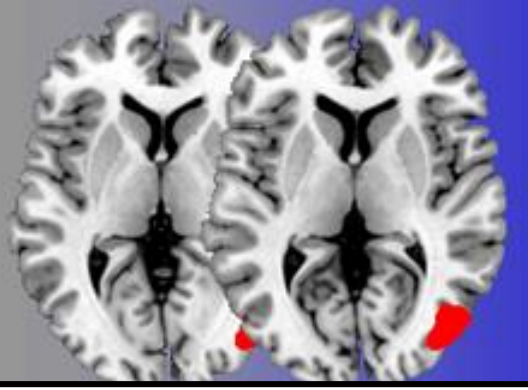
EMORY
ROLLINS SCHOOL OF PUBLIC HEALTH

CBIS
Center for Biomedical Imaging Statistics



BIOS 516
Neuroimaging Statistics

Introduction

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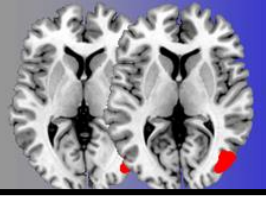
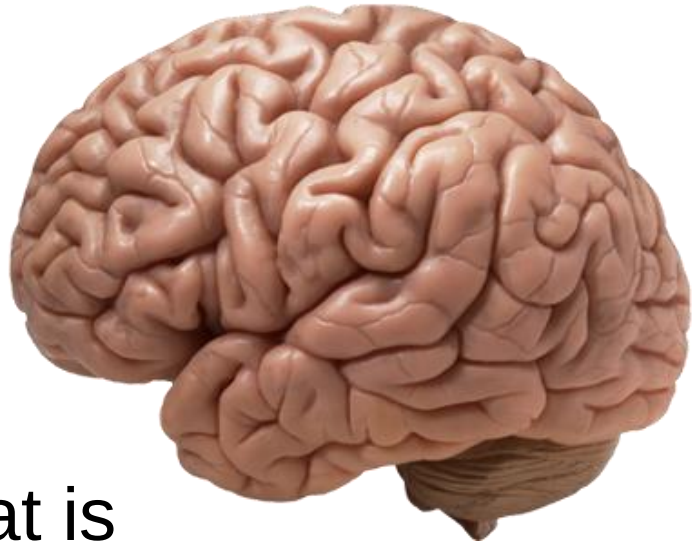


The Human Brain

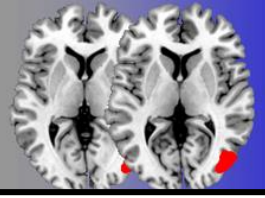
The Human Brain

- Controls all body activities
  - Heart rate, breathing, sexual function
  - Motor activities and senses
  - Learning, memory, language
  - Emotion, mood, behavior
  - Consumes ~20% of energy



- Daunting task for an organ that is
  - 3 pounds of fatty tissue
  - Cortex thick as 4 sheets of paper

The Human Brain



- How does this small package provide such a powerful punch?
  - Contains a network of an estimated 100 billion neurons
  - Highly sophisticated organization and system of communication
  - Each neuron has an estimated 7,000 synaptic connections (on average), giving up to 700 trillion connections!

The Neuron

- The brain achieves amazing functionality via networks of interconnected neurons
- Basic neuron structure:

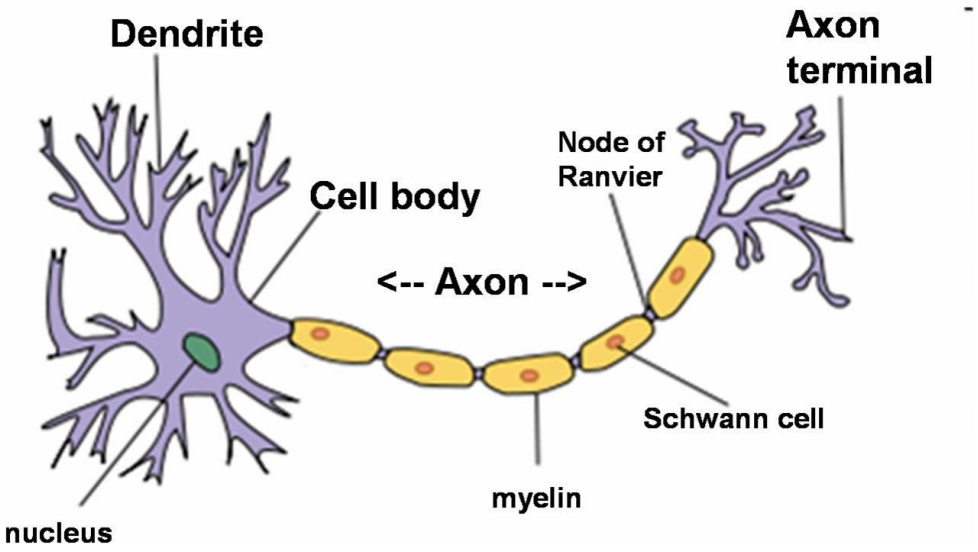


Figure from Wikepedia

Neuron Function

- Around the cell body are dendrites that receives signals from other neurons.

- A neuron transmits electrical signals along its axon, which is covered by the myelin sheath.

- At the axon terminals, this triggers the release of neurotransmitters from vesicles into the synaptic gap.

- The released neurotransmitters bind to receptor molecules on the surfaces of adjacent neurons. This signals a change, e.g. muscle contraction.

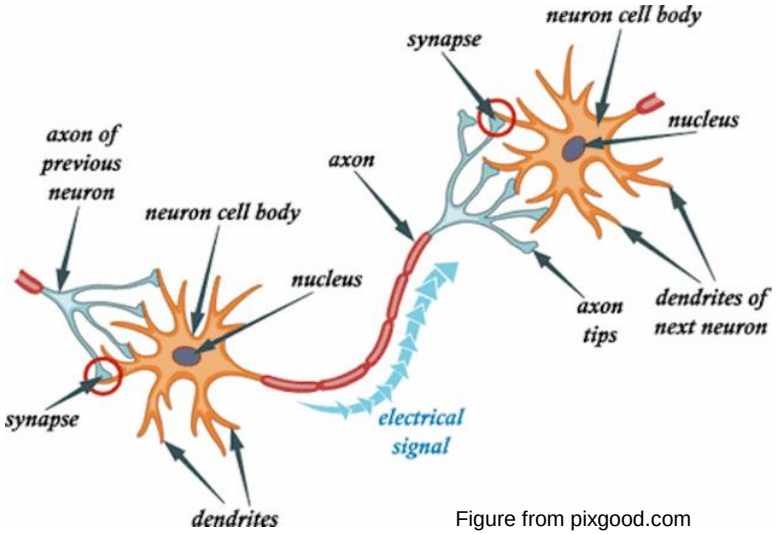


Figure from pixgood.com

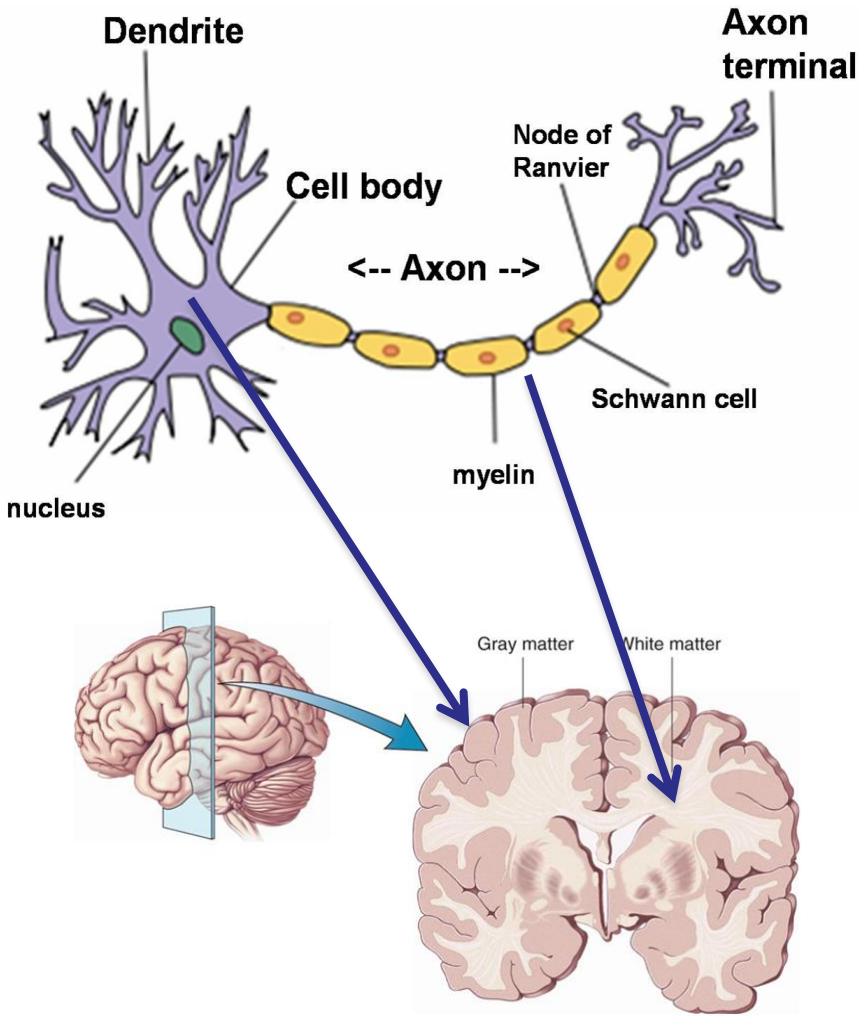
Figure from Brain Harmony Center

Gray vs. White Matter

Two main types of brain tissue:

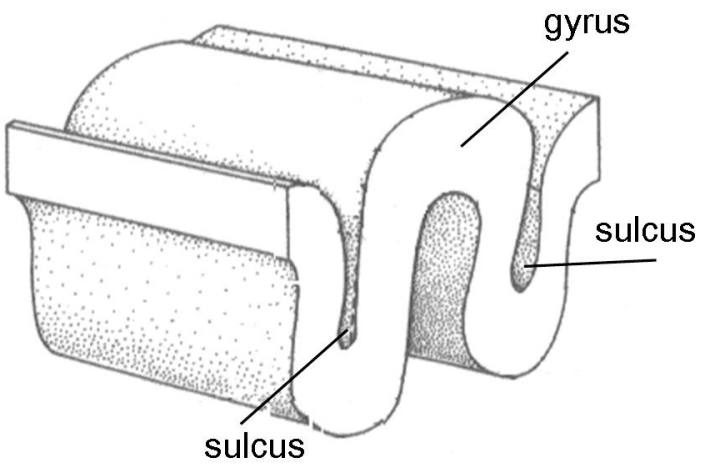
- **Gray Matter**
  - Makes up the surface of the cortex
  - Composed of neuron cell bodies, dendrites

- **White Matter**
  - Lies beneath the cortex
  - Composed of myelinated axons (fiber tracts) that connect nerve cells
  - Enables communication between grey matters by carrying electrical impulses.

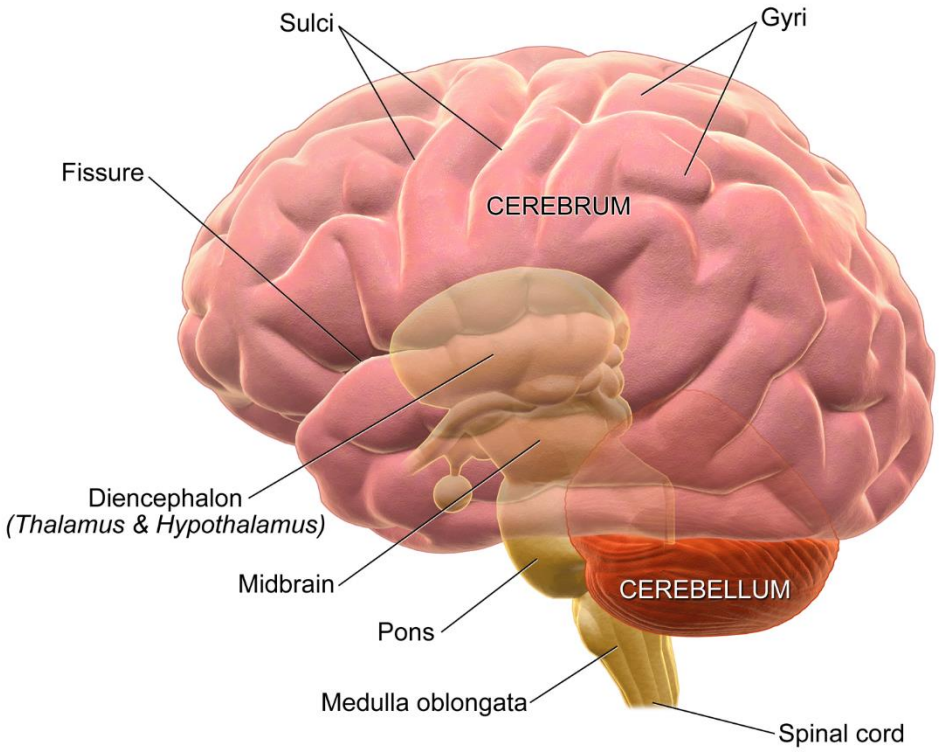


Brain Anatomy

Sulci and Gyri



An Introduction to Brain Structures

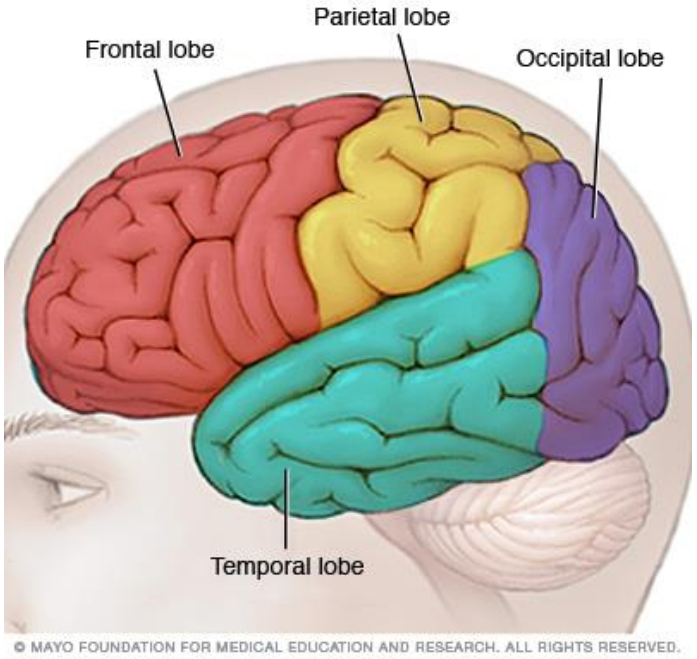


Wikipedia

Brain Function

Four lobes:

- Frontal (conscious thought, planning, decision making)
- Parietal (sensory info)
- Temporal (auditory)
- Occipital (vision)



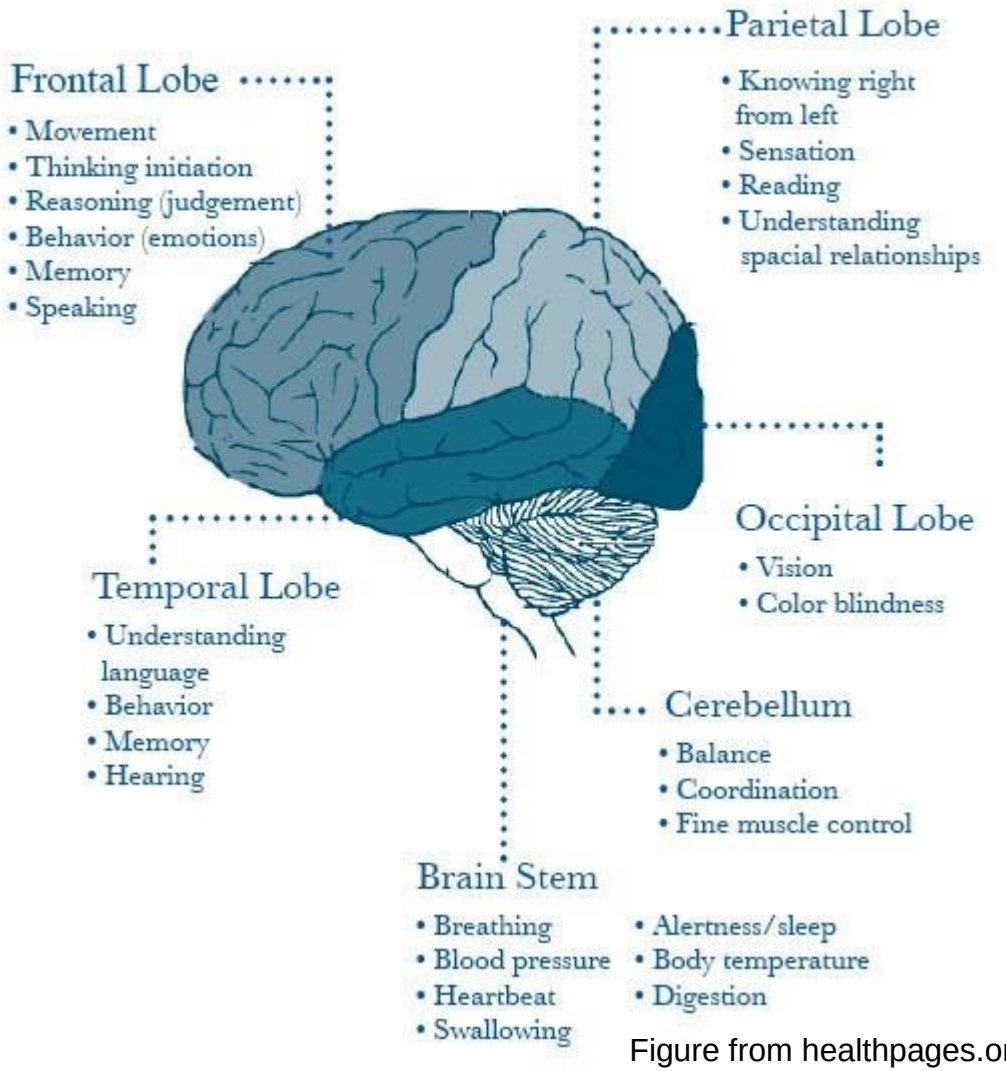
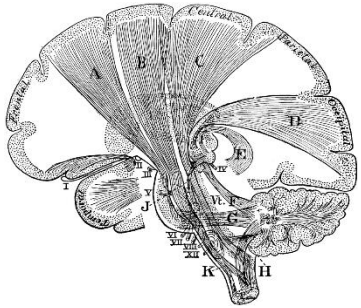


Figure from healthpages.org

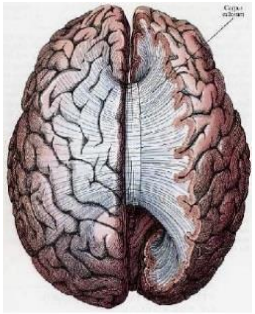
Brain Structure

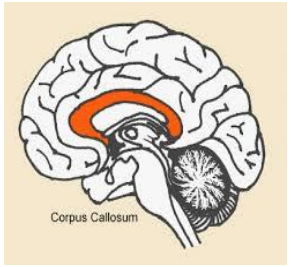
Three major kinds of white fiber bundles

- **Projection tracts:** vertical tracts that connects the cerebrum and lower brain and spinal cords (carry information between the cerebrum and the rest of the body)

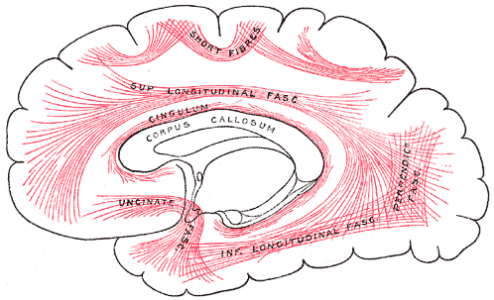


- **Commissural tracts:** mostly lie in corpus callosum which connects the two brain hemisphere (left or right)



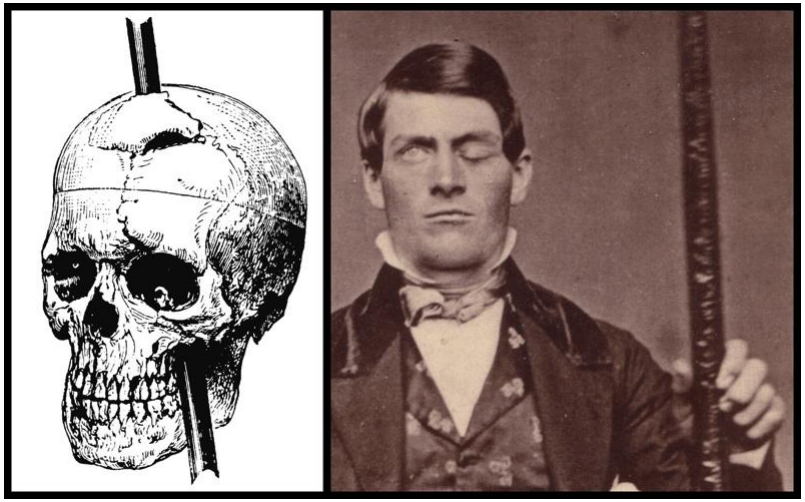


- **Association tracts**: connect different regions within the same hemisphere of the brain.



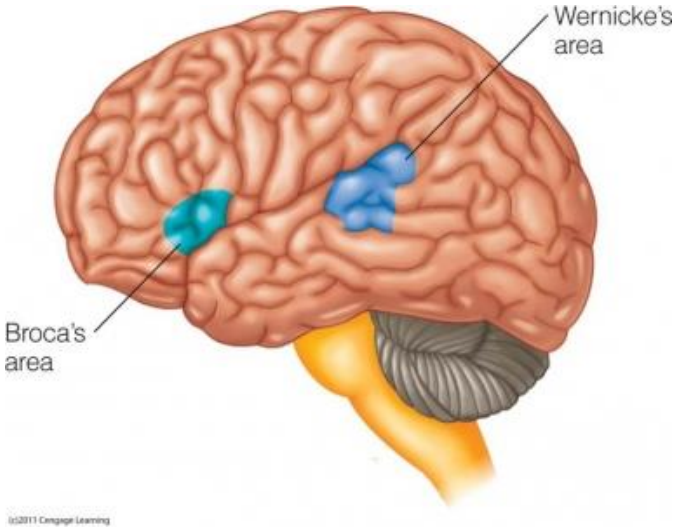
A Brief History of Brain Research

- **Before the advent of neuroimaging technology**, it was difficult to non-invasively study the brain *in vivo*.
  - **Dissection** studies of animal and human brains
- In **1848**, railroad worker **Phineas Gage** survives an accident in which the frontal lobe of his brain is pierced by an iron rod during an explosion.
  - He experiences profound mood and behavior changes.
  - Thus, **Frontal Lobe** responsible for key parts of personality

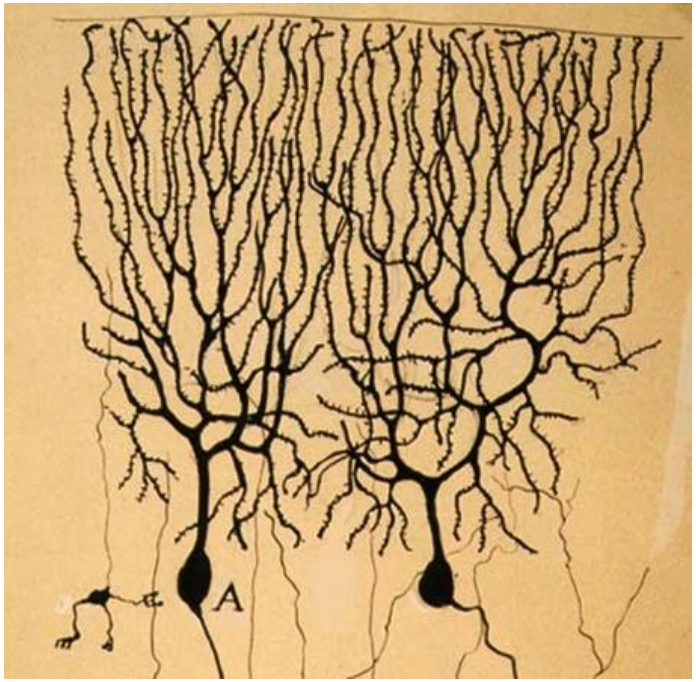


A Brief History of Brain Research

- **1862**: Paul Broca discovers an area of the brain related to speech
  - autopsied patient with speech impairment
  - Found LH lesion = Broca's area
- **1874**: Carl Wernicke finds an area related to understanding language
  - Autopsied patient with incoherent speech
  - Found LH lesion = Wernicke's area
- Conclusion: left hemisphere is important for language!

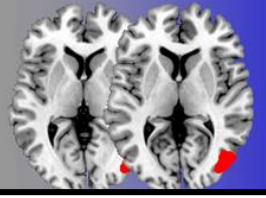


- **1906**: Santiago Ramon y Cajal wins the nobel prize for his work on the microscopic structure of the brain and his detailed illustrations of neurons.



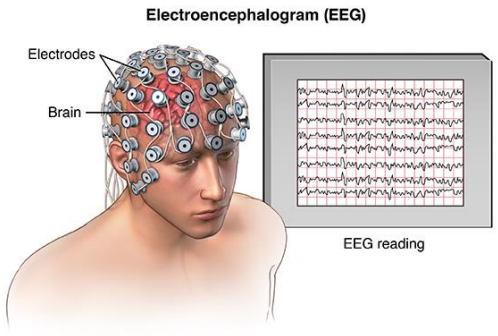
A Brief History of Brain Research

- **1929**: Hans Berger demonstrates the first **EEG**, now a common neuroimaging tool
- **1974**: first **PET** scanner developed
- **1990**: Pres. Bush declares the 90s the **"decade of the brain"** to promote brain research. **fMRI** has come to dominate the brain mapping field since this time.



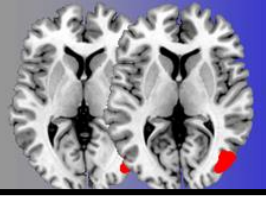
Neuroimaging Techniques and Modalities

Neuroimaging



- Neuroimaging methods allow us to understand interactions between the mind, brain, and body in a way we never have before.
- These interactions determine whether we are healthy or sick, energized or depressed, etc.
- Understanding these interactions is one of the most complex, important, and challenging issues in science today.

Neuroimaging



- Brain imaging can be separated into two major categories:
  - Structural neuroimaging
  - Functional neuroimaging
- There are a number of different modalities for performing each category

Imaging Modalities

1. *Metabolic* or *vascular* methods that measure brain activity by detecting a contrast agent in the blood

•fMRI (functional magnetic resonance imaging)

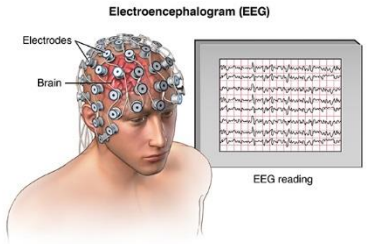
•PET (positron emission tomography)

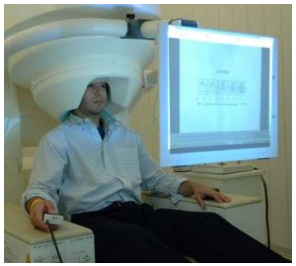
•SPECT (single photon emission computed tomography)

2. *Electrophysiological methods* that measure signals which arise as summations of electrical events in individual cells

•EEG (electro-encephalogram)

•MEG (magneto-encephalogram)

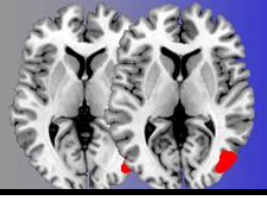




3. Structural Methods

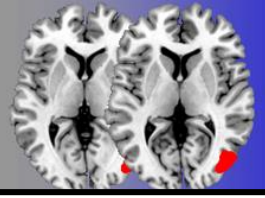
•MRI (magnetic resonance imaging)

•DTI (diffusion tensor imaging)



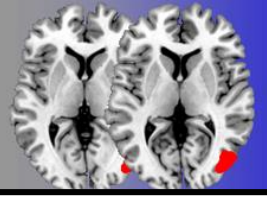
Functional Imaging

Functional Brain Imaging



- The process of mapping brain activity *in vivo* over time
- Useful for studying cognitive and affective processes.
- Popular non-invasive modalities include:
  - positron emission tomography (PET),
  - functional magnetic resonance imaging (fMRI),
  - electroencephalography (EEG), and
  - magnetoencephalography (MEG).

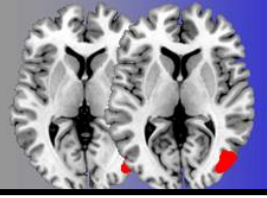
PET Overview



- PET is used to locate and quantify radioactivity emitted by radioactive tracers in the brain.

- Depending on the tracer, PET can be used to measure glucose metabolism, oxygen consumption, and regional cerebral blood flow – all correlates of neural activity.

PET Overview



- PET attempts to measure blood flow directly
- Inject a metabolically active tracer (biological molecule) that carries a positron-emitting isotope and is small enough to pass through the blood-brain barrier
- The injected tracer circulates through the blood (over a few minutes), and the radioactive isotopes emit positrons that interact with electrons and produce energy (divergent gamma rays)
- The PET detectors records this activity and enables calculation of the distribution of the positron-emitting tracer

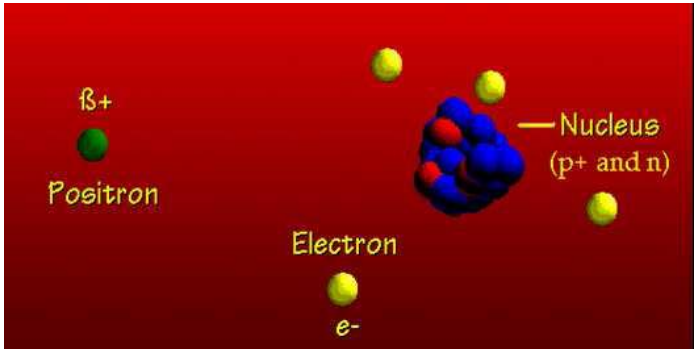
Depending on the tracer, PET can be used to measure glucose metabolism, oxygen consumption, and regional cerebral blood flow – all correlates of neural activity.

PET Overview

How does PET record signals?

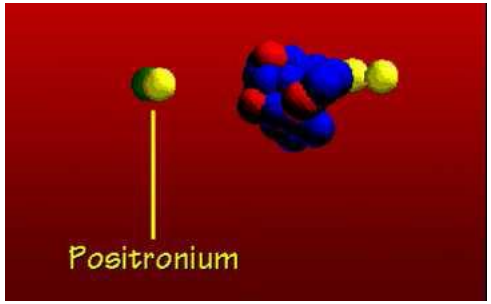
- Positron Emission

  Radioactive isotopes are unstable atoms that emit positrons to stabilize the nucleus.



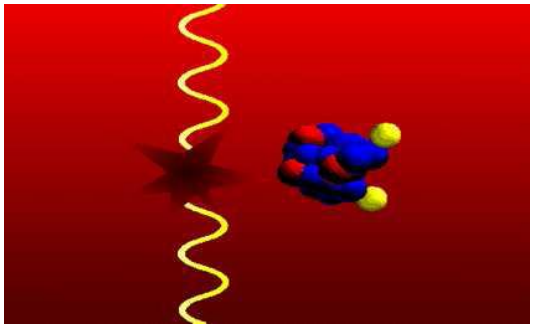
- Positron-Electron Interaction

  The positrons are susceptible to interaction with electrons that causes annihilation.



- Annihilation

  Coincident emission of two photon rays in opposite direction (almost 180°)

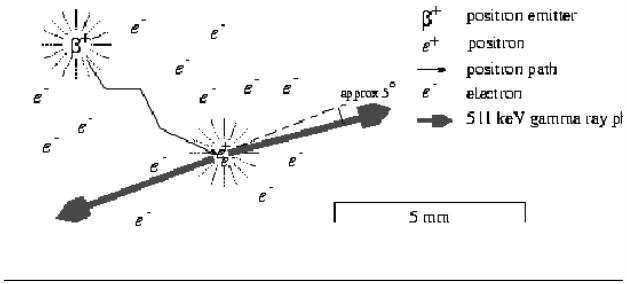


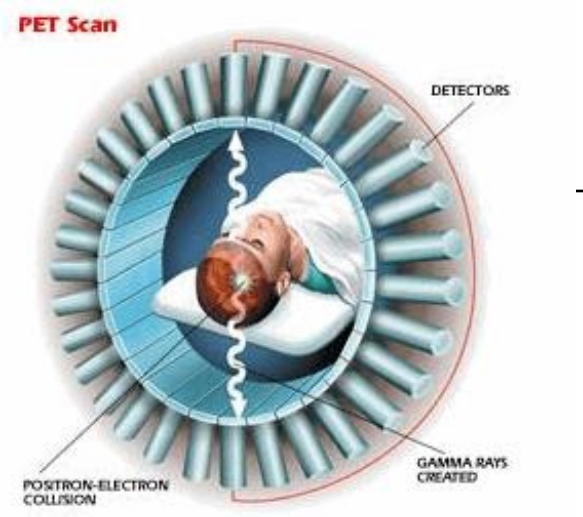
PET Overview

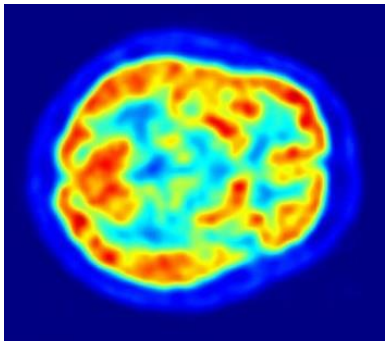
Signal Detection in PET

•After the tracer is injected, the isotope emits a positron, which finds a nearby electron and annihilates, producing two gamma rays in opposite directions.

•PET Scanner detects photon rays, determines location of annihilation, reconstruction of entire image







fMRI overview

- Structural image (MRI):
  - High spatial resolution
  - No temporal information

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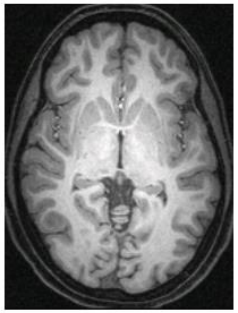
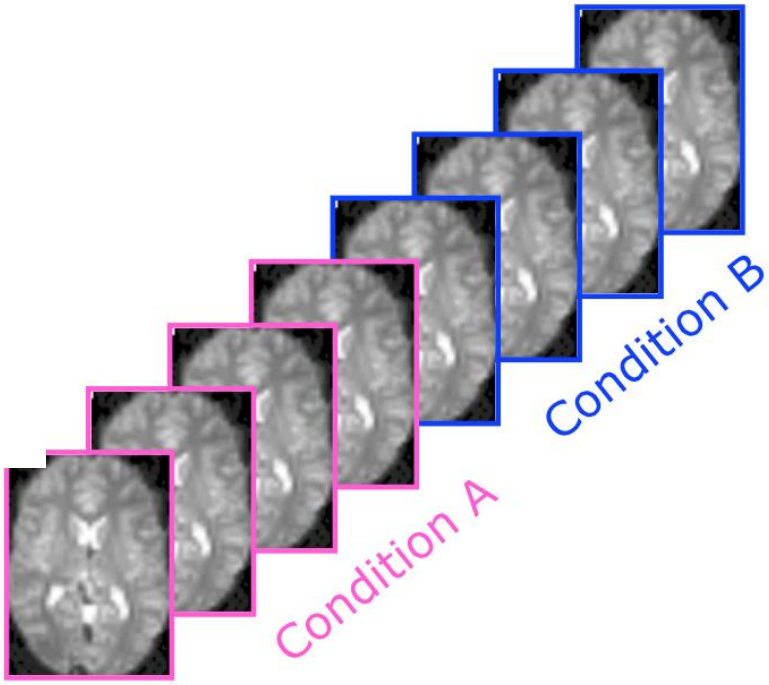
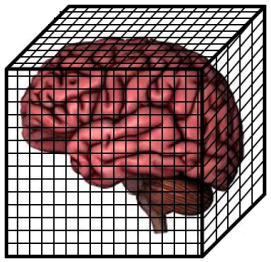


- Functional image (fMRI):
  - Lower spatial resolution
  - Higher temporal resolution
  - Can relate changes in signal to experimental task



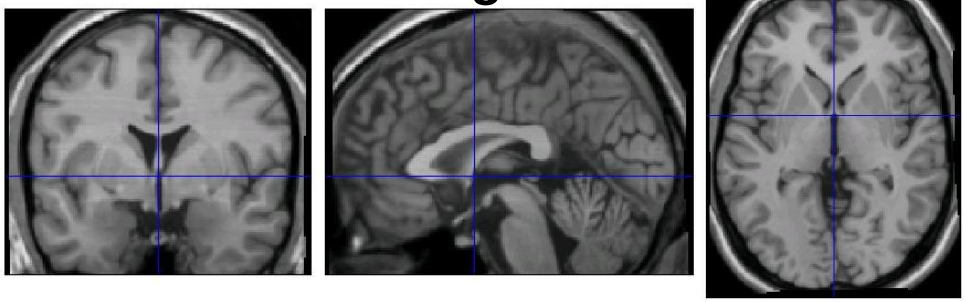
Brain Imaging Basics

- A brain image is represented by a 3D matrix of numbers that correspond to spatial locations
- Each location in the matrix is called a **voxel** (volumetric pixel)



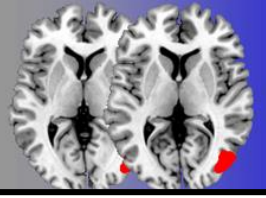
- Can be displayed in slices, in 3 orientations:

Coronal **Sagittal** **Axial**



(MRI)

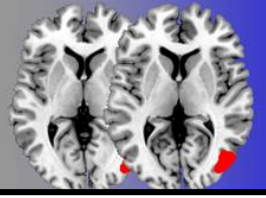
fMRI Overview



- Functional magnetic resonance imaging (fMRI) is a prominent non-invasive technique for studying brain activity.

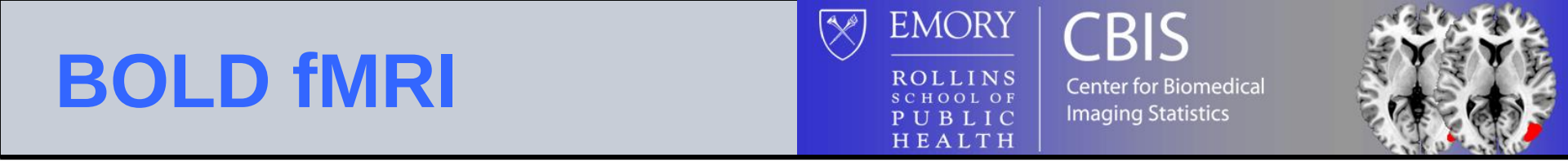
- It provides an attractive balance of spatial and temporal resolution compared to alternative methods.

BOLD fMRI

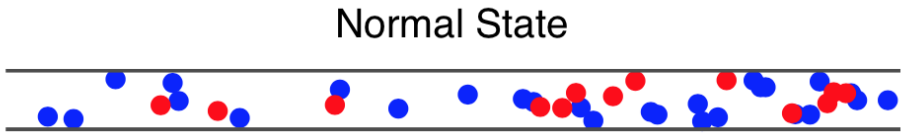


- fMRI measures the *blood oxygenation level dependent* **(BOLD) signal** as a correlate of neural activity
- Basis:
  - Neural activity causes localized increases in oxygen consumption
  - The body responds with an influx of oxygen-rich cerebral blood flow to fuel the increased metabolic activity
  - The increased oxygen supply actually outpaces the metabolic demand, resulting in an excess of oxygenated hemoglobin (oxyhemoglobin) in active brain tissue.
  - Therefore, there is relatively more oxyhemoglobin (OxyHb) than deoxyhemoglobin (deOxyHb) in these active areas

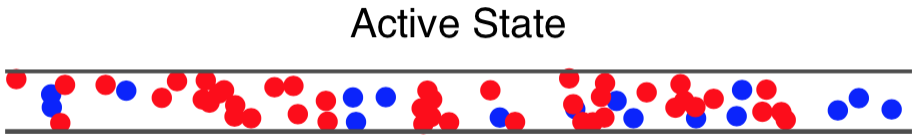
BOLD fMRI



- Normal State
  - Normal blood flow
  - deOxyHb is paramagnetic (small, positive susceptibility to magnetic fields)
  - Faster MRI signal decay, i.e. decreased MRI signal

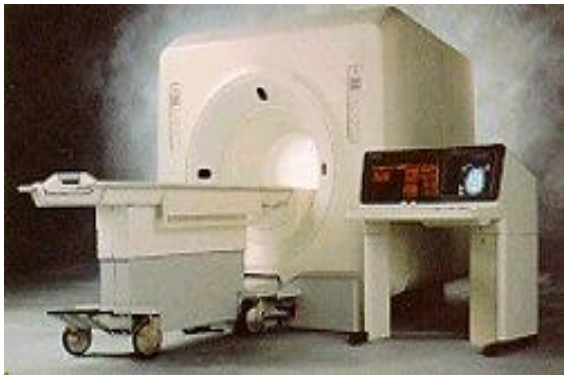


- Active State
  - Increased blood flow
  - Increased oxygenation
  - OxyHb is diamagnetic (very weak, negative susceptibility to magnetic fields)
  - Slower MRI signal decay, i.e. increased MRI signal



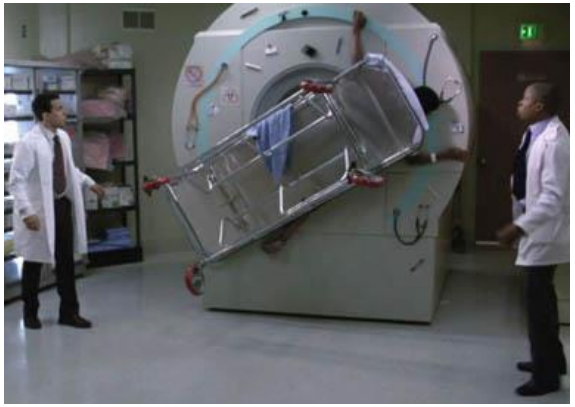
MRI scanner

An MRI scanner consists of an electromagnet with a very strong magnetic field (1.5 - 7.0 Tesla)



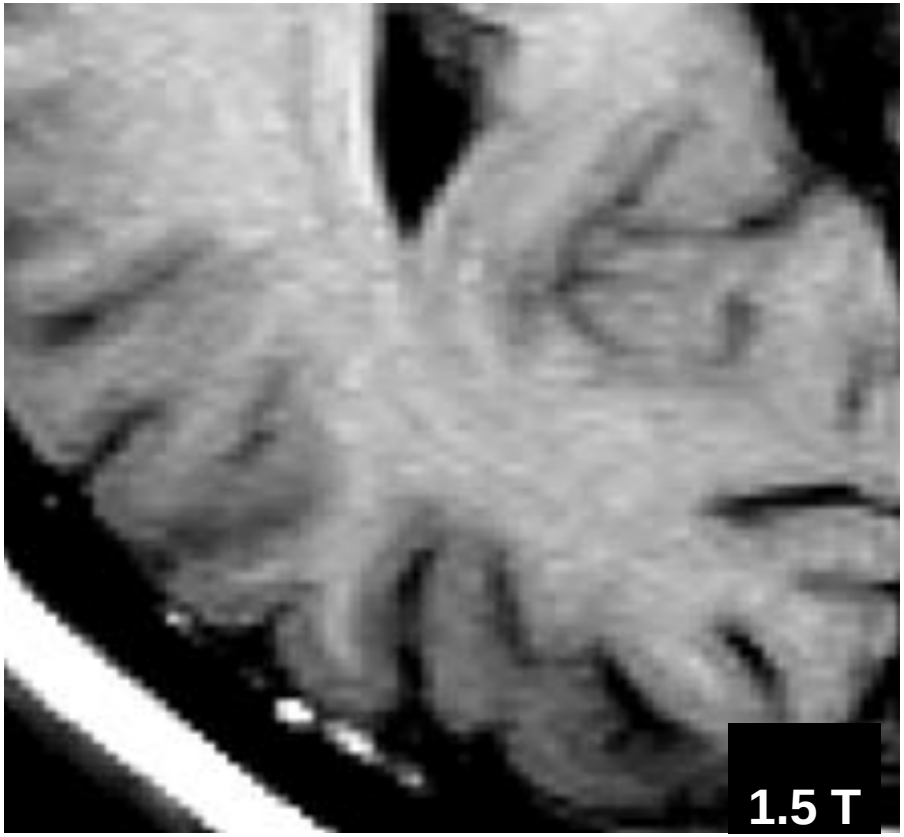
Earth's magnetic field = 0.00005 T

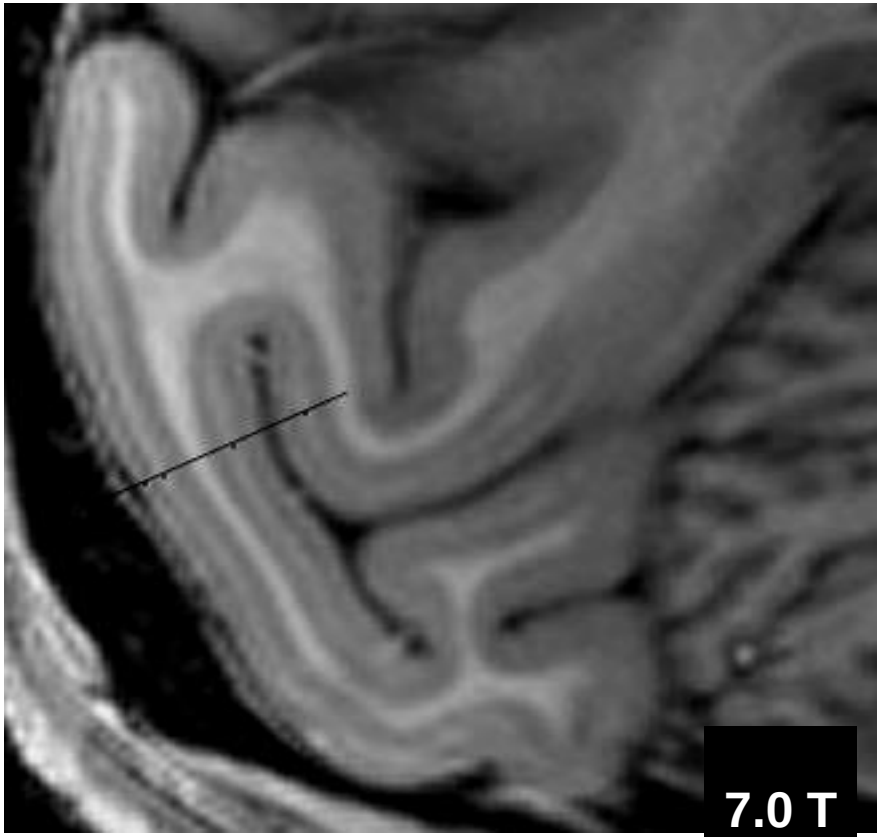
Be careful with metal objects……



Field Strength

Human V1 at 1.5 T vs. Monkey V1 at 7.0 T

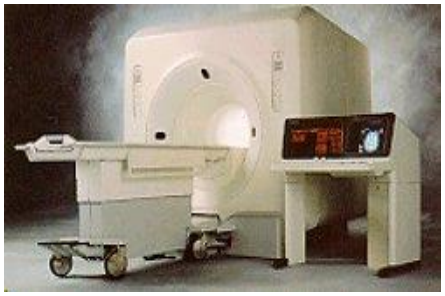


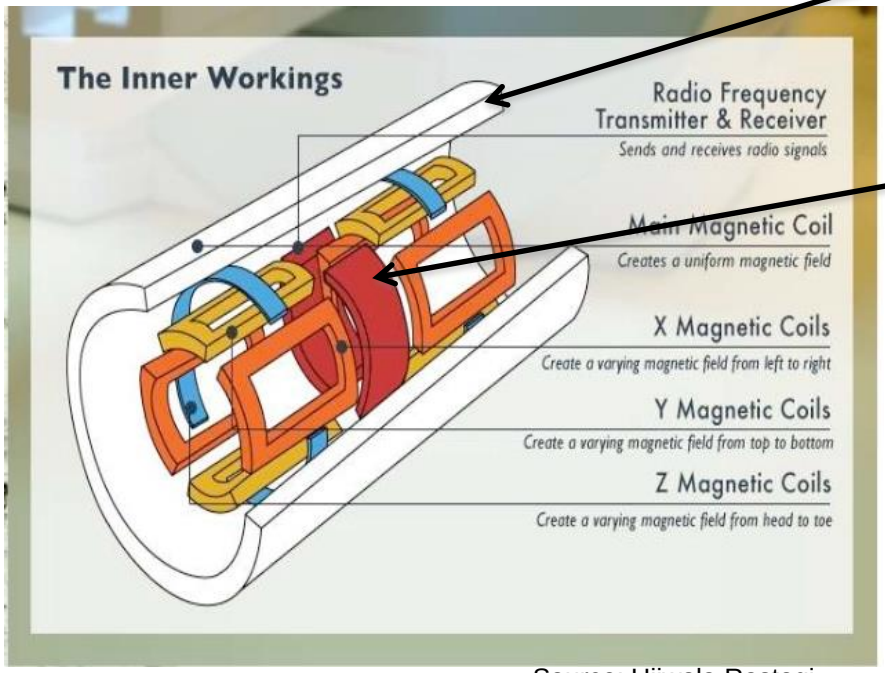


2D T_1 images 780um x 780um x 5,000um

3D T_1 images 250um x 250um x 750um

MRI scanner





Source: Ujjwala Rastogi

An MRI scanner generates three different magnetic fields:

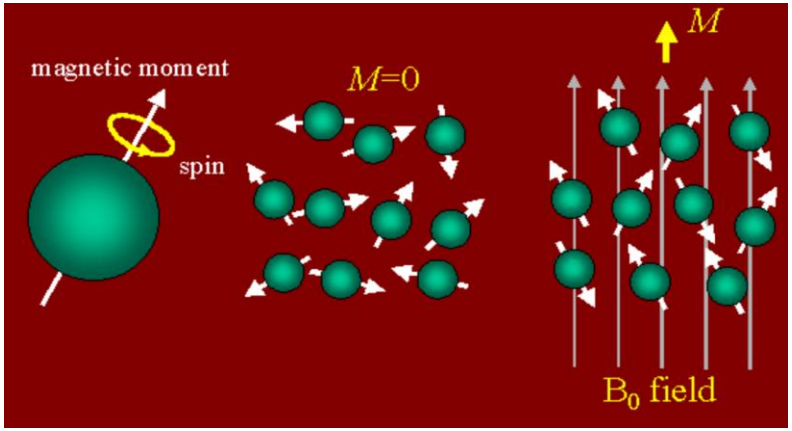
1. A strong static field B_0 (1.5 - 7.0 Tesla), often 3T, aligns the spins

2. An RF pulse, brief duration, used to excitation and refocusing

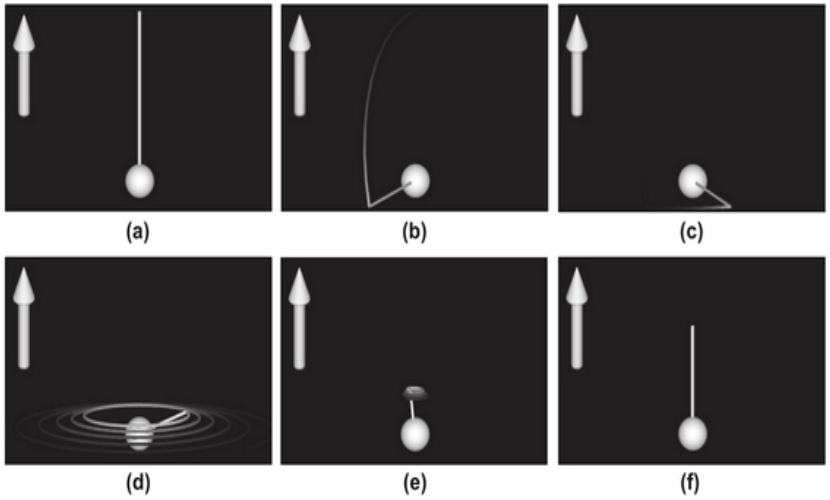
3. Gradients: create linear changes in the main field in 3 orthogonal directions x-, y- and z- planes

Physiology of MRI

- The subject is placed in the MRI scanner with a strong magnetic field (B0)
- The nuclei of ^{1}H atoms align with B0
- A short radio frequency (RF) pulse is applied that knocks the ^{1}H nuclei out of alignment.
- After the pulse, the ^{1}H nuclei fall back into their original alignment (equilibrium), and as they do, release a signal that is picked up by the receiver coil in the scanner.
- A short video to illustrate https://youtu.be/0YBUSOrH0lw



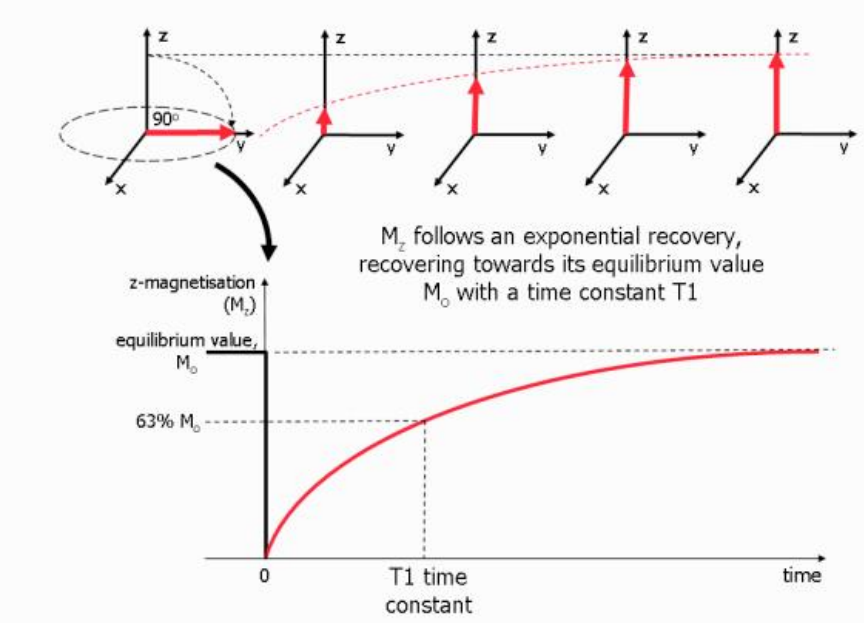
FMRIB, Oxford Univ.



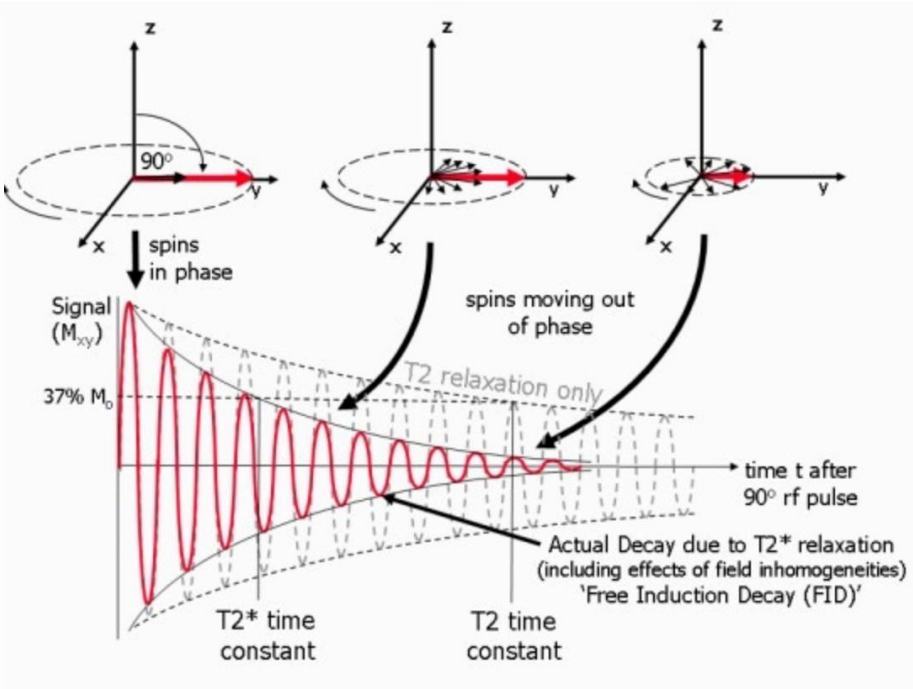
Berg and Behrens, 2014

Physiology of MRI

T1 relaxation time



T2 relaxation time



T1 relaxation is the process by which the *longitudinal magnetization is recovered*

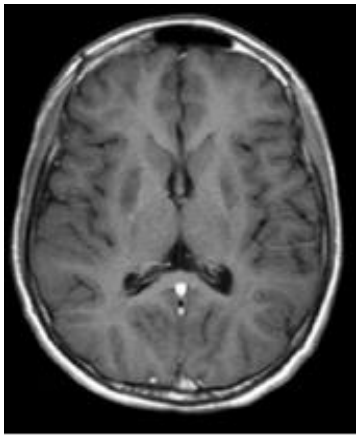
T2 relaxation is the process by which the *transverse magnetization decays* due to dephasing of proton spins

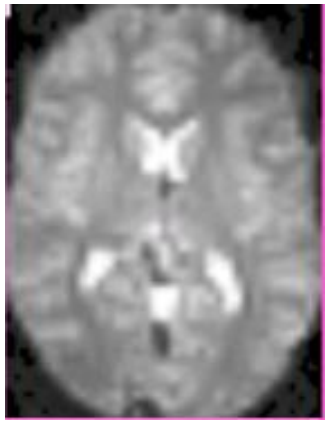
Figure: www.jcmr-online.com

Physiology of MRI

- **Relaxation**: time to reach equilibrium after RF pulse
- Measured in 2 directions:
- Longitudinal (**T1**) – parallel to B0
  - Best for **anatomical MRI** – high spatial resolution, provides good contrast between tissue types. Fatty tissue (WM) is bright; CSF is dark.
- Transverse (**T2**) – perpendicular to B0
  - Best for **functional MRI** since T2 is much faster than T1. low spatial resolution, CSF appears bright and fatty tissue is dark.

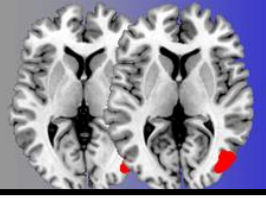
T1





T2

Physiology of MRI



- The subject is placed in the MRI scanner which forms a strong magnetic field (B0)
- The nuclei of ^{1}H atoms align with B0
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- A short video to illustrate...https://youtu.be/0YBUSOrH0lw

Physiology of MRI

- **Relaxation**: time to reach equilibrium after RF pulse
- Measured in 2 directions:
- Longitudinal (**T1**) – parallel to B0
  - Best for **anatomical MRI** – provides good contrast between tissue types. Fatty tissue (WM) is bright; CSF if dark.
- Transverse (**T2**) – perpendicular to B0
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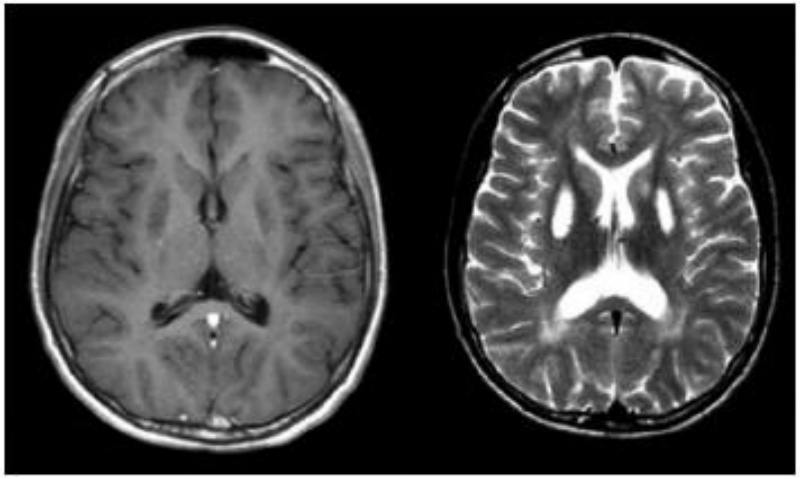
T1



T2

Physiology of MRI

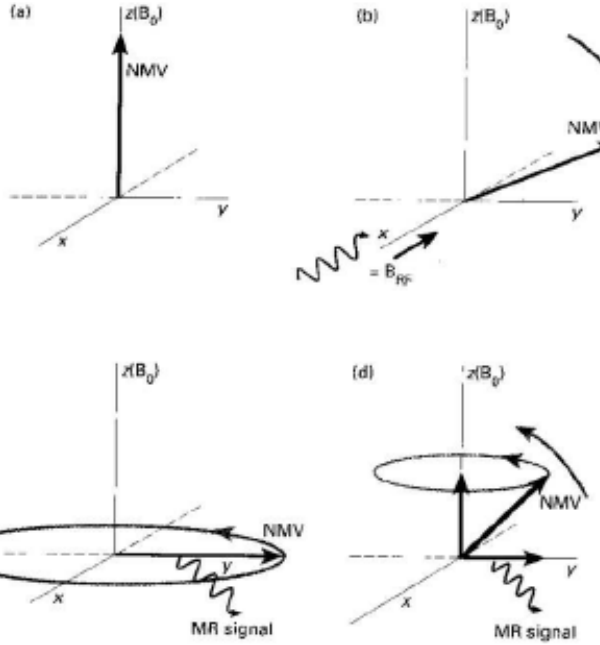
The basis of MRI is the mechanism by which RF radiation induces H+ atoms to precess in phase and the manner in which they return to equilibrium.

(a) Net magnetization vector (NMV) at equilibrium.

(b) RF input applied at right angles to external magnetic field. Exerts an additional magnetic force on the NMV, forcing it to move towards y.

(c) When RF turned off, the NMV has tilted by 90°. No longitudinal magnetization and maximum magnetization in transverse plane. Precession starts around longitudinal axis, producing the MR signal.

(d) The signal starts to fade as the NMV returns to equilibrium.



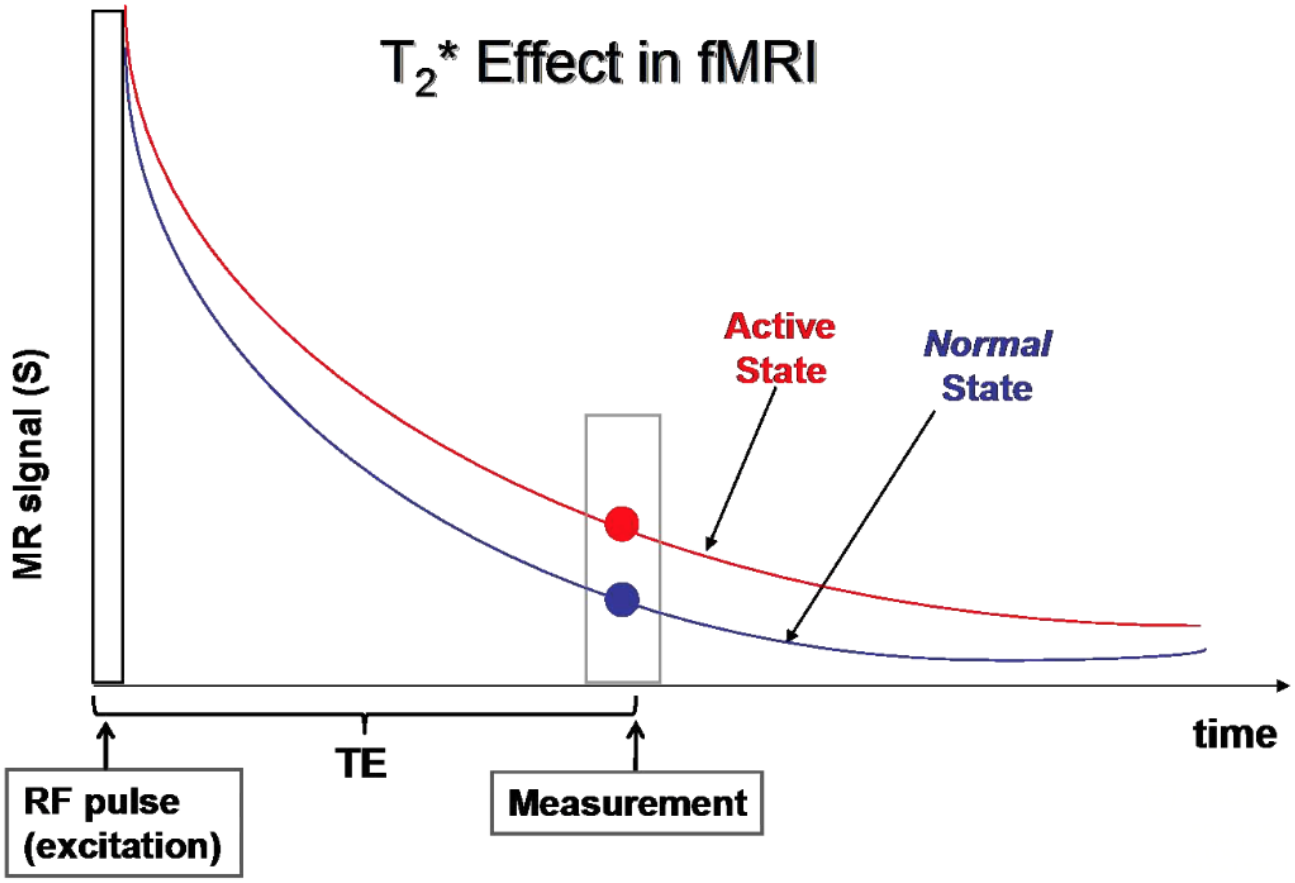
T1 relaxation defines the rate at which longitudinal Magnetization reappears

T2 relaxation defines the rate at which transverse Magnetization disappears

The decaying MRI signal is called free induction decay (FID).

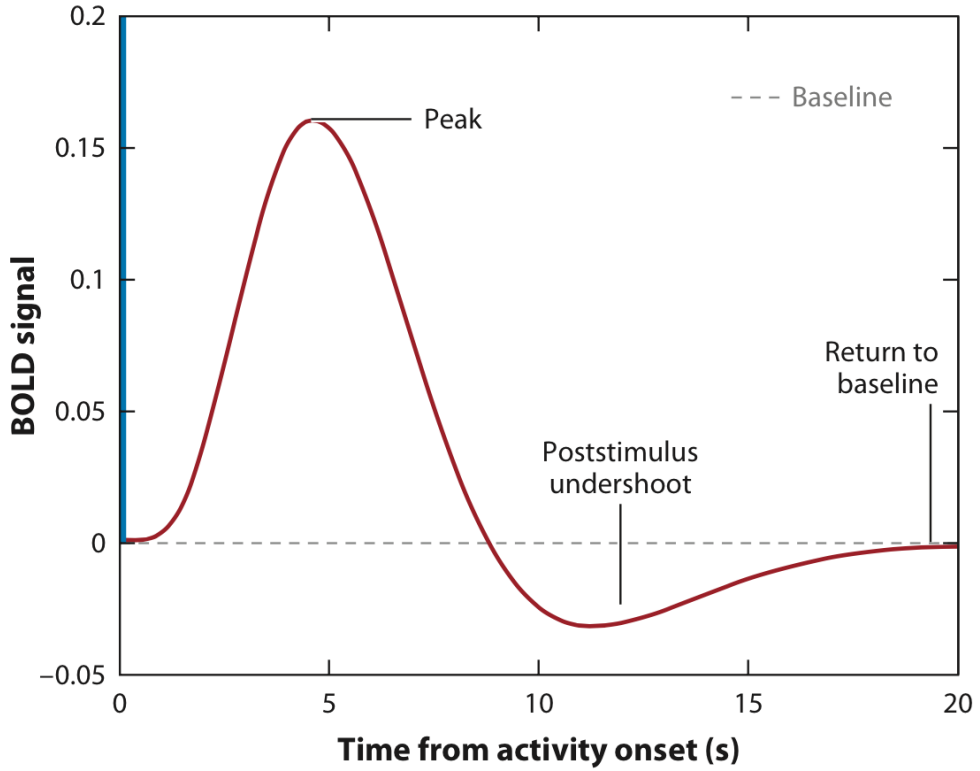
Physiology of fMRI

Deoxyhemoglobin suppresses the MRI signal. As the concentration of deoxyHb decreases (i.e. in active areas), the signal increases



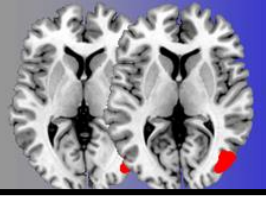
fMRI: HRF

The change in the MRI signal triggered by neural activity is known as the hemodynamic response function (HRF).



Bowman, 2014

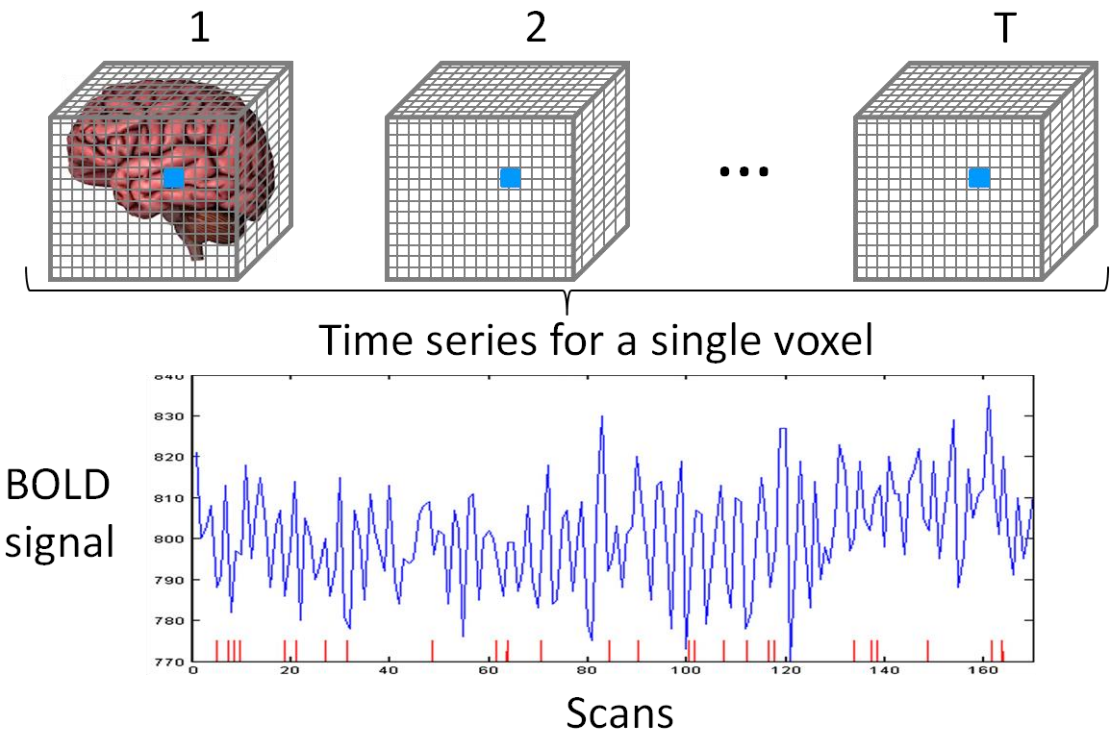
Properties of the HRF



- Magnitude of signal changes is quite small
  - 0.5 to 3% at 1.5 T
  - Hard to see in individual images

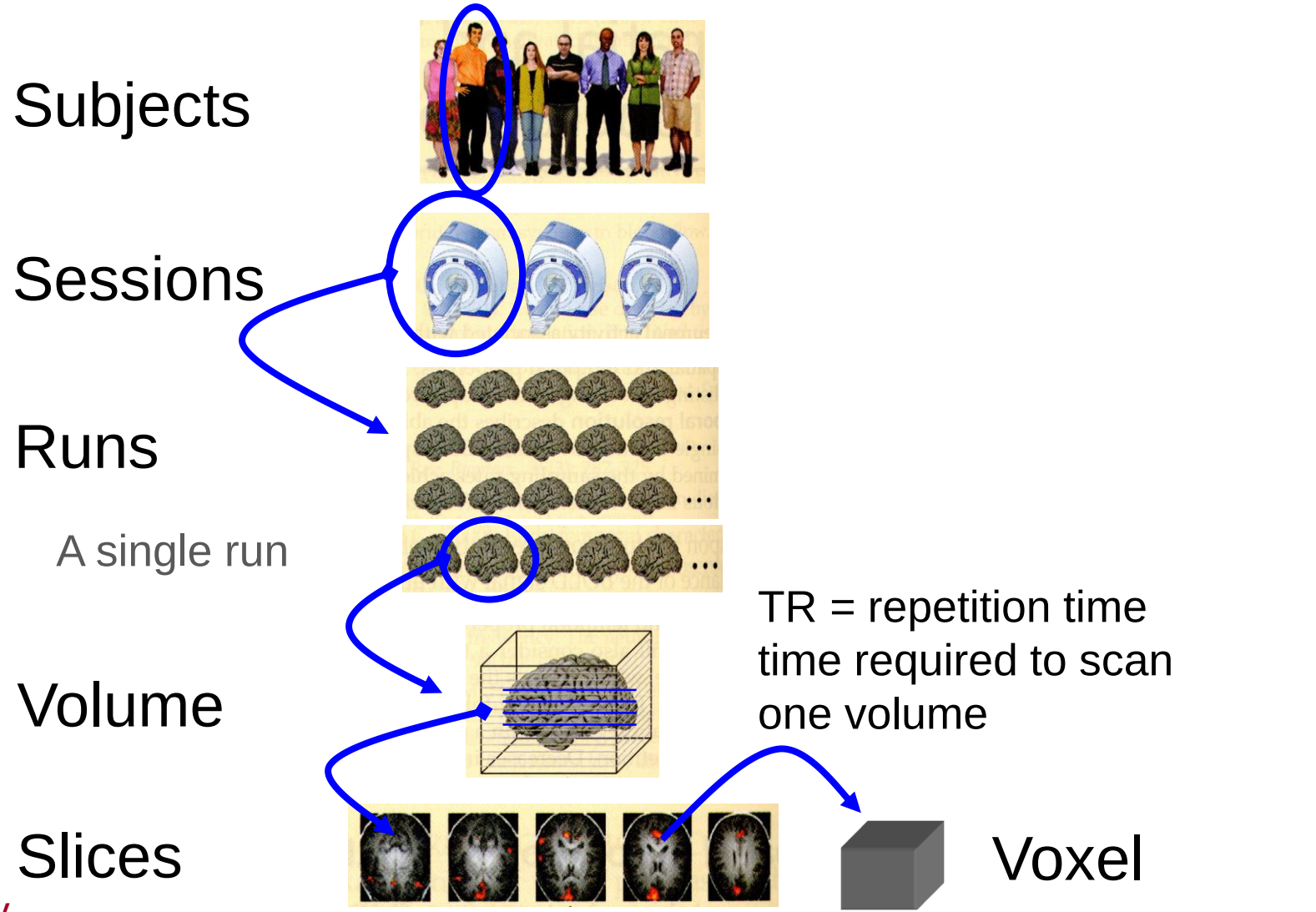
- Response is delayed and quite slow
  - Onset is ~2 sec after activity, and peaks 5-8 sec after the neural activity has peaked
  - Extracting temporal information is tricky, but possible
  - Even short events have a rather long response
  - Shape of HRF varies across brain regions and subjects

fMRI data structure



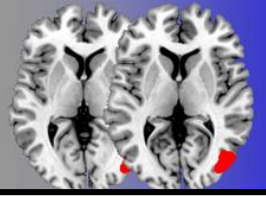
- 3D brain scans captured over time – each with ~100K voxels
- Usually, T=100-2K, with scans every 2 sec
- Each voxel has a BOLD signal time course

fMRI hierarchy



Ged Ridgeway

Challenges of fMRI data analysis

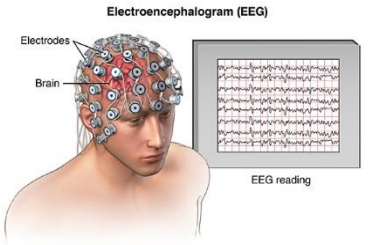


- The statistical analysis of fMRI data is challenging.
  - Data is massive and high dimensional.
  - The signal-to-noise ratio is low.
  - The data exhibits a complicated temporal and spatial noise structure.

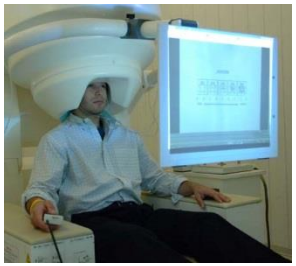
EEG and MEG

The electrical activity of neurons produces currents that spread throughout the brain.

- EEG measures voltage fluctuations sensed by an array of electrodes placed on the scalp.



- MEG measures the magnetic fields produced by the electrical currents using an array of sensitive magnetic field detectors.



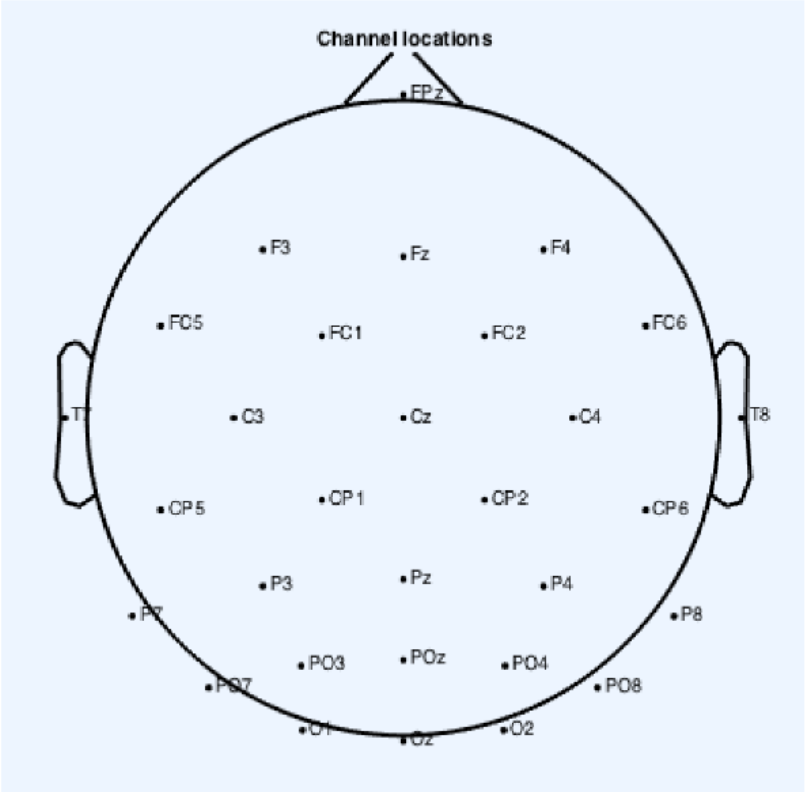
EEG and MEG data directly reflect current flows generated by neurons. These signals are measured with millisecond temporal resolution, and provide the most direct measurement of brain processing available noninvasively.

EEG Data

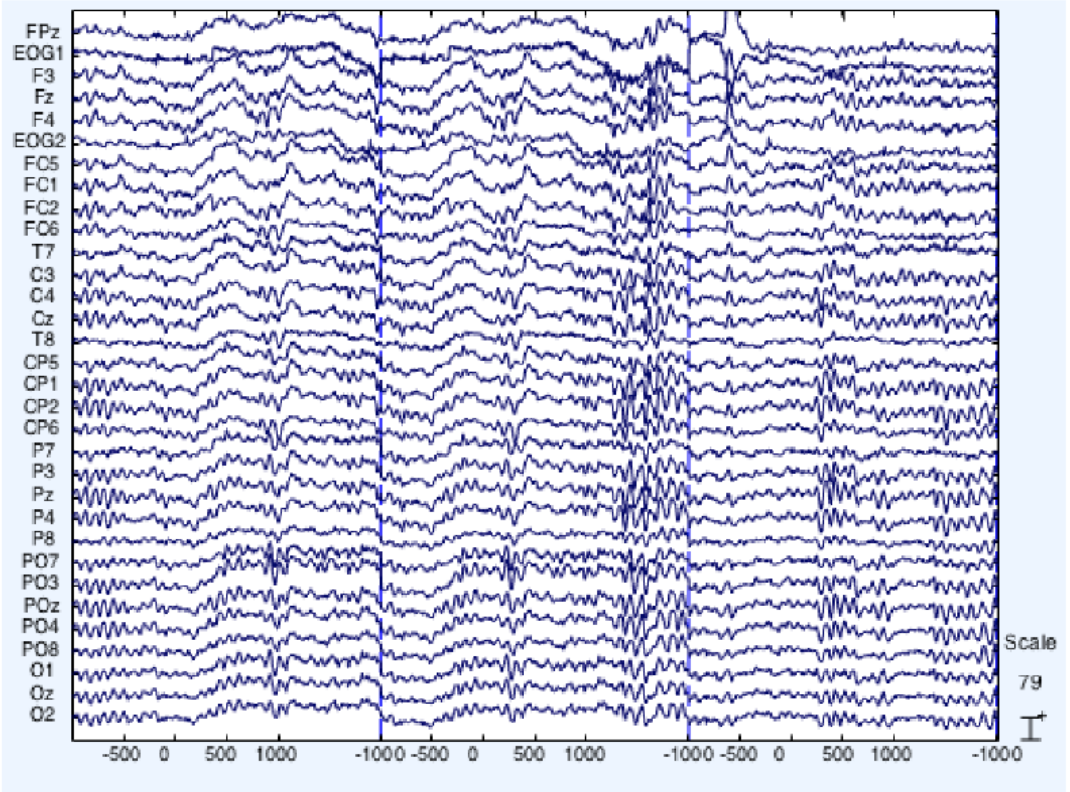
EMORY ROLLINS SCHOOL OF PUBLIC HEALTH

CBIS Center for Biomedical Imaging Statistics

EEG channel locations



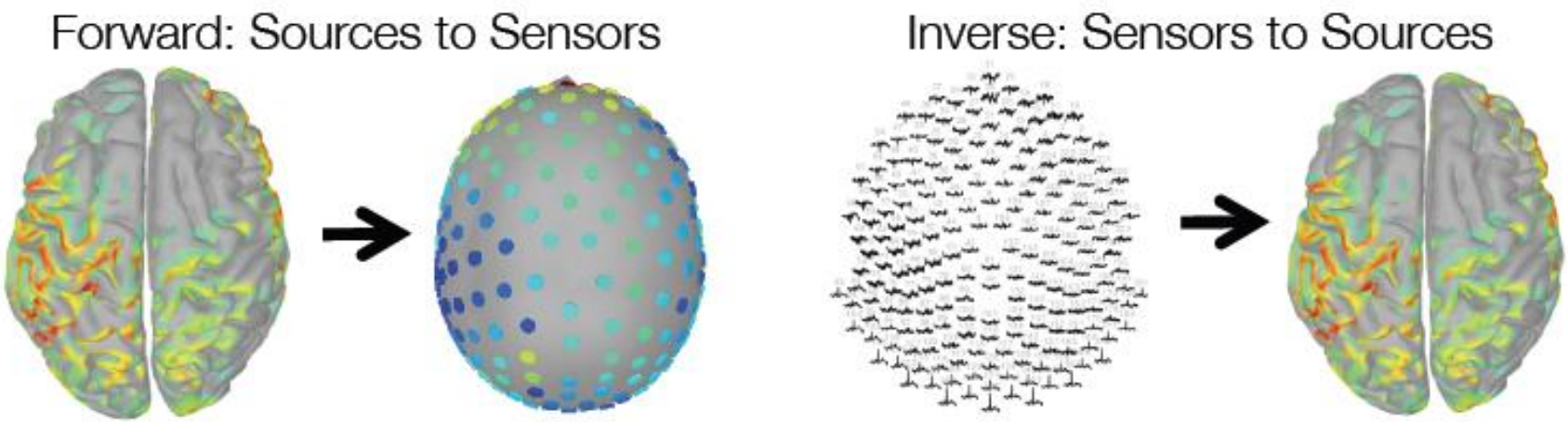
EEG signals at each location



EEGLab

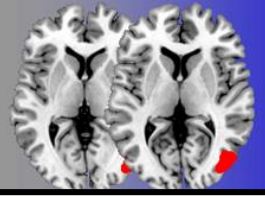
EEG/MEG

Constructing brain images from EEG/MEG signals requires the solution of an inverse source of localization problem.



Ombao

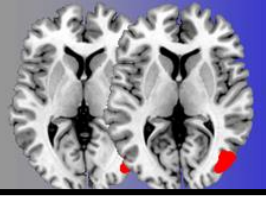
PET vs fMRI



- Activation in both PET and fMRI reflect changes in neural activity measured indirectly, and they measure different biological processes related to brain activity, which may be broadly defined as the energy-consumption of neurons.

- The spatial resolution of PET is on the order of 1-1.5 cm^3 and fMRI is typically on the order of 27-36 mm^3 for human studies.

PET vs fMRI



- Because PET computes the amount of radioactivity emitted from a brain region, enough time must pass before a sufficient sample of radioactive counts can be collected.
  - Temporal resolution limited to blocks of at least 30 sec
- fMRI has its own temporal limitations due largely to the latency and duration of the hemodynamic response to neural events.
  - HRF doesn't reach its peak until several seconds after local neuronal and metabolic activity has occurred.

PET vs fMRI

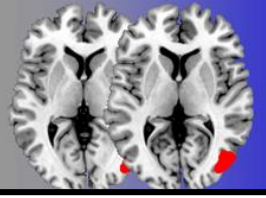


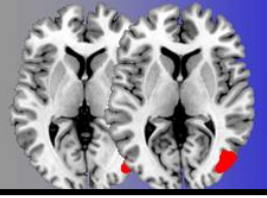
Table 2. Relative advantages of fMRI and PET

Advantages of fMRI	
Cost and availability	fMRI has lower cost, more facilities available
Spatial resolution	fMRI has higher resolution, but new PET scanners can have same functional resolution for group studies
Temporal resolution	fMRI is superior, permitting event-related designs
Brain connectivity analyses	fMRI permits time series connectivity analysis; PET and fMRI both permit individual differences analysis
Combination with other measures	Simultaneous time-series acquisition of fMRI and EEG provides most detailed mapping of relationships
Single-subject studies	fMRI permits detailed high-resolution studies of individuals
Repeatability	fMRI does not use radioactive substances, so frequent scans are considered safe

Advantages of PET	
Measuring neurochemistry	PET is superior; can be used to directly investigate neurochemistry
Transparency of activation measures	PET provides more direct measures of blood flow or metabolism
Artifacts	PET does not suffer from magnetic susceptibility artifacts and gradient- or RF-related artifacts
Combination with other measures	PET is not magnetic and can be combined with simultaneous EEG, MEG, and TMS
Studying baseline activity	PET provides quantitative measure of baseline state; ASL fMRI also can, but is less commonly available
Naturalness of environment	PET is quieter and has more open physical environment; advantage for auditory and emotion tasks

Wager et al, 2010

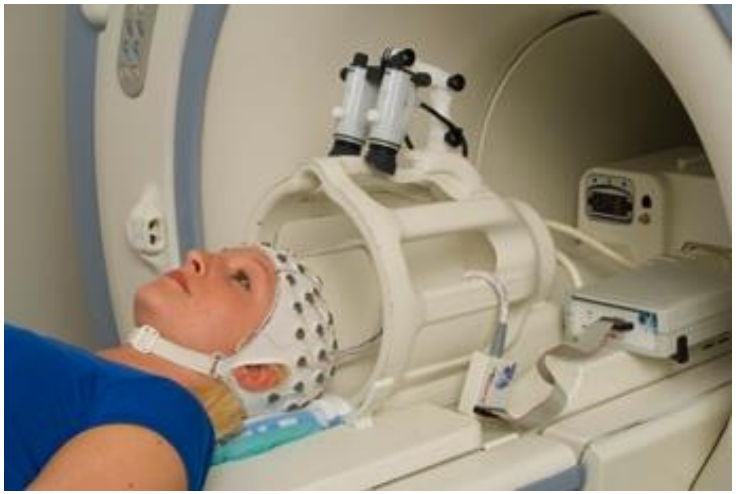
Comparing Modalities



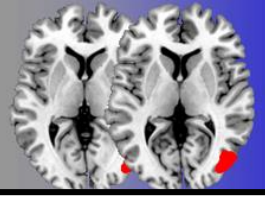
- Each functional neuroimaging modality provides a unique window into the brain
- PET and fMRI are the most widely used, and provide the most anatomically specific information across the entire brain.
- PET and fMRI has relatively better spatial resolution. However, the temporal resolution is not as good as EEG/MEG.
- EEG/MEG has better temporal resolution. However, the spatial resolution of EEG/MEG is poor (EEG around 6 cm^3). In addition, they only measures activity on the surface of the cortex, and not from deeper structures.
- EEG/MEG are less expensive and more convenient compared to fMRI and PET.

Combining modalities

- Recently, there is a trend towards using multiple imaging modalities to overcome some of the limitations of each method used in isolation.
  - EEG and fMRI: achieve best spatial and temporal resolution
  - fMRI and PET: requires a hybrid scanner
  - fMRI and DTI: study structure-function relationship
  - fMRI and Genetics (i.e. Imaging Genetics)

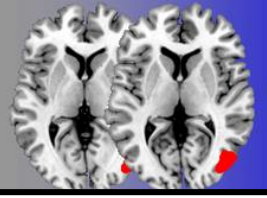


http://fmri.uib.no/



Structural Imaging

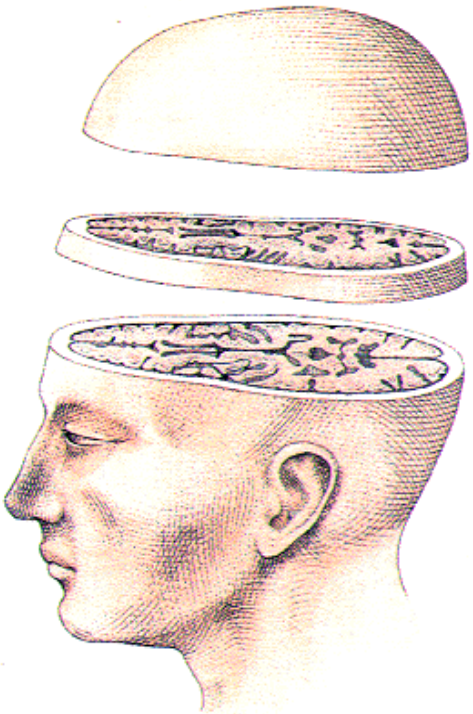
Structural Brain Imaging



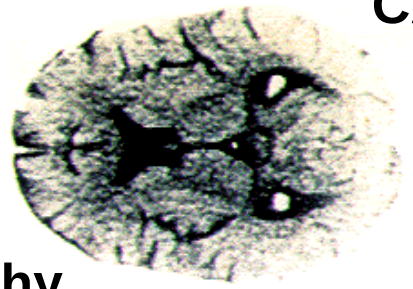
- **Structural brain imaging** deals with the study of brain structure and the diagnosis of disease (e.g. tumors) and injury.
- Modalities include:
  - computed axial tomography (CAT),
  - positron emission tomography (PET)
  - magnetic resonance imaging (MRI):

Diffusion-weighted MRI(**DWI**): is an MRI modality that maps **white matter fiber tracts** in the brain by measuring the diffusion of water molecules.

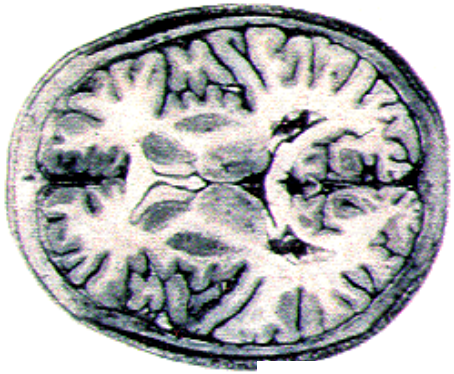
Structural Brain Imaging



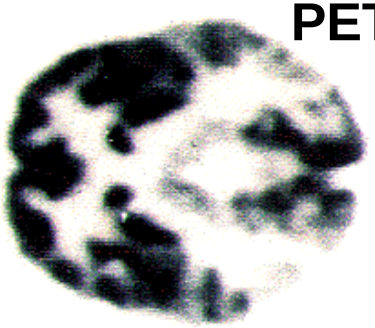
CAT



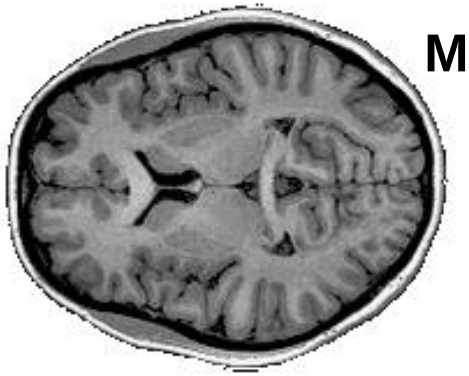
Photography



PET

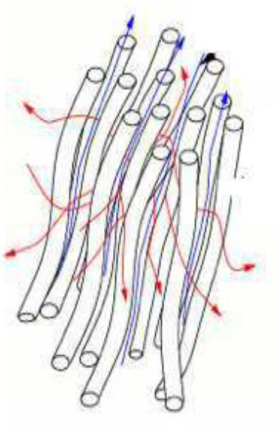


MRI



Structural Brain Imaging:
Diffusion Tensor Imaging (DTI)

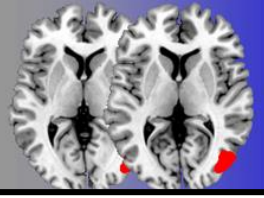
- An MRI technique that maps **white matter fiber tracts** in the brain by measuring the diffusion of water molecules.
- Water diffuses more quickly along axons than across them (water and fat don't mix!)



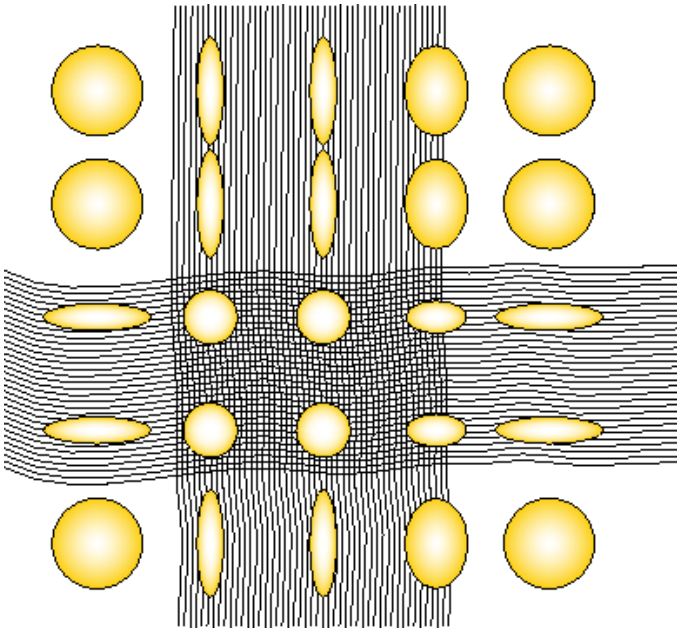
H_2O Brownian motion along the fibers [Poupon (1999)]

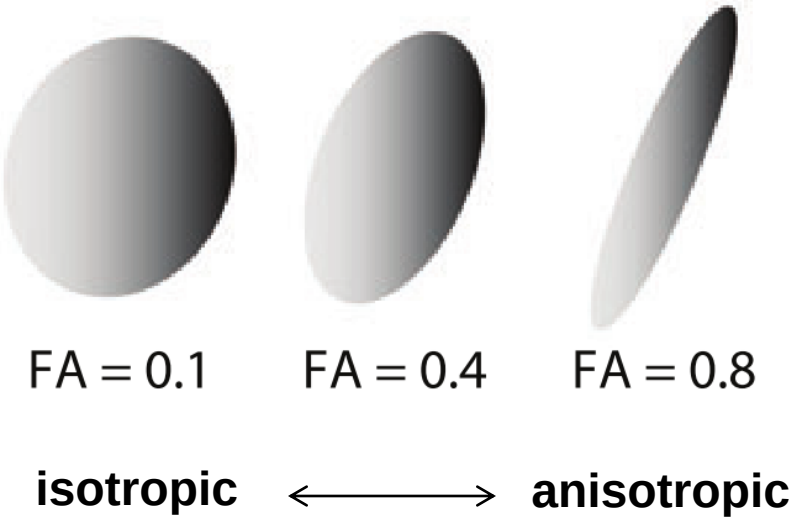
Eigen decomposition of the DT

Ellipsoidal visualization of the DT



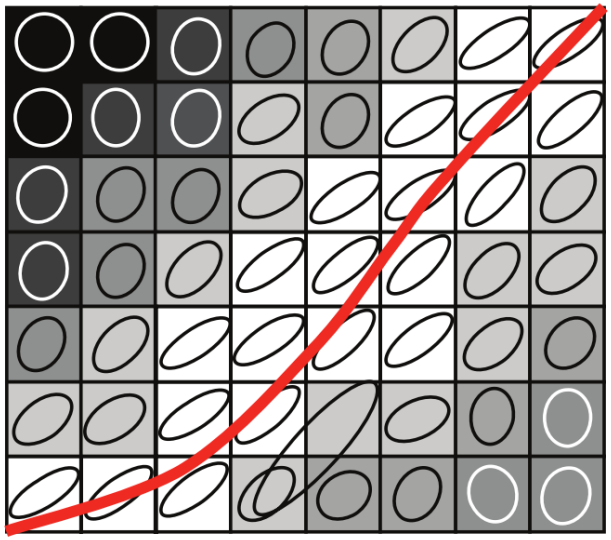
- Magnetic gradients are applied in different directions to calculate the **diffusion tensor** at each voxel location.
- **Fractional Anisotropy (FA)** – ranges from 0-1 and describes degree of diffusion restriction





DTI: Tractography

- We can trace streams through the tensor field to reconstruct the structural connections in the brain!



Water Diffusion

Brownian motion

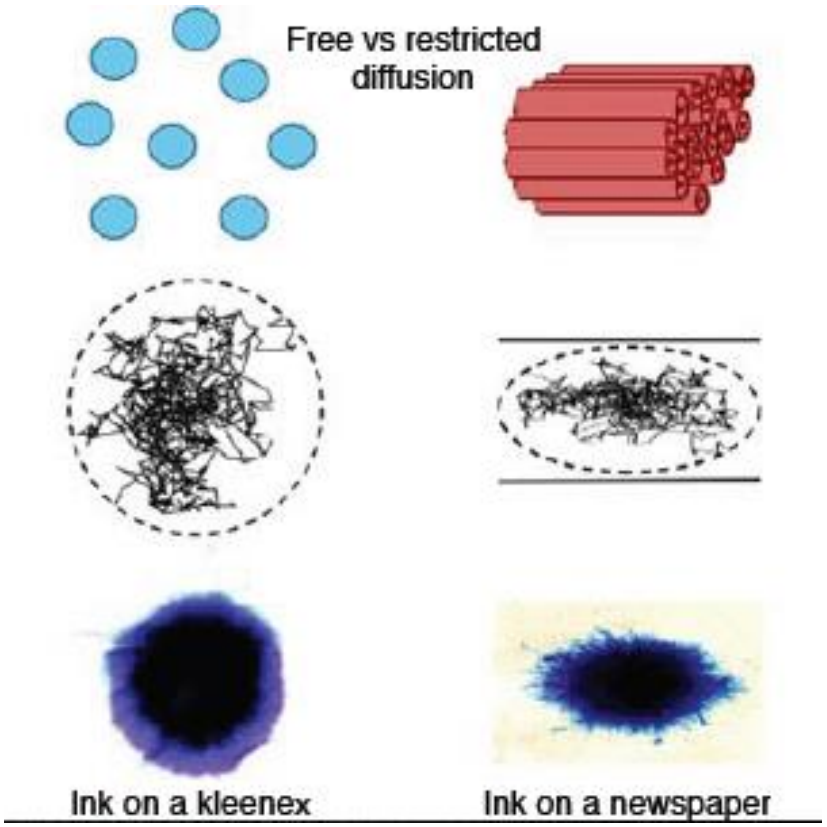
The displacement of self-diffusion of water molecules (Einstein,1956)

$$d = \sqrt{6Dt}$$

where d*: diffusion distance* D*:* diffusivity t: diffusion time

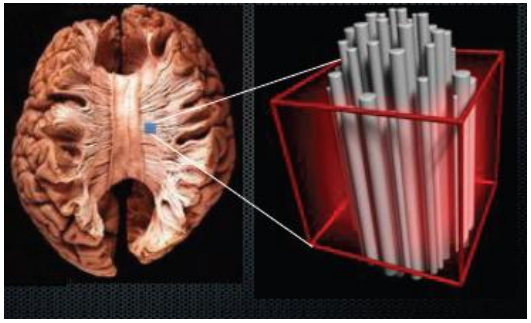
Assumptions:
(1) no structural restriction
(2) homogeneity in the diffusion environment

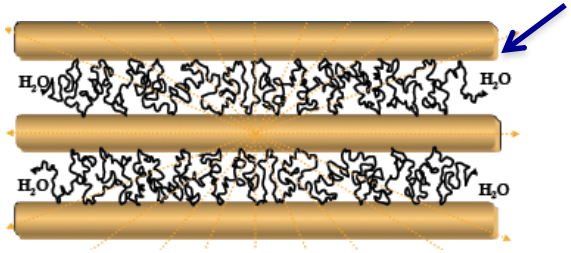
Diffusion

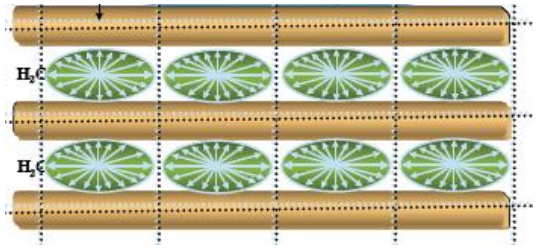


Descoteaux, 2015

Water diffusion in brain white matter is restricted





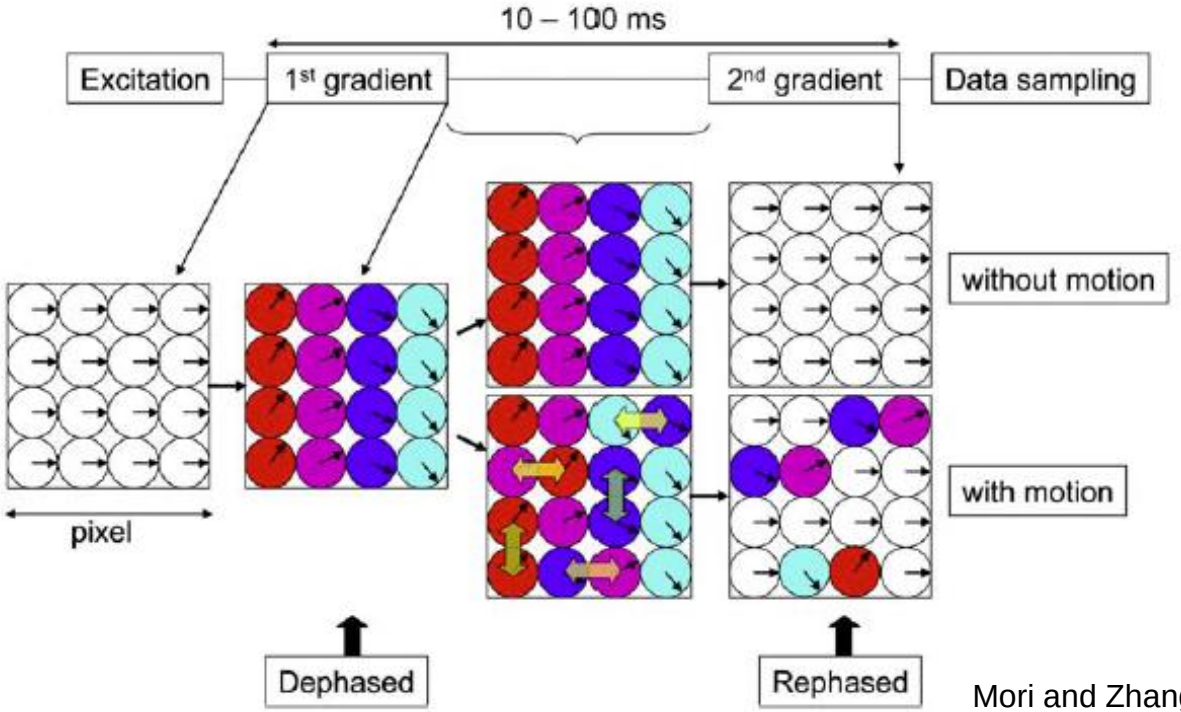


Diffusion tensor

Mark, Ulmer. AJNR 2002

- Water tends to diffuse faster along the fibers (Anisotropic diffusion)
- May infer white fiber directions based on water diffusion patterns

Physiology of diffusion-weighted MRI (DWI)

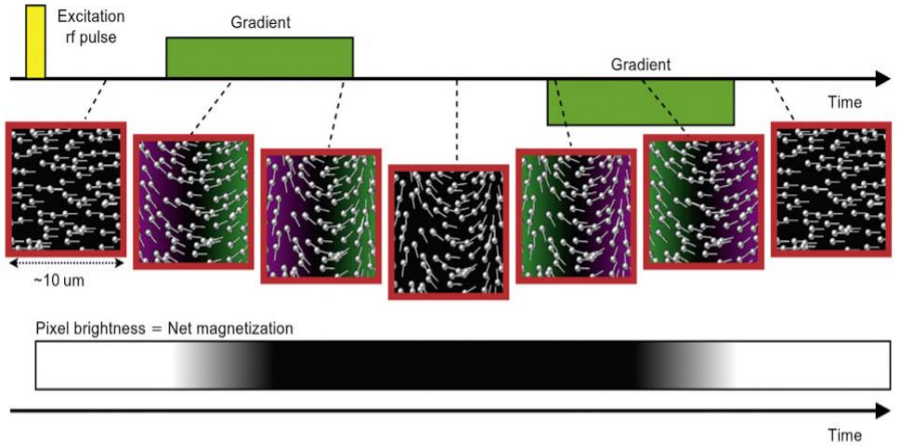


Mori and Zhang, 2006, Neuron 51

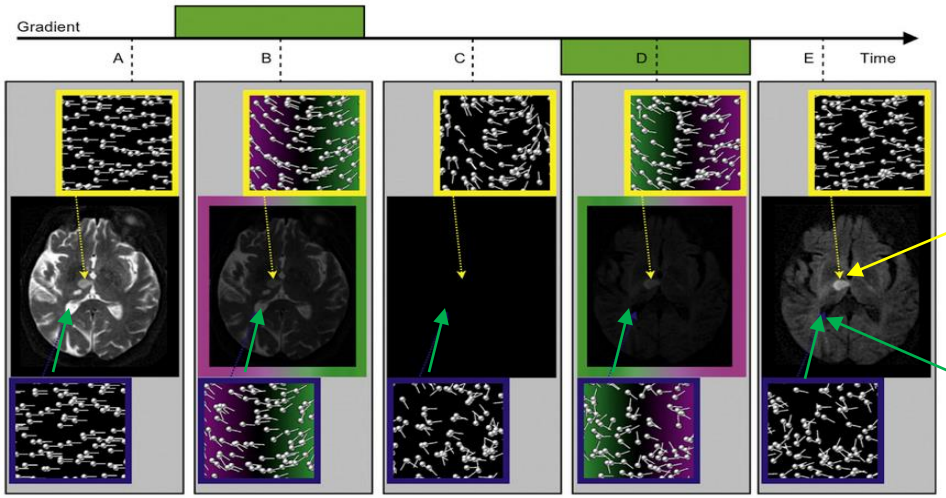
MRI can detect imperfect rephasing through signal loss

Physiology of diffusion-weighted MRI (DWI)

- Illustration of diffusion-weighted imaging signals without motion



- Illustration of diffusion MRI signals with diffusive motion

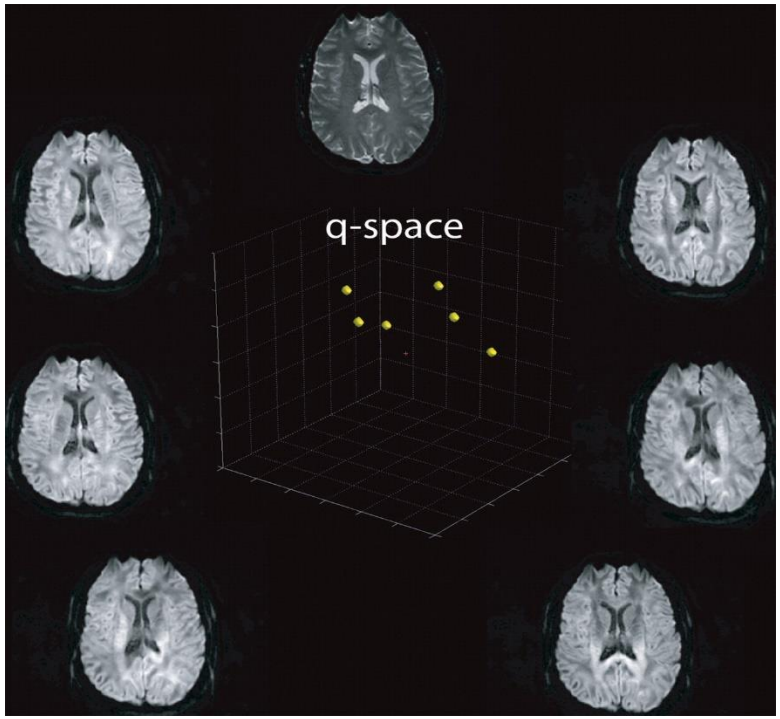


Area of stroke: low diffusion
Less signal attenuation

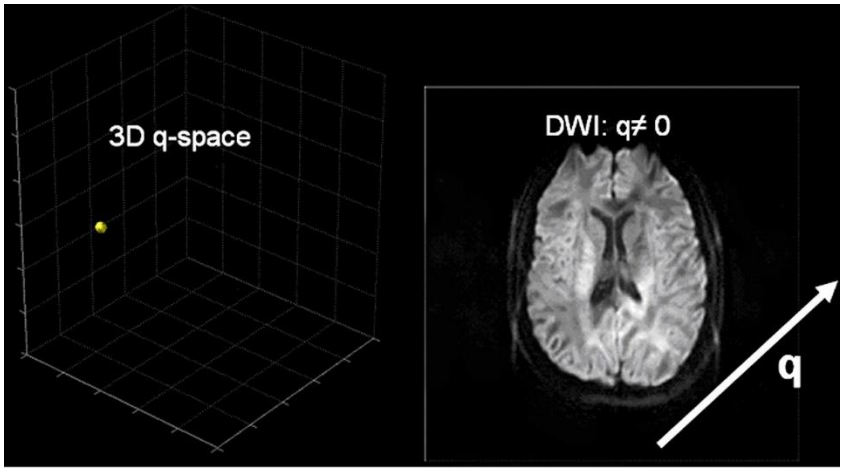
CSF: high diffusion
More signal attenuation

Johansen-Berg and Behrens, 2014

DTI data structure



Series of DWI obtained for DTI model, in which q-space is sampled in at least six different directions and in which a non–diffusion-weighted reference image is obtained.



DWI signal sampled at a single point in 3D q-space (i.e. a gradient $\vec{q}$). Brain areas where diffusion is intense in the direction of $\vec{q}$ appear darker due to larger signal attenuation.

Figures: Patric Hagmann et al., 2006