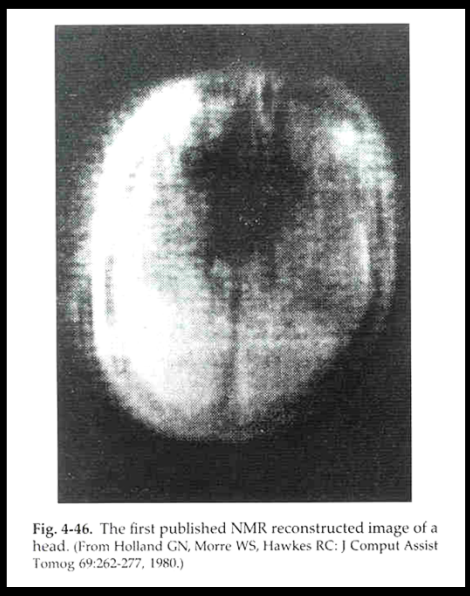
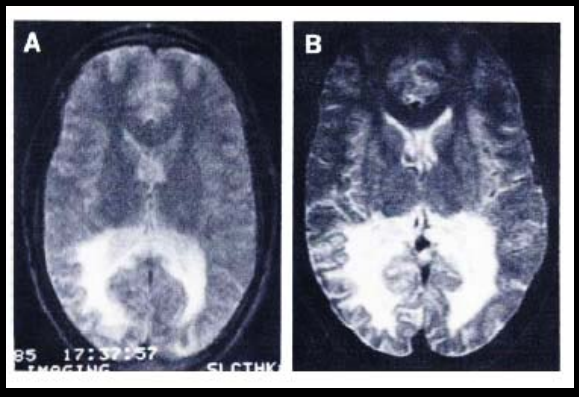


Fig. 4-46. The first published NMR reconstructed image of a head. (From Holland GN, Morre WS, Hawkes RC: J Comput Assist Tomog 69:262-277, 1980.)

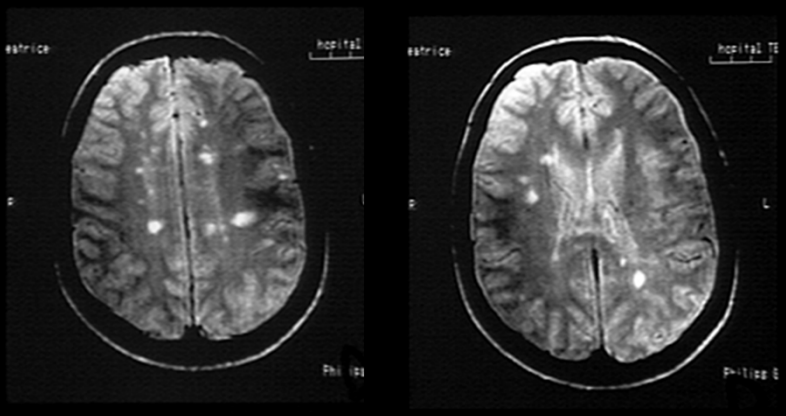
First published NMR image of the head (Holland et al., 1980)

FDA approved for clinical use, 1985.



1985 1986

FDA approved for clinical use, 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 computerized tomography: 10 to 1

Nuclear magnetic resonance

- When an electromagnetic (EM) pulse is applied to a nuclei in a magnetic field, the nuclei absorb energy from the EM pulse and radiate this energy back out again.
- The energy radiated back out is at a specific resonant frequency which depends on the number & types of nuclei, and the strength of the magnetic field.
- This allows the observation of specific quantum mechanical magnetic properties of an atomic nucleus.
- Many scientific techniques exploit NMR phenomena to study crystals and non-crystalline materials through *NMR spectroscopy*.

National laboratory's high magnetic field (18.8T) NMR spectrometer.

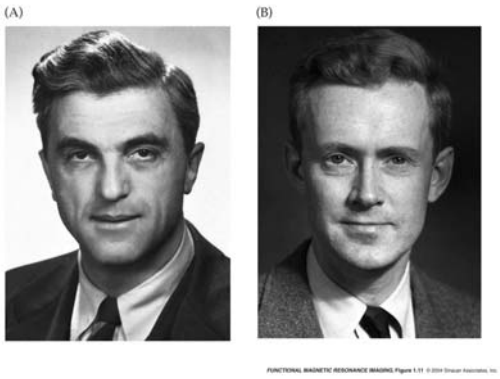
Magnetic resonance imaging

- A medical imaging technique using the principles of NMR to visualize structure and function of the body.

MRI requires:

1. a strong static magnetic field
2. a series of oscillating electromagnetic fields (pulse sequence)
3. a radio frequency receiver to measure radiated energy.

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



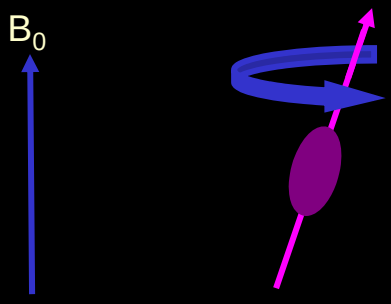
Felix Bloch and Edward Purcell: Nobel Prize in Physics, 1952: NMR

Bloch measured nuclear 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.

Nuclear magnetic resonance:

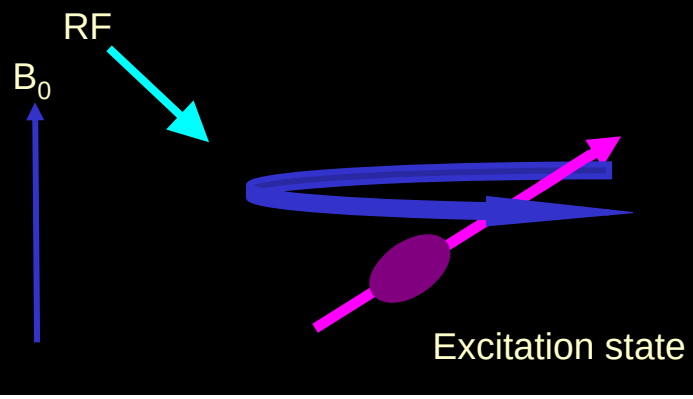
- *Step 1:* Atoms with an uneven number of protons act as dipoles. When placed in a strong static magnetic field, they will align with the field and precess around that axis.



Resting state

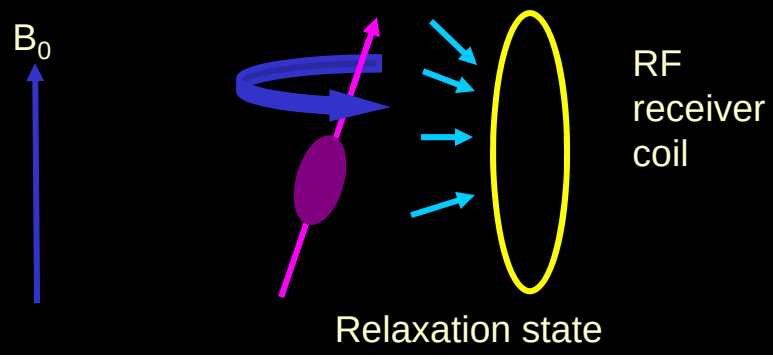
MRI Signal:

- *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:

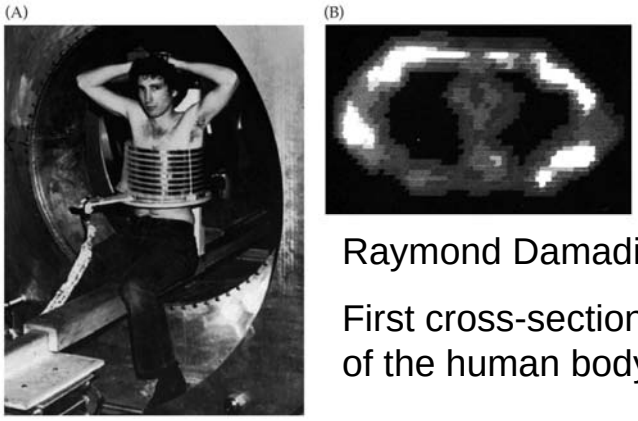
- *Step 3:* Turn off the RF pulse, and the molecule gives off the absorbed energy over time (relaxation rate), which can be measured with an RF receiver coil. This is *magnetic resonance.*



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
- Differential relaxation rates across tissue types will result in contrast – differences in signal intensity

The first MR image of the human body.

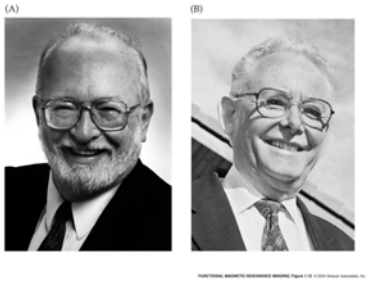


Raymond Damadian, 1977

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.

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

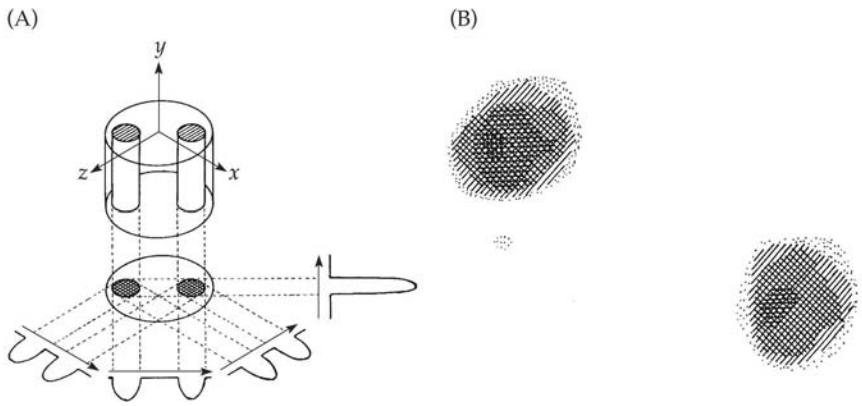


Paul Lauterbur and Peter Mansfield, Nobel Prize in Medicine, 2003: MRI

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.

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



A. 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.

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

The politics of science

- MRI 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, invented magnetic resonance imaging.

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.

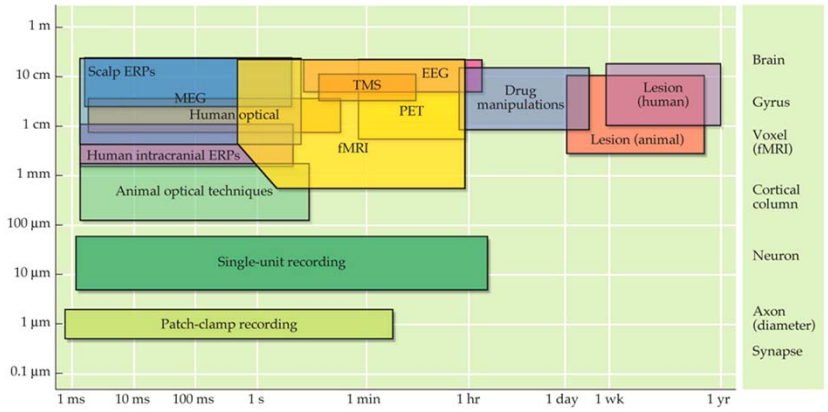
PET: Radioactive isotopes used to label metabolically active substances (glucose, oxygen, etc), injected, taken up by tissue, which then decay over time measured. Poor temporal and spatial resolution (also invasive).

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.

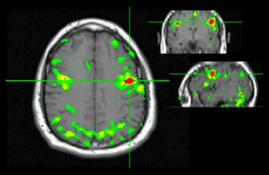
Diffusion MRI: Measures directional movement of molecules, tractography, identifying pathological conditions.

Neuroscience techniques differ in their spatial and temporal resolution.



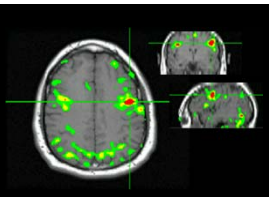
Where does fMRI fit? Functional measurement techniques compared by spatial and temporal resolution.

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

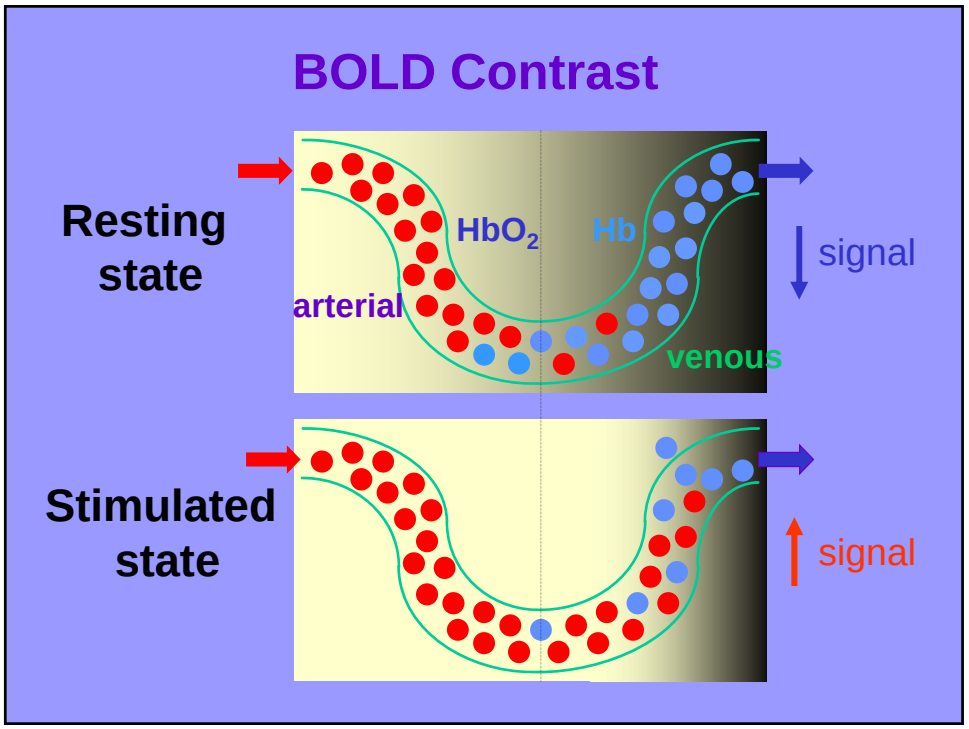
→ Uptake of O_2 less than supply

→ Surplus oxygenated hemoglobin

→ Decreased concentrations of deoxyhemoglobin

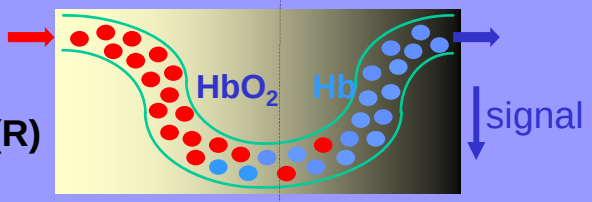
→ **Increased local fMRI T2* signal**

BOLD Contrast

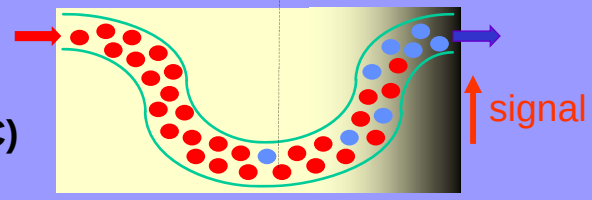


Determining Activation: A subtraction measure

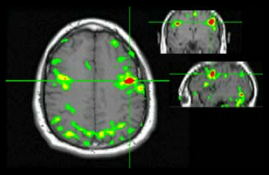
Subject is scanned at rest (R)



Subject is scanned during cognitive task (C)



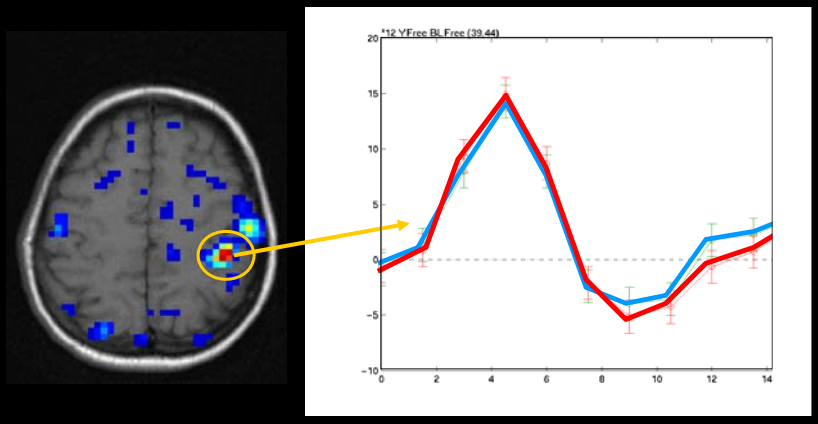
Regions of activity are determined the *differences* between scan R from scan C.



Caveats regarding fMRI:

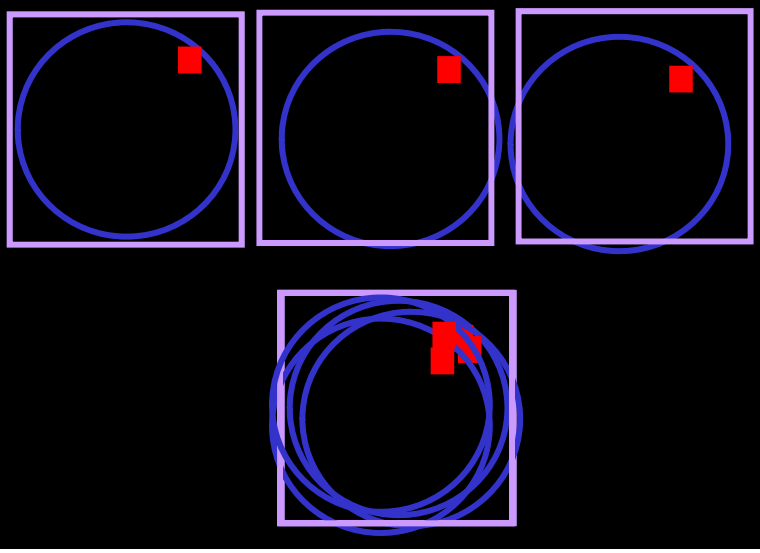
- Tertiary measure of neuronal activity.
- Very small signal changes, on order of 1 to 3%.
- Signal change predominates in region of large draining veins, not gray matter, and may vary in locality.
- Extremely sensitive to motion.
- Hemodynamic response is delayed – 15 msec scan, but 10-12 sec response (remember the Nyquist frequency?)

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



Motion: The magnetic field is static, but your subject is not….

time



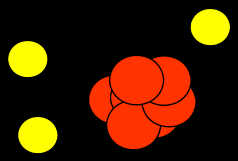
Positron emission tomography

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

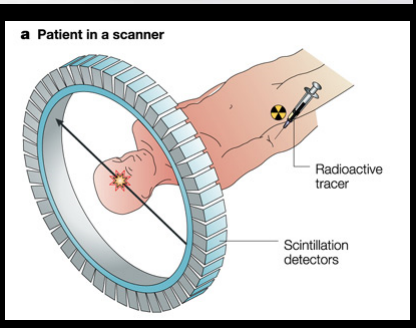
Isotope is connected to the compound of interest (such as oxygen or glucose) and injected.

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.

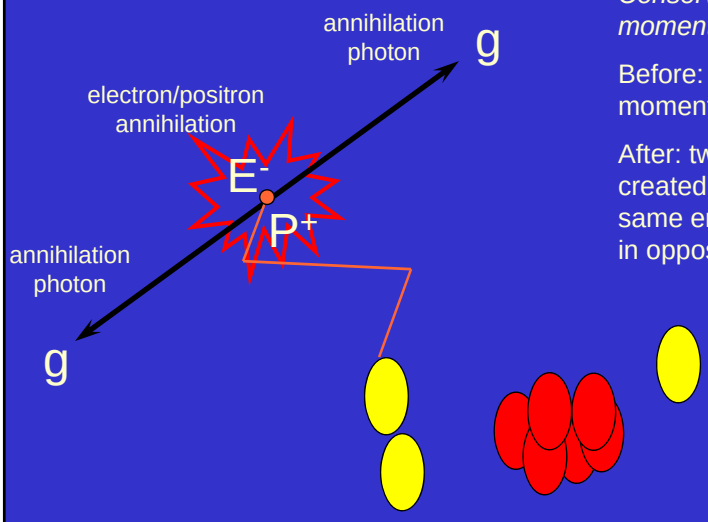


A cyclotron is used to create the isotope, adding additional protons to molecules of interest, such as oxygen, glucose, etc.



The radioactive isotope is injected into the subject, and is taken up by the brain into metabolically active regions. Detectors measure events as the isotope decays.

Annihilation: Decay via positron emission



Conservation of momentum:

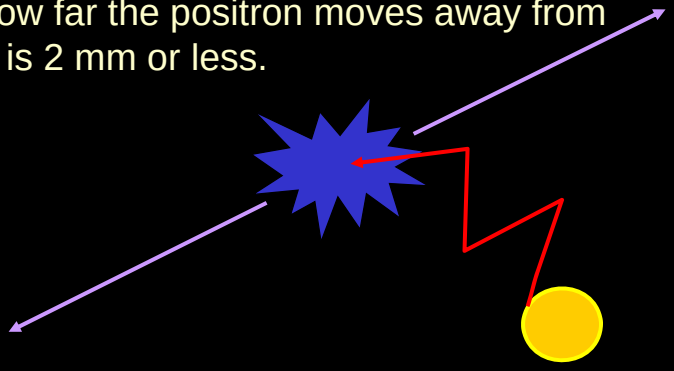
Before: system at rest; momentum ~ 0

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

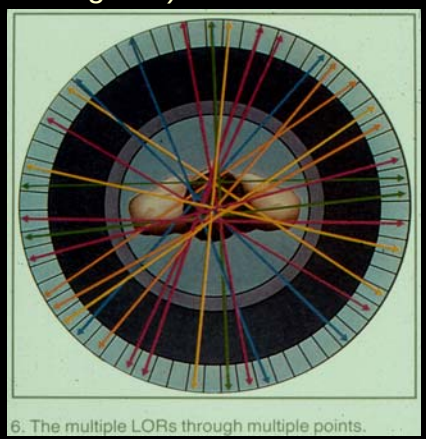
Scatter (how far the positron moves away from molecule) is 2 mm or less.



Coincident detection

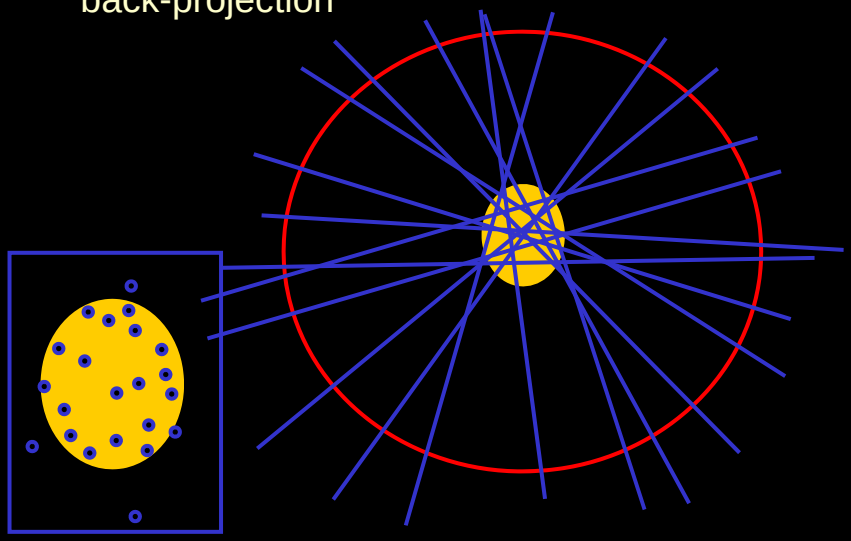
Scintillating crystal detectors in circumferential arrays, measure coincident events only.

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



6. The multiple LORs through multiple points.

Tomographic problem, reconstruction using back-projection



PET tracers:

1. Oxygen - HL is 1.5 mins.

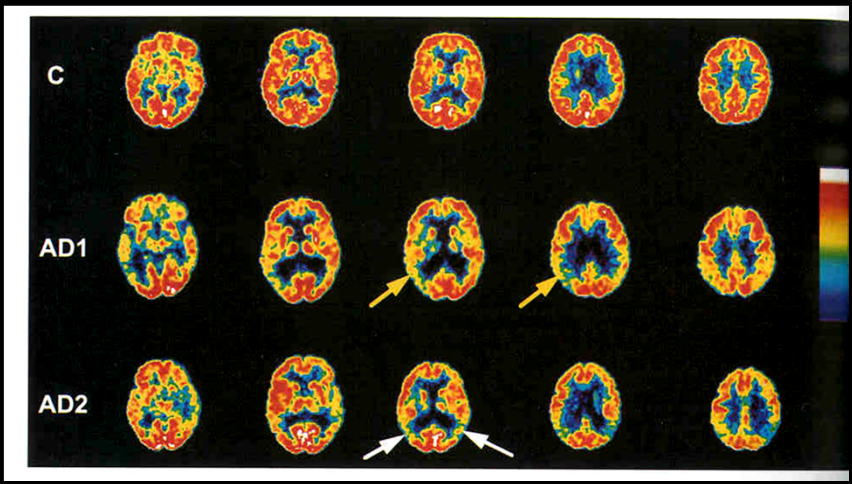
[15O]-labeled water and oxygen used in quantification of oxygen consumption.

2. Carbon - HL is 10.0 mins.

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

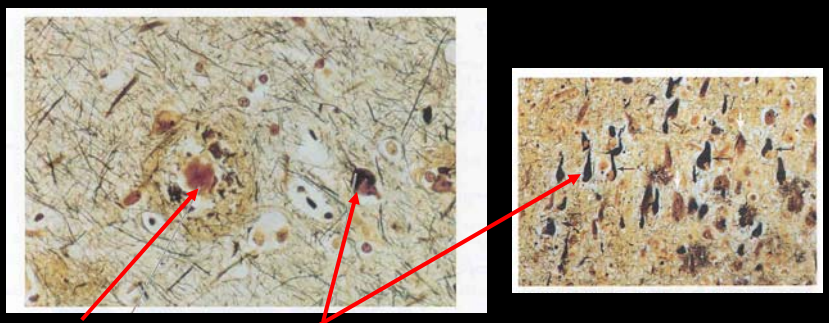
3. Flourine - HL is 109 mins.

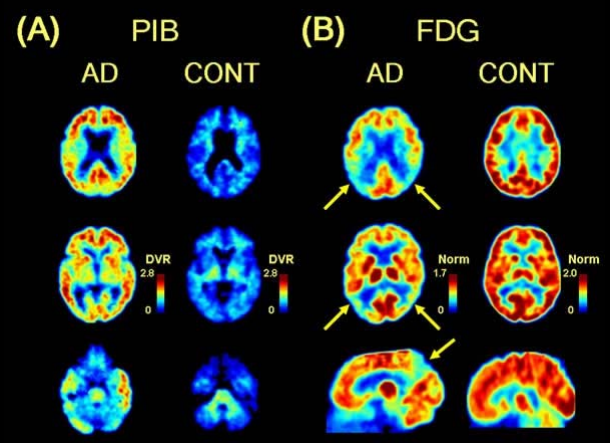
[18F]-2-deoxyglucose (FDG) most often used in activation studies. Also used to label L-Dopa and fluoroethylspiperone which bind to D2 dopamine receptors.



PET scans from a normal aged subject and two patients with probable AD. AD1 has a asymmetric metabolic lesion. AD2 shows decreased glucose metabolism bilaterally, also with a posterior distribution.

Measuring the pathology of AD: New tracer for A beta protein can measure the extent and distribution of plaques in human brains (University of Pittsburg)





(B) FDG images showing decreases in posterior regions for glucose metabolism in AD patient compared to control.
A) PIB imaging showing increased deposition of beta amyloid in the same AD patient compared to the control.

Voxel based morphometry

Basic Premise:

Spatial Normalization into standard space

↓

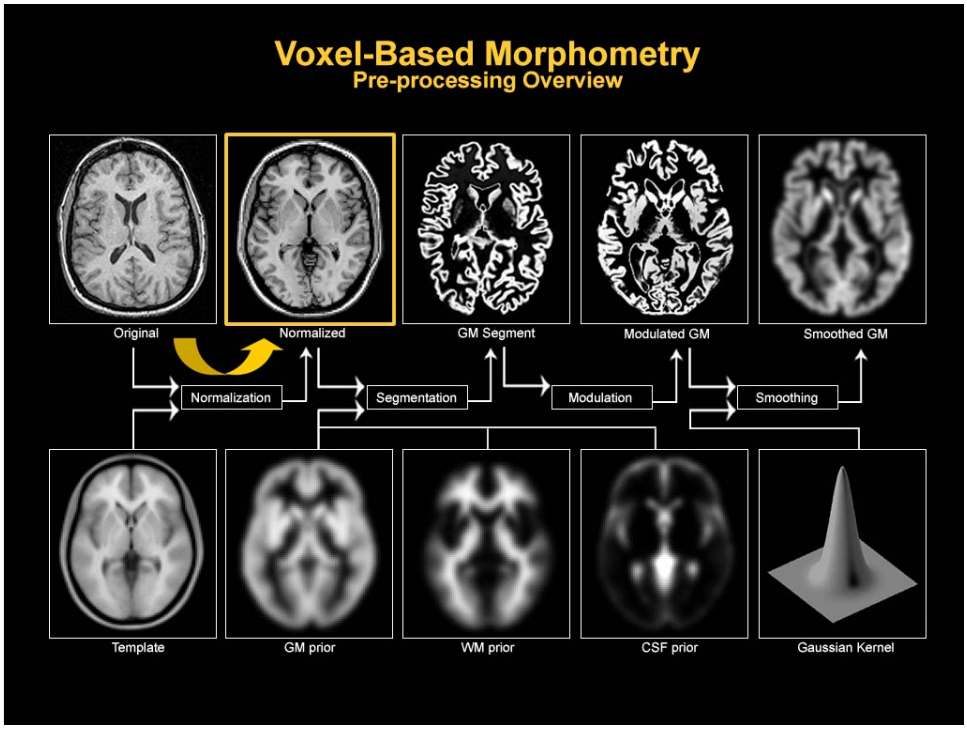
Segmentation of tissue classes

↓

Smoothing

↓

Voxel-wise parametric tests



Segmentation – Example final maps

T1 gray white CSF

Advantages

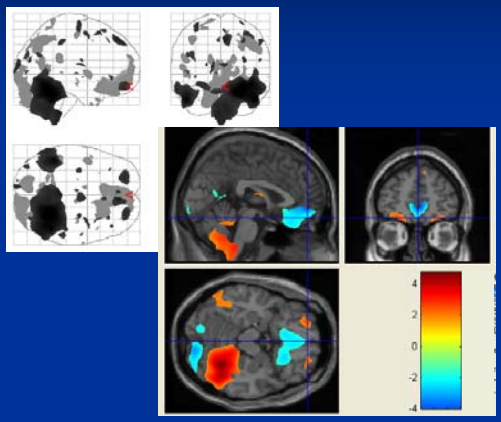
- Automated: fast and not subject to individual bias.
- Able to examine regions that are not anatomically well defined.
- Able to see the whole brain rather than choosing specific regions.
- Can be normalized for overall differences in brain volume, but also small regional variations in volume which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

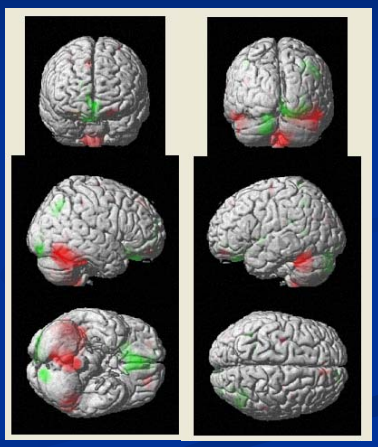
Disadvantages

- Crucially depends on accurate normalization.
- Shape errors: Gray matter sulcal folding patterns are very heterogeneous, thus registration is always poor.
- Crucially depends on a priori probability maps – which template do you use?
- Assumes normal gray-white contrast which is disrupted in presence of pathology and young/old.
- Assumes brain is gray, white, CSF, no model for strokes or tumor.
- Looks for differences in volume, which can be disrupted if shape of brain is different: problem for developmental disorders, aging.

Correlation between BMI and Gray Matter Volume

- p.05
- Covariate: Age, AI drug use, Hypertension, ICV



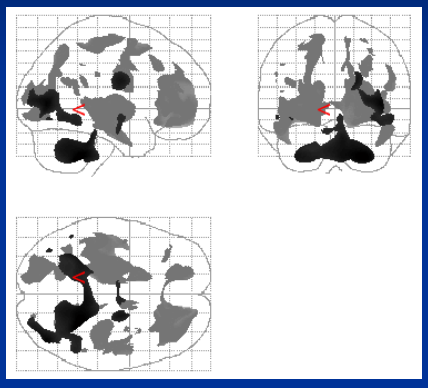


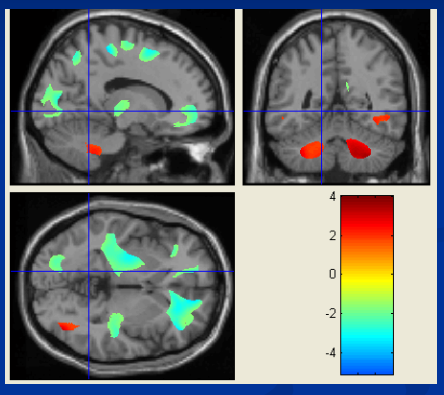
Decline Volume with Increasing BMI

Increase Volume with Increasing BMI

Correlation between BMI and Gray Matter Volume

- Multiple regression p.05
- Covariate: Age, AI drug use, Hypertension, ICV





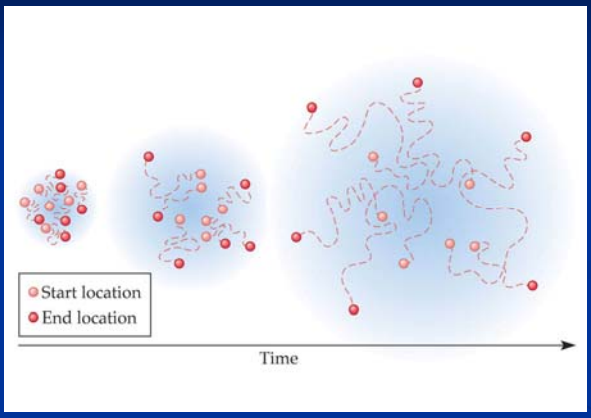
Decline Volume with Increasing BMI

Increase Volume with Increasing BMI

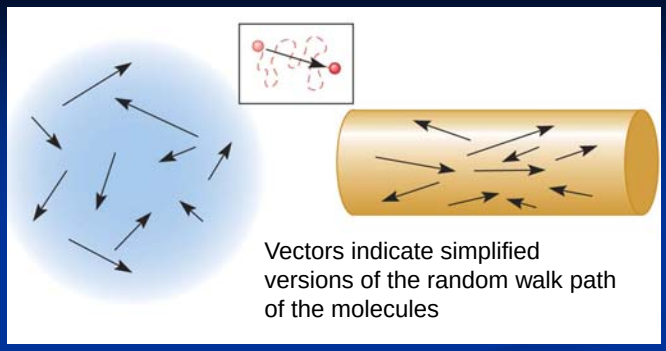
Diffusion-Weighted MRI

- Measures motion of water molecules
- It is sensitive to microstructural changes in gray and white matter
- Clearly identifies myelinated axons
  - Can be used to create maps of white matter tracts
- A measure of edema
  - Assessing strokes and other damage to brain tissue

- Diffusion. Over time, molecules within gases or liquids will move freely through the medium.



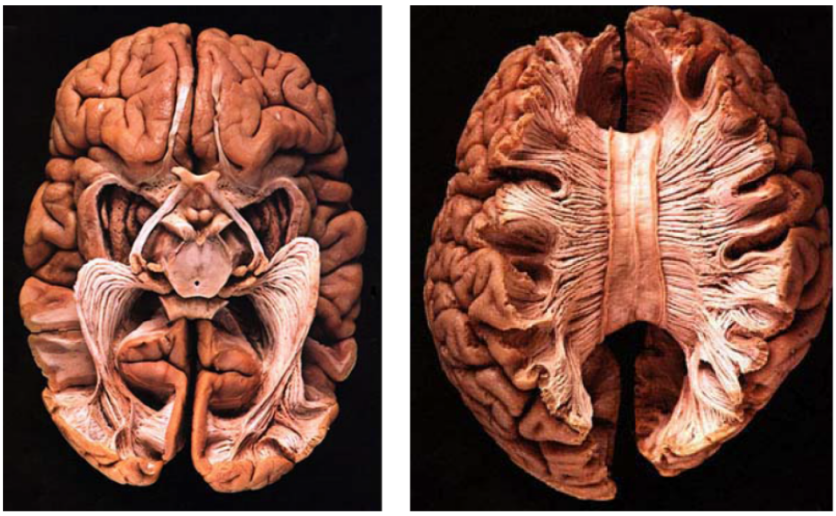
- MRI diffusion-weighted gradient causes changes in the MR signal that are dependent upon the amplitude and direction of diffusion



Vectors indicate simplified versions of the random walk path of the molecules

- 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

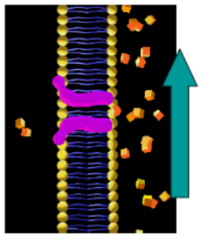
The White Matter



From: The Virtual Hospital (www.vh.org); TH Williams, N Gluhbegovic, JY Jew

H_2O Diffusion Probes Microscopic Structures In the Brain

Along the axon, within the cytoskeleton, there is a large Apparent Diffusion Coefficient (ADC)

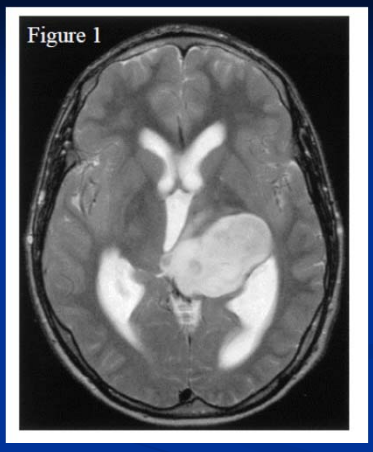


Measures:

- Density of axons
- Degree of myelination
- Average fiber diameter
- Directionality of axons

Mean Diffusivity (MD) summarizes diffusion in all directions

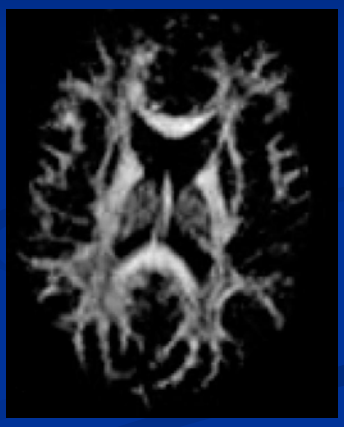
- Diffusion-weighted imaging common for clinical applications
- Measurements in only three directions



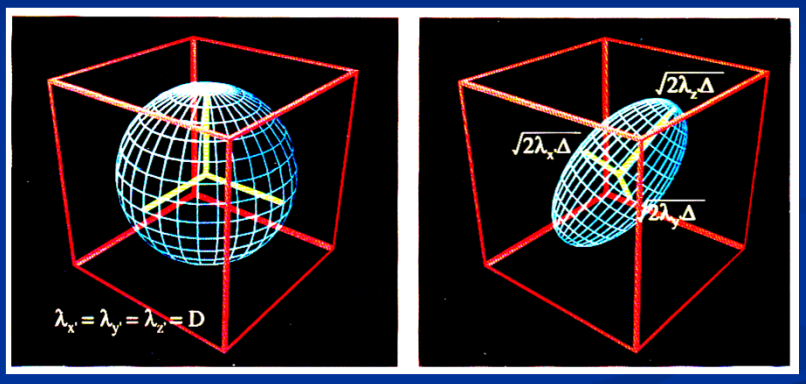
Fractional Anisotropy (FA)

- Measure of degree of anisotropy regardless of direction
- Brighter areas correspond to areas with high degree of diffusion

$$FA^2 = \frac{(l_x - l_y)^2 + (l_x - l_z)^2 + (l_y - l_z)^2}{2(l_x^2 + l_y^2 + l_z^2)}$$



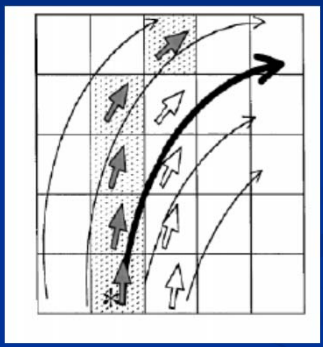
Tensor Model of Isotropy



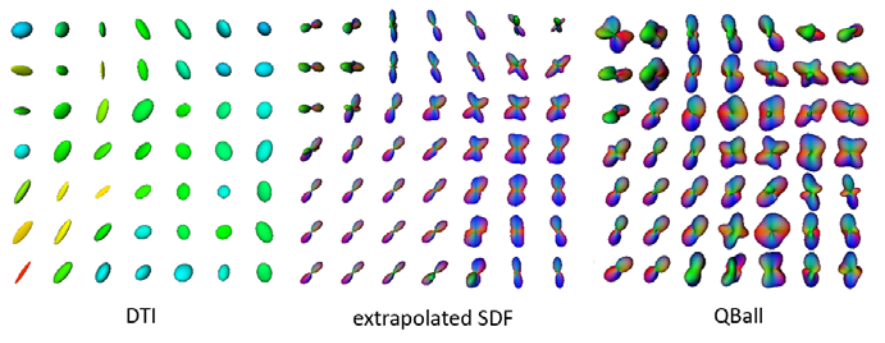
Isotropic **Anisotropic**

Fiber Assignment by Continuous Tracking FACT (Mori et al., 1999)

- Starting in a seed voxel, move to voxel edge in highest direction
- Use tensor from next voxel
- Continue until the next edge (with variable step size)
- Paths fall between data samples: separates tensor sampling resolution and path resolution



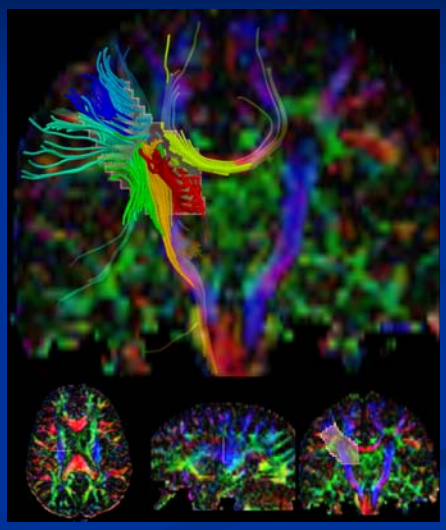
High-angular-resolution diffusion imaging and Q-ball vector analysis (Tuch)



- HARDI is a MRI imaging technique that is able to better capture the intra-voxel diffusion patterns.
- Instead of assuming a single ellipsoid, it considers multiple directions of fibers within a voxel
- Probabilistic tracking through multiple adjacent voxels

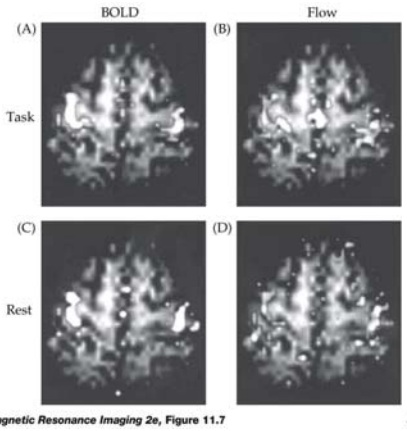
Diffusion tensor MRI -- Tractography

- 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)
- Requires very high numbers of directions (very minimum is 6 directions), small voxels (high resolution), extremely long imaging times



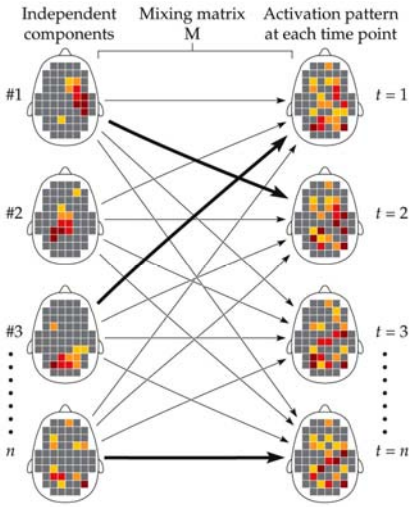
Resting state connectivity: Similar patterns of resting-state and task-related functional connectivity shown by Biswal et al. (1997)

Most often done by seed analysis during the task – asking which voxels are most strongly covarying with a voxel from a particular region



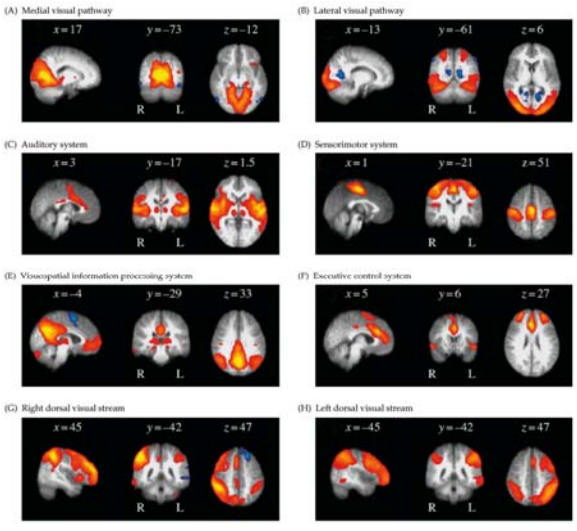
Functional Magnetic Resonance Imaging 2e, Figure 11.7

Resting state connectivity: Identifying stationary sets of voxels whose activity covaries across time and are maximally distinguishable from other sets of voxels.



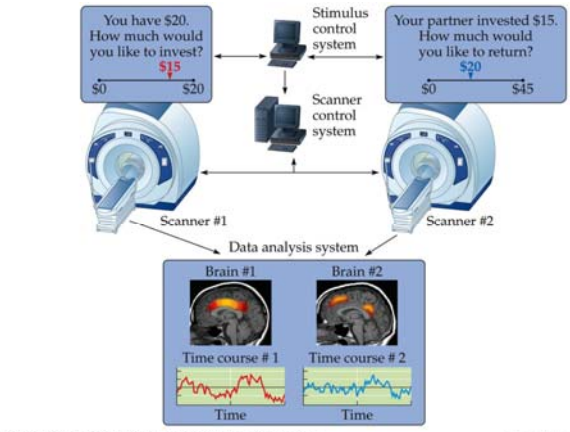
Functional Magnetic Resonance Imaging 2e, Figure 11.2

Using ICA to identify brain networks showing high resting-state connectivity (Beckmann et al., 2005)



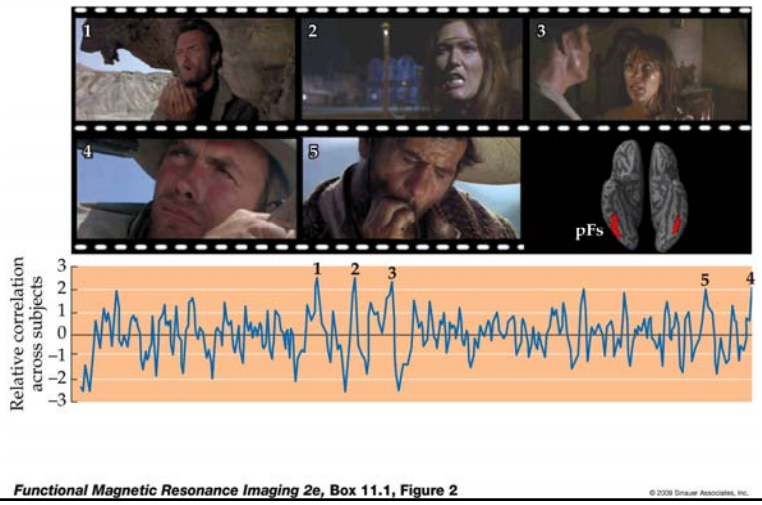
Functional Magnetic Resonance Imaging 2e, Figure 11.4

Hyperscanning fMRI: Two or more participants are scanned at the same time, scanners linked in time – allows more traditional experiments to occur, real interactions between subjects



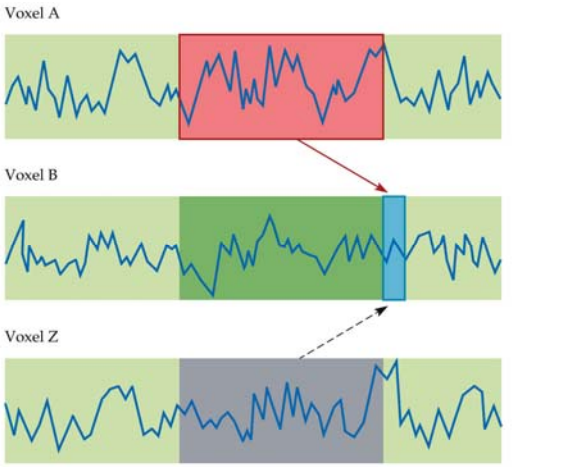
Functional Magnetic Resonance Imaging 2e, Figure 11.5

Free viewing: (Hasson et al., 2004) Identification of movie content that resulted in correlations of brain regions between subjects: An example of reverse inference.



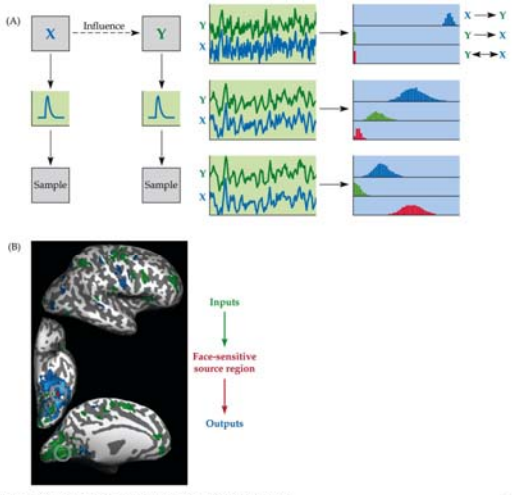
Functional Magnetic Resonance Imaging 2e, Box 11.1, Figure 2

Inferring causality across regions: Granger causality – when the activation in one region predicts subsequent activation in another region better than the same activation in the voxel of interest (B) or another reference voxel (Z).



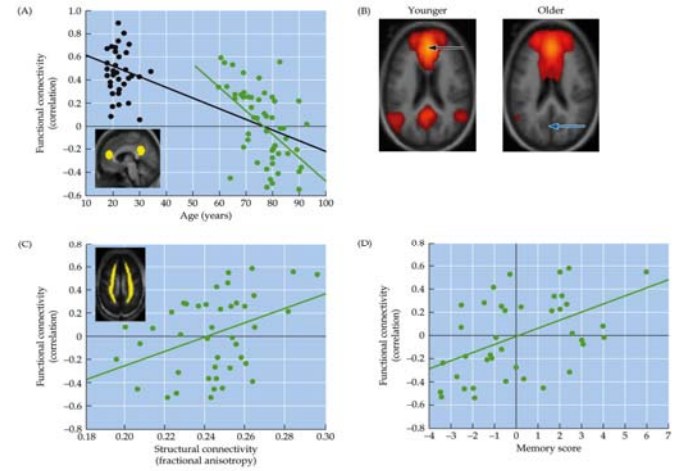
Functional Magnetic Resonance Imaging 2e, Figure 11.11

Roebroeck et al. 2005, showing input regions (X) that influence the output regions (Y) based on Granger causality analysis.



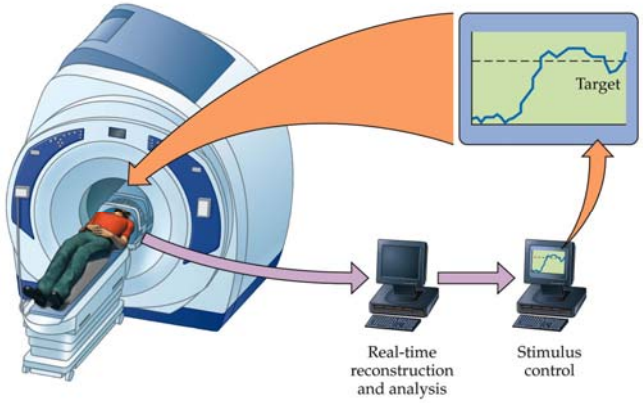
Functional Magnetic Resonance Imaging 2e, Figure 11.12

Combining functional and diffusion connectivity patterns in young and older adults.



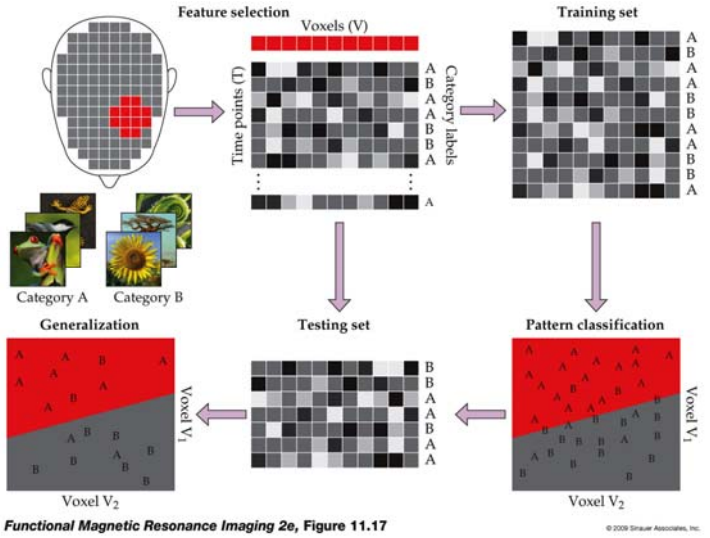
***Functional Magnetic Resonance Imaging 2e*, Figure 11.14**

Biofeedback in fMRI research: Using real-time reconstruction to provide information to subject – used to control emotional responses to stimuli, possibly teach older adults to engage frontal lobes....



***Functional Magnetic Resonance Imaging 2e*, Box 11.2, Figure 2**

Pattern classification: A conceptual overview of multi-voxel pattern classification of fMRI data



Functional Magnetic Resonance Imaging 2e, Figure 11.17