Vorlesung 1 – Introduction & Fundamentals

module contents

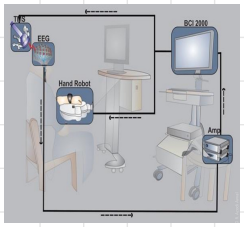
- fundamental anatomy & physiology of the sensorimotor nervous system
- basic theories & models of neuronal plasticity
- applications, advantages & disadvantages of transcranial neuromodulation (TMS, tES)
- applications, advantages & disadvantages of peripheral neuromodulation (pNS, NMES)
- clinical application examples

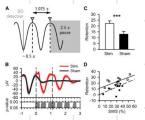
Learning objectives
- You understand the structure of the human nervous system, can define and localise the individual components and explain the mechanisms involved.
- You have learnt the theoretical principles and practical application of neuromodulatory procedures and you can present them in a comprehensible manner.
- You know the basic concepts of neuroplastic processes and you can categorise them.
- You know about the clinical fields of application and can present them.
- You can assess future medical technology fields and develop creative ideas.

- Parkinson → deep brain stimulation (invasive)
- non-invasive
  - → tDCS (transcranial direct current stimulation)
  - → tACS (transcranial alternating current stimulation)
  - → pNS (peripheral neurostimulation / neuromuscular stimulation (NMES)) → electrical stimulation → direct muscle stimulation
  - → TMS (transcranial magnetic stimulation) → magnetic field (cheapest of all methods) → induces action potential
  - → neuromodulation during sleep
  - → brain state-dependent stimulation







→ different brain-states
- δ → 0,5–4 Hz: deep sleep, restorative functions → less excitable (coma)
- θ → 4–8 Hz: light sleep, drowsiness, deep meditation
- α → 8–12 Hz: relaxed wakefulness, meditation, restful alertness
- β → 12–30 Hz: wakefulness, active thinking, focus
- γ → 30–100 Hz: high-level information processing, heightened awareness, complex mental activities → too excitable (Epilepsy)

Krankheitsbilder

relatively well researched: Parkinson, Tremor, Dystonie, Epilepsy, Pain

not well researched: stroke, Motor, Neglect, Aphasia

Dystonie: langanhaltende, unwillkürliche Kontraktionen der Skelettmuskulatur

Motorneuronerkrankung: auf Motoneuronen getroffen → beeinträchtigt nicht die Sensibilität

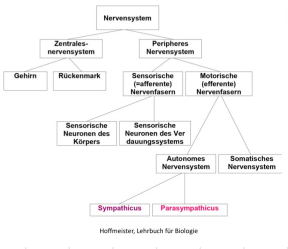
Neglect: durch Hirnschädigung (meist Schlaganfall) verursacht, Störung der Aufmerksamkeit für eine Körper- oder Raumhälfte

Aphasie: Sprachstörung

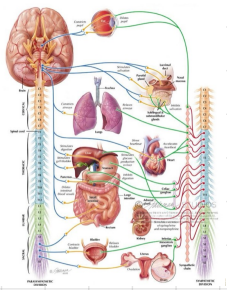
Vorlesung 2 – Neuroanatomy & -physiology

Nervous system overview

Learning objectives
- Students understand the structure and function of the human nervous system, can define and localise the individual components and explain the mechanisms involved.
- Students have learnt the theoretical principles and practical application of neuromodulatory procedures and can present them in a comprehensible manner.
- Students know the basic concepts of neuroplastic processes and can categorise them.
- Students know about the clinical fields of application and can present them.
- Students can assess future medical technology fields and develop creative ideas.



Hoffmeister, Lehrbuch für Biologie

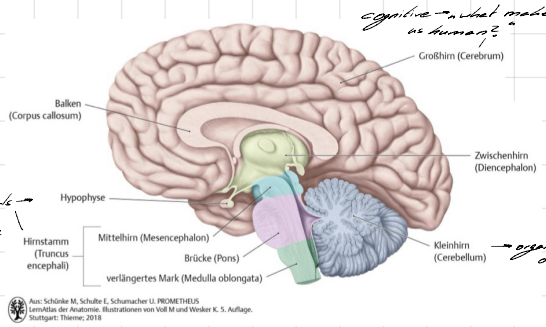


→ main efferent connection between gut/heart & brain: N. vagus

central nervous system → = brain & spinal cord

cognitive → „what makes us human?"

PNS: Nerves can grow again
ZNS: Nerves can't grow again



Aus: Schünke M, Schulte E, Schumacher U. PROMETHEUS LernAtlas der Anatomie. Illustrationen von Voll M und Wesker K. 5. Auflage. Stuttgart: Thieme; 2018

essentials → how to survive

→ organisation & orientation

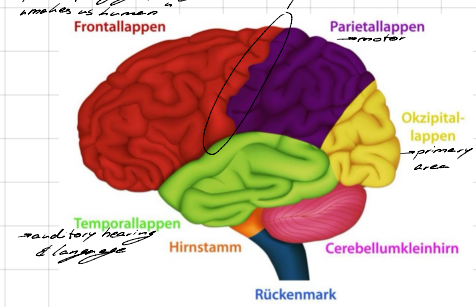


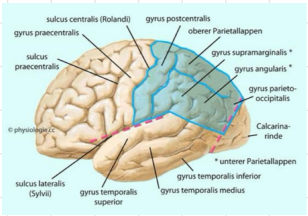
orientation in the cortex

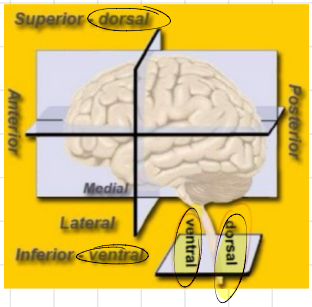
→ parts of language, planning makes us human

= central sulcus

gyrus = mountain
sulcus = Schlucht



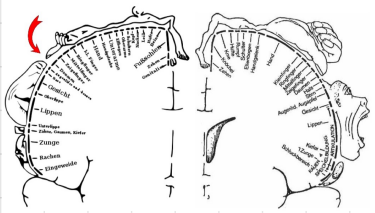


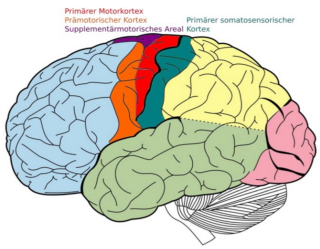


Sensorimotor cortex

Motorhomunculus

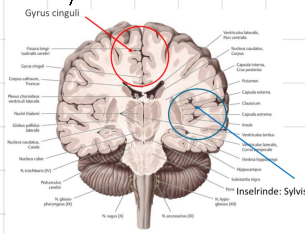
sensory-homunculus



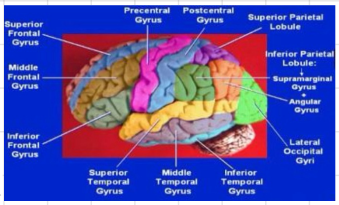


structure of the cortex

grey = neurons
white = axons

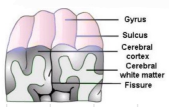


Thime Gruppe



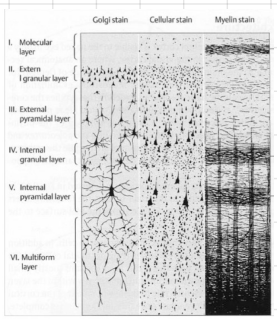
structure of the cerebral cortex



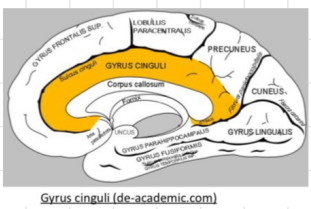


Grey matter: Cell body

White matter: Fibre connections



Cerebral Cortex | Neupsy Key

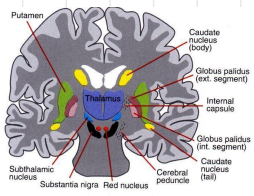


Gyrus cinguli (de-academic.com)

- 86 million neurons in brain with billion connections inbetween (dendrites & axons)
- which is the strongest principle? - the segregation or integration of the cortices?

Subcortical structures

very important!



basal ganglia: areas of grey matter in the white matter below the cerebral hemispheres

function: coordination of movements, synchronisation of movement sequences with sensory information

→ are affected in various neurological diseases, important target area for DBS

Thalamus: "a big big filter" → filters afferent information entering the brain → prevents overload → focus

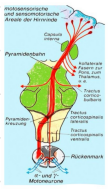
Savant-Syndrom

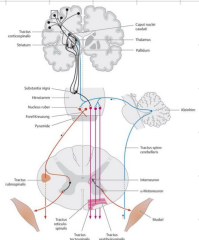
Inselbegabung = enables filter → can draw London by looking at it once

Feuerwehrproblem = will wissen, google nad

substantia nigra: place of dopamine → dopamine sent to striatum → Ursprungsort Parkinson

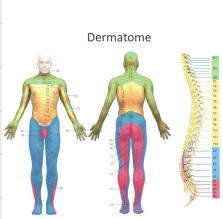
Pyramid track

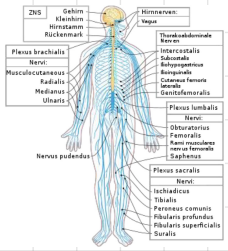




→ main function: activation of motor neurons for the execution of voluntary motor movements, fine motor skills & muscle tone

Peripheral nervous system

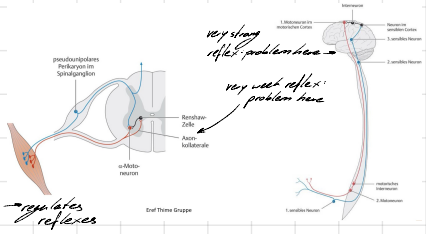




- spinal cord problems = Volkskrankheit
→ "You might have a disc colabs at the level of L5"

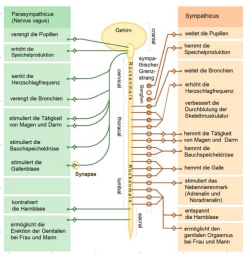
Interface central - peripheral nervous system

→ the nerv system is organized in loops



Autonomic nervous system

Function: to maintain vital functions such as heartbeat, respiration, digestion and metabolism. Organs and organ systems are innervated by the autonomic nervous system, e.g. the sexual organs, endocrine glands (hormones), exocrine glands, the vascular system (RR) or the pupil reaction.



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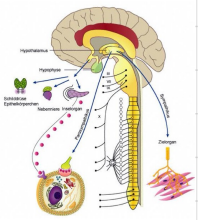
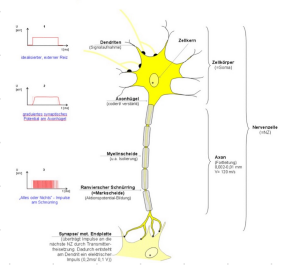
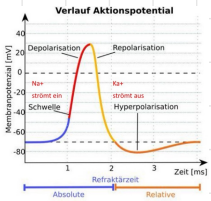


Neurophysiology

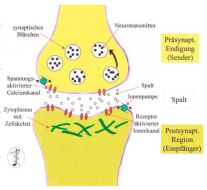
Nerve cell / Neurons

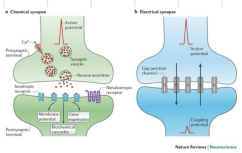




Sodium-potassium pump is the most important mechanism for the transport of ions across the cell membrane

Synapses





Chemical synapse: communication via neurotransmitters

Electrical synapse: direct electrical communication (less common)

→ pharmacology is supporting/inhibiting the synapsis → Agonists & Antagonists

→ Antidepressants are supporting Serotonin-transport

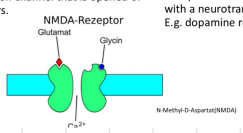
Neurotransmitters & receptors

Epilepsy: decrease of ZNS → give GABA (inhibitory)

1. Acetylcholin: most important transmitter in PNS
2. Glutamat (excitatory), Gamma-aminobutyric acid (GABA, inhibitory), Glycine (inhibitory), dopamine, noradrenaline, serotonin: most important transmitter in ZNS

Ionotropic receptor:
Receptor is itself an ion channel that is opened or closed by transmitters.

Metabotropic receptor:
Receptor activates a signalling cascade in the cell on contact with a neurotransmitter. (signalling cascade in the cell)
E.g. dopamine receptor D1

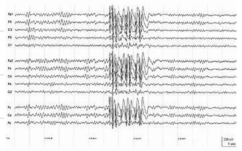


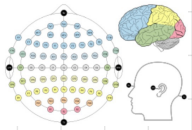
Elektrophysiology

Elektroencephalographie EEG

- firing happens in different frequences → 10Hz = 10 times/second
- not single neurons, but whole areas are firing synchrone
- sources of the EEG signal
  - → source reconstruction → take signals from all over the head & detect the source
  - → functional connectivity
- EEG records synchronised activity of many nerve cells (postsynaptic potentials) → picture 1

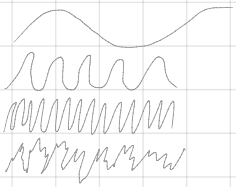


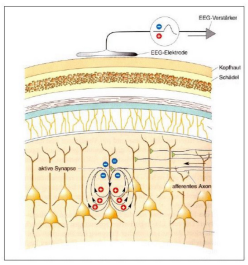


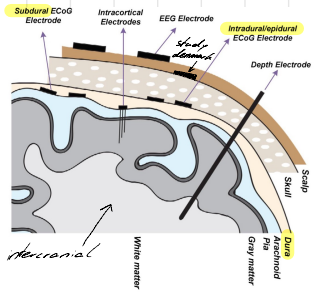


waveforms in EEG

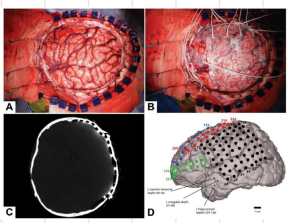
→ different brain-states
- δ → 0,5-3,5Hz: deep sleep, restorative functions → less excitable (coma)
- θ → 4-7Hz: light sleep, drowsiness, deep meditation
- α → 8-13Hz: relaxed wakefulness, meditation, restful alertness, "basic rythm"
- β → 14-30Hz: wakefulness, active thinking, focus
- γ → 30-100Hz: high-level information processing, heightened awareness, complex mental activities → too excitable (Epilepsy)





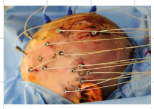


intracranial EEG



- detailed focus search
- Epi- or Subdural
- grid & stripelectrodes
- Recording & stimulation possible
- mapping of relevant regions
- can remain for about 2 weeks

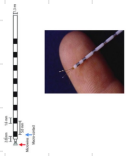
stereotactical EEG (SEEG)





- several deep electrodes
- individual implantation
- anatomical-clinical electrophysiologic correlation
- frameless, frame based or robot-assisted feasible
- → used if you can't find the area causing epilepsy or if it's too deep

→ robot-controlled SEEG





- enables planning of multiple trajectories with CCT or MRI2
- shorter implantation time

die Antworten mit * sind richtig

What does not belong to the subcortical structures?
a) Nucleus Pallidus
b) Motoneuron .
c) Nucleus Caudatus
d) Substantia Nigra
e) Putamen

What is not part of the central nervous system?
a) Spinal cord
b) Cerebellum
c) Plexus lumbalis .
d) Cerebrum
e) qqBrainstem

What is not a component of a nerve cell?
a) Dendrit
b) Myelin sheath
c) Axon
d) Cell nucleus
e) Melanozyt .

Which of the following is not controlled by the autonomic nervous system?
a) Pupil reaction
b) Digestion
c) Endocrine glands
d) Hand movement .
e) Heartbeat

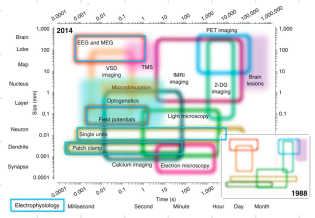
What is not one of the advantages of an intracranial EEG?
a) Can remain for about 2 weeks
b) Detailed focus search possible
c) Recording and stimulation possible
d) Cost-effective procedure .
e) Mapping of relevant regions possible

Motoneuron → starts in the cortex louder layer of the brain
plexus lumbalis → peripheren Nerven Hommes hier zsm

Vorlesung 3 – Fundamentals of Electrophysiology

methods of measuring brain activity

- brains are complex & have multiple ongoing processes
- Processes operate across spatial & temporal scales
- to face the challenge we can choose from a considerable pool of neuroscience methods



EEG doesn't capture AP, but postsynaptic potential

with EEG you measure the whole brain

what is Electrophysiology?

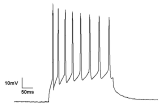
physiology = the study of living organisms

→ studies the electrical properties of cells & tissues in biological systems → from individual ion channels to entire organs

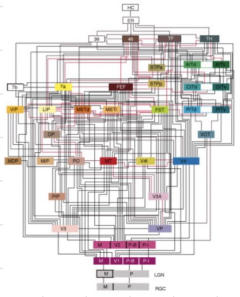
- Measures change in voltage or current flow

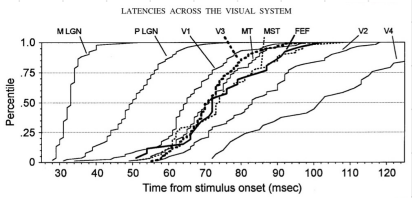
→ action potentials, postsynaptic potentials, ion channel activity, Neuromuscular communication (Electrooculography (EOG), Electromyography (EMG), Electrocardiography (ECG))

Measures of neural communication



- capabilities of Electrophysiology
  - → direct measure of neural signalling
  - → all methods create a electrical time series signal (voltage & current flow over time)
  - → all methods have high temporal resolution
  - → Spatial resolution depends on the method





Physics recap

Current (I or A): Ampere

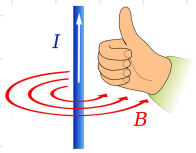
Voltage (U or V): Volt

Resistance (R or Ω): Ohm

Ohm's law: $U = R \cdot I$

Ampere's law: $\oint B\,dl = \mu_0 I_{enc}$

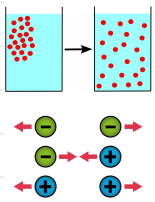
→ Electrophysiology relevance: an electrical current flowing through a (constant) resistor generates voltage drops & creates a magnetic field around it



Diffusion force: Ions move from a high-concentration to a low-concentration area to achieve a uniform concentration

Electrical force: Ions are attracted by the opposite charge & repulsed by the same charge

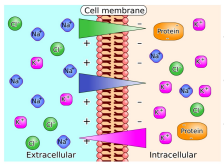
→ Diffusion force & Electrical force introduce potentials for ions to move → a chemical gradient (diffusion force) } Electrochemical gradient → an electrical gradient (electrical force) }



Bioelectrical Principles of Neurons: Chemical Gradients

- Ions are enveloped by water and cannot easily pass the lipid bilayer plasma membrane
- Ions are unevenly distributed between the cytosol (intracellular fluid) and the extracellular fluid
- The uneven distribution of ions is actively maintained by the Na⊕K⊕ATPase (Sodium-Potassium Pump)

Ion Type	More Abundant
$K^{\oplus}$	Intracellular
Protein-Aniones	Intracellular
$Cl^{\ominus}$	Extracellular
$Na^{\oplus}$	Extracellular

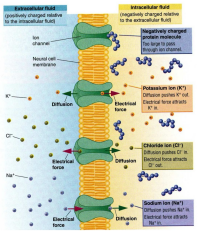


the resting membrane potential

- Selective ion channels cause ion specific membrane permeabilities
- At the equilibrium potential (~ -70mV) electrical and chemical gradients balance out, this means equally many ions are pushed out as are attracted in (zero net movement)
- The Resting Membrane Potential is driven by the concentration differences of the ions and the ion-specific permeability

Ion Type	Membrane Permeability for Ions*	More Abundant
$K^{\oplus}$	High permeability	Intracellular
Protein-Aniones	No permeability	Intracellular
$Cl^{\ominus}$	High permeability	Extracellular
$Na^{\oplus}$	Low Permeability	Extracellular

*in resting condition

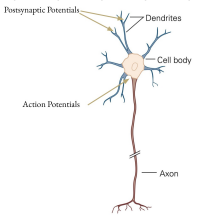


For further Interest: Goldman, Hodgkin and Katz Equation:

$$E_s = RT/zF \ln \frac{p_{Na}[Na^+]_o + p_K[K^+]_o + p_{Cl}[Cl^-]_i}{p_{Na}[Na^+]_i + p_K[K^+]_i + p_{Cl}[Cl^-]_o}$$

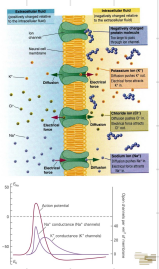
Neural Signaling

- Resting membrane potential is a stable equilibrium that is actively maintained (the body invests a lot of energy into it)
- For neural signalling, two types of events can perturb the system away from the resting potential
  - Action potentials
  - Post synaptic potentials



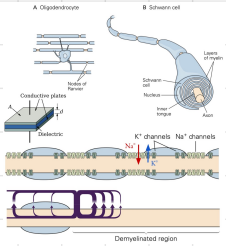
Action Potential

- Realized by voltage gated channels
- Triggered by depolarization of the membrane potential
- Voltage gated sodium channels have a fast response time but deactivate themselves after a short amount of time
- Voltage gated potassium channels react slower to the voltage change but do not inactivate
- Active signal propagation



Myelination

- Some axons are wrapped by Myelin sheaths
- Myelination by glial cells
- Faster and more energy efficient signal propagation:
  - Reduces leakage across membrane
  - Decreases membrane capacitance
  - → Signal jumps from node to node (saltatory impulse conduction)
- High density of voltage gated sodium channels at nodes of Ranvier



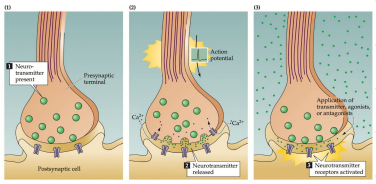
$$\text{capacitance } (C) = \varepsilon_0 \varepsilon_r \frac{\text{area } (A)}{\text{distance } (d)}$$

Postsynaptic Potentials (PSPs)

- Realized by ligand gated ion channels*
- Kation Influx: depolarization (excitatory postsynaptic potential EPSP)
- Anion Influx: hyperpolarization (inhibitory postsynaptic potential IPSP)
- Unspecific ion channels can also trigger secondary processes (like synaptic strengthening)
- Passive signal propagation (summation)
- Leaky integration

} ligand & ion channel determine the postsynaptic effects

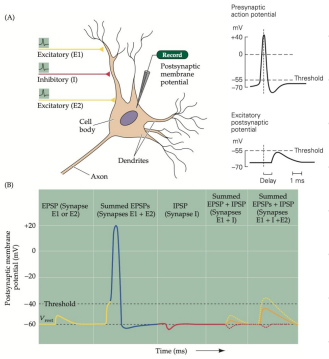
* there exist also other types of receptors relevant for synaptic signalling but we will focus on ion channels for this



Summation Properties

AP & Postsynaptic potentials have different temporal dynamics & therefore different summation properties

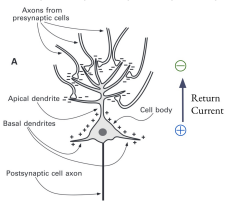
→ relevant for direct measure of the process that enable intercranial communication



the measured signal

- Ionic current flows across the plasma membrane create electrical potential
- Potential differences between two points cause return currents

Electrical signals can be measured on different scales:
- Across the plasma membrane
- Extracellularly along neurons
- Extracellularly between multiple neurons
- Across neuron populations/ brain regions

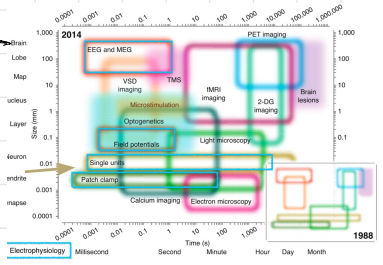


Summary:
- Action potentials and postsynaptic potentials are systematic deviations from the otherwise stable maintained resting membrane potential
- Ion influx and efflux of neurons, creates extracellular voltage fields
- These fields can summate over distances

Ion channel & neuron level

Measuring the signaling of individual neurons or neuronal compounds in response to stimuli or electricity →

Example measure: single channel activity & action potential frequency

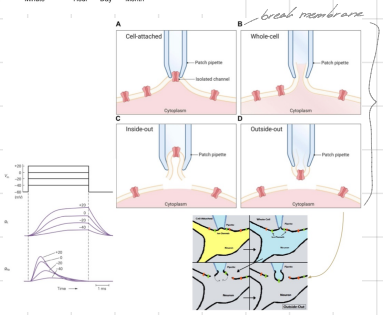


Patch clamp recording

- attach glass pipette to a patch of membrane to record activity of individual ion channels

Parameters

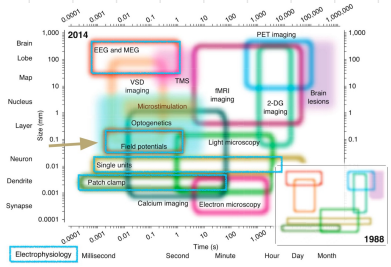
- fluid in glass pipette
- extracellular bath
- Voltage/Current in the pipette



field potentials

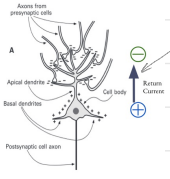
extracellular measures of the signaling of multiple nearby neurons →

example measure: local field potentials & multi unit activity

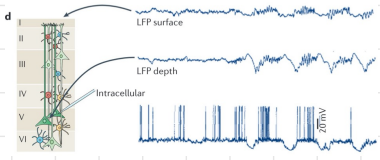


- Record voltage changes resulting from neuronal signalling extracellularly → extracellular electric field
- Field is the superposition of all ionic processes
- LFP gets less informative with distance from current source:
  - Amplitude decays with distance
  - Spatial averaging with other current fields





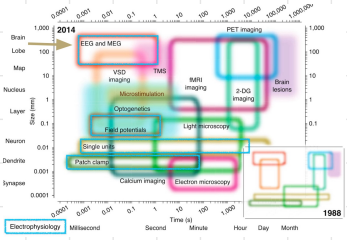
we bring an electrode in this space here



whole brain recording: EEG & MEG

measuring the signal of the whole brain areas simultaneously

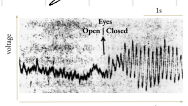
example measures: ECoG, EEG, MEG



EEG

the discovery

- Hans Berger, 1924

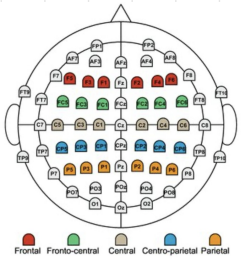


- Neural origins were disputed at first, but ultimately proven by 1934 after replication by Edgar Adrian and Bryan Matthews
- By the 1950s and 60s, EEG became established as a new tool in neurology and neuroscience

what do we measure?

→ voltage differences on the scalp

- reference measure between two electrodes
- (most often an additional ground electrode is added)



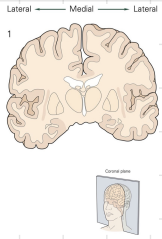


Anatomical Origins of EEG Signals

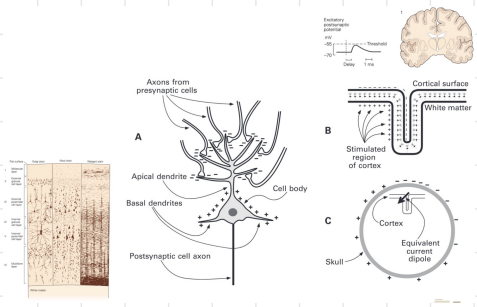
- Electrical Fields decay with the square of the distance
- Fields can summate or cancel each other out depending on their orientation

what are we actually measuring?
– question not solved yet

most easy part of the brain to analyse with EEG: cortex

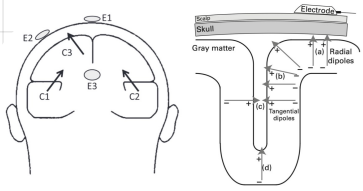


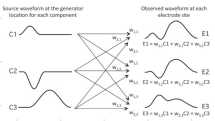
Scalp EEG signals are heavily influenced by PSPs of cortical pyramidal neurons due to
- Proximity
- Orientation
- Synchronization



Source summation

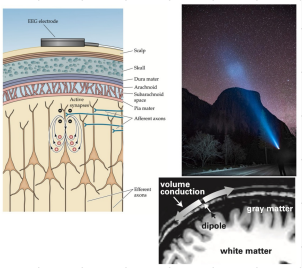
- sources of same orientation sum up,
  sources of opposite orientation cancel out
- angle between the source determines summation strength (maximal at 0° & cancellation at 180°)



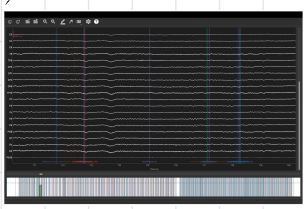


Volume conduction

- Distance between sources (pyramidal neurons) and sensors
- Voltage spreads through different tissues
- Volume conduction: tangential voltage spread when transitioning from skull to scalp
→ neighbouring channels are highly correlated in activity



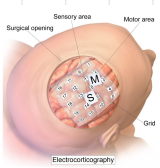
example Data EEG



related methods

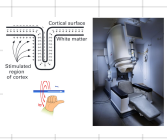
ECoG:

- Electrodes are placed under the skull
- Same sources as EEG
- Better spatial resolution due to lower volume conduction
- Invasive!



MEG:

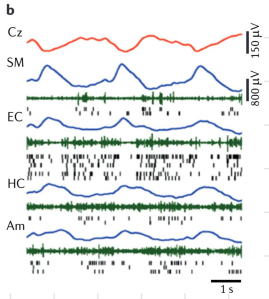
- Does measure the magnetic field instead of voltage
- Primarily measures tangentially oriented pyramidal neurons
- No volume conduction → better source localization



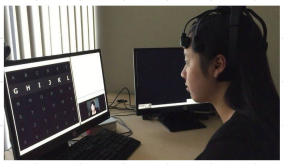
how are the measurements related? just interesting, no university learnen

the closer the neuron, the higher the frequencies can be resolved

Method	Spatial Resolution	Max. Frequency	Signal Amplitude
EEG	40 mm	< 100 Hz	5 - 300 µV
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 µV



- EEG in Medical Technologies: P300-Spellers:



What drives the resting membrane potential?

A) The action of voltage-gated sodium channels
B) The sodium-potassium pump, relative ion concentrations and selective membrane permeability .
C) Rapid depolarization of the cell membrane
D) Increased levels of calcium ions inside the cell
E) The refractory period

Which Ions drive the resting membrane potential?

A Calcium (Ca2+) and protein anions
B Sodium (Na) and calcium (Ca2+)
C Potassium (K+) and Chloride (Cl)
D Chloride (Cl) and protein anions
E Chloride (Cl) only

What primarily contributes to the termination of an action potential in a neuron?

A Opening of sodium channels and continued depolarization
B Influx of calcium ions to restore balance
C Opening of potassium channels and the self-inactivation of sodium channels .
D Continuous influx of sodium ions
E Closure of potassium channels and opening of chloride channels

Arrange the following electrophysiology methods in order from highest to lowest spatial resolution:

A) Patch clamp, Single-unit recording, LFP (Local Field Potential), EEG .
B) LFP, Patch clamp, Single-unit recording, EEG
C) EEG, LFP, Single-unit recording, Patch clamp
D) Single-unit recording, Patch clamp, LFP, EEG
E) Patch clamp, LFP, EEG, Single-unit recording

Which of the following is the primary source of EEG signals recorded from the scalp?

A Action potentials in subcortical neurons
B Postsynaptic potentials in cerebellar
Purkinje cells
C Action potentials in cortical pyramidal neurons
D Postsynaptic potentials in cortical pyramidal neurons .
E Synaptic activity in glial cells

How do we make sense out of the signal that we record?
How do we quantify the signal in order to use it to answer our scientific hypotheses?

Vorlesung 4 – Quantifying neural responses

Recap

Resting membrane potential

- Selective ion channels cause ion specific membrane permeabilities
- At the equilibrium potential (~ -70mV) electrical and chemical gradients balance out, this means equally many ions are pushed out as are attracted in (zero net movement)
- The Resting Membrane Potential is driven by the concentration differences of the ions and the ion-specific permeability

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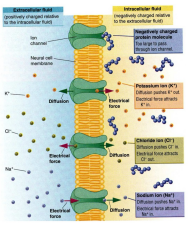
* in resting condition

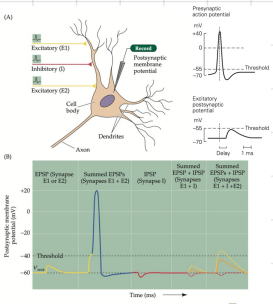


For further Interest: Goldman, Hodgkin and Katz Equation:

$$E_x = RT/zF \ \ln \frac{p_{x_0}[X^+]_o + p_K[K^+]_o + p_{Cl}[Cl^-]_i}{p_{x_0}[X^+]_i + p_K[K^+]_i + p_{Cl}[Cl^-]_o}$$

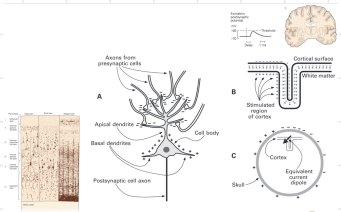
Summation properties

- Action potentials and Postsynaptic potentials have different temporal dynamics and therefore different summation properties
  Why is this so relevant?
- Direct measure of the processes that enable interneuronal communication



Anatomical origin of EEG Signals

Scalp EEG signals are heavily influenced by PSPs of cortical pyramidal neurons due to
- Proximity
- Orientation
- Synchronization



EEG

What do we measure?

- EEG measures voltage differences on the scalp
  - Reference measure: between two electrodes
  - (Most often an additional ground electrode is added)



The recorded signals

- For EEG we measure very small voltage differences between electrodes that are placed on the scalp.
- We learned that the EEG signal (mostly) represents activity of radially oriented cortical pyramidal neurons. (More specifically: their postsynaptic potential signalling)
- However, this is not the only signal that we pick up. The EEG signal most likely consists of neural activity (the signal of interest) and noise (other signals that we do not care about).

Physiological sources of noise

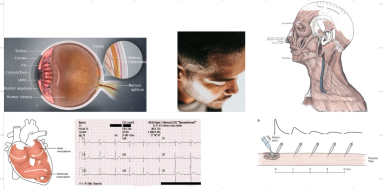
cardiac blood effects

muscle

artifacts evoked from neural stimulation

sweat → increases conductivity of the scalp

eye movement

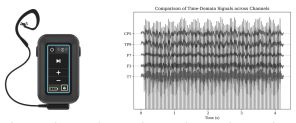


Environmental sources of noise

- screens
- ground disturbance → Linoleum floor (dancing next to the EEG system)
- florescent lights



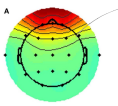
Neurostimulation currents



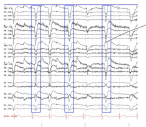
EEG Noise Artifacts

- EEG data represents a mixture of brain signal (source activity) and noise
- Some of the noise of an EEG recording can be assigned to true non-neuronal sources → we call this "artifacts"
- All artifacts have
  - Topographies (where the artifact occurs)
  - Temporal Patterns (when the artifact occurs)

So how do we separate brain signal of interest from background noise?



where the artifact appears and how strong

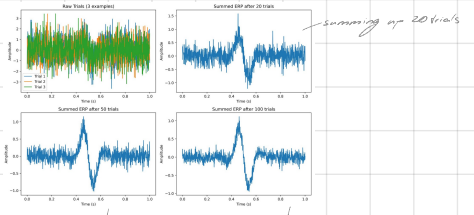


eye blinks → most intense in the frontal channel

→ website to visualize artifacts: https://www.learningeeg.com/artifacts

event-related potentials (ERPs)

Assumptions:
- EEG consists of both task relevant and unrelated activity
- Task relevant activity will be the same for each trial
- Averaging over trials will eliminate noise + task unrelated brain activity
- We precisely know when our cognitive processes of interest happen



summing up 20 trials

→ the noise cancels out by overlapping multiple trials

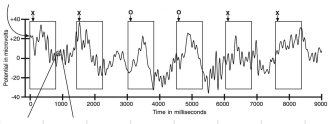
summing up 50 trials

summing up 100 trials

ERPs

ERPs: Averaging

- Epochs: Continuous EEG is segmented into short time windows around an event of interest (e.g. stimulus presentation)
- Each epoch is EEG signal from one trial
- Channel wise activity is averaged across trials



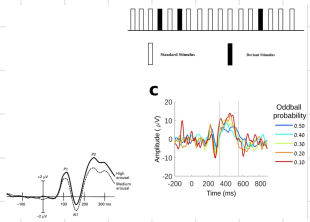
ERP-Nomenclature & Analysis

→ open & popular
→ not time efficient

- ERPs are characterized by their positive and negative peaks
- Individual peaks are characterized by
  - Polarity (positive or negative deflection)
  - Their latency (in milliseconds) or their number of occurrence

(= terminology)

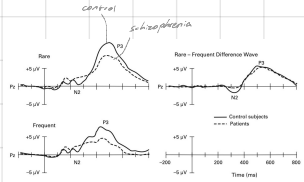
Example Analyses:
- Component latency
- Peak amplitude



ERP Analysis: Difference Waves

- Task related processing can be isolated into ERPs
- In neuroscience we want to compare brain activity between different conditions
- Therefore we compute ERPs for different conditions and subtract them
- Remaining signal: difference between the conditions

- anything irrelevant will be canceled out



intermediate evaluation

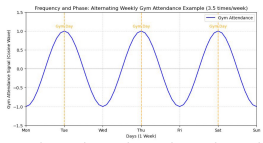
+ Fast, easy and low computational demand
+ Very high temporal resolution
+ Direct comparison of stimulus-related responses
+ Clinical utility (auditory evoked brainstem potentials)
+ Standard tool of cognitive neuroscience
+ Later potentials clearly modulated by cognitive processes

- Trial specific information is lost (assumes similarity)
- Non phase-locked information is lost (we will talk about this later)
- Single channel analysis
- Components can be influenced by a lot of factors
- Underlying neural mechanisms not well understood yet

- cognitive interpretation is quite advanced
- standard tool & very versatile
- first check

Frequency Analysis

Example: We go to the gym on the days Tuesdays, Thursdays and Saturdays
Q: Is there a more efficient way to describe the days than listing them?

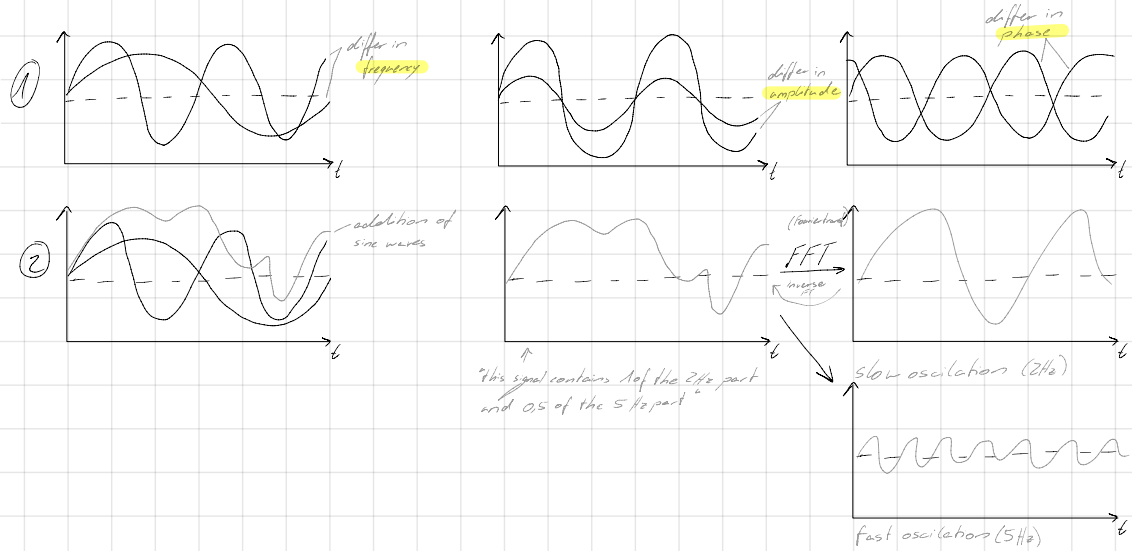


Frequency

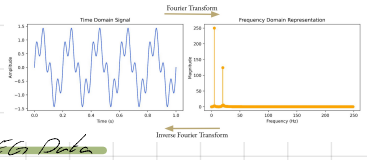
If we see patterns in a signal they can be described by a frequency

describing sine waves

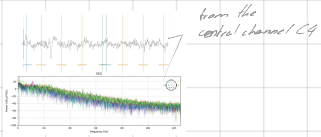
A sine wave can be perfectly described with the parameters:
- Frequency
- Amplitude
- Phase



Fourier Transform



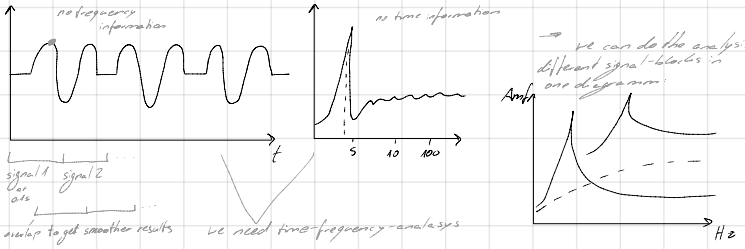
EEG Data



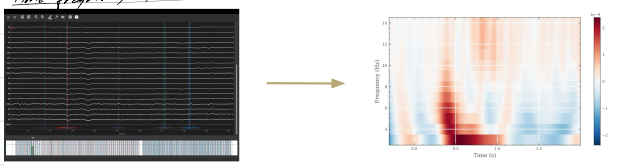
Intermediate Summary: Time & Frequency Domain

- Time and Frequency Domain are two representations of the same signal
- Time domain represents signal over time
- Frequency domain represents which frequencies make up the original signal
- Fourier transform perfectly decomposes the signal into sine waves of different frequencies
- Inverse fourier transform converts a signal from the frequency domain to the time domain

Time-Frequency



Time-frequency-plot:



Applications: ERPs



Example: Frequency Analysis

Example: Time-Frequency Analysis

Learning objectives
1. Students understand the structure and function of the human nervous system, can define and localise the individual components and explain the mechanisms involved.
2. Students have learnt the theoretical principles and practical application of neuromodulatory procedures and can present them in a comprehensible manner.
3. Students know the basic concepts of neuroplastic processes and can categorise them.
4. Students know about the clinical fields of application and can present them.
5. Students can assess future medical technology fields and develop creative ideas.

Vorlesung 5 – Clinical Cases

non-invasive neuromodulation techniques

tDCS – transcranial direct current stimulation

tACS – transcranial alternating current stimulation

TMS – transcranial magnetic stimulation

VNS – vagus nerve stimulation

disease patterns

Clinical conditions that can be treated with neuromodulation

Dystonia, Parkinson, Epilepsy, Traumata, Stroke, Pain

ADHS, Schizophrenia, Alzheimer, Depression, Autism, Tinnitus

Depression influences the behavior

difference Neurology/Psychology: measuring stg (current, voltage) (vs) interactive treatment

objective diagnosis (vs) not so objective, more of a feeling

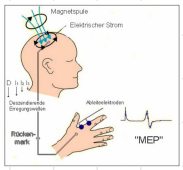
psychoanalysis: finding the root of the patients current problems

→ which brain areas are more

models take leading & training behaviour in less expensive

TMS & tACS

TMS:



tDCS:

- Low-amplitude direct current (usually 1 to 2.5 mA) via surface electrodes on the scalp
- Changes brain function by altering the neuronal resting membrane potential
- Causes either depolarisation (under the anode) or hyperpolarisation (under the cathode)

Possible targets:
- M1 (motor symptoms)
- DLPFC (cognition and mood)
- Combined M1 and DLPFC (motor symptoms)

→ all techniques make either an activation or deactivation



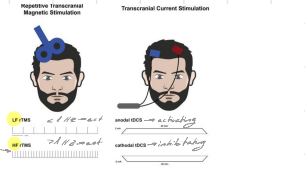


Abb. Aus: Non-invasive brain stimulation for Parkinson's disease: Clinical evidence, latest concepts and future goals: A systematic review, Madrid et al., 2021

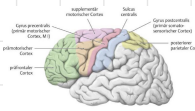
MDD

Approaches

forms of stimulation

Basic, memorize

Where?



How?

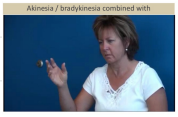
Excitation (excitatorisch)	Inhibition (inhibitorisch)
high frequency	low frequency
rTMS: > 5Hz	rTMS: <= 1Hz
Anodale tDCS	Kathodale tDCS

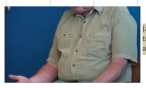
Parkinson's disease

motor deficits

→ becomes slower and slower with repetitive movement

Akinesia / bradykinesia combined with





(a) resting tremor and/or

left dominat tremor



(b) postural instability and/or

problems with standing



(c) rigidity

being very stiff

approaches

Clinical evidence for the treatment of PD by means of rTMS

Level	Recommendation
	Effective
Level B	HF-rTMS of M1 for the treatment of overall motor symptoms in PD
Level B	HF-rTMS over DLPFC for the treatment of depression in PD
Level B	cTBS over cerebellum for the treatment of dyskinesia in PD
Level C	HF-rTMS over SMA for the treatment of overall motor symptoms in PD
Level C	LF-rTMS over SMA for the treatment of dyskinesia in PD
	Ineffective
Level A	HF-rTMS over SMA for the treatment of depression in PD
Level B	HF-rTMS of M1 for the treatment of gait performance in PD
Level B	HF-rTMS of M1 for the treatment of depression in PD
Level B	HF-rTMS over the DLPFC for the treatment of overall motor symptoms in PD
Level B	HF-rTMS of M1+DLPFC for the treatment of overall motor symptoms in PD
Level B	LF-rTMS over the SMA for the treatment of overall motor symptoms in PD
Level C	LF-rTMS of M1 for the treatment of overall motor symptoms in PD
Level C	LF-rTMS of M1 for the treatment of depression in PD
Level C	LF-rTMS of M1 for the treatment of dyskinesia in PD

→ unwanted movement

Clinical evidence for the treatment of PD by means of tDCS

Level	Recommendation
	Effective
Level B	Anodal tDCS over M1 for the treatment of overall motor symptoms in PD
Level B	Anodal tDCS over M1+DLPFC for the treatment of gait performance in PD
Level C	Anodal tDCS over M1 for the treatment of gait performance in PD
Level C	Anodal tDCS + physical therapy for the treatment of cognitive function in PD
	Ineffective
Level B	Anodal tDCS + physical therapy for the treatment of overall motor symptoms in PD
Level B	Anodal tDCS + physical therapy for the treatment of gait performance in PD
Level C	Anodal tDCS + physical therapy for the treatment of bradykinesia in PD

Clinical evidence for the treatment of PD by means of tACS

Level	Recommendation
No recommendations are possible	

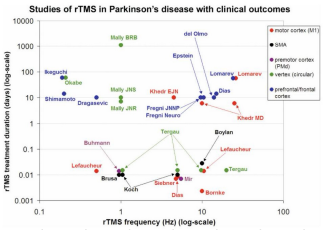
Abb. Aus: Non-invasive brain stimulation for Parkinson's disease: Clinical evidence, latest concepts and future goals: A systematic review, Madrid et al., 2021

Level A:

Level B:

Level C:

not memorize



Wirksame Ansätze nicht-invasiver Stimulation bei Parkinson
1. Exzitatorische Stimulation M1
2. Hemmende Stimulation SMA



activation worked

activation didn't work

	Excitatory	Inhibitory
M1	Benefit	No Benefit
SMA	No Benefit	Benefit

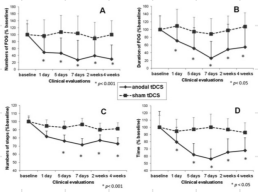
Excitatory stimulation of the motor cortex (anodale tDCS)

specific for effusion
→ motivated freezer with walk

tDCS über Motorkortex verringert 'Freezing of Gait' -Episoden durch anodale tDCS Stimulation

- randomisiert, doppelblind, cross-over, scheinkontrolliert
- n=10 PD mit FOG im "on"-Zustand
- 5 aufeinanderfolgende Tage mit anodaler tDCS M1/Scham
- Klinische Bewertung über einen Zeitraum von 1 Monat

Reduktionen in:
(A) Anzahl und (B) Dauer der FOG-Episoden
(C) Anzahl der Schritte während des "stand walk sit"-Tests (SWS)
(D) Zeit, die für die Durchführung des SWS-Tests benötigt wurde



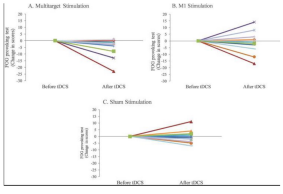
"crossed over study" = both groups go through treatment A & B, just in different time slots

Simultaneous stimulation of several areas

- Background: Stimulation M1 effective in freezing of gate (FoG)
- Question: Efficiency of simultaneous stimulation of motor and cognitive network?
- method:

N = 20 PD patients
3 consecutive days of tDCS (20 min)
- Conditions:
- A. M1+DLPFC
- B. M1
- C. Sham
- Result:

-Improvement in FoG-provoking test (P = 0.010), Timed Up and Go (P = 0.006), and the Stroop test (P = 0.016) only after combined stimulation



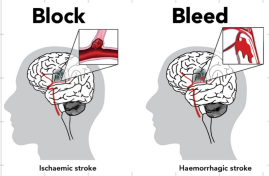
→ some patients improve, others decline

Stroke

Differentiation
- -ischaemic (occlusion) or
- -haemorrhagic (bleeding) stroke

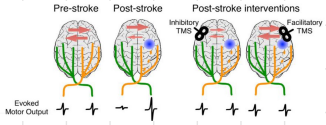
Causes
- Embolism (often of cardiac origin)
- Thrombus
- Aneurysma

consequences
- speech/language disorders
- -visual disorders
- -attention disorders, e.g. neglect
- -memory disorders
- -Personality changes



neuromodulation approaches after stroke

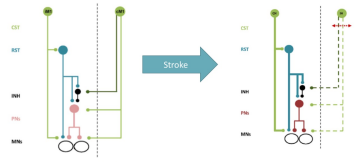
- **after Stroke** Hemispheres not in balance, but:
  - Strong inhibition healthy → affected hemisphere
  → **Overactivity healthy hemisphere**
- **Neuromodulation approaches: Restore balance, through:**
  - Strengthening the affected hemisphere, e.g. >1Hz TMS
  - Inhibition of healthy hemisphere, e.g. 1Hz TMS



if the crossing pathways are destroyed, there'll be others doing their job

perspectives

Current approaches not effective for stroke patients with severe motor impairments
Possible alternative approach:
Strengthening healthy hemisphere and ipsilateral pathways

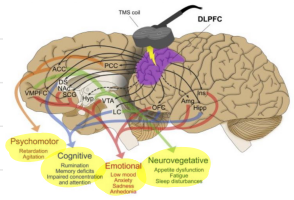


Abbreviations: cM1: contralateral M1, iM1: ipsilateral M1, CST: corticospinal tract, RST: reticulospinal tract, INH: inhibitory interneuron, PNs: propriospinal neurons, MNs: alpha motoneurons, CH: contralesional hemisphere, IH: ipsilesional hemisphere.

Depression

neurostimulation for depression

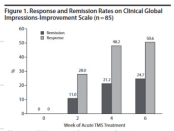
Approach: stimulation of the dorsolateral prefrontal cortex (DLPFC), e.g. with rTMS



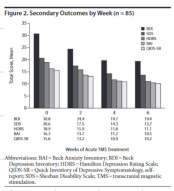
DLPFC stimulation with TMS for the treatment of depression

Since 2008: approved therapy for the treatment of major depression (FDA approved)
- Pre-condition: patients do not respond to drug treatment
- -Therapy: daily for 4-6 weeks (20-30 sessions)
- -Stimulation DLPFC with rTMS

Study on the effectiveness of TMS therapy for depression
- 100 Patients (2008-2011)
- Therapy: 5x/ week, maximum 30 sessions/6 weeks
- Protocoll:
- -TMS via left DLPFC-High
- -frequency rTMS (repeated 10 Hz for 5s stimulation with 15s pause in between; total: 4000 pulses/session)
- -Some patients: additional low-frequency rTMS via right DLPFC (300-1200 stimuli/session)
- -Protocol was customised (depending on clinical progress)



Abbreviation: TMS = transcranial magnetic stimulation.

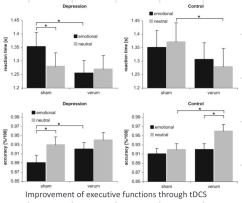


Abbreviations: BAI = Beck Anxiety Inventory; BDI = Beck Depression Inventory; HDRS = Hamilton Depression Rating Scale; QIDS-SR = Quick Inventory of Depressive Symptomatology, self report); SDS = Sheehan Disability Scale; TMS = transcranial magnetic stimulation.

Improved quality of life after TMS therapy (Solvason et al. 2014)
- 301 Patients
- Therapy vs. placebo therapy (randomised) for 6 weeks
- Questionnaires on functional status (including physical and mental health, pain) + quality of life
- Results/Conclusions:
  - Statistically significant improvement in functional status + quality of life for patients undergoing therapy (compared to sham therapy)
  - Improvements measurable both directly after therapy and after 6 months

DLPFC Stimulation with tDCS

Patients with depression receive tDCS and are tested with a distractor working memory task.
→ Performance improves after tDCS



Improvement of executive functions through tDCS

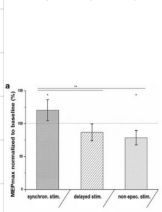
unanswered questions

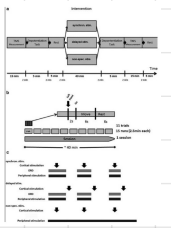
→ TMS well integrated in second-line therapy

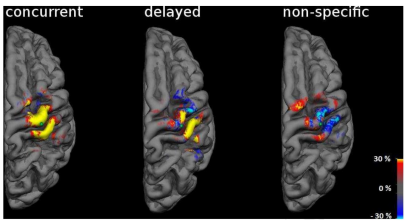
- Stimulate both hemispheres at the same time?
- Stimulate only one hemisphere?
- Stimulate the hemispheres one after the other?

Perspectives

brain state-dependent stimulation

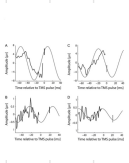


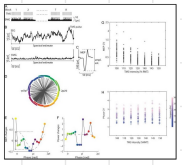


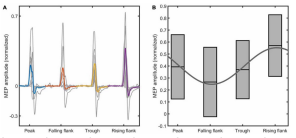


difference: another targeting activity-level

phase dependent stimulation







Which of the following methods is not a non-invasive stimulation technique?
a) tDCS
b) tACS
c) TMS
d) VNS
e) DBS .

What does not apply to DCS?
a) Stimulation with direct current with amplitude between 1-2,5 mA
b) Stimulation with direct current with amplitude between 5-10 mA .
c) Changes brain function by altering the neuronal resting membrane potential
d) Possible target is the primary motor cortex M1
e) Possible target is the dorsolateral prefrontal cortex DLPFC

The following symptoms may not occur as a result of a stroke:
a) Speech disorders
b) Cardiac Arrhythmia .
c) Memory disorder
d) Visual disturbances
e) Motor impairments

What effects does the stimulation of the DLPFC not have on depression?
a) Neurovegetative effects
b) Psychomotoric effects
c) Somatosensory effects .
d) Cognitive effects
e) Emotional effects

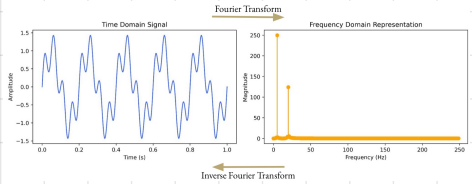
What is a possible therapeutic approach in the treatment of Parkinson's disease?
a) Inactivation of motor cortex
b) Activation SMA
c) Inactivation of the dorsolateral prefrontal cortex
d) Activation of occipital lobe
e) Activation of the motor cortex .

What is a possible therapeutic approach in the treatment of depression?
a) Activation of the motor cortex
b) Inactivation of motor cortex
c) Activation SMA
d) Activation of the dorsolateral prefrontal cortex .
e) Activation of occipital lobe

Vorlesung 6 – Methods of Neuromodulation I

Recap Fourier Transformation

→ every signal can be decomposed into a sum of sine waves of different frequencies



foundational thoughts on neurostimulation & -modulation

Modulating the nervous system

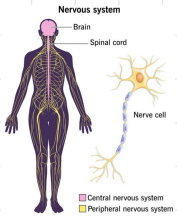
- Neural cells communicate with each other via electrical or chemical signals
- But cells can react to (i.e., sense) a variety of different physical stimuli, we can use a variety of different approaches to stimulate nervous tissue
- Signal Transduction: How externally applied energy (mechanical, magnetic, thermal, electrical ...) is transformed into a cellular signal
- Tissue reacts differently to different kinds of energy (e.g., think how mechanical stimuli such as vibration are transmitted through the skull compared to electromagnetic fields)

} how we get into the nerves

- Cells and cell ensembles can react over different time scales:
  - Immediate evoked responses (spikes, EPSPs, IPSPs)
  - Short-term synaptic plasticity changes
  - Long-term synaptic plasticity changes
  - Circuit reconfiguration
- Synaptic plasticity means that the coupling strengths between connected neurons change
- Plastic changes extend the duration of the effects of neuromodulation beyond the immediate time of application

clinical goal of neurostimulation: evoke changes that last

- We distinguish between three broad target systems
  - Specific brain regions
  - Peripheral nerves and muscles
  - (Spinal Cord)
- These targets differ in their functional roles, as well as in the anatomically given ease of access to interventions.



Precision in Neuromodulation

To achieve high precision in neurostimulation, two aspects matter:

1. Target Accuracy (or Sensitivity): → hitting the target you want to hit
We can effectively activate the desired neural circuits or regions.
2. Selectivity (or Specificity)
We avoid unintended activation of surrounding or unrelated neural structures.

Why does precision matter?
- Optimizing treatment response while minimizing side effects
- Making causal inferences about the role of brain regions in cognitive, sensory or motor processes

Control in Neuromodulation

Control here refers to our ability to bring our target system, e.g., the brain, into some state that we desire, using a 'controller', in our case, a neuromodulation system.

In general, we distinguish two kinds of control:
1. Open-loop control
Our stimulation is independent of the neural effects – whatever is happening in the brain in response to the stimulation doesn't change how we stimulate.
2. Closed-loop control
Our stimulation is modulated by the effects it evokes in the brain – we change the parameters depending on the difference between the current state and the target state.
We use feedback from the brain to guide stimulation.

Most current research is open-loop.

Controlling dynamical, non-linear systems

... is hard!

- The effects of our controller (the stimulator) on our system (the nervous system) are state-dependent.
- The same input (stimulation) can lead to different outputs (neural and behavioural effects) depending on the state and history of the system.

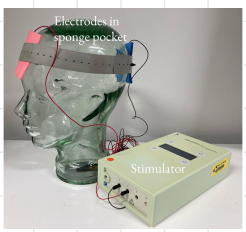
1. For example, stimulation applied during different phases of neural activity could have very different effects, even with the same intensity or frequency.
2. Previous experiences or ongoing conditions, like neuroplastic changes, can modify how the nervous system responds to stimulation.

Methods of brain modulation & stimulation

electrical modulation of the cortex

- Plan: We want to stimulate the cortex from the outside (i.e., 'noninvasively').
- Idea:
1. Neurons react to electricity
2. We can apply a voltage gradient across a pair of electrodes on the scalp to induce currents in the brain
3. The currents should be effective, but relatively low (0.5–2mA).

This general approach is called transcranial electrical stimulation (tES).
If we use direct current (Gleichstrom) we call the method transcranial direct current stimulation (tDCS)
If we use alternating current (Wechselstrom) we call the method transcranial alternating current stimulation (tACS)



the issue with the tissue

- The conductances of scalp and skull are relatively low, i.e., their resistances to current high
- This means we need to apply a lot of energy on the outside to get relatively little energy into the brain
- Often the loss is one or two orders of magnitude
- This limits the amount of current we can apply to the brain tissue, as we must avoid pain at the scalp. Currently, a maximum of 2mA is recommended.
- Depending on the montage (i.e, arrangement of electrodes), the electric field can be quite broad and unspecific, due to current spread.

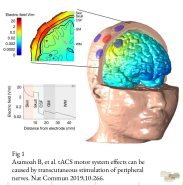


Fig 2
Asanteah B, et al. tACS-motor system effects can be caused by transcutaneous stimulation of peripheral nerves. Nat Commun 2019;10:266.

proposed mechanism of the tES

- Electric fields induced in the brain are sub-threshold for action potential generation (<1 V/m, more often around 0.2 V/m)
- Fields either depolarize or hyperpolarize neuron populations slightly
- This changes their excitability
- This means we modulate spontaneous activity, rather than inducing it directly
- Neurons form intricate interconnected networks, so (we hope) even minor interventions could shift dynamics substantially

Somatic Doctrine of tES

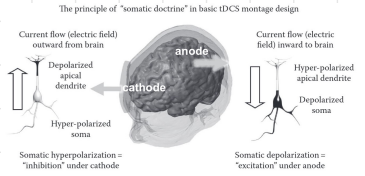


Fig 3.3a, Bikson et al., 2012, Cellular and Network Effects of Transcranial Direct Current Stimulation

Anode (+) depolarization of neuron soma (and apical dendrite hyperpolarization)
Cathode (-) hyperpolarization of neuron soma (and apical dendrite depolarization)

Effects of tES

- The 'somatic doctrine' describes a mechanism for the immediate online effects.
- Changes in excitability make neurons more or less responsive to input from other neurons (i.e, a probable if region B now is under anodal stimulation. depolarized soma needs now a little less excitatory input to fire, a hyperpolarized one a bit more)
- If for instance region A so far had limited success in activating region B, that might be more
- Here, hebbian plasticity ('what fires together, wires together') offers a way to transfer short-term effects to long-term effects
- This could lead to the induction of longer-lasting aftereffects, which are mediated by plastic changes at synapses (i.e., connection strength between neurons changes).
- These aftereffects are apparent even after the stimulation itself has ended, and increase with the current and duration of the stimulation.

Montages

- Montage refers to the spatial arrangement of stimulation electrodes on a subject's head
- The montage determines which regions are stimulated strongly, and which regions don't receive much current
- HD-tDCS (C) uses a ring configuration to achieve better localized fields compared to regular montages (A, B)
- Using software , the field strengths in different brain regions for a specific montage can be computed. (e.g., SimNIBS)

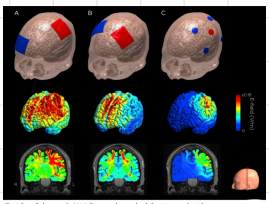
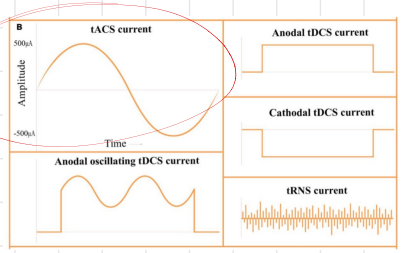


Fig 1 from Bikson et al., 2018. Rigor and reproducibility in research with transcranial electrical stimulation: An NIMH-sponsored workshop.

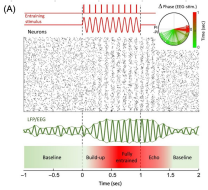
current waveforms



RNS = "random noise stimulation"

tACS

- tACS is the use of sinusoidal alternating currents in tES
- This means neuron populations go through regular cycles of enhanced and diminished excitability (via somatic de- or hyperpolarization, respectively)
- It is assumed that this can entrain frequencies (via constructive or destructive interference as well as resonance), so that internal oscillators follow the external oscillation
- Entrainment effects have been shown in single neurons in macaques, and are stronger with higher currents (Johnson et al., 2020)



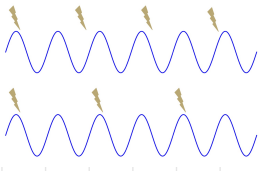
Simulated data from Hanslmayr et al., 2019. Modulating Human Memory via Entrainment of Brain Oscillations

rules of neural oscillation

- Frequently observed in different neuronal populations
  - Interaction between excitatory pyramidal cells and GABA interneurons
  - Observed in purely excitatory or inhibitory neural networks
  - Observed in single neurons under permanent depolarization
- Oscillations are implicated in a variety of functions
  - Synaptic plasticity changes at specific phases of theta oscillations (4-8Hz) in Hippocampus
  - LFP oscillations modulate individual neuron firing
  - Interregional synchronization between brain areas
  - ...
- Well understood neural mechanism

} this is why we do time-frequency analyses!

resonance phenomenon



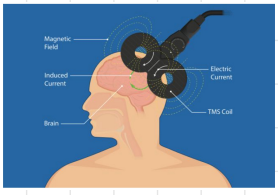
current issue with tDCS and tACS

- While the working mechanism is nice in theory, there are some concerns:
  - Current spread is wide, and nerves of the head such as the trigeminal nerve or occipital nerve can get suprathreshold stimulation, compared to subthreshold brain stimulation.
  - Some studies have shown that effects diminish or disappear under topical (i.e., local) anesthesia, which hints at somatosensory of peripheral nerve induced effects
  - However, some animal studies back-up the claim that tDCS or tACS can modulate neural firing (but their field strength often is at the very upper limit of what can be achieved in humans)

- tDCS mediated increases in cortical excitability are substantially weaker under topical anesthesia of the scalp (Lescrauwaet et al., 2024).
Effects of tDCS could partially be mediated by peripheral nerves, which are subject to much higher field strengths than cortical neurons.
"Depending on the location of the tDCS electrodes, several cranial and peripheral nerves can be affected, such as the occipital nerve, branches of the trigeminal nerve, and the cervical plexus. Afferent fibers from these nerves travel to the brainstem, where they project to the nucleus of the solitary tract (NTS) and trigeminal nuclei."
- Vanneste et al. (2020) show that noradrenergic activity evoked from the occipital nerve via tDCS is sufficient to modulate memory.
- Asamoah et al. (2019) show that for tACS, entrainment can be achieved solely via the peripheral effects of tACS, and is reduced under local anesthesia.

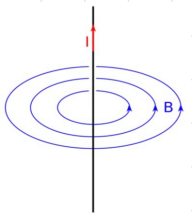
TMS

- Idea: We want to induce action potentials in a spatially limited region of the brain.
- Problem: Via scalp electrodes, it is not feasible to inject enough current to induce localized suprathreshold depolarizations (If we'd do that, we would have electroconvulsive treatment)
- Solution: One can circumvent that by inducing a current via a magnetic field. Magnetic fields are barely affected by the skin or the skull. This magnetic field in turn can be generated via a charged coil.
- This allows us to induce currents strong enough to make neurons fire in a well-circumscribed part of the brain, depending on the position and geometry of the magnetic field

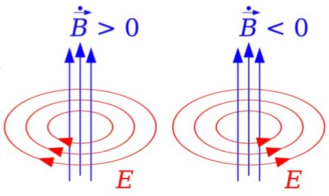


Physic recap: electromagnetic induction

Moving charges induce magnetic fields (cf. Biot-Savart law)

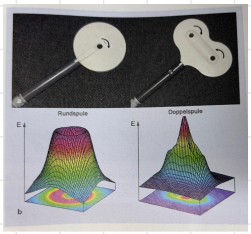


Changes in magnetic fields create currents opposing that change (cf. Lenz' rule)



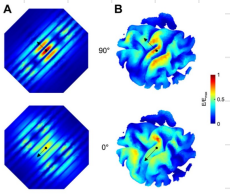
TMS coils

- There are round coils and figure-eight coils that produce different electrical fields:
  - The round coil produces an electrical field that is strongest in a ring shape concentric to the coil center, in the center, the field is zero
  - The figure-eight coil produces electrical fields that overlap only in a small area directly under the center of the coil
  - When using the figure-eight coil with low intensity, only the small part of the overlap between the electrical fields with be strong enough to alter neural activity allowing for high spatial precision neuromodulation



applying TMS: considerations

- Not just the overall position, but also the orientation relative to the geometry of the cortex, can greatly influence the stimulation effects.
- This is due to the different flow of the induced current across gyri and sulci, which are the most prominent macroanatomical features of the cortex.
- Both the location of the peak activation, as well as the extent of coactivated areas, can differ dramatically.
- Coil orientation hence must be controlled for, as it otherwise induces an unwanted source of variance between participants/patients (it is important for the precision, specifically for the specificity).



same position, different orientation:

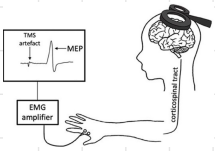


= Coil center

measure of TMS response

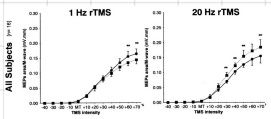
In the motor domain, it is easy to see a direct measure of the effect of our stimulation, so called motor evoked potentials (MEPs).
1. MEPs measure the excitability and connectivity of the motor pathways during TMS.
2. They are recorded using electromyography (EMG) after TMS pulses activate motor neurons.
3. MEP size reflects cortical and spinal cord responsiveness to TMS stimulation.

MEPs can be used to individualize stimulation strength, e.g. by defining the resting motor threshold (e.g., the intensity needed to achieve a MEP above 50μV in 50% of trials)
MEPs can also be used as readout of cortical excitability



repetitive TMS (rTMS)

- TMS devices can often send a series of magnetic pulses (up to 100 Hz)
- Depending on the frequency of pulses employed, this can result in excitation or inhibition of a target area
- Low frequency rTMS (<1Hz) is considered inhibitory, higher frequency rTMS (>5 Hz) excitatory



Gangitano et al. (2002). Modulation of input–output curves by low and high frequency repetitive transcranial magnetic stimulation of the motor cortex.
(*Circle*: baseline, *Square*: After TMS intervention)

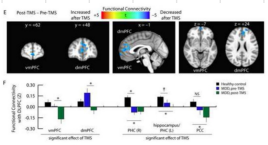
TMS: anatomical navigation

- Hitting the correct target is crucial for TMS.
- The coil must be positioned in the right position and orientation for the relevant area and the intended effects.
- Using infrared camera based measuring of the skull and tracking of positions.
- Can be supported by subject-specific MR scan for individual anatomy
- Representations of individual muscles or muscle groups can be found by closely

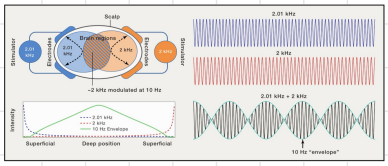


TMS: application examples

TMS in depressive patients applied over the DLPFC can changes the connectivity structure of the brain, especially between the so-called default mode network and central executive network. (Liston et al., 2014)



temporal interference stimulation



transcranial focussed ultrasound (tFUS)

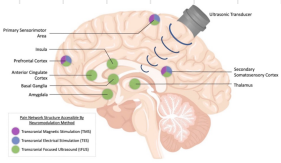


Fig 1 from Badran BW, Peng X. Transcranial focused ultrasound (tFUS): a promising noninvasive deep brain stimulation approach for pain.

contraindications

While most of these methods are quite safe, there are some contraindications that prevent or restrict the use of tES or TMS:

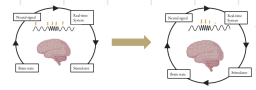
- Metal implants (near the head)
- History of seizures
- Pregnancy
- History of head injuries
- Cardiac pacemaker
- Implanted medication pumps
- Certain neurological or psychiatric disorders

what are we actually stimulating?

This is an area of ongoing research. While a lot research focuses on processes at the brain neuron (and often the cell body), we can also expect involvement of...

- Peripheral neurons
- Astrocytes
- Microglia
- Endothelial cells
- Axon terminals

closing the loop for neurostimulation



Open Loop:
Uses brain states to trigger stimulation.

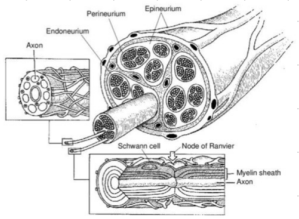
Closed Loop:
Stimulation is adjusted dynamically and continuously to reach and maintain a desired brain state.

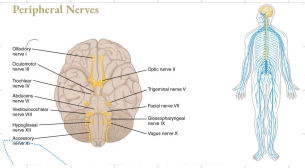
Vorlesung 7 – Methods of Neuromodulation II

Foundational Thoughts on peripheral Neurostimulation

Peripheral Nerves

- Nerves are bundles of parallel axons embedded in connective tissue.
- Nerves conduct information as electrical signals between the brain and the rest of the body
- Nerves that originate directly in the brain are called cranial nerves, nerves that originate from the spinal cord are called spinal nerves.
- Nerves can carry efferent (e.g., motor or secretory) information from the brain towards the body, or afferent (i.e., sensory) information towards the brain.
- Depending on the information they carry, we can refer to nerves as sensory, motor, or mixed nerves.



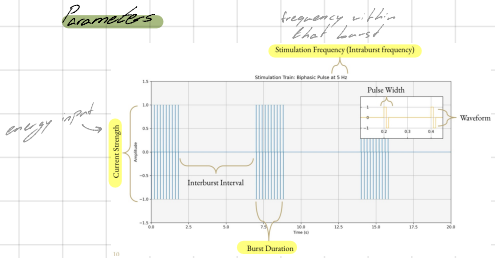


don't need to know these by heart

- Can be easy to stimulate for nerves directly under the skin surface (in contrast to cortical stimulation)
- We can achieve relatively high field strengths, i.e. use electrical stimulation to directly induce action potentials in the axons
- Induced action potentials travel along the axon in two directions: antidromic (back to its own cell body) and orthodromic (to its effector organ or sensory ending)
- For mixed nerves, we hence get both sensory and motor effects.



Parameters

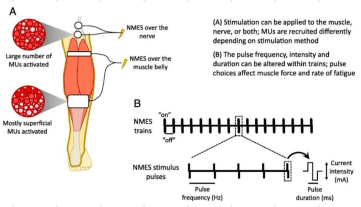


overview

most important: strength/frequency & burst

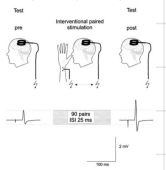
Neuromuscular or Functional Electrical Stimulation

- We apply biphasic stimulation either over the nerve directly above the muscle, or over the muscle belly using sticky electrodes
- Classically 20–50Hz
- Individually adjusted current strength (maximal tolerated intensity)
- Recruitment of motor units not in physiological order; muscles fatigue easier than normally for the same force
- NMES is this basic application; FES is the coordinated use of NMES to recapitulate whole, functional movements
- Used in rehabilitation and sports



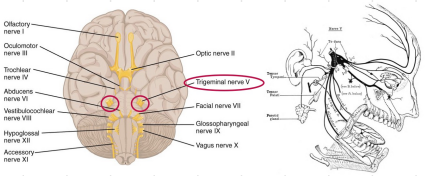
Applications of NMES with Neurostimulation

- We can use NMES/FES to modulate the motor pathway function between the brain and specific muscles
- Signals coincide in the spinal cord
- Hebbian principle: What fires together, wires together
- Pairing stimulation of the motor cortex (e.g., via TMS) or inducing motor imagery with a following muscle stimulation (usually ~25ms after the cortical activity) can enhance motor control in patients.
- This principle is referred to as paired associative stimulation.



"we stimulate the nerve to activate the muscle, not the other way around!"

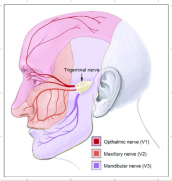
Trigeminal Nerve (Fifth Cranial Nerve)



- The trigeminal nerve is a mixed nerve
- It provides sensation to the skin of the face, scalp, and mucous membranes of the mouth and nose. It has three main branches:
- Ophthalmic (V1): Sensation from forehead, scalp, upper eyelid, and nose.
- Maxillary (V2): Sensation from cheeks, lower eyelid, upper teeth, and palate.
- Mandibular (V3): Sensation from jaw, lower teeth, chin, and part of the tongue (anterior 2/3).

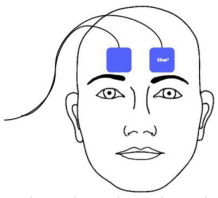
V3 additionally supplies innervation to muscles for chewing and some muscles for swallowing.

don't need to know details



Trigeminal Stimulation

- Can use sticky rubber electrodes with a regular tES- device (or other stimulus generator).
- Often, biphasic pulses are used for stimulation to evoke action potentials.
- In humans, often the ophthalmic branch of the trigeminal nerve is stimulated (see montage in picture), but the jaw is also used at times.
- Stimulation parameters vary widely, often 60–120Hz are used, with current intensities often between 5–20mA
- No consensus of parameters is given, and often justifications for choice are post-hoc. This makes comparing studies difficult.



Use case & effects

- Explored for use in headaches, migraine, epilepsy but also attention-deficit-hyperactivity disorder (ADHD), major depression, etc.
- Basic assumption: Modulation of sympathetic and parasympathetic system via brainstem circuits
- Here projections to the nucleus of the solitary tract (NTS), locus coeruleus (LC), raphe nuclei, reticular activation system in the brain stem are likely important for clinical effects.

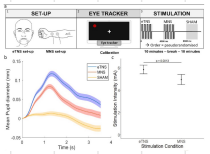
Reported Effects of TNS (in humans or in animals):

- Increase in Cerebral Blood Flow
- Decrease of Neuroinflammatory Responses
- Increase of noradrenaline signalling
- Increase in attention
- Decrease in depressive symptoms
- Modulation of cortical excitability and aberrant synchronization
- Peripheral vasoconstriction

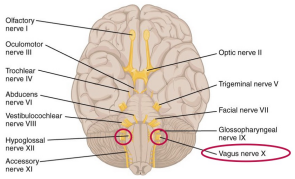
how to get white effects from very narrow stimulation

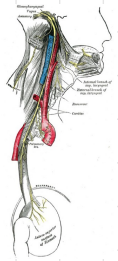
Pupil Response to TNS

- Pupil dilation is considered as an indirect readout of locus coeruleus (LC) activity
- Noradrenaline from the LC is a transmitter important for attention, arousal, threat response
- Seminck et al. have shown a larger pupil response to TNS, compared to stimulation of the median nerve (a spinal nerve at the lower arm) and 'no stimulation' sham.
- But median nerve stimulation also evoked a large pupil response!



Vagus Nerve (Tenth Cranial Nerve)





Vagus Nerve Stimulation



Vagus nerve efferent control

→ different on left & right side

→ has a lot of control about organs

- Vagus nerve is the main nerve of the parasympathetic nervous system
- Efferent control of target organs

Vagus nerve afferent relay

- VN has both parasympathetic control and sensory functions
- Majority of nerve fibres are afferent (~80 % afferent, ~20 % efferent)
- Gut-brain axis

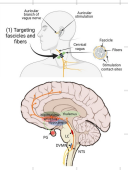
Four Vagal Nuclei in Brainstem

- Nucleus of the solitary tract (NTS) ← most important
  - Visceral sensory information
- Nucleus spinalis nervi trigemini (Sp5 N)
  - Somatic sensory information
- Dorsal Motor Nucleus of the Vagus (DMNV/DNV)
  - Parasympathetic motor output
- Nucleus Ambiguus (NA)
  - Motor control for swallowing and speech

Vagus nerve: how to stimulate?

- Invasive and non-invasive options
- Invasive VNS
  - Cervical VNS (cVNS)
- Transcutaneous VNS (non-invasive)
  - Transcutaneous Cervical VNS (cVNS)
  - Transcutaneous Auricular VNS (taVNS)





→ Vagus nerve stimulation enters brain at the lowest level

Vagus nerve stimulation (cVNS)

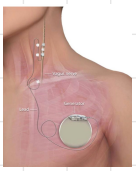
- Originally intended to treat epilepsy by blood flow modulation
- Needs implantation surgery
- Stimulation electrode is wrapped around the left cervical vagus branch
- Electrical pulses activate afferent fibers, transmitting signals to the brainstem

Neuroanatomical Pathway

- Signals travel preferentially to the Nucleus Tractus Solitarius (NTS) in the brainstem
- NTS sends projections to
  - Locus Coeruleus (LC) → Noradrenaline release
  - Substantia Nigra (SN) → Dopamine release
  - (Other areas like the hypothalamus and cortex)

cVNS in clinical applications

- FDA approval for treatment of
  - treatment-refractory epilepsy (TRE)
  - chronic treatment-resistant depression (TRD)
- Also used to treat Heart Failures
  - Implanted on the right cervical branch of the VN
- Allows for closed-loop applications
- VNS efficacy for many clinical indications is probed
- Implantation is costly and has (small) risks
- Overstimulation might damage the nerve



transcutaneous auricular Vagus Nerve Stimulation (taVNS) - Anatomy

- Transcutaneous = through the skin
- Stimulating the VN through a small sensory branch in the earlobe (Auricular branch of the Vagus Nerve, ABVN)
- Part of the outer ear is mostly innervated by the ABVN
  - Nearby nerves: Occipital nerves & Auriculo-temporal nerve
- ABVN joins the other Vagus Fibers at the Jugular Ganglion
- Signals are then relayed upstream to the brain taVNS as easy non-invasive alternative to cVNS?

