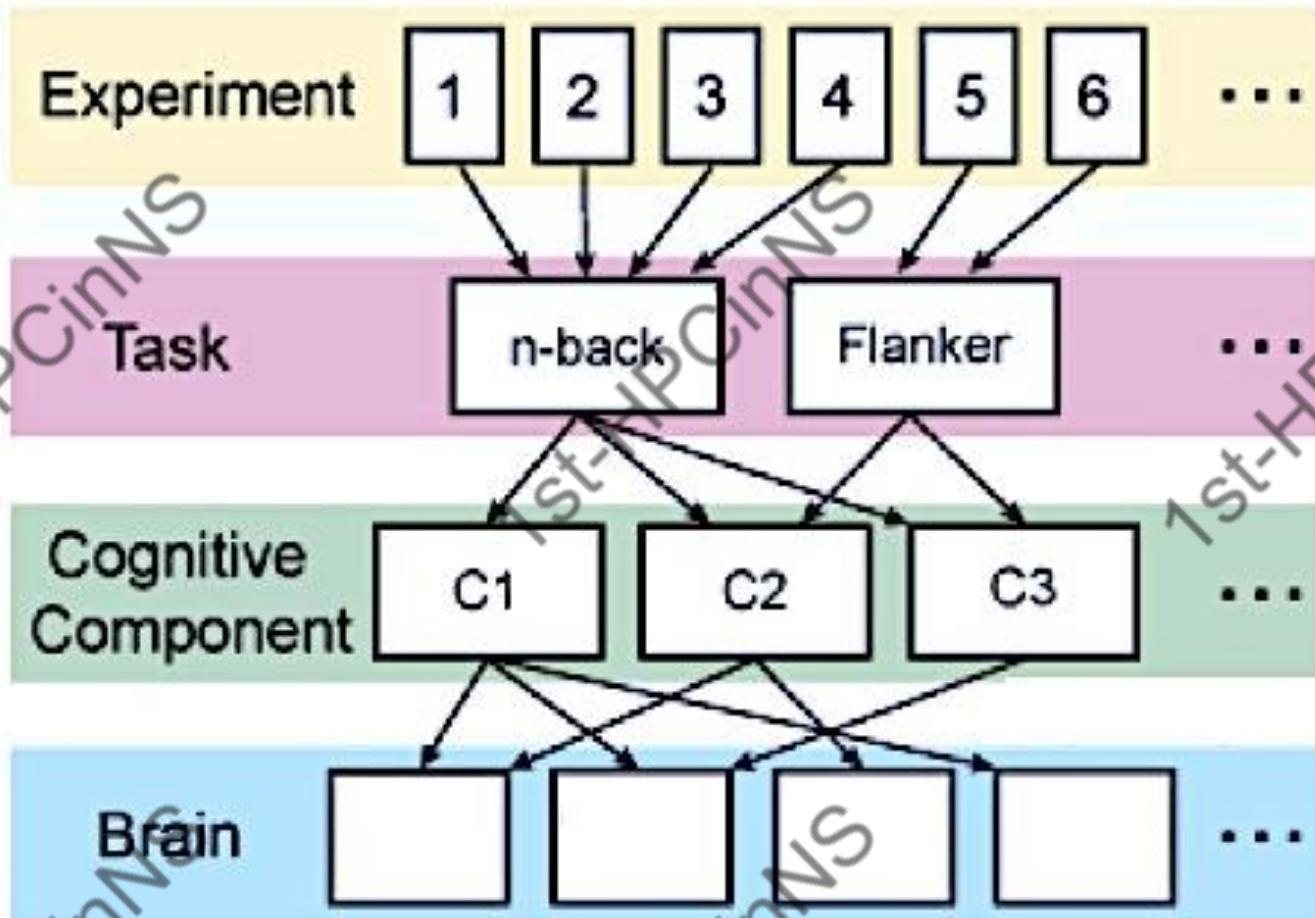


Computational approaches to fMRI data analysis

Reza Khosrowabadi

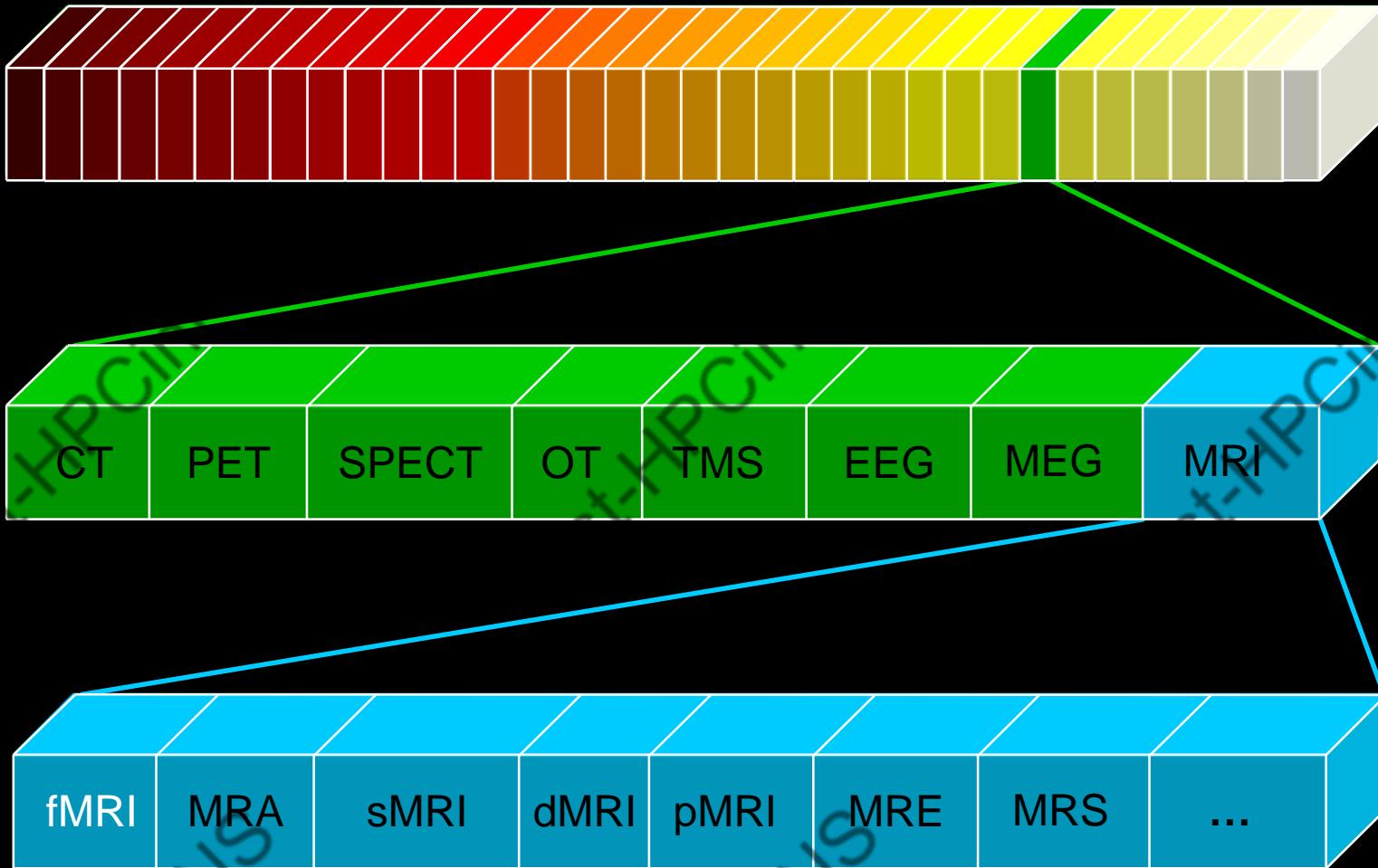
r.khosrowabadi@gmail.com

Behavior, Cognition, Neural activities

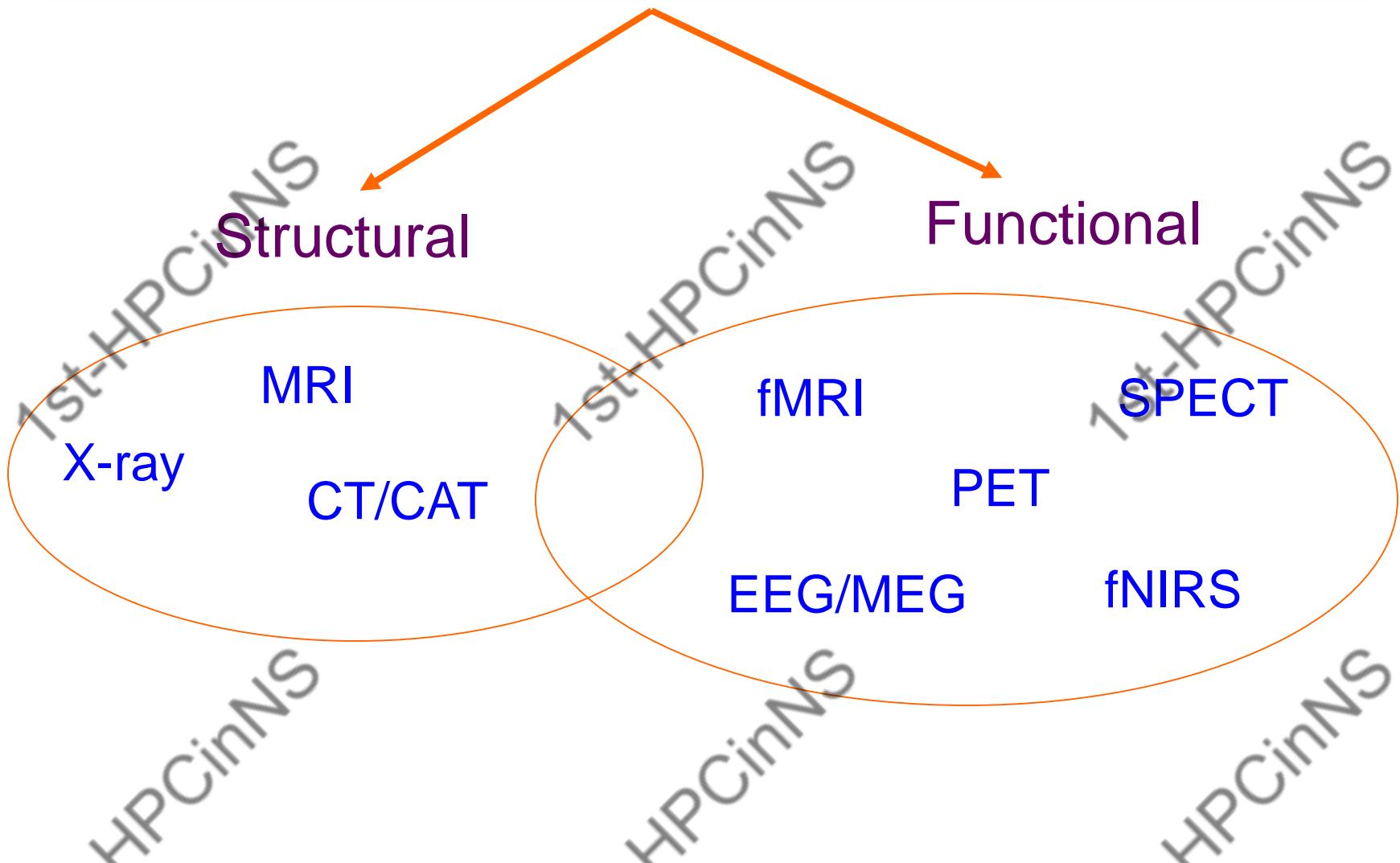


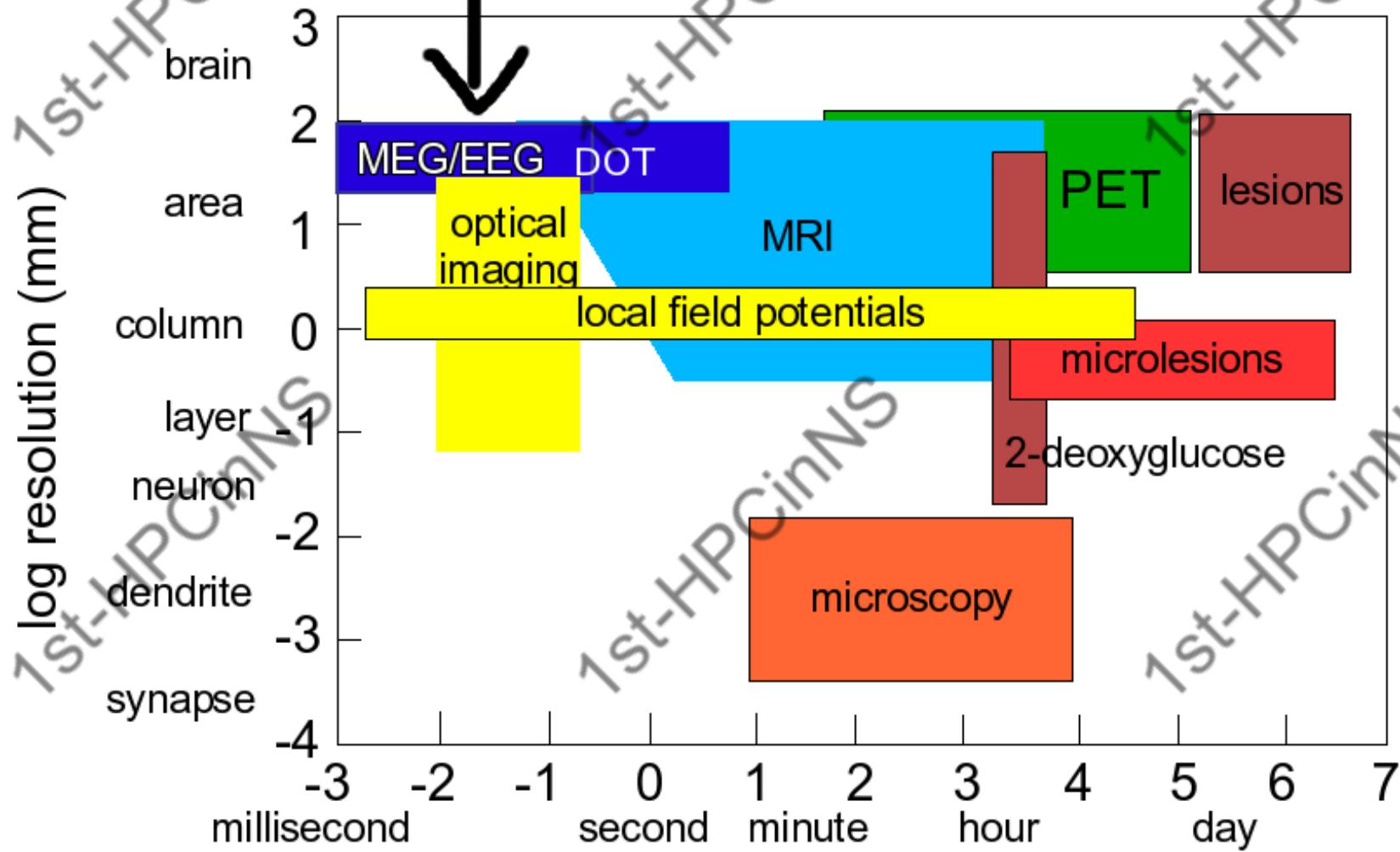
Brain Imaging

Neuroimaging



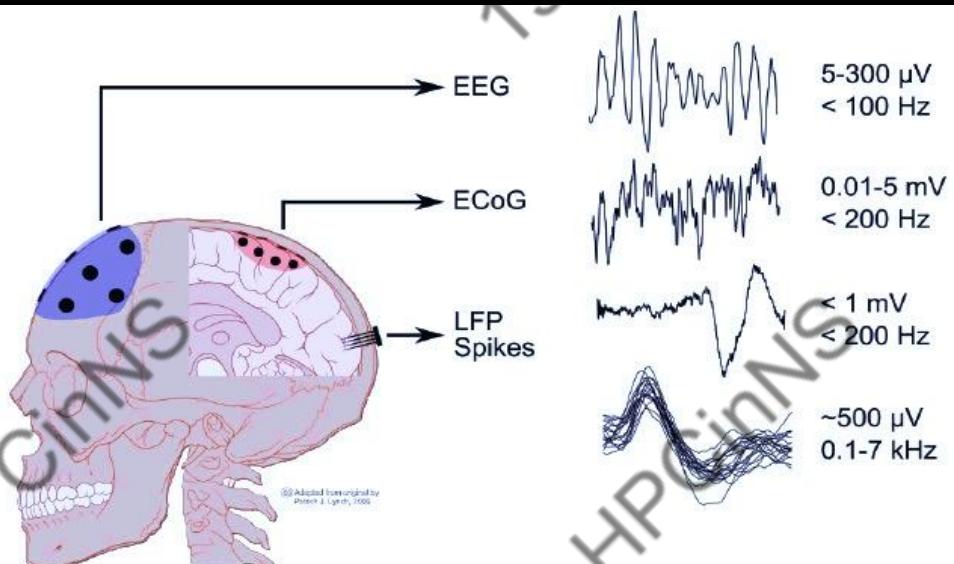
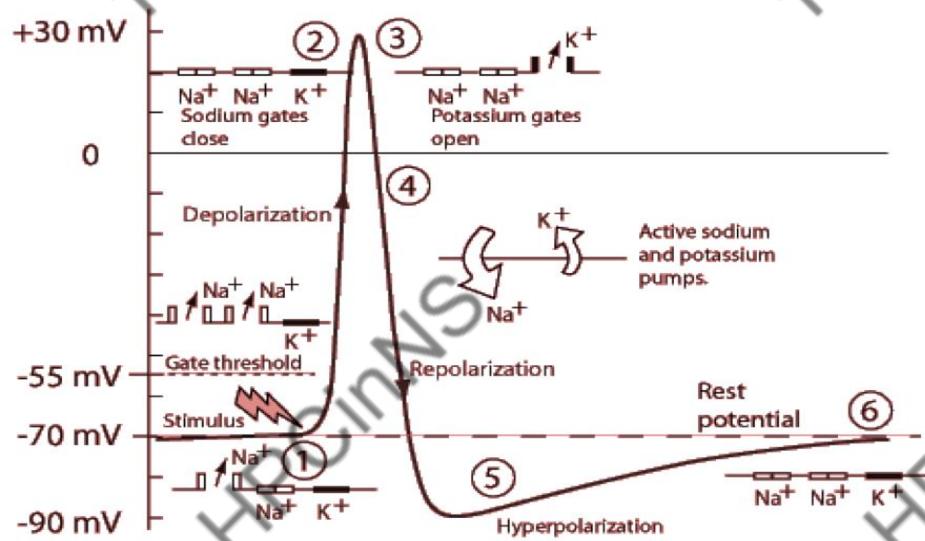
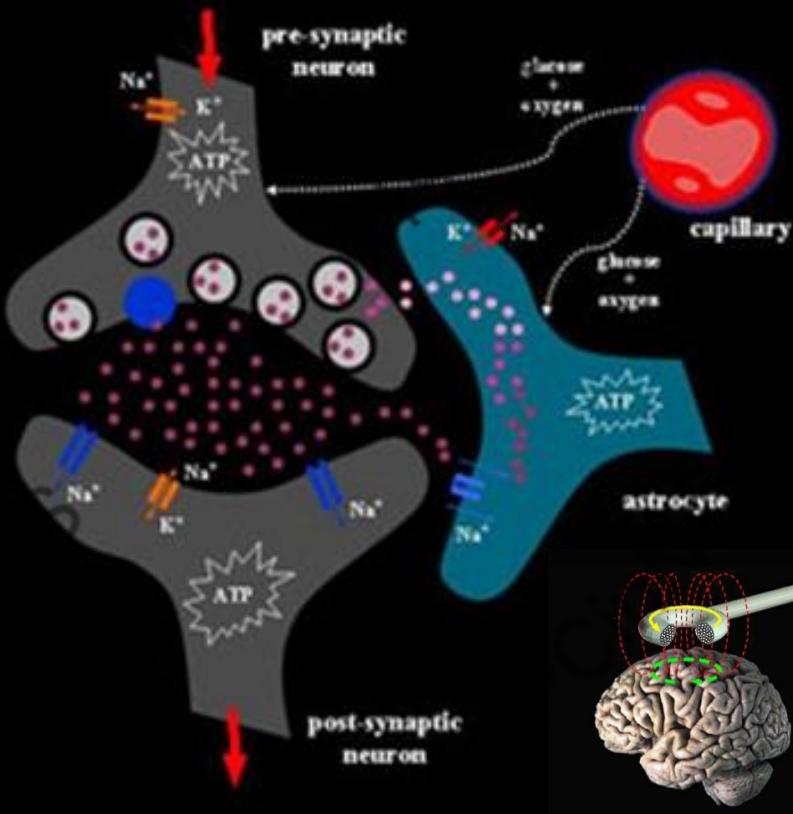
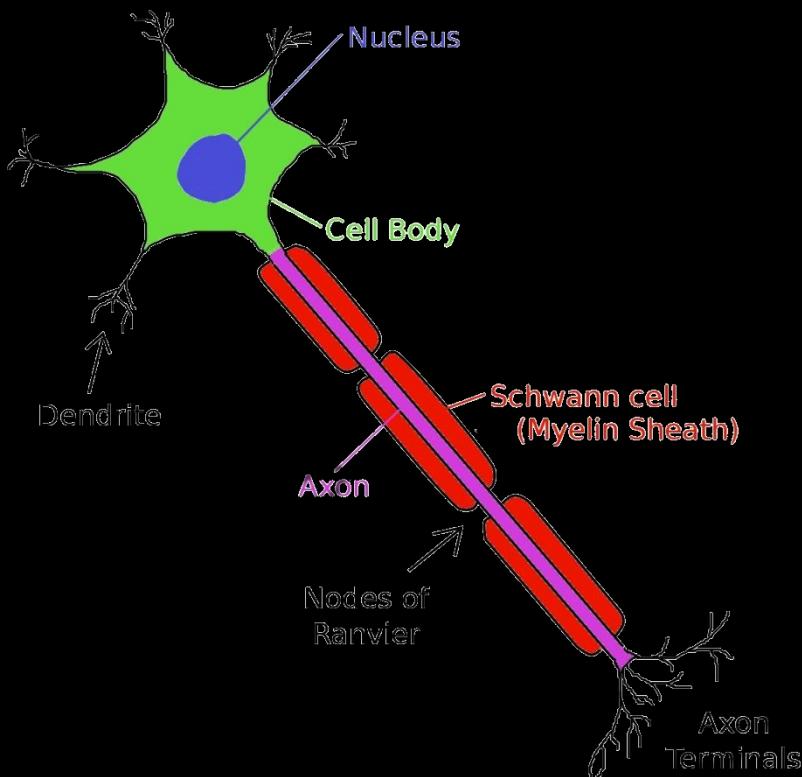
Imaging approaches



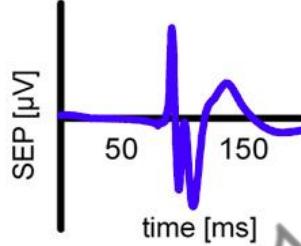


log time (second)

non-invasive invasive

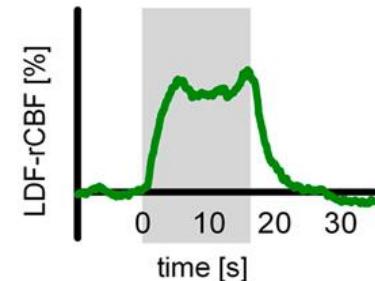


neuronal activity ↑



O₂ metabolism (CMRO₂) ↑

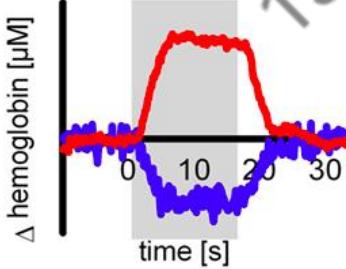
cerebral blood flow ↑↑↑



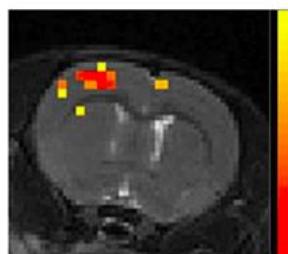
oxy-Hb ↓
deoxy-Hb ↑

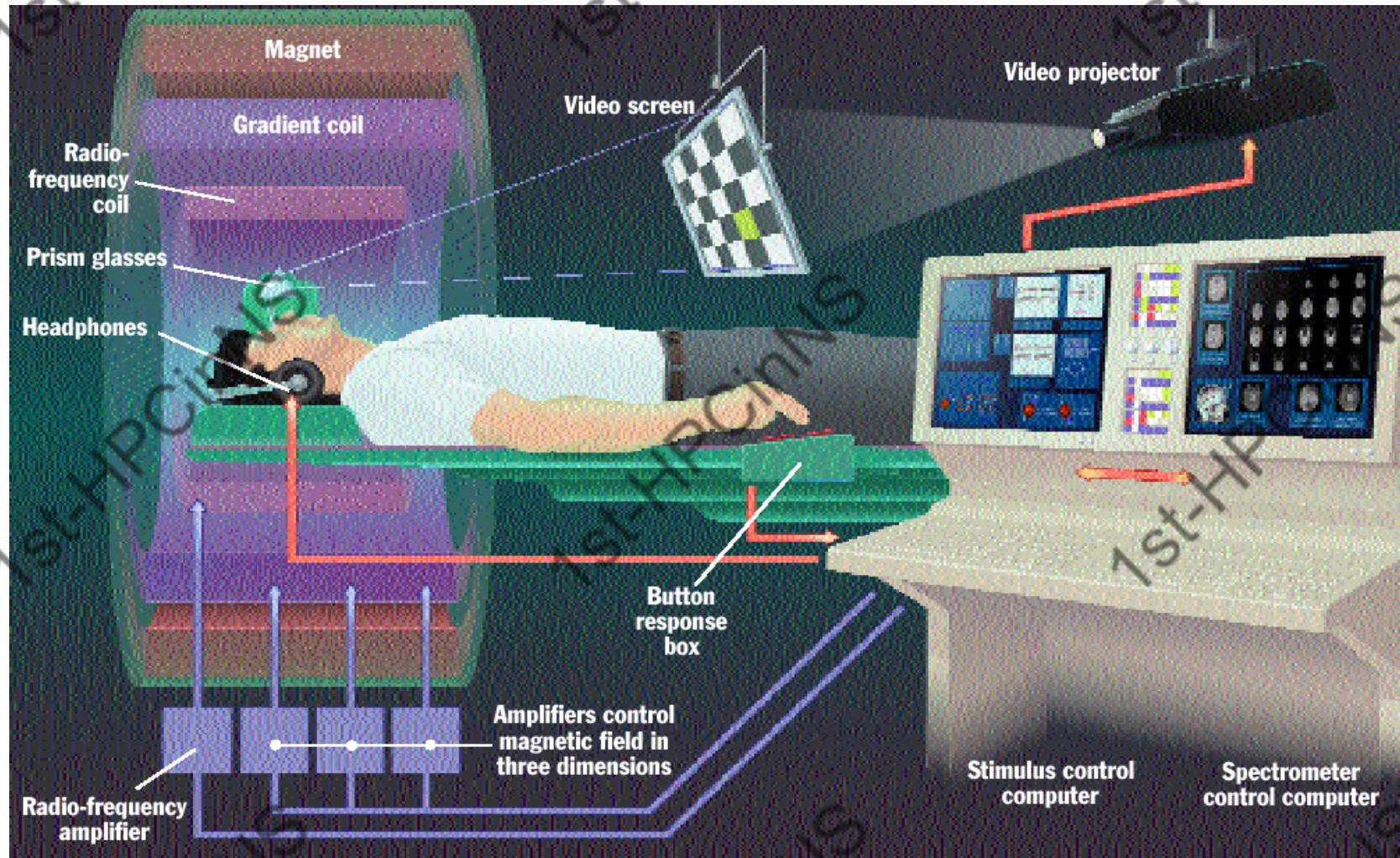
oxy-Hb ↑↑↑
deoxy-Hb ↓↓

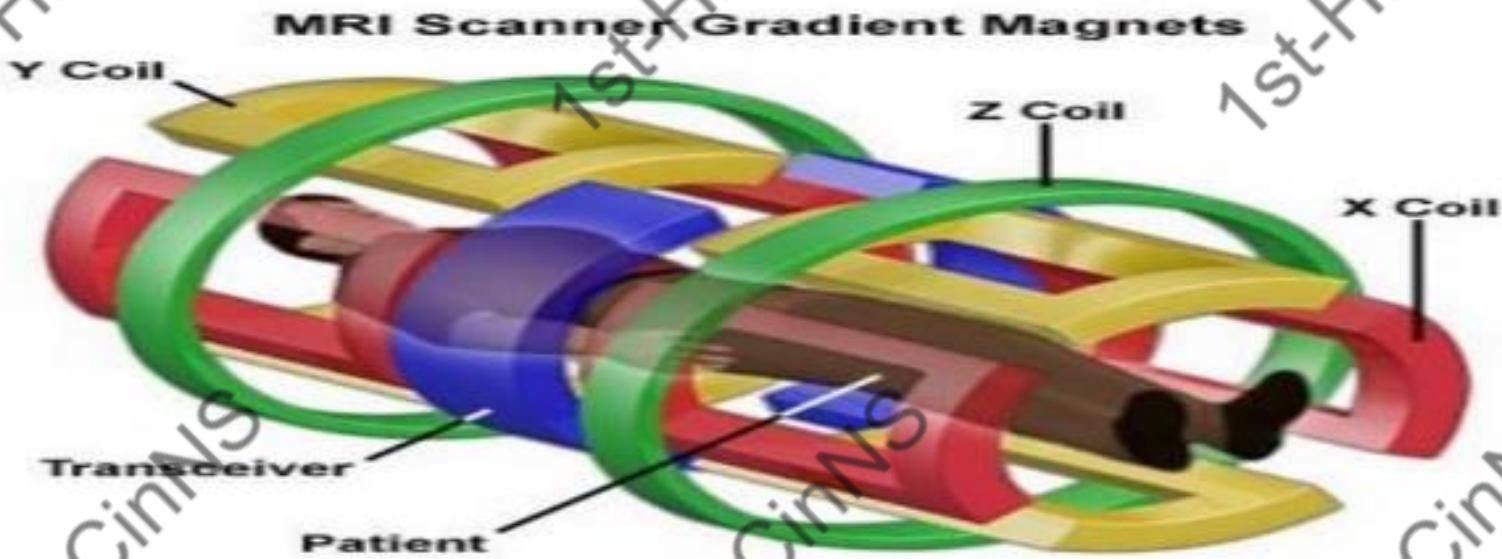
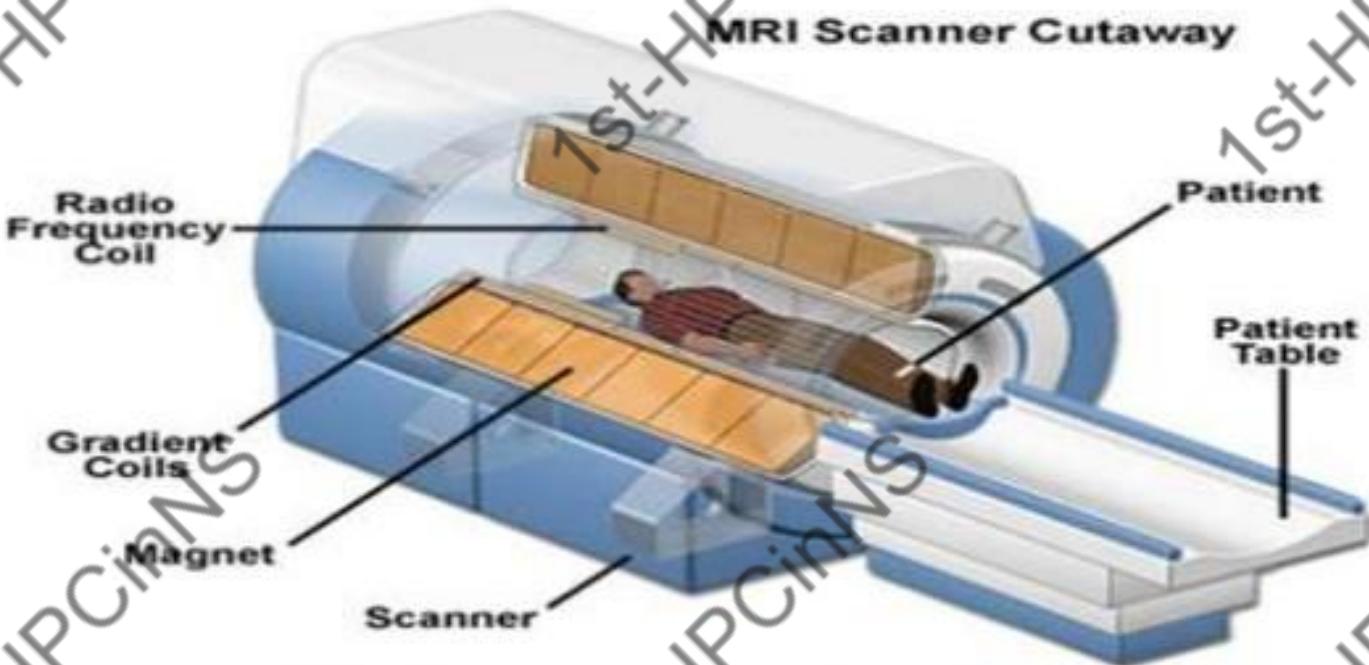
oxy-Hb ↑↑
deoxy-Hb ↓



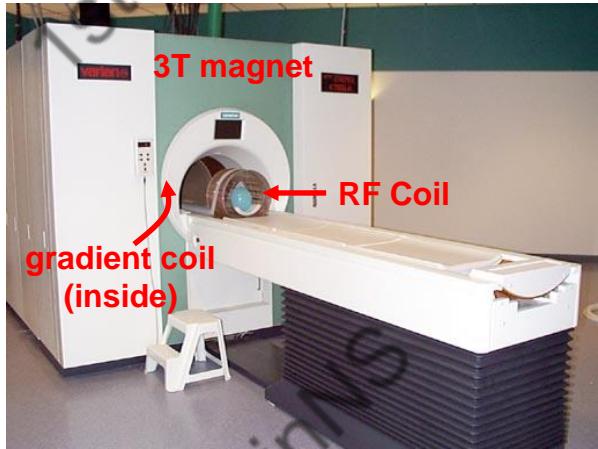
BOLD signal ↑



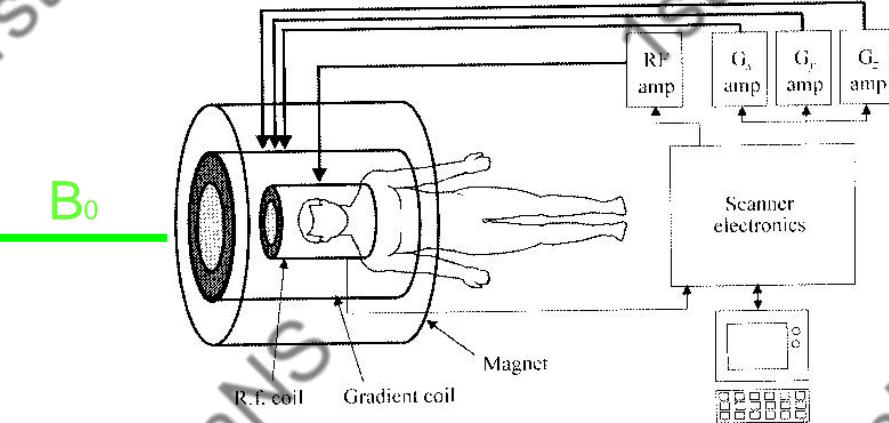
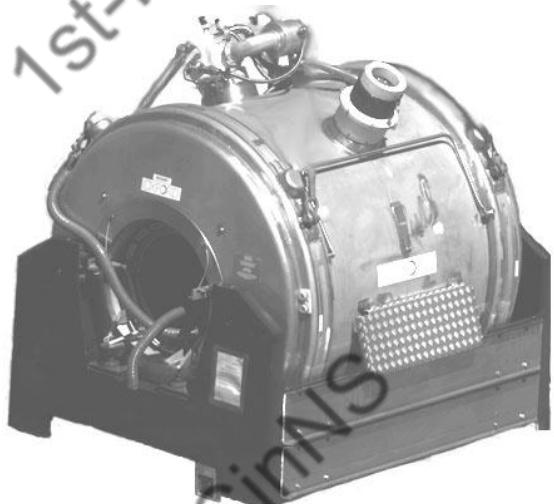




Equipment



Magnet



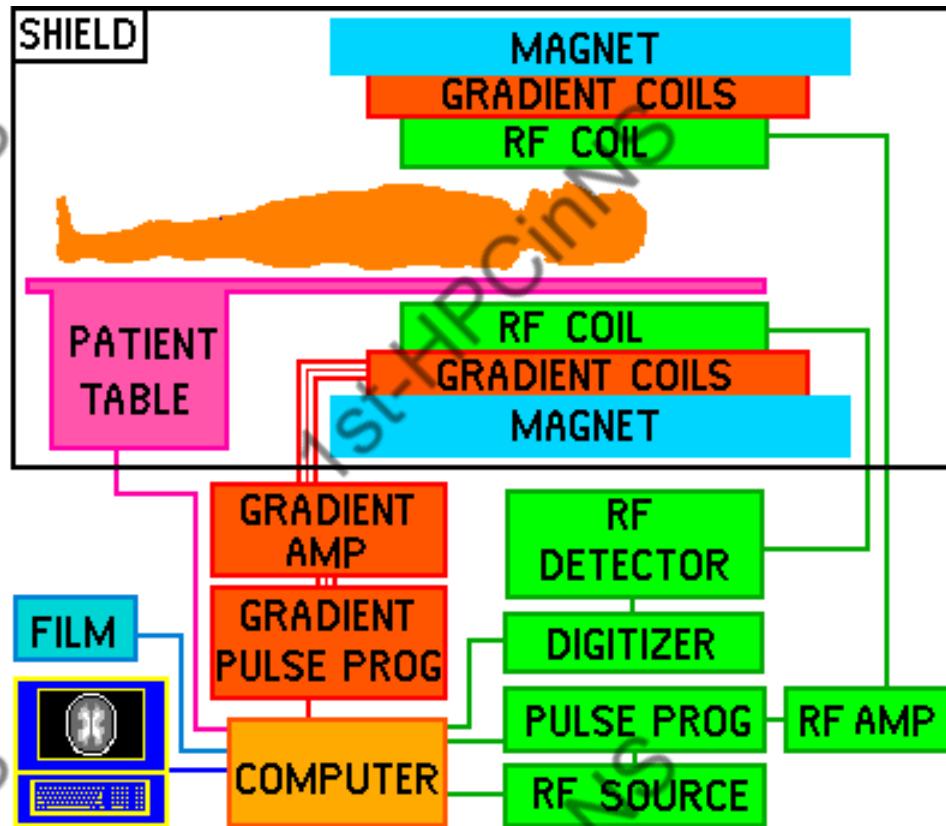
Gradient Coil



RF Coil



A schematic representation of the major systems on a magnetic resonance imager



Microscopic Principles

- The composition of the human body is primarily fat and water
- Fat and water have many hydrogen atoms
- 63% of human body is hydrogen atoms
- Hydrogen nuclei have an NMR signal
- MRI uses hydrogen because it has only one proton and it aligns easily with the MRI magnet
- The hydrogen atom's proton, possesses a property called spin
 1. A small magnetic field
 2. Will cause the nucleus to produce an NMR signal

Common nuclei with NMR properties

Criteria:

Must have ODD number of protons or ODD number of neutrons.

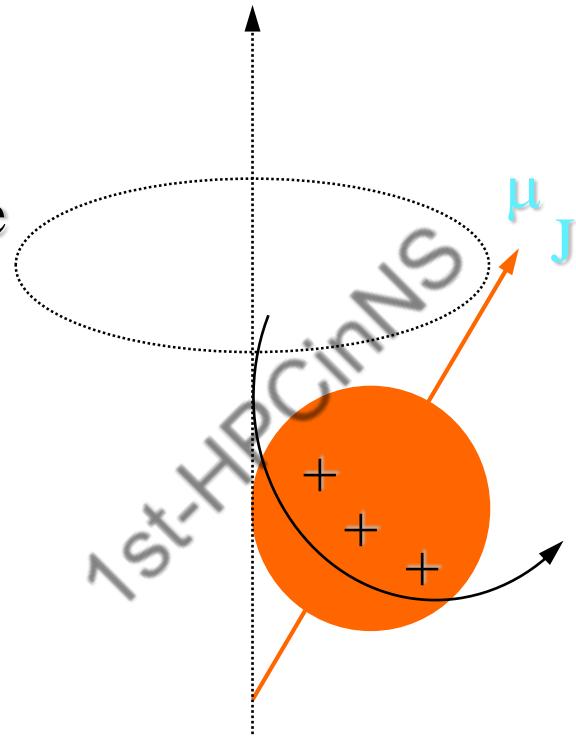
Examples:

^1H , ^{13}C , ^{19}F , ^{23}N , and ^{31}P with gyromagnetic ratio of 42.58, 10.71, 40.08, 11.27 and 17.25 MHz/T.

Since hydrogen protons are the most abundant in human body, we use ^1H MRI most of the time.

A Single Proton

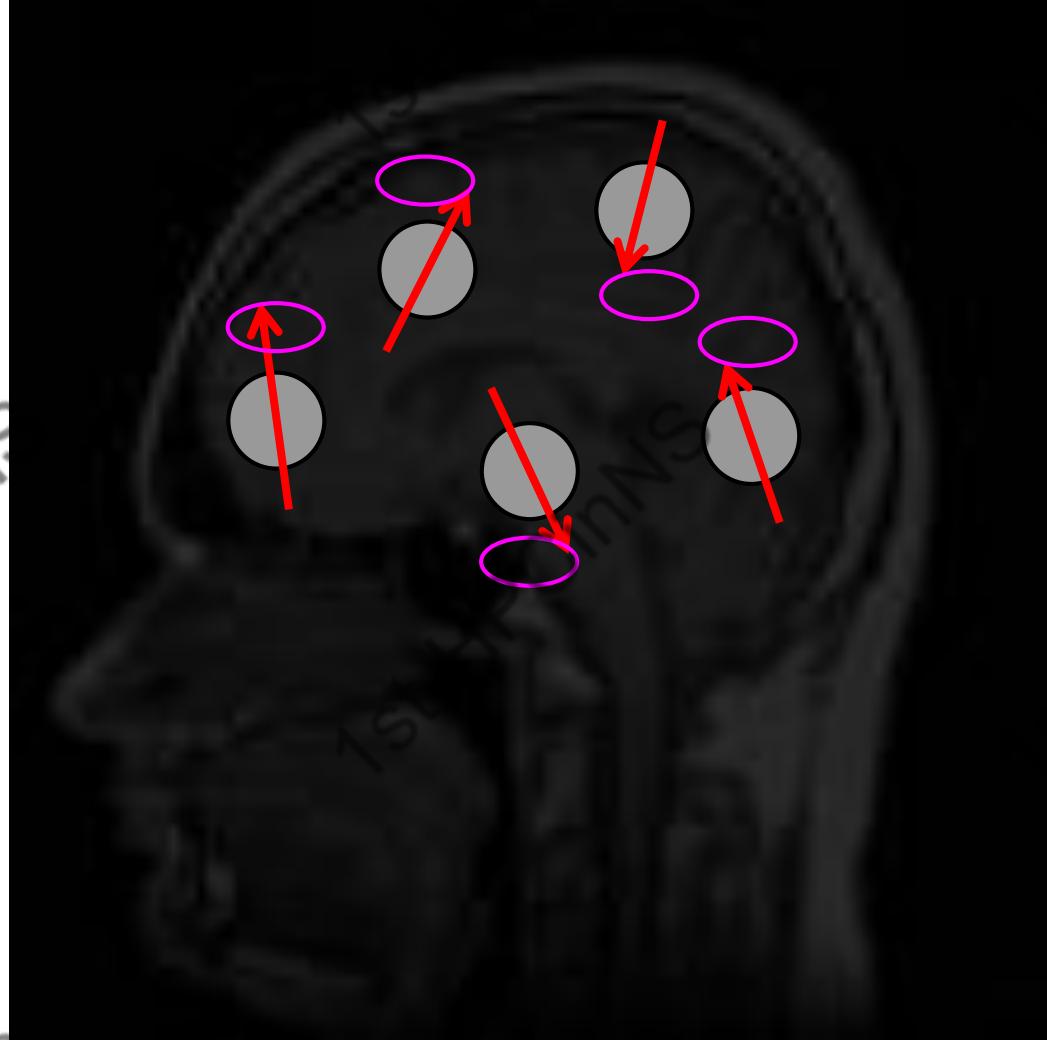
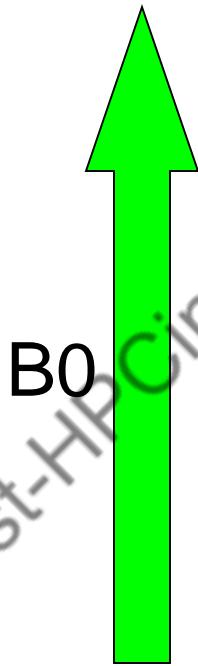
There is electric charge on the surface of the proton, thus creating a small current loop and generating magnetic moment μ .



The proton also has mass which generates an angular momentum J when it is spinning.

Thus proton “magnet” differs from a magnetic bar in that it also possesses angular momentum caused by spinning.

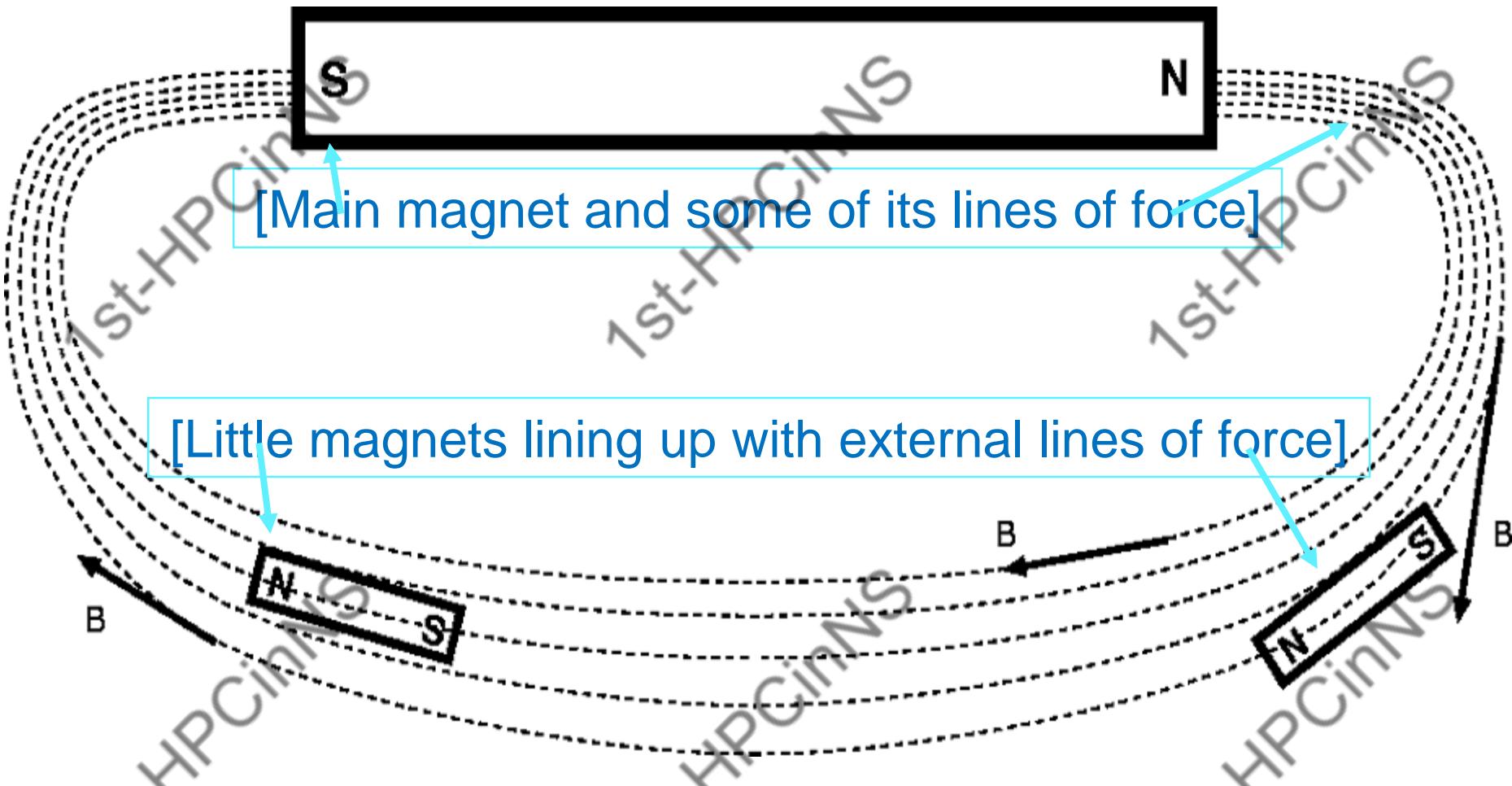
Within Magnetic Field



protons align parallel or anti-parallel to B_0 (parallel > antiparallel)
phase is random

Main Magnet Field B_0

Purpose is to align H protons in H_2O (little magnets)

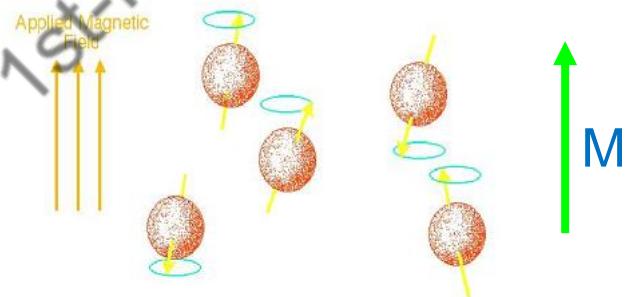


Protons align with field

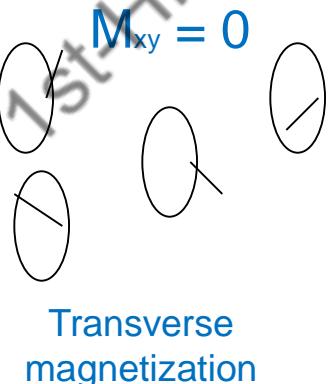
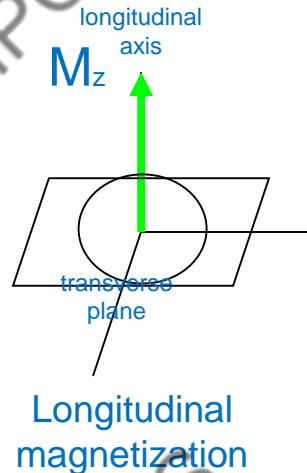
Outside magnetic field



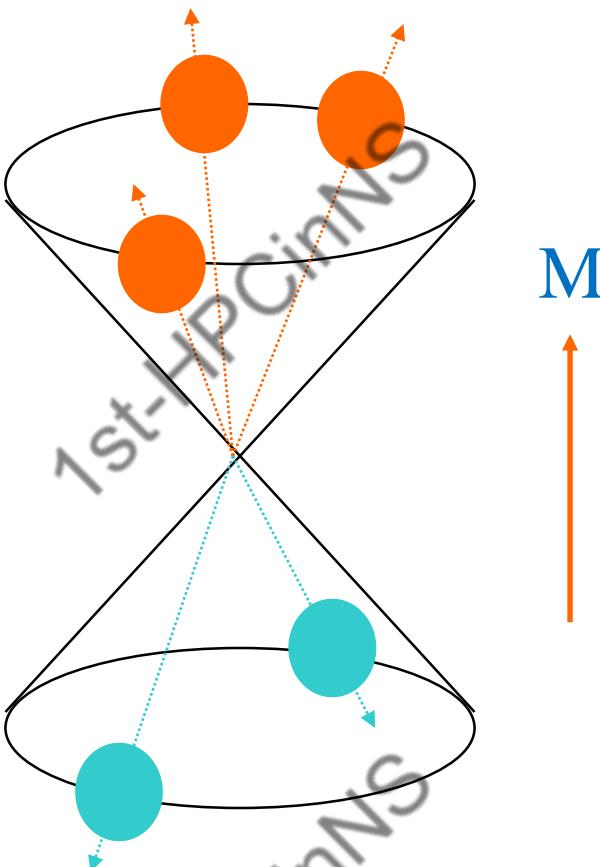
Inside magnetic field



- spins tend to align parallel or anti-parallel to B_0
- net magnetization (M) along B_0
- spins precess with random phase
- no net magnetization in transverse plane
- only 0.0003% of protons/T align with field



Net Magnetization



$$M = c \frac{B_o}{T}$$

Magnetic Principles

- The spinning hydrogen protons act like small , weak magnets.
- They align with an external magnetic field ($B\phi$).
- There is a slight excess of protons aligned with the field. (for 2 million , 6 excess)
- The # of protons that align with the field is so very large that we can pretty much ignore quantum mechanics and focus on classical mechanics.

Magnetic Principles

The spinning protons wobble or “precess” about that axis of the external B_o field at the precessional, Larmor or resonance frequency.

Magnetic resonance imaging frequency

$$\nu = \gamma B_o$$

where γ is the gyromagnetic ratio

The resonance frequency ν of a spin is proportional to the magnetic field, B_o .

Larmor Frequency

Larmor equation

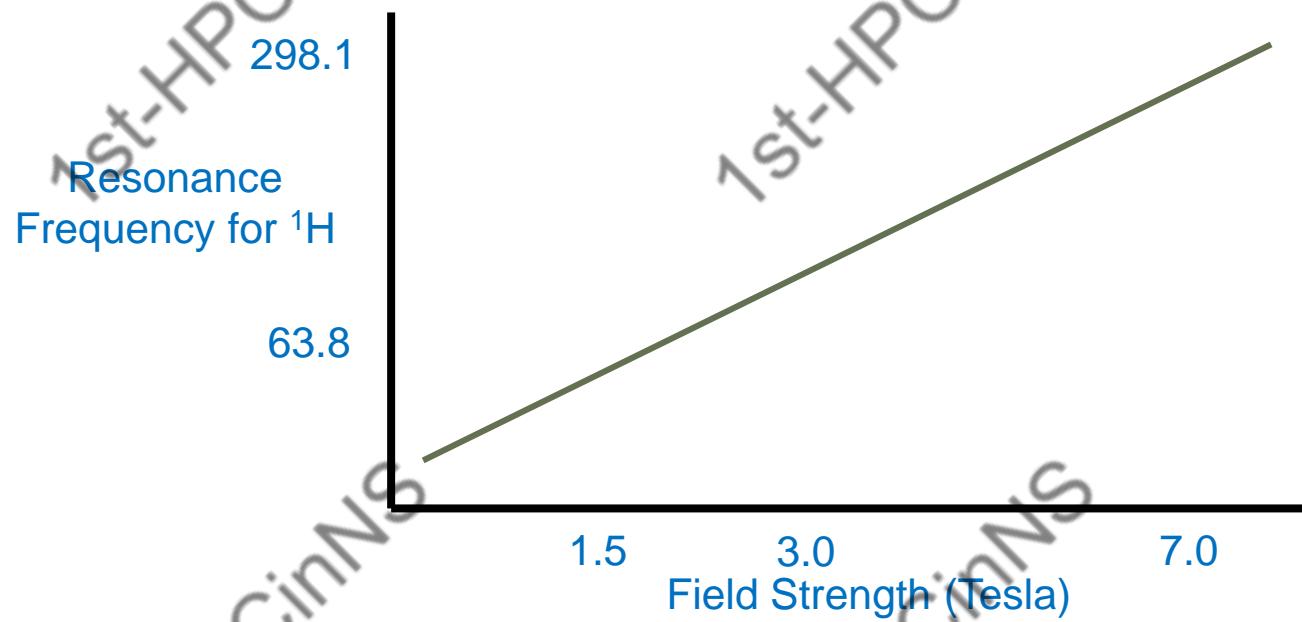
$$f = \gamma B_0$$

$\gamma = 42.58 \text{ MHz/T}$ for hydrogen

At 1.5T, $f = 63.8 \text{ MHz}$

At 3T, $f = 127.7 \text{ MHz}$

At 7T $f = 298.1 \text{ MHz}$

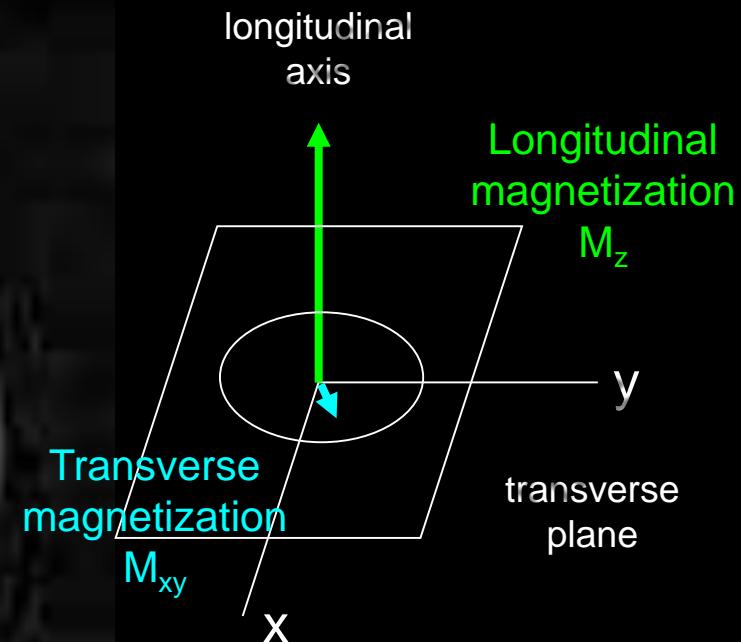
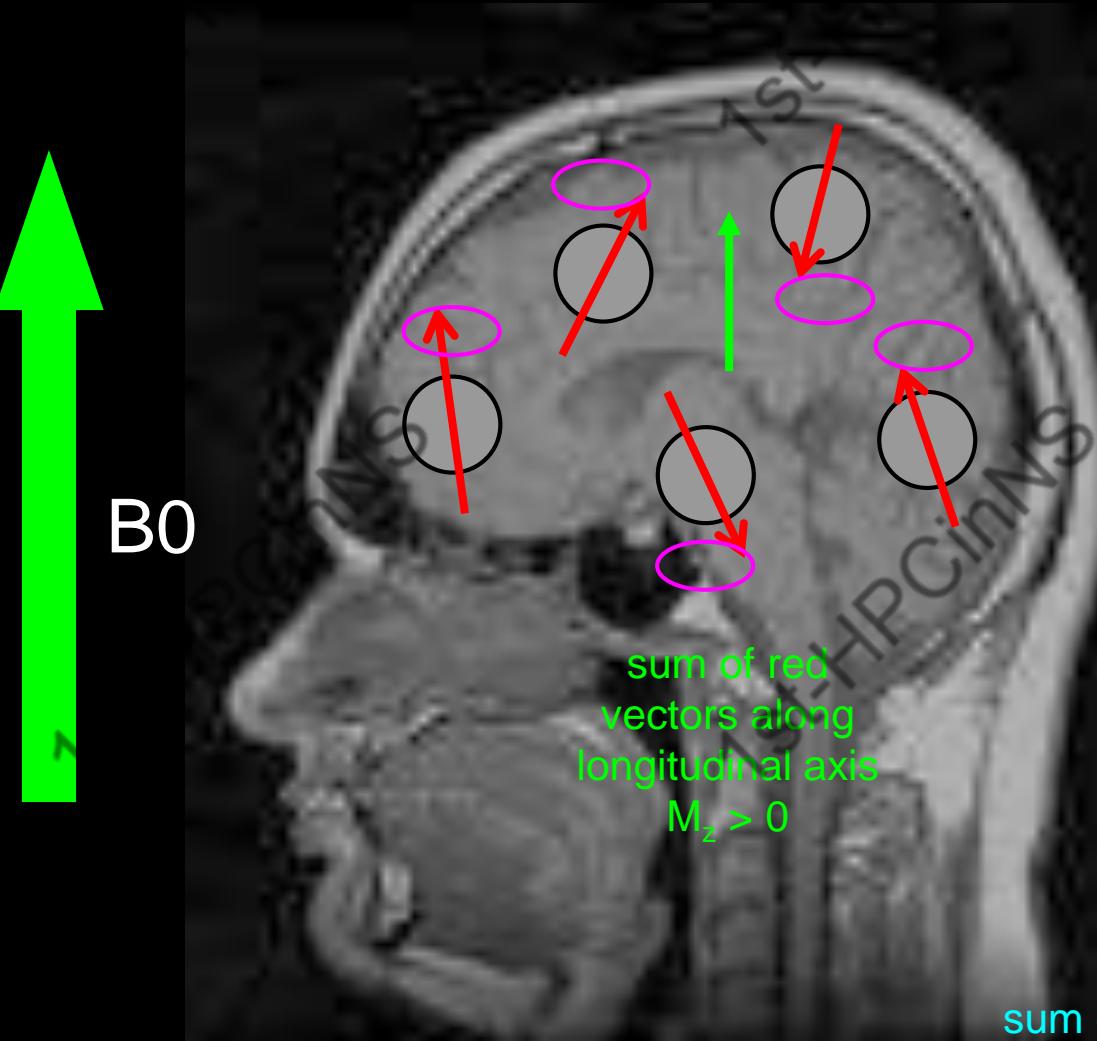


Magnetic Principles

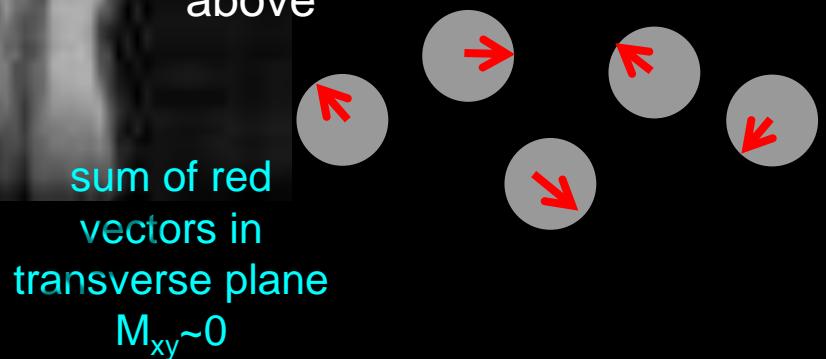
Now if an electromagnetic radio frequency (RF) pulse is applied at the resonance (Larmor, precession, wobble) frequency, then the protons can absorb that energy, and (at the quantum level) jump to a higher energy state.

At the macro level, the magnetization vector, M_ϕ , (6 million protons) spirals down towards the XY plane.

Within Magnetic Field



Now imagine viewing the spins from above



Principles of MRI

Before RF :

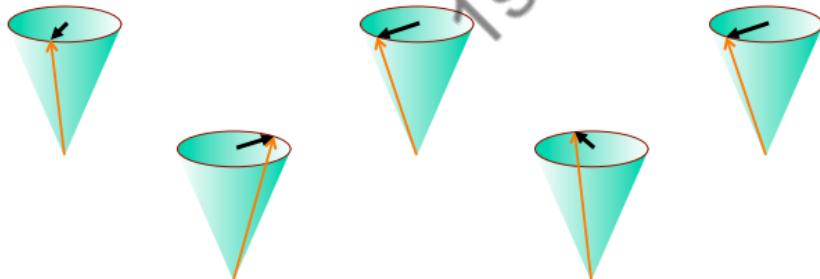
- Same frequency (Larmor)

- $\omega = \gamma B$

- Different Phase

- longitudinal magnetization = M

- Transversal magnetization = 0



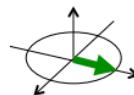
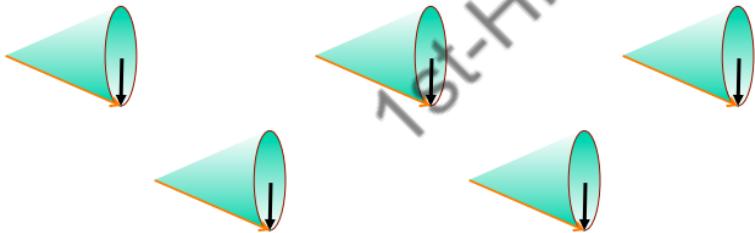
After RF:

- Same frequency (Larmor)

- Same Phase

- longitudinal magnetization = 0

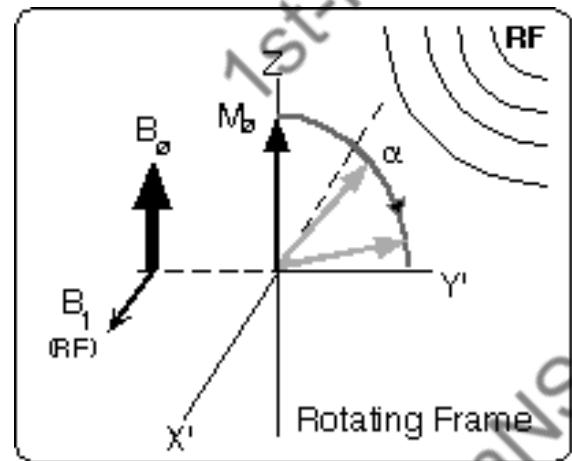
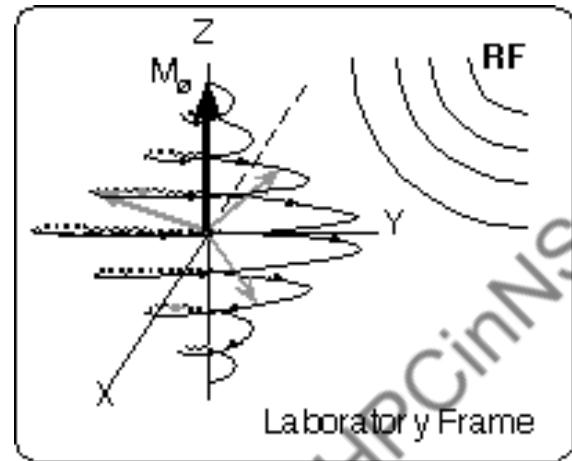
- Transversal magnetization = M



Magnetic Principles

Once the RF transmitter is turned off three things happen simultaneously.

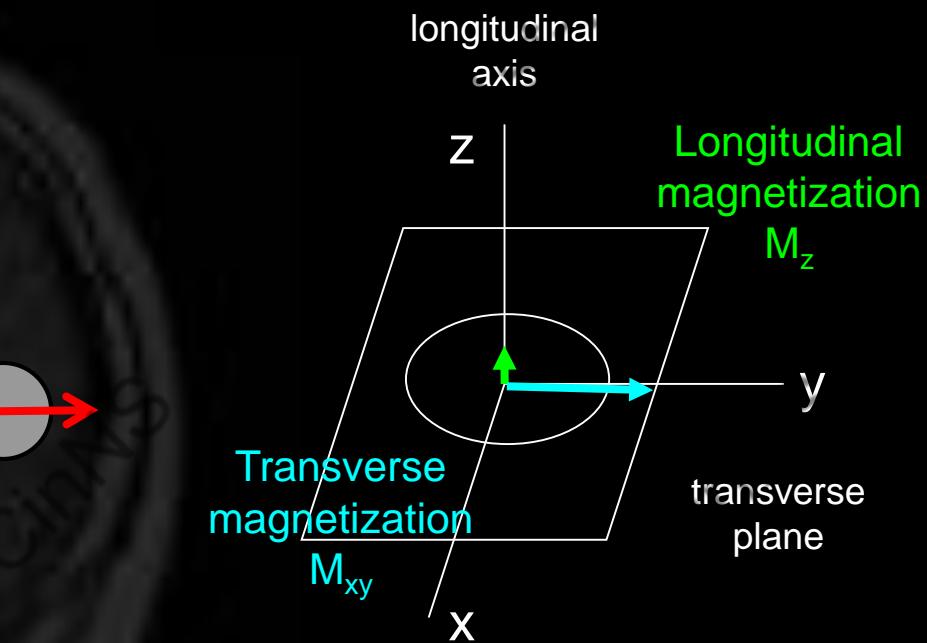
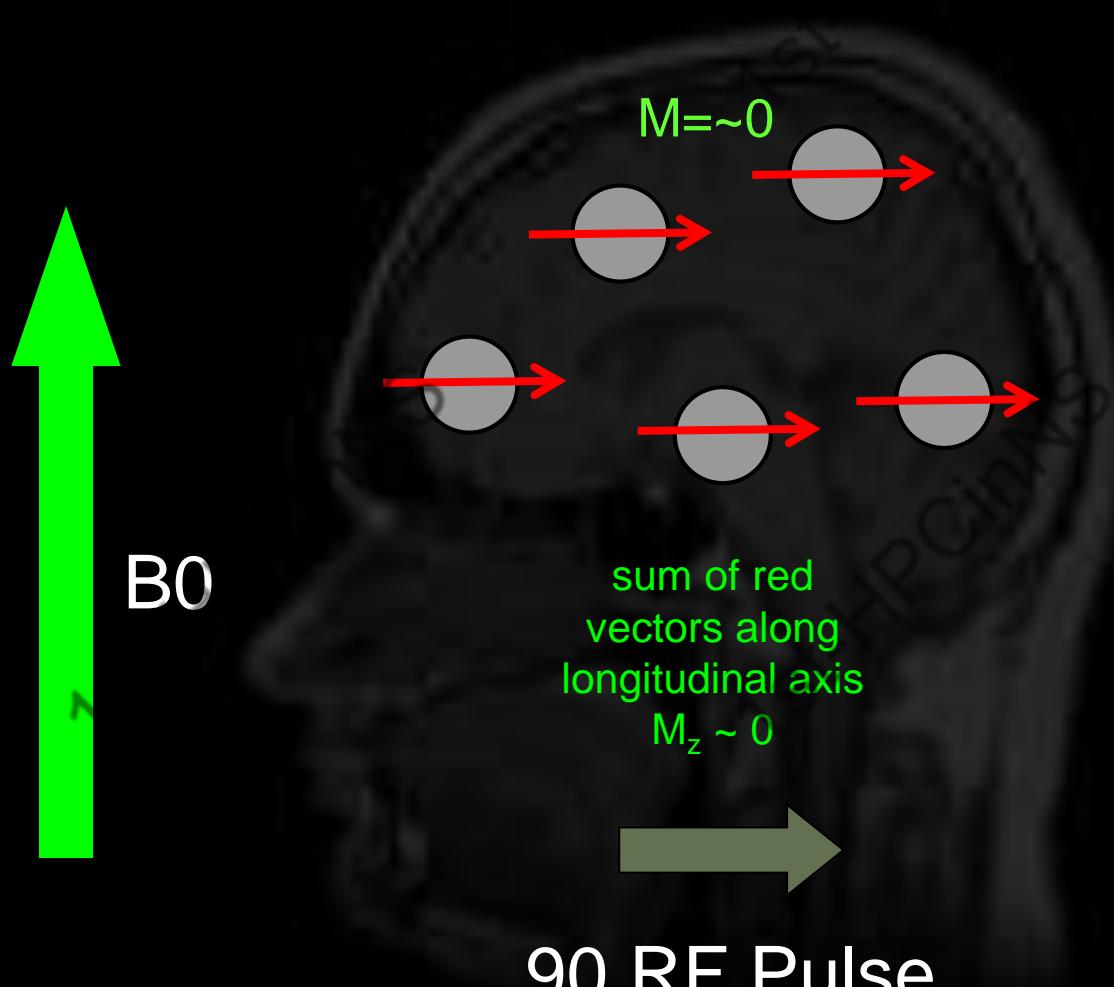
1. The absorbed RF energy is retransmitted (at the resonance frequency).
2. The excited spins begin to return to the original M_z orientation. (T_1 recovery to thermal equilibrium).
3. Initially in phase, the excited protons begin to dephase (T_2 and T_{2^*} relaxation)



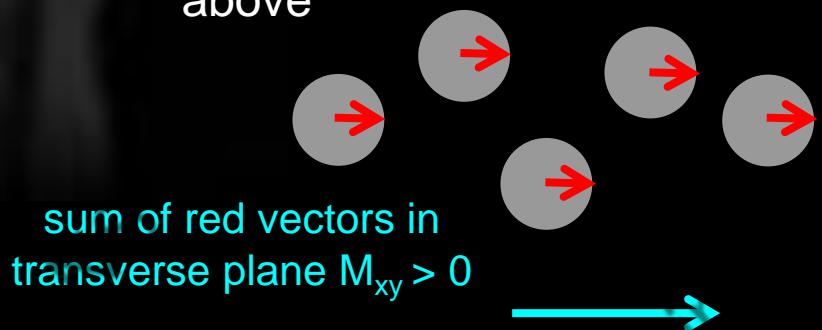
Magnetic Principles

The time course whereby the system returns to thermal equilibrium, or M_z grows to M_∞ , is mathematically described by an exponential curve. This recovery rate is characterized by the time constant T_1 , which is unique to every tissue. This uniqueness in M_z recovery rates is what enables MRI to differentiate between different types of tissue.

Apply Radio Waves

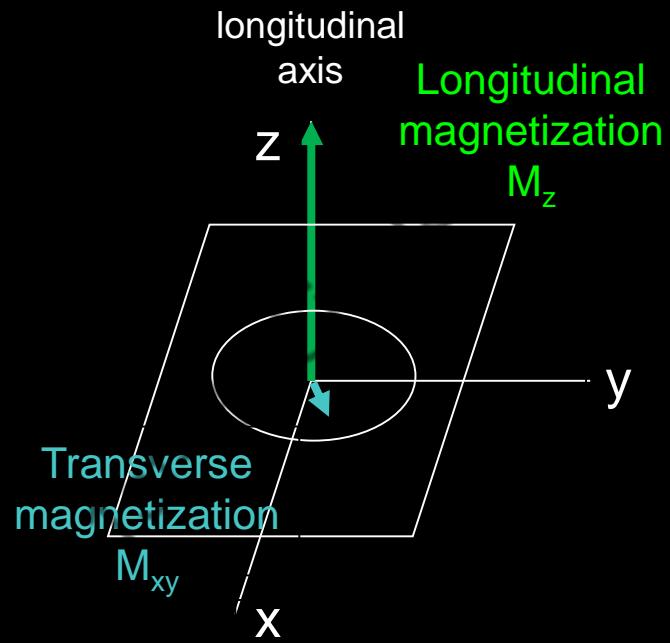


Now imagine viewing the spins from above

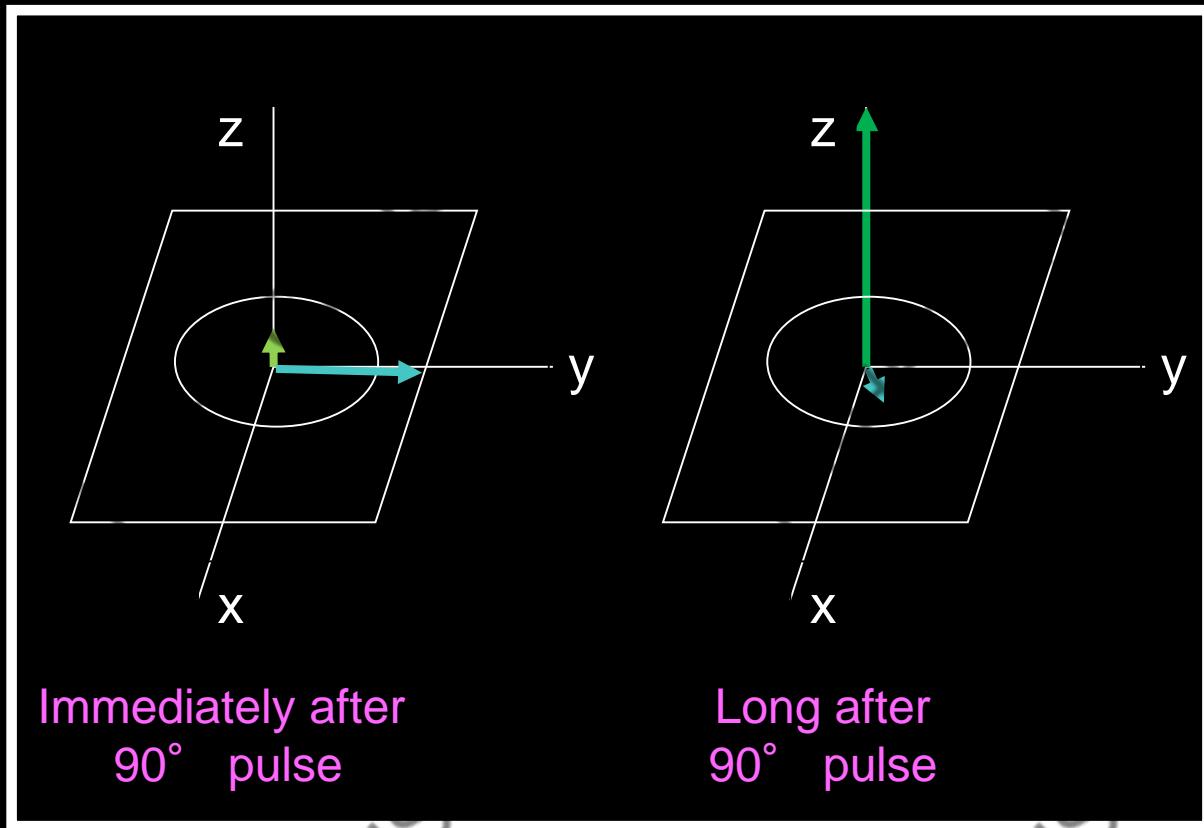


Measure Radio Waves

Measure during recovery period



Before
90° pulse

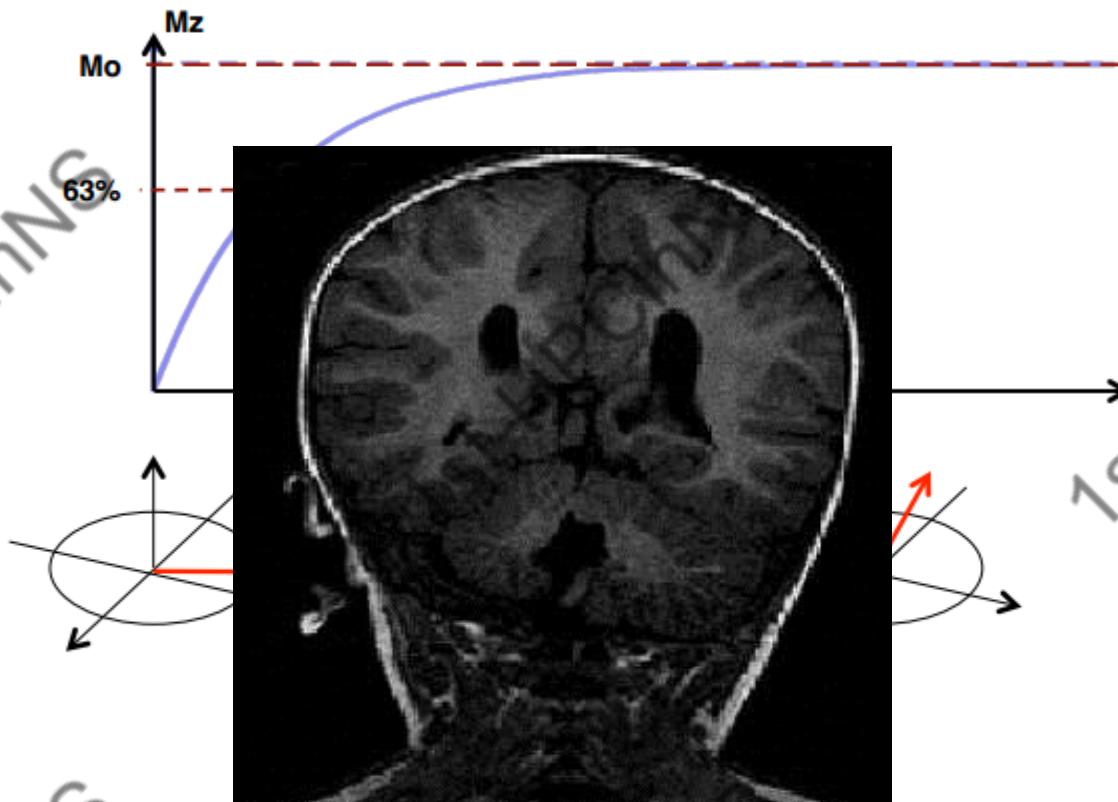


Immediately after
90° pulse

Long after
90° pulse

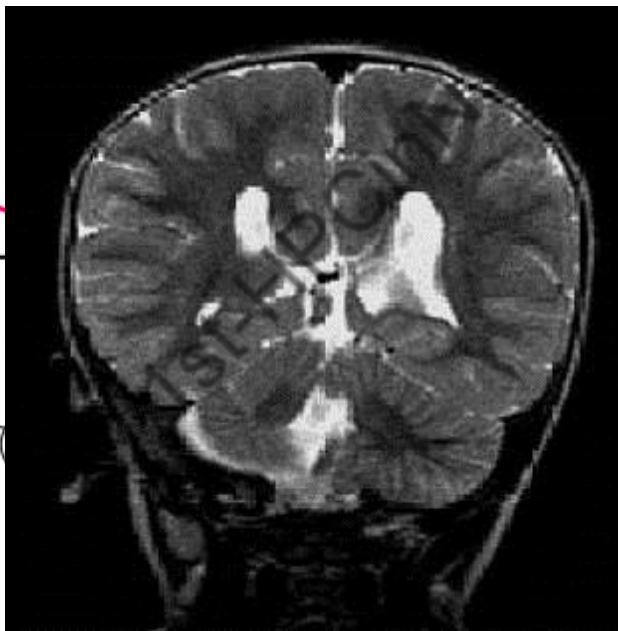
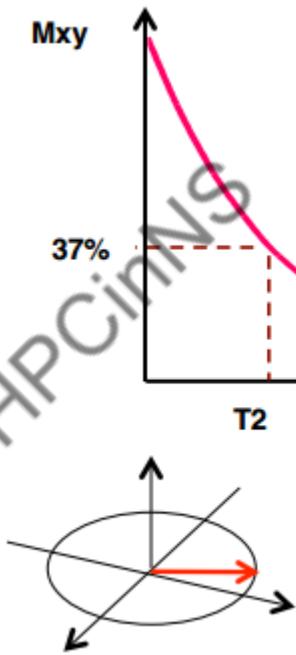
Longitudinal Relaxation Time

T1 measures how quickly the protons realign with the main magnetic field



Transverse Relaxation Time

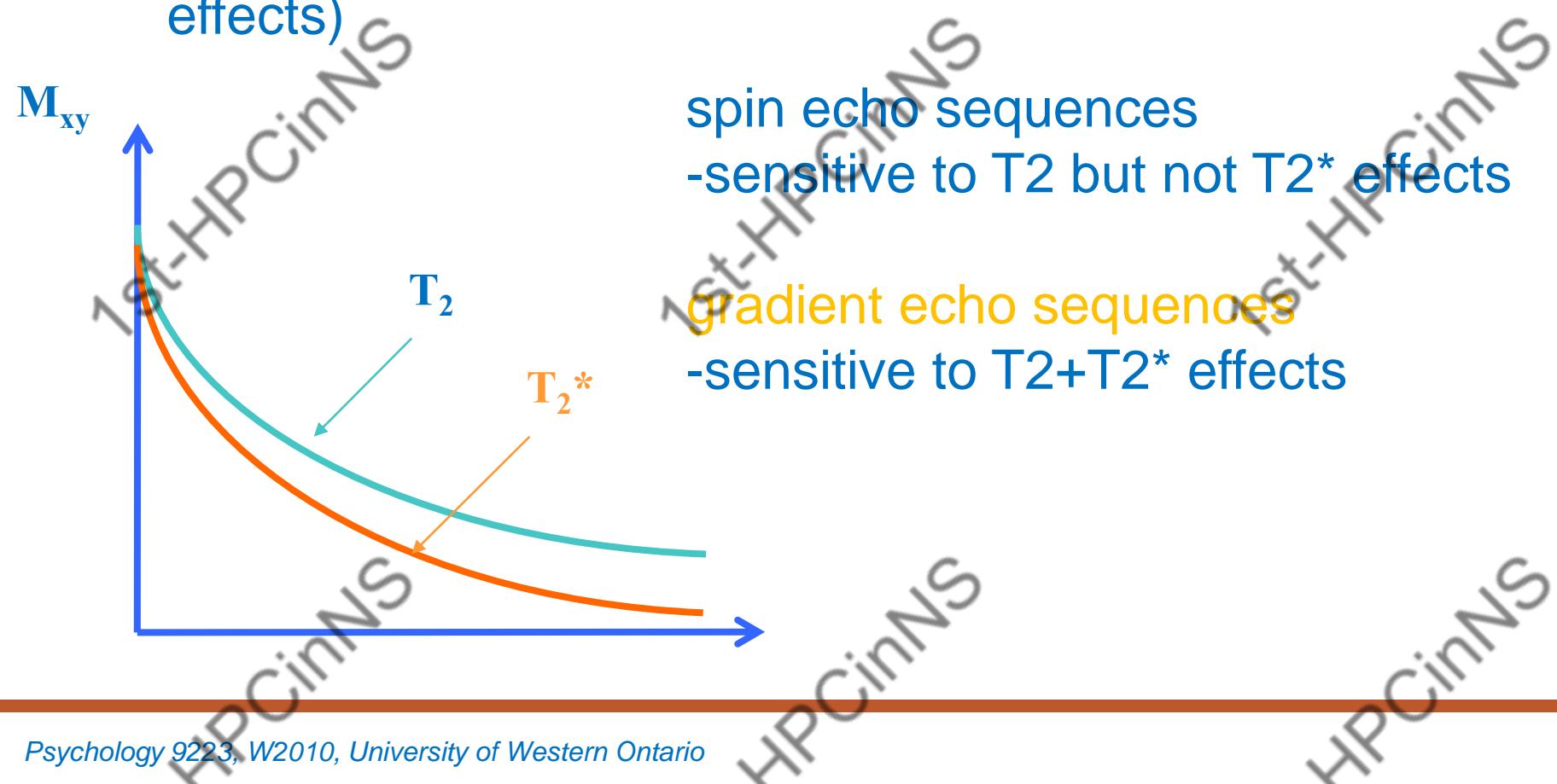
T2 measures how quickly the protons give off energy as they recover to equilibrium



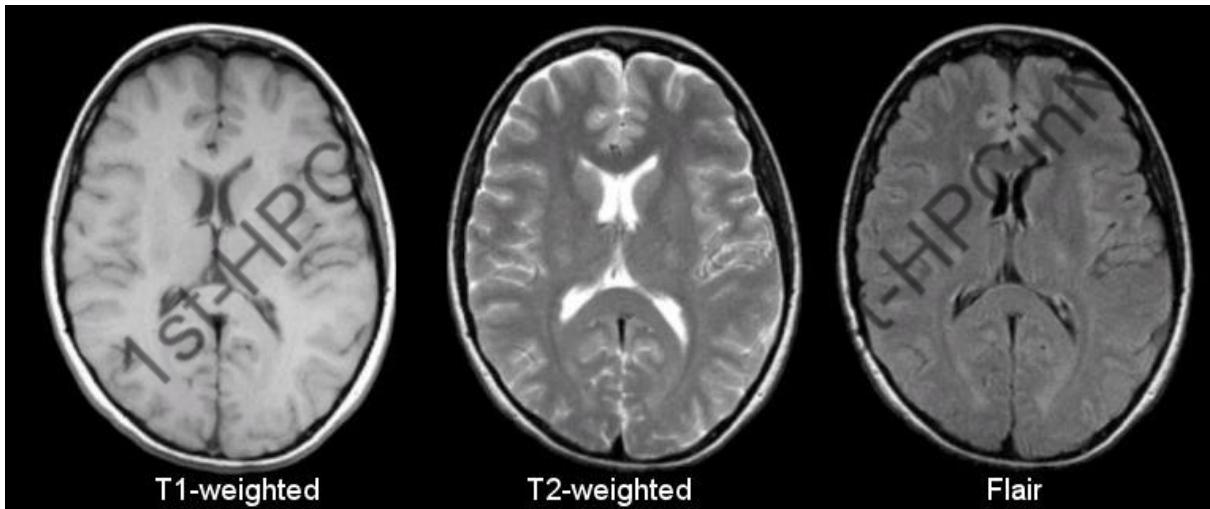
T2 VS T2*

Dephasing of transverse magnetization due to both:

1. spin-spin interactions (T_2)
2. static magnetic field inhomogeneities (additional T_2^* effects)

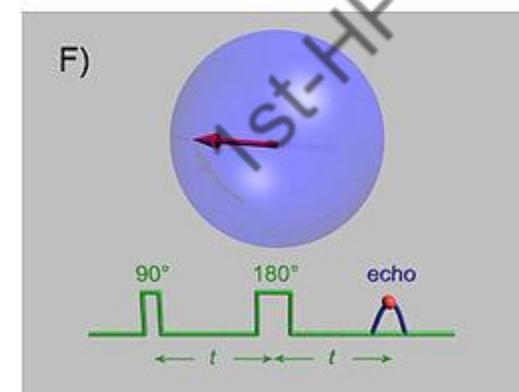
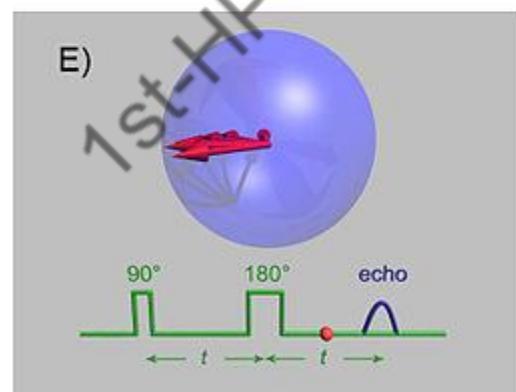
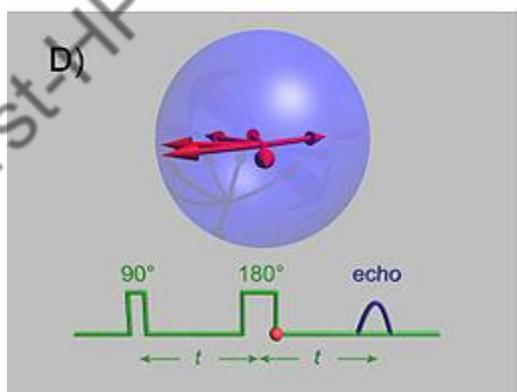
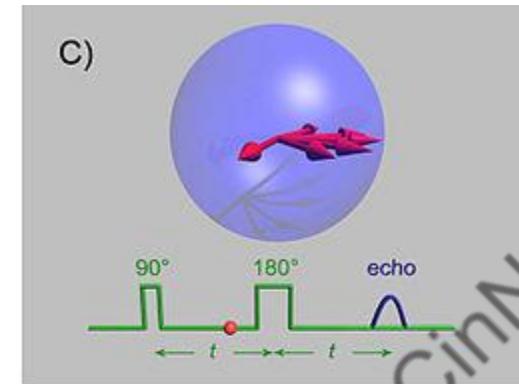
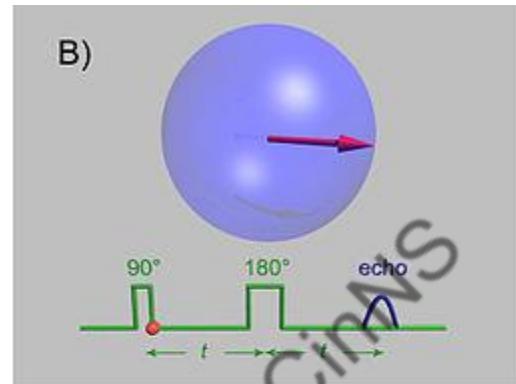
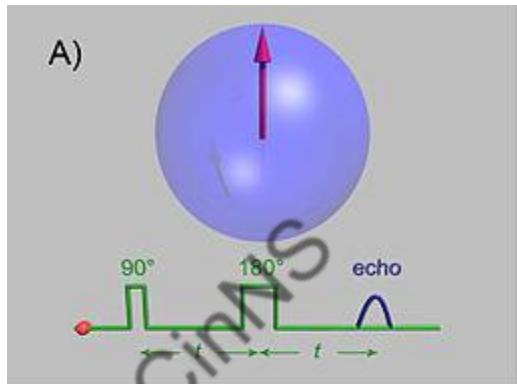


	TR (msec)	TE (msec)
T1-Weighted (short TR and TE)	500	14
T2-Weighted (long TR and TE)	4000	90
Flair (very long TR and TE)	9000	114



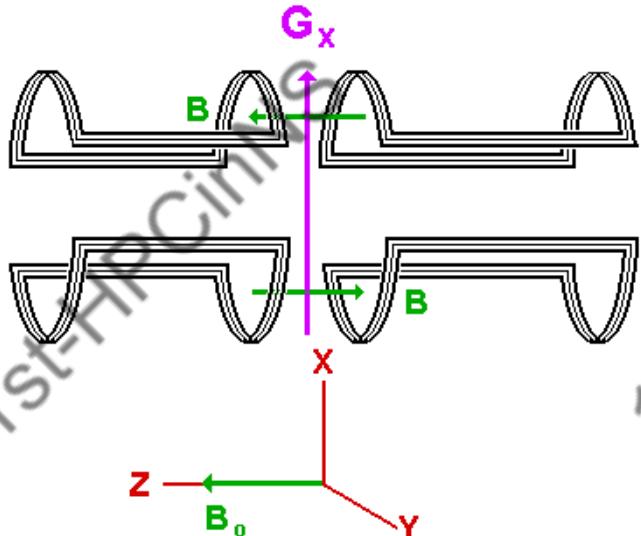
Tissue	T1-Weighted	T2-Weighted	Flair
CSF	Dark	Bright	Dark
White Matter	Light	Dark Gray	Dark Gray
Cortex	Gray	Light Gray	Light Gray
Fat (within bone marrow)	Bright	Light	Light
Inflammation (infection, demyelination)	Dark	Bright	Bright

spin echo sequence

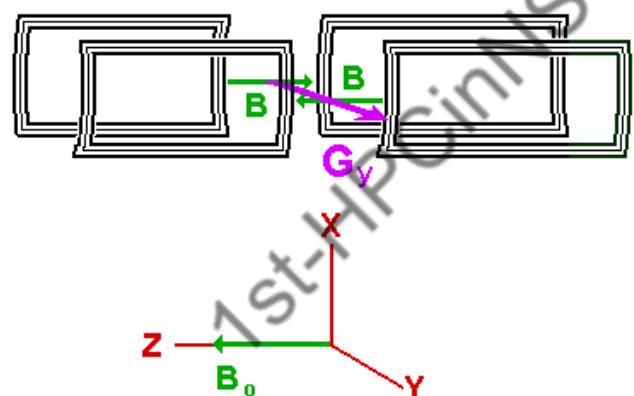


Gradient Coils

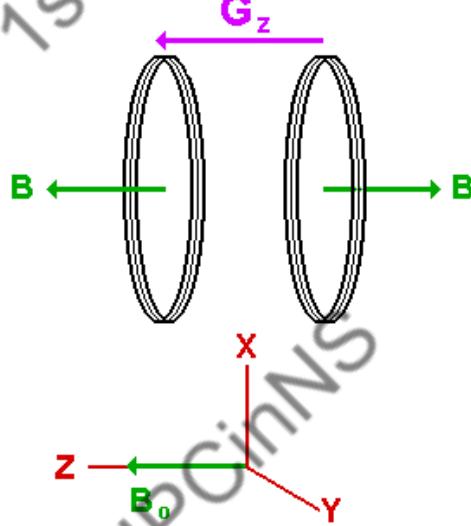
X Gradient Coil



Y Gradient Coil

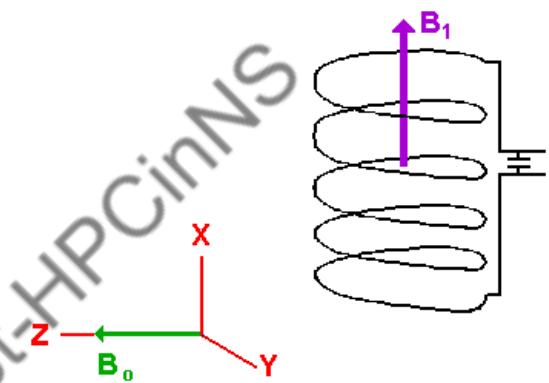


Z Gradient Coil

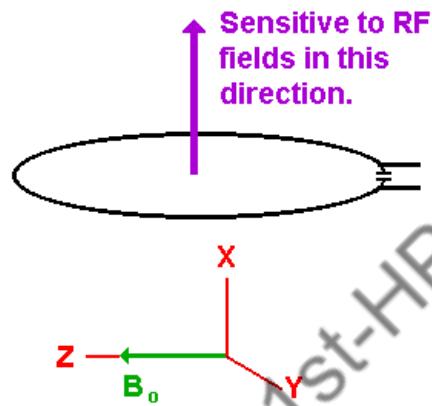


RF Coils

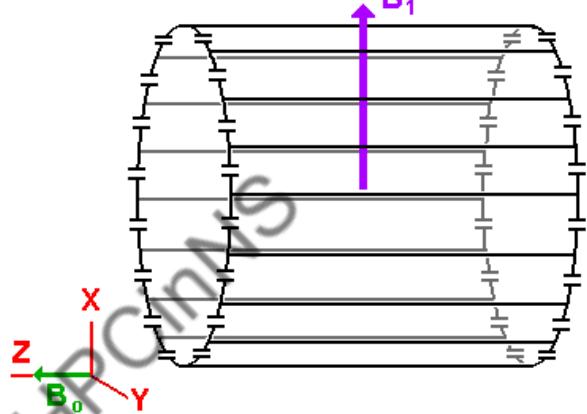
Multi-Turn Solenoid



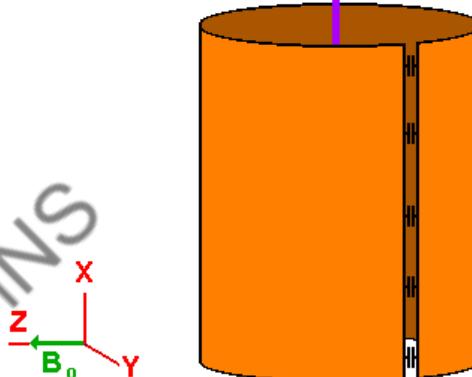
Surface Coil

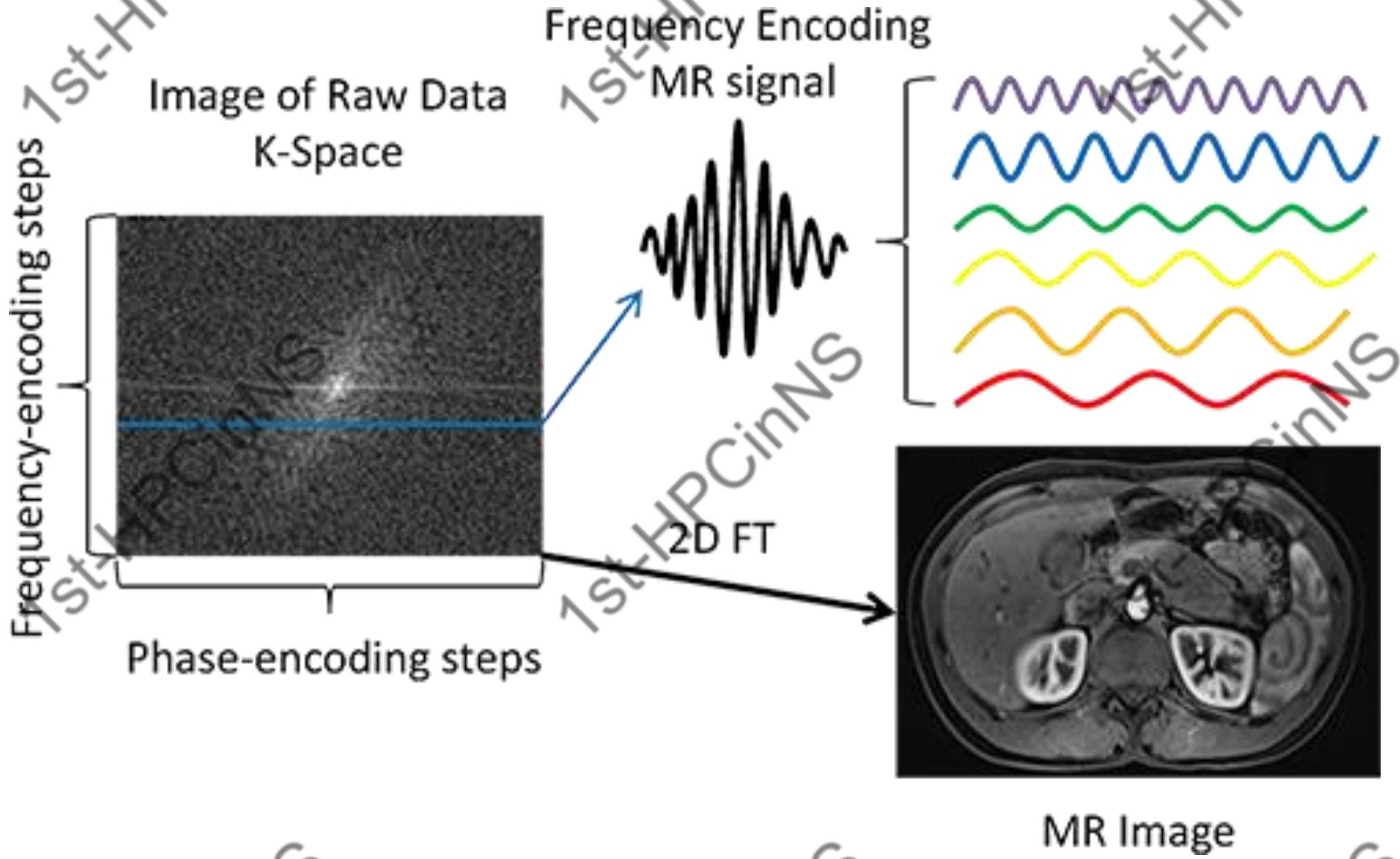


Bird Cage Coil



Single-Turn Solenoid



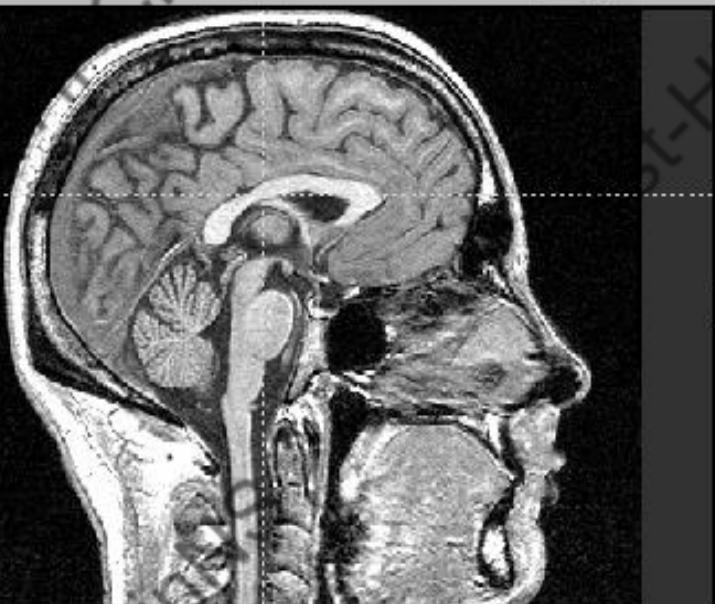


MR Image

Sagittal

S

62



Show Crosshairs Show Grid

Show Orientation Axes

Scaling Used: **Versus Unit Data**

A

I

Coronal

S

34



L

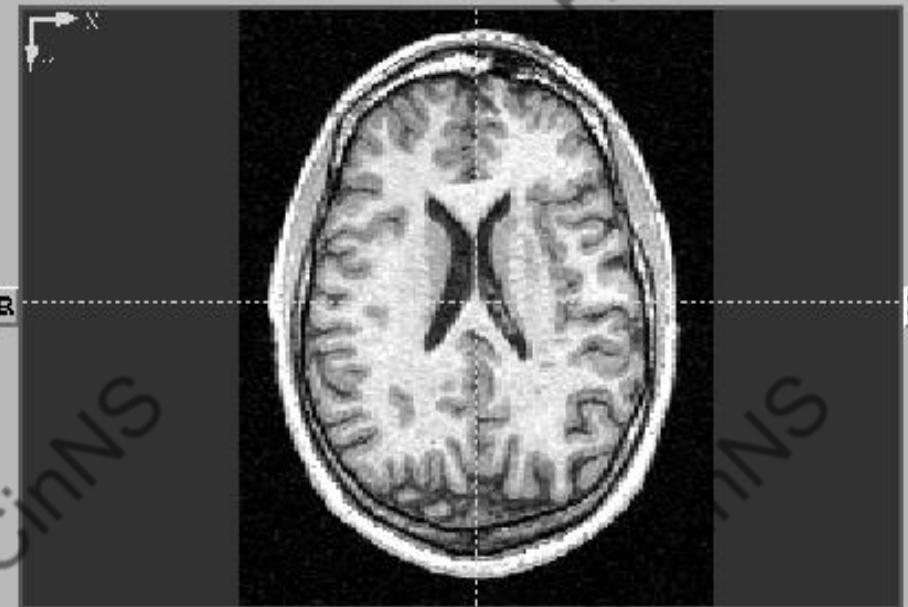
R

I

Transverse

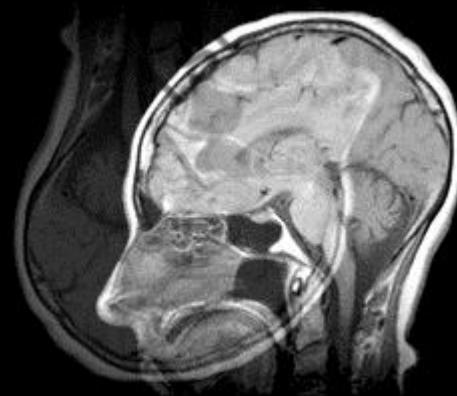
A

200



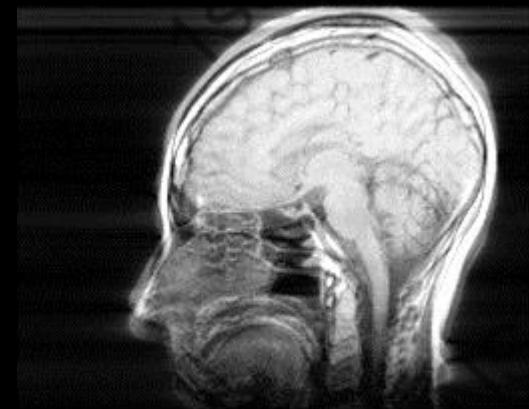
P

Ghost artifact

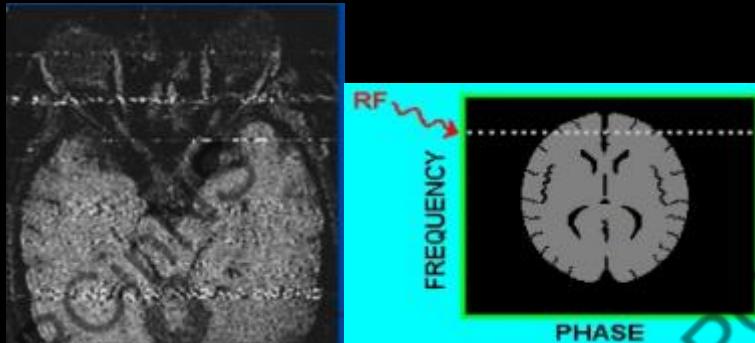


(c) BMRI, ILS

Motion artifact



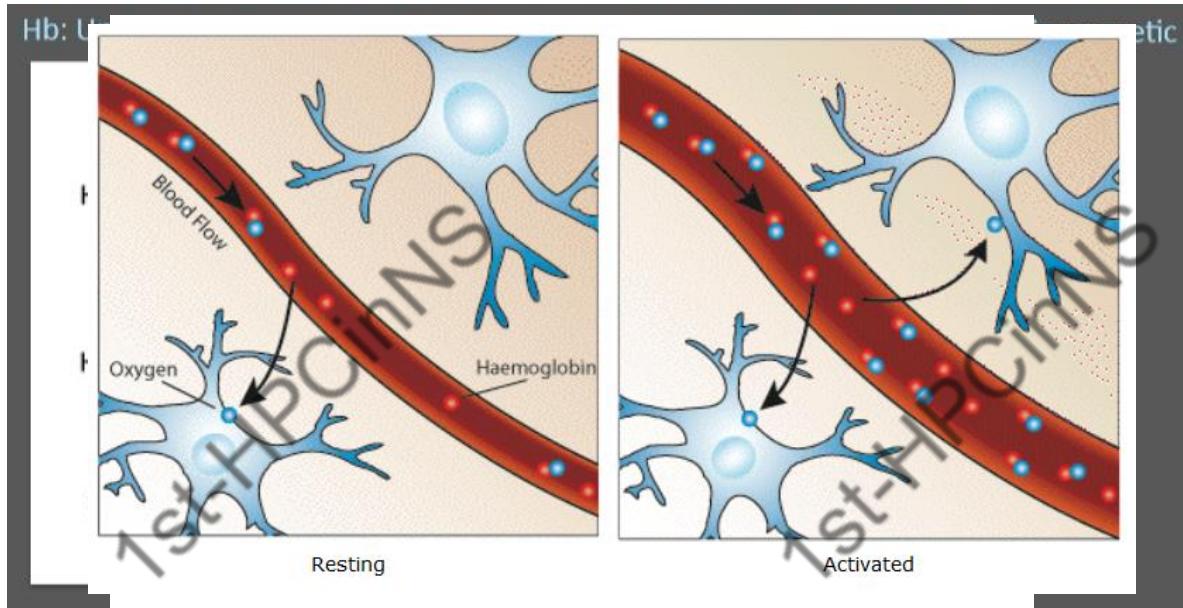
Zipper artifact



Magnetic susceptibility

Susceptibility (χ): degree of magnetization of a material in response to an applied magnetic field

- ❖ Ferromagnetism
- ❖ Diamagnetism
- ❖ Paramagnetism



BOLD fMRI

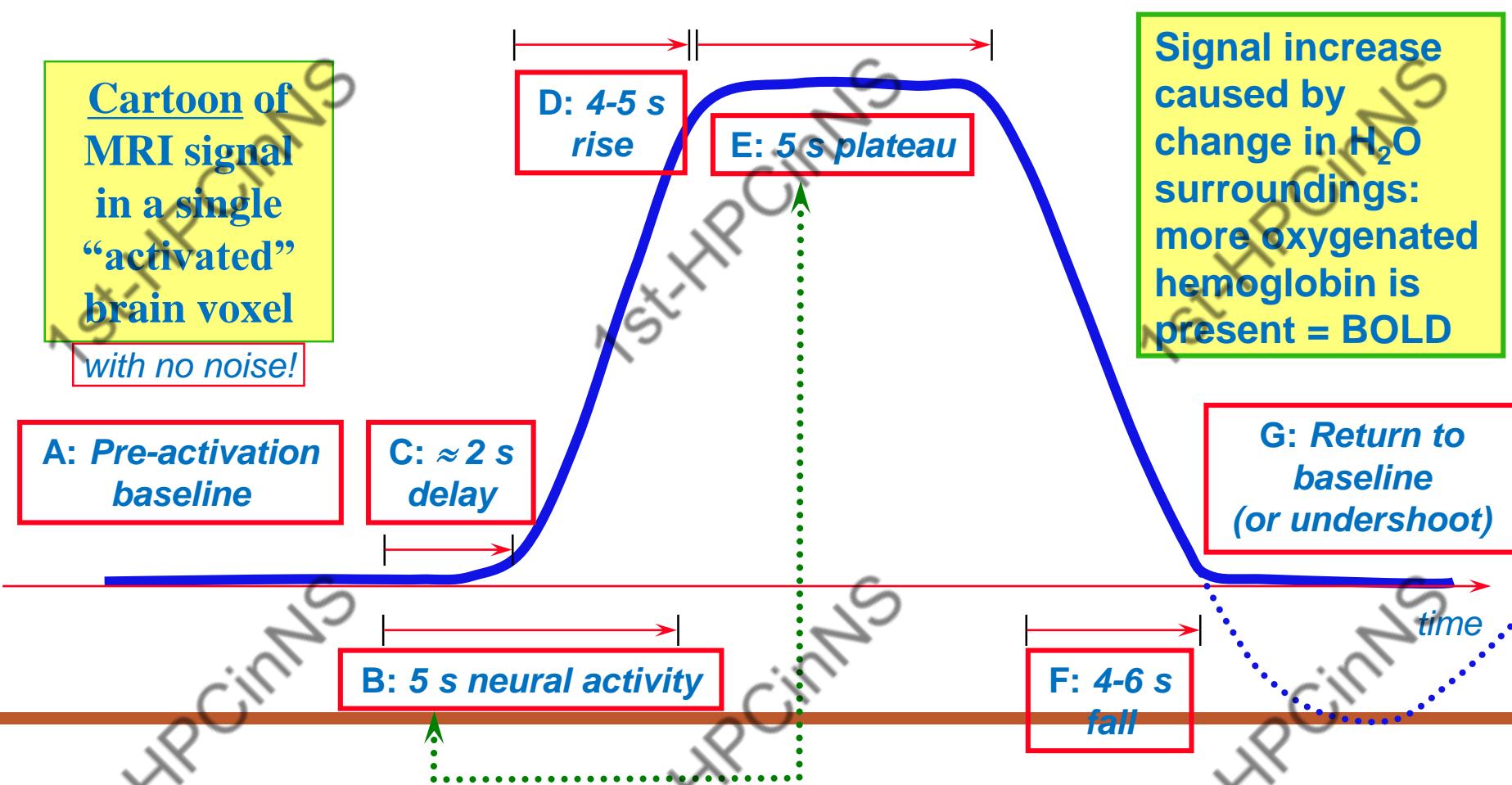
The most common approach: Blood Oxygenation Level Dependent (BOLD)

BOLD fMRI measures the ratio of oxygenated to deoxygenated hemoglobin in the blood.

It is important to note that BOLD fMRI doesn't measure neuronal activity directly, instead it measures the metabolic demands (oxygen consumption) of active neurons.

What is Functional MRI?

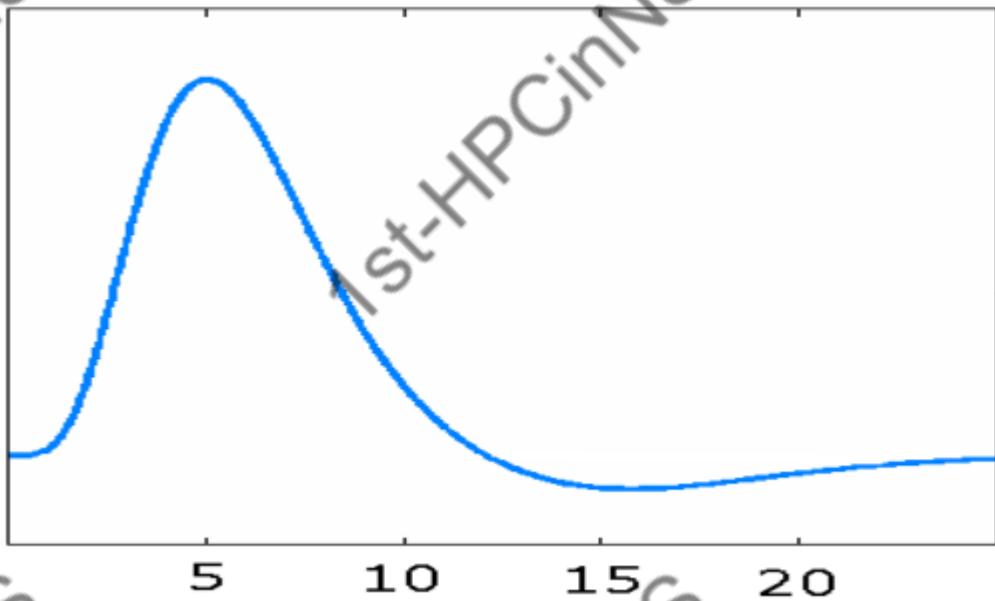
1991: Discovery that MRI-measurable signal increases a few % *locally* in the brain after increases in neuronal activity (Kwong, et al.)



Hemodynamic Response Function (HRF)

HRF represents changes in the fMRI signal triggered by neuronal activity.

- Different based on persons and regions.



LTI System

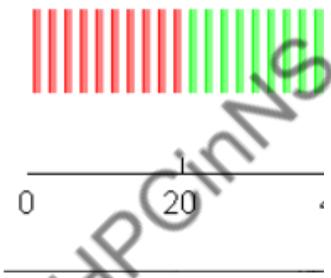
- The relationship between stimuli and the BOLD response is often modeled using a **linear time invariant (LTI)** system.
 - Here the neuronal activity acts as the input or impulse and the HRF acts as the impulse response function.
- In this framework the signal at time t , $x(t)$, is modeled as the convolution of a stimulus function $v(t)$ and the hemodynamic response $h(t)$, that is,

$$x(t) = (v * h)(t)$$

Experimental Design

- Blocked

Blocked



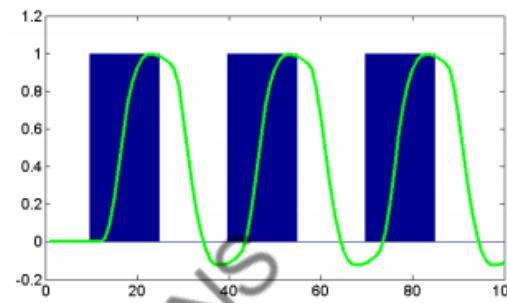
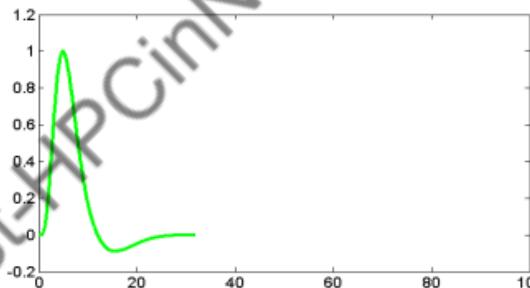
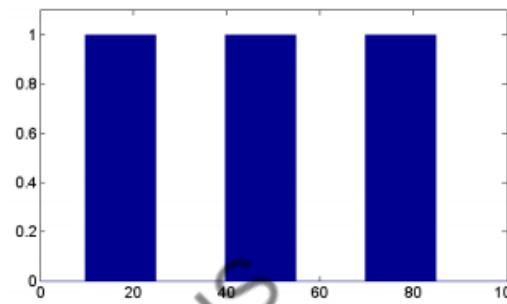
Experimental
Stimulus Function

Hemodynamic
Response
Function

Predicted
Response

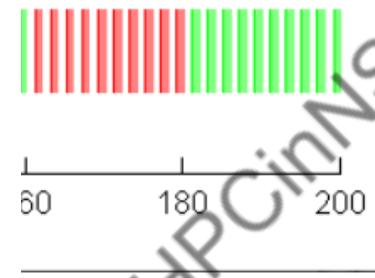
- High stat robust to
- Can't dire

Block Design



uped

Condition A
Condition B



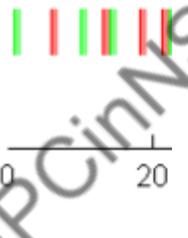
on and
HRF.

HRF.

Experimental Design

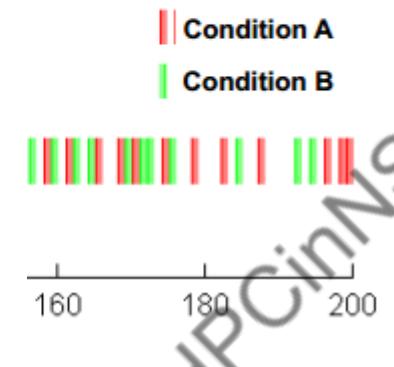
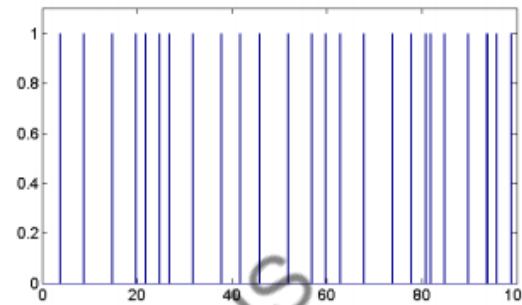
- Event

Event Stimulus Function



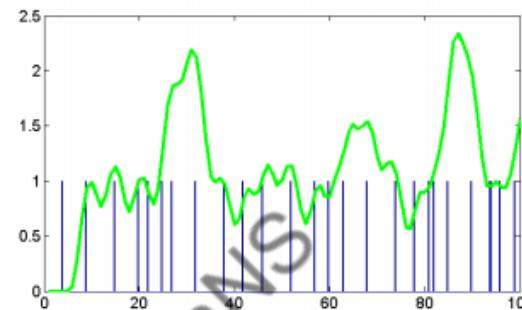
Hemodynamic Response Function

Event-Related

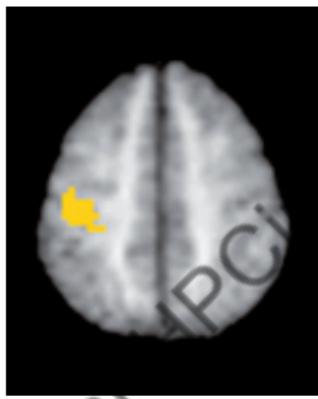
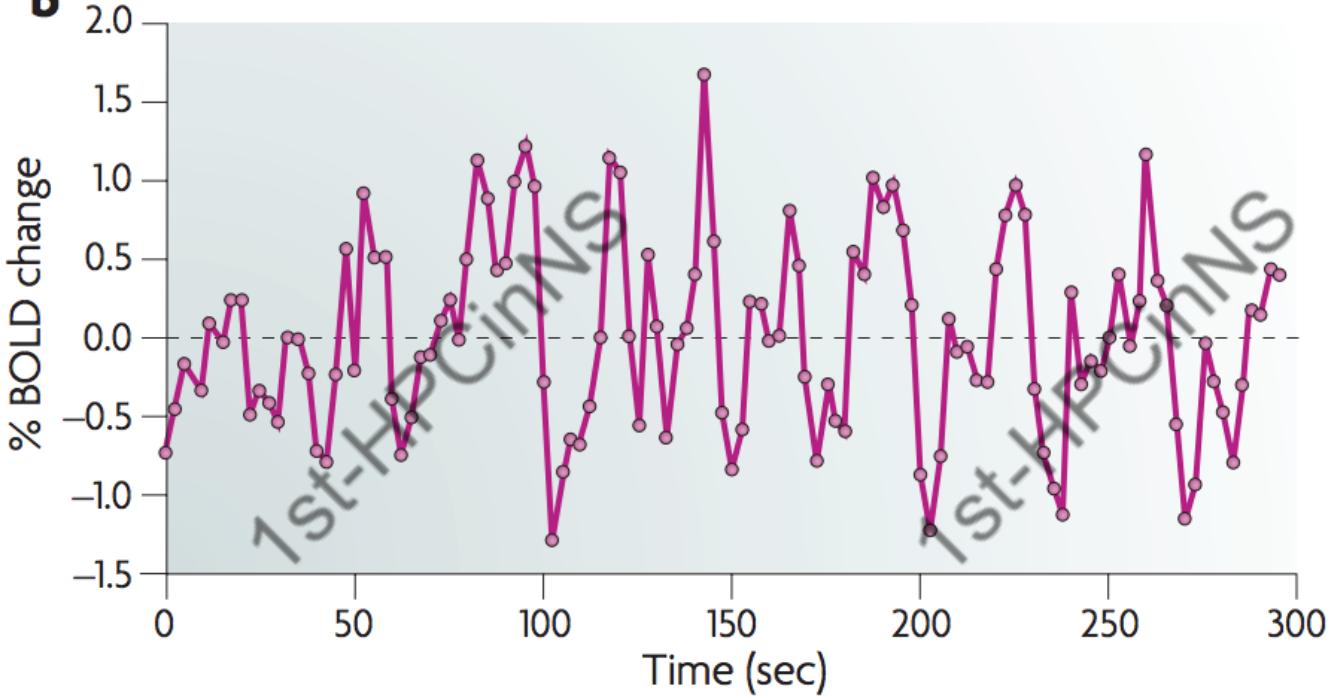


- Allow
- Decrease

Predicted Response



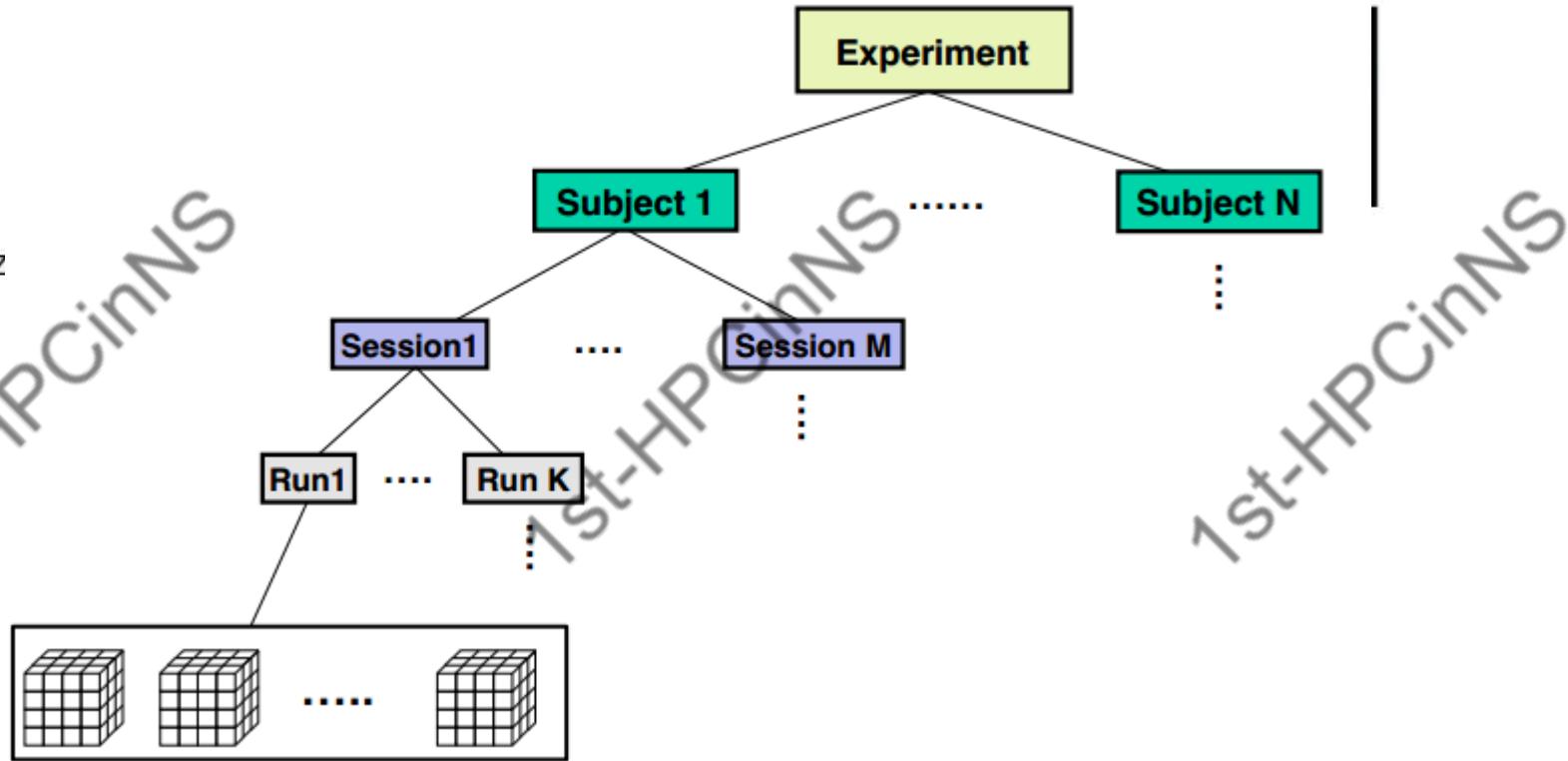
if the HRF.

a**b**

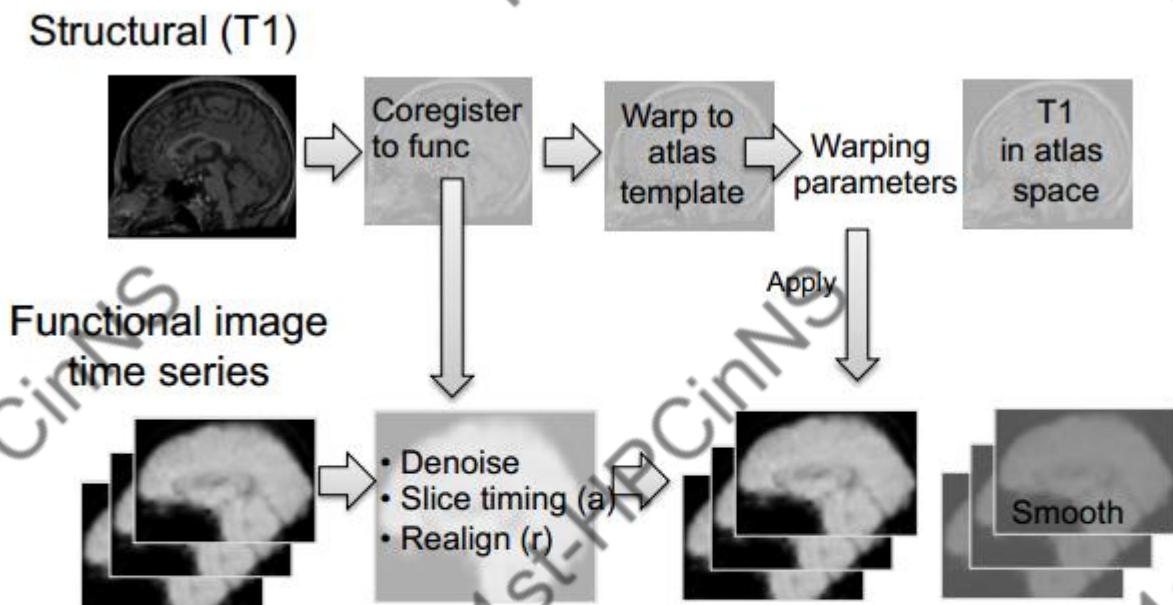
Five Guidelines for fMRI Design

1. Scan as many subjects as possible; scan as long as you can, considering psychological effects (fatigue, habituation).
2. Use short blocks (< 40 s) if you care about detecting differences, and event-related designs if you want to link activity to particular events.
3. Limit the number of conditions; pairwise comparisons far apart in time decrease power and overlap with low frequency noise
4. In event-related designs, randomize the ordering of events that are close together in time
5. Randomize ('jitter') intervals between events that need to be distinguished.

fMRI Data Structure- Terminology



Pre-processing Pipeline

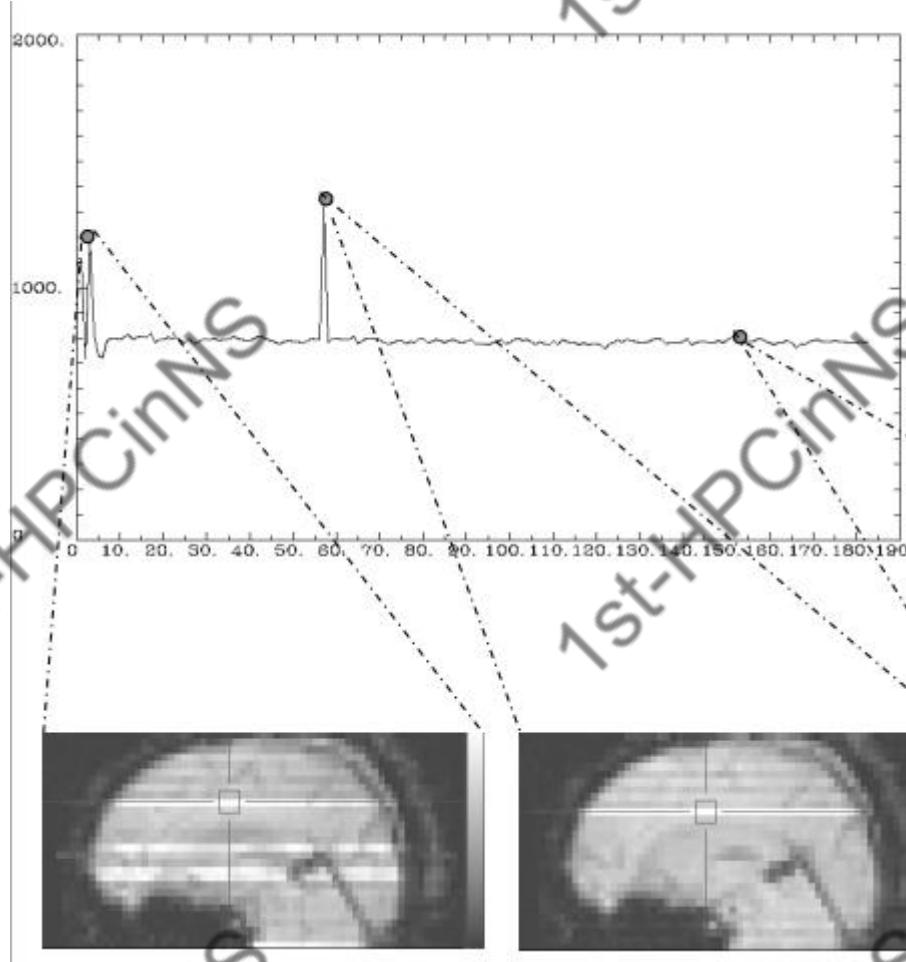


Preprocessing is performed both on the fMRI data and structural scans collected prior to the experiment.

Pre-processing Steps

- Visualization and Artifact Removal
- Slice Time Correction
- Motion Correction
- Physiological Corrections
- Co-registration
- Normalization
- Spatial Filtering
- Temporal Filtering

Visualization & Artifact Removal



Transient spike artifacts in the data during isolated volume acquisitions are apparent in certain slices, as shown by the bright bands in the sagittal slices (bottom). This suggests that gradient performance was affected during acquisition of some echo-planar images, which were acquired slice-by-slice in interleaved order in this experiment.

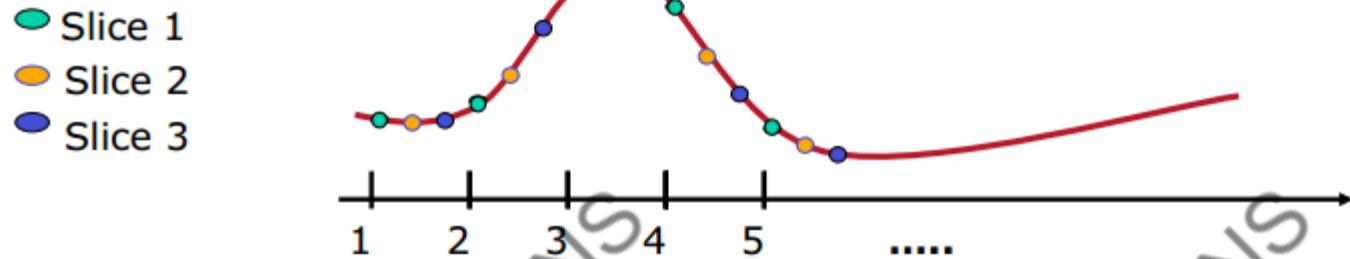
Slice Time Correction

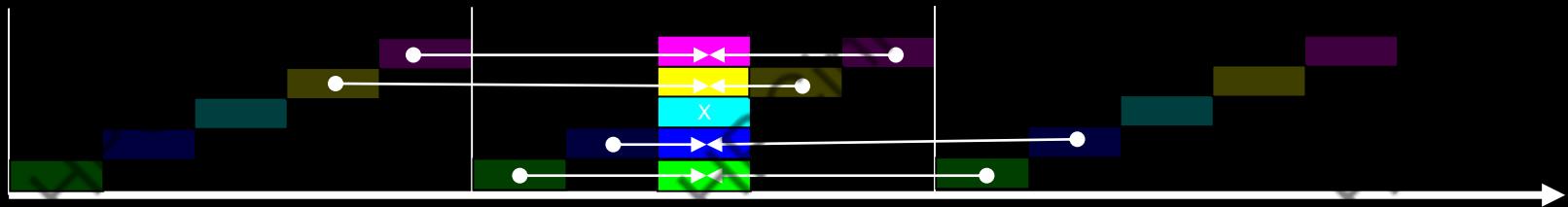
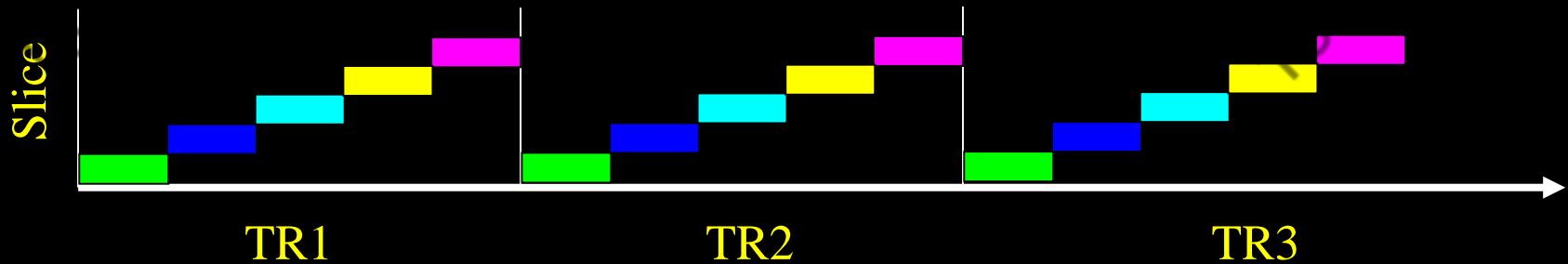
Temporal Interpolation

- Use information from nearby time points to estimate the amplitude of the MR signal at the onset of the TR.
- Use a linear, spline or sinc function.

Phase Shift

- Slide the time course by applying a phase shift to the Fourier transform of the time course.

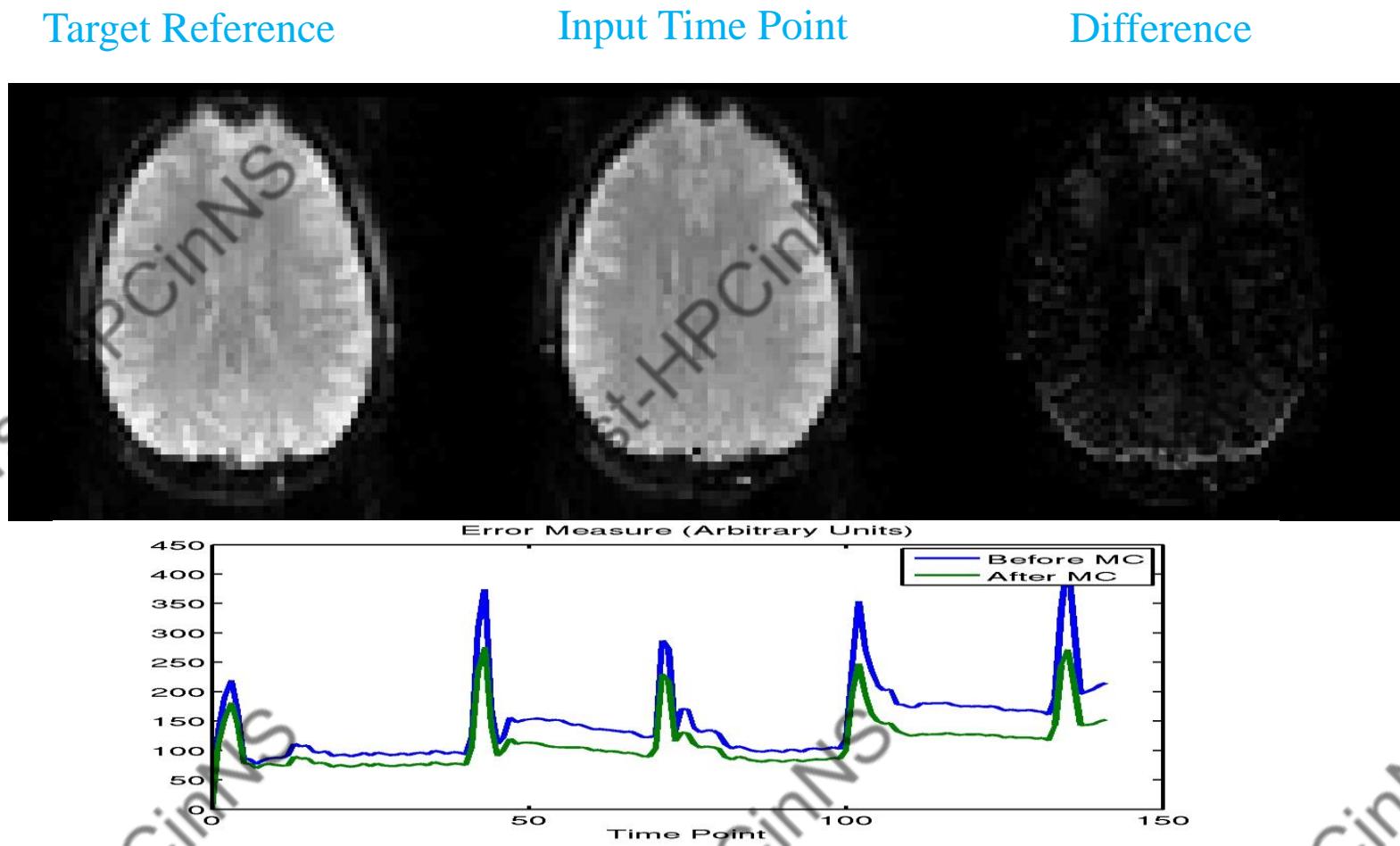




- Temporal interpolation of adjacent time points
- Usually sinc interpolation
- Each slice gets a different interpolation
- Some slices might not have any interpolation
- Can also be done in the GLM
- You must know the slice order!

Head Motion

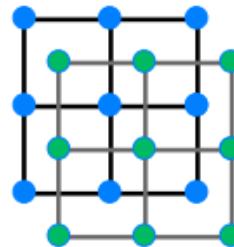
The goal is to find the best possible alignment between an input image and some target image.



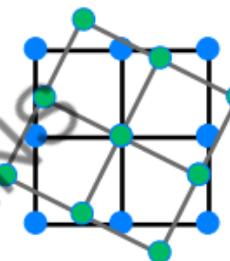
Head Motion

A rigid body transformation is used.

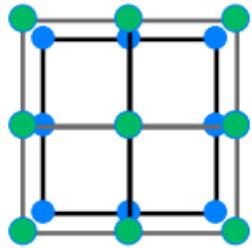
Translation



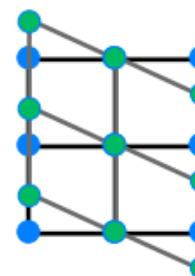
Rotation



Scaling



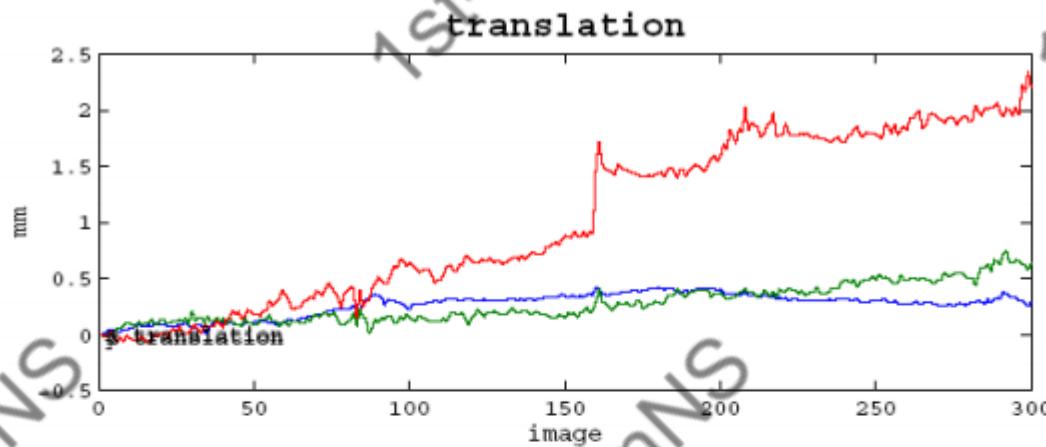
Shearing



Transformations

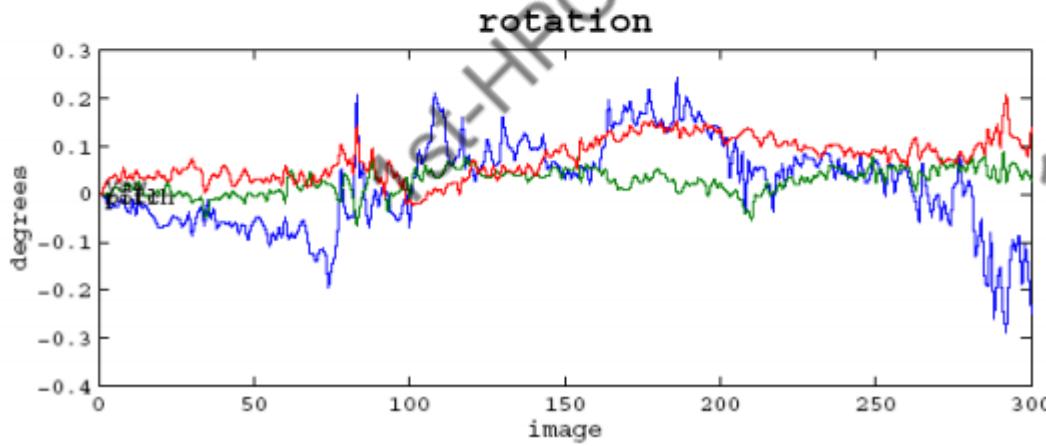
Linear transf

- Rigid body
- Similarity
- global scale
- Affine (12 degrees of freedom)
- shearing.

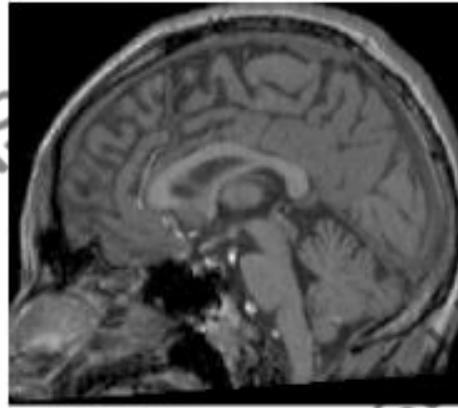
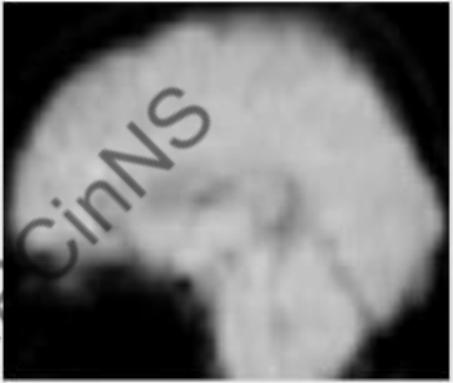


Warping

Transform coordinate



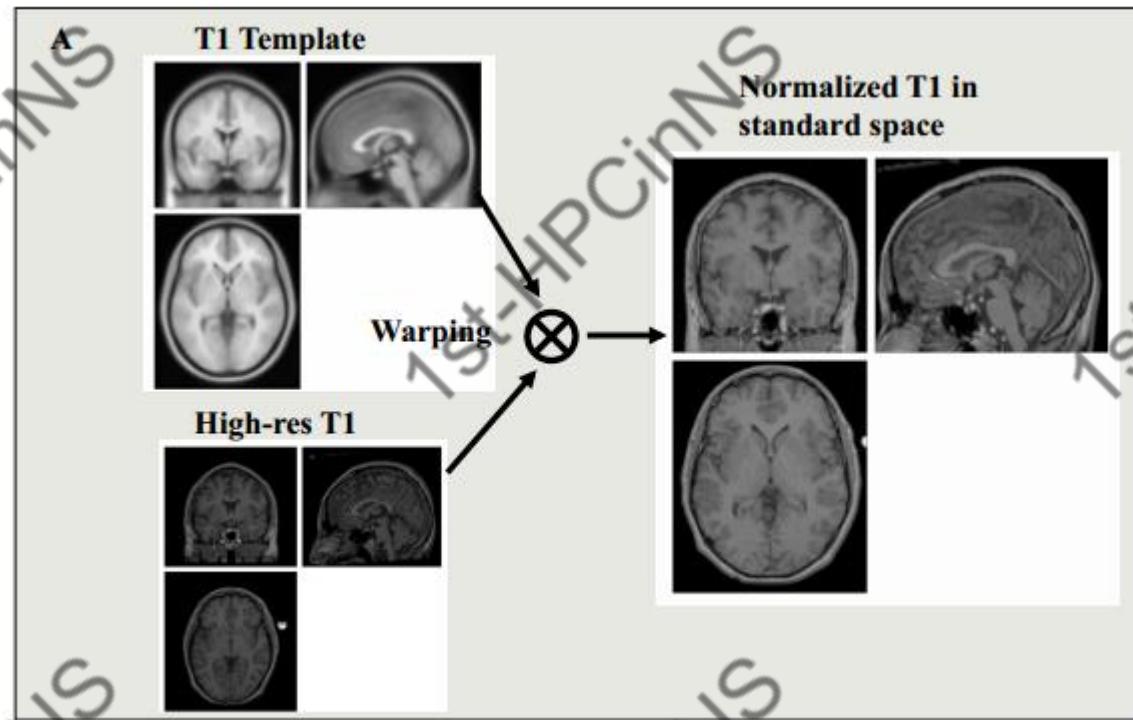
Coregistration



Spatial Normalization

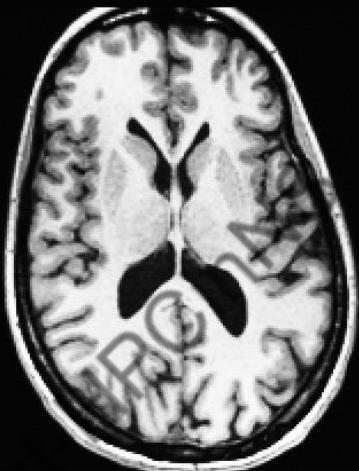
All brains are different. The brain size of two subjects can differ in size by up to 30%.

- There may also be substantial variation in the shapes of the brain.

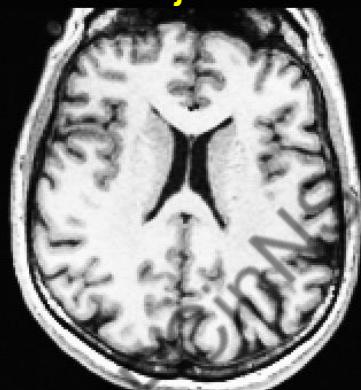


Native Space

Subject 1

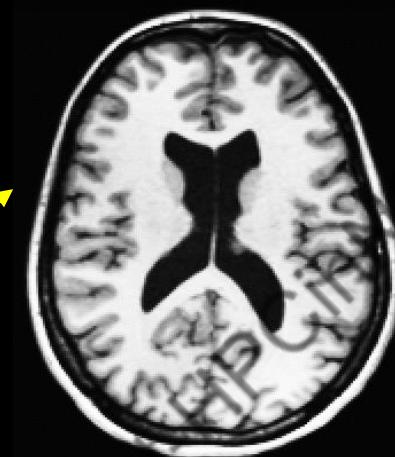


Subject 2

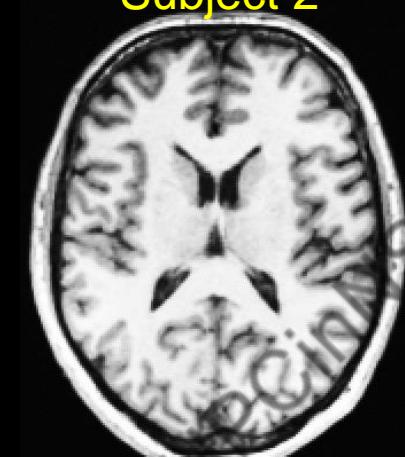


MNI Space

Subject 1



Subject 2



MNI152

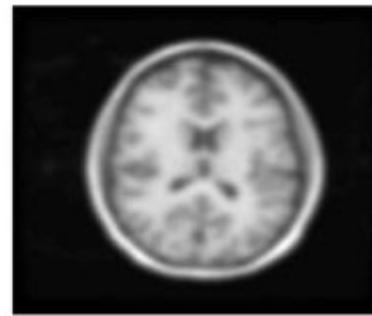
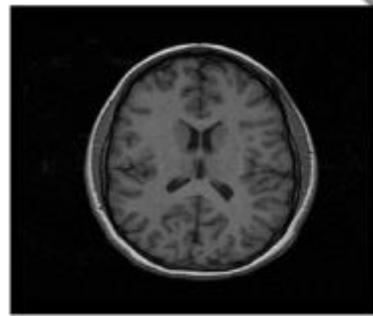
Affine (12 DOF) Registration

Normalization Methods

- Landmark-based methods
 - Align anatomical features in different brains
- Volume-based registration
 - Linear (e.g. affine) and nonlinear transformations
- Computational Anatomy
 - Diffeomorphic transformations
- Surface-based methods
 - Work on cortical surfaces

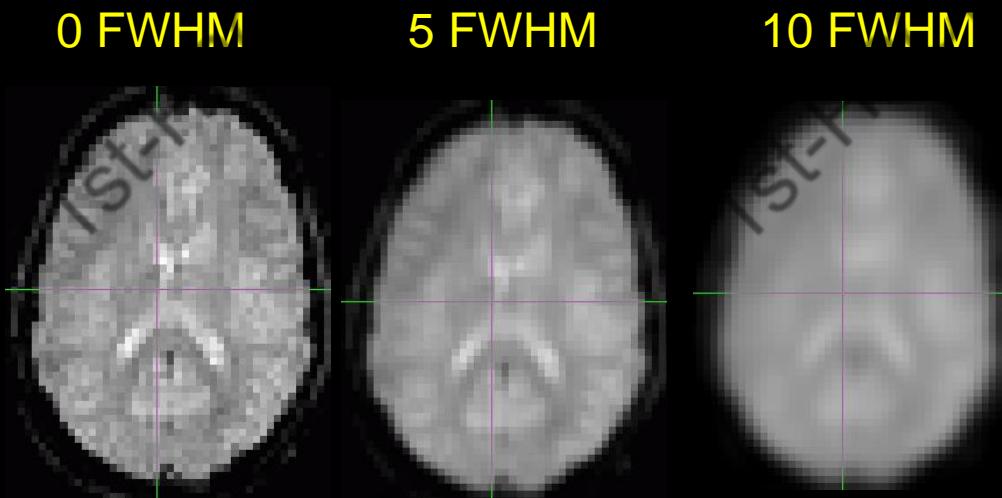
Spatial Smoothing

- In fMRI it is common to **spatially smooth** the acquired data prior to statistical analysis.
- Can increase signal-to-noise, validate distributional assumptions and remove artifacts.

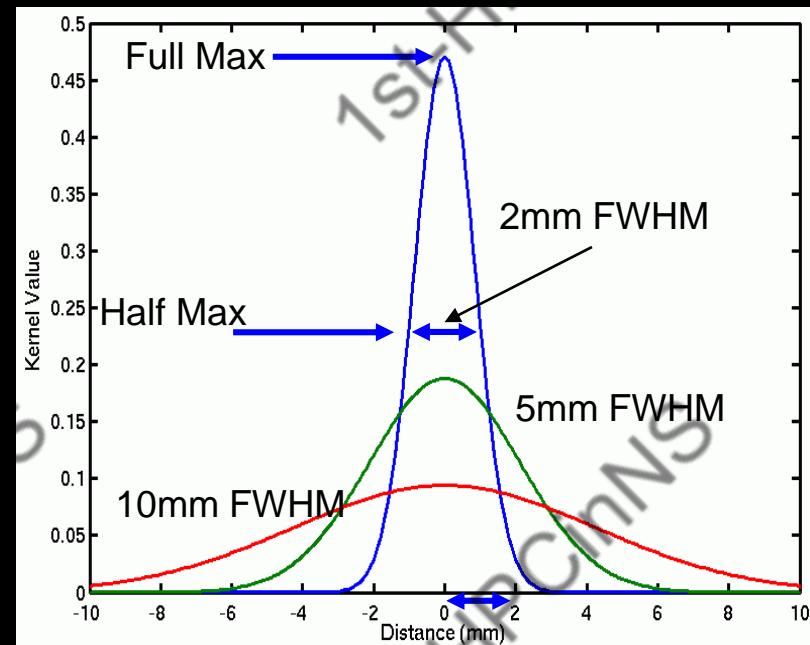


Spatial Smoothing

- Spatially convolve image with Gaussian kernel.
- Kernel sums to 1
- Full-Width/Half-max: $\text{FWHM} = \sigma/\sqrt{\log(256)}$
 σ = standard deviation of the Gaussian

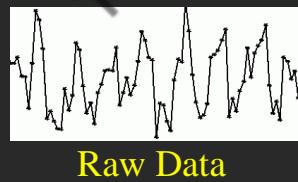


Full-Width/Half-max



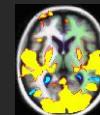
fMRI Analysis Overview

Subject 1



Preprocessing
MC, STC, B0
Smoothing
Normalization

First Level
GLM Analysis



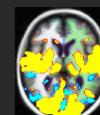
X C

Subject 2



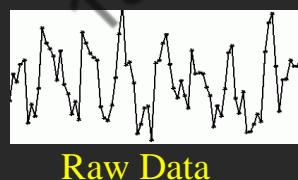
Preprocessing
MC, STC, B0
Smoothing
Normalization

First Level
GLM Analysis



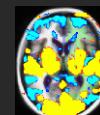
X C

Subject 3



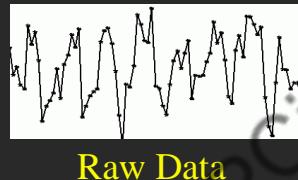
Preprocessing
MC, STC, B0
Smoothing
Normalization

First Level
GLM Analysis



X C

Subject 4

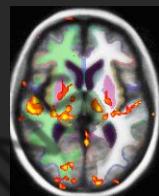
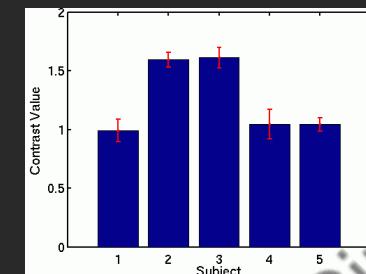


Preprocessing
MC, STC, B0
Smoothing
Normalization

First Level
GLM Analysis



X C



Higher Level GLM

X C

General Linear Model

9 authors are submitting papers for a special edition.

older authors are submitting their articles later than younger authors ?

y_i = Days after the deadline that author i submitted their article

x_i = Age of author i

First Guess -> straight line relationship between the number of days late y_i and age x_i

$$y_i = \beta_0 + \beta_1 x_i + \epsilon_i.$$

General Linear Model

$$\begin{bmatrix} y_1 \\ y_2 \\ y_3 \\ y_4 \\ y_5 \\ y_6 \\ y_7 \\ y_8 \\ y_9 \end{bmatrix} = \beta_0 \begin{bmatrix} 1 \\ 1 \\ 1 \\ 1 \\ 1 \\ 1 \\ 1 \\ 1 \\ 1 \end{bmatrix} + \beta_1 \begin{bmatrix} x_1 \\ x_2 \\ x_3 \\ x_4 \\ x_5 \\ x_6 \\ x_7 \\ x_8 \\ x_9 \end{bmatrix} + \begin{bmatrix} \epsilon_1 \\ \epsilon_2 \\ \epsilon_3 \\ \epsilon_4 \\ \epsilon_5 \\ \epsilon_6 \\ \epsilon_7 \\ \epsilon_8 \\ \epsilon_9 \end{bmatrix}.$$

$$\begin{bmatrix} y_1 \\ y_2 \\ y_3 \\ y_4 \\ y_5 \\ y_6 \\ y_7 \\ y_8 \\ y_9 \end{bmatrix} = \begin{bmatrix} 1 & x_1 \\ 1 & x_2 \\ 1 & x_3 \\ 1 & x_4 \\ 1 & x_5 \\ 1 & x_6 \\ 1 & x_7 \\ 1 & x_8 \\ 1 & x_9 \end{bmatrix} \begin{bmatrix} \beta_0 \\ \beta_1 \end{bmatrix} + \begin{bmatrix} \epsilon_1 \\ \epsilon_2 \\ \epsilon_3 \\ \epsilon_4 \\ \epsilon_5 \\ \epsilon_6 \\ \epsilon_7 \\ \epsilon_8 \\ \epsilon_9 \end{bmatrix}.$$

$$Y = X\beta + \epsilon \quad \epsilon \in N(0, \sigma^2 I)$$

Matrix Formulation

Write out equation for each observation of variable Y from 1 to J:

$$Y_1 = X_{11}\beta_1 + \dots + X_{1I}\beta_I + \dots + X_{1L}\beta_L + \varepsilon_1$$

$$Y_j = X_{j1}\beta_1 + \dots + X_{jI}\beta_I + \dots + X_{jL}\beta_L + \varepsilon_j$$

$$Y_J = X_{J1}\beta_1 + \dots + X_{JI}\beta_I + \dots + X_{JL}\beta_L + \varepsilon_J$$

Can turn these simultaneous equations into matrix form to get a single equation:

$$\begin{pmatrix} Y_1 \\ Y_j \\ Y_J \end{pmatrix} = \begin{pmatrix} X_{11} & \dots & X_{1I} & \dots & X_{1L} \\ X_{j1} & \dots & X_{jI} & \dots & X_{jL} \\ X_{J1} & \dots & X_{JI} & \dots & X_{JL} \end{pmatrix} \begin{pmatrix} \beta_1 \\ \beta_j \\ \beta_J \end{pmatrix} + \begin{pmatrix} \varepsilon_1 \\ \varepsilon_j \\ \varepsilon_J \end{pmatrix}$$
$$Y = X \beta + \varepsilon$$

Observed data

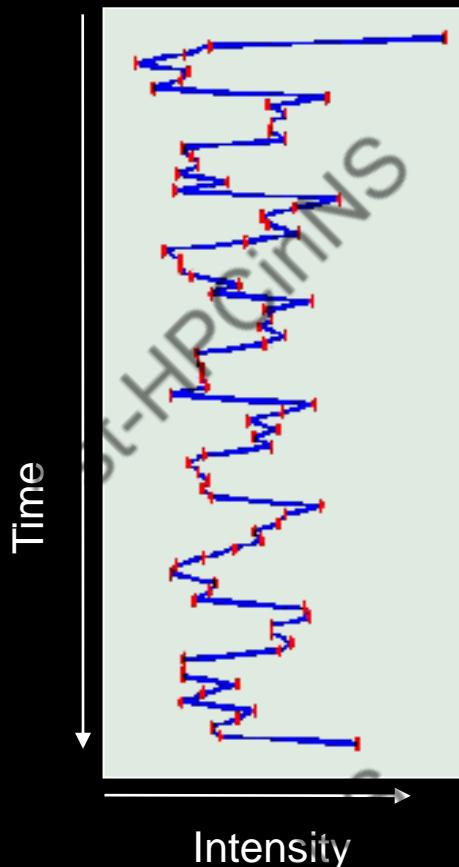
Design Matrix

Parameters

Residuals/Error

Getting the design matrix

Observations



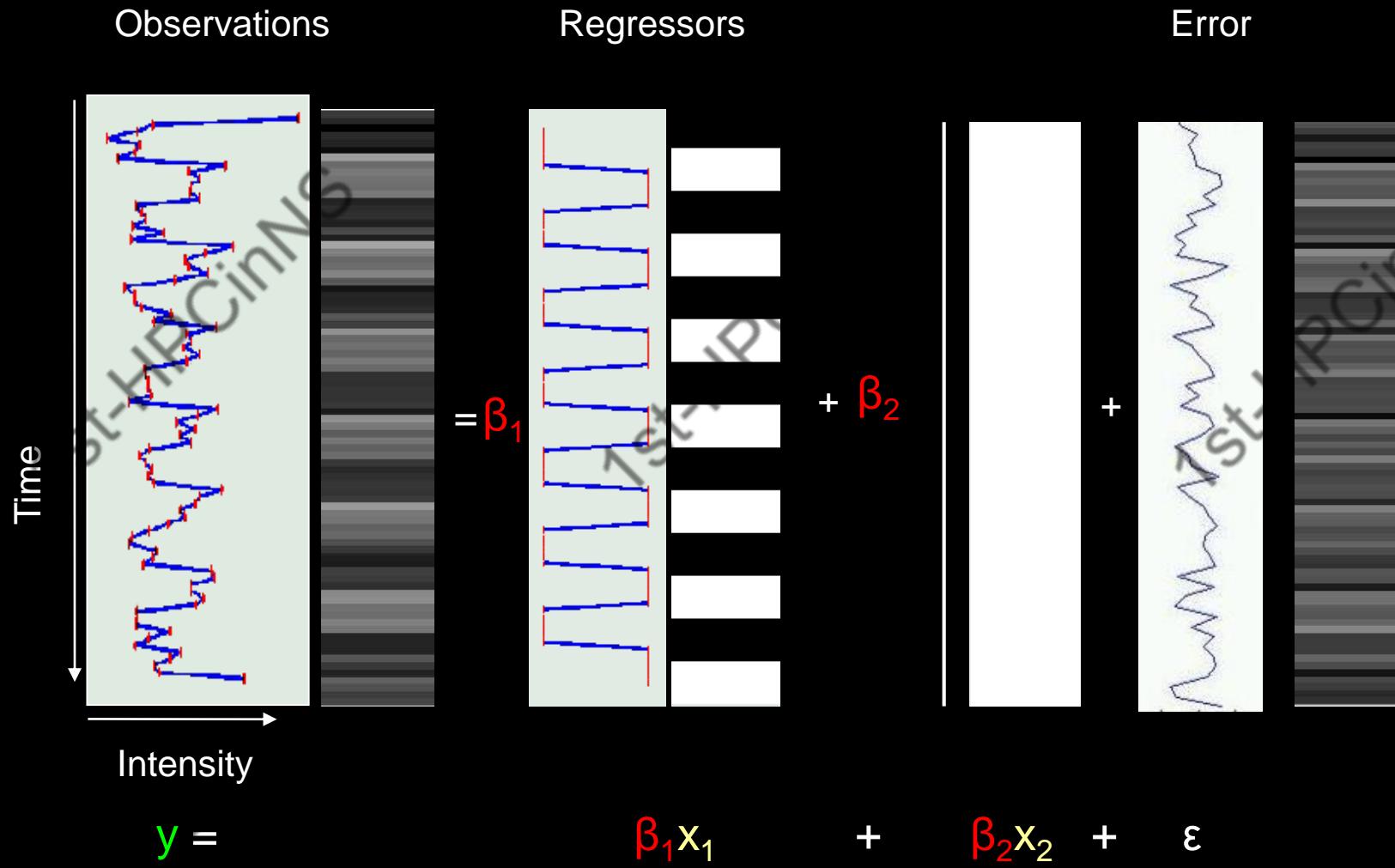
Regressors

$$y = \beta_1 x_1 + \beta_2 x_2 + \varepsilon$$

The equation illustrates the relationship between the observed data y and the regressors x_1 and x_2 . The term ε represents the error term, which is described as being normally and independently and identically distributed.

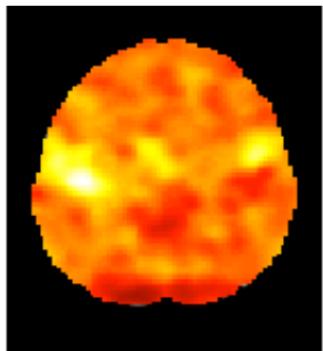
ε
Errors are
normally and
independently
and identically
distributed

Getting the design matrix

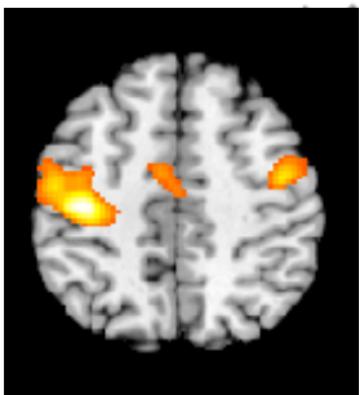


B map, z map

$$H_0 : \mathbf{c}^T \boldsymbol{\beta} = 0$$

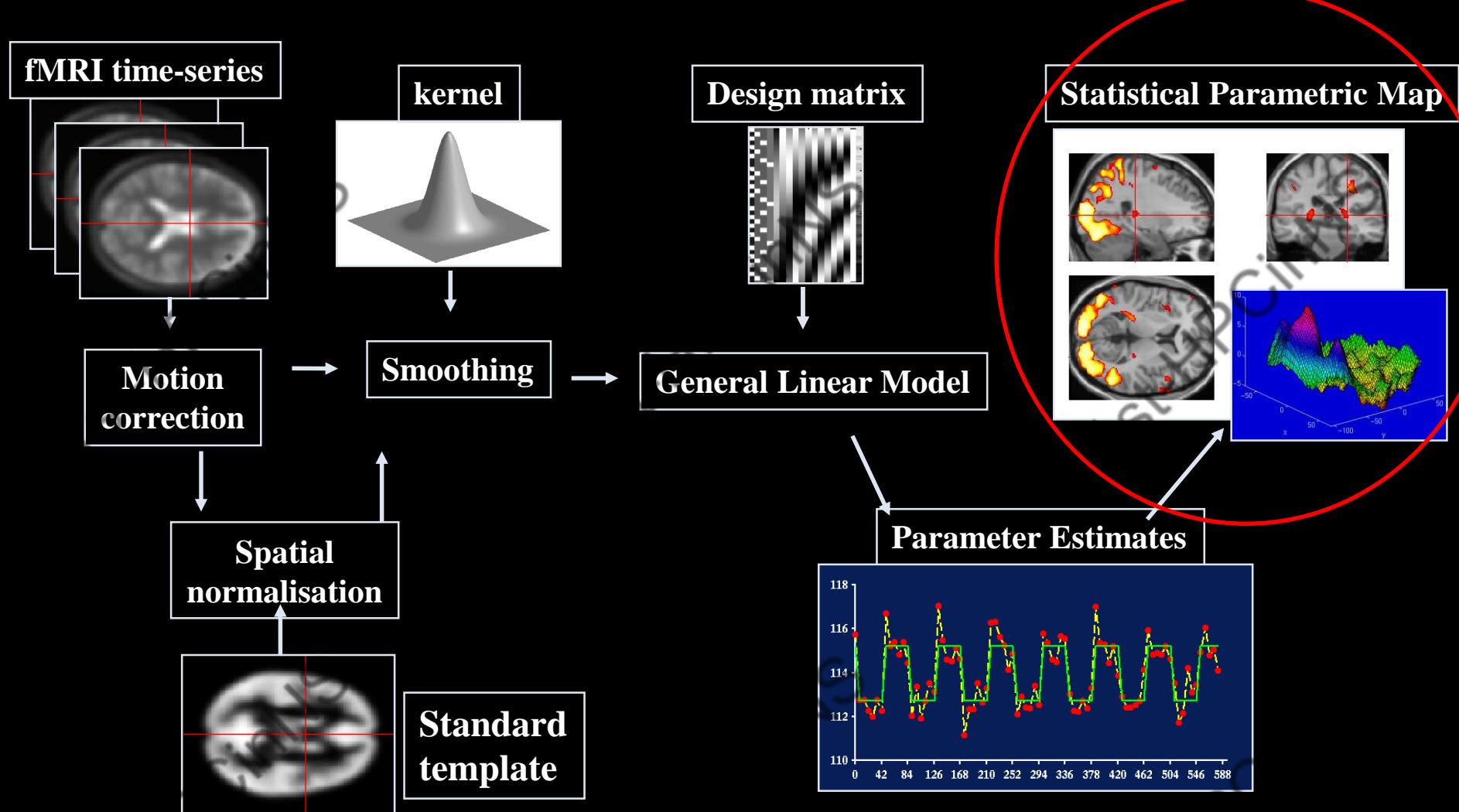


Statistical image:
Map of t-tests
across all voxels
(a.k.a t-map).



Statistical parametric map:
Each significant voxel is
color-coded according to
the size of its p-value.

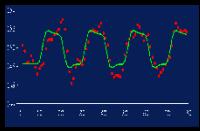
2nd Level Analysis



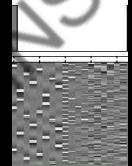
2nd Level Analysis

FIRST LEVEL (per person)

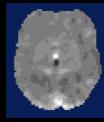
Data



Design Matrix

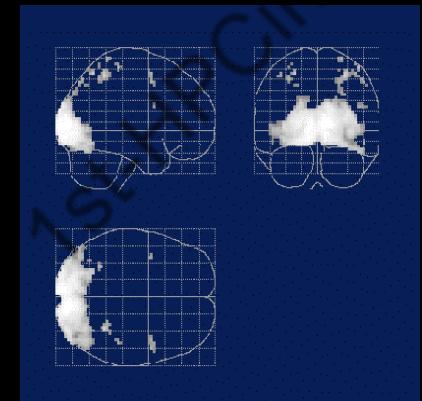
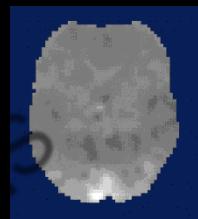
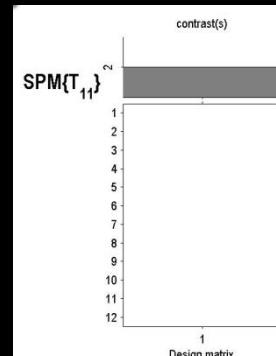
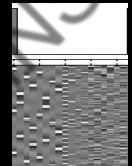
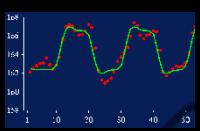
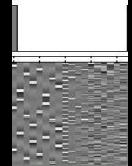
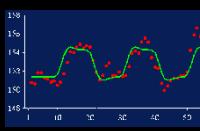
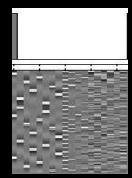
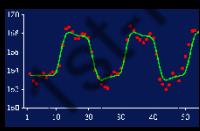


Contrast Image



SECOND LEVEL Group analysis

$$t = \frac{c^T \hat{\alpha}}{\sqrt{\text{Var}(c^T \hat{\alpha})}}$$

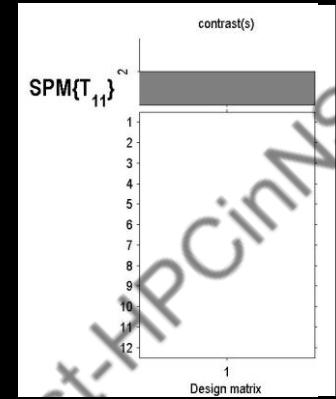


One-sample
t-test @ 2nd level

Stats tests at the 2nd Level

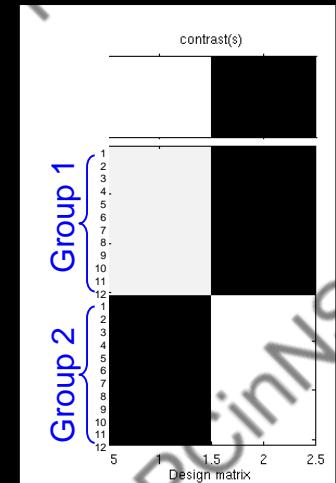
Choose the simplest analysis @ 2nd level : one sample t-test

- Compute within-subject contrasts @ 1st level
- Enter con*.img for each person
- Can also model covariates across the group
 - vector containing 1 value per con*.img,



If you have 2 subject groups: two sample t-test

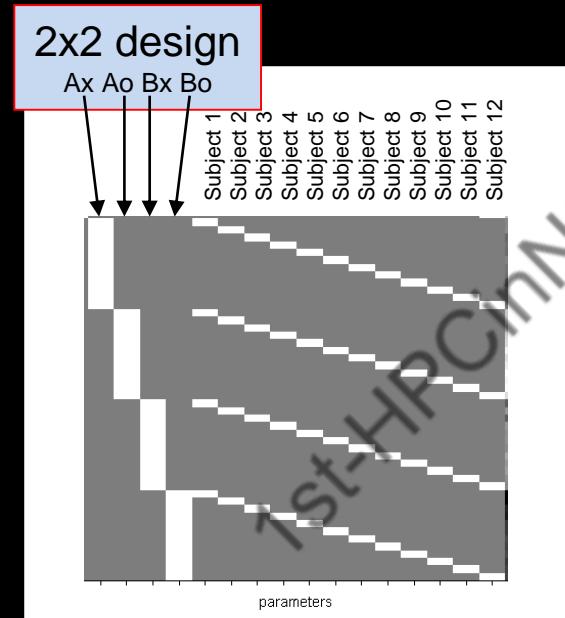
- Same design matrices for all subjects in a group
- Enter con*.img for each group member
- Not necessary to have same no. subject in each group
- Assume measurement independent between groups
- Assume unequal variance between each group



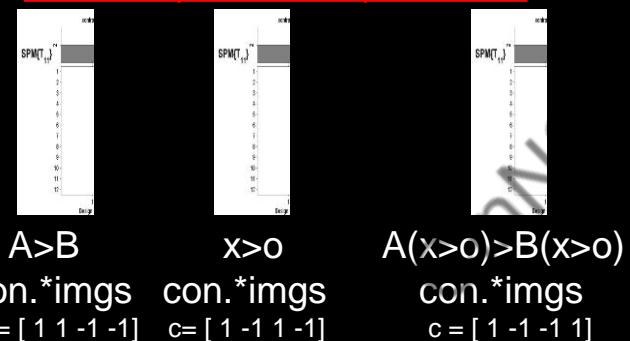
Stats tests at the 2nd Level

If you have no other choice: ANOVA

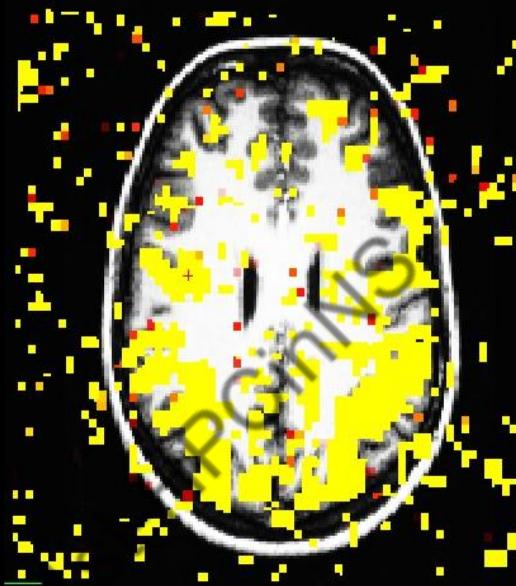
- Designs are much more complex
e.g. within-subject ANOVA need covariate per subject →
- **BEWARE** sphericity assumptions may be violated, need to account for
- Better approach:
 - generate main effects & interaction contrasts at 1st level
 $c = [1 \ 1 \ -1 \ -1]$; $c = [1 \ -1 \ 1 \ -1]$; $c = [1 \ -1 \ -1 \ 1]$
 - use separate t-tests at the 2nd level →



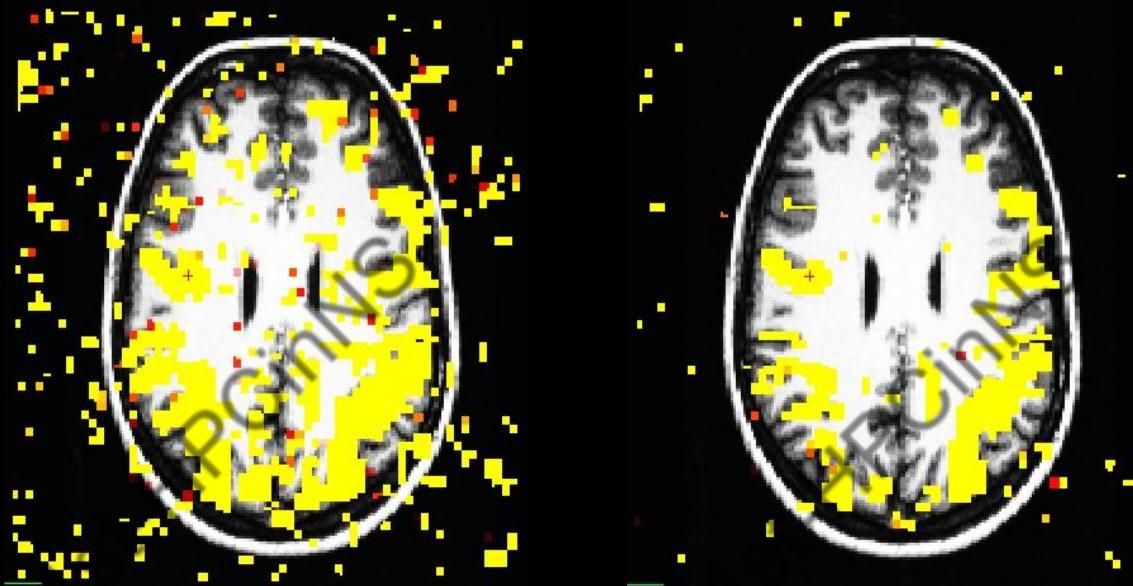
One sample t-test equivalents:



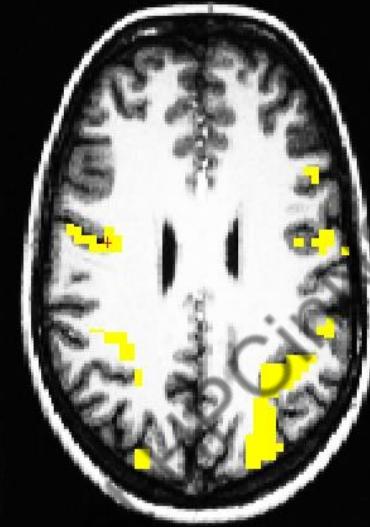
Problem of Multiple Comparisons



$p < 0.10$



$p < 0.01$



$p < 10^{-7}$

p value is probability that a voxel is falsely activated

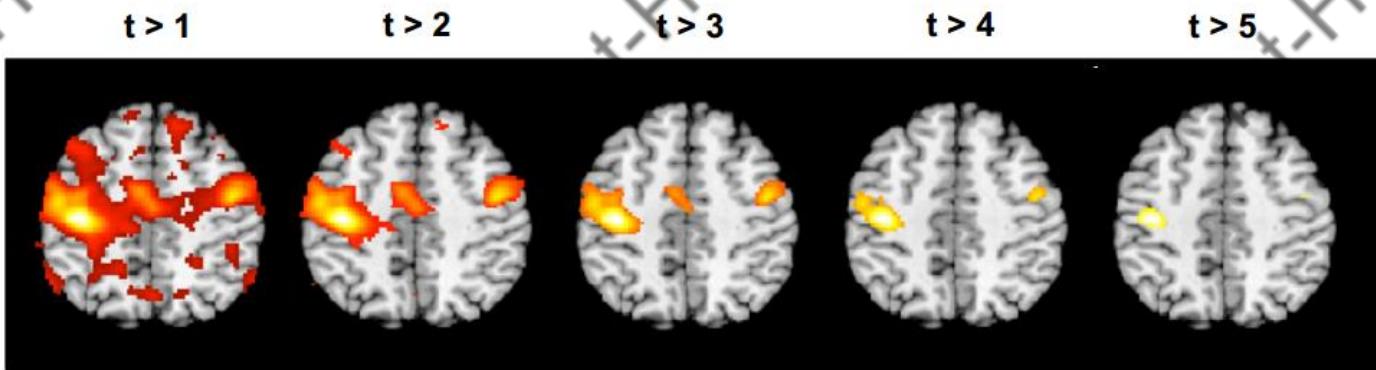
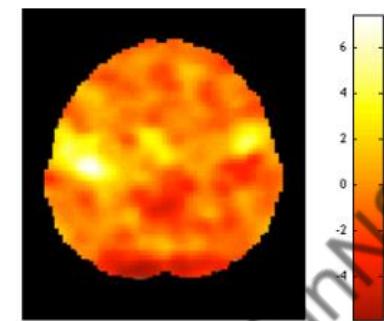
Threshold too liberal: many false positives

Threshold too restrictive: lose activation (false negatives)

Multiple Comparison

- F • Which of 100,000 voxels are significant?
 - $\alpha=0.05 \Rightarrow 5,000$ false positive voxels

- F • Choosing a threshold is a balance between sensitivity (**true positive rate**) and specificity (**true negative rate**).



	BV	SPM	FSL
Platform	All	All	Unix
Cost	\$\$\$	Free (\$)	Free
Interface	GUI/script	GUI/Matlab	GUI/Shell
Norm.	Talairach	MNI	MNI
Documentation	Good(ish)	Improving	Non-existent
Speed	V. Fast	Slow(ish)	Fast
Visualisation	Great	OK (add-ons)	Good
Advanced Features	Built-in	Add-on Toolboxes	DIY
Development	Agile	Cathedral	KISS/WIS

Further readings

Physics:

Kanal, E., and Michael L. Lipton. *Totally accessible MRI: a user's guide to principles, technology, and applications*. Springer Science & Business Media, 2010.

Hashemi, Ray Hashman, William G. Bradley, and Christopher J. Lisanti. *MRI: the basics*. Lippincott Williams & Wilkins, 2012.

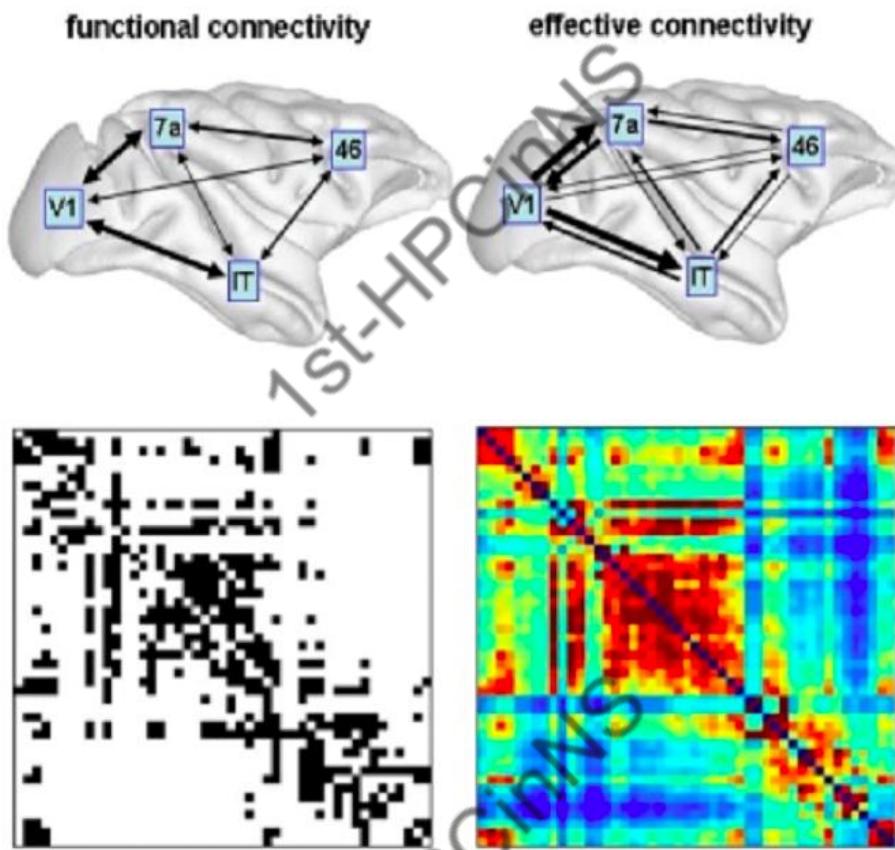
Brown, Robert W., et al. *Magnetic resonance imaging: physical principles and sequence design*. John Wiley & Sons, 2014.

Analysis:

Ashby, F. Gregory. *Statistical analysis of fMRI data*. MIT press, 2011.

Poldrack, Russell A., Jeanette A. Mumford, and Thomas E. Nichols. *Handbook of functional MRI data analysis*. Cambridge University Press, 2011.

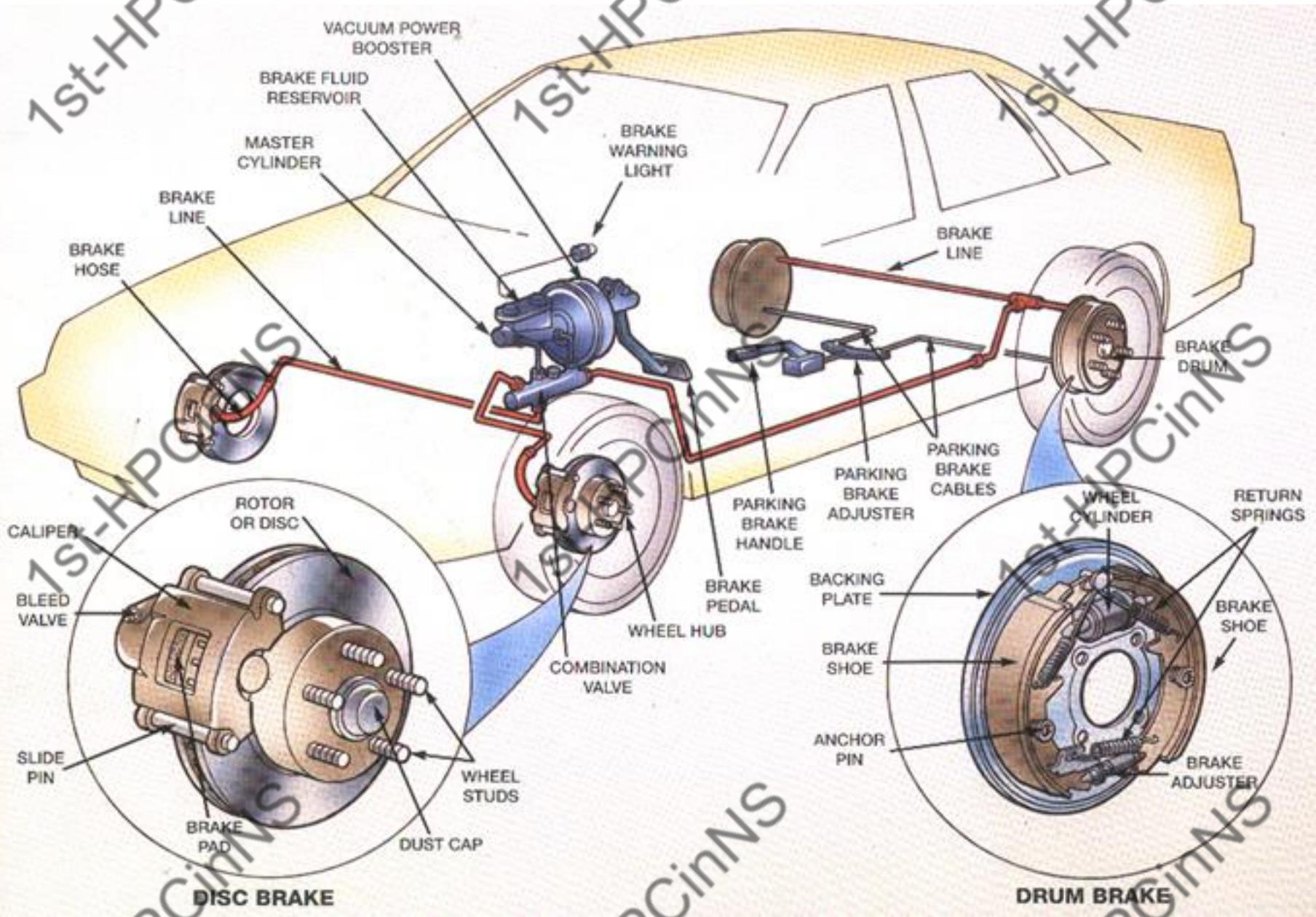
Functional connectivity & Graph theory



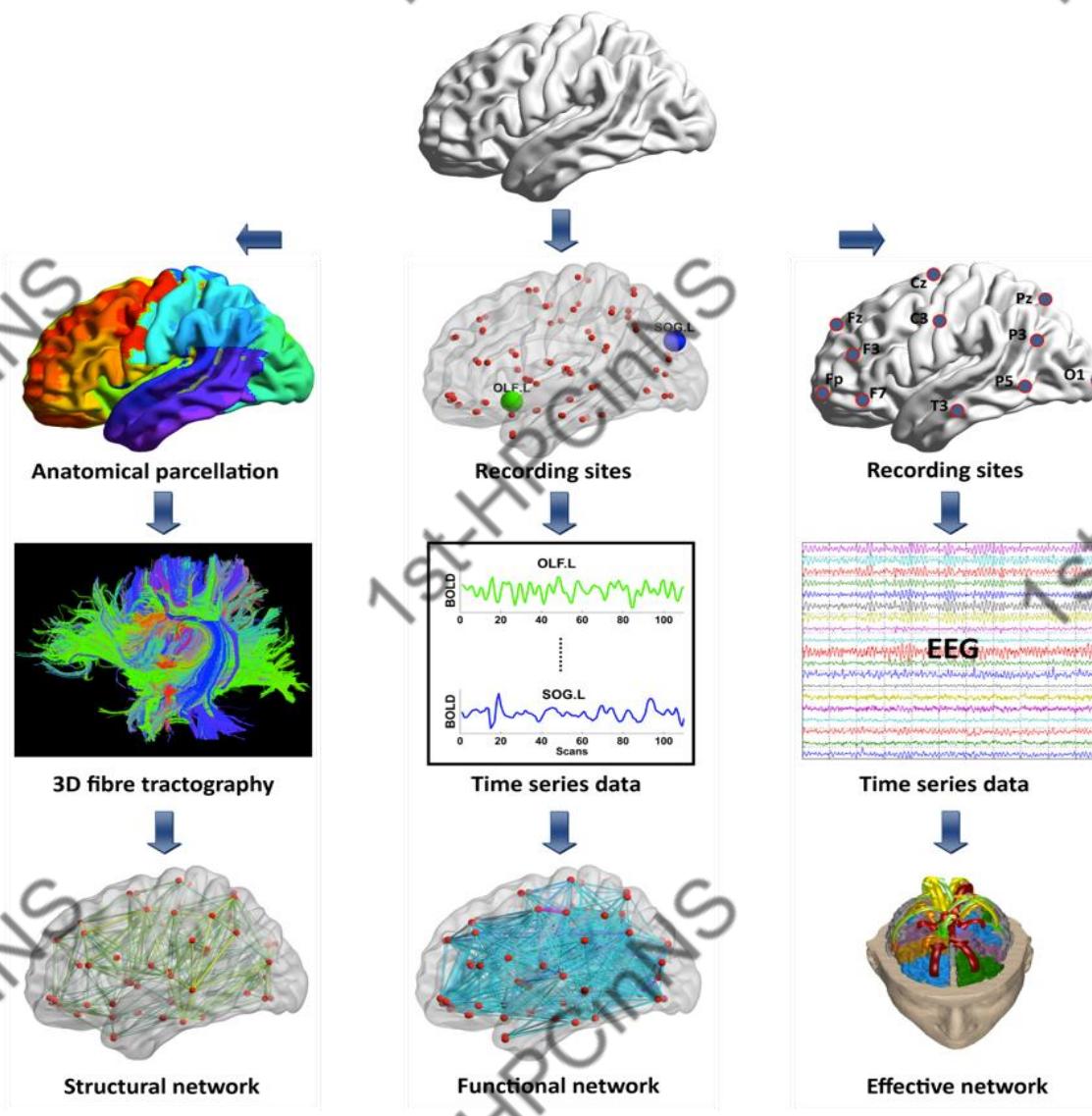






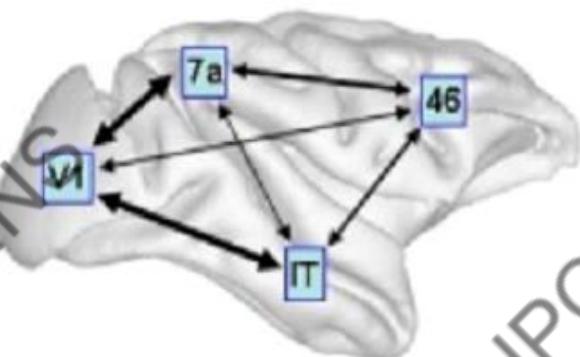


Brain Connectivity

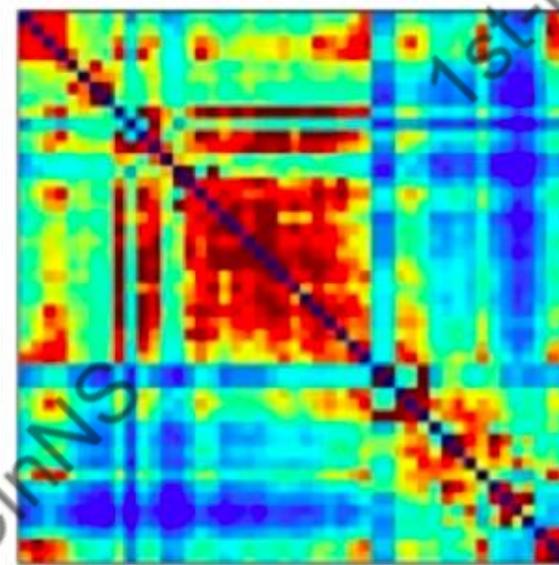
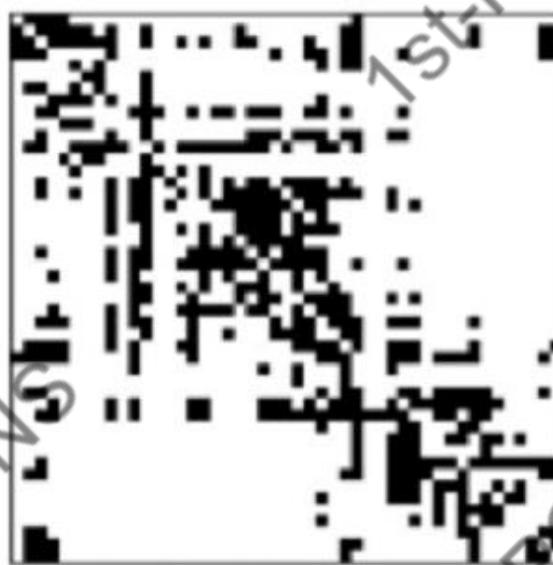
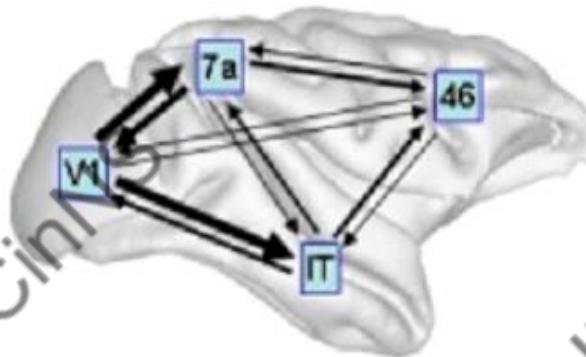


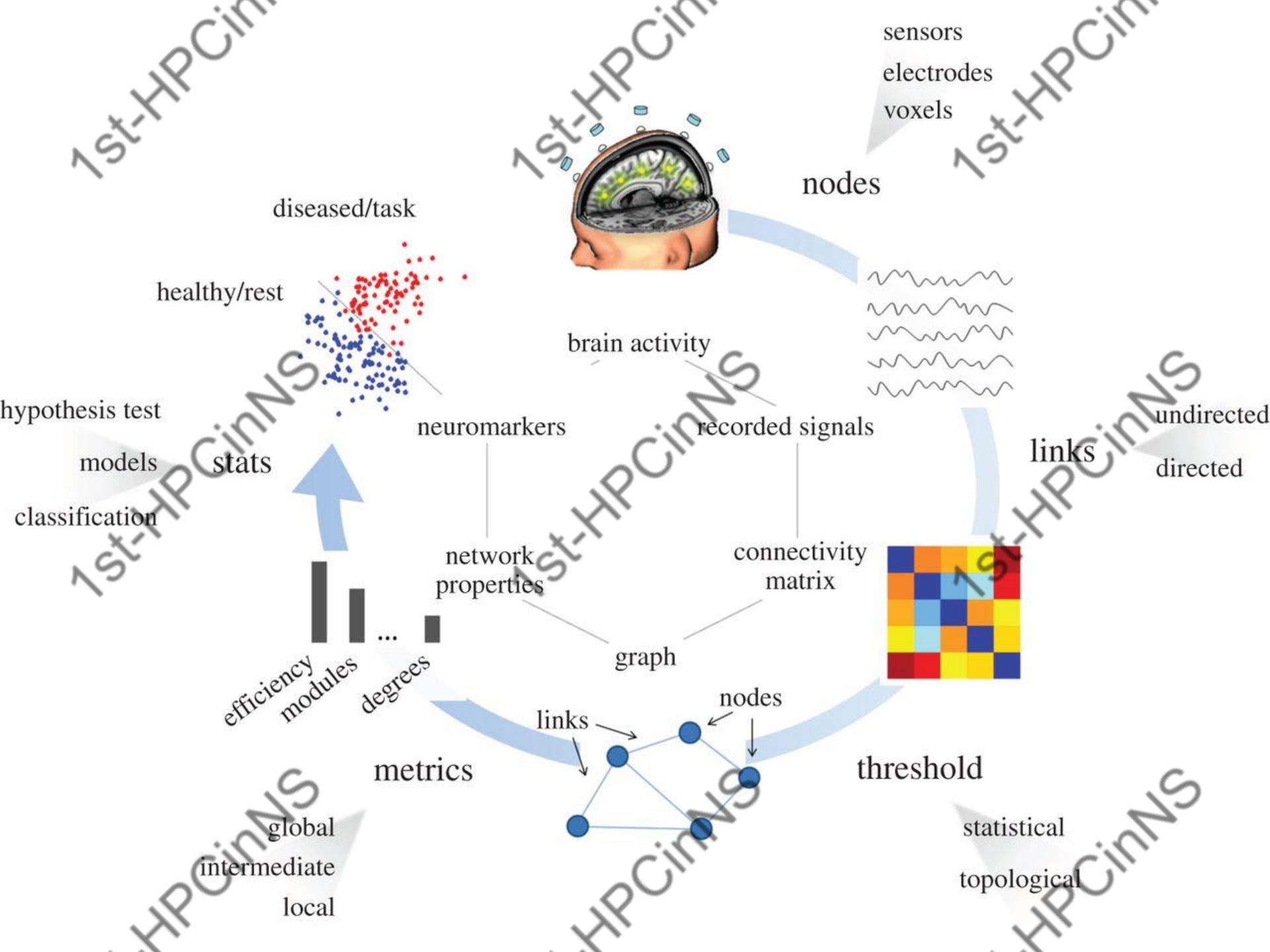
Brain Connectivity

functional connectivity



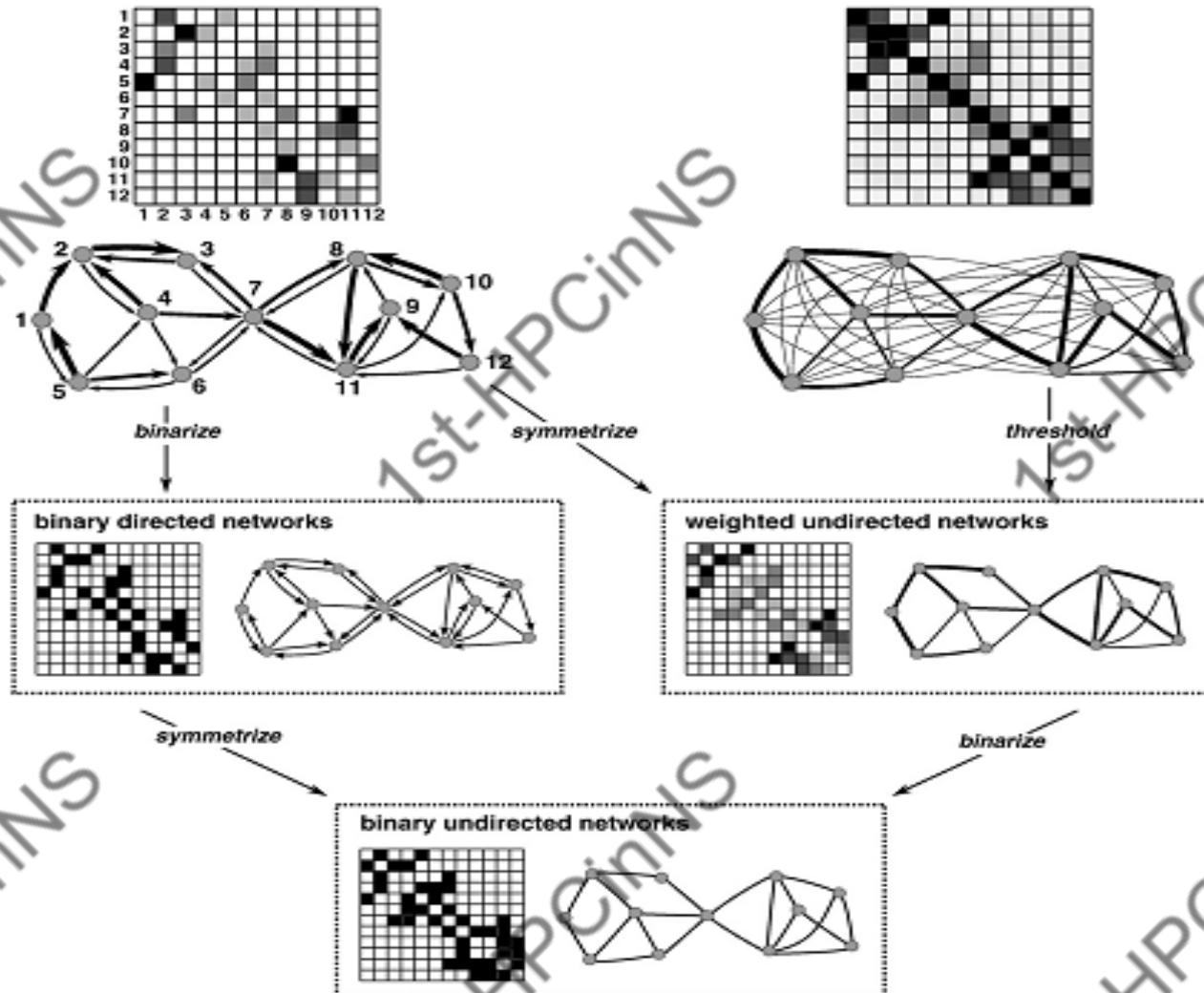
effective connectivity





Graph theoretical approaches

Weighted vs binary and Directed vs undirected



Global and local characteristics

- Functional segregation

Global clustering coefficient : number of triangles in the network

Local clustering coefficient : fraction of triangles around an individual node

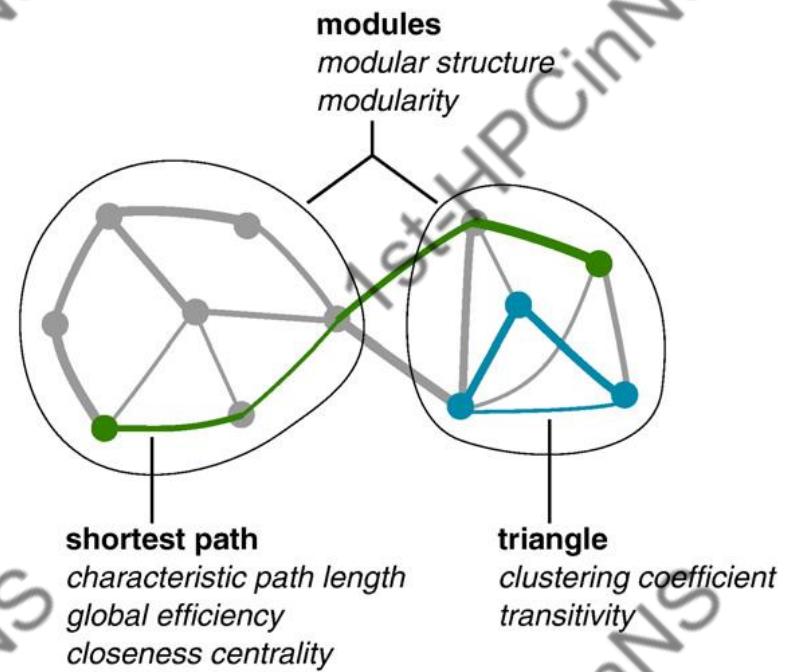
-Functional integration

Characteristic path length:

the average shortest path length between all pairs of nodes in the network

Global efficiency:

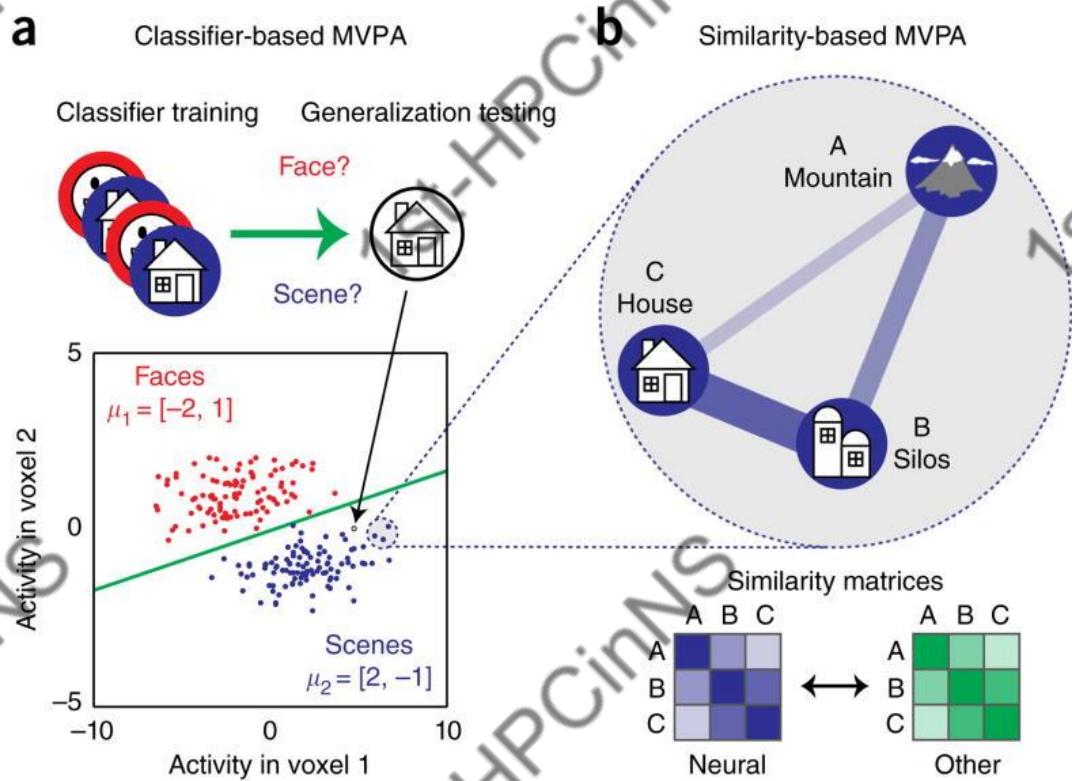
Inverse of CPL



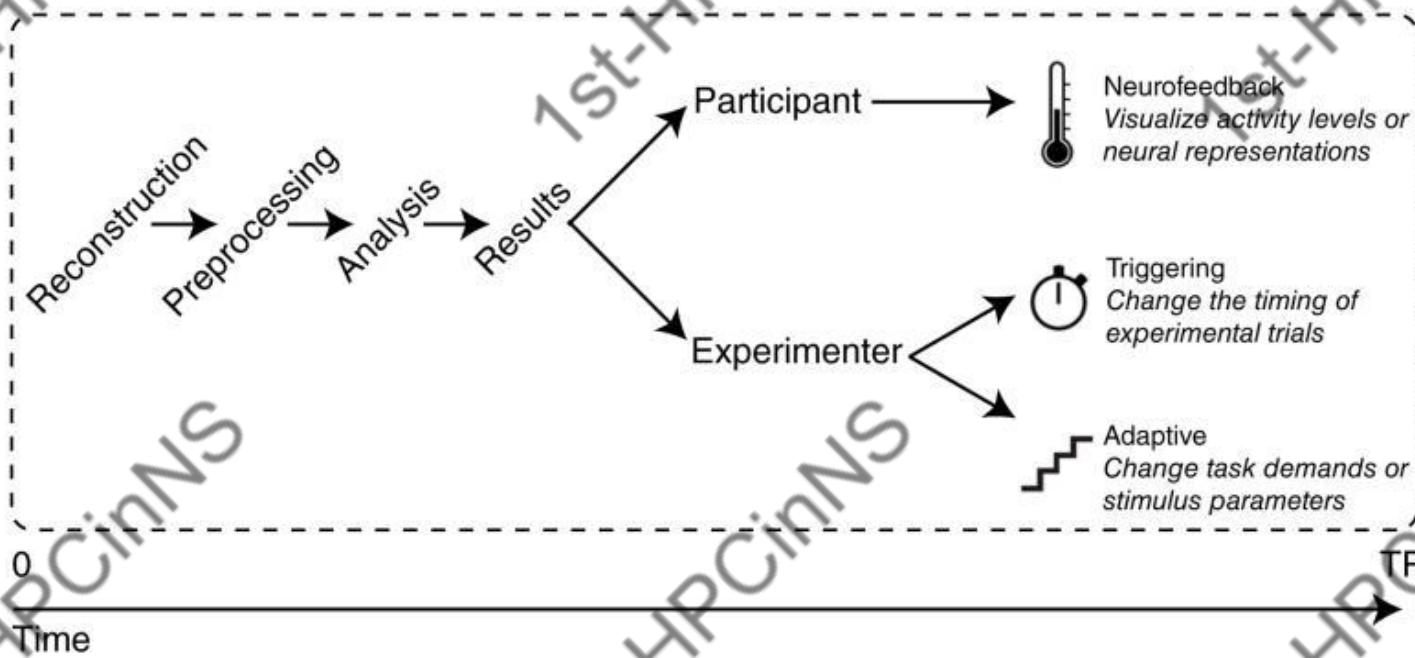
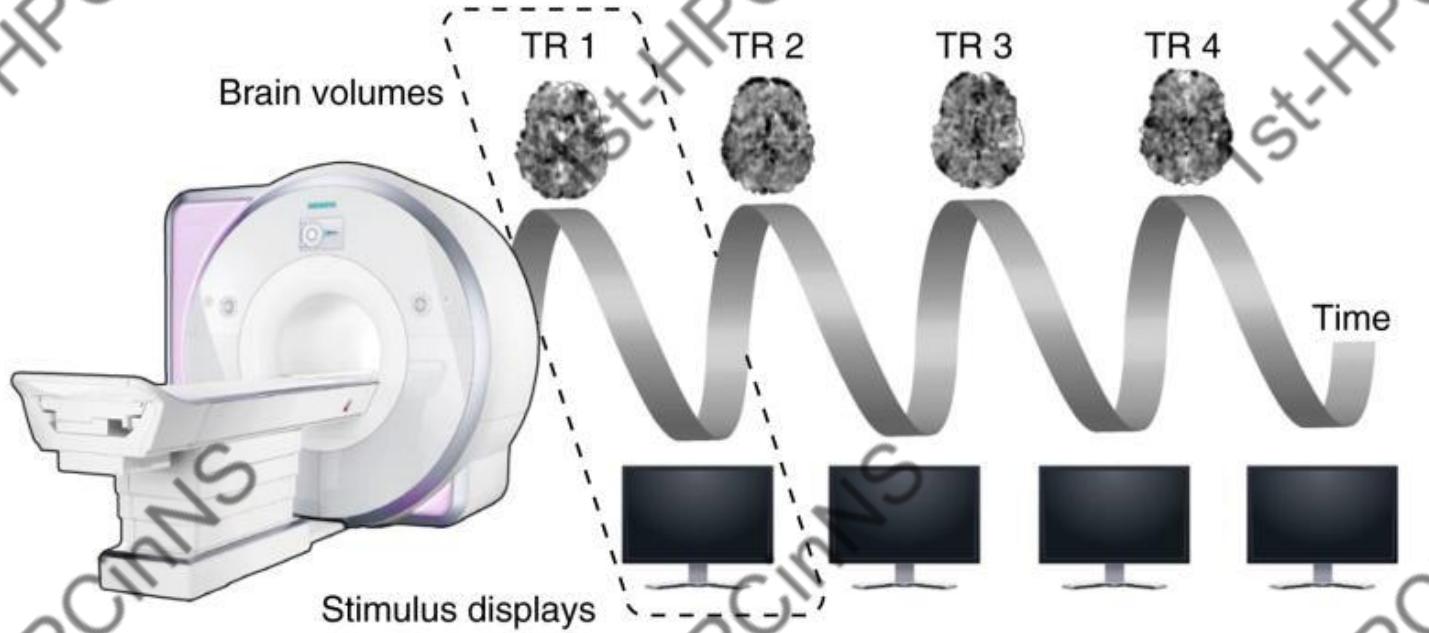
Computational approaches to fMRI analysis

These methods highlight the importance of computational techniques in fMRI analysis, especially machine learning, algorithmic optimization and parallel computing.

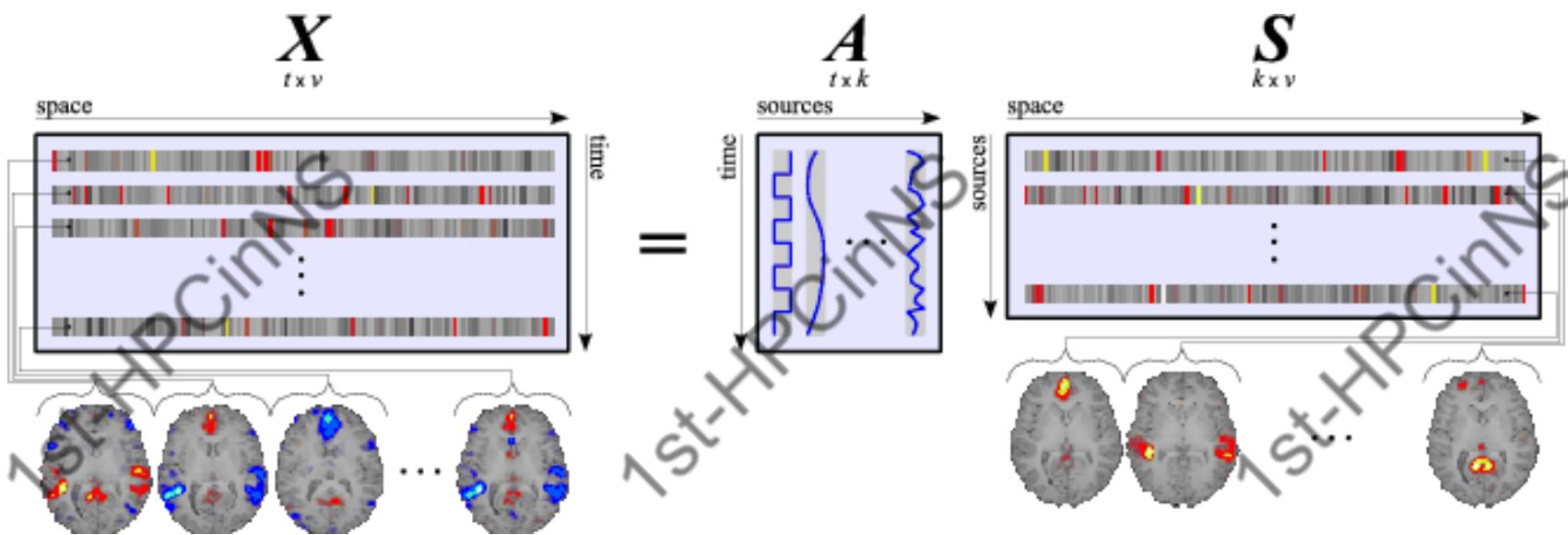
Multivariate analysis



Voxel-wise / Seed based data analysis

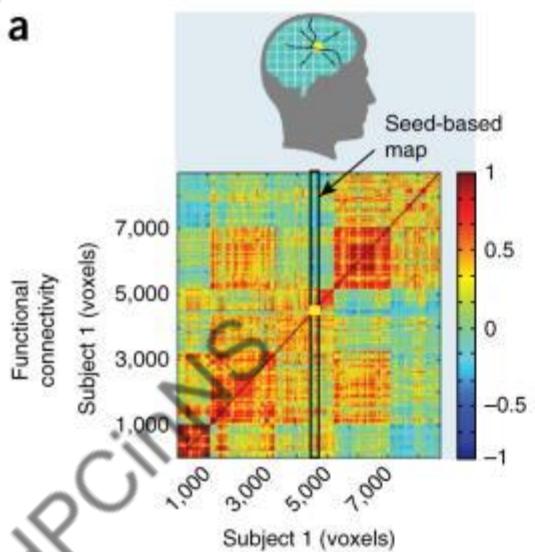


Independent component analysis

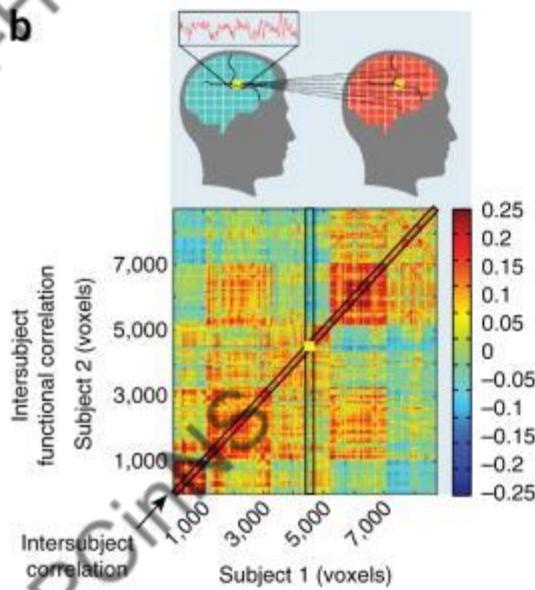


Functional connectivity

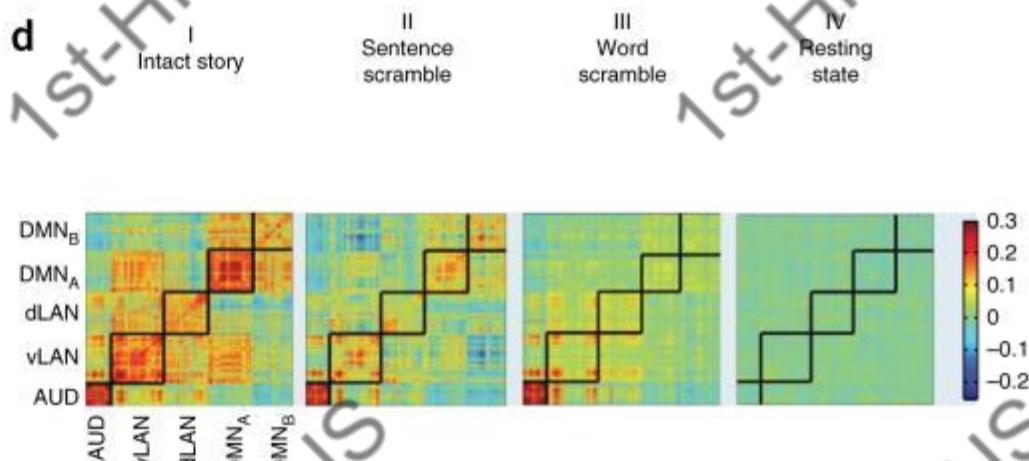
a



b



d



Multi-site classification

