• Neuroimaging techniques have changed the way neuroscientists address questions about functional anatomy, especially in relation to behavior and clinical disorders.
• **Neuroimaging** includes the use of various techniques to either directly or indirectly image the structure or function of the brain.

• **Structural neuroimaging** deals with the structure of the brain (e.g. shows contrast between different tissues: cerebrospinal fluid, grey matter, white matter).

• **Functional neuroimaging** is used to indirectly measure brain functions (e.g. neural activity).
• Example of Neuroimaging techniques:
  – **Computed Tomography** (CT),
  – **Positron Emission Tomography** (PET),
  – **Single Photon Emission Computed Tomography** (SPECT),
  – **Magnetic Resonance Imaging** (MRI),
  – **Functional Magnetic Resonance Imaging** (fMRI).

• Among other imaging modalities MRI/fMRI became largely used due to its low invasiveness, lack of radiation exposure, and relatively wide availability.
• **Magnetic Resonance Imaging (MRI)** was developed by researchers including Peter Mansfield and Paul Lauterbur, who were awarded the Nobel Prize for Physiology or Medicine in 2003.

• MRI uses magnetic fields and radio waves to produce high quality 2D or 3D images of brain structures/functions without use of ionizing radiation (X-rays) or radioactive tracers.

• By selecting specific MRI sequence parameters different MR signal can be obtained from different tissue types (structural MRI) or from metabolic changes (functional MRI).
MRI/fMRI scanner
MRI vs. fMRI

MRI studies brain anatomy.

Functional MRI (fMRI) studies brain function.

Source: Jody Culham’s fMRI for Dummies web site.
Examples of brain scans

MRI: high resolution (1 mm) - one image

fMRI: low resolution (~3 mm but can be better) - many images (e.g., every 2 sec for 5 mins)
3D example

Structural MRI

fMRI
fMRI: What it measures?
BOLD signal

↑neural activity → ↑ blood flow → ↑ oxyhemoglobin → ↑ T2* → ↑ MR signal

Source: fMRIB Brief Introduction to fMRI

Source: Jorge Jovicich
Physiology of the BOLD signal

- fMRI measures changes in the **Blood Oxygen Level Dependent (BOLD)** signal due to changing in neural activity.

- When neurons fire in response to sensory or cognitive process a sequence of events happens resulting in an increase in local cerebral metabolism.

- An increase in neural activity (and metabolism) causes an increased demand for oxygen. To compensate for this demand the vascular system increases the amount of oxygenated haemoglobin relative to the deoxygenated haemoglobin.

- Because the deoxygenated haemoglobin attenuates the MR signal an increase in the relation between oxygenated haemoglobin and deoxygenated haemoglobin leads to an increase of the BOLD signal.

Source: Arthurs & Boniface, 2002, *Trends in Neurosciences*
Temporal behaviour of the BOLD signal: Hemodynamic response

Time course of fMRI signal change in visual cortex in response to a visual stimuli

(i) Hemodynamic delay: ~2s
(ii) Time-to-peak of the response: ~13s
(iii) Width of the response
(iv) Amount of time to return to base line: ~20s
fMRI: How does it work?
fMRI Setup
During a standard fMRI experiment, hundreds of volumes or scans comprising brain activations at thousands of locations (voxels) are acquired.
Example of an fMRI experiment

**Question:** Which regions in the brain are involved in the representation and perception of objects?
A Simple Experiment

Intact Objects

Blank Screen

Lateral Occipital Complex
- responds when subject views objects

Scrambled Objects

One volume (12 slices) every 2 seconds for 272 seconds (4 minutes, 32 seconds)

Condition changes every 16 seconds (8 volumes)

Source: Jody Culham’s fMRI for Dummies web site
Standard Analysis

The most popular method is the **General Linear Model – GLM** (Friston et al., 1995), in which a linear regression is performed on the signal value at a voxel in order to determine whether the voxel’s activity is related to one stimulus or tasks.

**Typical question:** Which areas are related with one stimulus or task?

**Programs:** SPM (FIL-UCL), AFNI (NIH), XBAN (IOP-KCL), FSL (FMRIB-Oxford)…
Voxel Time course

Temporal series

fMRI

BOLD signal
General Framework
SPM (FIL-UCL)

- Image time-series
- Kernel
- Design matrix
- Statistical parametric map (SPM)

- Realignment
- Smoothing
- General linear model

- Normalisation
- Template
- Parameter estimates

- Statistical inference
  - Gaussian field theory
  - p < 0.05

Source: www.fil.ion.ucl.ac.uk
Voxel-wise time series analysis

- Single voxel time series
- BOLD signal
- Model specification
- Parameter estimation
- Hypothesis
- Statistic

Source: www.fil.ion.ucl.ac.uk
Single voxel regression model

\[ y = x_1 \beta_1 + x_2 \beta_2 + e \]

Source: www.fil.ion.ucl.ac.uk
Parameter estimation: Ordinary least squares

\[ y = X\beta + e \]

\[ \hat{\beta} = (X^T X)^{-1} X^T y \]

Ordinary least squares (OLS): Estimate parameters such that

\[ \sum_{t=1}^{N} e_t^2 \] is minimal

Source: www.fil.ion.ucl.ac.uk
Problem 1: Shape of BOLD response
Solution: Convolution model

Convolve stimulus function with a canonical hemodynamic response function (HRF):

\[ f \otimes g(t) = \int_{0}^{t} f(\tau) g(t - \tau) d\tau \]

Source: www.fil.ion.ucl.ac.uk
Problem 2: Low-frequency noise
Solution: High pass filtering

- blue = data
- black = mean + low-frequency
- green = predicted response, taking into account low-frequency
- red = predicted response (with low-frequency drift explained away)

Source: www.fil.ion.ucl.ac.uk
Discrete cosine transform basis functions

Source: www.fil.ion.ucl.ac.uk
Model: Design Matrix

discrete cosine transform (DCT) set

Source: www.fil.ion.ucl.ac.uk
Contrasts & Statistical Parametric Maps

Question: Is there an effect of interest after other modelled effects have been taken into account?

*contrast* — linear combination of parameters: $c^T \beta$

\[
c = \begin{bmatrix} 1 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 1 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \end{bmatrix}
\]

Is there activation during listening?

Null hypothesis: $\beta_1 = 0$

\[
t = \frac{c^T \hat{\beta}}{\text{Std}(c^T \hat{\beta})}
\]

In rejecting the null hypothesis at p-value<0.05, we accept 5% probability of type I error (false positives).

Source: www.fil.ion.ucl.ac.uk
Correction for multiple comparisons

- Mass-univariate approach: We apply the GLM to each of a huge number of voxels (usually > 100,000).
- Threshold of $p<0.05 \rightarrow$ more than 5000 voxels significant by chance!
- Massive problem with multiple comparisons!
- Solutions:
  - Bonferroni Correction (too conservative, voxels are not independent)
  - False Discovery Rate
  - Random Field Theory
  - Permutation Test
New approaches to analyze fMRI data

- Given that most brain functions are distributed processes, involving a network of brain regions, it would seem sensible to use the spatially distributed information contained in the fMRI data to aid our understanding of brain functions.

- Recently, **multivariate pattern recognition methods** have been applied to fMRI data.

- In these applications the fMRI scans are treated as spatial patterns and machine learning methods are used to identify statistical properties of the data that discriminate between brain states (e.g. task 1 vs. task 2) or group of subjects (e.g. patients vs. controls).