Neuroimaging

- Structural magnetic resonance imaging
  - How does it work?
  - Some applications of structural MRI
- Functional MRI
  - Measuring brain activity during cognitive tasks
- 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”

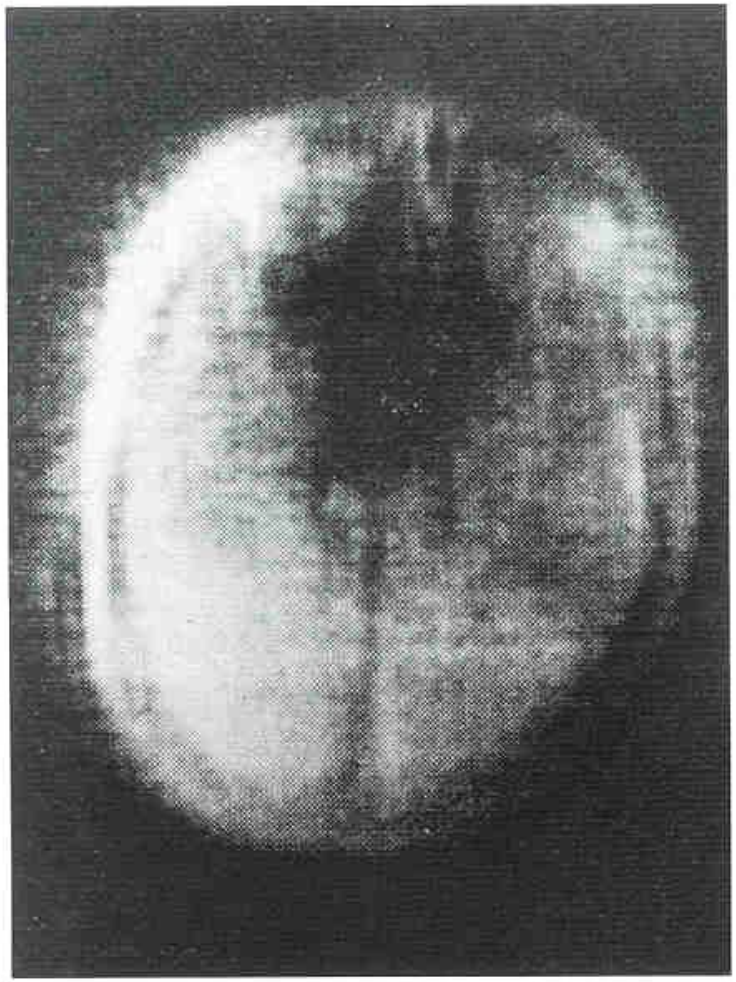
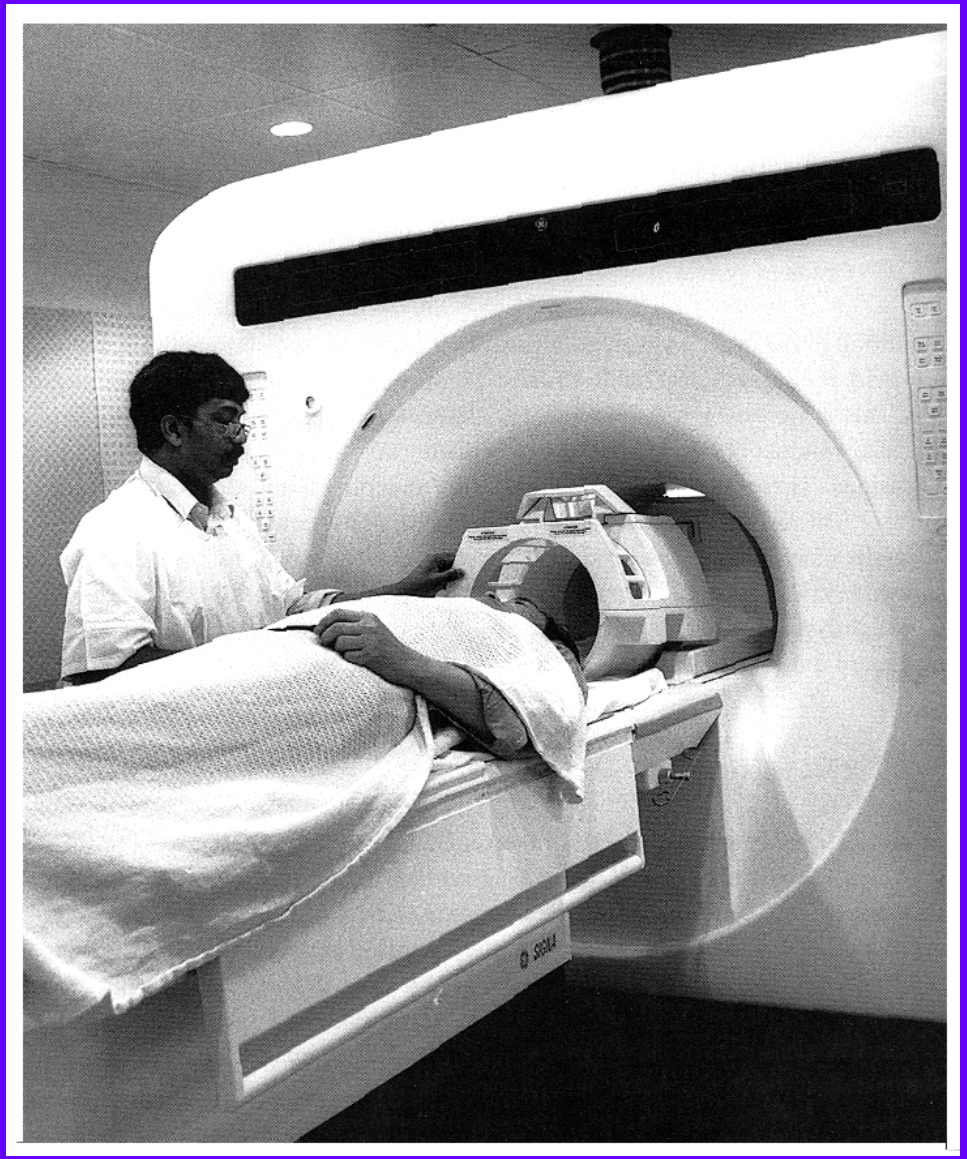
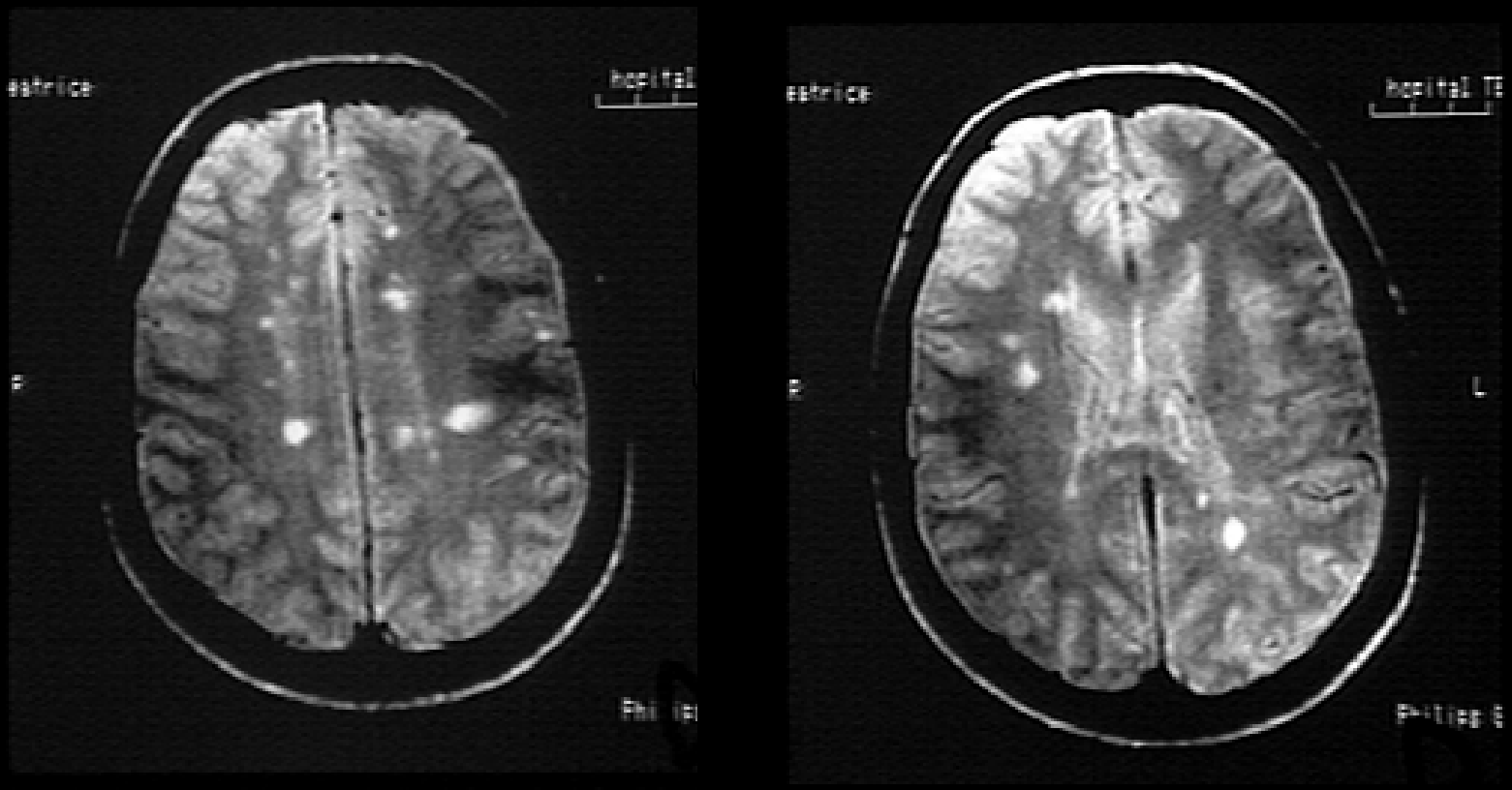


Fig. 4-46. The first published NMR reconstructed image of a head. (From Holland GN, Morre WS, Hawkes RC: J Comput Assist Tomog 69:262-277, 1980.)

Clinical magnetic resonance imaging magnet: 1.5 Tesla

MRI = Electromagnetic field + radio frequency waves

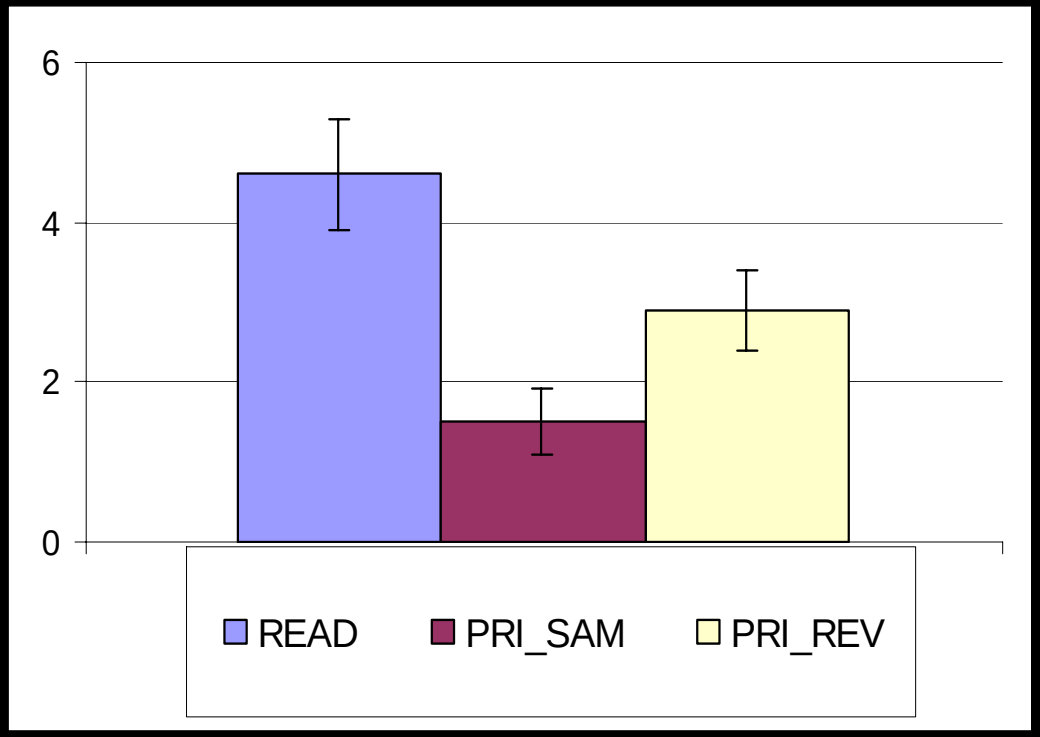


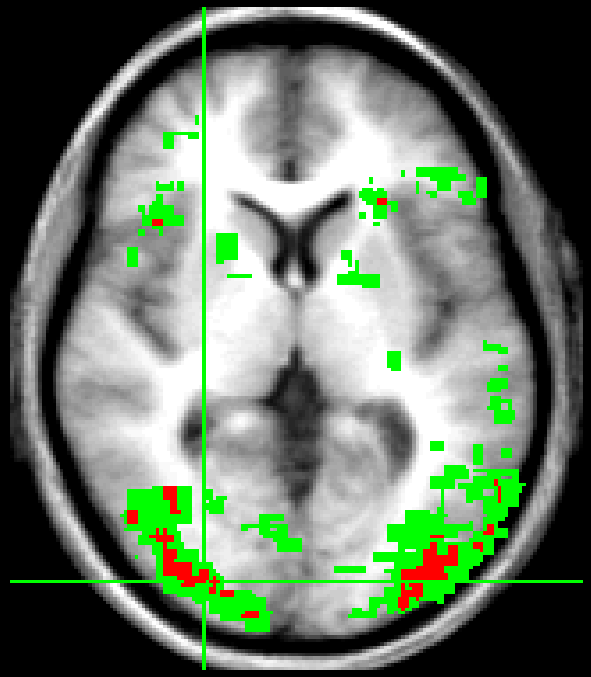


Multiple sclerosis – Clinical trials for MRI began in 1983, FDA approved two years later, in 1985.

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

Posterior cortical regions showed differential changes in neural activation resulting from format-specific priming.





Left occipital lobe

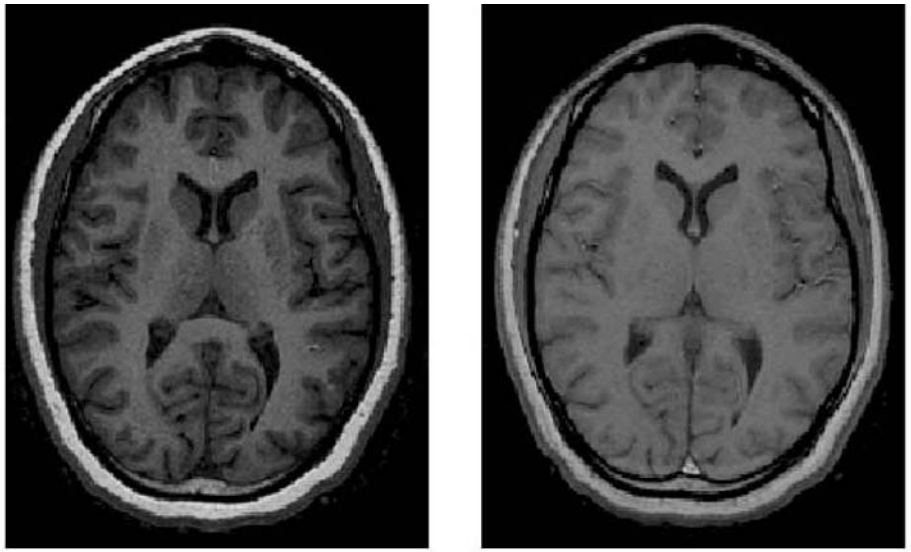
Ryan & Schnyer, 2005

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

1.4 Contrast and contrast-to-noise in MR images.

(A)

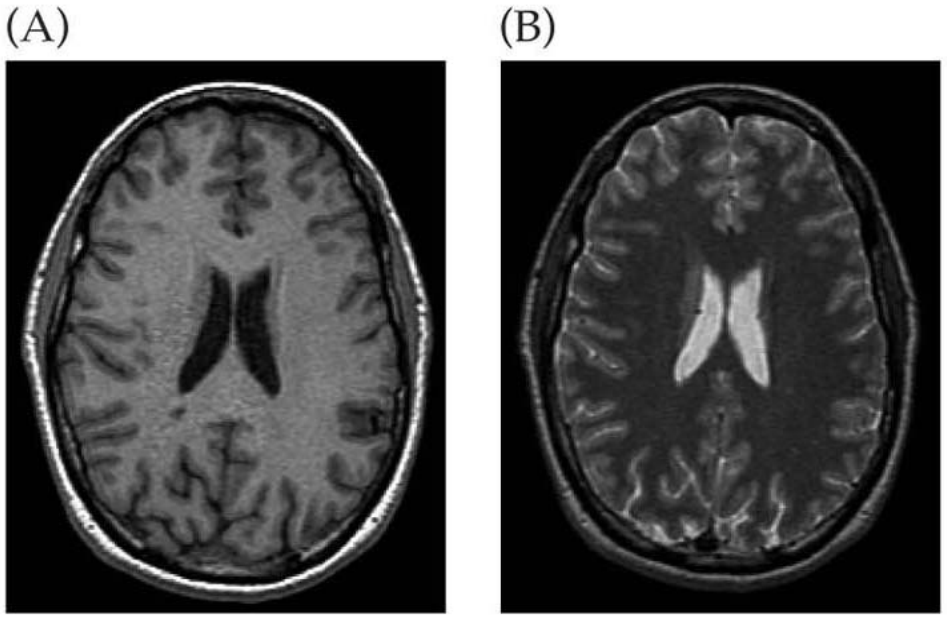


(B)

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

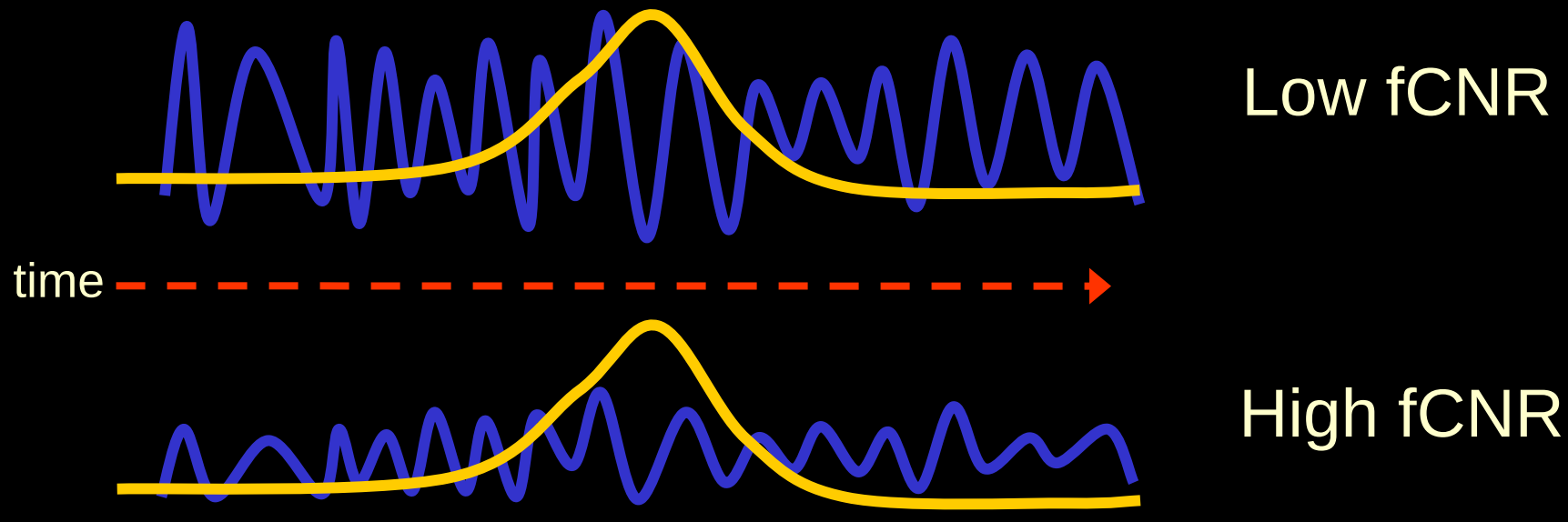
1.4 Contrast and contrast-to-noise in MR images.



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

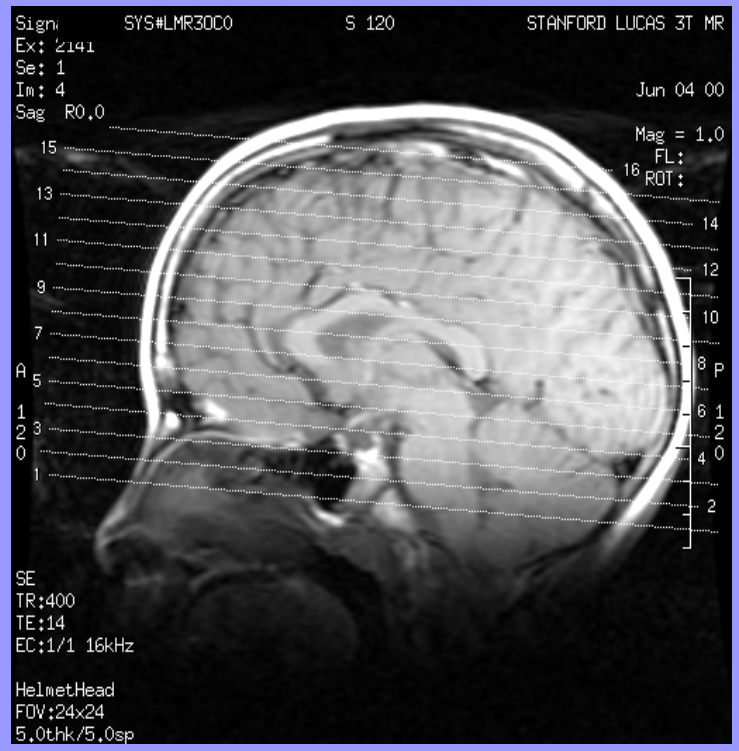


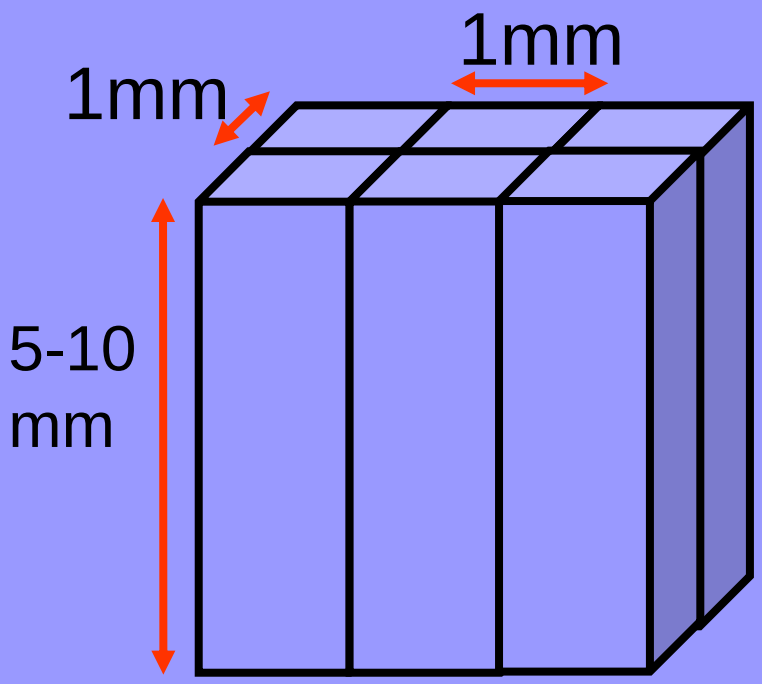
- The ability to detect a signal change against a background of noise, or variance in signal
- The variance may be due to measurement error, or physiological noise

Spatial resolution

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

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

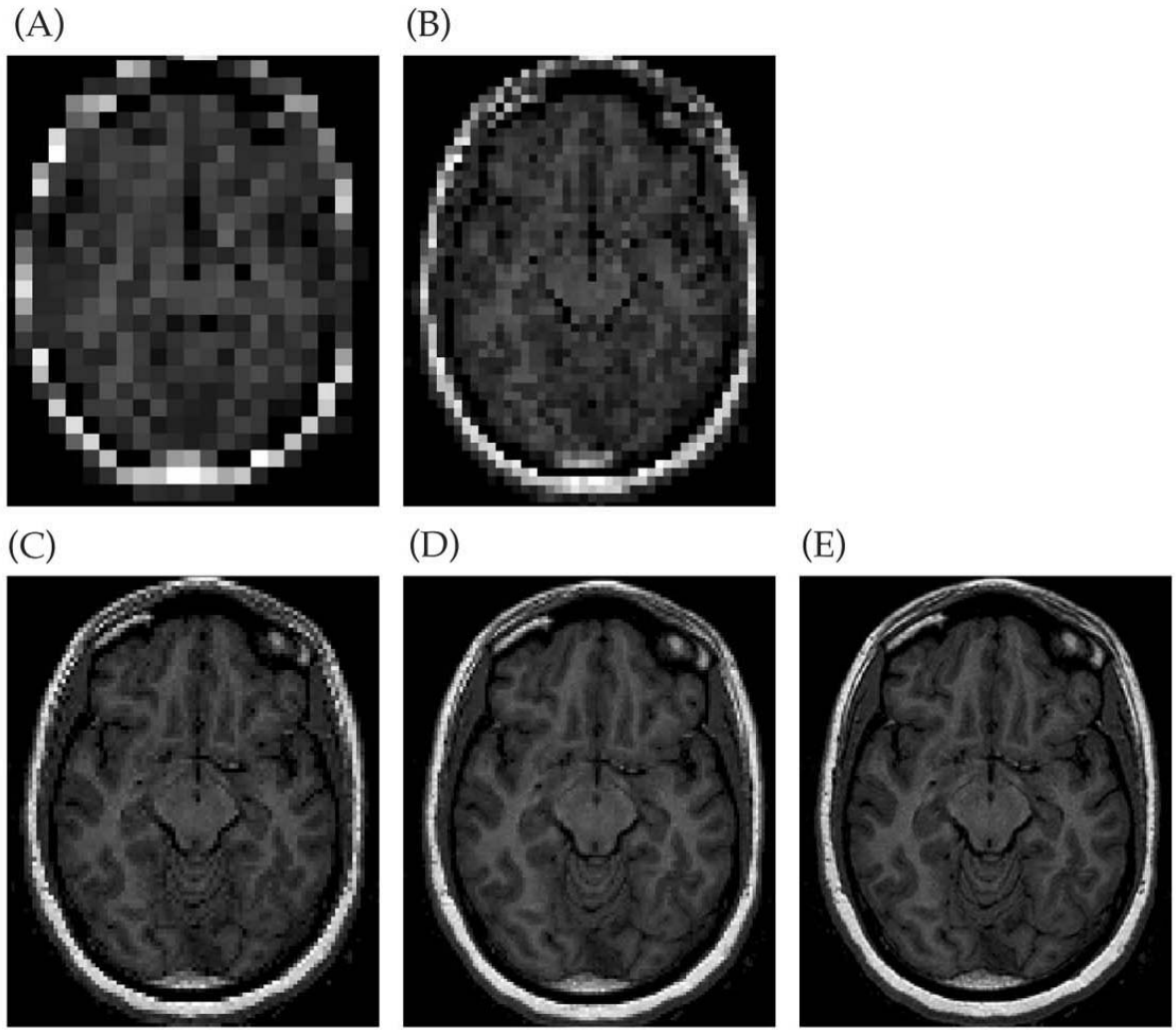




Voxel size: In-plane resolution x section thickness

1.6 The human brain at different spatial resolutions.

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



A. 8mm

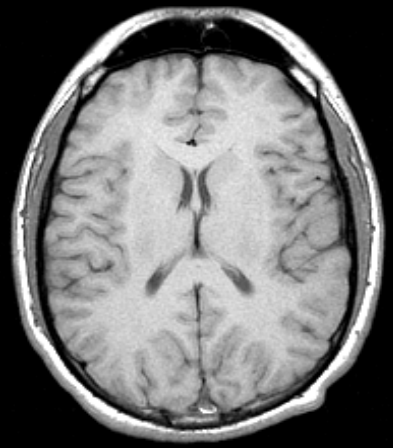
B. 4mm

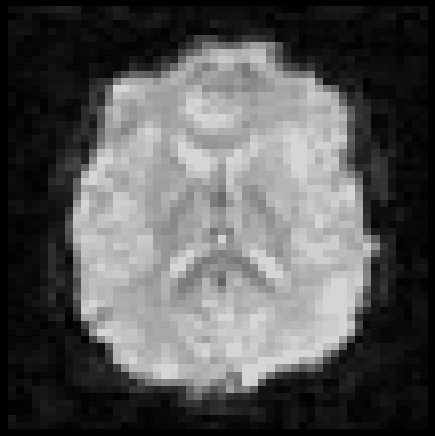
C. 2mm

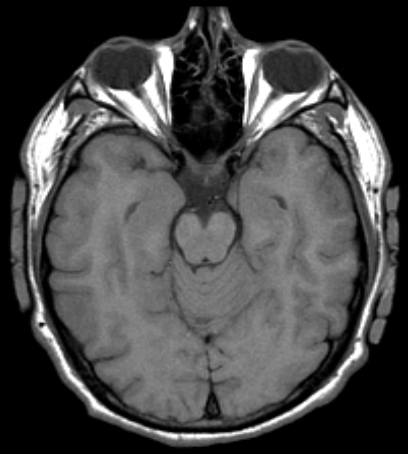
D. 1.5mm

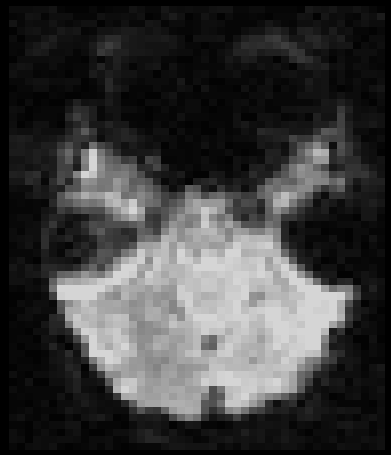
E. 1mm

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).

Measuring brain activity

ERP: Measuring electrical potentials in the brain through electrodes placed at the scalp. Excellent temporal resolution, but poor spatial resolution.

The "inverse problem"….

MEG: Measures small changes in magnetic fields caused by localized electrical activity of neurons, also through scalp recording. Moderate to good temporal resolution and spatial localization.

Inverse problem still applies.

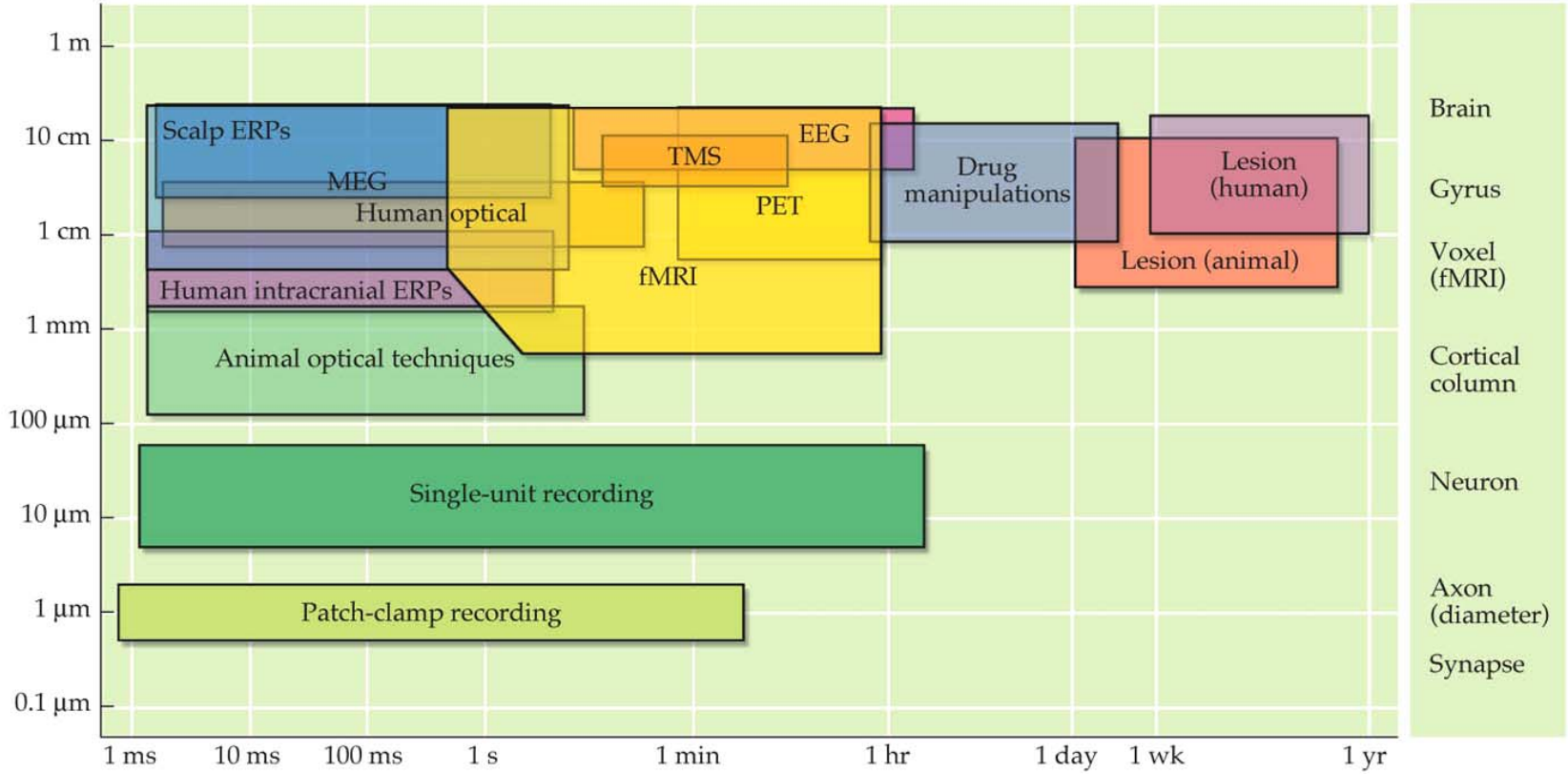
PET: Radioactive isotopes used to label metabolically active substances (glucose, oxygen, etc), injected, taken up by tissue, which then decay over time measured. Poor temporal and spatial resolution (also invasive).

fMRI: Measures changes in local hemodynamic changes due to neural activity using static magnetic field and oscillating transmit/receive radiofrequency coils. Good spatial localization, good temporal resolution, noninvasive.

Perfusion MRI: Measures local perfusion, has been used to measure hemodynamic responses to neural activity, much like fMRI. Possibly more directly localized response to active tissue than fMRI.

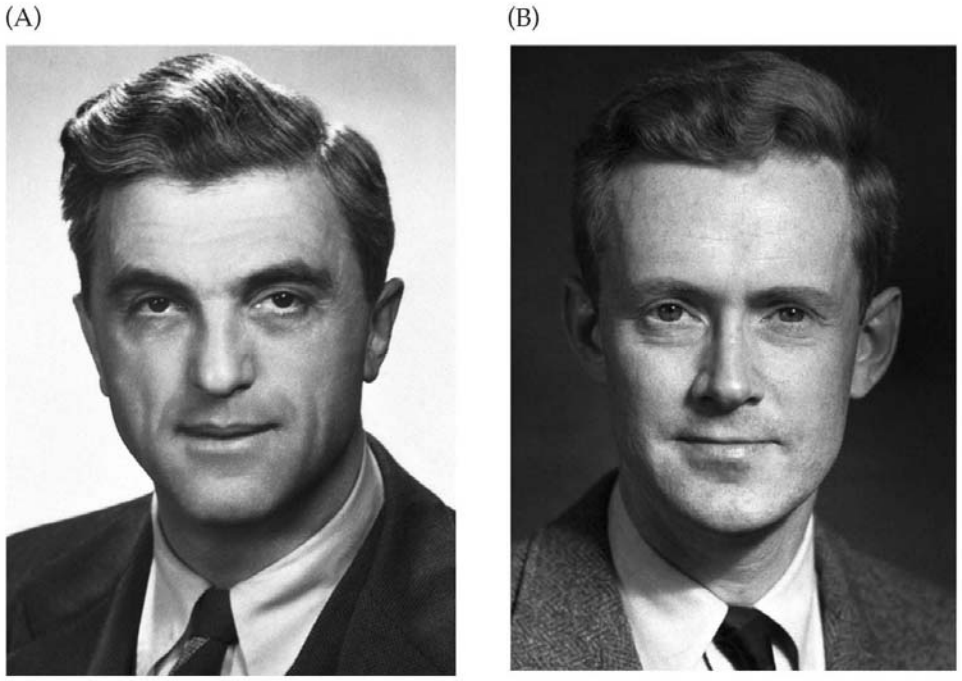
Diffusion MRI: Measures directional movement of molecules, tractography, identifying pathological conditions.

1.7 Neuroscience techniques differ in their spatial and temporal resolution.



Functional measurement techniques compared by spatial and temporal resolution

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



FUNCTIONAL MAGNETIC RESONANCE IMAGING, Figure 1.11

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

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

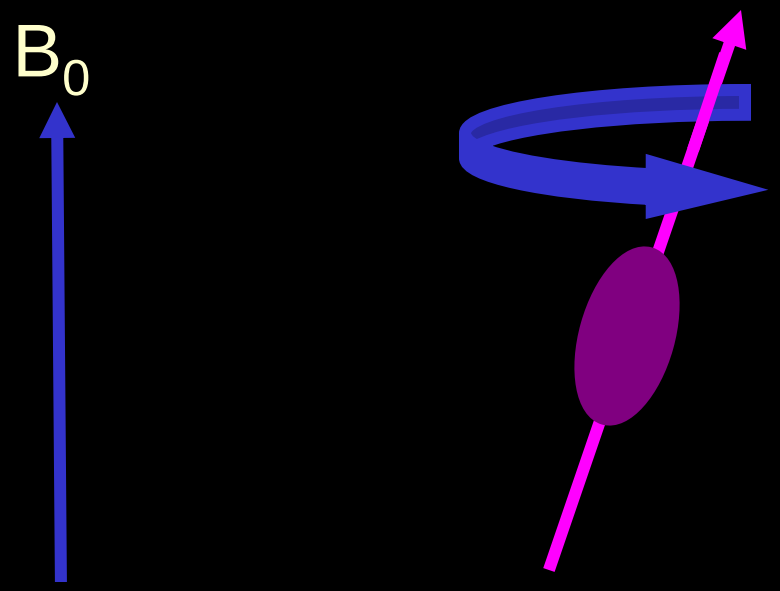
Purcell did the same with a container of water, devising a method that is identical to the basic MRI system: A static magnetic field, a transmit EM coil, and a coil for detecting emitted energy.

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:

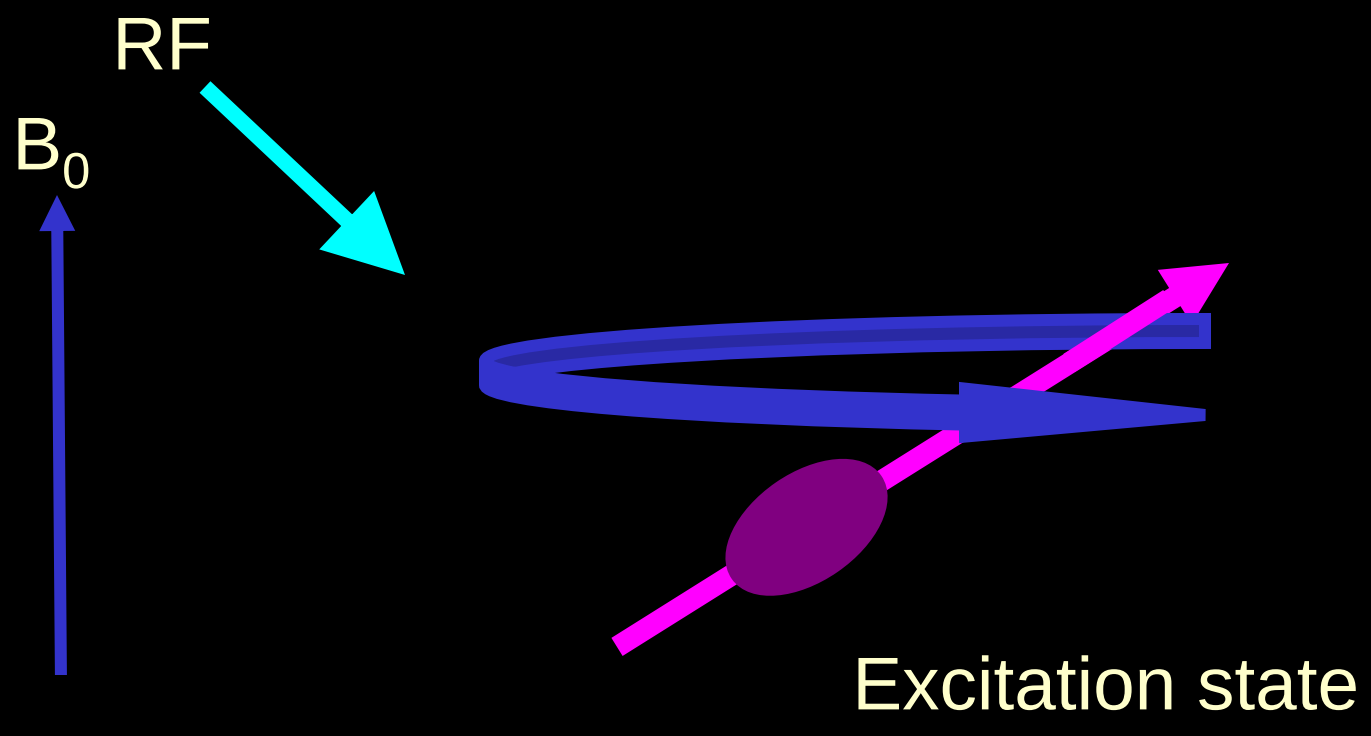
- *Step 1:* Atoms with an uneven number of protons act as dipoles – in a strong static magnetic field, they will align with the field and precess around that axis.



Resting state

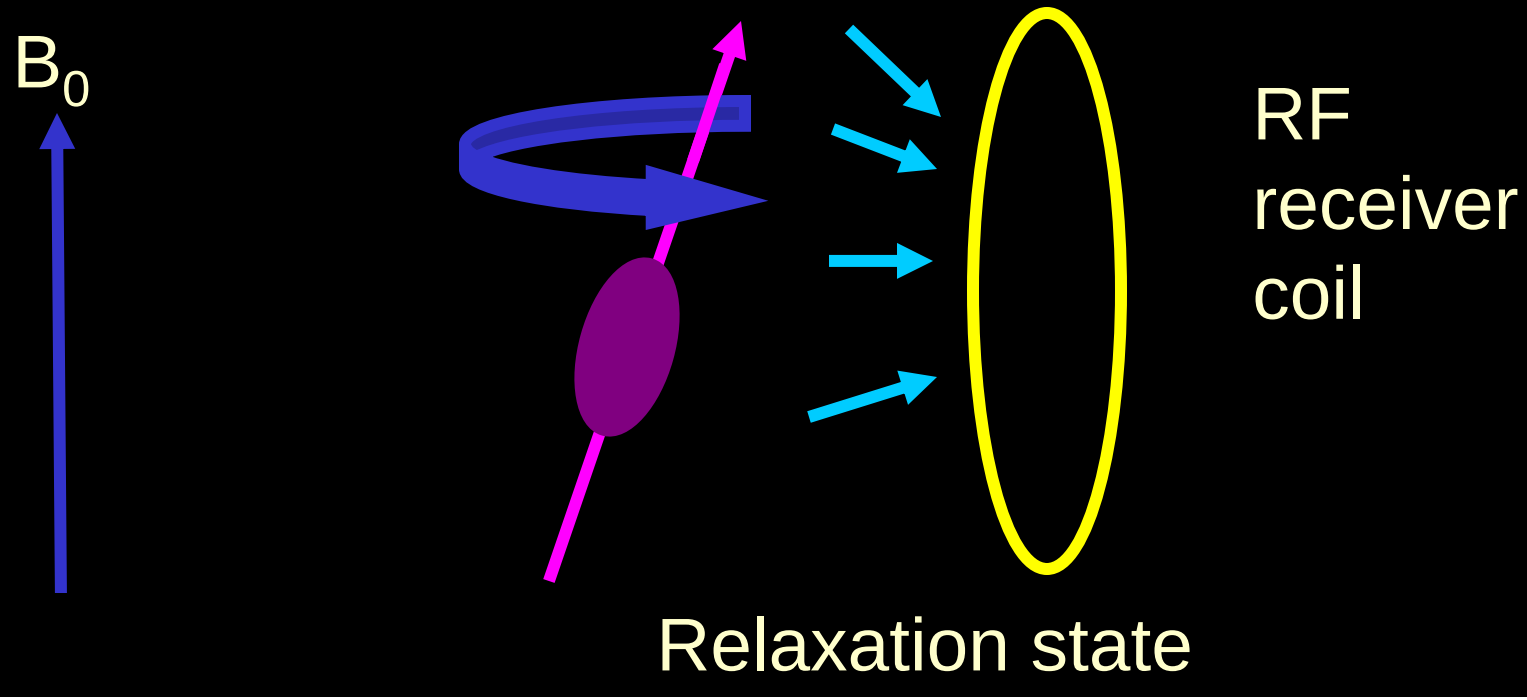
MRI Signal:

- *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.*



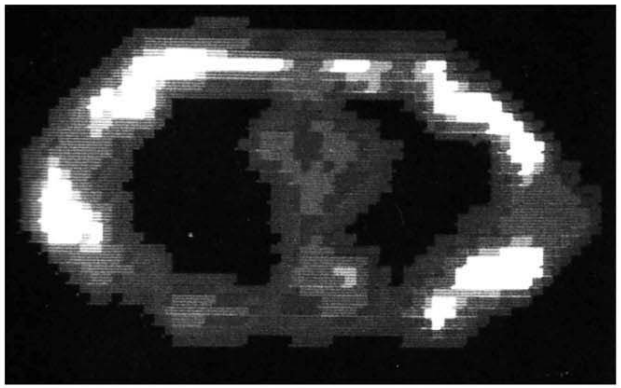
MRI Signal:

- *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)

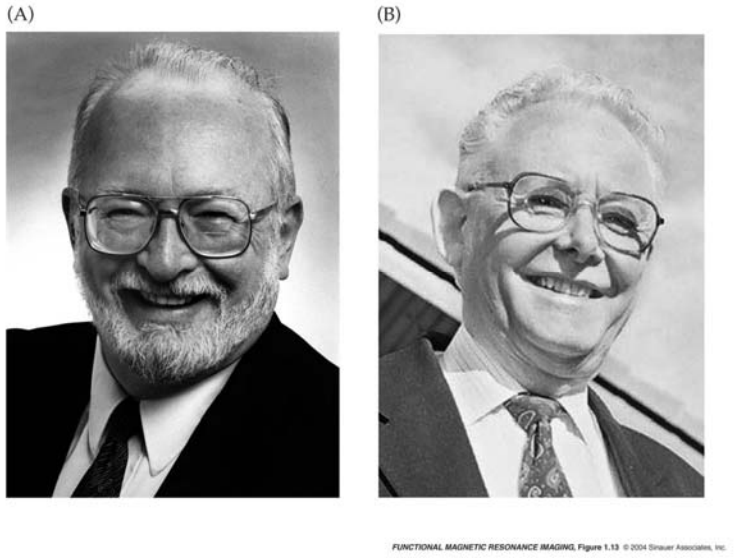


Raymond Damadian, 1977

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).



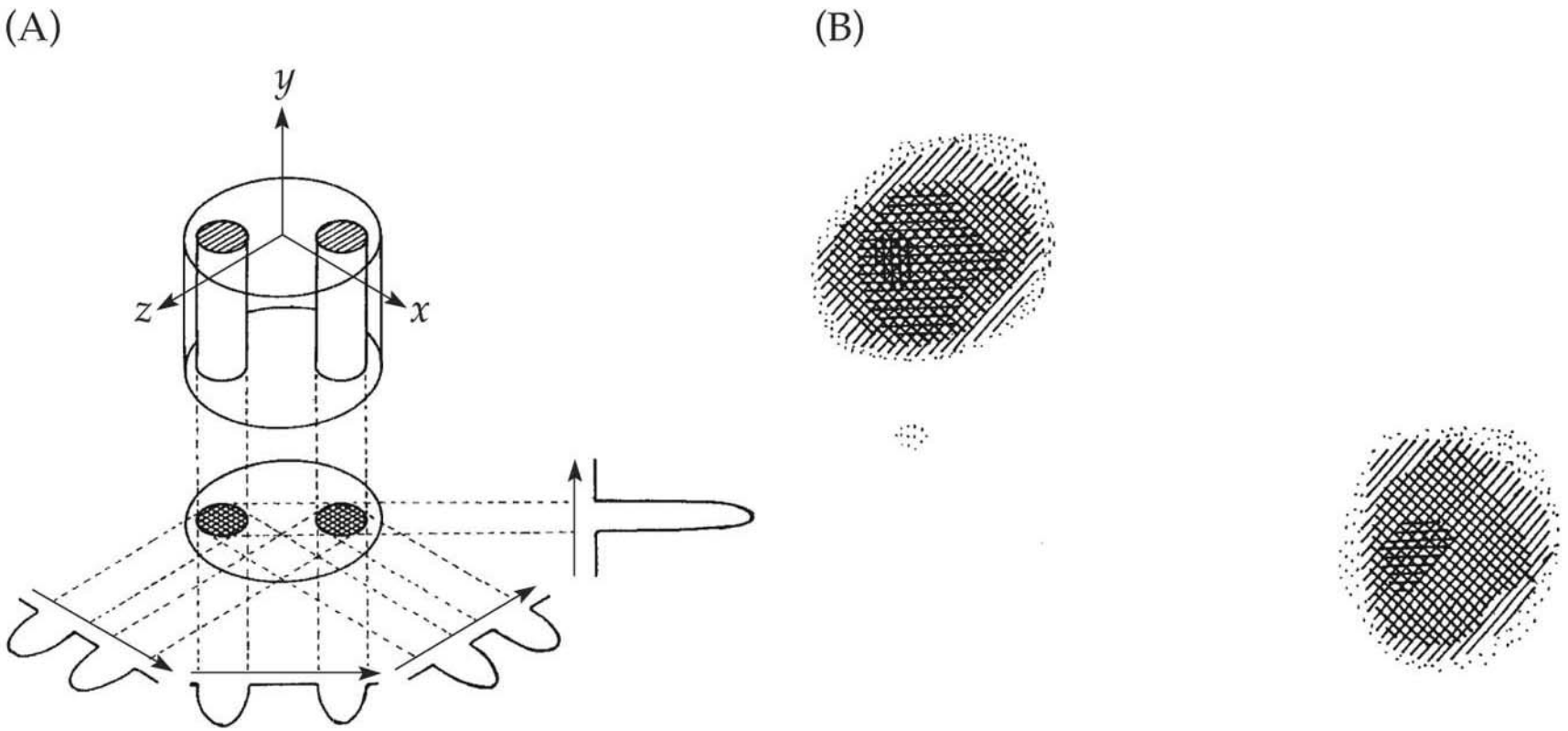
FUNCTIONAL MAGNETIC RESONANCE IMAGING, Figure 1.13 © 2004 Sinauer Associates, Inc.

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.

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



Lauterbur's imaging method: A beaker with two tubes of water. Signal was obtained from multiple angles around the object, with spatial gradients applied to the magnetic field. Backprojection methods were then used to reconstruct a 2D image of a cross-section of the water tubes.

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

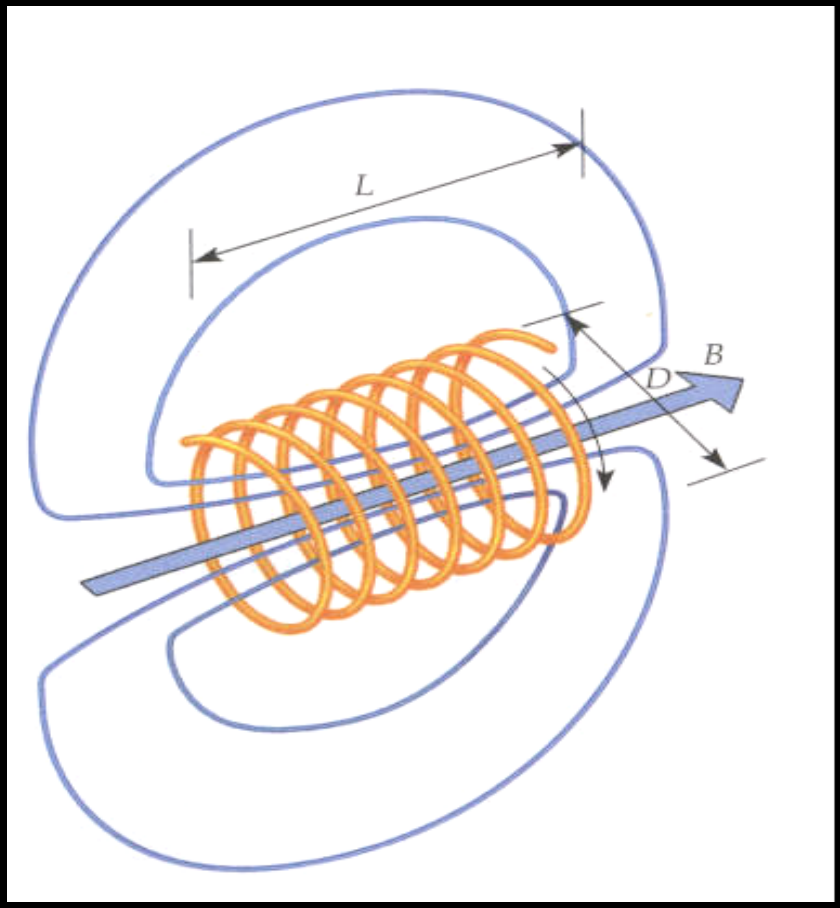
- MRI was approved for clinical use in 1985 at 1.5T.
- 3T was approved for clinical use in 1996.
- The Nobel Prize for Medicine was awarded jointly to Lauterbur and Mansfield in 2003 for the development of MRI. Damadian was not included in the prize, although he was also a nominee. Damadian took out a full-page ad in the New York Times explaining why he believed that he had, in fact, had invented magnetic resonance imaging.

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

- Goal: Homogeneity or consistency of field strength throughout the magnetic field, and
- Stability of the field over time.
- Superconducting electromagnet – a coil of wire, cooled with cryogens (helium, nitrogen) to near absolute zero, large current injected into wire
- Resistance is near zero, can sustain high current with no power requirements
- Field strength – proportional to the diameter of the coil and the strength of the current (nonlinearly related)

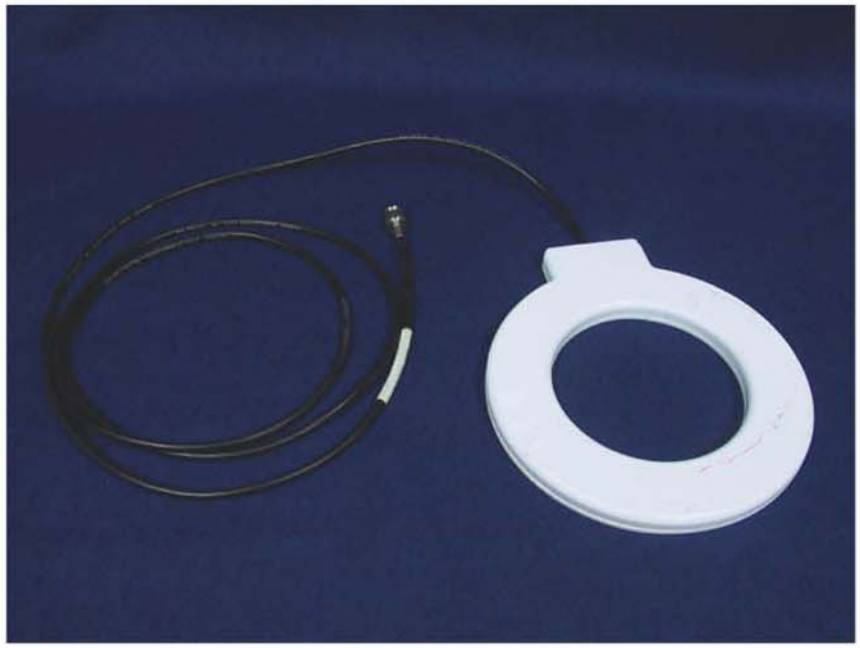


Electromagnet – solenoid with current that is maintained by supercooling, creates a magnetic field perpendicular to the axis of the coil. Housed in a vaccum chamber (dewar).

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.

(C)

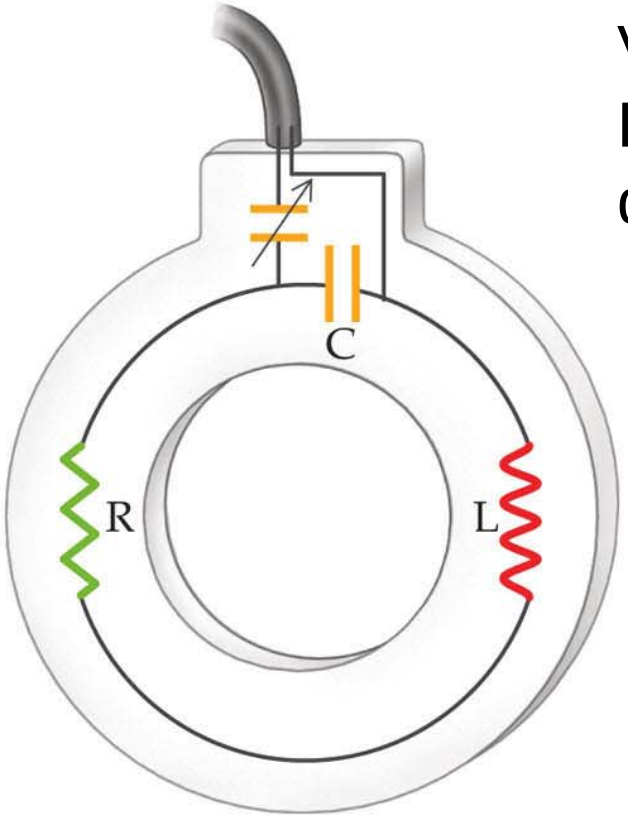


(D)

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.

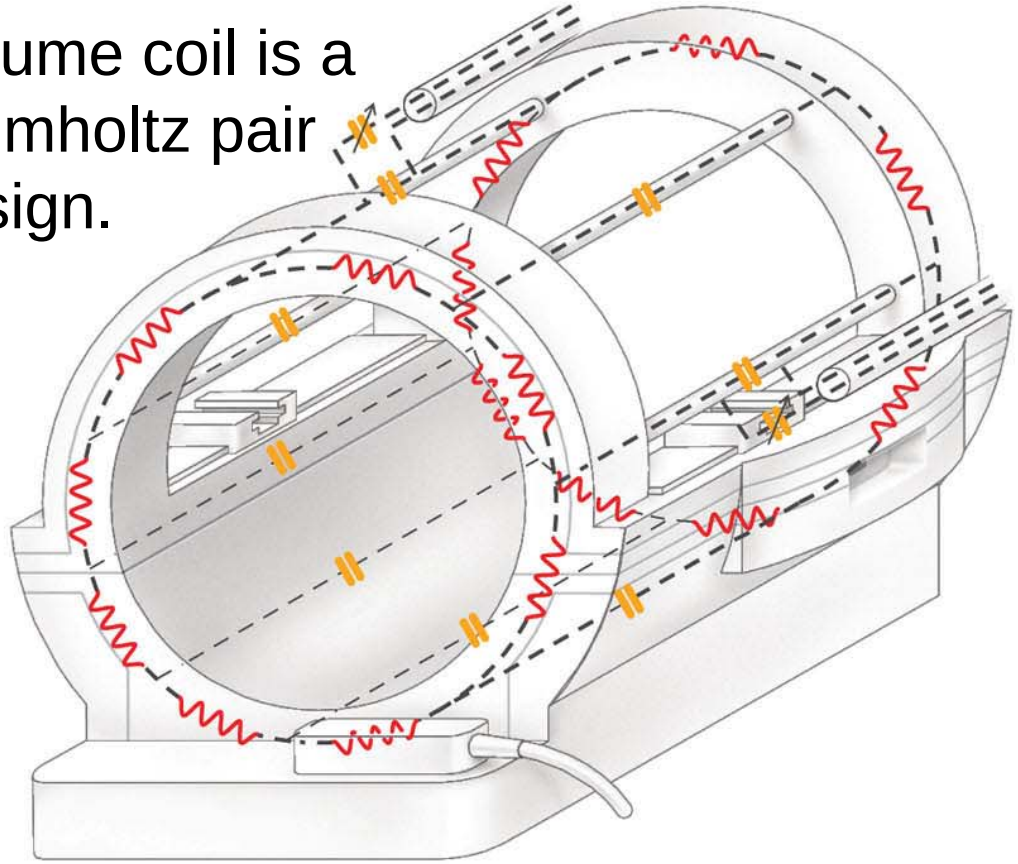
(A)



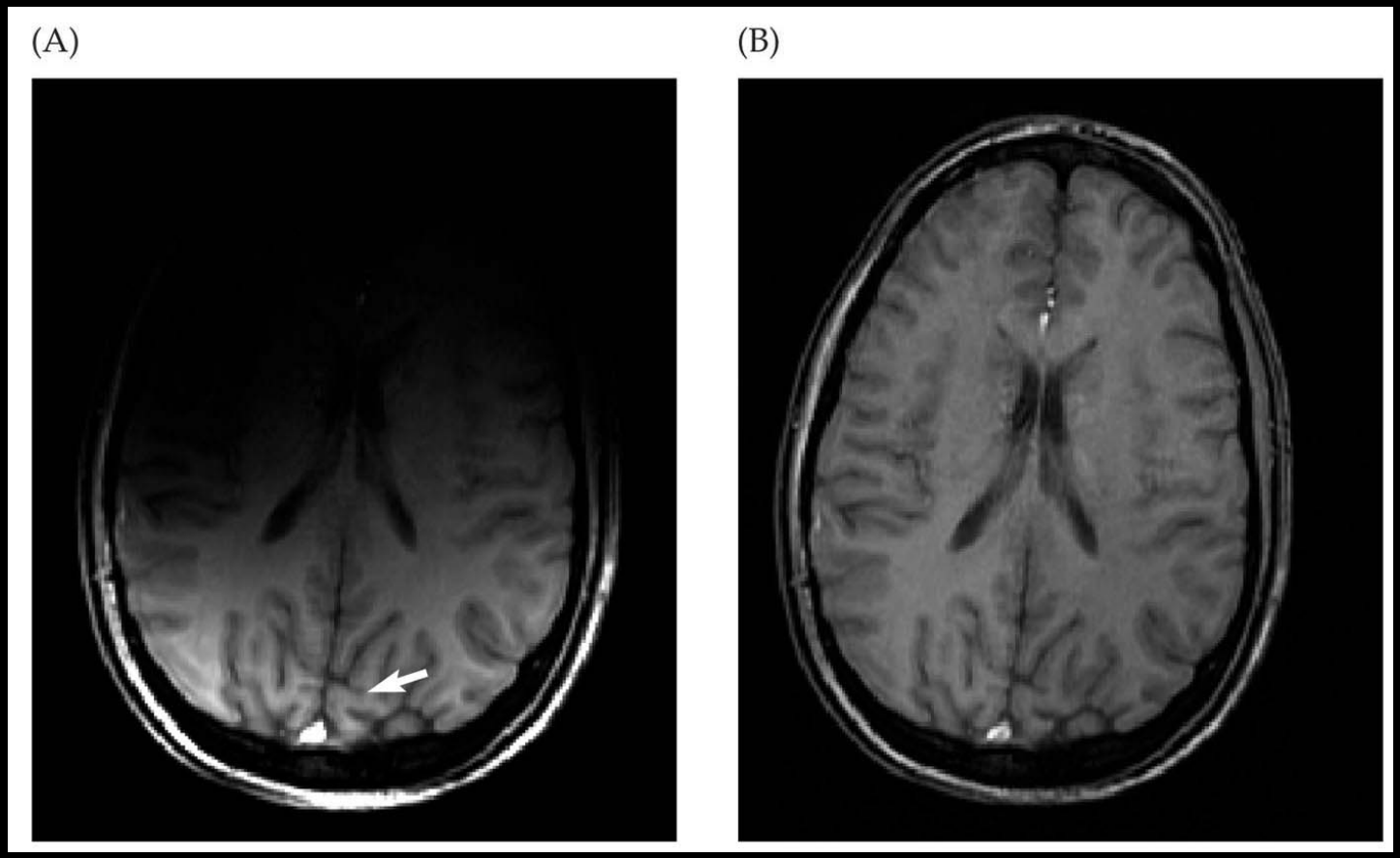
R = Resistor
C = Capacitor
L = Inductor
≠ = Adjustable capacitor

(B)

Volume coil is a Helmholtz pair design.



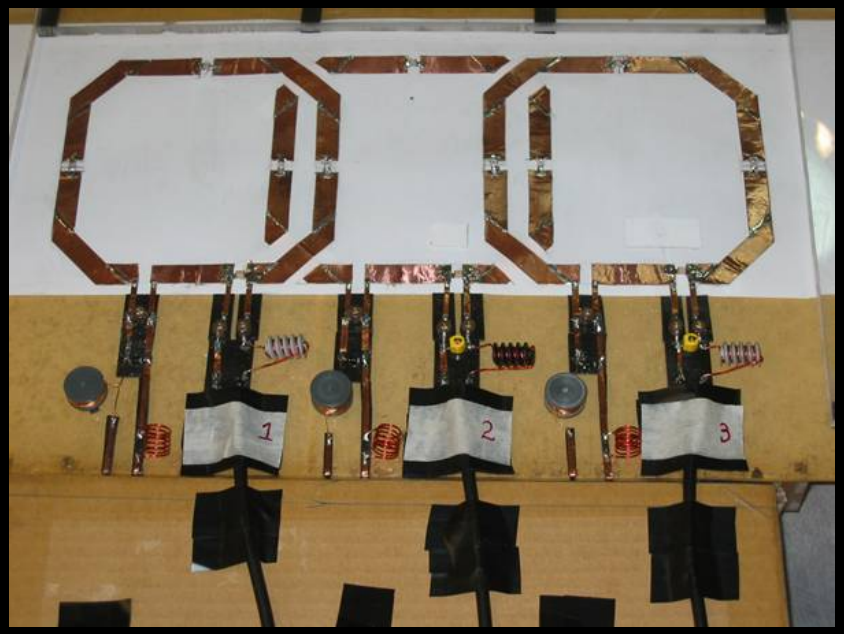
Rapid charge/discharge between inductor and resistor generates an oscillating magnetic field.



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.

Phased array coils:

- A phased array coil is essentially a number of overlapping coils (or *elements*), each with their own receiver detection circuitry.
- The term "phased array" comes from radar and is a bit confusing. A more appropriate name that you should use is "multi-coil array“. We use an 8-channel coil.



Three-element coil configuration designed at University of Queensland.

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

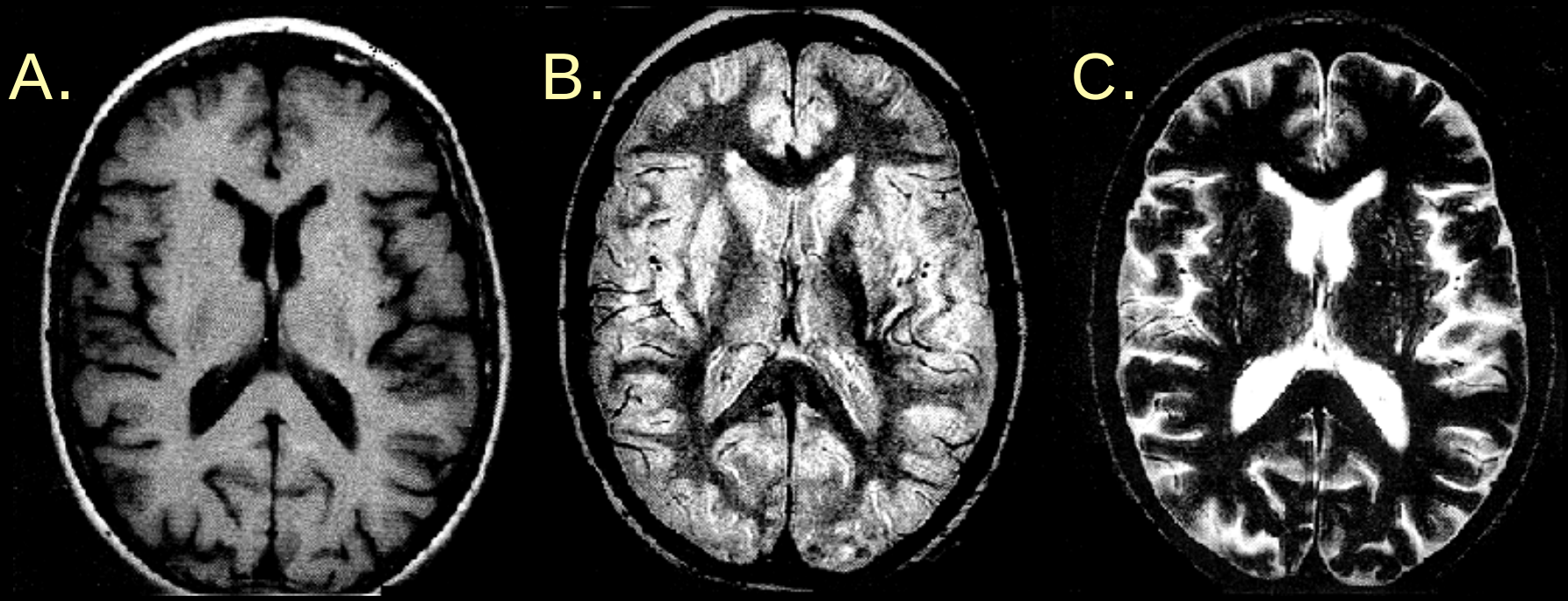
Temporal resolution of images

- 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)

MRI of a normal 73-yr-old female

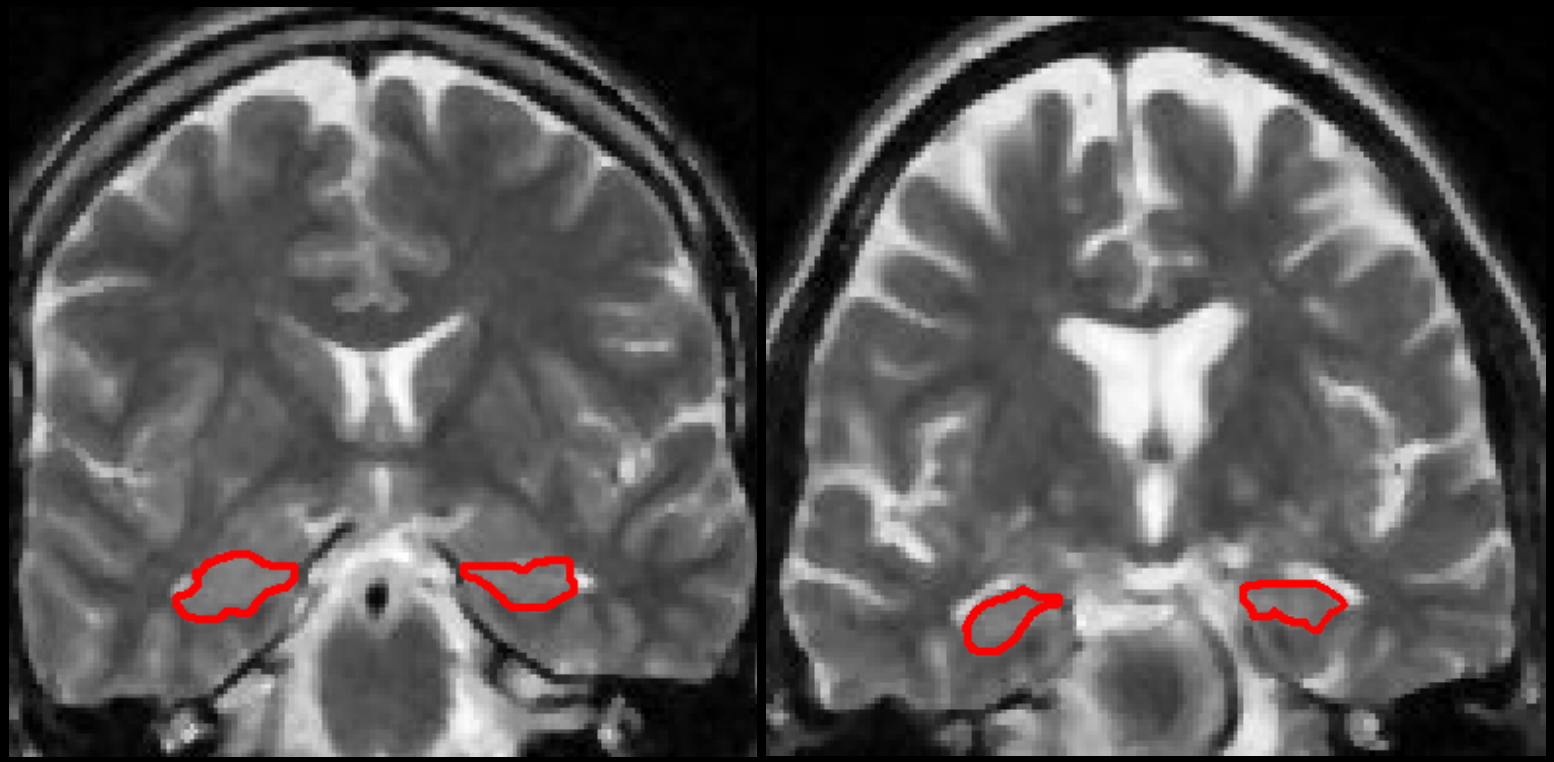


A. T_1 axial spin-echo image

B. Proton density-weighted image

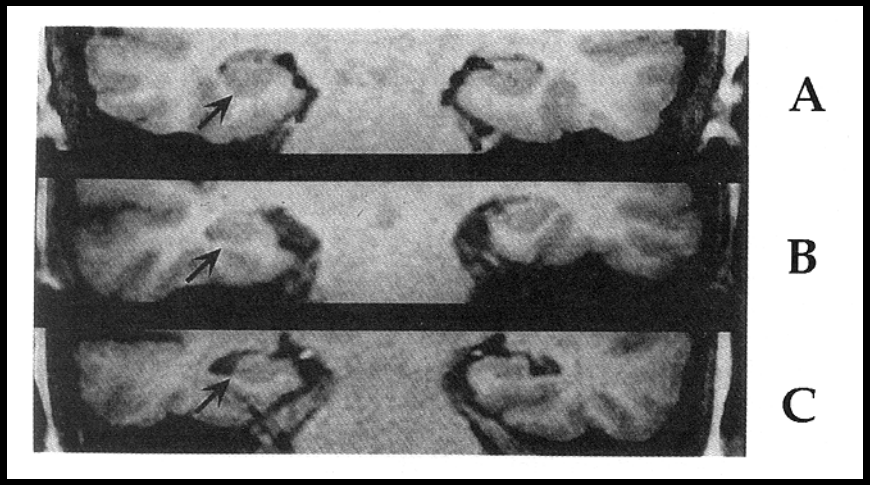
C. T_2-weighted image

From Ames, D., & Chiu, E. (1997)



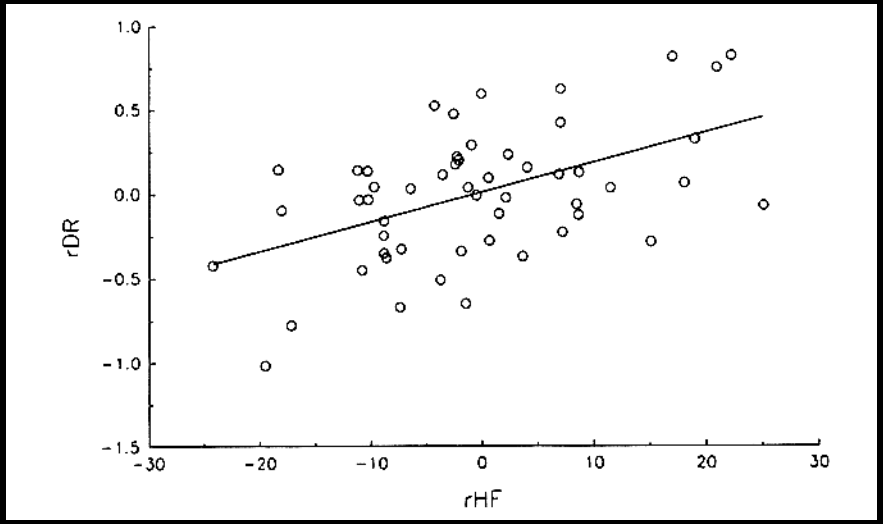
Measuring hippocampal volumes:

Predicts AD in patients who already have mild cognitive impairments.



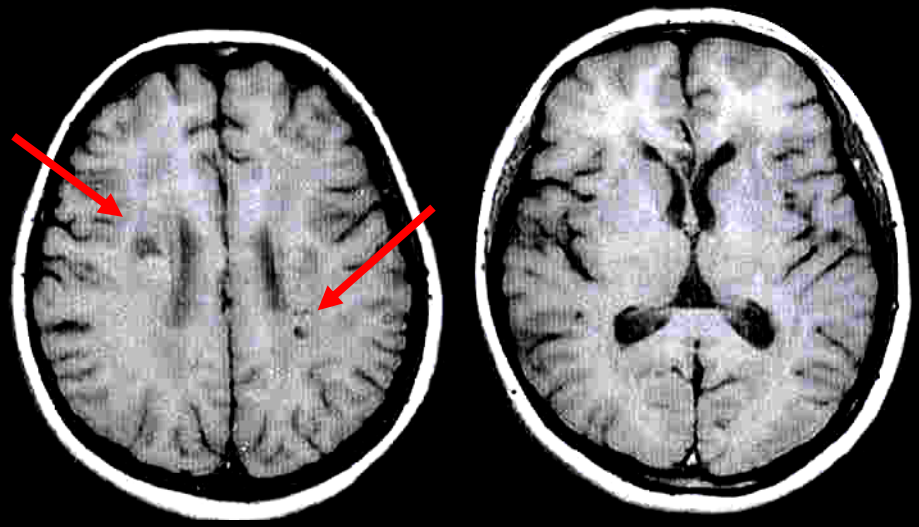
Golomb, Kluger, et al., (1994)

Coronal MRIs showing various levels of HC volumes in cognitively normal individuals.

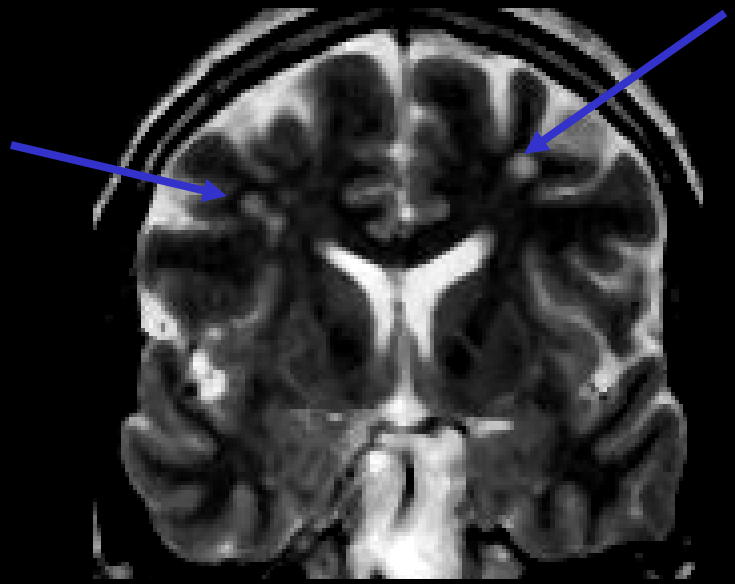


Scatterplot depicting relationship between HC volume and composite delayed recall performance in normal older adults.

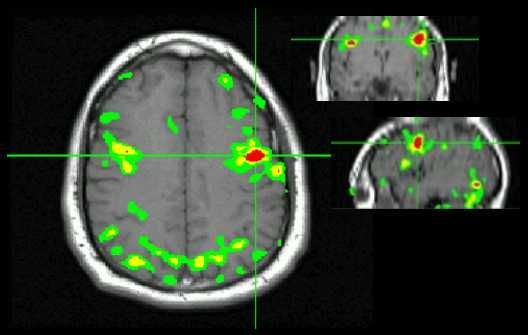
Decrease in volume > 2sd is a significant predictor of AD.



Multiple small infarcts (strokes) of the deep white matter, centrum semiovale and periventricularly (T1 MRI).



Also abnormal regions of white matter in disorders such as multiple sclerosis (T2 MRI).



fMRI: What is it?

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

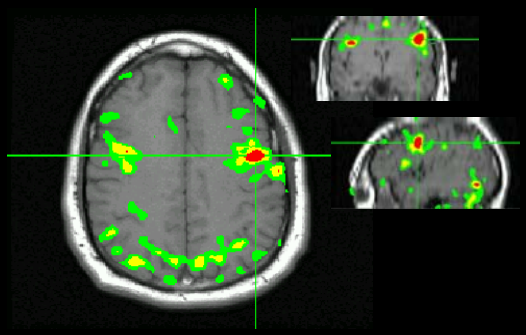
Good things:

- High resolution, fast scanning time, non-invasive

Not so good things:

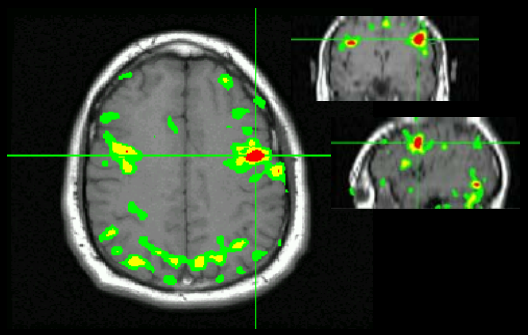
- Very low signal to noise ratio, sensitive to motion, susceptibility artifacts

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

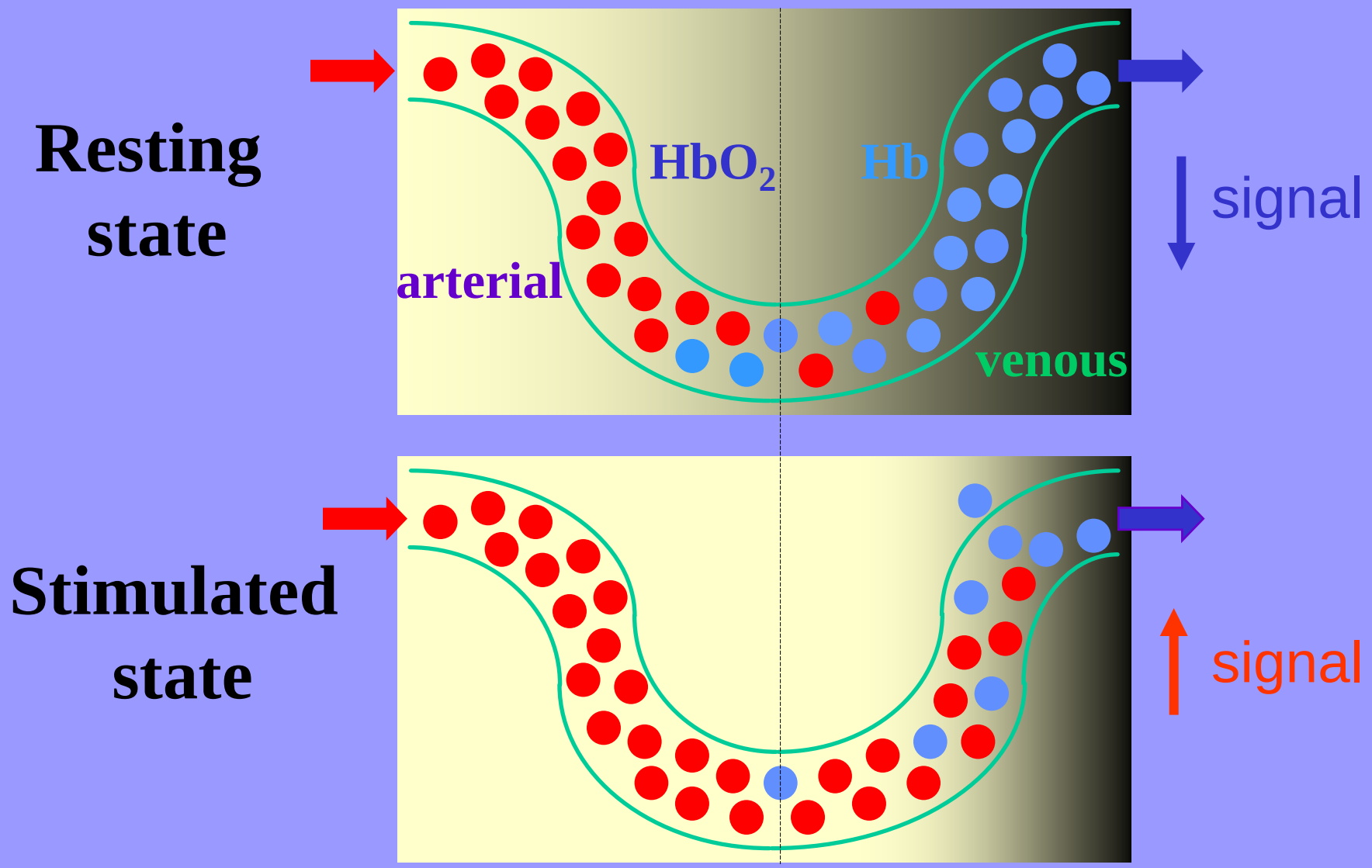
→ Uptake of O_2 less than supply

→ Surplus oxygenated hemoglobin

→ Decreased concentrations of deoxyhemoglobin

→ **Increased local fMRI T2* signal**

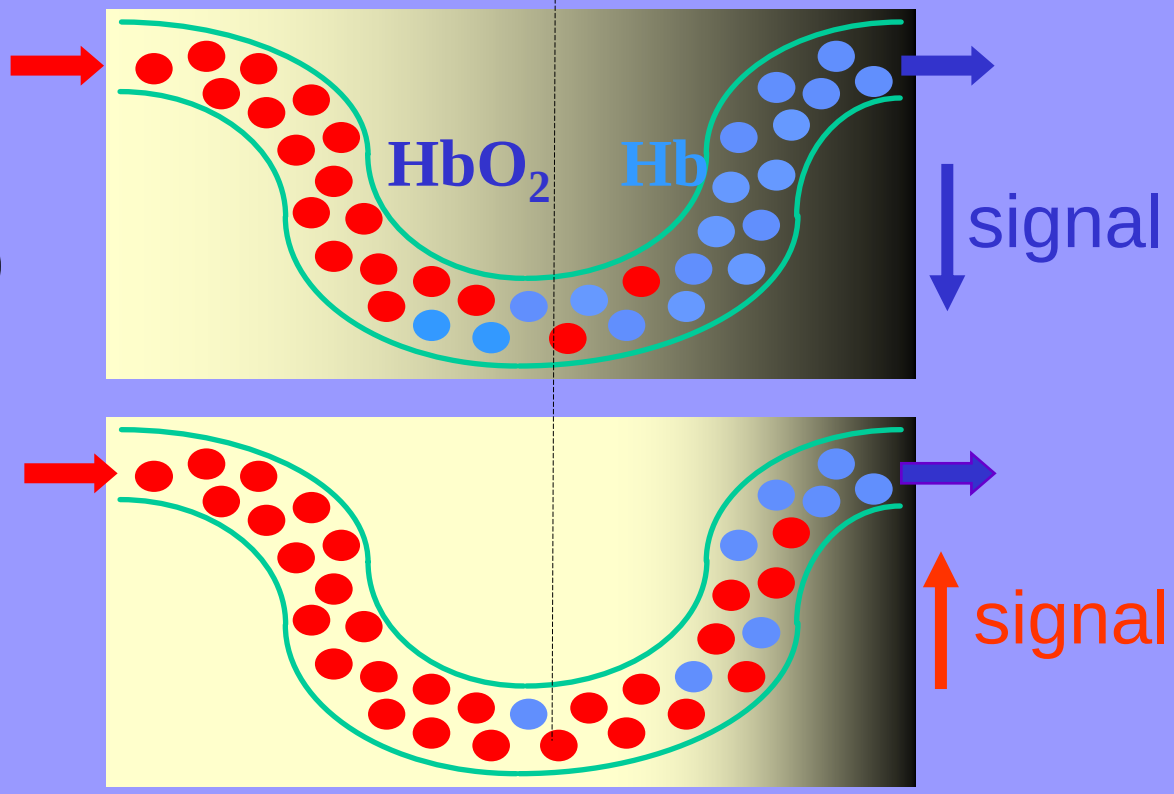
BOLD Contrast



Determining Activation: A subtraction measure

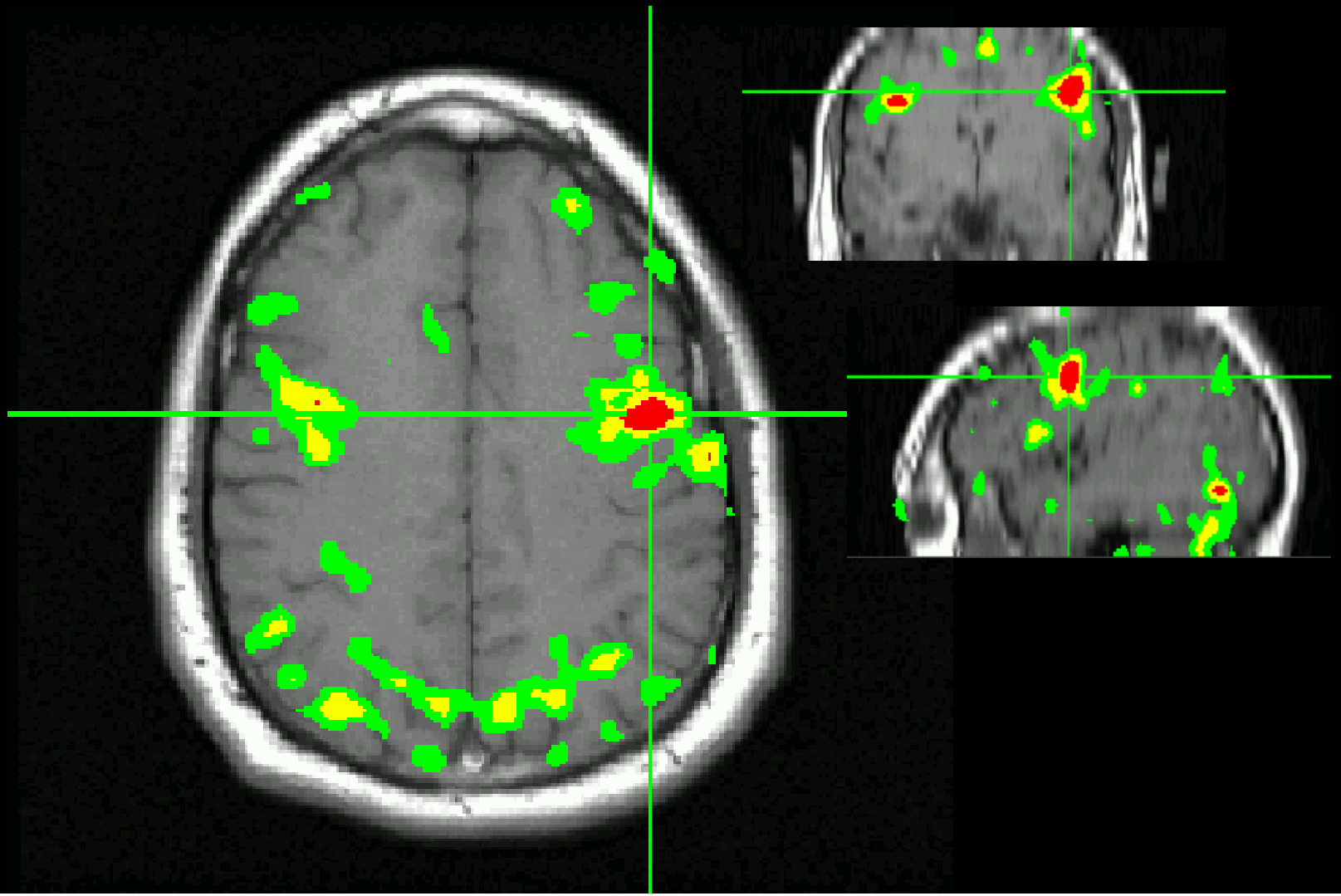
Subject is scanned at rest (R)

Subject is scanned during cognitive task (C)

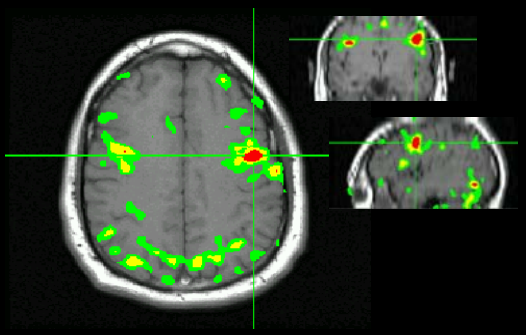


Regions of activity are determined the *differences* between scan R from scan C.

Activations: Regions of significant change in signal from one condition to another.



Caveats regarding fMRI:

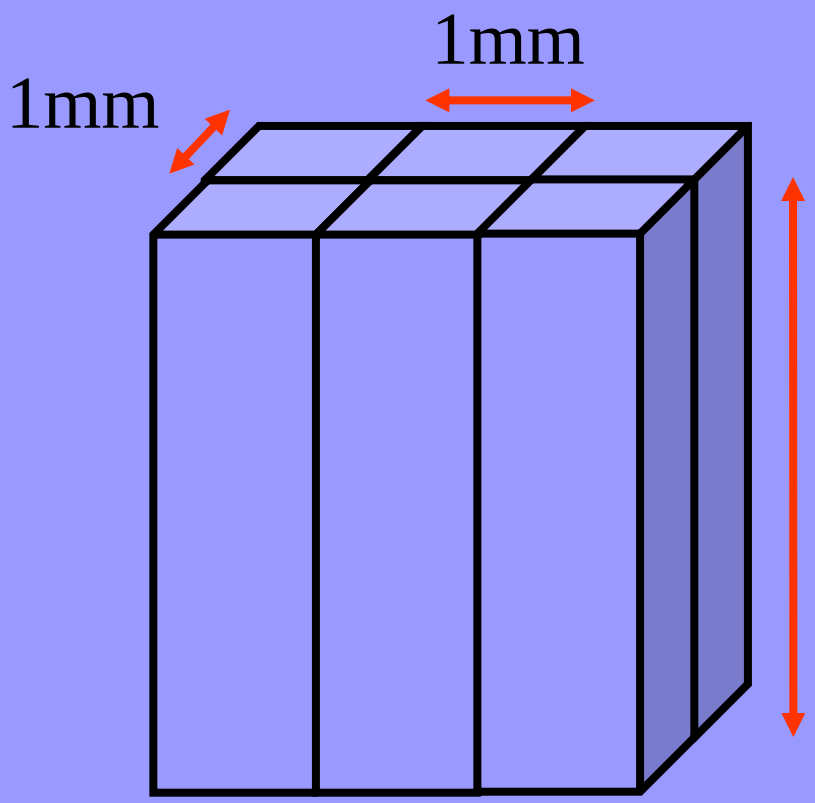


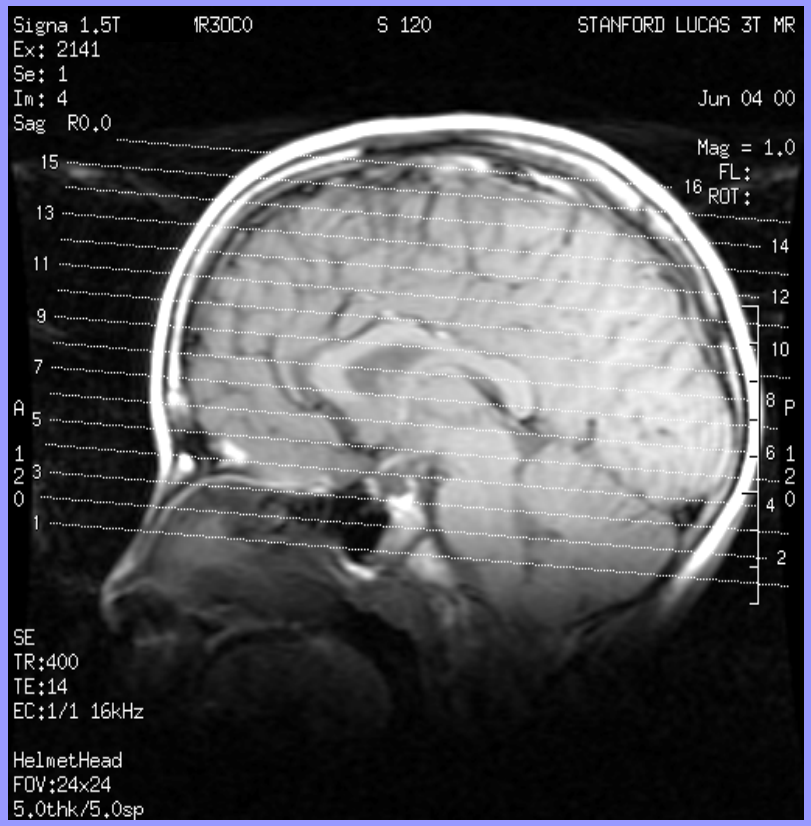
- Tertiary measure of neuronal activity.
- Very small signal changes, on order of 1 to 2%.
- Signal change predominates in region of large draining veins, not gray matter, and may vary in locality.
- Extremely sensitive to motion.
- Hemodynamic response is delayed -- 15 msec scan, but 10-12 sec response.

Voxel size in MRI:

Voxel size:

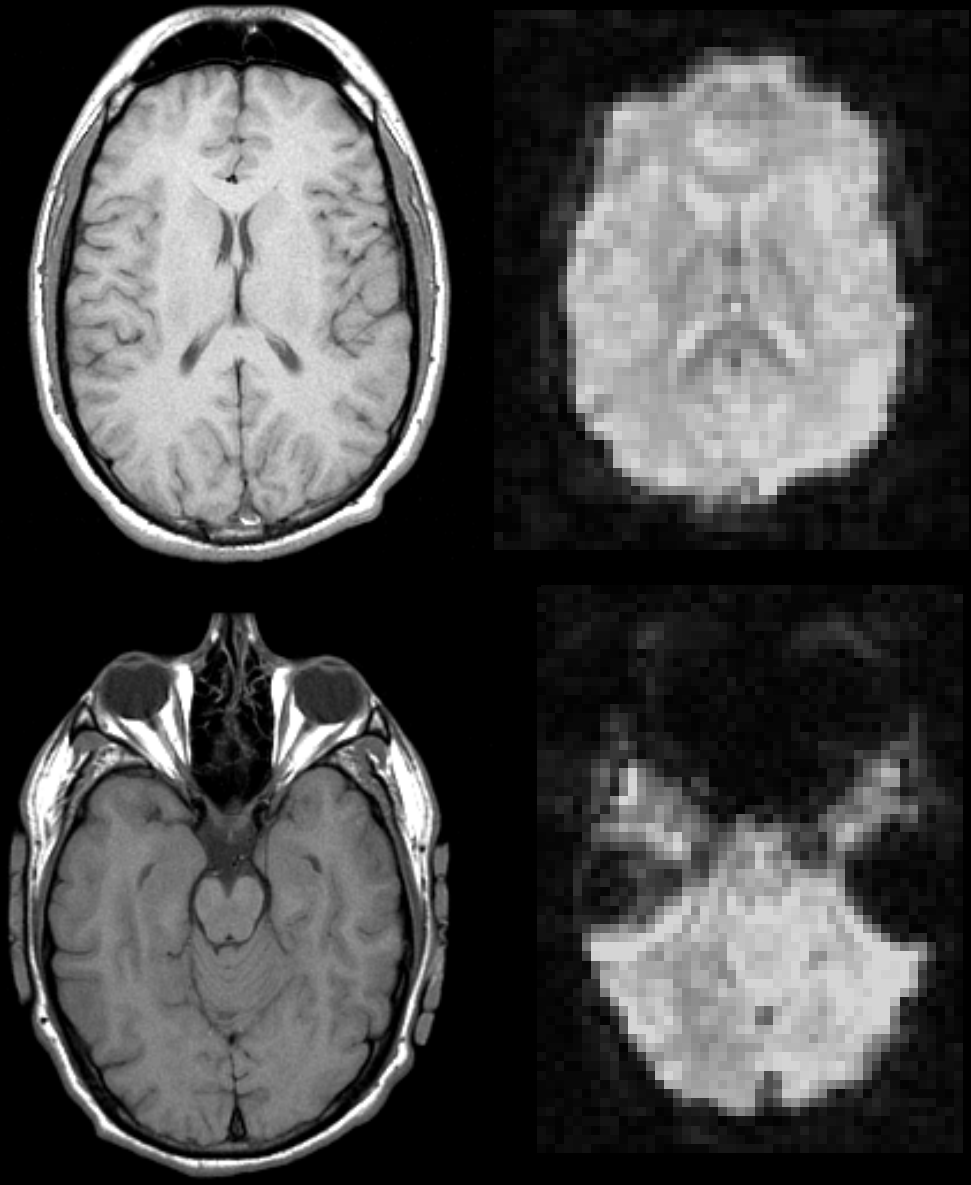
In-plane resolution x slice thickness





Anatomical:
1 x 1 x 5mm

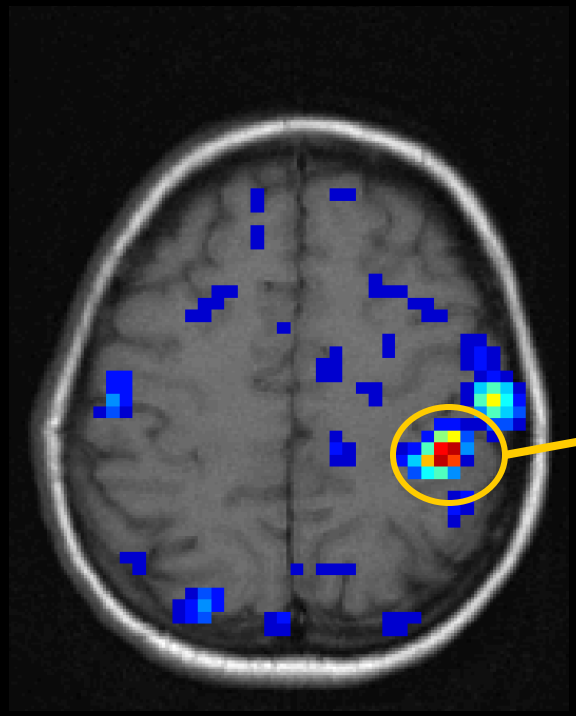
Functional: 3.4
x 3.4 x 5mm

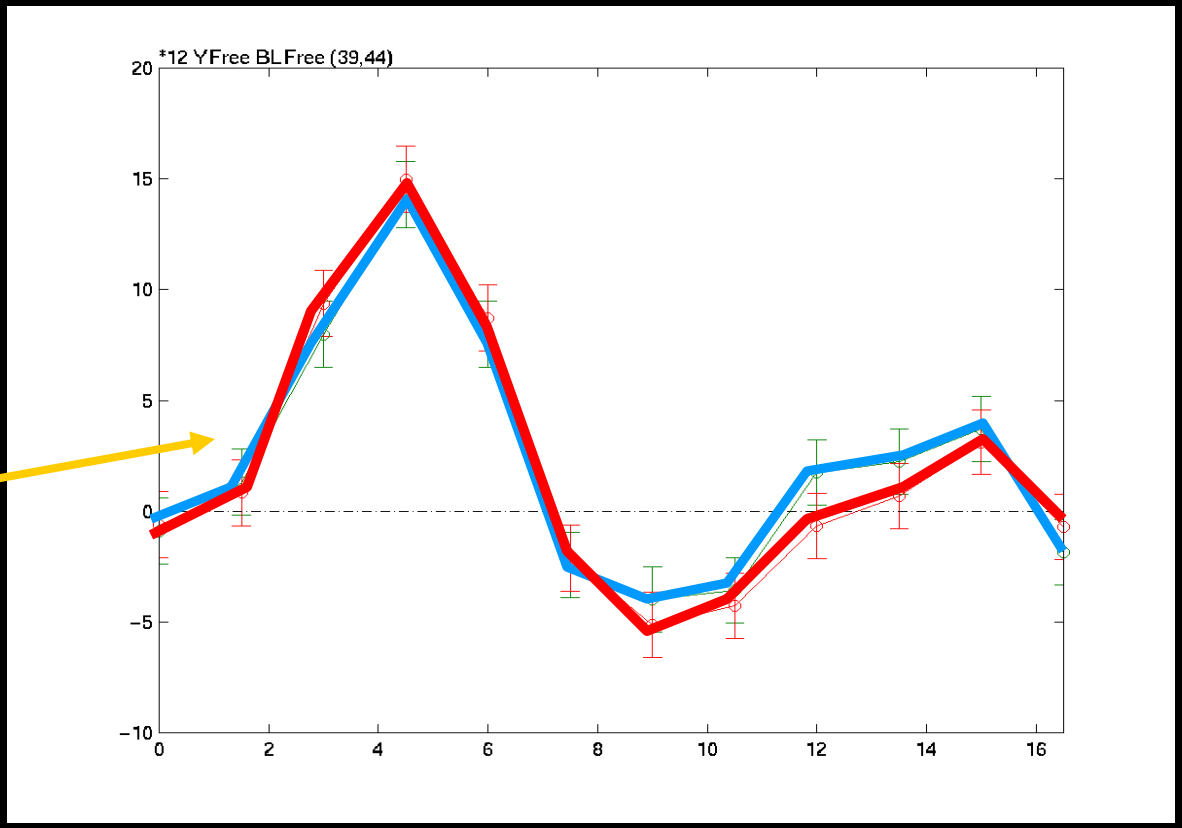


Dealing with low signal strengths:

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

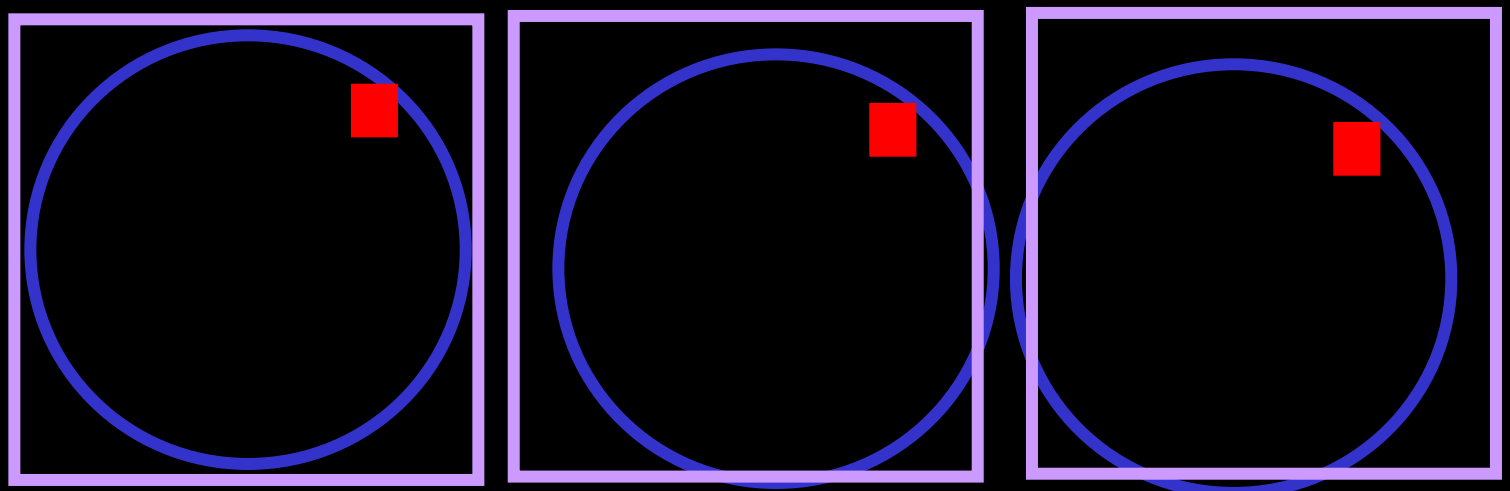
The hemodynamic response takes time, even for a single, fast behavioral response

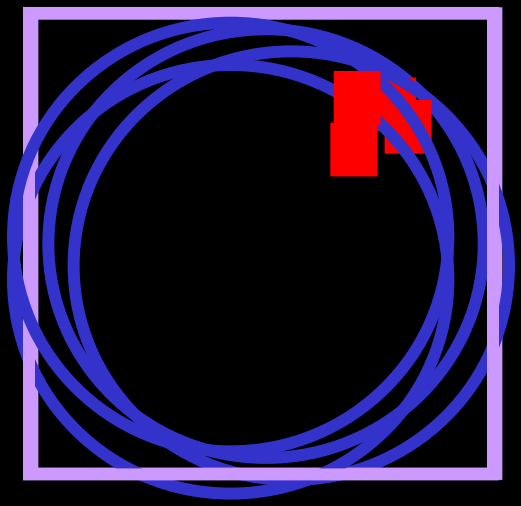




Motion:

time





Susceptibility Issues

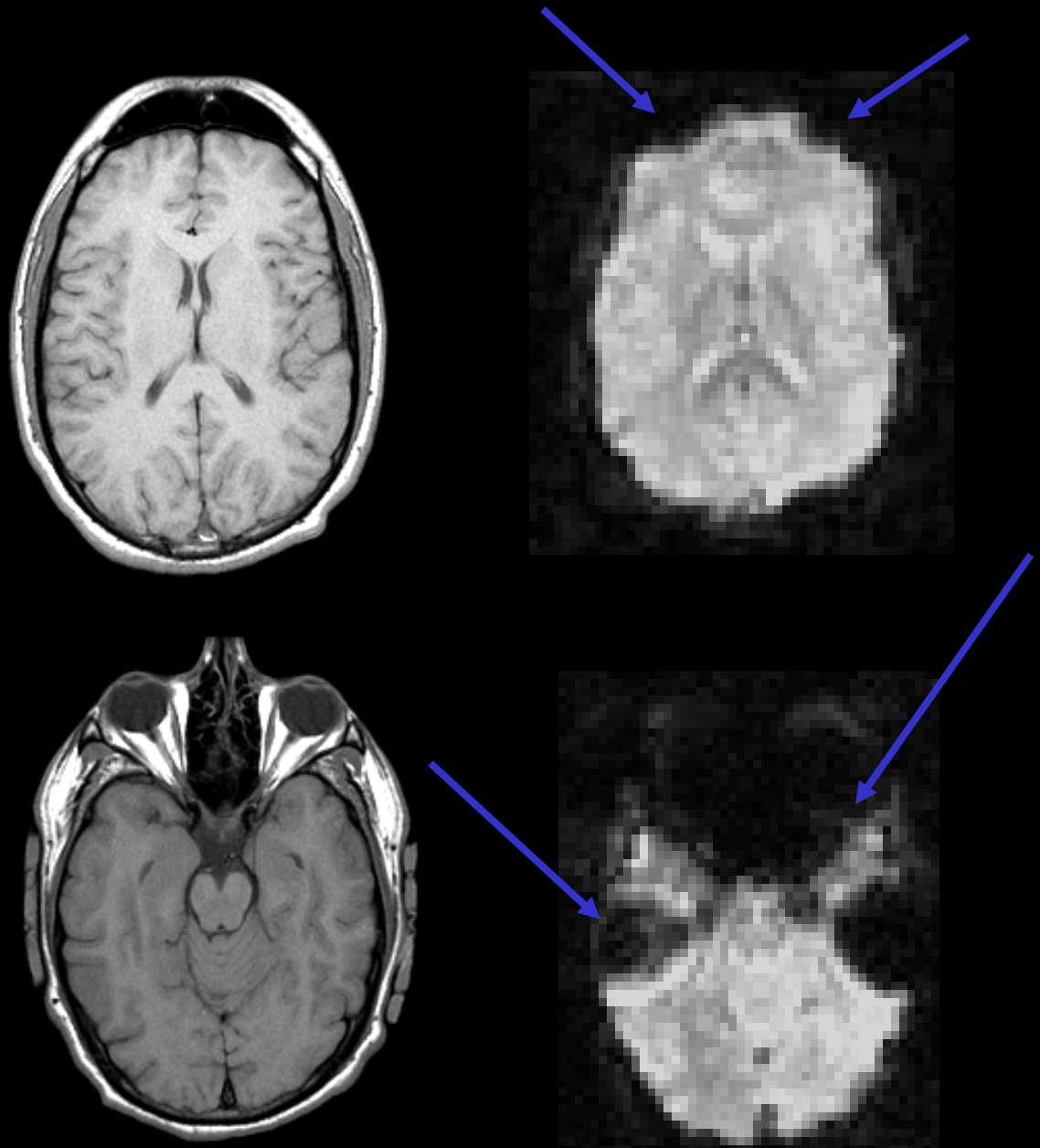
Increased at higher field strengths:

- **Affects choice of imaging parameters**

Leads to:

- **Signal loss near air/tissue interfaces**
- **Geometric distortion (EPI) or blurring (spiral)**

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

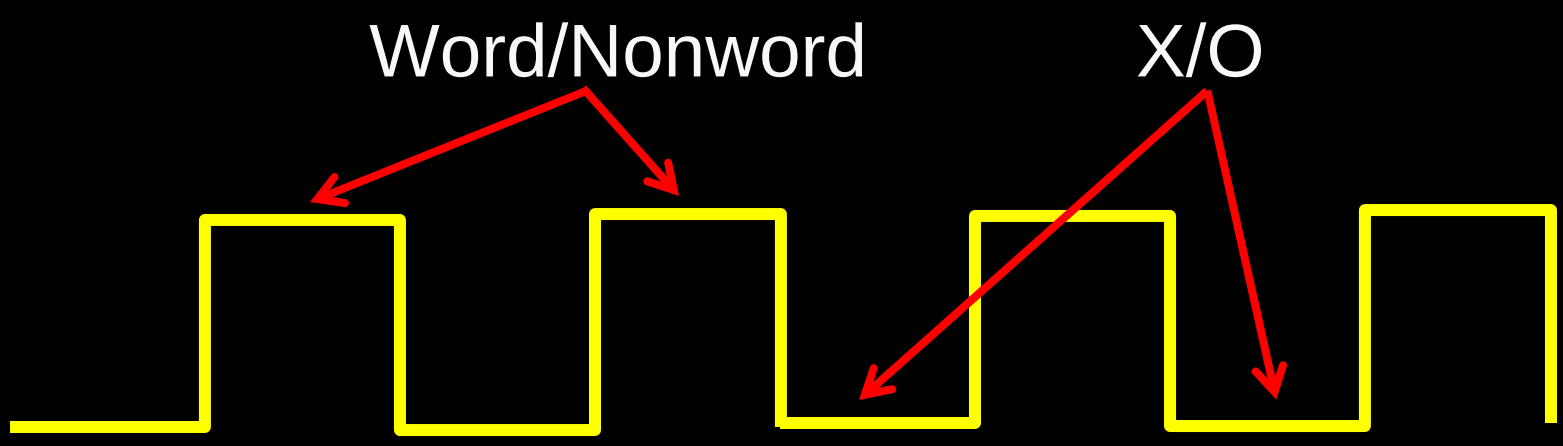


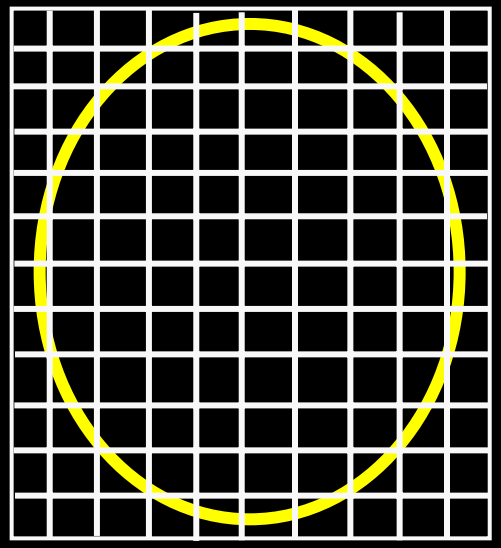
Simple fMRI experiment:

Word identification

20secs: Word/Nonword R/L button press

20 secs: XXXX/OOOO R/L button press



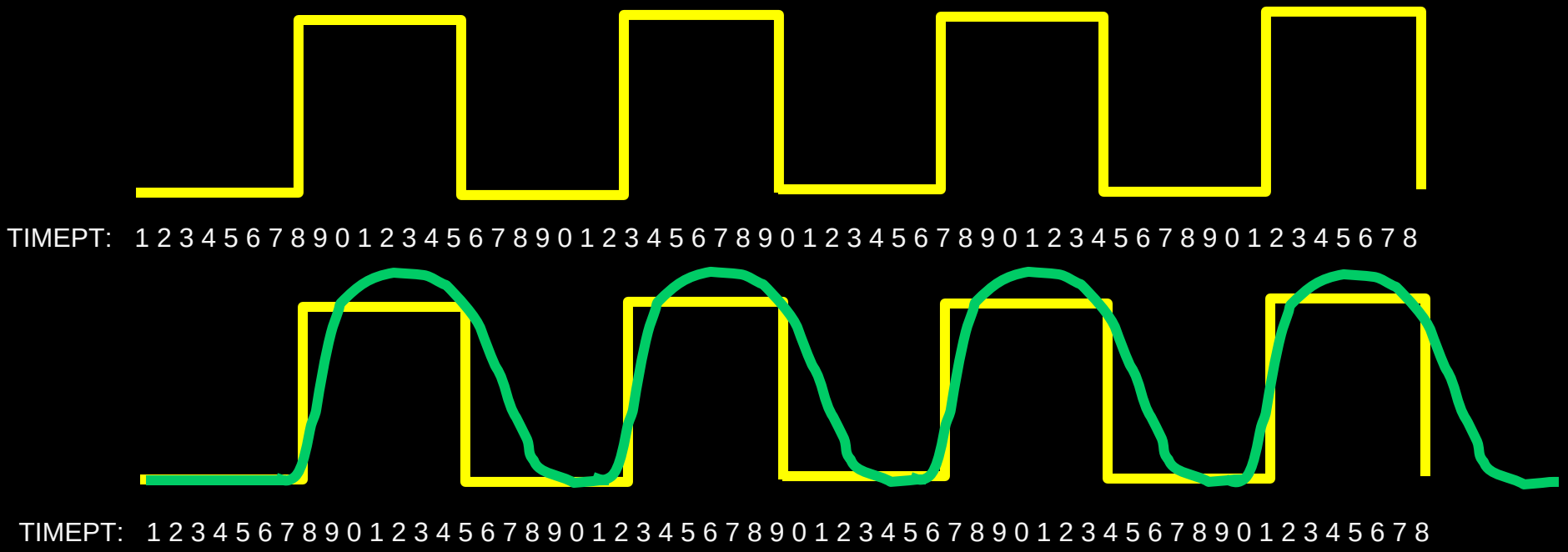


Statistical analysis:

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

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

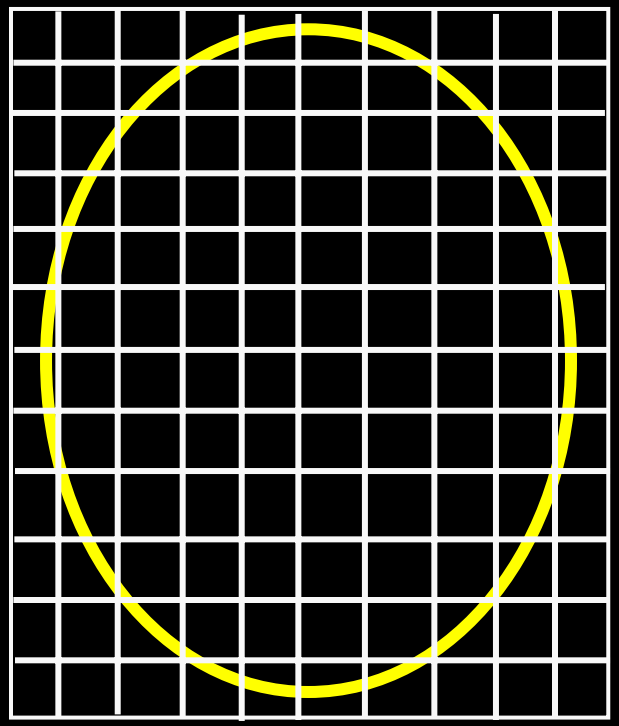
Alternatively, convolved function HRD with 0,1



Assumptions: Statistical

Independence across voxels

Dealing with many multiple comparisons



What is the true dependence across voxels?

Functional fields

Distribution of vessels

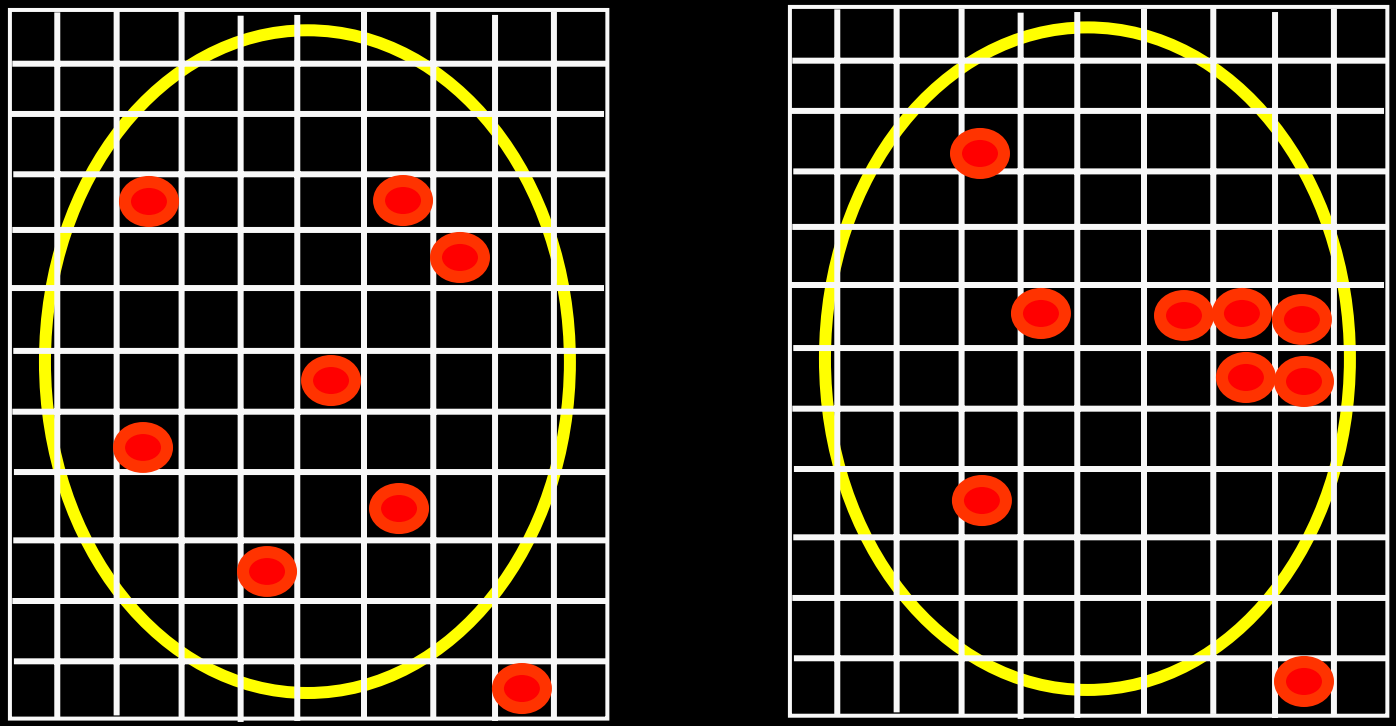
Approaches:

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.

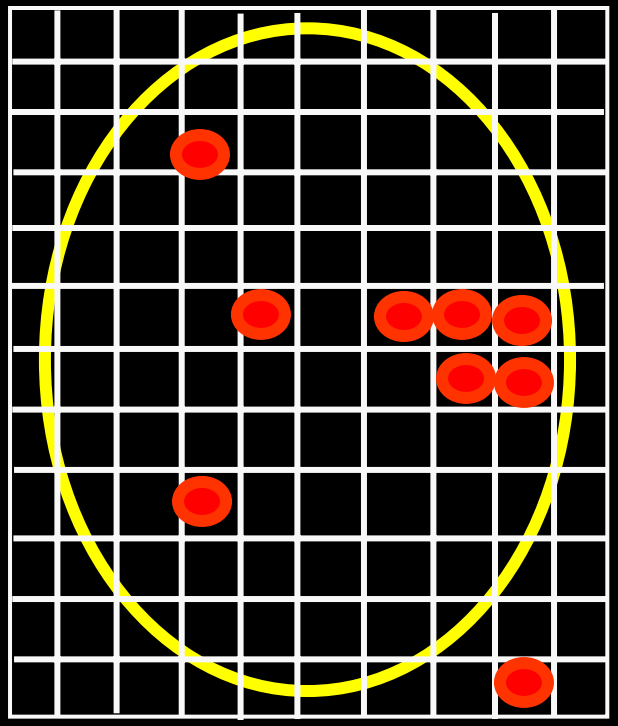
Upside is that smoothing deals with left-over-motion, and some partial voluming.

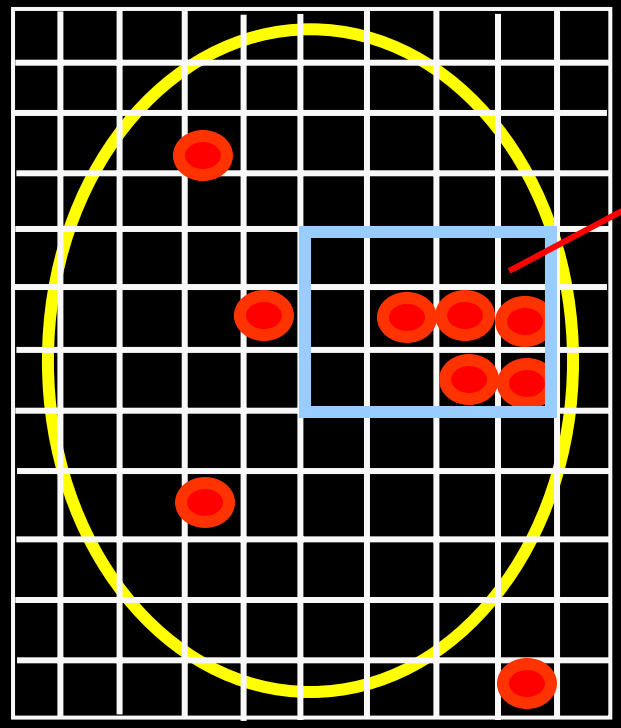
Clustering: Independent tests on each voxel, but estimate the probability by chance alone that voxels will occur side by side.



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.

Assumptions about cognition and brain:

"Pure insertion" A can be added to B without a change in B.

Example: pressing the button to words is equivalent to pressing the button to X/Os.

If not, then Mean[W/N] -- Mean [X/O] will not produce regions specific to W/N.

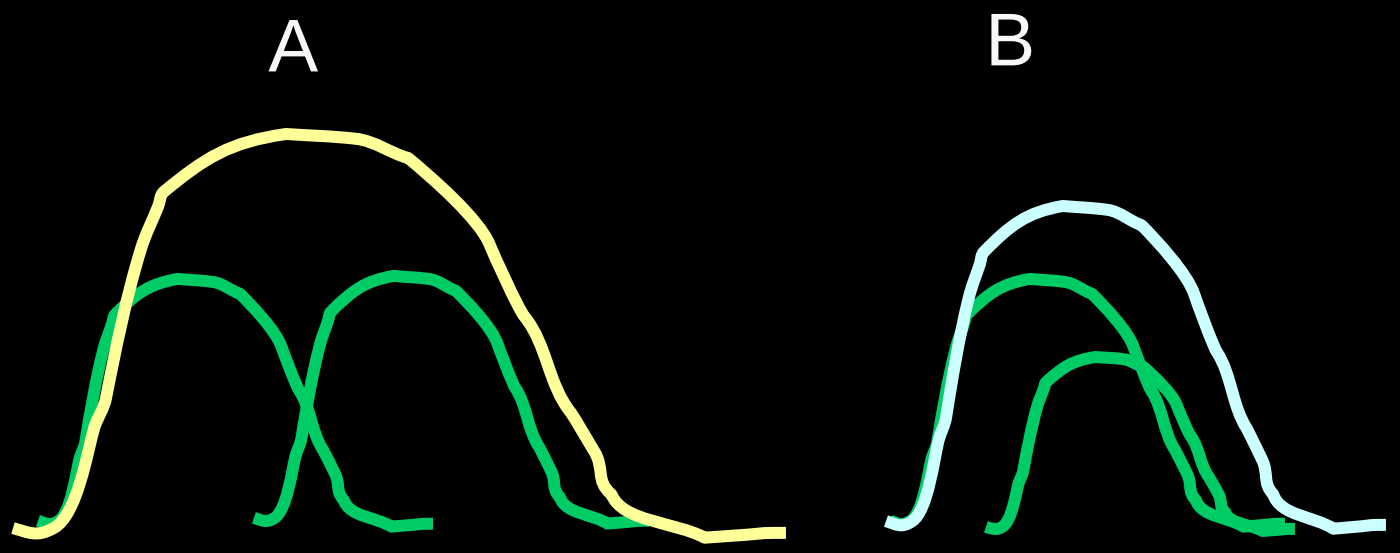
"Linearity" Response of the brain is not equivalent for two stimuli separated in time and the same two stimuli presented simultaneously or in close succession.

Example: Working memory

A. Stim -- delay ----- choice

vs

B. Stim -- choice ----- delay



Types of designs:

Blocked -- easy to set up, but limited

- Can't randomize trials
- Anticipation of effects (blocks of Yes vs No)
- Cannot remove incorrect responses

Factorial designs: Measuring interaction effects

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

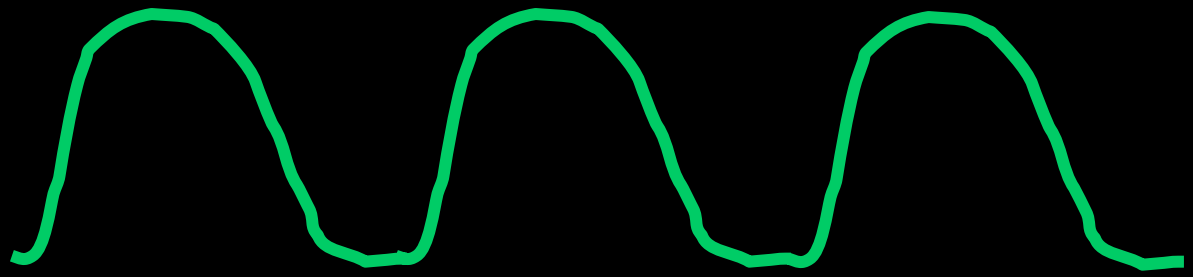
Cognitive conjunctions: Differing the control conditions or additive processes

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

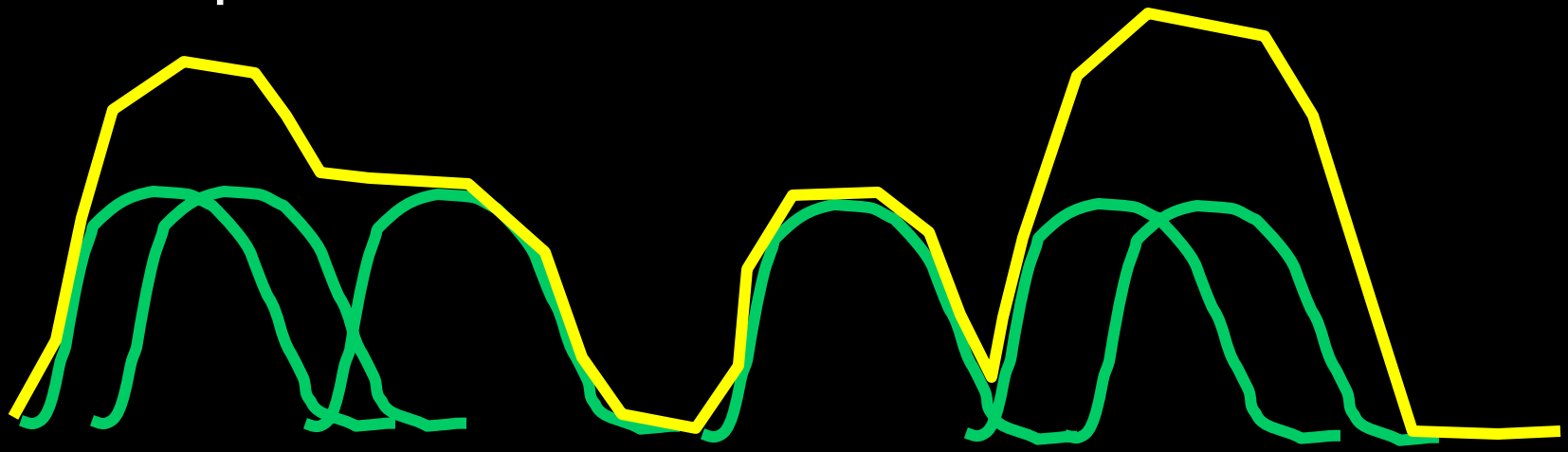
Parametric designs: Varying a parameter within a given variable, example, reaction time differences

Event related designs

Simplest case: 1.....1.....1.....



Faster presentation 1.2...2...1...1..2.....1.....11....2..



Good things about event-related designs:

Separate trials based on type, subject response

Random presentation decreases anticipatory effects

Presentation and responses can be self-paced

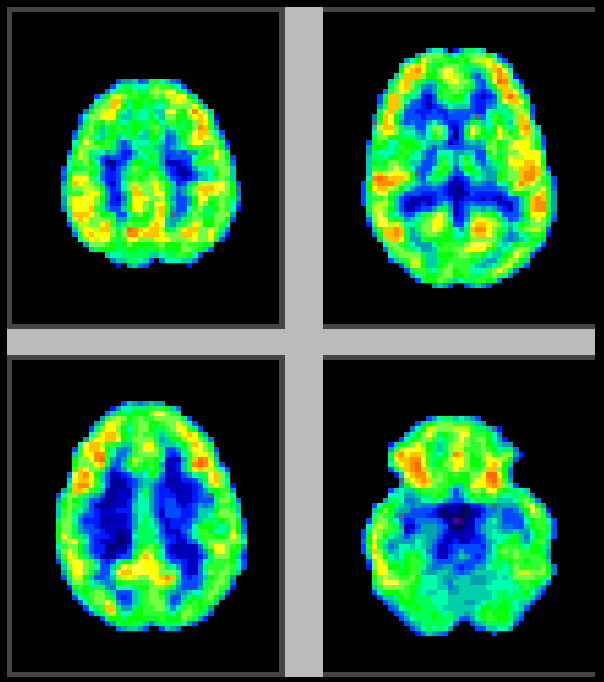
Difficulties:

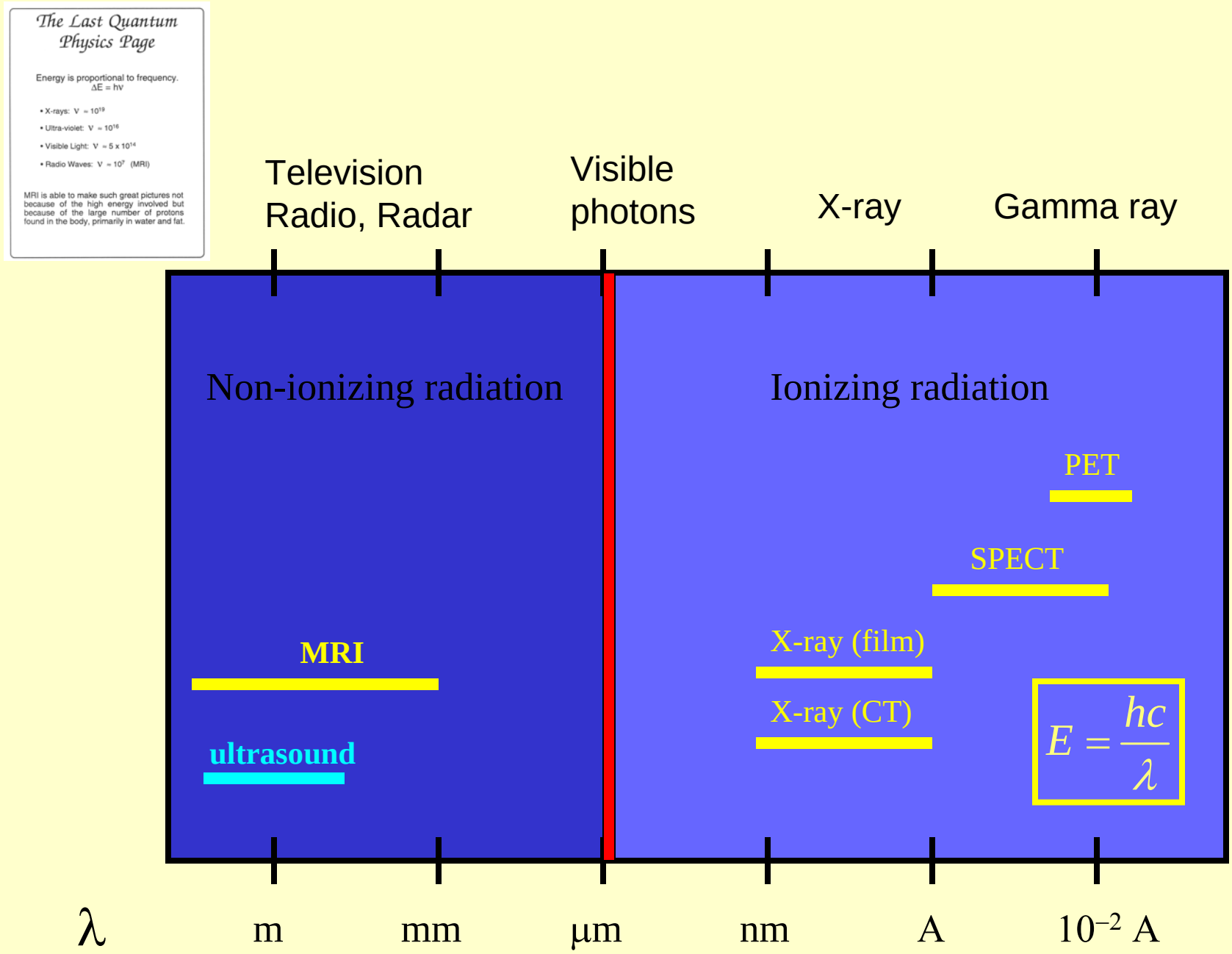
Dependencies amongst trials, e.g., yes/no recognition: Item.....Response

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

Positron Emission Tomography:

Measuring brain metabolism via radioactive tracers




The Last Quantum Physics Page
Energy is proportional to frequency.
ΔE = hν
• X-rays: ν ≈ 10^19
• Ultra-violet: ν ≈ 10^16
• Visible Light: ν ≈ 5 x 10^14
• Radio Waves: ν ≈ 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.
Television
Radio, Radar
Visible
photons
X-ray
Gamma ray
Non-ionizing radiation
Ionizing radiation
PET
SPECT
X-ray (film)
X-ray (CT)
MRI
ultrasound
E = hc/λ
λ
m
mm
μm
nm
A
10^−2 A

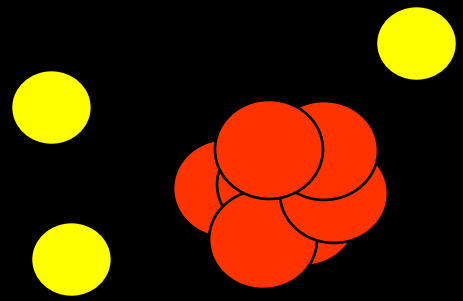
Positron emission tomography

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

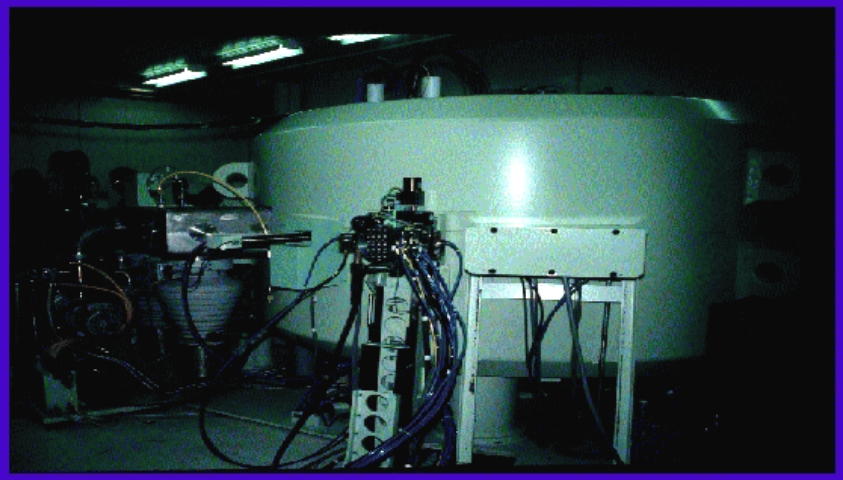
Isotope is connected to the compound of interest (such as oxygen or glucose) and injected.

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.

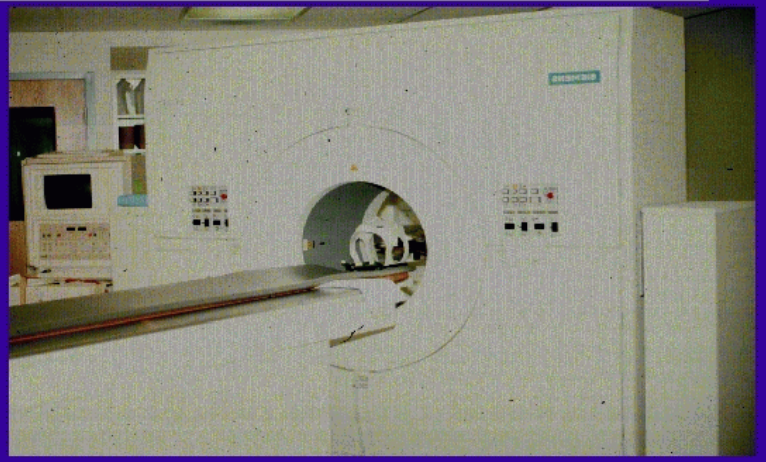


IBA 30MeV Cyclotron



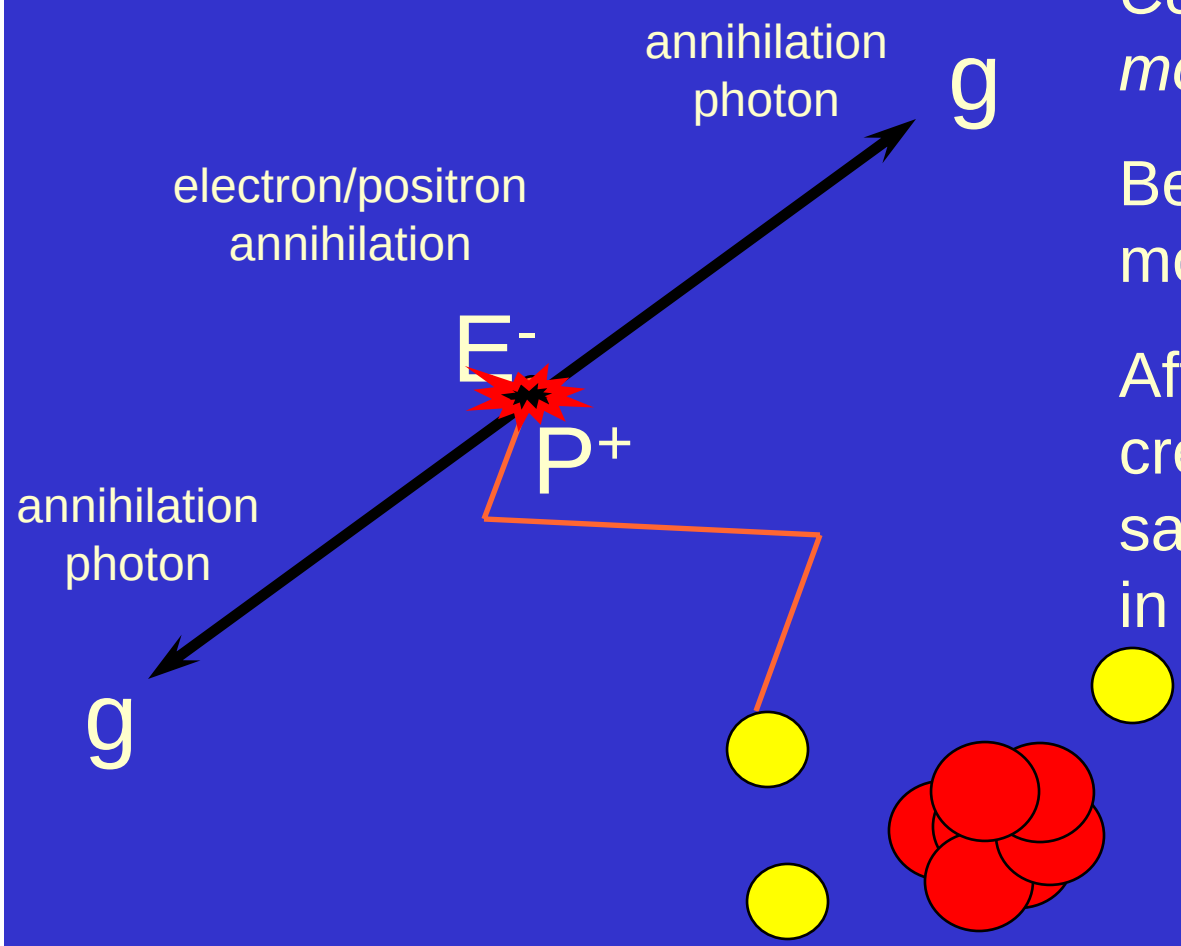
CPET; Buffalo, NY

Siemens/CTI ECAT 951-31R PET Camera



CPET; Buffalo, NY

Annihilation: Decay via positron emission



Conservation of momentum:

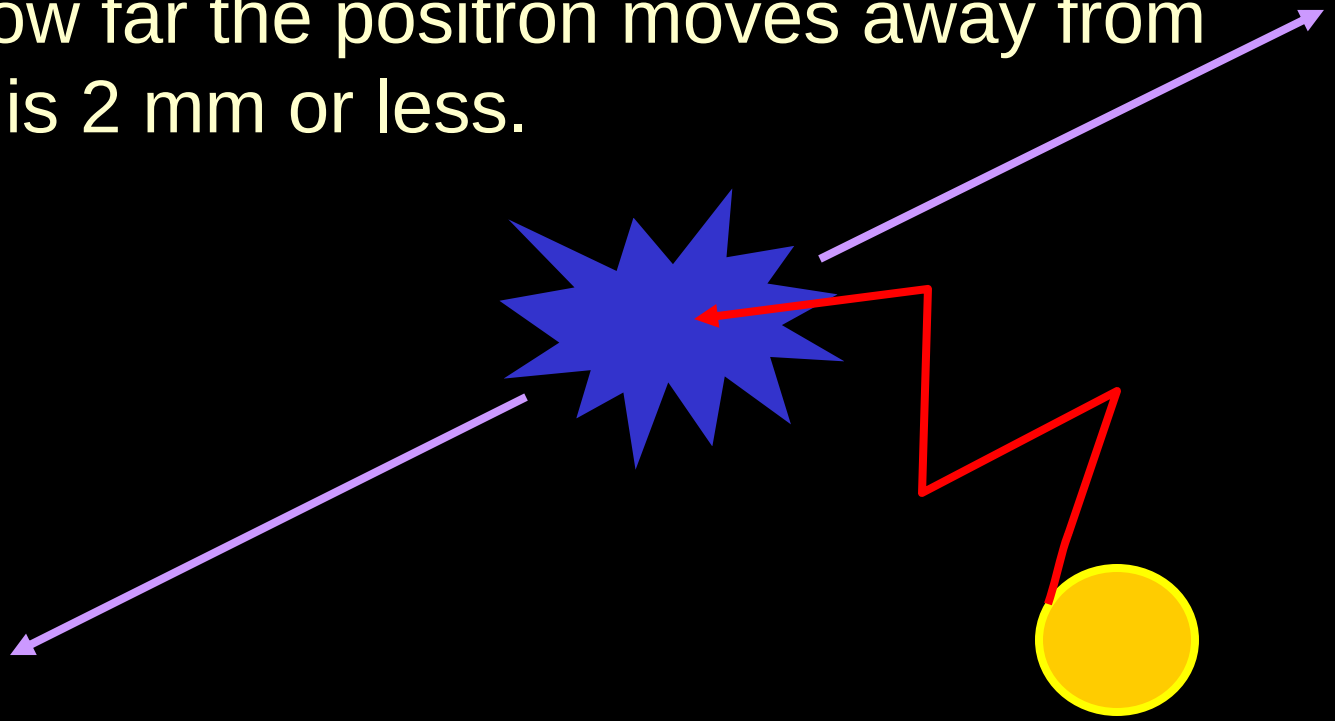
Before: system at rest; momentum ~ 0

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.

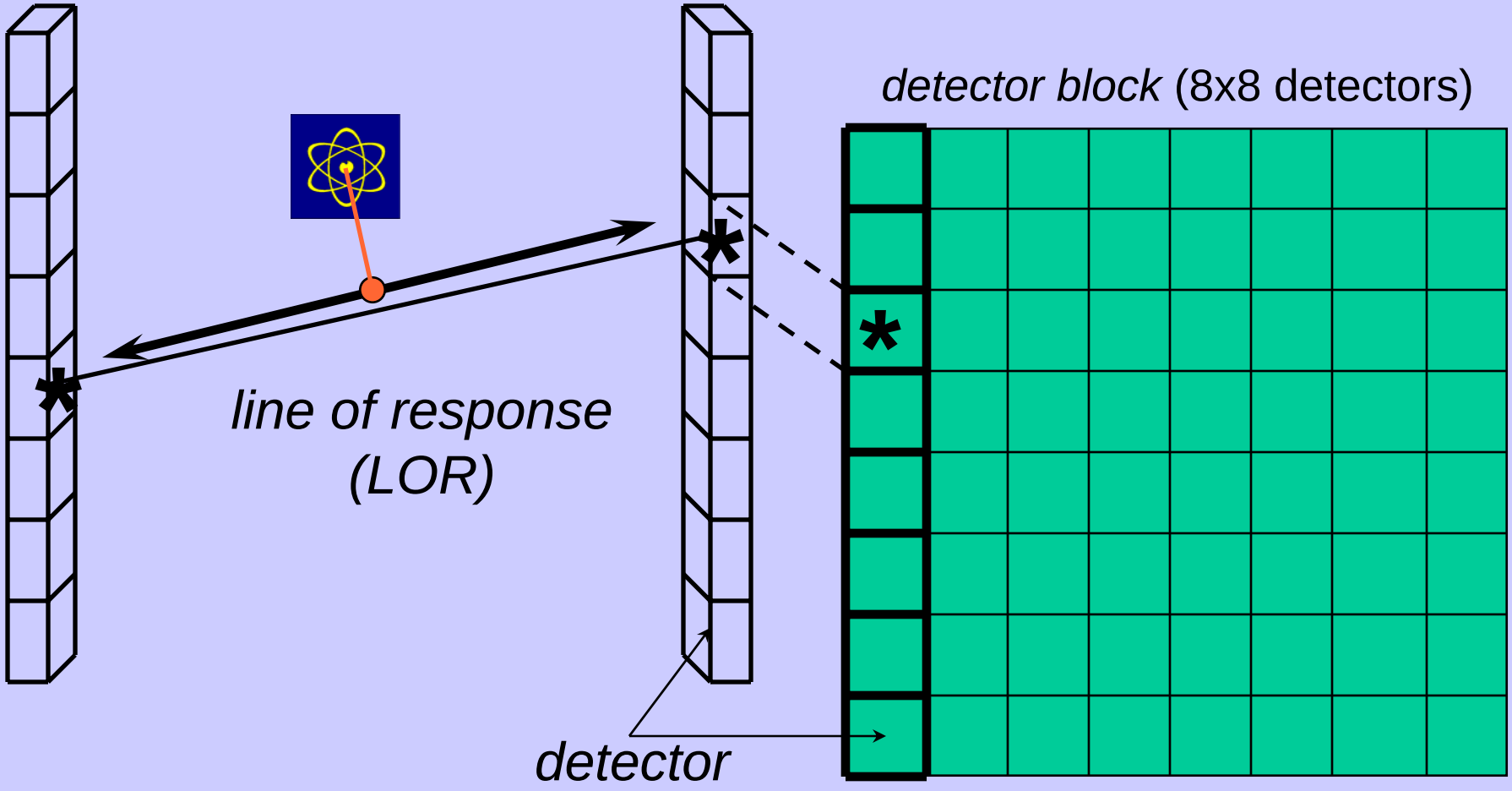
Scatter (how far the positron moves away from molecule) is 2 mm or less.



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?)

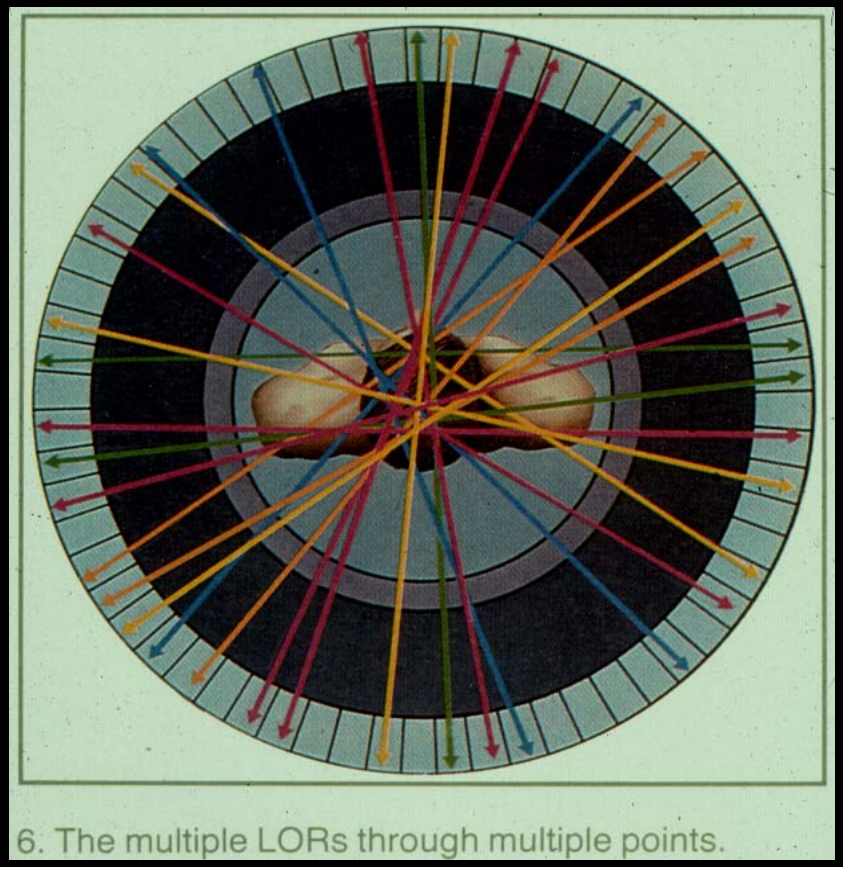
Annihilation detection



Coincident detection

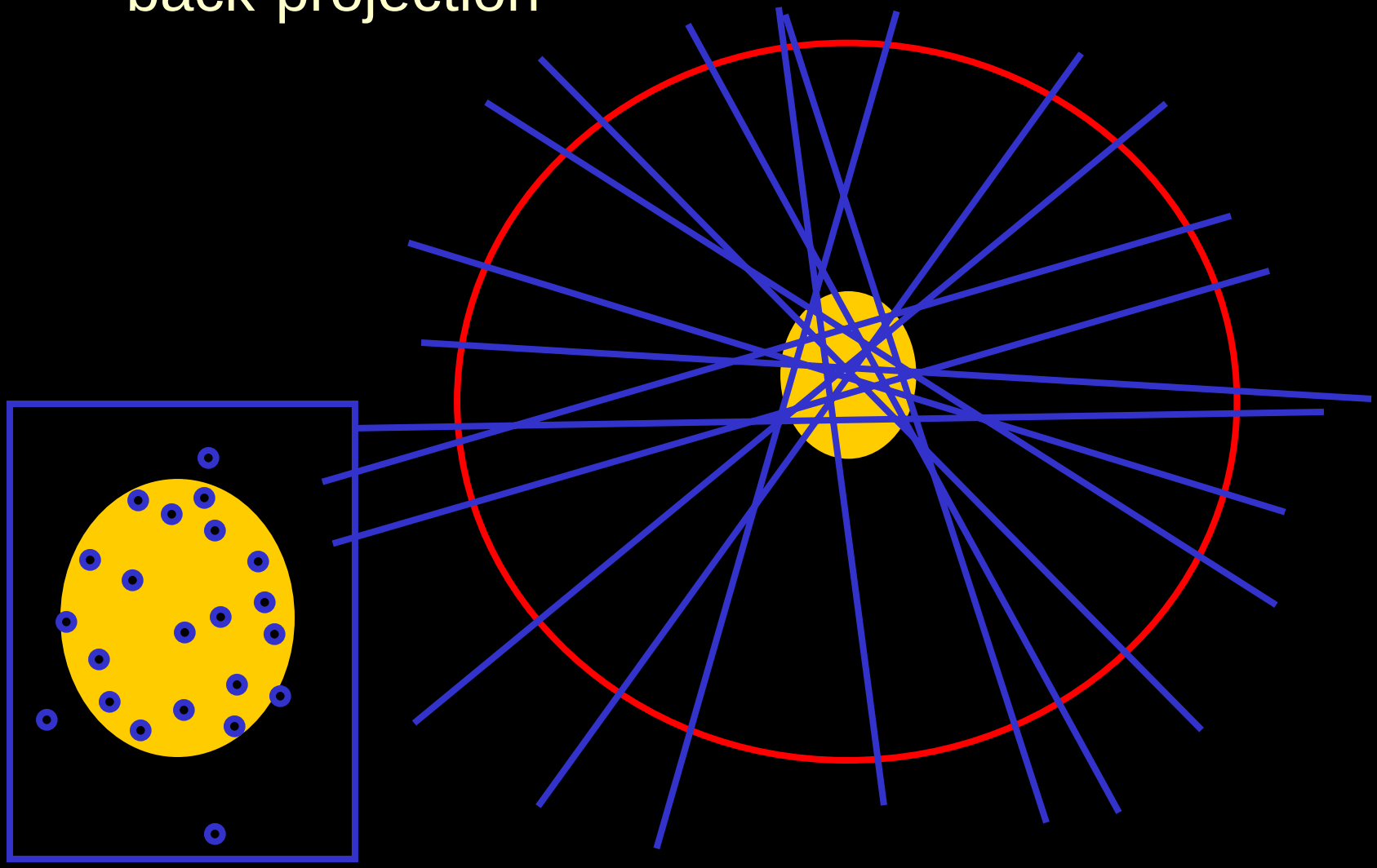
Scintillating crystal detectors in circumferential arrays, measure coincident events only.

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.

Tracer Compounds:

Carbon, nitrogen, oxygen, fluorine, all components of molecules in the body.

Fluorine 18 -- analog to hydrogen

Half life -- time taken for 50% of isotopes to decay, ideally half-life is within scanning time

PET tracers:

1. Oxygen - HL is 1.5 mins.

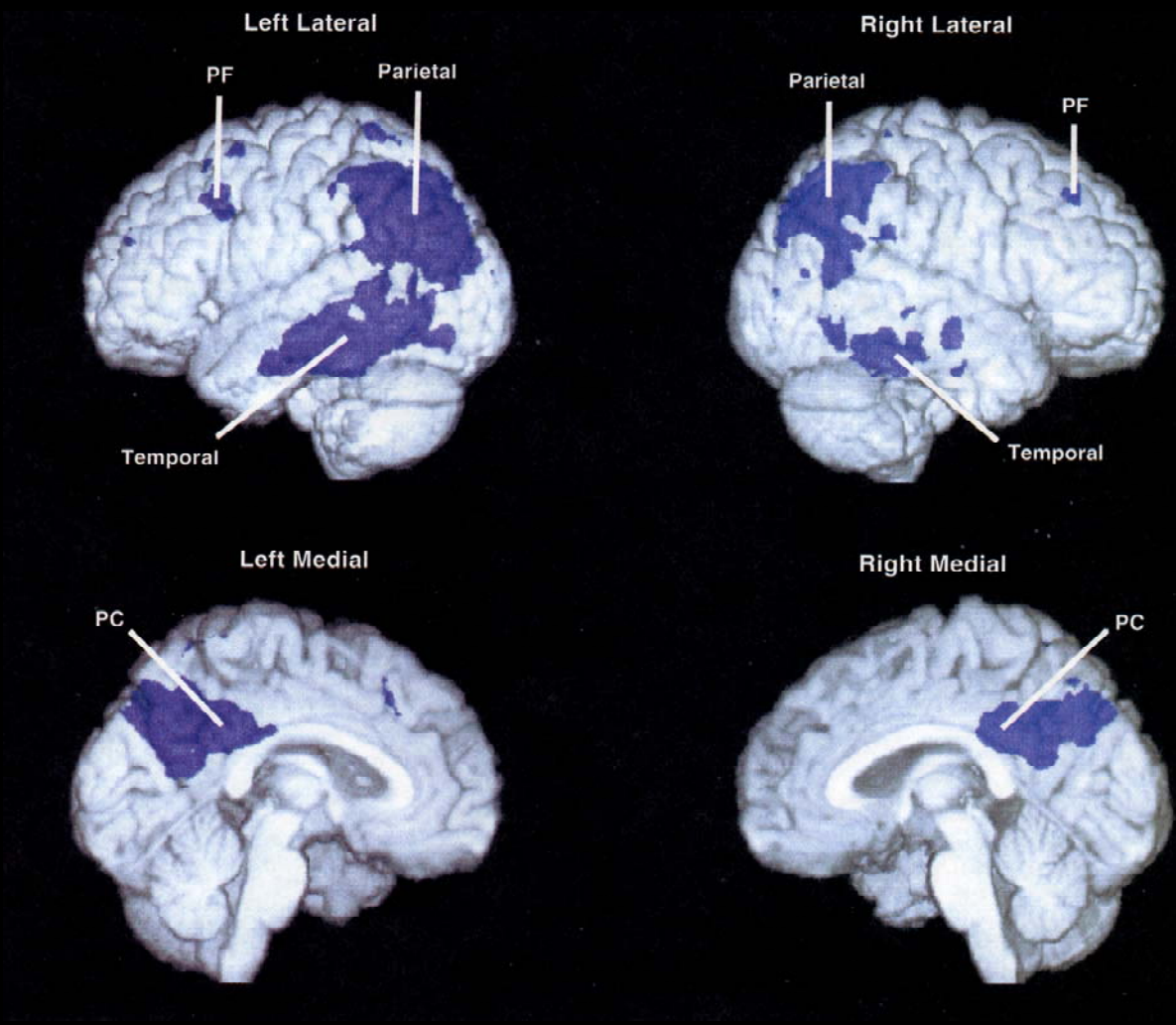
[15O]-labeled water and oxygen used in quantification of oxygen consumption.

2. Carbon - HL is 10.0 mins.

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

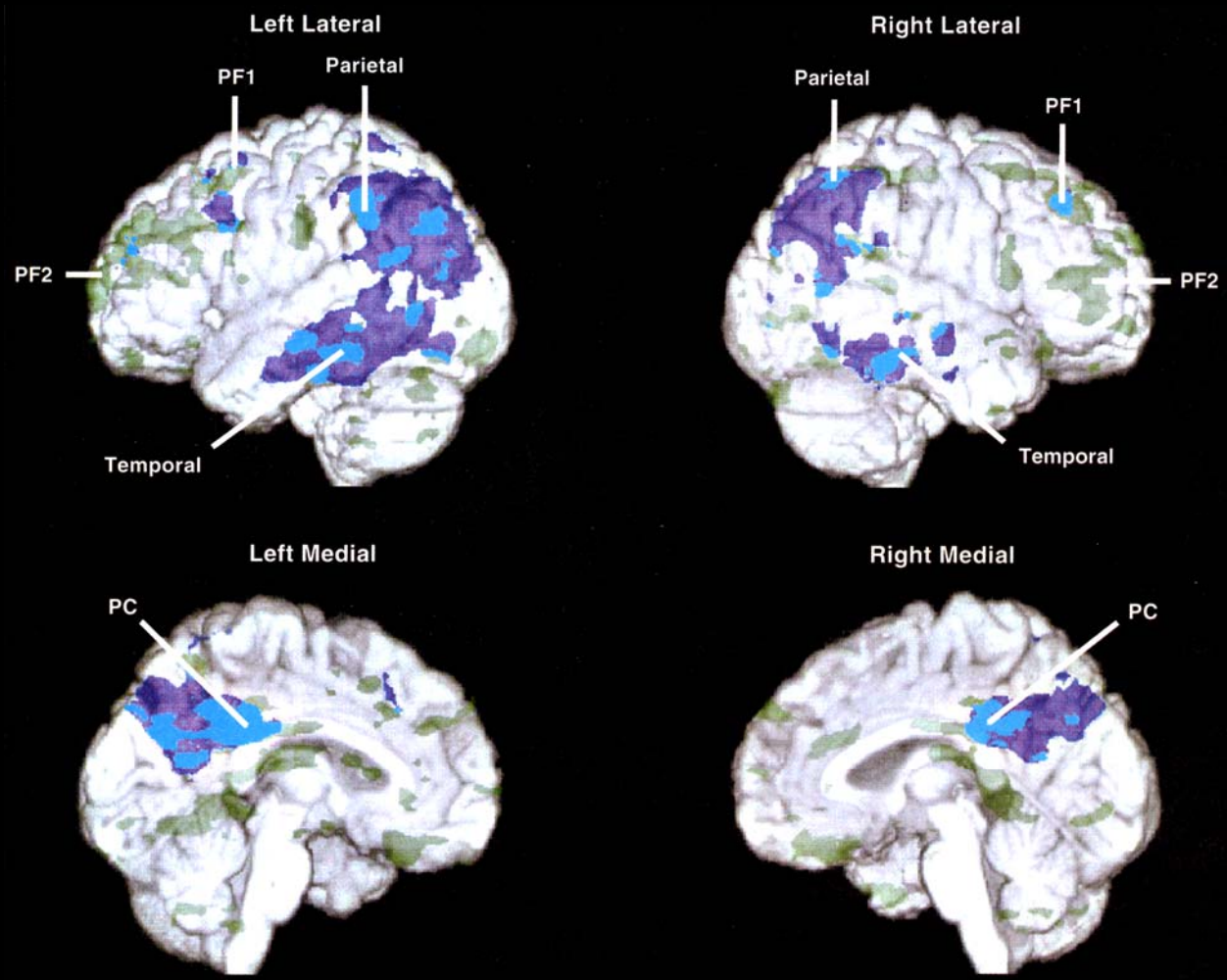
3. Flourine - HL is 109 mins.

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

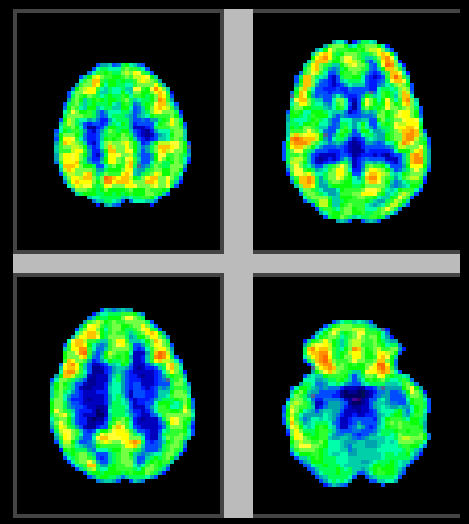


Preclinical detection of Alzheimer's disease:

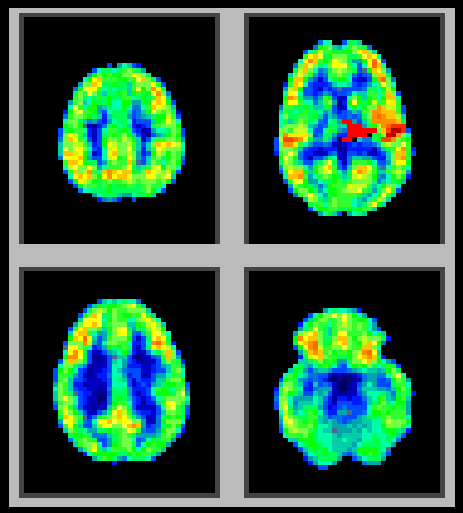
Reiman et al. (1996): Regions of brain with reduced rates of glucose metabolism in 37 patients with early stage probable AD.



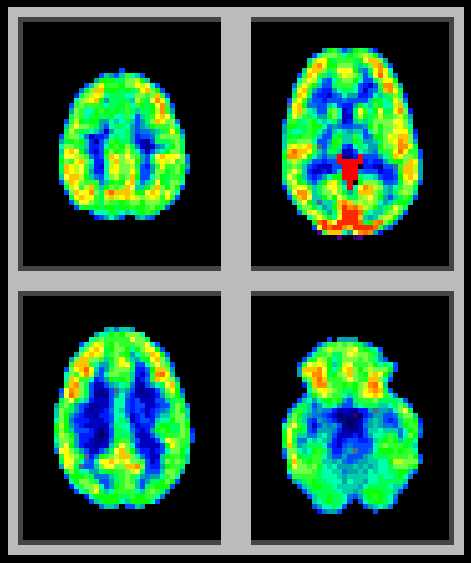
Regions of brain with reduced rates of glucose metabolism in 11 e4 homozygotes (light blue) and their relation to patients with probable AD (purple); Reiman et al., 1996.



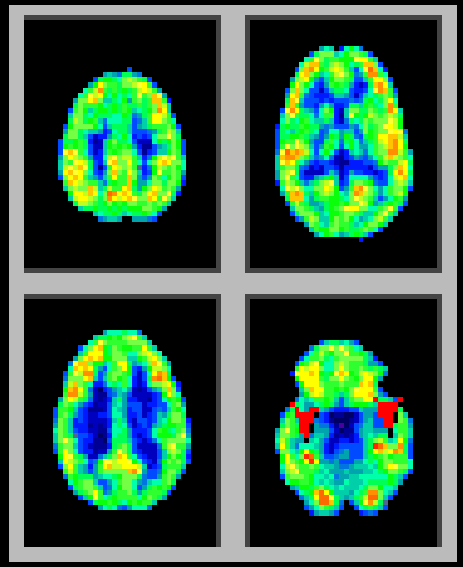
Rest



Motor

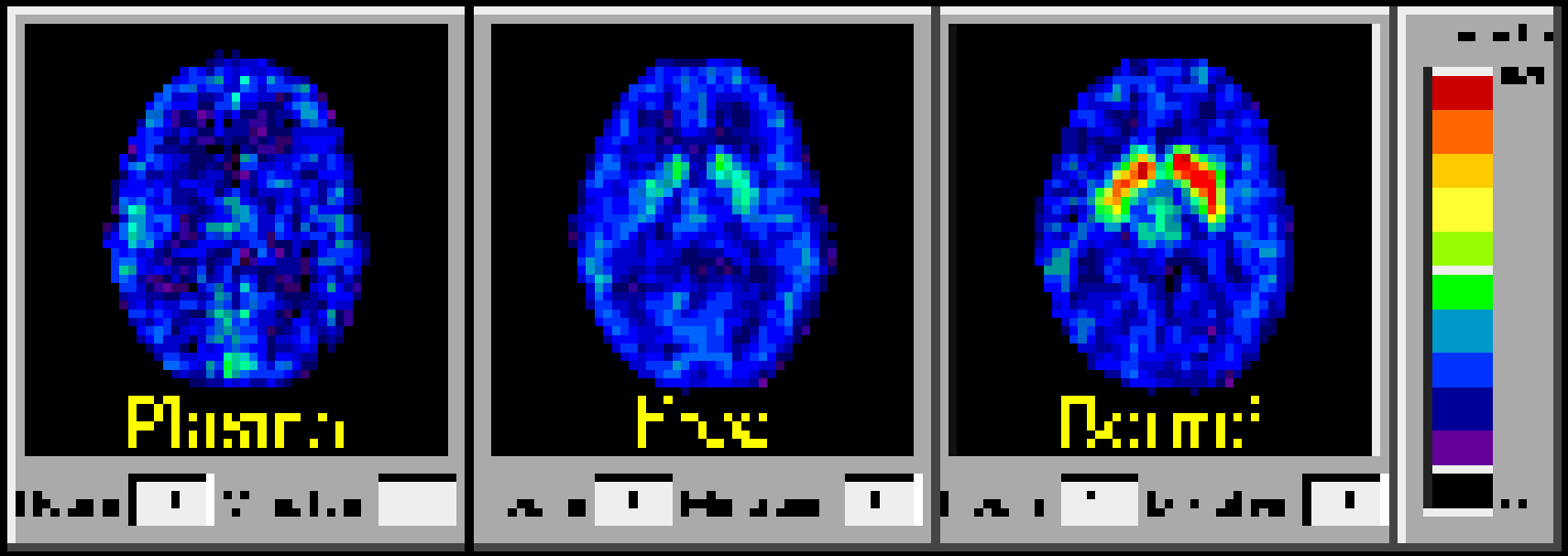


Visual



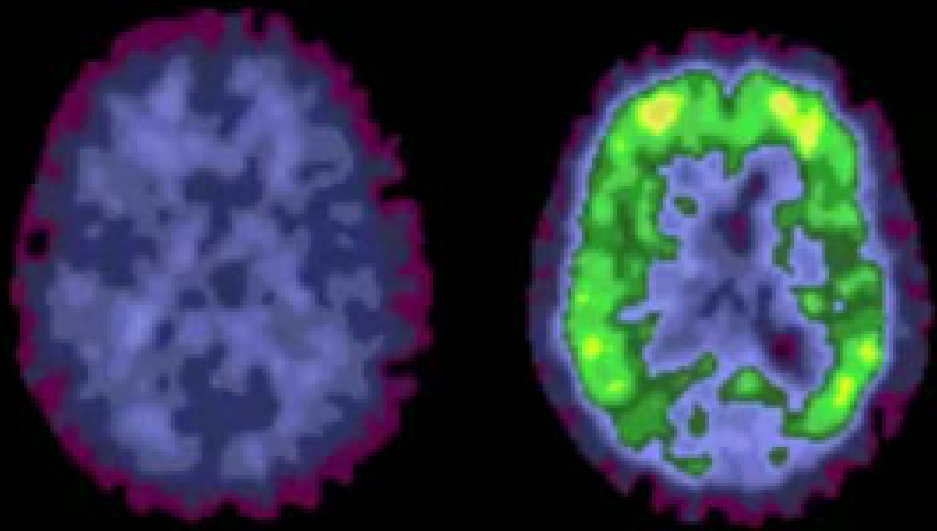
Recall

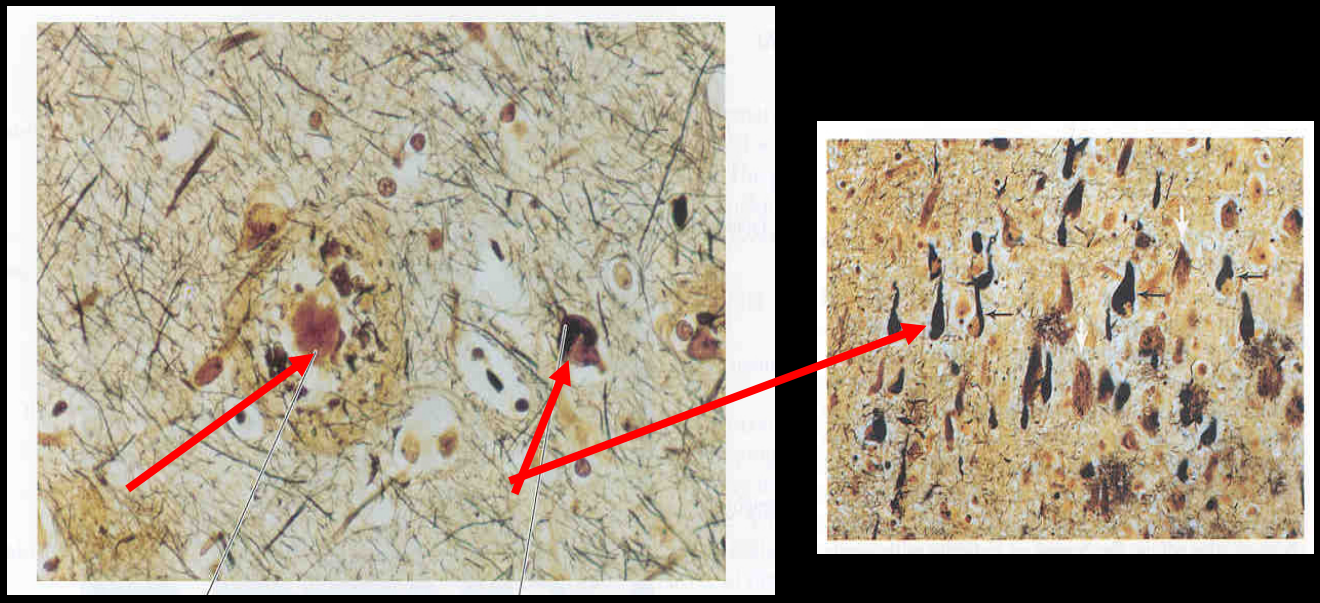
PET can be used to measure regional brain activity, similarly to fMRI, using subtraction designs.



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).





Plaques & Tangles