Considerations in Multi-site fMRI

Gary H. Glover

Radiological Sciences Laboratory
Center for Advanced MR Technology

Stanford University **School of Medicine**

Department of Radiology

National Center for Research Resources

Outline

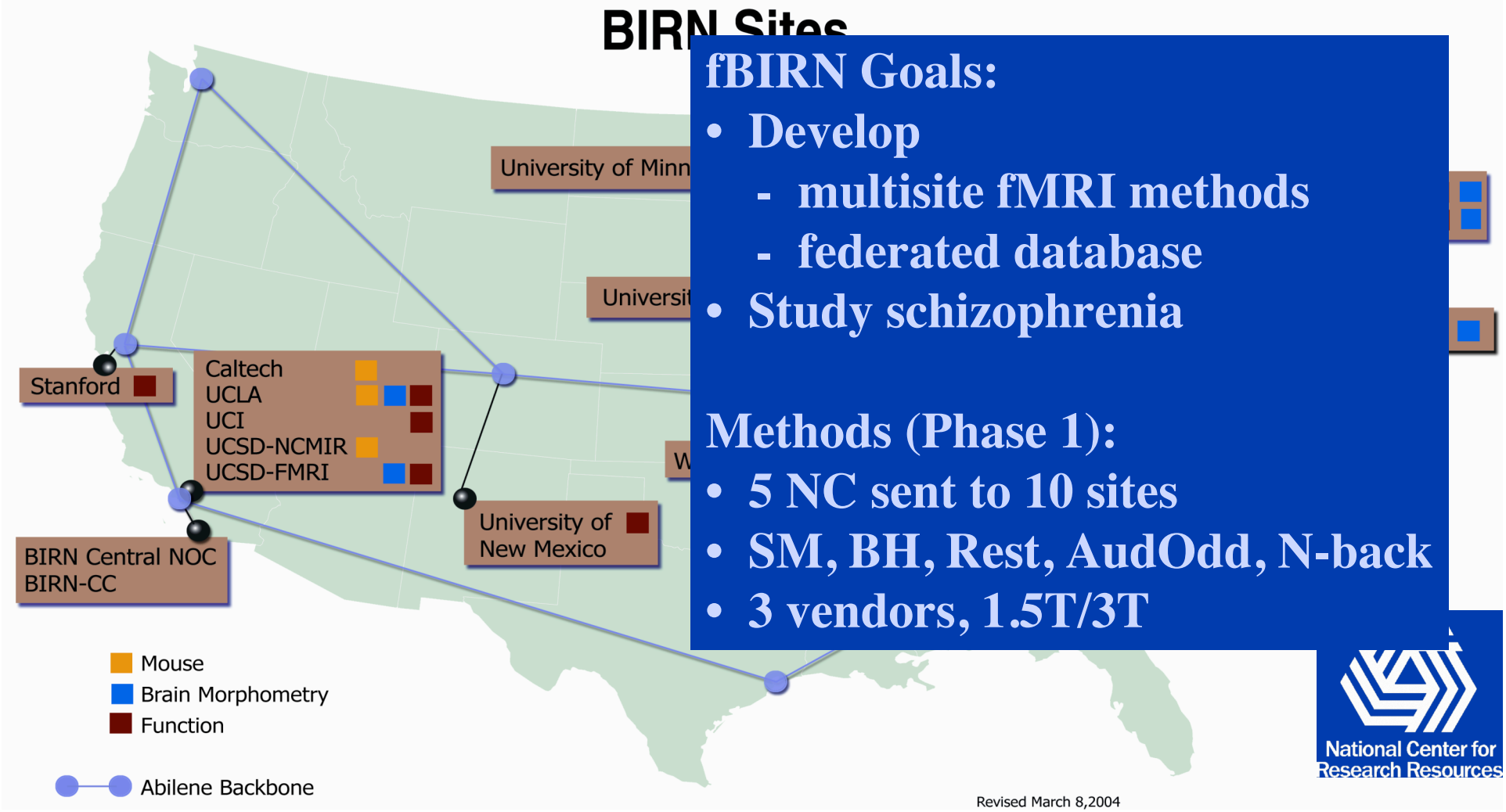
- **Motivation for multicenter imaging studies**
- **Issues in fMRI studies**
- **Standardization of protocols**
- **QA**
- **Site Equalization**
- **Calibration**

Context: 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

Functional Imaging Research in Schizophrenia Testbed
Biomedical Imaging Research Network



fBIRN Goals:

- Develop
  - multisite fMRI methods
  - federated database
- Study schizophrenia

Methods (Phase 1):

- 5 NC sent to 10 sites
- SM, BH, Rest, AudOdd, N-back
- 3 vendors, 1.5T/3T

National Center for Research Resources

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 venders 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
  - grad distortion correction
  - geometric calibration precision
  - temporal stability

Multicenter MRI/fMRI

- Need to qualify sites for entry into study
  - develop characteristics for acceptance

    e.g.
    - 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 (chances virtually 100% 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

Outline

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

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 mm^3)**
- **Structural image contrast uniformity**

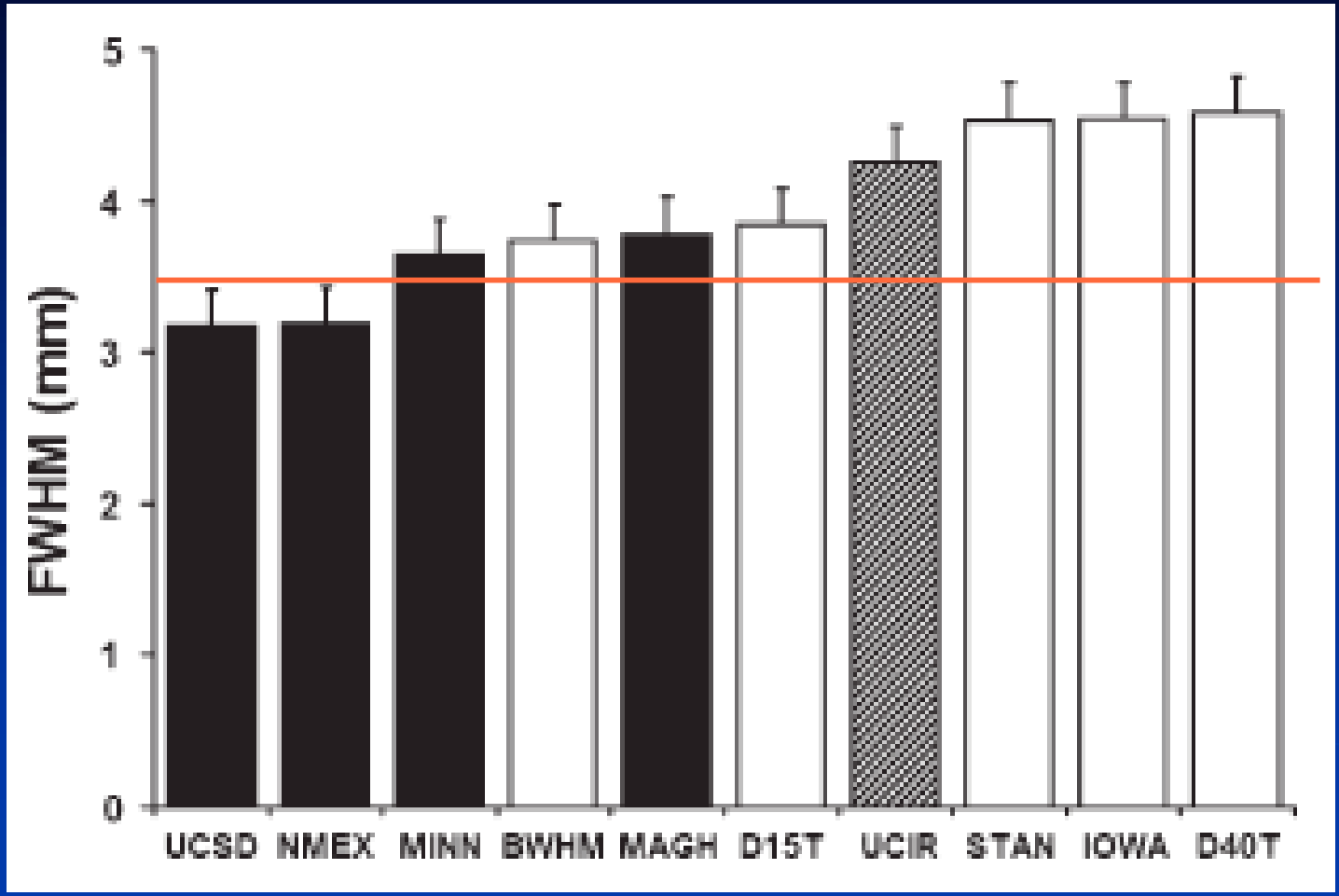
However,

- **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)

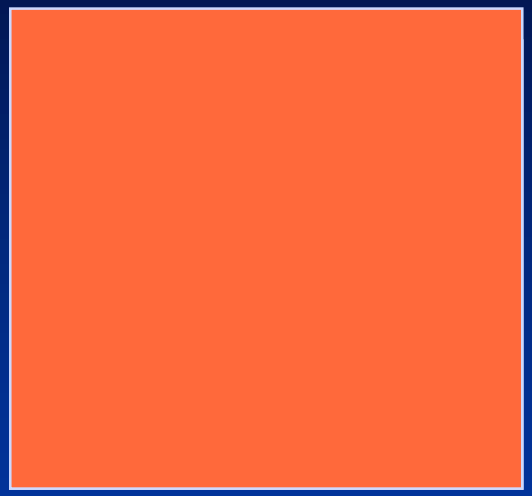
Intersite smoothness differences



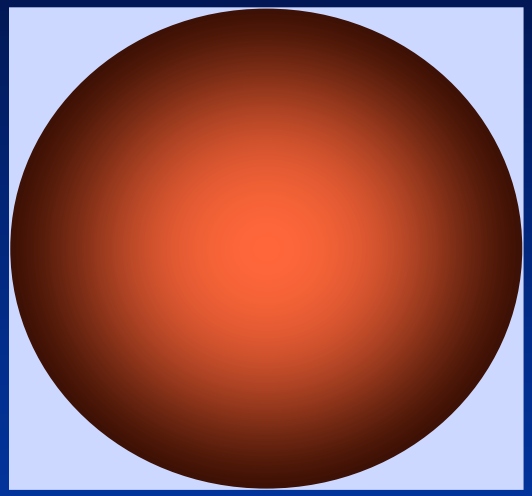
Friedman et al. NI (2006)

Why smoothness differences?

- k-space reconstruction kernel



Siemens



GE

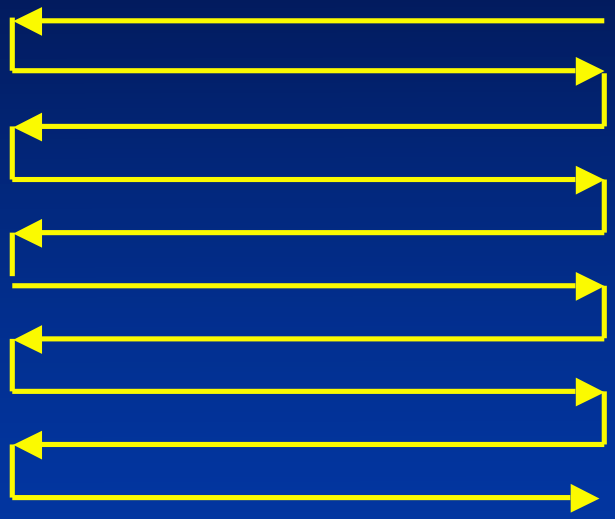
- Tacq
- T2* (Bo)

Important fMRI Characteristics

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

Why smoothness differences?

- k-space trajectory



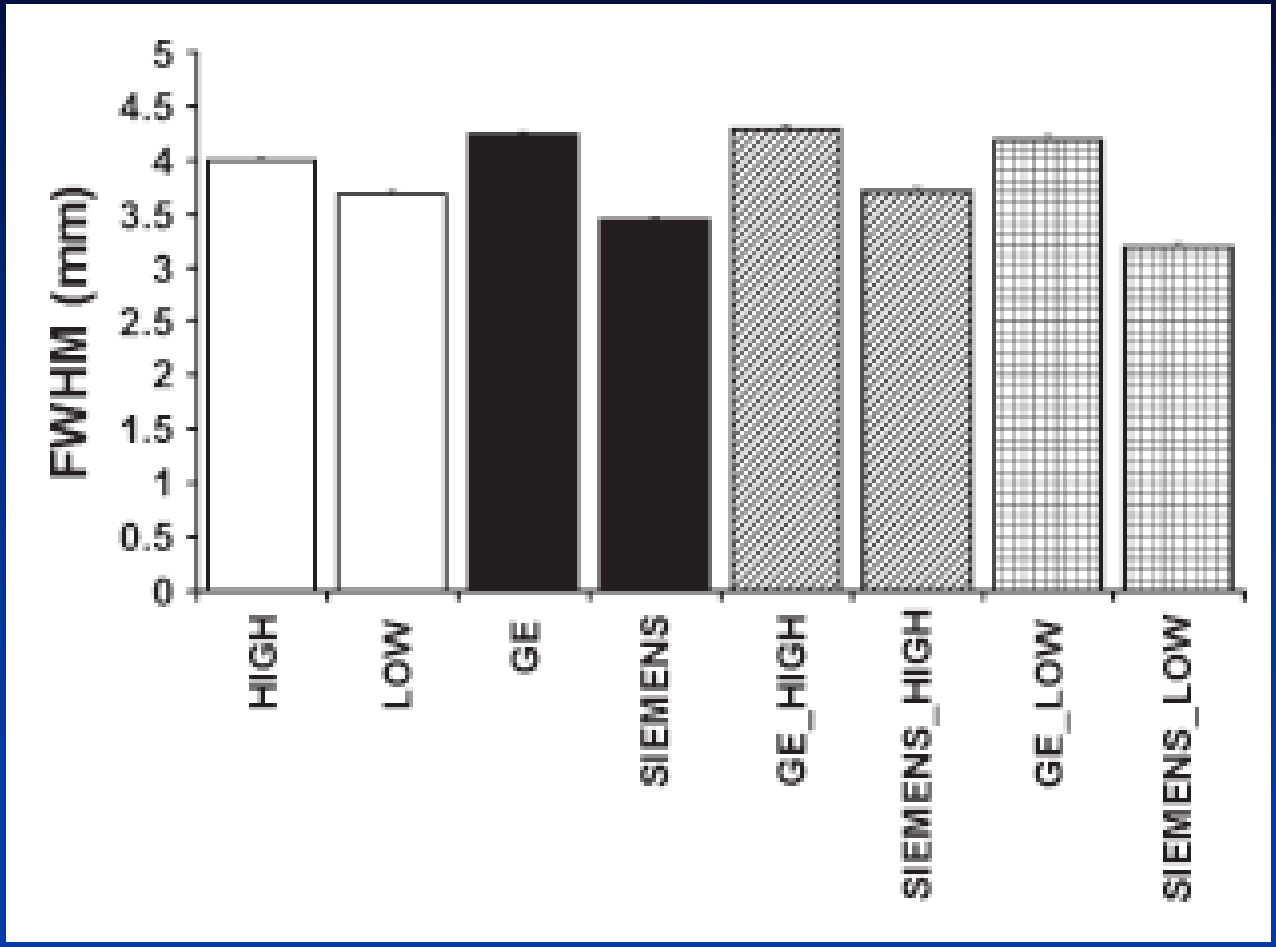
EPI

spiral

Important fMRI Characteristics

- fMRI acquisition contrast/smoothness
  - control parameters:
    - resolution/smoothness (resel may not = FOV/matrix_size)
    - BW: keep ESP constant across venders
    - 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)

Field Strength/Vender Differences

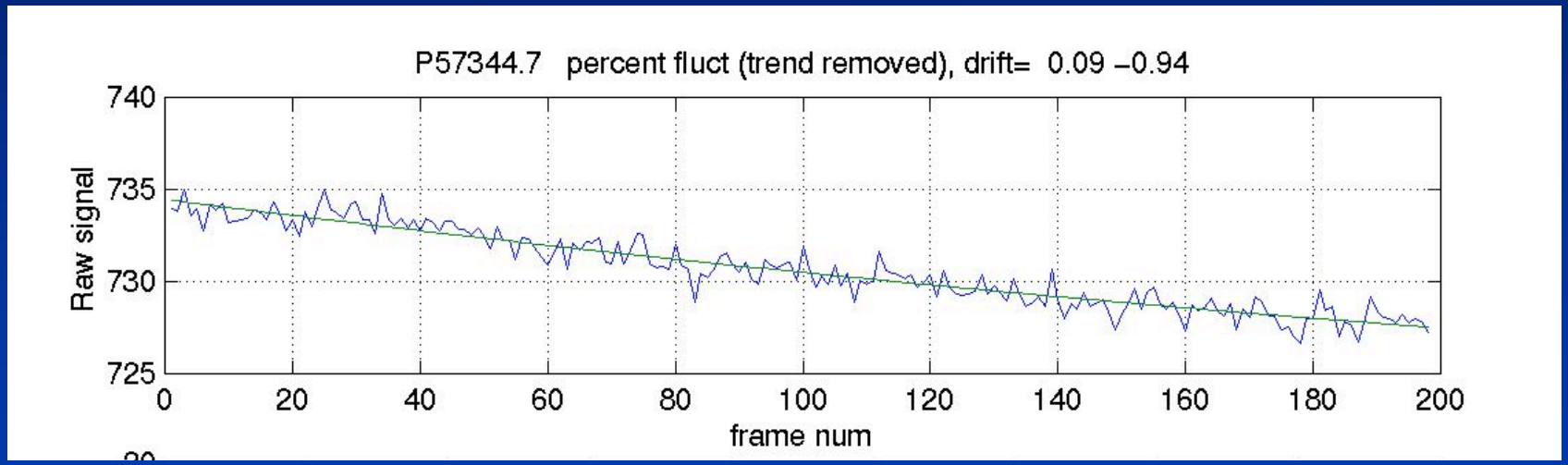


Friedman et al. NI (2006)

Important fMRI Characteristics

- **Dynamic image stability**

  fMRI & ASL depend on subtraction to compare conditions
  scanner stability must be < ll << brain noise



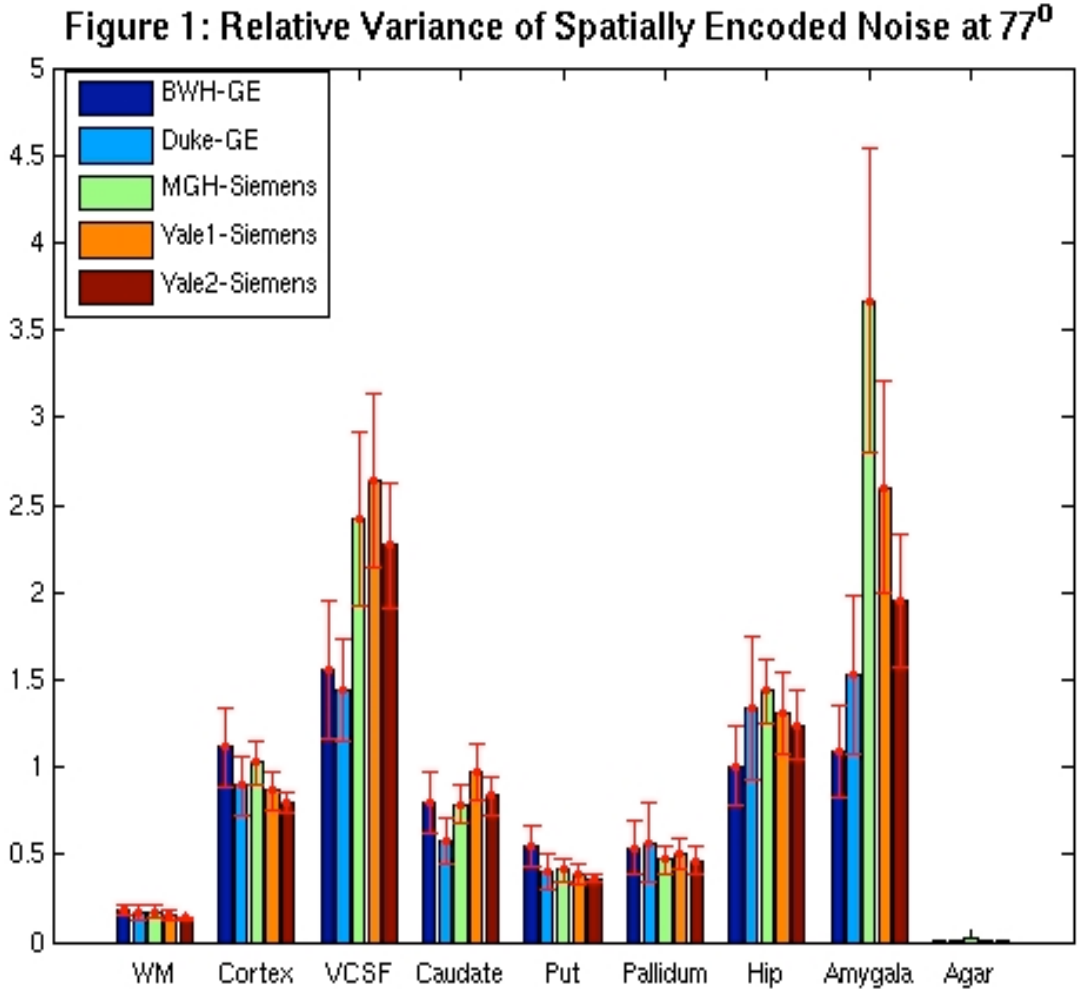
Brain noise relative to thermal noise

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

G. Krueger (2000)

- Acquire data at 10º, 77º
- Calc fraction of scanner/ brain noise vs. thermal noise, using human & phantom scans

D. Greve (ISMRM 2008)



Outline

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

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

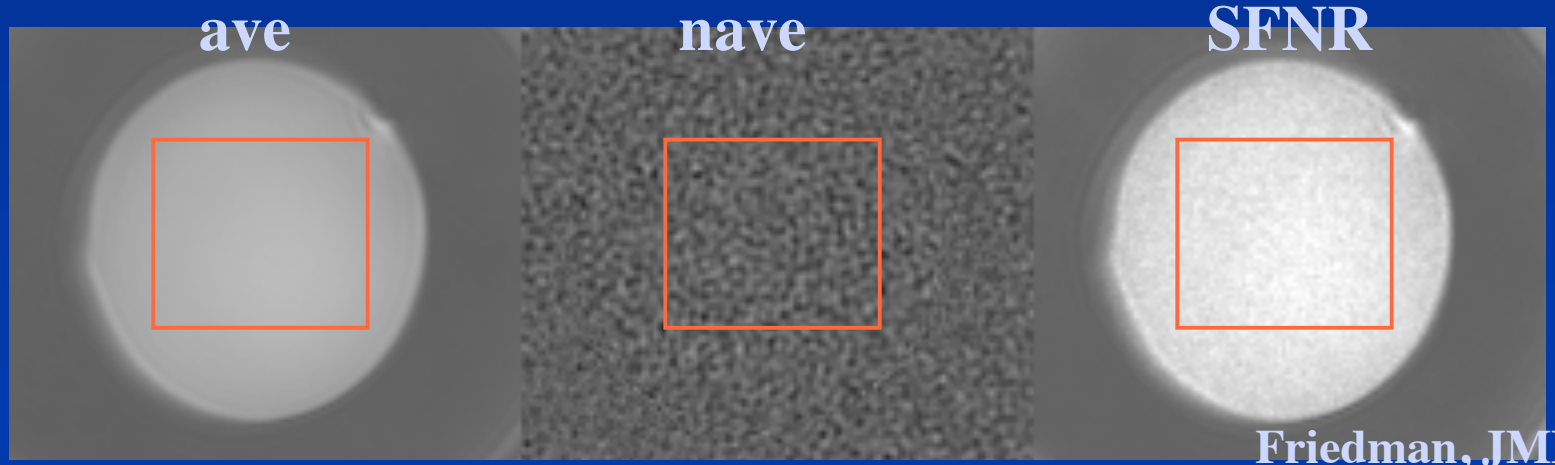
- Stability
  - acquisition
    - 17 cm agar gel phantom
    - fMRI acquisition, 2s TR, 240 time frames
      - (~8 min scan, ~55% grad slewing duty cycle)
  - analysis
    - plot time series in large ROI (31x31)
    - Weisskoff plot
    - SNR
    - SFNR

Analysis

$$I_{even} = \frac{2}{N}\sum_{even} I_i - I_{trend}(i) \qquad I_{odd} = \frac{2}{N}\sum_{odd} I_i - I_{trend}(i)$$

$$I_{ave} = \frac{1}{2}(I_{even} + I_{odd}) \qquad I_{nave} = \frac{1}{2}(I_{even} - I_{odd})$$

$$\sigma^2 = \frac{1}{N-1}\sum [I_i - I_{trend}(i)]^2 \qquad SFNR = I_{ave} / \sigma$$



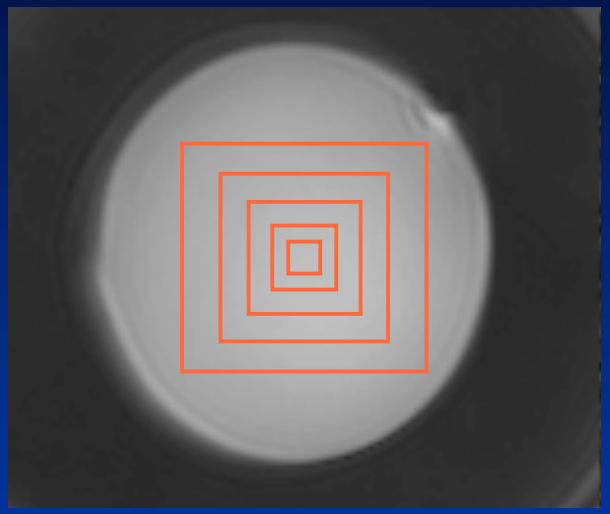
Friedman, JMRI 2006

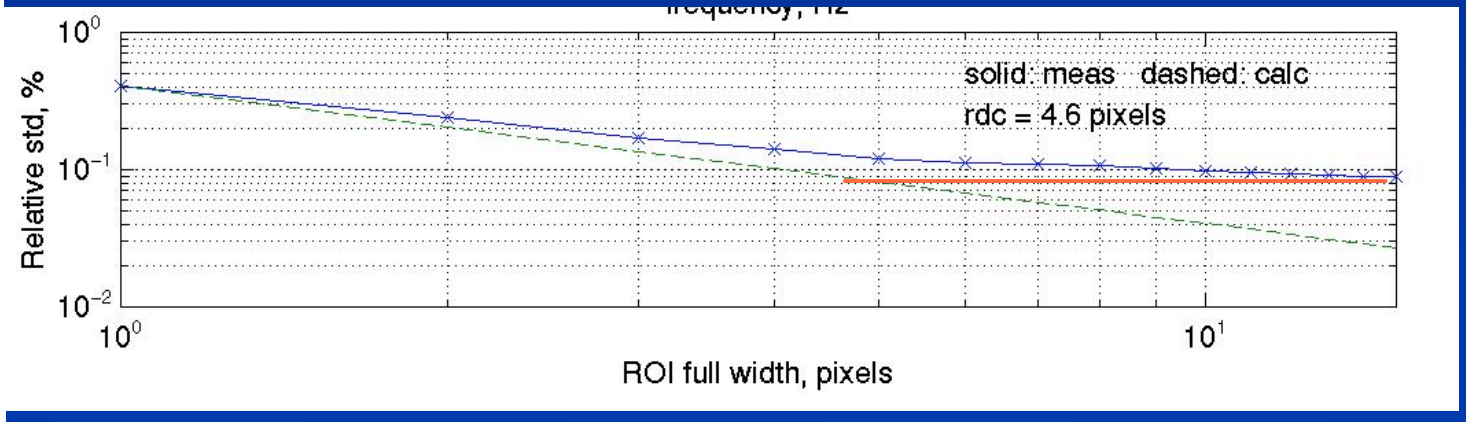
Weisskoff Analysis

$$\bar{I}_i(w) = mean_{(wx\,w)}[I_i - I_{trend}(i)]$$

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

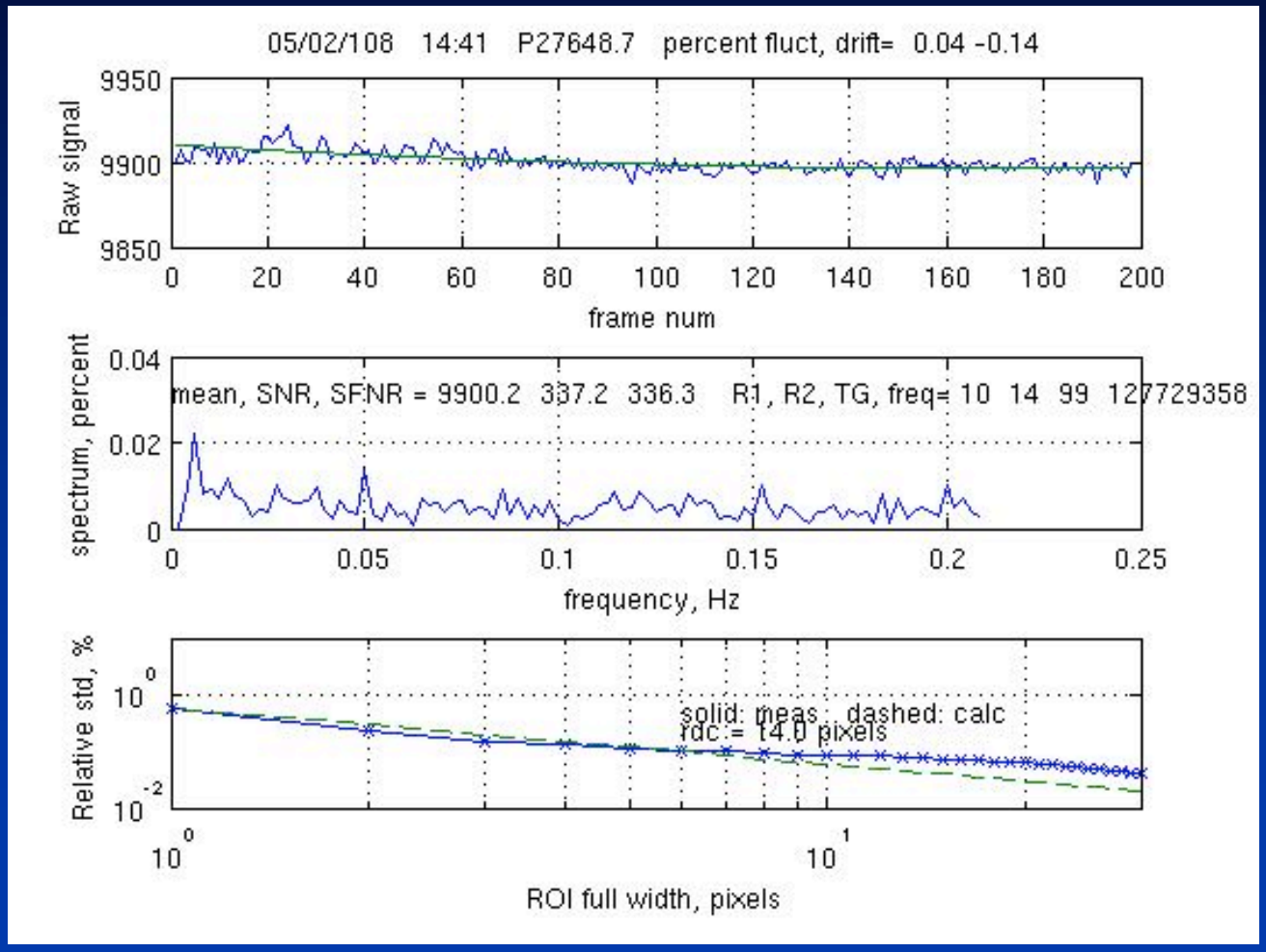
$$\sigma_{theory}(w) = \sigma(1)/w$$



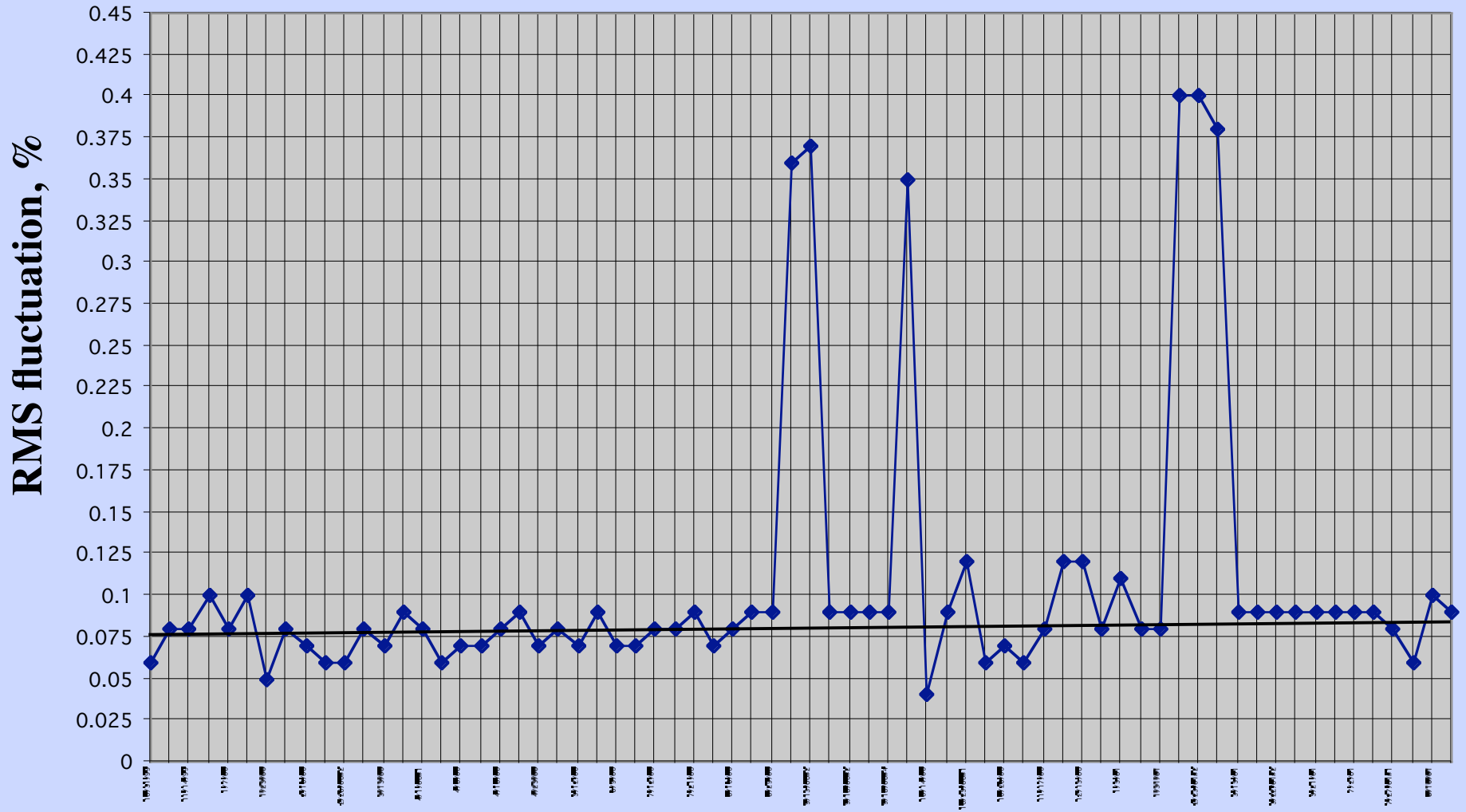


R. M. Weisskoff, *MRM* 36, 643-645 (1996).

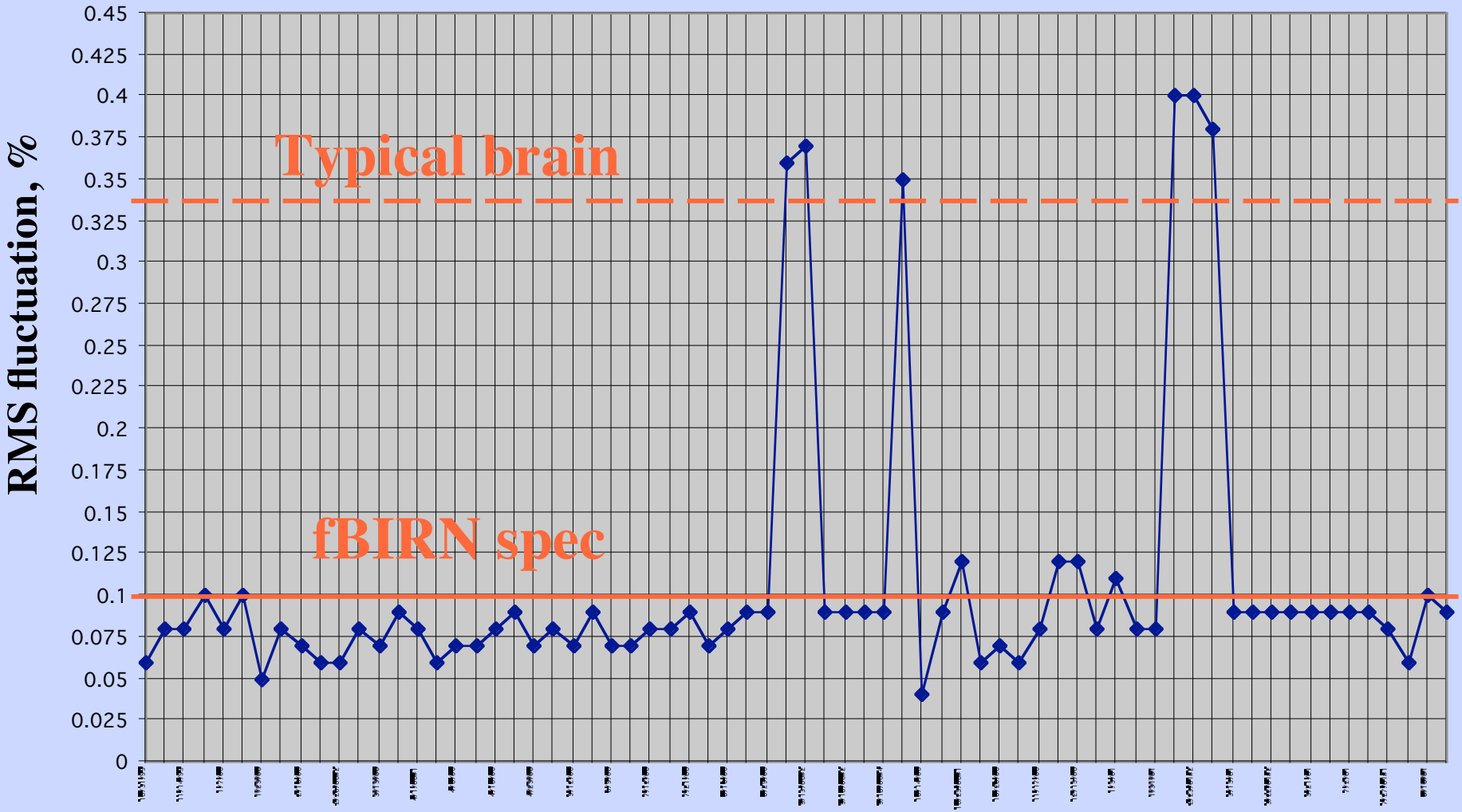
Stability


05/02/108 14:41 P27648.7 percent fluct, drift= 0.04 -0.14
Raw signal
9950
9900
9850
0 20 40 60 80 100 120 140 160 180 200
frame num
spectrum, percent
0.04
0.02
0
mean, SNR, SFNR = 9900.2 337.2 336.3 R1, R2, TG, freq= 10 14 99 127729358
0 0.05 0.1 0.15 0.2 0.25
frequency, Hz
Relative std, %
10^0
10^-2
solid: meas dashed: calc
rdc = 14.0 pixels
10^0 10^1
ROI full width, pixels

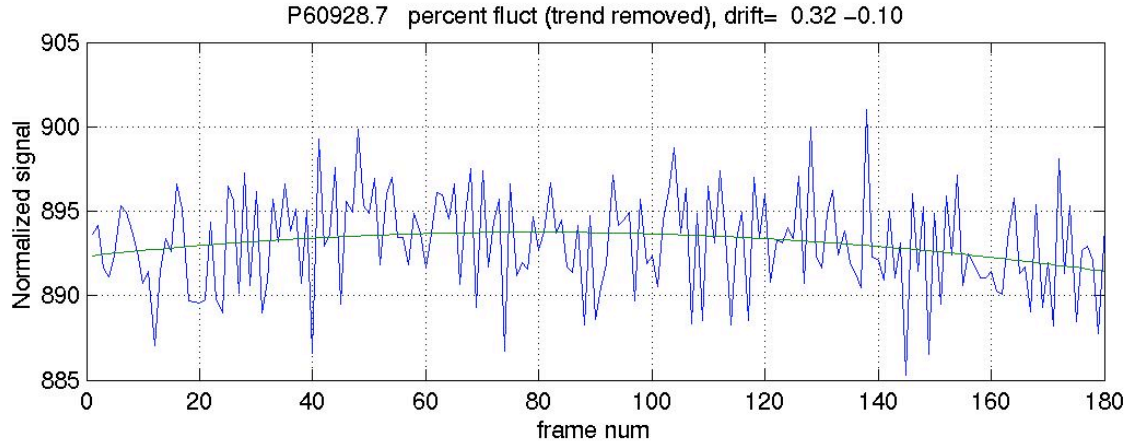
Time Series Stability

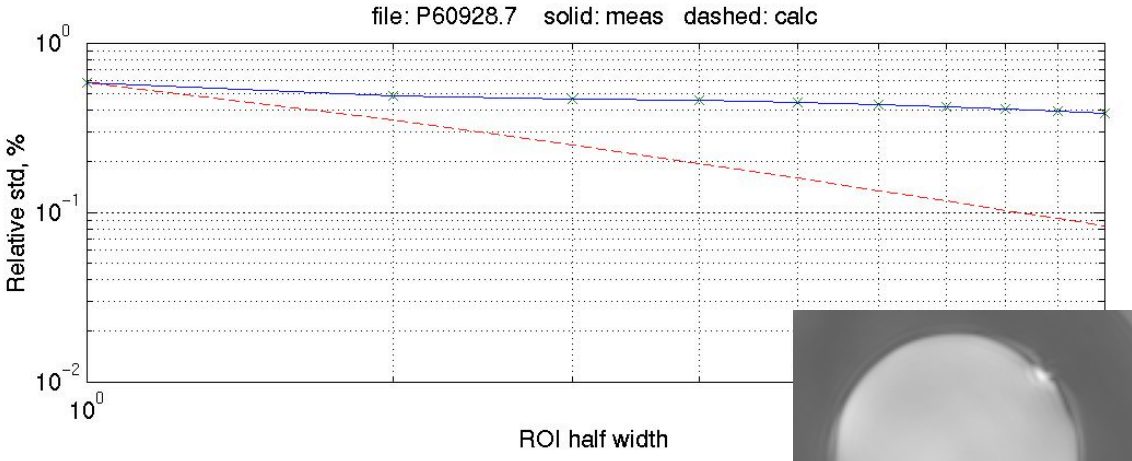


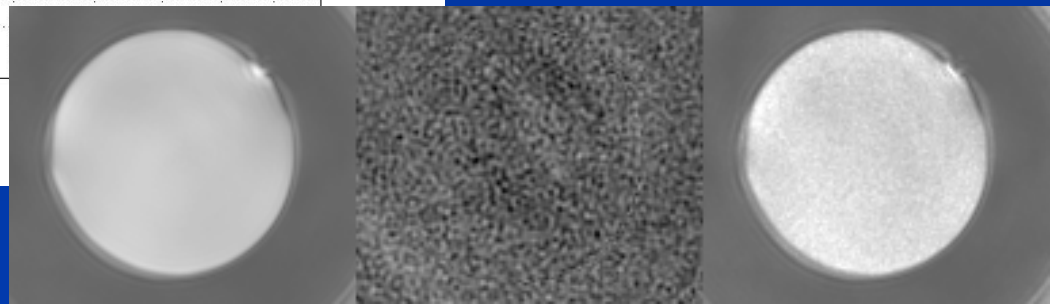
Time Series Stability



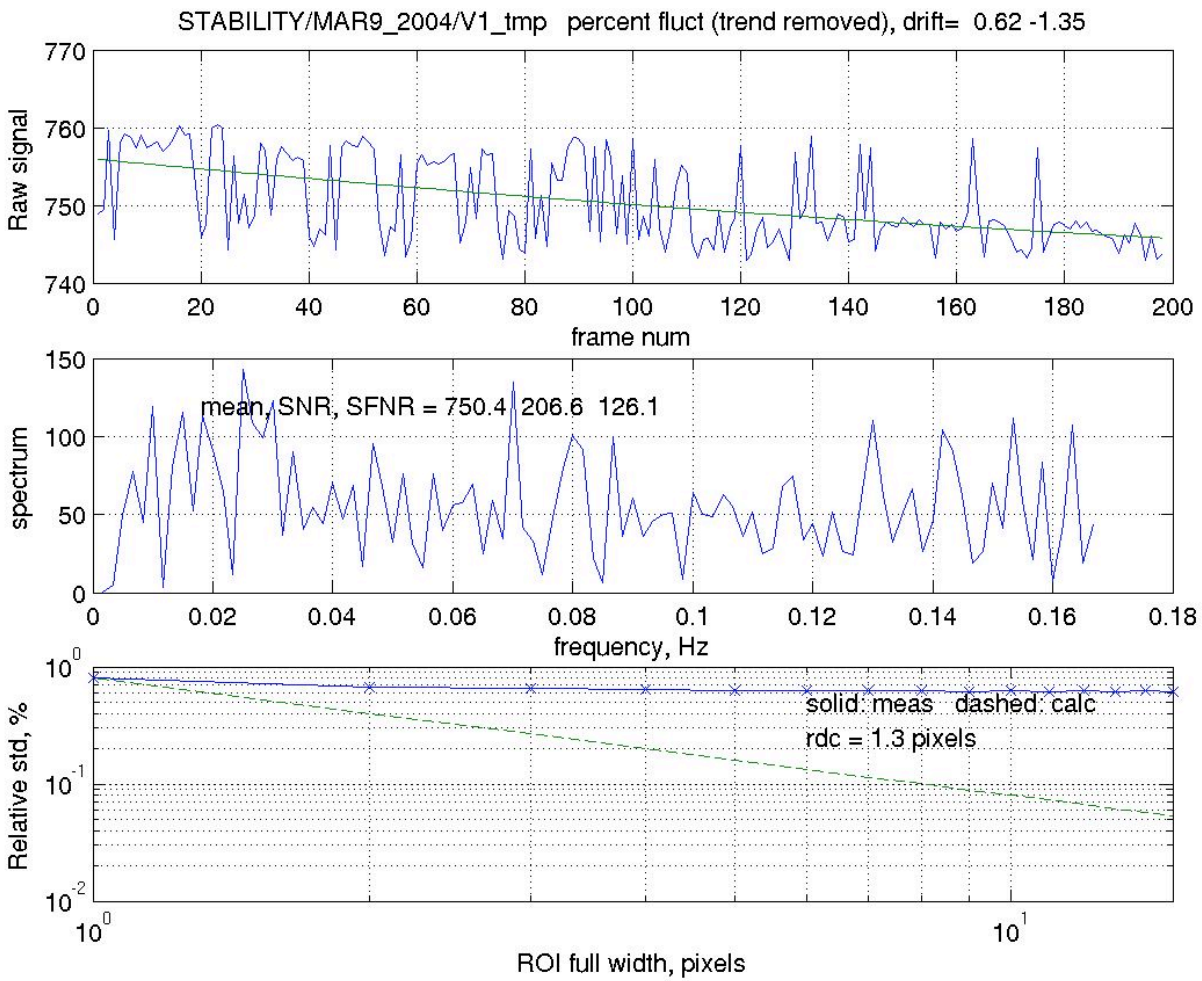
Bad Gradient Amps



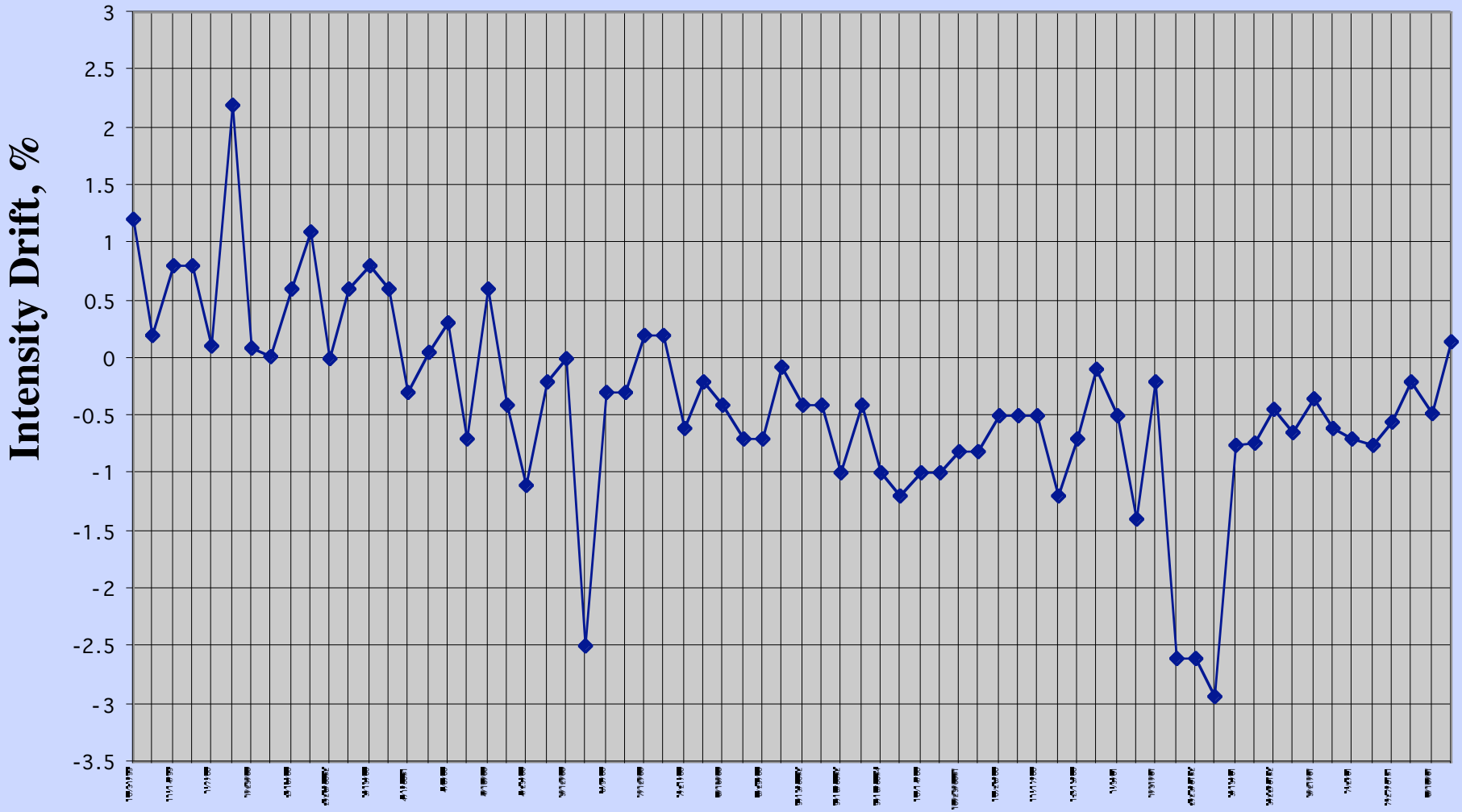




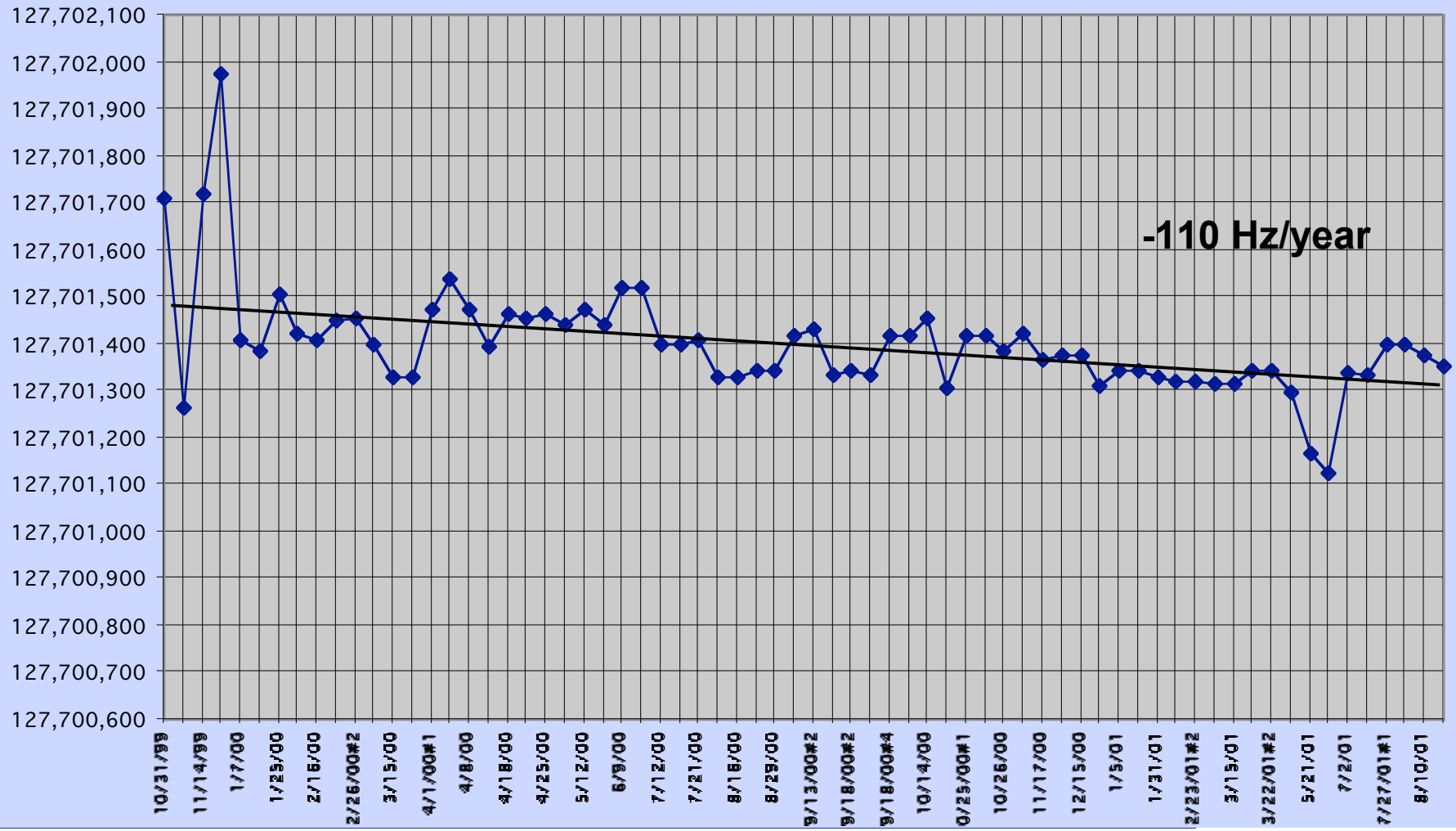
Bad Head Coil



Time Series Drift

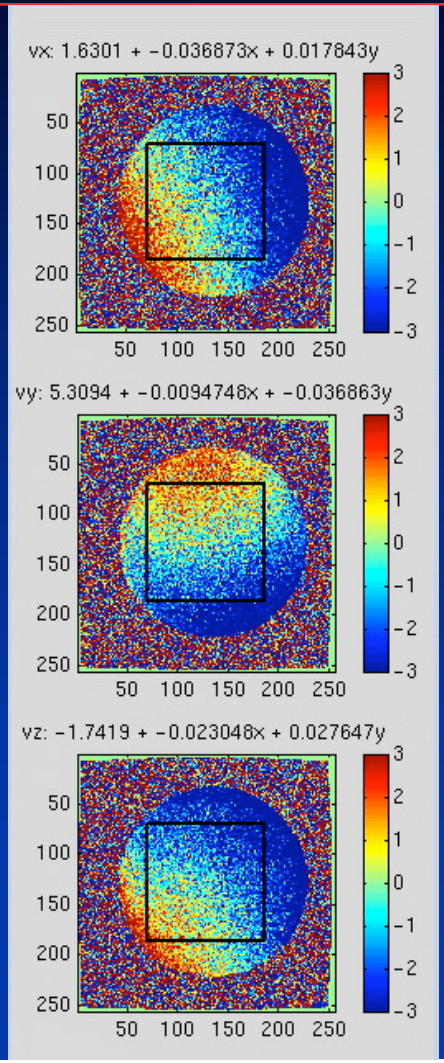


Frequency Drift



Eddy Current Maps

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



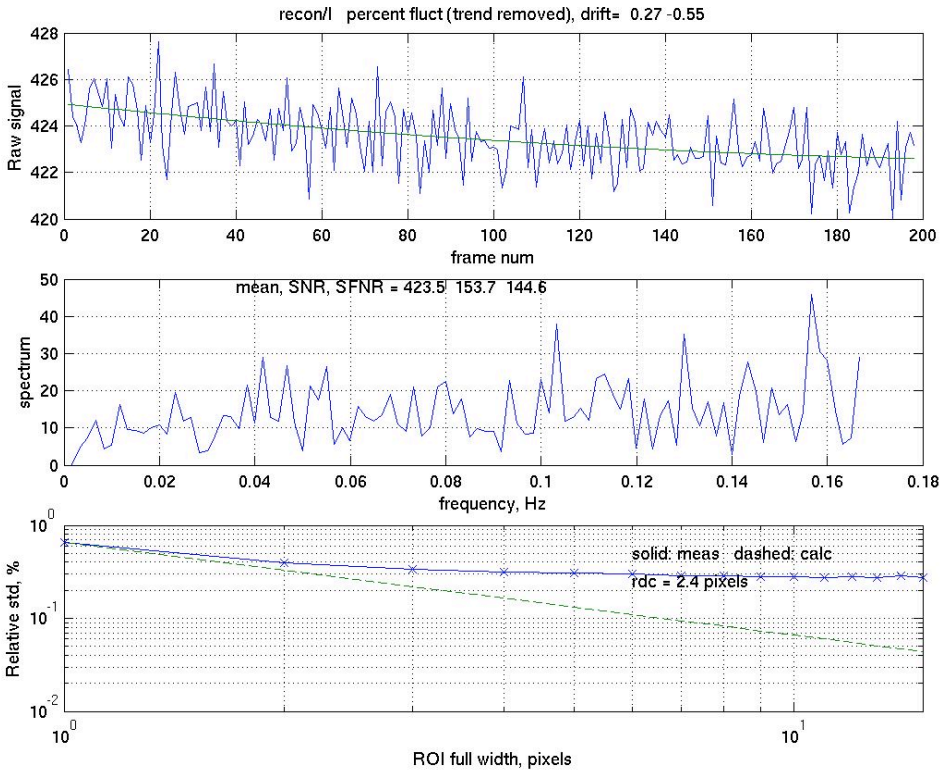
R/L

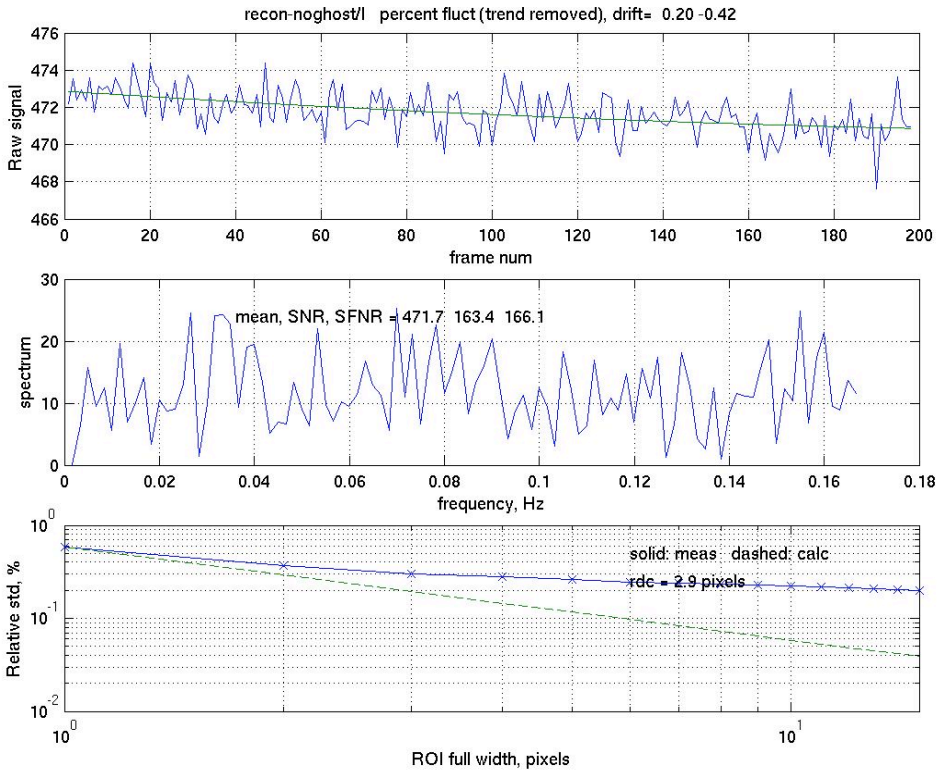
A/P

S/I

BIRN
BIOMEDICAL INFORMATICS RESEARCH NETWORK

Stability



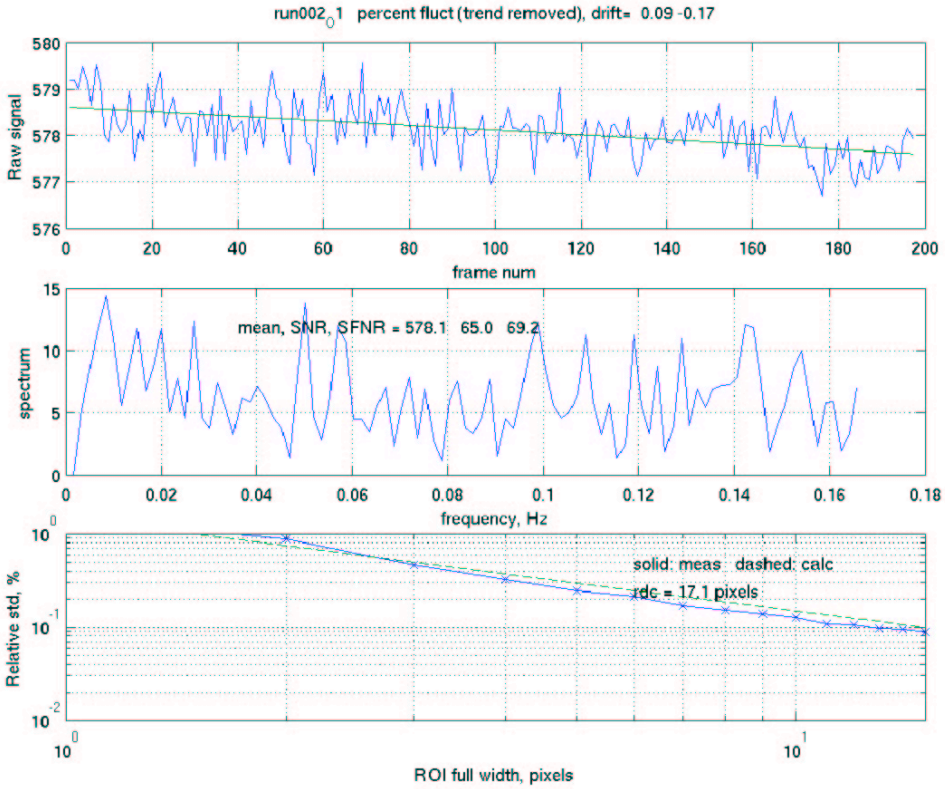


9/26/03 9/29/03 BWH, 3T

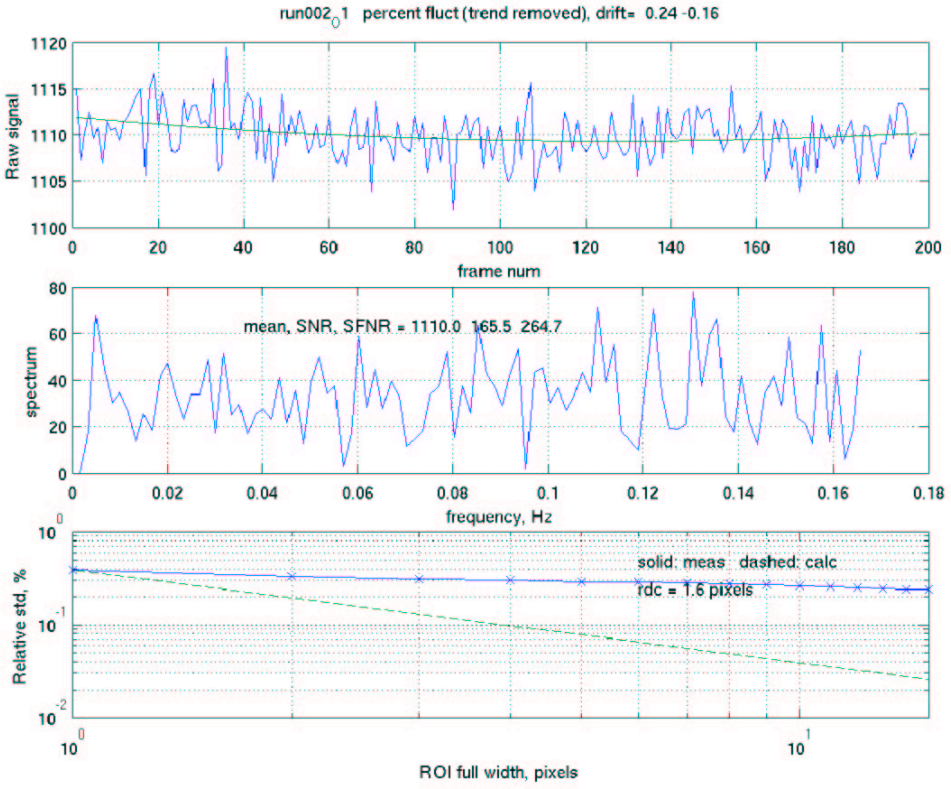
BIRN
BIOMEDICAL INFORMATICS RESEARCH NETWORK

Stability

1.5T



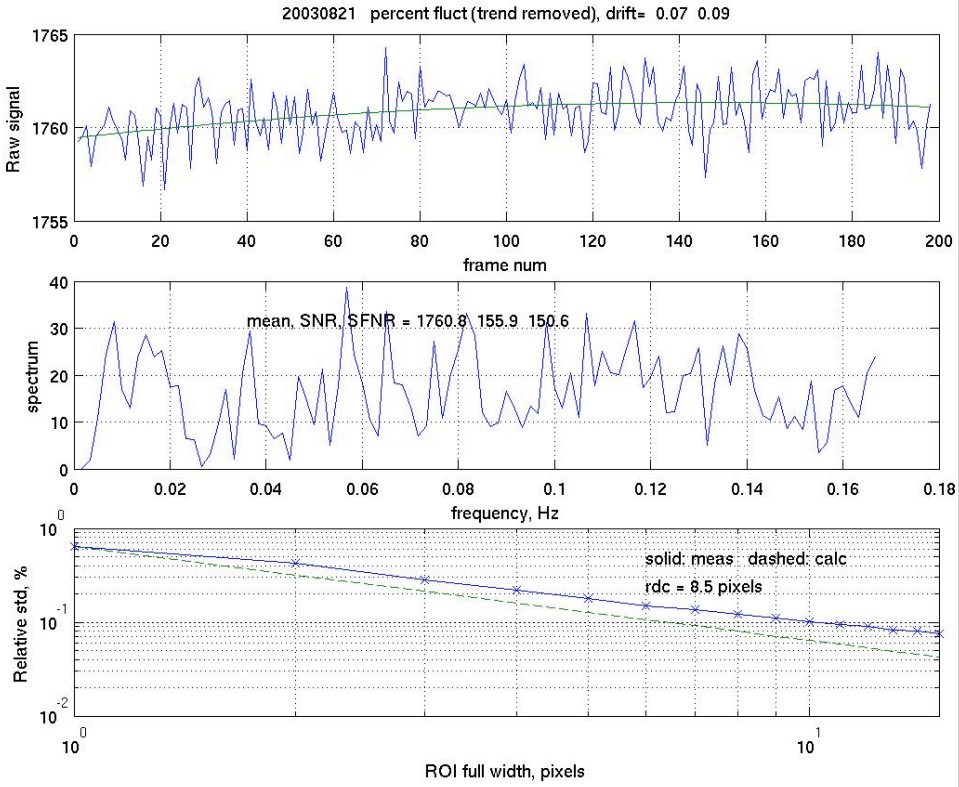
4T



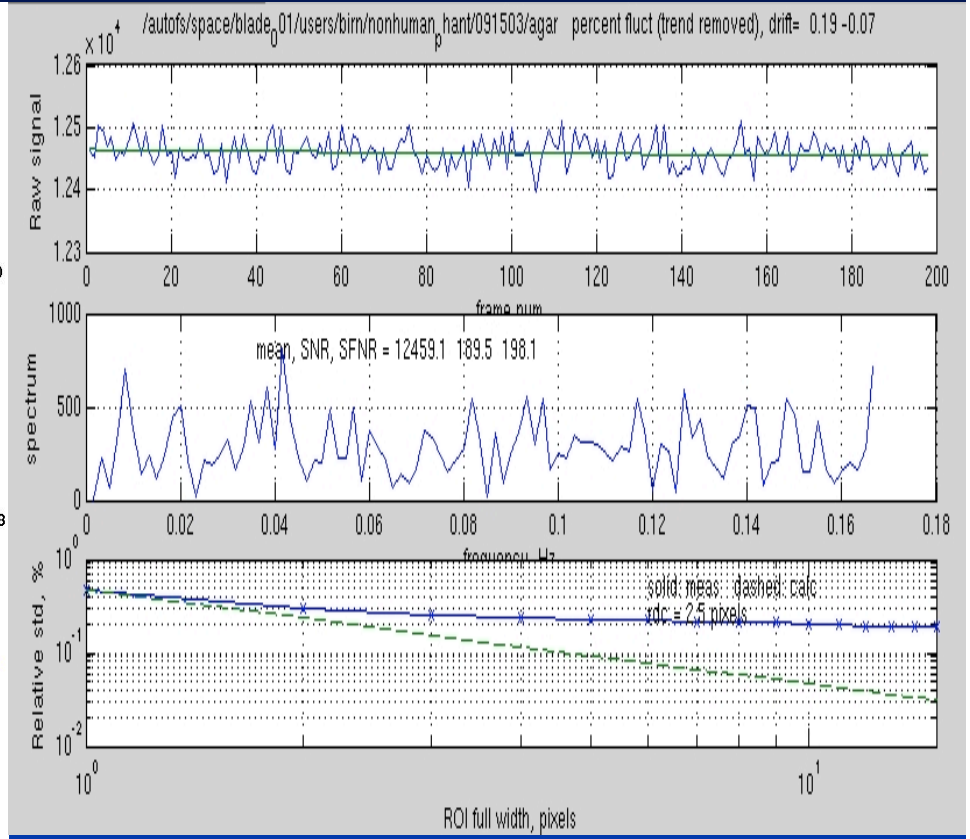
BIRN
BIOMEDICAL INFORMATICS RESEARCH NETWORK

Stability

Iowa, 1.5T



MGH, 3T

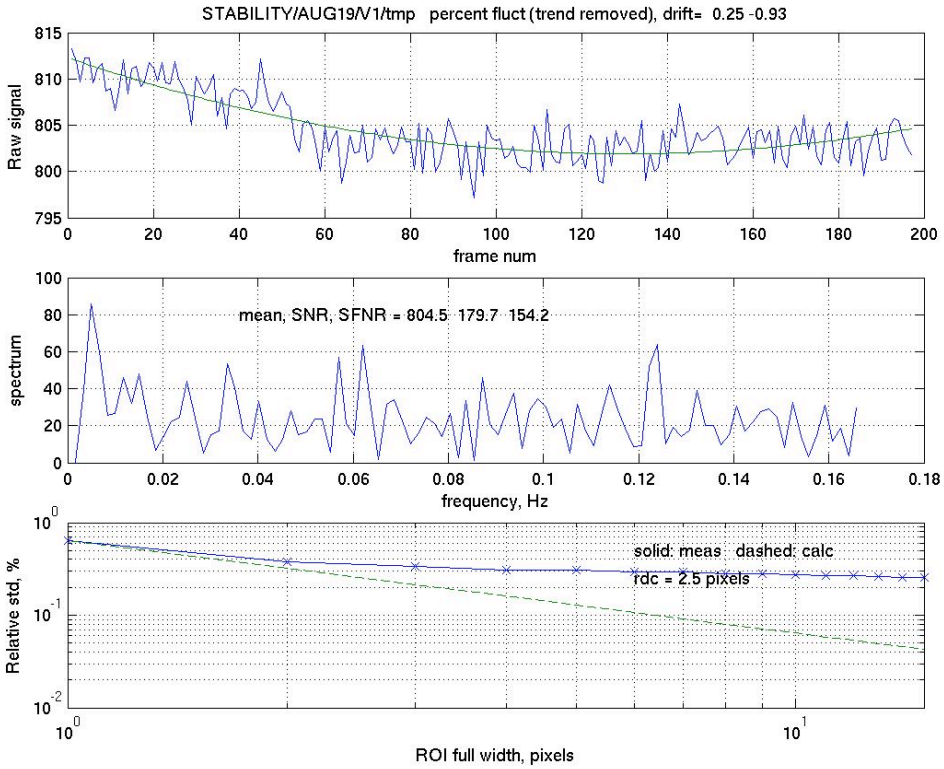


8/21/03 9/15/03

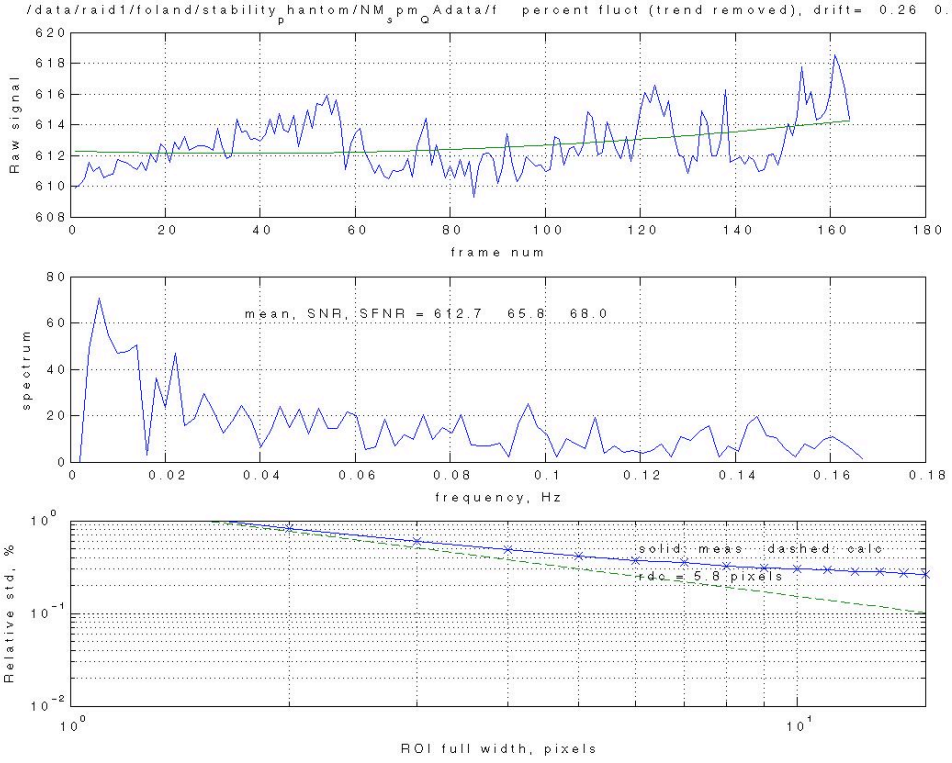
BIRN
BIOMEDICAL INFORMATICS RESEARCH NETWORK

Stability

Minnesota, 3T



NM, 1.5T

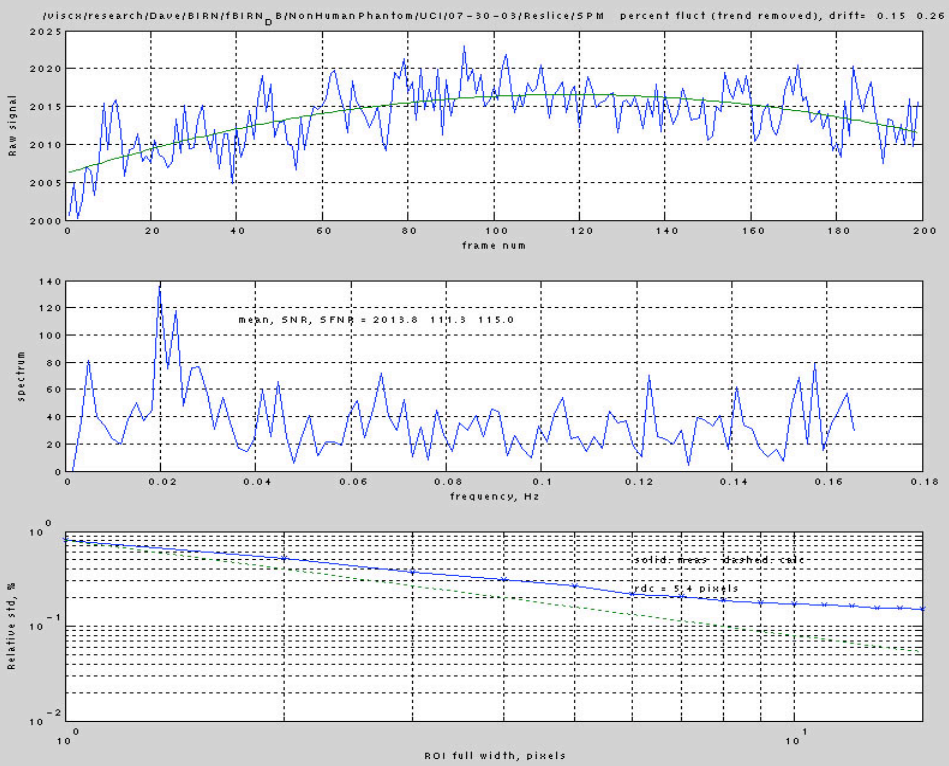


8/19/03 **8/27/03**

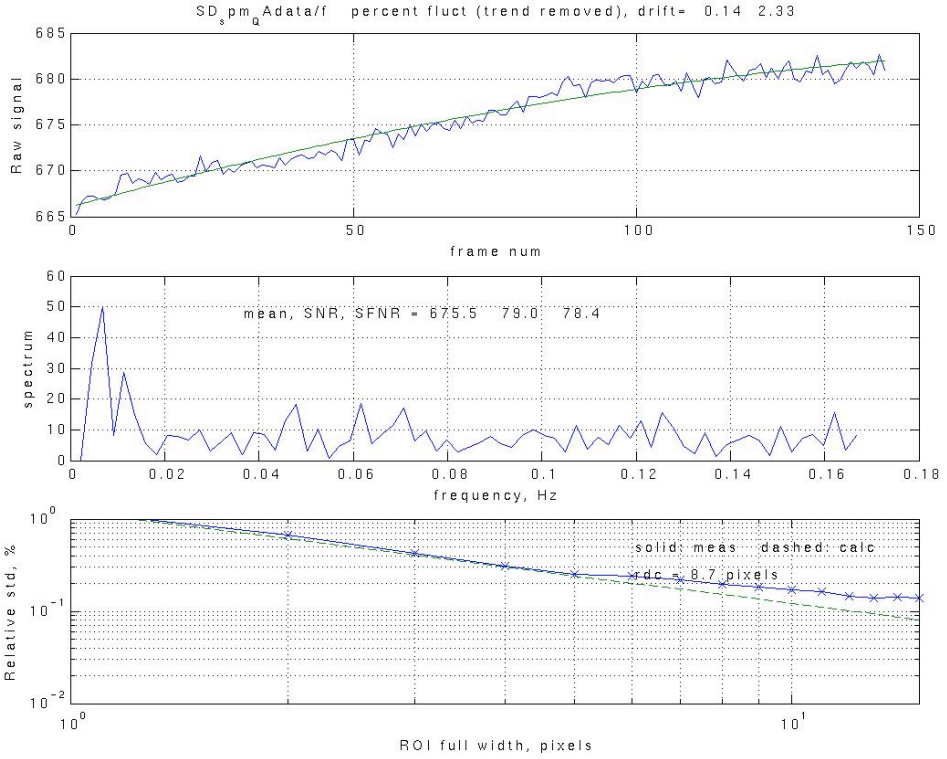
BIRN
BIOMEDICAL INFORMATICS RESEARCH NETWORK

Stability

UCI, 1.5T



UCSD, 1.5T

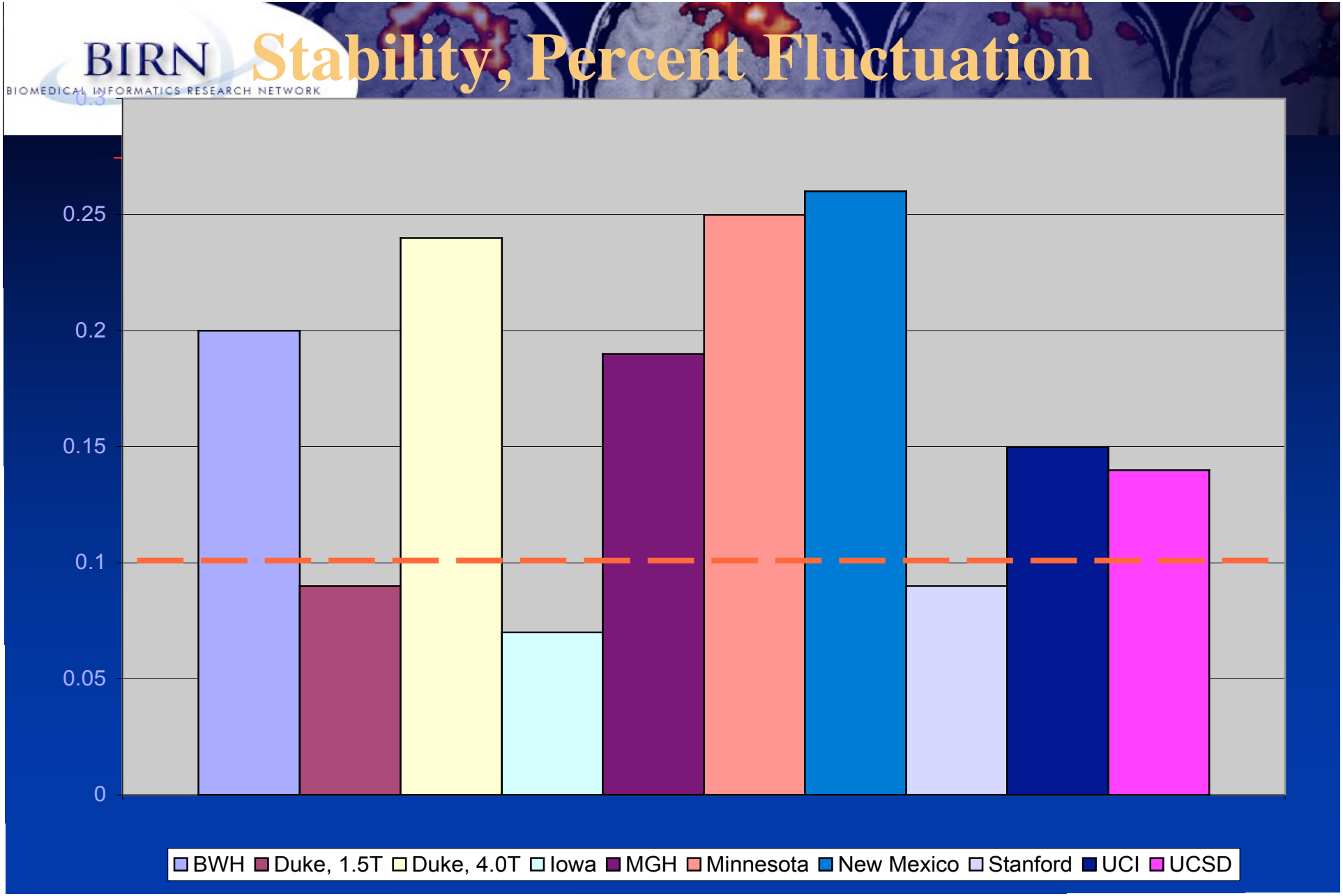


9/29/03

8/24/03

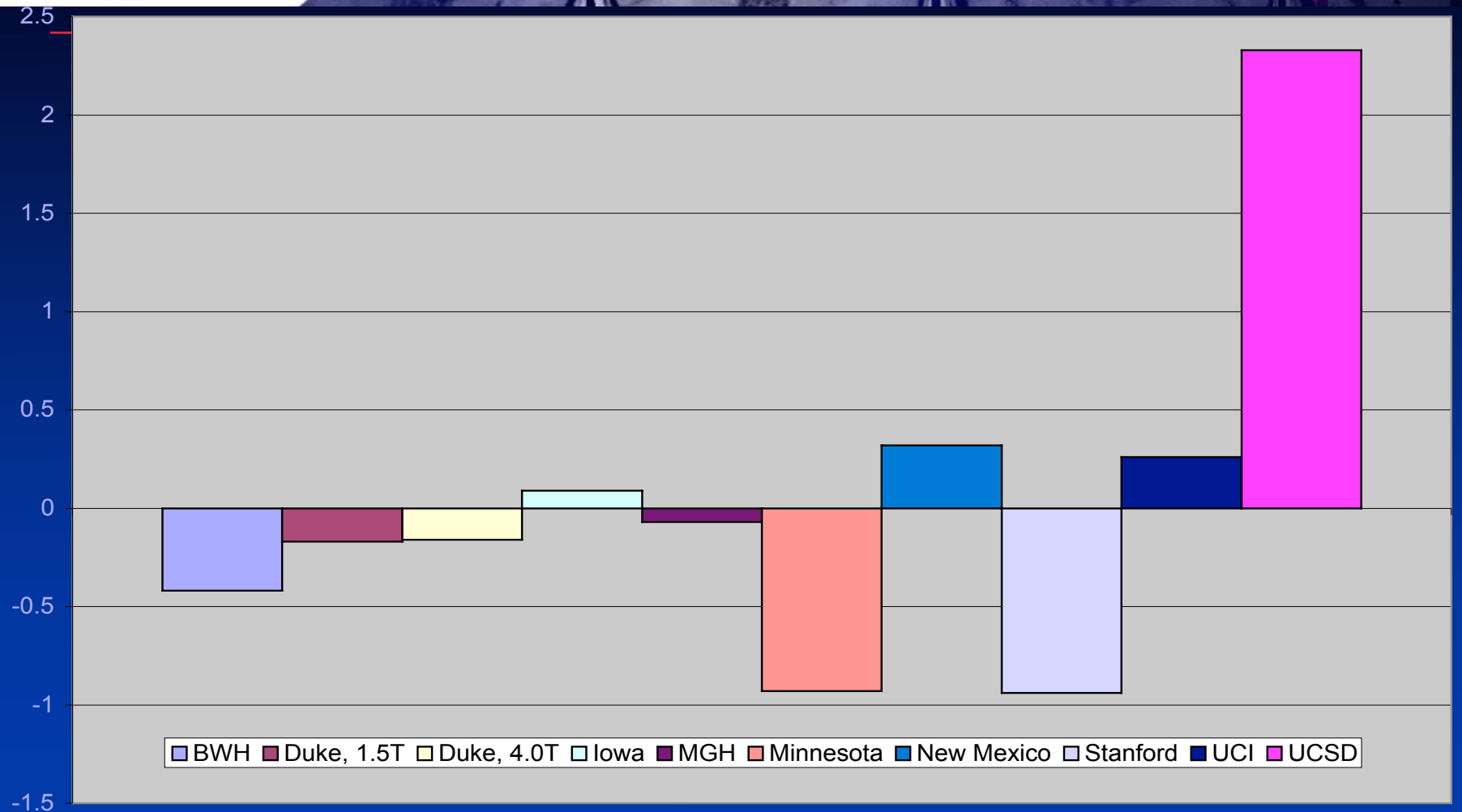
BIRN
BIOMEDICAL INFORMATICS RESEARCH NETWORK

Stability, Percent Fluctuation



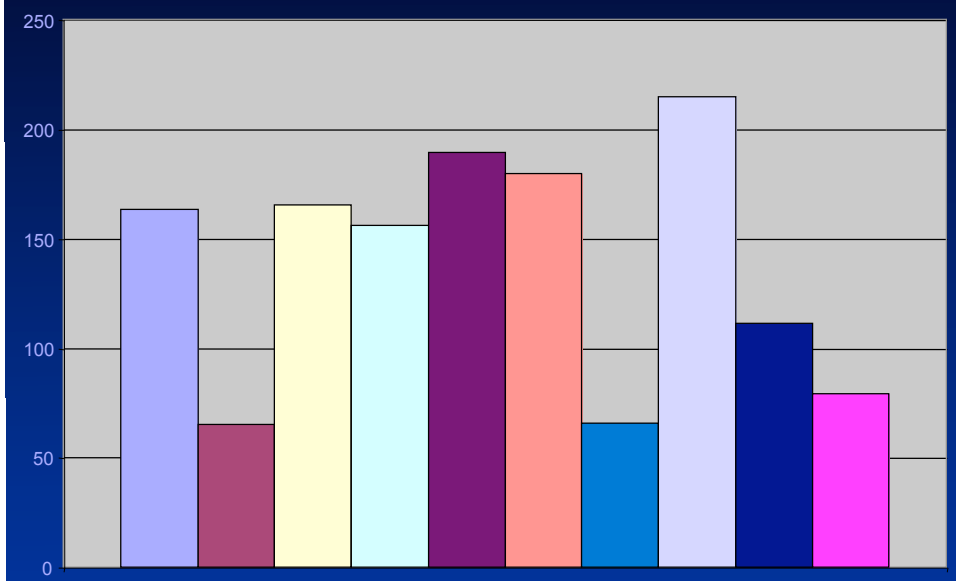
BIRN
BIOMEDICAL INFORMATICS RESEARCH NETWORK

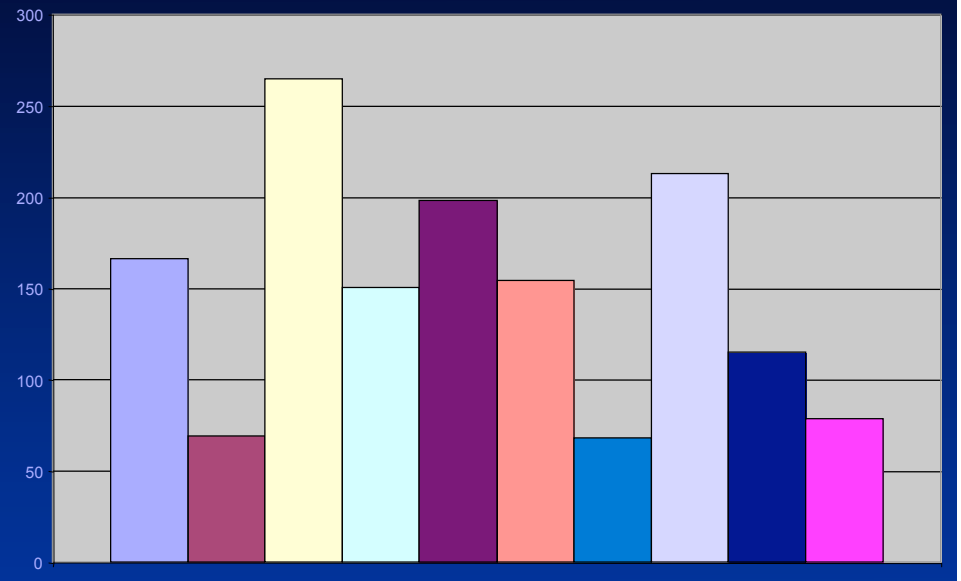
Drift, Percent



BIRN
BIOMEDICAL INFORMATICS RESEARCH NETWORK

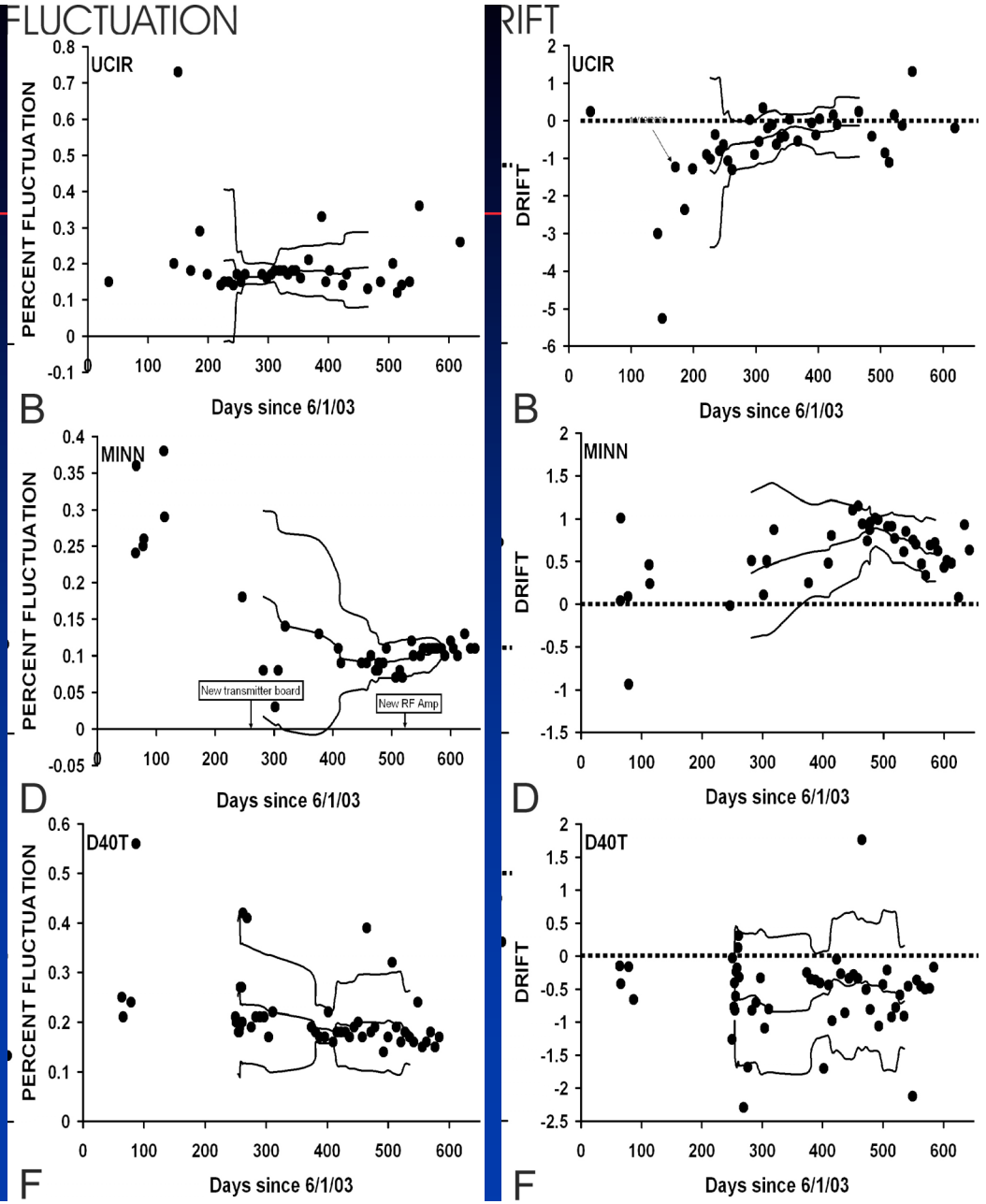
SNR, SFNR



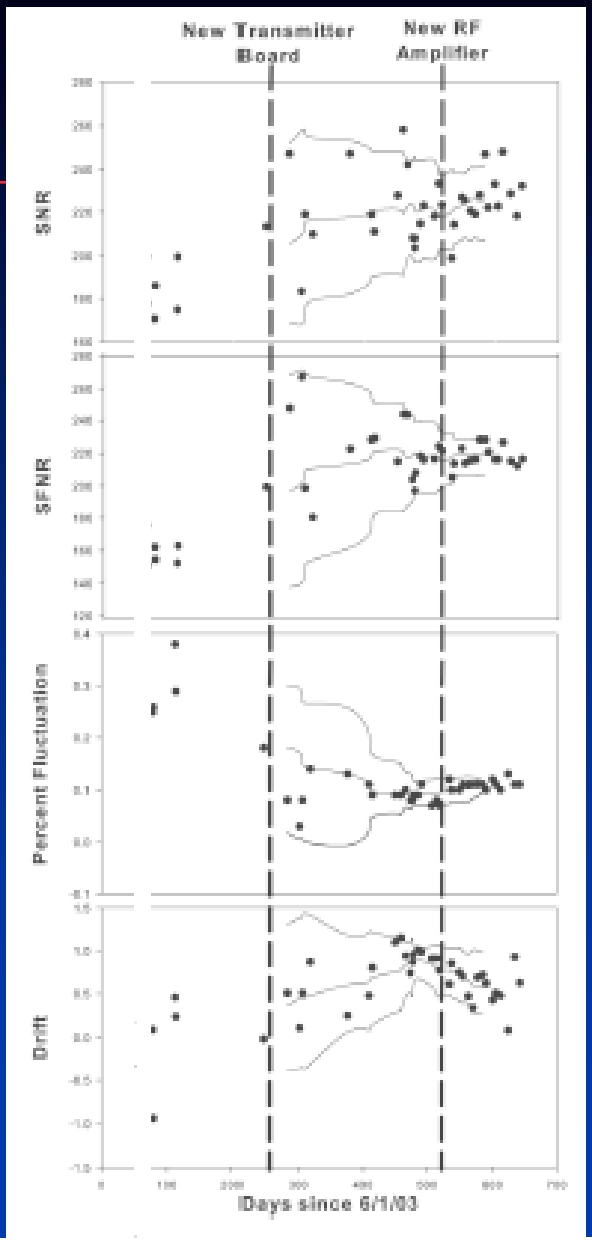


BWH | Duke, 1.5T | Duke, 4.0T | Iowa | MGH | Minnesota | New Mexico | Stanford | UCI | UCSD

QA helped to bring scanners into spec



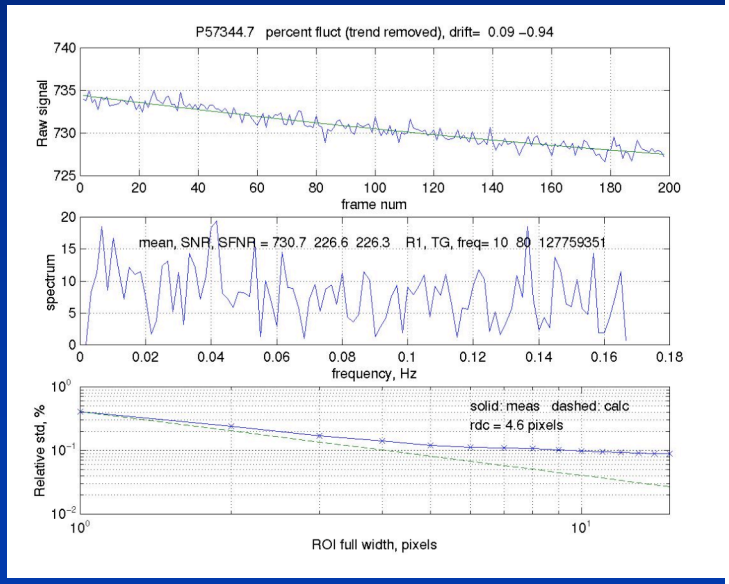
QA helped to debug site problems



BIRN
BIOMEDICAL INFORMATICS RESEARCH NETWORK

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



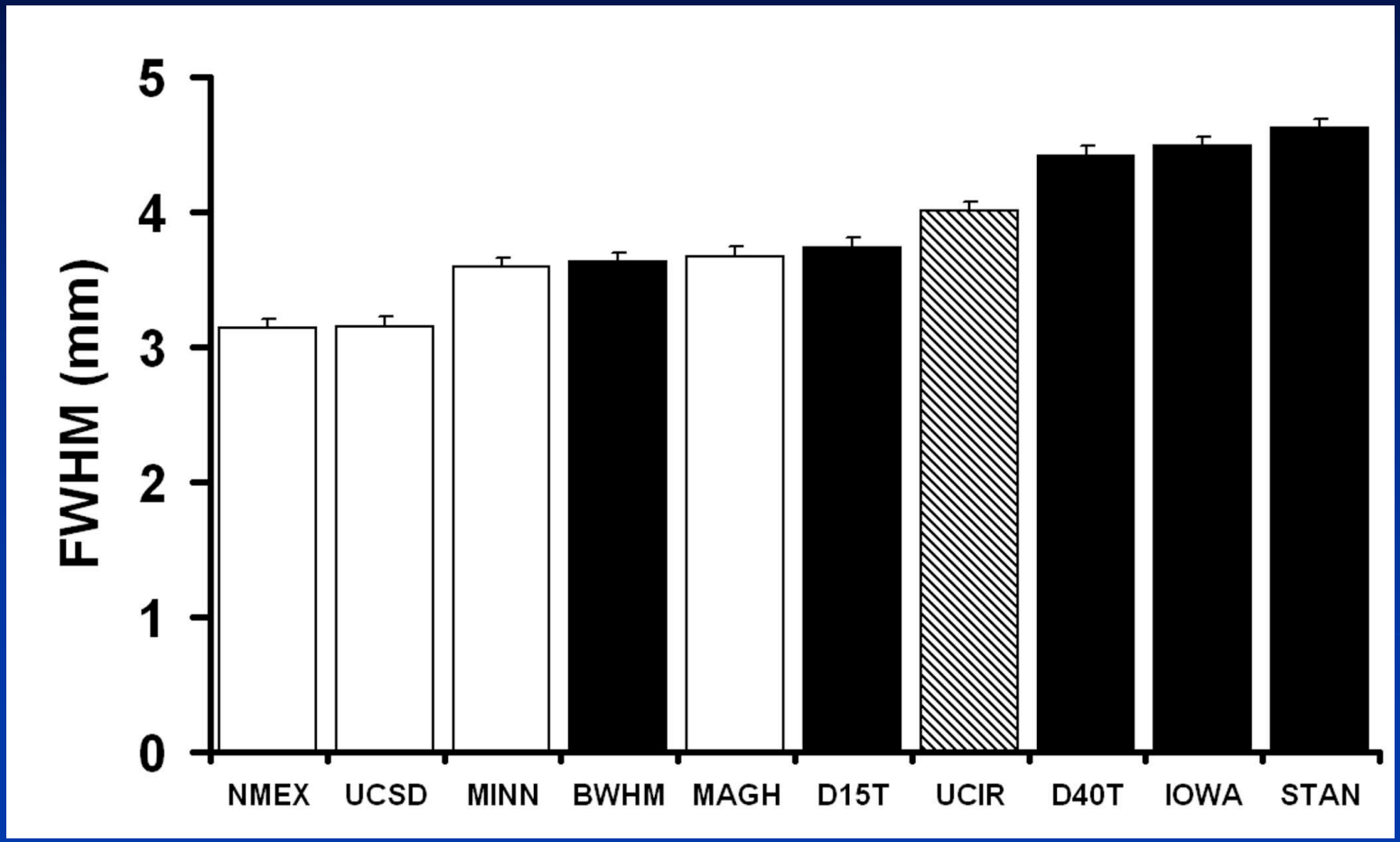
Outline

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

fMRI equalization across sites

- Compensation for smoothness
- Compensation by SFNR

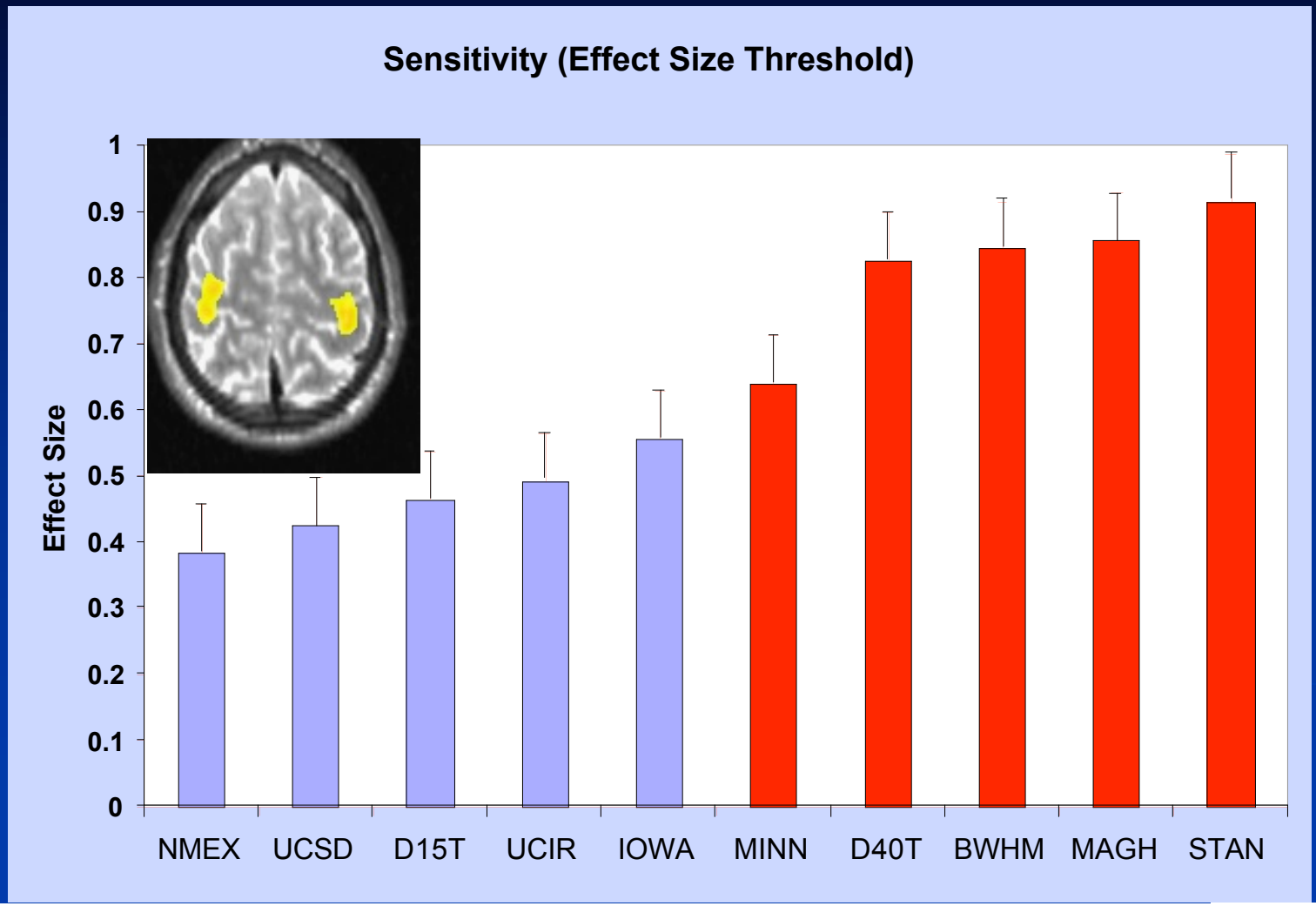
BOLD Smoothness Differences



Friedman, et al. 2006

BIRN
BIOMEDICAL INFORMATICS RESEARCH NETWORK

SM Sensitivity Differences



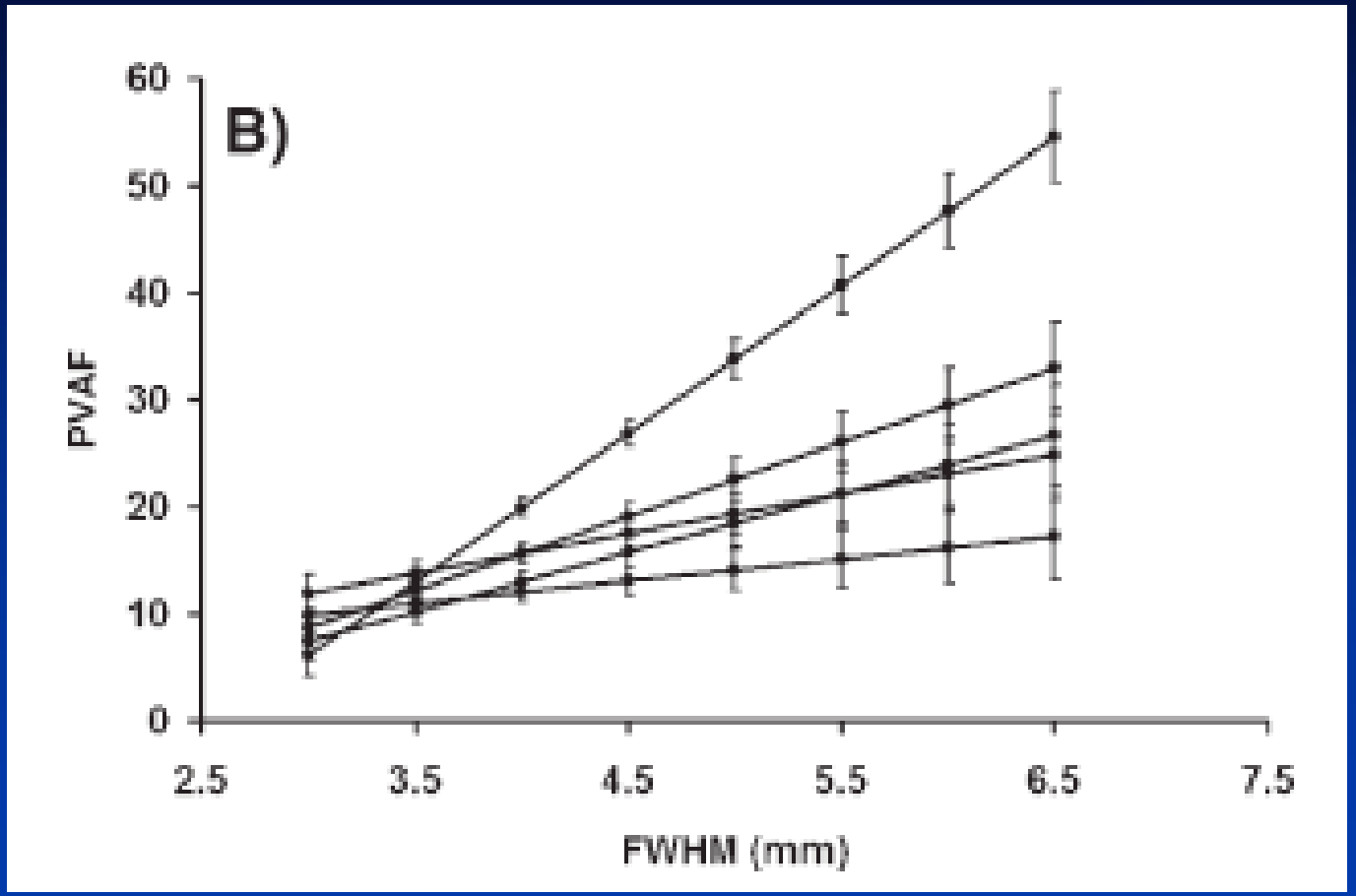
Red: 3T
Blue: 1.5T

Friedman, et al. 2006

BIRN
BIOMEDICAL INFORMATICS RESEARCH NETWORK

Sensitivity vs. Smoothness

5 traveling subjects at 10 sites performing sensorimotor task



Friedman, et al. 2006

Smoothness equalization

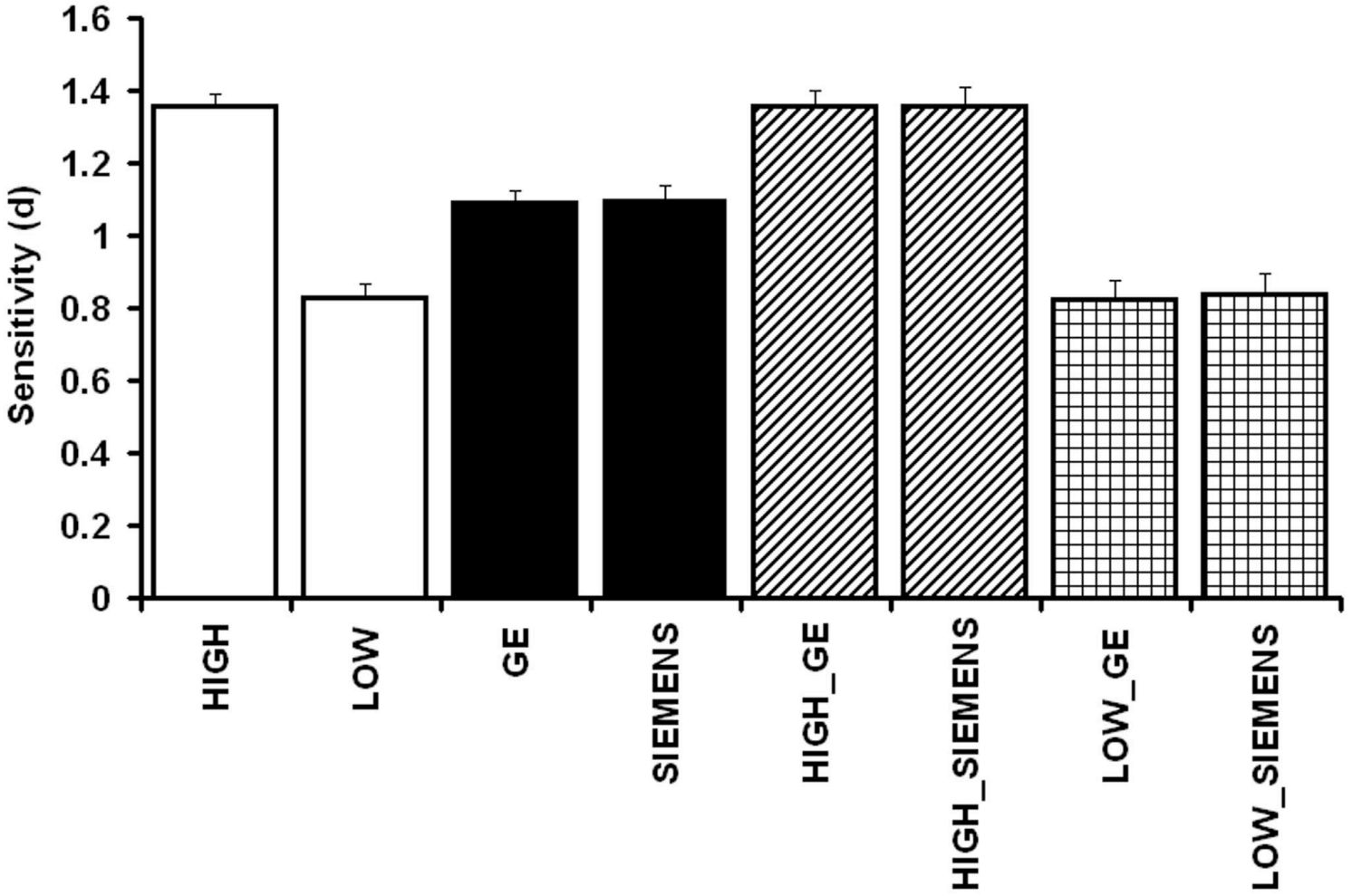
In first-level analysis: Use "smooth to" instead of "smooth by"

Smooth each site to largest FWHM using Gaussian filter

$$FWHM_{out}^{-2} = FWHM_{meas}^{-2} + FWHM_{filter}^{-2}$$

Friedman, et al. 2006

Sensitivity after smoothness equalization

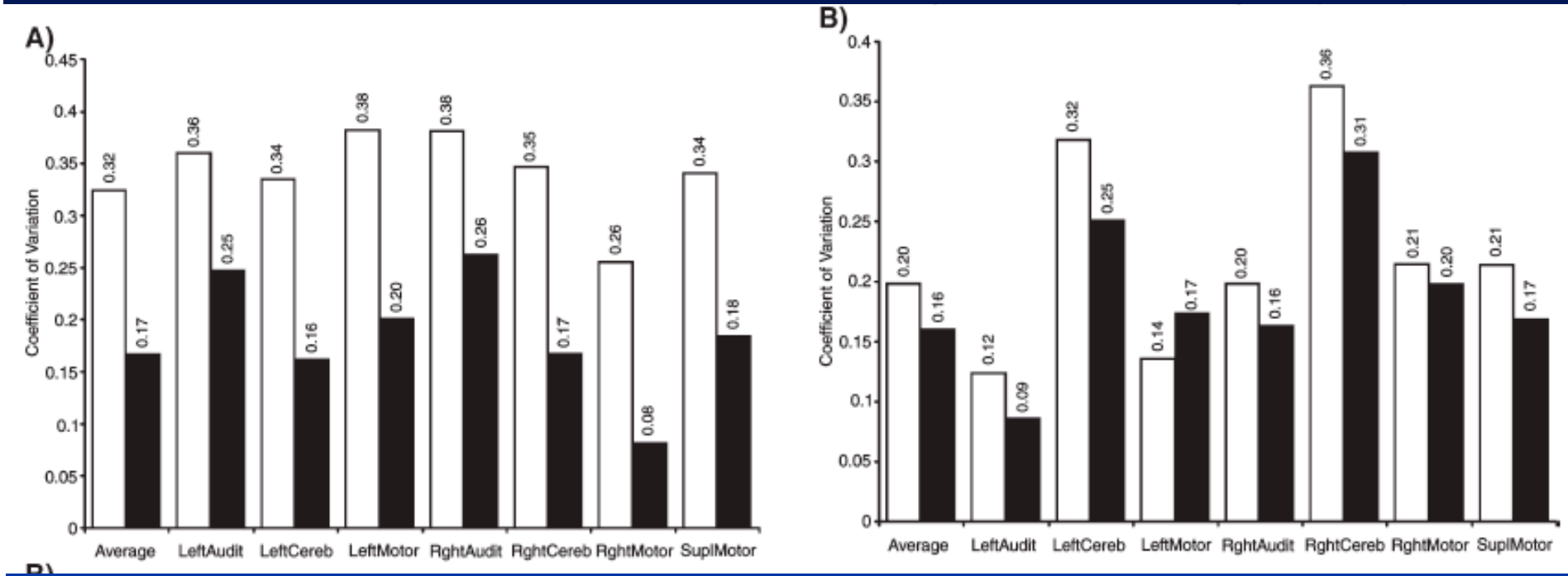


Friedman, et al. 2006

Intersite CV

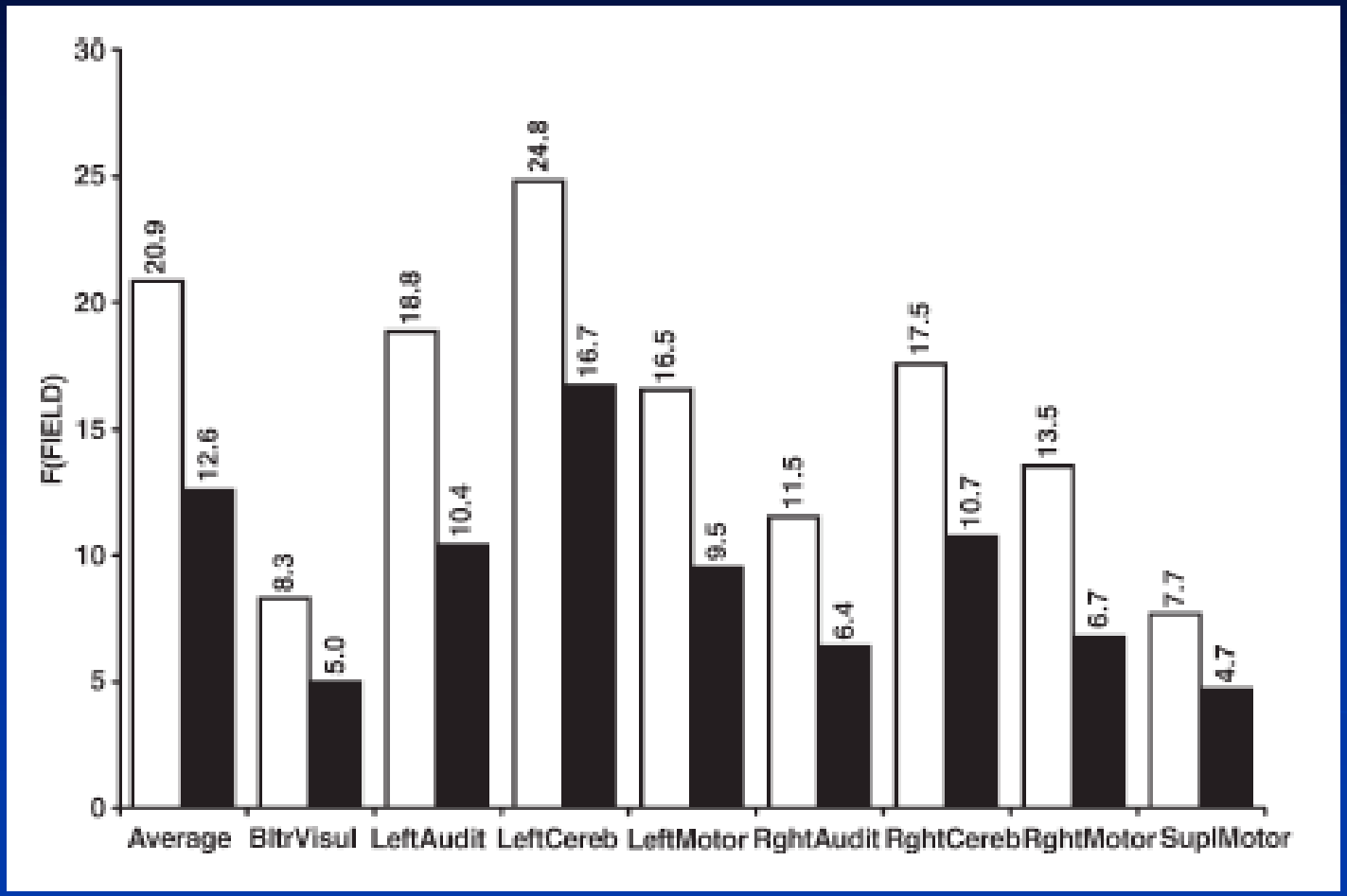
1.5T

3T



Friedman, et al. 2006

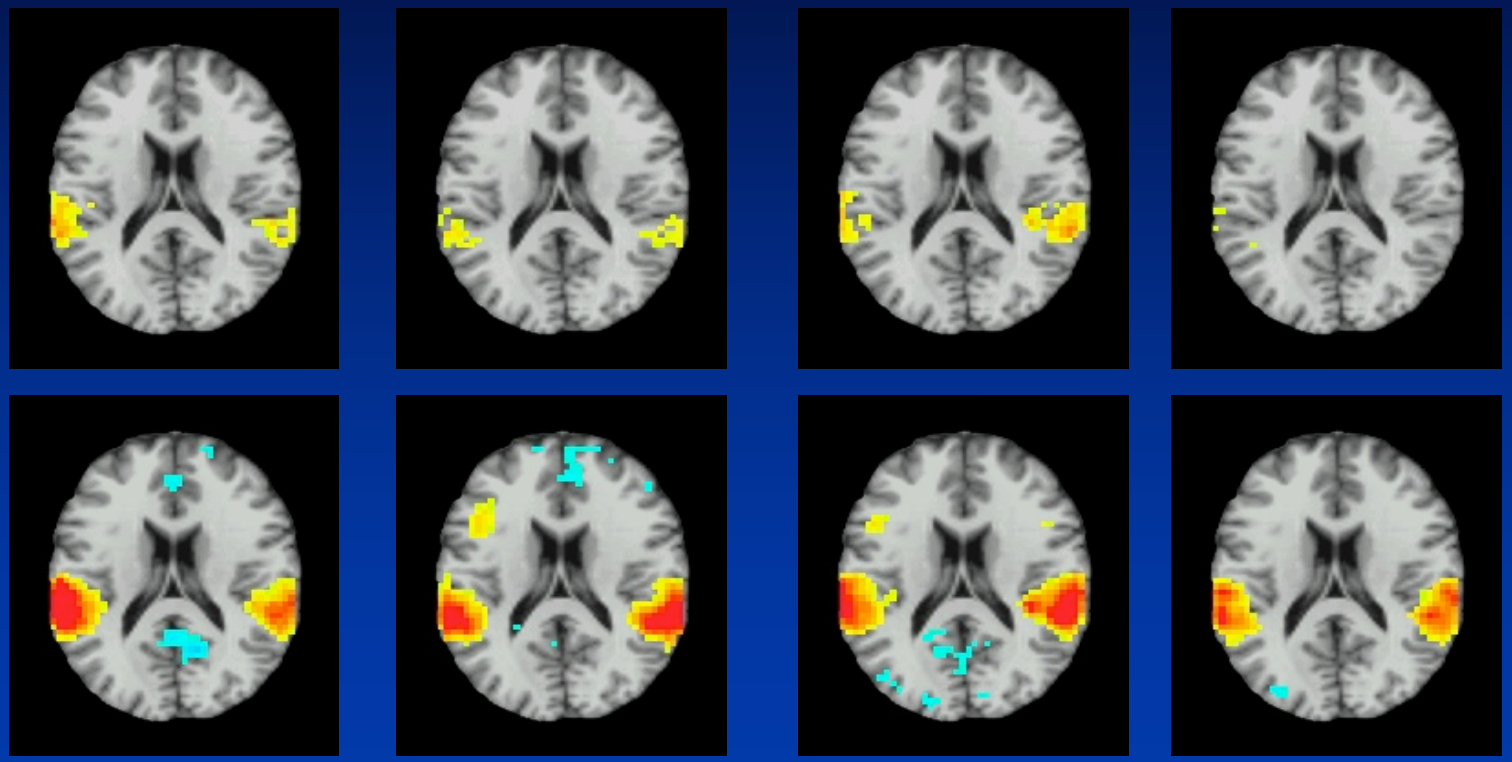
Intersite Effect of Field



Friedman, et al. 2006

BIRN
BIOMEDICAL INFORMATICS RESEARCH NETWORK

BOLD Sensitivity: Oddball Task

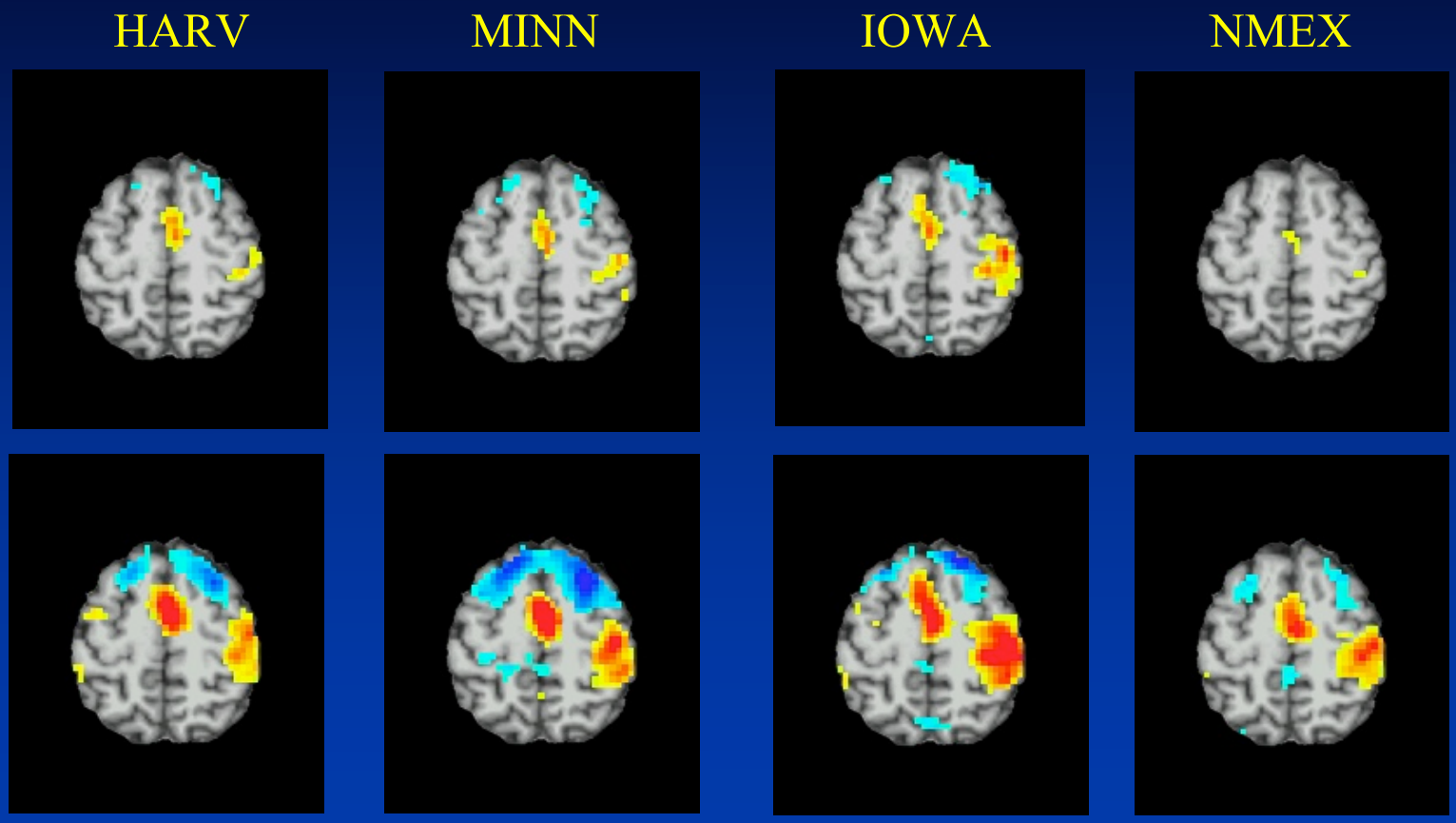


Novel Tones - Effect Size

Friedman, et al.

BIRN
BIOMEDICAL INFORMATICS RESEARCH NETWORK

BOLD Sensitivity: Oddball Task

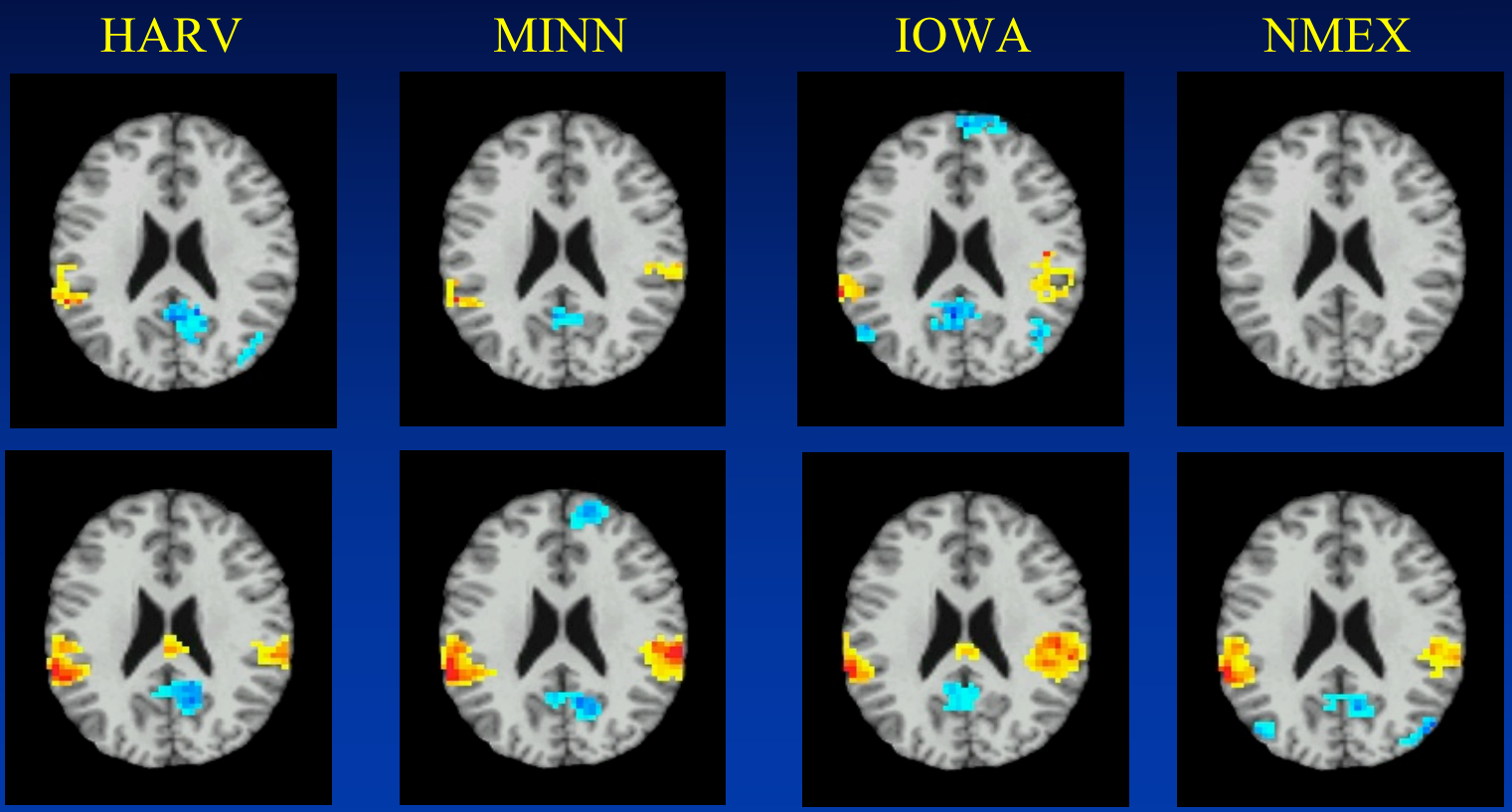


Target Tones- Effect Size

Friedman, et al.

BIRN
BIOMEDICAL INFORMATICS RESEARCH NETWORK

BOLD Sensitivity: Oddball Task



Target Tones - Cluster Maps

Voxel P = 0.001, Cluster Size = 8, Volumewise p = 0.05

Friedman, et al.

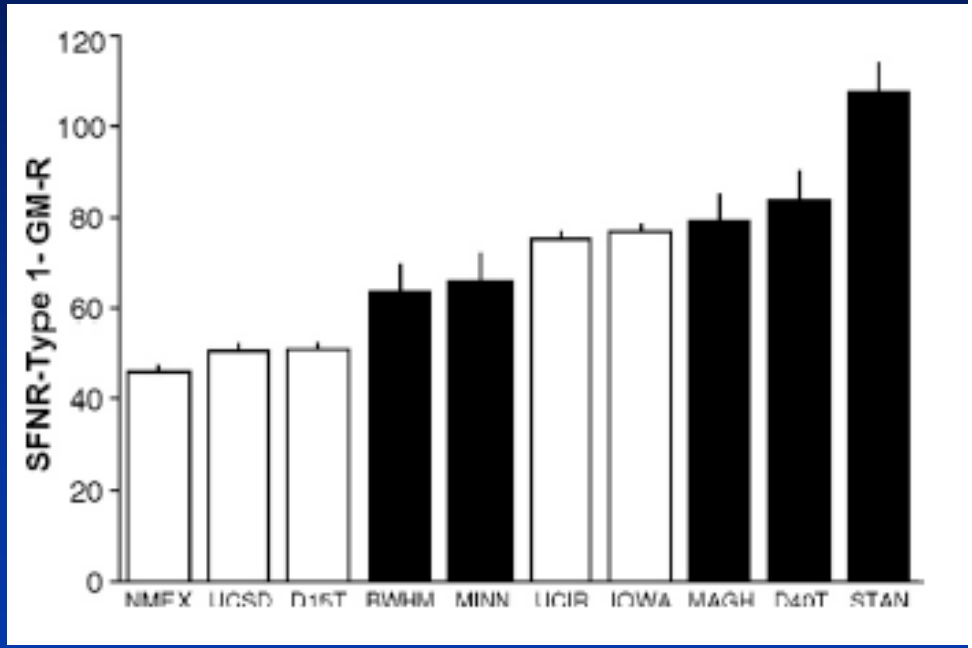
fMRI equalization across sites

- Compensation for smoothness
- Compensation by SFNR

fMRI equalization by SFNR

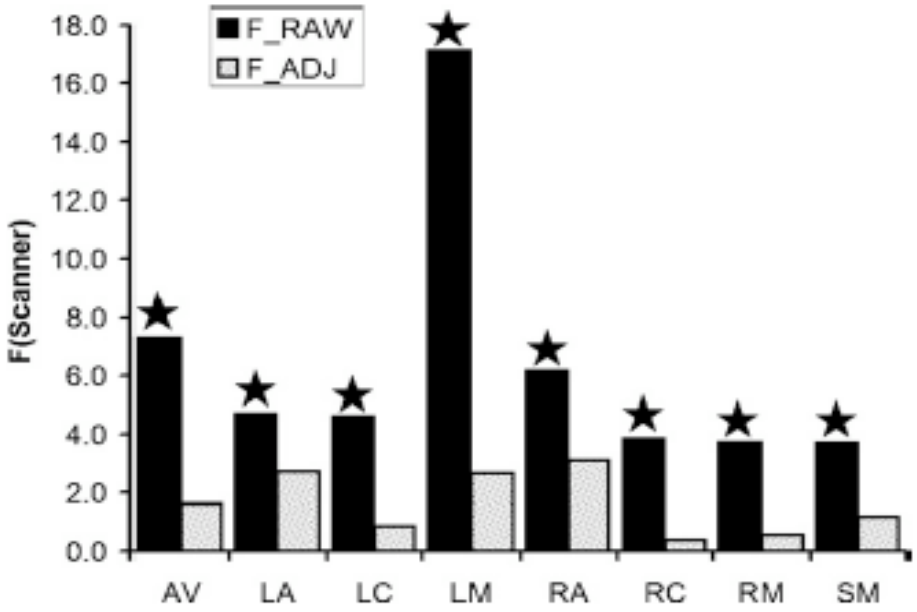
- Measure SFNR using
  - GM - Rest
  - WM - Rest
  - GM - SMresid
  - WM - SMresid
- Covary for SFNR

Original SFNR

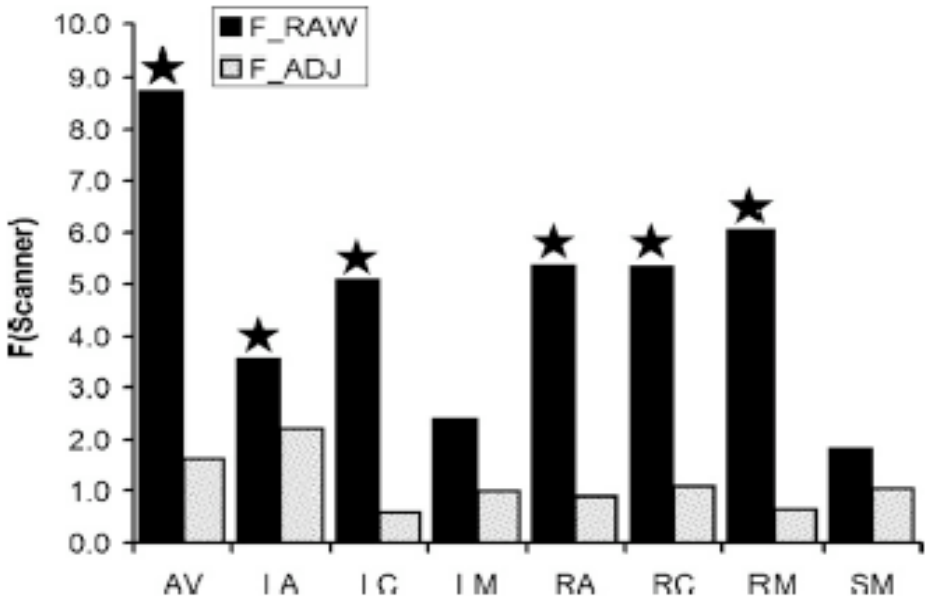


Site equalization by SFNR

1.5T



3T



Outline

- Motivation for multicenter imaging studies
- Issues in MRI or fMRI studies
- Standardization of protocols
- QA
- Site Equalization
- Calibration
- Site performance standardization

BIRN
BIOMEDICAL INFORMATICS RESEARCH NETWORK

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

BIRN
BIOMEDICAL INFORMATICS RESEARCH NETWORK

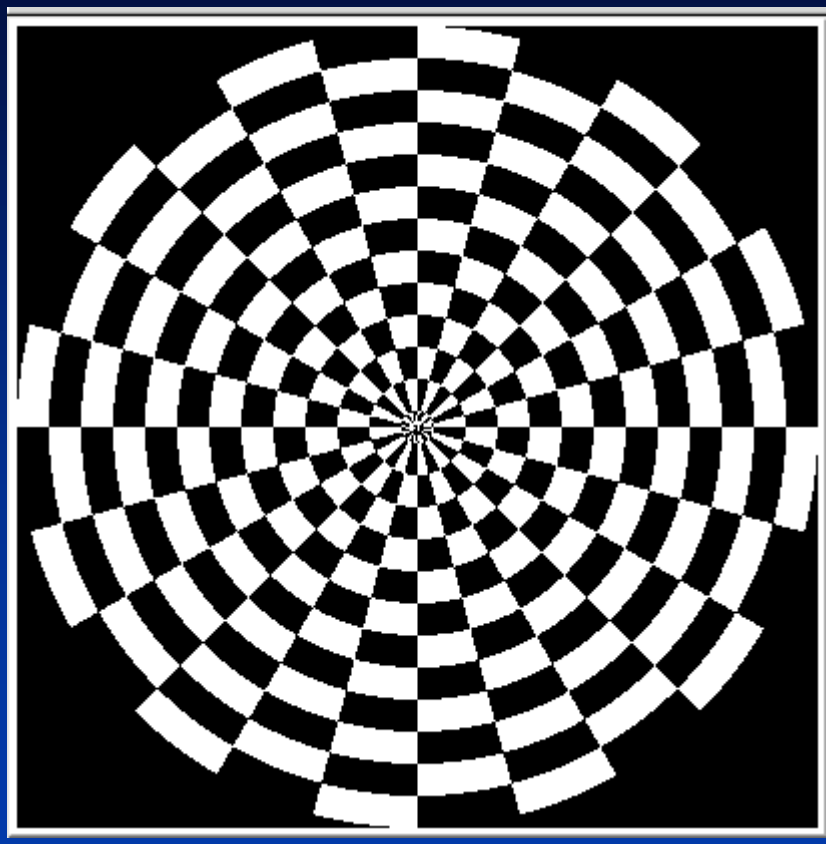
SM Task- Visual/Auditory/Motor

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, 86, 82, 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.

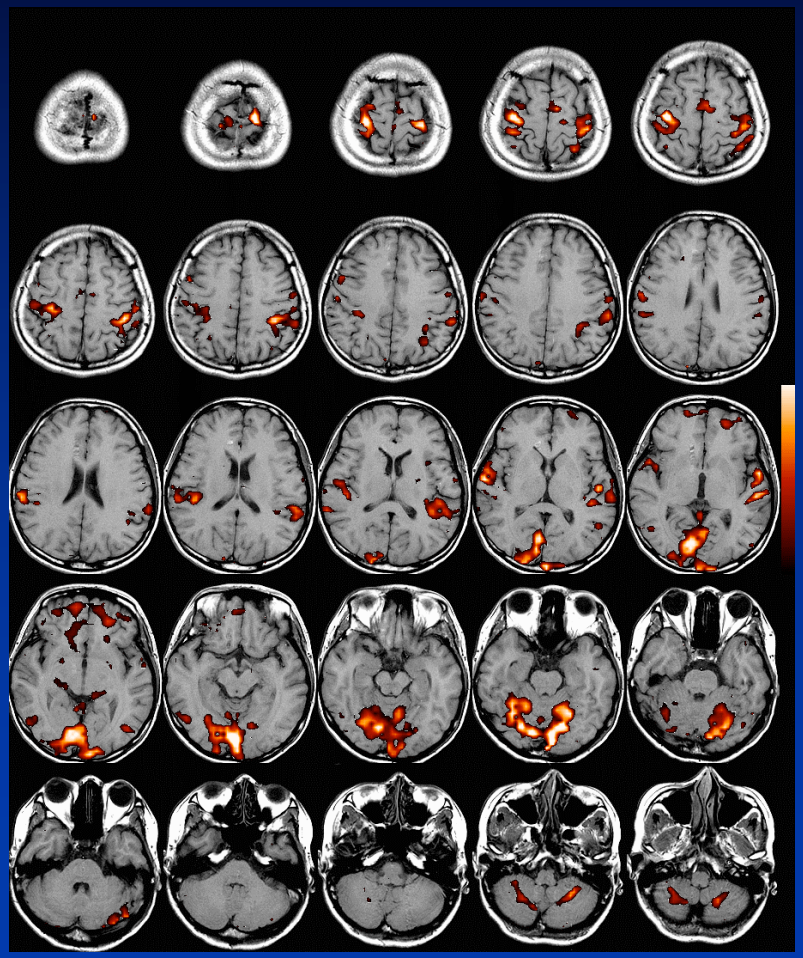
Off Block: Fixation cross, silence, no motion.



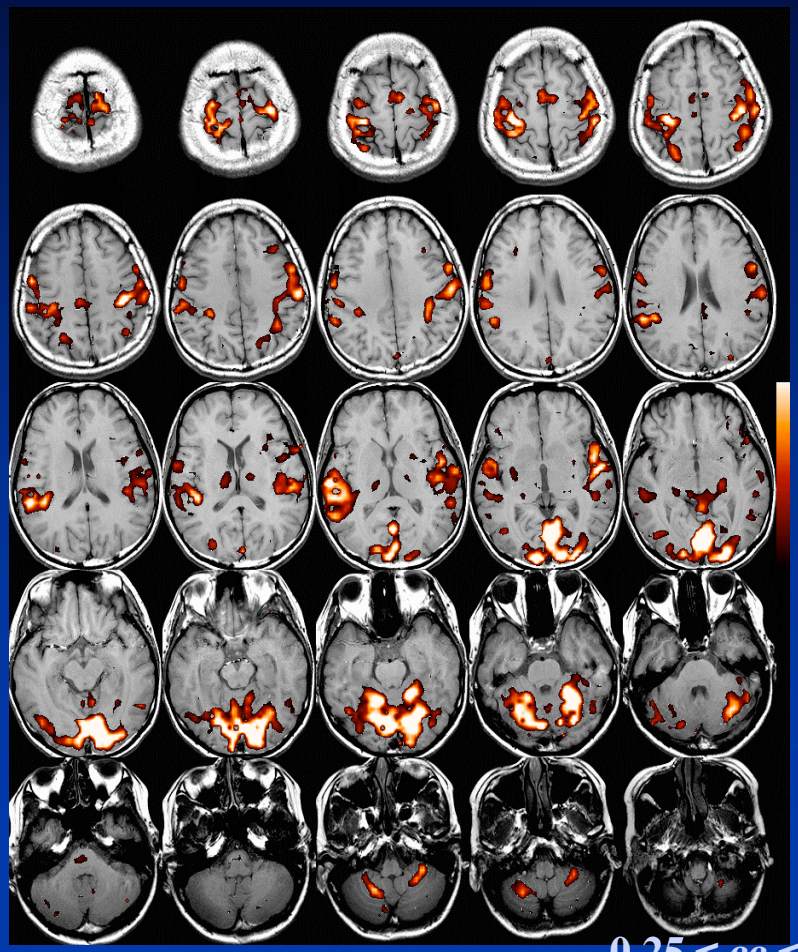
TR/TE/FA = 3000/(40/30)/90, 100 kHz BW, 64x64 matrix;
22 cm FOV, 35 slices, AC-PC orientation, 4 mm skip 0.

Activation

1.5T



3.0T



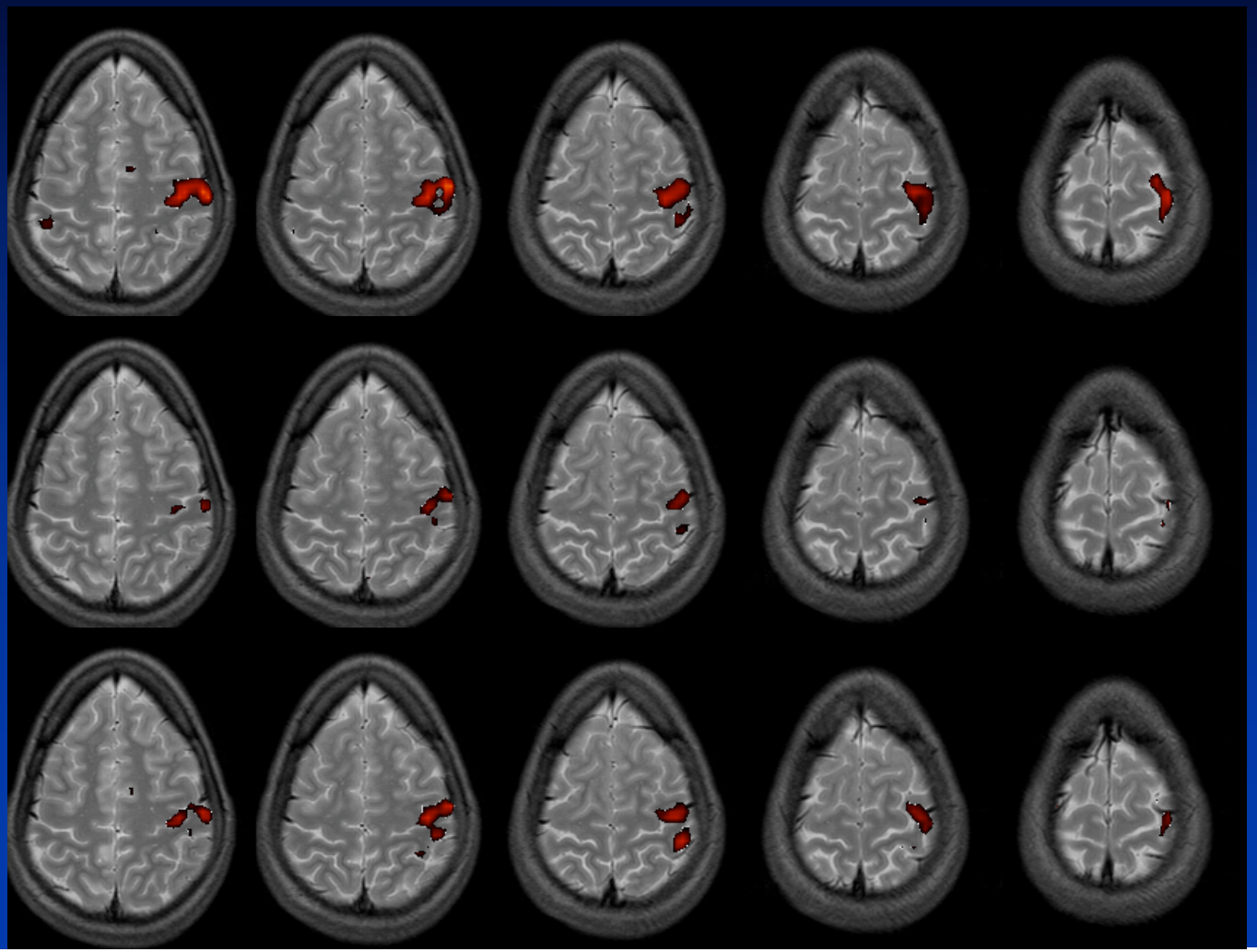
$0.25 \leq cc \leq 0.70$

Passive (pneumatic plungers) SM Calibration Task

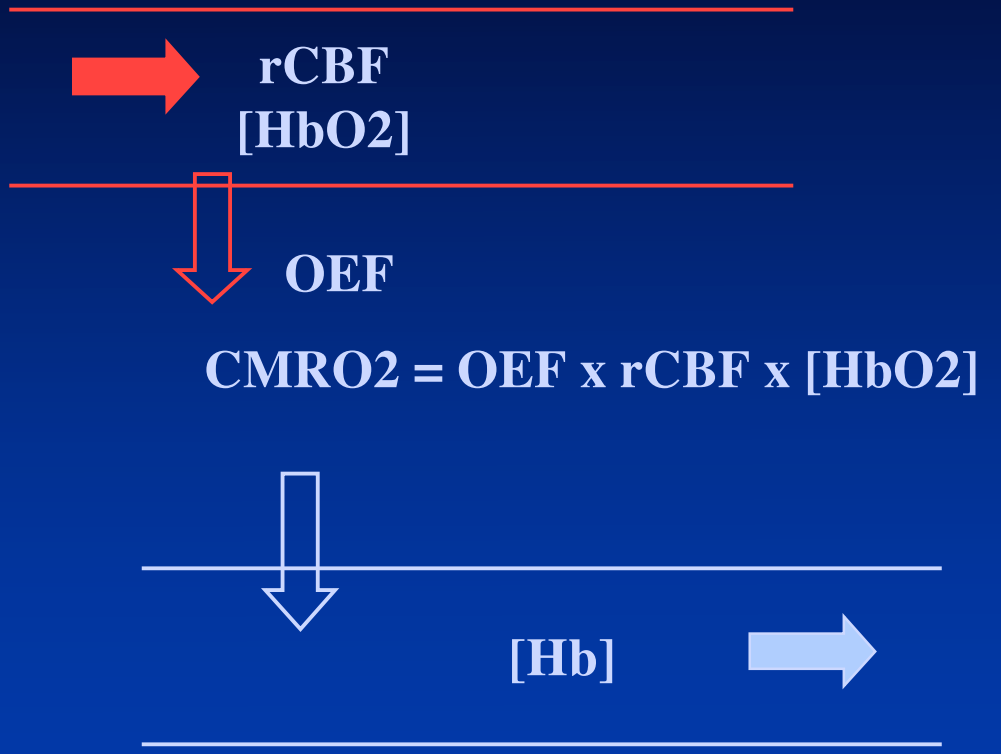
attend

not attend

attend



Calibration of BOLD Signal



Davis, PNAS (1998)
Buxton, 2003

$$\Delta R2^* \propto rCBV_a[Hb]_a^\beta - rCBV_0[Hb]_0^\beta$$

$$BOLD \propto -TE \cdot \Delta R2^*$$

$$rCBV \propto rCBF^\alpha$$

$$BOLD_a = S_0[f^\alpha(\frac{m}{f})^\beta - 1]$$

$$m \equiv CMRO2_a / CMRO2_0$$

$$f = rCBF_a / rCBF_0$$

$$BOLD_{BH} = S_0[f_{BH}^{\alpha-\beta} - 1]$$

$$BOLD_a = BOLD_{BH} \frac{[f_a^\alpha(\frac{m}{f_a})^\beta - 1]}{[f_{BH}^{\alpha-\beta} - 1]}$$

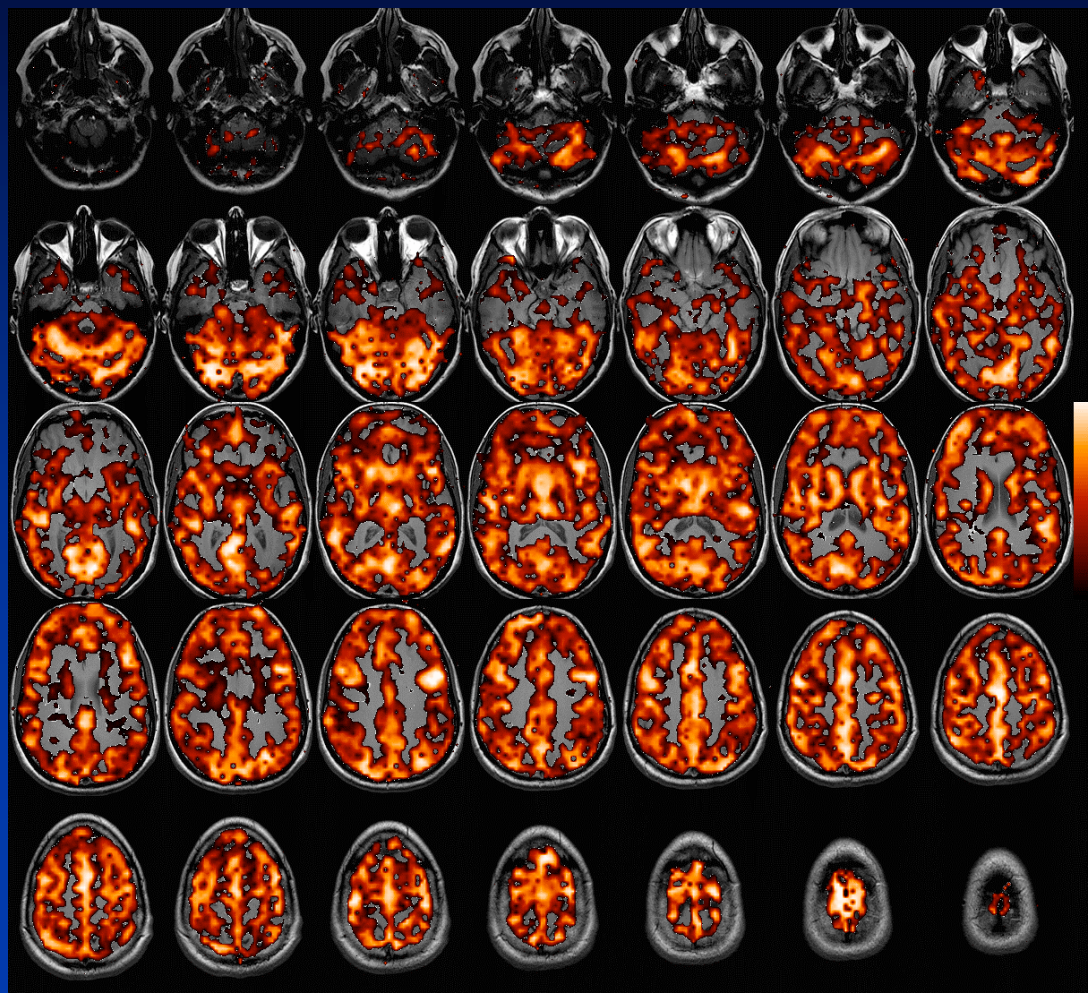
Calibration Breath-holding Task

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

On block: Hold breath while circle of diminishing size is projected.

Off Block: Fixation cross, breathe normally

Gray matter shows stronger response than white matter.



Calibration: Voxel-wise Normalization by BH Response

$$y_{meas}(j) = y_{metab}(j) \cdot B(j) + n, \quad j = 1 \cdots N_{sub}$$

$$y_{metab}(j) \approx y_{calib}(j) = y_{meas}(j) \frac{\overline{B}}{B(j)}$$

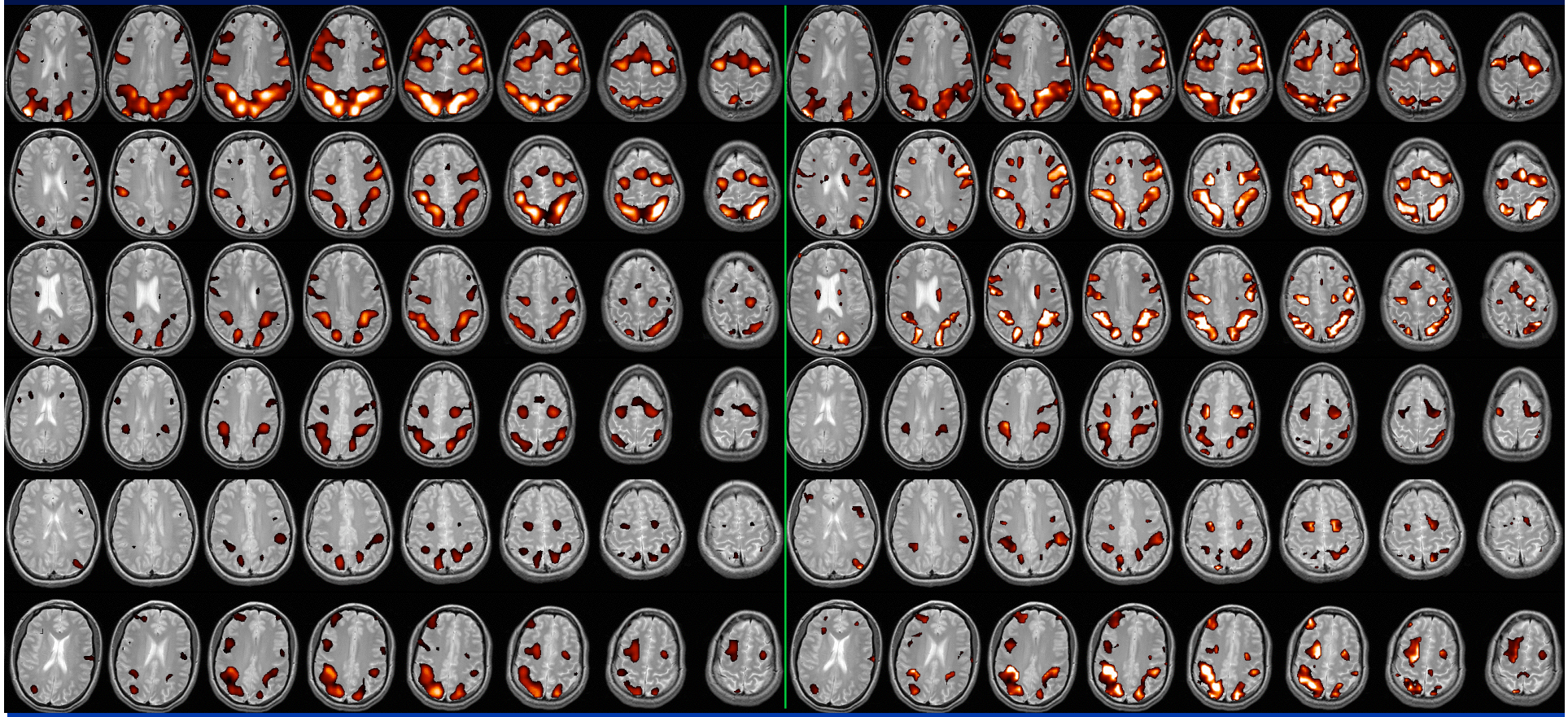
$$\sigma^2_{calib} = (1 - R^2)\sigma^2_{meas}, \quad R^2 = \mathrm{cov}(y_{meas}, B)$$

M. Thomason, 2007

BH Calibration: WM Task

No calib

Calib



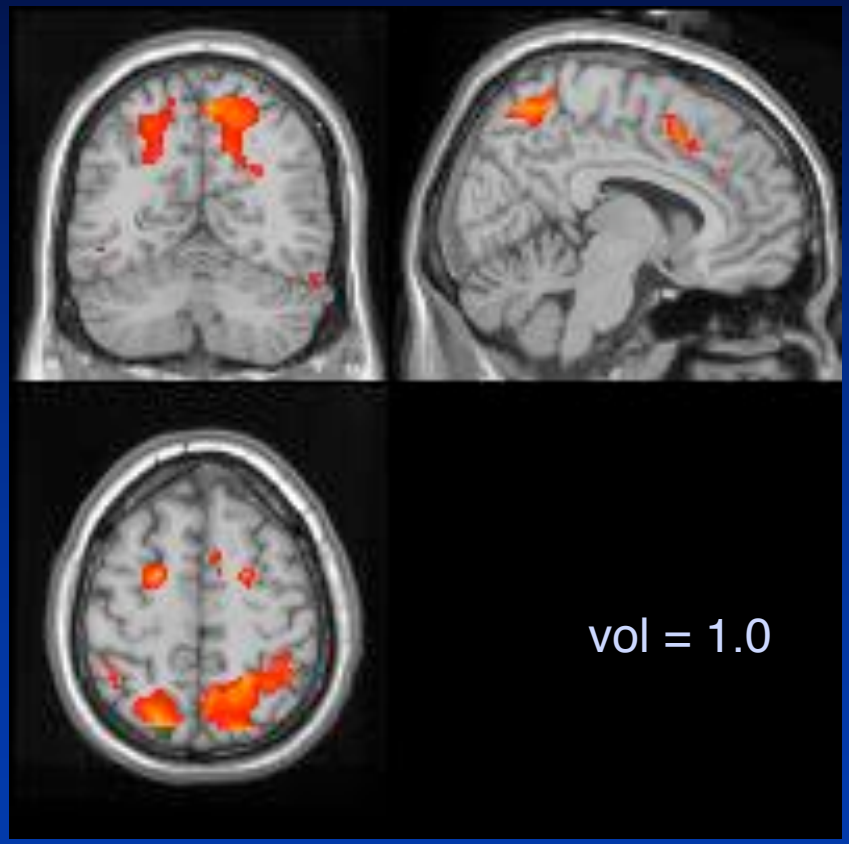
SWM task, fBIRN BH task

M. Thomason, 2007

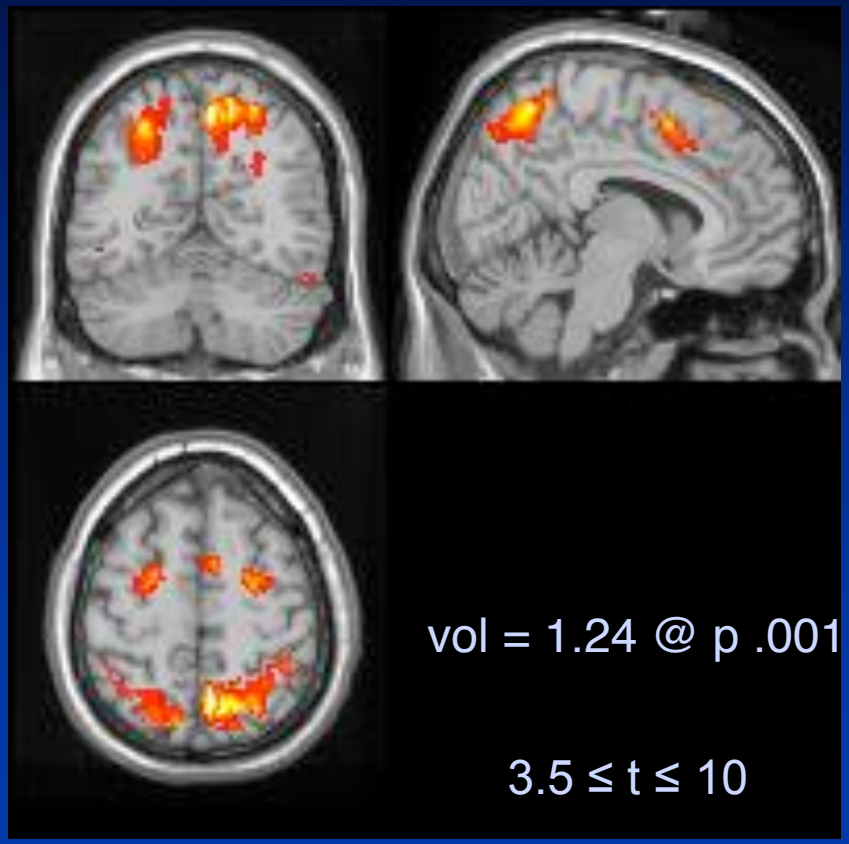
$5 \leq t \leq 20$

BH Calibration: Group Activation

No cal



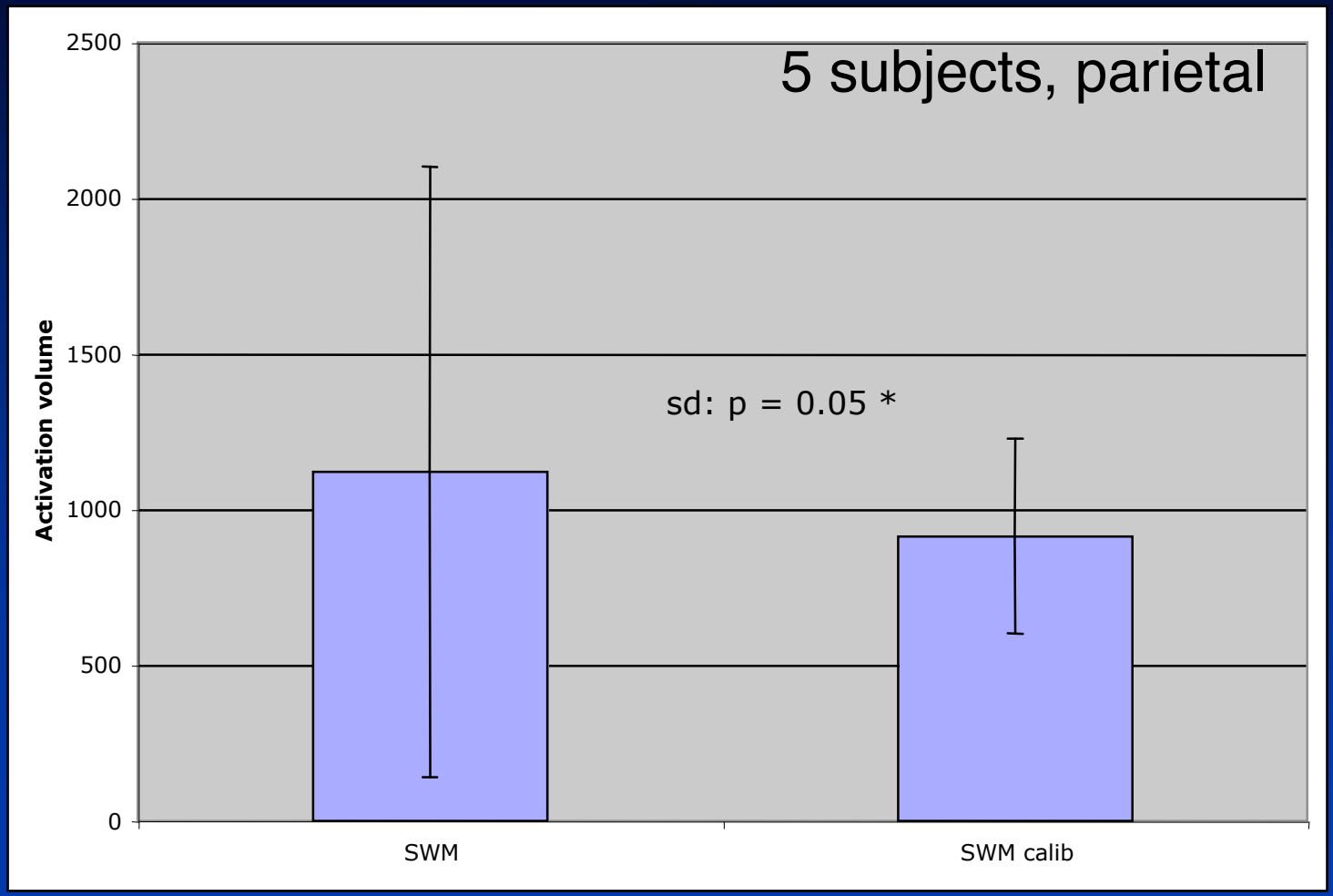
Calib



SWM task, fBIRN BH task, N = 7

M. Thomason, 2007

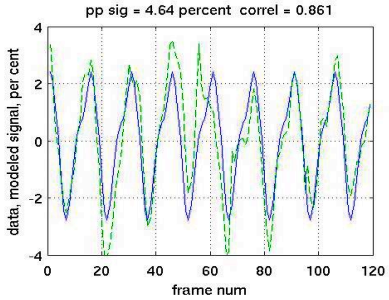
Calibration: SWM

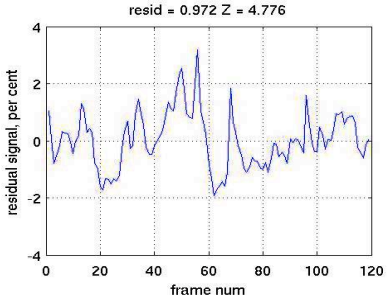


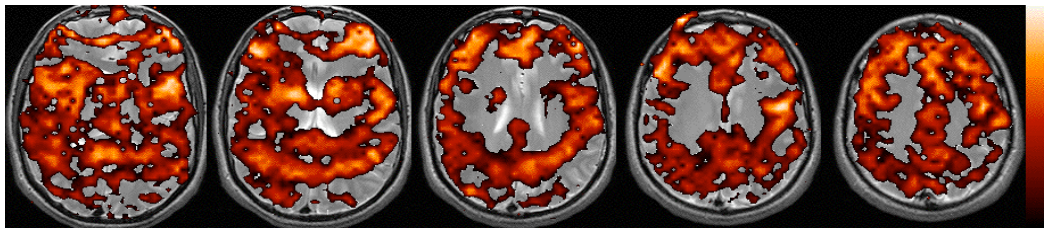
M. Thomason, 2007

BH Calibration: Inspiration control

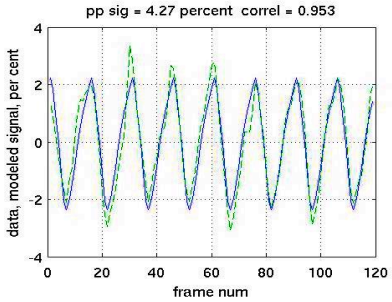
no control

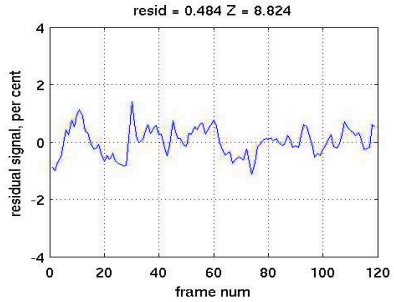


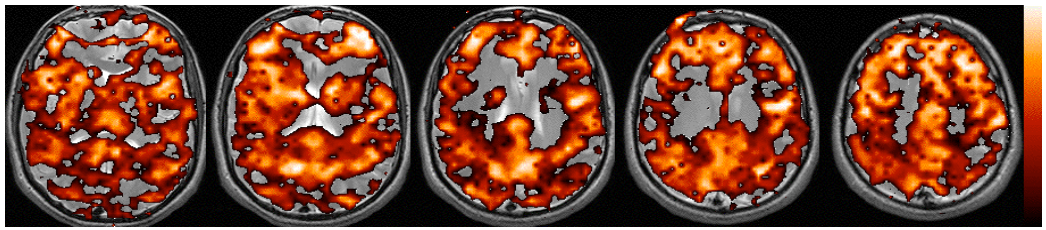




w/control





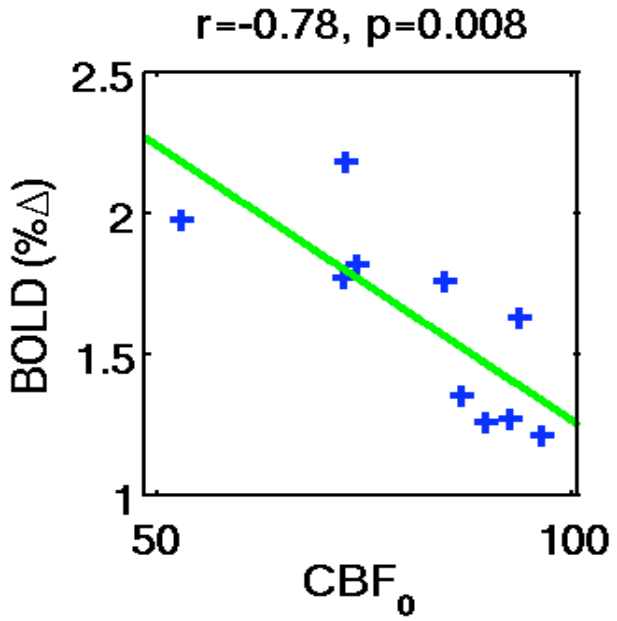


M. Thomason, 2008

BIRN

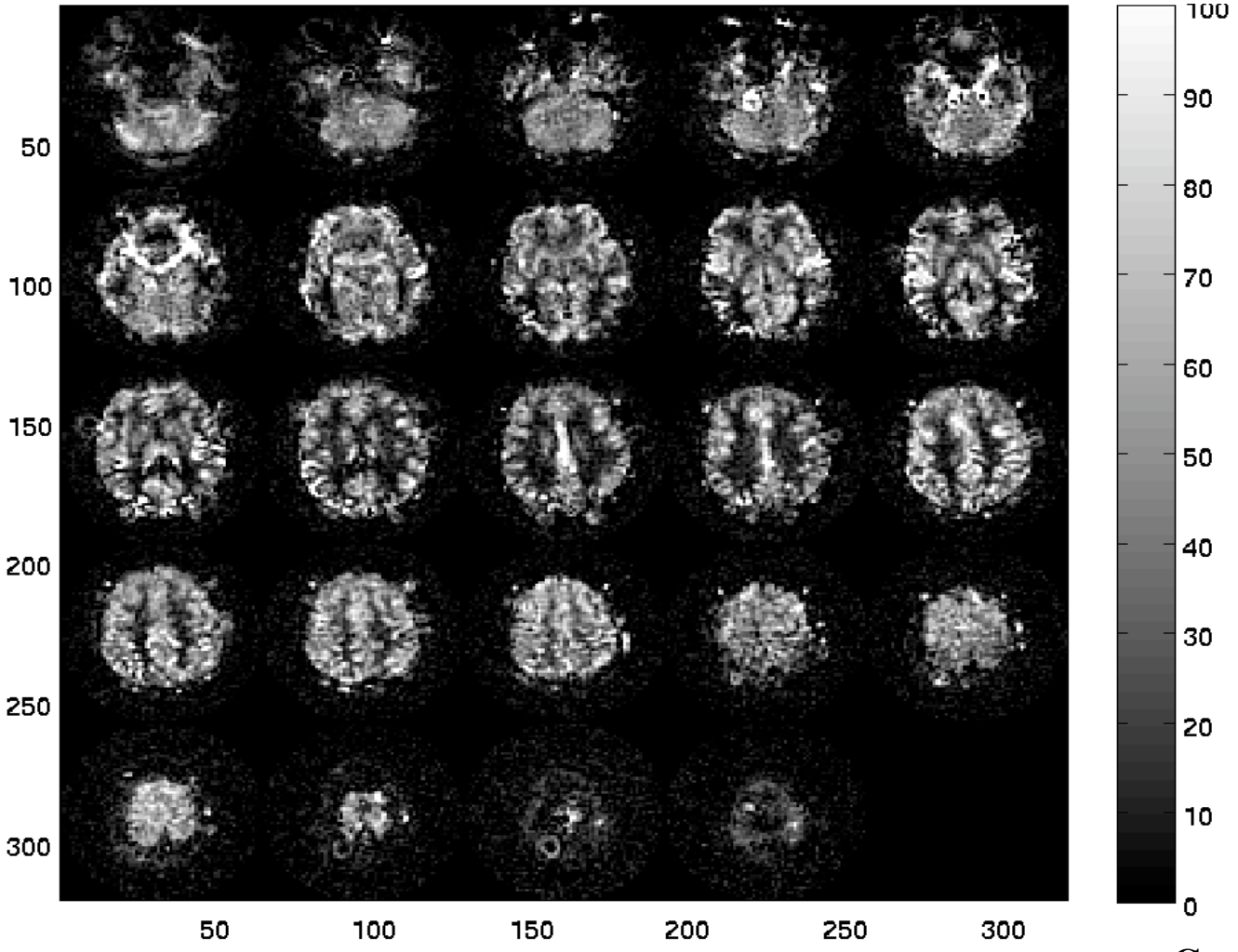
Cerebral Blood Flow

- 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.



Liau et al, Abstract 854, ISMRM 2008

ASL- quantitative rCBF maps



Courtesy T. Liu

Impact of Calibration

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

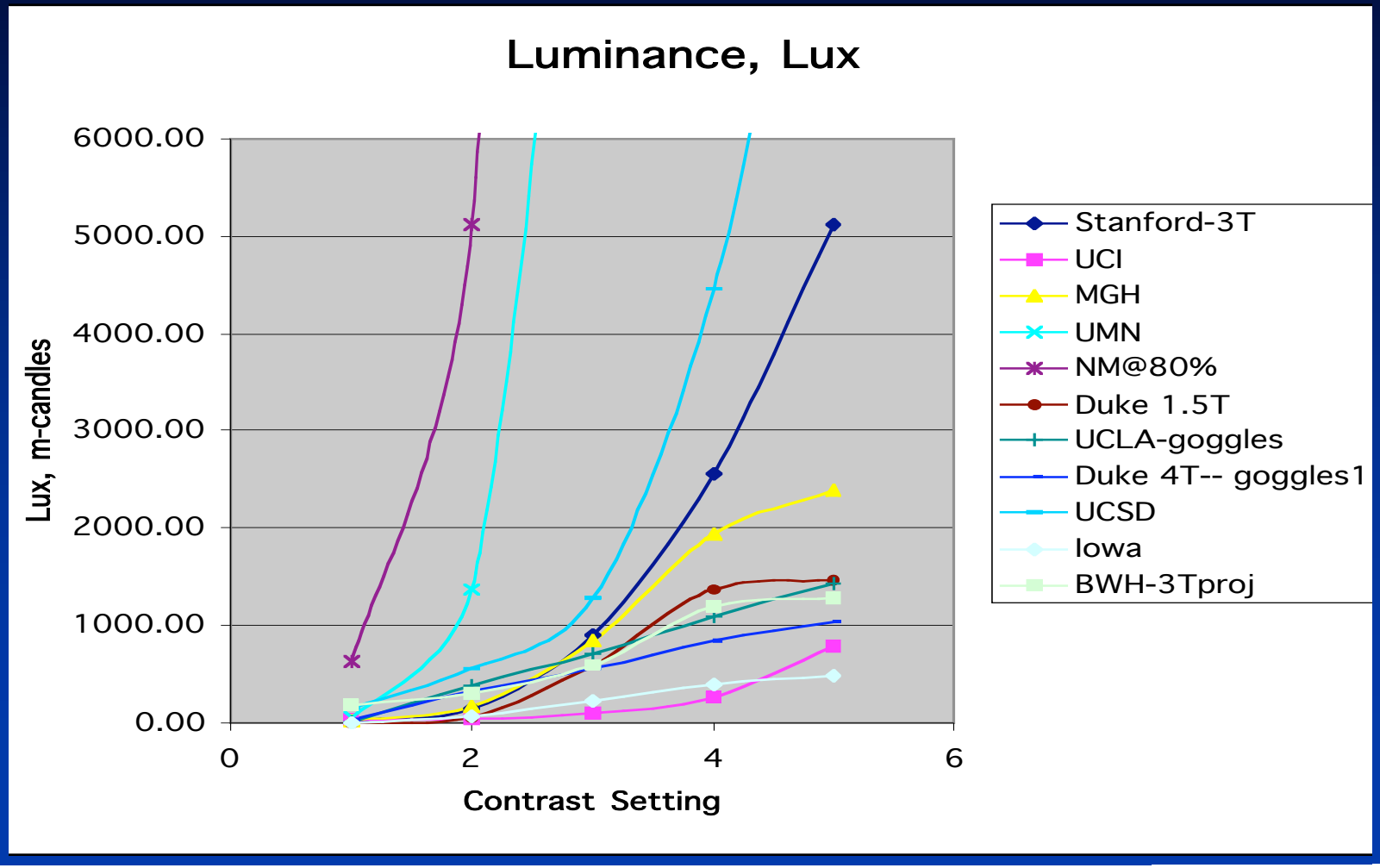
Outline

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

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

Site visual presentation



Conclusions

- Standardize scanner performance/ imaging params/ 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)

Acknowledgements:

fBIRN Calibration Working Group

Greg Brown @ucsd.edu
Lee Friedman @UCI.edu
Doug Greve @nmr.mgh.harvard.edu
Tom Liu @ucsd.edu
Bryon Mueller @cmrr.umn.edu
Jessie Turner @uci.edu
Jim Vovoyodic @duke.edu

My kids

Lara Foland
Moriah Thomason

National Center for Research Resources

NIH: National Center for Research Resources
P41-RR009784
U24-RR021992

Firenza