Eidgenössische Technische Hochschule Zürich
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ZNZ Introduction to Neuroscience II Spring 2017

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The Summary of the lectures in 2017

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Repository page: https://github.com/ssinhaleite/znz-intro-to-neuroscience-II-summary
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ZNZ - Institute of Neuroinformatics, ETH, UZH

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1 Cognitive Neuroscience

1.1 Research Methods in Cognitive Neuroscience - prof. Christian Ruff - 20.02.2017

There are various types of methods to acquire cognitive information. Those methods have different temporal resolution (can be acquired in milisseconds, seconds, hours, day, etc), spatial resolution (can get information of the brain, maps, columns, layers, cels, synapses, molecules) and invasiveness.

Techniques that record neuronal activity directly through electrophysiological means tend to have very good temporal resolution and techniques that manipulate brain function through drug effects or brain lesions tend to have the poorest temporal resolution.

Techniques that position electrode sensors directly within the brain have the highest spatial resolution and techniques that measure electrical signals that spread diffusely tend to have the lowest spatial resolution.

Non-invasive techniques record endogenous brain signals using sensors outside the body, thus they have almost no risk and can be conducted repeatedly in human volunteer participants. In the other hand, invasive techniques introduce a chemical or recording device into the body. Some invasive techniques can be used in humam volunteers (with significant attention) but other can be used only in human patients and/or non-human animals.

The main techniques that will be considered in this lecture are **correlative or measurement** and **causal or manipulation**. Both types of techniques provide distinct and complementary information about brain function.

Usually, the progress of cognitive neuroscience research happens quicly when measurement (correlative) techniques establish likns between brain structure and cognitive function and then manipulation (causal) techniques probe that relationtishp.

Correlative techniques

Measurements techniques measures changes in brain (information transmissionby neurons) function while a research participant (human or animal) engages in some cognitive activity. They are often described as being "correlational" because they can show that signals from a brain region co-occur with a function of interest, but they cannot show that a region is necessary for that function.

(f)MRI

(functional) Magnetic Resonance Imaging

MRI is a non-invasive imagin technique that employs principles of magnetic resonance to visualize different tissue types. Usually, one image is acquired. It is slow (minutes) but accurate (sub-mm

spatial resolution).

The fMRI employs special sequences that are i) sensitive to blood oxygenation and ii) fast to acquire (whole brain in 2-3 seconds). Numerous images are recorded and represent timecourse of blood oxygenation durig experimental task.

How the magnetic resonance works:

- Place an object (brain) in a strong **magnetic** field

  protons in the body have spins with a specific orientation and frequency, when the body is inside an MRI scanner, the protons align with the direction of the magnetic field.

- Deliver energy in form of radio waves

  radio frequence pulses with the appropriate frequency (that depends on the atomic nucleus being imaged, usually**Larmor frequency**) and change the orientation of the spins as the protons absorb the energy. The frequence used is called **resonant frequency**. When the pulse is turned off, the protons return to their original orientations, this process is called "relaxation", and during the (longitudinal $\rightarrow$ T1 and transverse $\rightarrow$ T2 1) relaxation, the protons emit energy in the form of radio waves.

- Measure radio waves emitted by object

  T1 is time constante of how quickly the protons realign with the magnetic field, for instance, CSF has low signal (dark) and fat has high signal (bright).

  T2 is time constante of how quickly the protons emit energy when recovering to equilibrium, for instance, fat has low signal (dark) and CSF has high sinal (bright).

The human scanners have a strong static magnetic field (around 1.5-7 Tesla). For reference, the earth's magnetic field is approximately 0.5 Gauss or 50-millionths of a Tesla.

The **T1 fMRI** images are structural images with high spatial resolution (less than 1 mm) and accurately distinguish different types of tissue. The **T2 fMRI** images have lower spatial resolution (2-3 mm) and relate changes in MR-signal to an experimental manipulation. Timeseries represents a large number of signals that are acquired in temporal order at a specific rate.

Some terminology:

- subjects: the item that will be scanned
- sessions: each time that the subject is inside of the scanner
- runs: all the images generated in one section for the whole subject. One complete scan of the subject is obtained in one single run.
- volume: the 3d images generated from one single run
- slices: each section of the volume is called slice.
- voxel: each single unit information in a slice

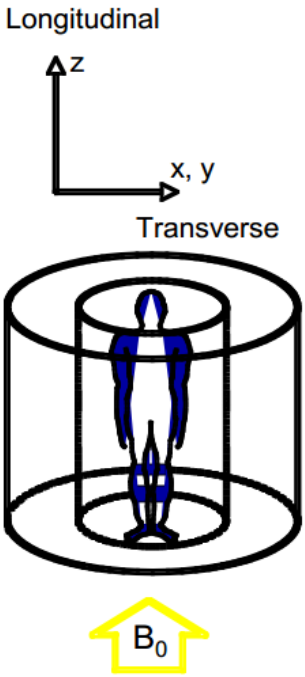

Figure 1: Orientation of the relaxation

the BOLD (Blood Oxygenation Level Dependent) contrast

measures inhomogeneities in the magnetic fiels (T2) due to changes in the level of O_2 in the blood. This way, fMRI measures neural activity indirectly via BOLD signal.

The oxygenated hemoglobine is diamagnetic (non magnetic) and produce no signal loss, however, the deoxygenated hemoglobine is paramagnetic (magnetic) and then produce a signal loss. When a specific region of the cortex increases its activity in response to a task, the extraction fraction of oxygen from the local capillaries leads to an initial drop in oxygenated hemoglobine (oxyHb) and an increase in local carbon dioxide (CO_2) and deoxygenated hemoglobine (deoxyHb).

Some properties of the BOLD signal:

- peaks 4-6 seconds after neural activity (delay)
- back to baseline after approx. 30 secs
- can vary in precise shape between regions and subjects
- often shows undershoot and sometimes shows initial undershoot

Due to an over-compensatory increase of rCBF(regional Cerebral Blood Flow), increased neural activity can decreases the relative amount of deoxyHB. This is called neuro-vascular coupling and it is an active area of research.

At present, the safest assumption is that BOLD relates to both spiking output and excitatory postsynaptic activity in neurons. Inhibitory activity is not assumed to lead to BOLD increases.

BOLD signal is not an absolute measure, but differs from session to session due to differences in scanner sensitivity, subject, etc. This way, BOLD signal needs to be compared between different conditions within the same experiment to infer BOLD changes (increase or decrease) due to neural process of interest P. **[Task with P] - [control task without P] = P**

For this "subtraction approach", there are assumptions of "pure insertion": i) cognitive (and neural) processes can be added to others without changing them and ii) changed behavior (and brain activity) reflects only added process.

Design of fMRI experiments

There advantages of fMRI are evident in its widespread acceptance among researchers and its visibility among the general public. fMRI allows us to **map complex cognitive functions in the brain of human volumteer participants with a good combination of spatial and temporal resolution**. However, fMRI has some disadvantages: it remains expensive, the scanner typicalli costs $500-$1000 per hour; also, some participants will be excluded based on issues related to safety (e.g., implanted devices) or comfort (e.g., claustrophobia). Moreover, even very small physiological variation (like head movements of only a few milimeters, breathing, or heartbeats) introduces noise into the BOLD signal.

they can be block-designs or event-related designs. In the block-designs, we measure constant BOLD response to a **series of stimuli**. In the event-related designs, we measure BOLD response to **each stimulus**.

Usually, fMRI experiments present a experimental stimuli displayed via MR-compatible monitor, head mounted display, or projection system, and the participant indicates his responses by moving a joystick or pressing a button.

- Block-designs:

  higher statistical sensitivity for detecting effects.

  some psychological process have to/may be better in blocks, for instance, if there is difficult to switch between states or to reduce surprise effects.

- Event-related designs:

  randomised trial order

  some events can not be blocked due to stimulus context.

In the fMRI designs, the predictions for BOLD signal can be categorical (identify classes), parametric (stimuli rotating, expanding) or model-based (check correlation between some model and BOLD signals). One can use a factorial desing and combine different factors (categorical, parametric and model-based) within one study, allowing study of context-dependent neural responses (can show a failures of pure insertion).

Sometimes, the resolution of the experiment is smaller than the MR image resolution, for this, we can consider the MVPA (multivariate activity pattern) or repetition suppression instead of the univariate signal in each voxel. The MVPA assumes that the signal in each voxel represents mixture of neuronal populations specialised for different features. Note that the pattern of increases and decreases may hence reliably differentiate different stimuli, even if each voxel by itself does not. The repetition suppression... ?

Analysis of fMRI experiments: SPM (Statistical Parametric Mapping)

it is a statistical approach instantiated in the most widely used software package for fMRI anaysis, it is implemented in MATLAB and it is open source. Allows standardised detection of **regional activity changes** in each voxel, associated with task parameters.

- Preprocessing

  Realignment (= registration): fix small head movements, assumes that the shape of the brain does not change.

  Spatial Normalisation: increase sensitivity with more subjects, extrapolate findings to the whole population and make results from different studies comparable (all in the same 'coordinate system')

  Smoothing: increase signal to noise, improve inter-subject averaging. In SPM, smoothing is a convolution with a Gaussian kernel. After smoothing, each voxel becomes the result of applying a weighted region of interest.

- Model estimation

  parameters estimation from GLM of voxel timeseries

- Contrasts and SPMs

  statistical inference

The results from fMRI are presented usually in three diferent ways, as shown in Figure 2. More specifically:

- Maps of activation

  the image is not a snapshot of the brain activity or a map of brain function. It simply indicates the results of a particular set of statistical tests, and the threshold for significance is (usually) corrected by the number of tests conducted.

- Time course of activation

  it shows the BOLD contrast MR signal changed over the duration of the experiment. The pattern of changes in BOLD signal over time is called a hemodynamic response.

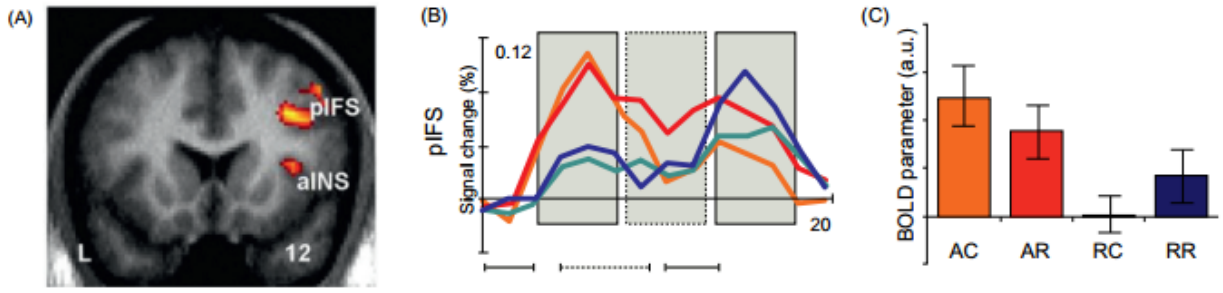

Figure 2: Common ways to present fMRI results. A) maps of activation, B) time courses of BOLD fMRI signal and C) parameter estimates of fMRI activation.

- Parameter estimates

  This involves creating a hypothesized model for the changes in brain activation that would be observed if there was an effect of the experimental condition. Its main advantage is that it provides a hypothesis-based statistical framework that can be adapted to any experimental design.

Advances in fMRI

Contrary to popular conception, advances in MRI technology have not been through stronger scanners, intead, the advances are changes in the hardware and procedures dor collecting fast and high-signal images. Rather than only recording signals from a single sensor around the sample object, new multi-channel scanners record MR signals from a large number of sensors at different points in space.

Causal Techniques

In order to address the impact of neural processes on behavior, neuroscients have developed several reserch thechniques to experimentally manipulate neural processing in specific brain areas. Causal or manipulation techniques examine how perturbations of the brain's function change cognitive functions or behavior. Pertubations on brain can be achieved either by transiently changing neuronal firing rates or neurotransmitter levels (**brain stimulation techniques**) or by permanently damaging tissue (**techniques that study the consequences of brain lesions**). Actually, there is a third technique: **neurophamacological intervetion**.

Brain Stimulation Techniques

Communication between connected neurons depends on the flow of electric charges. Neurons maintain an electric potential of about -70mV and when this potential rises above a fixed threshold voltage-gated ion channels open and trigger action potentials. This variation on membrane

potential is usually caused by synaptic input from other neurons, but an external electrical current can also affect membrane voltages and thus generate or inhibit action potentials. Brain Stimulation Techniques produce electrical currents in the brain in a controlled and locally specific fashion.

History of causal techniques: invasive stimulation

Fritsch & Hitzig in 1870 electrically stimulated an awake dog's brain via inserted wires and caused involuntary movements. The experiments were done in Frisch's home as the University would not allow the experiments. It was the first study to show that externally supplied electricity triggers neural function. Penfield and Rasmussen in 1950 attached electrodes to the cortical surface of human patients who were about to undergo neurosurgery and applied electrical current at various parts of the cerebral cortex. The behaviors and sensations elicited by stimulation of each area were documented in one of the first empirical maps of various motor, sensory and cognitive functions in the human cortex **Systematic "cartography" of brain-behavior (homunculus)**.

Nowadays, direct electrical stimulation of neurons via intracranial electrodes remains a routine technique in animal research, but most neuroscients use non-invasive brain stimulation techniques in human research as these techniques do not require surgery and can thus be employed routinely in health participants.

Causal Methods: Non-invasive stimulation

overcome need for invasive pre-surgical diagnosis, allow systematic testing of excitability and integrity of motor tracts, modulate function of the cortex for clinical purposes. Examples: TMS (transcranial magnetic stimulation) and tES (transcranial electric stimulation).

TMS

TMS: Biophysics

From Faraday's Law: a time-varying magnetic field induces an electric field in a conducting material. The induced electric field results in a measurable voltage and current flow. For TMS, the conducting material is the brain and the induced current activates neurons, as shown in Figure 3.

Brain is not homogenous conductor, but mixture of different materials (skull, liquor, gray and white matter) that have different conductivities. So, how does the electric field affect neurons?

- Activation of nerve fibre determined by the spatial derivative of the field component parallel to the fibre (the activating function)

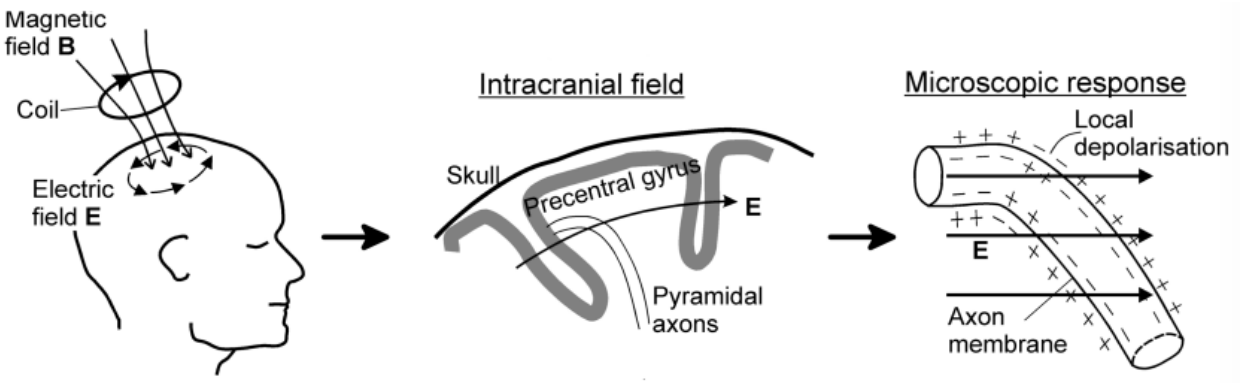

Figure 3: Basic principle of TMS

- Nerve bends are low-threshold points and therefore easiest to stimulate; the stronger the field, the stronger the stimulation.
- Cortical neurons have numerous bends, terminals and branches; these will all be affected most at the location where the induced fiels is maximal.
- The likely stimulation point in the cortex for random orientation of bends etc, is the field maximum.

TMS stimulates neurons by means of electromagnetic induction. By placing a looped copper coil against the part of the scalp overlying the site to be stimulated and running a strong, rapidly changing electrical current through the coil we generate a magnetic pulse perpendicular to the coil that permeates the skull and brain tissue. The rapid change of the magnetic pulse generates a complementary electric field in any conductive material (in this case, the neural tissue). **In other words, TMS uses a magnetic field, which can pass easily through the skull, to generate an electrical field inside the skull.** The likelihood that an action potential will be generated at any location depends on the orientation of these neurons with regard to the induced electrial field, this means, **some locations in the cortex are easier to stimulate than others using this technique**.

The two most common coil shapes are circular and figure-eight-shaped. Circular coils generate powerful but more difuse fields, whereas figure-eight coils result in more focal fields that produce the maximum current at the intersection of the two windings.

TMS: Neurophysiology and types of stimulation protocols

TMS pulses of hand representation in M1 (motor cortex area 1) cause measurable twitches in hand muscles. Non-motor cortical areas require different behavioral indices.

Finding the right area The first step of any TMS experiment involves localizing the scalp area overlying the cortical area that is to be stimulated. The experimenter needs to estimate where

on the scalp the TMS coil needs to be placed in order to induce currents in the target area. The stimulation area can also be identified as the site at which TMS has maximal behavioral effects in a separated task performed before the actual experiment begins.

Finding the optimal TMS intensity The optimal TMS intensity is usually determined for each participant individually as a fixed percentage of the motor threshold (MT), that is, the minimum intensity at which TMS applied over the motor cortex elicits hand twiches.

Influencing brain activity There are at least two different ways to influence brain activity.

- repeated TMS (rTMS) pulses can be applied *online* during task performance at a temportal frequency (5-20 Hz).

  The rTMS pulses elicit unspecific neural activity in the targeted area that disrupts cortical computations at that location.

- rTMS can also be applied just prior to the task (*offline*). The offline TMS generates after-effects offering a window in which the normal functional contribution of the stimulated area and possibly interconected areas are markedly reduced.

  rTMS can be applied for several minutes at low temporal frequency (1 Hz) $\rightarrow$ can reduce Motor Evoked Potentials for roughly the same duration as the length of rTMS application

  rTMS can be applied for less than a minute in a *theta burst pattern*, tipically 3-5 pulses at 100 Hz repeated at 5Hz. Theta-burst TMS (TBS) mimicks the theta rhythm that is expressed during memory storage. Also, TBS has been shown to lead to reductions (for continuous TBS) or enhancements (for intermittent TBS) of Motor Evoked Potential size lasting more than 30 minutes.

From slides notes:

It is necessary to be sure that the brain area is "at rest" during the stimulation (voluntary movements/contraction can reverse/abolishes the effects.

Advantages and Limitations of TMS

TMS allows non-invasive manipulation of neural processing with high spatial resolution (about one centimeter) and exceptional temporal resolution (milliseconds). However, nowadays it is only possible to target brain areas on the cortical surface. Also, for offline studies, there is some uncertainty about the precise duration of time window of TMS after-effects during which behavioral tests can be conducted.

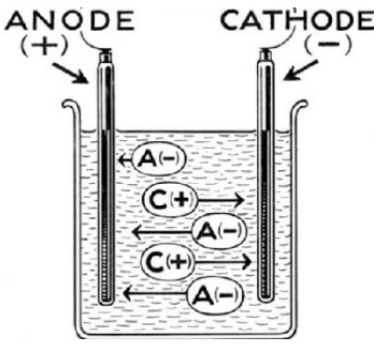

Figure 4: Basic principle of tES

tES: Biophysics

Two poles with electric potential difference (charge) connected through a conductive medium. The connection leads to discharge by electric current: negatively charged ions (anions) flow to anode and positively charged ions (cathions) flow to cathode, as shown in Figure 4.

tES envolves attaching two electrodes to the scalp and applying a constant electric potential difference, thus running a weak but constant electrical current between them. This affects the neurons along the path of the current, slightly changing their membrane voltages and thus their spontaneous firing. These effects are strongest directly beneath the electrodes where the current density is highest.

About 50% of the applied current reaches the cortex, the rest is shunted by the skull.

	TMS	tES
current	Induction of current by magnetic field	direct application of current
area	relatively focal	not very focal
induce	precisely timed burst of action potentials (+ physiological effects)	does not induce time-locked neural activity but modulates natural activity
threshold	suprathreshold stimulation	subthreshold stimulation
effects	phenomenological	physiological

Table 1: Differences between TMS and tES

History of causal techniques: lesion studies

Investigates causal brain-behavior relations (consequence of focal head wounds). They are measure in hypothesis-guided fashion cognitive and behavioral deficits of brain-lesioned patients.

Brain lesions in animals can also be experimentally induced in the laboratory, which enables scientists to test anatomically specific hypotheses about the relevance of the brain areas for specific behaviors.

Lesion studies in humans

The studiy of behavioral deficits in patients with brain damage (refered to as **neuropsychology**) originated in the neurological clinic.

One of the greatest challenges in neurological research is thus to determine the exact scope and extent of the neural damage associated with the given condition.

To test a hypothesis about the functional role of a given brain area using the lesion approach, researchers first identify a group of patients with more or less selective damage to that brain area. It is necessary, also, to identify a suitable control group for behavioral comparison (the control participants need to be closely matched to the patients with respecto to behaviorally relevant factors such as age, intelligence, socioeconomic status, cultural background, etc.

Advantages

The brain-behavior relationship is truly causal. Behavior deficits due to brain lesion can be very profound and can be evident to untrained observers. Moreover, the behavioral deficits resulting from naturally occurring brain damage can be very unexpected, leading to entirely new hypothesis. The knowledge gained from lesion studies is always relevant for medical care as it specifies behavioral deficits in patientes with specific types of brain damage, which may help the diagnosis and treatment of these disorders.

Limitations

Brain damage is often spatially diffuse, this can make it very difficult to find patients with overlapping damage in the structures of interest. Often litle is known about patients' behavior prior to the accident or illness. Brain injuries and ilnesses and their treatment can have nonspecific sequelae that may affect behavior, such as brain reorganization, medication effects, or an altered life situation.

Lesion studies in animals

In animals lesions are generated in clearly defined brain regions by various means so that therapeutic measures and the time course of recovery can be studied. A surgery is performed to produce a lesion at the designated site, usually the damage is irreversible.

Lesion experiments in animasl usually involve an experimental and a control group of animals that undergo matched procedures to rule out any unspecific effects of training, surgery, etc. The control group also undergoes surgery, but the procedures do not involve harm to the brain. At the

end of testing, the extent of the lesion is documented by detailed *post morten* neuroanatomical and neurochemical examination of the brain tissue.

Advantages

Full control over many variables that vary randomly in the context of pathological brain lesion in humans. Animals can be randomly assigned to either lesion or control group and can be perfectly matched in terms of experience, life situation, etc.

Limitations

Difficult to conduct: the training and keeping of experimental animals can be very labor-intensive and costly and surgery and behavioral testing require considerable infrastructure. It is generally difficult to compare behavior across species.

1.2 Perception and Attention - prof. D. Kiper - 27.02.2017

Perception

Perception is not a passive process (sensation is the passive process). Perception is the process by which people select, organize, interpret and respond to information from the world around them. It is selection and organization of environmental stimuli to provide meaningful experiences (we are not passive analyzers). The particular perception of itself is called proprioception. If you do not receive any stimulus (for instance, in a depravation tank), your brain creates it.

The perceptual process consists of six stages:5. (1-2)People receive stimuli from the enviroment throught their senses. (3) When the senses are activated, starts the perceptual selection. The perceptual selection is a filter, that allow us to deal with the most important matter. This is called **selective screening**: our system eliminates some factors because they are not important for us to be aware of. The "most important" is based on influencing factors that can be external or internal, as listed in Table 2. (4) When the most important stimuli is identified, starts the perceptual organization process by which people group the stimuli in recognizable patterns, listed in Table 3. (5-6) Then, we use the information received to interpret and respond to the stimuli. Perception is noisy and makes mistakes - very complex system. The most common types of perceptual errors are accuracy in judgment (main types listed in Table 4), perceptual defence, stereotyping, halo effect, projection, role of culture, etc.

Attention

Attention is the taking possession of the mind, in clear and vivid form, of one out of what sem several simultaneous possible objects or trains of thought. It is the focalization, concentration of consciouness. It implies withdraw from some things in order to deal effectively with others.

Internal	External
personality - strong factor	size
learning and perceptual sets - expectation of particular interpretation based on past experiences with the same or similar objects	intensity
motivation - the needs and desires at any particular time can influence perception (when you are hungry you can perceive a food as more delicious than when you are not hungry)	contrast
	motion
	repetition
	novelty
	familiarity

Table 2: Externals and internal influencing perception

continuity	lines are seen as following the smoothest path
closure	tendency to complete an object and perceive it as a constant
color constancy	your brain starts to iluminate the enviroment making you think the color is the same in different enviroments

Table 3: Examples of perceptual organization

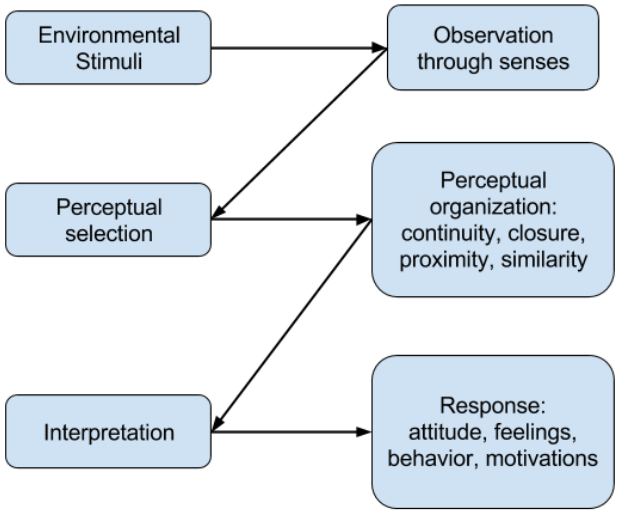

Figure 5: Stages of perception

similarity error	assuming that people are similar to us and then, will behave like us
contrast error	comparing people to others rather than to some absolut standard
overweighting of negative information	tendency to overreact to something negative
race, age, and gender bias	tendency to be more or less positive based on one's race, age or sex
first impression error	forming first impressions that are resistant to change

Table 4: Examples of perceptual organization

overt attention	selectively attending to an item or location over others by moving the eyes to point in that direction
covert attention	related with spotlight of attention, you can't pay attention to many things, this way when you pay attention in one thing, your capacity to pay attention in others decay.
feature attention	shadowing tasks, we can distinguish two mixed texts by focusing our attention on cues such as type style

Table 5: Types of attention

Attention can change rapidly, switching from one thing to another. It can be steered by our intentions ("top-down"), as when we look for a particular face in a crowd, or it can be steered by features of objects in the world ("bottom-up"), as when our attention is grabbed by a police car's flashing lights in our rearview mirror.

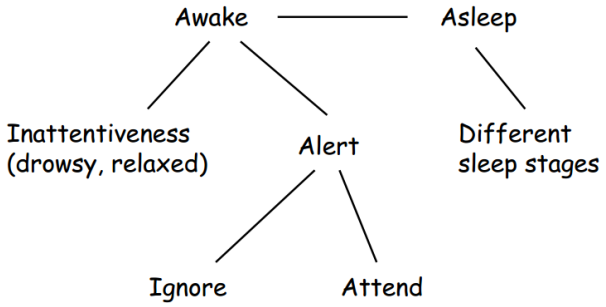

Figure 6: A definition of attention by exclusion

There are three main types od attention: overt, covert and feature attention. It one of them are explained in Table 5

Slide #18: frontal lobe → saccade eyes movements (overt attention); parieral lobe → covert attention.

Broadbent's filter theory - early selection

Broadbent (1958) argued that information from all of the stimuli presented at any given time enters a sensory buffer. One of the inputs is then selected on the basis of its physical characteristics for further processing by being allowed to pass through a filter, all the others are lost. Broadbent assumed that the filter rejected the non-shadowed or unattended message at an early stage of processing. It takes time to shift attention.

Treisman's theory - attenuation

physical characteristics are used to select one information for full processing but other messages are given partial processing.

Deutsch and Deutsch theory - late selection

All information get through but attention filters only act after meaning is analyzed.

Early or late experiments: Treisman and Geffen (1967) set about to test whether the filter was early or late in the processing stream. They had subjects shadow a message on one ear, and tap whenever they heard a certain word in either ear. When the key word appeared in the attended ear, subjects tapped 87% of the time, but when the key word appeared in the unattended ear, subjects tapped 8% of the time. This indicates that early selection is occurring.

A lot of simple experiments can be made to evaluate attention, for instance, pop out. It is easy to "find" elements based on one feature, more features (conjunction) $\rightarrow$ takes longer to find it. **pop out experiments can prove sinestesia because one can use one specific feature such as color, to find elements easily**. The more popout, more later selection (selection after meaning). Popout can be trained!

Effects in early visual cortex

Desimone experiments. MTA (medial temporal area) $\rightarrow$ prefered direction of motion $\uparrow$. Attention is like a weight to fire particular neurons.

Selective and divided attention

Attention is studied by presenting participants with two or more stimuli at the same time, this is called dual-task performance. In selective (focused) attention tasks, people are instructed to respond to one input only. In divided attention tasks, people are asked to process and respond to more than one input.

Gorila video:

innatentional blindness

1.3 Decision Making - 06.03.2017

What do we know about how the brain computes stimulus values at the time of decision-making? Recent meta-analyses: Positive effects of sv on BOLD are higher than negative effects. Also, the decision > outcome.

Becker-DeGroot-Marshack auctions to measure goal values.

Appetitive and aversive value

Multivoxel pattern analysis

PFC, LPFC, Parietal region

Deciding for self vs others

Executed:

decision for others

Model:

I'm not choosing for me but I'm still modeling. What I would choose for me?

vmPFC

= ventral medium pre frontal cortex

Areas on the brain that are not core for the type of the test but still may be part of the decision

comparison:

costs x bemefits

delay costs

effort costs

OFC

= orbital frontal cortex

ACC

= anterior cingulate cortex

Decision

related with learning: depends of what you have learned

Value (as in food) is not purely motor or sensory

how much people like chocolate after each square

All regions (on slide) receive input from VTA - dopaminergic neurons

long term memory

conditioning is impaired in amygdala but not in hippocampus (can not hold facts)

fear impairement (patient SM)

Similarity = shape, etc

positive and negative prediction errors

learning is proportional to prediction errors

dopamine neurons:

action potentials fires when unpredicted reward occurs; fewer action potentials than "normal" when no reward occurs.

learning from others

selfish = other = dorsal region

Representation → move from objective to subjective

dopamine neurons may represent values in a objective way

the same value has lower reward value if the subject needs to wait more for it

1.4 Emotion - 13.03.2017

Reference: Neuroscience, Purves et.al, chapter 28

Find methods to measure emotions

What is an emotion?

emotions are short lasting x mood are long lasting

emotion as everyday feeling

from psycology

from neuroscience: neurons controls behaviours

emotion as feelings

qualia → non communicative; verbal expression

comparative:

emotion is shared between humans and animals

fear conditionining x fear expression x fear prosody

Fear conditioning: conditioning stimuli and unconditioning stimuli inputs converge in amygdala. Amygdala neurons show long term potential (LTP), amygdala LTP facilitates CS conditioning.Amygdala LTP blocking blocks conditioning

common sense:

we do things because we feel

Physiological theory:

we feel because we sense things (attribution: think about the senses)

Facial feedback:

active some muscles leads to feeling

Appraisal theory:

automated no-consciouness that leads sensation to feeling

Affect theory:

framework to talk about subject feelings

Decision Theoretical View

emotions are actions:

adaptive to achieve goals.

Attention on two things:

goals and controls algorithms (that decide the actions)

rats cannot learn shock from taste, but they learn from be sick

many "algorithms" for many behaviours

game:

go pick a "piece" fast enough to not be hitted by "rock"

hippocampus lesion:

difficult approach

amygdala lesion:

return approach

Approximating algorithm:

optimal is too much complicated; why more time to go when is more difficult?

meta control:

how we decide what we decide?

Why study humans?

communication of emotions

Clinical application

fear extinction:

you can train the extinction of fear. However, the complete memory is not "removed".

memory reconsolidation:

memory consolidation needs proteins.

fear erasure:

where in the brain the fear seats? amygdala?

Multivariate fMRI analysis

benzodiapezines: ansiolitics

lesion on hippocampus make rats stay longer on open arm

slide: benzo:

red line; placebo: black line (human analogon)

1.5 Memory - Prof. Katharina Henke - 20.03.2017

Methods and Memory

fMRI

what structures support learning / tasks activities / retrieval activity?

Discover silent process (animals and humans)

Read the unconscionous mind using fMRI

Identify people with real memory problem

To identify areas on the brain essential for a task is necessary to analyze people with brain damage (in a specific area)

PET - Tomography:

used on study of learning and memory.

Patient:

23 years old - psycological trauma

No brain damage - no structural damage

Glucose pet indicates if area is working - functional amnesia

1.6 Learning during sleep - EEG

slowing sleep - delta waves

1.7 Multistore model

Sensory memory (up to 1s) $\rightarrow$ STM (15-20s to 1 min) $\rightarrow$ LTM (minutes and longer)

Hippocampus:

episodic memory $\rightarrow$ memory for personal episodies - autobiographical, what, where, when

Hippocampus - very vulnerable $\rightarrow$ lots of diseases by damage on hippocampus

ovulation invreases hyppocampus activity as in menstruation (?)

1.8 Declarative (explicit) memory

Semantic memory:

independent of hippocampus

through repetition is possible to learning new things using the neocortex and not passing throught the hippocampus

1.9 Nondeclarative (implicit) memory - unconsciouness

Procedural learning:

HM patient still able to ride a bike.

Priming:

tendency to process some perception in the same way. When you see a complex picture you need a longer time to identify things then in a second/third time.

1990-2000

Healthy patient do not show hippocampus activity during learning / memory

Hippocampus is speciallized in associate memory

anterior part: semantic and temporal association

posterior part: sensory and spatial

Parahippocampus gyrus:

individual objects - important for priming

Memory → new division → Model of Katharina (2010)

Encoding:

rapid / slow

Association:

flexible / rigid / no association (unique item)

Learning in sleep when the second word (?) is received in a moment where the neuron is polarized

1.10 Body Perception - 27.03.2017

Phantomology

Phantomology (is the name of the second chapter of Summa Technolofiae - 1964) and defines it as the science of the virtual reality of the body. "The science of the body in the brain, from out-of-limb to out-of-body experiences. Phantom limb sensation refers to the persistent experience of the postural and motor aspects of a limb after its physical loss.

- phantom body parts: the feeling of the body part after the removal of the body part
- hemiphantom: the feeling that half of the body is an entity that has its own life
- phantom double: the feeling of have a second body that imitates the original one.
- out of body experiences: the feeling of be disconnected with its own body.

The phantom limb is studied since 1510 (Paré) but the term "phantom limb" is from 1829 (Mitchell).

to read:

Finger and thustwitt, 2003, Neurosurgery 52.

Sensation is in the brain, not in the limb - Descartes

Even adult brains are capable to reorganize itself. In one experiment with adult monkeys, the cortical plasticity was identified: the monkeys lose a finger and the neighbors fingers took the "empty" area of the finger on the brain. In the maladaptive model, the pain is the price for the plasticity, the loss of input generates a "invasion" that causes pain. In the maintained representation model, the pain generates an increased input and then it is maintained the neural representation, in Nature 2013, an article was published saying that phantom pain is associated

with preserved structure and function in the former area (fMRI activation on phantom hand movement).

It is not very clear what is guided by phantom limb and why some people feel phantom limb pain. It is the peripheral nervous system or the central nervous system that origin the phantom limb sensation?

Phantomology

there are two types of phantom body parts: after amputation and also in congenital limb deficiency. Phantom limb can be feel even in congenital limb experiencies. Three main explanations: i) projection of enhanced motility of finger rudiments; ii) based on contralateral representation of intact limb; iii) based on innate schema for hand-mouth coordination. One patient has been feeling, as long as she can remember, a complete body. And she gets aware of hands in reflex movements and uses them to gesture. Also, she reports preference in posture (for instance in folding her arms) and says the inverted posture feels "awckward".

Scientific fact: does not mean remembering is not important, also does not mean "body schema" is "inate".

Negative phantom limbs

it happens when there is a physical limb but there is no "connection", the person do not recognize the existence of the body part, also called xenomelia.

One neglected phenomenal aspect of phantom limbs is the obstacle shunning: put a physical object at the same place as the phantom body part. Approximately 50% believes the phantom limb is still there even when a pile of books is placed at the same location of the limb, the others 50% perceive that the phantom limb is in his/her head. Experiment: ask for a person with phantom limb sensation to point out the location of the phantom body part, and then, add a physical object to the same place. The phantom body part vanishes but the phantom pain remains. **Even if the phantom limb sensations disappears the phantom limb pain can still holds** In some cases, the confrotation of the phantom limb with solid matter makes the person change the postural body as if the phantom limb changed its place. Also, there are cases where the kind of matter that is taking the place of the phantom limb matters. For instance, in one experiment with a man who lose the anterior part of his right foot, if he put his foot really close to a wall or other objects, the phantom sensation was there (but with the toes in different position), however, when the man put his foot behind his left foot, the sensation was different (as if the toes retracted into the foot).

To move the feet from an obstacle, if we do it in a fast way (brief interstimulus intervals) the foot appears to pass through the object. However, if we do it with longer interstimulus intervals, the foot appears to go around the object. Amputees with shunning show the long apparent motion trajectory with shorter interstimulus intervals. Shunning is associated with worse prothesis tolerance.

The phantom limb studies is relevant in research because the individual differences in visual-somesthetic interactions, but also has a clinical relevance considering the adjustment to a protesis.

Phantom limb without amputation

also called spinal phantom limb. The main difference to amputation phantom is the visual observation of dysfunctional but still present limbs.

supernumary

is a condition where the affected individual believes and receives sensory information from limbs of the body that do not actually exist, and never have existed. One of the patients have the sense of arms protruding from chest. Every time the patient tried to "slip into the phantom limb", she reports that the phantoms are evade laterally.

You do not need to physically lose a limb to experience phantom limb. Without the visual system we can simulate the feeling of phantom limb. Experiment 1: Pinocchio-illusion - with closed eyes, participant touch his/her nose, biceps is stimulated. Participants perceive arm or/and nose in different location. Experiment 2: Rubber hand - Place the rubber hand on a table in front of you and conceal your real hand behind a cardboard. A second person will, using identical movements, do the same thing with your hand and the fake hand. After a while, participants are convinced that the fake hand is their own hand.

until slide 17 of handout 06.01

Phantom moving is like imagine moving a limb - bilateral activation on brain

2 Clinical Neuroscience

2.1 Neurology: Ophthalmology, Otology, Epileptology and Parkinson - 03.04.2017

Neuro ophtamology

Clinical eye testing

- moviments
- smooth pursuit
- saccadic eye moviemnt - fast eye moviment

    disorders: velocity, metrics (can "pass" the point), latency

- nystagmus

  primary gaze: indicative of cerebellum loss $\rightarrow$ gaze holding and rebound

  vestibulo occular reflex: the head moves and the eyes move together and then, after a while the eyes turn to the object-goal position

Clinical balance testing

- spontaneous nystagmus: eyes drift to the side of the loss.
- head impulse test: negative $\rightarrow$ eye stays in position; positive: $\rightarrow$ eyes follow head and then turn.
- vertical: "close" one eye and the other stays in the same position
- dynamic: see letters moving the head

vertical occular deviation

dynamic visual acuity

sensorymotor balance:

romberg test: close eyes and balance is lost.

caloric testing

bimallolar (?) vibration sense

Epilepsy

What is epilepsy?

brain disorder, chronic condition

What is a seizure?

temporary disruption of normal brain function.

- eye moviment, body tension
- depending on the anatomical location of the seizure, can be all body or only an arm for instance

EEG

pyramidal cells in the cortex: sleep and close eyes produce high variations.

Seizures does not mean epilepsy.

Some seizures can be provocated.

Classification of seizures:

- focal: part of the brain
- generalized: whole brain; always without consciouness.

EEG measures synchrony post-synaptic potential

Hypersynchronization:

spikes and sharp edges (seizure)

generalized seizures:

neurons die

Treatment:

- surgery: small area
- pharmacotherapy
- disease specific treatment

Parkinson

Parkinson is a syndrome not a disease

Variety of symptons:

always related with a lack of dopamine. However, too much dopamine is also a disturb but it is not parkinson.

- slow movements

- tremor
- stiffness
- postural instability

Parkinson's disease:

the common reason for Parkinson's syndrome. Second most common degenerative disorder, just lose to alzheimer.

L-dopa is the most effective therapy to Parkinson's disease

it is like insuline for diabetes. However it is a symptomatic-therapy not a cause-therapy.

Manage the quantity of dopamine is not easy

2.2 Neurology: Multiple Sclerosis, Neuromuscular, Stroke and Neuropsychology - 10.04.2017

Multiple Sclerosis

- Most frequent CNS disease among young adults (20-40y)
- Relapses manifestation: coming and go
- distructive disease
- inflamation and other shrink (?) on brain
- enviromental effects: more common abouve equator line
- diagnostic depend of space and time

  space: not only one area of CNS lesion

  time: because come and go
- PPMS: primary progressive multiple scelerosis: CSF

  punctions of CSF: if you find bacteria (?) in the CSF and serum it is a general inflamation, if you find only in the CSF is MS.
- scale 0 to 10; 10 means death
- MS became a treatable disease in 90's
- de-myelination is necessary to diagnose MS: you need MRI information and additional signs.

Neuromuscular disorders

- diagnosis: medial (?) history, neurological examination, lab tests
- myotonic reaction: ?

Stroke

Any acute neurological sympton is a stroke unless proven otherwise

Stroke is not a seizure, and also is not a migraine

two type of strokes:

ischemia and hemorrhage

- ischemia: (80%) $\rightarrow$ block of a vessel - recanalization
- hemorrhage: (20%) blood pressure control / hematoma evacuation, reduction of intracranial pressure - cateter

cells in penumbra are potentially salvable

penumbra is an area around the vessel. After 270 mins of a stroke, recanalization can lead to hemorrhagia.

prognosis:

death + dependent (approx. 90% hemorragic and approx. 40% of ischemia)

Neuropsychological disorders

- aphasia (language disorders)

  broca $\rightarrow$ patient do not speak but understand

  wesnick $\rightarrow$ spontaneous speech is fluent but it is impossible to repeat phrases.
- alexia $\rightarrow$ can write but can not read
- apraxia $\rightarrow$ can use tools but can not immitate their uses
- anosognosia $\rightarrow$ no notion of its own deficience

2.3 Spinal Cord Injury - 25.04.2017 - Dr. Martin Schubert and Dr. Armin Curt

Clinical exam (padronized)

international grade of spinal cord injury (from A to E, where E is normal)

Neuro urology

Disfunction on urinary tract - spinal cord injury

paper to read:

"Lower urinary trait disfunction".

mickey mouse kidney (?)

leads to incontinency

disreflexia

above T6, vaso constriction. Increase on blood pressure leads to (parada cardiaca)

2.4 Epilepsy

2.5 Depression

2.6 Schizophrenia

2.7 Addiction Clinics - 15.05.2017 - Dr. Marcus

Global Burden of Disease (2010)

Alcohol + ilicit drugs $\rightarrow$ increased 5.4%. Tobacco $\rightarrow$ 3.7%.

Mortality in Switzerland

1. tobacco ¿¿¿ 2. alcohol ¿¿ 3. suicid ¿¿ 4. traffic accidents

Drugs most harm

1. alcohol ¿¿¿ 2. heroin ¿¿¿ 3. cocaine
Intoxication, dependence

Dependence Syndrome (six signs)

Need to present at least 3 signs during a month.

- Strong desire or compulsion
- Impaired capacity to control substance taking behaviour
- A physiological withdraw state with reduce or cease (?)
- Evidence of tolerance
- Preocupation with substance use by alternative pleasures (to not reduce or give up)
- Persistent use despite harmful consequence

Dependence

Environmental and genetic factors. First use is not enough to become dependent
Graph: probability to get dependent vs time (nicotine, cocaine, alcohol, cannabis)

Stigmas of Alcohol, Depression and Schizophrenia

to read: "Addiction is a Brain disease, and it matters"

Alcohol risks for health consequences

low $\rightarrow$ high

Treatment goals

preservation / restoration of health and social integration
Pharmacotherapy, Psycotherapy, Social Support.
+ 50% abstinence - 50% reduction

Heroin

pain killer open drug scene in Zurich (1980/1990)

Not drug free, but social acceptable

- prevention
- therapy
- harm reduction
- regression

33k people died of opioid in USA (when??)

Cocaine

issue in Zurich (top 3 cities in europe)

Patient interview

cocaine addicted

Recreational x addicted users

start of use drugs generate positive effects.
graph of positive/negative effects vs use

Berridge (?) et al, 2009

"want" vs "like" dissociates over time

want

dopamine

like

endogenous opioids

Addiction as pathological learning and memory

reward, memory, drive and control

Molecular target of drugs

- I - binds to G-protein - metabotropic - LSD
- II - binds to ionotropic receptors
- III - interacts with monoamine transporters (GABA receptors)

Addiction increase dopamine levels

mesolimbic projection (VTA - ventral tegmental area)

faster uptake

faster drug effect (reward)

place/people as trigger

if drig do not "come" the brain seeks the drug $\rightarrow$ absence of dopamine

Serotonin and addiction

without dopamine, one can still get addicted if there is serotonin in the body.

2.8 Addiction in Society

2.9 Neurosurgery - 22.05.2017 - Jorn Fierstra

Highly Specialized Medicine

most brain surgery but also spine surgery
UZH/ETH is an outstanding place

Brain pathologies

Aneurism

determine if must be treated. 50% of bleeding, some people do not need surgery.

bypass

80 years neurosurgery ?

Elana (?) laser system bypass

invented in zurich

Spine Pathologies

2nd image

neck

3rd image

tumor spinal cord

Brain tumor

30 cases per year

1st image

tumor from dura

3rd image

glioma (butterfly)

4th image

surgery, microscope, neural navigation

5th image

tumor that do not "appear", glowing tumor
Intraoperative MRI

Neurosurgery challenges

better imaging methods
BOLD fMRI Respiract: changes in CO2 to contract/dilate veins in brain
Neurovascular uncoupling finger tapping - image effects sensitive to threshold

3 Previous exams

2013

1. **FMRI**

2. **Microglia**

3. **Circadian Rhythms**

4. **Motor Learning**

5. **Parkinson**

6. **Multiple Sclerosis**

2011

1. **fMRI is routinely used to study the neural processes underlying behavior. Please describe all the procedures necessary for conducting and correctly interpreting an fMRI study, covering the following areas:**

   Data acquisition (what signals are measured in fMRI, and how?)

   Data analysis (which sequential routines are necessary to detect signal changes in fMRI images, using software packages such as SPM?)

   Results interpretation (what inferences about neuronal activity can be drawn from fMRI results? answer here.

2. **Please list the different types of long-term memory you know of. Describe their properties in humans, group them according to involved brain structures and give examples of behavioral tests that allow to model these memory types in rodents**

3. **Sleep regulation in physiological short and long sleepers: Explain the most important principles how sleep and wakefulness are physiologically regulated and how sleep-wake regulation may differ between habitual short and long sleepers.**

4. **Robotic tools have played a significant role in the investigation of human motor learning.**

   Describe the role of internal models in human motor control and how such models are acquired

   Identify three unique features of robotic systems that make them valuable tools to investigate human motor learning.

   Discuss how these unique features could be applied to clinical assessment and therapy of sensorimotor impairments answer here.

5. **The term "frontotemporal dementias" subsumes a heterogeneous group of disorders:**

   Please describe the clinical presentations of patients with frontotemporal dementia (major clinical syndromes, and characteristic features).

   Which genes/gene loci have been associated with frontotemporal dementia?

   Please summarize which major molecular subgroups of frontotemporal dementias can be defined and briefly discuss current knowledge and/or hypotheses on underlying pathomechanisms in the two most common subgroups. answer here.

6. **The maintenance of central and peripheral tolerance is the reason that autoimmune diseases are relatively rare. Please answer the following questions:**

   How does central T cell tolerance work (which organ performs T cell education, what is negative and positive selection)?

   What are the mechanisms of peripheral tolerance? Remember, we discussed four of them. Please shortly recapitulate.

Why does the inflammation in an MS-lesion subside after a while? What mechanisms can dampen an ongoing immune response (if you do not know, speculate!)? answer here.

3.1 All Question - topics

Methods

1. **fMRI is routinely used to study the neural processes underlying behavior. Please describe all the procedures necessary for conducting and correctly interpreting an fMRI study, covering the following areas:**

   fMRI (functional Magnetic Resonance Imaging) is a non invasive technique that employs principles of magnetic resonance that are sensitive to blood oxygenation and are fast to acquire.

   Data acquisition (what signals are measured in fMRI, and how?) To acquire data it is necessary follow three steps:

   a) Place an object (brain) in a strong magnetic field: protons in the body have spins with a specific orientation and frequency. When the body is inside an MRI scanner, the protons align with the direction of the magnetic field.

   b) Apply radio waves: radio frequences pulses with the appropriate frequence (Larmor frequency) change the orientation of the spins as the protons absorb the energy. When the pulse is turned off, the protons return to their original orientations (this process is called relaxation), and during relaxation the protons emit energy in the form of radio waves.

   c) Measure radio waves emitted by the object (brain): two measures can be acquired - T1 longitudinal and T2 transverse. T1 is how quicly the protons realign with the magnetic field and accurately distinguish different types of tissue, T2 is how quicly the protons emit energy when recovering equilibrium and relate changes in MR-signal to an experimental manipulation.

   One of the most commons signal used to relate changes in the MR-signal to the experimental manipulation is the BOLD (Blood Oxygenation Level Dependent) signal. This signal measures inhomogeneities in the magnetic field (T2) due to changes in the level of O_2 in the blood. This way, fMRI measures neural activity indirectly. The oxygenated blood is non magnetic while the deoxygenated blood is magnetic. When a specific region of the cortex increases its activity in response to a task, this region consumes the oxygen leading to an initial drop in oxygenated hemoglobine and an increase in local carbon dioxide and deoxygenated hemoglobine.

Data analysis (which sequential routines are necessary to detect signal changes in fMRI images, using software packages such as SPM?) The data analysis using software such as SPM allows standardised detection of activity changes in each voxel, and for this three macro steps are necessary:

a) Preprocessing: in the preprocessing phase we can realign the images to fix small head movements, normalise the data to increase sensitivity with more subjects, to extrapolate findings to the whole population, to make the results comparable among different studies, also, we can smooth the image to increase signal to noise, impreve inter-subject average.

b) Model estimation: calculate parameter for instance, from GLM of voxel timeseries.

c) Contrasts and SPM: do the statistical inference.

Results interpretation (what inferences about neuronal activity can be drawn from fMRI results? The fMRI results (using BOLD signal) are not an absolut measure, the results can differ from session to session due to differences in the scanner, in the subject, etc. This way, BOLD signals need to be compared between different conditions within the same experiment to infer BOLD changes, for example, we acquire signal for the task P and also signals from a control withou the task P. The difference between the two acquisition will be the result of the task P. This is an approach that assumes a "pure insertion" theory, where cognitive (and neural) process can be added to others withou changing them and the change in behavior (and in brain activity) reflects only the added process. Also, the fMRI results are correlative results, i.e., they can show that signals from a brain region co-occur with a task of interest but cannot show that a region is necessary for that function.

2. **What are the physiological correlations of fMRI signal? How does the fMRI signals correlate with neuronal activities?**

The physical correlation of fMRI is neural activity, resulting in an initial (about 0.5-2s) 'undershoot' of the proportion of oxygenated hemoglobin, due to the consumption of oxygen for the neural activity. This leads to a reduction of the BOLD (blood oxygen level dependant) signal. Neural activity seems to mediate vasodilation (maybe through to release of NO), leading to an increase of blood flow (after 2-10s), resulting in an increase of the BOLD signal due to the better blood supply. Studies comparing BOLD data with EEG data have shown that the BOLD signal rather reflects the information uptake and processing by neurons than their spiking output measured by EEG.

Memory

1. **Please list the different types of long-term memory you know of. Describe their properties in humans, group them according to involved brain structures and give examples of behavioral tests that allow to model these memory types in rodents**

Sleep

1. **Sleep regulation in physiological short and long sleepers: Explain the most important principles how sleep and wakefulness are physiologically regulated and how sleep-wake regulation may differ between habitual short and long sleepers.**

2. **Characteristics of sleep in mammals: Do they apply to invertebrates?**

   behavioural: Sleeping site Quiescence Body posture Elevated arousal threshold Rapid state reversibility Physiological: Altered EEG Reduced muscle tone Reduced heart rate Reduced respiration Reduced body temperature Regulatory: Compensatory response to sleep deficit or excess sleep

3. **Non-REM-REM sleep**

   REM: rapid eye movement. EEG low amplitude, mixed frequency (more similar to wake than to deep sleep EEG). Most prominent in the morning hours. non-REM: is subdivided into four substages 1-4 in human, deep sleep consists of stages 3 and 4. In deep sleep, he EEG contains prominent slow waves (0.5-4.5 Hz, high amplitude). cycles: REM sleep occurs every 90-100 mins during sleep (ultradian oscillator origins in the Pons). General term to describe cyclic alternation between REM and non-REM sleep. Healthy people usually start with stage 1, then 2, 3, 4, 2, REM, 2, 3, 4, REM etc.

4. **Sleep homeostasis and marker of sleep homeostasis on the sleep EEG**

   homeostasis has been defined as the coordinated physiological processes wich maintain most of the steady states in the organism; sleep homeostasis refers to the sleep need in dependance of the time spent awake. Sleep need rises exponentially during wake and declines exponentially during sleep. According to 2-process model of sleep regulation, sleep need is additionally dependant on circadian time. NREM-sleep is controlled thalamocortically. Marker of sleep homeostasis: slow-wave activity (power of slow waves rises in recovery sleep after sleep deprivation according to the 2-process model)

5. **Endogenous sleep-promoting components: comments**

   SCN (superchiasmatic nucleus of hypothalamus) clock genes: transcriptional/translational process melatonin: built during sleep Thalamus: control of NREM-sleep Pons: Regulation of REM-sleep Potential homeostatic sleep-promoting agents (Experiment: if CSF from a sleep-deprived animal is transferred to a rested animal, the rested animal becomes tired $\rightarrow$ there must be an agent in the CSF that accumulates during wakefulness and makes tired): adenosine, Interleukin-1b, TNFa, GHRH, prostaglandin.

6. **Role of thalamus-correlated rhythm in sleep: comments**

   Thalamus controls the NREM sleep rhythmus $\rightarrow$ EEG activation / desactivation

Schizophrenia

1. **Please describe shortly a neurobiological model of schizophrenia**

Depression

1. **Please describe briefly:**

   Some conceptional problems in studying depression from a neuroscientific point of view Depression is a disorder of subjective feeling (translation from first person perspective to third person perspective: epistemic problem). It is very difficult to evaluate the disease scientifically (animal models that are really adequate to depression, they can't talk to tell their feelings). The definition of psychiatry depends on social values and personal evaluation of suffering, but not depends on the organic disorder. No reliable bjective markers like genetic defects or metabolic disfunctions.

   Some changes of the neurobiology system in a depression state Change of HPA-axis (hypothalamus-pituitary-adrenal) The prominent mechanism by which the brain reacts to acute and chronic stress is the activation of HPA-axis $\rightarrow$ cortisol levels rise. Hypothalamus secretes CRH (corticotropin-releasing hormon) $\rightarrow$ pituitary (hypophysis) secrets adrenalcorticotropin (ACTH) $\rightarrow$ adrenal gland secrets cortisol

   Growth hormone is reduced. Sleep disorders (EEG!), disturbances of appetite regulation.

   different activation of brain areas (activation of medioorbital cortex and ventral anterior cingulate $\rightarrow$ limbic system activated)

Psychiatric disorders - general

1. **Animal models of behaviour allow us to investigate the symptoms of psychiatric disorders such as depression and schizophrenia. Discuss statements, giving examples of some specific model**

   You always have to ensure that the animal model is valid. There are different aspects of validity that have to be guaranteed: Face validity: quantifiable behavior and physiology in the animal model have to be similar to the symptoms in the investigated human illness. Construct validity: the quantifiable behavior and physiology in the animal model must be a result of the same central state as in the human patient. Theoretical rationale. Predictive validity: close correspondence between drug actions on behavior and physiology of the animal model and the human patient. Inter-laboratory validity Inter-species validity

   Schizophrenia: Impairment of working memory leads to symptoms like halluzinations: lack of references against associative memories. Selective attention is impaired, leading to delusions (misinterpretations), confusion of external and internal stimuli and retreatment to safety (neg. symptoms). Specific test: Latent Inhibition (LI) test. LI paradigm: repeated non-reinforced pre-exposure to a stimulus retards subsequent conditioning to that stimulus. This reflects the ability of 'learning not to attend'. In animals: rats reduce LI when given amphetamine $\rightarrow$ animal model for schizophrenia. Rats that get amphetamine, avoid the box where they got shocked previously in the CAR (conditioned avoidance response) and reduce licking water in the CER (conditioned emotional response) tests compared to control animals due to their impaired LI.

   Depression: Animal model of learned helplessness: animals are exposed to negative stimuli and don't get the possibility to escape. This leads to the 'learned helplessness' symptom, especially, if the animals are very young, which means, they give up very quickly and are not able to escape unwanted situations. Learned helplessness can be measured by the escape behavior in a two-way avoidance test. In this test, animals are placed in a shuttle box and exposed to a foot shock. They are allowed to escape to the save compartment of the shuttle box. If they get conditioned for the shock with a tone, starting shortly before the shock, animals learn to escape already at the presentation of the tone. 'Helpless' animals are not good in escaping compared to controls. Chronic mild stress: Animals are chronically exposed to mild stress like food / water deprivation for some hours, not enough space, over night illumination etc. The loss of pleasure (anhedonia) is measured with the ICSS (intra-cranial self-stimulation), the PRS (progressive reward schedule) or the sucrose preference test. Early life stress: Pups are stressed by separating them from mother for several hours per day etc.$\rightarrow$ anhedonia

2. **Describe methods for measuring motivation, attention and memory in rodents and/or primates. In which neuropsychiatric disease are these beavioural processes disrupted?**

Circadian Rhythm

1. **Circadian pacemakers, entrainment, Zeitgeber, phas-response curve**

   Pacemaker: SCN (superchiasmatic nucleus of hypothalamus) entrainment means that the 'inner clock', located in the SCN, is flexible in the way that it can adapt the phase (example: time-zone flights) and the frequency (example: bunker experiments, where one 'day' lasts 25 hours) of the circadian clock. Entrainment: via light, signalling from the eye to the SCN (possible photoreceptor: Melanopsin?). In the SCN, per transcription is activated upon light signal. Phase-response curve: depending on the circadian time, when a light pulse is presented, the phase of the circadian clock is shifted forward or backward. If the light pulse is presented shortly before the active period has started, then the phase is advanced and if the pulse is given shortly after the active period has ended, the phase is delayed (in humans). There is one time point during night when the phase shift swiches from delayed to advanced.

2. **Which physiological and endocrine variables in human are frequently used a phase-marker of circadian rhythm**

   endocrine: melatonin, adrenal gland (adrenalin, cortison); GHRH (Growth hormone releasing hormon) Physiological: body temperature; activity (via activity monitor); alpha-activity in the waking EEG

3. **What is the evidence that SCN is a circadian pacemaker**

   lesion method $\rightarrow$ arythmicity in vitro culture of a single SCN neuron SCN transplant reserves the rhythm in vitro SCN

4. **Which genes (gene?) are (is) involvedin generation of circadian rhythm**

   in mammals: Bmal1 is rhythmically expressed by the SCN. Clock and bmal1(basic helix-loop-helix transcription factor family) build heterodimers. These heterodimers bind to E-boxes of enhancers of the per and cry gene. Per and Cry proteins dimerize outside the nucleus and are phosphorylated. The dimers re-enter the nucleus and downregulate transcription of clock and bmal1 (negative feedback-loop). Situation is even more complex, also containing positive feedback-loops...) in fruit fly Cyc/Clk heterodimers activate per/tim gene transcription. Negative feedback-loop: Per/Tim heterodimers inhibit activation of their own genes via Cyc/Clk.

Models of Computation (?) → this topic was not covered in 2017

1. **Roles of automate as models for computation**

   The computational process in neurons can be investigated in neuroinformatics via automate models (as compared to the structural process via neuroscience)

2. **Automate suitable models for describing the operation of neurons and networks of neurons**

   Models for automates are transferable to neurons / neuronal networks:

   Feedforward processor: input → blackbox → output (without memory) In neuron: input correlates to the dentritic input (sum of input signals x weights), output correlates to the axonal output (fire or not fire)

   Finite State Machine: input → black-box (which remembers the state in which it is, memory!) → output In neuron: neurons also can feed back information to build up memory (this model accounts only for short-time memory (seconds)...). Feedback occurs, when axonal output is networked to dendrites of the very same neuron.

   Turing Machine: input → black-box containing unbounded memory → output Church-Turing-Thesis: this machine is able to compute all possible computations. Philosophic question: is the brain's memory unbounded???

   Universal Turing Machine: can simulate the computational process of any Turing Machine, when it knows the protocol of this machine, thus it can also simulate the computational process of a neuron... But the protocol is not known (e.g.: a bee can do computations leading to very various and complex behavior, there is no computational model that could do that with the limited recourses of a few thousand neurons that a bee needs to accomplish it)

   But: Neuronal networks have different weights for the 10 exp 14 axons/dentrite connections. This is not possible to be determined genetically (not enough resources), but dependant on the microenvironment of each neuron in the developmental process. Moreover, they can adapt to the environment by changing those weights or even establishing new connections between axons and dentrites. Synaptic release is additionally very versatile, can be modulated chemically, and be inhibitory or excitatory etc.

3. **What is the impact of W.I. and what information do we get from it?**

4. **(a) Describe the properties of a finite state machine. (b) Is a single neuron kind of a finite state machine? Explain your answer. (c) What kinds of model (artificial neurons) do you know about?**

4 References

The pictures used in this summary are from the class slide sets or internet, and belong to their respective owners. In the context of this summary they are used for educational purposes only.

4.1 Cognitive Neuroscience

- Christian C. Ruff and Scott A. Huettel, Chapter 6 - Experimental Methods in Cognitive Neuroscience, In Neuroeconomics (Second Edition), edited by Paul W. Glimcher and Ernst Fehr, Academic Press, San Diego, 2014, Pages 77-108, ISBN 9780124160088, http://dx.doi.org/10.1016/B978-0-12-416008-8.00006-1