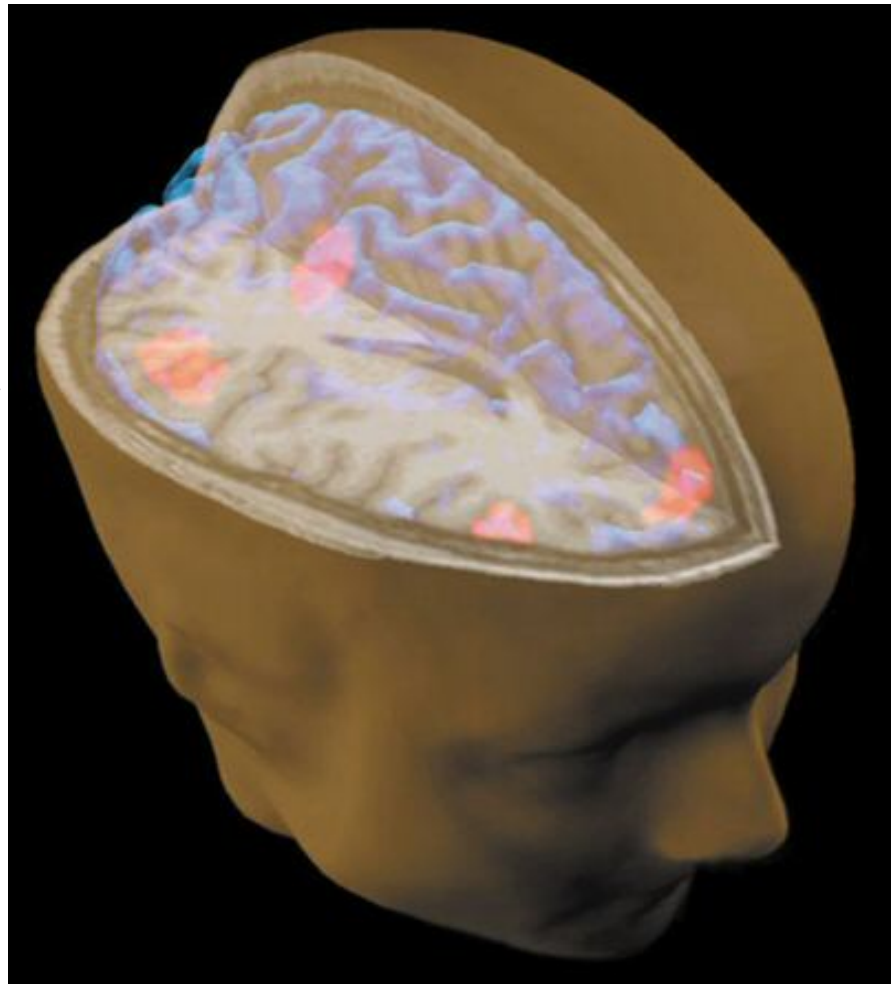
Functional Magnetic Resonance Imaging

fMRI



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Menu

- Introduction
- Some NMR Physics
- fMRI Hardware
- What fMRI really shows - BOLD Method
- Positives and Negatives of BOLD
- fMRI not BOLD Methods
- Discoveries and Results fMRI
- fMRI Software
- fMRI Data
- fMRI Analysis
- fMRI Visualization
- Fusion of Medical Imaging
- The future of fMRI

The Oxford physiologist Charles Sherrington made the observation that when a small area of exposed cat brain was stimulated electrically there is a flush of red blood.

This increases the blood supply to the brain locally, ensuring an adequate supply of oxygen to regions working harder in thinking.

IDEA!!

So, if we could measure the amount of oxygenated blood in a specific area we could have a measure of the underlined neural activity at this area.

Blood has a lot of water molecules and water molecules have a lot of hydrogen atoms that we can measure using MRI.

But what about oxygenation ? Oxygenation can be shown by T2*. Lets see why …

Decay (relaxation): *What Happens when the additional magnetic field is turned off?*

Spins begin to dephase…

$$M_{xy} = M_{xy_0}\, e^{-t/T2}$$

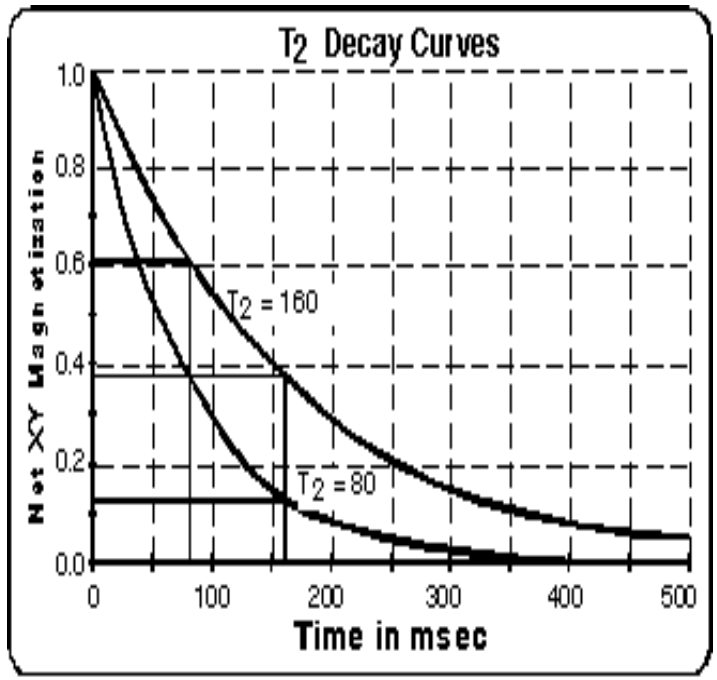
- At an Exponential rate defined by a certain formula

- This formula contains a different “Time constant” – T2

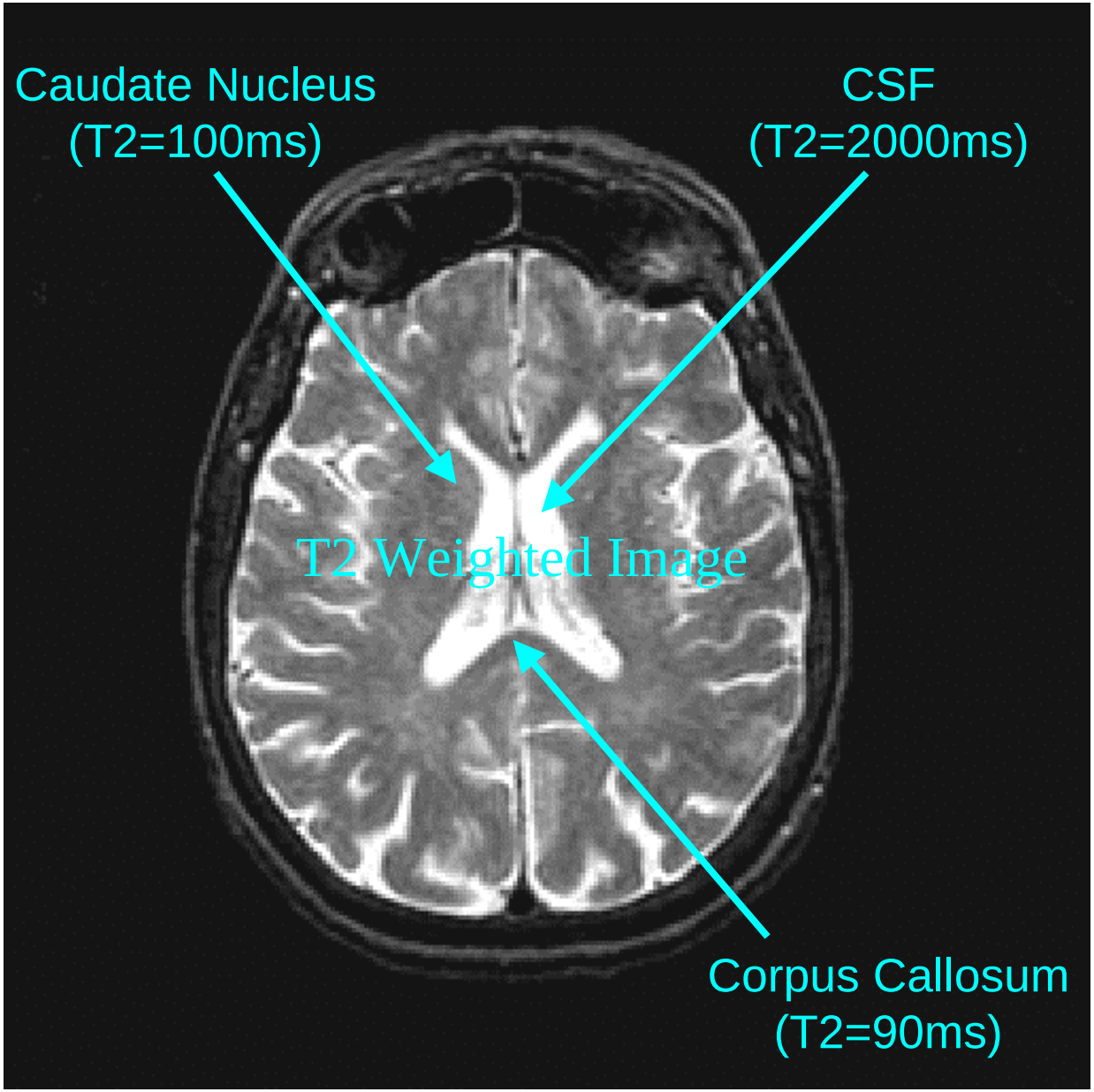
- Signal intensity decreases with decreasing T2

- The T2 rates are different for different tissues

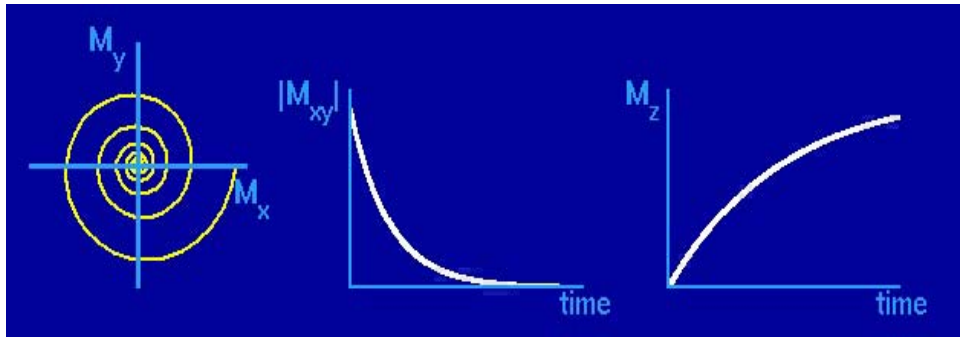
- The observed signal decay T2 is fast: a few msec to tens of msec



T2 Weighted Image



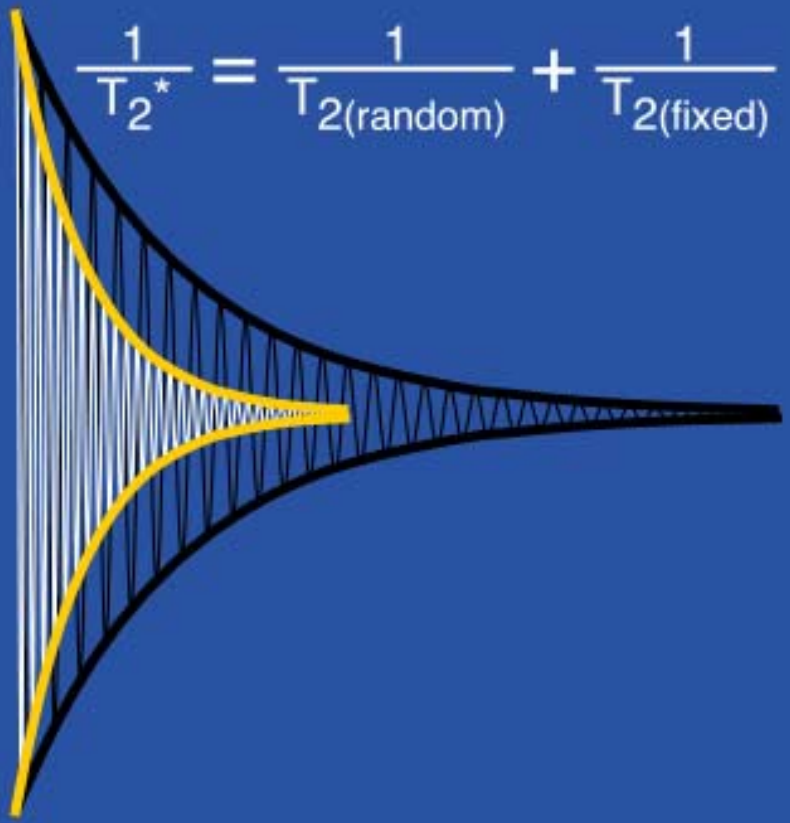
To sum up, Relaxation:



- In the real world, the NMR signal decays faster than *T2* would predict.
- There are many factors creating imperfections in the homogeneity of a magnetic field.
- Every tissue has a different magnetic susceptibility which distorts the field at tissue borders, particularly at air/tissue interfaces.
- The sum total of all of these random and fixed effects is called *T2**

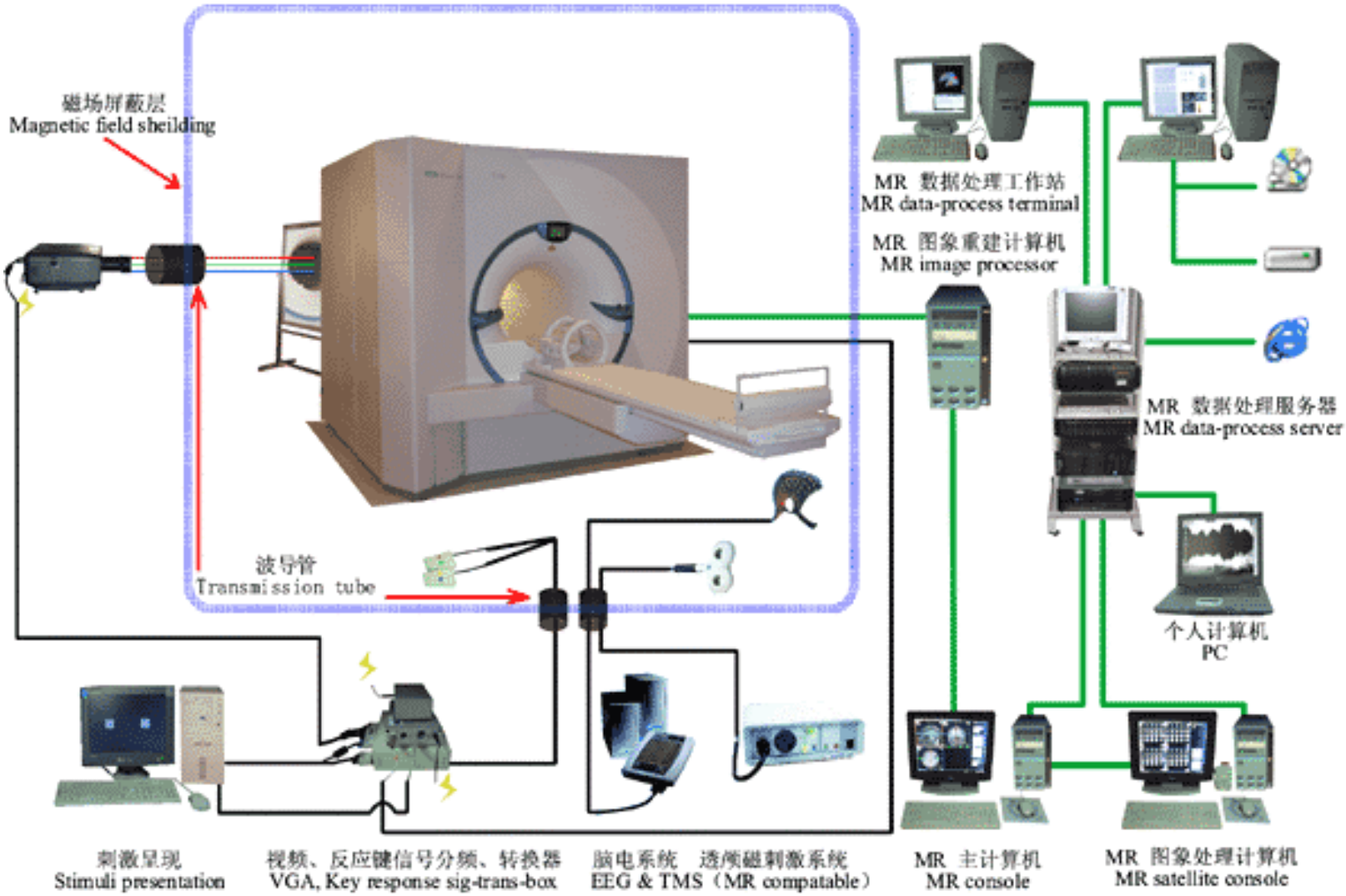
An Imperfect World - T_2^* Decay

$$\frac{1}{T_2^*} = \frac{1}{T_{2(random)}} + \frac{1}{T_{2(fixed)}}$$



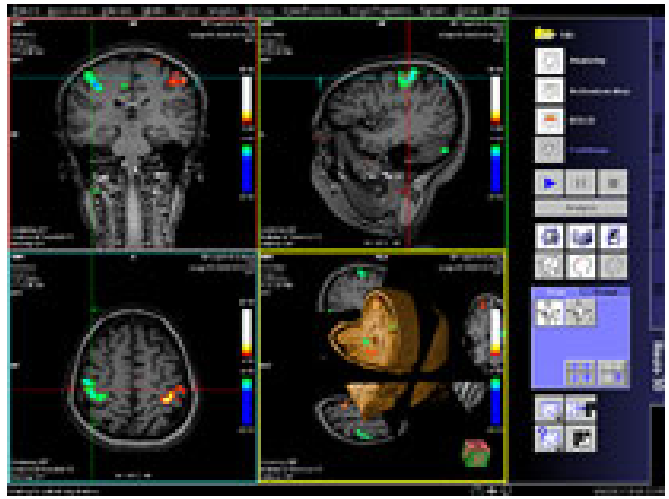
In the real world, the NMR signal decays faster than T2 would predict. Pure T2 decay is a function of completely random interactions between spins. The assumption is that the main external Bø field is absolutely homogeneous. In reality, there are many factors creating imperfections in the homogeneity of a magnetic field. The main magnet itself will have flaws in its manufacture. Every tissue has a different magnetic susceptibility which distorts the field at tissue borders, particularly at air/tissue interfaces. Patients may have some type of metal on or in them (dental work, clips, staples, etc.). The sum total of all of these random and fixed effects is called T2* (pronounced T - Two star).

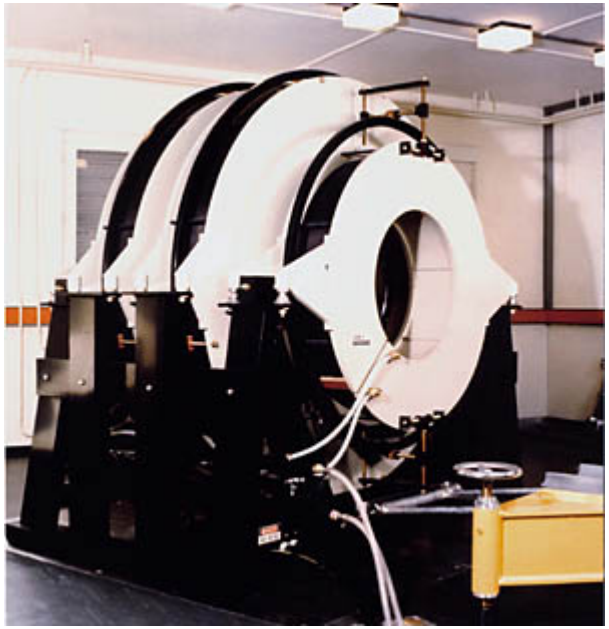
Hardware the basically the same as for simple MRI
Price about 1.6 million $ for 1.5 Tesla



The power of 3-Tesla (3T) MRI technology: "The magnetic strength is about 60,000 times as strong as Earth's magnetic field."

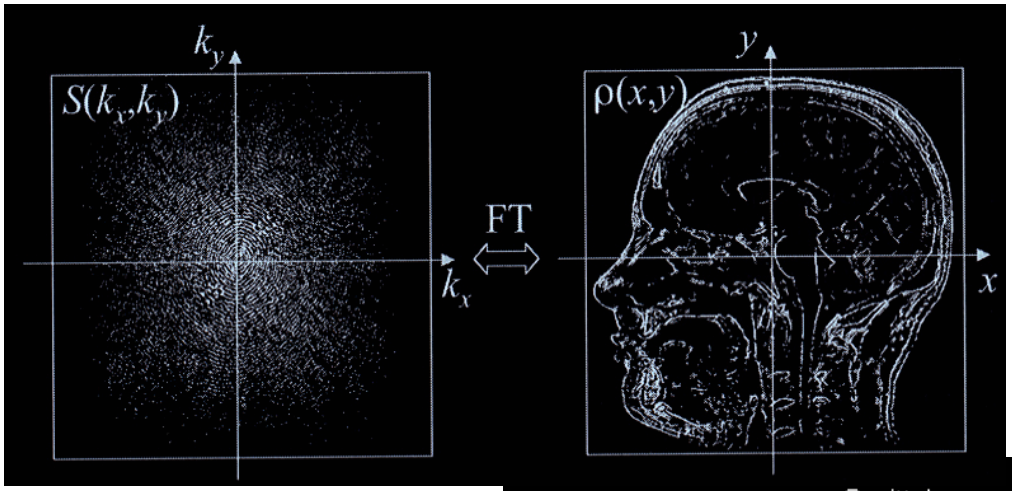
The magnet is supercooled ~ -270 degrees.





EPI & FLASH
Two Methods for Pulse Sequence Generation

The job of the particular pulse sequence is to navigate through the necessary (*kx* and *ky*) coordinates so that a signal can be collected at each point in k-space.



FLASH

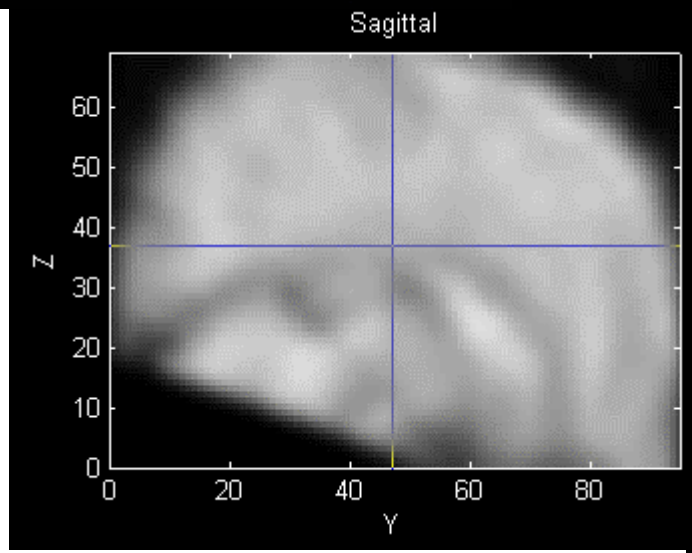
Fast Low Angle Shot

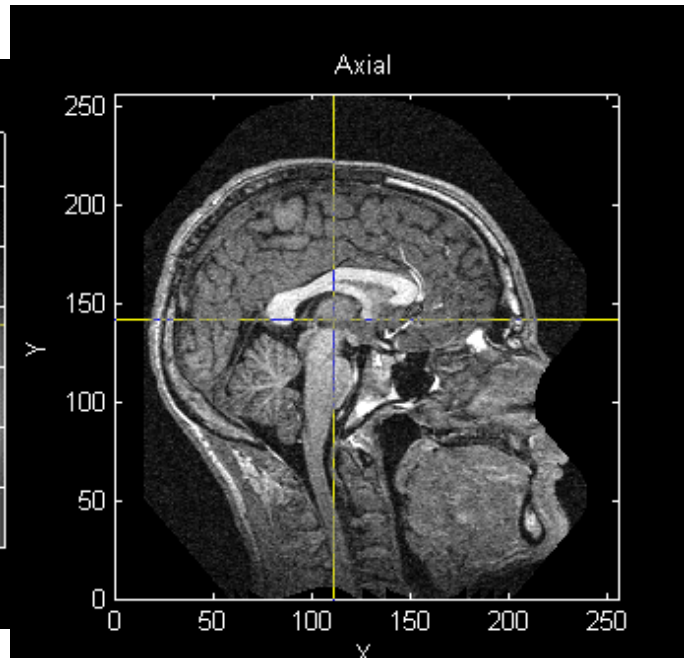
- 256x256 or 512x512 resol.
- 2.5 to 10 s per slice
- 60 to 240 s per volume

EPI

Echo Planar Imaging

- 64x64 or 128x128
- 30 to 50 ms per slice
- 2 to 6 s per volume





Ultra-fast BOLD fMRI

Ultra Fast Methods:
- Half-Fourier
- SENSE (Sensitive Encoding)
- SMASH (simultaneous acquisition of spatial harmonics)
- UNFOLD

'Block' paradigm

Which consists of alternated periods of activation (or task A) and rest (or task B). Each task is of roughly equal duration, typically the range 20-30 s.

'Single-event' paradigm

Much shorter periods of activation, alternated with longer periods of rest. Duration of activation can be about 6 s.

Given these time scales, why does one need ultra fast fMRI?

The answer relies in signal stability over time.

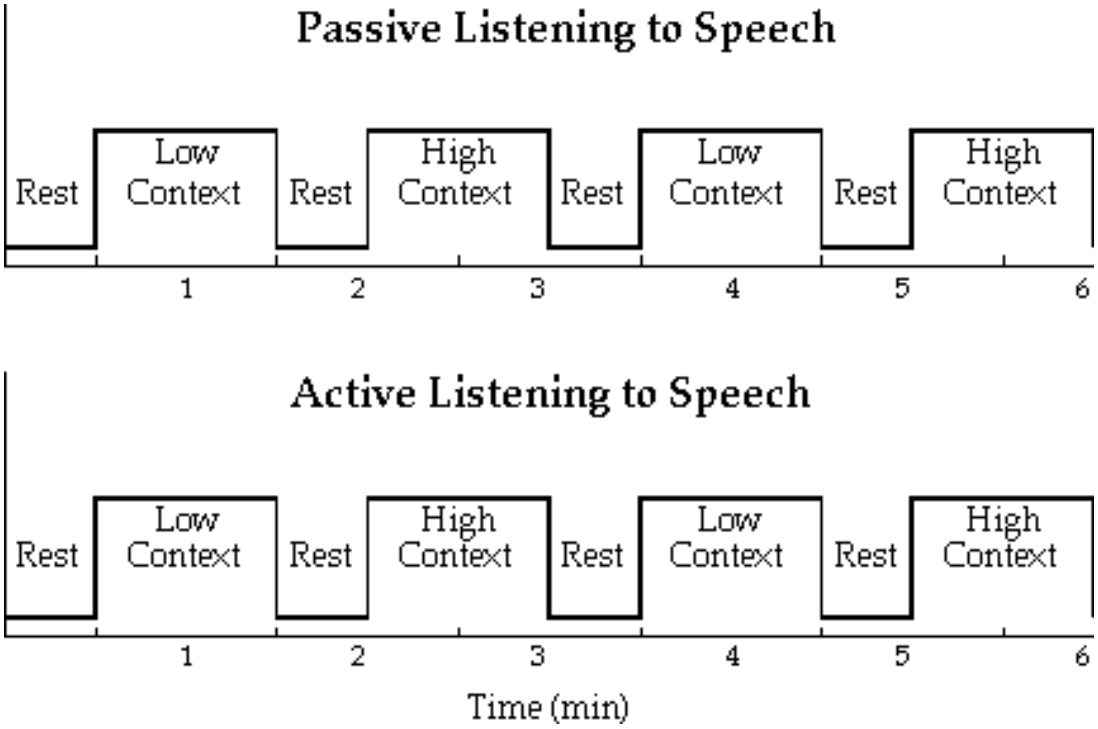
Signal Instabilities:
- Cardiac Cycle
- Respiratory motion
- Head motion

Why T2* and not T1?

MRI scanner is tuned to resonate and image hydrogen atoms as in conventional MRI; however, T2*-weighted images are performed which take advantage of the fact that deoxygenated hemoglobin is magnetic whereas oxygenated hemoglobin is not.

Because of the magnetic properties of the unflipped magnetic deoxyhemoglobin molecule which causes rapid dephasing, T2* signal is retained longer in a region when it has more oxygenated blood. Thus, an area with more oxygenated blood will show up more intense on T2*-weighted images compared to when there is less oxygenated blood around.

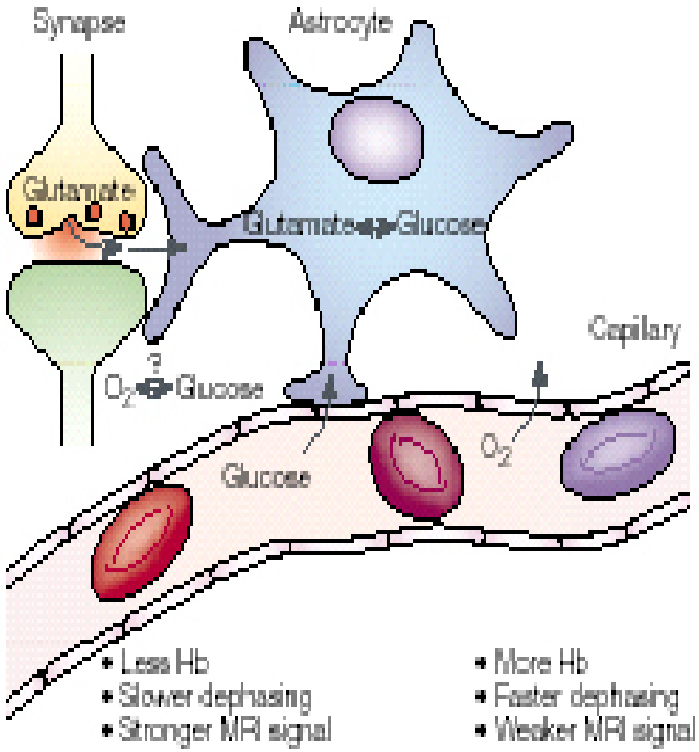
Design of fMRI Experiments



- fMRI-BOLD paradigms generally have several periods of rest alternating with several periods of activation.
- Images are then compared over the entire activation to the rest periods. Images over the first 3 to 6 seconds of each period are generally discarded due to the delay in hemodynamic response.
- Alternating paradims are used because the signal intensity generated by the MRI scanner drifts with time.

• fMRI-BOLD is best used for studying processes that can be rapidly turned on and off like language, vision, movement, hearing, and memory.

• The study of emotion is hampered by its slow and variable onset and its inability to be quickly reversed. Some have, however, succeed in using this technique to study fear (Whalen et al.)

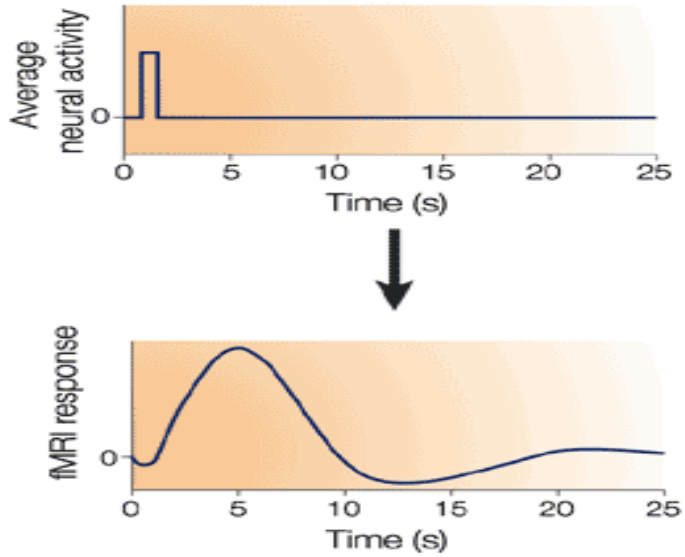


Neuronal activity results in:

1. *An initial increase in oxygen consumption owing to increased metabolic demand.*

2. *After a delay of ~2 secs, a large increase in local blood flow. which overcompensates for the amount of oxygen being extracted*

3. *Local increase in cerebral blood volume*



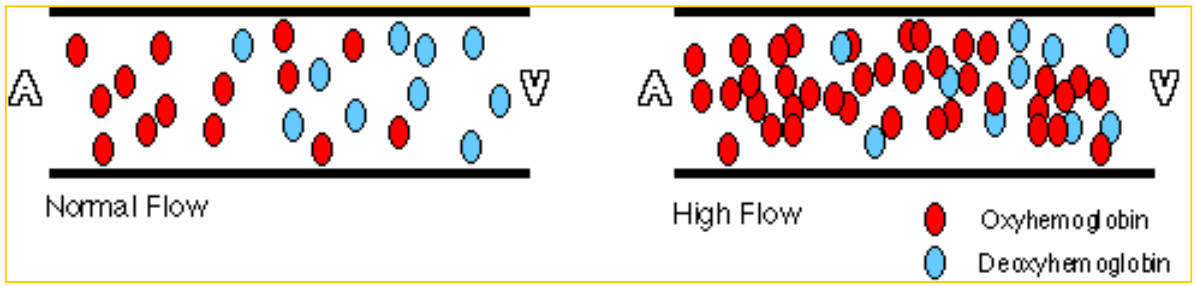
The increase in blood oxyhaemoglobin is what we measure in fMRI
This is called the BOLD (Blood Oxygen Level Dependent) response. (Ogawa et al. 1990)

Dr. Seiji Ogawa

BOLD (Blood Oxygen Level Dependent) contrast

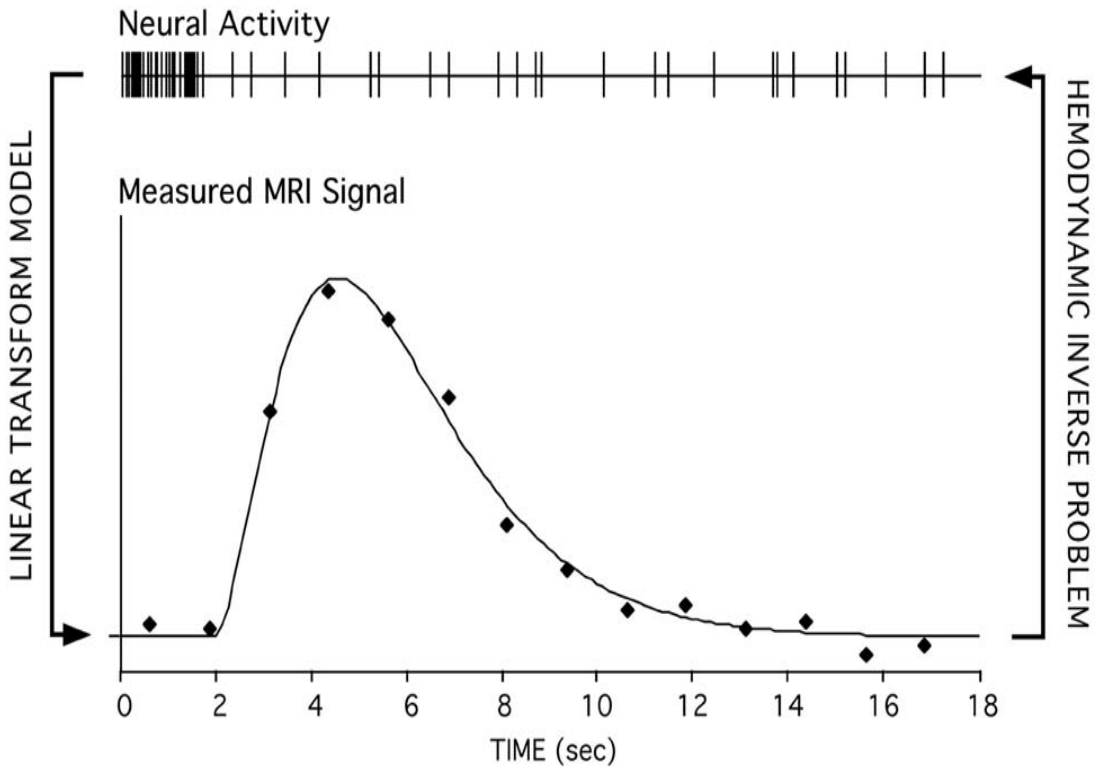
- Takes advantage of the different magnetic properties of oxyhemoglobin (HbO) and deoxyhemoglobin (Hb)

  Hb is *paramagnetic* and introduces an inhomogeneity into the nearby magnetic field, whereas HbO is weakly *diamagnetic* and has little effect.



Neuronal activity → local blood flow increases **overcompensating** for oxygen consumption → oxygen level in venous blood is elevated → larger MR signal.

What exactly does fMRI-BOLD tell us?



(Buckner, 2002)

- From sluggish Haemodynamic response to inferences on neural activity

- **The central assumption:** the fMRI signal is approximately proportional to some measure of the local neural activity, averaged over several millimeters and several seconds. This is sometimes referred to as the **linear transform model**

altered neuronal activity → changes in local haemodynamics → fMRI signal

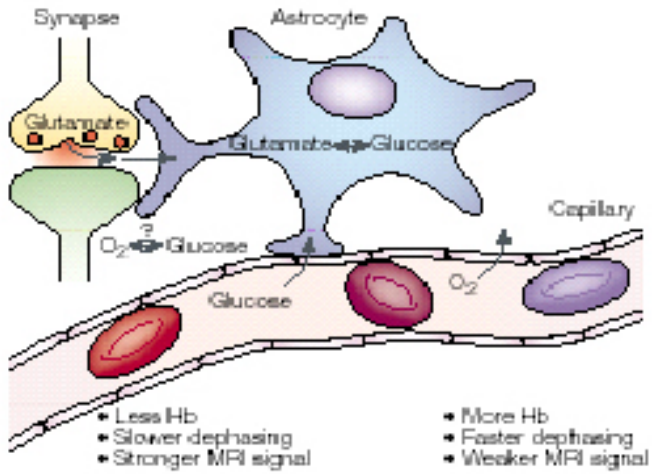
How the three are related is unclear

Altered neuronal activity → Changes in local haemodynamics:

- need for glucose?
- For oxygen?
- Some combination of both?

Various conflicting bits of evidence

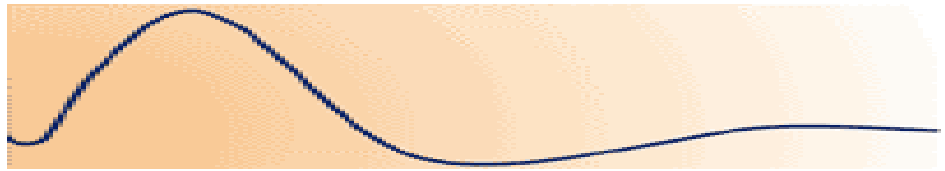
- In this talk: altered neuronal activity → fMRI signal
  (the linear transform model)



(Heeger & Ress, 2002)

- If the linear transform model were satisfactory, this would be *great (!):*

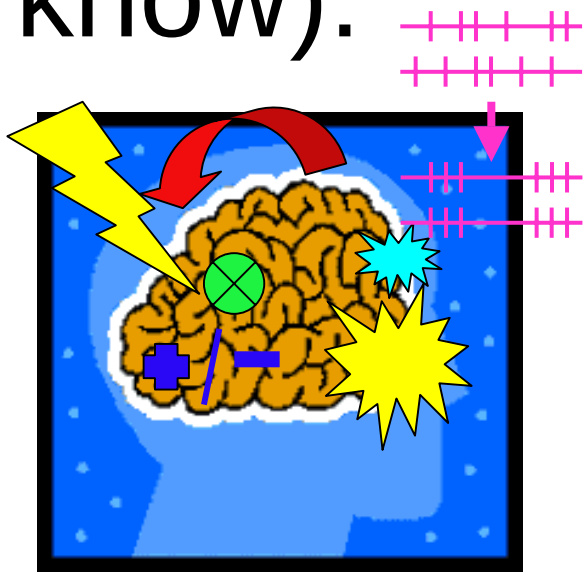
- it would mean we could reliably estimate the underlying neural activity from the Haemodynamic Response Function (HRF)



- But can we? most studies simply assume we can; if the model weren't a good approximation, this would make HRF measurements worthless

- This is important because some fMRI and neurophysiology experiments have yielded conflicting results

Things the fMRI signal MAY reflect (but we don't know):



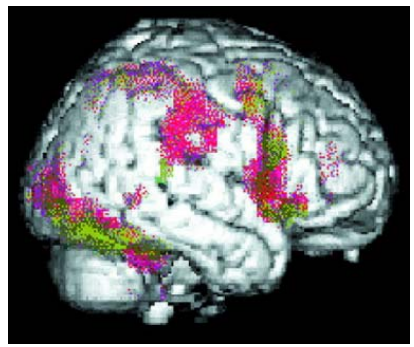
- Firing rates of the local neurons

but also activity that doesn't evoke spikes:

- Sub-threshold activity
- Simultaneous excitation and inhibition
- Modulatory inputs (e.g. top-down and feedback from higher cortical areas)

and other effects:

- Changes in neuronal synchrony without a concomitant change in mean firing rate
- Large changes in the firing rates of a few neurons
  OR
  small changes in the firing rate of many neurons



- To estimate the validity of the linear transform model, it is necessary to see how the fMRI signal correlates with measures of neural activity.

- But doing this is not so straightforward

- **The relationship of fMRI data and neural activity depends on a few factors:**

1. How ‘Neural activity’ is measured and quantified:

- fMRI: simultaneous activity of MANY neurons in a LARGE region of cortex (millimeters) over a LONG period (seconds). What component of the neural activity most predicts the fMRI signal?

- Average firing rate of all / a subpopulation of neurons?
- Degree of synchronous spiking?
- The Local Field Potential (LFP), believed to reflect dendritic currents?
- The Multi Unit Activity (MUA), believed to reflect spiking near the electrode tip?
- The current source density?
- Some measure of local average synaptic activity?
- Some measure of subthreshold electrical activity?

- All the above may correlate with each other under some circumstances, but can also vary independently of each other.

- Logothetis et.al. (Nature, 2001): simultaneous fMRI, LFPs and MUAs in rats. Concluded that BOLD fMRI signals “reflect the input and intracortical processing of a given area rather than its spiking output.”

2. fMRI acquisition technique

- BOLD (Blood Oxygen Level Dependent), the most common, provides a mixed signal dependant on:
  - blood FLOW
  - blood VOLUME
  - blood OXYGENATION.
- Variations on the technique can be used to emphasize or de-emphasize one or another of these components:
  - Pefusion-based fMRI → blood flow
  - Injections of various compounds → blood volume
  - Diffusion-based fMRI → cell swelling (after excitation)

3. Experimental protocol & data analysis

- Early days of fMRI: worry that the signal arises entirely/mostly from large draining veins
  → misleading on localization

- For example,
  visual stimuli at nearby locations →
  activity in nearby (but distinct) loci in V1

- But if the fMRI signal were only evident in a large vessel draining blood from V1, The activity from both points would seem to occur in the location of that vessel

Positives & Negatives of fMRI

Positives

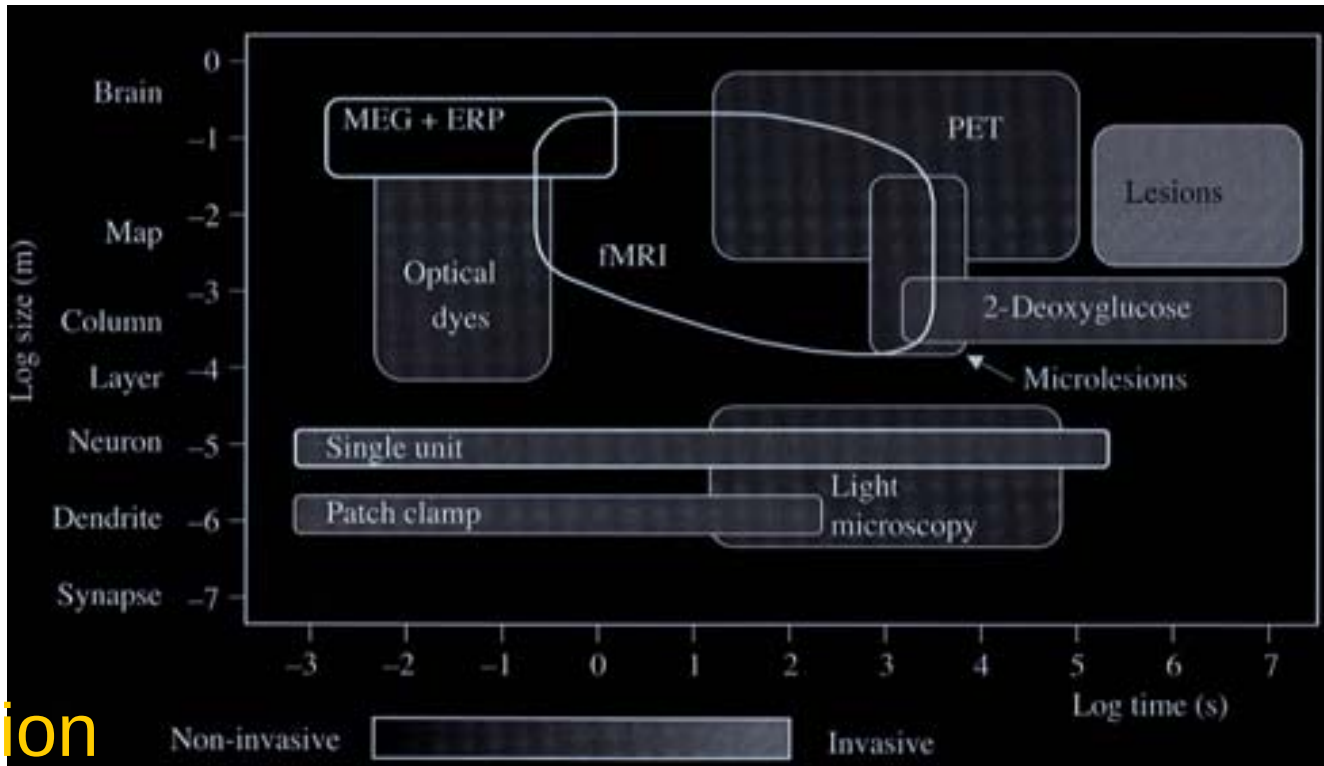
- Potential for high temporal and spatial resolution
- Lacks radioactivity and most techniques are noninvasive
- Can be repeated multiple times
- Performed on increasingly common state-of-the-art MRI scanners
- Better temporal resolution than PET

Negatives

- Extremely sensitive to head movements
- Awkward environment for emotional paradigms
- Contraindications:
  - Irremovable magnetic devices
  - Extreme claustrophobia
  - Loud sound from magnets
- Cannot perform receptor-ligand studies like PET and SPECT
- New technique with less track record than PET and SPECT
- There is a time lag of 3 to 6 s between when a brain region is activated and blood flow increases to it.

Comparing fMRI with other functional methods

- EEG and MEG define the underlying neuronal events in real time 10-100 msec, but provide relatively poor spatial resolution (many mm-cm).



- Invasiveness
- Spatial resolution

Non-BOLD Methods

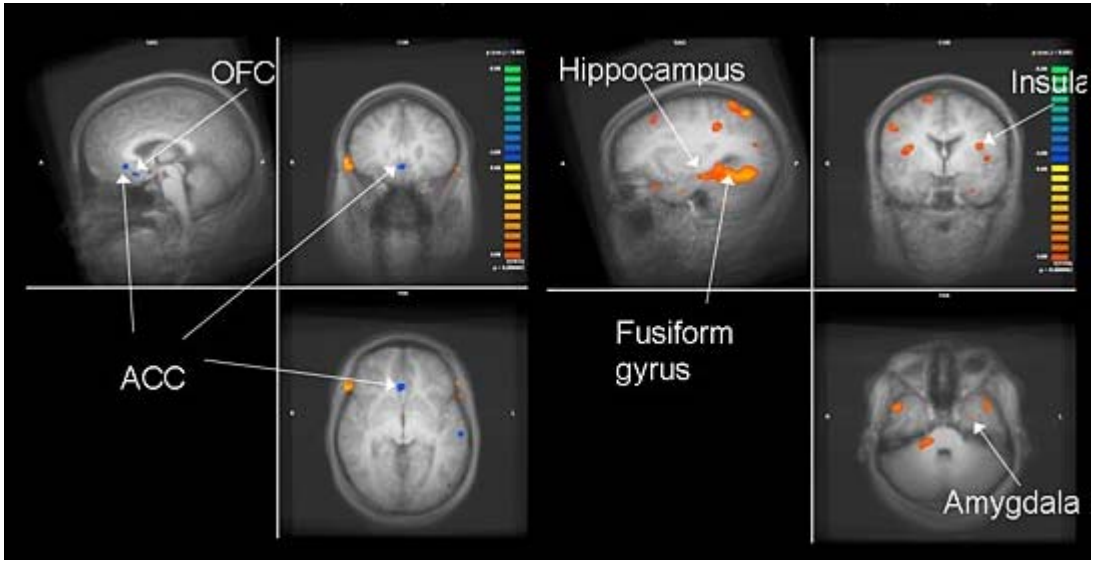
- Perfusion fMRI measures regional cerebral blood flow.
  - Intravenous Bolus-Tracking fMRI (T2*)
    - Injection of a magnetic compound (gadolinium-DTPA) . Areas perfused with the magnetic compound show less signal intensity as the compound creates a magnetic inhomogeneity that decreases the T2* signal.
    - The number of boluses can be given to an individual is limited by the potential for kidney toxicity.
    - Belliveau et al. (1991) first functional magnetic resonance maps of human task activation using a visual stimulation paradigm.
  - Arterial Spin-Labelling (T1)
    - Magnetic tagging of hydrogen atoms as they course through the blood and imaging them as they course through the slice of interest.
    - Can measure absolute blood flow.
    - Can directly compare data taken in different imaging sessions.
    - Takes several minutes to image a single slice.
    - More suited to measuring state differences between groups (i.e. bipolar euthymic versus bipolar depressed)
    - It is non-invasive.
- Diffusion-weighted fMRI which measures random movement of water molecules.
    - The amount of water diffusion for a given pixel can be calculated and is called the apparent diffusion coefficient (ADC).
    - It holds great promise for changing the clinical management of acute ischemic stroke by potentially refining the criteria for patients most likely to benefit form thrombolytic threrapy.

Non-BOLD Methods (cont.)

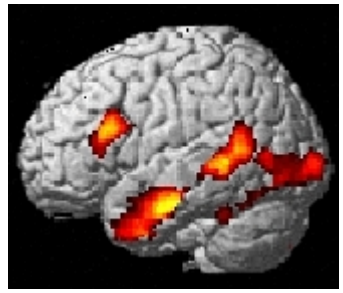
- MRI spectroscopy (MRSI) which can measure certain cerebral metabolites noninvasivelly and study tissue biochemistry.
  - Allows study of non-water hydrogen-containing molecules or molecules containing other magnetic elements
  - Relies on flipping non-water hydrogen atoms or other magnetic atoms
  - Magnetic compounds identified by spectographic peaks.
  - Single voxel and metabolic spatial techniques available.
  - Common types:
    - 1H-spectroscopy
      - Identifies lactate, creatine, cytosolic choline …
    - 31P-spectroscopy
      - ATP metabolism, intracellular pH and phospholipid metabolism
    - Li-spectroscopy
    - F-spectroscopy

Non-Bold Methods

- MRI spectroscopy
  - Restricted to study of mobile magnetic compounds
  - Receptor-ligand studies not currently possible
  - Limited spatial and temporal resolution but they will be improved by stronger magnets.
  - Can be used to identify regional biochemical abnormalities. When bipolar patients become either manic or depressed their PMEs (phosphodiesters) increase. These findings appear to be unrelated to medication treatment.
  - Differentiate Alzheimer Dementia from normal aging.
  - Measure changes in metabolic activity between sessions, such as before and after medication treatment
  - Is starting to be used in the characterization of tumor, stroke, and epileptogenic tissue and in presurgical planning.



Discoveries and Results

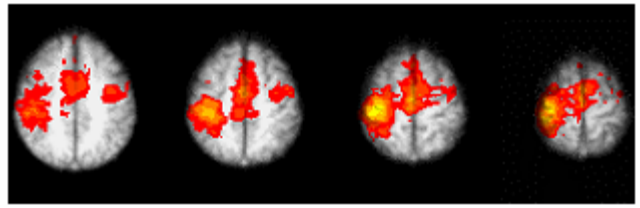


- **How do we remember?**
  - **Brewer et al.**
    - **Inside or an outside scene.**
    - **Whether a picture presented had been included in the original picture list.**
    - How well a picture was remembered was related to the amount of activity in a particular bit of the brain.
    - This suggests that the likelihood of us correctly remembering a piece of information is related directly to how well we absorb the information initially, or the strength of the encoding process.

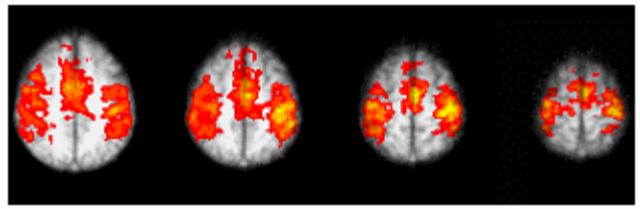
Discoveries and Results (2)

- **Recognising faces and objects**
  - *Andrews et al.*
    - Rubin vase ambiguous character
    - Familiar face -> activity in fusiform gyrus
    - When viewed as a vase the activity in fusiform gyrus disappeared
  - *Narain et al.*
    - Meaningless or noise sound is perceived more towards the front of superior temporal sulcus.
    - Meaningful sound interpreted as speech is heard behind this area.
- **Everything depends on context**
  - *Edmund Rolls et al*.
    - Bananas – pleasant taste – orbital frontal cortex activated.
    - Full of bananas – orbital frontal cortex activated in a different way.
  - *Tracey et al*.
    - Particular color -> painful burning.
    - Not to pay attention to pain or to focus on the pain.
    - When the subjects were distracted, the response to pain in the periaqueductal grey was changed. It appeared as though the brainstem was gating the responses. (child rescue)

Discoveries and Results (3)



Unaffected hand



Affected hand

- **Why do gamblers gamble?**

If we lost a lot of money we would be unlikely to keep gambling for fear of losing even more. However some people are unable to stop.

  - **O' Doherty et al.**
    - **Gambling experiment (high monetary reward and low monetary punishment).**
    - **Brain Regions involved in the representation of the size of rewards or punishments.**
    - **Damage to a region of the brain may lead to the inability to represent the size losses and consequently result in difficulty in judging the degree to which a particular choice is advantageous on the basis of a cumulative monetary gain.**

- **Learning how we learn**
  - **Learning involves strengthening new connections in the brain to change the relationship between brain input and output.**
    - **Motor skills of complex button pressing sequences**
    - **While learning they use motor areas on both sides of the brain, while when there is no learning they activate a much smaller region, in the hemisphere on the opposite side of the brain to that in which the hand is moved.**
    - **Repeated stimulus may lead to functional reorganization (blind Braille users).**
- **Watching the brain heal itself**
  - **Acute stroke**
    - **Maximize recovery after injury.**
    - **Subjects who have recovered successfully after a stroke increased activity in motor areas on the same side as the affected hand, rather than just in the opposite side of the brain normally used to move the hand.**

  - ***Multiple sclerosis***

Discoveries and Results (4)

- **Helping to guide the surgeon's knife**
  1. **Electrophysiological mapping of the cortex in the awake patient at the time of the operation.**
  2. **Wada test (sodium amytal)**
  3. **!! Localize activations associate with important tasks such as limb movement or speech production using non-invasive fMRI.**
- **Seeing disease before symptoms**

  The role of fMRI as a diagnostic tool.
  - Bookheimer et al.
    - Predict subsequent memory decline in patients genetically at risk for the Alzheimer's disease.
    - The magnitude and extent of brain activation in the regions of the brain commonly affected by Alzheimer's disease were greater amongst the genetically at-risk group.
- **Defining disease based on patterns of brain function**
  - **Dyslexia**
    - **Deficits in the integrity of the magnocellular pathway could be used as an objective clinical marker of the disorder.**

fMRI Software

- The creation of robust software for analysis, visualization and distribution of fMRI data is of great importance. Why?
- Open Source Tools
  - SPM (Matlab)
  - AFNI (Unix)
  - Caret (Multiplatform) – good for brain mapping
  - FSL (Oxford) & BET (brain extraction)

fMRI Data

- Many MBytes
  - For a single volume (100x100x100) we need about 16 Mbytes of memory
  - For 100 volumes ~ 1.6 Gbytes (16 x 100)
  - For 20 subjects ~ 32 Gbytes (1.6 x 20)

- Most popular formats
  - DICOM
    - Very general medical format.
    - Matlab commands: dicomread, dicomwrite.
    - Usually, one file for each slice.
    - *.dcm
  - Analyze 7.5
    - Usually, two files for each volume.
    - *.hdr & *.img
    - Matlab tools:mri_toolbox
      http://eeg.sourceforge.net/mridoc/mri_toolbox/

fMRI Analysis Overview

- Preparing fMRI data for statistical analysis.
- Statistical analysis of activation images.
  - GLM (General Linear Model)
- Inference (“Thresholding”)
  - Theshold the statistical map in order to decide at a given level of significance, which parts of the brain were activated.
  - Some voxels activate by chance.
    - Bonferroni Correction
    - Gaussian Random Field (GRF)
- Multi-subject statistics
  - Registration Tools used in raw data.
  - How many subjects are required ?
- Registration
  - Low resolution registered with high resolution
- Coordinate Systems
  - Talairach & Tournoux
- Templates
  - Average of many brains all registered to a common coordinate system.
- Brain Atlases
  - More sophisticated than templates.
  - Keep information about tissue type at each voxel, brain part, etc.
- Cortical Flattening
- Extracting Brain Connectivity

fMRI Preprocessing

1. K-space to Brain Images
2. Slice-timing Correction (voxels of the same volume must appear at the same time)
3. Alignment of Volumes (motion correction)
4. Smoothing (reduce noise)
5. Normalization (reduce the effect of global changes in intensity over time)
6. Reduction in low and high frequency
7. Remove unneeded brain parts.

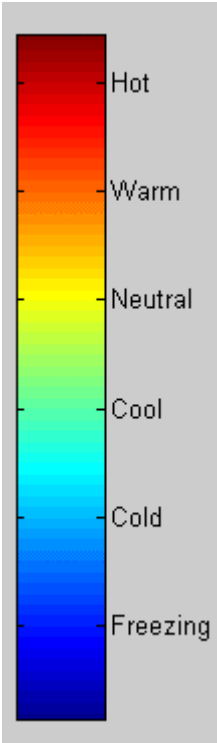
Statistical Analysis

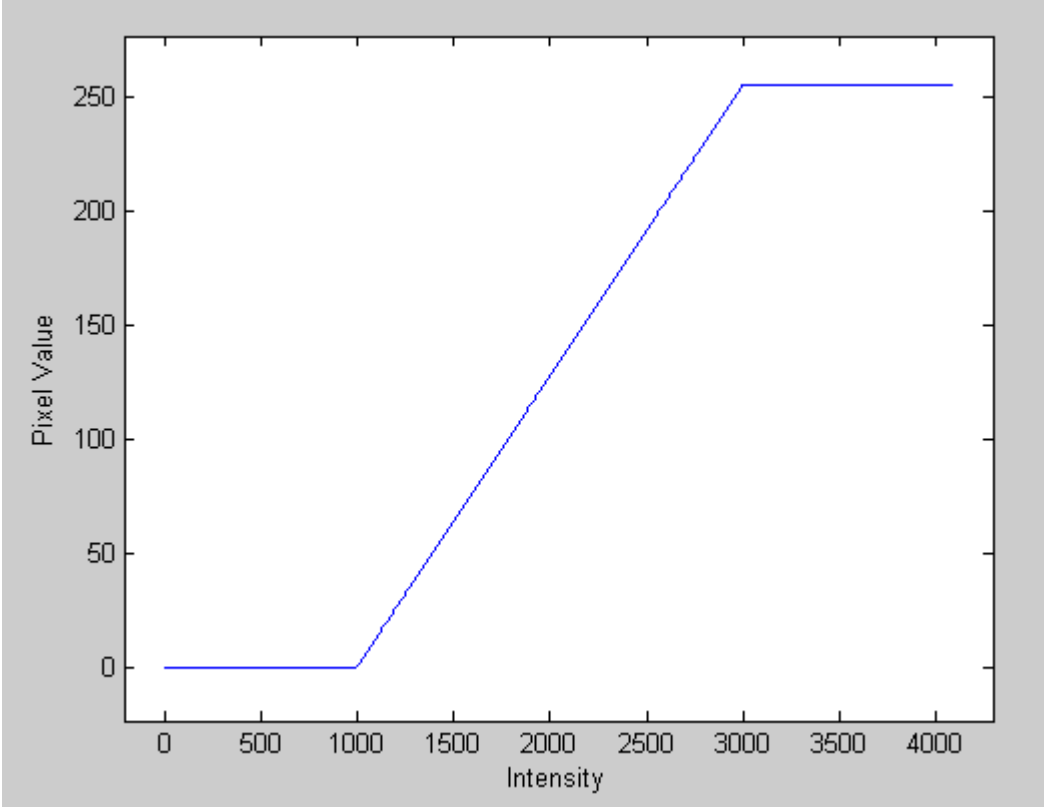
Statistical analysis is needed to determine which voxels are activated by the stimulation.

- Univariate analysis (analyze each voxel’s time independently)
- Multivariate
- Model Based Analysis
- Model Free Analysis

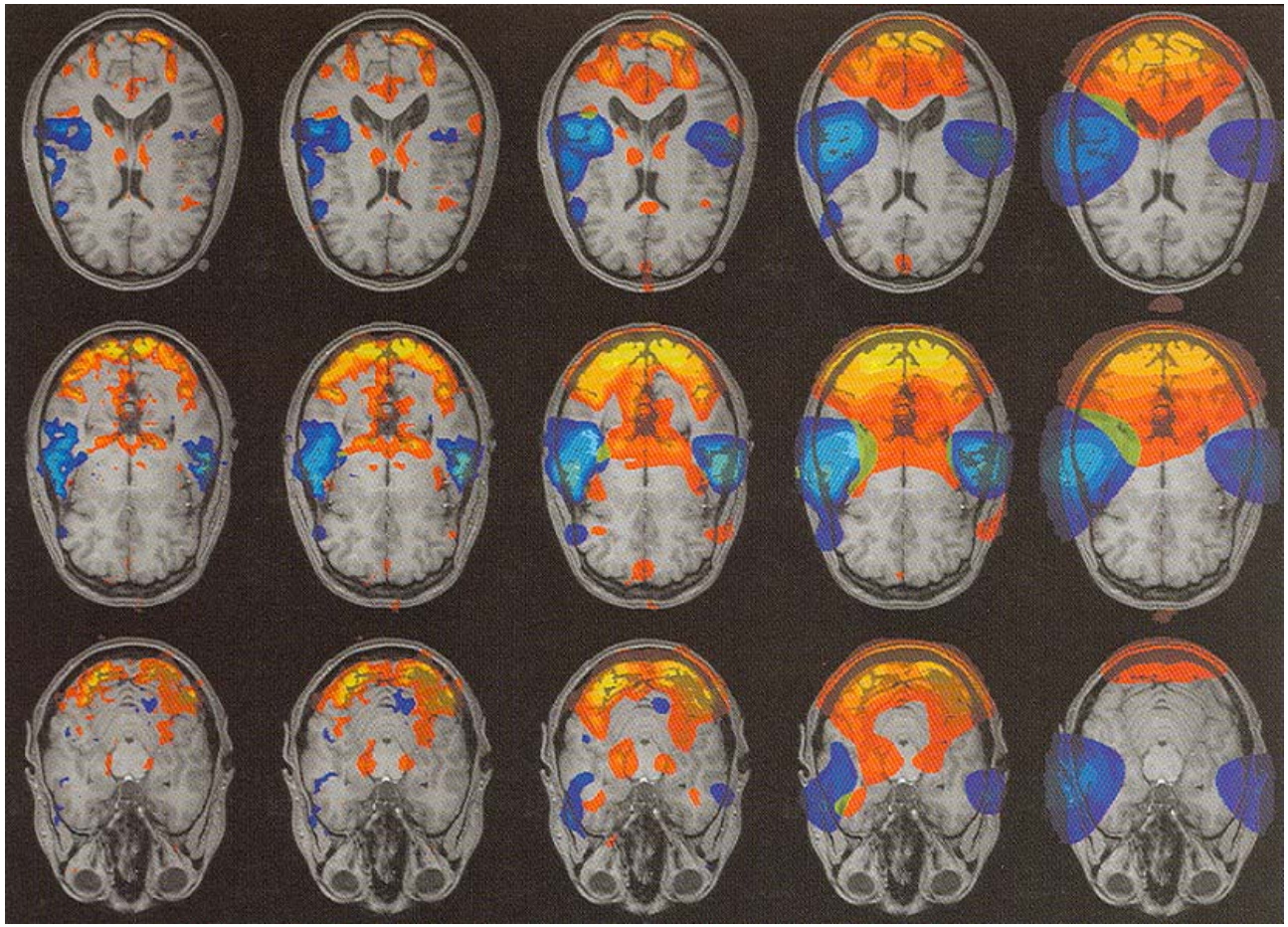
fMRI Visualization

- What you see on screen is not T1 or T2* intensity. It is a transformed intensity value into a pixel value (linear or non linear).
- Low and high threshold (e.g. in figure low=1000 & high 2000).
- Colormaps



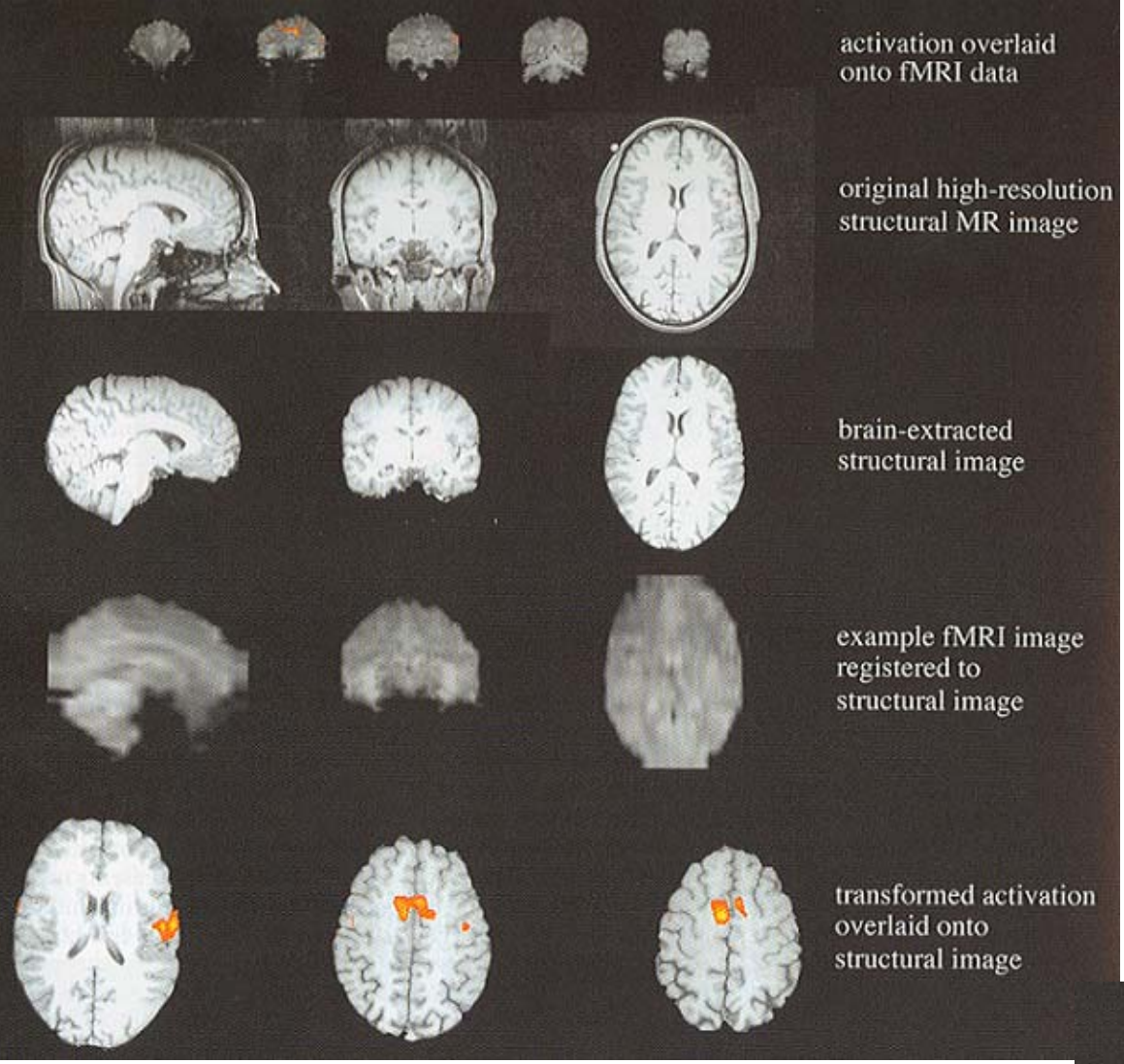


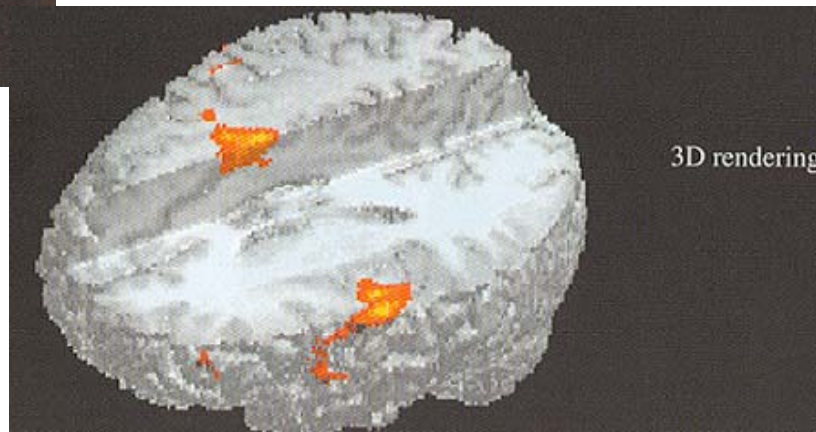
fMRI Visualization



Significant clusters of activation from and audiovisual experiment. The different rows were produced by processing with different spatial scales-filters.

Red clusters show visual activation; Blue clusters show auditory activation.

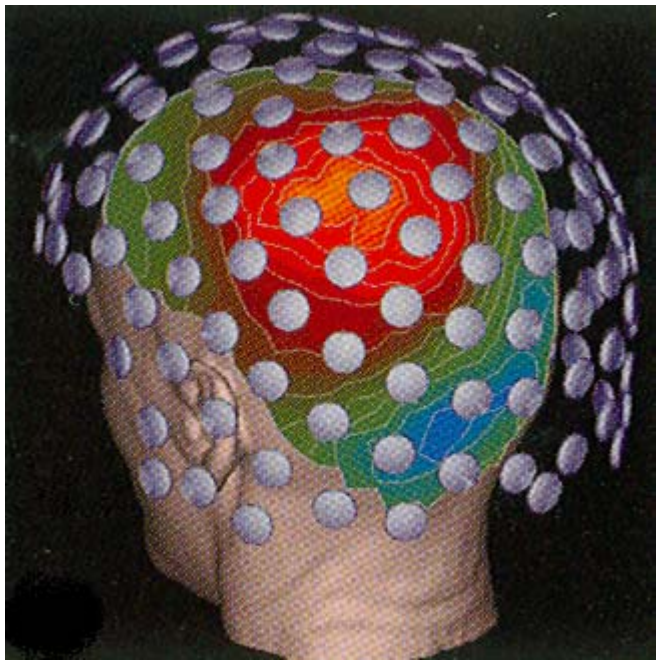


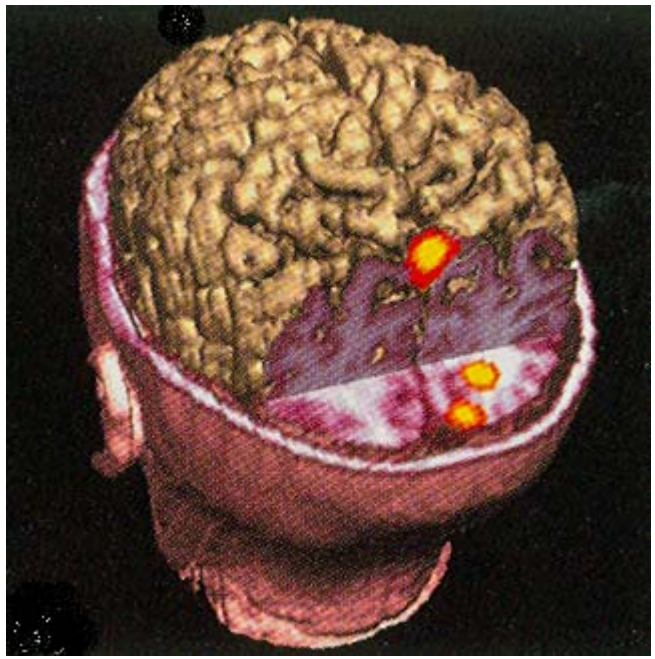


Various stages in the rendering of activation onto a high-resolution structural image.

Fusion of Medical Imaging

- MRI, fMRI , TMS, MEG, EEG, PET, SPECT, EIT, Optical Tomography, MRIS.





Fusion

- Co-registration
- Pitfalls fMRI & MEG/EEG
  - MEG/EEG need many trials
  - No guarantee that activation seen in one modality will be apparent in the other.
- Electrical Impedance Tomography
  - Inject small currents into the head and measure the electric potential at the remaining electrodes of a dense EEG sensor array.
- Trans-cranial magnetic stimulation
  - Transient lesion

And what about the future of fMRI?

- Smart Contrast Agents
- Very good time and spatial resolution
  - Cubic microns
  - Milliseconds
- Calcium and Gadolinium

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Books:

P Jezzard, PM Matthews, SM Smith, Functional MRI: an introduction to methods , Oxford 2001

Resources:

Front page image:
http://www.pubs.royalsoc.ac.uk/phil_trans_bio_content/images/law_brain.jpg

Ruth Stavy & David Channel : What are we measuring in fMRI? Powerpoint presentation

Tutorials:

http://homepage.mac.com/nankuei/functionalmri/
http://www.musc.edu/psychiatry/fnrd/primer_fmri.htm
http://www.fmrib.ox.ac.uk/fmri_intro/fmri_intro.htm

Acronyms:

BOLD : Blood Oxygen Level Dependance.
CBF : Cerebral Blood Flow.
CBV : Cerebral Blood Volume.
CVA : Canonical Variate Analysis.
CNR : Contrast to Noise Ratio
EC : Euler Characteristic.
EEG : ElectroEncephaloGraphy.
EPI : Echo Planar Imaging.
fMRI : Functional Magnetic Resonance Imaging.
FNI : Functional Neuroimaging.
FWHM : Full Width at Half Maximum.
gCBF : Global Cerebral Blood Flow.
GE : Gradient Echo.
GLM : General Linear Model.
Hb : Deoxyhemoglobin.
HbO2 : Oxyhemoglobin.
HRF : Hemodynamic Response Function.
ICA : Independant Composant Analysis.
IR : Inversion Recovery (time).
LCR : Liquide Cephalo-Rachidien.
ManCoVa : Multivariate Analysis of [Co]Variance.
MAP : Maximum A Posteriori.
MEG : MagnetoEncephaloGraphy.
MI : Mutual Information.
MRF : Markov Random Field.
MRI : Magnetic Resonance Imaging.
NMR : Nuclear Magnetic Resonance.
PCA : Principal Component Analysis
PET : Positron Emission Tomography.
rCBF : Regional Cerebral Blood Flow.
RFT : Random Field Theory.
ROI : Region Of Interest.
SE : Spin Echo.
SPECT : Single-Photon Emission Computed Tomography.
SPM : Statistical Parametric Mapping.
SVD : Singular Value Decomposition.
TR : Repetition Time (!).
TE : Time to Echo following the excitation pulse