

Introduction to Neuroscience – 2022/2023

Human Neuroanatomy – Lecture 01 – Juliet Richetto

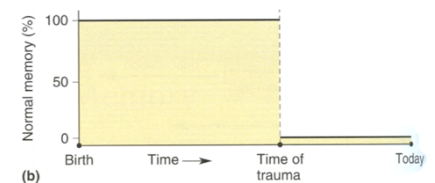
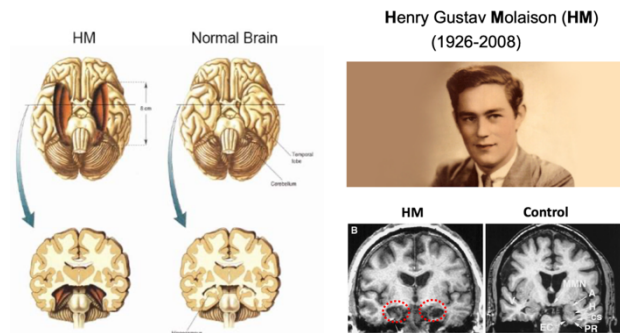
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Introduction: Why Do We Need to Know the Brain?

“There has been one striking and totally unexpected behavioral result: a grave loss of recent memory in those cases in which the medial temporal-lobe resection was so extensive as to involve the major portion of the hippocampal complex bilaterally ... in [H.M.] ... the loss was immediately apparent. After operation this young man could no longer recognize the hospital staff nor find his way to the bathroom, and he seemed to recall nothing of the day-to-day events of his hospital life... However, his early memories were apparently vivid and intact.”

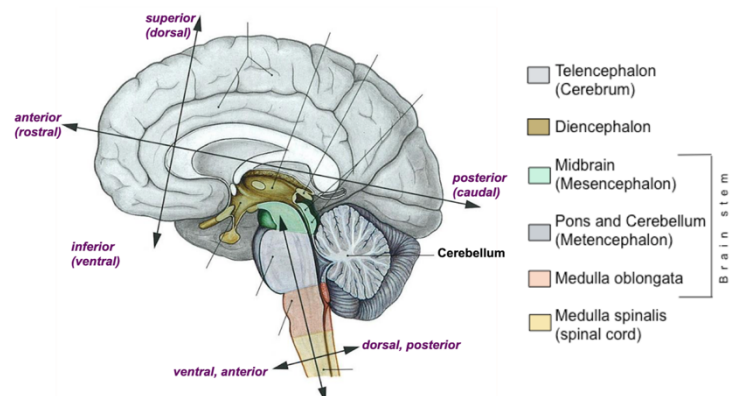
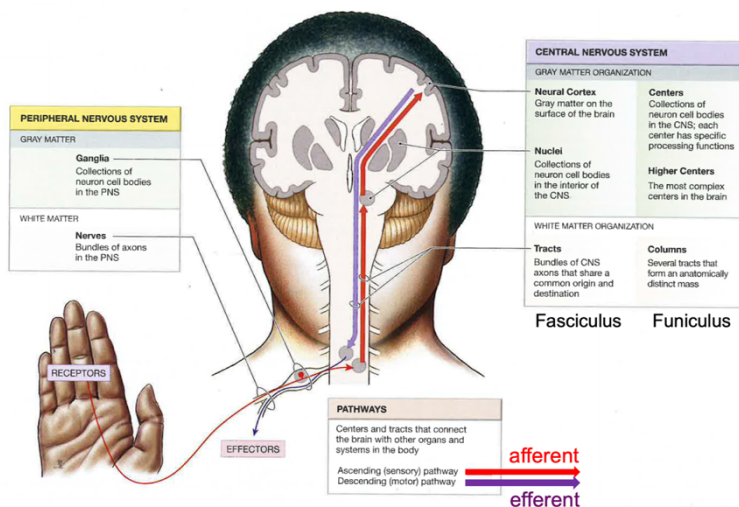
The bilateral removal of the hippocampal formation and allied structures caused a severe form of **anterograde amnesia**.



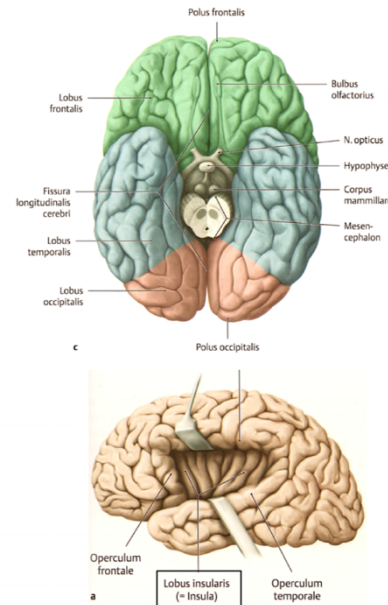
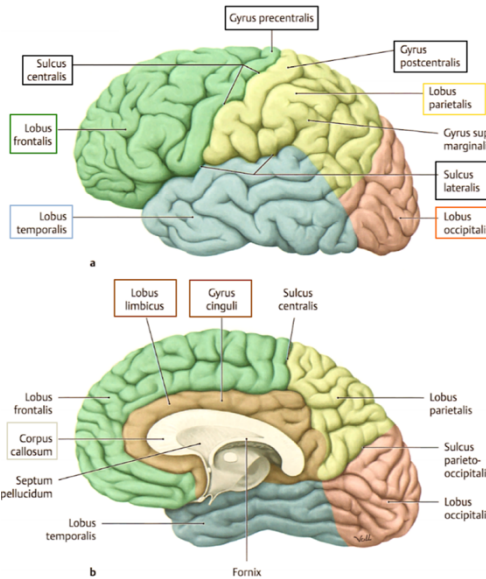
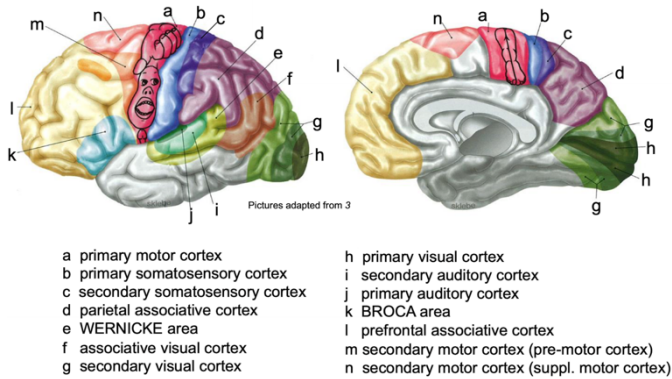
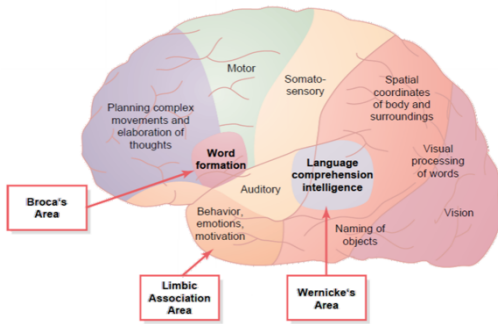
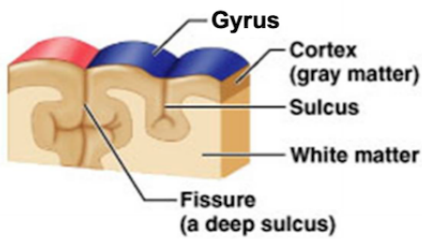
The Nervous System: Overview and Terminology

Nervous System

- Central Nervous System (CNS)
 - Brain
 - Spinal Cord
- Peripheral Nervous System (PNS)
 - Somatic and Autonomic Nervous System



Grey Matter of the Cortex



Korbinian Brodmann described in 1909 areas of the cerebral cortex on the basis of cytoarchitectural criteria. Areas differ in cell-types, layering and cell distribution, resulting in **52 Brodmann Areas**.

Examples: Brodmann Area 3,1,2 → Primary Somatosensory Cortex S1, Brodmann Area 17 → Primary Visual Cortex V1.

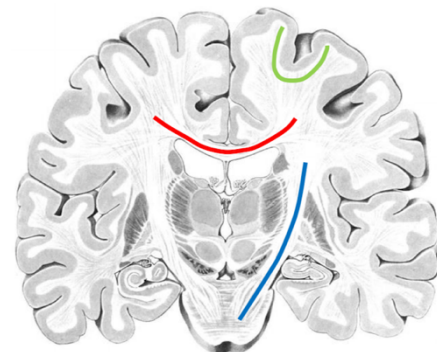
Cerebral Convolution: Species Differences

- **Gyrencephalic** (Human, Elephant).
- **Lissencephalic** (Rabbit, Mouse) (No gyrus structures).

Lissencephaly in Humans is due to a defective migration during early to mid-gestation (12th to 24th weeks), leading to impaired development of gyri and sulci.

White Matter: Macroscopic

- **Association Fibers (Green)** link cortical areas of the same hemisphere. Arcuate fibers run over short distances, long-distance association fibers have names, such as the Superior and Inferior Longitudinal Bundle/Fasciculus, the Cingulum and Uncinate Bundle.
- **Commissural Fibers (Red)** link areas of the two hemispheres (Corpus Callosum, Anterior Commissure, Posterior Commissure).
- **Projecting Fibers (Blue)** link the cortex with subcortical areas of the brain and the spinal cord (e.g., Internal Capsule).

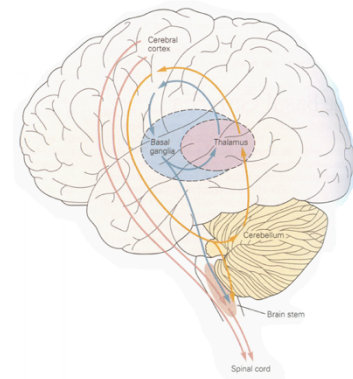


White Matter: Microscopic

- **Oligodendrocytes**
- **Microglia**
- **Astrocytes**

Telencephalon: Basal Ganglia

The basal ganglia are the principal **subcortical components** of a family of neuronal circuits which **link the thalamus and cerebral cortex**. The basal ganglia are crucial for the **initiation and modulation of voluntary movement** by sending their output to the motor cortex via the thalamus. In addition, the basal ganglia also contribute to a variety of behavioral and cognitive function other than voluntary movement.



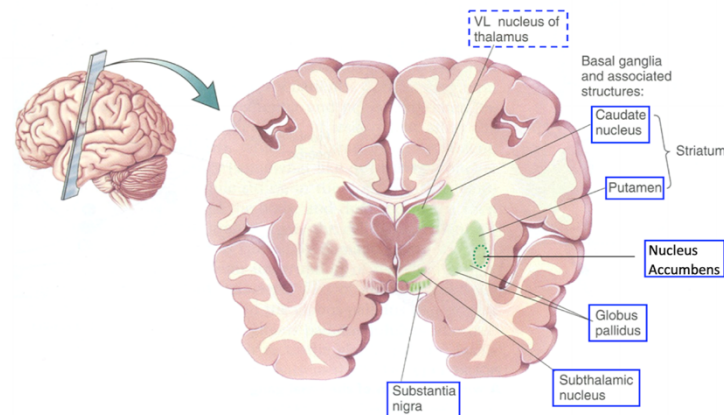
Basal Ganglia: Striatum

In humans (and most primates), the striatum consists of **three major subdivisions**: the **caudate nucleus**, the **putamen**, and the **nucleus accumbens**.

In rats and mice, the striatum is typically divided into two subdivisions: the **caudate putamen**, which is often referred to as the “**dorsal striatum**” (and which would correspond to the human caudate nucleus + putamen); and the **nucleus accumbens**, which is referred to as the “**ventral striatum**”.

The striatum is the **major recipient of inputs** from the substantia nigra, cerebral cortex, thalamus and brain stem.

Striatal neurons, which are primarily **GABAergic** spiny neurons (90/95%), send afferent **projections to the globus pallidus** and reciprocal projections to the substantia nigra.



Basal Ganglia: Globus Pallidus

The globus pallidus lies medial to the putamen and is divided into **external and internal segments**.

The globus pallidus give rise to the **major output projections** from the basal ganglia:

- The **Internal Segment (GPi)** sends projections to the thalamus and pedunculopontine nucleus (a group of cells located in the brain stem).
- The **External Segment (GPe)** sends projections to the internal segment of the globus pallidus and to the subthalamic nucleus.

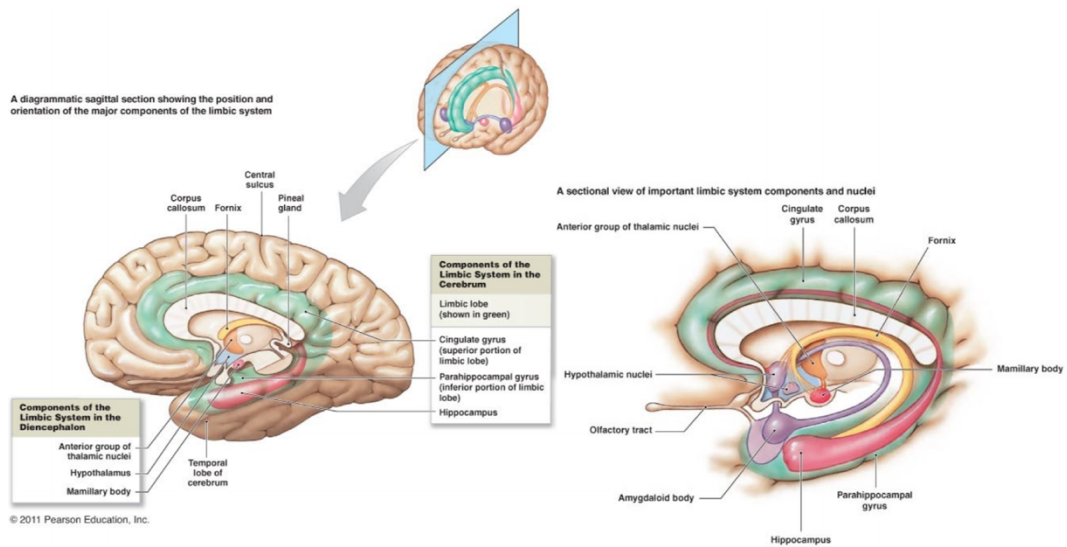
Basal Ganglia: Substantia Nigra

The substantia nigra is a **midbrain (mesencephalon) structure**, which contains a dense population of dopamine cells. The substantia nigra can be subdivided into substantia nigra **pars compacta** and **pars reticulata**. Dopamine cells in the **substantia nigra pars compacta** project to dorsal parts of the striatum (in humans: to caudate nucleus and dorsal part of putamen; in rats and mice: to caudate putamen), forming the **nigrostriatal dopamine pathway**.

Disorders of the Basal Ganglia: Parkinson's Disease

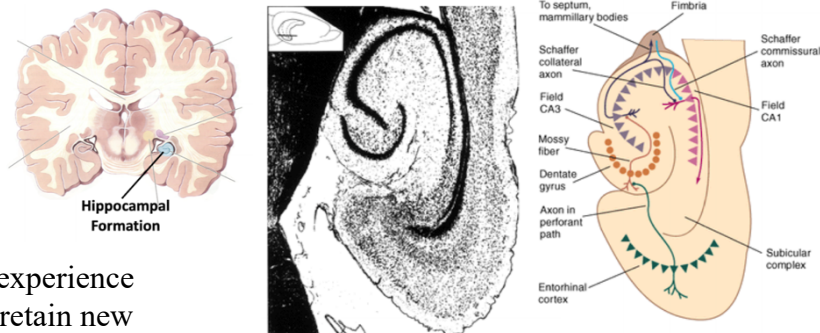
Parkinson's disease is a chronic and progressive degenerative disease of the brain that impairs motor skills, speech, and other functions. In patients with Parkinson's disease, the dopaminergic cells in the substantia nigra pars compacta are lost.

Telencephalon: Limbic System



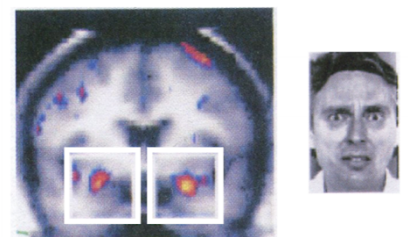
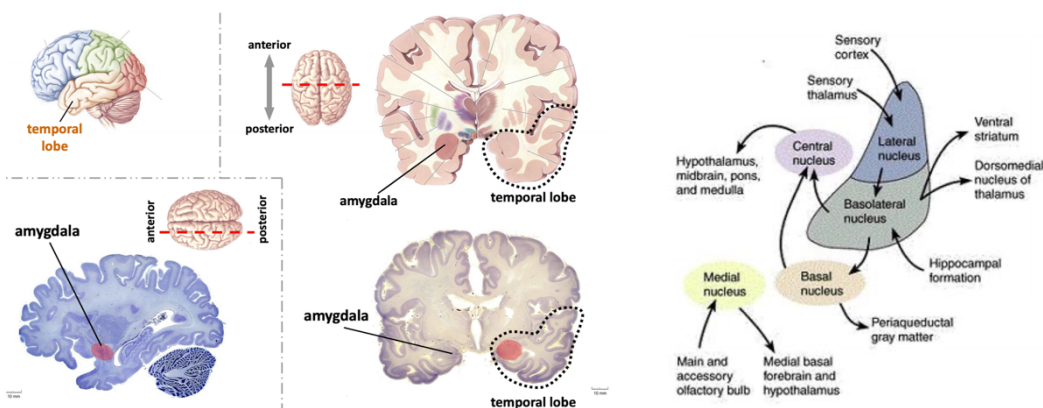
Limbic System: Hippocampal Formation

In Alzheimer's disease, the hippocampus is one of the first regions of the brain to suffer damage; memory problems (especially spatial memories) and disorientation appear among the first symptoms. People with extensive, bilateral hippocampal damage (such as in patients with progressed AD) may experience anterograde amnesia – the inability to form or retain new memories.



Limbic System: Amygdalar Complex

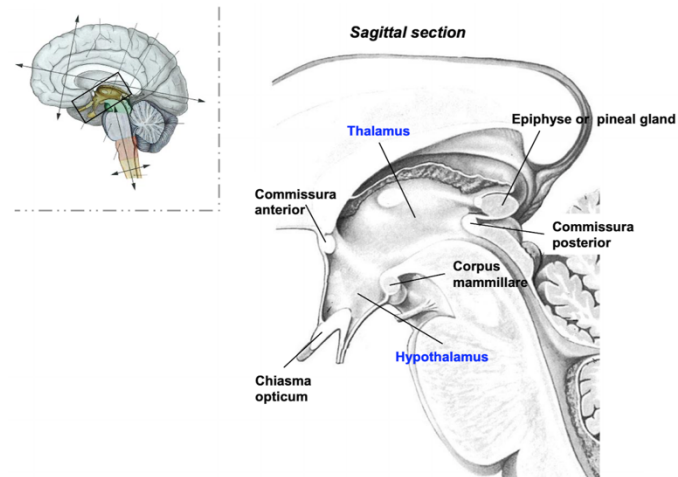
Functional involvement of amygdala in emotions. Human brain activity (measured by functional MRI) in response to emotional stimuli.



Human Neuroanatomy – Lecture 02 – Juliet Richetto

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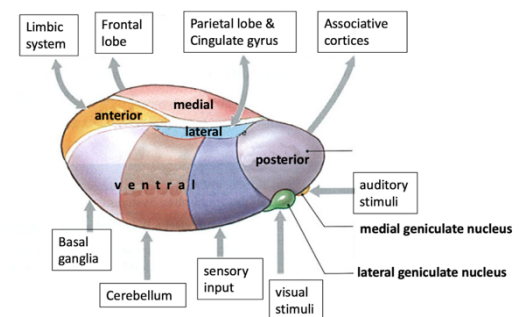


Diencephalon: Overview

Thalamus and **Hypothalamus** are the two main structures that constitute the Diencephalon. The main function of the **Epiphyse** or **Pineal Gland** is the production of melatonin. The **Chiasma Opticum** is the location where the optic nerves cross.

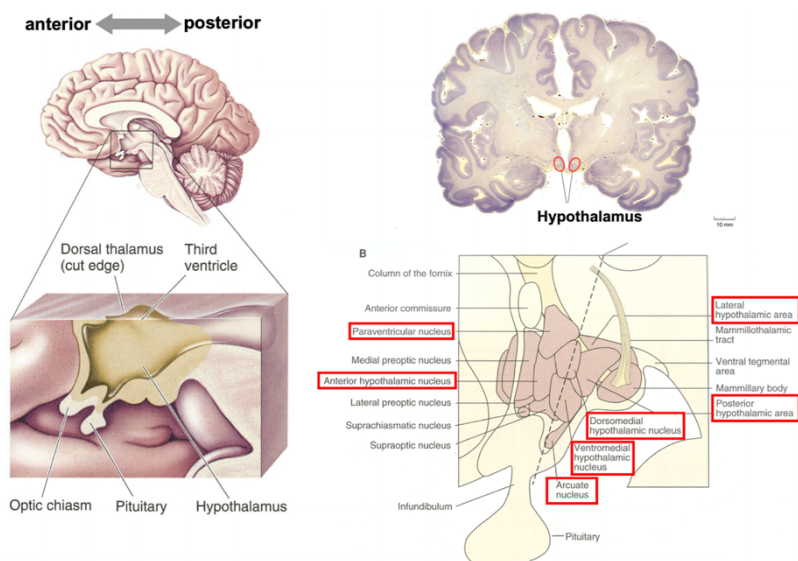
Diencephalon: Thalamus

- It receives inputs and sends outputs to various regions of the brain.
- It represents the “**Gatekeeper of the brain**”.
- It is important for the **transfer of information from the periphery to sensory processing regions** in the telencephalon.
- It has important **gating (filtering) functions**: it determines whether sensory information reaches conscious awareness in the neocortex.
- It participates in the **integration of motor information** from the cerebellum and basal ganglia and transmits this information to cerebral areas concerned with movement.

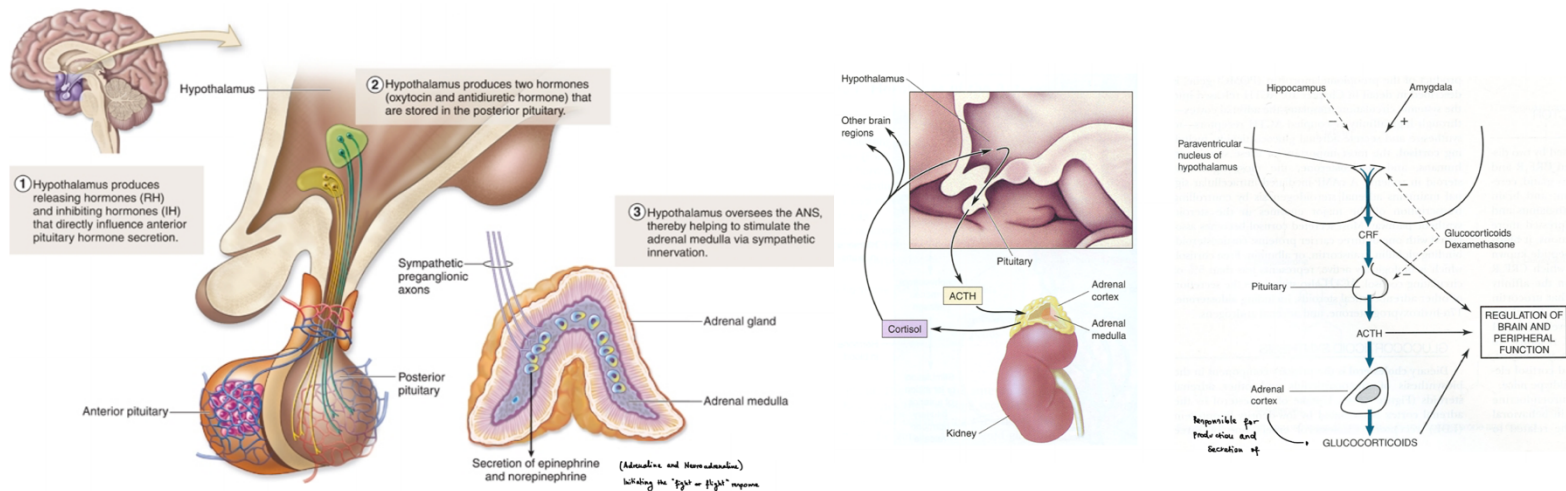


Diencephalon: Hypothalamus

- It regulates several behaviors that are essential for **homeostasis and reproduction**: it controls a variety of bodily and reproductive functions, including growth, eating, drinking and maternal behavior, by regulating hormonal secretions from the pituitary gland.
- It is an important **control center for the autonomic nervous system** and for the hypothalamus-pituitary-adrenal (HPA) **stress-response system**.



Diencephalon: Neuroendocrinology of the Hypothalamus



Diencephalon: epithalamus and Subthalamus

Epithalamus

- Epithelial roof of the third ventricle, habenula, pineal body and afferent/efferent connections.
- Secretion of melatonin, regulation of day-night cycles, information processing related to olfaction.

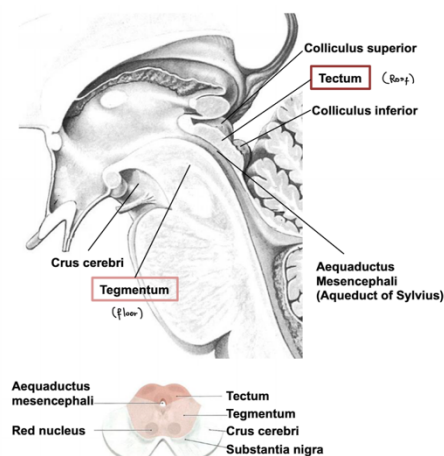
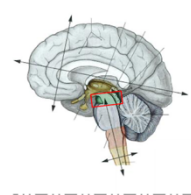
Subthalamus

- Continuation of the tegmentum.
- Functionally part of the basal ganglia (motor control).

Mesencephalon: Overview

A structure that can be found above the brain stem.

Colliculus Superior and **Colliculus Inferior** are a pair of nuclei that together form the reflexes associated with vision.



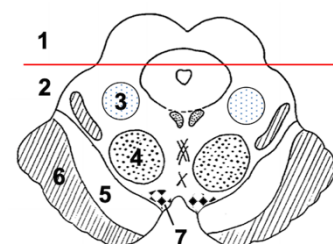
Mesencephalon: Functional Units

(1) Tectum (roof)

- **Superior Colliculus:** visual and oculomotor reflexes.
- **Inferior Colliculus:** relay auditory tract.

(2) Tegmentum (floor)

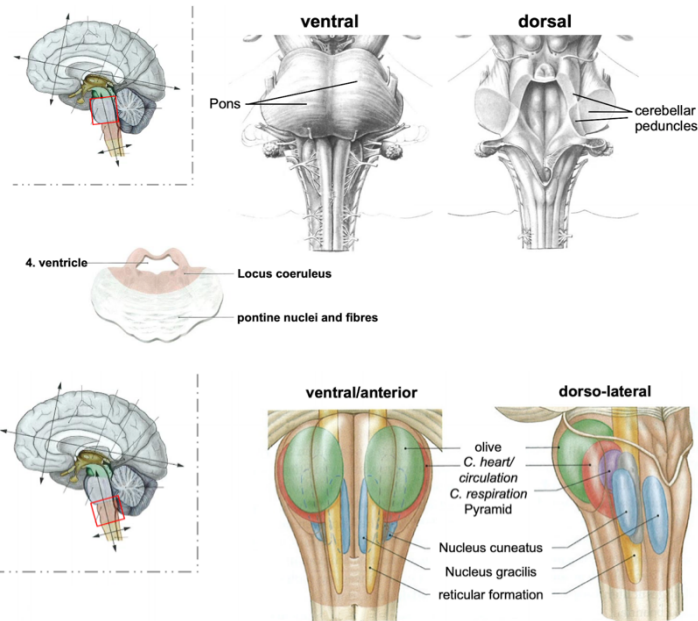
3. **Reticular formation:** automatic processing of incoming sensation and outgoing motor commands, helps to maintain consciousness, can initiate motor response to stimuli (see also medulla oblongata! Reflex center, some sensory information is directly processed in this area and sends motor commands even before consciousness).
4. **Red Nucleus:** involuntary control of background muscle tone and limb posture.
5. **Substantia Nigra:** regulates activity in the basal nuclei, degeneration of dopaminergic cells causes Parkinson's disease.
6. **Cerebral Peduncles:** connect primary motor cortex with motor neurons in brain and spinal cord, carry ascending sensory information to thalamus.
7. **Ventral Tegmental Area (VTA):** part of the limbic system, projects e.g. to Nucleus Accumbens and Amygdala, emotional reinforcement and reward function.



Pons: Overview

It is a collection of nuclei and fibers that form a bridge for information coming from one part of the brain and is relayed on the other side.

- **Pontine Nuclei** receive fibers from all cortical areas and relay to the contralateral cerebellum.
- **Locus Coeruleus** ("blue spot") contains noradrenergic cells innervating large portions of the brain, mediating physiological response to panic and stress. (secretion of neuroadrenaline).



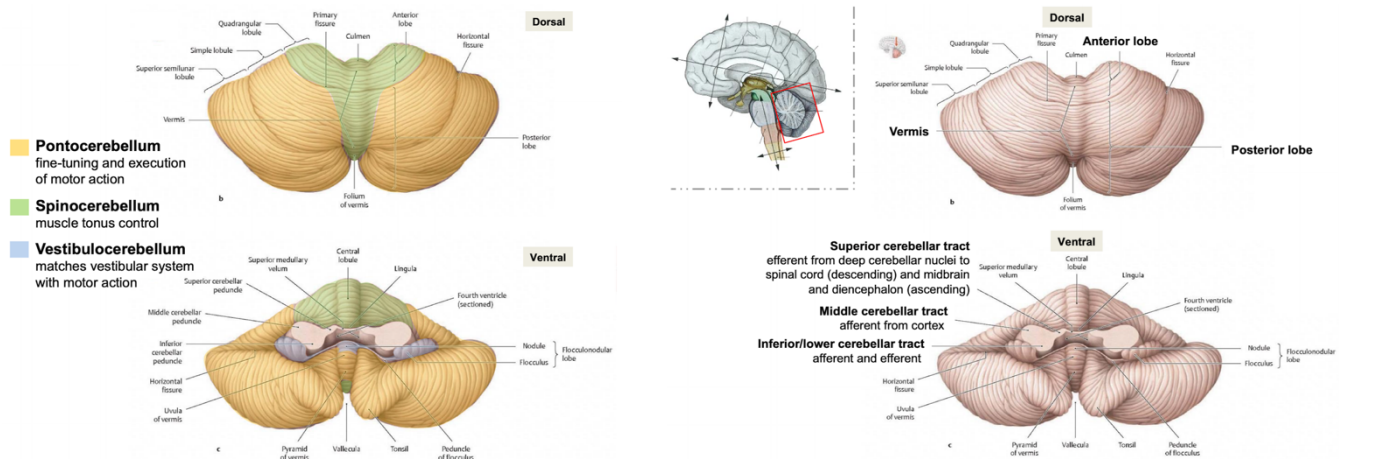
Medulla Oblongata: Overview

It is part of the brain stem, containing fiber tracks (group of axons).

- **Pyramid:** contains descending cortico-spinal fibers.
- **Olive:** relay nucleus for afferent connection from motor cortex and red nucleus, efferent to contralateral cerebellum.
- **Reticular Formation:** (entire brain stem!) containing the raphe nuclei and magno/parvocellular nuclei, which regulate respiration, circulation, vomiting, swallowing, and pain control. (Without necessarily reaching the conscious level).
- **Reflex Centers:** for heart and circulation (vasomotor/cardiac) and respiratory rhythmicity. (Without necessarily reaching the conscious level).

Cerebellum: Overview

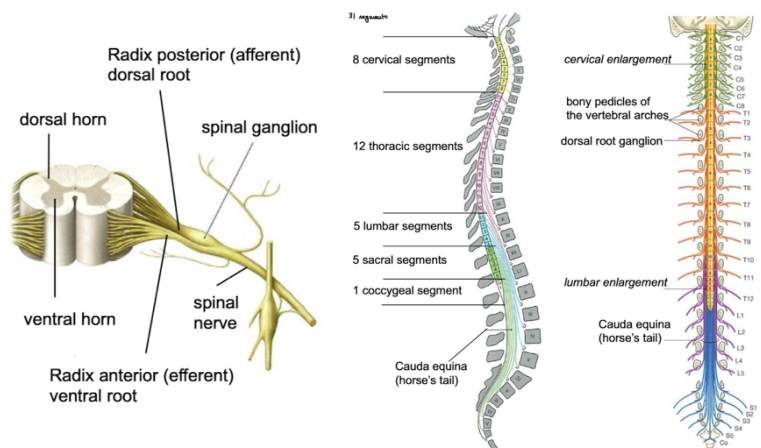
It is important for voluntary movement, posture, equilibrium and motor control.



Spinal Cord: Segmental organization

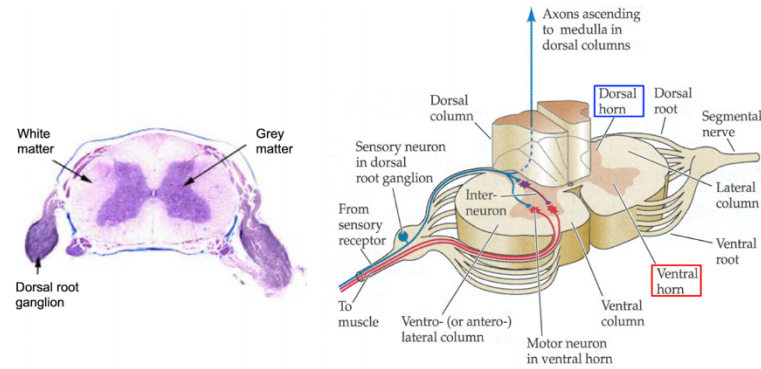
From each segment 2 spinal nerves are originated.

The **Radix Posterior (afferent) dorsal root** brings input from the periphery to the spinal cord. The **Radix Anterior (efferent) ventral root** brings motor information from the spinal cord to the periphery.



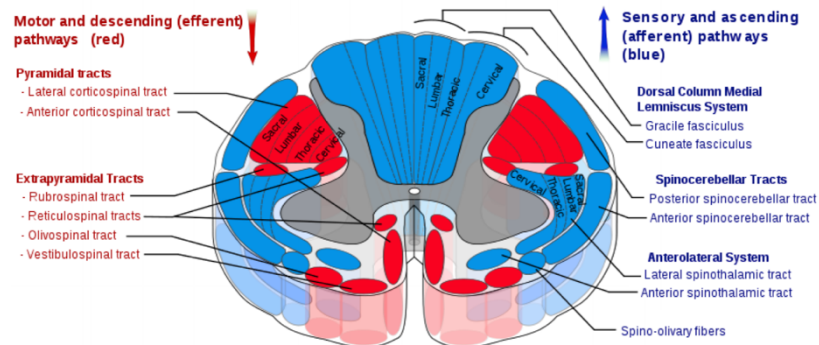
Spinal Cord: Grey Matter

The grey matter of the spinal cord consists of **cell bodies of interneurons, motor neurons** and **synaptic connections**. Fibers of the motor neurons in the **ventral horn** leave the spinal cord → **efferent/motor commands** to muscles. **Afferent/sensory axons** enter through the **dorsal horn** and either synapse on sensory interneurons in the **dorsal horn**, or join the ascending tracts in the white matter.



Spinal Cord: White Matter

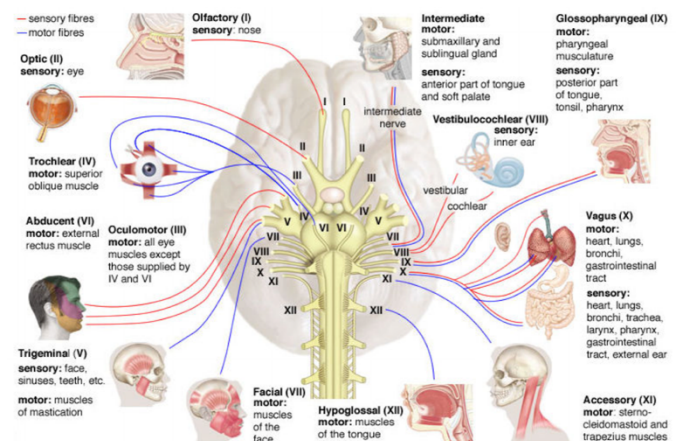
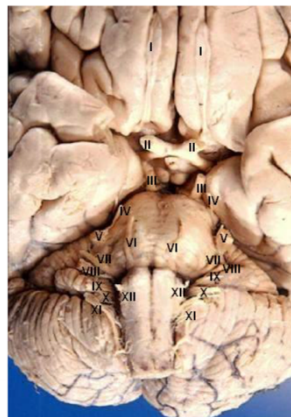
The white matter of the spinal cord mostly consists of **myelinated axons of motor and sensory neurons** → organized in columns (containing several fiber tracts) carrying information to (afferent/ascending) and from (efferent/descending) the brain.



Cranial nerves: Overview

Cranial nerves are the nerves that **emerge directly from the brain** (mostly from the brainstem), in contrast to spinal nerves (which emerge from segments of the spinal cord). Cranial nerves are **generally named according to their structure or function**. They usually innervate areas close to where they are originated from. The cranial nerves provide **motor and sensory innervation mainly to the structures within the head and neck**. The sensory innervation includes sensation such as temperature and touch, and innervation such as taste, vision, smell, balance and hearing. The **Vagus Nerve (X)** provides sensory and autonomic (parasympathetic) innervation to most of the **organs in the chest and abdomen**. (It doesn't innervate the head/neck area).

- I olfactory nerve
- II optical nerve
- III oculomotor nerve
- IV trochlear nerve
- V trigeminal nerve
- VI abducens nerve
- VII facial nerve
- VIII vestibulocochlear nerve
- IX glossopharyngeal nerve
- X vagus nerve
- XI accessory nerve
- XII hypoglossal nerve

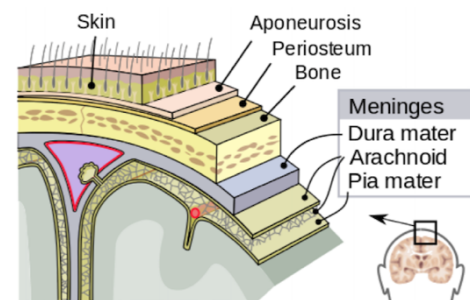


Meninges: Overview

The Meninges are the **three membranes that envelop the brain and spinal cord**. In mammals, the meninges are the **dura mater**, the **arachnoid mater**, and the **pia mater**. Cerebrospinal fluid is located in the subarachnoid space between the arachnoid mater and the pia mater.

- Dura Mater

- Leather-like, inflexible layer surrounding the CNS and spinal cord.
- Inner and outer layers, containing large venous sinuses (large veins that bring the blood back to the heart) (e.g., superior sagittal sinus).

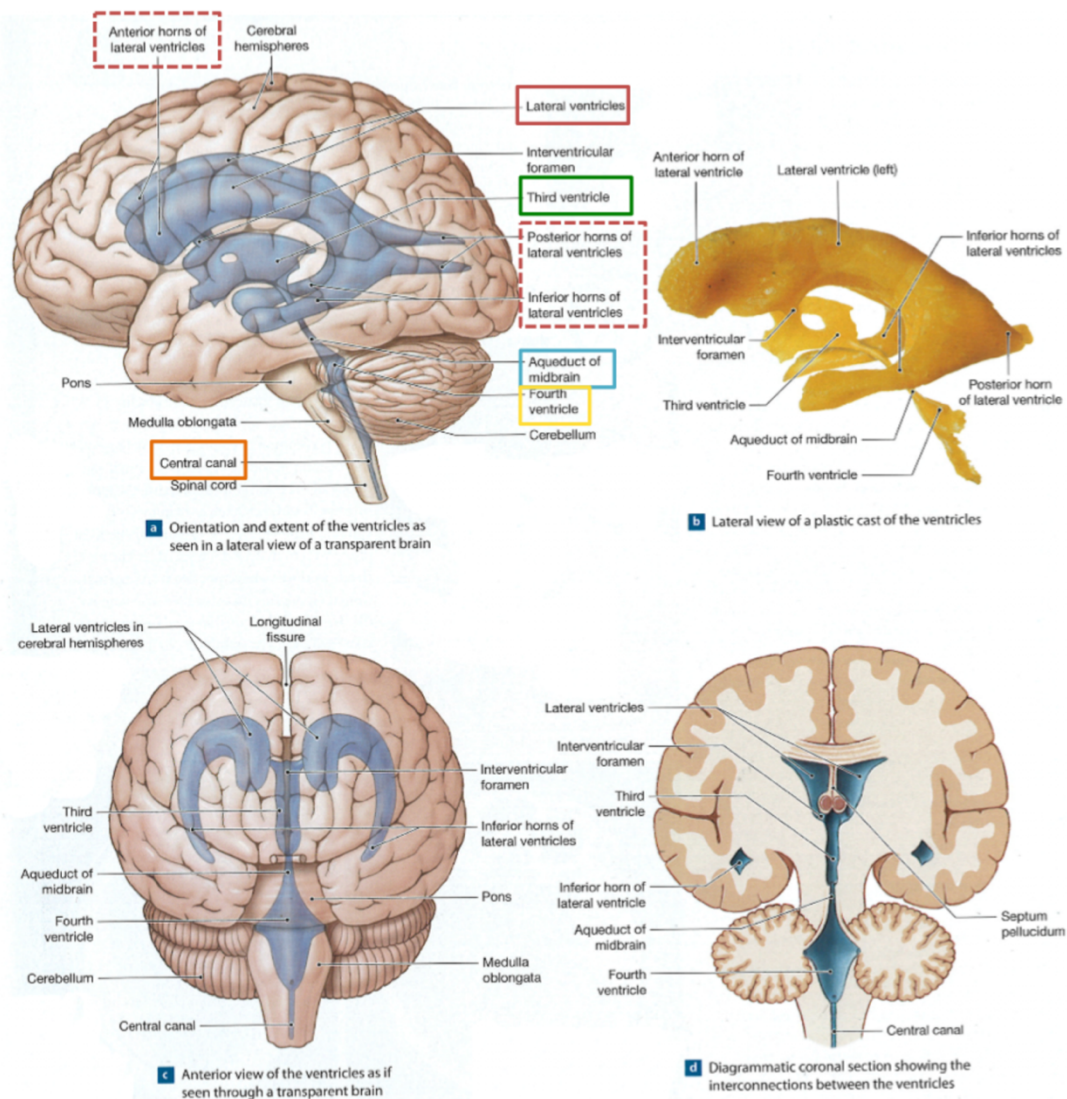


- **Arachnoid Mater**
 - Loose connective tissue bridging the liquor-filled space (subarachnoidal space) between dura mater and pia mater.
 - Contains all larger blood vessels.
- **Pia Mater**
 - Translucent, thin membrane directly covering the entire surface of the brain, follows all sulci and gyri.

Ventricles: Overview

They are cavities containing fluid.

- **Lateral Ventricles** (Cerebral Hemispheres)
- **3rd Ventricle** (Diencephalon)
- **Aequeductus Mesencephali** (Mesencephalon)
- **4th Ventricle** (Pons, Midbrain)
- **Central Canal** (Spinal Cord).



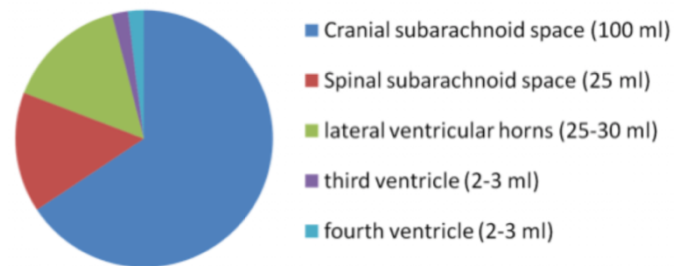
Ventricles: Pathologies

- **Neurodevelopmental Disorders** (e.g., Schizophrenia).
- **Neurodegenerative Disorders** (e.g., Alzheimer's Disease, AD).

Cerebrospinal Fluid: Overview

- It is a clear fluid, high content of NaCl, contains glucose and K⁺, low in proteins, very few cells (lymphocytes).
- It does a turnover three times a day.
- It flows throughout the ventricular system and is absorbed back into the bloodstream (via blood-brain-barrier).

Allocation of CSF in the CNS



Cerebrospinal Fluid: Main Functions

- **Buoyancy:** the actual mass of the human brain is approx. 1.5kg, however, the net weight of the brain suspended in the CSF is equivalent to a mass of 25gr. The brain therefore exists in neutral buoyancy, which allows the brain to maintain its density without being impaired by its own weight, which could cut off blood supply.
- **Protection:** CSF protects the brain tissue from injury when jolted or hit. In addition, it helps regulating intracranial pressure (lowering CSF production can help preventing brain ischemia).
- **Homeostasis:** through absorption back into the blood stream, CSF can rinse “metabolic waste” from the CNS allowing for a homeostatic regulation of the brain.

Cerebrospinal Fluid: Pathologies

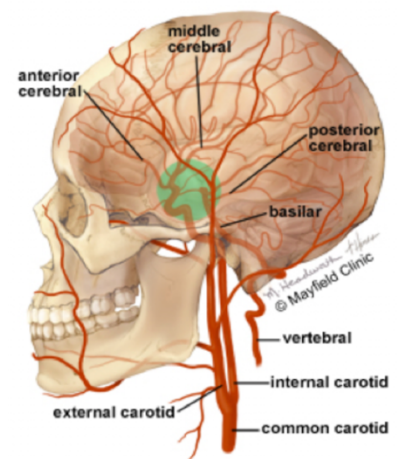
Hydrocephalus

- Abnormal accumulation of CSF within the brain.
- Congenital (neurodevelopmental disturbances) or acquired postnatally.
- Most common cause: **Aqueductal Stenosis** (mesencephalic passage between 3rd and 4th ventricles is blocked or too narrow to allow sufficient cerebral spinal fluid to drain → fluid accumulates in the upper ventricles).

Cerebral Circulation

The brain is one of the most metabolically active organs in the body!

- It uses approx. 20-25% of the body's total energy requirements (despite accounting for only 2% of the body's mass).
- The brain stores little energy as glycogen and relies mostly on circulating glucose.
- The rate of the cerebral blood flow in the adult is typically 750 milliliters per minute, representing 15% of the cardiac output.



Cerebral Circulation: Arteries

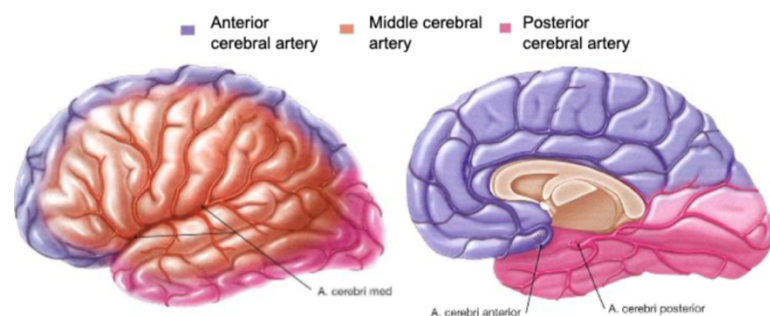
Main branches of the internal carotids

- Anterior Cerebral Artery
- Middle Cerebral Artery

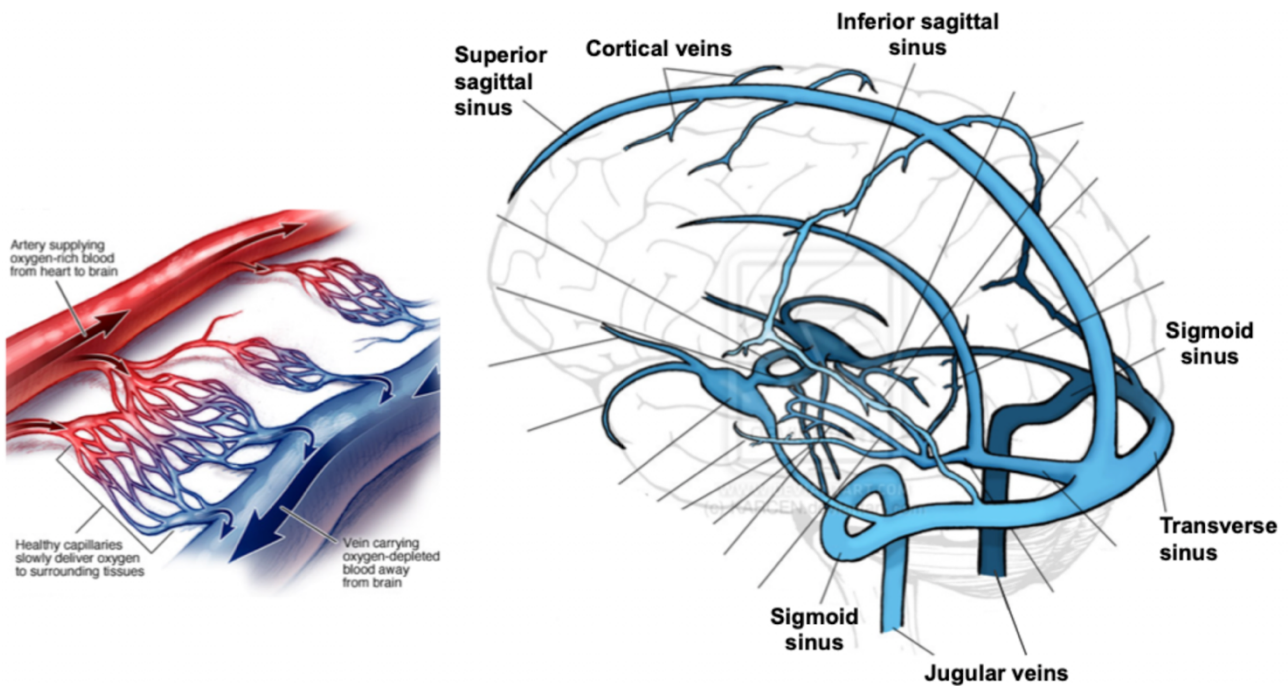
Main branches of the vertebral/basilar arteries

- 3 arteries supplying the cerebellum
- Posterior Cerebral Artery.

Brain areas supplied by



Cerebral Circulation: Veins



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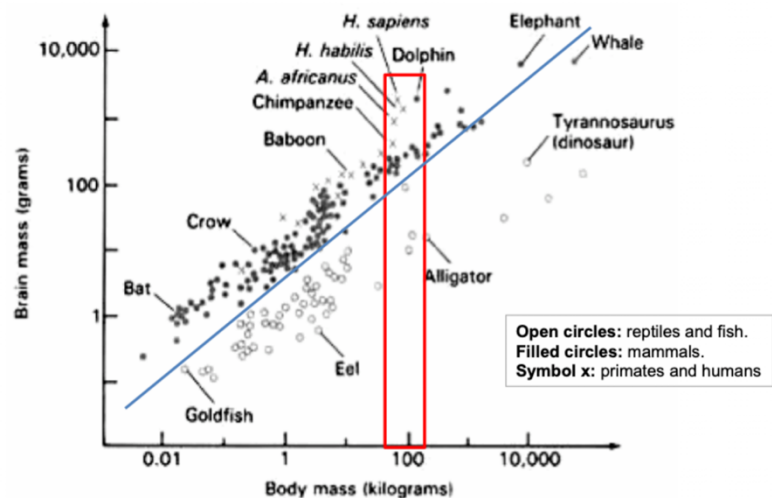
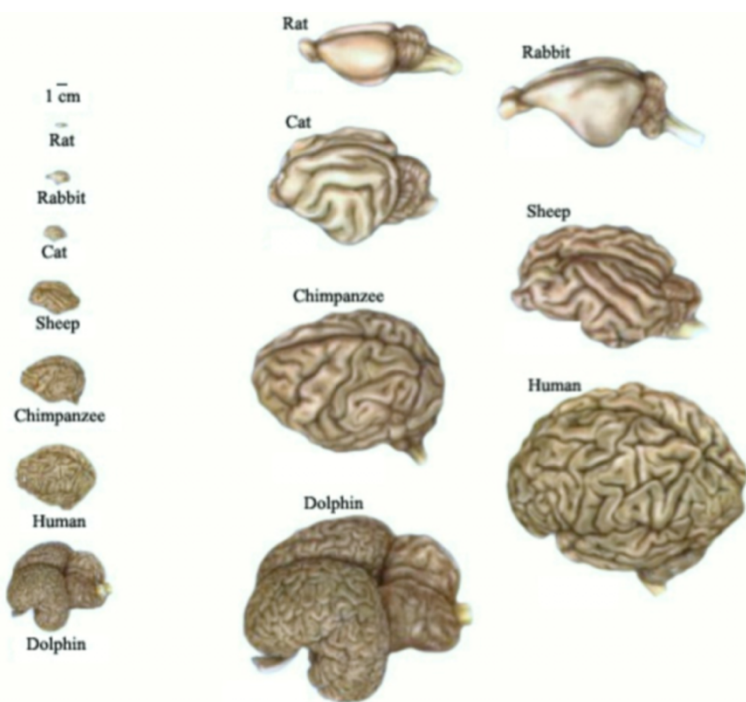
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- Brain Evolution in View of Cortical Expansion
- Cross-Species Comparison of Cortical Areas
- Cross-Species Comparison of Subcortical Areas
 - Hippocampus
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Absolute and Relative Differences

and

Brain Mass versus Body Mass

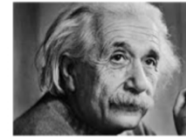


Encephalization Quotient (EQ)

It describes brain size as a **ratio of the expected average brain size relative to the actual body weight**. Some scientists argue that EQ correlates with the intelligence of a species.

Einstein:

- Average (or even smaller) total brain size
- Smaller neuron/glia ratio than average.



EQ of humans: ≈ 7.5

Human brains are 7.5 x bigger than what one would expect for species of this size.

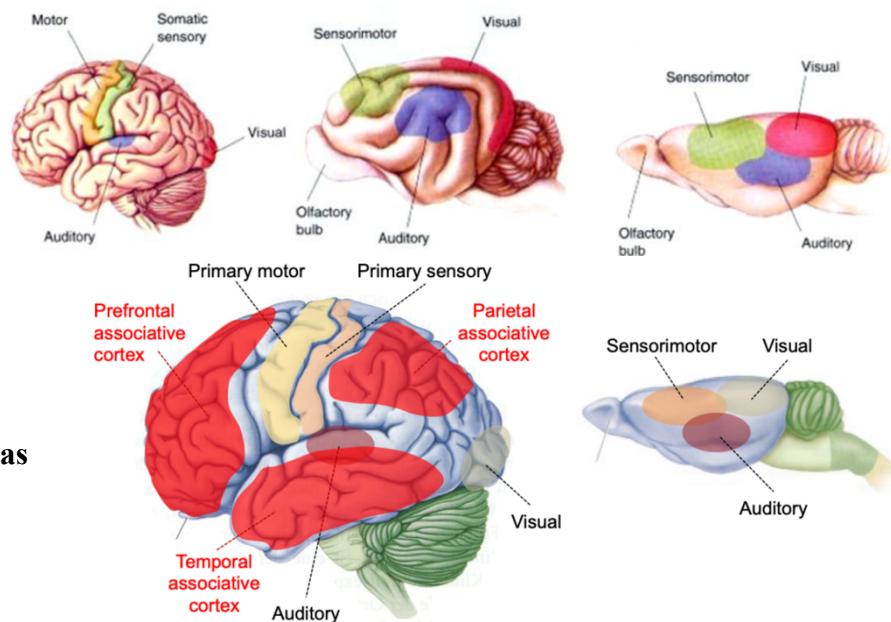


EQ of sq. monkeys: ≈ 1.1

“Our results also suggest that Einstein had relatively expanded prefrontal cortices, which may have provided underpinnings for some of his extraordinary cognitive abilities, including his productive use of thought experiments. From an evolutionary perspective, the specific parts of Einstein’s prefrontal cortex that appear to be differentially expanded are of interest because recent findings indicate that these same areas increased differentially in size and became neurologically reorganized at microanatomical levels during hominin evolution in association with the emergence of higher cognitive abilities.

Brain Evolution in View of Cortical Expansion

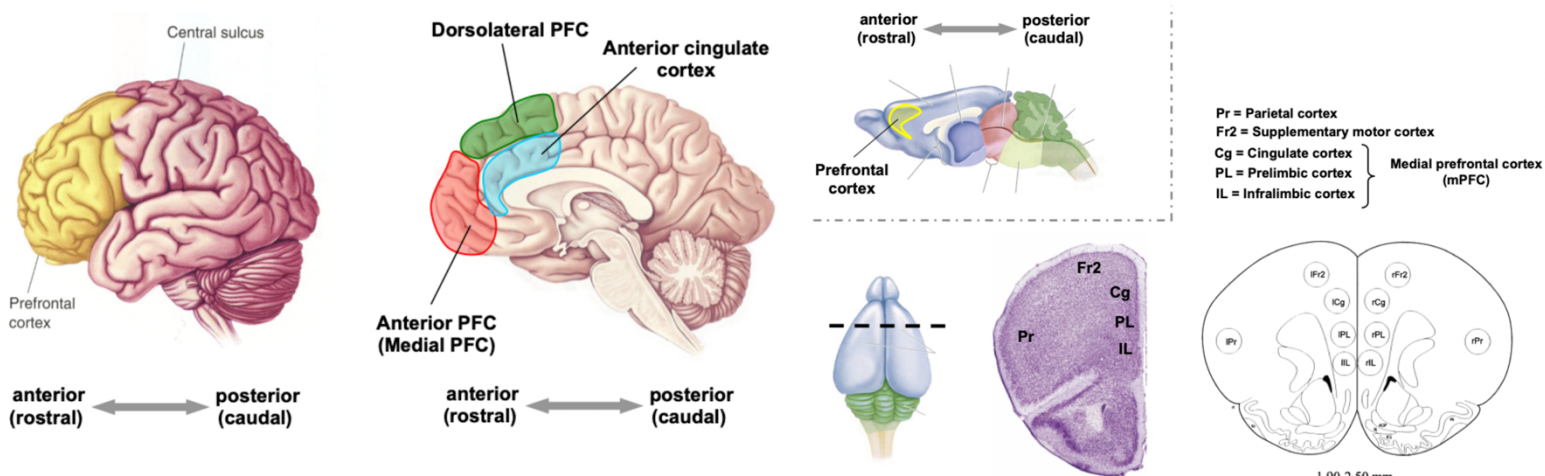
Cortical expansion is often equated with “brain evolution”, whereby the **relative size of the cerebral cortex increases while the relative size of the cerebellum remains fairly constant**. Human cortical expansion is relative but does not affect each region similarly!



Cortical Expansion of Associative Areas

Prefrontal Cortex: Human vs. Rats

Human Prefrontal cortex functions: Planning, Attention, Working Memory, Cognitive Flexibility and Impulsivity. Do rats have similar prefrontal structures and functions?



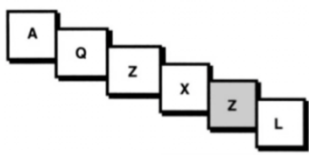
Assessment of Human prefrontal Cortical Functions

Example: Working Memory

- Short-term memory buffer with limited temporal capacity.
- Used to hold relevant information “online” in order to guide ongoing behavior, including strategic planning and problem solving.

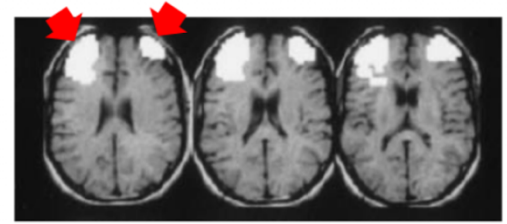
Cognitive tasks which demand working memory activate the PFC: an fMRI investigation in humans

Verbal memory task

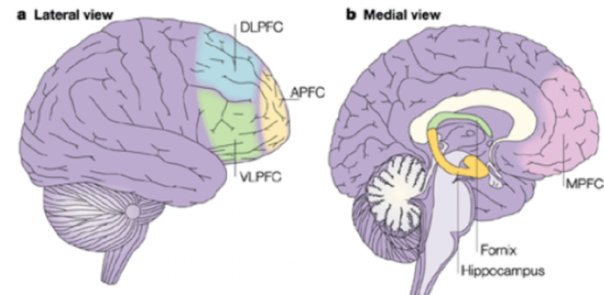


D'Esposito et al, 1998
Neuroimage 8:274-282

In the *verbal* condition (Fig. 1), stimuli were all the letters of the alphabet, presented in upper case. During the working memory task, subjects were instructed to determine whether each presented letter was the same as that presented two stimuli previously. In the corresponding nonworking memory task, subjects were instructed to identify an occurrence of the letter “X.”



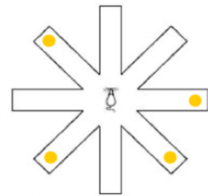
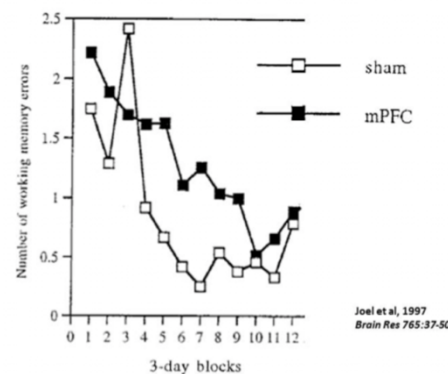
Activation of both left and right dorsolateral PFC during a verbal working memory task



Assessment of Rat Prefrontal Cortical Functions

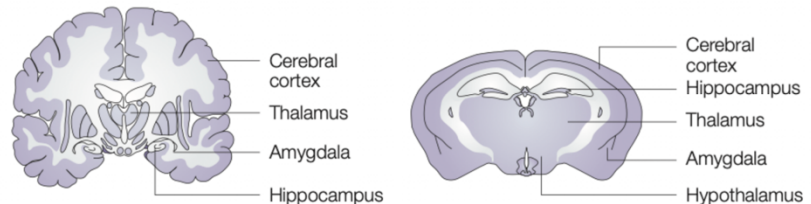
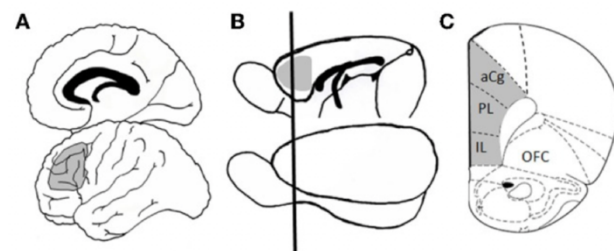
Effects of prefrontal cortex lesion on working memory in the 8-arm radial arm maze.

Lesions to the medial part of the prefrontal cortex (mPFC) lead to working memory impairments as evident by the **increased number of working memory errors** in the 8-arm radial arm maze.



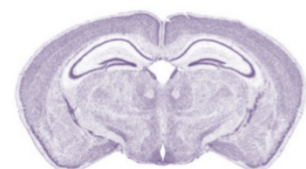
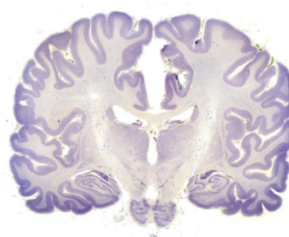
Prefrontal Cortex: Human vs. Rats

The rodent prefrontal cortex (PFC) is **not as anatomically complex** as the primate; however, **many of the critical neuroanatomical and functional characteristics are preserved in rodents**, which allow meaningful cross species comparisons relevant to study of the neurocognitive and neurobiological mechanisms that underlie changes in executive functioning across the lifespan. As indicated in the figure, the medial portion of rodent PFC (which includes anterior cingulate (aCg), prelimbic (PL), and infralimbic (IL) cortices) shares strong anatomical homology with primate dorsolateral PFC.



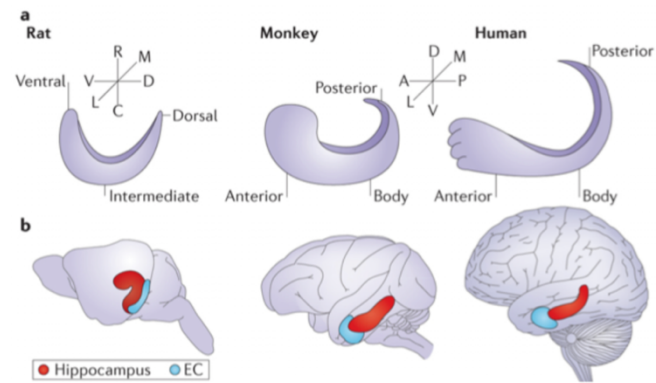
Adapted from: Cryan and Holmes (2005) Nat Rev Drug Discov

Cross-Species Comparison of Subcortical Areas



Cross-Species Comparison of Hippocampal Anatomy

Schematic illustrations of the orientation of the hippocampal long axis in rats, macaque monkeys and human. The **longitudinal axis** is described as **ventrodorsal in rodents** and as **anteroposterior in primates**. Note that a 90° rotation is required for the rat hippocampus to have the same orientation as that of primates.

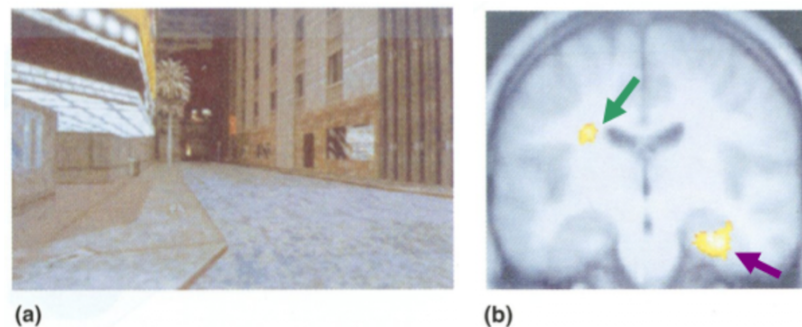


Cross-Species Comparison of Hippocampal Functions

“Recalling Routes around London: Activation of the Right Hippocampus in Taxi Drivers”

Positron Emission Tomography (PET) was used to examine the neural substrates of spatial memory retrieval in licensed London taxi drivers while they recalled complex routes around the city.

Activity in the human brain related to spatial navigation. (a) A virtual town was shown on a computer monitor, and subjects in a PET imaging machine used buttons to navigate the virtual environment. (b) Increased brain activity associated with spatial navigation was observed in the **right hippocampus (purple)** and left tail of the **caudate (green)**.



Effects of hippocampal lesions on reference learning and memory in the Morris water maze: deficits in the acquisition of spatial reference memory parallel the magnitude of dorsal hippocampal lesions, but is hardly present following ventral hippocampal lesions.

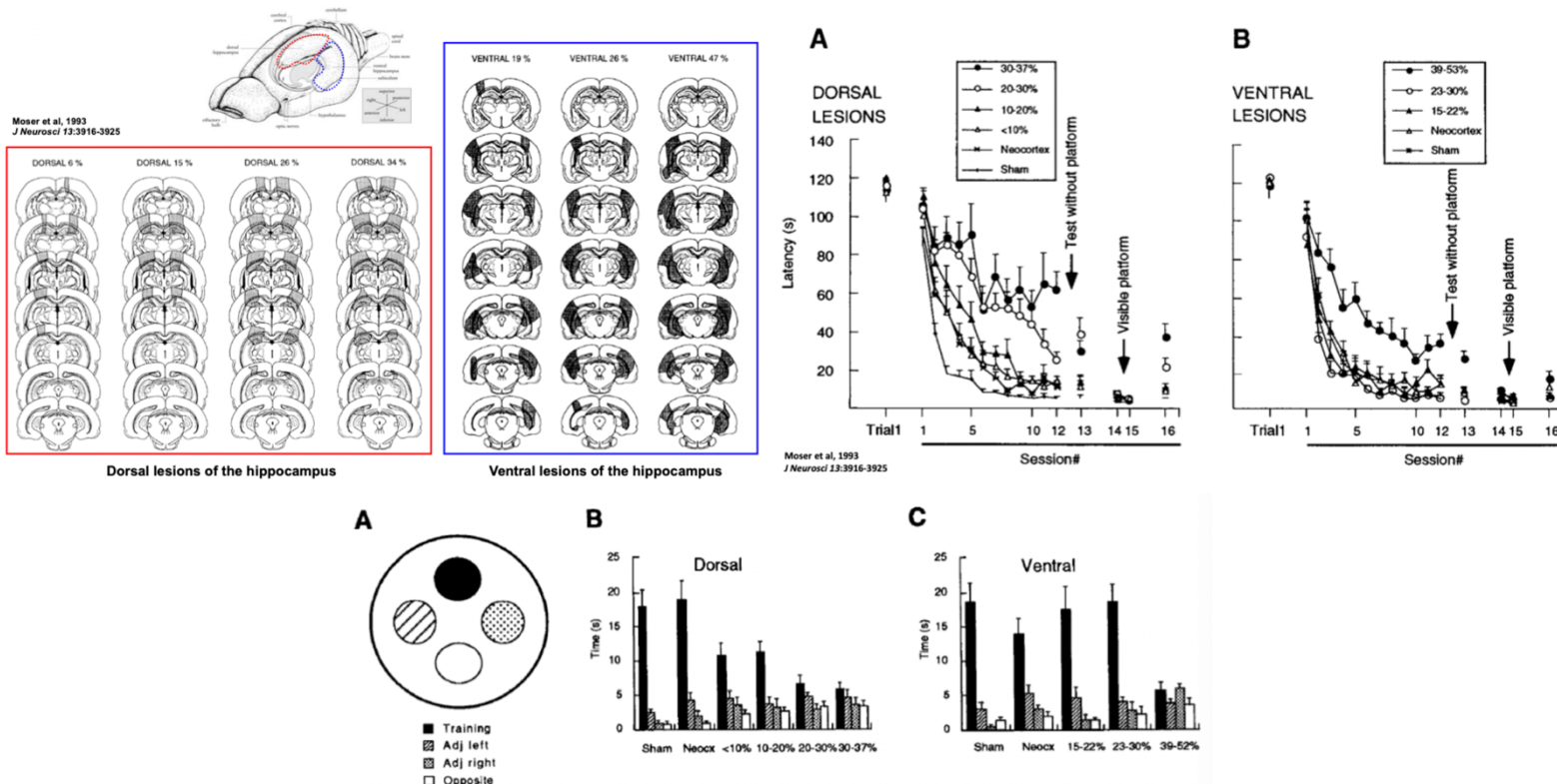


Figure 6. Performance of rats with dorsal and ventral hippocampal lesions on a spatial probe test. A, The swim time was measured inside a circular area (52 cm diameter) around the center of each quadrant (training quadrant, adjacent left, adjacent right, and the quadrant opposite to the training quadrant). During training, the platform had been located consistently in the center of the training quadrant. B and C, The mean time spent in the areas shown in A by groups with dorsal (B) or ventral (C) lesions.

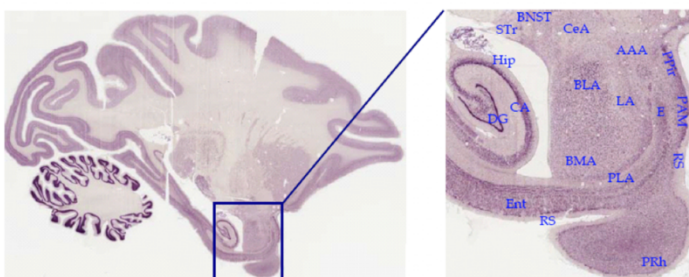
Moser et al, 1993, J Neurosci 13:3916-3925

Cross-Species Comparison of Amygdalar Anatomy

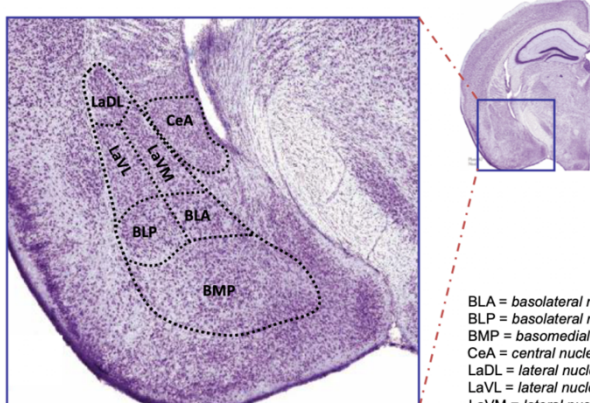
Primary amygdalar nuclei and basic circuit connections and function are **conserved across species**. An enlarged image of the basolateral complex of the amygdala (BLA) and central nucleus of the amygdala (CeA) or analogues are shown next to a coronal section from the brains of a lizard, rat, cat, monkey and human.

In Post-Traumatic Stress Disorders (PTSD), the amygdala is **hyperactive in response to negative (aversive) emotional stimuli** vs. neutral and positive stimuli.

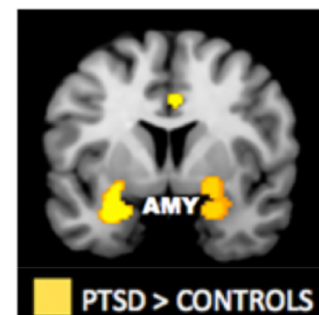
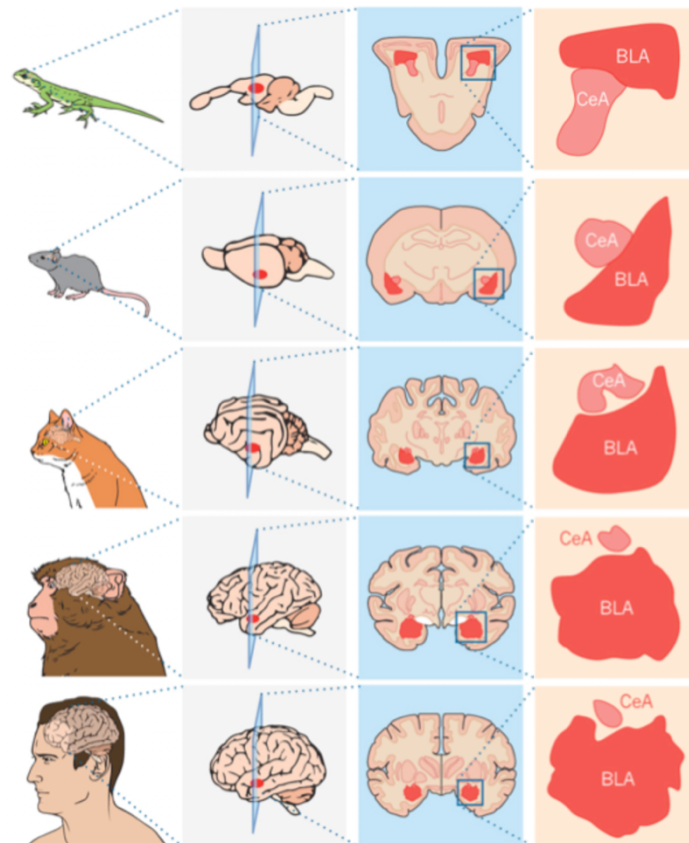
Rhesus monkey



Mouse



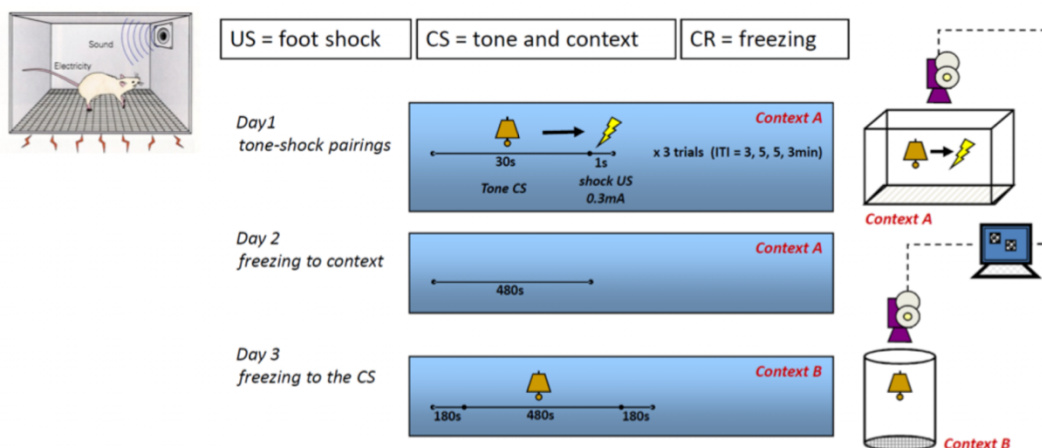
BLA = basolateral nuclei (anterior)
BLP = basolateral nuclei (posterior)
BMP = basomedial nuclei (posterior)
CeA = central nuclei (anterior)
LaDL = lateral nuclei (dorsolateral)
LaVL = lateral nuclei (ventrolateral)
LaVM = lateral nuclei (ventromedial)



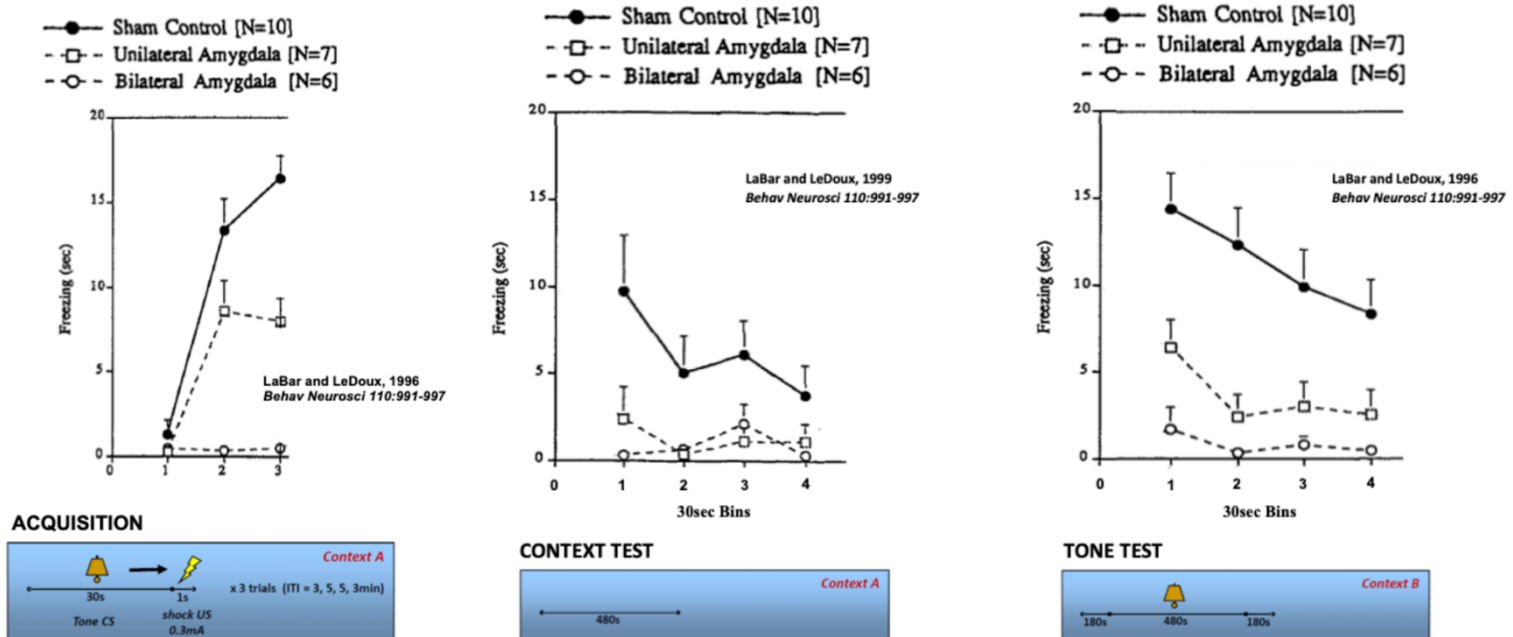
Hayes et al., 2012 *Biol. Mood Anxiety Disord.* 2, 9

Experimental investigations of amygdalar functions in rodents.

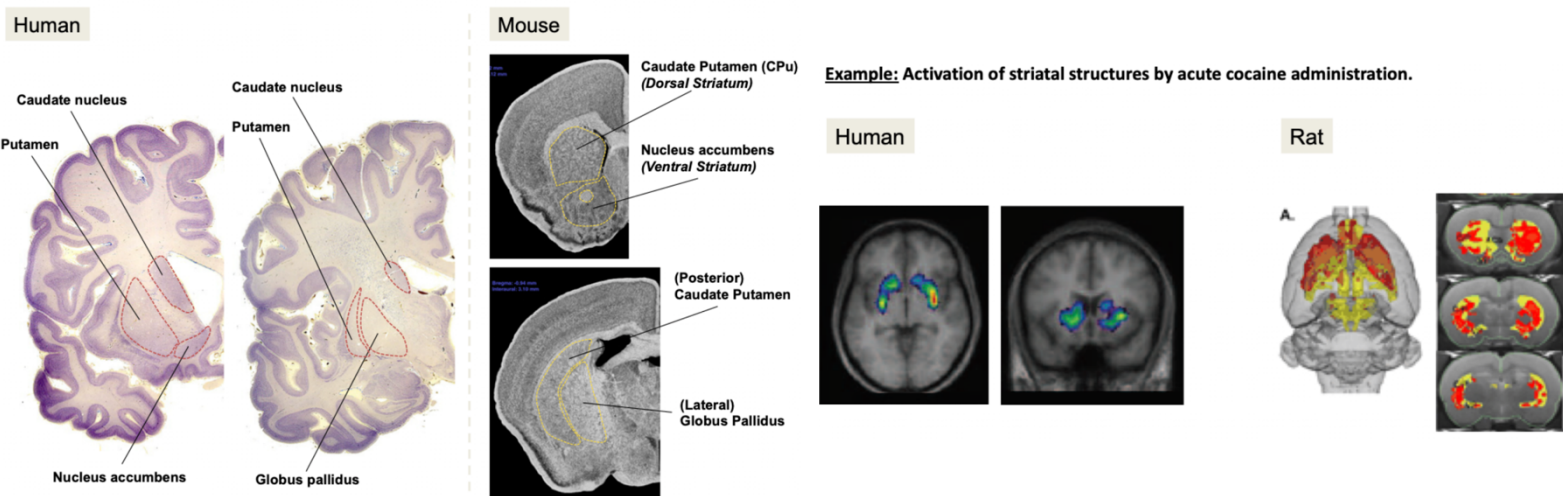
Classical (Pavlovian) fear conditioning



Classical Fear Conditioning: Effects of complete electrolytic lesions of the amygdala.



Cross-Species Comparison of Basal Ganglia Anatomy

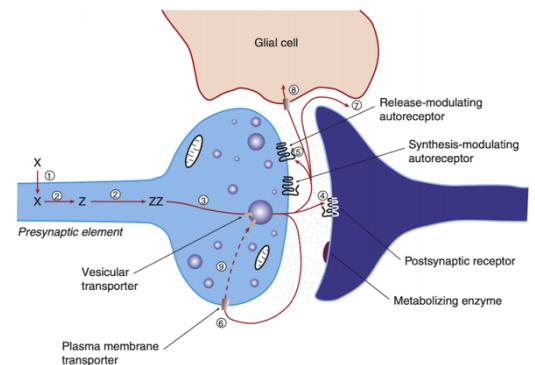


Synapses I – Lecture 05 – Csaba Földy

Chemical Transmission

Definition of Neurotransmitter

1. Synthesized and released from neurons → Localization of synthesizing enzymes.
2. Released from nerve terminals in a chemically or pharmacologically identifiable form → Must be possible to isolate it.
3. Reproduces events in the postsynaptic cells that are characteristically seen after stimulation of presynaptic neuron.
4. Its effect can be blocked by competitive antagonist for the receptor, in a dose-dependent manner.
5. Presence of active mechanisms to terminate action of neurotransmitters. → Uptake mechanisms and enzymatic inactivation.



Classical Neurotransmitters

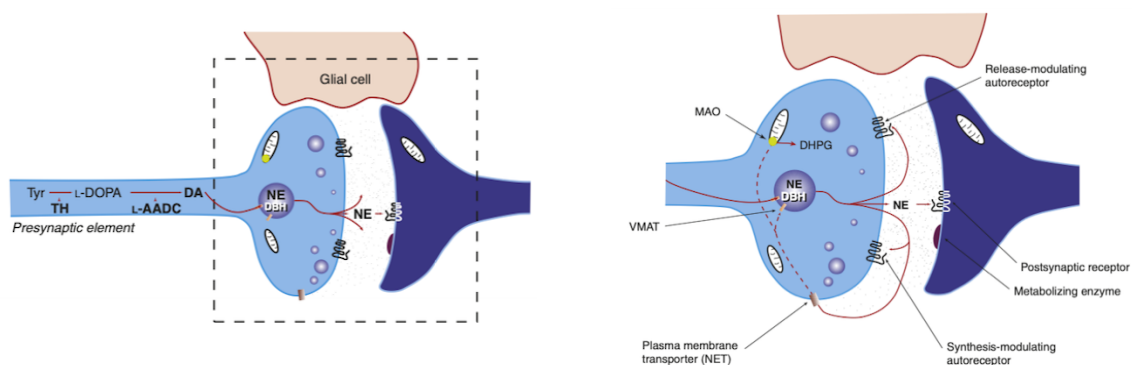
There are 5 classical neurotransmitters and are classified as classical because they satisfy the previously mentioned characteristics.

Catecholamines (Excitatory)

- Dopamine (DA), Norepinephrin (Noradrenaline) and Epinephrin (Adrenaline).
- Derived from the same precursor, but require separate enzymes.
- Storage and Release of Catecholamines and their enzymes:
 - Vesicular Storage
 - Release of Catecholamines
 - “Usual” Ca^{2+} dependent exocytosis
 - Reversal of DA and NE transporters to extrude Catecholamines
 - Apparent Ca^{2+} independent dendritic release
 - Regulation by Autoreceptors

These are broad ways in which NT can operate on the postsynaptic neurons

 - Synthesis-modulating autoreceptor
 - Release-modulating autoreceptor
 - Firing-rate-modulating autoreceptor
 - Inactivation/Catabolism
 - Two enzymes: monoamine oxidase (MAO) and cathchol-0-methyltransfrease (COMT). MAOs are drug targets in neuropsychiatric disorders.
 - Transporters (They might cross-bind or cross-activate with each other)
 - Facilitate transmitter re-uptake in an energy-dependent manner
 - High affinity transporters are neuron-specific
 - DAT: Dopamine transporter
 - NET: Norepinephrin transporter
 - Transporters are drug targets: Cocaine and Amphetamine both increase extracellular level of Catcholamines by blocking transporters. Cocaine has very high affinity for DAT, and Amphetamine reverses the normal direction, resulting in release
 - The Euphoria level from drug consume derives from the high concentrations of Catecholamines.



Serotonin (Excitatory)

- In blood, induced powerful contraction of smooth muscle organs.
- The brain accounts for only approx. 1% of total body serotonin.
- Serotonin inactivation:
 - Inactivated primarily by re-uptake through SERT, which belongs to the family of Catecholamine transporters.
 - Selective serotonin re-uptake inhibitors (SSRIs) block SERTs and widely used as antidepressants (such as fluoxetine aka Prozac).

- MAOs (monoamine oxydases) enzymatically degrade serotonin → MAO blockers elevate serotonin levels and are used as antidepressants.

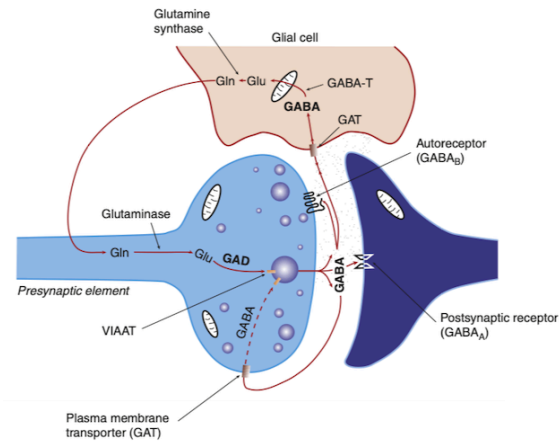
Acetylcholine (Excitatory)

It is important in neuromuscular junctions. Classic studies examining endplate potentials in neuromuscular junction.

- MAOs (monoamine oxydases) enzymatically degrade serotonin → MAO blockers elevate serotonin levels (antidepressants).
- Many of the rules that govern Ach transmission have found to be generally applicable to many neurotransmitters.

GABA (Inhibitory)

- Amino acid transmitter gamma-aminobutyric acid
- Derived from glucose metabolism
- GABA inactivation – the GABA shunt:
 - GABA is inactivated by GABA-T (which is both synthetic and degradative enzyme), but only if alpha-Ketoglutarate is present to receive the amino group that is removed from GABA. This unusual GABA shunt serves to maintain supplies of GABA. GABA uptake is mediated by GABA transporter (GATs), which are non-specific to GABA and take up other amino acids as well.



Glutamate and Aspartate (Excitatory Amino Acid Transporters)

- Account for most fast excitatory synaptic transmission in the brain
- Neither crosses the blood-brain barrier; need to be derived by local synthesis from glucose.
- Glutamine is exported from glia and need to be taken up by nerve terminals before being converted to glutamate.
- Vesicular uptake transporters VGlut1, 2, and 3 identify glutamatergic neurons, in most cases.
- Glutamate uptake after transmission is mostly by astrocytes, which have high levels of glutamate transporters. Glia can also release glutamate.

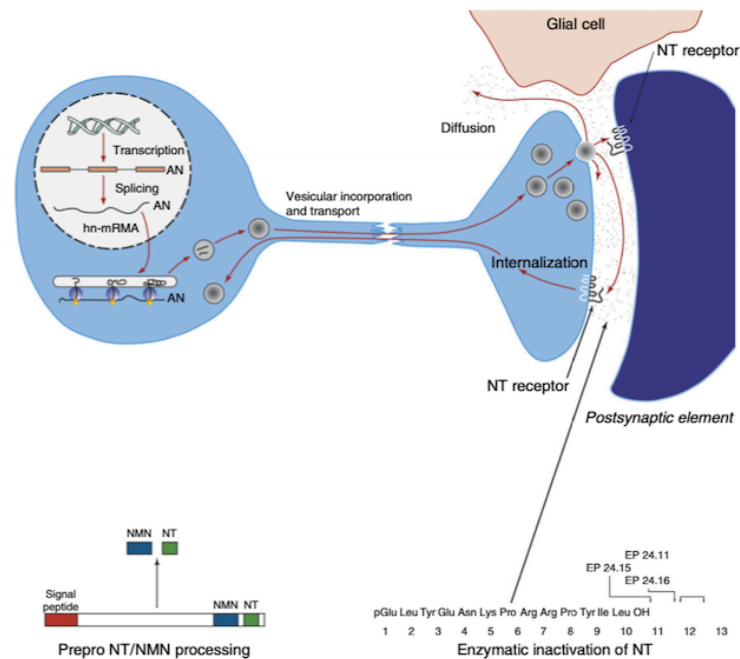
Non-classical neurotransmitters

- Fail most classical criteria, but still function as classical transmitters over restricted spatial and temporal domains.
- Can be also classical neurotransmitters used in “non-classical” ways. For example, in non-junctional appositions.

Peptide Transmitters

- Biosynthesis is mostly non-enzymatic and non-axonal, as classical neurotransmitters
- Gene → prohormone → uptake to secretory vesicles → peptidase on prohormone → peptide transmitter, which is then transported down the axon.
- Because transcription is required, peptide transmitters respond to demand slower than classical transmitters.
- Packaged to dense core vesicles (approx. 100nm diameter, vs approx. 50nm of classical), and released in response to high frequency stimulation.
- Inactivation: there are no uptake mechanisms. They are inactivated enzymatically, or by diffusion. However, certain fragments may remain biologically “active”.
- Synthesis, release, and termination of action of the neuropeptide transmitter neurotensin:

- Single gene yields two mRNAs: neurotensin (NT) and neuromedin (NMN)
- NT and NMN co-express, but molar ratios are different. Likely, because different processing of the precursor.
- There are no membrane transporters, but peptides can still accumulate in neurons, via internalization of receptor bound peptide, and subsequent dissociation.
- NT co-localizes with DA but their release is reciprocally regulated by actions of release-modulating DA autoreceptors.



Unconventional Transmitters

- Radically different from classical transmitters
- The original definition did not account for:
 - Multiple time scales (some transmitters can be present in low amounts and act on slow time scales).
 - Communication between neurons and non-neurons, such as glia.
 - Unconventional roles for neurotransmitters, such as regulation of neuronal development and intracellular signaling.
- No signaling and gaseous neurotransmitters (“gasotransmitters”).
- Endocannabinoid signalling
 - Major psychoactive component of marijuana is delta-9-tetrahydrocannabinol (THC); if psychoactive, there must be a receptor.
 - Search identifies CB1 receptor, if there is receptor, there must be endogenous ligand.
 - Search identifies 2-AG, and subsequently multiple other endocannabinoids, if there are ligands, there must be enzymes involved in synthesis and inactivation.
 - Search identifies respective enzymes.
 - ECs act as retrograde transmitters in synapses.

Release of Neurotransmitters

Transmitter Release is Quantal (Chemical signals can work as amplifiers)

- Chemical transmitter based synapses are highly diverse and modifiable (as opposed to electric coupling).
- Post-synaptic effect can be excitatory or inhibitory.
- Transmission has to be fast.
- A consequence of releasing transmitter by the exocytosis of vesicles is that synaptic transmission is quantal.

Transmission in the neuromuscular junction

- Profusion and docking of synaptic vesicles at approx. 1000 active zones.
- Action potential triggers release of transmitter of approx. 300 quanta into the synaptic cleft (approx. 100nm wide).
- Diffusion to postsynaptic receptors and reaching concentrations of 1mM within 2ms.
- Activation of up to 2000 receptors, resulting in ion channel opening.

- Action potential induced release of 300 quanta results in a peak of few 10mVs, enough to generate an action potential in the muscle fiber.

Transmission in Central Synapses (as opposed to the neuromuscular junctions)

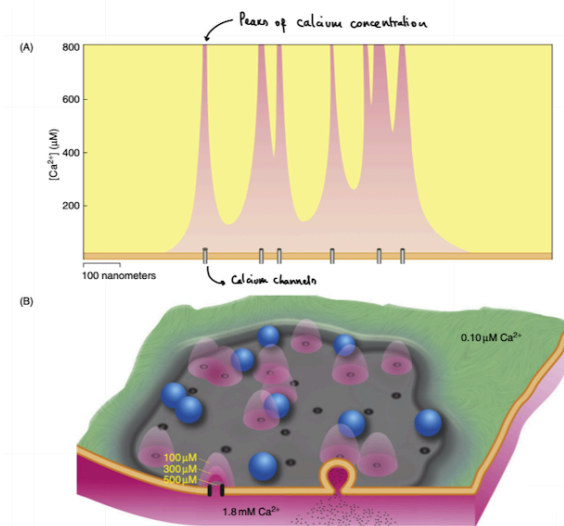
- A typical central synapse contains 1-4 active zones.
- Action potential triggers release of transmitter 5 to 10 vesicles.
- Cleft concentration also goes up to approx. 1mM, but typically there are less receptors, each vesicle activating approx. 30 receptors.
- Single evoked responses are in the range of few millivolts at most, clearly sub-threshold for excitatory responses to evoke postsynaptic action potential.

Excitation – Secretion Coupling

- Centrality of Ca^{2+} .
- Coupling is achieved by the use of Ca^{2+} as intracellular messenger.
- Normal intracellular Ca^{2+} is buffered very low. Extracellular Ca^{2+} is in the mM range $\rightarrow$ large driving force after Ca^{2+} channels open $\rightarrow$ up to 1000-fold increase in intracellular concentration (change intra/extra concentrations to test dependency).
- Probing with Ca^{2+} loading
- Probing with Ca^{2+} buffering
- Where is the Ca^{2+} sensor?

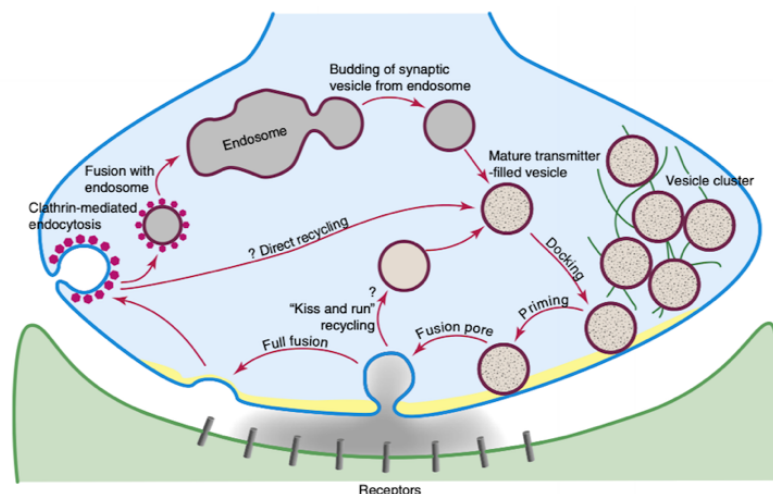
Ca^{2+} Microdomains

- Single active zone may have 100 Ca^{2+} channels.
- A single vesicle may be <5-nm from as many as 10 Ca^{2+} channels.
- Most prevalent Ca^{2+} channels for release are N- and P/Q-type channels.
- The exocytosis trigger must be fast (=fast on/off rate for speed).
- Cooperative Ca^{2+} binding; multiple Ca^{2+} sites need to be occupied for efficiency.



Molecular Mechanisms at the Nerve Terminal

- Neurons need an extremely efficient mechanism to recycle and reload vesicles within the terminal. (Otherwise they run out of readily releasable pool of vesicles).
- For most neurotransmitters, vesicles are refilled in approx. 30sec.
- A CNS synapse have only 2-20 fusion ready vesicles. These need to be replaced within seconds.

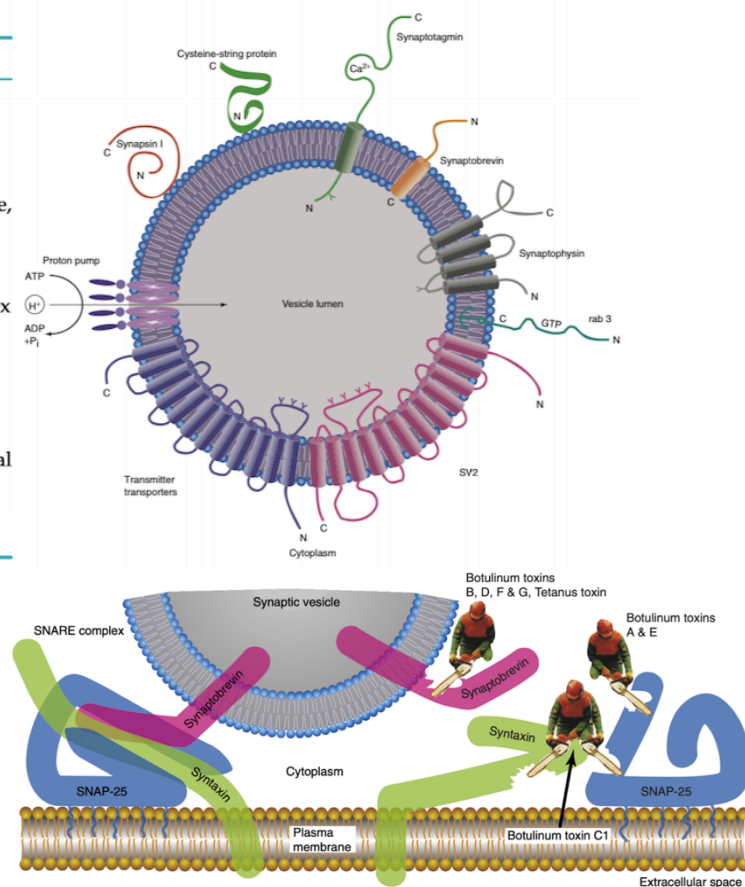


Structure and Topology of Major Synaptic Vesicle Membrane Proteins

- Protein compositions of synaptic vesicles are remarkably similar, independent of the neurotransmitter. (Extreme richness of different proteins).

TABLE 7.1 Function of Synaptic Vesicle Proteins

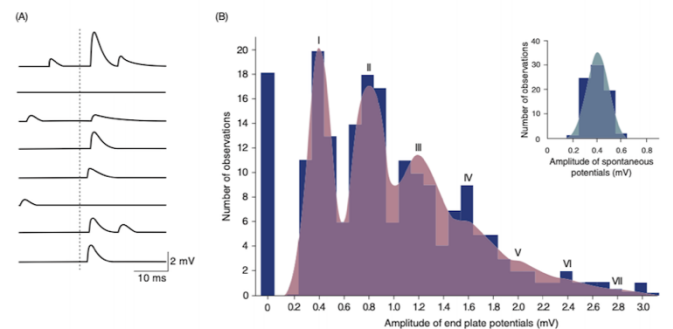
Protein	Function
Proton pump	Generation of electrochemical gradient of protons
Vesicular transmitter transporter	Transmitter uptake into vesicle
VAMP/synaptobrevin	Component of SNARE complex; acts in a late, essential step in vesicle fusion
Synaptotagmin	Ca ²⁺ -binding trigger for fusion and component of vesicle docking at release sites via interactions with SNARE complex and lipid; promotes clathrin-mediated endocytosis by binding AP-2 complex
Calcium "sensor"	
Rab3	Possible role in regulating vesicle targeting and availability
Synapsin	Likely to tether vesicle to actin cytoskeleton
Cysteine string protein	Promotes reliable coupling of action potential to exocytosis
SV2	Unknown
Synaptophysin	Unknown, endocytosis?



SNARE Proteins and Core Complex are Key to Membrane Fusions

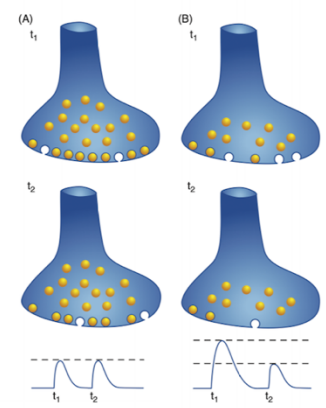
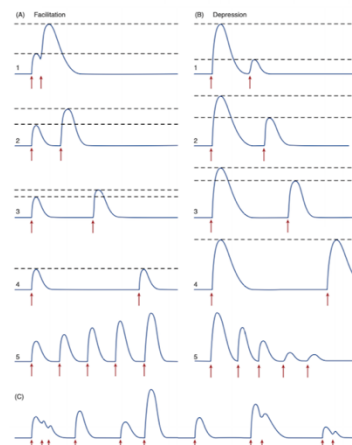
Quantal Analysis: Probing Synaptic Physiology (example: Neuromuscular Junction)

In the 60's they noticed that by recording synaptic signals in the neuromuscular junction, an histogram of the distribution of potential amplitudes showed multiple peaks. It depends on the number of vesicles released during a synaptic release.



Short-Term Synaptic Plasticity

Repetitive activation of the synapse, depending on the interval between the two stimulations, we can see a larger or smaller action potential amplitude in the second event, which are called "facilitation" (depends on the already higher concentration of calcium) and "depression" (which could be caused by a desensibilization of the synaptic site or depletion of the neurotransmitters vesicles).



(B) Readily-releasable pool is smaller and fusion probability is higher => synaptic depression

Synapses II – Lecture 07 – Theofanis Karayannis

Content of the Lecture

- How do we assess the function of neurons
- Types of synapses
- Synaptic transmission (post-synaptic)
- Post-synaptic integration

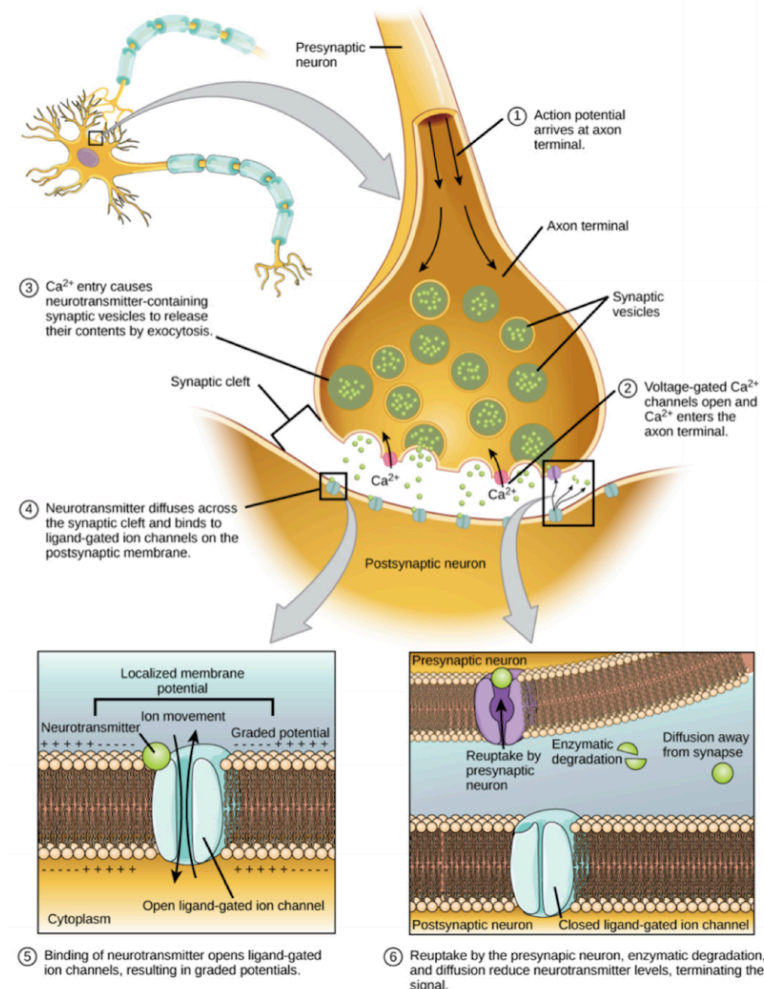
How Do We Assess the Function of Neurons

- By Electrophysiology because neurons generate and transmit electrical signals **via ions**.
- Neurons are polarized cells (resting membrane potential). The difference in voltage across the cell membrane when a neuron or muscle cells is not producing an AP.
 - A typical value is: -70mV (-50 to -90).
 - A cell that exhibits a membrane potential is said to be **polarized**.
- Why is the inside of the cell more negative? Because of the following:
 - The resting membrane is 10-100 times **more permeable to K^+ than to Na^+** .
 - **K^+ tends to leak out of the cell down its concentration gradient, carrying positive charge with it**, and unable to carry Cl^- with it because Cl^- has higher concentration outside.
 - The non-diffusible anion (protein, sulphate and phosphate ions) cannot leave the cell.
- The Action Potential is a very fast and transient change in the polarity of the neuronal membrane that **breaks the ionic equilibrium**.
- Synaptic transmission is the mode of communication between neurons.

Types of Synapses

- There are two types of synapses in the nervous system
 - **Chemical Synapses (2 types)**
 - **Excitatory (Asymmetric)**
 - **Inhibitory (Symmetric)**
 - Chemical Synapses physically connect across the cleft.
 - **Electrical Synapses (3 types of channels)**
 - Pannexin
 - Innexin
 - **Connexin (5 groups)**
 - Electrical synapses are gap junctions.
 - Electrical Transmission allows the rapid and synchronous firing of interconnected cells.

ELECTRICAL SYNAPSE	CHEMICAL SYNAPSE
Common in simple animals	Common in complex animals
Common in development	Common in adult
Fast	Slow
Bidirectional	Unidirectional
Excitatory	Excitatory or Inhibitory
Postsynaptic signal is similar to Presynaptic	Postsynaptic signal is different to Presynaptic



Synaptic Transmission (Post-synaptic)

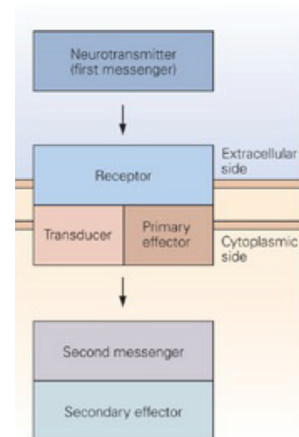
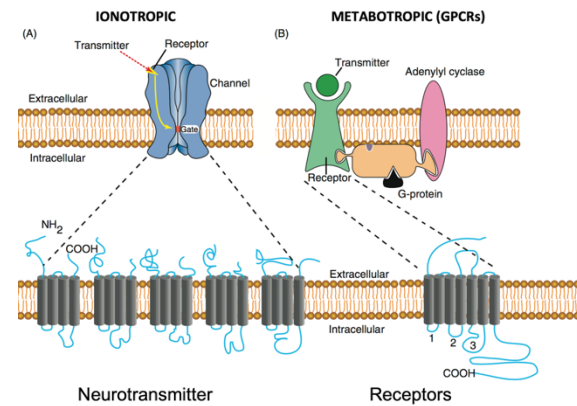
- Two different Neurotransmitter Receptor Types

- **Ionotropic (Ligand-Gated Ion Channels)**

- Short latency: rapid signals approx. 10ms.
- Localization: usually postsynaptic.
- Function: mediate fast synaptic transmission.
- They change their conformation upon binding of the NT.
- Typically 4/5 transmembrane domains

- **Metabotropic (GPCRs) (G-Protein Coupled Receptors)**

- Long latency: slow signals approx. 10sec.
- Divergence: amplification of weak signals.
- Convergence: integration of multiple inputs.
- Localization: presynaptic and postsynaptic.
- Function: modulate fast synaptic transmission.
- Typically 7 transmembrane domains.
- Three classes of GPCRs:
 - Class A (391 Olfactory)
 - Class B
 - Class C (GABA_B)
- The G-Protein has three subunits (alpha, beta, gamma).
- It generates a cascade of events: NT arrives to receptors → binds to G-protein → the G-Protein subunits splits (GTP to GDP) → Most of the work is done by the alpha subunit.
- **Divergent Roles for GPCRs:** There are 3 main sequences of events:
 - **cAMP System**
 - **Phosphoinositol System**
 - **Direct G Protein-Gating**
- **Benefits of GPCRs**
 - Amplification of the signal.
 - Modulation of cell function over a broad temporal range.
 - Diffusion of the signal to a large cellular volume.
 - Cross talk.
 - Coordination of diverse cell functions.



Glutamatergic-Excitatory

- **Ionotropic Glutamate Receptors – AMPARs.**
- Excitatory synapses depolarize the neuron.
- **The generation of an EPSP:** an impulse arriving in the presynaptic terminal causes the release of neurotransmitter. The molecules bind to transmitter-gated ion channels in the postsynaptic membrane. If **Na⁺ enters** the postsynaptic cell through the open channels, the membrane will become depolarized. The resulting change in the membrane potential (V_m), as recorded by a microelectrode in the cell, is the **EPSP**.
- Channels are very specific for certain ions, a small change in the gene code can block the passage of certain ions (e.g., Ca^{2+}).
- Receptors are affected by drugs (e.g., PCP blocks NMDA receptors giving hallucinations).

- Protein complexes allow receptors to be presented and work as channels, but such protein complexes can be removed by the cell (plasticity).

GABAergic – Inhibitory

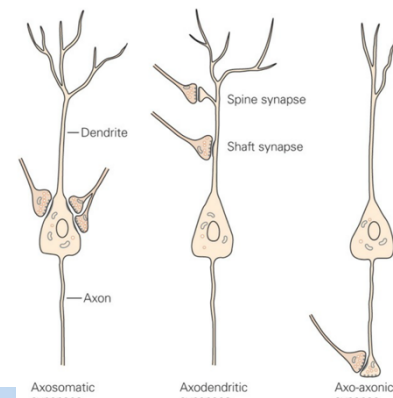
- **Ionotropic receptor type topological arrangement – GABA_ARs.**
- **The Generation of an IPSP:** an impulse arriving in the presynaptic terminal causes the release of neurotransmitter. The molecules bind to transmitter-gated ion channels in the postsynaptic membrane. If **Cl⁻** enters the postsynaptic cell through the open channels, the membrane will become hyperpolarized. The resulting change in membrane potential (V_m), as recorded by a microelectrode in the cell, is the **IPSP**.
- Several drugs to sleep better or relax are based on this concept, indeed these drugs target inhibitory receptors keeping them open for longer which allows more passage of Cl⁻, which in turn reduces the general spiking activity of the brain, thus inducing a sensation of relax which favors sleeping. Similar drugs are used also to cure Epilepsy.

Post-Synaptic Integration

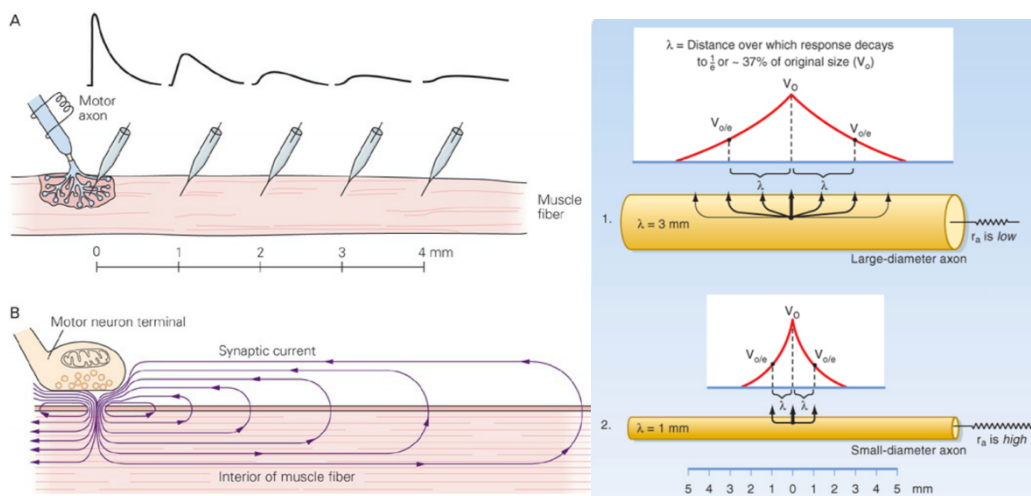
Effects of Spatial Location on Synaptic Impact

Different Types of Chemical Synapses based on Spatial Location

- Axosomatic Synapses
- Axodendritic Synapses
- Axo-axonic Synapses

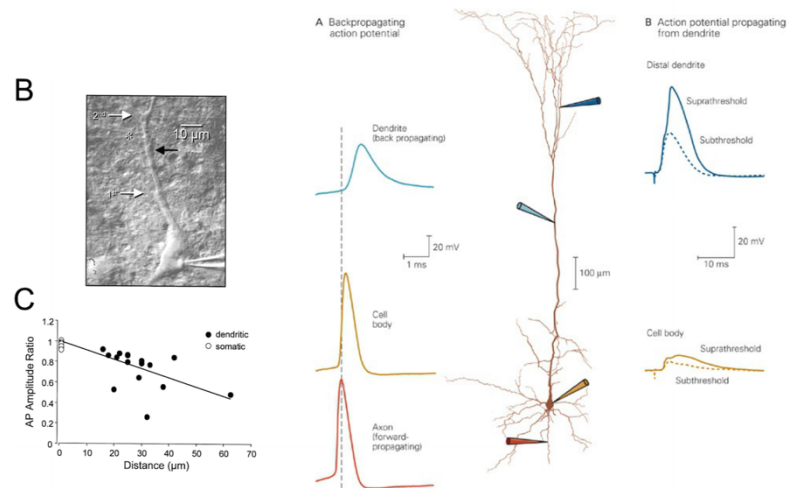


Electronic Attenuation of Electrical Signals with Distance



Place-Dependent Post-Synaptic Functional Impact

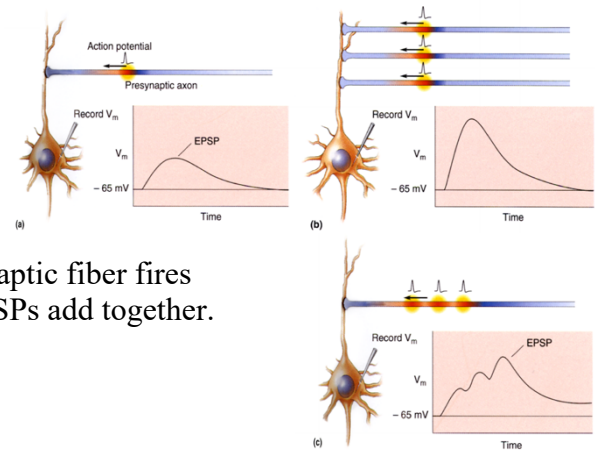
Signals are amplified in synapses through channels like NMDA, which is voltage-dependent.



Effects of Timing on Synaptic Impact

EPSP Summation

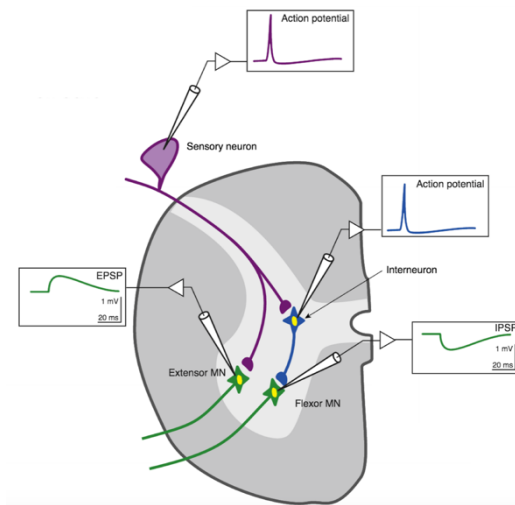
- A presynaptic action potential triggers a small EPSP in a postsynaptic neuron.
- Spatial summation of EPSPs:** When two or more presynaptic inputs are active at the same time, their individual EPSPs add together.
- Temporal summation of EPSPs:** When the same presynaptic fiber fires action potentials in quick succession, the individual EPSPs add together.



Integrating Synaptic Signals in a Simple Circuit

Feed-Forward Inhibition in the Reflex Spinal Cord Circuit

In the Spinal Cord reflex we have a circuit that induces opposite effects (excitation and inhibition) with respect to extensor and flexor muscular neurons. Indeed, when the sensory neurons sense a change in muscular stretch are excited and spike. The action potential generated from the sensory neuron, as shown in the image, generates an EPSP in the extensor MN which induces a muscle extension, at the same time the action potential excites an interneuron that inhibits the Flexor MN, thus relaxing the flexor facilitating the muscle extension.



Excitability – Lecture 08 – Martin Mueller

Membrane

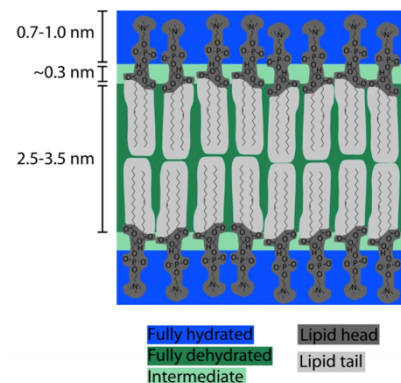
The membrane is a very thin bilipid layer that is absolutely impermeable for ions. The membranes are fluid.

Membrane Theory (Bernstein)

- Excitable Cells:** Membrane selectively permeable to K^+ ions at rest.
- Excitation:** Permeability for other ions increases.

Membrane Potential

The membrane potential at rest is approx. -80mv (-50 to -90). This value is mainly due to the high concentration of K^+ ions inside the cell compared to outside, which move outside the cell following their concentration gradient and bringing positive charges with them. At the same time, a contrary electrical gradient develops, since the inside is negatively charged, K^+ ions are subject to an electrical force that pushes them inside (membrane potential). When these two forces are in equilibrium, the net flux of K^+ is 0 and the cell is at its resting/equilibrium potential (E).



Equilibrium Potential (E)

It is the voltage at which chemical diffusional driving force is balanced by electrical driving force.

Nernst Equation can be used to calculate E:

$$E_K = \frac{RT}{F} \ln \frac{[K^+]_{out}}{[K^+]_{in}}$$

Since membrane potential is not simply due to K^+ , but also to other ions concentrations, a more comprehensive formula the **Goldman-Hodgkin-Katz Equation** has been developed. The membrane potential is indeed maintained by the **Na^+/K^+ Pump (ATP)** which pumps in $2K^+$ and pumps out $3Na^+$. The GHK equation can be used to calculate V_m :

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

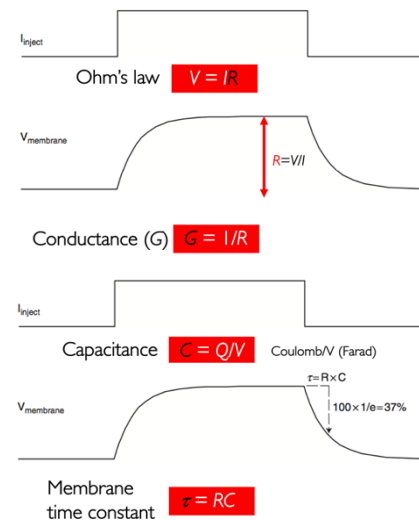
The membrane is mostly permeable to K^+ ions at rest, hence E_K dictates the Resting Membrane Potential. The Resting Membrane Potential represents the relationship between electric field and potential difference. It is the potential difference between two point separated by distance d : Hence, $E = -80\text{mV}/5\text{nm} = -16 \times 10^6 \text{ V/m}$.

$$E = -\Delta V/d$$

Passive Electrical Properties

Resistance

The Amplitude of V change is influenced by membrane resistance (R). For the same I , a larger R produces a larger potential difference.



Capacitance

The Capacitance is the voltage separation over the passive membrane. The Time course of V change is influenced by membrane capacitance and resistance (positive correlation).

RC Circuit

Membranes with ion channels are often schematized as RC circuits.

Cell Size

A larger cell usually has a smaller resistance, larger capacitance and larger time constant. A “leaky” membrane has a small resistance, while a thick membrane has a small capacitance.

Length Constant

The length constant (λ) is the point at which V_m has fallen to $1/e$ (or 37%) of its original value.

Measuring and Controlling V_m

Patch Clamp

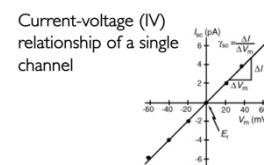
The patch clamp allows the active control of current (I) (Current Clamp) or V_m through I injection (Voltage Clamp). Indeed, through a patch clamp it is possible to measure the injected current and calculate V_m .

- Current injection to counteract changes in $I_m \rightarrow$ Measure membrane potential.
- Current injection to counteract changes in V_m (goal: $V_{\text{command}} = V_m$) $\rightarrow$ Measure current (clamp/fix V).

Current Clamp	Voltage Clamp
Current input	Current Input
Clamp current	Clamp voltage
Measure potential	Measure current
Measure V_m	
Measure C & R	
Sensitive to C error	Sensitive to R_s error (SEVC)
Physiological activity (EPSP)	Currents, Ion channels (EPSC)

Ion Channels and the AP

Ion channels are “digital”, they are either open or closed. The amplitude of single channel current (i) depends on single-channel conductance (g) and “driving force” ($V_m - E_{\text{ion}}$). The probability of a V-gated Channel is dependent on the voltage (Na^+ , K^+). The whole-cell current depends on single-channel conductance, driving force, number of open channels (n), and open probability (P_o):



Single channel conductance (g)
IV slope ($g = di/dV$)

$$i = g (V_m - E_{\text{ion}})$$

$$I = g (V_m - E_{\text{ion}}) n p_o$$

Ion Channels Requirements & Design Challenges

- Selectivity: Ion filter mimics hydration of ion
- High Conductivity (Speed): approx. speed of diffusion in H_2O but as a purely passive process.
 - Na^+ ions/channel = 10,000,000/s
 - Ions/channel = 1000/ms – 10,000/ms
 - More than 1000 times faster than membrane transporters and pumps. (Na^+/K^+ pump/ATPase = 100/s).

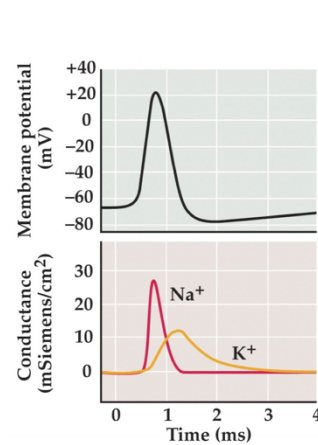
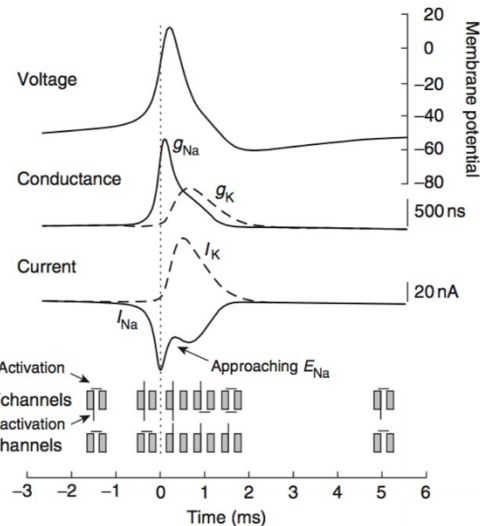
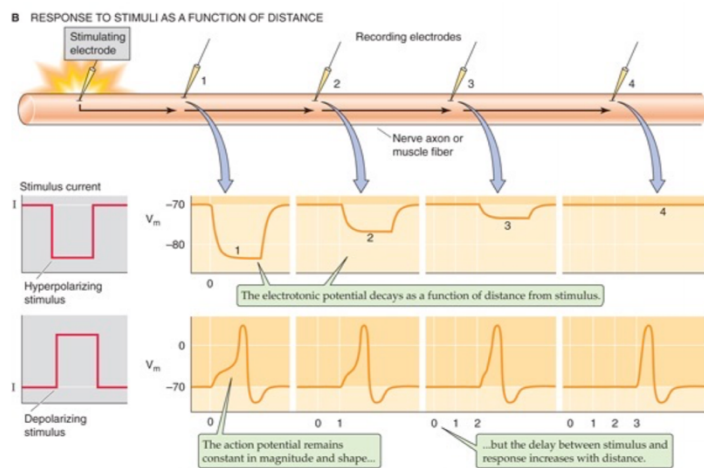
- Gating: Voltage gating involves V-dependent movement of charged channel structures.
 - Inactivation vs. Closure: during inactivation the channel does not conduct during the stimulus. The inactivation of V-gated ion channels involves charged channel structures (ball).
- Specificity (>90%): K⁺ channels 99.99% versus Na⁺ (Ionic Radius: K⁺ 152pm, Na⁺ 116pm).

The Action Potential

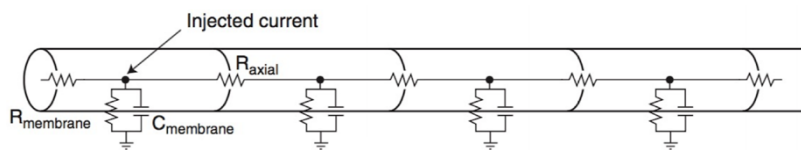
The action potential propagation:

$$t = x^2 / 2D$$

x Distance
D Diffusion coefficient



How can we increase conduction speed?



Solution 1
Diameter $\uparrow$
 $R_m \downarrow$
 $R_{ax} \downarrow \downarrow$
 $\Rightarrow \sim 25 \text{ m/s}$

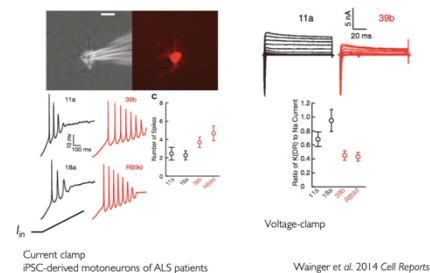
Solution 2
Insulation (myelin)
 $R_m \uparrow \uparrow$
 $C_m \downarrow \downarrow$
 $\Rightarrow > 200 \text{ m/s}$

High-Frequency Transmission

Short AP duration is required for high-frequency firing and transmission. This characteristic is very important to perform Rate Coding.

Examples (Physiology & Pathology)

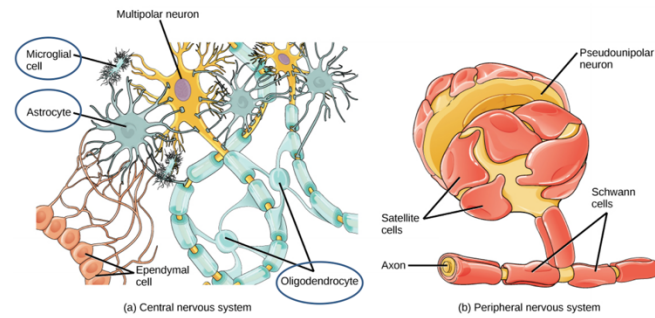
Hyperexcitability in ALS patient-derived iPS motoneurons due to decreased K⁺ current. In this experiment, sample of skin from patients with sclerosis were taken. Based on these samples, they made stem cells and transdifferentiated them in motoneurons. They did current clamps to analyze spiking patterns in these cells, which highlighted that these cells presented hyperexcitability compared to control ones. And voltage clamps highlighted a decrease of potassium currents over sodium currents. Hence, one of the problems of these cells may be related to a decreased number of potassium channels.



Glia and More – Lecture 09 – Bruno Weber

Glial Cells

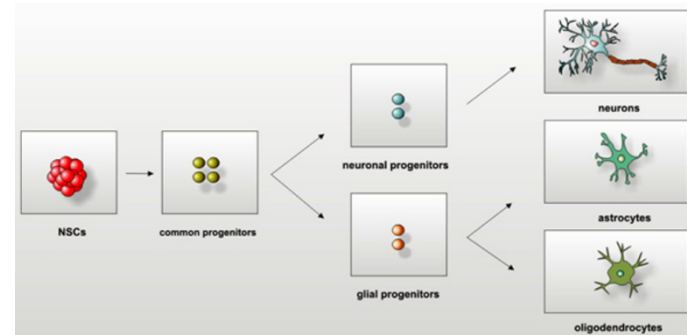
- **Central Nervous System**
 - Microglial cell
 - **Astrocyte**
 - **Oligodendrocyte**
- **Peripheral Nervous System**
 - Satellite cells
 - Schwann cells



Astrocyte

There exist two different main morphologies of astrocytes in grey and white matter.

- **Grey Matter Astrocytes (Protoplasmic)**
They have a spongy look and are difficult to represent. They touch on blood vessels as they have control over blood regulation.
- **White Matter Astrocytes (Fibrous)**



Astrocytes Form a Network

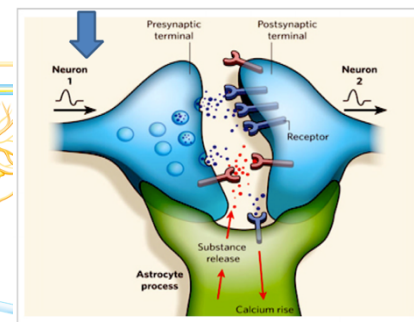
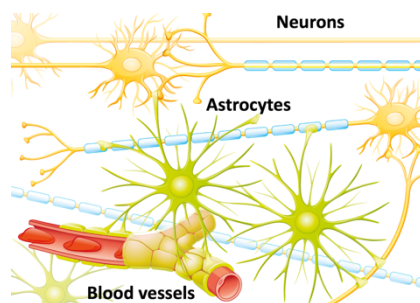
Astrocytes form networks through gap junctions: gap junctions form a channel between 2 membrane, they allow ions and metabolites to pass between cells and are made of connexin (Cx) proteins. Astrocytes: Cx30 and Cx43. They form sort of synapses between each other in a network even though they are not excitable cells.

Rodent vs. Human Astrocytes

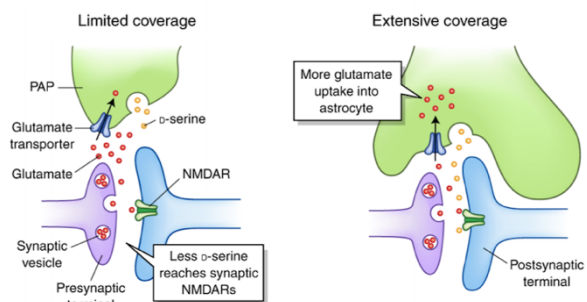
- **Structural Complexity:** human astrocytes are bigger than rodents ones and the number of the main processes is way bigger in humans.
- **Domains** are way bigger in humans.
- **Mice Implanted with Human Astrocytes:** about 10 years ago, human astrocytes were implanted into mice's and they found that LTP was enhanced.
 - Neurons displayed enhanced long-term potentiation (LTP).
 - Animals learned faster.

Astrocyte Structure

- The Astrocyte connects three parts in the **Neurovascular Unit**: Neurons, Astrocytes and Blood Vessels.
- **Tripartite Synapse:** Astrocytes surround synapses. Glia transmission, they are releasing neurotransmitters in the synaptic cleft.



They release transmitters and influence synapses through a morphological change in synapse coverage. It is a really plastic system with a lot of different **spatial** and **temporal scales** of how astrocytes modulate synaptic strength



Astrocyte Calcium Signaling

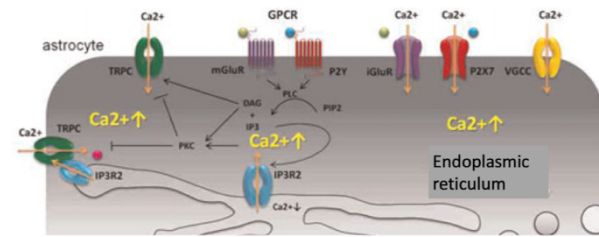
When a neuron spikes there is a concurrent increase in calcium concentration. Calcium concentrations in astrocytes is mirroring neuronal activation.

Two pathways:

- Direct calcium influx through ion channels.
- Release from the ER via GPCR and second messengers (IP₃).

The cell shows local domain increases due to its complex morphology, i.e., there are many subdomains. Calcium waves between astrocytes has also been reported:

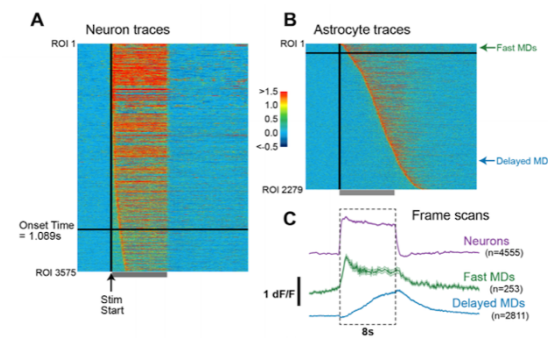
- Gap junctions.



Long-Term Two-Photon Imaging of Identical Cell Populations

Mice cortex has been exposed, genetically encoded viruses are injected to visual calcium concentrations with two-photon imaging.

Through whisker stimulation neurons shows spiking activity, sorting these neuronal traces by time they show to be pretty fast. On the contrary, astrocytes respond much slower to the whisker stimulation. However, there are neuronal subdomains that listen to the neuron activation. The correlation in time between the neuron and the astrocytes surrounding it, they show that the activation of the neuron likely elicits the activation of surrounding astrocytes.



Functional Roles of Astrocytes

- **Energy Metabolism**
- **Neurotransmission**
- **Biosynthesis**
- **Waste Recycling**
- **Local Blood Flow Regulation**

Energy Metabolism

Astrocytes are very nicely located to take up blood vessels energy substrates. They do so through GLUT1, which brings glucose into the astrocytes. Then, a cascade of metabolic processes takes place which brings to the formation of Lactate. The Lactate is then shuttled to neurons. We have to realize that glucose can also directly be delivered to neurons without the need of astrocytes to process it. Oxygen is passively diffused (it is not an active transport) through the entire tissue, with a high oxygen pressure in the vessel. All of the Lactate transport follows the chemical gradient, which implies that the astrocytes have an higher concentration of Lactate than neurons, which allows the flow.

Neurotransmission

Glutamate released from the neuron is taken up by astrocytes. If this process fails, a lack of astrocytic uptake of Glutamate leads to hyperexcitability. Also, GABA is mostly taken up by astrocytes.

- Glutamate-Glutamine Shuttle

- Synaptic glutamate is taken up through excitatory amino acid transporters (EAATs).
- Astrocytes either convert it to glutamine (via glutamine synthase, only present in the astrocytes) or intermediates of the TCA cycle.
- Glutamine is transported back to neurons.

- **GABA**
 - GABA is taken up through GABA transporters (GATs).
 - It enters the TCA cycle.

Biosynthesis

The nervous system always needs to form a lot of new stuff, which are provided in a large extent from astrocytic metabolism. In neurons, this is mainly done through Glutamate uptake.

- **Glucose:** diverted through the astrocytic PPP generates NADPH and precursors for the synthesis of nucleotides and amino acids.
- **Pyruvate:** carboxylated into the Krebs cycle intermediate oxalo-acetate (OAA), which is a precursor of multiple biosynthetic pathways in astrocytes and, through shuttling of glutamine, is also the main precursor for neuronal biosynthesis.

Waste Recycling

Astrocytic waste recycling is extremely important, tons of stuff happening to make sure that the neuron well-being is maintained. Astrocytes buffer potassium (very important), to avoid that there are excessive potassium ions which need to be cleared. K^+ ATPase pumps potassium ions into astrocytes. Another major thing is the scavenge reactive oxygen species produced in many processes in the neuron happens through astrocytes.

- **Reactive Oxygen Species (ROS)** in neurons are scavenged by ascorbate (AA) with the production of dehydroascorbic acid (DHA), which diffuses through the glucose transporters toward astrocytes to be recycled into AA, and is returned to neurons via anion channels and the SVCT2. **Glutathione (GSH)** reacts with ROS to generate glutathione disulfide (GSSG), or with xenobiotics to generate conjugated glutathione (GS-X), both of which are discarded via multidrug resistance proteins (MDR). GSH synthesized and released by astrocytes is cleaved in the interstice to cysteine, which controls the neuronal synthesis of GSH.
- Ammonia (NH_3) released by the deamidation of glutamine into glutamate leaves neurons by an unknown pathway and is captured as ammonium (NH_4), where it is recycled by glutamine synthase. K^+ released by neurons during synaptic activity enters astrocytes via K^+ channels and the Na^+/K^+ ATPase. Methylglyoxal is a side product of glycolysis, which is detoxified mostly in astrocytes by the glyoxalase system.

Oligodendrocytes

Oligodendrocytes are involved in the myelination of axons, which favors propagation speed and distance.

Myelin

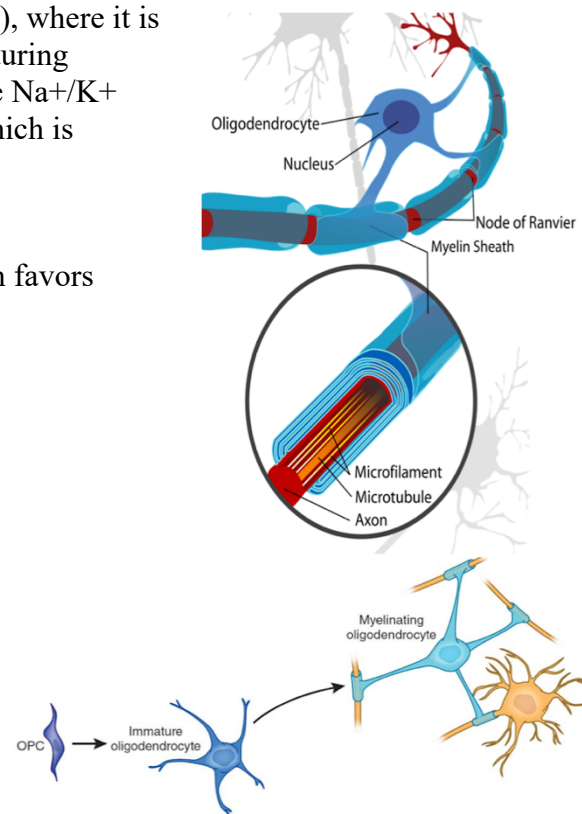
- White matter tracts.
- Schwann cells in the PNS
- Oligodendrocytes in the CNS.

Oligodendrocyte Maturation and Myelin Formation

- (1) Infiltration of oligodendrocyte precursor cells (OPCs).
- (2) Formation of immature oligos.
- (3) Immature oligos send out processes to axons.
- (4) Signals induce wrapping of membrane.

Oligodendrocytes Can Respond to Neurotransmitters

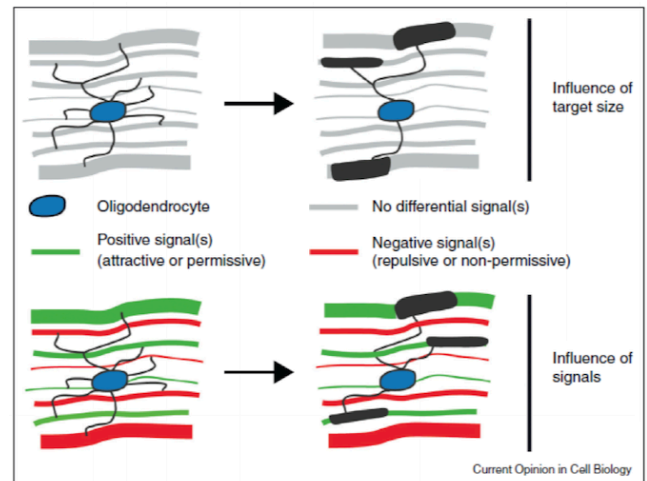
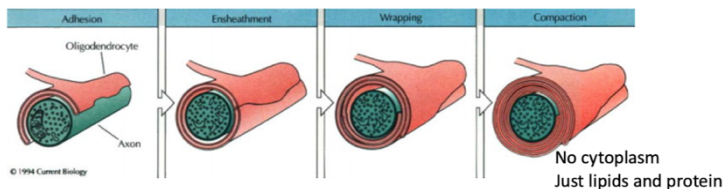
- OPCs express neurotransmitter receptors.
 - Glutamate, GABA, Acetylcholine, Dopamine, ...
 - May influence migration and proliferation.
- Mature oligos express glutamate receptors.



Immature Oligos Choose Axons Based on Size and Attractive Signals

They need to know what axons to wrap and that is probably done by attractive and repulsive signaling, which is probably performed by the neurons to attract or repel this oligos process.

Steps of Myelin Formation



Why Are Oligodendrocytes Important?

- Myelin formation is critical for increasing action potential conduction.
- But Oligodendrocytes also:
 - Provide metabolic support to axons through myelin.
 - Affect signal processing and long distance communication by modulating the degree of axonal myelination.

Oligos Provide Metabolite to Axons

- Oligos and astrocytes are connected by gap junctions (Cx): allows the flow of metabolites.
- Oligos express MCT1 (lactate transporter): knockout of this transporter induces axonal degeneration.

Myelin “Plasticity”

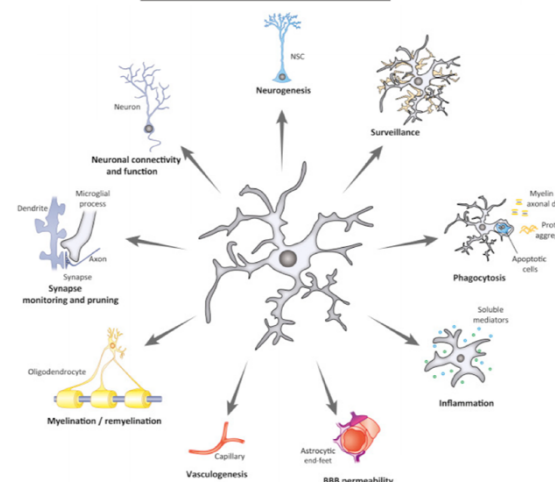
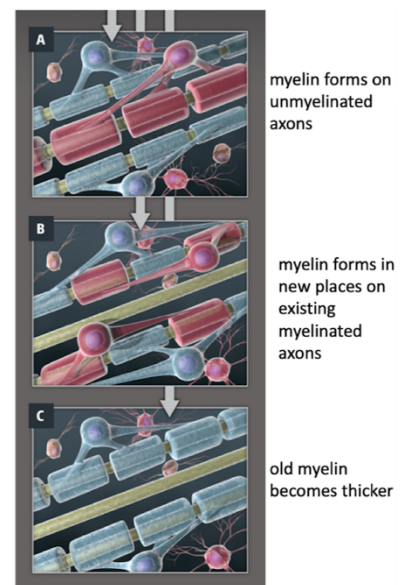
- Oligo coverage changes throughout adult life based on experience and neuronal activity.
- Neuronal activity appears to induce OPC proliferation and maturation (i.e., MORE oligos).
- This process is necessary for learning new motor tasks.

Summary Oligodendrocytes

- **Myelin Formation:** OPCs infiltrate tissue and immature oligos wrap membrane around axons.
- **Mature Myelin**
 - Oligos provide metabolic support for axons.
 - The degree of myelination may regulate information processing.
- **Myelin Plasticity**
 - Changes throughout life.
 - Necessary for learning new motor tasks.

Microglia

Microglia cells are involved in the “immune system” of the brain.



Three-Step Model of Microglial Phagocytosis

Microglia need to react to different signals to find “disturbing” elements (e.g., apoptotic cells) and they do so by reacting to chemoattraction. Then, they receive signals to eat (phagocytose) these elements and digesting them.

Microglial Phagocytosis in Health

Microglia are acting also when there is not necessary a lesion or something going “bad”, but also during pruning. There is always microglial activity also when there is not some major problem going on.

Microglial Phagocytosis in Disease

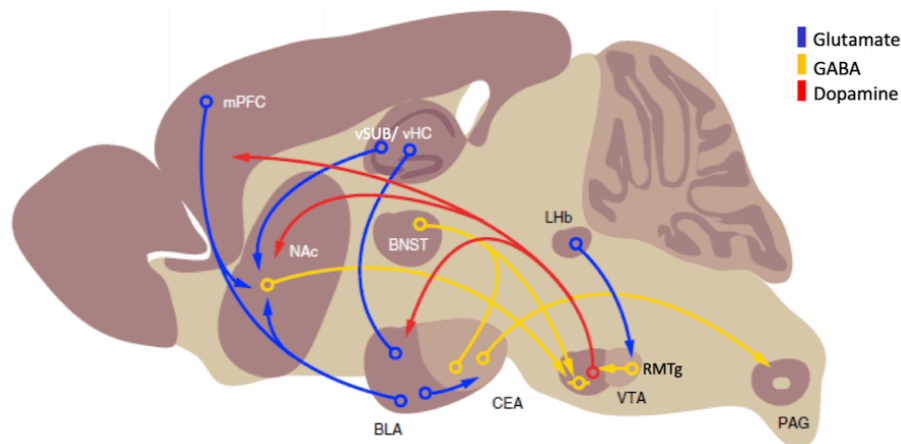
However, if there is something major going on, microglia play an important role in helping.

Cerebral Blood Vessels

The brain is very densely vascularized, mainly because it has a very high energy consumption, which is associated with high oxygen requirements. Not all areas are equally vascularized. There exist three main types of vessels: arteriole, capillary and venule. It is important to notice that blood vessels don't allow the passage of any elements if not for gas diffusion (O₂ and CO₂) and those mediated by protein channels passages. Blood flow is often use to analyze the brain activity through fMRI as a non-invasive technique.

Circuits Underlying Emotion – Lecture 10 – Christopher Pryce

Some major circuits underlying innate and learned behaviour directed at: **Aversion** and **Reward**



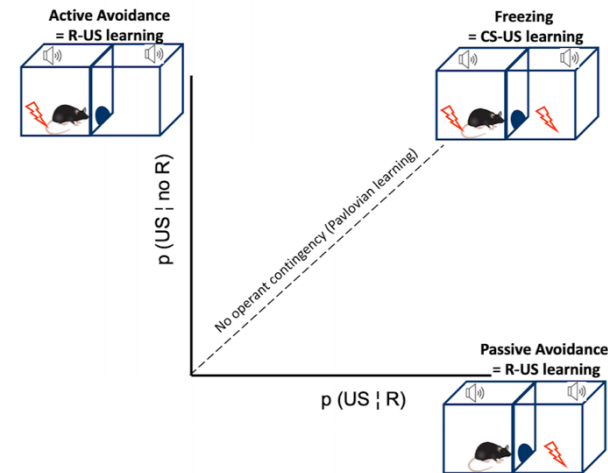
Some Major Psychological Components of Processing Aversive Stimuli

At psychological level stimuli can be either **Innate/Inborn** or **Learned**. An example of Innate stimuli is the communication of a danger through pheromones (chemosignals) which induces an **unconditioned response**, i.e., either **freeze** or **flight**. Built on genomically encoded response, a **conditioned response** can be learned.

- **Pavlovian Stimulus – Stimulus Learning**, in these experiments the animals learns to associate a conditioned stimulus (CS) (e.g., a bell ringing) to an unconditioned stimulus (US) (e.g., an electric shock). If this neutral stimulus (CS) can reliably predict the US, then such neutral stimulus will take on the emotional properties of the US. In this example, the response chosen by the mice is **freezing**.
- **Operant Learning Response – US – US – Response**, in this scenario the mice is in a conditioning where if a tone is presented the shock can occur in two situations:
 - In the first case, the shock occurs if the mice moves in another chamber of the cage and thus the mice learn to act **Passive Avoidance = R – US Learning**.

- Otherwise, if the shock occurs in the same chamber the tone appeared, the mice will move to another chamber, thus learning **Active Avoidance = R – US Learning**. In this scenario, the mice shows a goal-directed behaviour, however they have no self-awareness.

Aversion Learning: What Is Learned Determines the Emotional-Behavioral State

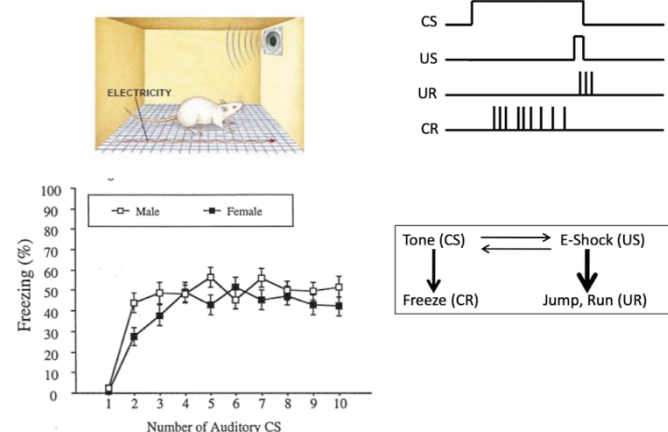


Some Major Circuits in Aversion Processing: Focus on Amygdala

People with lesioned amygdala face problems in feeling emotions. The amygdala is deeply involved in learning of aversive stimuli. The amygdala is made of several nuclei and the most important ones involved in learning aversive stimuli are: **Basolateral Complex (BLA)** and **Central Nucleus (CEA)**. The amygdala is mainly composed of **Glutamate** and **GABAergic inhibitory neurons**.

Pavlovian, Classical or Stimulus-Stimulus Conditioning: Tone-Electroshock Conditioned Freezing

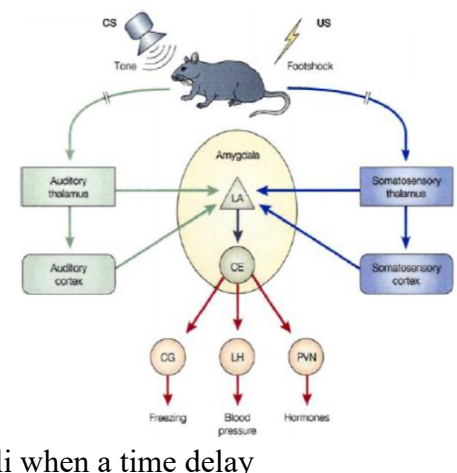
We know the importance of amygdala from these experiments: we have the animal in a chamber where a tone is played and a shock is exerted. If we present a neutral stimulus such that the end of the tone coincides with the shock, then we will quickly see not just an unconditioned response, but also a conditioned one. The conditioned stimulus takes on the emotional properties of the unconditioned one. At the first trial, the mice won't have any conditioned response, but already from the second trial the mice will learn (with a certain probability) and show a conditioned response. By increasing the salience of the unconditioned stimuli, the learning drastically increase as well. (Approx. from 50% after first trial to approx. 80% after first trial).



Amygdala Microcircuitry

Cortex-like structure comprising glutamate long-range projections neurons (80%) and GABA interneurons (e.g., parvalbumin, somatostatin) (20%).

It is an example of Hebbian Associative Learning, when pavlovian conditioning is performed both the auditory system and the somatosensory system are involved, both projecting to thalamus, then cortices and then to through glutamate neurons in amygdala. As a result of some trials, the auditory neurons stimulated by the conditioned stimulus are capable of exciting the lateral amygdala neurons that were before only stimulated by the unconditioned one. However, the amygdala is not efficient in detecting and predicting unconditioned stimuli when a time delay



occurs between the tone and the electroshock, in such cases the Hypothalamus plays a major role in predicting the unconditioned stimulus. So, the stimulus arrives to the central amygdala which in turn excites the lateral Hypothalamus (LH) that controls blood pressure, the Para-Ventricular-Nucleus (PVN) where Hormones are causing release of Cortisol are synthesized, which will then go back into the Amygdala to fixate emotional memory.

Optogenetic Investigation of Neural Circuits Underlying Emotional Behaviour

AAV transduction-expression of light-sensitive proteins (opsins) in a specific regions/cell populations allows for the experimental regulation of the firing activity of those regions/cells. Optogenetic has been widely utilized to increase understanding of Pavlovian Aversion Learning.

Pavlovian Aversion Learning: Importance of Amygdala

In Mouse, Optogenetic Inhibition (halorhodospin) of Basolateral amygdala (BLA) Glutamate neurons projecting to Central Nucleus (CeM) reduces Pavlovian (CS-US) aversion learning. Hence, they used an optic light to induce optogenetic inhibition when the unconditioned stimulus was presented. The inhibition of such pathway reduced learning, demonstrating that this pathway is important in the regulation of pavlovian aversive learning conditioning.

Some Major Circuits in Aversion Processing: Focus on Habenula and Tegmentum

In order to understand more of the behavioral responses, we have to go in the **Periaqueductal Gray (PAG)** or the **Rostromedial Tegmental Nucleus (RMTg)**. There is a projection from the central amygdala to the PAG, so the GABAergic neurons are sending long-range projections.

Some Major Circuits in Aversion Processing: Focus on PAG, LHb, RMTg

The **Periaqueductal Gray** contains GABAergic neurons targeted by GABA neurons from the central amygdala which are projecting to glutamate neurons in the PAG. When the neurons in central amygdala fires (i.e., when the lateral amygdala detects a CS or US) then they will inhibit GABA neurons in PAG, which will disinhibit Glutamate neurons in the PAG, these neurons project then to the Lateral Habenula (LHb) which excites VTA GABA interneurons and Rostromedial Tegmental Nucleus (RMTg), which is in turn capable of inhibiting the dopamine neurons in the Ventral Tegmental Area (VTA). Hence, one of the key features of aversive stimuli processing is the inhibition of dopamine release, which is one of the main neurotransmitters underlying reward behavior.

Neural Circuitry of Pavlovian Aversion Behaviour

Unconditioned response is Flight, Conditioned response is Freezing. If the neural circuitry underlying conditioned and unconditioned stimuli is the same, how is it possible that the reaction elicited is different?

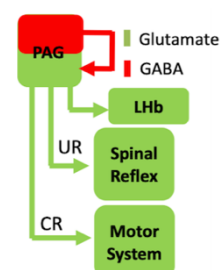
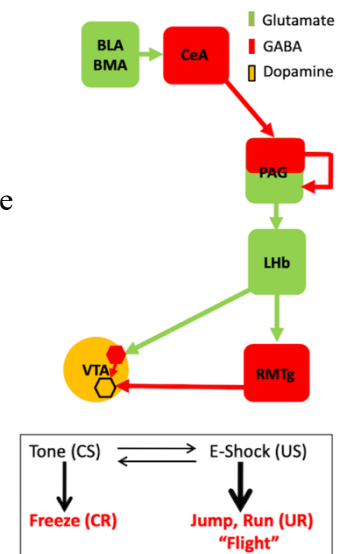
Amygdala to PAG Pathway

In Mouse, optogenetic excitation (ChR2) of dorsal Periaqueductal gray (dPAG) glutamate neurons causes:

- (1) Increased Running/Flight during dPAG neuronal firing.
- (2) Increased Freezing after dPAG neuronal firing.

It suggests 2 separate populations of neurons in dPAG:

- (1) Neurons for UR = Flight.
- (2) Neurons for CR = Freeze.



Importance of LHb/RMTg to Dopamine-Neuron Circuit to Aversion Processing

Experiment in Macaques: a point is showed on a computer screen. If the point moves in a direction, then it is predictive of a tone and a reward. If the point moves in the other direction, then there is a different tone and no reward coming. Here the absence of reward is the aversive stimulus.

What was seen is that:

- No-Reward CS results in phasic excitation of LHb neurons and phasic inhibition of VTA DA neurons.
- Reward CS results in phasic inhibition of LHb neurons and phasic excitation of VTA DA neurons.

In the case of rats:

- Aversive CS or US results in phasic excitation of RMTg GABA neurons.
- Reward CS or US results in phasic inhibition of RMTg GABA neurons.

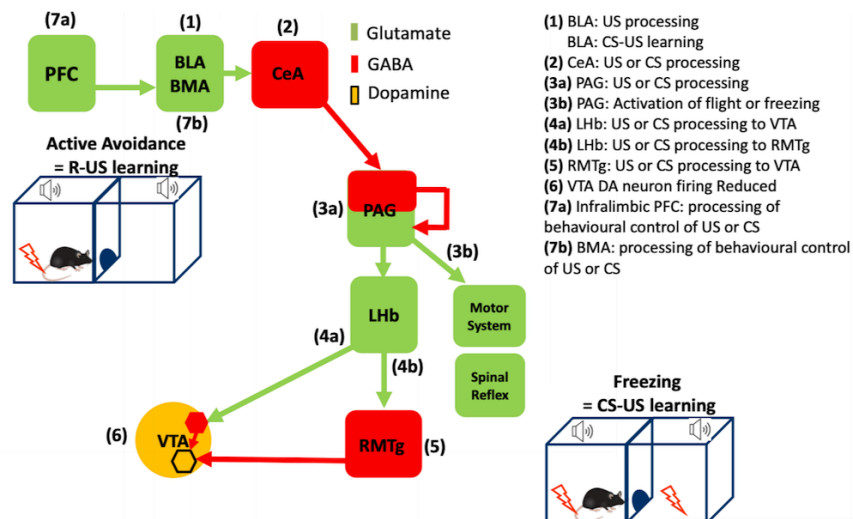
Some Major Circuits in Aversion Processing: Focus on Prefrontal Cortex

Medial Prefrontal Cortex has long-range Glutamate connections to the Amygdala Basolateral complex (BLA) and the Nucleus Accumbens. It also receives dopaminergic neurons from **VTA**. PFC is fundamental in goal-directed behaviour.

Aversion Learning: Importance of Prefrontal Cortex to Amygdala Circuit

In Mouse, Optogenetic excitation of infralimbic Prefrontal Cortex (vmPFC) glutamate neurons projecting to Basomedial amygdala (BMA) decreases freezing behaviour related to Pavlovian (CS-US) aversion learning – increased extinction learning (gradual decrease in response to a conditioned stimulus that occurs when the stimulus is presented without reinforcement) (Similar behavioural effect is observed with optogenetic excitation of BMA Glutamate neurons directly).

Overview of a Major Neurocircuit in Aversion Processing and Subsequent Behaviour



Some Major Psychological Components of Processing Reward Stimuli

The **Innate** and **Learning** responses underlying reward systems are the same of the aversive stimuli learning. However, experiments show that **Pavlovian to Operant Transfer** is possible, i.e., mice can learn to combine the two types of stimuli to reach the reward.

Pavlovian Reward Learning: Importance of VTA-NAc Dopamine Neurons

Pavlovian learning involves acquisition by a neutral stimulus of the emotional properties of an US based on their close temporal association. Dopamine neurons responding to UCS (Unconditioned Reward Stimulus): High VTA Dopamine Neuron Burst firing. Once the association is learned, dopamine neurons respond shifts towards the conditioned stimulus (CS) and only slightly fire when reward is delivered. Thus, dopamine neurons respond to “**Reward Prediction Error**”.



The Visual System – Lecture 11 – Daniel Kiper

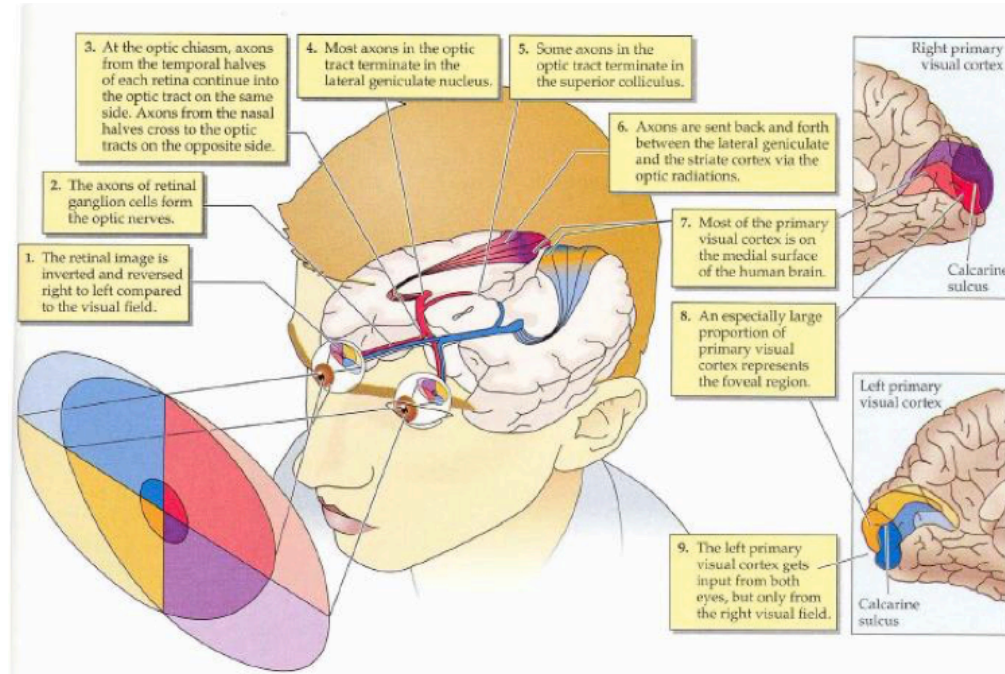
“All systems in the brain always interact. Every neuron can interact with any other neuron through no more than seven neurons.”

“Humans are “visual animals” (primates in general). Parts of visual cortex are easily accessible because they can be found at the outside/back of the cortex”

Retinocortical Pathways

The retinocortical pathways give rise to conscious vision

1. Visual field (approx. 180°). The same point is projected onto the nasal and the temporal part of the retina. The retinal image is inverted and reversed right to left compared to the visual field.
2. The axons of retinal ganglion cells form the optic nerves.
3. At the optic chiasm, axons from the temporal halves of each retina continue into the optic tract on the same side. Axons from the nasal halves cross to the optic tracts on the opposite side.

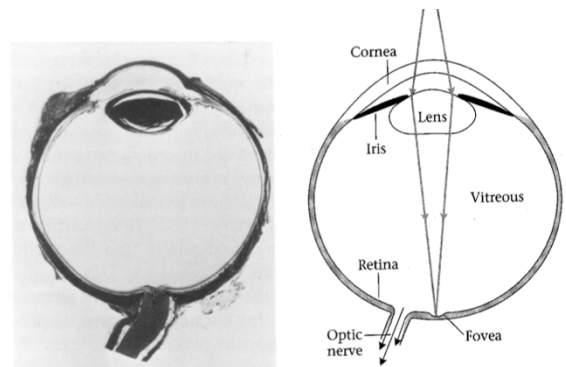


4. Most axons in the optic tract terminate in the lateral geniculate nucleus.
5. Some axons in the optic tract terminate in the superior colliculus.
6. Axons are sent back and forth between the lateral geniculate and the striate cortex via the optic radiations.
7. Most of the primary visual cortex is on the medial surface of the human brain. It is buried into the calcarine sulcus. And everything below the calcarine sulcus processes the lower quadrant of the visual field.
8. An especially large proportion of primary visual cortex represents the foveal region.
9. The left primary visual cortex gets input from both eyes, but only from the right visual field.

There is approximately a 40/50 ms delay until the visual signals/information is transmitted from the eye to the first neuron of the visual cortex.

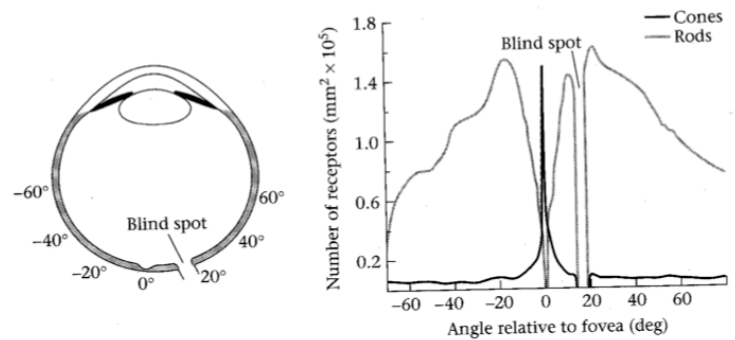
The Human Eye

The **optic nerve** represents a “blind spot” as there are no photoreceptors in its location. However, the brain compensates by “filling” the missing information. The **fovea** is involved in focused vision and allows only a few degrees of visual angle.



Distribution of Rods and Cones: a View from the Side

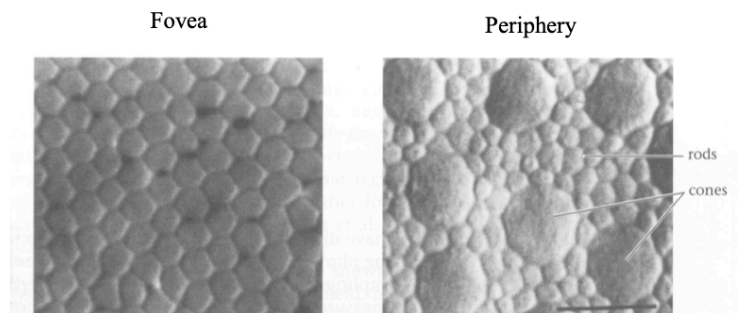
A different distribution of cones and rods is present on the retina. The **cones** work in day light (higher light levels) and are capable of color vision, while the **rods** are saturated during day time (low light levels), but they provide un-colored night vision. There exist 3 types of cones (short-wavelength sensitive, middle-wavelength sensitive and long-wavelength sensitive) and only 1 type of rods.



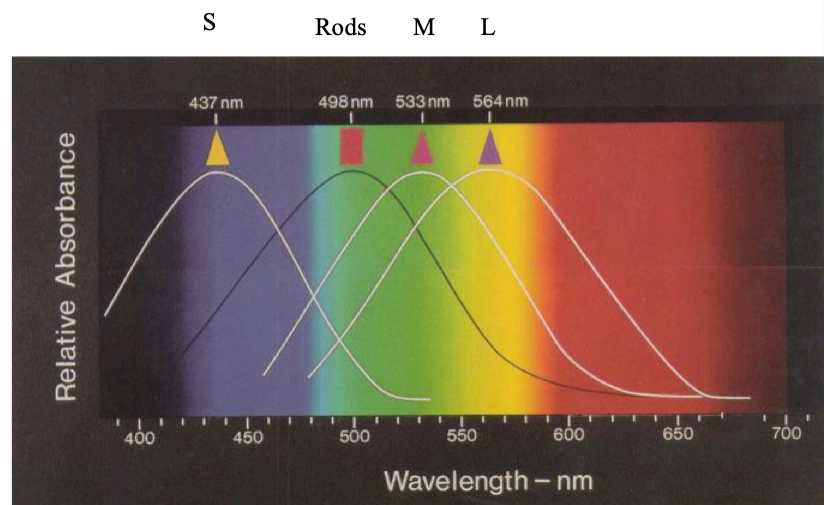
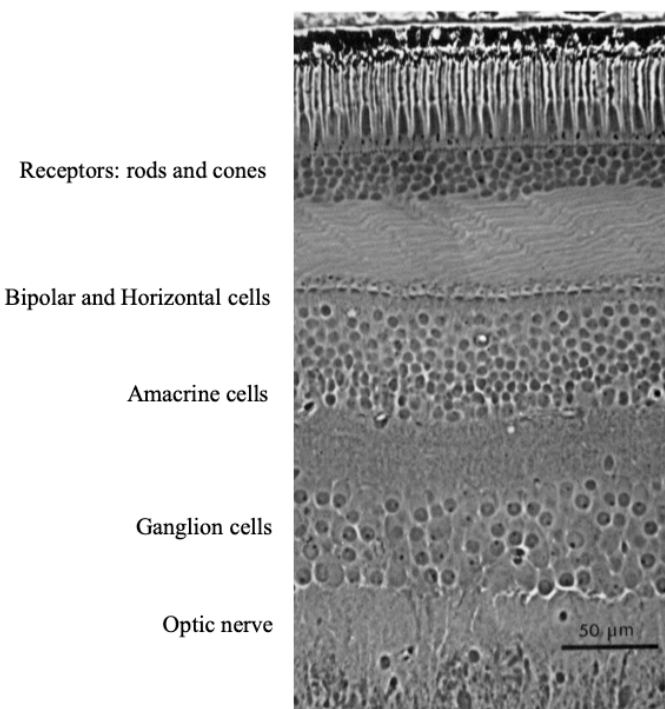
The figure shows the distribution of rods and cones in the retina. We can notice that the fovea is rod-free and has a very high density of cones. The density of cones falls off rapidly to a constant level at about 10-15 degrees from the fovea. Notice the blind spot which has no receptors. At about 15-20 degrees from the fovea, the density of the rods reaches a maximum.

Distribution of Rods and Cones: a View from the Front

As it can be seen from the picture, the fovea presents only cones, while in the periphery both cones and rods can be observed. In particular, cones density decreases with distance from the fovea.



Sensitivity for Wavelength of the 3 Types of Cones



A Section Through the Human Retina

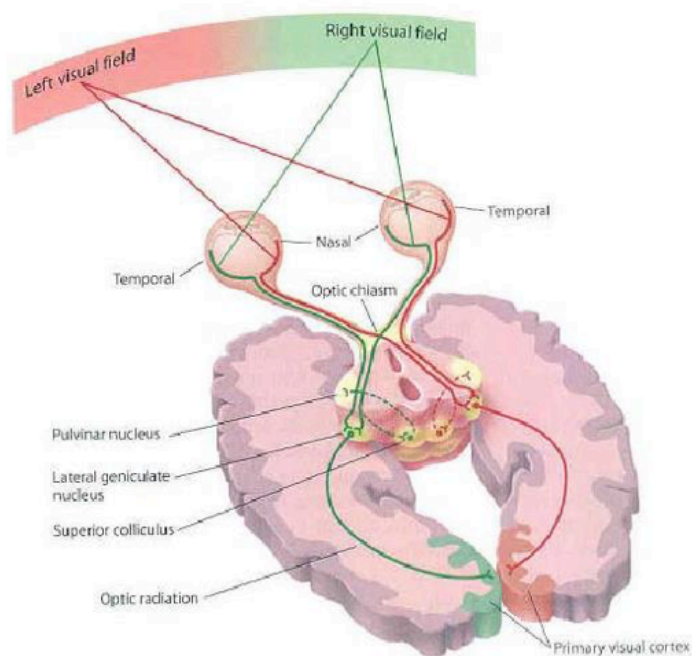
Horizontal cells modulate the output of photoreceptors and play many roles in early visual processing contributing to contrast enhancement, color opponency, and the generation of center-surround receptive fields in cones. In the human retina there are approx. 1 million ganglion cells, which collect information about the visual world from bipolar and amacrine cells (retinal interneurons). There are many types of amacrine cells that are distinguished based on the way they

respond to visual inputs. Then the layer of photoreceptors responds to changes in membrane potential. Indeed, when the membrane changes potential, photoreceptors release neurotransmitters (they don't communicate through APs). Since they need nutrients, they are located closely to blood vessels, i.e., at the back of the eye in humans.

Basic Retinal Circuitry

The eye already processes the visual information before it sends it to the brain.

The Visual Pathways



Receptor terminals (RT)

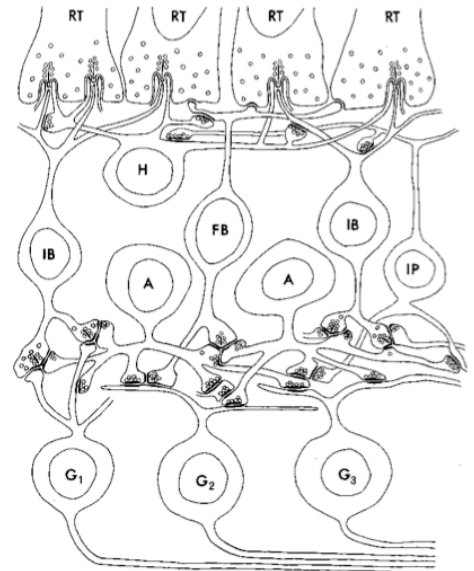
Horizontal cells (H)

Bipolar cells (B)

Amacrine cells (A)

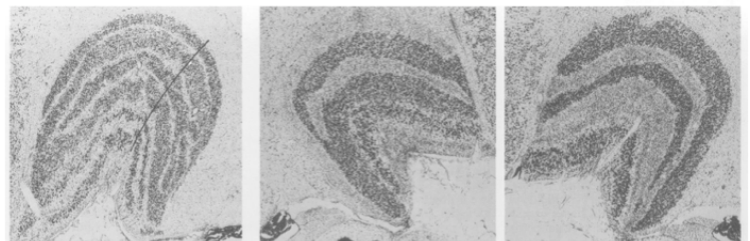
Ganglion cells (G)

Optic nerve



Within the visual pathways plays an important role the **Lateral Geniculate Nucleus (LGN)**, it belongs to the thalamus and it is composed of approx. a million of nerve nuclei. These cells respond more or less the same way ganglion cells do. Furthermore, each LGN receives signals from both eyes.

The Lateral Geniculate Nucleus (LGN)

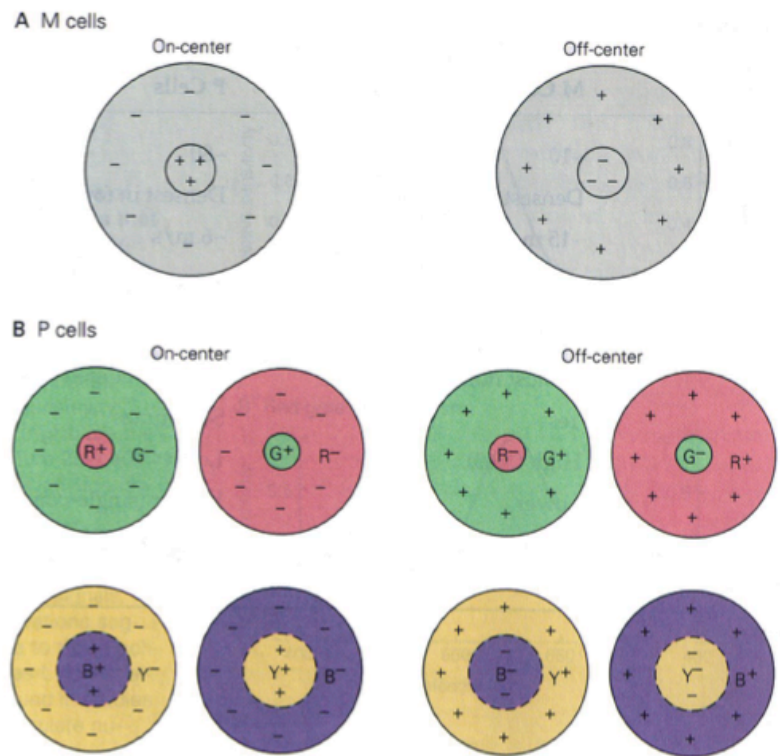


From this cross-section frame of LGN in a primate, it is possible to notice that it has a layer structure, where each layer receives input from one eye (three layers per eye), hence each layer is “monocular”. The two bottom layers contain anatomically big cells: Magnocellular, Parvocellular and Koniocellular. M cells do not care about the color, but rather about light intensity differences. They are extremely contrast sensitive. P cells are less contrast sensitive, but they are sensitive to color and are more capable of discriminating fine details than their M counterparts. Finally, K cells deal with short wavelength information. Hence, there is an anatomical segregation according to the information treated.

Each cell in the visual pathway responds to just stuff happening in the receptive field of the cell. Each cell doesn't receive information from all the photoreceptors. It is important to notice that the receptive fields of ganglion cells are round.

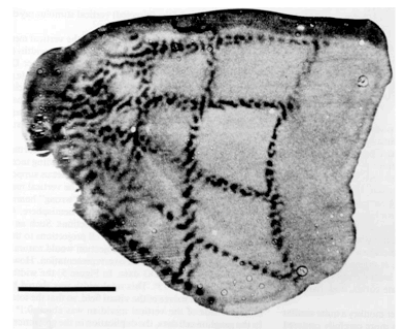
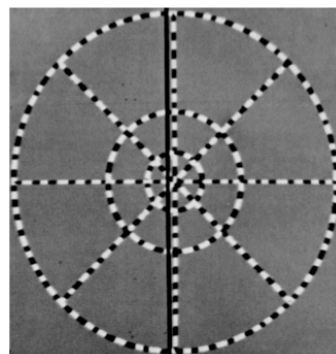
Receptive Fields of Ganglion Cells and LGN Neurons

Approximately 50% of Ganglion cells have an on-center, where the cell strongly responds to an increase of light intensity. While the other 50% shows off-center, where the cell strongly responds to a decrease in light intensity. This type of receptive field is great to detect contrast. The study of this structure provided insights on the process of adaption of the retina to the overall light level. While M-cells and Ganglion cells show very similar receptive fields, P-cells have round receptive fields that discriminate between middle and long wavelengths. Furthermore, the size of the centers of the receptive fields changes depending on the location of the cell in the retina. Finally, K-cells show again round receptive fields which distinguish among short wavelengths.



Cortical Representation Measured with 2-Deoxy-Glucose

Part of a monkey left hemisphere cortex. The black regions show regions of the brain that have been activated by the visual input. In particular, it demonstrates the **retinotopic visualization**, i.e., a faithful projection of the image. Furthermore, we can notice the **cortical magnification**, i.e., in the cortex, the center of vision is “amplified” and a great percentage of brain tissue is dedicated to the center of vision. (2% of the visual field (the central 10deg) occupy 50% of V1).

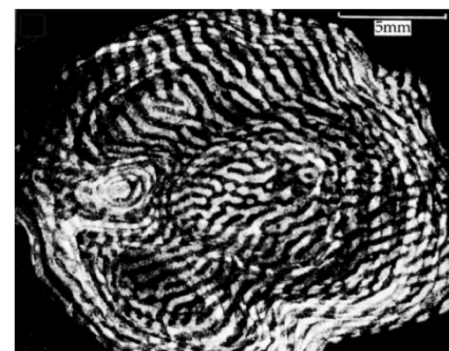


Hubel and Wiesel, circa 1969

They were performing an experiment, studying the receptive fields of cells located in the primary visual cortex of different animals. These two researchers understood what the primary visual cortex is doing. Current vision papers often still cite them and some of the questions they posed are still unanswered. The visual system is thanks to them one of the best understood system of the brain.

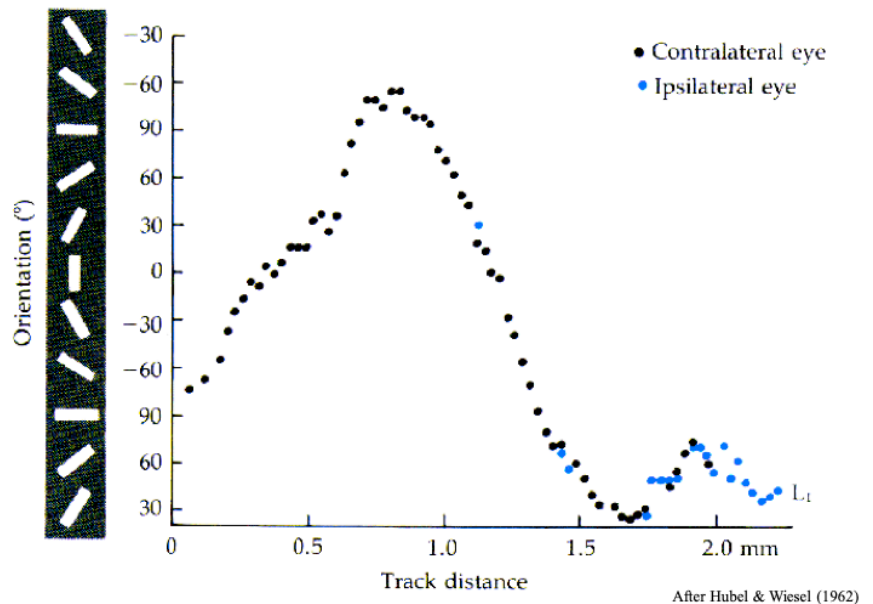
Ocular Dominance Columns Measured with Radioactive Proline

The picture shows a piece of V1, black bands respond to the left eye and white to the right eye. Contrary to what's happening in the LGN, here the vast majority of cells in the primary visual cortex are binocular, i.e., each cell receives inputs from both sides. For most cells one eye is more important than the other (**ocular dominance**). This was one of Hubel & Wiesel discoveries.



The second thing they discovered is that cells in the primary visual cortex are elongated, they are not round anymore. Which means that the best way to excite one of these cells is to use lines of lights rather than round dots. Individual cells are line detectors. And they also discovered that each cell has a preference over the orientation of the line. Each cell strongly responds to lines of a specific orientation (**orientation selectivity**). That's important because it gives real insights into what the visual cortex does, because it "looks in the image to see where there are edges and lines". Then they analyzed the orientation selectivity through the following experiment:

Each point represents the preferred orientation of a cell in the visual cortex as they are encountered by inserting an electrode in the visual cortex. It is peculiar that the preferred orientation changes smoothly as you go deeper, they realized that it depends on the oblique direction of penetration with the electrode. So, they moved from one "orientation column" to the other.

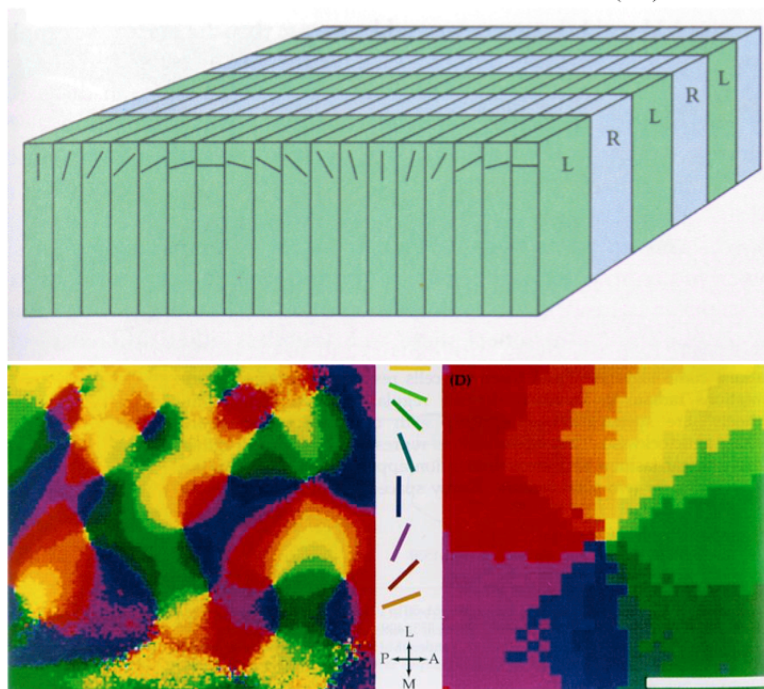
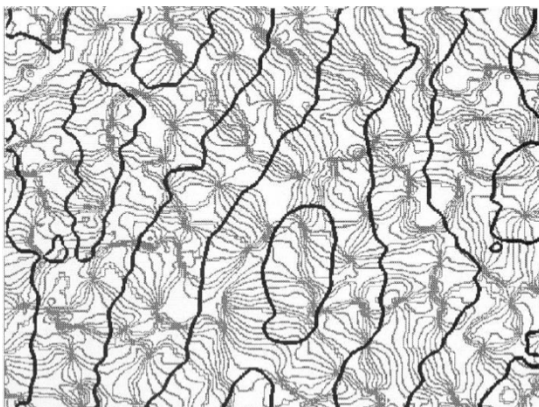


The "ice-cube" Model of Hubel and Wiesel

This is the proposal they made about the organization of the visual cortex. Within each band the cells prefer a specific orientation. In particular, each set of binocular bands analyze a specific part of the visual field. This organization is valid for humans and primates, but it's not true for all animals, e.g., rodents, indeed they do not present orientation columns.

Orientation Columns Measured with Optical Imaging

Each color represents a preference for a different orientation. This is a more accurate representation of the orientation columns.



This represents the relation between ocular dominance (thick black lines) columns and orientation columns (grey lines). It seems as intersecting with perpendicular lines.

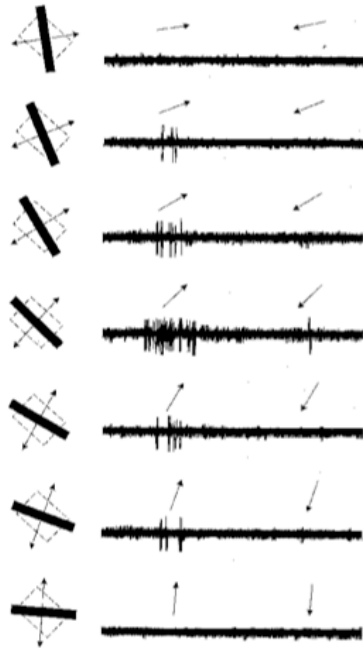
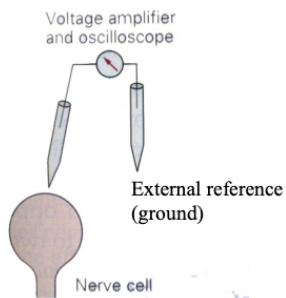
Receptive Fields of LGN and V1 Simple Cells

Taken from Hubel & Wiesel, we can see two examples of LGN receptive fields. Crosses are the on-centers, surrounded by off triangles. While LGN receptive fields are round. In V1, the on and off regions are elongated as shown in the picture.



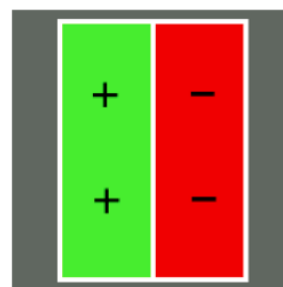
Extracellular Recordings

Selectivity for Stimulus Orientation and Direction in Area V1

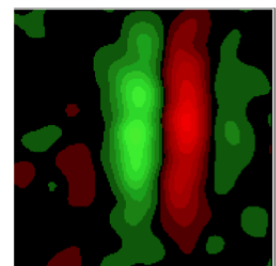


Receptive Field of a Simple Cell

The following pictures show the schematic example of on/off regions measured through reverse correlation, which allows to map spatial/temporal characteristics.



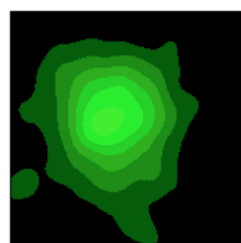
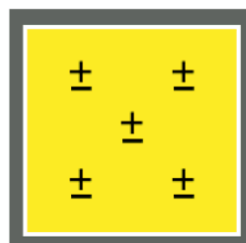
Schematic of the receptive field



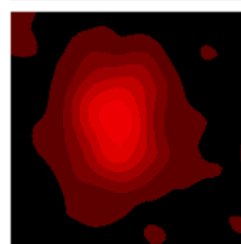
Responses to white dots - responses to black dots

Receptive Field of a Complex Cell

Sometimes cells have overlapping on and off regions, in such a case they are called **complex cells**. If you look at the receptive field, it's difficult to tell which preferred orientation they have, even though they are strongly orientation selective. The receptive field of complex cell is the result of summation and integration of the receptive fields of many input simple cells.



Responses to white dots



Responses to black dots

Cortical Visual Areas of The Macaque Monkey

Schematic picture showing the right hemisphere of a macaque, with V1 represented by the big red area on the back (top left sketch), while at the bottom we can see the left hemisphere.

A lot of our cortex is dedicated to analyze visual signals. It's called Primary Visual Cortex because that's where most of the visual inputs end up first.

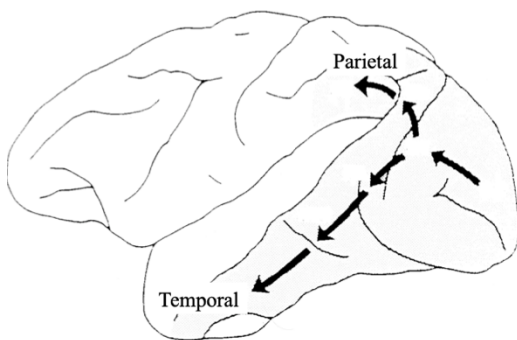
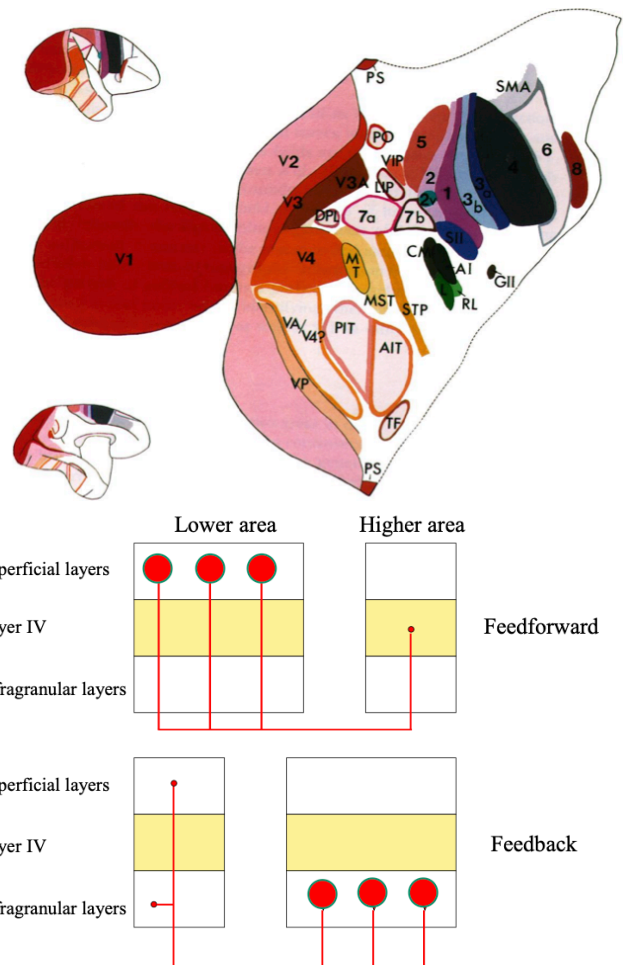
Just like monkeys, also Humans have many different visual areas

Lots of signals travel from the superficial layers of one region to the layer 4 of the next region, this sort of connection is called **feedforward** (it travels under infragranular layers).

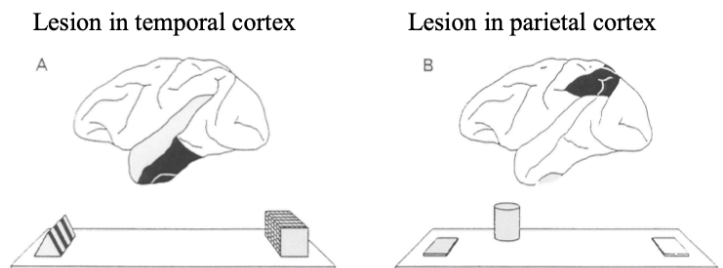
Other signals travel from the infragranular layers of one region to the superficial and infragranular layers of a different region, this is called a **Feedback**.

Two Cortical Functional Streams

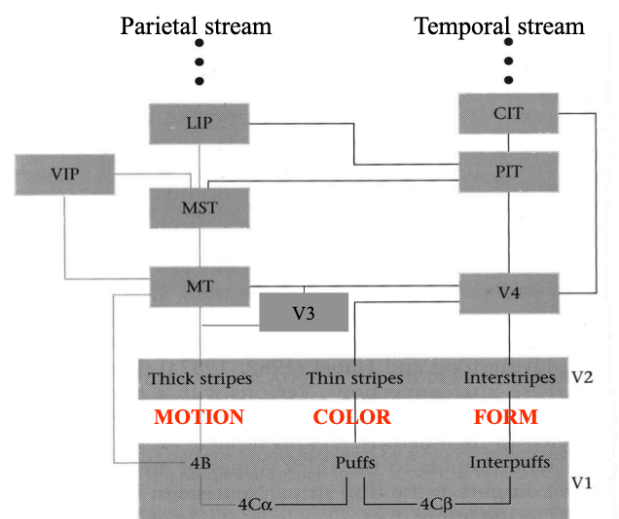
These two pathways are doing different things and it has been found through lesion studies.



Effects of Lesions in Two Cortical Regions



Monkeys with parietal cortex lesions were not able to perform tasks associated with object localization, but they were capable of object identification. On the contrary, monkeys with temporal cortex lesions were still capable of object localization but were defecting of object recognition skills. Hence, the conclusion that temporal and parietal cortices are both involved in processing visual information, but they have distinct roles. The **temporal cortex** is primarily involved in processing information about the **objects and scenes that we see**, while the **parietal cortex** is involved in **spatial processing**, including spatial attention and orientation.



The Auditory System – Lecture 12 – Stefan Elmer

Prologue: The Fascination of Hearing

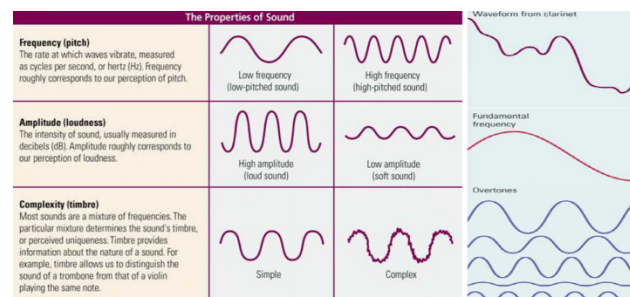
The vibration of an object (e.g., tuning fork) causes changes in air pressure. Hence, acoustic sound waves can be described as fluctuations in air pressure due to compression and rarefaction of air molecules. The auditory system transforms sound waves into distinct patterns of neural activity, which are then integrated with information from other senses (and cognition) to guide behavior and promote communication. The auditory system is not only essential for speech, but also for music, emotion recognition, sound localization, etc.

- Frequency range of hearing across species.
- Sound Localization:
 - Having two ears (instead of one) is important for sound localization.
 - Due to the perception of interaural time (ITD) and level (ILD) differences between the two ears we are able to localize sound sources in the environment.
 - Sound localization in the horizontal plane (azimuth) is based on ITD and ILD, while sound localization in the vertical plane is based on spectral filtering by ears, head and shoulders.
- Hearing enables:
 - To perceive and identify object from far away, vision doesn't.
 - To perceive sounds from all around the body with an angle of 360 degrees (vision only 180 degrees).
 - To map the sound in space and to identify the spatial location of objects.
 - To recognize emotional states (e.g., speech prosody, sad, happy, fear, etc.)
 - Complex human faculties like music and language.

However, there is also a “dark side” of hearing such as hearing loss, tinnitus, amusia, etc.

The Basic Building Blocks of Acoustic Signals: Air Pressure and Waves

- Soundwave as variation in air pressure.
- Complex sound waveform: Each complex signal can be decomposed into sine and cosine waves.
- Each oscillation can be described in terms of amplitude and frequency. Frequency (Hz) = number of periods (cycles) per second.

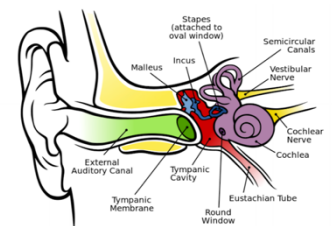


Sound Processing Along the Hierarchy of the Auditory System

- **Peripheral Auditory System:** Outer, Middle and Inner Ear.
- **Central Auditory System:** Auditory Brainstem and Cortex.

The Outer Ear

The outer ear consists of the **pinna**, the **ear canal** and the **tympanic membrane**. The funnel-shaped pinna “collects” air pressure fluctuations from the environment and directs them through the ear canal to the tympanic membrane (eardrum), which constitutes the transition to the middle ear. The tympanic membrane vibrates in response to sounds (air pressure changes), and this vibration is transmitted to three ossicles situated in the middle ear (**malleus**, **incus** and **stapes**). The length and shape of the ear canal plays an important role in sound amplification.



- **Outer ear:** pinna, ear canal and tympanic membrane (eardrum)
- **Middle ear:** malleus, incus, stapes (ossicles)
- **Inner ear:** oval window, cochlea, Corti-organ and round window

The Middle Ear

The middle ear is separated from the outer ear by the tympanic membrane (eardrum), and is responsible for the conversion of air pressure fluctuations into mechanical energy. The transmission of sounds from the outer to the middle ear takes place through the deflection of the tympanic

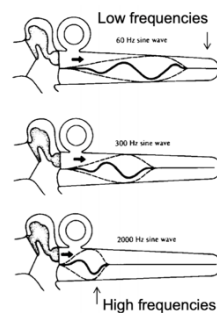
membrane. The deflection of the tympanic membrane results in vibrations of the three ossicles (malleus, incus and stapes), which in turn convey energy to the fluid-filled cochlea in the inner ear.

The Inner Ear: Cochlea

The cochlea is a **fluid-filled tube** which is divided into two major compartments by the **basilar membrane**, namely the **scala vestibuli** and **tympani**. The movement of the ossicles transfers the mechanical energy to the oval window of the cochlea, which sets the fluid in motion, from the oval to the round window (pressure compensation). The two liquid-filled tubes that run along the cochlea are separated by the basilar membrane. The basilar membrane moves up and down in response to incoming sound waves, which are converted into traveling waves on the basilar membrane. The Corti organ, which is situated on the basilar membrane, is responsible for the transduction of auditory signals into action potentials. The location-specific deflection of hair cells in the Corti organ activated calcium and potassium channels which lead to action potentials.

The Inner Ear: Tonotopic Organization of the Cochlea

Basilar membrane vibration to sinusoids varies with frequency because its mechanical properties vary along its length. The basilar membrane is wider at the apex (most responsive to low frequencies) and stiffer at the base (most responsive to high frequencies). The mechanical properties of the basilar membrane are the initial source of tonotopic organization (frequency coding).

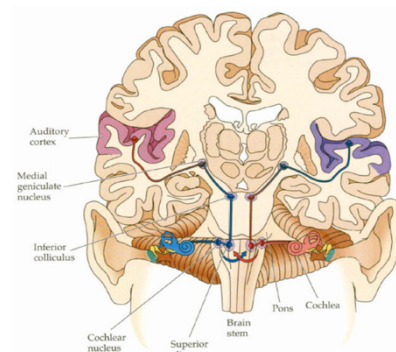


Recap

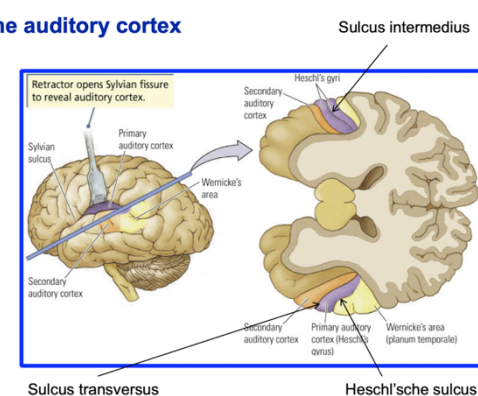
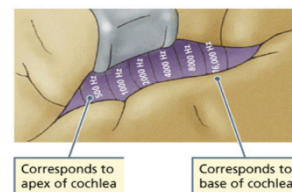
The pinna catches sound waves and deflects them into the external ear canal. Waves are amplified and directed to the eardrum, causing it to vibrate, which in turn vibrates ossicles. Ossicles amplify and convey vibrations to the oval window. Vibration of oval window sends waves through cochlear fluid causing the basilar and tectorial membranes to bend, which in turn cause cilia of outer hair cells, embedded in the tectorial membrane, to bend. This bending generates neural activity in hair cells.

Brainstem and Central Auditory Pathway

- (1) **Cochlear Nucleus** (start sound feature processing, frequency and sound onset/offset).
- (2) **Superior Olfives** (Interaural Intensity Differences).
- (3) **Inferior Colliculi** (Somatosensory connections, multisensory).
- (4) **Medial Geniculate** (Integration and connecting to A1).
- (5) **Auditory Cortex** (A1).



The auditory cortex



Mapping of Elementary Auditory Functions in the Cortex

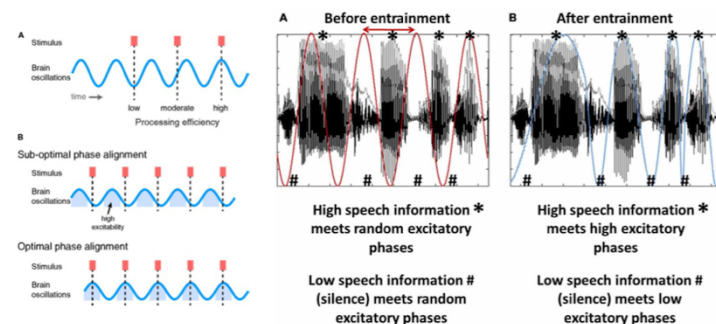
- Spectral and Temporal Auditory Processing:

- Spectral processing involves the analysis of the frequency content of a sound, which is related to the perception of pitch.
- Temporal processing involves the analysis of the timing and sequencing of sound events, which is related to the perception of rhythm, tempo and sound onset/offset.
- The left auditory cortex favors the extraction of information from short temporal integration windows, whereas the right counterpart primarily relies on long integration windows.

- **Intensity Coding**
 - It refers to the way that the auditory system represents the loudness or amplitude of a sound. Neurons respond to different levels of sound intensity, with some neurons specifically sensitive to low-level sounds and others responsive to high-level sounds. The brain uses this information to construct a representation of the sound intensity and to determine the loudness of the sound.
- **Timbre and Complexity Coding**
- **Auditory Object Recognition and Spatial Location (“What” and “Where” Streams)**
 - “What” and “Where” streams in the auditory cortical system of primates (and humans). Similar to “what” and “where” streams in the visual system.
- **Motor Perception**
 - Moving vs Stationary auditory objects.

Speech Processing and Neural Oscillations

- Speech processing is mediated by neural tracking, which refers to the alignment of neural oscillations with the speech signal.
- High excitability phases of neurons align with information in speech (e.g., syllables, words, regularities, etc.).
- Neural oscillations track different linguistic units of the speech signal. Neural tracking of speech takes place at different time scales. Different methods, for example cross-correlation between the envelope of the speech signal and the EEG signal, phase coherence, etc.



Speech Segmentation

Speech is a continuous acoustic signal without reliable gaps in between words or linguistic entities. The challenge is how to recognize word boundaries when no lexicon is available for word recognition. Once the word forms have been recognized, meaning assignment can be achieved through associative and contextual learning.

- **Statistical Learning:** Computation of transitional probabilities between adjacent syllables.
- **Prosodic Bootstrapping:** Detection of word boundaries based on rhythm, intonation or lexical stress cues.

The Vestibular System: Rotational Movements and Linear Accelerations

Functions of the Vestibular System: register body motions, postural control (Vestibulo-spinal tract), maintain upright posture, measure gravity field, keep eyes still when head moves.

Two organs in the inner ear (labyrinth):

- Semicircular tubes filled with fluid:
 - Oriented in three planes, one for each dimension in which we move the head (pitch, roll, yaw). Responsible for the coding of **rotational movements**.
- Otolith organs containing hair cells, and consisting of utricle and saccule:
 - Responsible for the coding of **linear accelerations**.
 - Infer body position in relation to gravity.
 - Detect changes in the direction and speed of movements.

Conclusions

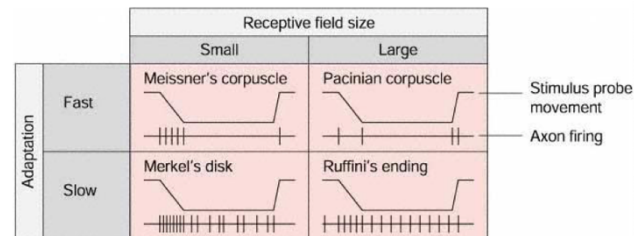
The auditory system enables to perceive air pressure fluctuations (frequency and amplitude) through complex processing steps in the outer, middle and inner ear. The cochlea is characterized by an excellent spectral (tonotopy) and temporal resolution. The neural codes are transmitted from the cochlea to the cortex via brainstem and central auditory system. Several specialized cortical

modules contribute to different aspects of hearing (intensity, timbre and complexity coding, auditory object identification, speech and language processing, etc.). The vestibular system is fundamentally involved in balance and posture processing.

Somatosensory and Motor Systems – Lecture 13 – Fritjof Helmchen

Sensory Receptors

- Vision, Smell, Taste, Touch, Thermal Senses, Pain, Hearing, Balance, Proprioception.
- The Somatosensory encapsulated receptors are 4:
 - **Meissner Corpuscle**
 - **Merkel-Neurite Complex**
 - **Ruffini Corpuscle**
 - **Pacinian Corpuscle**



Some of these receptors quickly adapt, while others don't. Fibers are classified as either:

- **Rapidly Adapting (RAs)**
- **Slowly Adapting (SAs)**
- Also in terms of the size of their **Receptive Field** (The size of the area on the skin from which they can be activated) (it is also related to the position of the receptor, indeed superficial receptors tend to have smaller RF than deeper ones).

RAs respond only at the beginning and end of sustained displacements (i.e., to transients) but respond well to higher frequency vibrations. Two types:

- **RA I: Meissner Corpuscles** (10 – 200 Hz) (small RF)
- **RA II (PC): Pacinian Corpuscles** (70 – 1000 Hz) (large RF)

SAs respond throughout sustained displacements of the skin, and are thus suited to coding the duration and magnitude of mechanical stimuli. Two types:

- **SA I: Merkel Receptors/Disks** (small RF)
- **SA II: Ruffini Endings** (large RF).

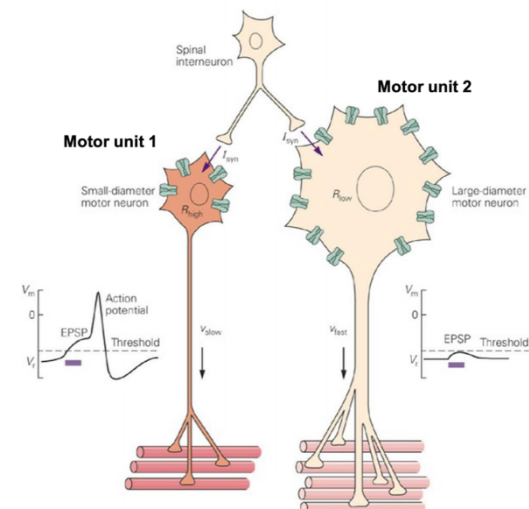
Spinal Cord Circuitry

Motor Unit 1

- Small diameter motor neuron.
- High input resistance.
- Needs small drive from spinal interneuron (and thus M1) to drive an AP in the postsynaptic neuron.

Motor Unit 2

- Large diameter motor neuron.
- Low input resistance.
- Needs large drive from spinal interneuron (and thus M1) to drive an AP in the postsynaptic neuron.



Gray Matter

Gray matter can be found in the inner part of the spinal cord. It presents a localized representation of the different limbs in the spinal cord.

White Matter

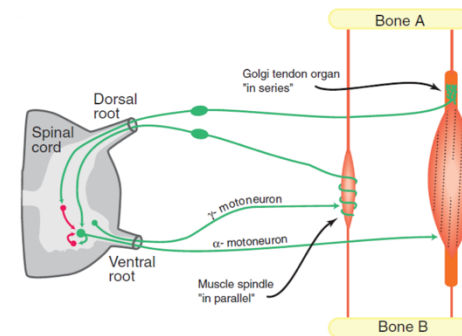
It presents two different pathways:

- **Motor and Descending (efferent) Pathways**
 - Pyramidal Tracts
 - Extrapyramidal Tracts

- **Sensory and Ascending (afferent) Pathways**
 - Dorsal Column Medial Lemniscus System
 - Spinocerebellar Tracts
 - Anterolateral System

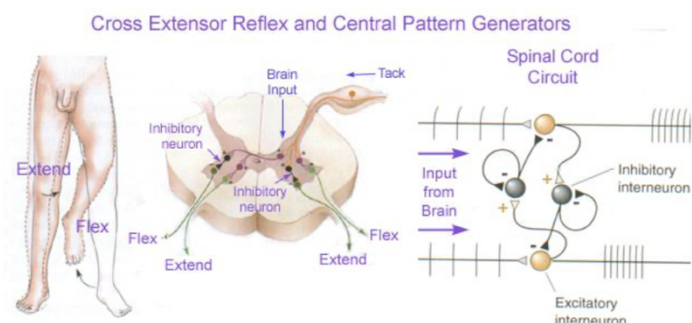
Spinal Cord Reflex ARC

For reflexes, there is a loop directly within the spinal cord (does not go all the way up to the CNS). The dorsal root of the spinal cord receives sensory signals from Golgi tendons (muscle stretch sensor) and directly projects to the ventral root, which through gamma and alpha motoneurons induce muscle movements.



Central Pattern Generator (CPG)

This is some kind of circuitry between the right and left side of the spinal cord which induces the ability to do some movements that involve both sides of the body (e.g., walking or swimming). Flexing and extending muscles alternatively on both sides through excitation and inhibition via interneurons.



Dermatomes

Dermatomes are areas of skin that connect to a specific nerve root of the spine. There are 31 pairs of spinal nerves, forming nerve roots that branch from the spinal cord. Spinal nerves are named and grouped by the region of the spine that they are associated with (cervical nerves, thoracic nerves, lumbar nerves, sacral nerves, coccygeal nerves). There is some redundancy transmitted to the dorsal root of the spinal cord. There is essentially some **re-bundling** of skin nerves together and they are overlapping. Nerve fibers of the skin are rebundled and mixed together and sent to spinal cord. Because if one of the dorsal roots is damaged (accident/tumor), then you have redundancy, which allow to avoid losing all the sensation in that area.

Modality Segregation

It is the basic principle of organization of the somatosensory system. Information from each class of receptors reaches a different group of neurons in the CNS and these neurons project to higher levels along segregated “parallel” pathways. This segregation begins with the place of termination of different classes of afferent axon in the spinal cord. It continues with two major ascending pathways:

- **The Dorsal Column – Medial Lemniscal Pathway** (Touch information).
- **The Spino – Thalamic Pathway** (Pain & Temperature information).

The Dorsal Column – Medial Lemniscal Pathway

- The ascending branches of **Aβ axons** (conveying discriminative touch information, i.e., carrying mechanoreceptive information) ascend in the dorsal columns (the **gracile and cuneate fasciculi**), and synapse on cells in the **dorsal column nuclei (DCN)** in the medulla (the **gracile and cuneate nuclei**, respectively).
- The axons of DCN cells cross the midline and ascend in the **medial lemniscus** to the **lateral division of the ventro-posterior nucleus (VPL)** of the thalamus.
- **VPL** cells in turn project to the primary somatosensory cortex (**SI**).

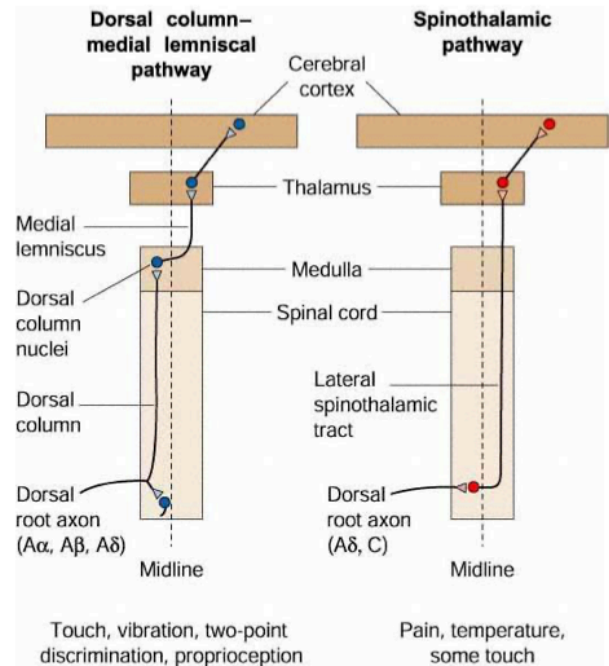
Things to Note About Dorsal Column – Medial Lemniscal Pathway

- The **Gracile Fasciculus** extends the entire length of the spinal cord; it and the **Gracile Nucleus** contain a representation of the feet, legs, and lower trunk.

- The **Cuneate Fasciculus** begins at the cervical level; it and the **Cuneate Nucleus** contain a representation of the hands, arms, and upper trunk.
- The entire system is topographically organized (i.e., adjacent parts of the body surface are represented by adjacent neurons – **Somatotopy**).
- The decussation (crossing over) of the medial lemnisci results in a representation of the **contralateral** body surface on each side of the brain at levels above the DCN.

The Spino – Thalamic Pathway

- It represents the second-major pathway.
- Small-diameter myelinated and unmyelinated axons (**A δ** (first pain) and **C** (second pain) fibers serving temperature sensitivity and nociception) terminate in the spinal cord itself.
- The axons of the spinal neurons then cross the midline and ascend as **the anterolateral system**.
- Most of these fibers (constituting the **spino-thalamic system**) terminate in VPL and in the intralaminar and posterior groups of thalamic nuclei.
- Other ascending fibers terminate in the reticular formation (the **spino-reticular system**) and in the midbrain.
- The VPL neurons receiving spino-thalamic input are segregated from those receiving medial lemniscal input and project to both primary and secondary somatosensory cortex (**SI** and **SII**).

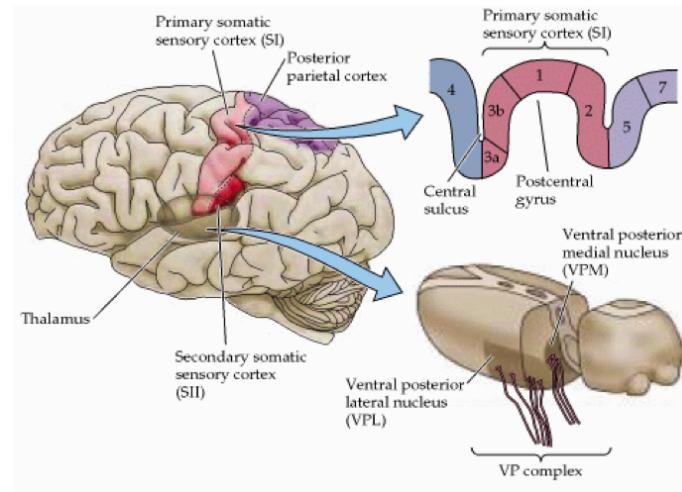


The Trigeminal System

- It is dedicated to the brain and the neck. Conveys somatosensory input from the face.
- Large-diameter myelinated axons of the trigeminal ganglion conveying discriminative touch information terminate in the principal trigeminal nucleus.
- The axons of these cells then cross the midline, join the medial lemniscus, and terminate in the **medial division of the Ventro-Posterior Nucleus (VPM)**.
- Small diameter lightly-myelinated and unmyelinated axons of the trigeminal ganglion conveying thermal and nociceptor information descend in the spinal trigeminal tract and terminate in the spinal trigeminal nucleus.
- The axons of these cells then project to VPM and to the posterior and intralaminar thalamic nuclei (i.e., rather like the anterolateral system).
- Hence, we have a separation again of mechanoreceptors from thermoreceptors.

The Somatosensory Thalamus

- The **ventrobasal** complex of the thalamus has the two major divisions previously described:
 - **VPL** (somatosensory information from the body)
 - **VPM** (somatosensory information from the face)
- Both are somatotopically organized.
- Thalamic neurons have adaption properties (SA vs RA) like those of peripheral neurons, but the RFs are larger than those of dorsal root ganglion cells and are commonly concentric, with a central excitatory area and a surrounding inhibitory area.



Thalamo-Cortical circuit

It is a neural pathway that connects the thalamus, a relay station in the brain, with the cortex. In this circuit, sensory information from the body is transmitted to the thalamus, which processes and filters the information and then sends it to the relevant regions of the cortex for further processing. The cortex, in turn, sends feedback to the thalamus to regulate the flow of incoming information. This loop allows for the integration of sensory information and the generation of conscious perception and action.

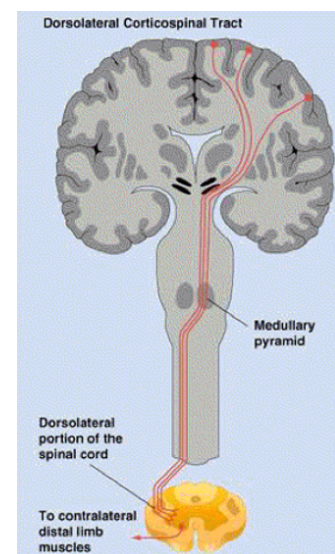
Cortical Association Areas

These areas represent the high-level processing in the cortex, which take care of communicating between sensory cortex processing and motor processing. The corpus callosum connects the two brain hemispheres integrating both parts of the body. The association areas can be found in the **posterior parietal cortex**, **anterior parietal cortex**, **temporal association cortex** etc... A major role in the process of integrating multisensory information is played by interneurons.

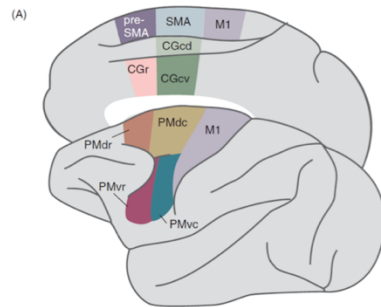
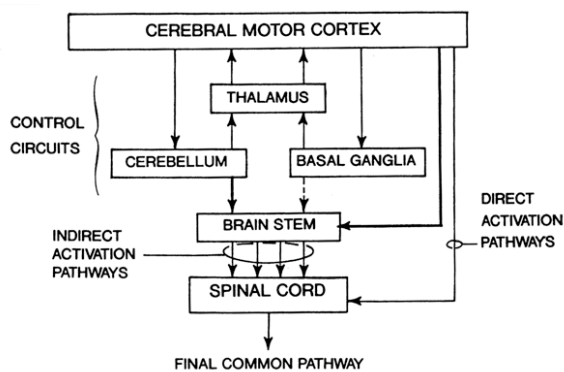
Motor System

Corticospinal Pathway

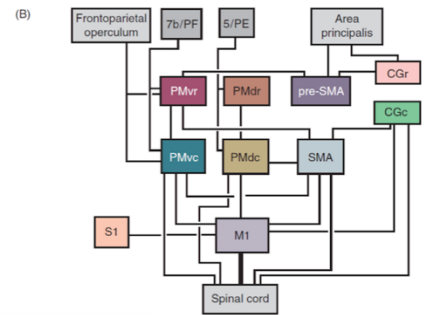
- Origins: Primary Motor Cortex (MI), Premotor Cortex, Supplemental Motor Cortex, Anterior Paracentral Gyrus, Parietal Lobe (including SI) and Cingulate Gyrus.
- Collaterals: Small percentage of Corticospinal Neurons
 - 1. Midbrain (primarily red nucleus)
 - 2. Trigeminal Nuclei
 - 3. Pontine Nuclei
- Termination is Spinal Cord: mostly laminae 3-7, few in ventral horn and laminae 1-2; mostly innervating interneurons, although some innervation of alpha motor neurons.
- If you measure from a muscle with an EMG and pyramidal neuron in the cortex – we find correlation between spikes and that the muscles are directly controlled from the cortex.



A Hierarchy of Motor Areas



*M1 primary motor cortex
PM premotor areas
SMA supplementary motor areas*



Representation of Movements in M1

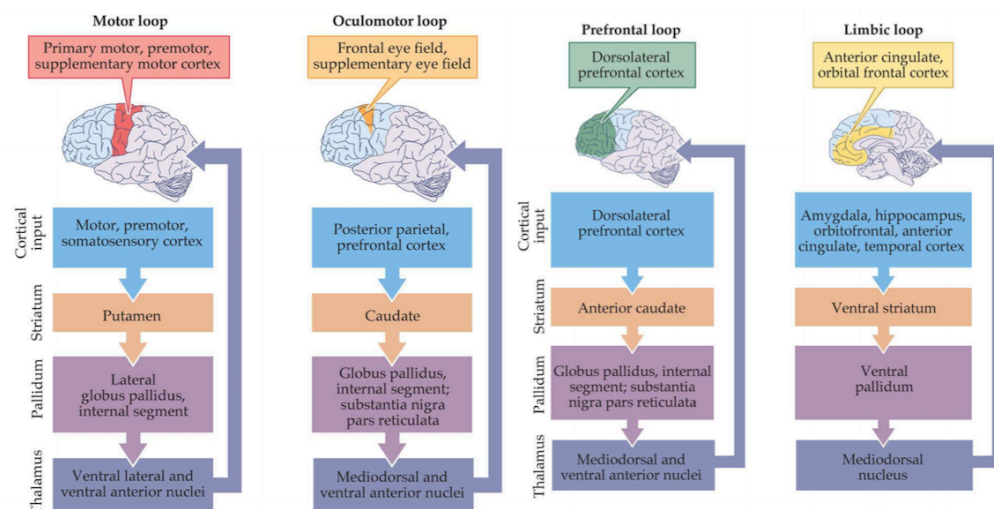
Single unit activity upon arm movements in different directions. There exist some kind of population vector representation of neurons in M1. If we have to move an arm in a specific direction, we have specific neurons that fire a lot and others that do not fire at all. In general, all neurons have some preferred direction and certain strength to a specific angle. This means that, for example, a neuron will fire maximally for movement of right arm at 90 degrees, and decreases gradually in response for 80/100 degrees, 70/110 degrees, and so on.

Inputs to the Basal Ganglia

Basal ganglia receives widespread input from cortical areas. It integrates inputs from motor and sensory areas. It presents some topographic organization and shows both divergence and convergence. In the case of divergence, information from many neurons in the cortex projects to a smaller number of neurons in the basal ganglia, allowing for integration and processing of information from many sources. In the case of convergence, information from a single neuron in the basal ganglia projects to many neurons in the thalamus and cortex, distributing the processed information to multiple targets. This processing of information by the basal ganglia contributes to the regulation of movement and the selection of appropriate motor response.

The **cortico-basal ganglia-thalamic network** refers to a group of interconnected brain regions that play a critical role in motor control, attention and decision-making. The network consists of the **cortex**, the **basal ganglia** (group of subcortical nuclei including caudate-putamen and globus pallidus) and the **thalamus**. In this network, the information flows from the cortex to the basal ganglia, where it is processed and integrated with other information. The processed information then flows to the thalamus, which distributes it to different areas of the cortex.

Basal Ganglia Loops and Non-Motor Brain Functions



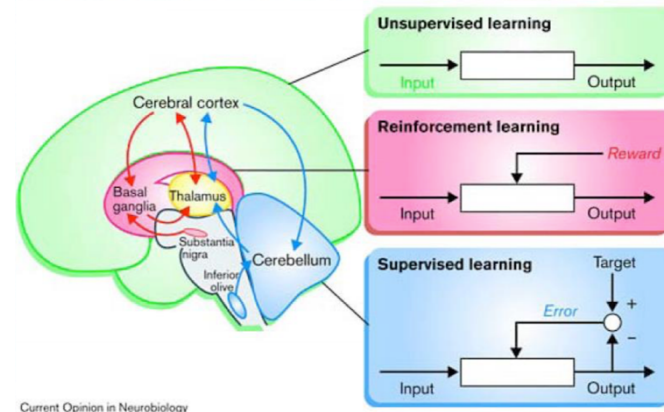
Organization of the Cerebellum

- **Vestibulocerebellum:** Evolutionary oldest, inputs from vestibular organ, affects balance and eye movements, if lesioned vomiting and spontaneous eye movements.
- **Spinocerebellum – Vermis:** Cooperates with vestibulocerebellum, it receives inputs from spinal cord, coordinates posture and locomotion via the deep cerebral nucleus fastigii and the formation reticularis, it is involved in the rough control of limb movements.
- **Spinocerebellum – Intermediate Hemisphere:** It receives inputs from spinal cord, it is involved in the fine control of distal members like fingers, it provides sensory information from extremities, it controls dorsolaterally descending pathways (rubrospinal, corticospinal).
- **Cerebrocerebellum:** it receives inputs from cerebral cortex via pontine nuclei, it projects to motor and premotor cortical areas.

Motor Coordination by Cerebellum and Basal Ganglia

The cerebellum and basal ganglia play complementary roles in motor coordination and are intricately interconnected. The cerebellum is involved in fine-tuning of movements, ensuring that they are accurate, smooth and coordinated. It does this by receiving sensory information about limb position and movement using that information to adjust motor output from the cortex. The cerebellum also helps to learn and store motor skills and habits, allowing for automatic and efficient movements.

The basal ganglia are involved in the selection and initiation of movements. They receive input from the cortex and other brain regions, process that information, and then output signals that either facilitate or inhibit movement. The basal ganglia plays a critical role in controlling voluntary movement. The relationship between the cerebellum and basal ganglia can be thought of as a feedback loop. The basal ganglia select and initiate movements, while the cerebellum fine-tunes and modulates those movements based on sensory information. This interaction allows for smooth and coordinated execution of movements.



Formatio Reticularis (Reticular Formation)

It is a complex network of nerve cells that is found throughout the brainstem and is involved (among many functions) in the control of movements and maintaining posture by integrating sensory information about the body's position in space.

Descending Brainstem Pathways

- **Ventromedial System**
 - **Vestibulospinal tract:** it originates in the vestibular nuclei of the brainstem and is involved in the regulation of balance and posture.
 - **Reticulospinal** (mainly mesencephalic and pontine part): it originates in the reticular formation of the brainstem and is involved in the regulation of autonomic functions, such as blood pressure, respiration and reflexes.
 - Mostly bilateral
 - Control of erect posture
 - Coordination of body movements (arms and legs)
- **Dorsolateral System**
 - **Rubrospinal tract:** it originates in the red nucleus of the brainstem and is involved in the regulation of movement and the modulation of spinal reflexes.
 - **Reticulospinal** (mainly medullary part): it originates in the reticular formation of the brainstem and is involved in the regulation of autonomic functions, such as blood pressure, respiration and reflexes.
 - Activate flexors, inhibit extensors

- Cooperate with corticospinal tract
- Facilitate flexion-based movements
- Support fine motor control
- **Monoaminergic System**
 - Noradrenergic
 - Serotonergic
 - Relevant for locomotion control

Connectivity of Descending Pathways

- Further support function of the medial and lateral pathways.
- Medial interneurons innervate multiple spinal cord segments and project bilaterally.
- Lateral interneurons are confined to few segments and remain unilateral.

LDABNN – Lecture 13 – Benjamin Grewe

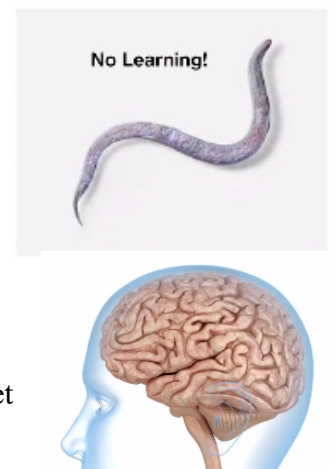
Why do we need plasticity/learning?

The C.Elegans genome stores all synaptic connections. The simple worm C. Elegans, for example, has 302 neurons and about 7000 synapses and in each individual of an inbred strain, the wiring pattern is exactly the same (Chen et al., 2006).

Connections in the human Brain are mostly learned:

The human brain has about 10^{11} neurons, and more than 10^3 synapses per neuron. Specifying a connection target requires about $\log_2 10^{11} + 35$ bits/synapse. Thus, it would take 3.5×10^{15} bits (approx. 400TB) to specify all 10^{14} connections in the brain. However, the human genome only has about 3×10^9 nucleotides, so it cannot encode more than approx. 1GB of information (Wel et al., 2013).

Conclusion: Even if every nucleotide of the human genome were devoted to efficiently specifying brain connections, the information capacity is orders of magnitude too small to encode all synaptic connections.



Why do we need learning! We need learning to survive and adapt to new situations in a changing environment.

Learning as evolutionary survival strategy. Is the brain a Universal Learning Machine?

A species using the mixed strategy may thrive if that strategy achieves a higher asymptotic level of performance.

Suggested paper: A Critique of Pure Learning: “*What Artificial Neural Networks can Learn from Animal Brains*” – Zador



Intelligent Behaviour Emerges with Learning!

Defining Plasticity/Learning (Learning & Memory vs. Plasticity)

- **Learning:** The acquisition/storage of knowledge/information or the formation of a memory through experience.
- **Memory:** Stored information that can be recalled at a later stage in time
 - Learning results in memory – which itself has a further outcome – a change in future behaviour.
 - Learning does not always imply a conscious attempt to learn. Simple observation can lead to the creation of a new memory.

- **Plasticity:** the biological implementation of learning. Plasticity allows us to form a memory.

Learning in Computer Science

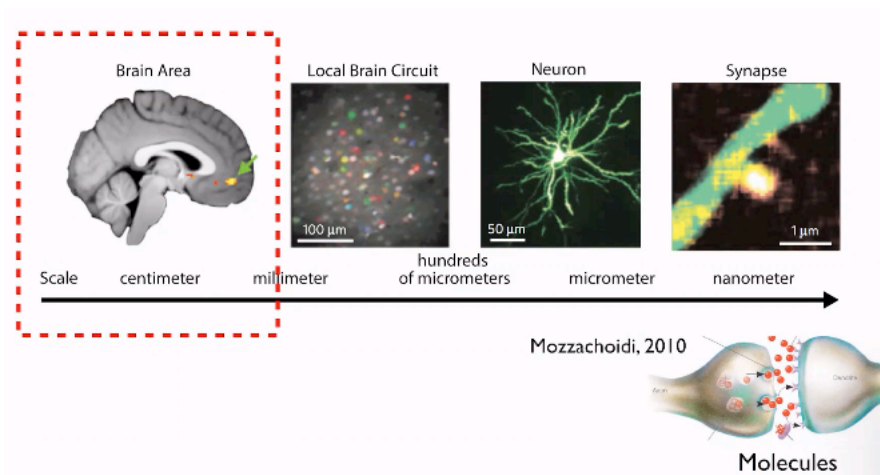
- Machine Learning
 - Supervised Learning (Regression & Classification)
 - Unsupervised Learning (Clustering & Dimensionality Reduction)
 - Reinforcement Learning

Learning in Neuroscience

- Pavlovian Conditioning
- Instrumental Conditioning
- Reward/Aversive Learning
- Social Learning
- Perceptual Learning
- Motor Learning

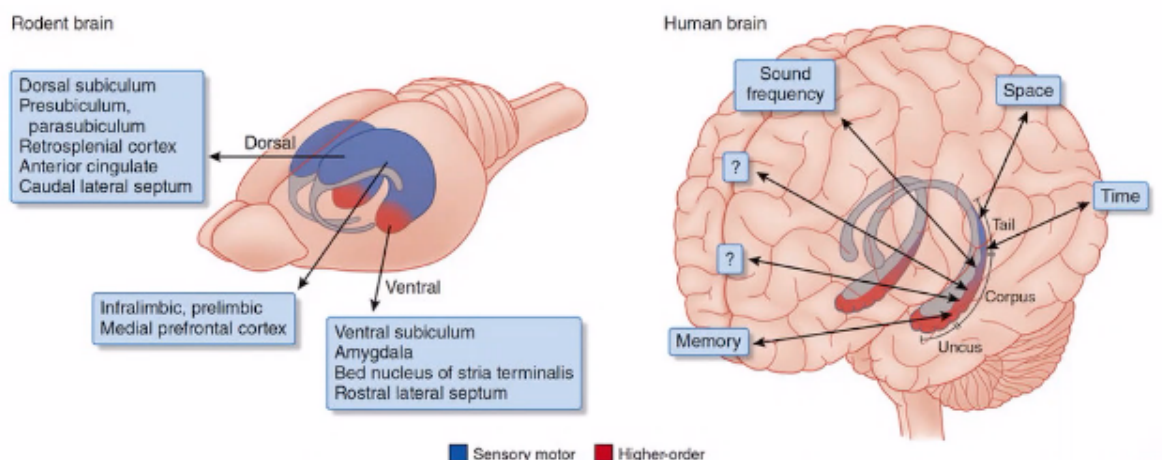
Network and Systems Plasticity

Neural Substrates of Plasticity



How does the brain implement a learning?

The Hippocampus as a Model System to Study Learning and Memory



Henry Gustav Molaison (H.M.) 1926 – 2008

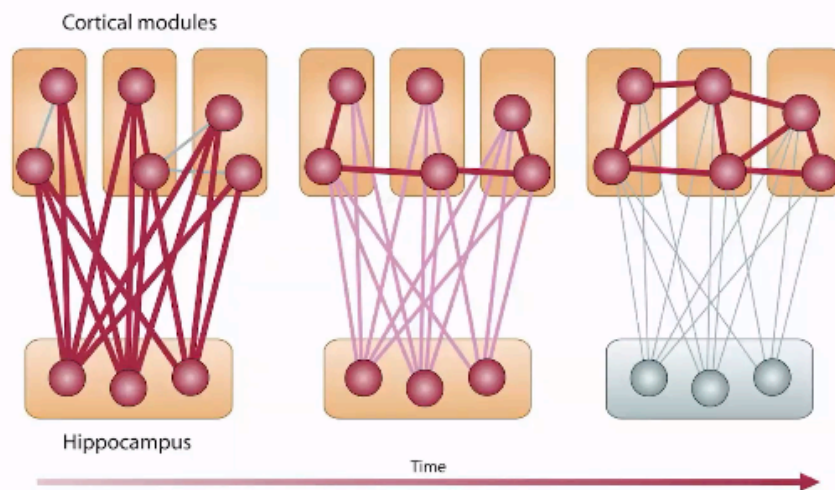
Amygdala, hippocampal gyrus, and anterior two third of the hippocampus were removed.

Diagnosis: Severe anterograde amnesia

- Normal STM
- Normal LTM (for events prior to surgery)
- Problem: transfer from STM to LTM
- Could not consolidate new declarative knowledge
- Capable of acquiring implicit knowledge

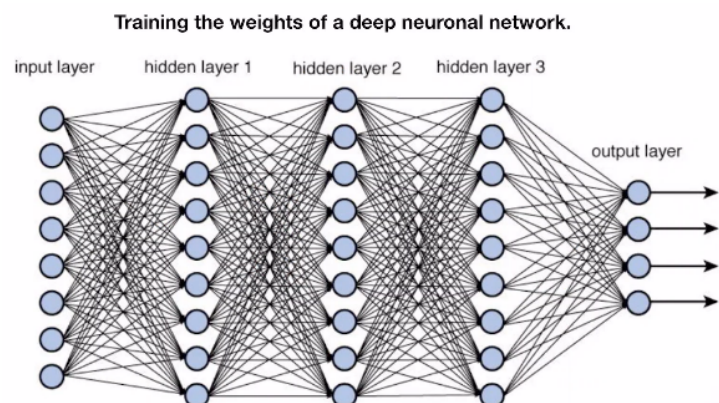
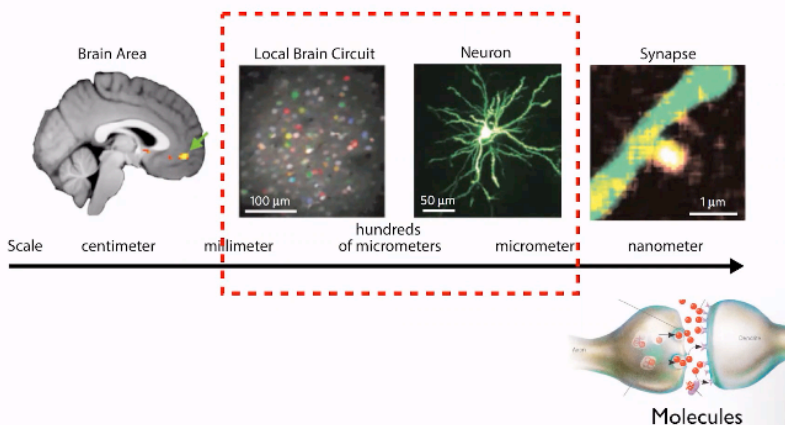
Conclusions:

- The Hippocampus is not a permanent storage area for explicit knowledge.
- The Hippocampus is involved (with other cortical areas) in consolidation, a longer term process taking months to years (note retrograde amnesia in hippocampus lesion patients for up to 3 years).
- Consolidation is understood to involve biological changes taking place in those other areas of cortex.
- Once this has fully taken place, the hippocampus is not required for retrieval.

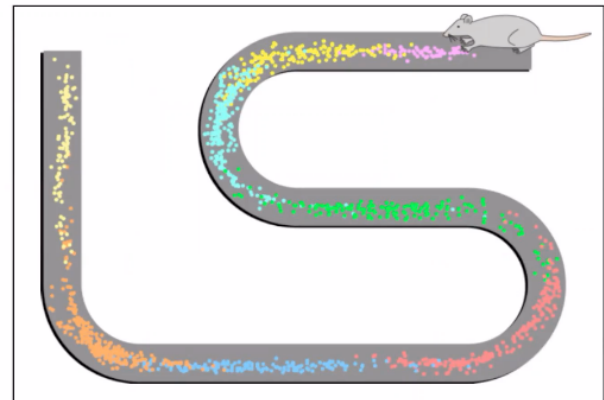
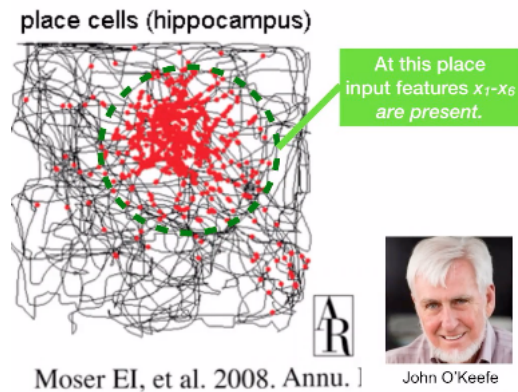


Review Article | Published: 26 August 2018
Mechanisms of systems memory consolidation during sleep
Jens G. Klinzing, Nils Niehuth & Jan Born
Nature Neuroscience 22, 1698–1810(2019) | Cite this article
18k Accesses | 57 Citations | 338 Altmetric | Metrics

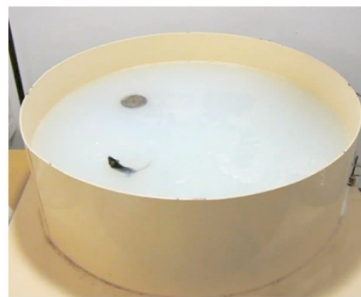
Cellular Plasticity, the Perceptron



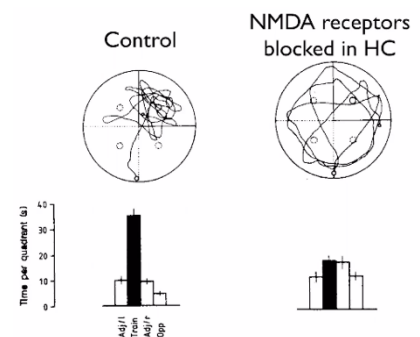
The Hippocampus and Spatial Memory



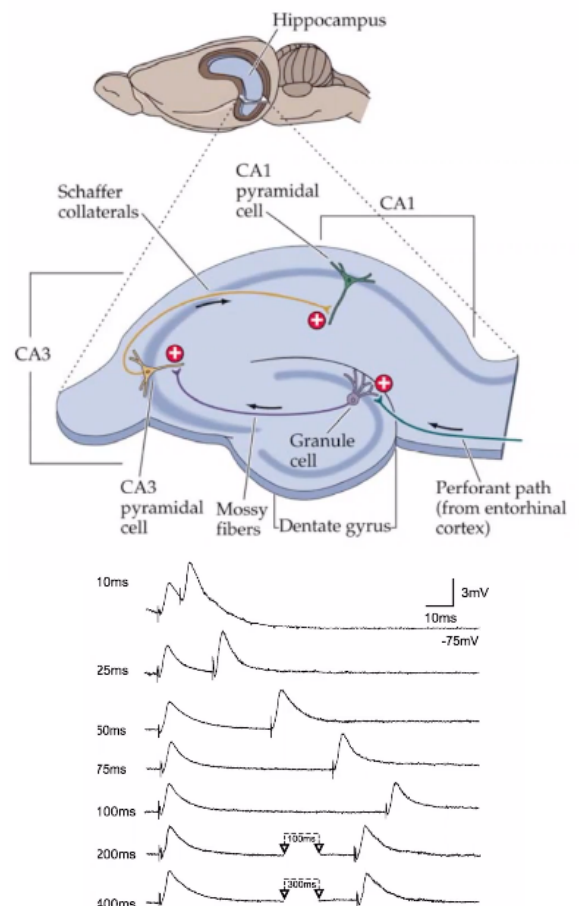
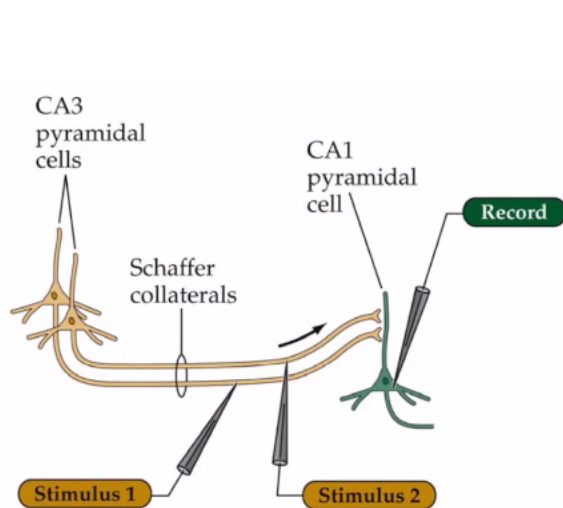
Morris Water Maze



Morris et al. Nature 1986



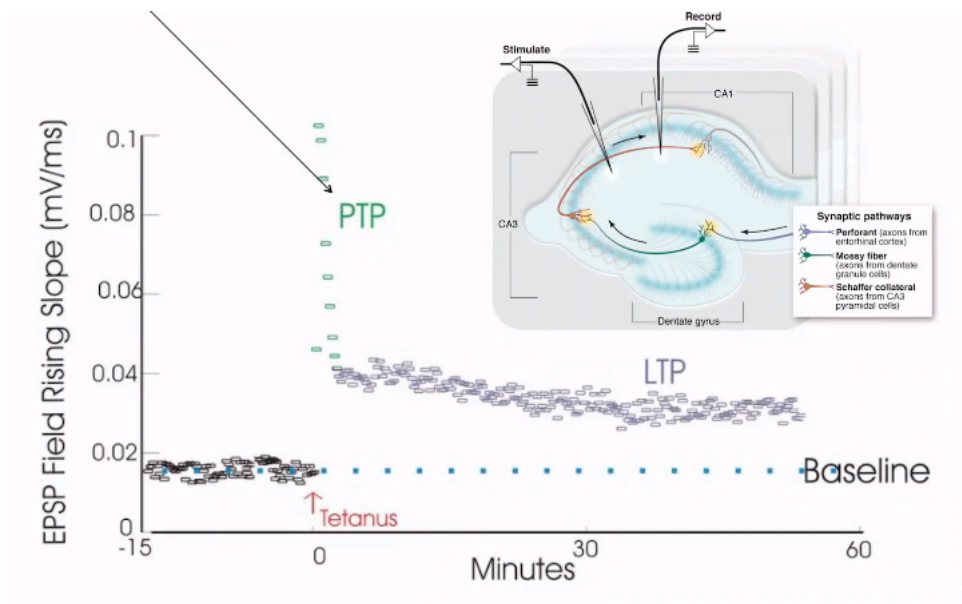
How can we measure neuronal plasticity in the Hippocampus?



Short-term Plasticity: Paired Pulse Facilitation

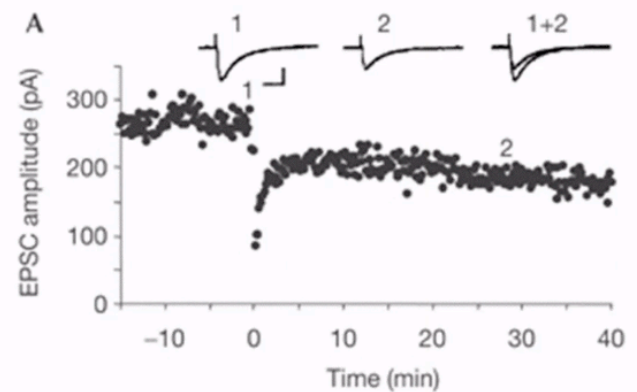
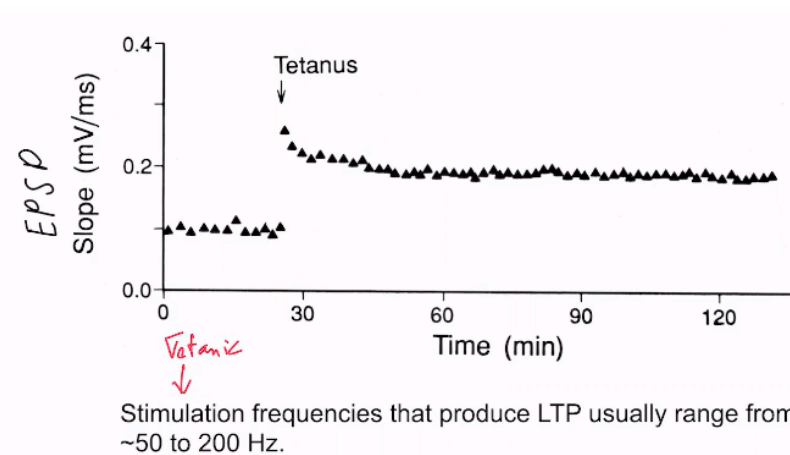
Paired activations of a synapse onto a CA1 neuron.
 “Residual Ca^{2+} ” in terminal for 10 to 100 ms after first stimulus increases probability of release.

Post Tetanic Potentiation and Long-Term Potentiation



PTP believed to be caused by a large accumulation of Ca^{2+} in the terminal caused by a high frequency tetanic stimulation.

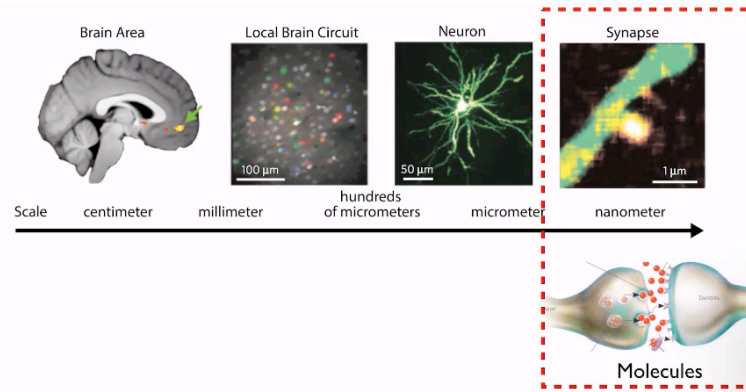
Recording of LTP in a Hippocampal Slice & of LTD in the Hippocampus



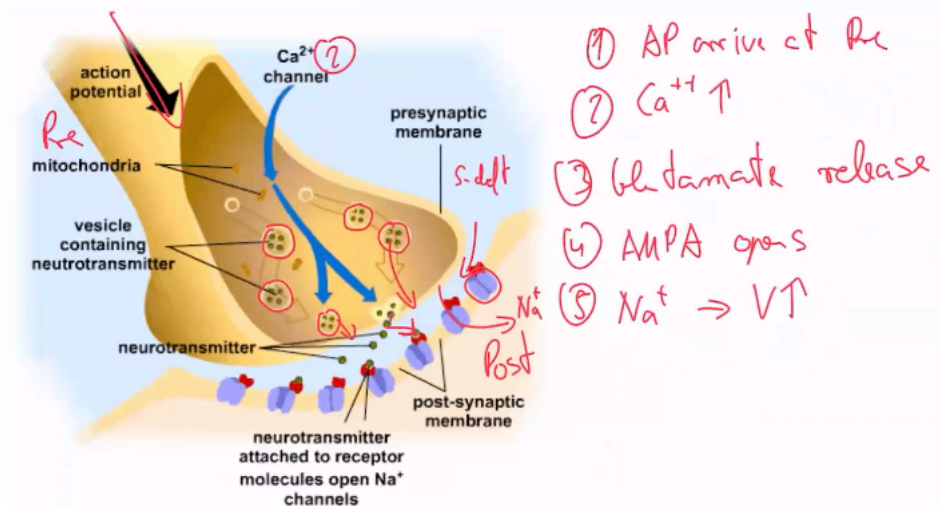
Summary of LTP and LTD

- **LTP**
 - LTP after tetanic stimulation is (high) frequency dependent.
 - LTP involves multiple mechanisms across time all of which induce long-term synaptic strengthening.
 - LTP mechanisms last from 30min to several hours, but do not involve protein synthesis.
 - LTP mechanisms lasting longer than a few hours require protein synthesis.
- **LTD**
 - LTD after tetanic stimulation is (low) frequency dependent.
 - LTD also involves several different mechanisms acting in concert to induce synaptic depression.
 - LTD and LTP act in concert to change information coding and to implement new memories in the brain.
 - STDP is thought to arise from the same mechanisms governing LTP and LTD.

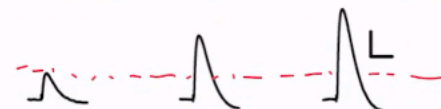
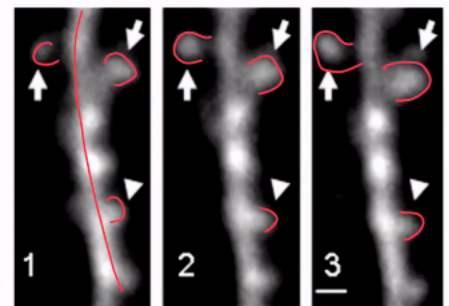
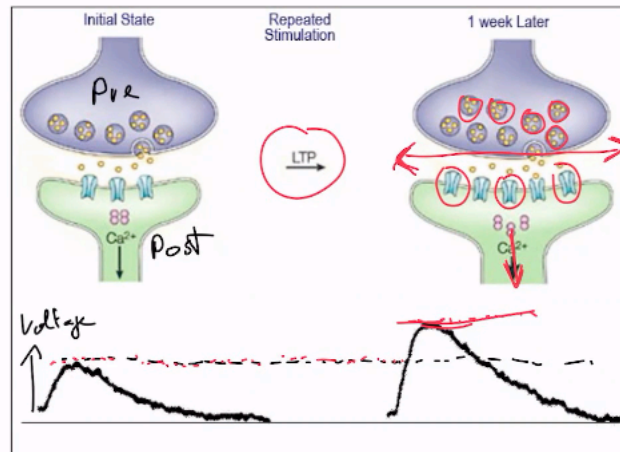
Synaptic plasticity, the Hebbian Synapse



Synaptic Plasticity – A Short Recap of Synaptic Function

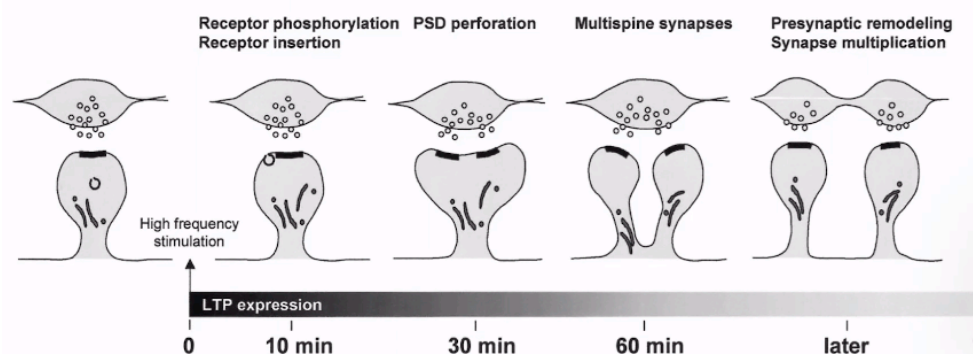


Plasticity (LTP) at the Synapse

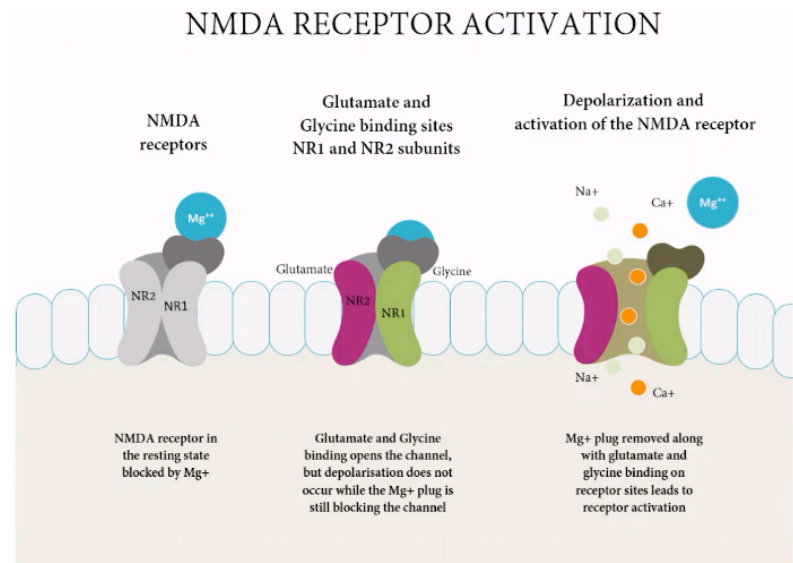


1. Synapse size changes. (Long-term)
2. AMPA/NMDA ratio changes / More vesicles. (Long-term)
3. Number of spines changes. (Very Long-term)

Time Scales of Synaptic Plasticity

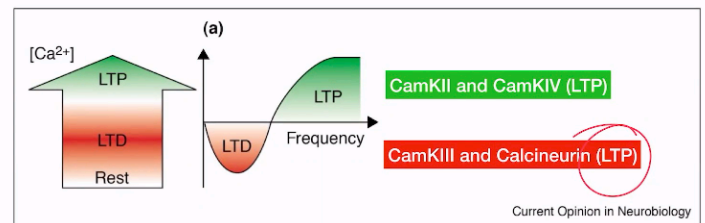


Synaptic Plasticity – The NMDA Receptor

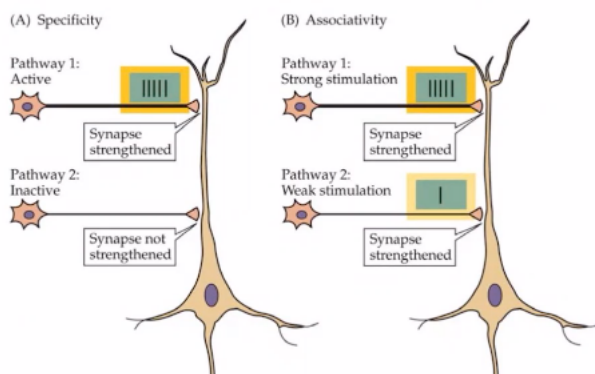


1. Calcium ions flow through the activated NMDA receptor.
2. One of its targets is calcium/calmodulin-regulated Protein Kinase.

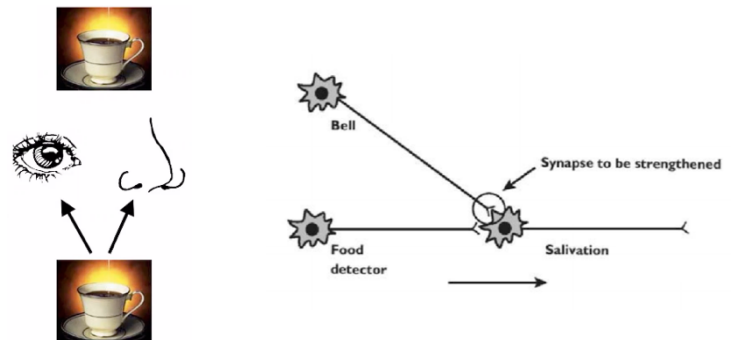
The Role of Calcium in LTP/LTD



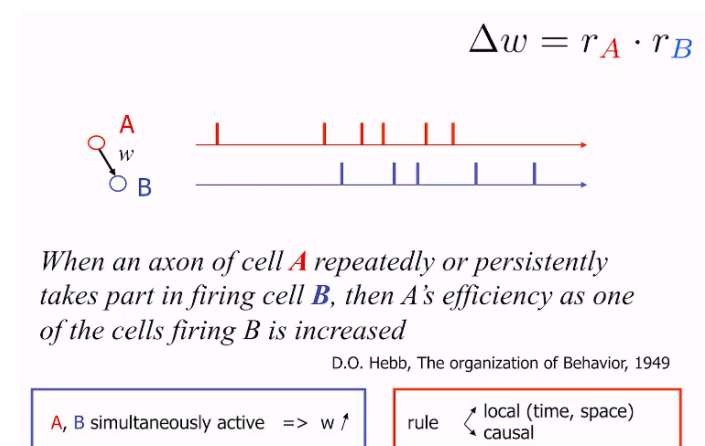
Hebb's Idea



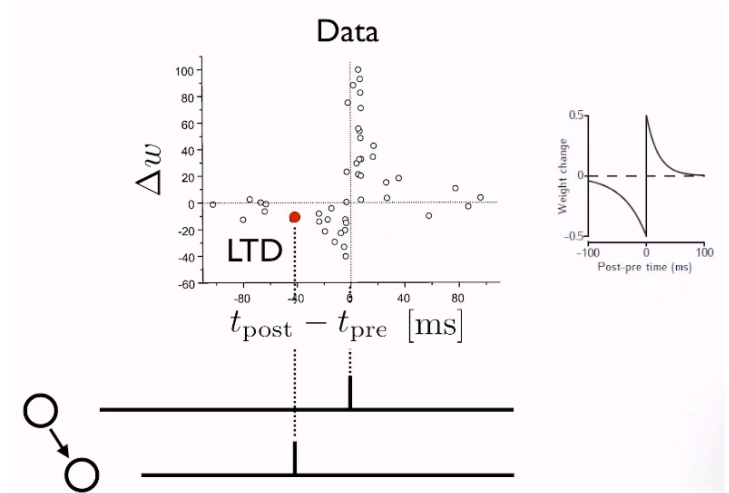
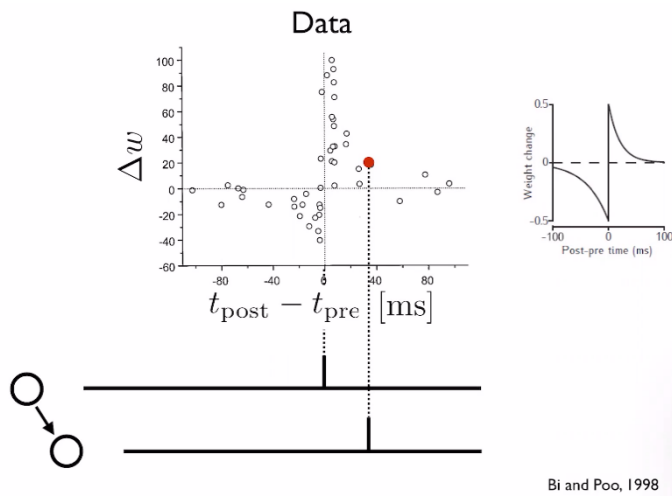
3. Level and timing of Ca^{2+} rise in spine determines LTD or LTP.
4. Low frequency synaptic firing (~ 5 Hz) produces LTD; high frequency synaptic firing (~ 50 to 100 Hz) produces LTP.



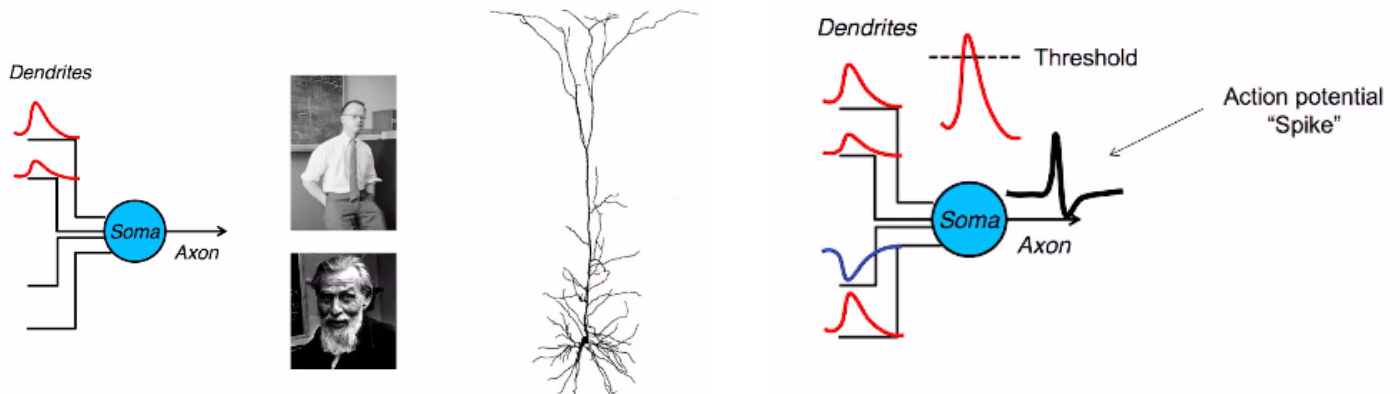
Hebb's Postulate



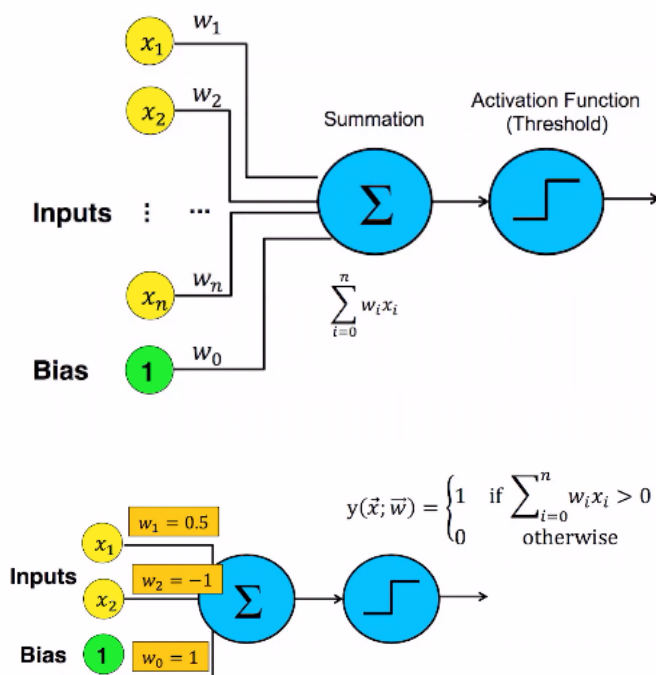
Spike-Timing Dependent Plasticity (STDP)



What can we learn from the Brain?

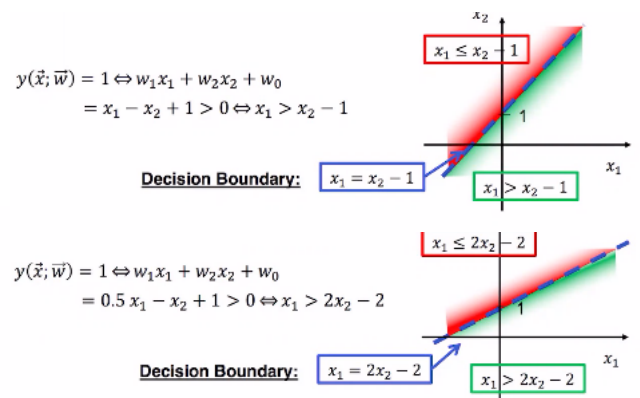


The McCulloch & Pitts Neuron AKA The Perceptron



$$\text{output} = \begin{cases} 0 & \text{if } \sum_j w_j x_j \leq \text{threshold} \\ 1 & \text{if } \sum_j w_j x_j > \text{threshold} \end{cases}$$

$$\text{output} = \begin{cases} 0 & \text{if } w \cdot x + b \leq 0 \\ 1 & \text{if } w \cdot x + b > 0 \end{cases}$$



The Perceptron Learning Algorithm

Can all logical operations be implemented by a McCulloch Pitts Neuron?

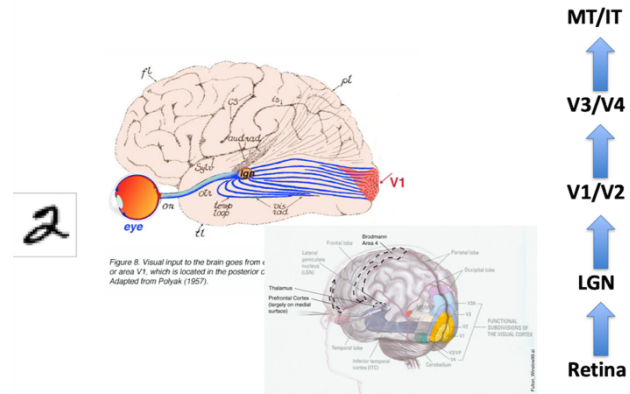
OR yes, EQUALITY yes, AND yes, NOT yes, but it cannot implement XOR. Since there is no line which perfectly separates the two classes in the XOR problem. We can overcome this problem by combining multiple neurons in networks -> Neural Networks.

The Perceptron – Summary

- McCulloch-Pitts neurons implement a linear decision boundary (separating hyperplane)
- The weights and bias define the decision boundary
- They can implement many logical operations (AND, OR, NOT)
- They cannot implement XOR (not linearly separable)
- They can be trained on labeled datasets (supervised learning).

Learning to Recognize Handwritten Numbers (MNIST)

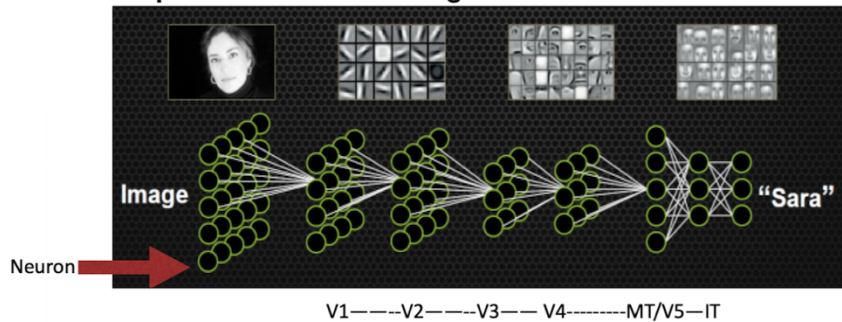
- Machine Learning Approach:
 - Linear Classifier: 88 – 92 accuracy.
 - K-Nearest Neighbor: 95 -98 accuracy.
- Human: 99.8 accuracy.



A Neuronal Network for Classifying Handwritten Digits

We can train a multi-layer NN through gradient descent (backpropagation) to minimize the error by changing the weights between neurons.

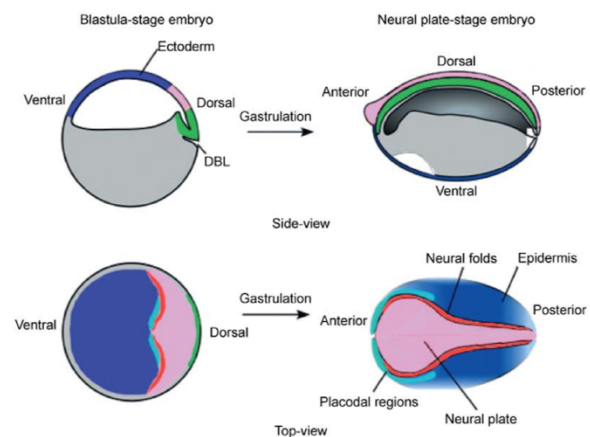
Deep Network - Brain Analogies



Building a CNS I – Lecture 4 – Stephan Neuhauss

Gastrulation

Gastrulation is defined as an early developmental process in which an embryo transforms from a one-dimensional layer of epithelial cells (blastula) and re-organizes into a multi-layered and multi-dimensional structure called the **gastrula**. In reptiles, avians and mammals, which are triploblastic organisms, gastrulation derives a three tissue-layered organism composed of **endoderm**, **mesoderm** and **ectoderm**. Each derm layer corresponds to the development of specific primitive systems during organogenesis. In addition to setting the embryo up for organ formation, gastrulation provides a mechanism to develop a multi-leveled



body plan that demarcates anatomical axis formation with dorsal/ventral and cranial/caudal axis (also termed anterior or rostral/posterior, respectively), retention of global left/right symmetry, and the loss of bilateral symmetry in specific systems (e.g., heart).

The Famous Spemann Organizer

In the 1930's, Mangold and Spemann discovered neural induction during experiments in which they transplanted small pieces of tissues from one amphibian embryo to another at pregastrulae stages. The key observation was made when they transplanted a small piece of tissue from a region called the dorsal blastopore lip (DBL), and the host embryo responded to the grafted tissue by forming a complete secondary dorsal axis. Importantly, most of the tissues in the secondary dorsal axes were not derived from the transplanted tissue but rather from the tissue in the host embryo. In particular, the secondary dorsal axis contained a complete nervous system that was derived entirely from the ventral ectoderm of the host embryo, a tissue that would have differentiated into skin in the absence of a graft. The implication of this observation was that the transplanted tissue can act as a source of inducing signals that can cause ventral ectoderm to form neural tissue, and that this inductive interaction normally occurs on the dorsal side of the embryo. Tissues in the DBL was later termed the **organizer** because of its ability, when transplanted, to reprogram the ventral side of the embryo to form dorsal tissue, not only in the ectoderm but also in the internal mesodermal tissues.

Following Mangold and Spemann's lead, it was subsequently found all vertebrate embryos appear to contain a region, called **Spemann's organizer**, which can induce ectoderm to form neural tissue.

Anterior-Posterior (AP) Patterning

The neural plate is a morphologically homogeneous sheet of epithelial cells derived from dorsal ectoderm, which acquires its neural potential and fate as a result of inductive signaling. As the neural plate rolls up and closes into a tube, a series of constrictions appear in its wall, subdividing the anterior end of the tube into a series of vesicles representing the anlagen of fore-, mid- and hindbrain. Further subdivision ensures, most conspicuously in the hindbrain region (rhombencephalon), where a series of segment-like swellings, rhombomeres, are formed. Caudal to the hindbrain, the neural tube forms a long narrow cylinder that is the precursor of the spinal cord. These early morphological features of the neural tube dictate the overall plan of the CNS and predict its later regional specializations. The neuroepithelium then commences with the production of a huge diversity of region-specific cell types, each having a distinct identity in terms of morphology, axonal trajectory, synaptic specificity, neurotransmitter content, and so on. Different neuronal cell types also carry distinctive surface labels that may ensure accuracy of axonal navigation and the formation of appropriate connections with other cells. Perhaps most strikingly, individual neurons or groups of similar neurons originate at predictable times and at precise positions within the various regions of the neural tube. In some cases, neurons remain in their position of origin during and following differentiation; in other cases, young neurons or their precursors are directed to migrate along stereotypic paths to settle in locations distant from their position of origin. Correct specification of this intricate spatial ordering, or pattern, of cells is crucial to later events in CNS development when neurons establish complex arrays of specific interconnection that constitute functional networks. Activity-dependent processes and regressive events, such as the pruning of axons and cell death, later reinforce and refine initial patterns of connectivity, but a high-degree of precision is achieved from the outset, dependent on, and as a direct result of, appropriate cell patterning.

AP Polarity

The initial establishment of AP polarity along the neuraxis is coupled intimately to the establishment of the main body axis during early embryonic development. Although AP axis formation in the vertebrate embryo remains poorly understood, it may have conceptual similarities with the strategies used for axis determination in the *Drosophila* embryo, where genetic studies have produced a detailed understanding. In *Drosophila*, AP polarity is first established by a gradient

of positional information produced by the maternal morphogen Bicoid emanating from the anterior pole of the egg. The gradient of the Bicoid transcription factor initiates a cascade of transcription factor activation that progressively subdivides the body axes further into smaller segmental units.

Neural Induction

AP patterning of the CNS begins during the process of neural induction as dorsal ectoderm takes on a neural fate. This process divides nascent neural tissue into prechordal (anterior) and epichordal (posterior) neural plate regions based on signals that come from adjacent head and tail organizing tissues. Formation of the prechordal plate requires two inhibitory signals produced by the head organizer: one that inhibits BMP and the other WNT signaling. Tail organizer tissue produces potent posteriorizing agents, including WNTs, FGFs and RA. The extent of signals required for generating AP polarity, however, is not fully known and the details of their action remain to be explored. Interestingly, both neural and anterior-neural are default states, requiring specific molecular activity to become non-neural (BMP) or posterior-neural (WNT).

Following the establishment of polarity along the AP axis of the embryo and the delineation of prechordal and epichordal regions of the neural plate, the AP axis becomes further regionalized into smaller and smaller domains, as revealed by the expression of developmental control genes. This process of progressive regional refinement involves two general classes of mechanisms – the establishment of local organizers as sources of diffusible factors (morphogens) that inform neighboring cells about their position and fate, and the partitioning of the neuroepithelium into small modules or segments in which development can proceed with a degree of autonomy. IN both cases, a conspicuous and important feature is the setting up of boundaries, which position a local organizer, contain cells within a compartment, or both.

The Notochord

It is a **ventral organizer**. Crucially involved in patterning the ventral neural tube is the notochord, a mesodermal skeletal structure that occupies the midline of the embryo directly beneath the neur ectoderm. Grafting experiments in avian embryos have shown that both floor plate and motor neuron differentiation depend on notochord signals. Early removal of the notochord results in a normal-sized spinal cord in which both of these ventral cell types are absent, with dorsal cell types and dorsal specific markers appearing in their place. Similarly, implanting a supernumerary notochord alongside and in contact with the lateral neural plate results in formation of an additional group of floor plate cells at the point of contact, with clusters of motor neurons on either sides. These experiments show not only the power of the ventral midline signal to influence fate choice, but also the multipotent competence of responding neural tube cells at different DV positions. At a slightly later developmental stage, the floor plate itself acquires the same inductive capabilities – it can also induce motor neurons and will induce itself homeogenetically. The floor plate thus becomes an organizing center for a ventral pattern that is built into the neural tube itself.

Dorsal Blastopore Lip (DBL)

The Dorsal Lip of the Blastopore is a structure that forms during early embryonic development and is important for its role in organizing the germ layers. The dorsal lip is formed during early gastrulation as folding of tissue along the involuting marginal zone of the blastocoel forms an opening known as the blastopore. It is particularly important for its role in neural induction through the default model, where signaling from the dorsal lip protects a region of the epiblast from becoming epidermis, thus allowing it to develop to its default neural tissue.

Building a CNS II – Lecture 6 – Sebastian Jessberger

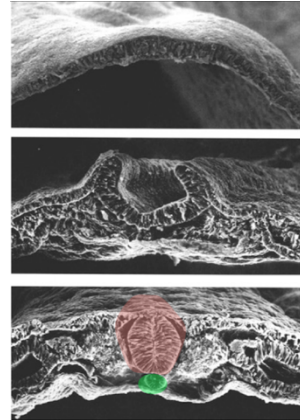
How do you get from a fertilized egg and pluripotent cells to the highly specialized neural structures?

Principles of Mammalian Neural Development

- **Tissue Polarity:** The tissue is polarizing.
- **Cellular Polarity:** also cells have to be polarized.

Neurulation

It is the start of the formation of the CNS. It is the formation of the vertebrate nervous system in embryos. The notochord induces the formation of the CNS by signaling the ectoderm above it to form the thick and flat neural plate. The neural plate then folds in on itself to form the neural tube, which will then later differentiate into the spinal cord and brain. In the figure: (top) Neuro-epithelial layer already showing signs of elongation of cells (notochord not present). (middle) Neural groove forming. (bottom) Neural tube formed with overlying ectoderm and underlying notochord.



How to visualize dividing cells (and their progeny)?

Dividing cells like stem cells are those that give rise to neurons. To visualize them we can use:

- **Endogenous marker (pH3, Ki67, mitotic figures):** are proteins that selectively express when the cell is dividing.
- **Thymidine analogues (BrdU):** these analogues are integrated into the DNA when it is doubling and they can be detected through antibodies.
- **Retroviruses:** they cannot cross nuclear membrane, so they can only enter the cell when it is dividing and can be later identified.
- **Transgenic Lineage Tracers**
- **Fusion Plasmids (tubulin, histones).**



Radial Glia as Neural Stem Cells?

How could you identify if these cells give rise to neurons within the developing cortex.

It is done through **Transgenic Fate Tracing**.

Transgenic Fate Tracing

It is a method used in developmental biology to study the development and differentiation of cells in an organism. It involves creating genetically modified organisms that express a certain gene or set of genes specifically in certain cell types of interest. The gene used for fate tracing are typically linked to a fluorescence or other type of reporter molecule, which allows the cells of interest to be visualized and tracked over time. The basic steps of transgenic fate tracing are:

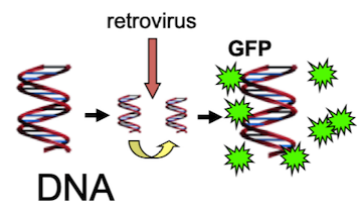
- Identification of a gene that is specifically expressed in the cell type of interest.
- Creation of a transgenic organism that expresses the gene in the cells of interest.
- Observing the expression of the gene and the development and differentiation of the cells in the organisms.

By tracking the cells that express the fate-tracing gene, researchers can gain insights into the origins and developmental pathways of different cell types.

In Malatesta 2003, it is done through Cre-recombinase, which are bacterial enzymes normally not present in the body that can cut DNA or recognize specific DNA patterns (loxP). You express this Cre-recombinase under GFAP (highly expressed in Glia cells), thus now driving also Cre-recombinase. The researchers generated transgenic mice that expressed a green fluorescent protein (h-GFAP) under the control of a promoter that was specifically active in neuronal precursors. Using these transgenic mice, the authors were able to visualize and track the development and differentiation of neuronal precursors in the hippocampus in real-time, and to demonstrate that these cells gave rise to both neurons and astrocytes.

Retroviruses

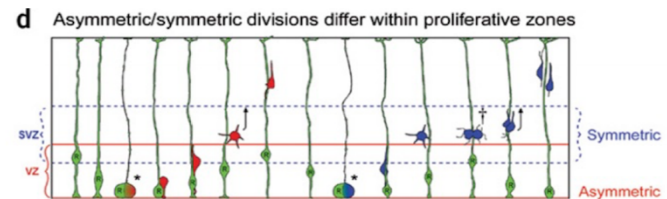
Moloney murine leukemia (MML) viruses cannot cross nuclear membrane: specific for dividing cells. Then, when the cell divides, the retrovirus can enter the nuclear membrane and fluorescent protein (GFP) can be used to evidence it (**Retroviral Labelling**).



Radial Glia Divide and Generate Neuronal Progeny

There are two main ways in which Radial Glia divides:

- Asymmetric: in this case, the radial glia cell divides into two daughter cells, one of which retains the characteristic of a radial glia cell and can continue to divide and support neuronal migration, while the other differentiates into a neuron. (Most common scenario).
- Symmetric: it generates a “daughter” which is a basal progenitor that can be divided again and it usually give rise to two neurons.



“Once development was ended, the fonts of growth and regeneration of the axons and dendrites dried up irrevocably. In the adult centers, the nerve paths are something fixed, and immutable: everything may die, nothing may be regenerated” – Ramon y Cajal, 1928.

Early Evidence for Cell Division in the Adult Brain

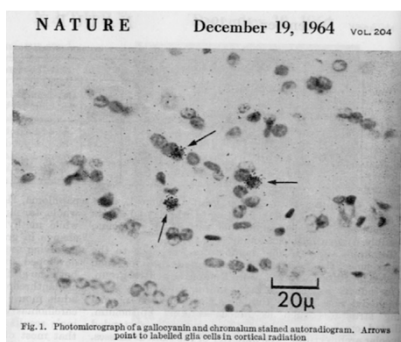
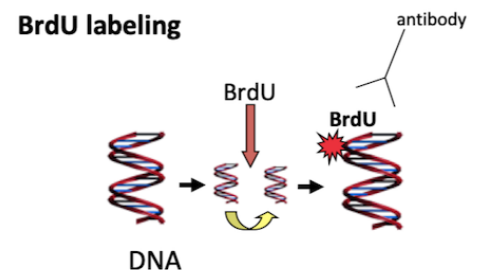


Fig. 1. Photomicrograph of a gallosyanin and chromosom stained autoradiogram. Arrows point to labeled glia cells in cortical radiation.

Before



After

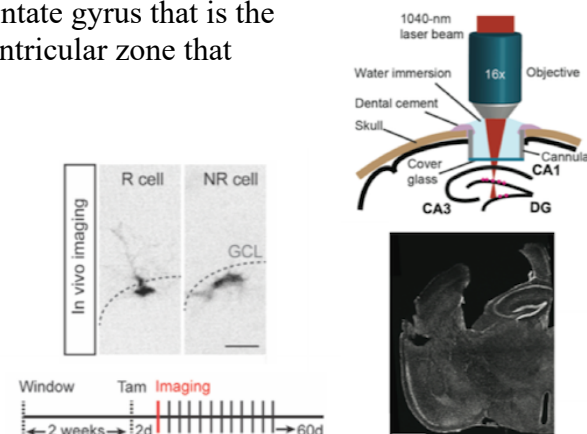


Plasticity and Repair of the Mammalian Brain

- Life-long neurogenesis in the adult hippocampus in mammals including humans. (still largely controversial).
- Involved in certain forms of learning and memory.
- Reduced and/or altered neurogenesis in neuro-psychiatric disease (e.g., depression, ageing).
- Areas involved in neurogenesis in adult human brains: dentate gyrus that is the entrance door to hippocampus, adult rodent brains: subventricular zone that migrate and differentiate in olfactory bulb cells.

In order to identify neural stem cells in the Dentate Gyrus of Hippocampus **Intravital Imaging** can be used, which allows to very deep within the tissue with a 2-photon technique. tdTOMATO is injected to identify the cells.

This technique allows for the construction of a **lineage tree** of adult neural stem cells deriving from the same mother cell.



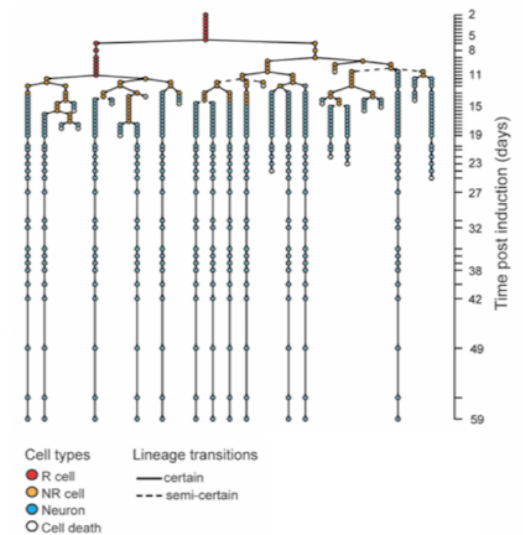
One mother and her daughters

Things to look at:

- Stem cell dynamics
- Mode of cell division
- Migration and Integration
- Functional Properties (combined with GECIs)
- **Self-Renewal Potential**

There is evidence suggesting long-term self-renewal, but there is also evidence suggesting the contrary, i.e., rather quick depletion.

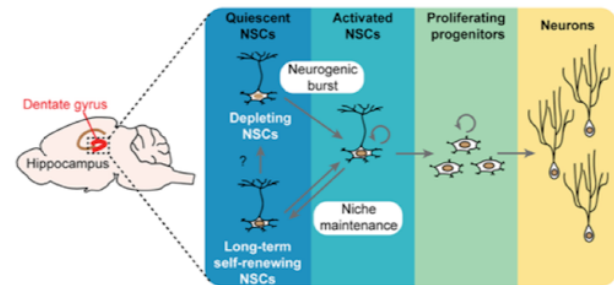
Distinct Behaviour of Neural Stem Cells in the Hippocampus



These two types of cells can be identified through molecular signature.

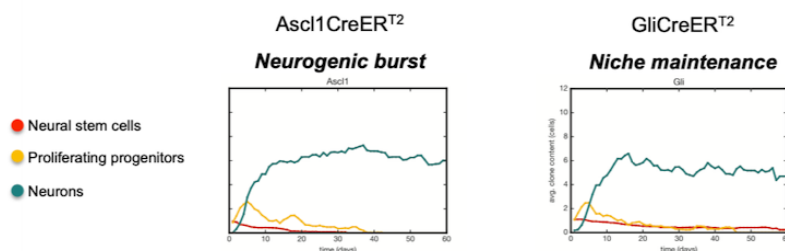
Diversity of Hippocampal Stem Cells

- Functional and molecular diversity of hippocampal neural stem cells.
- Long-term (>100 days) self-renewing stem cells exist in the adult mammalian hippocampus.
- How do they contribute to life-long neurogenesis?
- What are the stem cell dynamics with advancing age?



However, a main question is the prior history of a given cell and this can be investigated through iCOUNT.

Dynamic Regulation of Adult Neurogenesis



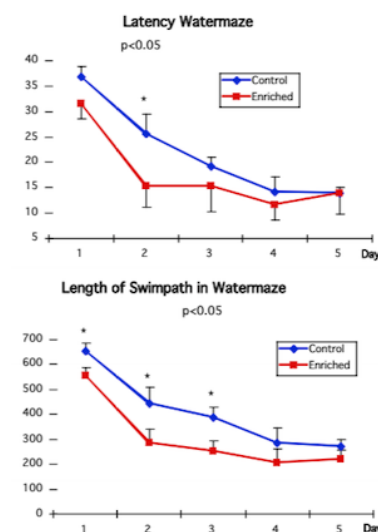
doubles the amount of neurons generated in the hippocampus.

- **Learning**
- Housing of mice in an **environmental enrichment**, where they live in a much larger cohorts with more mice.

One experiment demonstrating how enriched environment enhances learning based on Hippocampus is the **Morris Water Maze**. Indeed, mice grown in an enriched environment showed much faster learning curves in finding the platform in the water maze compared to mice grown in less “fancy” environments. Hence, there is some kind of correlation between increased hippocampus neurogenesis and performance in learning spatial locations, even though it has not yet been demonstrated a causality. Other examples, Cab driving increases hippocampal size: hippocampal volume correlates with the time spent behind the wheel. Students learning increases brain size.

The number of neurons generated is not static but dynamically regulated. Elements that induces an increase in the amounts of neurons generated are:

- **Voluntary physical exercise**



There are however also negative regulators of neurogenesis (also involved with neurodegenerative diseases):

- Alcohol
- **Stress**: if you stress mice it dramatically reduces the amount of neurons generated in the hippocampus, which in turn has control over mood and can be implicated in depression. Indeed, studies demonstrated that antidepressant treatment are correlated with increased neurogenesis in adult rat hippocampus. Further studies, showed that there has to be neurogenesis happening in the hippocampus for antidepressants to work.
- Age
- Hit-Damage.

Irradiation Ablated Neurogenesis

By using ionizing radiation, which divides cells (like those used in cancer therapy), dramatically reduces neurogenesis in the HC.

In Santarelli et al. 2003, they studied mice that were treated with ionizing radiation to ablate neurogenesis in the hippocampus and then administered the antidepressant fluoxetine (Prozac). The results showed that ablation of neurogenesis in the hippocampus prevented the behavioral effects of fluoxetine, suggesting that neurogenesis in the hippocampus is required for the antidepressant effects of this drug.

Other approaches to ablate neurogenesis involve **transgenic mice** (using TK or suicide genes under the control of stem cell promoters) and **local cell ablation** (e.g., lentiviral vectors). All of these approaches are not perfect and present disadvantages, hence they are often used in combination to mitigate cons.

The Dentate Gyrus as a Pattern Separator

The Dentate Gyrus represents very similar inputs distinctly within the brain. What it has been shown is that mice with **decreased neurogenesis are impaired at spatial pattern separation**.

