Clinical applications of fMRI: Present and Future

James Voyvodic, Ph.D.
Brain Imaging and Analysis Center
Duke University Medical Center
Functional MRI (fMRI) is primarily used clinically to map speech and motor function prior to brain surgery.
Diffusion tensor imaging (DTI) is used to map major white matter tracts.
**fMRI & DTI**

**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 & DTI
Technical goals

- 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 connectivity
- Measure brain function (or change in function)
fMRI – Patient performs tasks using simple visual cues and alternating block designs

Bilateral hand motion task

Silent sentence-completion task

Old MacDonald had a ________.

Bnd MwjGhdchkj ckr n ________.

15s vs 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.
Image signal pre-processing

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

- Filter out high-frequency noise
  - 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
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
  - fMRI statistical analysis of “active” voxels
  - Overlay of fMRI and DTI on anatomical images
- Neuroradiological interpretation
Patient compliance is a bigger issue for fMRI than other scans

- **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

Real-time MRI analysis

Head motion & mean intensity

Activation maps

Direct observation of eye and hand movements

Voyvodic et al., Frontiers Neuroinfo. (2011)

Voyvodic, NeuroImage (1999)
Silent sentence-completion reading task

Real-time fMRI mapping and head-motion plots
Summary fMRI maps can combine multiple task areas and pathology
fMRI validation by direct comparison with intraoperative mapping
Acquire diffusion-weighted images at multiple diffusion orientations (6-60)

Calculate diffusivity and orientation at each voxel

Color-code orientations
Can overlay color-coded FA map on anatomy
DTI – fiber tracking

Start at any ‘seed’ and connect voxels with similar orientations

Overlay fiber tracks on anatomy
Clinical fMRI – Localization of language and motor areas (e.g. 12 yo with epilepsy)
Language and motor -- RH 82 yo with parietal tumor
Language -- LH 34 yo with insular tumor
In resting-state fMRI, a person lies still for ~10 minutes. Low frequency (<0.1 Hz) oscillations in BOLD signal are correlated in interconnected brain regions. Oscillations in 1 area can be used to find connected areas. ICA analysis can be used to identify “networks” based on similarity of resting-state oscillations.

Goodyear et al., 2014
fMRI & DTI
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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
Head motion is the most common source of problems in fMRI.

The best solution for excessive head motion is to stop scanning and help the patient to stay still.

Intermittent motion can be dealt with by omitting problem images.
Consistency of performance across multiple task cycles

Mean active signal
Cycle amplitude
Cycle correlation
Mean single cycle
Passive language tasks

Receptive and expressive language areas can be activated using passive tasks such as listening to a story or watching a video.

4 min video with narration
In alternate 15s blocks

Red – sentence-completion task
Green – video narration
Measuring BOLD amplitude differences

Within one scan

Two different scan sessions
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.
Statistical significance of activation changes as a function of scan time

Fixed-threshold mapping

Relative-threshold mapping

Activation mapping as percentage of local excitation (AMPLE)
Activation mapping as percentage of local excitation (AMPLE)

A

B

C

D

Voyvodic, MRI, 2006
AMPLE maps are consistent across scans or scanners.

Voyvodic, MRI, 2006
Anatomical spread of active voxels

Voyvodic et al, JMRI, 2009
AMPLE maps improve language reproducibility
Language AMPLE maps improve reproducibility

Upper 40% of AMPLE peaks are most reproducible
Simulation studies

Generate simulated fMRI data with known activity levels

Voyvodic, MRI, 2006
Sources of 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).

A. Network Fluctuations: Based on known brain networks, add random low-frequency signal for each network to gray matter voxels.

B. Cardiac Fluctuations: Use recorded respiratory data and empirical analyses of respiratory BOLD effects and add these to voxel time series.

C. Respiratory Fluctuations: Use recorded cardiac data and empirical analyses of cardiac BOLD effects and add these to voxel time series.

D. Neurovascular Uncoupling: Vary the shape and magnitude of hemodynamic response function across voxels.

A. Attention (within scan)
B. Arousal (across scan)
C. Response Time

A. Attention: fMRI magnitude varies within/across task epochs either randomly or correlated with task condition.

B. Arousal: fMRI magnitude varies across scans.

C. Response Timing: fMRI response waveform shape and timing Varies relative to task onset/offset. (Behavioral & hemodynamic)
Same scan analyzed at 8 clinical fMRI sites
Scan analyzed at 8 fMRI sites + AMPLE
Currently, clinical fMRI can locate eloquent cortex. In the future, clinical fMRI will be used to measure changing levels of brain activity. Doing so will require improved reproducibility, improved tasks, and improved analysis methods (improved acquisition methods will also help). Once able to measure brain activity, fMRI could be used clinically to assess neurological or psychiatric disorders, disease progression, and patient response to therapies.
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
  - How task is performed affects activity pattern
Making fMRI reproducible and more quantitative

- Develop methods more closely linked to neuronal activity
  BOLD vascular signals are highly correlated with optical imaging and electrophysiological recordings; but more direct methods may be possible

- Continue to improve BOLD image acquisition methods
  Greater specificity and sensitivity to microvasculature to improve resolution

- Improved task design and behavioral control
  Consistent spatial patterns of brain function should yield consistent spatial patterns of BOLD signals

- Improved analysis methods
  Filter out non-task variables
  fMRI activation measurement should reflect brain activity levels