
- it means that the different parts of this little subthalamic nucleus have different functions

Functional connectivity maps



Intrathecal drug delivery

- drug delivery pumps
- we insert the tube into the spinal canal and put the drug into the 20-40 ml container.
- we build in the device under the skin.
- we program the device telemetrically.
- it is pumping the drug through the catheter into the CSF.

Neuroendocrinology

Lecture 19

Neuroendocrine regulation

- endocrine glands target organs, which are regulated by the CNS.
- endocrine glands produce hormones and release them into the blood vessels.

System of endocrine glands

- *Hypophysis / Pituitary gland*
  - master gland
  - below the hypothalamus
  - Anterior pituitary
    - growth hormone
    - thyroid-stimulating hormone
    - adrenotropic hormone
    - follicle-stimulating hormone
    - luteinizing hormone
    - prolactin
  - Intermediate pituitary
    - melanocyte-stimulating hormone
  - Posterior pituitary
    - oxytocin
    - vasopressin
- *Corpus pineal / Pineal body*
  - in the skull
  - epithalamic structure
  - melatonin
- *Glandular thyreoidea / Thyroid gland*
  - triiodothyronine
  - thyroxine
- *Glandular parathyreoidea / Parathyroid gland*
  - 4 parathyroid glands
- *Thymus*
  - in the chest
- *Glandular suprarenalis / Adrenal gland*
  - abdominal cavity
- *Pancreas*
  - behind the stomach
  - insulin
  - glucagon
  - somatostatin
  - pancreatic polypeptide

- *Ovarium*
    - progesterone
    - androstenedione
    - oestrogens
    - inhibin
- *Testis*
    - androgens
    - oestradiol
    - inhibin
- *Gastrointestinal tract with endocrine cell populations*

Targets of hormone action

- autocrine regulation
    - secretes hormone that binds to autocrine receptors on that same cell.
- paracrine regulation
    - released hormones influence other cells in the vicinity.
- endocrine regulation
    - the target and production site are far from each other.
    - delivered by blood.

Hormones

Gland	Hormone	Target Tissue	Principal Actions
Hypothalamus	Releasing and inhibiting hormones	Anterior lobe of pituitary gland	Stimulates or inhibits secretion of specific hormones
Anterior lobe of pituitary	Growth hormone (GH)	Most tissues in the body	Stimulates growth by promoting protein synthesis
	Thyroid-stimulating hormone (TSH)	Thyroid gland	Increases secretion of thyroid hormone; increases the size of the thyroid gland
	Adrenocorticotropic hormone (ACTH)	Adrenal cortex	Increases secretion of adrenocortical hormones, especially glucocorticoids, such as cortisol.
	Follicle-stimulating hormone (FSH)	Ovarian follicles in the female; seminiferous tubules in male	Follicle maturation and oestrogen secretion in the female; spermatogenesis in the male
	Luteinizing hormone (LH); called interstitial cell–stimulating hormone (ICSH) in males	Ovary in females, testis in males	Ovulation; progesterone production in female; testosterone production in male
	Prolactin (PRL)	Mammary gland	Stimulates milk production

Posterior lobe of pituitary (storage only: ADH and oxytocin are synthesized in the hypothalamus)	Antidiuretic hormone (ADH)	Kidney	Increases water reabsorption (decreases water lost in urine)
	Oxytocin	Uterus; mammary gland	Increases uterine contractions; stimulates ejection of milk from mammary gland
Thyroid gland	Thyroxine and triiodothyronine	Most body cells	Increases metabolic rate; essential for normal growth and development
	Calcitonin	Primarily bone	Decreases blood calcium by inhibiting bone breakdown and release of calcium, antagonistic to parathyroid hormone.
Parathyroid gland	Parathyroid hormone (PTH) or parathormone	Bone, kidney, digestive tract	Increases blood calcium by stimulating bone breakdown and release of calcium; increases calcium absorption in the digestive tract; decreases calcium lost in urine
Adrenal cortex	Mineralocorticoids (aldosterone)	Kidney	Increases sodium reabsorption and potassium excretion in kidney tubules; increases water retention
	Glucocorticoids (cortisol)	Most body tissues	Increases blood glucose levels; inhibits inflammation and immune response.
	Androgens and oestrogens	Most body tissues	Secreted in small amounts; effect is generally masked by the hormones from the ovaries and testes
Adrenal medulla	Epinephrine, norepinephrine	Heart, blood vessels, liver, adipose tissue	Helps cope with stress; increases heart rate and blood pressure; increases blood flow to skeletal muscle; increases blood glucose.

Pancreas (islets of Langerhans)	Glucagon	Liver	Increases breakdown of glycogen to increase blood glucose levels
	Insulin	General, but especially liver, skeletal muscle, adipose tissue	Decreases blood glucose levels by facilitating uptake and utilization of glucose by cells; stimulates glucose storage as glycogen and production of adipose tissue
Testes	Testosterone	Most body cells	Maturation and maintenance of male reproductive organs and secondary sex characteristics
Ovaries	Oestrogens	Most body cells	Maturation and maintenance of female reproductive organs and secondary sex characteristics; menstrual cycle
	Progesterone	Uterus and breast	Prepares uterus for pregnancy; stimulates development of mammary gland; menstrual cycle
Pineal gland	Melatonin	Hypothalamus	Inhibits gonadotropin-releasing hormone, which consequently inhibits reproductive functions; regulates daily rhythms, such as sleep and wakefulness
Thymus	Thymosin	Tissues involved in immune response	Immune system development and function

- Other organs can produce biologically active hormones as well:
    - adipose tissue
        - hormones:
            - resistin, leptin, angiotensinogen
    - gastrointestinal tract
    - heart
    - kidney
    - skeleton
    - skin

Hypothalamic regulation of eating and appetite

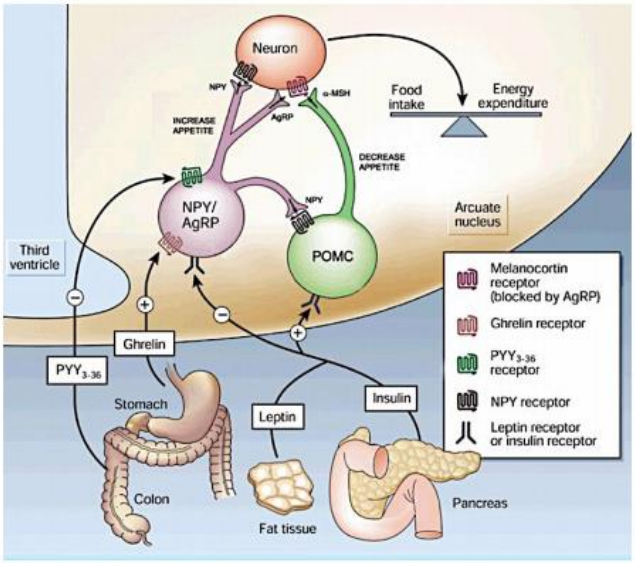


Figure 12.16 Hormones that control eating

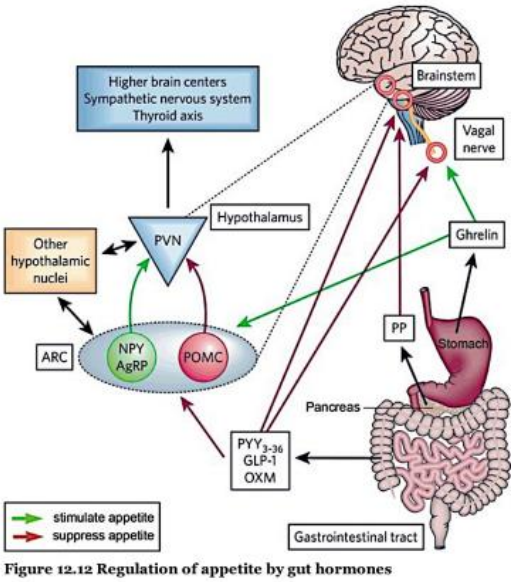
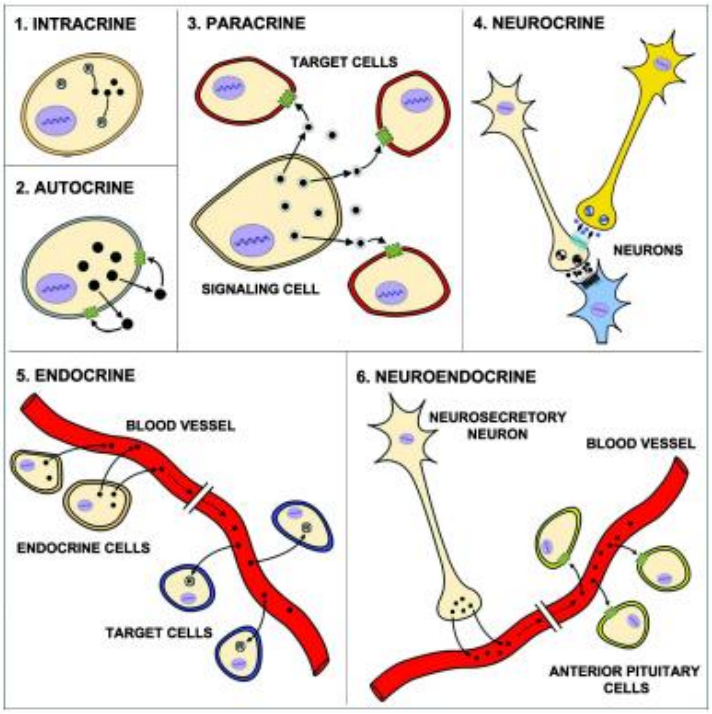


Figure 12.12 Regulation of appetite by gut hormones

Oxytocin and vasopressin

- influence behaviour
  - emotional
  - social behaviour
  - cognitive processes

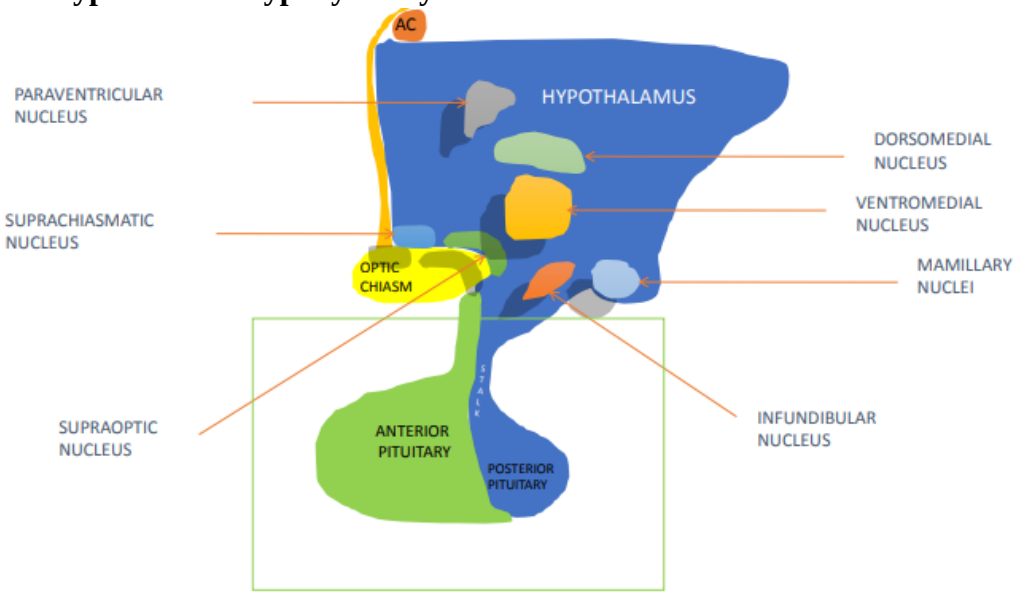
Target of endocrine gland hormones



Central regulation of the endocrine system

- *limbic system* is heavily interconnected with the hypothalamus.
- hypothalamus is integrated within the limbic system.
- beneath the hypothalamus is the hypophysis
- *hypothalamo-hypophisis unit* is a functional unit.

The hypothalamo-hypohyseal system

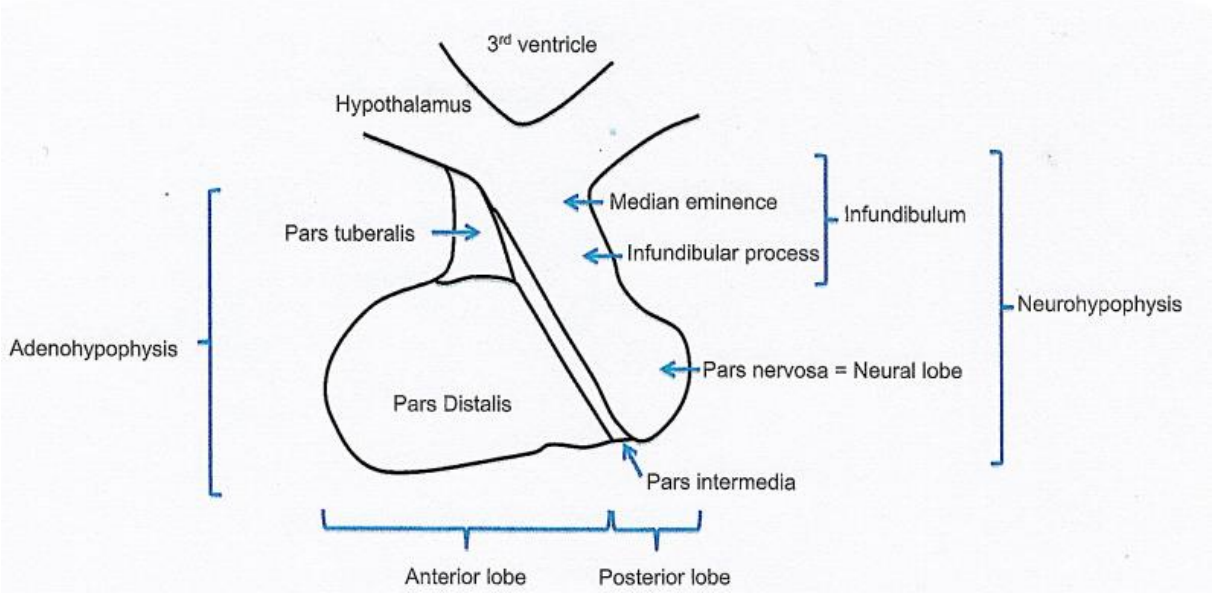


Significance

HPG-system Hypothalamic–pituitary–gonadal axis	Reproduction	Sterility
HPT-system Hypothalamic–pituitary–thyroid axis	Metabolism	Graves' disease
HPA-system Hypothalamic–pituitary–adrenal axis	Adaptation	Addison disease
HPP-system Hypothalamic-posterior-pituitary axis	Water, salt balance	Diabetes insipidus
Endocrine pancreas	Carbohydrate metabolism	Diabetes mellitus

Parts of adeno-and neurohypophysis

- Adenohypophysis
  - tuberal part
  - huge distal part
  - intermedial part
- Neurohypophysis
  - median eminence
  - infundibular process
  - neural lobe



Blood supply of the pituitary gland

- anterior pituitary is supplied by the *superior hypophyseal artery*.
- posterior pituitary is supplied by the *inferior hypophyseal artery*.
- magnocellular hypothalamic neurons project to the posterior pituitary
- axons from the infundibular region projecting to the median eminence terminating on the capillary loops and, then the blood vessels transfer the hormones to the anterior pituitary

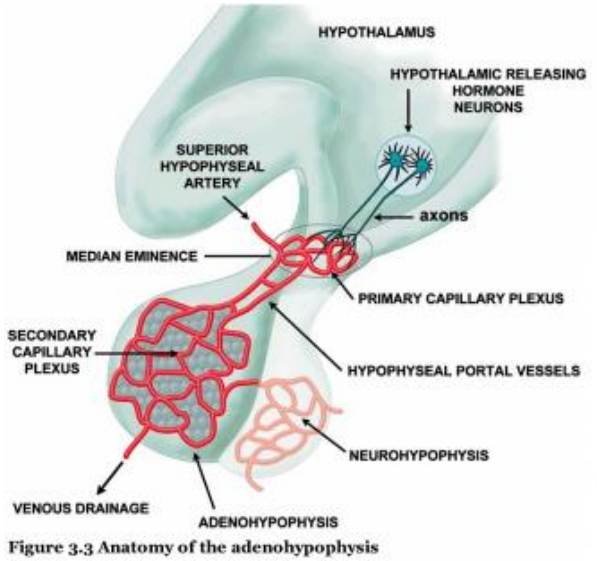


Figure 3.3 Anatomy of the adenohypophysis

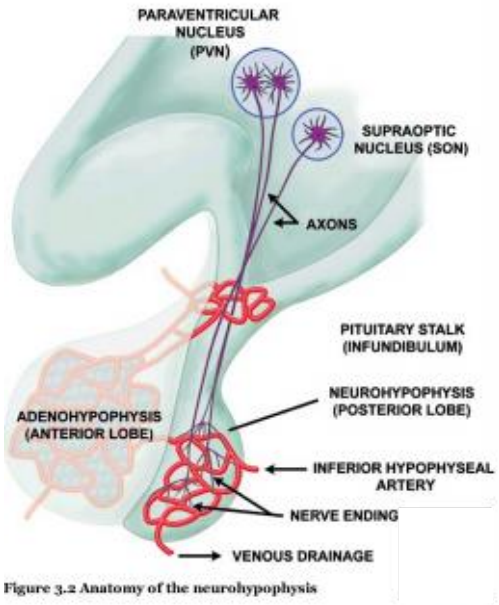
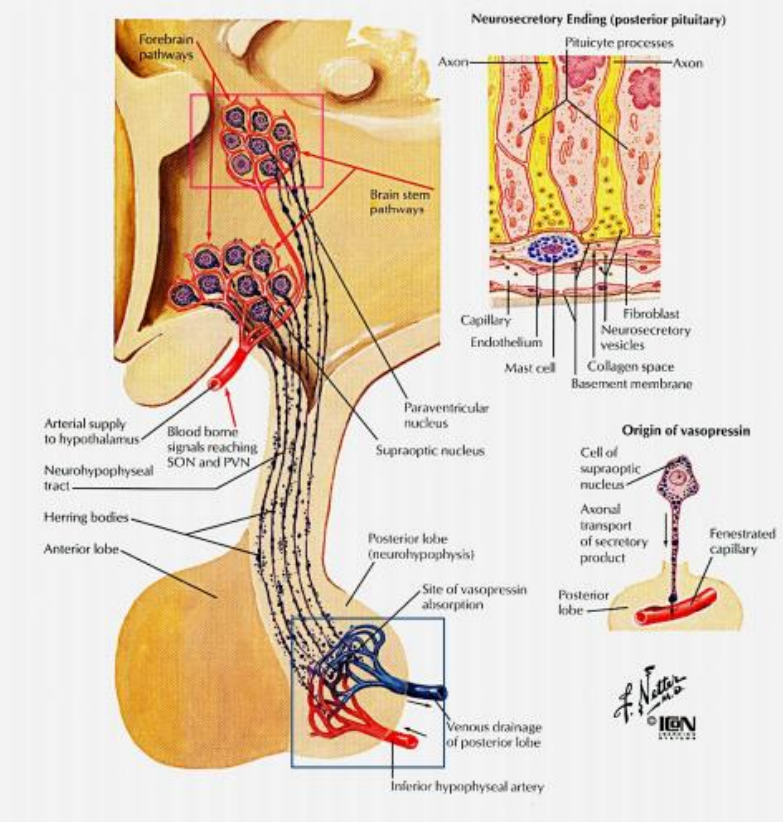
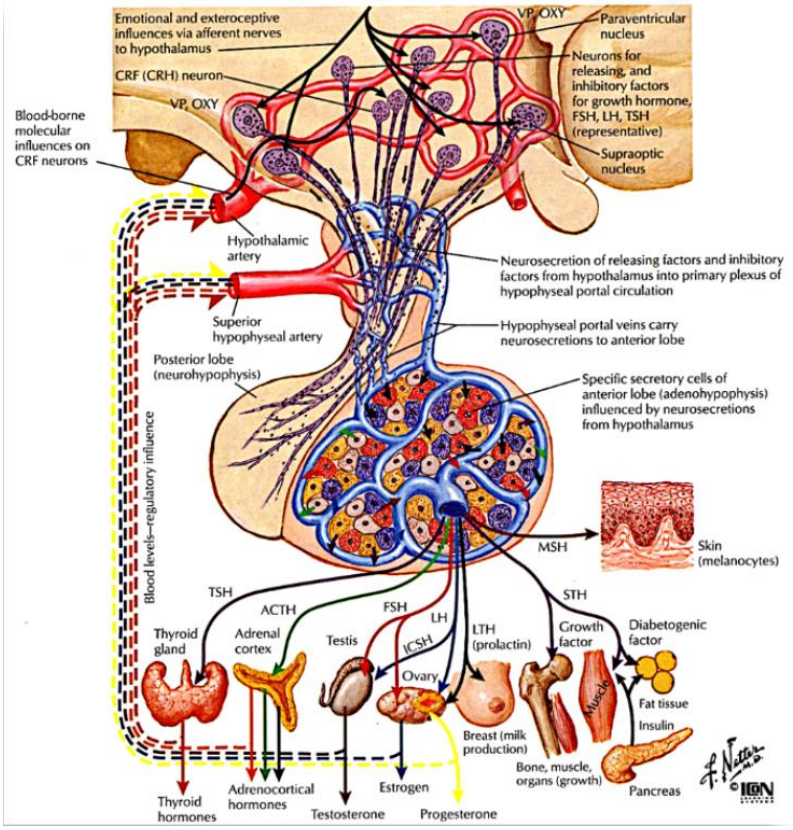


Figure 3.2 Anatomy of the neurohypophysis

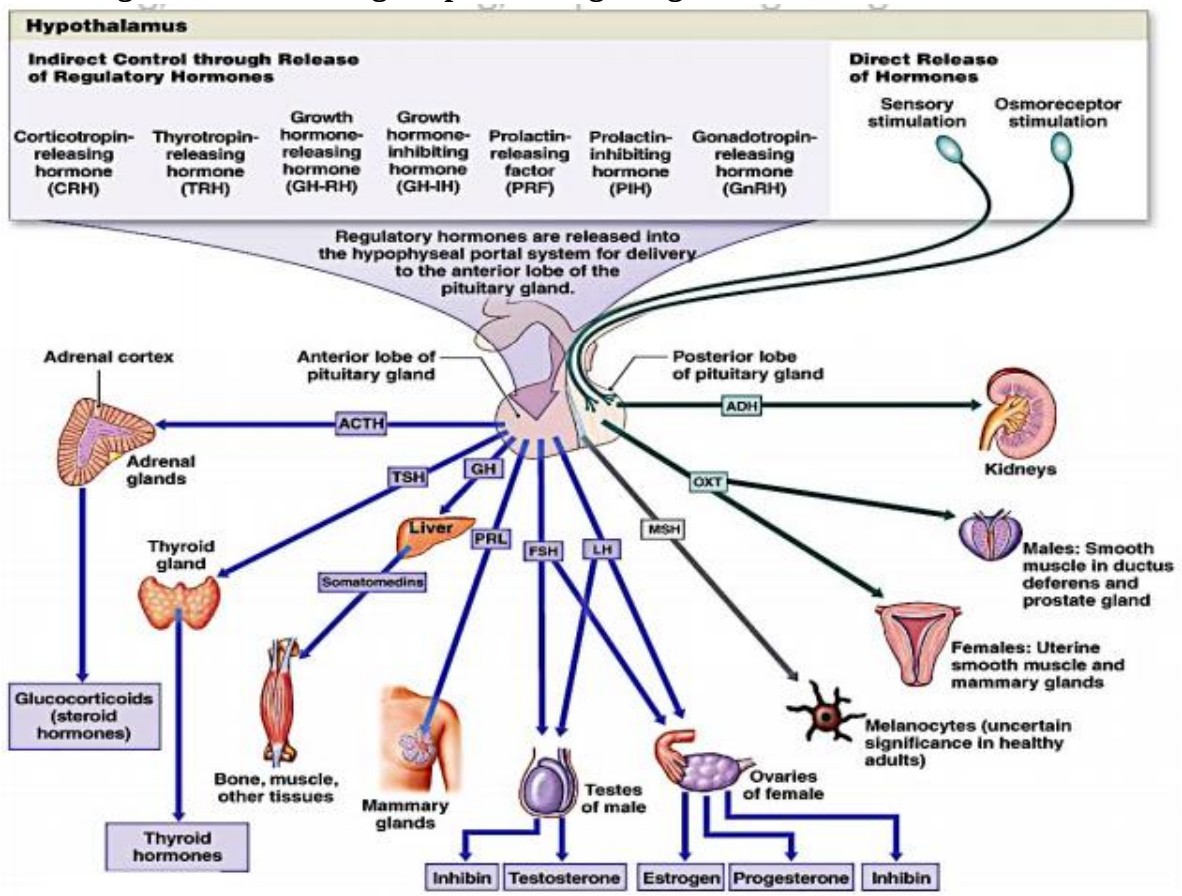
Neurosecretion



Hypothlamo-pituitary-endocrine gland axes



Releasing, release-inhibiting, troph and target organ hormones



Signalling mechanisms

Hypothalamus — Parvicellular neurosecretory cells

↓ Releasing hormons
Release-inhibiting hormons

Pars distalis — Troph cells — GPCRs

↓ Troph hormones

Endocrine gland — Target cells — GPCRs

↓ Peptide hormones
Steroid hormones
Derivatives of aminoacids

2

GnRH receptor

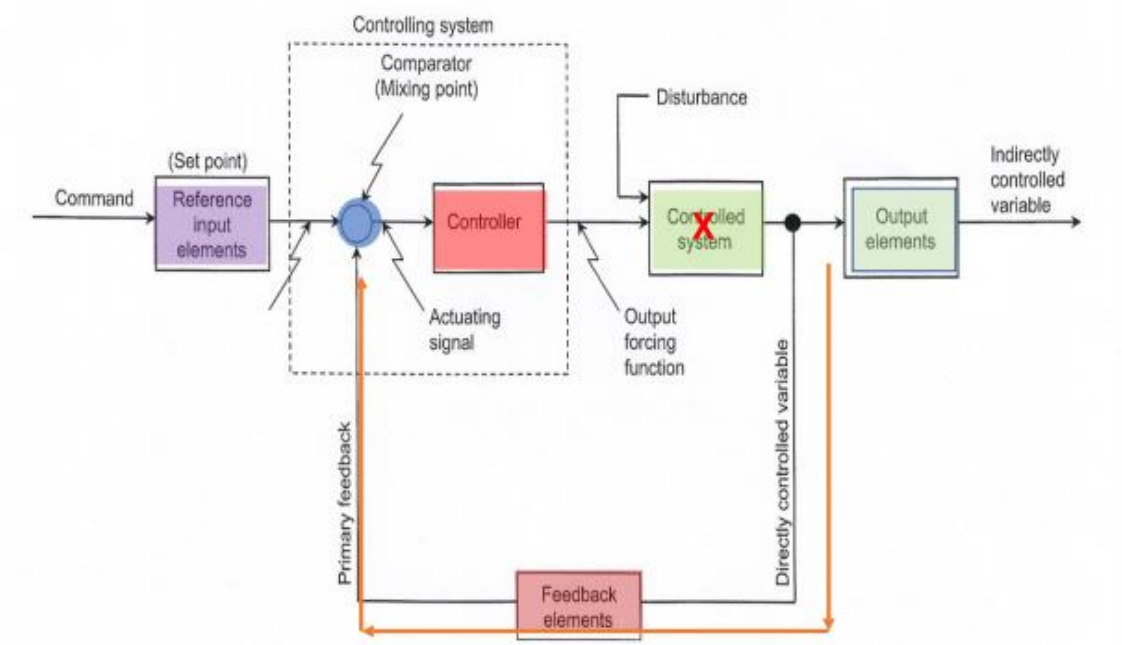
- 7 transmembrane receptor protein
- ligand binding pocket
- GnRH receptors are expressed in the cell membrane of gonadotroph cells in the anterior pituitary in LH and FSH cells

Secretion

- pulsatile in nature

Principle of feedback regulation

- key components:
    - reference input elements
        - they control the controlling system.
        - processes command and information arriving from different units.
    - comparator
        - part of the controlling system
        - also called mixing point unit
        - and this mixing point talks to the controller
    - controller
        - part of the controlling system
        - regulates the controlled system.
        - the output determines the operation function of the output elements.
    - controlled system
        - gets information from the controller
    - feedback element
        - the output of a controlled system in addition to informing the output elements also feeds back to the comparator unit.

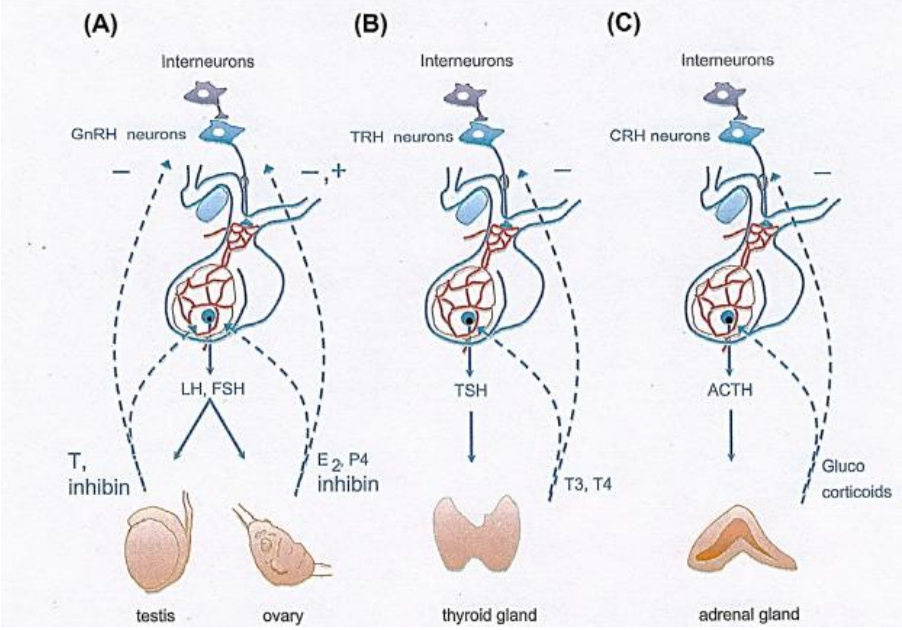


Feedback mechanisms

- hypothalamus – pituitary – target gland cascade
- ultrashort feedback
    - released inhibiting hormones secreted from the hypothalamus do feed back to the hypothalamus.
    - short feedback mechanism: troph hormones produced by the pituitary gland also informs the hypothalamus.
    - long feedback mechanism: the target gland also reports to the pituitary and the hypothalamus
    - direct long feedback mechanism: target gland to pituitary
    - indirect long feedback mechanism: target gland to hypothalamus

Three-level regulation

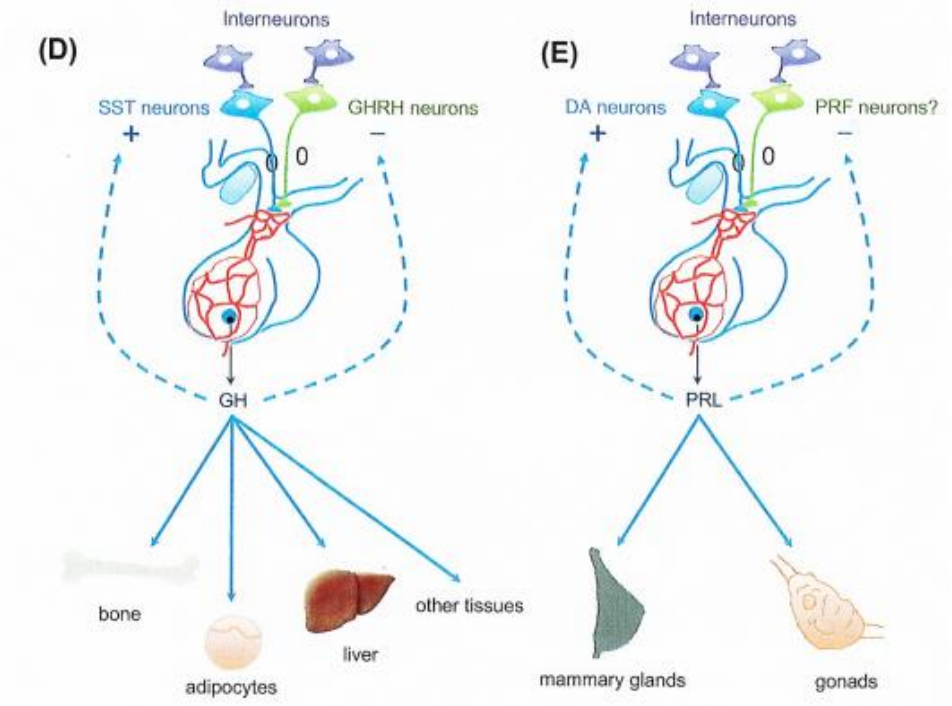
- hypothalamic pituitary gonadal axis (A)
- hypothalamic pituitary thyroid axis (B)
- hypothalamic pituitary adrenal axis (C)



1. level at the pituitary
    - where the corresponding releasing hormones (GnRH, TRH, CRH) act upon troph cells
    - with these troph cells inturn discharge LH, FSH, TSH and ACTH into a circulation, that reach the peripheral endocrine organs.
2. level at the peripheral endocrine organs
    - the produced hormones (T, inhibin, E, P, etc.) feed back to the pituitary
3. level at the peripheral endocrine organs
    - the produced hormones (T, inhibin, E, P, etc.) feed back to the hypothalamus

Two-level regulation

- production of growth hormones (GH) depends on hypothalamic hormones (SST (inh), GHRH (exc))
- these hormones reach the pituitary and as a result we facilitate the GH.
- hormone reaches the peripheral organs, but they do not sign back.
- 1st level: in the pituitary at the level of GH cells
- 2nd level: SST neurons and GHRH neurons



Neurosecretory system

- Magnocellular system
- Parvicellular system

Magnocellular system

Hypothalamic neurosecretory substances

- produced by hypophysiotropic neurons
  - Gonadotropin-releasing hormone (Gn-RH)
  - Corticotropin-releasing hormone (CRH)
  - Thyrotropin-releasing hormone (TRH)
  - Growth hormone-releasing hormone (GH-RH)
  - Somatostatin
- produces in magnocellular neurons
  - Vasopressin
  - Oxytocin
- other transmitters in hypophysiotropic neurons
  - Galanin
  - CART
  - Dopamine
  - Glutamate

- other regulatory substances
    - neurotransmitters
    - neuropeptides
    - steroids
    - cytokines
    - lymphokines
    - growth factors

Hypothalamic neurosecretory hormones

- Synthesized in neurons
- Transported via axo-plasmic flow
- Stored and released from axon terminals
- Secreted into the blood stream
- Have specific receptors
- Influence target structures via receptor coupled mechanisms
- Biologically active

Retrograde labelling of neurosecretory cells

- retrograde trace molecule (e.g., Fluoro-Gold)
- injected into the animal
- the substance gets into the circulation, this way it approaches the medial eminence where the parvicellular neurosecretory processes end
- the substances get out of the blood vessels and picked up via axon terminals
- and the neuron transports it in a retrograde manner toward the peripherals

Hypothalamic nuclei rich in hypophysiotropic neurons

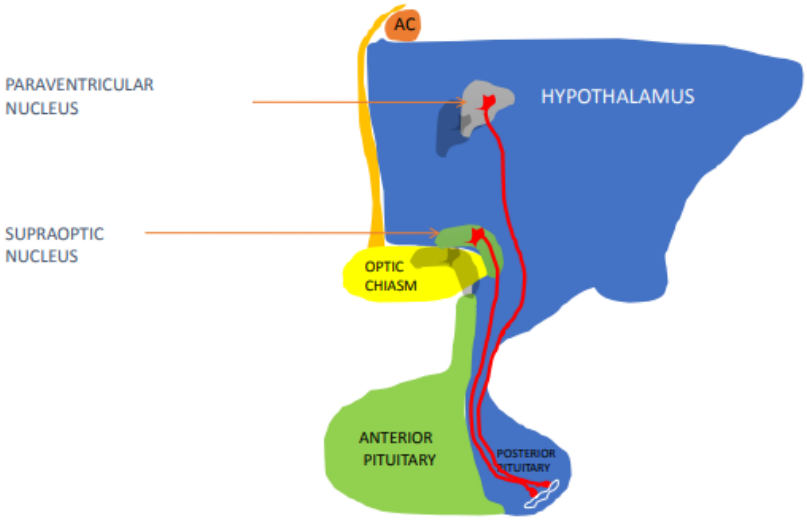
- OVLT-MPOA
- paraventricular nucleus
- periventricular nucleus
- arcuate nucleus

Division of hypothalamic paraventricular nucleus (PVN)

- magnocellular
- parvicellular
- autonomic

The magnocellular neurosecretory system

- Magnocellular neurons located in the supraoptic and paraventricular nuclei synthesize oxytocin, vasopressin, neurophysins and transport them down to the posterior pituitary.
- Upon specific stimuli, the hormones are released to the systemic circulation.
- They control smooth muscle functions and absorption of water in kidney.

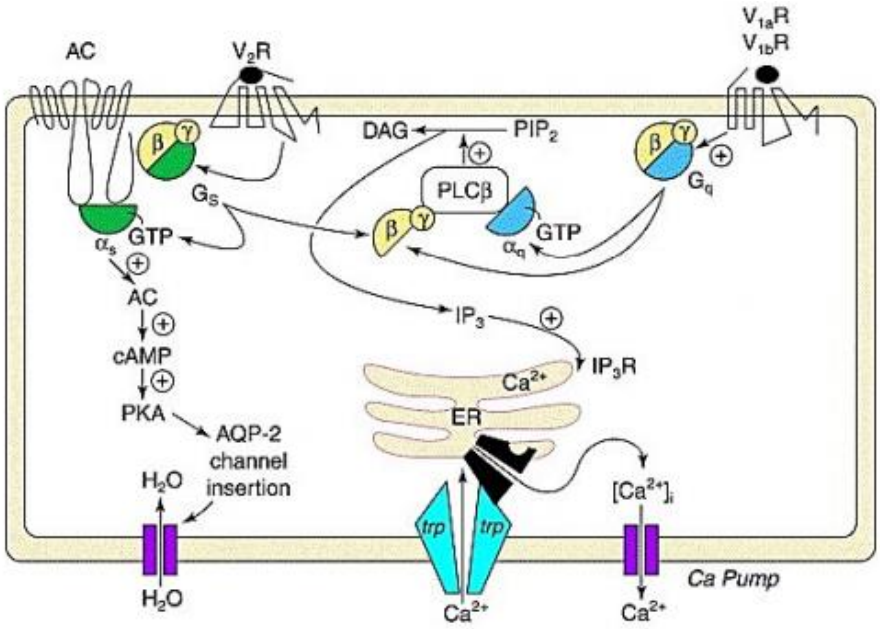


Magnocellular system

- magnocellular neurons (MCN) synthesize hormones:
  - oxytocin (OT)
  - arginine vasopressin (AVP)

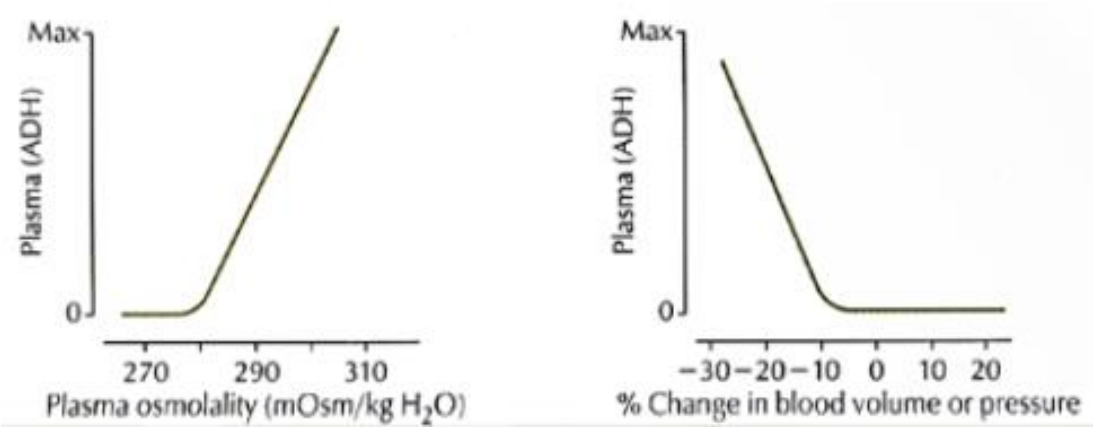
Vasopressin (VP) receptors

Receptor Subtype	Site(s) of Action	Physiological Effect(s)
V_{1a}	Vascular smooth muscle, platelets, cardiac myocytes	Vasoconstriction, platelet aggregation, positive inotropism
V_{1b}	Anterior pituitary	Release of ACTH and β-endorphins
V_2	Renal collecting ducts	Increased water absorption

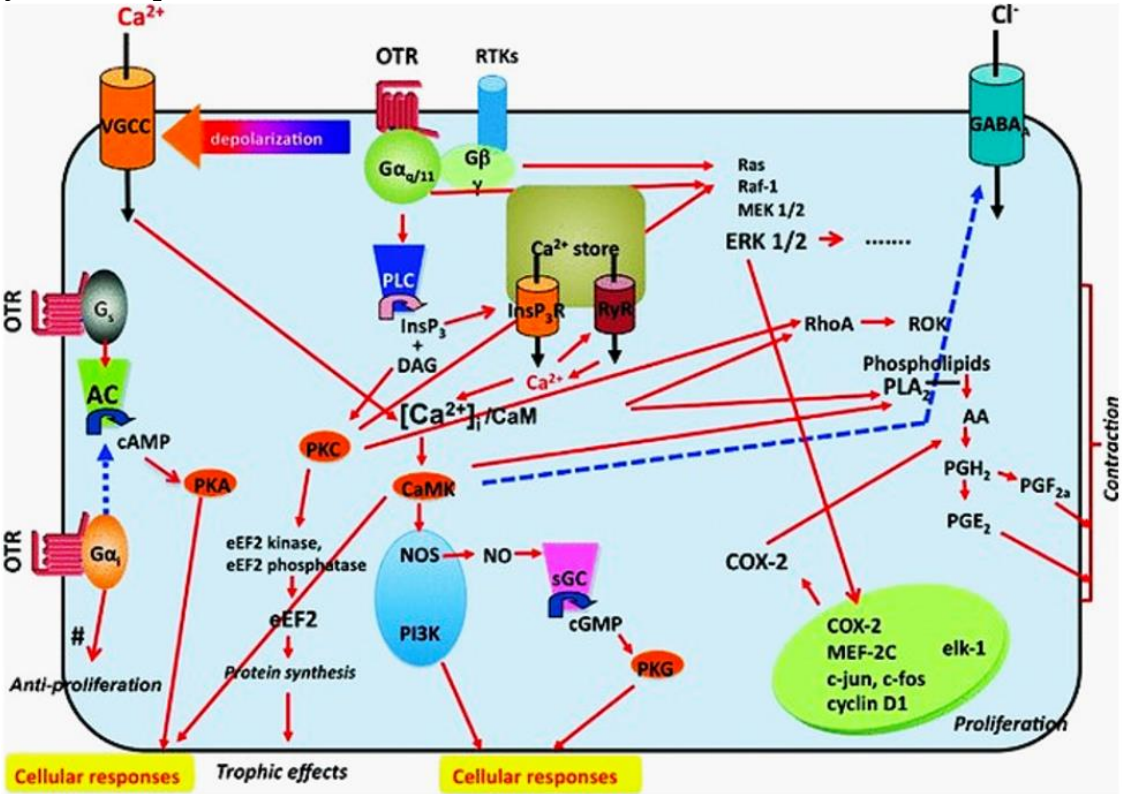


Vasopressin in the kidney

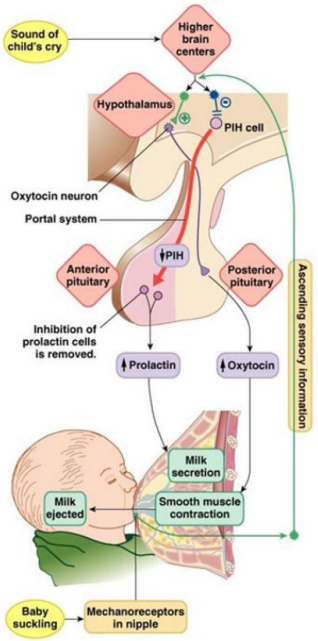
- collecting ducts become more permeable to water and thus permits osmolar equilibrium and absorption of water into the hypertonic interstitium
- a small volume of highly concentrated urine is excreted

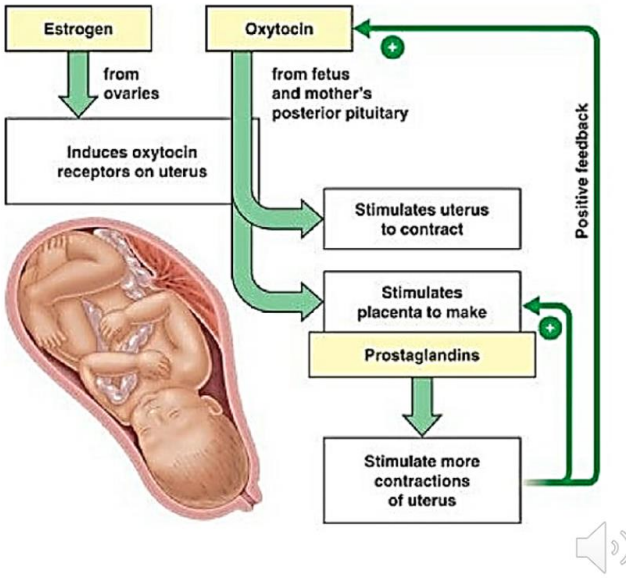


Oxytocin receptors



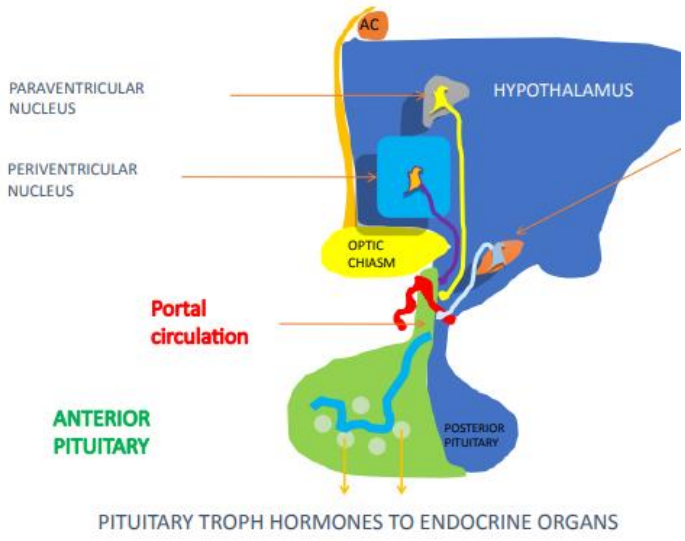
Oxytocin





The parvicellular neurosecretory system

- Parvicellular neurons secret releasing (LHRH, CRH, TRH, GHRH) and release-inhibiting (SS) hormones into the portal circulation.
- The hormones control the troph hormone output of different anterior pituitary gland cells.
- The system regulated reproduction, stress, adaptation, body growth and metabolism.



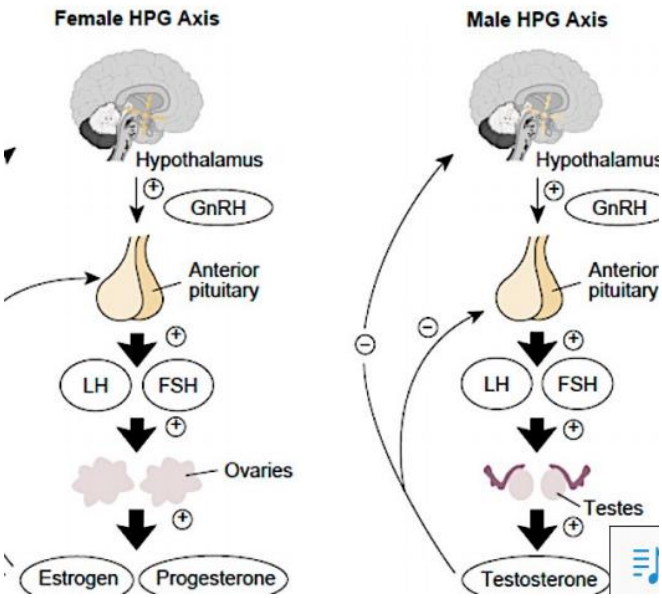
Classic parvicellular hypophysiotropic hormones

- Gonadotropin-releasing hormone (GnRH)
    - regulation of reproduction
- Thyrotropin-releasing hormone (TRH)
    - regulation of metabolism
- Corticotropin-releasing hormone (CRH)
    - operation of adrenal gland
- Growth hormone-releasing hormone (GHRH)
    - stimulatory substance
- Somatostatin (SS)
    - inhibitory substance

Hypothalamic nuclei rich in parvicellular neurosecretory neurons

- OVLT-MPOA
- Paraventricular nucleus
- Periventricular nucleus
- Arcuate nucleus

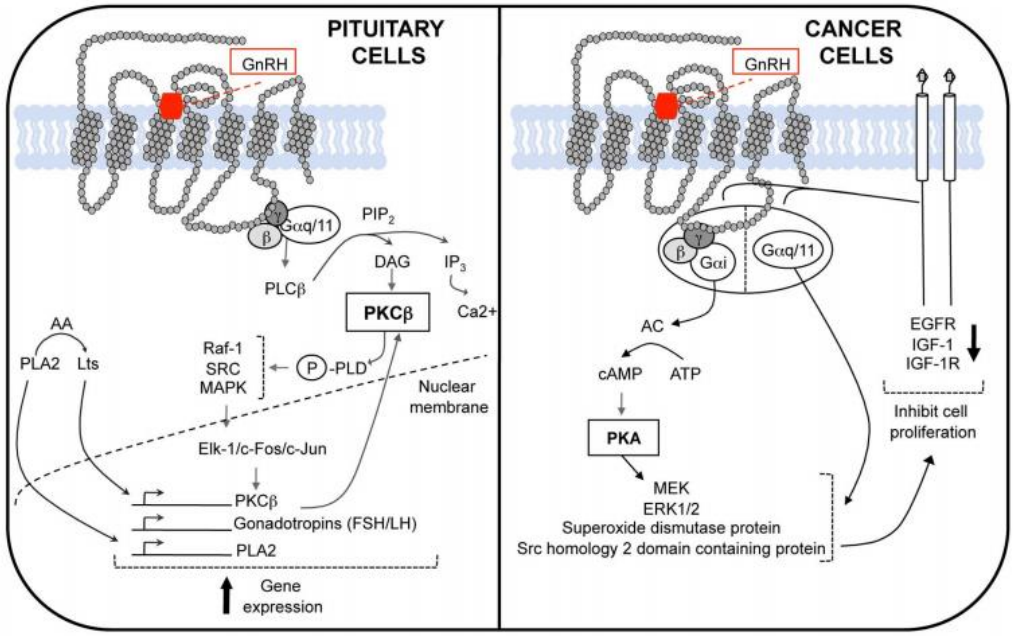
GnRH system



Gonadal regulation

- in the OVLT
    - triangle shaped region between the anterior commissure (CA) and the optic chiasm (OCH)
    - contains the majority of GnRH neurons.

GnRH receptor-linked signalling



Pulsatile GnRH and LH secretion

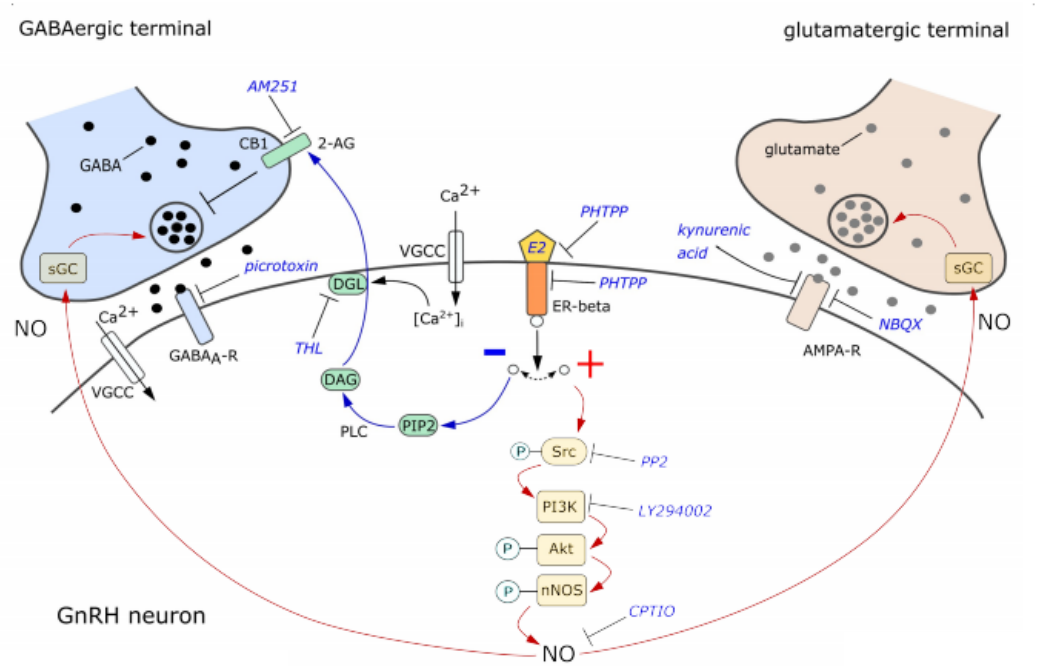
- higher amount of GnRH than LH in approximately every hour
- GnRH pulses are vital / essential for the induction of LH release.

Surge release of GnRH and LH

- sudden action of release, when relatively large amount of hormone release occurs.
- e.g., during menstrual cycle (LH levels are very high)

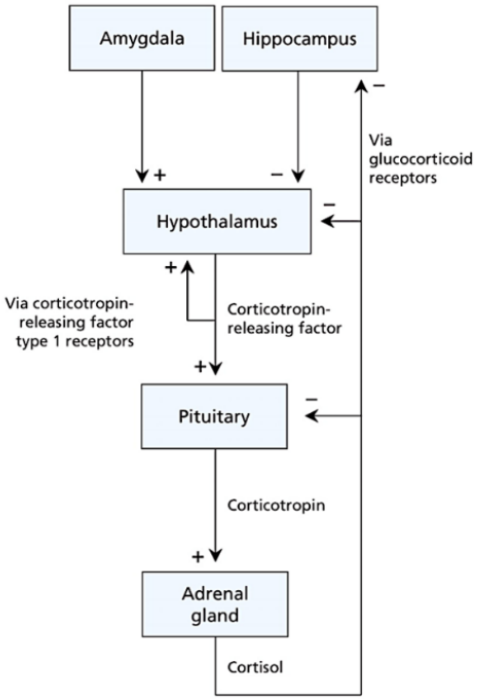
Molecular pathways involved in the negative and positive oestradiol feedback regulatory mechanisms of GnRH neurons

- increase the probability of GABA release
- NO excited GnRH neurons



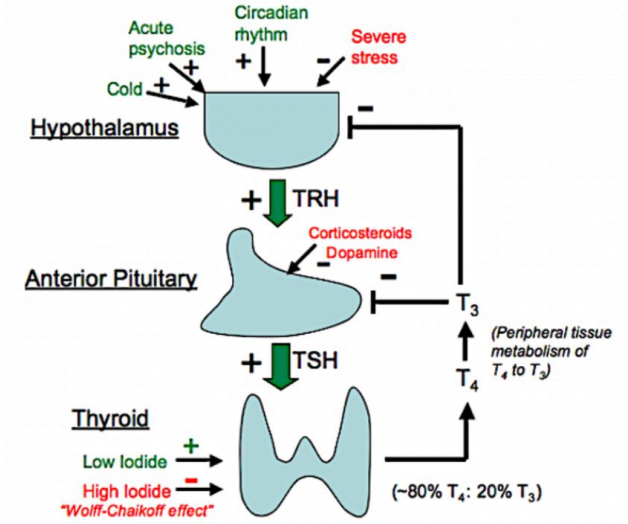
Corticotropin-releasing hormone CRH system

- responsible for stress and adaptation
- hypohysiological CRH neurons are synthesized in the PVN.
- adrenal regulation
- CRH receptor
  - 2 subtype
  - CRH uses subtype 1
- CRH neurons receive input from peptides and transmitters as well

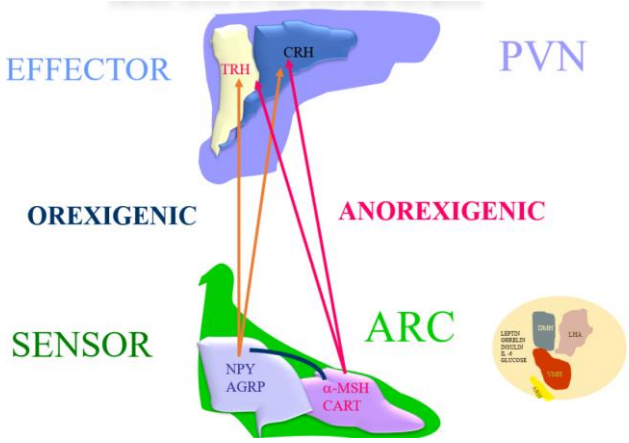


TRH system

- regulate energy and metabolism
- T_3 inhibits the hypothalamus and the pituitary as well



- TRH neurons receive GABAergic and glutamatergic sources and communicate with other neurons from the medulla, and with arcuate nucleus
- the actual level of energy and feeding state of the animal is highly determines the operation of the adrenal gland and the thyroid gland



- from thyroid gland T4/T3 regulate:
  - Thermogenesis
  - Mitochondrial uncoupling
  - Basal oxygen consumption
  - Fat stores
  - Lipogenesis Lipolysis
- from adrenal gland glucocorticoids regulate gluconeogenesis; lipolysis; glucose uptake inhibition
- metabolic signals reach arcuate nucleus and activate orexigenic and anorexigenic cell populations.
- metabolic signal populations project toward the PVN and evoke endocrine responses, they also communicate with magnocellular neurons that project toward autonomic centres.
- some other cell populations project to the lateral hypothalamus where the neurons project to the cortex and the brainstem and spinal cord