Functional Magnetic Resonance Imaging

Christophe@pallier.org (http://www.pallier.org)

1) Practical Aspects : a typical scanning session, the scanner hardware, risks, costs, ...

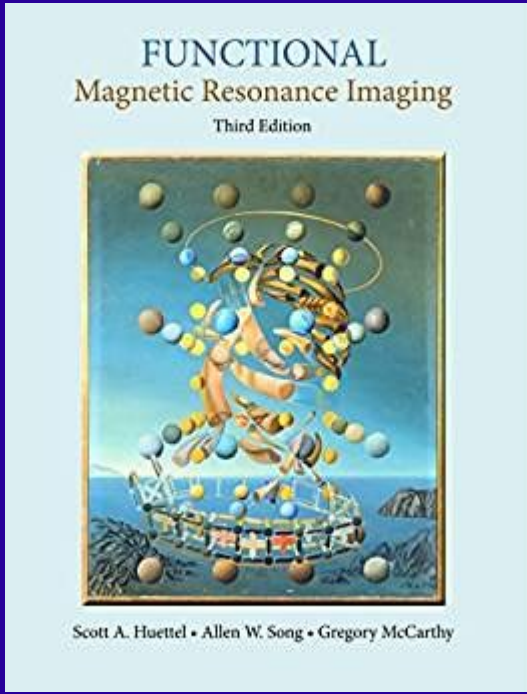
2) Rudiments of Nuclear Magnetic Resonance and how are MRI images obtained.

3) fMRI : the BOLD effect

4) Preprocessing of images

5) Data analyses

Resources



Textbook on fMRI (3rd edition) by Huettel, Song & McCarthy

fMRI for Dummies

http://www.fmri4newbies.com/ by Jody Culham

MRC | Cognition and Brain Sciences Unit

http://imaging.mrc-cbu.cam.ac.uk/imaging/CbuImaging

http://www.fil.ion.ucl.ac.uk/spm/course

Practical Aspects

A typical fMRI experiment

1. The volunteer is interviewed by a doctor.

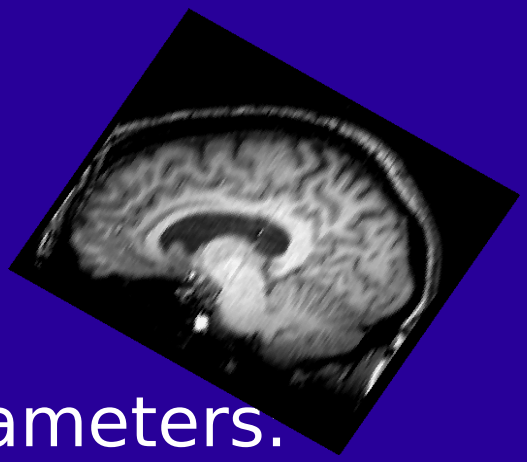
2. s/he is installed in the scanner (pulse detection/respiration belt/eye tracker/...)

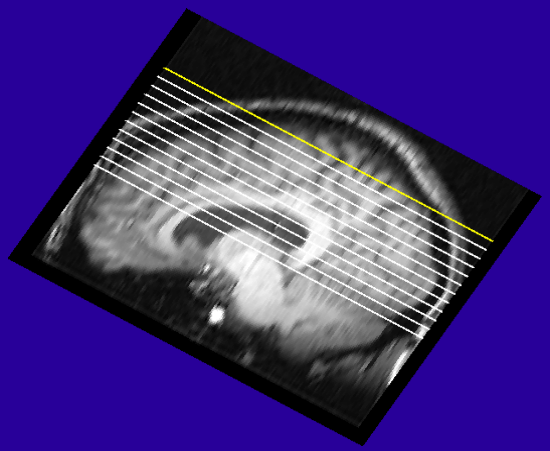
3. Data acquisition lasts about 1 hour: One anatomical scan lasting 8 minutes and a series of functional scans, each lasting about 2 seconds*

Note: The subject can receive visual and auditory stimulation and move his hands and fingers. But it crucial that s/he does not move the head.

Controling at the console

Acquire a quick pilot image to find the location of the brain.



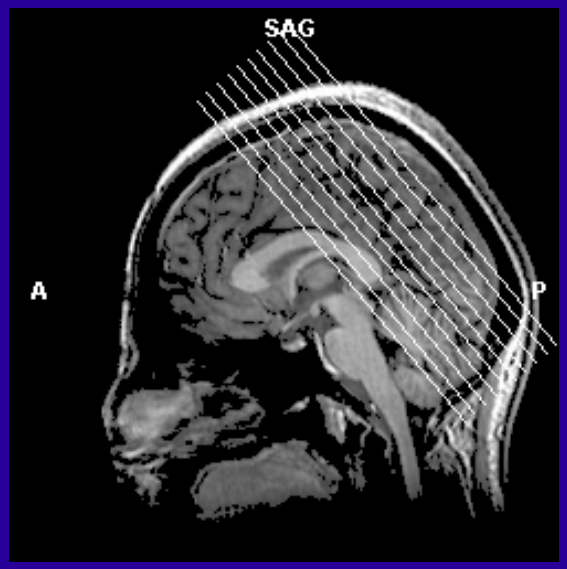


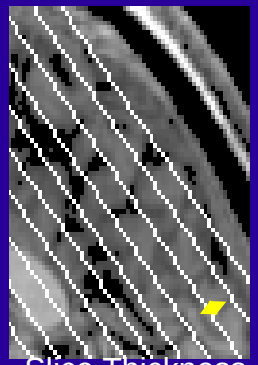
Define scan parameters.

- choose the resolution of the images (slice thickness...)
- position the slices
- duration of a scan (TA=time of acquisition)
- number of repetitions

If there is some stimulation, synchronize it with data acquisition.

Slice Terminology

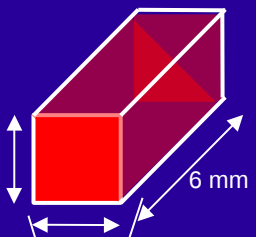




Slice Thickness
e.g., 6 mm

In-plane resolution
e.g., 192 mm / 64
= 3 mm

VOXEL
(Volumetric Pixel)

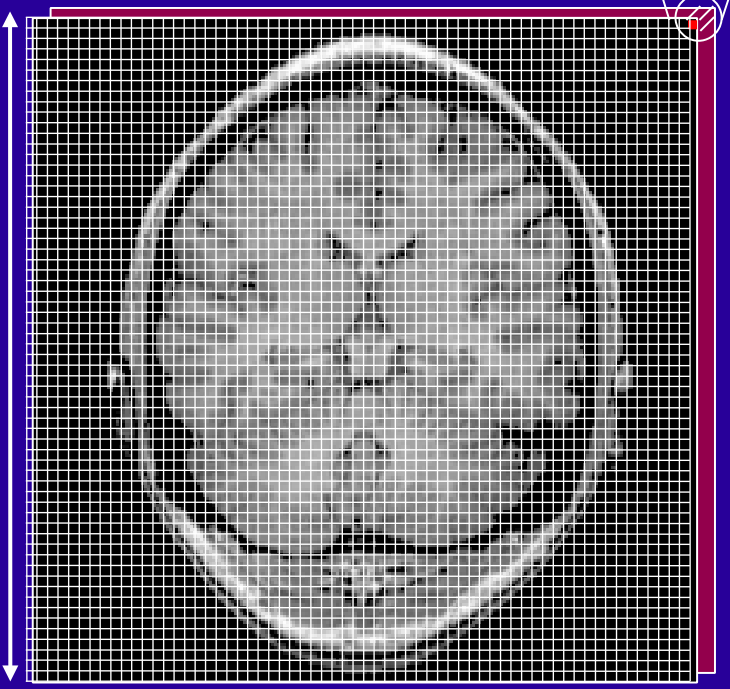


IN-PLANE SLICE

Number of Slices
e.g., 10

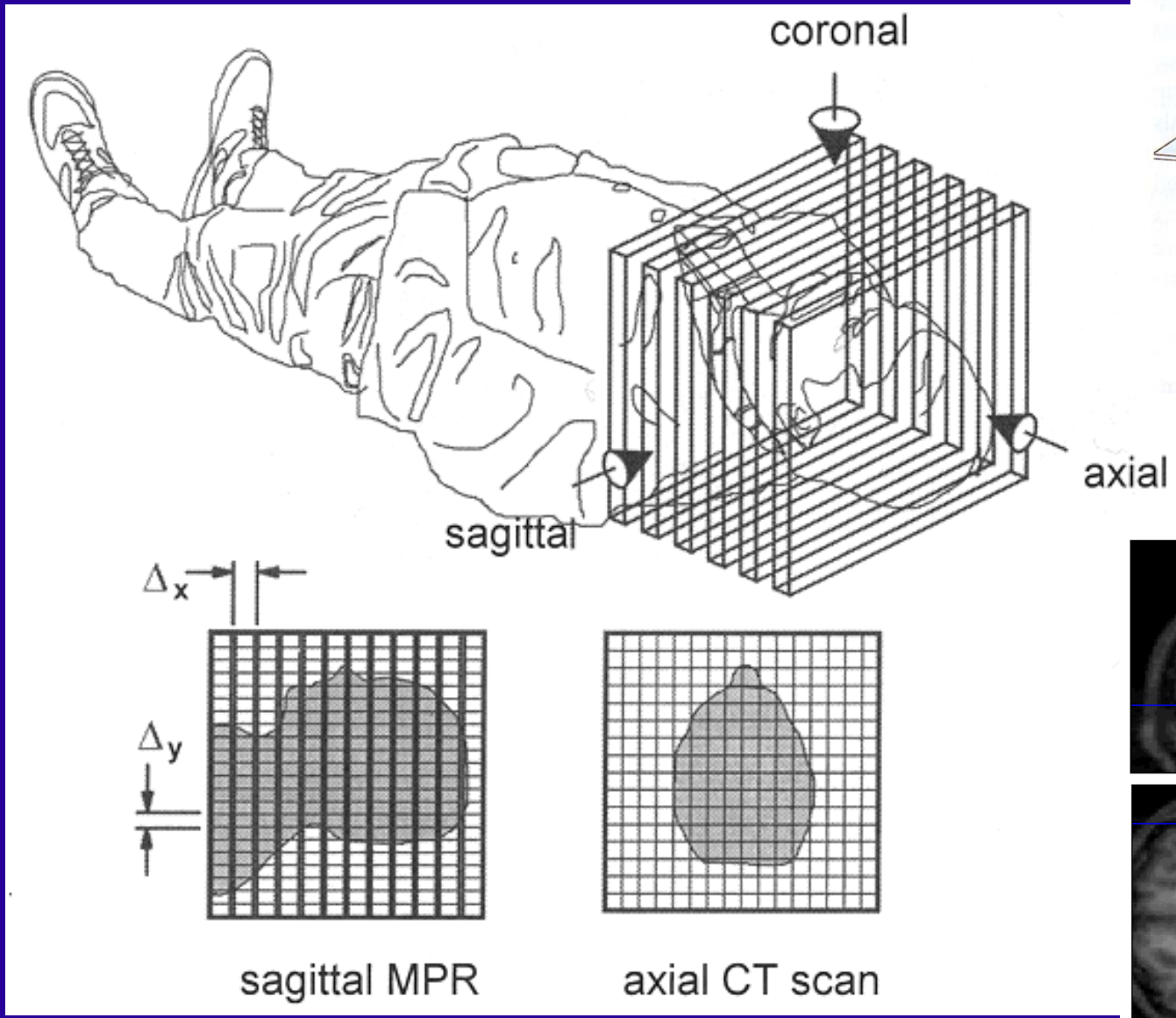
Matrix Size
e.g., 64 x 64

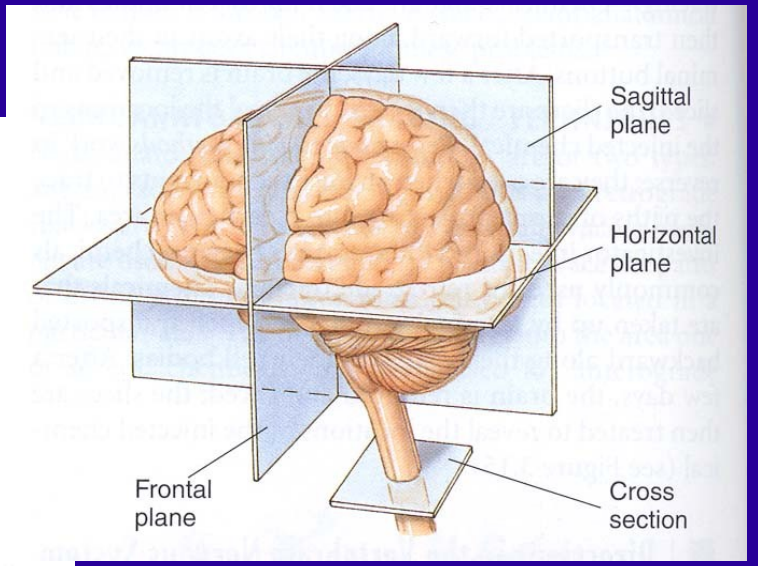
Field of View (FOV)
e.g., 19.2 cm

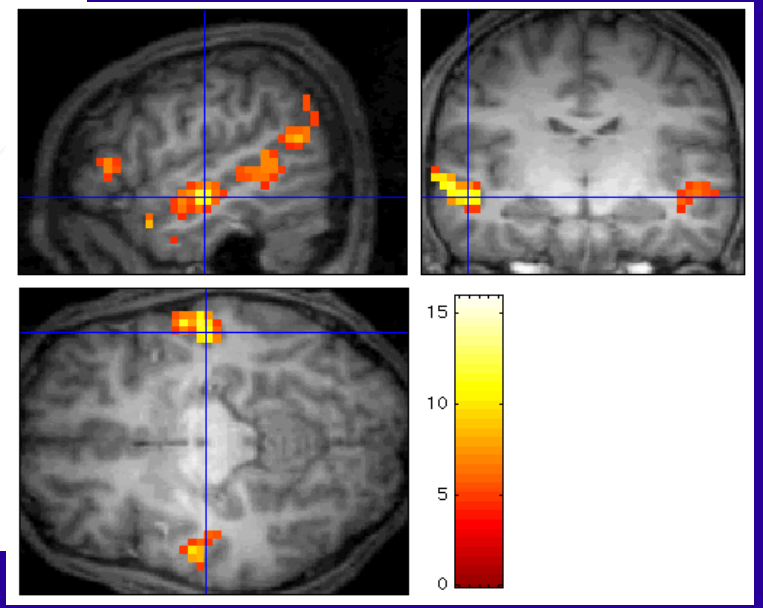


fMRI for Dummies

Sagittal/Coronal/Axial views





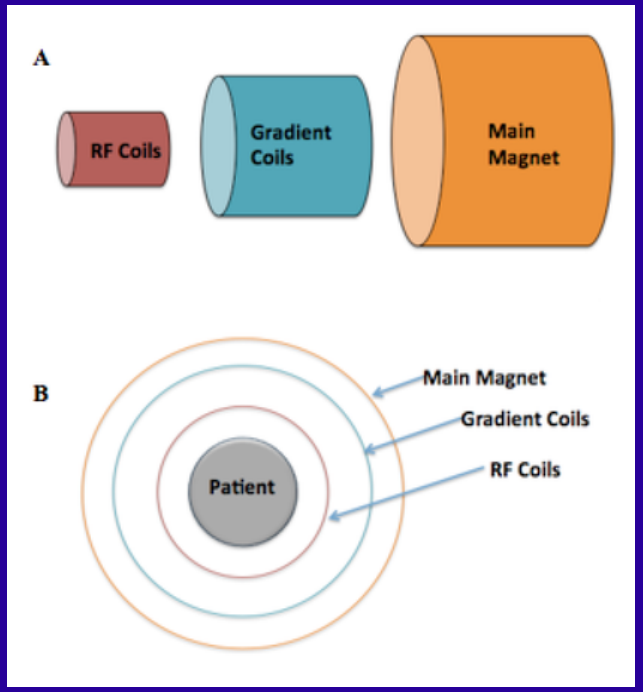


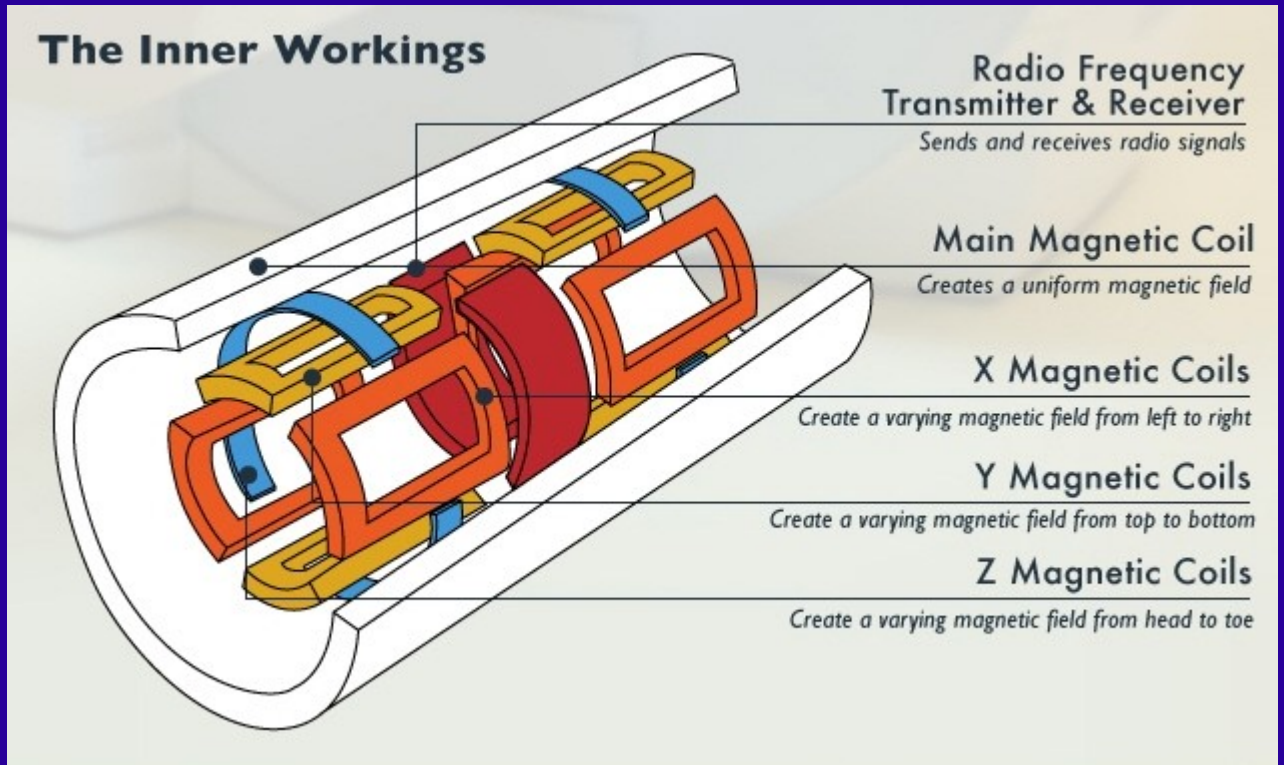
Hardware of an MRI scanner

1) A main **magnet** creating a strong static field (~ 1 to 17 T ; for humans, maximum = 9.4T in Chicago & Maastrich, soon 11.7T in Neurospin).

2) **Gradient coils** generating small magnetic field (e.g. 50mT/m)

3) An **RF transmitter / receiver** (or **Antenna)** used to « excite » the brain, then measure the re-emitted signal.



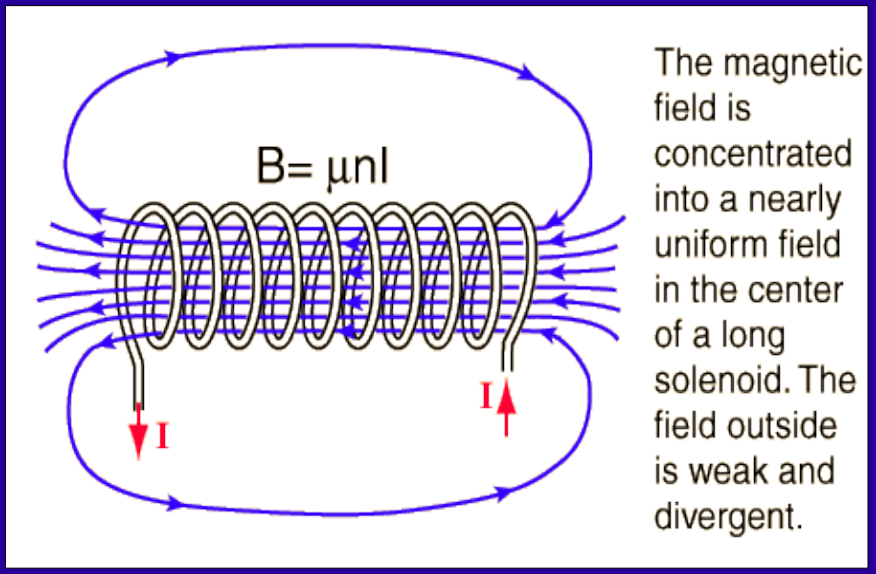


The main magnet

Generate a strong **static** magnetic field (1.5T, 3T, 7 Telsa,...) tht must be as homogenous as possible in the volume to image.

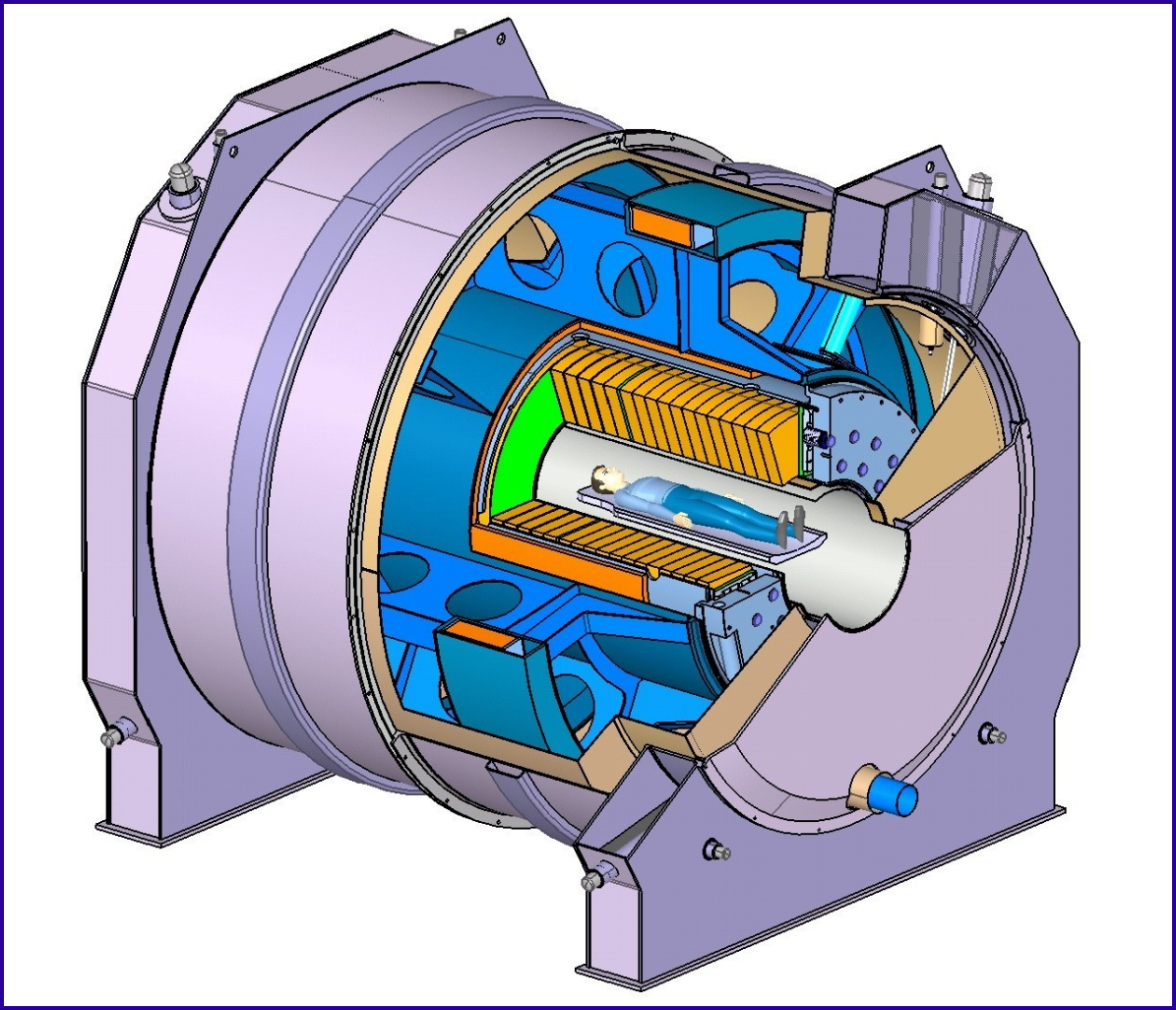
There exists 3 types of magnets:

- Permanent (~ 100 tons)
- Electric (resistive)
- Electric (with supraconductors : no electrical resistance). **These magnet are always on (unless stopped for maintenance)**



The magnetic field is concentrated into a nearly uniform field in the center of a long solenoid. The field outside is weak and divergent.

Neurospin's 11.75T magnet for humans (due in 2017)



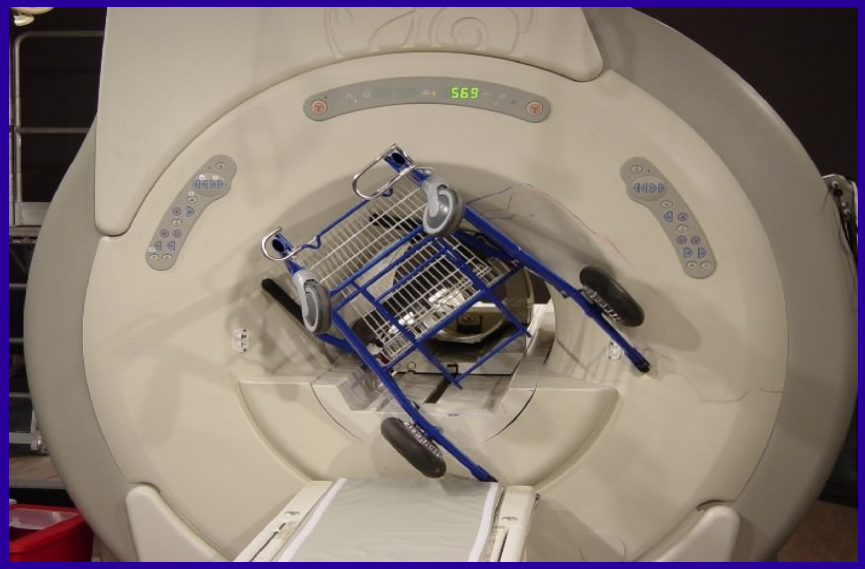
Coil : 230 km of niobium-titanium wire assembled with a precision of a few micrometers.

45 tons

Current = 1400 A
Temperature = 1.8 K

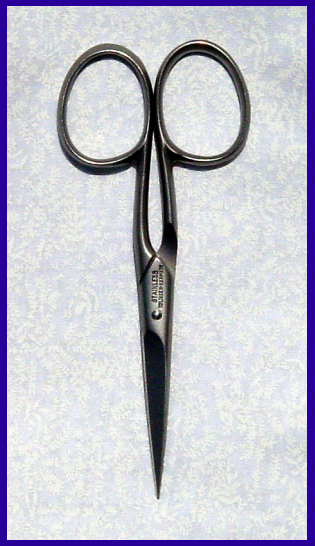
http://irfu.cea.fr/Sacm/en/Phocea/Vie_des_labos/Ast/ast_visu.php?id_ast=3377

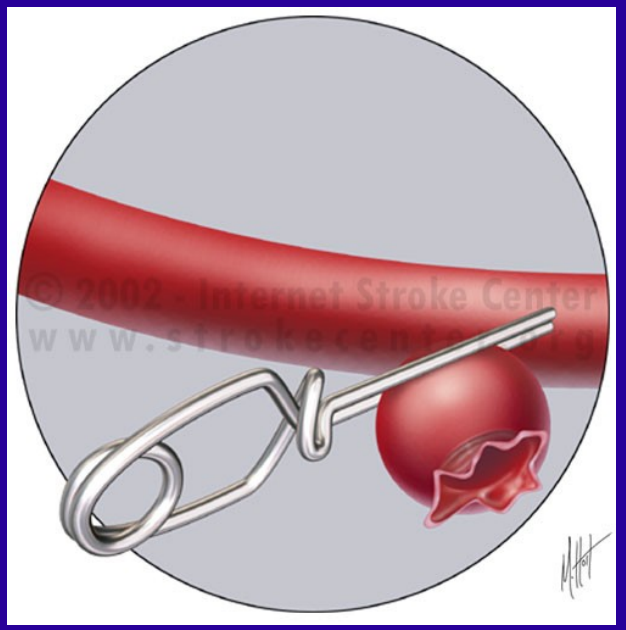
The main risk: missile effect



Search youtube for « magnetic resonance missile effect »

Magnet Safety: Little Things





Aneurysm clips can be pulled off vessels, leading to death

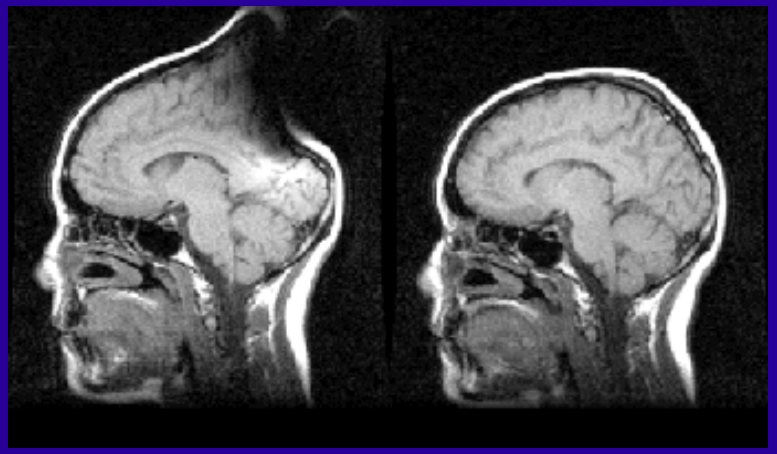
Flying things can kill people.
Even in less severe incidents, they can fly into the magnet and damage it or require an expensive shutdown.

Subject Safety

Anyone going near the magnet – subjects, staff and visitors – must be thoroughly screened:

Subjects must have no metal in their bodies:
- pacemaker
- aneurysm clips
- metal implants (e.g., cochlear implants)
- interuterine devices (IUDs)
- some dental work (but fillings are okay)

Subjects must remove metal from their bodies
- jewellery, watch, piercings
- coins, etc.
- wallet
- any metal that may distort the field (e.g., underwire bra)

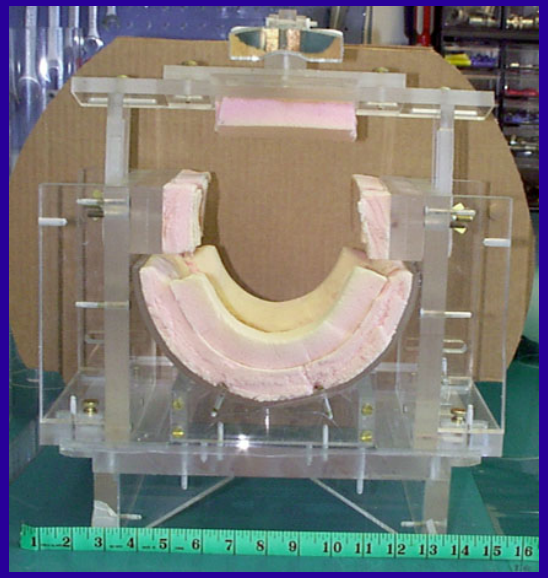


This subject was wearing a hair band with a ~2 mm copper clamp. Left: with hair band. Right: without.
Source: Jorge Jovicich

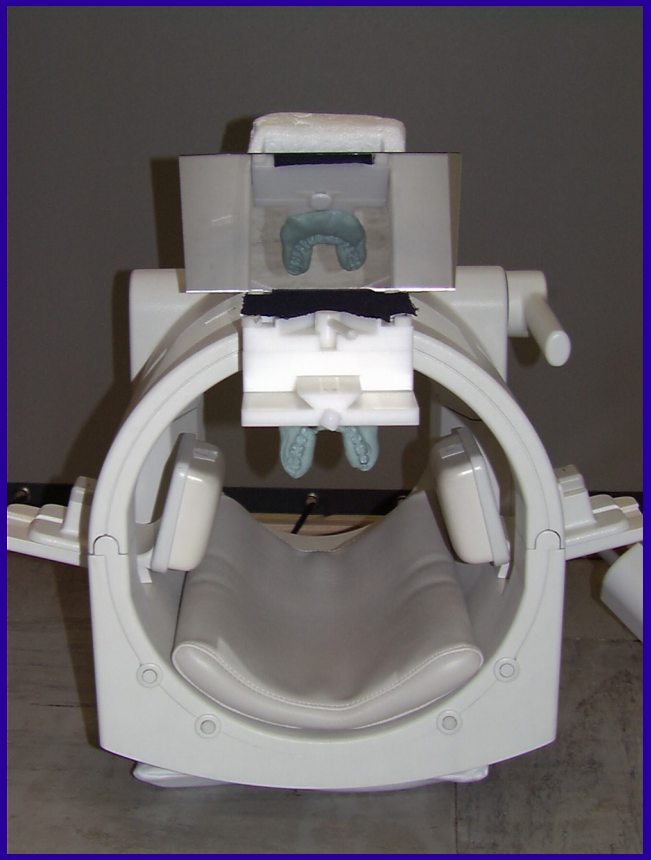
Females must not be pregnant or at risk of conceiving
- Some institutions even require pregancy tests for any female, every session

Subjects must be given ear plugs (acoustic noise can reach 120 dB)

Head Restraint



Head Vise
(more comfortable than it sounds!)



Bite Bar

Thermoplastic mask

Cost

Cost of a 3T magnet ~ 2 million euros

Cost of an antenna ~ 10.000-100.000 euros

Cost of maintenance (liquid Helium and Nitrogen, support) ... ~ 150.000 euros/year.

In my institution, the cost of a scientific experiment with 20 subjects ~ 16.000 euros (ignoring the salaries of the researchers...)

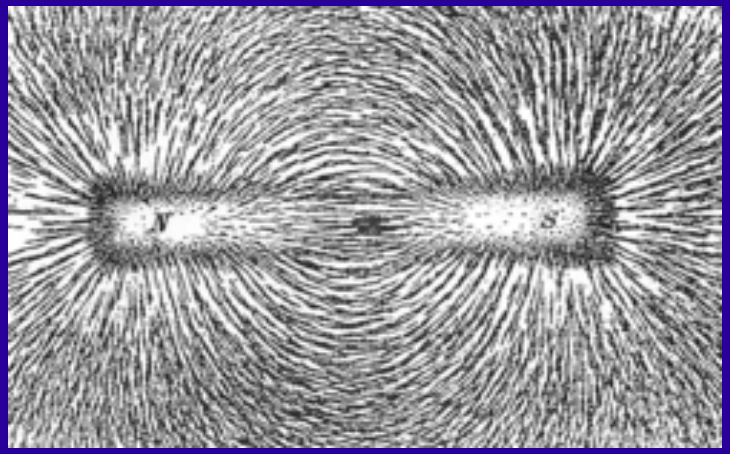
After data acquisition

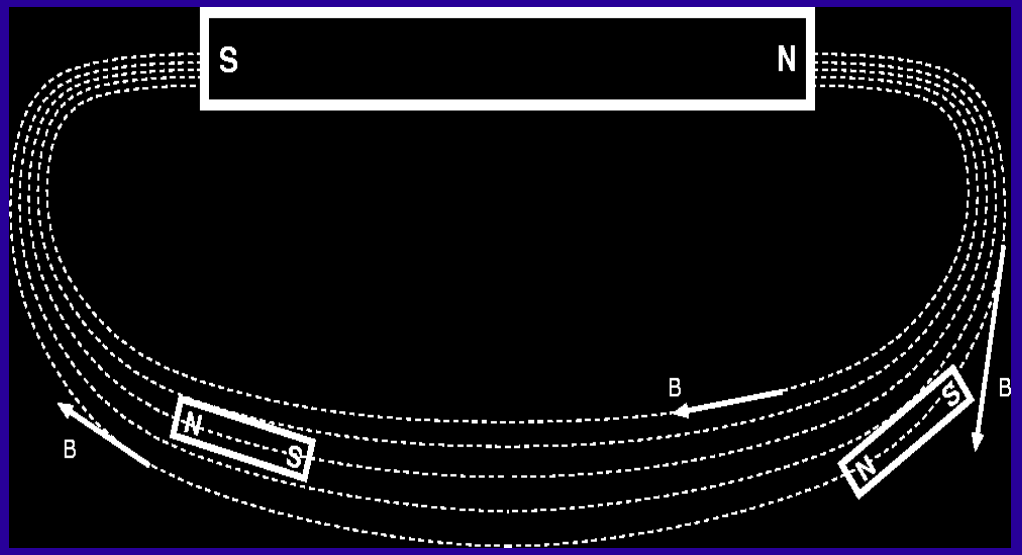
- Data (typically several hundred megabytes, or a few gigabytes) are uploaded to a central server
- On your workstation, you download the data and start the processing pipeline.
- When the analysis pipeline is automatized, single Ss analyses typically take a few hours or less on a cluster (used to take 2 days in 1999...)

(Note: Nowadays, it is sometimes possible to perform « Real time analyses », simultaneously with data acquisition (biofeedback)).

Principles of Image acquisition

Magnetic field

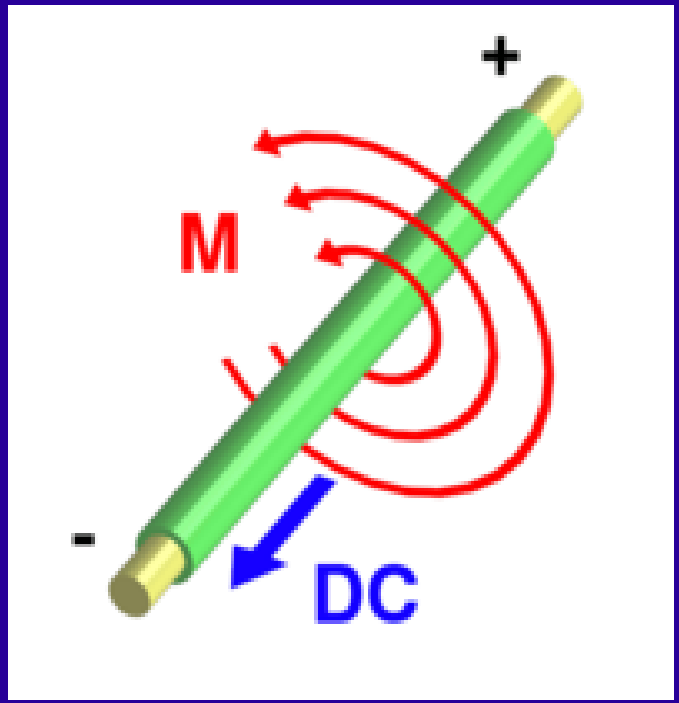




Magnetic lines of force of a bar magnet revealed by iron filings (little magnets themselves, the magentic force orients them to align with the field lines)

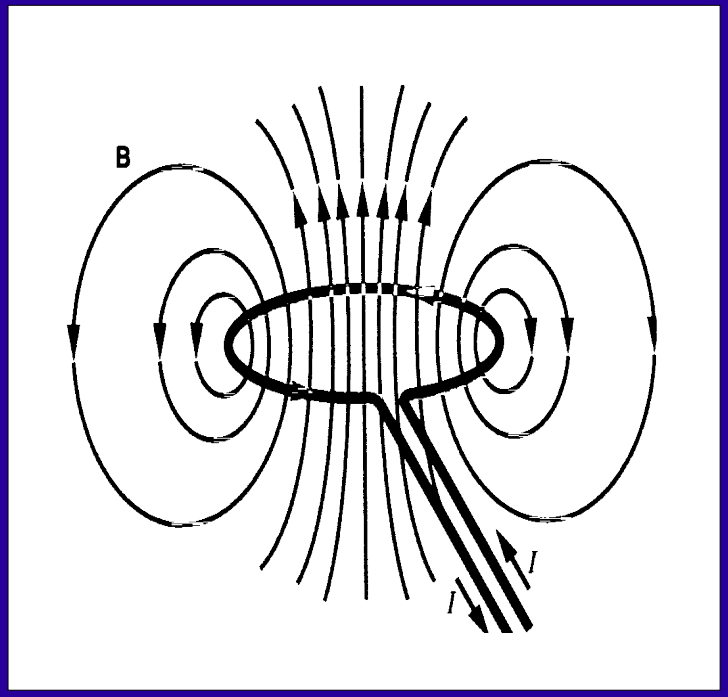
Magnetic fields are produced by currents (that is movement of electric charges)

Linear current



Remark: reciprocally, a particle moving with speed **v** in a magnetic field **B**, is subjected to a force $\mathbf{F} = q(\mathbf{v} \times \mathbf{B})$

A coil (a wire forming a loop) is equivalent to a small magnet.



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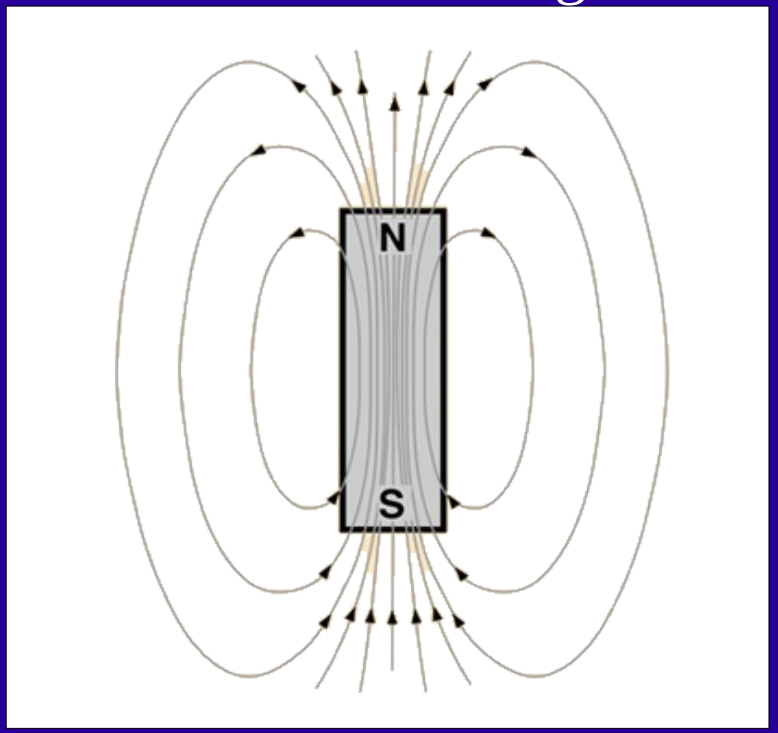
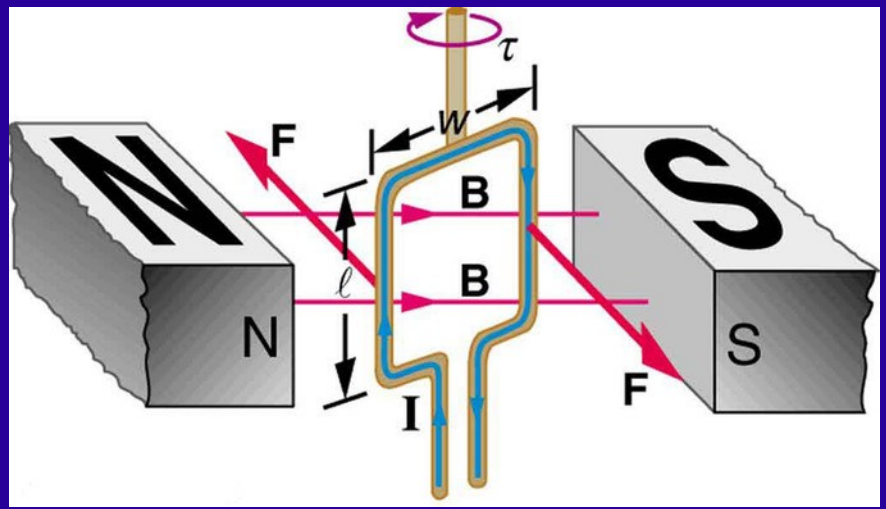
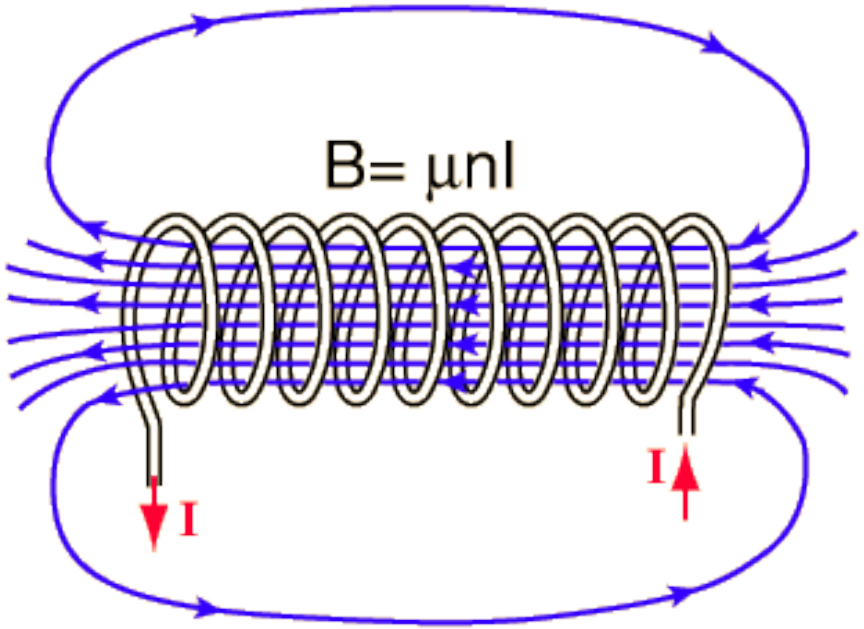


A coil with running current has a **magnetic moment** (vector ⊥ to its area): A magnetic field B will exert a torque (rotative force) to align the magnetic moment to B



Solenoid ‘s definition

multiple loops to create a spatially uniform field

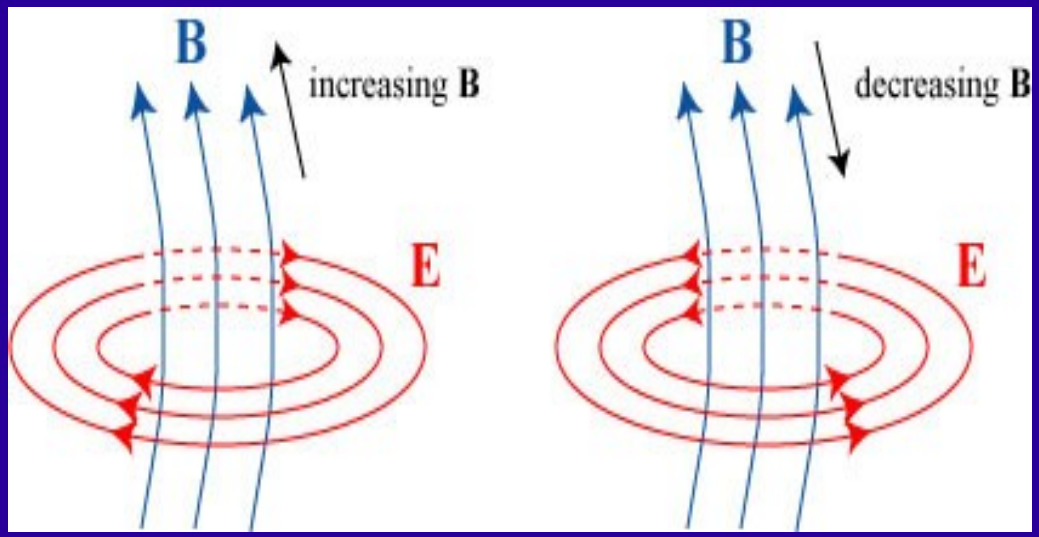


The magnetic field is concentrated into a nearly uniform field in the center of a long solenoid. The field outside is weak and divergent.

The phenomenon of induction: Time-varying magnetic fields can produce electric currents

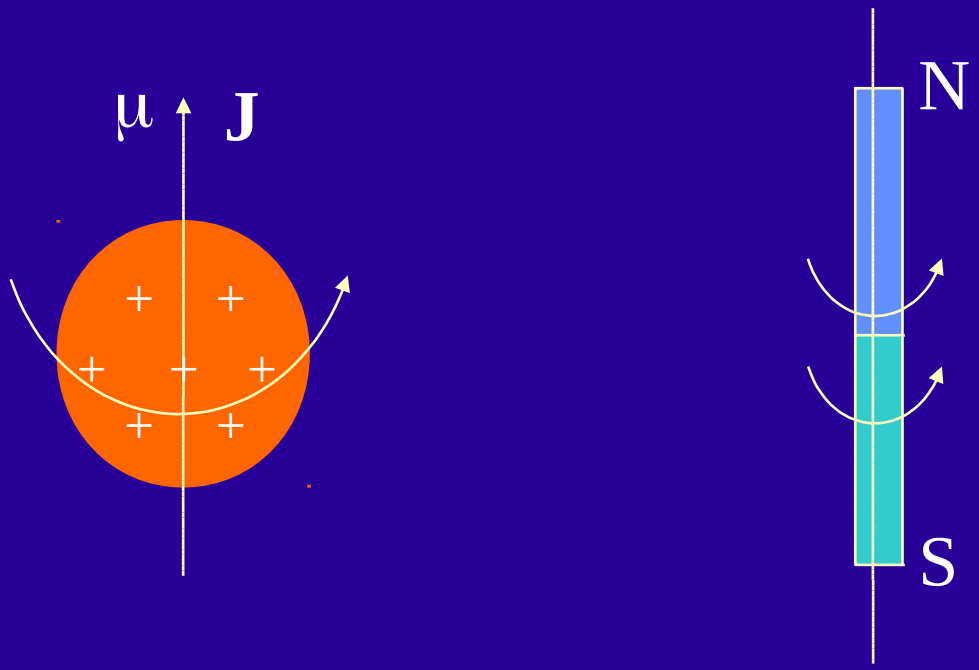
$$\nabla \times \mathbf{E} = -\frac{\partial \mathbf{B}}{\partial t}$$

Maxwell–Faraday equation



This allows to build a receiving antenna with a loop wire that detects changes in magnetic field (for ex. MEG)

Similarity between a spinning proton and a spinning magnetic bar



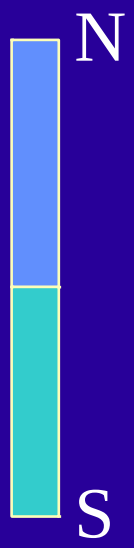
Because a proton has a charge and is spining on itself,
it has an **angular momentum** J and a **magnetic moment** μ.

$$\boldsymbol{\mu} = \gamma \, \mathbf{J}$$

where γ is an experimental constant called the gyromagnetic ratio (which varies with the type of atomic nucleus)

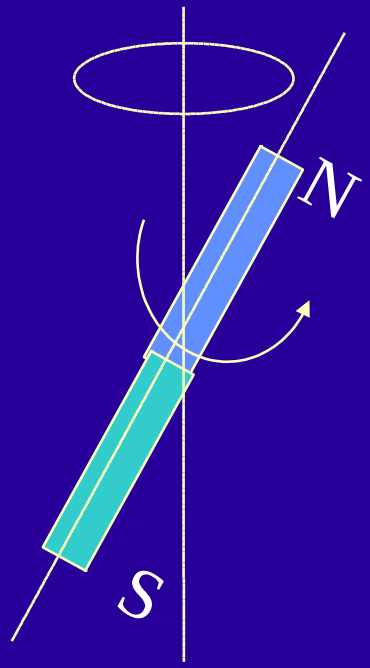
Behavior of a Magnetic Bar in a Magnetic Field

Magnetic field



Static magnetic bar

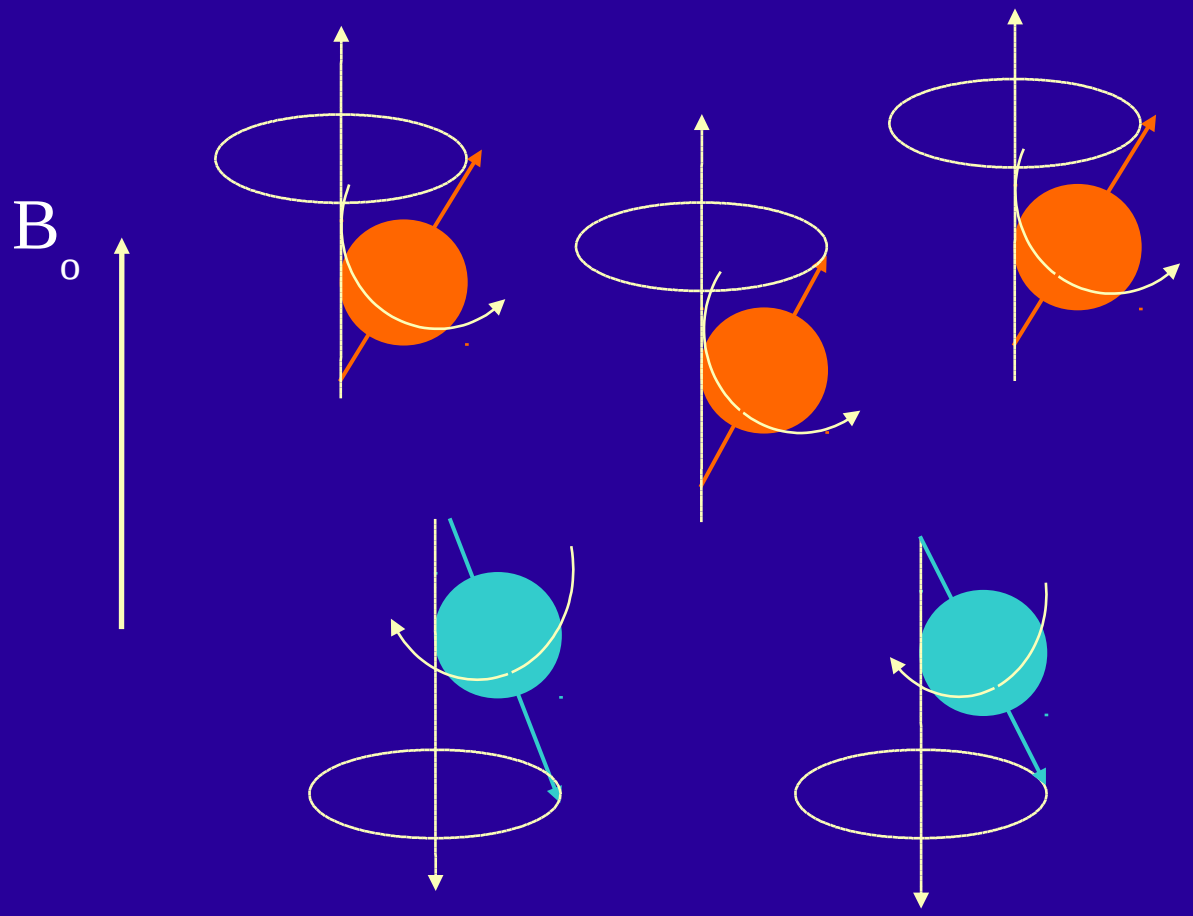
Orients itself
along the vector **B**



Spinning magnetic bar

Has a movement
of precession

Protons in a Magnetic Field

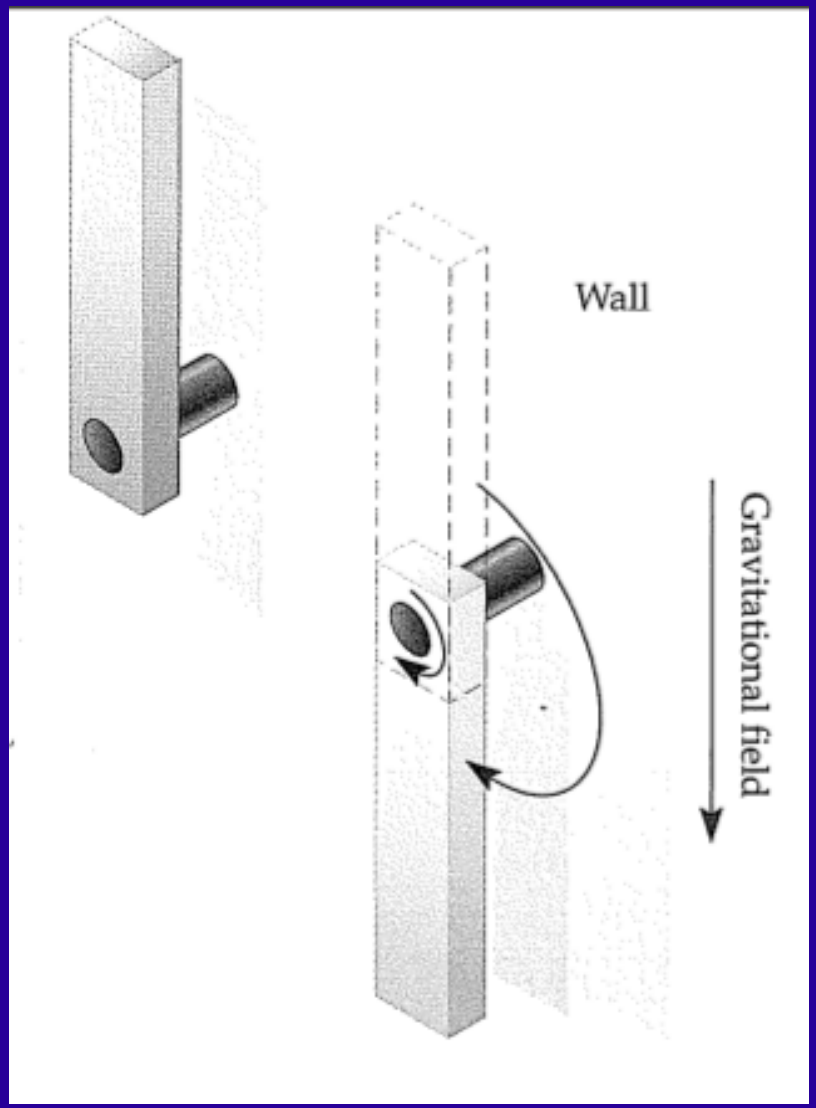


Parallel (low energy)

Anti-Parallel (high energy)

Spinning protons in a magnetic field will assume **two** states. (It is a quantum mechanics property: The angular momentum of protons is quantified, that is can only take 2 discrete values)

Example of a discrete states system

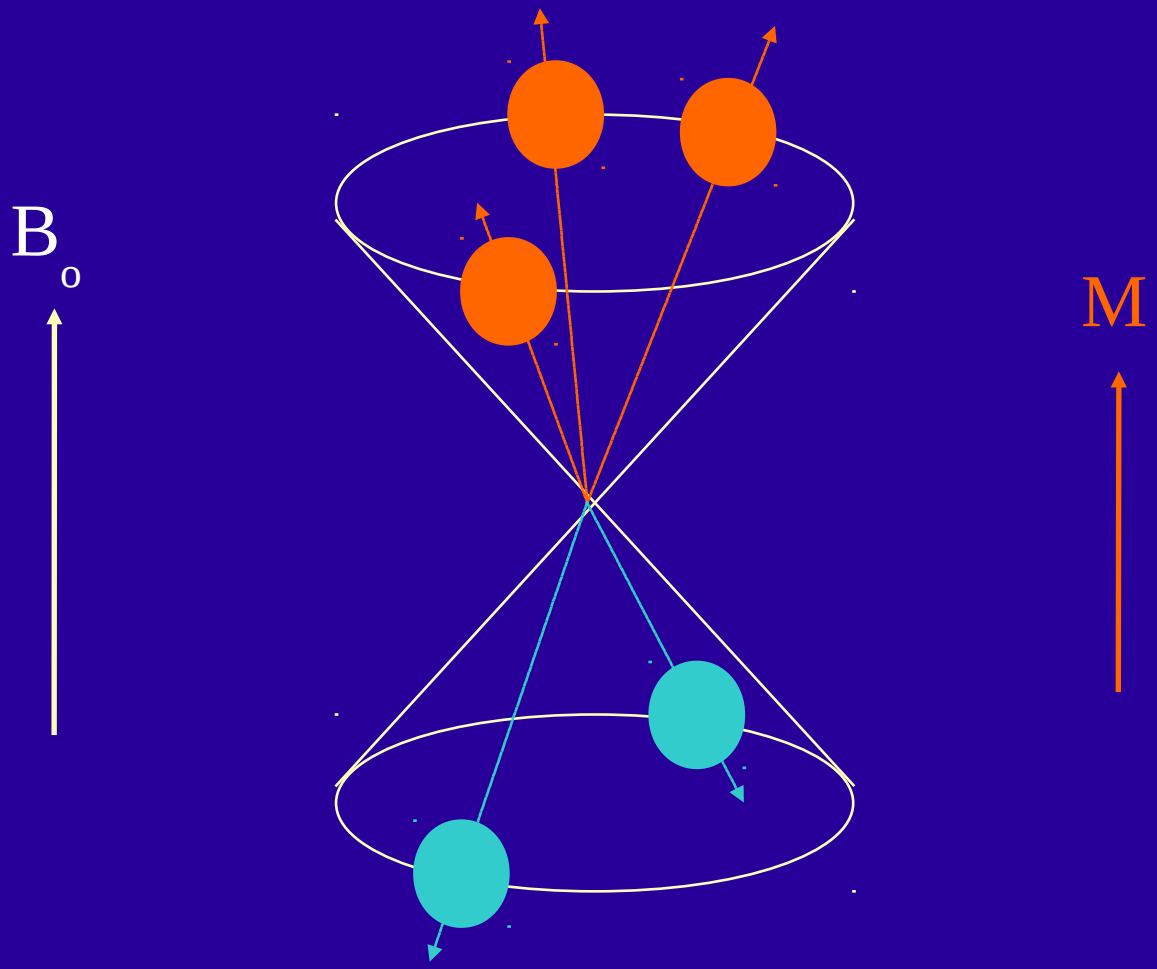


A handle bar within the earth gravitational field can assume two states :

The antiparallel state (up) with high potential energy

The parallel state (down) with low potential energy (but more stable)

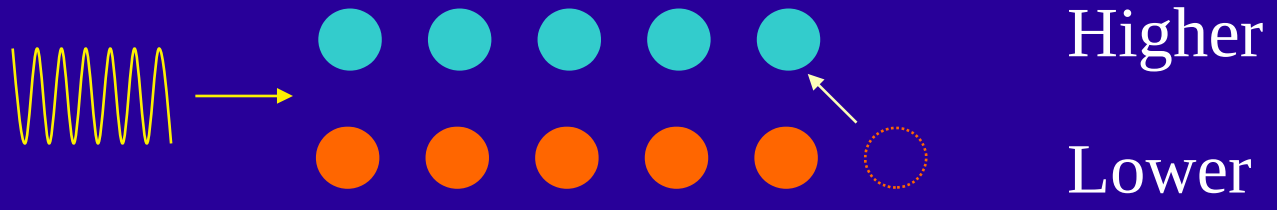
More protons in the low energy state
=> the sum of all magnetic moment create a Net Macroscopic Magnetization ‘M’ aligned with B0



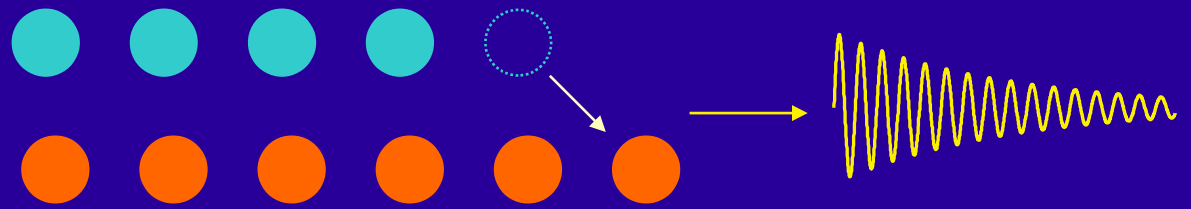
Nuclear Magnetic resonance

1) Spin system before irradiation:

2) Transitions induced by electromagnetic field (EM)



3) Return to steady steady state after the end of irradiation



To induce transitions between the energy states, the electromagnetic wave must have a very precise frequency:

$$\Delta E = h\nu$$

h = Planck's constant

ν = frequency

with

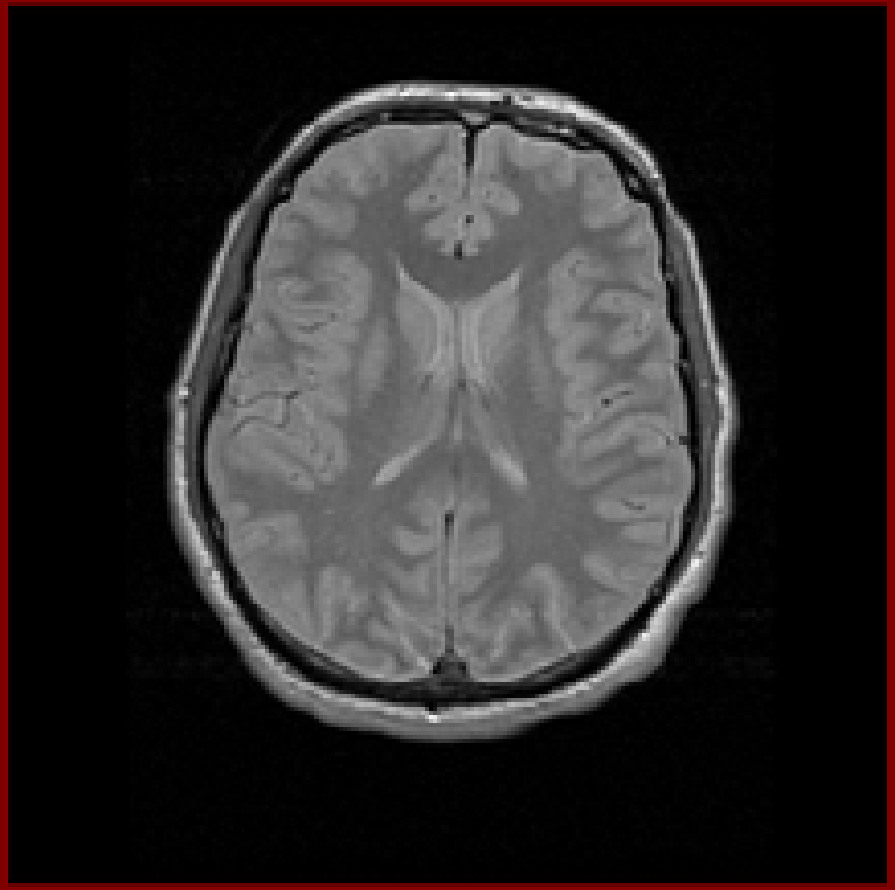
$$\nu = \gamma/2\pi B_o$$

γ = gyromagnetic ratio

ν is known as the Larmor frequency (resonance frequency)

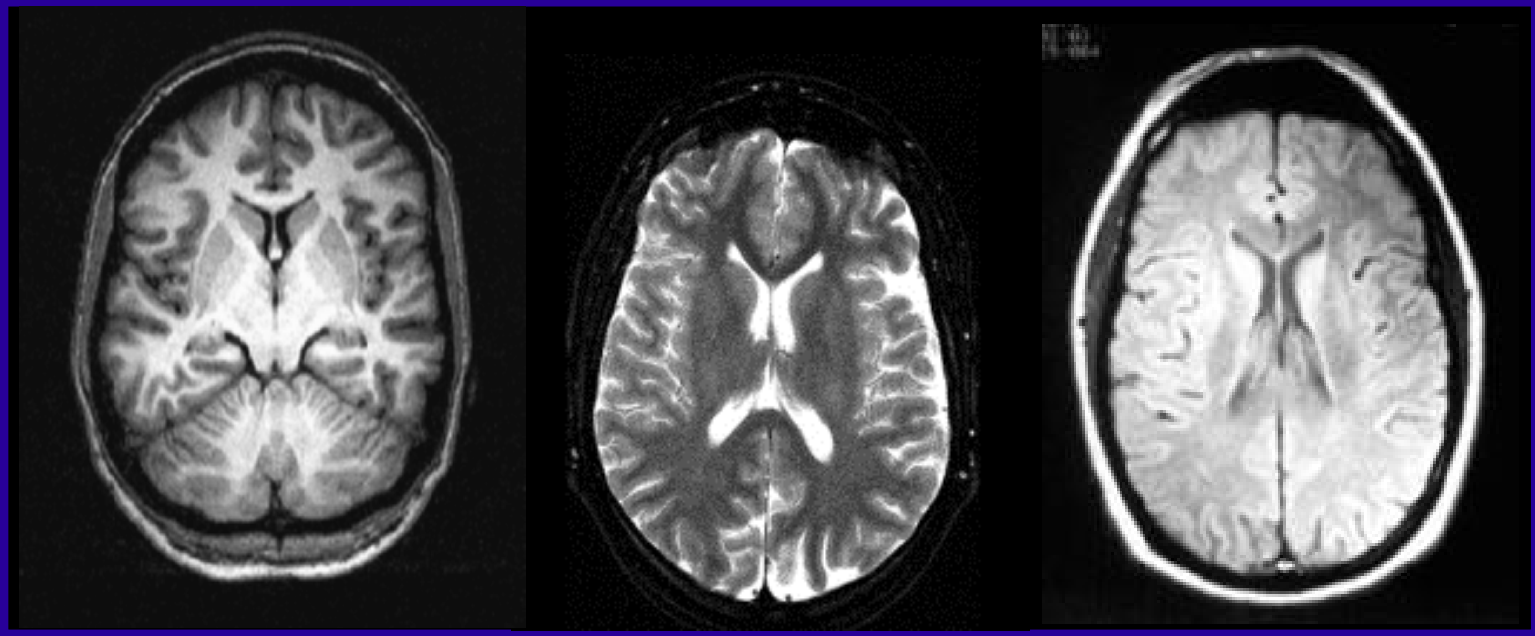
$\gamma/2\pi$ = 42.57 MHz / Tesla for **protons in H2O**

If you measure the amplitude of the reemitted signal, you get... the density of protons from H2O (that is, the density of water)



	Proton Density
CSF	1
grey matter	0.92
white matter	0.79

Classical MRI is essentially based on measures of various **relaxation times** of the Net magnetization vector M.

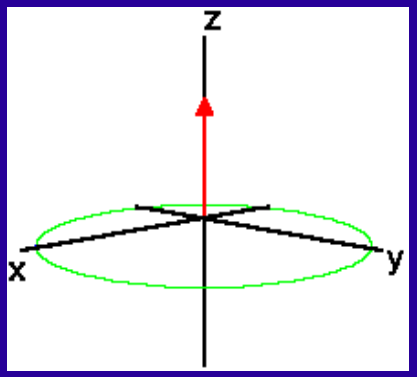


T1 T2 T2*

At 3 Tesla:

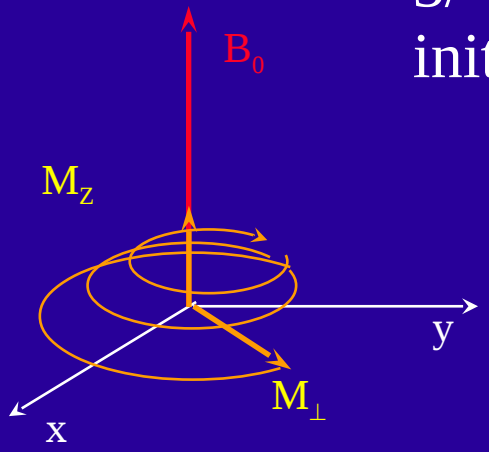
White matter:	1100 msec	55 msec
Grey matter:	1400 msec	70 msec

NMR classic view



1/ In the presence of only B_0, the net magnetization M_0 (the sum of all magnetic moments) is // to B_0 (z).

2/ The RF pulse («excitation») flips the Magnetisation vector which becomes **transversal**



3/ Without further excitation, the system returns to initial state (« relaxation »)

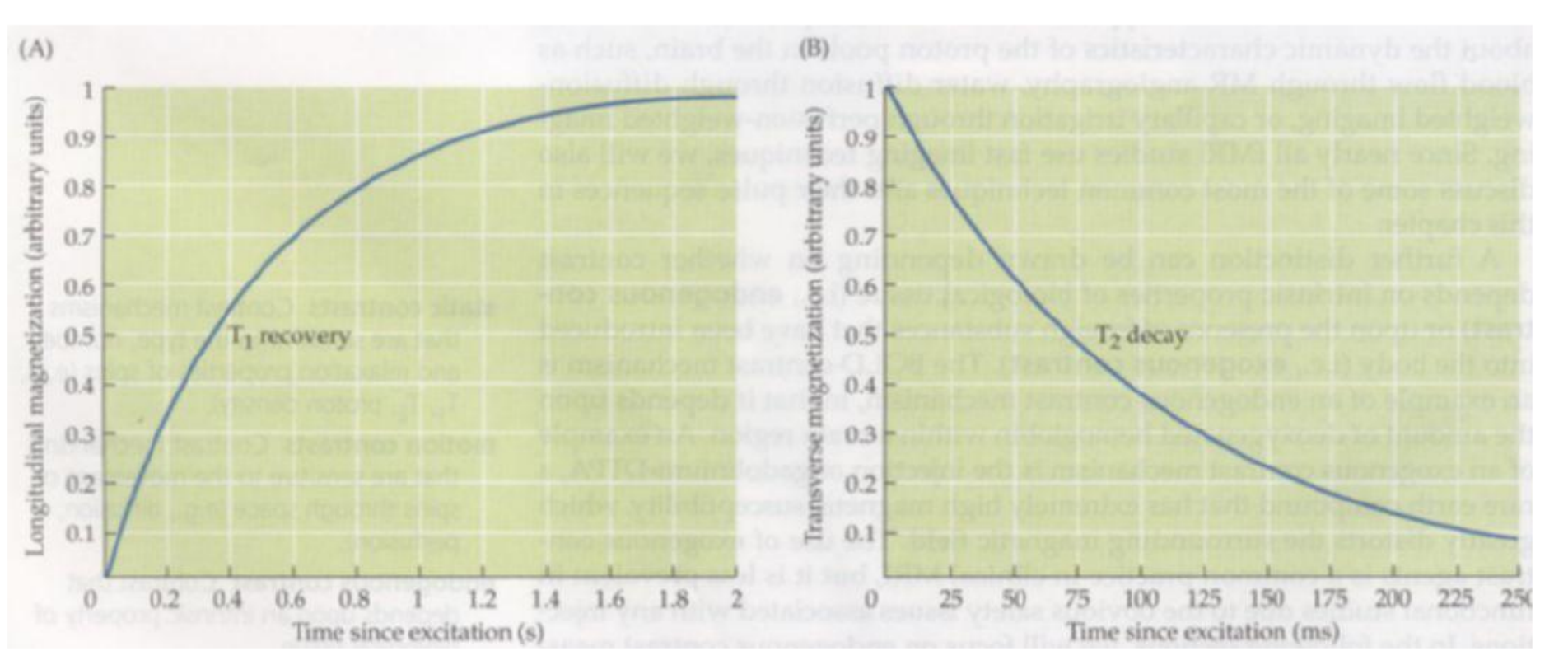
T1 = relaxation time for the longitudinal component M_Z

T2 = relaxation time for the transverse component $M_\perp$

Relaxation of longitunal (M_z) and transverse (M_{xy}) components of M in grey matter

$$M_z = M_0(1-e^{-t/T1})$$

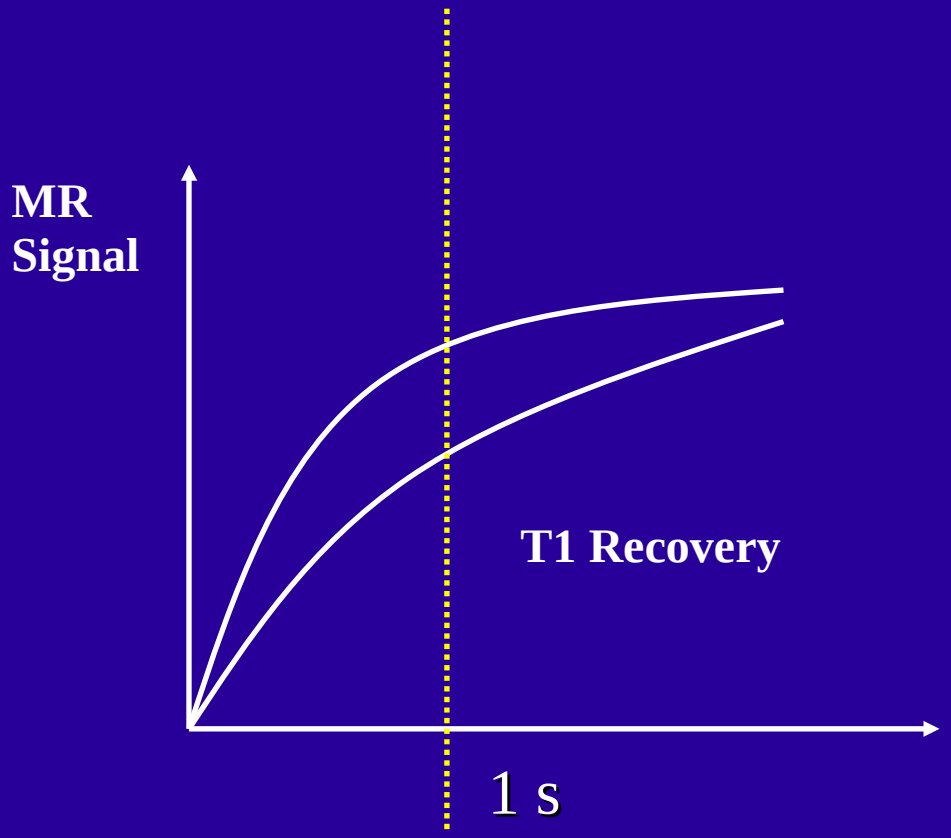
$$M_{xy}=M_0e^{-t/T2}$$



Manipulating the time between two excitations (TR) to contrast two tissues with differing T1 values

With a short TR (< T1), the longitunal magnetic moment has not yet completly recovered when the second excitation occurs.

The amplitude of the measured signal is proportional to M_z, therefore tissues with different T1 values will produce different signal intensities.



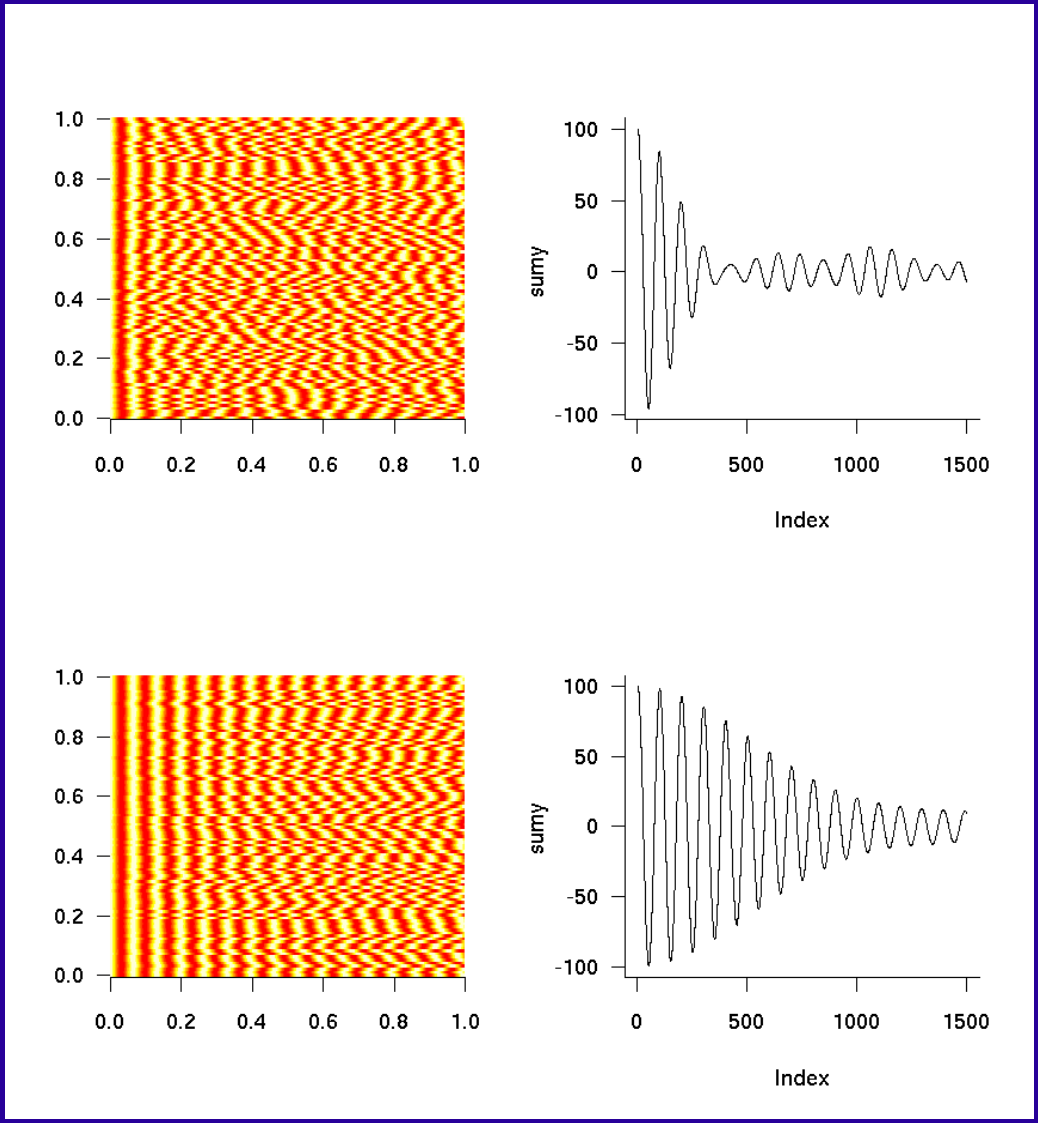
T2* relaxation

T2* is the time of the decrease of the Free induced decay (FID).

It is related to the speed at which protons become *out of phase*.

Protons become out of phase faster in presence of B_0 inhomogeneities (because they spin at different frequencies).

The more inhomogenous the B_0 field is, the less signal you observe.



Summary: Different tissues have different relaxation times. These relaxation time differences can be used to generate image contrast.

- T1 - Gray/White matter
- T2 - Tissue/CSF
- T2* - Susceptibility (functional MRI)

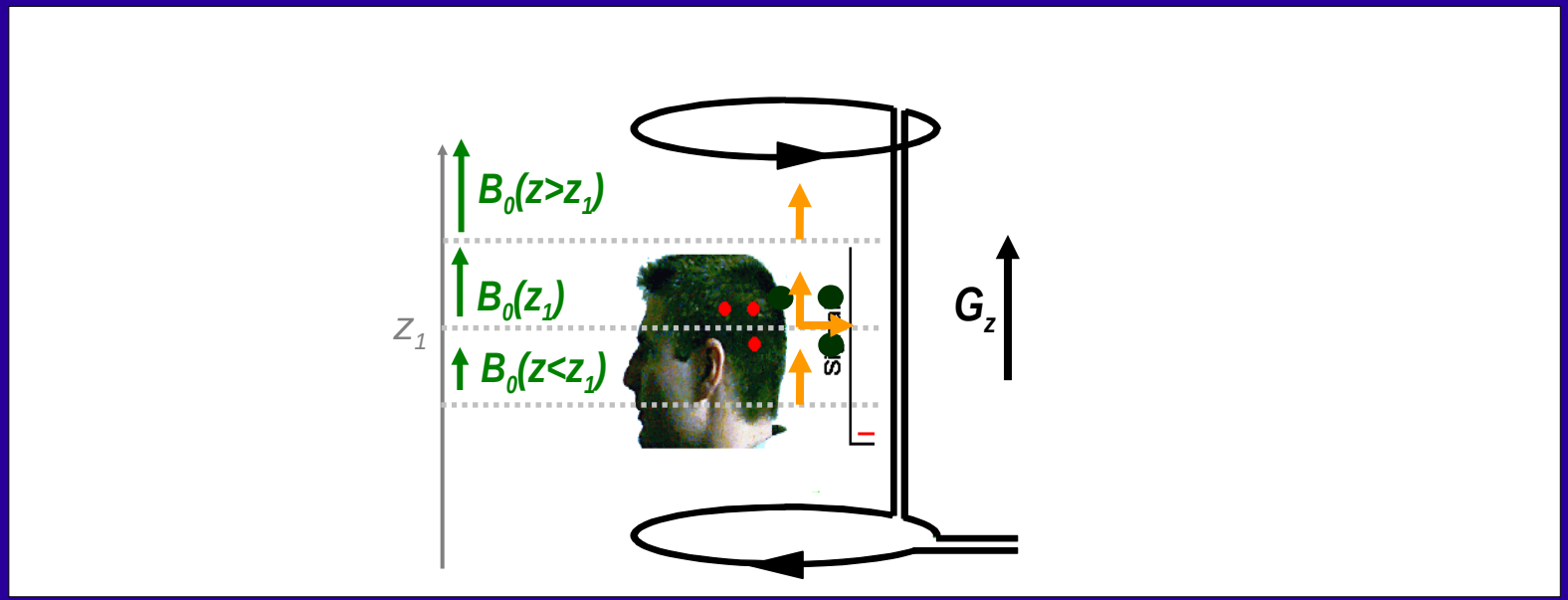
One essential ingredient of the MRI method is missing. Which ?

Spatial encoding of images

- There is only one signal for the whole Brain !!!
- Then, how to get spatial information ???

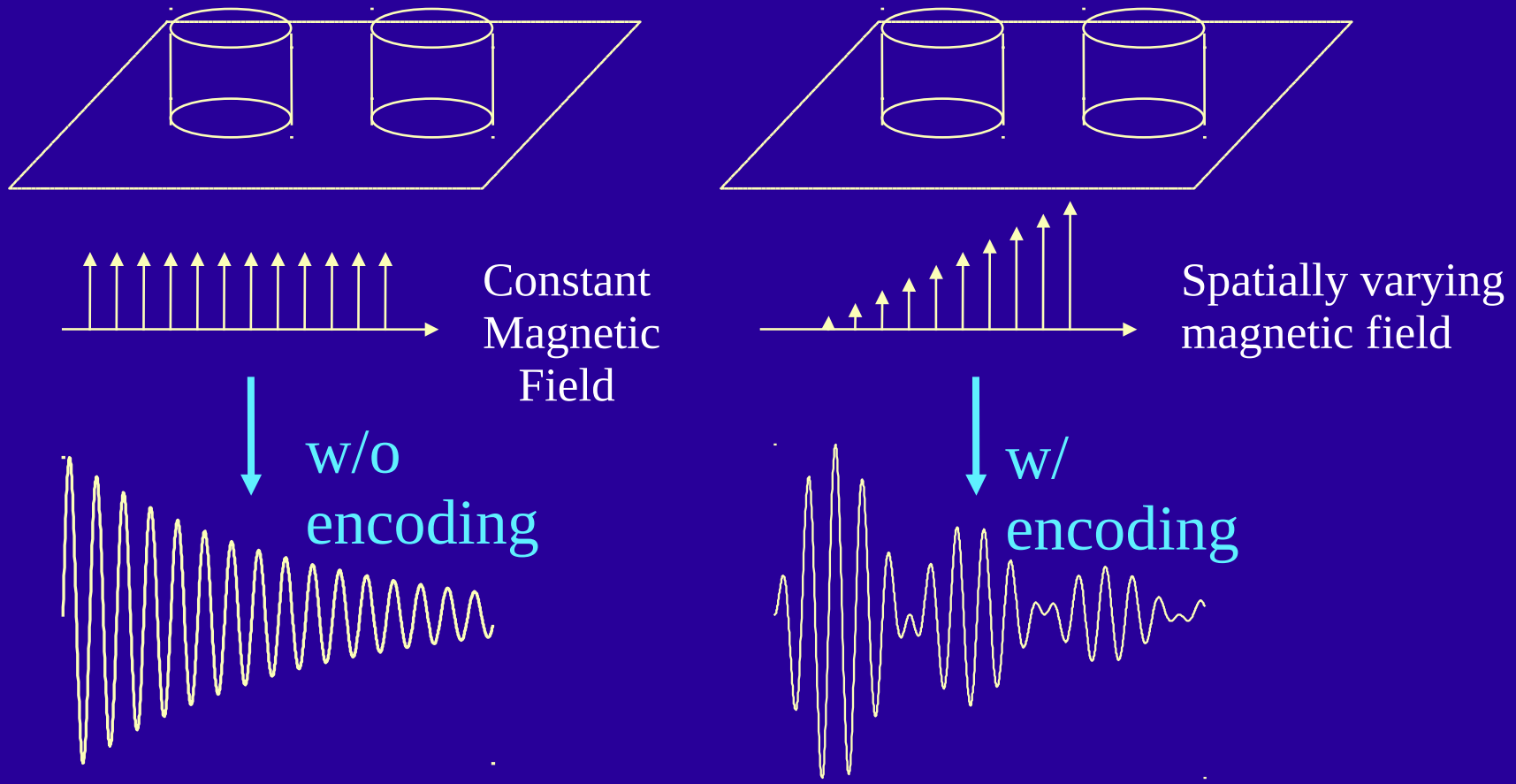
Spatial encoding 1: slice selection

- By creating a spatial gradient of B, different slices (plane perpendicular to B) have different Larmor frequencies.
- By sending a RF at a given frequency, it possible to excite protons only in the relevant slice.

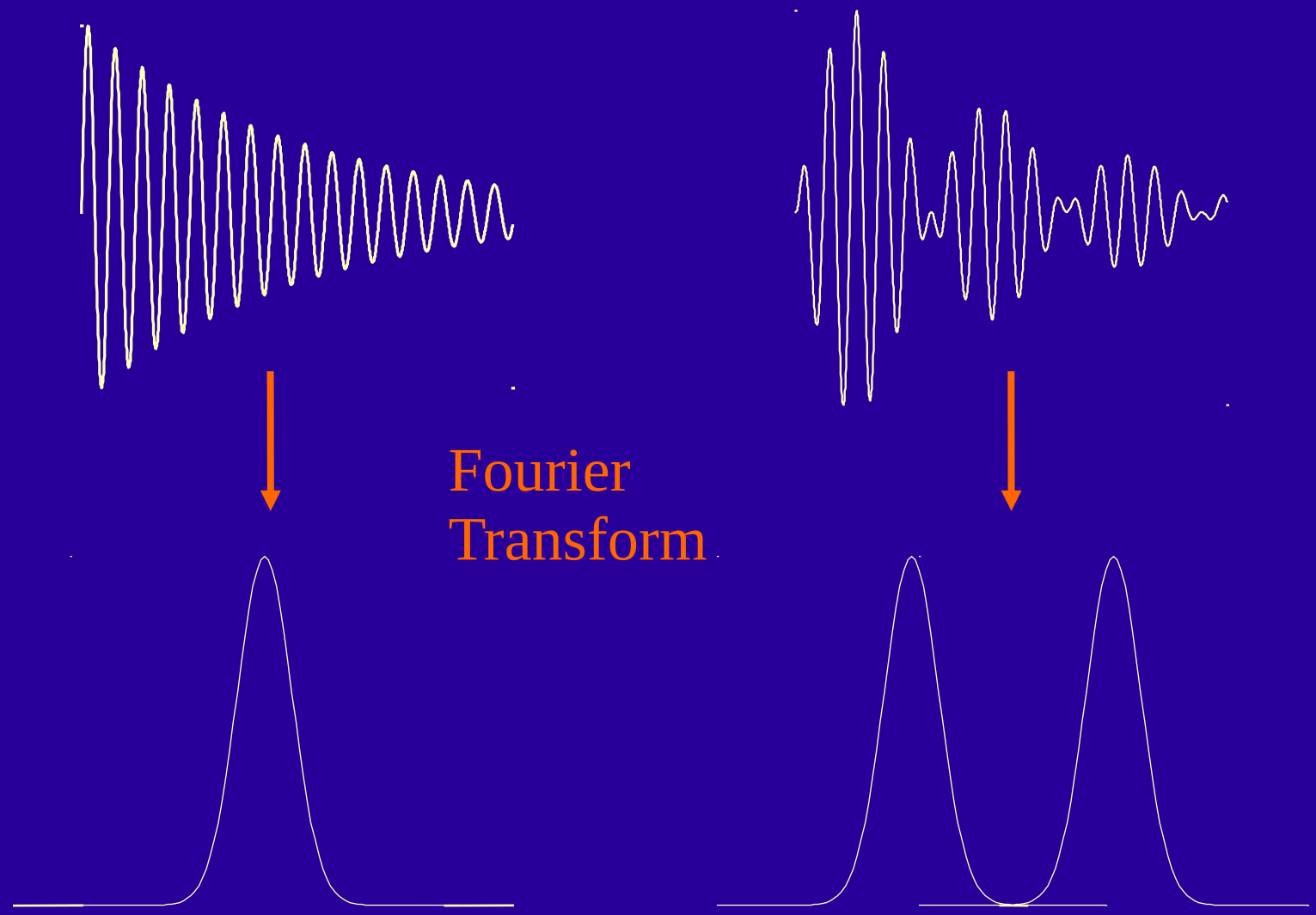


Using frequency to encode spatial position

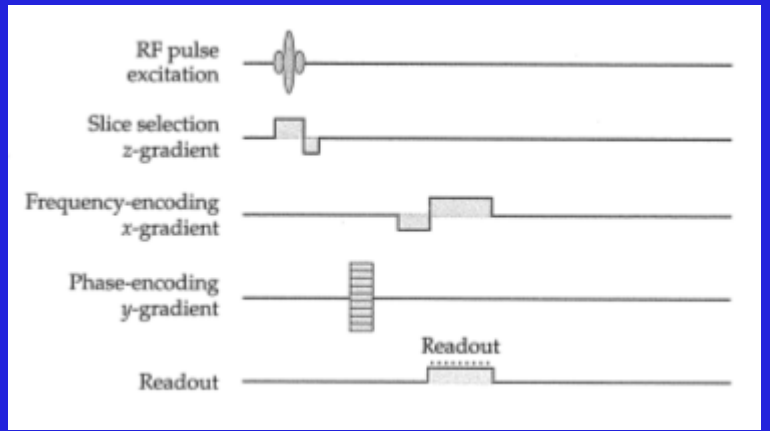
- With a gradient along the x axis: the Larmor frequencies will vary along the 'x' axis.
- frequency information <=> spatial information



Readout of the MR Signal



Summary of image formation



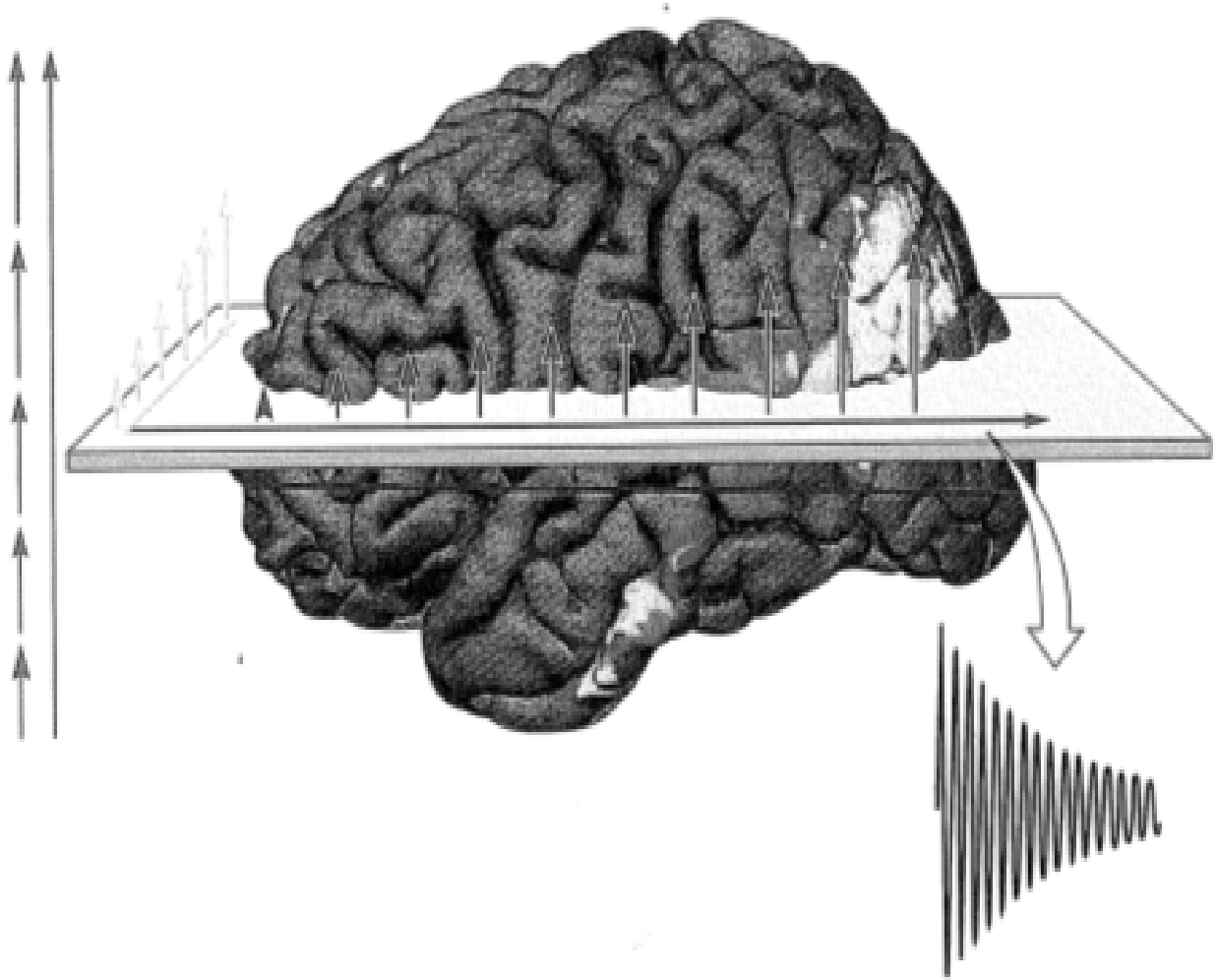


Figure 4.8 Summary of image formation. For most images acquired during fMRI experiments, three steps are used: initial selection of a two-dimensional slice (blue), and combined phase encoding (yellow) and frequency encoding (red). Data acquisition is typically done concurrently with encoding.

The general MRI Signal Equation

$$S(t)=\int_x \int_y \int_z M_{xy0}(x,y,z)e^{-t/T_2}e^{-i\omega_0 t}e^{-i\gamma\int_0^t (G_x(\tau)x+G_y(\tau)y+G_z(\tau)z)d\tau}dxdydz \quad (4.14)$$

Equation 4.14 can be read as stating that the total MR signal measured at any point in time reflects the sum across all voxels of the net magnetization at time point zero, multiplied by a decay factor based on T_2, with the accumulated phase given by the combined strength of the static magnetic field and of the gradient field at that point in space. This vastly important equation is known as the MR signal equation, because it reveals the relationship between the acquired signal, *S(t)*, and the properties of the object being imaged, *M(x,y,z)*. It is important to recognize that this equation is sufficiently general to describe the MR signal in virtually all imaging methods.

Huettel, Song & McCarthy *Functional Magnetic Resonance Imaging*

Video (6min) : https://www.youtube.com/watch?v=wrlQxlo0uT4

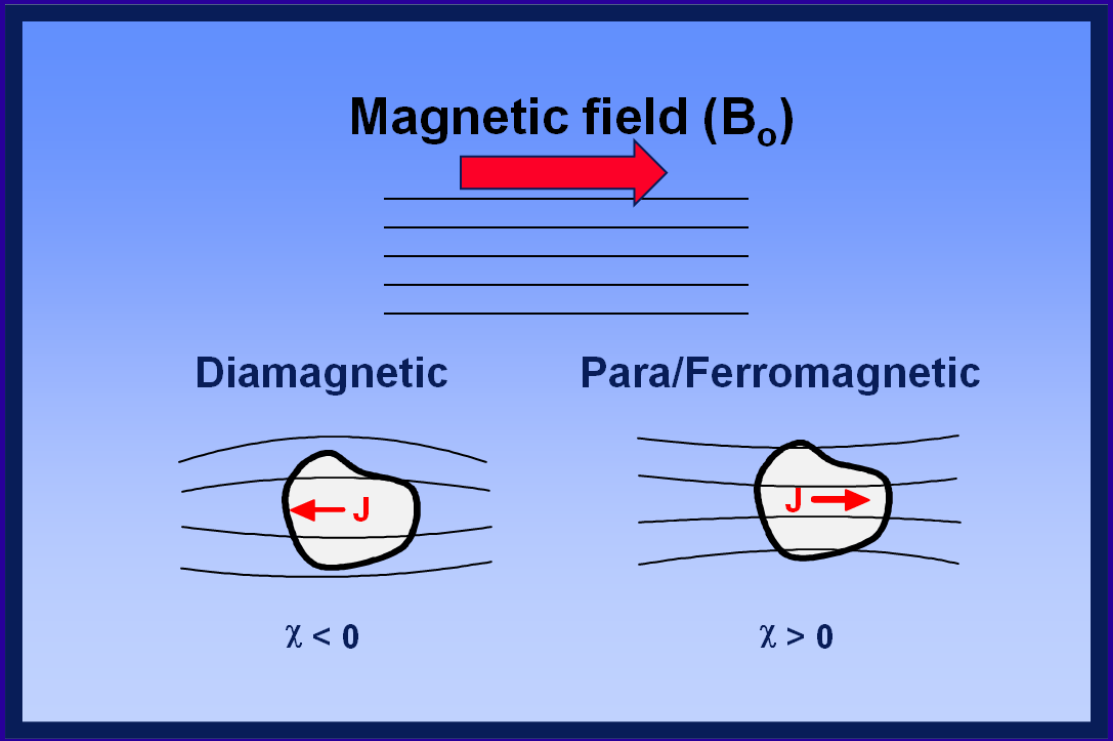
Functional MRI

The basis of functional MRI images

Oxyhemoglobin and Deoxy-hemoglobin have different magnetic properties :

- OxyH is diamagnetic (it repels magnetic field)

- DeoxyH is paramagnetic (it attracts magnetic field).



A change in the local concentrations of oxy/deoxy haemoglobin creates **local distortions** of the magnetic field.

Increase in deoxy-Hb => smaller T2*

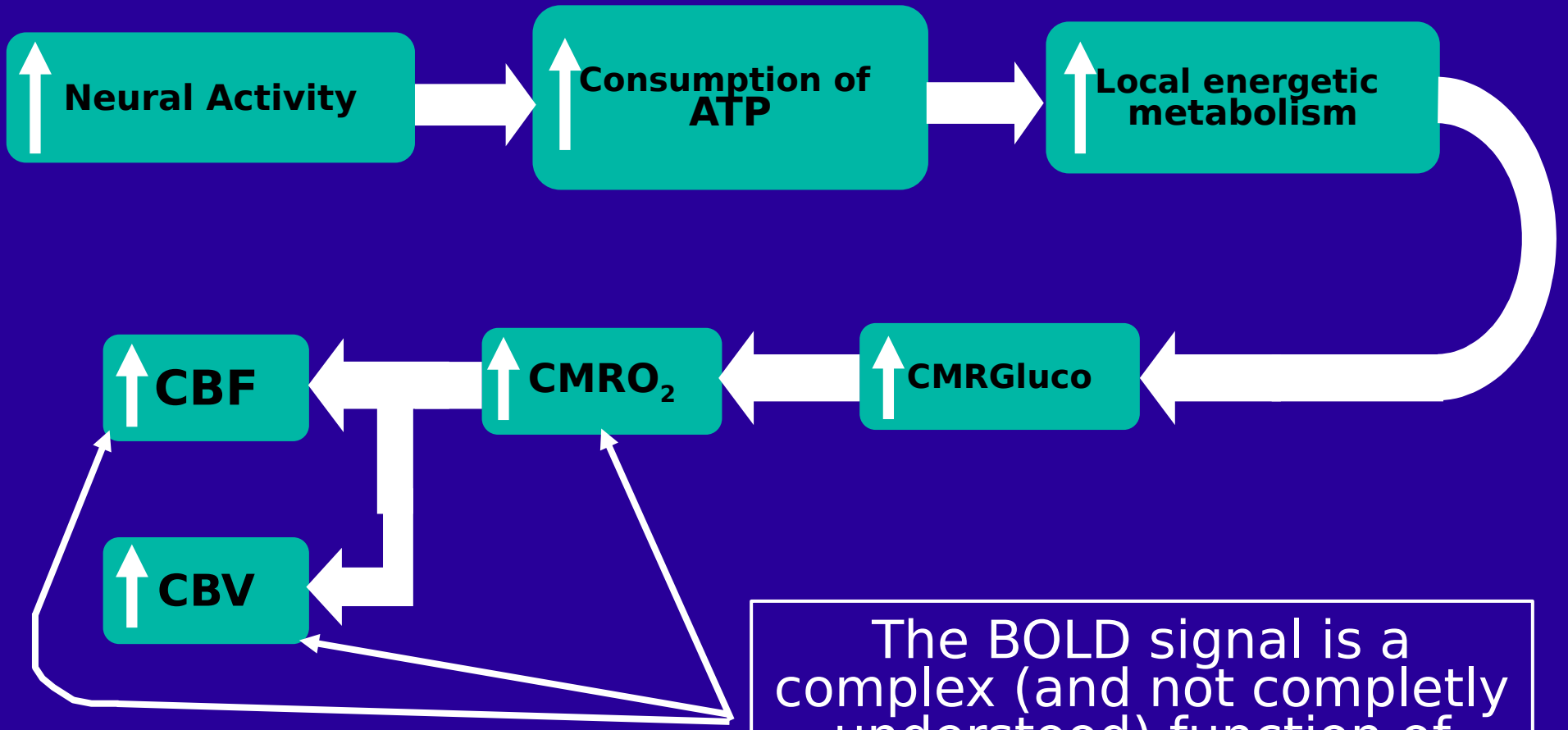
Increase in oxy-Hb => larger T2*

fMRI is based on the Blood Oxygen Level Dependent (BOLD) signal endogenous contrast

- BOLD signal = differences in T2* between two conditions

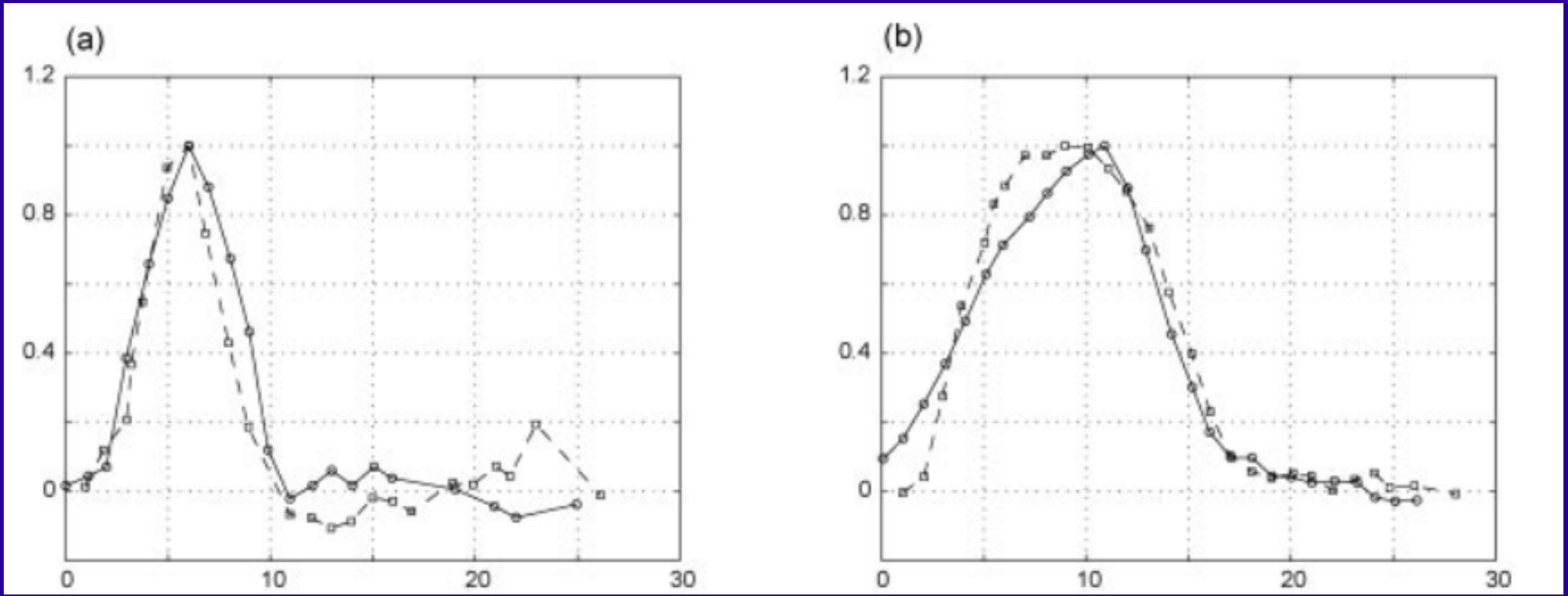
=> SHOW an example of an 4D fMRI scan

Cerebral activation



The BOLD signal is a complex (and not completly understood) function of these parameters.

The BOLD response to sensory events



Time course of the BOLD response. Data are replotted from experiments in motor cortex (open circles) and visual cortex (open squares). The two panels show measurements in response to a **visual stimulus** or **movement** of 2 s (a) or 8 s duration (b).

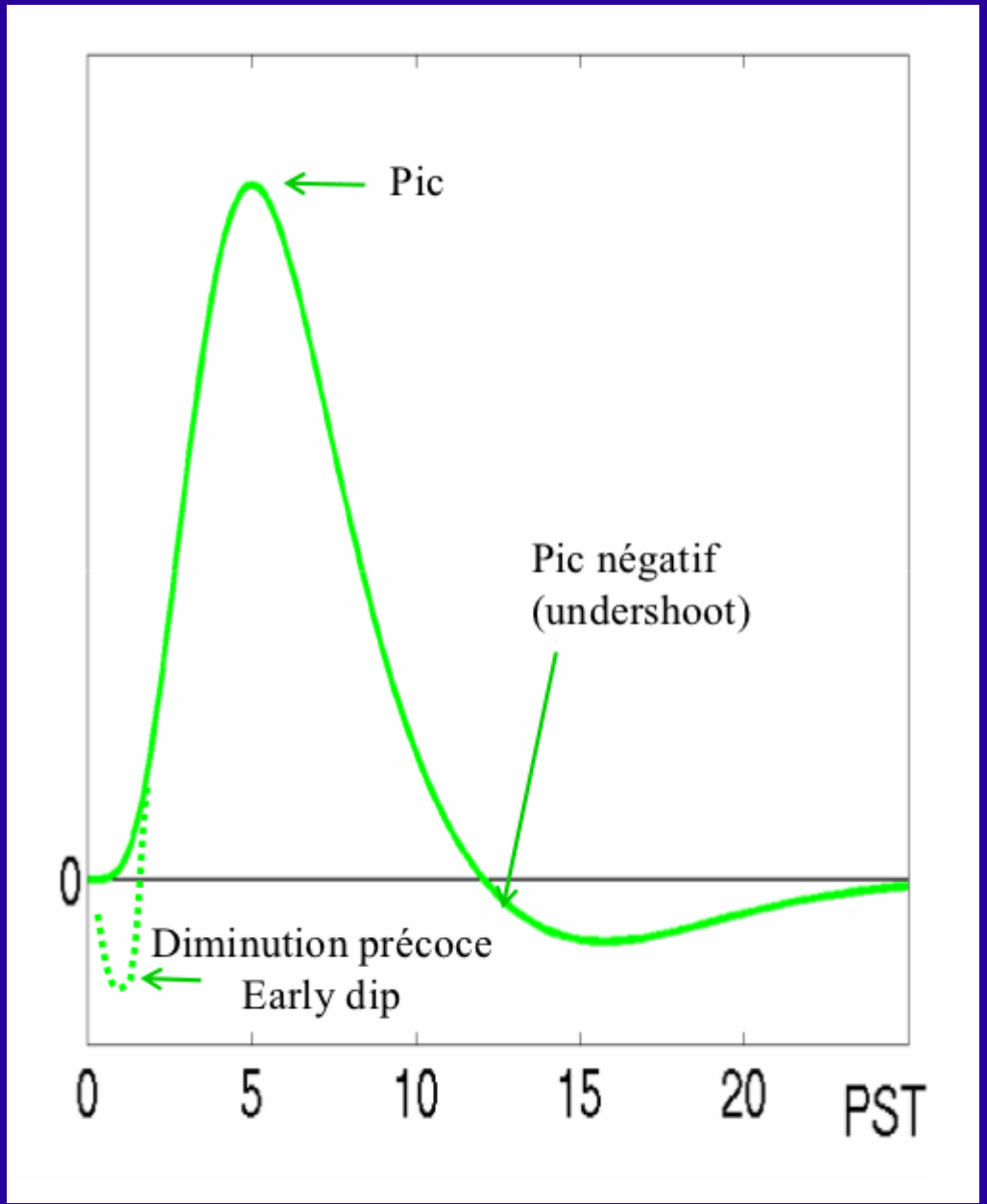
Logothetis (2004) *Ann. Rev. Neurosci*

The “impulse” BOLD response (response to a very short event)

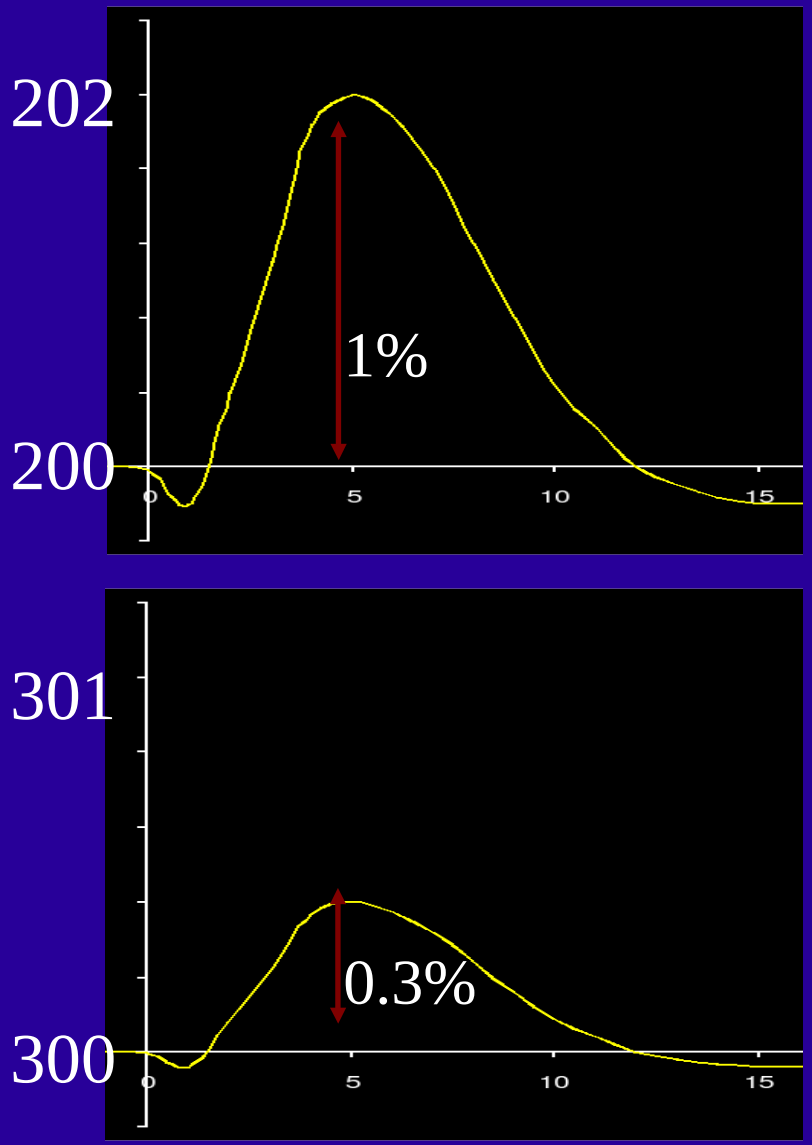
Reaches a peak 4~6 seconds after the event then goes back to baseline (in ~20 sec)

Sometimes, it is possible to detect an 'early dip'

It is similar, but varies, across brain regions and individuals



Percent Signal Change

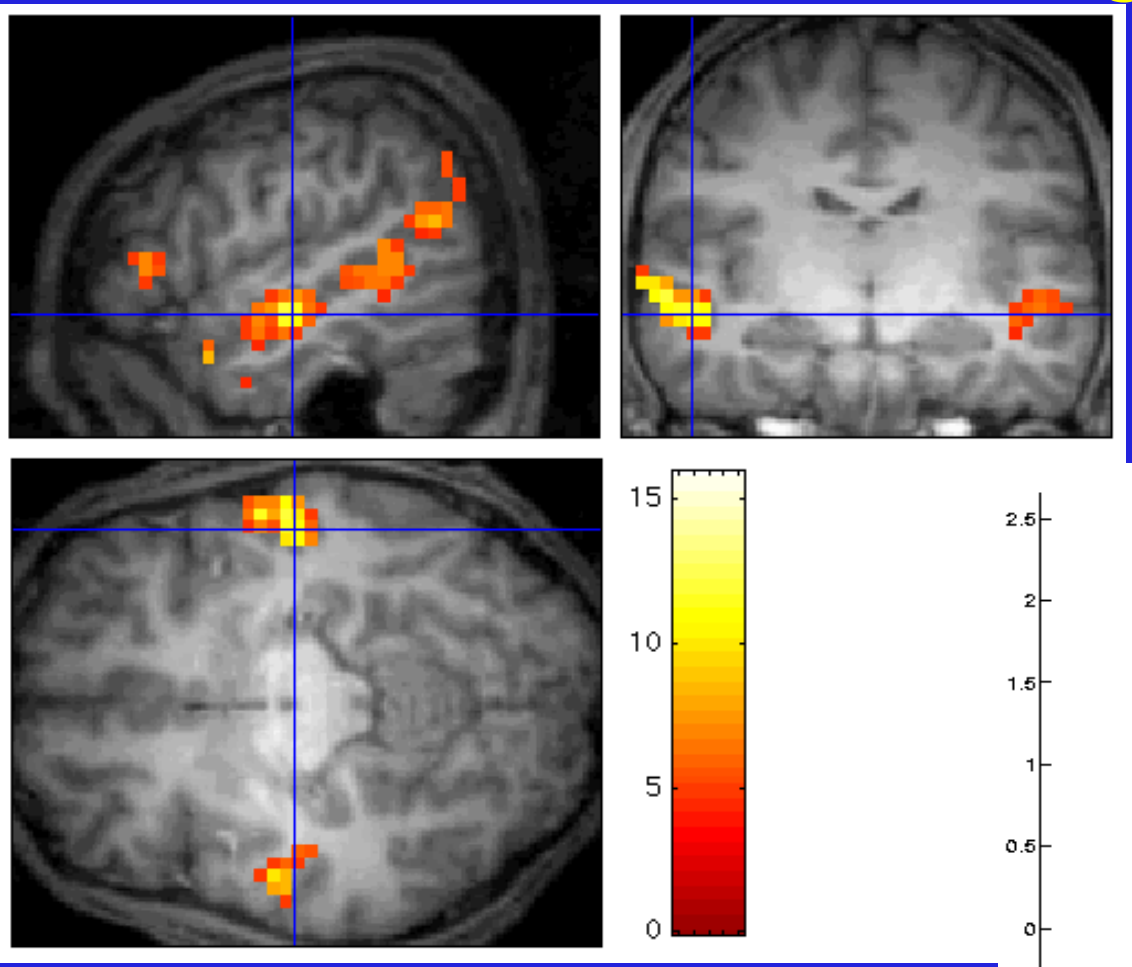


- Peak / mean(baseline)
- Often used as a basic measure of “amount of activity”
-
- To compare two experimental conditions one compares the signal changes.

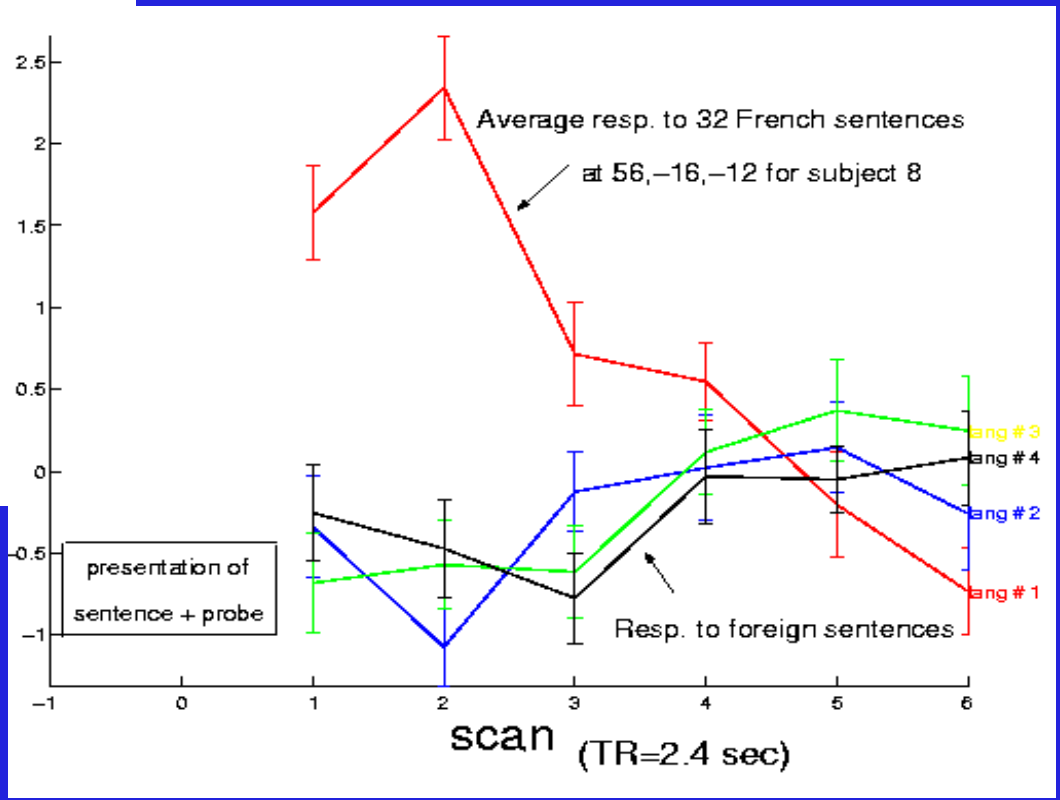
The delay is good news for auditory fMRI:

- The scanner makes a lot of noise when an image is being taken.
- As the haemodynamic response is delayed, it is possible to present auditory stimuli in **silent periods between scans.**

Example of data in one French subject: areas showing more activation following French sentences than foreign sentences.



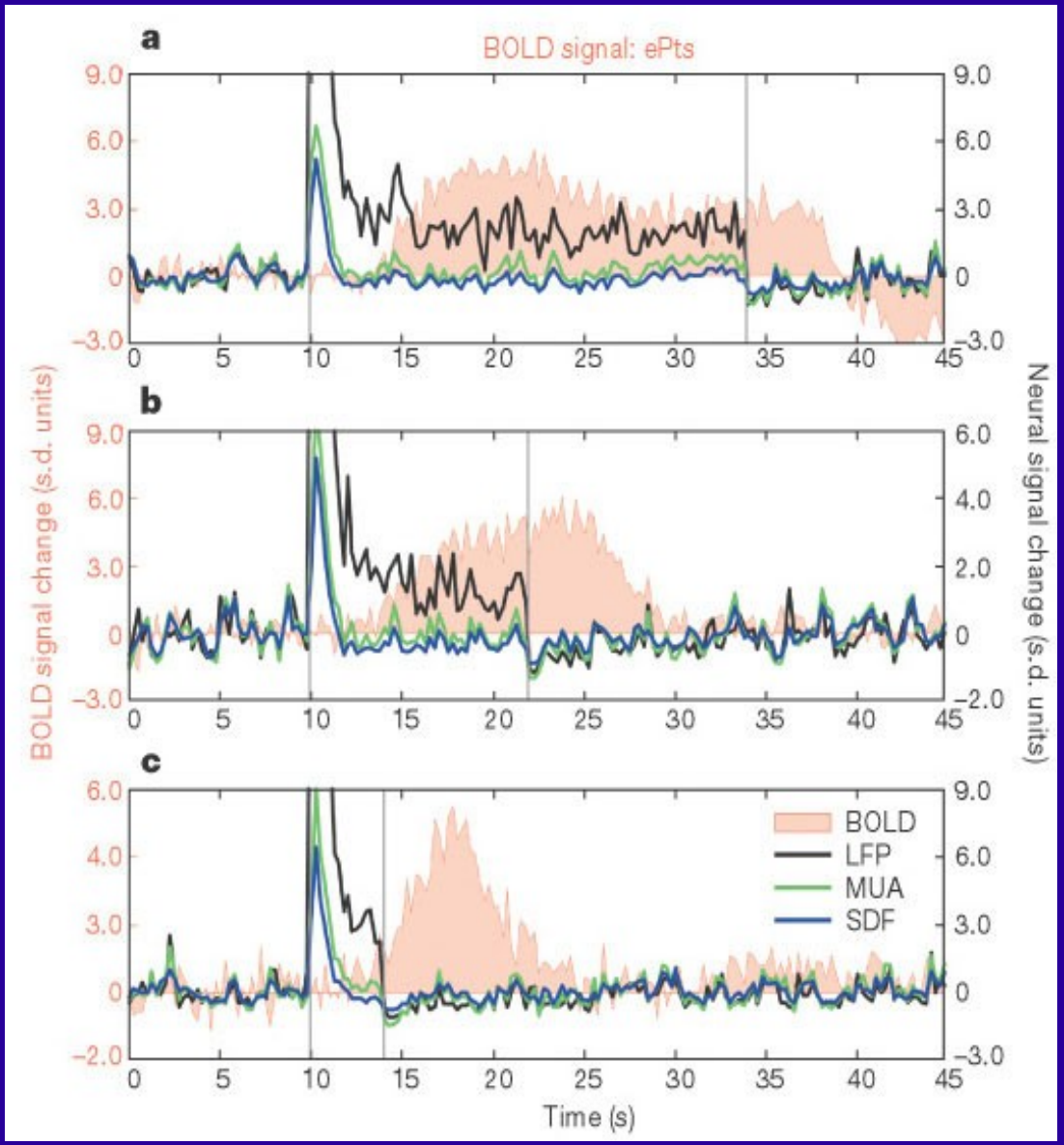
(threshold: p<0.05 FWE-corrected)



Relationship between neural activity and the BOLD signal

Simultaneous recordings of fMRI and electrical activity (!!!) in cells of monkey visual cortex revealed that fMRI correlates more with Local Field Potentials (LFP), than with spiking activity.

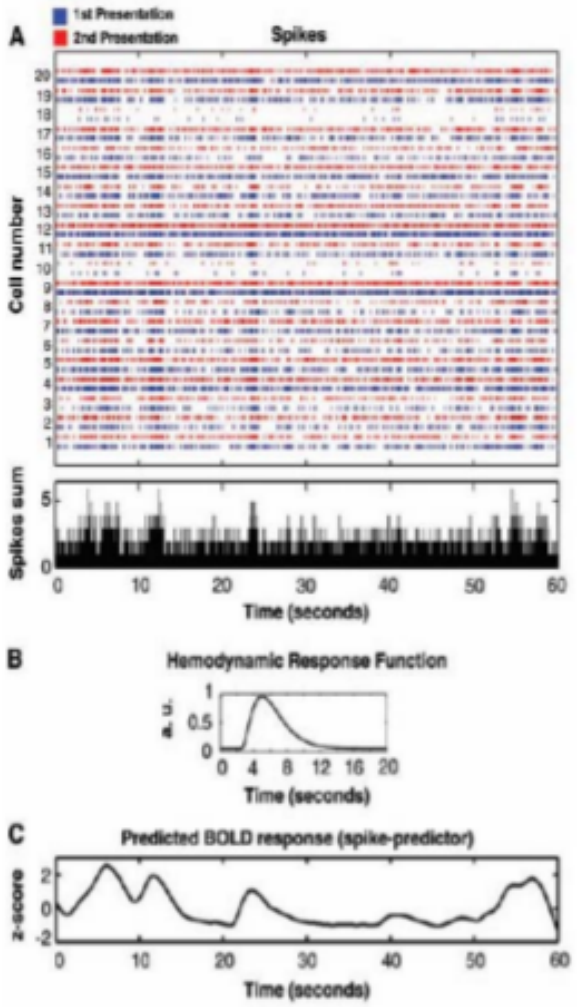
FMRI may mostly reflect postsynaptic activity (like EEG/MEG).



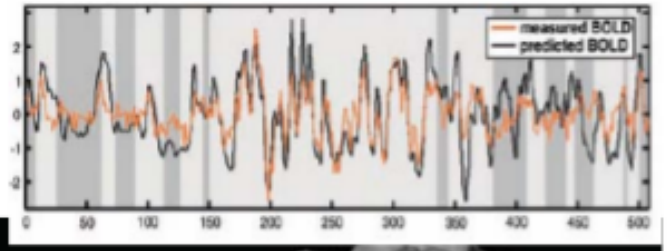
(Logothetis et al. 2001 *Nature*)

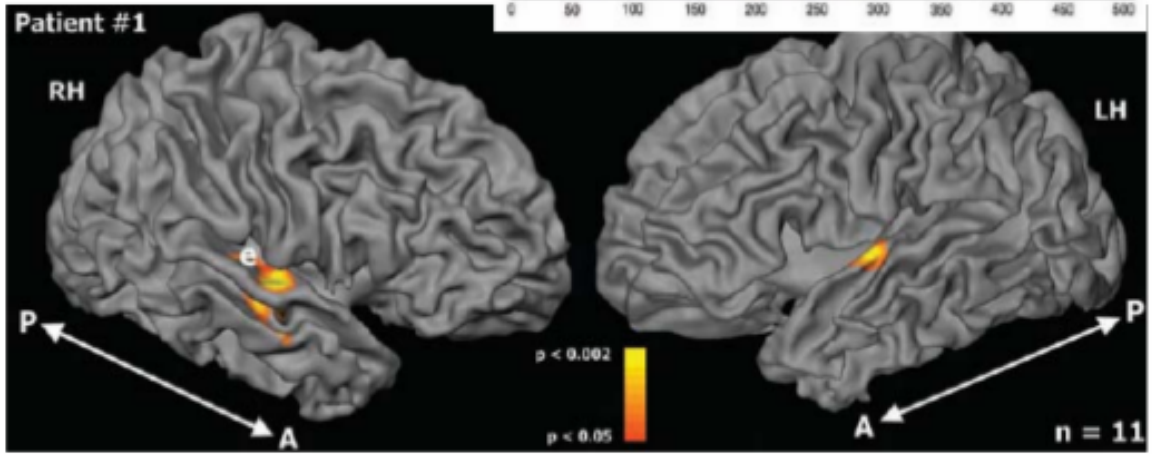
Chez l'homme, corrélation entre l'activité neuronale et l'IRM fonctionnelle

Décharges neuronales multi-unitaires enregistrées chez deux patients avec électrodes implantées dans le cortex auditif lors de la vision d'un film « Le bon, la brute et le truand »

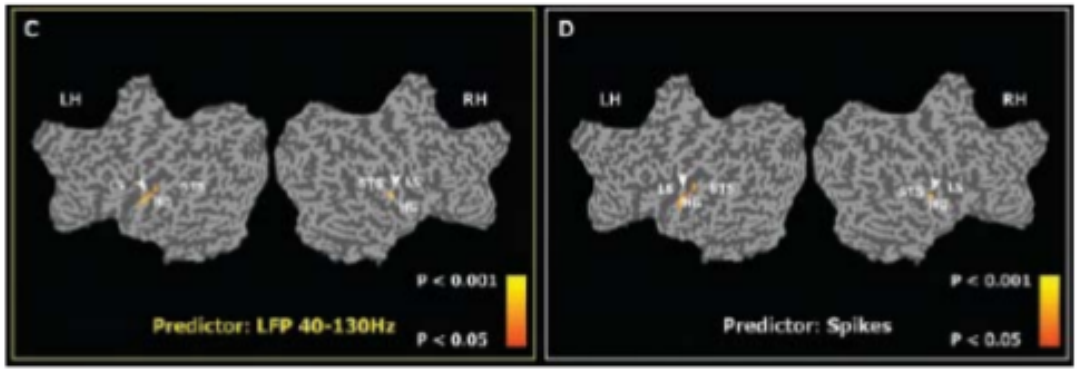


Prédiction du signal IRMf observé chez 11 *autres* sujets



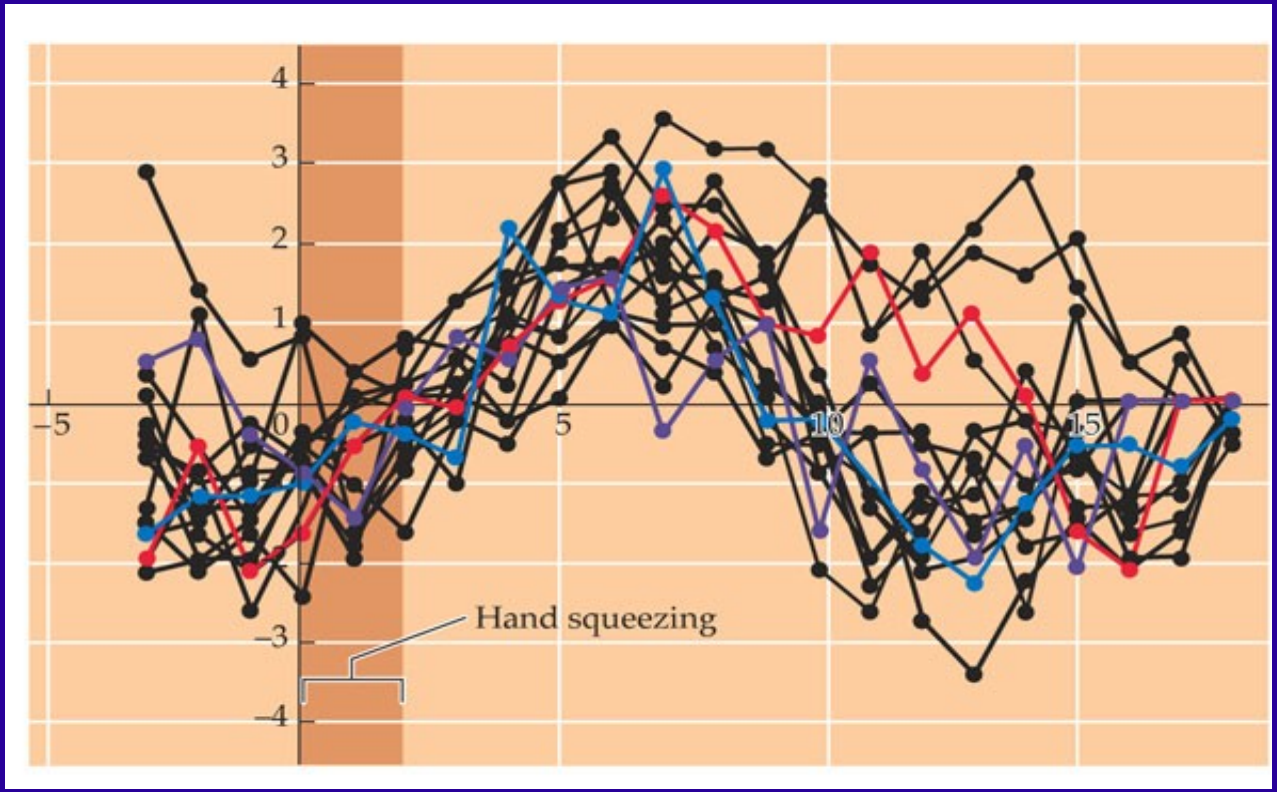


La prédiction est comparable avec les décharges et le champ de potentiel local



Mukamel, R., Gelbard, H., Arieli, A., Hasson, U., Fried, I., & Malach, R. (2005). Coupling between neuronal firing, field potentials, and FMRI in human auditory cortex. *Science, 309*(5736), 951-954.

Trial to Trial Variability



Huettel, Song & McCarthy, 2004, Functional Magnetic Resonance Imaging

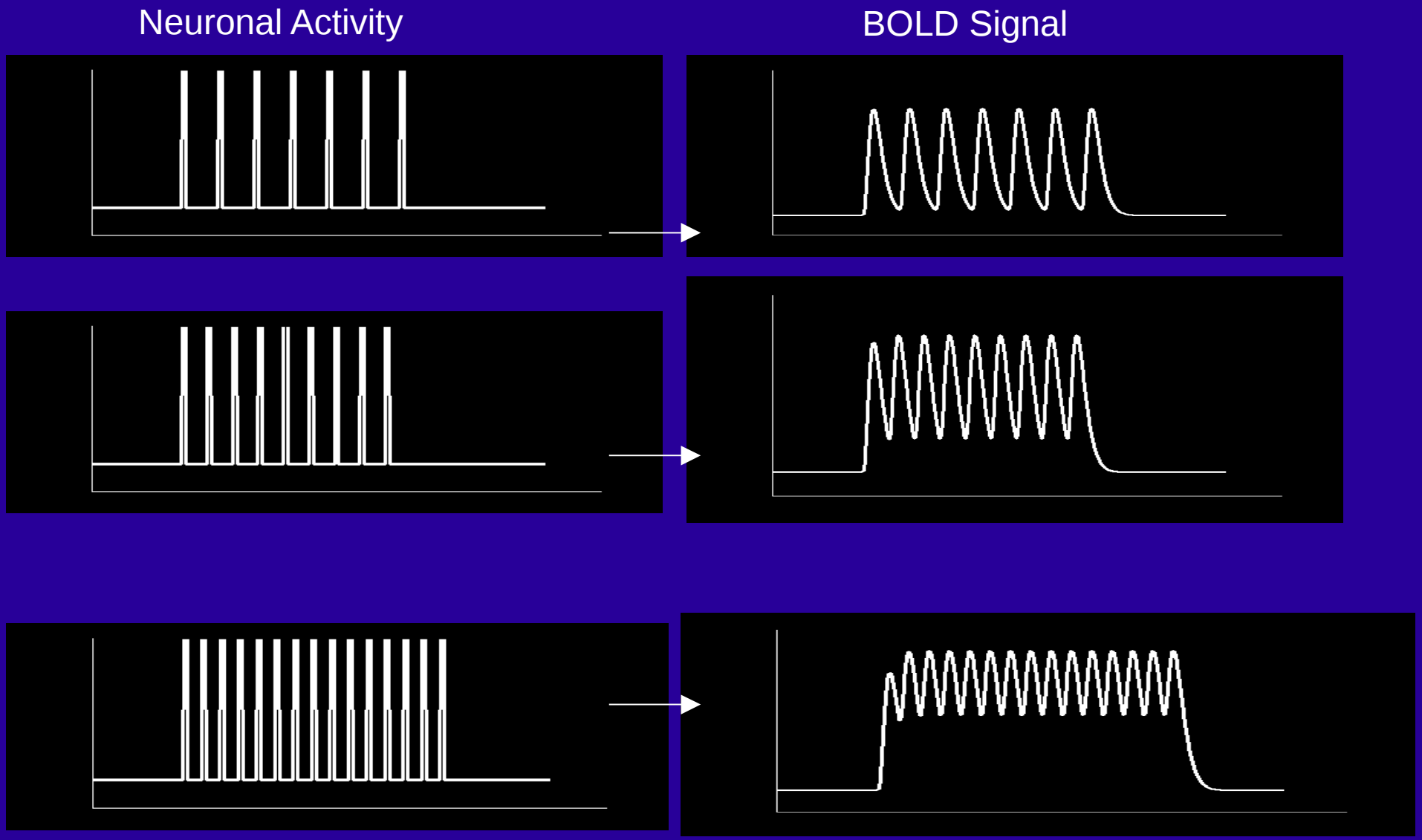
From trial to trial, the measured signal varies.

You need several trials to make sure that variation is not due to random fluctuations of the signal.

The number of trials depends on the amplitude of the effect.

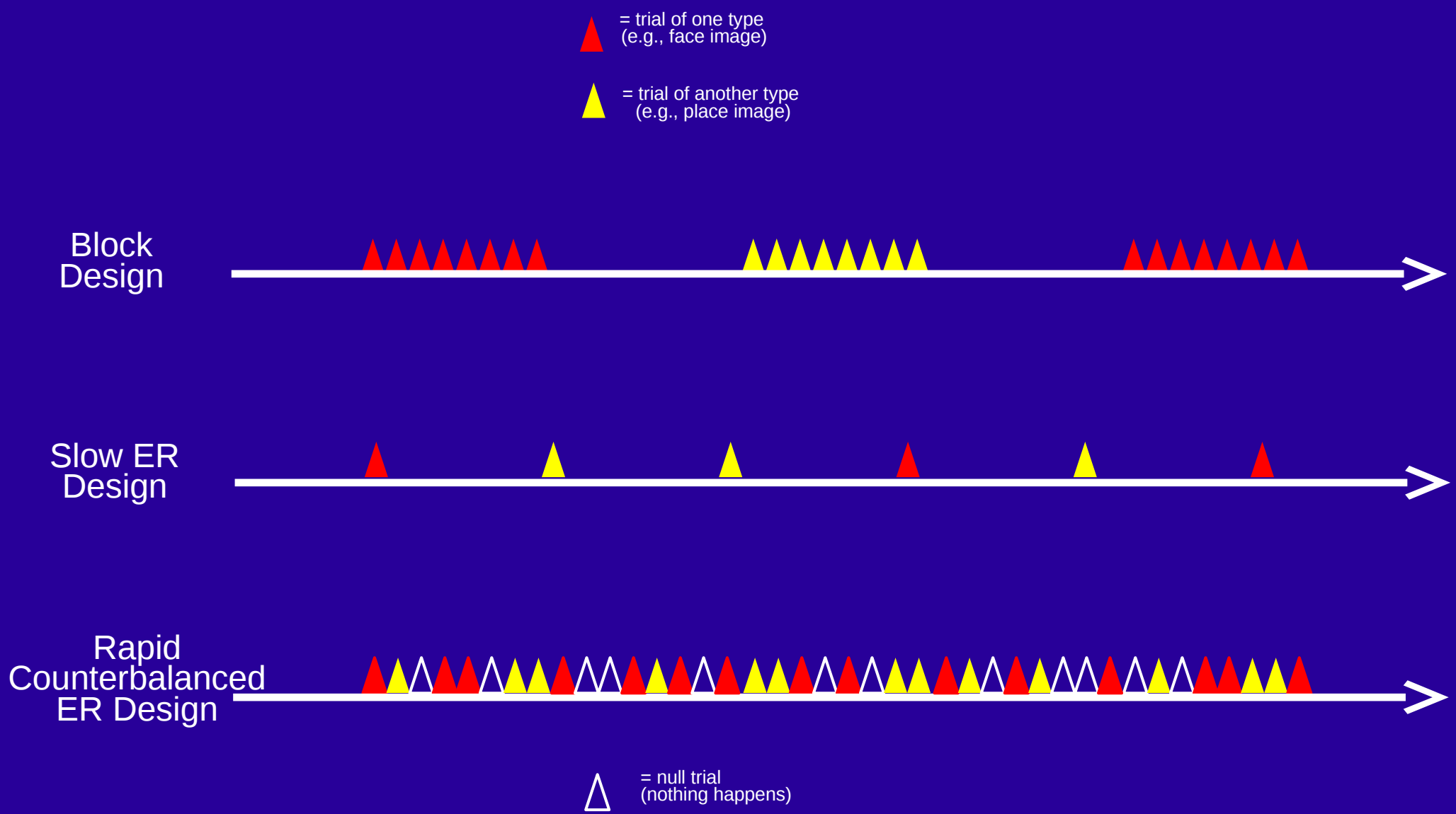
need of statistical tools...

BOLD Summates



Slide from Matt Brown

Design Types



Most important concepts

What does the intensity in MRI images represent ?

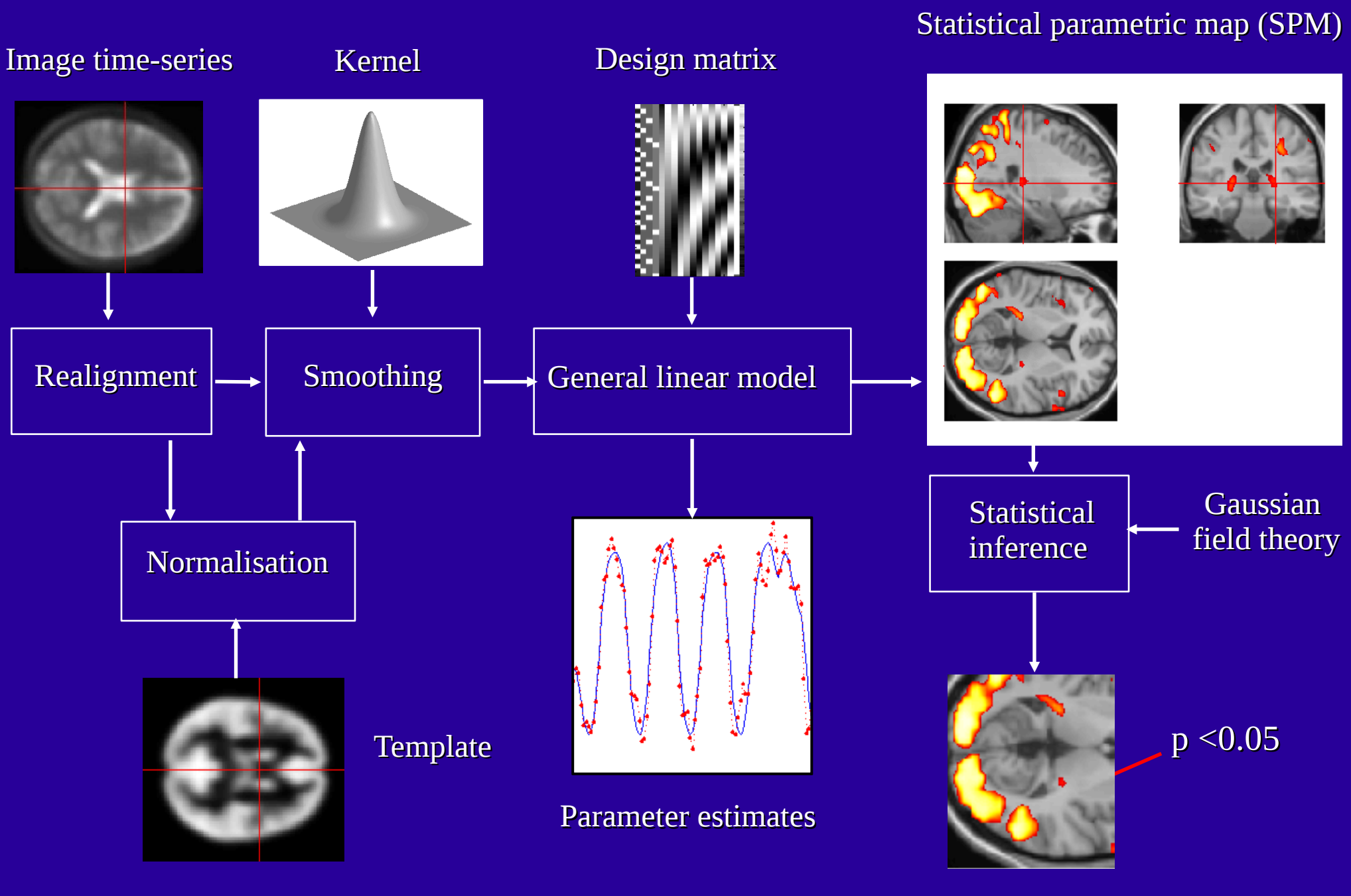
What property of blood makes functional MRI possible ?

What is the temporal profile of the BOLD response ?

What are the basic experimental designs in fMRI ?

Processing of Images

SPM processing pipeline for functional images

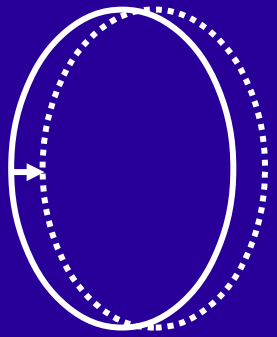


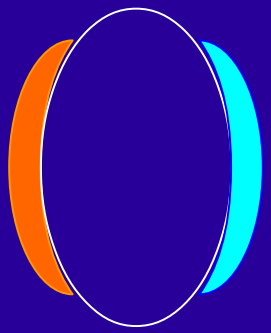
Head Motion: Main Artifacts

1. Head motion leads to spurious activation (particularly at the edges)
2. Regions move over time
3. Motion of head (or any other large mass) leads to changes to field map

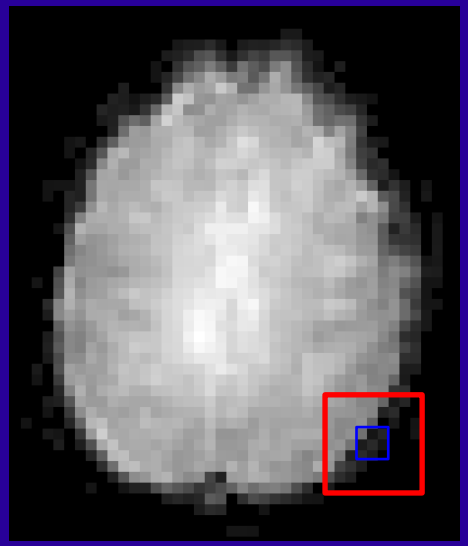
Spurious Activation at Edges

time1 → time2

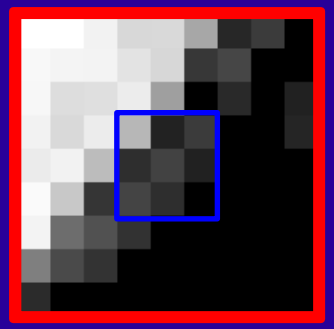




A

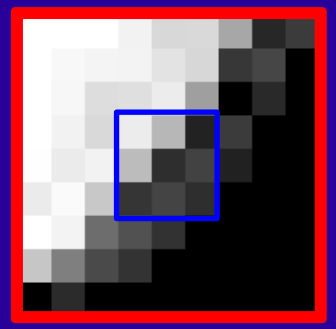


B



507	89	154
119	171	83
179	117	53

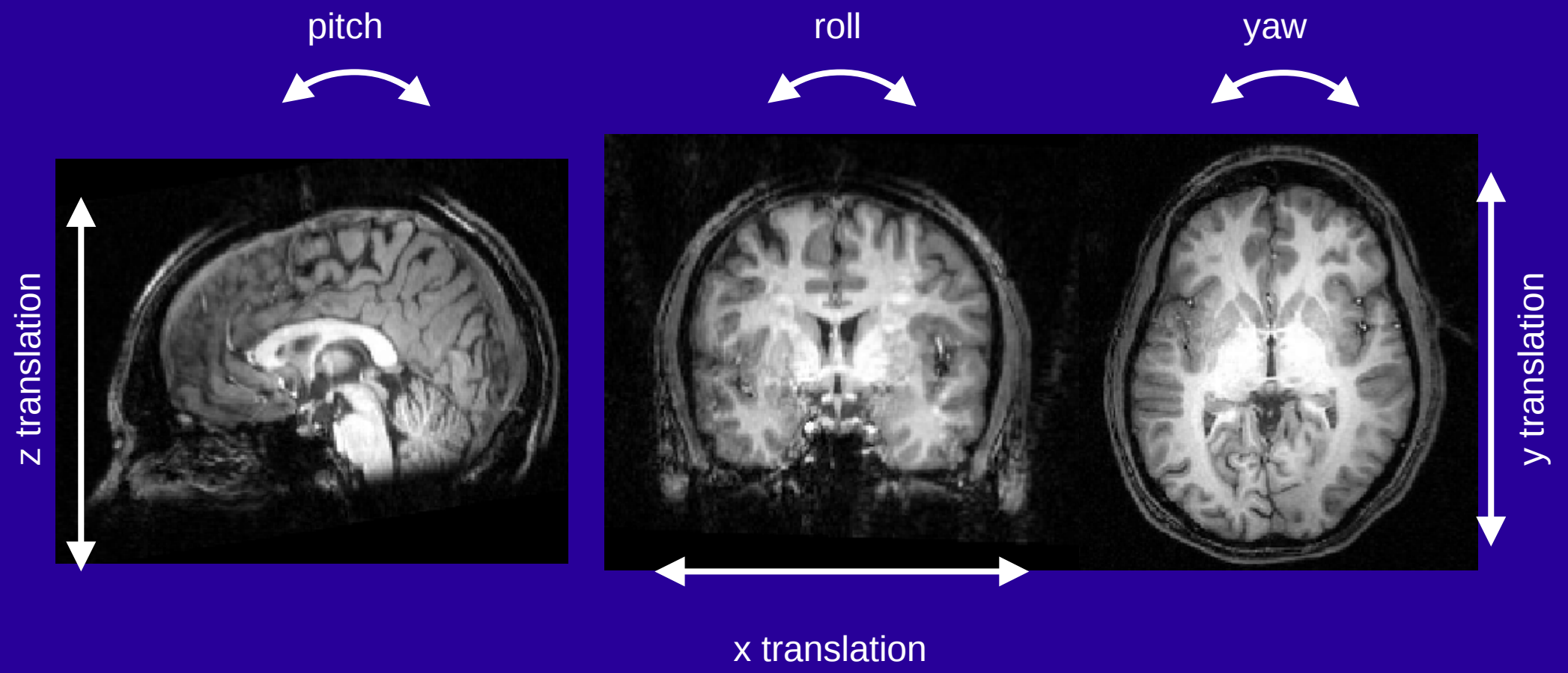
C



663	507	89
520	119	171
137	179	117

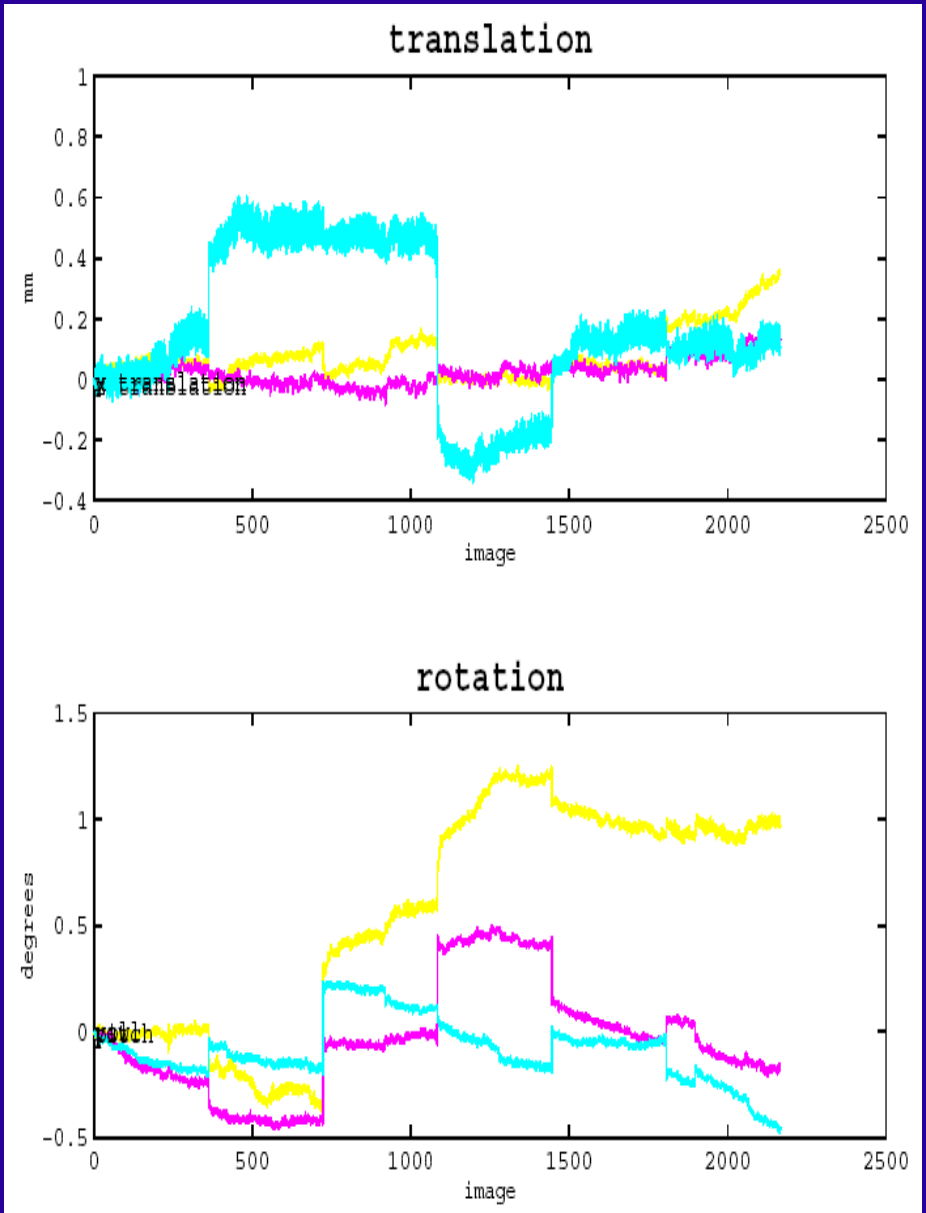
Slide modified from Duke course

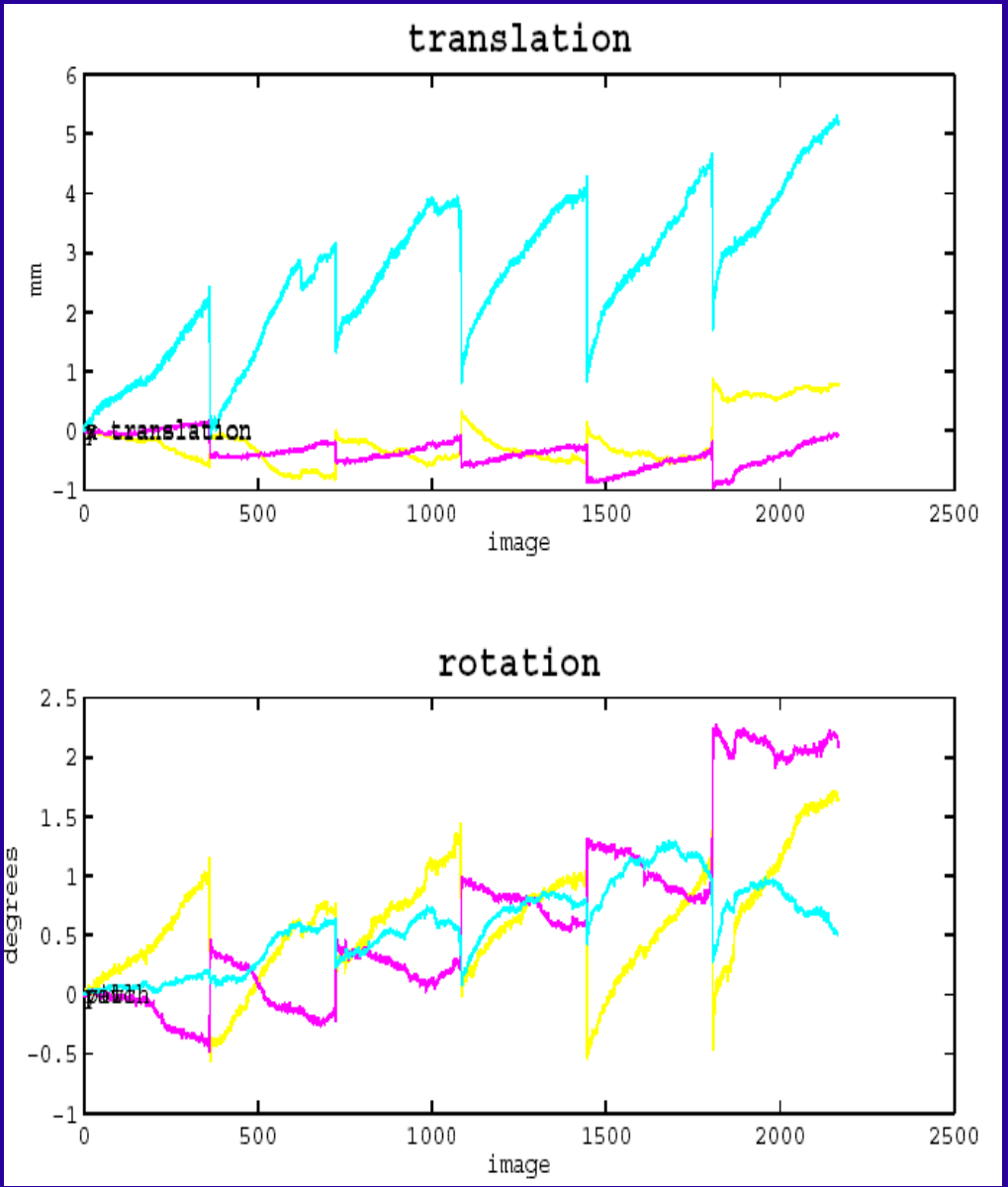
Motion Correction Algorithms



- Align each volume of the brain to a target volume using six parameters: three translations and three rotations
- Target volume: the functional volume that is closest in time to the anatomical image

Head Motion: Good, Bad,…





Slide from Duke course

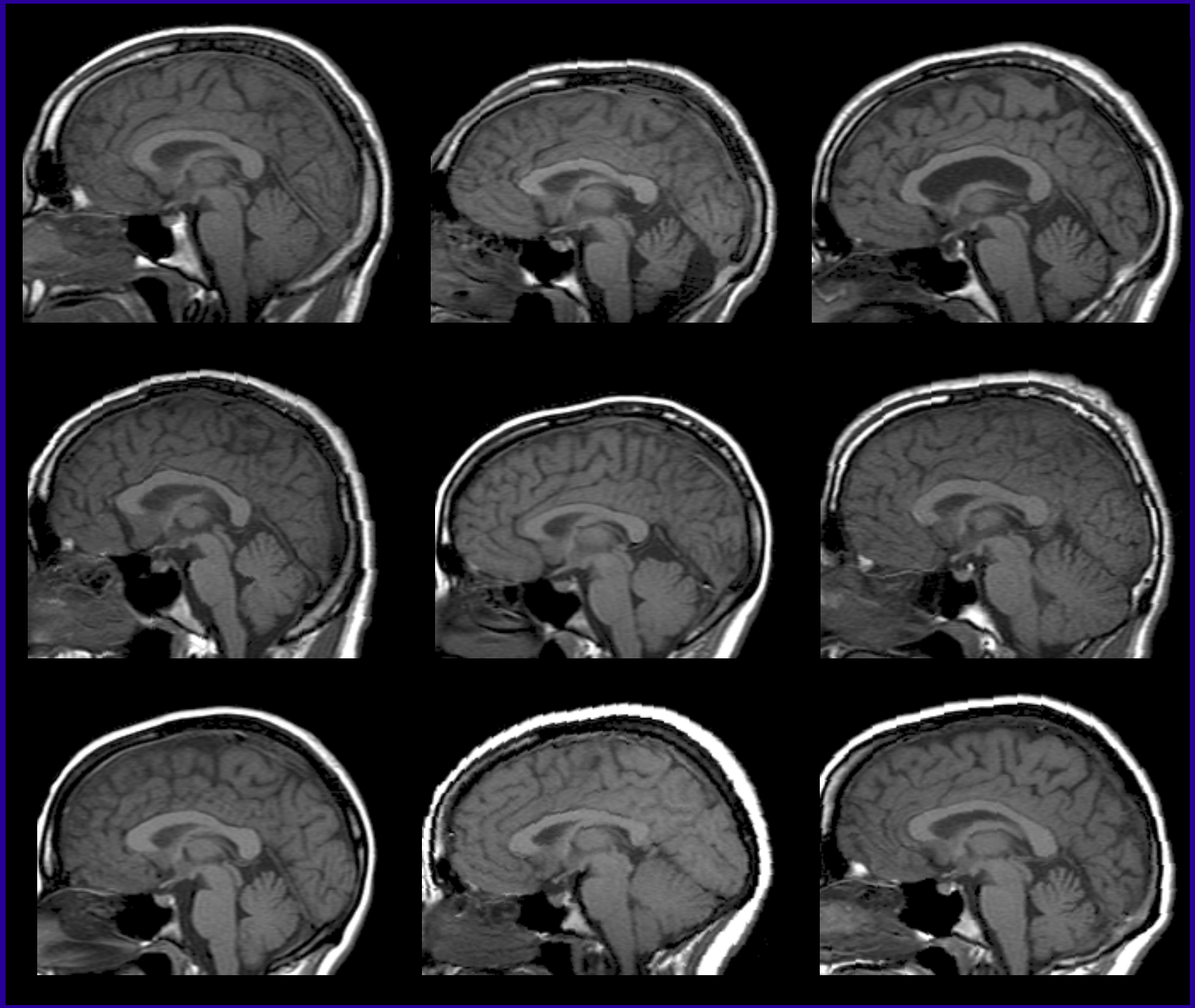
Correcting Head Motion

- Rigid body transformation
  - 6 parameters: 3 translation, 3 rotation
- Minimization of some cost function
  - E.g., sum of squared differences

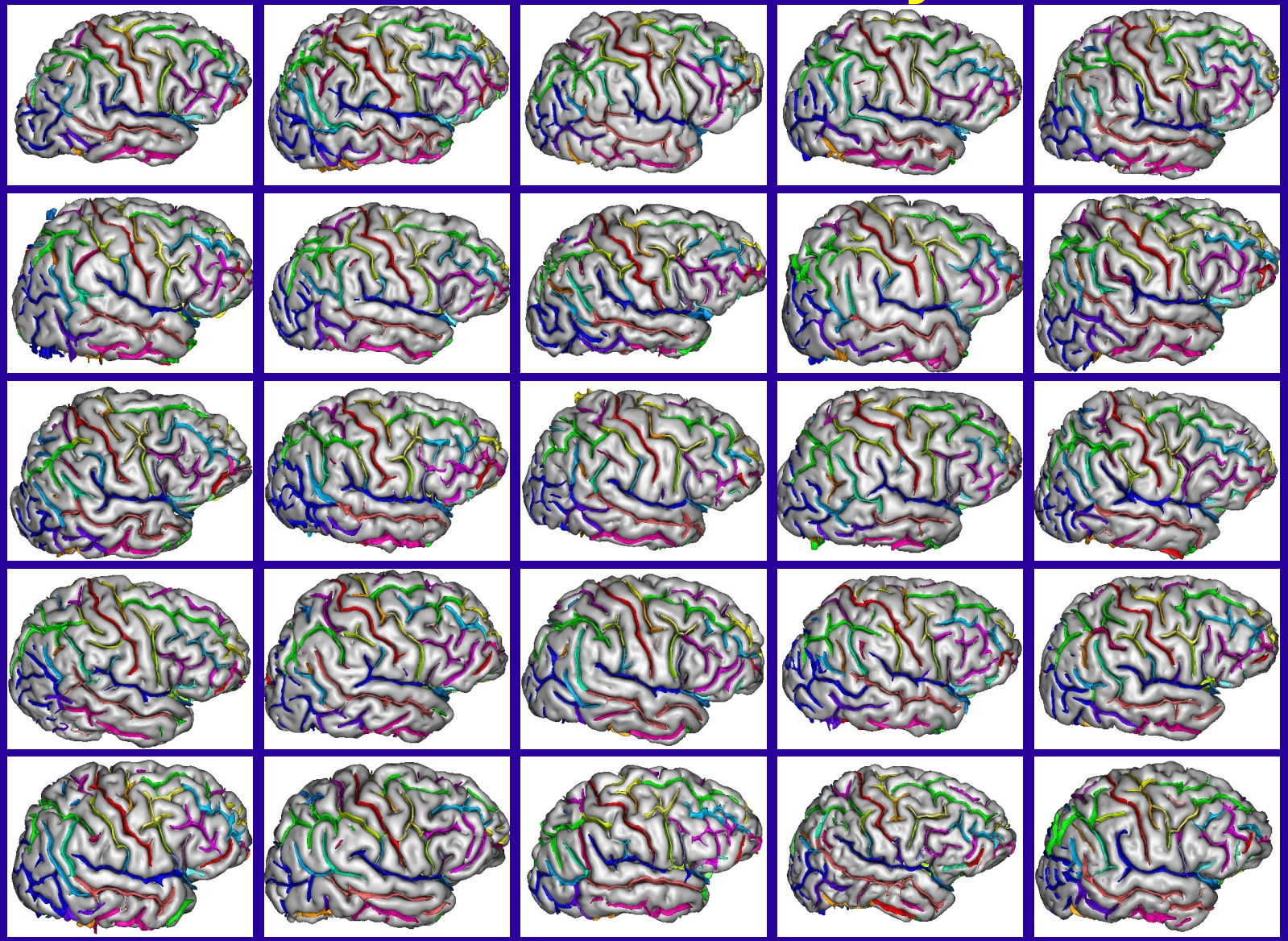
Correction for slice timing.

- Corrects for differences in acquisition time within a TR
  - Especially important for long TRs (where expected HDR amplitude may vary significantly)
  - Accuracy of interpolation also decreases with increasing TR

Spatial normalisation

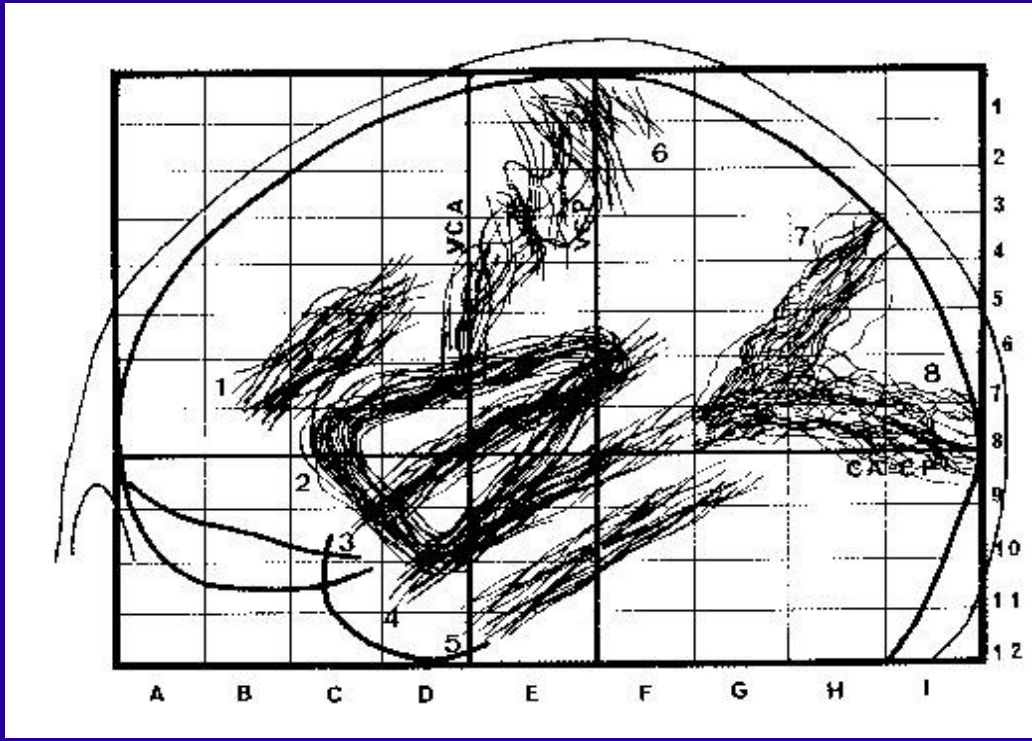


A database of manually labelled

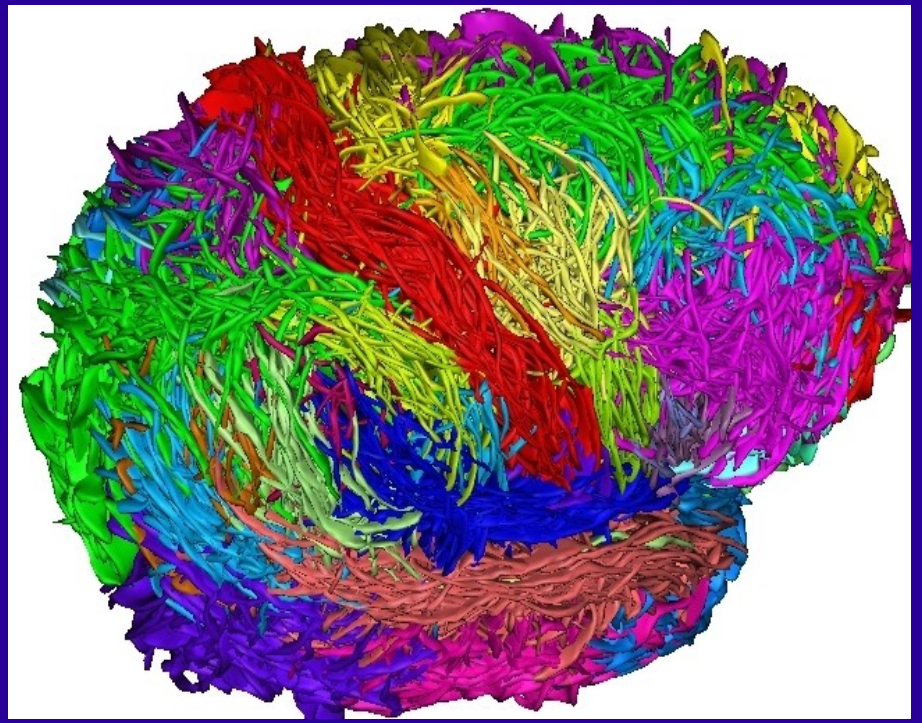


Jean-Francois Mangin & Denis Riviere, SHFJ, Orsay

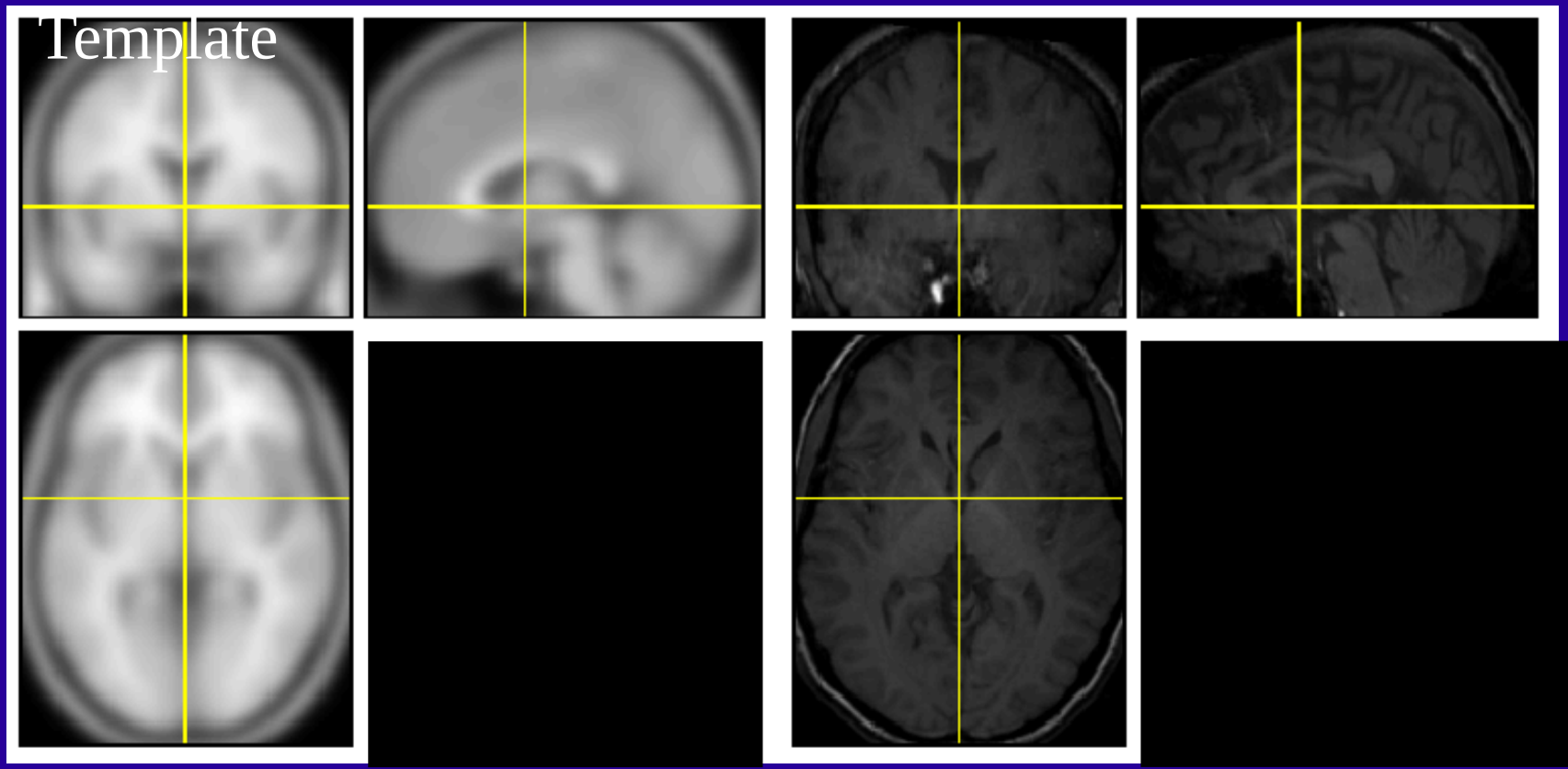
Variability of Sulci



Source: Szikla et al., 1977 in Tamraz & Comair, 2000

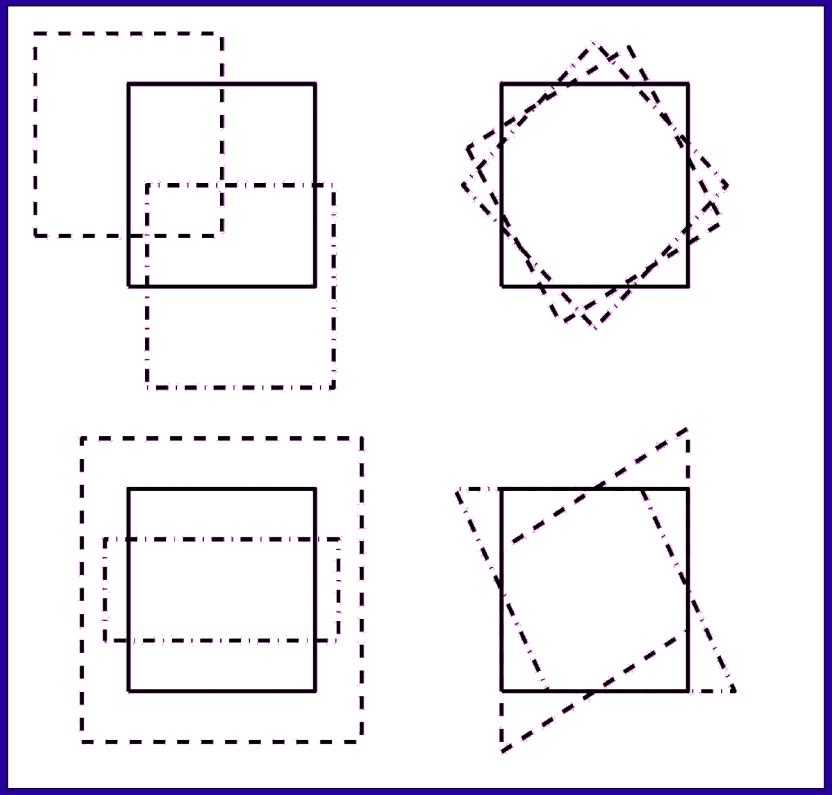


Normalization to Template



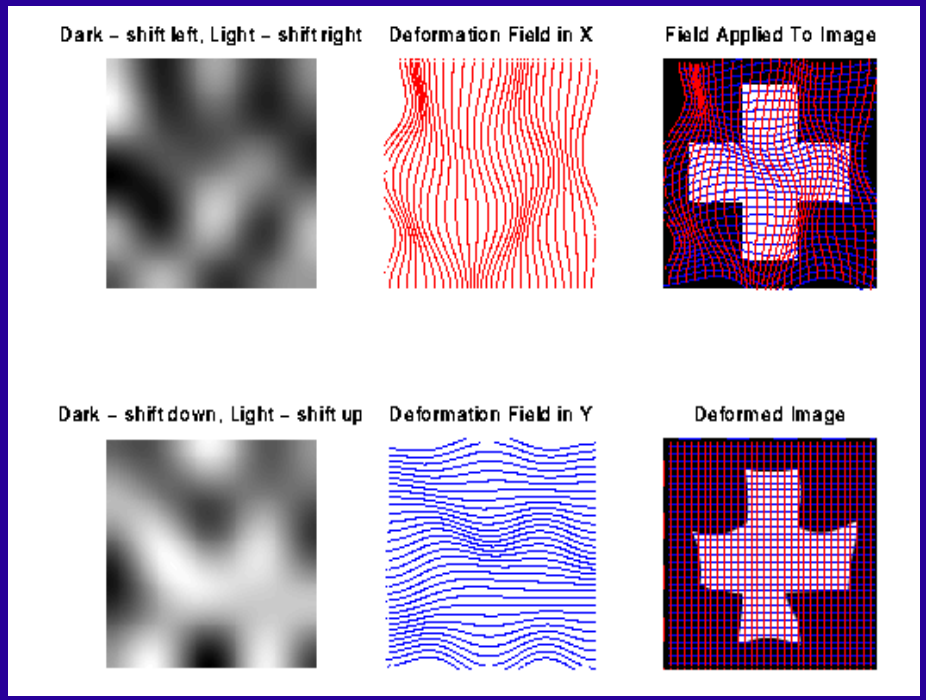
Spatial Normalisation - Affine

- The first part is a 12 parameter affine transform
  - 3 translations
  - 3 rotations
  - 3 zooms
  - 3 shears
- Fits overall shape and size



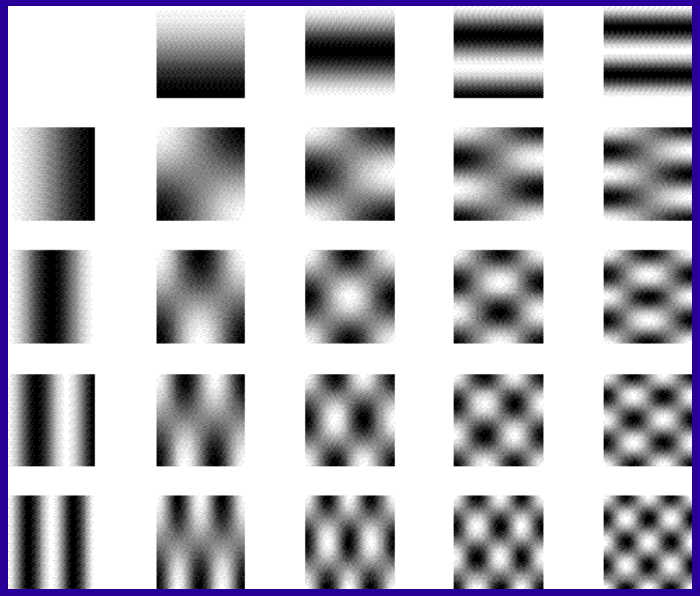
- Algorithm minimises the mean-squared difference between template and source image

Spatial Normalisation - Non-linear



Deformations consist of a linear combination of smooth basis functions

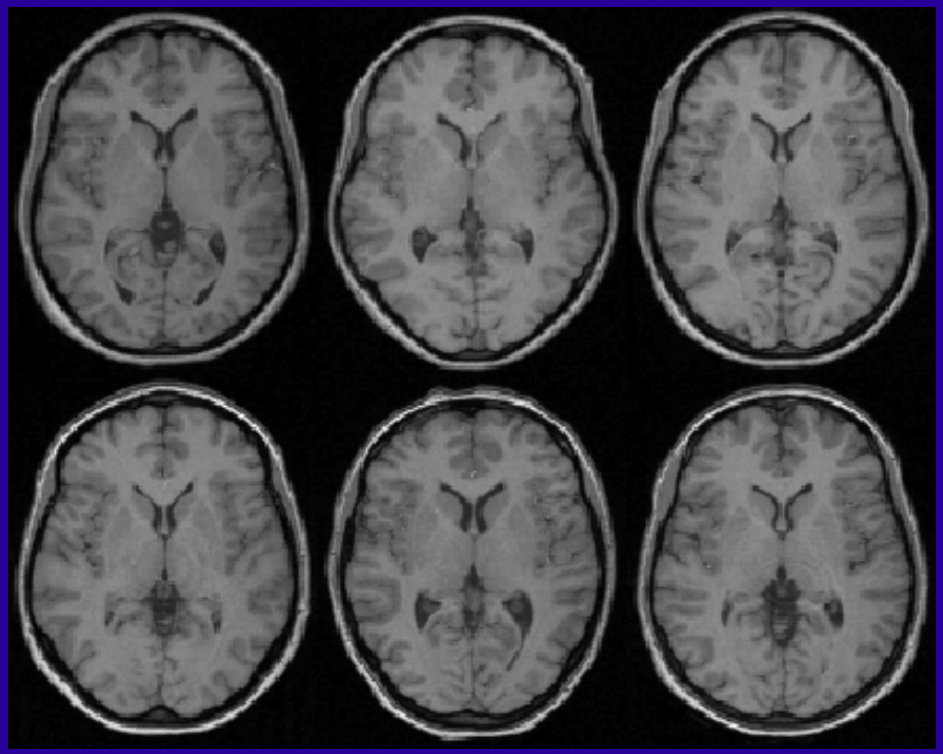
These are the lowest frequencies of a 3D discrete cosine transform (DCT)



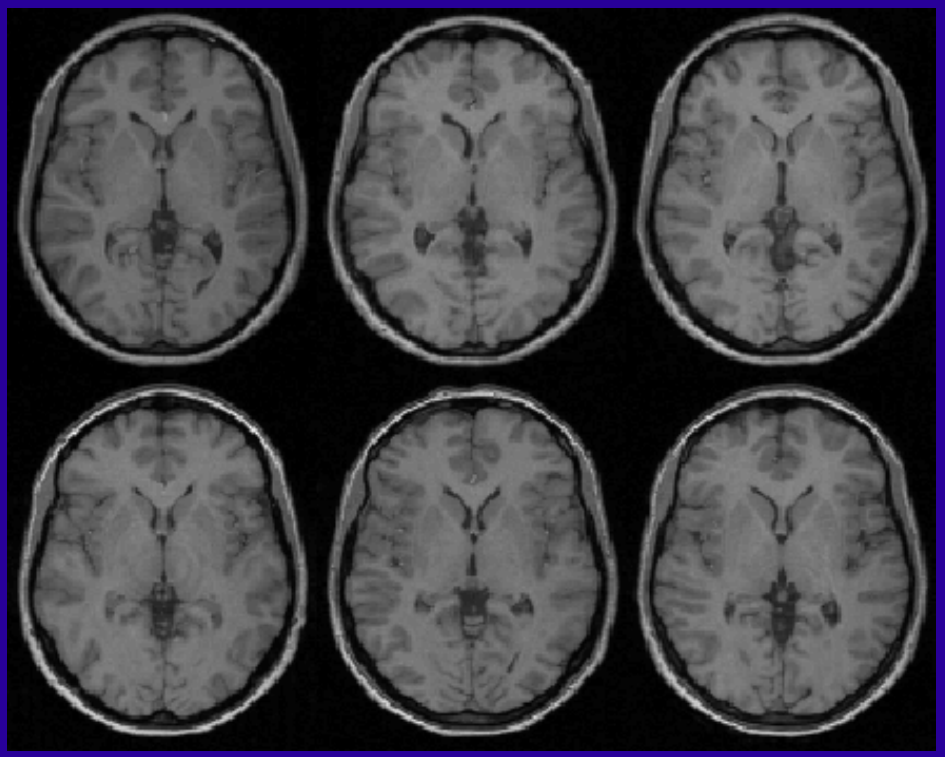
Algorithm simultaneously minimises

- Mean squared difference between template and source image
- Squared distance between parameters and their known expectation

Spatial normalisation (affine vs. Non-linear registration)



Affine registration



Non-linear registration

Spatial normalization

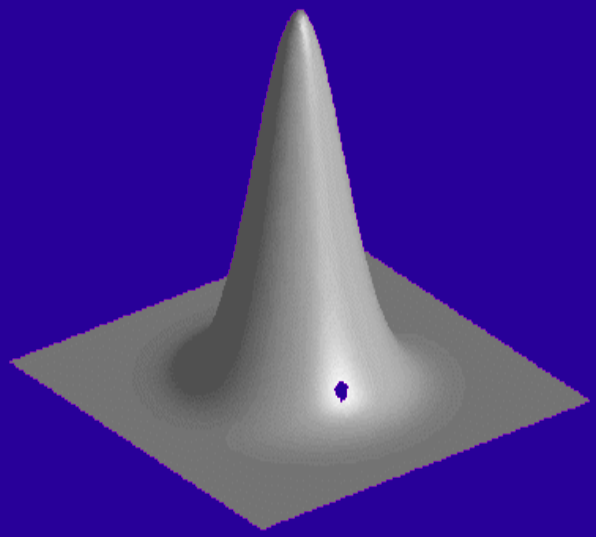
- Allows generalization of results to larger population
- Improves comparison with other studies
- Provides coordinate space for reporting results
- Enables averaging across subjects

- But
  - Reduces spatial resolution
  - Can reduce activation strength by subject averaging.
  - Group statistics are typically less sensitive than within Ss analyses (lower number of degrees of freedom)

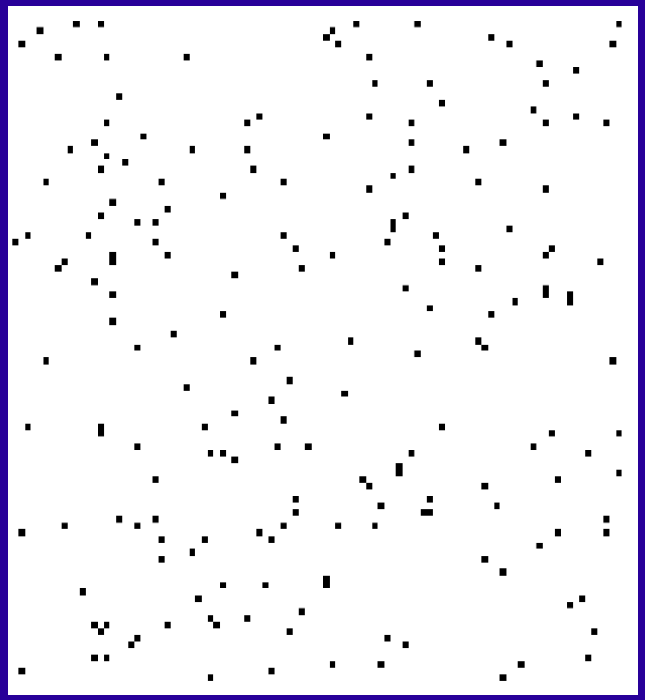
Smoothing

Smoothing is done by convolution.

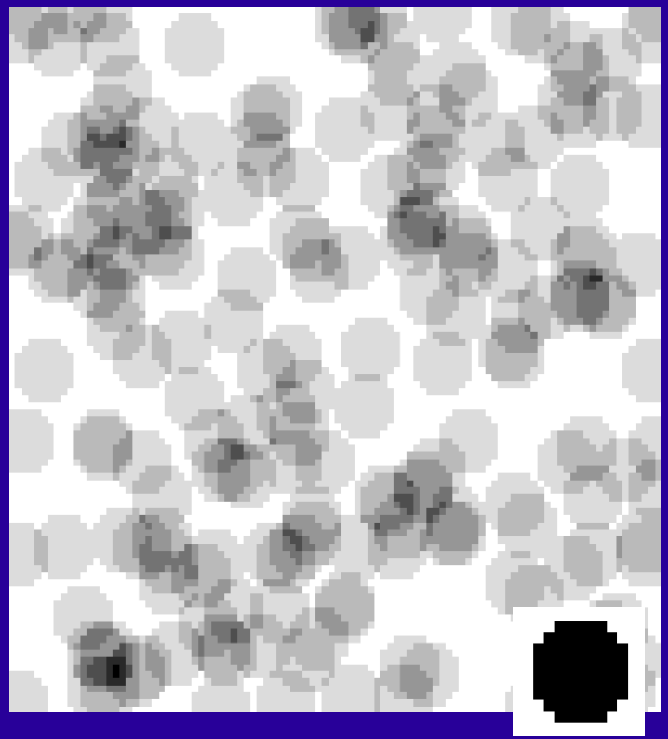
Each voxel after smoothing effectively becomes the result of applying a weighted region of interest (ROI).



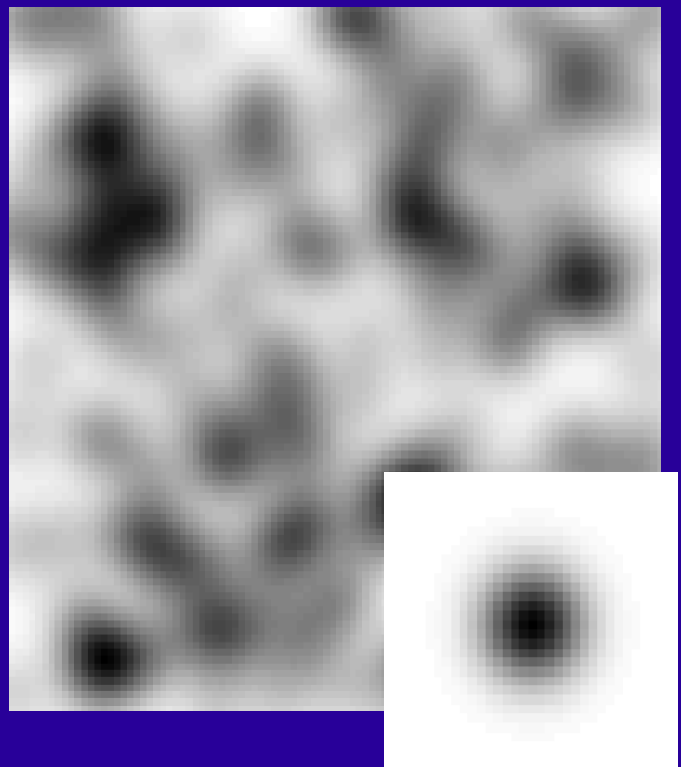
Before convolution



Convolved with a circle

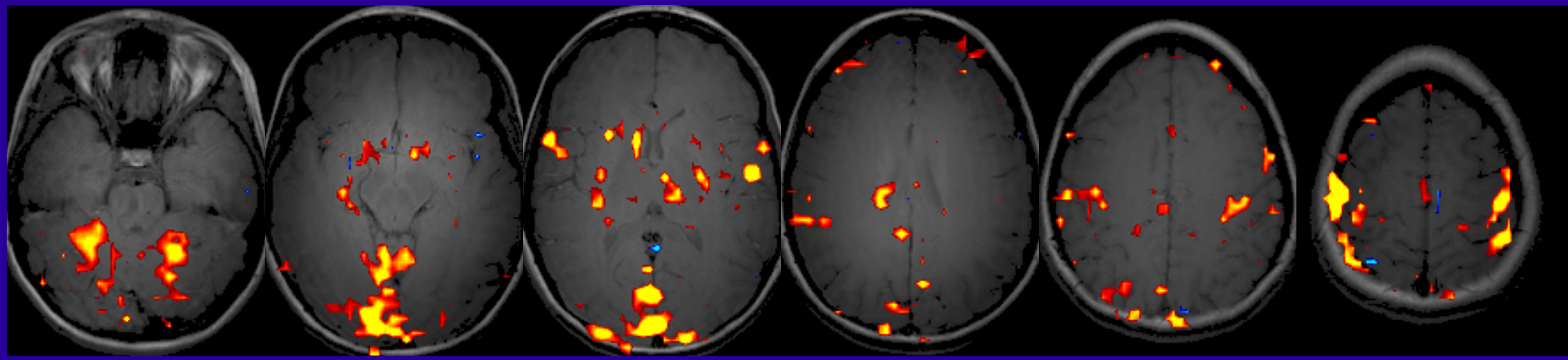


Convolved with a Gaussian

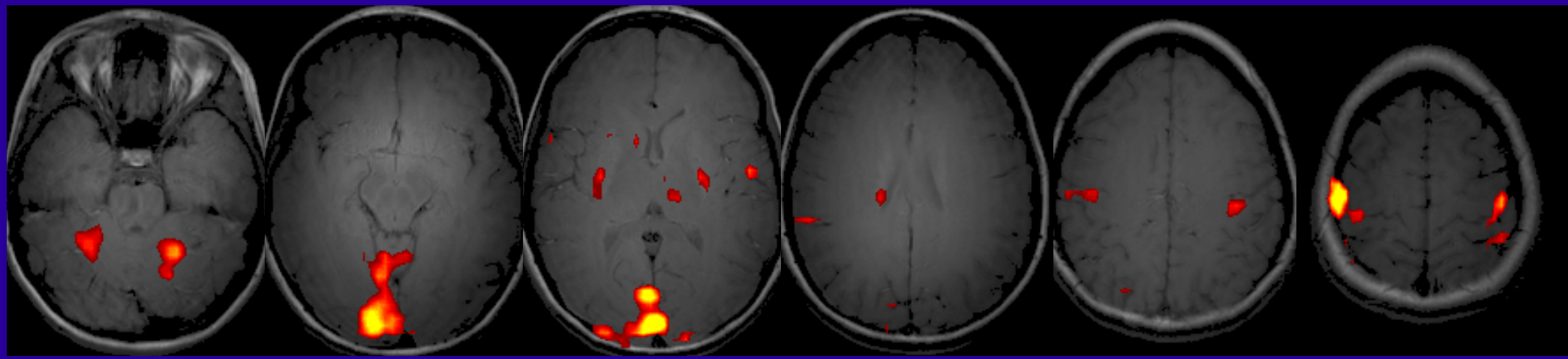


Effects of Spatial Smoothing on Activity

Unsmoothed Data



Smoothed Data (kernel width 5 voxels)



Slide from Duke course

Plan

1)MRI in practice

2)What does (f)MRI measure ?

3)Processing of images

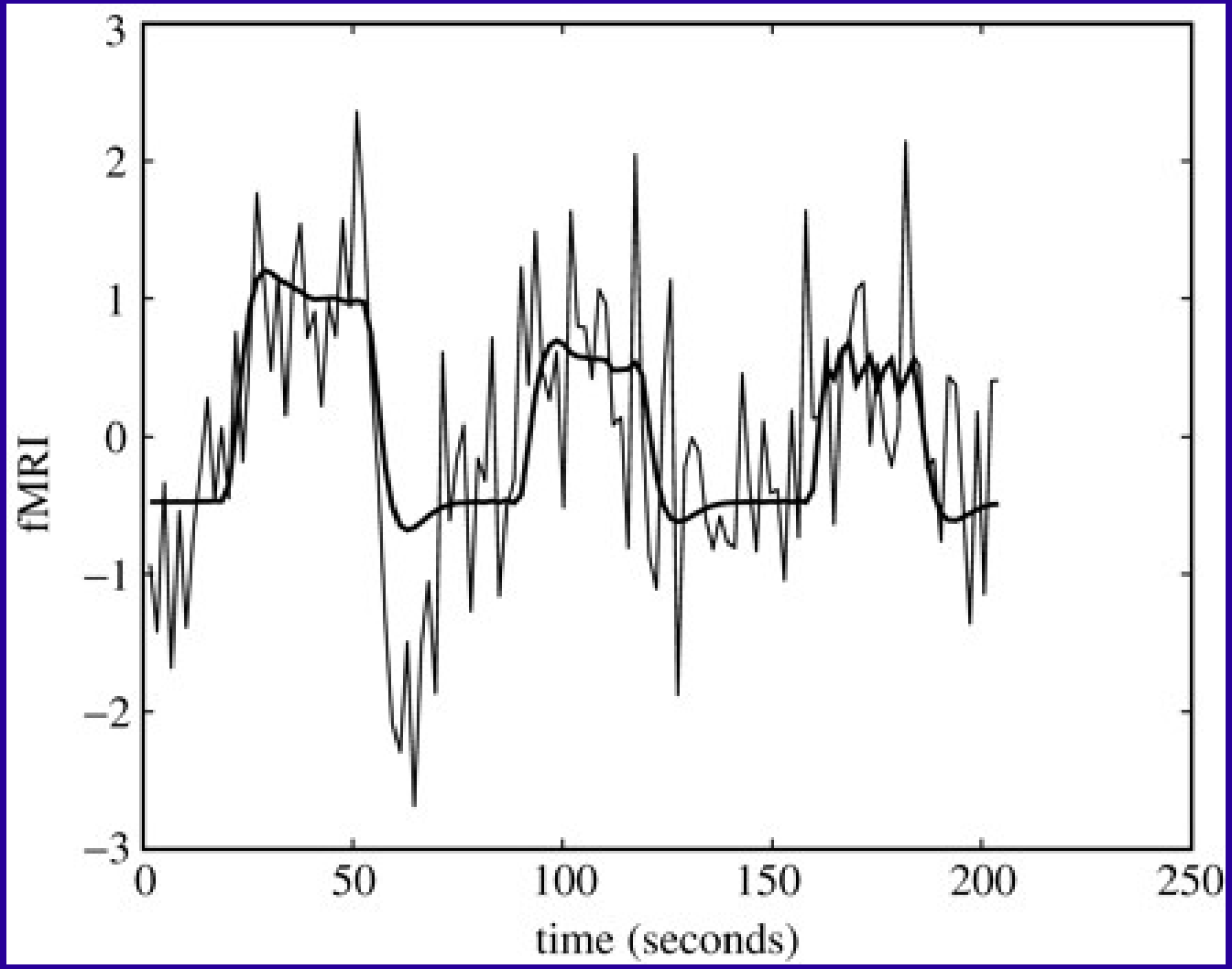
4) Creation of Statistical Maps

Aim: detecting voxels with higher activation in condition A than in condition B.

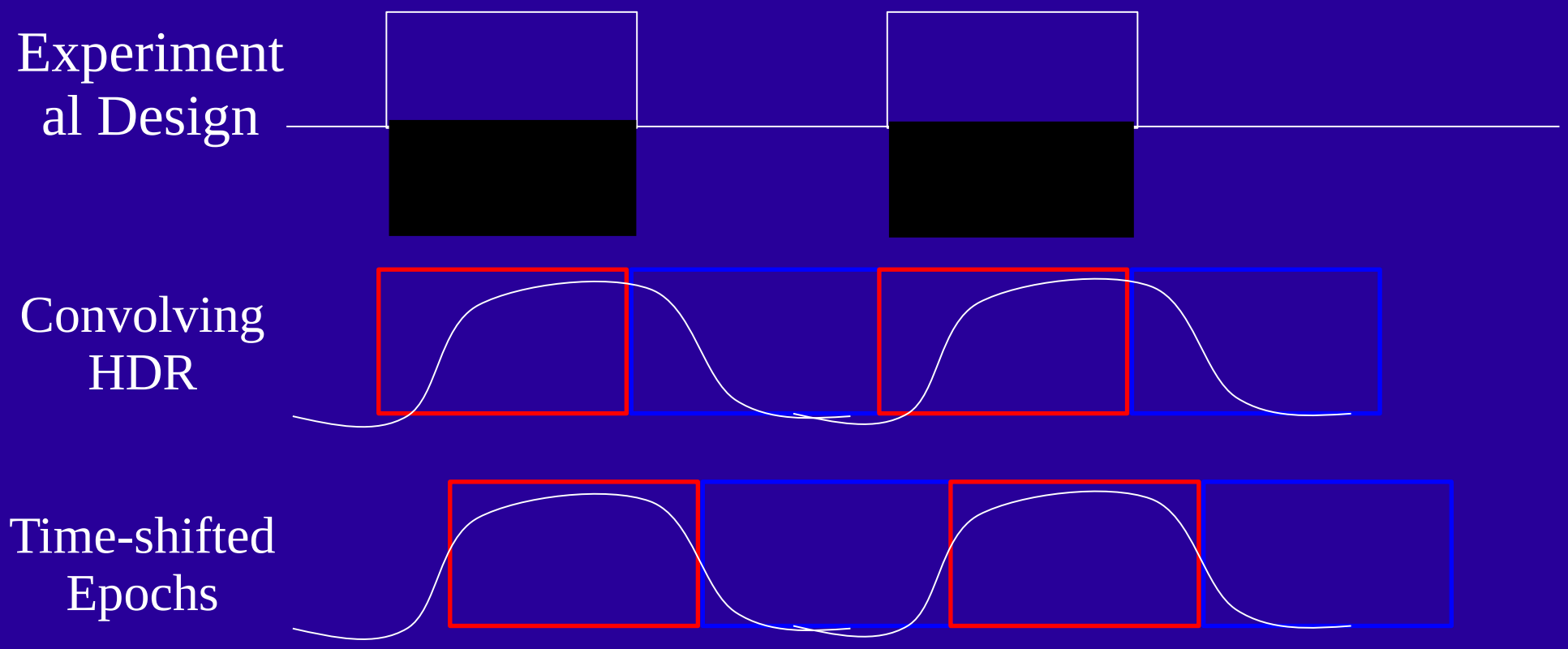
- Data consist of N timeseries (1 per voxel) containing t points in time (typically a few hundred)

- If alternance of two conditions, you could think of using N **t-tests** to compare the scans in condition A versus the scans in condition B.

Example of an fMRI time series (voxel in the auditory cortex, alternation of silent and noisy periods)



The Hemodynamic Response Lags Neural Activity



Statistical modeling with the General Linear Model

- For each experimental condition (i), create a theoretical neural activation profile.
- Convolve this by a theoretical hemodynamic impulse response function.
- Use the resultant profile as a regressor (X_i) in a multiple regression with the observed signal (Y_{vox}) as the dependent variable, that is find a set of a_i such that :

$$Y_{vox} \cong \sum a_i . X_i$$

- Interpretation : ai represents the amplitude of response to condition 'i'

Design Matrix
BOLD Timeseries
Regressors of Interest
Nuisance Regressors
Amplitude parameter (unknown)
Error Term
time
=
x
+

Two Problems

- Lack of temporal independence: the signal is autocorrelated because of the **smoothing by heamodynamic response.** (actually not a big problem. It can easily be taken care of : for example, one can diminish the degrees of freedom of the test)

- Multiple comparisons problem:
  - One is performing N (~ 50000 voxels) statistical tests in parallel !

Probability that a “5%” event (False Alarm) is observed at least one time in 'n' trials

This probability called the « family-wise error » (for a family of tests)

Solutions

1)Do nothing...

2)Use a more stringent statistical threshold at the voxel level (e.g., Bonferroni correction : to assure an FWE-threshold of alpha for N tests, set the threshold alpha/N for individual test).

3)Theory of random gaussian fields to test the size of activated cluster (a large cluster of 'weakly' activated voxel can reveal a true activation).

4)False Discovery Rate (FDR) procedure

5)Permutation tests.

In papers and figures, **always check if the results are corrected for multiple comparisons**