Connecting to the Networks of the Human Brain

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ConnectToBrain

European Research Council
Established by the European Commission

Aalto University
School of Science

Università degli Studi "G. d'Annunzio"

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ITAB

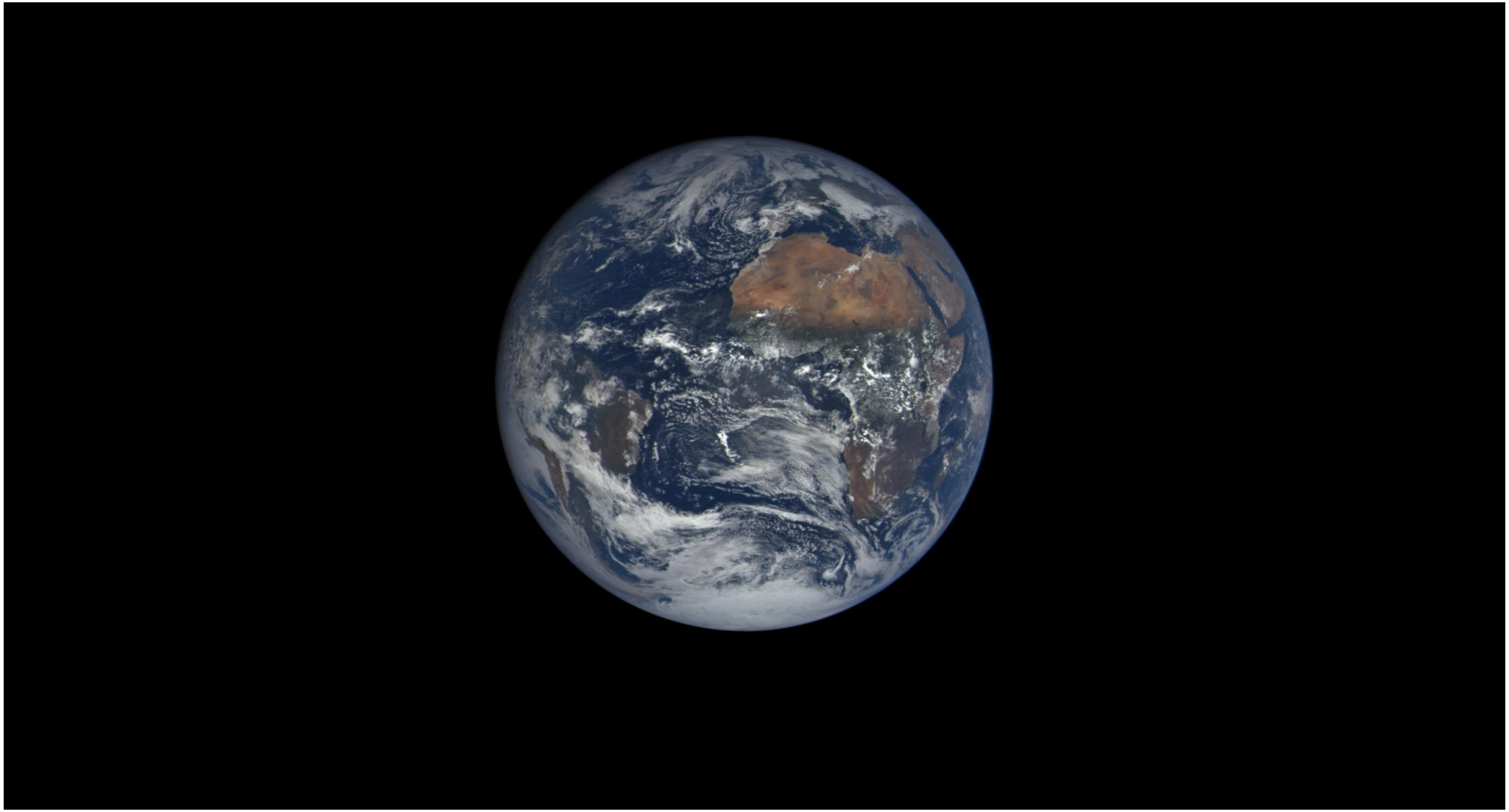
INFN LNGS

LNGS '25

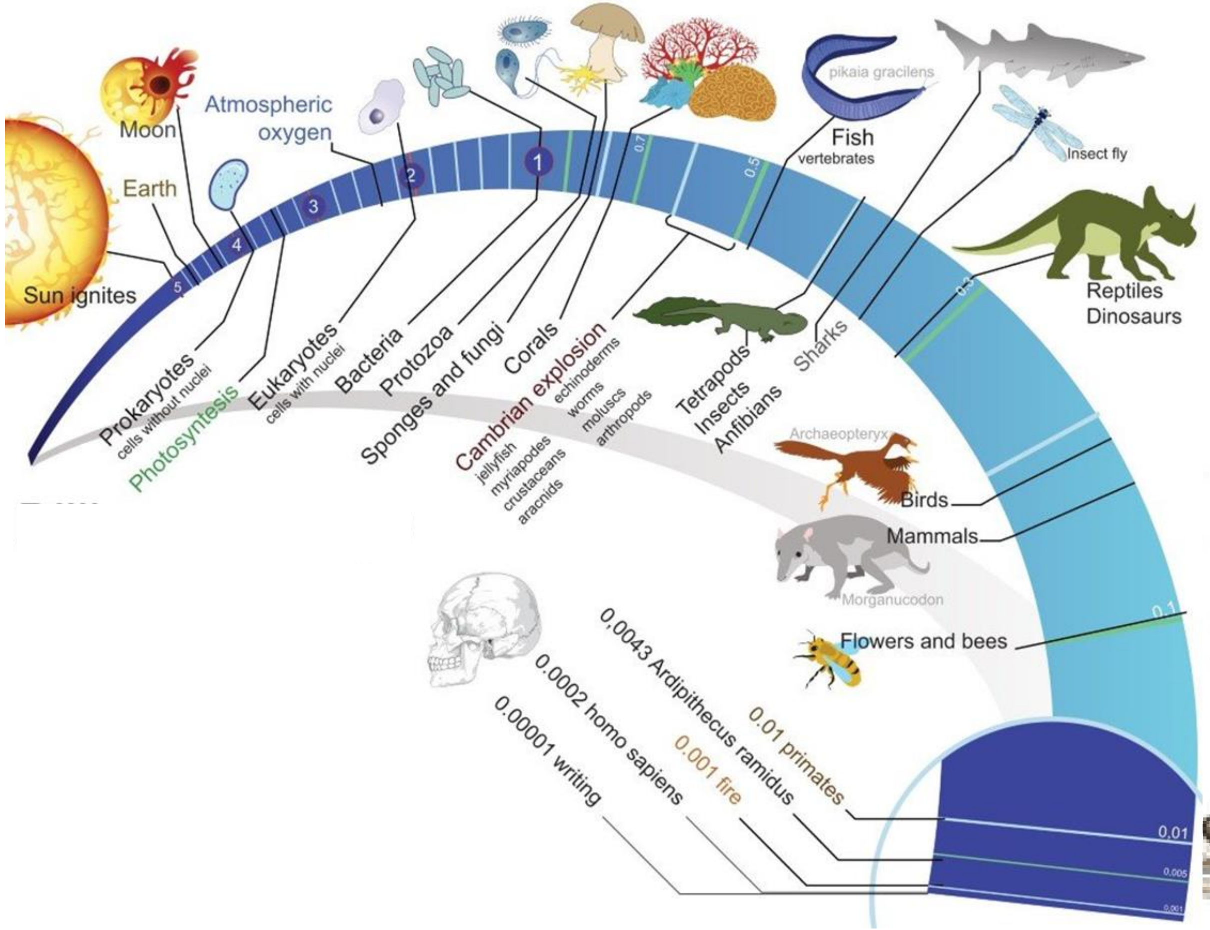
The big-bang

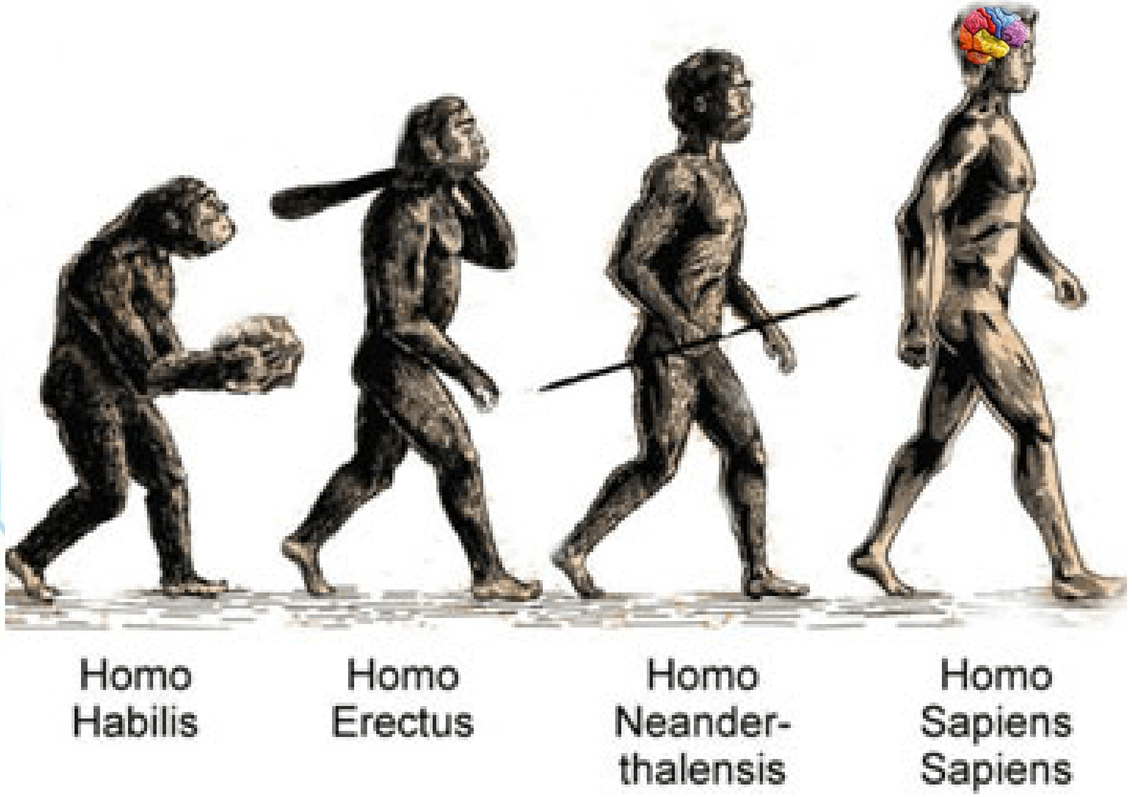
The solar system

The earth

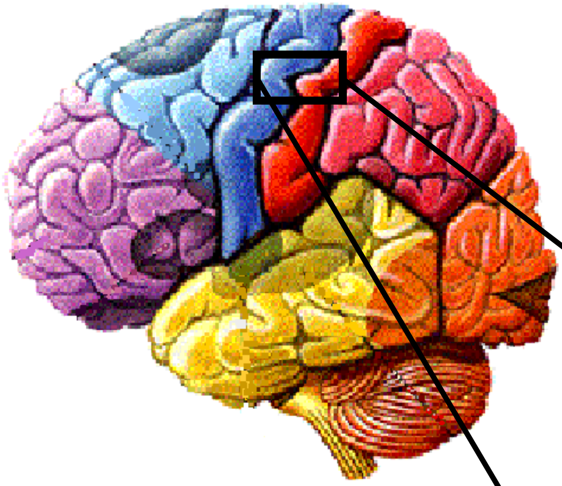


Life develops and evolves

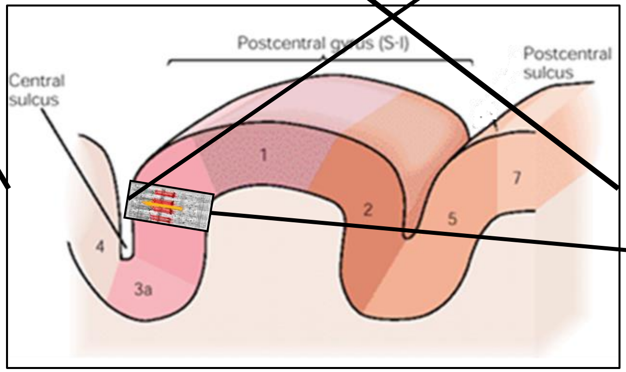


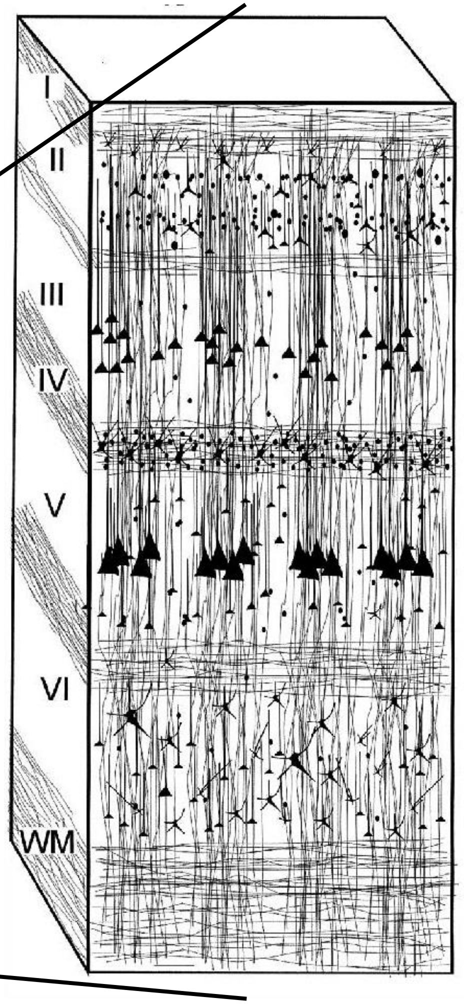


The brain



100 billion neurons packed in about 1300 cm^3 space

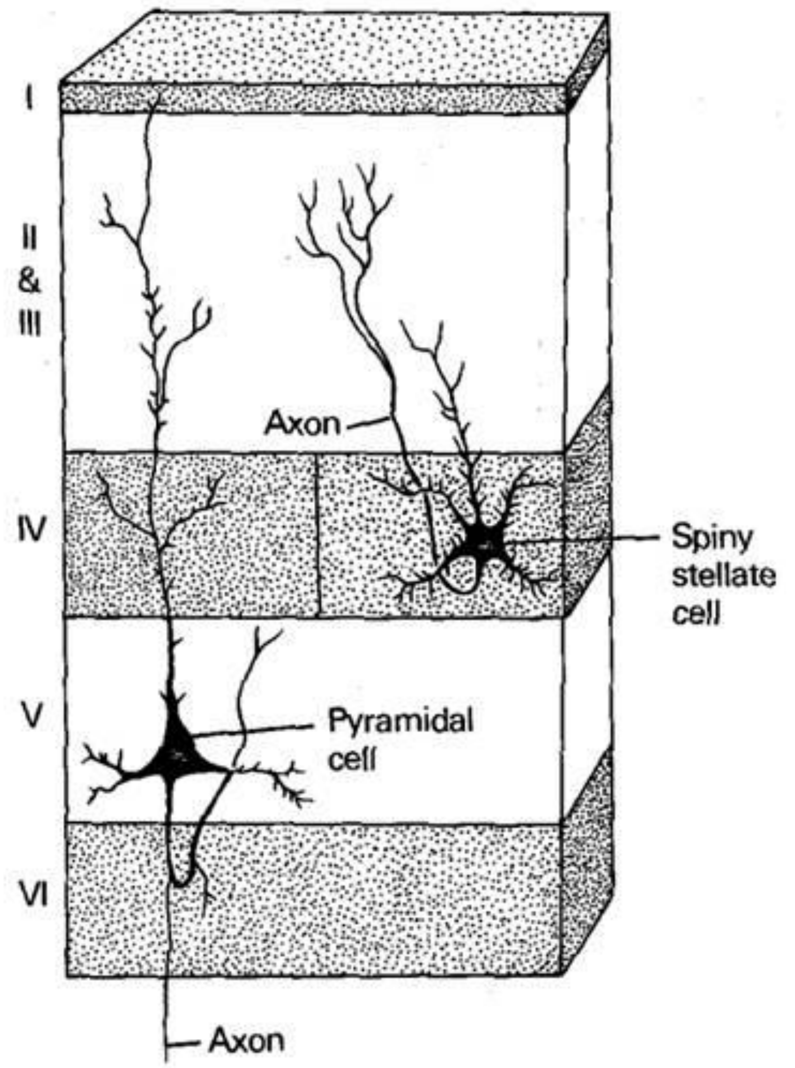




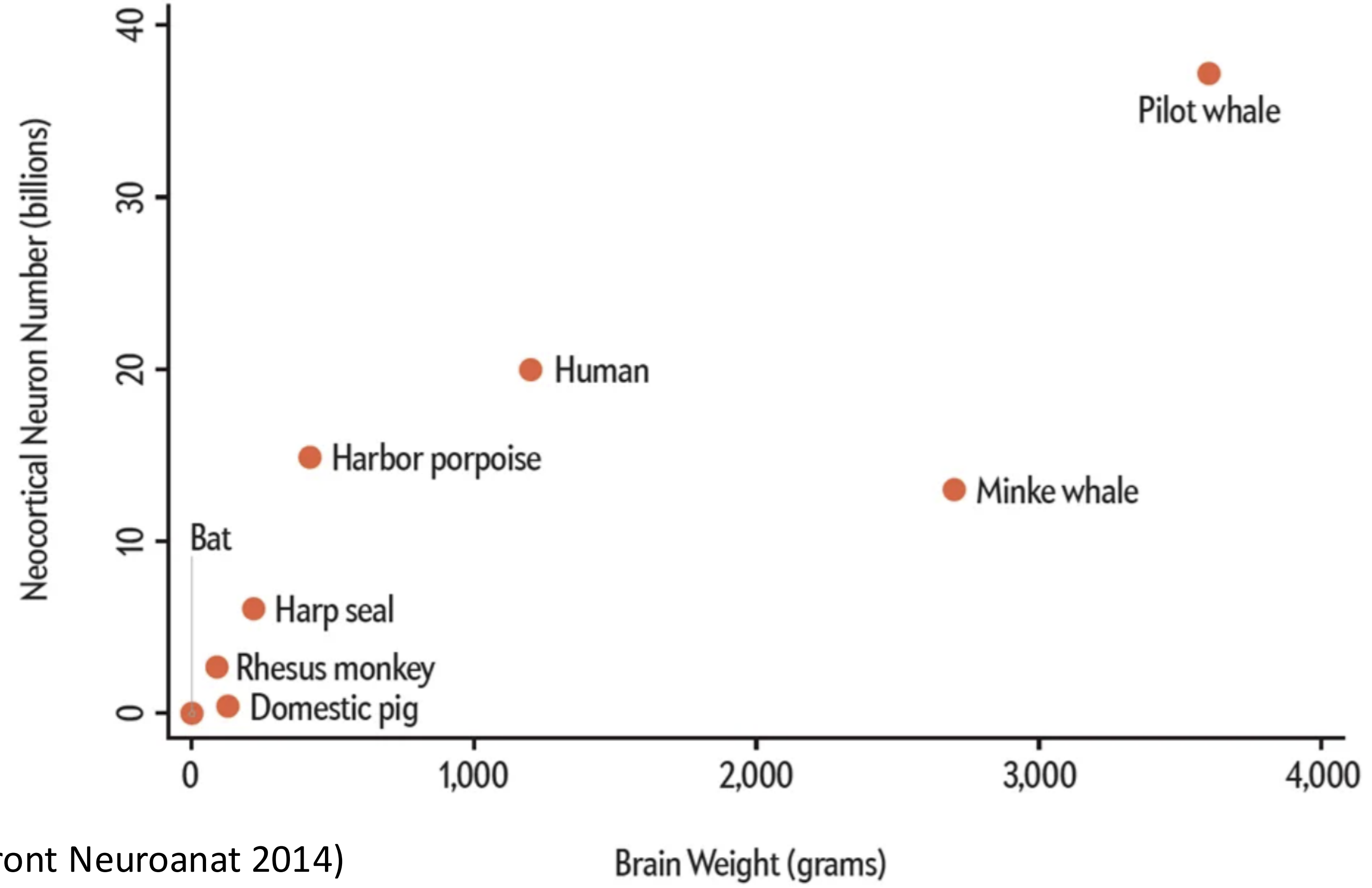
The neuron

A neuron is an electrically excitable cell that processes and transmits information by electrical and chemical signaling.

Neurons are the core components of the nervous system, which includes the brain, spinal cord, and peripheral ganglia.



Brain size is only partially related to “intelligence”



SCIAM (from Mortensen et al, Front Neuroanat 2014)

I am my connectome

Main difference between *Homo Sapiens Sapiens* and other species is not specifically linked to the brain size or the number of neurons within the brain, but rather to how the neurons are interconnected.

The human neocortex contains approximately $\sim 2 \cdot 10^{10}$ neurons and $\sim 10^{14}$ synapses connecting them (Pakkenberg et al, 2003).

I am my connectome (Sebastian Seung)

https://www.youtube.com/watch?v=HA7GwKXfJB0

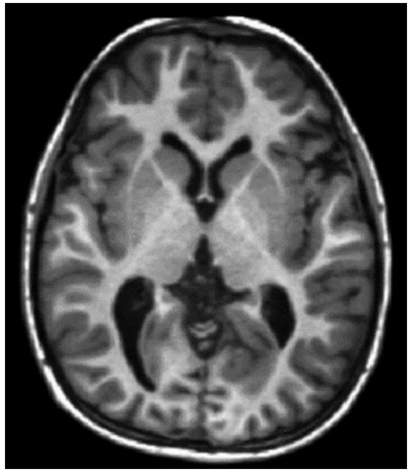
Brain imaging techniques

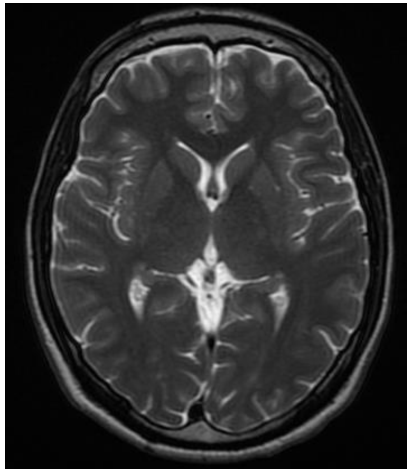
Non-invasive brain images are manly obtained by Magnetic Resonance Imaging (MRI)

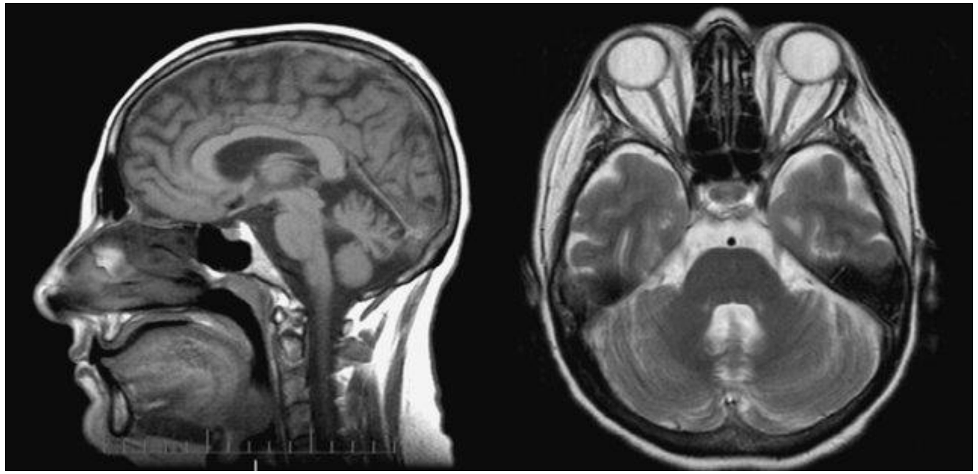
Lauterbur and Mansfield, the 2003 Nobel laureates, successfully exploited the phenomenon of nuclear magnetic resonance to generate biomedical images.

Paul Lauterbur

Peter Mansfield



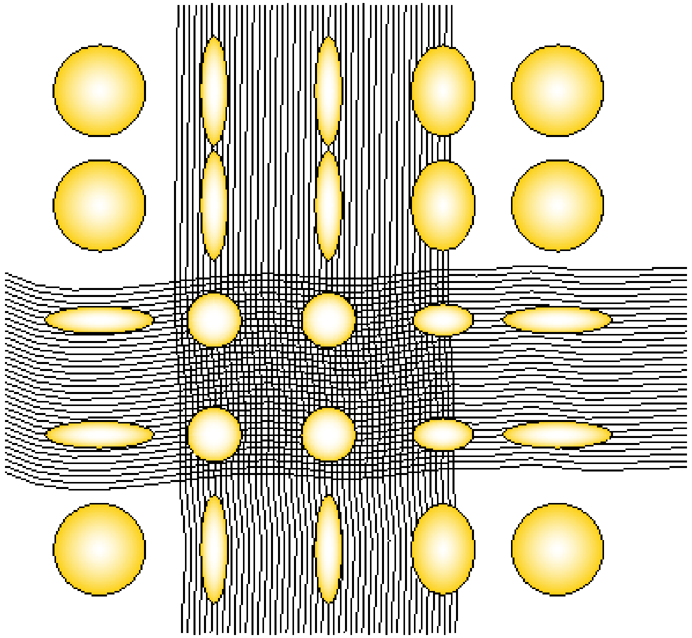


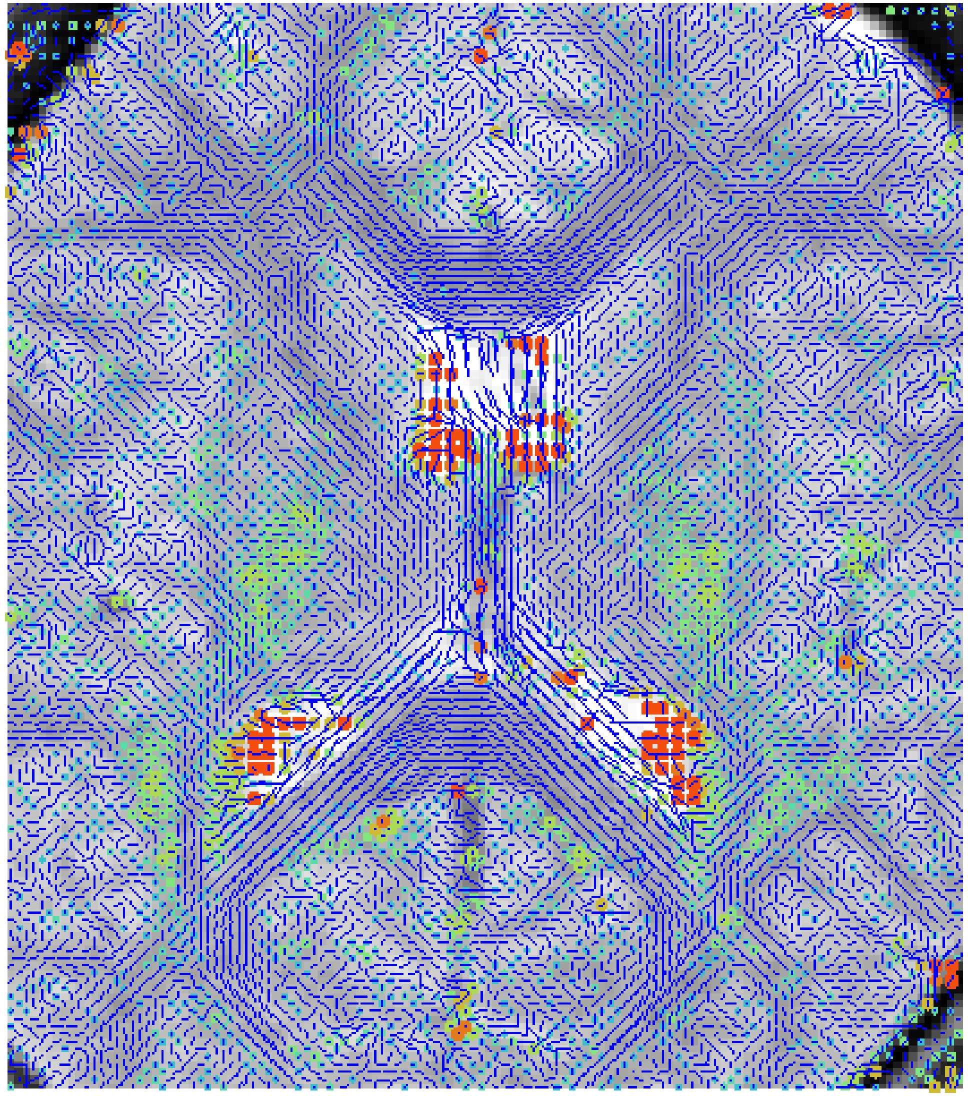


Brain imaging techniques

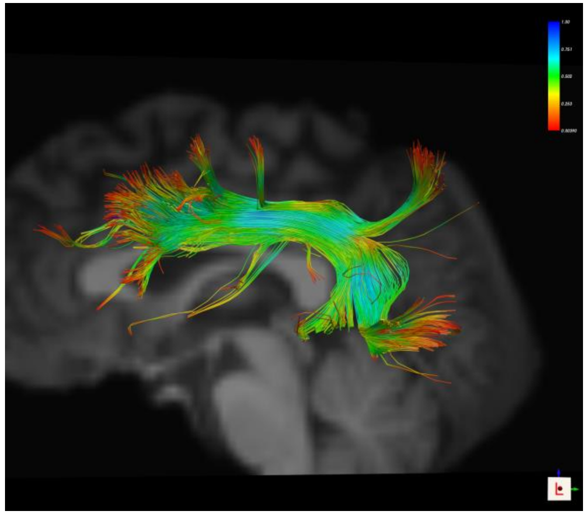
MRI can also be used to obtain data of water diffusion in the brain tissue.

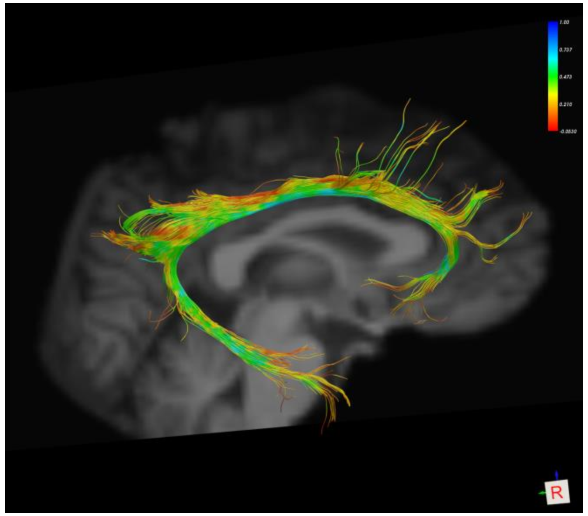
Large axonal fibers may be reconstructed by measuring the anisotropy they cause in the Brownian motion of water molecules.



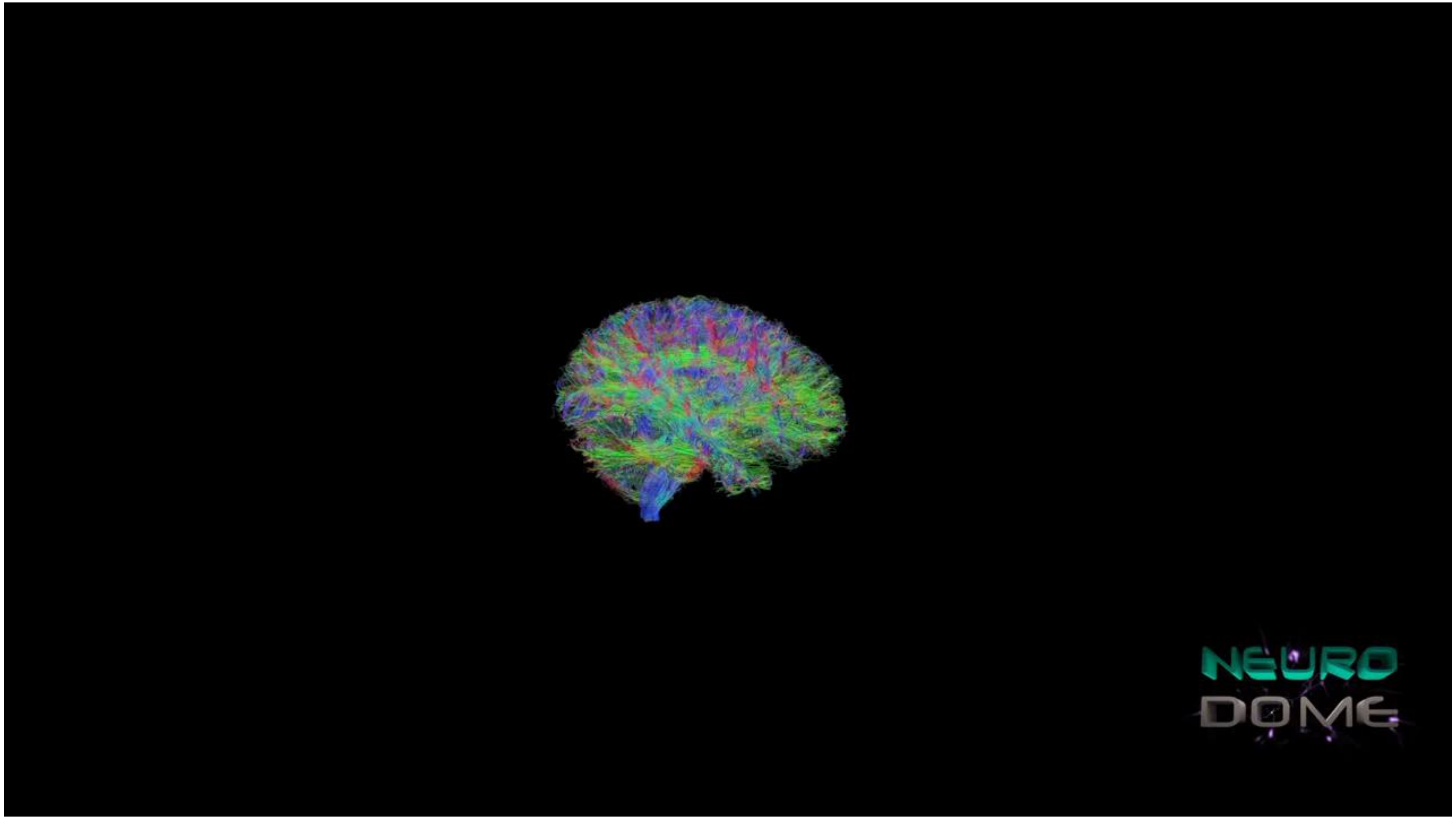


Brain imaging techniques



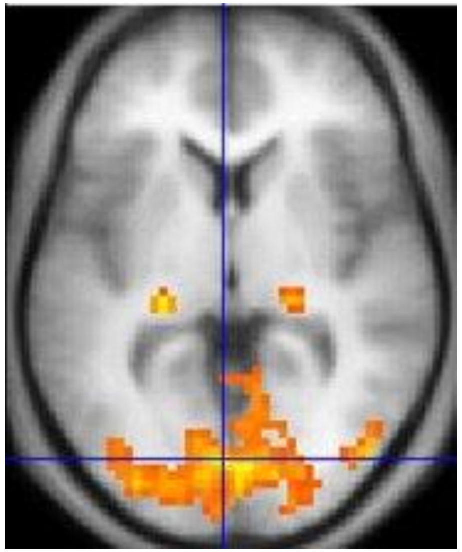


Diffusion Tensor Imaging (DTI)

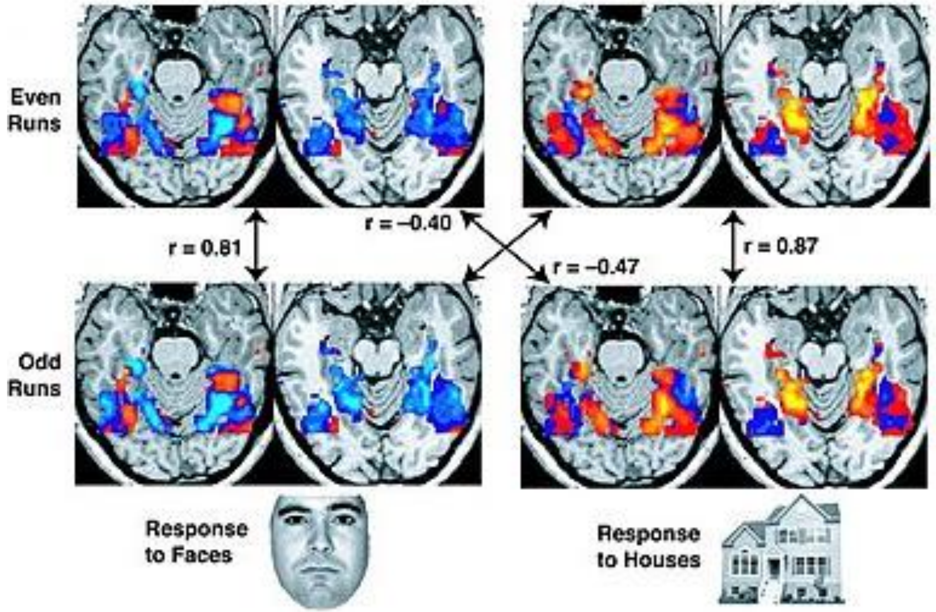


Structural vs functional connectivity

Brain imaging techniques



Brain functional information can be obtained using MRI to map the concentrations of deoxyhemoglobin and oxyhemoglobin. The primary form of fMRI uses the blood-oxygen-level dependent (BOLD) contrast.



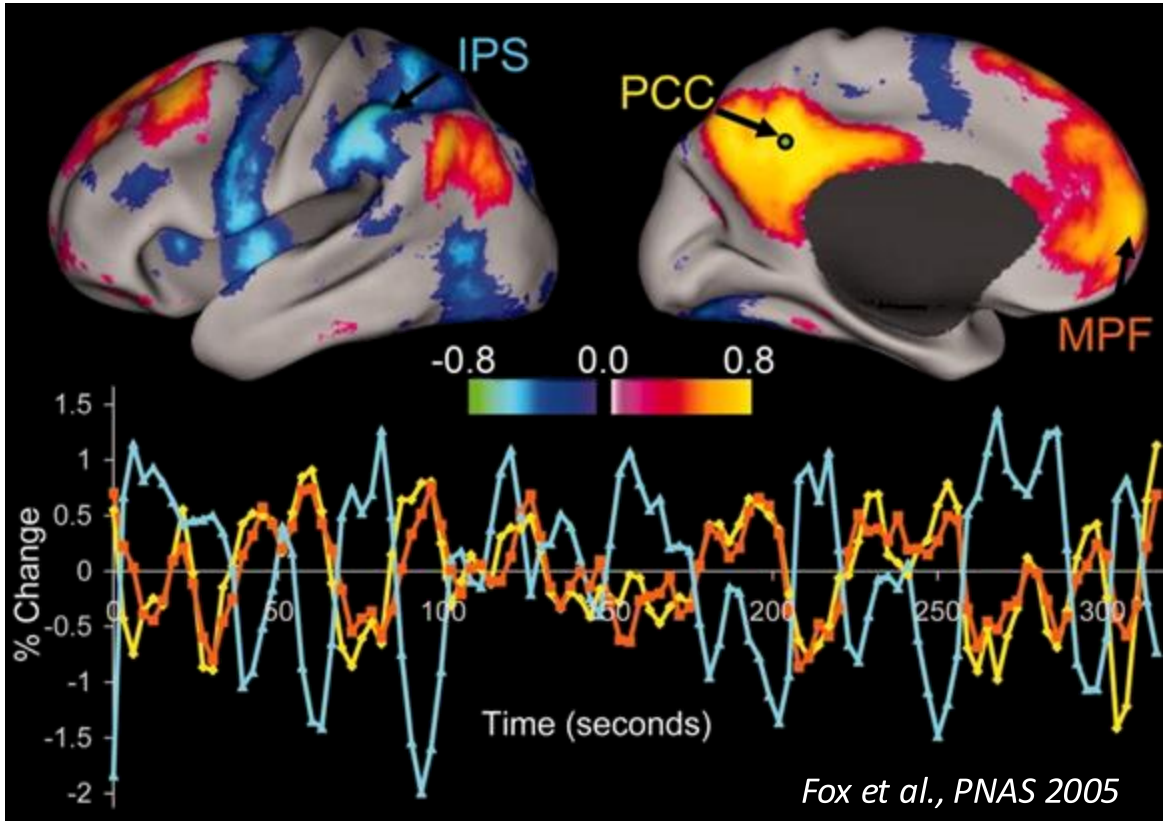
BOLD technique is often used to contrast two different conditions, e.g.:

- task vs rest
- task1 vs task 2

Functional connectivity

BOLD signal correlation is a method widely used in neuroscience to measure the functional connectivity between different regions of the brain.

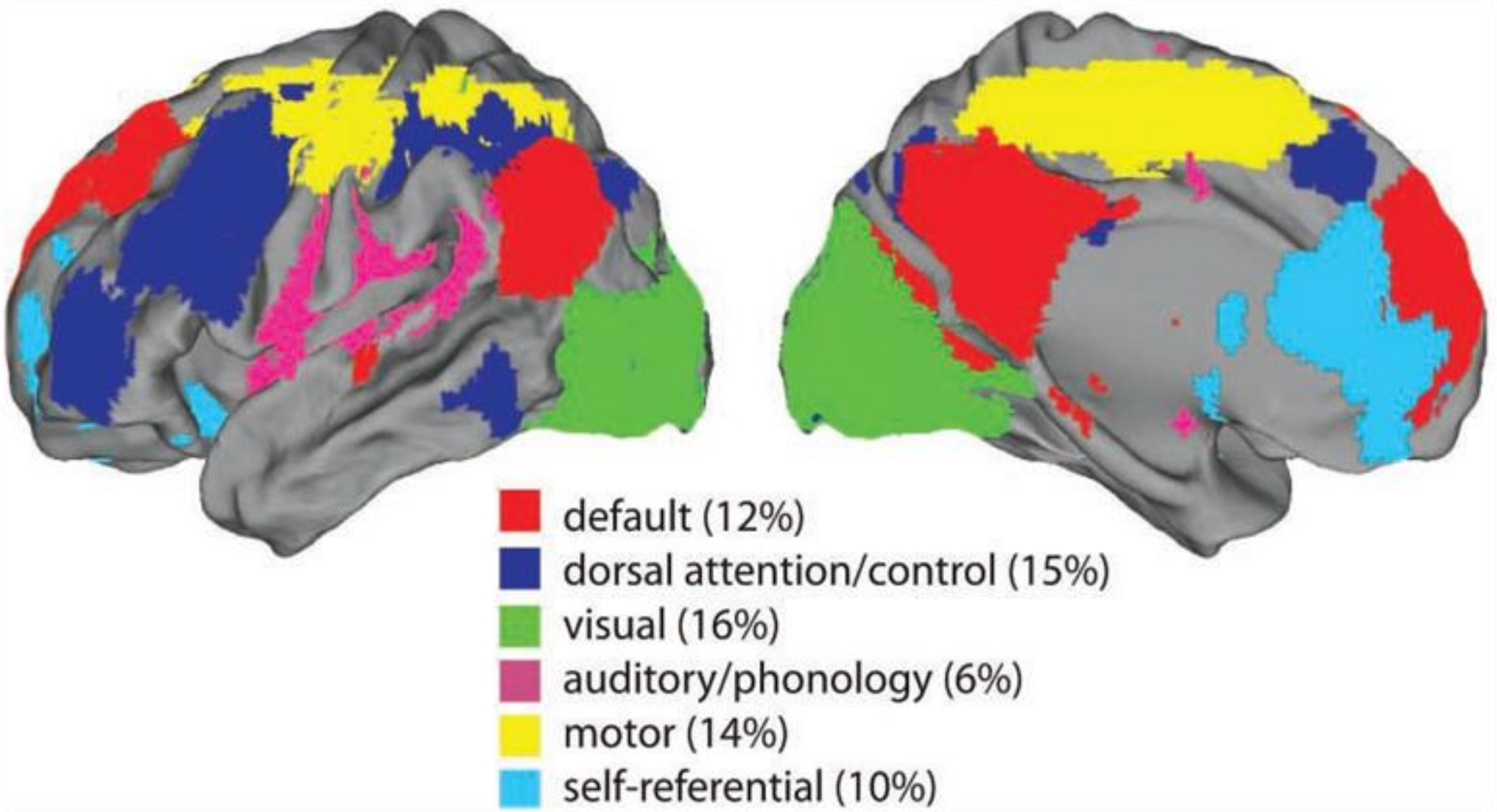
It involves the computation of the Pearson correlation coefficient between the BOLD signals (proxy for neuronal activation) from different brain regions.



Intrinsic correlation between Posterior Cingulate Cortex (PCC) and all voxels for a single subject during rest fixation.

Brain networks

Resting State Networks



Deco and Corbetta 2011

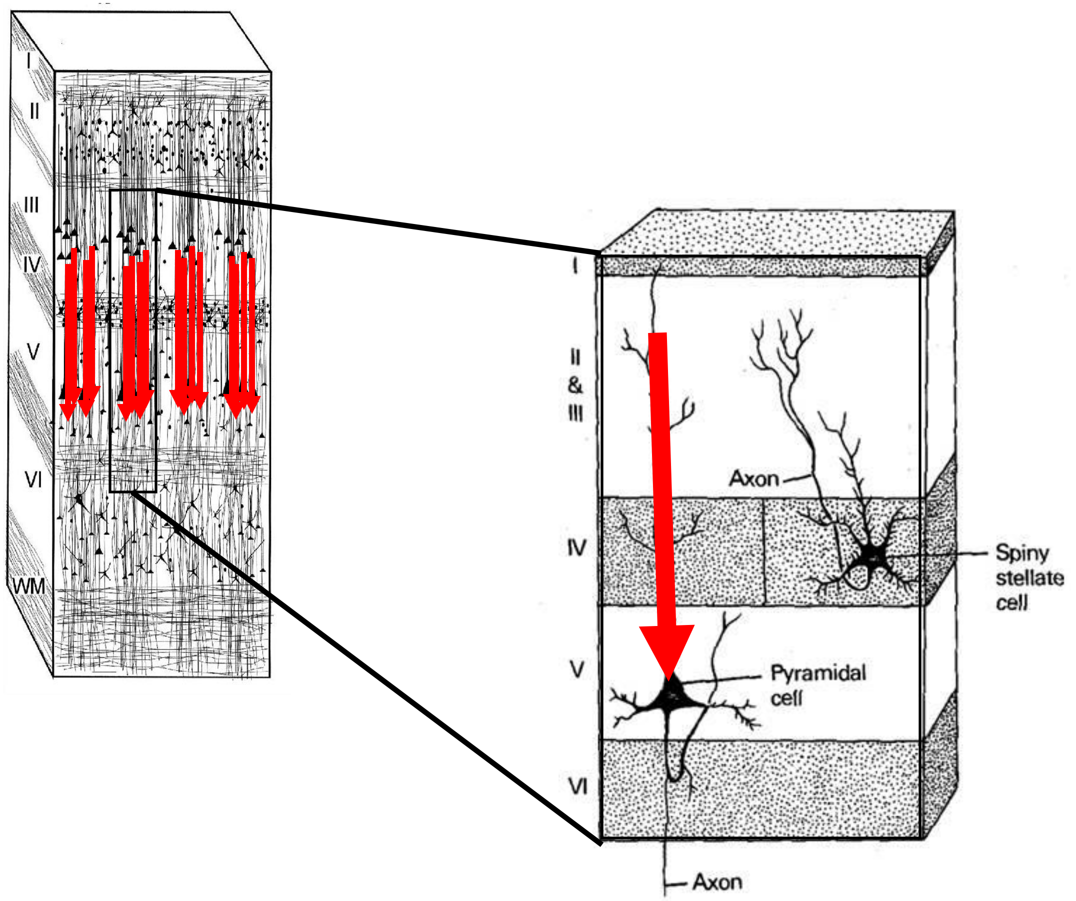
Brain imaging techniques

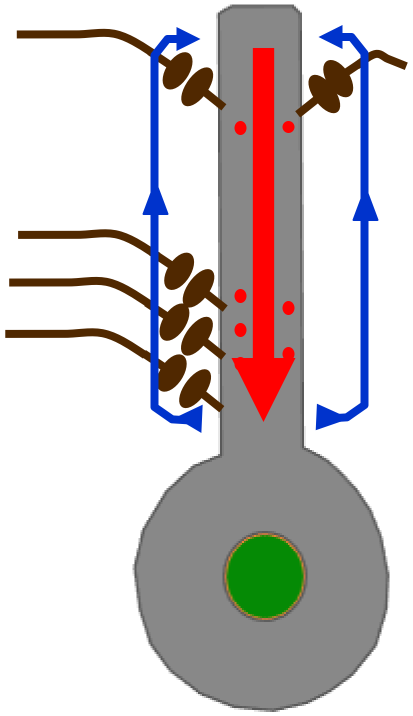
Brain functional information can be obtained also using electrophysiological techniques such as ElectroEncephaloGraphy (EEG) and MagnetoEncephaloGraphy (MEG).

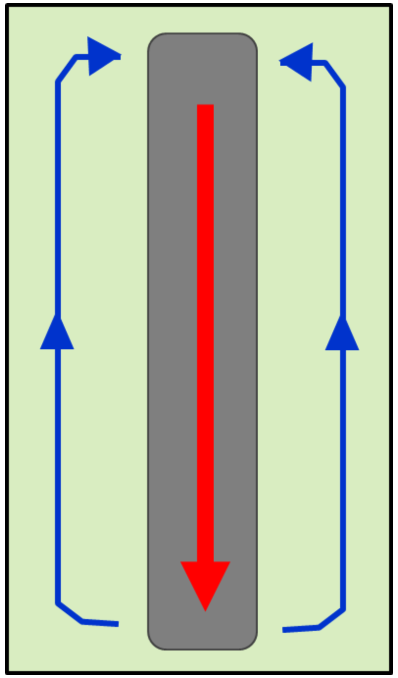
Strictly speaking, these techniques are not "brain imaging techniques" but can be effectively used to assess brain functionality.

EEG and MEG

EEG and MEG signals are generated by neuronal activity.

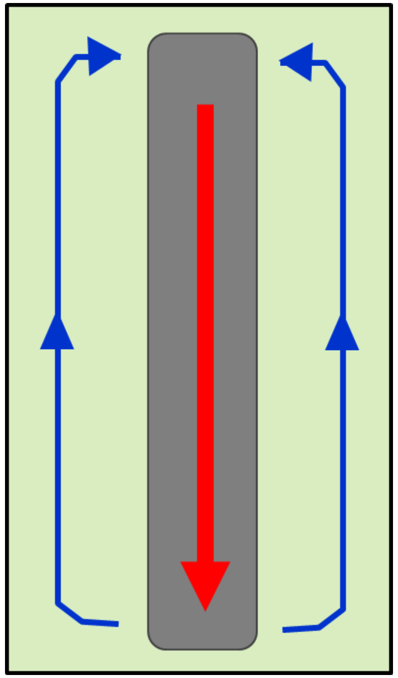






Current dipole model

EEG and MEG



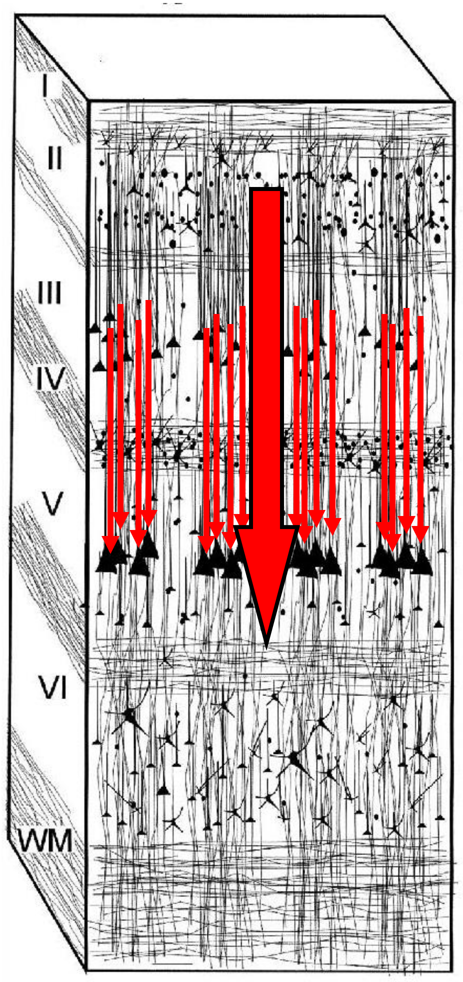
Quasistatic approximation holds

$$\boldsymbol{B}(\boldsymbol{r}) = \frac{\mu_0}{4\pi}\frac{\mathbf{Q} \times (\mathbf{r}-\mathbf{r}_0)}{(\mathbf{r}-\mathbf{r}_0)^3} + \frac{\mu_0}{4\pi}\int \frac{\nabla\sigma(\mathbf{r}') \times \nabla V(\mathbf{r}')}{(\mathbf{r}-\mathbf{r}')} d\mathbf{r}'$$

$$V(\boldsymbol{r}) = \frac{1}{4\pi\sigma}\sum(\sigma_i - \sigma_j)\int V(\boldsymbol{r}')\frac{(\boldsymbol{r}-\boldsymbol{r}')}{|\boldsymbol{r}-\boldsymbol{r}'|^3} dS_{ij}$$

$\mathbf{J}(\mathbf{r}) = \mathbf{Q}\,\delta(\mathbf{r}-\mathbf{r}_0) + \sigma(\mathbf{r})\,\mathbf{E}(\mathbf{r})$

EEG and MEG



Given the typical current dipole strength (Q ~ 0.2 pA·m) and the Biot-Savart law, each neuron is expected to generate a magnetic field (at 4 cm distance) of

$$B \approx 2 \cdot 10^{-18}\ T = 2 \cdot 10^{-3}\ fT$$

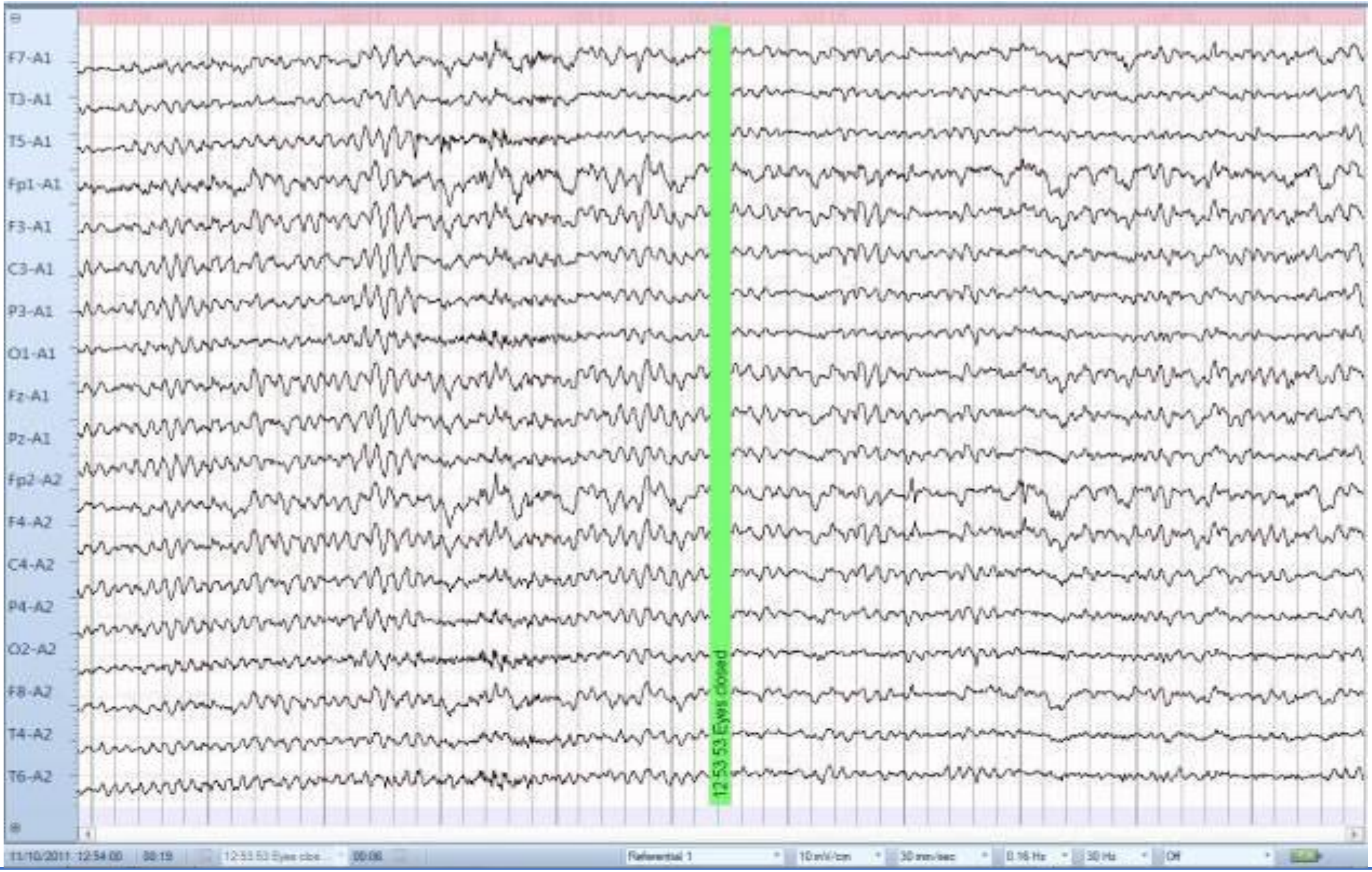
If the pyramidal neurons enclosed in one square mm of the cortex (about 10^5 neurons) are active together, the order of magnitude of the resulting magnetic field (at 4 cm distance) is:

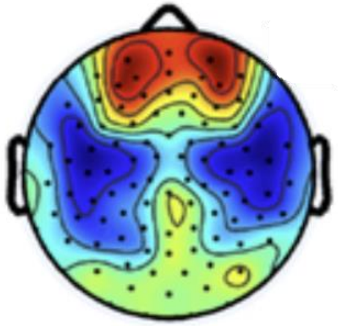
$$B \sim 10^{-13}\ T = 100\ fT$$

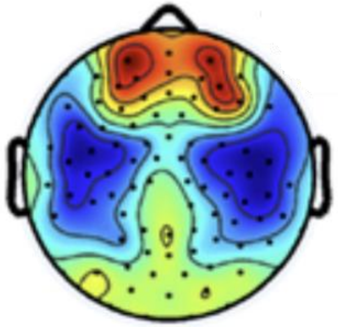
The electric potential recorded on the scalp is about:

$$V \sim 10\ \mu V$$

EEG and MEG

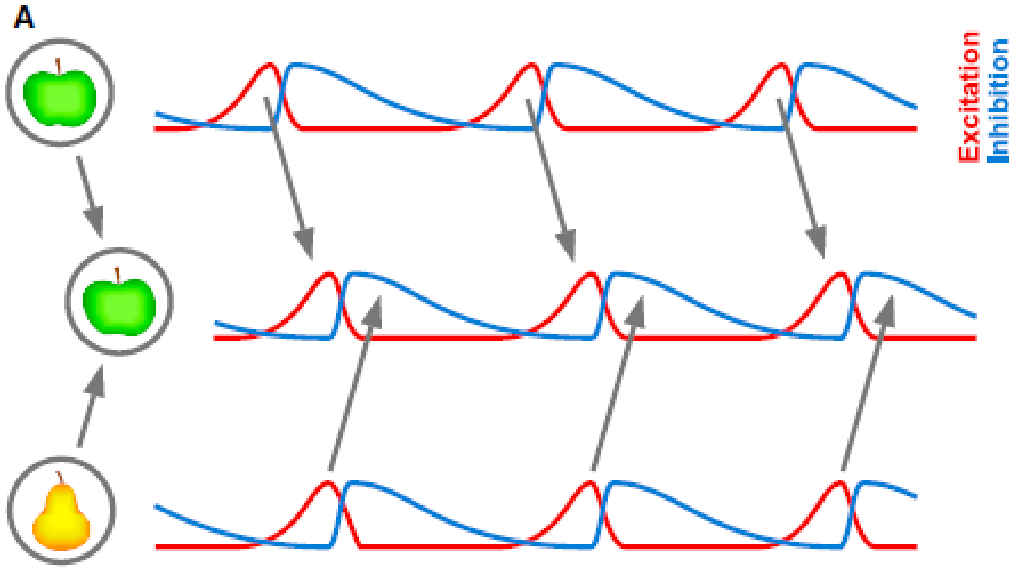

F7-A1
T3-A1
T5-A1
Fp1-A1
F3-A1
C3-A1
P3-A1
O1-A1
Fz-A1
Pz-A1
Fp2-A2
F4-A2
C4-A2
P4-A2
O2-A2
F8-A2
T4-A2
T6-A2
12:53:53 Eyes closed

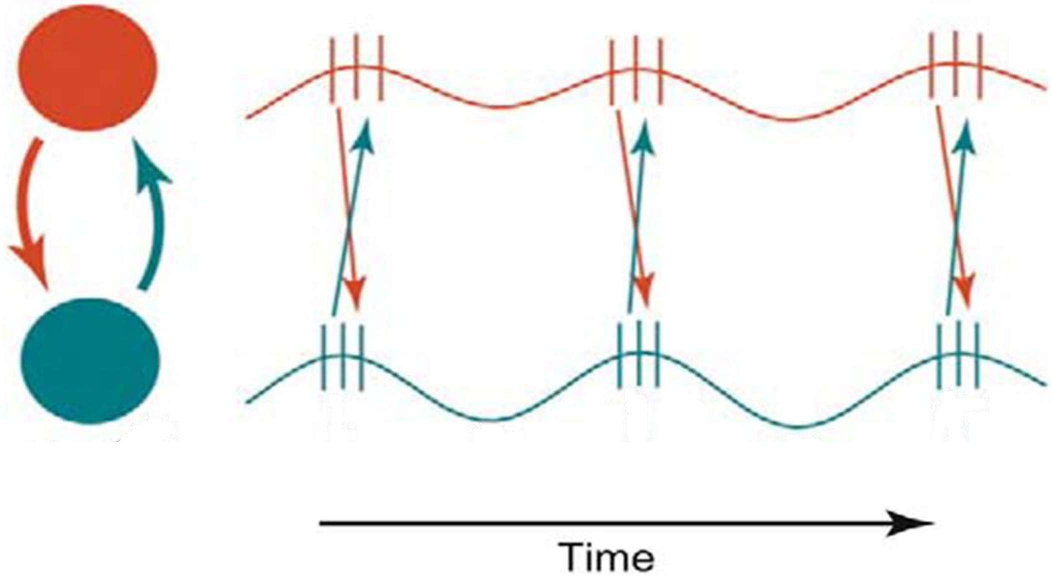




EEG-MEG functional connectivity

Only neurons that oscillate in-phase can effectively communicate

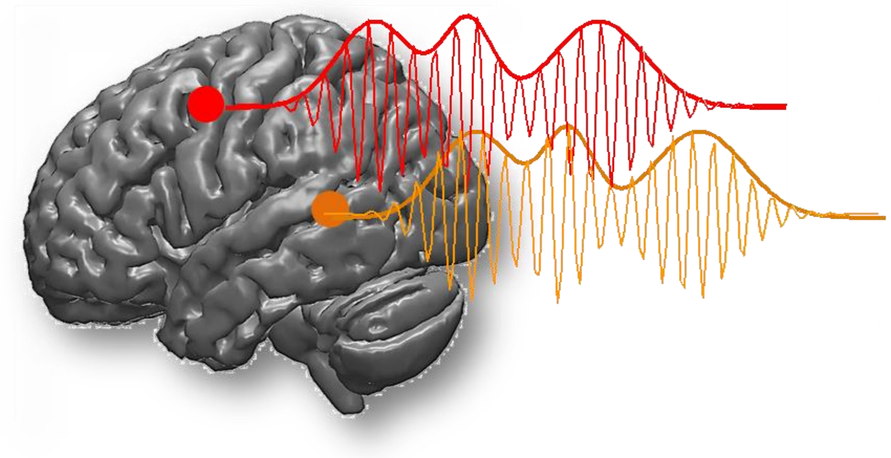




Adapted from Fries *TICS* 2005

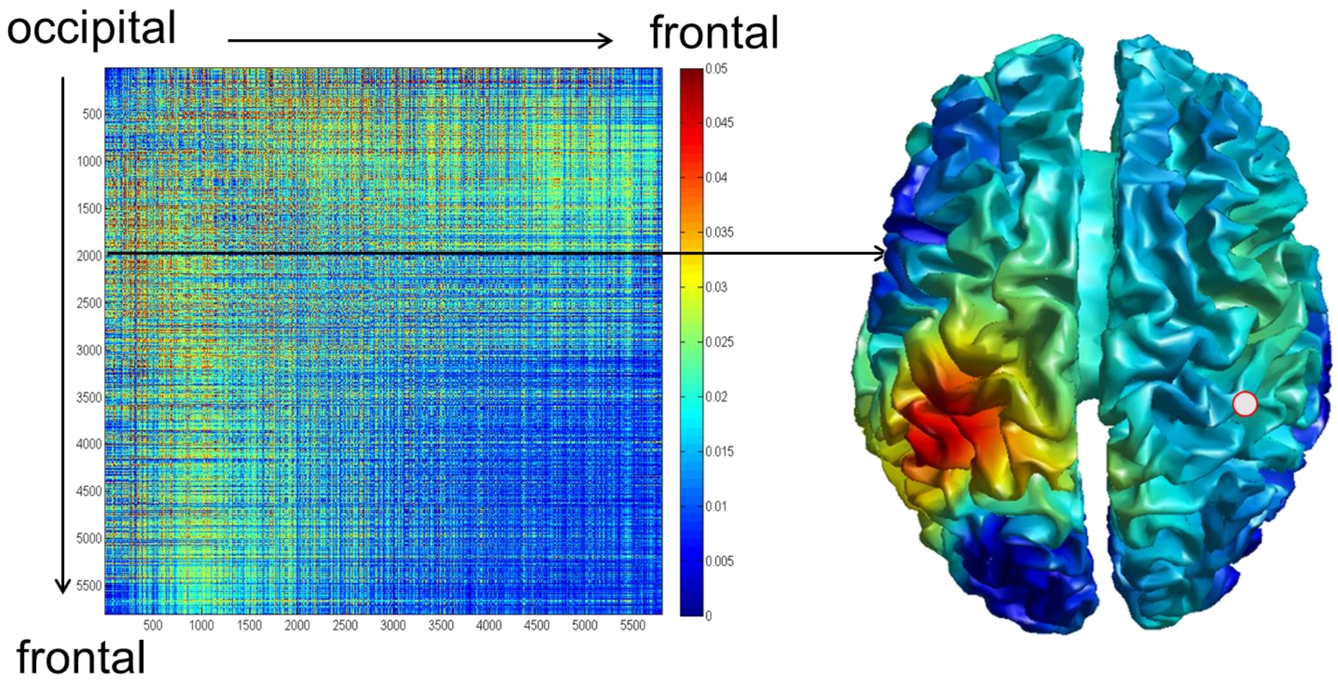
Fries *Neuron* 2015

(EEG)-MEG functional connectivity

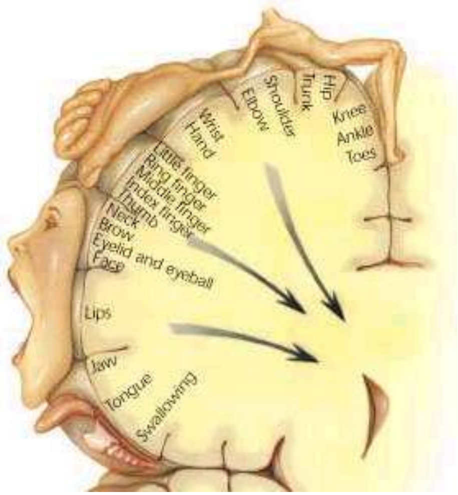


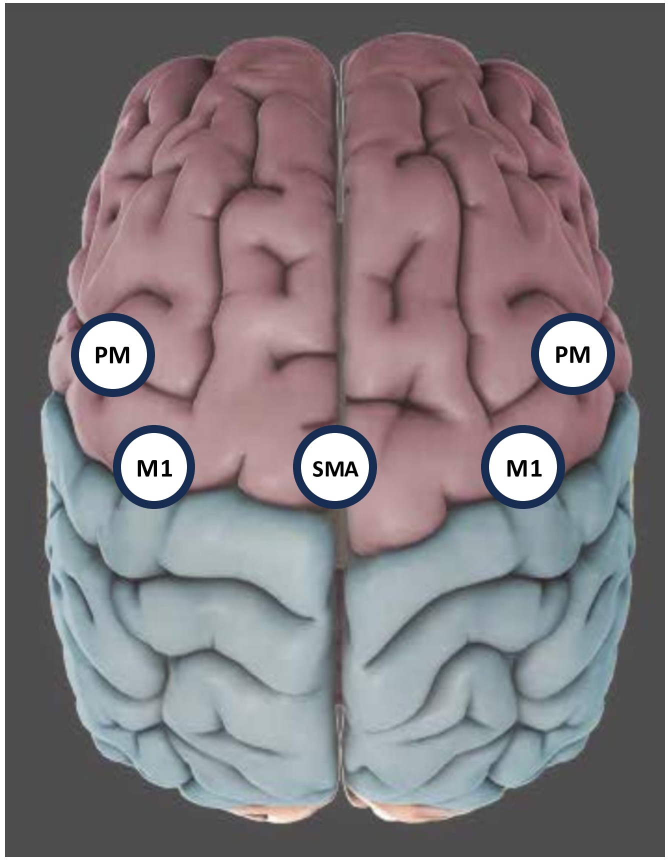
$$\mathrm{iPLV_{ij}}(f) := \left|\langle \Im\left(e^{\iota\,\Delta\theta_{ij}(f)}\right)\rangle\right|$$

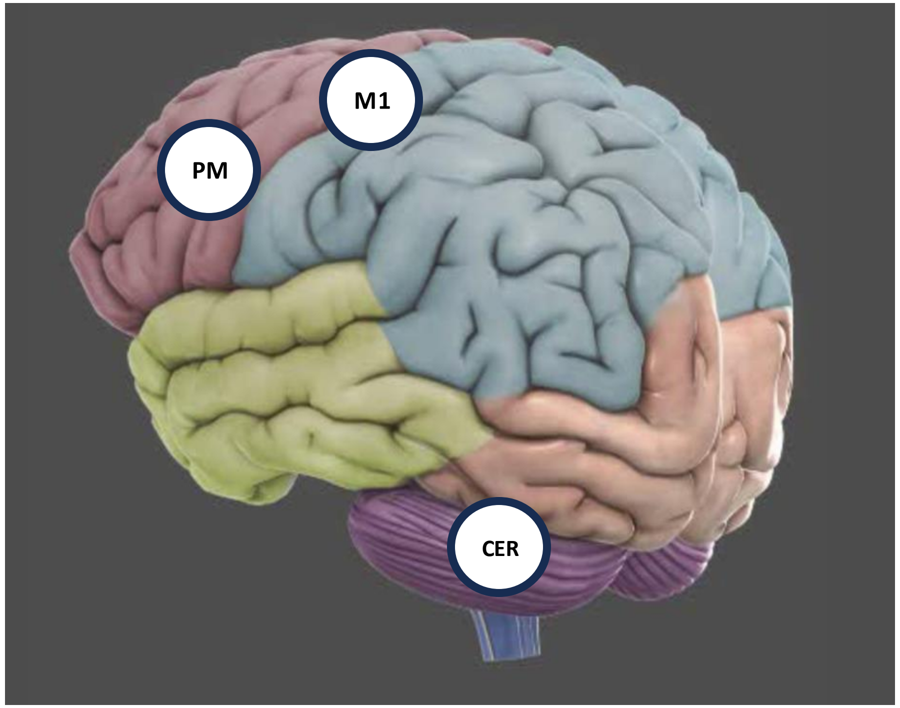
$\Delta\theta_{ij}$ phase difference between the two oscillations



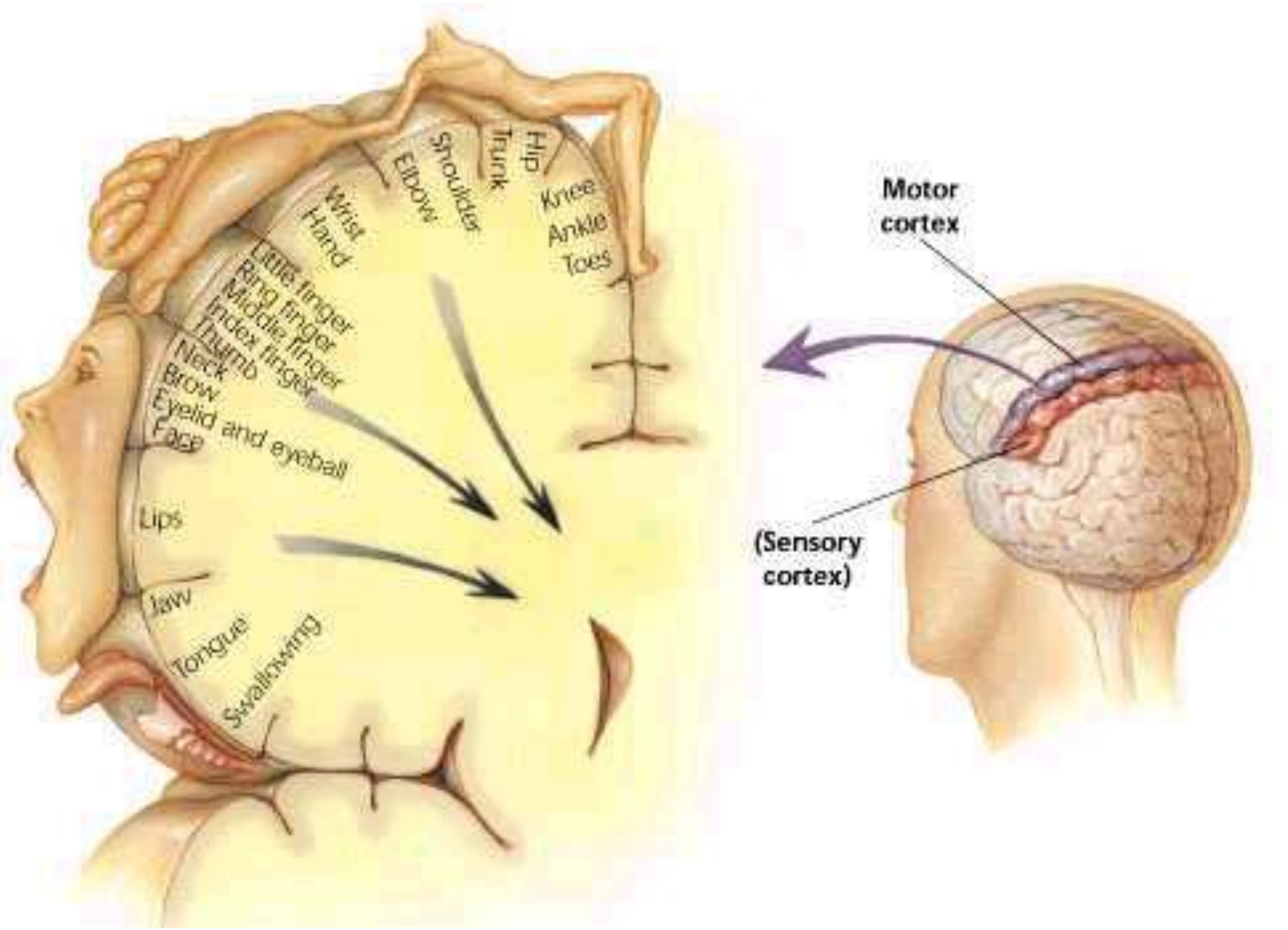
Motor network



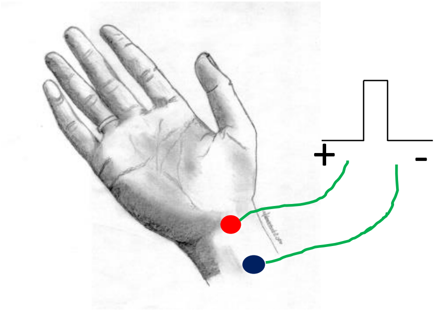


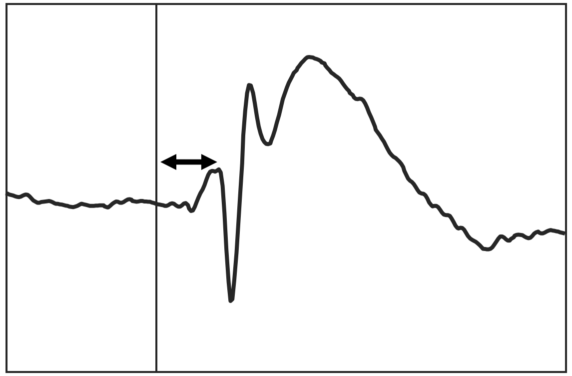


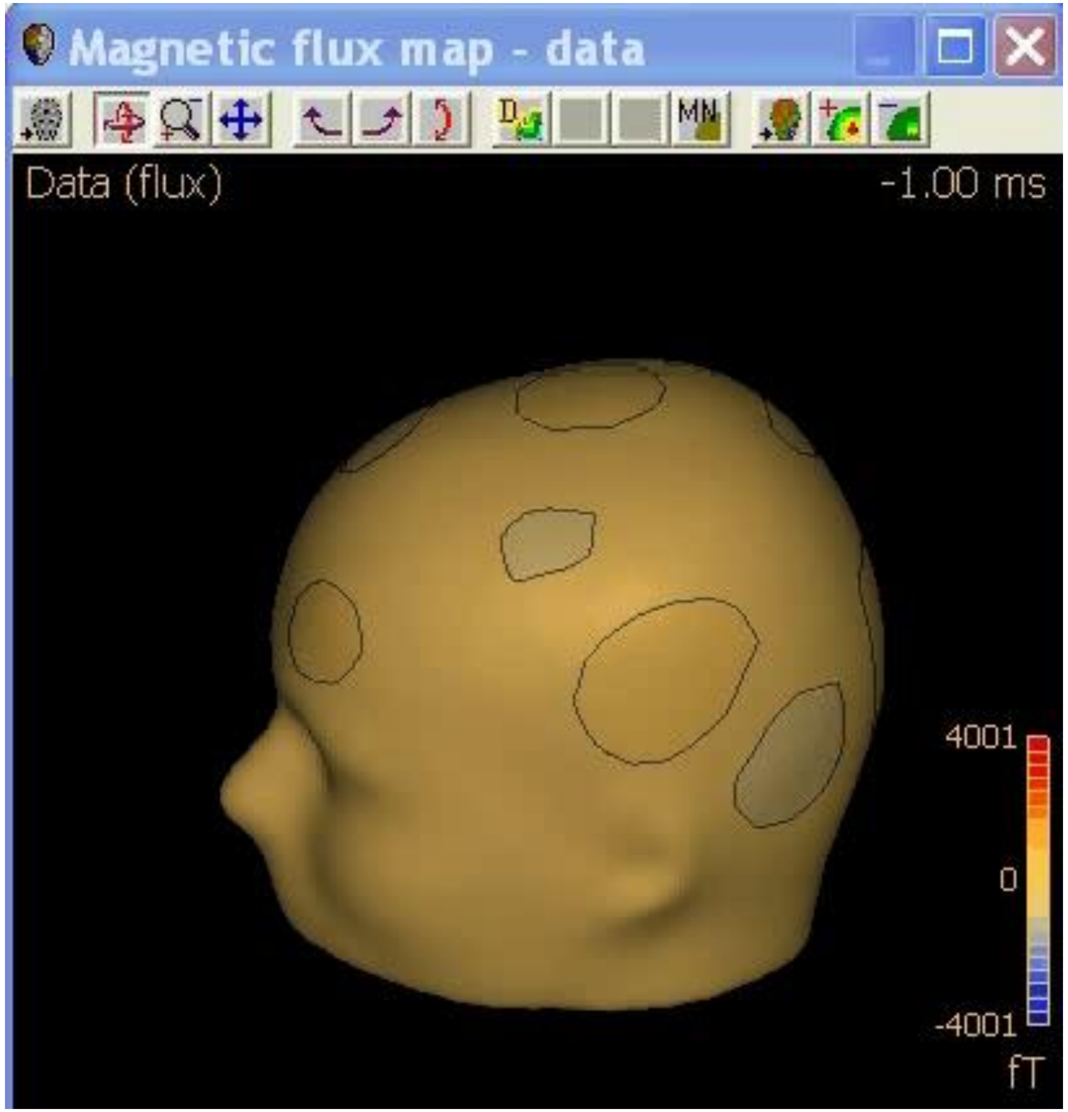
Motor and sensory homunculus



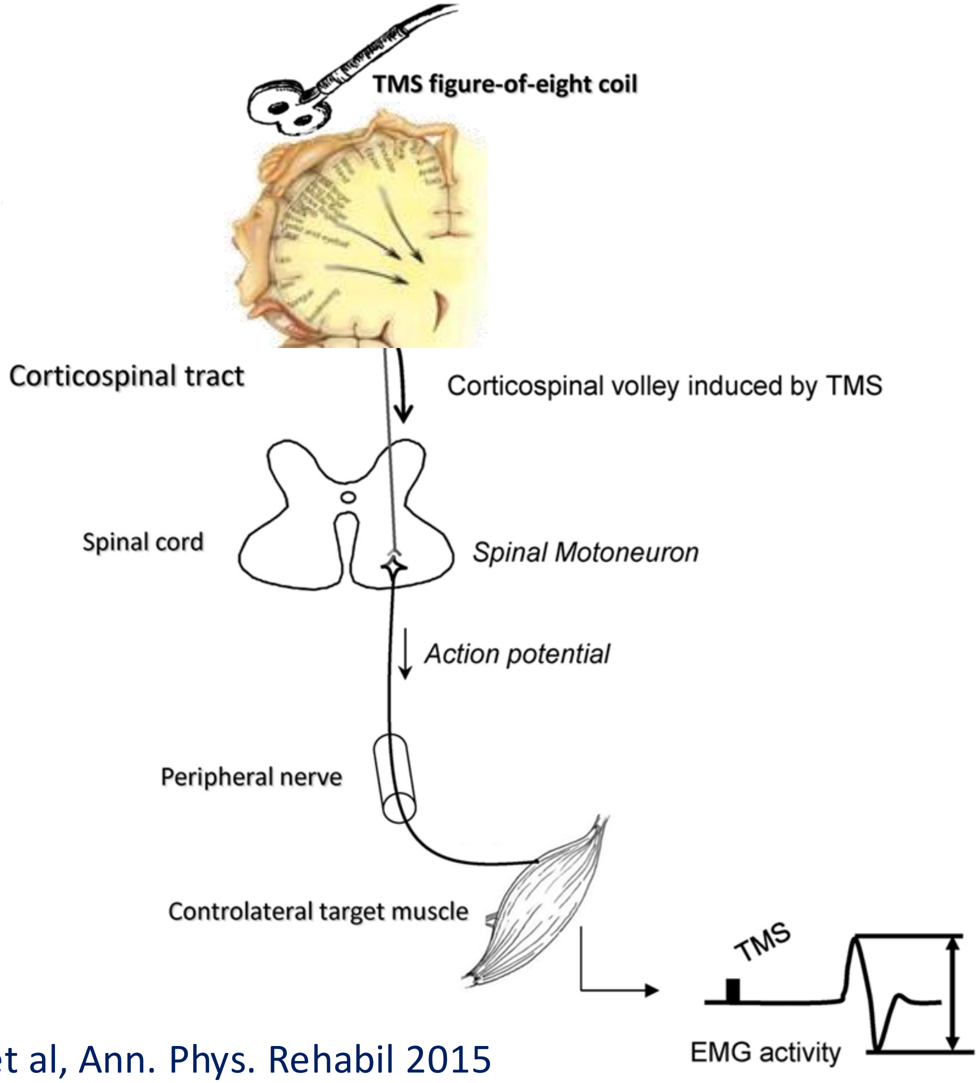
Somatosensory evoked fields







Motor evoked potential



Stimulation of an area of the motor cortex produces a contraction of the muscle controlled by that area.

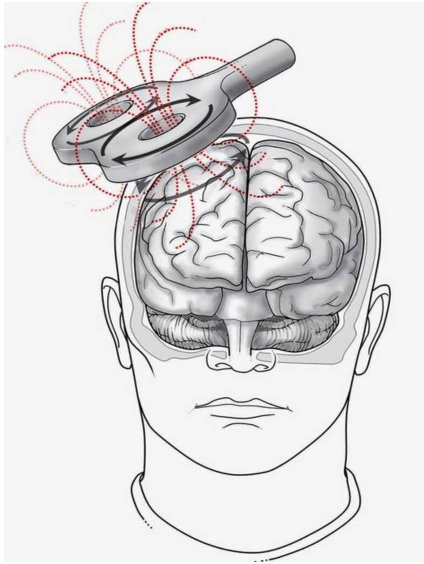
Modified from Klomjai et al, Ann. Phys. Rehabil 2015

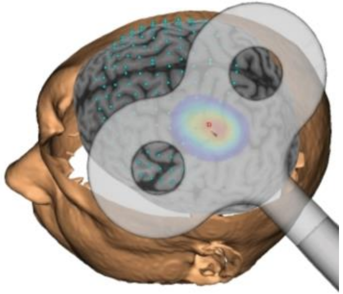
Transcranial Magnetic Stimulation

Transcranial Magnetic Stimulation (TMS) applies brief magnetic pulses, inducing localized intracranial electric fields (E-fields).

→ Non-invasive technique
→ E-field depends on the coil geometry and stimulation parameters

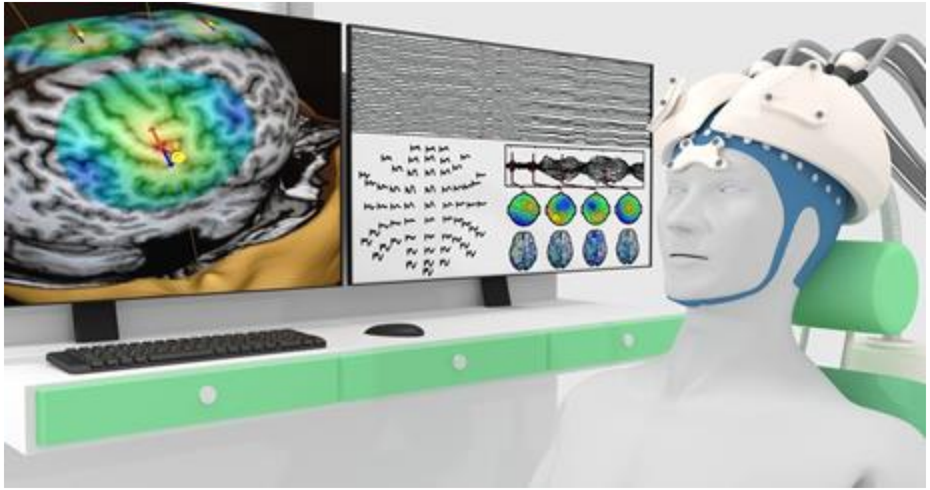
Snap! I don't feel any pain or notice anything unusual other than the sound, but my arm jumps again, seemingly of its own accord…





ConnectToBrain in a nutshell

- 📍 ERC Synergy Grant project
- 💰 Funding: ~10 M€
- ✅ Started in: Sept ‘19
- 🏁 Ending in: Aug ‘26
- 🤝 Partners:
  - FI Aalto University
  - DE Universitaet Tuebingen
  - IT Università d’Annunzio



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Multi-locus TMS

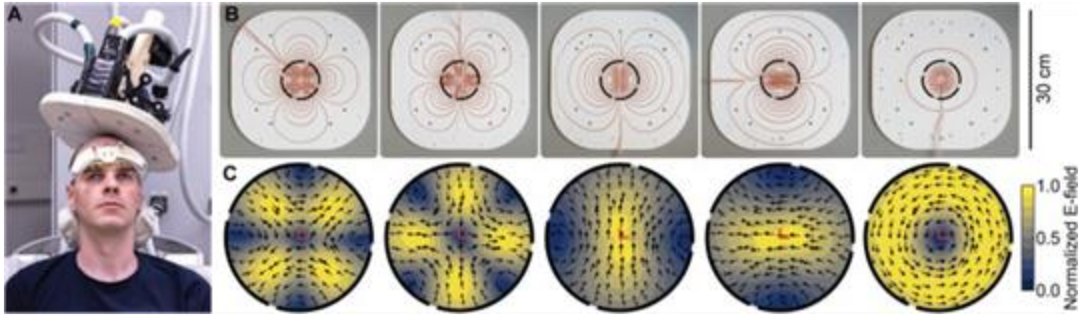
Development of innovative multi-locus TMS device.

Classical TMS devices do not allow to automatically change stimulation parameter without the help of the operator.

The mTMS enables the fast stimulation of different nodes of functional brain networks:

- ➔ a set of large overlapping coils
- ➔ 2 coil mTMS transducer
- ➔ 5 coil mTMS transducer

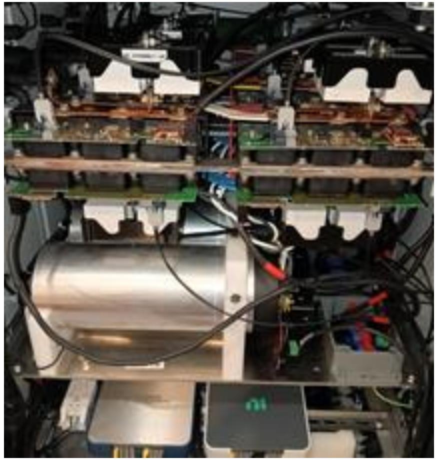
Nieminen J. O. et al., 2019
Nieminen J. O. et al., 2022
Tervo A. E. et al, 2022
Souza V.H. et al, 2022
Matsuda R.H., 2022



mTMS electronics

The mTMS system is based on independently controlled H-bridge circuits:

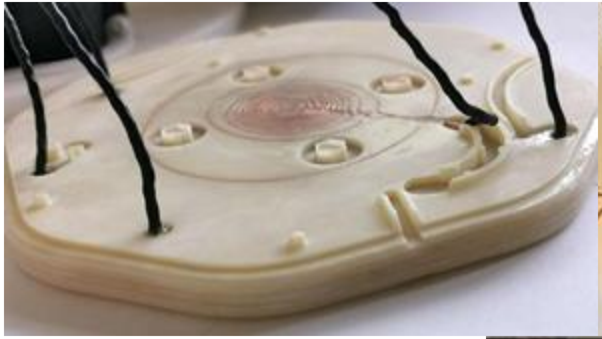
- ➔ Control unit: FPGA
- ➔ Charging unit: high-voltage charger, capacitors
- ➔ Channels: pulse module and discharge controller
- ➔ Coils: 5 channels
- ➔ Auxiliary Electronics: Digital temperature sensors, power distribution module.



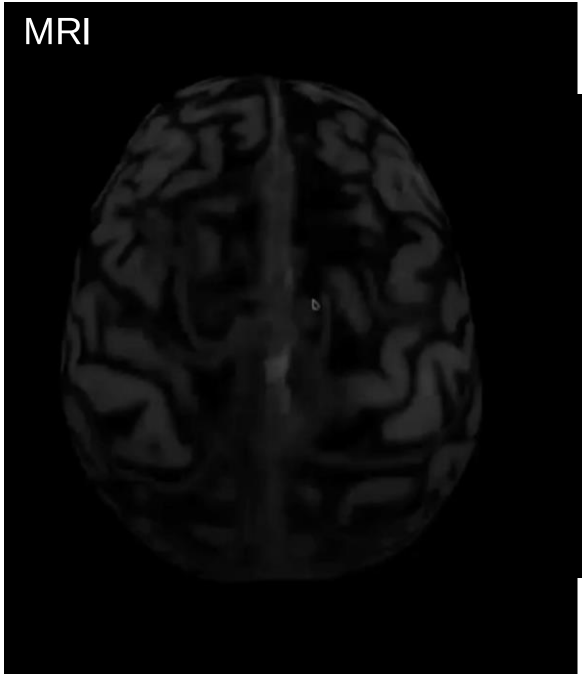
mTMS 5 coil transducer

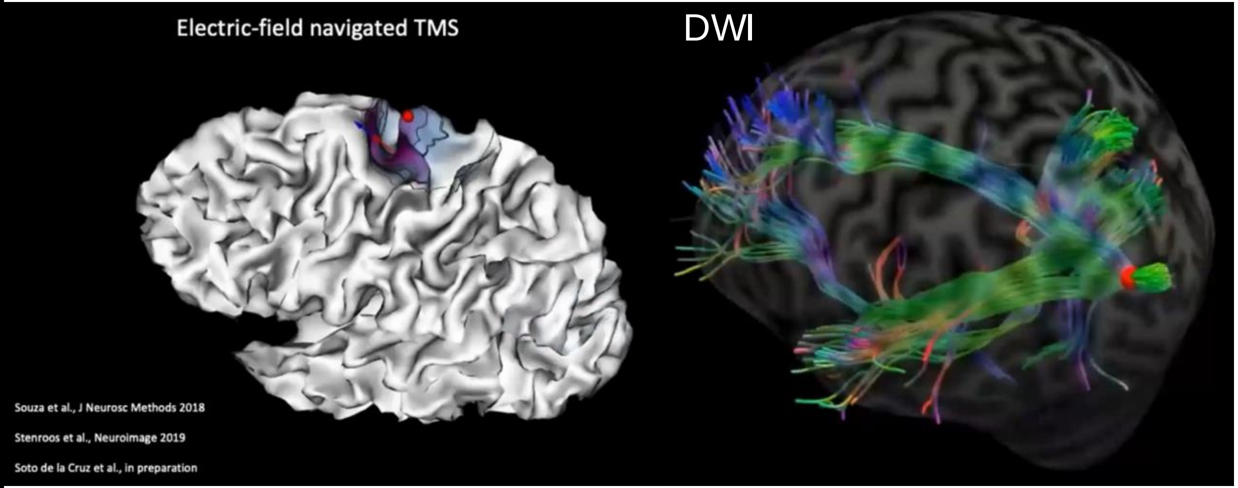
5 coil transducer to control the location and orientation of the induced E-field:

- ➔ 30 mm diameter, 360°
- ➔ five coil formers, 3 mm
- ➔ polyamide
- ➔ copper litz wire



Neuronavigation software: InVesalius

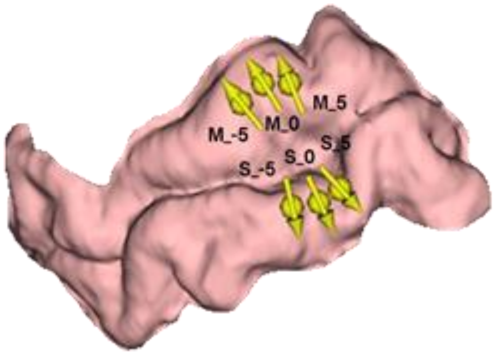


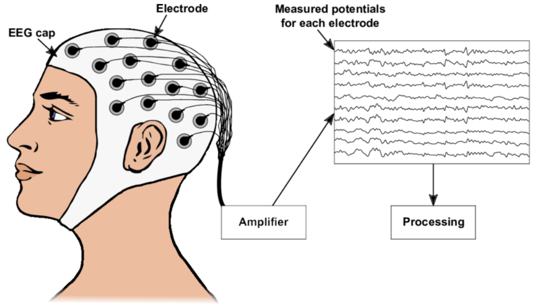


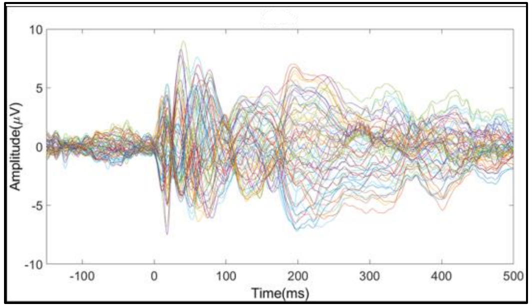
Mapping FUNctional in the Motor and Somatosensory Areas: FUN-mTMS

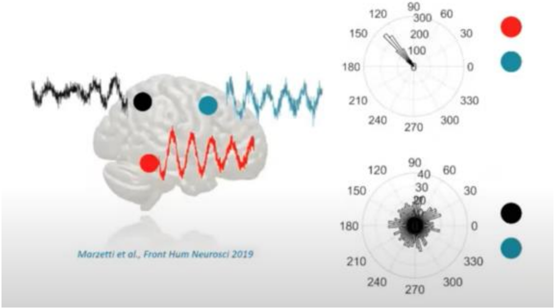
Investigate spatial specificity of mTMS-induced EEG connectivity modulations:

- ➔ Stimulation of three sites 5 mm apart, in both M1 and S1.
- ➔ Prediction of stimulation site from post-stimulus functional connectivity
- ➔ 7 functional connectivity metrics
- ➔ Linear SVM for prediction
- ➔ Evaluation: accuracy and recall
- ➔ Connectivity Importance Inspection









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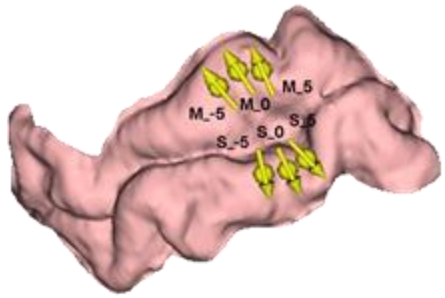
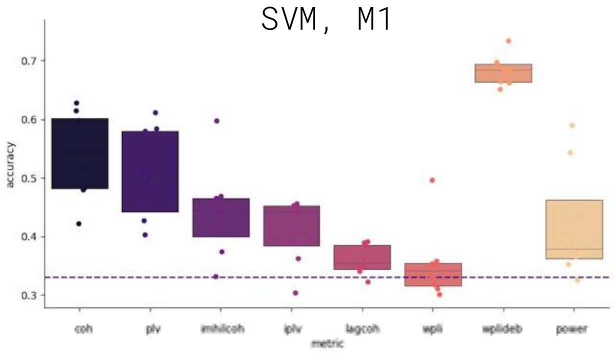
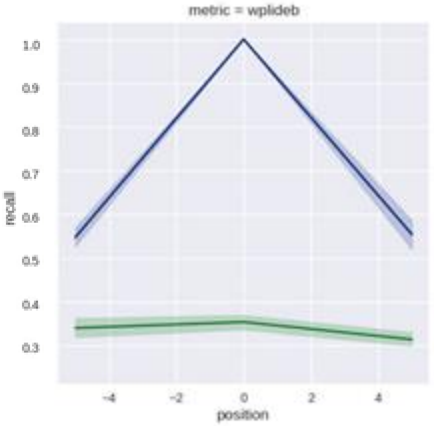
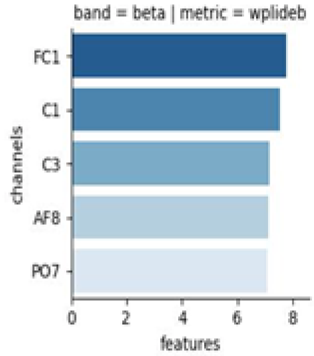
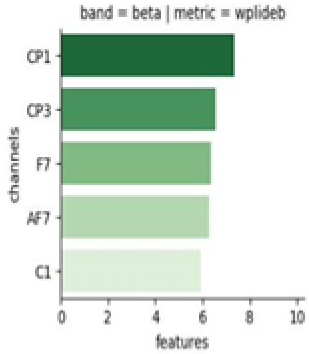




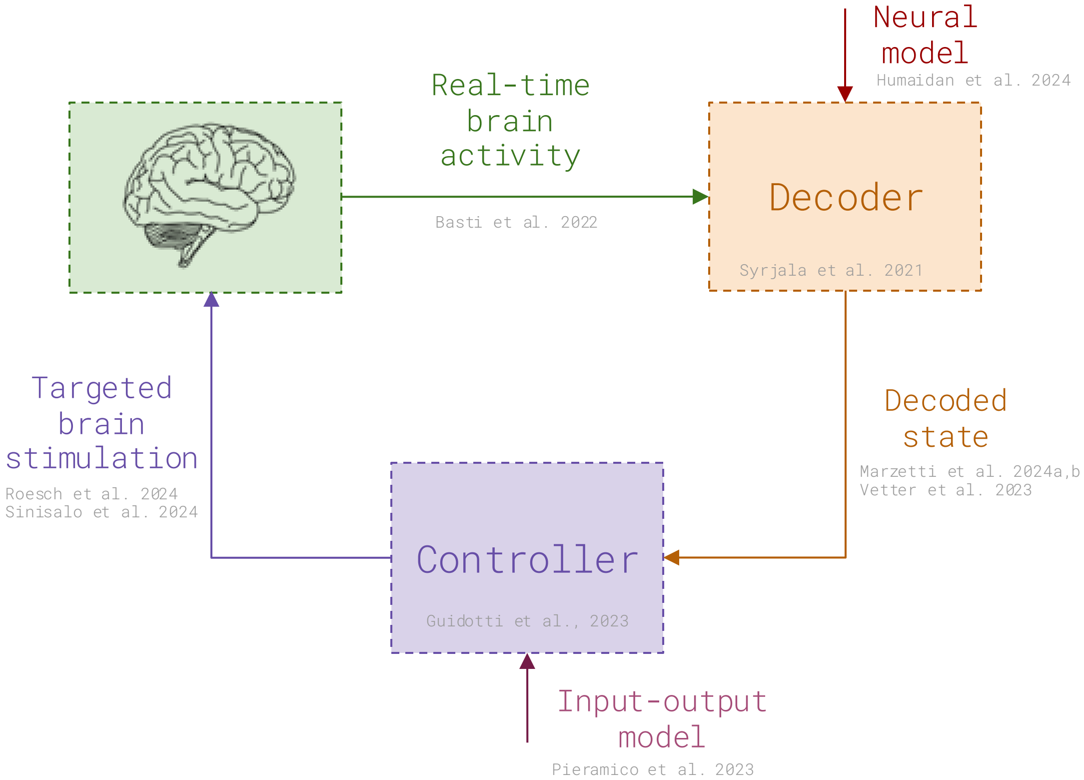






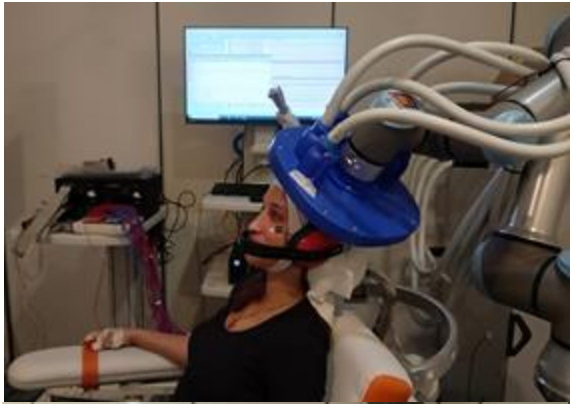
Closed-loop neuromodulation

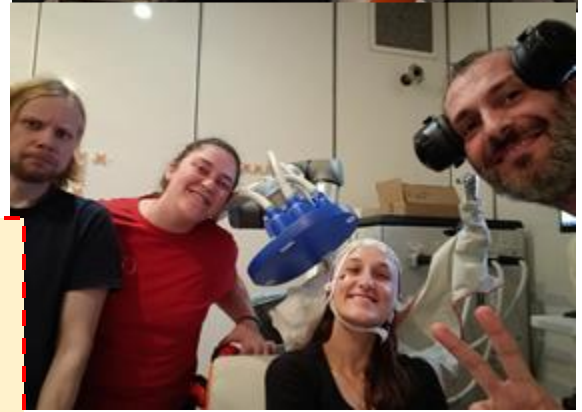
- ➔ Real-time Brain activity is captured
- ➔ A machine-learning algorithm decode the brain state
- ➔ The AI-driven controller will choose the stimulation parameters to drive the brain into a target state.



Lab setup + experiments

- ➔ Lab setup
- ➔ First PoC experiment on connectivity triggered closed-loop mTMS/EEG
- ➔ Acquisition of massive multimodal dataset [EEG/TMS, DWI, fMRI, sMRI]





First EEG connectivity-triggered closed-loop mTMS proof-of-concept experiment in Europe

Thank you

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