Methods of neuroimaging

Lecture 6

Aim and Outline

Aim is study of classical and modern methods of functional neuroimaging

- Invasive and non-invasive methods
- Registration of single units activity
- Non-invasive methods
  - Hemodynamics
  - Electric activity of brain

Neuroimaging

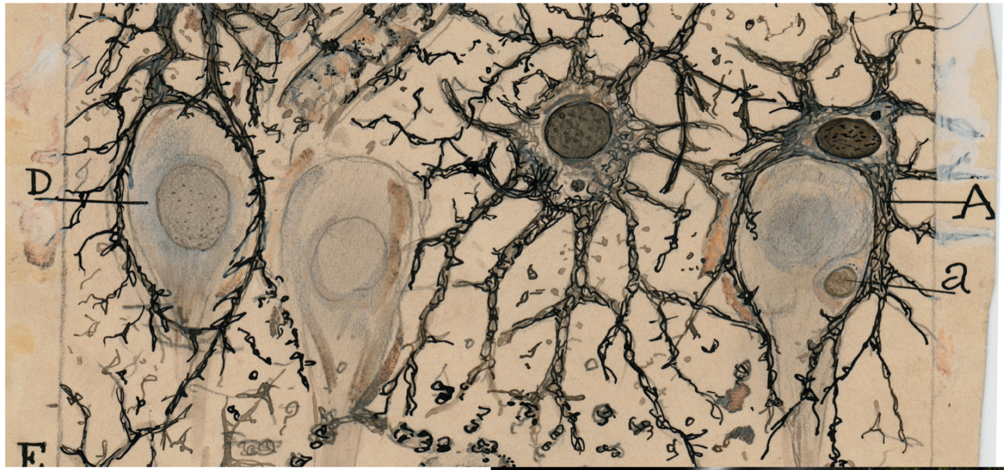
- The active use of various types of neuroimaging is a new paradigm in neurophysiology

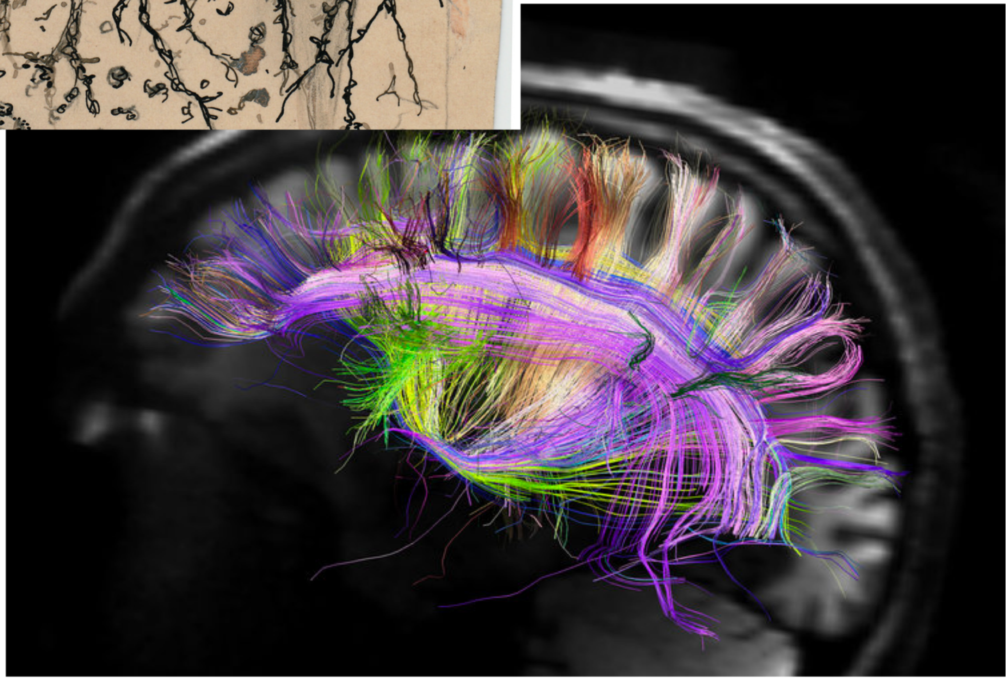
- **Neuroscience:** restoration of the connectome of the brain, detecting patterns of brain activity during rest-state or making the cognitive tasks, analyzing in vivo the dynamics of individual neurons and the brain as whole
- **Medicine:** detecting damage to brain tissue, brain injuries, and today it is increasingly being used to diagnose behavioral and cognitive problems (for example, neurodegenerative changes in the brain related to the patient’s age), metabolic disorders and brain lesions on a smaller scale (for example, detection of epileptic foci).

Structural and functional neuroimaging

- Imaging the anatomical infrastructure to support neural interaction is the complex network of axonal projections (the human connectome)

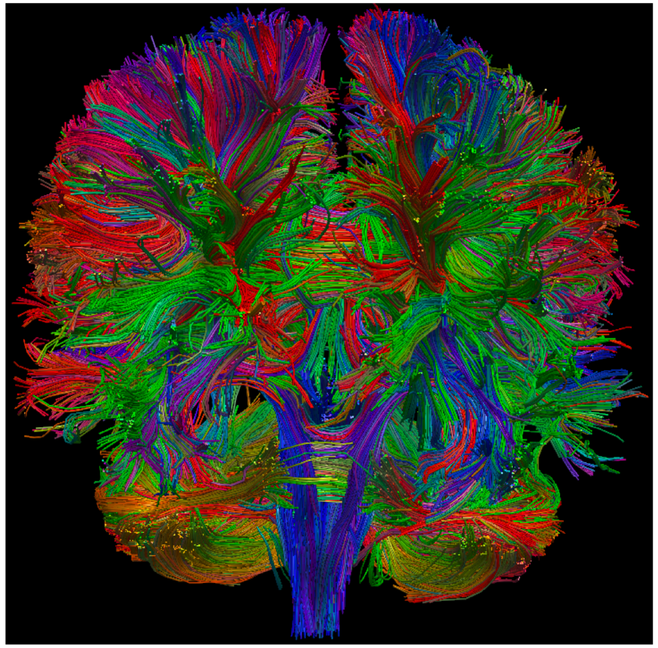
- Imaging brain function in real time (not just the structure of the brain)

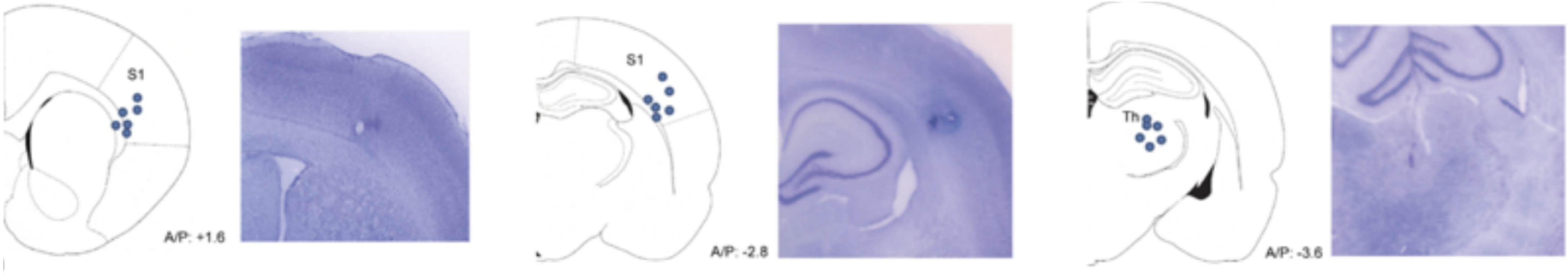




Imaging brain connectome

- Macroscale structural connections of the brain can be reconstructed **in vivo** using diffusion-weighted imaging (DWI). This technique estimates the diffusion of water molecules in the brain, which is constrained by large-scale white matter fiber tracts, allowing these tracts to be delineated
- Slices of the brain in vitro that allow us to evaluate the characteristics of the brain or our surgery





The brain is bloody and electric

Blood

- **increase in neuronal activity –> increase in metabolic demand for glucose and oxygen –> increase in cerebral blood flow (CBF) to the active region**
- Blood is an indirect, slow (because blood flows slowly), measure of neural activity

Electricity

- **the brain works because neurons communicate with each other and they do this by sending out tiny electrical impulses**
- Electricity is a direct measure of neural activity

Invasive and non-invasive recording from brain

Invasive

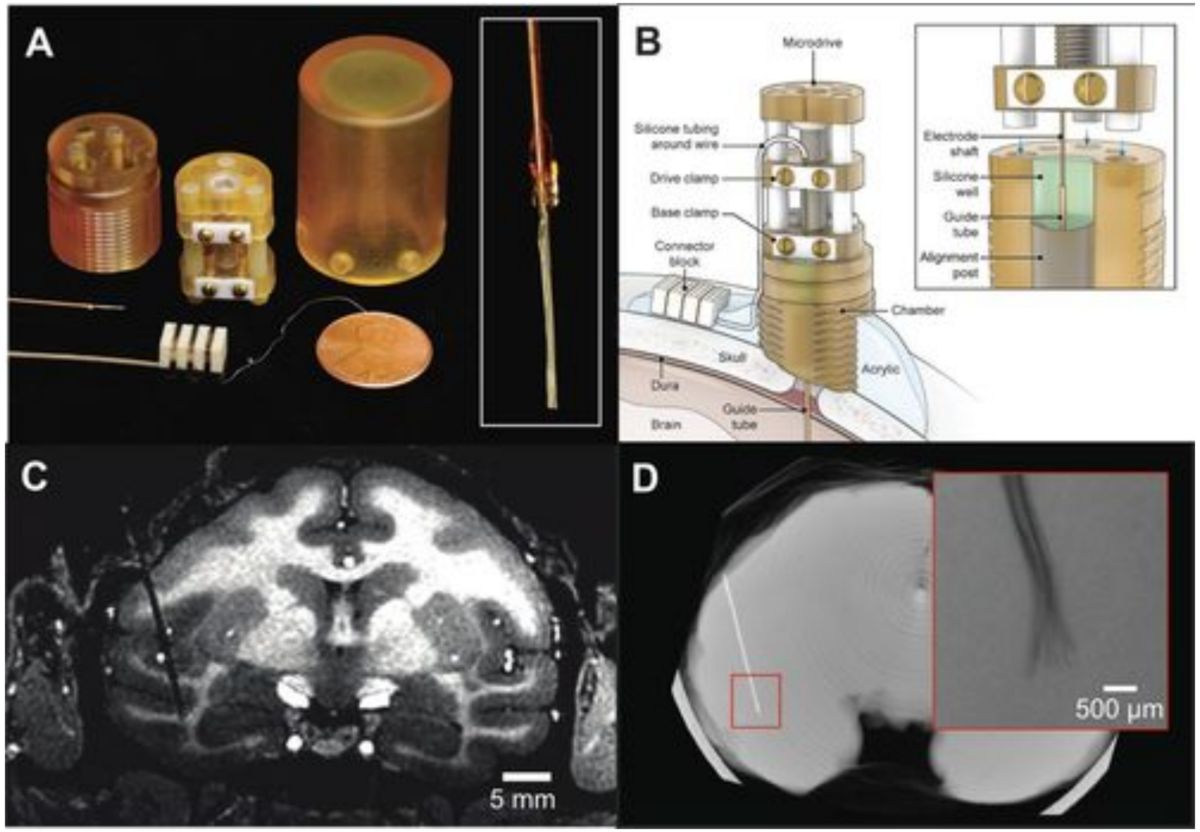
- Invasive method of monitoring of the brain activity when electrodes is placed (implanted) inside the brain.

Non-invasive

- Non-invasive methods is based on recording brain activity without some damage of CNS or its integument

Implanted systems

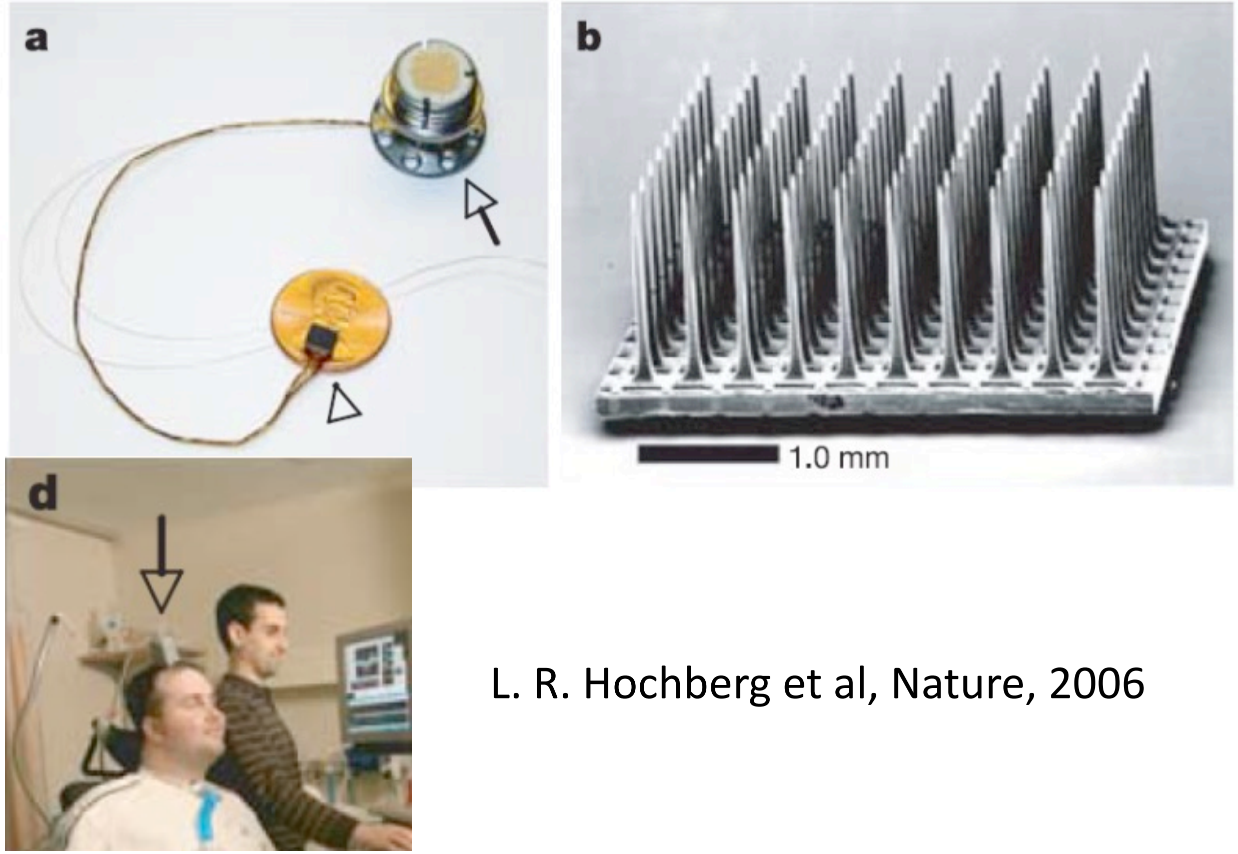
- The simplest scheme is a set of wires implanted in the region of interest.
- Initially, this is a formed wire harness.
- Due to the resistance of the gray matter, the wires diverge.



D. B. T. McMahon et al, JNP, 2014

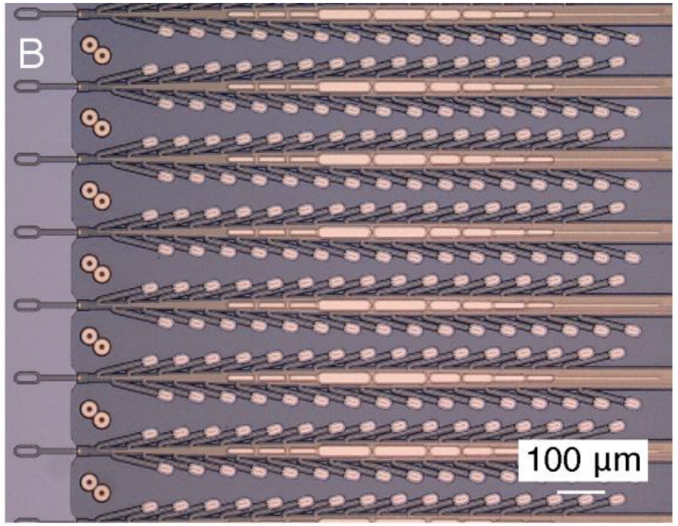
Implanted systems

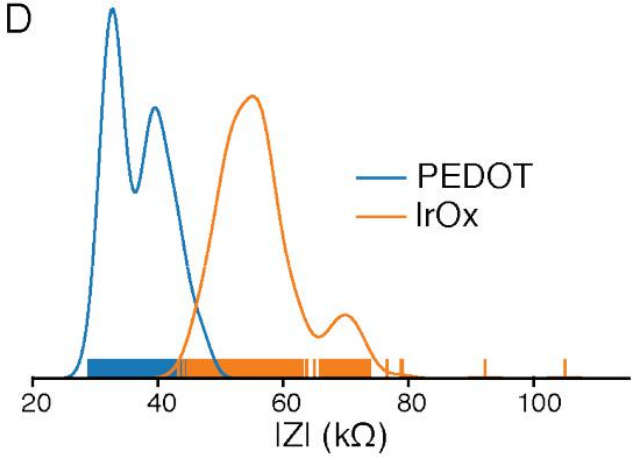
- More accurate method is the use of multi-electrode arrays
- Miniature systems
- The number of electrodes can reach up to 300 pieces
- Widely used when working with people with complete paralysis (e.g. the last stage of amyotrophic lateral sclerosis or severe form of cerebral palsy)

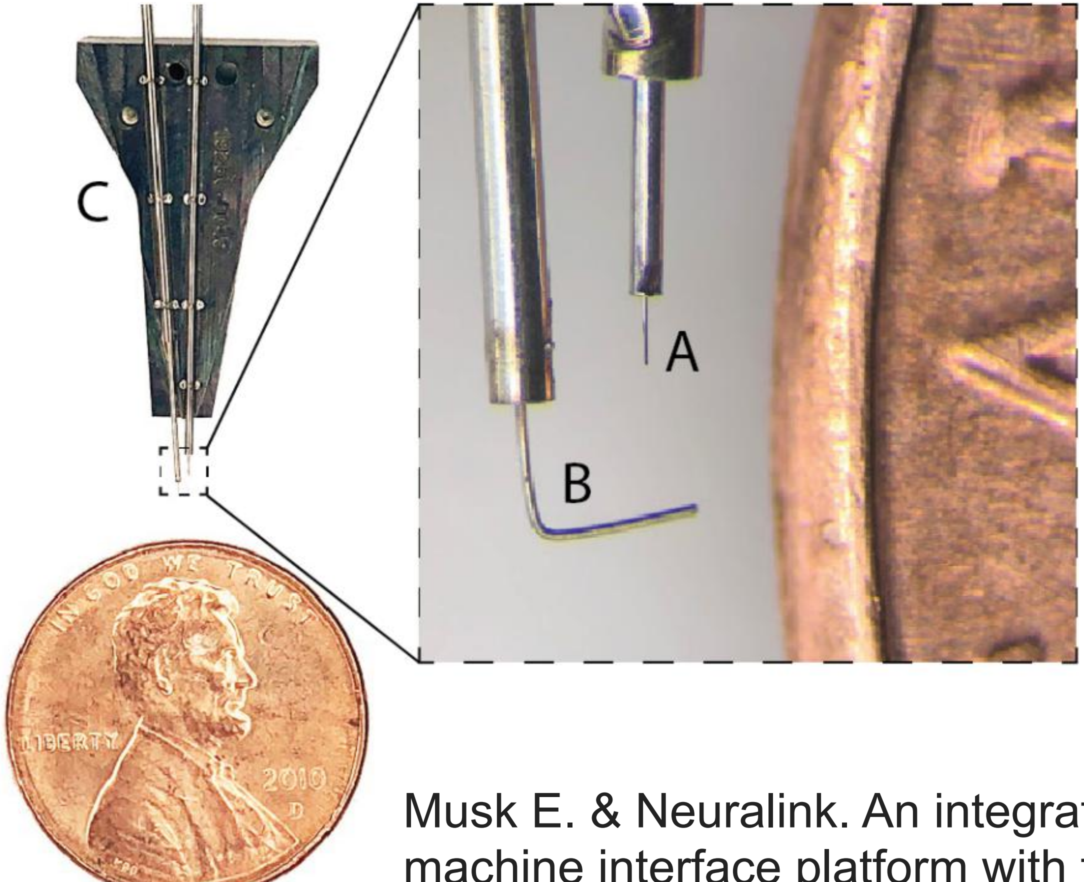


L. R. Hochberg et al, Nature, 2006

Integrated platform with thousands channels: Neuralink & Elon Mask

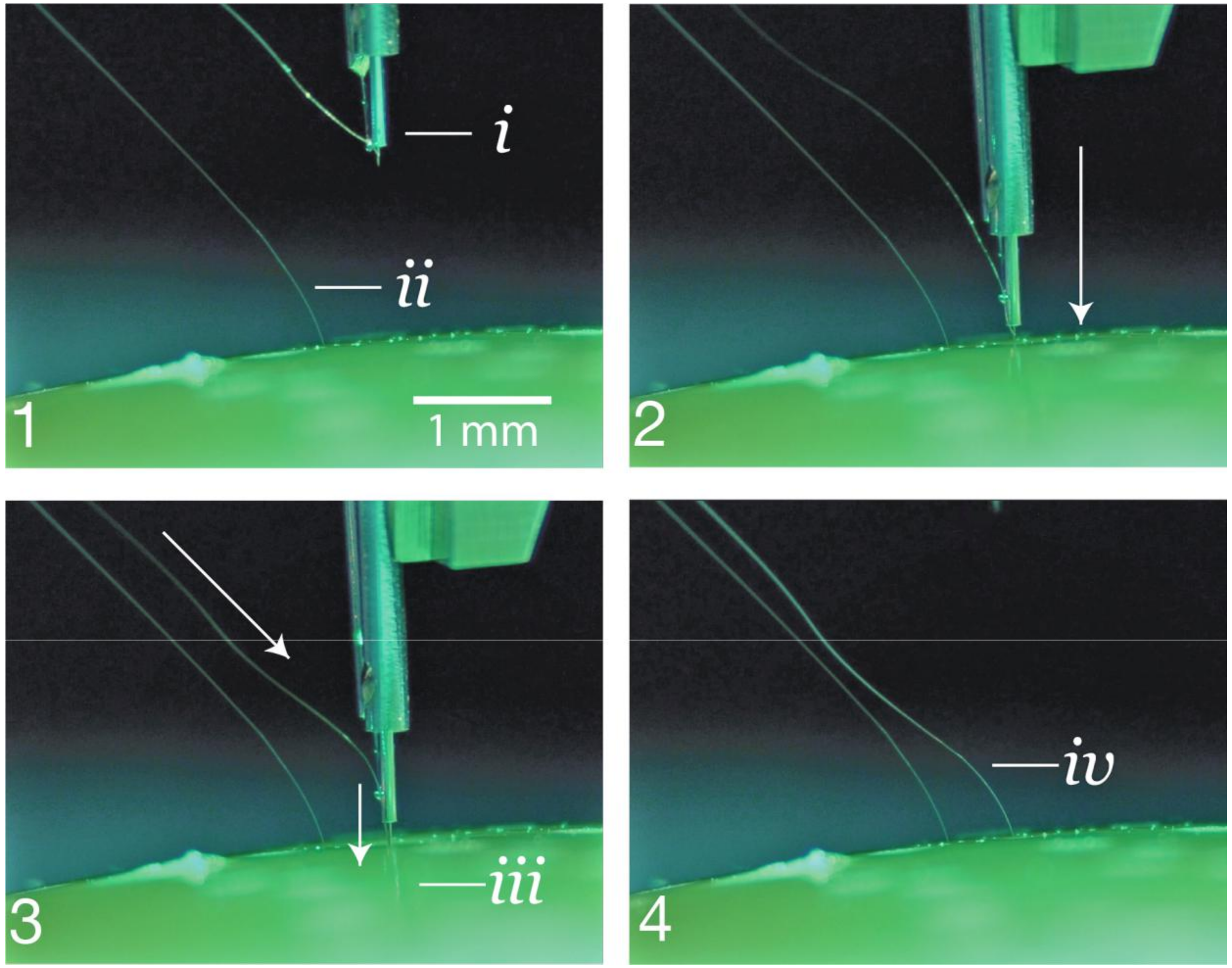






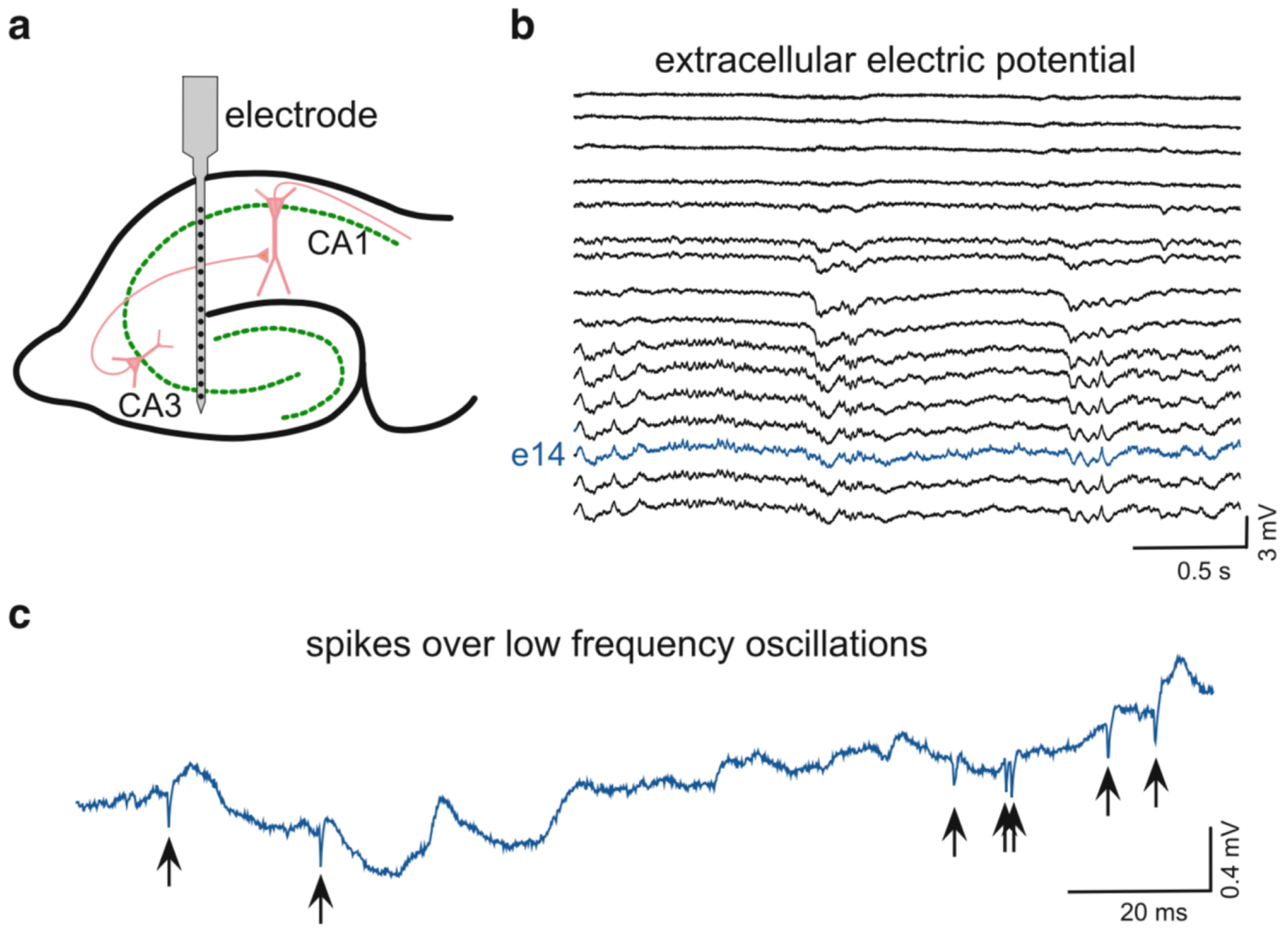
Musk E. & Neuralink. An integrated brain-machine interface platform with thousands of channels //Journal of medical Internet research. 21 (2019) e16194.

Integrated platform with 4000-channels: Neuralink & Elon Mask



Example of extracellular recordings in the CA1–CA3 regions of the rat hippocampus

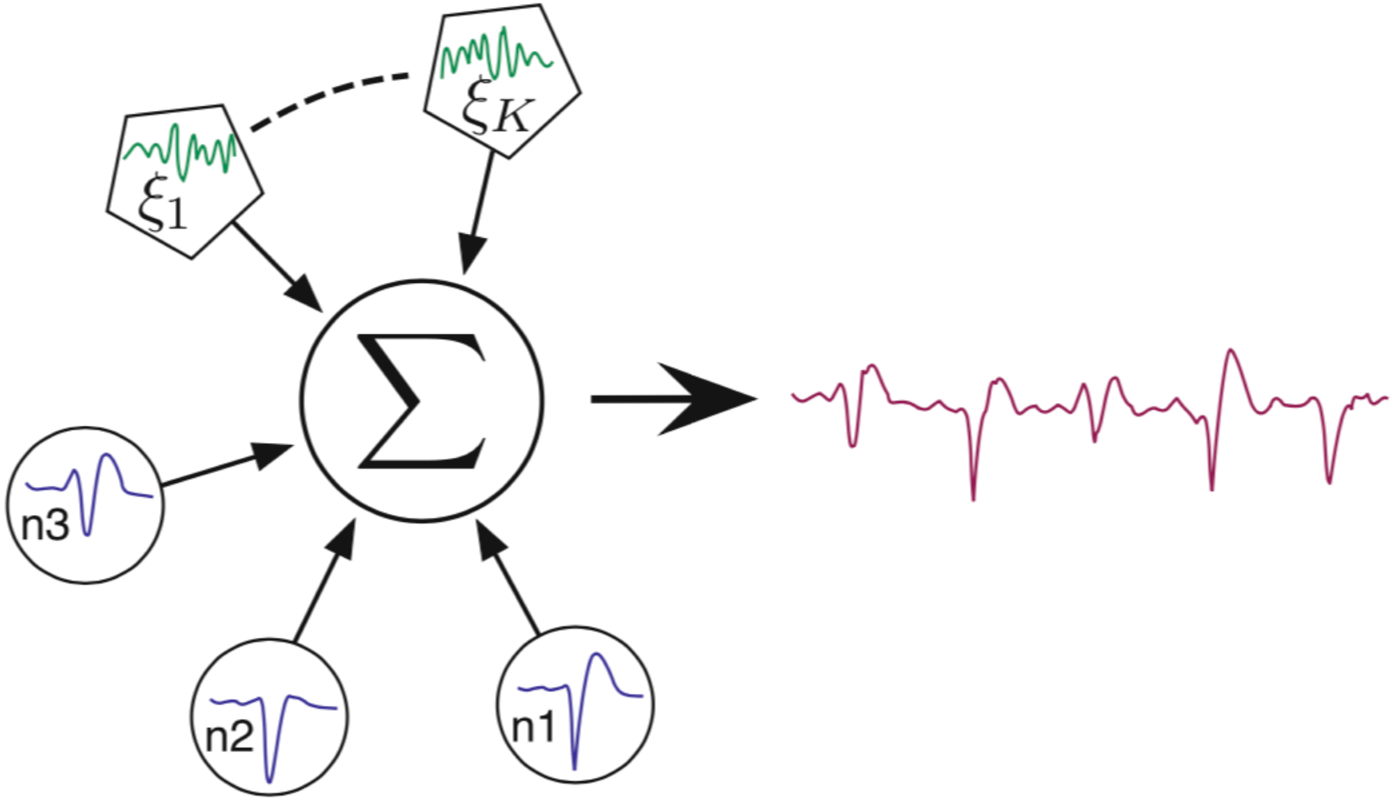
- In vivo experiments usually provide recordings of the extracellular field potential that contains multi-unitary activity coming from nearby neurons
- This activity, besides spikes, contains low-frequency oscillations (<1 kHz), so-called **local field potentials** (LFPs) produced by synaptic currents in principal cells



(**a**) Sketch of the recording setup. A linear micro-electrode with 16 tips is lowered into the hippocampus along the main cell axis. (**b**) Epoch of electrical potentials recorded by the electrode (16 traces). (**c**) Zoomed trace from the electrode tip #14. Several neuronal spikes can be observed with the naked eye (*arrows*)

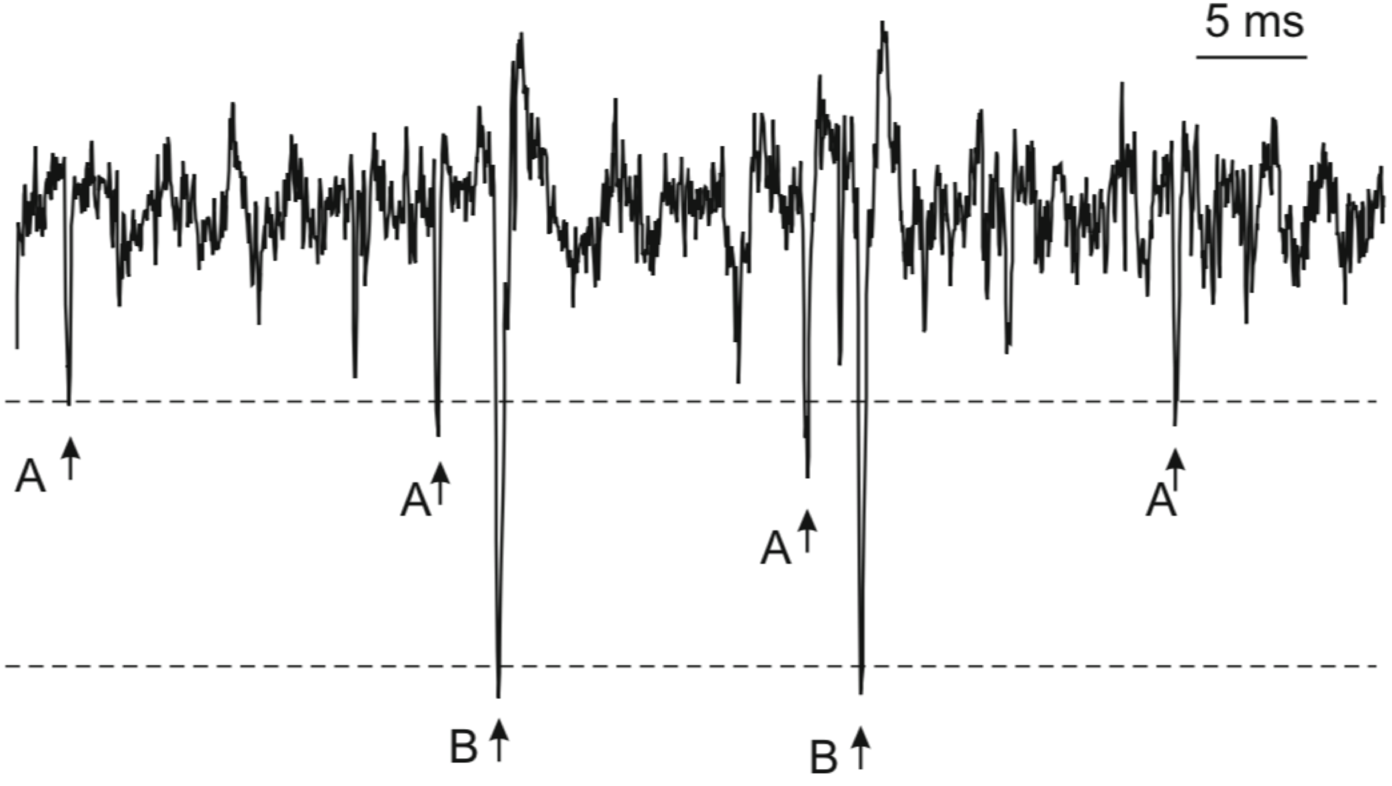
Spike sorting problem

- The extracellularly recorded signal is a sum of spikes generated by neurons 1–3 and fluctuations produced by noise sources ξ_1 ,..., ξ_K

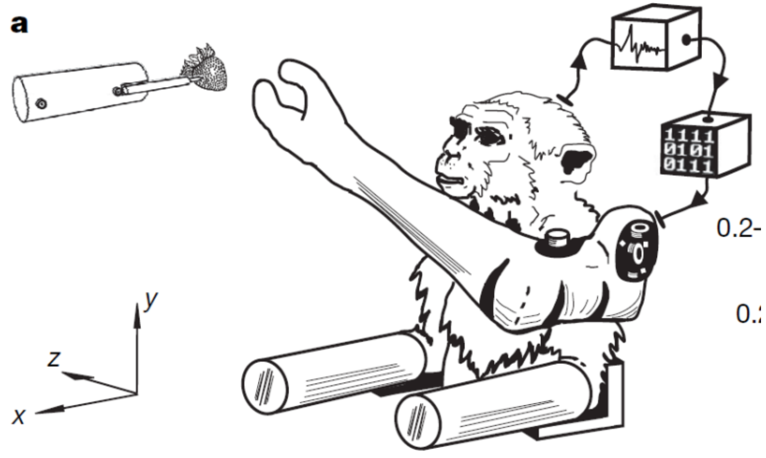


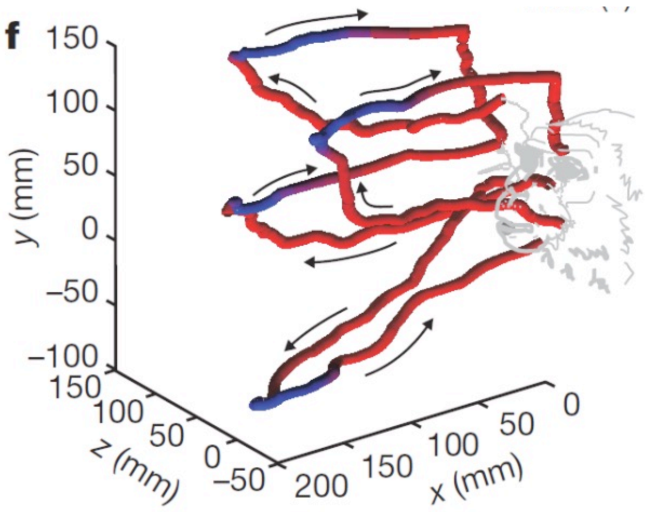
Spike sorting problem

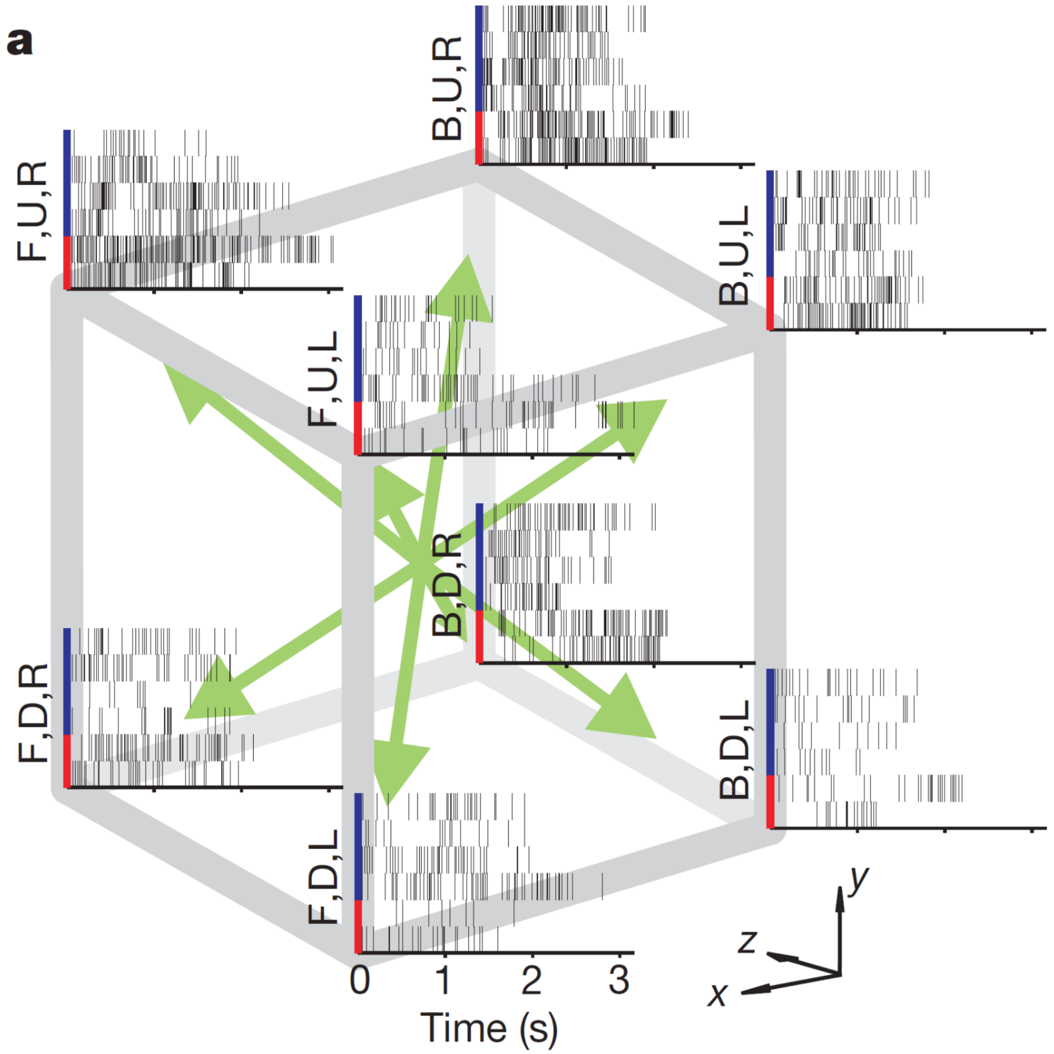
- A typical example of the extracellular potential recorded from the rodent hippocampus. The simplest way to sort spikes (marked by *arrows*) is by amplitude thresholding (two *dashed lines*)



‘Mental’ control of robotic hand







M. Velliste, S. Perel, M. C. Spalding, A. S. Whitford, A. B. Schwartz, Nature 453 (7198) (2008) 1098

Electrocorticography (ECoG) or intracranial EEG (iEEG)

- **Invasive method of monitoring of the brain activity when electrodes is placed inside the brain.**
- ECoG has high spatial resolution, wide bandwidth, high amplitude and small sensitivity to artifacts.
- ECoG signals are recorded by placing a series of electrodes (usually multi-electrode matrices) under the skull directly on the surface of the cerebral cortex

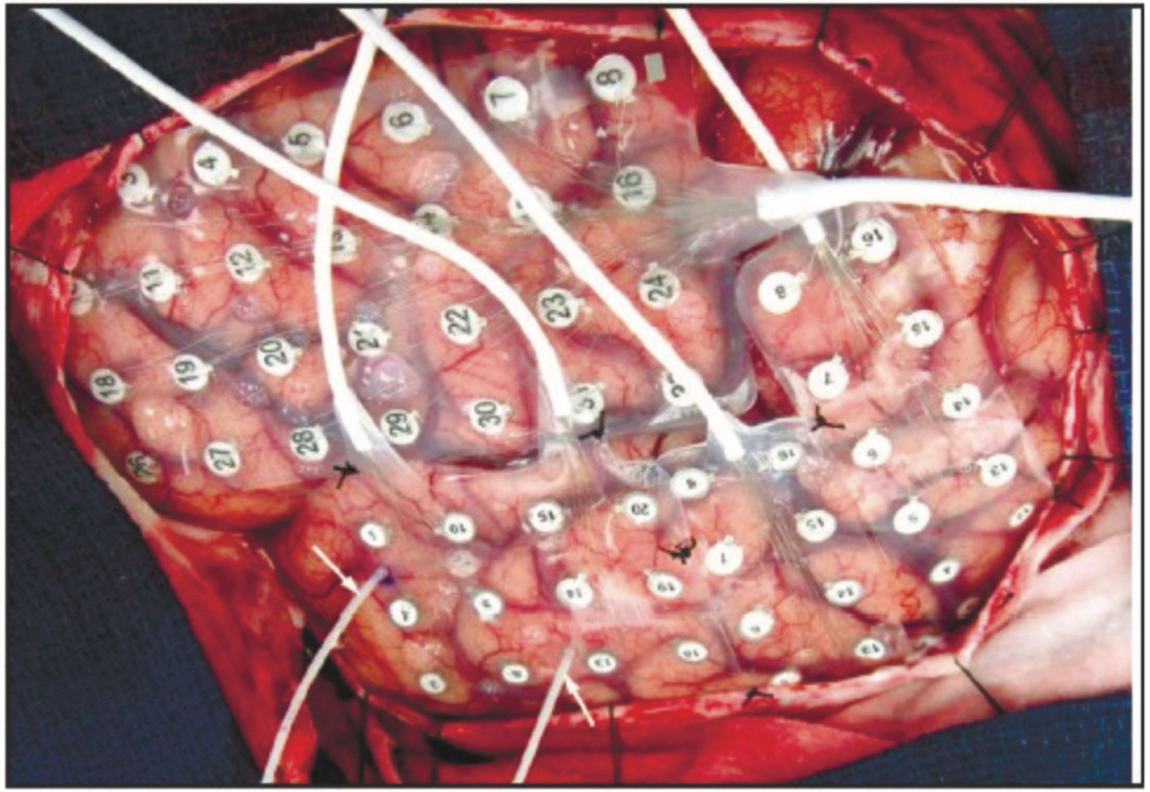
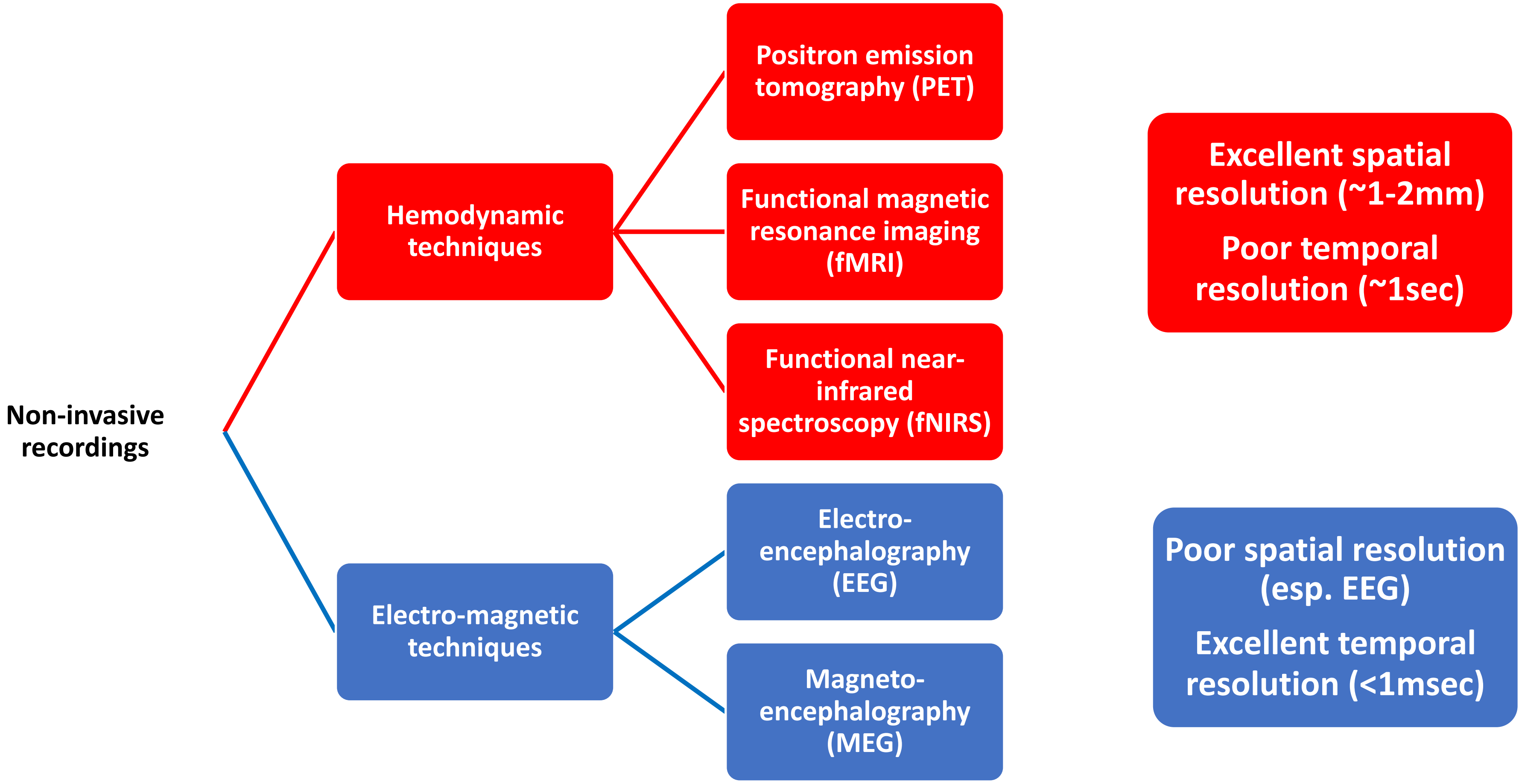


Photo taken during neurosurgical operation, showing the left hemisphere of the brain with multielectrode matrices superimposed on its surface

Non-invasive recording from brain



Hemodynamics methods history

- Roy and Sherrington first showed in 1890 that brain stimulation led to a local increase in blood flow to active populations of neurons.
- Landau and others subsequently used radioactive tracers to measure regional cerebral blood flow (rCBF) in animals (1955), and in 1963 this technique was first applied to humans.
- The spinning atom effect is known as nuclear magnetic resonance (NMR). It was first observed during the late 1930s, but medical applications were not found for the NMR technique until the 1970s. In 1973, Paul Lauterbur showed NMR could produce body images. British scientist Peter Mansfield developed the mathematical processes that turned MRI into a useful rapid imaging technique
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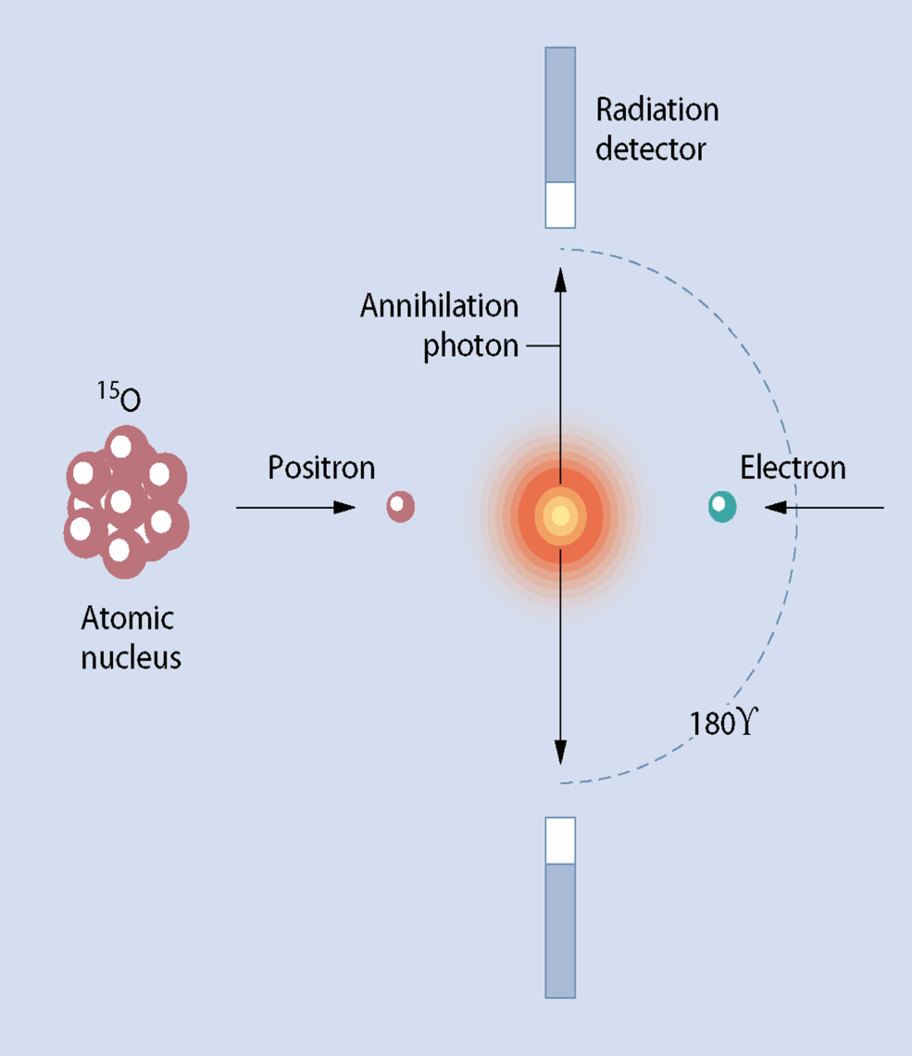
PET (Positron Emission Tomography)

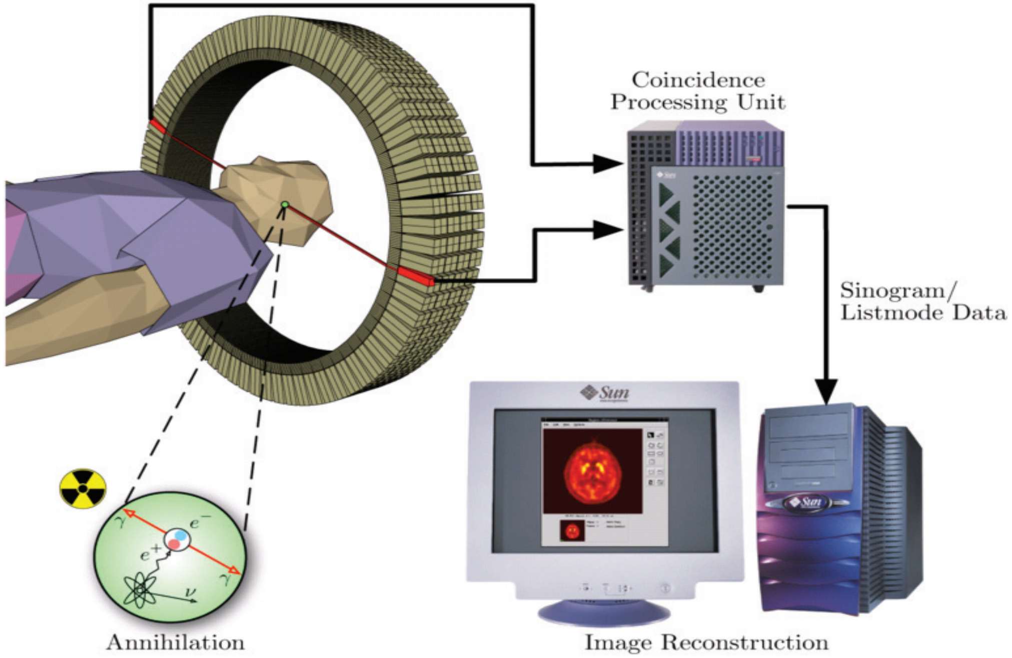
- Radioactive labeling of some compound that is familiar to the body (such as glucose or water).
- The radioactive material (PET radioisotopes) - a positron emitting radionuclide (e.g., 2-deoxyglucose,

  ^{15}O radioactive oxygen) - is injected.
- PET images the electromagnetic radiation induced by the decay of the PET radioisotopes.



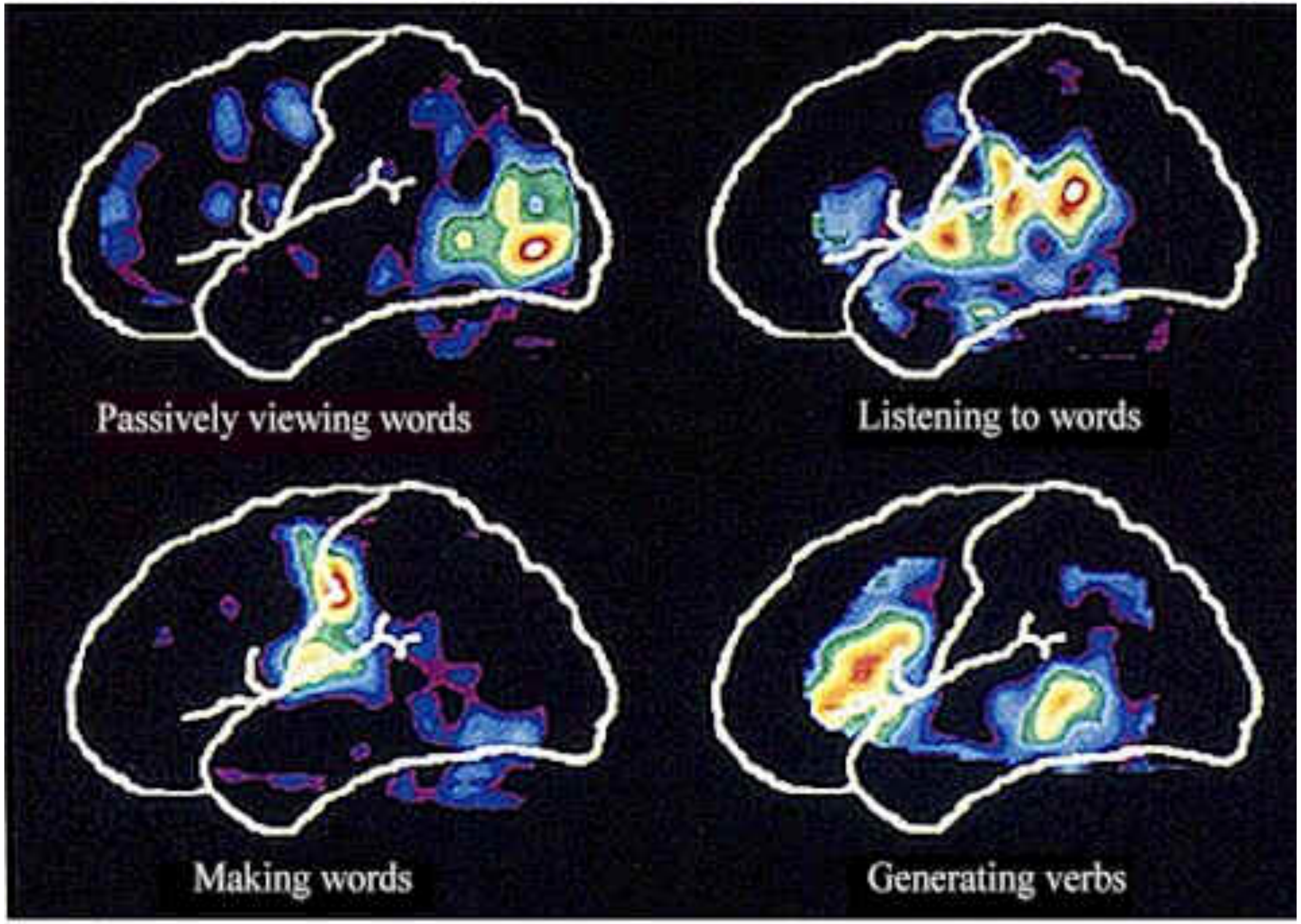
PET scans

- Positrons interact with electrons which produce photons (gamma rays) traveling in opposite directions.
- PET scanner detects the photons.
- Computer determines how many gamma rays from a particular region and a map is made showing areas of high to low activity.



Examples of PET images

- Dependent measure: regional Cerebral Blood Flow (rCBF).
- Spatial resolution about 4-10 mm throughout the brain.
- Temporal resolution very bad (~30-40 sec).



PET pros and cons

PRO

- Very good spatial resolution

CONs

- Basically no temporal resolution
- Invasive.
- Cost; PET facilities require not only a PET camera but also a cyclotron, which is used to produce the radioactive tracers

These days it’s hard to get human subjects approval for PET studies, given that noninvasive alternatives exist: fMRI (based on MRI).

The greatest advantage of PET over the more recent method is the choice of radioactive tracer

- Researchers can synthesize radiopharmaceutical compounds that bind to dopamine or serotonin receptors (C-11 or F-18 N-methylspiperone), opiate receptors (C-11 carfentanil), etc.
- PET is likely to continue to be important for understanding the role of various neurotransmitters in cognition.

Magnetic Resonance Imaging (MRI) and functional MRI (fMRI)

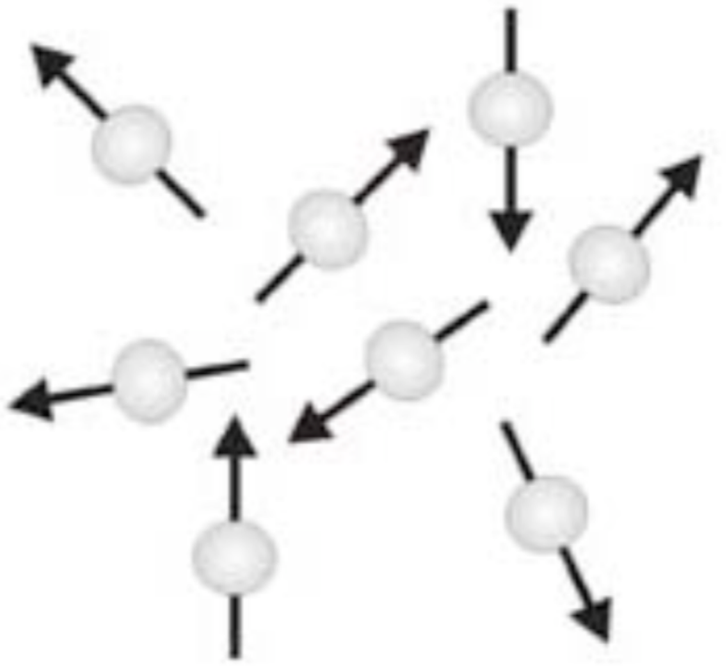
- An MRI scanner uses a strong magnetic field and radio waves to create pictures of the tissues and other structures inside the brain
- An MRI scanner can create clear detailed pictures of the structure of the brain and detect any abnormalities or tumours.
- Sometimes a dye, or tracer, such as gadolinium may be introduced via a vein in the arm, to improve contrast in the image.

A 3 tesla clinical MRI scanner

Basics of MRI

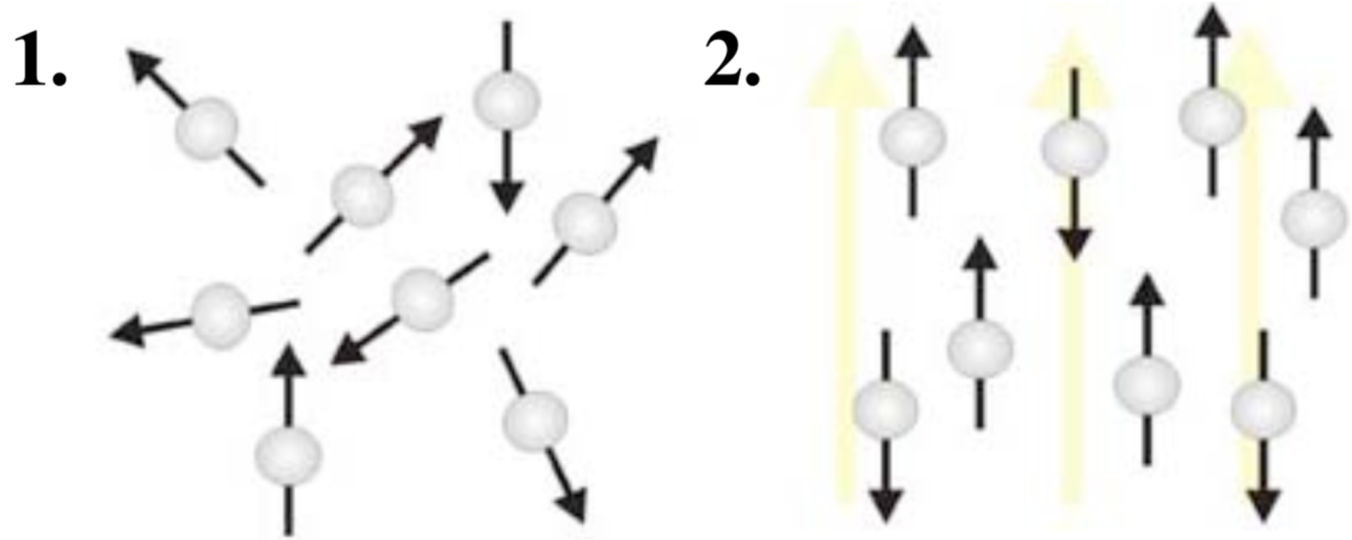
Our bodies are mostly water and have a high concentration of hydrogen nuclei (called protons)

- The nuclei of hydrogen atoms (called protons) normally point randomly in different directions.



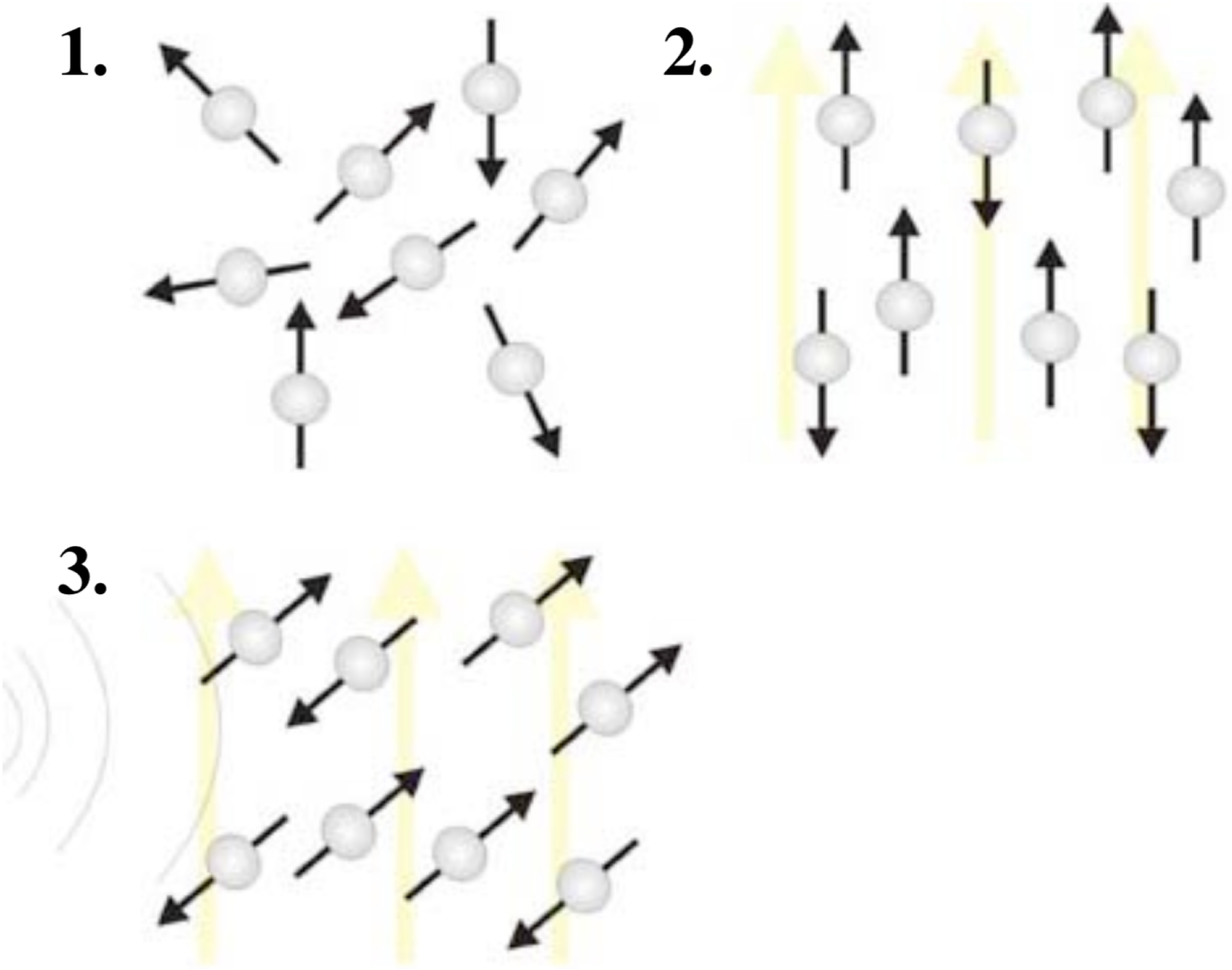
Basics of MRI

- When exposed to a strong static magnetic
  field, the nuclei line up in parallel formation, like rows of tiny magnets.
- In an MRI set-up, a strong external static magnetic field is applied across the brain in order to line up the hydrogen nuclei. (*This field can be up to 80 000 times stronger than the earth's magnetic field.*)



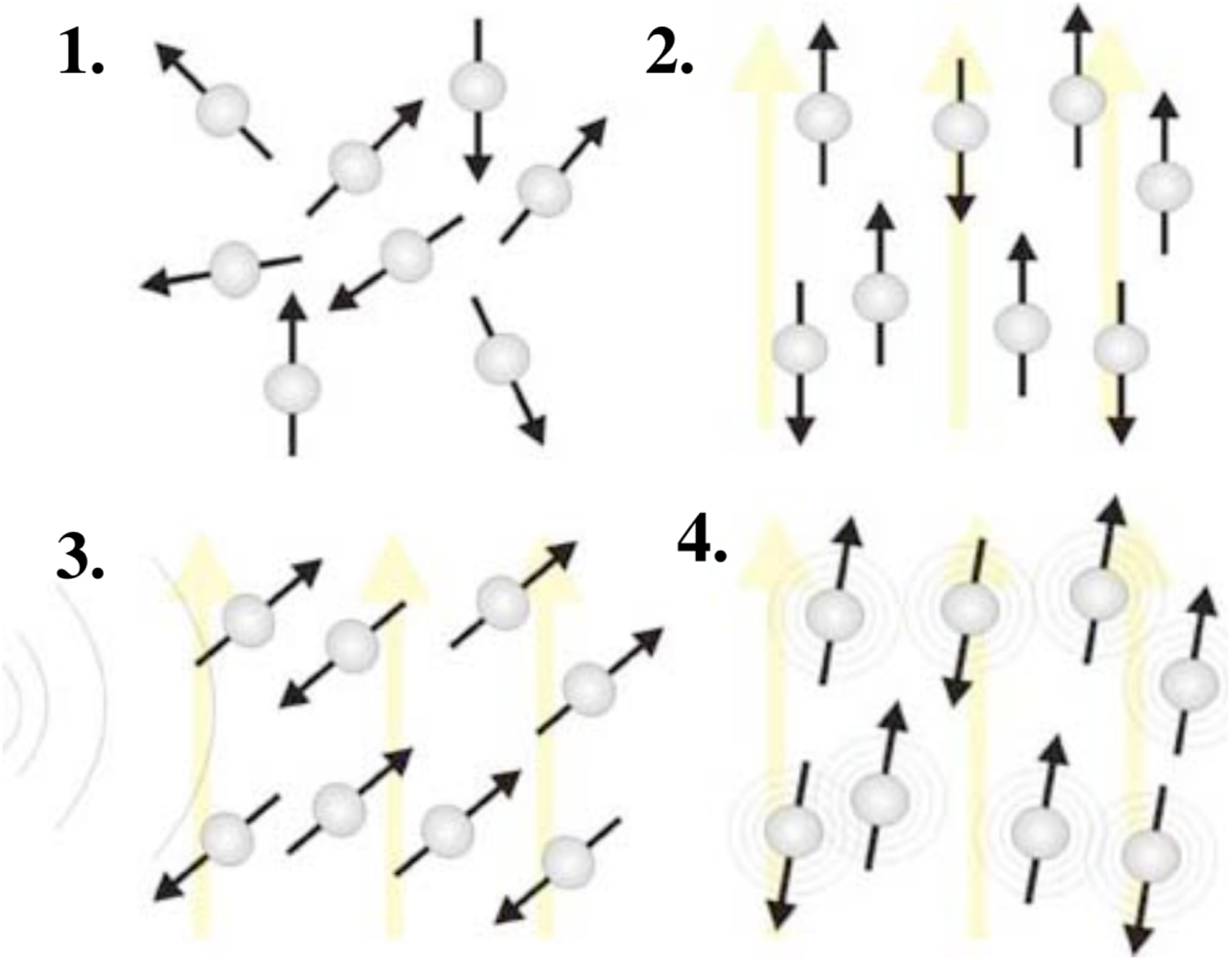
Basics of MRI

- Then this parallel formation, called *equilibrium*, is disturbed by sending out radio waves from the MRI machine

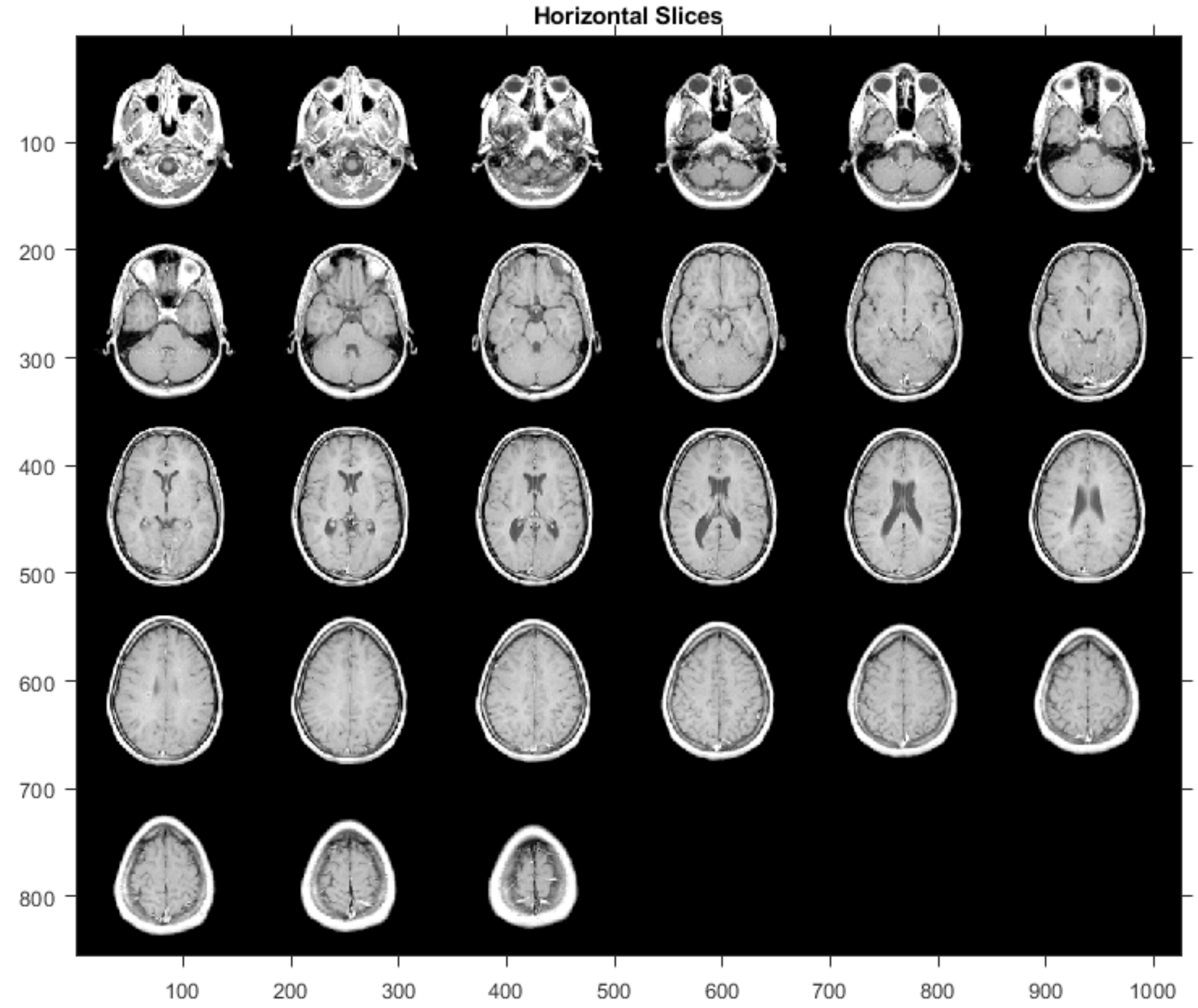


Basics of MRI

- As the hydrogen nuclei fall back into alignment, they produce a detectable radio signal.
- The MRI scanner is tuned to detect radiation emitted from the hydrogen molecules.
- Different types of tissue produce different RF signals
- For example, tissues that contain little or no hydrogen (such as bone) appear black. Those that contain large amounts of hydrogen (such as the brain) produce a bright image.



MRI image example



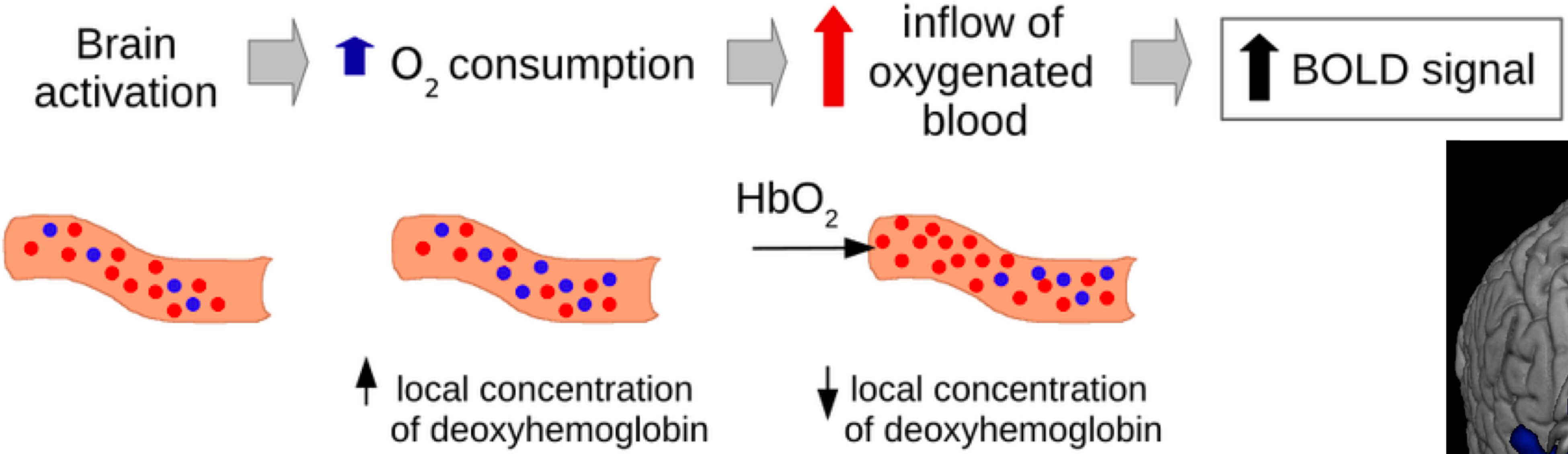
Functional magnetic resonance imaging (fMRI)

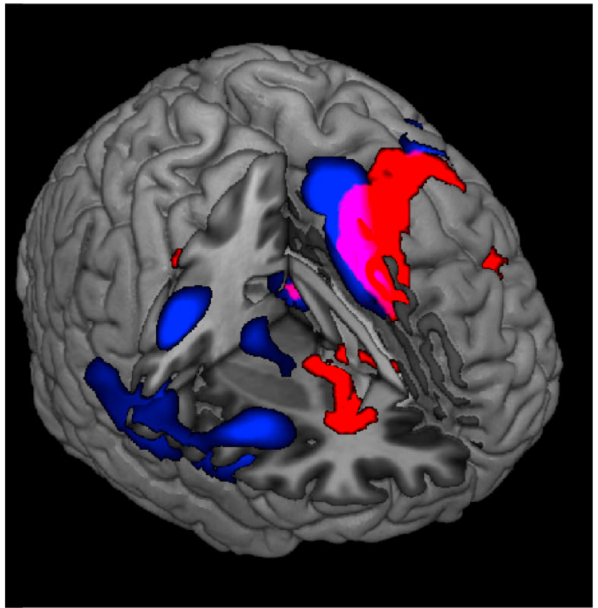
- Functional magnetic resonance imaging can show which part of the brain is active, or functioning, in response to the patient performing a given task, by recording the movement of blood flow.

- Different molecules have different magnetic resonance and two components of blood are tracked to observe brain activity.
- Hemoglobin in the blood carries oxygen; oxyhemoglobin, around the brain and when it is used up, it becomes desoxyhemoglobin.

Blood oxygenation level–dependent (BOLD) imaging

The BOLD signal measures the local changes in blood oxygenation ocurring during brain activity:

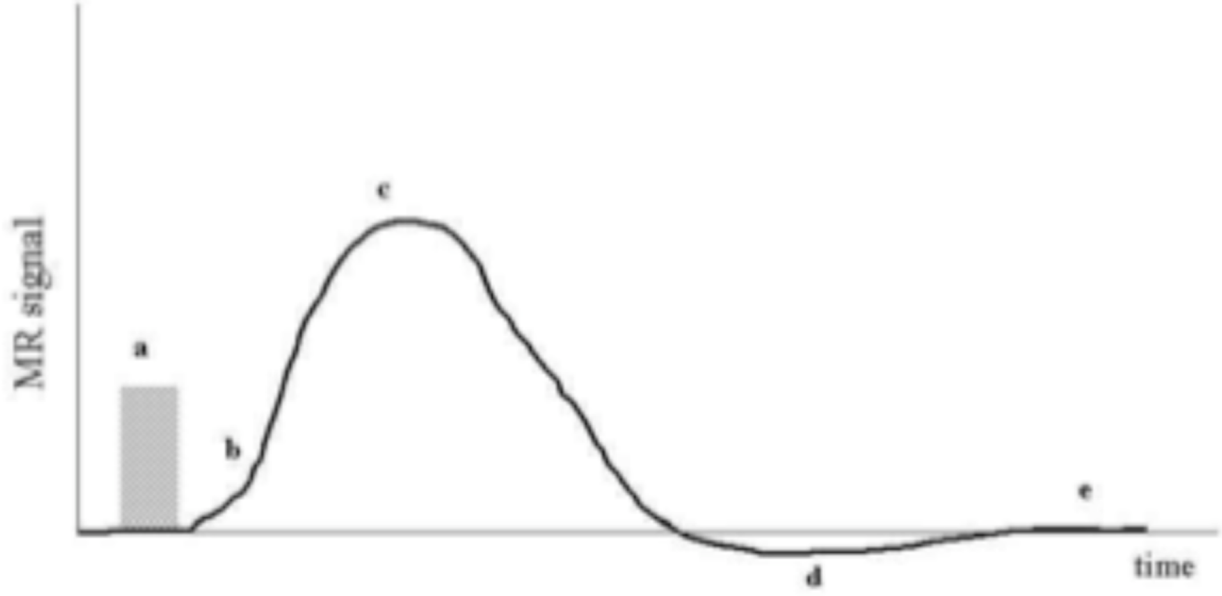




Hemodynamic lag

Lag (3-6 seconds):

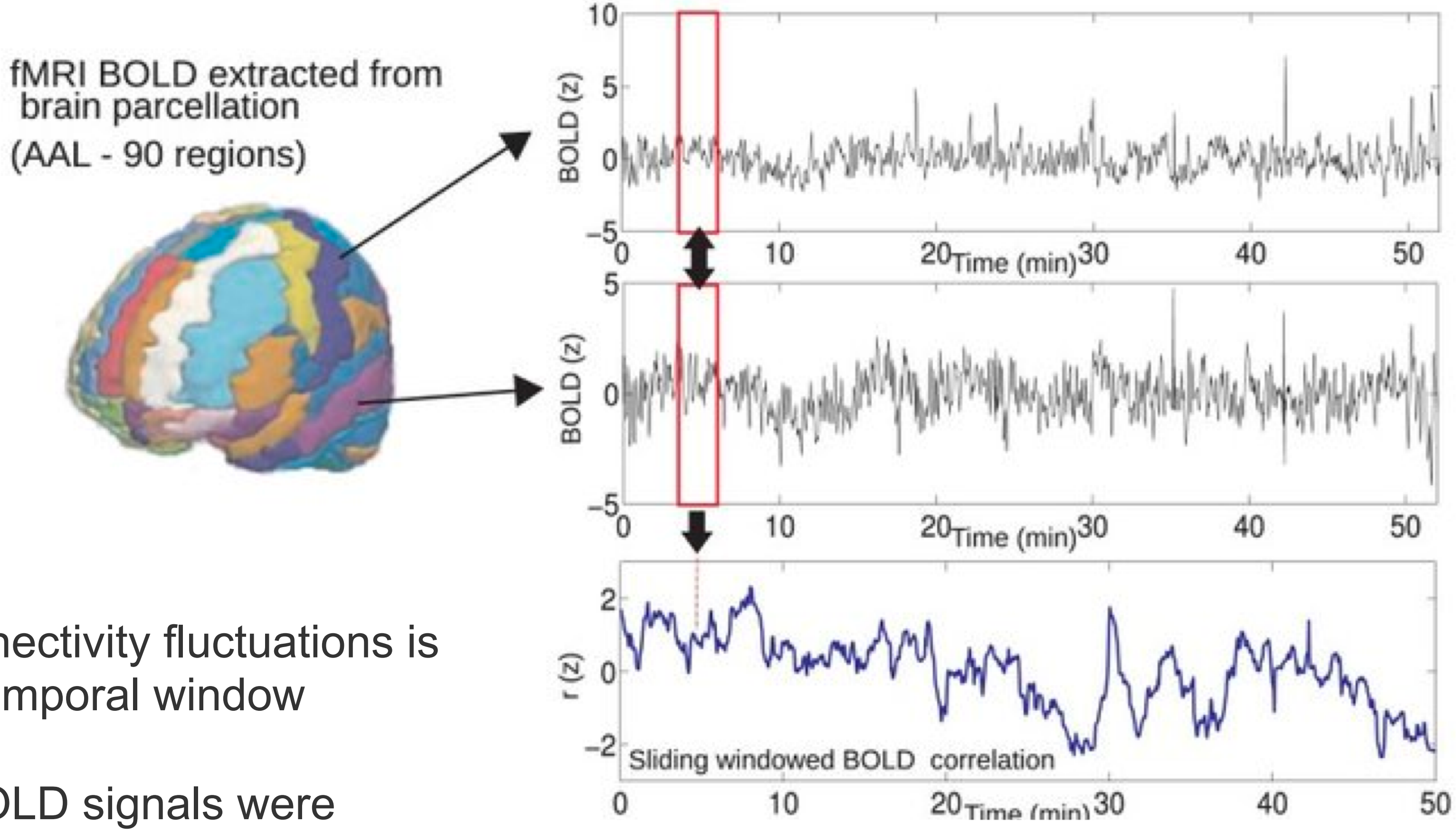
- short stimulus
- rise, 6-9 s
- return to baseline, 8-20 s
- undershoot



Temporal resolution: in the order of seconds.

- Fast enough to distinguish between trials (i.e. event-related designs are possible)
- Not fast enough to distinguish between the activation patterns associated with different stages of stimulus processing.

BOLD signal example: rest-state analysis



Method used to compute BOLD connectivity fluctuations is based on analysis of correlation in temporal window

For each pair of regions, average BOLD signals were extracted and correlated using a sliding window of 60 volumes (≈2 min). This resulted in a connectivity estimate over time.

fMRI pros and cons

PROs

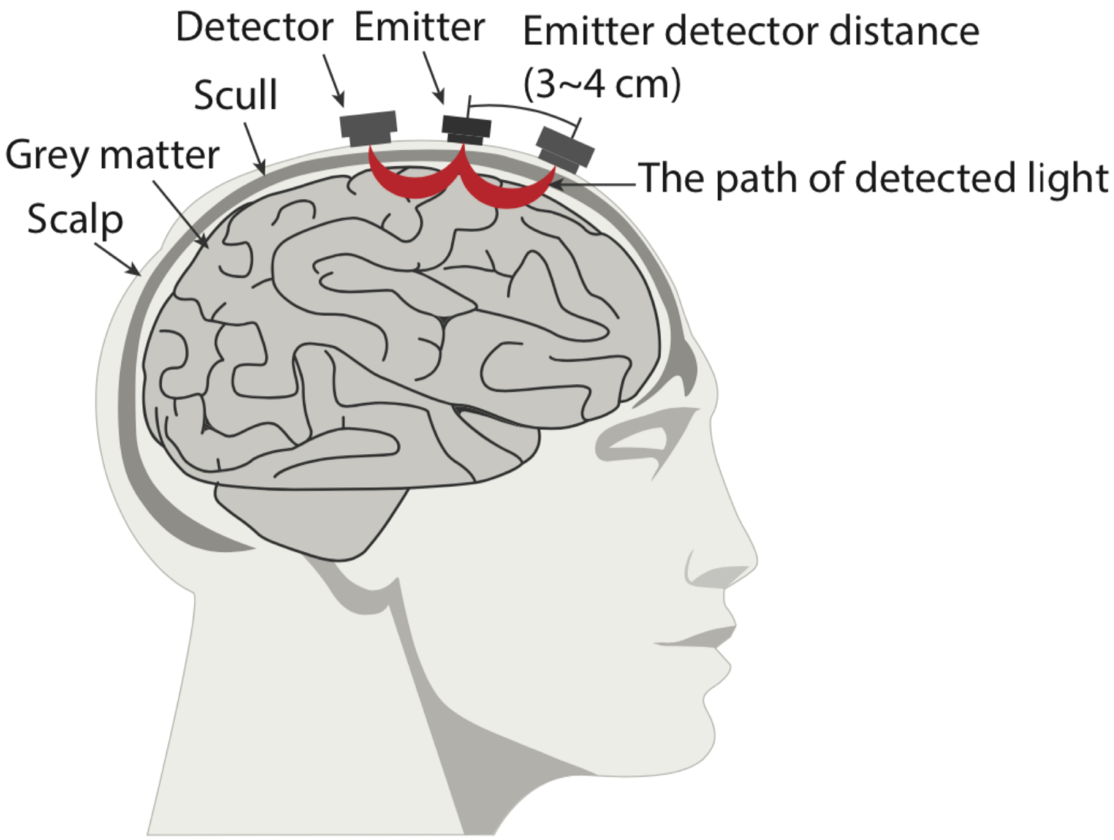
- No radioactive tracers are needed
- Spatial resolution: 3-6mm (in most applications)

CONs

- Poor temporal resolution
- here is no way to register activity during normal daily activities

Functional near-infrared spectroscopy

- Using fNIRS, brain activity is measured through hemodynamic responses associated with neuron behaviour.
- fNIRS is sensitive to the hemodynamic response to cerebral activation.
- This technology also has the ability to distinguish oxy- and deoxyhemoglobin changes.



Non-invasive recording from brain

- **Non-invasive recordings**
  - **Hemodynamic techniques**
    - Positron emission tomography (PET)
    - Functional magnetic resonance imaging (fMRI)
    - Functional near-infrared spectroscopy (fNIRS)
  - **Electro-magnetic techniques**
    - Electro-encephalography (EEG)
    - Magneto-encephalography (MEG)

Hemodynamic techniques:

Excellent spatial resolution (~1-2mm)

Poor temporal resolution (~1sec)

Electro-magnetic techniques:

Poor spatial resolution (esp. EEG)

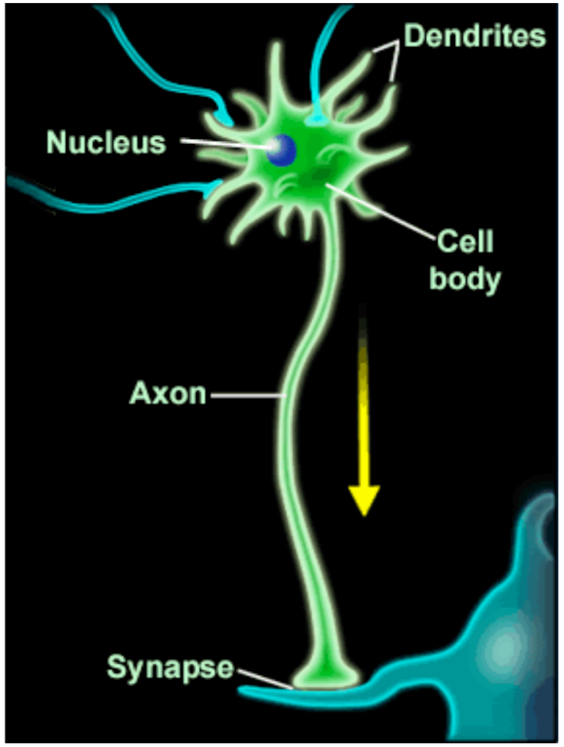
Excellent temporal resolution (<1msec)

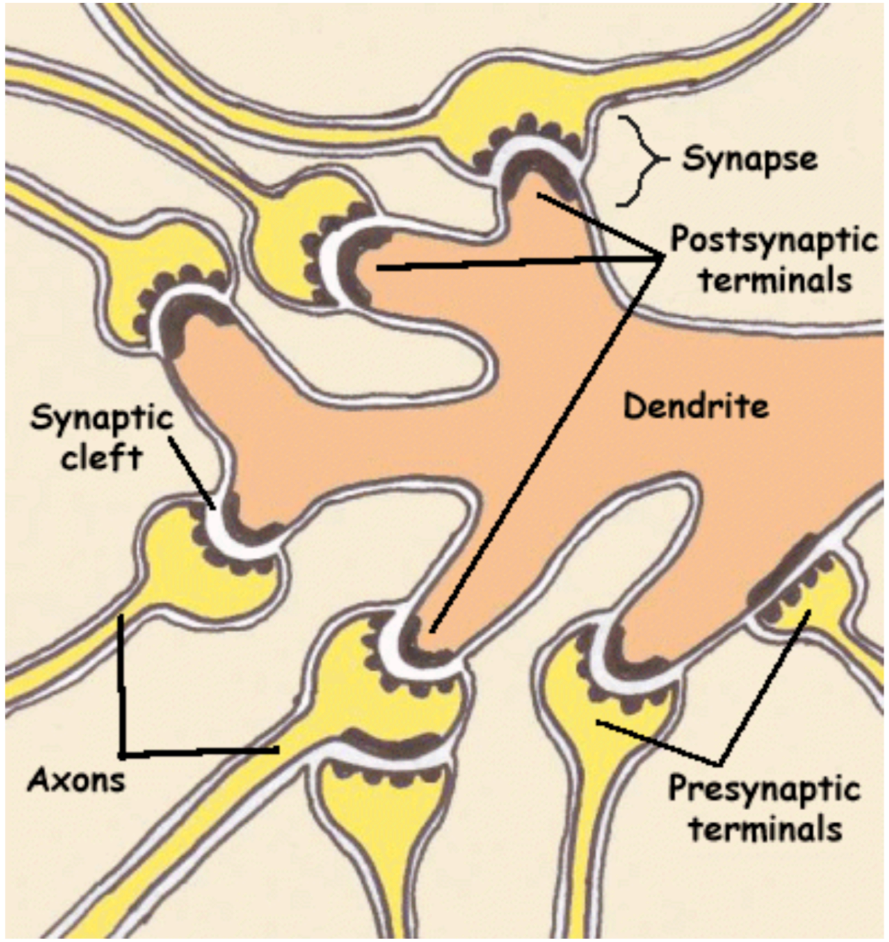
Electromagnetism: EEG and MEG (MEEG)

- Millisecond temporal resolution.
- Neurons communicate with each other thousands of times per second by sending each other tiny electrical impulses
- Populations of neurons are connected into networks
- When networks fire ***in synchrony***, the dynamics of the electric activity can be detected and recorded outside the skull.

Main source of the signal

- Post-synaptic current flow along the dendrites of (pyramidal) nerve cells

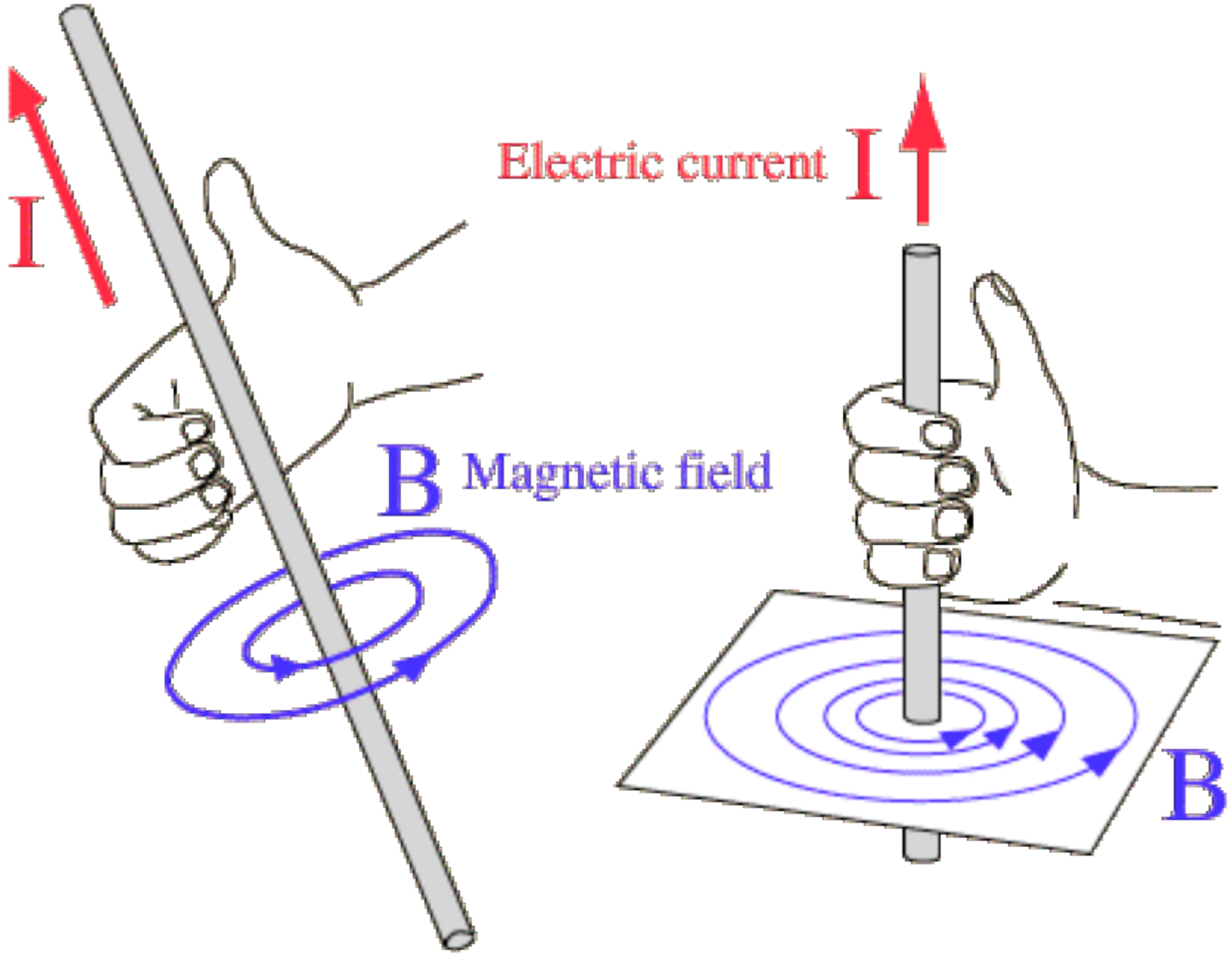




Where does the magnetic field come from?

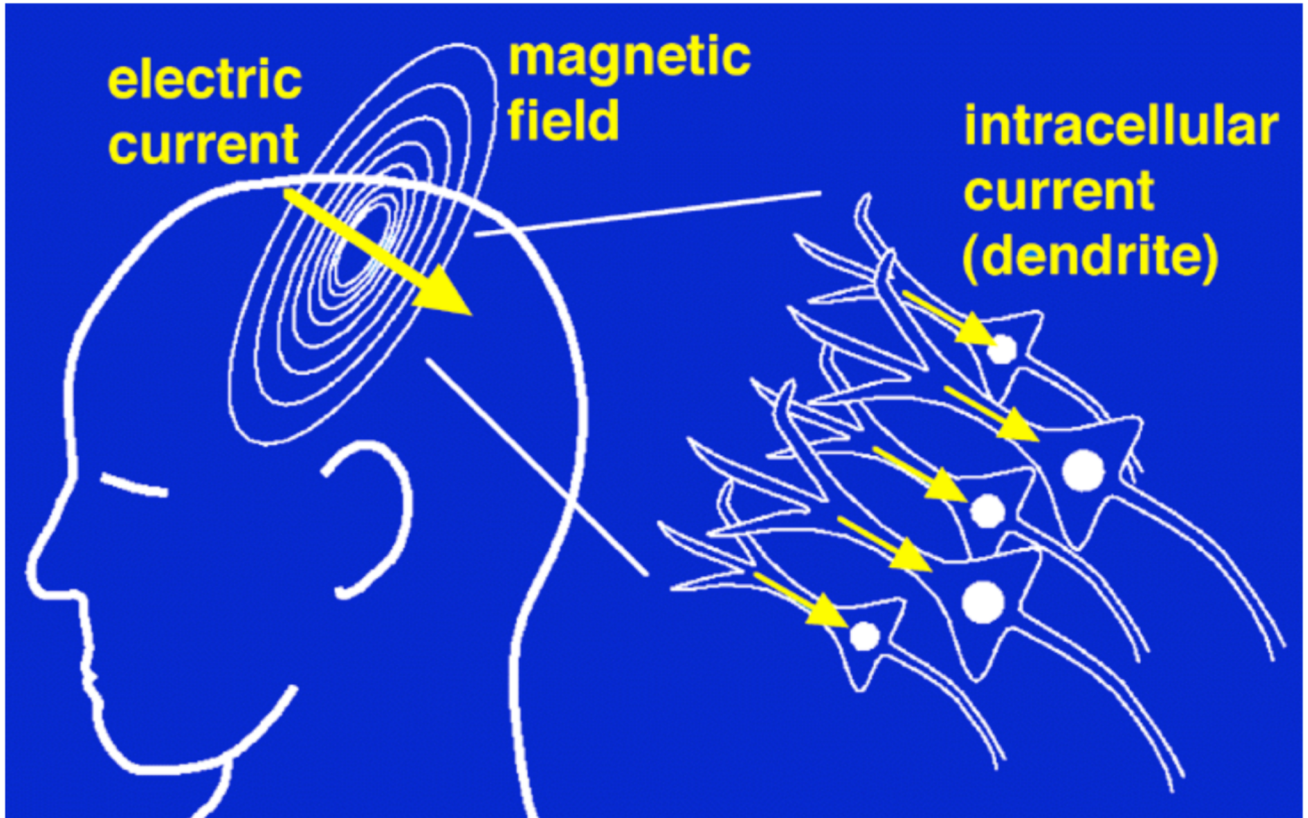
An electric current creates a magnetic field around it

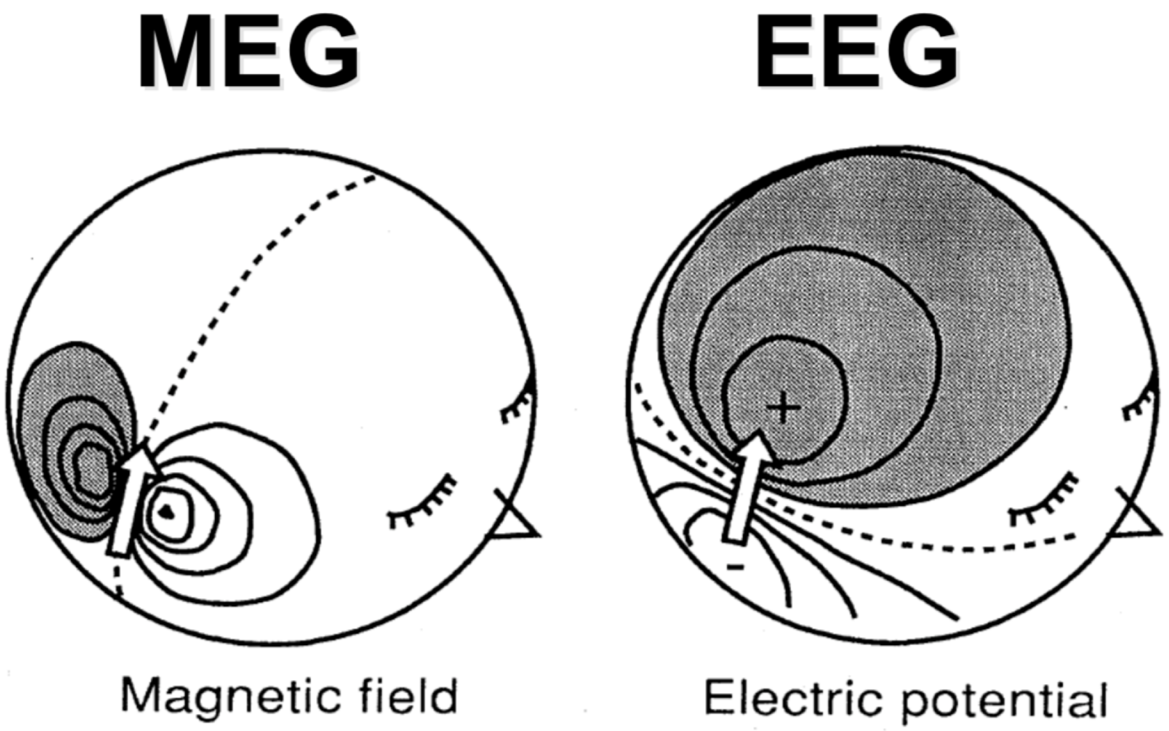
- **The right-hand rule:** When the thumb of the right hand is pointing in the direction of the current, the fingers of the right hand curl in the direction of the magnetic field



Electromagnetics technics

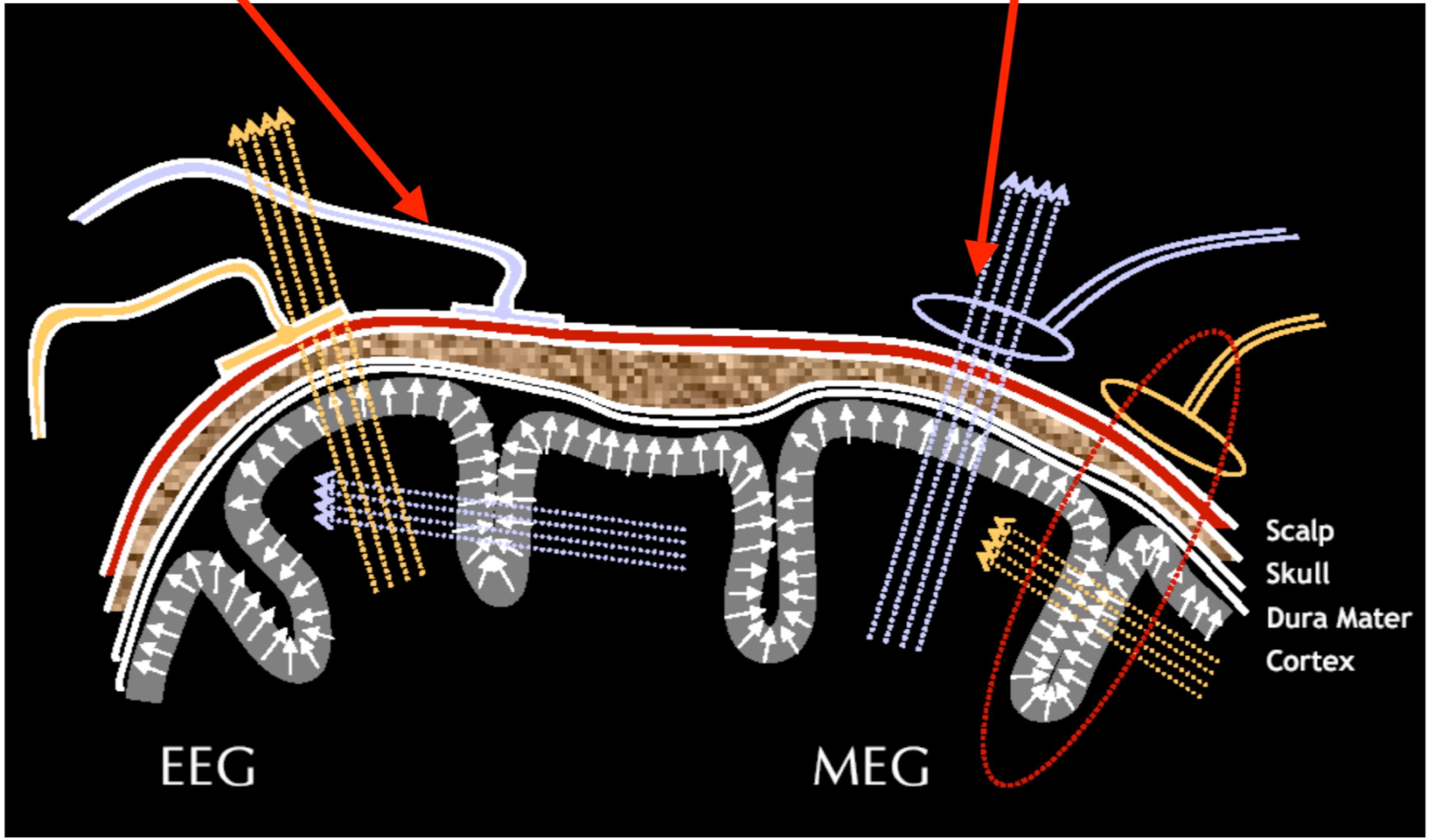
- EEG (electroencephalography): electric potentials
- MEG (magnetoencephalography): magnetic fields





EEG electrodes on the scalp

MEG sensors outside the head, in a tank containing liquid helium to enhance superconductivity



Source: http://www.allgpsy.unizh.ch/graduate/mat/180102/Lecture1.pdf

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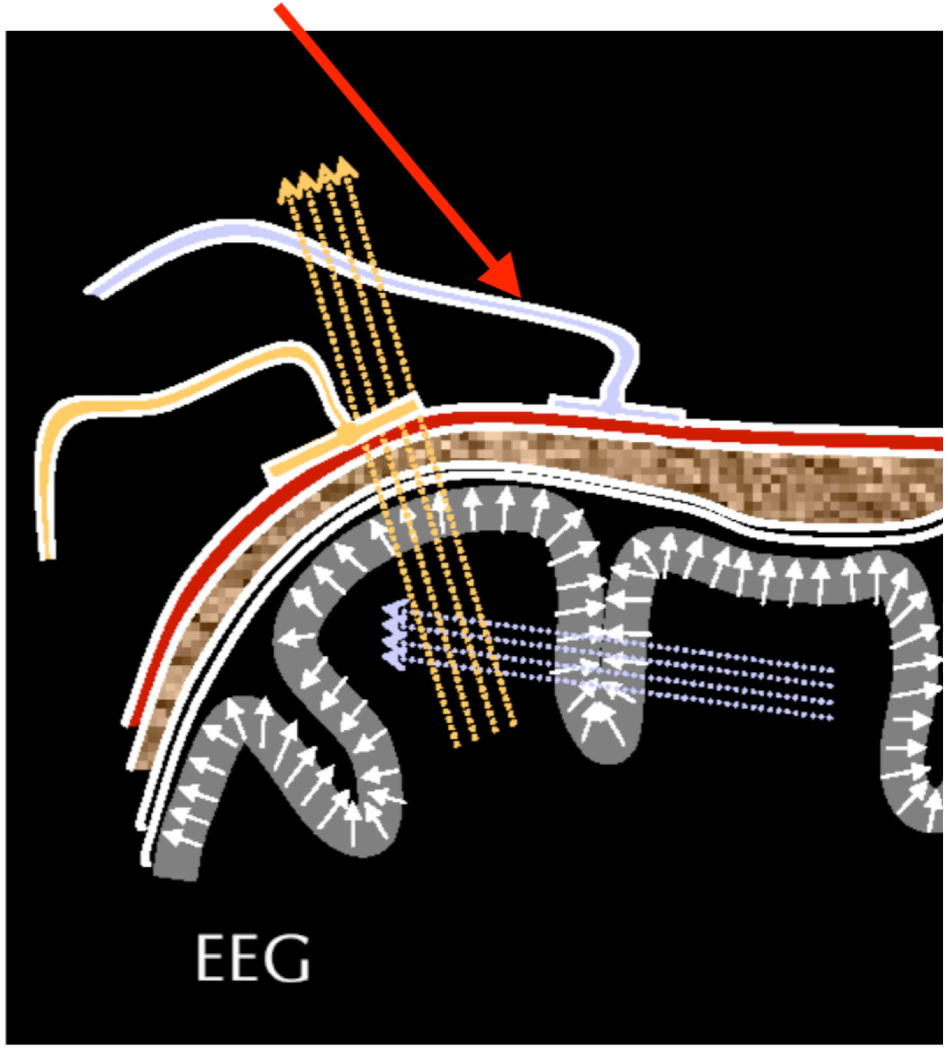

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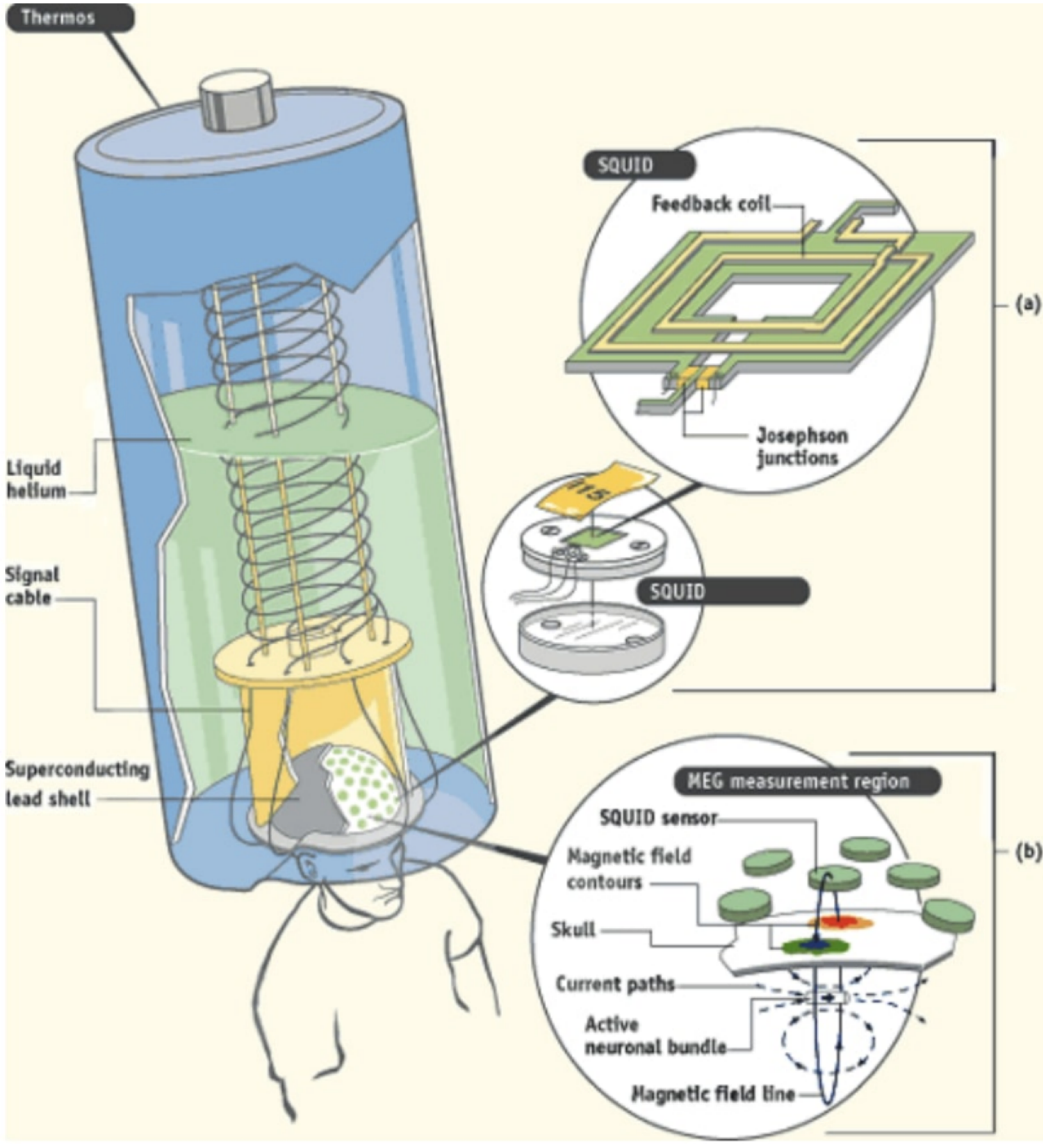
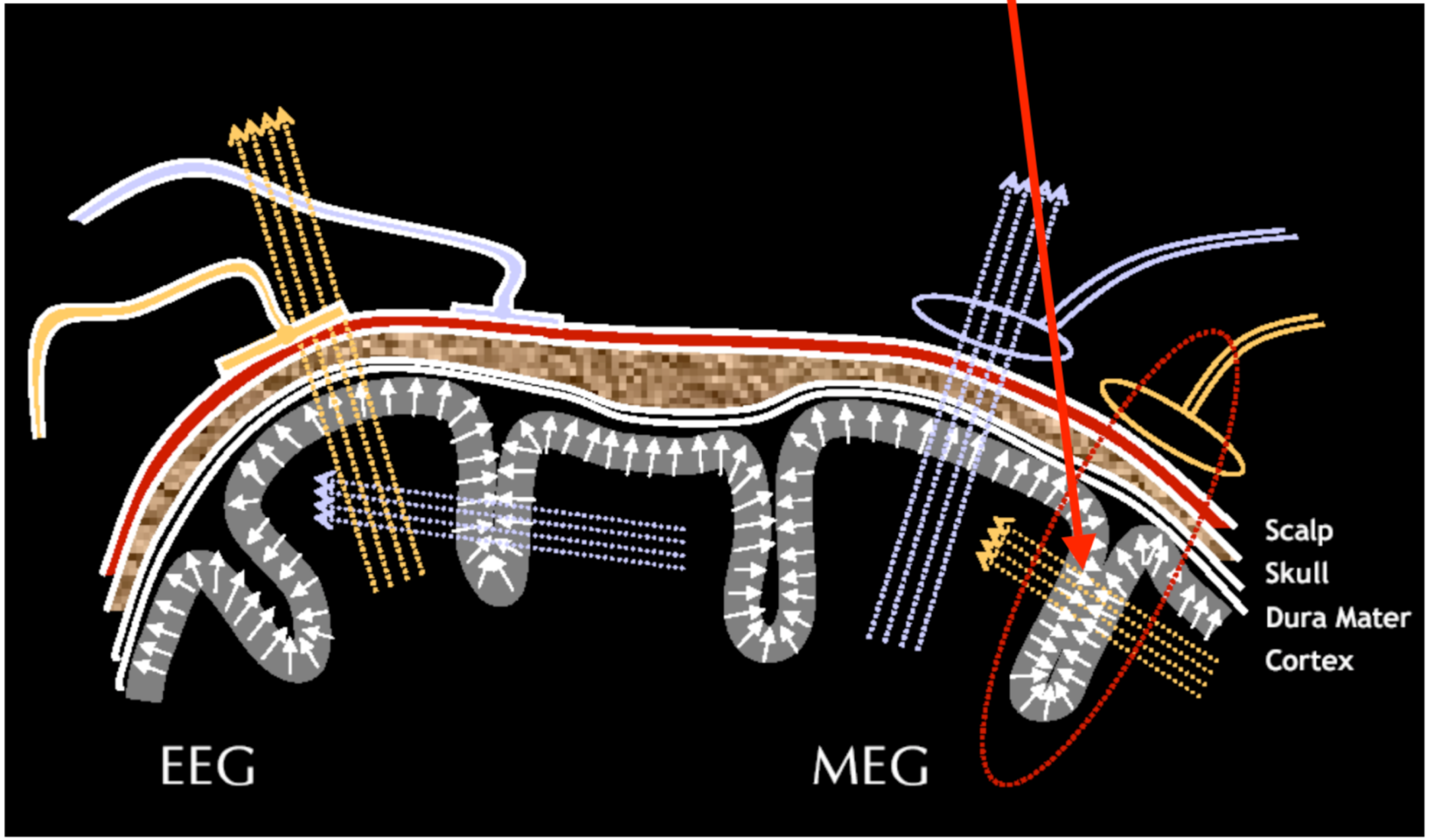
MEG sensors outside the head, in a tank containing liquid helium to enhance



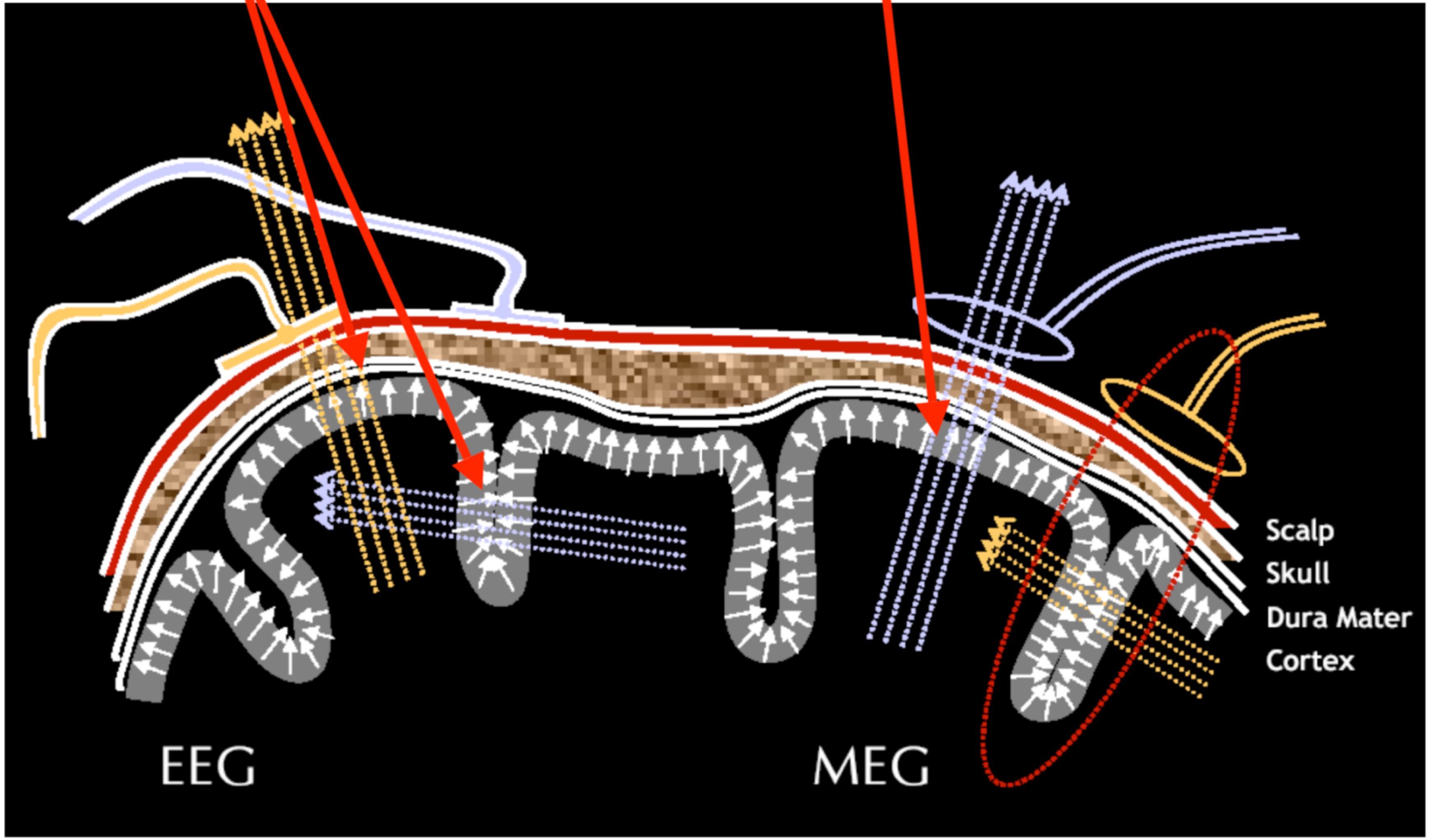
MEG signal is dominated by currents oriented tangential to the skull.



Source: http://www.allgpsy.unizh.ch/graduate/mat/180102/Lecture1.pdf

EEG picks up tangentially and radially oriented currents equally.

Currents oriented perfectly radial to the skull are missed in MEG. But there is very little signal that is so perfectly radial.



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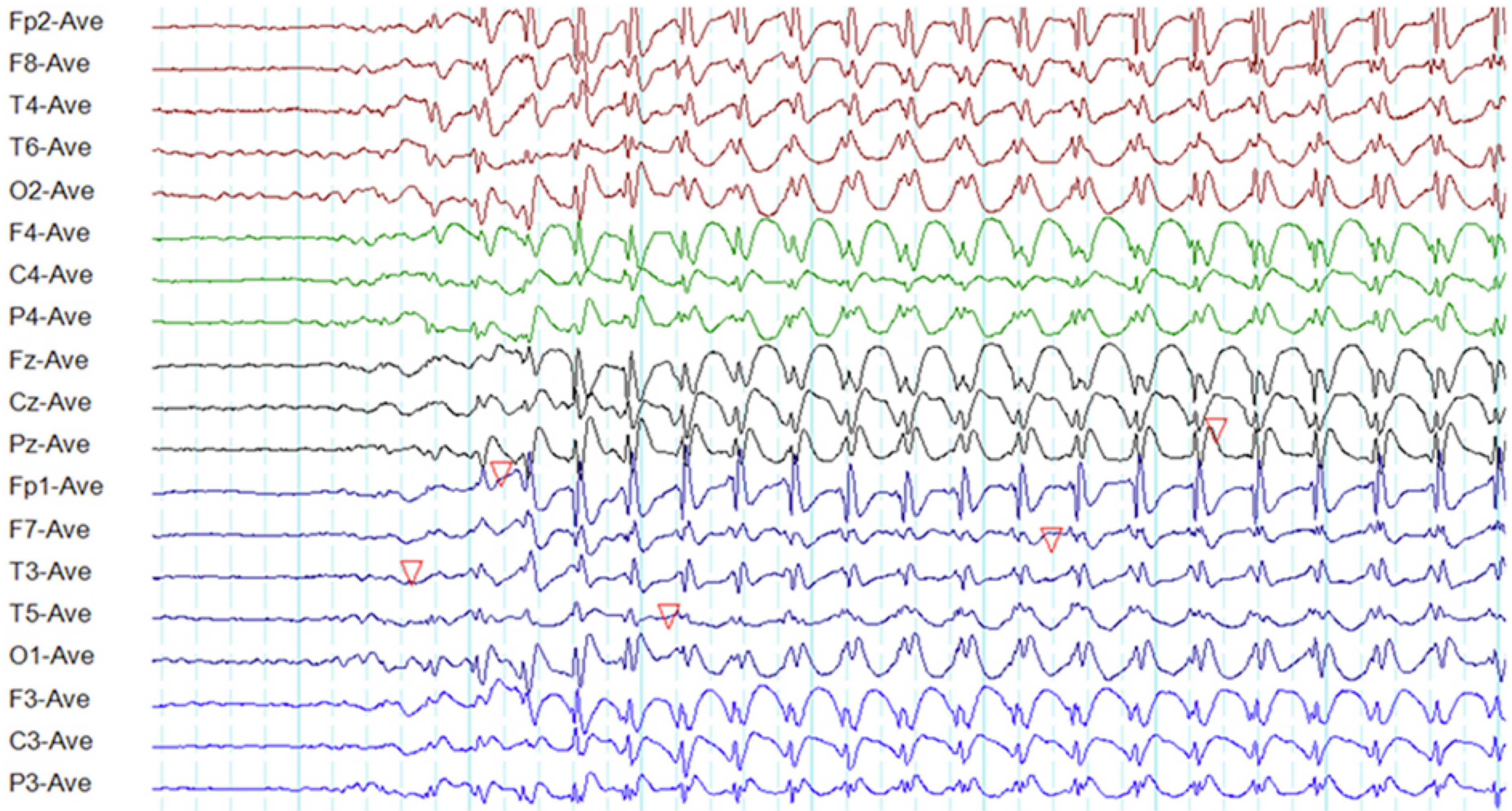
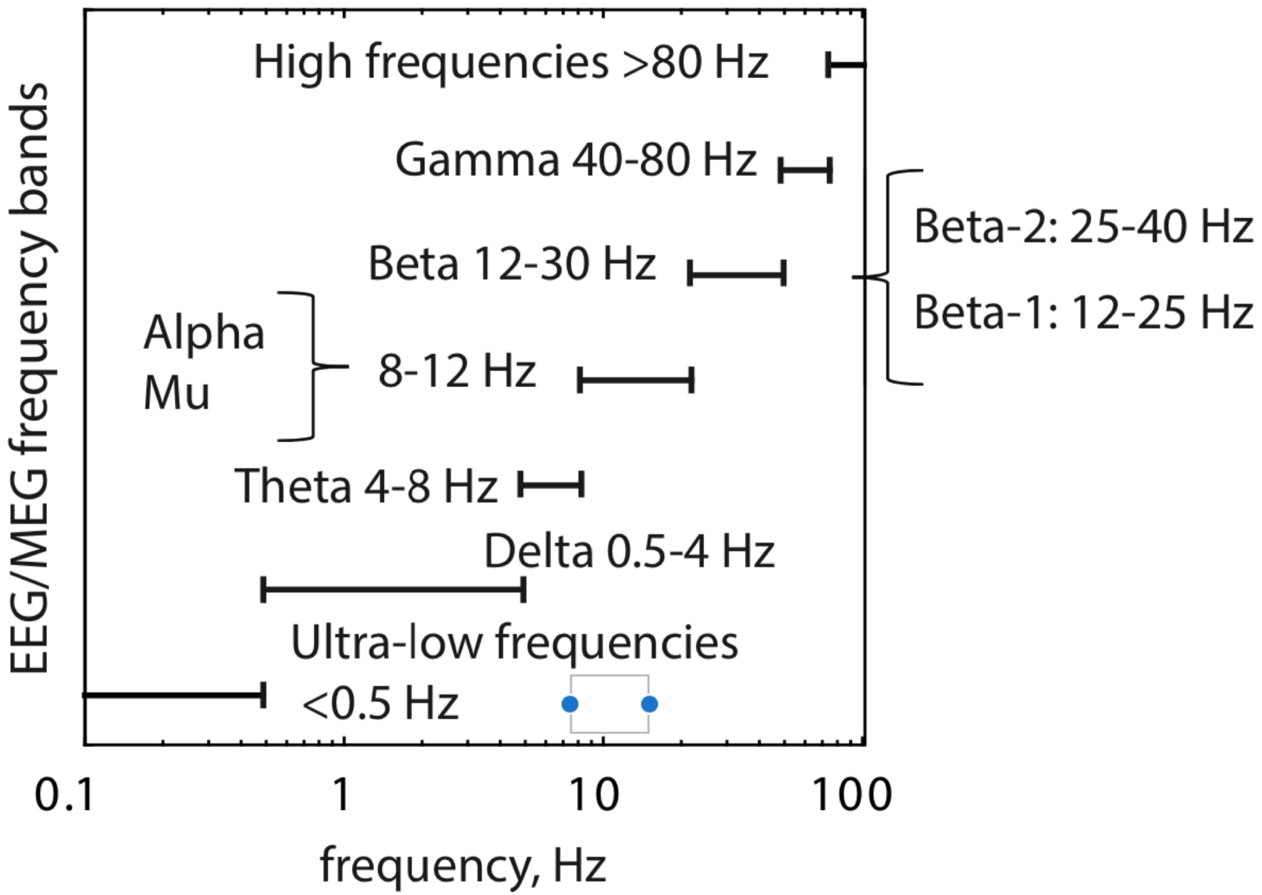
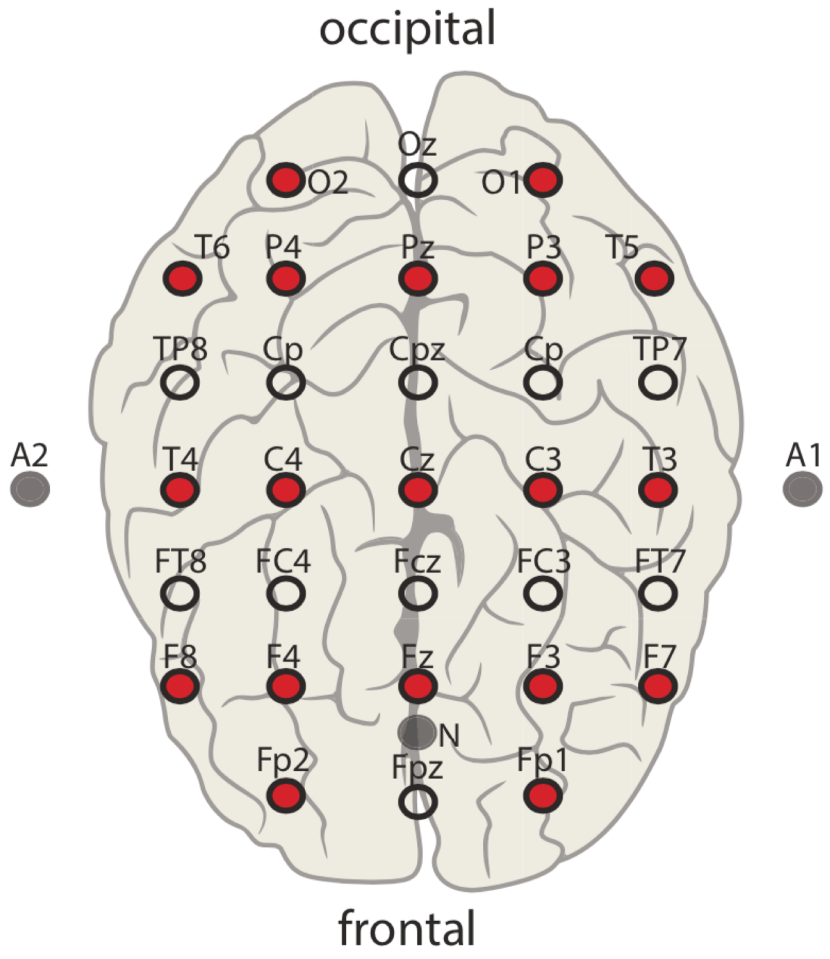
EEG and MEG

Epileptic EEG



Frequency ranges, traditionally allocated on EEG/MEG signals





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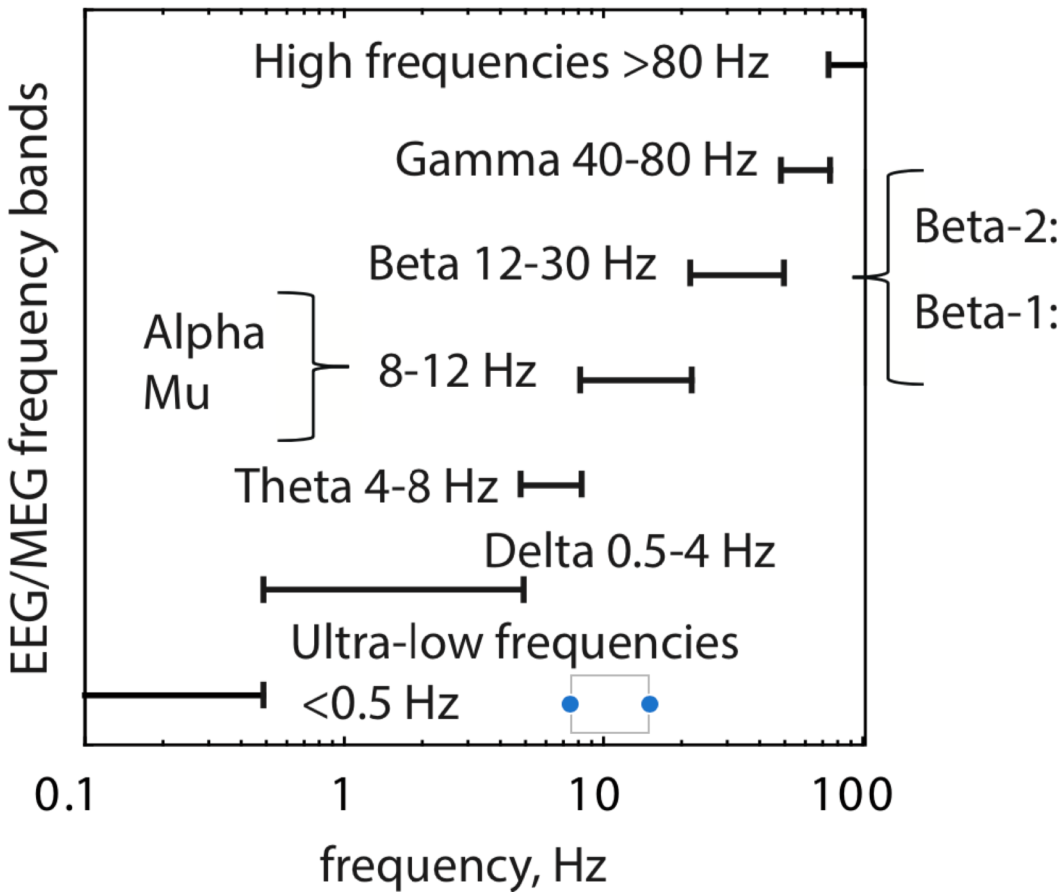
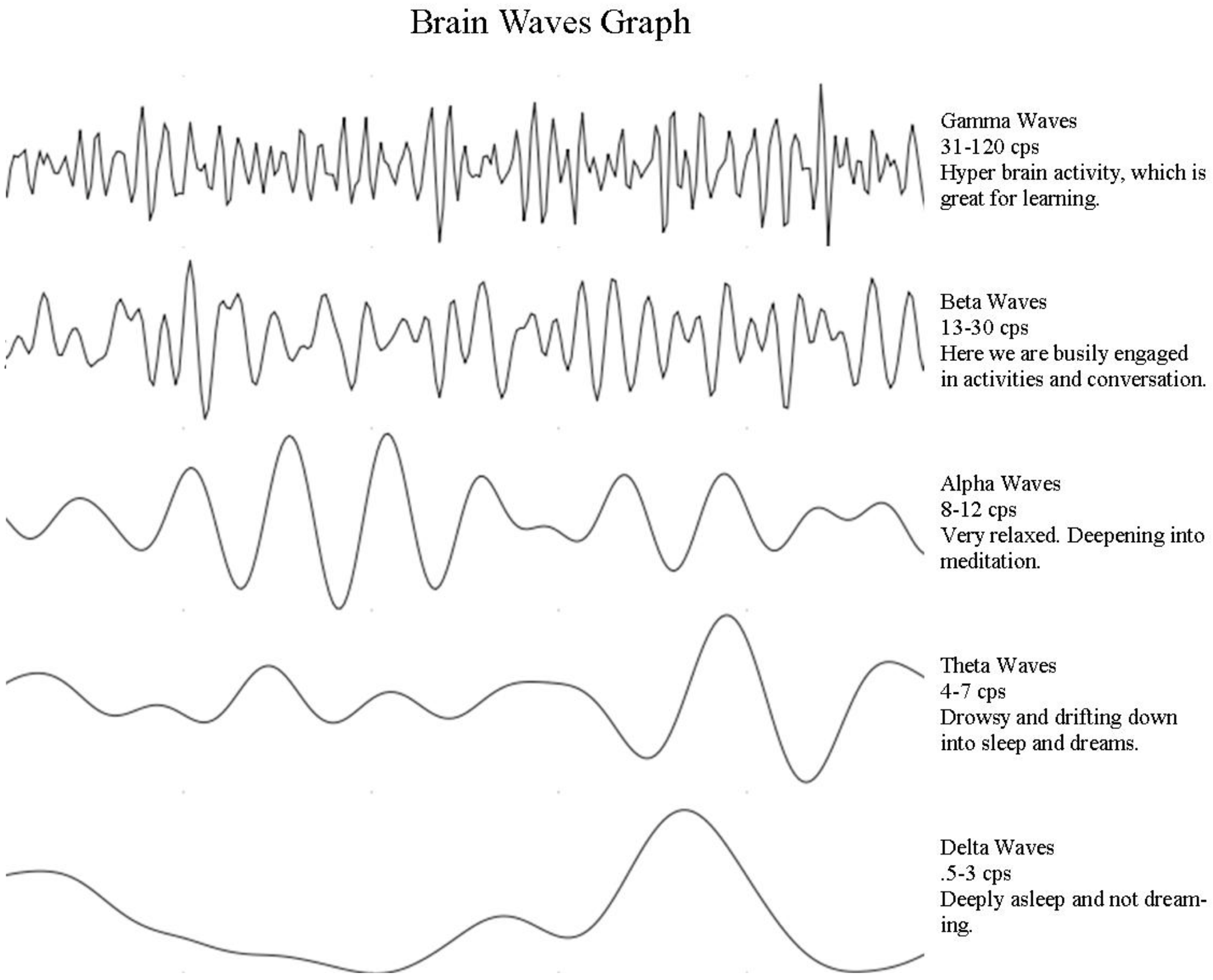
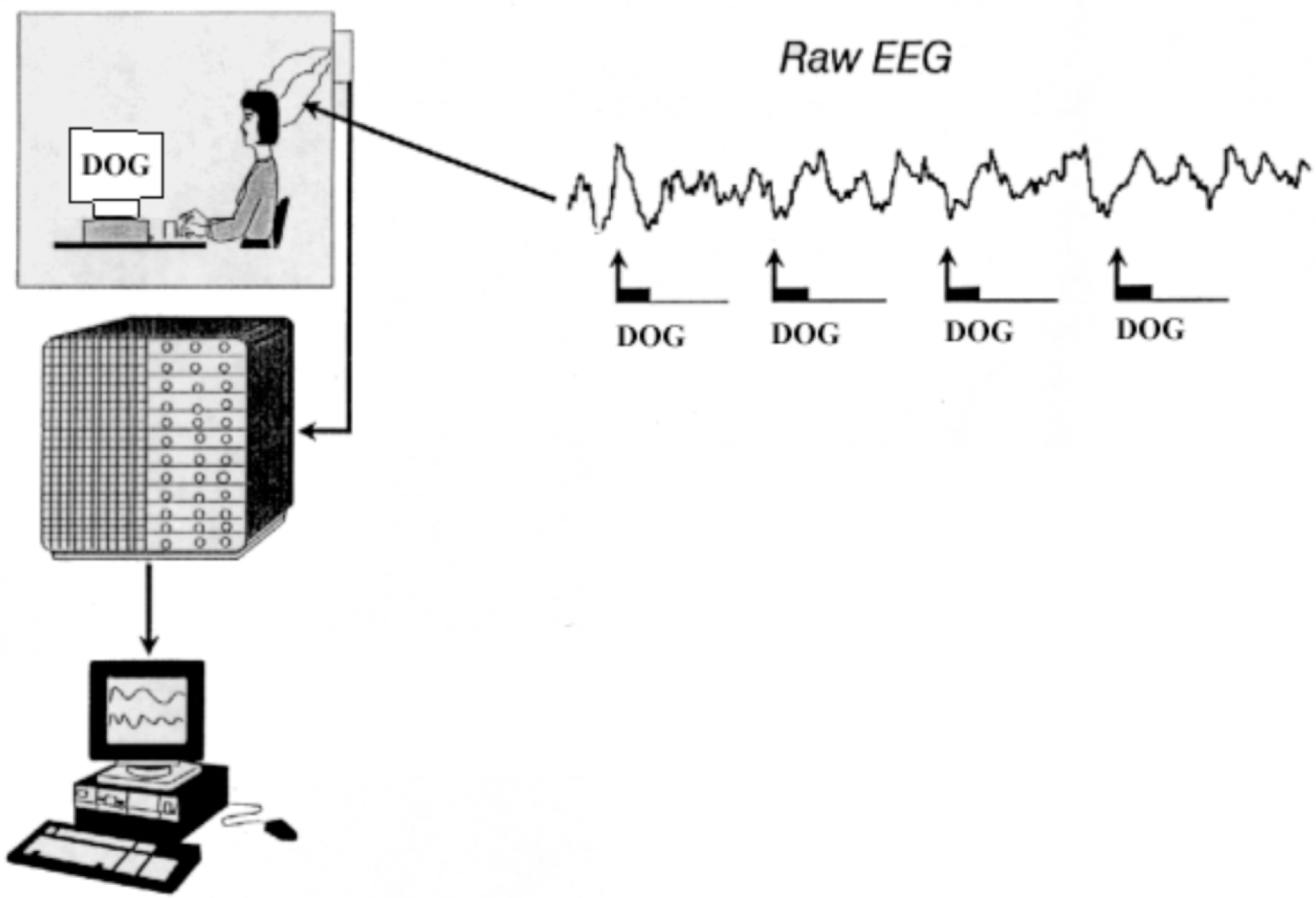


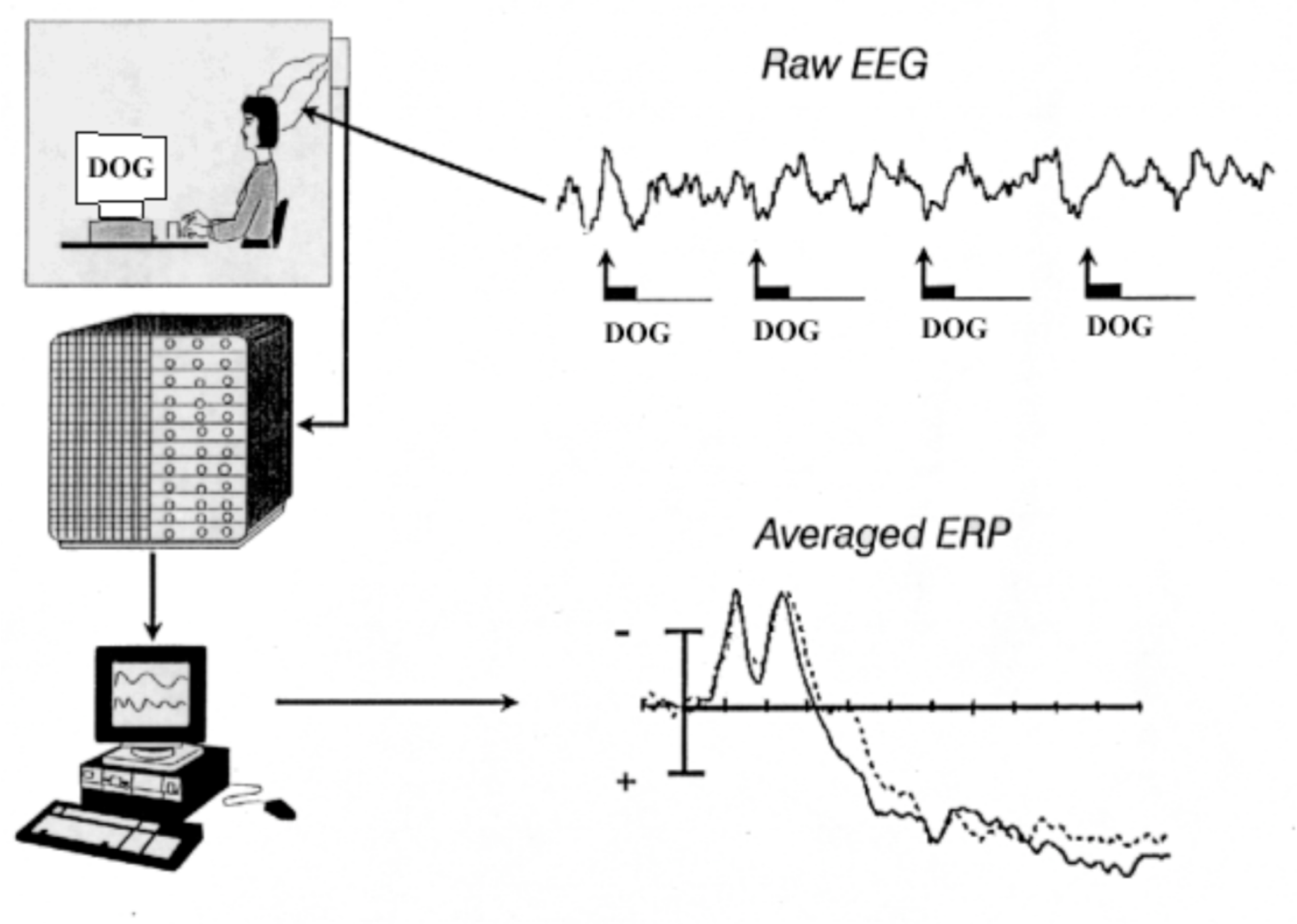


Event-related potential technique



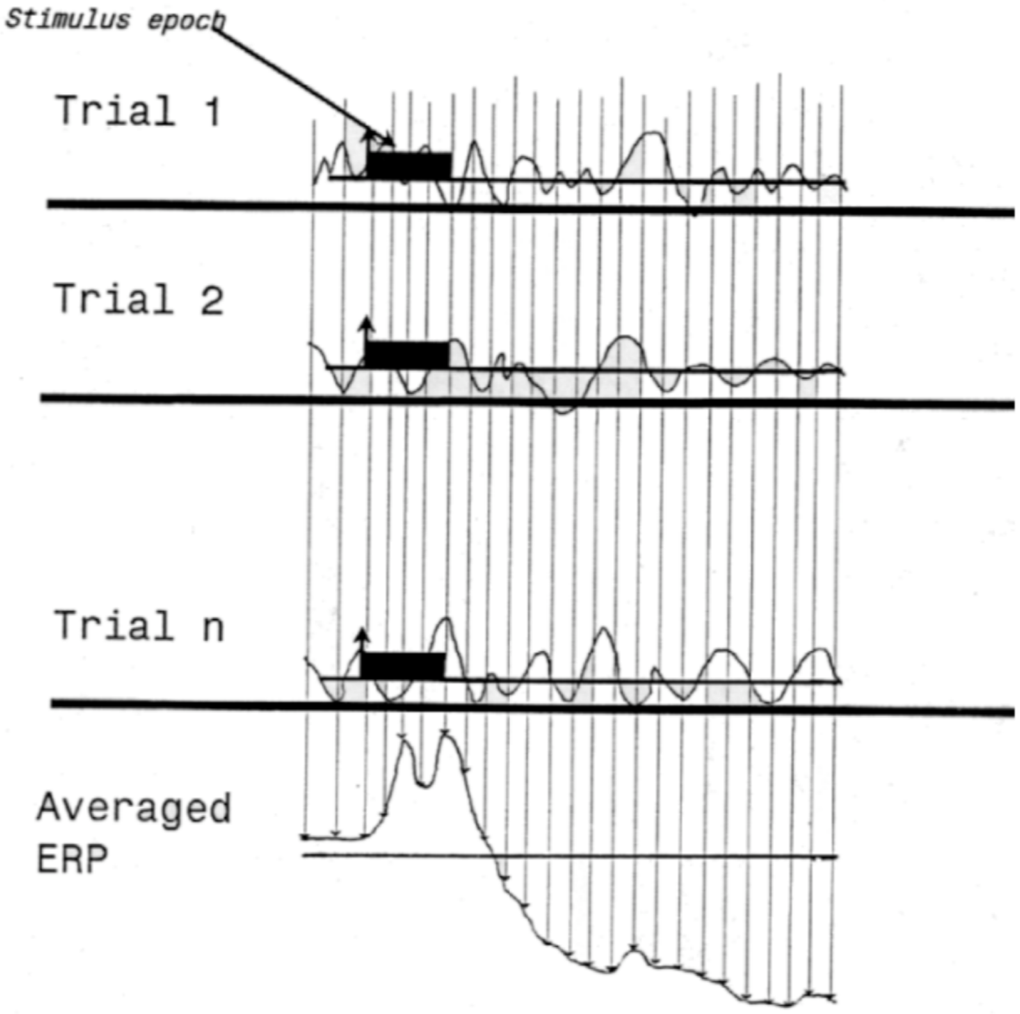
http://neurocog.psy.tufts.edu/images/ERP_technique.gif

Event-related potential technique



http://neurocog.psy.tufts.edu/images/ERP_technique.gif

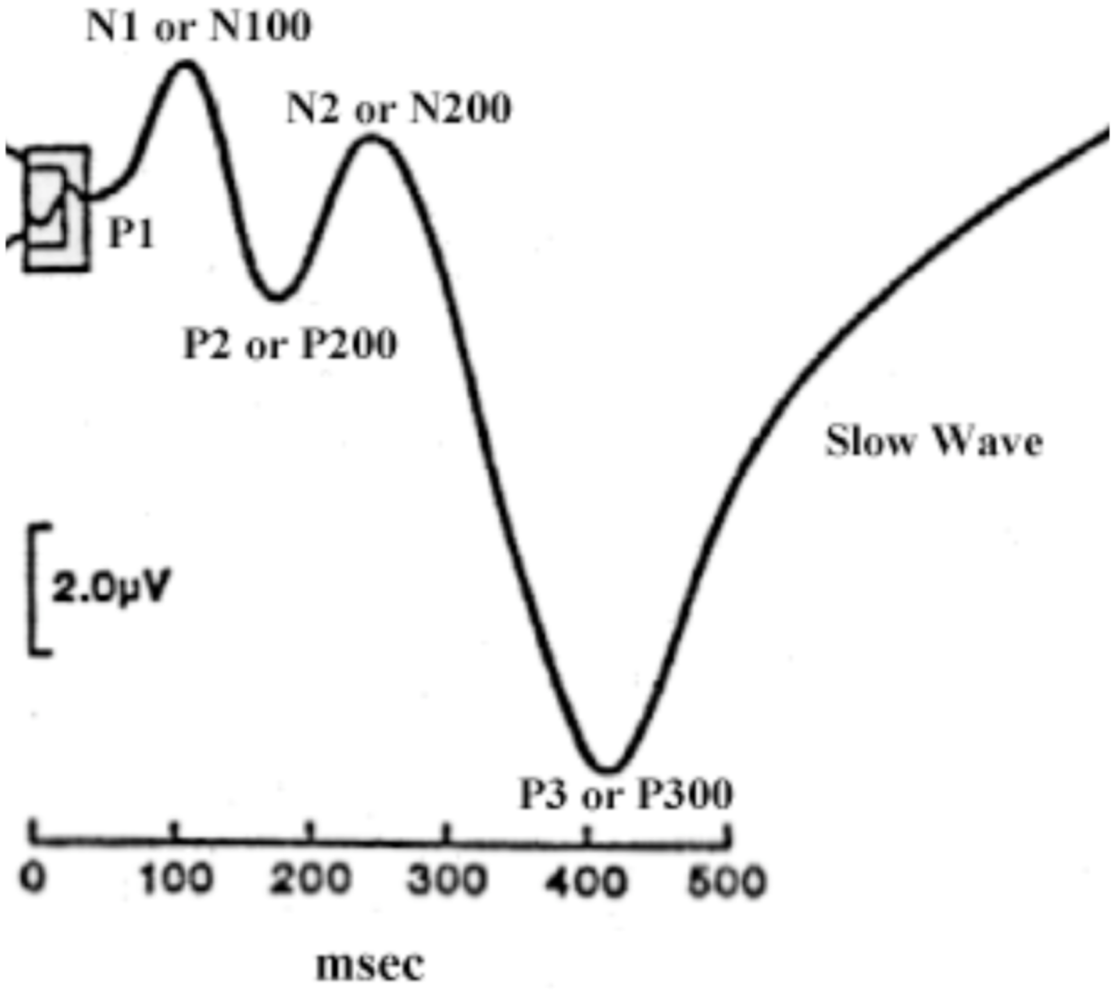
Averaging to obtain ERP



http://neurocog.psy.tufts.edu/images/ERP_averaging.gif

Labelling of ERP components

- P or N: whether the component is negative or positive going
- Number after the letter: indicates the approximate peak latency of the components. 1, 2, 3, etc. are short for 100ms, 200ms, 300ms and so forth.
- Traditionally, negative is plotted up and positive down



http://neurocog.psy.tufts.edu/images/ERP_components.gif

EEG pons and cons

PONS

- Millisecond temporal resolution
- Direct reflection of neuronal activity
- Less expensive than fMRI or PET

CONS

- Localization of neural generators complicated (and usually not done).
- **Different tissues and the skull differ in their conductivity: Electric potentials do not pass through these structures undistorted.**
- Localization requires realistic head models.

EEG pons and cons

Electroencephalography is better suited to answering questions about “when” cognitive processes work not **where** they work

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MEG

- Main advantage over EEG: better spatial resolution (millimeters for cortex, worse for deeper sources)
- Magnetic fields pass through skull and various tissues undistorted.
- Distribution of the magnetic field around the head tells you a lot
- about the underlying current generators.

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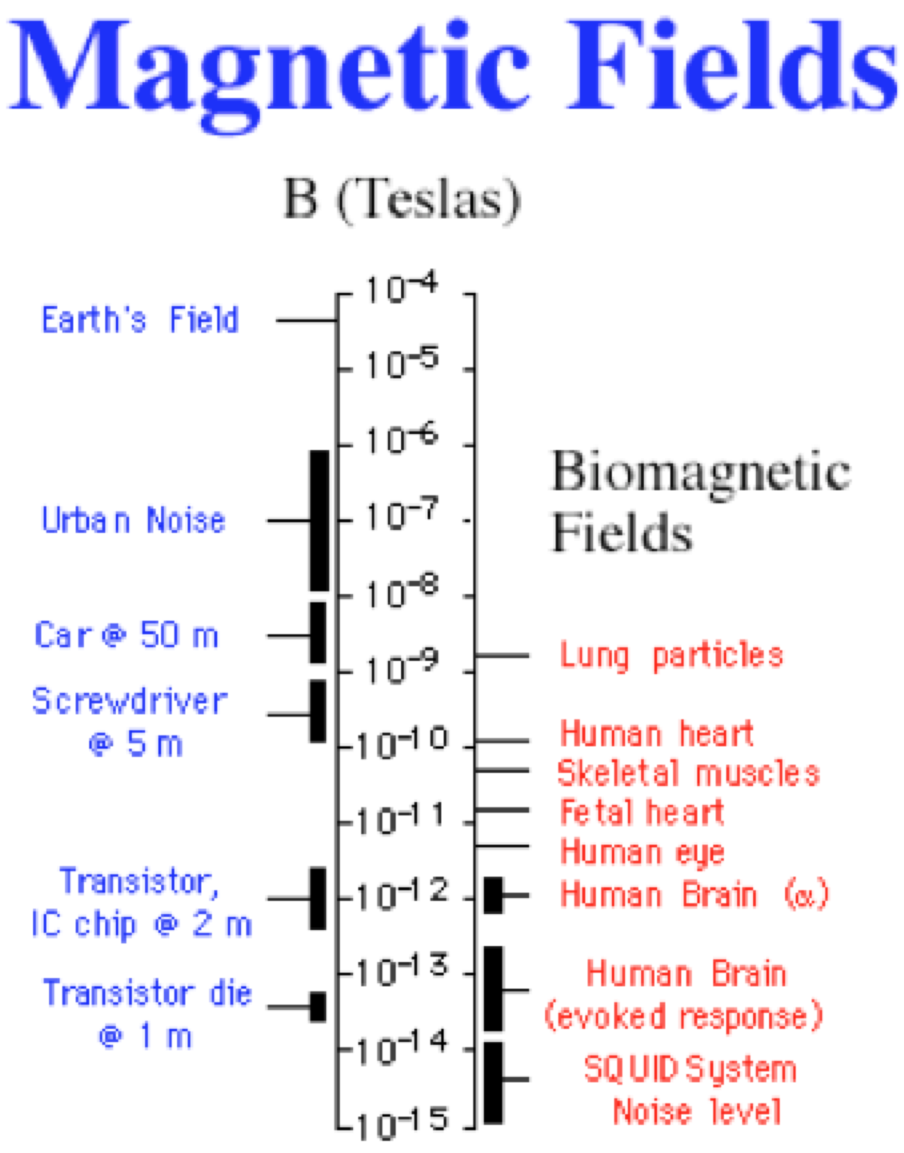

The magnetic fields generated by neural activity are 100 million times smaller than the earth's magnetic field and 1 million times smaller than the magnetic fields produced in an urban environment.

How to capture the tiny signal

- Superconductive sensors
- Reference channels
- Magnetically shielded room

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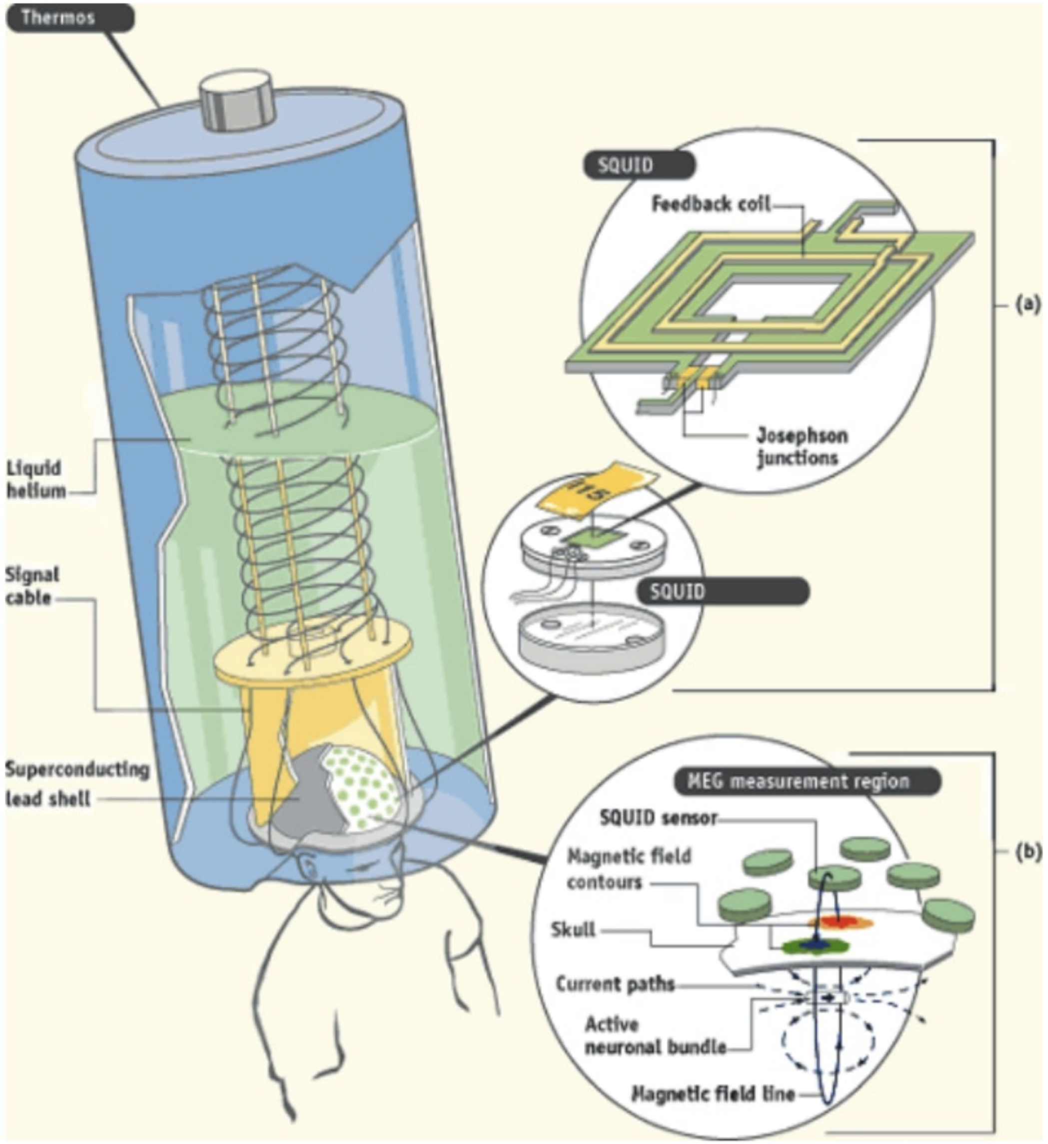

How to capture the tiny signal

- **Superconductive sensors**
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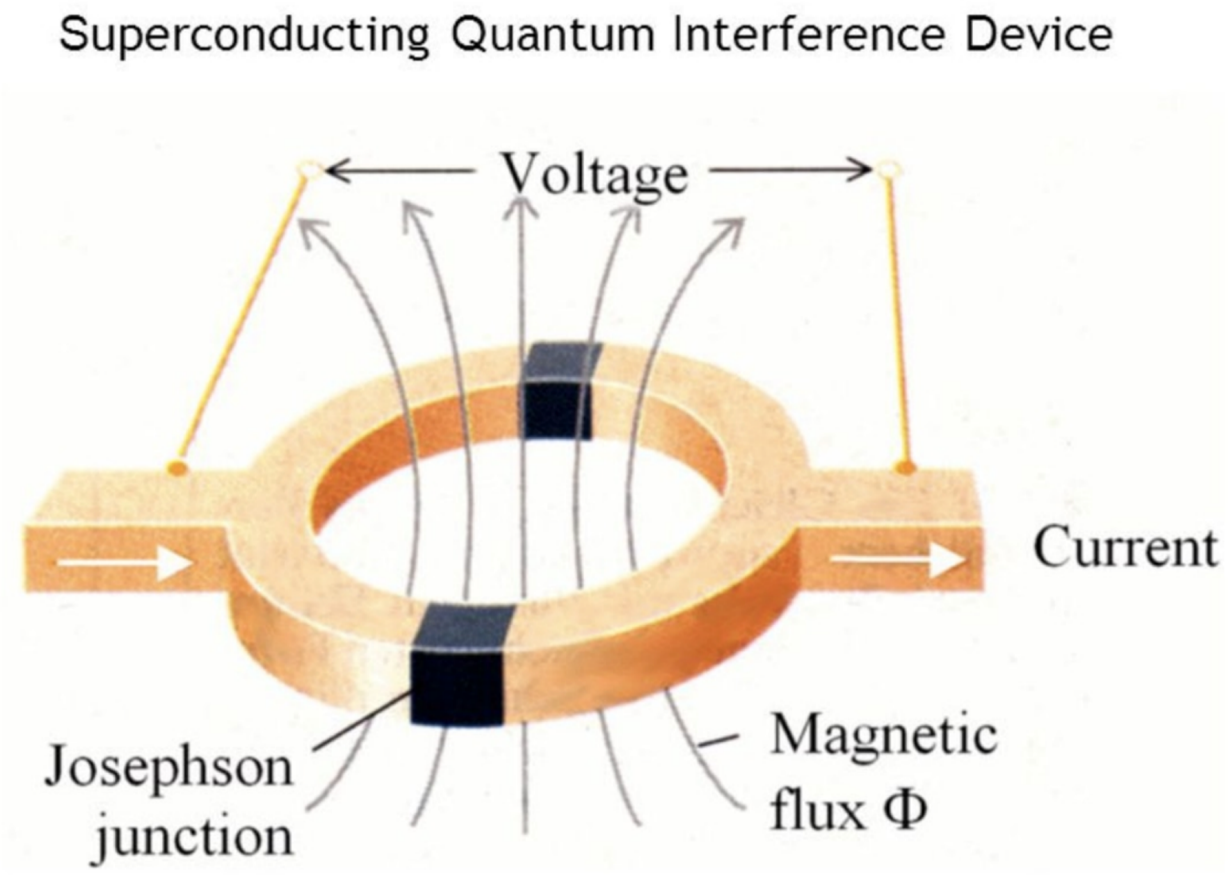


- Most sensitive sensors for magnetic flux and magnetic field.
- Small superconducting ring (< 1 mm in diameter)
- Very small current can flow through the weak link without dissipation

How to capture the tiny signal

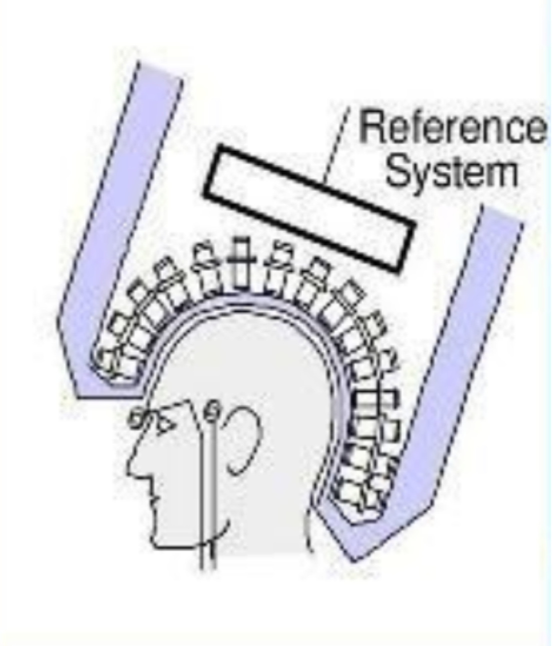
- **Superconductive sensors**
- Reference channels
- Magnetically shielded room

306-channel (102 magnetometers and 204 planar gradiometers**) Vectorview MEG** system (Elekta AB, Stockholm, Sweden) in the magnetically shielded room.

How to capture the tiny signal

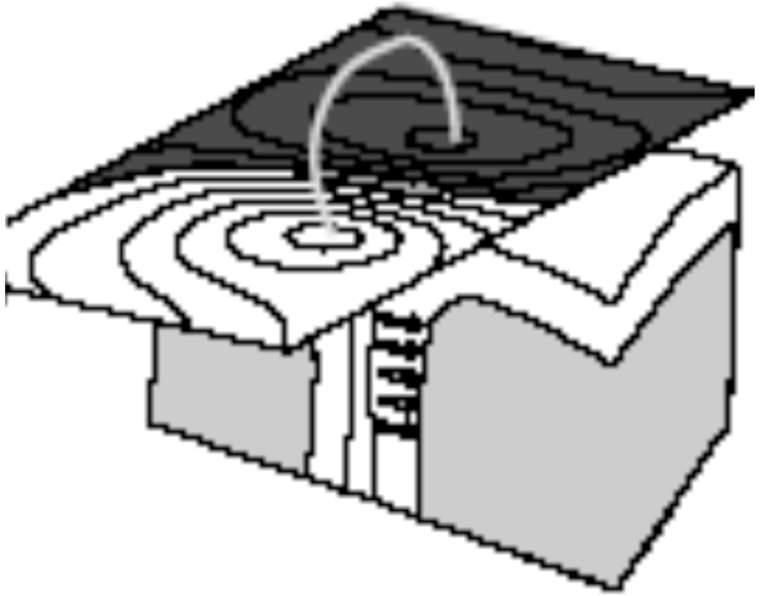
- Superconductive sensors
- **Reference channels**
- Magnetically shielded room

Placed somewhere close to the head but far enough to not measure any brain activity. Signal measured by the reference channel subtracted from the raw data during acquisition.

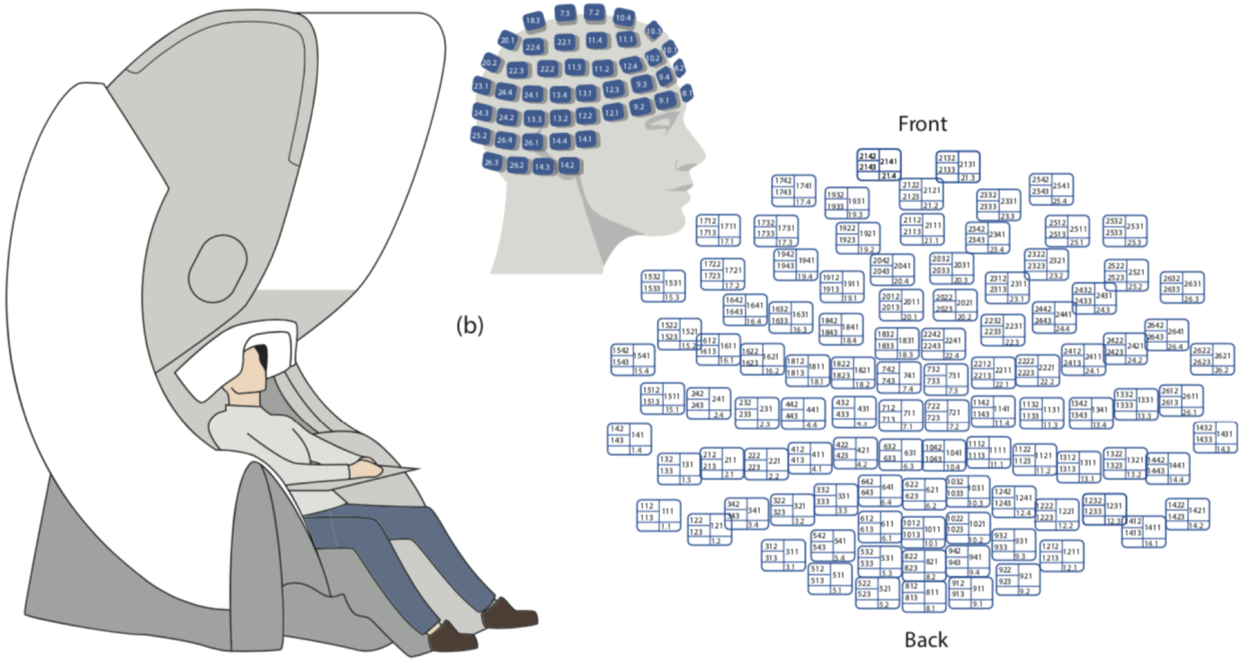


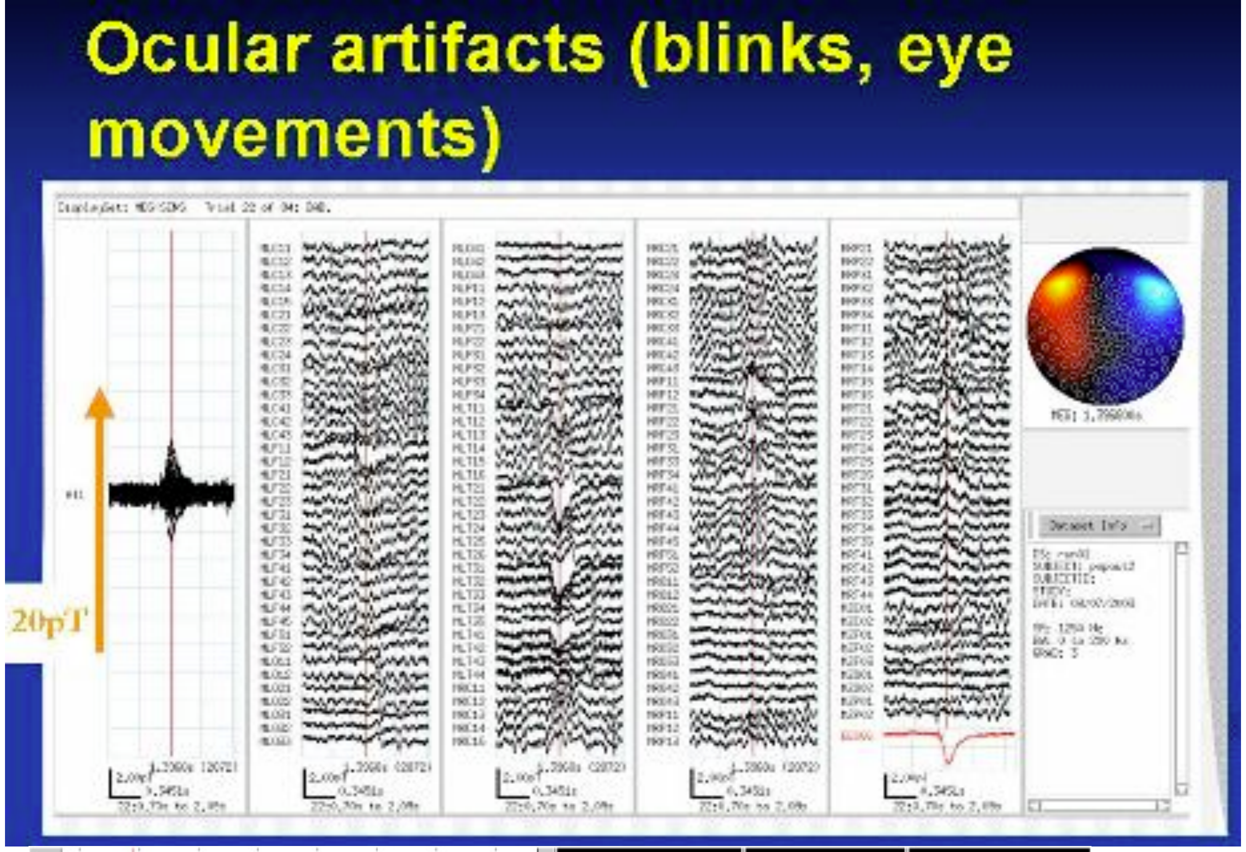
How to capture the tiny signal

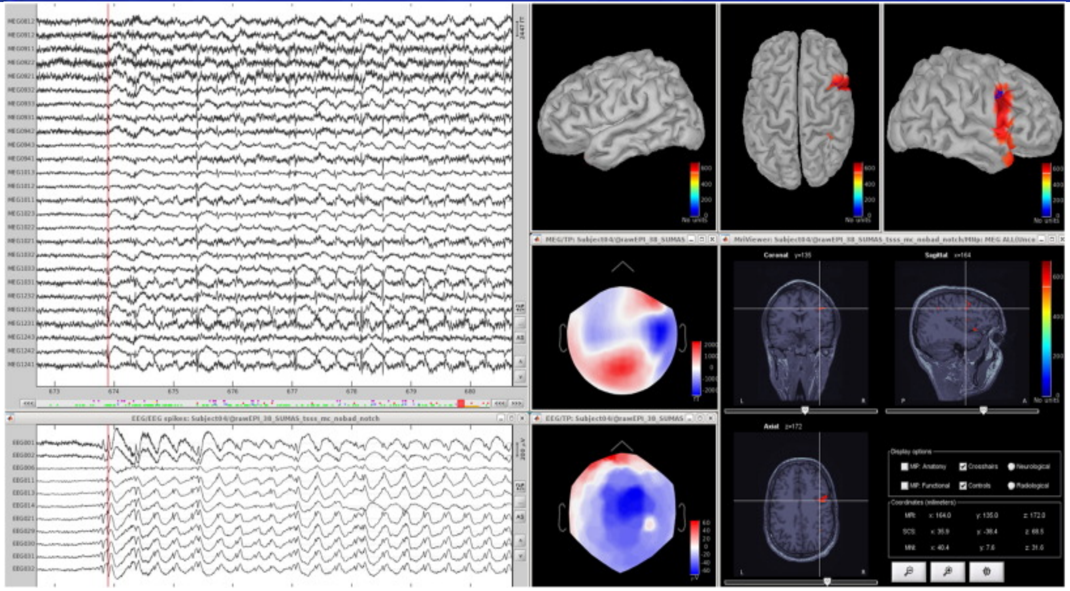
- Superconductive sensors
- Reference channels
- **Magnetically shielded room**



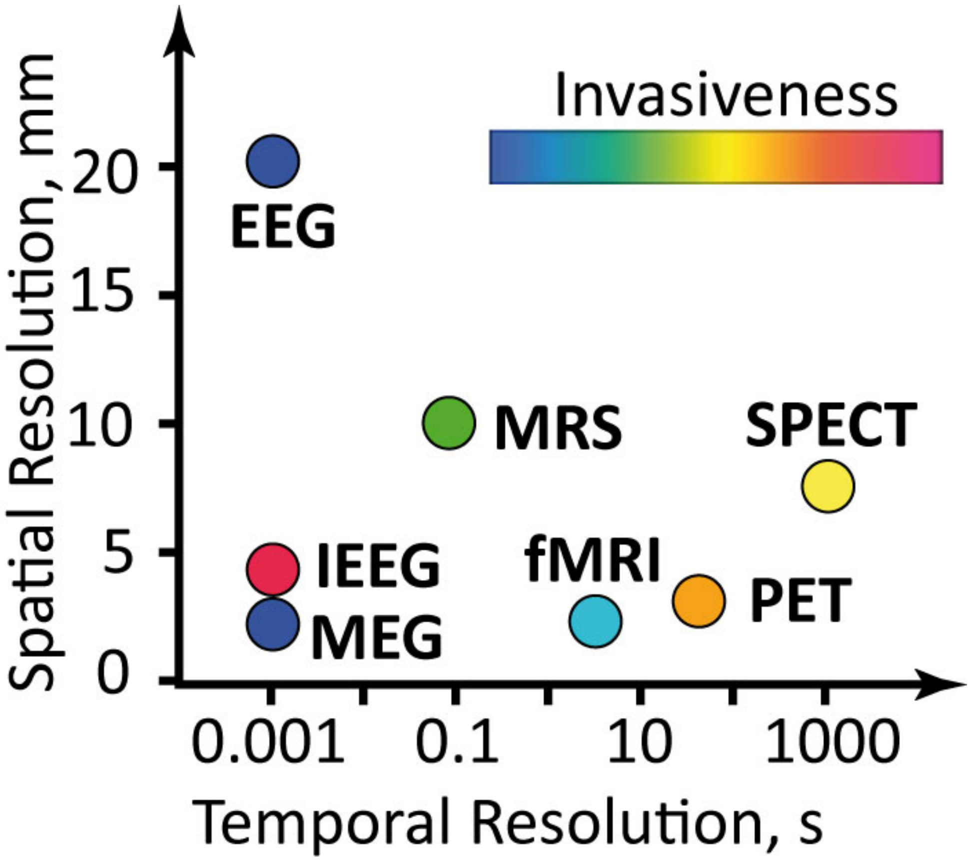
MEG Data







Spatial-frequency resolution of different neuroimaging technics



Positron emission tomography (PET)
Single-photon emission computed tomography (SPECT)