fMRI as a Biomarker
Reliability, QA, Multisite

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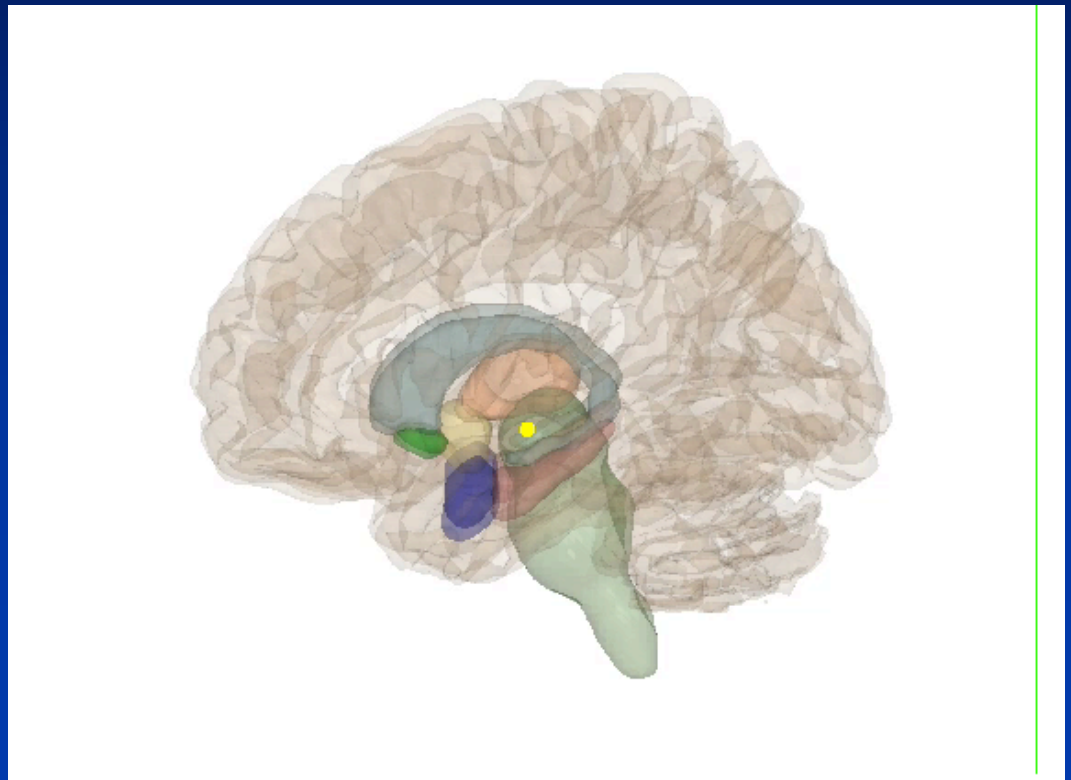
The consistency problem

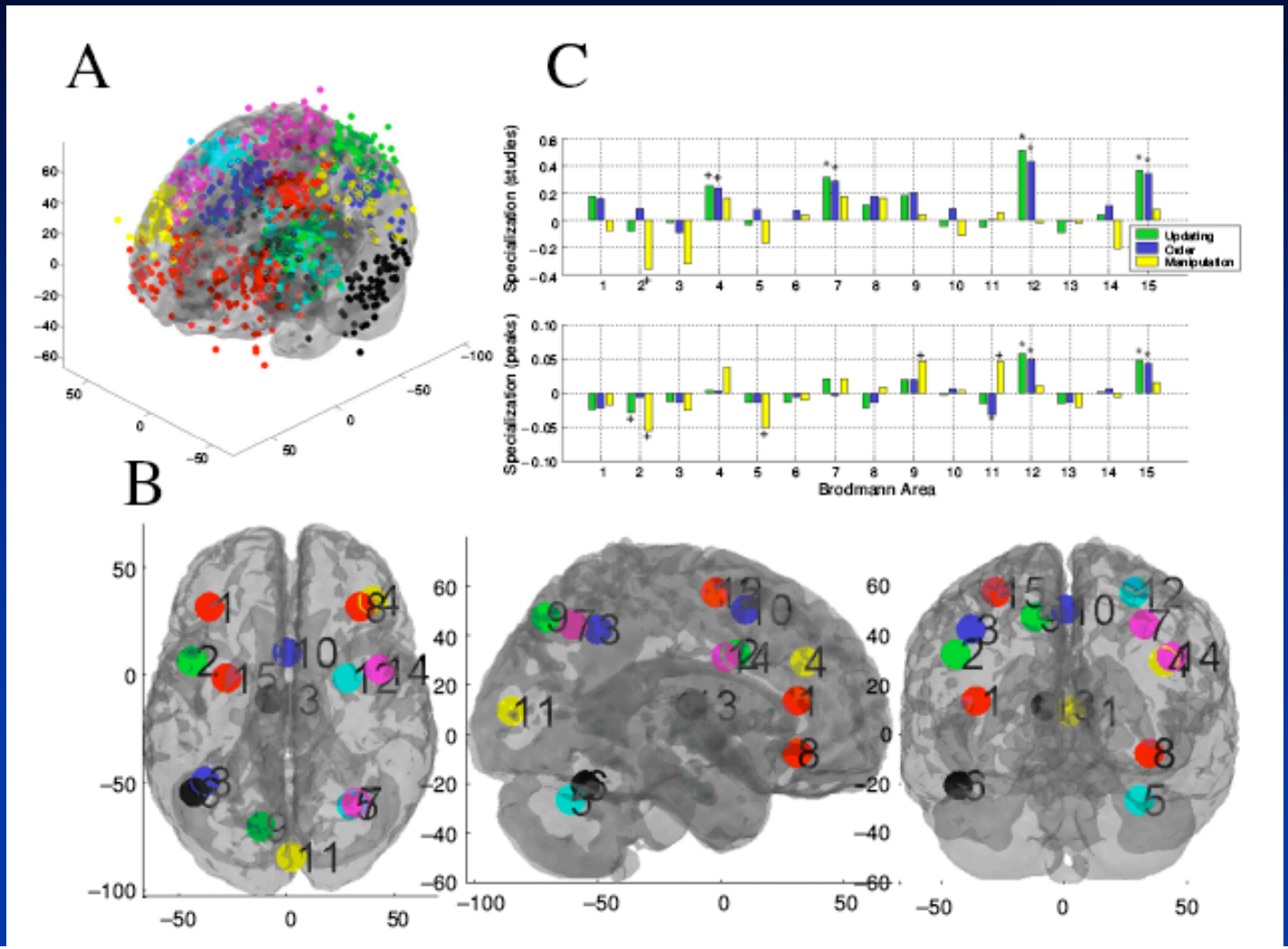
- Where are the “emotion regions?”
- Look at coordinates reported in published studies of emotion:



163 studies of emotion

Slide courtesy
Tor Wager

Consistency: fMRI of WM



60 PET/fMRI studies
TD Wager, 2003

The Scientist, July 19, 2004 v18 i14 p64(1)

Fake Method for Research Impartiality (fMRI): behavioral sciences bid for enhanced status falls short. (Closing Bell) *Sam Jaffe.*

Full Text:

For decades, the behavioral sciences have been at a dramatic disadvantage to the hard sciences. When a biologist hypothesizes that the addition of a particular ligand to a cell will cause a certain gene to turn on and thus produce a certain protein, all she has to do is to introduce the enzyme and then test for the protein. If it's there, she publishes a paper; if it's not, she quietly discards the work.

The psychologist has a much steeper hill to climb. Let's say he's trying to prove his hypothesis that most people who hate their fathers also secretly desire their mothers. Relying on the subject to tell you how he feels has too many obvious landmines that can corrupt the data. How can the psychologist scientifically prove that the connection exists?

Well, now he can. Or at least he can claim that it's a provable hypothesis. Thanks to fMRI (functional magnetic resonance imaging), dozens of studies are pouring out of the humanities aisle of academia claiming that the yellow and red blotches on fMRI scans reveal scientific evidence that can be used to

Outline

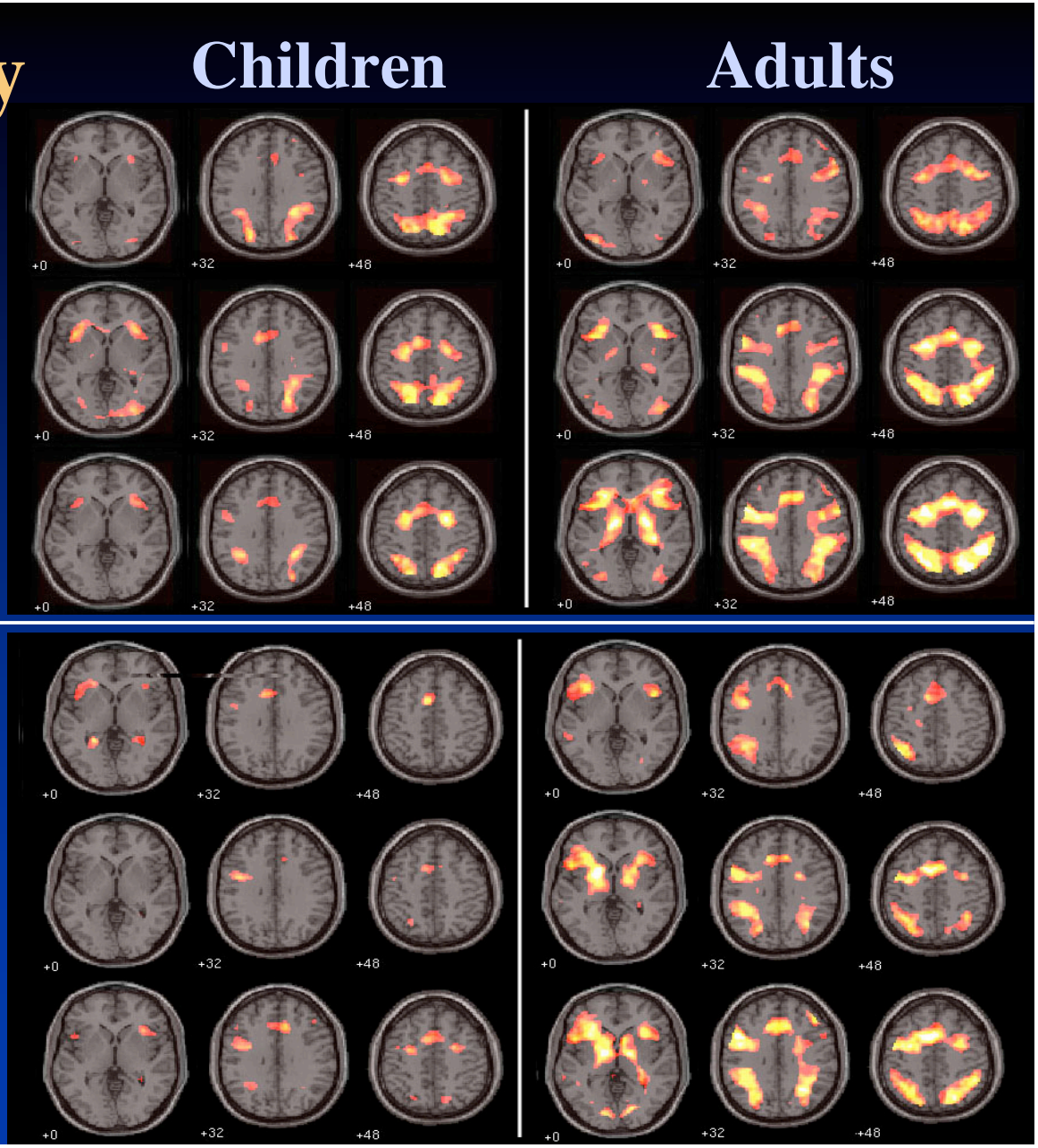
- **Issues with fMRI reliability**
- **Reducing confounds**
  - **HRF**
  - **calibration of vasoreativity**
  - **latency**
- **Physiological noise**
- **Multicenter studies**

fMRI as a biomarker: Motivation

Examples where quantifying activation may be important in drawing inferences about cognition:

- Inter-group comparisons
  Age, health
- Longitudinal studies
  normal/abnormal development, therapy
- Multi-center studies
  fBIRN schizophrenia fMRI trial

Working Memory



M. Thomason, NI 2009

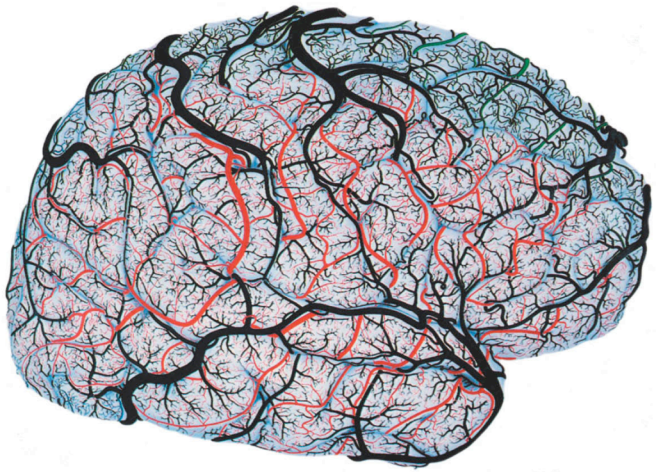
Variance in fMRI

- inter-subject variability (probably what you want)
- inter-trial variability (attention, behavior)
- inter-run/session variability (attention, behavior, scanner)
- hemodynamic confounds (calibration)
- physiologic noise (measure and remove)
- small effect size (average)
- task design (control for unrelated effects)
- a lot more…

fMRI Calibration: Motivation

What's the problem?

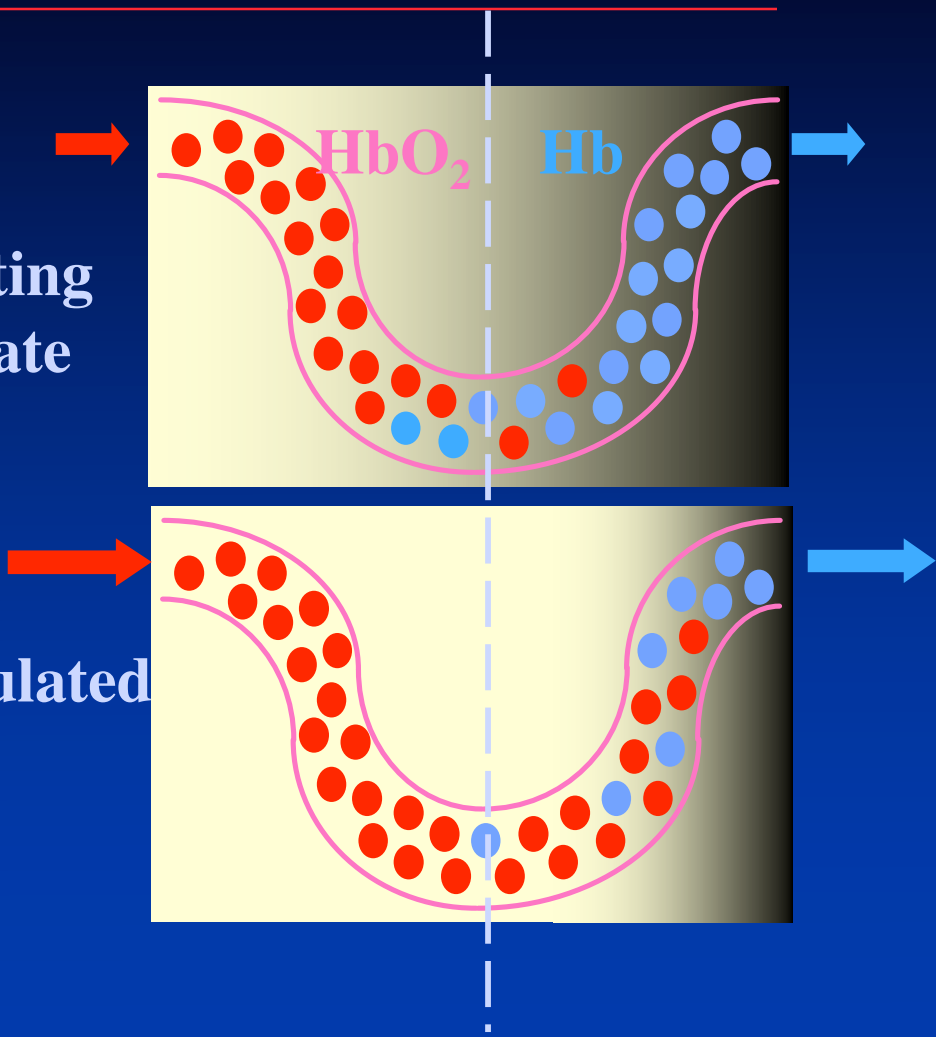
Vascular response to upregulated metabolism



↑ $CMRO_2$ →

↑ $[CO_2]$, ↑ [Hb], ↓$[HbO_2]$

→ ↑ rCBF, rCBV
→ ↑ $[HbO_2]$
→ ↑ T2, T2*
→ BOLD contrast



BOLD Contrast

∴ BOLD signal is an epiphenomenological indicator of neural processing: many confounds to quantification

- HRF characteristics
  - Amplitude -> calibration
  - Latency
  - Baseline rCBF
- Physiological noise
  - cardiac pulsation -> denoising
  - respiration
  - head motion

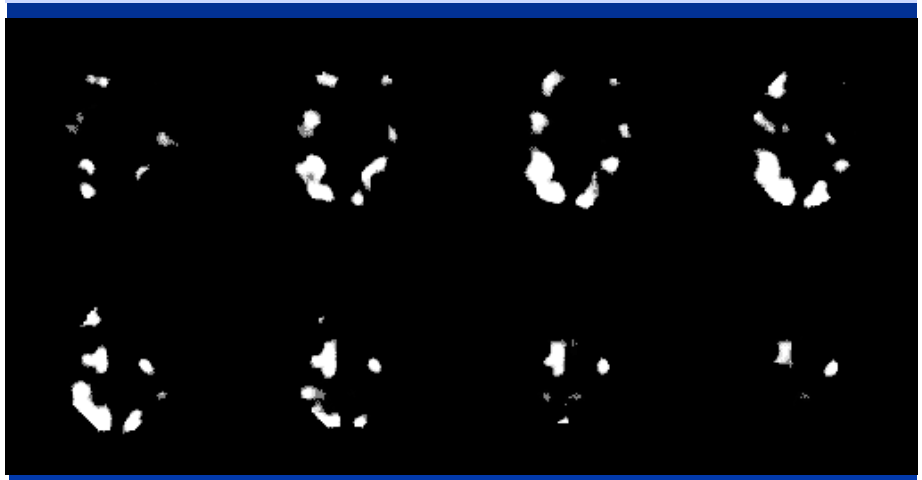
Activation map derives from thresholding a statistical estimate of BOLD CNR:

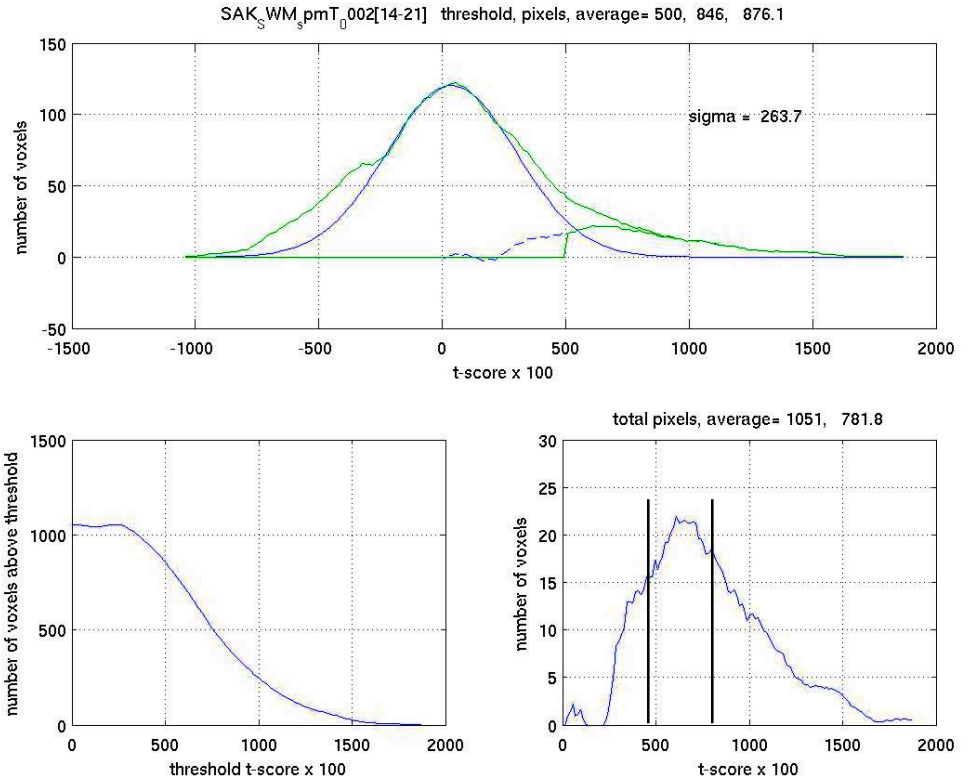
$$y_{meas}(t) = \beta_{\exp} d_{\exp}(t) + \beta_{cntl} d_{cntl}(t) + \beta_0 + \varepsilon(t)$$

$$GLM \Rightarrow \beta' s$$

$$T = \frac{\beta_{\exp} - \beta_{cntl}}{\sigma} = \frac{effect}{resid}$$

$$T_{crit} = tpdf(p, df)$$





What does it mean?

Does "activation"
= metabolic up-regulation consequent to
neural firing?

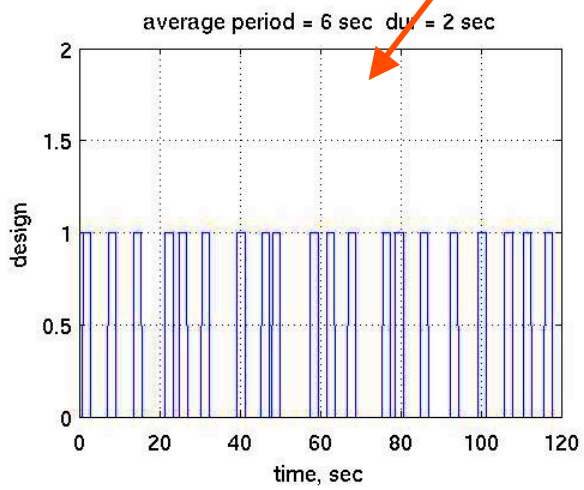
$$y_{meas}(t) = \beta d(t) + \varepsilon(t)$$

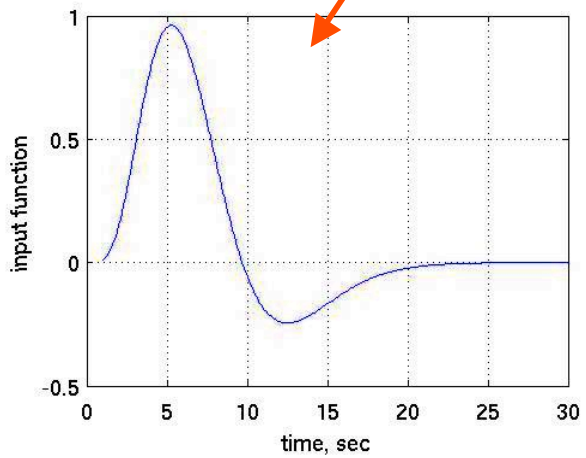
No, not directly… HRF is in the way

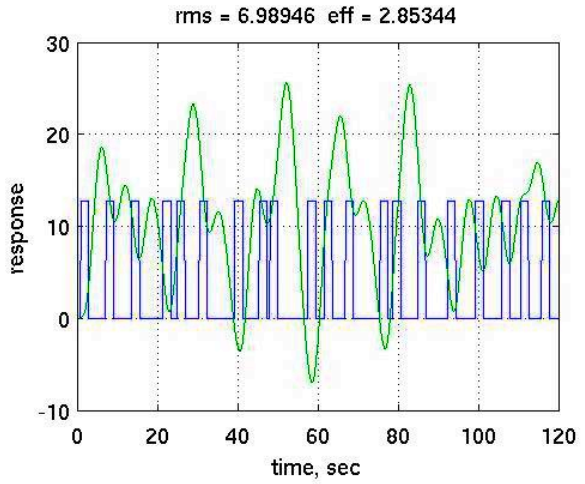
$$y_{meas}(t) = \beta(d(t) * h(t)) + \varepsilon(t)$$

General Linear Model

$$y = (\beta_1 d_1 + \beta_2 d_2 + \beta_3 d_3 \cdots + \beta_n d_n) * h + \beta_0 + \tilde{n}$$







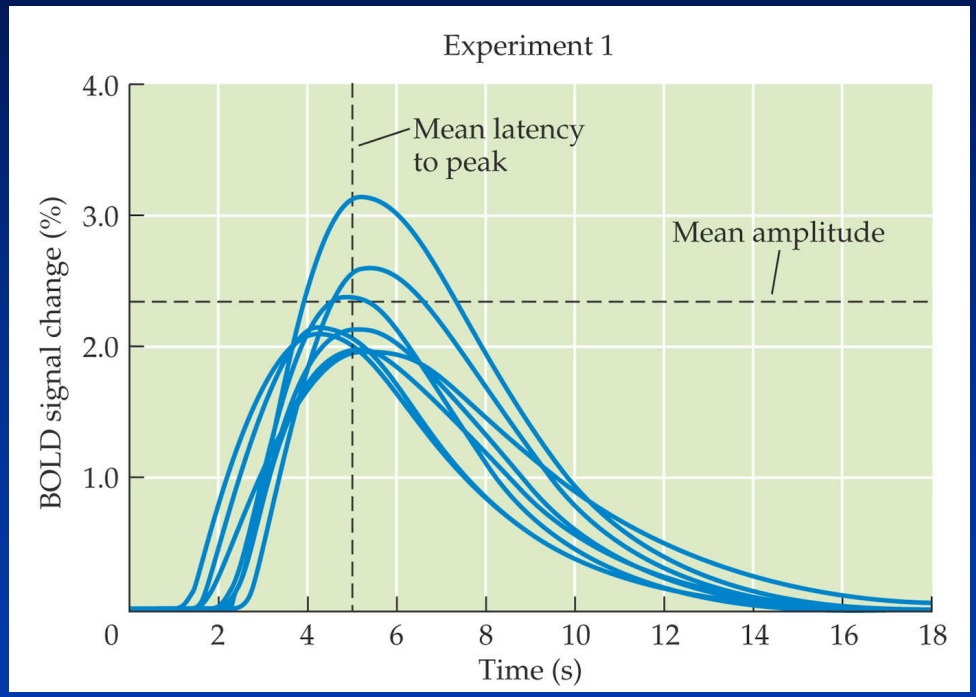
Hemodynamic Response Function

- Definition: BOLD response to an impulsive stimulus

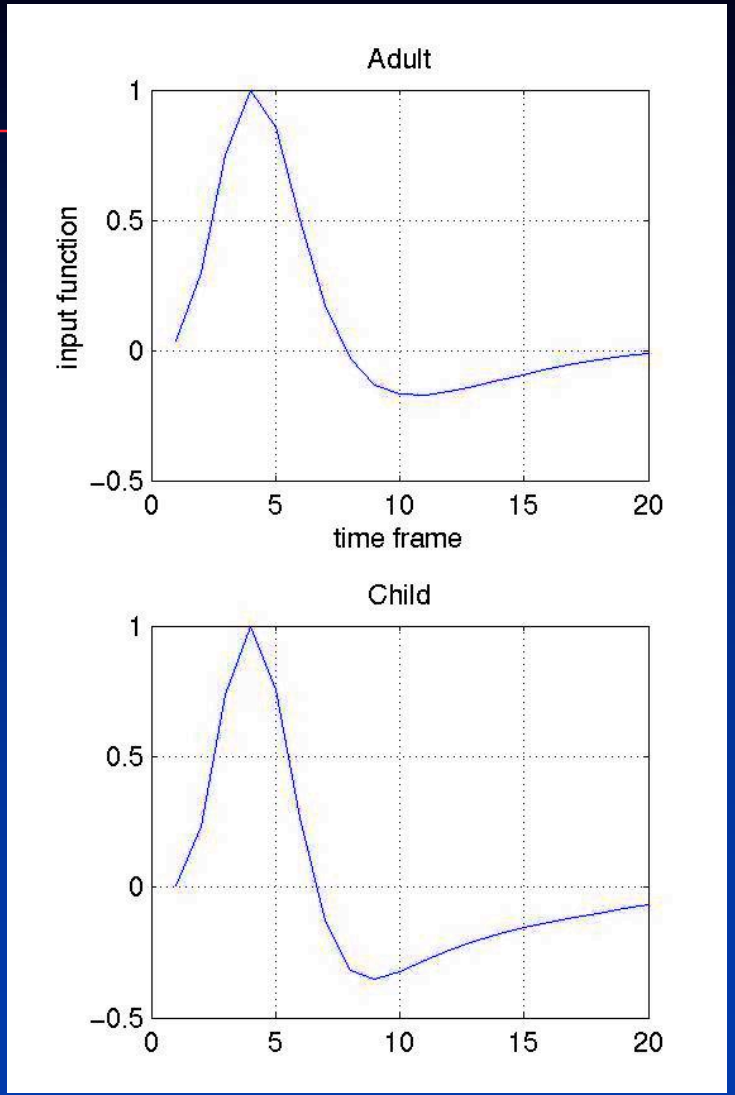
- may include neuronal and vascular responses
  -> use a cognitively simple task to reduce neuronal component

- may be nonlinear
  -> superposition does not hold

Variability of HRF

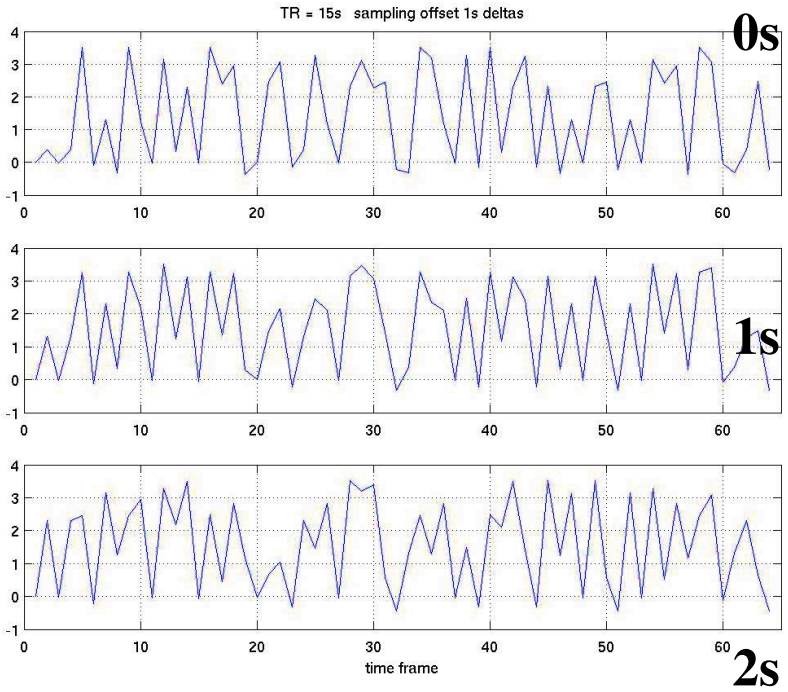


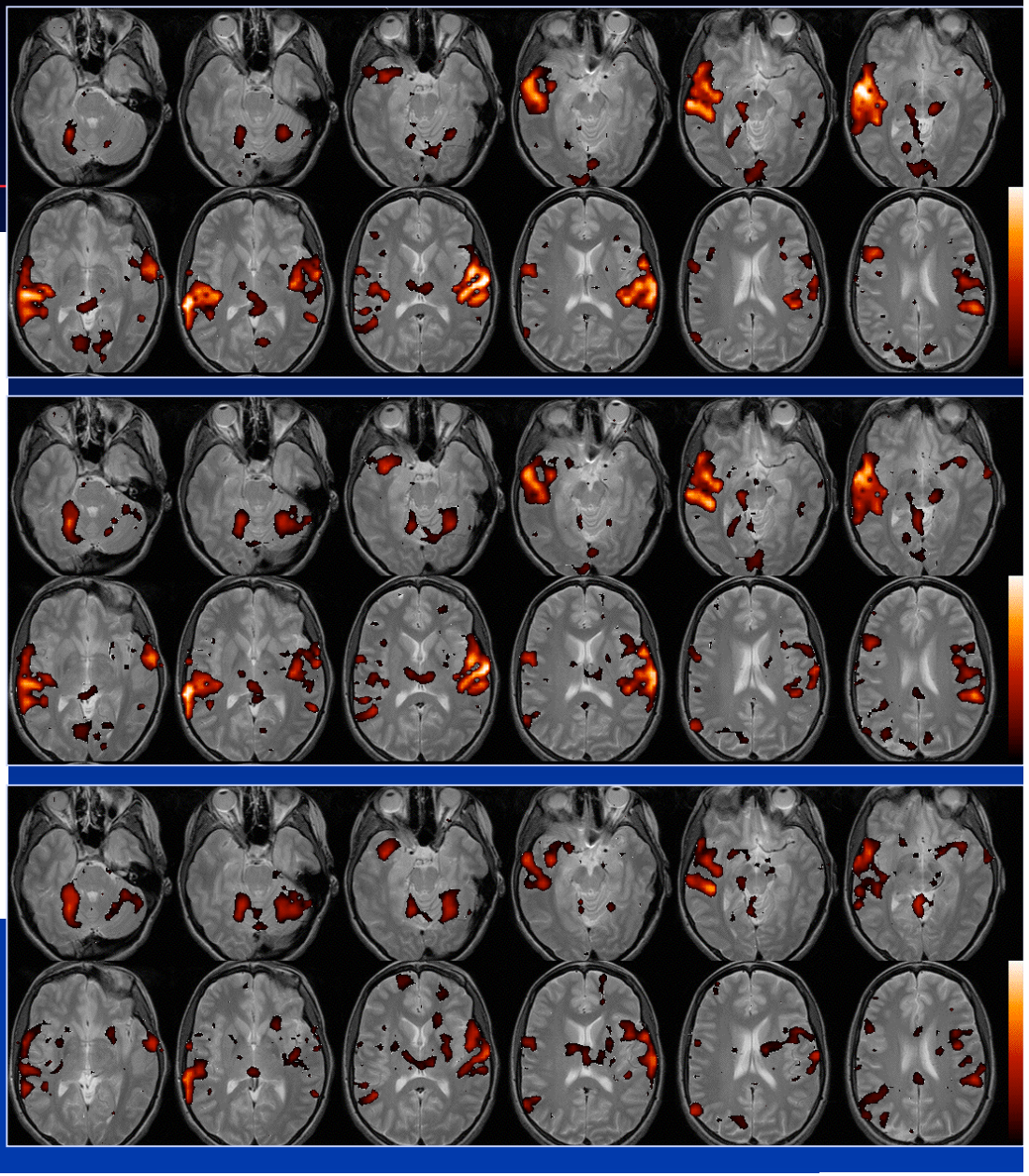
Miezen, et al. (2000)



M. Thomason

Timing error

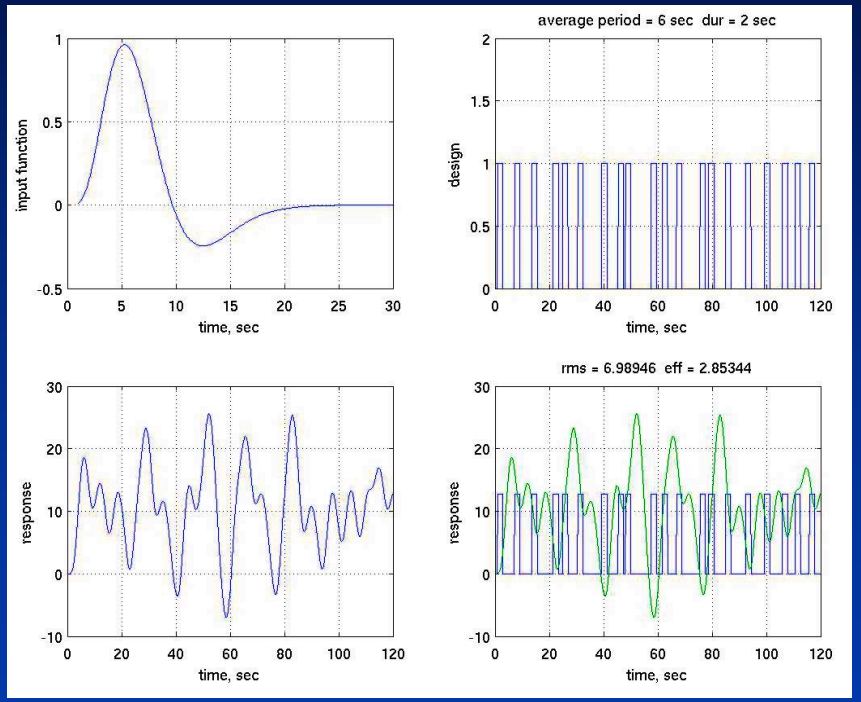




Individual differences: HRF

- temporal differences in HRF important in event-related designs

-> measure individual HRFs

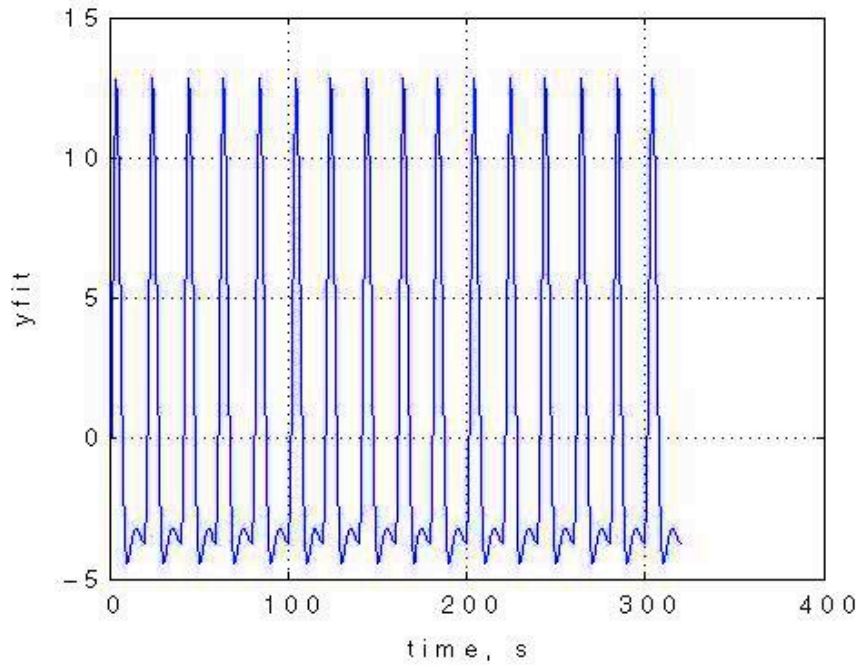


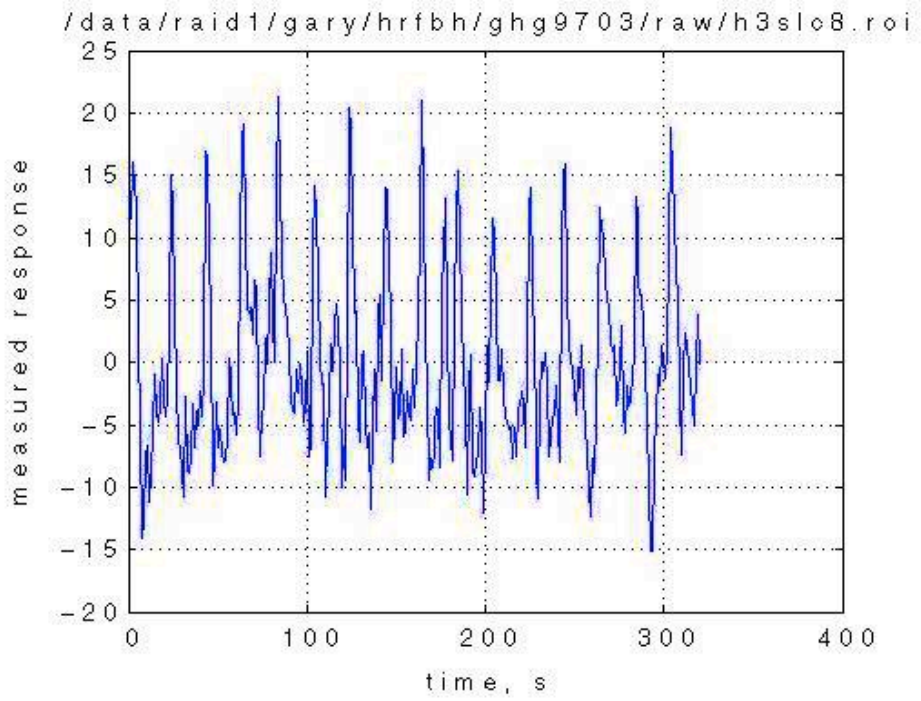
Outline

- Issues with fMRI reliability
- Reducing confounds
  - HRF
  - calibration of vasoreativity
  - latency
- Physiological noise
- Multicenter studies

Measurement of HRF

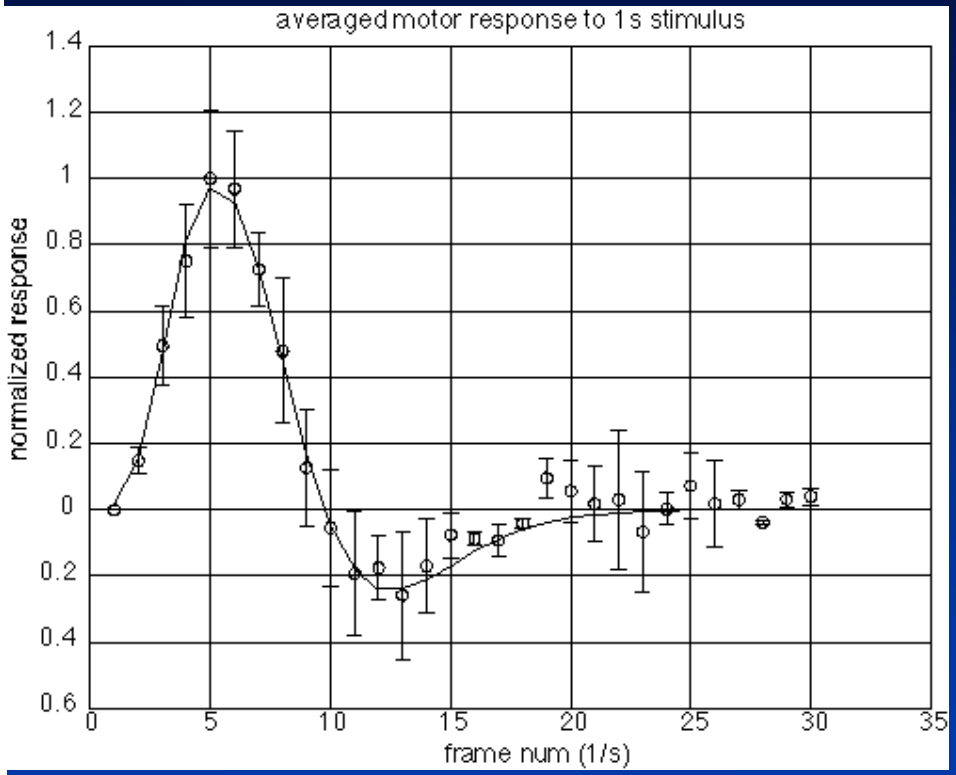
Use short stimulus, long ISI:





HRF: Measure h(t) with 1s task

motor



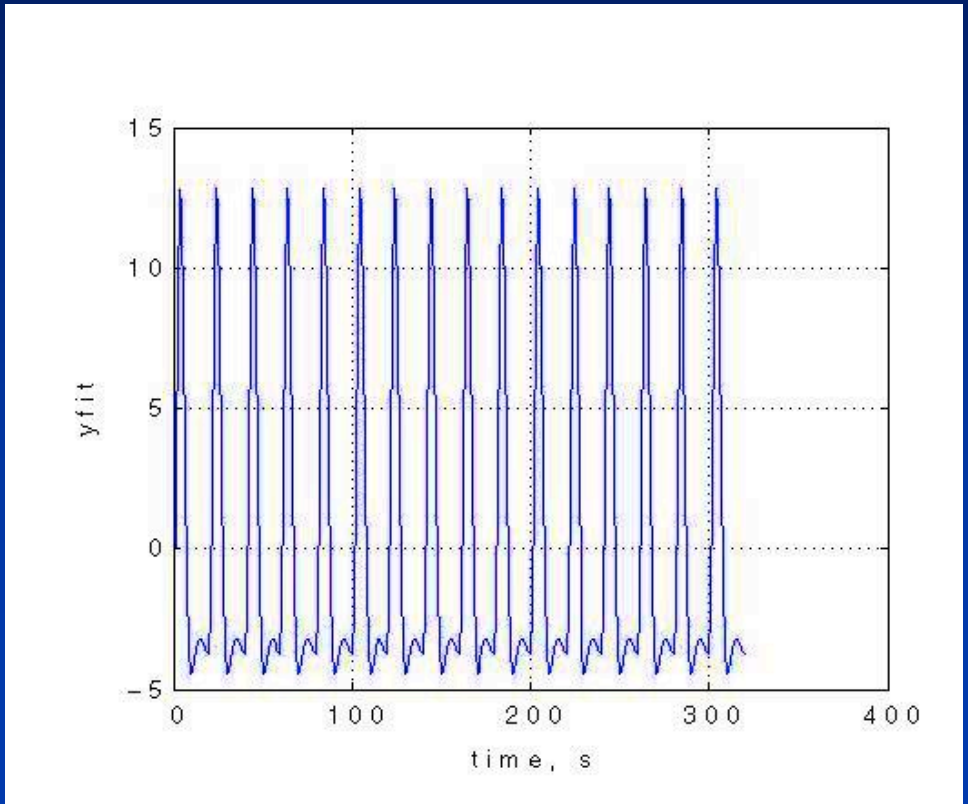
auditory

Finger tapping & tones at 3Hz, N=5

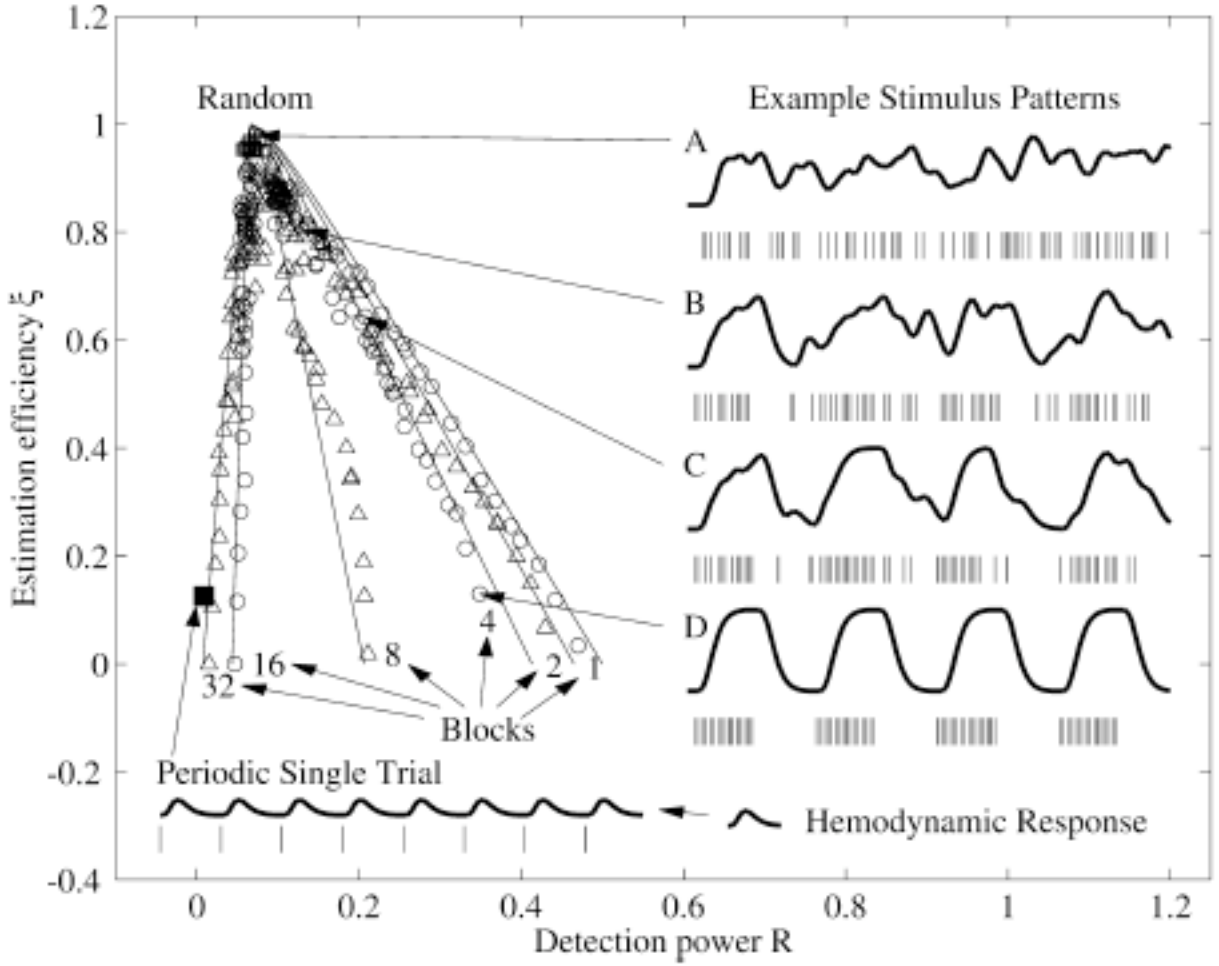
Glover, NI 1999

Measurement of HRF

- **Event related designs are inefficient (T. Liu)**



Detection or Estimation?

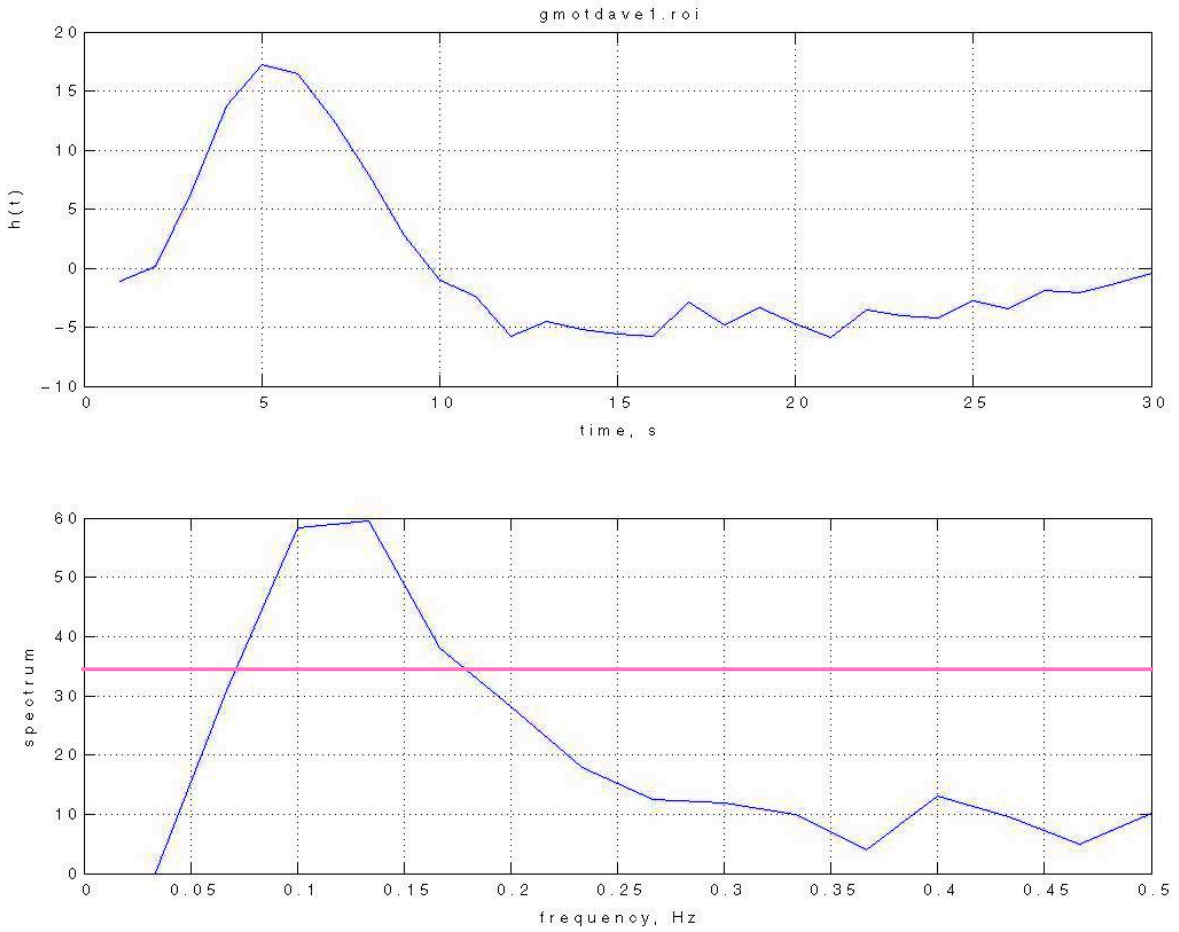


Jittered (random) **designs** → maximum estimation efficiency

Block designs → maximum detection power

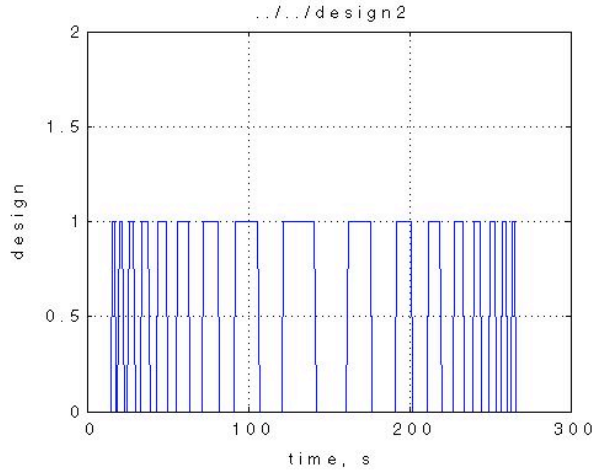
Liu et al. NI (2001)

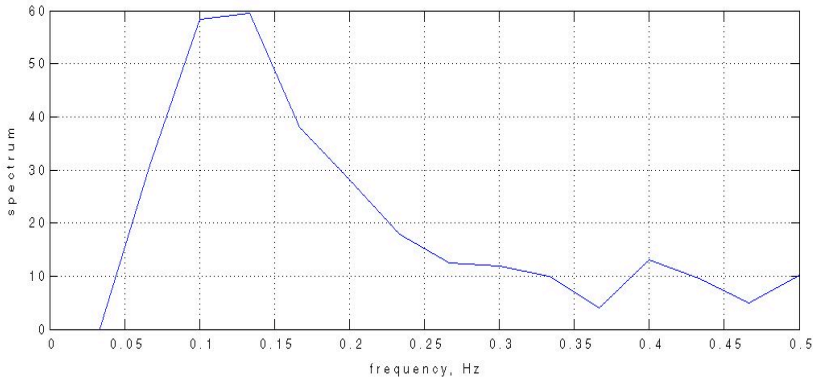
Spectral content of h(t)

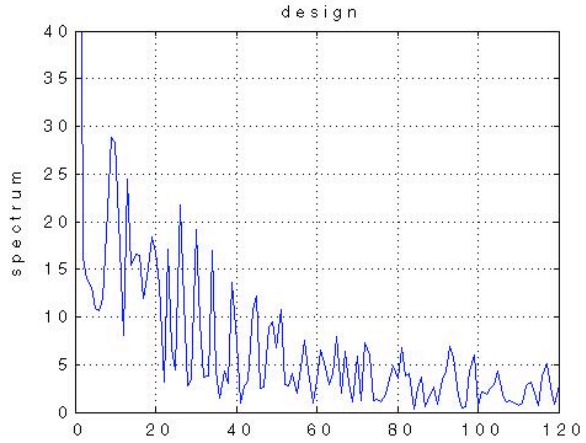


Fourier Measurement of HRF: (FHRF)

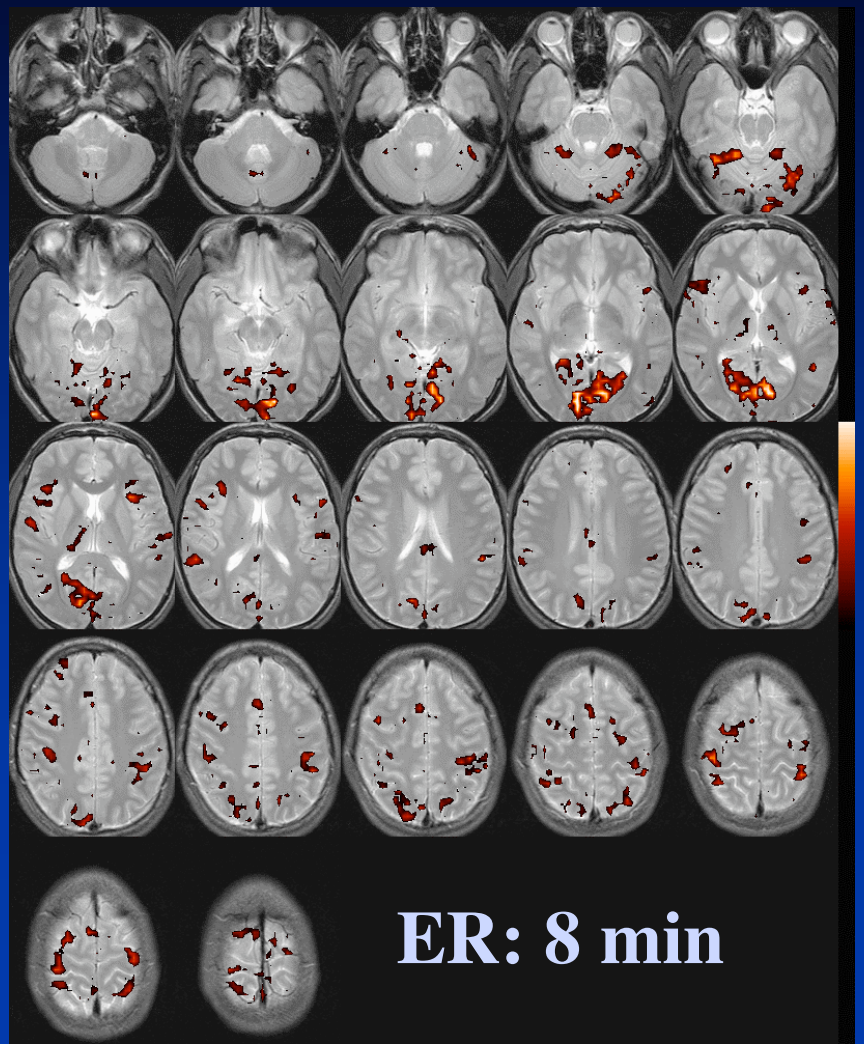
Design has on/off blocks of duration 4s, 6s, 8s, 10s, 12s, 16s, 20s, 30s, 40s, …4s

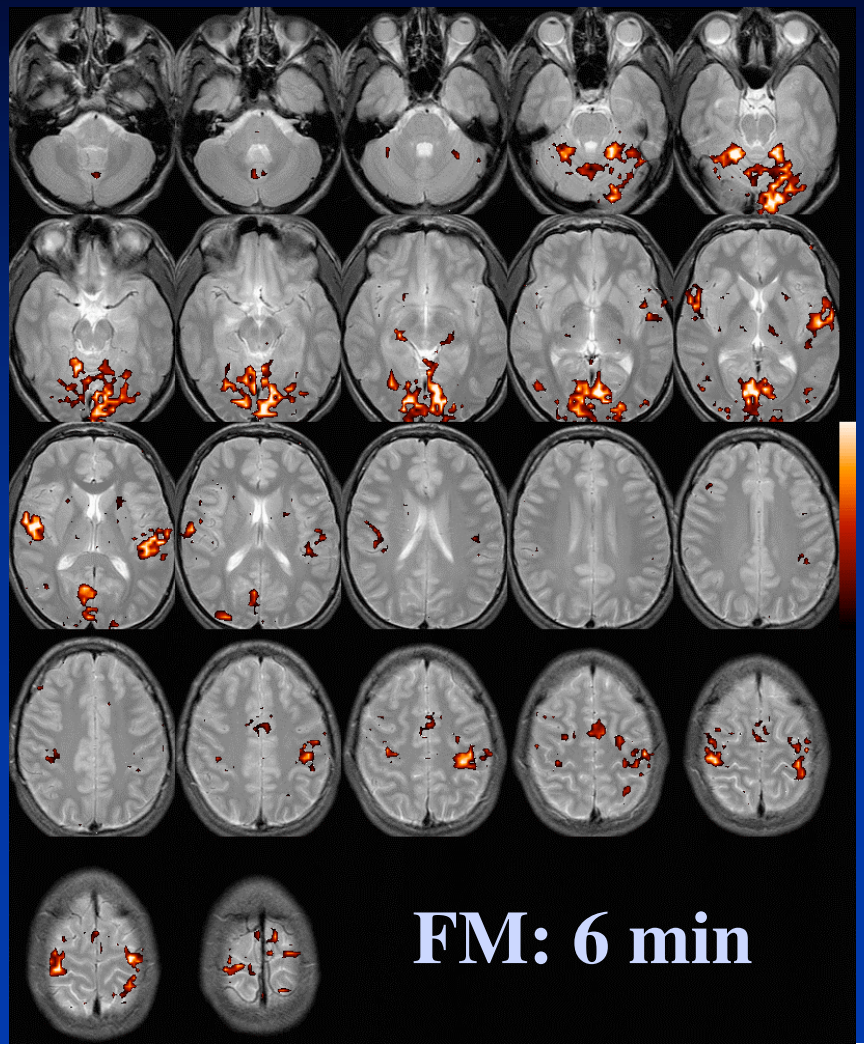






Measurement Efficiency

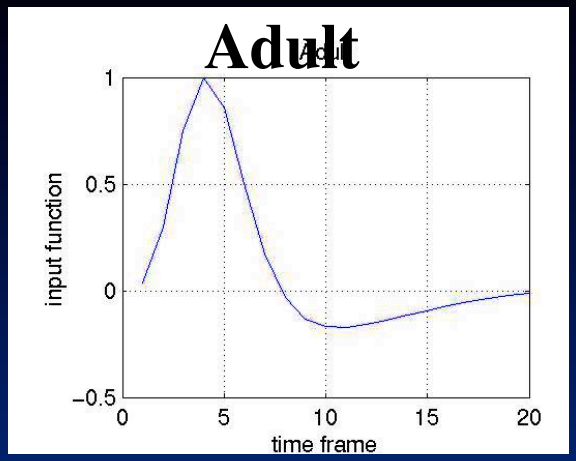


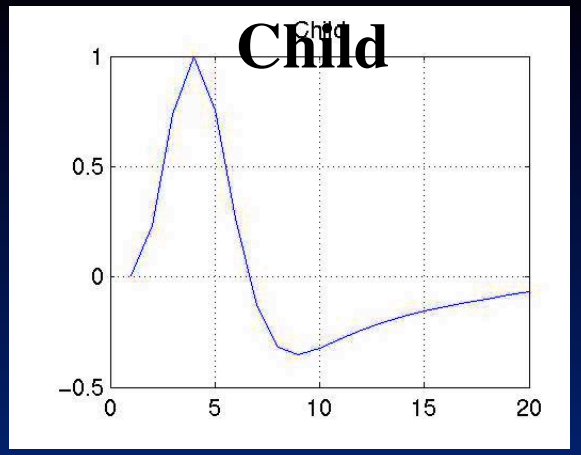


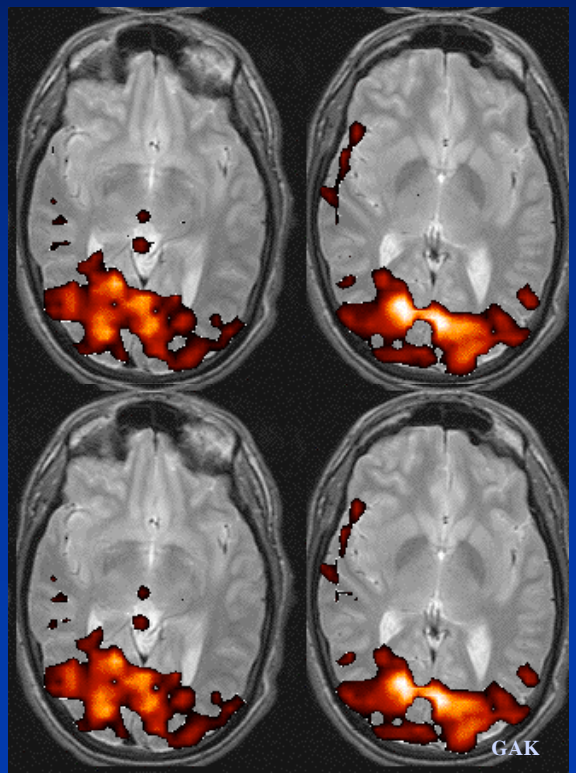
Effect of HRF on Activation

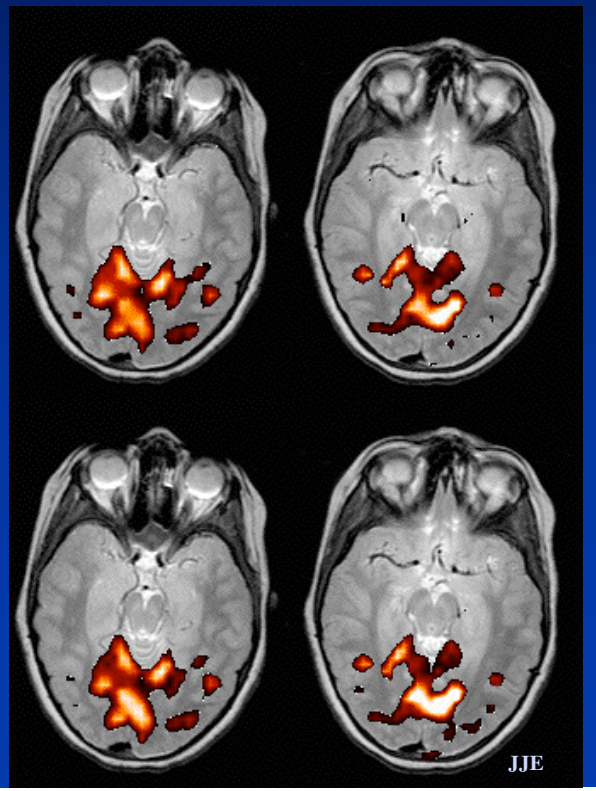
Canonical
Gamma variate

Measured
Linear HRF









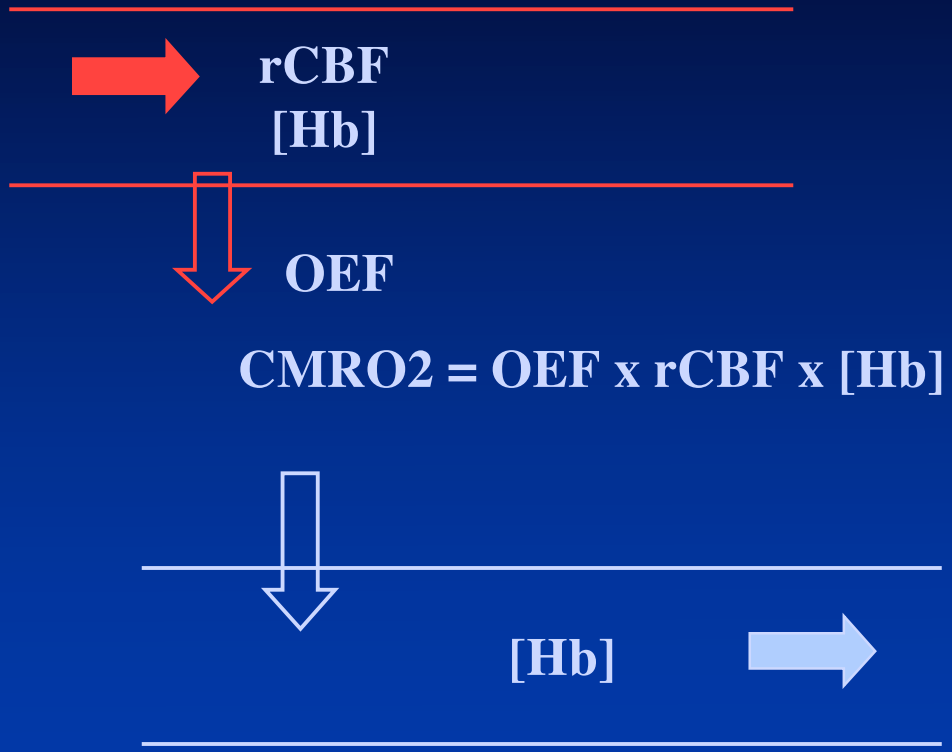
Measurement of HRF

- Can provide characteristic info for each subject
  - requires a task
  - may be difficult to obtain in relevant regions
- Key features are amplitude & latency
  - may be obtained without invoking a task

Outline

- Issues with fMRI reliability
- Reducing confounds
  - HRF
  - calibration of vasoreativity
  - latency
- Physiological noise
- Multicenter studies

Vasoreactivity



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

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

$$rCBV \propto rCBF^\alpha$$

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

$$m \equiv CMRO2_a / CMRO2_0$$

$$f = rCBF_a / rCBF_0$$

M **represents a 'gain' factor related to vascular reactivity**

Davis, PNAS (1998)
Buxton, 2003

Measuring vasoreactivity

Use a task that does not involve change in metabolism:

- **Hypercapnia**
  - **O2 or CO2**
  - **Breath holding**

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

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

$$m \equiv CMRO2_a / CMRO2_0$$

$$f = rCBF_a / rCBF_0$$

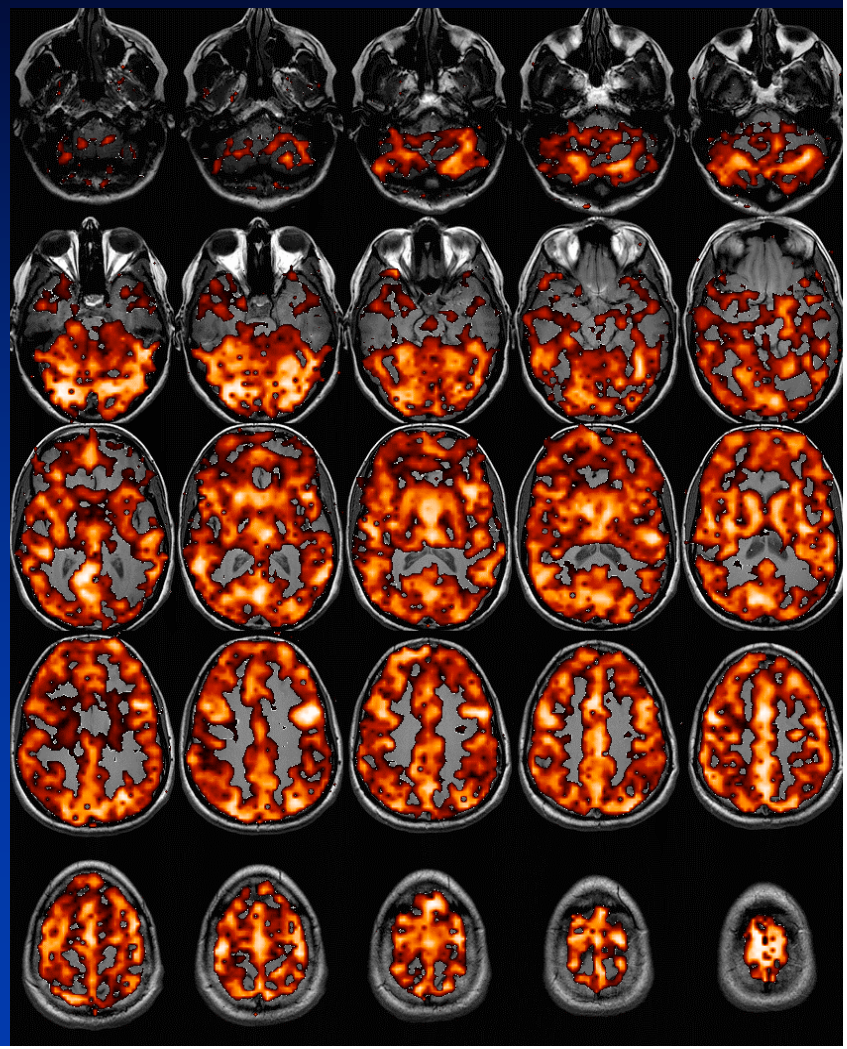
BH Task

Block trial: 15s off/on
8 cycles, 4 min, 15 s

breathe 14s

Breath in & hold 2s

Hold 14s

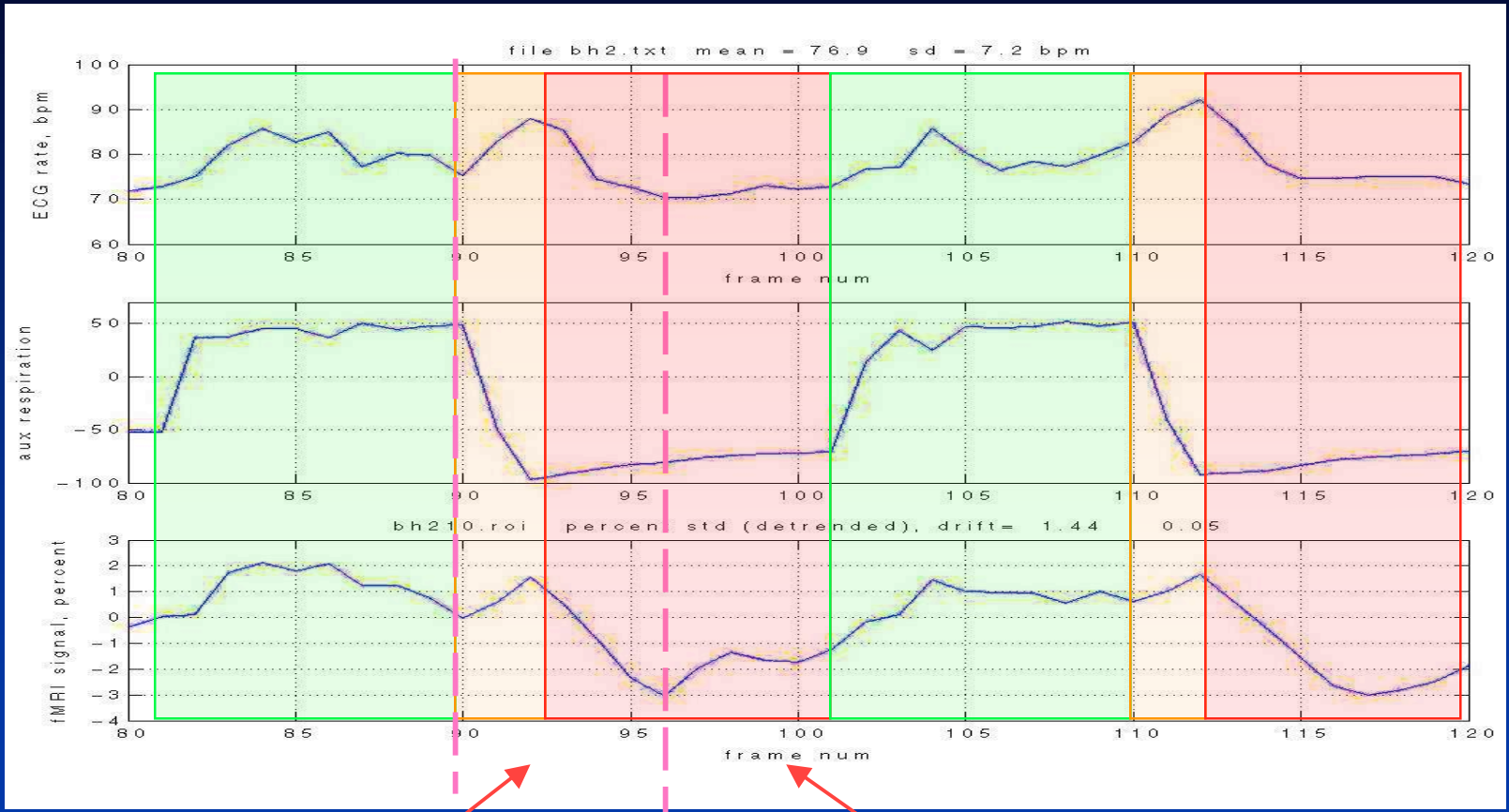


BH-induced BOLD signal

HR

Resp

BOLD

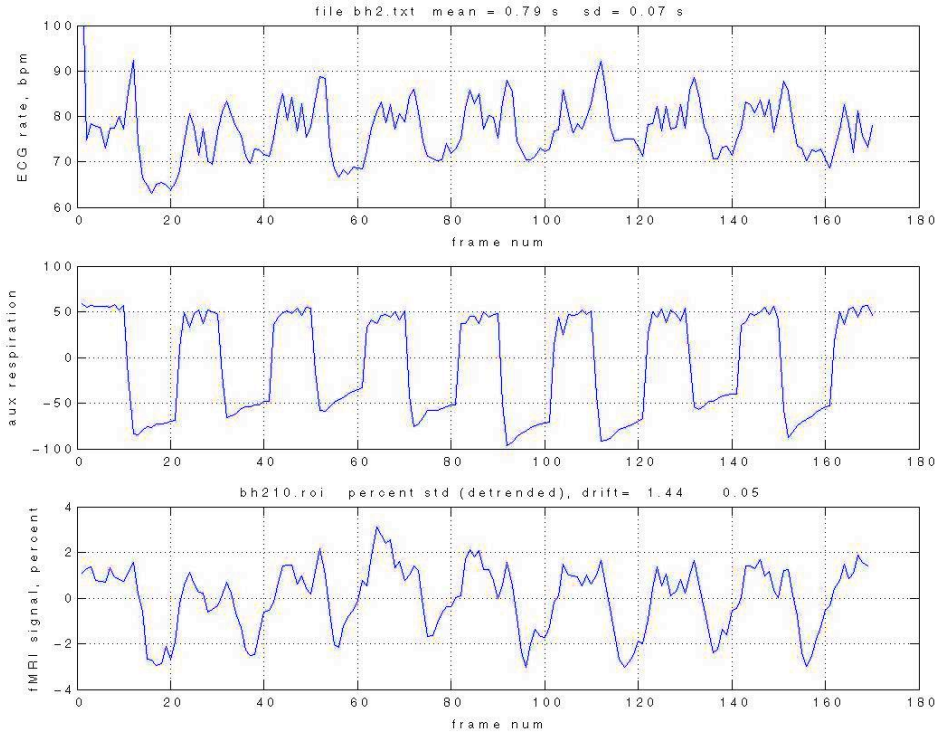


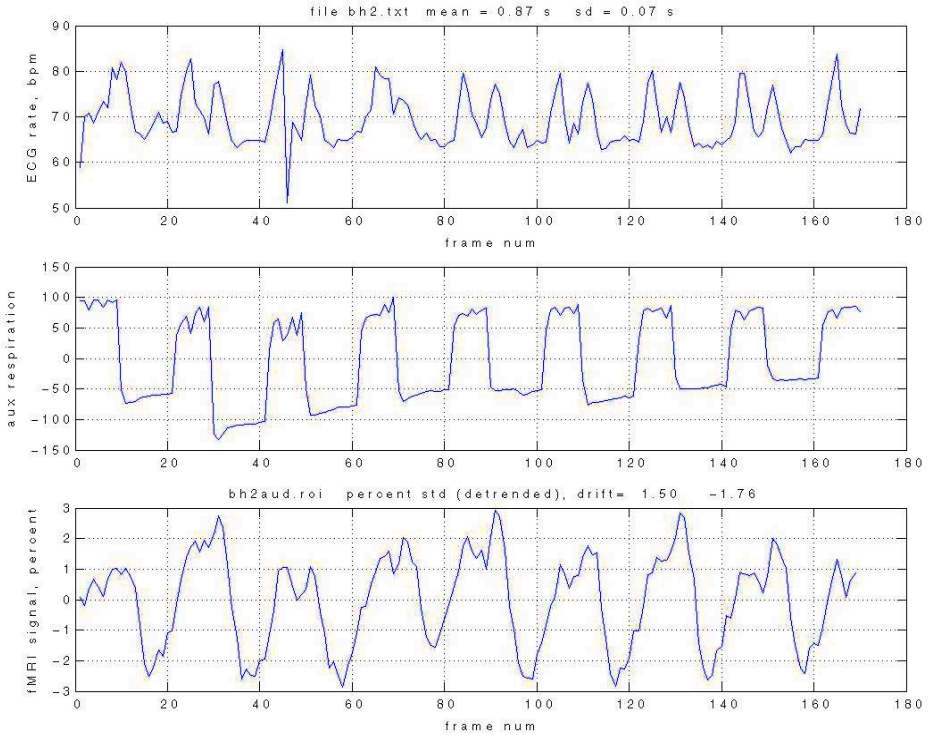
Thomason, et. al, 2007

Vascular res. ↓ ⇒ HR↓ ⇒ ↓ CBF ⇒ hypoxia

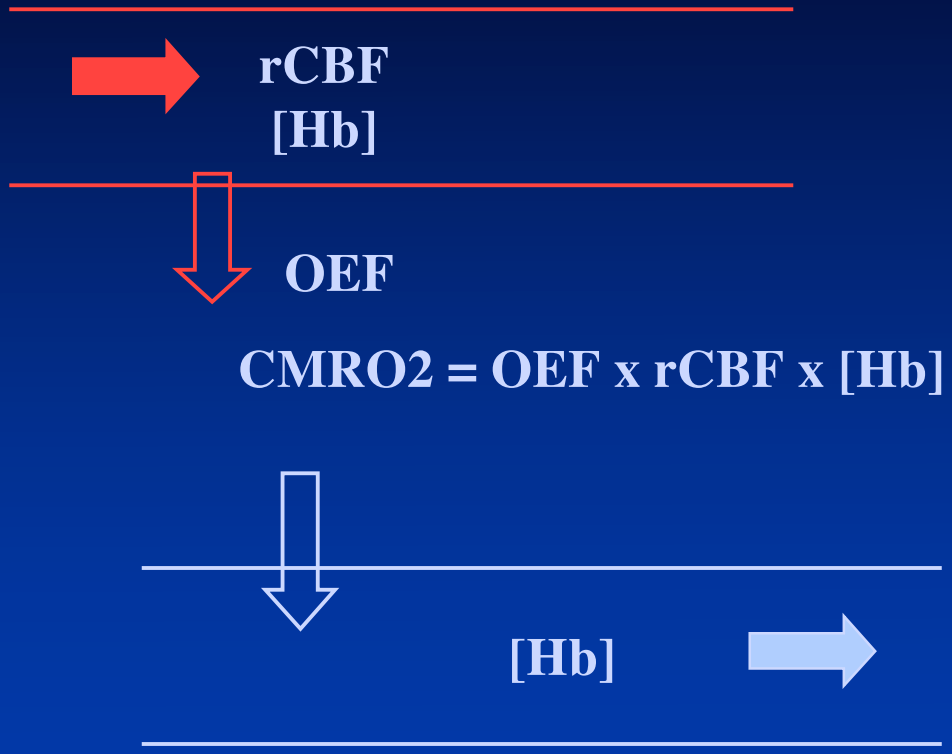
Basal metab. ⇒ O_2↓, CO_2, NO, H^+↑ ⇒ vasodilation ⇒ ↑ rCBF

Vascular Responsivity: BH





BOLD Signal



Davis, PNAS (1998)
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$$BOLD \propto -TE \cdot \Delta R2^*$$

$$rCBV \propto rCBF^\alpha$$

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

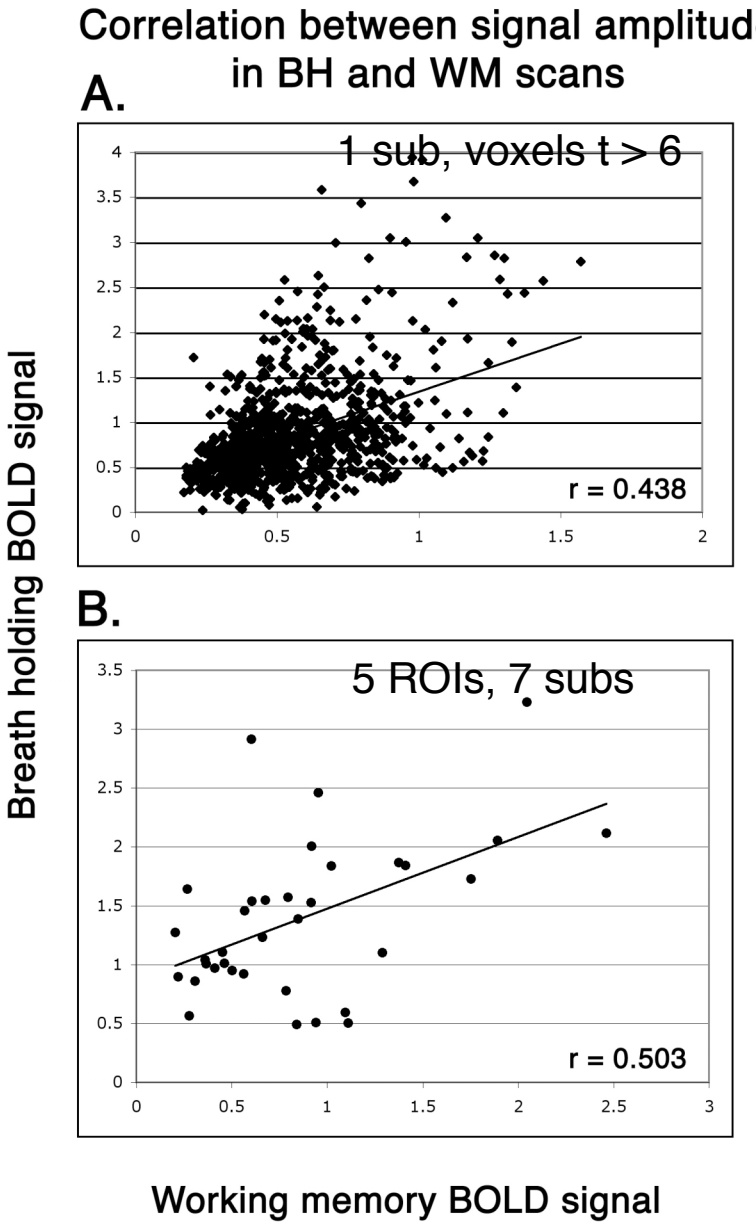
$$m \equiv CMRO2_a / CMRO2_0$$

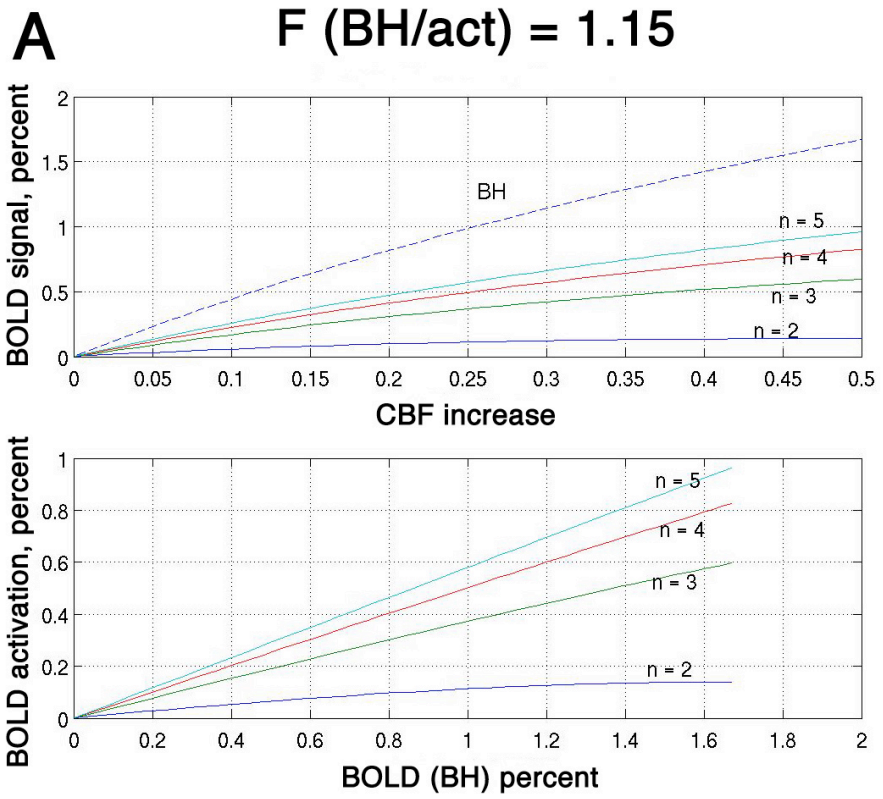
$$f = rCBF_a / rCBF_0$$

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

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

BH Calibration



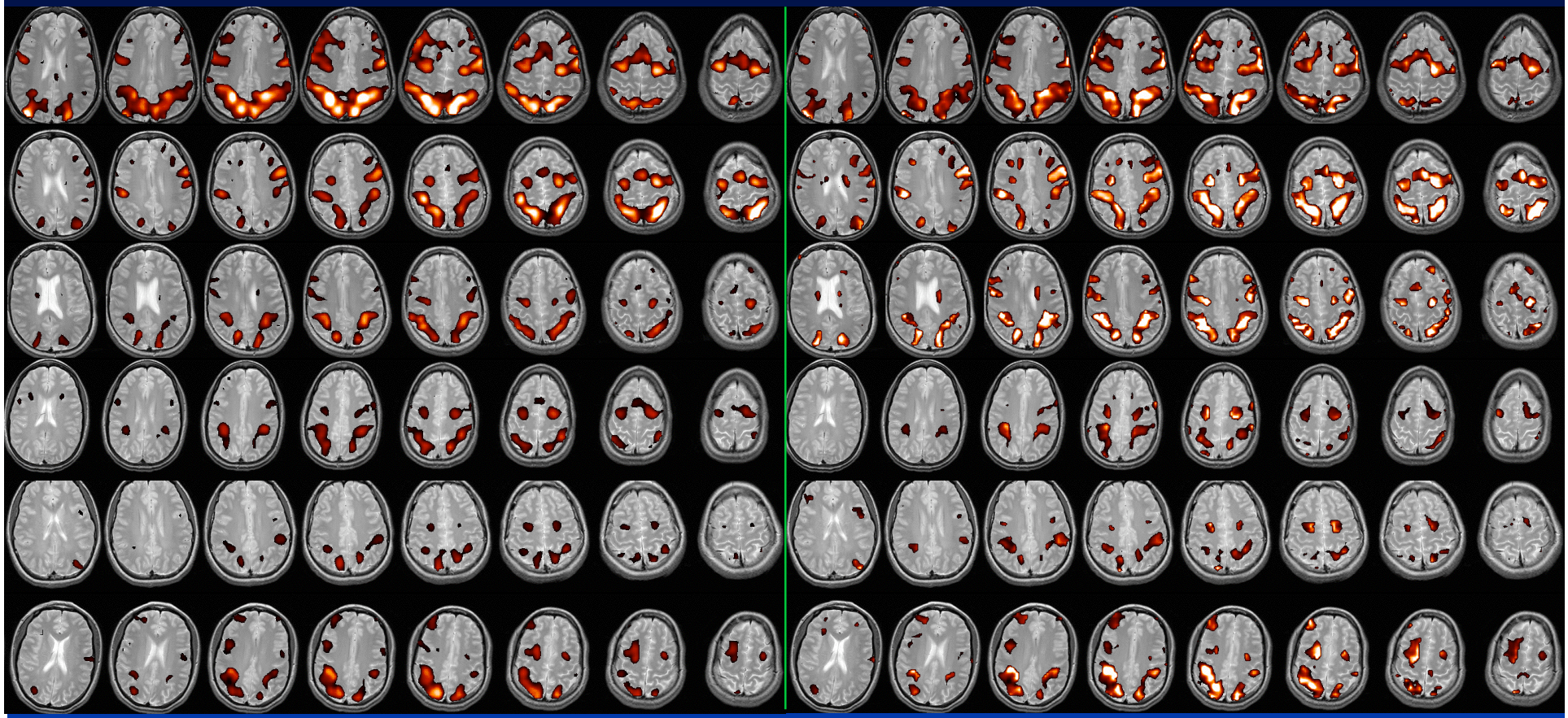


M. Thomason et al., 2007

BH Calibration: Individual Subs

No calib

Calib

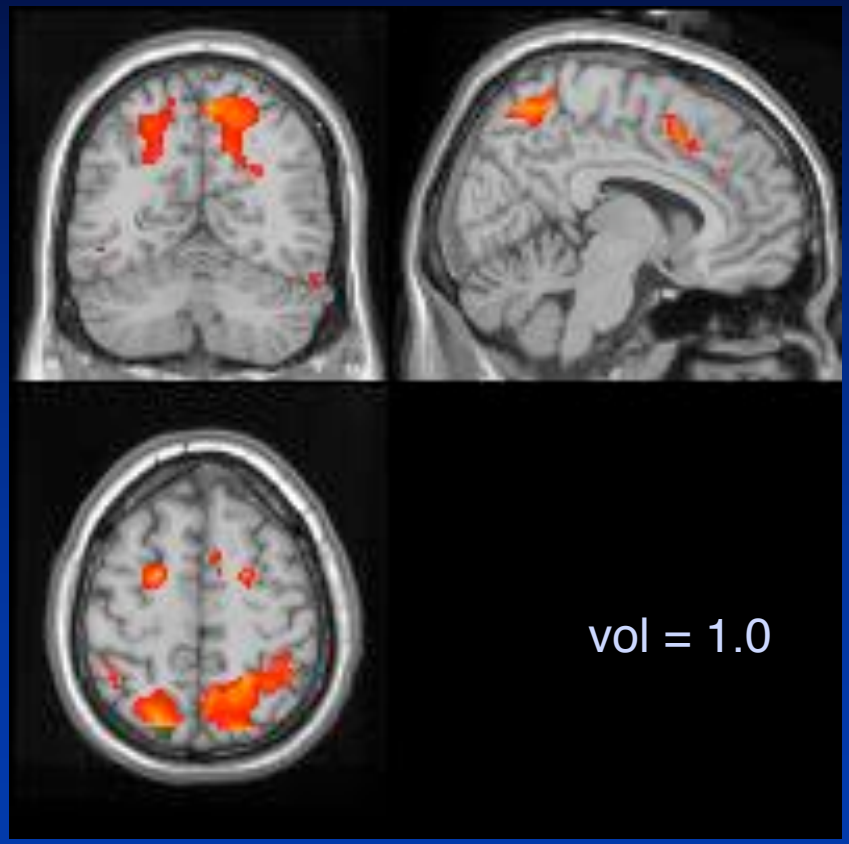


M. Thomason et al., 2007

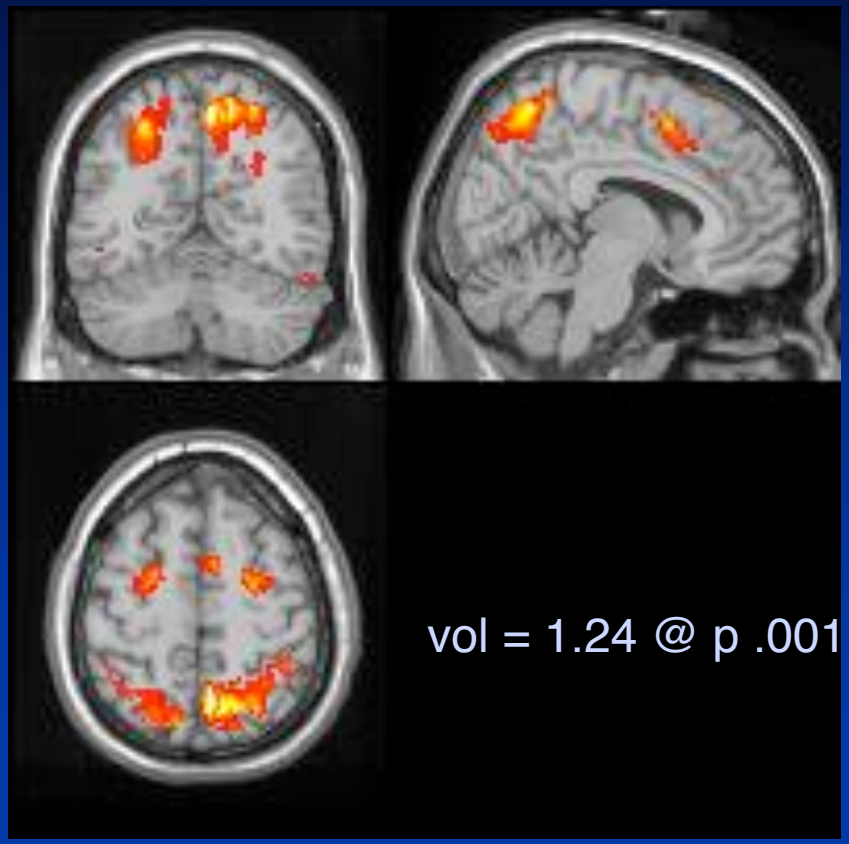
$5 \leq t \leq 20$

BH Calibration: Group Activation

No cal



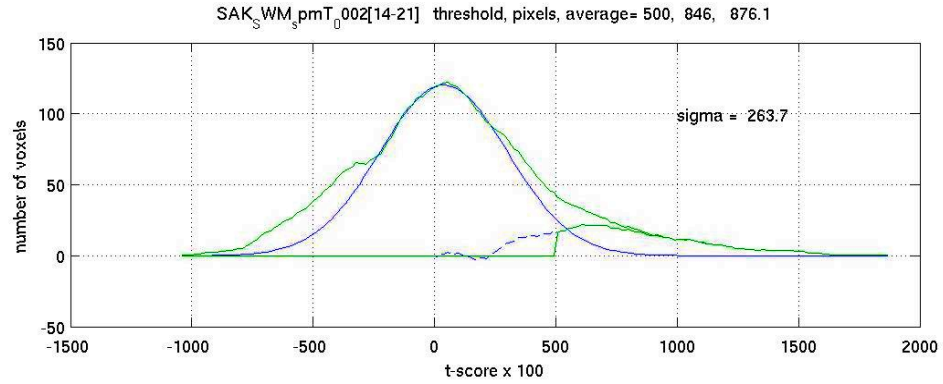
Calib

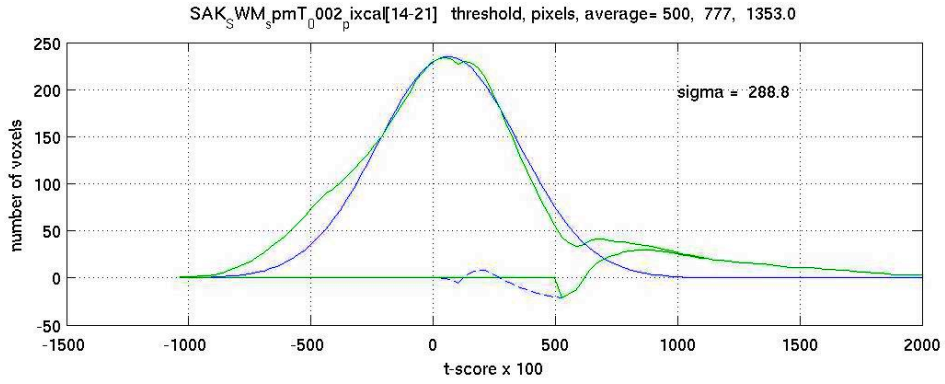


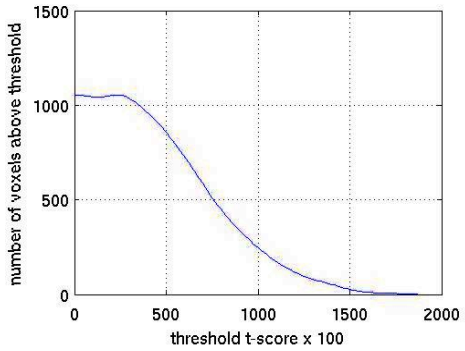
M. Thomason et al., 2007

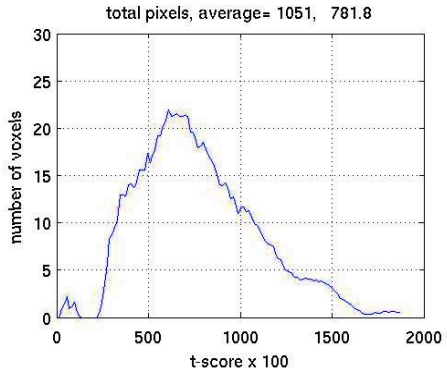
$3.5 \leq T \leq 10$

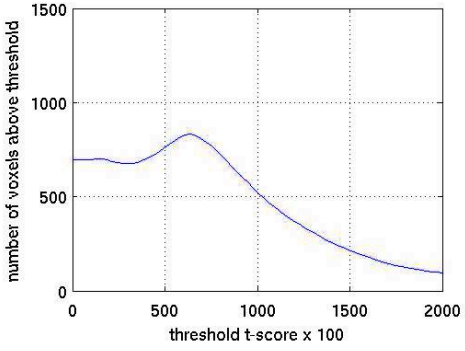
Activation Response

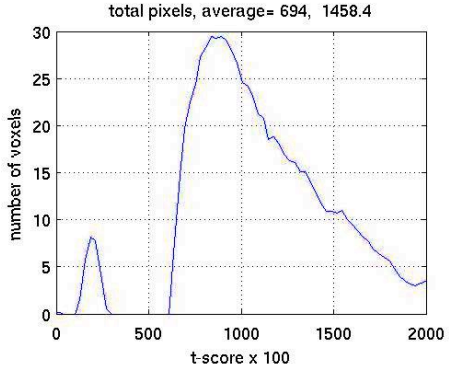




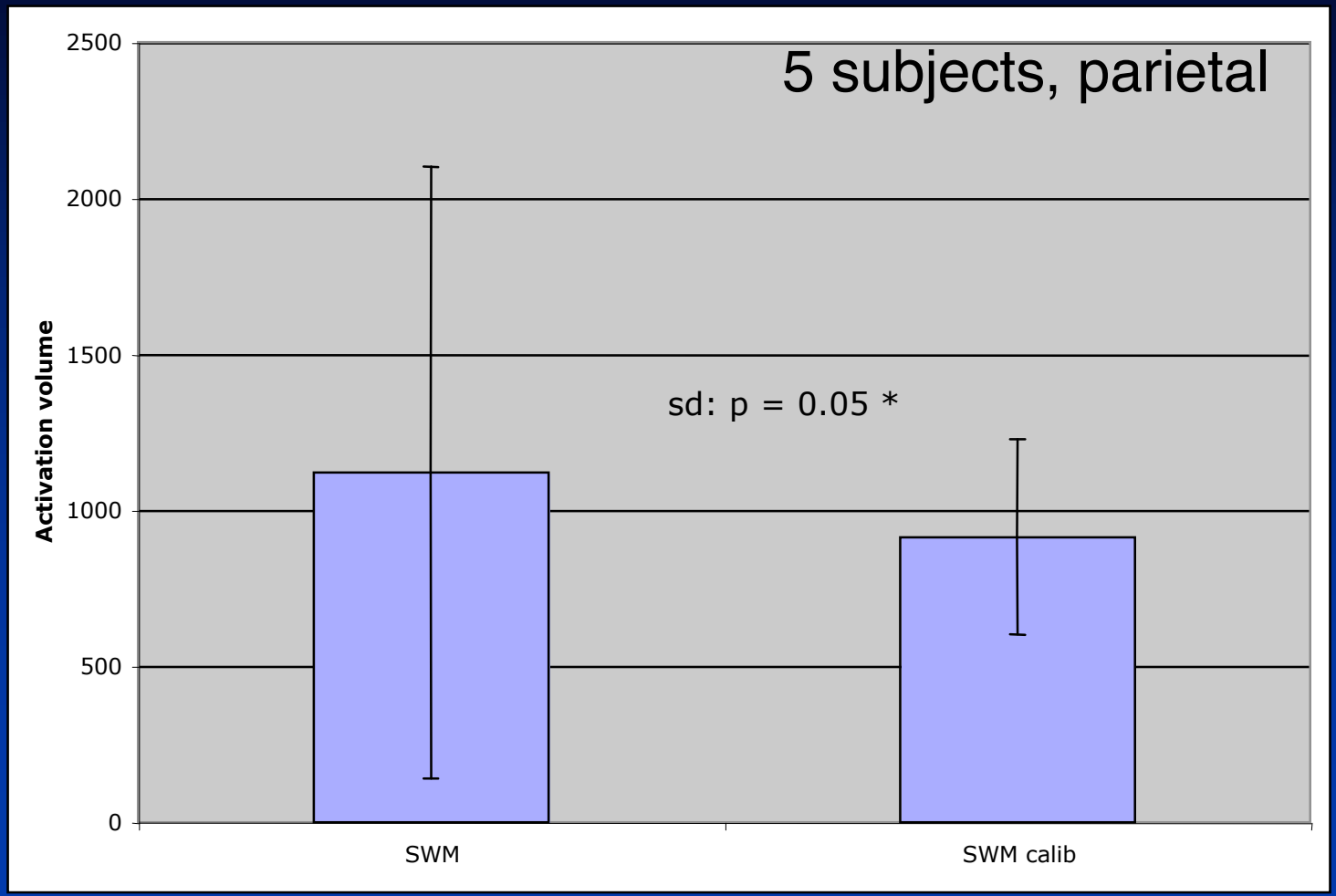








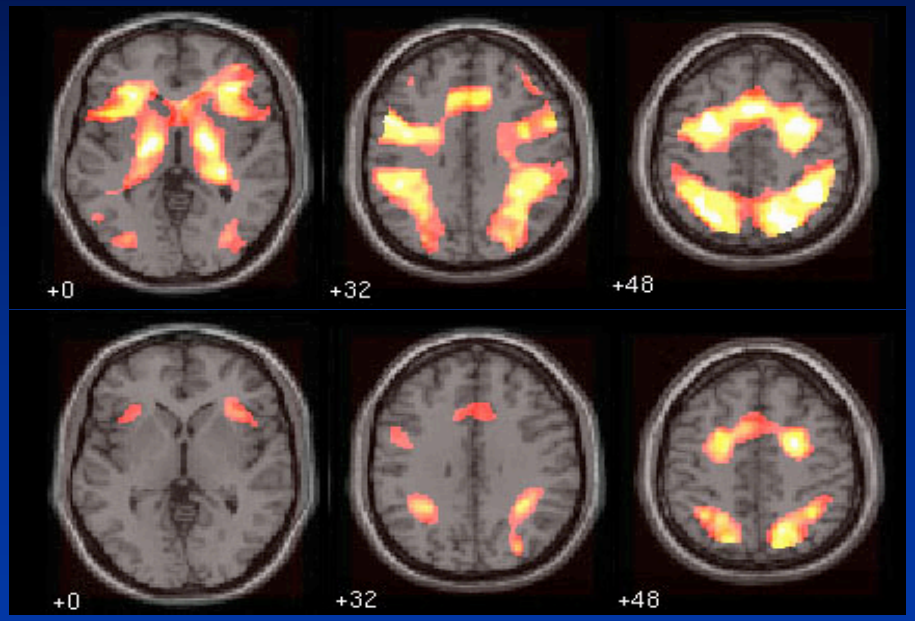
Calibration: SWM

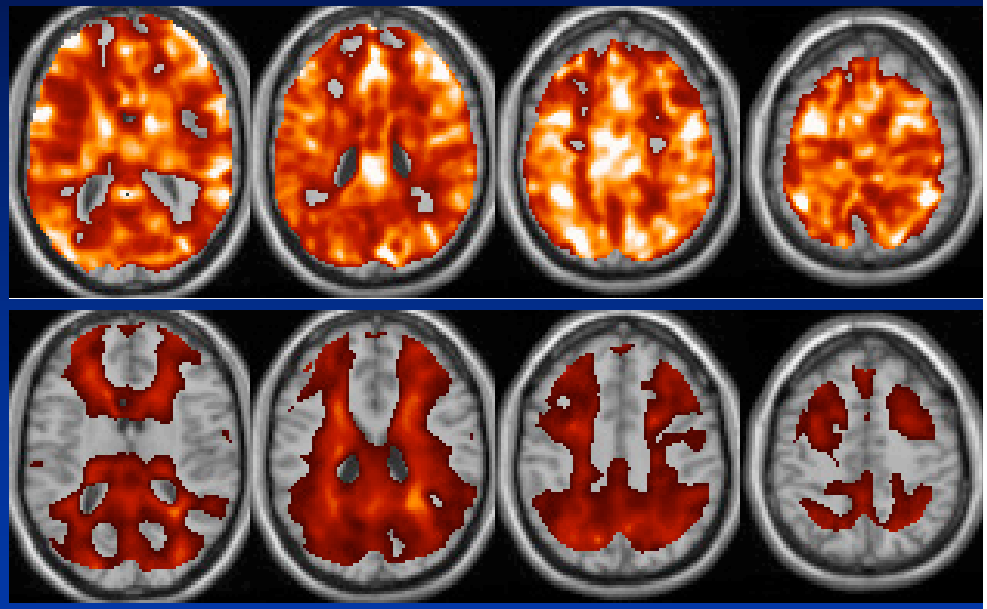


M. Thomason, 2007

Correlation: WM & BH

SWM **BH**





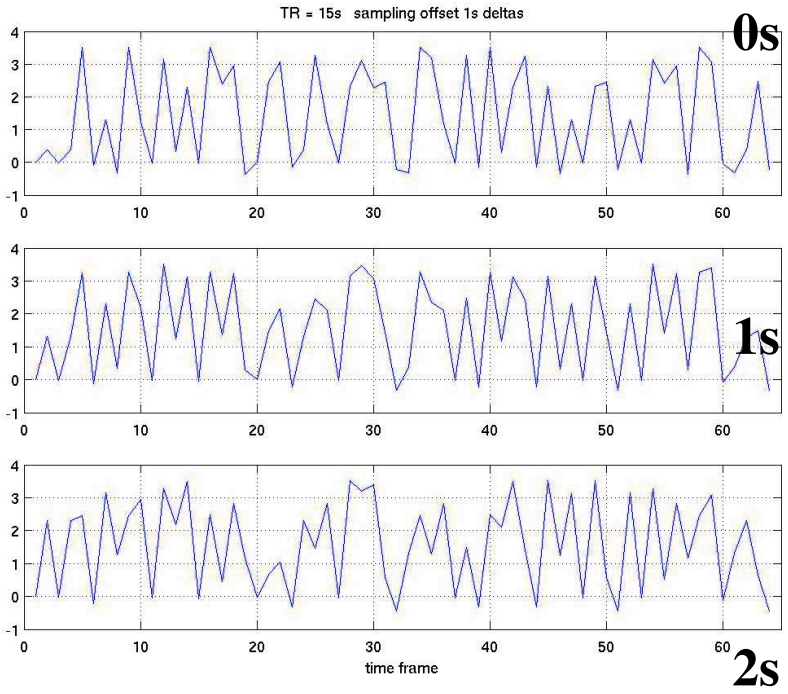
Top: adults
Bottom: children

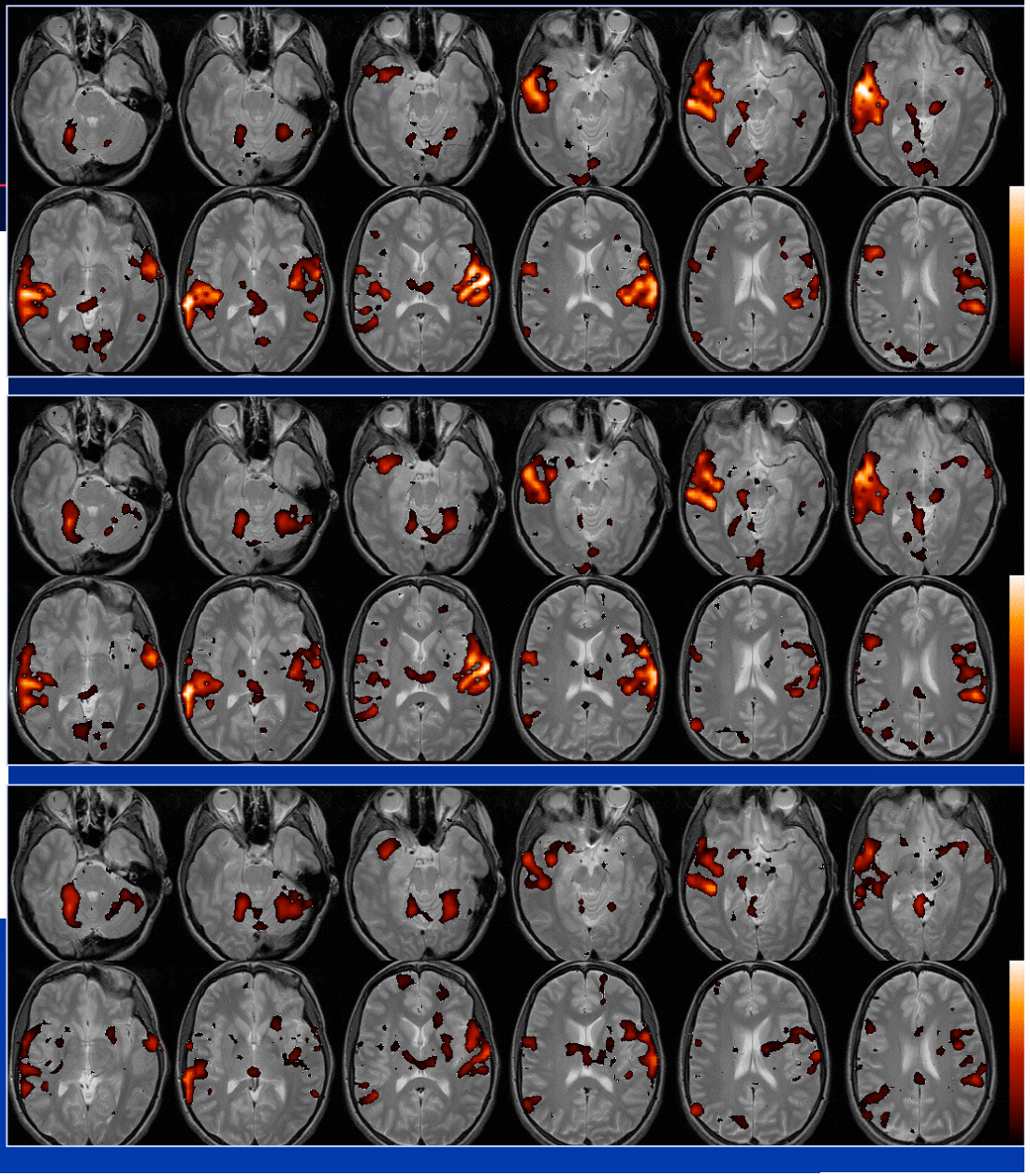
Thomason, et. al, 2005

Outline

- Issues with fMRI reliability
- Reducing confounds
  - HRF
  - calibration of vasoreativity
  - latency
- Physiological noise
- Multicenter studies

Timing error



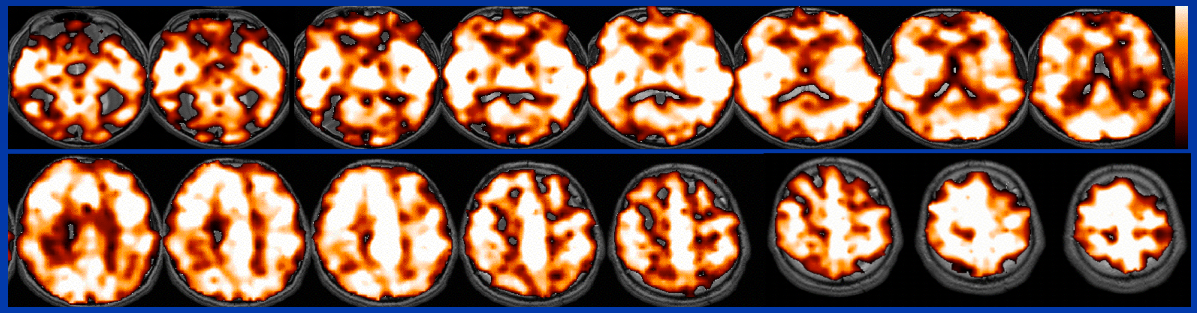


Auditory WM (N. Gaab)

BH to measure vascular latency

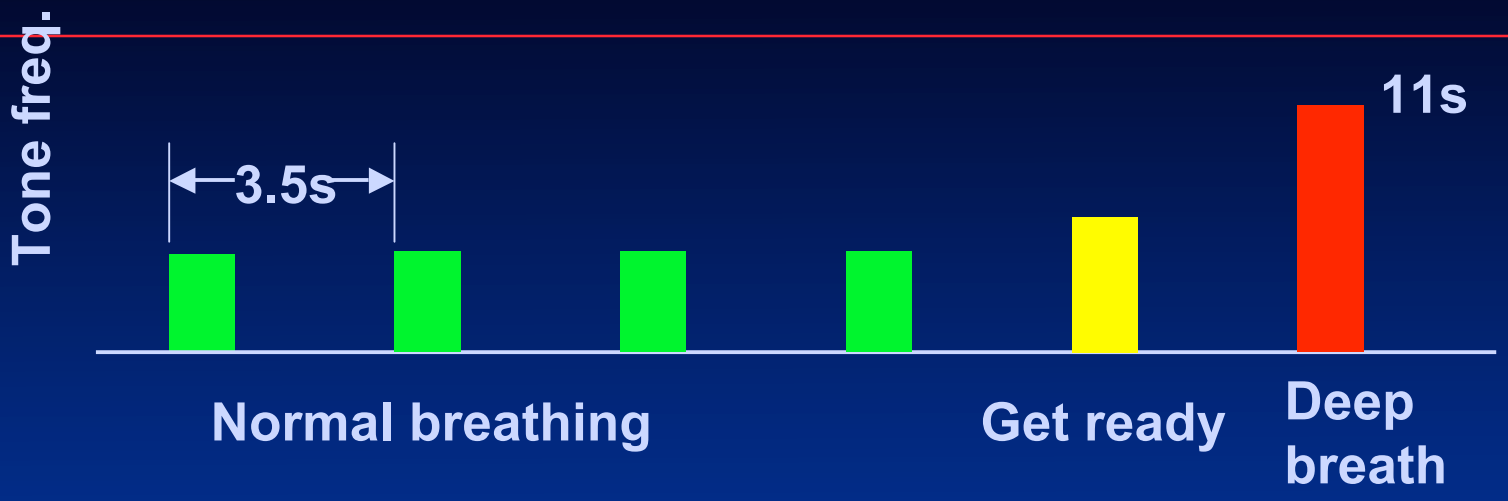
Can a BH task be used to quantify relative differences in vascular latency across the brain?

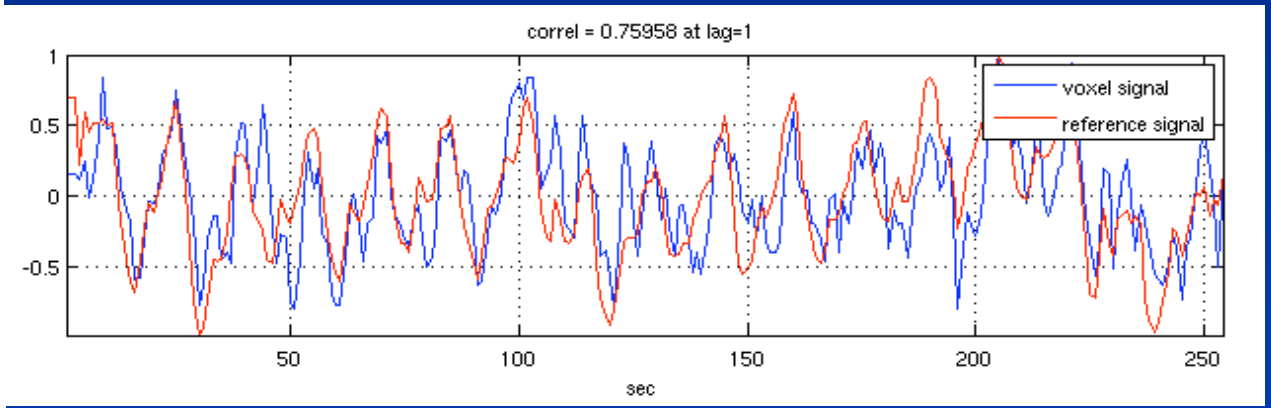
BH causes activation “everywhere”
BH causes a BOLD signal response that is uncoupled from neural activation (CMRO2)

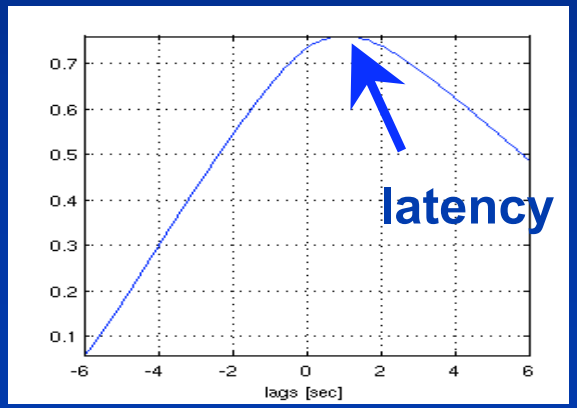


C. Chang (2008)

Latency Measurement

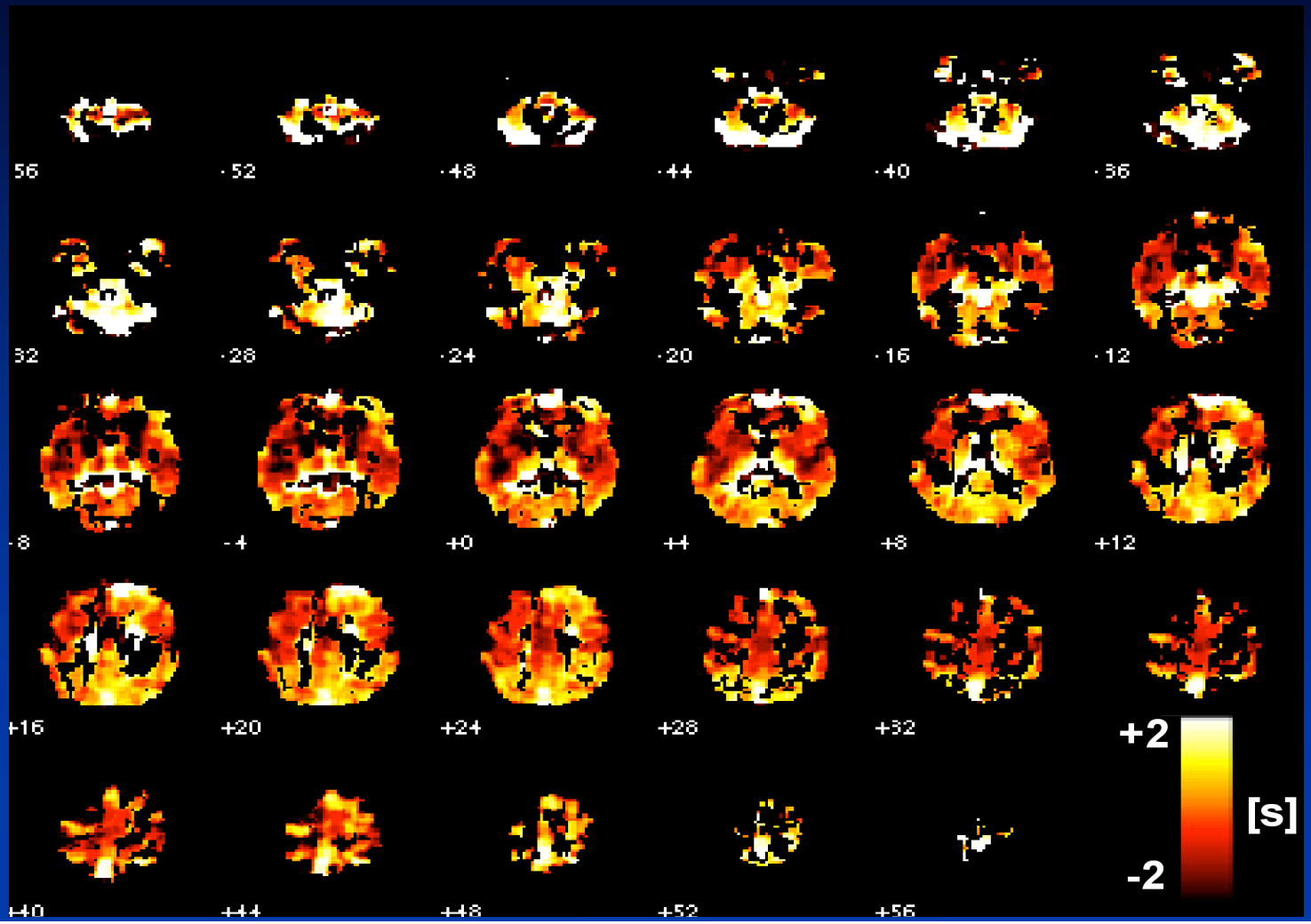




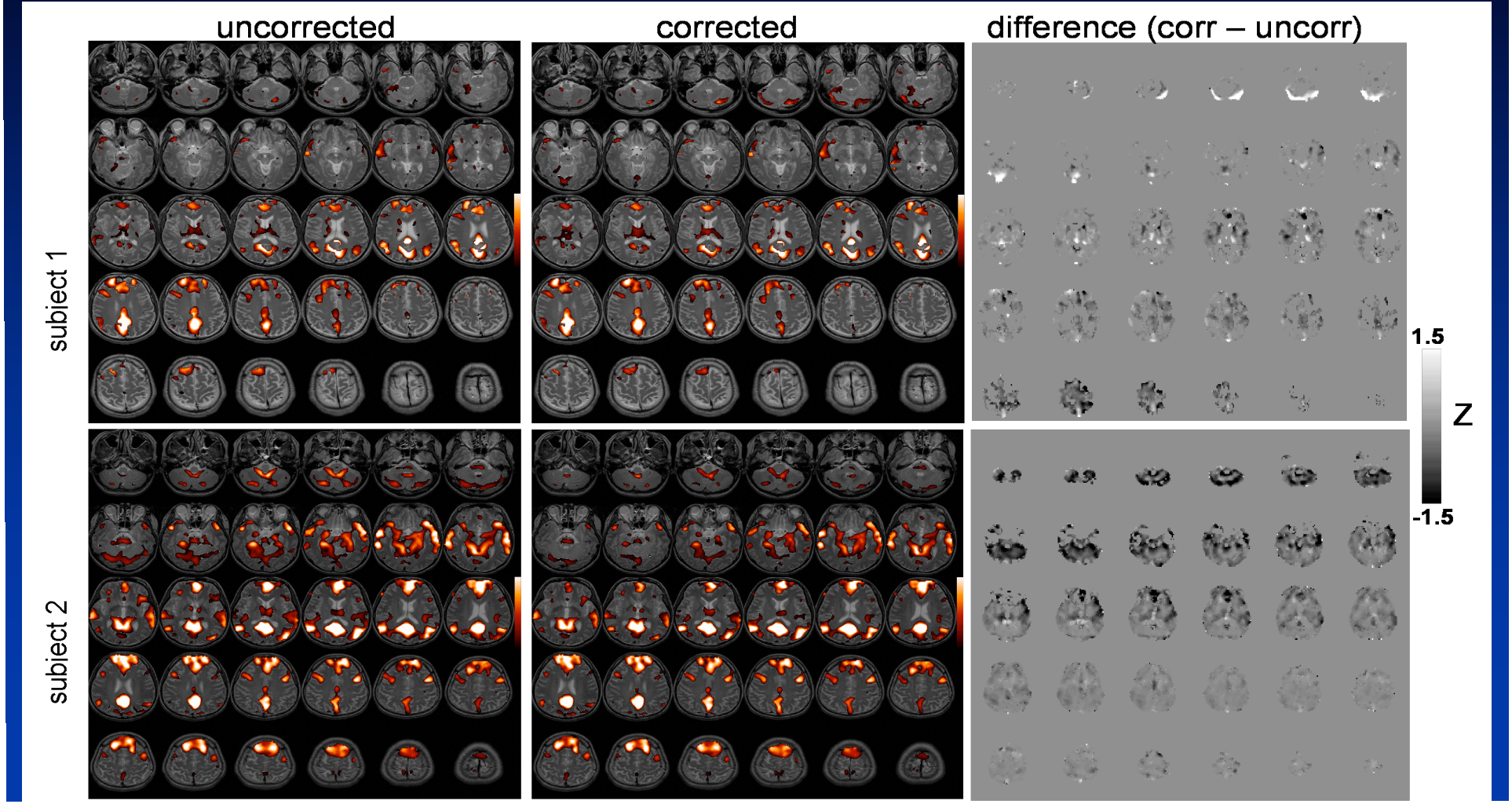


Chang et al., 2008

Latency Map

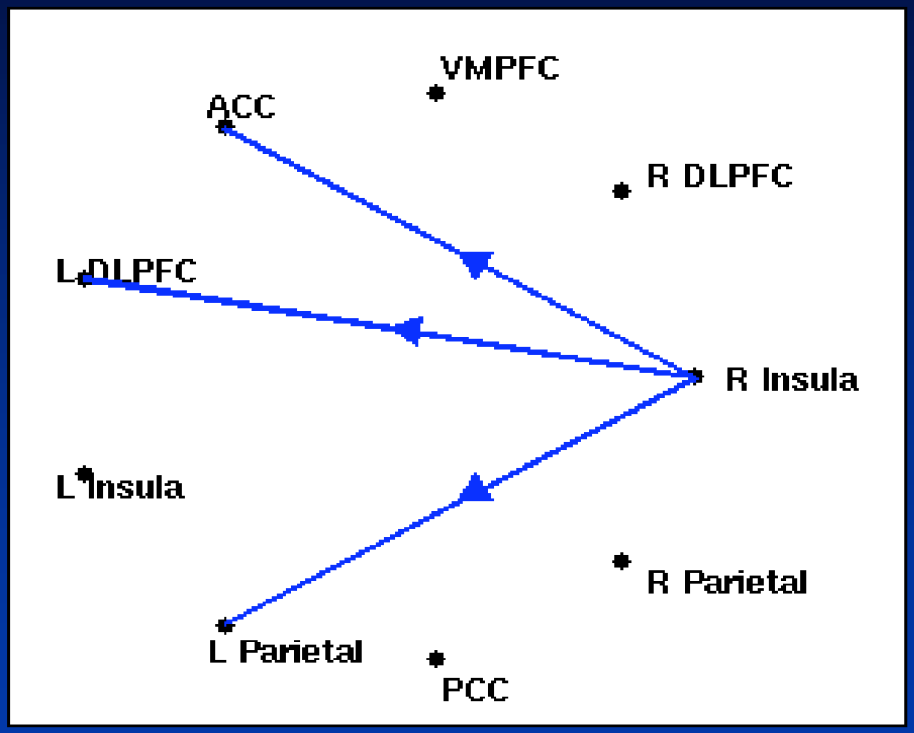

-56
-52
-48
-44
-40
-36
-32
-28
-24
-20
-16
-12
-8
-4
+0
+4
+8
+12
+16
+20
+24
+28
+32
+40
+44
+48
+52
+56
+2
-2
[s]

Impact on default-mode network

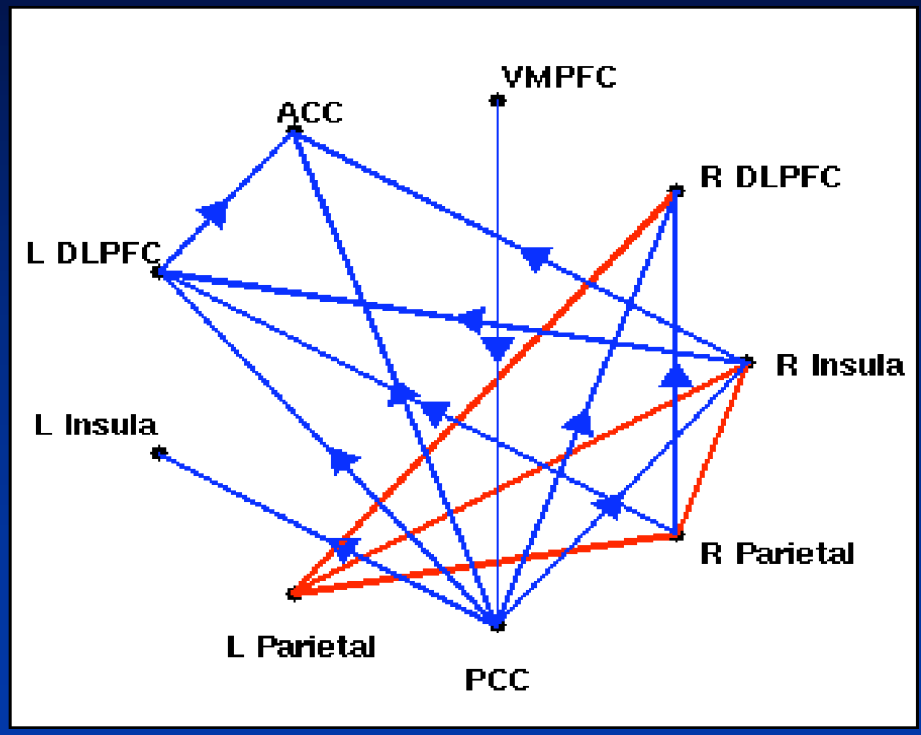


Impact on Granger causality

Before correction



After correction



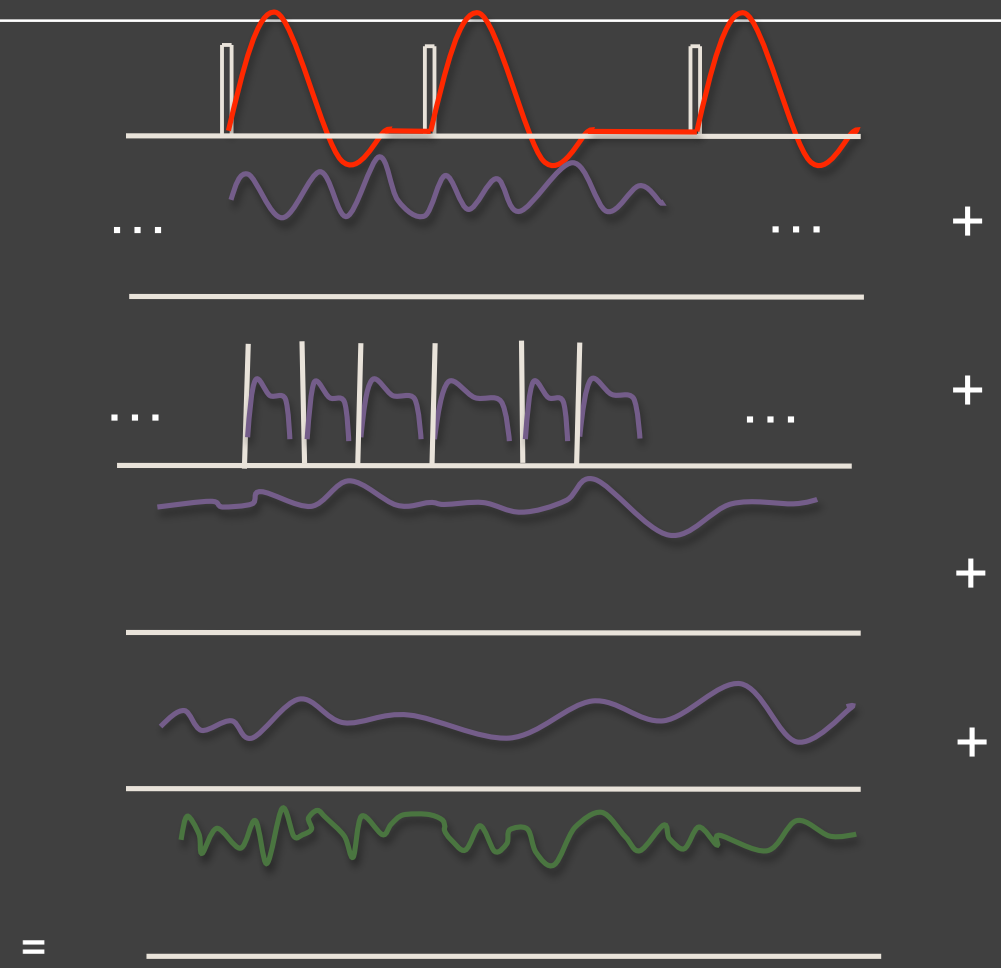
Chang et al., 2008

Outline

- Issues with fMRI reliability
- Reducing confounds
  - HRF
  - calibration of vasoreativity
  - latency
- Physiological noise
- Multicenter studies

BOLD/Physio noise: sources

- Neuronal activation
- Respiration cycle
- Cardiac cycle
- Respiration volume ($\approx CO_2$)
- Heart rate



Physio noise: reduction

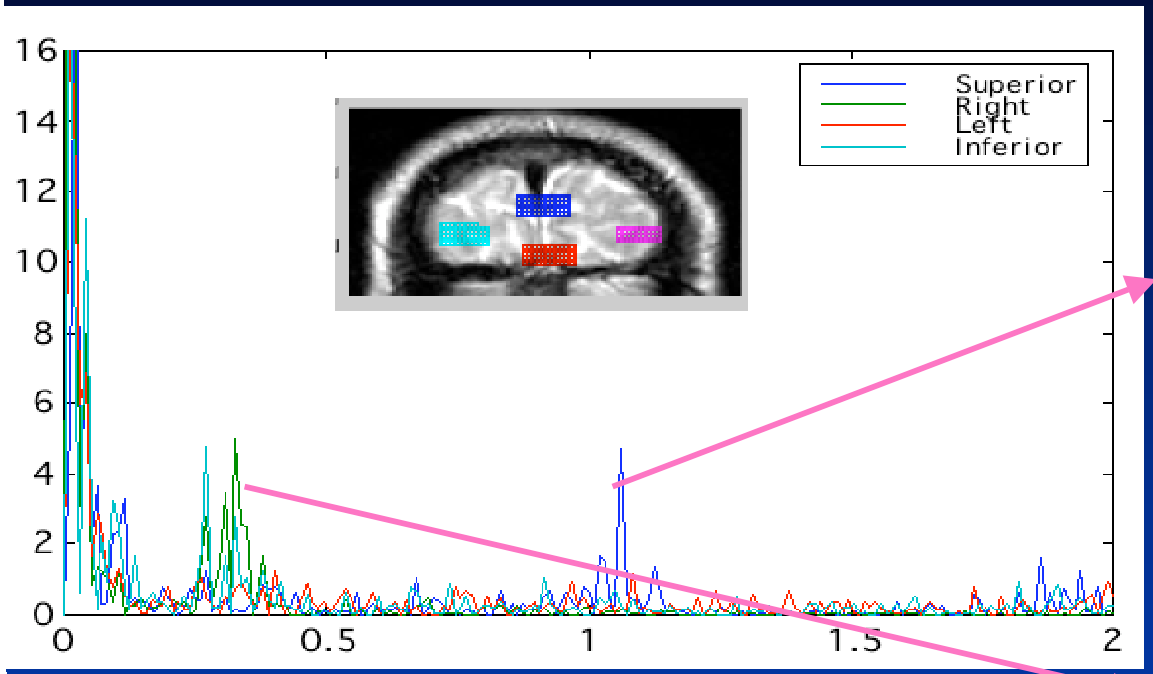
- Neuronal activation
- Respiration cycle
- Cardiac cycle

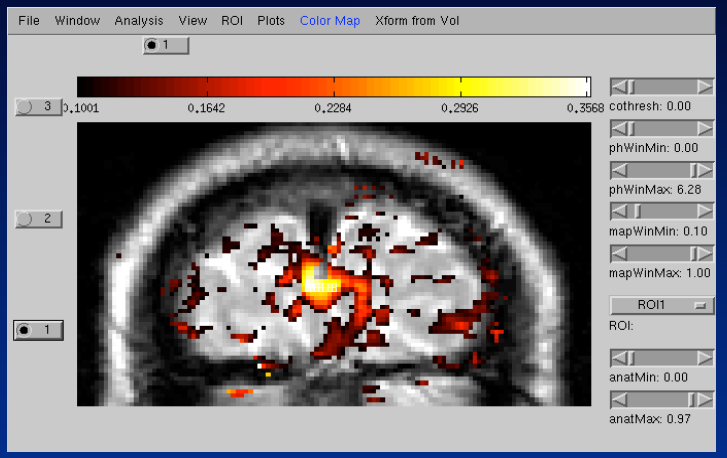
RETROICOR

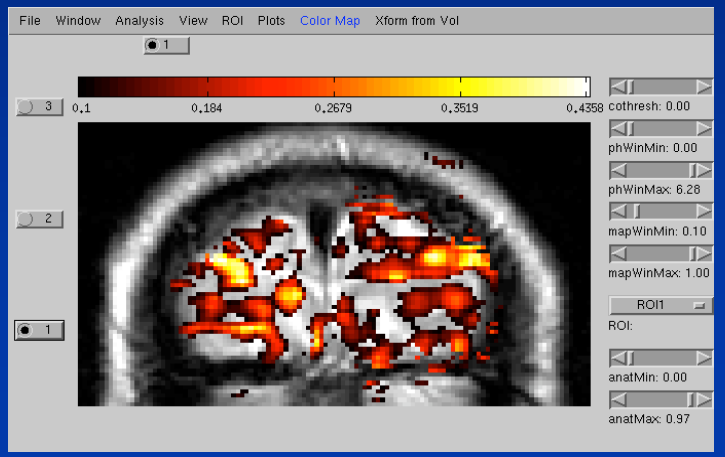
- Respiration volume ($\approx CO_2$)
- Heart rate

RVHRCOR

Cardiac/Respiratory Noise

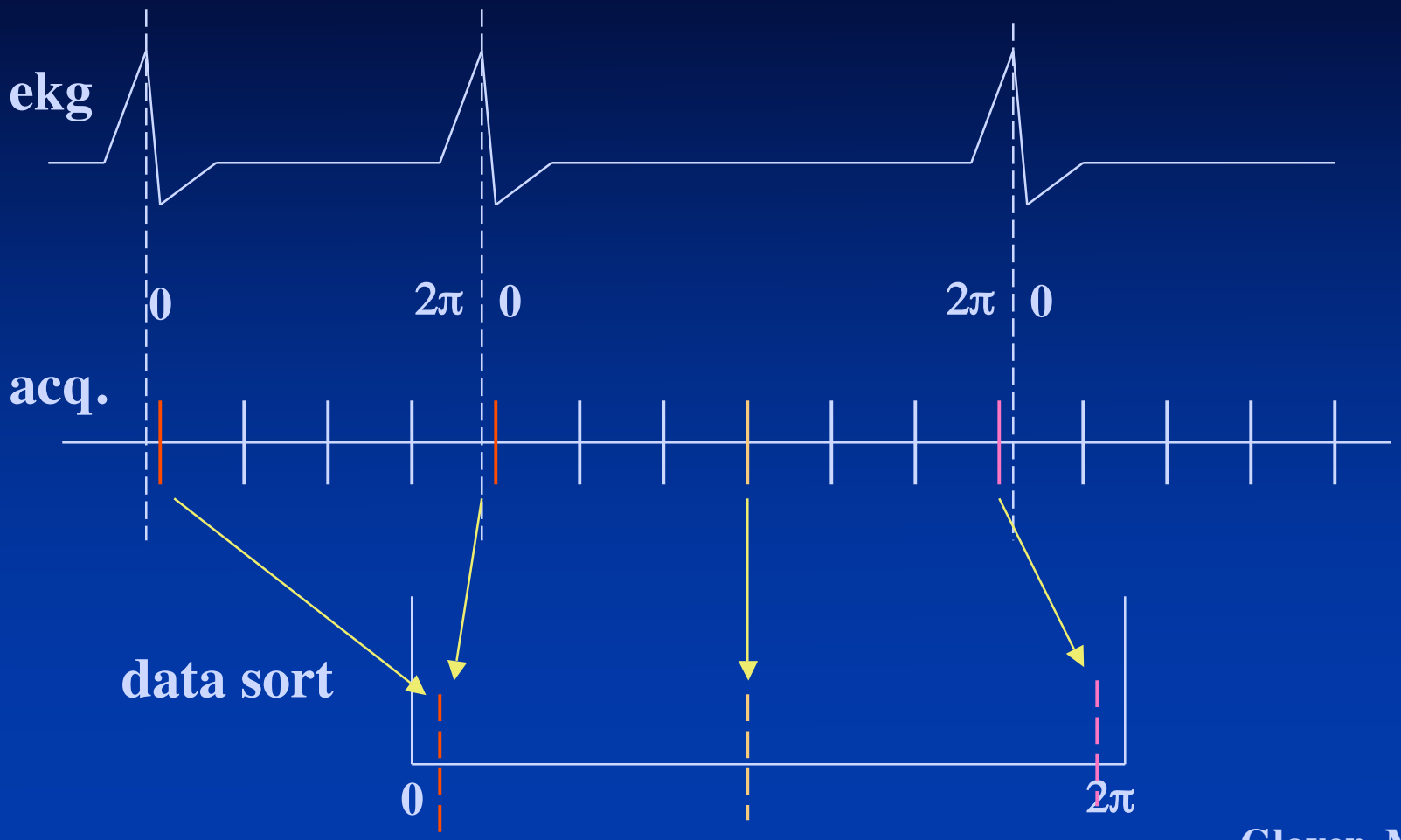






TR 250ms

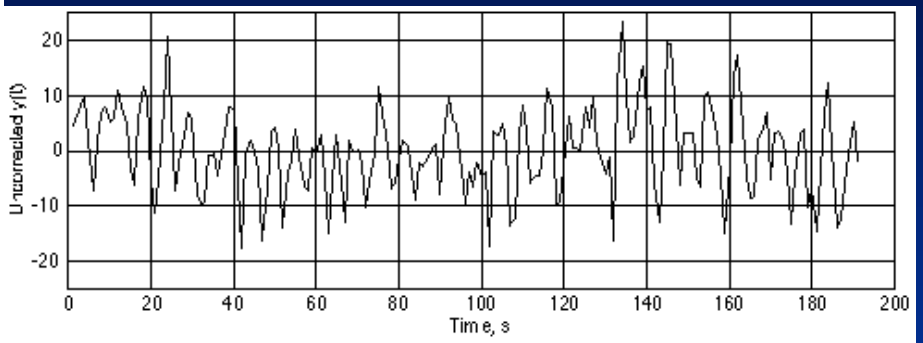
Retrospective sorting by cardiac phase



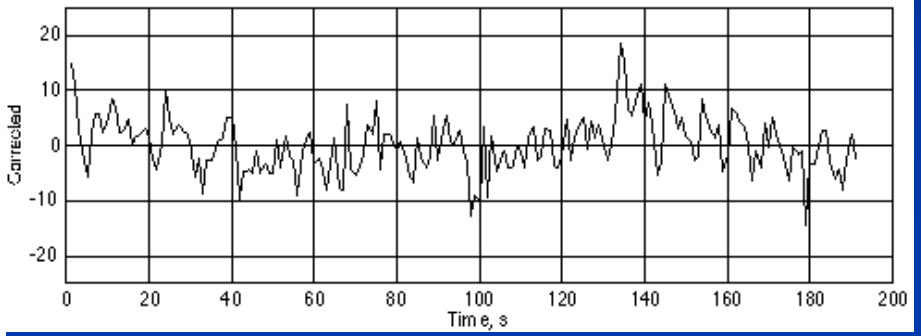
Glover, MRM 2000

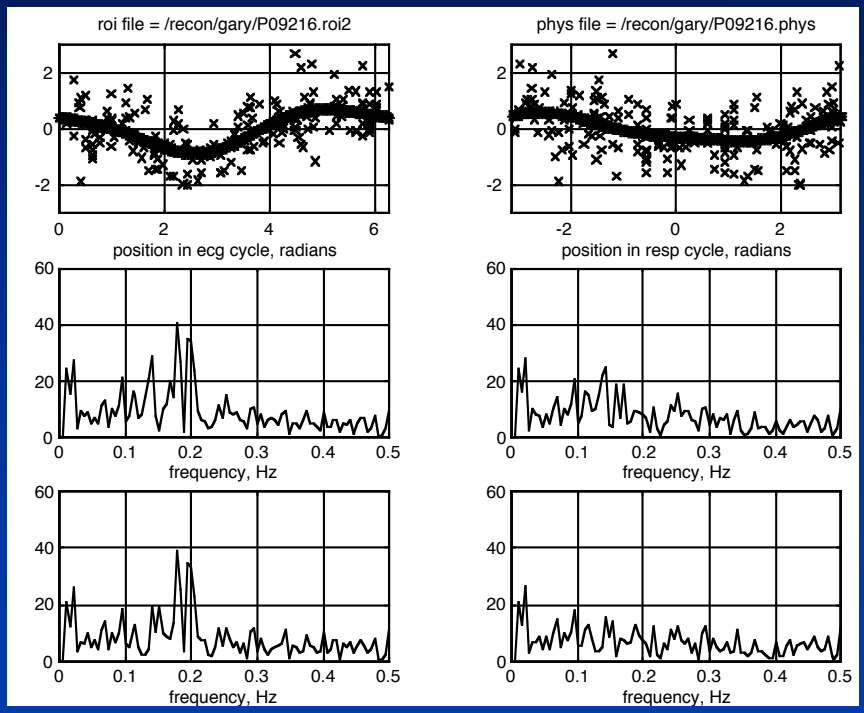
Cardiac/Respiratory Motion Correction

Timeseries in a voxel



after correction





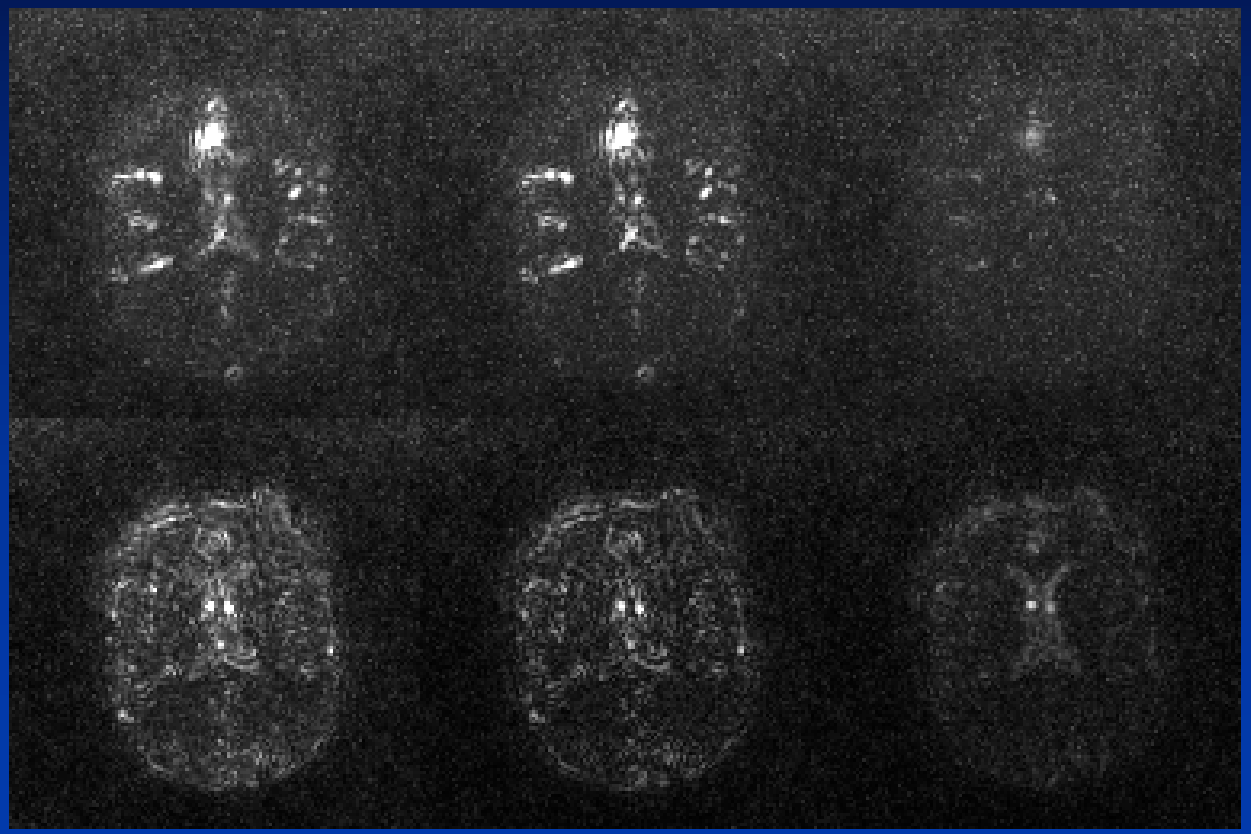
TR 1000ms

Retrospective Corrections

Before K-space I-space

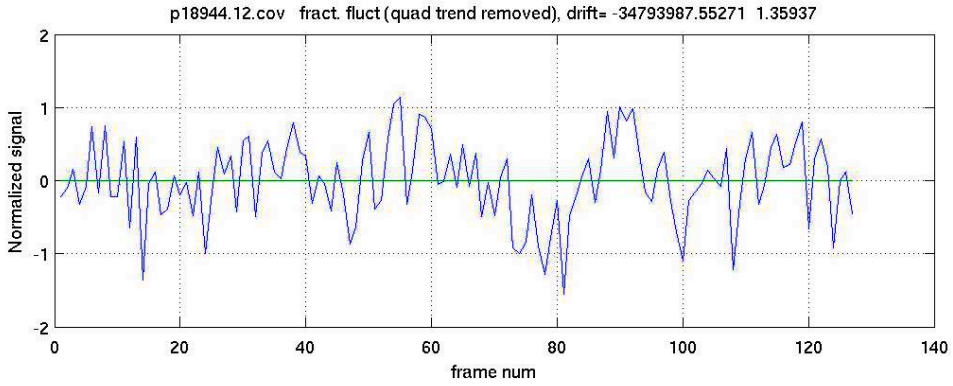
ECG

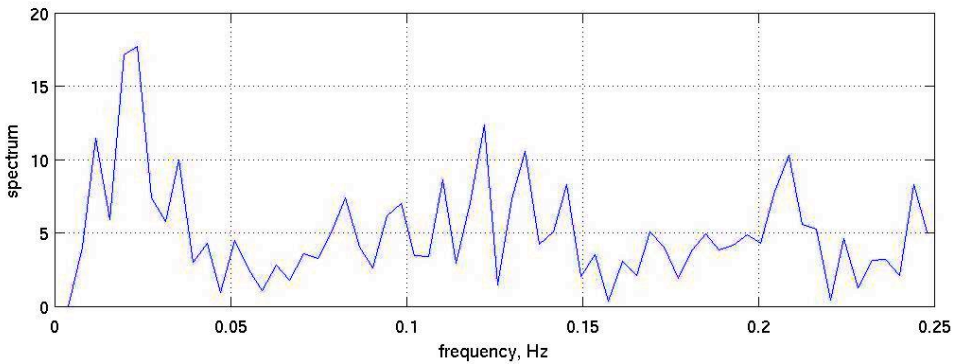
Resp



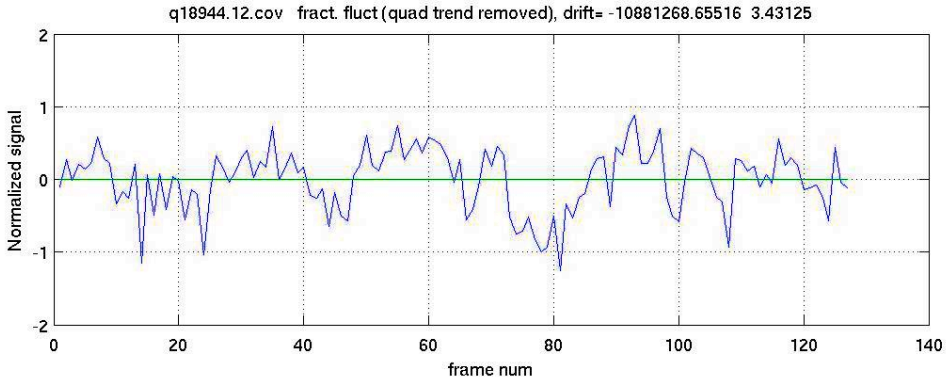
Resting State

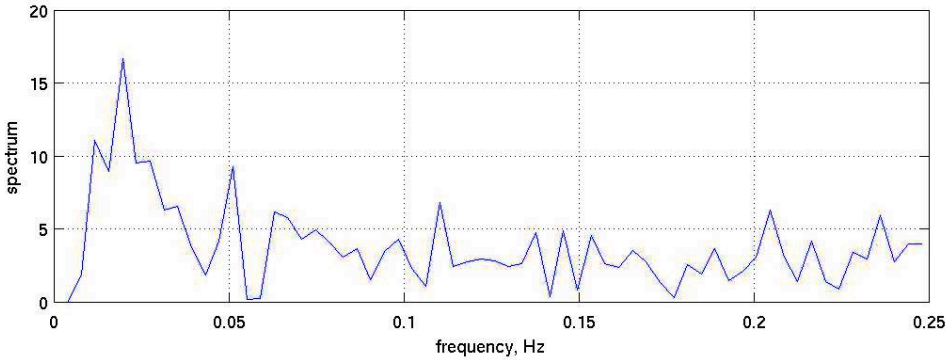
No retroicor





With retroicor

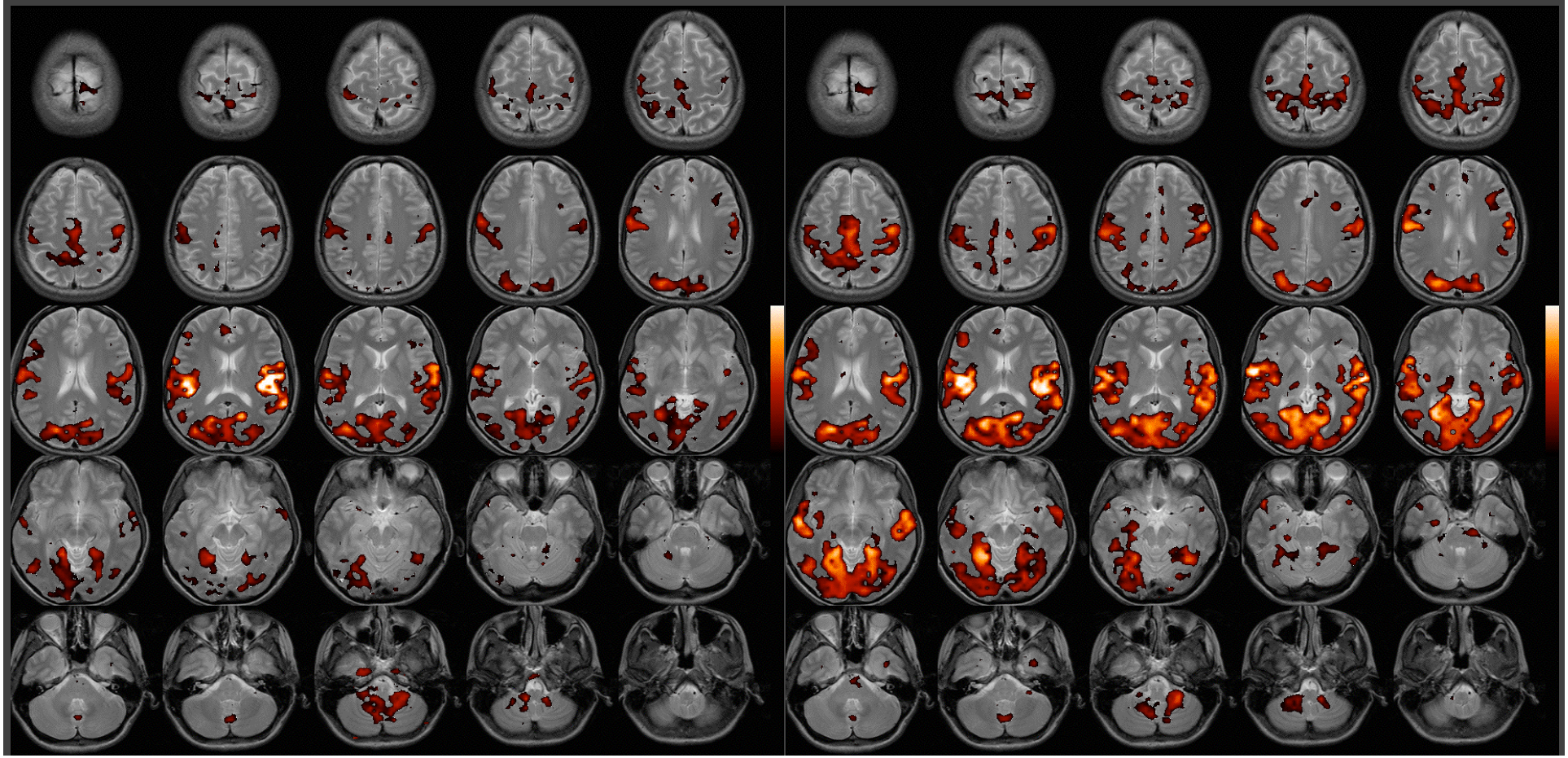




RETROICOR

No retroicor

With retroicor



Physio noise: reduction

- Neuronal activation
- Respiration cycle
- Cardiac cycle

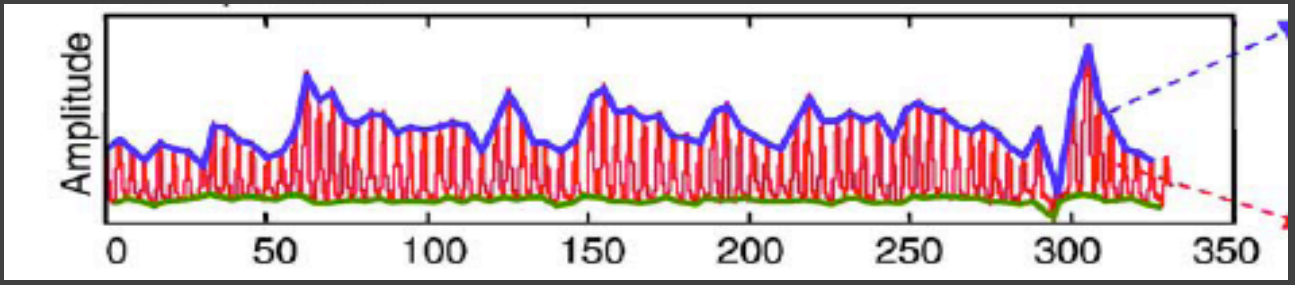
RETROICOR

- Respiration volume ($\approx CO_2$)
- Heart rate

RVHRCOR

Physio noise: sources

- Variation in respiration volume (per time)



Birn 2006

  - Air intake is inversely related to the amount of CO_2 in your blood.
    - CO_2 is a vasodilator (causes blood vessels to expand); this decreases vascular resistance, causing blood flow to increase
    - Known to affect BOLD (Wise, 2004)
- Heart rate
  - Affect cerebral blood flow (CBF)/volume; coupled to respiration
  - Not well known!

Physio noise: RVHRCOR

- Method to remove artifacts due to low-frequency respiration (RV) and heart rate (HR) (Chang et al, 2009, Birn et al., 2008)
- Model:

RV-related HR-related

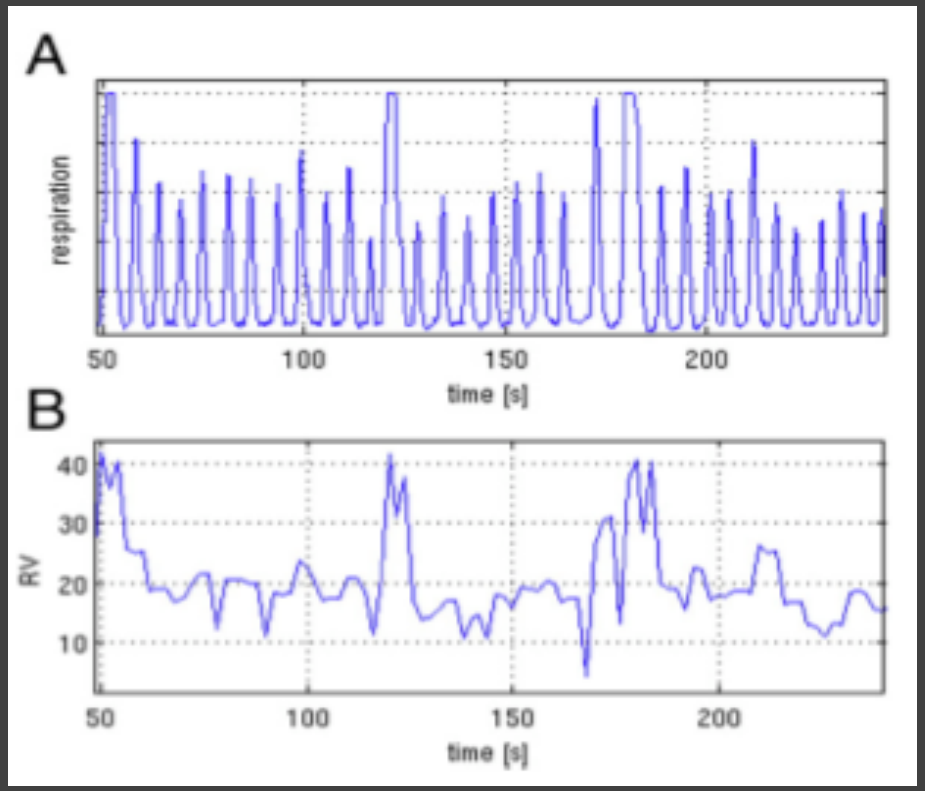
Voxel time series = RV ⊗ RRF + HR ⊗ CRF + (brain signal,etc.)

Remove these

  - Ä denotes convolution.
  - RRF and CRF are impulse responses that describe the mapping between RV ←→ BOLD signal, and HR ←→BOLD signal, respectively (just like the hemodynamic response function (HRF) maps between stimuli ←→ BOLD signal)

RVHRCOR: RV

1. Compute RVT from the raw respiration trace



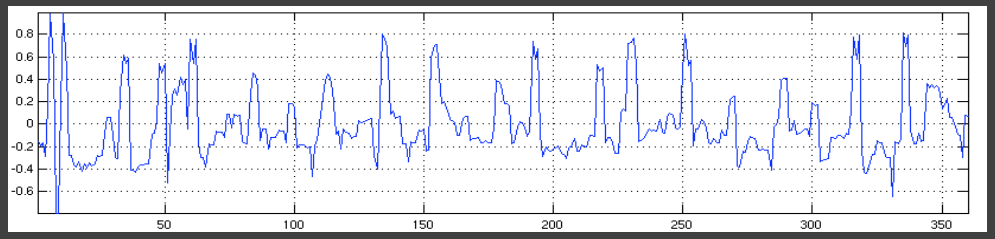
resp

RVT

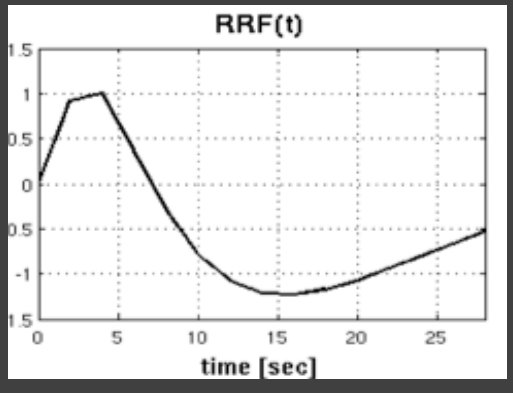
RVHRCOR: RV

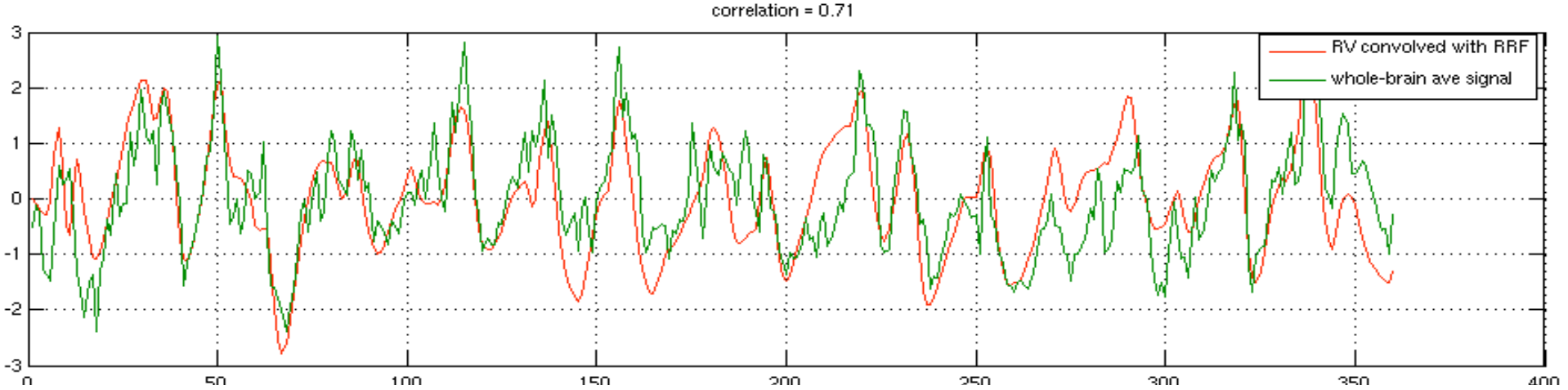
2. Convolve RVT with the RRF

RV

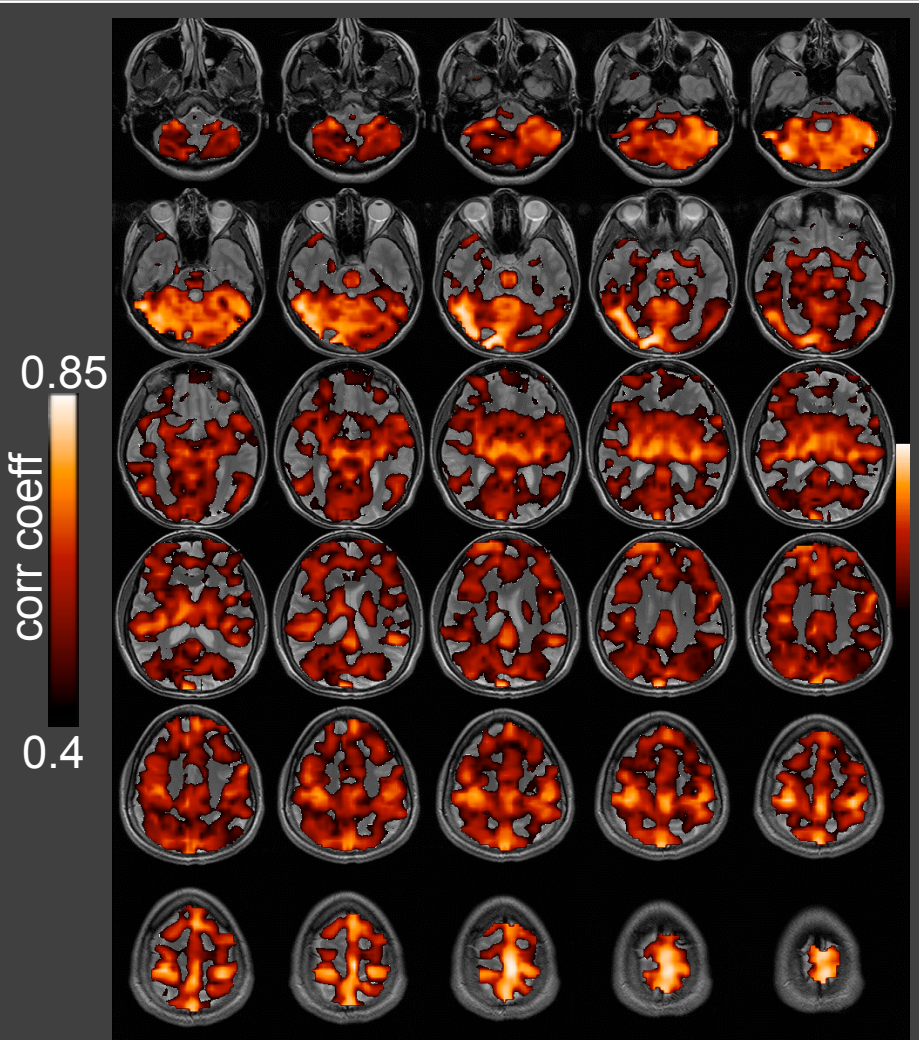


✪





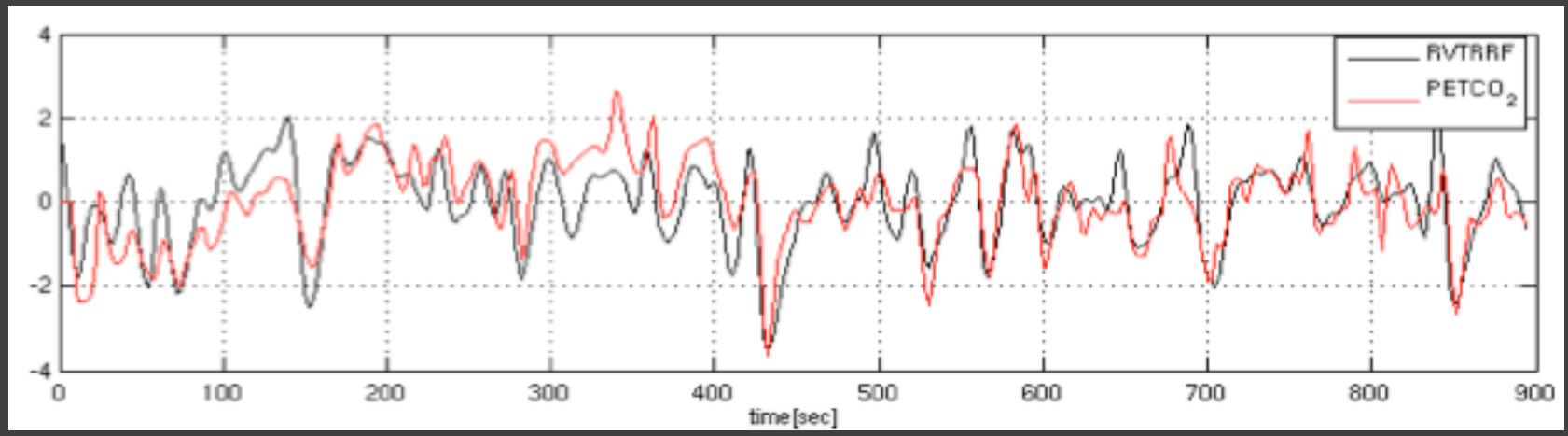
RVHRCOR: RV



- Correlation between RVx and each voxel

RVx ≈ CO2

(after shifting CO_2 forward by about 10s)



- RV(T) ~ ventilation ~ 1/$PaCO_2$
- So, model could be: RV → CO_2 changes → BOLD changes

Chang, 2009

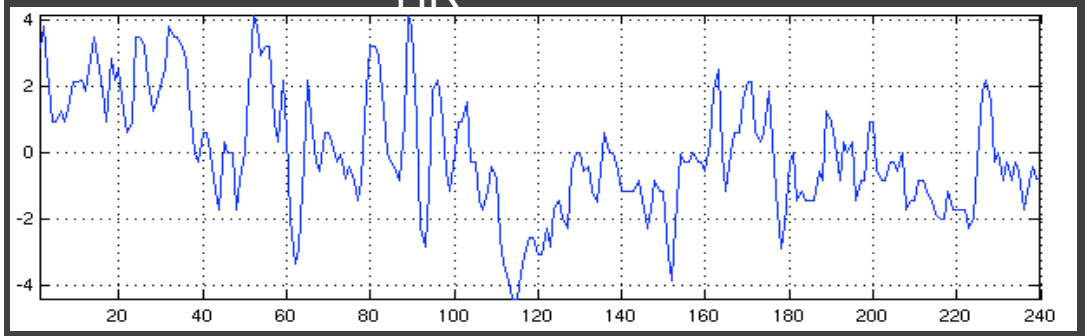
RVHRCOR: HR

- RV:
  1. Compute RV from the raw respiration trace
  2. Convolve RV with the RRF

- HR:
  1. Compute HR from the cardiac/PPG triggers
  2. Convolve HR with the CRF

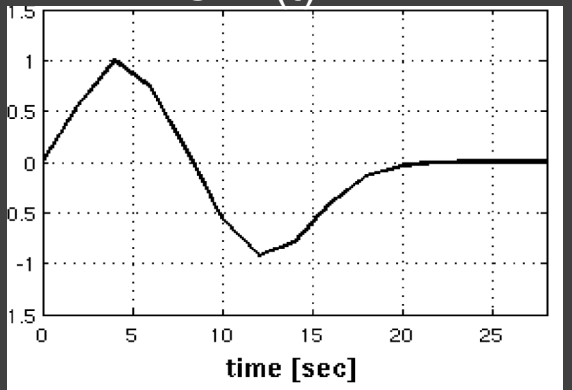
Cardiac response function (CRF)

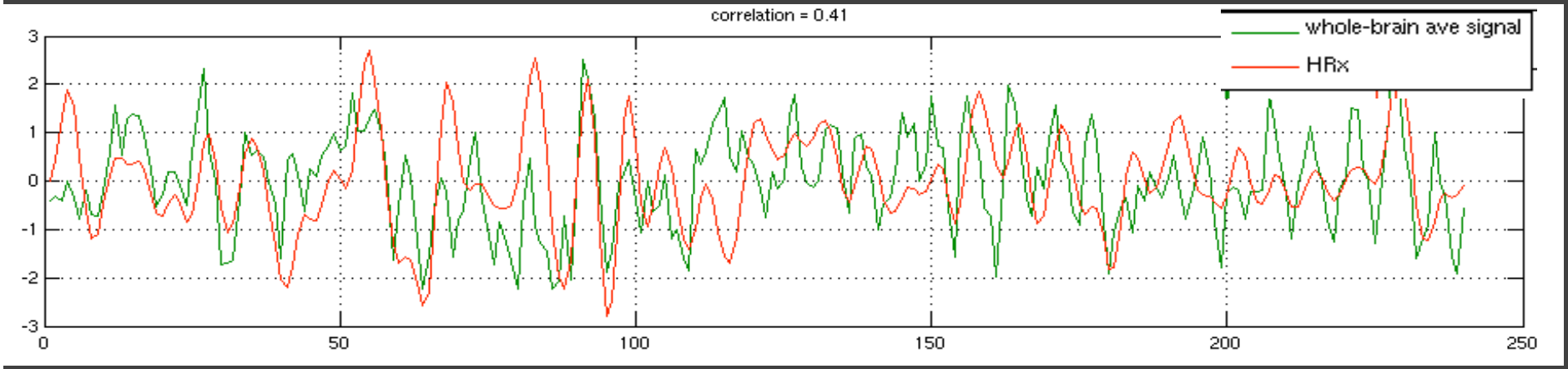
HR



✪

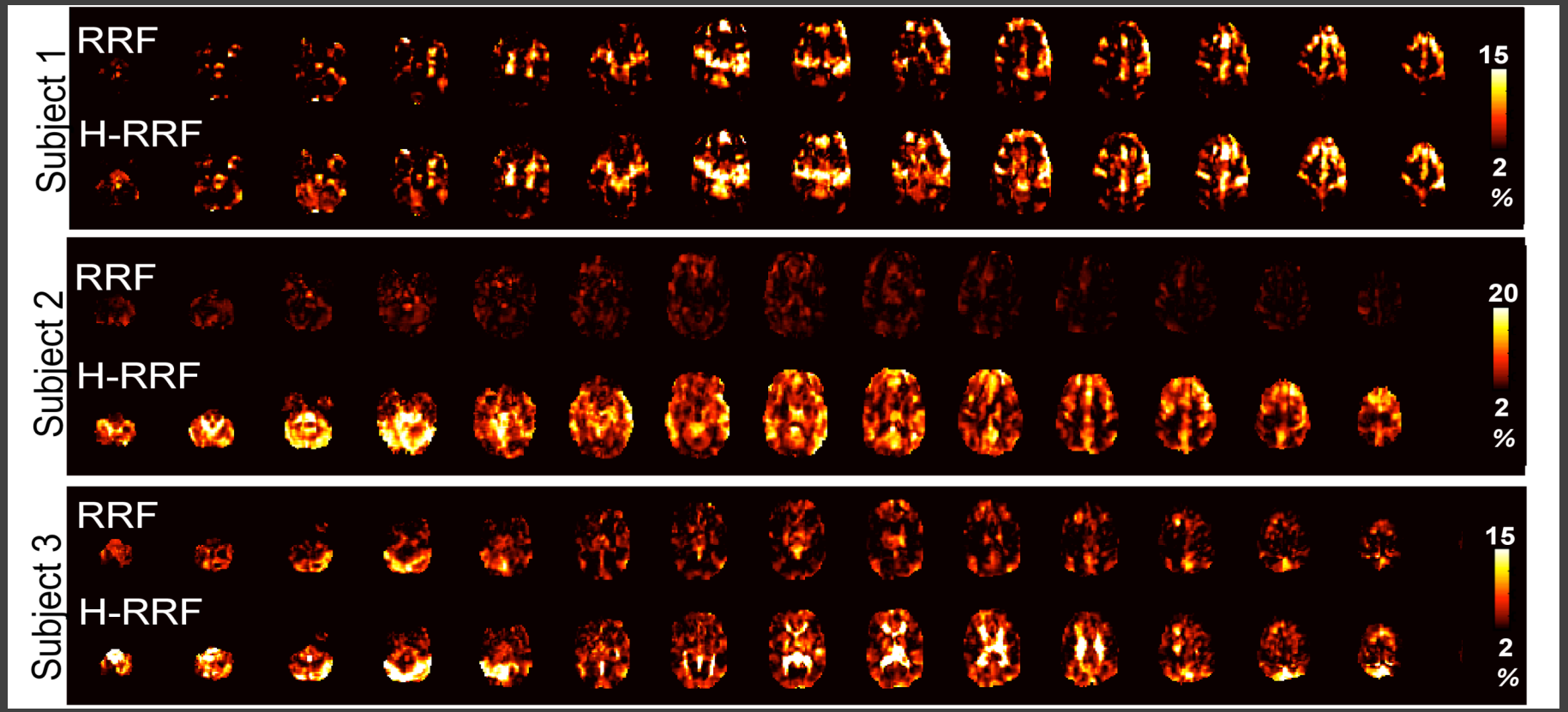
CRF(t)





Chang, 2009

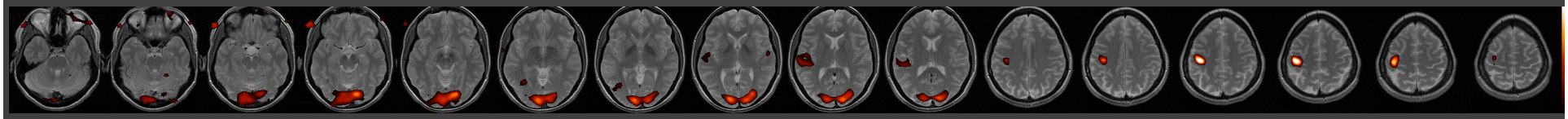
Variance explained: RVx & HRx



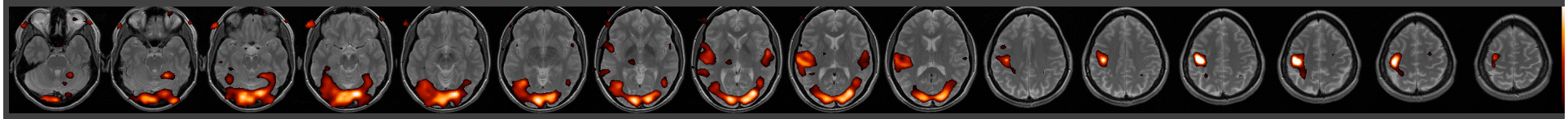
Chang et al., 2009

Impact on activation: SM task

Retroicor only

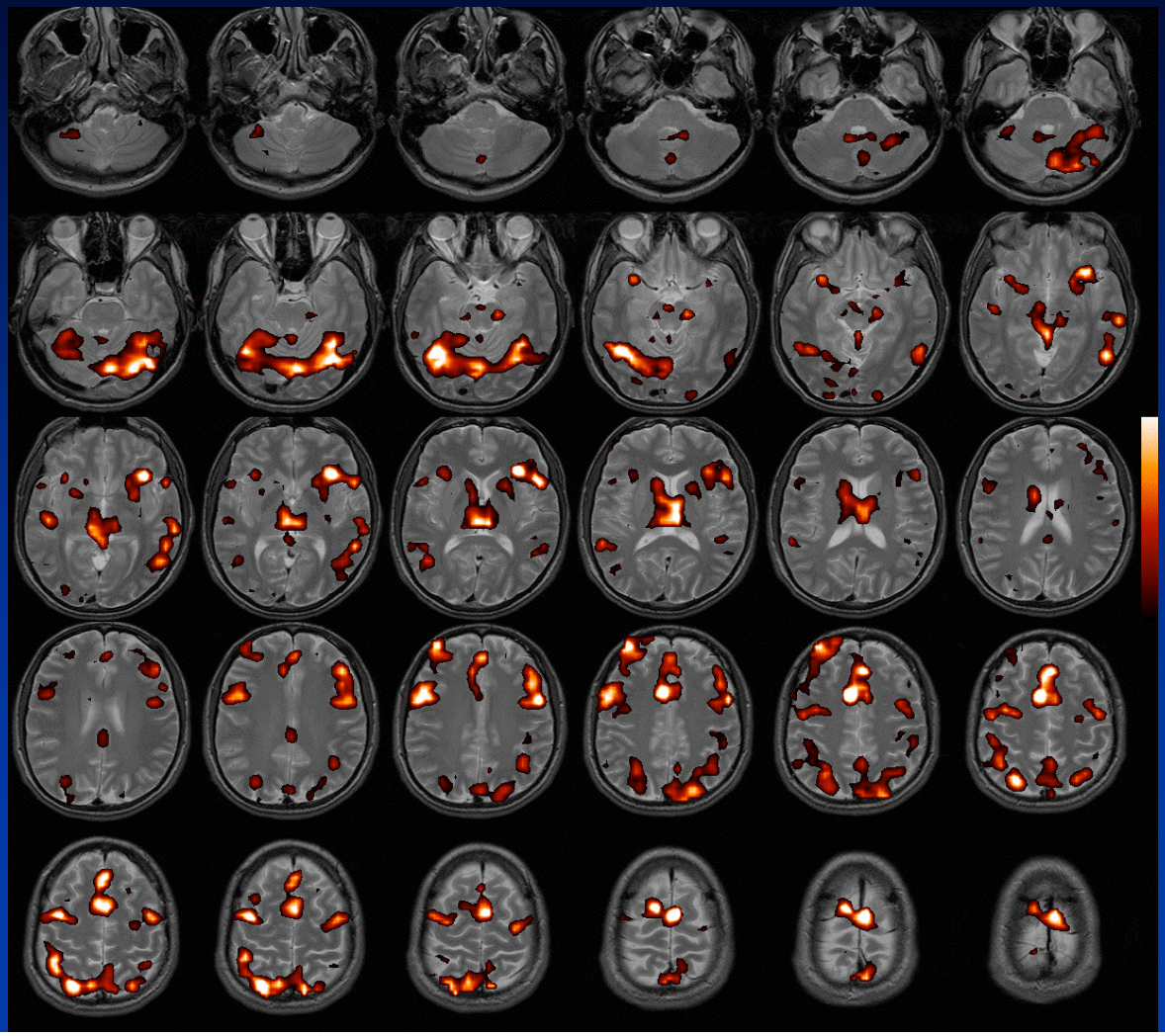


Retroicor & rvhrcor



T maps: after - before

Impact on WM task

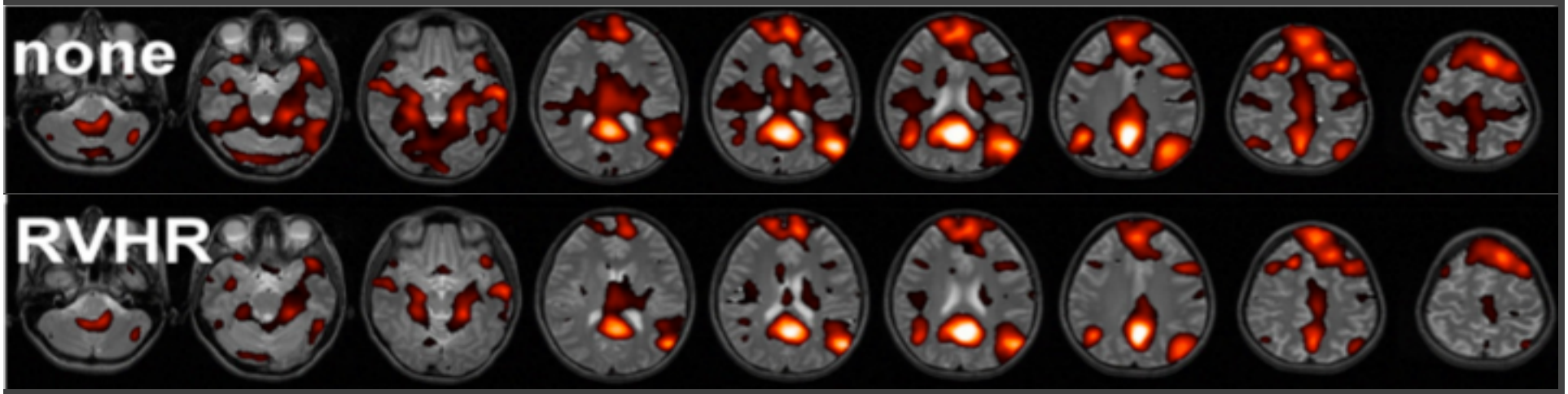


WM Activation increases
(corrected - uncorrected)
T=0.1-1.0

Chang et. Al
(2009)

Impact on resting-state networks

- Decreases “false” positive correlations w/ default-mode



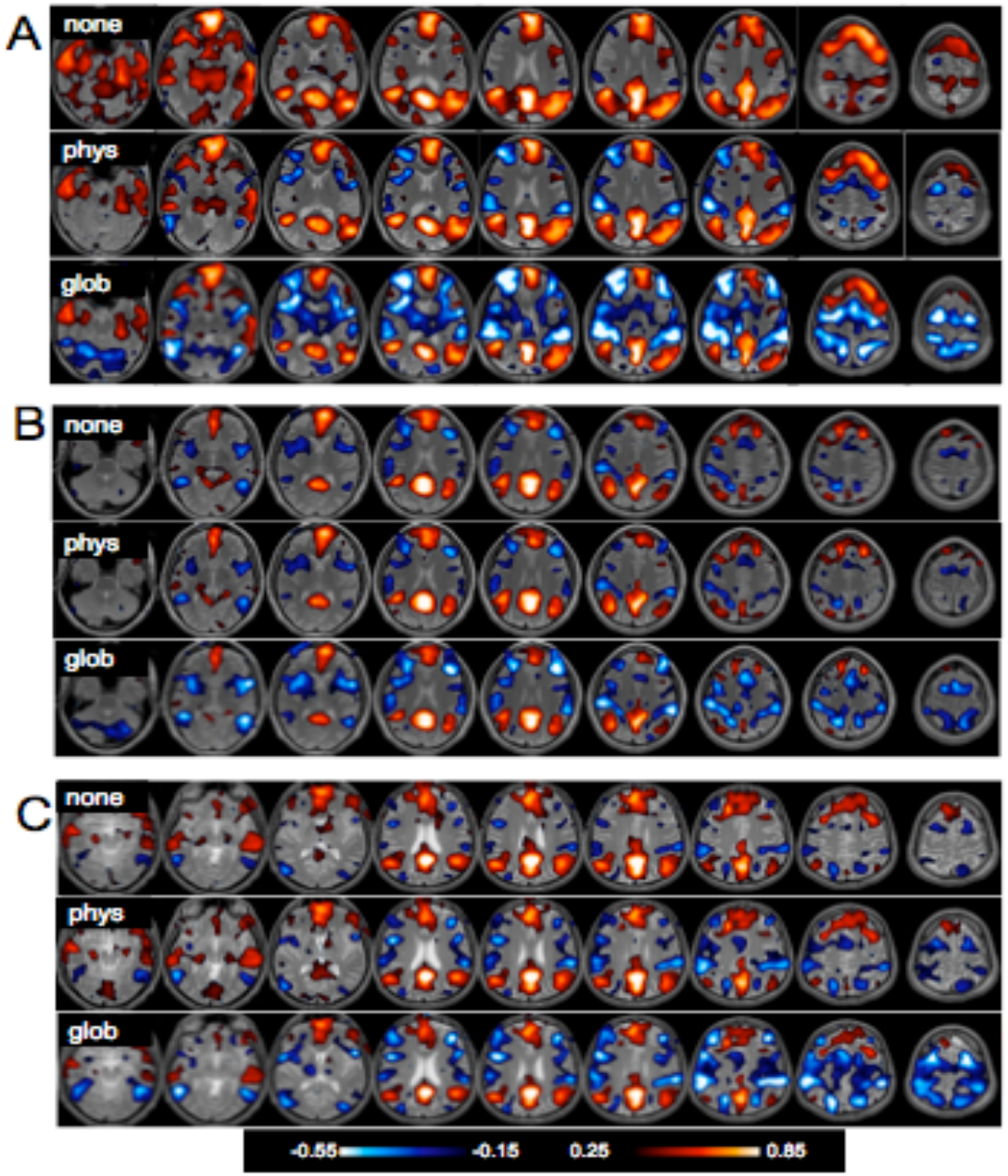
Chang et al., 2009

Impact on resting-state networks

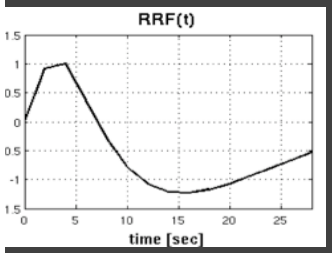
Correction can

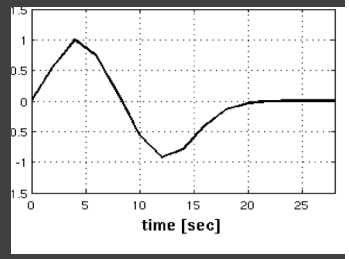
- reduce spurious "connectivity" in DFM
- increase anticorrelated network connectivity

Chang et al., 2009



RVHRCOR: Summary





resp

PPG

RV

HR

RRF

CRF

RVx

HRx

β_r

β_h

voxel time series

-

-

"clean" voxel time series

Chang, 2009

Outline

- Issues with fMRI reliability
- Reducing confounds
  - HRF
  - calibration of vasoreativity
  - latency
- Physiological noise
- Multicenter studies

Multicenter Neuroimaging Studies

- Potential use of MRI/fMRI as a biomarker
  - structural/functional differences may predict disease; large study numbers are necessary for biodiversity
  - monitoring drug efficacy or other therapy
- Generate large data sets rapidly
- Access wide or targeted demographic characteristics
- Provide image databases for other analyses

Multicenter MRI

- 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

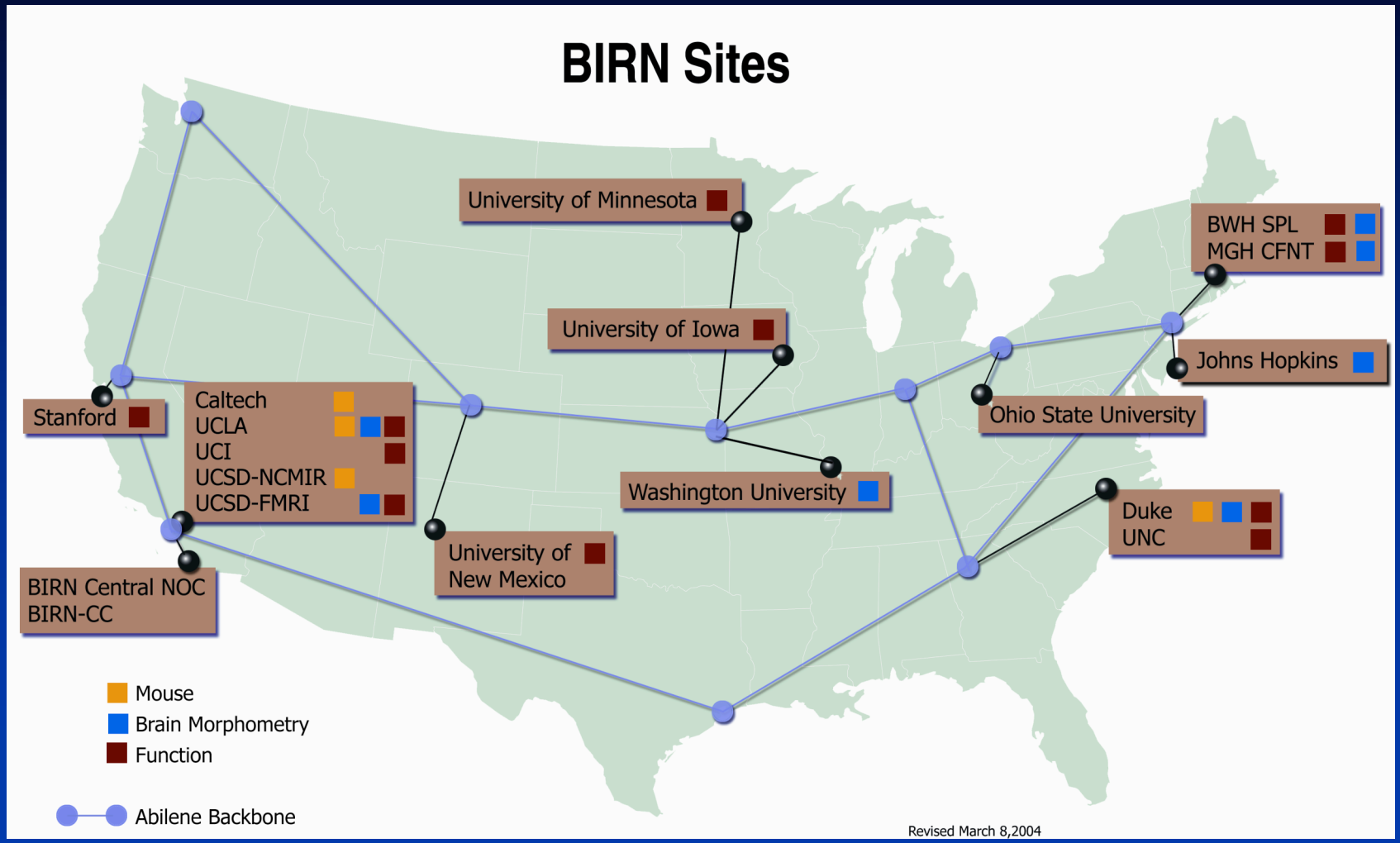
- Need to qualify sites for entry into study
  - characteristics for acceptance
    - geometric accuracy
    - contrast/resolution
    - SNR, CNR, tSNR (SFNR)
    - temporal stability
    - reliability/reproducibility
    - artifacts (ghosts/distortion/eddy current-related, …)
  - understand sensitivity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

Multicenter MRI

- 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- test scientific question

BIRN
BIOMEDICAL INFORMATICS RESEARCH NETWORK

Multicenter MRI



fBIRN

- Goal: Develop methods for pooling fMRI data on schizophrenics at each of 11 centers
  - load manipulation in emotional WM
- Approaches: Reduce intersite/intersubject variability
  - scanner QA
  - measure/calibrate/normalize
    - BOLD sensitivity
    - HRF/vasoreactivity

Issues in multicenter studies

- Standardization of protocols
- QA
- Site Equalization

Standardization

- Study design
- Acquisition parameters
- Scanner characteristics
- Study procedures
- Analysis pipeline
- Database structures

fMRI Imaging Characteristics

Modest importance:

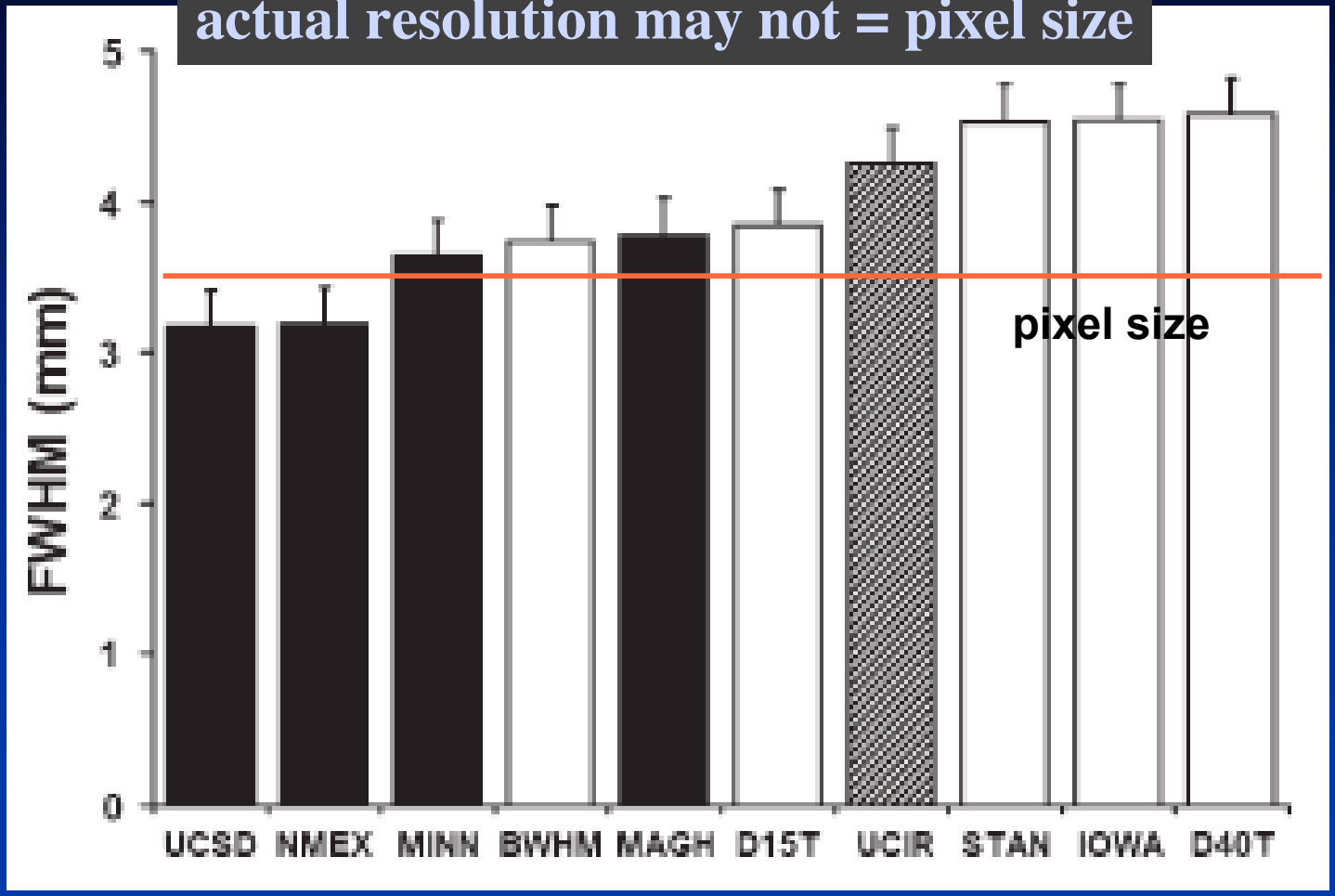
- **Geometric accuracy (since fMRI is low resolution- e.g. 3.4x3.4x4 mm^3)**

Highest importance:

- **Stability (short/long term)**
- **BOLD CNR- B1 uniformity (coil choice)**
- **Susceptibility-induced distortion/dropout (seq. params)**
- **Ghost/spike noise/other artifacts**
- **Standardization across vendors**

Intersite smoothness differences

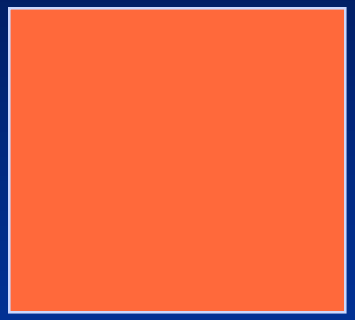
actual resolution may not = pixel size

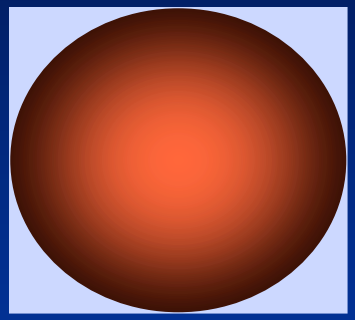


Friedman et al. NI (2006)

Why smoothness differences?

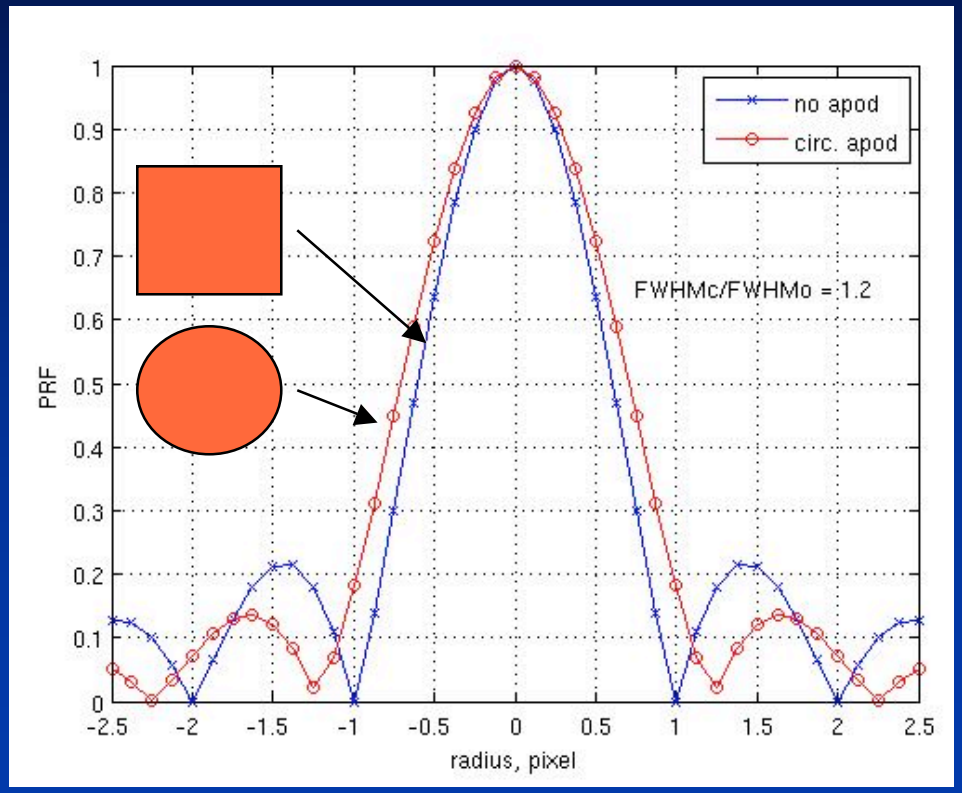
- k-space reconstruction kernel





Vender “S”

Vender “G”



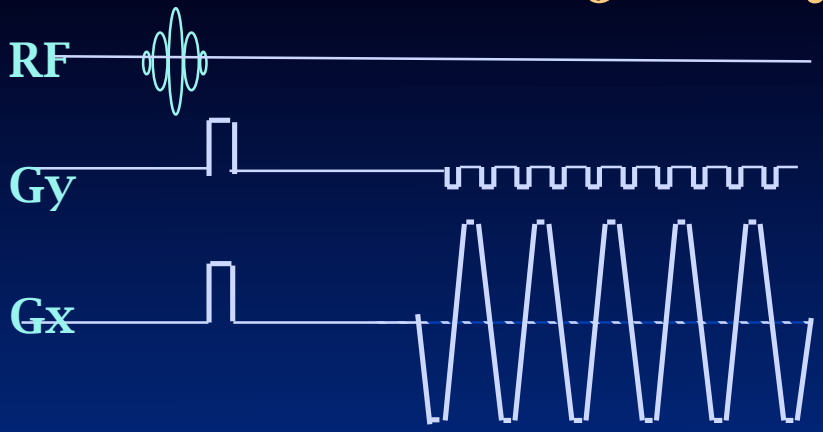
- Apodization- lower resolution, higher SNR

Important fMRI Characteristics

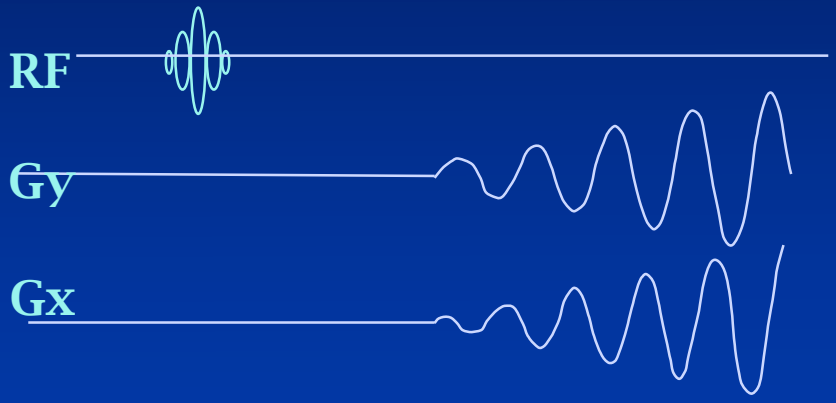
- fMRI acquisition contrast/smoothness
  - control parameters:
    - resolution/smoothness (resel != FOV/matrix_size)
    - BW: keep ESP constant across venders
    - slice spacing/skip/orientation
    - fat saturation vs. water excitation
    - readout trajectory (EPI vs. spiral), affects smoothness, artifacts
    - field strength (affects SNR, CNR, vessels vs. tissue, artifacts)

Trajectory

EPI



Spiral

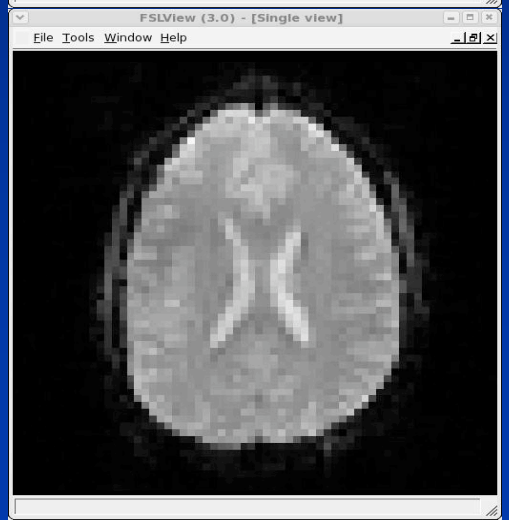


- affects resolution, motion sensitivity, SNR, num slices/TR

RF Excitation/Slice Select

Spectral-Spatial
(default for
GE EPI)

FATSAT
(default for
Siemens EPI)

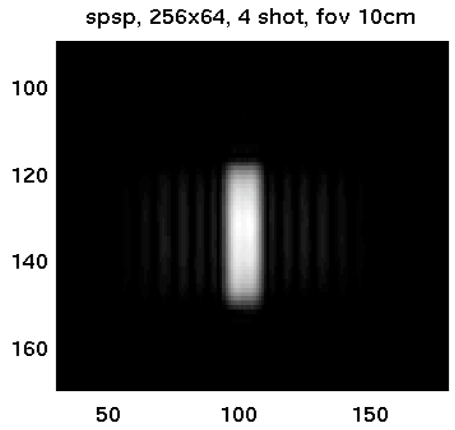


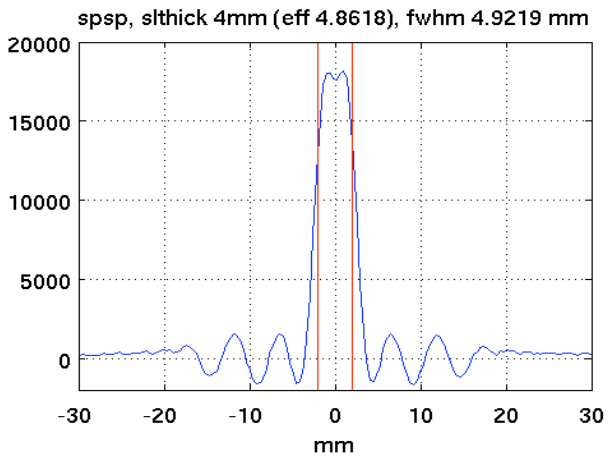
Bryon Mueller
(UMinn)

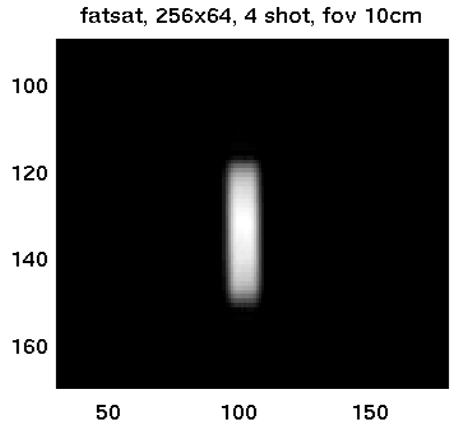
Measured Slice Profile

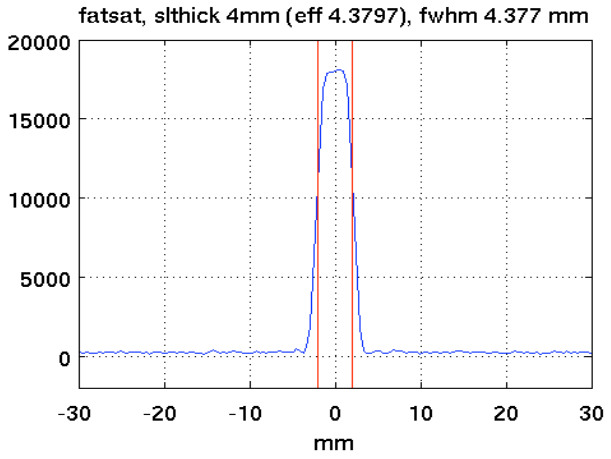
spectral-spatial

fat sat





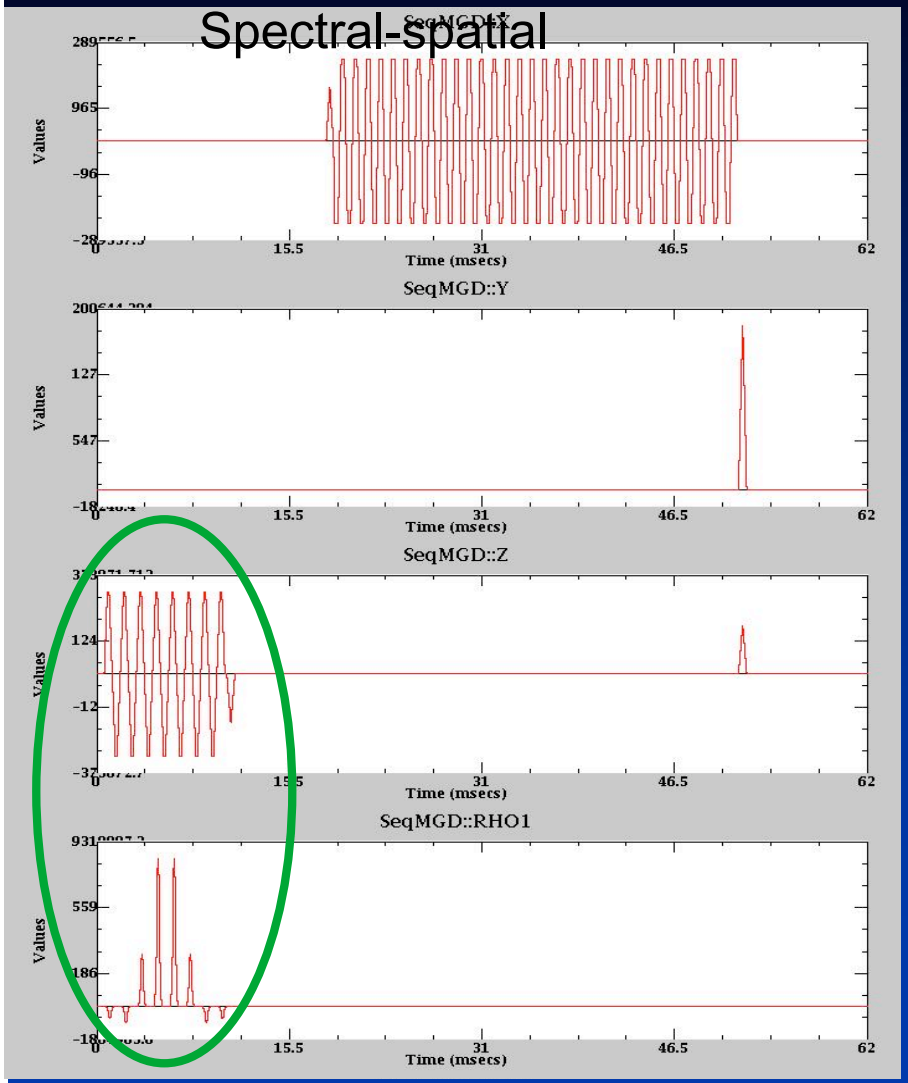




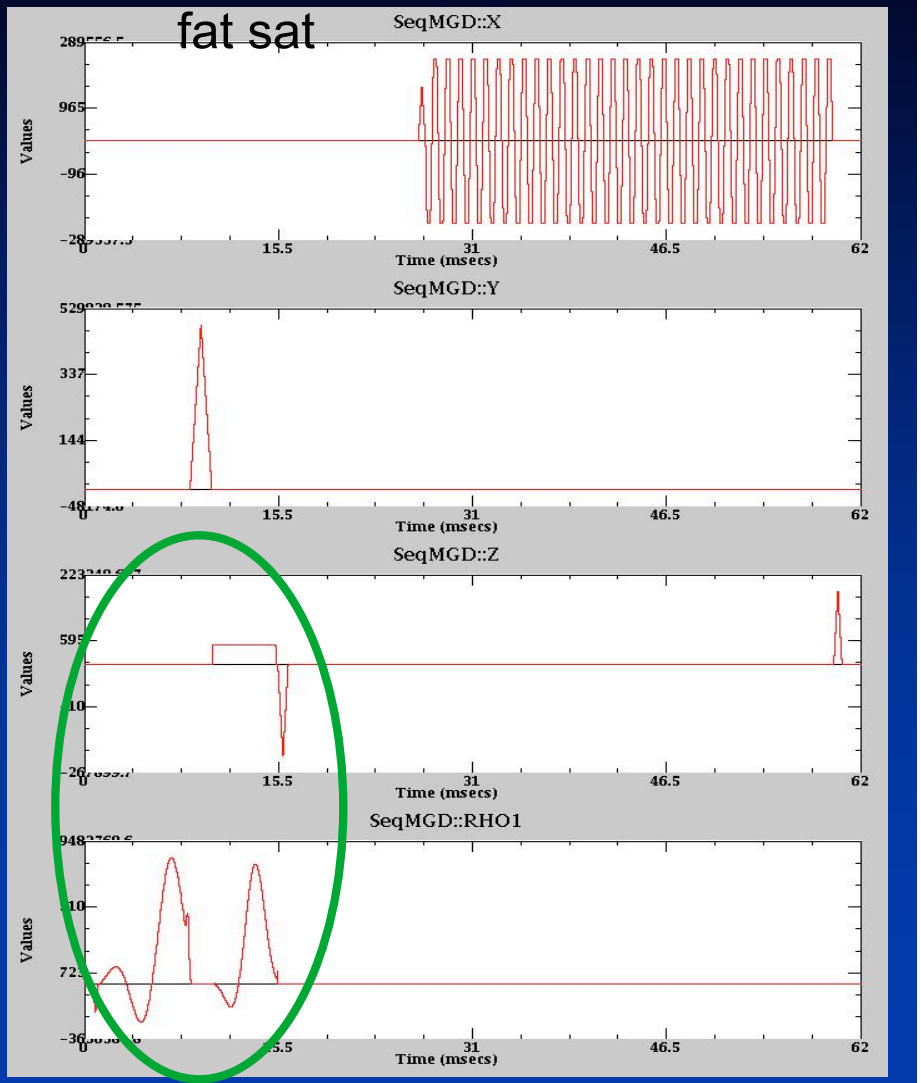
Kun Lu, Tom Liu (UCSD)

Slice select

Spectral-spatial



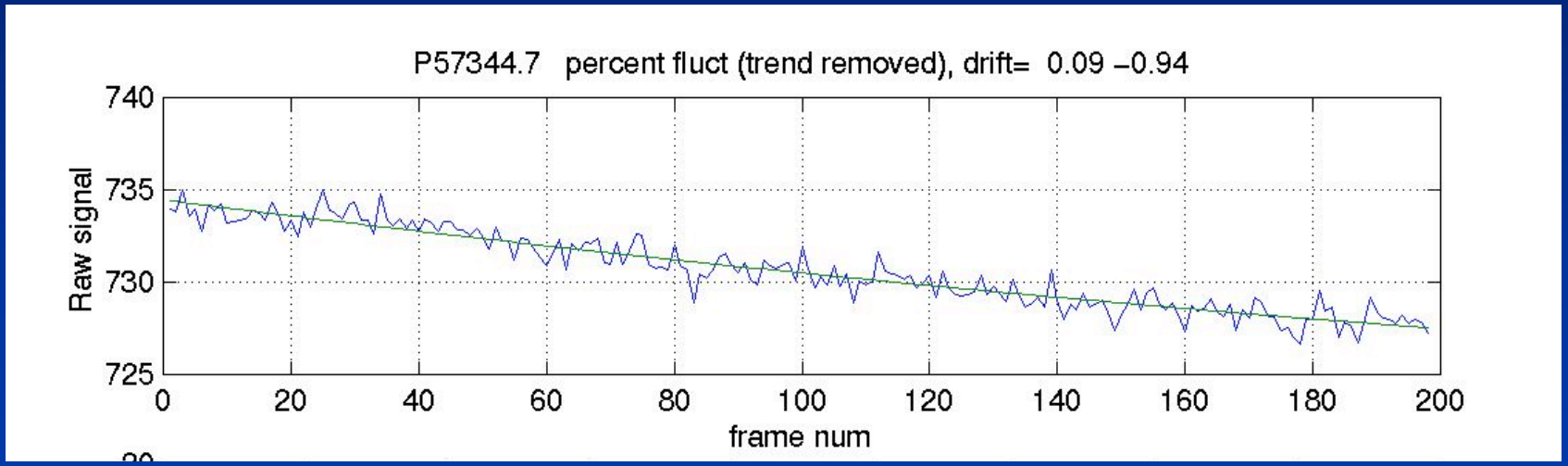
fat sat



Important MRI Characteristics

- **Dynamic image stability**

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



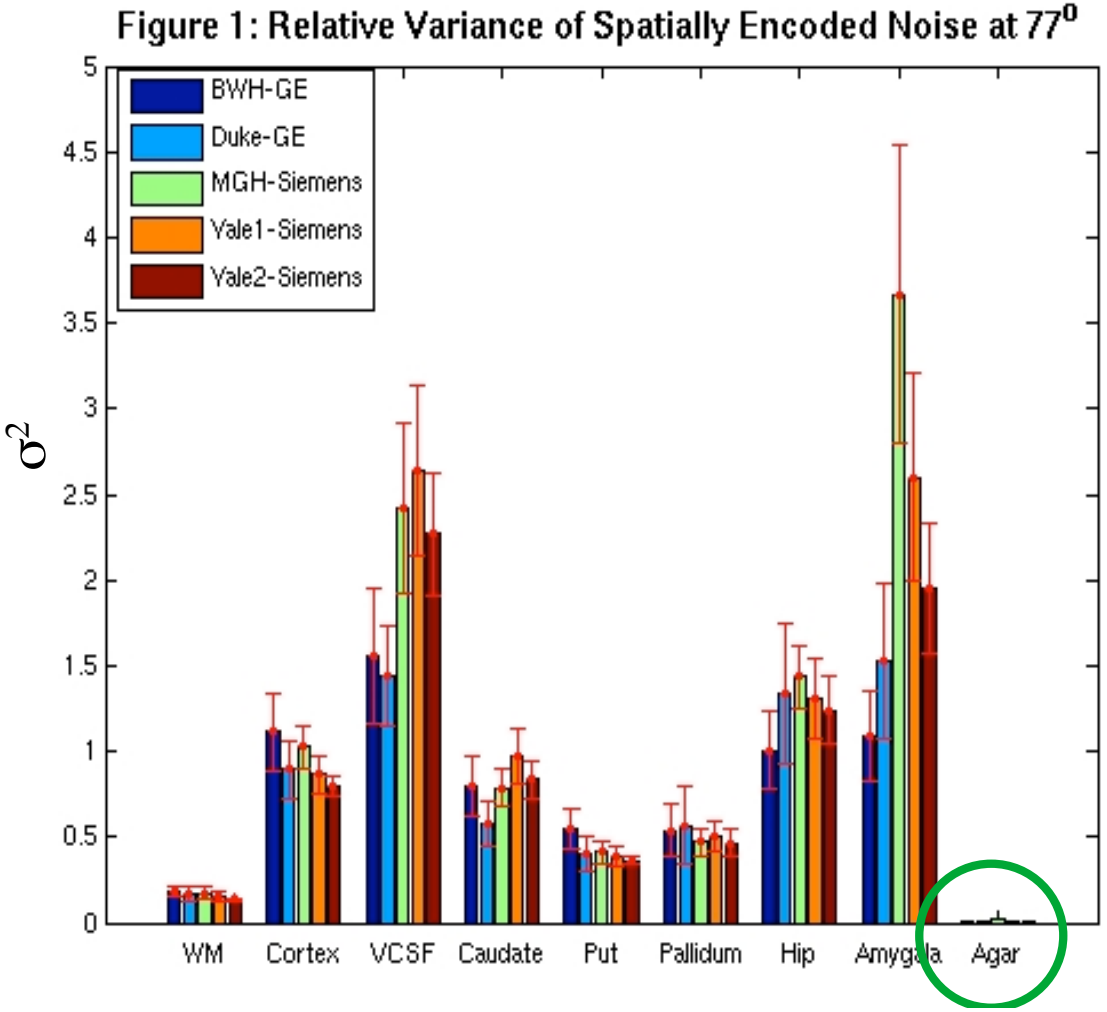
Brain noise relative to thermal noise: to set acceptance criteria

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

G. Krueger (MRM 2000)

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

D. Greve (MGH, ISMRM 2008)



Issues in multicenter studies

- Standardization of protocols
- QA
- Site Equalization

QA: What to measure?

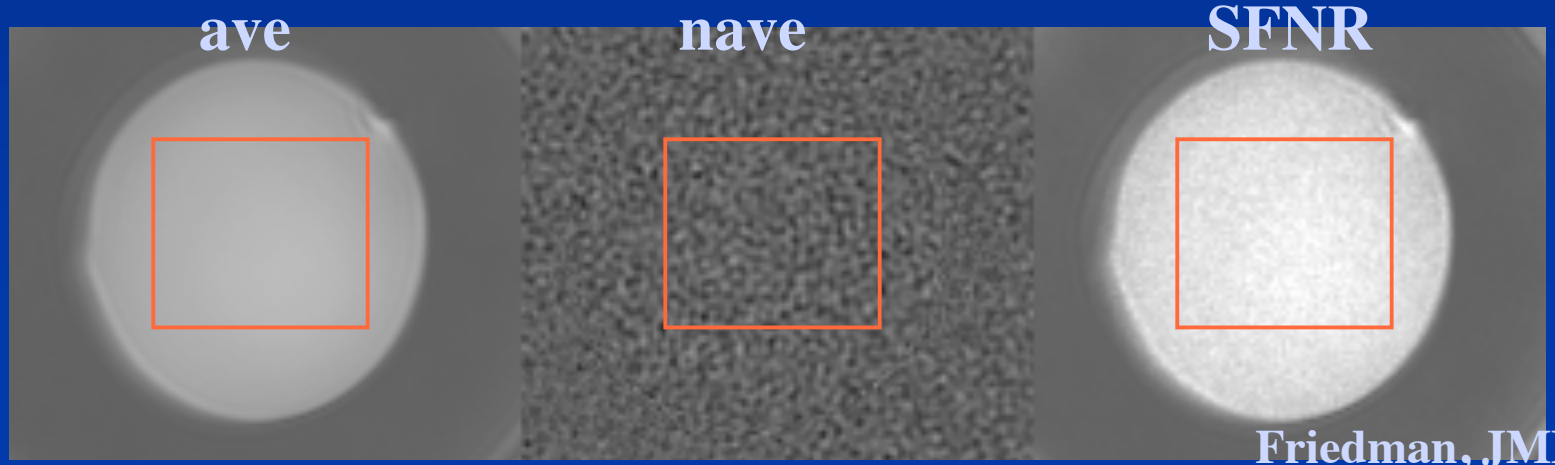
- Time series image stability
- Signal to noise ratio
- Signal intensity
- Xmtr/Rcvr Gains
- MRS characteristics
- Eddy currents
- Geometric accuracy

SNR, SFNR

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

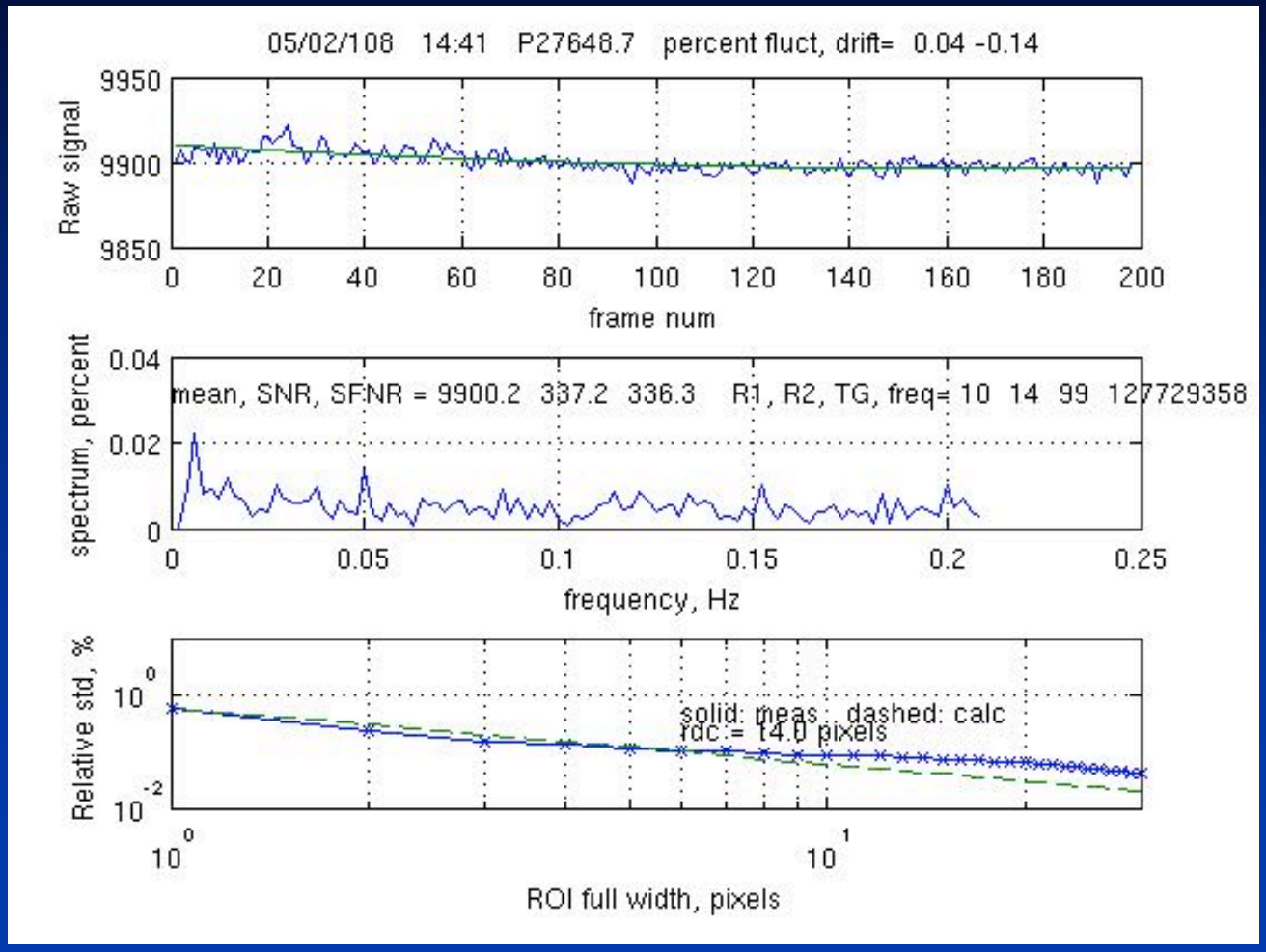
$$I_{ave} = \frac{1}{2}(I_{even} + I_{odd}) \qquad I_{nave} = \frac{1}{2}(I_{even} - I_{odd})$$

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



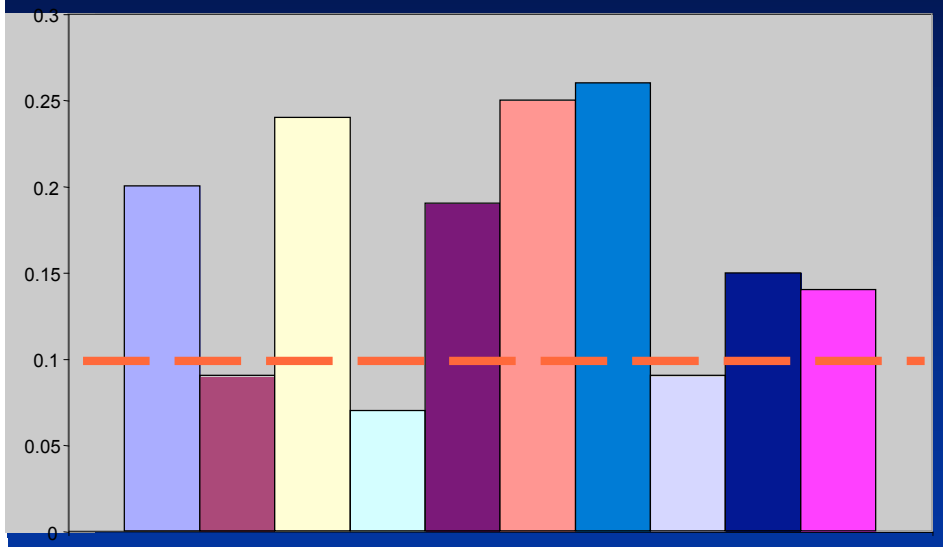
Friedman, JMRI 2006

Stability

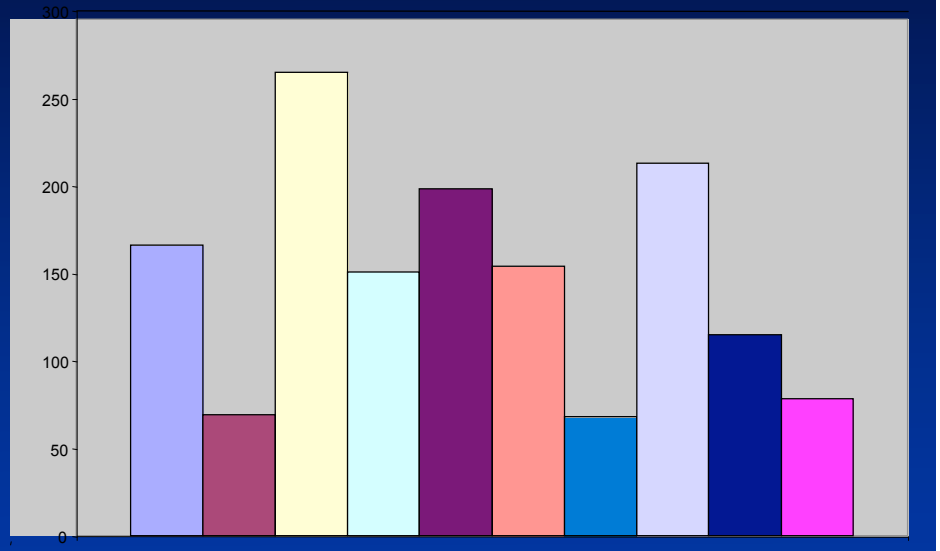

05/02/108 14:41 P27648.7 percent fluct, drift= 0.04 -0.14
Raw signal
9950
9900
9850
0 20 40 60 80 100 120 140 160 180 200
frame num
spectrum, percent
0.04
0.02
0
mean, SNR, SFNR = 9900.2 337.2 336.3 R1, R2, TG, freq= 10 14 99 127729358
0 0.05 0.1 0.15 0.2 0.25
frequency, Hz
Relative std, %
10^0
10^-2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

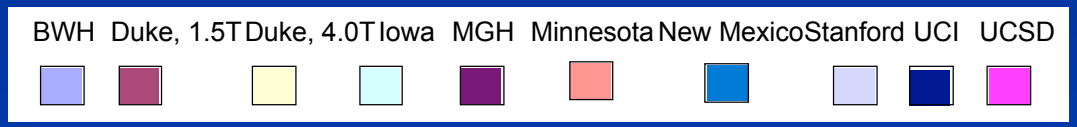
Site differences

RMS instability, %

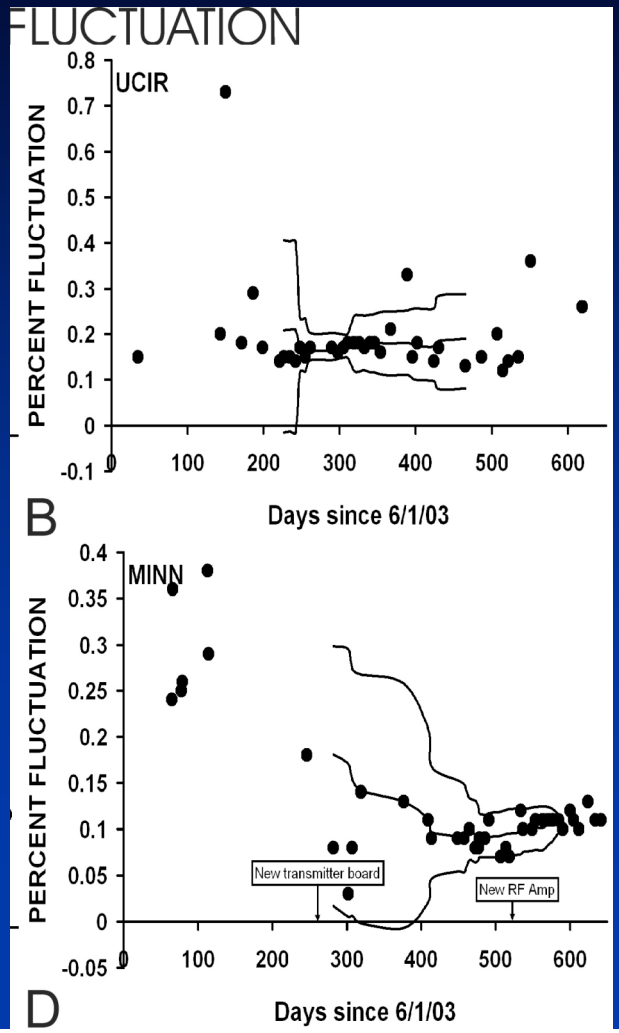


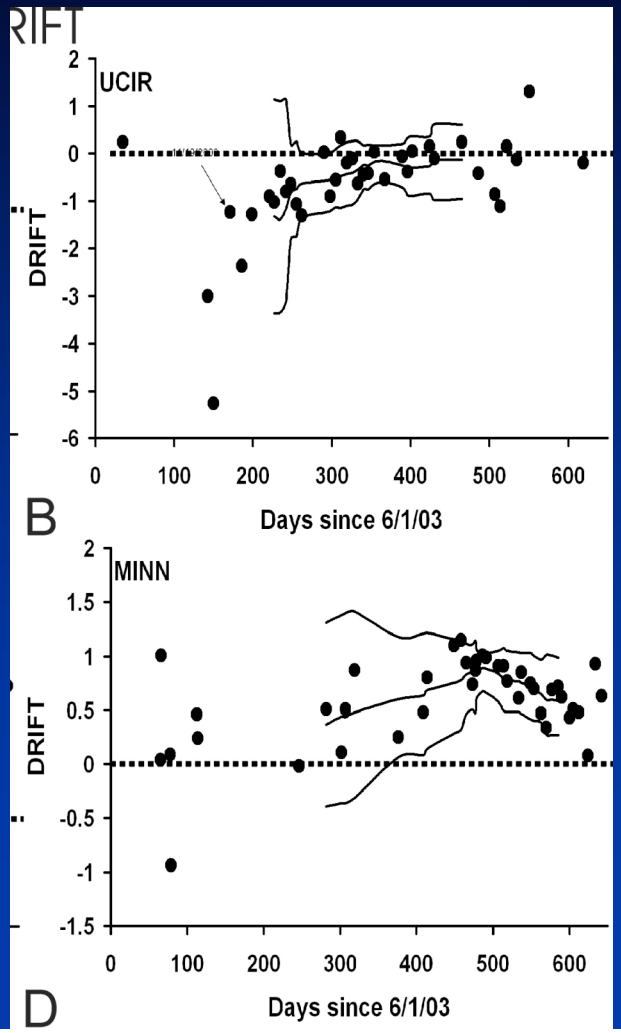
SFNR





QA helped to bring scanners into spec



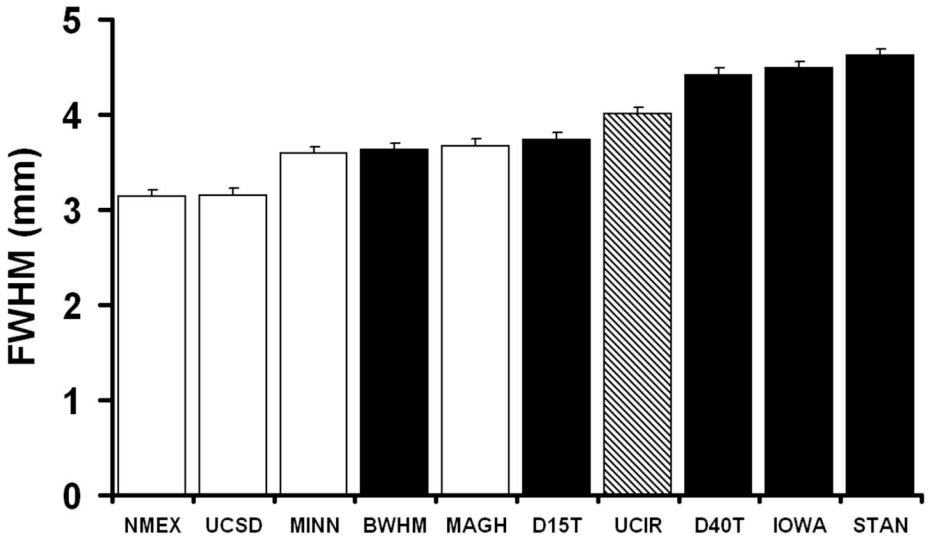


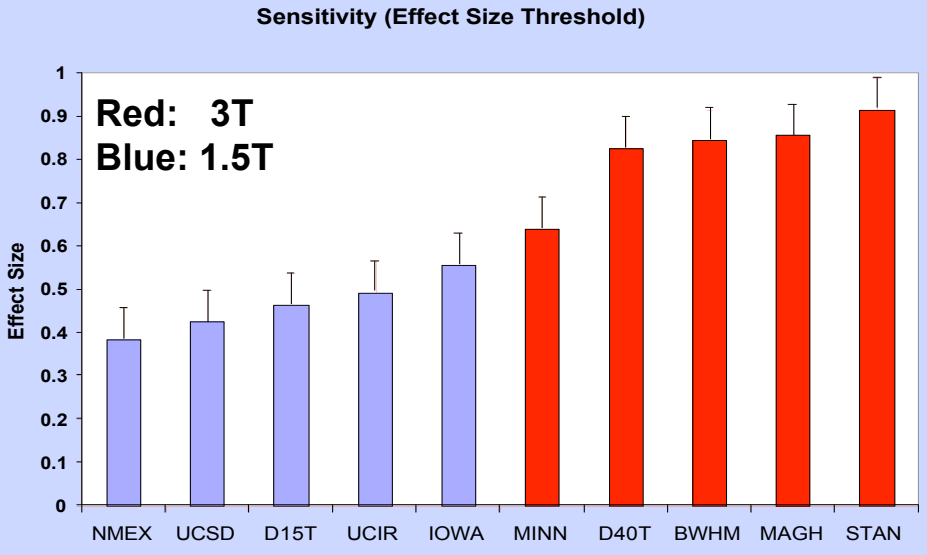
Friedman, JMRI 2006

Issues in multicenter studies

- Standardization of protocols
- QA
- Site Equalization
  - smoothness compensation
  - SFNR compensation

Smoothness/BOLD Differences

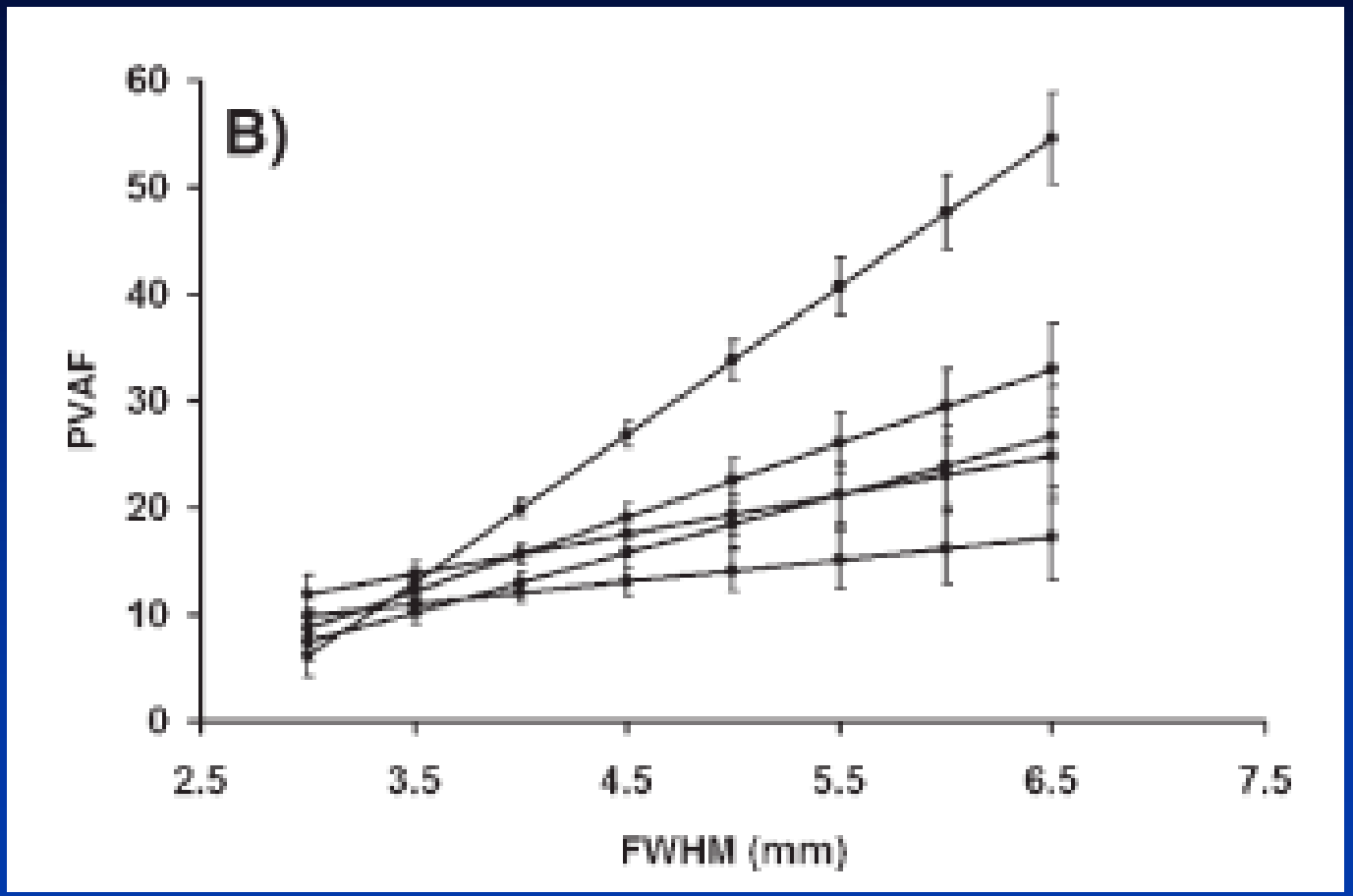




Friedman, et al. 2006

Sensitivity vs. Smoothness

5 traveling subjects at 10 sites performing sensorimotor task



Friedman, et al. 2006

Smoothness equalization

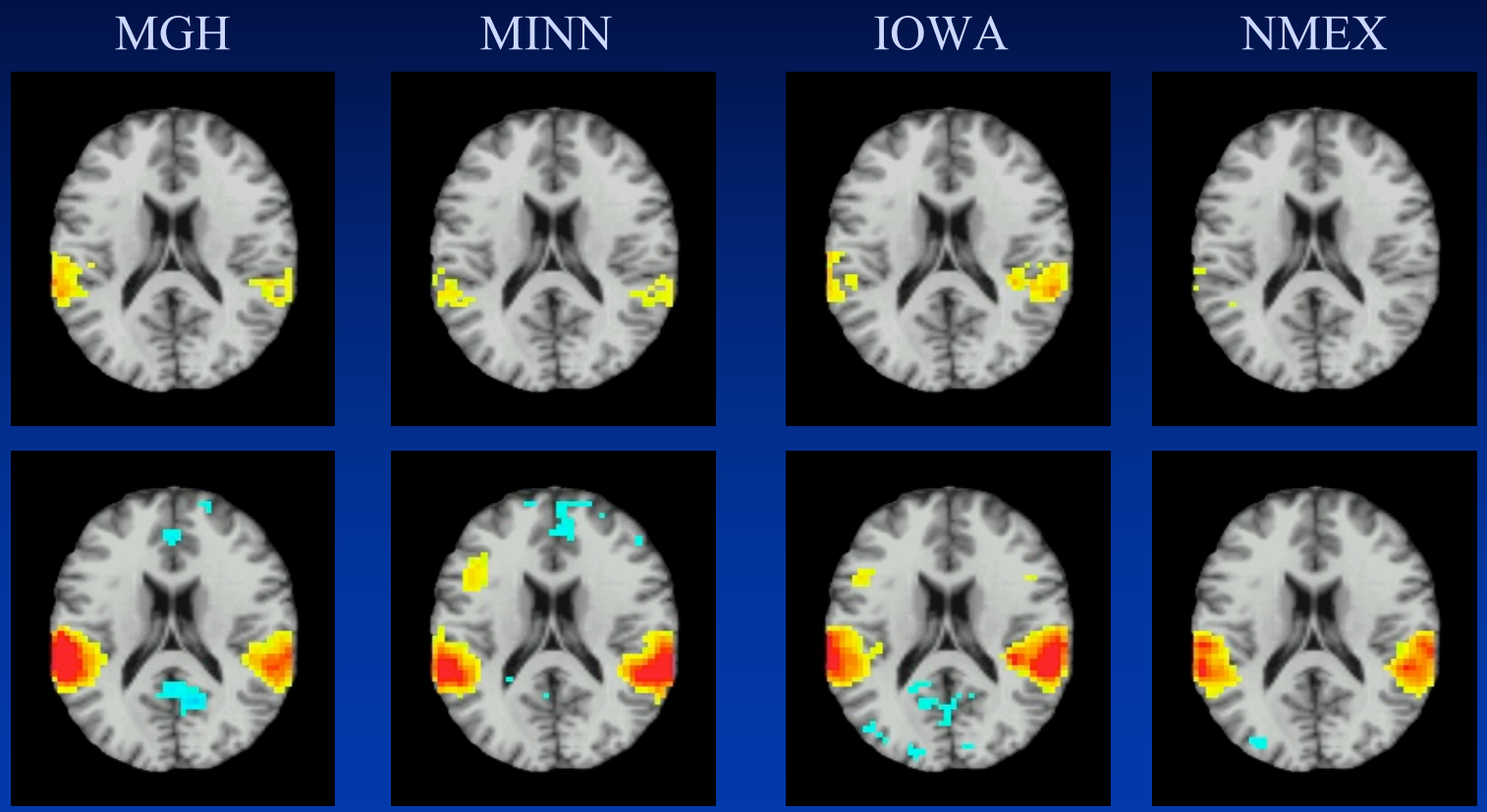
- In first-level analysis: Use "smooth to" instead of "smooth by"
- Smooth each site to largest FWHM using Gaussian filter

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

e.g., AFNI program (thanks to R. Cox)

Friedman, et al. 2006

BOLD Sensitivity: Oddball Task



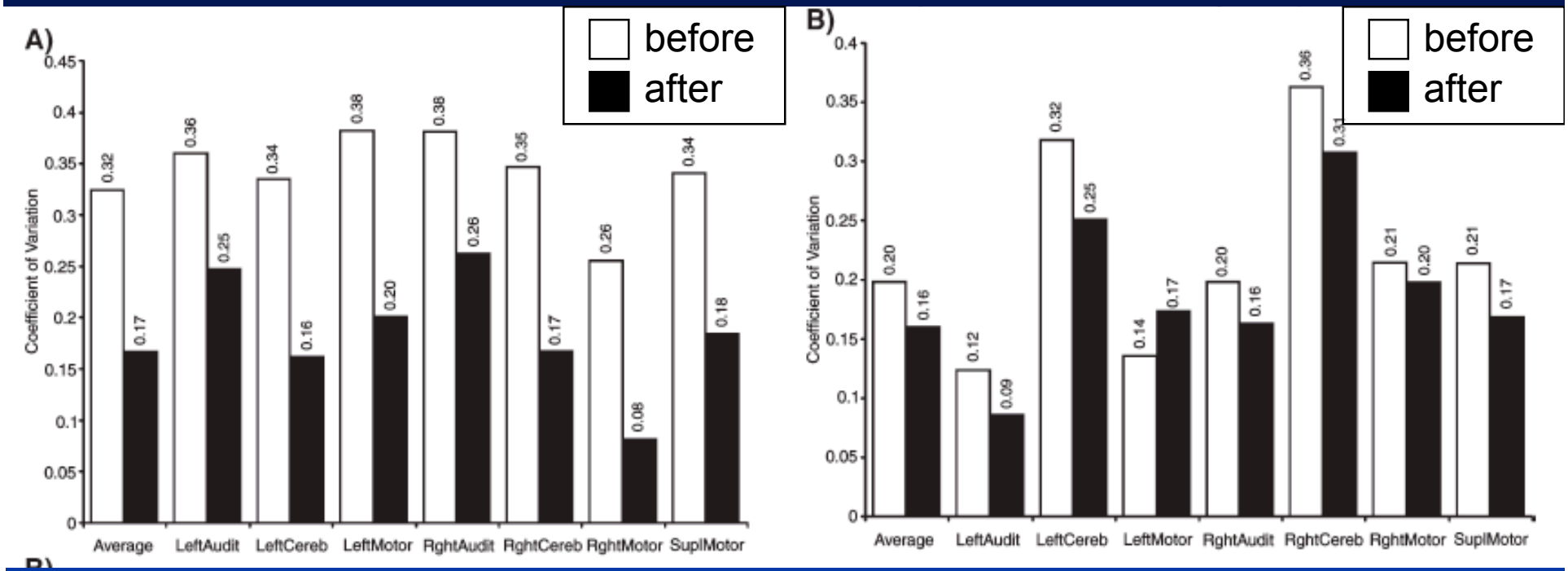
Novel Tones - Effect Size

Friedman, et al.

Intersite CV

1.5T

3T



Friedman, et al. 2006

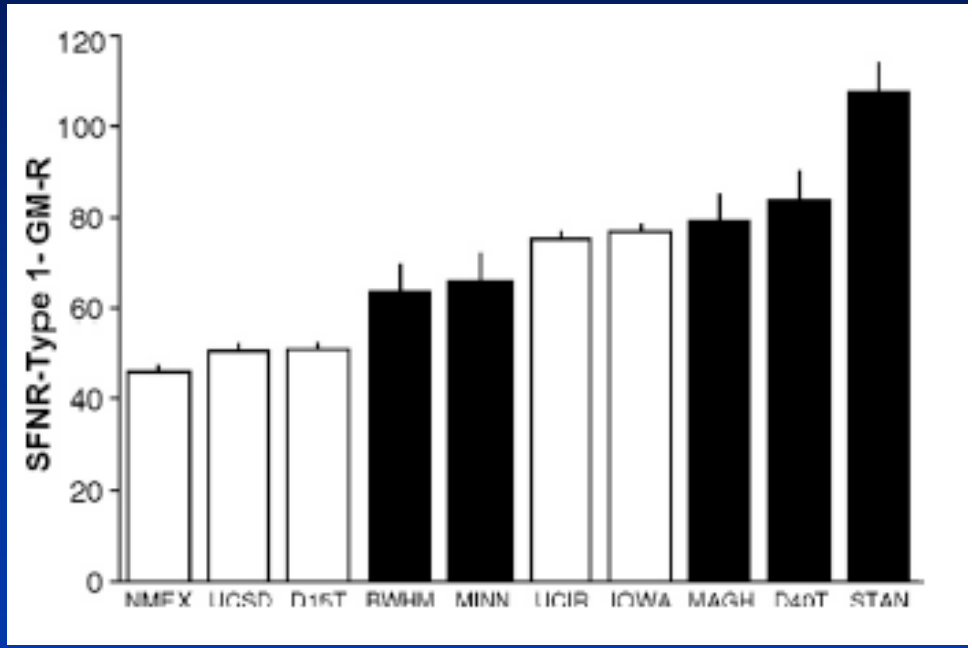
fMRI equalization across sites

- Compensation for smoothness
- Compensation by SFNR

fMRI equalization by SFNR

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

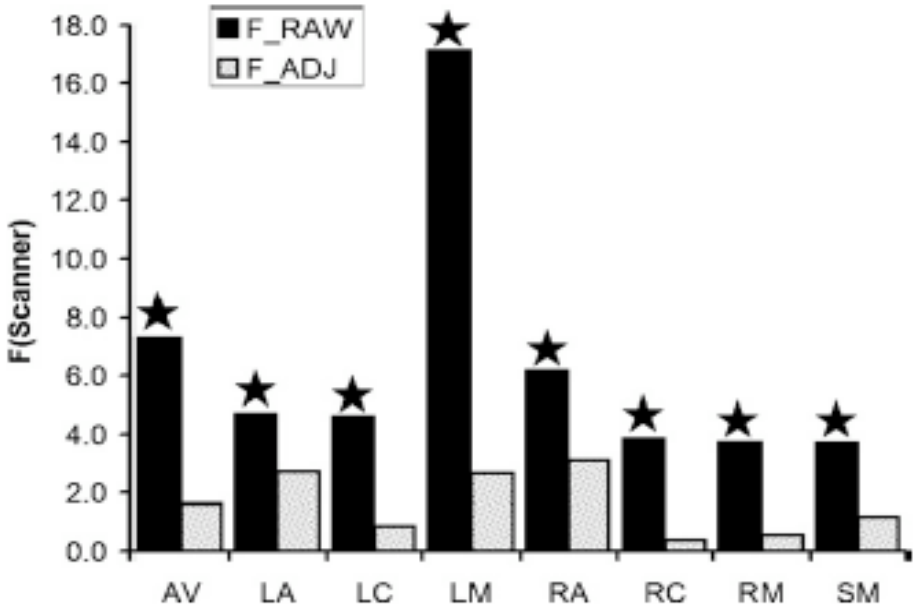
Original SFNR



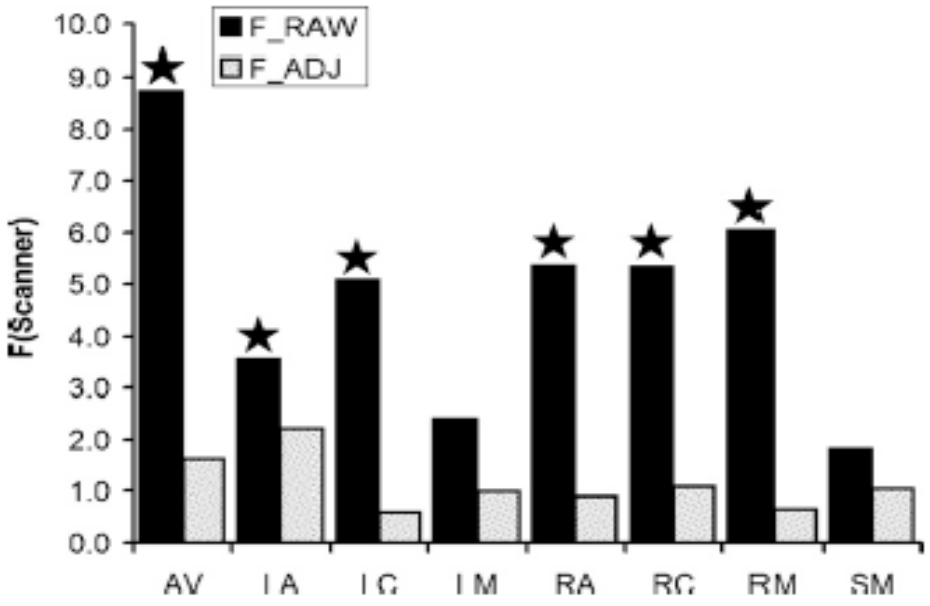
Friedman,
et al. 2006

Site equalization by SFNR

1.5T



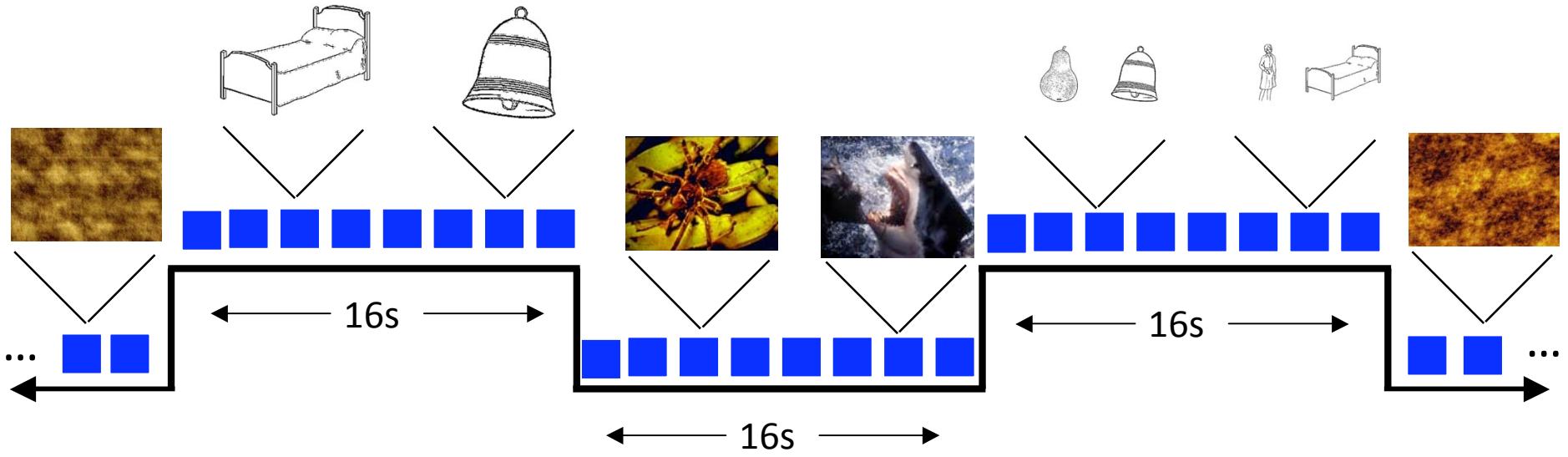
3T



Friedman, et al. 2006

fBIRN Emotional Working Memory Task:

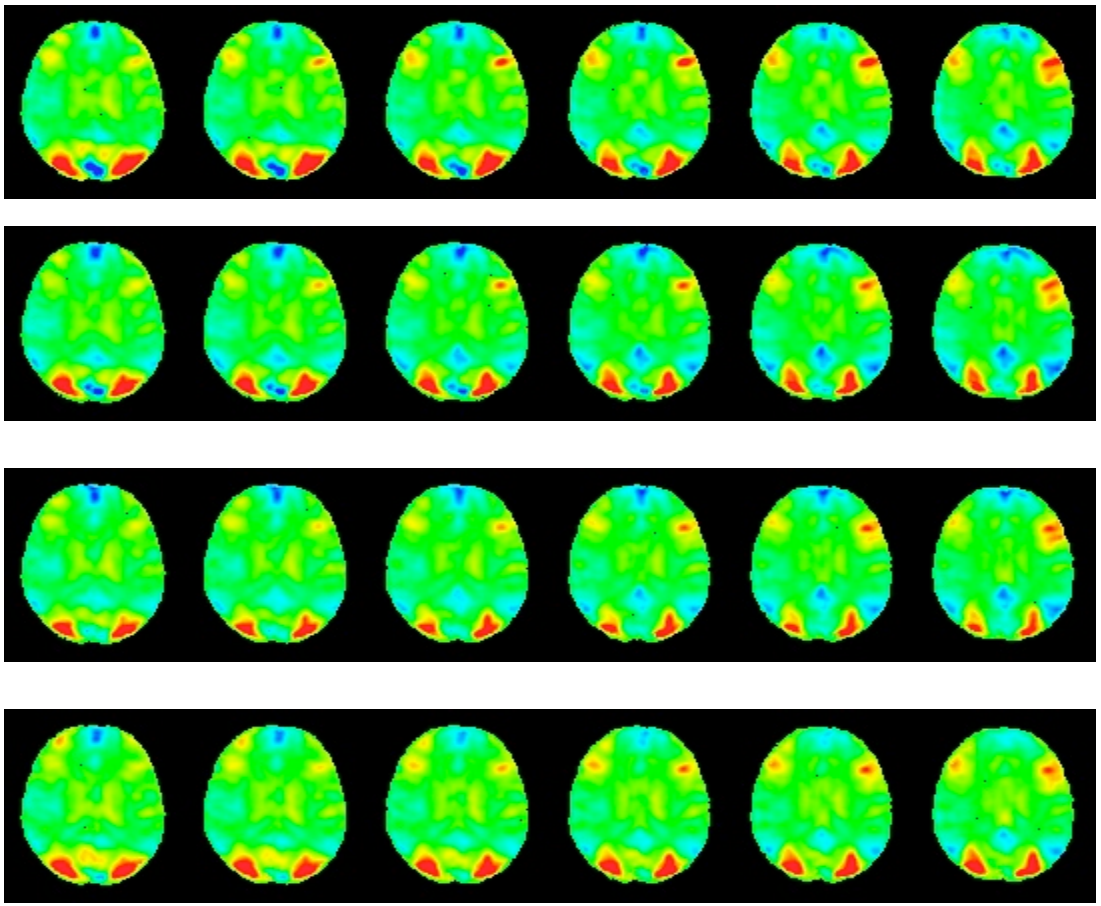
Emotional Distraction



Eight pictures presented during the encode period.

Eight picture pairs presented during the forced choice period.

Mean of Contrast 1 at Four Study Sites



0003

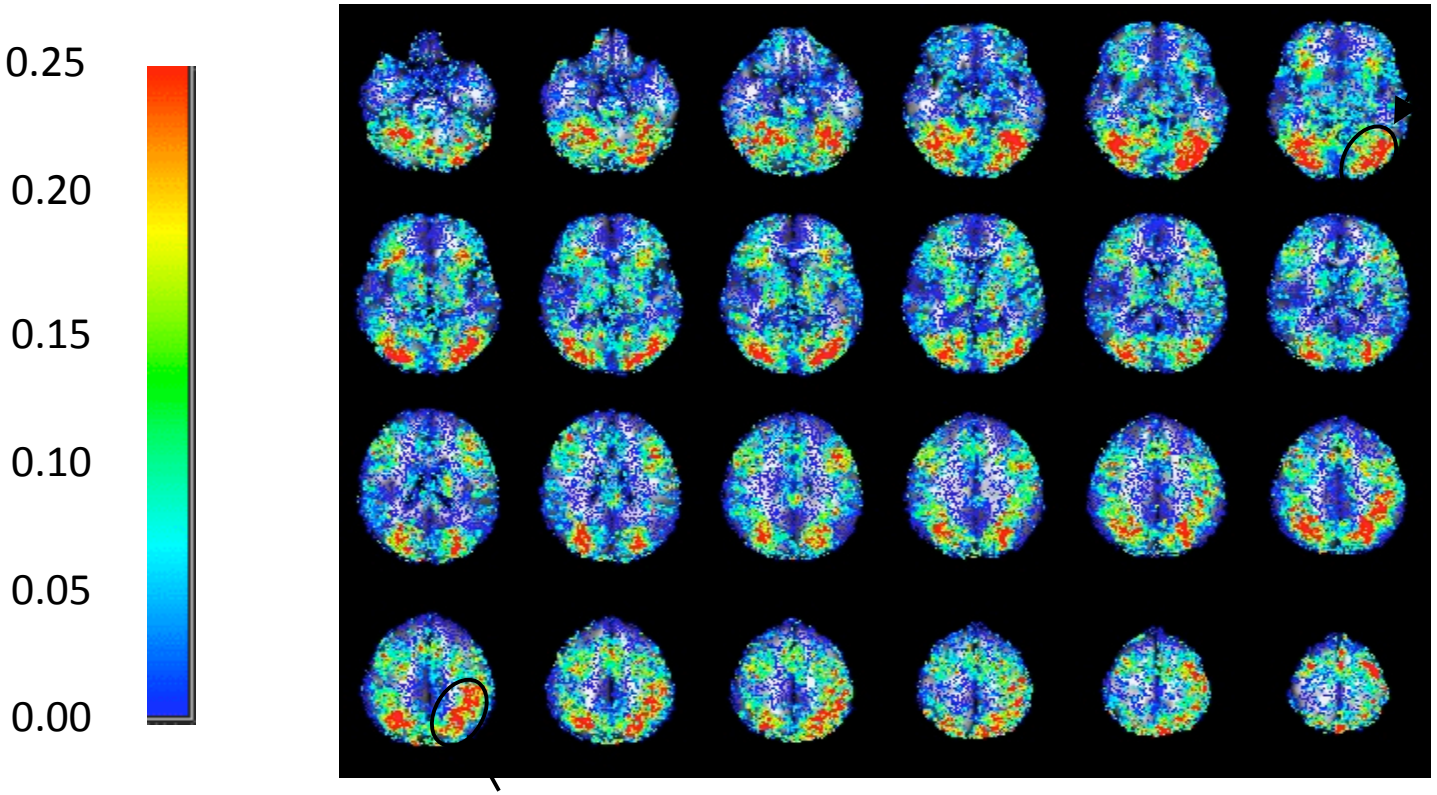
0005

0006

0018

G. Brown, et al.

ICC Unadjusted Minus ICC w/BH Calib: Site effects



Functional Contrast 1

G. Brown, et al.

Multisite Studies- items not discussed

- Task design
- Ancillary hardware: projection, sound, button box, physiological, bite bar/stabilization
- Acquisition script
- Data integrity:
  - QA of all scan data
  - automated upload of scan and meta data
  - automated analysis pipeline
- Employ a traveling site coordinator/scannee

Summary

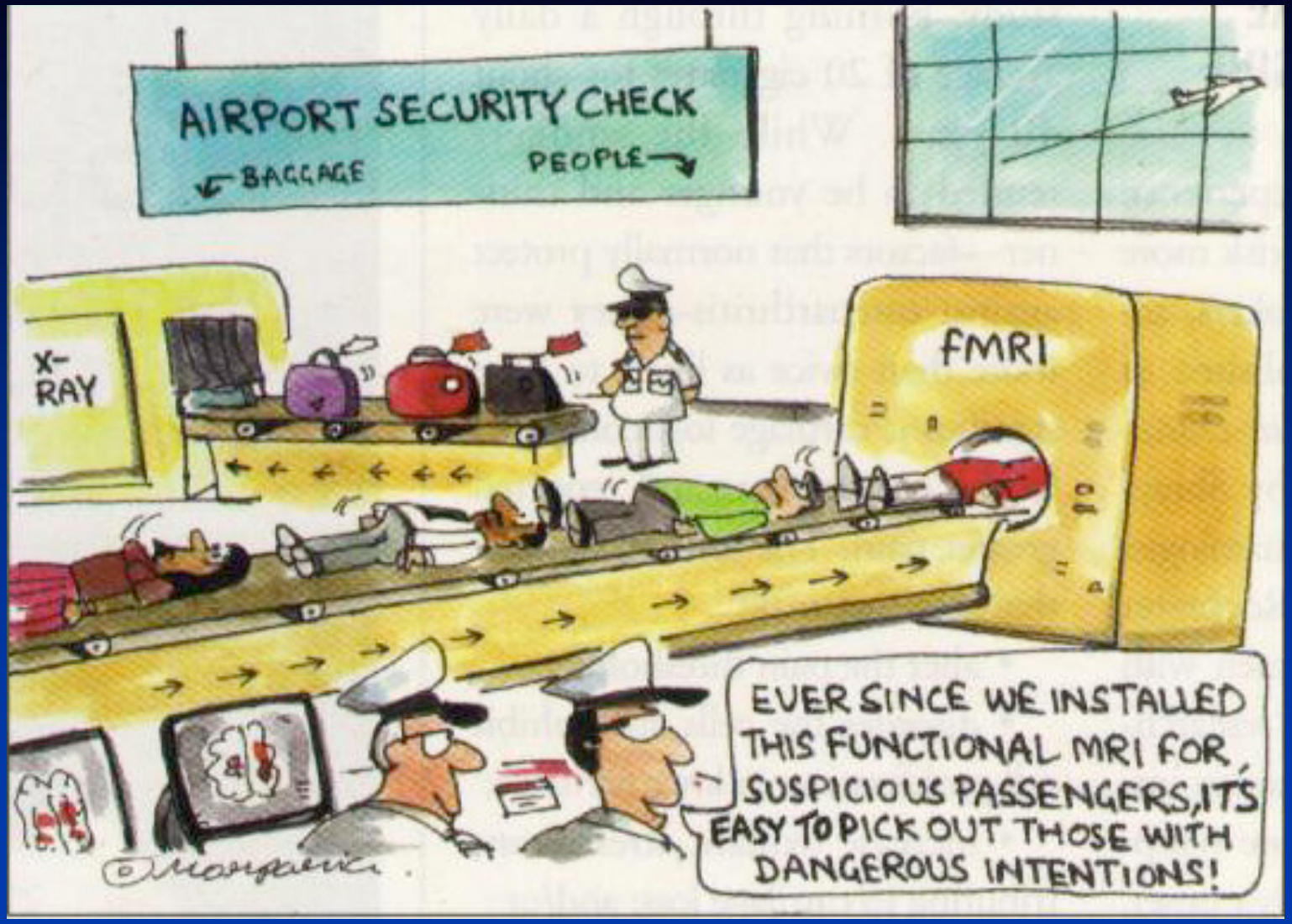
BOLD contrast confounded by

- **inter-subject, inter-regional variations in hemodynamic response amplitude/latency**
  - **use hypercapnic calibration (e.g. BH) or ASL to reduce vasoreactivity 'gain factor' variance**
- **respiratory- and cardiovascular-induced BOLD signal changes**
  - **use RETROICOR and RVHRCOR (must measure card. and resp. functions)**
- **site differences in stability, SNR, pulse sequence, parameters, study administration**

Summary

- Reduction of these confounds can improve confidence in activation maps
- Calibration important in group comparisons, longitudinal studies
- QA, standardization, calibration crucial in multicenter studies

fMRI: Many biomarker applications



Acknowledgements:

fBIRN Calibration Working Group

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

My kids

Catie Chang
Lara Foland
Jason Hsu
Christine Law
David Ress
Moriah Thomason
Caires

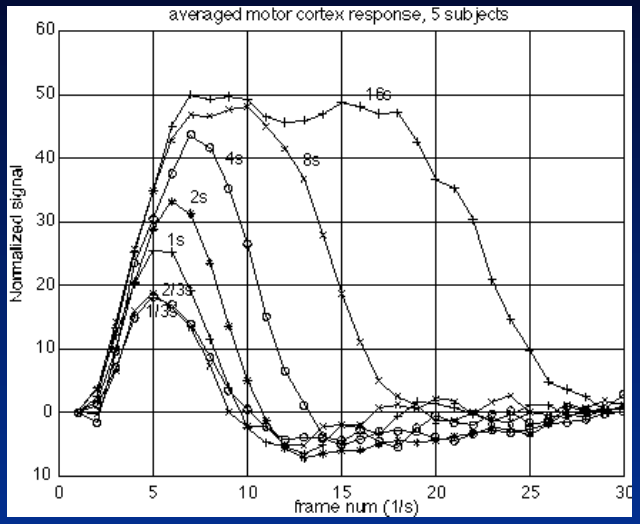
National Center for Research Resources

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

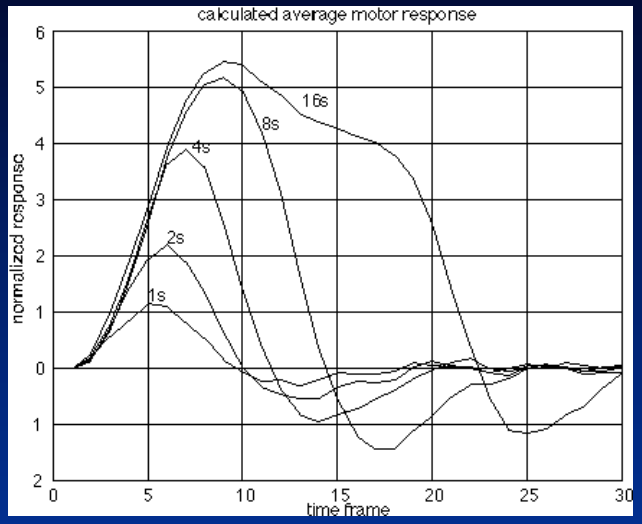
Firenza

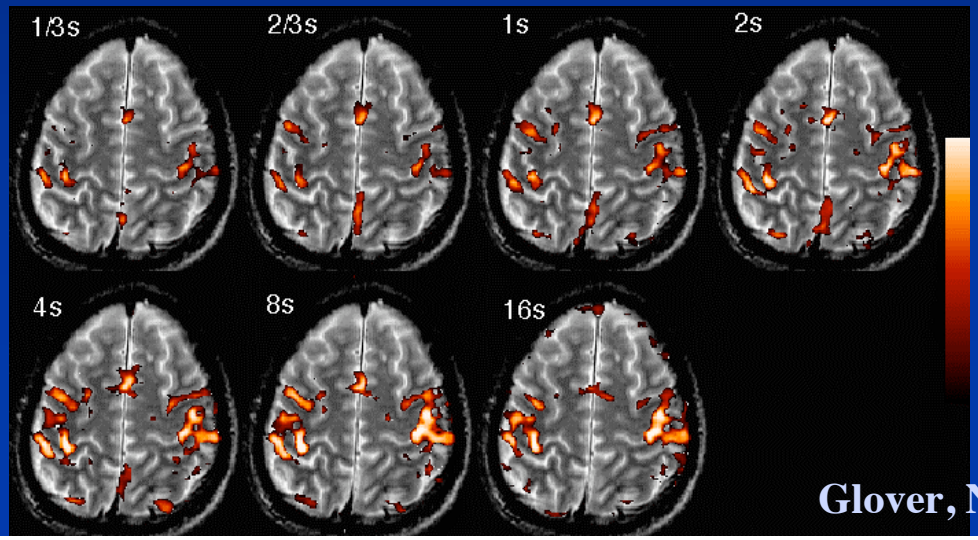
Nonlinearities- Motor

Measured- average of 5 subjects



Calculated using h(t)*rect(T)



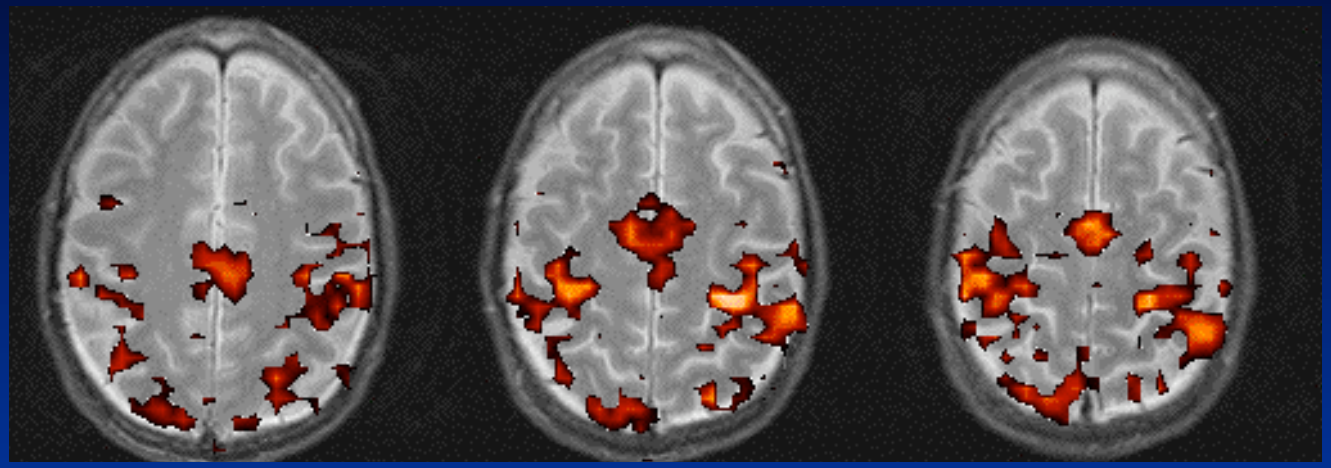


Finger tapping at 3Hz: 1/3s, 2/3s, 1s, 2s, 4s, 8s, 16s

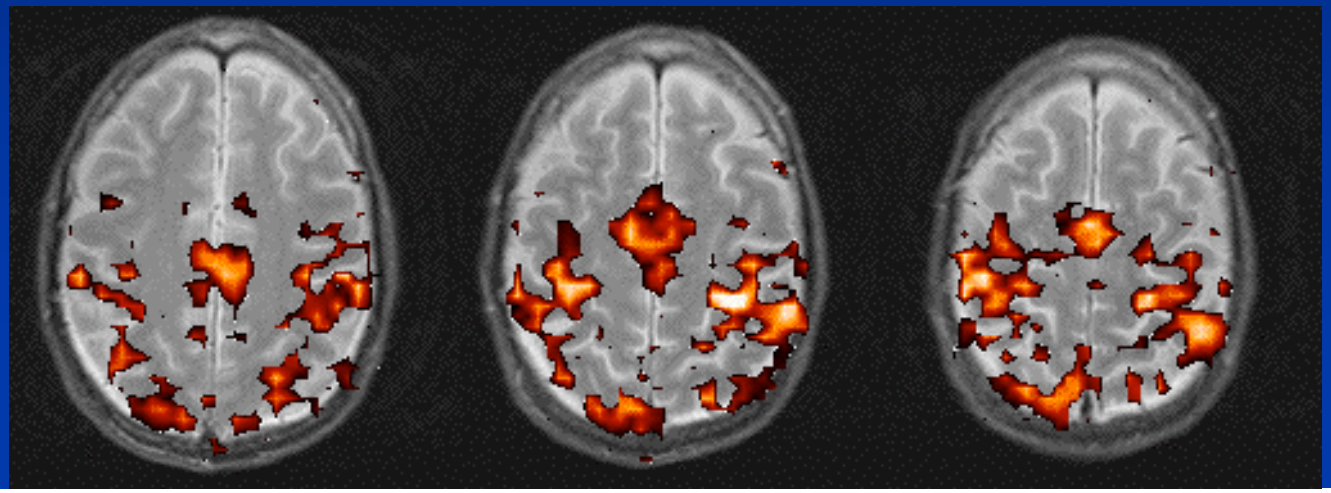
Glover, NeuroImage 9:416 (1999)

Effect of HRF on Activation

Linear HRF



Nonlinear HRF



BH Calibration Method

- Use BH task (non-neuronal, no change in CMRO2) to normalize cognitive task
- Reduces signal change related to vasoreactivity
- Should reduce inter-subject variance