Principles of Functional Neuroimaging Data

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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

• Neuroimaging allows us to understand interactions between the mind, brain, and body in a way we have never been able to before.

• These interactions determine whether we are healthy or sick, energized or depressed, resilient or fragile, whether or not we age gracefully.
  
  - Nearly all of the top causes of death in the U.S. are influenced by our decisions, emotions, and behavior.

• Understanding these interactions is one of the grand challenges of our time.
A Multidisciplinary Community

- Physicists
- Neuroscientists
- Engineers
- Clinicians
- Public health
- Psychologists
- Statisticians
- Mathematicians
- Computer scientists
- Behavioral scientists
- Philosophers
- Biologists

- Need experts in each discipline working together.
- Need individuals with multiple types of expertise.
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).
MRI

Proton Density  T1  T2
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.
  - Direction encoded in a 3×3 matrix at each location.
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

**Space (mm):**
- 1 mm
- 10 um
- 100 um
- 1 cm
- 10 cm
- 100 cm

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

- BOLD
- Functional maps
- Large-scale networks
- Columns
PET
PET Overview

• PET is used to locate and quantify radioactivity emitted by radiolabeled tracers in the brain.
  – Tagged compounds that bind to particular proteins expressed in the brain, such as dopamine receptors or transporters.

• Depending on the tracer, PET can be used to measure glucose metabolism, oxygen consumption, and regional cerebral blood flow.
  – Makes inferences about the location of neural activity based on the assumption it is accompanied by changes in metabolism, oxygen consumption, or blood flow.
PET Overview

- The PET camera consists of a number of detector elements positioned on a circular array surrounding the patient.

- Once the tracer is introduced into the patient, it is deposited to the tissue of interest in proportion to the local uptake.

- As the isotope decays, it emits a positron, which finds a nearby electron and annihilates.
PET Overview

- This produces two photons propagating from the point of annihilation in opposite directions.

- Each photon 'hits' one of the detectors. If two photons are detected within a narrow time window, an event is recorded to have occurred along the line connecting the two detectors.
PET Overview

• Once a large number of events have been recorded, the density of the emitting compound can be estimated, allowing for the creation of an image of the uptake of the compound.

• By acquiring a sequence of PET images, one can quantify tracer kinetics and estimate the density of a neuroreceptor throughout the brain.
What does PET measure?

- The most common radioactive tracers:
  - $^{15}$O PET measures the rate of water uptake into tissue.
  - $^{18}$F (FDG) PET measures glucose uptake.
  - $^{11}$C Raclopride PET measures dopamine binding.

Nordberg, et al.
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.

Lindquist et al., 2008
HRF Properties

- Magnitude of signal changes is quite small
  - 0.1 to 5%
  - Hard to see in individual images

- Response is delayed and quite slow
  - Extracting temporal information is tricky, but possible
  - Even short events have a rather long response

- Exact shape of the response has been shown to vary across subjects and regions.
Interpretation

- How well does BOLD signal reflect increases in neural firing?

- The BOLD signal corresponds relatively closely to the local electrical field potential surrounding a group of cells, which is likely to reflect changes in post-synaptic activity, under many conditions.

Logothetis et al, 2001
fMRI Data

- Each image consists of \(~100,000\) brain voxels.
- Several hundred images are acquired; typically one every 2s.
- Each voxel has a corresponding time course.
EEG/MEG
EEG/MEG Basics

- The electrical activity of neurons produces currents that spread throughout the brain.

- When these currents reach the scalp, in the form of voltage changes and magnetic fields, they can be measured non-invasively.

- EEG measures voltage fluctuations sensed by an array of electrodes placed on the scalp.

- MEG measures the magnetic fields produced by the electrical currents using an array of sensitive magnetic field detectors.
EEG Data

EEG channel locations

EEG signals at each location
EEG/MEG Basics

- The signals recorded by EEG and MEG directly reflect current flows generated by neurons within the brain.

- These signals are measured with millisecond temporal resolution, and provide the most direct measurement of brain processing available non-invasively.
  - The spatial resolution of these methods is limited.
EEG/MEG Basics

• Building maps of brain activity from EEG/MEG signals requires the solution of an inverse source localization problem.
• Typical EEG/MEG studies involve the presentation of repeated stimuli.

• MEG and EEG data is often averaged over trials to form event-related fields (ERFs) and event-related potentials (ERPs), respectively.

• ERFs and ERPs are typically characterized by a series of deflections in their time course, which are differentially pronounced at different recording sites on the scalp.
COMPARING MODALITIES
Comparing Modalities

• Each functional neuroimaging modality provides a unique window into the brain.

• PET and fMRI are the most widely used and provide the most anatomically specific information across the entire brain.

• The relatively good spatial resolution of PET and fMRI complement the precise timing information provided by EEG and MEG.
PET vs fMRI

• Activation in both PET and fMRI reflect changes in neural activity only indirectly, and they measure different biological processes related to brain activity, which may be broadly defined as the energy-consumption of neurons.

• The spatial resolution of PET is on the order of 1-1.5 cm$^3$ and fMRI is typically on the order of 27-36 mm$^3$ for human studies.
PET vs fMRI

• Because PET computes the amount of radioactivity emitted from a brain region, enough time must pass before a sufficient sample of radioactive counts can be collected.
  – Temporal resolution limited to blocks of at least 30s.

• Functional MRI has its own temporal limitations due largely to the latency and duration of the hemodynamic response to neural events.
  – HRF does not reach their peak until several seconds after local neuronal and metabolic activity has occurred.
  – The locking of neural events to the vascular response is not very tight.
## PET vs fMRI

### Table 2. Relative advantages of fMRI and PET

<table>
<thead>
<tr>
<th>Advantages of fMRI</th>
<th>Advantages of PET</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cost and availability</td>
<td>fMRI has lower cost, more facilities available</td>
</tr>
<tr>
<td>Spatial resolution</td>
<td>fMRI has higher resolution, but new PET scanners can have same functional resolution for group studies</td>
</tr>
<tr>
<td>Temporal resolution</td>
<td>fMRI is superior, permitting event-related designs</td>
</tr>
<tr>
<td>Brain connectivity analyses</td>
<td>fMRI permits time series connectivity analysis; PET and fMRI both permit individual differences analysis</td>
</tr>
<tr>
<td>Combination with other measures</td>
<td>Simultaneous time-series acquisition of fMRI and EEG provides most detailed mapping of relationships</td>
</tr>
<tr>
<td>Single-subject studies</td>
<td>fMRI permits detailed high-resolution studies of individuals</td>
</tr>
<tr>
<td>Repeatability</td>
<td>fMRI does not use radioactive substances, so frequent scans are considered safe</td>
</tr>
<tr>
<td>Measuring neurochemistry</td>
<td>PET is superior; can be used to directly investigate neurochemistry</td>
</tr>
<tr>
<td>Transparency of activation measures</td>
<td>PET provides more direct measures of blood flow or metabolism</td>
</tr>
<tr>
<td>Artifacts</td>
<td>PET does not suffer from magnetic susceptibility artifacts and gradient- or RF-related artifacts</td>
</tr>
<tr>
<td>Combination with other measures</td>
<td>PET is not magnetic and can be combined with simultaneous EEG, MEG, and TMS</td>
</tr>
<tr>
<td>Studying baseline activity</td>
<td>PET provides quantitative measure of baseline state; ASL fMRI also can, but is less commonly available</td>
</tr>
<tr>
<td>Naturalness of environment</td>
<td>PET is quieter and has more open physical environment; advantage for auditory and emotion tasks</td>
</tr>
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Wager et al, 2010
Comparing Modalities

• The signals recorded by EEG/MEG directly reflect current generated by neurons within the brain.

• The spatial resolution of EEG is around $6 \text{ cm}^3$. In addition, it only measures activity on the surface of the cortex, and not from deeper structures.

• However, it is less expensive and more convenient for using with patients than fMRI and PET.

• Due to its excellent temporal resolution, it is useful for monitoring online activity, and ideal for Brain-Computer Interface (BCI).
MEG vs EEG

• The main advantage of MEG over EEG is that has a relatively better spatial resolution.
  – Magnetic fields are less distorted than electric fields by the skull and scalp.

• EEG tends to be sensitive to activity in more brain areas, but activity visible in MEG can also be localized with more accuracy.
  – MEG only detects tangential components of the current.
STATISTICAL/MATHEMATICAL ISSUES
Several approaches exist to solving the ill-posed electromagnetic inverse problem.
Once a large number of events have been recorded, the goal is to use this information to estimate the density of the emitting compound across the object, allowing for the creation of an image of the uptake of the compound.

- Filtered back-projection
- EM-algorithm (Shepp and Vardi)
Images acquired in the frequency domain (or k-space).

- Compressed sensing
- Parallel Imaging
- Multiband
Preprocessing

- All neuroimaging data undergoes a large amount of pre-processing before it is ready to be analyzed.

![Flowchart of preprocessing steps for fMRI and EEG data.]
• Much of the focus of neuroimaging research has been on finding regions that are active during a specific task or related to certain behavioral measure.
Brain Mapping

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.
   - Massive multiple comparison problem.
In the past few years significant focus has been placed on determining how different brain regions are connected with one another.

Cribben et al. (2012)
Varieties of Connectivity

**Structural connectivity**
- Presence of axonal connections
- Tractography

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

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

**Dynamic connectivity**
- Assess state changes

*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.
Recently, interest has focused on using a person’s brain activity 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)
Example

Comparing social and physical pain

Woo et al. 2015
MULTI-MODAL METHODS
Multi-modal Analysis

• All methods used in the human neurosciences have limitations.

• A current trend is to use multiple methodologies to overcome some of the limitations of each method used in isolation.
  – Simultaneous fMRI / EEG or MEG
  – Simultaneous MRI / PET
Simultaneous EEG-fMRI

- EEG-fMRI allows for simultaneous acquisition of electrophysiology and hemodynamic information.
  - Provides high spatial and temporal resolution.
  - Requires the presence of MRI compatible EEG amplifiers and electrodes.
  - Artifacts in the EEG recordings due to switching on and off the MRI gradients.

http://fmri.uib.no/
Simultaneous PET-MRI

- PET-MRI incorporates the spatial resolution of MRI with the functional capabilities of PET.
  - Requires an MRI-compatible PET camera.

http://medicalphysicsweb.org/
Future Directions

• The field surrounding 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.

• Coming this fall: Neuroimaging specialization on Coursera!

Joint course with Tor Wager, UC Boulder