INTRODUCTION TO FUNCTIONAL NEUROBIOLOGY

2016-2017

1. L1: The resting membrane potential of the neuron. Generation of the action potential. Synaptic signal transduction. Synaptic plasticity.

PRESENTER: **Norbert Hájos, Ph.D., D.Sc.**

BRIEF SUMMARY:
The first lecture describes the basic **electrophysiological methods** and the **membrane properties** of neurons at „resting" and „activated" states.
The second lecture demonstrates the structural elements and the function of the **pre- and postsynaptic structures** and explains the significance of the **„anterograde" and „retrograde" neurotransmission.**
The third lecture explains and demonstrates with experimental data, that the effectiveness of **signal transduction** can increase (potentiation, facilitation) or decrease (depression) in a short and/or a long term in response to alteration of afferent neuronal activity.

ESSENCE:

1) The physico-chemical forces, which determine the membrane potential of neurons.

- The membrane potential is the difference in electric potential between the intracellular and the extracellular space.
- The lipid bilayer is a diffusion barrier to the movement of ions = insulator.
- Ion transporter/pump push ions across the membrane establishing concentration gradient.
- Ion channels allow ions to move across the membrane→concentration gradient decreases.

2) The biological properties of the cell membrane, which provide the neurons with the capability to generate resting and action potentials (semipermeability, ion channels and pumps).

Ion composition of neuronal tissue:

- Resting membrane potential = (-60) – (-75) mV

Ion	Inside concentration [mM]	Outside concentration [mM]	Equilibrium Potential [mV]
Na^+	18	145	+56
K^+	135	3	-102
Cl^-	7	120	-76
Ca^{2+}	100 nM	1.2	+125

- The Nernst Equation: The equilibrium potential for an ion can be calculated. Equilibrium is the balance of diffusion and electricity.

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

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

- The Goldman Equation: If the relative permeabilities are known, it is possible to calculate the membrane potential at equilibrium by using Goldman equation.

$$V_m = 61.54\ mV \cdot \log \frac{P_K[K^+]_o + P_{Na}[Na^+]_o}{P_K[K^+]_i + P_{Na}[Na^+]_i}$$

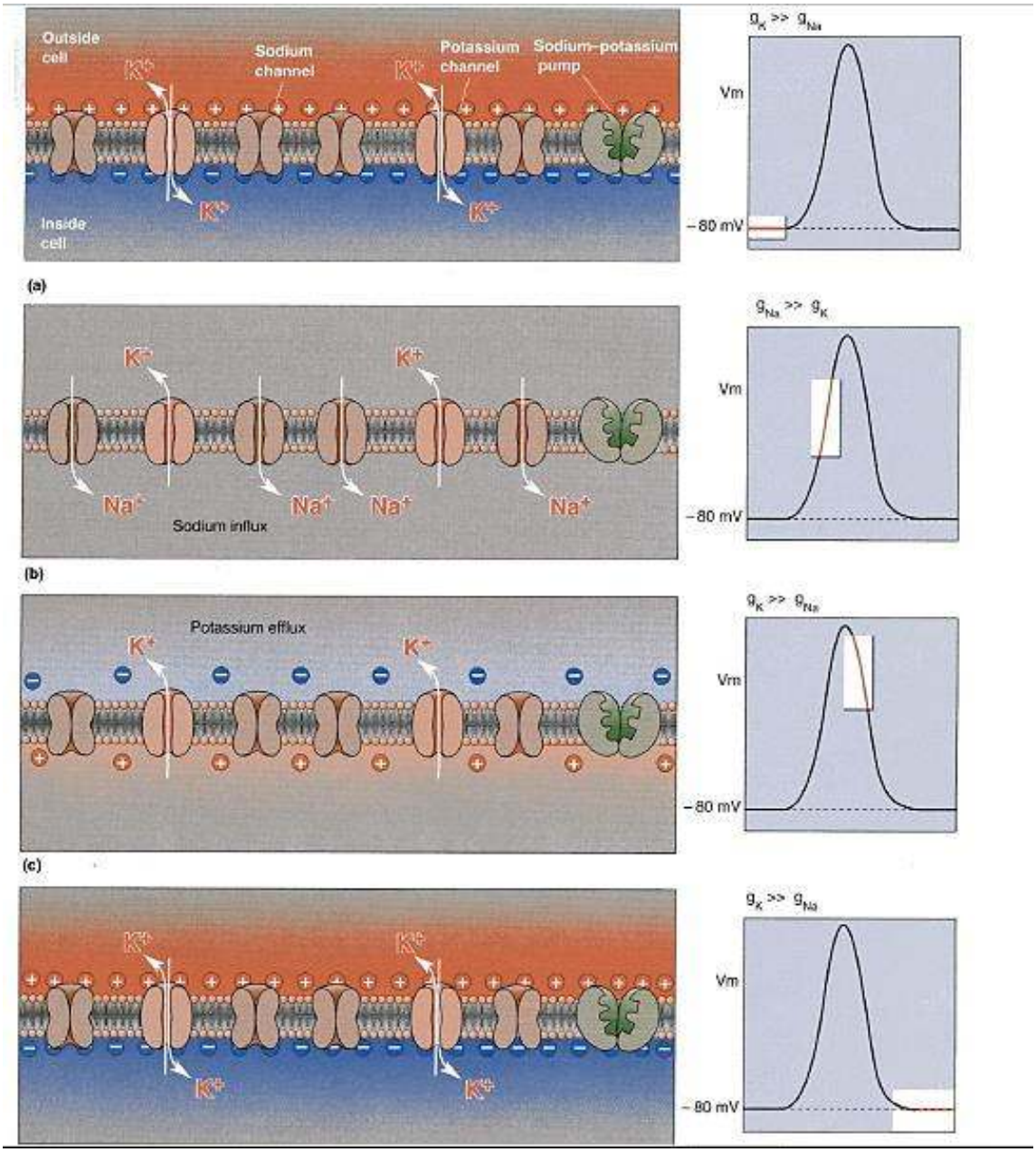
V_m = membrane potential
P_k/P_{Na} =relative permeabilities to K^+ and Na^+

Action Potential:

- Nobel Prize 1963 (Eccles, Hodkin, Huxley): determining of ion movements during AP, with voltage-clamp method → Membrane voltage kept constant, measuring injected current. (How much ionic current crosses the membrane at a given voltage.) Voltage dependency of ion channels can be determined.
- Diverse types of AP in the nervous system (e.g. thalamus: burst firing)
- Linear summation of asynchronous excitatory inputs, while synchronous inputs give rise to supralinear summation in the dendrites
- Backpropagating AP: soma→ dendrit

Ion channels and transporters

- Nobel prize 1991 (Nehert, Sakmann) development of patch-clamp, single ion channels in the cell membrane.
- Patch-clamp method: Cell membrane sealed to the electrode by suction. Electrodes are filled with solution with similar ion composition to the intracellular medium. With the help of micropipette isolate a tiny area of the cell membrane and record molecular events of ion channels located there and measure transmembrane current. Types: cell attached, whole cell recording, inside-out recording, outside-out recording.
- Ion channels: voltage gated, ligand gated, phosphorylation-gated, strech or pressure gated
- Ion transporters : sodium-potassium pump (takes three Na back to the extracellular, two K into the intracellular space, uses ATP).



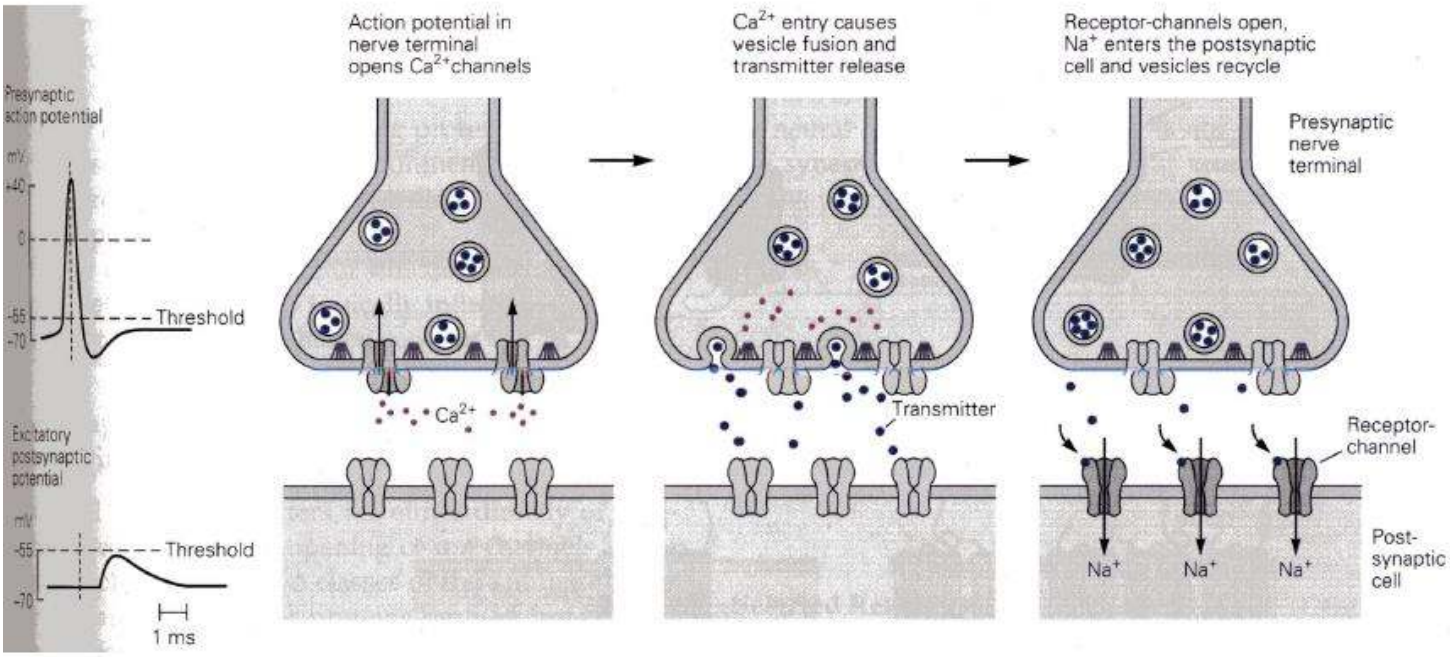
3) The parameters measured during electrophysiological recordings. Characteristics of the records.

4) Targets of electrophysiological recordings.

5) Passive and active properties of the electrotonic conductance in the neuronal processes.

6) Structure and function of the presynaptic element.

The mechanisms of neurotransmission



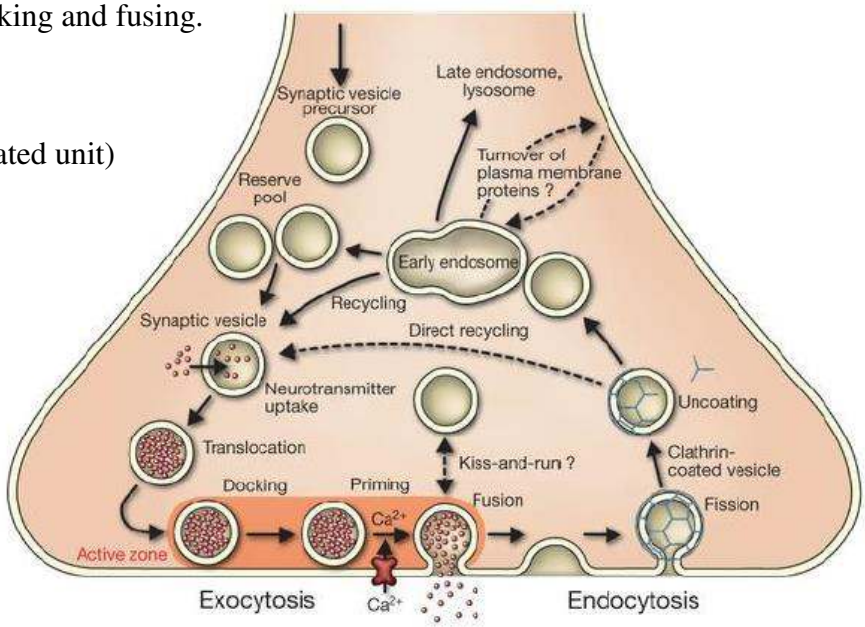
Presynaptic element:

1. synaptic vesicle in reserve pool
2. docking
3. priming
4. fusion with the membrane: exocytozis, transmitter release (after Ca2+ influx)
5. synaptic vesicle membrane recycling: endocytosis-> ensure the proper reserve pool

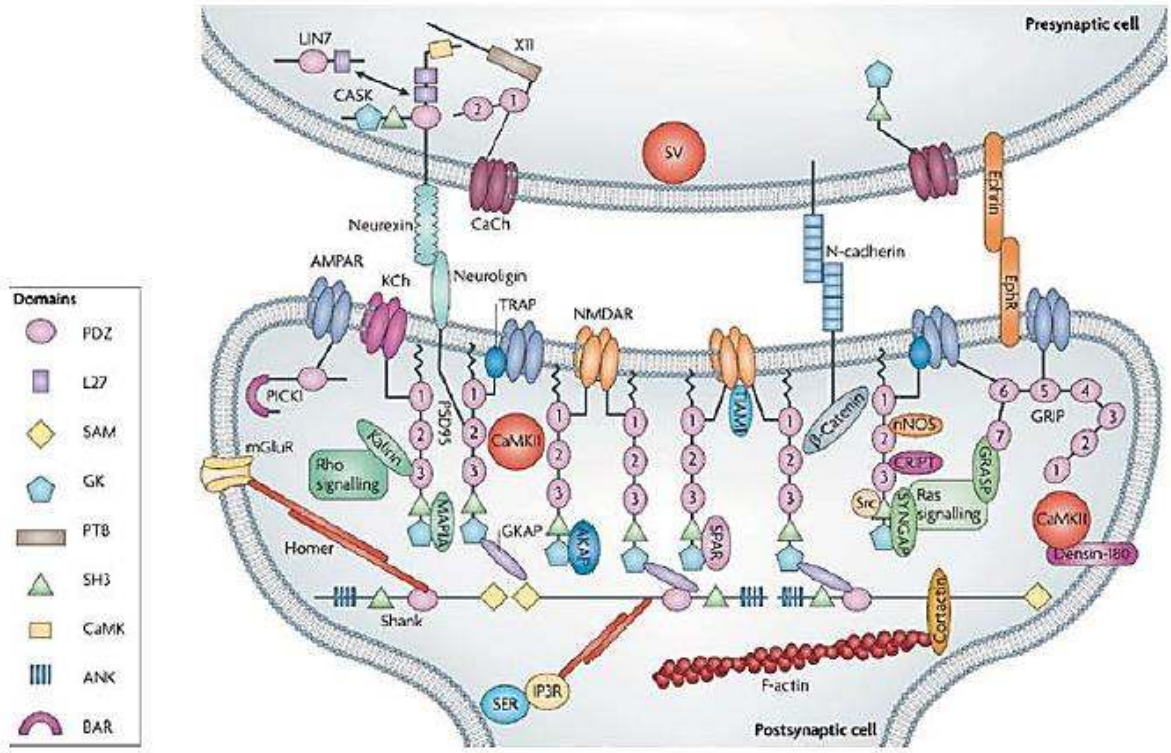
SNARE proteins: pivotal role in docking and fusing.

V-SNARE (vesicular components),

T-SNARE (target membrane associated unit)



7) Structure and function of the postsynaptic element.



Receptors:

- iontropic (direct gating) - fast transmission (10ms)
  excitatory:
  - glutamate : AMPA r., kainate r., NMDA r.
  - Ach: nicotinic r.

  inhibitory:

  - GABA r.
  - glycine r.
- metabotropic (indirect gating) – slow transmission (100 ms) – G-protein coupled-second messengers
  excitatory:
  - glutamate: mGlu r.,
  - Ach: muscaranic r.

  inhibitory:
  - GABA r.
- Quantal release of neurotransmitters -> postsynaptic potential
- Extrasynaptic neurotransmission (role in short- and long-distance communication between nerve cells, release neurotransmitters to the extracellular space)
  - raphe nuclei-> serotonin

  - midbrain cholinergic cells (basal forebrain) -> Acethylcholine
  - locus coeruleus -> norepinephrine
  - ventral tagmental area -> dopamine
- Second messengers : intracellular signaling molecule whose concentration increases (or decreases) in response to binding of an extracellular ligand to a cell-surface receptor. -> trigger physiological changes
  - cAMP-> PKA (protein kinase A)
  - cGMP -> PKG
  - IP3-> Ca2+ release, DAG(diacylglycerol)-> PKC
  - Arachidonic acid -> Lipoxygenase, Cyclooxigenase

8) Retrograde neurotransmission.

Postsynaptic ->Presynaptic, primary purpose: regulation of chemical neurotransmission, mainly inhibiting

- Gaseous molecules: NO, CO o
- Peptides: BDNF, dynorfine (inhibit dopamine)
- Lipids: endocannabinoids, arachidonyl acid
- Classical neurotransmitters: GABA, glutamate

9) Short term plasticity.

Plasticity: is the ability of synapses to strengthen or weaken over time, in response to increases or decreases in their activity

Short-term plasticity (STP) - Depends on the target selectivity, acts on a timescale of ms to few s

- short-term depression (STD)
  - weakens the synapse (we have the same stimuli but response will be lower)
  - caused by: depletion of the readily releasable vesicles, de-sensitisation of postsynaptic receptors, intracellular factors
- short-term facilitation
  - Synapses will strengthen for a short time
  - caused by Ca accumulation

10) Long term plasticity.

(LTP) – long lasting change. Mechanisms: NMDA receptor dependent, Spike timing-dependent (=precise temporal interval between presynaptic and postsynaptc spikes)

- Long term potentiation (LTP): strengthening of synapses induces long-lasting increase in signal transmission between two neurons
- Long term depression (LTD): long-lasting decrease in synaptic strength

2. S1: *In vitro* and *in vivo* recording techniques.

PRESENTER: **János Szabadics, Ph.D.**

BRIEF SUMMARY:
This seminar describes electrophysiological recording techniques, which allowed and still allows the experimental understanding of the operating principles of the neuronal circuits. These rules include how analog and digital signals propagate and integrated by the excitable neurons. It is also explained (and exemplified), how specificity and selectivity of the electrophysiological recordings can be increased by introducing pharmacological and genetic manipulations of the target area.

ESSENCE:

1) How the patch-clamp technique is used and capable to measure input events (i.e. inward or outward currents, activation of electric or chemical synapses).

2) How the propagating electrotonic (graded) potential (anterograde and retrograde) is processed within the somatodendritic compartment of the neurons.

3) The quantal release of neurotransmitters.

4) Operation of voltage- and ligand gated ion channels.

3. L2: Structure of the retina. Information processing in the retina. Thalamic relay of the retinal projection

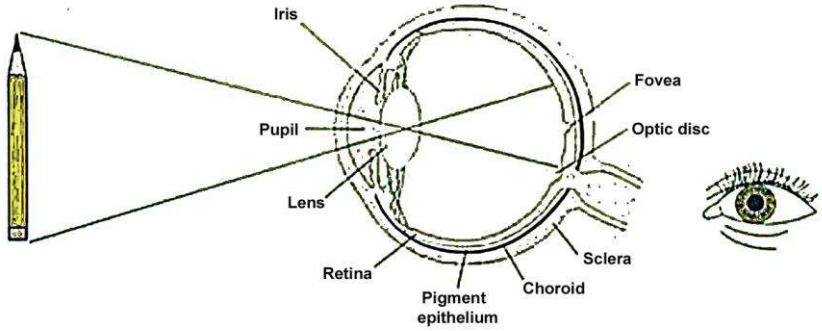
PRESENTER: **Dr. Béla Völgyi**

BRIEF SUMMARY:
This series of lectures explains the visual information processing in the vertebrate **inverted retina, in which the light reaches the photoreceptor layer the last**. Retinal cells are characterised by their position, connectivity, phenotype (morphology and transmitters, neuromodulators, receptors, intracellular signalling molecules produced) and electrophysiological responses to light. The term "**receptive field**" is introduced and the function of the two types of centre-surround structures i.e. **on-centres** and **off-centres** are described.

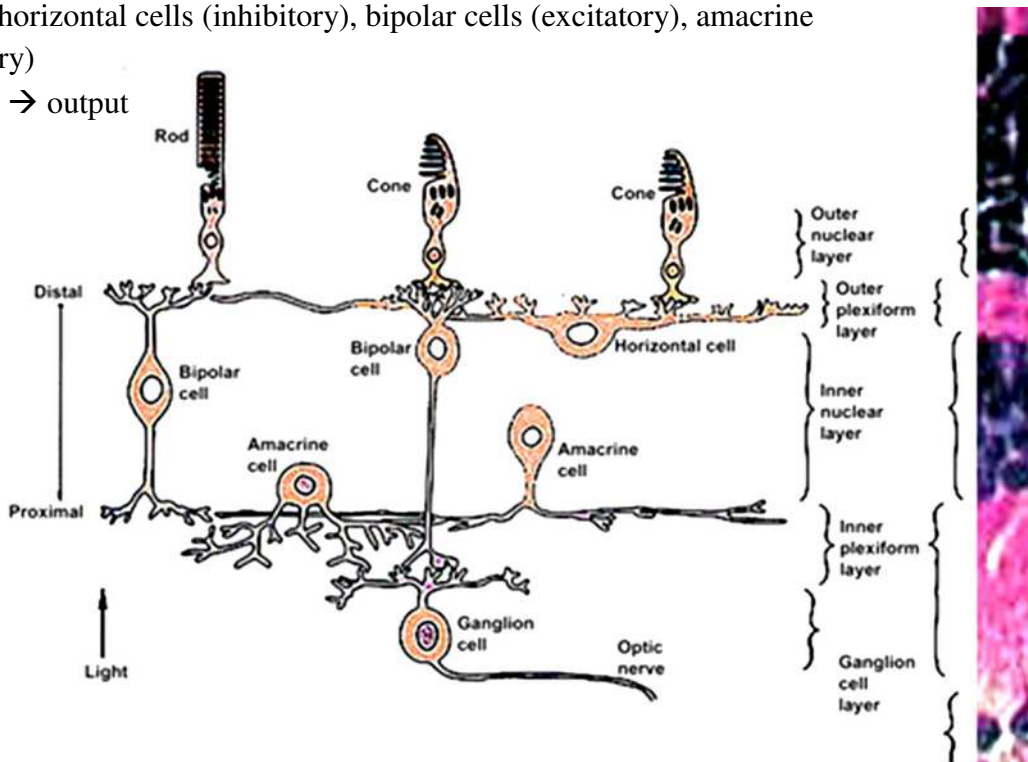
ESSENCE:

1) Light passes through a series of refractory media, creating a minimised, and upside-down image of the objects on the retina.

The retina:



- Fovea (sárga folt): responsible for sharp central vision
- Optic disc(vakfolt): exit point of the optic nerve
- 10 layers including:
  - 3 somatic
  - 2 synaptic
- cell types:
  - photoreceptors(back of retina): rods, cones
  - interneurons: horizontal cells (inhibitory), bipolar cells (excitatory), amacrine cells (inhibitory)
  - ganglion cells → output

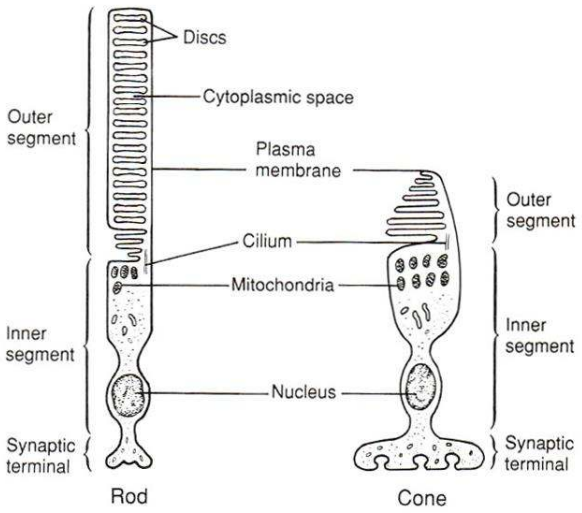


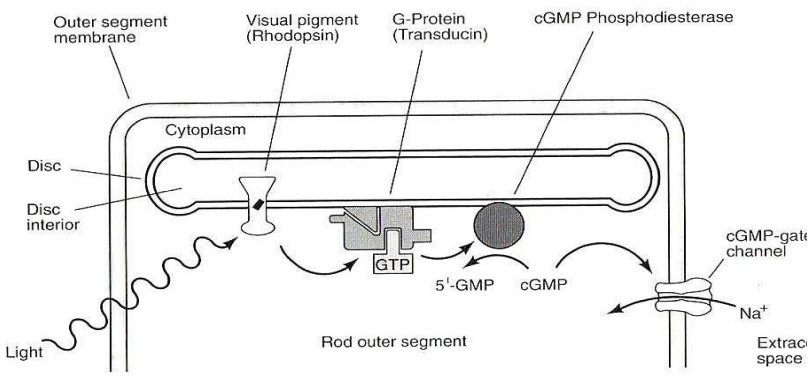
2) The spectrum and luminance of visible light are limited and two basic photoreceptor types with different characteristics and retinal distribution are specialised for detection.

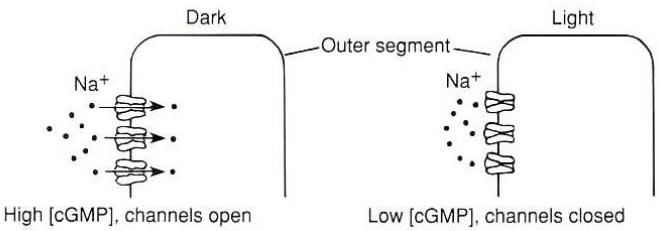
Rods (pálcikák)		**Cones (csapok)**
Processing of low intensity light	**Function**	Fast processing of high intensity light
Long outer segments, closed endomembrane system with disks, rhodopsin (on the disks): opsin (transmembrane protein) + cis-retinal	**Structure**	Open membrane system with folds, rhodopsin (photopsin) in the outer membrane's folds
1: green light	**Types**	3: blue, green, red lights → cones are responsible for colour detection
Invaginated (independent of ON/OFF types)	**Synapse** (Ribbon synapse*)	Invaginated: postsyn. cell fold to the presyn. cell(ON BP cell), Flat: "normal" synapse(OFF)
2 horizontal cells, 1 bipolar cell	**Postsynaptic partner**	2 horizontal cells, 1 bipolar cell

* ribbons (szalagok) are vertical; vesicles are collected on them. Rods' ribbon synapse is smaller.

- normally rods and cones are depolarized (~40mV). In dark: cGMP keeps open the Na^+ channels in their membranes.
- Light → trans retinal from cis retinal (conformation change) → transducin (G protein) activation → cyclic phosphodiesterase → GMP from cGMP → Na^+ channels close → hyperpolarization (not action potential!)
- dark → NT release
  light → NT release stops







3) The retina spatially encodes the image and compresses the visual information via converging signalling to ganglion cells.

Photoreceptors→interneurons→ganglion cells

4) Function of retinal cells in on-centre or off-centre structures. Dark currents and signal inversion.

Bipolar cells:

- ON and OFF type
- OFF bipolar cells:
  - fire by darkness
  - hyperpolarize to light → sign conserving cells
  - AMPA and KA receptors
  - flat contact
- ON bipolar cells:
  - fire by light
  - depolarize to light → sign-inverting cells
  - mGluR6 glutamate receptor
  - invaginated contact
- receptive field: center (receptors have direct contact with BCs) and surround (receptors have contact with BCs through horizontal cells)
- BCs are contrast detectors

Horizontal cells:

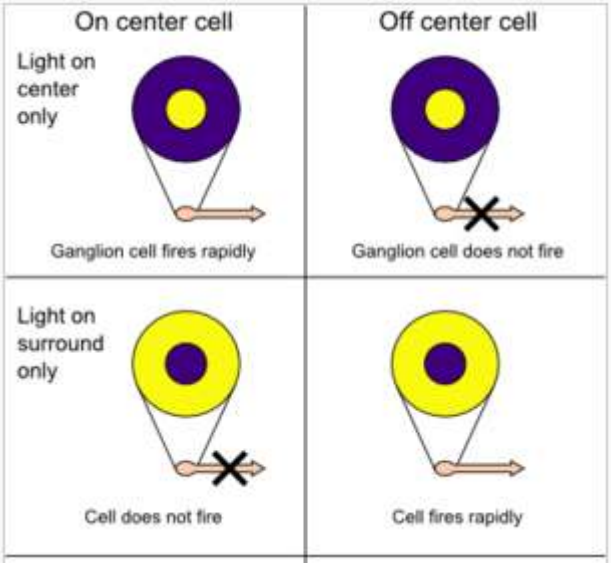
- hyperpolarize to light
- glutamatergic input (AMPA receptor), GABAergic output
- their lateral inhibition generate the center-surround receptive field

Amacrine cells:

- major inhibitory interneurons of inner retina
- 30-40 subtypes
- mainly GABA and glutamate transmitters, capable to coexpression
- neuromodulation
- narrow-, medium- or wide-field dendritic arbor
- one axonic, **axonless** or multiaxonic

Ganglion cells:

- ON, OFF and ON-OFF cells
- they fire first in the retina
- transient or sustained response
- ganglion cell mosaics
- minimal overlap between GCs
- inhibitory cells: amacrine cells



5) Participation of retina in light adaptation and orientation selectivity.

4. S2: Stem cells and potential applications

PRESENTER: **Prof. Emília Madarász**

BRIEF SUMMARY:

This seminar describes the development of nervous system from the viewpoints of cellular fate. It explains the **prevailing regulatory mechanisms during cell proliferation and differentiation** in the embryonic primordia and the mature nervous system. It explains also the **selection processes** (elements produced in excess, and reduced to the level of the biological need), which determine the final set of cells and synapses for building functional networks. Finally, the ethical questions, and the biological problems related to the use of cells with the capability to produce **new, differentiated neurons or glial cells** for clinical and/or research purposes, are also discussed.

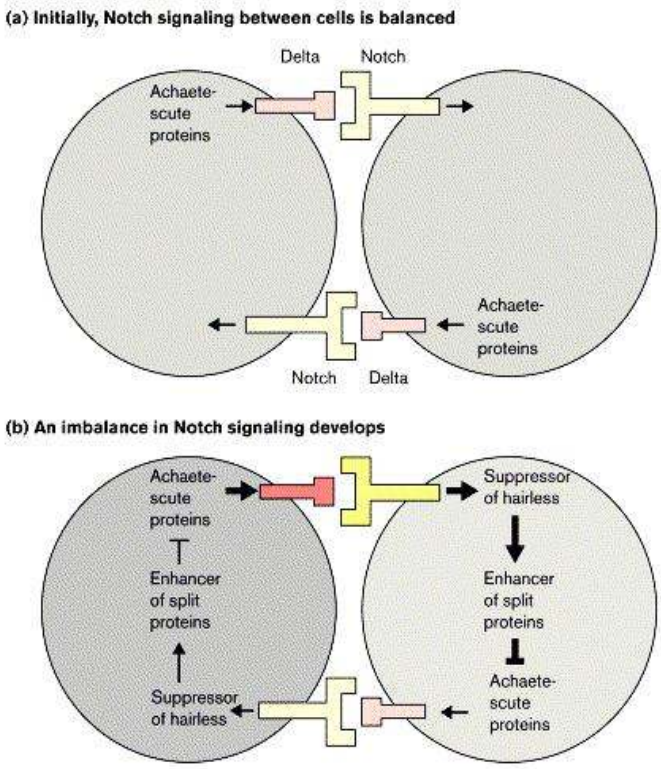
ESSENCE:

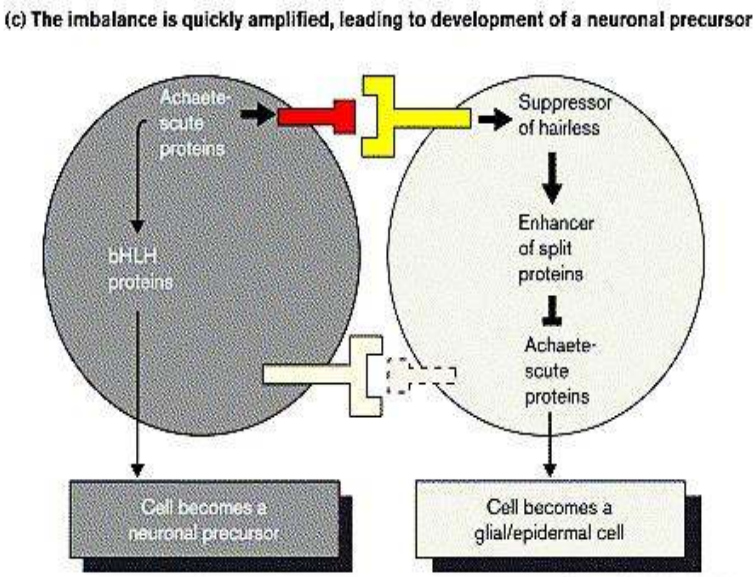
1) There are cells in the embryonic, as well as in the mature nervous systems, which can reproduce themselves, and can produce cells differentiating into specialized cells.

- Stem cells: can divide by asymmetric mitosis
  - one daughter cell will be the same
  - the other will differ in phenotype →progenitor cell
- 2 types of stem cells:
  - embryonic stem cell (daughter cell is either haploid or diploid)
  - tissue stem cell (daughter cell is only diploid) → neural stem cell is tissue stem cell
- IPSC (Induced Pluripotent Stem Cell): eg. fibroblast can be reconverted to stem cell in vitro
  aim: curing diseases (Alzheimer, Parkinson, Huntington…)
- Neurons and glia cells are formed from neural stem cells
- Neural stem cells are also found in adult brain (neurogenic zones): SVZ (SubVenticular Zone), olfactory bulb, hippocampus (granule cells)

6) The balance between cell proliferation and differentiation is regulated by direct cell to cell signaling via the notch/delta system, and by several environmental factors including growth-factors, small molecular weight regulatory compounds and cell to extracellular matrix interactions.

- Notch/Delta system: stem cells get the neurulation signs from the neighboring cells (direct cell to cell signaling). The Notch-Delta system regulates whether there will be proliferation or differentiation.
  - eg. AVE (Anterior Visceral Endoderm) organizing cell → head – not head region
  - eg2: Shh (Sonic hedgehog) morphogen → responsible for shape development





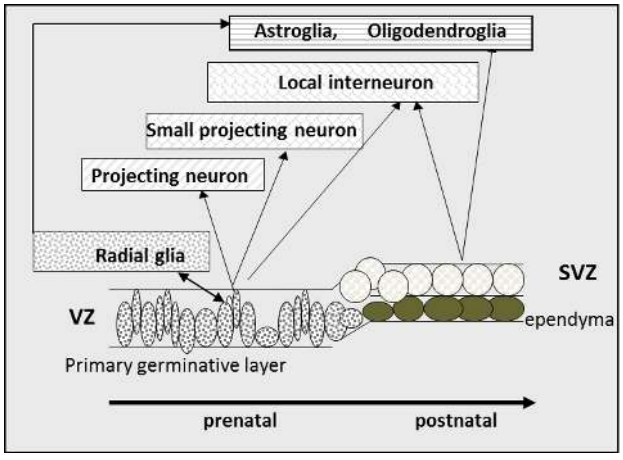
Differentiating cells **Non-differentiating cells**

- differences between neighbouring cells caused by stochastic events and intrinsic or extrinsic factors are stabilized or amplified through Notch and Delta signals
- Lateral inhibition (by N/D system)

7) Regulated cell migration of post-mitotic neuronal precursors is crucial for the formation of specific regions in the nervous system.

Migration of neurons:

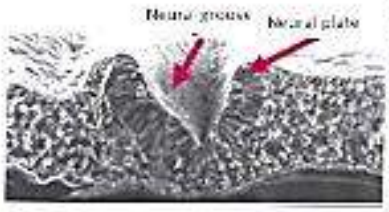
- CNS: with the help of radial glia cells
  In response to tissue damages, large-scale cell production occurs in the CNS.
- PNS: migration of cells of neural crest (they migrate to different spots of the body depending on their differentiation→(regulated by factors)

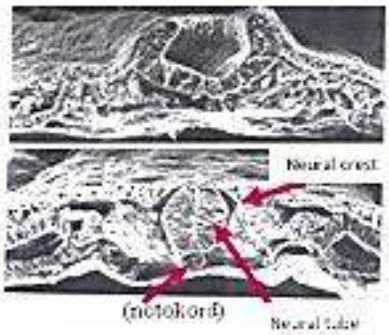


Embryonic cell migration from the primary germinative zone → Neuronal precursors derived from the primary germinative zone migrate along the radial glia cells → The secondary germinative zone derives from the primary zone.

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

Embryonic neuroectodermal stem cells



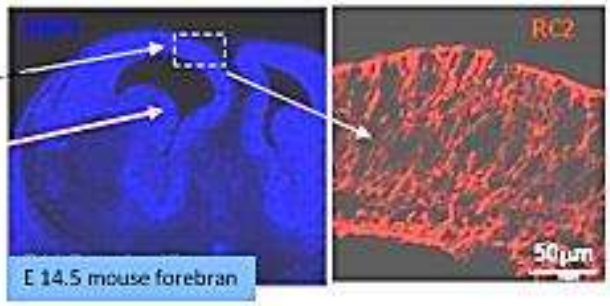


= Neuroepithelial stem cells

Embryonic/fetal neural tissue stem cells

Primary neural stem cells

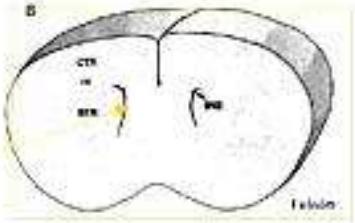
Secondary neural stem cells



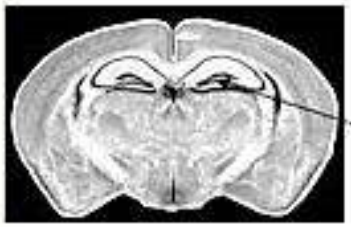
= radial glia cells in the ventricular zone

= neural stem cells in the subventricular zone

Adult-hood neural stem cells



subventricular zone



subgranular zone

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

8) Building functional networks for the mature nervous system is a result of multiple selection processes, which involve programmed cell death, directed migration, axonal growth and withdrawal, synapse formation and elimination.

- factors regulate the development of axons and dendrites
- growth cone: the membrane expansion is continuous where the actin cone is attached (receptors at the surface → determination of growth direction)
- Programmed cell death (apoptosis)→ adult brain has more less neurons but these form more synapses
- Formation of synapses (which cell, how many) → formation and continuous changing of networks

- Synapses can be formed and maintained between synchronously active partners, role of GDP (Giant Depolarizing Potential), ”Fire together, wire together”

9) Neural stem cells and newly generated neurons are standard components of the mature nervous tissue. Besides expanding our understanding on the processes of neural cell fate decisions, the use of neural stem/progenitor cells for future clinical cell replacement requires strict scientific and ethical control.

Stem cells can be used for:

In vitro

- drug testing;
- assessing individual drug reaction of own-derived iPSC generated neurons
- academic 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

5. L3: Olfactory receptors. Networks of the olfactory bulb. Network activity in the olfactory bulb.

PRESENTER: Prof. **Zoltán Nusser**

BRIEF SUMMARY:

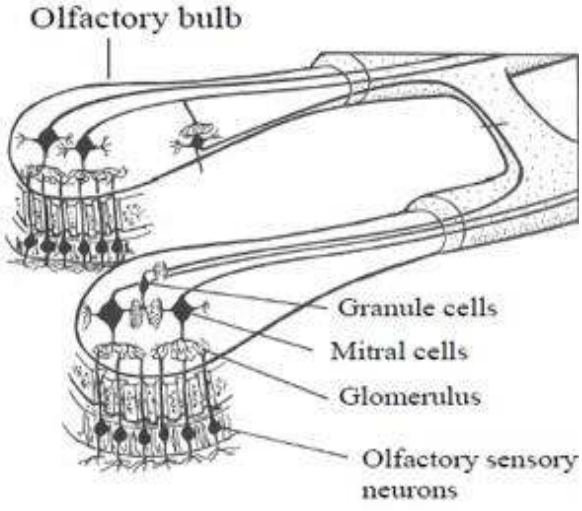
The first lecture describes the **olfactory epithelial cells (OECs)** with special emphasis on the olfactory genes, signal transduction cascades and electrophysiological responses involved in transforming the chemical information to electrical signals.
The second lecture demonstrates the **neuronal elements and their synaptic connections in the main olfactory bulb**, which participates in the processing and transmitting the olfactory information to **higher brain centres**.
The third lecture explains the encoding mechanism of **the olfactory signals** (temporal code) and the role of **field potential oscillation** played in this process.

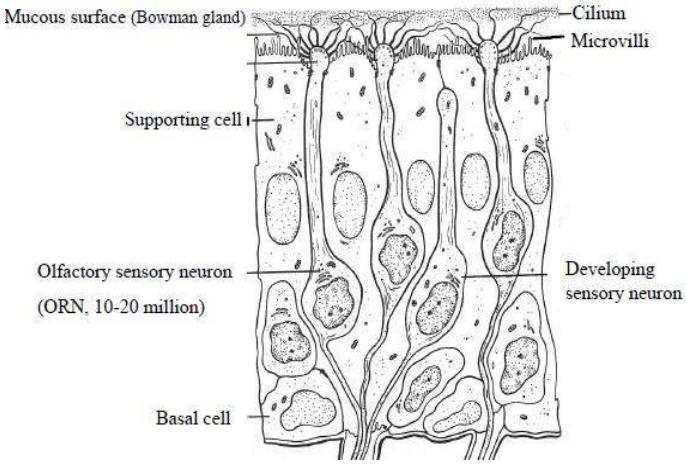
ESSENCE:

1) The phenotype and the location of epithelial cells involved in olfaction.

- Cilium and microvilli on the surface, Browman gland → mucous surface
- olfactory sensory neuron/OSN (10-20 million in human, 200 in dogs), supporting cells
- basal cell, which produce ~ 60 new olfactory sensory neuron daily

The Jacobson organ (vomeronasal organ) is a sensory organ specialized for detecting pheromones → presence in human is questioned





2) The expression and molecular pathways activated by the olfactory receptors.

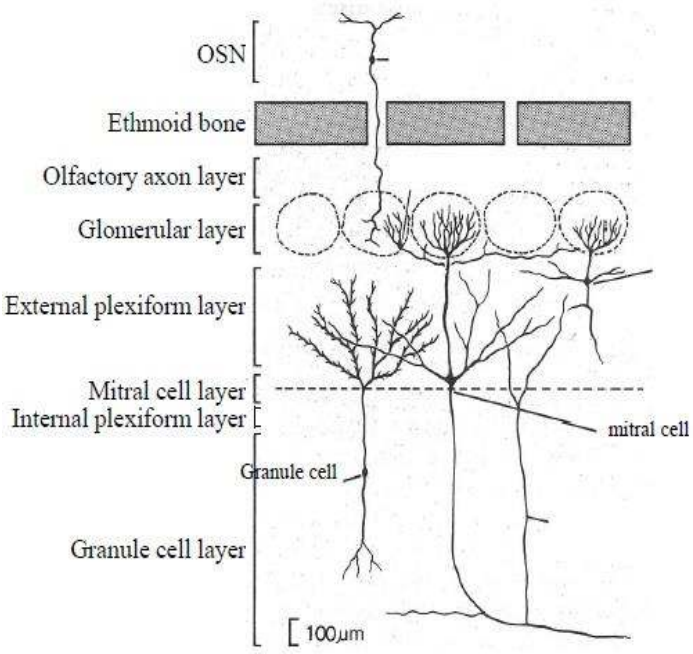
- More than 1000 genes responsible for olfaction (3% of the total number of genes in human)
- OSNs that express a given olfactory receptor/OR gene show widespread distribution in the epithelium, but send their axons in two well defined glomeruli

- ORs are seven transmembrane, G protein ($G_{\alpha olf}$) coupled receptors that activate adenylyl cyclase and increase the intracellular concentration of cAMP → cAMP activates cyclic nucleotide-gated ion channel → Ca^{2+} ions activate either nonselective cation or Cl^{-} channels
- One OSN expresses only a single type of OR gene. However, one OR binds and gets activated by many different odors/chemical molecules
- Each odor evokes a specific spatio-temporal activity of the OSN population
- The electric responses of OSNs show adaptation.
- The concentration of an odor is encoded by the latency and frequency of the AP

3) The electrophysiological properties and responses to single and repeated stimuli of olfactory epithelial cells. Ligand specificity. Adaptation.

4) The neuronal elements and their synaptic connections within the olfactory bulb.

The Main Olfactory Bulb (MOB):



- <u>Glomerulus:</u> OSN + mitral/tufted dendrit + PGC axon/dendrit
- <u>Mitrall cells (excitatory, glutamergic):</u> principal cells of the MOB, providing the main output of the bulb. The primary dendrite arborizes in a single glomerulus, many secondary dendrites are in the external plexiform layer, where they receive dendro-dendritic inhibition from granule cells
- <u>Tufted cells (excitatory, glutamergic):</u> principal cells of the MOB. Provide an extensive local collateral system in the internal plexiform layer.
- <u>Granule cells (inhibitory, GABAergic):</u> They receive excitatory inputs form mitral/tufted cells and inhibitory from dSACs (deep short-axon cells = GABAerg (dis)inhibitory) through their dendrites. Axonless!
- <u>Periglomerular cells (inhibitory, GABAergic):</u> small cell bodies located around the glomeruli. Excitatory input from OSN/mitral/tufted cell dendrites, GABAergic, inhibitory outputs to mitral/tufted and other

5) Synaptic mechanisms: dendro-dendritic inhibition.

6) The connectivity of olfactory bulb with other brain regions.

7) Theory for encoding different odorant stimuli.

8) The putative role of field potential oscillations played in the encoding process.

6. S3. Cellular models of nerve cells

PRESENTER: **Szabolcs Káli, Ph.D.**

BRIEF SUMMARY:

This is the first of two seminars introducing some of the key ideas and methodology of computational neuroscience, which aims to provide the necessary mathematical and computational tools for a quantitative description and understanding of neural functions. Following a brief survey of some of the most popular topics in computational neuroscience, we focus on the methods which enable the detailed simulation of the behavior of single neurons.

ESSENCE:

1) What physical laws govern ionic currents and the changes in the membrane potential of neurons.

2) How passive neuronal properties, voltage-gated and synaptic conductances can be described mathematically, and how these equations can be used to understand the generation of the action potential and the spread of electrical signals in dendrites and axons.

3) How multicompartmental models can be used to describe neurons in a morphologically and biophysically realistic manner.

https://users.itk.ppke.hu/neurobiologia/2016-2017_SEMESTER_2/Notebook_IntroductionFuncNeurobiol_2017/S3_NEURONAL_MODELING_K%C3%A1liSzabolcs_ShokoyaMimi.PDF

7. E4: Motor control at spinal cord level. Supraspinal motor control.

PRESENTER: **Imre Kalló, M.D., Ph.D.**

BRIEF SUMMARY:
After a short introduction to motor functions from phylogenetic and ontogenetic points of view, the organization and operation of the musculoskeletal system and its connection with the central nervous system are briefly summarized. The neuronal network regulating human gait is described and network phenomena are exemplified in phylogenetically simpler neuronal systems. The second part of the lecture describes the three sensory systems and their interaction to maintain posture and balance to any conscious or unconscious activity. The third part of the lecture demonstrates the cortical regions involved in motor control and characterizes the elements of the movement regulated by these regions.

ESSENCE:

1) Properties of active movements are determined by the complexity of the regulating nervous system and the bio-chemico-physico- characteristics of the musculoskeletal system.

2) Muscle force can be dynamically adjusted to the real and expected load.

3) Human gait is controlled by motor pattern generators (MPGs); neuronal networks capable to maintain rhythmic output without rhythmic sensory or central inputs.

4) Peripheral and central inputs of MPGs.

5) Maintenance of posture and balance requires a continuous sensory input.

6) Multiple cortical areas are involved in motor control.

7) Motor control is achieved in functional relationship with other cortical areas and subcortical centres.

8) Cortical neurons specialised for encoding different aspects of motor control.

8. L5-S5: Hippocampal microcircuitry and connections .Structure of hippocampal networks. Specialised functions of hippocampal inhibition

PRESENTER: **Tamás Freund, Ph.D., D.Sc.**

BRIEF SUMMARY:
After a short introduction to higher brain functions with some scientific and philosophic speculations, the organization and operation of the hippocampal formation are explained. Two basic cell types are distinguished in the different subdivisions i.e. (1) the principal neurons and (2) the interneurons and their functionally important types are characterised on the basis of their location, connections, morphological, biochemical and electrophysiological properties. Network phenomena supporting signal-noise distinction, plasticity and different cortical activity states are described.

ESSENCE:

1) The properties of principal neurons organised in a single layer of the dentate gyrus (DG) and the CA1-3 regions – trisynaptic loop and its afferent and efferent connections
2) Recurrent connections of the DG and CA3 region.
3) Postsynaptic target-specificity of interneurons. Input- or output-selective inhibition of principal neurons.
4) Synchronisation of neuronal activity. Inhibition and disinhibition.
5) Spike-time dependent neuronal plasticity. The role of NMDA receptors.
6) Mediators and roles of feed-forward and feed-back inhibition.
7) Theta oscillation - noise and signal transmission phase.
8) Phase precession – transmission of specific signals.
9) Functional states of the cerebral cortex - influence by our inner world.

9. L6. Structure of the thalamocortical networks. Function of. the thalamocortical networks. Information Processing in the thalamus

PRESENTER: **László Acsády, Ph.D., D.Sc.**

BRIEF SUMMARY:
In the first part of this series of lectures, the thalamus will be described with certain simplification; i.e. the thalamic nuclei will be classified as they belong to either of two basic operational units; to a group of subnuclei (1) working relatively independently and relaying sub-thalamic (mainly sensory) inputs to primary sensory cortical areas; or to the other set of subnuclei (2), the higher order nuclei, which function only in mutual relationship with other cortical areas. The elements of the thalamocortical-corticothalamic circuit and the generation of different oscillations within the circuit will also be explained. The second part of the presentation will focus on the "less known part", the higher order nuclei of the thalamus; it will characterise the conditions at which their neurons are activated, as well as the dominant (driver and inhibitory) afferents, which can dramatically change the firing activity of neurons. Comparisons between the two units will be made, with special attention to potential signal integration at thalamic levels.

ESSENCE:

1) The cortico-centric concept *versus* thalamo-cortical concept
2) Relay function of the thalamus – "driver afferents" from the periphery, "modulators" from the cortex
3) Thalamic inhibition
4) Thalamo-cortical circuits and rhythms – generation of oscillations
5) Firing properties of relay neurons; generation of tonic and burst activities
6) Putative signal integration at higher order thalamic neurons - the role of peripheral and cortical drivers
7) Putative gating of signal transmission in the higher order nuclei from the periphery to the cortex – the role of extra-thalamic inhibition

10. S6: Molecular mechanisms of memory formation . Mechanisms of learning at cellular and network levels

PRESENTER: **László Acsády, Ph.D., D.Sc.**

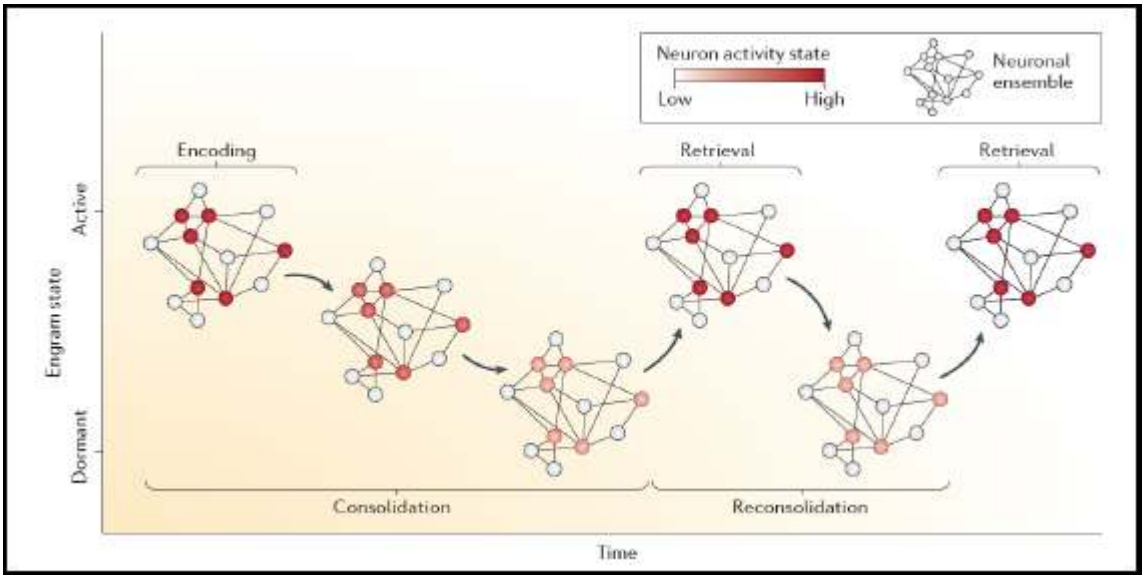
BRIEF SUMMARY: This series of lectures exemplifies different memory types by demonstrating human cases, animal experiments and behavioural tests. It describes the neuronal circuitries involved, the employed learning mechanisms and the evolutionary pressure leading to the two basic memory types, the **procedural and declarative memories**. The elements of memory procedures i.e. learning, consolidation, storage and retrieval are explained in details, with special attention paid to the role of hippocampus and sleep.

ESSENCE:

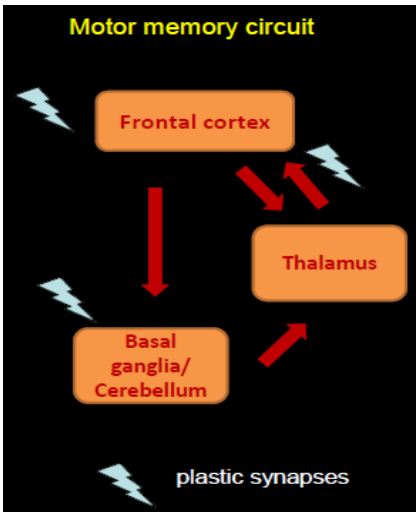
1) Memory has developed under evolutionary pressure ensuring usage of previous experience (procedural or event-related) for the beneficiary of the individuum or the species.

Engram:

- The engram is in a dormant state between encoding and retrieval.
- Engram is a persistent alteration in the brain as a result of a specific event
- The content is the engram is linked to the information perceived during encoding and predict what can be recalled later.
- A major feature of engram is ecphory, the ability to change behaviour when reactivated with the appropriate keys.

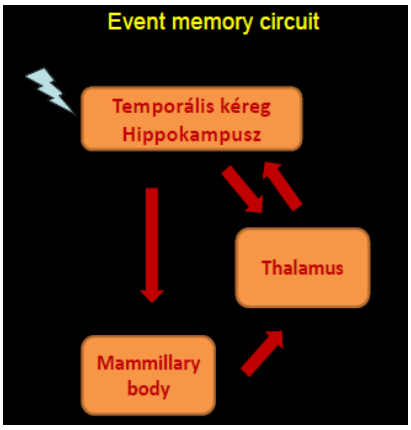


2) Procedural and declarative memories are fundamentally different.



Motor memory (Procedural, implicit):

- Requires training, practice
- Can be recalled in situation identical to the learning situation (rigid)
- Can be destructed by learning similar things
- Can display plasticity in case of brain damage (other brain region can learn the same thing)
- Sport, typing, driving, dancing, priming, operant and classic conditioning

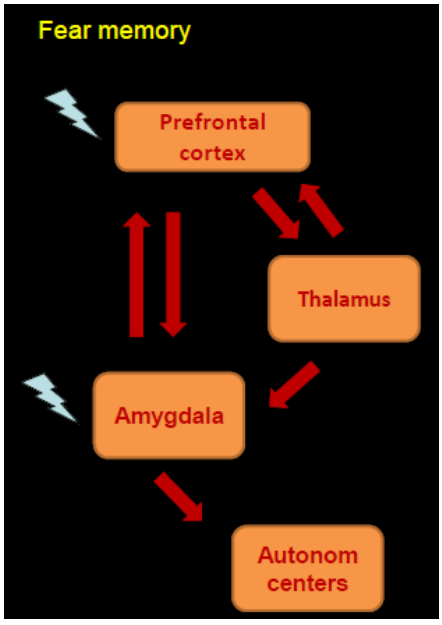


Event memory (Declarative, explicit):

- Requires a single event
- Can be recalled in various situations
- More difficult to destruct
- No recovery after damage
- Personal events, people, data, spatial navigation, words

Fear memory, reward memory:

- In case of significant events single association may be sufficient
- can be recalled on situation identical to the learning situation
- highly pronounced vegetative responses (heart, breathing, sweat)
- foot schock, kokain



3) Characteristics of the hippocampal neurocircuit, which allows information selection/reduction to be stored, encoding the information, storage and fast retrieval.

4) The existence of a hippocampus-independent memory.

Consolidated memory that comes from the hippocampus and stored in the neocortex.

5) Memory formation involves four basic elements; learning, consolidation, storage and retrieval.

6) The role of slow wave sleep in memory consolidation.

11. L7. Functional brain mapping

PRESENTER: **Zoltán Vidnyánszky, PhD., DSc.**

BRIEF SUMMARY:
The seminar will give a short introduction to the different magnetic resonance imaging (MRI) techniques, with a special emphasis on the functional MRI. Next, major application fields of the fMRI methods will be discussed. What can and cannot be investigated with MRI will be explained using examples from fMRI studies investigating the organization of the human visual cortex. Clinical and translational neuroimaging applications of fMRI will also be discussed.

ESSENCE:

1) Structural and functional MRI.

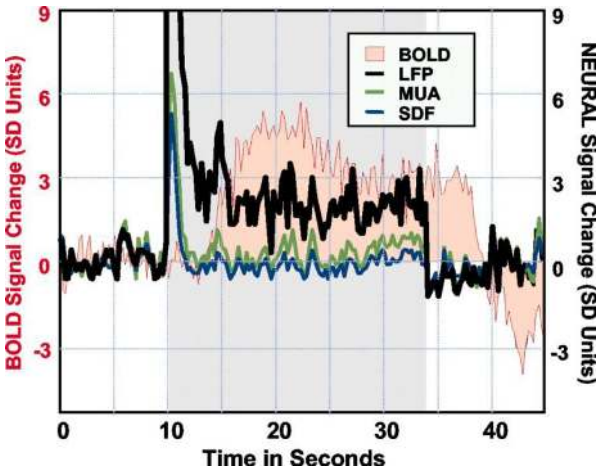
2) The BOLD signal and its neural basis

The Blood Oxygenation Level Dependent method

- The BOLD signal is determined by the balance of deoxygenated (paramagnetic) to oxygenated (diamagnetic) hemoglobin in blood within a voxel
- oxygenated hemoglobin: diamagnetic → increases the local homogeneity
- deoxygenated → decreases the homogeneity
- 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 hemodynamic state and activation-induces adjustments in metabolism and hemodynamics

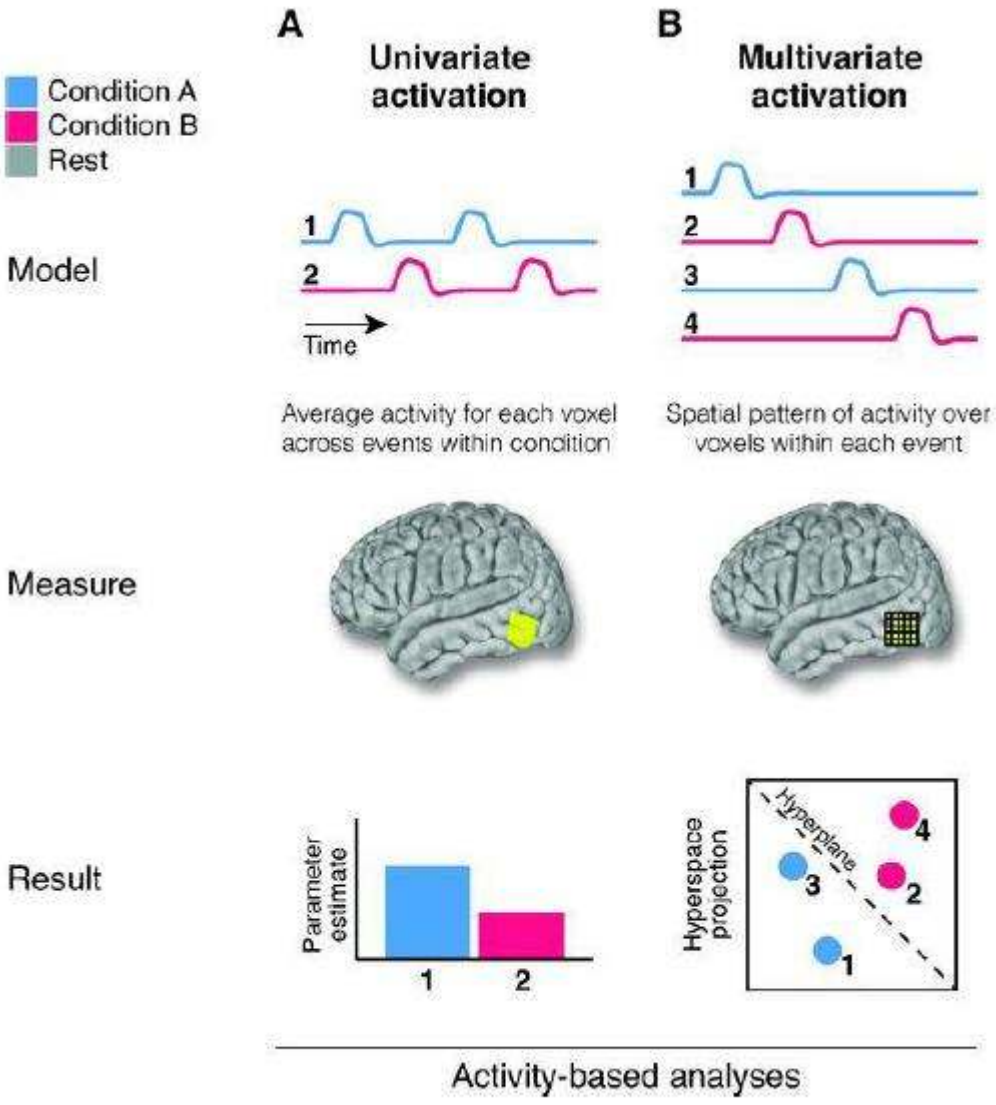
Neural Basis:

- BOLD signal strongly correlates with the local field potential(LFP)
- LFP is a mass neural signal reflecting multitude of neural process, including:
  - synaptic potentials,
  - afterpotentials of somatodendritic spikes,



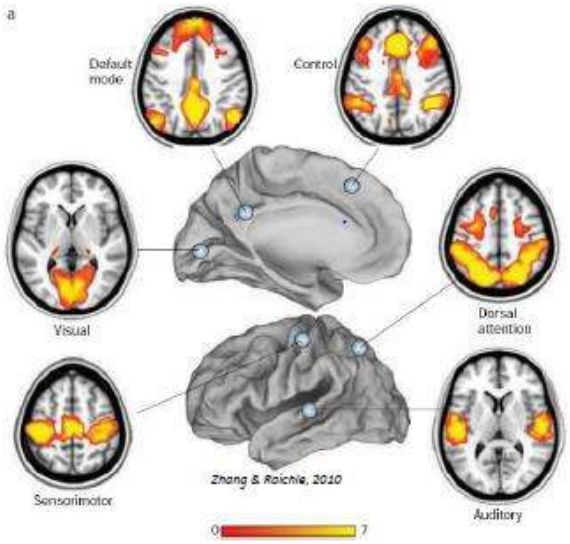
  - voltage-gated membrane oscillations.
- Thus BOLD reflects:
  - the input of a given cortical area
  - its local intracortical processing, including the activity of excitatory and inhibitory interneurons
  - the effect of neuromodulatory pathways
- BOLD signal is also affected by spiking activity of local, excitatory neurons: Direct excitation of optogenetically defined local cortical excitatory neurons triggers BOLD responses that faithfully capture all of the phase- and timing-relationships of the complex dynamics of previously measured sensory-triggered BOLD. i.e no need to evoke processes not initiated by spiking of local, excitatory neurons to explain the complexity of BOLD signal dynamics.

3) Univariate and multivariate analysis of the fMRI data



4) Measuring intrinsic functional connectivity using resting state fMRI

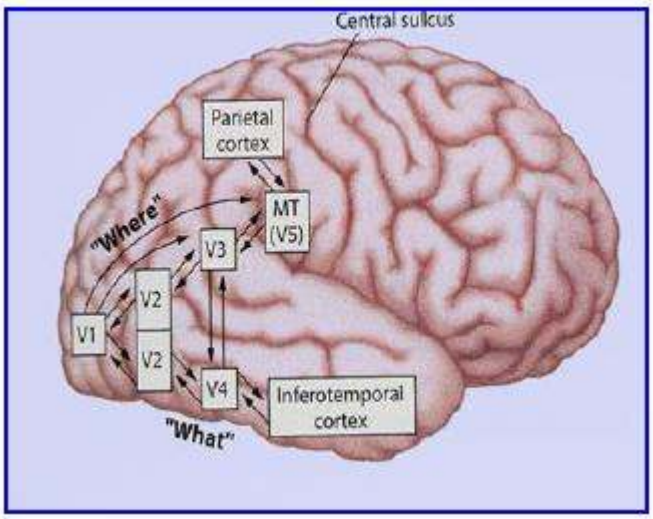
- Functional connectivity (FC):
  Statistical (undirected) interdependence of signals between distinct brain regions
- Resting-state fMRI:
  studying FC by measuring the correlation of spontaneous slow (below 0.1Hz) fluctuations in the BOLD signal across various brain regions during wakeful rest, with no explicit task.
- Major networks revealed:
  - Visual
  - Sensorimotor
  - Auditory
  - Default mode network
  - Dorsal attention
  - Executive control
- Functional newtworks found in rs-fMRI research studies are characterized by alpha/neta and high-gamma-band (65-100 Hz) coherence at infra-slow (<0.1 Hz) frequencies.
  It suggests that quasi-periodic, infra-slow changes in local cortical activity ight form the neurophysiological basis for rs-fMRI network.



5) fMRI investigation of the topological representation and neural selectivity of different visual cortical areas

Stages/levels of visual information processing:

- Low level: local feature detection(V1-V3)
- Intermediate level: grouping and segmentation (V4, MT/MST)
- High level: object recognition/biological motion (IT, STS, PC)



Two visual pathways

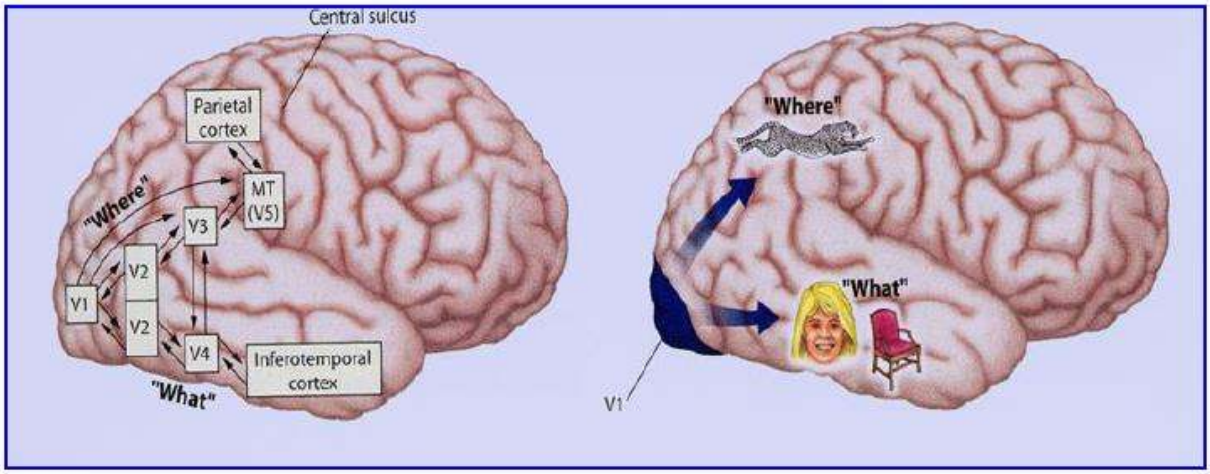
The two visual processing streams for different visual percepts:

"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



Source: Mishkin & Ungerleider, 1982

6) Active vision and the visual attentional network

Active vision:

- The visual input is ambiguous: Vision could only be the result of some form of unconscious inferences→a matter of deriving a probable interpretation for incomplete data, based on previous experiences.
- There is not enough neural capacity to process all the information entering our senses at any given time. A large part of the visual information is redundant and task irrelevant.
- Vision is a mode of exploration of the world. Its main functions:
  - acquire information about the visual environment
  - visually guide our actions

  it is achieved with the help of: eye movement, attention, learning.

Attentional networks:

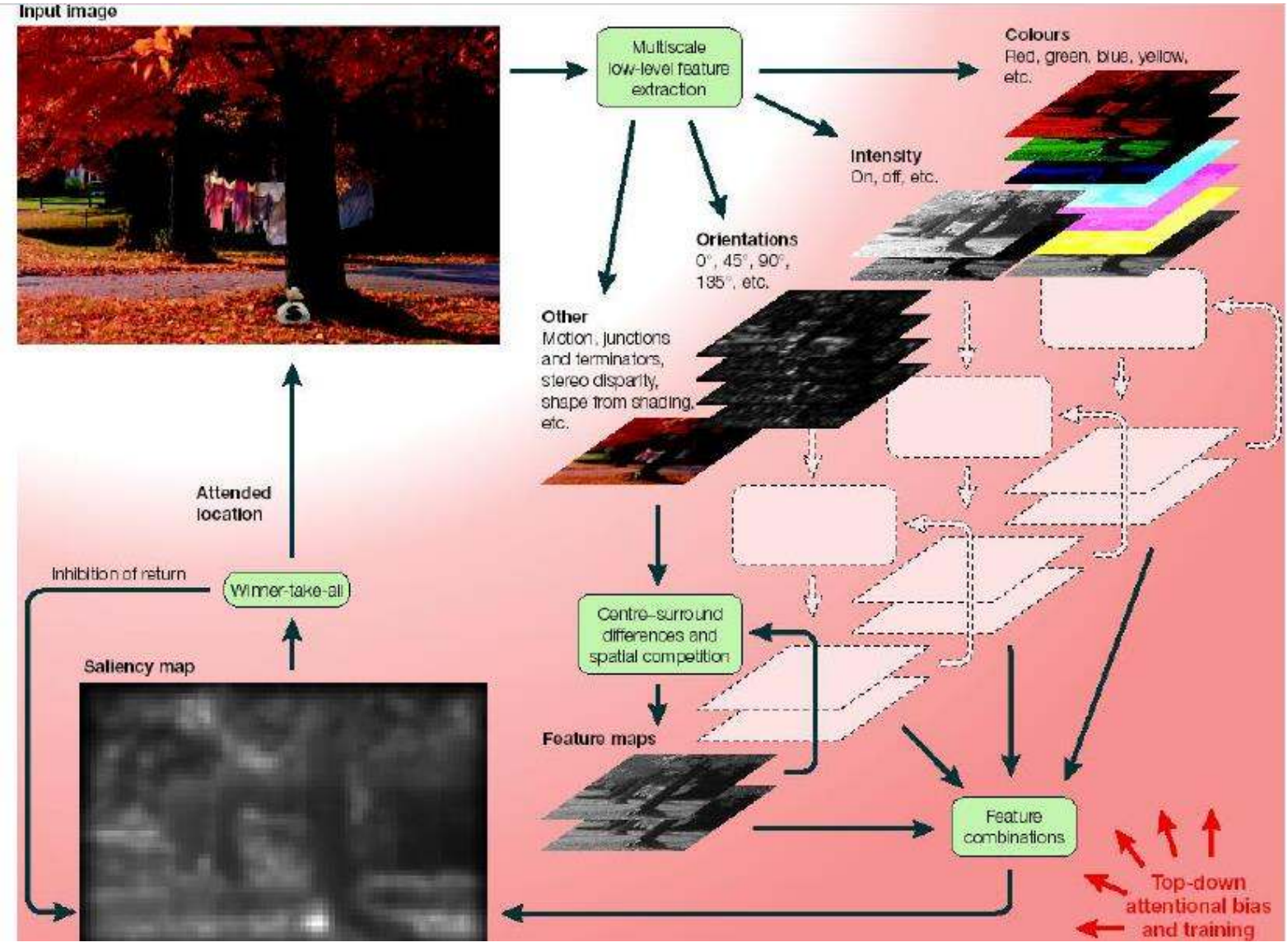
- Alerting:

Sustained attention, to increase and maintain response readiness in preparation for an impending stimulus.

- Orienting/Selection:
  The ability to select specific information from among multiple sensory stimuli; exogenous and endogenous orienting
- Executive functions
  Includes supervisory functions, conflict resolution and focused attention.

Visual attentional selection:

- Function:
  To select that part of the visual input that will be processed in detail and will guide behaviour
- Types:
  - Stimulus driven (bottom-up) → Saliency map:



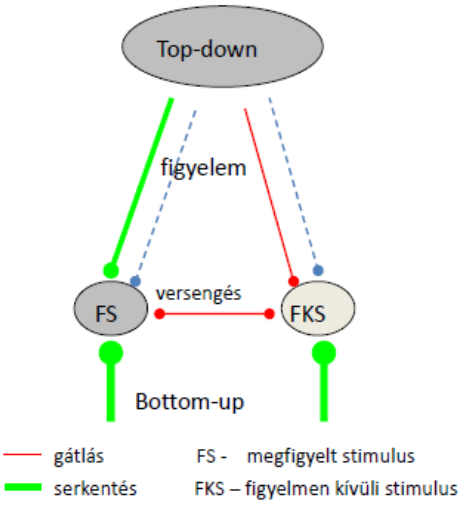
– Volitional (top-down):

Biased competition model
[Desimone & Duncan, 1995]

multiple stimuli in the visual field automatically engage in competitive interactions

attention can biase the competition in favor of the attended stimulus

as a result, processing of the attended stimulus is enhanced while ignored stimuli are suppressed.



- Units of attentional selection:
  - particular locations in the visual field
  - visual features (color, motion, etc.)
  - visual objects
- Mechanisms of attentional modulation:
  - Response enhancement
  - Noise reduction
  - Efficient selection

7) Clinical and translational neuroimaging using different MRI methods

Clinical fMRI

- Planning of lesional surgery : ASL + BOLD together
  ASL (Arterial Spin Labeling): it is like a PET but the marker is noninvasive: the monitored water molecules are labeled magnetically
- Weighting of depression and schizophrenia
- Examination of plasticity
  application: for a given free area they build up new functions, and see whether it was successful.
- The discovery of default mode network made possible the comparison of pairs (before-after, normal-abnormal)
  (The function of the default mode network is the alignment of the acquired informations)

- Developing of biomarkers (e.g. measurement of the stage of the disease, efficiency of therapies)
  it is a method which characterizes a given neural process
- The volume of the hippocampus is in correlation with the memory disorder
- Pain: the activity of the insula is a useful marker (the activity of the insula predicts the strength of the pain)