Neuroimaging

- Structural magnetic resonance imaging – measuring volumes of brain and brain regions
- Functional MRI – measuring brain activity during cognitive tasks
- Diffusion MRI – measuring motion of water molecules along diffusion gradients
- Positron emission tomography -- measuring metabolic processes, including changes in metabolism during cognitive tasks

First published NMR (MRI) image of the brain: 1980

“A shadow of the brain”

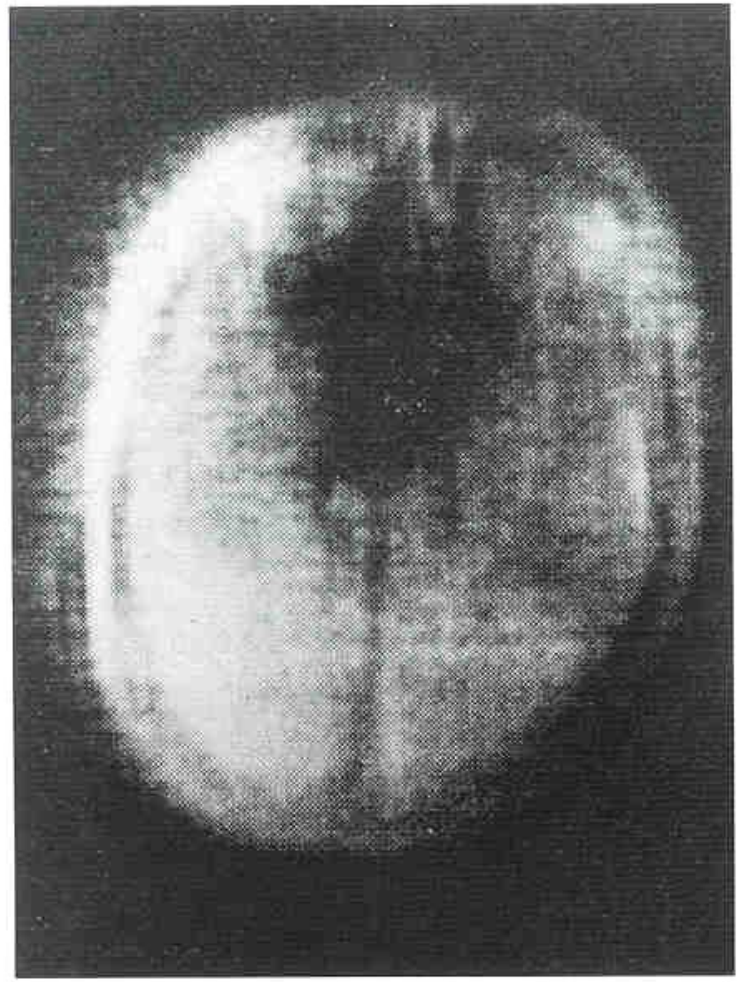
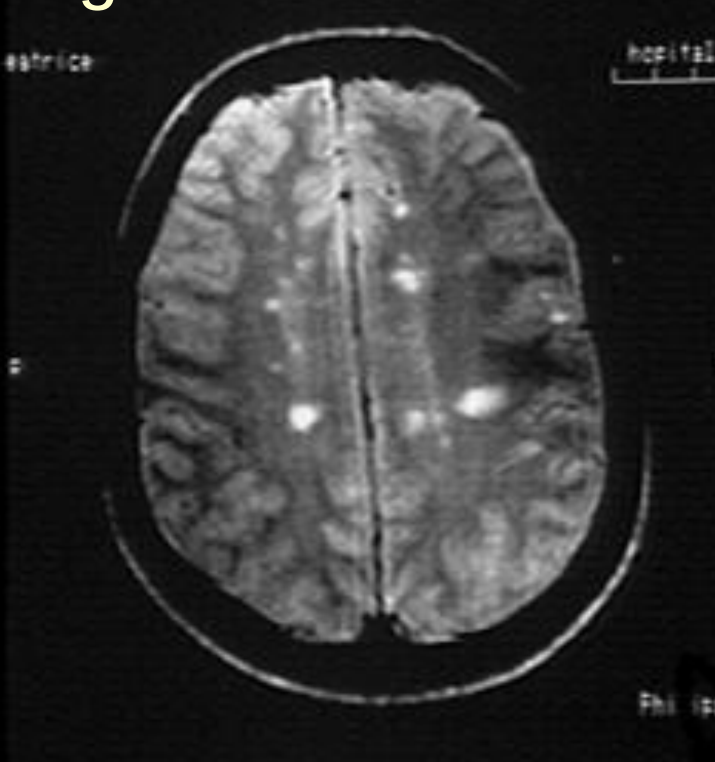
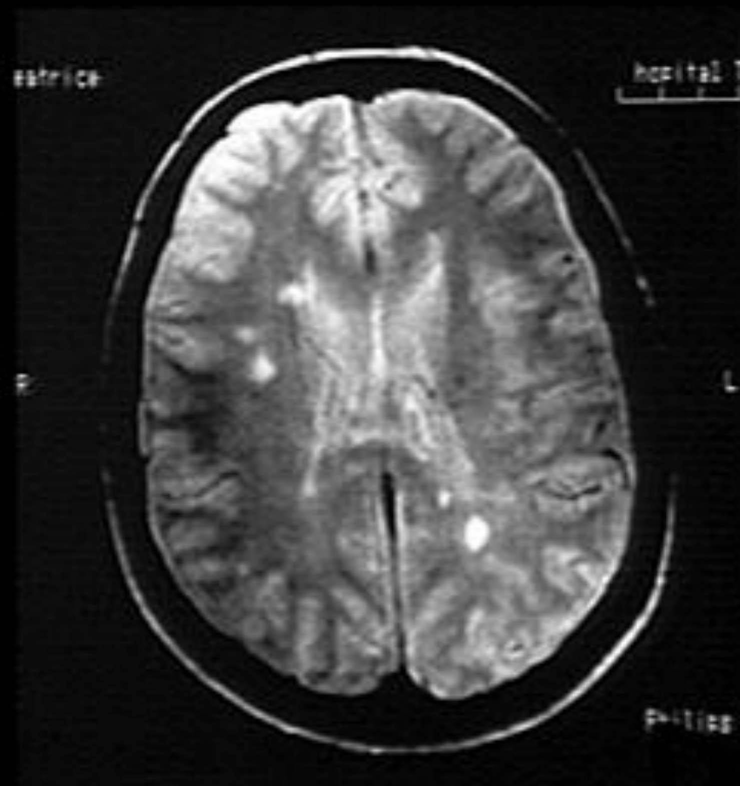


Fig. 4-46. The first published NMR reconstructed image of a head. (From Holland GN, Morre WS, Hawkes RC: J Comput Assist Tomog 69:262-277, 1980.)

Images collected in 1985

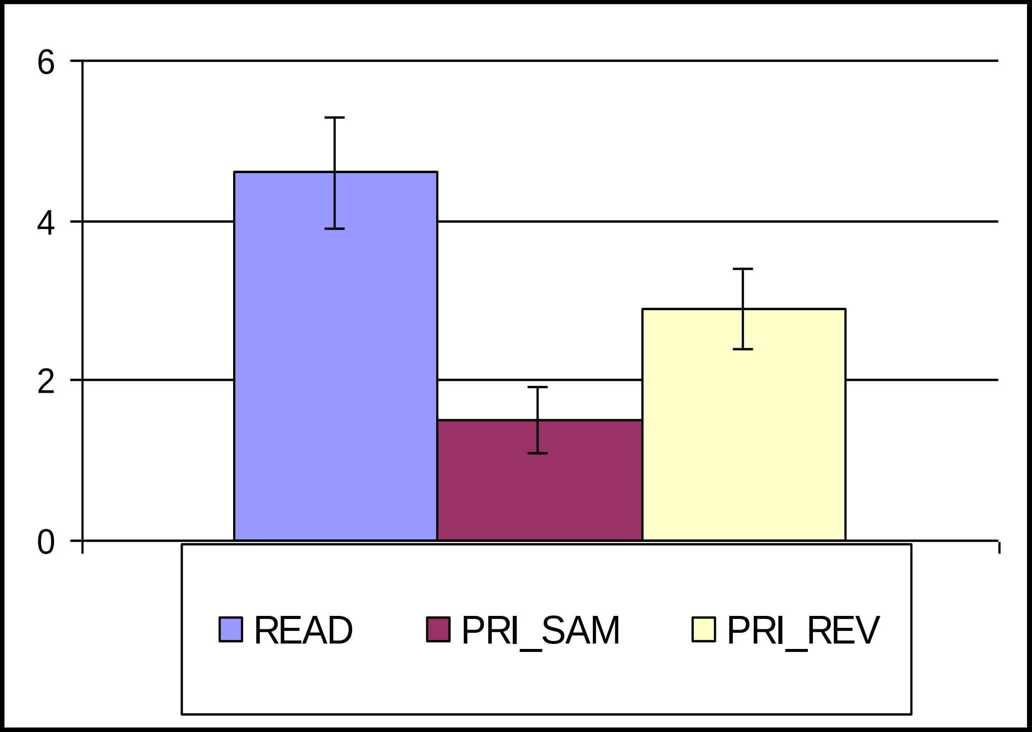




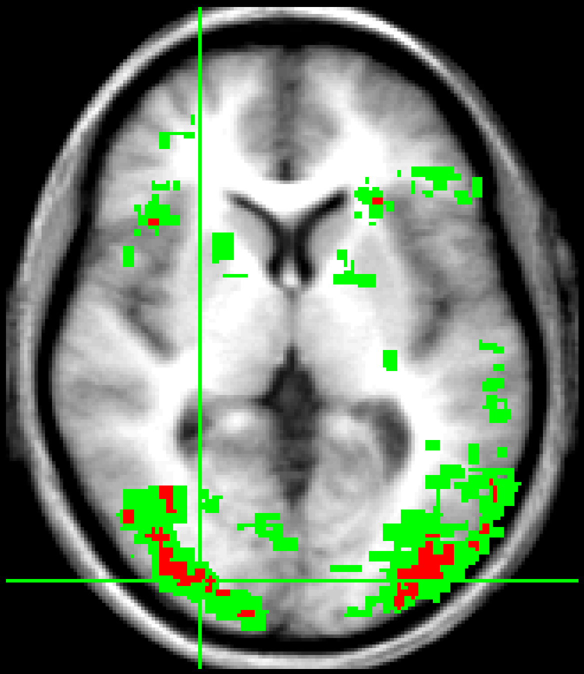
Multiple sclerosis – Clinical trials for MRI began in 1983, FDA approved two years later, in 1985.

Sensitivity of MRI to MS lesions compared to CT: 10 to 1

First human functional MRI paper: Bandettini, Wong, et al. (1992)



Left occipital lobe



Ryan & Schnyer, 2005

Functional image properties

- What does it measure (light transmittance, quantity of a specific material)
- Contrast sensitivity – the smallest difference in quantity that is measurable, resulting in a difference in image intensity
- Spatial resolution – the ability to distinguish changes in signal across different spatial locations
- Temporal resolution – the sampling rate, or how fast you can detect a change in signal

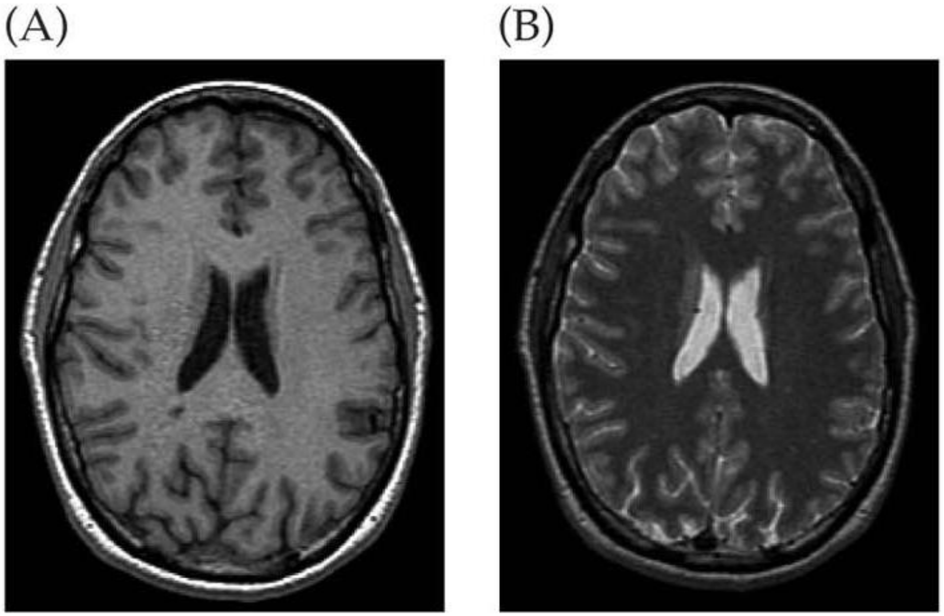
(A)

(B)

FUNCTIONAL MAGNETIC RESONANCE IMAGIN

Two MRI's (same image) at different contrast sensitivities, with greater signal intensity differences across gray white matter boundaries (A) compared to image (B).

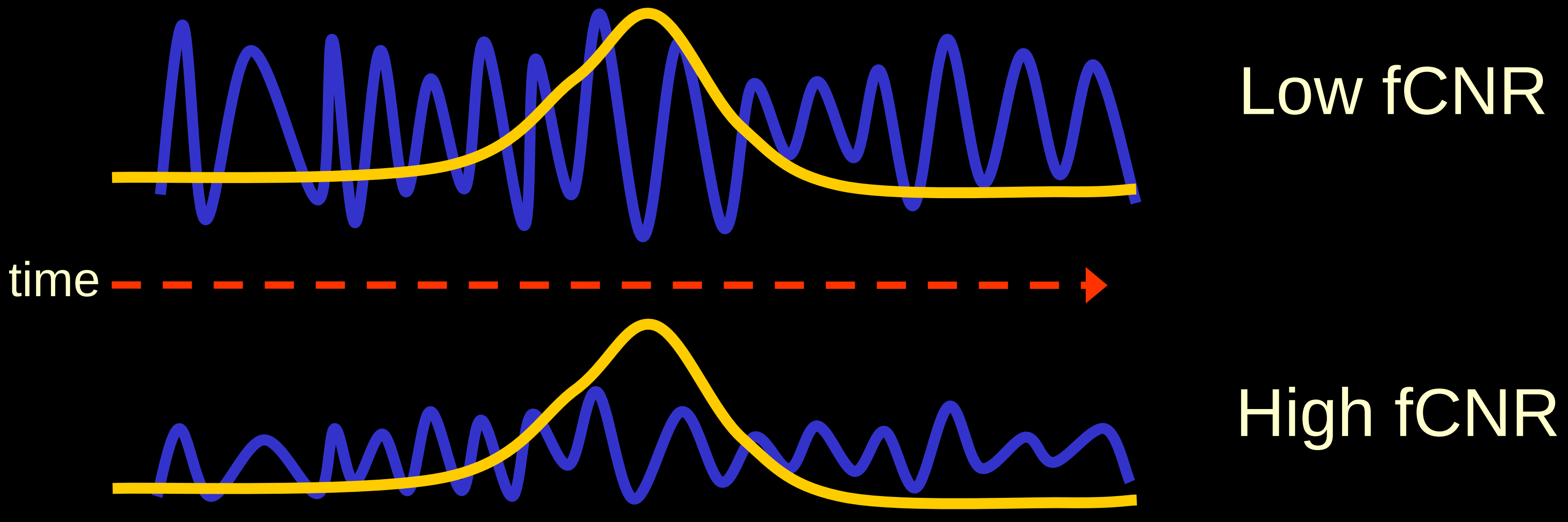
Contrast to noise ratio – magnitude of intensity differences divided by background signal variance



In MRI, contrast also refers to sensitivity to a specific physical property of the nuclei

For example, two images that are differentially sensitive to two properties of relaxation rates of hydrogen, T1 (A) and T2 (B).

Functional contrast to noise

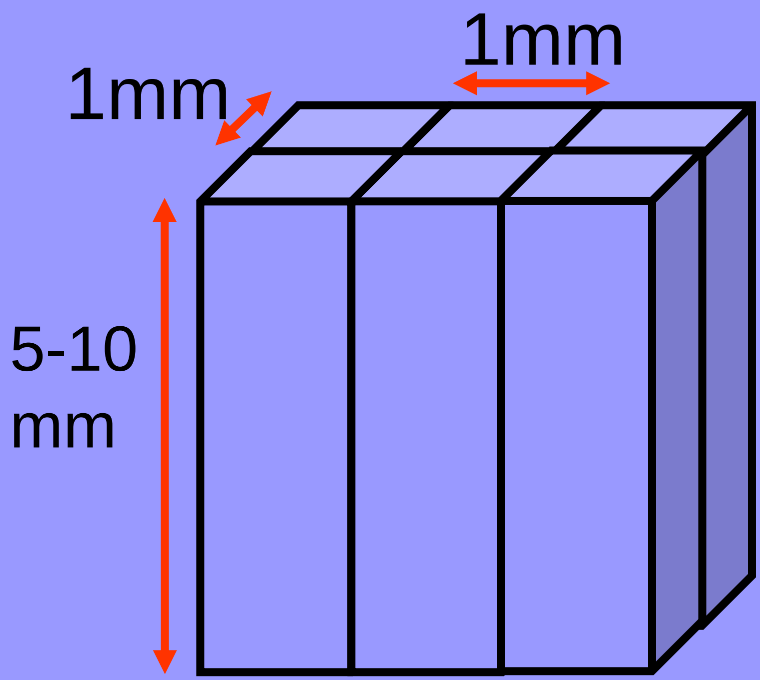


- The ability to detect a signal change against a background of noise, or variance in signal
- The variance may be due to measurement error, or physiological noise

Spatial resolution

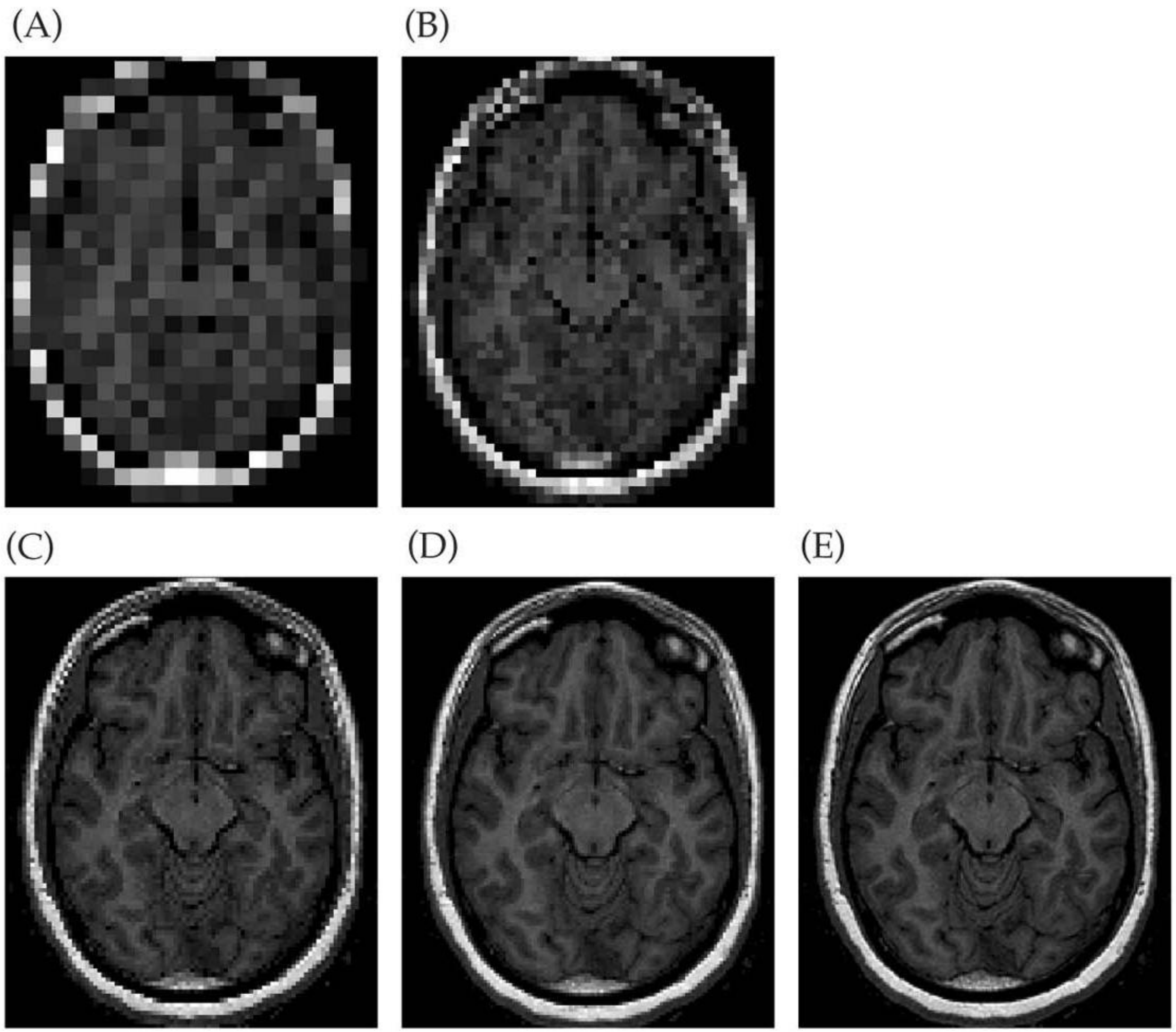
Pixel: Smallest element in a 2D image – in-plane resolution

Voxel: 3D sample from which signal is collected and averages



Voxel size: In-plane resolution x section thickness

MRI images at various spatial resolutions. Note resolutions 1.5mm or smaller appear similar to us.



A. 8mm

B. 4mm

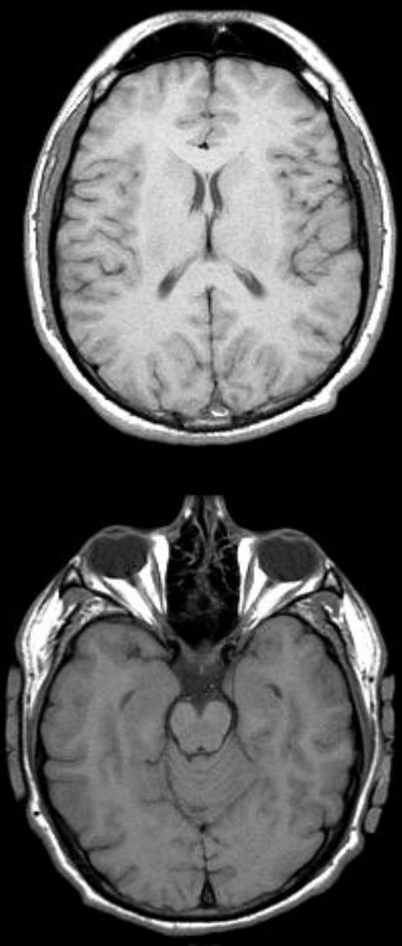
C. 2mm

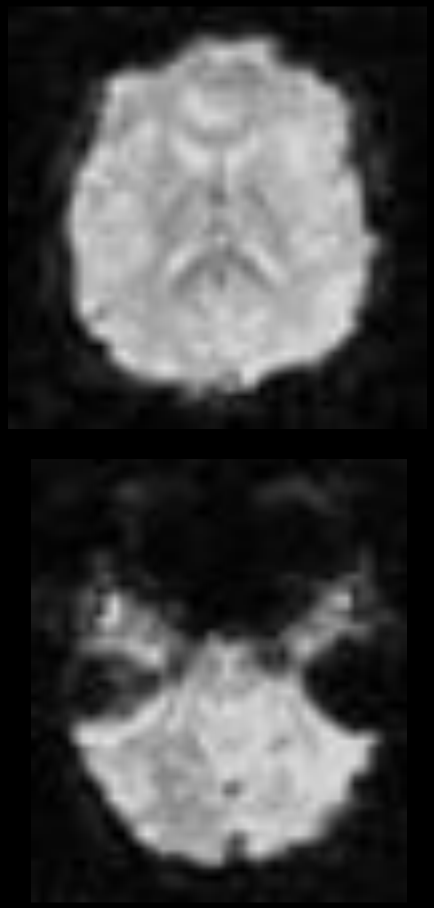
D. 1.5mm

E. 1mm

Anatomical: 1 x 1 x 5mm

Functional: 3.4 x 3.4 x 5mm





Functional images are lower resolution (larger voxels) and also have lower CNR because of the way the images are collected (echo-planar).

Temporal resolution of images

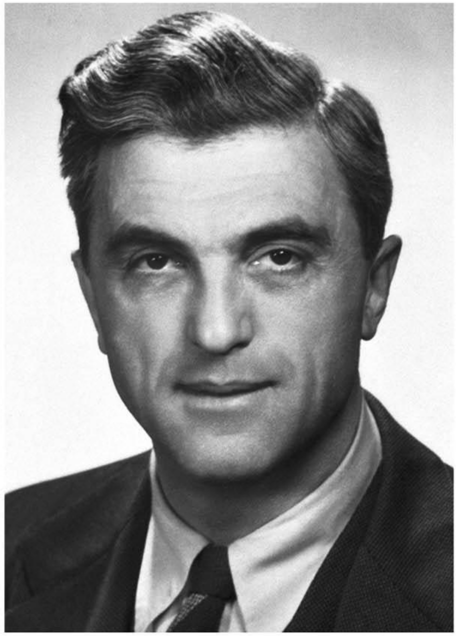
- Sampling rate: The frequency in time with which a measurement is made – MRI can sample as quickly as 30 msecs
- Temporal resolution: The ability to distinguish changes in an image across time.
- Two limits to temporal resolution:

Nyquist frequency – a fundamental rule that a signal must be sampled twice as frequently as the fastest change in the signal that you wish to measure

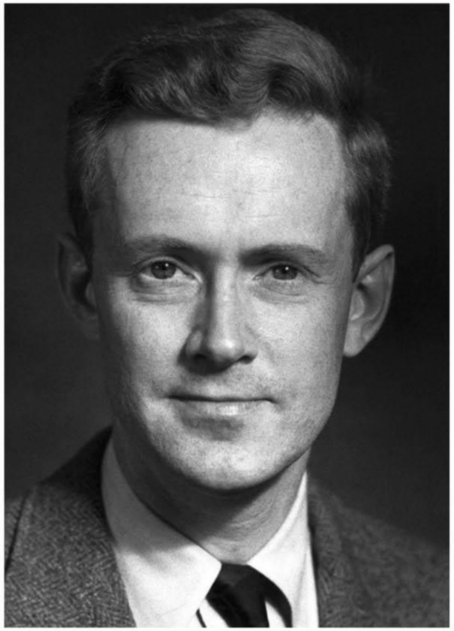
Signal frequency – fast sampling does not matter if the signal change is slow (hemodynamic response is 12 secs)

1.11 Nobel laureates Felix Bloch (A) and Edward Purcell (B) shared the 1952 prize in Physics.

(A)



(B)



Felix Bloch and Edward Purcell: Nobel Prize in Physics, 1952.

FUNCTIONAL MAGNETIC RESONANCE IMAGING, **Figure 1.11**

Purcell measured magnetic resonance in a block of material (paraffin wax) that was placed in a magnetic field.

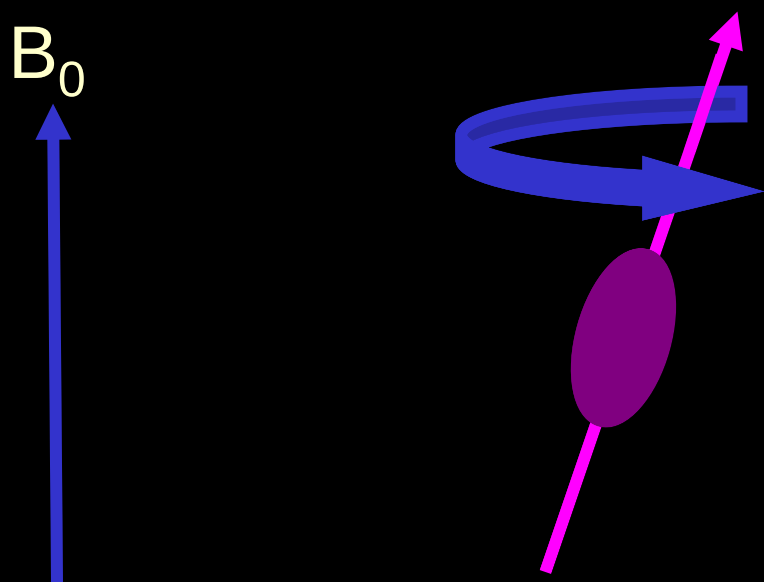
Purcell did the same with a container of water, devising a method that is identical to the basic MRI system: A static magnetic field, a transmit EM coil, and a coil for detecting emitted energy.

Magentic resonance:

- *Resonant frequency* – the frequency at which a particular molecule precesses or “spins” like a top around its axis. AKA “Larmor frequency”
- Energy at that frequency will be absorbed (“excitation”).
- Once the energy source is removed, the molecule will return back to its normal resting state, giving off energy (“relaxation”).
- Magnetic resonance – measureable energy emitted during relaxation.

MRI Signal:

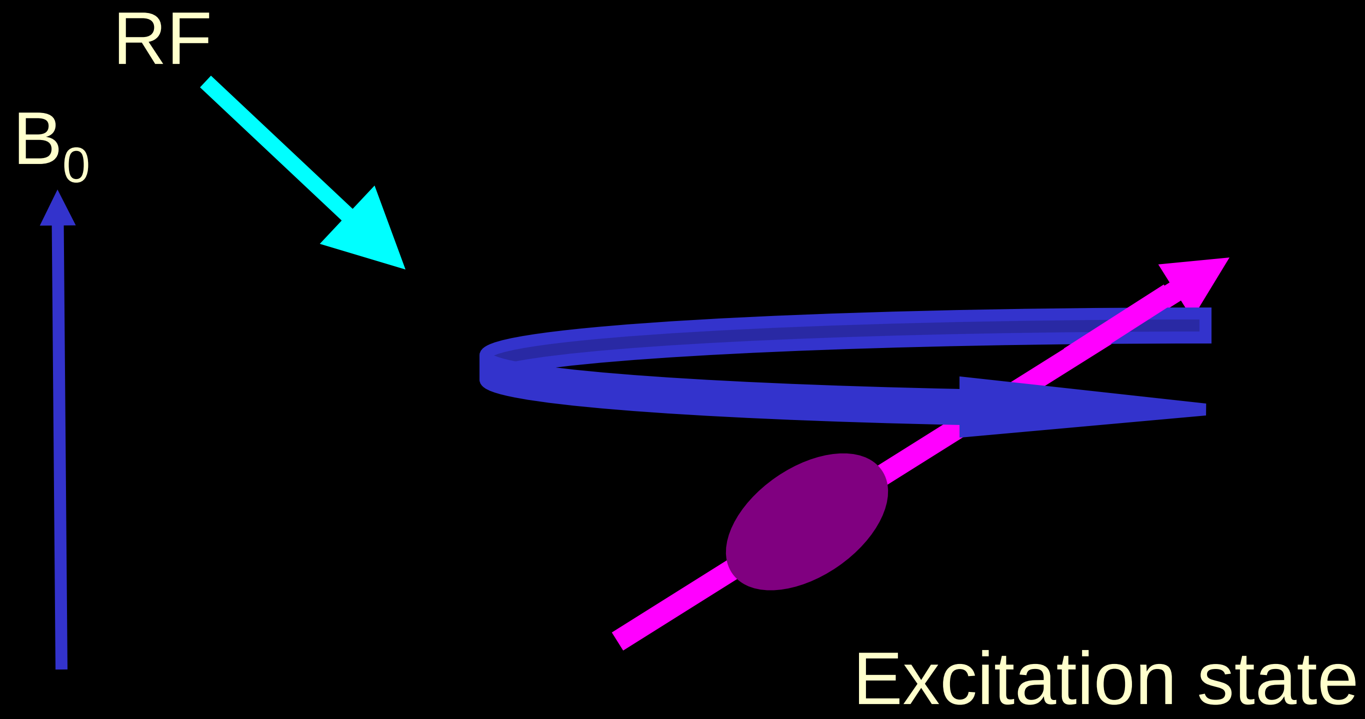
- *Step 1:* Atoms with an uneven number of protons act as dipoles – in a strong static magnetic field, they will align with the field and precess around that axis.



Resting state

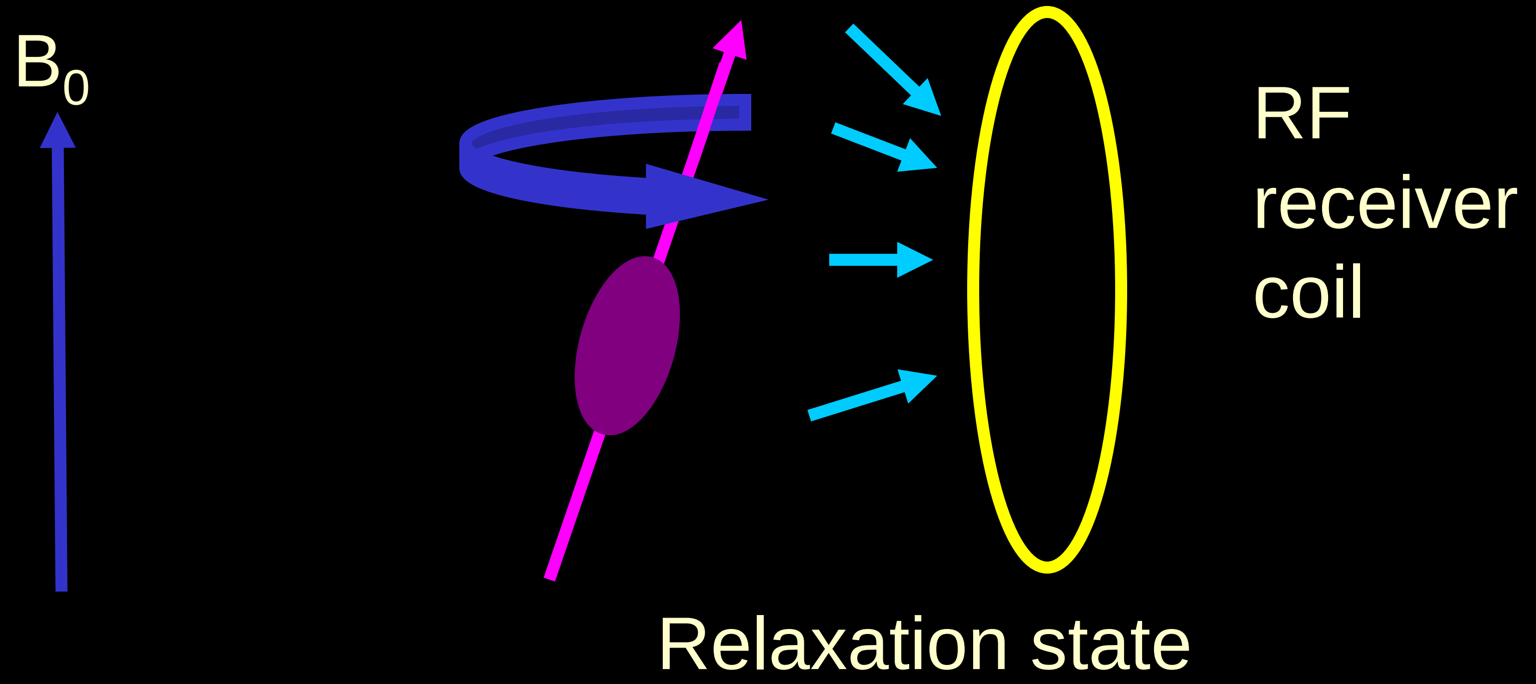
MRI Signal:

- *Step 2:* Apply energy pulse (normally in the radio frequency range) at the resonant frequency of the molecule – the energy will be absorbed.



MRI Signal:

- *Step 3:* Turn off the RF pulse, and the molecule gives off the absorbed energy over time (relaxation rate), which can be measured with an RF receiver coil. This is *magnetic resonance.*

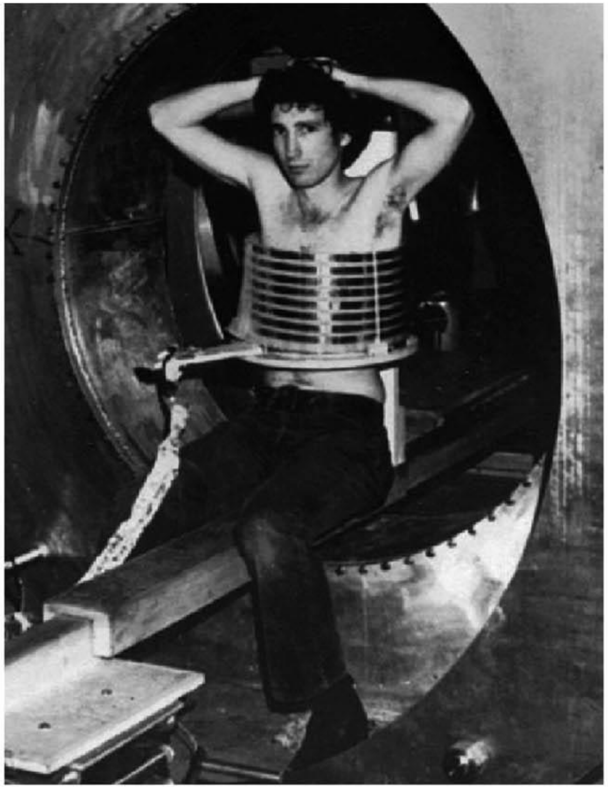


MRI Signal:

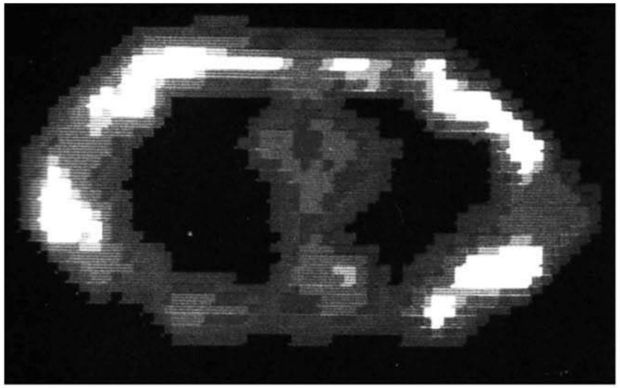
- *Molecule of interest:* Hydrogen
- Why hydrogen? Lots of it in the brain (water)
- Differs in densities across tissue types (least in white matter, more in gray matter, most in CSF)
- Also differs in the strength of bonds (water is freely diffusing in CSF, but more tightly bound in fatty tissue such as myelin)
- Both these properties will affect the *relaxation rate* – how fast the water molecule returns to its low energy state

1.14 The first MR image of the human body.

(A)



(B)



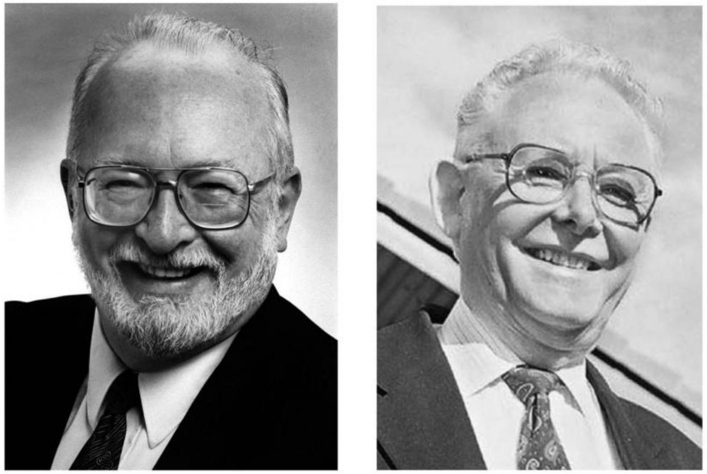
Raymond Damadian, 1977

First cross-sectional image of the human body.

Damadian showed that magnetic resonance of water differed depending on the type of biological tissue in which it was bound (Science, 1971). He built the first large-bore magnet called “Indomitable”, producing a cross-sectional image of the human body composed of 106 voxels. Each voxel was obtained separately, by moving the person’s position slightly. Total imaging time was 4 hours.

1.13 Nobel laureates Paul Lauterbur (A) and Peter Mansfield (B).

(A) (B)



Paul Lauterbur and Peter Mansfield, Nobel Prize in Medicine, 2003

Lauterbur (1976) applied gradients to the static magetic field so that the field strength differed depending on the spatial location. The resonant frequency of hydrogen would therefore differ across spatial locations. The amount of energy emitted at a given frequency would determine where it was located in 2D space.

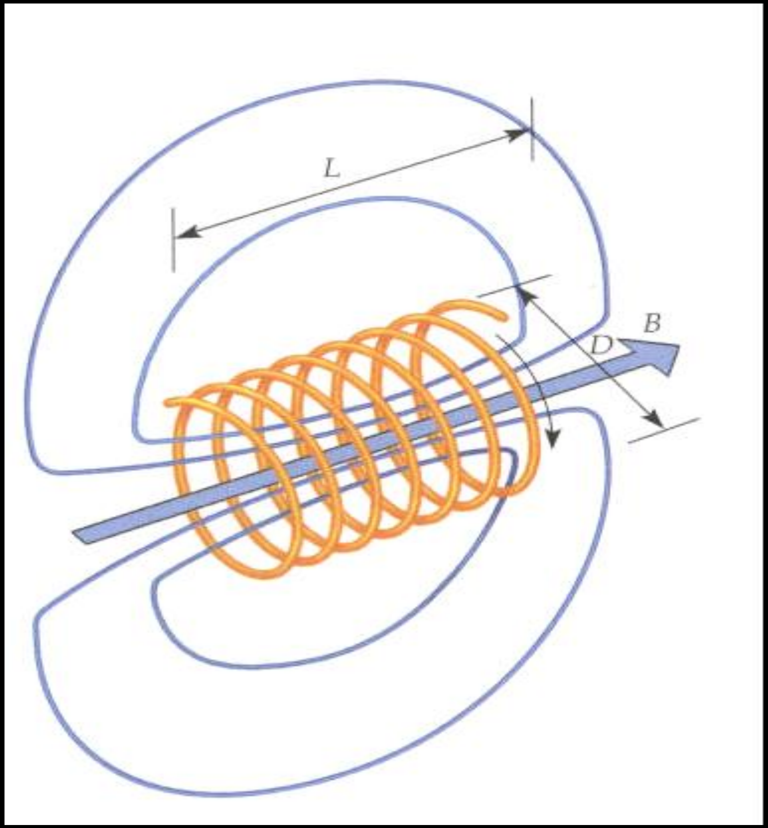
Peter Mansfield (1976) found a more efficient way of collecting the signal, by applying a single EM pulse, and then acquiring signal continuously while you changed the spatial gradients. Then the complex signal could be reconstructed with Fourier analysis.

Components of MRI scanner:

- Static magnetic field
- Transmit radiofrequency coil
- Receiver radiofrequency coil
- Gradient coils (z, x, y)
- Shimming coils (1^{st}, 2^{nd}, 3^{rd} order)

Static magnetic field:

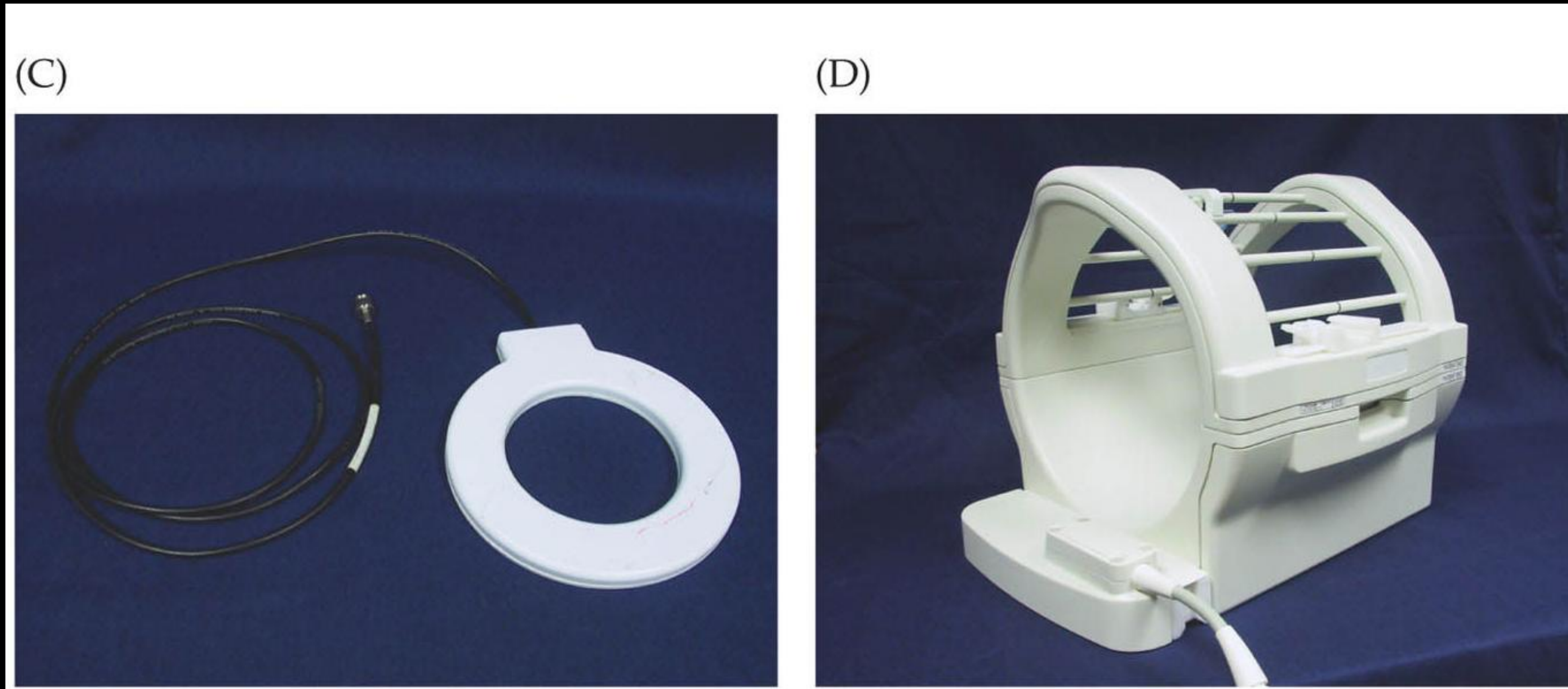
Electromagnet – solenoid with current that is maintained by supercooling, creates a magnetic field perpendicular to the axis of the coil. Housed in a vaccum chamber (dewar).



Field strength – proportional to the diameter of the coil and the strength of the current (nonlinearly related).

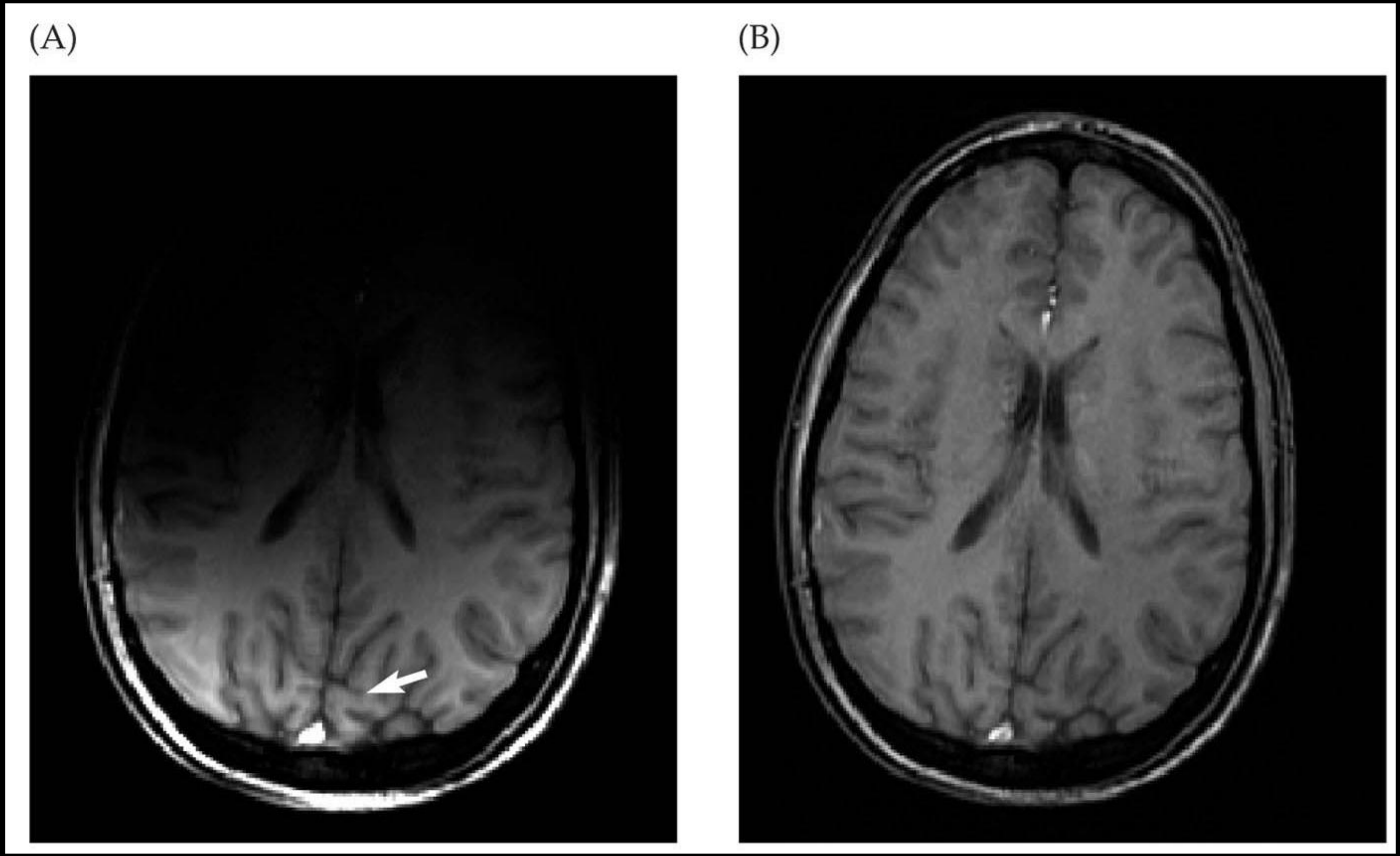
Radiofrequency coils

- Transmit coil: Electromagnetic coil used to generate oscillating energy (radiofrequency range) at the resonant frequency of a sample being measured (excitation).
- Receive coil: EM coil used to measure energy emitted by a sample as it returns to its lower energy state (relaxation) once the excitation pulse is turned off.



Surface coil, simple inductor-capacitor circuit used to produce strong magnetic field over a limited region of brain.

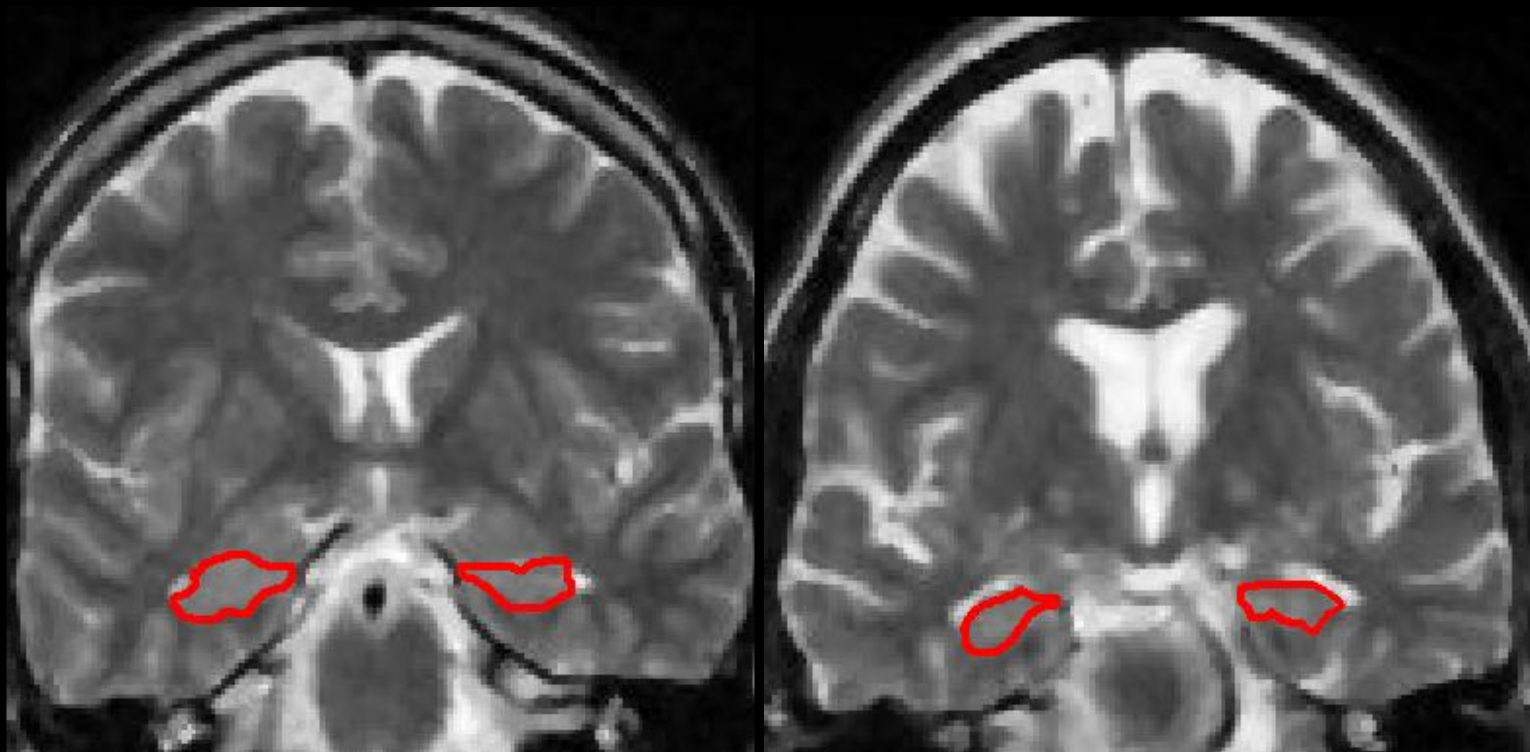
Volume or “birdcage” coil, used to produce consistent images across the whole brain. Contains both transmit and receive RF coils.



Amount of energy that can be transmitted or received depends on distance between the coil and the sample. A) Surface coil obtains strong local signal but limited area. B) Volume coil obtains relatively uniform signal at expense of local strength.

Gradient and shim coils

- Gradient coils – superimpose small and consistent variations in the strength of the static magnetic field
- Used for spatial localization of the signal (more soon….)
- Three directions, x, y, z
- Shim coils – small EM coils that are used to keep the static field homogeneous
- These are adjusted for each subject in the scanner, since each person's head will distort the field differently



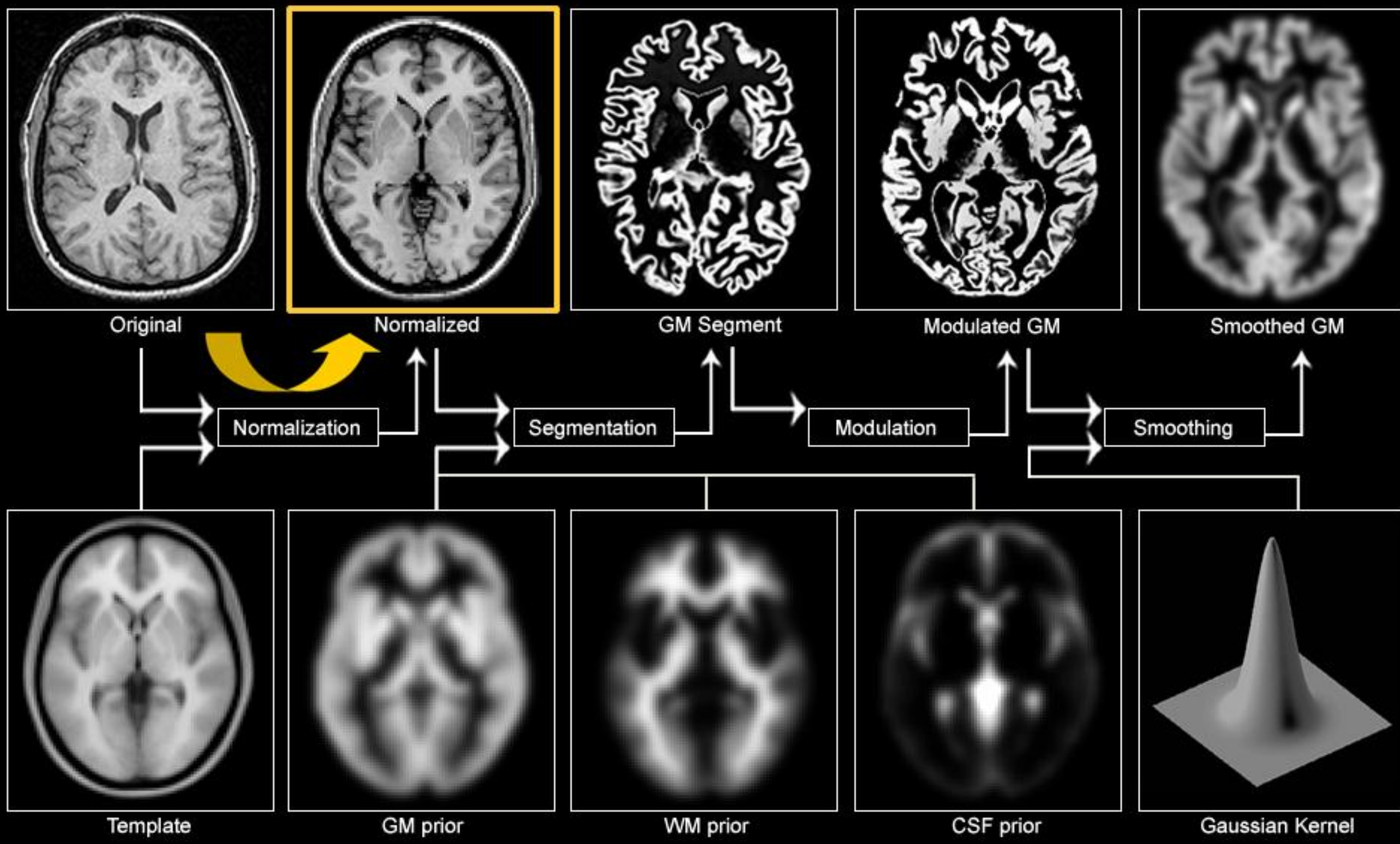
Measuring hippocampal volumes:

Predicts AD in patients who already have mild cognitive impairments.

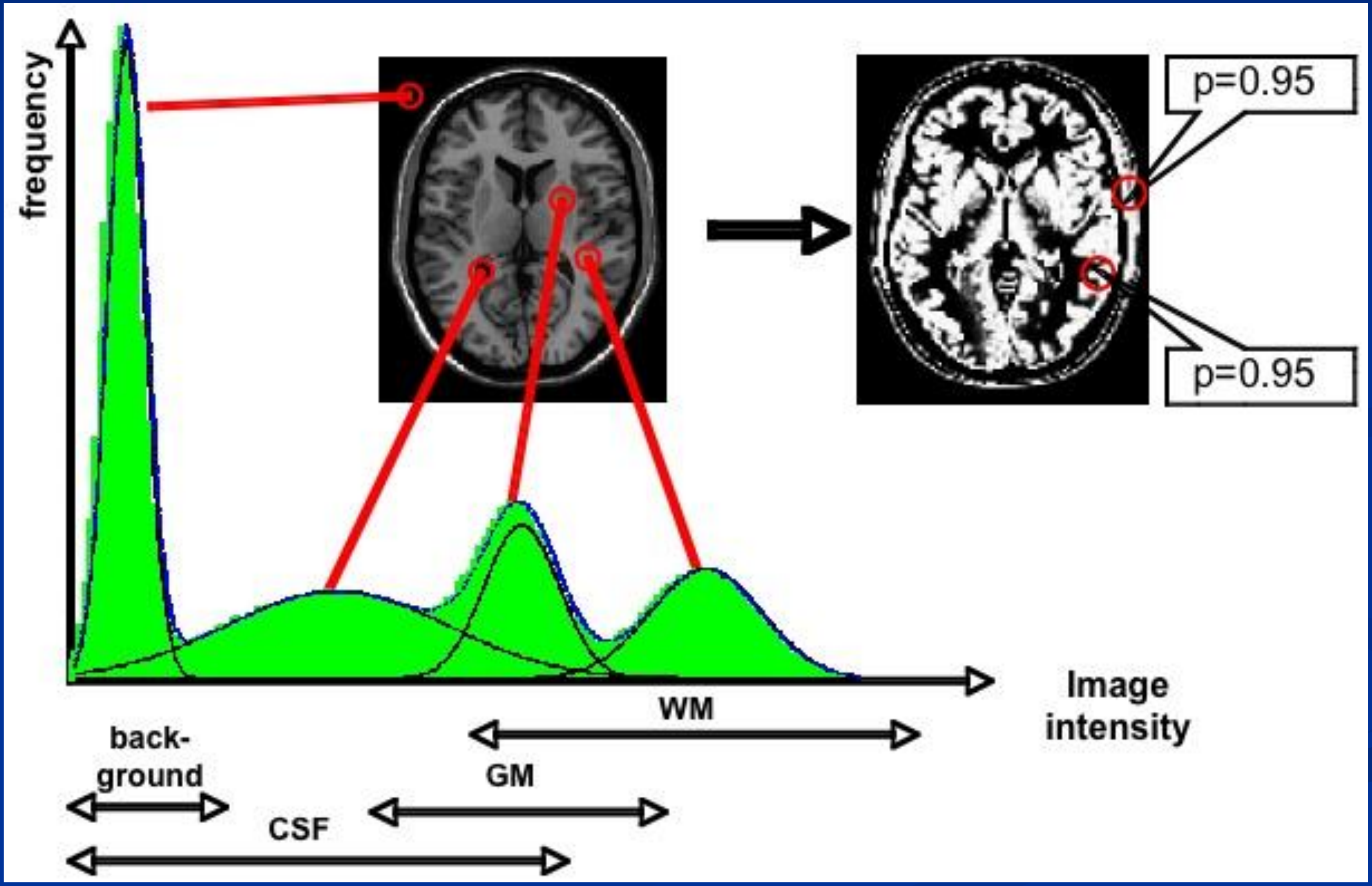
Voxel based morphometry

- Traditional ROI based morphometry is time consuming, observer dependent, provides measures of large areas and implies a priori hypotheses regarding the structures to assess.
- VBM is an automated method that lets you test for volume differences across the entire brain, voxel by voxel.
- Examines local volume differences in different tissue types that may be independent of larger volumetric differences in gross anatomy.
- A voxel by voxel statistical analysis is used to detect regional differences in the amount of gray and white matter between populations.

Voxel-Based Morphometry
Pre-processing Overview

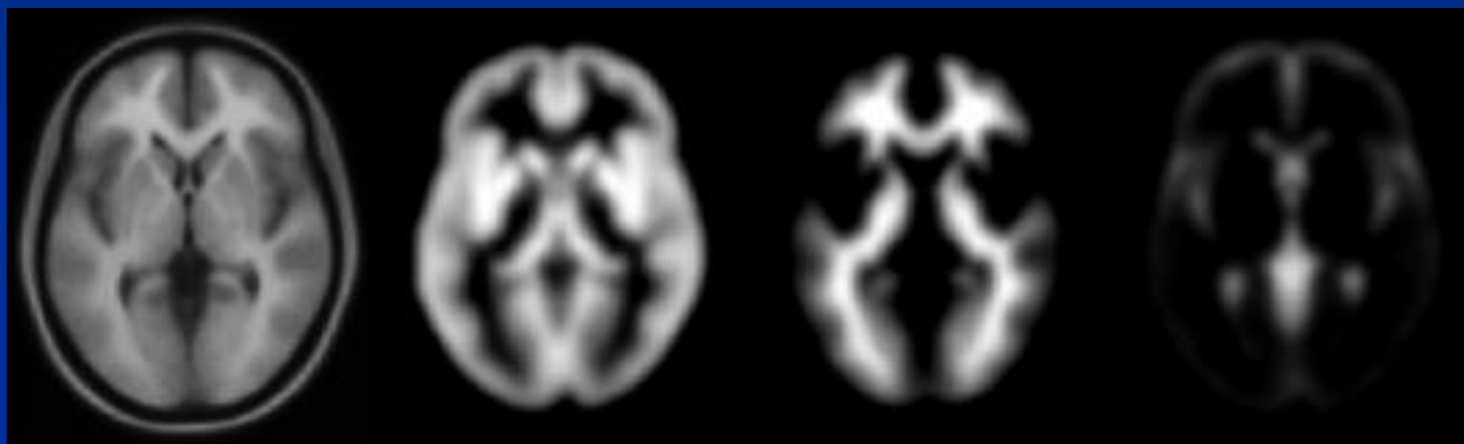


Segmentation – Based on image intensity distributions

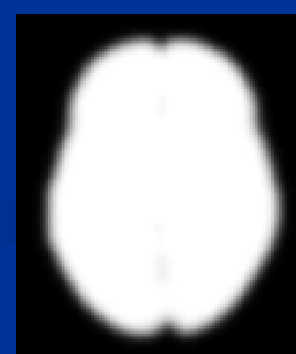


Segmentation – use of priori information

Tissue probability maps (TPMs) are used in addition to intensity information to enhance segmentation.



T1 GM WM CSF

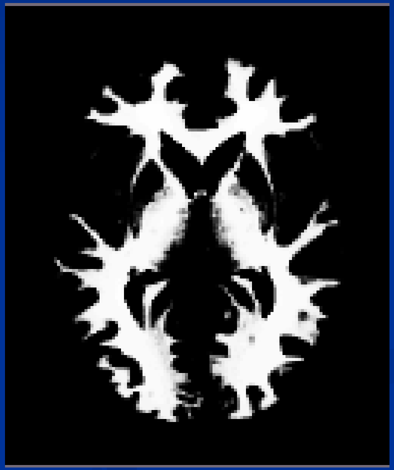


Mask for cleaning up non brain

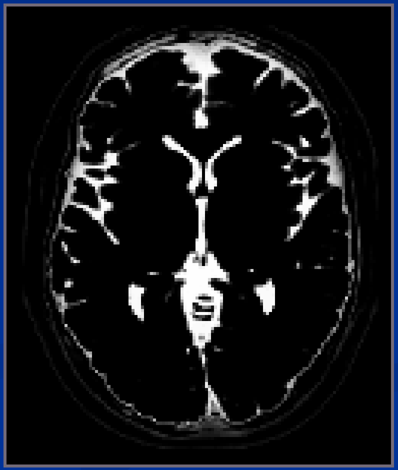
Segmentation – Example final maps

T1

gray



white

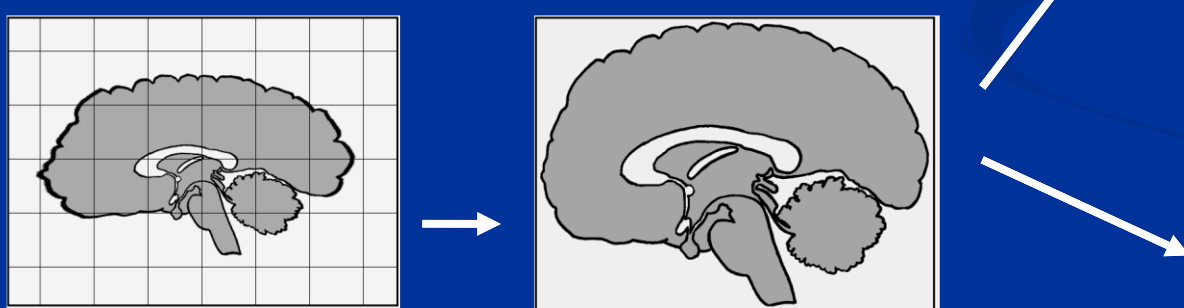


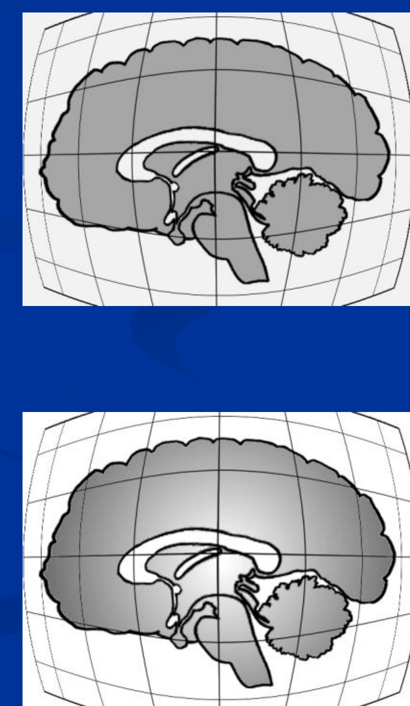
CSF

Modulation

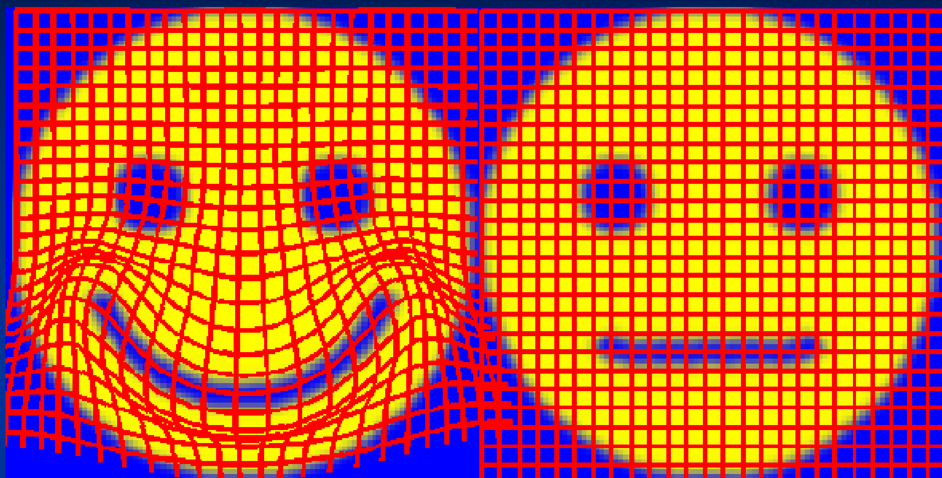
Corrects for distortions and changes in volume induced by nonlinear normalization.

– Analogy: as we blow up a balloon, the surface becomes thinner. Likewise, as we expand a brain area it's volume is reduced.

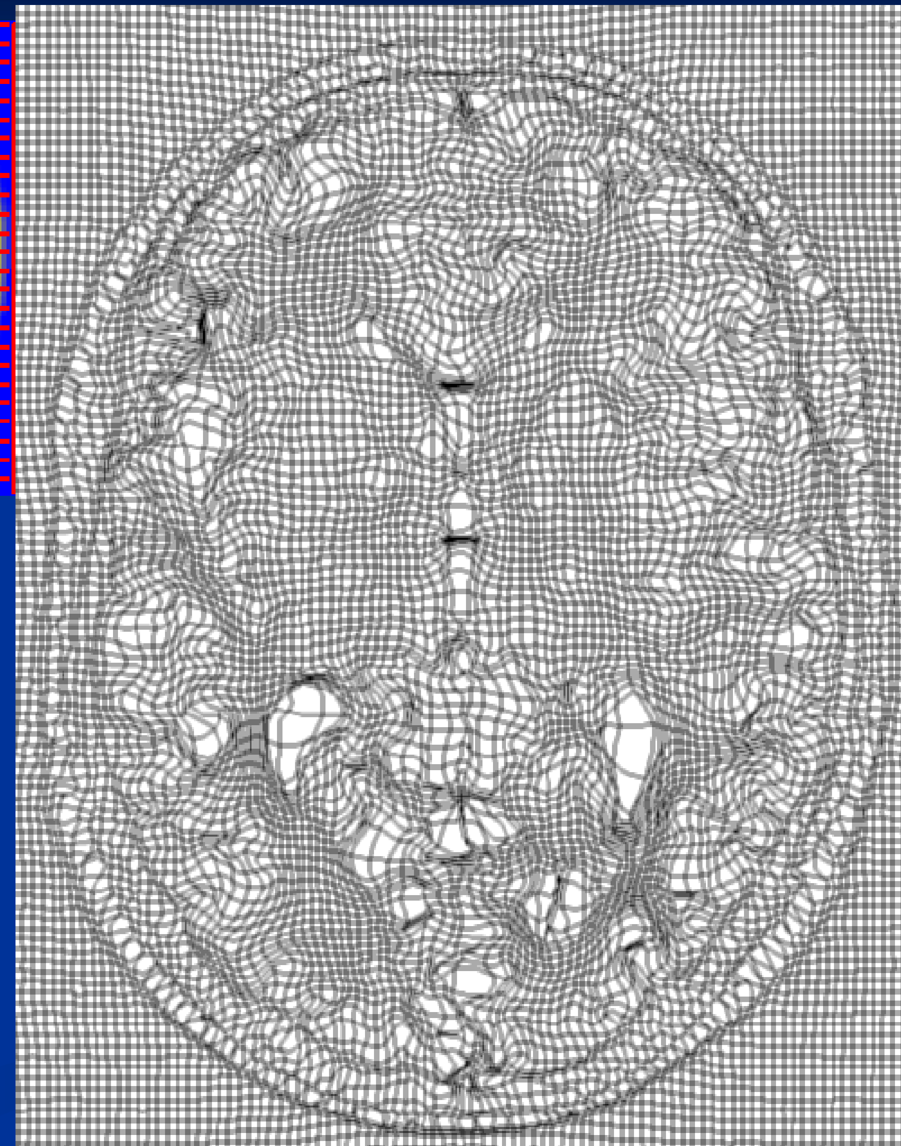




Deformation Field



Original Warped



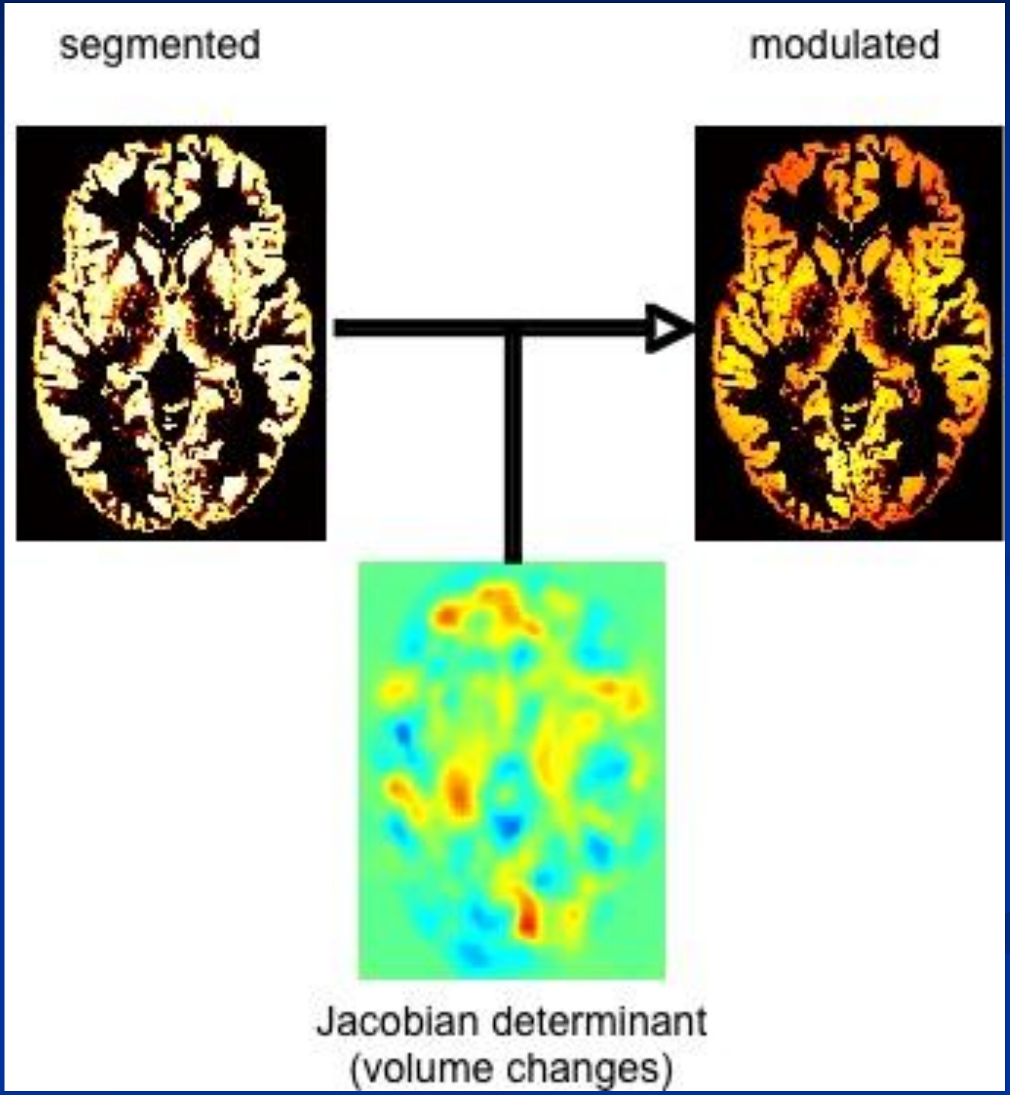
Deformation field

$$\begin{bmatrix} x' \\ y' \\ z' \end{bmatrix} = \begin{bmatrix} t_1(x,y,z) \\ t_2(x,y,z) \\ t_3(x,y,z) \end{bmatrix}$$

Modulation

Effect of modulating segmented images. The Jacobian determinant in the center represents the volume changes due to non-linear spatial normalization.

These volume changes are used to modulate the segmentation result on the left and the modulated image is shown on the right side.

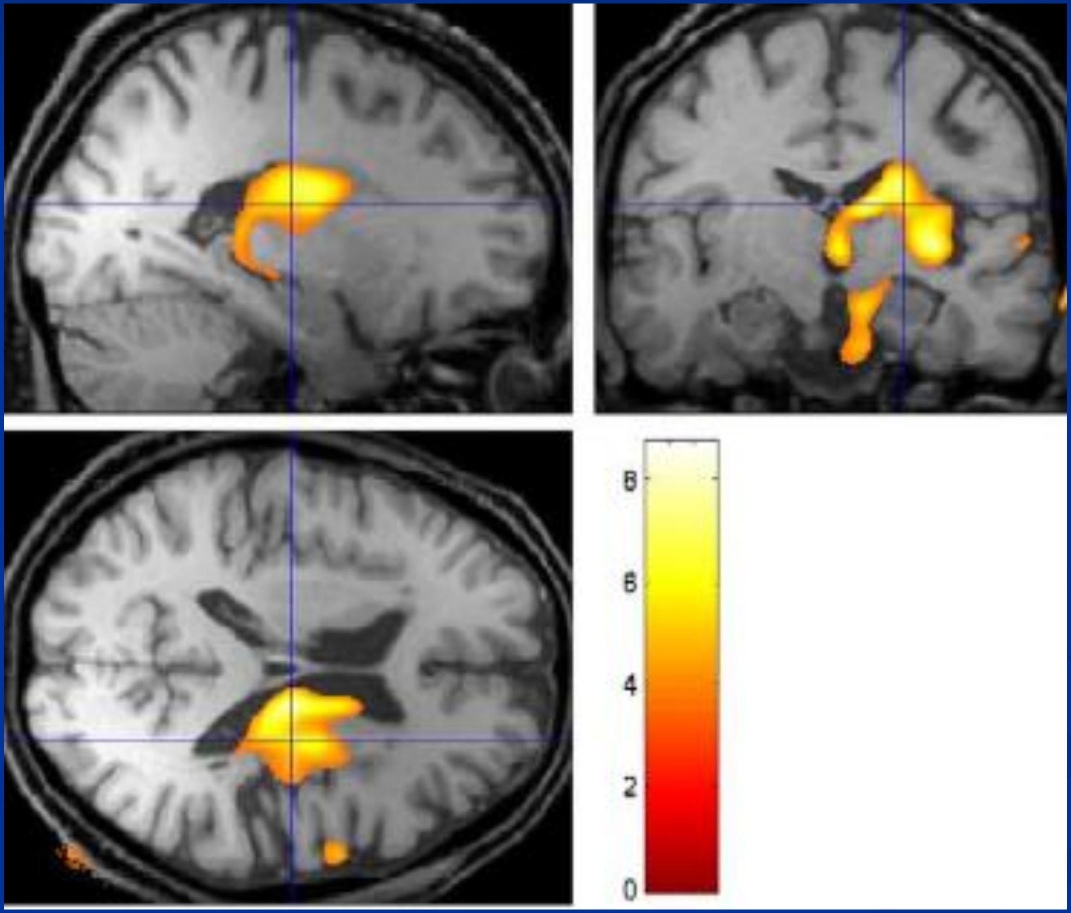


Advantages

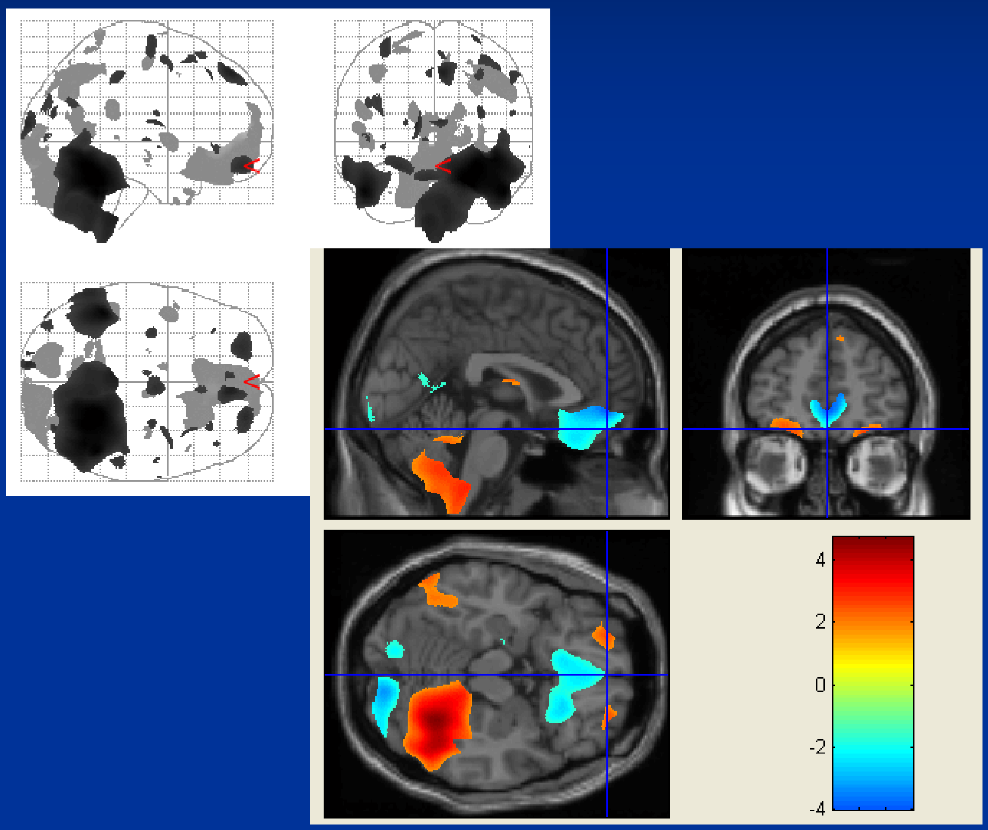
- Automated: fast and not subject to individual bias.
- Able to examine regions that are not anatomically well defined.
- Able to see the whole brain rather than choosing specific regions.
- Can be normalized for overall differences in brain volume, but also small regional variations in volume which will otherwise add variance to regional measurements.

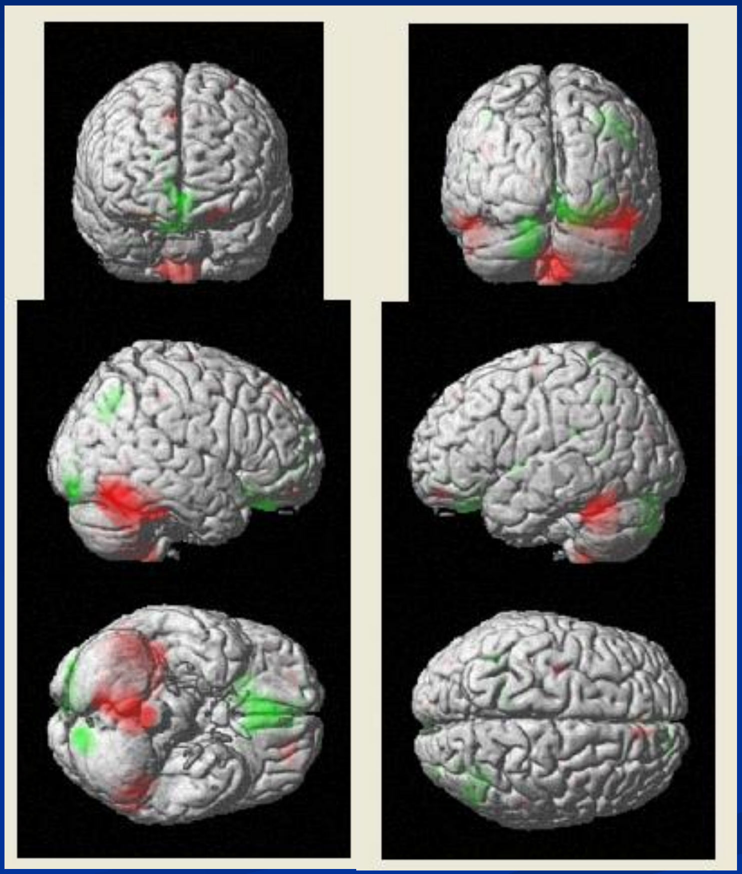
Measuring stroke (Shen et al. 2007)

- Stroke patient vs. controls



Correlation between BMI and Gray Matter Volume

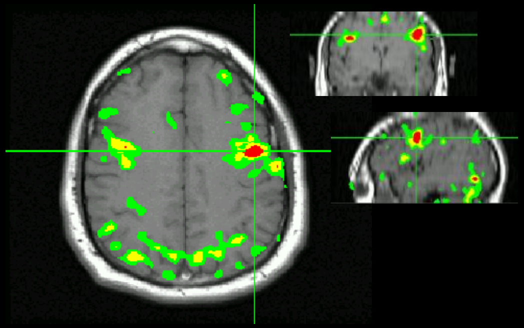




Decline Volume with Increasing BMI

Increase Volume with Increasing BMI

fMRI: What is it?



- Measures changes in signal intensity that arise from oxygenated blood in a region.

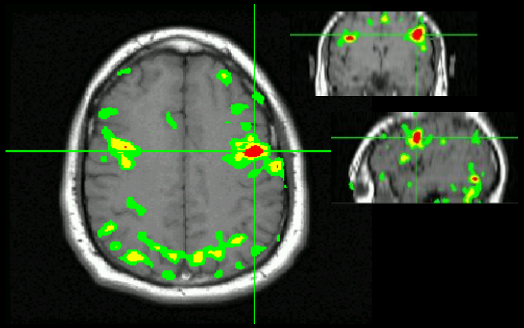
Good things:

- High resolution, fast scanning time, non-invasive

Not so good things:

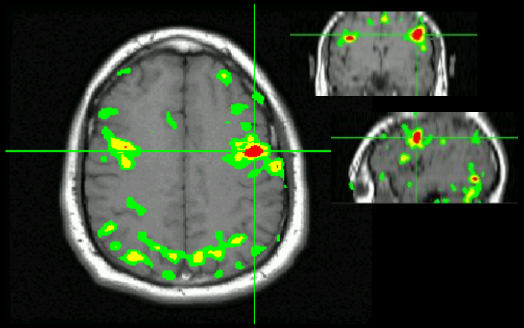
- Very low signal to noise ratio, sensitive to motion, susceptibility artifacts

Functional MRI signal



- MRI signal is dependent on field strength of the magnet and the properties of the tissue.
- Also dependent upon changes in local environment
- Paramagnetic substances (such as deoxyhemoglobin) will lead to loss of local signal on T2* weighted image.

Functional MRI signal



Local neuronal activity

→ Increased local metabolic rate

→ Increased blood flow

→ Increased oxygenated hemoglobin

→ Uptake of O_2 less than supply

→ Surplus oxygenated hemoglobin

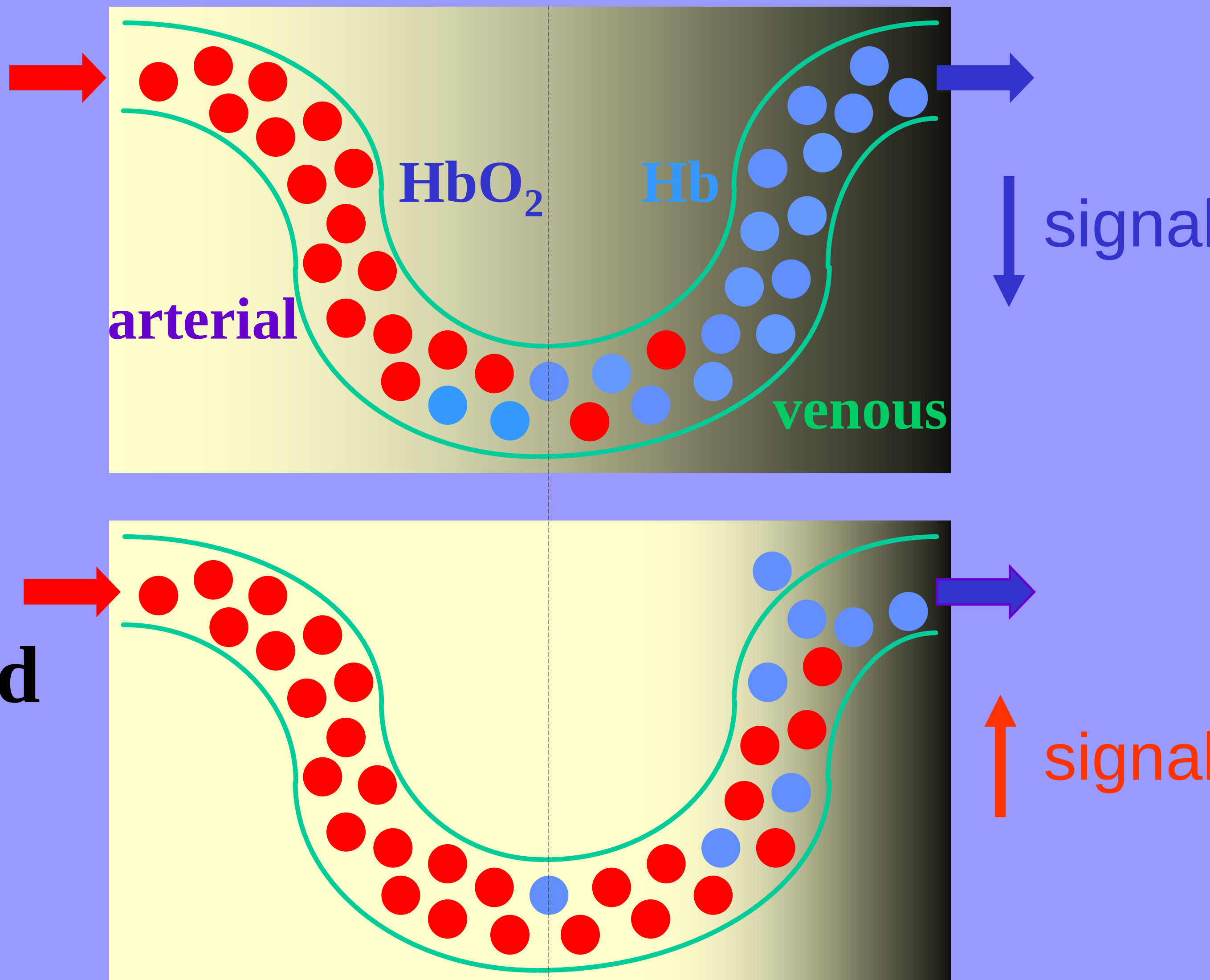
→ Decreased concentrations of deoxyhemoglobin

→ **Increased local fMRI T2* signal**

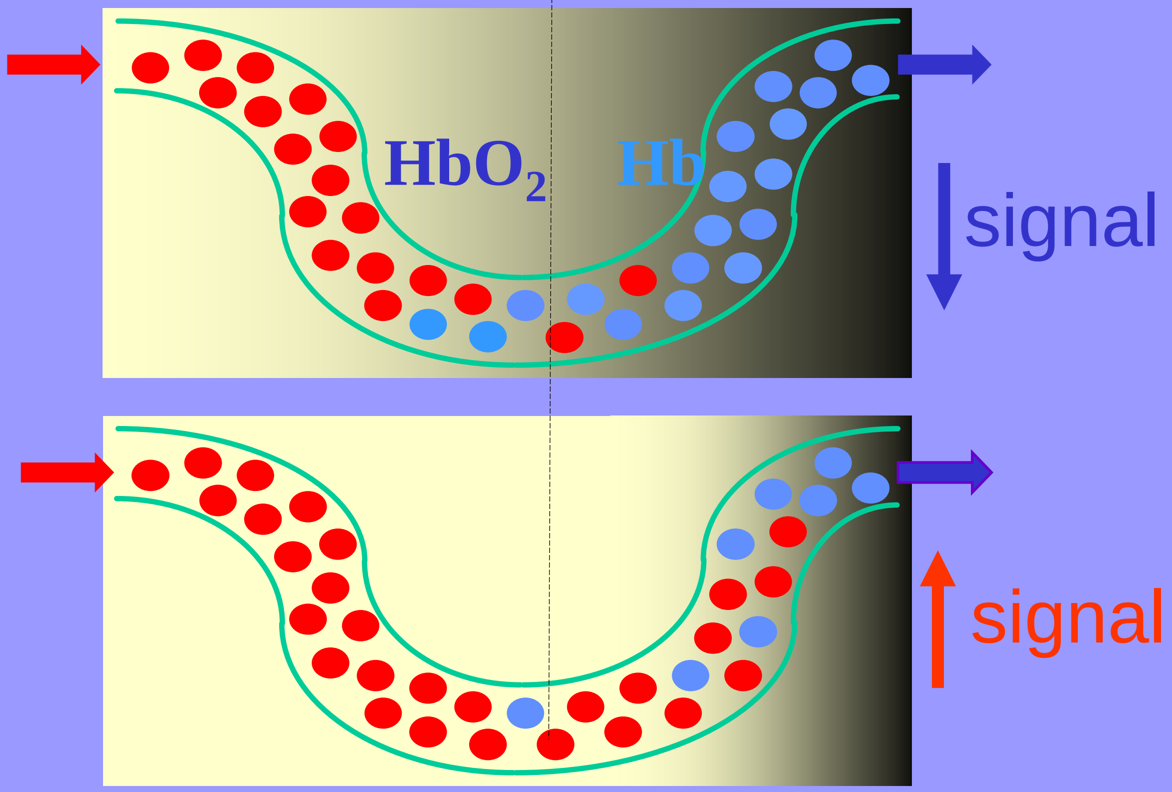
BOLD Contrast

Resting state

Stimulated state



Determining Activation: A subtraction measure

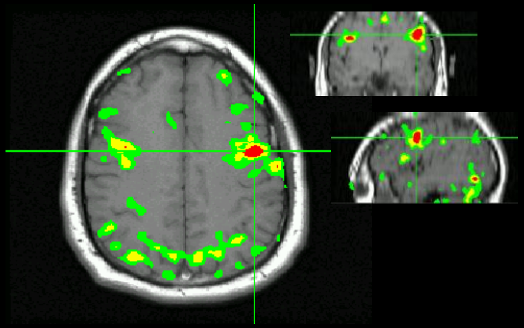


Subject is scanned at rest (R)

Subject is scanned during cognitive task (C)

Regions of activity are determined the *differences* between scan R from scan C.

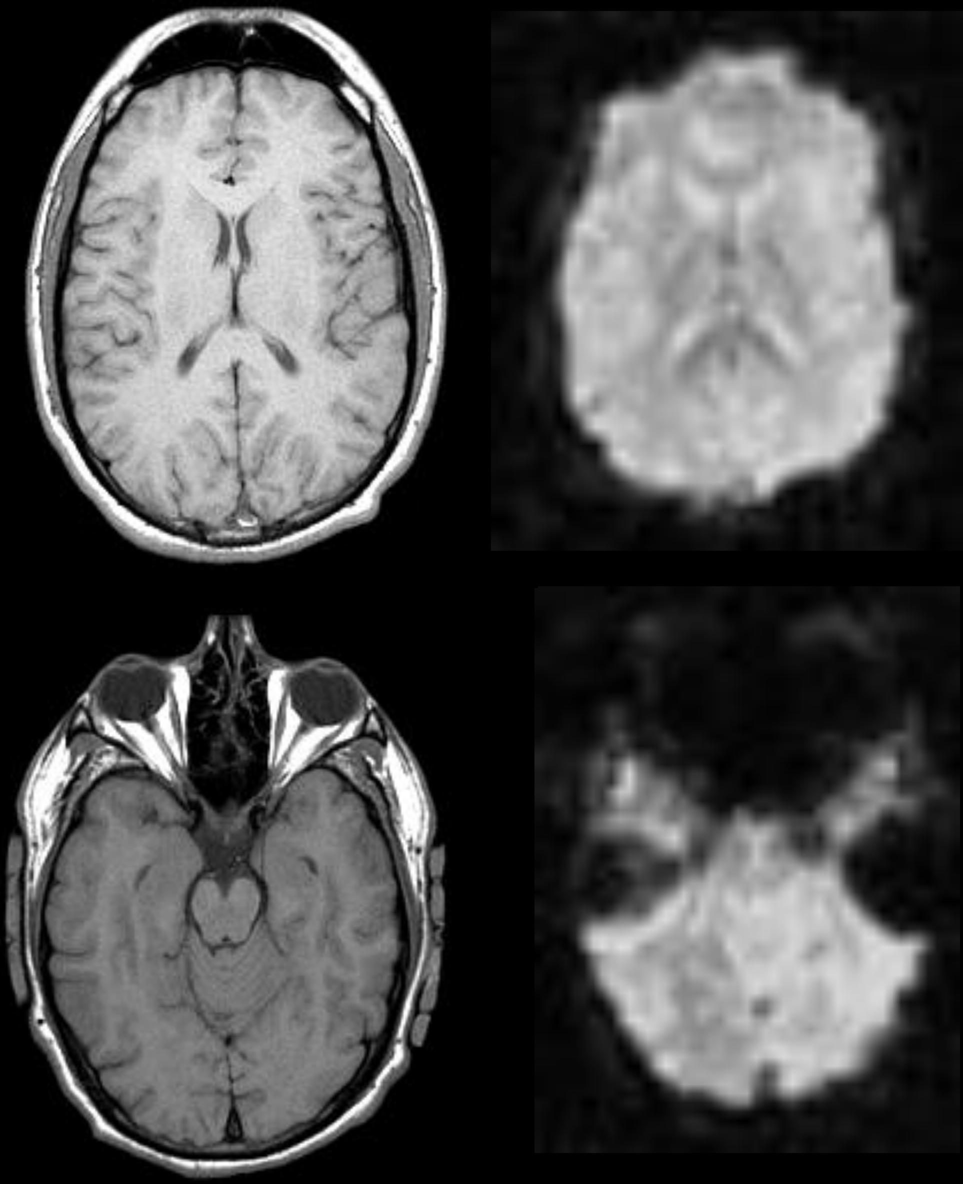
Caveats regarding fMRI:



- Tertiary measure of neuronal activity.
- Very small signal changes, on order of 1 to 2%.
- Signal change predominates in region of large draining veins, not gray matter, and may vary in locality.
- Extremely sensitive to motion.
- Hemodynamic response is delayed -- 15 msec scan, but 10-12 sec response.

Anatomical: 1 x 1 x 5mm

Functional: 3.4 x 3.4 x 5mm

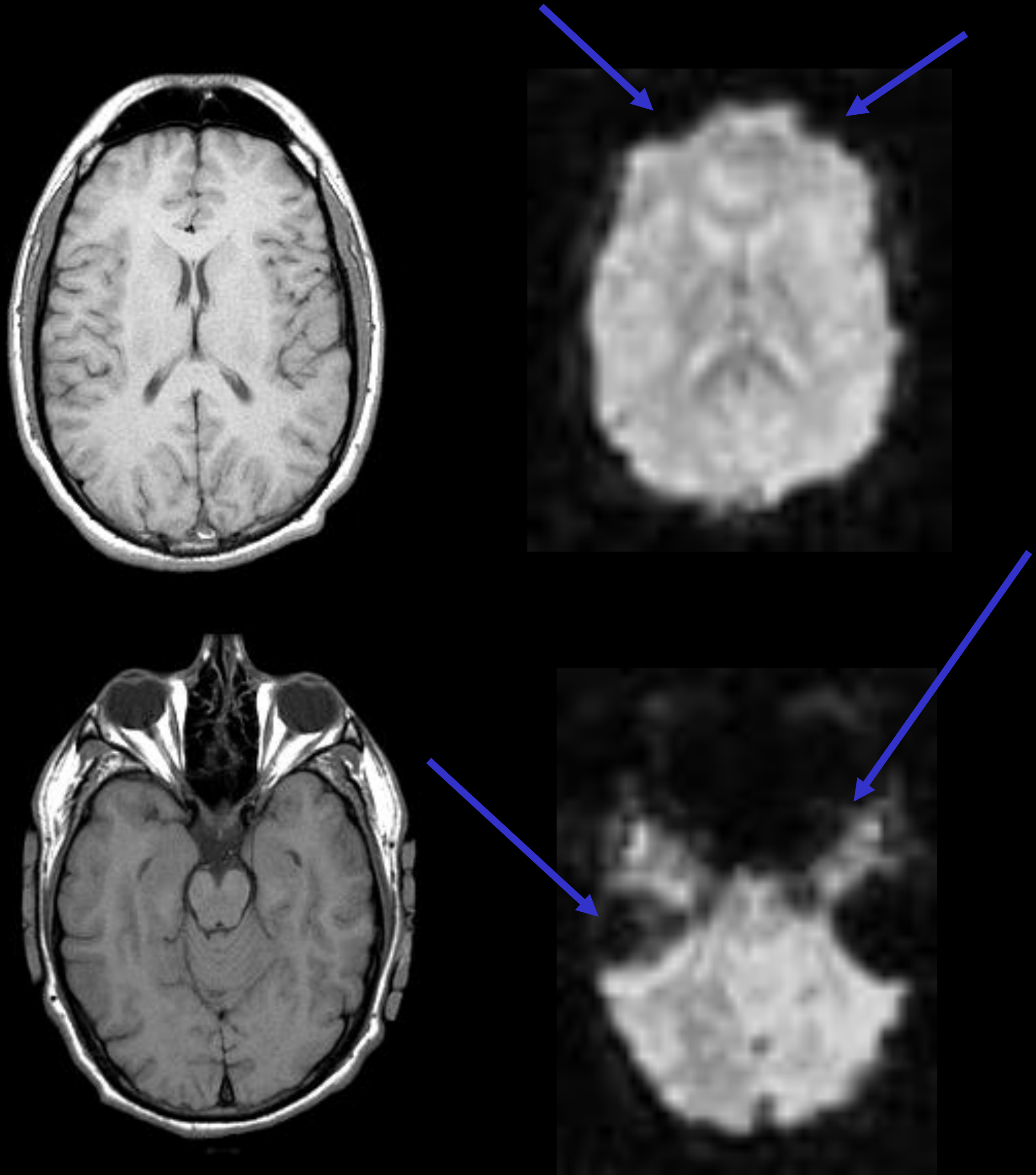


Dealing with low signal strengths:

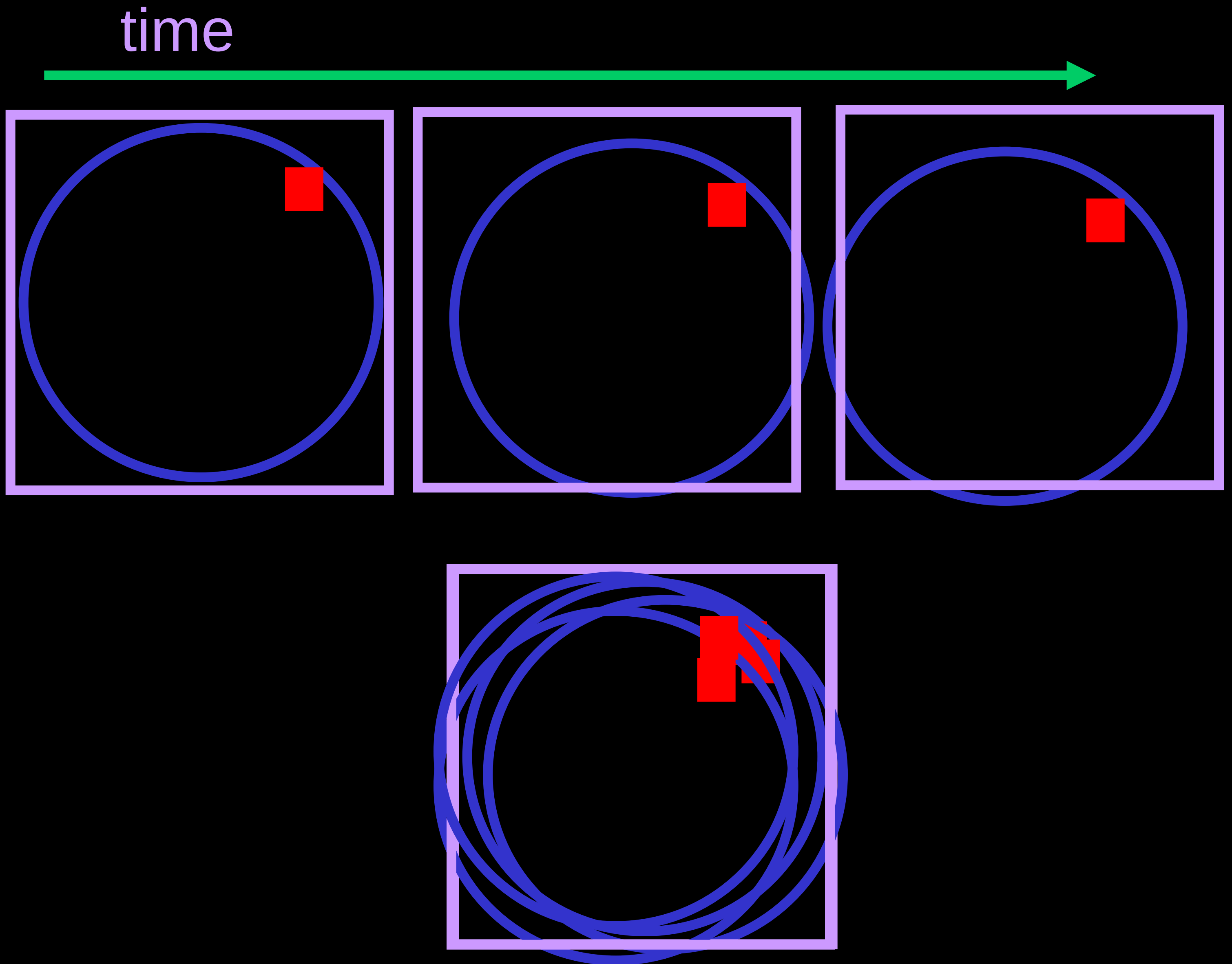
Larger voxel size increases signal to noise (sensitivity), but results in lower resolution images.

Susceptibility:

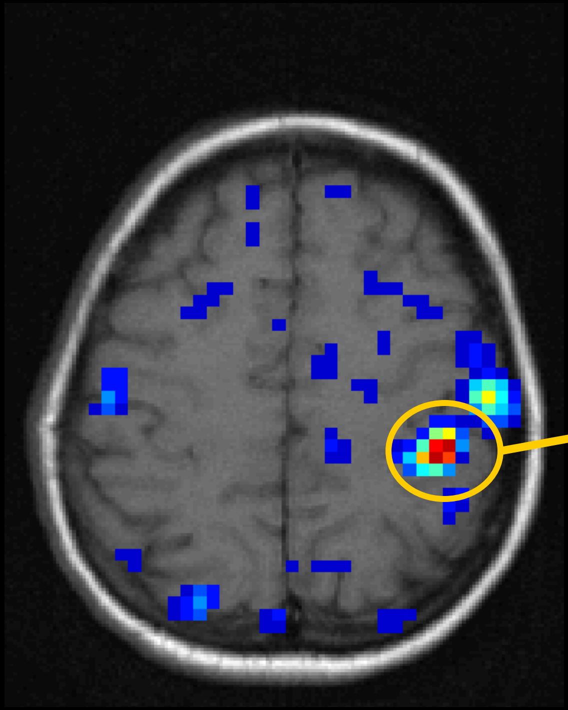
Regions near transitions between brain and air (sinuses) will cause signal dropoff.

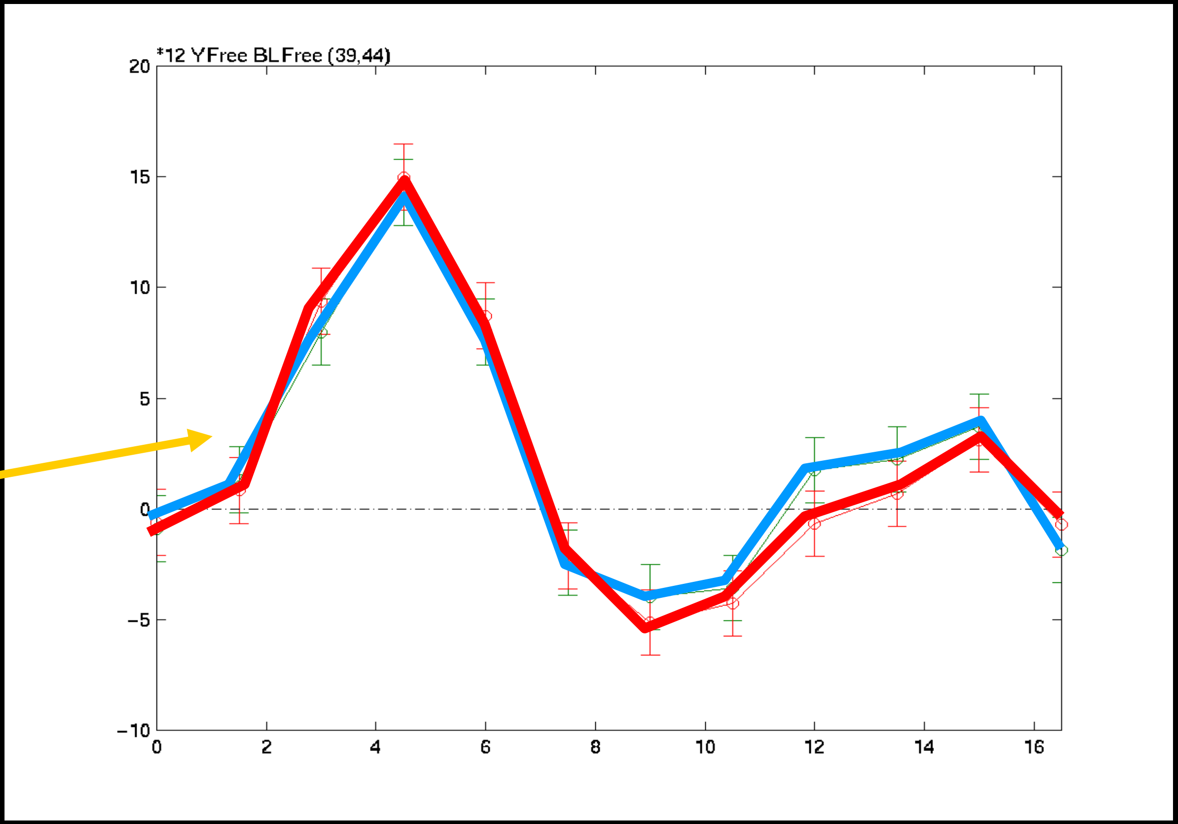


Motion:



The hemodynamic response takes time, even for a single, fast behavioral response



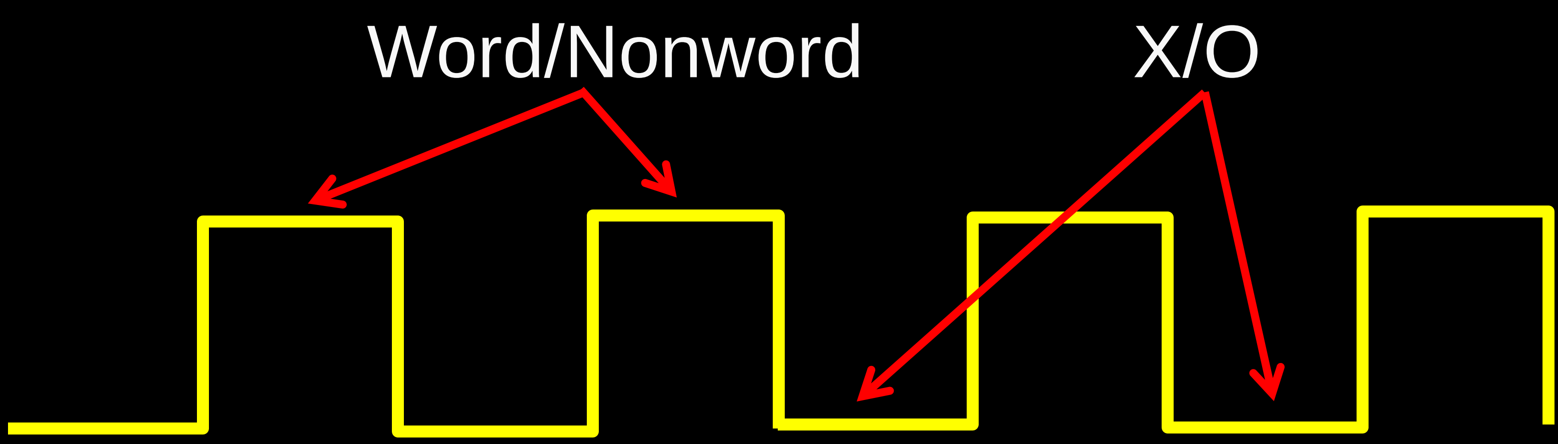


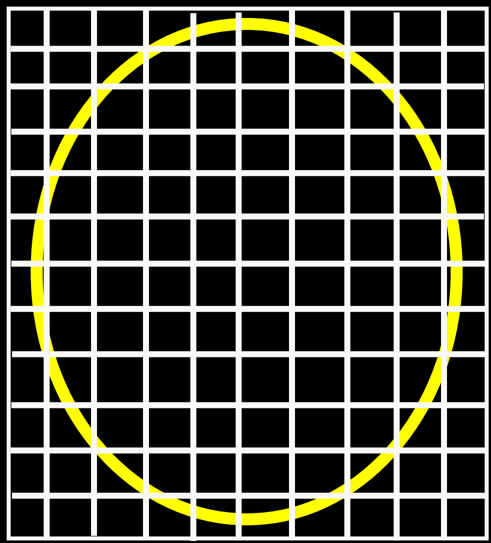
Simple fMRI experiment:

Word identification

20secs: Word/Nonword R/L button press

20 secs: XXXX/OOOO R/L button press



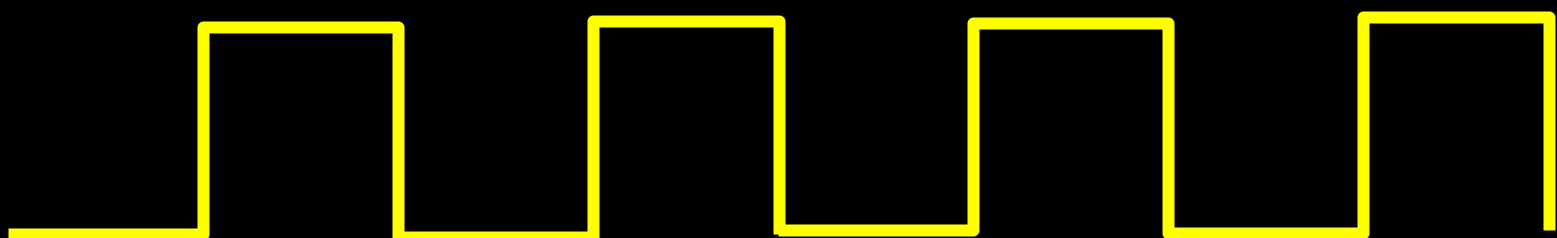


Statistical analysis:

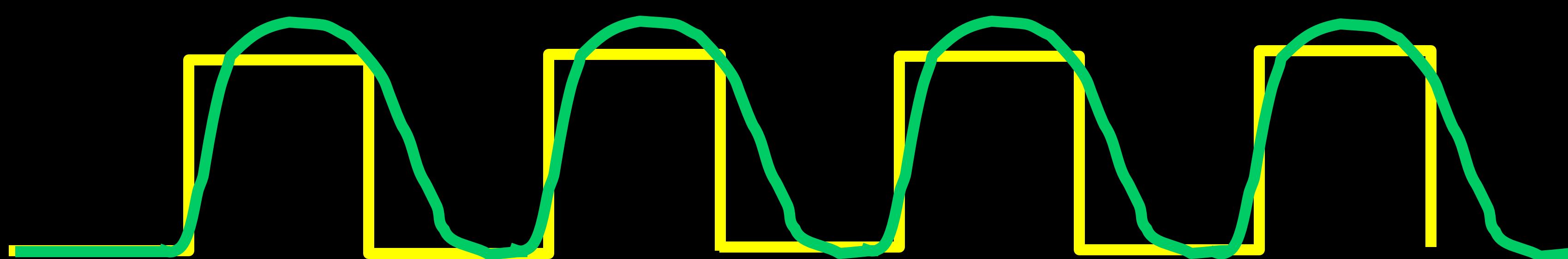
Mean[W/N], Mean[X/O]

Paired t-test = Pearson r (function 0,1)

Alternatively, convolved function HRD with 0,1

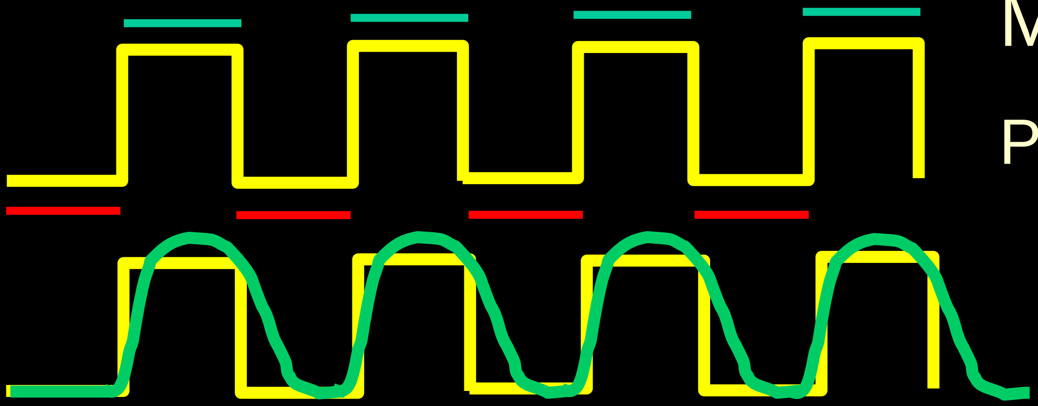


TIMEPT: 1 2 3 4 5 6 7 8 9 0 1 2 3 4 5 6 7 8 9 0 1 2 3 4 5 6 7 8 9 0 1 2 3 4 5 6 7 8 9 0 1 2 3 4 5 6 7 8 9 0 1 2 3 4 5 6 7 8



TIMEPT: 1 2 3 4 5 6 7 8 9 0 1 2 3 4 5 6 7 8 9 0 1 2 3 4 5 6 7 8 9 0 1 2 3 4 5 6 7 8 9 0 1 2 3 4 5 6 7 8 9 0 1 2 3 4 5 6 7 8

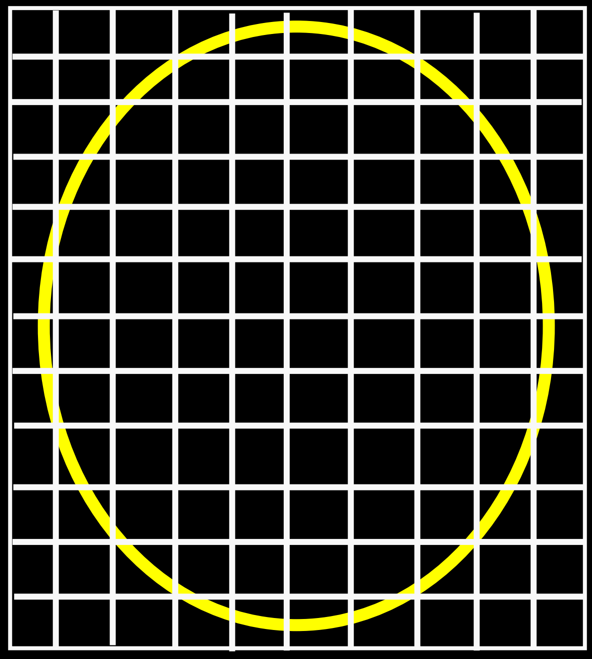
An immediate problem of experiment-wise error



Mean[W/N] > Mean[X/O]

Paired t-test or correlation

p(voxel) < .05, .01, etc



How many tests?

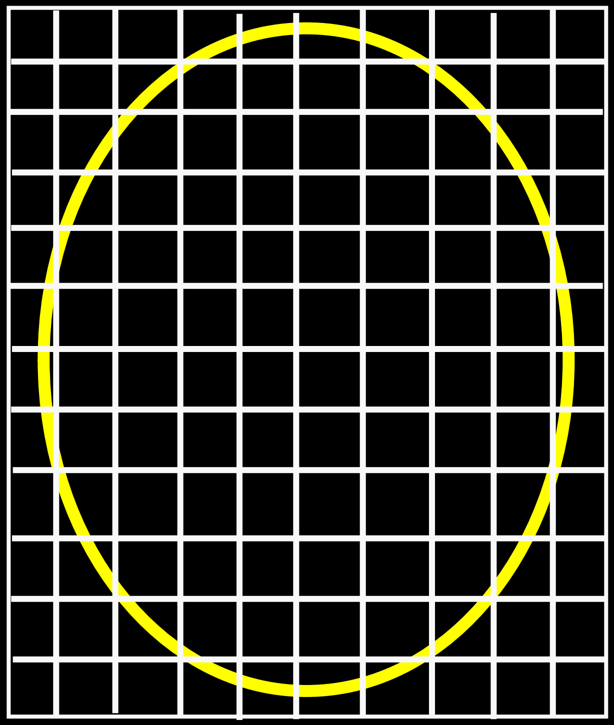
Volume: 5mm section, 64x64, 20 sections

81,920 voxels x 60% (brain)

Total tests: 49,152

Statistical assumptions:

Independence across voxels: Critical issue in dealing with multiple comparisons and assessing true p value



What is the true dependence across voxels?

Functional fields: Regions of cortex work in concert; the degree of independence is an empirical question

Distribution of vessels: BOLD may be correlated across regions due to shared blood flow

Approaches:

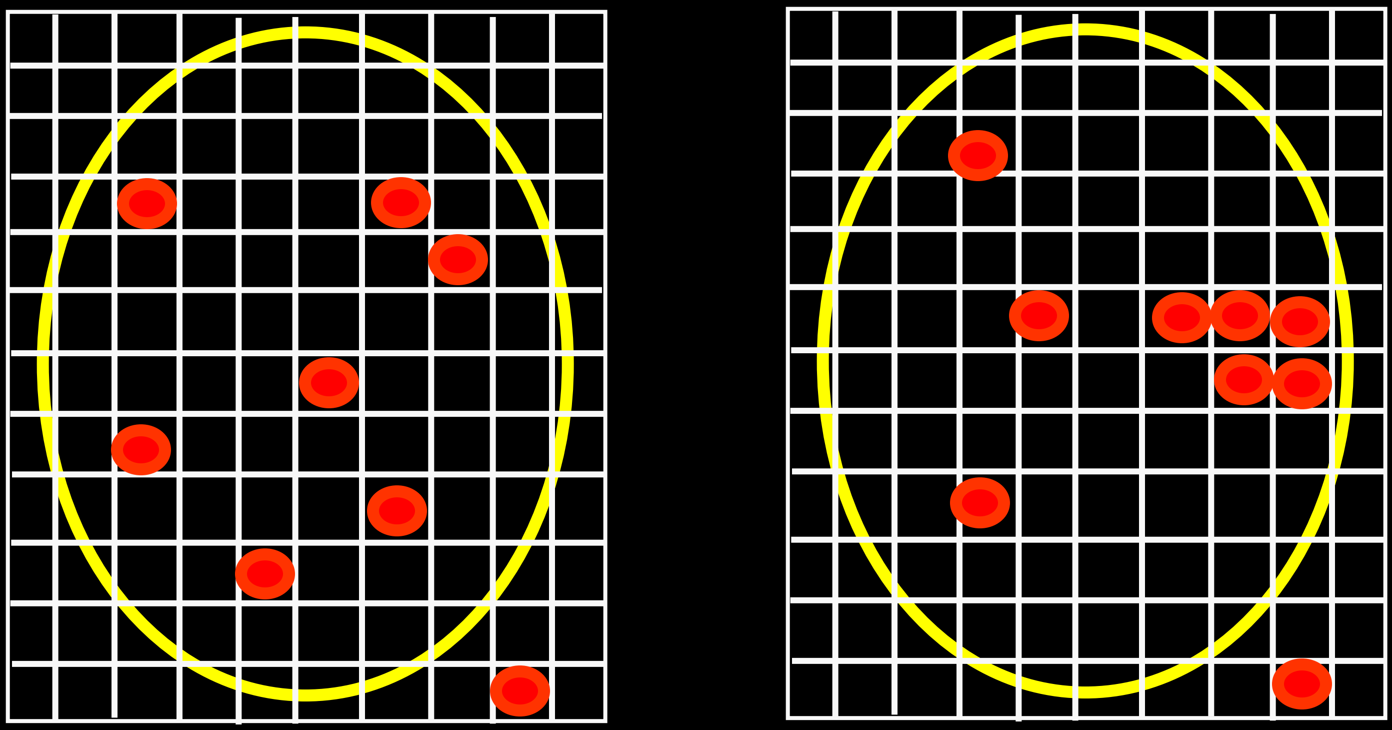
Smoothing: SPM imposes a covariance structure across all voxels, in order to estimate the change in degrees of freedom.

Downside is that covariance is not uniform.

Upside is that smoothing deals with left-over-motion, and some partial voluming.

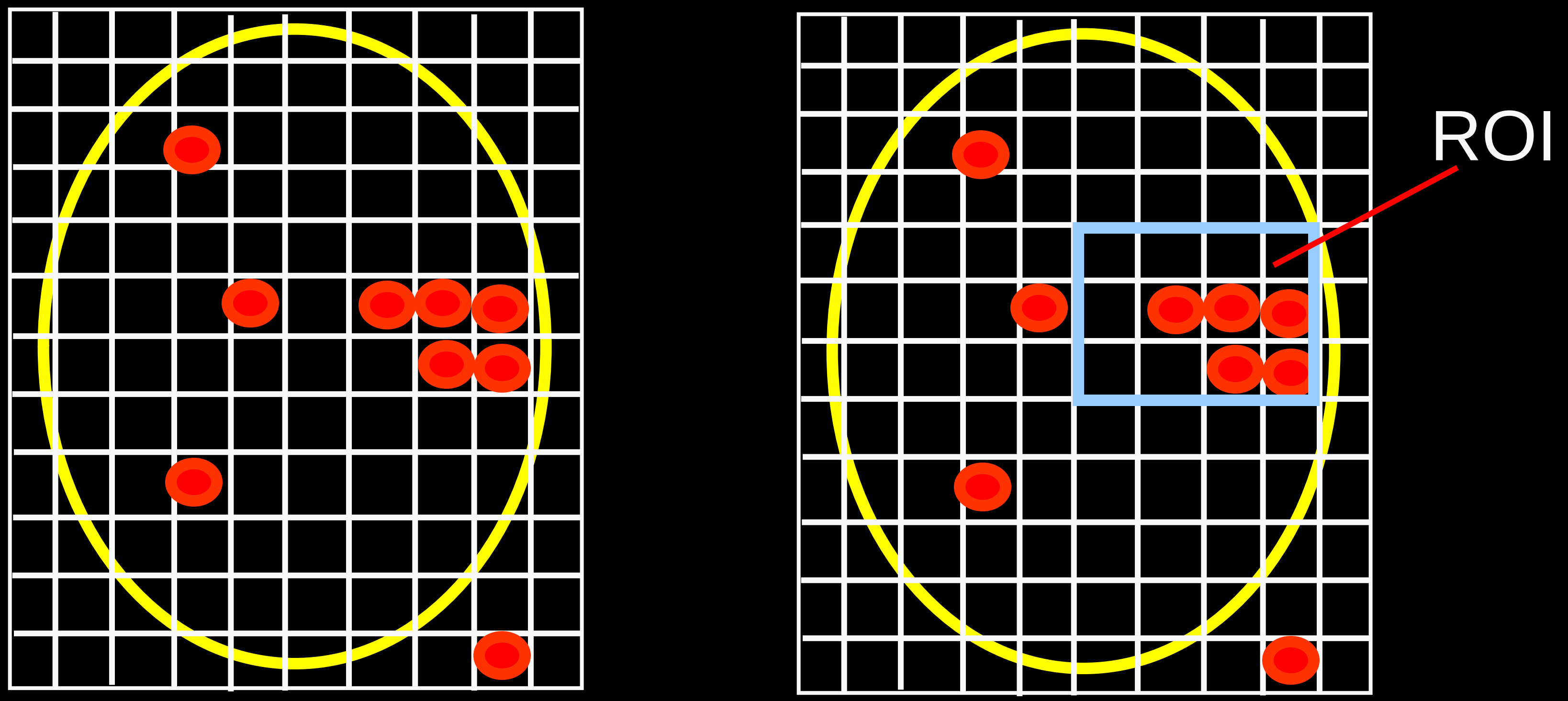
Then apply FDR or FWE correction based on the “known” DF.

Clustering: Independent tests on each voxel, but estimate the probability by chance alone that voxels will occur side by side.



At p = .05, 2048 voxels, chance alone = 102

Chance that 12 cluster continguously? Much less



Another approach: Region of interest analysis

Identifying a priori based on anatomy or prior research the regions to analyse -- greatly reduces experimentwise error rate.

Types of designs:

Blocked -- easy to set up, but limited

Factorial designs: Measuring interaction effects

[A+B+X] - [B+X] = [A+X] - [X]

Cognitive conjunctions: Varying the control conditions to identify common cognitive processes

[A+B] - [B] compared to [A+C] - [C]

Parametric designs: Varying a parameter within a given variable, example, reaction time differences or confidence judgements

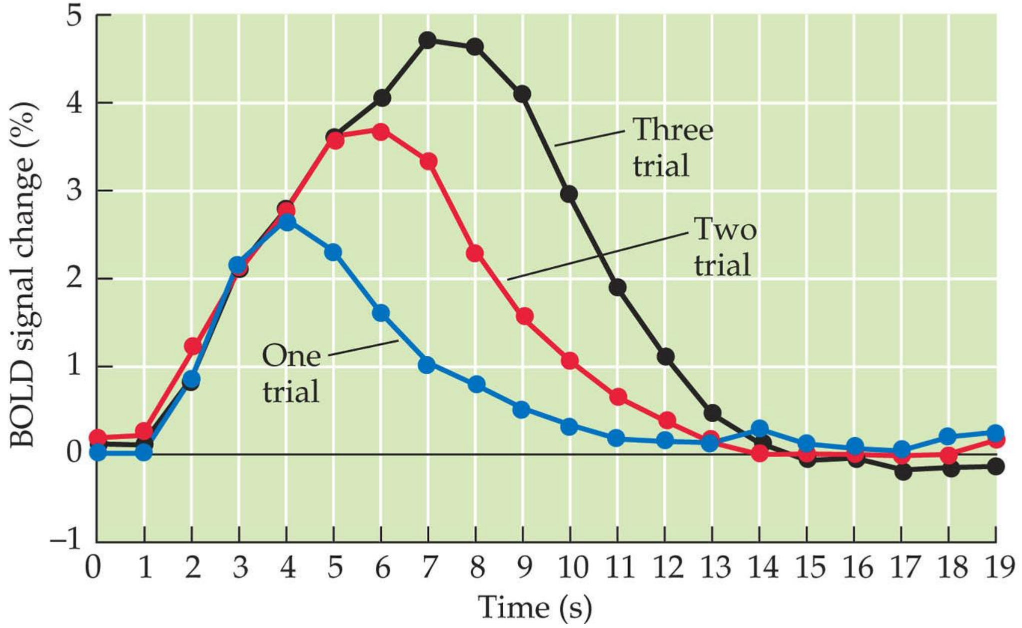
Blocked designs -- easy to set up, but limited

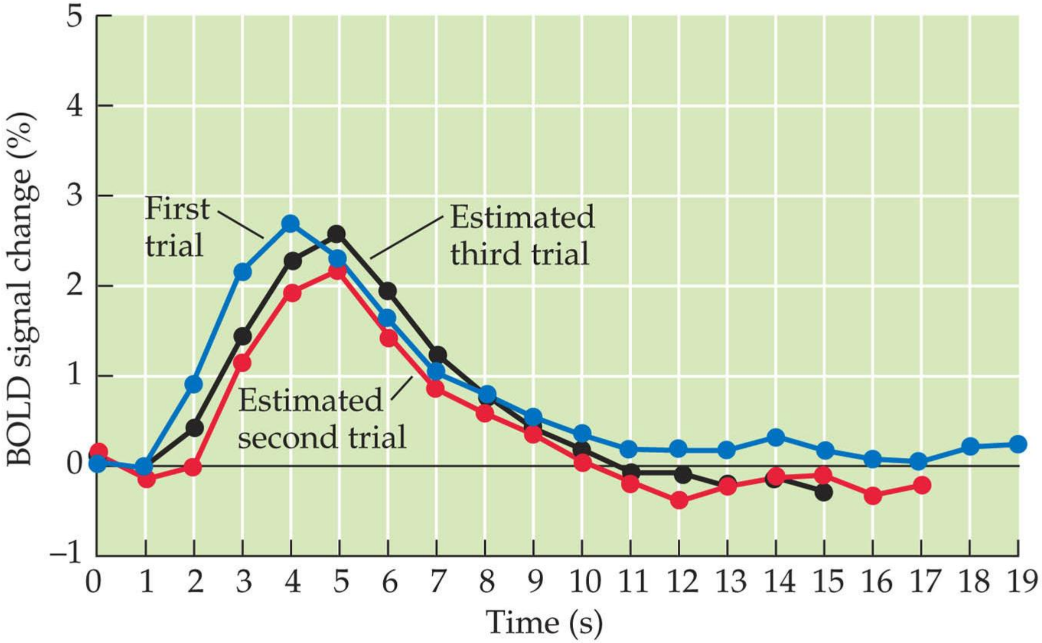
- Can't randomize trials
- Anticipation of effects (blocks of Yes vs No)
- Cannot remove incorrect responses
- But, greater power to detect changes in signal
- Why? Signal amplitude increase is (somewhat) additive)
- Insensitive to the shape of the HDR – a bonus

How do you increase power in a blocked design?

- Allowing activation to return to baseline
- Switching as often as possible

8.20 Linear addition of hemodynamic responses to individual stimulus events. (Part 1)





Dale & Buckner, 1997

One, two, or three stimuli presented at ISI of 2 or 5 sec.

Generally linear and additive respones, especially with ISI=5.

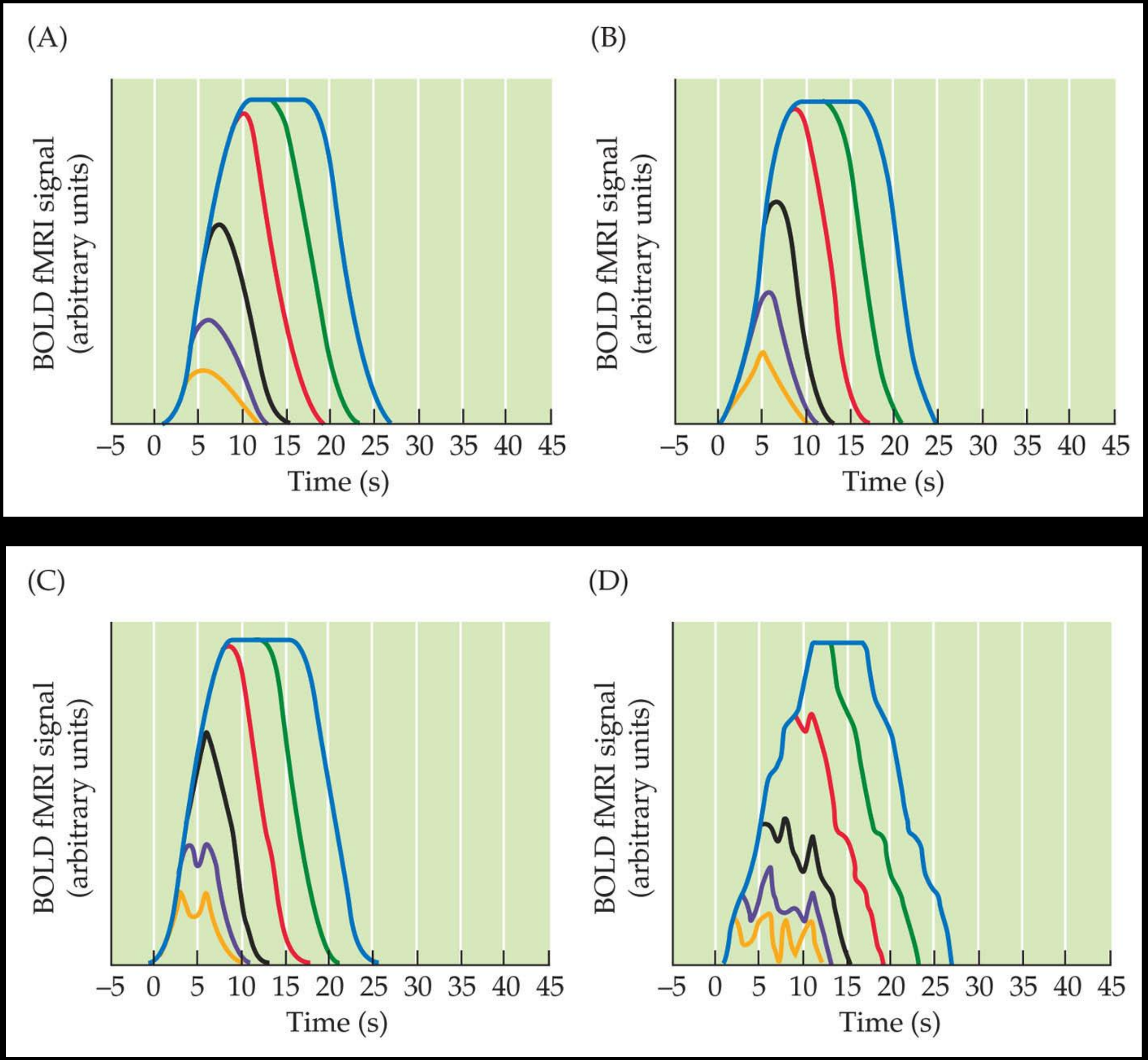
Note that for 2 sec data (shown here), subtraction of the one trial HDR results in subsequent responses that are smaller amplitude and delayed.

Not a perfectly linear system, particularly at short intervals.

Varying stimuli presented from 1 to 32

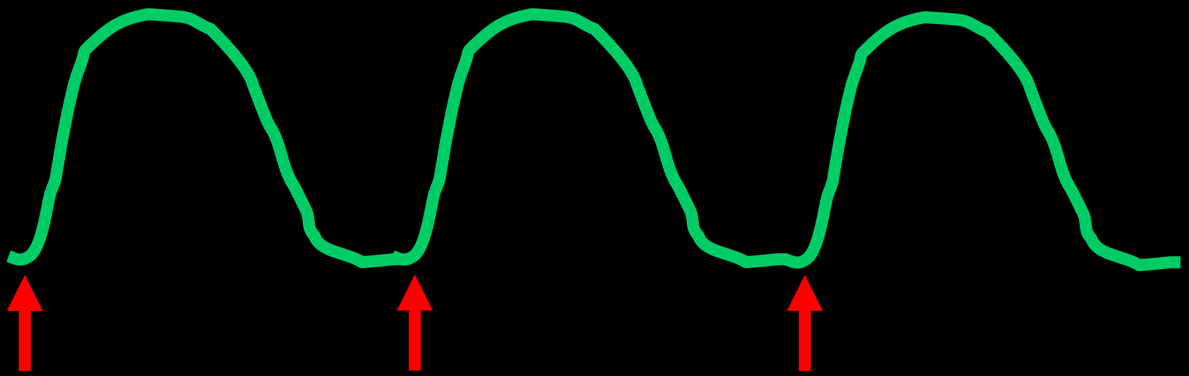
A. Standard HDR form

B-C Other possible HDR forms



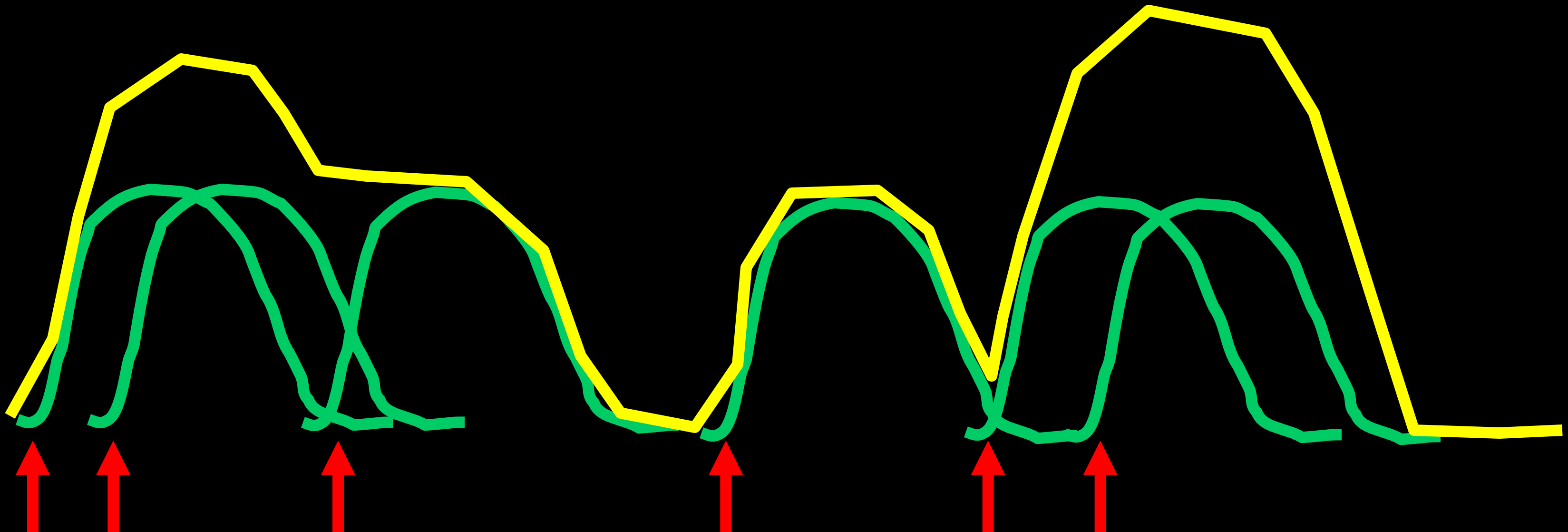
Event related designs

Simplest case: 1….(12-18secs)……1……….1……etc



Faster presentation with jitter

1…1.x…x…1…..1..x…x..1.x.x..11….x.. etc



Good things about event-related designs:

Trials can be regrouped in various ways, based on condition, subject's responses, reaction times, etc

Random presentation decreases anticipatory effects

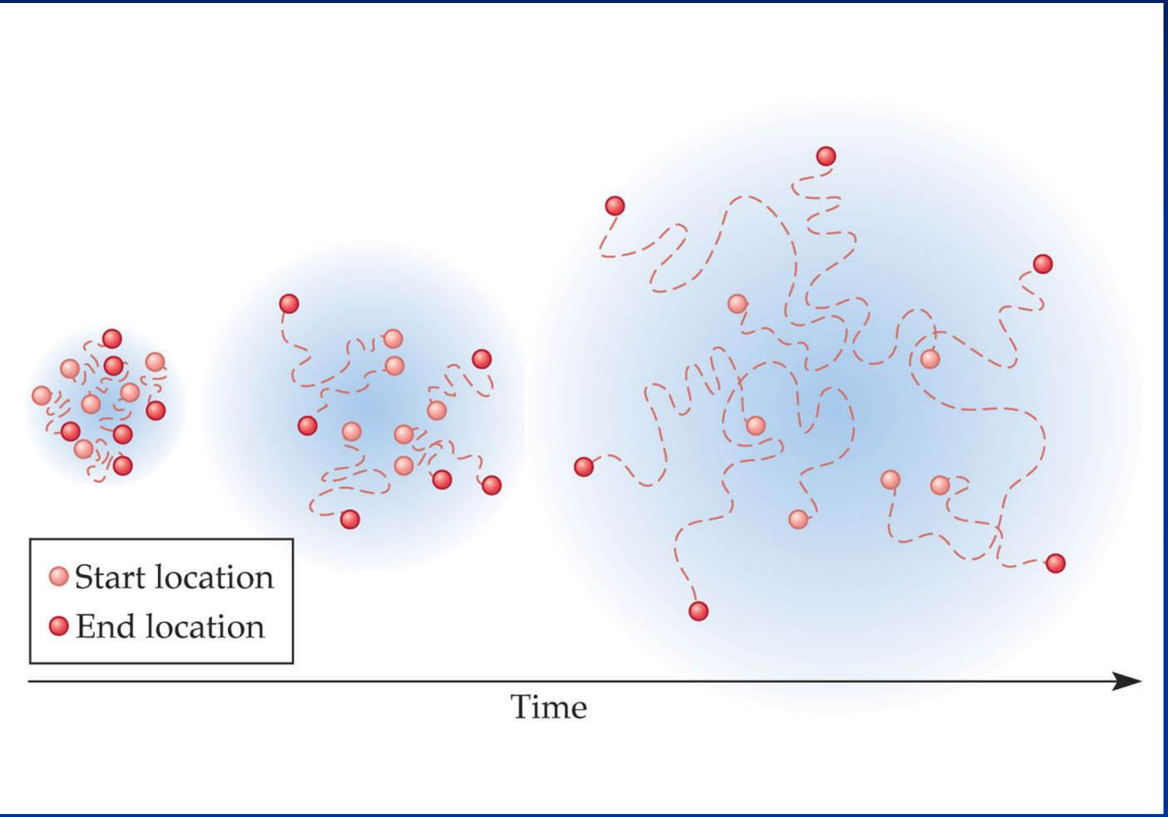
Presentation and responses can be self-paced, more like typical cognitive experimental designs

Difficulties:

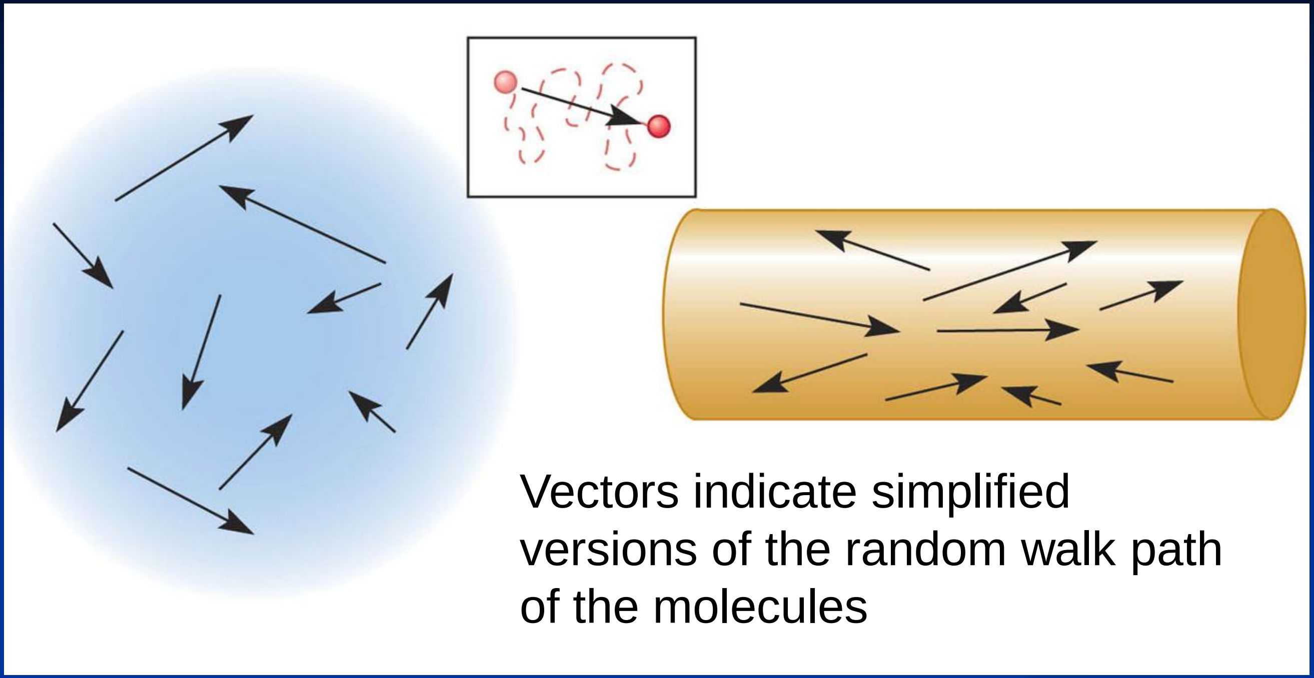
Dependencies amongst trials, e.g., yes/no recognition: *Item......Decision…Response*

Problem: If two regions are hypothesized to play different roles in the decision vs response components of the task, how can you separate them?

- Diffusion MRI: Over time, molecules within gases or liquids will move freely through the medium via Brownian motion



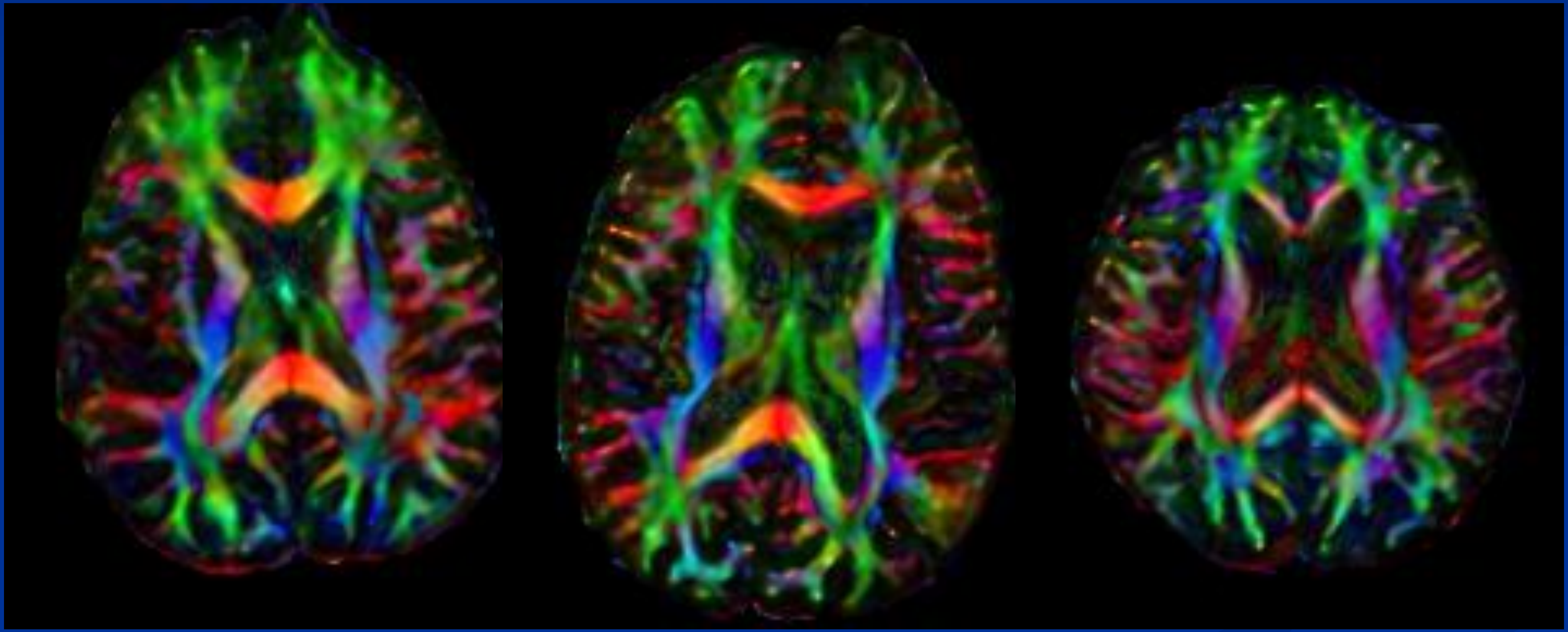
- MRI diffusion-weighted gradient causes changes in the MR signal that are dependent upon the amplitude and direction of diffusion



- Isotropic diffusion – no restrictions in the direction of movement, measured as the apparent diffusion coefficient (ADC)
- Anistropic diffusion – movement is restricted in one or more directions, measured as fractional anisotropy (FA)
- Where movement is relatively unrestricted, ADC will be high and FA will be low
- Where movement is relatively restricted (e.g., in a myelinated axon), ADC will be lower and FA will be high

Changes with Age

3T, 25 directions, 2 B0, 2 averages

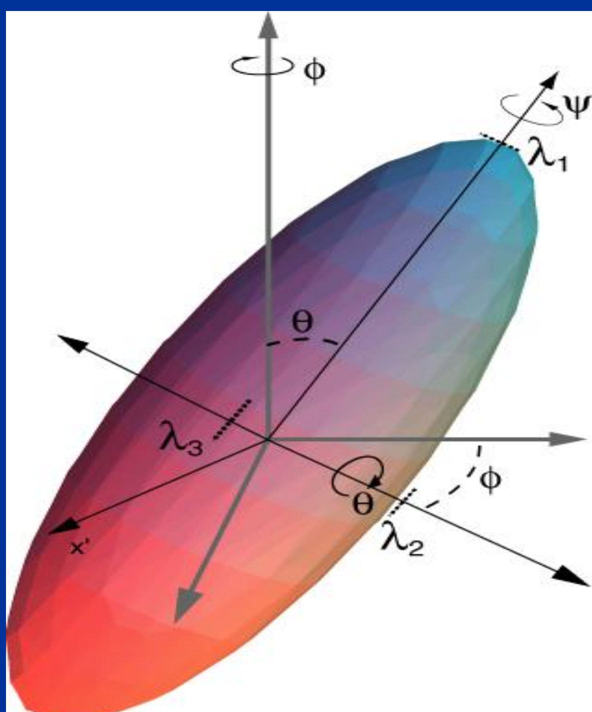


29 years　　75 years　　92 years

Eigen-system Analysis of Diffusion Tensor

$$\vec{\mathbf{D}} = \begin{pmatrix} D_{xx} & D_{xy} & D_{xz} \\ D_{xy} & D_{yy} & D_{yz} \\ D_{xz} & D_{yz} & D_{zz} \end{pmatrix} = \begin{pmatrix} V_{1x} & V_{1y} & V_{1z} \\ V_{2x} & V_{2y} & V_{2z} \\ V_{3x} & V_{3y} & V_{3z} \end{pmatrix} \bullet \begin{pmatrix} \lambda_1 & & \\ & \lambda_2 & \\ & & \lambda_3 \end{pmatrix} \bullet \begin{pmatrix} V_{1x} & V_{2x} & V_{3x} \\ V_{1y} & V_{2y} & V_{3y} \\ V_{1z} & V_{2z} & V_{3z} \end{pmatrix}$$

$$\lambda_1 \geq \lambda_2 \geq \lambda_3$$

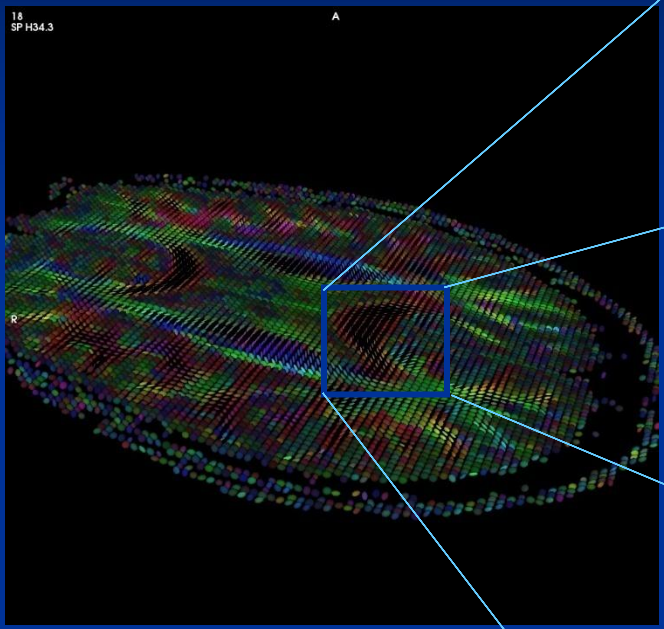


- Major Eigen-Value : λ_1
- Major Eigen-Vector: $\left[V_{1x} \quad V_{1y} \quad V_{1z} \right]^T$

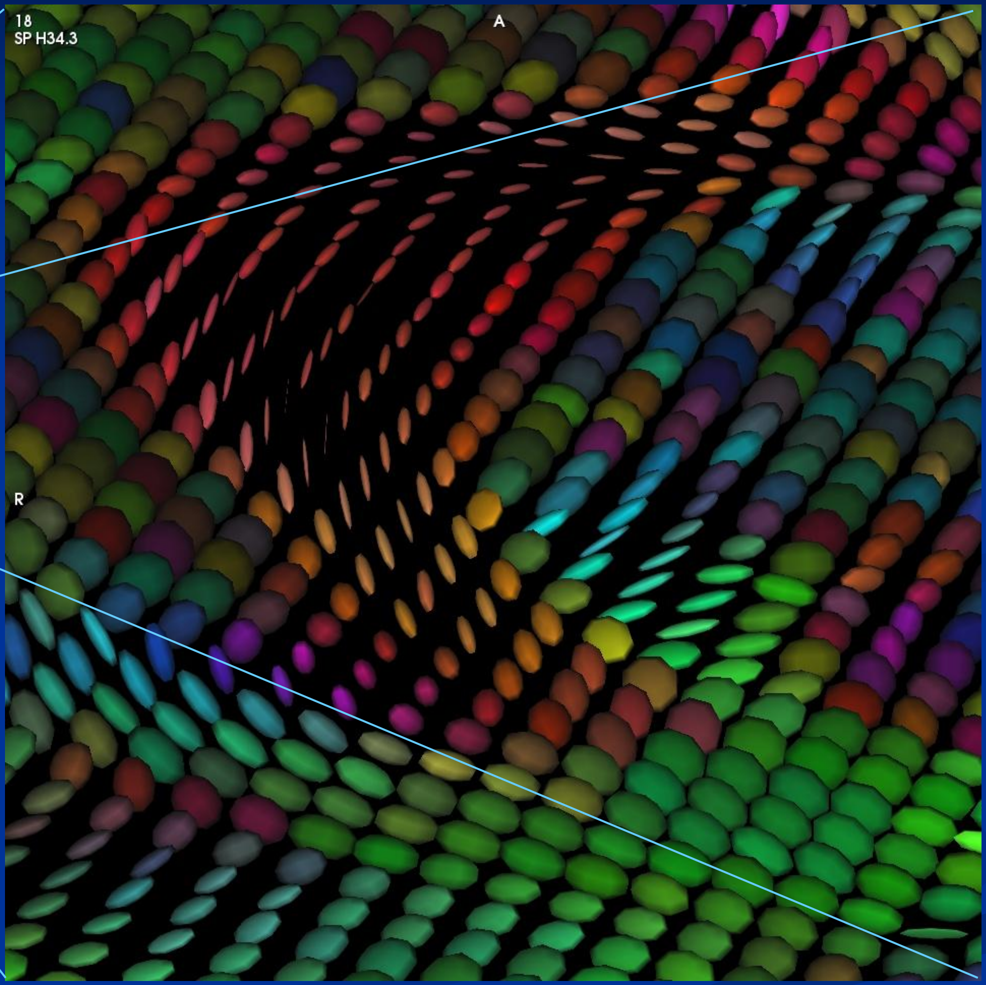
$$FA = \sqrt{\frac{3 \bullet \sum_{i=1,2,3} (\lambda_i - \bar{\lambda})^2}{2 \bullet \sum_{i=1,2,3} \lambda_i^2}}$$

$$\bar{D} = \frac{\lambda_1 + \lambda_2 + \lambda_3}{3}$$

Field of Diffusion Tensor Ellipsoids



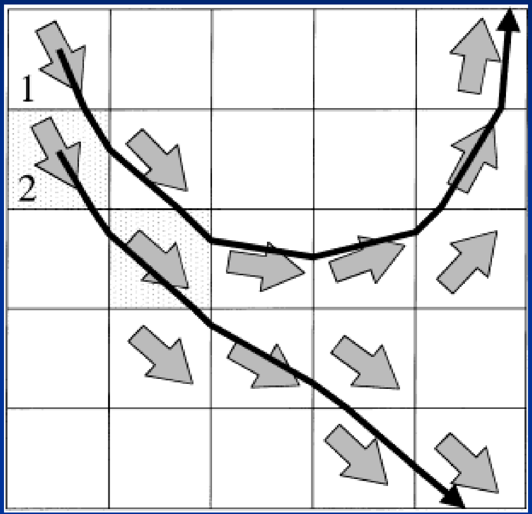
Whole Slice



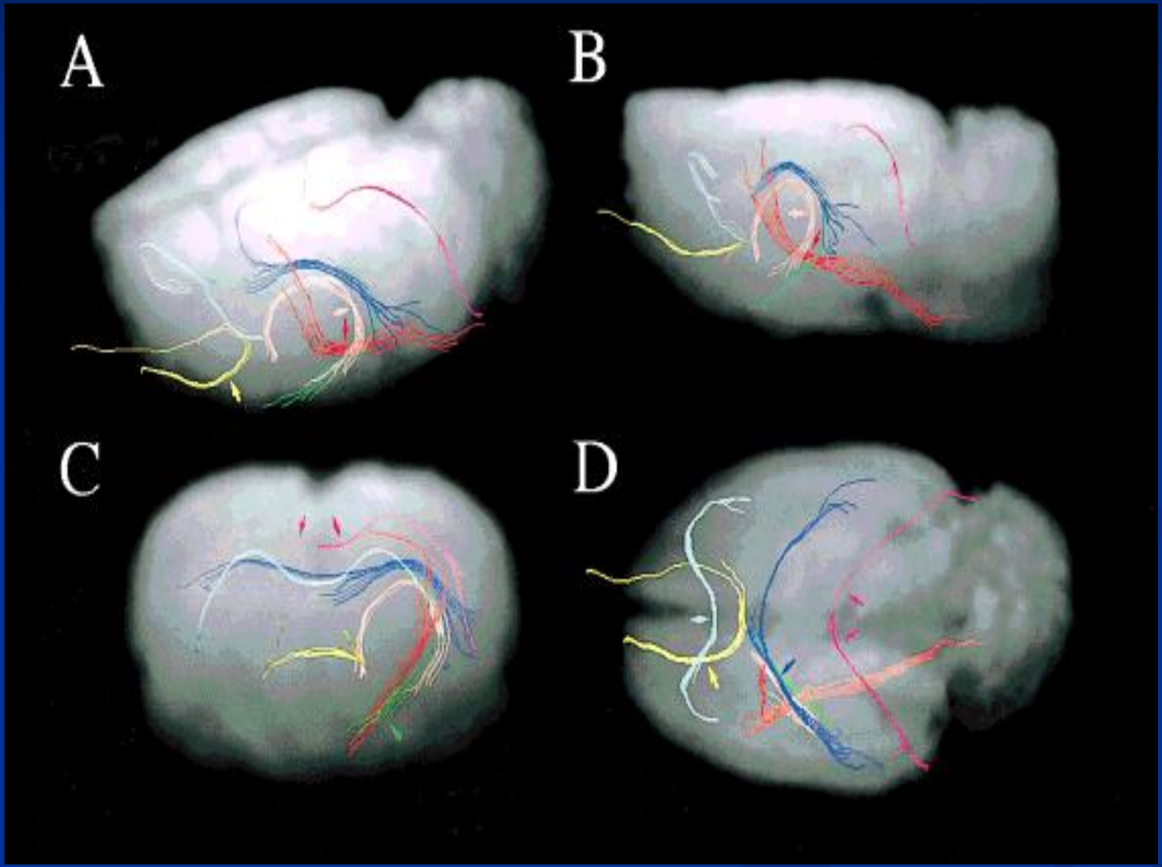
Local Structures

W.Zhan et. al.

Fiber Assignment by Continuous Tracking



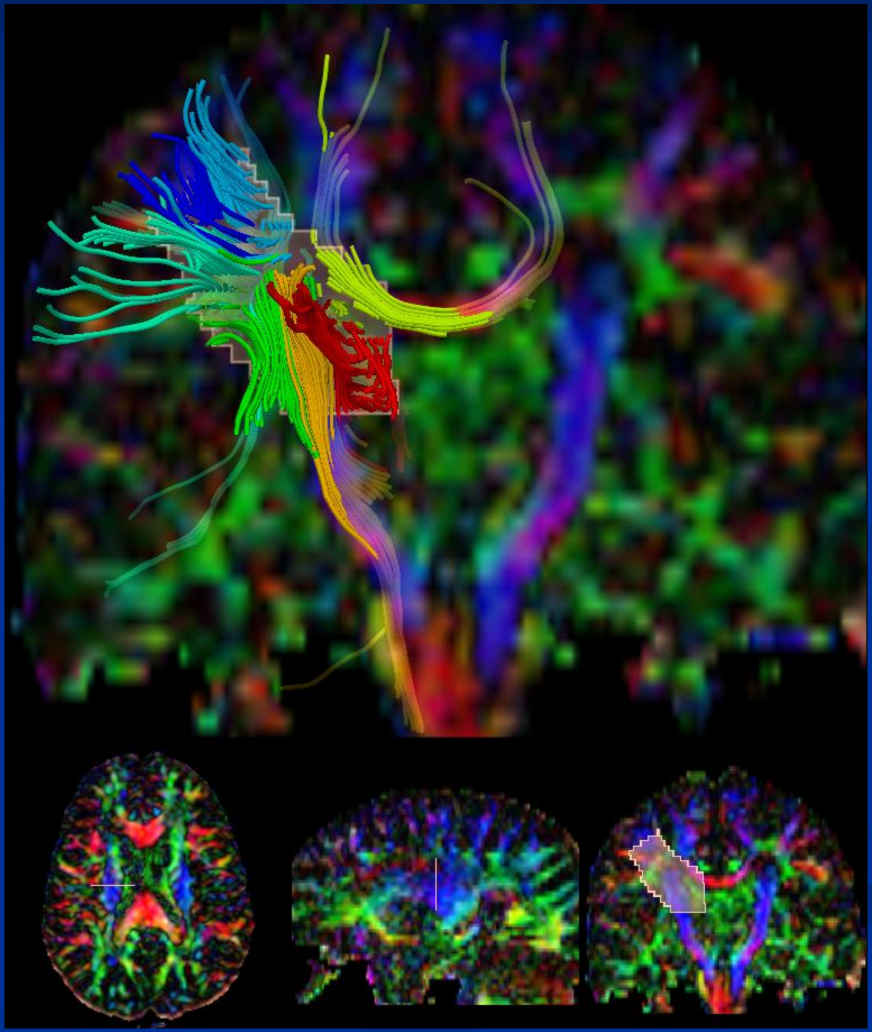
FACT Algorithm



Xue R., et.al., *Magn. Reson. Med.* 42 (1999), 1123–1127

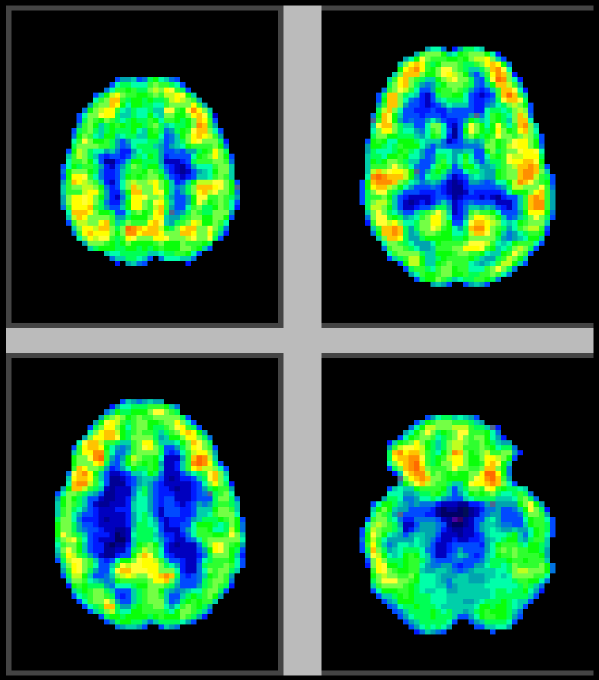
Diffusion tensor MRI -- Tractography

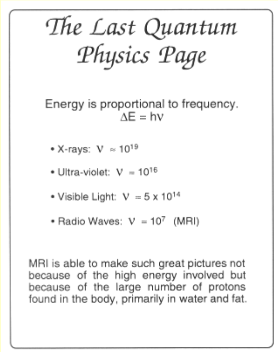
- Red – movement along the X axis (right to left)
- Green – movement along the Y axis (anterior to posterior)
- Blue – movement along the Z axis (superior to inferior)



Positron Emission Tomography:

Measuring brain metabolism via radioactive tracers

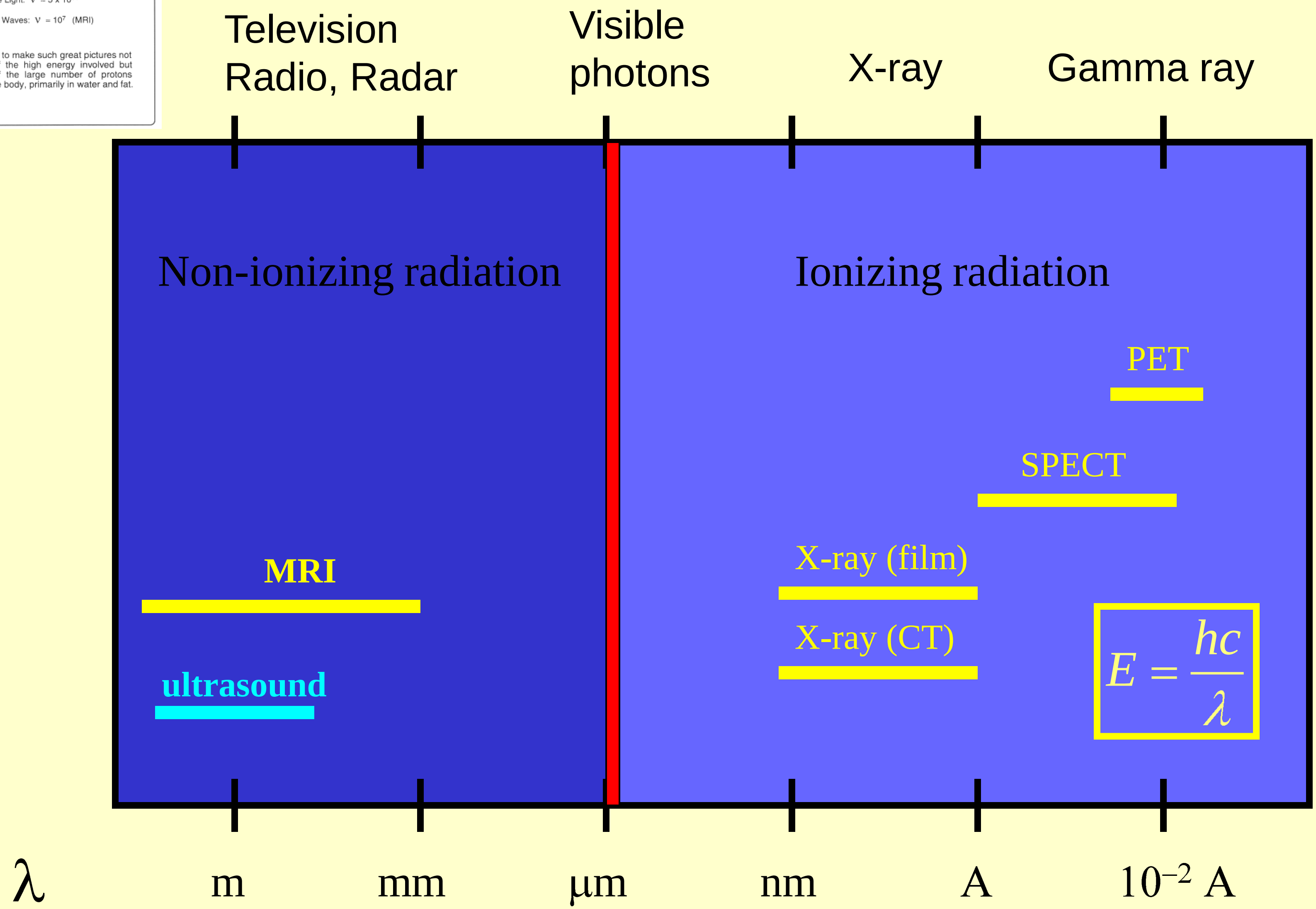



The Last Quantum Physics Page

Energy is proportional to frequency.
$\Delta E = h\nu$

- X-rays: $\nu \approx 10^{19}$
- Ultra-violet: $\nu = 10^{16}$
- Visible Light: $\nu = 5 \times 10^{14}$
- Radio Waves: $\nu = 10^{7}$ (MRI)

MRI is able to make such great pictures not because of the high energy involved but because of the large number of protons found in the body, primarily in water and fat.



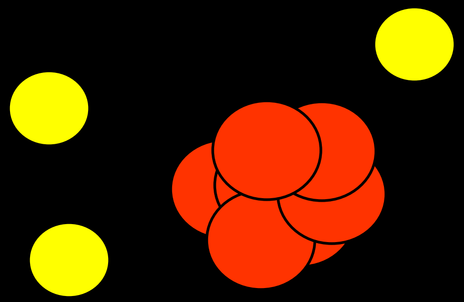
Positron emission tomography

Cyclotron creates an isotope, where extra protons are added to the nucleus, creating instability.

Isotope is connected to the compound of interest (such as oxygen or glucose) and injected.

As the molecule decays, it emits a positron which is annihilated when it collides with an electron.

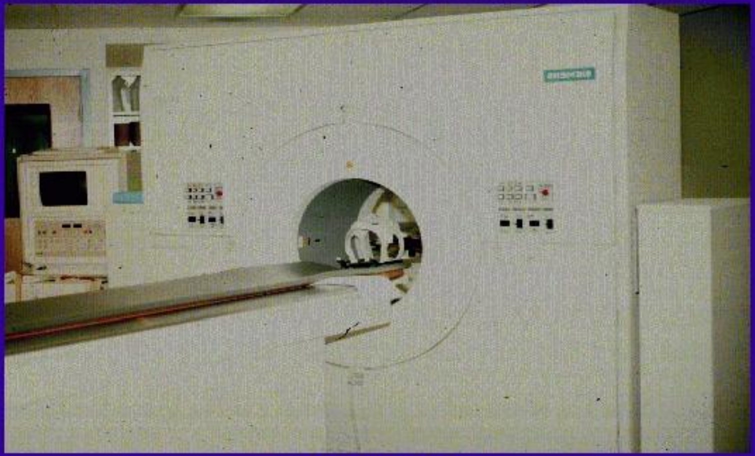
Annihilation event releases energy (photons) that can be measured with detectors.



IBA 30MeV Cyclotron

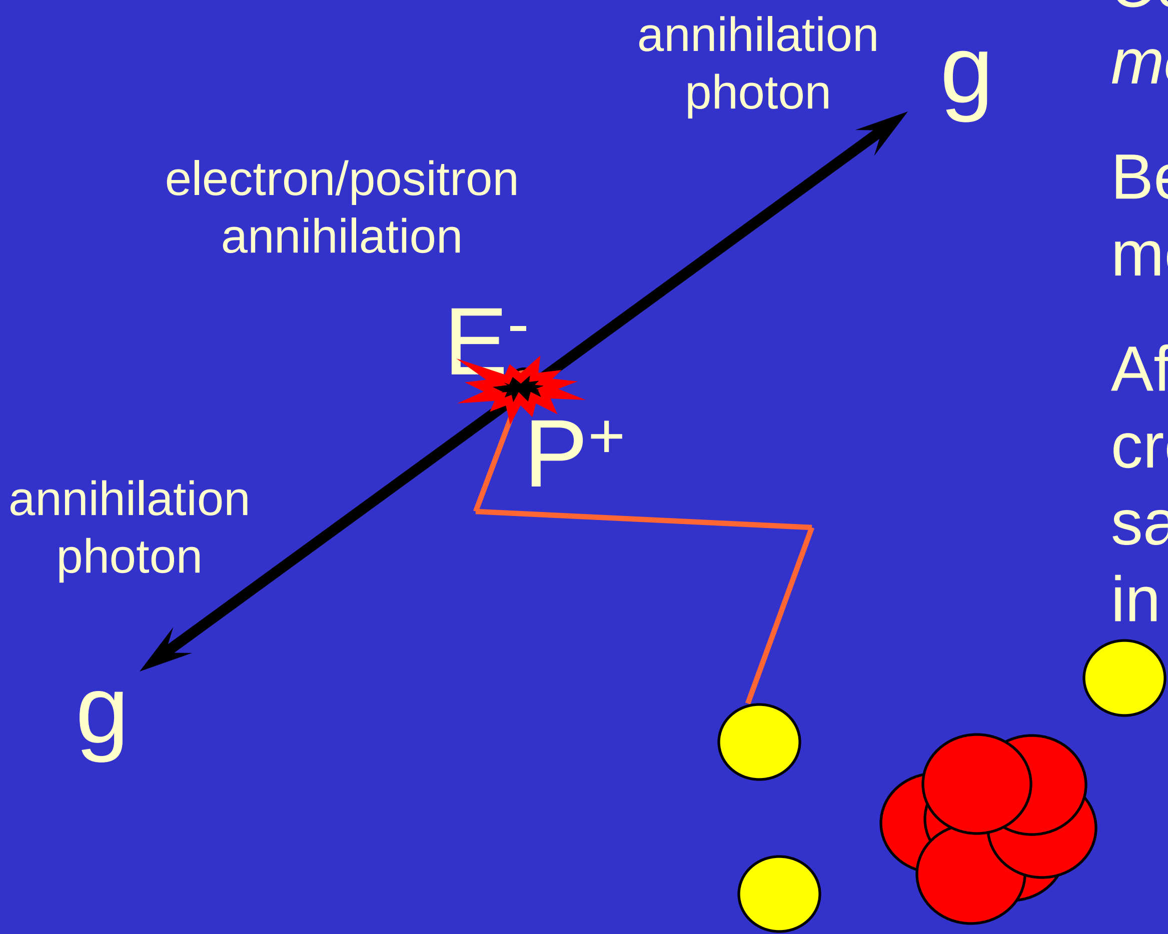
CPET; Buffalo, NY

Siemens/CTI ECAT 951-31R PET Camera



CPET; Buffalo, NY

Annihilation: Decay via positron emission



Conservation of momentum:

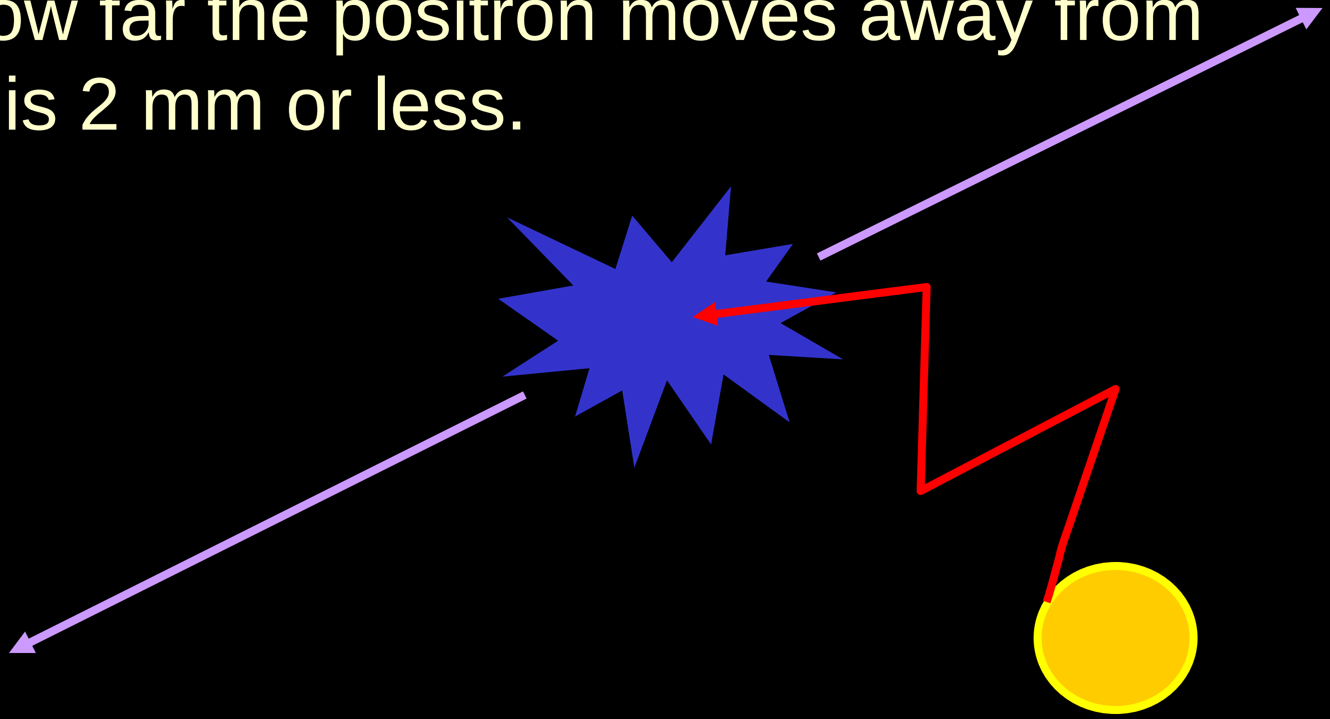
Before: system at rest; momentum ~ 0

After: two photons created; must have same energy and travel in opposite direction.

Emits gamma ray (two photons), travelling a path 180 degrees from the site of annihilation.

Sufficient energy in gamma rays to increase probability of passing out of brain without attentuation.

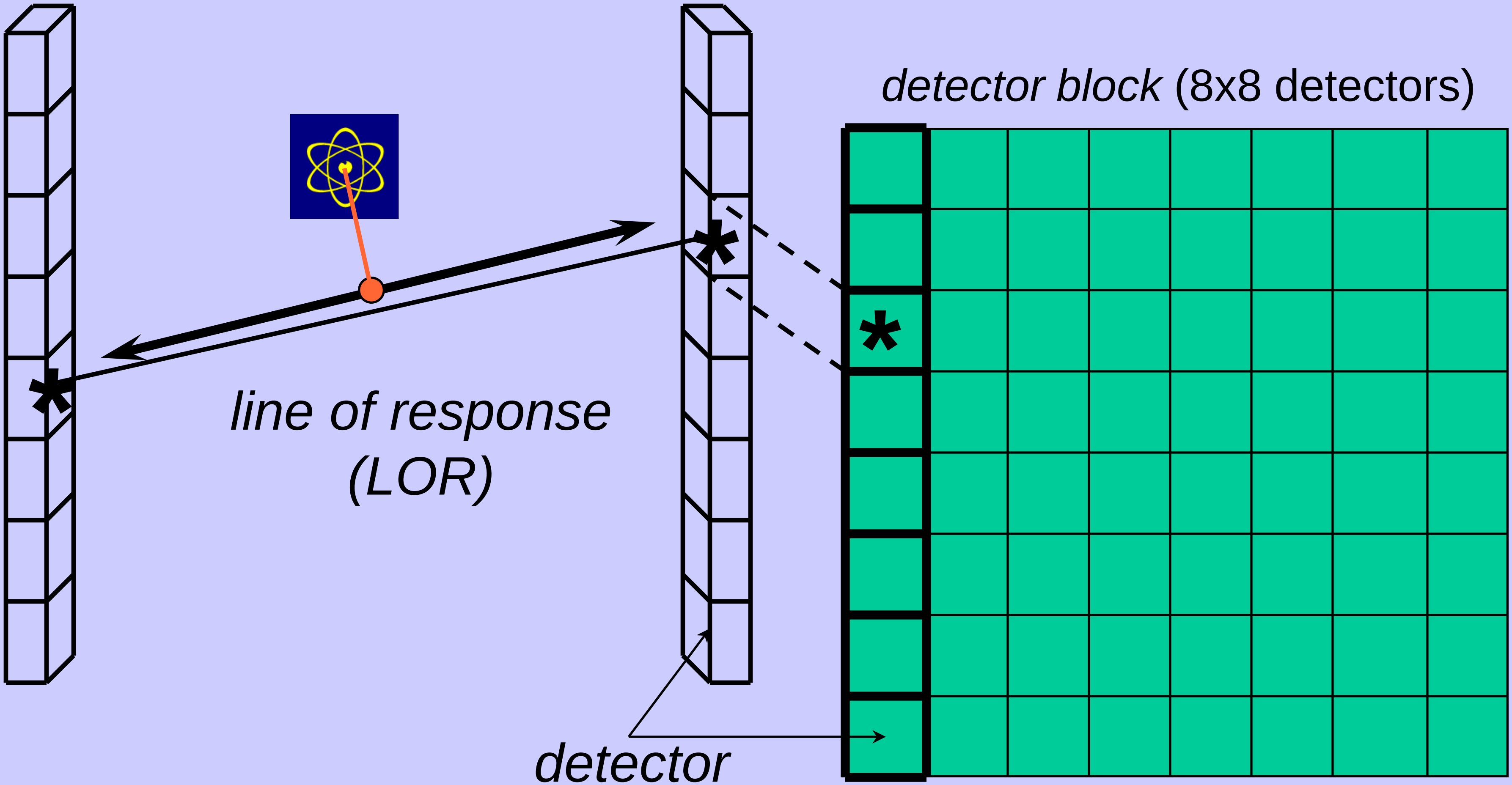
Scatter (how far the positron moves away from molecule) is 2 mm or less.



LOR determination

- Determining the line along which the two annihilation photons travel, known as the “Line of Response” or LOR, is a prerequisite step of any PET imaging modality and requires:
  - Event detection (did an event occur?)
  - Event positioning (where did it occur?)
  - Coincidence determination (did two events occur in a straight line?)

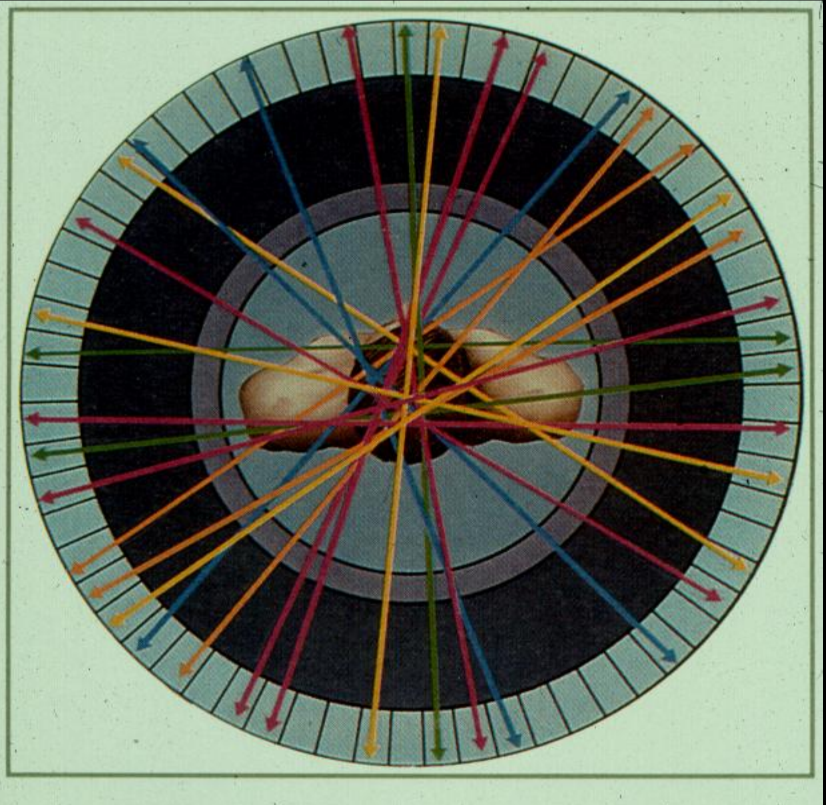
Annihilation detection



Coincident detection

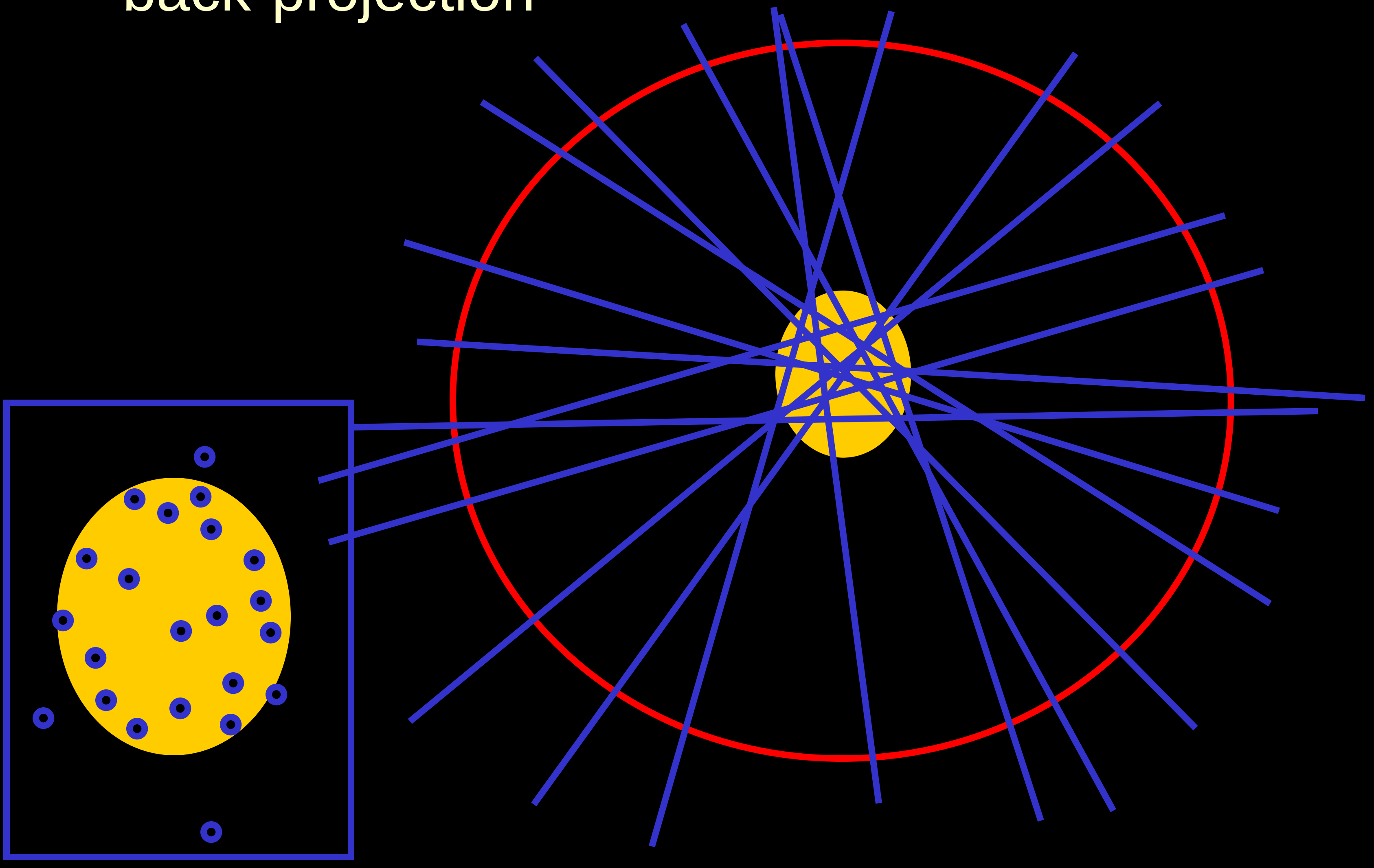
Scintillating crystal detectors in circumferential arrays, measure coincident events only.

Essentially counts coincident events, assumes a line of events (180 degrees).



6. The multiple LORs through multiple points.

Tomographic problem, reconstruction using back-projection



Parameters affecting image quality

Sensitivity (SNR) or number of detectable counts:

- Dependent upon dose, scan length, kinetics of tracer, efficiency and number of detectors

Spatial resolution

- Dependent upon resolution of detectors, small detector elements (bounded by the scatter at annihilation and the tracer kinetics)

Reconstruction

Quantitative if corrections made for:

1. Gamma ray attenuation (1 in 5 from center of brain versus 4 in 5 at edge of brain).
2. Random incidences -- two unrelated gamma rays strike detectors simulataneously.
3. Scattered events - scattering (deflection) through tissue of gamma ray but still detected, thus incorrect position.
4. Differential efficiency of each detector, measured using uniform radiation source.
5. Dead time -- at high count rates, electronics limit the number of events countable.

PET tracers:

1. Oxygen - HL is 1.5 mins.

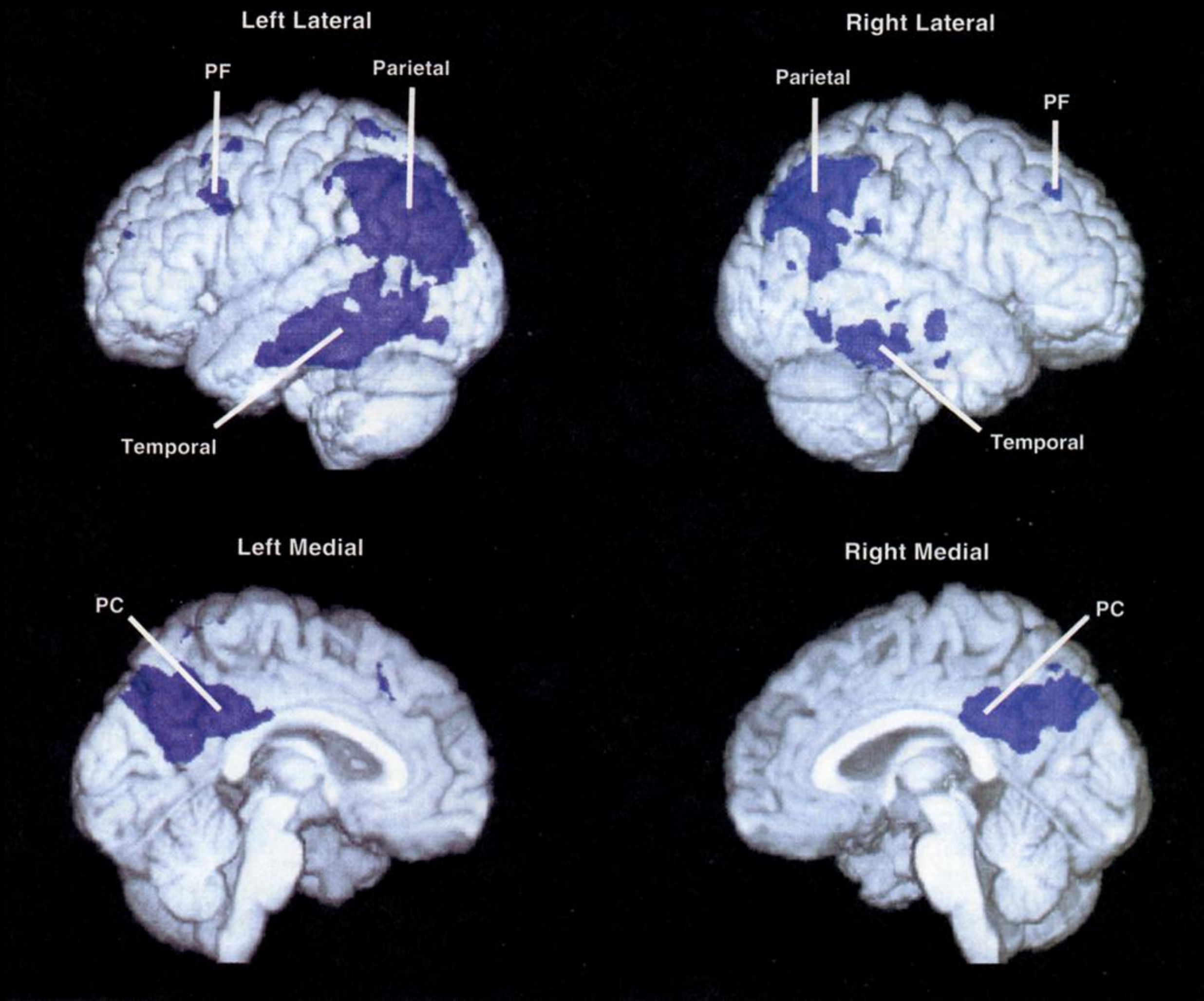
[15O]-labeled water and oxygen used in quantification of oxygen consumption.

2. Carbon - HL is 10.0 mins.

[11C]-labeled cocaine used to measure responses of dopamine D2 receptors during acute and chronic drug use.

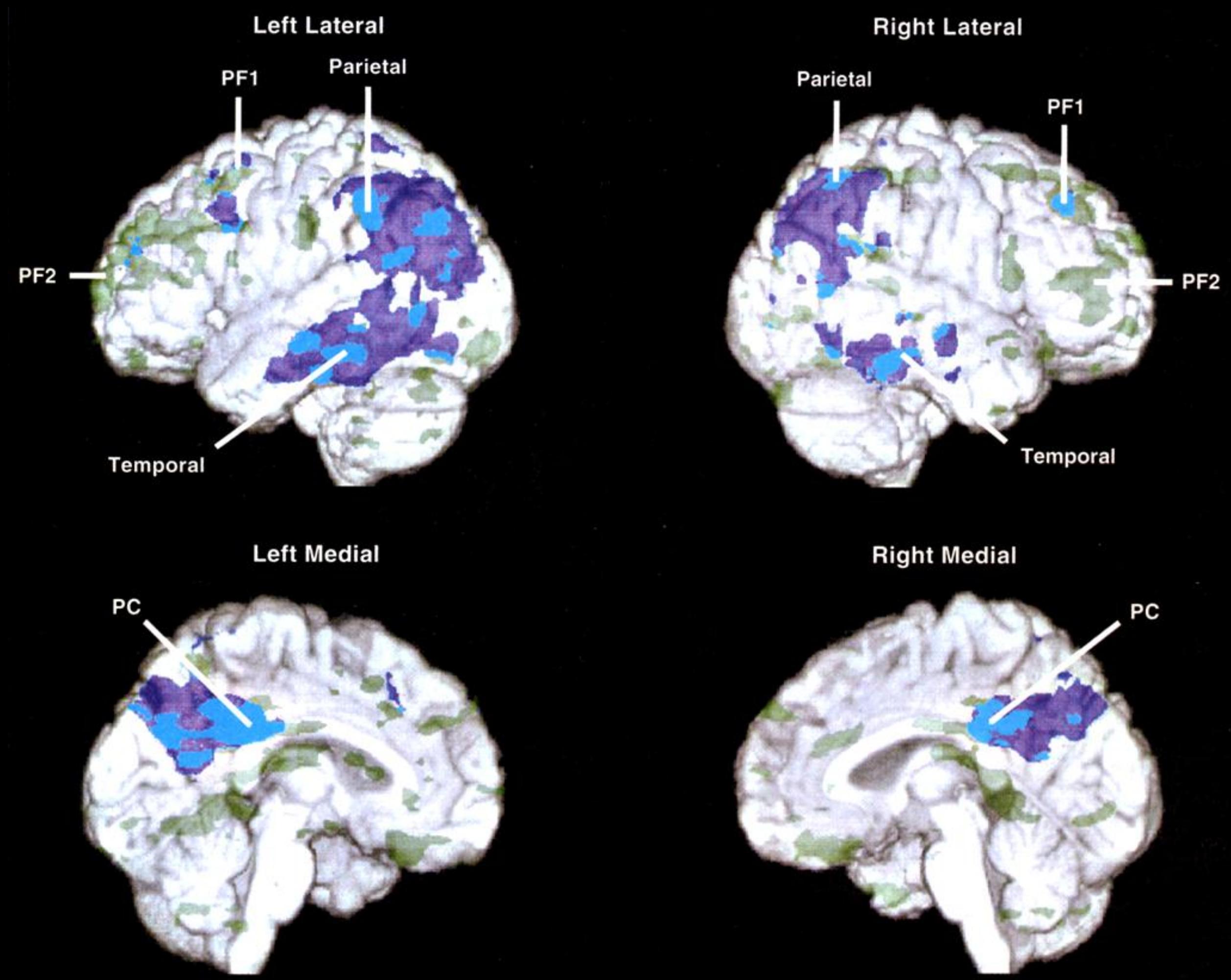
3. Flourine - HL is 109 mins.

[18F]-2-deoxyglucose (FDG) most often used in activation studies. Also used to label L-Dopa and fluoroethylspiperone which bind to D2 dopamine receptors.

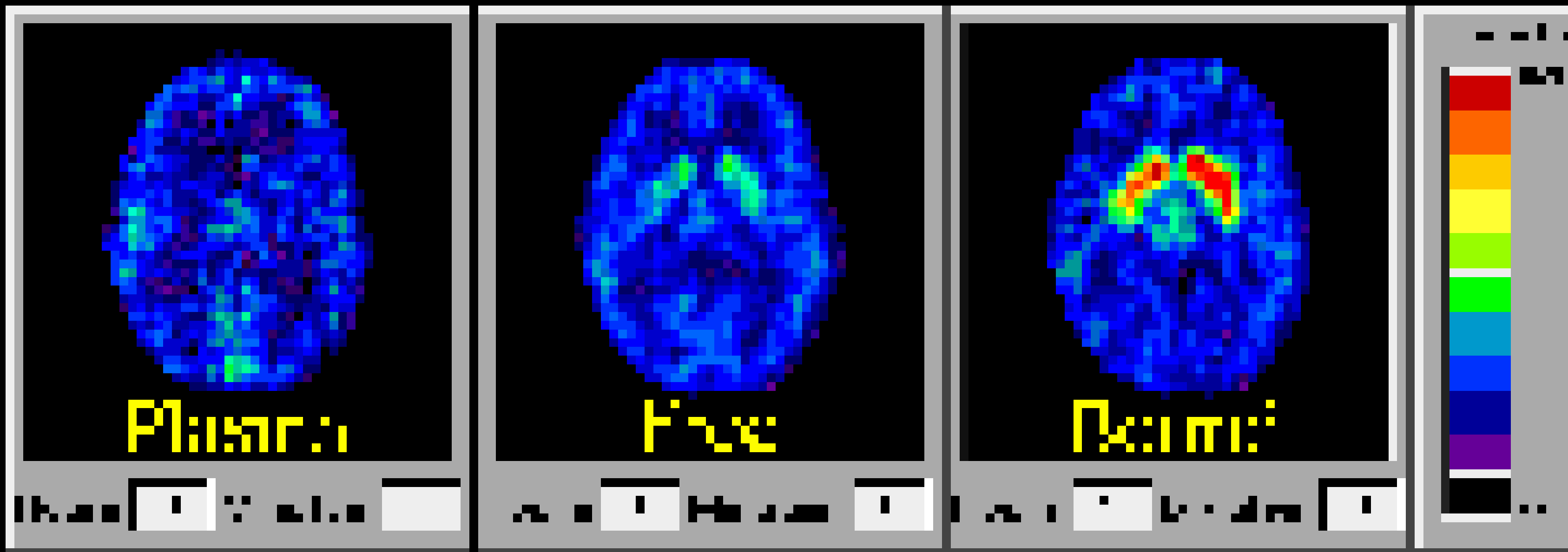


Preclinical detection of Alzheimer's disease:

Reiman et al. (1996): Regions of brain with reduced rates of glucose metabolism in 37 patients with early stage probable AD.

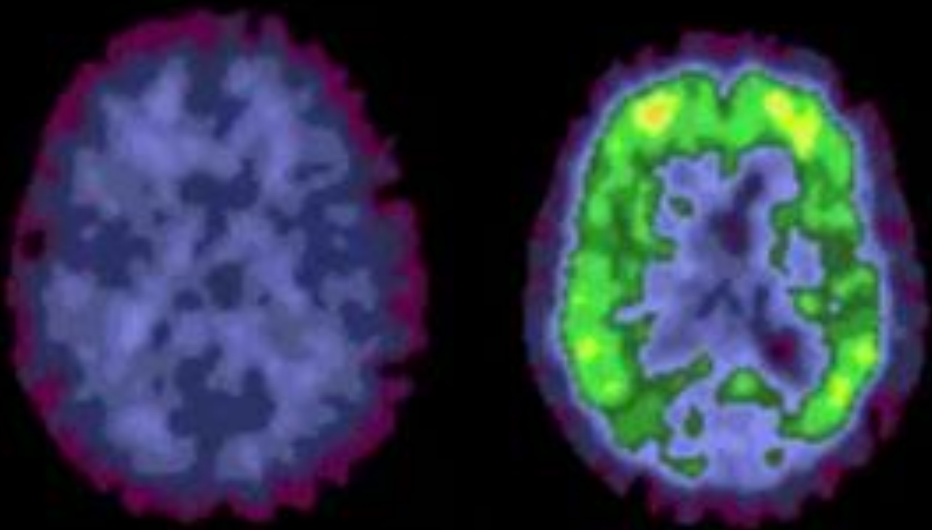


Regions of brain with reduced rates of glucose metabolism in 11 e4 homozygotes (light blue) and their relation to patients with probable AD (purple); Reiman et al., 1996.

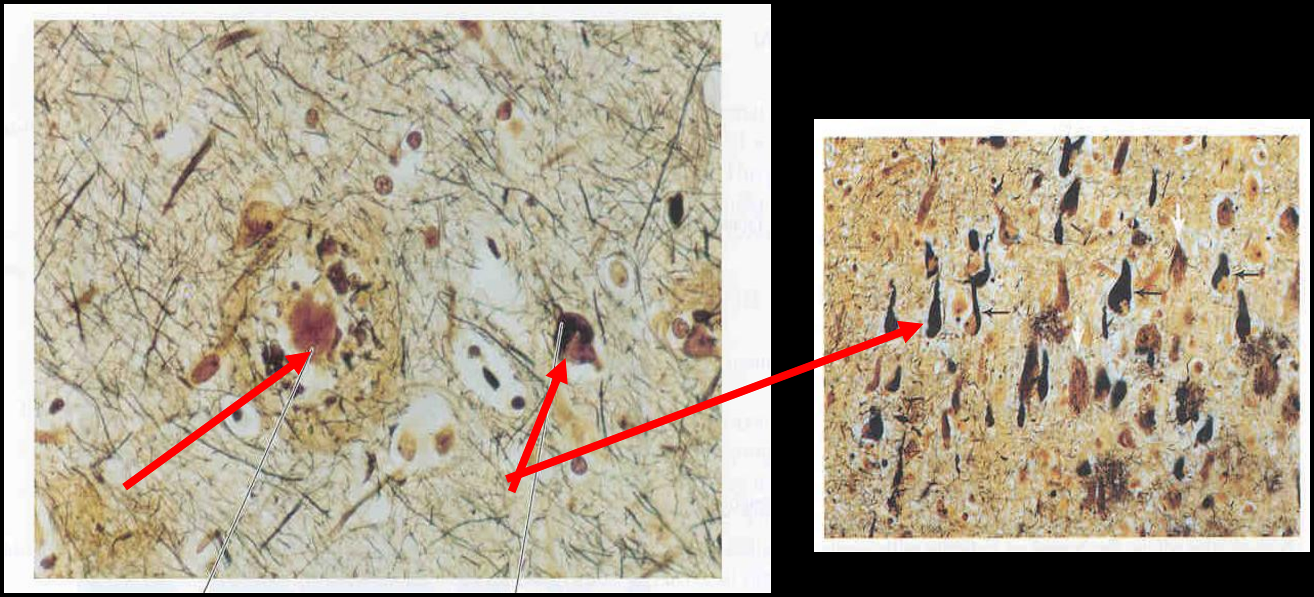


Unique uses of PET: Dopamine uptake using [18F]-Fluoroethylspiperone

Comparing the absorption of PIB (Pittsburg Imaging Compound) in the brains of subjects
without dementia (left) and with Alzheimer's disease (right).



This compound binds to the proteins contained in beta amyloid plaques



Plaques & Tangles

Neuroimaging methods:

Provide many ways to measure structure and function of the human brain.

What do you have to know to use them?
-- how they work: physics
-- how to analyse them: statistics
-- how to interpret them: physiology
-- how to apply them: cognitive neuroscience