Neuroinformatics

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Lecture 4: Case study - Deep brain stimulation for Parkinson's disease

Overview

Why this lecture?

- Because...

Parkinson's disease

- Disease basics
- Symptoms
- Patophysiology
- Therapy

Deep brain Stimulation (DBS)

- Basics
- Stimulators
- Targetting

μEEG: processing and evaluation methods

- μEEG
- μEEG recording of patient data
- Processing μEEG
- Conversion of μEEG to a spike train
- Statistics
- Spike train statistics
- Applications
- Mechanism of DBS STN

Why this lecture?

We included this in order to

- Show you a case study:
  - how can the methods you will learn be applied?
  - are they good for basic research of bran function?
  - are there some applications?
- Show you how we came to computational neuroscience
- Give you some insight into what we do

Parkinson’s disease (PD)

Review of Patophysiology, Diagnosis and Therapy

Historical perspective

Dr. James Parkinson (1755-1828)

1817:

- ”involuntary tremulous motion”
- ”pass from a walking to a running pace”
- ”shaking palsy”

Epidemiology

- Average incidence is 20 per 100,000 in North America
- 1 Million affected in the United States, about the same in Europe
- 50,000 new cases per year
- Cost estimated to exceed $5.6 Billion annually

- Average age of onset around 60
- Men affected slightly more than women
- Genetic Link
- African-Americans and Asians slightly less likely than Caucasians to develop PD
- Caffeine and smoking shows some protective effects

- **Continuous Progressive Neurological Disease**, thereby causing increasing disability of movement
- **no cure**

Symptoms

- Four cardinal symptoms
  - T remor
  - R igidity
  - A kinesia and bradykinesia
  - P ostural instability
- **Tremor** - Usually tremor at rest, when person sits, arm shakes, tremor stops when person attempts to grab something
- **Rigidity** - Increased muscle tone and increase Resistance to movement (arms and legs stiff)
- **Akinesia and Bradykinesia** - Lack of movement or slowness in initiation and execution of voluntary movements
- **Postural instability** - Abnormal fixation of posture (stoop when standing), equilibrium, and righting reflex
- **Gait disturbances** - shuffling feet

Characteristic Problems

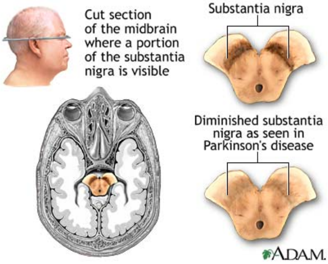
- Hypomimia - decreased facial animation
- Hypophonia - soft speech
- Dysarthria - unclear pronunciation
- Dyspnea - labored breathing
- Festination - Shuffling gait
- Micrographia - small handwriting

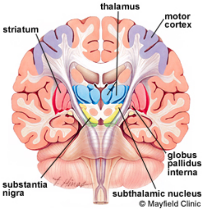
- Change in facial expression (staring, lack of blinking)
- Failure to swing one arm when walking
- Flexion (stooped) posture
- ”Frozen”painful shoulder
- Limping or dragging of one leg
- Numbness, tingling, achiness or discomfort of the neck or limbs
- Subjective sensation of internal trembling
- Resting tremor

Most symptoms may affect one or both sides of the body

Patophysiology

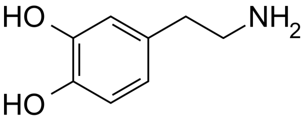
- Loss of dopaminergic cells located in Substantia Nigra in Basal Ganglia
- Most symptoms do not appear until striata dopamine levels decline by at least 70-80%
- **imbalance** primarily between the **excitatory** neurotransmitter **Acetylcholine** and **inhibitory** neurontransmitter **Dopamine**.
- **Cause** of this neurodegenerative process **unknown**

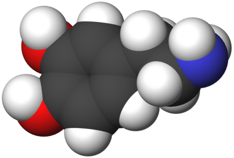




Dopamine

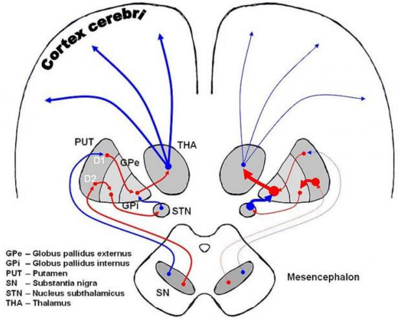
- Neurotransmitter (chemical infomation transmission at synapses)
- Role in reward-motivated behavior
- Role in motor control
- Levels increased by stimulants(incl. drugs: cocaine, amphetamine)
- Probably connected with schizophrenia
- Dopaminergic neurons rather rare (est. 400 000 in human brain)





Basal Ganglia I - Movement control

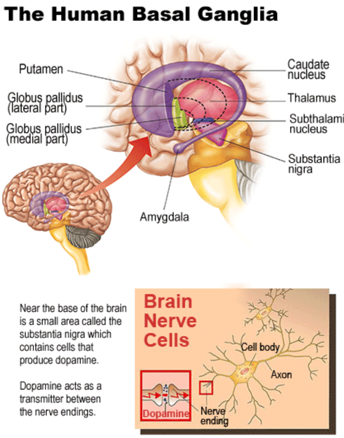
- The Basal Ganglia Consists of Five Large Subcortical Nuclei That Participate in Control of Movement:
  - Caudate Nucleus
  - Putamen
  - Globus Pallidus
  - Subthalamic Nucleus
  - Substantia Nigra

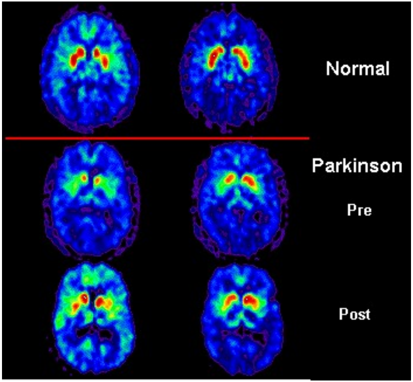


Neuronal pathways of the human brain in normal condition (left) and Parkinson's disease (right). Red Arrows indicate suppression of the target (GABA), blue arrows indicate stimulation of target structure (glutamate).

Basal Ganglia II

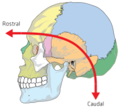
18F PET scan(right) shows decreased dopamine activity in the basal ganglia

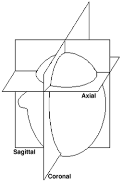


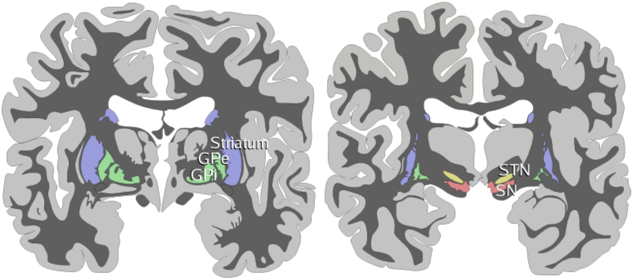


Subthalamic nucleus (STN)

- Subthalamic nucleus:
  - small lens-shaped nucleus (several mm in size)
  - ventral to the thalamus
  - function not well understood
- Below: Coronal slices of human brain showing the basal ganglia.
  - ROSTRAL: striatum, globus pallidus (GPe and GPi)
  - CAUDAL: subthalamic nucleus (STN), substantia nigra (SN)







Therapy

- No no definitive cure known
  (=no possibility to stop or revert the process)
- Current therapies only suppress symptoms

Therapeutic options

1. Drug treatment
   - **Levodopa** - dopamine precursor
   - Dopamine agonists - stimulate dopamine receptors directly
2. Pallidotomy - destruction of cells in the GP
3. Deep brain stimulation - application of electrical pulses to STN or GP
4. Nerve cell transplantation (Experimental, research only)
5. Genetic engineering (Experimental, research only)

Levodopa (L-dopa)

- **Increasing the synthesis of dopamine**
- Introduced in the late 1960s
- "Gold Standard" in drug therapy
- Crosses the blood-brain barrier
- Adverse effects: nausea, vomiting, postural hypotension, involuntary movements, restlessness, and cardiac arrhythmias
  - Behavioral disturbances in 20 to 25% of population
  - Trouble in thinking (cognitive effects)
  - L-dopa can induce: Psychosis, Confusion, Hallucination, Anxiety, Delusion
- Some Individuals develop hypomania (inappropriate sexual behavior); "Dirty Old Man", "Flashers"

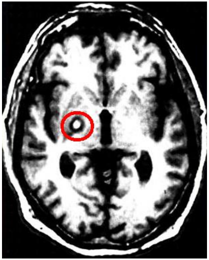
”On/Off switching”

After long-term therapy with levodopa:

- **”On/off”Effect**: like a switch ; without warning, suddenly person goes from full control back to bradykinesia tremor etc. Lasting 30min to several hours, then gets control again.
- ”On/off”Effect usually after 2 or more years on L Dopa
- related to denervation hypersensitivity

Pallidotomy

- **Destruction of cells in the globus pallidus** (GP)
- Until the late 1990s, most common type of PD surgery. DBS is now being performed more often (reversible)
- May help to restore the balance in basal ganglia.
- **Procedure:**
  1. Position of GP located using medical imaging techniques (such as MRI and/or CT)
  2. Insertion of a wire probe into the GPi.
  3. Placement confirmed by electrical tests (microrecording)
  4. Tissue surrounding the Probe heated by emission of electromagnetic field. The heat destroys nearby tissue.



Pallidotomy II - effects

- Almost immediate effect
- Improvements:
  - 70% to 90% reduction of dyskinesias and dystonia
  - 25% to 50% for tremor, rigidity, bradykinesia, and gait disturbance
  - Levodopa dose may be reduced after the surgery, and dyskinesia improvement is based partly on this reduction.

- **Adverse side effects:** hemorrhage, weakness, severe visual and speech deficits and confusion
- **Irreversible!** Not much performed anymore...

Experimental techniques

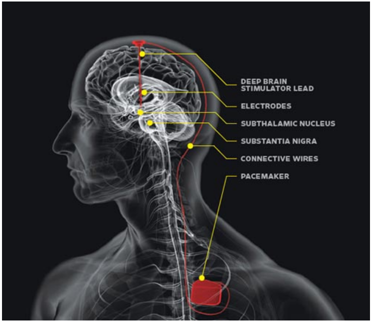
Possible future techniques under research include:

- **Neural tissue transplants:**
  - Researchers are studying ways to implant neural tissues from fetal pigs into the brain to restore the degenerate area.
  - In a clinical trial conducted in part at Boston University School of Medicine, three patients out of 12 implanted with the pig tissues showed significant reduction in symptoms.
  - Connected with risks and side effects...
- **Genetic engineering:**
  - Scientists are modifying the genetic code of individual cells to create dopamine-producing cells from other cells, such as those from the skin.

Deep brain Stimulation (DBS)

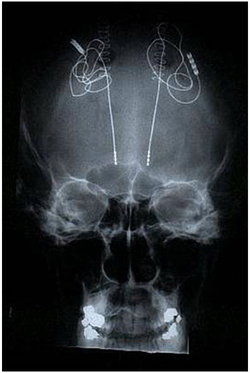
Overview of the therapeutical technique

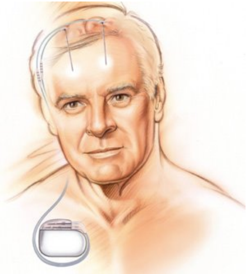
DBS basics



- Modern **treatment technique for Parkinson's disease** (PD), Essential tremor, clinical depressions and other.
- **Stimulation electrodes** implanted into patient's brain
- Supports or replaces medication when insufficient or contraindicated
  - Typical case: patient with long-term progressive PD.

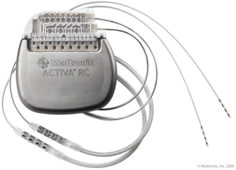
DBS implants



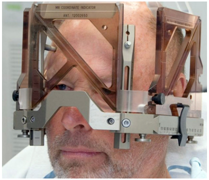


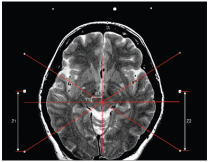
Stimulator device

- Device similar to heart pacemaker
- Implanted in the chest cavity
- Leads below skin to top of the head
- Battery-operated
- Remote-controlled
  - Most devices need to be reoperated once in every 2-5 years
  - Some devices remotely rechargeable



Targetting





Problem: locate and implant the target structure accurately

- Target structure very small (STN - several mm)
- Far away from head surface
- Soft tissue (may shift + hard to see on CT)

Procedure:

1. Fitting patient with stereotactic frame ($\rightarrow$ patient coordinate system)
2. Imaging using MRI and CT (low accuracy)
3. Planning trajectory
4. Microrecording ($\rightarrow$ accurate identification of target position)
5. Implantation of stim. electrode
6. Implantation of dbs device (few days after)

Microrecording

Aim: refine on position of the target structure

- Set of microelectrodes shifted through patient's brain
- Electrophysiological properties along trajectory recorded
- Activity evaluated by trained physician
- Accurate location of target nucleus boundaries identified.

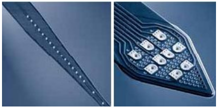
μEEG: processing and evaluation methods

Tomáš Sieger (updates: E. Bakštein)

μEEG

EEG	μEEG
	
$\sim$10 000μm	$\sim$1μm
$\sim$1$\div$100Hz	$\sim$10 000Hz

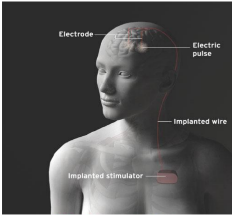
- microelectrodes
  - neuron $\sim$10μm (10-25μm)
  - electrode tip $\sim$1$\div$10μm
  - one / more conacts (tetrodes)



  - bipolar / unipolar
  - recording / stimulatory

Application: research of DBS STN mechanisms in Parkinson's disease

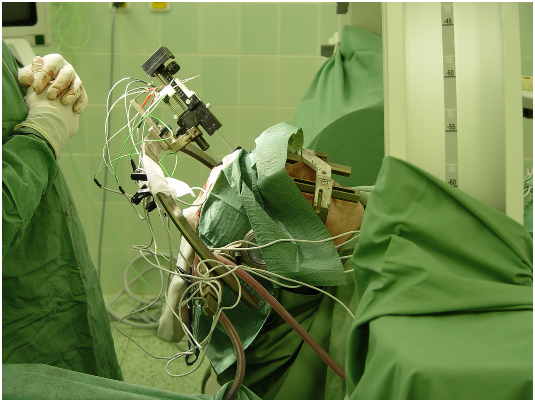
- Parkinson's disease: neurodegenerative disorder
- Deep brain stimulation (DBS)



  - non-motoric side effects: depression, emotional lability
  - hypothesis: STN neurones are connected to cognitive processes

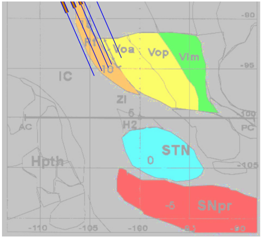
μEEG - recording of patient data

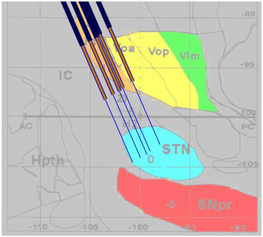
- 5 paralell mikcoelectrodes (cross), 2mm apart
- sampling rate 24kHz

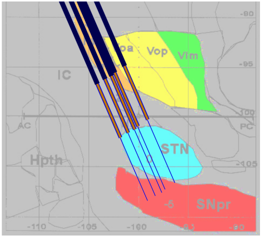


Microregistration - shifting electrodes

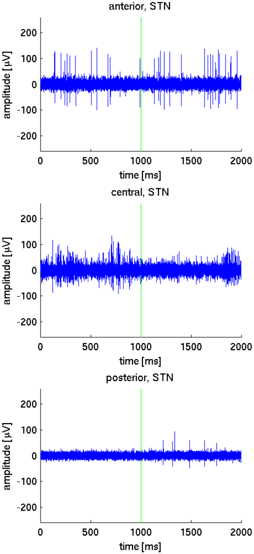
- 3 recording positions:





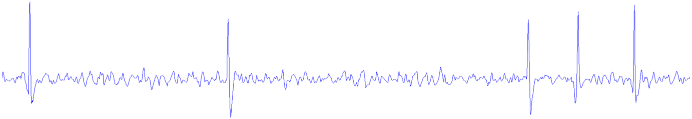


μEEG example

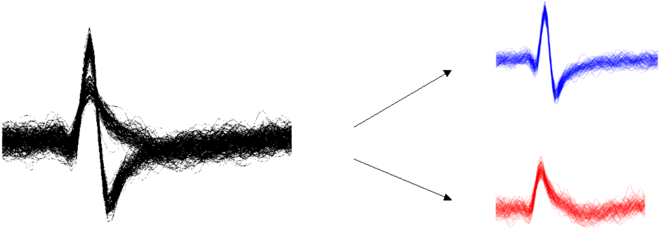


Spike detection and spike sorting

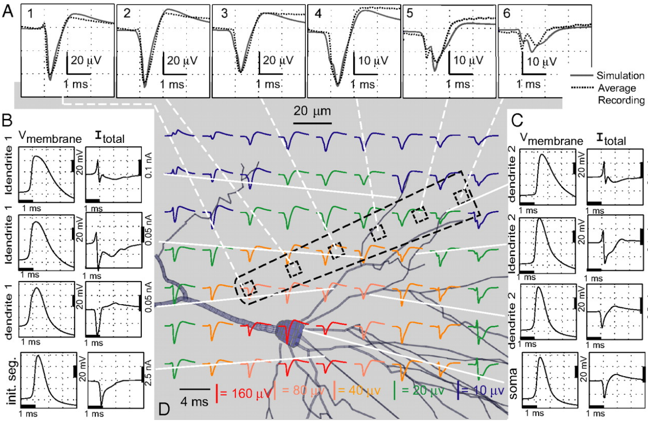
- μEEG



- spike detection
- sorting of detected spikes to neurons



Recorded spike shape depends on the neuron-electrode positioning



► Carl Gold, D.A. Henze, Ch. Koch and G. Buzsáki, On the Origin of the Extracellular Action Potential Waveform: A Modeling Study. J.Neurophysiol 95:3113-3128, 2006.

Spike sorting

Selected methods

method	spike detection	spike sorting	
		features	clustering
WaveClus[1]	amplitude	koef. WT AP	superparamg.
KlustaKwik[2]	N/A	ad hoc	Gauss mix fit + AIC
OnlineSort[3]	energy	AP	min. LS of AP differences, threshold
Spike2[4]	amplitude manual	ad hoc	manual / k-means

[1] R. Quian Quiroga, Unsupervised Spike Detection and Sorting with Wavelets and Superparamagnetic Clustering. Neural Computation 16, 1661–1687 (2004)

[2] Kenneth D. Harris, Accuracy of Tetrode Spike Separation as Determined by Simultaneous Intracellular and Extracellular Measurements. Neurophysiol 84:401-414, 2000.

[3] Ueli Rutishauser, Online detection and sorting of extracellularly recorded action potentials in human medial temporal lobe recordings, in vivo. Journal of Neuroscience Methods 154 (2006) 204–224.

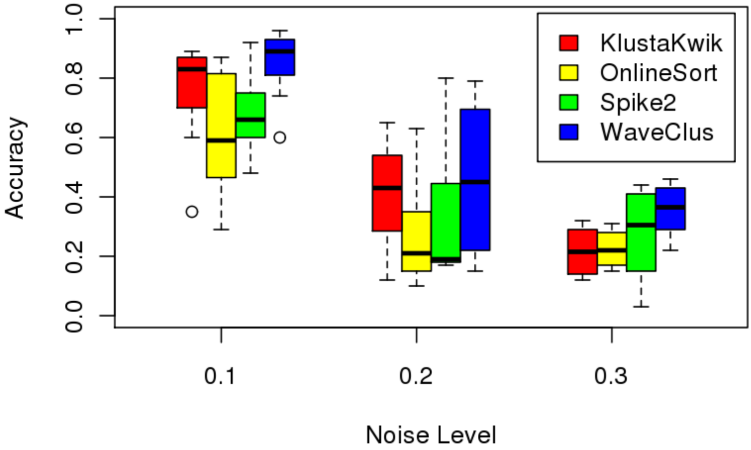
[4] CED Spike2 SW, http://www.science-products.com/Products/CatalogC/Acq&AnaSoftware/Spike2/Spike2.html

Spike sorting
Problems

- guarantee?
  - did we detect all true spikes?
  - did we include noise spikes (false positives)?
  - were the spikes sorted correctly?
- which method should we choose?
  - how should we set the parameters?
- method comparison:
  - processing of artificial/simulated signal
  - problem: how to generate signal, sufficiently similar to real one

Spike sorting

Methods: comparison of accuracy

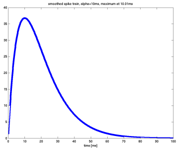


Spike train statistics

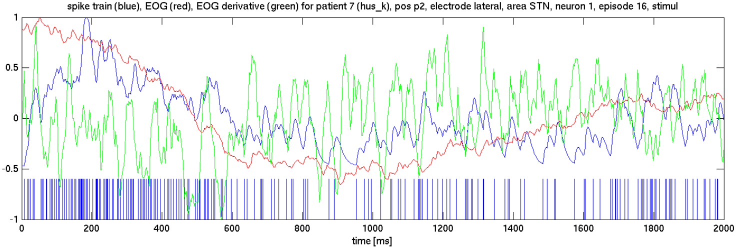
- tasks:
  - compare spike train to other quantity:
    - single number
    - continuous signal
  - compare two spike trains
- how to characterize a spike train?
  - mean firing rate
  - median ISI
  - ISI coefficient of variance
  - ISI index of assymetry
  - Fano faktor
  - ...
  - the spike train itself!
    - holds most information

Comparing spike train to continuous signal

- spike train $\rightarrow$ continuous function (instantaneous firing rate)
  - convolution of spiketrain with alpha funcition $w(\tau) = \alpha^2 \tau e^{-\alpha\tau}$

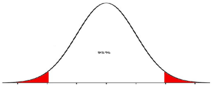


- Compute relation between signal and instantaneous firing rate



Comparing spike train to continuous signal (2)

- Compute relation between signal and instantaneous firing rate
  - correlation (Pearson, Spearman)
  - mutual information
- statistical significance
  - correlation coefficients
    - watch out for assumptions (normality)
    - watch out for degrees of freedom
- Monte-Carlo simulation: bootstrap
  - repeat many times (5000x):
    - generate artificial signals
    - compute correlation coefficient
  - result: distribution of correlation coefficients



  - we deem coefficients outside of 95% interval significant

Comparing two spike trains

- ad-hoc methods
  - spike train metrics (Victor, Purpura)
  - comparison of spike train features
- Statistical tests
  - testing difference in spiketrain intensities (testing frequency coding)
  - testing difference in spiketrain distribution (testing temporal coding)
  - advantage: statistical significance

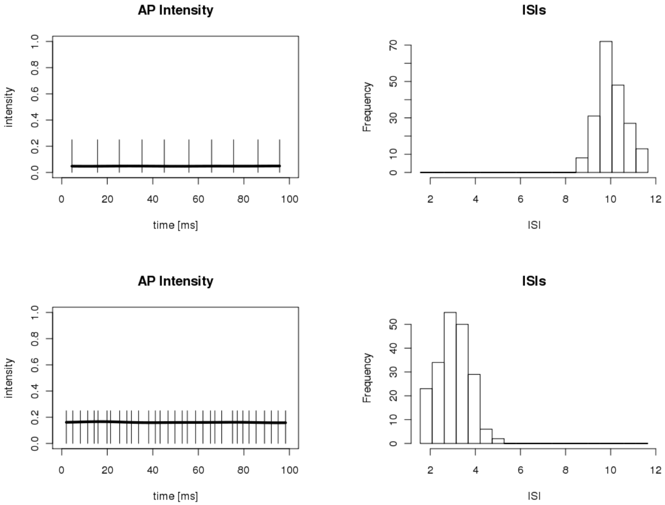
Victor metric

- Jonathan D. Victor and Keith Purpura. Metric-space analysis of spike trains: theory, algorithms, and application. Network 8,

127-164 (1997)

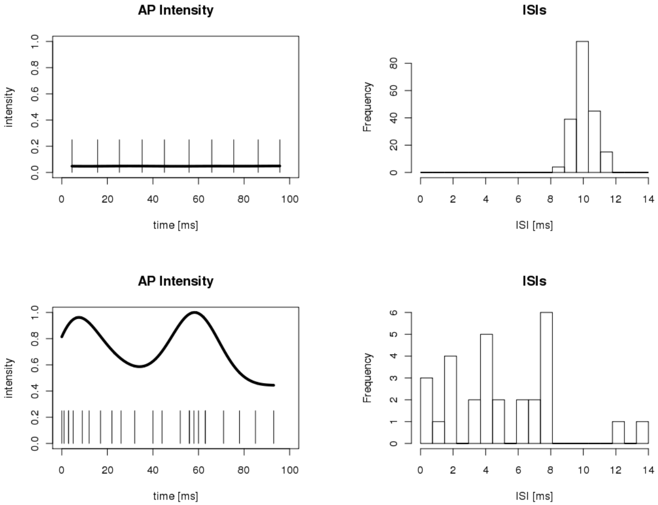
Testing spiketrain intensities

Wilcoxon 2-sample test



Testing ISI distribution

Kolmogorov-Smirnov 2-sample test

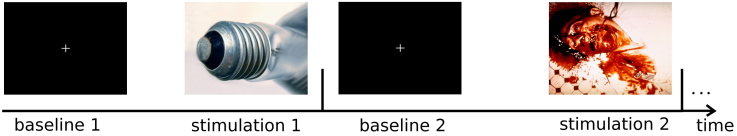


Test of spike train differences

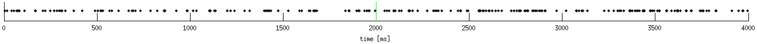
- combination of previous two tests
  - we want a single test at significance level α
- procedure:
  1. test of AP intensities at significance level $\frac{\alpha}{2}$
  2. test of ISI distribution at significance level $\frac{\alpha}{2}$
- the resulting test yields a significance level α

Visual stimulation + recording μEEG

- visual stimulation



- recorded μEEG



Statistics

- data
  - 10 patients
  - 43 recording positions
  - 141 recordings (74 in STN)
  - 173 recording minutes (89 minutes in STN)
  - 176 neurons (101 in STN)
- results: counts of identified **significant** neurons
  - by comparing spiketrain characteristics: 6
  - by comparing spiketrains: 20

Team

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  - Igor Varga, MSc.
  - (Ing. Jiří Wild, PhD.)
- Department of neurology, 1st Faculty of Medicine, Charles University
  - Prof. MUDr. Robert Jech, PhD.
  - MUDr. Tereza Serranová, PhD.
  - MUDr. Filip Růžička, PhD.
- Na Homolce hospital, Prague
  - MUDr. Dušan Urgošík, CSc.

Thank you for your attention!