Clinical fMRI at Duke

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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.
Clinical context of use

- Treatment planning for brain surgery
  - Brain tumors (> 90% of fMRIs at Duke)
  - Arteriovascular malformations
  - Epilepsy
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 (future)
- Measure change in brain function (future)
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 MwjGhdchkj ckr n ________.
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:
- General Linear Model (analysis of variance)
- t-test differences
- frequency analysis (FFT)
- temporal correlation
- image subtraction

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

Thresholded “map” of active voxels is overlaid on MR images
Summary fMRI maps can combine multiple task areas and pathology.

Yellow – Language areas
Blue – Mouth areas
Green – Hand areas
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
  - DTI fiber-tracking (if requested)
- Neuroradiological interpretation
A clinical fMRI exam produces many different types of images

Anatomy & pathology

fMRI maps & 3D reconstructions

DTI Maps & Fiber tracks
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
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 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
Standard fMRI tasks at Duke

- **Silent sentence-completion** (also have audio version)
  - Bnd MwjGhdchkj ckr
  - n ________ .
  - vs
  - Old MacDonald had a ________ .

- **Bilateral hand movement**
  - vs
  - vs

- **Antonym word generation**
  - vs
  - upstairs

- **Foot movement (unilateral)**
  - vs
  - <<< +

- **Mouth movement**
  - vs
  - <<< +++

All tasks preceded by short practice reminder (<1min); actual tasks are 4mins.
Passive language tasks

Receptive and expressive language areas can also 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 – passive video task
Diffusion tensor imaging (DTI) How does it work?

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
As traditionally performed, fMRI is not quantitatively reproducible.

Liu et al., “Reproducibility of fMRI at 1.5T in a Strictly Controlled Motor Task”, MRM 2004
Language fMRI is typically more variable than motor fMRI.

Overlap of same language task performed twice in one session:
- Red – first scan
- Green – second scan
- Yellow – overlap
Analysis methods at different hospitals vary

Same scan data analyzed at 8 clinical fMRI sites
Obstacles to fMRI reproducibility

- **BOLD is an indirect measure of neural activity**: Many factors intervene between activity and BOLD.
- **Traditional analysis sets threshold solely based on statistical significance**: Significance is very sensitive to noise components.
- **Brain function is complex and variable**: Task design affects activity pattern; task performance affects BOLD signal.
Statistical thresholding is a major source of variability

Setting the threshold determines which voxels are considered active.

Changing the statistical threshold can result in very different activation maps, despite a constant pattern of brain activity.

Voyvodic, MRI, 2006
To improve reproducibility we have developed a threshold normalization method

Activation mapping as percentage of local excitation (AMPLE)

Traditional fixed-threshold mapping yields different activation profiles as significance increases with scan duration.

The AMPLE method sets thresholds relative to the peak activity (e.g. 50% of the peak value), which results in less variable activation maps.

Statistical significance is affected by any factor that affects either signal or noise levels (e.g. scan duration, motion, attention, anxiety, practice effects, caffeine, tobacco, etc).
AMPLE results in more consistent fMRI maps

Activation maps are relatively independent of scan duration. The number of active voxels at any AMPLE level reaches a stable plateau.
AMPLE maps are consistent across scan sessions, scanners, or scan method.
Anatomical spread of active voxels

The upper 50% AMPLE peak of a hand motor map is consistently at the expected anatomical location in the pre- and post-central gyri.
Simulation studies, where true brain activity is known, show that once the number of voxels at any AMPLE level stabilize (plateau), the map accurately matches the true active voxels.

Generate simulated fMRI data with known activity levels

Voyvodic, MRI, 2006
AMPLE maps improve language reproducibility

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<th>AutoLobe ROIs</th>
<th>AMPLE (≥60%)</th>
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Subject 1

[Brain images showing AMPLE maps and comparison with other methods]
Same scan analyzed at 8 clinical fMRI sites
Scan analyzed at 8 fMRI sites + AMPLE
Current research projects

- We have a database of over 900 patient fMRI exams
- Quantify reproducibility metrics for repeated tasks
- Generate metrics of scan quality
  - BOLD signal contrast
  - Task performance consistency
  - Subjective assessment (5 raters)
- Create digital reference objects (DROs) and test
  - DROs look like real brain scans, except “Truth” is known
  - Components can be manipulated to test sources of variance
- Use DROs to assess effects of head motion and variability in task performance
- Goal is to improve reproducibility, reduce bias, and identify objective criteria for assessing scan quality
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 clinical and research potential