Clinical fMRI as a quantitative imaging biomarker of brain function

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Collaborators

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- QIBA fMRI Biomarker Committee
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 _______ | vs | Bnd MwjGhdckj ckr n _______ | 15s | 15s |
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.
Image signal pre-processing

- Filter out known nuisance signals (usually)
  - Head motion (measure motion - realign images)
  - Regression filter (heartbeat, respiration, drift)

- Filter out high-frequency noise (always)
  - Spike filter
  - Spatial smoothing
  - Temporal smoothing
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
Functional maps can be overlaid on brain anatomical images, resampled, and viewed from any orientation.
Motor cortex mapping prior to neurosurgery

$T = 0 \text{ s}$
T = 13.5 s
$T = 38.0 \text{ s}$
Clinical fMRI exam

- 10 min pre-scan assessment and training
- 45 min MRI session
  - 10 min anatomical scans (T1 & FLAIR)
  - 15-20 min fMRI – 3-4 tasks (4 min each)
  - 5 min 30-direction DTI scan
- 30-60 min post-scan image analysis
  - Registration of fMRI and DTI with T1 images
  - Definition and statistical analysis of “active” voxels
  - Overlay of fMRI and DTI on anatomical images
- Neuroradiological interpretation
Clinical fMRI exam

Anatomy & pathology

fMRI maps & 3D reconstructions

DTI Maps & Fiber tracks
Diffusion tensor imaging (DTI) is used to map major white matter tracts.
When all goes well fMRI is easy

Statistical significance provides map of brain activity

This fMRI map was computed from ~13,000 images.
Clinically, how do we assess whether all went well?
fMRI -- Clinical goals

- Determine location and borders of eloquent (essential) cortical areas relative to lesions
- Determine location of major white-matter tracts connecting eloquent areas
- Evaluate risk of post-surgical functional deficits
- Decide whether surgery is advisable
- Plan surgical approach and extent of resection
- Decide whether intraoperative mapping is necessary
fMRI -- Technical goals

- Tasks that selectively activate eloquent brain areas
  [appropriate and effective]
- Detect BOLD signals to identify eloquent brain areas
  [sensitivity & specificity]
- Map location relative to anatomy and pathology
  [image registration]
- Evaluate laterality of language dominance
  [relative activation]
- Map edges of areas and proximity to lesion
  [thresholding & quantitative reproducibility]
- Measure brain function (or change in function)
How to do quantitative fMRI?

- How best to acquire images?
- How best to analyze images?
- How to assess image quality?
  - What data quality metrics can distinguish good scan from bad?

Goal is to make fMRI a quantitative biomarker of brain function.
Collaborative efforts to make fMRI quantitative & reproducible

Organizations:
  BIRN (Biomedical Informatics Research Network)
  ASFNR (American Soc. of Functional Neuroradiology)
  QIBA (Quantitative Imaging Biomarkers Alliance) of the RSNA (Radiol. Soc. of N. America)

Strategies:
  Standardize acquisition and analysis
  Improve quality assessment metrics (QA)
  Assess and reduce sources of signal variance
  Determine reproducibility claims
On a test-retest basis, BOLD fMRI can be performed reproducibly to a level such that:

- the **center of mass of activation** of a focus of interest can be determined with a ?? mm repeatability coefficient
- the **spatial extent** half-maximum border of activation clusters can be determined with a ?? mm repeatability coefficient
- the **relative magnitude** of activation in homologous regions across hemispheres can be determined with a ?? % repeatability coefficient
Sources of variance affecting fMRI

- Scanner*
- Task design*
- Training procedures*
- Stimulus presentation system*
- Physiology
- Pathology
- Patient movement
- Task performance
- Analysis procedures

* Controlled by standardization
Patient compliance is a bigger issue for fMRI than other scan procedures

- **Training**
  - Patients must actively participate in fMRI
  - Tasks must be appropriate and understood
  - Task fMRI is done on patients 5yo to >80yo

- **Task performance**
  - Anxiety affects fMRI results
    - Getting patients relaxed is important
  - Head motion is most common problem
  - Important to assess performance in real-time
Real-time monitoring is critical for successful clinical fMRI

Dual screen real-time behavioral display

Direct observation of eye and hand movements

Real-time MRI analysis

Activation maps

Head motion & mean intensity

Voyvodic et al., Frontiers Neuroinfo. (2011)

Voyvodic, NeuroImage (1999)
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
Obstacles to fMRI reproducibility

- BOLD is an indirect measure of neural activity
  - Many factors intervene between activity and BOLD

- Brain function is complex and variable
  - Task design affects activity pattern
  - Task performance affects BOLD signal

- Traditional analysis methods emphasize statistical significance over signal amplitude
  - Significance is used to define active areas
  - Significance is very sensitive to noise components
Statistical thresholding is a major source of variability.

Even a constant pattern of brain activity can result in very different activation maps, depending on statistical threshold.

Voyvodic, MRI, 2006
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
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</strong> (t ≥ 4.0)</td>
<td><img src="image1.png" alt="Image" /></td>
<td><img src="image2.png" alt="Image" /></td>
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<tr>
<td><strong>AMPLE t-maps</strong> (t ≥ 50%)</td>
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Voyvodic, MRI, 2006
Activation mapping as percentage of local excitation (AMPLE)

Voyvodic, MRI, 2006
Threshold Reproducibility DROs

Generate simulated fMRI data with known activity levels

Conclusion: Once AMPLE time plots stabilize activation is reliable.
Anatomical spread of active voxels

Voyvodic et al, JMRI, 2009
Central sulcus profiles

- t-values - 2 task cycles
- t-values - 10 task cycles
- AMPLE - 2 task cycles
- AMPLE - 10 task cycles
AMPLE maps improve language reproducibility

<table>
<thead>
<tr>
<th>t (≥4) Maps</th>
<th>PctSig (≥1%)</th>
<th>AutoLobe ROIs</th>
<th>AMPLE (≥60%)</th>
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<tr>
<td><strong>Right</strong></td>
<td><strong>Left</strong></td>
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<td>4T Spiral Out</td>
<td>4T Spiral In</td>
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Subject 1
Language AMPLE maps improve reproducibility

Upper 40% of AMPLE peaks are most reproducible
Assessing fMRI results: QA metrics

- Identifying useful metrics
  - Stability of activation signal
  - Head motion
    - Average or Maximum displacement and rotation
    - Fraction of images with motion greater than X
  - Task performance
  - Image SNR
  - BOLD signal contrast (between vs within blocks)
  - Pathology – neurovascular uncoupling

- Determining threshold values
  - E.g. How much motion is too much?
Determine sources of signal variance

A. Instrument (raw) Noise: Add varying amounts of Rician or 1/f noise to voxel time series.

B. Ghosting: Alias voxels at each time point along the phase encoding direction.

C. Geometric Distortion: Local warping of images (due to poor shim or locally heterogeneous susceptibility).

D. Signal Drift: Introduce linear and/or low frequency signal drifts.

A. Random Rigid Motion: Introduce varying amounts of head motion to shift each voxel’s “true” BOLD response to different nearby voxels. Model “partial voluming”.

B. Task Correlated Motion: Add additional head motion that is correlated with task start and stop times.

C. Brain Motion within Skull: Use empirical motion data to introduce elastic brain motion (may be related to respiratory or regional cardiac pulsation).

Scanner Noise
- A. Instrument Noise
- B. Ghosting
- C. Geometric Distortion
- D. Signal Drift

Head Motion
- A. Random Rigid Motion
- B. Task Correlated Motion
- C. Brain Motion within Skull

Physiological Noise
- A. Network Fluctuations
- B. Cardiac Fluctuations
- C. Respiratory Fluctuations
- D. Neurovascular Uncoupling

Task Dependent Noise
- A. Attention (within scan)
- B. Arousal (across scan)
- C. Response Time

DRO’s: Synthetic realistic fMRI time series

C. Response Timing: fMRI response waveform shape and timing varies relative to task onset/offset. (Behavioral & hemodynamic)
Digital reference objects (DROs)
Synthetic realistic imaging data

Brain anatomy + Static EPI images + Physiological noise

Map of active areas + Task-dependent signals + Analysis

→ fMRI maps
Same data analyzed at 8 clinical fMRI sites
Hand-movement task

“Standard” threshold

AMPLE 50% threshold

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DRO1
Sentence language task

“Standard” threshold

AMPLE 50% threshold
Sentence language task

“Standard” threshold

AMPLE 50% threshold
Registering functional and anatomical images
Quantifying center of mass of activation (CMA)

Hand Motor Cortex -- dCenter of Activation

Standard Threshold

Ample 50% Threshold

Single activation cluster CMA displacement for 8 sites for each DRO
Quantifying spatial extent of activation

Hand Motor Cortex -- Volume of Activation

Standard Threshold

 RH

LH

Ample 50% Threshold

 RH

LH

Single activation cluster volumes for 8 sites for each DRO
Quantifying language hemispheric dominance

Language Cortex -- Weighted Laterality Index

Receptive and expressive laterality for 9 site maps for each DRO
Task performance DROs: 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

Conclusion: Consistency index > 0.5 is good task performance
Consistency of performance across multiple task cycles

- Mean active signal
- Cycle amplitude
- Cycle correlation
- Mean single cycle

![Graph showing consistency of performance across multiple task cycles with specific values for mean active signal, cycle amplitude, cycle correlation, and mean single cycle.](image)
Head motion is a pervasive problem in fMRI.

Examples of different Patterns of head motion.
Motion Issues

- How to avoid motion
- Head motion complexity
- How to measure (estimate) motion
- How to compensate for motion
- Effectiveness of "motion correction"
- How much motion is too much?
Creating motion phantoms (DROs)

Base images with no activity and no motion

Add activation pattern, activation time course, and motion
Digital motion phantoms – added motion is very similar to original actual.

Human Phantom

Base

Human Phantom
Motion correction: Motion between volumes is correctable.
Realign image volumes to “correct” motion
Choice of reference volume can affect motion correction

Measure “residual motion” by recalculating motion metrics after realignment.

Residual motion varies as a function of realignment reference volume.
Motion within volume is not correctable by realignment

Conclusion: Use image registration to reposition volumes between movements, and omit volumes when head is actively moving. Problem scan if more than ~10% of volumes actually moving.
Combining realignment and censoring can enhance signal detection.
Conclusions

- To be reproducible and quantitative, clinical fMRI should satisfy specific QA metrics:
  - BOLD signal amplitude is significantly above noise (AMPLE 50%: p < .05), and
  - Task performance is reasonably consistent (CI > 0.5), and
  - The spatial pattern stabilizes over time, (AMPLE 50% reaches plateau), and
  - Residual head motion after correction is minimal (no motion > 1mm?)
Once it is quantitative and reproducible fMRI will be able to actually measure brain activity (not just locate activity)

Then fMRI could be used clinically to assess neurological or psychiatric disorders, disease progression, and patient response to therapies