Principles of Functional Neuroimaging

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Neuroimaging

• Understanding the brain is arguably among the most complex, important and challenging issues in science today.

• **Neuroimaging** is an umbrella term for an ever-increasing number of minimally invasive techniques designed to study the brain.
  – Can be used to measure structure, function and disease pathophysiology.

• These techniques are being applied in a large number of medical and scientific areas of inquiry.
Neuroimaging can be separated into two major categories:

- Structural neuroimaging
- Functional neuroimaging

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

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

• Modalities include:
  – computed tomography (CT),
  – magnetic resonance imaging (MRI), and
  – positron emission tomography (PET).
Structural Neuroimaging

- CT
- PET
- MRI
MRI

Proton Density  T1  T2
Diffusion MRI

• 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 MRI allows one to measure directional diffusion and reconstruct fiber tracts of the brain.
Diffusion MRI
Recently there has been explosive interest in using functional neuroimaging to study both cognitive and affective processes.

Modalities include:

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

Structural images:
- High spatial resolution
- No temporal information
- Can distinguish different types of tissue

Functional images:
- Lower spatial resolution
- Higher temporal resolution
- Can relate changes in signal to an experimental task
Properties

- Each functional imaging modality provides a different type of measurement of the brain.
  - PET: brain metabolism
  - fMRI: blood flow
  - MEG/EEG: electromagnetic signals generated by neuronal activity

- They also have their own pros and cons with regards to spatial resolution, temporal resolution and invasiveness.
Human Neuroimaging

- MEG & EEG
- PET
- ASL
- fMRI
- BOLD

Log(Space (mm))
- 100 cm
- 10 cm
- 1 cm
- 1 mm
- 100 um
- 10 um
- 1 um

Log(Time (s))
- 1 msec
- 1 s
- 10 s
- 2 min
- 3 h
- 1 Day
- 12 Days

Large-scale networks
Functional maps
Columns
Growth of fMRI

- In the past decade fMRI has become the dominant tool for functional imaging.
Functional MRI

- 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.
fMRI Data

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

• Each voxel has a spatial location and a value representing its intensity.
fMRI Data

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

- Each voxel has a corresponding time course.
fMRI Data

• The analysis of fMRI data is an example of a modern statistical ‘big data’ problem.
  – The data from each subject consists of tens of millions of measurements.
  – Each subject may be brought in for multiple sessions.
  – The experiment may be repeated for multiple subjects (e.g., 10–100).
  – The data is not only large but also has a complex correlation structure in both space and time.

• Statistics plays a crucial role in understanding the data and obtaining relevant results that can be used and interpreted by neuroscientists.
BOLD fMRI

- The most common approach towards fMRI uses the **Blood Oxygenation Level Dependent (BOLD)** contrast.

- It allows us to measure the ratio of oxygenated to deoxygenated hemoglobin in the blood.

- It doesn’t measure neuronal activity directly, instead it measures the metabolic demands (**oxygen consumption**) of active neurons.
BOLD Contrast

- Hemoglobin exists in two different states each with different magnetic properties producing different local magnetic fields.
  - Oxyhemoglobin is diamagnetic.
  - Deoxyhemoglobin is paramagnetic.

- BOLD fMRI takes advantage of the difference in contrast between oxygenated and deoxygenated hemoglobin.
  - Deoxyhemoglobin suppresses the MR signal.
  - As the concentration of deoxyhemoglobin decreases the fMRI signal increases.
• The change in the MR signal triggered by instantaneous neuronal activity is known as the hemodynamic response function.
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.
fMRI Noise

• The measured fMRI signal is corrupted by random noise and various nuisance components that arise due to hardware reasons and the subjects themselves.

• 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.
fMRI Noise

- Some of these noise components can be removed prior to statistical analysis, while others need to be included as covariates in subsequent models.

- It is difficult to remove/model all sources of noise and therefore significant autocorrelation will be present in the signal.

- Characteristics of the noise:
  - “1/f” in frequency domain
  - Nearby time-points exhibit positive correlation
Pre-processing

• Prior to analysis, fMRI data undergoes a series of preprocessing steps aimed at identifying and removing artifacts and validating assumptions.

• The goals of preprocessing are
  
  – To minimize the influence of data acquisition and physiological artifacts;
  
  – To check statistical assumptions and transform the data to meet assumptions;
  
  – To standardize the locations of brain regions across subjects to achieve validity and sensitivity in group analysis.
Preprocessing is performed both on the fMRI data and structural scans collected prior to the experiment.
Human Brain Mapping

- The most common use of fMRI to date has been to localize areas of the brain that activate in response to a certain task.

- These types of human brain mapping studies are necessary for the development of biomarkers and increasing our understanding of brain function.
Localizing Activation

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

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

3. Choose an appropriate threshold for determining statistical significance.
The General Linear Model (GLM) can be written:

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

where

\[
\begin{bmatrix}
Y_1 \\
Y_2 \\
\vdots \\
Y_n
\end{bmatrix}
= \begin{bmatrix}
1 & X_{11} & \cdots & X_{1p} \\
1 & X_{21} & \cdots & X_{2p} \\
\vdots & \vdots & \ddots & \vdots \\
1 & X_{np} & \cdots & X_{np}
\end{bmatrix}
\begin{bmatrix}
\beta_0 \\
\beta_1 \\
\vdots \\
\beta_p
\end{bmatrix}
+ \begin{bmatrix}
\varepsilon_1 \\
\varepsilon_2 \\
\vdots \\
\varepsilon_n
\end{bmatrix}
\]

\(V\) is the covariance matrix whose format depends on the noise model.

The quality of the model depends on our choice of X and V.
Example

Famous vs. non-famous face example:

\[ \text{fMRI Data} = \text{Design matrix} \times \begin{bmatrix} \beta_0 \\ \beta_1 \\ \beta_2 \end{bmatrix} + \text{Residuals} \]
Example

- A **contrast** is a linear combination of GLM parameters.
  - A **t-contrast** is a single, planned contrast -> t-test
  - Specified by weights ($c$), so that $c^T\beta = a$ scalar value
  - Use a t-test to perform tests on effects of interest.

\[
\text{fMRI Data} \quad = \quad \begin{bmatrix} \text{Intercept} \\
\text{Task regressors} \\
\text{Betas (slopes)} \end{bmatrix} \times \begin{bmatrix}
\beta_0 \\
\beta_1 \\
\beta_2 
\end{bmatrix} + \text{Residuals}
\]

Test:

\[
H_0 : \beta_1 - \beta_2
\]
Multiple Comparisons

- Which of 100,000 voxels are significant?
  - $\alpha=0.05 \Rightarrow 5,000$ false positive voxels

- Choosing a threshold is a balance between sensitivity (true positive rate) and specificity (true negative rate).
Measures of False Positives

- There exist several ways of quantifying the likelihood of obtaining false positives.

  - **Family-Wise Error Rate (FWER)**
    - Probability of any false positives
      - Bonferroni
      - Random field theory
      - Permutation tests

  - **False Discovery Rate (FDR)**
    - Proportion of false positives among rejected tests
      - Benjamini-Hochberg procedure
Brain Connectivity

• Human brain mapping has primarily been used to construct maps indicating regions of the brain that are activated by certain tasks.

• Recently, there has been an increased interest in augmenting this with connectivity analysis.

• They seek to describe how brain regions interact and how this depends on experimental conditions and behavioral measures.
Varieties of Connectivity

**Structural connectivity**
- Presence of axonal connections

**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.

Roy et al. 2014 DCM
Varieties of Connectivity

**Structural connectivity**
- Tractography

**Functional connectivity**
- ‘Seed’-analysis
- Graphical Models
- Independent/principal components

**Effective connectivity**
- Path analysis, mediation
- Granger causality
- Dynamic causal modeling (DCM)

Roy et al. 2014 DCM
Network Analysis

• Network analysis tries to characterize networks using a small number of meaningful summary measures.

• The hope is that comparisons of network topologies between groups of subjects may reveal connectivity abnormalities related to neurological and psychiatric disorders.
More recently, interest has turned towards using a person’s brain activity or structure to predict their perceptions, behavior, or health status.

Emerging applications

- Alzheimer’s disease
- Depression (e.g., Craddock et al. 2009)
- Chronic pain (e.g., Baliki et al. 2012)
- Anxiety (e.g., Doehrmann et al. 2013; Siegle et al. 2006)
- Parkinson’s disease
- Drug abuse (Whelan et al. 2014)
- Acute pain (e.g., Wager et al. 2013)
- Emotion (Kassam et al. 2011; Kragel et al. 2014; Wager et al. 2015)
Multi-modal Analysis

• In neuroscience there is a general trend toward using multiple imaging methods in tandem to overcome limitations of each approach in isolation.
  – Examples include: joint EEG and fMRI, imaging genetics

• Each of these multi-modal approaches promise to be important topics of future research, and to fully realize their promise, novel statistical techniques will be needed.
Future Directions

• The field surrounding functional neuroimaging is constantly evolving.
  – More and more increasingly ambitious experiments are being performed each day.
  – With this rapid development, new research questions are opening up every day.

• This is creating a significant new demand, and an unmatched opportunity, for quantitative researchers working in the neurosciences.
Thanks

- Thank you for your attention.

- Coursera fMRI class available on demand.

Joint course with Tor Wager, UC Boulder