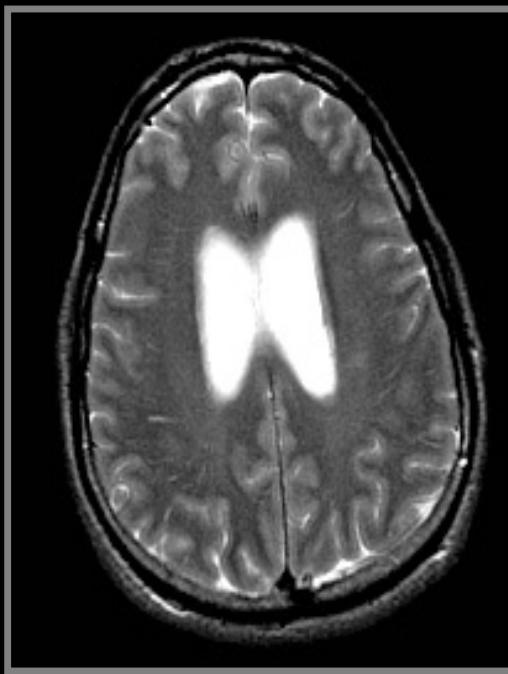


# Spatial, Temporal, and Interpretive Limits of Functional MRI

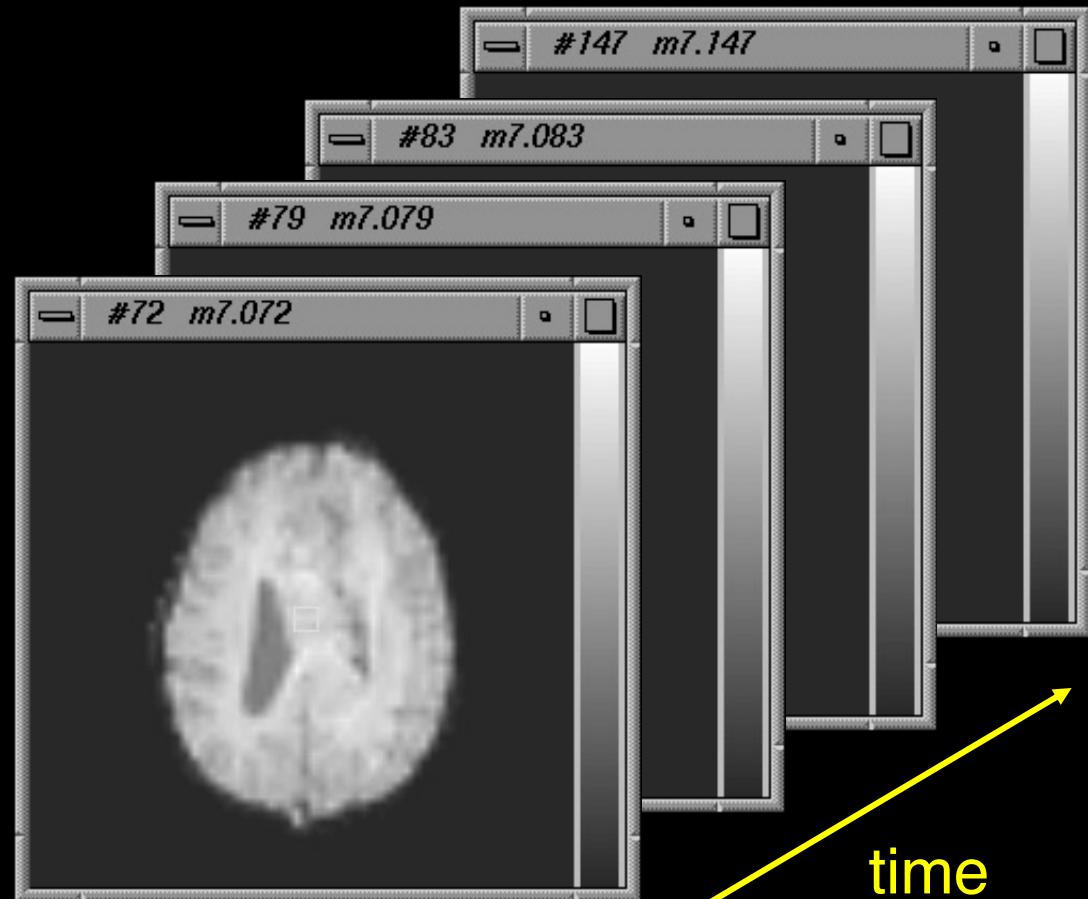
Peter A. Bandettini, Ph.D

Unit on Functional Imaging Methods  
&  
3T Neuroimaging Core Facility

Laboratory of Brain and Cognition  
National Institute of Mental Health

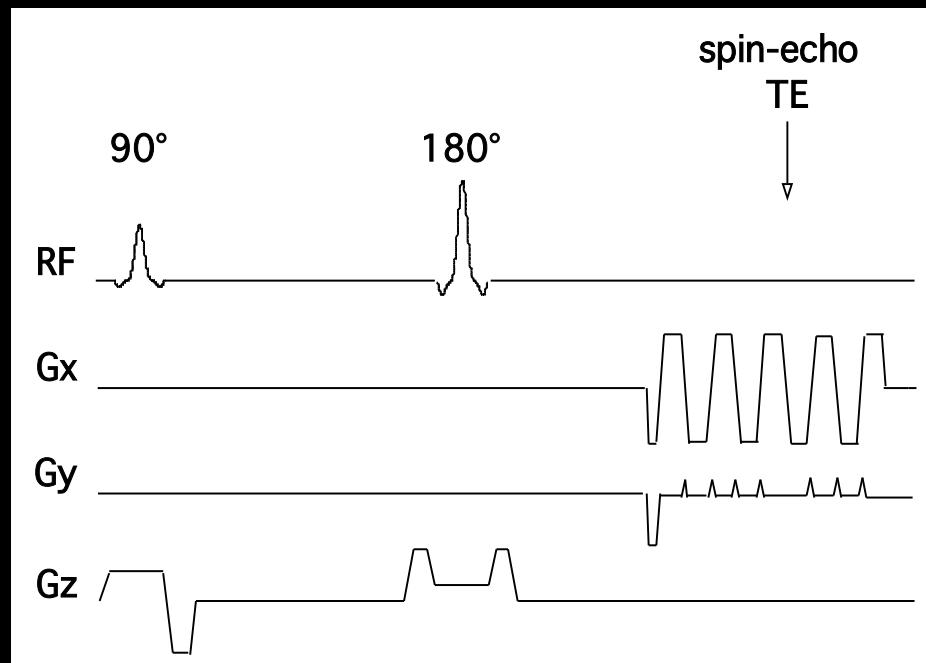
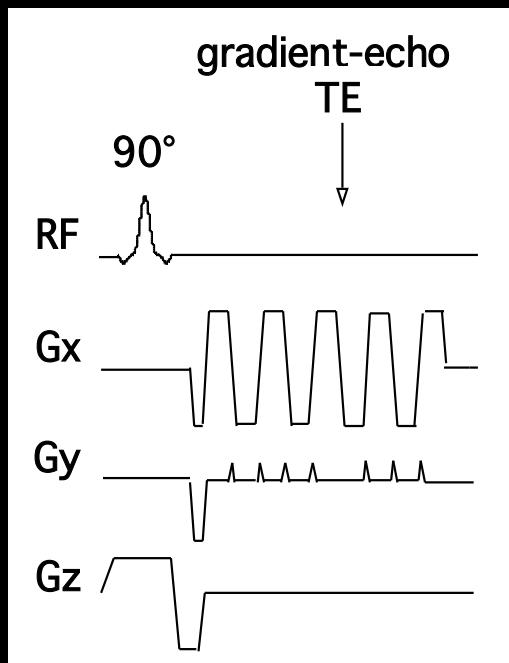


Anatomic



Functional

# Echo-Planar Imaging

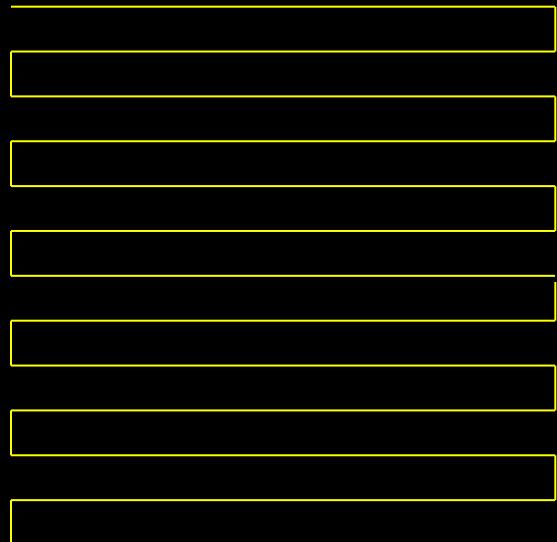


# Single Shot Imaging

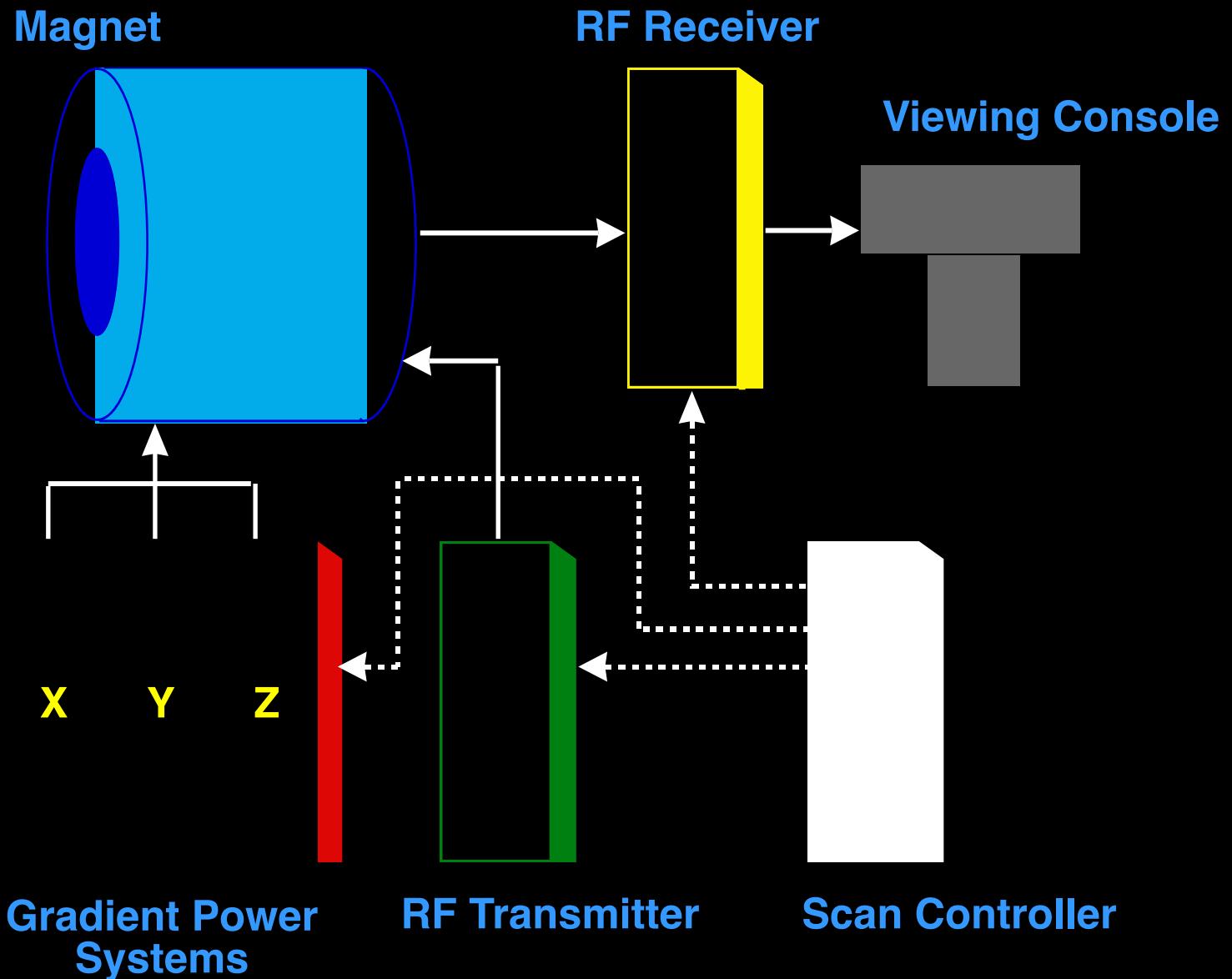


EPI Readout Window

$\approx 20$  to 40 ms



# Imaging System Components



**1991-1992**



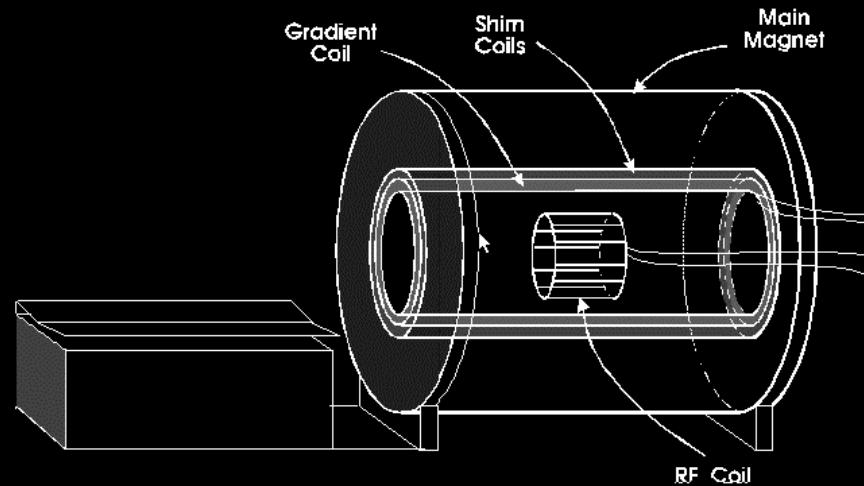
**1992-1999**



2 G/cm, 350 T/m/s



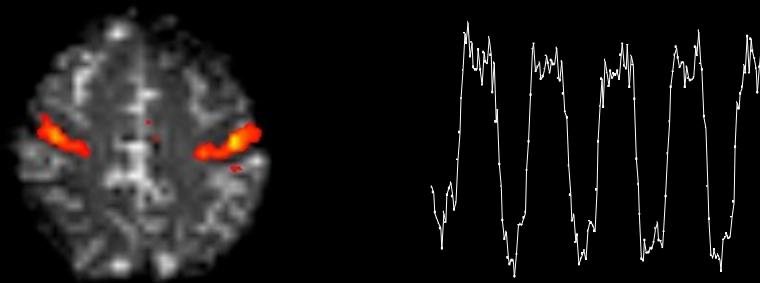
4 G/cm, 150 T/m/s



10 G/cm, 1000 T/m/s

# The use of fMRI to Investigate Brain Function

Where?



When?

How much?

---

**How to get the brain to do what we want it to do in the context of an fMRI experiment?**

# A Primary Challenge:

...to make progressively more precise inferences using fMRI without making too many assumptions about non-neuronal physiologic factors.

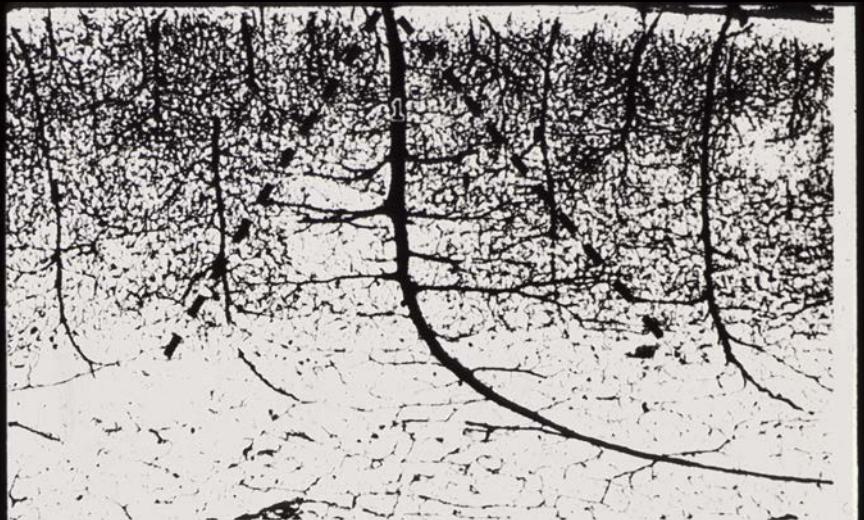
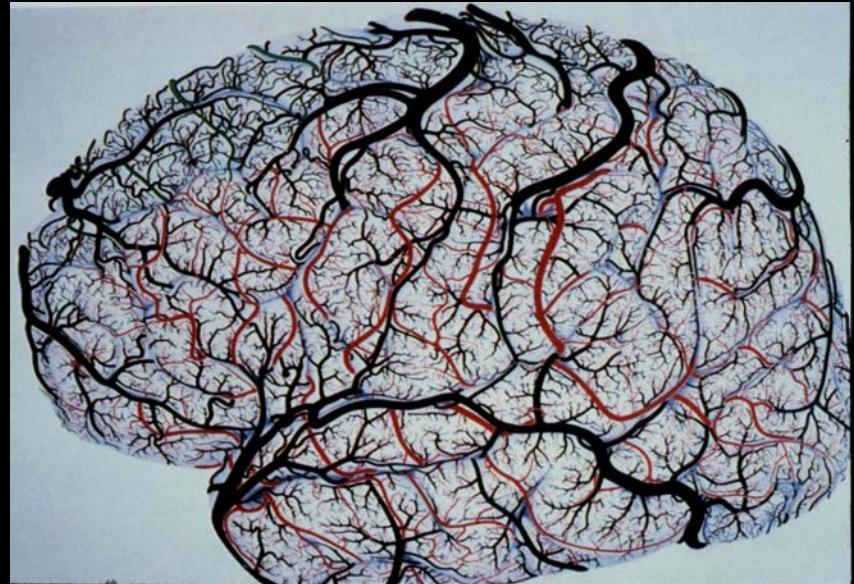


FIG. 43. Middle temporal gyrus. Female, 60 years. (1) Principal intracortical vein. The branches length regularly decreases from deep to superficial cortical regions, thus the vascular territory of the principal vein has a conical appearance (dotted line) ( $\times 28$ )



- Contrast in fMRI

*Hemodynamic Specificity*

- The Hemodynamic Transfer Function

*Location, Latency, Magnitude*

- Best Results So Far

*Temporal Resolution, Spatial Resolution*

- Neuronal Activation Input Strategies

*Block Design*

*Phase and Frequency Encoding*

*Orthogonal Designs*

*Parametric Designs*

*Event-Related Designs*

*Free Behavior Designs*

- Contrast in fMRI

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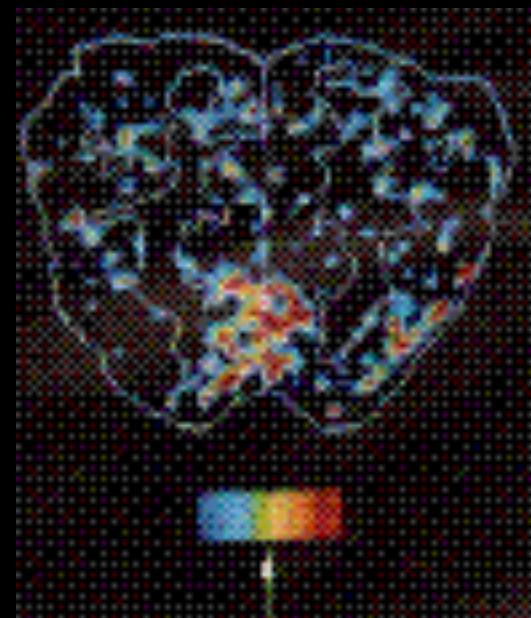
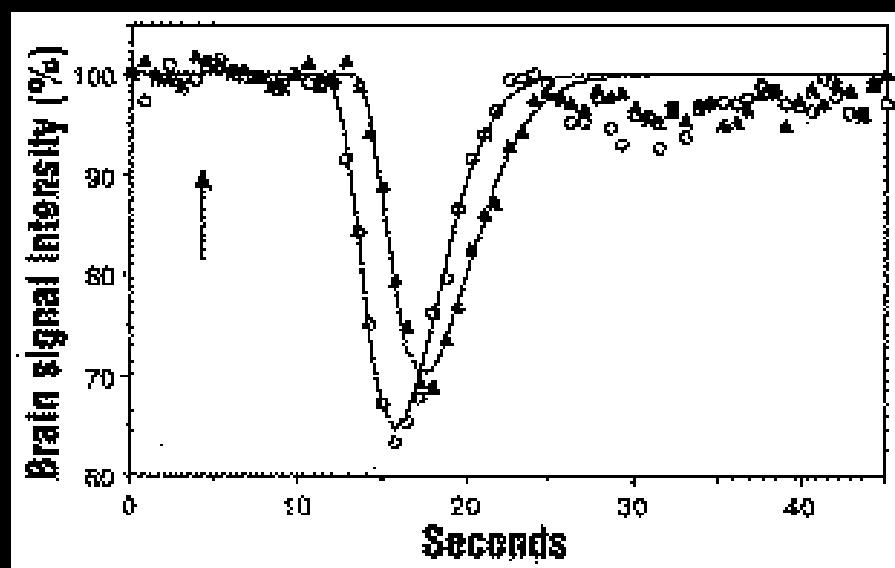
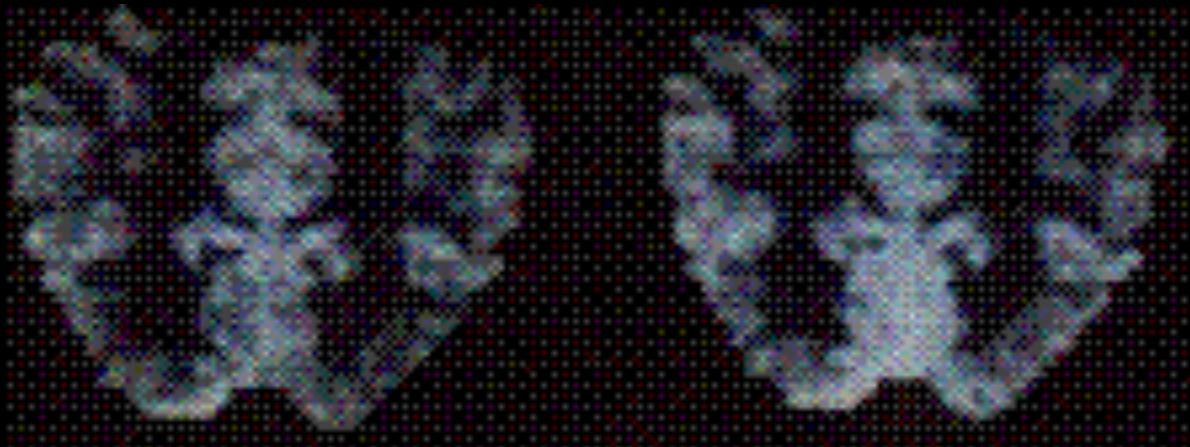
*Free Behavior Designs*

# Contrast in Functional MRI

- **Blood Volume**
  - Contrast agent injection and time series collection of T2\* or T2 - weighted images
- **BOLD**
  - Time series collection of T2\* or T2 - weighted images
- **Perfusion**
  - T1 weighting
  - Arterial spin labeling
- **CMRO<sub>2</sub>**
  - BOLD and Perfusion w/  
Normalization to Global Perfusion Change

**Resting**

**Active**

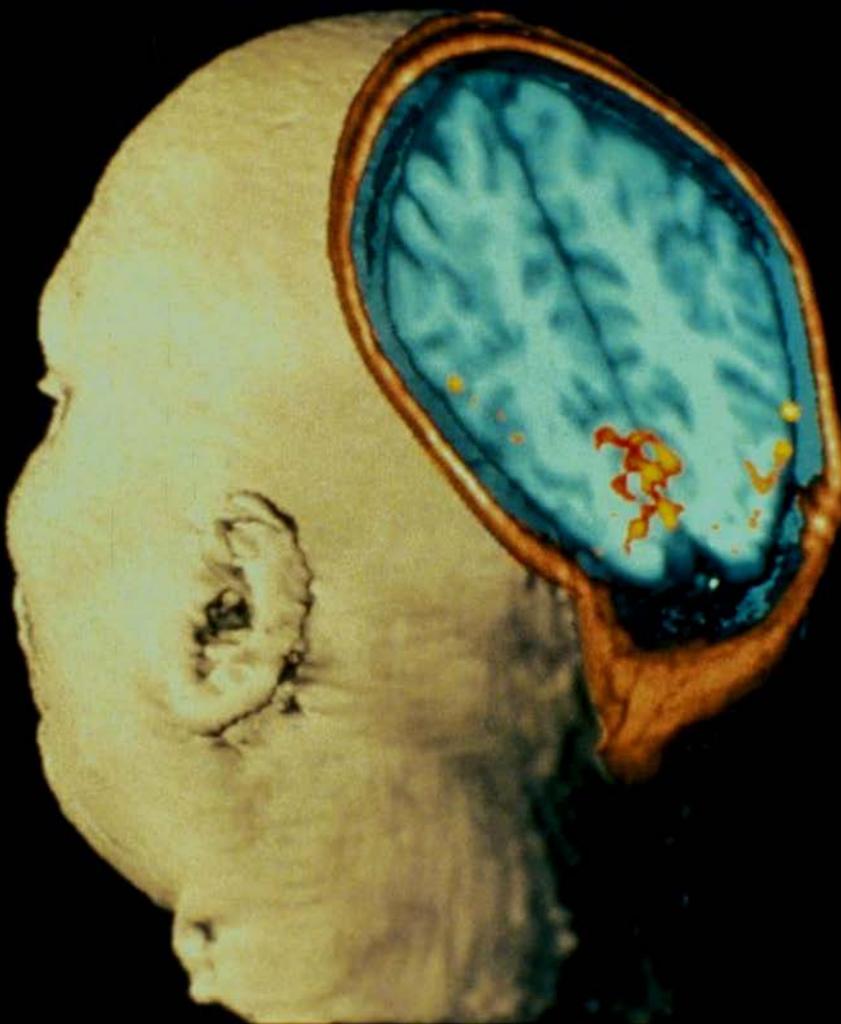


# Photic Stimulation

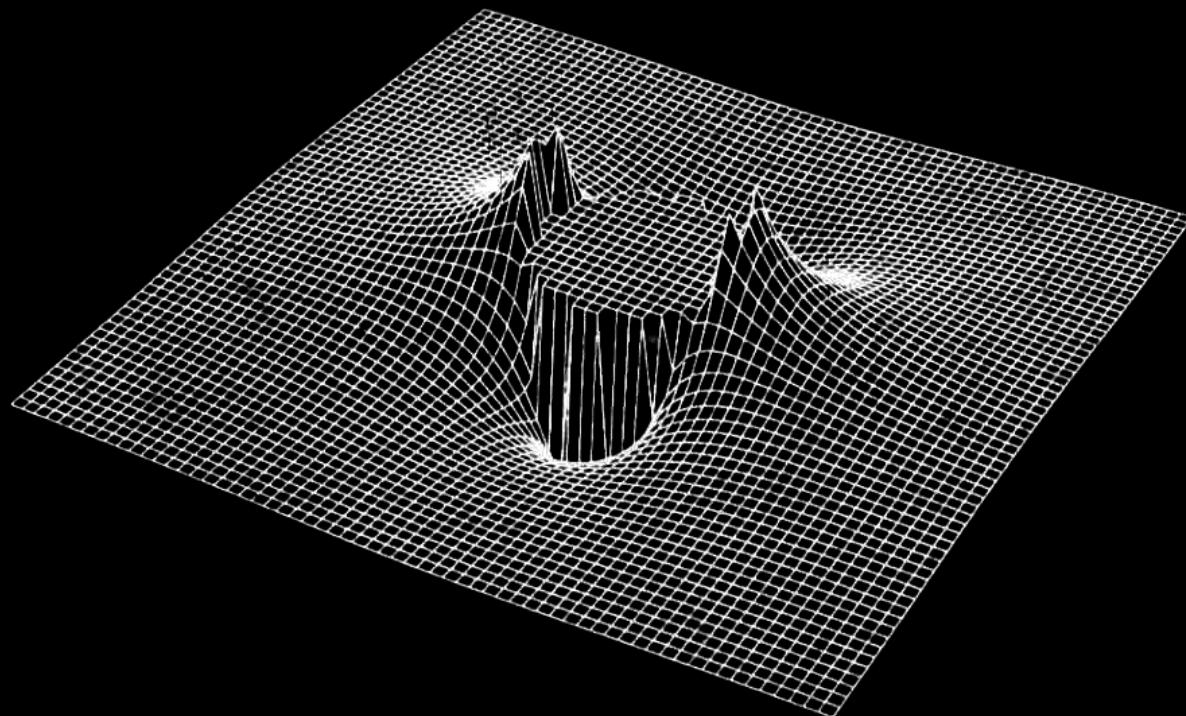
MRI Image showing  
activation of the  
Visual Cortex

From Belliveau, et al.  
Science Nov 1991

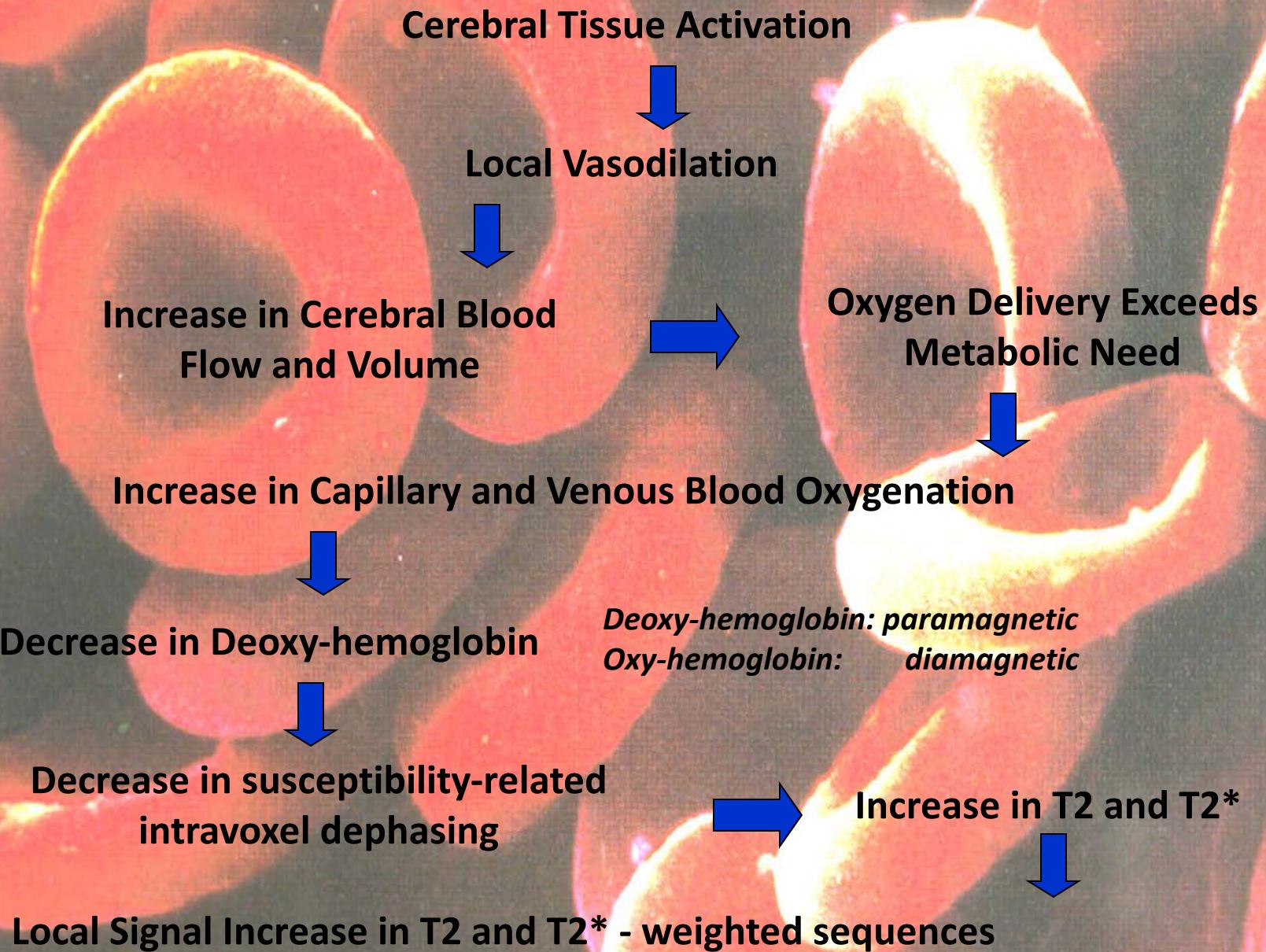
MSC - perfusion



Susceptibility-Induced Field Distortion in the  
Vicinity of a Microvessel  $\perp$  to  $B_0$ .

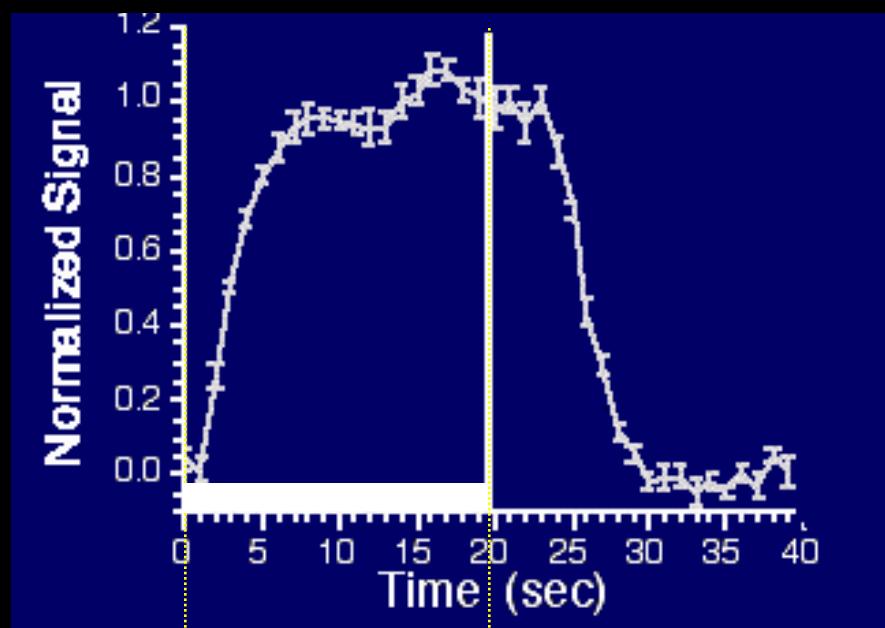


# BOLD Contrast in the Detection of Neuronal Activity

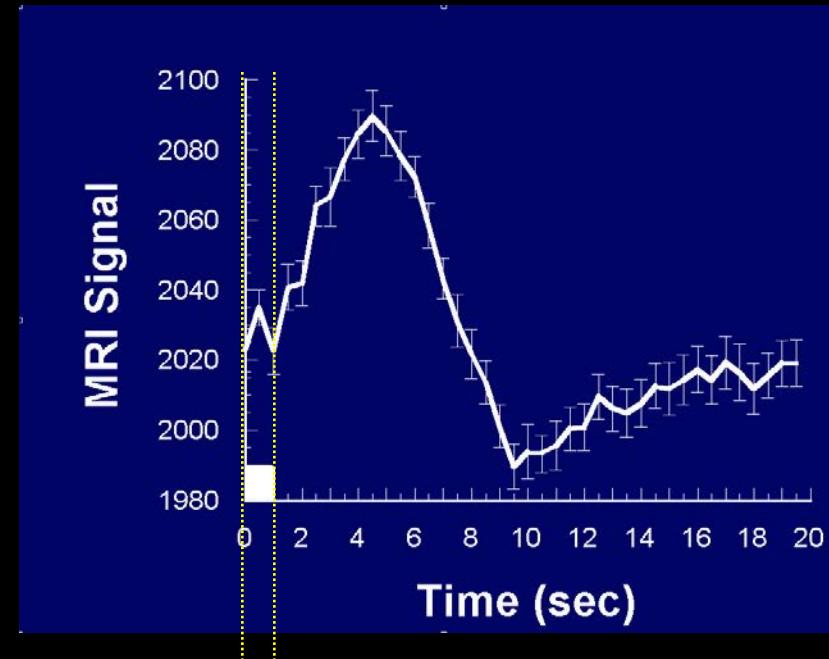


# The BOLD Signal

Blood Oxxygenation Level Dependent (BOLD) signal changes



*task*



*task*

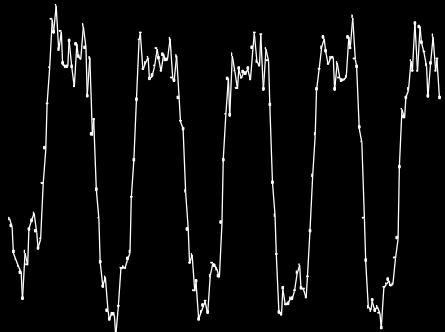
# Alternating Left and Right Finger Tapping



~ 1992

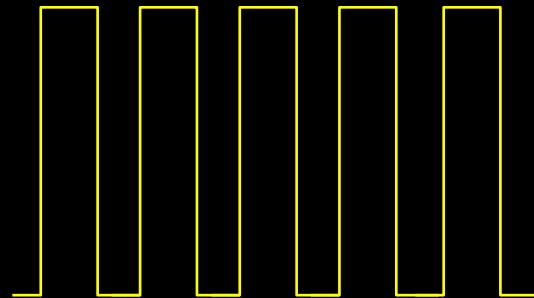
# Creating a Functional Image

ON ON ON ON ON



Signal Time Course

X



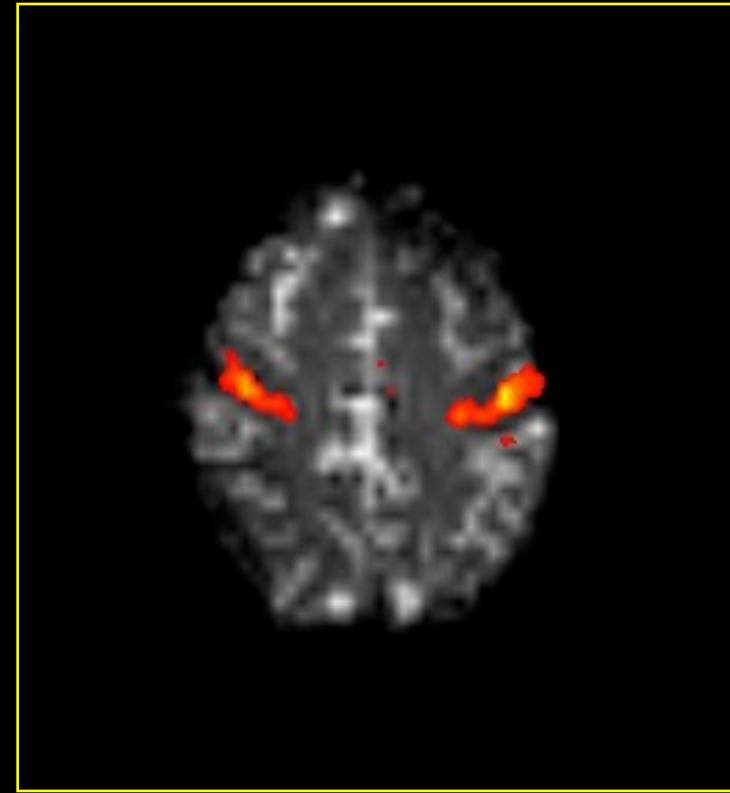
Reference Function

=



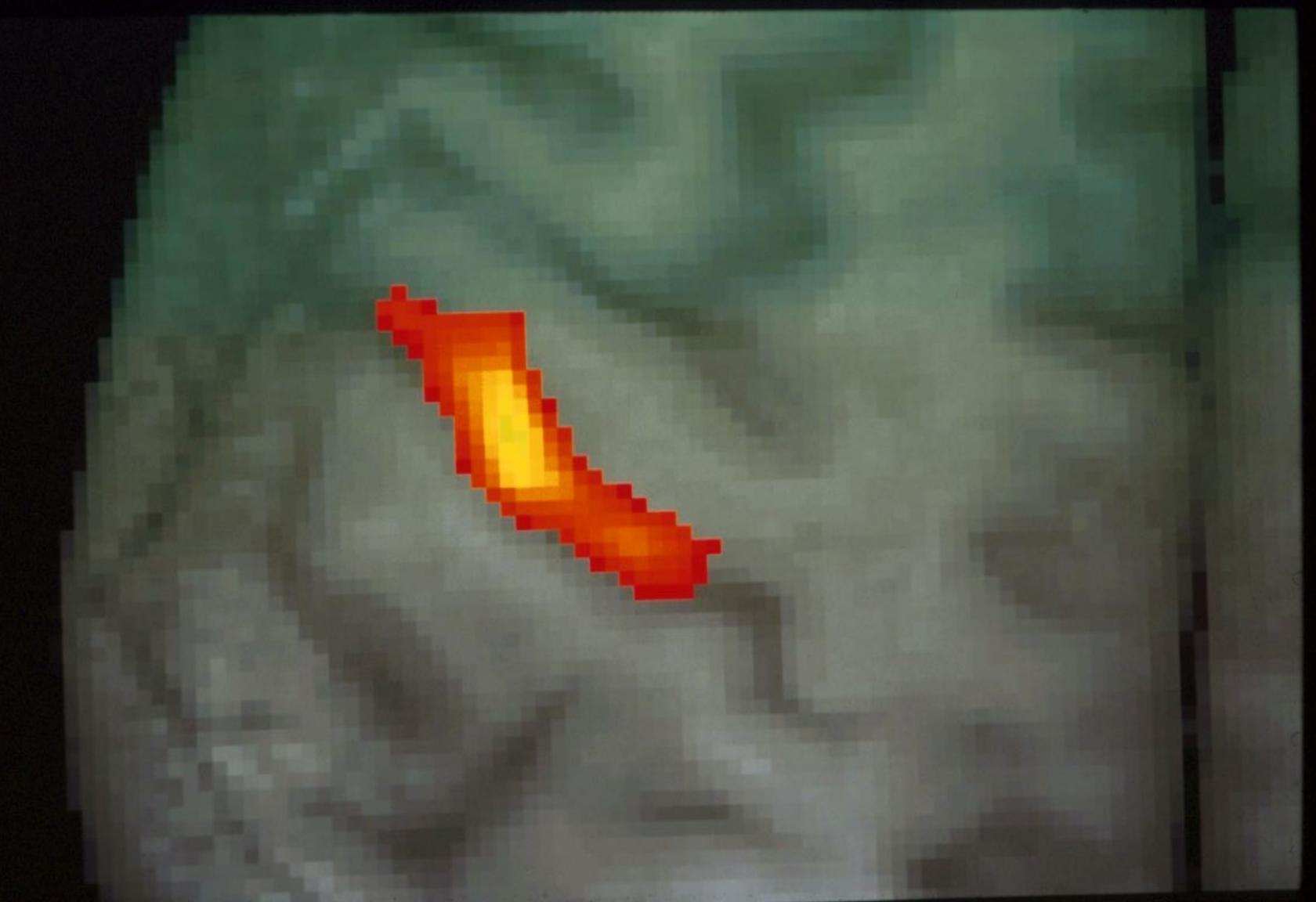


Cross Correlation Image



Cross Correlation Image

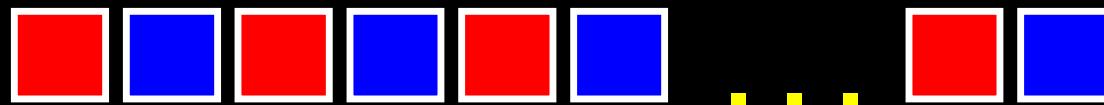
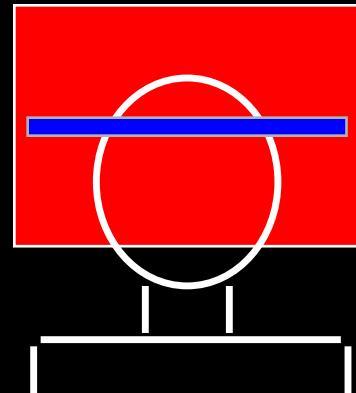
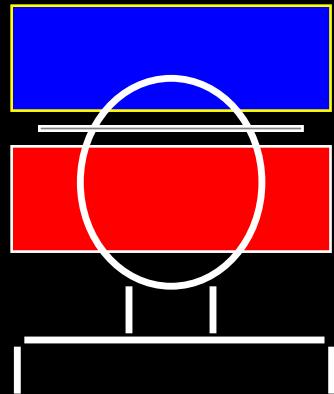
Anatomical Image



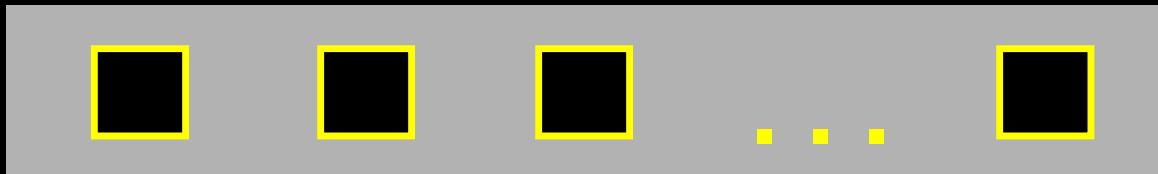
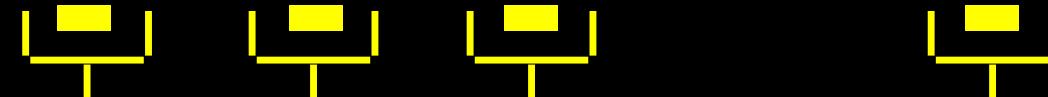
# Perfusion / Flow Imaging

EPISTAR

FAIR

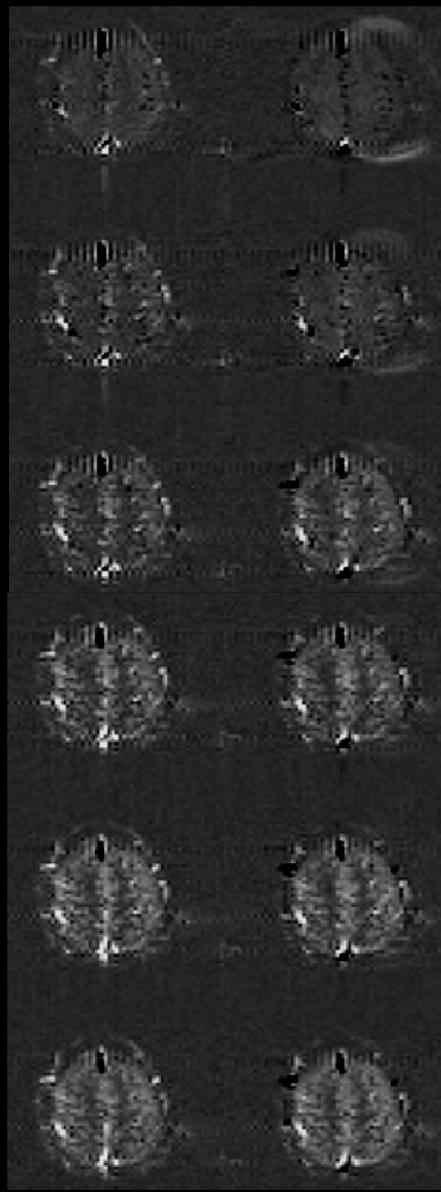


...



**TI (ms) FAIR EPISTAR**

**200**



**400**

**600**

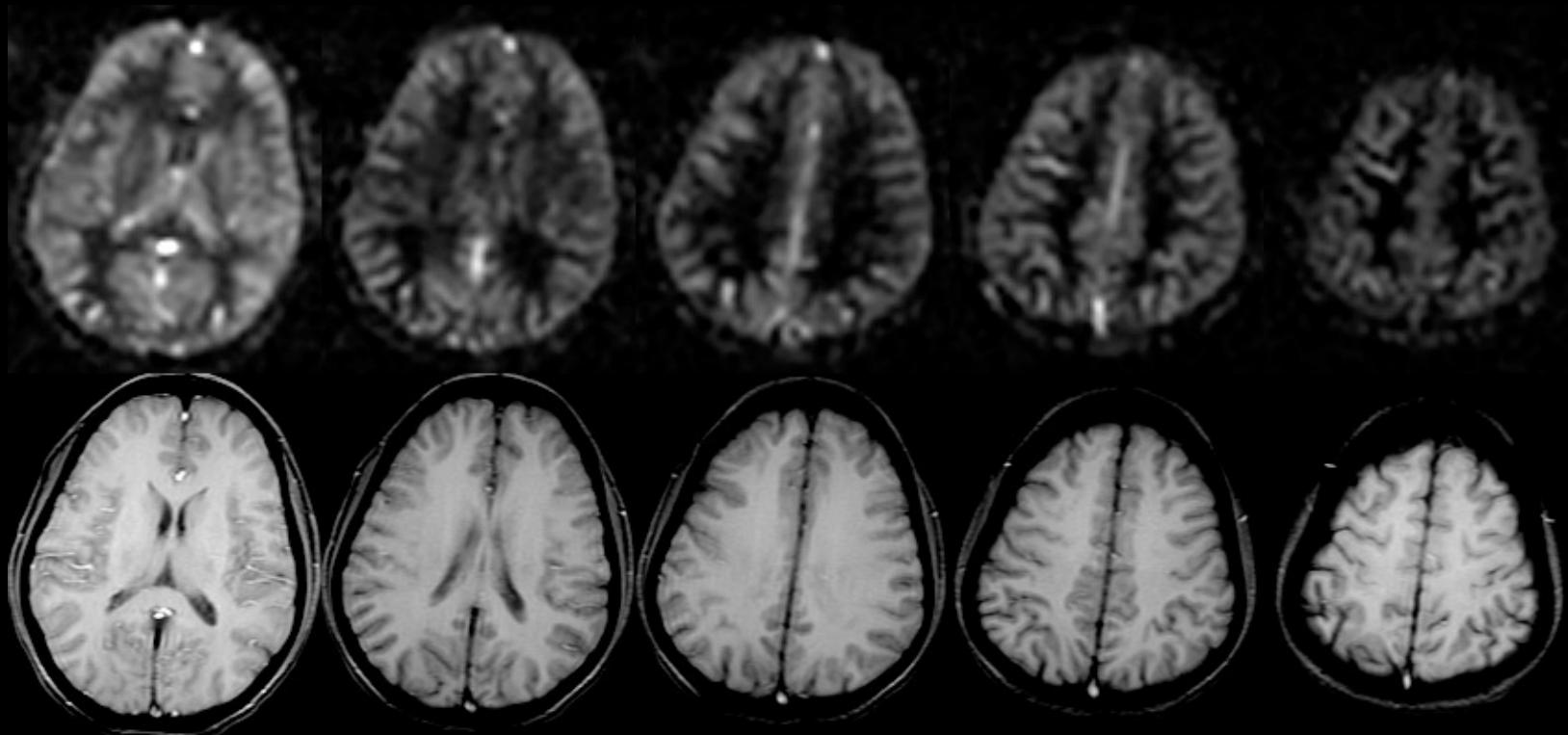
**800**

**1000**

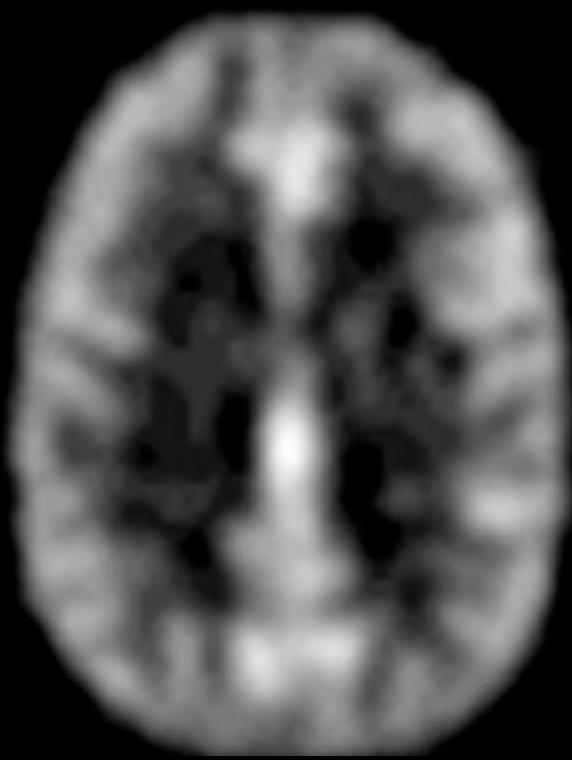
**1200**

# Resting ASL Signal

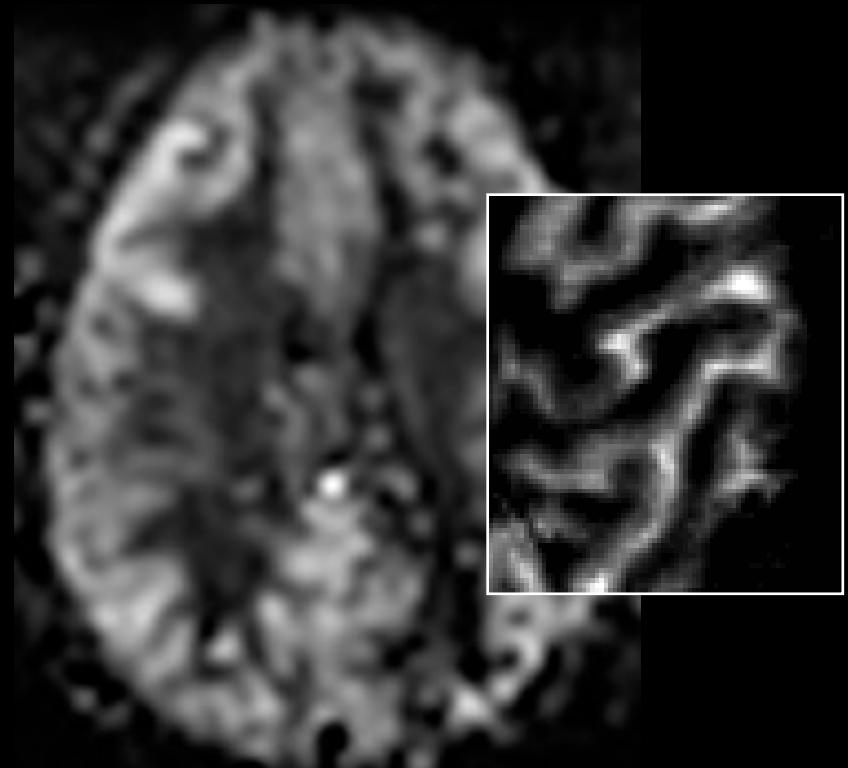
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# Comparison with Positron Emission Tomography



PET:  $\text{H}_2^{15}\text{O}$



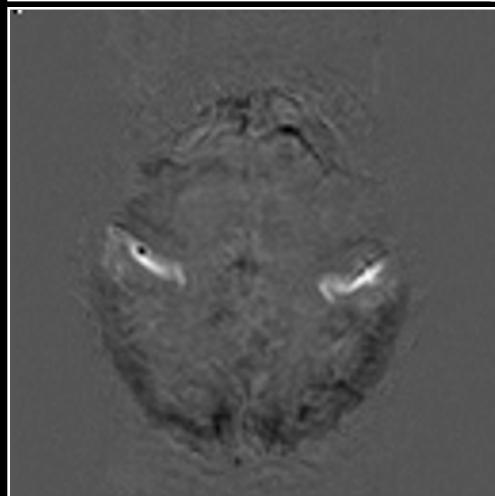
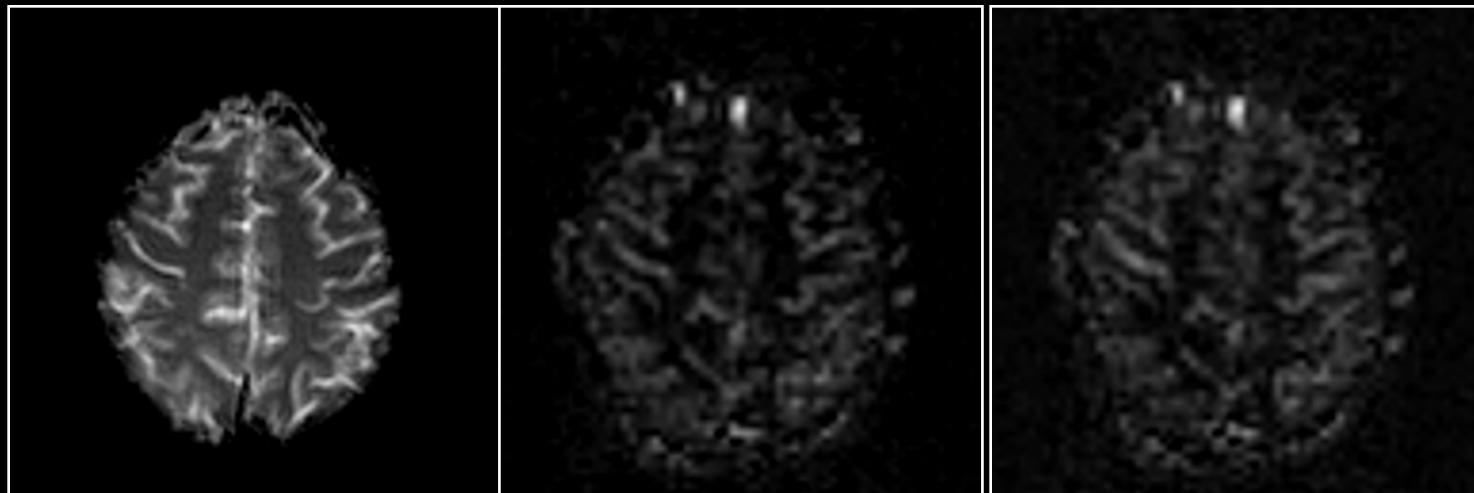
MRI: ASL

# Perfusion

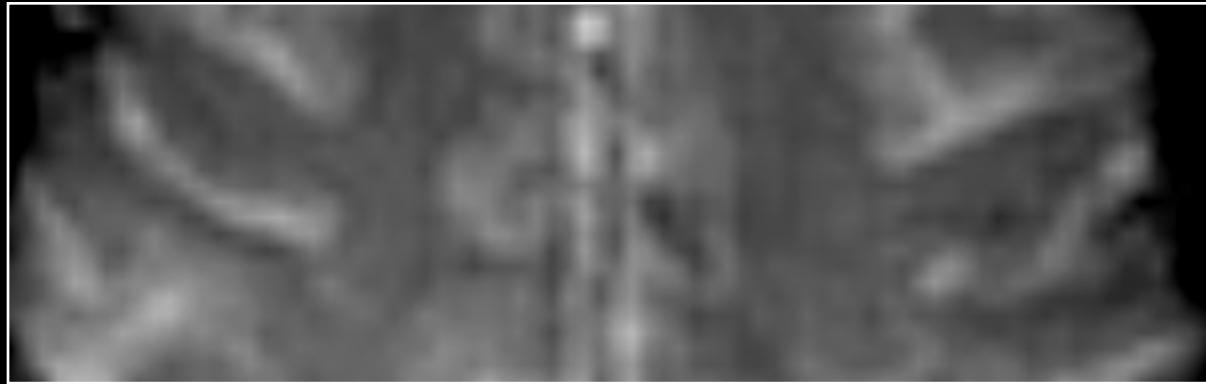
**BOLD**

*Rest*

*Activation*



# **Anatomy**



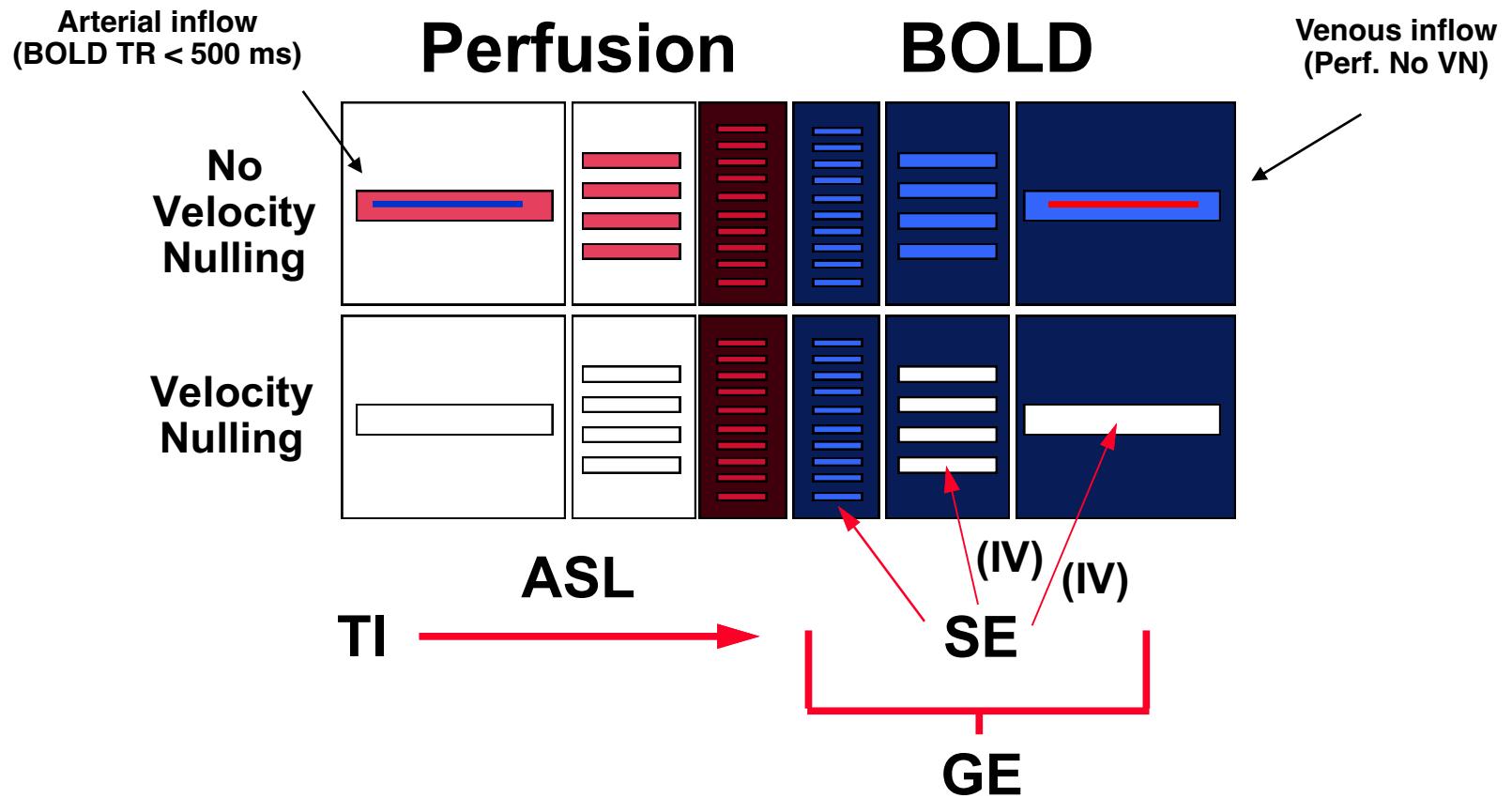
# **BOLD**



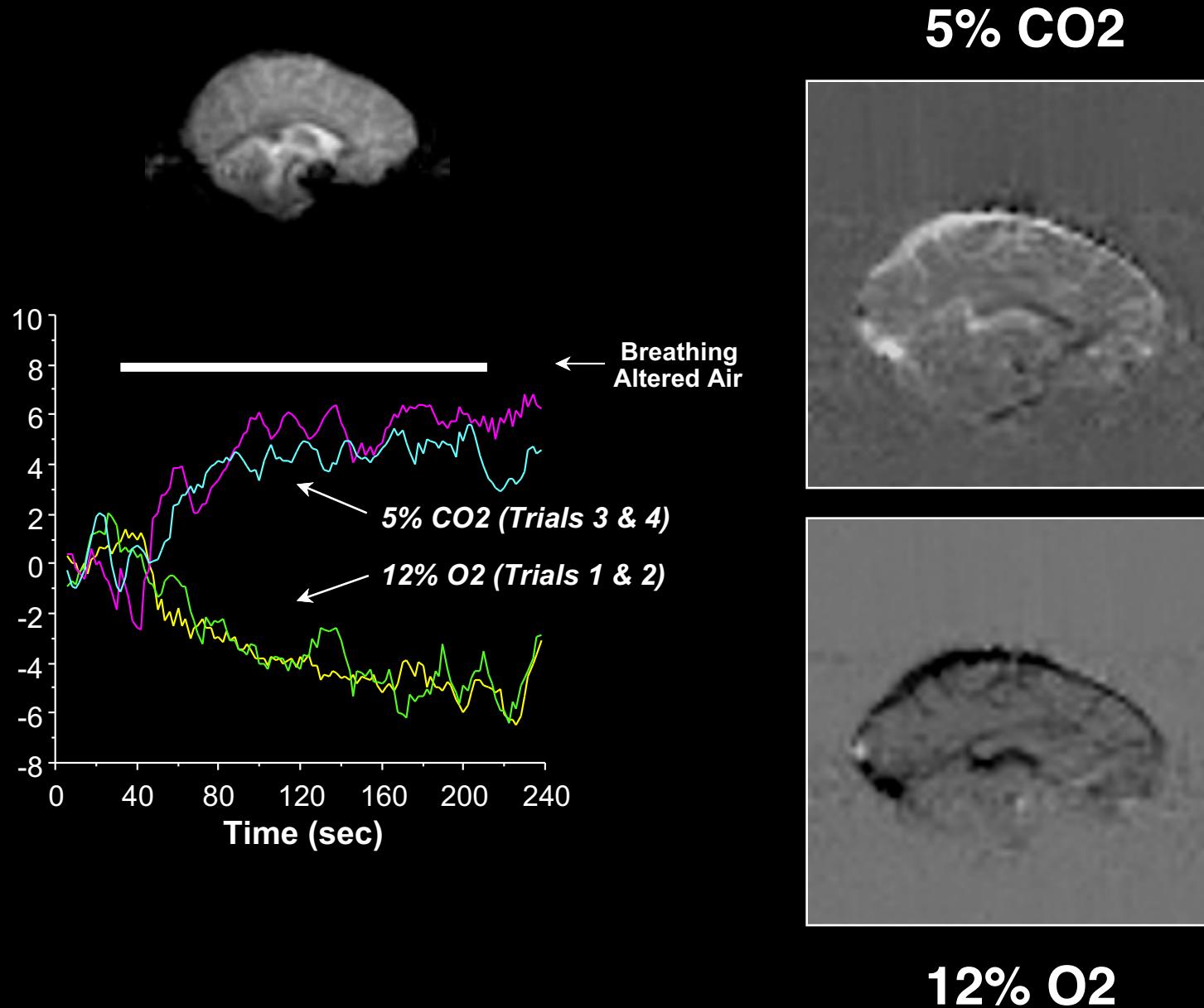
# **Perfusion**



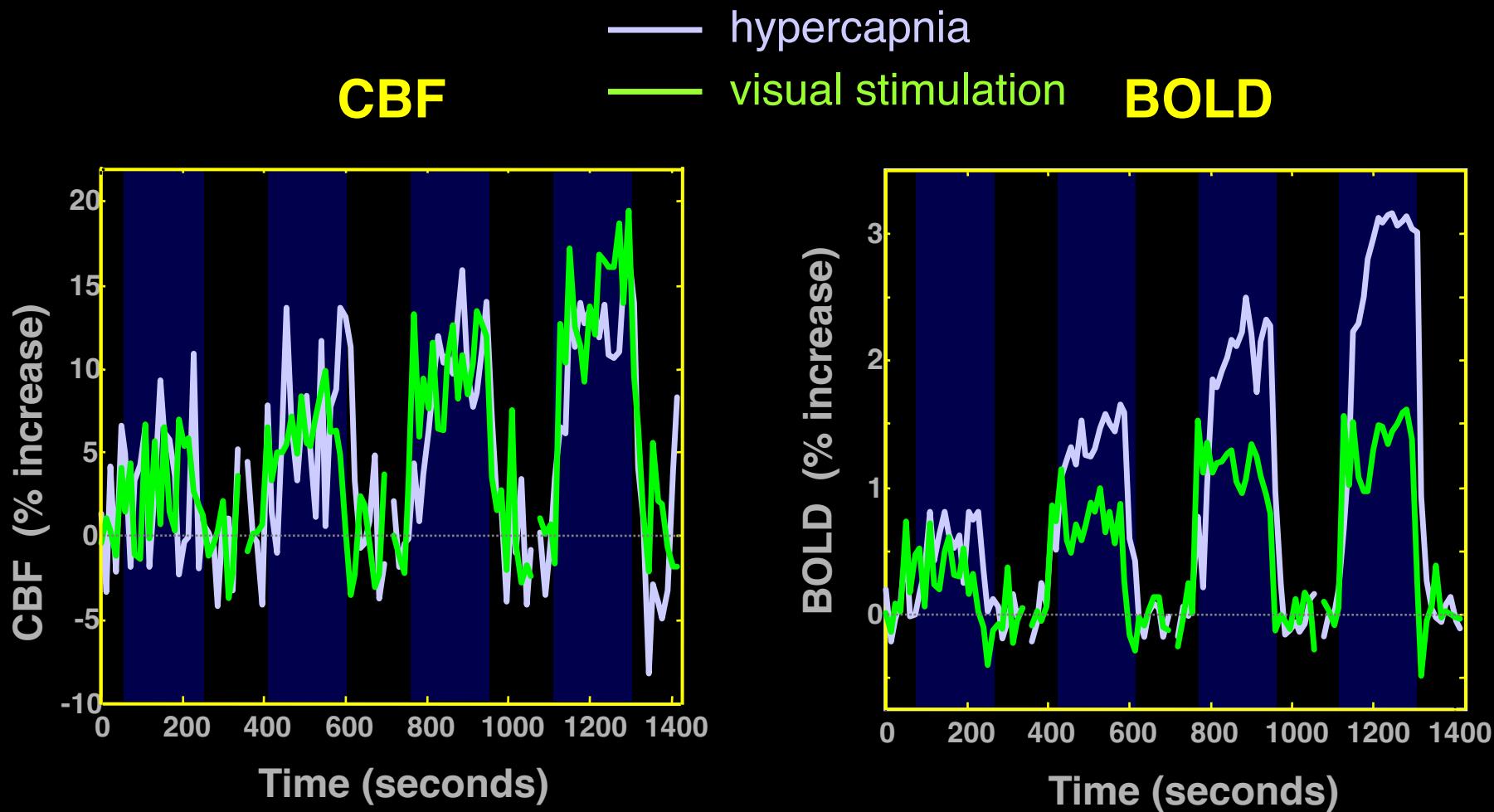
# Hemodynamic Specificity



# Hemodynamic Stress Calibration



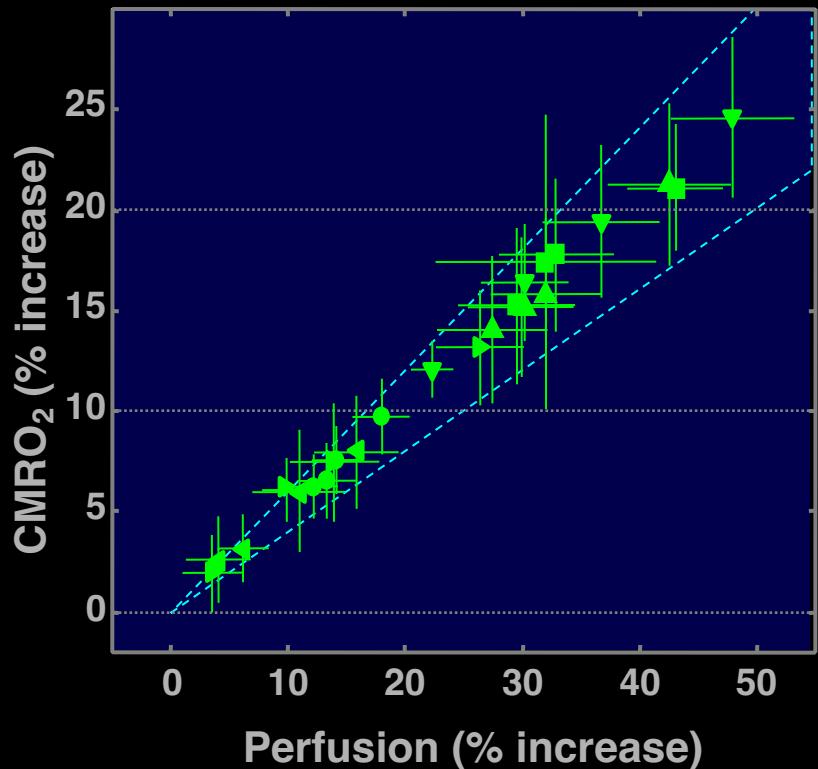
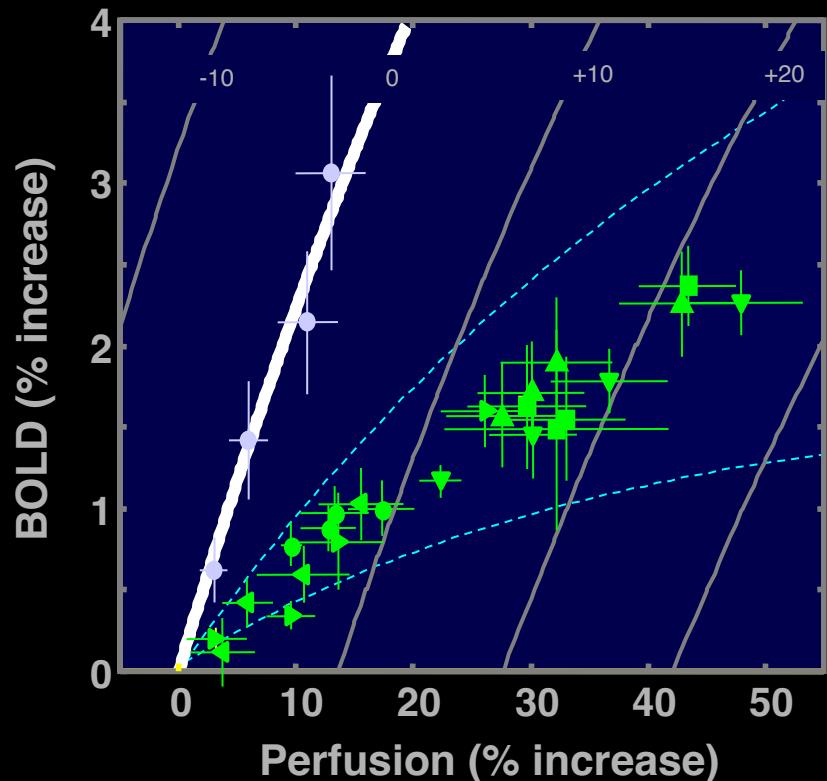
# CMRO<sub>2</sub>-related BOLD signal deficit:



Simultaneous Perfusion and BOLD imaging  
during graded visual activation and hypercapnia

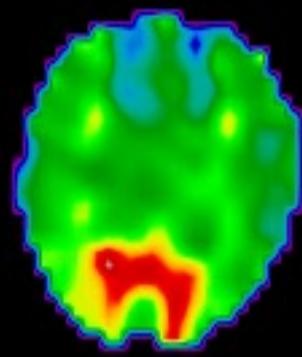
N=12

# CBF-CMRO<sub>2</sub> coupling

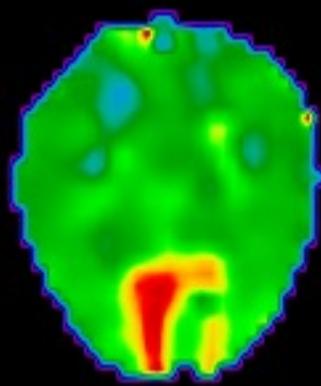


**Characterizing Activation-induced CMRO<sub>2</sub> changes using calibration with hypercapnia**

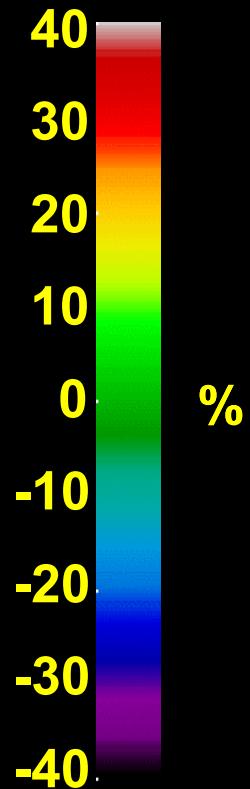
# Computed CMRO<sub>2</sub> changes



Subject 1



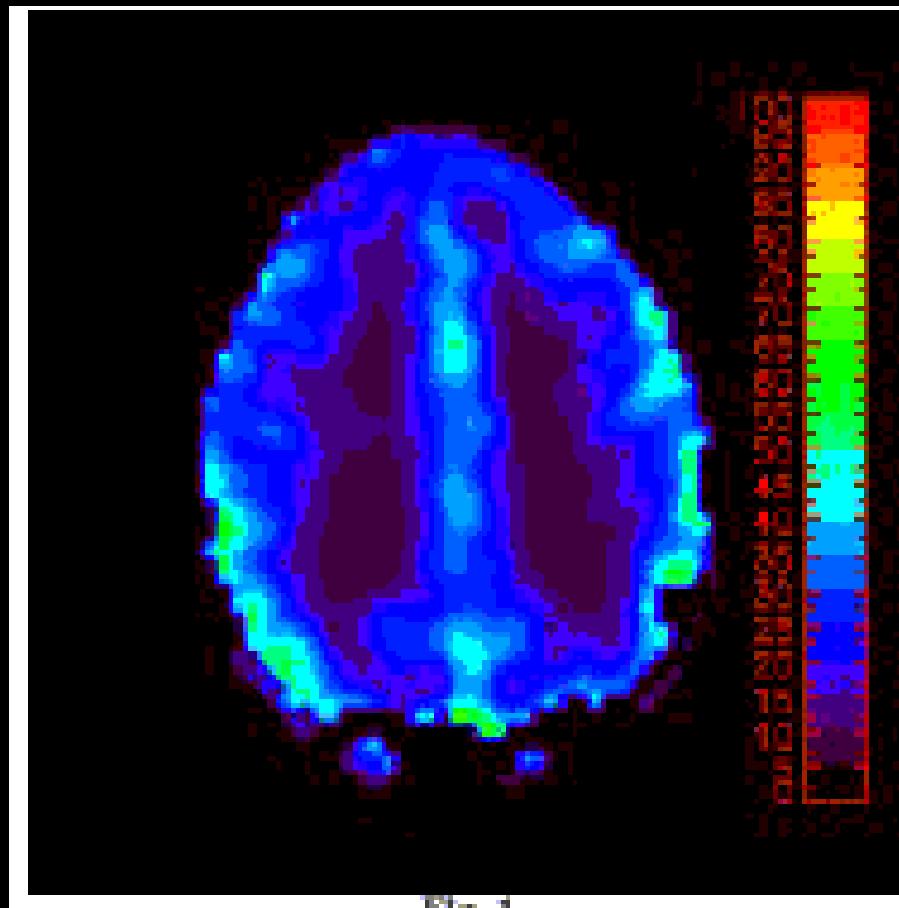
Subject 2



# Quantitative Measurements of Cerebral Metabolic Rate of Oxygen (CMRO<sub>2</sub>) Using MRI: A Volunteer Study

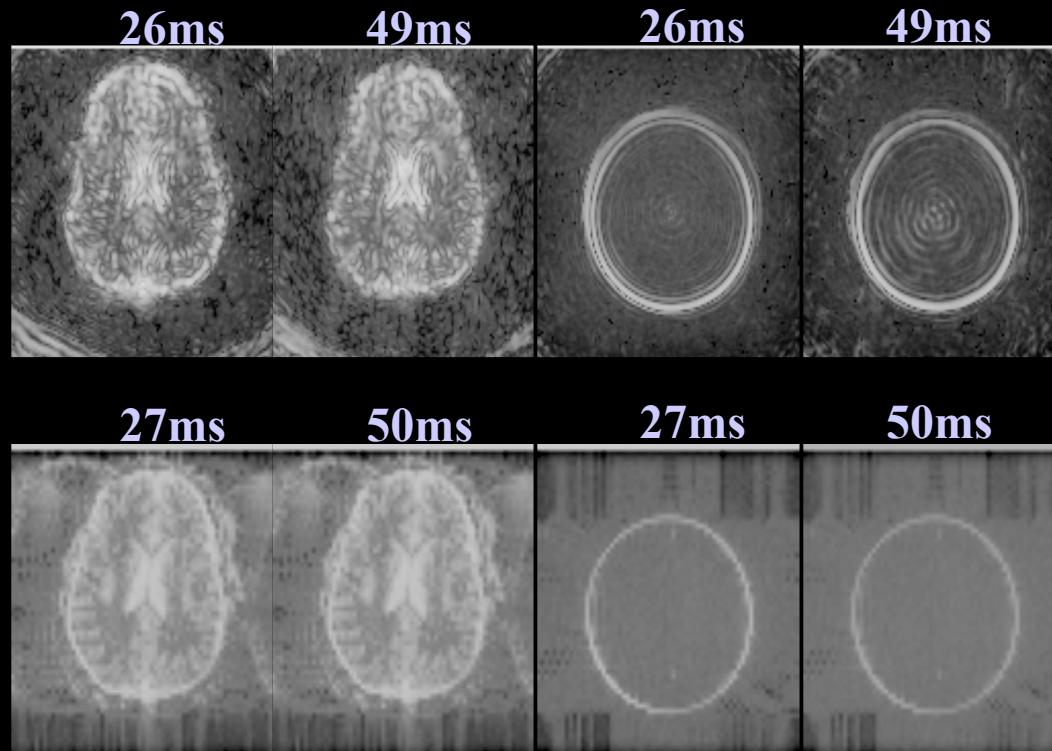
Honeyan AN<sup>1</sup>, Weili LIN<sup>2</sup>, Azim CELIK<sup>3</sup>, Yuesh Z. LEE<sup>4</sup>

<sup>1</sup>Washington University, 600 Airport Road, Chapel Hill, NC USA; <sup>2</sup>UNC-Chapel Hill, Department of Radiology, CB#7515, Chapel Hill, NC USA; <sup>3</sup>GE Medical Systems; <sup>4</sup>UNC-Chapel Hill, ;

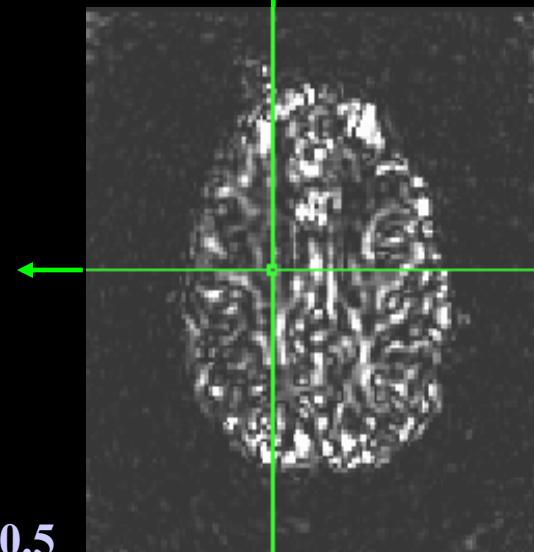
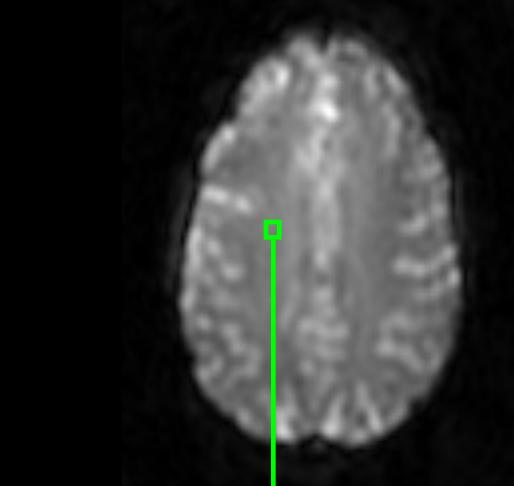
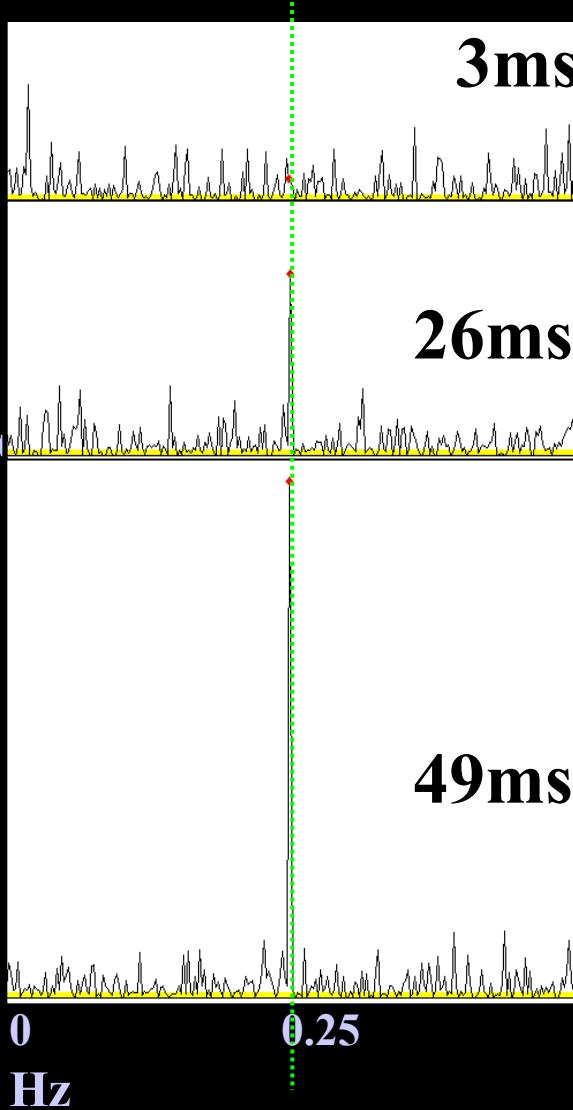


Higher Signal to Noise **in a single image** does not necessarily translate to higher Signal to Noise **over time**.

### Temporal vs. Spatial SNR- 3T



# 0.25 Hz Breathing at 3T



# Image Respiration map

# 0.68 Hz Cardiac rate at 3T

## Power Spectra

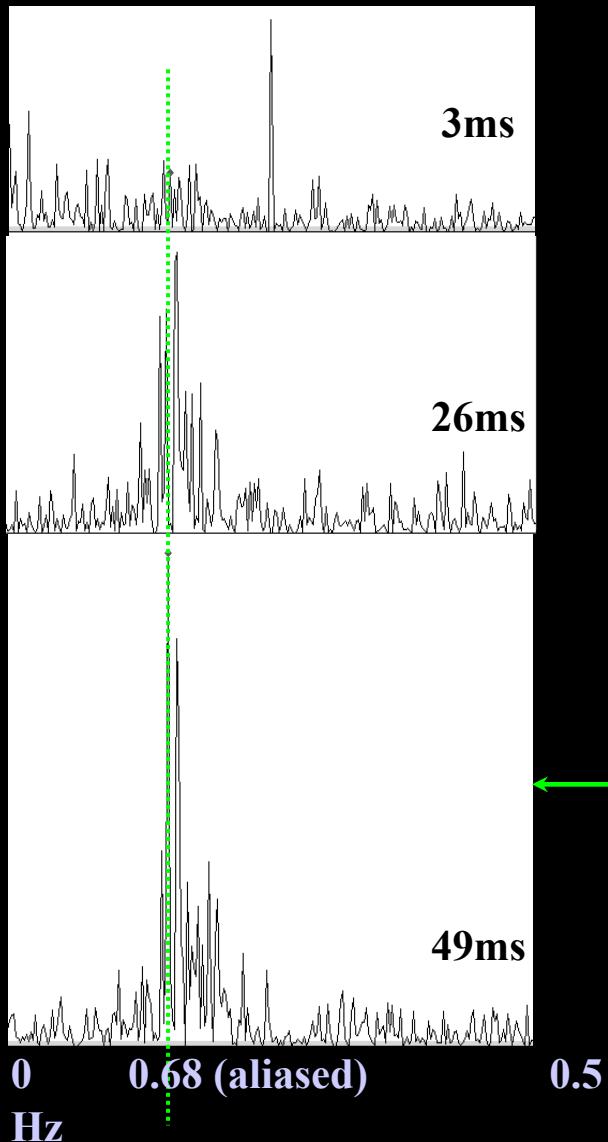
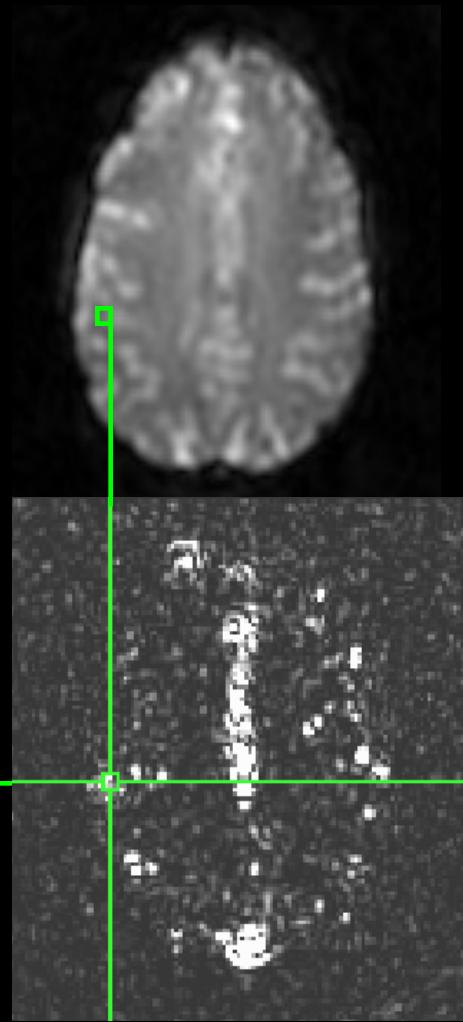
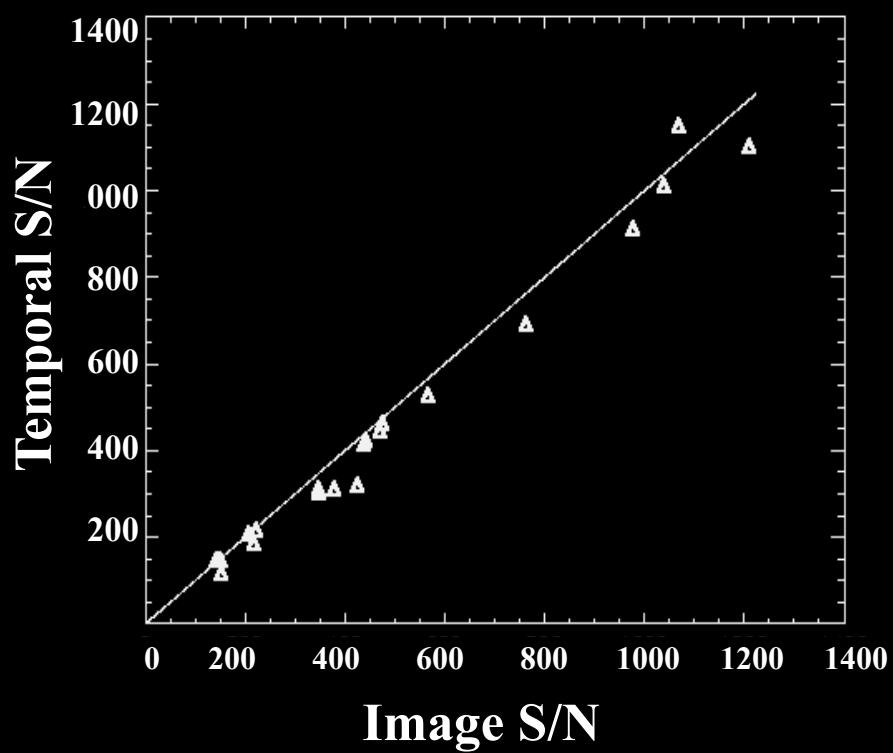


Image  
Cardiac map

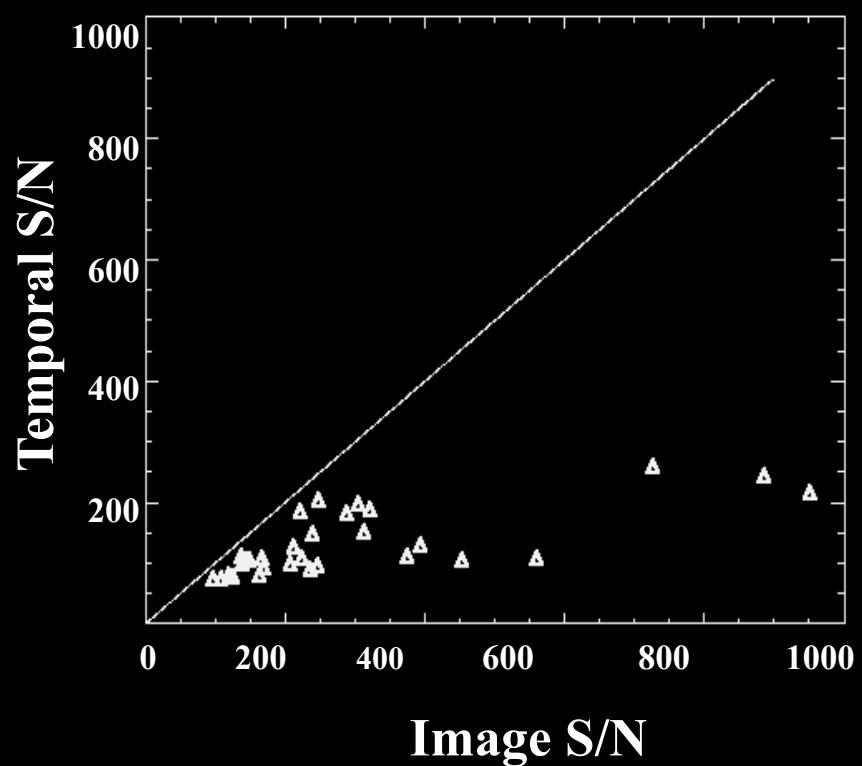


# Temporal S/N vs. Image S/N

PHANTOMS

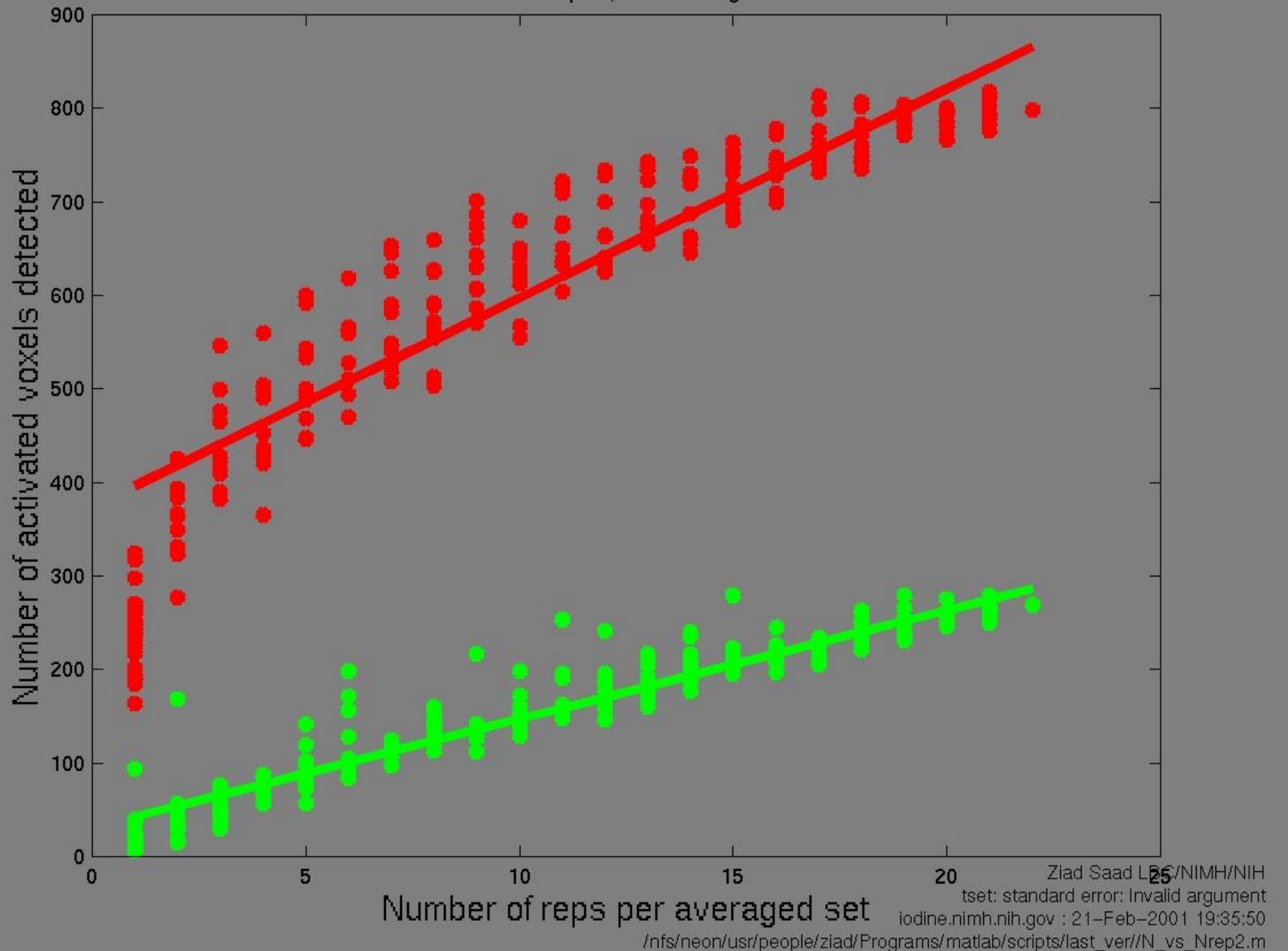


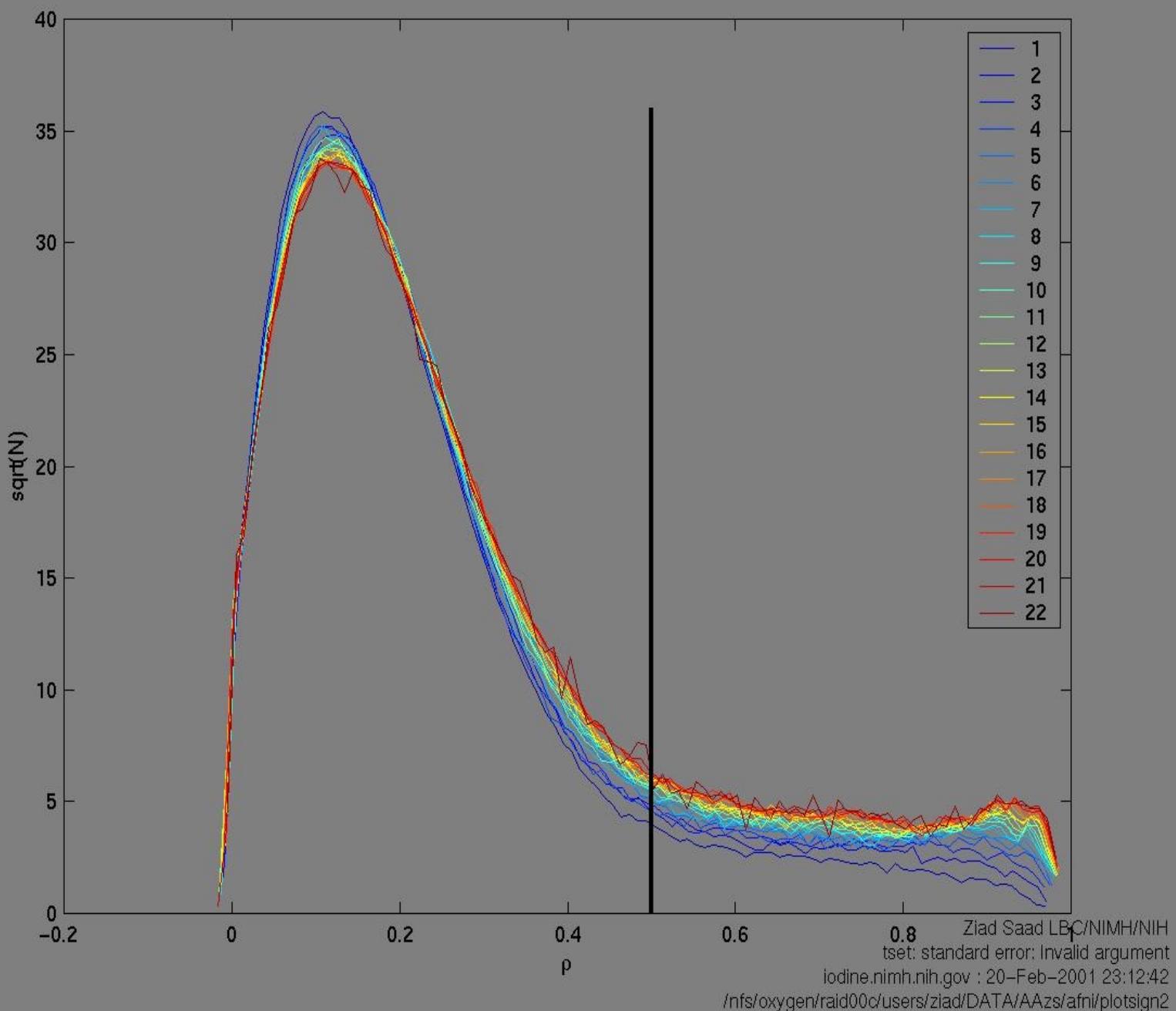
SUBJECTS



N. Petridou

Fit curve: Pos: 22.347 Nrep + 373.782 -- Neg: 11.6126 Nrep + 30.8055  
Fit corr. coeff. (pos, neg) : (0.948073, 0.989839).  
Red->pos., Green->neg.





- Contrast in fMRI

*Hemodynamic Specificity*

- The Hemodynamic Transfer Function

*Location, Latency, Magnitude, Linearity*

- Best Results So Far

*Temporal Resolution, Spatial Resolution*

- Neuronal Activation Input Strategies

*Block Design*

*Phase and Frequency Encoding*

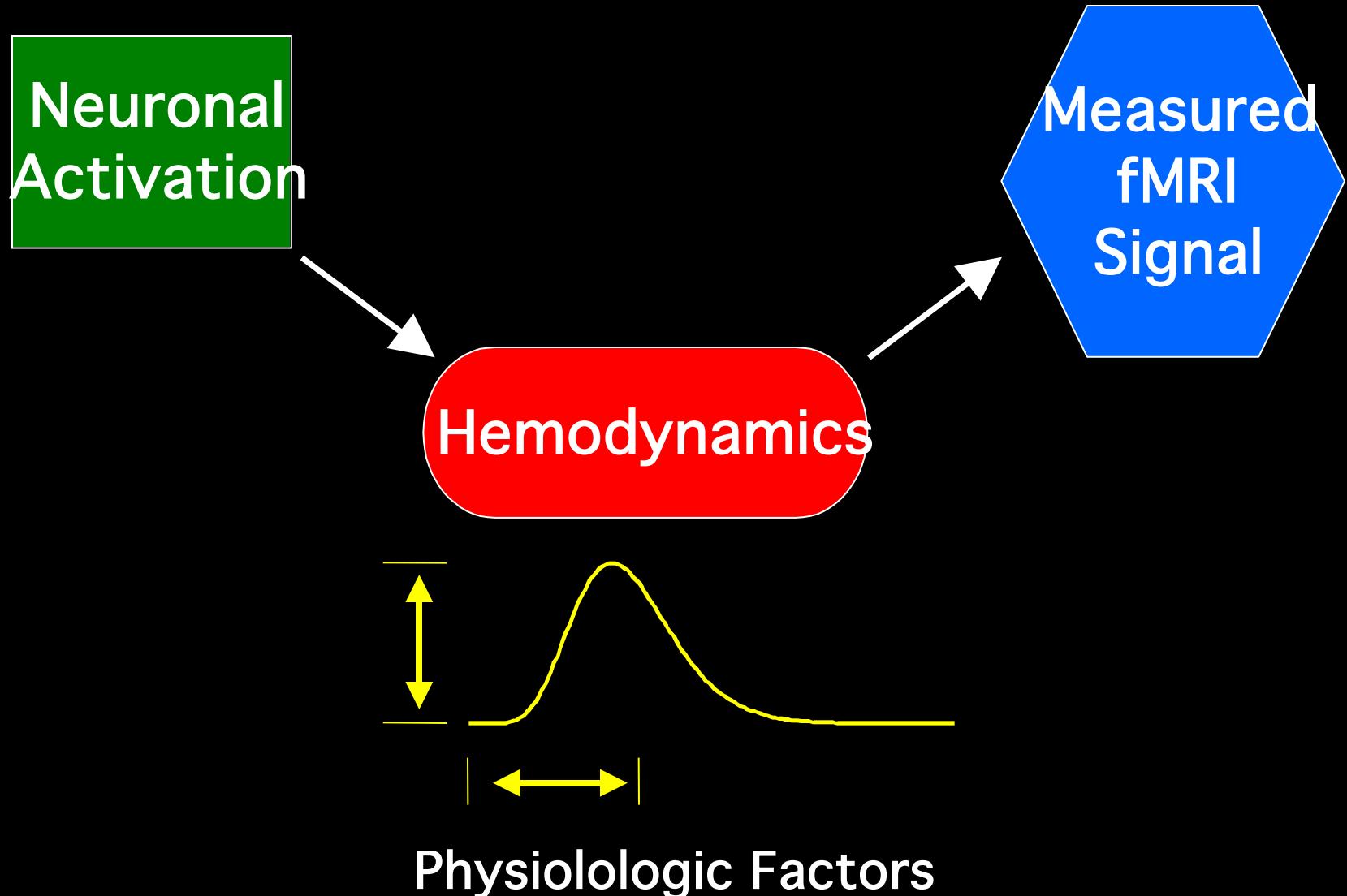
*Orthogonal Designs*

*Parametric Designs*

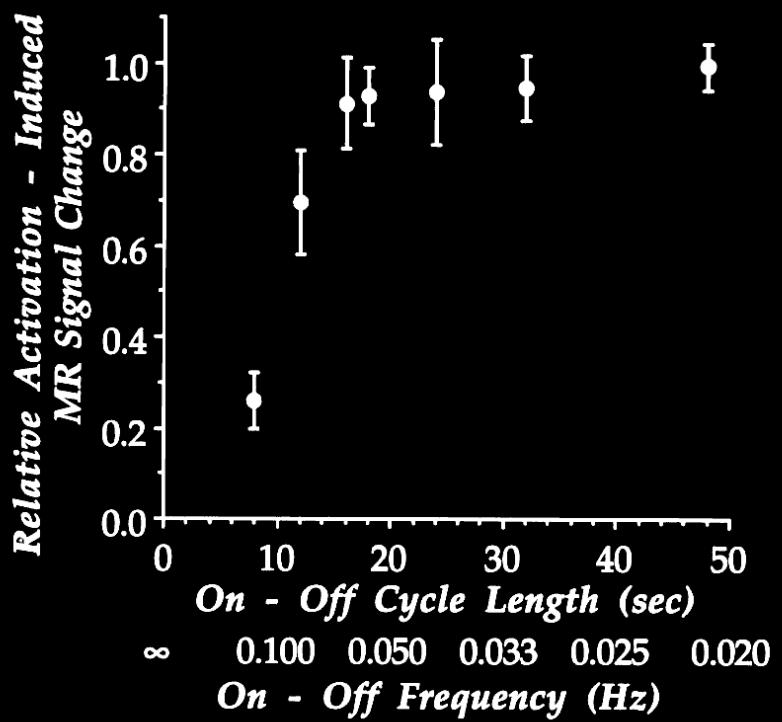
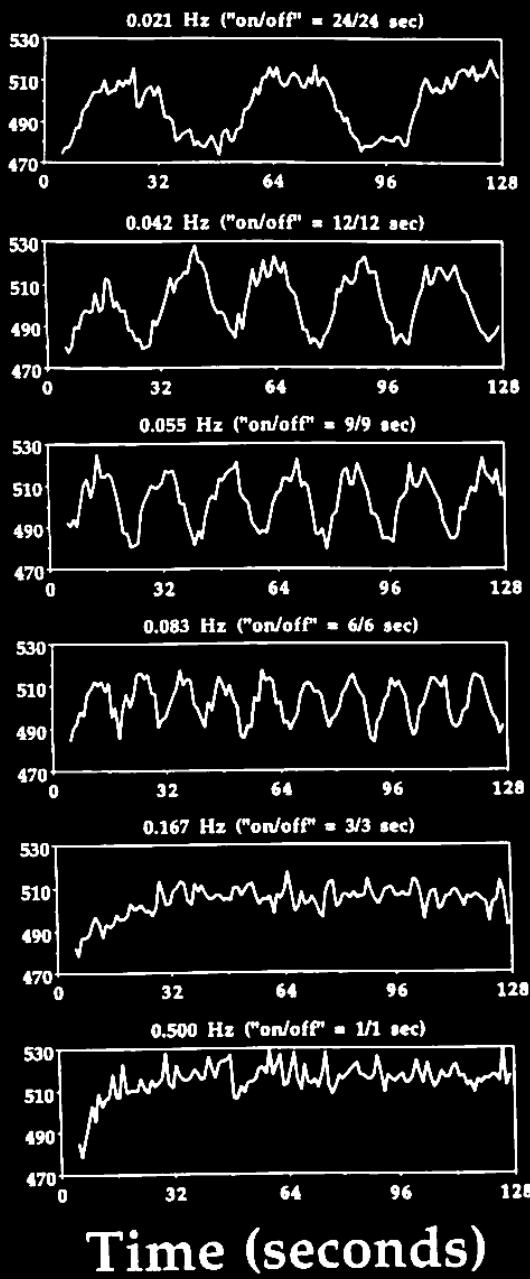
*Event-Related Designs*

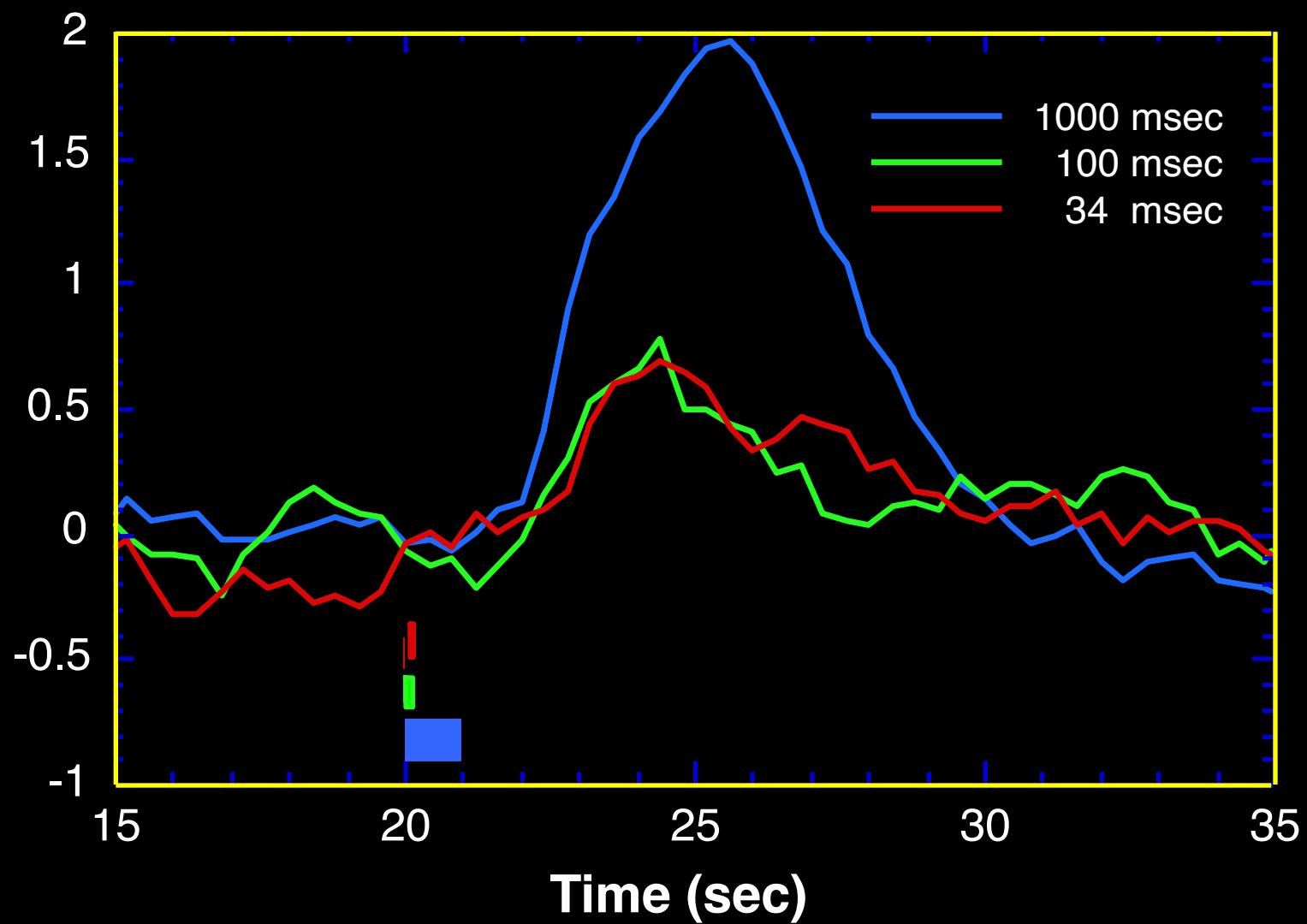
*Free Behavior Designs*

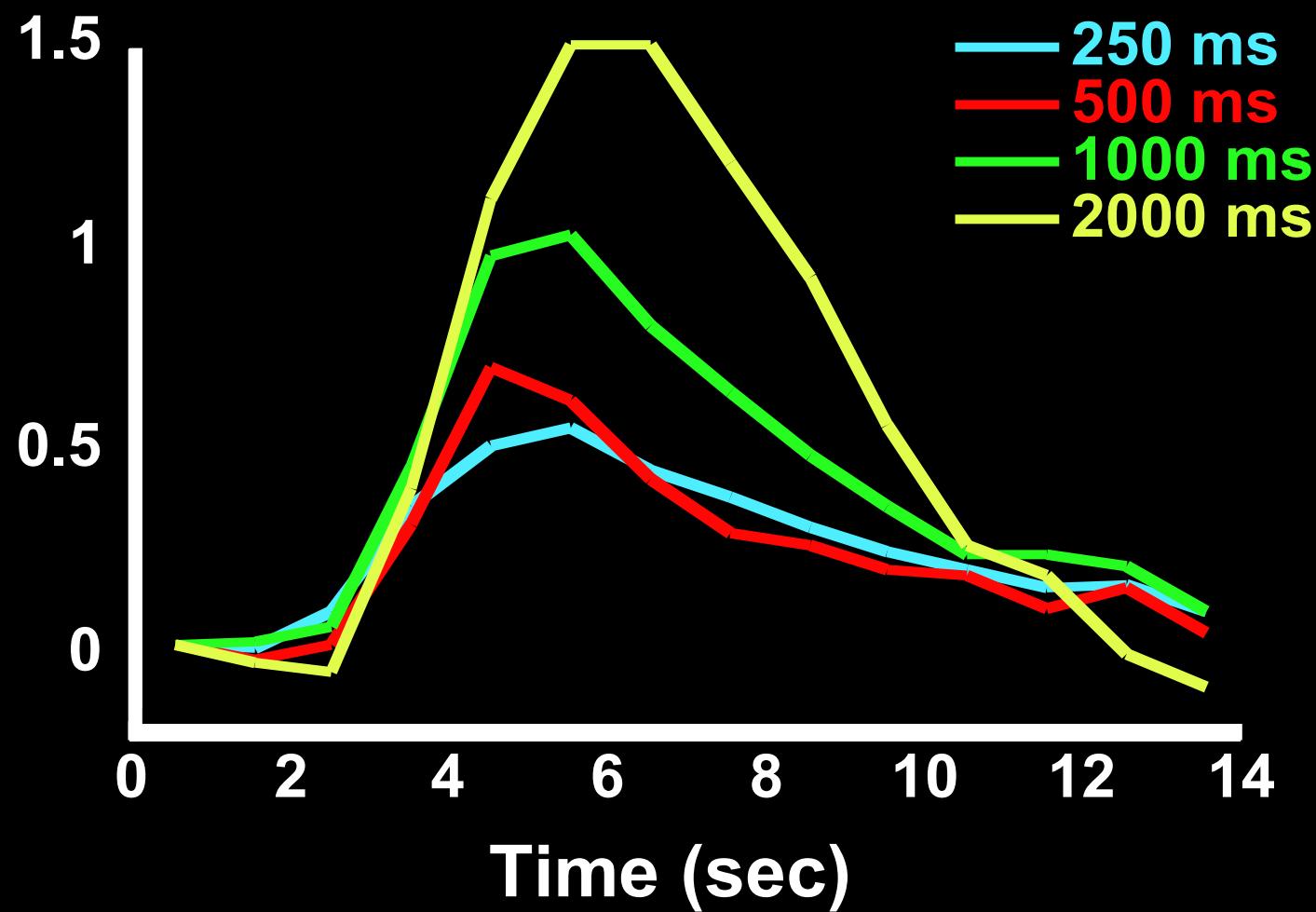
# Hemodynamic Transfer Function



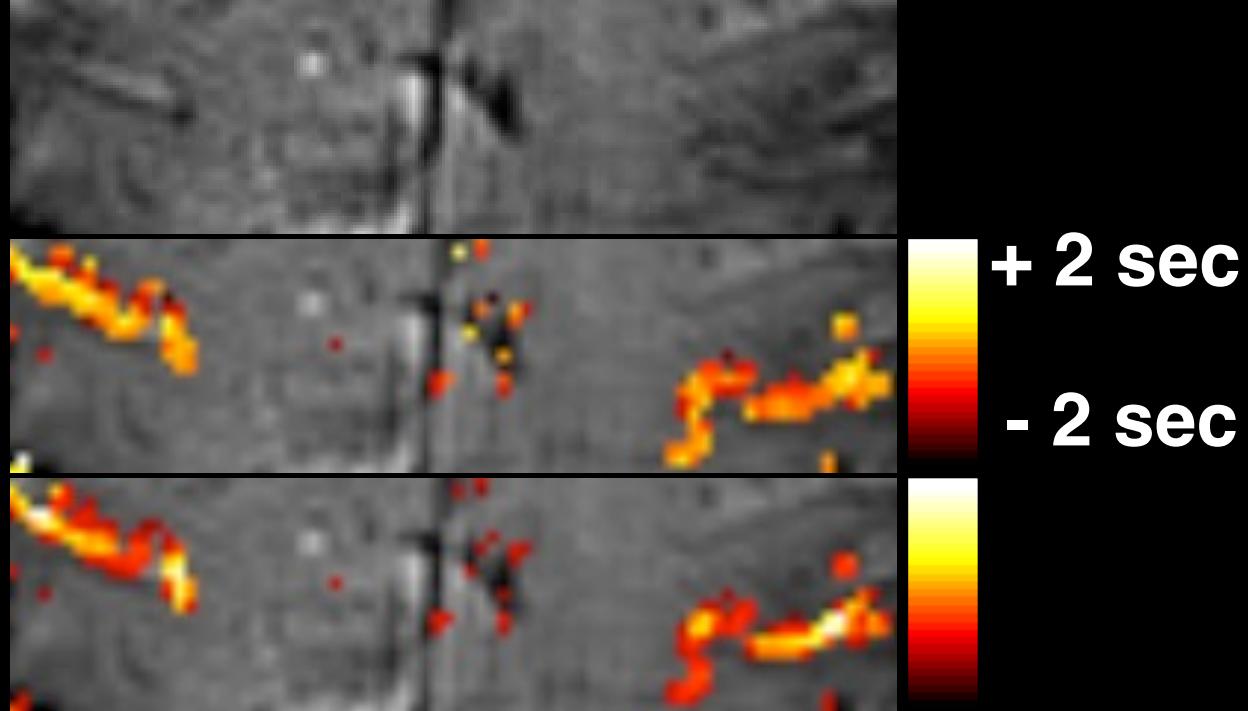
# MRI Signal



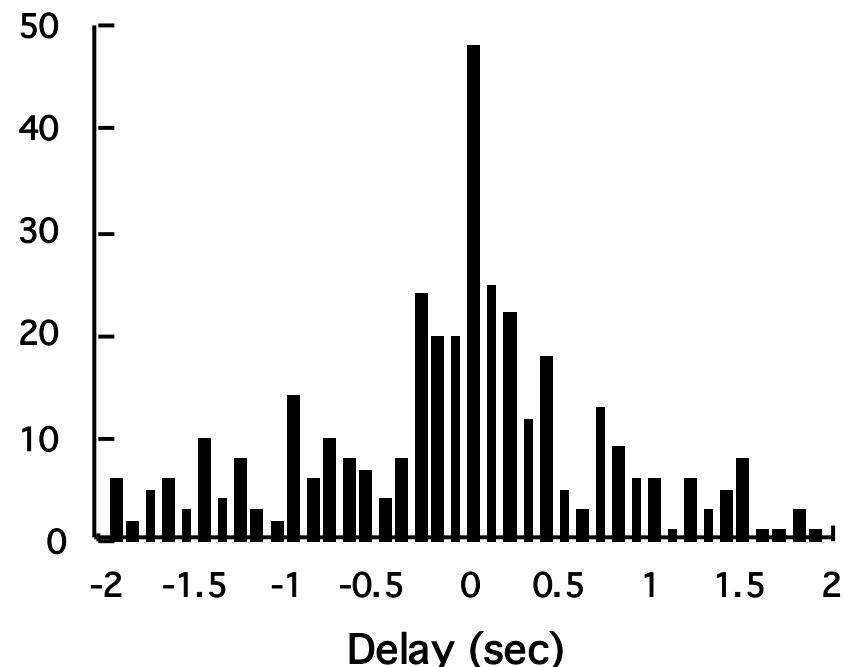
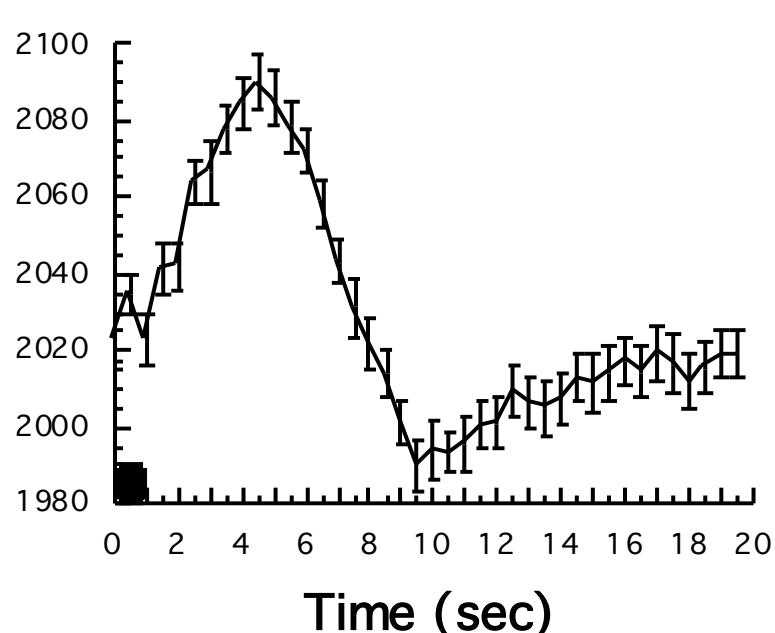




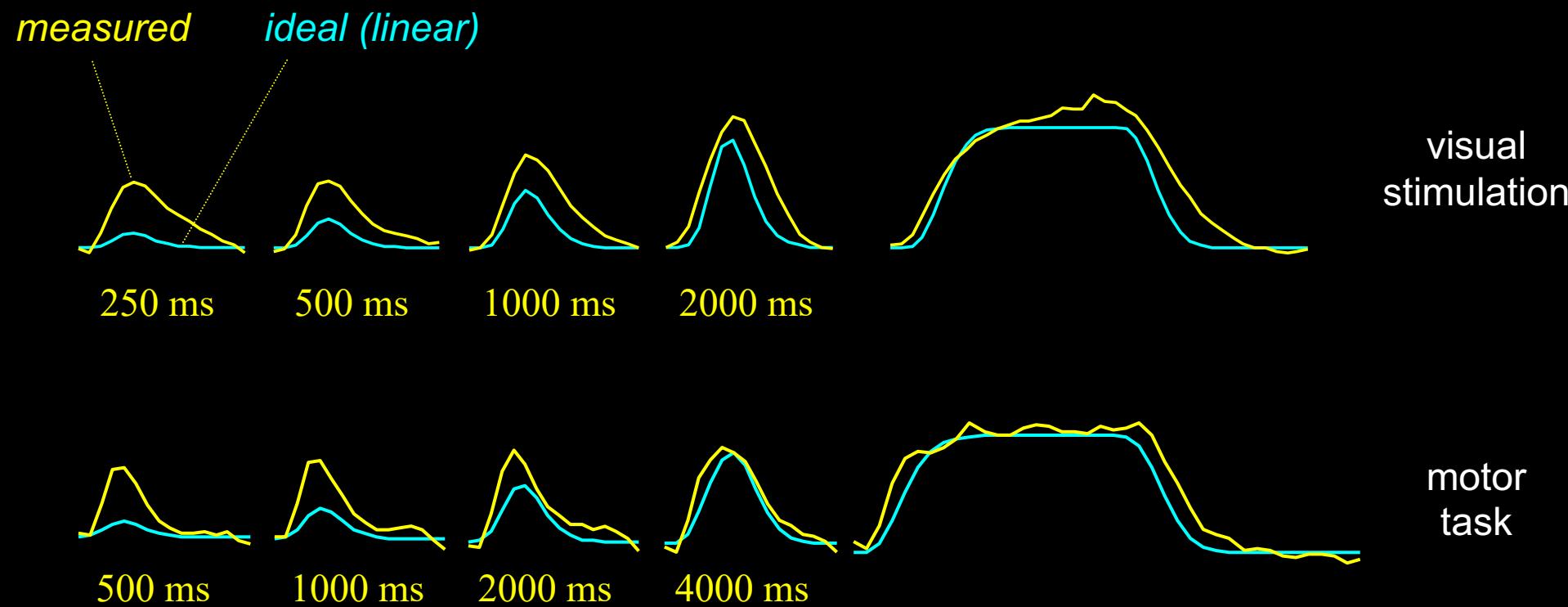
# Latency



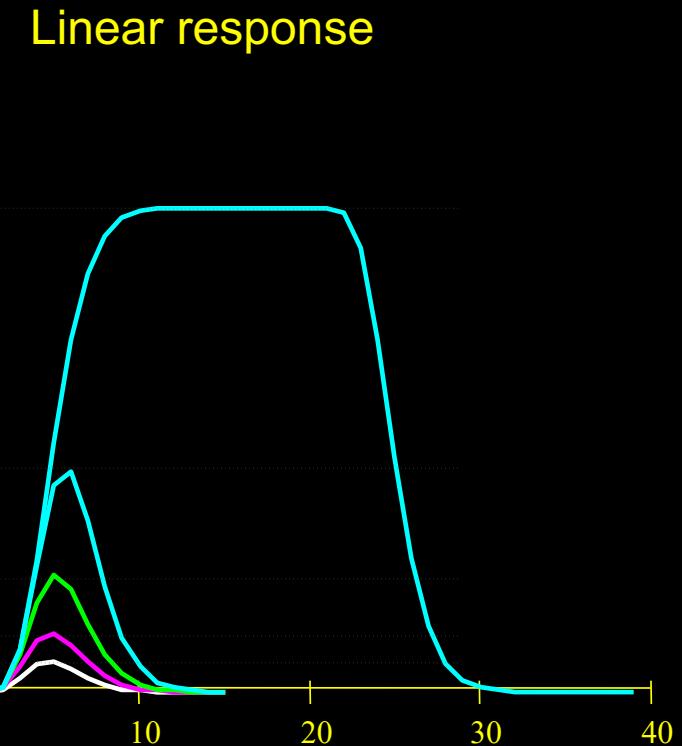
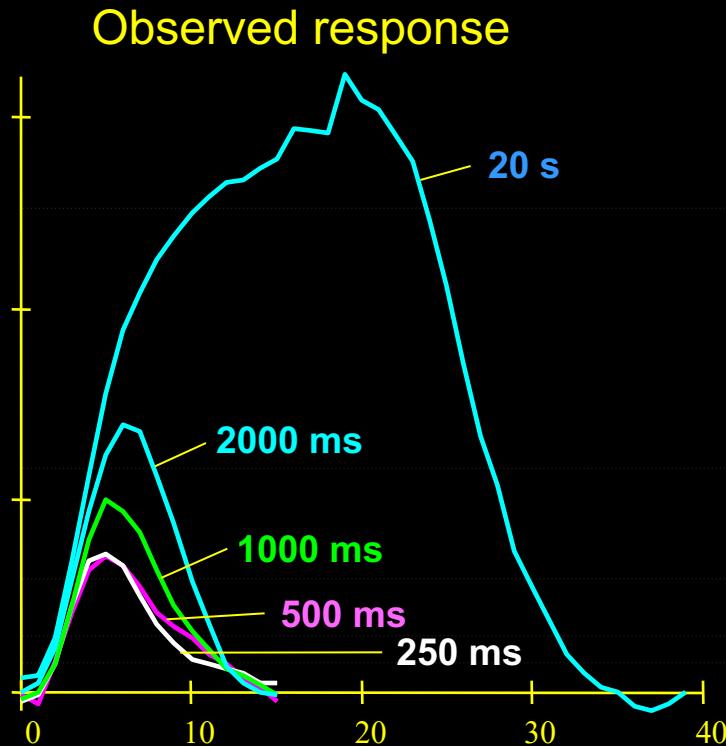
# Magnitude



# Observed Responses

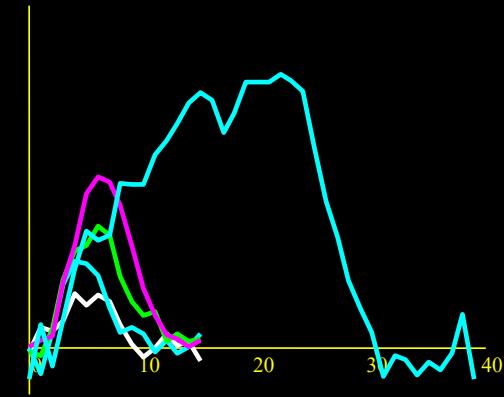
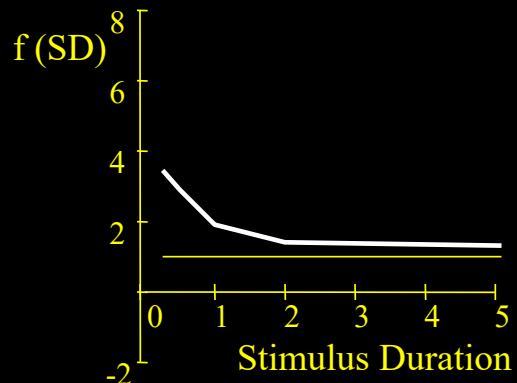
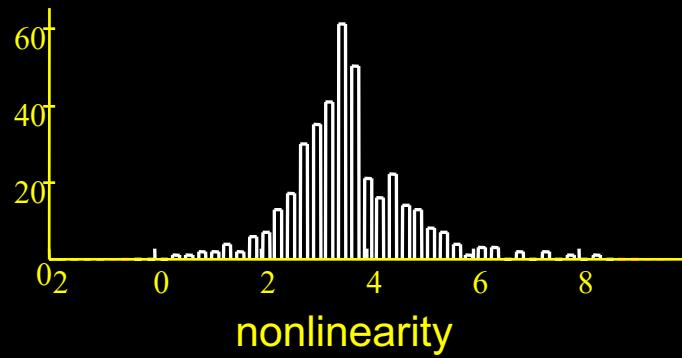
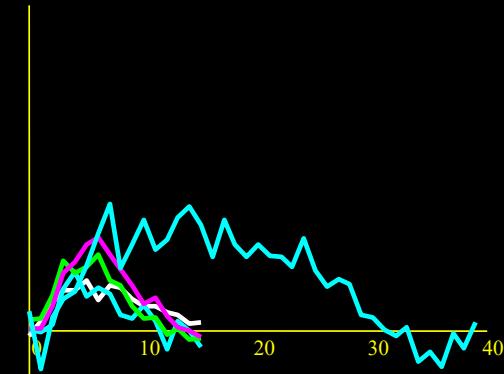
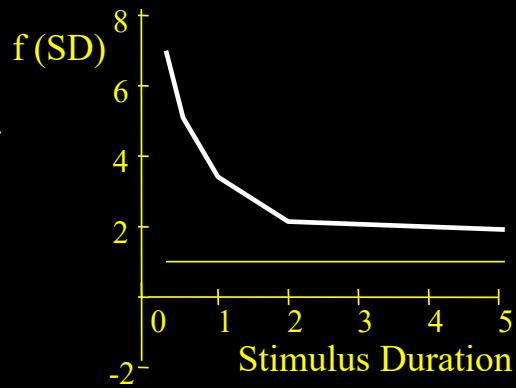
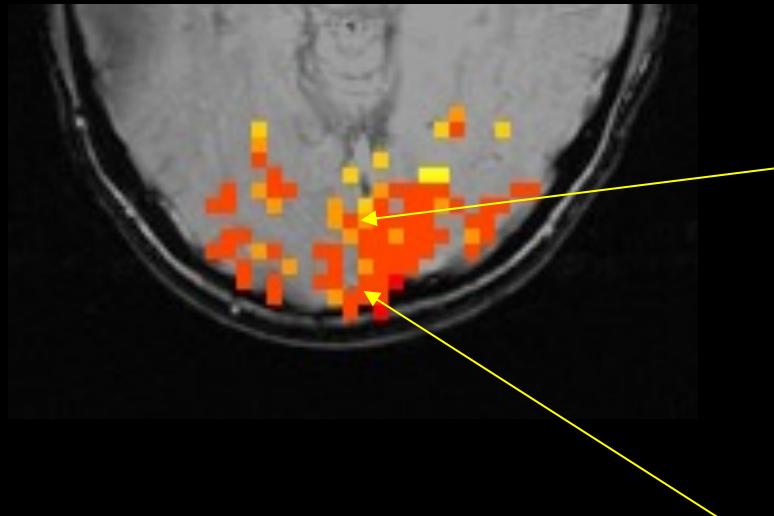


# BOLD response is nonlinear



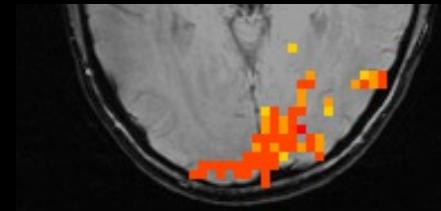
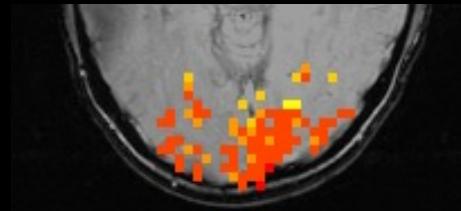
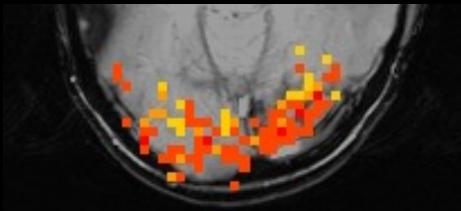
*Short duration stimuli produce larger responses than expected*

# Results – visual task

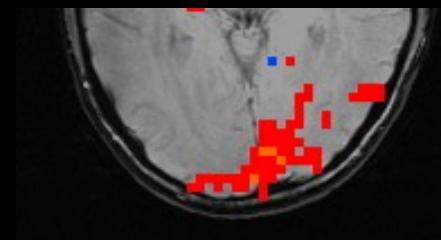
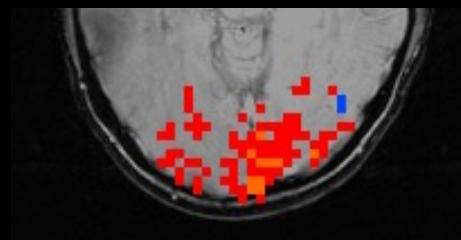
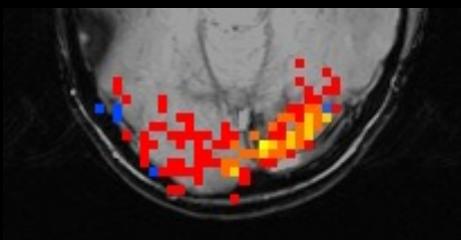


# Results – visual task

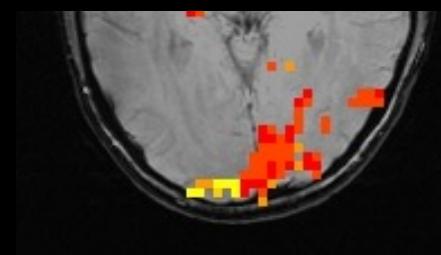
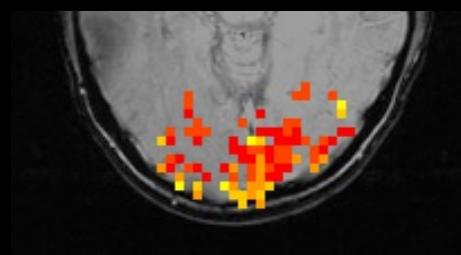
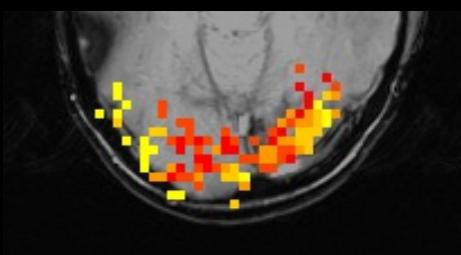
Nonlinearity



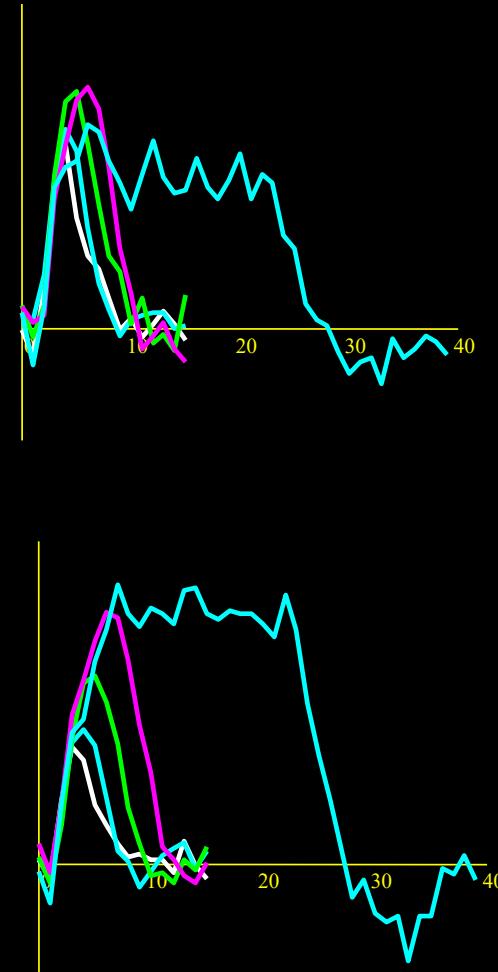
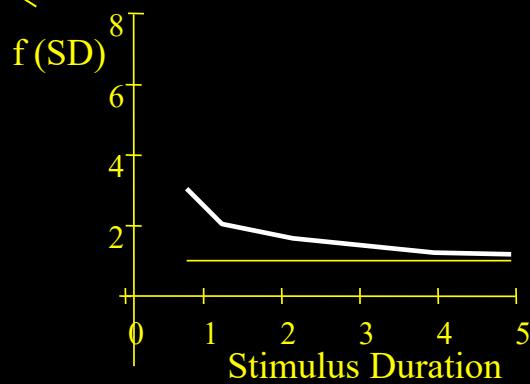
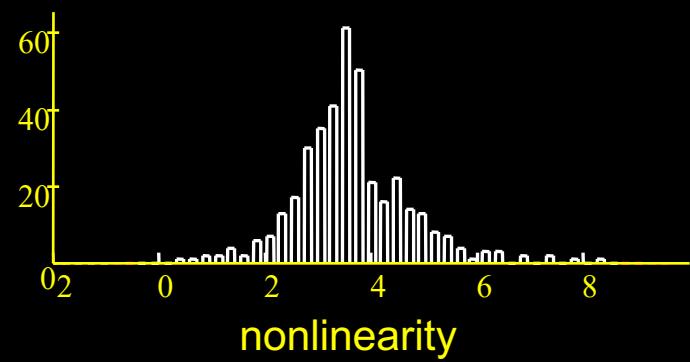
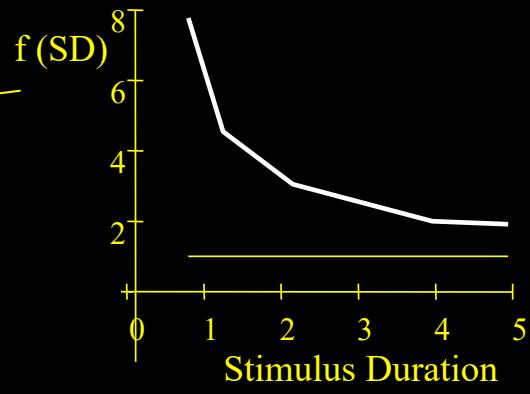
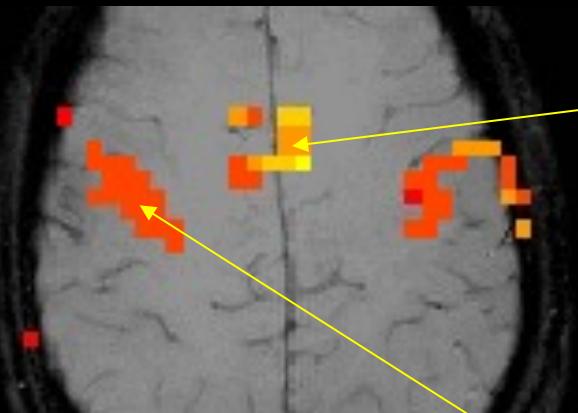
Magnitude



Latency

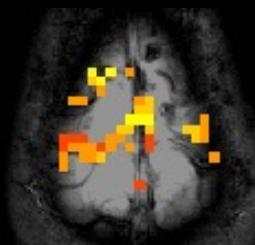
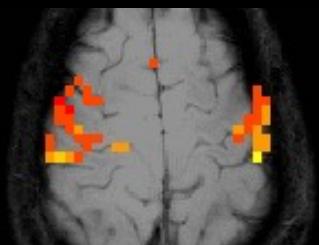
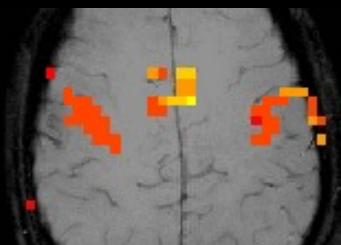


# Results – motor task

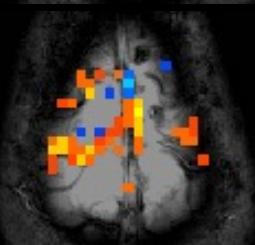
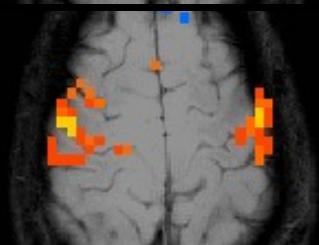
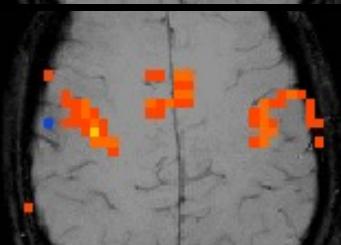


# Results – motor task

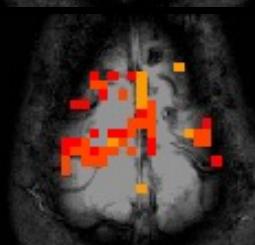
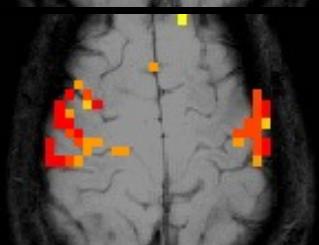
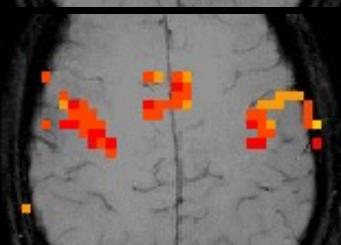
Nonlinearity



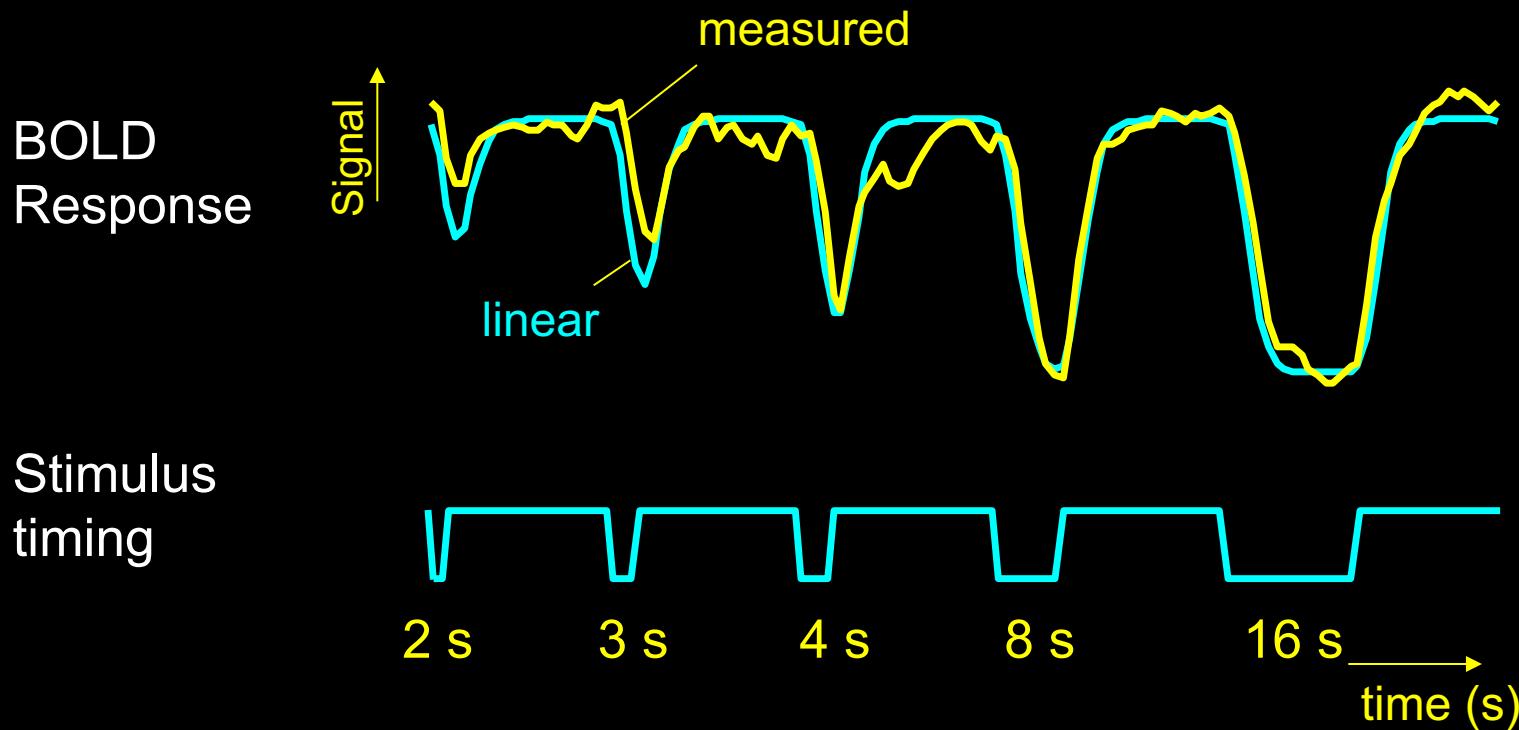
Magnitude



Latency



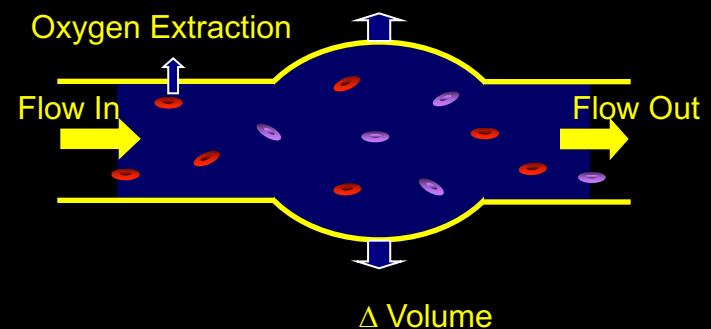
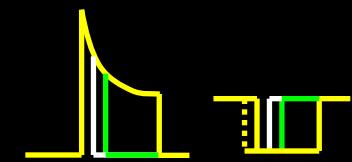
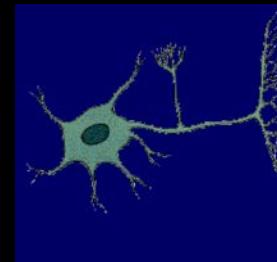
# Different stimulus “ON” periods



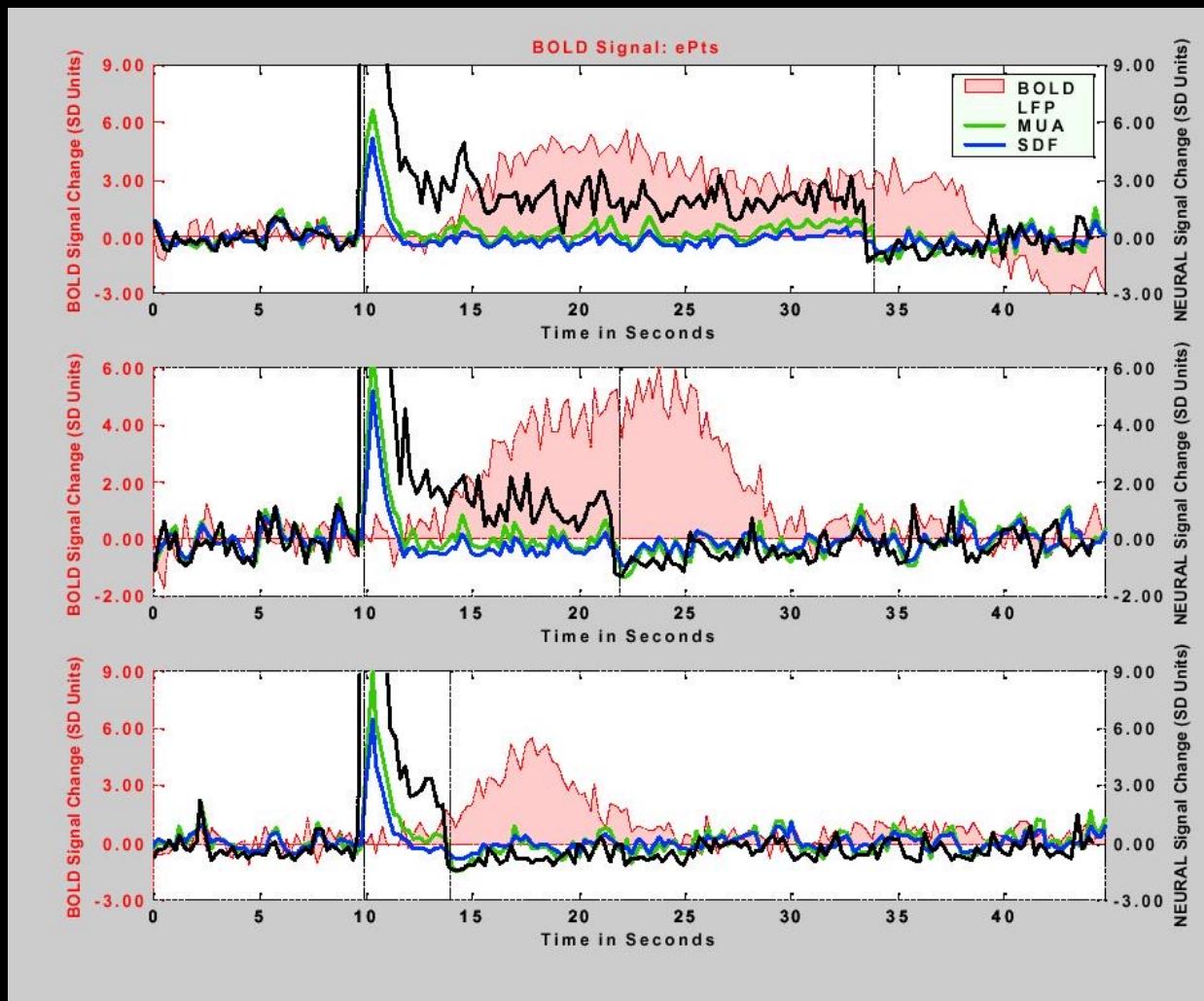
*Brief stimulus OFF periods produce smaller decreases than expected*

# Sources of this Nonlinearity

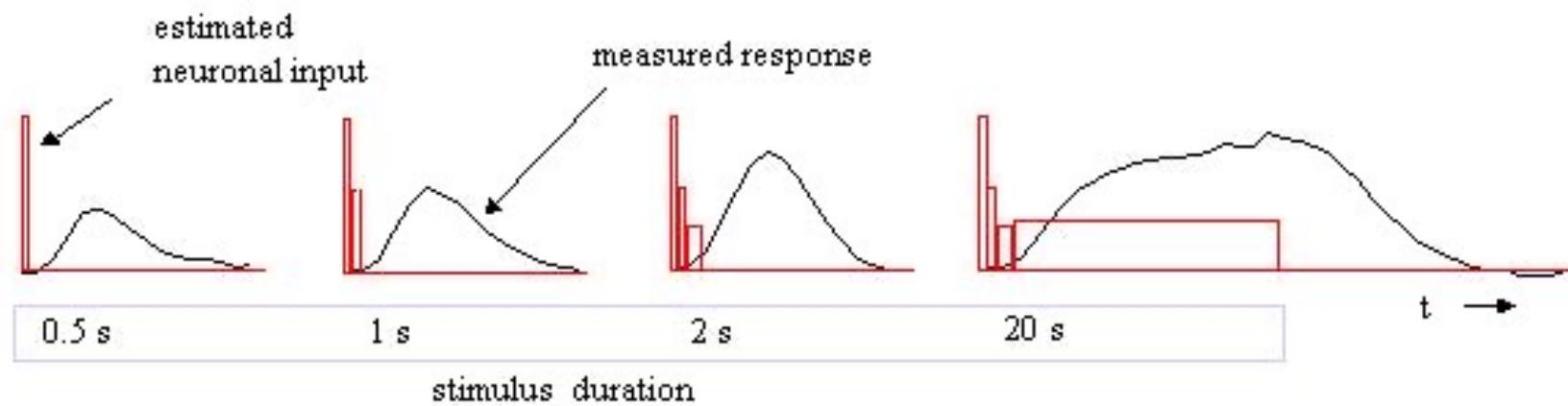
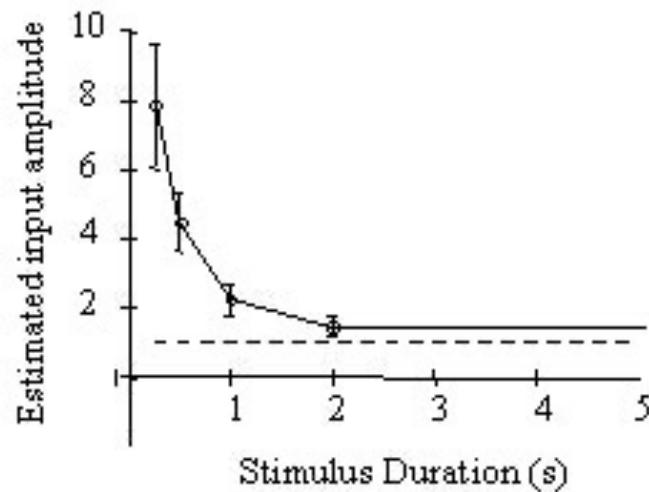
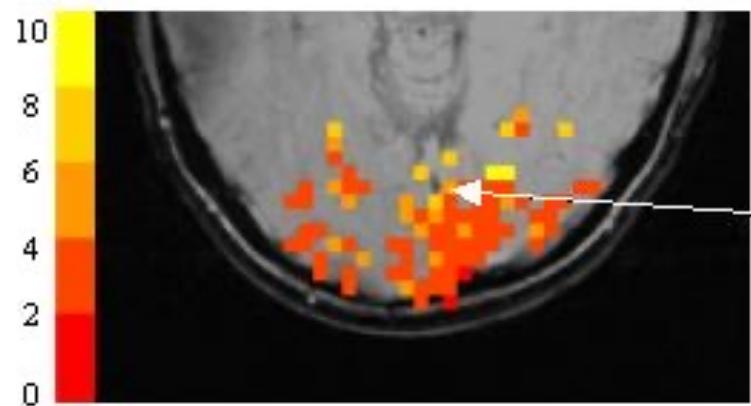
- Neuronal
- Hemodynamic
  - Oxygen extraction
  - Blood volume dynamics



# BOLD Correlation with Neuronal Activity



Logothetis et al. Nature, 412, 150-157

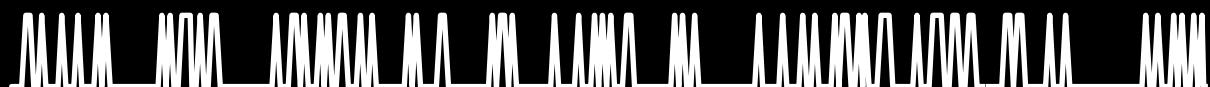


# Varying “ON” and “OFF” periods

- *Rapid event-related design with varying ISI*



8% ON



25% ON

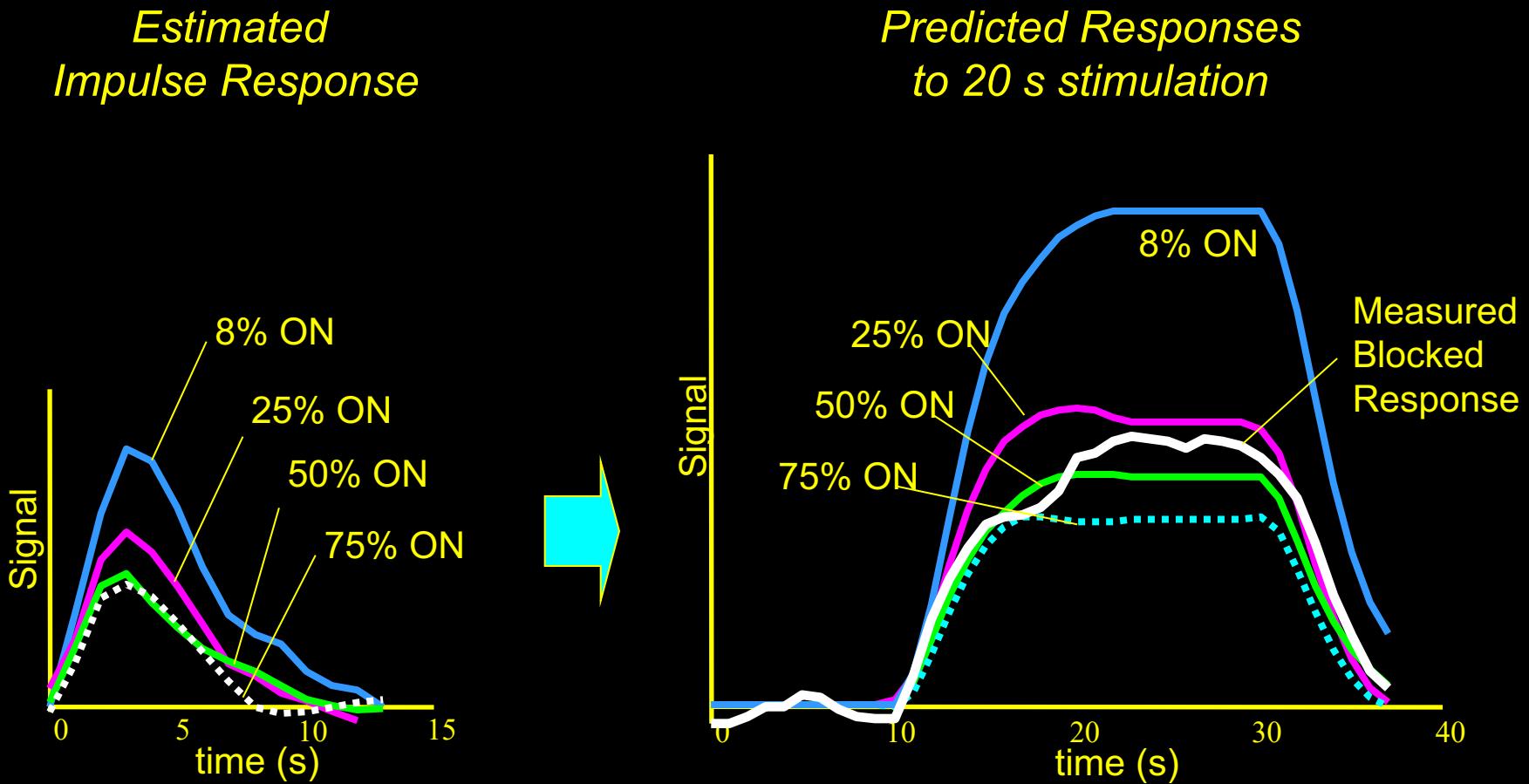


50% ON

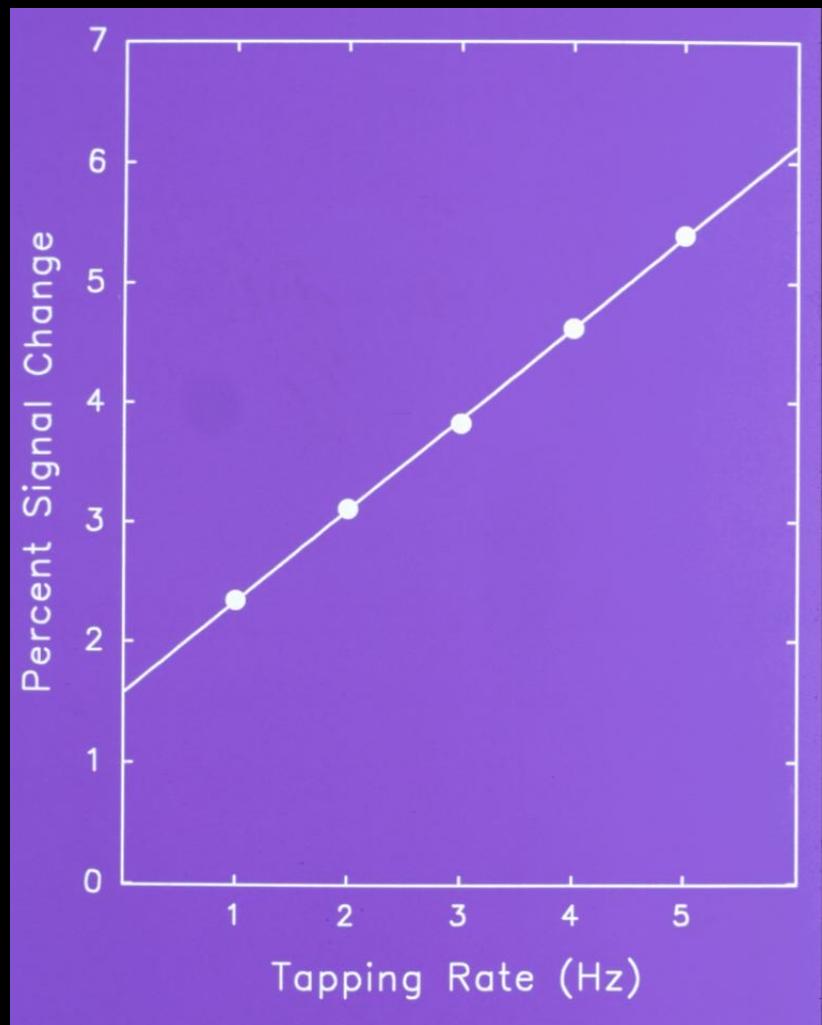


75% ON

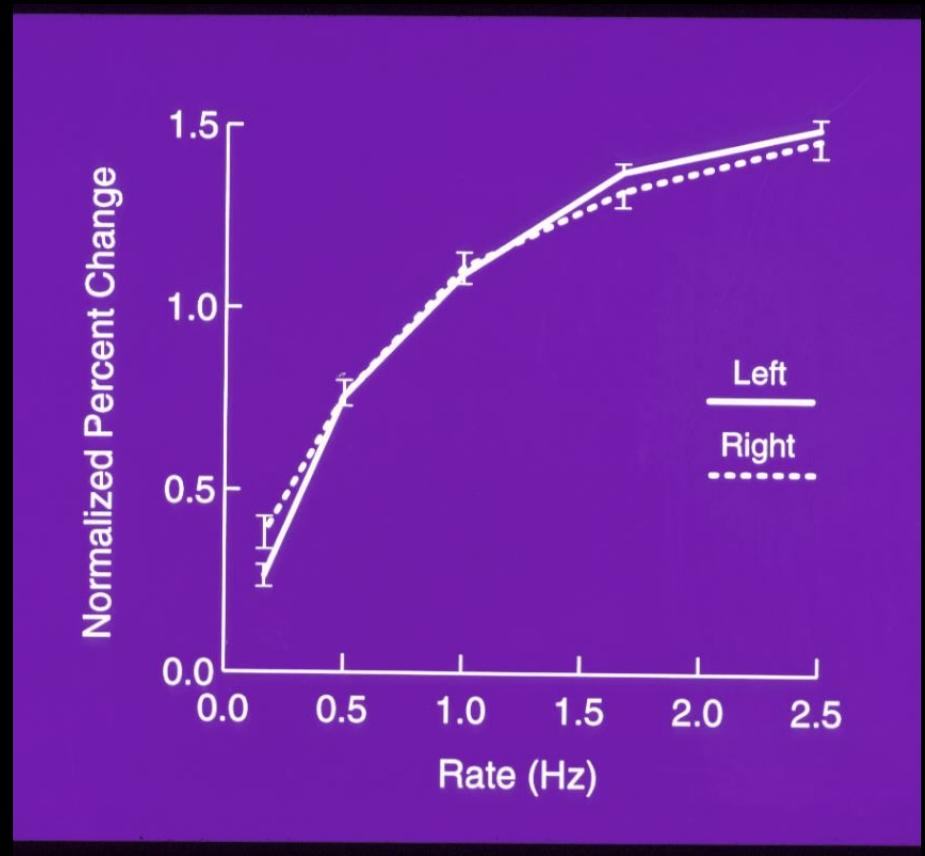
# Varying “ON” and “OFF” periods

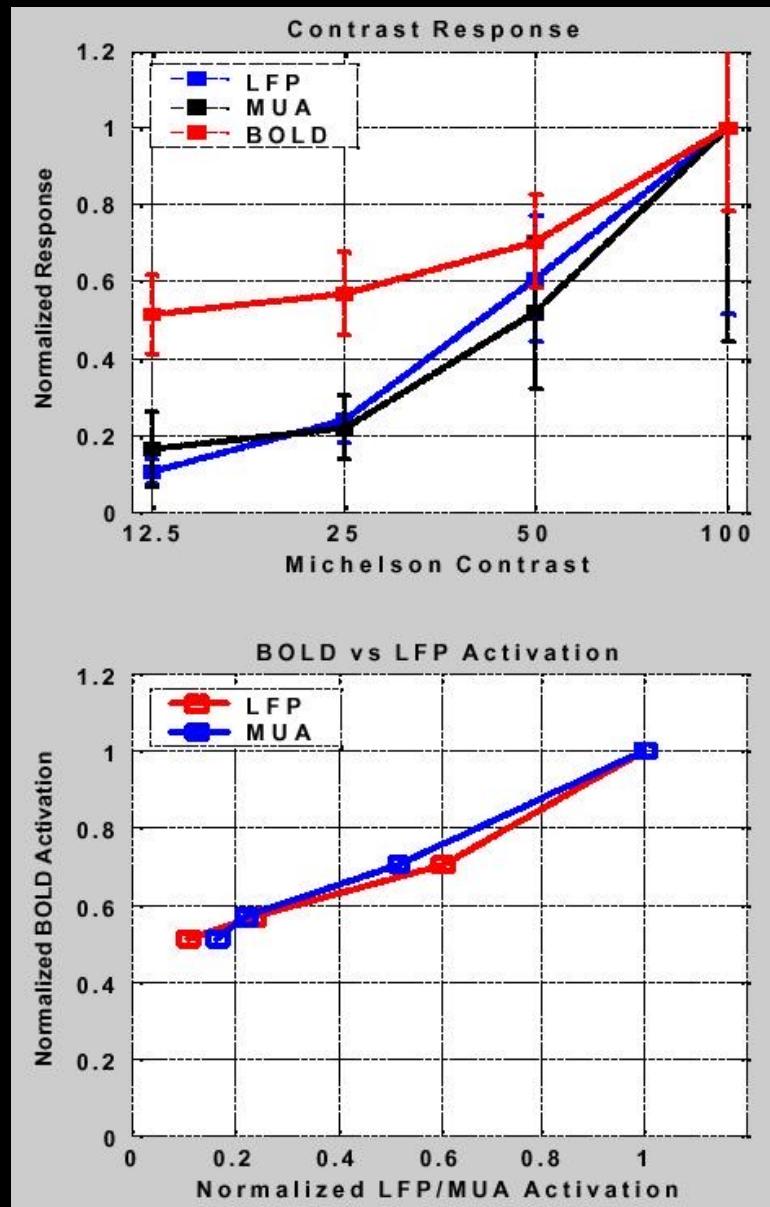


# Motor Cortex



# Auditory Cortex





Logothetis et al. Nature, 412, 150-157

- Contrast in fMRI

*Hemodynamic Specificity*

- The Hemodynamic Transfer Function

*Location, Latency, Magnitude*

- Best Results So Far

*Temporal Resolution, Spatial Resolution*

- Neuronal Activation Input Strategies

*Block Design*

*Phase and Frequency Encoding*

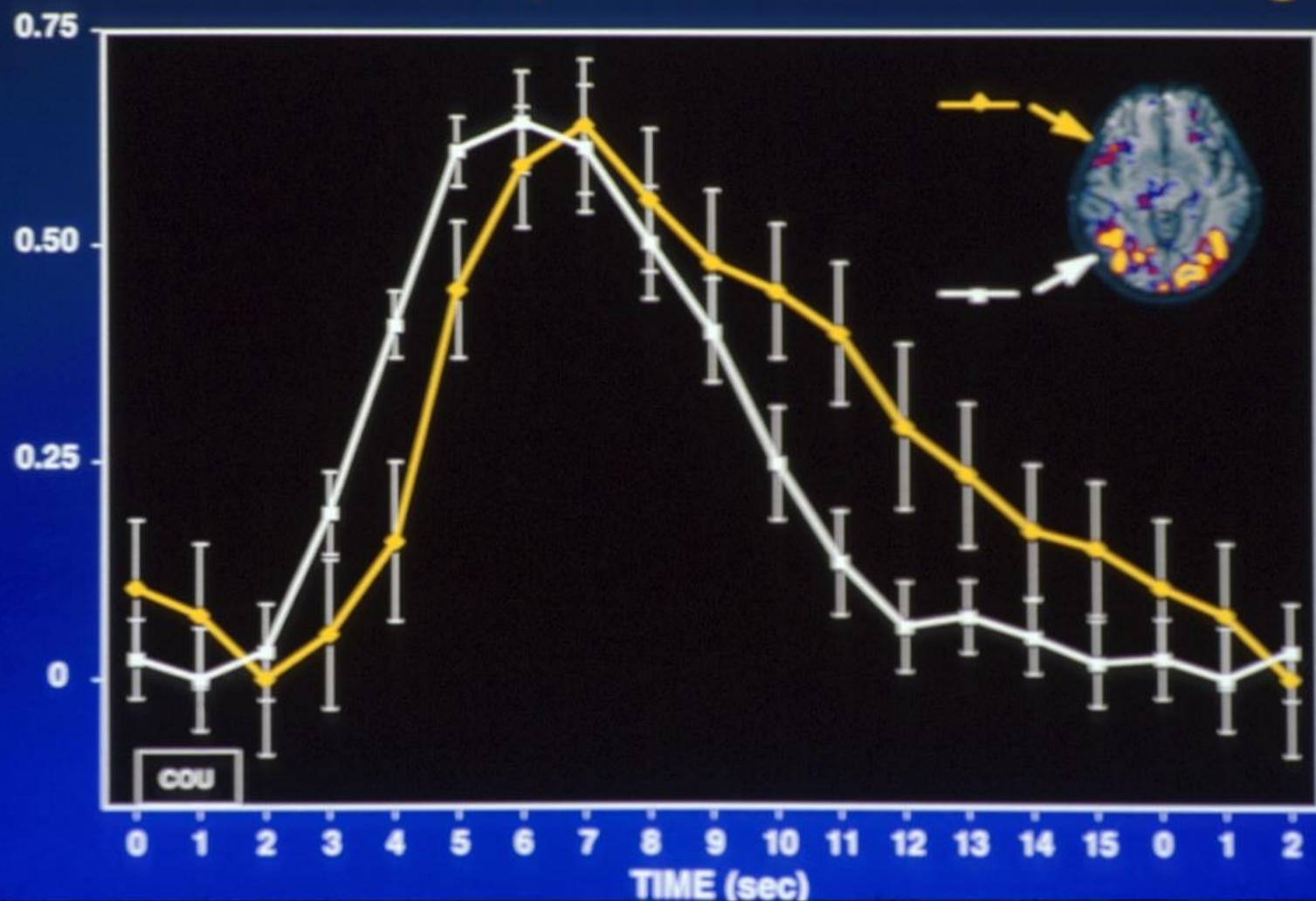
*Orthogonal Designs*

*Parametric Designs*

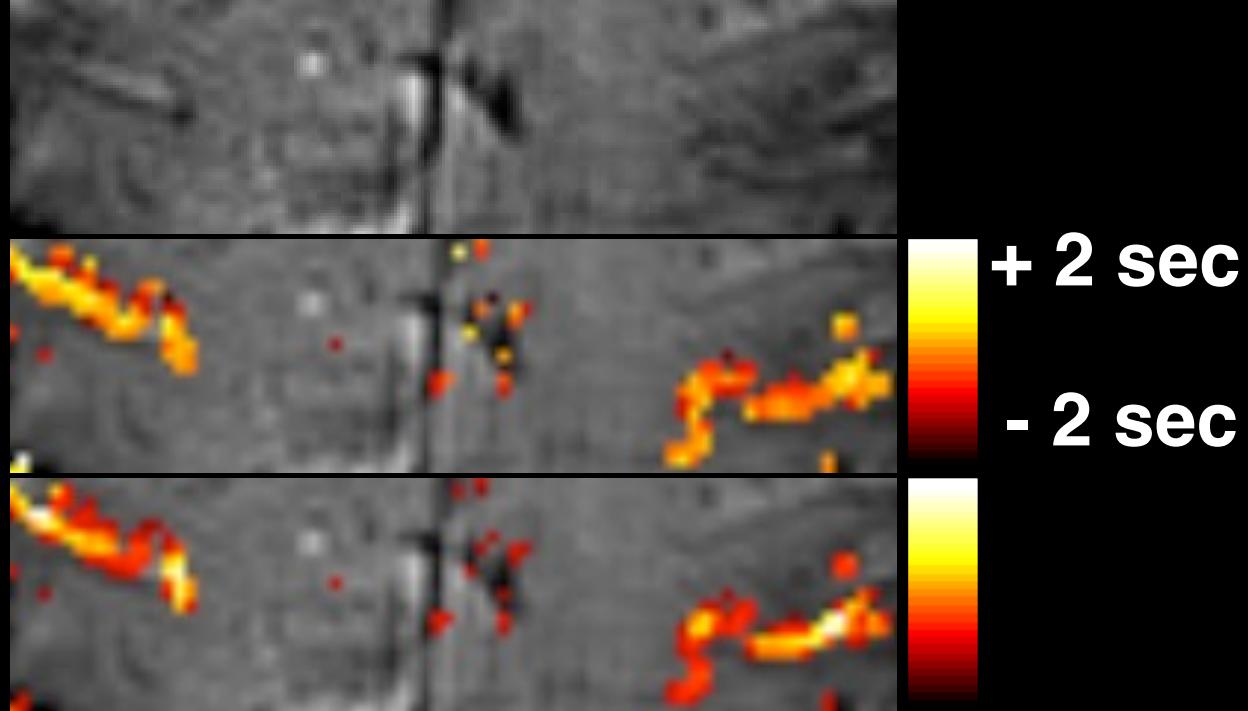
*Event-Related Designs*

*Free Behavior Designs*

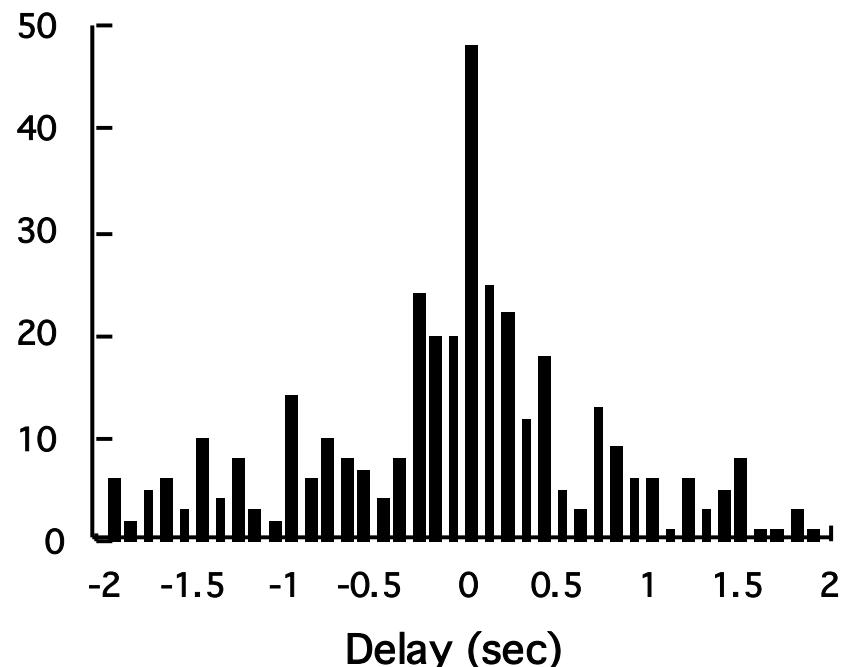
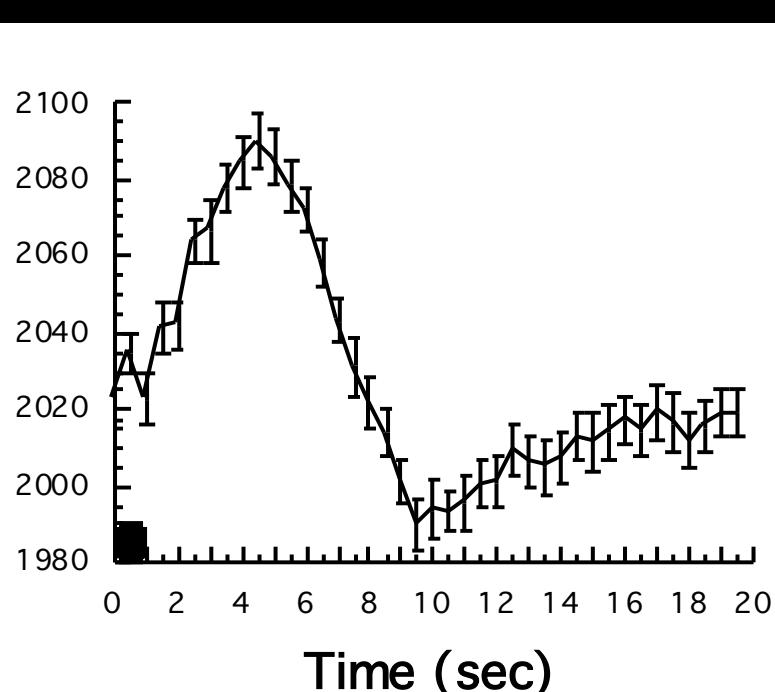
## Time Course Comparison Across Brain Regions



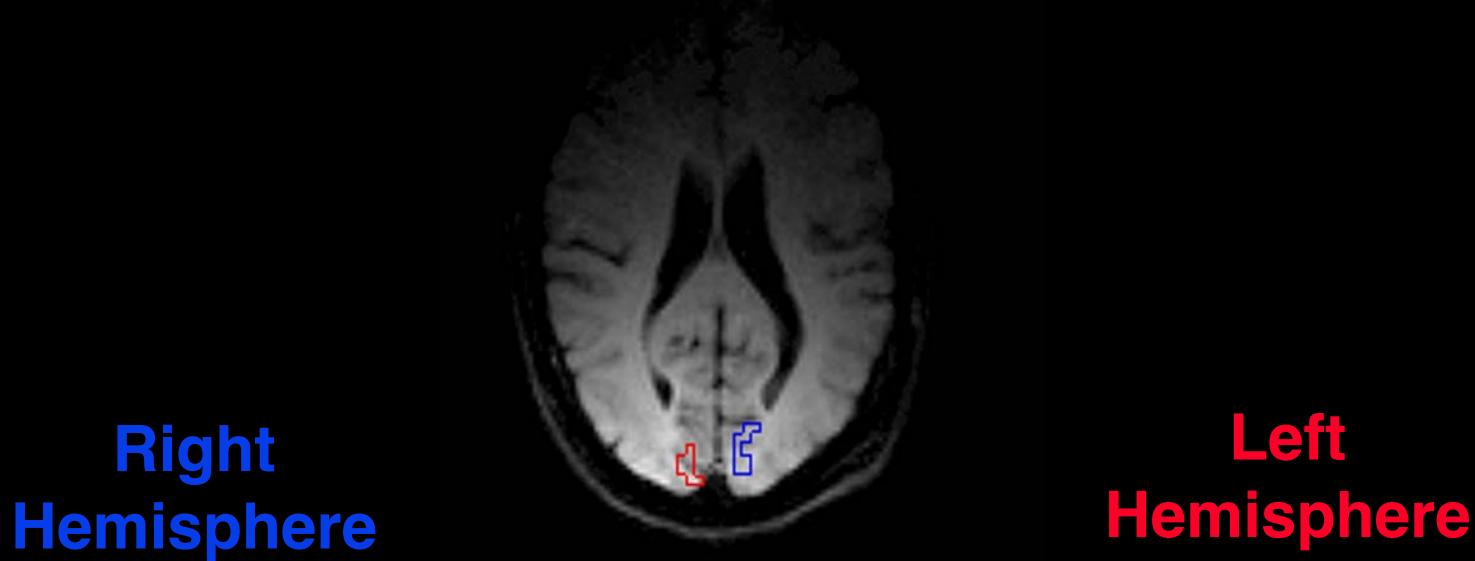
# Latency

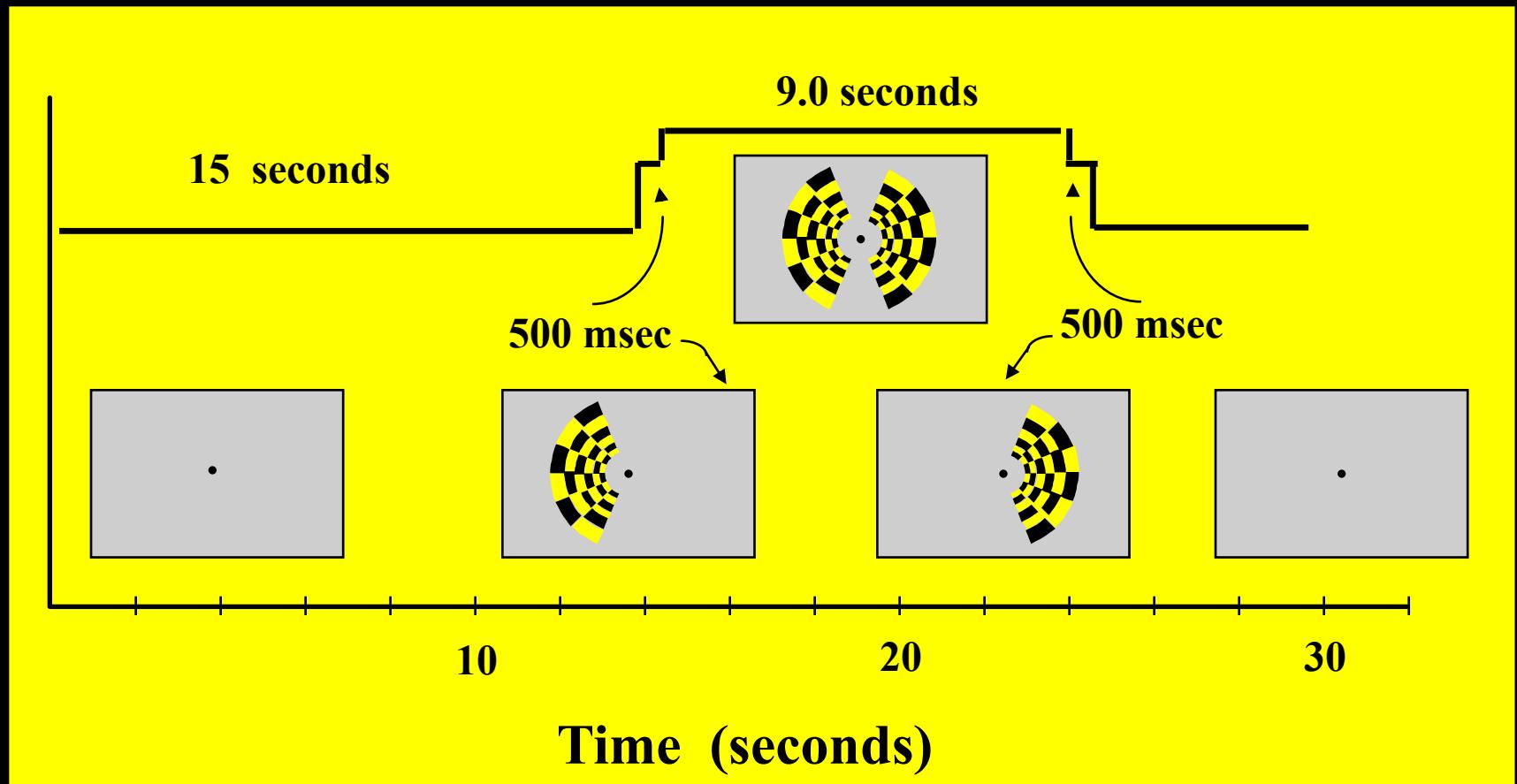


# Magnitude



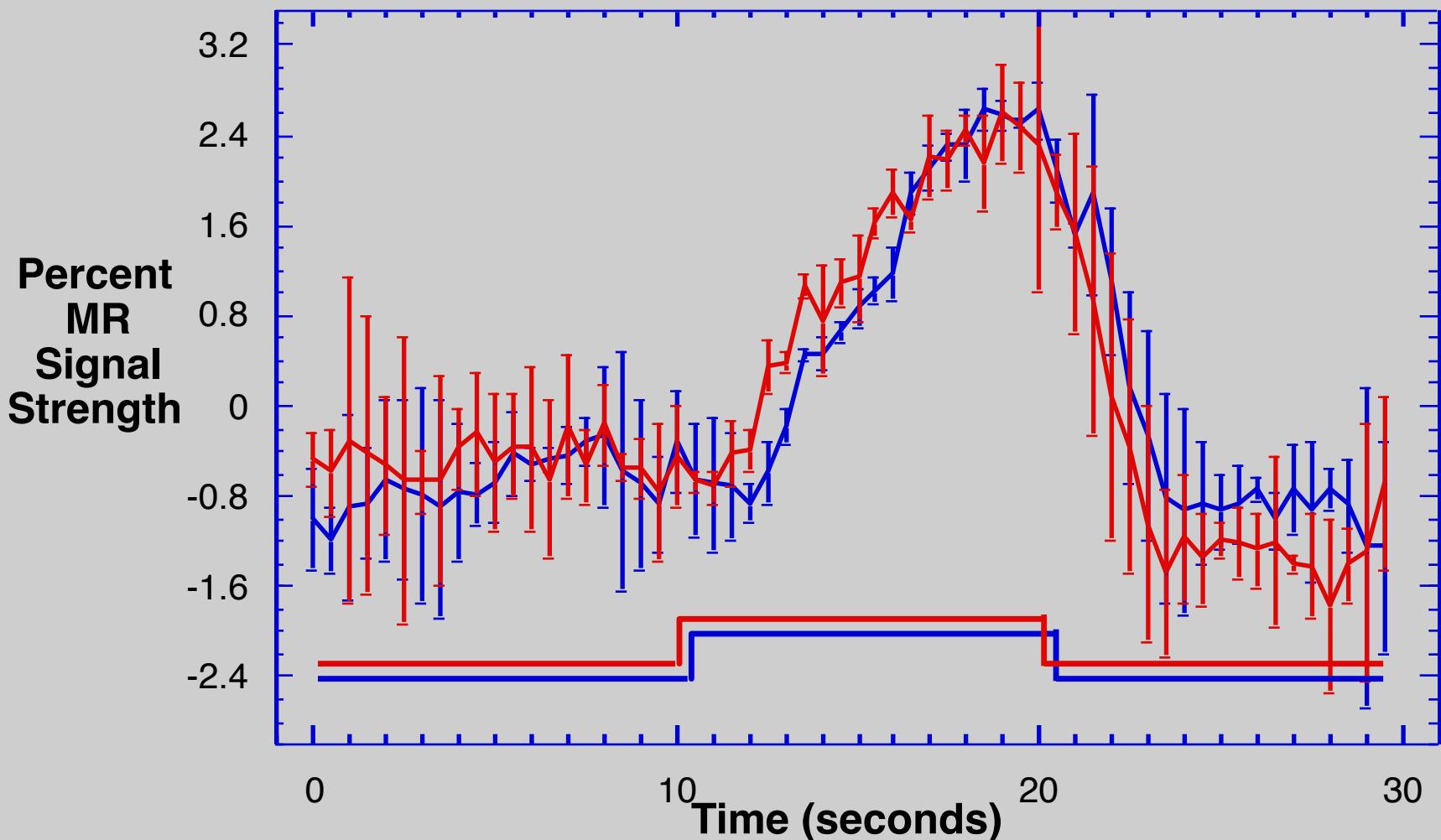
# Regions of Interest Used for Hemi-Field Experiment

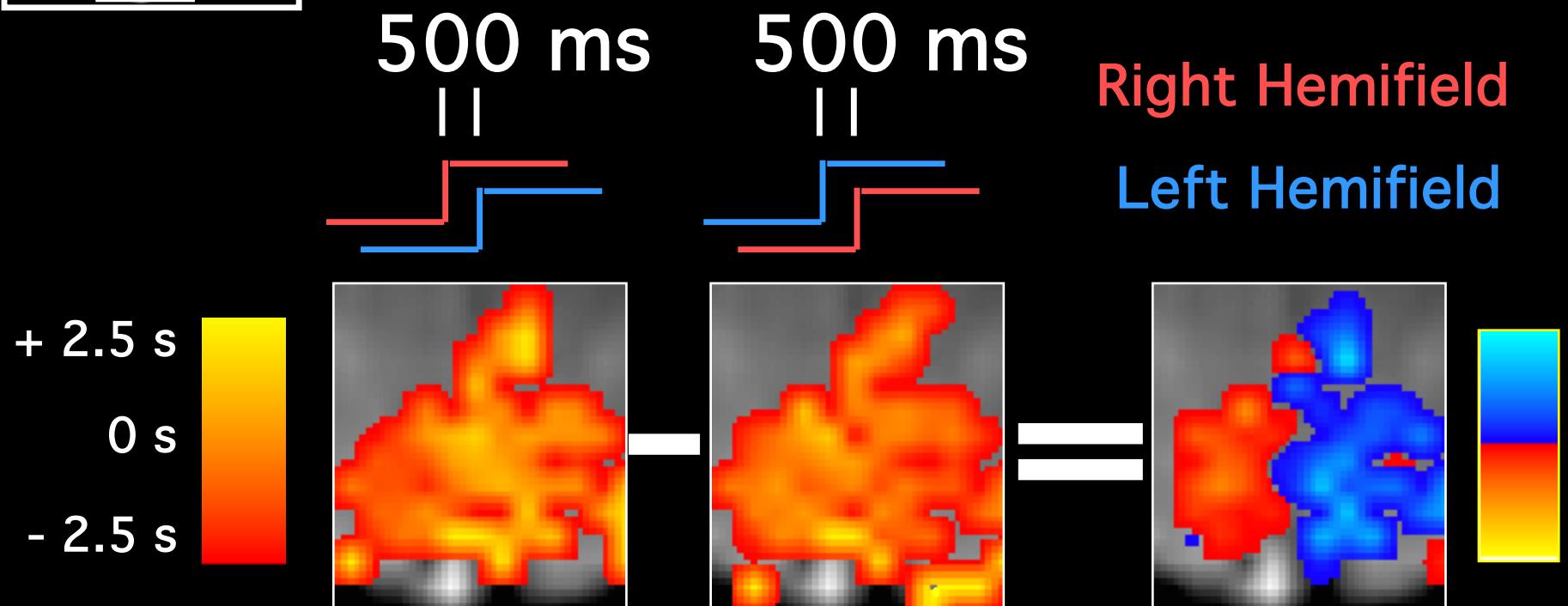
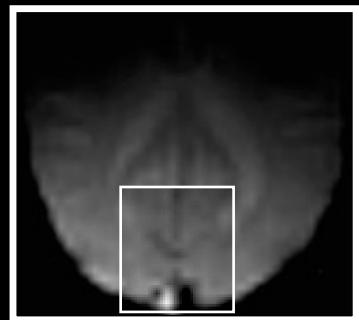


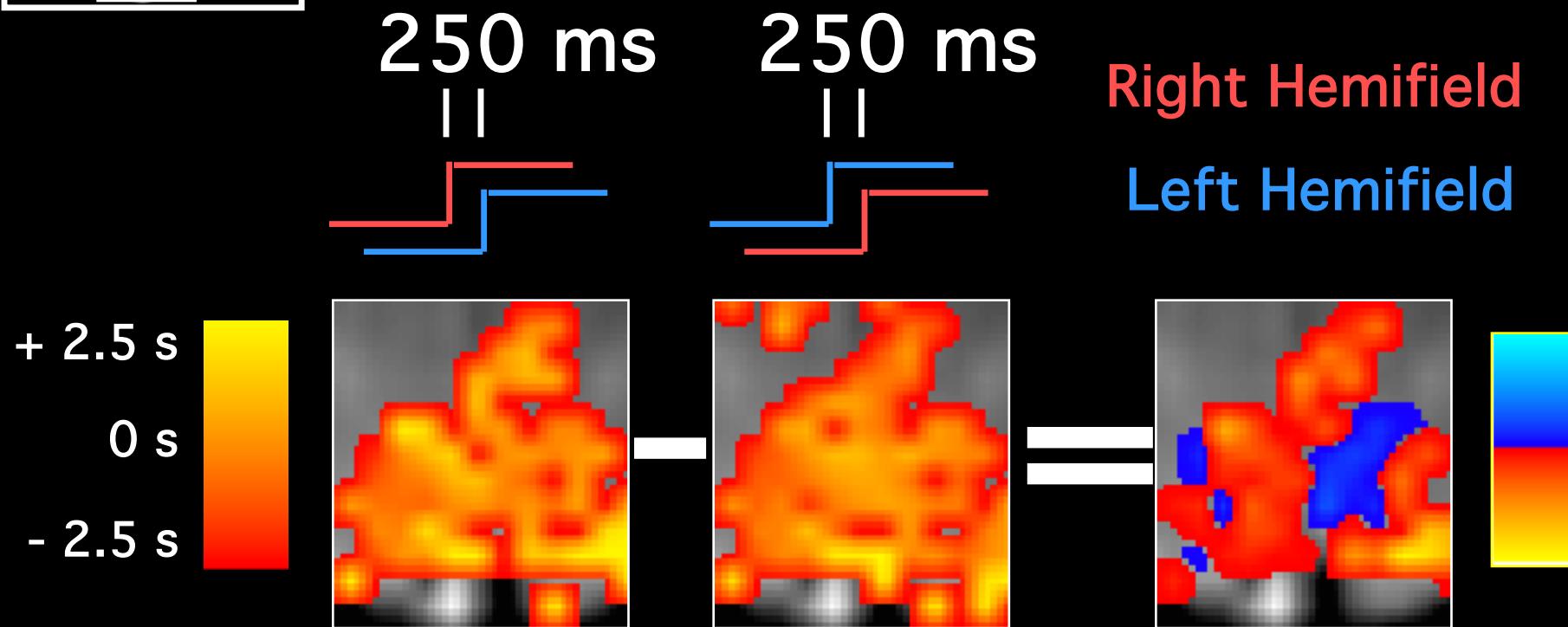
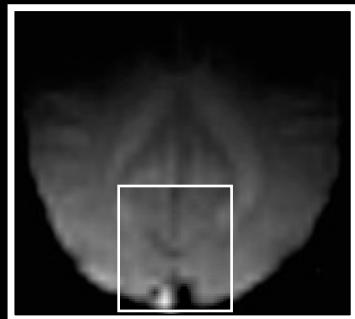


# Hemi-field with 500 msec asynchrony

Average of 6 runs    Standard Deviations Shown





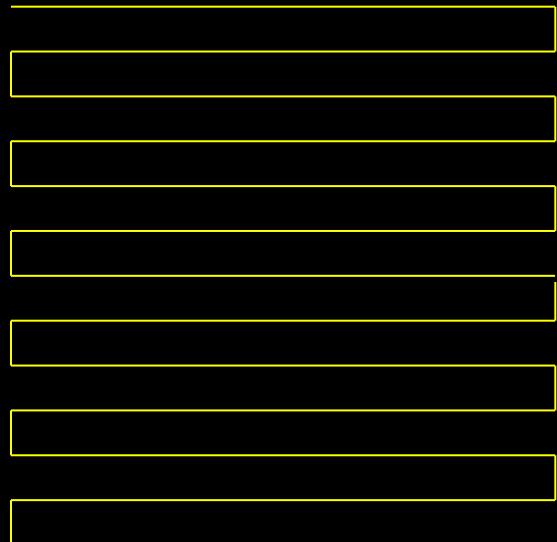


# Single Shot Imaging

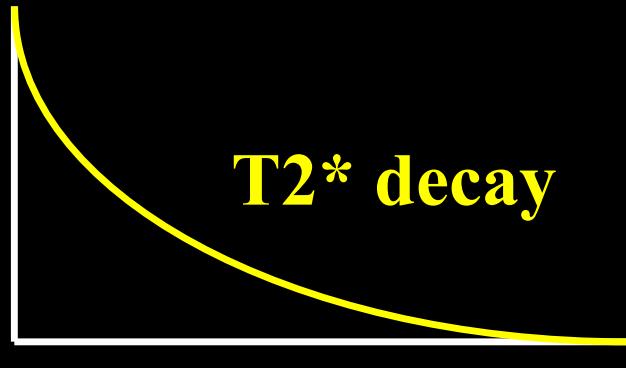


EPI Readout Window

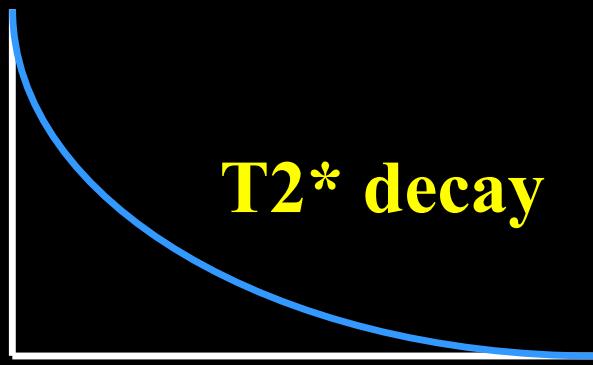
$\approx 20$  to 40 ms



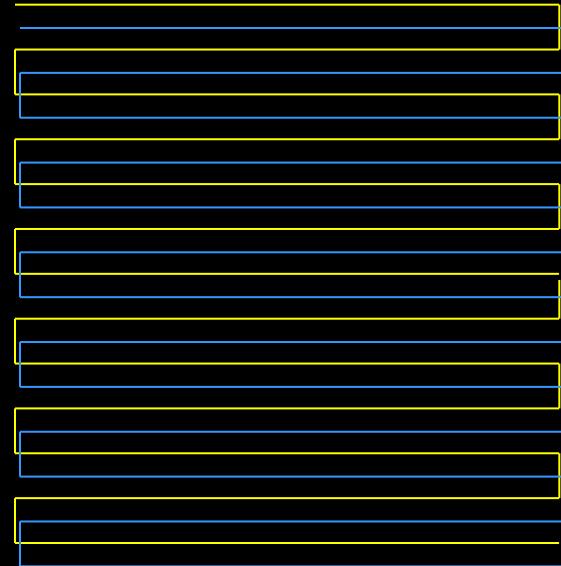
# Multishot Imaging



EPI Window 1



EPI Window 2



# Multi Shot EPI

Excitations

1

2

4

8

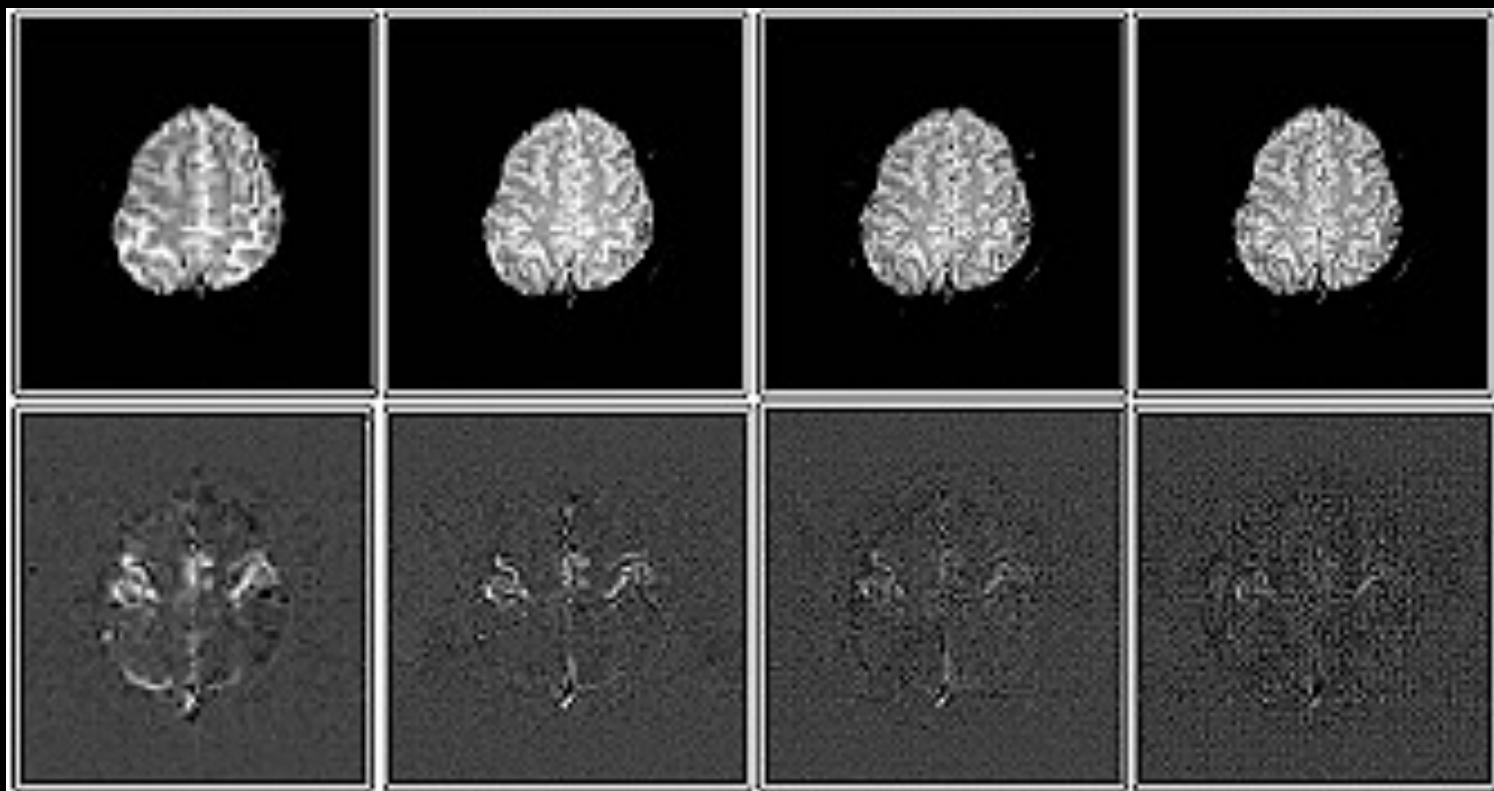
Matrix Size

64 x 64

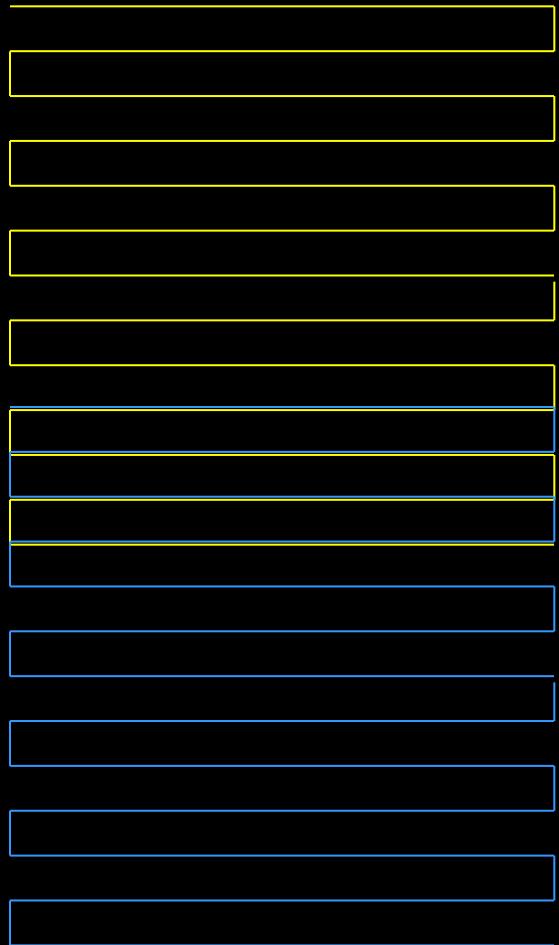
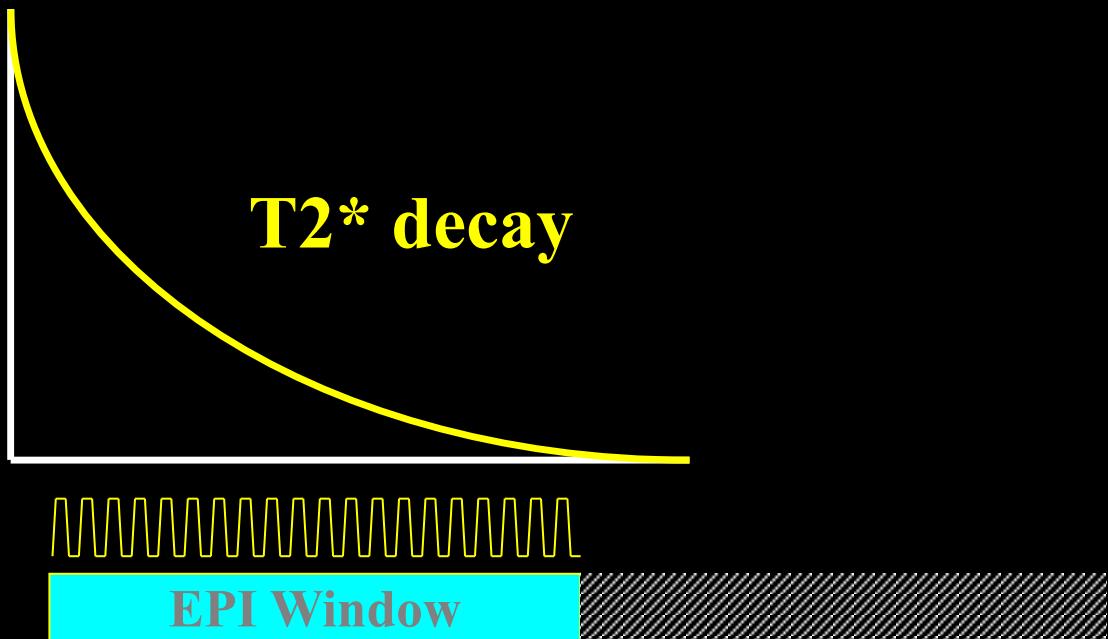
128 x 128

256 x 128

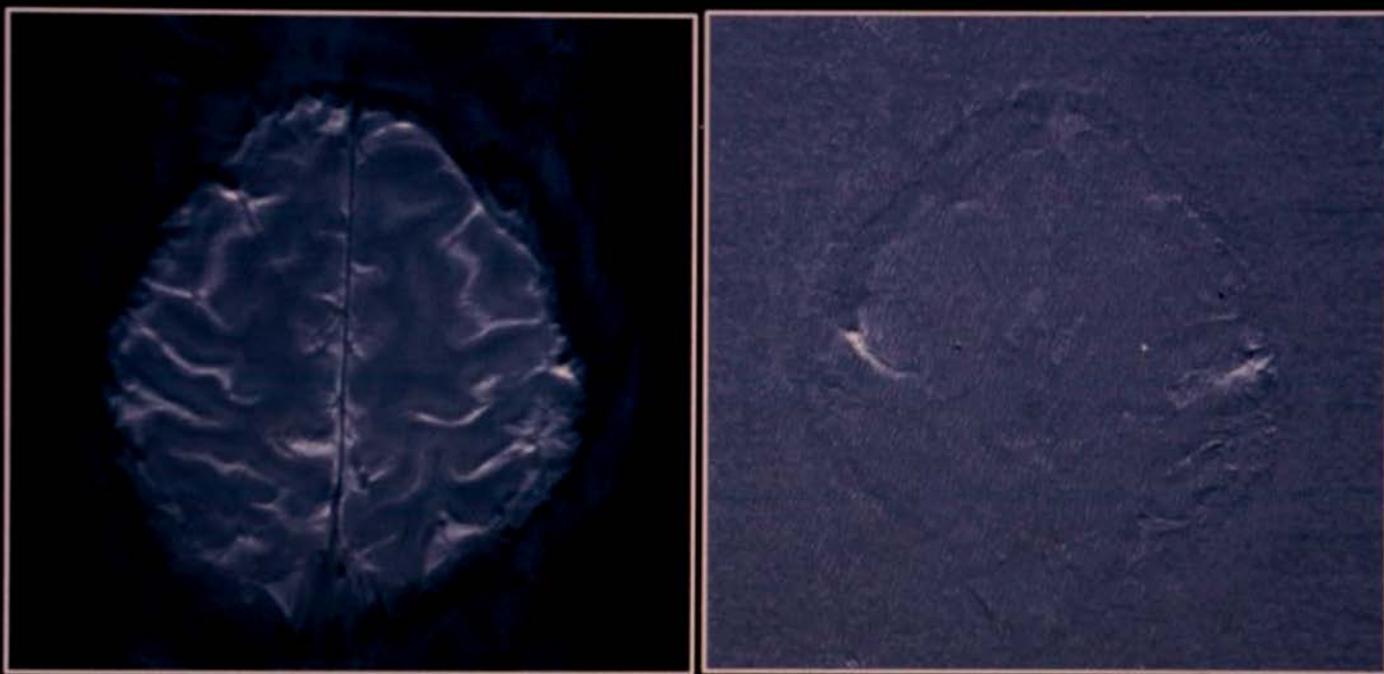
256



# Partial k-space imaging

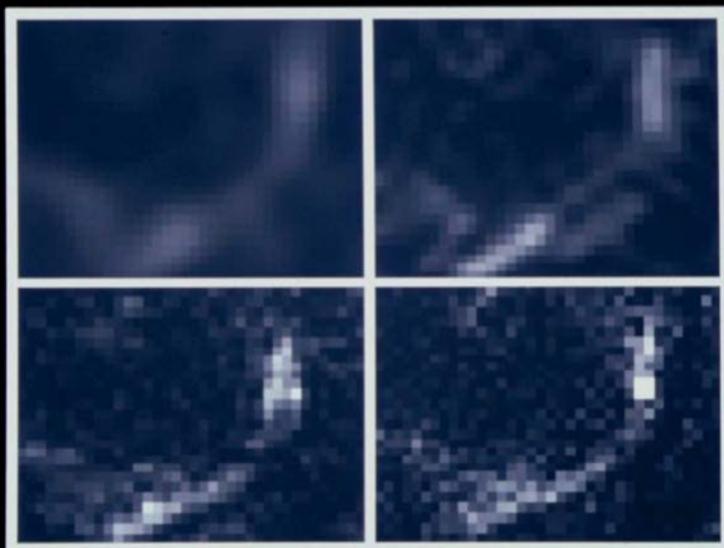


**Single - Shot EPI at 3T:  
Half NEX, 256 x 256, 16 cm FOV**



## Fractional Signal Change

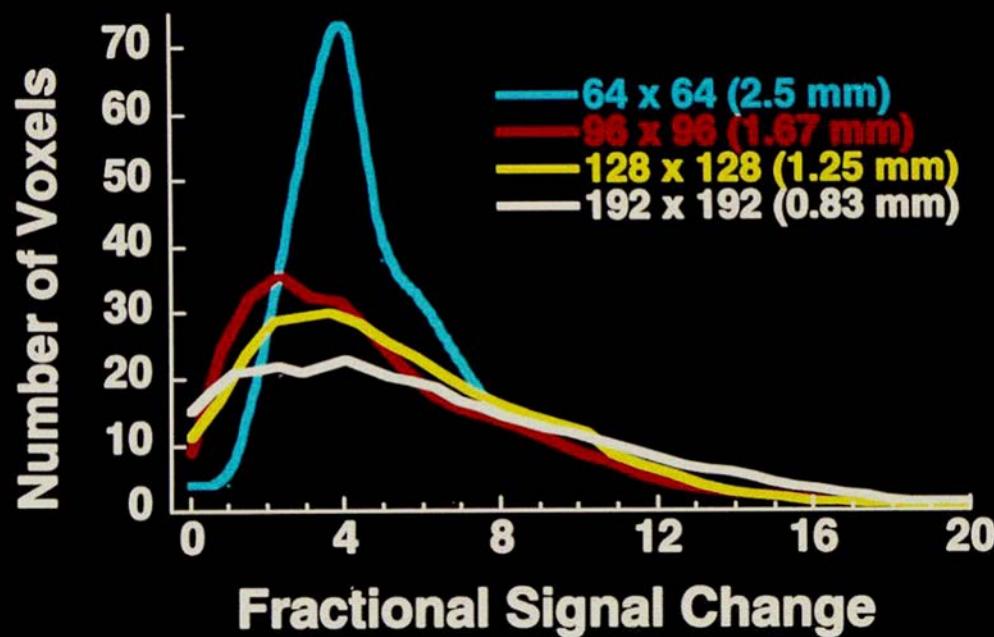
$2.5 \text{ mm}^2$



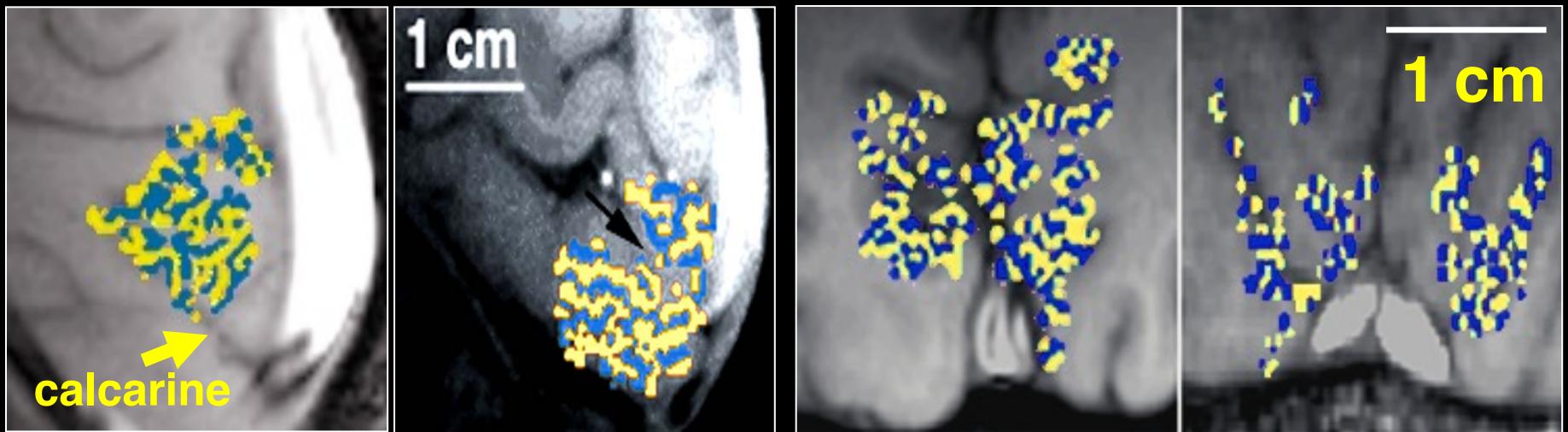
$1.25 \text{ mm}^2$

$0.83 \text{ mm}^2$

$0.62 \text{ mm}^2$



# ODC Maps using fMRI



- Identical in size, orientation, and appearance to those obtained by optical imaging<sup>1</sup> and histology<sup>3,4</sup>.

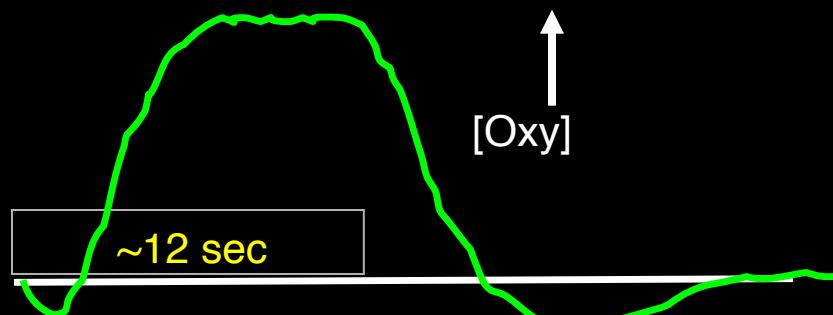
<sup>1</sup>Malonek D, Grinvald A. *Science* 272, 551-4 (1996).

<sup>3</sup>Horton JC, Hocking DR. *J Neurosci* 16, 7228-39 (1996).

<sup>4</sup>Horton JC, et al. *Arch Ophthalmol* 108, 1025-31 (1990).

# Why short is better than long

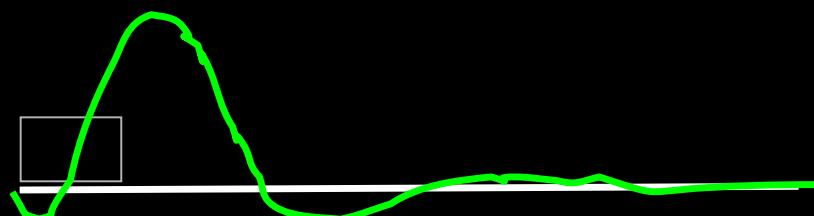
The vascular response to prolonged neural stimulation



It is argued that fMRI cannot achieve submillimeter functional resolution because a saturated hyperoxic vascular response to neural activity spreads over many millimeters<sup>1,2</sup>.

However, optical imaging has demonstrated that the hyperoxic response can yield well-localized maps when using short duration stimuli (<5 sec)<sup>1</sup>.

The vascular response to brief neural stimulation



<sup>1</sup>Malonek D, Grinvald A. Science 272, 551-4 (1996).

<sup>2</sup>Kim D-S, Duong T, Kim S-G. Nat Neurosci 3, 164-9 (2000).

- Contrast in fMRI

*Hemodynamic Specificity*

- The Hemodynamic Transfer Function

*Location, Latency, Magnitude*

- Best Results So Far

*Temporal Resolution, Spatial Resolution*

- Neuronal Activation Input Strategies

*Block Design*

*Phase and Frequency Encoding*

*Orthogonal Designs*

*Parametric Designs*

*Event-Related Designs*

*Free Behavior Designs*

# Neuronal Activation Input Strategies

1. Block Design

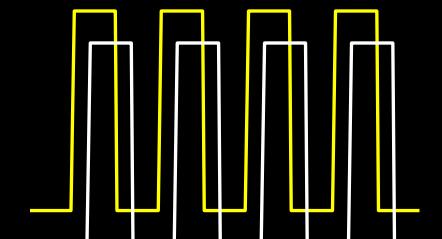
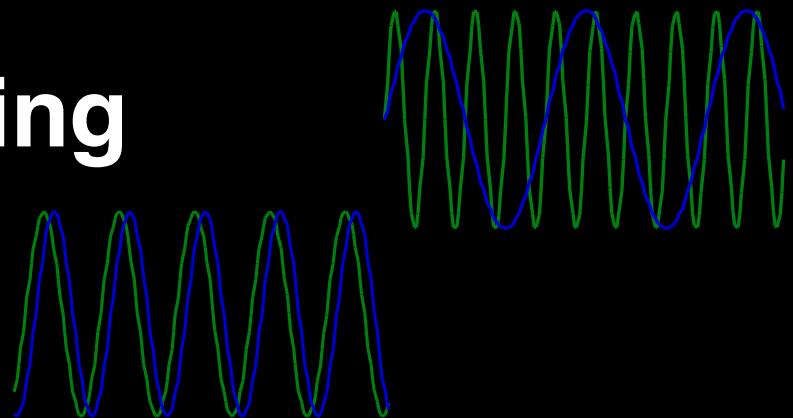
2. Frequency Encoding

3. Phase Encoding

4. Single Event

5. Orthogonal Block Design

6. Free Behavior Design.



# Neuronal Activation Input Strategies

1. Block Design

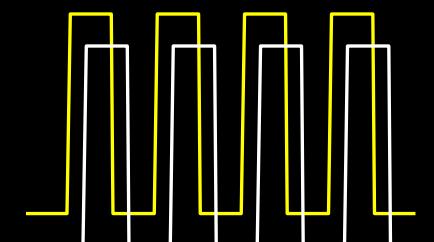
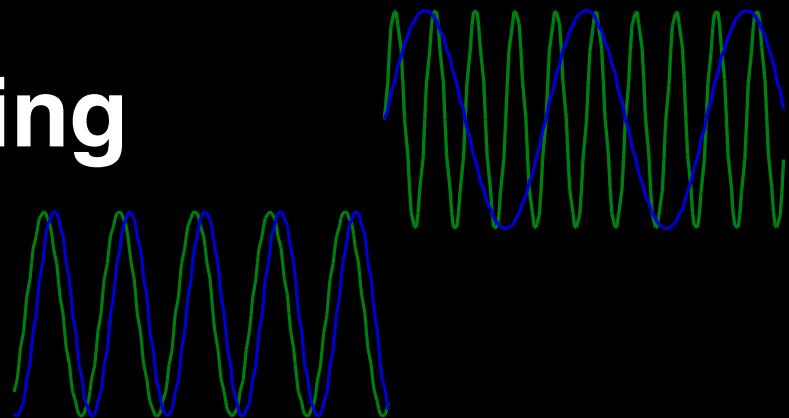
2. Frequency Encoding

3. Phase Encoding

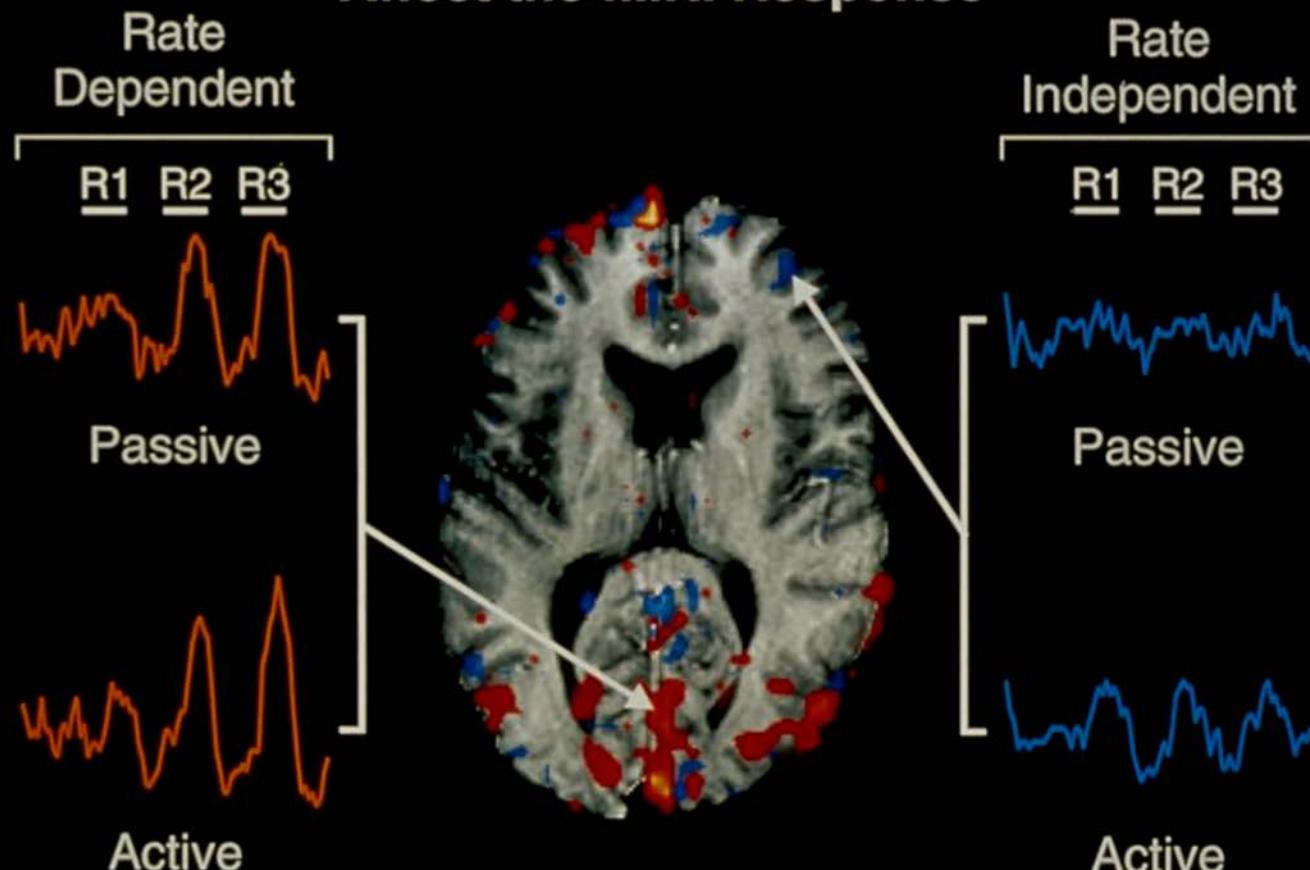
4. Single Event

5. Orthogonal Block Design

6. Free Behavior Design.



## Both the Task and Presentation Rate Affect the fMRI Response



DeYoe et al.

# Neuronal Activation Input Strategies

1. Block Design

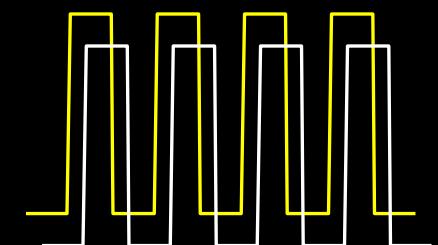
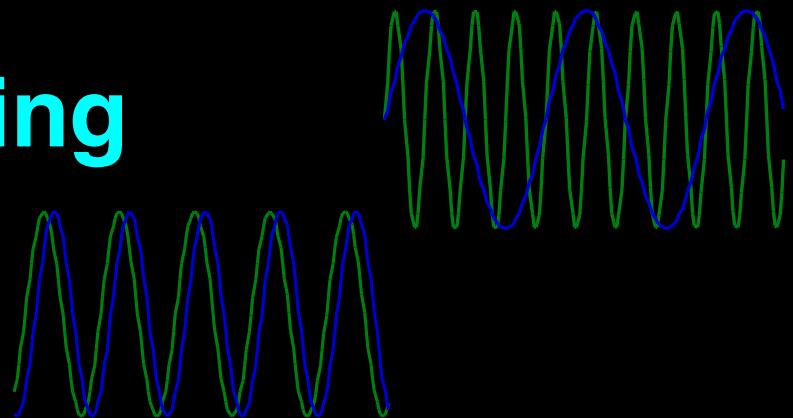
2. Frequency Encoding

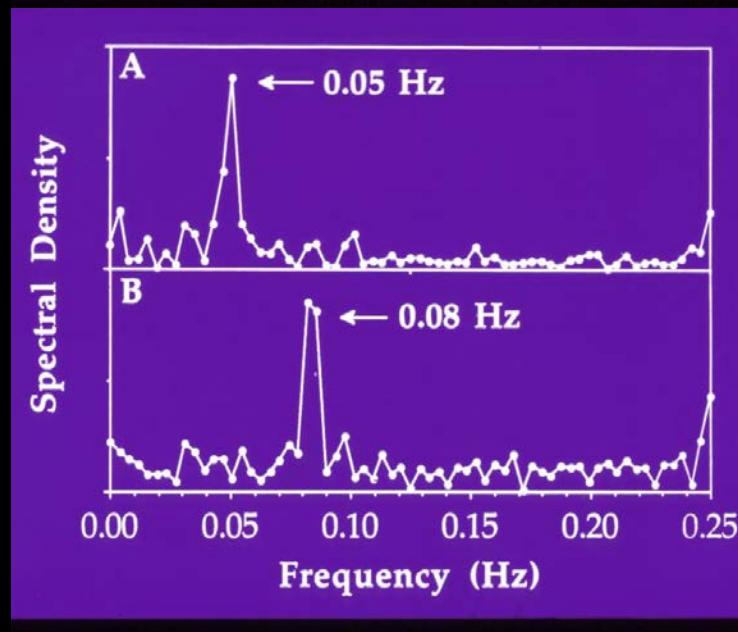
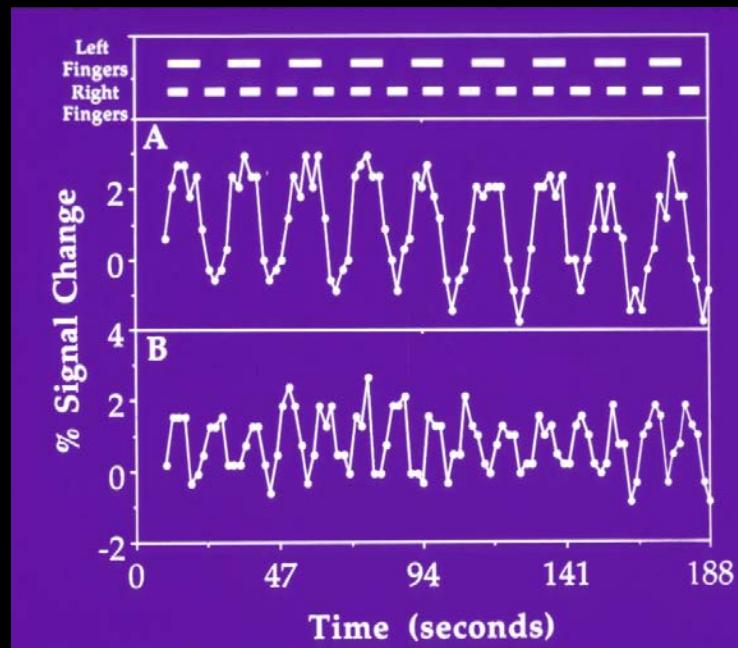
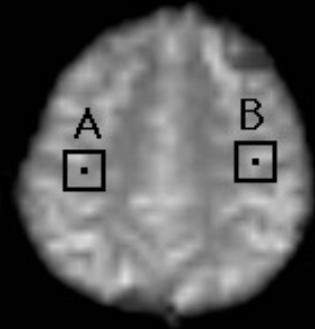
3. Phase Encoding

4. Single Event

5. Orthogonal Block Design

6. Free Behavior Design.

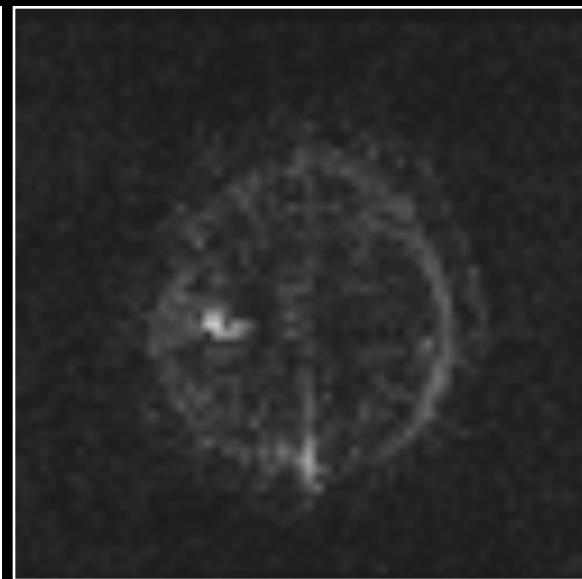
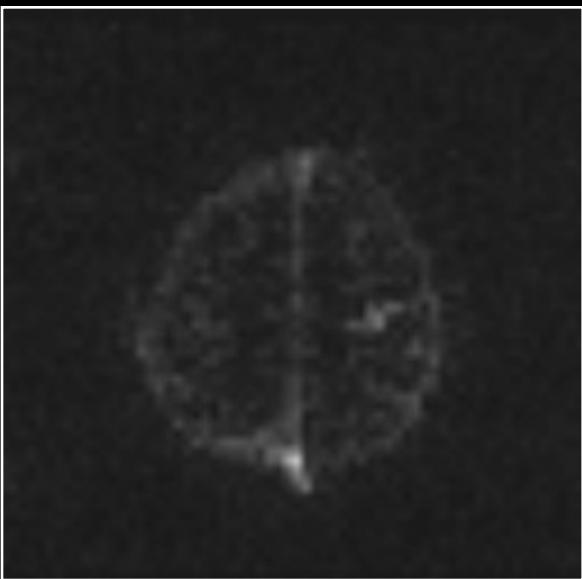




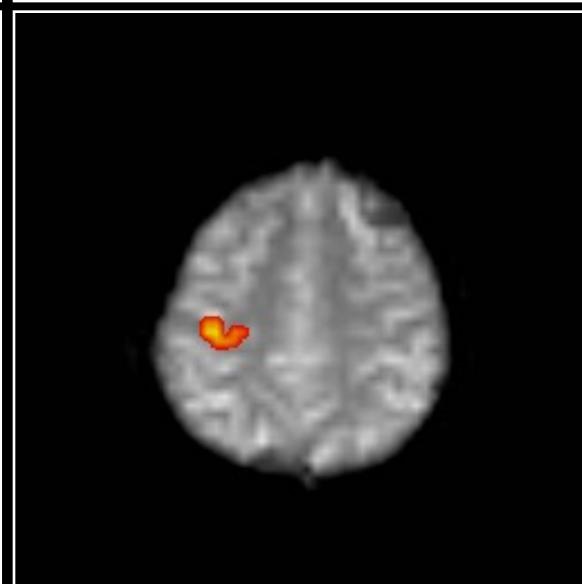
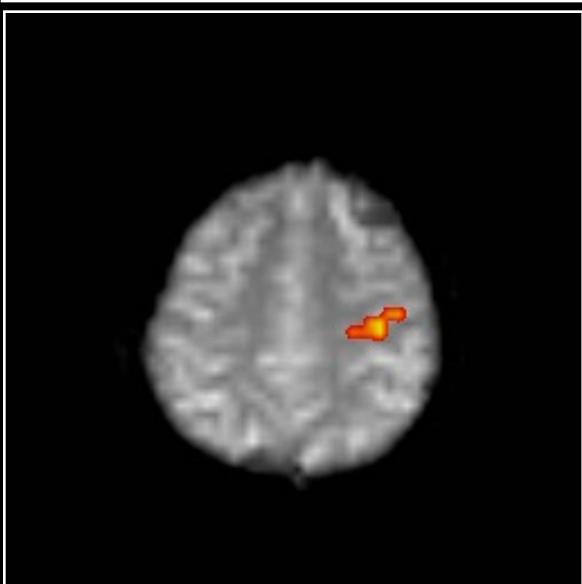
**0.08 Hz**

**0.05 Hz**

**spectral  
density**



**c.c. > 0.5  
with spectra**



# Neuronal Activation Input Strategies

1. Block Design

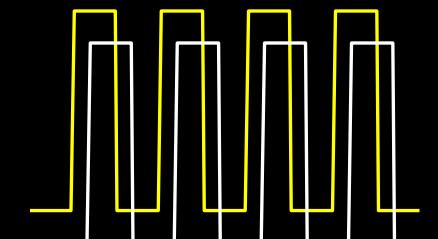
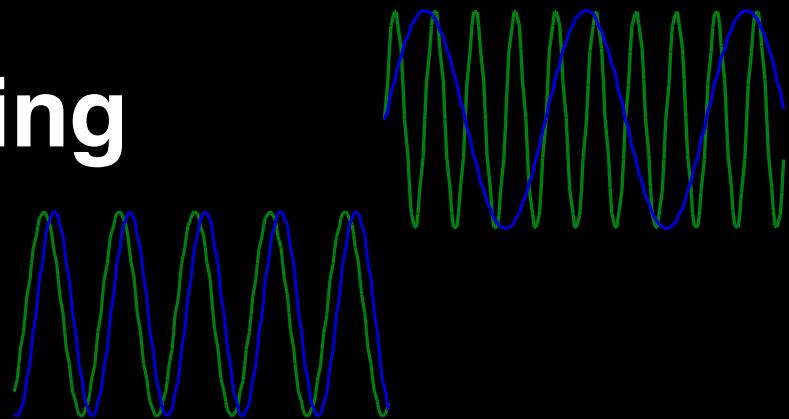
2. Frequency Encoding

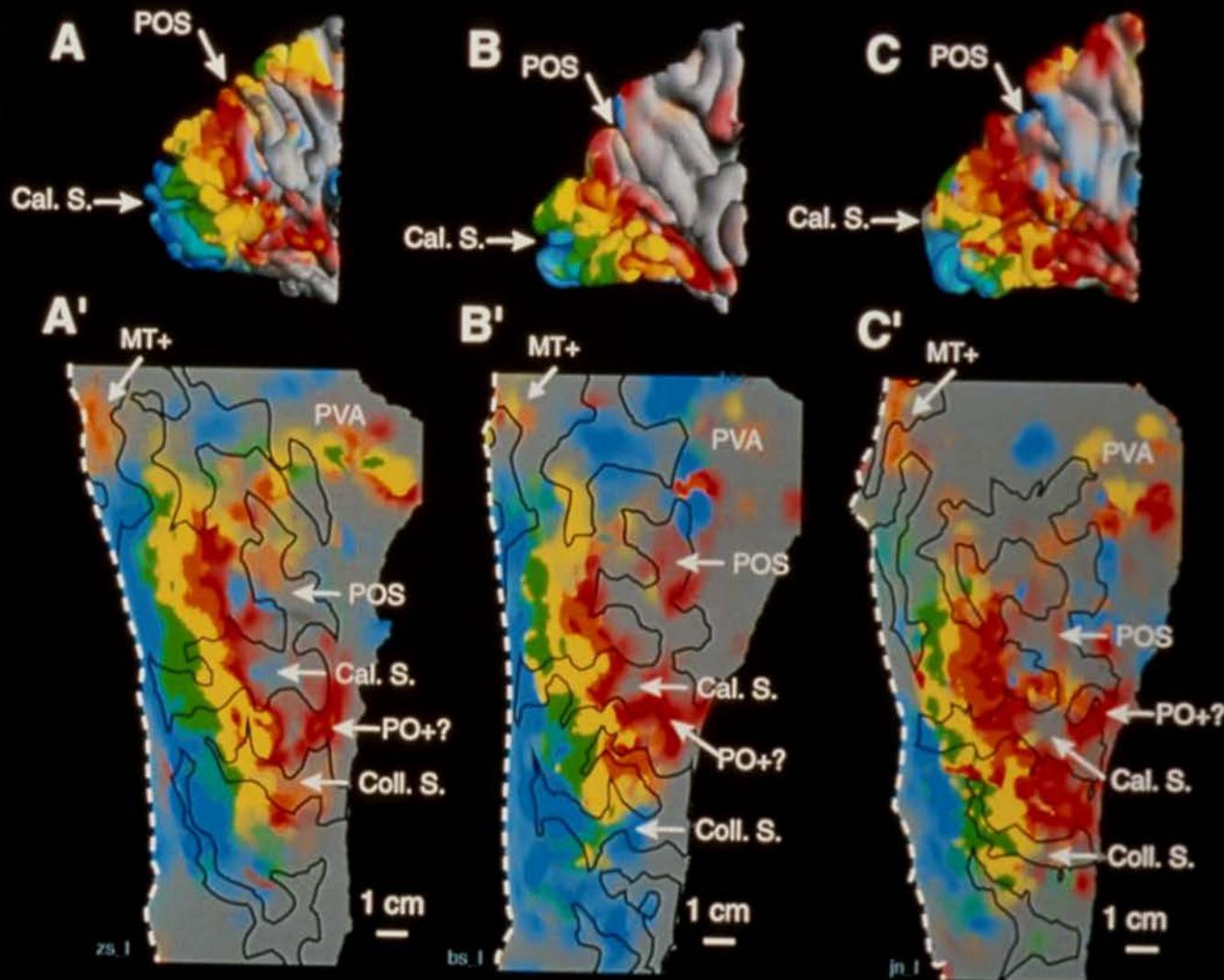
3. Phase Encoding

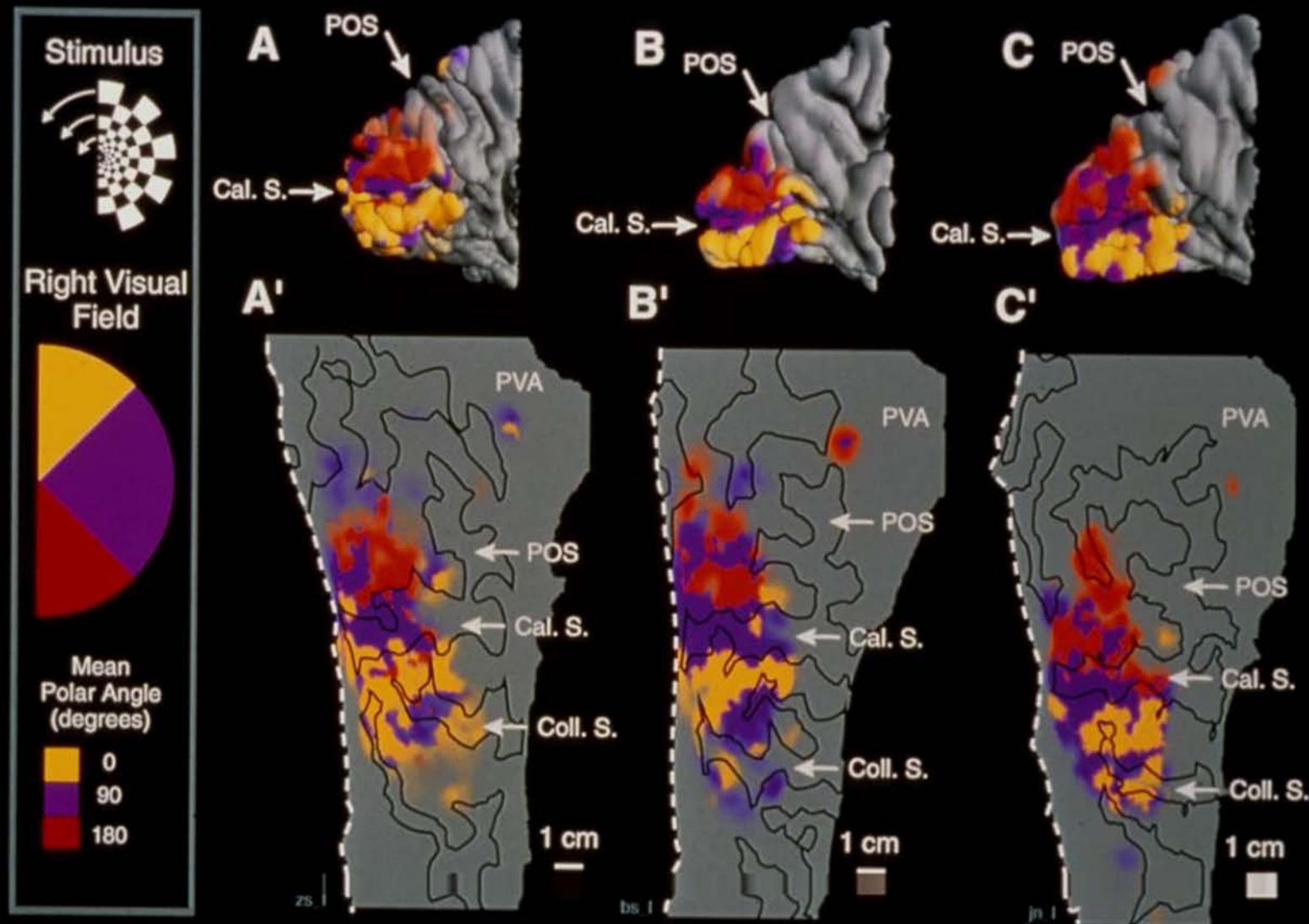
4. Single Event

5. Orthogonal Block Design

6. Free Behavior Design.







# Neuronal Activation Input Strategies

1. Block Design

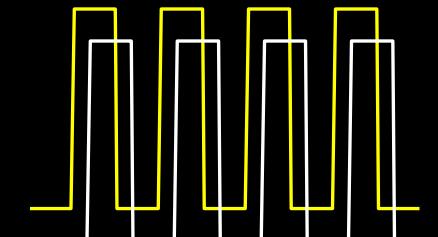
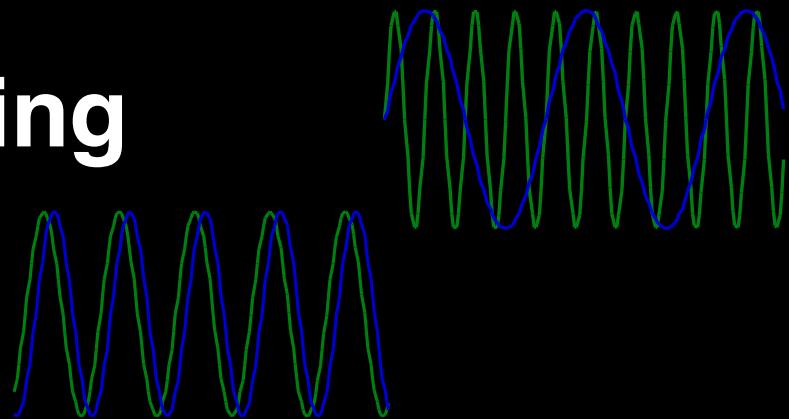
2. Frequency Encoding

3. Phase Encoding

4. Single Event

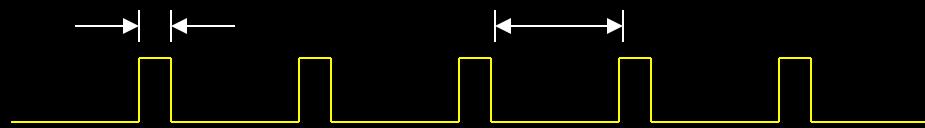
5. Orthogonal Block Design

6. Free Behavior Design.

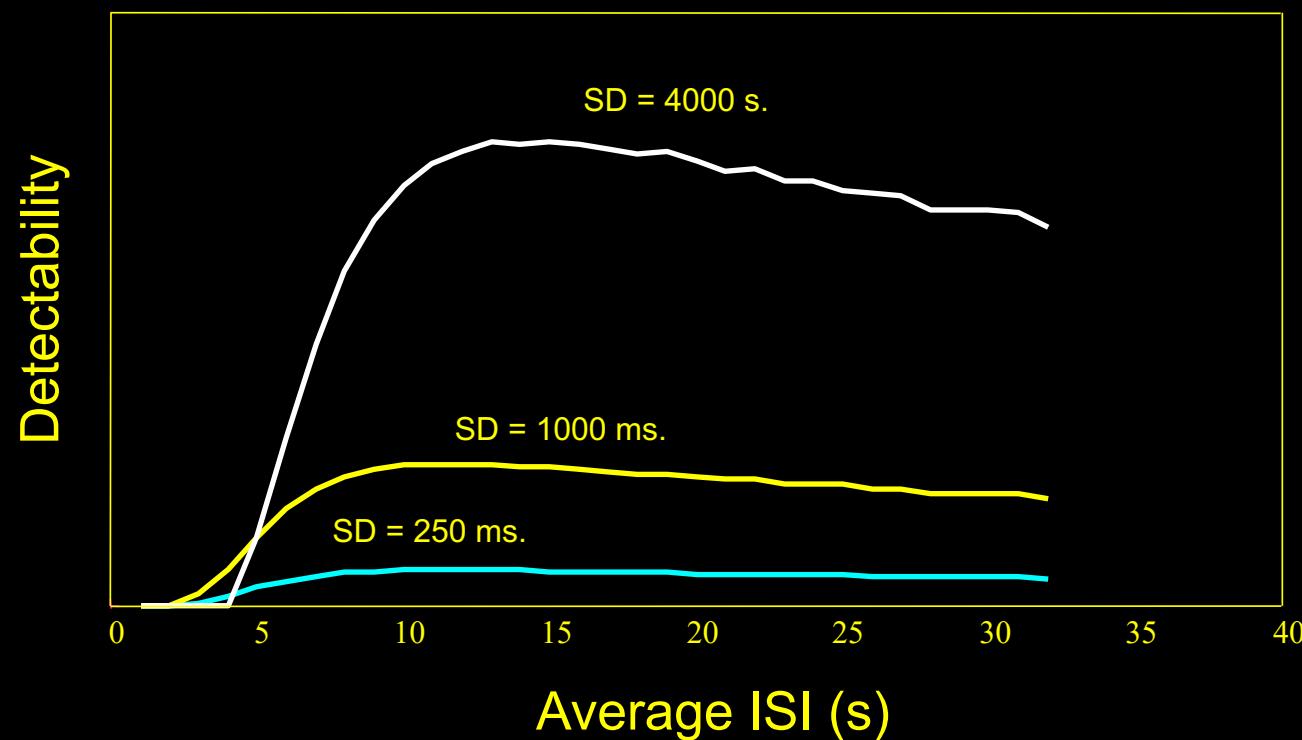


# Detectability – constant ISI

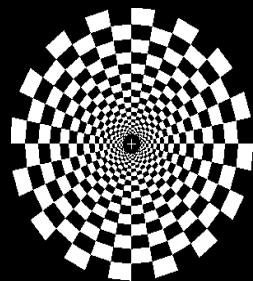
SD – stimulus duration



ISI – inter-stimulus interval

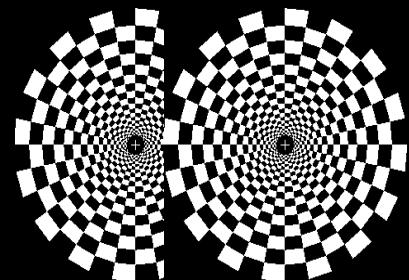


# Visual Activation Paradigm: 1 , 2, & 3 Trials



0 sec

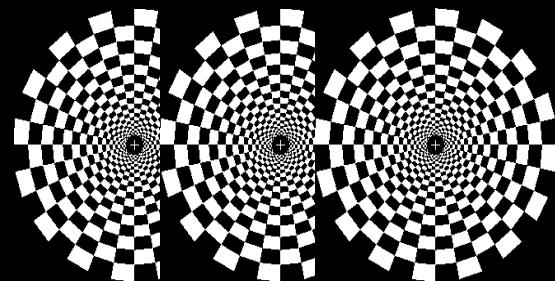
20 sec



0 sec

2 sec

20 sec



0 sec

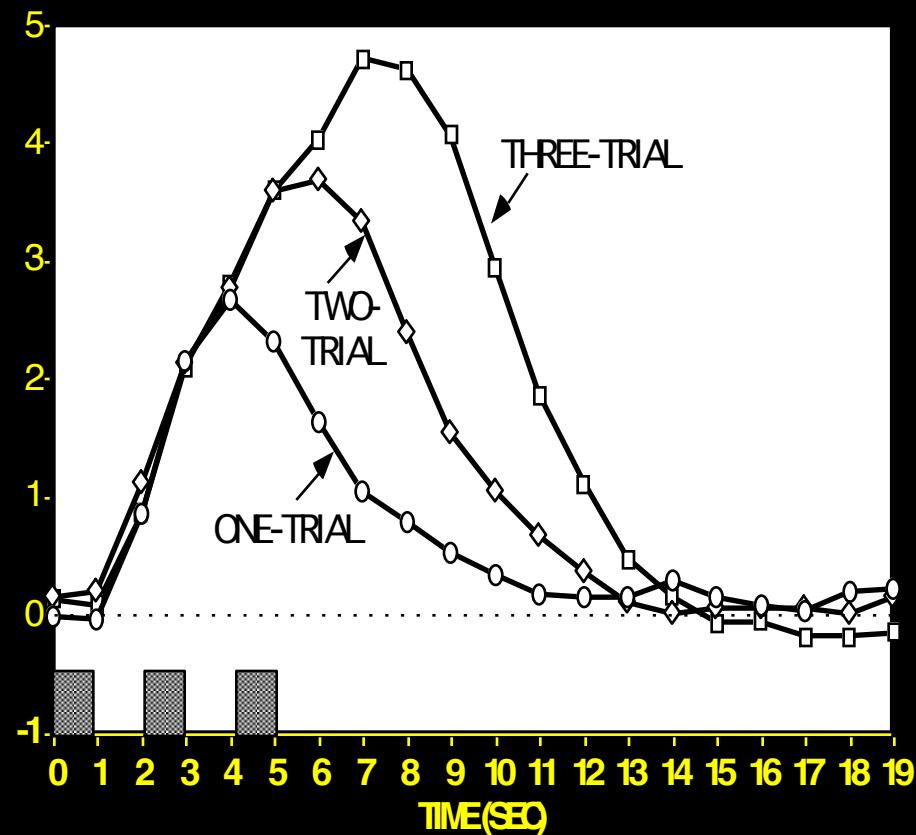
2 sec

4 sec

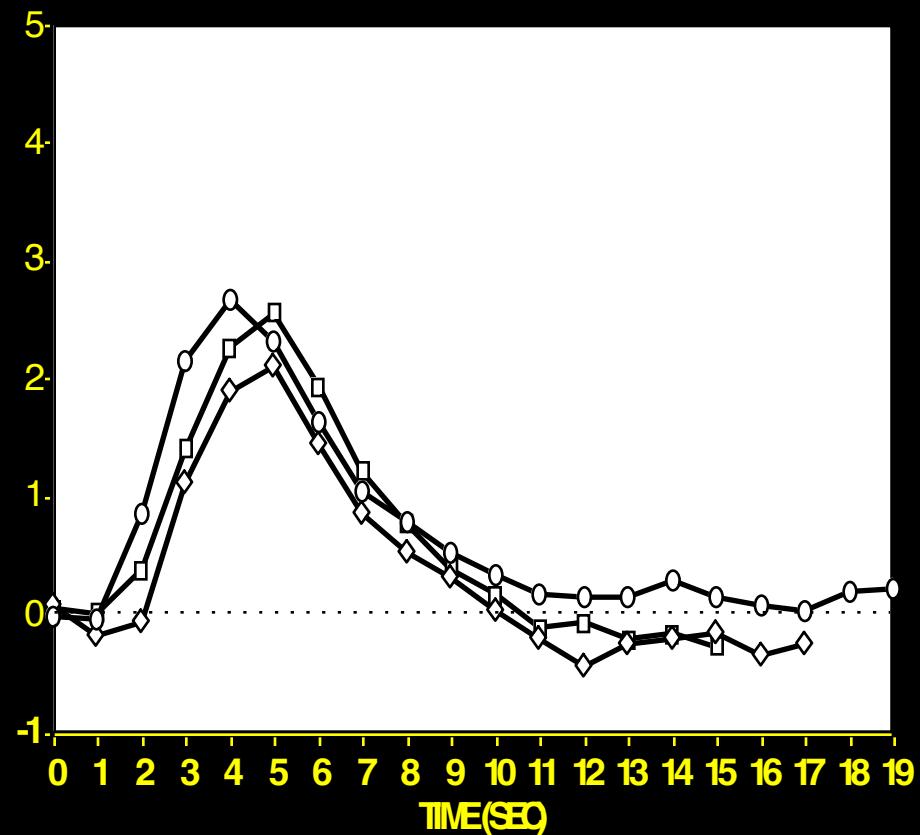
20 sec

# Response to Multiple Trials: Subject RW

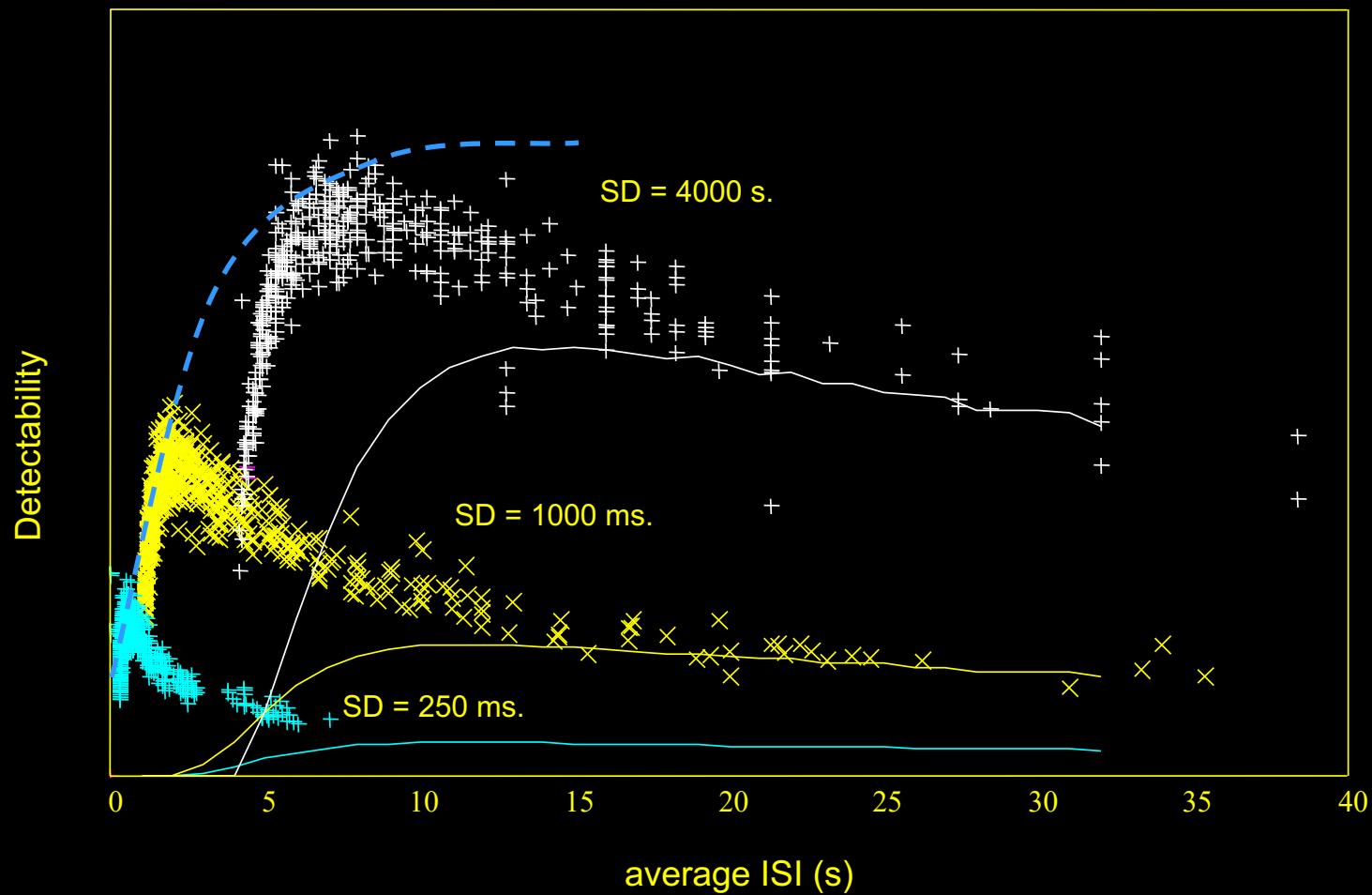
**RAW DATA**



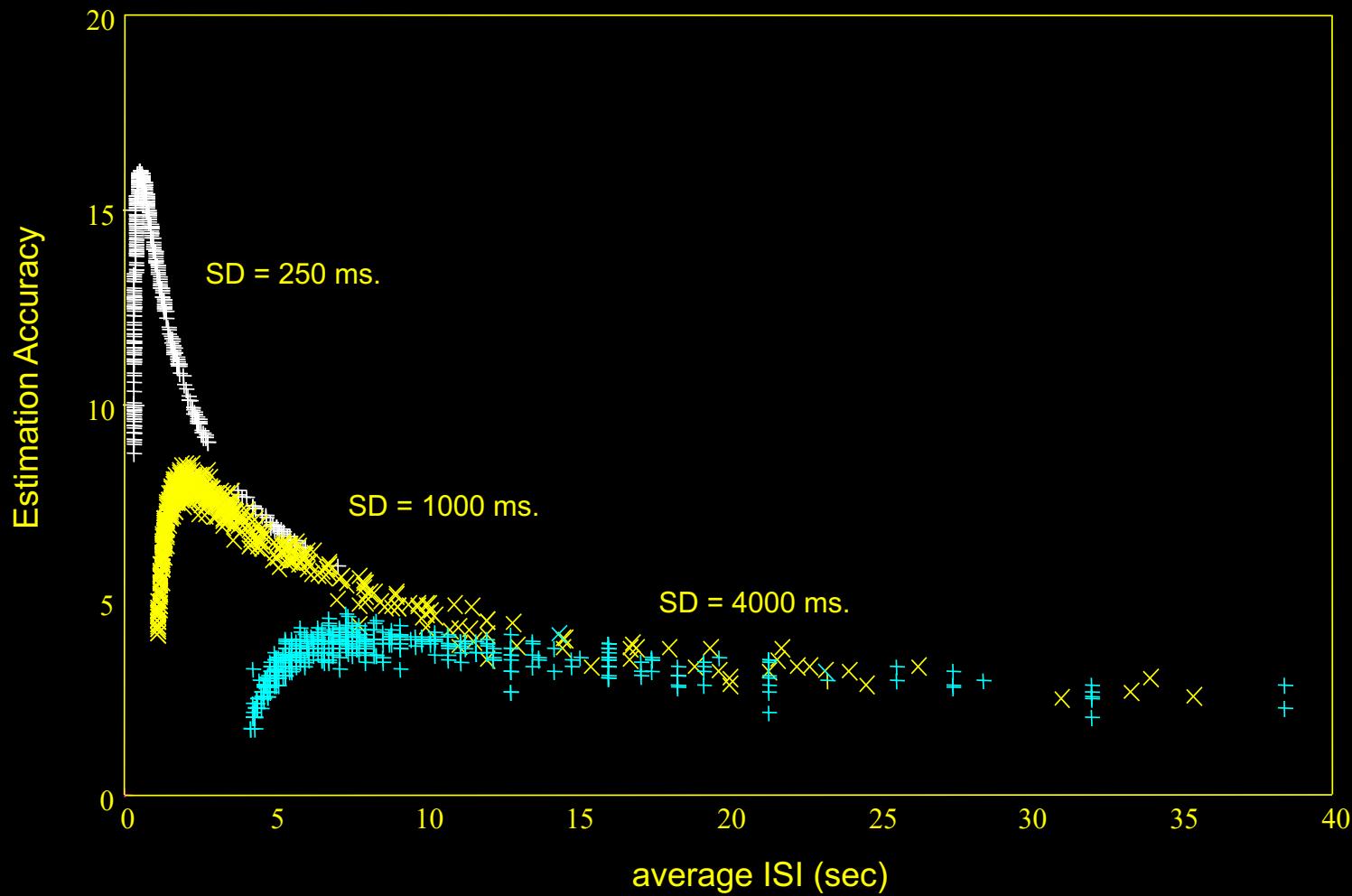
**ESTIMATED RESPONSES**



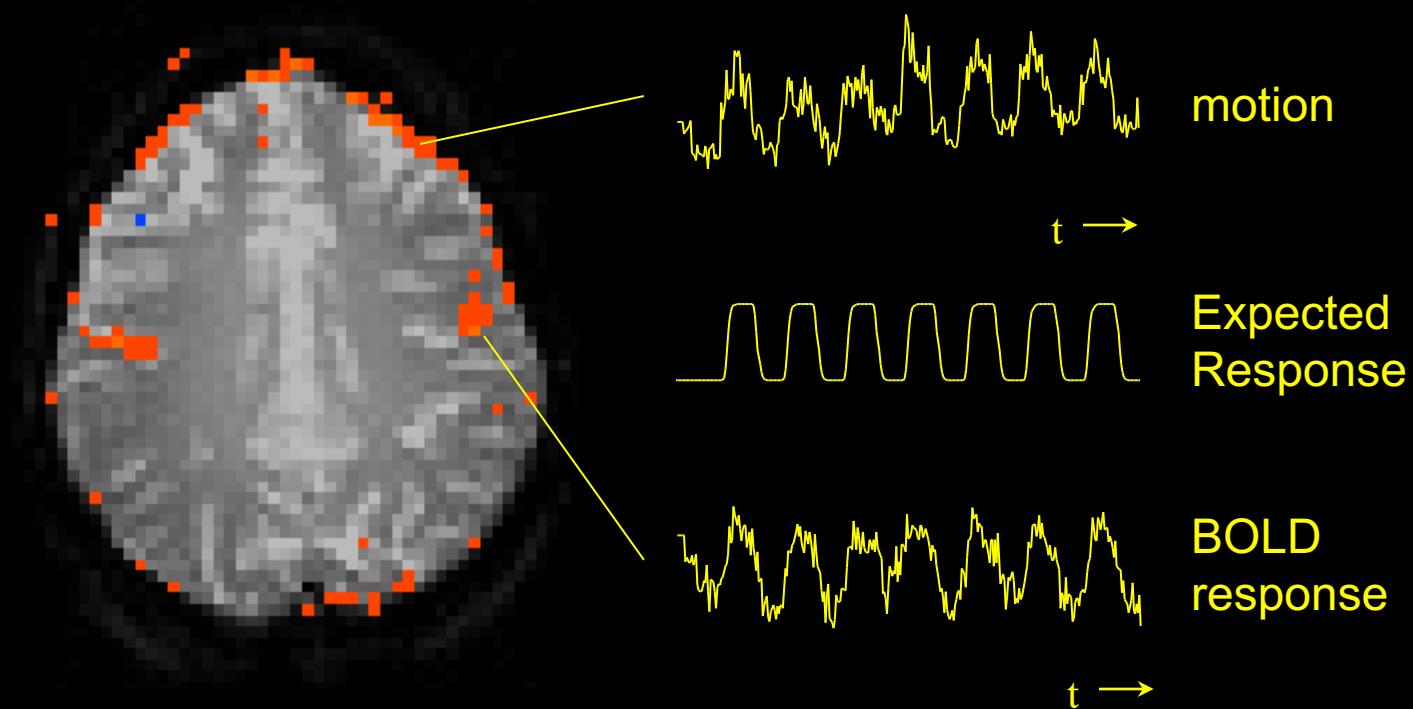
# Detectability vs. Average ISI



# Estimation accuracy vs. average ISI

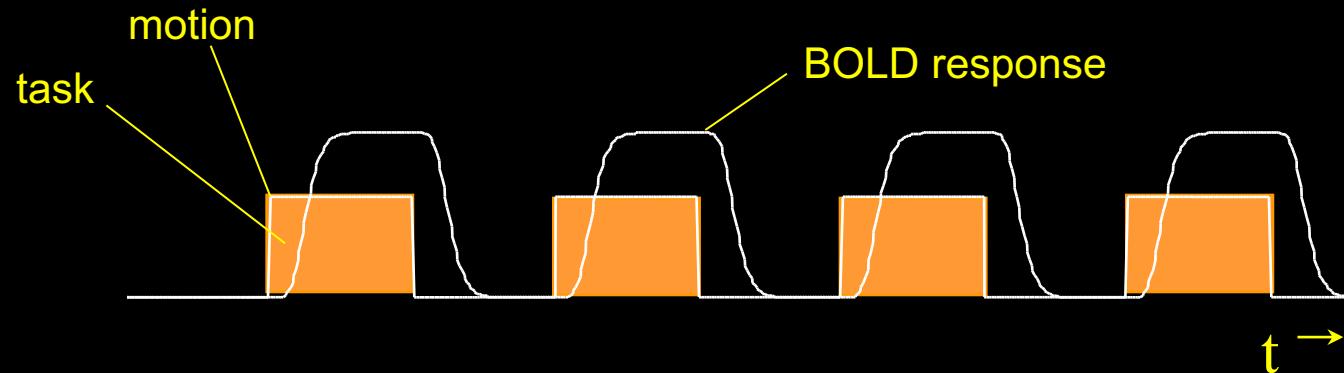


# Speaking - Blocked Trial

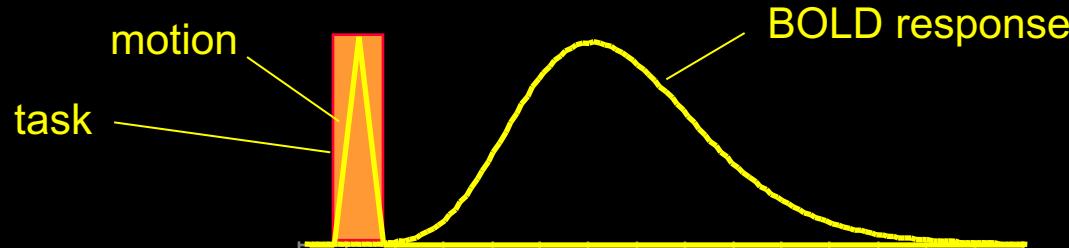


# fMRI during tasks that involve brief motion

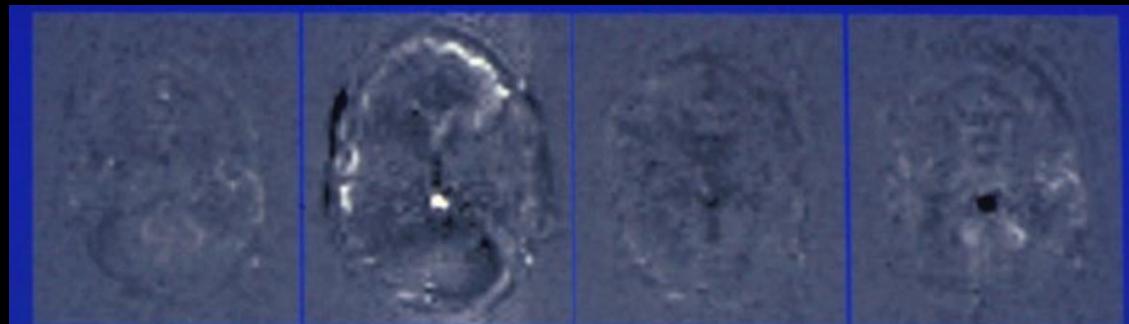
## Blocked Design



## Event-Related Design



# Overt Word Production



2

3

4

5



6

7

8

9



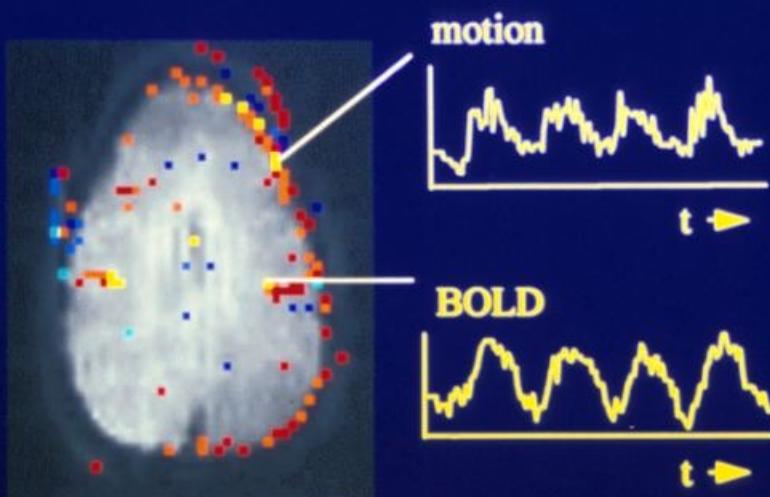
10

11

12

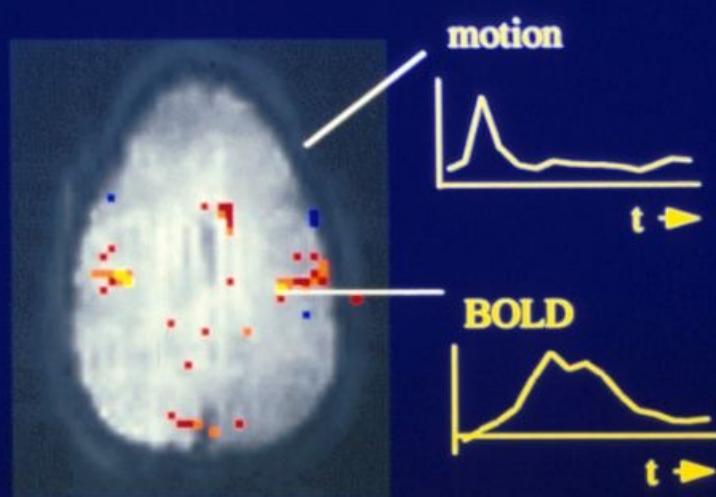
13

## Motion-Decoupled fMRI: Functional MRI during overt word production



### "block-trial" paradigm

Motion induced signal changes resemble functional (BOLD) signal changes

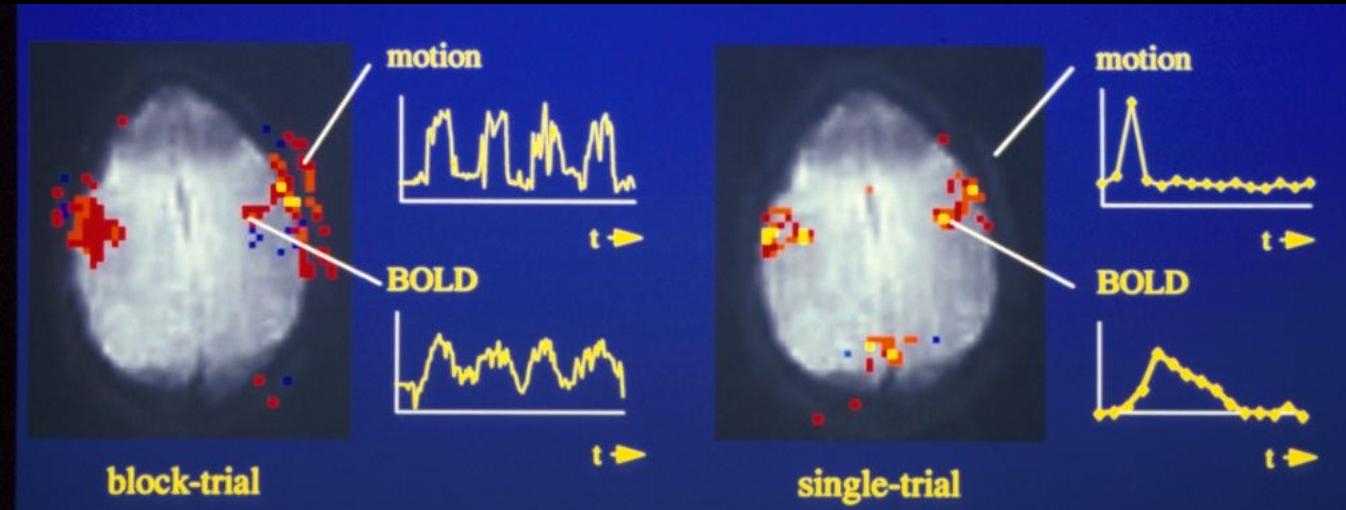


### "single-trial" paradigm

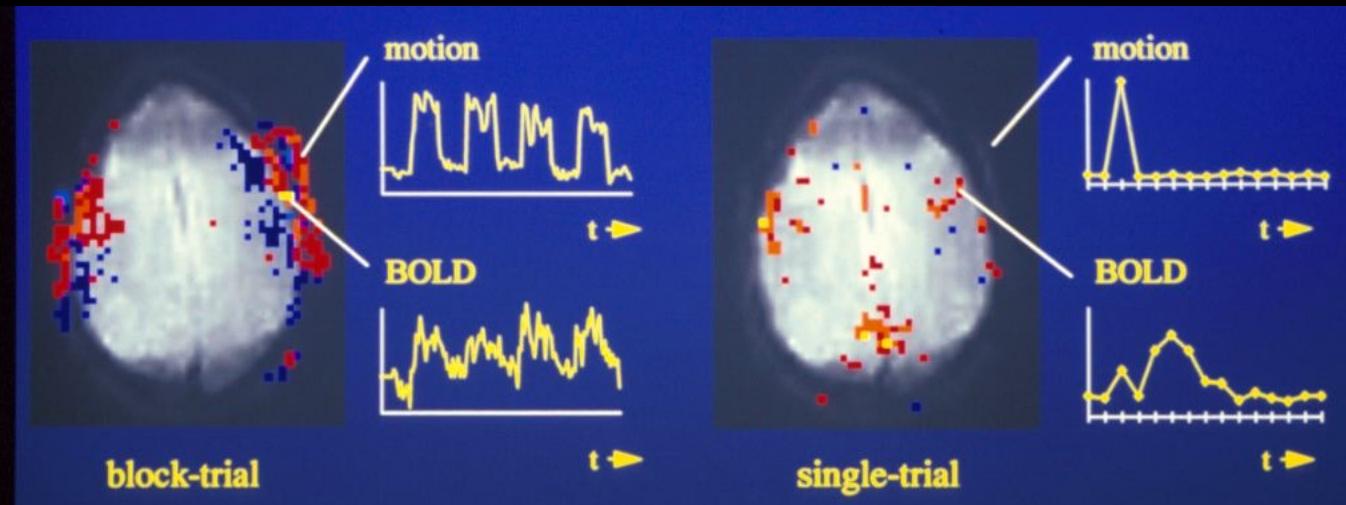
Motion induced and BOLD signal changes are separated in time

R.M. Birn, et al.

# Tongue Movement

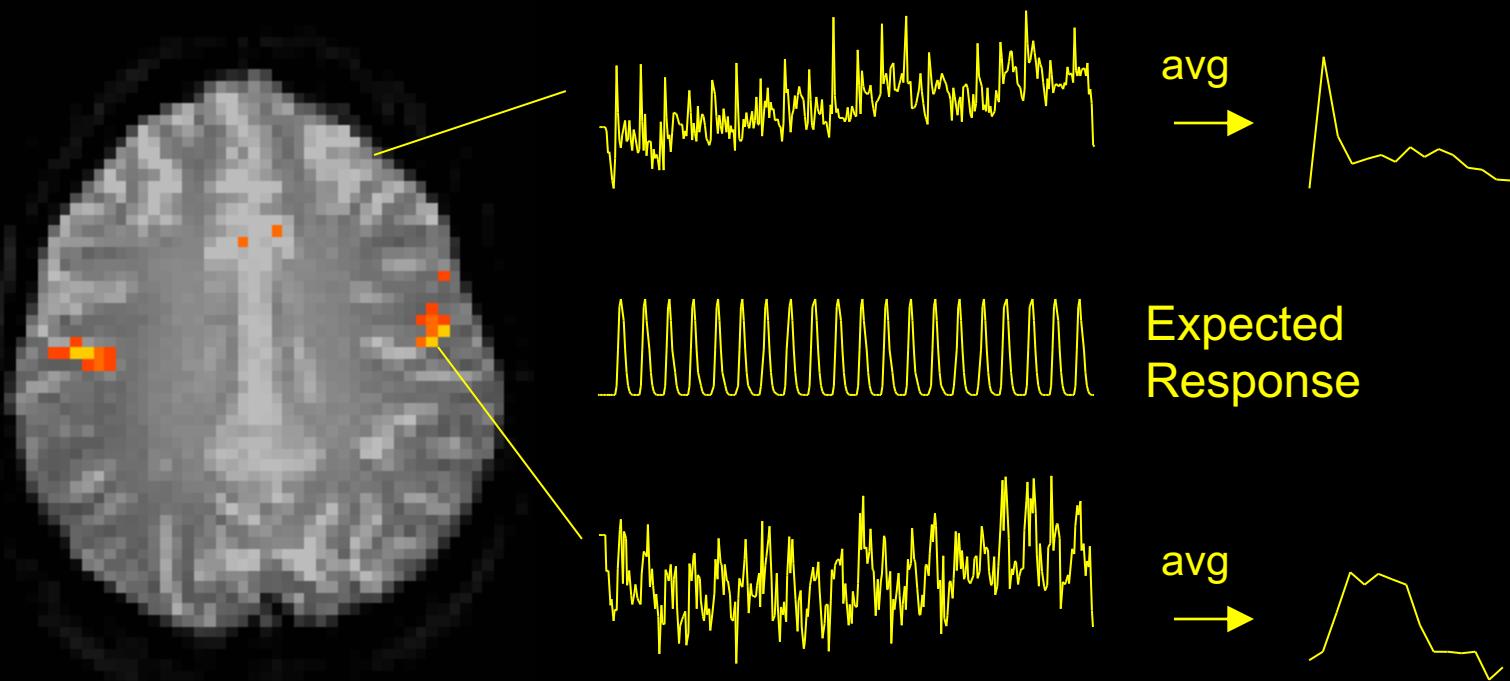


# Jaw Clenching



*Constant ISI*

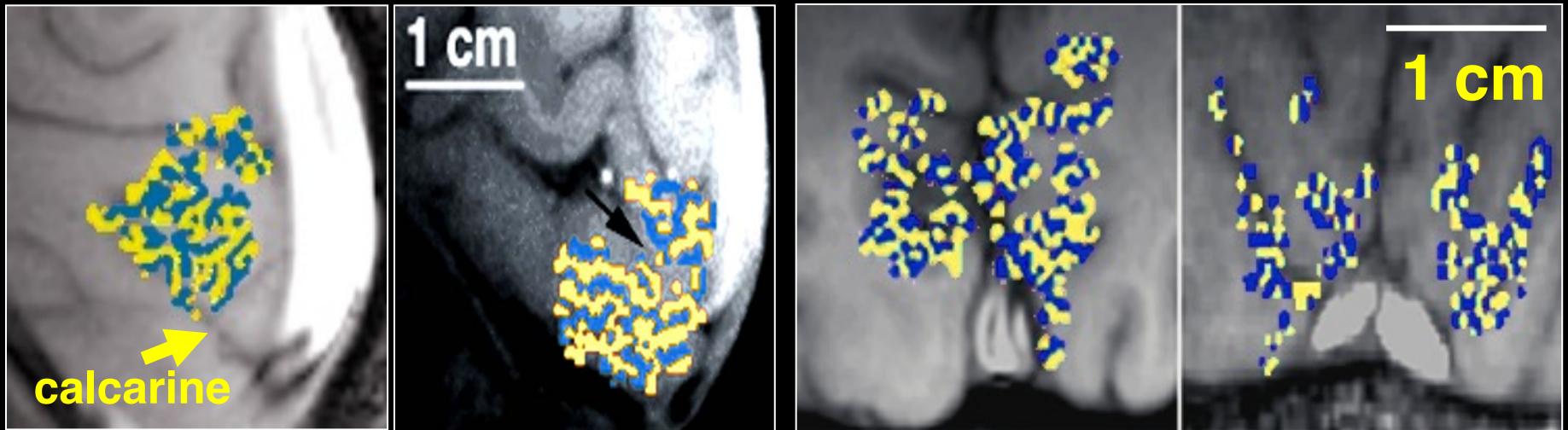
# Speaking - ER-fMRI



# Swallowing - Event-Related



# ODC Maps using fMRI



- Identical in size, orientation, and appearance to those obtained by optical imaging<sup>1</sup> and histology<sup>3,4</sup>.

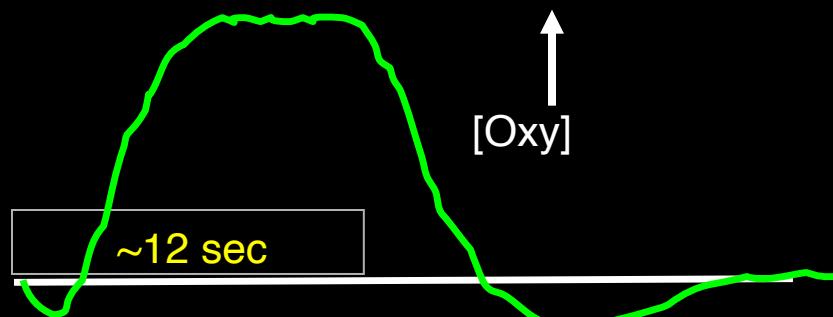
<sup>1</sup>Malonek D, Grinvald A. *Science* 272, 551-4 (1996).

<sup>3</sup>Horton JC, Hocking DR. *J Neurosci* 16, 7228-39 (1996).

<sup>4</sup>Horton JC, et al. *Arch Ophthalmol* 108, 1025-31 (1990).

# Why short is better than long

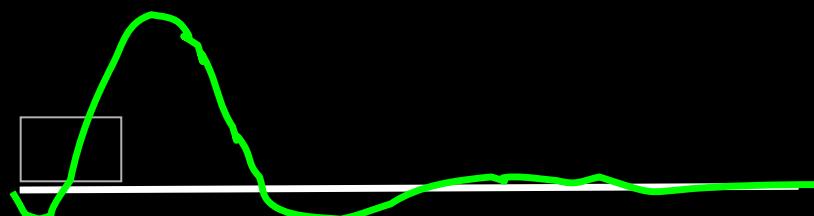
The vascular response to prolonged neural stimulation



It is argued that fMRI cannot achieve submillimeter functional resolution because a saturated hyperoxic vascular response to neural activity spreads over many millimeters<sup>1,2</sup>.

However, optical imaging has demonstrated that the hyperoxic response can yield well-localized maps when using short duration stimuli (<5 sec)<sup>1</sup>.

The vascular response to brief neural stimulation



<sup>1</sup>Malonek D, Grinvald A. Science 272, 551-4 (1996).

<sup>2</sup>Kim D-S, Duong T, Kim S-G. Nat Neurosci 3, 164-9 (2000).

# Neuronal Activation Input Strategies

1. Block Design

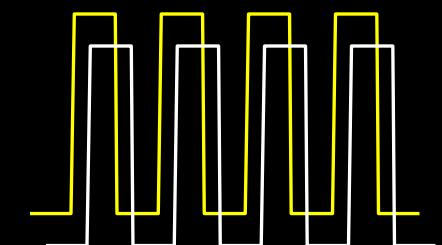
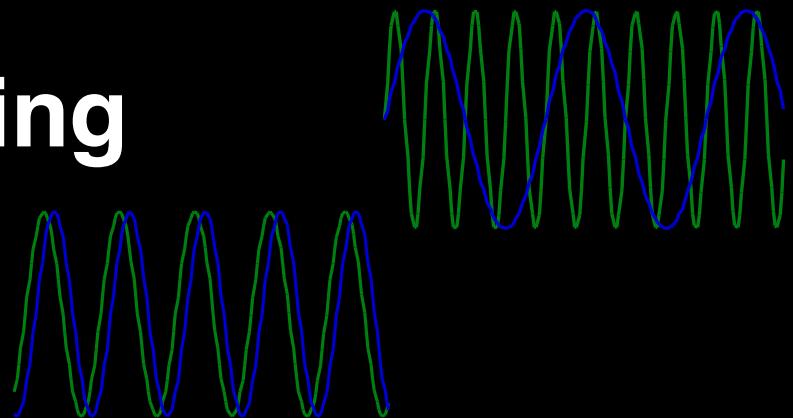
2. Frequency Encoding

3. Phase Encoding

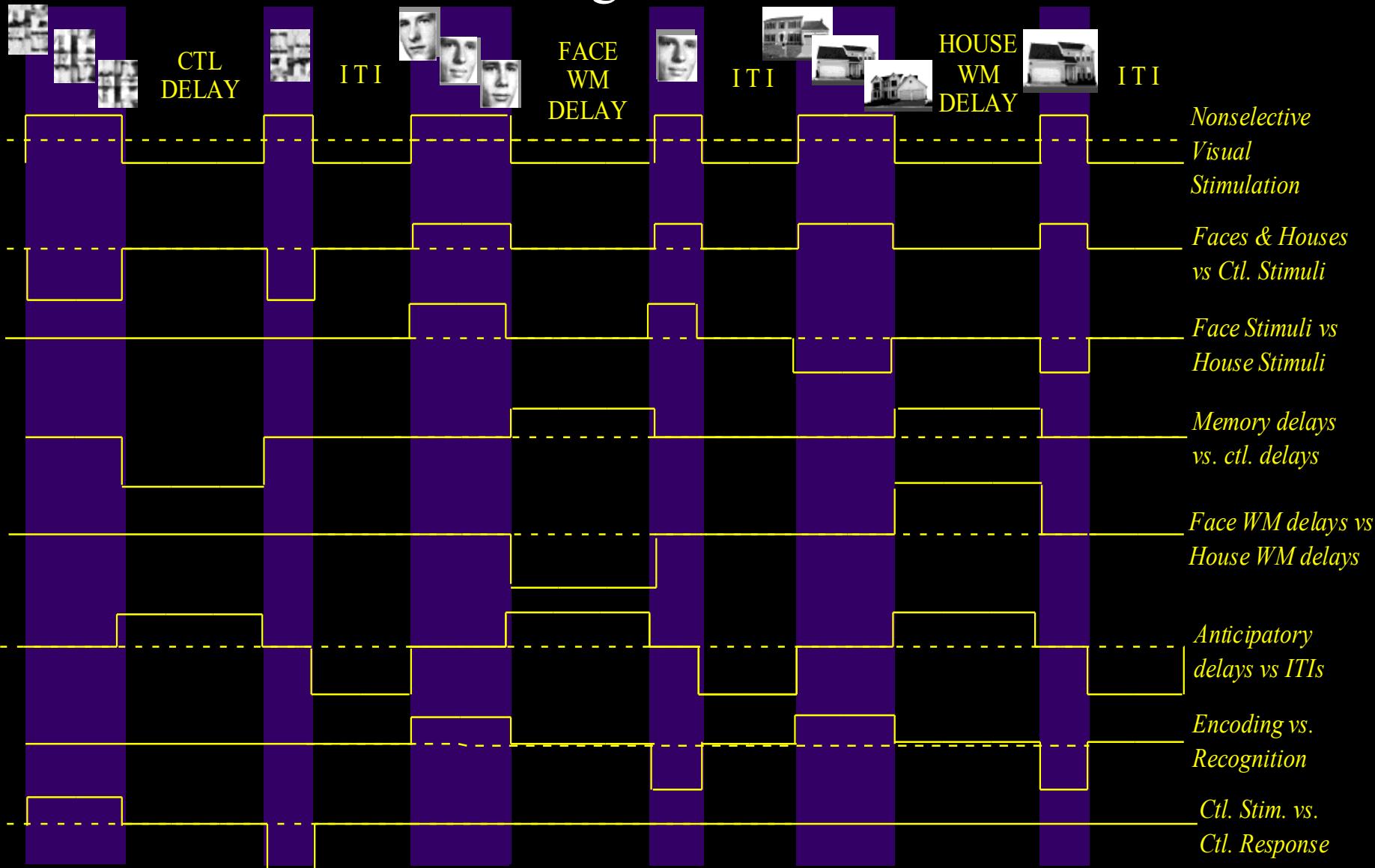
4. Single Event

5. Orthogonal Block Design

6. Free Behavior Design.



# Example of a Set of Orthogonal Contrasts for Multiple Regression



# Neuronal Activation Input Strategies

1. Block Design

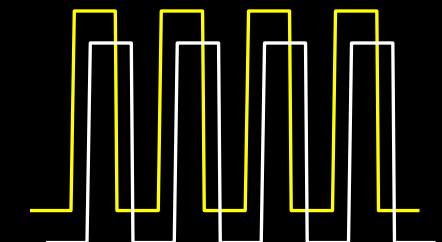
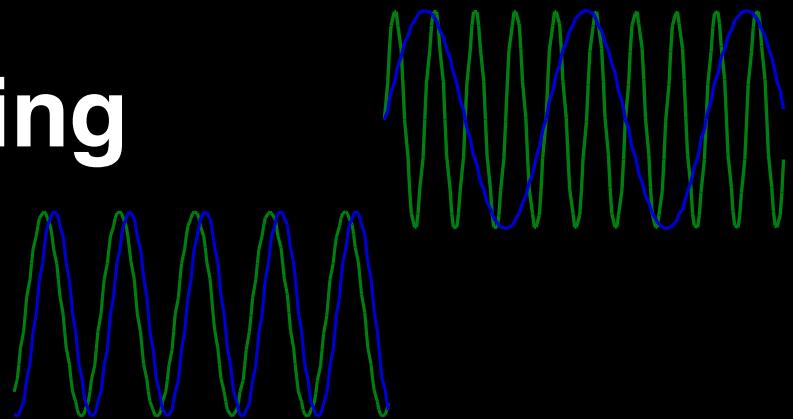
2. Frequency Encoding

3. Phase Encoding

4. Single Event

5. Orthogonal Block Design

6. Free Behavior Design.

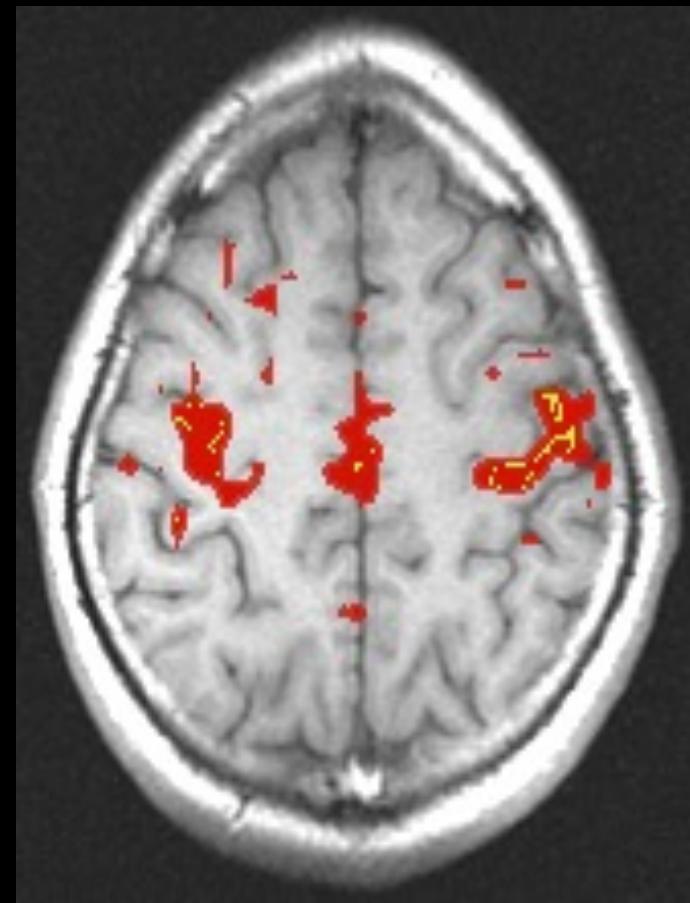
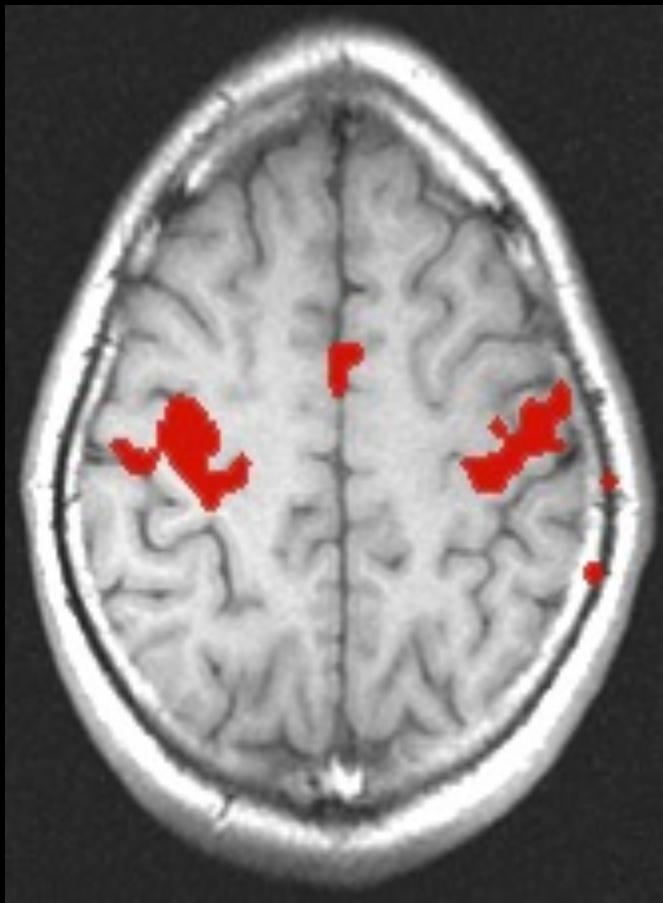


# Free Behavior Design

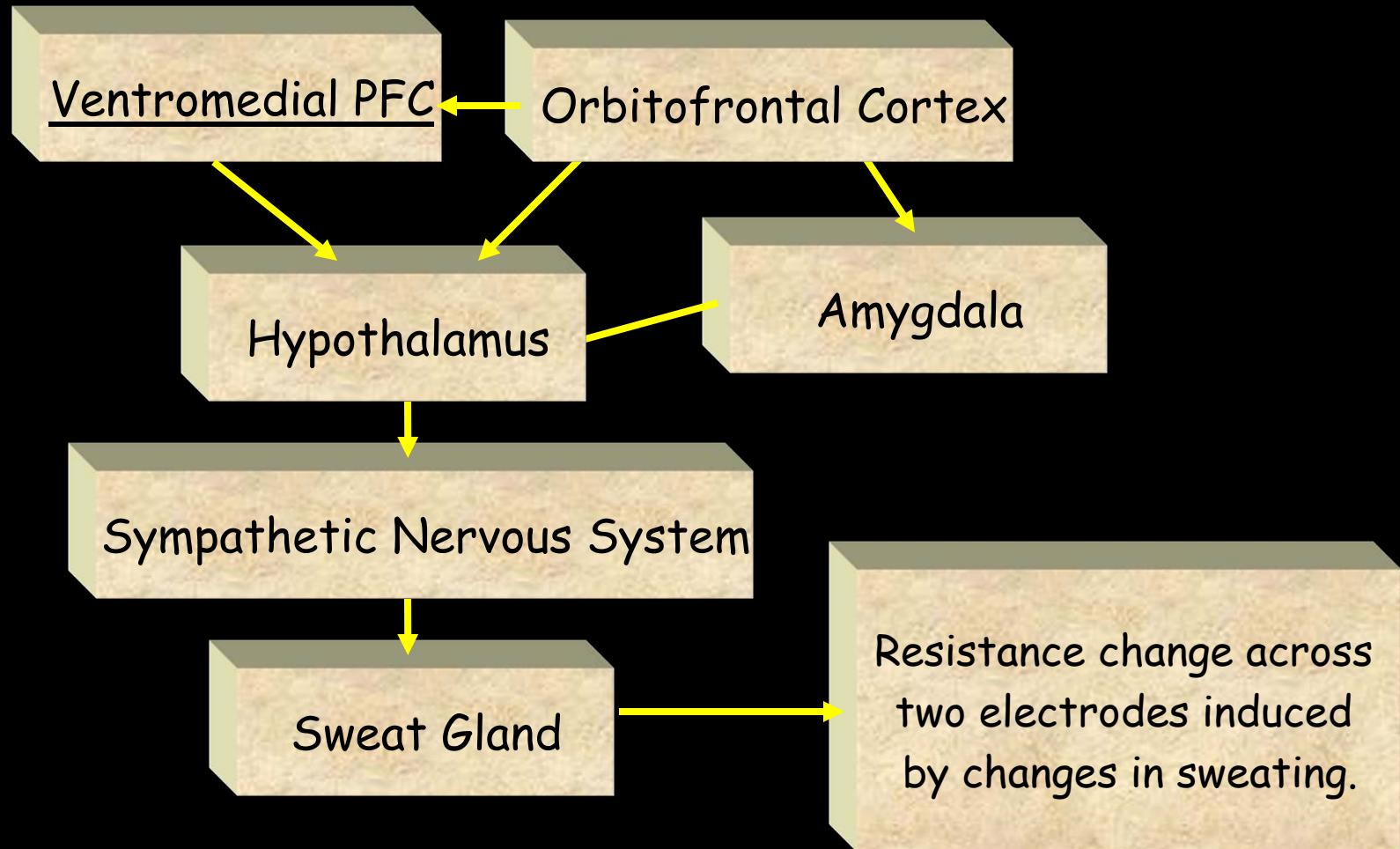
Use a continuous measure as a reference function:

- Task performance
- Skin Conductance
- Heart, respiration rate..
- Eye position
- EEG

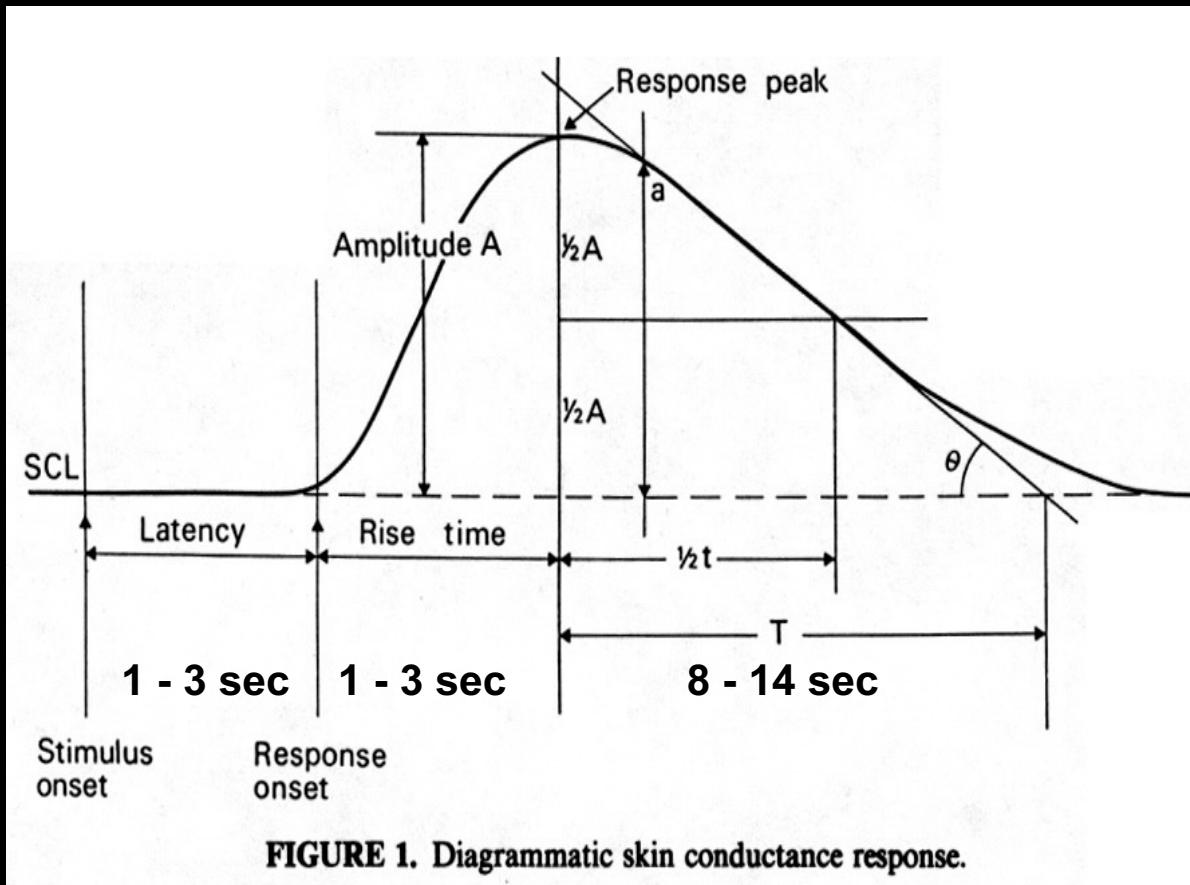
# Resting Hemodynamic Autocorrelations



# The Skin Conductance Response (SCR)

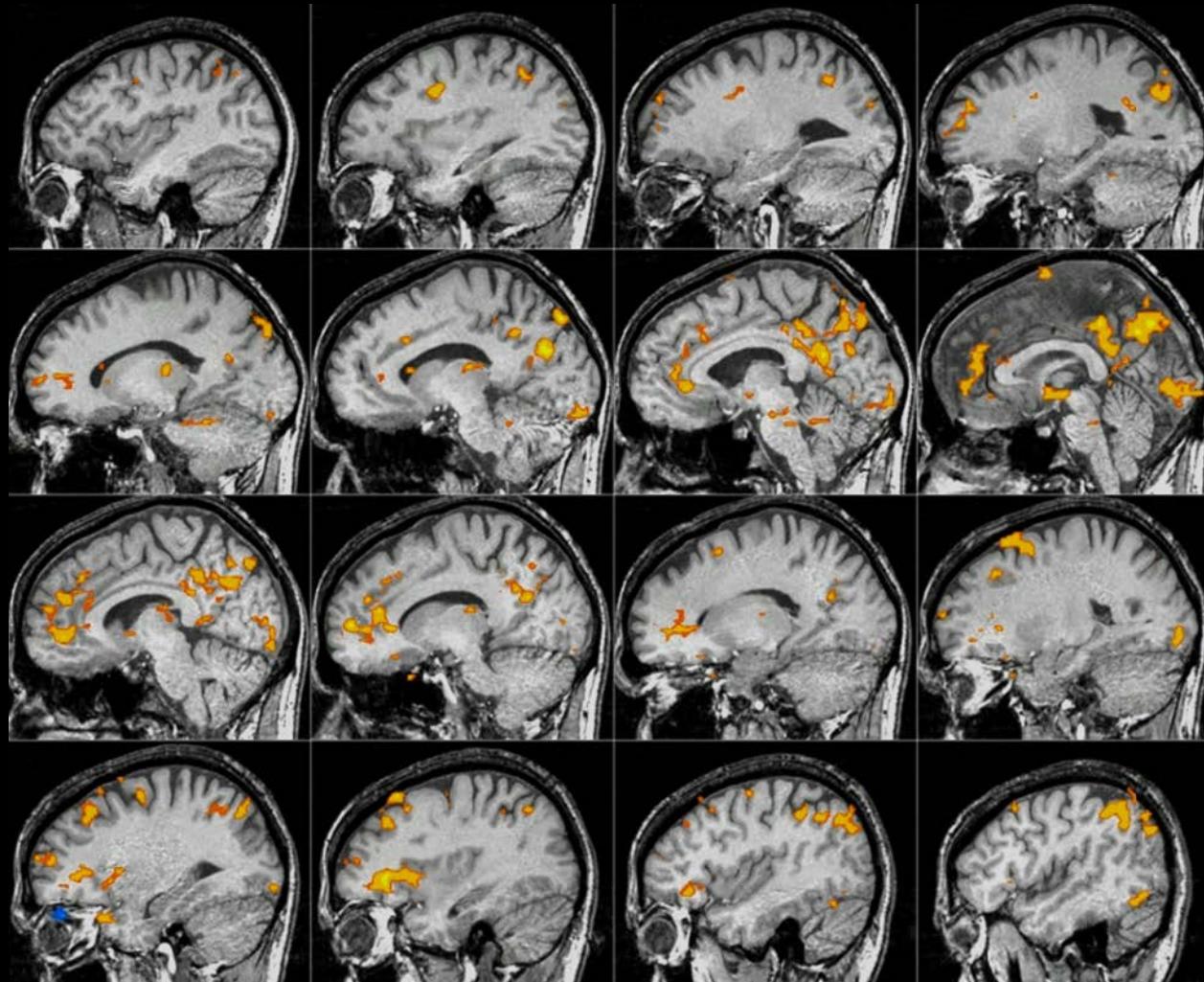


# Skin Conductance Dynamics



- Boucsein, Wolfram (1992). Electrodermal Activity. Plenum Press, NY
- Venables, Peter, (1991). Autonomic Activity ANYAS 620:191-207.

# Brain activity correlated with SCR during “Rest”



- Contrast in fMRI

*Hemodynamic Specificity*

- The Hemodynamic Transfer Function

*Location, Latency, Magnitude*

- Best Results So Far

*Temporal Resolution, Spatial Resolution*

- Neuronal Activation Input Strategies

*Block Design*

*Phase and Frequency Encoding*

*Orthogonal Designs*

*Parametric Designs*

*Event-Related Designs*

*Free Behavior Designs*

## Additional Thanks To...

Eric Wong, UCSD

Robert Savoy, MGH

Richard Hoge, MGH

Randy Buckner, Wash. U.

Ted DeYoe, MCW

Sue Courtney, Johns Hopkins U

Rasmus Birn, NIH

Ziad Saad, NIH

Patrick Bellgowan, NIH