Brain Imaging

• Brain imaging can be separated into two major categories:
  – Structural brain imaging
  – Functional brain imaging

• There exist a number of different modalities for performing each category.

Structural Brain Imaging

• Structural brain imaging deals with the study of brain structure and the diagnosis of disease and injury.

• Modalities include:
  – computed axial tomography (CAT),
  – magnetic resonance imaging (MRI), and
  – positron emission tomography (PET).

Diffusion Tensor Imaging

• An MRI scanner can also be used to study the directional patterns of water diffusion.

• Since water diffuses more quickly along axons than across them this can be used to study how brain regions are connected.

• Diffusion tensor imaging (DTI) is a technique for measuring directional diffusion and reconstructing fiber tracts of the brain.
Recently there has been explosive interest in using functional brain imaging to study both cognitive and affective processes.

Modalities include:
- positron emission tomography (PET),
- functional magnetic resonance imaging (fMRI),
- electroencephalography (EEG), and
- magnetoencephalography (MEG).

Functional magnetic resonance imaging (fMRI) is a non-invasive technique for studying brain activity.

During the course of an fMRI experiment, a series of brain images are acquired while the subject performs a set of tasks.

Changes in the measured signal between individual images are used to make inferences regarding task-related activations in the brain.

Each image consists of ~100,000 brain 'voxels' (cubic volumes that span the 3D space of the brain).

During the course of an experiment several hundred images are acquired (~ one every 2s).
fMRI Data

- In addition, the experiment may be repeated for multiple subjects (e.g., 10–40) to facilitate population inference.

- The total amount of data that needs to be analyzed is staggering.

Statistical Analysis

- The statistical analysis of fMRI data is challenging.
  - It is a massive data problem.
  - The signal of interest is relatively weak.
  - The data exhibits a complicated temporal and spatial noise structure.

Spatial and Temporal Resolution

- When designing an fMRI experiment one must balance the need for adequate spatial resolution with that of adequate temporal resolution.

- The temporal resolution determines our ability to separate brain events in time.
  - In fMRI the temporal resolution is determined by how quickly each individual image is acquired (TR).

- The spatial resolution determines our ability to distinguish changes in an image across different spatial locations.

Terminology

**Structural (T1) images:**
- High spatial resolution
- Low temporal resolution
- Can distinguish different types of tissue

**Functional (T2*) images:**
- Lower spatial resolution
- Higher temporal resolution
- Can relate changes in signal to an experimental manipulation

**Scan Volume:**
- Field of View (FOV), e.g., 192 mm

**Matrix Size**
- e.g., 64 x 64

**In-plane resolution**
- 192 mm / 64 = 3 mm

**Axial slices**
- e.g., 3 mm

**Slice thickness**
- e.g., 3 mm

**Voxel Size**
- 3 mm

Ged Ridgeway
**Terminology**

- **Subjects**
- **Sessions**
- **Runs**
  - A single run
- **Volume**
  - TR = repetition time
  - Time required to scan one volume
- **Slices**

**BOLD fMRI**

- The most common approach towards fMRI uses the **Blood Oxygenation Level Dependent (BOLD)** contrast.
- BOLD fMRI measures the ratio of oxygenated to deoxygenated hemoglobin in the blood.
- It is important to note that BOLD fMRI doesn’t measure neuronal activity directly, instead it measures the metabolic demands (oxygen consumption) of active neurons.

**HRF**

The hemodynamic response function (HRF) represents changes in the fMRI signal triggered by neuronal activity.

**Properties of the HRF**

- Magnitude of signal changes is quite small
  - 0.5 to 3% at 1.5 T
  - Hard to see in individual images
- The amplitude of the dip is even smaller
  - ~15% of the amplitude of the rise
  - More localized to areas of neural activity
- Response is delayed and quite slow
  - Extracting temporal information is tricky, but possible
  - Even short events have a rather long response

**LTI System**

- The relationship between stimuli and the BOLD response is often modeled using a linear time invariant (LTI) system.
  - Here the neuronal activity acts as the input or impulse
  - and the HRF acts as the impulse response function.
- In this framework the BOLD response at time $t$ is modeled as the convolution of a stimulus function $v(t)$ and the hemodynamic response $h(t)$, that is,

$$x(t) = (v * h)(t)$$
Noise

- In fMRI the noise can be due to both hardware reasons and to the subject.

- Sources of noise:
  - Thermal motion of free electrons in the system.
  - Patient movement during the experiment.
  - Physiological effects, such as the subject’s heartbeat and respiration.
  - Low frequency signal drift.

- Significant autocorrelation present.

Data Processing Pipeline

Experimental Design

- Block design: Similar events are grouped

  Blocked design Condition A Condition B
  0 20 40 60 80 100 120 140 160 180 200

  • High statistical power to detect activation and robust to uncertainties in the shape of HRF.
  • Can’t directly estimate features of the HRF.

Experimental Design

- Event-related design: Events are mixed

  Event-related design Condition A Condition B
  0 20 40 60 80 100 120 140 160 180 200

  • Allows for the estimation of features of the HRF.
  • Decreased power to detect activation.

Pre-processing

- Prior to statistical analysis fMRI data undergoes substantial pre-processing.

- Pre-processing steps include:
  - Slice Time Correction
  - Motion Correction
  - Normalization
  - Spatial Filtering
  - Temporal Filtering

Statistical Analysis

- There are multiple goals in the statistical analysis of fMRI data.

- They include:
  - localizing brain areas activated by the task;
  - determining networks corresponding to brain function; and
  - making predictions about psychological or disease states.
Localizing Activation

1. Construct a model for each voxel of the brain.
   - “Massive univariate approach”
   - Regression models (GLM) commonly used.

\[
Y = X\beta + \epsilon \quad \epsilon \sim N(0, V)
\]

2. Perform a statistical test to determine whether task related activation is present in the voxel.

\[H_0 : \mathbf{c}^T \beta = 0\]

3. Choose an appropriate threshold for determining statistical significance.
   - Massive multiple comparisons problem.

Statistical Parametric Map

• The results of the thresholded statistical images are presented in a statistical parametric map.

• Each significant voxel is color-coded according to the size of its p-value.

Brain Networks

• Human brain mapping has primarily been used to provide maps showing regions of the brain activated by specific tasks.

• Recently, there has been an increased interest in augmenting this type of analysis with connectivity studies that describe how various brain regions interact and how these interactions depend on experimental conditions.

Brain Connectivity

• The strength of these interactions vary from correlations to causal relationships.

Undirected Relationships

Directed Relationships

Connectivity

Functional Connectivity

Undirected association between two or more fMRI time series.

Effective Connectivity

Directed influence of one brain region on the physiological activity recorded in other brain regions.
Functional Connectivity

- Functional connectivity analysis is usually performed using data-driven transformation methods which make no assumptions about the underlying biology.

- Methods include:
  - Seed Analysis
  - Principal Components
  - Partial Least Squares
  - Independent Components Analysis

Effective Connectivity

- Effective connectivity analysis is performed using statistical models which make anatomically motivated assumptions and restricts inference to networks comprising of a number of pre-selected regions of interest.

- Methods include:
  - Structural Equation Modeling
  - Dynamic Causal Modeling
  - Granger Causality
  - Graphical Models

Prediction

- There is a growing interest in using fMRI data for classification of mental disorders and predicting the early onset of disease.

- Various multivariate pattern classification approaches have successfully been applied to fMRI data.
  - A classifier is trained to discriminate between different brain states and used to predict the states in a new set of data.
Multi-modal Experiments

- There is a trend towards using multiple imaging modalities to overcome some of the limitations of each method used in isolation.
  - Combined EEG and fMRI
  - Combined DTI and fMRI
  - Combined TMS and fMRI
  - Imaging genetics (combined fMRI and genetics)

- All very promising, but even more data intensive than fMRI alone.

Major Analysis Packages

<table>
<thead>
<tr>
<th>Package</th>
<th>Details</th>
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<tbody>
<tr>
<td>SPM</td>
<td>Open source, but requires Matlab, which is expensive and comparatively slow. Widespread. Large variety of add-ons. Very active development community. Runs on all platforms. Emphasis on fast processing. Free.</td>
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<tr>
<td>AFNI</td>
<td>Open source, written in C. Part command-line, part GUI. Free.</td>
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Class Software

- Software:
  - SPINN (Statistical Plug-In for Neuroimaging analysis)
    - Preliminary development version is currently known as canlab_tools
    - Library of MATLAB scripts and toolboxes developed by Tor Wager’s lab and myself
    - Documentation: http://wagerlab.colorado.edu/wiki/doku.php?title=core/can_core_tools
    - Calls some functions from SPM
  - SPM8