Functional Neuroimaging with PET

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Seeing the Brain

Just look at it!

Anatomic Images (MRI)

Functional Images

PET

fMRI

EEG

(Just try to get informed consent!)
What is a Functional Image?

Anatomic Image

<table>
<thead>
<tr>
<th>Live volunteer</th>
<th>Functional Image</th>
</tr>
</thead>
<tbody>
<tr>
<td><img src="image1.png" alt="Anatomic Image" /></td>
<td><img src="image2.png" alt="Functional Image" /></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Dead volunteer</th>
</tr>
</thead>
<tbody>
<tr>
<td><img src="image3.png" alt="Anatomic Image" /></td>
</tr>
</tbody>
</table>

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Parametric Images

Associating a parameter of interest with locations (voxels) throughout the brain.

**PET:** concentration of radioactivity (mCi/cc brain tissue)

**fMRI:** paramagnetic signal from deoxygenated hemoglobin (~volts)

**EEG:** electrical signal strength (volts)

**MRI:** T1-weighted paramagnetic spin realignment (~volts)
A Functional Image starts with a Measurement

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Extracting Data from Images

Examine values at specific locations (voxels) throughout the image volume.
Extracting Data from Images

ROI Analysis: Extracting the average value for all voxels within a Region-of-Interest.

ROI is drawn on MRI image.

ROI value is extracted from functional image.

Average value of voxels inside ROI is 6.7 microCi/cc
ROI Analysis

[Image: Brain scans with ROI analysis software interface]
ROI Analysis: Morphometry

Measuring the volume of an anatomic structure.
Extracting Data from Images

Time series: examining how data in a voxel changes over time.

fMRI image with overlay showing degree of correlation to ideal response function.

Time series over 17 sec for 9 voxels shown inside green rectangle. (Ideal response function shown in green.)
Extracting Data from Images

ROI time series: examining how data in a ROI changes over time.

[Images of ROI time series and graph showing [F-18]-F-L-DOPA uptake]
Some modalities (PET) are said to be quantitative because the values are in terms of basic physical units, and these can be directly compared across time and/or subjects.

Furthermore, these images can be converted into other (more interesting) units, such as a biochemical or physiological rate-constant.

\[
\text{ICMRglu} = \left( \frac{C_g}{LC} \right) \left( \frac{k_1 k_3}{k_2 + k_3} \right) \left( \frac{C_i(T) - C_e(T)}{C_m(T)} \right)
\]

\[
\text{ICMRglu} = L \ast C_g \left( \frac{C_i(T) - C_e(T)}{C_m(T)} \right)
\]
Quantitative Images

Images which represent an underlying physiological process are (usually) more interesting than images of the "raw" measured data. There may be little visual difference between raw and quantitated images, but it is the underlying values that are important.
The Challenge: how to reduce a vast amount of data to a few pithy numbers.

Example: A typical fMRI study consists of 209 scans, each with 64x64x23 voxels. This is 20 million pieces of data!

For many studies, examining individual voxels or drawing ROIs is prohibitively time-consuming.
Data Reduction: Statistical Parametric Map (SPM)

Goal: Find brain regions that are activated by a tone.

Model for Listening task:

- tone is off on off on off on off on off on off on off on

Fitted and adjusted responses test

SPM results:
- SPM(T_{73,91})
- Height threshold: T = 5.22
- Extent threshold: k = 0 voxels

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Data Reduction: Statistical Parametric Map (SPM)

- Where is the activation?
- How strong is it?
- How significant is it?
- Is it repeatable?
- Can these results be generalized to a larger population?

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Functional Volumes

PET slices

Healthy

Parkinsonian

MRI slices

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Visualisation: 4D

Areas of the brain activated when mothers view pictures of their own infants (red) and of other infants (blue)
Part II: PET Particulars

• How does the PET scanner work?
• What is a tracer?
• How do you make a tracer?
• What types of tracers do we have?
• What types of studies do we do?
• What types of studies COULD we do?
Positron Annihilation

- Positron emitting atom
- Neighboring atom
- Positron annihilation
- Gamma-Ray range: 10 mm - ∞
- Positron range: 1-10 mm

∠ #1

180°

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A Functional Image starts with a Measurement

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Dynamic Scan

4 x 0.5 min
4 x 2 min
10 x 10 min
A Tracer...

- Mimics (follows, traces) a physiologically interesting molecule or process
- Is related in a known way to a naturally-occurring analog
- Does not alter the process being studied
  - it is inert, or
  - it is present in extremely low concentrations.
- Must yield a concentration measurement in tissue.
  - Tracer molecule must be labeled with a special atom or molecule.
So many tracers, so little time...

Physiological Processes

- Blood Flow
- Blood volume
- Perfusion
- Metabolism
- Lung, liver, kidney function
- Cardiac output
- DNA / RNA and protein biosynthesis
- Neurotransmission

Physiologically relevant positron emitters

- $^{17}$F (t$_{1/2} = 1$ min)
- $^{15}$O (t$_{1/2} = 2$ min)
- $^{13}$N (t$_{1/2} = 10$ min)
- $^{11}$C (t$_{1/2} = 22$ min)
- $^{18}$F (t$_{1/2} = 110$ min)
Neurotransmission

Processes:
- Postsynaptic / Presynaptic
- Agonist / Antagonist
- Specific neurotransmitter sub-types
- Synthesis
- Transport across cell membranes
- Reuptake
- Displacement
- Vesicular storage

Systems
- Dopamine
- Seratonin
- Choline
- Opiate
- Benzodiazepine
How to make a PET tracer

1. Make a positron emitter
2. Label a precursor
Radiosynthesis rig for $\left[{^{11}C}\right]$-methyl iodide

- 90% N$_2$ + 10% H$_2$
- 6 MeV protons
- NH$_3$ Trap -70°C
- Drierite
- 14N(p,a)11C
- 700°C Oven
- $I_2$ + CH$_4$ → CH$_3$I
- Recirculation Loop
- CH$_3$I Trap (Porapak) and heater (PC control)
- Ascarite CO$_2$ Trap
- Radiation Monitors (PC read)
- Pressure and Flow Sensors (PC read)
- Dallas Trap

PC for valve and temp. control, and sensor reading

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Radiosynthesis rig for $[^{11}\text{C}]-\text{methyl iodide}$
Current PET studies

• Metabolism:
  • $[^{18}\text{F}]$-FDG (glucose analog): the workhorse
  • $[^{15}\text{O}]$-O$_2$
  • $[^{18}\text{F}]$-FLT (fluoro-levo-tyrosine: DNA synthesis => oncology)
• Blood flow
  • $[^{15}\text{O}]$-H$_2$O
  • $[^{15}\text{O}]$-CO (blood volume)
  • $[^{17}\text{F}]$-CH$_3$, $[^{18}\text{F}]$-CH$_3$
• Dopaminergic system
  • $[^{18}\text{F}]$-fluoro-L-DOPA (vesicular storage)
  • $[^{18}\text{F}]$-FMT (fluoro-meta-tyrosine: dopamine synthesis)
  • $[^{18}\text{F}]$-fallypride (high-affinity post-synaptic D2 receptor)
  • $[^{18}\text{F}]$-desfallypride (medium-affinity post-synaptic D2 receptor)
  • $[^{11}\text{C}]$-raclopride (low-affinity post-synaptic D2 receptor)
• Benzodiazepine
  • $[^{11}\text{C}]$-PK11195 (activated macrophages)