fMRI as a Biomarker: Quantitation and Reproducibility

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Functional MRI (fMRI) is primarily used clinically to map speech and motor function prior to brain surgery.
fMRI – Patient performs tasks using simple visual cues and alternating block designs

Bilateral hand motion task

Silent sentence-completion task

Old MacDonald had a ________.

15s

vs

Bnd MwjGhdckj ckr

n ________.

15s
How does fMRI work?

T2*-weighted Blood Oxygenation Level Dependent (BOLD) imaging is sensitive to local changes in blood flow.

“Rest”

“Task”

from Mosley
During a ~5-minute fMRI scan the patient performs many cycles of a simple task.
20-30 echo-planar images are acquired every TR (~1.5s),
This yields a time series of ~200 brain image volumes.
Image intensity varies with the task in some voxels.
Statistical image processing

Compare the timing of the observed fluctuations in the fMRI images to the expected fluctuations of the BOLD response.

Task timing

Predicted response

Actual response

Comparison methods:
- image subtraction
- t-test differences
- frequency analysis (FFT)
- temporal correlation
- General Linear Model (analysis of variance)

Statistical significance identifies “active” voxels (statistical value above some minimum threshold)

Thresholded “map” of active voxels is overlaid on MR images
Examples
Language – LH 34 yo with insular tumor
Language & motor – RH 82 yo parietal tumor
Language & motor – RH 12 yo with epilepsy
fMRI as a Quantitative Biomarker
Things we would like to quantify:

- Localization of brain activity
  - Brain coordinates of the speech/motor centers?
- Spatial extent of active brain region
  - What can be resected without impairing function?
- Relative activation of different brain areas
  - Which cortical hemisphere is dominant (essential)?
- Amplitude of activation within brain areas
  - Diagnostic: Is activation level abnormal?
  - Treatment monitoring: Is treatment effective?
  - Research: How does experiment affect brain activity?
- To be quantitative, results must be reproducible
Obstacles to fMRI reproducibility

- BOLD is an indirect measure of neural activity
  - Many factors intervene between activity and BOLD
- Traditional analysis methods emphasize statistical significance over signal amplitude
  - Significance is used to define active areas
  - Significance is very sensitive to noise components
- Brain function is complex and variable
  - Task details affect activity pattern
- Scanners differ by manufacturer, field strength
- Scans depend on sequence parameters, technologist
- Etc...
Traditionally, fMRI is quantitatively not reproducible.

Liu et al., “Reproducibility of fMRI at 1.5T in a Strictly Controlled Motor Task”, MRM 2004
Language – first scan
Language -- rescan
Overlap of 2 Language t-maps
Can fMRI be reproducible or quantitative?

- BOLD signal is closely linked to neuronal activity
  - Good correlations between BOLD and optical imaging or electrophysiological recordings
- Improved image acquisition methods
  - Greater specificity and sensitivity to microvasculature
- Improved task design and behavioral control
  - Consistent spatial patterns of brain function should yield consistent spatial patterns of BOLD signals
- Improved analysis methods (normalization)
  - Need to control for non-task variables
- Goal is reproducible quantitation, not necessarily absolute quantitation
Quantitative Imaging Biomarker Alliance (QIBA) is a research effort of the Radiological Society of N. America (RSNA)

Developing a QIBA biomarker:
- Identify imaging methods that could be biomarkers
- Define the biomarker
- Specify a context of use for the biomarker
- Establish quantitative “claims” for the biomarker
- Formalize procedures for how to achieve the claims
  - Device specifications
  - Imaging protocol
  - Data quality assessment criteria
Simple biomarker example (non-imaging)

- Biomarker
  - Body temperature
- Context of use
  - Diagnosis of fever
- Quantitative claim
  - Measured body temperature will be within 0.1°C of the true body temperature with 95% confidence
- Procedures
  - Performance specifications for the thermometer
  - Place under the tongue with patient at rest for 1 min.
  - Read value, place under tongue for 30s more, read again
- QA constraints
  - Both values read must be the same (within 0.1°C)
fMRI Biomarker

- **Biomarker**
  - T2*-weighted BOLD signal response to a task ("activation")

- **Context of use**
  - Quantify location and spatial extent of language or motor areas to assess risk of causing aphasia or paralysis in brain surgery

- **Quantitative claim**
  - Location of the peak of BOLD activation can be measured to within 5mm of the true peak with 95% confidence
  - Location of the half-maximum border of BOLD activation can be measured to within 1cm of the true border with 95% confidence

- **Procedures**
  - Performance specifications for the MR scanner
  - Task specifications, MR scanning protocol, patient training, positioning
  - Patient performance monitoring
  - Image processing protocol

- **QA constraints**
  - Head motion, task performance, image SNR, scanner drift, ...
Real-time fMRI – Acquisition quality control

Monitoring task performance is crucial for successful fMRI.

Activation Maps

Head motion & Mean intensity

Monitor eye and/or hand movements

Record cardiac and Respiratory oscillations
Monitor sources of signal variance
Variability due to image processing methods:
Same scan data analyzed at 8 clinical fMRI sites
Statistical maps measure **significance**. Want maps that measure **signal**.

Even a constant pattern of brain activity can result in very different statistical activation maps, depending on significance threshold.
Statistical significance of activation changes as a function of scan time

Activation mapping as percentage of local excitation (AMPLE)

Fixed-threshold mapping

Relative-threshold mapping
Activation mapping as percentage of local excitation (AMPLE)
AMPLE maps are consistent across scans or scanners

<table>
<thead>
<tr>
<th>Subject 1</th>
<th>1.5T Spiral In</th>
<th>1.5T EPI</th>
<th>1.5T Spiral Out</th>
<th>4.0T Spiral Out</th>
<th>4.0T Spiral In</th>
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<tbody>
<tr>
<td><strong>Standard t-maps (t ≥ 4.0)</strong></td>
<td><img src="image1.png" alt="Image" /></td>
<td><img src="image2.png" alt="Image" /></td>
<td><img src="image3.png" alt="Image" /></td>
<td><img src="image4.png" alt="Image" /></td>
<td><img src="image5.png" alt="Image" /></td>
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<tr>
<td><strong>AMPLE t-maps (t ≥ 50%)</strong></td>
<td><img src="image6.png" alt="Image" /></td>
<td><img src="image7.png" alt="Image" /></td>
<td><img src="image8.png" alt="Image" /></td>
<td><img src="image9.png" alt="Image" /></td>
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Voyvodic, MRI, 2006
Simulation studies

Generate simulated fMRI data with known activity levels

Voyvodic, MRI, 2006
Anatomical spread of active voxels

Voyvodic et al, JMRI, 2009

- >= 30%
- >= 50%
- >= 70%
- >= 90%
Overlaid Repeat Language t-maps

1st scan

2nd scan

3rd scan

4th scan
Overlaid Repeat Language AMPLE
Language overlap and motor AMPLE – 34 yo
Language AMPLE maps improve reproducibility

Upper 40% of AMPLE peaks are most reproducible
Same scan analyzed at 8 clinical fMRI sites
Scan analyzed at 8 fMRI sites + AMPLE
Current research projects

- We have a database of over 800 patient fMRI exams
- Quantify reproducibility metrics for repeated tasks
- Generate overall metrics of scan quality
  - Subjective assessment (5 raters)
  - Task performance consistency
  - BOLD signal contrast
- Correlate head motion metrics with above
- Create digital reference objects (DROs) and test
  - DROs look like real brain scans
  - They are synthesized by combining known components
  - “Truth” is known
  - Components can be manipulated to test sources of variance
Assessing fMRI results: QA metrics

- Identifying useful metrics
  - Head motion
    - Average or Maximum displacement
    - Average or maximum rotation
    - Fraction of images with motion greater than X
  - Task performance
  - Image SNR
    - BOLD signal contrast (between vs within blocks)
- Determining threshold values
Head motion is the most common source of problems in fMRI

The best (only) solution for excessive head motion is to stop scanning and convince the patient to stay still.

Intermittent motion can be dealt with by omitting problem images.
Task performance: signal consistency

Activation-weighted average time course signal for different patients

Consistency index:

Consistency index (B correl A): 0.64
Simulations using average time course signals from 400 different patients

Standard t-maps

AMPLE t-maps
Conclusion

- fMRI can be reproducible
- Reproducibility is essential for clinical use
- Converting reproducibility to a quantitative biomarker is still a challenge
- Quality control is critical for reliable results
  - Statistical significance for confidence threshold
  - Local signal consistency as reproducibility measure
  - BOLD signal amplitude for relative activation
- Quantitative fMRI has great potential