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ZNZ Introduction to Neuroscience II

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The Summary of the lectures in 2017

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1 Cognitive Neuroscience

1.1 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 milliseconds, seconds, hours, day, etc), spatial resolution (can get information of the brain, maps, columns, layers, cells, 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 human 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 here 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 quickly when measurement (correlative) techniques establish links between brain structure and cognitive function, and then manipulation (causal) techniques probe that relationship.

Correlative techniques

Measurements techniques measure changes in brain function (information transmitted by neurons) 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 imaging 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 during 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
pulses of radio frequency with the appropriate frequency (that depends on the atomic nucleus being imaged, usually **Larmor frequency**) change the orientation of the spins as the protons absorb the energy. The frequency 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 → T1 and transverse → T2) relaxation, the protons emit energy in the form of radio waves (Figure 1).
- Measure radio waves emitted by the object
T1 (longitudinal) is time constant of how quickly the protons realign with the magnetic field, for instance, CSF has low signal (dark) and fat has high signal (bright).
T2 (transverse) is time constant of how quickly the protons emit energy when recovering to equilibrium, for instance, fat has low signal (dark) and CSF has high signal (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 session 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

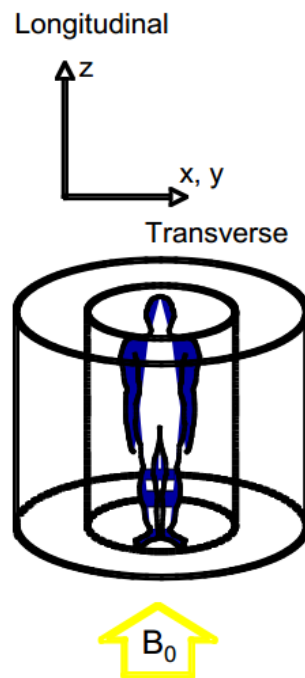


Figure 1: Orientation of the relaxation

the BOLD (Blood Oxygenation Level Dependent) contrast

BOLD measures inhomogeneities in the magnetic fields (T_2) 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 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 temporal 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 decrease the relative amount of deoxyHB. This is called neurovascular 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. In other words: **[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

The 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 volunteer participants with a good combination of spatial and temporal resolution**. However, fMRI has some disadvantages: it remains expensive, the scanner typically 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 millimeters, breathing, or heartbeats) introduces noise into the BOLD signal.

The design of fMRI experiments 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 an 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 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 design use decreases in BOLD signal for 2nd vs 1st presentation of stimulus as index for functional specialization of neurons within the voxel.

Analysis of fMRI experiments: SPM (Statistical Parametric Mapping)

SPM is a statistical approach instantiated in the most widely used software package for fMRI analysis, 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 different 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 changes over the duration of the experiment. The pattern of changes in BOLD signal over time is called a **hemodynamic response**.

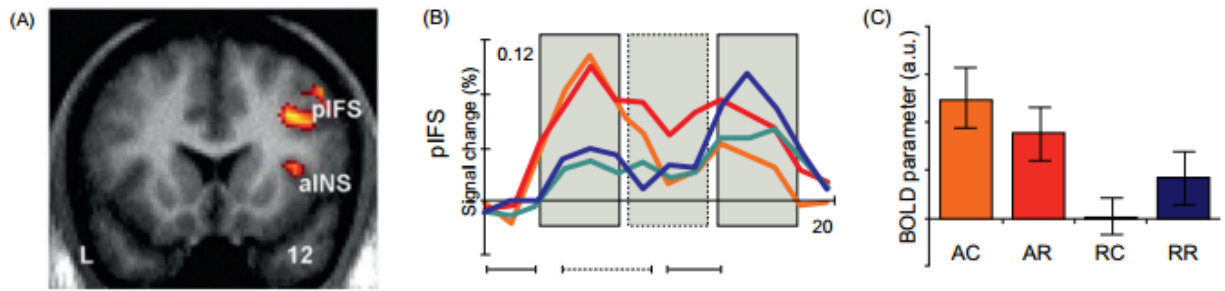


Figure 2: Common ways to present fMRI results. A) maps of activation, B) time courses of BOLD fMRI signal and C) parameter estimates of fMRI activation.

- 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, instead, the advances are changes in the hardware and procedures for 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, neuroscientists have developed several research techniques 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. Perturbations 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**). There is also a third technique: **neuropharmacological intervention**.

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 Fritsch'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 neuroscientists use non-invasive brain stimulation techniques in human research as these techniques do not require surgery and can thus be employed routinely in healthy 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 a homogeneous 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)
- Nerve bends are low-threshold points and therefore easiest to stimulate; the stronger the field, the stronger the stimulation.

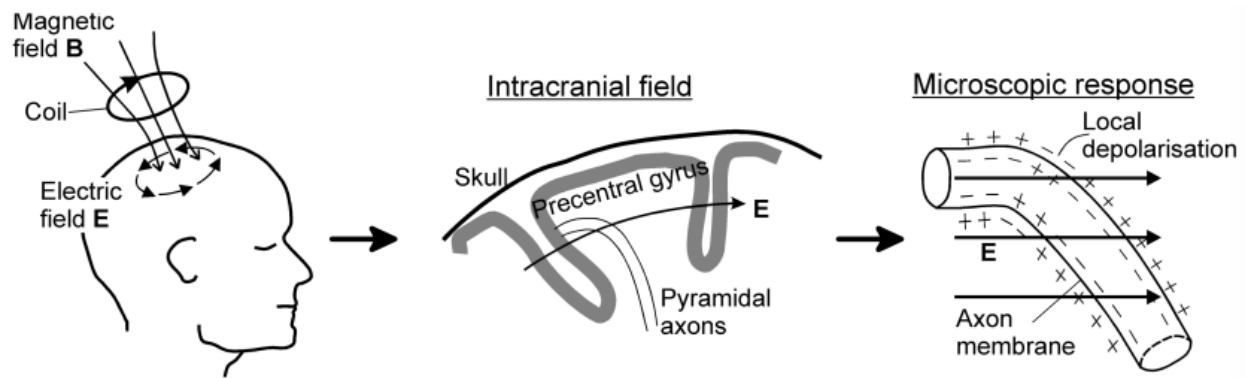


Figure 3: Basic principle of TMS

- Cortical neurons have numerous bends, terminals and branches; these will all be affected most at the location where the induced field 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. A looped copper coil is placed against the part of the scalp overlying the site to be stimulated. By running a strong, rapidly changing electrical current through the coil we generate a magnetic pulse perpendicular to the coil. This pulse 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 electrical 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 diffuse 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 twitches.

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 temporal 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 interconnected areas are markedly reduced.

rTMS can be applied for several minutes at low temporal frequency (1Hz) → 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*, typically 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.

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 (cations) flow to cathode, as shown in Figure 4.

tES involves 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

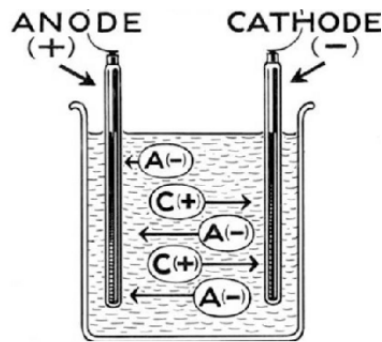


Figure 4: Basic principle of tES

neurons along the path of the current, slightly changing their membrane voltages and thus their spontaneous firing. These effects are stronger 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)	it 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

Lesion studies are used to investigate causal brain-behavior relations (consequence of focal head wounds). They are measure in a hypothesis-guided fashion, where cognitive and behavioral deficits of brain-lesioned patients are studied.

Brain lesions in animals can 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 study of behavioral deficits in patients with brain damage (referred to as **neuropsychology**) originated in the neurological clinic.

One of the greatest challenges in neurological research is 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 the 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 respect to behavior 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 patients 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 little is known about patients' behavior prior to the accident or illness. Brain injuries and illnesses 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 animals 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 mortem* 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. Surgery and behavioral testing require considerable infrastructure. It is generally difficult to compare behavior across species.

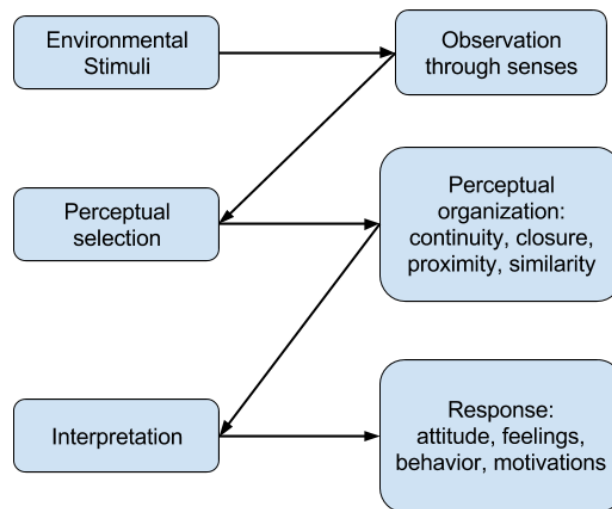


Figure 5: Stages of perception

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 deprivation tank), your brain creates it.

Perception is essentially the interface between the outer and inner worlds. The outer environment creates signals that can be sensed and the perceiver receives these signals and converts them into psychologically meaningful representations that define our inner experience of the world.

The perceptual process consists of six stages (Figure 5):

- (1-2) People receive stimuli from the environment through 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.

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

perceptual grouping or 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 illuminate the environment making you think the color is the same in different environments

Table 3: Examples of perceptual organization

- (5-6) Then, we use the information received to interpret and respond to the stimuli. Perception is noisy and makes mistakes, it is a very complex system.

The most common types of perceptual errors are:

- accuracy in judgment (main types listed in Table 4).
- perceptual defence: the tendency for people to protect themselves against ideas, objects or situations that are threatening.
- stereotyping: the belief that all members of a specific group share similar traits and behaviors.
- halo effect: tendency to color everything we know about a person because of one recognizable (un)favourable trait.
- projection: tendency to see one's trait in others.
- role of culture: culture influences our perception in selecting information and exhibiting a behavioral pattern in situations.

This simple perception-appraisal-response sequence is implemented innumerable times in the course of any given day and, to a great extent, is completed without effort.

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 absolute 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 error in accuracy of judgment

Attention

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

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.

The bottom-up stimulus usually seems to require immediate behavioral responses (e.g., a rock flying in your direction). It seems quite functional that the attentional system is tuned to attend quickly to moving and looming stimuli as those stimuli will commonly have more immediate survival implications than the more stable ones.

Not all stimuli in the perceptual field receive equal attention; instead, some stimuli are selected for relatively intense scrutiny, making them more likely to reach the threshold of awareness. When an individual encounters stereotype/ inconsistent information, attention is drawn, and the perceptual details of an event are encoded.

We can enhance perception, if we focus our attention on a location in the visual field, this is called **spotlight of attention**. However, enhancing perception in one part of the visual field takes place at the expense of other areas.

Shadowing task is an experiment where two "signs" are presented to the participant and one of the signs will "hide" the other.

There are three main types of attention: overt, covert and feature attention. Each one of them are explained in Table 5. The common area for saccade eye movements (overt attention) and covert attention is the frontal lobe; the area preferentially activated by covert attention is the parietal lobe.

There are two orienting mechanisms: **exogenous or reflexive** and **endogenous or voluntary**. Table 6 lists the main differences between them.

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

exogenous	endogenous
peripheral cues	central cues (e.g, arrows)
fast (100 ms)	slow (300 ms)
occurs even with uninformative cues	occurs only with informative cues

Table 6: Two orienting mechanisms

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 rejects the shadowed or unattended message at an early stage of processing. It takes time to shift attention.

Deutsch and Deutsch theory - late selection

All information get through but attention filters only act after meaning is analysed, for example, each ear receives a different message and it is asked to the participant to say the message. The message can be recovered if it is the only thing with meaning.

Treisman's theory - attenuation

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

Early or late experiments: Treisman and Geffen (1967) tested whether the filter was early or late in the processing stream. They had subjects shadowing 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, and 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. Adding more features (conjunction) will make it

longer to find elements. **Pop out experiments can prove sinesthesia because one can use one specific feature such as color, to find elements easily.** The more popout, more late selection (selection after meaning). Popout can be trained!

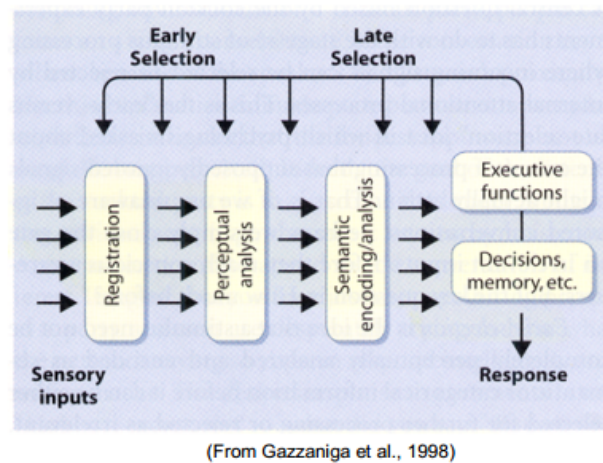


Figure 6: Different models of selection in attention

Another definition of attention

Attention is what enables us to process information about the world around us. We can only be aware of things around us if we pay attention to them. **Preattentive** processes help us to decide what to pay attention to and what to filter out and ignore.

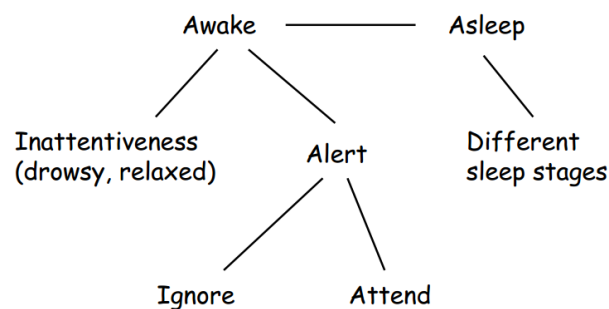


Figure 7: A definition of attention by exclusion

Effects in early visual cortex

Desimone experiments. MTA (medial temporal area) → preferred direction of motion ↑. 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

Two main activities for decision making: **valuation** and **action selection**. Valuation: what is the value of each action. Action selection: choose action based on valuations.

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

What brain areas encode the stimulus value computation in simple choices between primary rewards (e.g., foods)? Use of Becker-DeGroot-Marshack (BDM) auctions to measure goal values. Critical to have a real-time and incentive compatible measure of goal values.

Experimental design

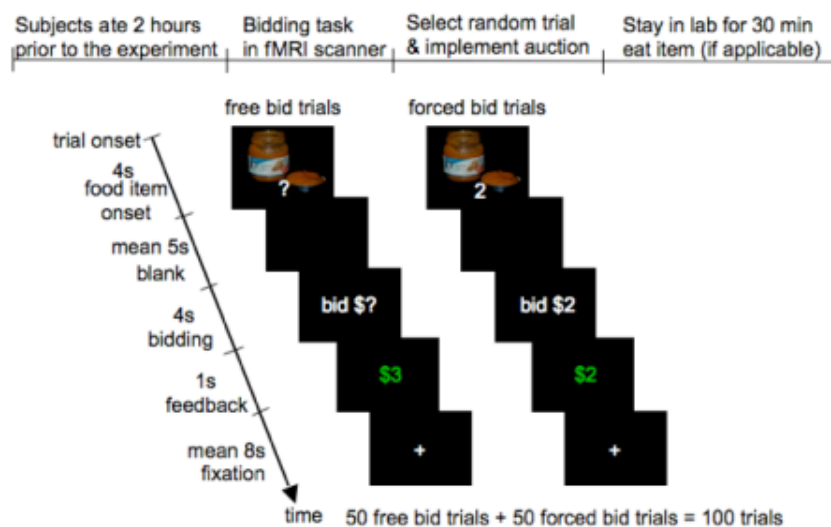


Figure 8: Experimental design - free bid and forced bid trials

Subjects were instructed to eat at most 2h before the experiment to decrease the attractiveness of the foods. During the informed consent period, subjects agreed to eat whatever food item they would eventually have to eat as determined by the auction mechanism described below.

Subjects were instructed that they would have to remain in the laboratory for 30 min at the conclusion of the experiment and that they will have to eat whatever food was shown on a randomly selected trial unless they purchased the right not to do so. In addition to a \$50/h participation fee, each subject received three \$1 bills in “spending money” to place bids to purchase the right to avoid eating disliked food items. Whatever money they did not spend was theirs to keep. Subjects placed bids for the right to avoid eating particular foods in 100 different bidding trials. In each trial, they were allowed to bid \$0, \$1, \$2, or \$3. At the end of the experiment, one of those trials was randomly selected, by drawing a ball from an urn, and only

the outcome of that trial was implemented. As a result, subjects did not have to worry about spreading their \$3 budget over the different items and they could treat each trial as if it were the only decision that counted.

The rules of the auction were as follows. Let b denote the bid made by the subject for a particular item. After the bid is made, a random number n was drawn from a known distribution (in our case, \$0, \$1, \$2, and \$3 were chosen with equal probability). If $b \geq n$, the subject did not have to eat the item and paid a price equal to n . In contrast, if $b < n$, the subject had to eat the entire portion of the food shown but also did not have to pay anything.

There is no incentive to bid less than the willingness-to-pay (WTP) since the price paid is determined by the random number n , and thus the bids do not affect the price paid. There is also no incentive to increase the bid above the WTP since this may lead to a situation in which the subject avoids having to eat the item but ends up paying a price larger than his WTP (e.g., consider the case of $WTP = \$1$, $b = \$3$, and $n = \$2$). Since bidding the exact WTP is the best strategy, the bids provide a good measure of the aversive goal value computed by the brain for every subject and item at the time of decision making. Thus, we could use the bids as a behavioral measure of aversive goal value to correlate with the blood oxygen level-dependent (BOLD) signal on a trial-by-trial basis. As a result, any area that encodes for goal values in free, but not in forced trials, is a good candidate for the goal value computation.

Free bid trials vs forced bid trials A key difference between the two types of trials is that, whereas subjects were free to select the amount of their bid in the free trials, they were told how much to bid in the forced trials. The forced bids were drawn uniformly and independently from \$0, \$1, \$2, \$3 on each trial. As a result, subjects need to make an aversive goal value computation in free trials to decide how much to bid, but they do not necessarily need to do so in forced trials.

vmPFC and dlPFC encode for WTP in free trials, but not in forced trials.

Valuation

Appetitive and aversive value

Which brain areas encode for aversive goal values? Are these the same areas that encode for appetitive goal values? Robustness to non-primary rewards and more complex decision problems: Is the ventral medial pre frontal cortex (vmPFC) a common area of stimulus valuation across decision problems?

Multivoxel pattern analysis

PFC, LPFC, Parietal region

Deciding for self vs others

vmPFC reflects the values you would assign when choosing for yourself. vmPFC reflects the values you have learned, another area would assign the values when choosing for others. The values computed are those that are appropriate for the situation.

Model

I'm not choosing for me but I'm still modeling. What I would choose for me? There are some areas on the brain that are not core for the type of the test but still may be part of the decision.

How much people like chocolate after each square? The value decreases.

vmPFC and vStr are among the most consistently found regions in human neuroimaging studies, however, value representations are not limited to these regions.

Action selection

All costs are not created equal.

comparison:

costs x benefits

delay costs

effort costs Orbital Frontal Cortex (OFC) lesions decrease willingness-to-wait. Anterior Cingulate Cortex (ACC) lesions decrease willingness to expend physical effort.

These experiments highlight both the power and complexity of using the lesion method to examine brain function. Clear dissociation between ACC and OFC lesions. Interactions between lesions and experience.

dmPFC/ACC, dlPFC, and IPS activity is consistent with regions implementing a value comparison process. These regions are functionally connected with value computation areas such as vmPFC and these regions modulate motor output in favor of the selected action.

There is growing evidence that the brain makes goal-directed choices using a process of valuation-action selection (Figure 9).

Learning and perception in decision making

We can think in many types of decisions: figuring out the number of an approaching tram, or deciding what to eat in a new restaurant, or trading in the stock market, or even playing poker.

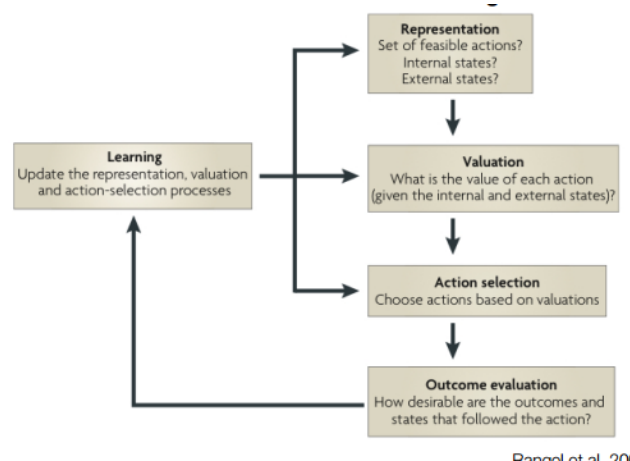


Figure 9: Value based decision making process

Decision

Make a decision is related with learning: depends of what you have learned. The value of an decision (as in food) is not purely sensory or motor.

Reward system is divided in three parts:

- planning, judgment: prefrontal cortex and frontal cortex
- reward: nucleus accumbens, medial forebrain bundle and ventral tegmental area.
- emotions, conditioned effects: amygdala

What is learned and how?

What: Focus on value representations (aversive, appetitive) How: Learning rules (rescorla-wagner, temporal difference learning rule)

Consequence of learning: long term memory

Implicit memory as associative learning: classical and operant conditioning with emotional responses in amygdala. Classical conditioning: Before conditioning the dog only salivates (unconditioned response) in the presence of the food (unconditioned stimulus). The same way, with the presence of a sound (neutral stimulus), there is no salivation (no conditioned response). During conditioning, the sound is presented together with the food, which makes the dog salivates. After conditioning, only the presence of the sound (conditioned stimulus) is enough to produce salivation (conditioned response).

Memory functions of the temporal lobe

Patient H.M.: ablation of temporal lobe, particularly hippocampus caused strong anterograde amnesia, but intact working memory and procedural memory.

Conditioning is impaired in amygdala but not hippocampus. The inverse holds for declarative knowledge acquisition.

Fear impairment (patient SM)

Lesion in amygdala generates inability to recognize fearful faces but intact recognition of different emotions. Also, impaired attention to eye region and an inability to experience fear (except if it is elicited “internally” through CO₂).

The amygdala is involved in value learning (particularly fear conditioning).

Learning mechanisms

Hume: temporal contiguity, spatial contiguity and similarity (shape, etc). Rescorla: contingency. Kamin: prediction error (blocking paradigm).

Learning by prediction errors In the learning phase, it is learned that with the sound, we will receive one euro. In a next phase, if when we heard the sound, we gain 10 cents, the prediction error is negative, if we gain one euron, the prediction error is zero, and if we gain more than one euro, the prediction error is positive. Prediction error response is sensitive to predicted reward magnitude.

This way, $\text{predictionerror} = \text{outcome} - \text{prediction}$, and $\text{newprediction} = \text{previousprediction} + \text{predictionerror}$.

Learning is proportional to prediction errors. $\Delta V = \alpha\beta(\lambda - \Sigma V)$ Where,

- ΔV is the change in associative strength of conditioned stimulus (learning)
- α, β learning rate
- λ is the amount of processing of unpredicted unconditioned stimulus
- ΣV is the summed current associative strength of conditioned stimuli presented (amount learned)

Temporal difference learning It is the difference in expected and actual outcome: prediction error signal in relation to time $t, t + 1, \dots$

Predicted value: $V(t) = \Sigma w_i x_i(t)$, where w_i is the weight and $x_i(t)$ is the stimulus representation (presence of CS). Prediction error: $\delta(t) = (r(t) + \gamma V(t+1)) - V(t)$, where $r(t)$ is the reward

at time t and γ is the discount factor. $\Delta w_i = \alpha \sum x_i(t) \delta(t)$ it is the correspondence to recortla-wagner rule $\Delta V = \alpha \beta (\lambda - \Sigma V)$.

Dopaminergic neurons

Dopaminergic neurons appear to code a (signed) reward prediction error. Action potentials fires when unpredicted reward occurs; fewer action potentials than “normal” when no reward occurs. Increasing reward probability leads to increasing CS response and decreasing reward response.

Reward prediction carries temporal information: delayed and early reward activates dopaminergic neurons thus, prediction error response is computed moment by moment.

L-Dopa enhances prediction error responses in ventral striatum, haloperidol reduces them, dopamine release depends on prediction.

Activity of dopaminergic neurons, dopamine concentrations in target structures and BOLD-activity in target structures such as the striatum process prediction errors as described by temporal difference learning rules.

Altruistic learning

Nicer people process value for others more than the value for themselves. The spatial gradient (on ventral-dorsal regions) of altruistic value representation is more pronounced for selfish than for altruistic participants.

selfish = other = dorsal region

Reinforcement learning is driven by prediction errors, as captured by formal learning models.

Representation

What do we mean with representation? What is represented? Sensory/percetual features, blood sugar, objective choice option paramteters, pre-decision. What if subjective processes are represented or impact representations in absence of choice?

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
Representations occur at various processing stages. The orbitofrontal cortex, the hypothalamus and other regions (e.g. the insula) represent internal states. Single neurons represent magnitude and probability of rewards and punishments. Representations can be influenced by learning.

1.4 Emotion - Prof. Dominik Bach - 13.03.2017

What is an emotion?

Emotions are the subjective feelings that are associated with physiological states. Emotions are short lasting and mood are long lasting. Some of the most devastating psychiatric problems involve emotional (affective) disorders.

What is a feeling? qualia (non communicative) + verbal expression.

Emotion as everyday feeling, different theories: neuroscience, comparative and psychological. From neuroscience, neurons control behaviors; from comparative, emotion is shared between humans and animals.

Physiological changes associated with emotion

All emotions are expressed through both visceral motor changes and stereotyped somatic motor responses. Examples of changes in the activity of the visceral motor are increase or decrease in heart rate, cutaneous blood flow (blushing or turning pale), sweating, and gastrointestinal motility. Activation of the visceral motor system, particularly the sympathetic division, was long considered an all-or-nothing process. More recent studies have shown that the responses of the autonomic nervous system are actually quite specific, with different patterns of activation characterizing different situation and emotional states. For example, if subjects are given muscle-by-muscle instructions that result in facial expressions recognizable as an emotion without being told which emotion they are simulating, each pattern of facial muscle activity is accompanied by specific and reproducible differences in visceral motor activity (as measured by indices such as heart rate, skin conductance, and skin temperature).

In 1928, Phillip Bard, removed both cerebral hemispheres (including the cortex, underlying white matter and basal ganglia) in a series of cats. When the anesthesia had worn off, the animals behaved as if they were enraged. This behavior was called **sham rage**, because it had no obvious target. Bard suggested that whereas the subjective experience of emotion might depend on an intact cerebral cortex, the expression of coordinated emotional behaviors does not necessarily entail cortical process. Conclusion: basic circuits for organized behaviors accompanied by emotion are in the diencephalon and the brainstem structures connected to it. In short, the somatic and visceral activities associated with unified emotional behavior are mediated by the activity of both the somatic and visceral motor neurons, which integrate parallel, descending inputs from a constellation of forebrain sources.

The left hemisphere is more importantly involved with what can be thought of as positive emotions, whereas the right hemisphere is more involved with negative ones. Also, the right hemisphere is more intimately concerned with both the perception and expression of emotions than is the left hemisphere.

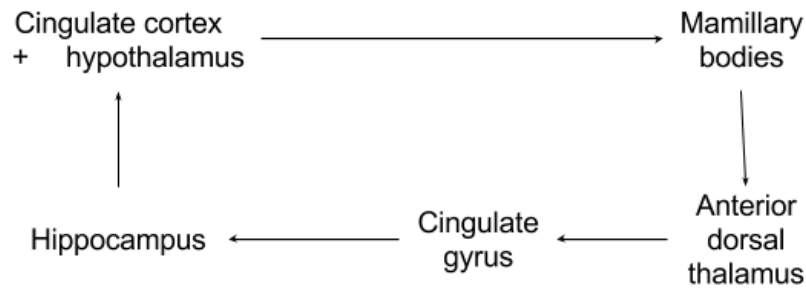


Figure 10: Papez circuit

Papez circuit

It is a circuit suggested by Papez. He believed that these pathways provided the connections necessary for cortical control of emotional expressions. Figure 10 shows the Papez circuit: the cingulate cortex and hypothalamus are interconnected via projections from the mammillary bodies (part of the posterior hypothalamus) to the anterior nucleus of the dorsal thalamus, which projects in turn to the cingulate gyrus. The cingulate gyrus (and many other cortical regions as well) projects to the hippocampus. Finally, the hippocampus projects via the fornix (a large fiber bundle) back to the hypothalamus. Over time, some of the structures that Papez originally described (for instance, hippocampus) now appear have little to do with emotional behavior, whereas the amygdala (that he hardly mentioned) clearly plays a major role in the experience and expression of emotion.

fear conditioning 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. Amygdala neuron firing relates to freezing behaviour. Amygdala lesions disrupt fear acquisition and lesions post training erase fear memory.

Fear expression: detection of fear expression is impaired in bilateral amygdala lesions.

Fear prosody: is unimpaired in bilateral amygdala lesions.

Find methods to measure emotions

What criteria should we use to decide if a particular behavior is emotional or not?

Comparative theories

Basic emotion theory: facial expression of basic emotions, and their recognition, are organised in categories of basic emotions and they are mostly culture-unspecific.

Common sense

We do things (behavior) because we feel. (sensation → subjective feeling → behavior)

Physiological theory

we feel because we sense things. Attribution: think about the senses. (sensation → body response → subjective feeling)

James-Lange event → body reaction → feeling

Schachter-Singer event → body reaction → attribution → feeling

Facial feedback

active some muscles leads to feeling. sensation → expression (face, posture, prosody) → subjective feeling

Appraisal theory:

automated no-consciousness that leads sensation to feeling: "I felt fear because I evaluated a situation as dangerous". (sensation → automated appraisal → subjective feeling /body response)

Richard Lazarus 1. Is the event relevant for the agent? 2. Can the agent cope with the event?

Klaus Scherer Sequential Stimulus Evaluation Checks (SECs): 1. Relevance (novelty, (un)pleasantness); 2. Consequence (causes of the event, probability of consequences, urgency); 3. Coping potential (control, power); 4. Normative significance.

Affect theory:

meta-cognitive representation of inner states, including emotions, framework to talk about subject feelings (inner states, including emotions → subjective feeling)

Decision Theoretical View

What we can observe in emotions are internal and external actions. How are they decided upon and coordinated?

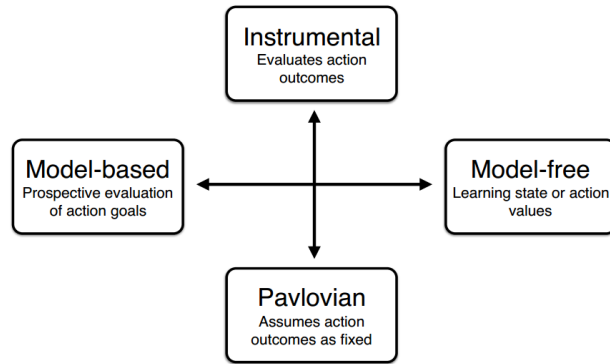


Figure 11: Types of approximating algorithms

Emotions are actions

As actions, emotions are adaptive, and can be optimised to achieve goals. **Attention on two things:** goals and controls algorithms (that decide the actions).

For non-discrete problems, computations are often analytically intractable. The (numerical) computations are often extremely time-consuming and many variables (including possible actions) are unknown. Use of approximating algorithms, optimal is too much complicated; why more time to go when is more difficult? The approximating algorithms are listed in Figure 11.

Approximating algorithm:

Requirements:

- Need for speed: high-dimensional distributions problematic
- Learning from errors often impossible: reinforcement learning problematic
- Lots of information missing: need to integrate over many variables.

Some possible solutions for this approximating algorithms are pre-programming algorithms to 1. operate on selected sensory input; 2. consider only a selected action; 3. remove/reduce plasticity. That means: we need multiple algorithms.

- Preprogramming sensory input: rats cannot learn to freeze from taste (but they learn to freeze from shock). They cannot be conditioned to avoid audiovisual CS, but they can learn from be sick.
- Preprogramming action menu: nose-poking cannot be conditioned to avoid threat (shock), but nose-poking can be conditioned to avoid starvation.

- Limited plasticity: startle eye blink cannot be conditioned to CS, but airpuff eye blink can be conditioned to CS.

Discrete algorithms

Which sensory input? Which actions? Action-outcome relation fixed (pavlovian vs. instrumental)? What kind of algorithm (model-free vs model-based)?

Should we restrict “emotions” to humans? Rodent anxiety models: elevated plus maze, open field test, novelty, suppressed feeding test, successive alleys test, etc.

many “algorithms” for many behaviours

game:

go pick a “piece” fast enough to not be hit by “rock”

hippocampus lesion:

difficult approach

amygdala lesion:

return approach

meta control:

how we decide what we decide?

Why study humans?

Communication of emotions (facial expression, prosody, body posture), attentional capture, induction of feelings, influence of ‘emotional stimuli’ on deliberate decision-making, and clinical application (fear conditioning, anxiety-like behavior).

Clinical application

Fear extinction

You can train the extinction of fear. However, the complete memory is not “removed”. Extinction builds a competing memory.

Memory reconsolidation

Memory consolidation needs proteins, with this we can “unlearn” responses to CS.

Fear erasure

Memory erasure goal: specific memory re-activation in psychotherapy context; drug intervention to prevent reconsolidation. Where in the brain the fear seats? amygdala?

Multivariate fMRI analysis

benzodiazepines: anxiolytics

lesion on hippocampus make rats stay longer on open arm

slide: benzo:

red line; placebo: black line (human analogon)

Anxiety

Subjective feeling with physiological responses.

1.5 Memory - Prof. Katharina Henke - 20.03.2017

One of the most intriguing of the brain's complex functions is the ability to store information provided by experience and to retrieve much of it at will.

Learning is the name given to the process by which new information is acquired by the nervous system and is observable through changes in behavior. Memory refers to the encoding, storage, and retrieval of learned information.

Methods and Memory

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

fMRI

Good spatial resolution throughout the brain. Measures blood oxygenation (see BOLD in 1.1). The aims of the fMRI study are:

- to find the structures that support learning/tasks activities/retrieval activity (detect a task-relevant network of brain structures and functional specialization of a brain region)
- to discover silent process (animals and humans)
- to read the unconscious mind using fMRI (detect mental process that do not reflect in behavior)
- to identify people with real memory problem (it can detect simulation in patients)

PET - Positronen Emission Tomography

Used on study of learning and memory, measures metabolites and neurotransmitter concentrations (most common: glucose uptake).

example of patient - 23 years old with psychological trauma No brain damage (structural damage) observed, glucose PET indicates if area in the brain is working or not - functional amnesia.

Electro encephalography - EEG

EEG has good temporal resolution, and is used on study of learning and memory consolidation during sleep, measures excitatory and inhibitory postsynaptic potentials in neocortex.

Multistore model

Three temporal classes of memory are generally accepted. Sensory memory (up to 1s) is the routine ability to hold ongoing experiences in mind for fractions of a second. The Short Term Memory (STM, sometimes working memory) is the ability to hold information in mind for seconds to minutes (15-20s to 1 min) once the present moment has passed. The Long Term Memory (LTM) entails the retention of information in a more permanent form of storage for days, weeks or even a lifetime (minutes and longer).

The capacity of working memory very much depends on what the information in question means to the individual and how readily it can be associated with information that has already been stored.

Forgetting Were it not for forgetting, our brains would be impossibly burdened with the welter of useless information that is briefly encoded in our immediate memory "buffer". In fact, the human brain is very good at forgetting. Although forgetting is a normal and apparently essential mental process, it can also be pathological, a condition called **amnesia**.

Amnesia is defined as the inability to learn new information (anterograde amnesia) or to retrieve information that has already been acquired (retrograde amnesia).

Hippocampus

It is important to establish new declarative memories. Spatial learning and memory is related with hippocampus. Rats with lesion in the hippocampus cannot learn to find the platform in a pool. However, it is not used to recall nondeclarative memory (patient HM case).

episodic memory → memory for personal episodes - autobiographical, what, where, when. Hippocampus is very vulnerable, i.e., there are lots of diseases by damage on hippocampus. The larger hippocampal resections, the worse the resulting learning impairments.

ovulation increases hippocampus activity as in menstruation (?)

Long Term Memory

The LTM is divided in two types: declarative (or explicit) and nondeclarative (or implicit). The complete division of memory (based on consciousness) is shown in Figure 12.

Declarative (explicit) memory Declarative memory is the storage (and retrieval) of material that is available to consciousness and can be expressed by language (hence, "declarative"). It is divided in two: semantic and episodic memory.

The **semantic memory** is independent of hippocampus and through repetition is possible to learn new things using the neocortex and not passing through the hippocampus. The semantic

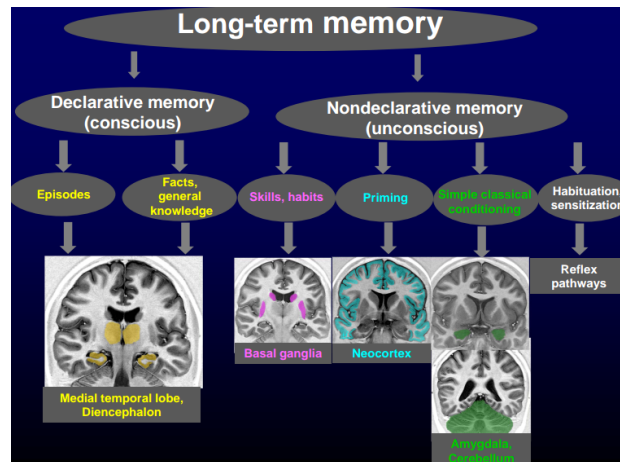


Figure 12: Memory model based on consciousness

memory holds facts, general knowledge, no context and refers to the present. Brain structures: **lateral temporal lobe** and **parahippocampal gyrus**.

The **episodic memory** holds happenings, temporal and spatial context, personal information and mental time travel into the past. Brain structure: hippocampus.

Nondeclarative (implicit) memory - unconscious Nondeclarative memory (sometimes referred to as procedural memory) is not available to consciousness. Such memories involve skills and associations that are, by and large, acquired and retrieved at an unconscious level. Is divided in three memories: procedural, priming and classical conditioning.

- Procedural: striatum, motor and premotor cortex and cerebellum.
HM patient still able to ride a bike.
- Priming: neocortex
tendency to process some perception in the same way. When you see a complex picture for the first time you need a longer time to identify things then in a second/third time.
- classical conditioning: amygdala and cerebellum

Role of hippocampus in episodic memory

Hippocampus is specialized in associate memory. This association can be spatial, semantic, temporal or sensory.

anterior part: semantic and temporal association

posterior part: sensory and spatial Hippocampus is necessary for uncounscious relational encoding and retrieval. It is highly active during deep sleep. Specific patterns of activity observed in the hippocampus while rats were awake were observed to “replay” during both REM sleep and slow wave sleep.

Knowing the precise function of a brain structure allows for a precise diagnosis of brain function.

New memory model - Katharina (2010)

This model divides memory based on processing modes, not consciousness. Three characteristics: number of learning trials, associations and flexibility. Figure 13 shows the new memory division.

- Encoding (number of learning trials): rapid (1 trial) or slow (many trials)
- Association & flexibility: flexible associations, rigid associations, or no associations (unique item)

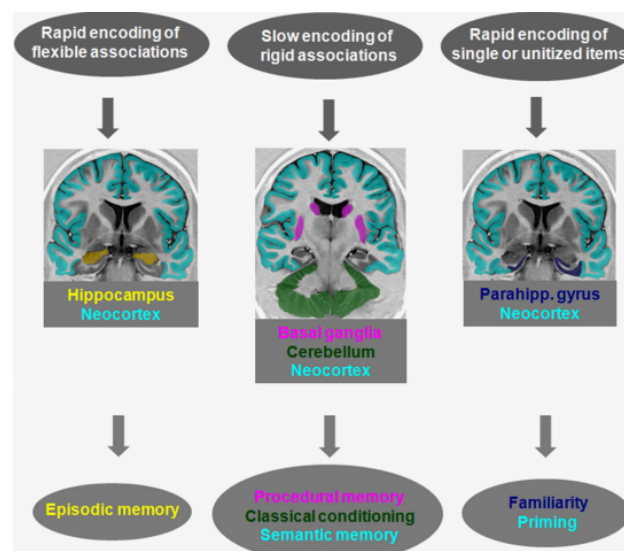


Figure 13: Memory model based on processing modes

1.6 Body Perception - 27.03.2017

Phantomology

Phantomology (is the name of the second chapter of Summa Technologiae - 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.

Nearly all patients have an illusion that the missing limb is still present, following the amputation. Phantom sensations are not limited to amputated limbs. Many types of phantom sensations are reported, such as:

- phantom body parts: the feeling of the body part after the removal of the body part (not necessarily a limb).
- 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).

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?

Phantom pain

Phantoms might simply be a curiosity, or a provocative clue about higherorder somatic sensory processing, were it not for the fact that a substantial number of amputees also develop phantom pain. Phantom pain is, in fact, one of the more common causes of chronic pain syndromes and is extraordinarily difficult to treat. Because of the widespread nature of central pain processing,

ablation of the spinothalamic tract, portions of the thalamus, or even primary sensory cortex does not generally relieve the discomfort felt by these patients.

Phantomology

There are two types of phantom body parts: after amputation and in congenital limb deficiency. Phantom limb can be felt even in congenital limb deficiencies. 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 "awkward". Natural phantom limbs obey the "lawfulness of limbs", but amputees can learn to "execute" impossible limb movements.

fMRI of phantom hand movements Task: rhythmic opening/closing of the right phantom hand. Showed bilateral activation in premotor and parietal cortices, but no M1 and S1 activations. **Phantom moving is like imagine moving a limb - bilateral activation on brain.**

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

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% believe 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 disappear the phantom limb pain can still hold** In some cases, the confrontation 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 lost 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 prosthesis 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 prosthesis.

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

It 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.

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.

Strong desire for amputation, it happens almost exclusively in men, well-educated, elevated incidence of non-heterosexuality and non-righthandedness. Xenomelia is accompanied by reduced response to tactile stimulation below the desired amputation line, also, is accompanied by reduced thickness and volume in Superior Parietal Lobe (SPL) and smaller area in Inferior Parietal Lobe, primary somatosensory (S1) and secondary somatosensory (S2). Xenomelia: cause or consequence?

Hemiphanton

Patients with a sensorimotor hemisindrome often do not perceive/acknowledge the disorder called **anosognosia**. They often deny ownership over paralyzed side, they speak of other person: **somatoparaphrenia**. This other person frequently behaves in a hostile way, is disliked by the patient and aggressively treated: **misoplegia**.

Whole-body phantom or phantom double or doppelgänger

The phantom double or doppelgänger is purely somaesthetic illusion (it is felt but not seen). Patients usually point a very precise localization in space, in a neurological context it is almost

exclusively after **parietal lobe lesions**. Indirect evidence that “felt presence” is another self: vague sense of familiarity, shared feelings, imitation of body movements.

Autoscopic phenomena It is defined as a visual experience where the subject sees an image of him/herself in external space, viewed from within his/her own physical body. Autoscopic phenomena consist of out-of-body experience (OBE), autoscopic hallucination (AH), and heautoscopy (HAS). Figure 14 shows graphically the difference between the three types.

- OBE: During an OBE, people seem to be awake and feel that their “self”, or center of awareness, is located outside of the physical body and somewhat elevated. It is from this elevated extrapersonal location that the subjects experience seeing their body and the world.
- AH: During an AH, people experience seeing a double of themselves in extrapersonal space without the experience of leaving one’s body.
- HAS: The individual experiencing an HAS also has the experience of seeing a double of himself in extrapersonal space. However, it is difficult for the subject to decide whether he/she is disembodied or not and whether the self is localized within the physical body or in the autoscopic body (usually lesions on left posterior insula).

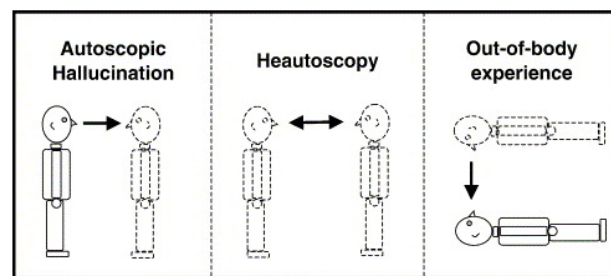


Figure 14: Types of autoscopic phenomena. Figure from [2].

Whole-body phantom experiments

To induce the whole-body phantoms one can use the following experiments:

- out-of-hand experience: mirror box after Ramachandran enables movement in a paralyzed phantom hand by visual observation of the reflection of the still existing hand.
- out-of-body experience: feeling of being “out of body” induced by observing own body in front of oneself. Also, touch observed on other body simultaneously to touch felt on own body induces feeling of being at the place of seen touch.

phantom limbs can reflect perceptuo-motor memories, innate or empathically acquired programs and phantom sensations can be induced by intersensory conflicts.

todo

Finger and thustwitt, 2003, Neurosurgery 52.

2 Clinical Neuroscience

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

Neuro ophtamology

Clinical eye testing

- movements
- smooth pursuit
- saccadic eye movement - fast eye movement
 - disorders: velocity, metrics (can “pass” the point), latency
- nystagmus
 - primary gaze: indicative of cerebellum loss → gaze holding and rebound
 - vestibulo ocular 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 → eye stays in position; positive: → 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 ocular deviation

dynamic visual acuity

sensorymotor balance:

romberg test: close eyes and balance is lost.

caloric testing

bimalleolar vibration sense

Epilepsy

What is epilepsy?

It is a brain disorder, a chronic condition.

What is a seizure?

It is a temporary disruption of normal brain function.

- eye movement, 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 provoked.

Classification of seizures:

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

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. A disease can be defined as a health condition that has a clearly defined reason behind it. A syndrome (from the Greek word *súndromos* meaning “run together”) however, may produce a number of symptoms without an identifiable cause.

Variety of symptoms

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

- slow movements (bradykinesia)
- tremor at rest
- stiffness (rigidity of the extremities and neck)
- postural instability

Parkinson's disease

The common reason for Parkinson's syndrome. It is the second most common degenerative disorder of the nervous system (Alzheimer's disease is the leader).

The defects in motor function are due to the progressive loss of dopaminergic neurons in the substantia nigra pars compacta, a population that projects to and innervates neurons in the caudate and putamen. The cause of the progressive deterioration of these dopaminergic neurons is not known, but genetic investigations are providing clues to the etiology and pathogenesis. Whereas the majority of cases of Parkinson's disease are sporadic, there may be specific forms of susceptibility genes that confer increased risk of acquiring the disease. Two genes are best studied linked with Parkinson: *α-synuclein* and *parkin*.

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

Dopamine is like insuline for diabetes, however it is a symptomatic-therapy not a cause-therapy and manage the quantity of dopamine is not an easy task. In Parkinson the spatial distribution

of the degenerating neurons is largely restricted to the substantia nigra pars compacta, this way, one therapy for Parkinson's disease would be to enhance release of dopamine in the caudate and putamen.

In contrast to most other neurodegenerative disorders, there is effective temporary symptomatic treatment for PD consisting of DA replacement with levodopa or DA agonists and adjunctive medications or surgical approaches. To achieve a true cure, the underlying mechanisms of neuronal cell death need to be understood, strategies for enhancing neuronal survival and regrowth need to be developed, and consideration needs to be made toward the replacement of cells lost during the degenerative process. If these goals can be obtained, a full recovery could be achieved.

2.2 Multiple Sclerosis, Neuromuscular, Stroke and Neuropsychology

- 10.04.2017

Multiple Sclerosis

Multiple sclerosis (MS) is a disease of the central nervous system characterized by a variety of clinical problems arising from multiple regions of demyelination and inflammation along axonal pathways, **demyelination is necessary to diagnose MS: you need MRI information and additional signs**. MS as a demyelinating disease is deeply accepted in the clinical literature, although precisely how the demyelination translates into functional deficits is poorly understood.

A possible explanation of the human disease is that a genetically susceptible individual becomes transiently infected (by a minor viral illness, for example) with a microorganism that expresses a molecule structurally similar to a component of myelin. An immune response to this antigen is mounted to attack the invader, but the failure of the immune system to discriminate between the foreign protein and itself results in destruction of otherwise normal myelin.

MS commonly manifests between ages 20 and 40. It is the most frequent CNS disease among young adults. The signs and symptoms of MS are determined by the location of the affected regions.

Abnormalities are often apparent in the cerebrospinal fluid, which usually contains an abnormal number of cells associated with inflammation and an increased content of antibodies (a sign of an altered immune response).

The diagnosis of MS generally relies on the presence of a neurological problem that remits and then returns at an unrelated site, **MS is characterized by relapses manifestation: the neurological problem comes and goes**.

- destructive disease
- inflammation and shrink (loss of myelin and axons) on brain
- environmental effects: more common above equator line
- diagnostic depend of space and time
 - space: not only one area of CNS lesion
 - time: because it comes and goes
- PPMS: primary progressive multiple sclerosis: CSF
 - punctuations of CSF: if you find antibodies in the CSF and serum it is a general inflammation, if you find only in the CSF is MS.
- scale 0 to 10; 10 means death
- MS became a treatable disease in 90's

Neuromuscular disorders

- diagnosis: medical history, neurological examination, lab tests
- myotonic reaction: is a symptom of a small handful of certain neuromuscular disorders characterized by delayed relaxation (prolonged contraction) of the skeletal muscles after voluntary contraction or electrical stimulation.

Stroke

Any acute neurological symptom is a stroke unless proven otherwise. However, stroke is not a seizure, and also is not a migraine.

Types of stroke

There are two types: ischemic and hemorrhagic.

- ischemic: (80% of the cases) → block of a vessel - recanalization
- hemorrhagic: (20% of the cases) blood pressure control / hematoma evacuation, reduction of intracranial pressure - catheter

cells in penumbra are potentially salvable

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

prognosis

death or be in a dependent state (approx. 90% hemorrhagic and approx. 40% of ischemia)

Neuropsychological disorders

- aphasia (language disorders)
 - broca → patient does not speak but understands
 - wernicke → spontaneous speech is fluent but it is impossible to repeat phrases.
 - apraxia → patients speak in a monotone, no matter the circumstances or meaning of what is said.
- alexia → can write but cannot read
- apraxia → can use tools but cannot imitate their uses

- anosognosia → no notion of its own deficiency

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

25.04.2017

Spinal cord injury (SCI) can be divided into traumatic and non-traumatic aetiologies.

Traumatic SCI

Occurs when an external physical impact acutely damages the spinal cord. The primary injury damage cells and initiates a complex secondary injury cascade, which produces the death of neurons and glial cells, ischemia and inflammation.

Non-traumatic SCI

Occurs when an acute or chronic disease process, such as a tumor, infection or degenerative disc disease, generates the primary injury.

Regardless of the cause, **SCI can lead to permanent and severe neurological deficits**. SCI have devastating physical, social and vocational consequences for patients and their families. Prevention is the most important intervention today. For SCI that cannot be prevented, the development of effective treatments become crucially important.

The incidence of SCI varies worldwide. The incidence of traumatic SCI is higher in North America, than Australia or Western Europe. The incidence of non-traumatic SCI is also higher in Canada than in Australia, for instance. Traumatic SCI occurs more commonly in males ($\approx 80\%$) than in females ($\approx 20\%$). The age profile of individuals with traumatic SCI has a bimodal distribution, with one peak between 15 and 29 years of age and the second, smaller but growing, above 50 years.

Diagnosis

Fractures on the spinal column are often described by their vertebral level, but the neurological injury is described by the spinal cord level at which the nerve roots emerge. Different levels of the spinal cord innervate distinct muscle groups; in general, SCI results in the partial or complete loss of function below the level of injury. SCIs generally result in loss of sensorimotor function, but can also affect the sympathetic nervous system.

Sympathetic Nervous System

Sympathetic Nervous System (SNS) is responsible for up- and down-regulating in many homeostatic mechanisms in living organisms. Fibers from the SNS innervate tissues in almost every

organ system, providing at least some regulatory function to things as diverse as pupil diameter, gut motility, and urinary system. It is perhaps best known for mediating the neuronal and hormonal stress response commonly known as the fight-or-flight response. This response is also known as sympatho-adrenal response of the body, as the preganglionic sympathetic fibers that end in the adrenal medulla (but also all other sympathetic fibers) secrete acetylcholine, which activates the great secretion of adrenaline (epinephrine) and to a lesser extent noradrenaline (norepinephrine) from it. Therefore, this response that acts primarily on the cardiovascular system is mediated directly via impulses transmitted through the SNS and indirectly via catecholamines secreted from the adrenal medulla.

High thoracic or cervical injuries can lead to severe hypotension and bradycardia. The loss of innervation to secondary lymphatic organs can induce secondary immunodeficiency.

Spinal Shock

It is a temporary clinical state of flaccid paralysis post-SCI, including loss of motor, sensory, autonomic and reflex function at or below the level of injury. Spinal shock can affect the accuracy of the initial neurological examination (used to define the severity of the SCI).

Neurogenic Shock

It is typified by hypotension, bradycardia, wide pulse pressure and warm pink extremities. It is most clinically relevant with a neurological level of injury above T6.

After any traumatic injury, the advanced trauma life support protocols dictate initial care, which includes airway, breathing and circulation support (along with immobilization of the spinal cord using a rigid cervical collar and backboard).

Patients with suspected traumatic SCI undergo neurological examination (which includes a voluntary motor and sensory examination of each limb and a rectal examination) to assess for neurological dysfunction and radiographic imaging to look for damage to the vertebrae and/or spinal cord. Plain X-ray, CT and MRI are the most commonly used radiological tools. X-ray and CT are useful to detect gross fracture dislocation injuries, MRI is well suited for evaluate the integrity of soft tissue, such as intervertebral discs, ligaments and the spinal cord and nerve roots. Also, MRI can evaluate for the presence of oedema and/or haemorrhage.

If the SCI is detected, the grade of the injury is classified according to the American Spinal Injury Association (ASIA) Impairment Scale, which ranges from A (most severe) to E (least severe).

SCI Syndromes

Central cord syndrome is the most common incomplete SCI syndrome (15% to 25% of SCIs). Most commonly diagnosed in elderly patients with pre-existing cervical spondylosis who after a

fall results in cervical hyperextension. Central cord syndrome is characterized by disproportionate motor impairment of the upper limbs, rather than the lower limbs.

Brown-Sequard syndrome is most commonly observed in individuals with penetrating traumatic SCI (as gunshots or knife wounds). It is characterized by loss of motor function, light touch, proprioception and vibration sensation ipsilateral to the injury and loss of pain and temperature sensation contralateral to the injury.

Prognosis

Neurological recovery in patients with SCI is typically observed within the first six months after injury (continuous improvements can be seen up to five years later). In general, thoracic injuries are associated with reduced potential for motor recovery compared with injuries in the cervical or lumbar spinal cord. Patients with ASIA Impairment Scale grade A, are generally predict to have less than 5% chance of walking 1 year after the injury. There are some tools that predict neurological recovery and long-term walking potential considering for instance age, neurological examination and MRI feature.

Pathophysiology

The initial trauma (first injury) causes displacement or dislocation of the vertebral column, which causes compression or transection of the spinal cord. This causes a focal region of cell death and blood-spinal cord barrier disfunction (it initiates a cascade of secondary injury mechanisms). Secondary injury mechanisms includes vascular changes, inflammation, loss of ionic homeostasis and oxidative stress (increasing the damage to the spinal cord). Cell death contributes to the formation of cystic cavities, which are surrounded by a glial scar (a deposition of astrocytes and molecules that inhibit neuronal regeneration), which interfere with neuronal regeneration and functional recovery.

Traumatic SCI is pathophysiologically divided into primary and secondary injuries. And can also be temporally divided into the acute (< 48 hours), subacute (48 hours to 14 days), intermediate (14 days to 6 months) and chronic (> 6 months). The pathophysiology of the traumatic spinal cord is shown in Figure 15.

The first injury damage neurons and oligodendrocytes (myelinating cell type of the CNS), disrupts the vasculature and compromises the blood-spinal cord barrier. Together, these events immediately initiate a secondary injury cascade.

Acute phase

Secondary cellular changes in the acute phase are caused by cell permeabilization, pro-apoptotic signalling and ischaemic injury due to the destruction of the microvascular supply of the spinal cord within minutes of injury. In addition, blood vessel injury can cause severe haemorrhages, which can expose the cord to an influx of inflammatory cells, cytokines and vasoactive peptides.

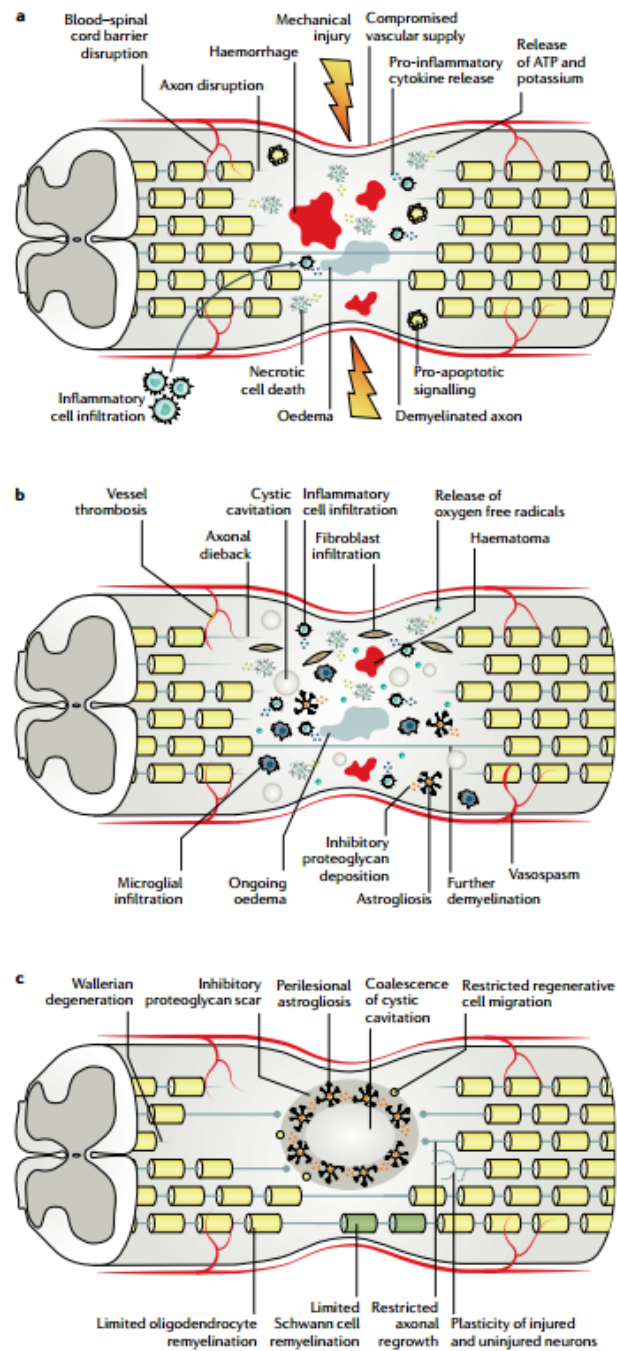


Figure 15: Pathophysiology of the traumatic spinal cord

The inflammatory response in the acute and subacute phases, combined with the disrupted blood-spinal cord barrier, progressively add to spinal cord swelling, leading to further mechanical compression of the cord, which can extend for multiple spinal segments and worsen the injury.

Subacute phase

In this period, ischaemia and excitotoxicity contribute to a loss of intracellular and extracellular ionic homeostasis. Ongoing necrosis of neurons and glia due to ischaemia, inflammation and excitotoxicity releases ATP, DNA and potassium, which can activate microglial cells. Activated microglia infiltrate the injury site, where they propagate the inflammatory response and contribute to ongoing apoptosis of neurons and oligodendrocytes. Phagocytic inflammatory cells can clear myelin debris at injury site but can also induce further damage to the spinal cord. High levels of the neurotransmitter glutamate are released from dying neurons and astrocytes and are poorly reabsorbed by surviving astrocytes. This causes a receptor overactivation, which combined with the loss of ATP-dependent ion pump functions and subsequent resultant sodium dysregulation, can lead to excitotoxic cell death.

The multiple causes of cell death that occur during the acute and subacute phases of SCI can produce greater damage than the original primary injury and form the basis for the neuroprotective interventions.

Intermediate-chronic phase

The spinal cord lesion evolves to intermediate through to chronic phases that are marked by attempts at remyelination, vascular reorganization, alterations in the composition of the extracellular matrix (ECM) and remodelling of neural circuits.

In humans, cell death in acute phase promotes **cystic cavities**, which contain extracellular fluid. These cavities become a formidable barrier to directed axonal regrowth and are a poor substrate for cell migration. In the acute phase, signalling from activated microglia, astrocytes and macrophages causes the secretion of proteins that are inhibitory to axonal growth, which condense with astrocytes to form the **glial scar**, that potentially restricts axon regeneration. But also, the glial scar isolates the injury site to reduce the spread of cytotoxic molecules and inflammatory cells.

Even if regenerative efforts are able to overcome spinal cord lesions, properties of the adult mammalian CNS can still limit neurite regrowth. Molecules present in myelin are potent inhibitors of axon regeneration, and several molecules released by degenerating oligodendrocytes can contribute to failure of regeneration. Although severe SCI can destroy substantial portions of the spinal cord white matter, a surviving subpial rim of demyelinated axons can persist in rodent models of injury. Endogenous mechanisms exist for at least partial regeneration of the injured spinal cord. CNS neurons exhibit both anatomical and synaptic plasticity, which might contribute to ongoing functional recovery for years after injury. These and other mechanisms can be supple-

mented by the neuroprotective and neuroregenerative strategies but barriers to regeneration still exist, meaning additional therapies to remove or overcome these barriers are necessary.

Animal models

Animals models have contributed to our understanding of the pathophysiology of SCI and have been useful for the preclinical testing of new therapies. The ideal animal model should anatomically and pathophysiologically resemble humans SCI, require minimal training, be inexpensive and produce consistent results. Rat models are the most commonly used for SCI research, however, differences in size, molecular signalling, anatomy and the recovery potential following SCI have made direct translation challenging. Large animal models, such as non-human primates, overcome some of these barriers, but substantial differences in cost and unique housing requirements make their use less common and even they are unable to exactly mimic human SCI.

Management of patients with SCI

Functional neural tissue is progressively lost during the hours after SCI, making it crucially important to rapidly diagnose patients and implement neuroprotective interventions during the acute phase.

The management of patients includes monitoring of haemodynamics and decompressive surgery to limit the damage to the spinal cord. In addition, patients can receive a neuroprotective agent (its use is controversial). Long term management includes monitoring and treating systemic complications of injury as autonomic dysreflexia, neuropathic pain, pressure sores, respiratory complications, gastrointestinal and urinary disturbance, etc.

Decompressive Surgery

Surgical intervention is an essential basis of the acute treatment for patients with spinal trauma and acute SCI. Surgery typically involves open reduction and decompression paired with an instrumented fusion to stabilize the spinal column in an anatomical position. Decompressing the spinal cord early after SCI should help to limit the zone of injury and improve clinical outcomes (some studies shown better prognosis when the decompression is done within 24 hours than after 24 hours).

Complications

Can be **local** or **systemic**.

Locals:

Neuropathic arthropathy

Slow progressive destruction of a joint. Can lead to deformity, overlying skin ulceration and potentially fatal infections. The loss of sensation that is common after SCI allows repeated microtraumas to go unnoticed, which promotes bone resorption.

Spasticity

Is the velocity-dependent increase in muscle tone with exaggerated deep tendon reflexes that results from injury to upper motor neurons. Can substantially affect mobilization, activities of daily living and sleep. Treatment may include physical therapy, systemic pharmacological treatments, local botulinum toxin injections or surgery.

Systemics:

Cardiovascular

Compromise of sympathetic flow can lead to hypotension. As a result, 60% of the patients experience symptomatic hypotension (dizziness, weakness and syncope). Treatment includes the use of lower extremity compression stockings, medical management (such as the use of hydration, salt tablets etc) and/or peripheral vasoconstriction.

Disreflexia

It is an urgent condition that most commonly occurs in patients with injuries at or above T6. It is caused by the presence of a noxious stimulus, which causes a reflex overstimulation of spinal sympathetic neurons, leading to vaso constriction and dangerous acute hypertension. Increase on the blood pressure can lead to heart attack. Treatment requires upright positioning of the patient, removal of the triggering stimulus and pharmacological anti-hypertensives.

Respiratory

Paralysis of the phrenic nerve, intercostal muscles and/or abdominal muscles leads to reduced lung capacity, ineffective cough and accelerated fatigue with respiratory demands. As a consequence, recurrent pneumonia and pleural effusion happens. Respiratory complications are the leading cause of mortality in patients with chronic SCI. In individuals with high cervical injuries, or those with poor respiratory reserve, lifeloong ventilator dependency can be used.

Secondary immunodeficiency

The disruption of CNS input to immune organs can result in the systemic dysfunction of macrophages and natural killer cells in a process known as immune paralysis. This increase susceptibility to infections (pneumonia, urinary tract or wound infections).

Genitourinary and gastrointestinal

Dysfunction of the genitourinary and gastrointestinal system increases care requirements, the risk of infection and can be a source of substantial social and psychological stress in patients. Injuries at or above L1-L2 interrupt innervation of the detrusor, or the bladder muscle, and urinary sphincters, which can cause an inability to empty the bladder, acontractile bladder, urinary incontinence and recurrent infections. Management includes urethral catheterization every few hours, surgical creation of a urinary stoma, injections of botulinum toxin and pharmacological therapies. The neurological level of injury can also affect sexual function, injuries above T11 can affect psychological erection or vaginal lubrication and ability to orgasm, even with preservation of the reflexive erection/vaginal lubrication. SCI can interrupt the voluntary control of the anal sphincter and or the parasympathetic innervation of the bowel. Both cases lead to constipation, an increased risk of infection and stress. Treatments range from dietary fibre intake, digital rectal stimulation and the use of suppositories.

Pressure sores

It cause pain, increased care requirements and can be life-threatening if not promptly treated. Prevention of pressure sores requires daily inspection and cleaning of the skin, but also a relief of the pressure on each region every few hours.

Neurogenic heterotopic ossification

It is a process that form ectopic bone in the connective tissue around joints. This ossification occurs most commonly on large joints and presets with localized pain, redness, low-grade fever and increased spasticity.

Neuropathic pain

It is experienced by up to 40% of patients with chronic SCI and can have a substantial effect on the psychological well-being and quality of life of patients. Neuropathic pain can be treated pharmacologically (antidepressants, anticonvulsants and/or opioids), surgically (implanted spinal cord stimulator) or through non-allopathic treatments (acupuncture, massage etc).

2.4 Epilepsy - 02.05.2017

Epilepsy is one of the most common neurological disorders affecting about 8 in 1000 inhabitants (prevalence of epilepsy: approxi. 0.8%). It is characterized by recurrent **seizures**.

In some patients epilepsy seizures may not be the only symptoms. Especially syndromes like temporal lobe epilepsy can also have **psychiatric aspects**, i.e, mood disorders and anxiety disorders can often be associated with epilepsies while ictal (during the seizure) or interictal (between the seizures) psychotic disorders are less frequent.

Typical ictal (during the seizure) symptoms are alterations of consciousness, motor, sensory and psychic events. After the seizure (postictal) there is a complete recovery or transient functional deficit as Todd's paralysis, aphasia, depression, fatigue etc. Between seizures (interictal) there are few symptoms (if any) as depression, cognitive deficits, etc.

It seems likely that abnormal activity generates plastic changes in cortical circuitry that are critical to the pathogenesis of the epilepsy. The importance of neuronal plasticity in epilepsy is indicated most clearly by an animal model of seizure production called kindling. To induce a kindling, a stimulating electrode is implanted in the brain, often in the amygdala. At the beginning of the experiment, weak electrical stimulation, in the form of a low-amplitude train of electrical pulses, has no discernible effect on the animal's behavior or on the pattern of electrical activity in the brain. As this weak stimulation is repeated once a day for several weeks, it begins to produce behavioral and electrical indications of seizures. By the end of the experiment, the same weak stimulus that initially had no effect now causes full-blown seizures. This phenomenon is essentially permanent; even after an interval of a year, the same weak stimulus will again trigger a seizure.

The behavioral manifestations of epileptic seizures in human patients range from mild twitching of an extremity to loss of consciousness and uncontrollable convulsions.

Modern thinking about the causes (and possible cures) of epilepsy has focused on where seizures originate and the mechanisms that make the affected region hyperexcitable.

Prejudices

The most common prejudices are: epilepsy is contagious, is a mental disease, patients with epilepsy are mentally retarded and every seizure is life-threatening.

Many names in history had epilepsy such as Alexander, the Great, Julius Cesar, Dante Alighieri, Alfred Nobel and many others.

Epidemiology

5 to 10% of the population have seizures and approximately 0.6 to 1% of the population have epilepsy. The first manifestation occurs equally in the childhood/adolescence, in adulthood or at an older age. The mortality rate between epilepsy patients is almost three times as high as healthy individuals in Switzerland. In Switzerland, the mortality rate is 7.8/1000 individuals per year, while for epilepsy patients is 23/1000 per year.

Epilepsy

Strictly speaking, epilepsy is not a single disease but a disorder that can have many different causes. **Epilepsy is a chronic disease defined by recurring and unprovoked seizures.** So there are many types of epilepsies that can be classified e.g. according to their different etiologies (origins). Using this criterion we can distinguish between two main classes of epilepsies: **idiopathic** and **symptomatic**.

Idiopathic epilepsies

Idiopathic epilepsies are genetically determined and cannot be treated surgically. However, most patients with such syndromes respond very well to medical treatment. Although we know, that idiopathic epilepsies usually run in families, the **genetics of epilepsies** has only begun to be explored: while some special syndromes have been identified (e.g. “autosomal dominant nocturnal frontal lobe epilepsy” with mutations on chromosomes 1, 15, and 20) the genetic mechanisms of idiopathic epilepsies are still unclear.

Symptomatic epilepsies

Symptomatic epilepsies are caused by identifiable alteration of brain tissue (tumors, scar, inflammation etc). For patients with symptomatic epilepsies who do not respond well to antiepileptic drugs the surgical treatment can be investigated as a possible treatment.

Seizure

Seizure are caused by transient functional disturbances of cerebral neurons leading to excessive and/or synchronous discharges.

There are many different types of seizures whose symptoms depend on the specific brain regions involved. Note that **seizures are not always a sign of epilepsy**, they can sometimes also be provoked by high fever, substance abuse, sleep deprivation or metabolic disorders like diabetes in persons who do not suffer from epilepsy.

Among epileptic seizures we can again distinguish between two main classes: **generalized** and **focal**.

Generalized seizures

Show signs of involvement of both cerebral hemispheres from beginning onward and are usually associated with loss of consciousness.

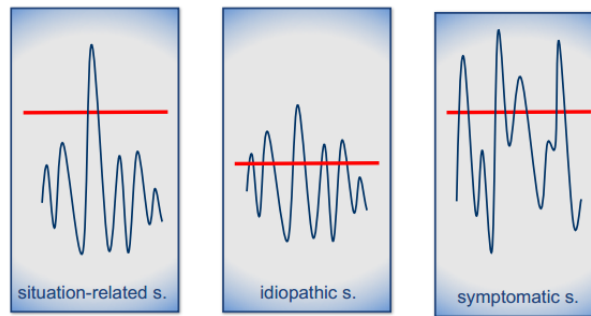


Figure 16: Seizure threshold for different types of seizures

Focal (or partial) seizures

Show signs of involvement of only one specific brain region – at least initially. These seizures may or may not be associated with impaired consciousness.

The seizure threshold for each seizure type is shown in Figure 16.

First aid

It is necessary do not panic if one sees a person during a seizure. Watch the person and consult a watch, usually seizures don't last longer than 2-3 minutes. If necessary rescue the person out of danger zone and protect his/her head. Do not restrain the person and do not put anything in the person's mouth. Observe the person after the seizure, if necessary position he/she in the lateral recumbent position. If the seizures continues for longer than 5 minutes, call emergency physician.

Diagnosis

The diagnostic work-up tries first to establish whether a patient really suffers from epilepsy. If he or she does, we try to define the specific epilepsy syndrome: the symptoms and findings that comprise a particular type of epilepsy defined by its etiology, occurring types of seizures, course and prognosis etc.

Since the specific symptoms of seizures depend on the functions of the brain regions involved in the epileptic brain activity, the **semiology of focal seizures**, i. e. the signs and symptoms of a seizure and their temporal sequence can be analyzed with the aim of localizing the seizure origin in the brain. Other examinations usually performed during the diagnostic work-up include checking the patient history, blood and CSF tests, **magnetic resonance imaging (MRI)** of the brain in search of morphological correlates of the epileptogenic focus and, especially **electroencephalography**, recordings of brain electrical activity in search of epileptiform potentials like spikes or sharp waves. These examinations are also performed to exclude non-epileptic attacks indicative of differential

diagnoses like syncope, movement disorders, non-epileptic psychogenic seizures etc., which should not be confused with epilepsy.

Treatment

Epileptic seizures are symptoms of epilepsies, and medical treatment aims at preventing seizures. Thus, antiepileptic drugs can make a patient seizure-free but they cannot treat the underlying cause of the epilepsy.

Seizure freedom can be accomplished medically in about 60% to 70% of all epilepsy patients. In those patients, in whom seizures recur in spite of adequate medical treatment, it is sometimes possible to offer epilepsy surgery, which can be very successful in certain epilepsy syndromes like e.g. medial temporal lobe epilepsy.

Presurgical evaluation relies not only on imaging and EEG-studies including seizure recordings but also on neuropsychological examinations, which can demonstrate specific cognitive deficits like, for example, memory deficits induced by epileptogenic activity and/or lesions in specific brain areas. Therefore, **neuropsychology in epileptology** can help to localize the epileptogenic focus, to predict potential risks of epilepsy surgery and to identify possible cognitive side effects of antiepileptic drugs.

Palliative epilepsy surgery

Aims at reducing the frequency and/or the severity of seizures not controlled by other means.

Curative epilepsy surgery

Aims at removing the epileptogenic zone to establish seizure-freedom without causing any additional neurological or neuropsychological deficits. Before it is possible to decide for or against surgical treatment, the chances and risks of the operation must be evaluated presurgically. In some patients this also necessitates the implantation of intracranial electrodes to record seizures directly from within the brain. In addition, intracranial electrodes can be used for functional electrostimulation mapping of motor, sensory and cognitive functions to increase the safety of cortical resections. Thus, in the presurgical evaluation of pharmacoresistant focal epilepsies the frontiers between neurophysiology and neuropsychology become blurred. This becomes especially clear in mesial temporal and mesial frontal epilepsies, which show that **limbic seizures and functions** tap aspects of declarative memory and emotional processing. In the **temporal lobe epilepsy** the declarative (conscious) memory is impaired while the procedural (unconscious) memory is intact.

2.5 Depression

Feeling sad and blue are common and universal moods experienced in response to transient loss, stress, or disappointment. The clinical diagnosis of major depressive disorder (MDD) involves a persistent symptom complex that includes some combination of depressed mood, diminished interest or pleasure, changes in sleep and appetite, excessive guilt, agitation or retardation, loss of energy, diminished ability to think or concentrate, thoughts of death, and thoughts of suicide. The community lifetime prevalence is approximately 12 to 15%, with the lowest rates in Asian countries and the highest in the Americas, Europe, and Australia.

The rates of MDD are two- to threefold higher in women than men.

Different subtypes of major depression have been identified, including depression with psychotic features and a typical depression. Depression is an extremely disabling disorder. About 75% of patients have recurrent episodes. Ten to 30% recover incompletely, with persistent residual symptoms. MDD also complicates the course of cardiovascular illness, diabetes, hypertension, and other chronic medical conditions. Suicide, accidents, and the risk of death from heart disease are highest among the depressed.

Three common questionnaires for depression:

- Beck depression inventory
- Hamd questionnaire
- one more ??

Self, future, not be able to feel joy.

Health people have positive bias. Realistic people are subdepressed.

2.6 Schizophrenia - 08.05.2017

Schizophrenia is a catastrophic illness with an onset typically in adolescence or early adulthood. It was identified and defined by Eugen Bleuler (Swiss psychiatrist) in 1911. The combination of significant incapacity, onset early in life, and chronicity of illness makes schizophrenia a particularly tragic disorder, occurring in 0.5 to 1% of the population.

A substantial body of evidence indicates that schizophrenia is associated with both **genetic and environmental factors**. Currently, it remains an open question whether these environmental factors play a necessary role in the neurodevelopmental abnormalities responsible for psychotic brain disorders or whether their role is additive or interactive with genetic contributions.

People with schizophrenia are more likely than others to have schizophrenic relatives. The most compelling evidence is the 50% concordance rate for monozygotic twins relative to 15% concordance for dizygotic twins.

Some risk factors:

- heritability (DISC1/2, COMT)
 - Disc - hippocampus alteration
 - Comt - dopamine dysregulation
- Lower social status
- Paternal age (father)
- pregnancy/birth complications and postnatal infections

Characteristics and Symptoms

The clinical symptoms are divided into two categories: **positive** and **negative**. The positive symptoms represent distortions or exaggerations of normal cognitive or emotional functions. The negative symptoms reflect a loss or diminution of normal function.

Some of the positive symptoms are:

- delusions (false beliefs that don't go away even with evidence that they aren't true)
- hallucinations (hearing or seeing things that are not real)
- incoherence
- disorganized speech
- disorganized or bizarre behavior
- psychomotor disturbance

Negative symptoms:

- attention deficits (attentional impairment)
- lack of willpower/initiative
- apathy
- social withdrawal
- alogia: poverty of speech or speech devoid of coherent content
- affective flattening: diminution in the ability to express emotions
- anhedonia: inability to experience pleasure
- avolition: inability to initiate or persist in goal-directed behavior

The profound and pervasive cognitive and emotional disturbances that characterize schizophrenia suggest that it is a serious brain disease affecting multiple functions and systems (for instance, auditory hallucinations and disruptions in linguistic expression suggest involvement of the auditory cortex and perisylvian language regions). Other symptoms, such as delusions or disorganized behavior, are more difficult to localize to specific regions and suggest dysfunction distributed across multiple neural systems and circuits. Negative symptoms may be related to the prefrontal cortex, which mediates goal-directed behavior and fluency of thought and speech.

* Usually related with religion

* Mixing topics - interpolation - can not keep one subject (usually people say thought is getting louder)

Neuropathological alterations

The most consistently described structural alterations in schizophrenia are ventricular enlargement and decreases in the volume of temporal lobe structures, including the hippocampus, amygdala, and entorhinal cortex. Some structural differences were found in the brain:

- less activity in Prefrontal cortex: helps people think logically and organize their thoughts.
- activity on visual and auditory cortices: the pattern of an hallucination is equivalent to when people are really seeing or hearing. For the schizophrenic there is almost no way to distinguish them.
- large basal ganglia: might affect movement patterns.
- small amygdala: responsible for basic feelings (like fear, lust and hunger). Schizophrenics usually have few emotion.

Also, there are some neurotransmitters differences like:

- dopamine: among other things, it is responsible for feeling pleasure. Links the basal ganglia with the prefrontal cortex. In some parts of the brain the level of dopamine is low (might affect the pleasure state) and in other parts are high (maybe responsible for hallucinations).

Diagnosis

Difference between American system and European: symptoms for one month or two months respectively. It must be clear that any of these symptoms are not due to depression or to neuroleptic medication.

One of the symptoms for at least one month:

- thought echo
- delusions of control, influence (body or limb movements)
- hallucinatory voices giving a running commentary on the patient's behavior
- persistent delusions of other kinds that are culturally inappropriate (or impossible: e.g. be able to control weather, communication with aliens from another world, etc.)

Two of the symptoms for at least one month:

- persistent hallucinations
- breaks or interpolations in the train of thought (resulting in incoherence, irrelevant speech or neologisms)
- catatonic behavior
- "negative" symptoms

Therapy

The therapy of psychotic disorders is based on medication, psychotherapy, rehabilitation.

Medication

Antipsychotic drugs are used but they must be with low dosage start (to reduce side effects), use of tranquilizer (benzodiazepines) during the acute phase. The treatment in adequate dosage until remission, sometimes, there is a treatment resistance (need to change to another antipsychotic drug). In the long term treatment side effects are crucial, as the psycho-social reintegration (rehabilitation), for this, family therapy has an important role.

Psychoterapy

The goals of psychoterapy are separated in categories like: diagnostics (“what is happening to me?”), symptom reduction (“the voices should disappear”), well-being (“I want to feel better”), optimism (“my future is important, I want to live a normal life”), work (“I want to complete my training”) and becoming an adult (“I want to be independent of my parents”).

10% of patients suicide in the first year of schizophrenia - need to take care of medications.

In Switzerland (and some other countries) you can't medicate (treat) patients against their will.

Dopamine in Schizophrenia

Schizophrenia is associated with abnormalities in the dopaminergic synapses of the brain. The strongest link between dopamine synapses and schizophrenia comes from studies of drugs that alleviate the symptoms of schizophrenia. A large number of antischizophrenic (or neuroleptic) drugs have been found, most of them belong to two chemical families: phenothiazines (including chlorpromazine) and butyrophenones (including haloperidol). These drugs have two properties in common: they block postsynaptic dopamine receptors and they inhibit the release of dopamine from the presynaptic neuron. One interpretation of these results is that schizophrenia is due to excess activity at dopamine synapses. Another possibility is that the underlying problem in schizophrenia is not an excess of dopamine activity at all, but a deficit of glutamate activity ¹. If glutamate release is reduced in the schizophrenic brain, one way to correct this deficiency would be to block activity at dopaminergic receptors, relieving glutamate synapses from inhibition.

¹Glutamate is the predominant excitatory amino acid released by neurons in the cerebral cortex that project widely throughout the limbic system, and dopamine synapses are known to inhibit glutamate release in these target regions.

2.7 Addiction Clinics - Dr. Marcus - 15.05.2017

Drug addiction is a chronic, relapsing disease with obvious medical, social, and political consequences. Addiction (also called substance dependence) is a persistent disorder of brain function in which compulsive drug use occurs despite serious negative consequences for the afflicted individual.

General Information

Global Burden of Disease (2010)

Alcohol and illicit drug use account for 5.4% of world's annual disease burden (impact of a health problem as measured by financial cost, mortality, morbidity, or other indicators), with tobacco responsible for 3.7%.

Mortality in Switzerland (2007)

1. Tobacco (9.201 deaths)
2. Alcohol (1.993 deaths)
3. Suicid (1.360 deaths)
4. Traffic accidents (384 deaths)

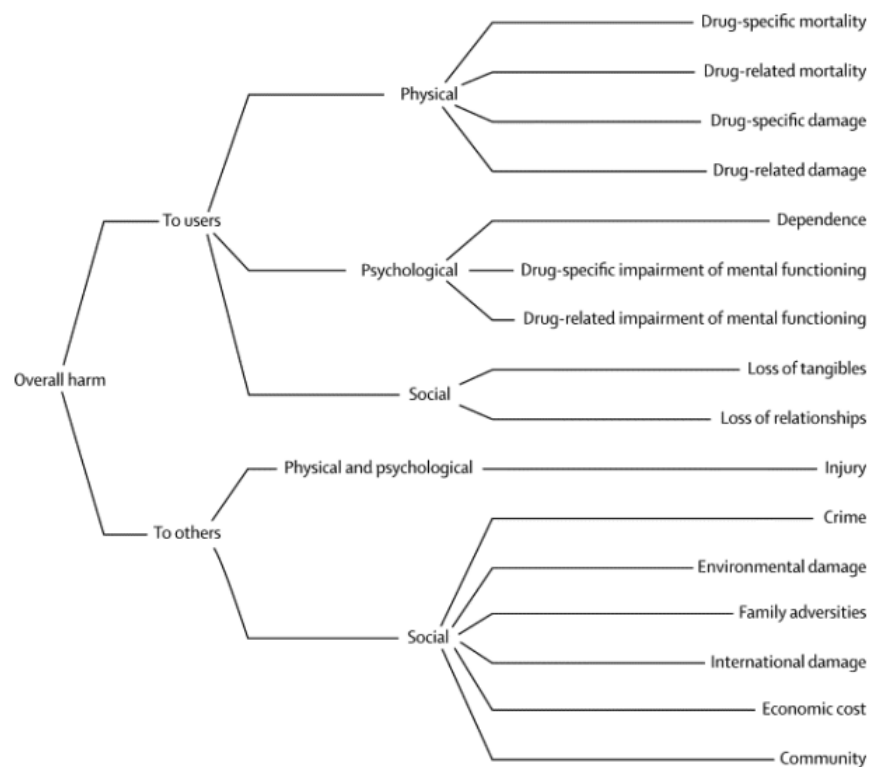
Harm related to the use of drugs

The harm caused by drugs can be divided in two categories: to the user itself and to others, the subdivision of each categorie is shown in Figure 17.

Considering the overall harm caused by drugs (to the user + to others), the drugs that cause most harm are:

1. Alcohol (72 pts harm score)
2. Heroin (55 pts harm score)
3. Crack-cocaine (54 pts harm score)

The cocaine itself appears in the fifth position with 27 pts of harm score.



[Nutt et al. The Lancet 2010; 376:1558-1565](#)

Figure 17: Different types of harm related to the use of drugs

Dependence Syndrome (ICD-10)

To consider that exist a **dependence syndrome**, **three of more of the following manifestations should have occurred together for at least one month** or if persisting for periods of less than one month, should have occurred together repeatedly within a 12-month period.

- Strong desire or compulsion to take the substance
- Impaired capacity to control substance taking behaviour
- A physiological withdraw state when substance use is reduce or ceased
- Evidence of tolerance to the effects of the substance (need for significantly increased amounts of the substance)
- Preoccupation with substance use by alternative pleasures (pleasures or interests being given up or reduced because the substance use)
- Persistent substance use despite harmful consequences

risk	men	women
low	0-4 drinks per day (40g alcohol concentration)	0-2 drinks per day (20g alcohol concentration)
medium	4-6 drinks per day (40-60g alcohol concentration)	2-4 drinks per day (20-40g alcohol concentration)
high	6-10 drinks per day (60-100g alcohol concentration)	4-6 drinks per day (40-60g alcohol concentration)
very high	>10 drinks per day (>100g alcohol concentration)	>6 drinks per day (>60g alcohol concentration)

Table 7: Alcohol risks for health consequences

From first use to dependence

The dependence is caused by environmental and genetic factors. A single (first) use is not enough to become dependent. However, some drugs need less time to create a dependence. In order of most addictive drugs: cocaine → alcohol/nicotine → cannabis.

Alcohol

The alcohol abuse/dependence is the mental disorder that shows the highest gap (92%) between policy and practice (not only in Europe).

Stigmas of Alcohol, Depression and Schizophrenia

todo: "Addiction is a Brain disease, and it matters"

Alcohol risks for health consequences

Table 7 shows the level of risk that the consumption of alcohol represents for the health. For comparison, one bottle of wine (750ml, 12% vol) corresponds to 70g of alcohol and 7 drinks. In general, 10g of alcohol is found in 100ml of wine with 12% vol, or 330ml of beer with 4% vol, or 30ml of alcohol beverages with 40% vol.

Treatment goals

In the early 19th century started the **temperance movement** promoting abstinence and a "moral" life, aiming at a society without alcohol and drugs. In the early 20th century, this movement spread around Europe and became a popular social movement. Alcohol use was considered a lack of virtue, the treatment was based on work therapy and pedagogic measures to overcome "lack of willpower".

At the beginning of the treatment, approximately half of the patients with alcohol abuse, would like to stop drinking completely (abstinence), and the other half would like to reduce the consumption of alcohol (moderate drinking, without dependency). However, preferences change over time, after four weeks, 49% of the patients change from reduction to abstinence as preferred treatment goal.

Nowadays, current guidelines suggest that it is best to engage the patient in reducing the alcohol consumption at first than force an abstinence.

The general **treatment goals** are preservation or restoration of health and social integration. Abstinence or a moderate use that does not substantially affect health and social environment as well as the treatment of concurrent diseases (psychiatric and somatic) are suited to reach this goal.

Some treatments are pharmacotherapy, psychotherapy and social support.

Heroin

It was used as a pain killer. There was an open drug scene in Zurich around 1980/1990. In 1991 was introduced the **Four Pillar Strategy**: not drug free, but drug use that is socially compatible.

- prevention
- therapy
- harm reduction
- regression

Opioid agonist treatment

Opioid agonist therapy (OAT) is an effective treatment for addiction to opioid drugs such as heroin, oxycodone and others. The therapy involves taking the opioid agonists methadone (Methadose) or buprenorphine (Suboxone). These medications work to prevent withdrawal and reduce cravings for opioid drugs. People who are addicted to opioid drugs can take OAT to help stabilize their lives and to reduce the harms related to their drug use. Methadone and buprenorphine are long-acting opioid drugs that are used to replace the shorter-acting opioids the person is addicted to. Long-acting means that the drug acts more slowly in the body, for a longer period of time. By acting slowly, it prevents withdrawal for 24 to 36 hours without causing a person to get high. OAT also helps to reduce or eliminate cravings for opioid drugs. Treatment works best when combined with other types of support, such as individual or group counselling.

This treatment has good evidence of efficacy resulting in reduction of heroin/ cocaine use, reduction of mortality, improvement in quality of life, increase in treatment retention.

In 2015, 33k people died of opioid in USA.

Cocaine

Cocaine is still an issue in Zurich, top 3 cities in Europe (first place: Antwerp, Belgium, second place: Amsterdam, Holland).

Patient interview

cocaine addicted, the interview was in German, without translation.

2.8 Addiction in Society - Prof. Boris Quednow - 15.05.2017

The vast majority of the people who regularly consume psychoactive drugs are NOT addicted nor will they ever become addicts.

Psychoactive drug consumption

The American Psychiatric Association defines addiction in terms of both physical dependence and psychological dependence (in which an individual continues the drug-taking behavior despite obviously maladaptive consequences).

In addition to a compulsion to take the agent of abuse, a major feature of addiction for many drugs is a constellation of negative physiological and emotional features, referred to as "withdrawal syndrome," that occur when the drug is not taken.

Although positive reinforcement is clearly necessary for the development of drug use, it may fall short in explaining the development of compulsive use. So, what drives the drug consumption in some people and why/how do some of them become addicted? What factors distinguish drug use from abuse and dependence or addiction?

Opponent-process theory

According to **opponent-process theory**, drug addiction is the result of an emotional pairing of pleasure and the emotional symptoms associated with withdrawal. At the beginning of drug or any substance use, there are high levels of pleasure and low levels of withdrawal. Over time, however, as the levels of pleasure from using the drug decrease, the levels of withdrawal symptoms increase, thus providing motivation to keep using the drug despite a lack of pleasure from it.

Incentive-sensitization model

According to **incentive-sensitization model**, the motivation to abuse substances must be a force a lot stronger than merely liking something. Everybody will have things they like but it won't change their behavior in the same way that an addicted will. Liking is not a good explanation for addiction. Instead addicts have developed a powerful motivation that is called

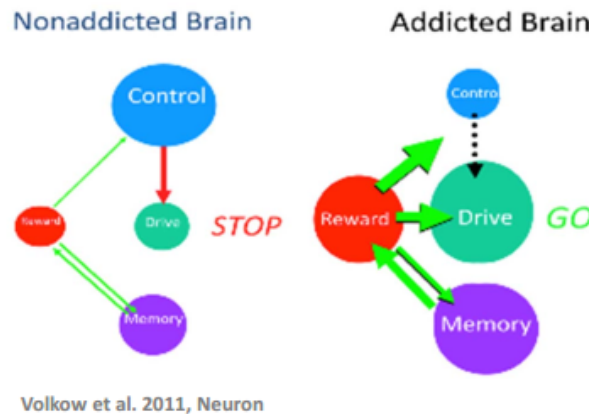


Figure 18: Circuits underlying addiction

incentive salience. Incentive salience is an intense type of wanting because the brain develops a strong association between a stimuli and a reward (pathological reward learning). This association develops subconsciously but it can soon start to influence outward behavior. This compulsion to get more of the stimuli can be incredibly strong. Thus, addicts may no longer even like the substance but they still feel compelled to use it.

This way, **“want” vs “like” dissociates over time**. The wanting sensation is mediated by dopamine and the liking sensation is mediated by endogenous opioids.

Addiction as pathological learning and memory

The transition from occasional to compulsive drug use and the persistent vulnerability to relapse are due to neuroadaptations in brain circuits implicated in reward, memory, drive, and control.

Figure 18 shows a schematic relation between the circuits underlying addiction. Reward (nucleus accumbens and ventral pallidum), memory (amygdala and hippocampus), control (pre frontal cortex and anterior cingulate gyrus) and drive (orbital frontal cortex and subcallosal cortex). In a nonaddicted brain, these circuits are balanced, this results in proper inhibitory control and decision making. However, during addiction, the enhanced expectation value of the drug in the reward, drive, and memory circuits overcomes the control circuit, this favors a positive-feedback loop initiated by the consumption of the drug and perpetuated by the enhanced activation of the drive and memory circuits.

Stages of addiction

Drug addiction, also known as substance dependence, is a chronically relapsing disorder characterized by (1) compulsion to seek and take the drug, (2) loss of control in limiting intake, and (3) emergence of a negative emotional state when access to the drug is prevented. Drug-taking behavior progresses from impulsivity to compulsivity in a three-stage cycle: binge/intoxication,

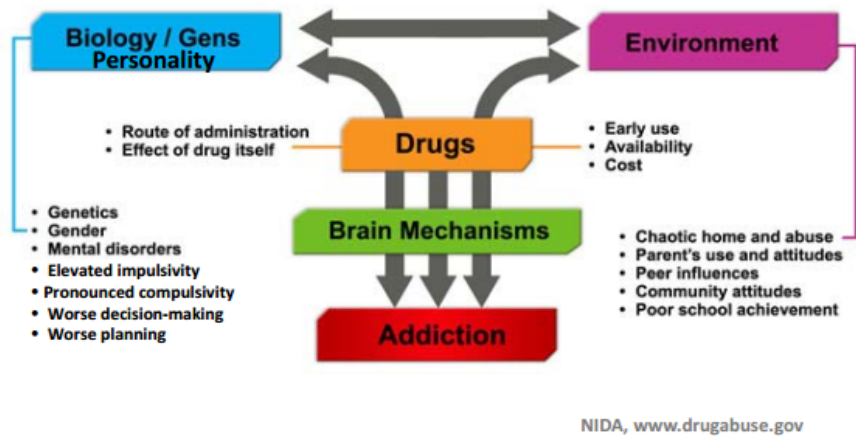


Figure 19: Factors leading to drug addiction

withdrawal/negative affect and preoccupation/anticipation. Positive reinforcement (pleasure/gratification) is more closely associated with impulse control disorders. Negative reinforcement (relief of anxiety or relief of stress) is more closely associated with compulsive disorders.

Stage I

The stage I is the binge/intoxication stage. It is marked by a positive reinforcement by the drug, rewarding effects mediated by dopamine and endogenous opioids (VTA to Nacc), the stimulus-response habit learning is enhanced, and associative learning of context cues happens.

Stage II

The stage II is the withdrawal/negative effect stage. In this stage there is a negative emotional state involving the extended amygdala. This can induce stress and anxiety-like effects, it projects to hypothalamus and brain stem. The endogenous opioids decrease, and then the negative reinforcement happens (drug seeking to avoid withdrawal).

Stage III

The stage III is the preoccupation/anticipation (craving) state. It is a state with high vulnerability to relapse (even after prolonged abstinence) where conditioned drug-associated cues or stress can elicit strong drug craving, which in turn makes relapse more likely. Disrupted PFC function is crucial for this stage.

Approximately 10 to 20% of drug users become addicted at some point during their lifetime. Among the factors leading to addiction, there are biological/gens and environmental factors, some are listed in Figure 19.

Molecular target of drugs

There are three classes of drugs according to their mechanism of action.

- I - binds to G-protein - metabotropic receptors - Opioids, Cannabinoids, Hallucinogens
- II - binds to ionotropic receptors - Nicotine, Alcohol, Benzodiazepines
- III - interacts with monoamine transporters (GABA receptors) - Cocaine, Amphetamine

All addictive drugs increase dopamine levels (in animal models). Addiction liability and reinforcing effects are mainly mediated by i) mesolimbic projection (VTA - ventral tegmental area to NAc - Nucleus Accumbens), ii) mesostriatal projection (substantia nigra to dorsal striatum) and iii) mesocortical projection (VTA to PFC).

Dopamine and reward: pharmacokinetic profile of drug

Drugs with fast uptake leads to a fast drug effect (reward), more intense high and stronger reinforcing effects. The reward elicits approach and consumatory behavior, increases frequency and intensity of behavior leading to reward a maintain learned behavior and induces subjective feelings of pleasure. But, when the reward is predict but doesn't happens, dopaminergic neurons code the discrepancy between the prediction and occurrence of rewards, that is crucial for approach behavior. If the drug do not "come" the brain seeks the drug → absence of dopamine.

The dopamine release facilitates learning. Drugs elicit more dopamine release for greater duration than natural resources of reward (food, sex, social interaction). Upon repeated administration tolerance does not develop to drug- induced dopamine release, but natural rewards are weaken.

By blocking reuptake or enhancing release, cocaine and amphetamine increase the synaptic availability of dopamine, norepinephrine and serotonin. However, the acute reinforcing effects of these drugs depend critically on dopamine. Low doses of dopamine receptor antagonists injected either systemically or centrally into the nucleus accumbens, amygdala, or bed nucleus of the stria terminalis block cocaine and amphetamine self-administration in rats.

Perpetuation of drug addiction

Why do addicts continue to take drugs if reward is mediated by dopamine release in the mesolimbic pathway and addicts exhibit attenuated drug-induced when dopamine increases?

Because of the conditioning. Association of environmental cues with the drug may underlie intense desire for drug. The dopamine increase by conditioned cues are larger than those produced by drugs itself. The use of drugs is compulsive when exposed to drug cues.

Serotonin and addiction

Without dopamine, one can still get addicted if there is serotonin in the body. Cocaine and other psychostimulants increase serotonin activity in the brain. Serotonin depletion in PFC reduces the reinforcing properties of cocaine in conditioned place preference (CPP) in rats. **A functional serotonin system is required for establishing psychostimulant consumption and related behaviors in animals.**

2.9 Neurosurgery - Jorn Fierstra - 22.05.2017

Highly Specialized Medicine

Applying and mastering the most modern and complex techniques and cutting edge knowledge currently available.

Specialized in surgeries for brain and spinal pathologies (most brain surgery). Brain: Neurovascular (Aneurysms), Neuro-oncology (Tumors), Epilepsy, Hydrocephalus, Deep Brain Stimulation, Trauma, Infectious diseases. Spine: Spinal canal stenosis, Herniated discs, Neurovascular, Neuro-Oncology.

UZH/ETH is an outstanding place.

Brain pathologies

Aneurism

An aneurysm is an arterial condition in which the wall of an artery weakens, creating a bulge, or distension of the artery. An aneurysm can occur in important arteries such as those supplying blood to the brain, and the aorta. The bulge in an artery forms as a result of a weakening of the artery wall, which allows the blood pressure to distend the artery wall wider than usual. A cerebral aneurysm is usually saccular. This shape also accounts for most cases of ruptured brain aneurysms. Ruptured cerebral aneurysms are the most common cause of a type of hemorrhagic stroke. This type of stroke is less common than ischemic strokes - strokes caused by a blocked artery rather than an internal bleed.

Most aneurysms do not themselves cause any symptoms, however, a large aneurysm may obstruct circulation to other tissues. An aneurysm can also contribute to the formation of blood clots that then obstruct smaller blood vessels, potentially causing ischemic stroke or other serious problems; this is known as thromboembolism. Otherwise, aneurysms tend to produce symptoms only when there are complications such as rupture. Brain aneurysm can lead to hemorrhage; a symptom of the stroke bleed is a sudden extreme headache.

When an aneurism is found, it is necessary determine if it must be treated. Many people do not have any symptom and can live with it. Approximately 50% of aneurism will result in bleeding, this way some people do not need surgery.

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

Bypass

Cerebral bypass surgery is performed to restore, or “revascularize”, blood flow to the brain. A cerebral bypass is the brain’s equivalent of a coronary bypass in the heart. The surgery connects a blood vessel from outside the brain to a vessel inside the brain to reroute blood flow around a damaged or blocked artery. The goal of bypass surgery is to restore blood supply to the brain and prevent strokes.

Elana - Excimer Laser Assisted Non Occlusive Anastomosis

The only proven non-occlusive bypass technique in Neurosurgery, only technique available to make a bypass in the brain without temporary occlusion of the blood-flow. This can significantly diminish the risk of stroke. The Elana procedure is designed to make traditional bypass procedures safer and easier.

Spine Pathologies

Neck Injuries and Disorders

Tumor spinal cord

Intraoperative MRI

Intraoperative magnetic resonance imaging (iMRI) refers to an operating room configuration that enables surgeons to image the patient via an MRI scanner while the patient is undergoing surgery, particularly brain surgery. iMRI reduces the risk of damaging critical parts of the brain and helps to confirm that the surgery was successful or if additional resection is needed before the patient’s head is closed and the surgery completed.

Neurosurgery challenges

- Understanding the origin of neurological disease
- advance treatment and thereby outcome of patients with neurological disease
- advance current diagnostic and therapeutic modalities available to us

It is necessary to have better imaging methods that auxiliate to figure out the precise area to be removed in a surgery, for instance.

Novel MRI - clinical neuroscience research

An emerging technique for mapping cerebrovascular re-activity (CVR) is blood oxygen level-dependent MRI (BOLD MRI) of changes in cerebral blood flow (CBF) during manipulation of end-tidal partial pressure of carbondioxide. It uses a 3 Tesla MRI together with RespirAct device that change CO₂ and O₂.

Respiract: changes in CO₂ to contract/dilate veins in brain. RespirAct™ is an investigative tool that's designed to control end-tidal gas concentrations in the lungs and blood. Failure of the blood vessels to dilate or contract at the necessary time can starve tissue for oxygen. RespirAct™ is involved in researching diagnostic procedures that measure vascular reactivity, i.e., the ability of the blood vessels to regulate blood flow in reaction to varying circumstances which affect blood supply and demand. We're currently investigating the control of CO₂ and O₂ for a number of applications.

Neurovascular uncoupling finger tapping - image effects sensitive to threshold

3 Previous exams

Note: this answers were provided by students and were not verified by a teacher. Use them at your own risk.

2005

1. **NeuroImmunology** - A student in a major Neurobiology lab attempts to generate and purify recombinant rabbit myelin basic protein (MBP). He uses a eukaryotic expression system. Suddenly, his cell-cultures become contaminated by bacteria. He has already spent a lot of time on his project and does not want to tell his supervisor about his mishap. The student decides to ignore the contamination and purify his protein. He further decides to assess the level of contamination by injecting the protein into mice. He reckons that if they developed septic shock syndrome, he would have to tell his boss and start from scratch. If the mice were fine, he would not tell his boss about his blunder and go ahead as planned. After injecting his protein, the mice do not develop septic shock and the student is ecstatic. However, after one week, the mice develop hind-limp paralysis and a student from the Neuroimmunology lab next door tells him that his mice appear to suffer from EAE. The student now wonders whether this is to be expected after MBP injection or not. You can surely help:

Why did the mice develop this autoimmune disease? Please name step-by-step events leading to CNS-inflammation.

Does the contamination have anything to do with the mice developing EAE? Explain the four mechanisms of peripheral tolerance and provide examples! Hint: the narrative above provides one of the four examples you need.

2.

Imaging - Abstract of a paper (Goel V. and Dolan RJ: The functional anatomy of humor: segregating cognitive and affective components.

Explain why we have auto-aggressive T cells and the events occurring in the thymus “usually” lead to central tolerance. What is positive and negative selection?

What is shown in figure 1 (statistical map) - explain how it is generated.

what is shown in figure 2 (modulation in ROI) - explain.

3.

Psychiatry II - Explain pathogenesis of Alzheimer and reveal therapeutic approaches.

4.

Different aspects of MS are listed. Weight the importance of the different aspects and their impact for treatment

How do you interpret the activation in ventromedial prefrontal cortex? See answer 2.

5. **Neuroinformatics - What are the organizing principles of neural systems? Explain on examples of retinal stereopsis and why the brain uses them.**

6. **Sleep research - Why is sleep divided into REM and non-REM? Why is slow-wave-activity meaningful in non-REM-sleep?**

2006

1. **Imaging - Abstract from Nature: A general mechanism for perceptual decision-making in the human brain (2004). Figure 1 (behavioral data) and Figure 2 (fMRI data) were given.**

explain behavioral results

explain fMRI results

what is the signal measured with fMRI?

What is a statistical map and to what extent does it reflect neuronal activity?

2.

Disease models - What are the arguments in favour and against the protein-only hypothesis of prion propagation?

3.

Brain and behavior - Compare and contrast two research strategies in the study of schizophrenia with an emphasis on how they may complement each other

4.

Sleep and circadian rhythm

is the conclusion drawn from this study supported by data?

Define terms: sleep homeostasis; circadian sleep-wake rhythm

5.

Neuroinformatics

Describe: their main physiological markers; their practical manifestations

differences in organising principle between electronic and neural computation

6.

Multiple Sclerosis

illustrate neural computation principles by specific examples (e.g. retina), explain functional utility.

Where are the predilection sites in MS lesion? (Where are Plaques most frequently? Reasons?

Which cellular or histological features are typical for MS plaques?

What is the role of the BBB (blood brain barrier) in MS pathogenesis and by which techniques can it be elucidated?

Describe mechanisms of demyelination and axonal damage and mechanisms of remyelination and axonal repair.

Which forms of MS do you know and how are they characterized?

What is the prevalence rate in Switzerland and how are such figures determined?

Main clinical features (typical symptoms) of chronic MS. See answer 3.

Forms of therapy

2013

In what respect are therapies effective and in which respect less so?

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? See answer 1.

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**

See answer 1.

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.**

See answer 1.

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?

- 6.

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

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.

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.

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 frequencies pulses with the appropriate frequency (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 quickly the protons realign with the magnetic field and accurately distinguish different types of tissue, T2 is how quickly 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 O₂ 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, improve inter-subject average.
- b) Model estimation: calculates parameter for instance, from GLM of voxel timeseries.
- c) Contrasts and SPM: does 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 absolute 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 without the task P. The difference between the two acquisitions will be the result of the task P. This is an approach that assumes a “pure insertion” theory, where cognitive (and neural) processes can be added to others without 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 signal 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 dependent) signal. Neural activity seems to mediate vasodilation (maybe through the 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.

3. Functional magnetic resonance imaging (fMRI) is one of the most widely-used techniques for non-invasive studies of human brain function. fMRI exploits the so-called “blood oxygen level dependent” (BOLD) contrast.

Please discuss the biophysical basis of BOLD: how is BOLD linked to changes in regional magnetic field inhomogeneities and regional blood flow during neuronal activation? BOLD measures inhomogeneities in the magnetic field due to changes in the level of O₂ 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.

Please discuss what aspects of neuronal activity are most closely respected by BOLD and which biochemical processes link neuronal activity to vasodilation and vasoconstriction. Neurovascular coupling refers to the relationship between local neural activity and subsequent changes in cerebral blood flow (CBF). The BOLD signal is based on this coupling and measures neural activity indirectly. The cerebral metabolism depends on a constant supply of both glucose and oxygen. A continuous supply of these two energy substrates is maintained by cerebral blood flow (CBF), which delivers glucose and oxygen to neural tissue through the complex web of blood vessels in the brain's vascular system. During neural activity, increases in oxygen and glucose consumption are followed by an increase in CBF. Action potentials at pre-synaptic cell leads to neurotransmitter release (e.g., glutamate, GABA) that open ion-channels on post-synaptic cell. Re-uptake of glutamate and pump ions out of cell again uses energy and oxygen, this triggers blood vessel dilation and decrease ratio of deoxygenated/oxygenated blood, i.e, decrease in magnetism, increasing the BOLD signal strength. A neuronal activity inhibition will lead to a vasoconstriction correspond to a decrease in blood oxygenation, and a decrease in the BOLD signal.

Please summarize the basic principles of statistical parametric mapping, the standard approach to analyzing fMRI images. The SPM identify functionally specialized brain responses and is the most prevalent approach to characterizing functional anatomy and disease-related changes. The basic pipeline includes three steps:

- preprocessing: images are spatially aligned to each other to correct for the effect of subject movement during scanning (realignment/motion correction), then spatially normalised into a standard space and smoothed.
- modelling: parametric statistical models are applied at each voxel (a volume element, the three-dimensional extension of a pixel in 2D) of the data, using a general linear model (GLM) to describe the data in terms of experimental effects, confounding effects and residual variability.
- statistical inference: classical statistical inference is used to test hypotheses that are expressed in terms of GLM parameters. This results in an image in which the voxel values are statistics: this is a statistical parametric map (SPM).

4. What is the neurological basis for BOLD fMRI?

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 (T_2) 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.

Perception and Attention

1.

Decision Making

1. Describe the process of decision making and the areas of the brain with significant BOLD signal during the process

The decision-making process is the ensemble of computations performed in the brain in order to take an action in response to external stimuli. It can be schematized as:

REPRESENTATION → VALUTATION → ACTION SELECTION → ACTION PERFORM AND EVALUATION → LEARNING

It is strongly related to the perception process, due to the necessity to get a proper representation of the outer world before taking an action. Important stage in this process is the learning phase, that influences how all the other steps are performed. Complex meta-analyses of the brain during experiments show how the areas most involved are:

- vmPFC - ventral medial prefrontal cortex
- dlPFC - dorsal lateral prefrontal cortex
- PCC - posterior circular cortex

Several experiments show also relationships with striatum and amygdala, in particular referring to the learning phase, and OFC (occipital frontal cortex) and ACC (anterior cingulate cortex) referring to willingness to face some kind of cost in action selection.

2. Describe an experimental setup to study the decision process in humans

Evaluation of the decision process in humans can be done using the BDM auctions. The experiment structure is:

- Keep away the subject from food, to increase the attractiveness of the foods
set the subjects in an “hungry state”, so we ensure they have interest n getting the food the bid for.
- Show them food (100 trials, 50 items) and ask them to bid to get it

- Force them to wait 30 mins and provide them with food
the wait prevent them from thinking to eat immediately after the experiment is done.

The core of the experiment is the auction, in which subjects have to bid to get the food they see. The bids can be \$0, \$1, \$2 or \$3. A random number P is selected for each object, being B the subject bid, if $B \geq P$, the food is won and P is paid, otherwise the food is not won and 0 is paid. The bid becomes what in economics is called WTP (Willingness To Pay). In order to get a control group, half of the trials use the free bid system previously described while the other half uses a forced bid system, where the subject can't decide the amount of its bid.

Experimental results show an increase in the BOLD signal in the vmPFC and in the dlPFC for the free bid trials that doesn't occur in the forced bid trials, indicating that these areas are involved into the active decision process.

3. Describe an experimental setup to study the decision process in primates

In order to study the decision-making process in primates, the following experimental setup is prepared:

- Monkey prevented from drinking
- Two groups of coloured dots are shown
- The monkey has to select one of the two groups
- Reward based on monkey selection is provided

Each group represent a different kind of liquid (e.g. water and juice) and the number of dots represent the amount (e.g. 4 drops vs 1 drop). What the monkey learns is the relative value of the liquids against each other. Analyses of BOLD signal of the brain during this task show how vmPFC and dlPFC are activated during the task. Further, it is possible to perform single neuron measurement in the monkey OFC (occipital frontal cortex) and see direct relationship with the task performed and a single neuron activity.

4. Describe an experimental setup to study aversive decision process in humans

In order to verify if aversive decision process involves different brain areas, the BDM auctions can be modified replacing "desirable" food with "undesirable" ones (e.g. children food), also, instead of keep the subjects away from food, instruct them to eat at most 2 hours before the test, to decrease the attractiveness of the food. The resulting BOLD signal is similar to standard BDM experiment, showing that same brain areas are involved.

5. Comment about complex decision process (multiple factors to be evaluated) and differences in rewards offered

Extra experiments have been done to verify differences in activated brain areas for complex choices (e.g. evaluating color+shape+regularity), showing again a strong involvement of the vmPFC. It is interesting to note, however, that when we change the kind of reward (e.g. money vs food) the areas of the vmPFC that are activated are slightly different, indicating a different processing according to the kind of reward the subject is going to get.

6. Describe an experimental setup to study the decision process when deciding for someone else

The experimental setup to verify if we decide differently if we or someone else is going to be rewarded is the following:

- Subjects are coupled. Partners are chosen such that they often make opposite choices.
- The subject is informed about who is going to get the reward, if himself or the coupled subject
- A dual choice between small, short term reward and large, long term reward is shown

Due to the coupling rule, subjects have to model what they expect the partner is going to do. Measurements during this experiment show how there is no real difference in brain activation when deciding for ourselves or for someone else, but there is a relevant difference when it gets to take a decision or model the partner decision scheme.

7. Describe an experimental setup to study the action selection process on rodents

The experimental setup to evaluate the decision-making process in rodent is based on a small T structure with two rewards, one large and the other small, at its ends. To get the large reward there is some sort of price the mice have to pay: it could be a delay (e.g. 15 seconds) or a physical effort (e.g. climb a wall). Placed in this setup with a properly tune reward size, the mice show a preference of the larger reward, accepting the “cost” of the delay/effort. Afterwards, the mices are divided in 3 groups:

- Control group (surgery without brain lesions)
- OFC group (lesion to occipital frontal cortex)
- ACC group (lesion to anterior cingulate cortex)

The test is the repeated and the results show:

- no behaviour difference for the control group

- decreased willingness of facing a delay in the OFC group (with a minor degrade of physical willingness too)
- decreased willingness of facing a physical effort in the ACC group

This indicates an active role of these two areas in the decision process. It is interesting to notice that despite the damaged brain, the mice can afterwards learn again their preference for the higher reward, indicating how the learning process is able to somehow compensate the physical injuries.

8. Describe the sequential sampling process and an experimental setup to verify its hypothesis

The sequential sampling process hypothesis describes the decision-making as an accumulation of evidences, until a certain threshold of certainty is reached and an action is taken. In order to verify this, the following experimental setup is prepared:

- The subject is placed in front of randomly moving dots
- Some dots are set to move only to right or to left
- As soon as the subject identifies the direction of movement, it takes a decision and select the side
- The delay of the decision is measured

This experiment tries to show how faster the decision becomes when the number of coherent dots is higher, showing that more information lead to a faster accumulation of evidence and then decision, modelling the process with a drift diffusion model.

9. Describe what is it meant with conditioning and what brain areas are involved, bringing examples to support your thesis

There are two kinds of conditioning: classical (or Pavlovian) and operant (or instrumental). Classical conditioning is related to the learn of unconscious or automatic answer to some external stimuli, while operant conditioning is a conscious behaviour in which a response is learned due to a reward system (procedure also called "Reinforcement Learning").

The first one can be demonstrated in the classical Pavlov's dog experiment. Classical conditioning is usually related to amygdala and the case of H.M. shows it isn't related to hippocampus. Similarly, the case of S.M. showed the importance of amygdala: her lesioned brain was unable to learn to react to fear stimuli.

10. Give a model for learning processes

A model for learning process is the prediction-error model. The concept behind it is that every time the brain predicts the outcome of an action, it compares the prediction with the actual outcome and updates its internal prediction model. It is described as $\Delta V = \alpha\beta(\lambda - \Sigma V)$, where:

- ΔV is the change in learning (prediction error update)
- α and β are learning rates
- λ is the amount of unpredicted outcome
- ΣV is the amount learned (accumulated learning)

This model sees the learning as an accumulation of evidences that leads to a minimization of the prediction error. The prediction is updated at each time step. In humans, the learning phase is often correlated to Striatum/OFC activity.

Emotions

1. How, on a conceptual level, do fear conditioning and extinction work?

Fear conditioning is a behavioral paradigm in which organisms learn to predict aversive events. It is a form of learning in which an unconditional stimulus (e.g. an electrical shock) is associated with a conditional (neutral) stimulus (e.g., a tone), resulting in the expression of fear responses to the originally neutral stimulus. Eventually, the neutral stimulus alone can elicit the state of fear. Conditioning stimuli and unconditioning stimuli inputs converge in amygdala. Amygdala neurons show long term potential (LTP) that facilitates CS conditioning.

Fear extinction works the same way as fear conditioning but, instead of generate a response (fear), the response is extinct. This can be obtained by present the conditioned stimulus alone, so that it no longer predicts the coming of the unconditioned stimulus, and the conditioned response gradually stops. However, the complete memory is not "removed". Extinction builds a competing memory.

2. How is it implemented in a human / rodent brain? What are some empirical findings?

It is necessary a protein synthesis to keep the memory. If you present, after a CS conditioning, the tone with a protein synthesis inhibitor, we observe a disruption in memory and in the paired condition.

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.**

Long term memory is the retention of information in a more permanent form of storage (days, weeks, or even lifetime). The LTM is divided in two types: declarative (or explicit) and nondeclarative (or implicit). The declarative memory is that one available to consciousness and it is divided in two types: semantic and episodic. The nondeclarative memory is not available to consciousness and it is divided in four types: procedural, priming, classical conditioning and habituation/sensitization. Semantic memory refer to facts and general knowledge while episodic memory refer to personal memories. Semantic memory is related with lateral temporal lobe and parahippocampal gyrus. Episodic memory is related with hippocampus.

The procedural memory refers to skills and habits, and it is related with striatum, premotor cortex and cerebelum. The priming memory refers to the tendency to process some perception in the same way, it is related with the neocortex. The classical conditioning memory refers to the associations and it is related with amygdala and cerebelum. Lastly, the habituation/sensitization refers to ignore or pay more attention to determined situations, and it is related with the reflex pathways.

In rats, we can access the classical conditioning memory using the classical pavlovian conditioning, this way, we can observe the associated behavior.

2. **List techniques used to investigate memory working principles**

Most used techniques to investigate memory are fMRI, PET and Electroencephalography (EEG).

fMRI is used to find the structures that support learning/tasks activities, also used to detect mental process that do not reflect in behavior, can be used to identify people with real memory problems (detect simulations).

PET is used on study of learning and memory, measures metabolites and neurotransmitter concentrations.

EEG is used on study of learning and memory consolidation during sleep. It measures excitatory and inhibitory postsynaptic potentials.

3. **Describe the multistore model**

The multistore model is a memory model that take into account the time that a memory is stored. It is divide in three classes:

- sensory memory, it is up to 1s, used for routine experiences
- short term memory (aka, working memory), it is up to 1 minute. It is the ability to hold information once the present moment has passed.
- long term memory, over 1 minute and longer.

It is important to notice that long term memory is not permanent: forgetting is a key process necessary to keep the amount of information stored under control and avoid memorizing useless concepts and data. Although forgetting is a normal and essential mental process, it can be pathological, a condition called amnesia.

4. Describe HM disease and symptoms

HM was a patient suffering of seizures preventing him from having a regular life. For this reason, he was subject of a brain surgery, with the removal of hippocampus. Despite the success of the treatment (he didn't have any more seizures) it suffered of a serious retrograde and anterograde amnesia: he was unable to remember events immediately before the surgery and he lost the ability to remember new events. This clinical case has been a fundamental step in understanding the role of hippocampus in episodic memory, which is defined as the memory allowing us to remember specific events ("episodes") of our life. Also, during the analysis of HM impairment, it came out that he was still able to acquire other kinds of knowledge (e.g. to perform some kind of drawing task) but without the ability to remember he learned it (e.g. being surprised by how easy a task was at first attempt, when he actually trained on it several times before).

5. Provide a scheme of existing long-term memories, with a brief description of each one and which brain areas are involved in each of them, based on consciousness memory model

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refers to the associations and it is related with amygdala and cerebellum. Lastly, the habituation/sensitization refers to ignore or pay more attention to determined situations, and it is related with the reflex pathways.

6. Describe the role of hippocampus in unconscious memory retrieval and sleep

HM case demonstrated that hippocampus plays a central role in episodic memory. Several experiments show how hippocampus become active in particular during REM sleep, working on the consolidation of the memory and how it is important for associative memory.

7. Provide a scheme of memory based on processing modes

The model based on processing modes is divided in three classes:

- Rapid encoding of flexible associations: responsible for episodic memories, related with hippocampus and neocortex.
- slow encoding of rigid associations: procedural memory, classical conditioning and semantic memory, related with basal ganglia, cerebellum and neocortex.
- rapid encoding of single or unitized items: familiarity and priming, related with parahippocampal gyrus and neocortex

Body Perception

1. Define phantomology

Phantomology is the science of the virtual reality of the body. It is the science of the body in the brain, from out-of-limb to out-of-body experiences.

2. What is phantom limb? What types of phantom sensations exist?

Phantom limb refer to a sensation/persistend experiences of the postural and motor aspects of a limb after its physical loss. There are four groups of phantom sensations:

- phantom body parts: the feeling of the body part without the body part itself. Can occur after amputation or even in congenital limb deficiency.
- 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.

Also, even the loss of the limb, one can have phantom sensation, it is called spinal phantom limb.

3. What is phantom pain? Describe some theories about why it happens.

Phantom pain is the feeling of a pain in the body part that it is not attached to the body. It is not well clear why phantom pain happens. One theory (maladaptive model) says that the pain is the price for the plasticity of the brain. The loss of inputs in a determined area generates an "invasion" from neighbors areas that causes pain. Another theory (maintained representation model) states that the representation of the phantom in the brain is maintained give the pain as input.

4. Why some people with congenital limb deficiency experience phantom sensation?

It is not well know why this happens, but there are three main explanations.

- projection of enhanced motility of rudiments (if some part of the limb is there but not enterily)
- contralateral representation of intact limb
- innate body schema

5. What is the obstacle shunning?

It is when a physical object is placed at the same location as the phantom body part. Approximately 50% of the patients believe the phantom limb is still there, and the other half realize that the phantom limb is in his/her head. In some cases, the confrontation of the phantom limb with an obstacle makes the person change the postural body as if it is necessary to move the phantom limb of place. However, it is interesting to notice that even if the phantom sensation disappears, the phantom pain can still holds. Shunning is associated with worse prothesis tolerance.

6. Explain what is supernumary and negative phantom limbs.

Supernumary is a condition where the individuo believes and receives sensory information from limbs that do not exist and never have existed. This can be simulated by the pinochio illusion or by rubber hand experiment. In the pinochio ilusion, the participant close his/her eyes and touches his/her nose and have the biceps stimulated. The participant will perceive arm and/or nose in different location. In the rubber hand experiment, a rubber hand is placed in front of the participant and his/her real hand is hided by a cardboard. A second person will, using identical movements, do the same thing with the fake and real hand. After a while, participants are convinced that the fake hand is their own hand.

Negative phantom limbs happens when the limb exists but the person do not recognize the existence of the body part. This phenomenon is also called xenomelia. This sensation is accompanied by reduced response to tactile stimulation in the "unconnected" limb. Also

is related with reduced thickness and volume in Superior Parietal Lobe and smaller area in Inferior Parietal Lobe, S1 and S2 areas.

7. What is whole-body phantom? How can one induce it?

The whole-body phantom is purely somaesthetic illusion, i.e, one can feel but cannot see. Patients usually point a precise localization in space and it happens almost exclusively after Parietal Lobe Lesions. The visual experience of whole-body phantom is called autoscopic phenomena, represents a dissociation between the image of him/herself and the body. It is divided in three groups:

- Out-of-body experience: people feel their self outside the physical body and somewhat elevated.
- Autoscopic Hallucination: people experience seeing a double of themselves, without “leave” the original body.
- Heautoscopy: people experience seem a double of themselves. However, the subject cannot point out where the self is localized.

To induce the whole-body phantom we can use the out-of-body experience: observe the own body in front of oneself (for example, using a head mounted display) and simultaneously touch the real and fake bodies. After a while, the participant will felt that he/her is at the place of seen touch.

Neurology

Ophtalmology

1. How we can use saccadic eye information to diagnose disorders?

Saccadic disorders may produce abnormal latency to initiate eye movements, abnormal speed of eye movements (generally slow), or abnormal accuracy of eye movements (hypometria or hypermetria). The specific type of abnormality relates to the pattern of neural activity delivered to the ocular motoneurons.

2. Explain nystagmus

Nystagmus is a condition of involuntary eye movement, acquired in infancy or later in life, that may result in reduced or limited vision. Due to the involuntary movement of the eye, it has been called "dancing eyes". Can be related with a loss of vestibulo-ocular reflex, when the head moves, the eyes move together and then, after a while, the eyes turn to the object-goal position. In spontaneous nystagmus, eyes drift to the side of the loss.

3. What is the Romberg's test?

Romberg test is a test to identify loss of balance. The Romberg test is based on the premise that a person needs two of three of the following senses to maintain balance: proprioception, vestibular function and vision. If a person loses the balance when close the eyes, then exists a disorder on proprioception or on the vestibular system.

Otology

1. What is otology?

Otology is the study of the anatomy and disease of the ear. It is related with hearing and vestibular systems. Neurotology is a focused study of diseases of the inner ear.

2. Describe some tests used in neurotology.

There is two common tests used: the caloric test and the bimalleolar vibration sense.

In the caloric test, the external auditory canal is irrigated with cold or warm water or air. The difference in temperature between the body and the injected substance should mimics a head turn. If the water is warm (44°C or above) it mimics a head turn to the ipsilateral

side, and thus both eyes must turn toward the contralateral ear. If the water is cold (30°C) it mimics a head turn to the contralateral side, and thus both eyes must turn toward the ipsilateral ear. Absent reactive eye movement suggests vestibular weakness of the side being stimulated.

Parkinson

1. What is Parkinson? It is a syndrome or a disease?

Parkinson is the syndrome of having a combination of slowness of movement, stiffness, tremor at rest and postural instability. Many related diseases can cause the parkinson syndrome. The most common reason is the Parkinson disease. Parkinson disease is the second most common degenerative disorder of the nervous system.

2. What causes the parkinson disease?

The symptoms of parkinson are due to the progressive loss of dopaminergic neurons in the substantia nigra pars compacta, that projects and innervates neurons in the caudate and putamen. The cause of the deterioration of these dopaminergic neurons is not known. Some genes are been studied and linked with Parkinson: *α-synuclein* and *parkin*.

3. What are the treatments for parkinson?

Since the symptoms are caused by loss of dopamine, the most common treatment is medication to increase dopamine in the caudate and putamen. However, this treatment is a symptomatic-therapy, not a cause-therapy. To achieve a true cure the mechanisms of neuronal cell death need to be understood and strategies for enhancing neuronal survival and regrowth need to be developed.

Neuromuscular disorders

1. What are neuromuscular disorders?

Neuromuscular disorders affect the nerves that control the voluntary muscles. When the neurons that control the muscles become unhealthy or die, communication between the nervous system and muscles breaks down. As a result, the muscles weaken and waste away.

2. How neuromuscular disorders can be diagnosed?

The diagnostic of neuromuscular disorders can use medical history, neurological examination and laboratory tests. A common test is the Nerve Conduction Studies (NCS), it is a measurement of the speed of conduction of an electrical impulse through a nerve. NCS can determine nerve damage and destruction. During the test, the nerve is stimulated, usually with surface electrode patches attached to the skin. Two electrodes are placed on the skin over the nerve. One electrode stimulates the nerve with a very mild electrical impulse and the other electrode records it. The resulting electrical activity is recorded by another electrode. The nerve conduction velocity (speed) is then calculated by measuring the distance between electrodes and the time it takes for electrical impulses to travel between electrodes. Another test that may be performed is electromyography (EMG). An EMG measures the electrical activity in muscles and is often performed at the same time as NCS. Both procedures help to detect the presence, location, and extent of diseases that damage the nerves and muscles.

3. What is myotonic reaction?

Myotonia is a symptom of certain neuromuscular disorders characterized by delayed relaxation (prolonged contraction) of the skeletal muscles after voluntary contraction or electrical stimulation.

Stroke

1. What is a stroke? Types and treatments.

A stroke, also known as a cerebrovascular accident, is a medical emergency. Any acute neurological symptom is a stroke unless proven otherwise. Strokes happen when blood flow to the brain stops. Within minutes, brain cells begin to die. There are two kinds of stroke. The more common kind (80% of the cases), called ischemic stroke, is caused by a blood clot that blocks a blood vessel in the brain. The other kind, called hemorrhagic stroke, is caused by a blood vessel that breaks (changing in blood pressure control) and bleeds into the brain. The symptoms of a stroke usually are related with trouble walking, speaking and understanding, as well as paralysis or numbness of the face, arm or leg. For ischemic stroke a treatment is the recanalization of the vessel or use of a catheter. For hemorrhagic stroke, an option is the use of a clipping or a coiling.

2. What is a penumbra in a ischemic stroke?

The penumbra is an area around the direct affected area. It is an area of moderate reduction of the blood flow. Cells in penumbra are potentially salvageable. However it needs to be

treated as soon as possible. After 270mins, recanalization of a ischemic stroke can lead to hemorrhagia.

3. Constraint Induced Movement Therapy - limitations and describe.

The term Constraint-Induced Movement Therapy (CIMT) describes a package of interventions designed to decrease the impact of a stroke on the upper-limb function of some stroke survivors. It is a behavioural approach to neurorehabilitation based on "Learned-Nonuse". CIMT is typically performed for individuals following a stroke as between 30-66% of the survivors will experience some functional loss in their impaired limb. Furthermore, CIMT has also been performed for individuals with other injuries and even for multiple sclerosis. The aim of CIMT is to improve and increase the use of the more affected extremity while restricting the use of the less affected arm. The three major components of CIMT include;

- Repetitive, structured, practice intensive therapy in the more affected arm
- Restraint of the less affected arm
- Application of a package of behavioural techniques that transfers gains from the clinical setting to the real world, thus CIMT uses operant training techniques applied in the context of rehabilitation medicine.

The limitations of CIMT come from the way the therapy is proposed. Patients are expected to wear a mitt or sling to restrict movement of the unimpaired arm for 90% of waking hours, which is very restrictive. Also, Therapy sessions of 6 hours per day for 2 weeks is very intensive and increases patient and caregiver burden. Given these challenges, some patients and therapists have expressed concerns about the therapy.

Neuropsychological disorders

1. Cite language disorders that you know.

Aphasia are language disorders that affects a person's ability to communicate. Some types of aphasia are:

- Broca's aphasia: a person with Broca's aphasia knows what he or she wants to say, but is unable to accurately produce the correct word or sentence. Expressing language in the form of speech and writing will be severely reduced.
- Wernicke's aphasia: a persons with Wernicke's aphasia can produce many words and they often speak using grammatically correct sentences with normal rate and prosody. However, often what they say doesn't make a lot of sense or they pepper their sentences with non-existent or irrelevant words.

- aprosodia: a person with aprosodia has an inability to properly convey or interpret emotional prosody. Prosody in language refers to the ranges of rhythm, pitch, stress, intonation, etc.
- alexia: a person with alexia loses the ability to read or understand words, sentences, or, in some cases, even letters. It is also called visual aphasia or word blindness. Interestingly, the person still have the ability to write.

2. What is apraxia?

Apraxia is a motor disorder caused by damage to the brain (specifically the posterior parietal cortex), in which the individual has difficulty with the motor planning to perform tasks or movements when asked, provided that the request or command is understood and he/she is willing to perform the task. A person can use a tool but cannot imitate their use when asked.

3. What is anosognosia?

Anosognosia is a deficit of self-awareness, a condition in which a person with some disability seems unaware of its existence. It is a neurological disorder and distinguishes from denial, which is a psychological defense mechanism.

Multiple Sclerosis

1. In which way may the pathological and pathophysiological disturbance in MS help to explain the clinical course of the disease?

Multiple sclerosis is an inflammatory demyelinating disease of the CNS in which activated immune cells invade the central nervous system and cause inflammation, neurodegeneration and tissue damage. Multiple sclerosis can be pathologically defined as the presence of distributed glial scars (or sclerosis) in the central nervous system disseminated in time and space. Currently it is unknown what the primary cause of MS is. Current models can be divided into two groups: Inside-out and Outside-in. In the first ones, it is hypothesized that a problem in the CNS (like an inflammation or viral illness) produces an immune response that destroys myelin and finally breaks the BBB. In the second models, an external factor produces BBB leaks, immune cells enter the CNS, and destroys myelin and axons. Progression of MS is linked to increasing neurologic dysfunction which by current understanding reflects neurodegenerative processes.

2. Different aspects of MS are listed. Weight the importance of the different aspects and their impact for treatment.

There is no cure for multiple sclerosis. Treatment typically focuses on speeding recovery from attacks, slowing the progression of the disease and managing MS symptoms. Some people have such mild symptoms that no treatment is necessary. Some treatments that can be used in MS are:

- Physical therapy: a physical or occupational therapist can teach the patient stretching and strengthening exercises and show him/her how to use devices to make it easier to perform daily tasks. Also, together with the use of a mobility aid when necessary can also help manage leg weakness and other gait problems often associated with MS.
- Muscle relaxants: the patient may experience painful or uncontrollable muscle stiffness or spasms, particularly in legs. Muscle relaxants such as baclofen (Lioresal) and tizanidine (Zanaflex) may help.
- Medications to reduce fatigue
- Other medications: medications also may be prescribed for depression, pain, sexual dysfunction, and bladder or bowel control problems that are associated with MS.

3. Main clinical features (typical symptoms) of chronic MS?

Classic MS symptoms are:

- Sensory loss (ie, paresthesias): usually an early complaint
- Motor symptoms: muscle cramping secondary to spasticity
- Autonomic symptoms: bladder, bowel, and sexual dysfunction
- Optic neuritis: loss of vision (or loss of color vision) in the affected eye and pain on movement of the eye.
- Eye symptoms: including diplopia on lateral gaze
- Heat intolerance
- Constitutional symptoms: fatigue and dizziness; fatigue must be differentiated from depression (which may, however, coexist), lack of sleep, and exertional exhaustion due to disability
- Pain
- Subjective cognitive difficulties: with regard to attention span, concentration, memory, and judgment
- Depression

4. What are treatment and therapies for MS?

There is no cure for MS, but some treatment and therapies can slow down the advance of the disease and reduce the symptoms. Experiencing a relapse is discouraging, so ending it as quickly as possible benefits both the body and the mind. Inflammation is a key feature of MS relapses, and it can lead to many of the secondary symptoms. Corticosteroids and interferons are often used to ease inflammation and reduce the severity of attacks. Interferons dampen the overactive immune system. Also some therapies can help with the symptoms as: physical therapy (can help manage leg weakness and other gait problems), speech therapy (for speech difficulties, such as long pauses or slurred language, but also for swallowing) or injections of botulinic toxin (alleviating bladder and bowel problems).

5. How does the blood brain barrier (BBB) function in MS?

The blood-brain barrier (BBB) is a cellular and metabolic barrier located at the capillaries in the brain that alters permeability, restricting the passage of some chemical substances and microscopic objects from the bloodstream into the neural tissue, while allowing other substances to pass into the brain. For example, the blood-brain barrier restricts the passage of bacteria, red-blood cells, and certain toxins and water-soluble molecules into the brain while allowing the passage of oxygen, glucose and amino acids. Normally, a person's nervous system would be inaccessible for the white blood cells due to the blood-brain barrier. However, it has been shown using MRI that, when a person is undergoing an MS "attack", the BBB has broken down in a section of the brain or spinal cord, allowing white blood cells called T lymphocytes to cross over and destroy the myelin.

6. What is a BBB test in MS?

CSF shows oligoclonal bands and elevated IgG synthesis in over 80% of patients. Evoked potentials that may show problems with sensory systems that are not known from clinical exam. However, none of these (except serial MRIs) can show whether lesions are separated in space and time.

7. In which points are treatments satisfactory? In which points not so?

8. What is the prevalence / incidence in Switzerland?

The prevalence is 110 per 100.000 inhabitants. The average incidence in Europe is 108 per 100.000 inhabitants.

9. What is the prevalence rate in Switzerland and how are such figures determined?

The prevalence is 110 per 100.000 inhabitants. The average incidence in Europe is 108 per 100.000 inhabitants. The prevalence rate is defined as the number of people that have the disease at a specific point in time.

10. Describe mechanisms of demyelination and axonal damage and mechanisms of remyelination and axonal repair?

The early stages of MS involve relapsing-remitting where patient experience demyelination associated with loss of function (i.e., vision and gait), which is usually regained following remyelination. In the progressive stages of MS, irreversible functional deficit occurs which has been associated with progressive loss of axons and neurons. Demyelination in multiple sclerosis occurs by two major mechanisms: primary injury to the myelin sheath with relative preservation of oligodendrocytes, or direct injury to oligodendrocytes (oligodendrogliaopathy). Following demyelination of the axon there is either (i) remyelination with axonal preservation, or (ii) axonal death. Remyelination can take place by either surviving mature oligodendrocytes, or more likely by the recruitment of progenitor oligodendrocytes that mature into myelinating cells. Axonal death occurs as a result of either the inflammatory response, in particular MHC Class I restricted CD8 positive T cells, or by the failure of local neurotrophic support as a result of injury to glial cells. The majority of white matter tract axons were entirely enwrapped by myelin; therefore, it is likely that axons cannot obtain proper nutrient support from their external environment on their own and require metabolic support from glial cells. Following demyelination, there is an overall increased demand for ATP. The energy required to maintain the intra-axonal ionic balance and the resting membrane potential by the Na^+/K^+ ATPase pump were increased, due to redistribution and an overall increase in the number of Na^+ channels. Increased metabolism requirements for demyelinated axons may make these axons more susceptible to death through disease mechanisms such as inflammation.

11. Where are the predilection sites in MS lesion (where are the plaques most frequently)? Reasons?

Plaques are randomly distributed. They have a predilection for the periventricular white matter, optic nerves, and spinal cord but spare no part of the CNS. The predilection for these sites may be explained in part by the distribution of venules where blood–brain barrier breakdown takes place.

12. What cellular or histological features are typical for MS plaques?

Long-lasting chronic MS lesions are characterized by a relatively uniform appearance of extensive primary demyelination with variable axonal loss, gliosis and minor infiltration by

lymphocytes and macrophages/microglia. Early MS lesions show a profound inflammatory reaction consisting of T cells, a variable but low number of B cells and massive infiltration by foamy macrophages at the sites of demyelination.

13. What is the role of the BBB in MS pathogenesis and by which techniques can it be elucidated?

The presence of a blood–brain barrier (BBB) restricts the movement of soluble mediators and leukocytes from the periphery to the CNS. Despite the presence of this tightly regulated BBB, leukocyte entry into the CNS is an early event in multiple sclerosis (MS), an inflammatory disorder characterized by the formation of multifocal lesions in the brain and spinal cord. Acute MS lesions, featuring areas of demyelination, axonal loss and immune cell infiltrates, display BBB disruption. The BBB breakdown is a crucial and obligatory step in the pathogenesis of MS.

14. Which forms of MS do you know and how are they characterized?

There are four types of MS:

- Relapsing-Relapsing MS (RRMS): this is the most common form of multiple sclerosis. About 85% of people with MS are initially diagnosed with RRMS. People with RRMS have temporary periods called relapses when new symptoms appear.
- Secondary-Progressive MS (SPMS): in SPMS, symptoms worsen more steadily over time, with or without the occurrence of relapses and remissions. Most people who are diagnosed with RRMS will transition to SPMS at some point.
- Primary-Progressive MS (PPMS): this type of MS is not very common, occurring in about 10% of people with MS. PPMS is characterized by slowly worsening symptoms from the beginning, with no relapses or remissions.
- Progressive-Relapsing MS (PRMS): a rare form of MS (5%), PRMS is characterized by a steadily worsening disease state from the beginning, with acute relapses but no remissions, with or without recovery.

15. 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!)?

In MS, subsequent to the demyelination and degeneration, the remyelination and neurogenesis are stimulated and progenitor cells migrate into damage sites. Remyelination is the default spontaneous process in which demyelinated axons are ensheathed with new myelin sheaths. Remyelination is not only found in inactive lesions but can also be observed in lesions with ongoing demyelinating activity. However, repair processes are especially characteristic of the early disease phase. Remyelination may even begin within a month or

two after active demyelination. In contrast, remyelination in late stage MS appears sparse and restricted to borders of inactive lesions. Thus, myelin repair, termed remyelination, occurs in acute inflammatory lesions in MS and is associated with functional recovery and clinical remissions. The new myelin sheath may either act as a protective physical barrier to damaging inflammatory molecules, or restore trophic support to the axon.

16. How MS can be diagnosed?

To diagnose MS is necessary find demyelination. MRI information and additional signs can be used. Also, the presence of antibodies in the CSF and its absence in the serum indicates MS.

Spinal Cord Injury

1. What are the two main aetiologies of SCI?

SCI can be traumatic or non-traumatic. The traumatic SCI occurs when an external physical impact acutely damages the spinal cord as primary injury. In the non-traumatic SCI, a chronic disease process, such as a tumor or infection generates the primary injury. In both cases, the primary injury damage cells and initiates a complex secondary injury cascade, which produces death of neurons and glial cells, ischemia and inflammation.

2. How is SCI diagnosed?

A suspicion of SCI includes identification of an injury (or a process that generates a primary injury) and the presence of some of the symptoms: acute head, neck, or back pain; decline of feeling in the extremities; loss of control over part of the body; urinary or bowel problems; walking difficulty; pain or pressure bands in the chest area; difficulty breathing; head or spine lumps.

Patients with suspected SCI undergo neurological examination (including voluntary motor and sensory examination of each limb and a rectal examination) and radiographic imaging to look for damages. The images techniques commonly used are X-ray, CR and MRI. X-ray and CT are useful to detect gross fractures and MRI is used to evaluate soft tissues, such as discs, ligaments and nerve roots.

3. Why SCI can sometimes cause urinary problems?

Regulatory functions as pupil diameter, gut motility, and urinary system are controlled by the sympathetic nervous system. Sympathetic pathways start in the spinal cord. Some SCI can interrupt this pathways and then generates a variety of side effects as urinary problems, gastrointestinal problems, and even sexual function.

4. Cite two SCI syndromes and its characteristics.

- Central cord syndrome: most commonly diagnosed in elderly patients. It is characterized by disproportionate motor impairment of the upper limbs rather than the lower limbs.
- Brown-Sequard syndrome: most commonly observed in individuals with penetrating traumatic SCI. It is characterized by loss of motor function, proprioception and vibration sensation ipsilateral to the injury, and loss of pain and temperature sensation contralateral to the injury.

5. How a SCI develops from the primary injury?

The primary injury causes displacement or dislocation of the vertebral column, which causes compression or transection of the spinal cord. This causes a focal region of cell death and blood-spinal cord barrier disfunction, which causes a cascade of secondary injury mechanisms. This secondary injury mechanisms includes vascular changes, inflammation, loss of ionic homeostasis and oxidative stress (increasing the damage to the spinal cord). Cell death contributes to the formation of cystic cavities, which are surrounded by a glial scar (a deposition of astrocytes and molecules that inhibit neuronal regeneration), which interfere with neuronal regeneration and functional recovery.

6. Describe the temporal phases of the SCI.

SCI can be temporally divided into the acute (< 48 hours), subacute (48 hours to 14 days), intermediate (14 days to 6 months) and chronic (> 6 months) phases.

In the acute phase blood vessel injury can cause severe hemorrhages, which can expose the cord to an influx of inflammatory cells. The inflammatory response combined with the disrupted blood-spinal cord barrier, progressively creates a swelling, leading to further mechanical compression of the cord, which can extend for multiple spinal segments and worsen the injury. Cell death in acute phase promotes cystic cavities. These cavities become a barrier to directed axonal regrowth and are a poor substrate for cell migration.

In the subacute phase ischemia and excitotoxicity contribute to a loss of homeostasis, and ongoing necrosis of neurons and glia releases ATP and potassium, which can activate microglial cells. Activated microglial cells infiltrate the injury site, where they propagate the inflammatory response. Phagocytic inflammatory cells can clear myelin debris at injury site but can also induce further damage to the spinal cord.

The multiple causes of cell death that occur during the acute and subacute phases of SCI can produce greater damage than the original primary injury and form the basis for the neuroprotective interventions.

Lastly, the chronic phase is marked by attempts at remyelination, vascular reorganization, alterations in the composition of the extracellular matrix (ECM) and remodelling of neural circuits.

7. How animal models can be applied to study of SCI?

Animals models are useful for the preclinical testing of new therapies. The ideal animal model should anatomically and pathophysiologically resemble humans SCI, require minimal training, be inexpensive and produce consistent results. Rat models are the most commonly used for SCI research, however, differences in size, molecular signalling, anatomy and the recovery potential following SCI have made direct translation challenging. Large animal models, such as non-human primates, overcome some of these barriers, but substantial differences in cost and unique housing requirements make their use less common and even they are unable to exactly mimic human SCI.

8. Cite some complications of SCI.

Complications can be local or systemics. Examples of local complications are neuropathic arthropathy (slow progressive destruction of a joint) and spasticity (can affect mobilization, activities of daily living and sleep). Some systemics complications are cardiovascular, respiratory (leading cause of mortality in patients with chronic SCI), secondary immunodeficiency, genitourinary and gastrointestinal problems, pressure sores etc.

Epilepsy

1. What is epilepsy?

It is a disorder in which nerve cell activity in the brain is disturbed, causing seizures.

2. What is a seizure?

A seizure happens because of abnormal electrical activity in the brain. It is a temporary disruption of normal brain functions. A seizure usually change the eyes moviment and the body tension. Seizures does not mean epilepsy. In epilepsy the seizures are unprovoked. Seizures are caused by transient functional disturbances of cerebral neurons leading to excessive and/or synchronous discharges.

3. How do seizures are classified?

The seizures can be classified in focal or generalized. The focal seizures are disturbs that starts in a specific part of the brain. These seizures can often be subtle or unusual and

may go unnoticed or be mistaken for anything from intoxication to daydreaming. The generalized seizures are the result of abnormal activity in both hemispheres and usually associated with unconsciousness.

4. What is EEG for test seizures? How it works?

An electroencephalogram (EEG) is a test that measures and records the electrical activity of the brain. Electrodes are attached to the patient's head and the brain's electrical activity is recorded. EEG measures synchrony post-synaptic potential. A hypersynchronization indicates neuron participation in the generation and propagation of the seizure. Spikes and sharp waves are an epileptiform of brain electrical activity.

5. What are the treatments for epilepsy?

There are some treatments for epilepsy. The treatment aims at preventing seizures, and can make a patient seizure-free but cannot treat the underlying cause of the epilepsy. The most common is pharmacotherapy, where drugs can control the seizures. If the area on brain that cause the seizures is small, well defined and do not control speech, sight, movement or hearing, surgery can be a treatment option or even a palliative option, just to reduce the frequency and/or severity of seizures. More than that, depending on the type of the seizure, a specific treatment can be used as diets or nerve stimulation.

6. Compare idiopathic vs symptomatic epilepsies.

Idiopathic epilepsies are genetically determined and cannot be treated surgically. However, most patients with such syndromes respond very well to medical treatment. On the other hand, symptomatic epilepsies are caused by identifiable alteration of brain tissue (tumors, scars, inflammation etc). Patients with symptomatic epilepsies who do not respond well to antiepileptic drugs, can see the surgical treatment as a possibility.

Depression

1. Every sadness is a depressive state? How depression can be diagnosed?

Feeling sad is a common mood in response to loss, stress or disappointment. The Major Depressive Disorder (or depression) involves persistent symptoms that includes a combination of depressed mood, diminished interest or pleasure, changes in sleep and appetite, loss of energy, thought of death and suicide, etc.

2. Please describe briefly:

Some conceptional problems in studying depression from a neuroscientific point of view Depression is a disorder of subjective feeling. It is very difficult to evaluate the disease scientifically, or even create animal models that are adequate to depression because 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 objective markers like genetic defects or metabolic disfunctions exist to analyse the depression in a objective way.

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 that rises cortisol levels. Hypothalamus secretes CRH (corticotropin-releasing hormon) leading the pituitary gland (hypophysis) to secrets adrenalcorticotropin (ACTH). The ACTH interacts with receptors in the adrenal gland stimulating the production and release of cortisol. Cortisol is the adrenal glucocorticoid stress hormone secreted in humans and other primates.
- Reduction of growth hormone: causes sleep disorders, disturbances of appetite regulation and functioning of limbic system.

Schizophrenia

1. Please describe shortly a neurobiological model of schizophrenia

Imaging studies shows some consistently structural alteration in the brain of schizophrenic patients, for instance, less activity in prefrontal cortex, activity on visual and auditory cortices, differences in size of basal ganglia, hyppocampus and amygdala. Also, some differences in dopamine was found. Each one of this differences can be used to justify the symptoms of schizophrenia. The prefrontal cortex helps people to think logically and organize their thoughts, so, less activity in this area can be related with the common symptom of disorganized speech/behavior. Also difference in size of basal ganglia, amygdala and hippocampus can affect the movement patterns and basic feelings, (causing inability to express emotions and attention deficits, for instance). More than that, the variation in dopamine can be related with apathy and inability to experience pleasure.

2. **Describe two different approaches in schizophrenia research. How do they contrast/complement?**

3. **Positive symptoms, how are they linked to dopamine?**

The positive symptoms represent distortions or exaggerations of normal cognitive or emotional functions. Some positive symptoms of schizophrenia are delusions, hallucinations, disorganized speech and psychomotor disturbance. They can be linked with an excess of dopamine in some parts of the brain. This excess in dopamine can activate some brain areas as visual or auditory cortex leading to hallucination for instance.

4. **Negative symptoms, how are they linked to dopamine?**

The negative symptoms reflect a loss or diminution of normal cognitive and emotional functions. Some negative symptoms of schizophrenia are attention deficits, lack of initiative, apathy, social withdrawal, diminution in the ability to express emotion and inability to experience pleasure. These symptoms can be associated with a lack of dopamine. Since dopamine is responsible for feeling pleasure and reward-motivated behavior, a lack of dopamine can lead to loss of emotions, for instance.

5. **How can dopamine release be influenced (pharmacologically, by the environment)?**

Some stimulants (pharmacologics) can change the dopamine level by inhibit dopamine uptake, resulting in increased dopamine concentration. An animal's social environment and stress level actually can change the number of D2 receptors in the brain and change the proportion of the nucleus accumbens that is dedicated to pleasure. Thus, the environment can alter how pleasurable a given reward can be.

6. **How to diagnose schizophrenia?**

There is no definitive test to diagnose schizophrenia, but if some symptoms persist for at least one month and are clearly not due to depression or neuroleptic medication, it can be schizophrenia. The symptoms that must persist are: delusions of control, hallucinatory voices giving a running commentary on the person's behavior, delusions that are culturally inappropriate or that are impossible, incoherence of speech, or one of the negative symptoms.

7. **What are the treatments for schizophrenia?**

The therapy treatment is based on medication, psychotherapy and rehabilitation. Some antipsychotic drugs can be used but with low dosage start (to reduce side effects). Tran-

quilizers can be used during acute phases. In the long term, control the treatment side effects is crucial to the rehabilitation (reintegration) of the patient in society. Psychotherapy helps the patient to deal with his/her thoughts and behavior, learning more about the illness and learning how to differentiate what is real and what is not.

8. How dopamine is related with schizophrenia?

The strongest link between dopamine and schizophrenia comes from studies of drugs that alleviate the symptoms of schizophrenia. A large number of antischizophrenic drugs have two properties: block postsynaptic dopamine receptors and inhibit the release of dopamine from presynaptic neurons. One interpretation of these results is that schizophrenia is due to an excess of dopamine. Another possibility is that the problem is not an excess of dopamine, but a deficit of glutamate. If glutamate release is reduced, one way to correct this deficiency would be block activity at dopaminergic receptors, relieving glutamate synapses from inhibition.

Psychiatric disorders - general

1. What is the neurobiological system in schizophrenia and depression?

See answers 1 from Schizophrenia and 2 from Depression.

2. 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.

Modeling of human neuropsychiatric disorders in animals is extremely challenging given the subjective nature of many key symptoms, the lack of biomarkers and objective diagnostic tests, and the early state of the relevant neurobiology and genetics. Many of the symptoms used to establish psychiatric diagnoses in humans (e.g., hallucinations, delusions, sadness, guilt) cannot be convincingly ascertained in animals. When there are reasonable correlates in animals, (eg., abnormal social behavior, motivation, working memory, emotion, and executive function), the correspondence may only be approximate.

Also, you always have to ensure that the animal model is valid. There are different aspects of validity that have to be guaranteed:

- Face validity: the 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 in the human patient.

- Inter-laboratory validity
- Inter-species validity

There are three major clusters of symptoms in Schizophrenia: positives, negatives and cognitive. Positive symptoms include hallucinations and delusions, experiences that are not characteristic of normal mental life. Negative symptoms represent deficits in normal functions such as impoverished speech, asocial behavior, and diminished motivation. Cognitive symptoms include deficits in working memory and conscious control of behavior. One common symptom is the attentional impairment, this happens because the schizophrenic patient has an inability to focus on important stimulus. A specific test, Latent Inhibition (LI), was proposed. In the LI, a neutral stimulus is presented much before the unconditioned stimulus. Healthy people take too longer to learn the correlation between the stimulus. However, a schizophrenic patient learns the relation rapidly (as the stimulus were presented paired). In animals: Rats were present with a tone followed by a shock, but not paired. Rats are not able to learn to avoid the shock this way. However, rats treated with amphetamine learn to avoid the box where they got shocked, due to their impairment on LI.

In depression, the symptoms are related with diminished interest, loss of energy, diminished ability to think or concentrate. The most common animal model for depression is the **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, this lead to anhedonia (inability to experience pleasure).

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

Motivation, attention and memory are commonly affected by neuropsychiatric disorders. Depression is the disorder most related with changes in motivation, however, schizophrenia and sometimes parkinson patients also present lack of motivation. Attention is mainly impaired in schizophrenia, but also in depression. Memory is affected by Alzheimer and some cases in Parkinson, and also commonly in aging.

Measuring motivation: Learned Helplessness Test: 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.

Measuring attention: One method to measure attention in rodents is the Multiple Choice Serial Reaction Time Test. In this test, a rodent is positioned in front, for instance, of five doors in which one of them will be briefly illuminated. The rodent needs to poke the right door in order to receive the food. This test address the attention of the animal.

Measuring memory: Spatial memory - Morris Water Maze Test: In this task, a tank is filled with milky water with a platform concealed somewhere beneath the surface. When a rat is placed in the tank, he will swim around until he finds the platform. When this task is repeated many times, he learns to use cues from outside the tank and can find the platform almost immediately from any spot in the tank. He can do this because he has created a spatial map of the tank and its surroundings. If the rat's hippocampus is lesioned after he learns the task, there will be no effect; if it is lesioned before (when he is naive), however, he is unable to learn it. Working memory - Radial Arm Maze Test: In this test, a mouse is placed in the middle of a radial maze that contains food in some arms. The working memory is assessed when the mouse visits each arm only once.

4. 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). Frontotemporal dementia (FTD) is a term for a diverse group of uncommon disorders that affect the frontal and temporal lobes (areas generally associated with personality, behavior and language). In FTD portions of these lobes shrink. Signs and symptoms vary, depending upon the portion of the brain affected.

The disorders grouped into FTD fall into three subtypes:

- Behavior variant frontotemporal dementia: characterized by prominent changes in personality, interpersonal relationships and conduct.
- Primary progressive aphasia: affects language skills, speaking, writing and comprehension. It can be semantic (individuals lose the ability to understand or formulate words in a spoken sentence) or agrammatic (a person's speaking is very hesitant, labored or ungrammatical).

- Disturbances of motor (movement or muscle) function: produce changes in muscle or motor functions with or without behavior or language problems.

The most common signs and symptoms of frontotemporal dementia involve extreme changes in behavior and personality.

Which genes/gene loci have been associated with frontotemporal dementia?
Mutations in three genes **MAPT**, **GRN**, and **C9orf72** have been associated with FTD.

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. FTD is characterized by abnormal protein deposits and almost all cases can now be classified into three major molecular subgroups based on specific accumulating proteins with the most common being FTD-tau and FTD-TDP (accounting for 40% and 50%, respectively) and FTD-FET (accounting for 5–10%).

Tau is a microtubule-associated protein that promotes microtubule assembly and stability which are crucial for maintaining neuronal integrity and axoplasmic transport. Abnormal intracellular accumulation of hyperphosphorylated tau is a characteristic feature of a number of neurodegenerative disorders (tauopathies), including several conditions that may present as FTD (FTLD-tau).

TDP-43 was identified as the protein that accumulates in the vast majority of cases of FTLD with tau-negative, ubiquitin-positive inclusions (then referred to as FTLD-U), and in most cases of amyotrophic lateral sclerosis (ALS).

5. Describe the major diagnostic procedures and tools in the differential diagnosis of dementias.

No single test can diagnose dementia, so it is necessary to run a number of tests that can help pinpoint the problem. Some of them are:

- Cognitive and neuropsychological tests: to evaluate the cognitive function. A number of tests measure memory, orientation, reasoning and judgment, language skills, and attention.
- Neurological evaluation: to evaluate memory, language, visual perception, attention, problem-solving, movement, senses, balance, reflexes and other areas.
- Brain scans: to check for evidence of stroke or bleeding or tumor or hydrocephalus. Also to check patterns of brain activity.
- Laboratory tests: blood tests can detect physical problems that can affect brain function, such as vitamin B-12 deficiency or an underactive thyroid gland. Sometimes the spinal fluid is examined for infection, inflammation or markers of some degenerative diseases.

6. **Please give a detailed account of the process by which prions, upon entering the body, reach the CNS.**

The term “prion” is derived from proteinacious infectious particle. This small infectious particle is a disease-causing form of a protein called cellular prion protein (PrP^c). Prion diseases are contracted by exposure to prion infectivity. There are many ways to the prions enter the body, for example by direct brain exposures (on neurosurgery), by oral or parenteral uptake etc. After replication and accumulation in lymphoid organs, prions invade the nervous system through sympathetic and parasympathetic nerves.

7. **What is the significance of the blood brain barrier (BBB) in infectious disease of the CNS?**

The blood–brain barrier (BBB), composed mainly of specialized brain microvascular endothelial cells, maintains biochemical homeostasis in the CNS by regulating the passage of nutrients, molecules and cells from the blood to the brain. The restrictive nature of the BBB provides an obstacle for drug delivery to the CNS, and, thus, major efforts have been made to generate methods to modulate or bypass the BBB for delivery of therapeutics. Loss of some, or most, of these barrier properties during neurological diseases including stroke, MS, brain traumas, and neurodegenerative disorders, is a major component of the pathology and progression of these diseases. BBB dysfunction can lead to ion dysregulation, altered signaling homeostasis, as well as the entry of immune cells and molecules into the CNS, processes that lead to neuronal dysfunction and degeneration. Although the BBB protects against CNS-directed inflammation by restricting immune cell access to the brain, it can also regulate the local inflammatory response by expressing proinflammatory molecules that promote the recruitment of peripheral immune cells into the CNS.

Addiction

1. **What are the primary causes of mortality in Switzerland (2007)?**

- Tobacco
- Alcohol
- Suicid
- Traffic accidents

2. **What drugs cause the most overall harm? What are the types of harm?**

- Alcohol
- Heroin
- Cocain

The harm caused by drugs is divided in two categories: to the user itself and to the others. In both categories there are physical, psychological and social harm.

3. What defines a dependence syndrome?

To consider the existence of a dependence syndrome, it necessary at least three of the following symptoms together for at least one month (or in a small period but repeatedly within a year).

- strong desire or compulsion to take the substance
- impaired capacity to control substance taking behavior
- physiological withdrawal state when substance use is reduced or ceased
- evidence of tolerance to the effects of the substance
- preoccupation with substance use by alternative pleasures
- persistent substance use despite harmful consequences

Addiction is the physical and psychological dependence, in which an individual continues the drug-taking behavior despite obviously harmful consequences.

4. What is/are the cause(s) of the dependency?

Dependence is caused by environmental and genetic factors. A single use is not enough to create a dependency, however some drugs need less time to create it.

5. Cite treatments for dependency and its goals.

The general treatment goal are preservation and restoration of health and social integration. To achieve this goal, treatment of concurrent diseases and abstinence or moderate use (without dependence) are suited.

6. What is the Four Pillar Strategy?

It was a policy to reduce the number of drug users in Zurich. The strategy was based in a not drug free society but in drug use that is socially compatible. The four pillars are: prevention, therapy, harm reduction and regression.

7. What is the Opioid Agonist Treatment?

It is an effective treatment for addiction to opioid drugs. The therapy involves taking the opioid agonists. These medications work to prevent withdrawal and to reduce cravings for opioid drugs. People addicted to opioids can take OAT to help stabilize their lives and to reduce harms related to their drug use. Usually the agonists are long-acting opioids that replace the short-acting opioids the person is addicted to. By acting slowly, it prevents withdrawal for at most 36h without causing a person to get high, also it helps to reduce or eliminate cravings for opioids drugs.

8. Explain how addiction occurs.

Positive reinforcement is clearly necessary for the development of drug use, but it is not sufficient to explain the development of compulsive use. There are two theories to explain how the dependence occurs: the opponent-process theory and the incentive-sensitization model. In the opponent-process theory, drug addiction is the result of emotional pairing of pleasure and emotional symptoms of withdrawal. At the beginning of drug use there are high levels of pleasure and low levels of withdrawal. Over time, as the level of pleasure decrease, the levels of withdrawal increase, thus providing motivation to keep using the drug, despite a lack of pleasure from it. The incentive-sensitization model considers the motivation to abuse substances must be more stronger than just like it. It states that addicts developed a motivation called incentive salience. Incentive salience is an intense type of wanting because the brain develops a strong association between a stimuli and a reward. This association develops subconsciously but it can influence outward behavior. Thus, addicts may no longer even like the substance but they still feel compelled to use it (want sensation is mediated by dopamine and like sensation is mediated by endogenous opioids).

In any case, addiction is a pathological learning and memory, that involves reward (nucleus accumbens and ventral pallidum), memory (amygdala and hippocampus), control (prefrontal cortex and anterior cingulate gyrus) and drive (orbital frontal cortex and subcallosal cortex). During addiction, the enhanced expectation value of the drug in the reward, drive and memory circuits overcomes the control circuit, favoring a positive-feedback loop initiated by the consumption and enhanced by activation of the drive and memory circuits.

9. What are the stages of addiction?

The addiction is characterized by three stages: compulsion to seek and take the drug (binge/intoxication), loss of control in limiting intake (withdrawal/negative effects) and emergence of a negative emotional state when access to the drug is prevented (preoccupation/anticipation). The first stage (binge/intoxication) is marked by a positive reinforcement by the drug rewarding effects mediated by dopamine and endogenous opioids (VTA to Nacc), the stimulus-response habit learning is enhanced and associative learning of context

cues happens. In the second stage (withdrawal/negative effects) there is a negative emotional state involving the extended amygdala. This induces stress and anxiety-like effects, it projects to hypothalamus and brain stem. The endogenous opioids decrease and then the negative reinforcement happens. The third stage (preoccupation/anticipation) represents high vulnerability to relapse (even after prolonged abstinence). Conditioned drug-associated cues or stress can elicit strong craving. Disrupted PFC is crucial for this stage.

10. What are the molecular targets of drugs?

There are three classes of drugs according to their mechanism of action. There are drugs that bind with G-protein (metabotropic receptors) as opioids, cannabinoids and hallucinogens. There are drugs that bind to ionotropic receptors like nicotine and alcohol. And there are drugs that interact with transporters (GABA receptors) like cocaine and amphetamines.

11. What is the relation between addiction and dopamine?

The dopamine release facilitates learning. Drugs elicit more dopamine release for greater duration than natural resources of reward (food, sex, social interaction). Upon repeated administration tolerance does not develop to drug-induced dopamine release, but natural rewards are weakened. By blocking reuptake or enhancing release, cocaine and amphetamine increase the synaptic availability of dopamine, norepinephrine and serotonin. However, the acute reinforcing effects of these drugs depend critically on dopamine. Low doses of dopamine receptor antagonists injected either systemically or centrally into the nucleus accumbens, amygdala, or bed nucleus of the stria terminalis block cocaine and amphetamine self-administration in rats. However, without dopamine, one can still get addicted if there is serotonin in the body. Cocaine and other psychostimulants increase serotonin activity in the brain.

Neurosurgery

1. What is an aneurysm? How it can be treated?

An aneurysm is an arterial condition in which the wall of an artery weakens, creating a bulge, or distension of the artery. Most aneurysms do not themselves cause any symptoms, however, a large aneurysm may obstruct circulation to other tissues. An aneurysm can also contribute to the formation of blood clots and then obstruct smaller blood vessels. When an aneurysm is found, it is necessary to determine if it must be treated. Many people do not have any symptom and can live with it. Approximately 50% of aneurysms will result in bleeding, this way some people do not need surgery.

2. How a bypass surgery is performed?

Cerebral bypass surgery is performed to restore blood flow to the brain. The surgery connects a blood vessel from outside the brain to a vessel inside the brain to reroute blood flow around a damaged or blocked artery. The goal of bypass surgery is to restore blood supply to the brain and prevent strokes. Elana is the only technique available to make a bypass in the brain without temporary occlusion of the blood-flow.

3. What are neurosurgery challenges and research?

Some challenges are:

- understanding the origin of neurological disease
- advance in treatments and outcomes of patients
- advance in diagnosis and therapies
- better imaging methods to figure out precise areas to remove in a surgery

One tool used in neurosurgery is the fMRI that is based on neurovascular coupling. However, in some cases (brain tumor, for instance) this coupling doesn't hold and then, new techniques are necessary. The respiract for instance, is an tool that controls the amount of CO₂ consumed, and thus, be able to measure vascular reactivity.

Motor Learning and robot-assisted neurorehabilitation

1. 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 No answer.

Identify three unique features of robotic systems that make them valuable tools to investigate human motor learning. No answer.

Discuss how these unique features could be applied to clinical assessment and therapy of sensorimotor impairments No answer.

2. Properties of motor learning - name them. How is this used in therapy?

No answer.

3. What is one advantage and one disadvantage of robot-assisted rehabilitation?

Some advantages:

- Intensive high repetitive tasks can be performed by robots with high precision and endurance.
- robotics tools increases training intensity
- can be combined with engaging social and gaming features
- enables a higher patient throughput by allowing the treatment of several patients by one therapist in parallel
- can facilitate guided motor training remotely through telerehabilitation
- robots can even provide tactile feedback that corrects the impaired movements
- data collected during the robot training sessions can be quantified with ease to complement the subjective and qualitative observation of clinicians

Some disadvantages:

- the acceptance by patients and physicians is still low
- cannot provide some sensory inputs, such as temperature, touch, stroking and psychological support.
- robotic training is less flexible than hands-on therapy
- it is necessary a specific robot for each type of therapy, i.e., the robot used in shoulder therapy cannot be used for wrist therapy, for instance

Neuroimmunology

This topic was not covered in 2017.

1. 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)? The tolerance of T cells begins as soon as a T-cell receptor is formed and expressed on the cell surface of a T-cell progenitor in the thymus. Tolerance mechanisms that operate in the thymus before the maturation and circulation of T cells are referred to as “central tolerance”. However, not all antigens that T cells need to be tolerant of are expressed in the thymus, and thus central tolerance mechanisms alone are insufficient. Fortunately, additional tolerance mechanisms exist that restrain the numbers and or function of T cells that are reactive to developmental or food antigens, which are not thymically expressed. These mechanisms act on mature circulating T cells and are referred to as “peripheral tolerance”. The thymus is the organ

necessary to perform cell education. Thymocytes enter the cortex and undergo T cell receptor (TCR) gene rearrangement and display both CD4 and CD8. These cells interact with cortical thymic epithelial cells (CTEC) and undergo apoptosis unless they receive a survival signal generated via TCR/self-peptide—MHC interaction. Positively selected thymocytes progress to single-positive CD4 or CD8 cells and enter the medulla. High-avidity TCR/self-peptide—MHC ligation in the presence of medullary thymic epithelial cell (MTEC) or dendritic cell (DC) co-stimulatory molecules in the medulla lead to negative selection of self-reactive thymocytes.

What are the mechanisms of peripheral tolerance? Remember, we discussed four of them. Please shortly recapitulate. No answer.

Circadian Rhythm

This topic was not covered in 2017.

1. Circadian pacemakers, entrainment, Zeitgeber, phase-response curve

Pacemaker: SCN (suprachiasmatic 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 switches from delayed to advanced.

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

endocrine: melatonin, adrenal gland (adrenalin, cortisol); GHRH (Growth hormone releasing hormone) 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 → arrhythmicity in vitro culture of a single SCN neuron SCN transplant restores the rhythm in vitro SCN

4. Which genes (gene?) are (is) involved in 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.

Sleep

This topic was not covered in 2017.

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.**

No answer.

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, the 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 which maintain most of the steady states in the organism; sleep homeostasis refers to the sleep need in de-

pendance 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 (suprachiasmatic 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 → 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 rhythm → EEG activation/desactivation

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 dendritic 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 feedback 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).

However, neuronal networks have different weights for the 10×14 axons/dendrite 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 dendrites. 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?

No answer.

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?

No answer.

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

- 1 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>
- 2 Olaf Blanke and Christine Mohr, **Out-of-body experience, heautoscopy, and autoscopic hallucination of neurological origin**, In Brain Research Reviews, vol 50, 2005, Pages 184 - 199, <http://www.sciencedirect.com/science/article/pii/S0165017305000792>
- 3 Neuroscience, Purves et.al, chapter 28 - **Emotions**
- 4 Neuroscience, Purves et.al, chapter 30 - **Memory**
- 5 Fundamental Neuroscience, 4th edition, chapter 48 - **Learning and Memory**