COMPUTATIONAL NEUROSCIENCE
Research group at the University of Tartu

Introduction to Computational Neuroscience

Lecture 3: Windows to the brain

Lesson	Title
1	Introduction
2	Structure and Function of the NS
3	Windows to the Brain
4	Data analysis
5	Single neuron models
6	Network models
7	Artificial neural networks
8	Artificial intelligence
9	Learning and memory
10	Perception
11	Attention & decision making
12	Brain-Computer interface
13	Neuroscience and society
14	Future and outlook
15	Projects presentations
16	Projects presentations

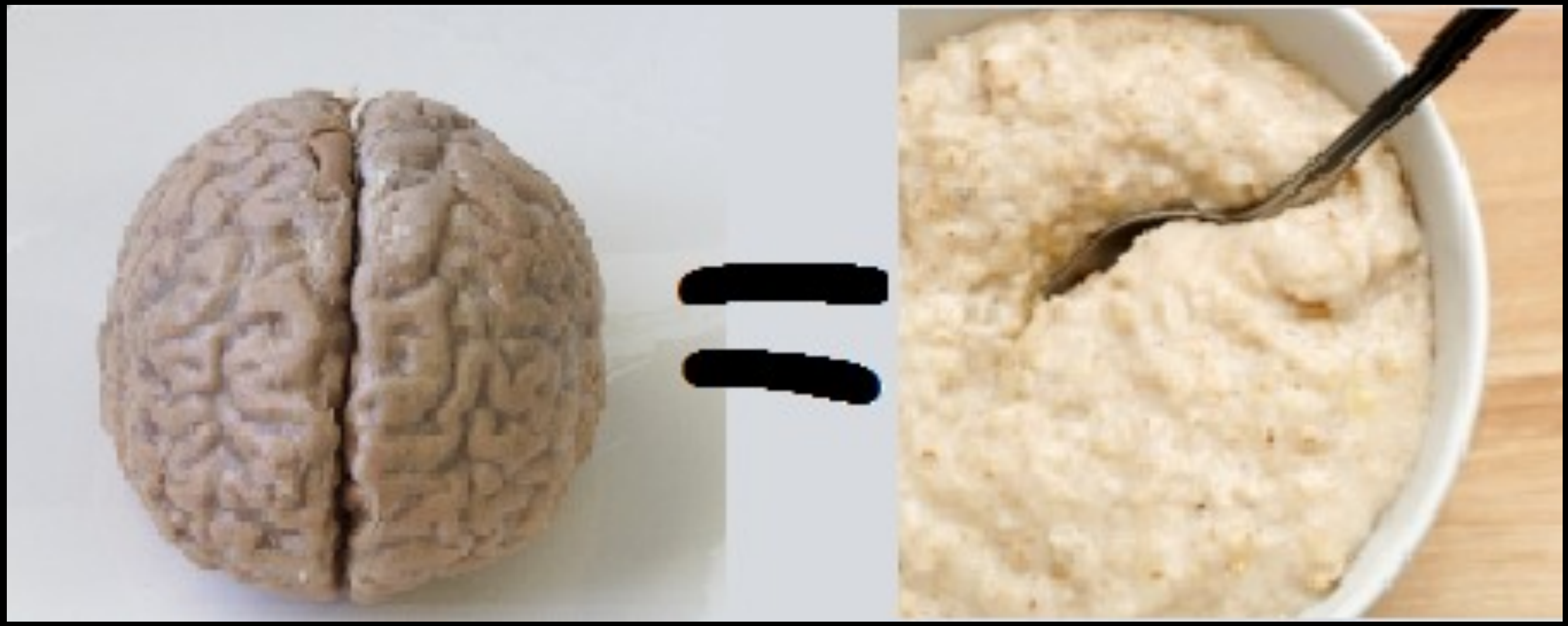
Basics

Analyses

Models

Cognitive

Applications



“One of the difficulties in understanding the brain is that it is like nothing so much as a lump of porridge”

R.L. Gregory

Eye and the Brain: the psychology of seeing, New York, 1966, McGraw-Hill

Measurement is the first step that leads to control and eventually to improvement.

If you can’t measure something, you can’t understand it.

If you can’t understand it, you can’t control it.

If you can’t control it, you can’t improve it.

Every leap forward in knowledge about the NS has been based on a leap forward in technology

Some leaps forward

Ramon y Cajal (1900s) → **Golgi staining** → **Structure of the NS**

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Eccles, Hodgkin, Huxley (1940s)	→	Intracellular recordings	→	Ionic basis of membrane potential

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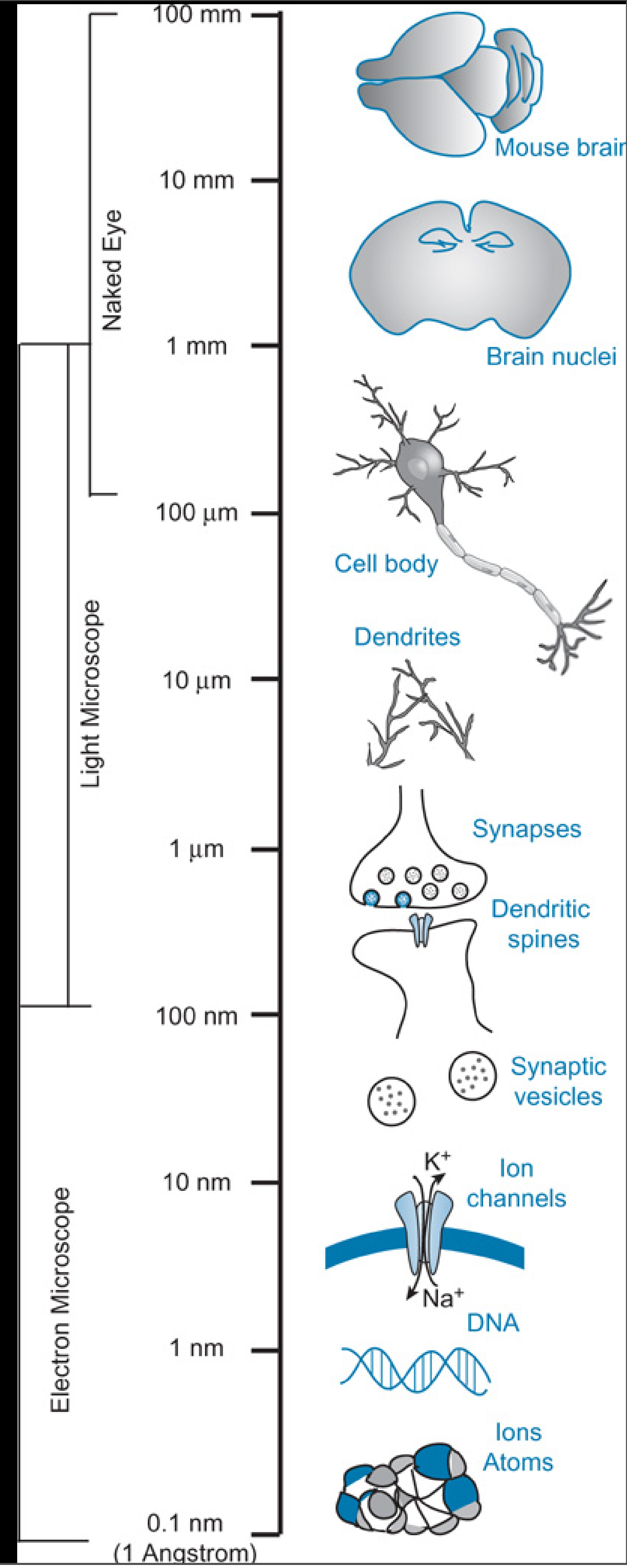
Hubel, Wiesel (1960s) →	**Extracellular recordings** →	**Information processing in visual system**
Neher, Sakmann (1970s) →	**Patch-clamp** →	**Physiology of single-ion channels**

Learning objectives

- Explain the different ways of studying the NS
- Compare strengths and limitations of different techniques to measure brain structure and activity
- Understand the basic mechanisms behind different brain imaging techniques and electrophysiology

Levels of study

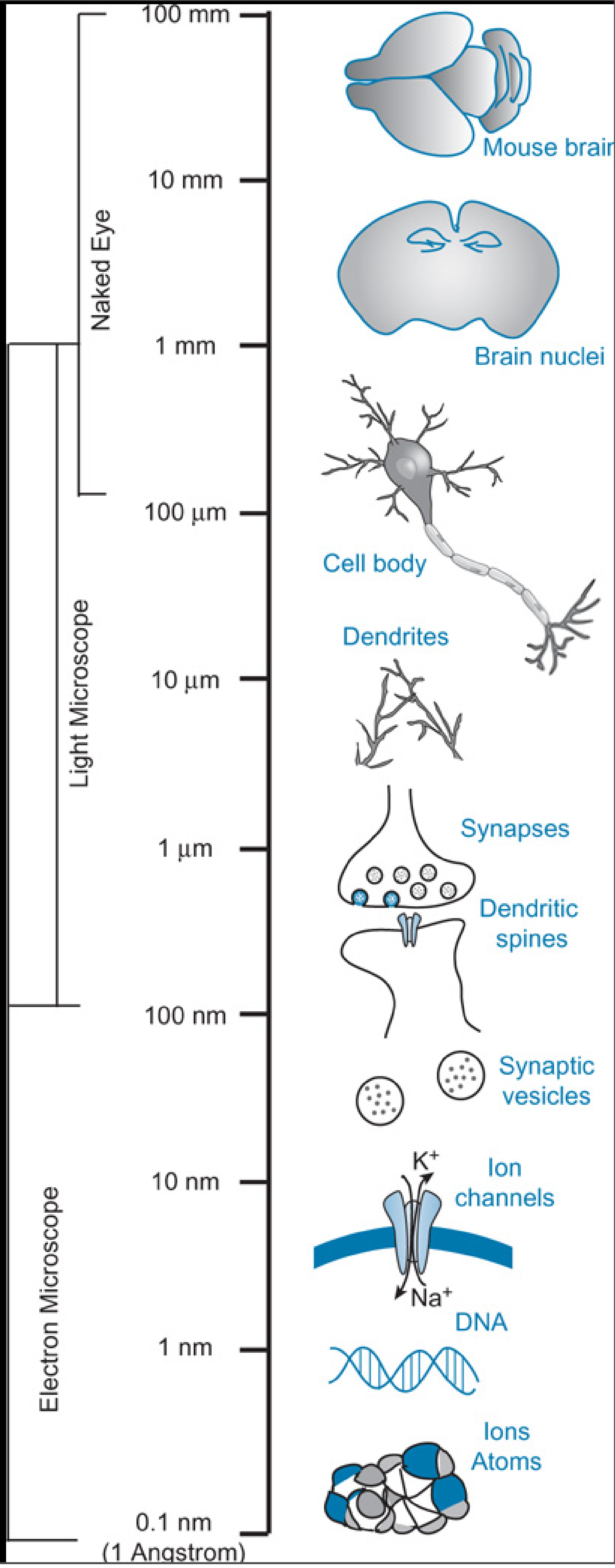


Levels of study

A neuroscientist can study the NS through any level of organization

Different techniques are appropriate for different scales

However, irrespective of the technique the basic scientific approach is consistent from level to level



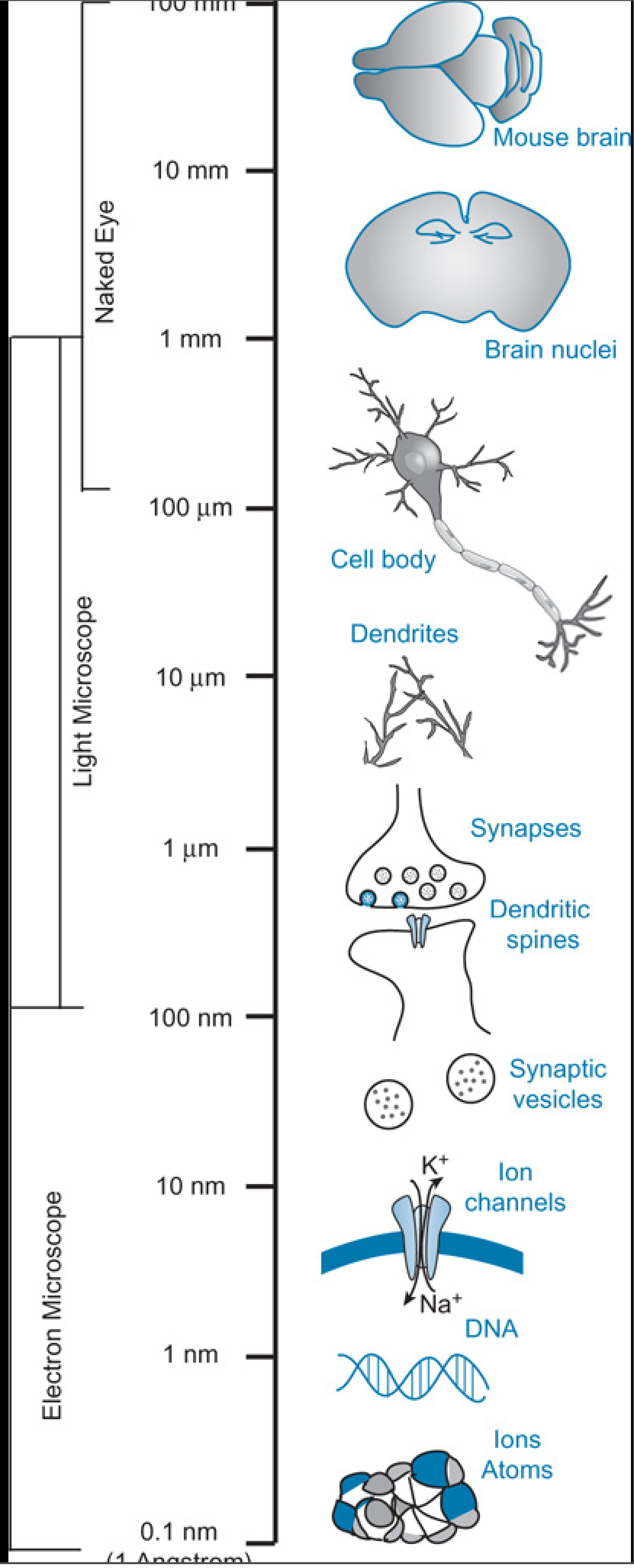
Methods of studying the NS

1) Examining case studies

2) Screens

3) Descriptions

4) Manipulations



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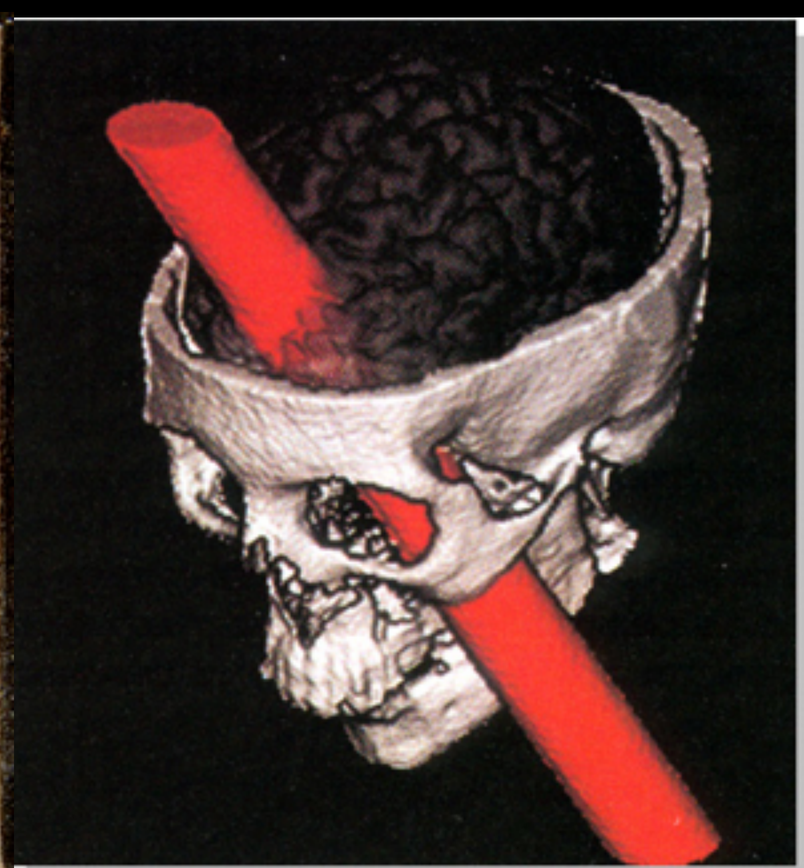

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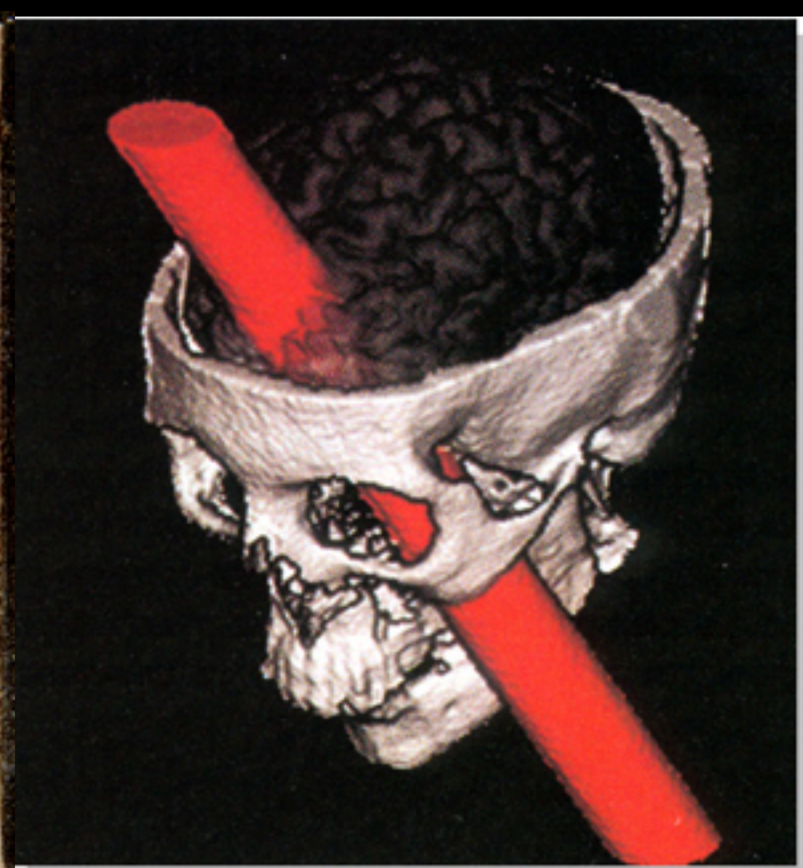

Methods of studying the NS

2) Screen: is a search for anatomical structures, neurons, proteins or genes that may play a role in a biological process of interest.

* Often explorative rather than driven by hypothesis
* Identifies candidates for future hypothesis-driven research

Methods of studying the NS

3) Description: is the act of simply observing properties of the NS without manipulation.

* Foundation for understanding structure-function
* Provides insight about what variables manipulate

Ex.: quantifying the number or types of neurons belonging to one region, etc...

Methods of studying the NS

4) Manipulation: consists of varying one aspect of the NS or environment and examining the effect this perturbation has on a separate aspect of the NS

* Tests the effect of *X* (independent variable) on *Y* (dependent variable)

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Loss-of-function (necessity) experiments

Is the activity in region X necessary for behavior Y?

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Loss-of-function (necessity) experiments

Is the activity in region X necessary for behavior Y?

Gain-of-function (sufficiency) experiments

Can stimulation of region X cause behavior Y?

Techniques for imaging and recording the brain

Whole brain imaging

Electrophysiology

Neuronal manipulation

Neuroimaging

Structural brain imaging techniques are used to resolve the anatomy of the brain in a living subject without physically penetrating the skull

* Measure anatomical changes over time
* Diagnose diseases such as tumors or vascular disorders

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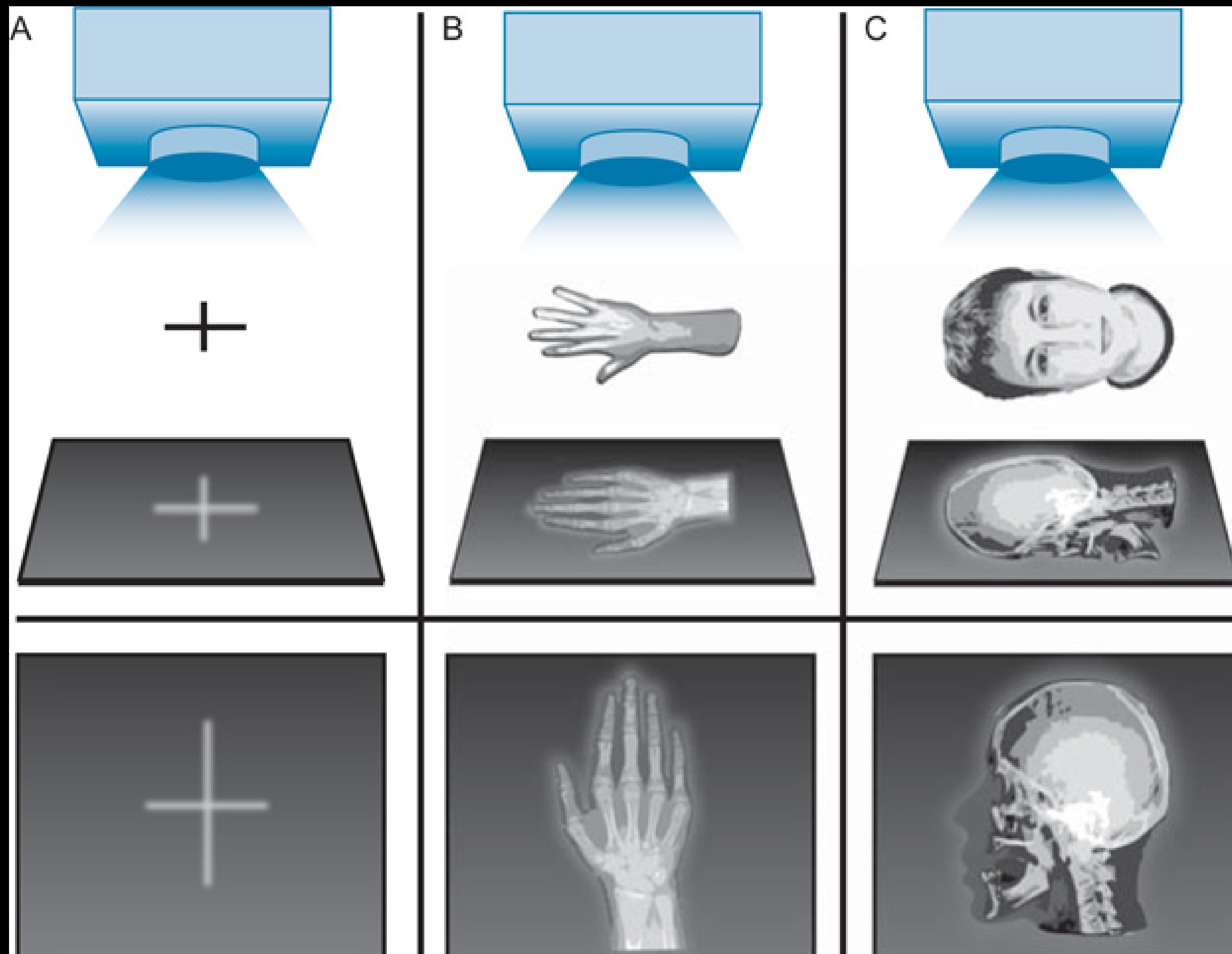
Structural brain imaging

Contrast:
absorption
of X-rays



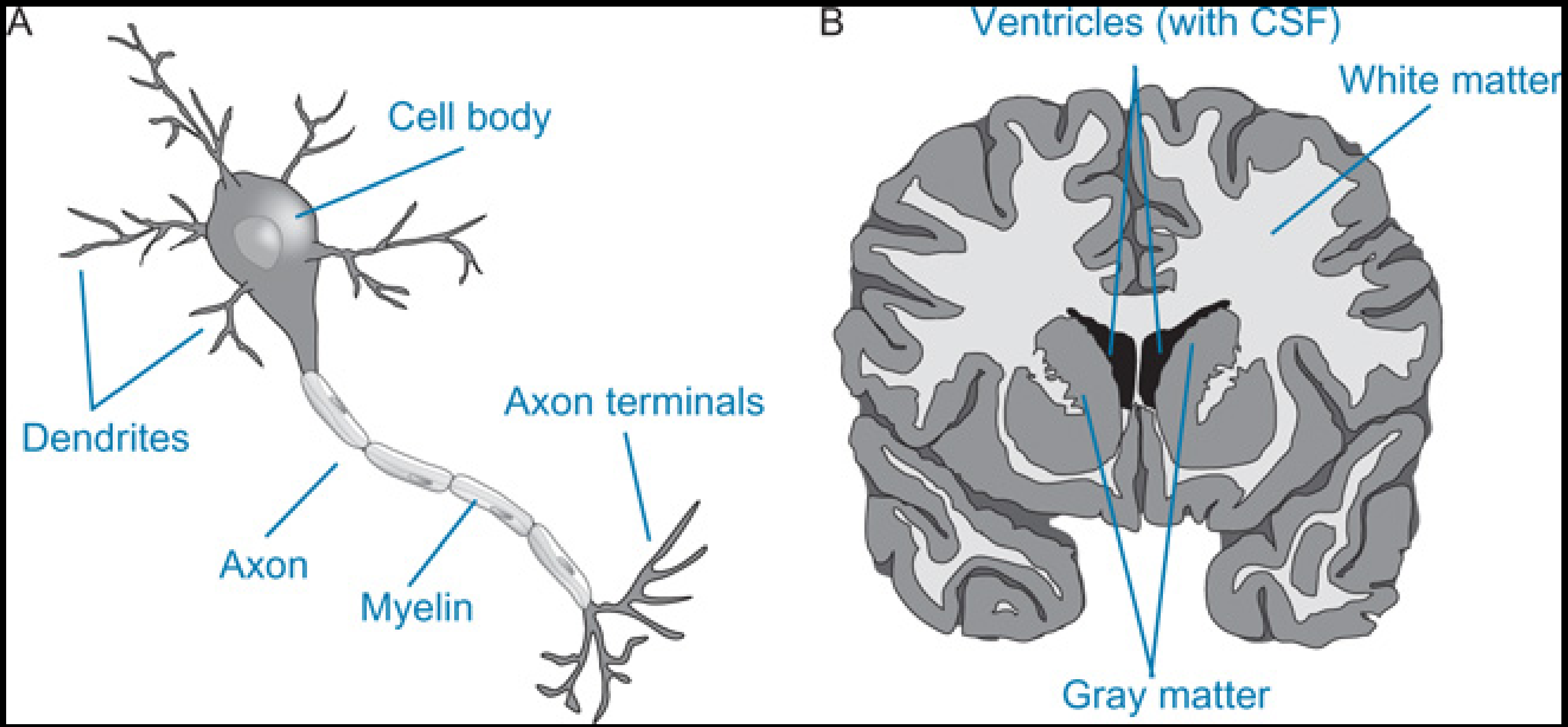
Standard X-ray technology alone cannot produce detailed images of the brain (poor soft-tissue contrast)

Structural brain imaging

Neural cell bodies: biomolecules + proteins + carbohydrates

Axons: fat (myelin)

Ventricles: cerebro-spinal fluid (saline solution)



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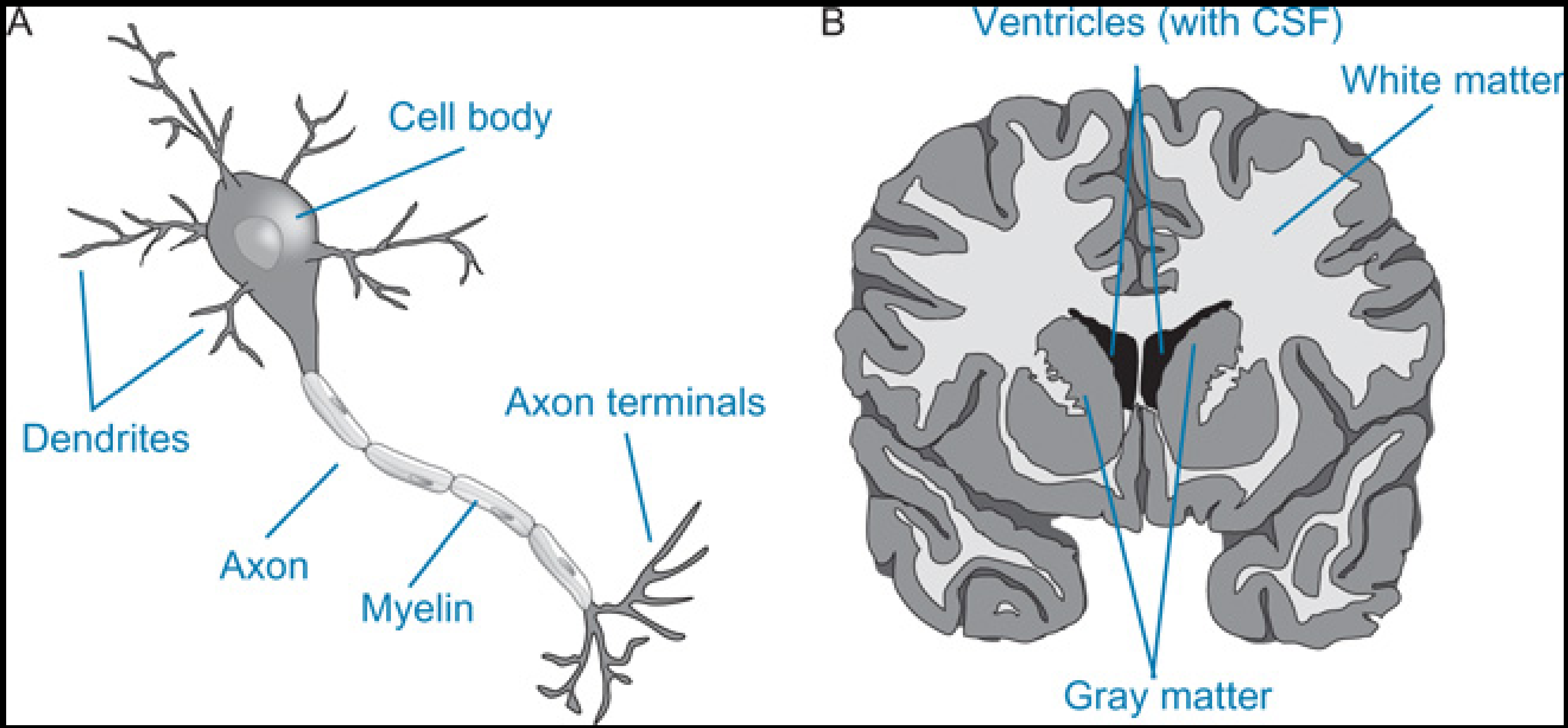
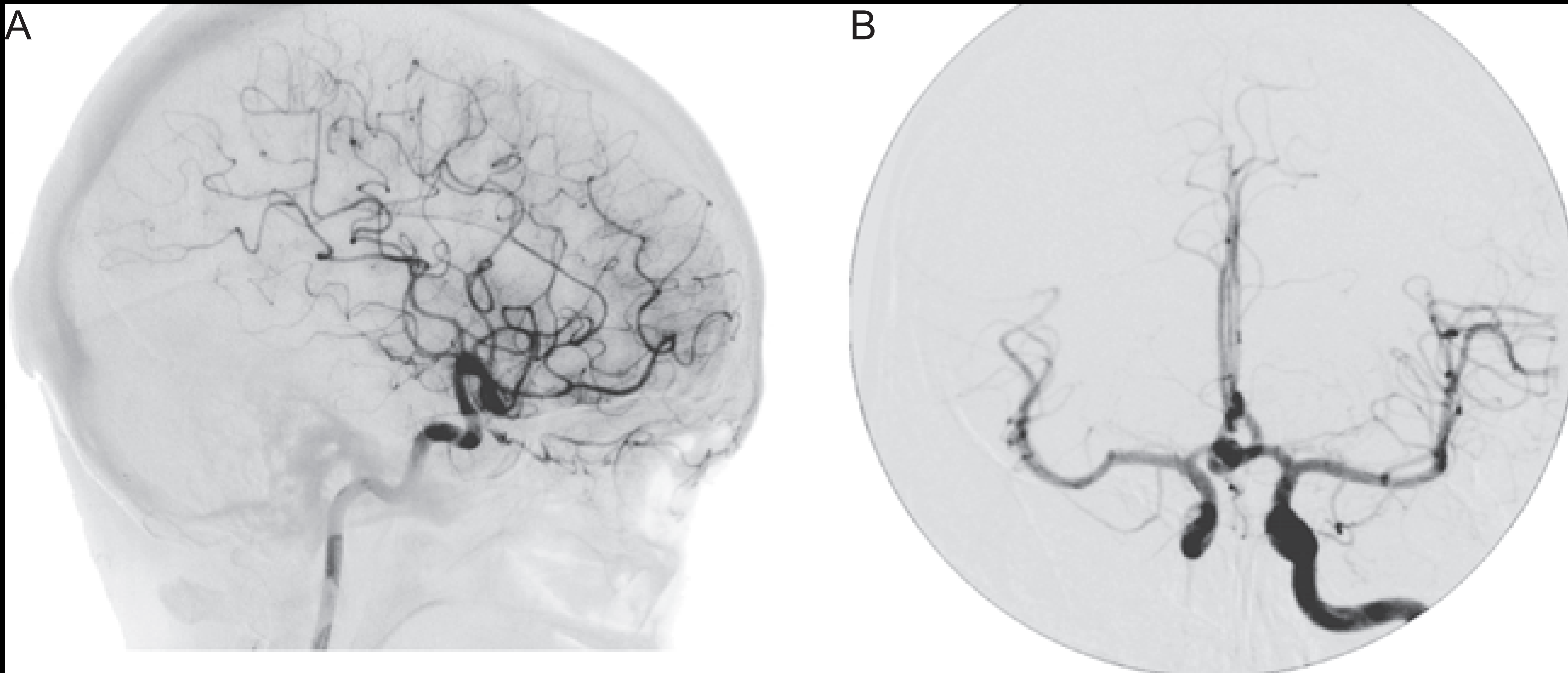


The goal: to use these differences in composition to form the basis of an image

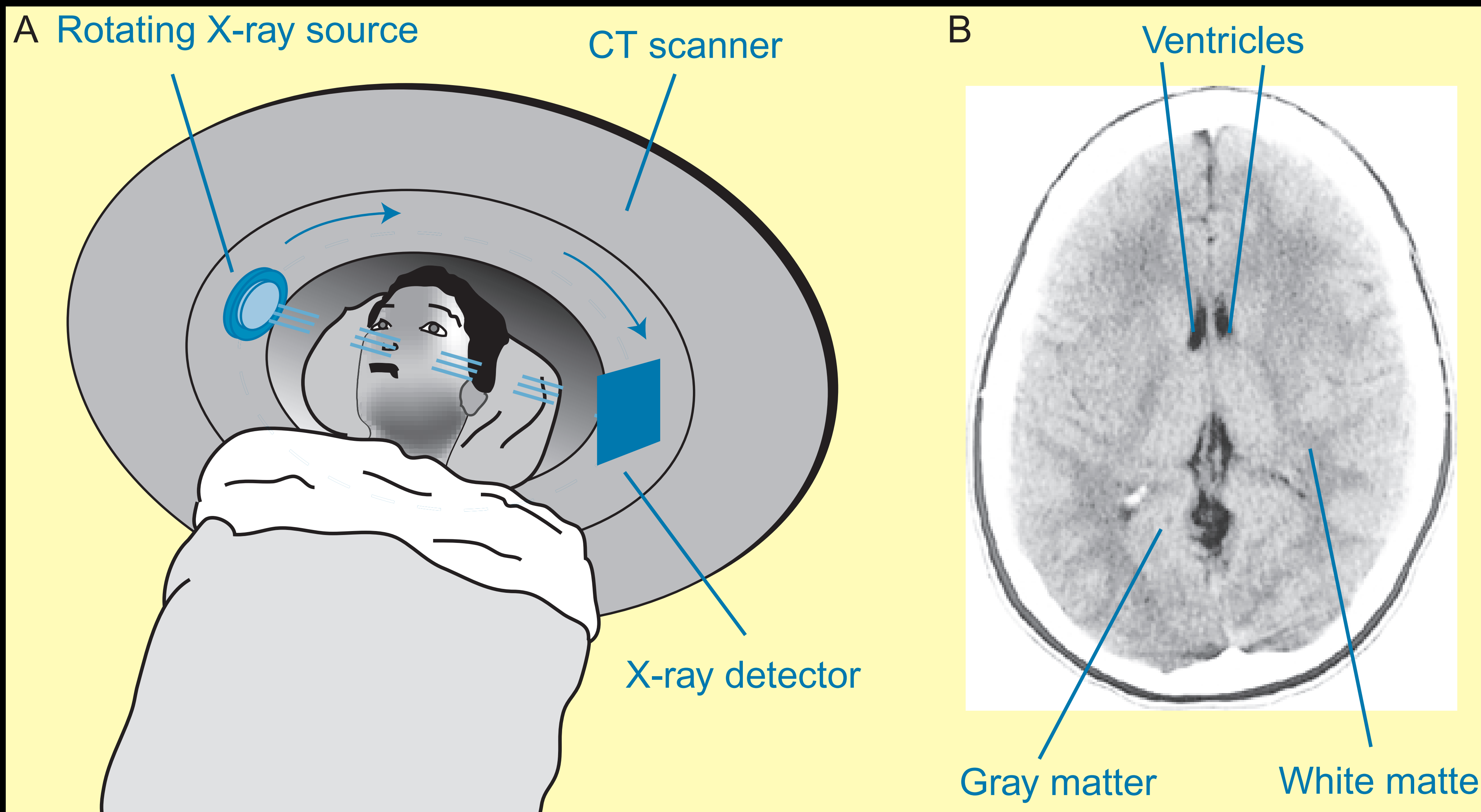
Structural brain imaging



Cerebral angiography

Solution 1: insert a dye that absorbs X-ray better than surrounding tissue

Structural brain imaging



Computerized tomography

Solution 2: take multiple scans from multiple angles and combine them

Structural brain imaging

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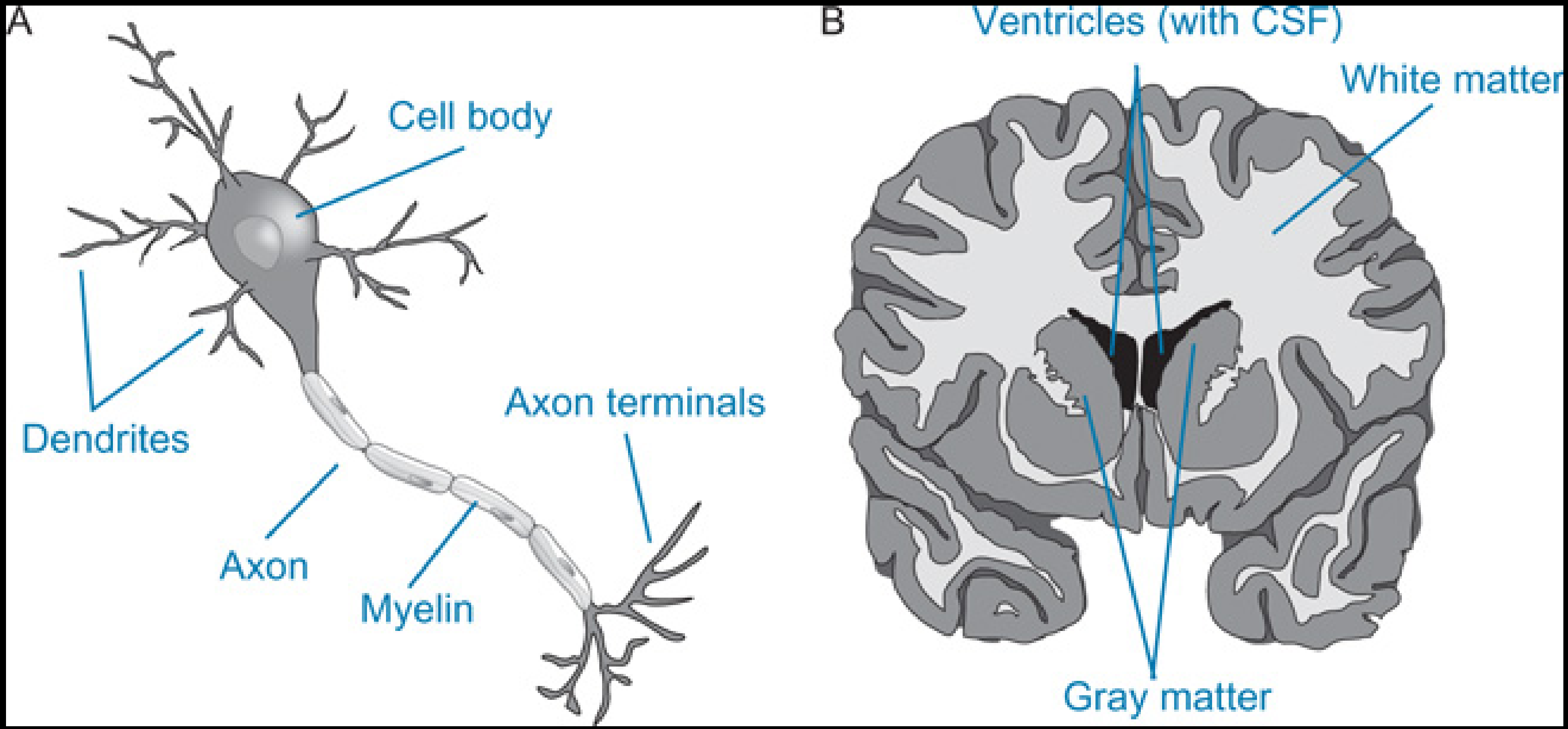

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Magnetic Resonance Imaging

Contrast:
magnetic
properties

The Method of
imaging the brain
in clinics and research

Resolution < 1mm

Magnetic Resonance Imaging

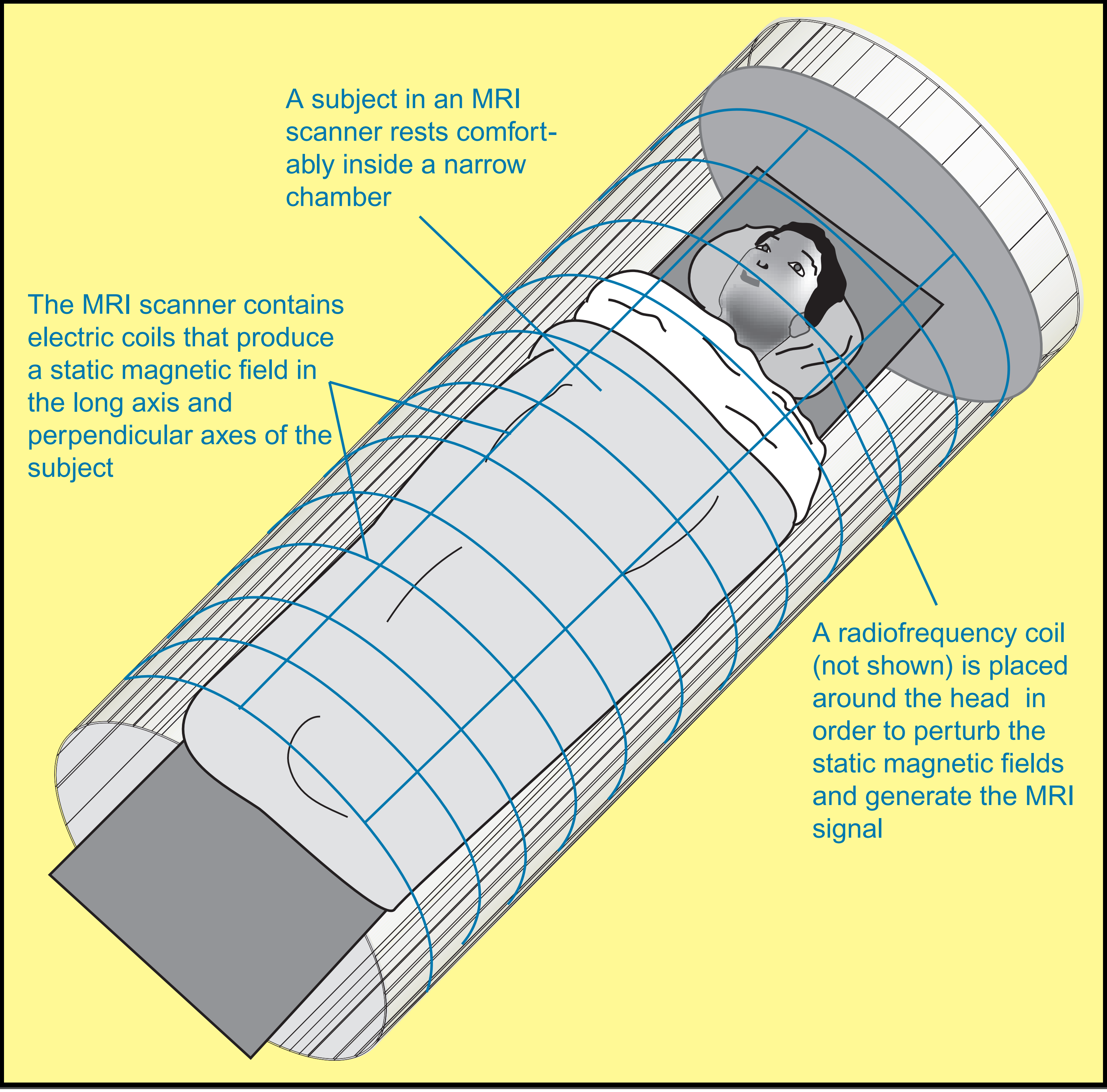
MRI takes advantage of the differential magnetic properties of neural tissue to produce an image

Utilizes magnetic properties of H^+ (abundant)

Artificially excite H^+ and measure their relaxation

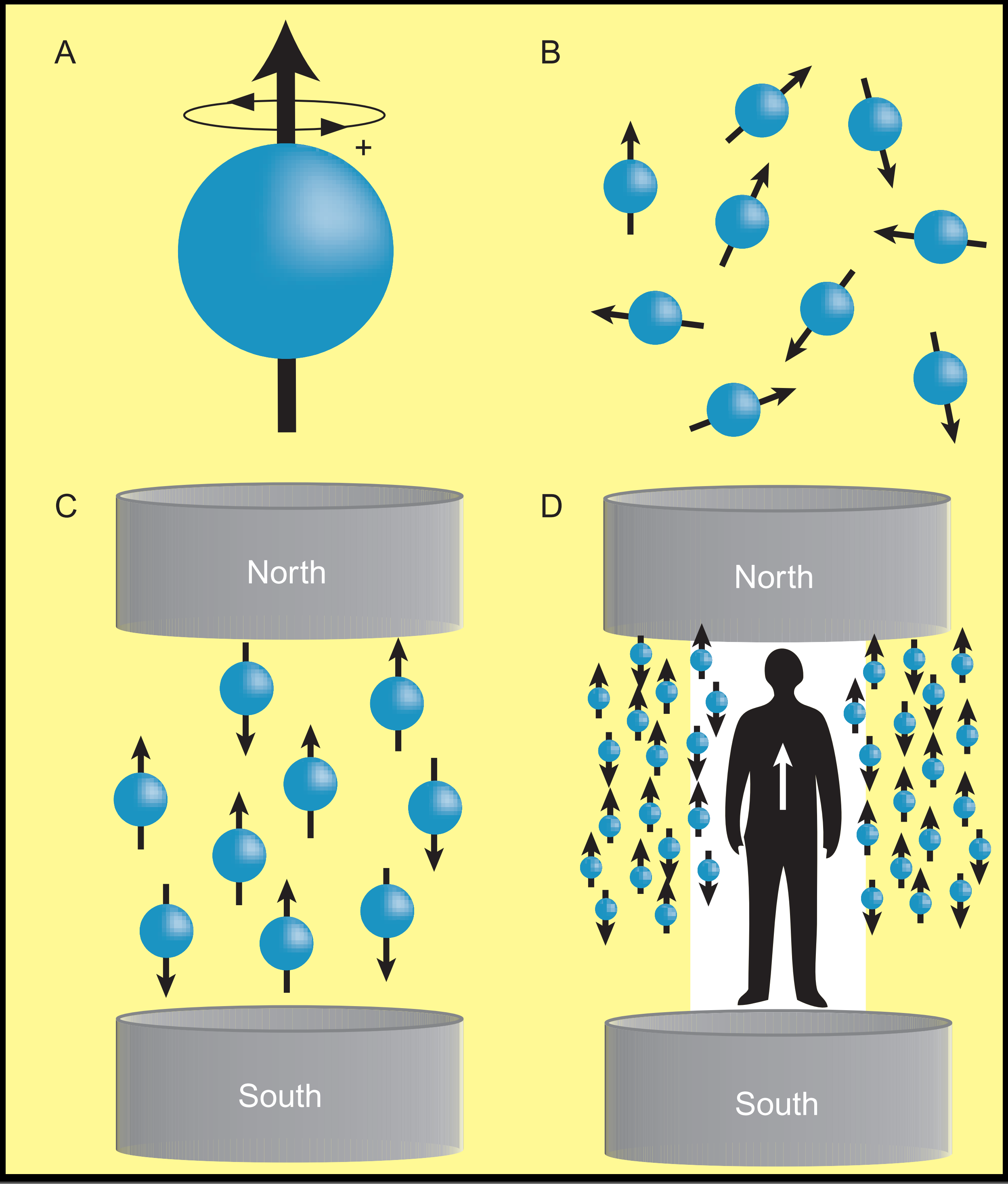
MRI: physical basis (I)

Subject is placed in a magnetic field to affect the hydrogen protons in subject's tissues



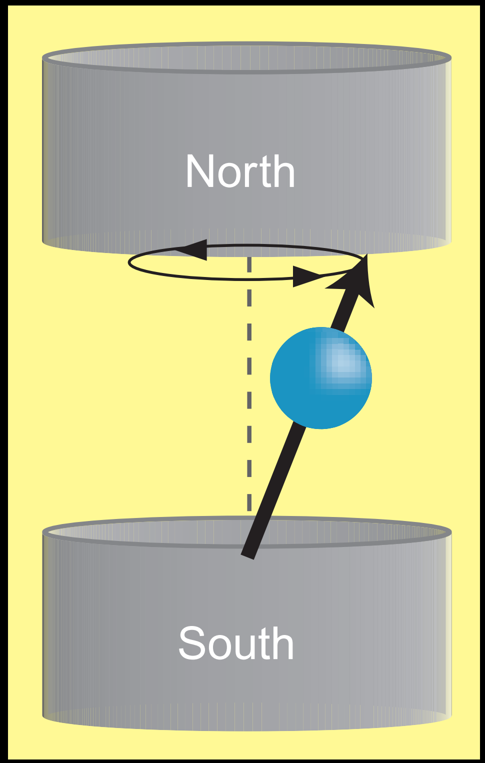
MRI: physical basis (2)

Protons can be thought as miniature magnets that align in the presence of a strong magnetic field



MRI: physical basis (3)

Protons precess with a frequency that depends on the external magnetic field (generated by the MRI scanner; 1.5-3 Teslas)



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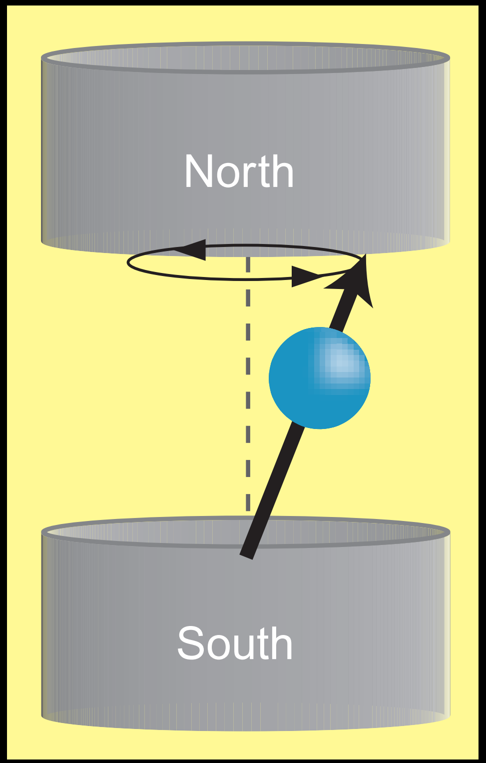

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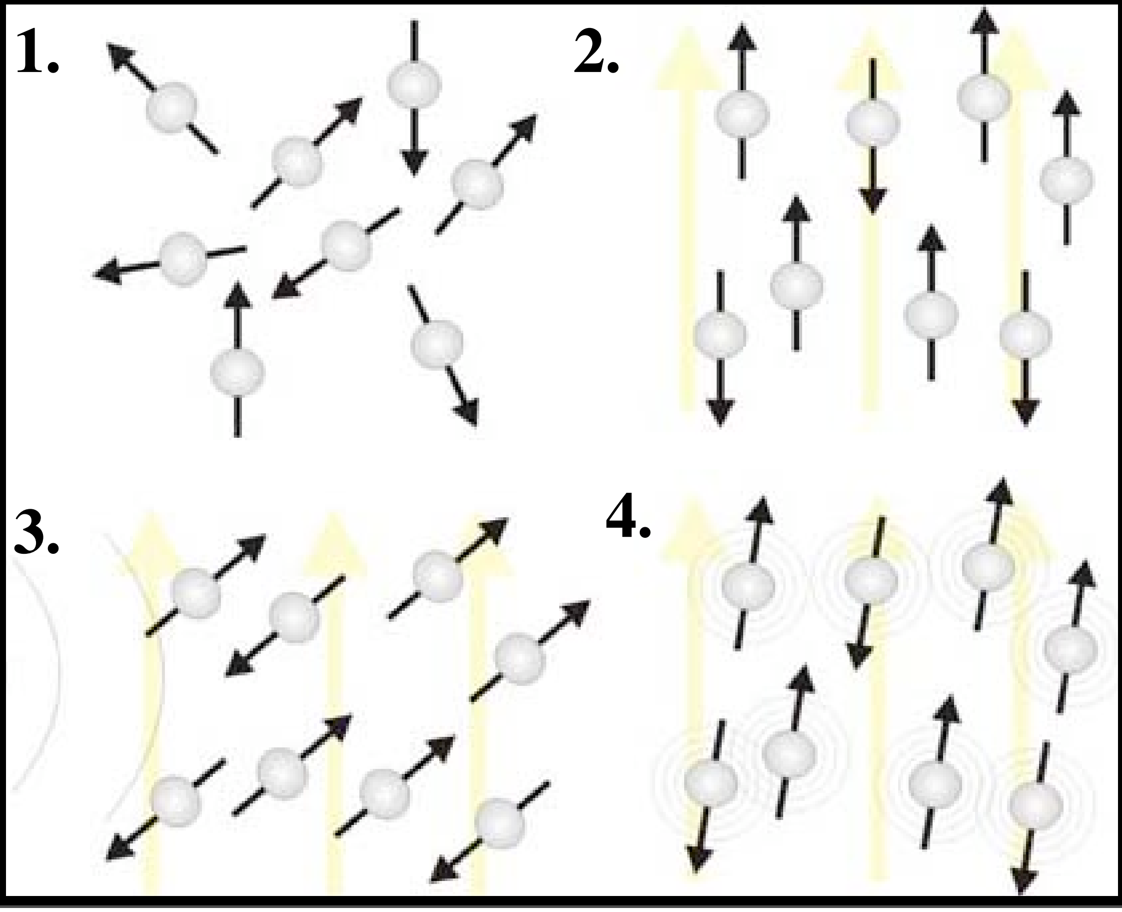
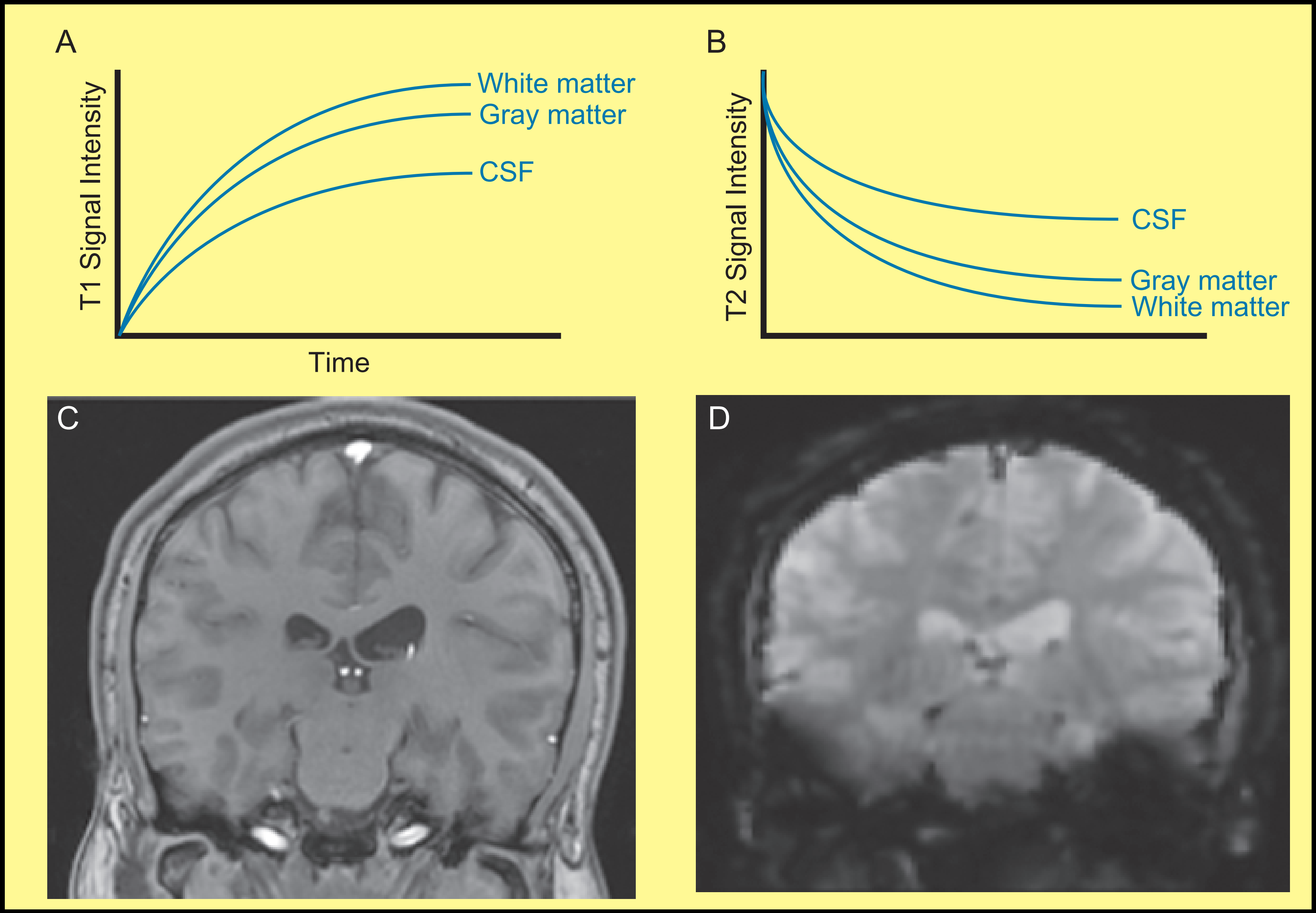


A RF pulse at the same precession frequency perturbs the protons. The times of relaxation in the longitudinal (T1) and transversal (T2) axes are measured.

MRI: generating the image

Different substances have different T1 and T2 time constants



MRI: selecting a slice of brain

RF pulse only excite protons with the same precession frequency

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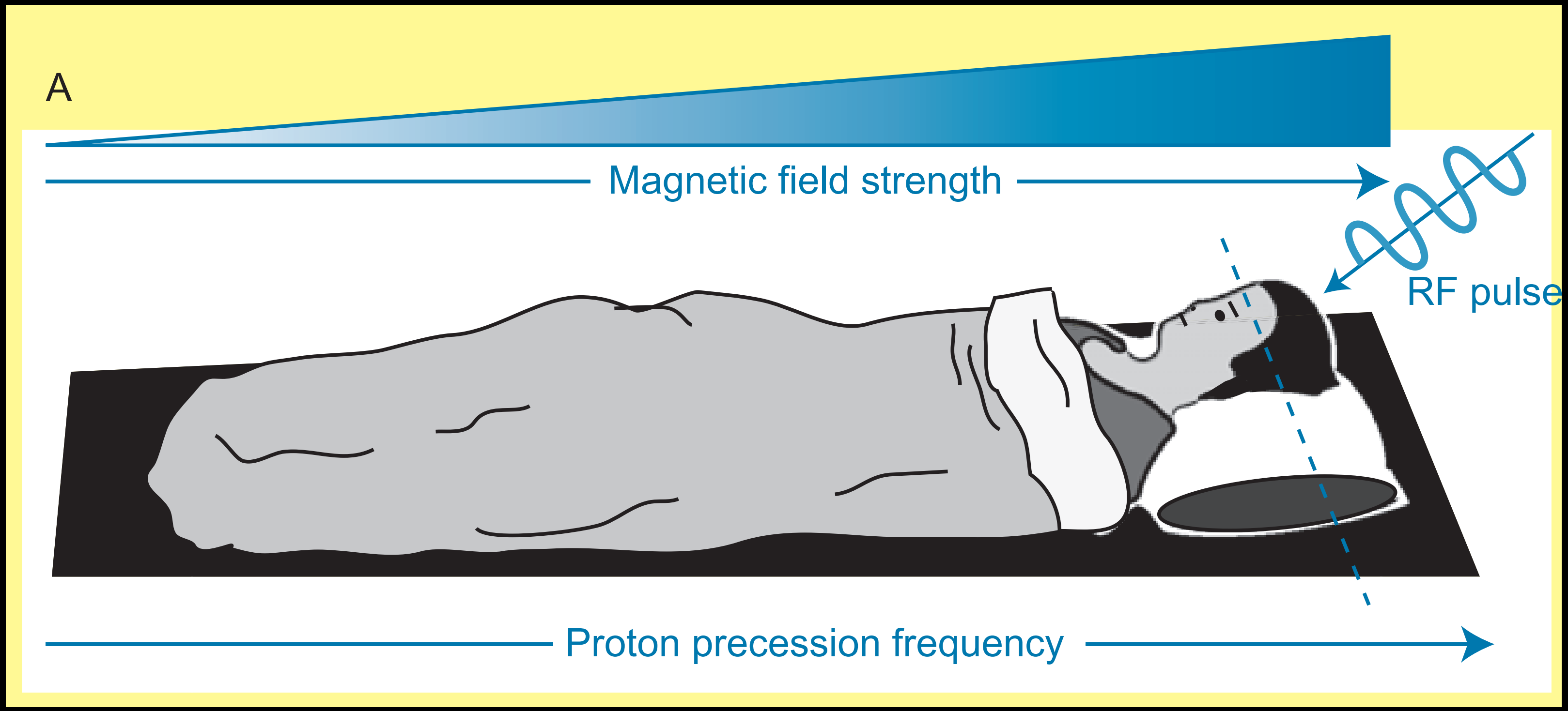
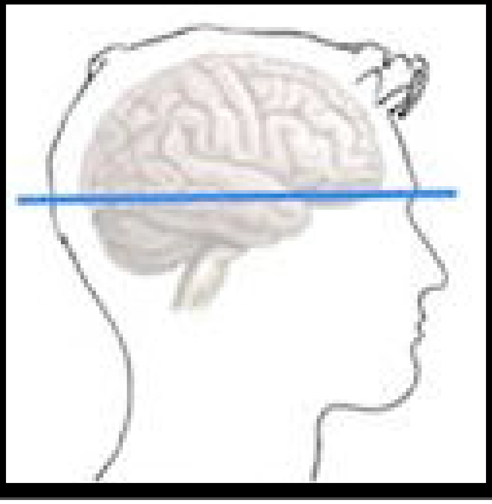
Apply an external magnetic field at a gradient, the RF affects only an specific plane





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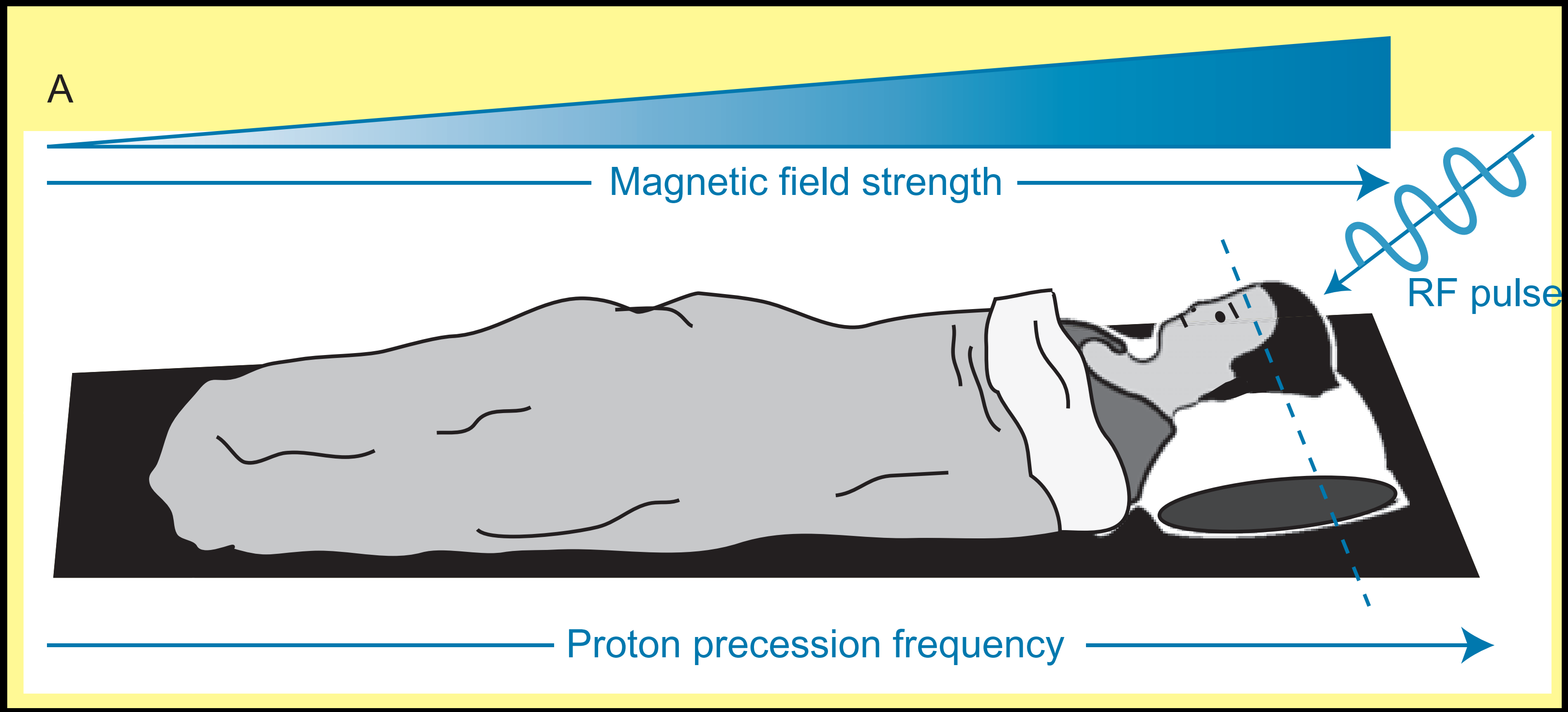
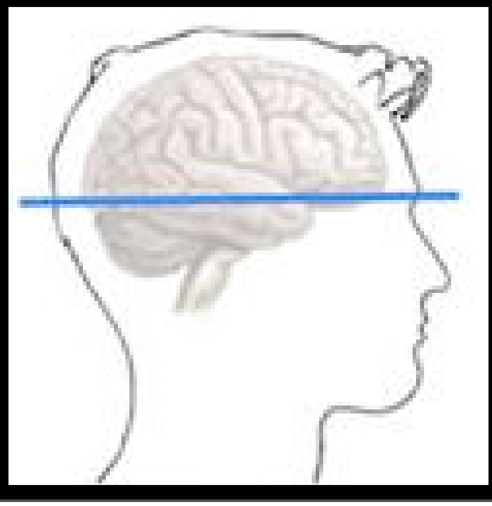


Voxel: 3d version of pixel represents cubic volume of brain space



MRI: + and -

Advantages

Beautiful images with great resolution

Entirely non-invasive

No X-rays applied

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Disadvantages

Expensive

CT better at bony structures

Not for everybody (e.g. pacemakers)

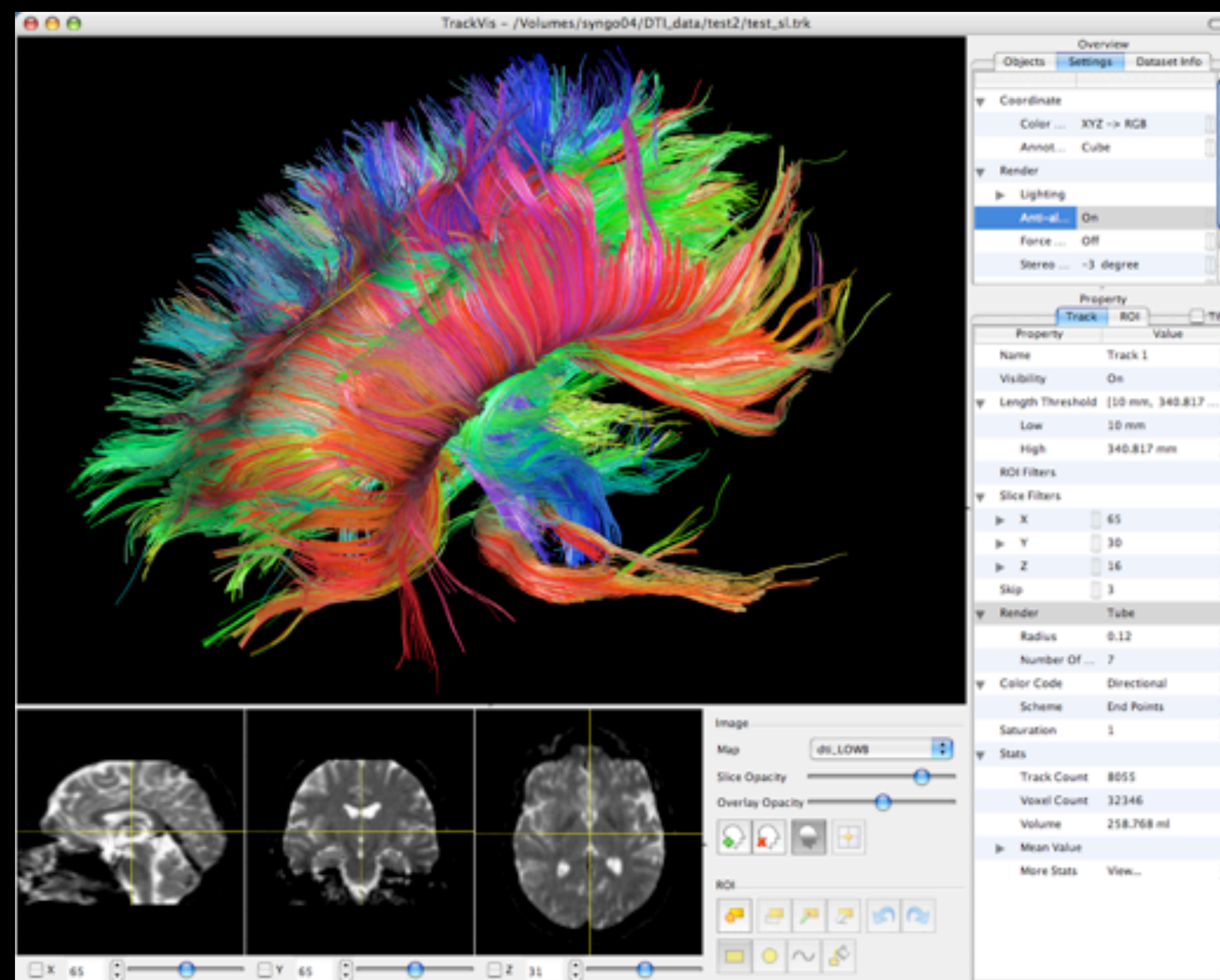
MRI: tracing connections

MRI can be tweaked to track fiber tracts (bundles of axons)

Diffusion tensor imaging: takes advantages that diffusion of water molecules is faster along fibers

Which areas of the brain are connected

No direction of the connections



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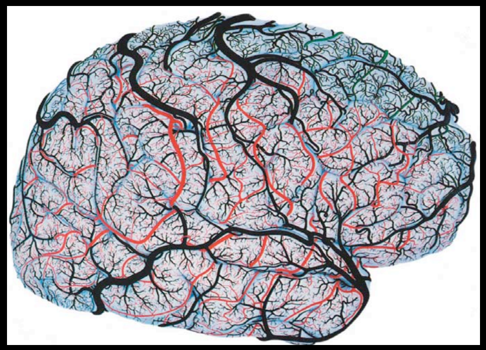
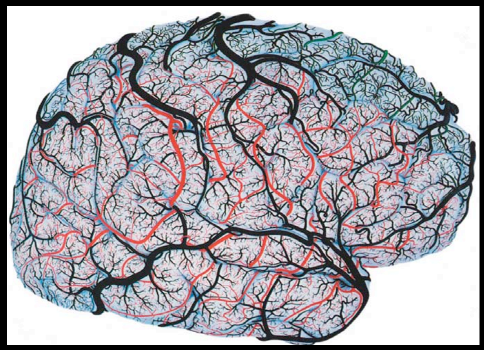
Functional brain imaging



The brain is **bloody** and **electric**

Functional brain imaging



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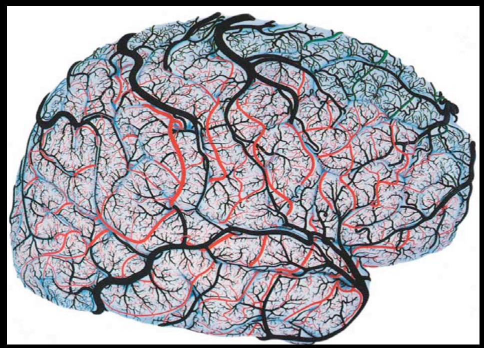
Blood

Increase in neuronal activity ⟶ increase in metabolic demand for glucose and oxygen ⟶ increase in cerebral blood flow to the active region

Blood flow is an indirect, slow measure of neural activity

Functional brain imaging



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Blood

Increase in neuronal activity → increase in metabolic demand for glucose and oxygen → increase in cerebral blood flow to the active region

Blood flow is an indirect, slow measure of neural activity

Electricity

Neurons communicate by producing tiny electrical impulses

Electricity is a direct measure of neural activity

Functional brain imaging

Non-invasive recording from human brain (Functional brain imaging)

Hemodynamic techniques

Positron emission tomography (PET)

Functional magnetic resonance imaging (fMRI)

Excellent spatial resolution (~1-2mm)
Poor temporal resolution (~1sec)

Electro-magnetic techniques

Electro-encephalography (EEG)

Magneto-encephalography (MEG)

Poor spatial resolution (esp. EEG)
Excellent temporal resolution (<1msec)

First functional brain imaging

Functional MRI (fMRI)

Contrast:
magnetic
properties (Blood Oxygenation Level Dependent (BOLD) signal)

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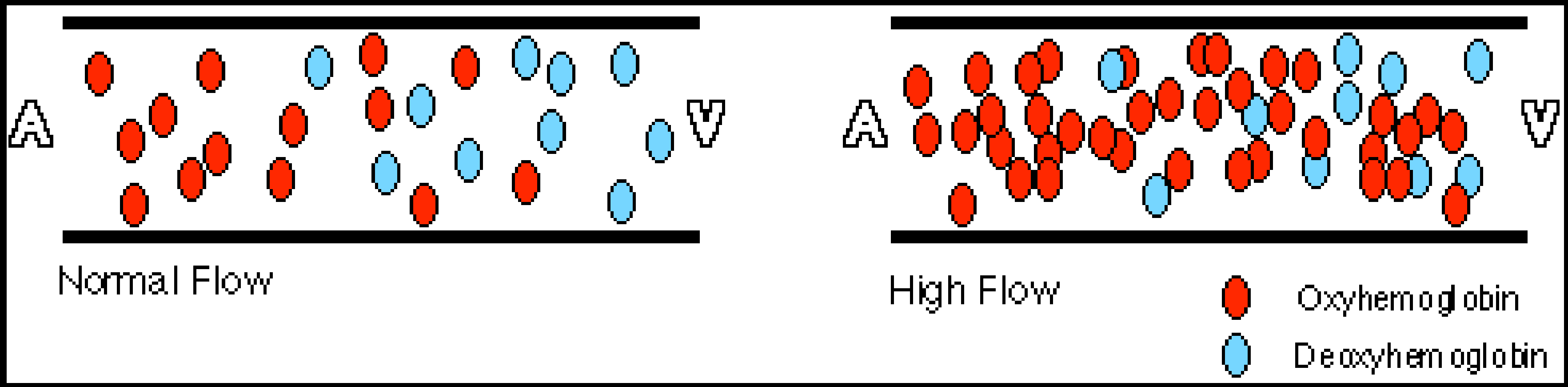
Blood is more oxygenated in an activated region of the brain than in a nonactivated region



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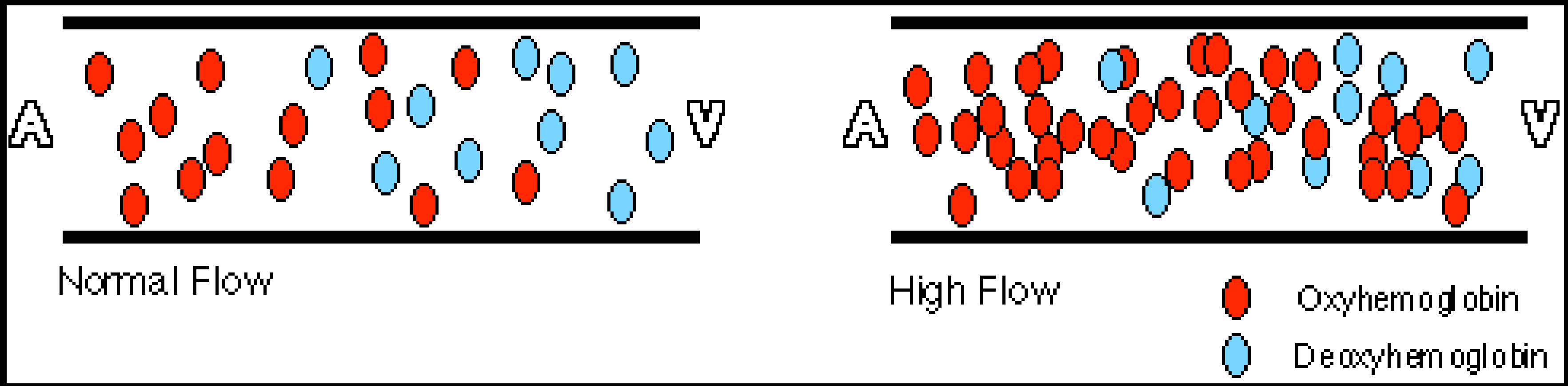
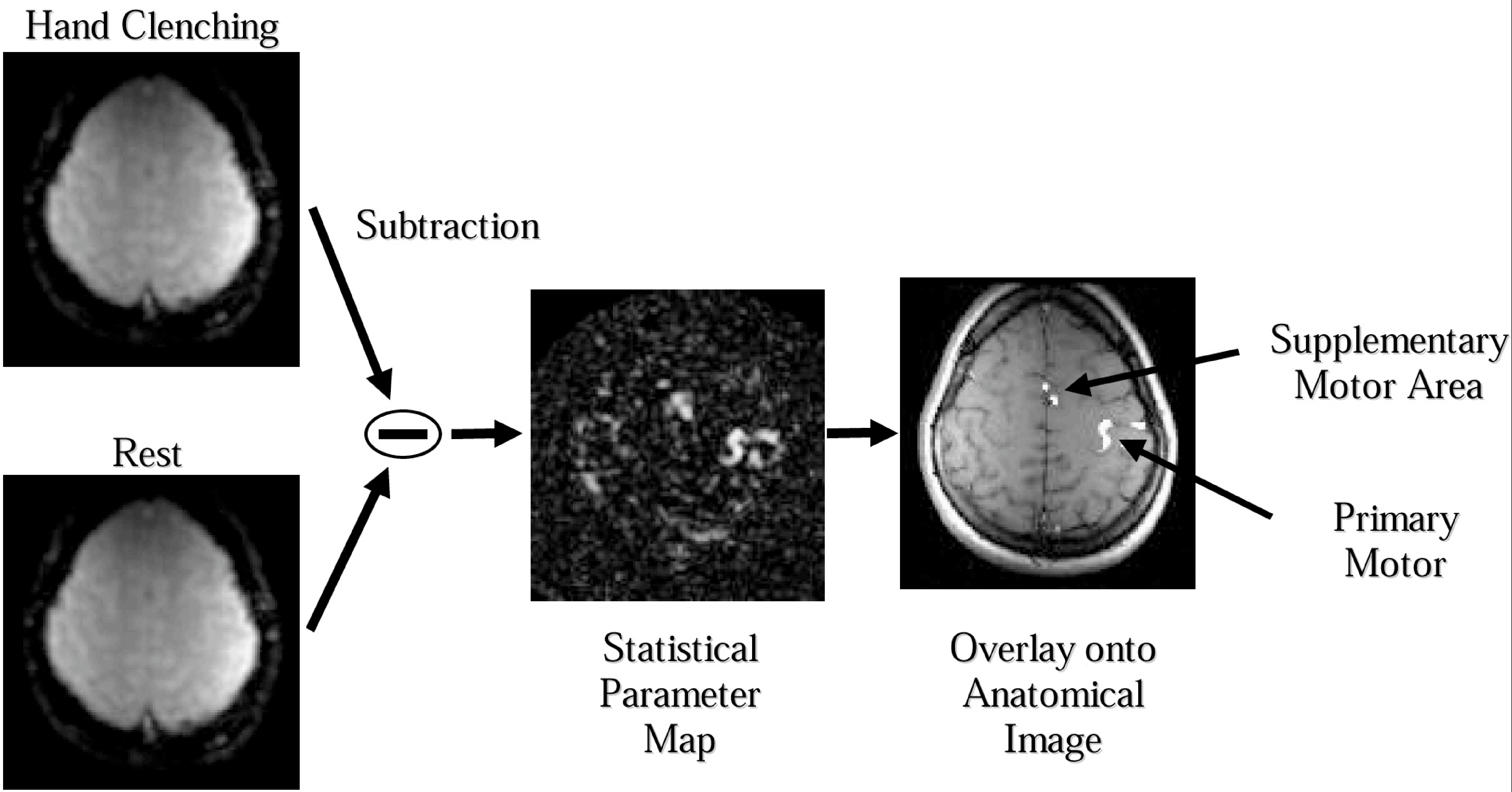


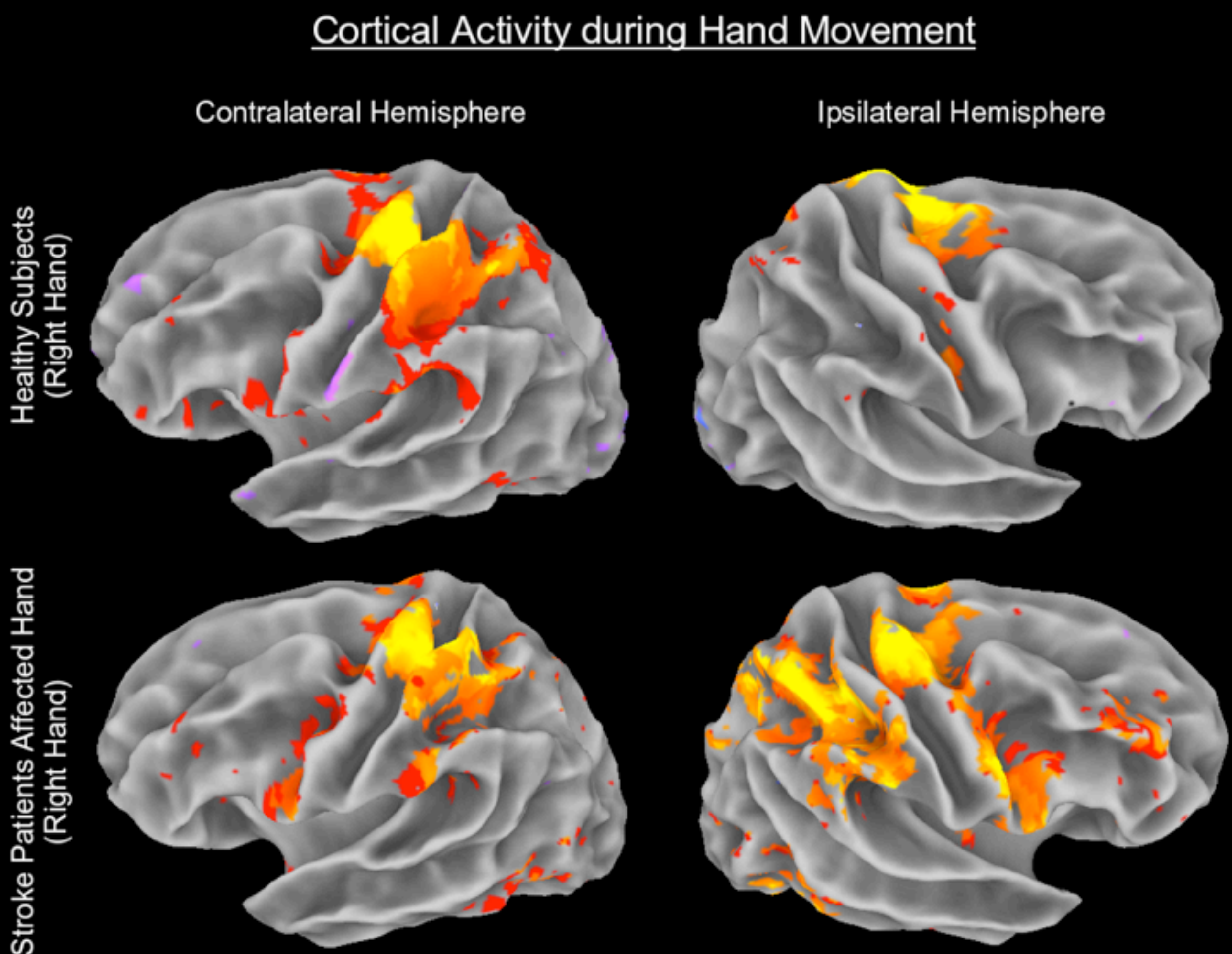
Oxyhemoglobin and deoxyhemoglobin differ in their magnetic susceptibility: Deoxy Hb has a higher magnetization decay rate than Oxy Hb

Functional MRI (fMRI)

Subtraction method



Functional MRI (fMRI)



fMRI: + and -

Advantages

Good spatial resolution (1-5 mm)

Entirely non-invasive

Rich data analysis

fMRI: + and -

Advantages	**Disadvantages**
Good spatial resolution (1-5 mm)	Temporal resolution (seconds due to the hemodynamic lag)
Entirely non-invasive	Expensive
Rich data analysis	Geography not mechanisms

Functional brain imaging

Non-invasive recording from human brain (Functional brain imaging)

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Electromagnetic techniques

MEG

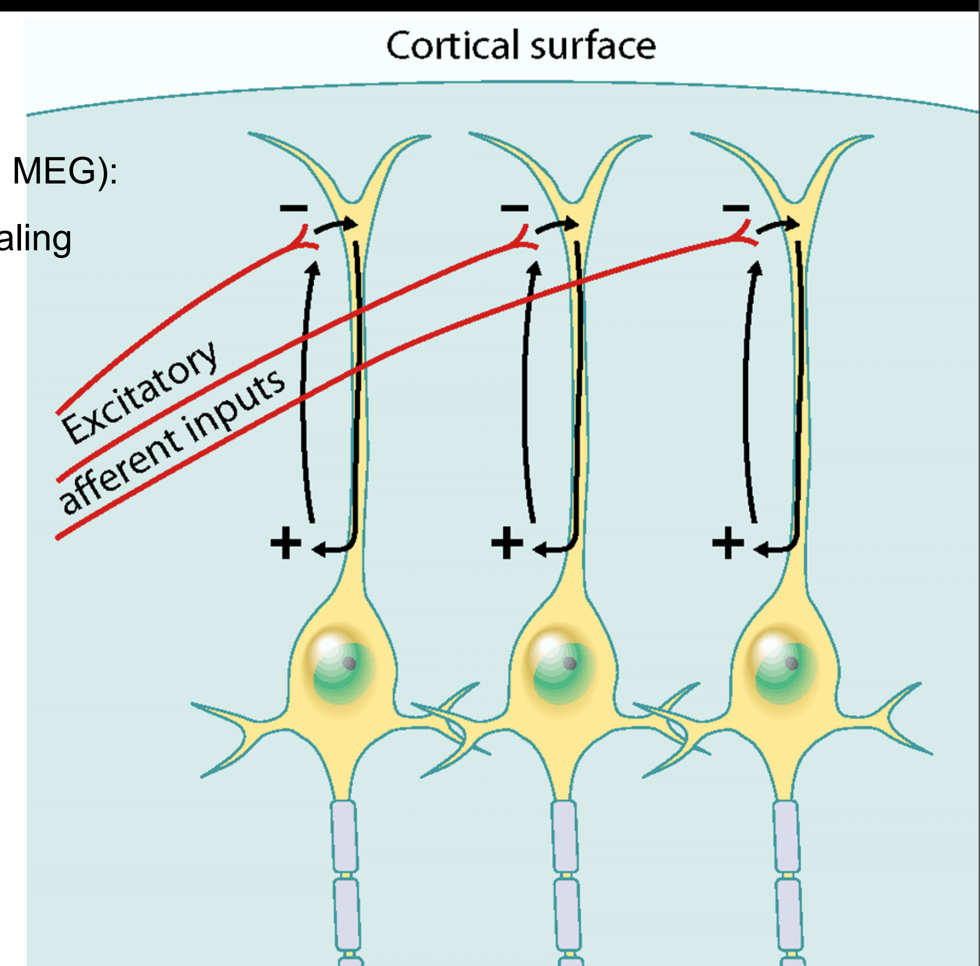
EEG

Electromagnetic techniques

Main source of the signal: post-synaptic current flow along the dendrites of (pyramidal) neurons

Local field potential (ERP, MEG):

Integrative activity (+ signaling activity)



Electromagnetic techniques

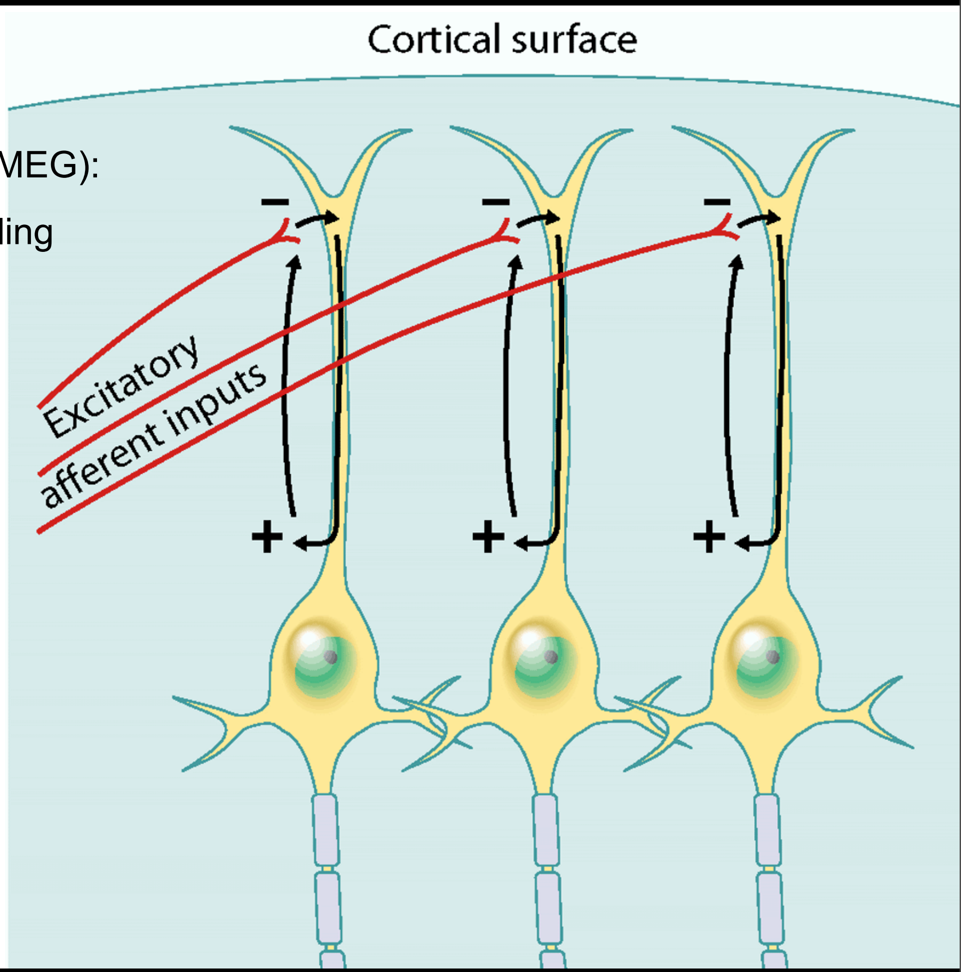
Main source of the signal: post-synaptic current flow along the dendrites of (pyramidal) neurons

Temporal resolution: <1 ms

For the electric activity to be detected outside the skull, populations of neurons must fire in synchrony (50k for MEG, millions for EEG)

Local field potential (ERP, MEG):

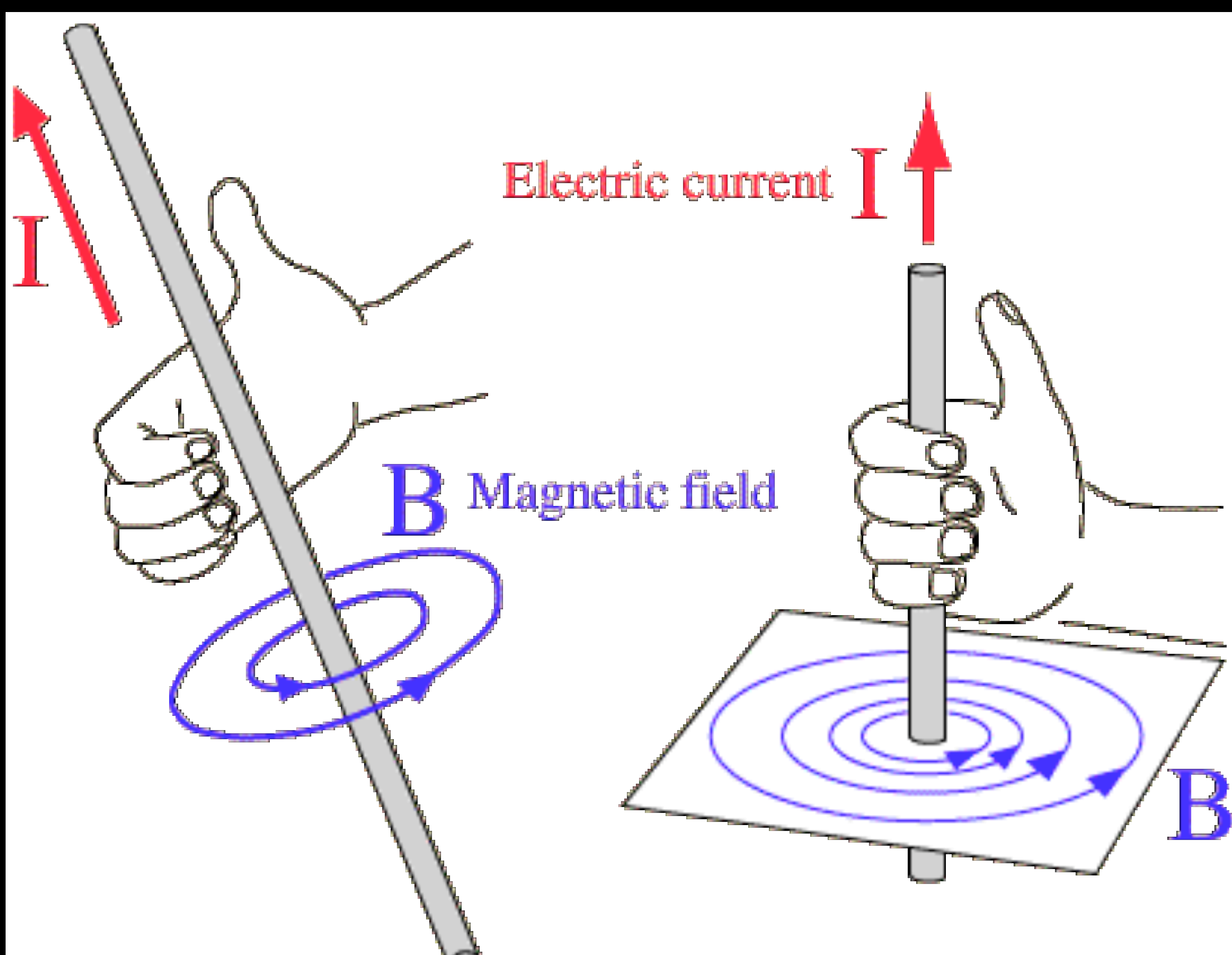
Integrative activity (+ signaling activity)



Electromagnetic techniques

An electric current creates a magnetic field around it

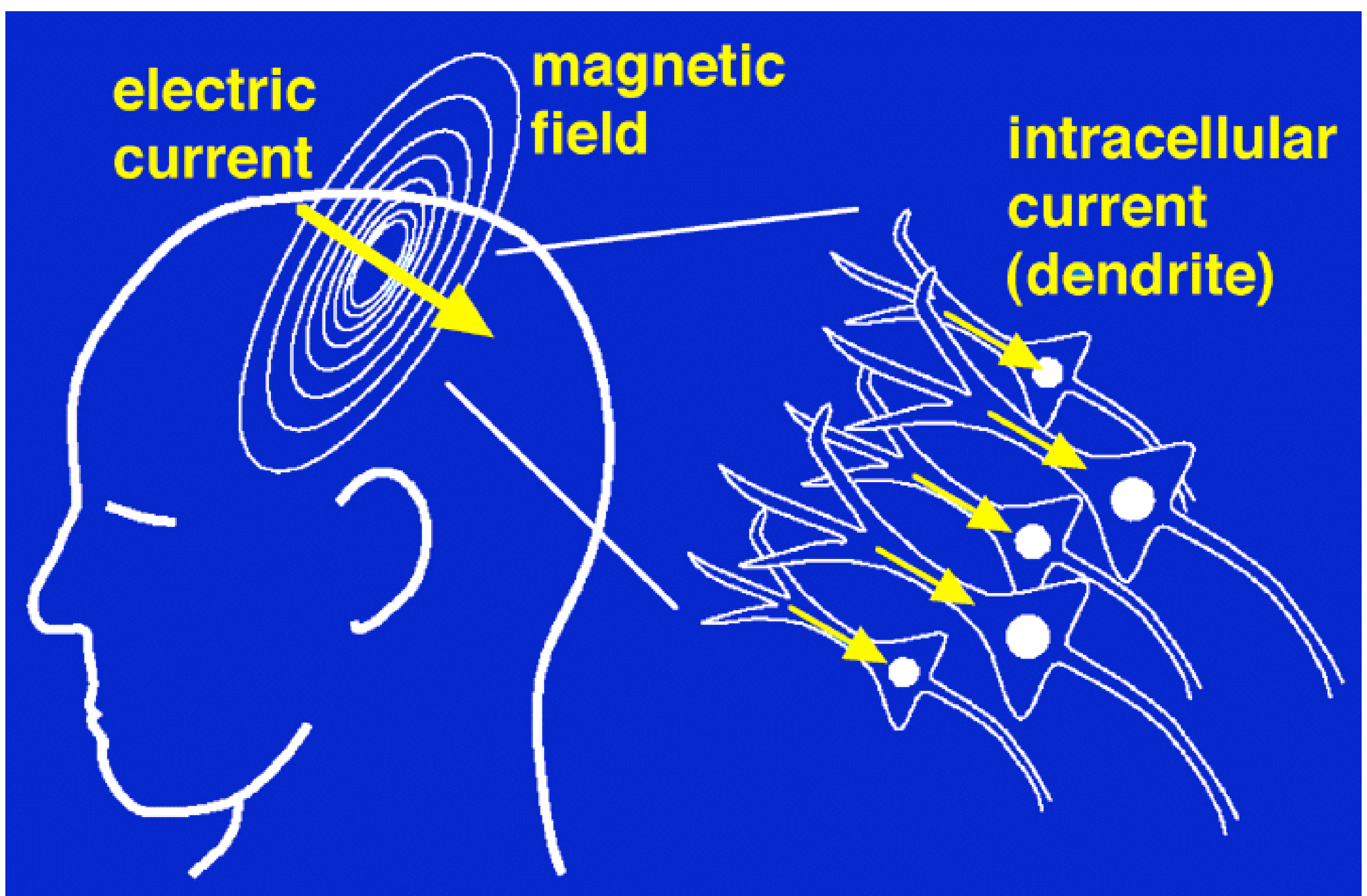
The right-hand rule:

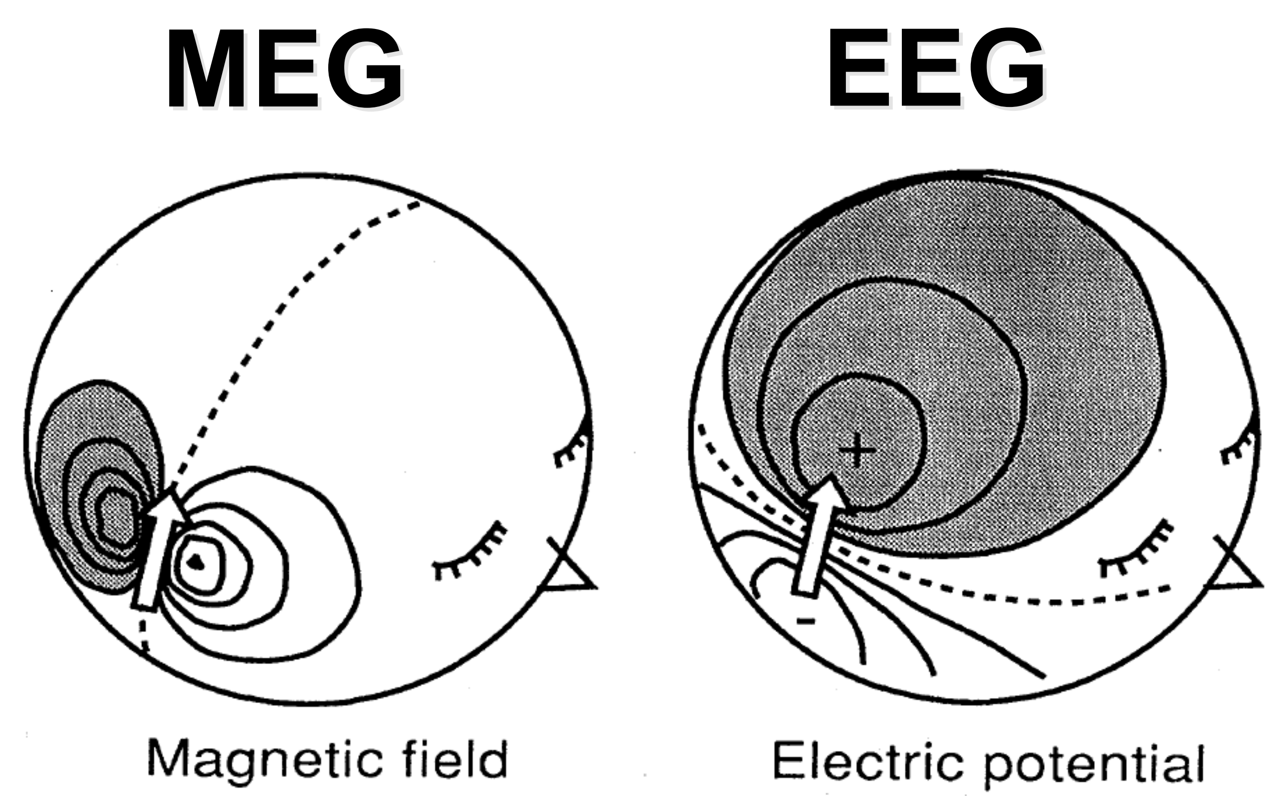


Electromagnetic techniques

EEG (electroencephalography): electric potentials

MEG (magnetoencephalography): magnetic fields

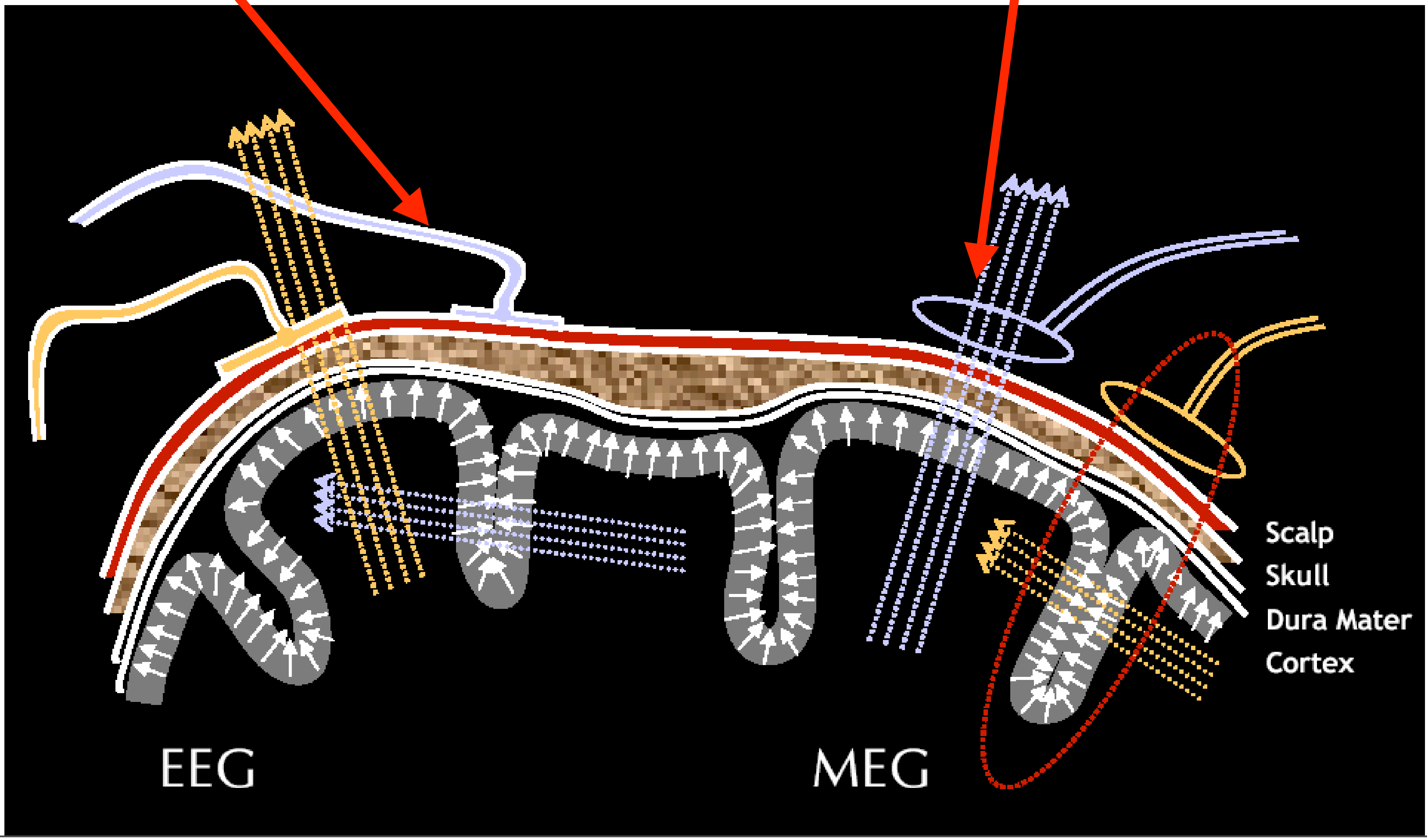




Electromagnetic techniques

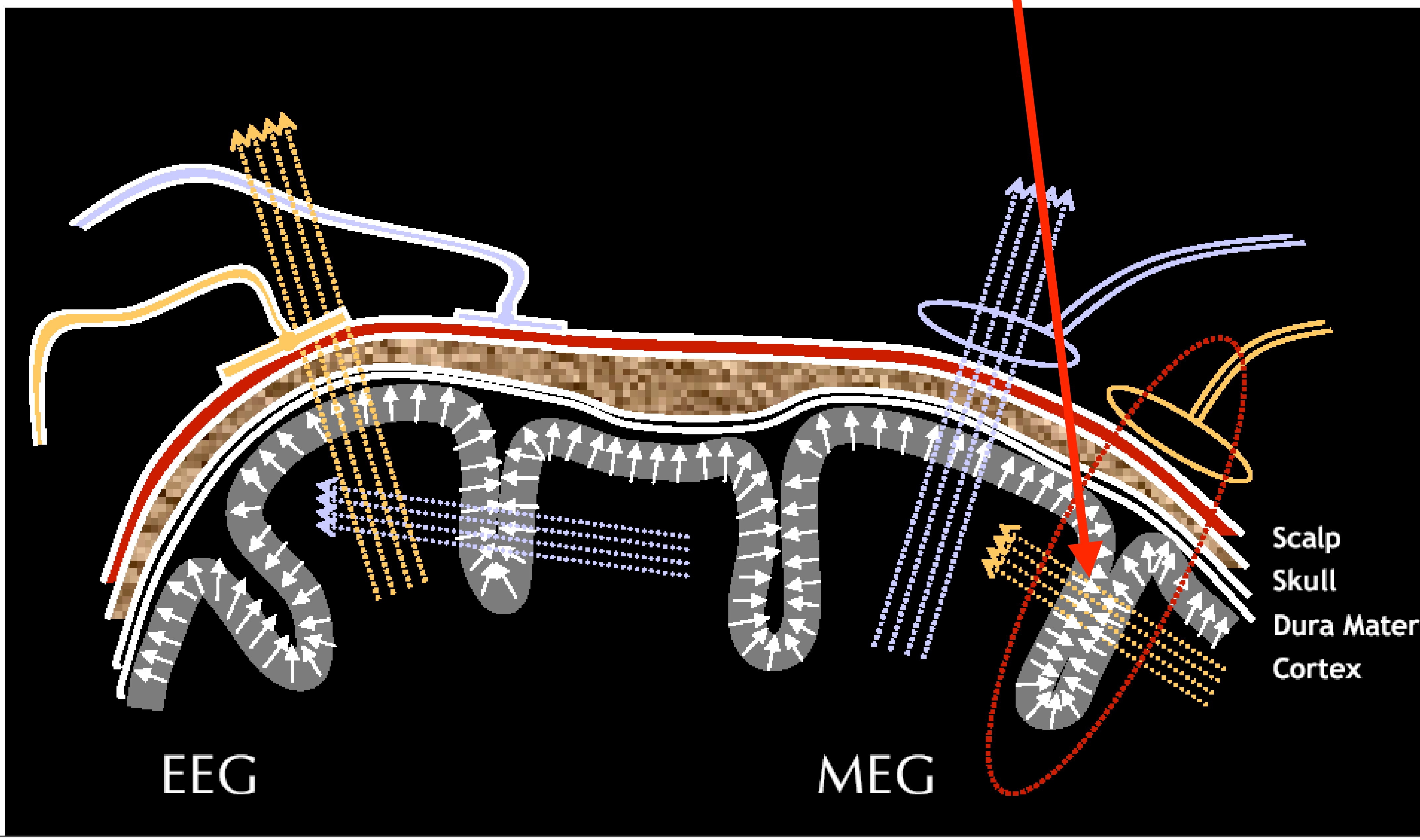
EEG electrodes on the scalp

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



Electromagnetic techniques

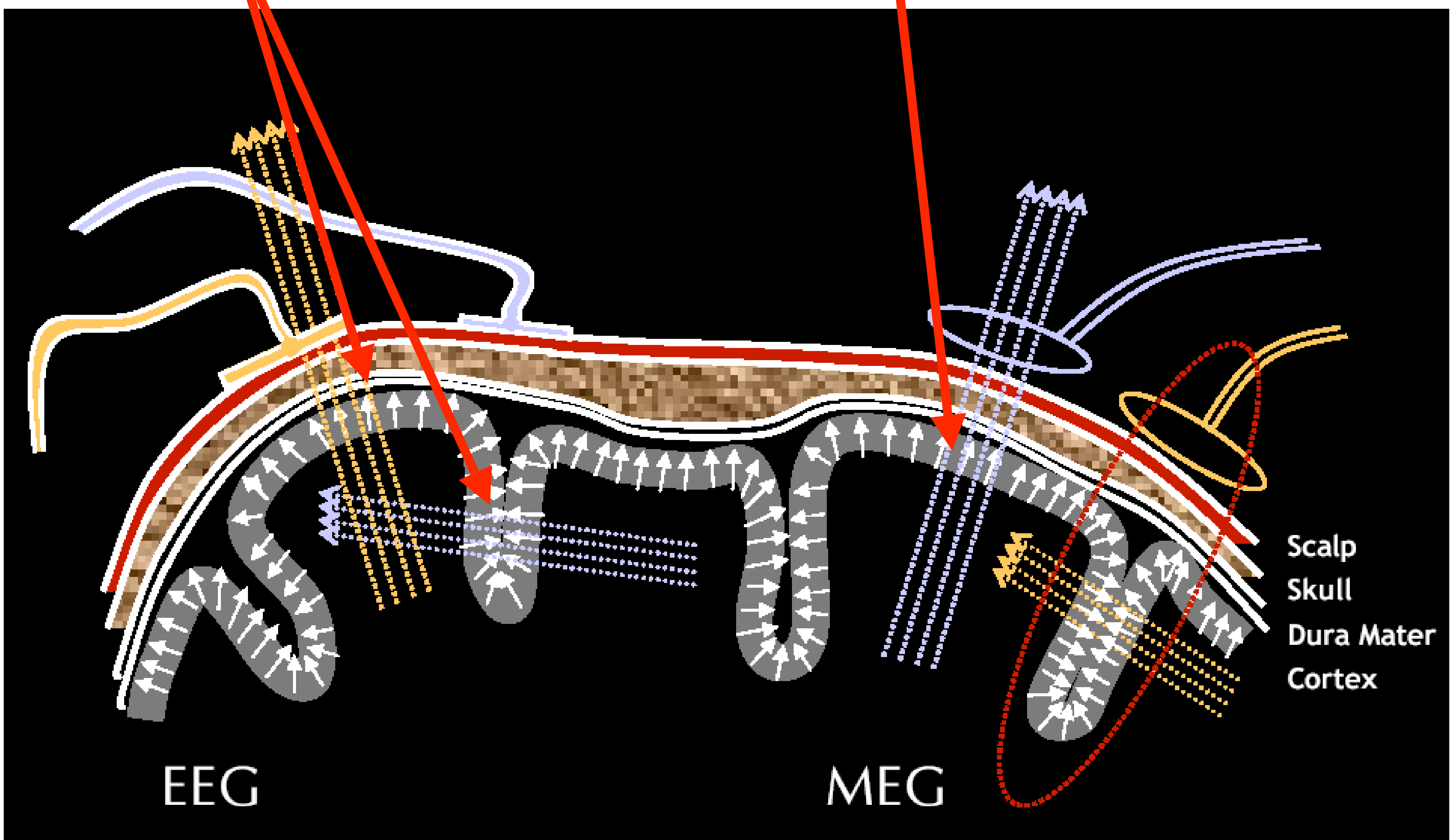
MEG signal is dominated by currents oriented tangential to the skull.



Electromagnetic techniques

EEG picks up tangentially and radially oriented currents equally.

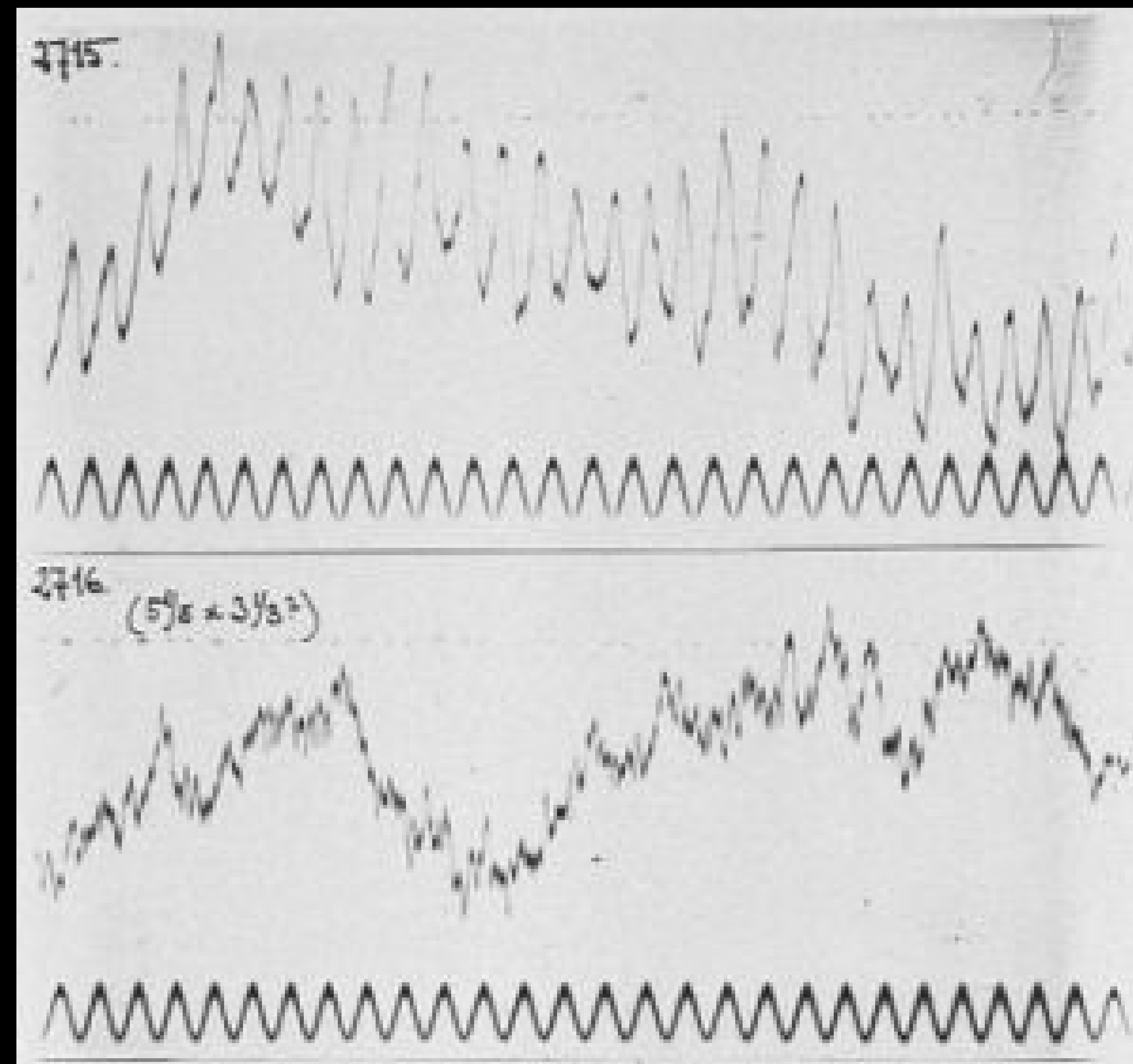
Currents oriented perfectly radial to the skull are missed in MEG. But there is very little signal that is so perfectly radial.



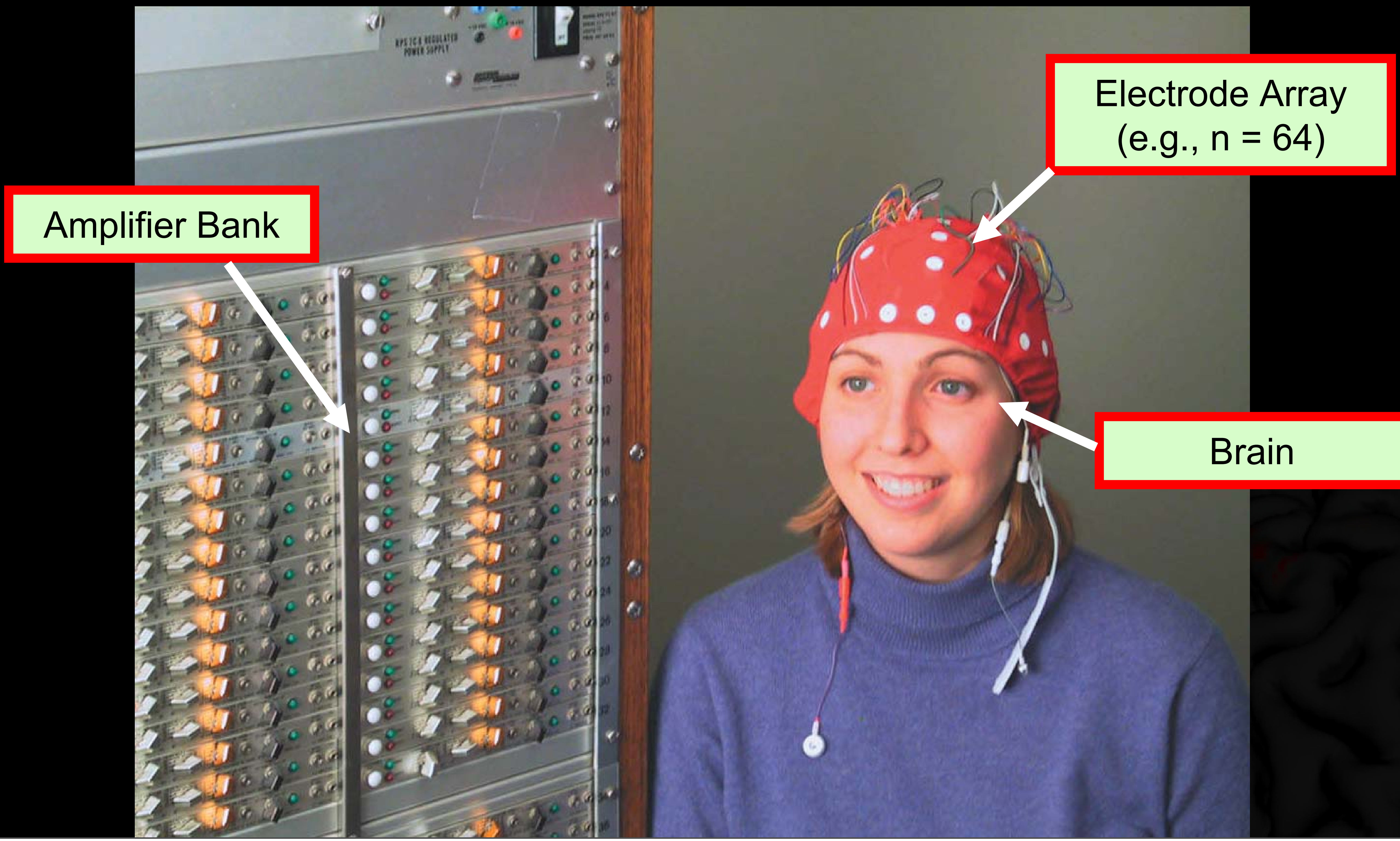
EEG

EEG recordings

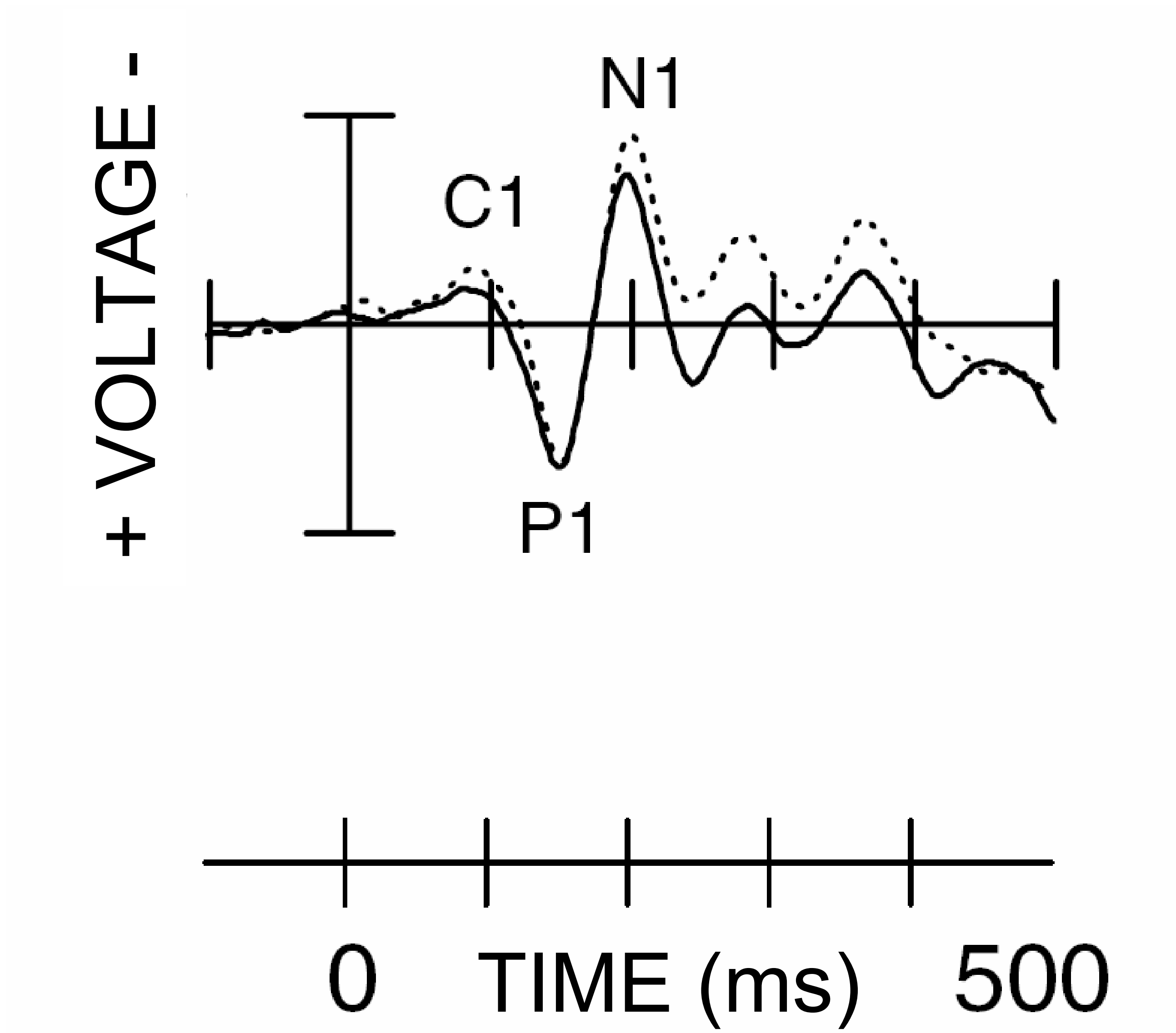
Hans Berger
(circa 1925-1935)

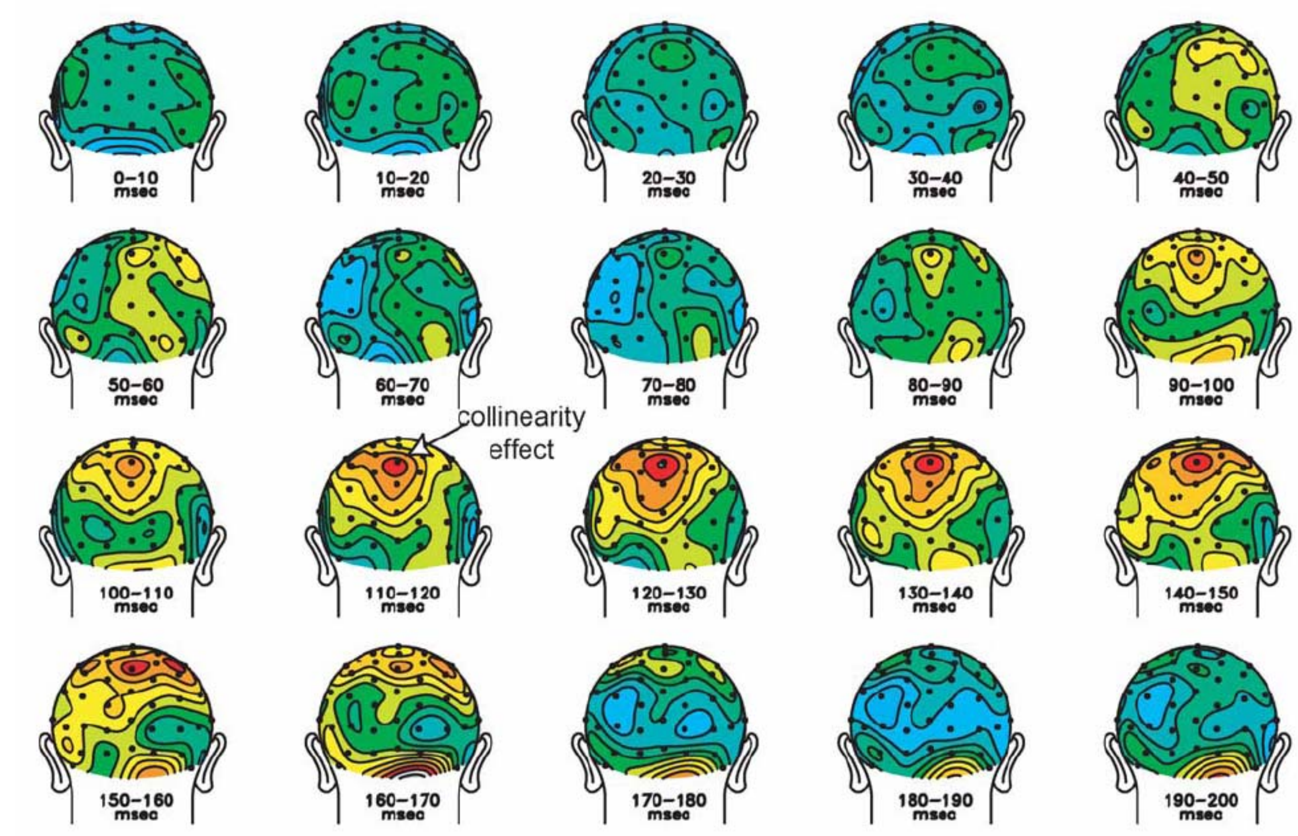


EEG



EEG





TIME
(in 20ms Intervals)

Averaging over similar trials, Event Related Potentials (ERPs) have excellent temporal resolution (but coarse spatially)

EEG

Temporal and spatial resolution of EEG:

* Millisecond temporal resolution

* Localization of neural generators is complicated. Different tissues in the skull differ in their conductivities and electric potentials get distorted when passing through these structures)

* EEG + fMRI = powerful method to detect the precise timing and location of neural activity within the brain

MEG

Distribution of the magnetic field around the head tells you a lot about the underlying current generators

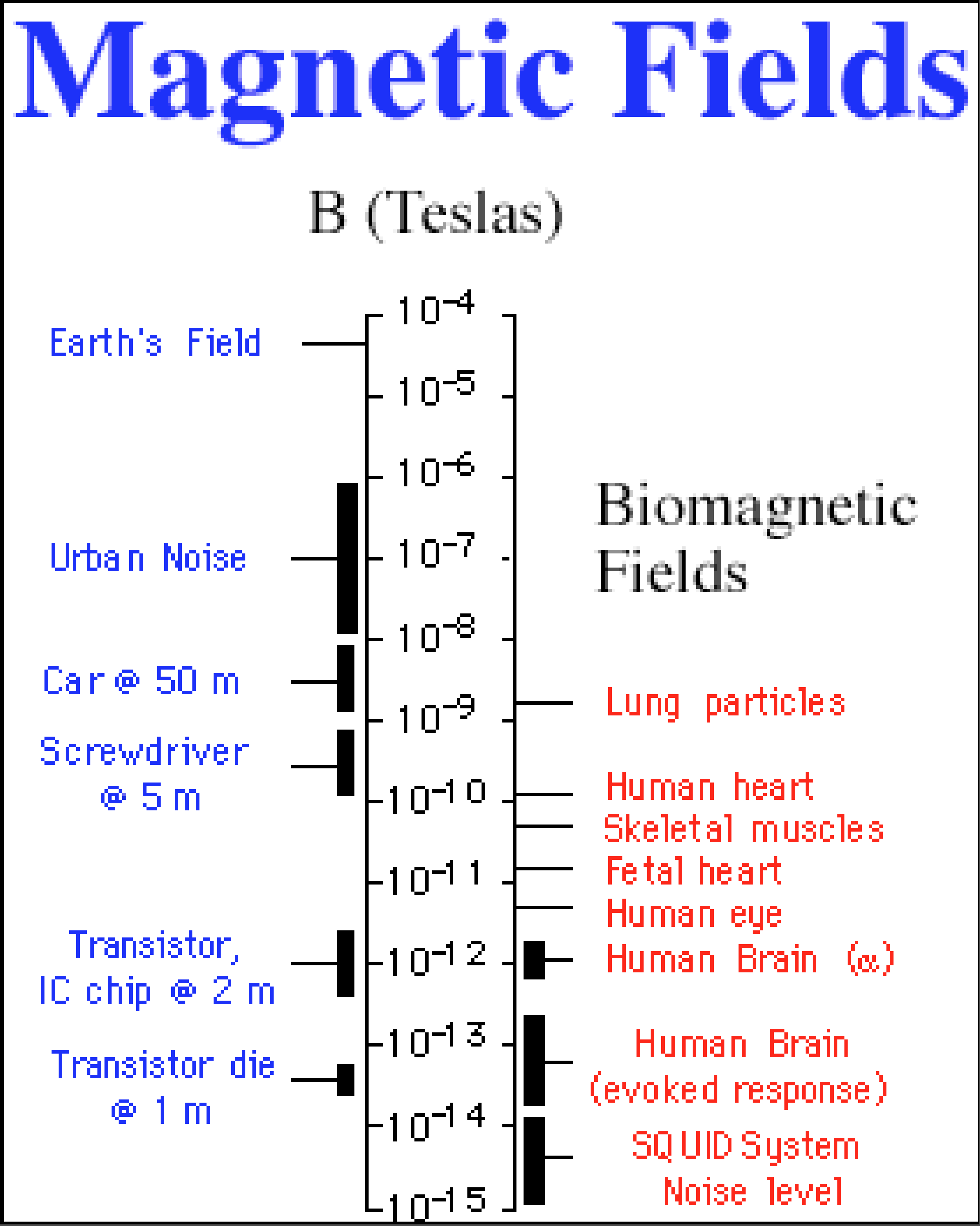
Magnetic fields pass through skull and various tissues undistorted

The main advantage over EEG: better spatial resolution (mm for cortex, worse for deeper sources)

MEG

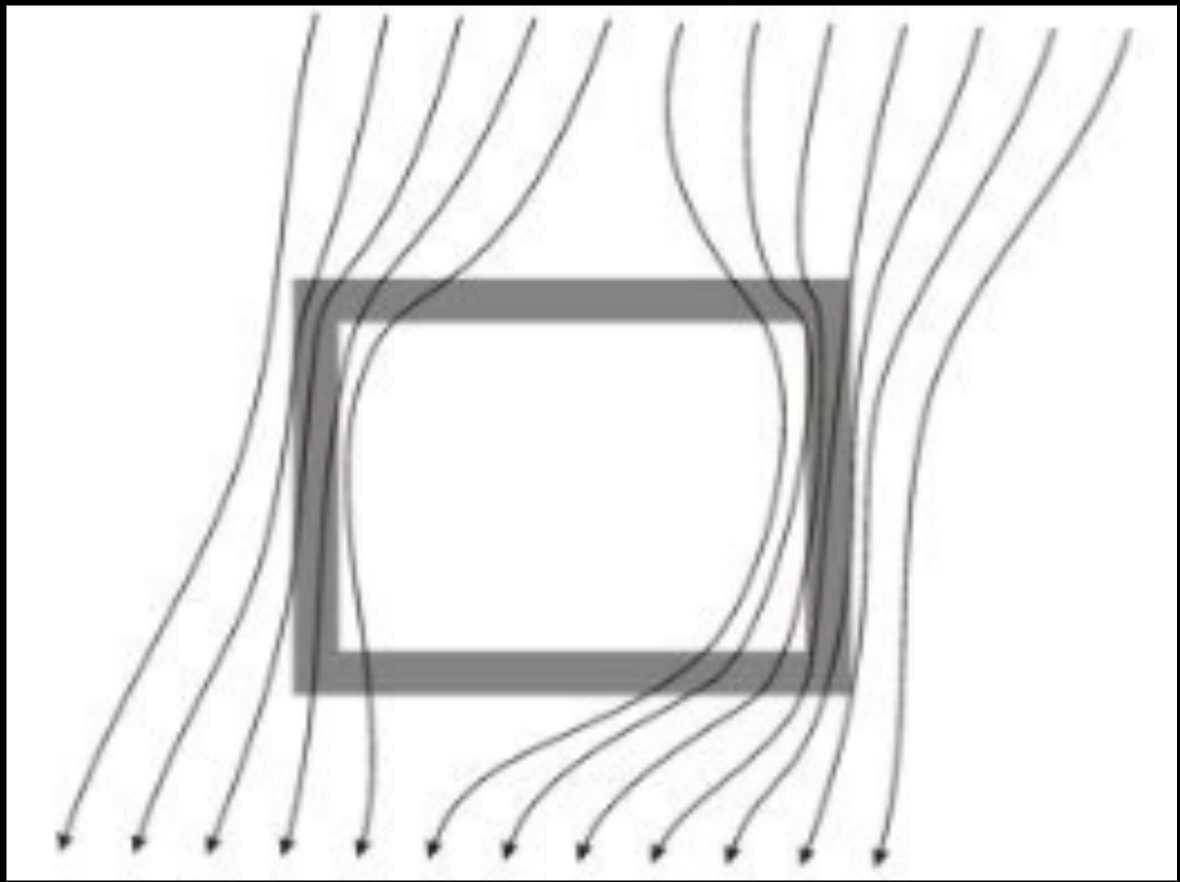
Problem: magnetic fields generated by brain are 100 million times smaller than the Earth's magnetic field

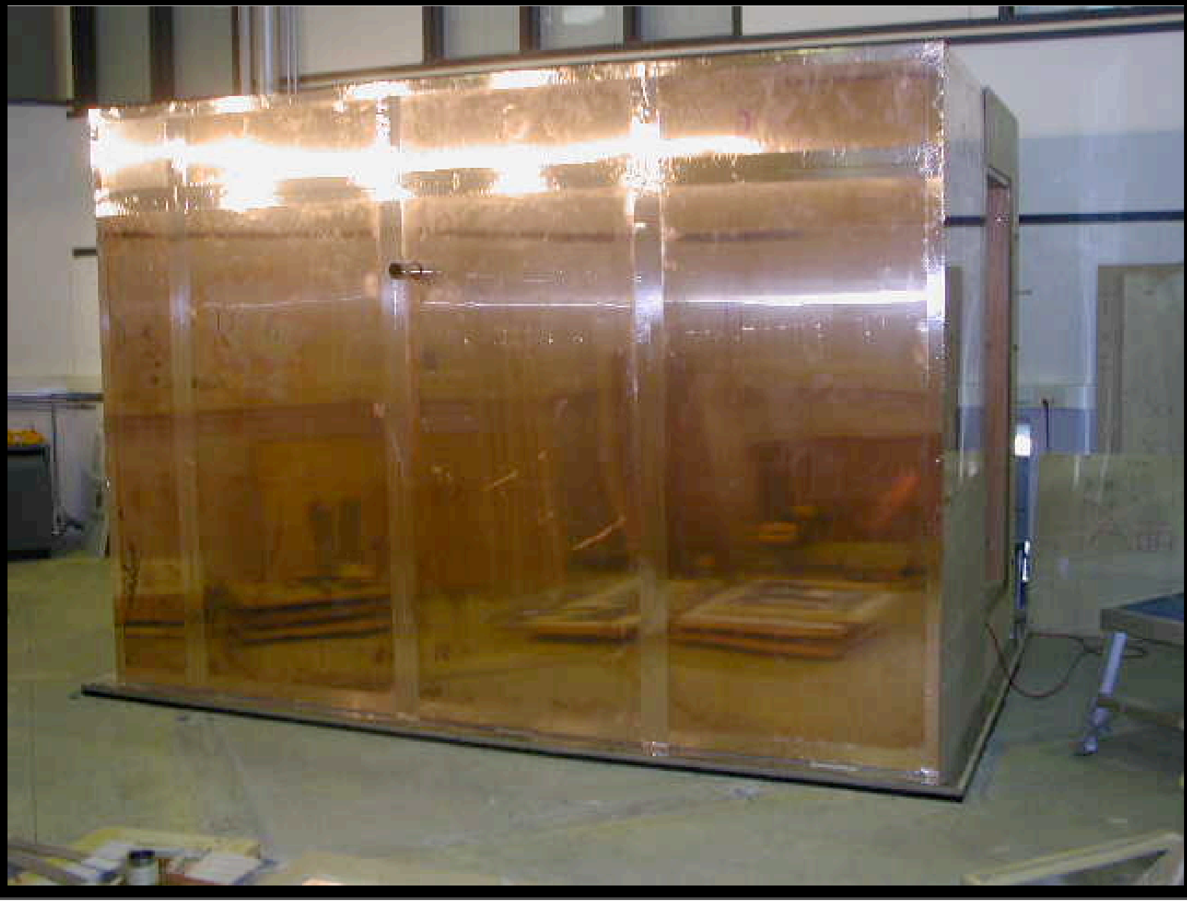
How do we pick up the tiny magnetic fields generated by the brain?



MEG

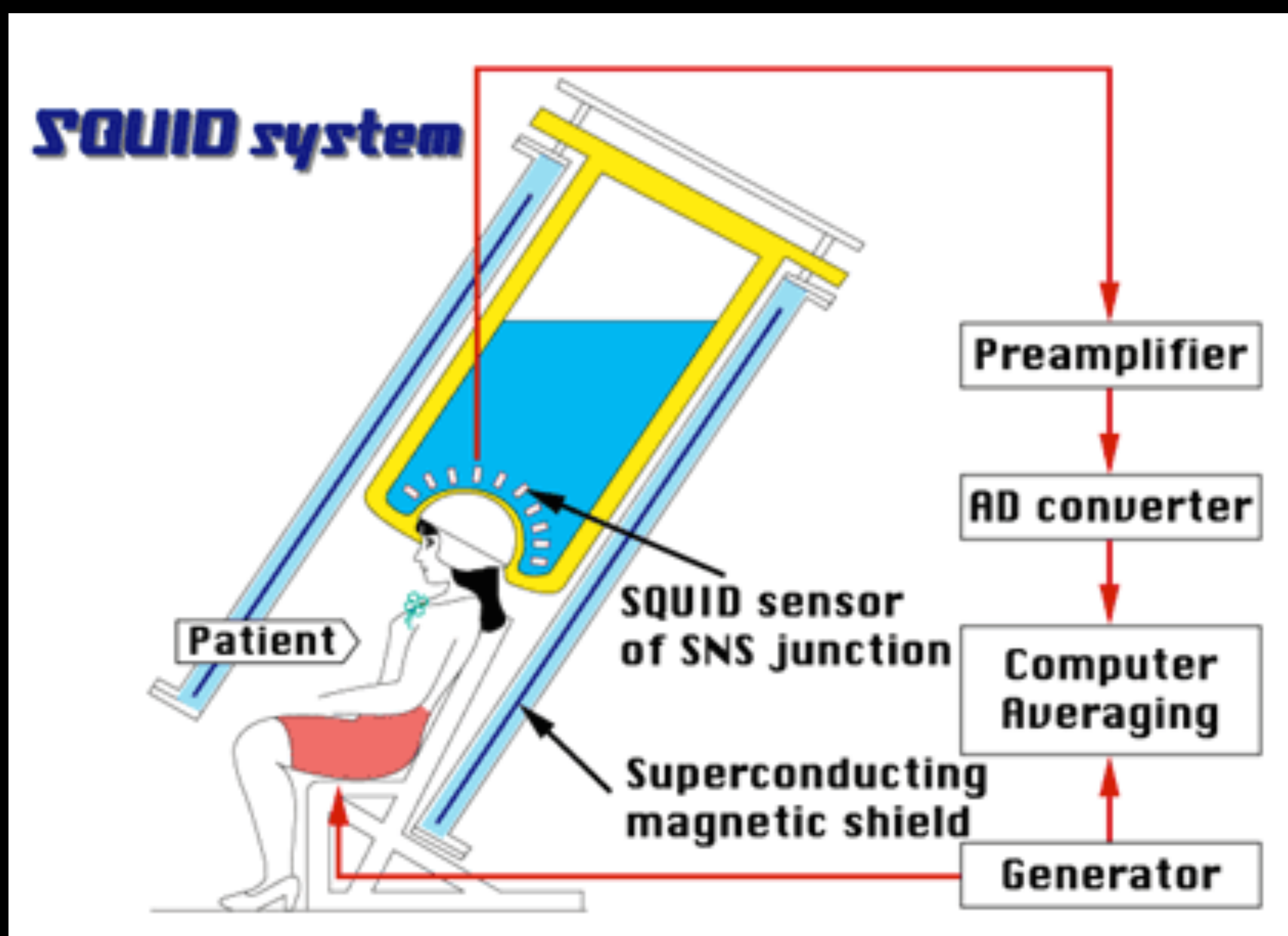
Solution part 1:
magnetically shielded room



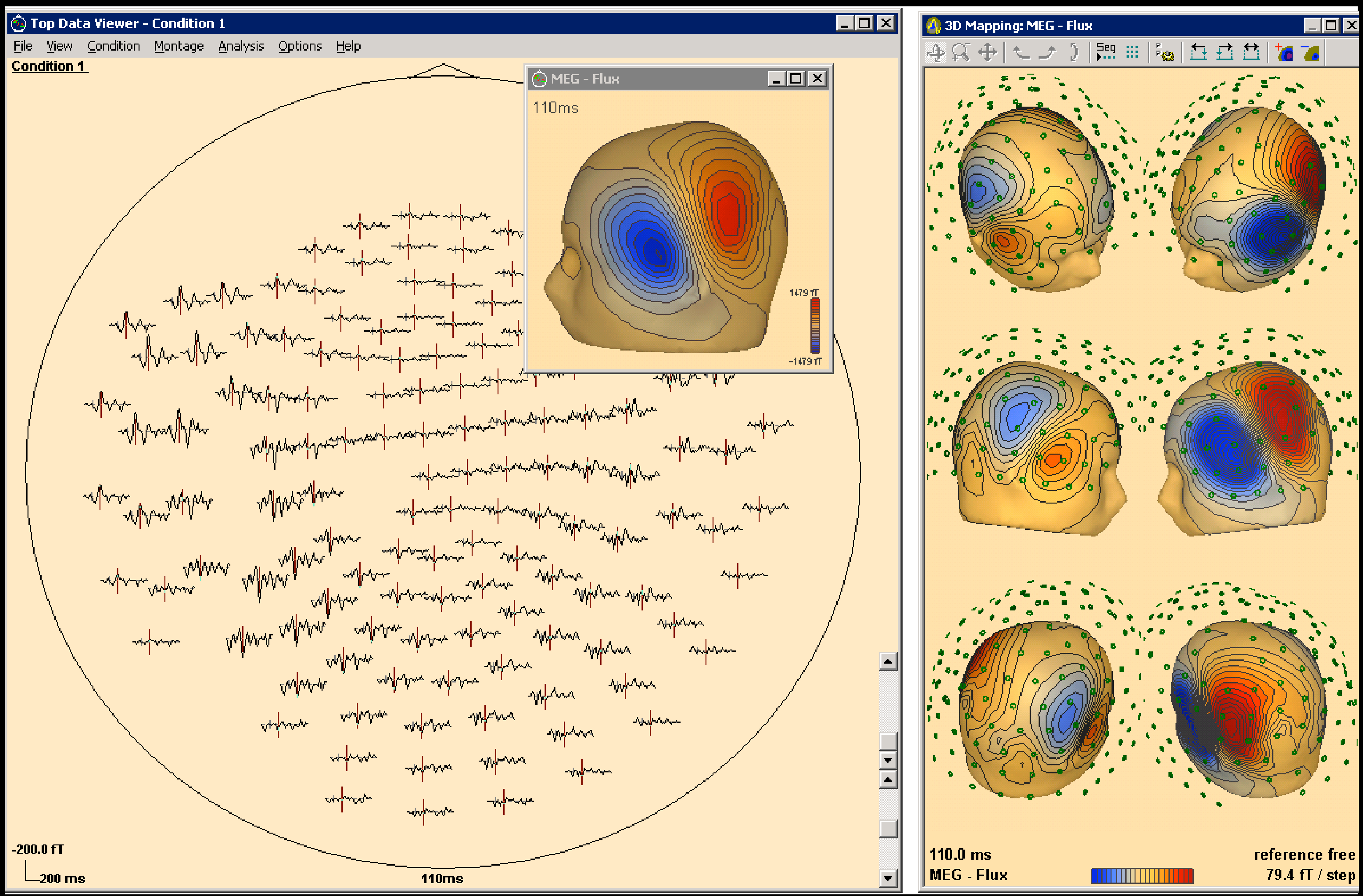


MEG

Solution part 2:
superconductive sensors



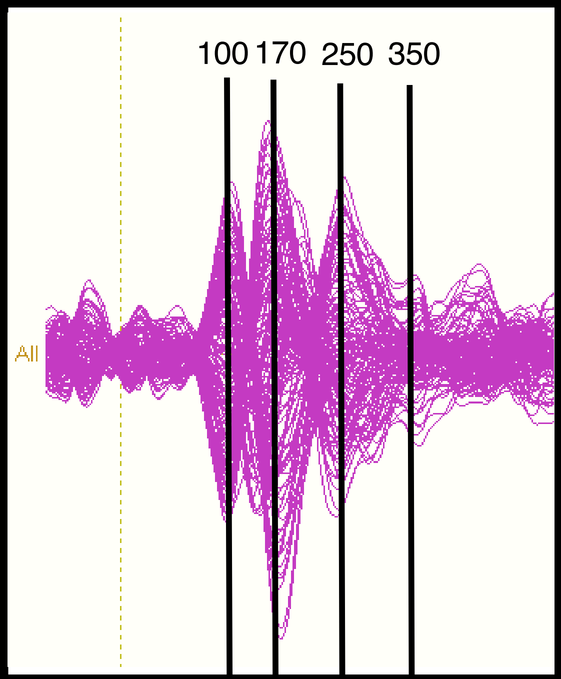
MEG

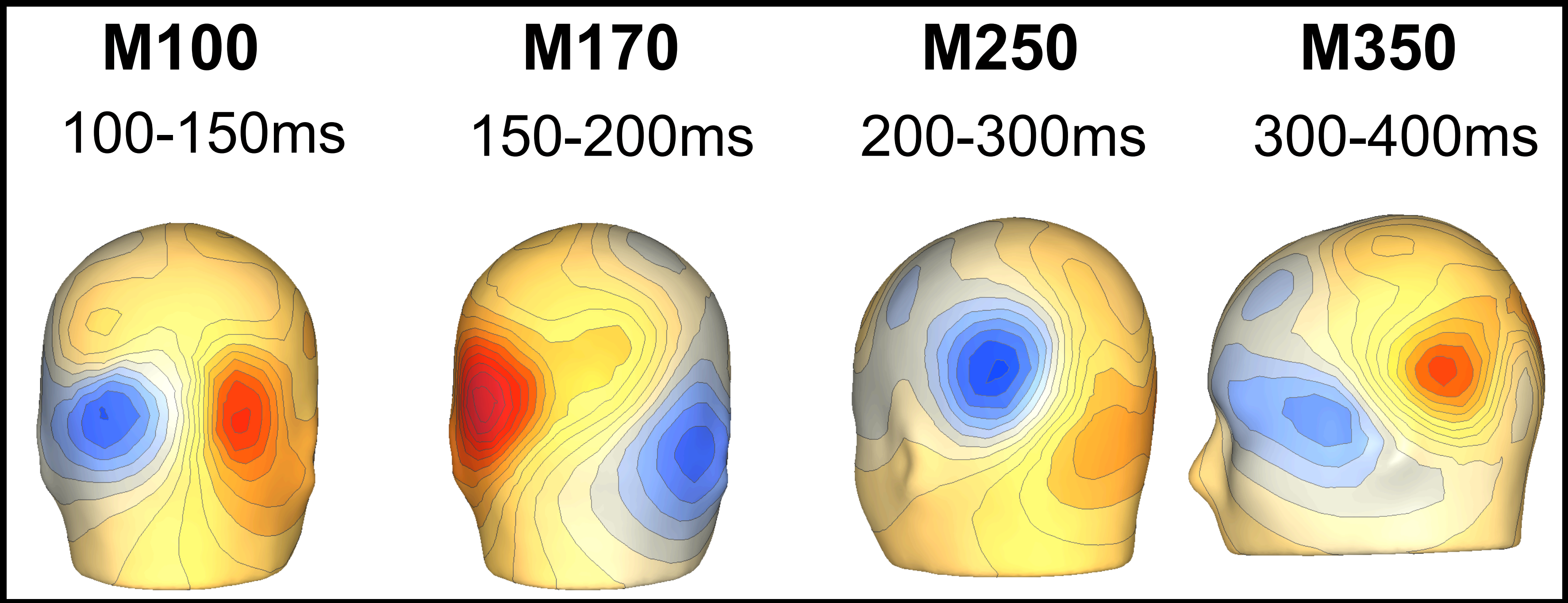


Averaged response to 1 kHz tone

MEG

Averaged response to visual words





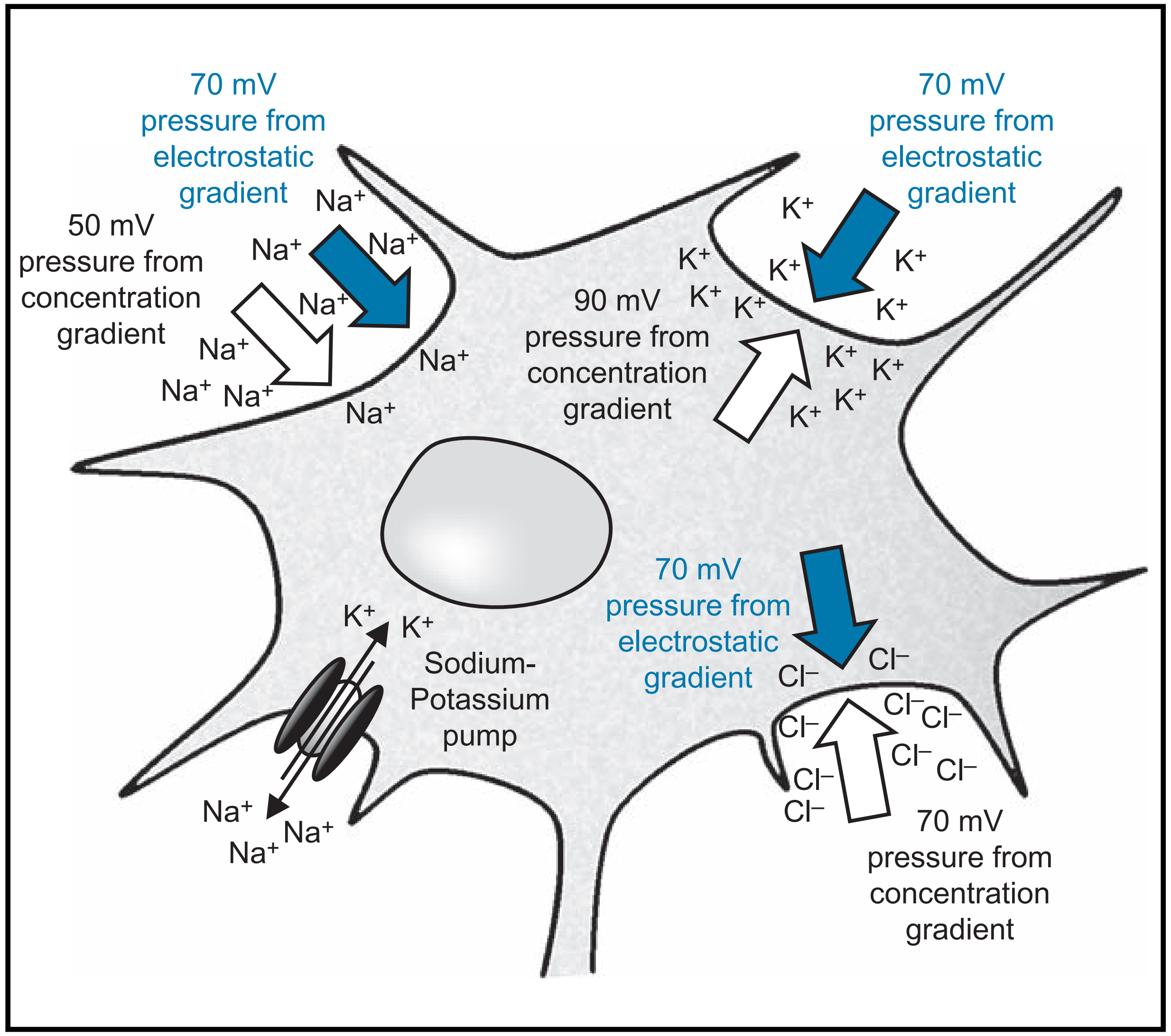
One can analyze the sensor data or the neural currents underlying the magnetic fields (inverse problem)

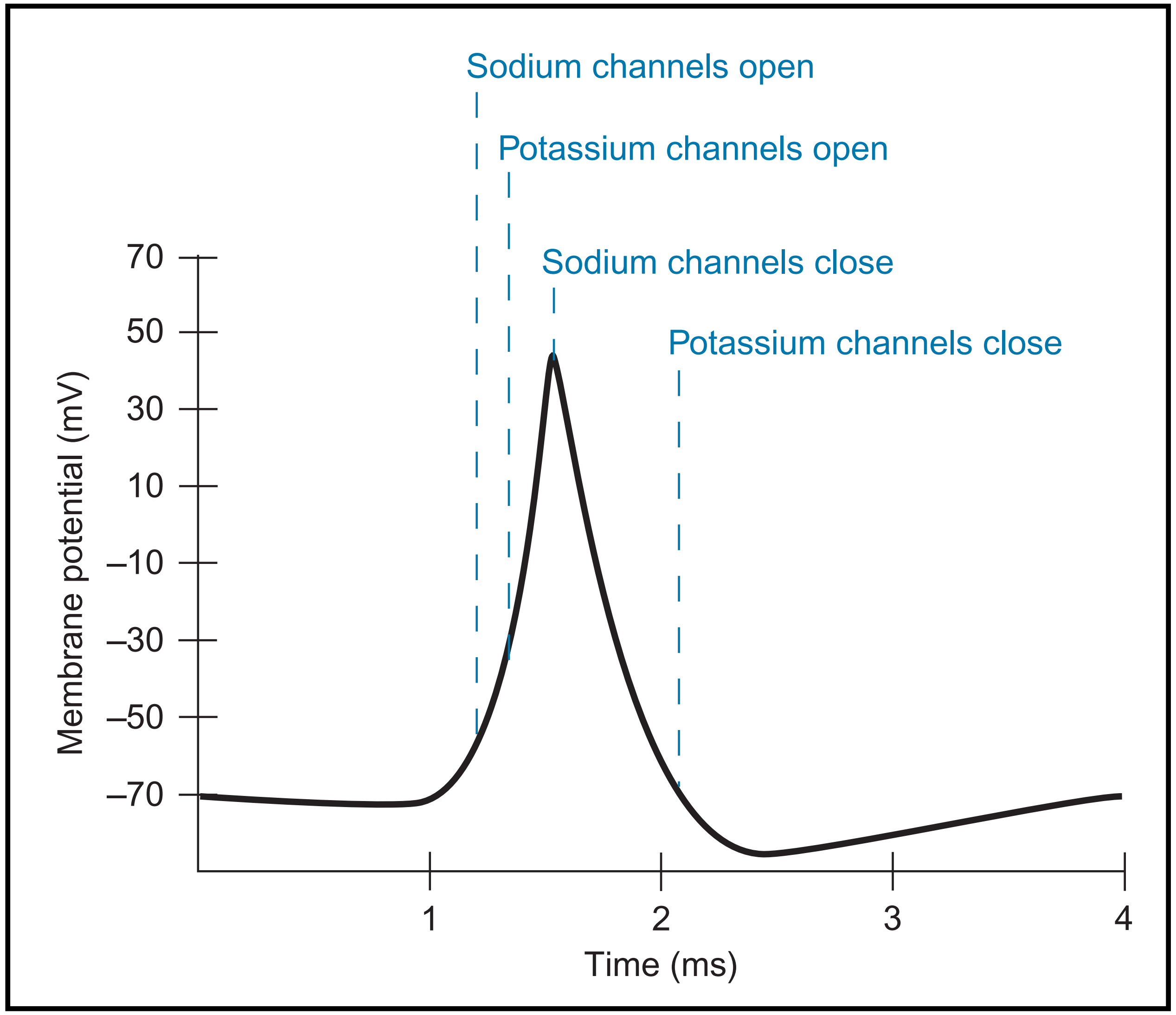
Whole brain imaging

Electrophysiology

Neuronal manipulation

Electrical properties (review)





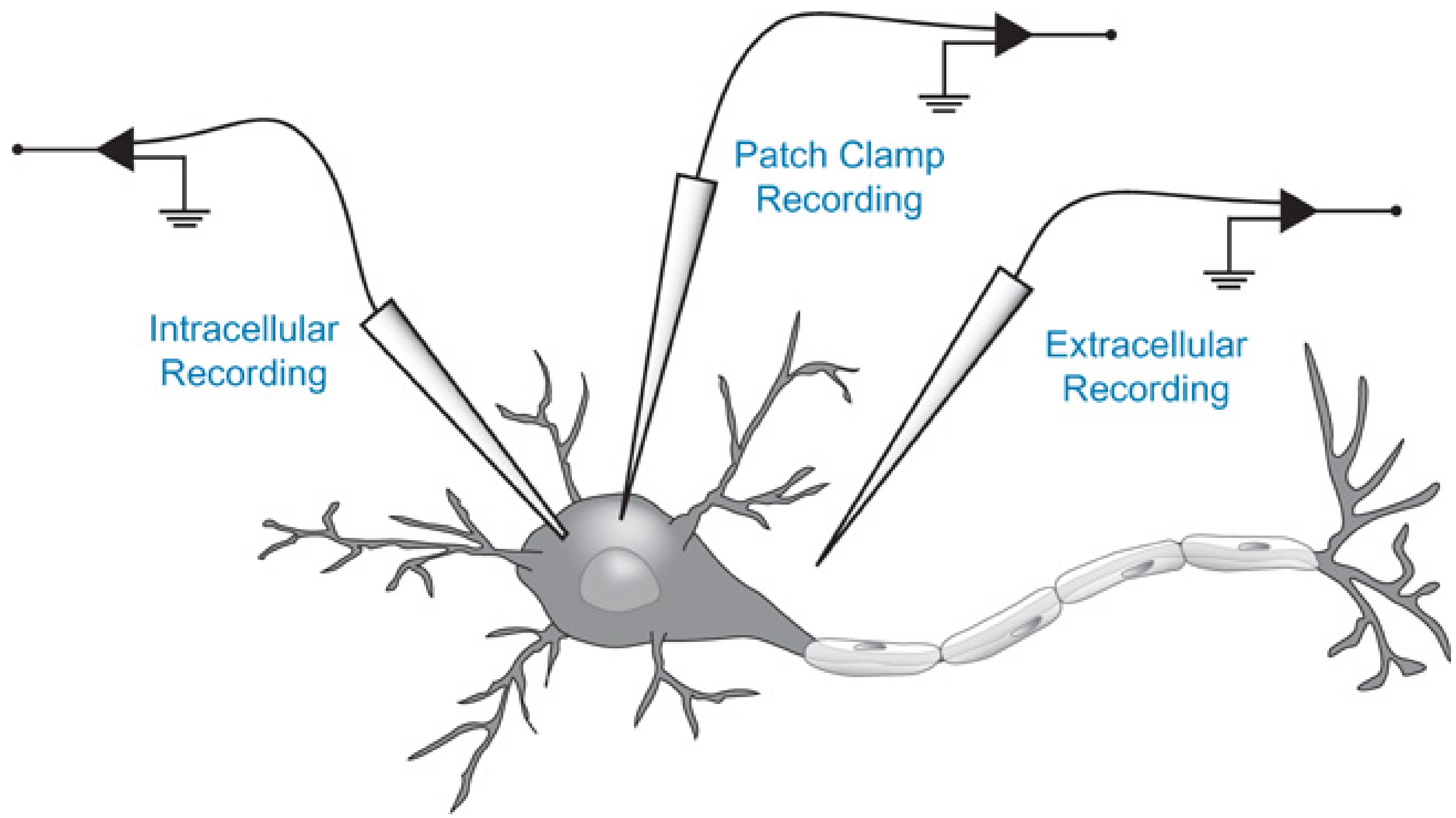
Types of electrophysiology

Three types of electrophysiology recordings (invasive)

Extracellular: outside the neuron

Intracellular: inside the neuron

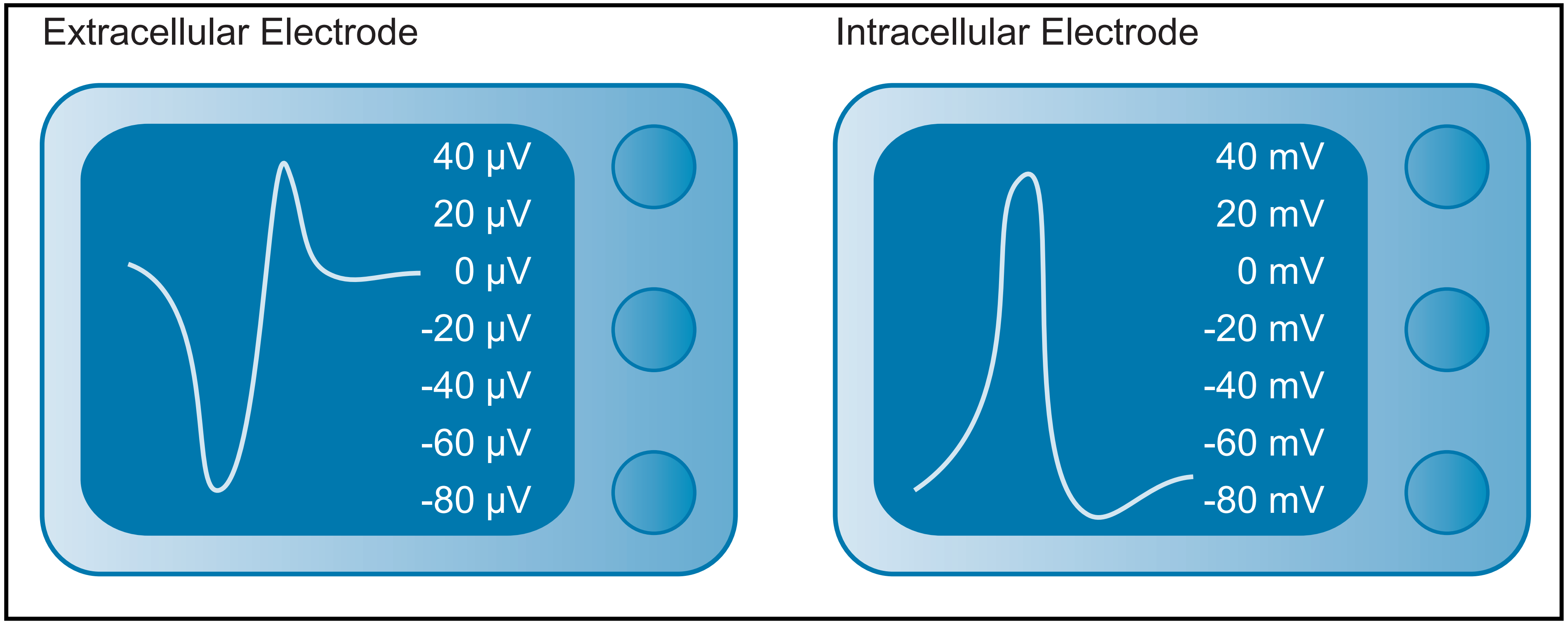
Patch-clamp: adjacent to the membrane



Backbone of neuroscience research

Types of electrophysiology

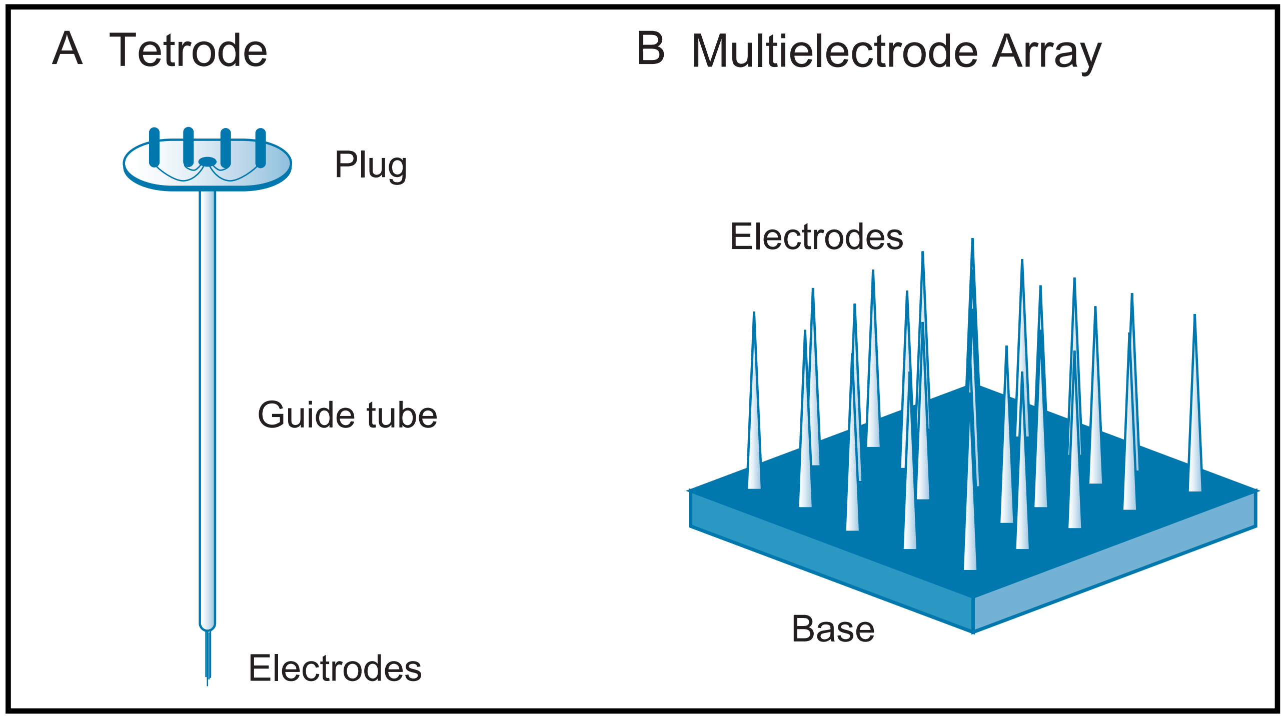
Different types of recording capture different information and can answer different questions

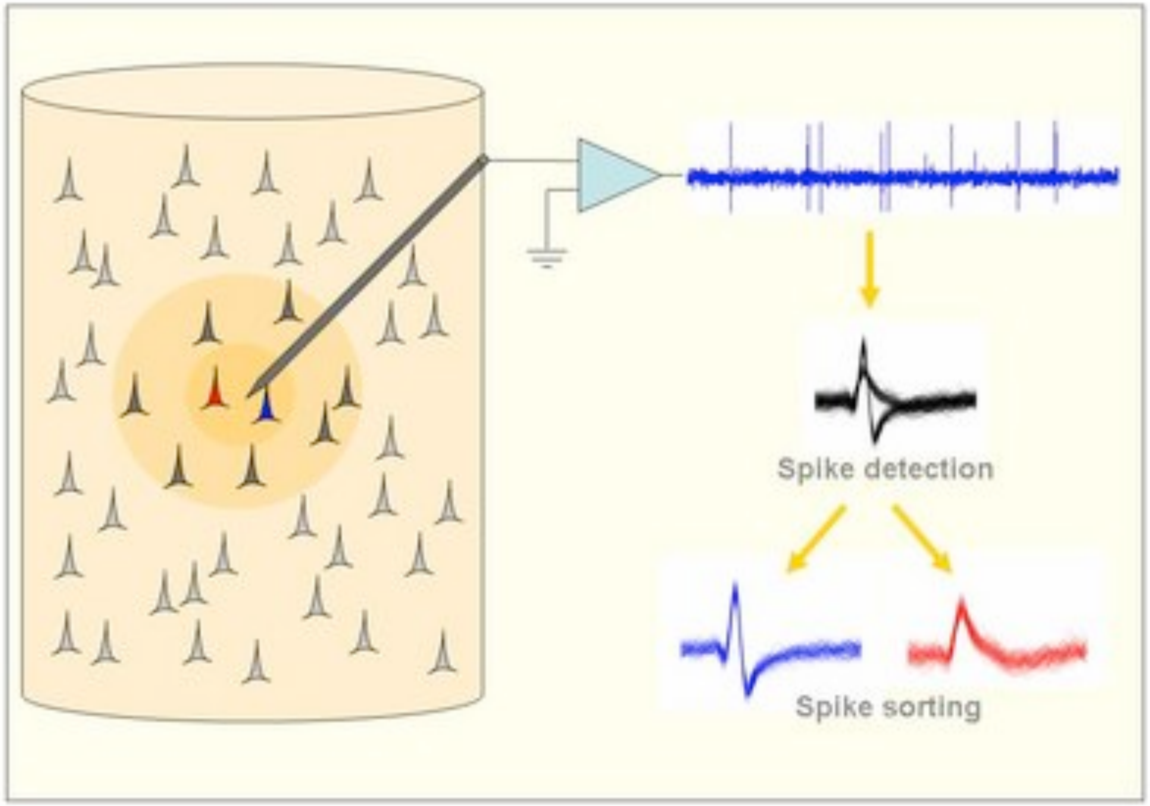


Extracellular: action potentials of groups of neurons + LFP

Intracellular: action potentials + EPSP + IPSP of a single cell

Extracellular recordings





Easier in vivo

Records a few tens up to hundreds neurons

Requires spike sorting to identify which cell fire which a.p.

Whole brain imaging

Electrophysiology

Neuronal manipulation

Manipulating neurons

Some techniques perturb neural activity (inhibit or stimulate certain neurons) to test their role

Manipulating neurons

Some techniques perturb neural activity (inhibit or stimulate certain neurons) to test their role

Types:

Physical: cooling down a brain region to deactivate it

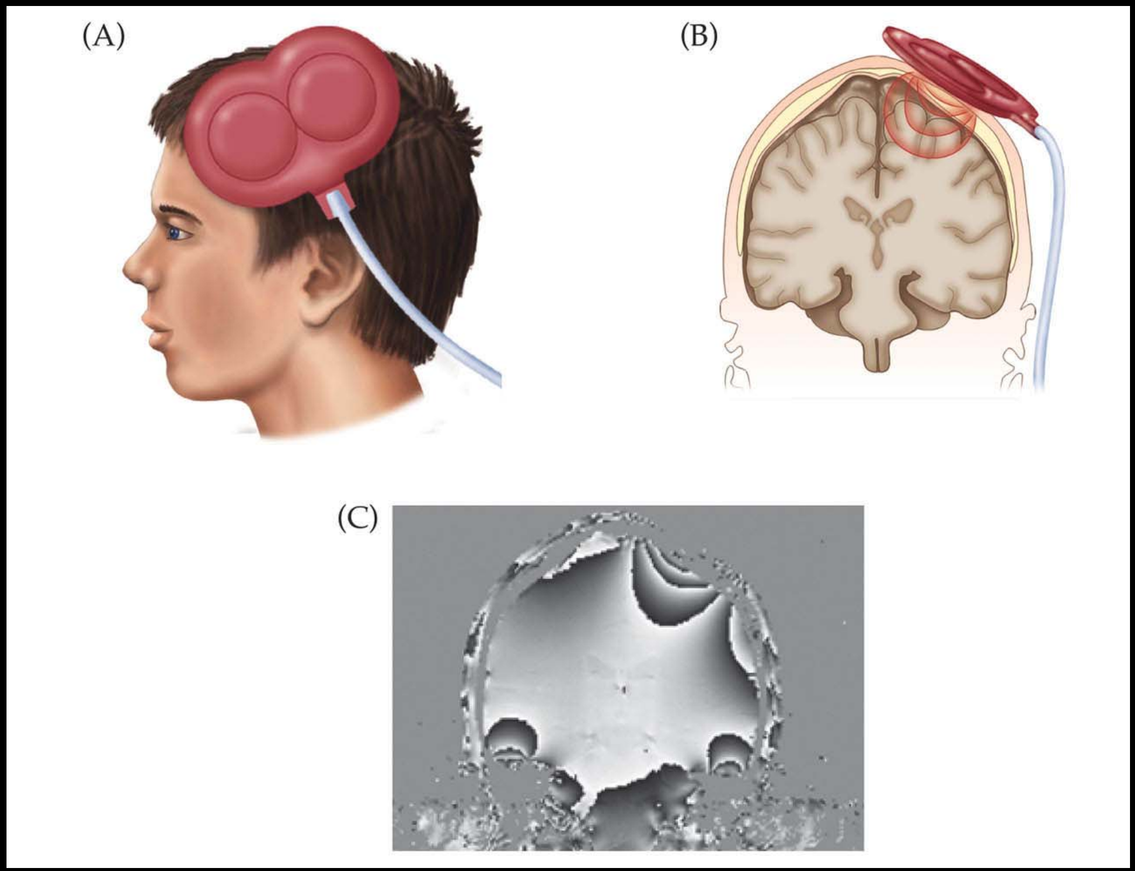
Pharmacological: applying drugs to block channels

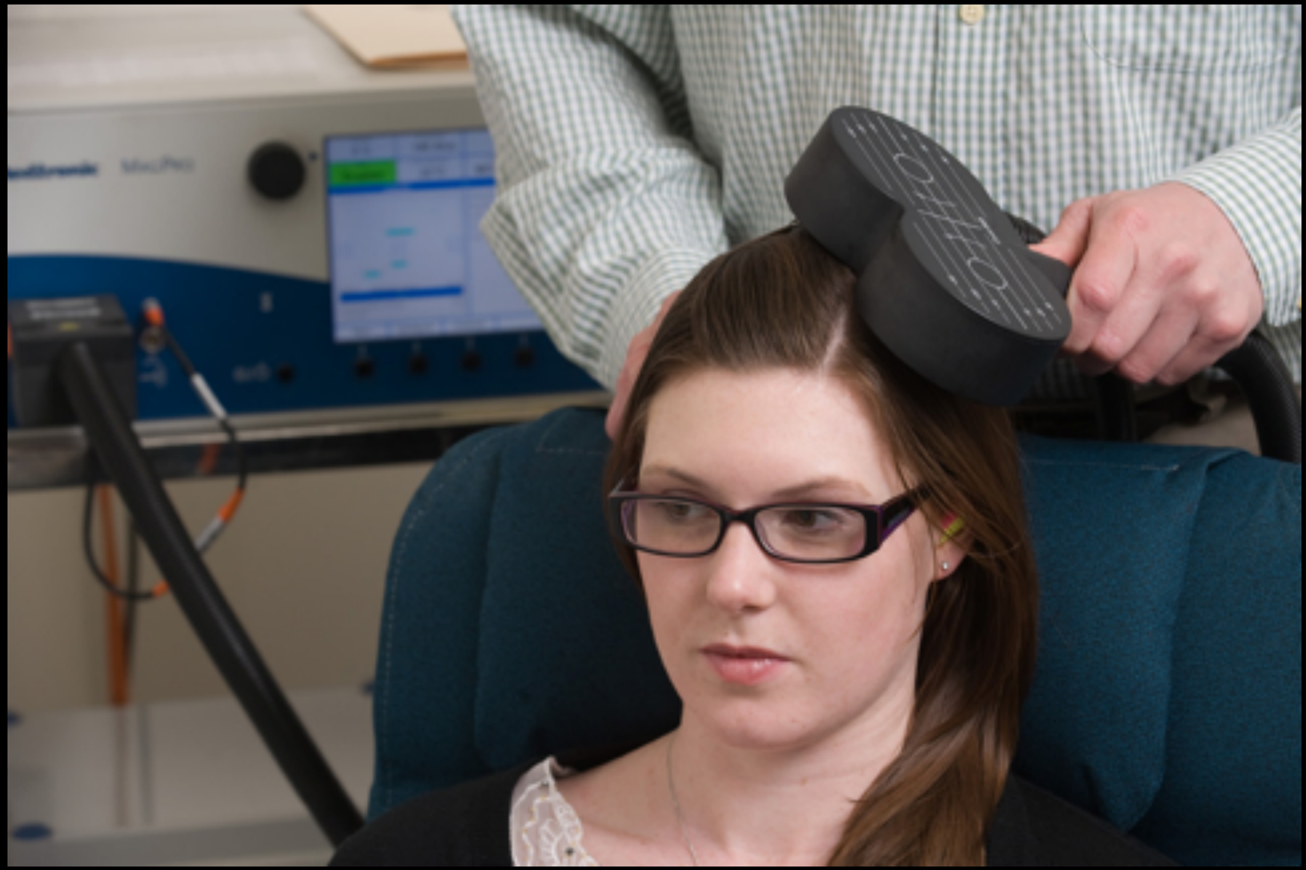
Electrical: applying electrical currents to stimulate neurons

Magnetic: applying magnetic fields (TMS)

Optic: laser (optogenetics)

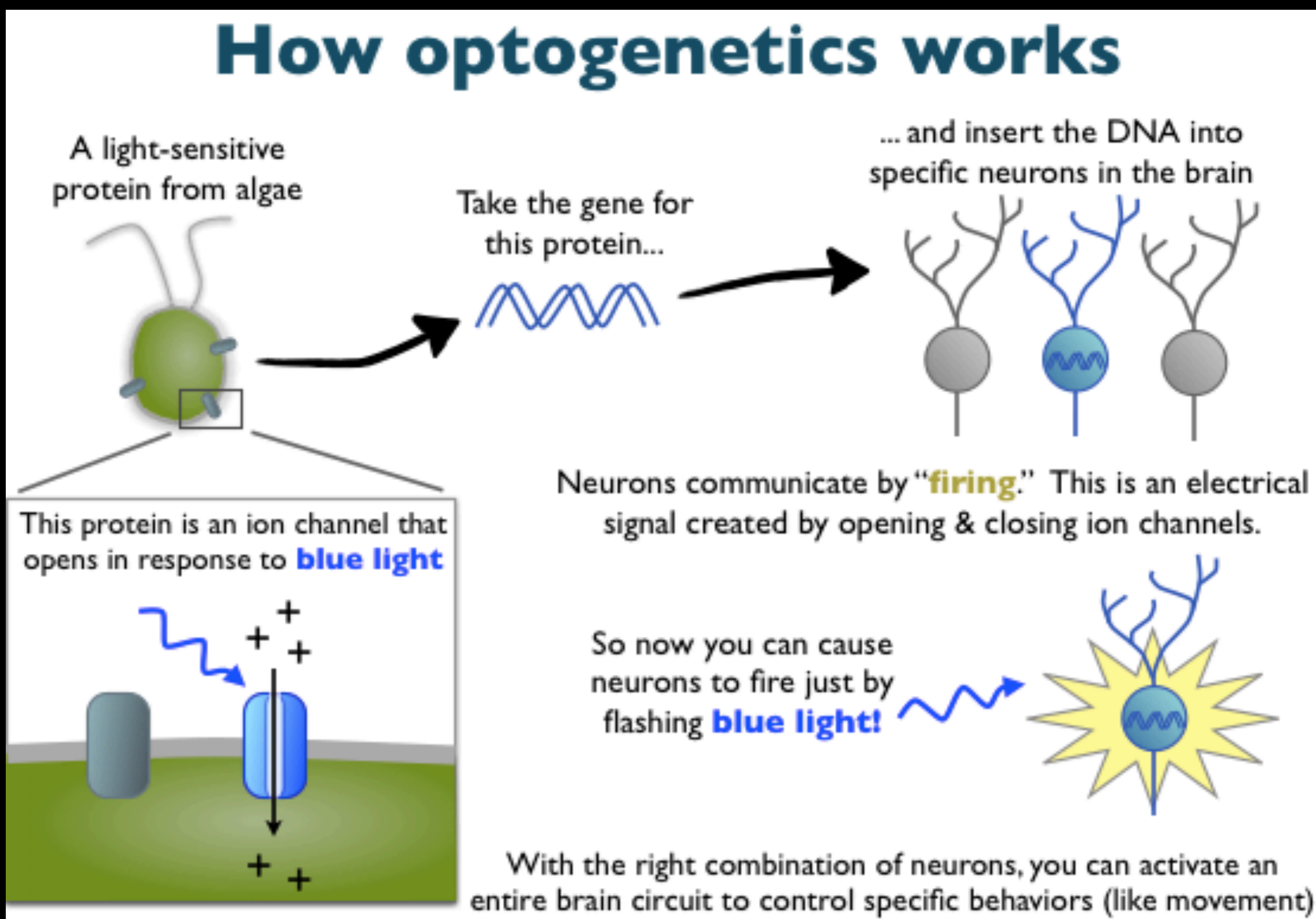
Transcranial Magnetic Stimulation (TMS)

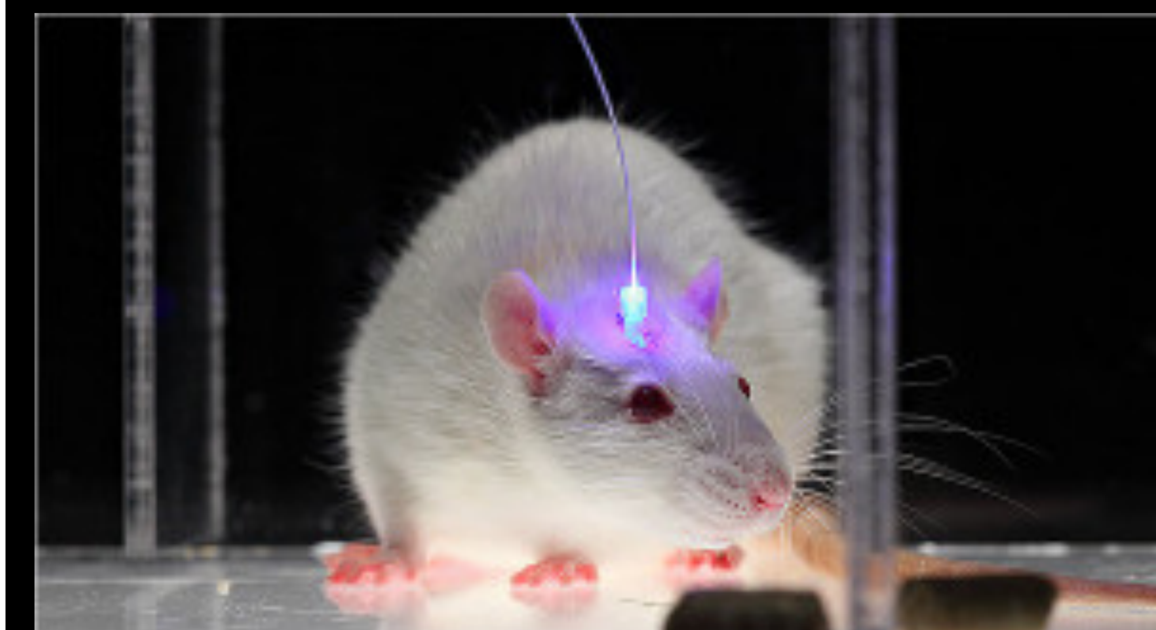




TMS allows transient* and safe* disruption of local neural activity, in effect creating reversible lesions (loss-of-function and gain-of-function experiments)

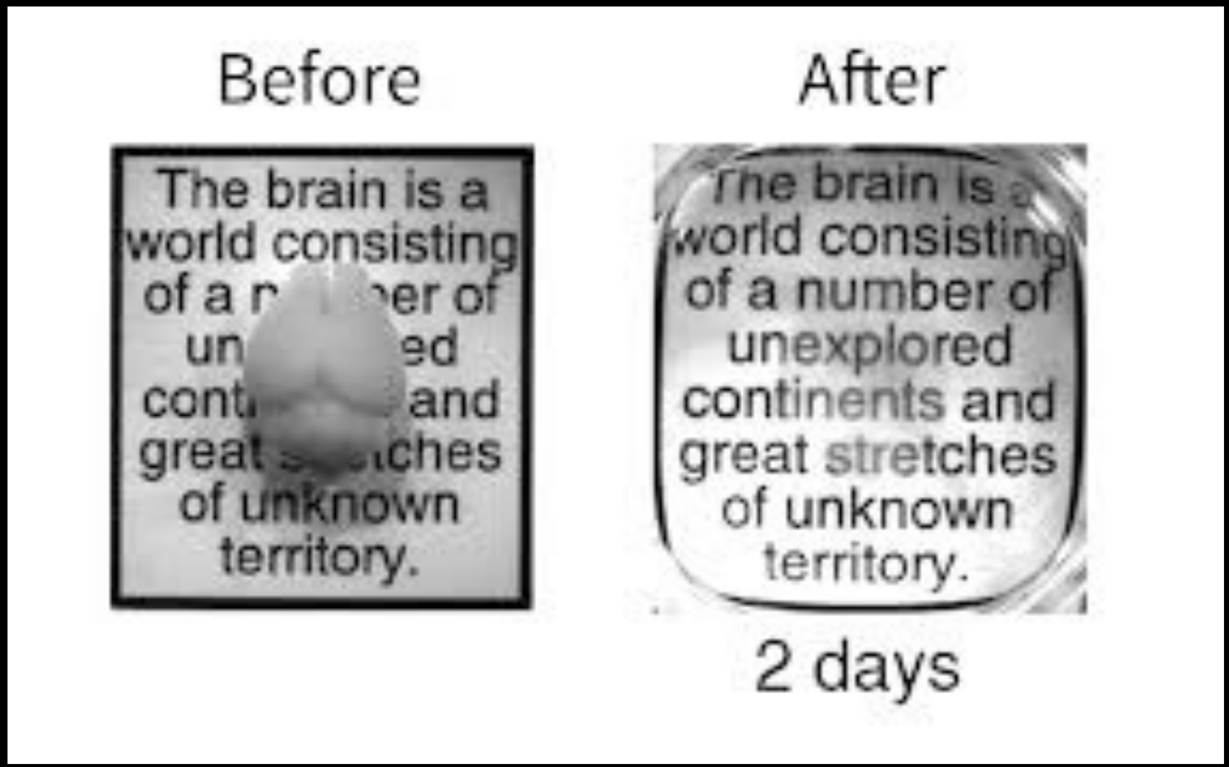
Optogenetics: a light switch for the brain

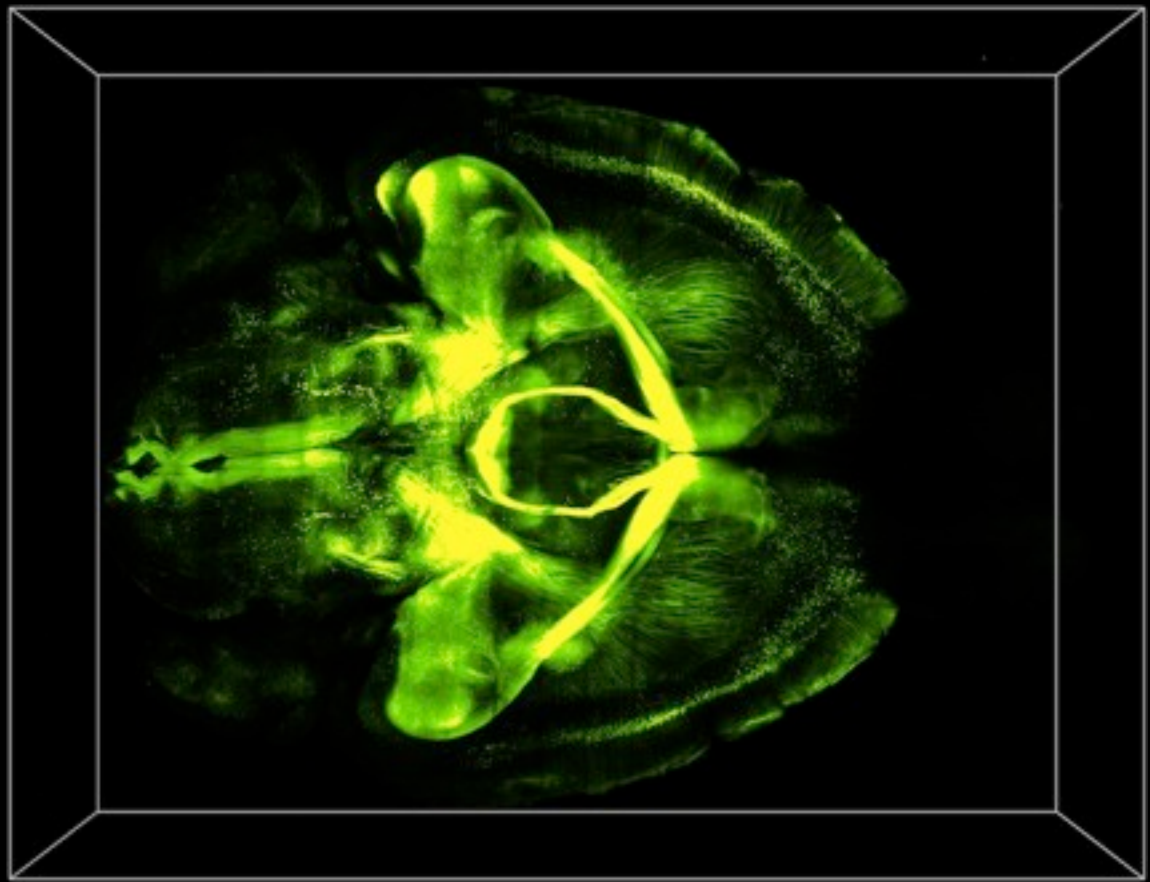




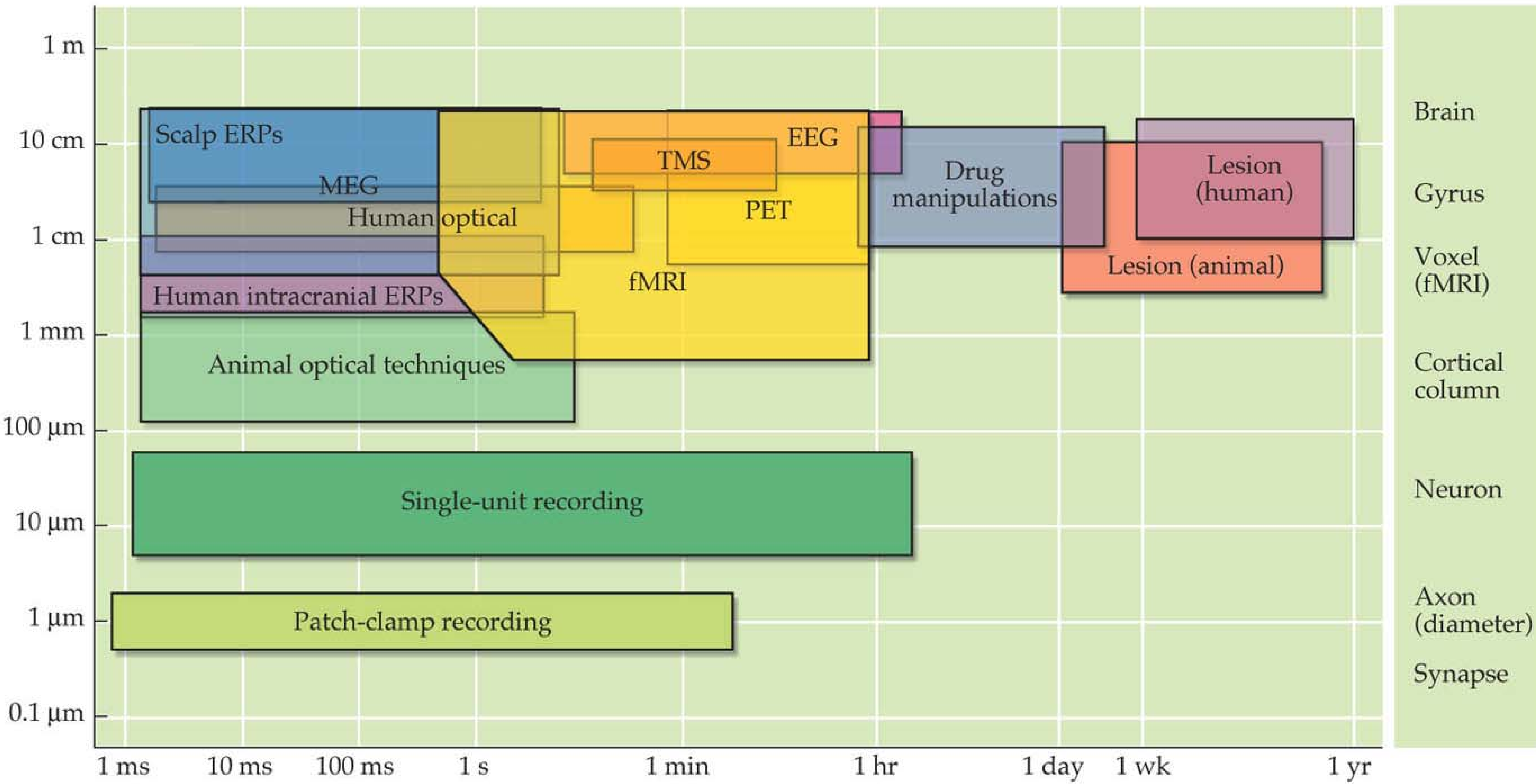
It allows the millisecond-precise control of selected groups of neurons

CLARITY: the future to visualize brain structure?





Overview



1 m
10 cm
1 cm
1 mm
100 µm
10 µm
1 µm
0.1 µm
1 ms
10 ms
100 ms
1 s
1 min
1 hr
1 day
1 wk
1 yr
Scalp ERPs
MEG
Human optical
Human intracranial ERPs
Animal optical techniques
EEG
TMS
PET
fMRI
Drug manipulations
Lesion (human)
Lesion (animal)
Single-unit recording
Patch-clamp recording
Brain
Gyrus
Voxel (fMRI)
Cortical column
Neuron
Axon (diameter)
Synapse

Summary

- Structural (functional) brain imaging capture the anatomy (activation) of different brain regions
- MRI (fMRI) technique of choice for good spatial resolution
- EEG and MEG have excellent temporal resolution
- Electrophysiology techniques measure activity at the neuron level
- No perfect technique allows yet to monitor extensive regions of brain circuits with a single-neuron resolution

To know more

Chapters 1 and 4

Guide to research techniques in neuroscience, Matt Carter and Jennifer Shieh, Academic Press, 2010

Lesson	Title
1	Introduction
2	Structure and Function of the NS
3	Windows to the Brain
4	Data analysis
5	Single neuron models
6	Network models
7	Artificial neural networks
8	Artificial intelligence
9	Learning and memory
10	Perception
11	Attention & decision making
12	Brain-Computer interface
13	Neuroscience and society
14	Future and outlook
15	Projects presentations
16	Projects presentations

Basics

Analyses

Models

Cognitive

Applications