**Learning on a molecular level**

Long term potentiation (=: LTP) is necessary and sufficient for learning to occur on a molecular level: Learning on neuronal level = more AMPAR on postsynaptic cell or the formation of new synapses. NMDAR are blocked by Mg2+ (Ca2+ flows in when unblocked). NMDAR are used as coincidence detectors in learning when the time difference of the activation of the pre- and postsynaptic side is below 100ms. This allows Ca2+ to flow in and starting a protein kinase cascade and transcriptional changes. CamKII is translated, which drives the formation of new AMPAR on the postsynaptic cell. AMPARs allow the inflow of Na+ ions (⬄ depolarization of the postsynaptic cell = activation). ATP needed to pump out Na+ and Ca2+ afterwards.

Also, within the postsynaptic cell when Ca2+ has entered via NMDAR, there are changes to the cytoskeleton (more scaffolding proteins like PSD-95 and SAP-102, because more AMPARs), protein phosphorylation, local protein synthesis and AMPAR trafficking.

LTP occurs constantly for 1-2h. Afterwards, new gene expression is required (this can be inhibited by, e.g. cycloheximide which binds to ribosomes and renders them dysfunctional).

How can we verify, LTP is sufficient for learning? Optogenetics allow us to study learning: Inject amygdala of mice with adenovirus containing the DNA for light sensitive ion channels. Blue light activates these and allows influx of cations. Couple blue light radiation with electric shock. LTP occurs, because blue light induces LTP on a molecular level. After some time, blue light is sufficient to induce a fear response in mice.

Associativity during activity induces LTP in weakly activated pathways when coupled to a strongly activated pathway. Therefore, LTP occurs in both pathways. Specificity during activity induces LTP only in the strongly activated pathway. Eventually, the weakly active pathway might be eliminated.

Two types of memory storage systems: Declarative memory (involved hippocampus and amygdala; hippocampus necessary for long term memory formation (not needed for retrieval specifically, but it is indespensable for the formation of long term memory) – memories include events, episodic memory, language, words, meaning of words, recognition and other consciously accessible memory data) and non-declarative memory (neural substrates of their formation unknown, but assumed to be widespread; includes motoric functions, associations, puzzle solving skills, priming cues etc. – storage is in cerebellum, basal ganglia, premotor cortex and other sites related to motor activity).

**Strokes destroy neural tissue**

Two major types of strokes can be differentiated: ischemic and hemorrhagic stroke. Ischemic strokes are blood clots jamming arteries which leads to areas of reduced blood supply (reduced supply of O2 and glucose). Hemorrhagic strokes are ruptures in vessels which leaks bloods, builds up pressure and can finally lead to mechanical damage of the neurons.

A transitory ischemic attack (=: TIA) has the similar or the same symptoms like an ischemic stroke, but they pass often <24h.

Ischemic strokes: Embolic: Blood clots from arteries (e.g. heart) leave their place and are translocated in the brain where they clog up the vessels. Often occurs without a TIA.

Thrombotic: Over time due to poor nutritioning, brain arteries clog up (often with arteriosclerosis). Often, TIAs precede. Happens in 80% of the ischemic strokes.

Hemorrhagic stroke: Rupture of blood vessels leads to leakage of blood. Subarachnoid: Blood leaks between skull and brain. Intracerebral: Blood leaks in the brain into the brain. Both conditions are dangerous because of reduced supply of oxygen and glucose etc. and danger of mechanical damage to neurons.

Primary and secondary pathomechanisms and their consequences: Primary pathomechanisms: Reduced oxygen and glucose supply to neurons leads to apoptosis eventually.

Secondary pathomechanisms: Reduced O2 supply leads to activation of HIF1-alpha (transcription factor during hypoxic conditions) and reduced glucose supply leads to changes in the metabolism. Also, further complications arise with ion gradients in neurons:

Acidosis: Activation of anaerobic metabolism produces lactate from glucose and H+. Lactate locally decreases the pH environment (makes it more acidic), which leads to protein instability and other problems.

Ion channels: Proper depolarization cannot occur anymore: ion gradients are disturbed; Na+ spontaneously leaks out of neurons (increased hyperpolarization), intracellular glutamate levels decrease while extracellular glutamate levels increase (due to Na+ dependent glutamate transporters), Ca2+ influx depolarizes the cell (further excitation, activation of Ca2+ dependent proteases, lipases; and production of free radicals and ROS).

ROS: ROS, NO and free radicals destroy macromolecules and can lead to apoptosis. Also, oligodendrocyte cell death leads to glial injury (demyelination).

The core zone compromises all irreversibly damaged or destroyed neurons. The penumbra is the target of therapy, since this zone is endangered by a stroke, but it can still be saved and the damage is normally reversible. Most often, the middle cerebral artery (=: MCA) is occluded, so the damage is restricted to the cerebral cortex.

Spontaneous recovery and compensation: Compensation: Compensation can occur on different levels: Distal areas which are related to destroyed brain tissue can compensate for the loss of function (EEG: those areas show an increased activity when compared to controls). In some cases, the neural activity can return to normal in affected areas (spontaneous recovery). Furthermore, reorganization (of the somatotopic map for example) can occur. Lastly, reduction in laterality (e.g. motor functions become contralesional and less lateral) – also a form of reorganization.

Most improvement occurs within 30 days. After 7 days, predictions about final improvement are most reliable.

Hemiplagia: One side of the body is affected by the consequences of the stroke. The unaffected side functions normally (obvious in gait, face expression, arm and hand control).

Possible treatments and therapies: Reperfusion – restoration of normal blood supply. Neuroprotection – protect penumbra. Prevent the formation of new blood clots with aspirin (anti-platelet; inhibits activation of platelets) or heparin (anti-coagulant; indirectly inhibits thrombin to blood clot). A thrombectomy removes the blood clot directly by guiding a catheter to the blocked site. In hemorrhage, surgery removes aneurysms and closes ruptured blood vessels.

**Multiple Sclerosis**

Multiple sclerosis is characterized by frequent inflammations of the nervous system mediated by an autoimmune response that results in the oligodendrocyte-induced death and axonal degeneration. Patients often have compromised cognitive and motor functions over the course of the disease (depends on where the site of inflammation is located).

Immune-mediated pathogenesis: Antigen presentation and T cell activation. B cell activation and antibody production. Chemotaxis, adhesion, migration (through BBB to brain site). Activation of macrophages and autoimmune response against myelin and attack on oligodendrocytes: demyelination. Axonal degeneration (oligodendrocytes not only have protective functions for neurons but also metabolic support due to high energy expenditure of neurons). Apoptosis.

Pathomechanisms: Perivascular inflammation, acute axonal transection, phagocytosis: microglia- and macrophage mediated removal of myelin, remyelination, further axonal loss in chronic regions, gliosis: proliferation of astrocytes and formation of scars.

Several processes lead to demyelination: Attack from cytotoxic T cells, NO and ROS attack on myelin, B cells produce antibodies against myelin, macrophages and microglia phagocyte myelin.

Control mechanisms in immunology: BBB: immunological ignorance – lymphocytes cannot normally pass the BBB. Anergy mediated by CD152. Suppression through T reg cells. Apoptosis.

Risk factors: Hypovitaminosis D (low vitamin D levels), smoking, Epstein-Barr virus, little exposure to sun (individuals living farther away from the equator are at increased risk of developing MS – the first 15 years are defining though). Hygiene hypothesis: Having expierenced more illnesses previously makes the body more resistant to developing MS.

Available treatments: Basic therapy: Fingolimod, Glatirameracetat, beta-Interferone. Advanced therapy: Natalizumab, Mitoxantron, Fingolimod. Pulse therapy with Cortisol also possible.

Types of MS: RRMS – SPMS – PPMS:

RRMS : Characterized by frequent (every 2 years) inflammations in the nervous system. Inflammation normally lasts for more than a week to be classified as a relapse. Also, some degree of remyelination may occur afterwards. RRMS can develop into SPMS after 10-15 years.

SPMS: After RRMS, axonal loss, death of oligodendrocytes and neurons occurs continously due to persistent inflammation without autoimmune attacks.

PPMS: Only few inflammations are necessary to induce constant loss of white and gray matter due to inflammations.

Experimental autoimmune encephalomyelitis (=: EAE): active immunization: injection of CNS myelin peptide, Freund’s adjuvant, BBB weakener. This activates the endogenous immune system, resulting into massive autoimmunity towards the CNS.  
Adoptive transfer: Create T helper cells specific for CNS myelin peptide and adoptively transfer these cells. The transferred cells induce immune reaction, resulting into massive autoimmunity towards CNS.

**Higher Functions of the brain and their mental disorders**

The association cortex: The association cortex is involved in processing inputs from different brain areas that allow for recognition and integration of information and transmit it to other brain areas.

Loss of function is therefore very specific when lesions occur in the association cortex, since it gets information ipsilaterally and contrallaterally in a series and parallel nature (leads to agnosia, specific loss of recognition of objects, such as faces, sounds, objects etc.).

The association cortex receives information from thalamic regions, which themselves actually project information to the association cortex. Also, the pulvinar and dorsomedial nucleus receive information from the sensory and motor cortex, which they process and send it onwards to the association cortex. The association cortex need not receive unprocessed information, but can receive transformed information inputs.

The parietal association cortex: involved in attention: The division of labor is ipsilateral, the right hemisphere is predominantly occupied with attention processing. The left hemisphere is occupied with language processing and has only a little involvment in attention processing. If damage to left side in the parietal cortex, then the right hemisphere can compensate (since the right side takes care of attention processing from both sides already anyway and the left side is only slightly involved in attention processing in general). If damage occurs in the right hemisphere, the left side cannot compensate and one has to deal with contralateral neglect syndrome: The inability to attend to specific parts of the body or objects despite sensory input from other areas (sensory, motor, somatic sensation etc.). It is sometimes coupled with apraxia (difficulty to perform complex motor tasks on the neglected side).

The temporal association cortex: Involved in recognizing stimuli that are attended to, especially complex stimuli. Damage results in agnosias (individual becomes unable to recognize certain categories of objects – prosopagnosia: inability to recognize faces).

The prefrontal cortex: Involved in planning and decision making amongst others (impaired in ADHD, PD, MDD, schizophrenia, AD).

ADHD: ADHD has a significant genetic component (concordance: 70%, only 30% is environment). In ADHD, patients have a reduced PFC and there are deficits in the neuronal circuits involving the PFC and striatum. It has been show ritalin (:= methylphenidate) is effective (dopamine/noradrenaline reuptake inhibitor).

Environmental factors: pre-natal smoking, low birthweight, diet (food deficiency or different metabolism in ADHD patients?), early deprivation/neglect, gene-environment interactions (epigenetics), TV/games/media.

**The study of stress**

Stress reaction on a macro level: first phase (Alarm reaction): shrinkage of thymus, spleen, liver, lymph nodes; drop in body temperature; acute erosions in digestive tract; removal of chromaffin from adrenal glands; fat tissue disappears. Time scale: Stress exposure < 6h.  
Second phase (Resistance): Adaption: adrenal glands are greatly enlarged and organ functions return to normal. Time scale: stress exposure 6-48h.  
Third phase (Exhaustion): same symptoms as in first phase + disease and death. Time scale: stress exposure > 1 month.

The fight-or-flight response: Following things can be observed easily: pupils dilate and eye lids retract such that more light can be absorbed, bronchies dilate, blood flow is reorganized: less blood flow in skin and gut, but more in muscles for maximal performance, vegetative functions are shut down so that more energy is available for catabolic processes, catabolic processes are upregulated by cort and NE: gluconeogenesis in the liver, the adrenal medulla releases epinephrine and NE and mediates glucagon release (for gluconeogenesis) in the pancreas, hairs stand on end (fearsome look), heart rate accelerates and strength of pumping increases to deliver more blood (oxygen and nutrients) to brain and muscles.

Sweat glands, arterial blood vessels, piloerector muscle and the adrenal medulla are only innervated by the sympathetic division.

The neuropsychological pathway of stress on a molecular level: Amygdala -> stria terminalis -> paraventricular nucleus (=: PVN) of the hypothalamus  
Bed nucleus of stria terminalis -> key limbic hub that activates PVN

PVN activates the following: HPA axis: release of cortisol/corticosterone; Sympathetic nervous system: adrenaline; In the brain: PVN activates CRH-containing neurons -> locus coeruleus: release of brain noradrenaline.

Functions of cortisol: suppresses the immune system (innate and adaptive), induces gluconeogenesis in the liver, inhibits lipogenesis (at the same time, catechoramine promotes lipolysis). After long and persistent exposure of cortisol: increased risk of formation of blood clots (thrombosis).

Surjective response space in NE: The effects of NE are dependent on the receptors in the target tissue and their exact location (pre- or postsynaptic).

**Parkinson’s Disease**

95% of PD cases are idiopathic while only 5% have a genetic origin.

MPTP: Drug that is metabolized. In mice and apes, it leads to human like symptoms of PD: Bradykinesia, postural instability, compromised gait, muscular rigidity (later on: hypokinesia or even akinesia).

Non-motor associated symptoms: depression, hallucinations, bladder dysfunction, no response to dopaminergic treatment, dementia, psychosis.

The PD phenotype can be improved to some extent through visual cues and kinaesthetic feedback.

MPTP is metabolized to MPP+ which ultimately inhibits the respiratory chain in the mitochondria resulting into oxidative stress within. Then, it is transported in vesicles via vesicle monoamine transporter (=: VMAT), where it will bind to negatively charged proteins in the cytoplasm.

In mice, the normal phenotype can be recovered when superoxide dismutase 1 (=: SOD1) is overexpressed in the mitochondrial genome.

The basal ganglia is responsible for the initiation of voluntary movement. Final downstream target of the basal ganglia network is the brainstem. The STN and GPi are target of DBS therapy, which can partially recover the normal phenotype. In the putamen, the D2 and D1 receptors are the main target for optogenetics therapy.

Biomarkers in PD: Loss of olfactory function in 70-100% of all patients and they do not respond to dopaminergic treatment at a later stage.

Concordance: 30% vs. 5% (monozygotic vs. dizygotic).

L-DOPA: A precursor of dopamine which is applied in PD to recover the normal phenotype. It acts on the striatum (putamen/caudate) on the D2 and D1 receptors . Permanent use of L-DOPA has dyskinesia as a side effect. Life expectancy is typically reduced by 10 years.

Cell biological and genetic factors in PD: Lewy bodies are observed in the SNpc. They originate from the misfolding of proteins leading to filament formation and aggregation of amyloid bodies finally. Often, alpha-synuclein is involved synucleinopathy. Other proteins are tau, amyloid-beta and TDP-43 (only in ALS though). Bradykinesia will occur only if more than 60% of the neurons are affected by synucleinopathy in the SNpc (synucleinopathy probably leads to cell death in striatal neurons).

Genes: PARKIN, PINK1, ubiquitine C-terminal hydrolase 1, alpha-syn.

**Motor systems and spinal cord injury**

Lesion levels and their consequences: Damage on a level affects all levels below.

C1-4: breathing

C2: neck movement

C5: shoulder movement

C6-7: elbow and wrist movement

C7-T1: hand and finger movement

T1-12: sympathicus

T2-T12: trunk stability

T11-L2: parts of sexual function

L2: hip movement

L3: knee extension

L5: knee flexion

L4-S1: ankle movement

S2-3: sexual functions

S2-4: bladder functions

Consequences of SCI: hypokinesia or hyperkinesia, depression, sexual dysfunction, bladder dysfunction, clonus, spasticity.

Spinal disk: left upper side: motor associated functions, left lower: posture and stability, right upper: sensory functions (like touch), right lower: pain and temperature. These things are of course symmetric.

Syndromes: Central cord syndrome: incomplete damage, different things can be targeted.

Brown-Séquard syndrome: one side is damaged: ipsilateral loss of motor functions and proprioception and contralateral loss of pain and temperature sensation.

Anterior cord syndrome: Only dorsal part undamaged (sensory functions) – loss of motor functions, pain, temperature and postural balance.

Posterior cord syndrome: All but dorsal part intact – loss of sensory functions.

Cauda equina syndrome: lower motor neurons affected.

Conus medularis syndrome: lower and upper neurons affected.

Tetraplagia: arms, limbs, upper and lower motoneurons affected. Paraplagia: legs, upper and lower motoneurons affected. Conus medularis: upper and lower motoneurons affected (lowest part of the spinal cord). Cauda equina: lower motoneurons (nerve fibers lying within the spinal cord) affected.

Ration: 3,8 : 1 (male : female) – most injuries occur at C4/C5 level and around T11-L1.

Motor unit: alpha-motoneuron with innervated nerve. There are also gamma-motoneurons that innervate intrafusally (alpha-motoneurons innervate extrafusally) which are needed for proprioception. When alpha-motoneurons activate without gamma-motoneurons, there will be a shortening of the Ia fiber as the muscles contracts and when activation occurs with the activation of a gamma-motoneuron, then there will be no decrease in Ia fiber while contracting.

Ia fiber: type 1 a sensory fiber (primary afferent nerve fiber).

Basal ganglia needed for proper initiation of movement and gait. Cerebellum needed for comparing intended and performed movement and correcting the error so that movement is smooth and nice. Also, the cerebellum is involved in motor skill learning (there are stem cells and ongoing cell proliferation in the granule cell layer).

Local motor circuits are needed for complex movements. There is a central pattern generator that works autonomously when it is stimulated/activated. Cats can be completely decerebrated and put on a treadmill and they will generate normal movement as long as they are on the treadmill. Humans cannot, but experiments have shown that there is a human CPG which can be used for recovery. The CPG also works independently of sensory feedback or supraspinal centres, but they help modulate the CPG.

Flexion: Activation of flexors and inhibition of extensors is ipsilateral. Inhibition of flexors and activation of extensors is contralateral.

Targets of therapy: neuroprotection, rewiring, goal-directed therapy (physiotherapy), reactivation.

A dermatome is a segment of skin that is provided by one spinal nerve (collective representation of skin not discrete representation of every single skin cell).

Corticospinal tract exam: let arm work against gravity and see how well it does.

Dorsal column exam: light touch.

Spinothalamic exam: stinging with safety pin.

Severity of lesion evaluated with the ASIA scale: integrates motor and sensory functions: AIS A is complete loss of function and AIS E is normal function (healthy).

MEP: motor evoked potential to test the pyramidal tract. SSEP: Somatosensory evoked potential to test dorsal column. CHEP: contact heat evoked potential to test spinothalamic tract (pain especially).

Lower motoneuron syndrome: paralysis/paresis, areflexia, loss of muscle tone, denervation signs.

Upper motoneurons syndrome: paresis, minor atrophies due to disuse, spasticity, Babinski’s sign, loss of fine voluntary movements.

Upper motoneurons are found in the brainstem and cerebral cortex.

The Corticospinal tract (=: CST, also known as pyramidal tract) is directly linked to hand and finger movement which makes it the model system of choice to test movement after an injury since the patient does not need to move all of his body and risk further damage (only hand). The CST can be disrupted at the pyrimdal decussation or at spinal levels.

The visceral nervous system: involved in sympathetic (T1-L2/3) and parasympathetic (S2-4) autonomous functions.

Lesions at T6 and above lead to severe cardiac dysfunctions. Also, tetraplegia patients have a disturbed circadian rhythm (problems falling asleep?).

In the sympathicus, the preganglionic axon (the one descending from the CNS) is short and cholinergic and the postganglionic axon (the one closer to the organs) is long and noradrenergic. In the parasympathicus, the preganglionic axon is long and postganglionic axon is short and both are cholinergic. The hypothalamus is a key structure in the visceral nervous system. (Cholinergic: acetylcholine is the neurotransmitter acting. Noradrenergic: norepinephrine is involved in transmitting the nerve impulses as a neurotransmitter.)

Functions of sympathetic and parasympathetic nervous system:

Sympathetic: increase heart rate, dilate pupils, inhibit salivation, relax airways, inhibit digestion, stimulate release of insulin and glucagon, stimulate gluconeogenesis and release, stimulate secretion of norepinephrine and epinephrine.

Parasympathetic: slow down heart rate, increase salivation, promote digestion, constrict airways, stimulate gall bladder for bile release, dilate blood vessels in intestines and rectum.

Autonomic dysreflexia: life-threatening, noxious (or non-noxious) stimuli below the lesion level (it does not reach the brain, but signalling is still ongoing locally).