

# A closer look at fMRI

## dynamics, fluctuations, and patterns

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1991

Neuronal Activation



Measured Signal

?

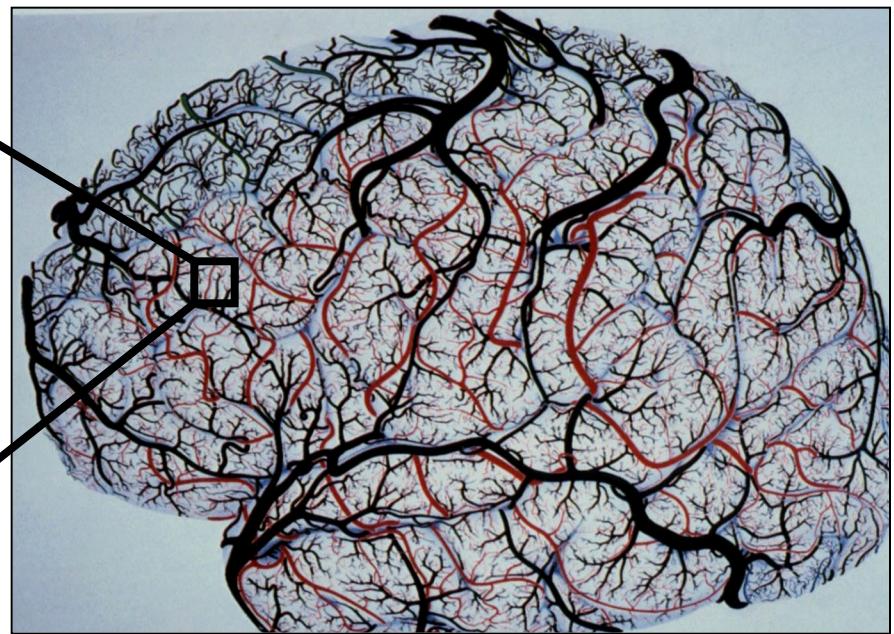
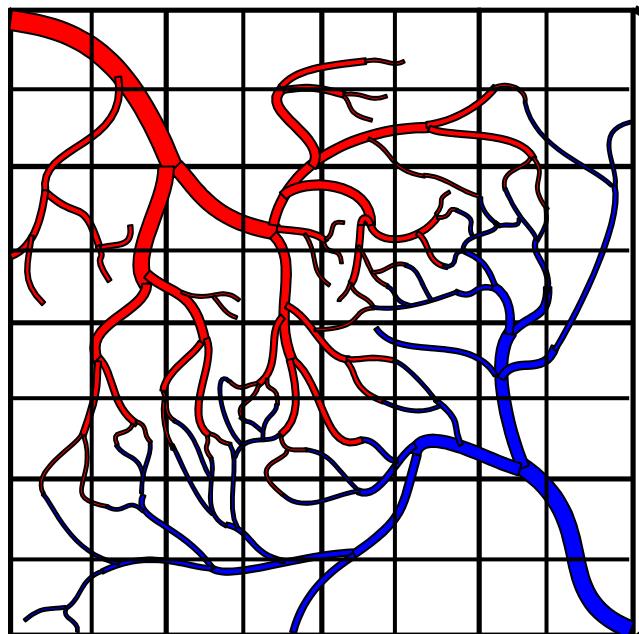
?

Hemodynamics

?

?

Noise



1. Dynamics

2. Fluctuations

3. Experimental Design

4. Pattern Information

5. Neuronal Current MRI

# 1. Dynamics

## Motivation:

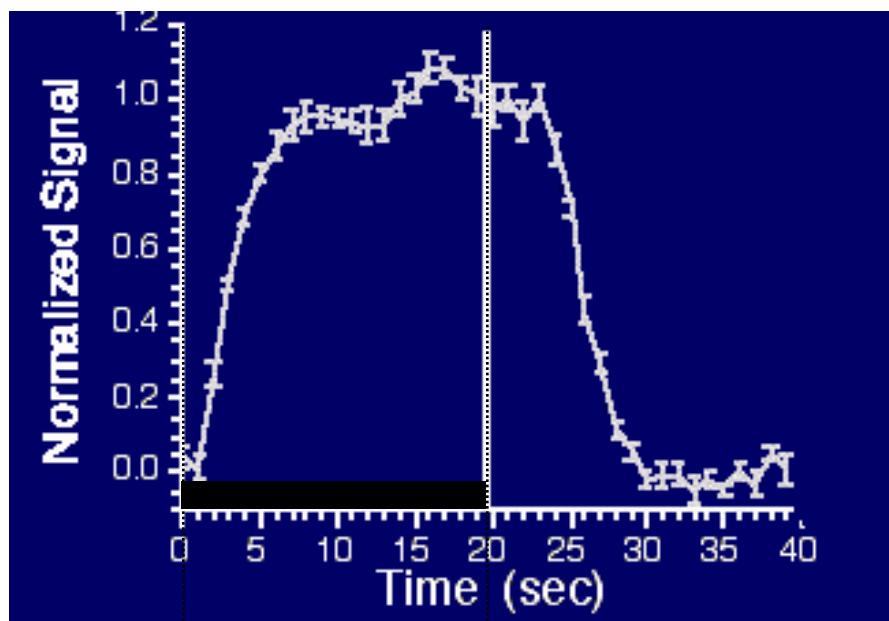
- To understand the neuronal and non-neuronal influences on the fMRI signal.

## Studies:

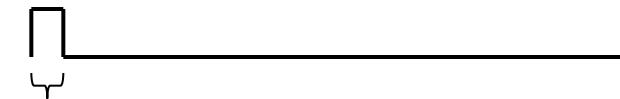
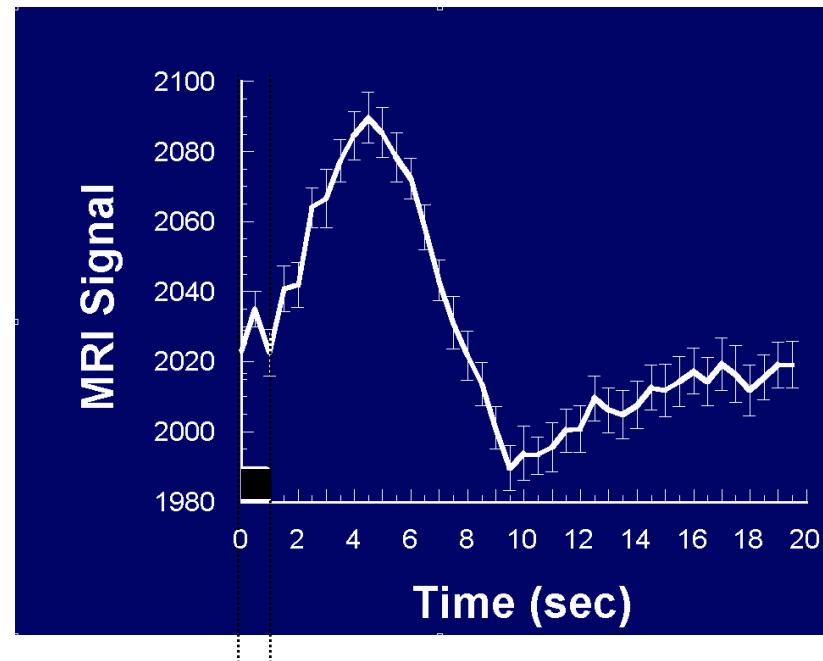
- Modulate timing: "on" duration, "off" duration, and duty cycle of visual cortex activation.
- Neuronal and Hemodynamic Modeling.
- MEG and fMRI Comparison.

# The BOLD Signal

Blood Oxygenation Level Dependent (BOLD) signal changes

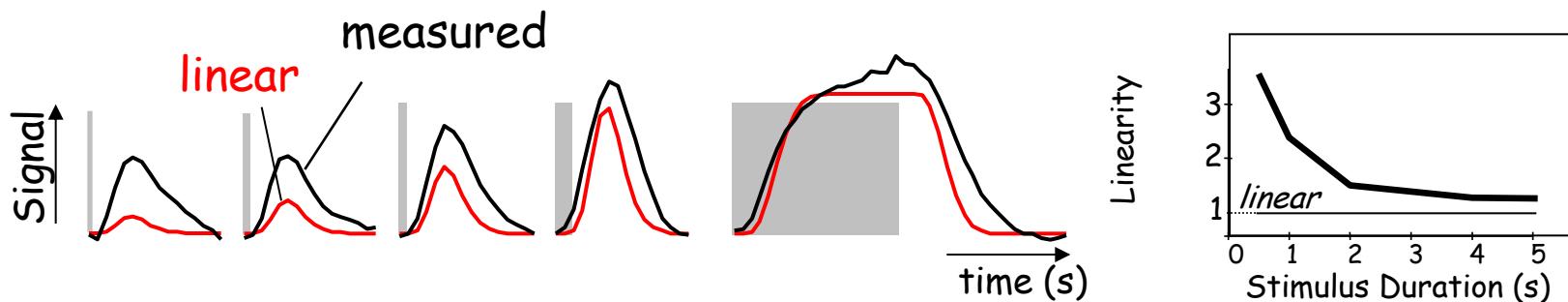


*task*



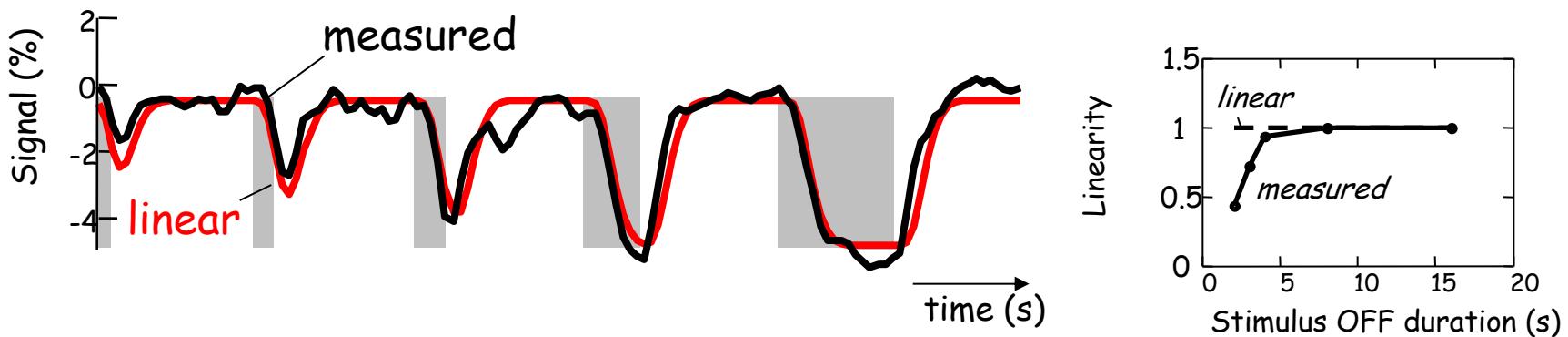
*task*

Brief "on" periods produce **larger** increases than expected.



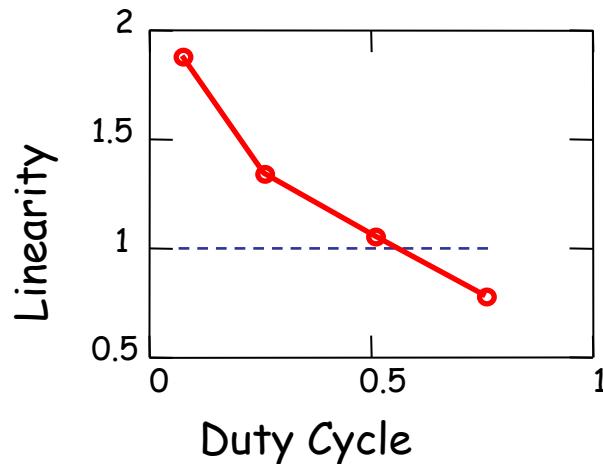
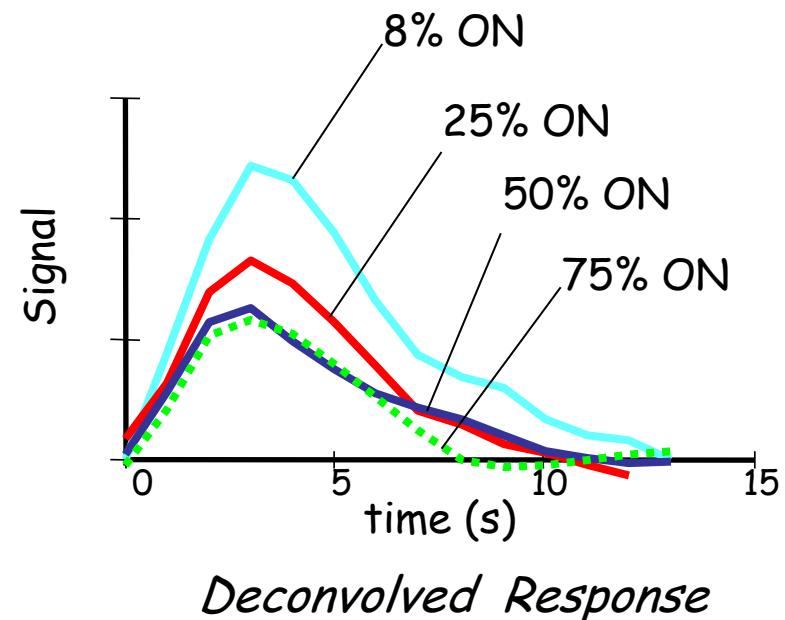
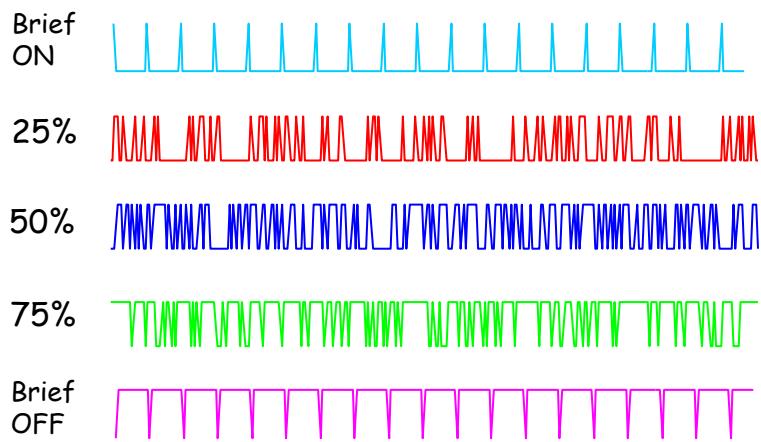
R. M. Birn, Z. Saad, P. A. Bandettini, NeuroImage, 14: 817-826, (2001)

Brief "off" periods produce **smaller** decreases than expected.

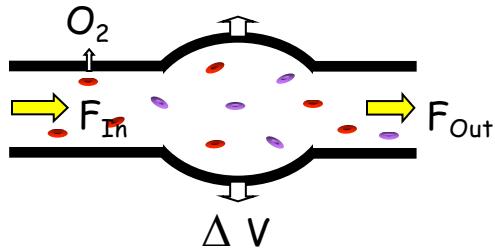


R.M. Birn, P. A. Bandettini, NeuroImage, 27, 70-82 (2005)

# Varying the Duty Cycle

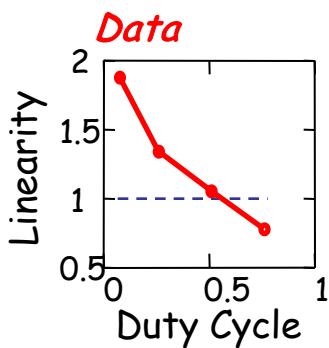
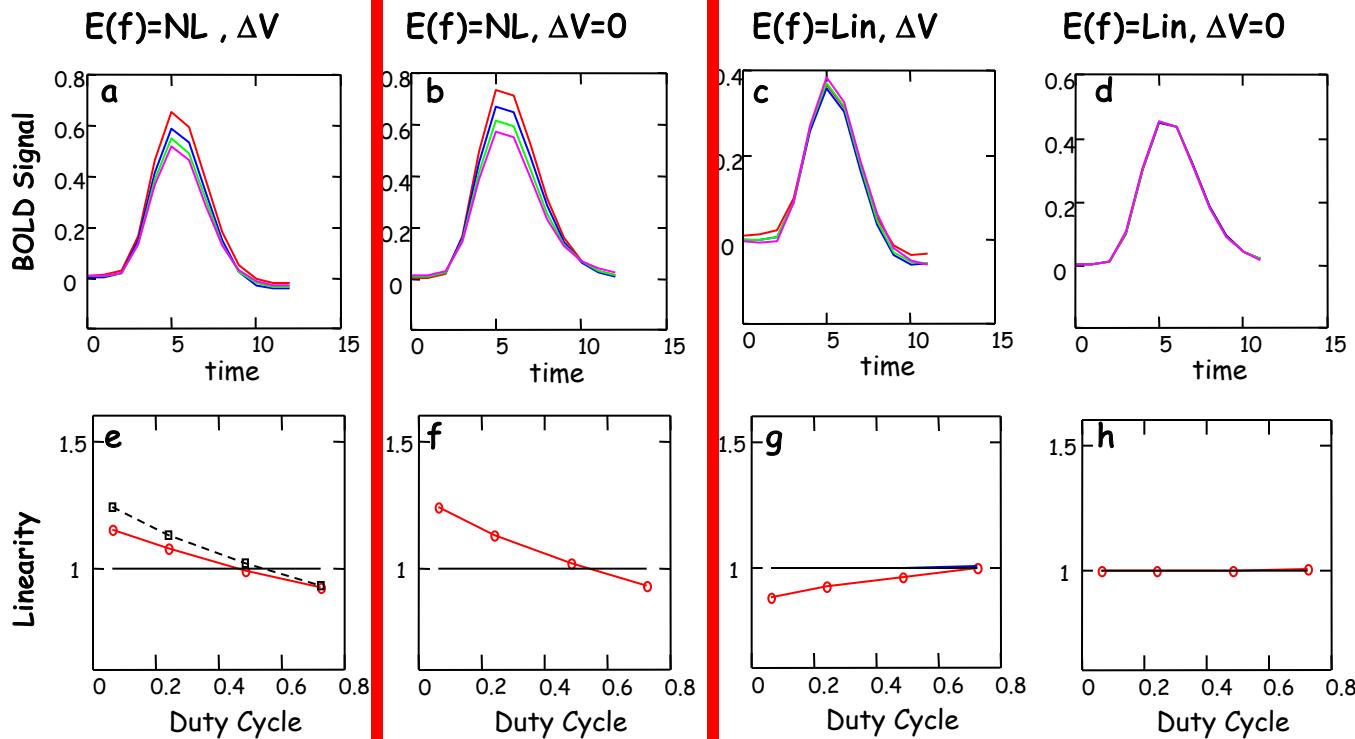
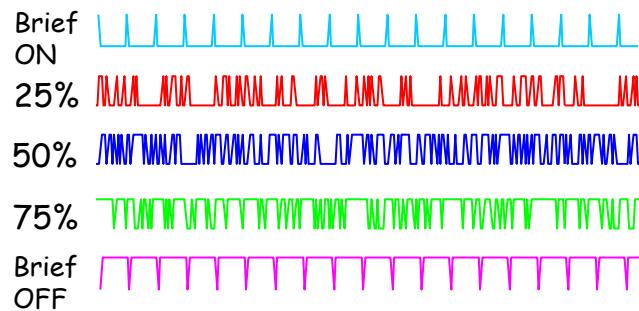


# Simulation of Hemodynamic Mechanisms (Balloon model)

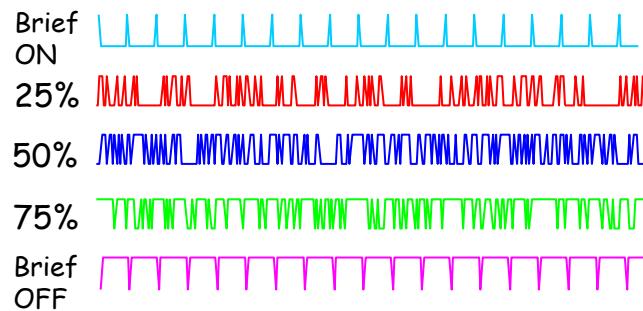
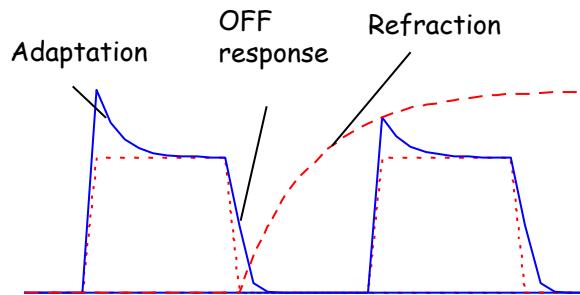


$E(f)$  = oxygen extraction fraction

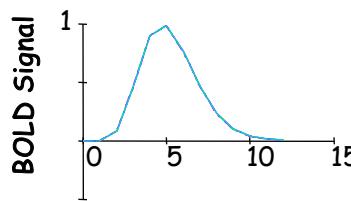
$V$  = blood volume



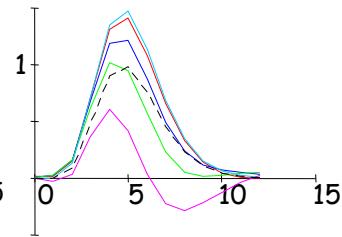
# Simulation of Neuronal Mechanisms



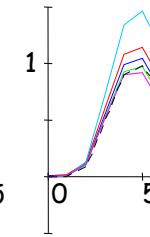
Linear



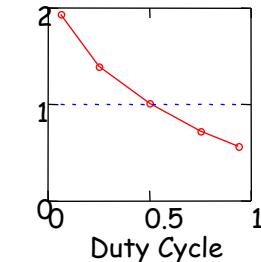
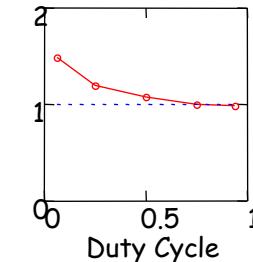
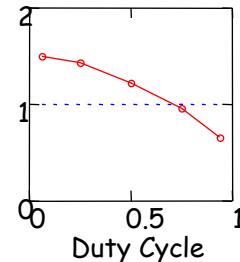
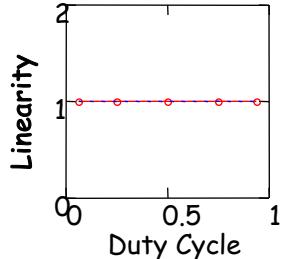
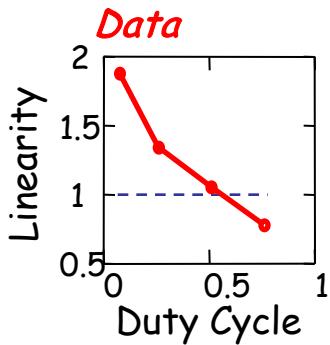
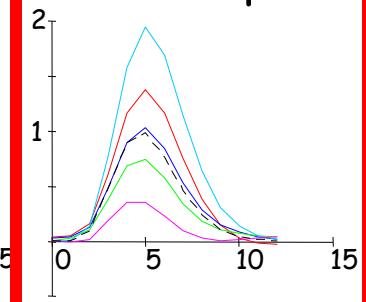
Adaptation



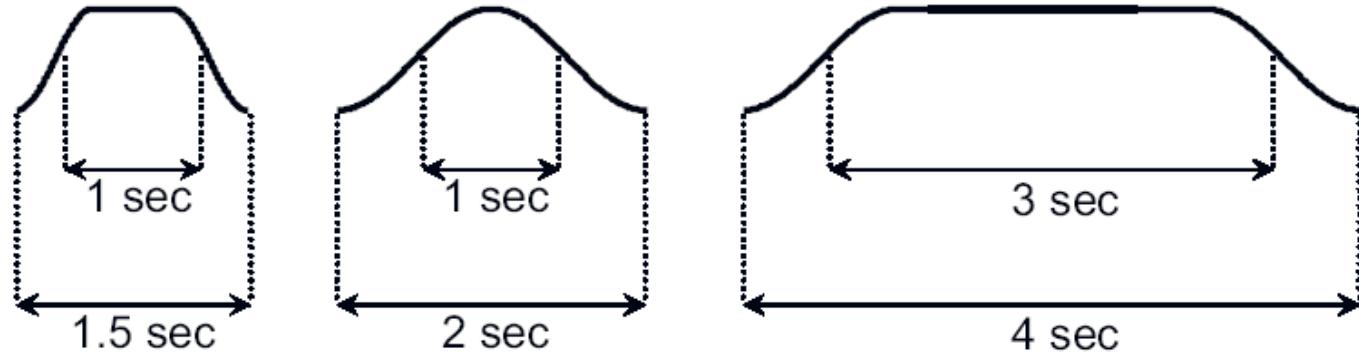
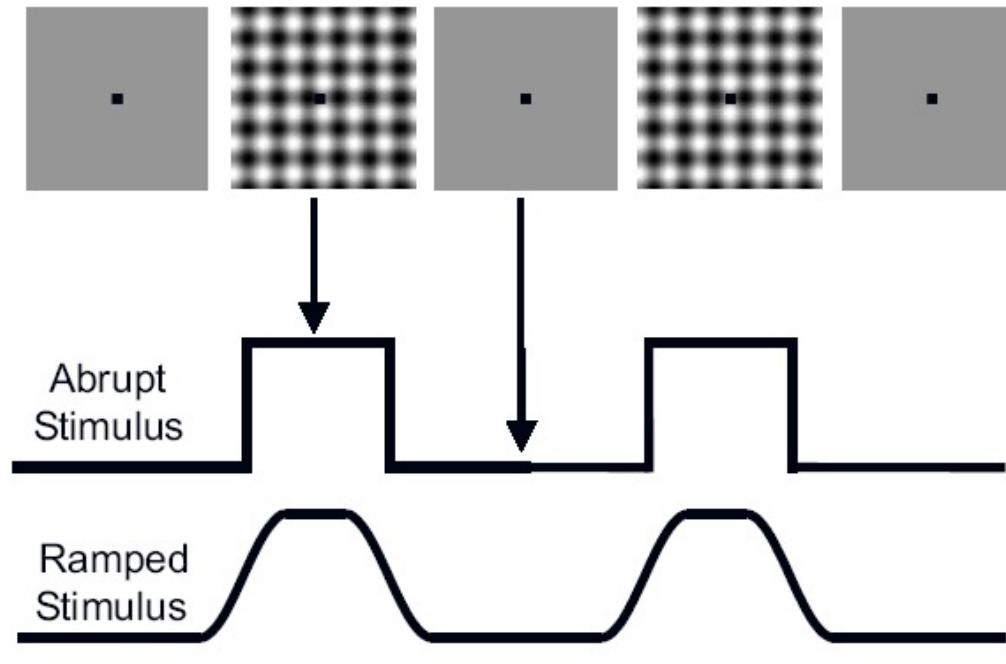
Adaptation + Refraction



Adaptation  
+ Refraction  
+ OFF response

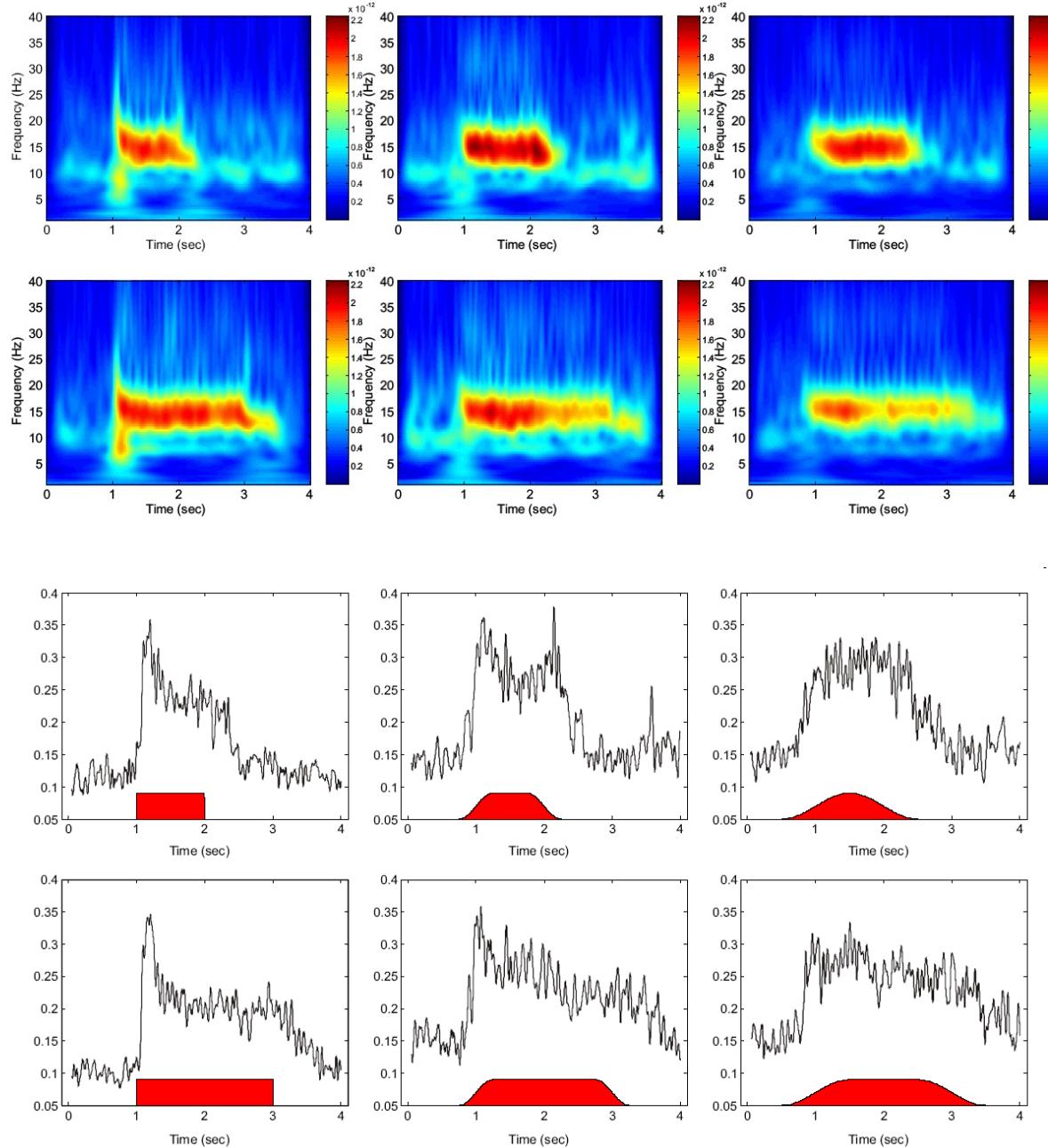


# MEG & fMRI Linearity Comparison



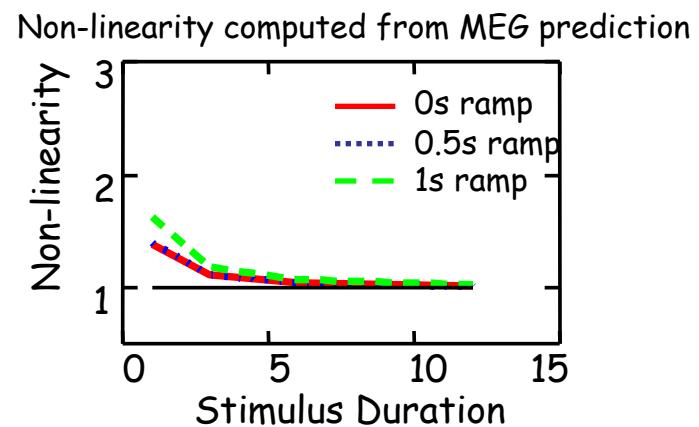
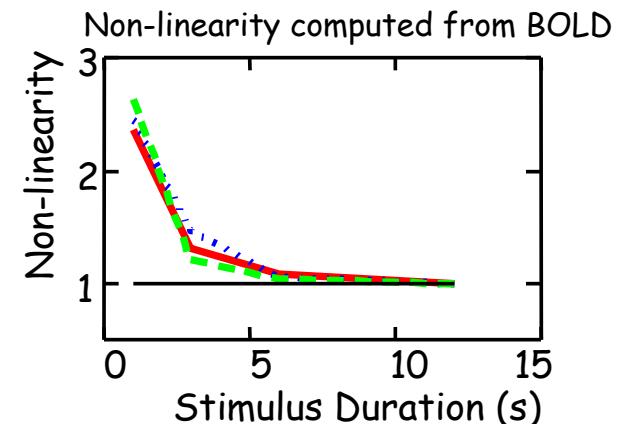
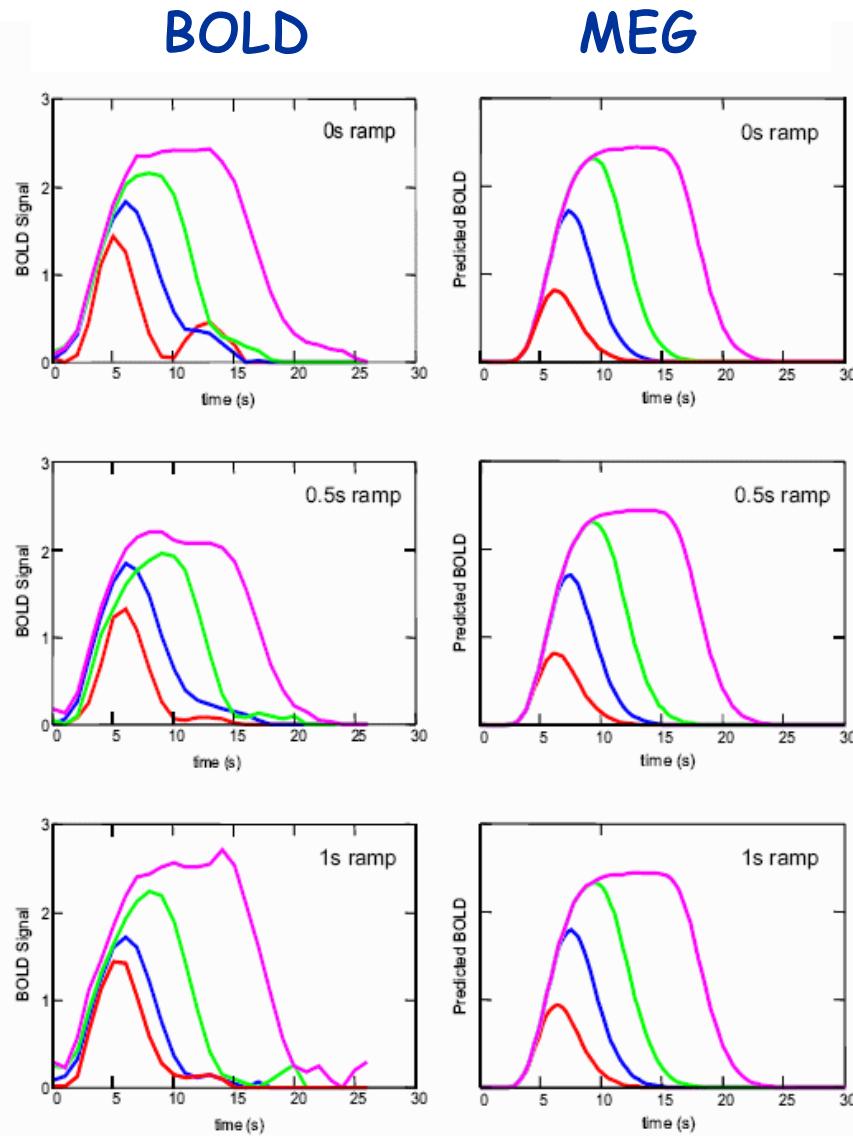
A. Tuan, R. M. Birn, P. A. Bandettini, G. M. Boynton, (submitted)

# MEG Results



A. Tuan, R. M. Birn, P. A. Bandettini, G. M. Boynton, (submitted)

# Measured and Predicted BOLD responses



## 2. Fluctuations

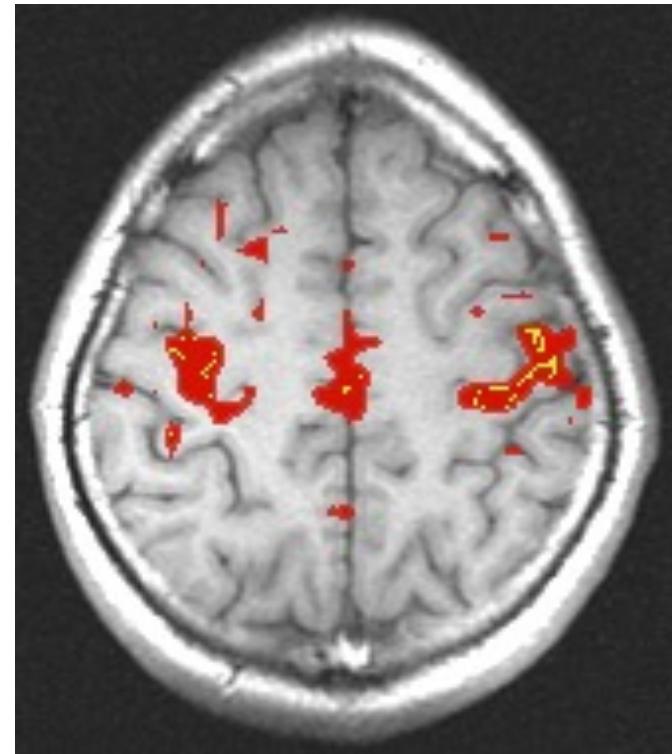
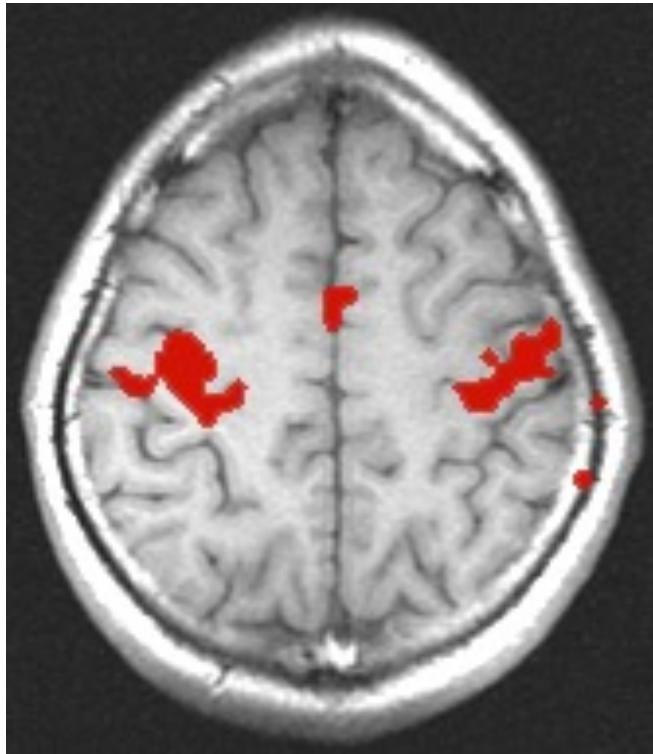
### Motivation:

- Applications of connectivity mapping (autism, schizophrenia, Alzheimer's, ADHD) have exploded - need for better interpretation.
- Distinguish neuronal activity-related fluctuations from non-neuronal physiological fluctuations.
  - *reduce false positives in resting state connectivity maps*
  - *increase functional contrast to noise for activation maps*
- fMRI *activation magnitude* calibration using fluctuations rather than hypercapnic or breath-hold stress.

### Studies:

- Time course of respiration volume per unit time (RVT)
- The Respiration Response Function (RRF)
- FMRI Calibration using RRF

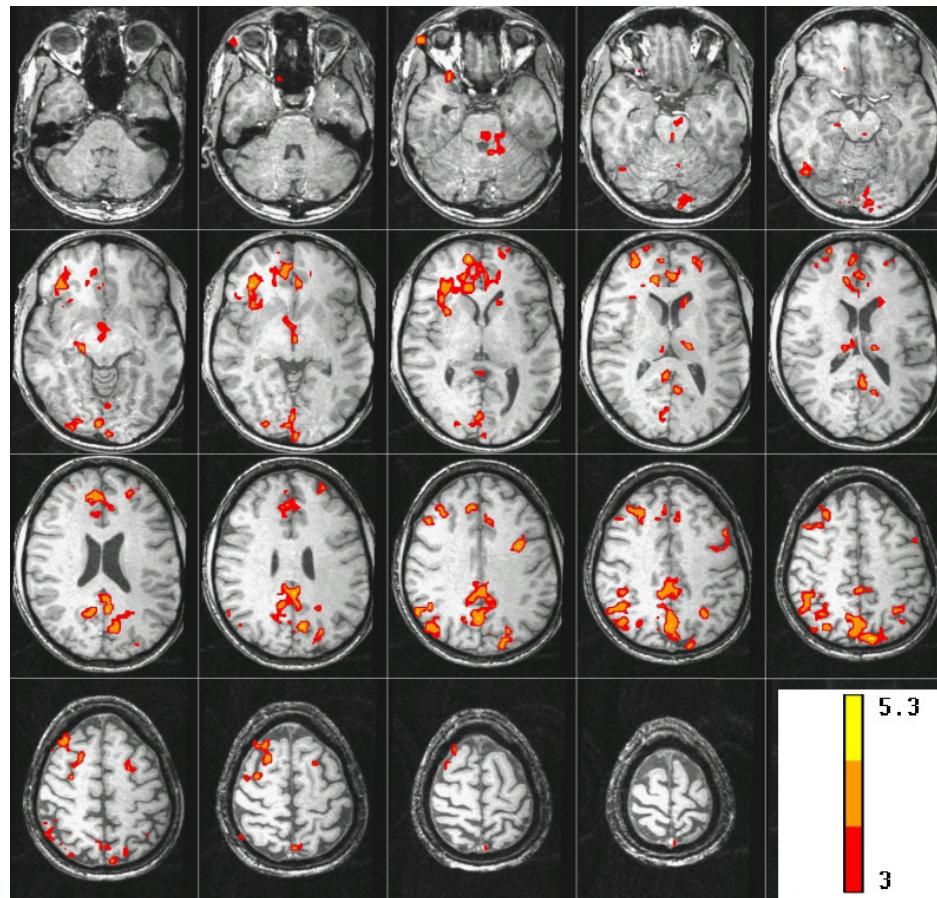
# Resting State Correlations



Activation:  
correlation with reference function

Rest:  
seed voxel in motor cortex

BOLD correlated with SCR during "Rest"

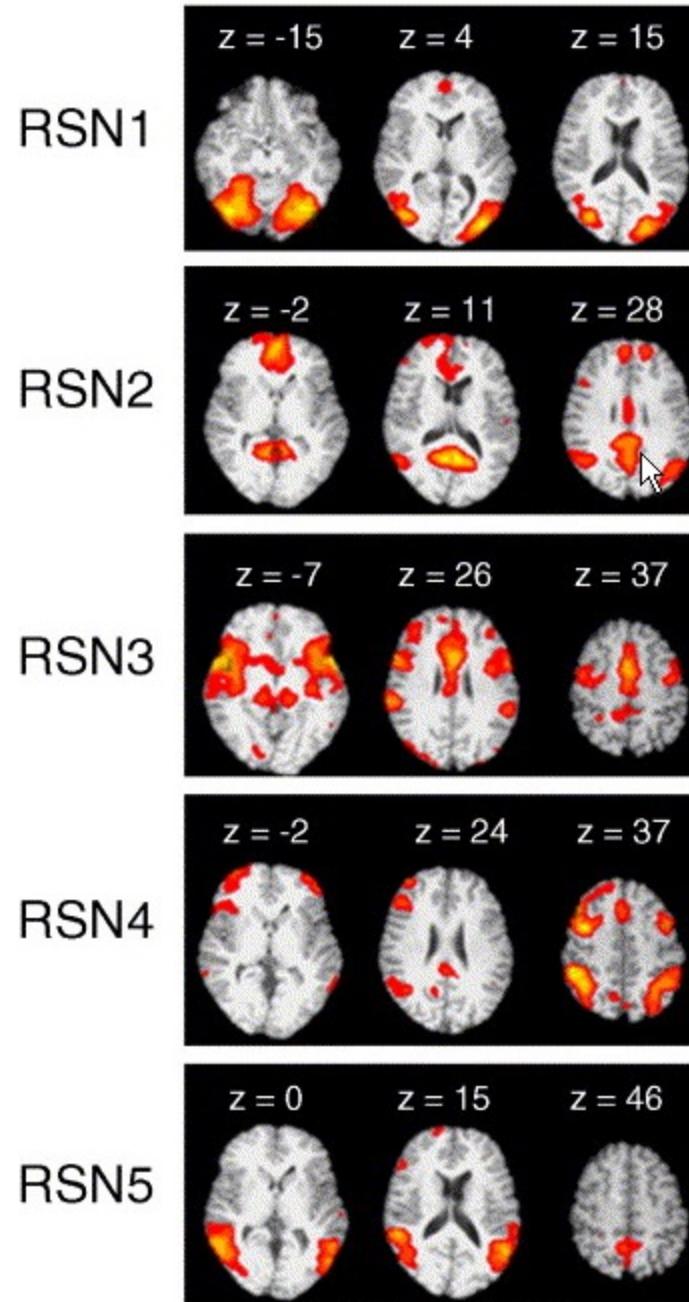
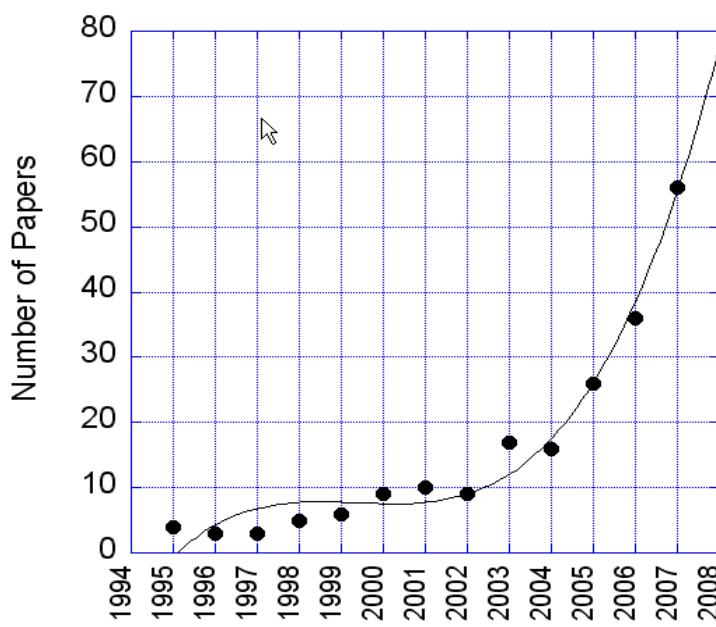


J. C. Patterson II, L. G. Ungerleider, and P. A Bandettini,  
*NeuroImage* 17: 1787-1806, (2002).

# Methodology

## Resting state networks identified with ICA

M. DeLuca, C.F. Beckmann, N. De Stefano, P.M. Matthews, S.M. Smith, fMRI resting state networks define distinct modes of long-distance interactions in the human brain. *NeuroImage*, 29, 1359-1367

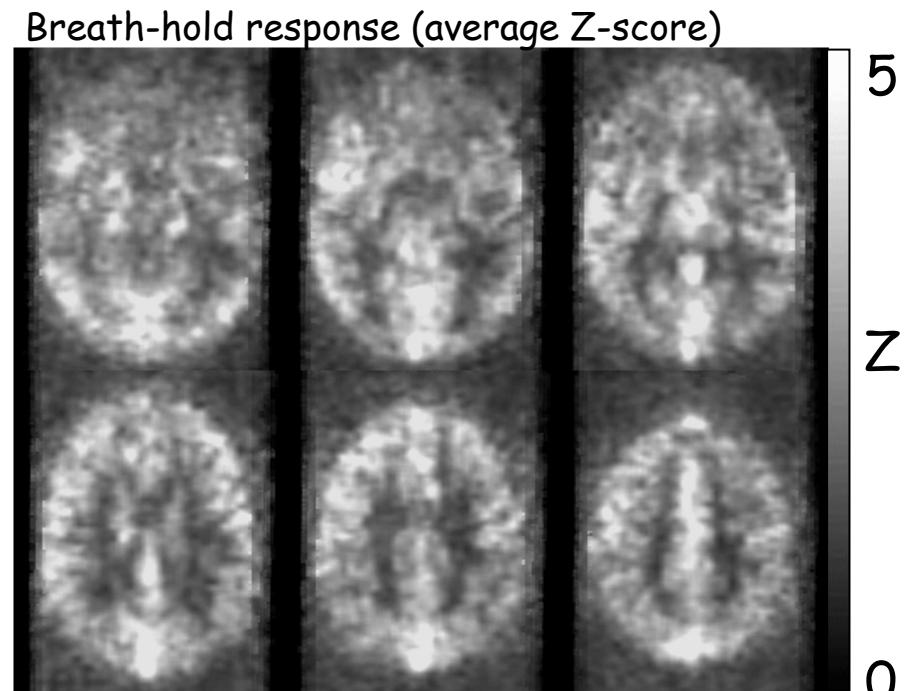
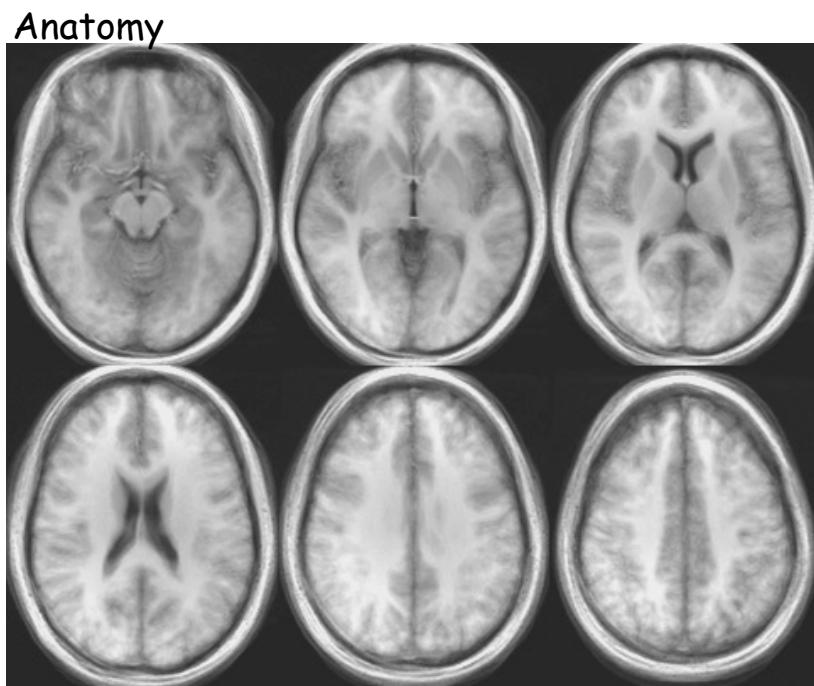
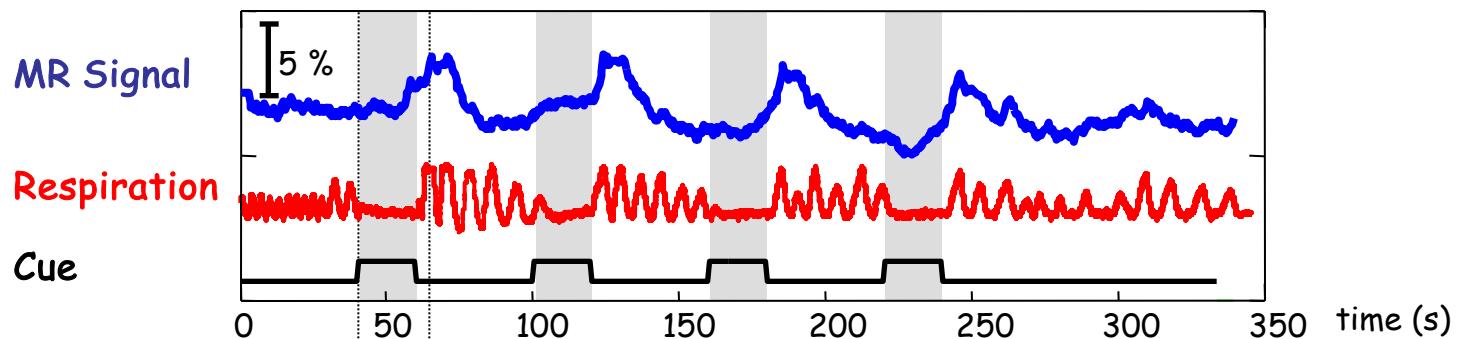


## Sources of time series fluctuations:

- Blood, brain and CSF pulsation
- Vasomotion
- Breathing cycle ( $B_0$  shifts with lung expansion)
- Bulk motion
- Scanner instabilities
- Changes in blood  $\text{CO}_2$  (changes in breathing)
- Spontaneous neuronal activity

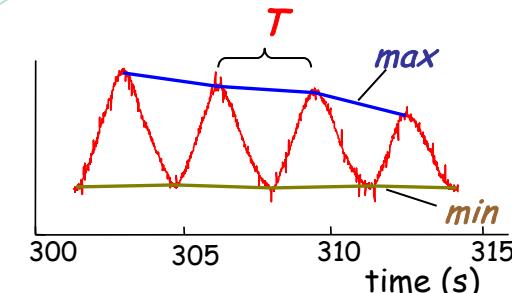
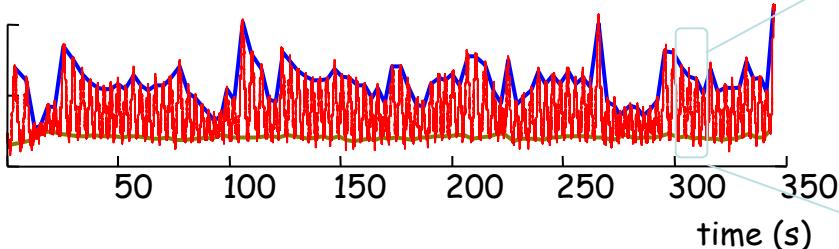
# Breath-holding

Group Maps (N = 7)

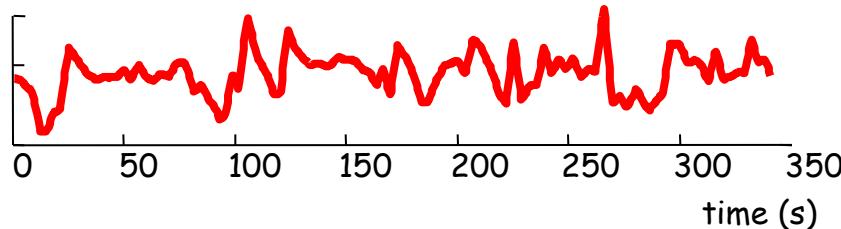


# Estimating respiration volume changes

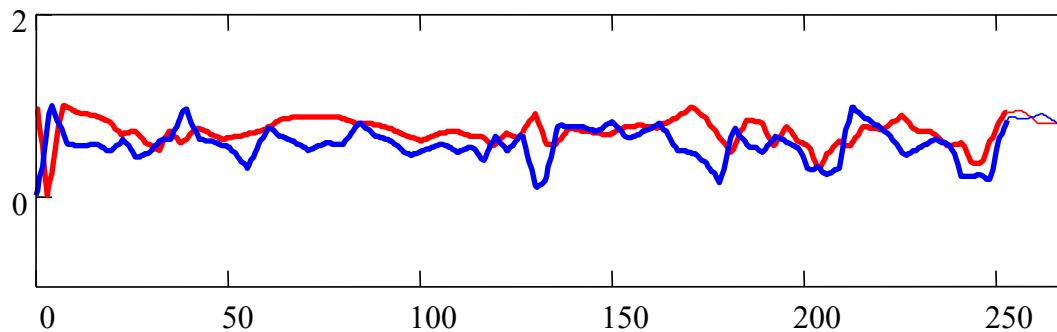
Respiration



Respiration Volume / Time (RVT)

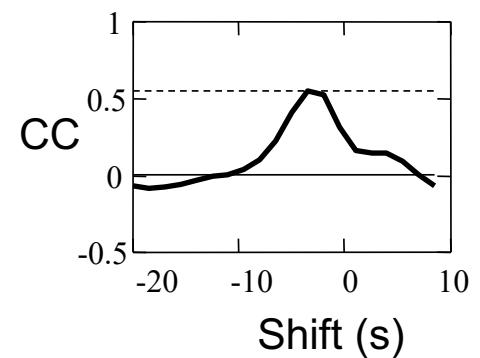


$$RVT = \frac{\text{max} - \text{min}}{T}$$



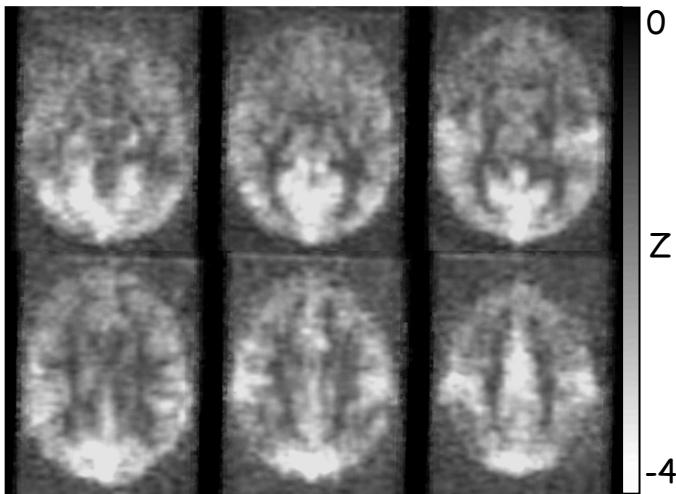
RVT precedes end tidal  $\text{CO}_2$  by 5 sec.

—  $\text{CO}_2$   
— RVT

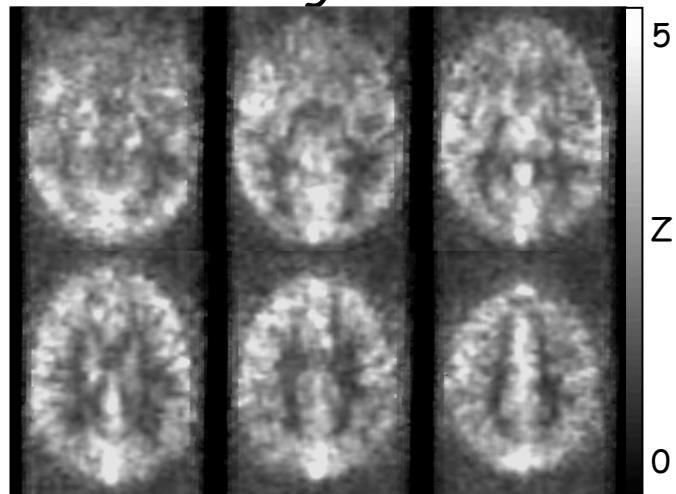


# Respiration induced signal changes

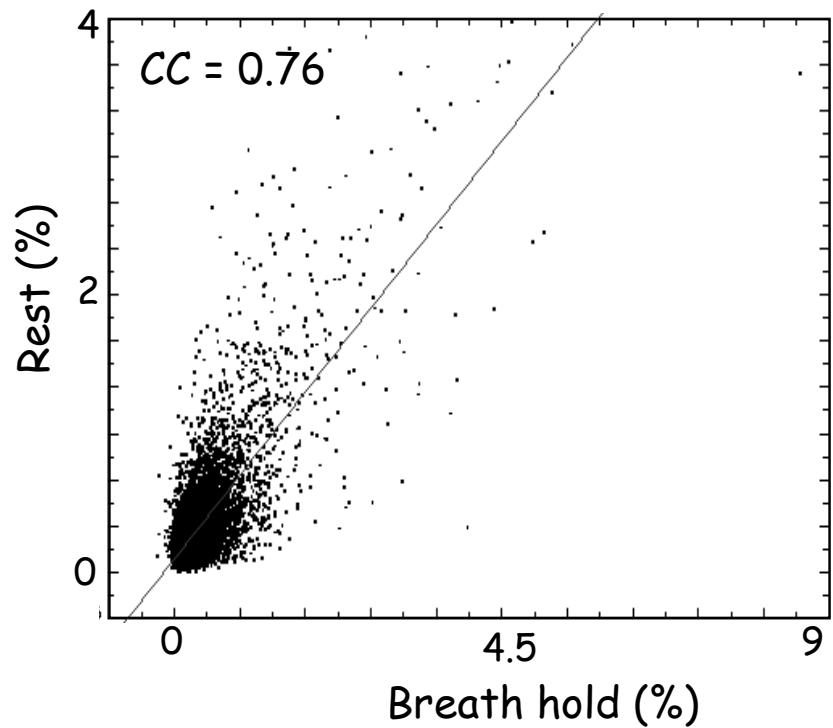
*Rest*



*Breath-holding*

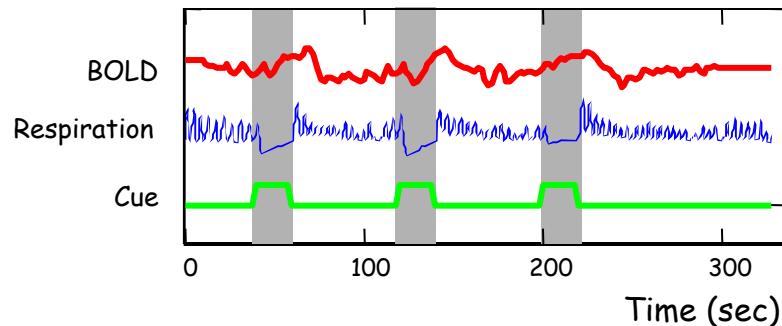


(N=7)

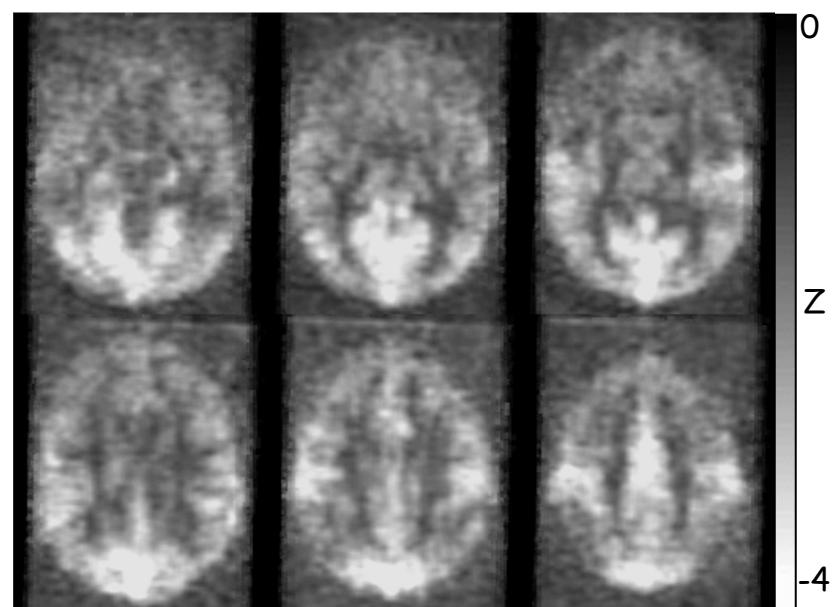
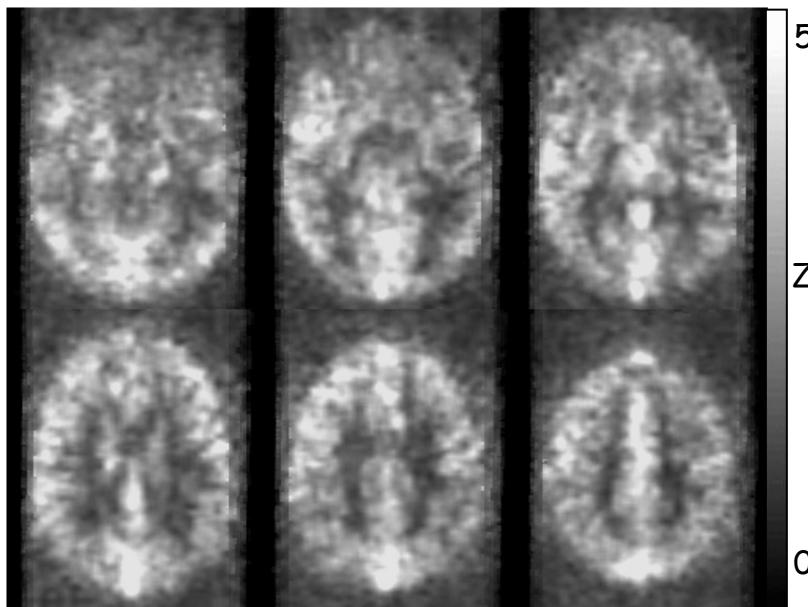
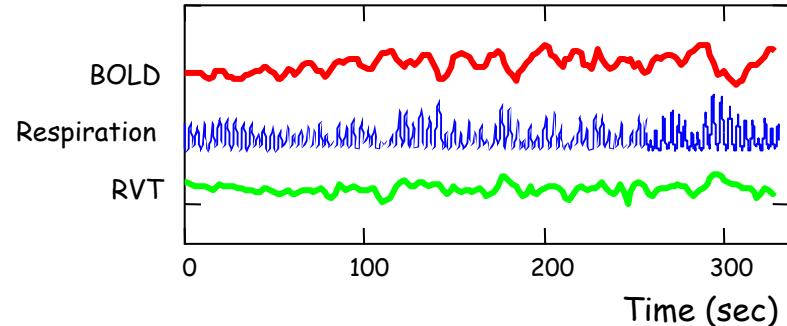


# Respiration induced signal changes

## Breath-holding



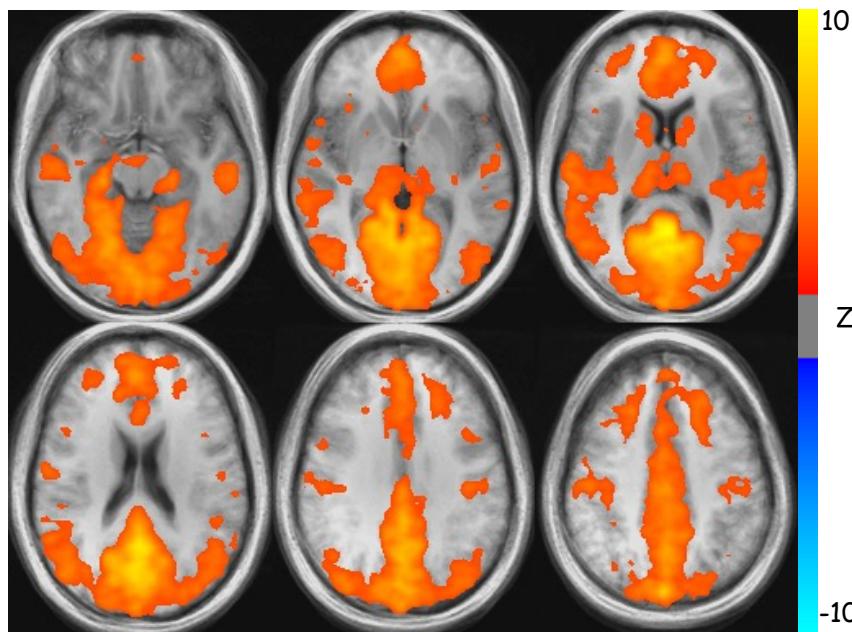
## Rest



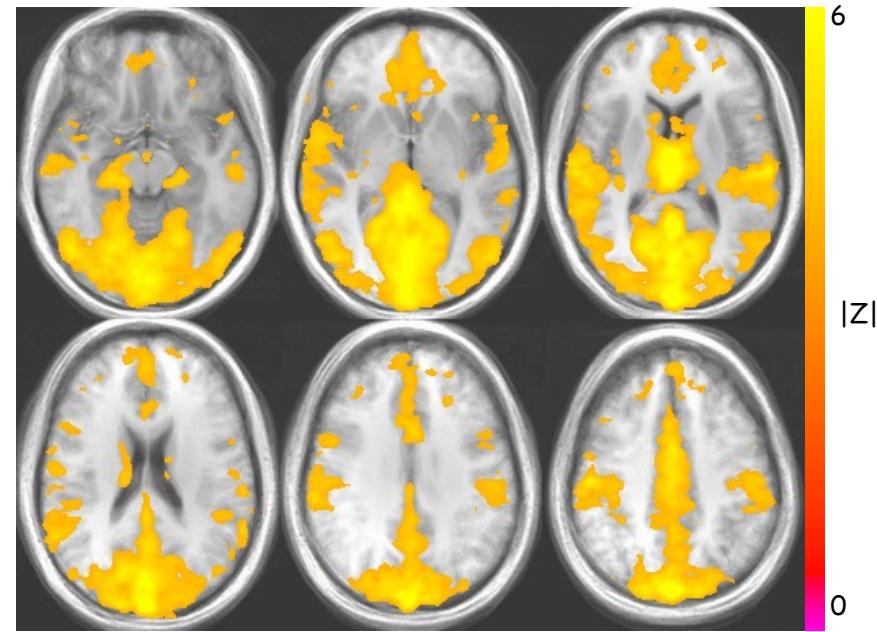
(N=7)

# RVT Correlation Maps & Functional Connectivity Maps

Resting state correlation with signal from posterior cingulate

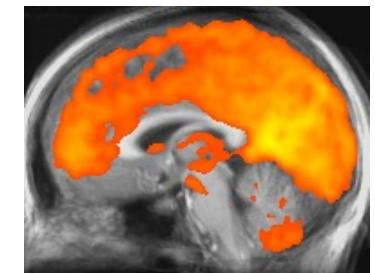


Resting state correlation with RVT signal



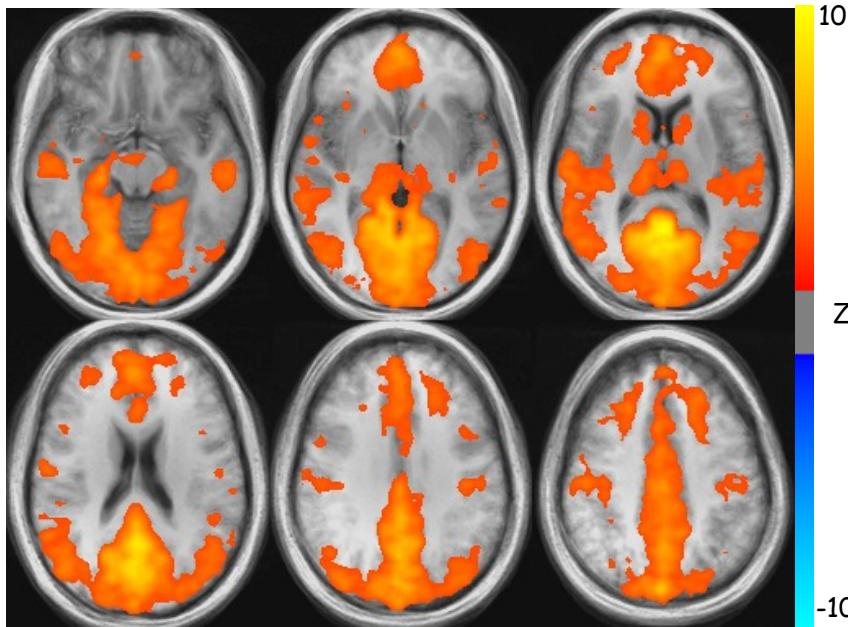
*Group (n=10)*

R.M. Birn, J. A. Diamond, M. A. Smith, P. A. Bandettini,  
*NeuroImage*, 31, 1536-1548 (2006)

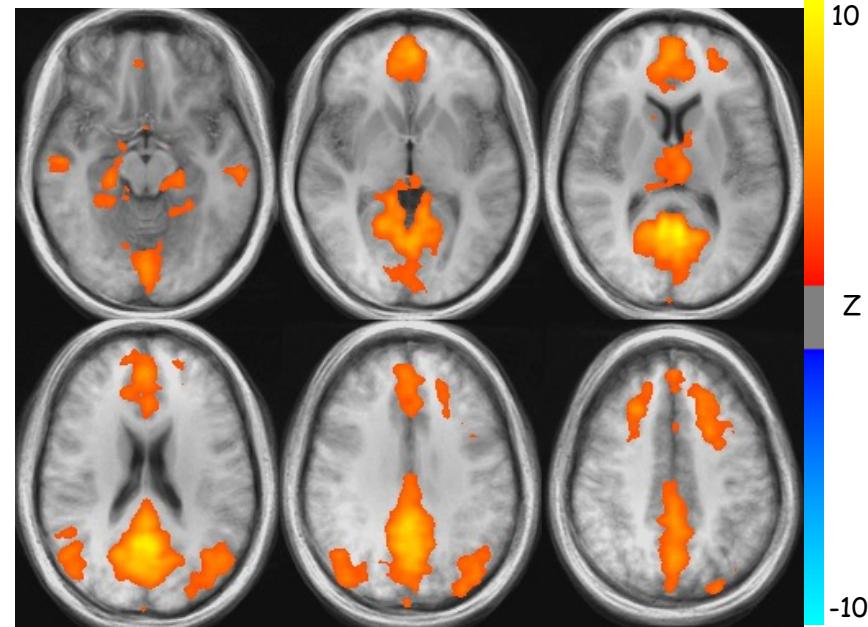


# Effect of Respiration Rate Consistency on Resting Correlation Maps

Spontaneously Varying Respiration Rate

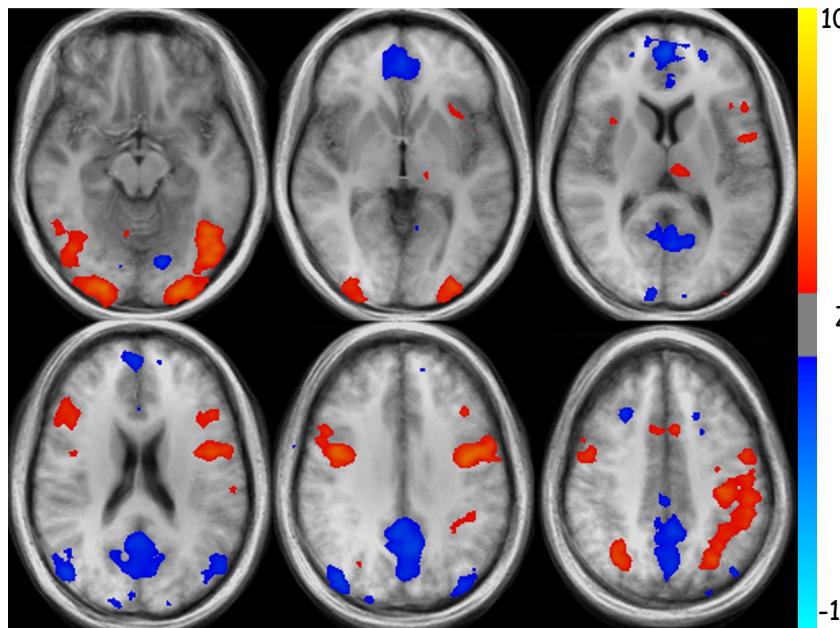


Constant Respiration Rate



Lexical Decision  
Making Task

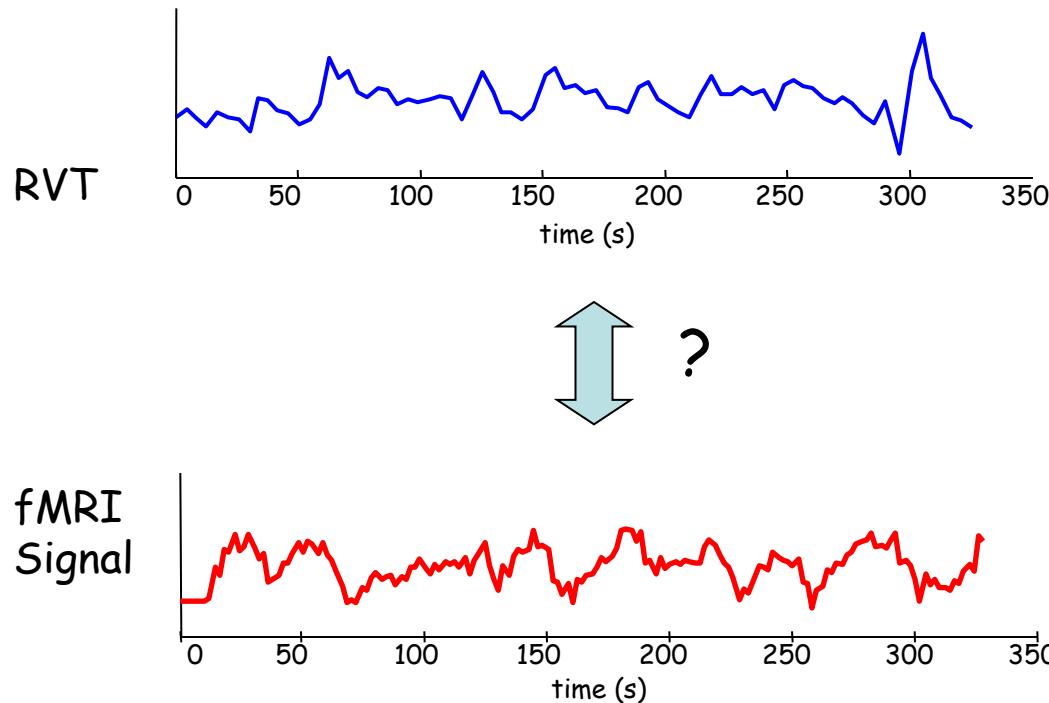
Group ( $n=10$ )



Blue: deactivated  
network

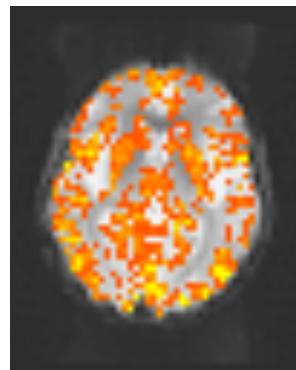
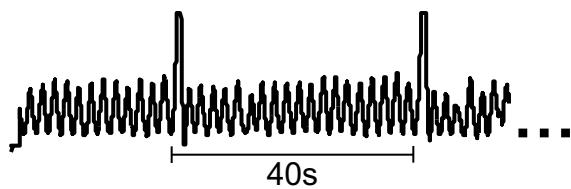
# Respiration Changes vs. BOLD

*How are the BOLD changes related to respiration variations?*

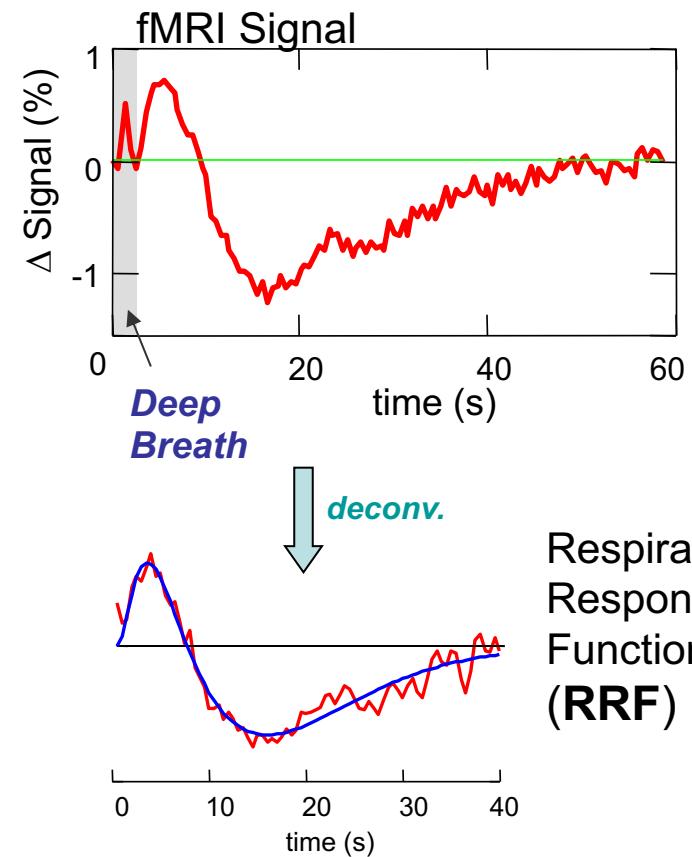


# fMRI response to a single Deep Breath

Respiration

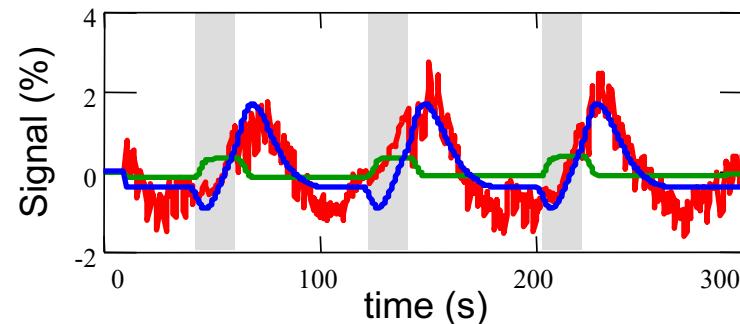
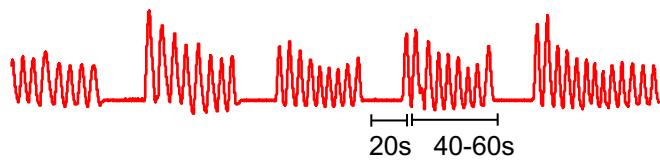


$$RRF(t) = 0.6 t^{2.1} e^{-1.6} - 0.0023 t^{3.54} e^{-4.25}$$

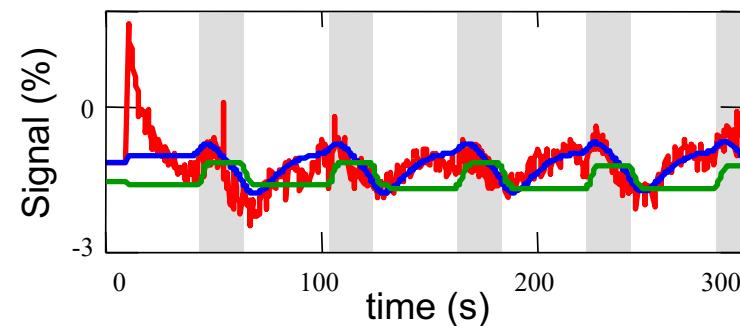
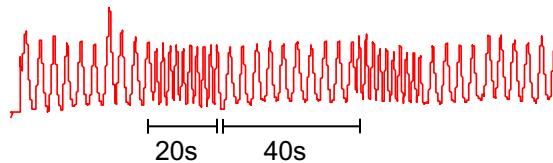


Respiration response function predicts BOLD signal associated with breathing changes better than activation response function.

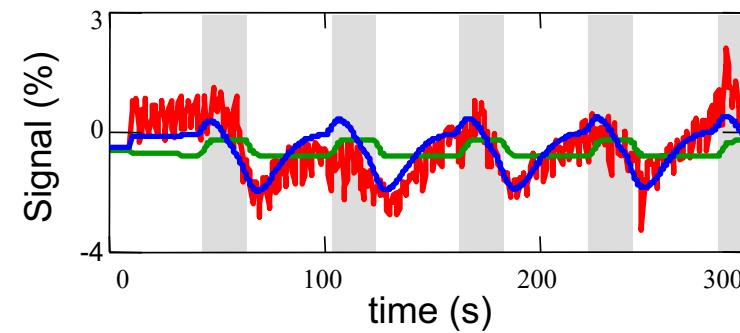
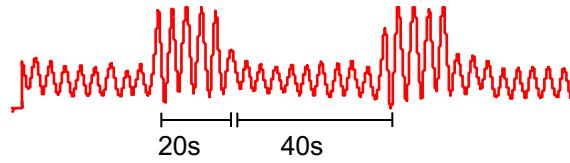
### Breath-holding

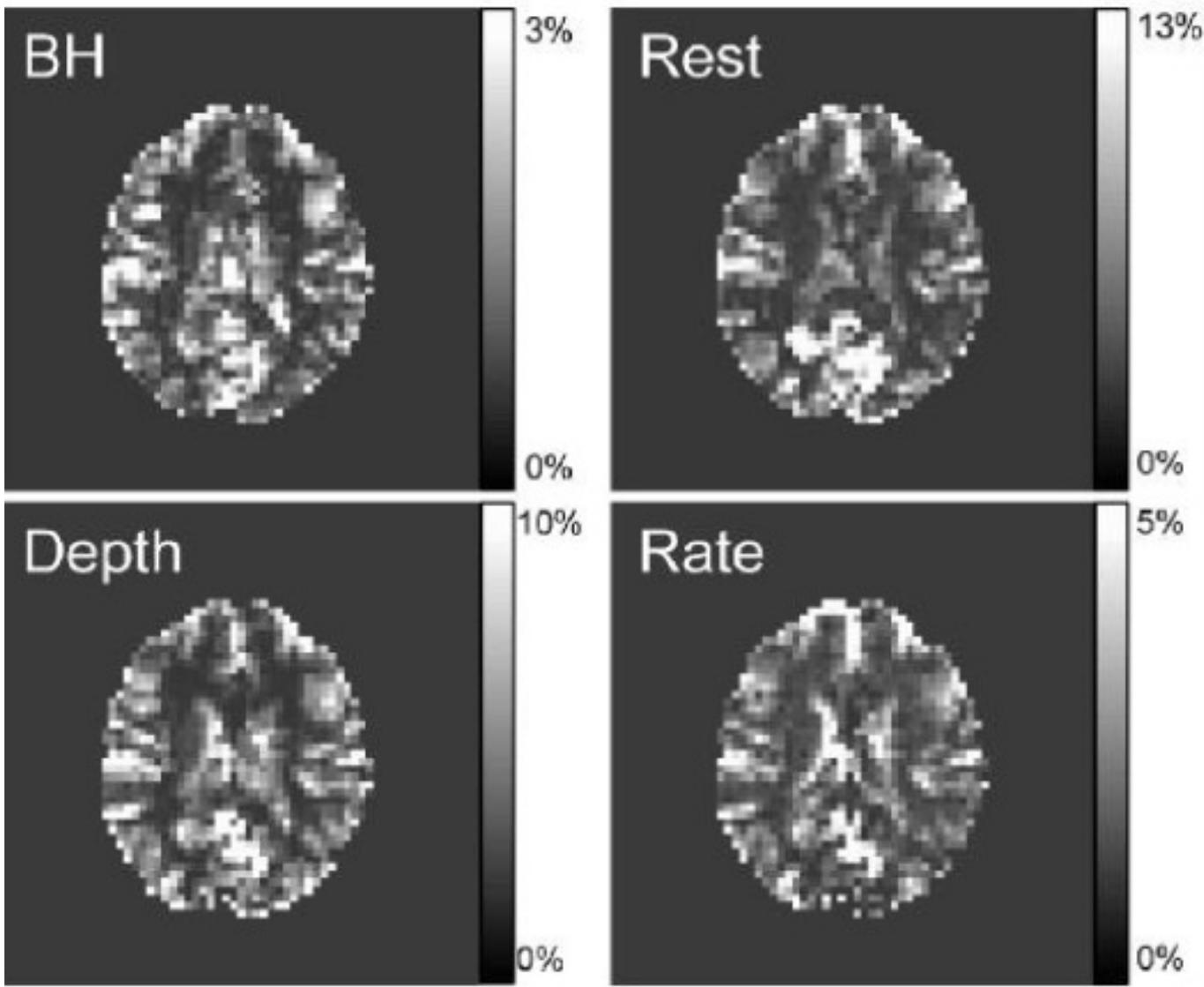


### Rate Changes

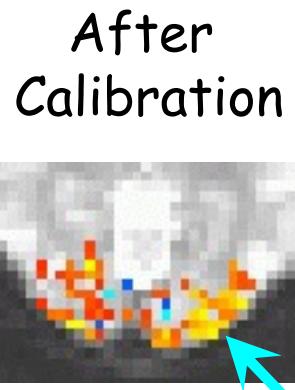
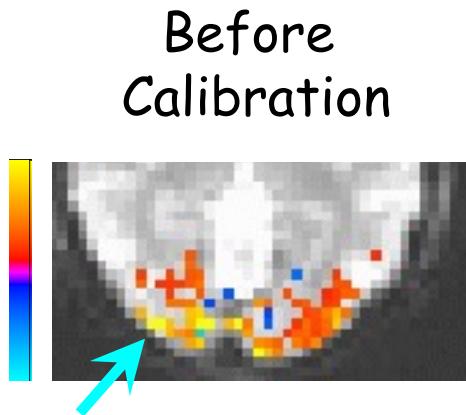


### Depth Changes

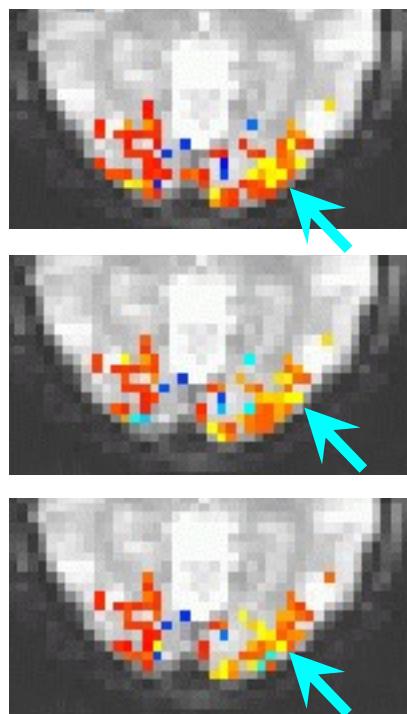




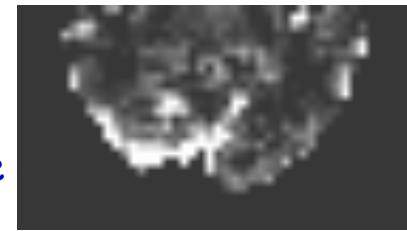
# BOLD magnitude calibration



$$\text{BOLD}_{\text{calib}} = \frac{\% \Delta S (\text{BOLD})}{\% \Delta S (\text{Resp})}$$



*Respiration-induced  $\Delta S$*



# 3. Experimental Design

## Motivation:

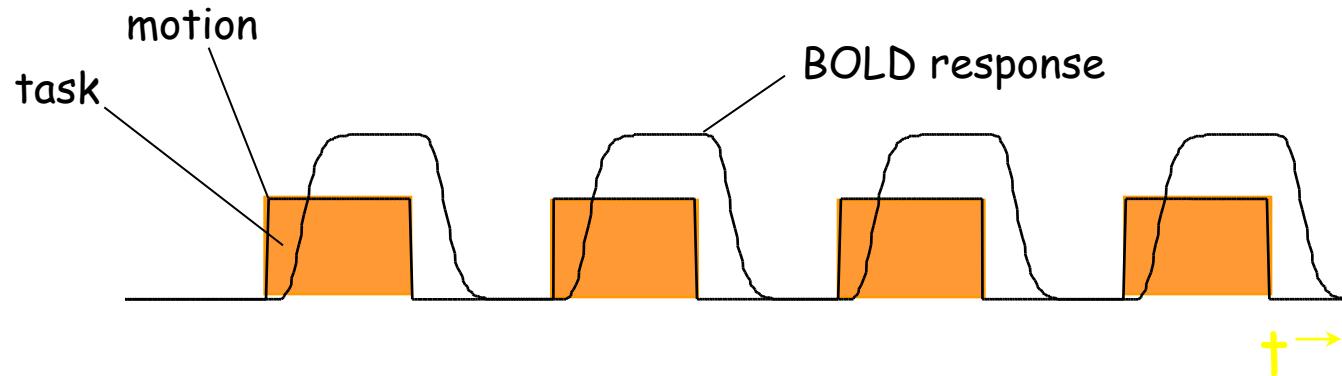
- Guides for *individual* subject scanning at the limits of detectability, resolution, available time, and subject performance.

## Studies:

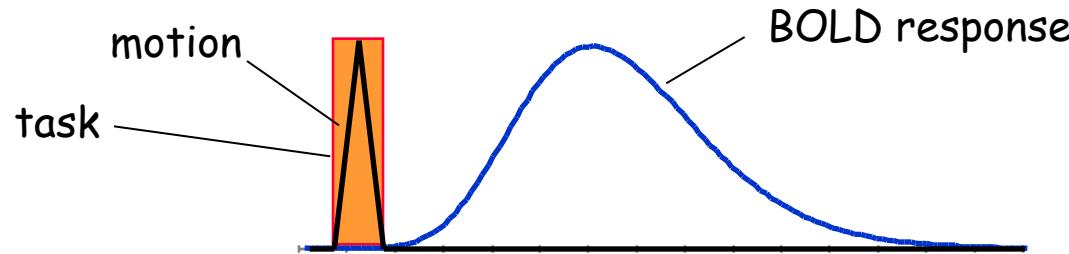
- Overt response timing
- Suggested resolution

# fMRI during tasks that involve brief motion

## Blocked Design

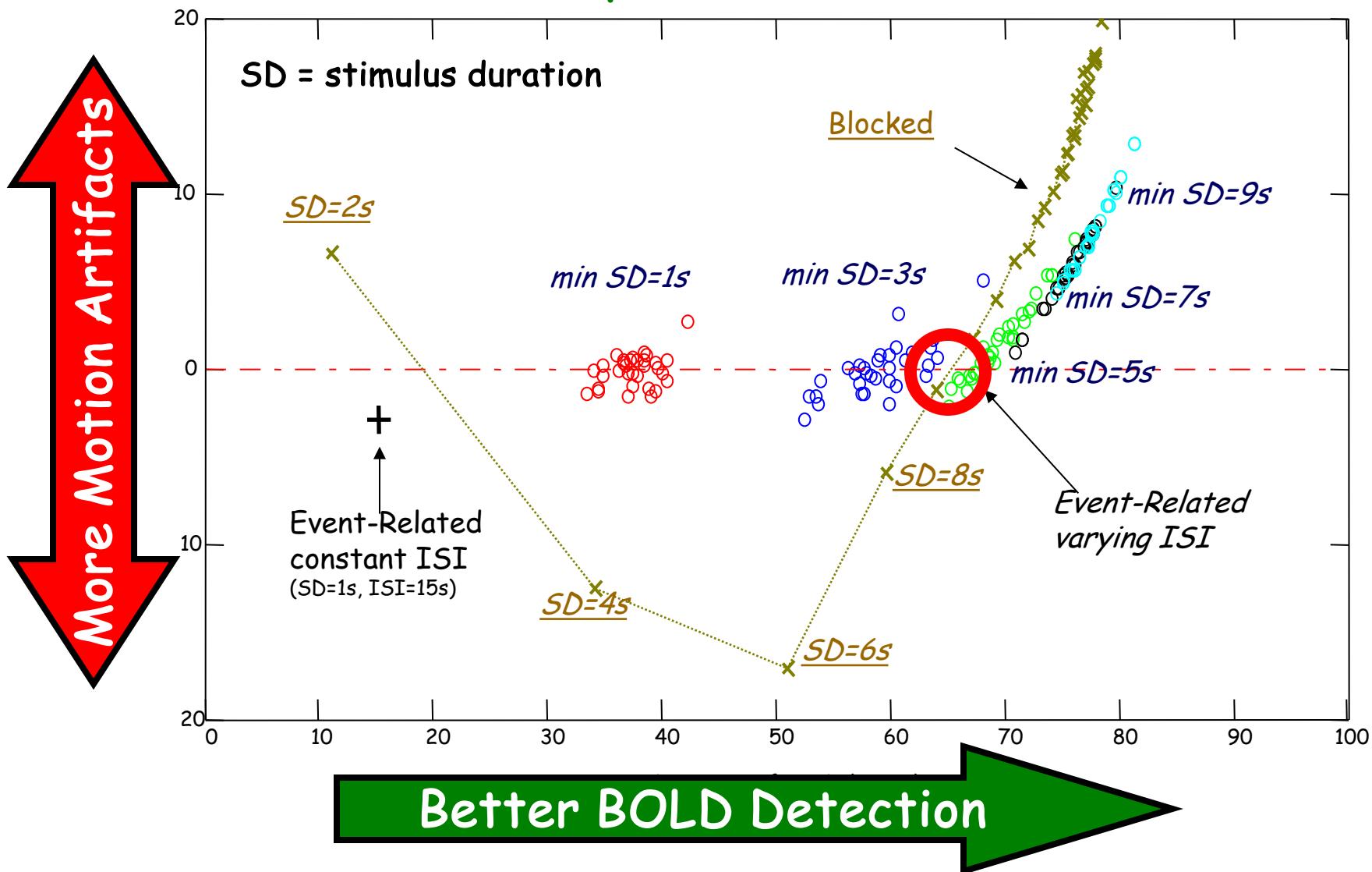


## Event-Related Design

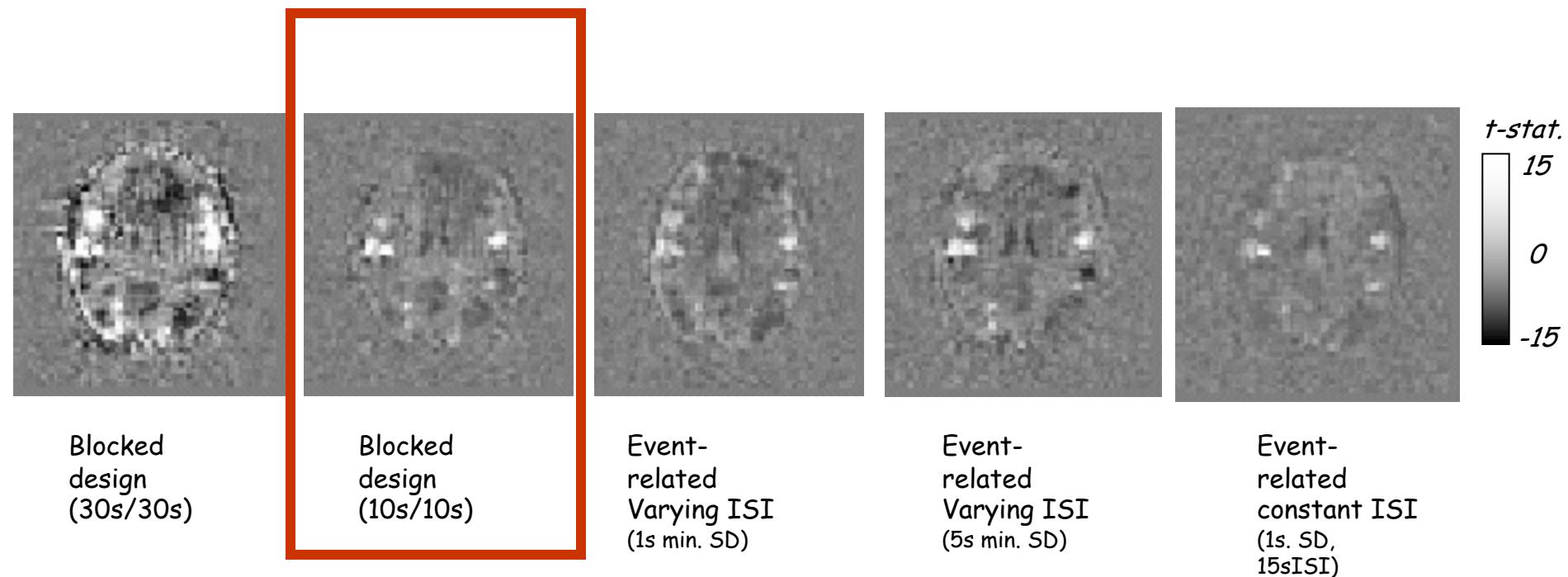


R. M. Birn, P. A. Bandettini, R. W. Cox, R. Shaker, *Human Brain Mapping* 7: 106-114 (1999).

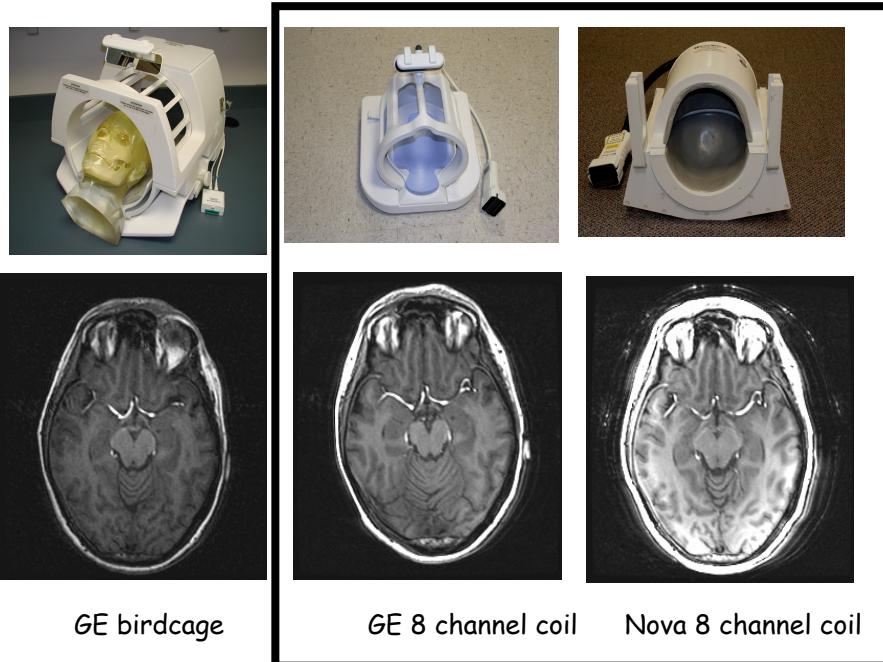
# Overt Responses - Simulations



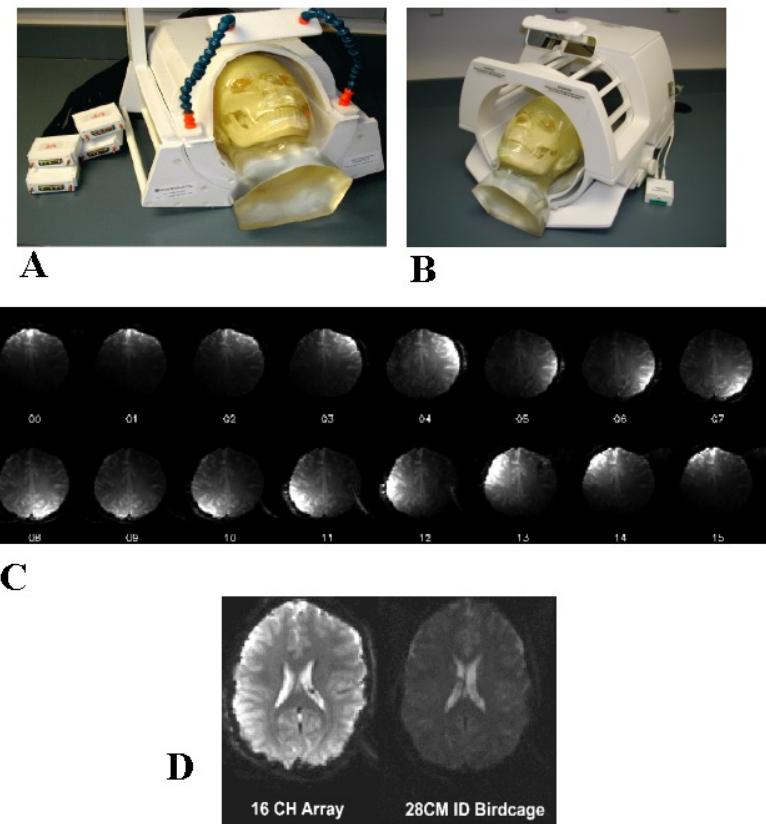
# Overt Responses



8 channel parallel receiver coil



16 channel parallel receiver coil

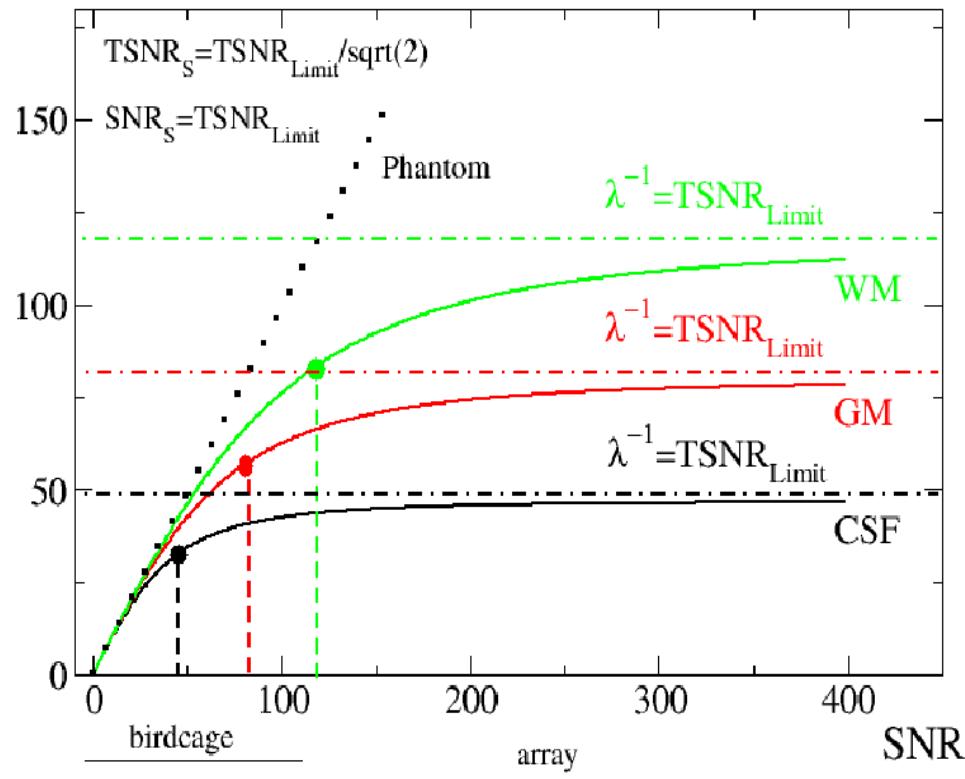


J. Bodurka, et al, Magnetic Resonance in Medicine 51 (2004) 165-171.

# Finding the “suggested voxel volume”

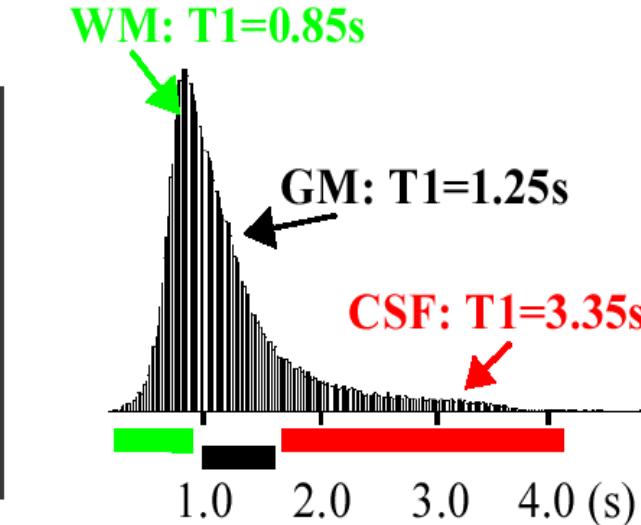
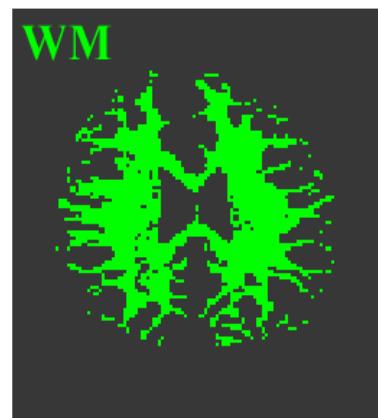
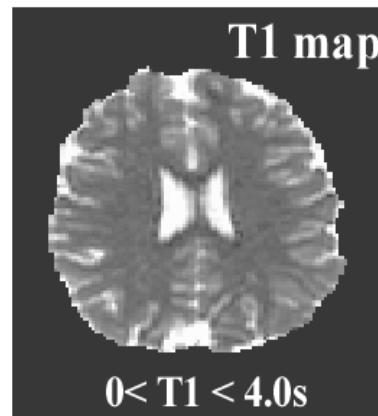
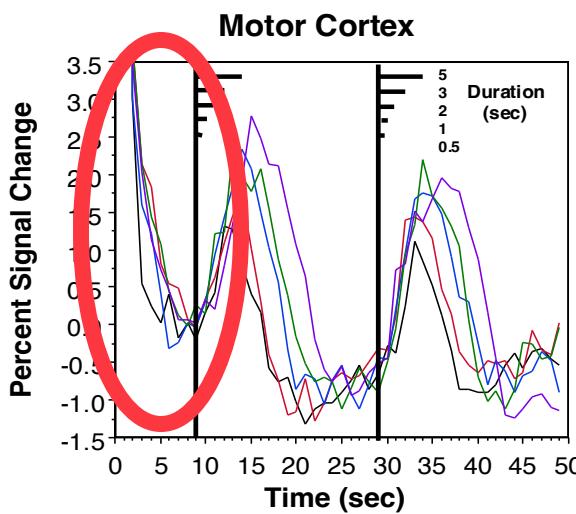
## Temporal Signal to Noise Ratio (TSNR) vs. Signal to Noise Ratio (SNR)

TSNR

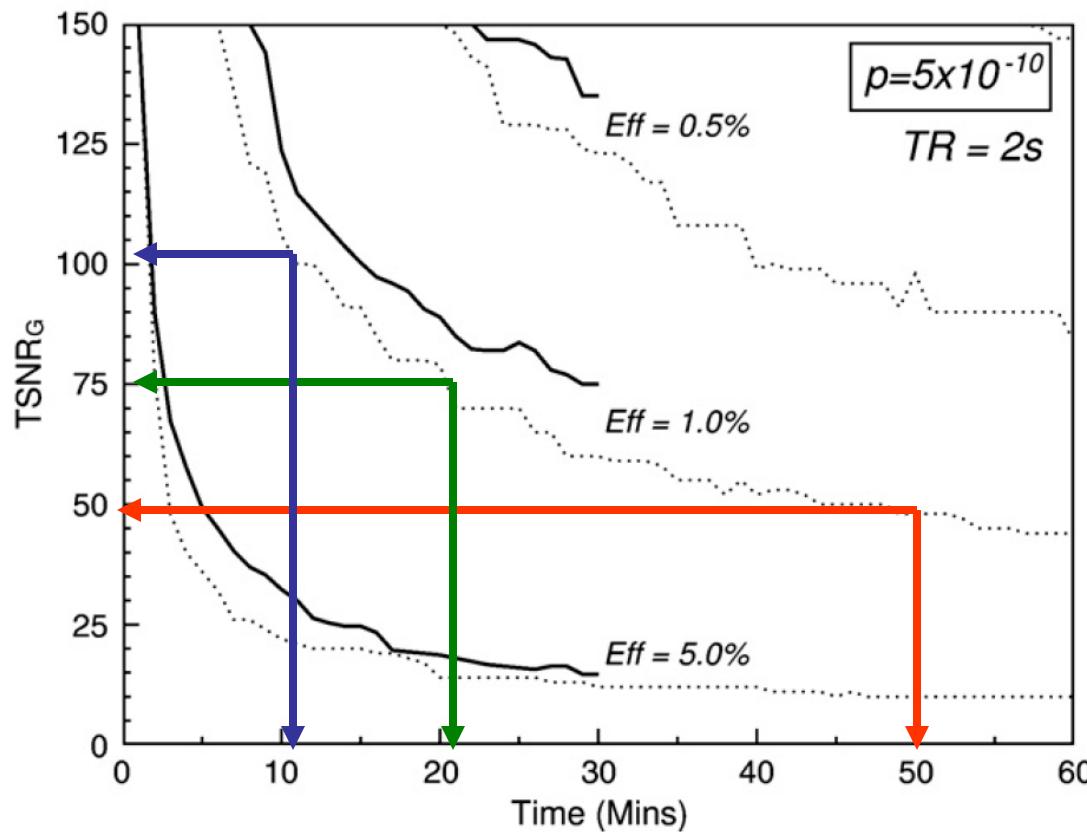


3T, birdcage:	2.5 mm <sup>3</sup>
3T, 16 channel:	1.8 mm <sup>3</sup>
7T, 16 channel:	1.4 mm <sup>3</sup>

# Segmentation using EPI Transient



# Sensitivity, Scan Time, and Temporal Signal to Noise



# 4. Pattern-Information Analysis

## Motivation:

- Classical fMRI analysis:

*Is a region activated during a task?*

- Pattern-information analysis:

*Does a region carry a particular kind of information?*

## Study:

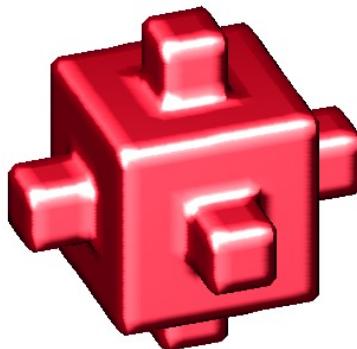
- Pattern-Information Mapping

- Dis-similarity matrix

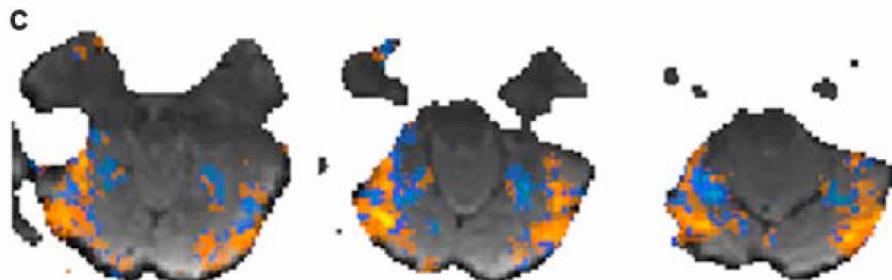
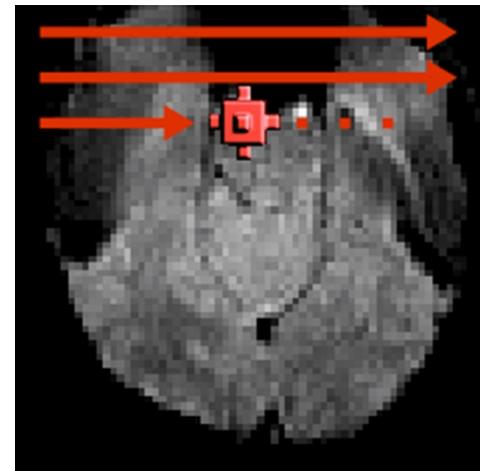
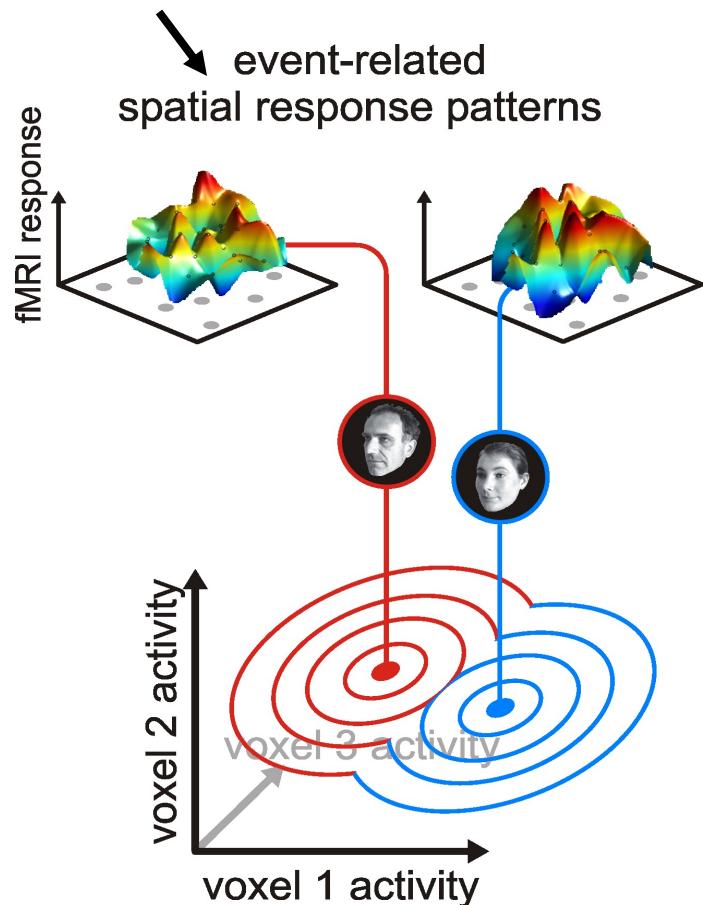


# Pattern Information Mapping

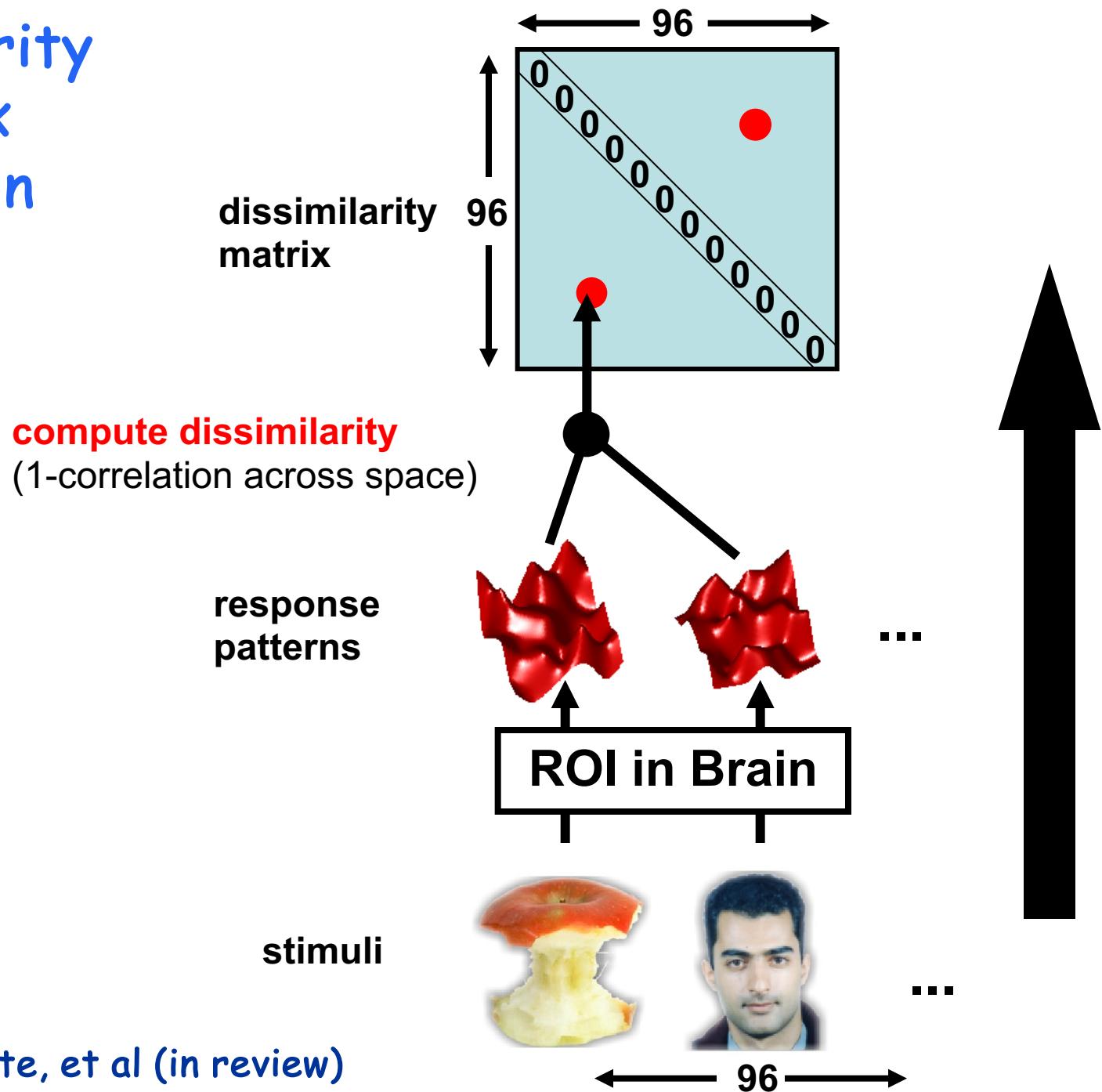
"searchlight" ROI →



From fixed ROI



# Dissimilarity Matrix Creation

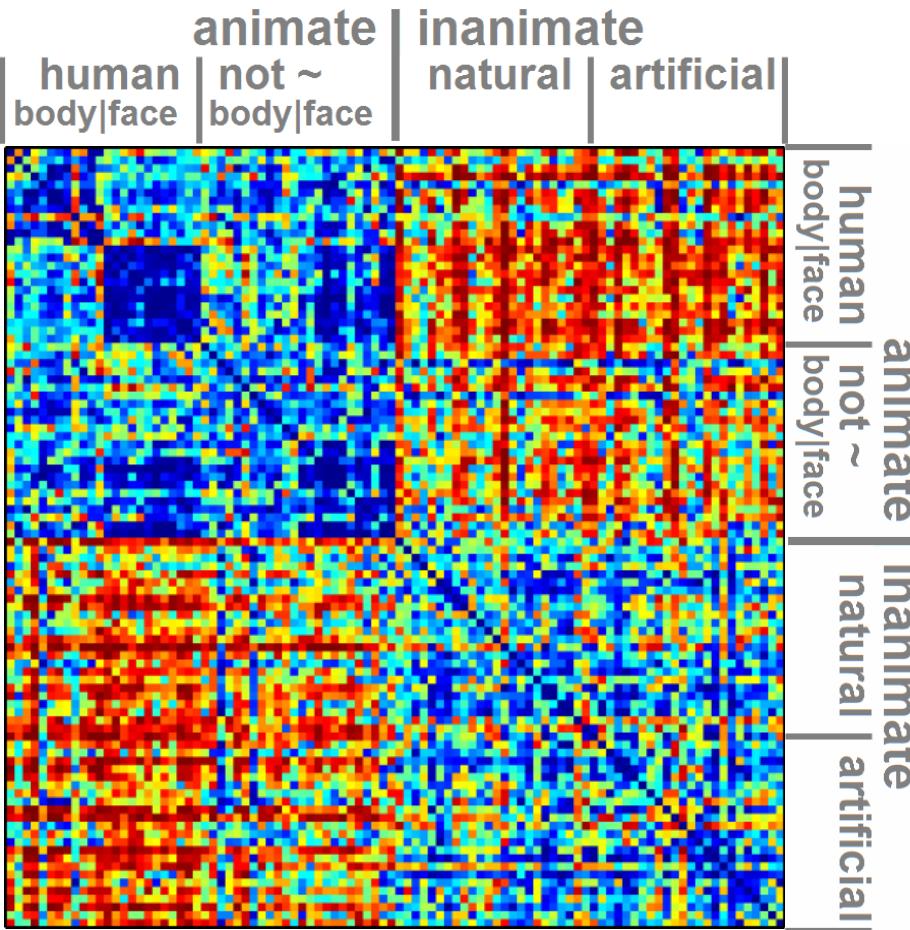


# Visual Stimuli



## Human IT

(1000 visually most responsive voxels)



dissimilarity

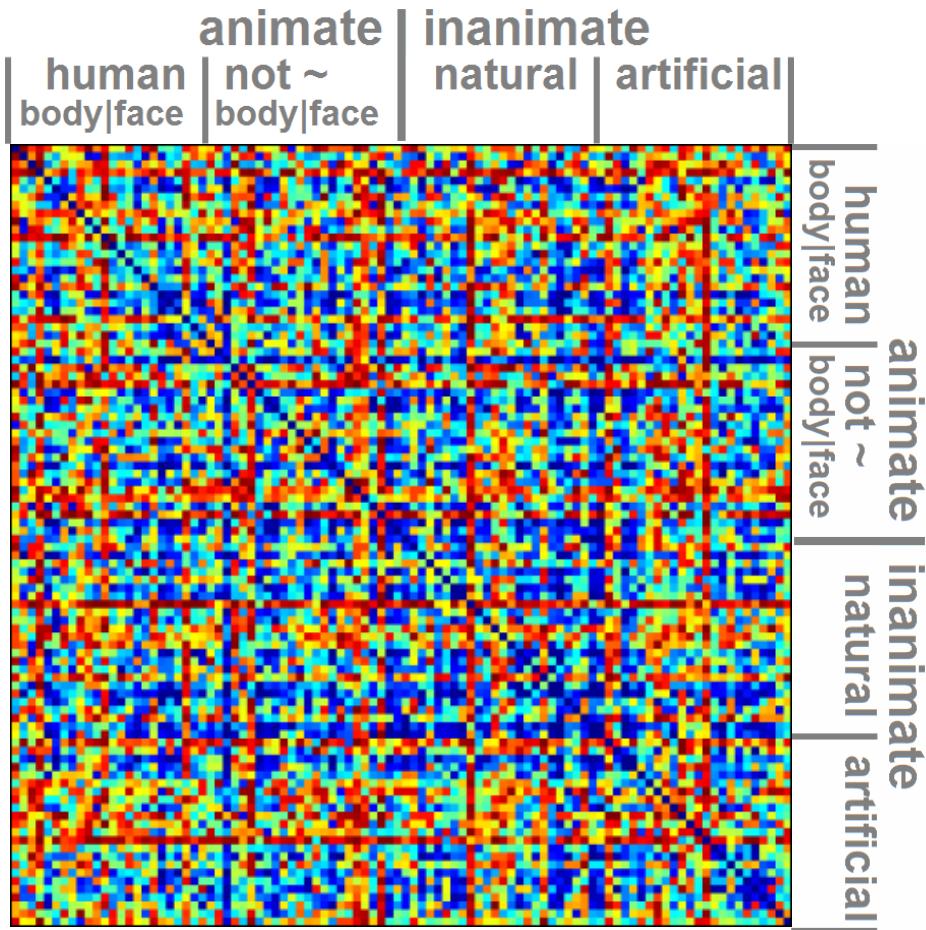
0

[percentile]

100

## Human Early Visual Cortex

(1057 visually most responsive voxels)



animate | inanimate  
natural | artificial

human | not ~  
body|face | body|face

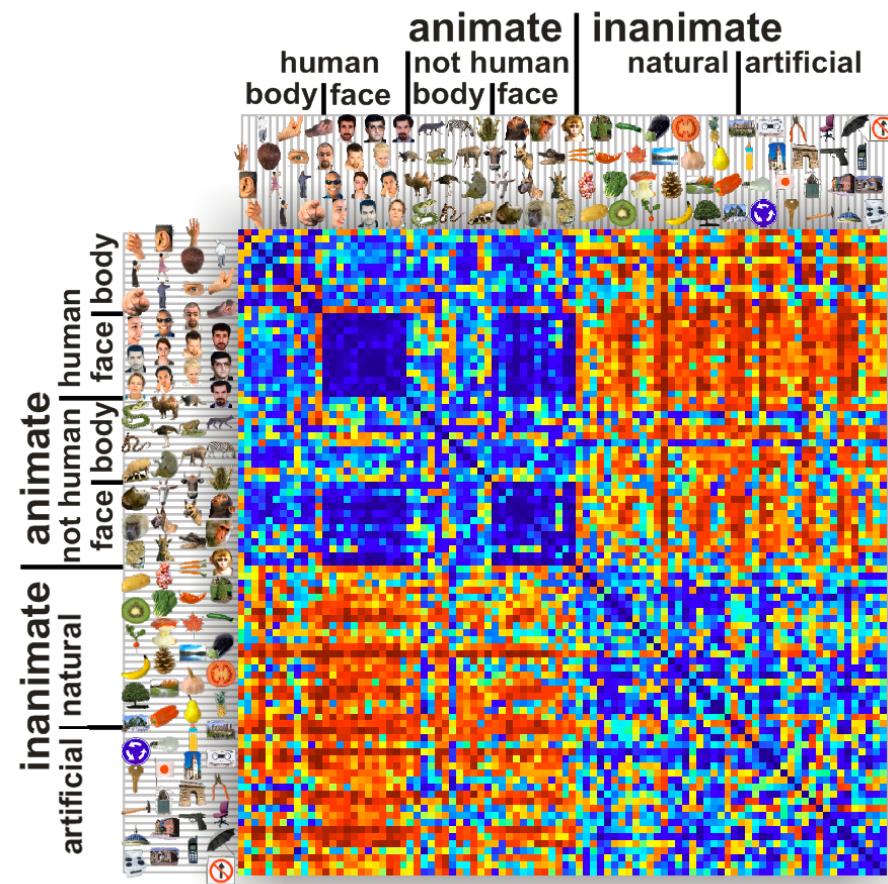
# Monkey-Human Comparison Procedure

## Human

- fMRI in four subjects  
(repeated sessions,  
>12 runs per subject)
- "quick" event-related  
design  
(stimulus duration: 300ms,  
stimulus onset asynchrony: 4s)
- fixation task  
(with discrimination of fixation-point  
color changes)
- occipitotemporal  
measurement slab  
(5-cm thick)
- small voxels ( $1.95 \times 1.95 \times 2 \text{ mm}^3$ )
- 3T magnet, 16-channel coil  
(SENSE, acc. fac. 2)

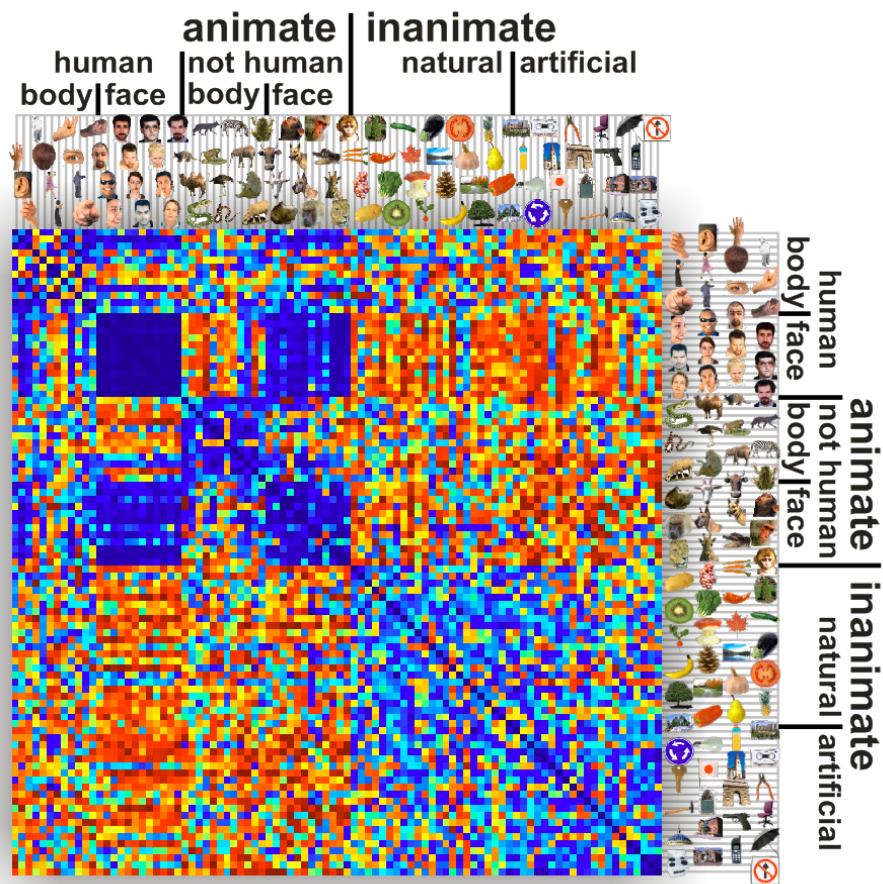
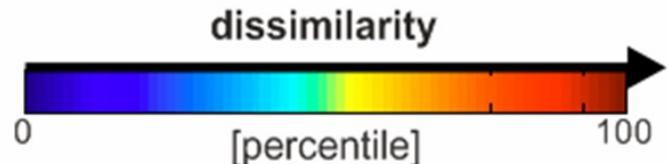
## Monkey (Kiani et al. 2007)

- single-cell recordings  
in two monkeys
- rapid serial presentation  
(stimulus duration: 105ms)
- fixation task
- electrodes in anterior IT  
(left in monkey 1, right in monkey 2)
- 674 cells total
- windowed spike count  
(140-ms window starting 71ms after  
stimulus onset)



average of 4 subjects  
fixation-color task  
316 voxels

**man**



average of 2 monkeys  
fixation task  
>600 cells

# monkey

# 5. Neuronal Current MRI

## Motivation:

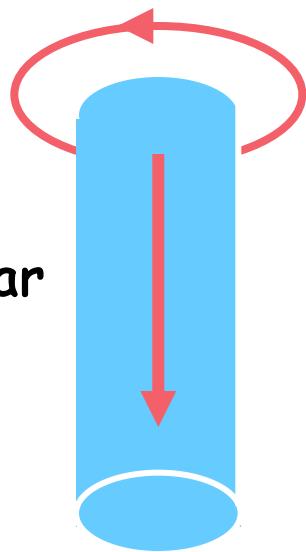
- Direct fMRI of neuronal activity.

## Studies:

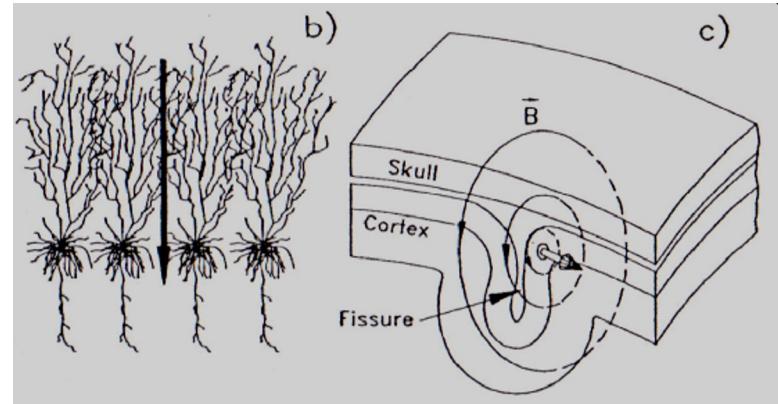
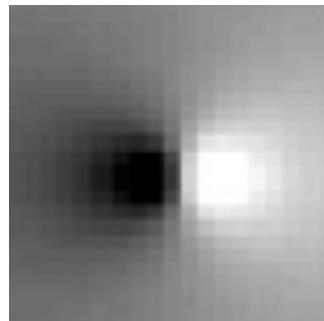
- Model
- Phantom Studies
- Cell Cultures at 7T and 3T

## Magnetic Field

Intracellular Current



## Surface Fields

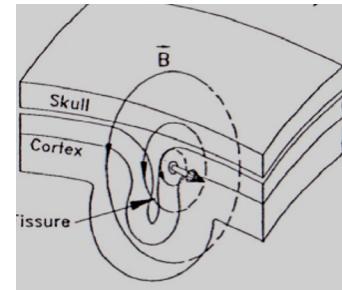


100 fT at on the scalp

J.P. Wikswo Jr et al. *J Clin  
Neurophys* 8(2): 170-188, 1991

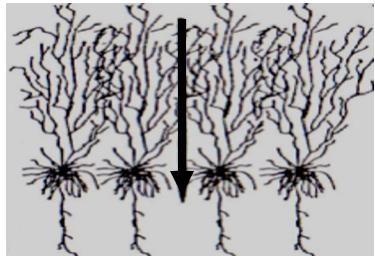
# Magnetic field associated with a bundle of dendrites

Because  $B_{MEG} = 100 \text{ fT}$  is measured by MEG on the scalp

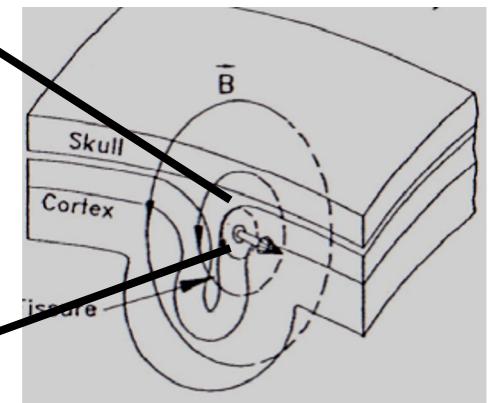
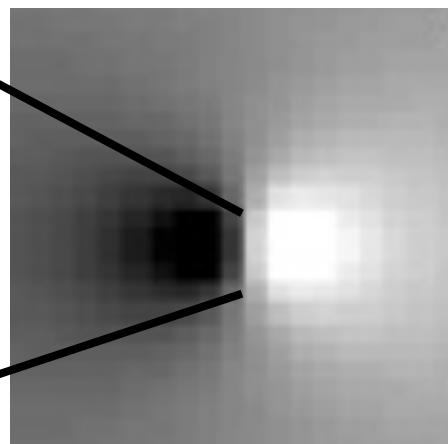
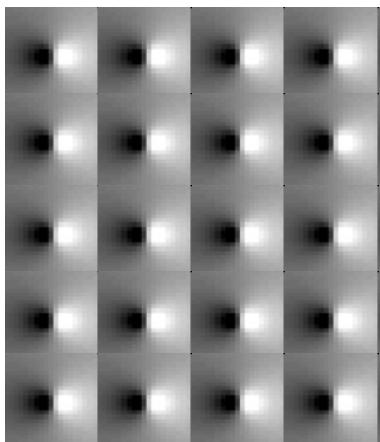


at least 50,000 neurons ( $0.002 \text{ fT}$  (per dendrite)  $\times 50,000 = 100 \text{ fT}$ ), must coherently act to generate such field. These bundles of neurons produce, within a typical voxel,  $1 \text{ mm} \times 1 \text{ mm} \times 1 \text{ mm}$ , a field of order:

$$B_{MRI} = B_{MEG} \left( \frac{r_{MEG}}{r_{MRI}} \right)^2 = B_{MEG} \left( \frac{4 \text{ cm}}{0.1 \text{ cm}} \right)^2 = 1600 B_{MEG} \quad B_{MRI} \approx 0.2 \text{nT}$$

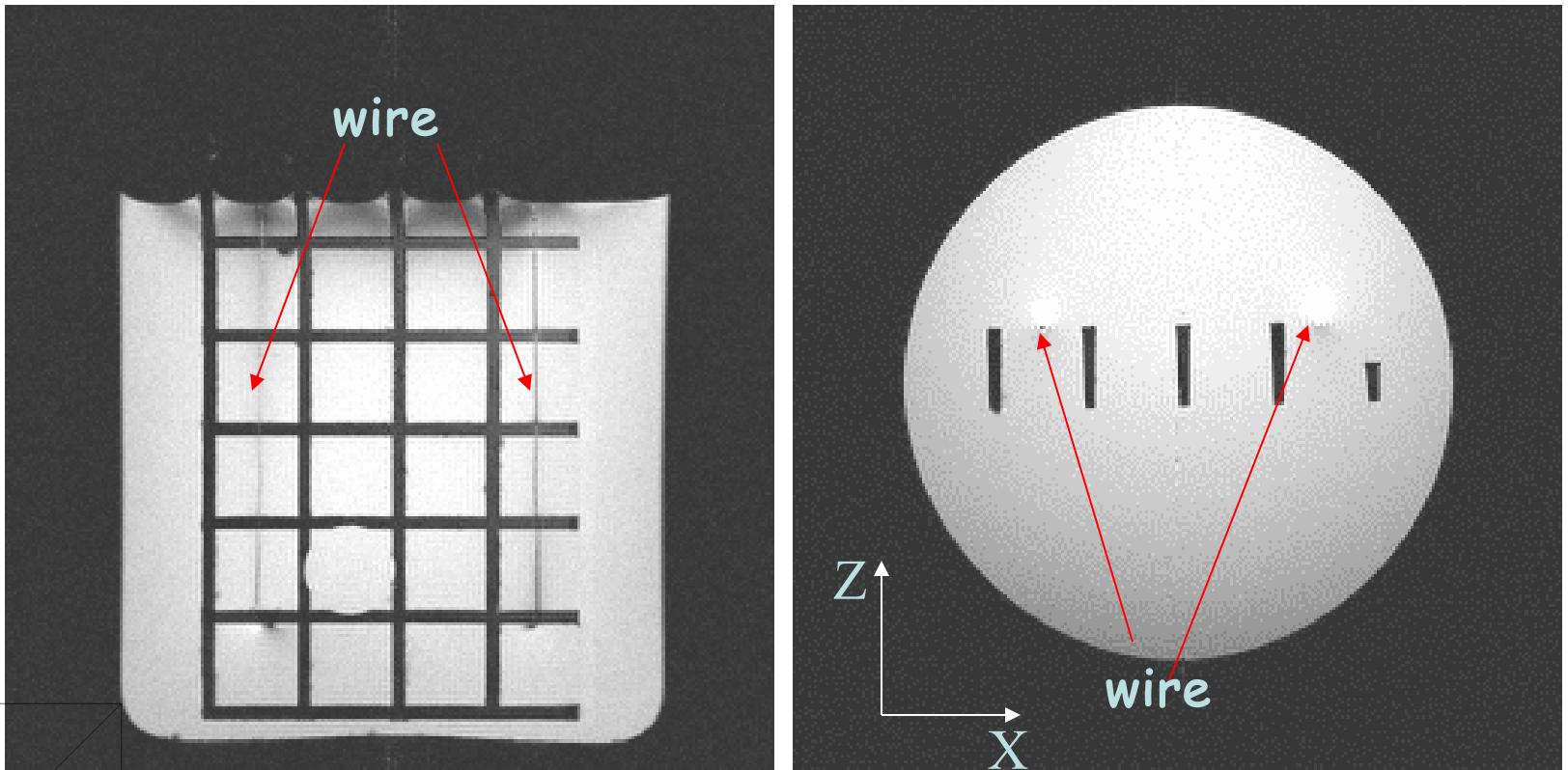


## Surface Field Distribution Across Spatial Scales

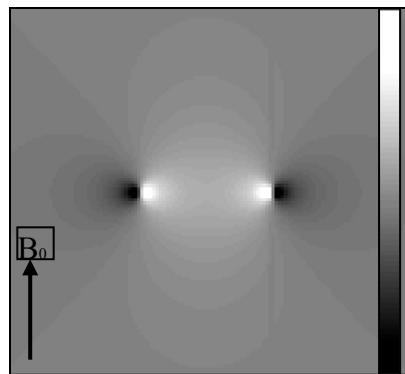


Adapted from: J.P. Wikswo Jr et al.  
*J Clin Neurophys* 8(2): 170-188, 1991

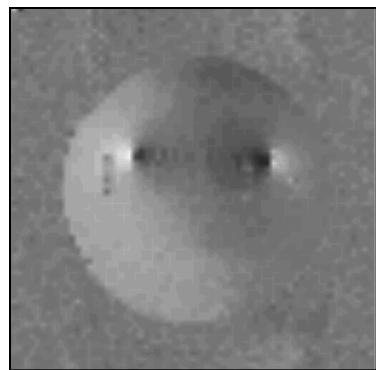
# Current Phantom Experiment



calculated  $B_c \parallel B_0$

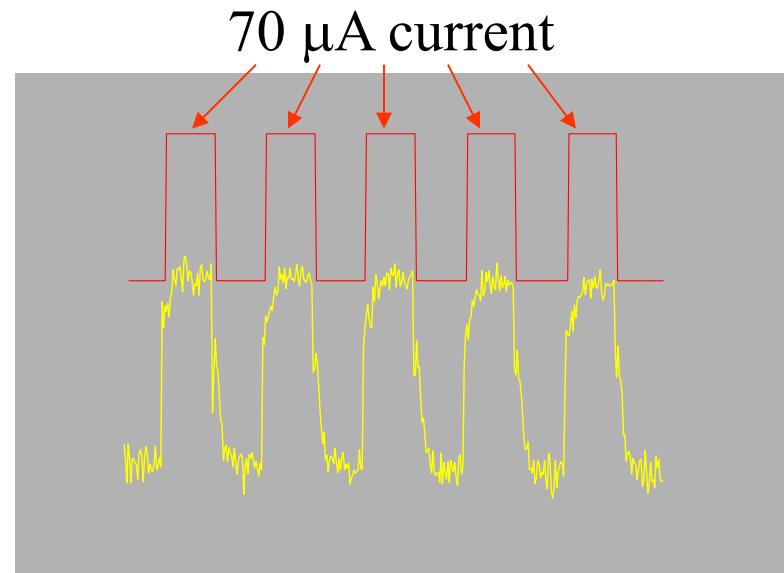


$$\Delta\phi \approx 20^\circ$$



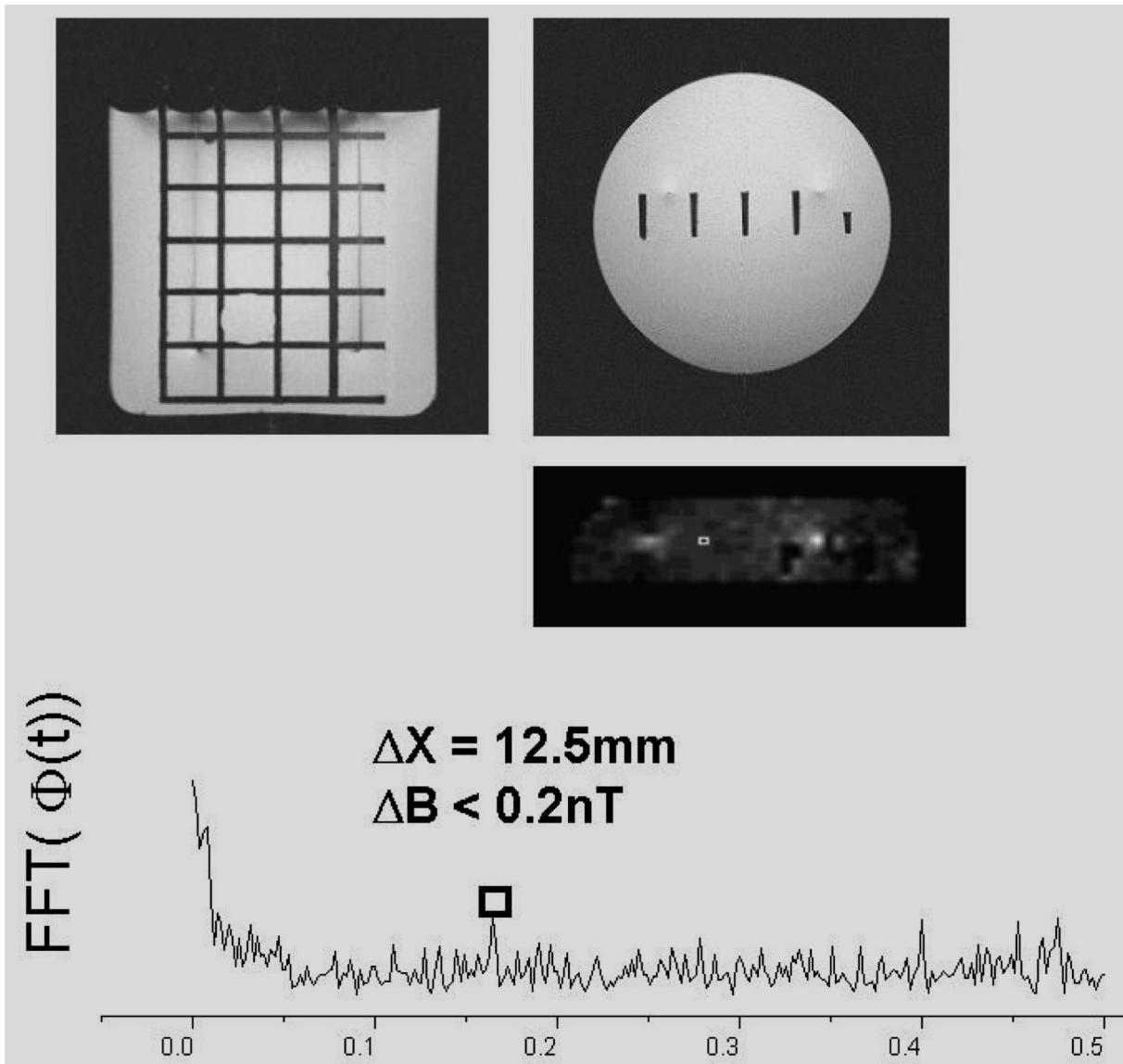
Correlation image

## Measurement



Single shot GE EPI

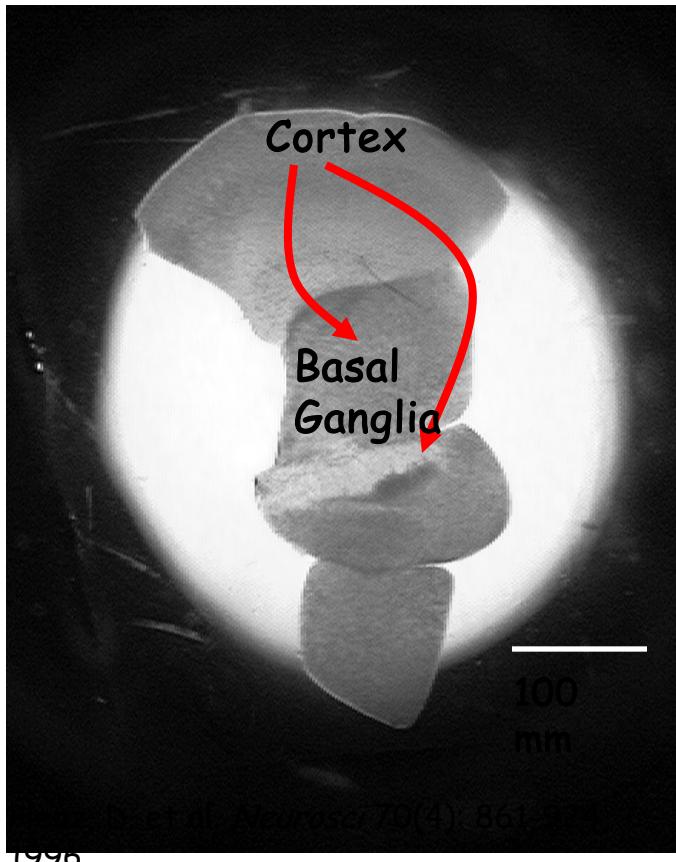
J. Bodurka, P. A. Bandettini. Magn. Reson. Med. 47: 1052-1058, (2002).



J. Bodurka, P. A. Bandettini. Magn. Reson. Med. 47: 1052-1058, (2002).

# *in vitro* model

Organotypic (*no blood supply or hemoglobin traces*) sections of newborn-rat somato-sensory Cortex & Basal Ganglia



- Size: in-plane:~1-2mm<sup>2</sup>, thickness: 60-100μm
- Neuronal Population: 10,000-100,000
- Spontaneous synchronized activity < 2Hz
- Epileptiform activity
- Spontaneous beta freq. activity (20-30Hz)
- Network Activity Range: ~ 0.5-15μV

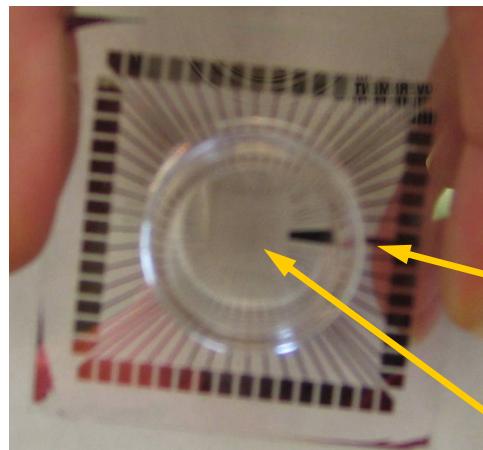
## *Culture Preparation*

Multi-Electrode Arrays (MEA)

Multichannelsystems Germany 8x8 electrodes

0.8ml culture medium

Multi-Electrode Array

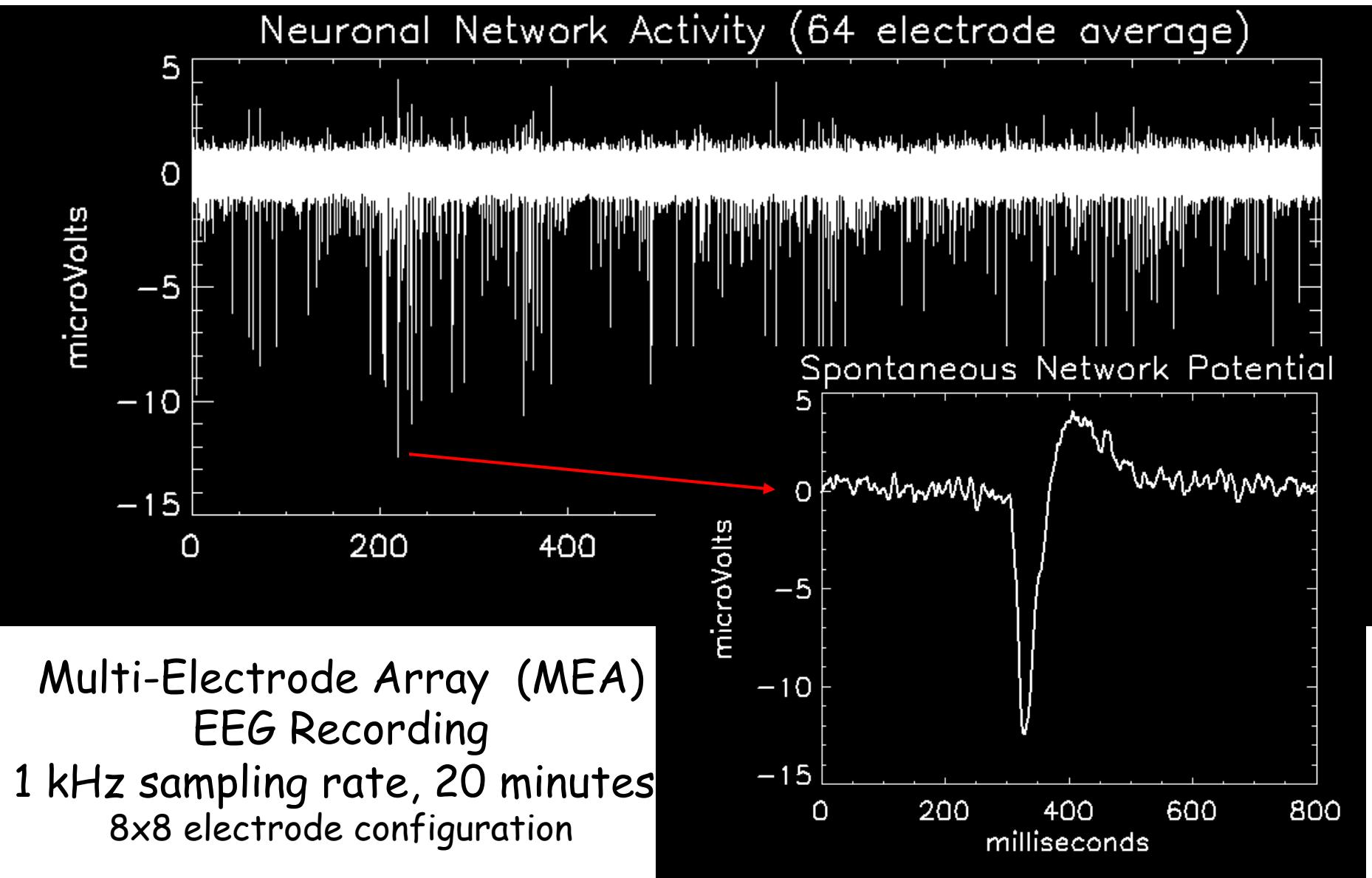


Reference  
electrode

Culture site

10mm

# Multi-Electrode Array EEG recording



# in vitro MR protocol

## Imaging (3T)

- Spin-Echo EchoPlanar Imaging

SE EPI  
image

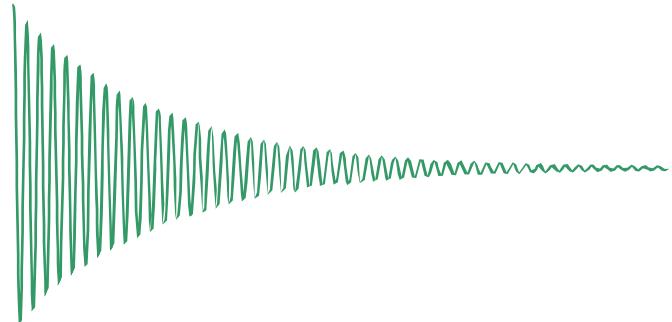


- voxel size: ~3x3x3 mm
- Sampling Rate :1 Hz (TR: 1sec)
- TE: 60 ms
- Readout :44 ms

## NMR (7T)

- free induction decay (FID) acquisition

FID



- slab size: ~2x10x1mm
- Sampling Rate :10 Hz (TR: 100ms)
- TE : 30 ms
- Readout : 41 ms

# *in vitro* MR experiment design

## Imaging (3T)

Six Experiments

Active : 10 min (600 images) neuronal activity present

Inactive : 10 min (600 images) neuronal activity terminated via TTX administration

## NMR (7T)

Six Experiments

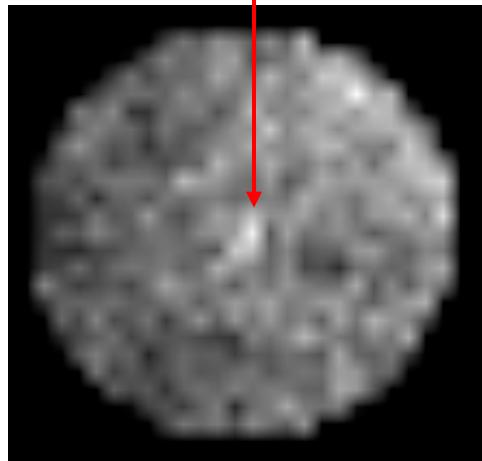
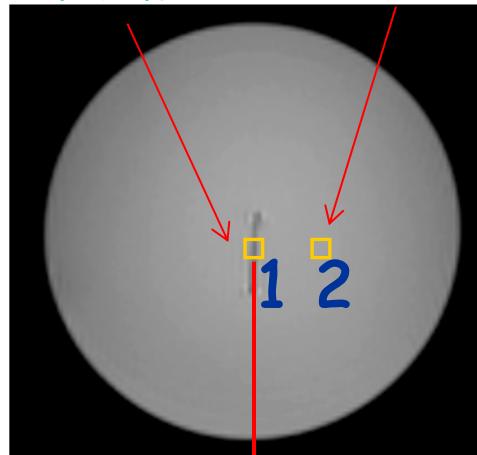
Active : ~17 min (10,000 images) neuronal activity present

Inactive : ~17 min (10,000 images) neuronal activity terminated via TTX administration

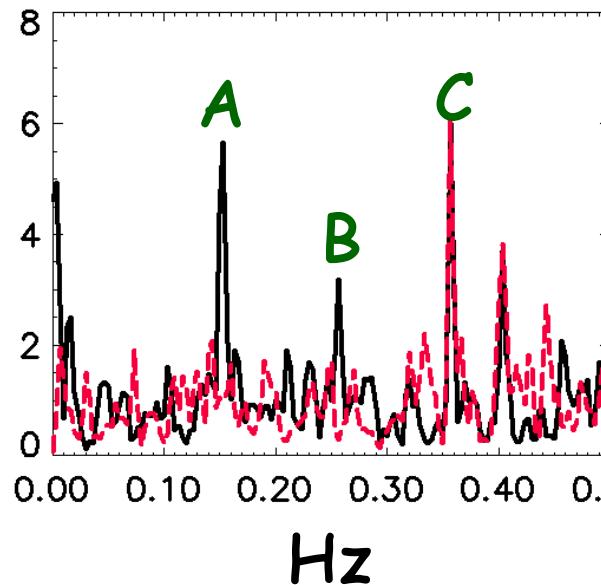
*Pre- and Post- MR scan electrical recordings*

### 3 Tesla data

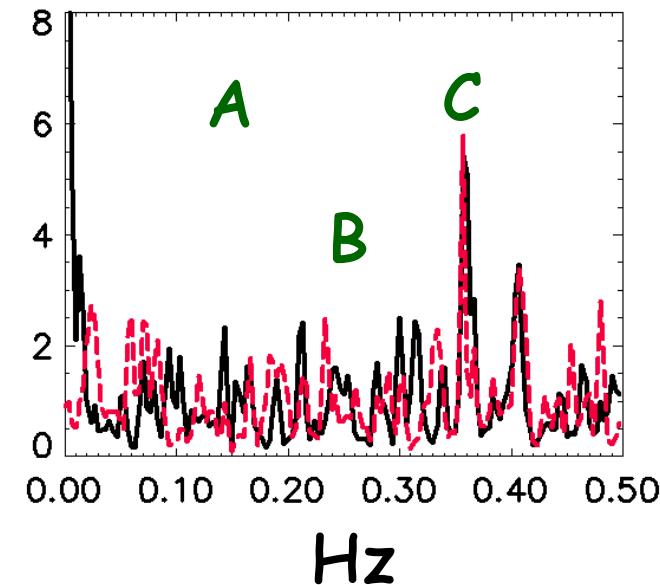
Culture      ACSF



*1: culture*



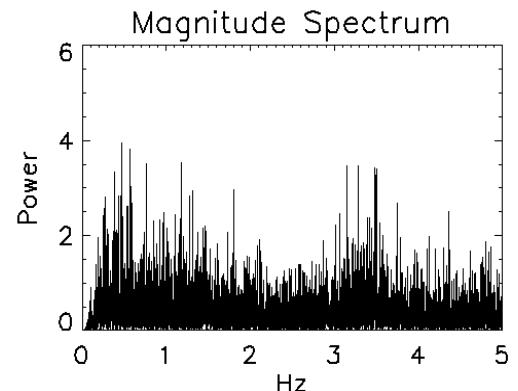
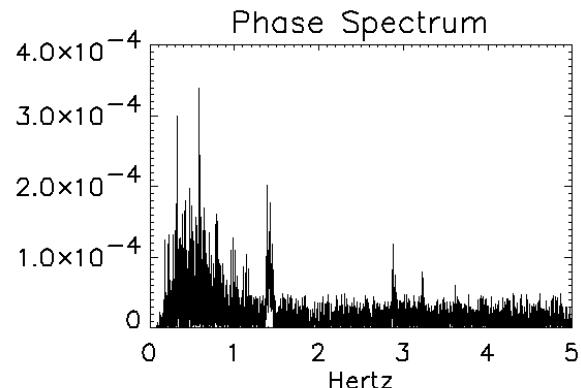
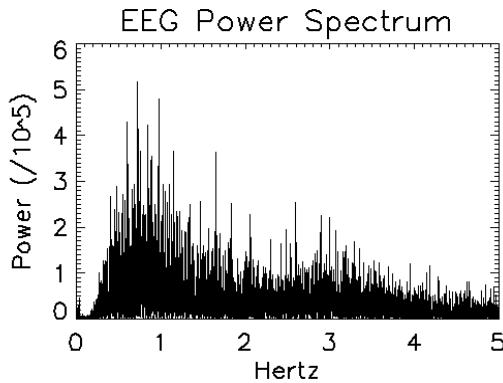
*2: ACSF*



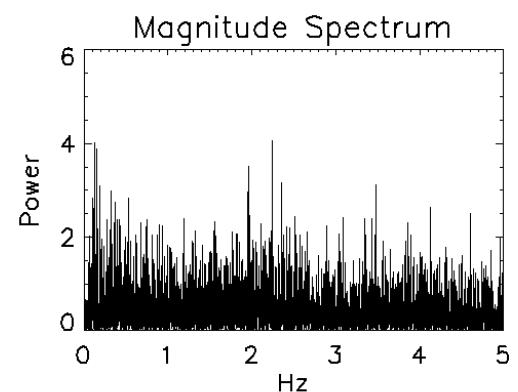
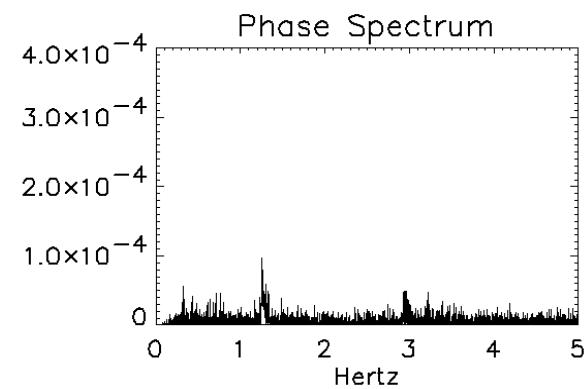
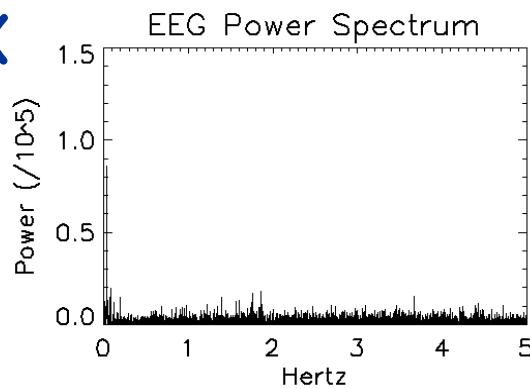
Active condition: black line  
Inactive condition: red line

- A: 0.15 Hz activity, on/off frequency
- B: activity
- C: scanner noise (cooling-pump)

# 7 Tesla data



TTX



Power decrease between PRE & TTX EEG : ~ 81%

Decrease between PRE & TTX  
MR phase: ~ 70%

Decrease between PRE & TTX  
MR magnitude: ~ 8%

N. Petridou, D. Plenz, A. C. Silva, J. Bodurka, M. Loew, P. A. Bandettini,  
Proc. Nat'l. Acad. Sci. USA. 103, 16015-16020 (2006).

1. Dynamics

2. Fluctuations

3. Experimental Design

4. Pattern Information

5. Neuronal Current MRI



September, 1991

## Section on Functional Imaging Methods

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Anthony Boemio	post doc
Justin Edmands	system admin
Dan Handwerker	post doc
Tyler Jones	post bac IRTA
Youn Kim	post bac IRTA
Niko Kriegeskorte	post doc
Marieke Mur	student IRTA
Kevin Murphy	post doc
Alissa Par	post bac IRTA
Vikas Patel	system admin
Dorian Van Tassell	program assistant

Javier Castillo-Gonzalez Summer Student	
Jason Diamond	Howard Hughes Fellow
Thomas Gallo	Summer Student
Hauke Heekeren	post doc
David Knight	post doc
Ilana Levy	post bac IRTA
Marta Maierow	visiting fellow
Hanh Nguyen	post bac IRTA
Natalia Petridou	student IRTA
Douglass Ruff	post bac IRTA
Monica Smith	post bac IRTA
August Tuan	post bac IRTA
Naja Waters	post bac IRTA

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Jerzy Bodurka	staff scientist
Ellen Condon	technologist
Janet Ebron	technologist
Kenny Kan	technologist
Kay Kuhns	admin. lab manager
Wenming Luh	staff scientist
Sean Marrett	staff scientist
Marcela Montequin	technologist
Sandra Moore	technologist
Sahra Omar	technologist
Alda Ottley	technologist
Paula Rowser	technologist
Adam Thomas	system admin

Karen Bove-Bettis	technologist
James Hoske	technologist

Parameter	Description	Default value	Range evaluated
$E_0$	Resting oxygen extraction fraction	0.4	0.3–0.6
$v_0$	Resting blood volume fraction	0.03	0.03–0.18
$f_0$	Resting relative blood flow	0.01 s <sup>-1</sup>	0.01 s–0.16 s
$\Delta f$	Fractional blood flow change	0.4	—
$\alpha$	Steady-state flow–volume relationship	0.4	0.25–1.0
$\tau_{MTT}$	Blood mean transit time ( $v_0/f_0$ )	3 s	1.1 s–18 s
$\tau_+$	Viscoelastic time constant (inflation)	20 s	10 s–40 s
$\tau_-$	Viscoelastic time constant (deflation)	20 s	10 s–40 s
$a_1$	Weight for deoxyhemoglobin change	3.7	2.8–5.6
$a_2$	Weight for blood volume change	1.1	0.7–1.9

ON response amplitude: initial amp:	1.5 times steady state amp
Adaptation time constant:	1.5s
Refractory period:	5s
OFF response amplitude:	initial amp 0.5 times steady state amp
OFF response time constant:	0.5s

The initial overshoot amplitude and decay time were chosen to roughly match the local field potential change measured in macaque visual cortex in response to rotating checkerboard, as measured by Logothetis et al. (2001).

The refractory period was chosen to produce results somewhat consistent with observed BOLD refractory period (Huettel et al., 2000).