

Neuromodulation and Neuroplasticity

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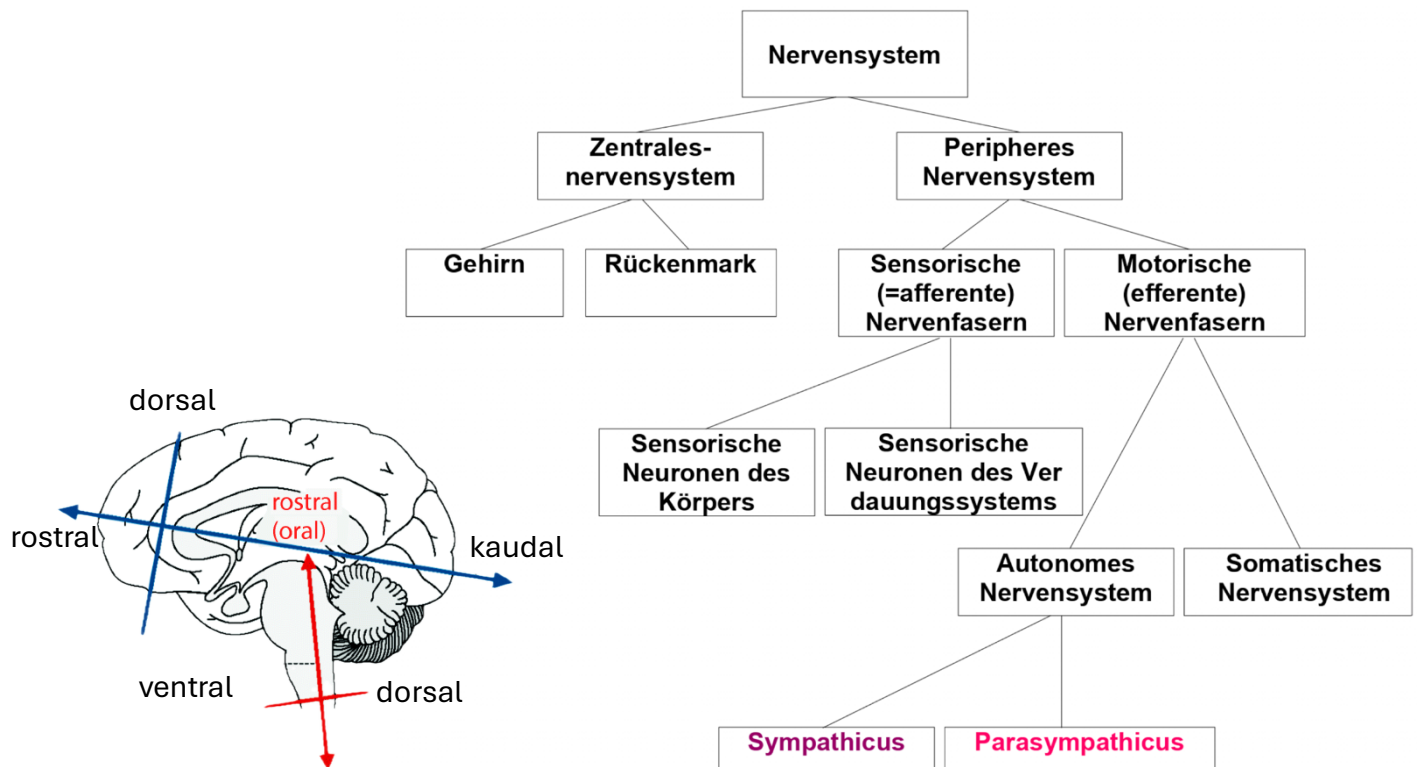
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WS 24/25

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Nervous system



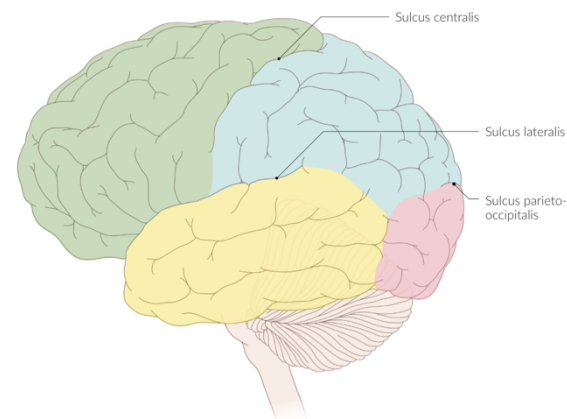
Anatomical overview

Central nervous system

- consists of brain (Cerebrum) and spinal cord (Medulla spinalis)
- less likely to regenerate (unlike PNS)

Lobe overview

Lobe	Function
■ Frontal lobe	- higher cognitive functions - primary motor cortex
■ Parietal lobe	- primary somatosensory cortex
■ Temporal lobe	- auditory functions - memory functions
■ Occipital lobe	- visual functions



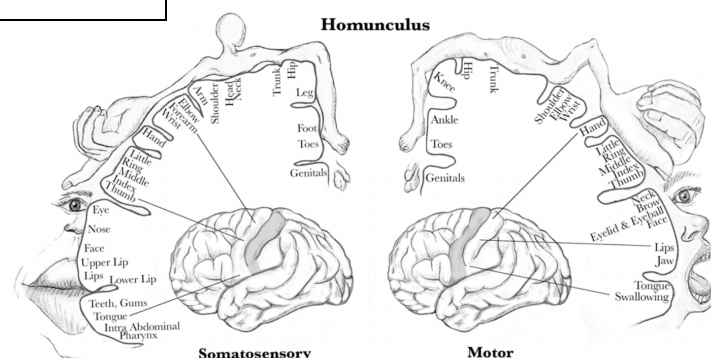
Sensorimotor cortex:

Somato-sensory functions:

- pain perception
- general sensory functions

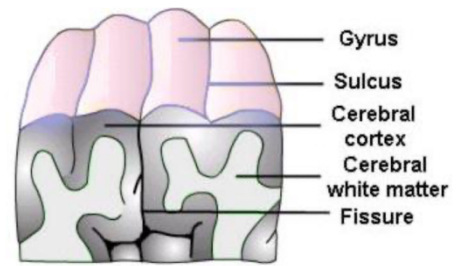
Somato-motor functions:

- voluntary motor functions of the musculature



Structure of the cerebral cortex

- 80 billion neurons << connections
- grey matter (subst. grisea): cell body (neurons)
- white matter (subst. alba): connections (axons)

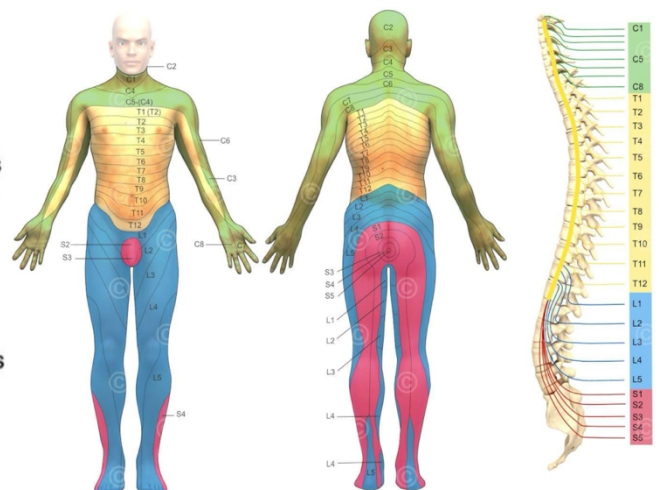
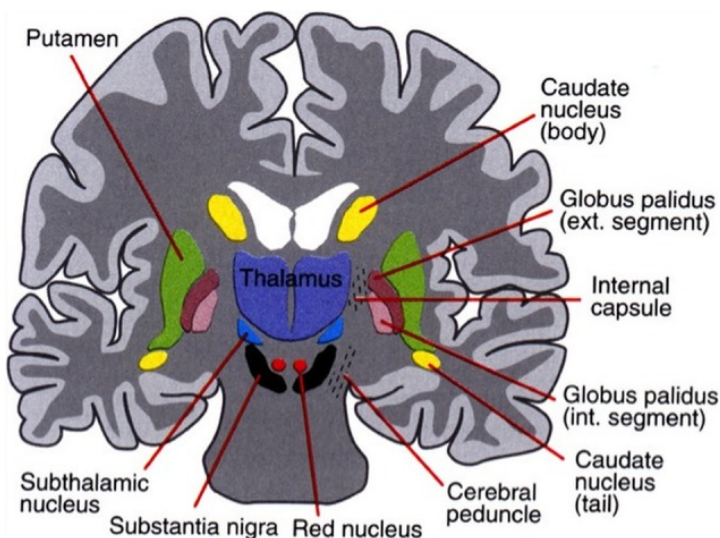


Gyri and sulci

- Gyrus cinguli: limbic system, psychomotoric function
- **Sulcus centralis**: separates motor/sensory cortex
- Sulcus lateralis (sylvii): separates temporal from frontal/parietal lobe
- Gyrus $\triangleq$ "mountain"
- Sulcus $\triangleq$ "valley"

Subcortical structures

- Thalamus: afferent filter function
- Basal ganglia: areas of grey matter in the white matter below the cerebr. hemispheres
 - movement coordination/synchronization with sensory information
- Substantia nigra: dopaminergic neurons (degeneration causes Parkinson -> DBS)



Pyramid track

Main function is the **activation of motor neurons** for:

- voluntary motor movements
- fine motor skills
- muscle tone

Peripheral nervous system

Body area split into **dermatomes**, **distinctive** of the innervating **spinal nerve**. Specific dermatomal problems might indicate an injury in the associated vertebral region.

Autonomic nervous system

- sympathetic/parasympathetic system (N. vagus)
- maintain vital functions: heartbeat, respiration, digestion, metabolism
- innervation of: organs, endo-/exocrine glands, vascular system, pupils, sex. organs

Neurophysiology

Action potential

- Na^+ influx -> depolarization, K^+ efflux -> hyperpolarization
- formation at the axon hillock
- **discrete** "all or none" event with **fixed duration** (comp. PSP) -> **they do not sum!**

Synapses

- **chemical synapses**: communication via neurotransmitters, vesicles
- **electrical synapses**: direct elect. communication, gap junction channels, less common

Neurotransmitters and receptors

- **ionotropic** receptor: receptor itself is the **transmitter dependent ion channel**
- **metabotropic** receptor: activates **signaling cascade** on **transmitter contact**

Central nervous system

- glutamate (excitatory)
- gamma-aminobutyric acid (GABA, inhibitory)
- glycine (inhibitory)
- dopamine, noradrenaline, serotonin

Peripheral nervous system

- acetylcholine

Electrophysiology

- measures **change** in **voltage** or **current flow** -> **neural communication**
- > action/postsynaptic potentials, ion channel activity, neuromuscular communication
- spatial scale from single ion channels to entire organs (method dependent)
- methods achieve **high temporal resolution**
- equilibrium potential (**-70 mV**) where **electrical** and **chemical gradients** balance out
- resting potential can be perturbed by **action potential** or **post synaptic potential**

Myelination

- by glia cells
- faster/more efficient
- saltatory impulse conduction

Chemical gradient

- uneven distribution of ions
- ions are enveloped in water
- > cannot easily pass lipid bilayer
- actively maintained by $\text{Na}^+\text{K}^+\text{ATPase}$

Ion Type	Membrane Permeability for Ions*	More Abundant
K^+ fast voltage activ. channel	High permeability	Intracellular
Protein-Anions ⁻	No permeability	Intracellular
Cl^- slow voltage activ. channel	High permeability	Extracellular
Na^+	Low Permeability	Extracellular

Postsynaptic potentials

- **graded** and **transient** change in membrane potential -> **summable!**
- realized by **ligand gated channels**
- **cation** influx (Na^+ , K^+): depolarization (**excitatory** postsynaptic potential **EPSP**)
- **anion** influx (Cl^-): hyperpolarization (**inhibitory** postsynaptic potential **IPSP**)

The measured signal

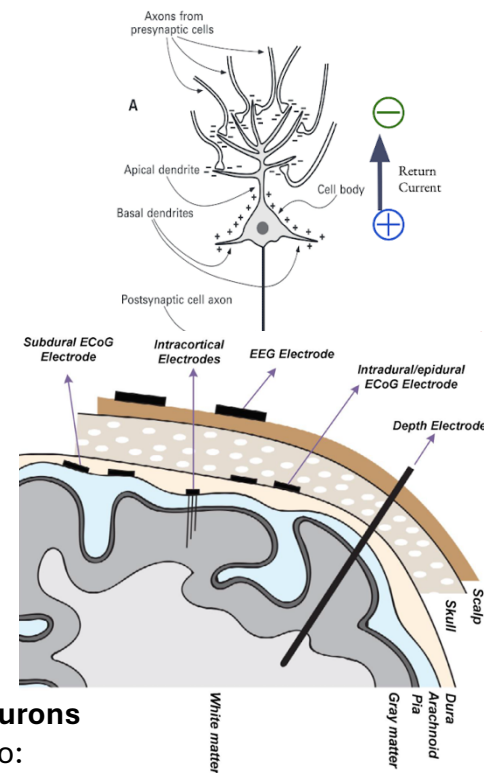
- ionic currents flowing across the **plasma membrane** create **electric potential**
- **extracellular voltage fields** form (local field potentials (**LFP**))
- **potential difference** between two points causes measurable **return currents**

Local field potentials

- field is the **superposition** of all **ionic processes**
- **amplitude decays with distance** ($\frac{1}{r^2}$) -> less informative
- **spatial averaging** with other fields
- summation/cancellation depending on **orientation** (vector)
- well understood

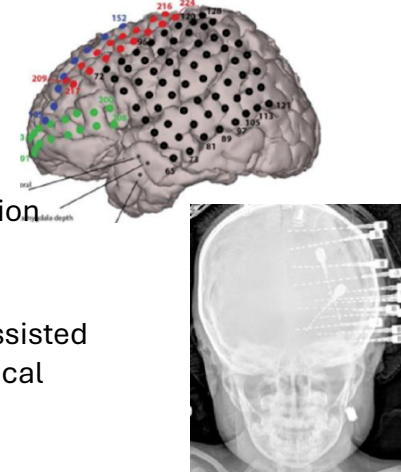
Electroencephalography (EEG)

- measures **voltage difference** on the scalp (with reference!)
- records synchronized activity of many cortical nerve cells
-> **postsynaptic potentials!**
- many electrode types:
 - EEG electrode
 - Subdural Electrocorticography (ECoG) electrode
 - intra-/epidural ECoG electrode
 - intracortical electrode
 - depth electrode
- signal mostly from **radially oriented cortical pyramidal neurons**
- heavily influenced by cortical pyramidal **neuron PSPs** due to:
 - proximity
 - orientation
 - synchronization
 - neuron shape
- volume conduction: tangential **voltage spread** when transitioning through skull/scalp



Intracranial EEG (iEEG)

- detailed focus search
- epi-/subdural
- grid and strip electrodes
- ECoG has better spatial resolution due to lower volume conduction
- recording/stimulation possible
- mapping of relevant regions
- can remain for up to 2 weeks

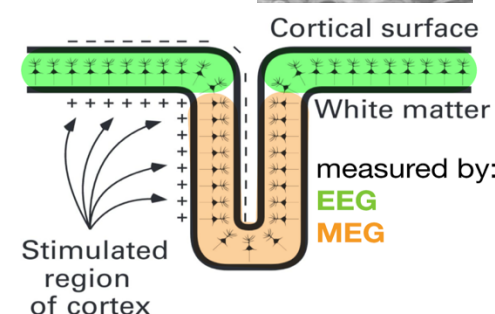


Stereotactic EEG (SEEG)

- several deep electrodes
- individual implantation
- frameless, frame based, robot assisted
- anatomical-clinical-electrophysical correlation

Magnetoencephalography (MEG)

- measures **magnetic field** instead of voltage
- primarily measures **tangential oriented pyramidal neurons**
- **no volume conduction** -> better source localization



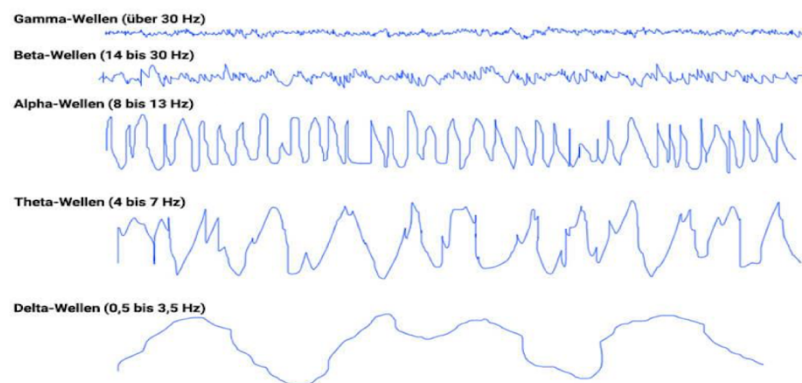
Comparability of measurement methods

- the closer to the neuron, the higher the frequencies that can be resolved

Method	Spatial Resolution	Max. Frequency	Signal Amplitude
EEG	40 mm	< 100 Hz	5 - 300 μ V
ECoG	4 mm	< 200 Hz	0.01 - 5 mV
LFP	0.4 mm	< 200 Hz	< 1 mV
Single Unit	< 0.01 mm	< 7000 Hz	~ 500 μ V
Patch clamp	~ 1 μ m	< 10000 Hz	

Waveforms

- gamma waves (> 30 Hz): heightened attention, learning process
- beta waves (~20 Hz): mental activity, sensory stimuli
- alpha waves (~10 Hz): awake brain activity with closed eyes (basic rhythm)
- theta waves (~5 Hz): when falling asleep or very tired
- delta waves (1.5-3.5 Hz): slow, synchronized waves signal deep sleep



Artifacts

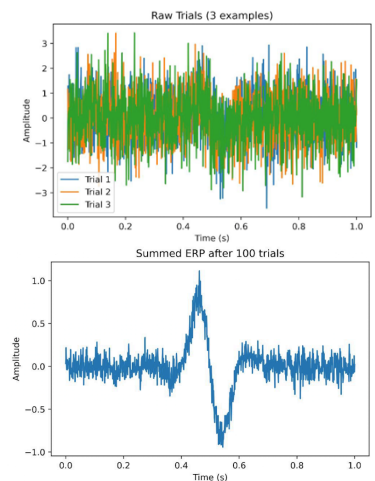
EEG data represents a mixture of **brain signal** and **noise** caused by:

- increased conductivity due to sweat -> **electrode interconnection**
- muscle action (cardiac, cranial, eye movement)
- neural stimulation methods
- ambient electronics (computers, lights, etc.)

To get rid of noise and view the desired data, **event-related potentials** are used.

Event-related potentials (ERPs)

- epochs are a given time frame around an **event of interest**
- relevant neural activity over **many trials** will be **temporally constant** in the epochs
- **averaging** over many trials will therefore **eliminate noise**
- ERPs are characterized by their **polarity** ($\pm$) and **latency**
- "difference wave" by subtracting ERPs of different conditions
- (+) very high **temporal resolution** (no add. filtering required)
- (+) fast, easy, low computational demand
- (-) non-phase-locked information is lost (due to averaging)
- (-) trial specific information is lost



Fourier transformation (FT)

- **decomposition** of time series signal into sum of sine waves of different frequencies
- time and frequency domain are the **representations of the same signal**
- temporal information is lost in frequency domain
- only for "**stationary**" signals of constant frequency

Short time Fourier transformation (STFT)

- for **non-stationary signals** with temporal and frequency variations (e.g. **EEG**)
- FT applied over small overlapping time windows
- shorter windows improve temporal resolution but reduce frequency resolution (v.v.)

Modulation of the nervous system

- neural **communication** via **electrical/chemical signals**
- **signal transduction**: transformation of externally applied energy into **cellular signal**
- cells react to a variety of physical signals over different timescales:
 - immediate evoked response (spikes, EPSPs, IPSPs)
 - synaptic **plasticity** changes (short/long term)
 - circuit reconfiguration
- change of synaptic plasticity (interneural "coupling strength")
-> **duration extension** of neuromodulation effects beyond application
- distinction between three broad target systems:
 - specific brain regions (CNS)
 - spinal cord (CNS)
 - peripheral nerves/muscles (PNS)

Precision

- to optimize treatment response with minimal side effects
- to take causal inferences between brain region and motor processes
- controlled by two key aspects:

Target accuracy (sensitivity)

- spatial precision
- effectively reaching the desired physical location (brain regions, nerves, etc.)

Selectivity (specificity)

- functional precision
- minimizing off-target activation and therefore side-effects like headaches or dizziness

Control

- the ability to bring target system in into desired state
- same input can lead to different output depending on system state and history like:
 - different phases of neural activity
 - neuroplastic changes

Open loop control

- no knowledge of system state
- independent from brain response
-> no change in stimulation
- most research is open loop

Closed loop control

- stimulation is modulated by evoked neural effects (target state difference)
-> dynamic stimulation parameters
- technical challenges
- future perspectives

Methods of brain modulation

Electrical Modulation of the cortex

- application of **voltage gradient** across pair of **scalp** electrodes (tES)
-> **induced current** in the brain
- effective but relatively low currents (0.5-2 mA)
- transcranial **direct current** stimulation (tDCS)
- transcranial **alternating current** stimulation (tACS, 50-60 Hz)

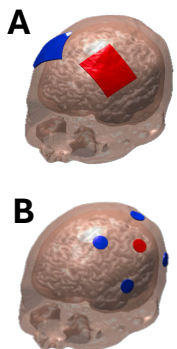


Issue with the tissue

- relatively **low conductance** of scalp and skull and hence **high resistance** to current
-> **high energy loss** from outside to inside of the skull (two orders of magnitude)
- limited amount of current to avoid pain (max. 2 mA)
- **not precise** due to **current spread** (for gross brain regions)

Mechanism of tES (somatic doctrine)

- induced electric fields are **sub-threshold** for action potential generation
- changed **excitability** (altered resting membrane potential)
-> **modulation** of **spontaneous activity** rather than induction
- anode (+): **depolarization** of neuron soma (**more responsive**)
- cathode (-): **hyperpolarization** of neuron soma (**less responsive**)
-> **cycles** of enhanced/diminished **excitability** with tACS
- no numerical change in **ions** but **redistribution**
- **lasting aftereffects** because of **plastic changes** at synapses during stimulation
- aftereffects increase with current and duration of stimulation
- better **localized fields** with **ring** (B) instead of regular (A) **configuration**
- issues with **current spread** and overstimulation of some brain nerves
- effect may also come through peripheral nerve mediation into the brain rather than actual stimulation of neurons

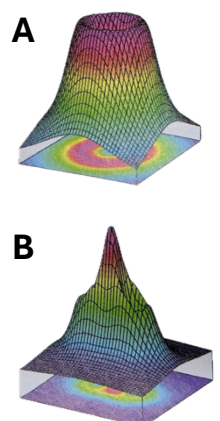


Transcranial magnetic stimulation (TMS)

- evocation of **action potentials** in spatially limited region of the **cortex**
- induced **current** via **magnetic field** (not effected by skull/scalp)
- geometry and **orientation** dependent (different current flow across gyri and sulci)
- contraindicated with cranial metal implants, seizure/disorder history

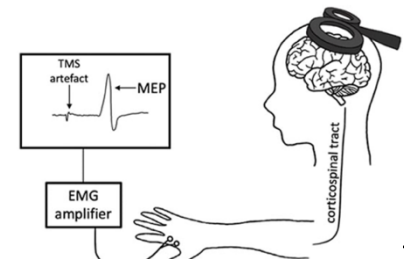
Coil

- **round** (A) and **figure-eight** (B) coil configuration
- overlapping fields of **figure-eight coil** allow for **high spatial precision**
- but everything in the field's "path" is excited, not just the tip



Measurement

- motor evoked potentials (MEPs) can be measured by electromyography after motor neuron activation by TMS
- MEP reflect cortical/spinal cord **responsiveness** to TMS
- repetitive TMS (rTMS) can result in **inhibition** (LF: <1 Hz) or **excitation** (HF: >5 Hz)

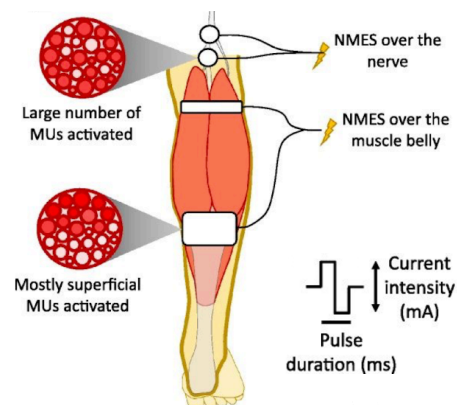


Peripheral nerves

- bundles of parallel axons embedded in connective tissue
- conduction of information between brain and body as **electrical signals**
- of different origin (cranial/spinal)
- **sensory** (afferent), **motor** (efferent) or **mostly of mixed type**
- easy stimulation of nerves near the skin's surface (compared to cortical stimulation)
-> use of high field strength -> **directly induced action potentials** in axon
- induced **AP travels along the axon** either to the **effector organ/sensory ending** (**orthodromic**) or back to its **cell body** (**antidromic**, refractory period $\frac{1}{2}$)

Neuromuscular electric stimulation (NMES)

- biphasic stimulation of either the direct **muscle** or its **nerve**
- current adjusted till maximal tolerated intensity
- unphysiological motor unit recruitment (all at once $\frac{1}{2}$)
- **functional electric stimulation** (FES) to achieve whole, functional movements (rehabilitation/sports)

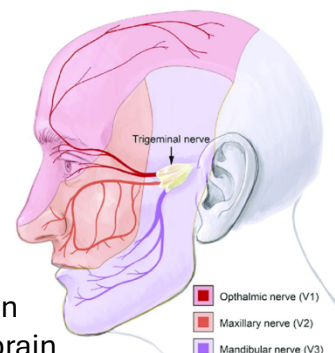


Paired associative stimulation

- paired stimulation of the **motor cortex** (e.g. via TMS) with following **muscle stimulation** (NMES/FES)
- Hebbian principle: "**what fires together, wires together**"
-> enhanced motor control
- plastic change in the corticospinal cord and primary motor cortex

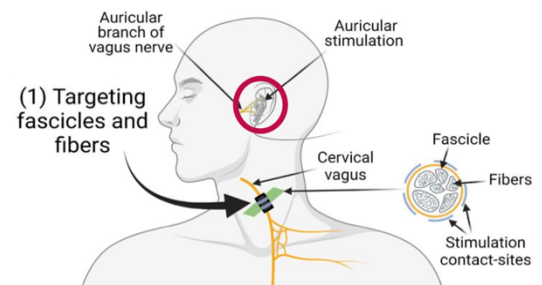
Trigeminal nerve

- provides sensation to face and scalp skin and mucous membranes of the mouth and nose
- mixed cranial nerve
- stimulation with biphasic tES pulses mostly on forehead to evoke action potentials
-> explored for use in **headaches, migraine, epilepsy, ADHD, depression**
- wide effects from narrow stimulation due to nerve projections into the brain



Vagus nerve

- main nerve of the parasympathetic nervous system
-> control and sensory functions
- "gut brain axis"
- mixed cranial nerve (~80% afferent, ~20% efferent)
- different options of vagus nerve stimulation (VNS)
- modulation at lowest level of the brain (medulla)



Cervical VNS

- either invasive or transcutaneous
- activation of afferent fibers
- treatment of epilepsy and depression
- closed-loop applications

Transcutaneous auricular VNS

- stimulation through small sensory branch in the earlobe (auricular)
- treatment of trauma patients
- increased learning performance

Clinical cases

Clinical conditions that can be treated with neuromodulation

Neurological

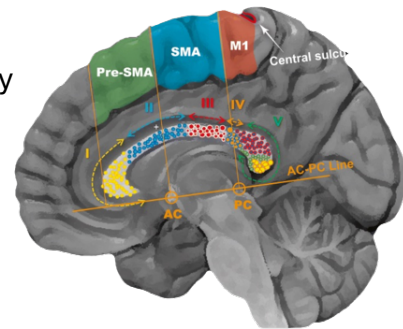
- influence on body functions
-> easy to quantify
- Parkinson, stroke, epilepsy, dystonia, pain, traumata

Psychiatric

- influence on behavior
-> difficult to quantify (subjective)
- Alzheimer, depression, autism, ADHD, schizophrenia, tinnitus

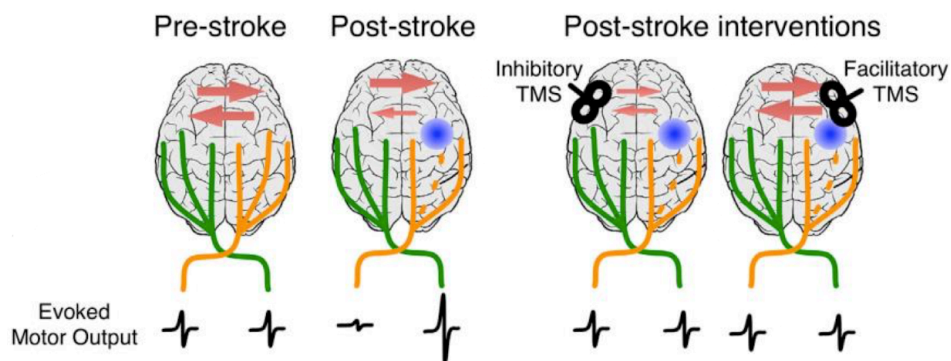
Parkinson's disease

- **restrained motion** with resting tremor, postural instability or rigidity
- approach of **excitatory** stimulation of **primary motor cortex (M1)** and **inhibitory** stimulation of **supplementary motor cortex (SMA)**
- improvement of "freezing of gait" with **tDCS** of **motor cortex**
- best result with **simultaneous stimulation** of motor and cognitive network



Stroke

- ischemic (blockade) or hemorrhagic (bleeding) type of stroke
- caused by embolism, thrombus or aneurysm
-> disorders of speech, vision, attention, memory or personality
- **disbalance** between **hemispheres** (overactivity of healthy hemisphere)
- **balance restoration** by **strengthening** of **affected** and **inhibition** of **healthy** hemisphere via rTMS



Depression

- FDA approved treatment of drug-resistant depression via rTMS of **dorsolateral prefrontal cortex (DLPFC)**
- **reactivation** of areas with reduced activity resulting in release of neurotransmitters
- daily sessions for 4-6 weeks
- improved quality of life "measurable" both directly and 6 months after therapy