Cross-site image acquisition: fMRI

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Outline

• Motivation for multicenter imaging studies
• Issues in MC-fMRI studies
• Standardization of protocols
• QA
• Site Equalization
• Calibration

Context example: fBIRN

Why do Multicenter Neuroimaging Studies?
• Potential use of MRI/fMRI as a biomarker
  - structural/functional differences may predict disease;
    large study numbers are necessary for biodiversity
  - ADNI study using VBM methods to study cortical thickness
  - BJ Casey study using fMRI to examine ADHD
• Generate large data sets rapidly
• Access wide or targeted demographic characteristics
• Provide image databases for other analyses/data mining

Functional Imaging Research in Schizophrenia Testbed
Biomedical Imaging Research Network

fBIRN Goals:
• Develop
  - multisite fMRI methods
  - federated database
• Study schizophrenia
Outline

- Motivation for multicenter imaging studies
- **Issues in fMRI studies**
  - Standardization of protocols
  - QA
  - Site Equalization
  - Calibration

Multicenter MRI/fMRI

- Desire to pool results across sites equally requires standardization
- Different vendors may have incompatible characteristics/definitions - e.g.
  - pulse sequence contrast in FSPGR vs MPRAGE
  - meaning of BW/echo spacing in EPI imaging - artifacts/SNR
  - k-space apodization filters -> smoothness/CNR
  - gradient distortion correction differences
  - geometric calibration precision
  - temporal stability

Multicenter MRI/fMRI

- Need to qualify sites for entry into study
  - develop characteristics for acceptance
    - geometric accuracy
    - contrast/resolution
    - SNR, CNR, tSNR (SFNR)
    - temporal stability
    - reliability/reproducibility
  - understand sensitivity of scanner characteristics relative to desired measurements
- Set criteria for acceptance
- Need to maintain minimum performance standards
  - develop a QA program

Multicenter MRI/fMRI

- Decide policy for upgrades (depending on size, chances good for at least one site to upgrade)
  - minor: software only
  - major: hardware & software
- Develop procedures to control for/reduce site effects
- Develop procedures to reduce data acquisition confounds, e.g. hemodynamics in BOLD fMRI
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Standardization

• Acquisition parameters
• Scanner characteristics
• Study procedures
• Analysis pipeline
• Database structures

fMRI Imaging Characteristics

Modest importance:
• Structural accuracy (since fMRI is low resolution- e.g. 3.4x3.4x4 mm³)
• Structural image contrast uniformity

However,
• Both must be adequate for tissue segmentation and normalization to template

Important fMRI Characteristics

• fMRI acquisition contrast/smoothness
  - control parameters:
    resolution (FOV & matrix size), but…
    measured smoothness (resel) may
    NOT = FOV/matrix_size
Intersite smoothness differences

Friedman et al. NI (2006)

Why smoothness differences?

- Resolution (nominally) = FOV / npix
  - Smoothing can diminish actual resolution

Why smoothness differences?

- k-space reconstruction kernel
  - Siemens
  - GE ("Fermi filter")
  - Tacq
  - T2* (Bo)

Why smoothness differences?

- Resolution (nominally) = FOV / npix
  - Smoothing can diminish actual resolution
  - T2* apodizes k-space
**Why smoothness differences?**

- Resolution (nominally) = FOV / npix
  - Smoothing can diminish actual resolution
- T2* apodizes k-space
- k-space Trajectory
Why smoothness differences?

- Resolution (nominally) = FOV / npix
- Smoothing can diminish actual resolution
- T2* apodizes k-space
- k-space Trajectory
- Field strength and pulse sequence

Comparison: GRE vs. SE @ 3T

GRE
SE

64x64, 3.43 mm

Comparison: GRE vs. SE @ 7T

GRE
SE

128x128, 1.72 mm, 3 shots

Activation autocorrelation function

<table>
<thead>
<tr>
<th></th>
<th>GRE</th>
<th>SE</th>
<th>Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>3T</td>
<td>2.04 pixels</td>
<td>1.75 pixels</td>
<td>1.17</td>
</tr>
<tr>
<td>64x64</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
**Activation autocorrelation function**

- **GRE**
  - 1.88 pixels
- **SE**
  - 1.90 pixels
- Ratio 0.99

7T 128x128, 1.72 mm

---

**Important fMRI Characteristics**

- fMRI acquisition contrast/smoothness
  - control parameters:
    - resolution/smoothness (resel may not = FOV/matrix_size)
    - BW: keep ESP constant across vendors
    - slice spacing/skip/orientation
    - fat saturation vs. water excitation
    - readout trajectory (EPI vs. spiral), affects smoothness, artifacts
    - field strength (affects SNR, CNR, vessels vs. tissue, artifacts)

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**Field Strength/Vender Differences**

<table>
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<tr>
<th>Field Strength/Vender Differences</th>
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<td>Friedman et al. NI (2006)</td>
</tr>
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</table>

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**Important fMRI Characteristics**

- Dynamic image stability
  - fMRI & ASL depend on subtraction to compare conditions
  - scanner stability must be < || << brain noise
Brain noise relative to thermal noise

\[ \sigma^2 = \sigma_0^2 + \sigma_s^2 + \sigma_p^2 = \sigma_0^2 + (\lambda_s + \lambda_p)S^2(\alpha) \]

G. Krueger (2000)

- Acquire data at 10\(^\circ\), 77\(^\circ\)
- Calc fraction of scanner/brain noise vs. thermal noise, using human & phantom scans

D. Greve (MRM 2011)

Standardization: Slice selection

Glover, et al., JMRI 2012

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Reconstruction artifacts
QA: What to measure?

- Time series image stability
- Signal to noise ratio
- Signal intensity
- Xmtr/Rcvr Gains
- MRS characteristics
- Eddy currents
- Geometric accuracy

Scan protocols

- Stability
  - acquisition
    - 17 cm agar gel phantom
    - fMRI acquisition, 2s TR, 240 time frames
      (~8 min scan, ~55% grad slewing duty cycle)
  - analysis
    - plot time series in large ROI (31x31)
    - Weisskoff plot
    - SNR
    - SFNR

Analysis

\[
\begin{align*}
I_{\text{even}} &= \frac{2}{N} \sum I_i - I_{\text{trend}}(i) \\
I_{\text{odd}} &= \frac{2}{N} \sum I_i - I_{\text{trend}}(i) \\
I_{\text{ave}} &= \frac{1}{2} (I_{\text{even}} + I_{\text{odd}}) \\
I_{\text{nave}} &= \frac{1}{2} (I_{\text{even}} - I_{\text{odd}}) \\
\sigma^2 &= \frac{1}{N-1} \sum (I_i - I_{\text{trend}}(i))^2 \\
\text{SFNR} &= \frac{I_{\text{ave}}}{\sigma}
\end{align*}
\]

Weisskoff Analysis

\[
\bar{I}_i(w) = \text{mean}_{(w,w)}[I_i - I_{\text{trend}}(i)]
\]

\[
\sigma(w) = \text{stdev} [\bar{I}_i(w)]
\]

\[
\sigma_{\text{theory}}(w) = \sigma(1) / w
\]

Friedman, JMRI 2006

### Bad Head Coil

![Bad Head Coil Image](image)

### Time Series Drift

![Time Series Drift Image](image)

### Frequency Drift

![Frequency Drift Image](image)

### Eddy Current Maps

- 3-directions phase contrast scan on agar phantom
- Analyze velocity maps for error
- Useful as on-going QA
Stability

BWH, 3T
9/26/03  9/29/03

Iowa, 1.5T
8/21/03  9/15/03

Stability

MGH, 3T

Stability

Minnesota, 3T
8/19/03  8/27/03

Stability

NM, 1.5T

Stability

UCI, 1.5T
9/29/03  8/24/03

Stability

UCSD, 1.5T
QA helped to bring scanners into spec.

QA helped to debug site problems.
fBIRN QA Program

• Initial tests resulted in vendor efforts to improve stability
• Daily/weekly QA highlighting problems
• QA protocols being used for magnet acceptance testing
• One vendor using stability scans for own testing

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fMRI equalization across sites

• Compensation for smoothness
• Compensation by SFNR

BOLD Smoothness Differences

Friedman, et al. 2006
SM Sensitivity Differences

Sensitivity vs. Smoothness

Smoothness equalization

In first-level analysis: Use “smooth to” instead of “smooth by”

Smooth each site to largest FWHM using Gaussian filter

\[ FWHM_{\text{out}}^{-2} = FWHM_{\text{meas}}^{-2} + FWHM_{\text{filter}}^{-2} \]

Sensitivity after smoothness equalization
Intersite CV

1.5T  3T

Intersite Effect of Field

Friedman, et al. 2006

BOLD Sensitivity: Oddball Task

Target Tones- Effect Size

Original  Equalized

Novel Tones - Effect Size

Original  Equalized

Friedman, et al.
**BOLD Sensitivity: Oddball Task**

Original

Equalized

Target Tones - Cluster Maps
Voxel $P = 0.001$, Cluster Size = 8, Volumewise $p = 0.05$

Friedman, et al.

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**fMRI equalization across sites**

- Compensation for smoothness
- Compensation by SFNR

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**fMRI equalization by SFNR**

- Measure SFNR using
  - GM - Rest
  - WM - Rest
  - GM - SMresid
  - WM - SMresid
- Covary for SFNR

**Site equalization by SFNR**

<table>
<thead>
<tr>
<th>Original SFNR</th>
<th>1.5T</th>
<th>3T</th>
</tr>
</thead>
<tbody>
<tr>
<td>AV</td>
<td><img src="image1" alt="Graph" /></td>
<td><img src="image2" alt="Graph" /></td>
</tr>
<tr>
<td>LA</td>
<td><img src="image3" alt="Graph" /></td>
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</tr>
<tr>
<td>LC</td>
<td><img src="image5" alt="Graph" /></td>
<td><img src="image6" alt="Graph" /></td>
</tr>
<tr>
<td>LM</td>
<td><img src="image7" alt="Graph" /></td>
<td><img src="image8" alt="Graph" /></td>
</tr>
<tr>
<td>RA</td>
<td><img src="image9" alt="Graph" /></td>
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<tr>
<td>RC</td>
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</tr>
<tr>
<td>RM</td>
<td><img src="image13" alt="Graph" /></td>
<td><img src="image14" alt="Graph" /></td>
</tr>
<tr>
<td>SM</td>
<td><img src="image15" alt="Graph" /></td>
<td><img src="image16" alt="Graph" /></td>
</tr>
</tbody>
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• Site performance standardization

Calibration Goals

Goals of Calibration process

• Use fMRI tasks and traveling subjects (‘human phantoms’) to develop data with which to characterize inter-site differences
• Develop calibration methods with which to reduce inter-site variance in fMRI results

Tasks should

• require minimal cognitive input
• be robust (good repeatability, control for attention/behavioral level)
• be performable by schizophrenic subjects

SM Task- Visual/Auditory/Motor

Block trials, 15s “on”, 15s “off”, 8 blocks.

On block:
• Alternating contrast checkerboard.
• Binaural tones generated with Mac internal squarewave synthesizer. Each tone is 166 ms long with 167 ms of silence.
• Tones and visual contrast change at 3Hz. Tone sequence is Midi notes: \{60, 64, 68, 72, 76, 80, 84, 88, 92, 78, 74, 70, 66, 62, 58\}. This is an auditorily annoying, mistonal scale.
• Subject performs bilateral finger apposition at 3Hz, in time with visual and auditory cues.

Off Block: Fixation cross, silence, no motion.

TR/TE/FA = 3000/(40/30)/90, 100 kHz BW, 64x64 matrix; 22 cm FOV, 35 slices, AC-PC orientation, 4 mm skip 0.
Passive (pneumatic plungers) SM Calibration Task

- Attend
- Not attend

Calibration of BOLD Signal

\[ \Delta R^2 \propto rCBV_0 [Hb]^{\alpha} - rCBV_0 [Hb]^{\beta} \]
\[ BOLD \propto -TE \cdot \Delta R^2 \]
\[ rCBV \propto rCBF^\alpha \]
\[ BOLD_{BH} = S_0 [f^\alpha (m)^\beta - 1] \]
\[ BOLD_{BH} = BOLD_{BH} \frac{[f^\alpha (m)^\beta - 1]}{[f_{BH}^\alpha - 1]} \]

Gray matter shows stronger response than white matter.

Calibration: Voxel-wise Normalization by BH Response

\[ y_{meas}(j) = y_{metab}(j) \cdot B(j) + n, \quad j = 1 \cdots N_{sub} \]
\[ y_{metab}(j) = y_{calib}(j) = y_{meas}(j) \cdot \frac{B}{B(j)} \]
\[ \sigma^2_{calib} = (1 - R^2) \sigma^2_{meas} \quad R^2 = \text{cov}(y_{meas}, B) \]

\[ M. \text{ Thomason, 2007} \]
BH Calibration: WM Task

No cal | Calib

SWM task, fBIRN BH task
M. Thomason, 2007
$5 \leq t \leq 20$

BH Calibration: Group Activation

No cal | Calib

SWM task, fBIRN BH task, N = 7
M. Thomason, 2007
vol $= 1.0$
vol $= 1.24 @ p .001$
$3.5 \leq t \leq 10$

Calibration: SWM

5 subjects, parietal

sd: $p = 0.05 *$

Cerebral Blood Flow

- Cerebral blood flow (CBF) is a measure of the delivery of blood to brain tissue.
- A number of recent studies have shown that the BOLD signal measured in fMRI studies can depend on baseline CBF.

Liu et al, Abstract 854, ISMRM 2008
ASL- quantitative rCBF maps

Impact of Calibration

- Controlling for subject-specific vasoreactivity differences leads to reduced group variances, ironically may decrease inter-site reliability

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Site Procedures

- Standardize scanners, imaging params, coil type
- Standardize ancillary equipment- bbox, A/V stimulus delivery equipment/SW, bite bar
- Standardize scan procedure- order of scans, scan script, subject preparation, slice prescription QA scans
- Use cross site visiting coordinator
- Use automated upload scripts, processing pipeline
**Conclusions**

- Standardize scanner performance/imaging parameters/site procedures as much as possible
- Compensate inter-site differences in SFNR, etc.
  - smooth-to
  - SFNR covariation
- Use inter-subject compensation for HRF confounds
  - hypercapnic calibration (BH)
  - ASL baseline rCBF compensation
    (may increase site effects)

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  - Moriah Thomason

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