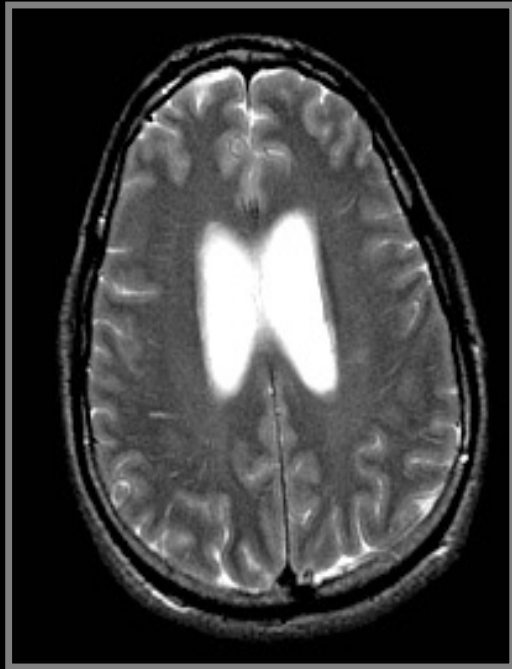


Spatial, Temporal, and Interpretive Limits of Functional MRI

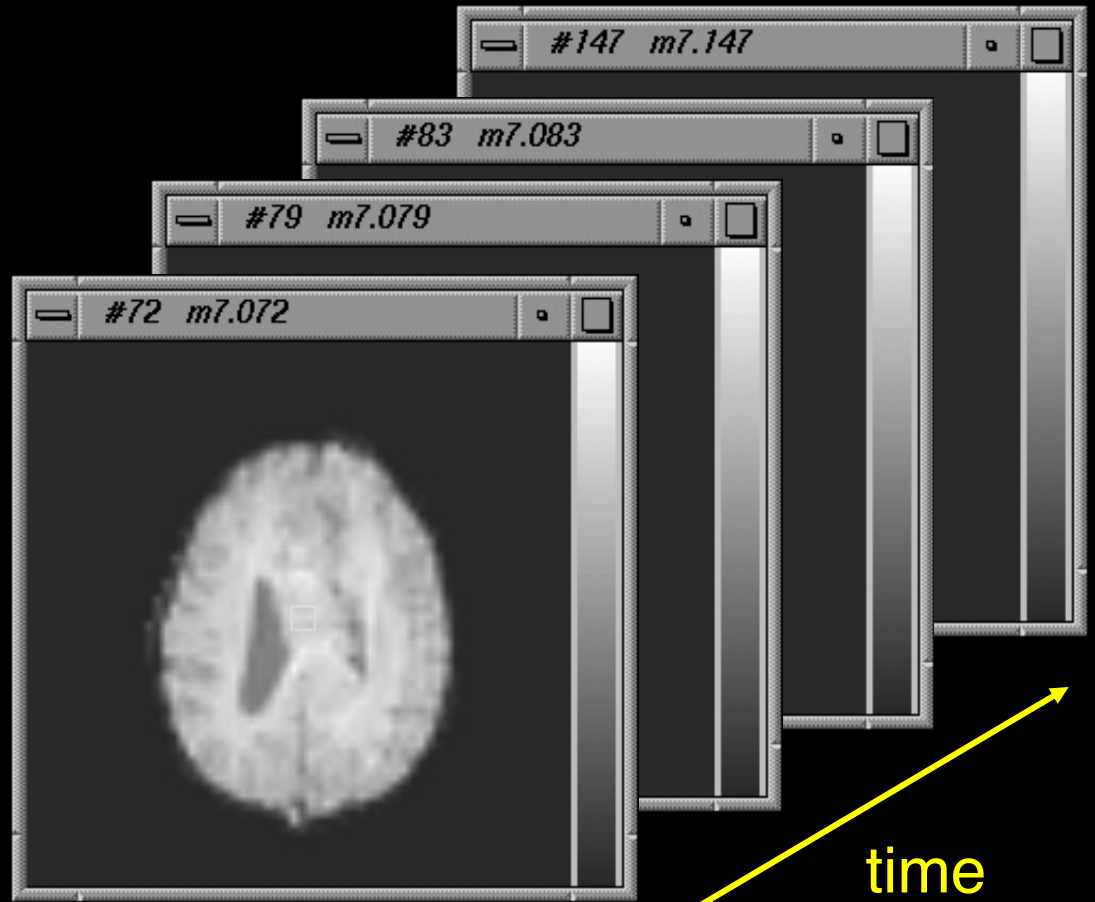
Peter A. Bandettini, Ph.D

Unit on Functional Imaging Methods
&
3T Neuroimaging Core Facility

Laboratory of Brain and Cognition
National Institute of Mental Health

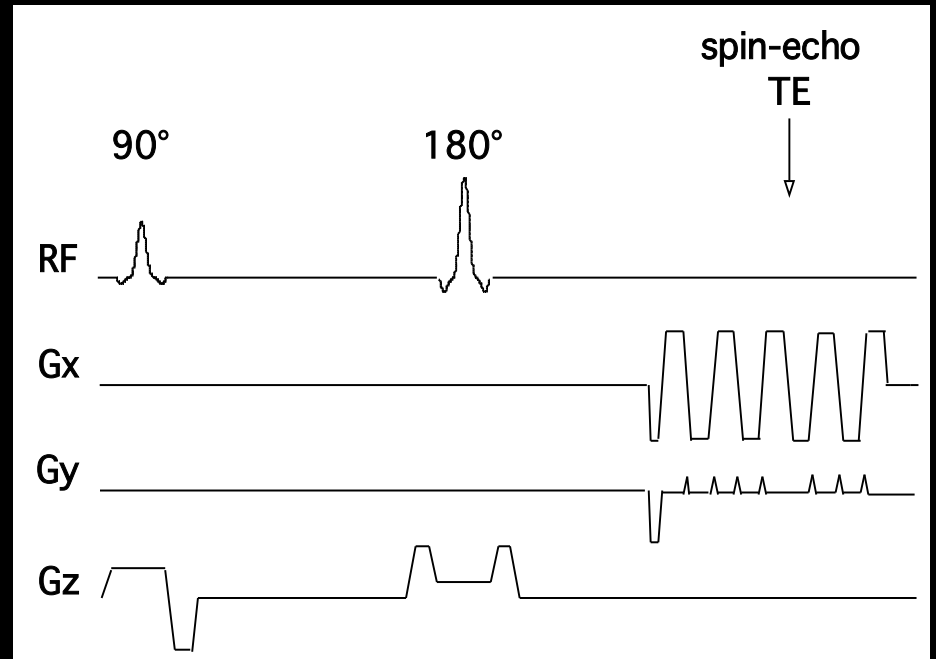
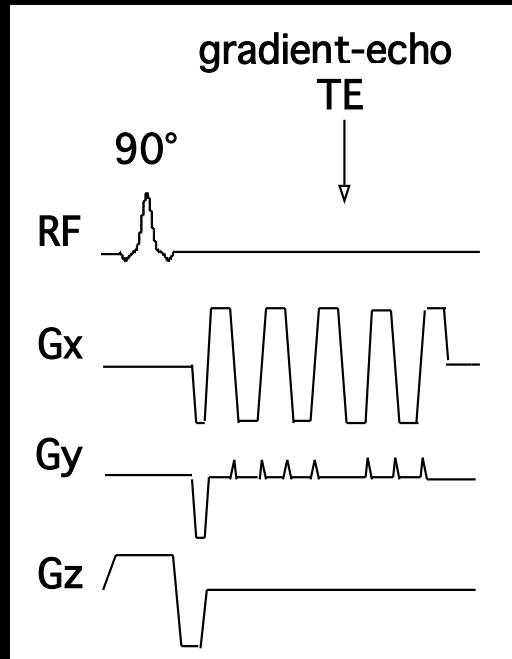


Anatomic

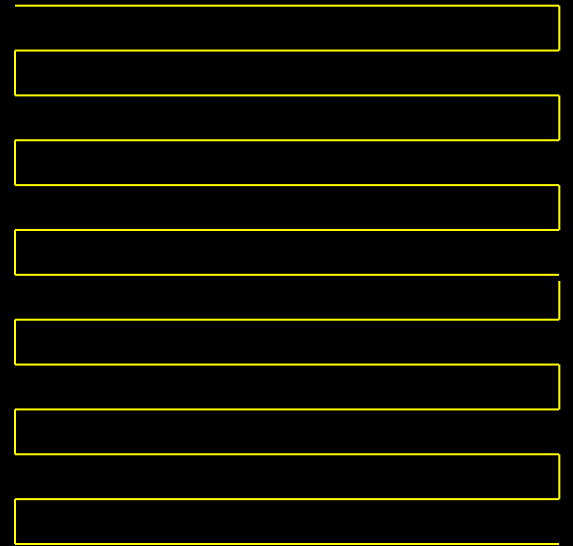
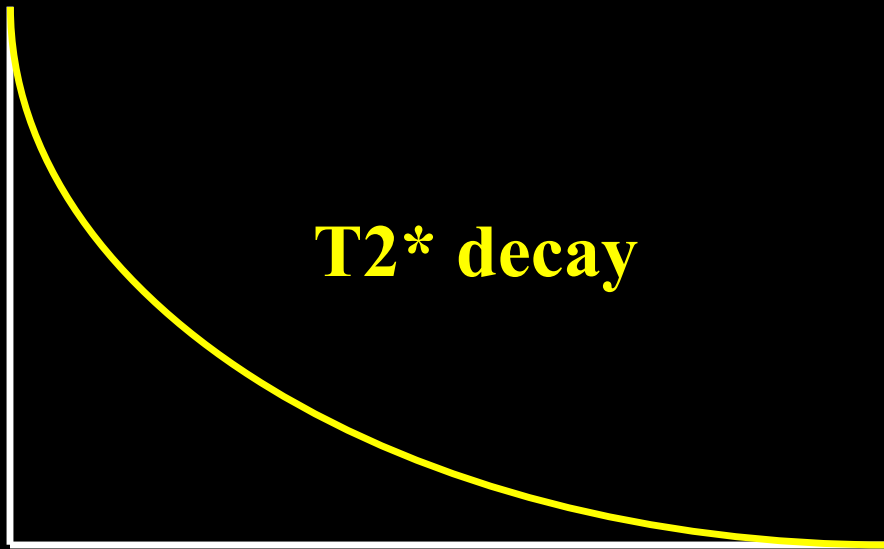


Functional

Echo-Planar Imaging



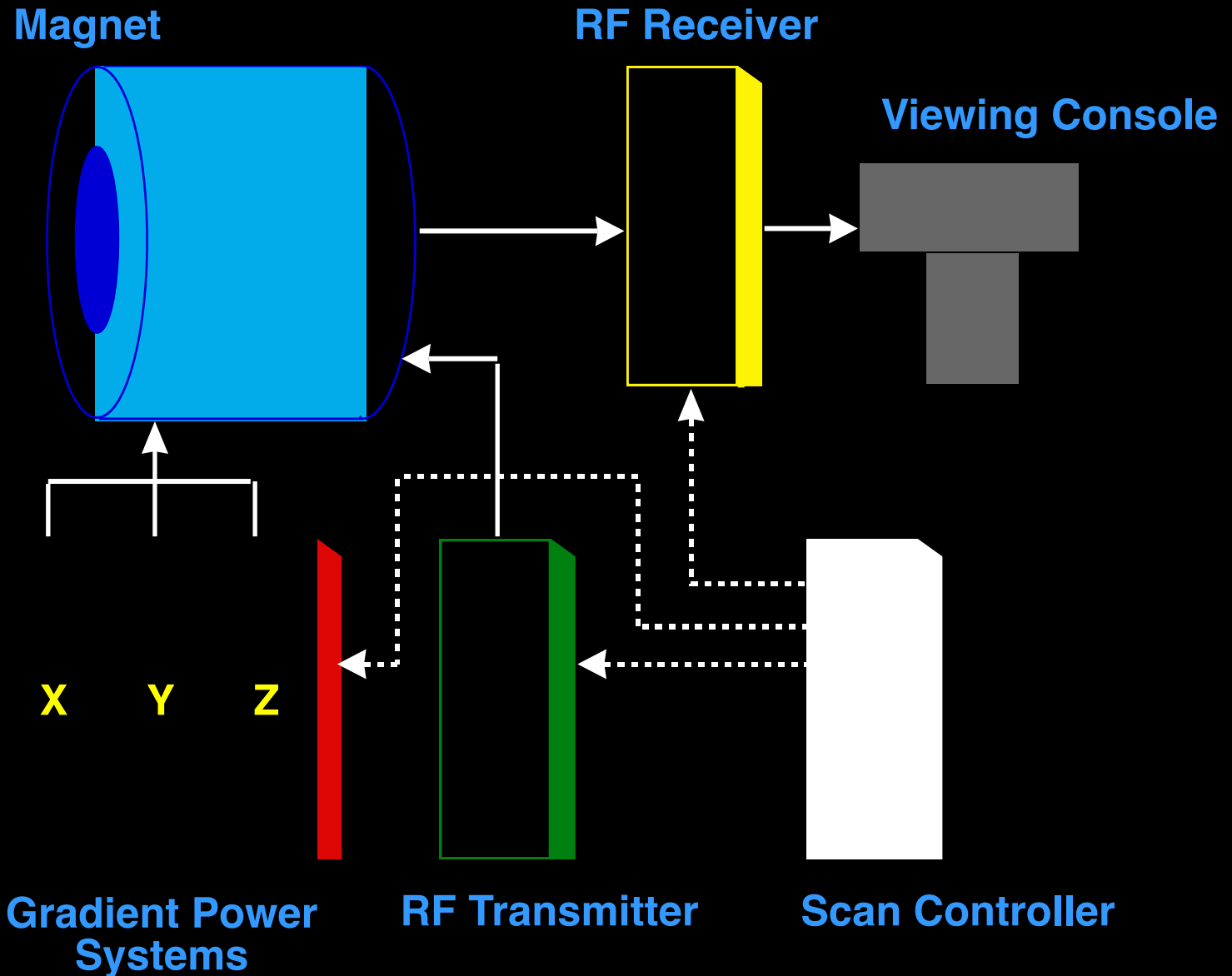
Single Shot Imaging



EPI Readout Window

≈ 20 to 40 ms

Imaging System Components



1991-1992

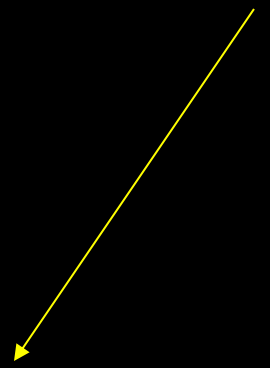
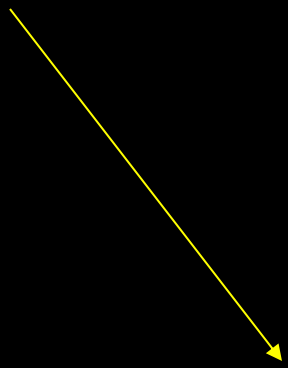
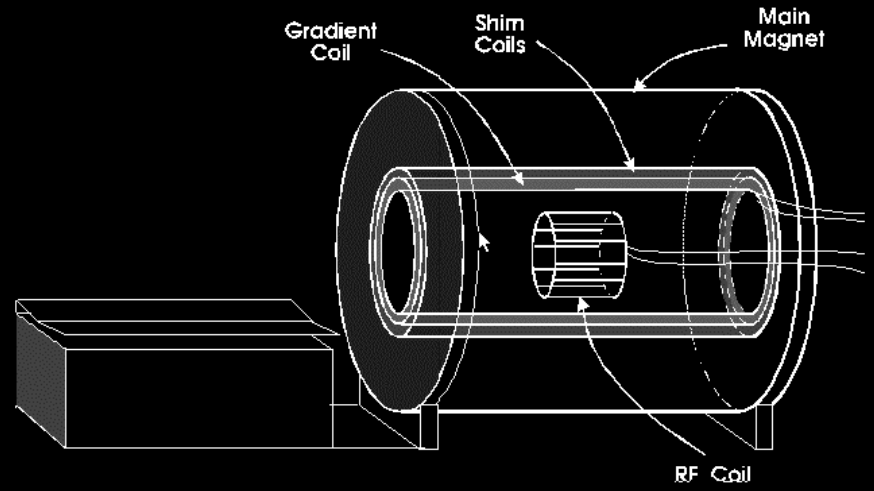


1992-1999



2 G/cm, 350 T/m/s

4 G/cm, 150 T/m/s

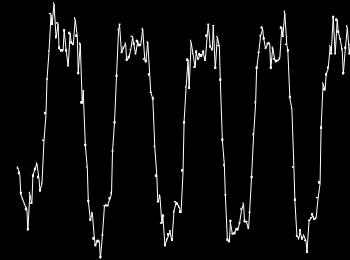
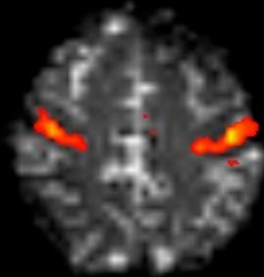


10 G/cm, 1000 T/m/s

The use of fMRI to Investigate Brain Function

Where?

When?

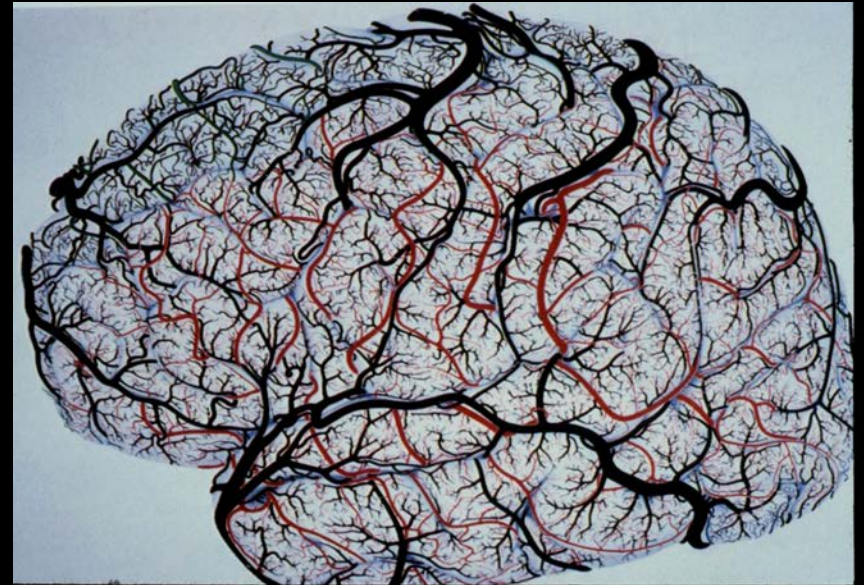
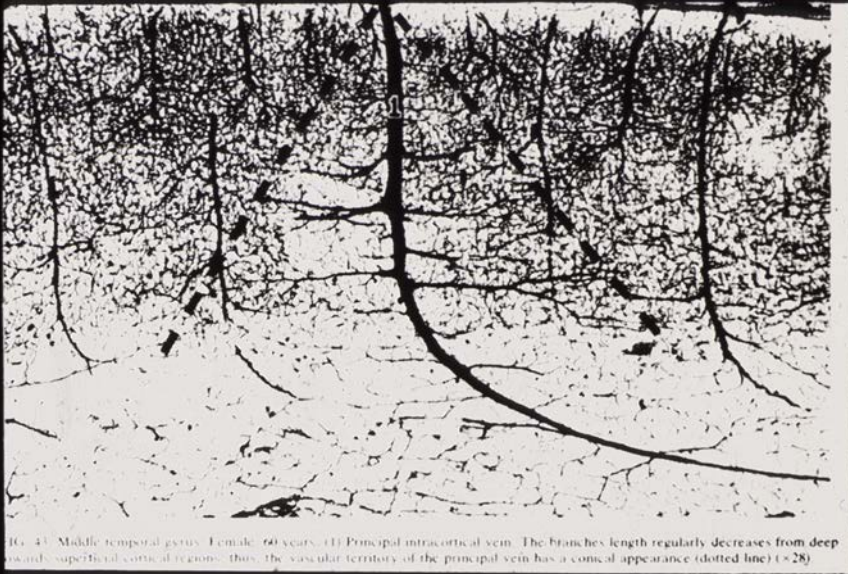


How much?

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.



- **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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Event-Related Designs

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**

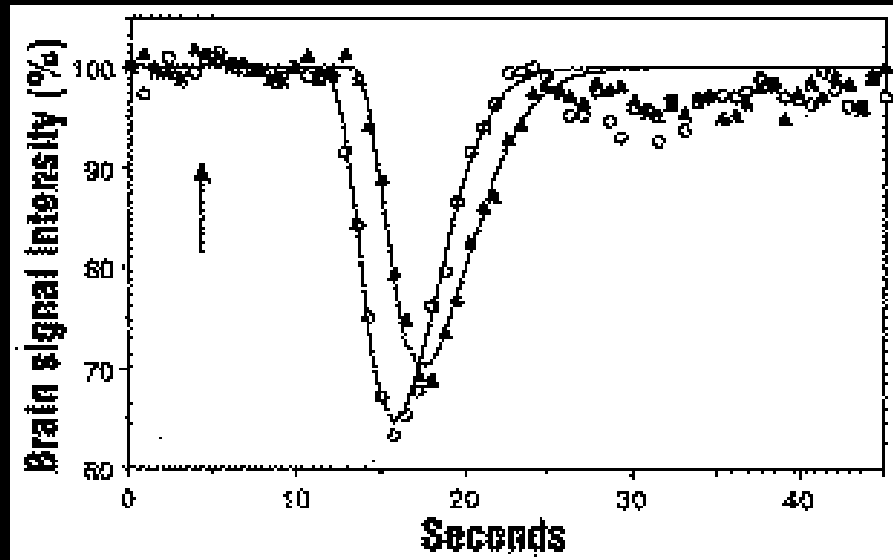
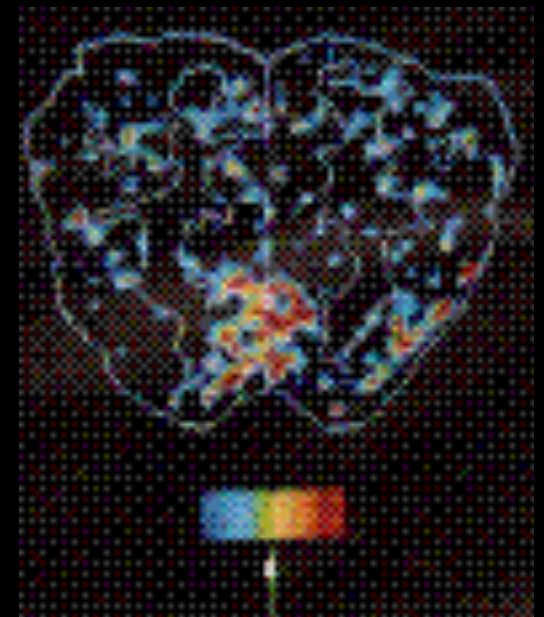
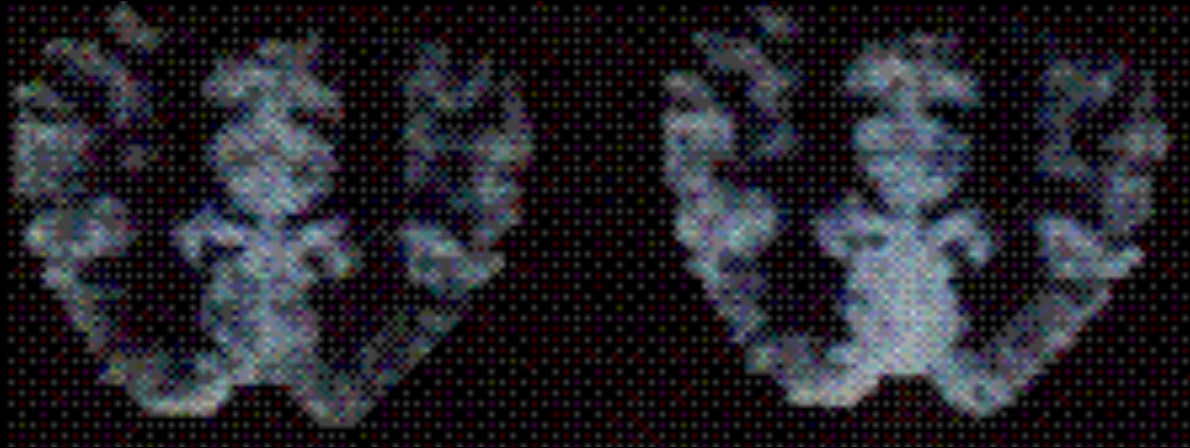
- T1 weighting
- Arterial spin labeling

- **CMRO₂**

- BOLD and Perfusion w/
Normalization to Global Perfusion Change

Resting

Active

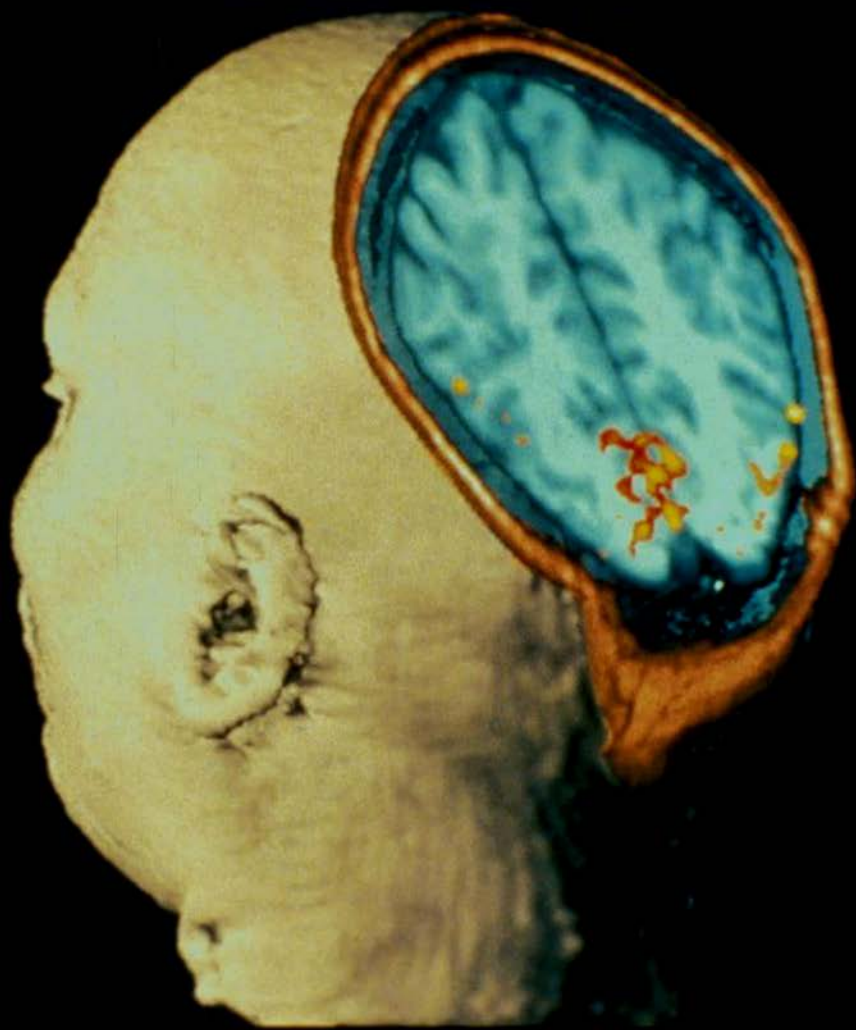


Photic Stimulation

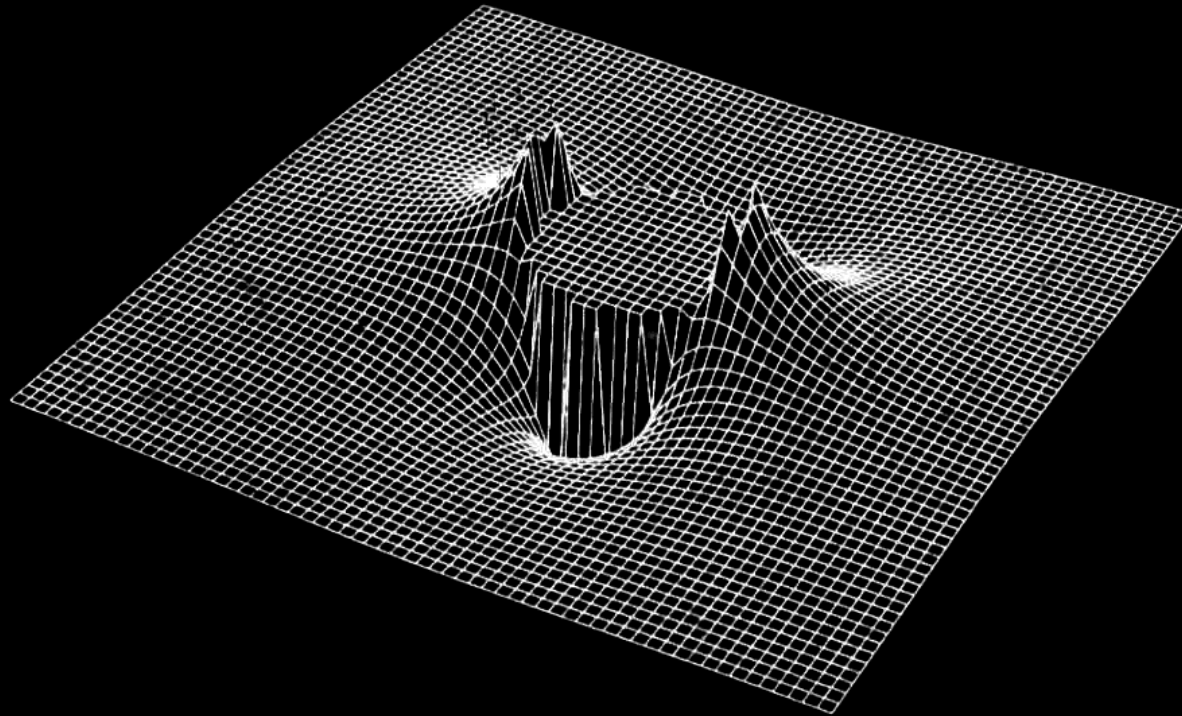
MRI Image showing
activation of the
Visual Cortex

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

Cerebral Tissue Activation



Local Vasodilation



Increase in Cerebral Blood Flow and Volume



Oxygen Delivery Exceeds Metabolic Need



Increase in Capillary and Venous Blood Oxygenation



Decrease in Deoxy-hemoglobin

Deoxy-hemoglobin: paramagnetic
Oxy-hemoglobin: diamagnetic



Decrease in susceptibility-related intravoxel dephasing



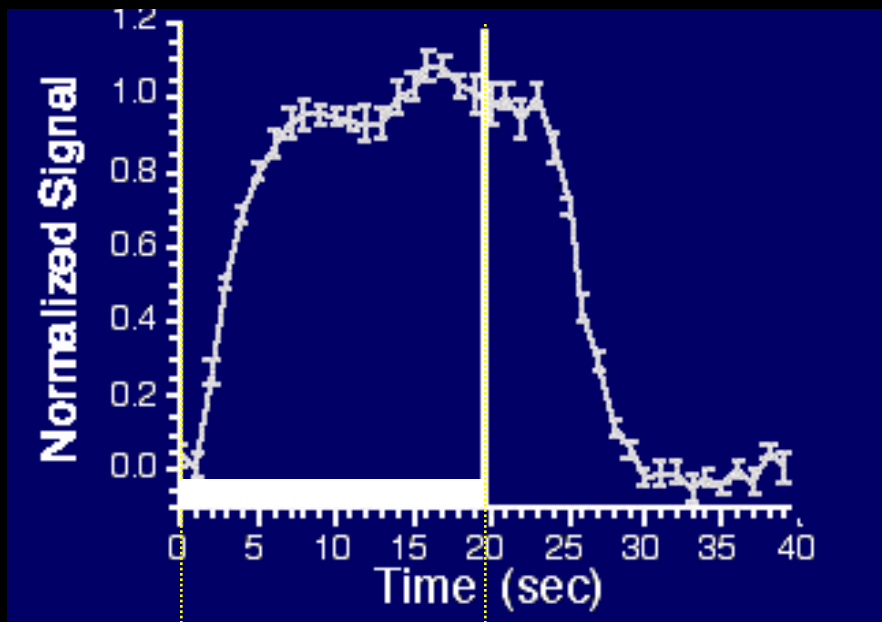
Increase in T2 and T2*



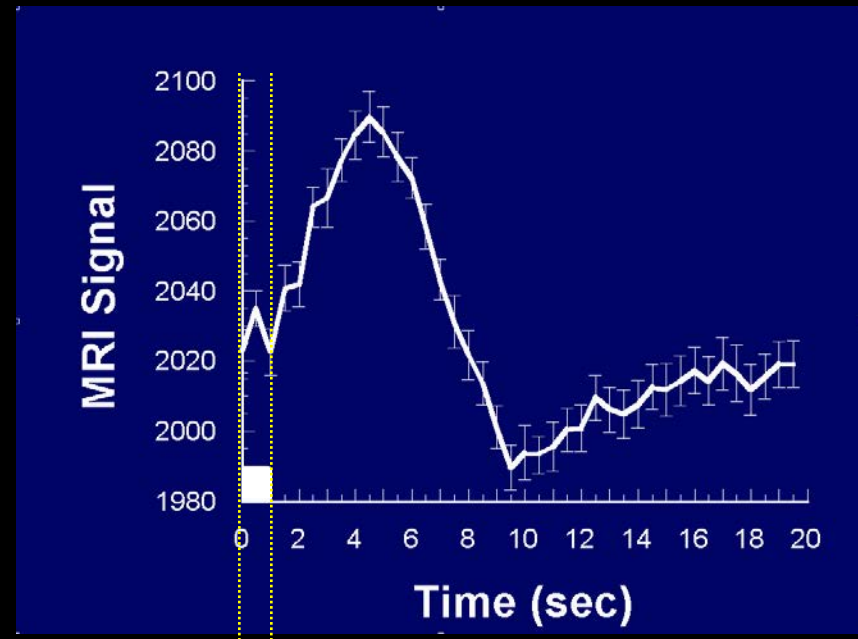
Local Signal Increase in T2 and T2* - weighted sequences

The BOLD Signal

Blood Oxygenation Level Dependent (BOLD) signal changes



task



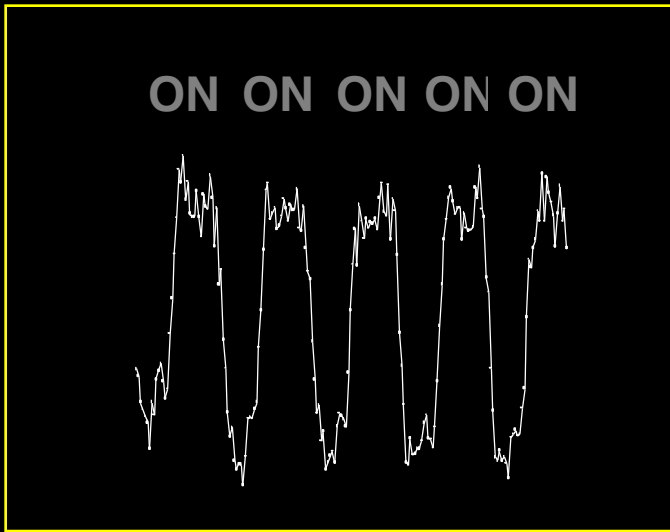
task

Alternating Left and Right Finger Tapping



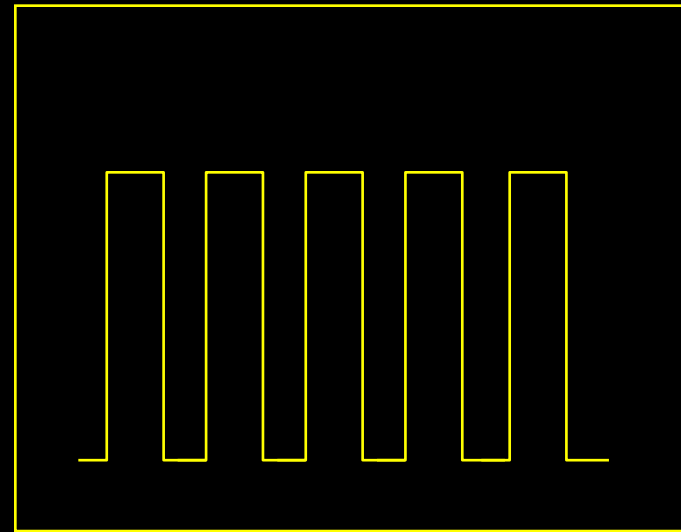
~ 1992

Creating a Functional Image



Signal Time Course

X



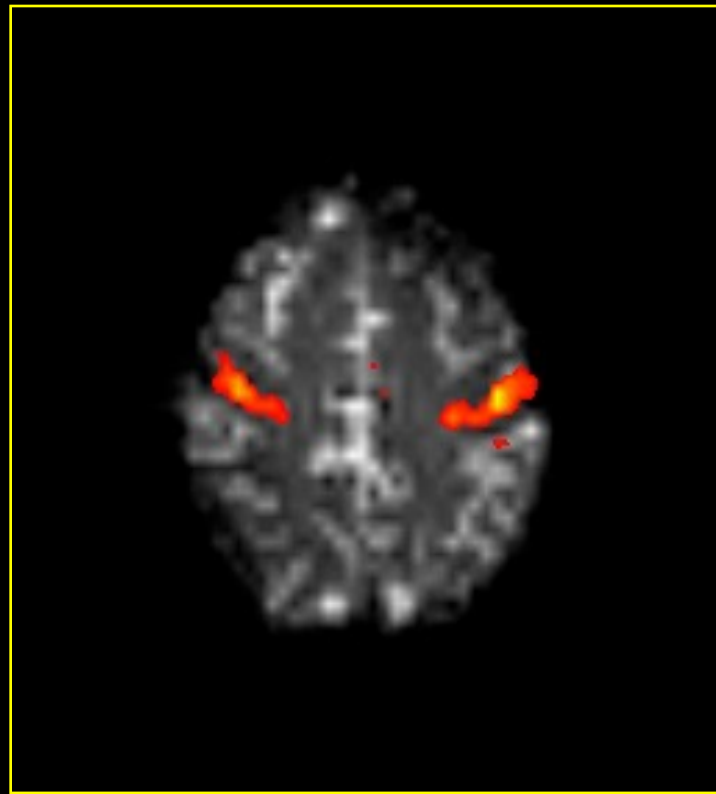
Reference Function

=





Cross Correlation Image

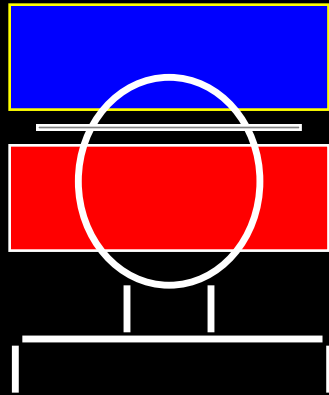


Cross Correlation Image
Anatomical Image

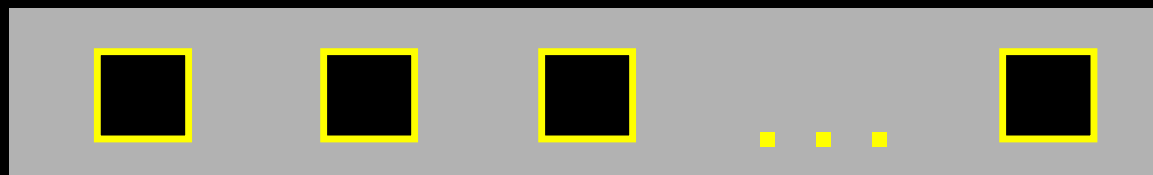
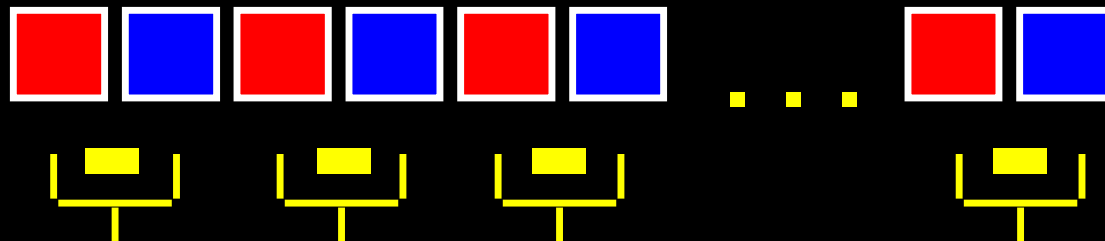
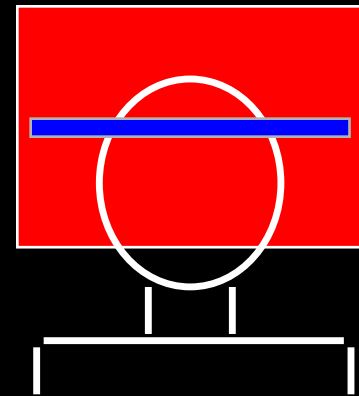


Perfusion / Flow Imaging

EPISTAR



FAIR



**Perfusion
Time Series**

TI (ms)

FAIR

EPISTAR

200

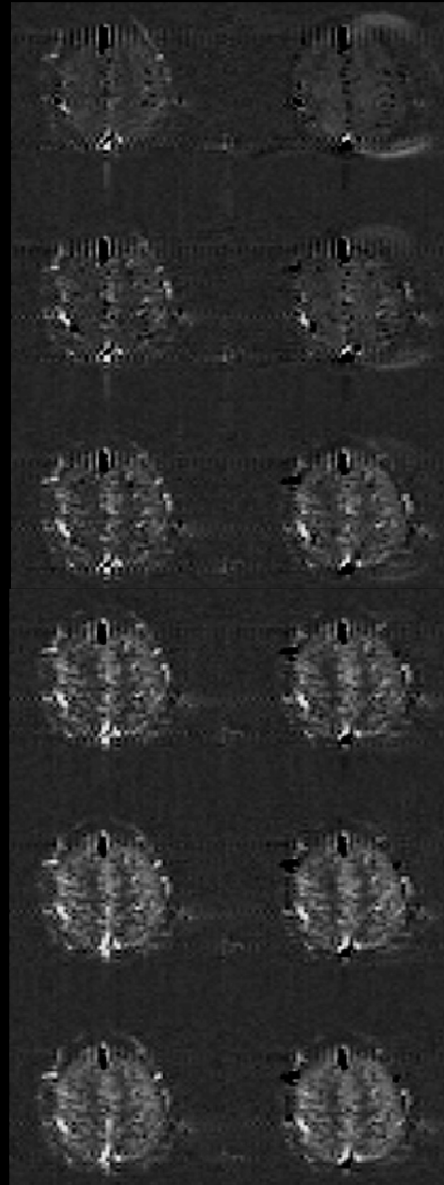
400

600

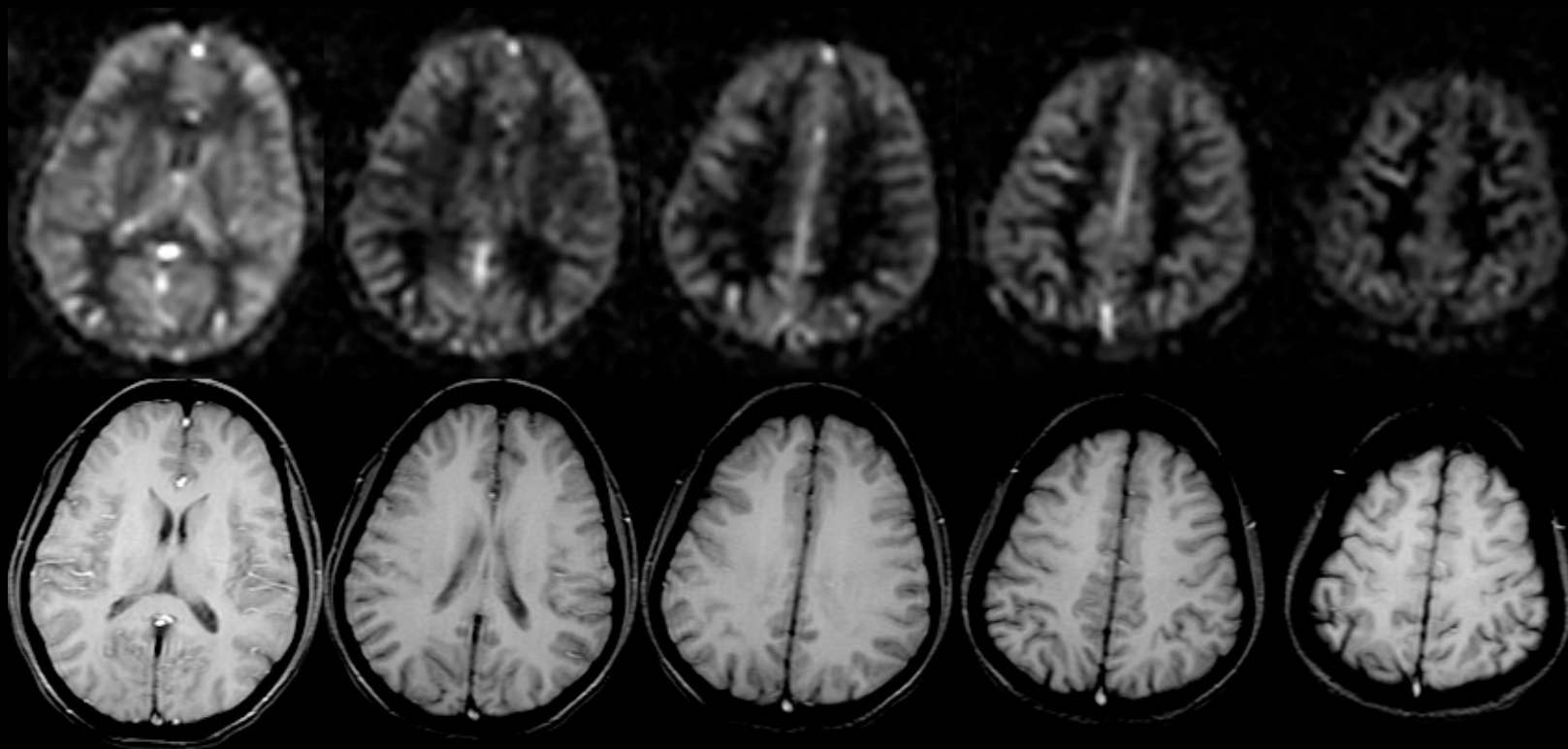
800

1000

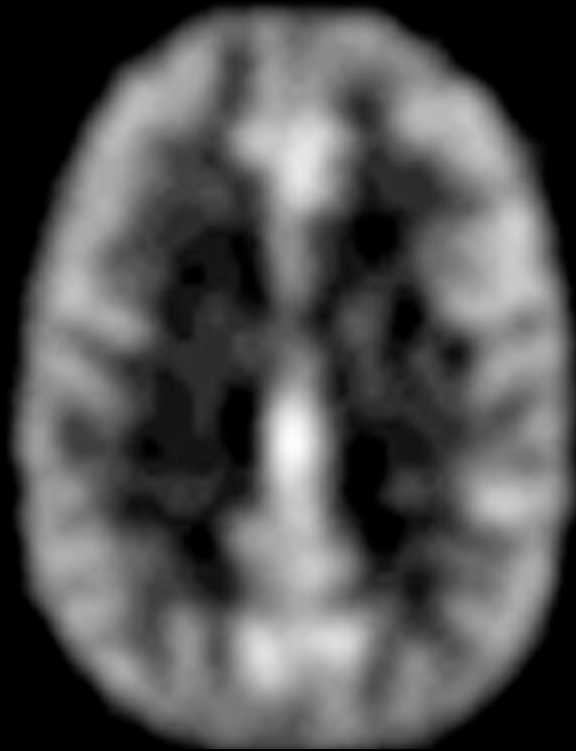
1200



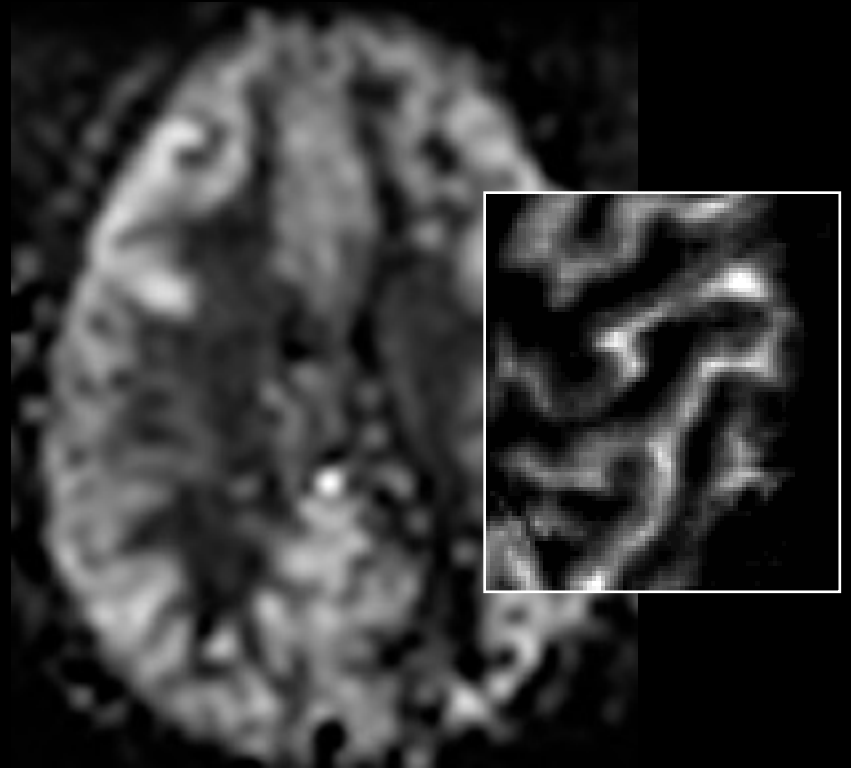
Resting ASL Signal



Comparison with Positron Emission Tomography



PET: H_2^{15}O



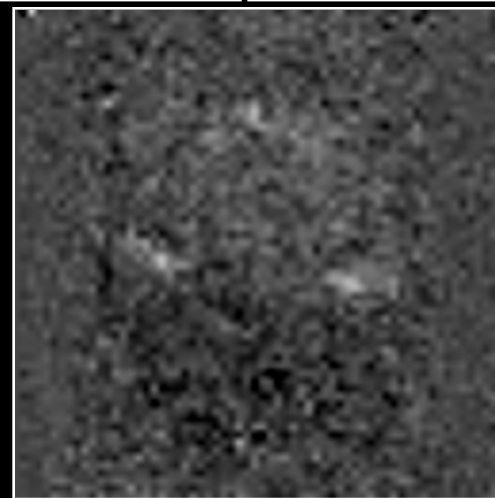
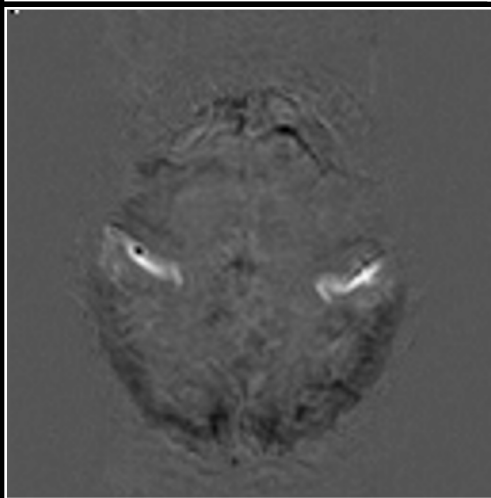
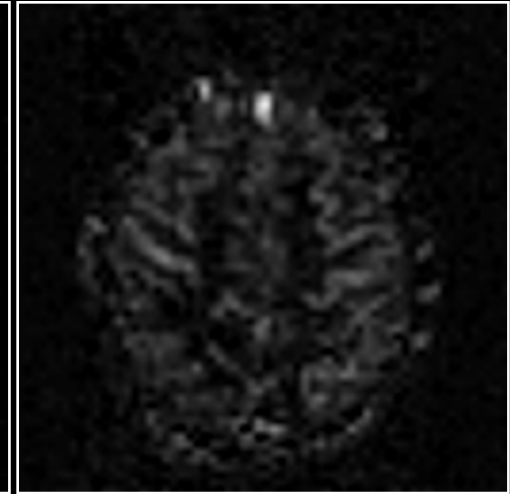
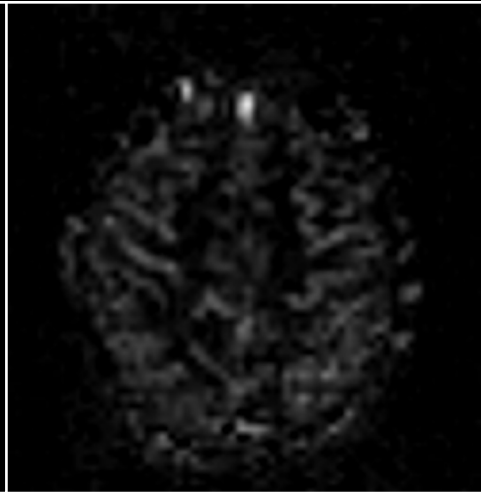
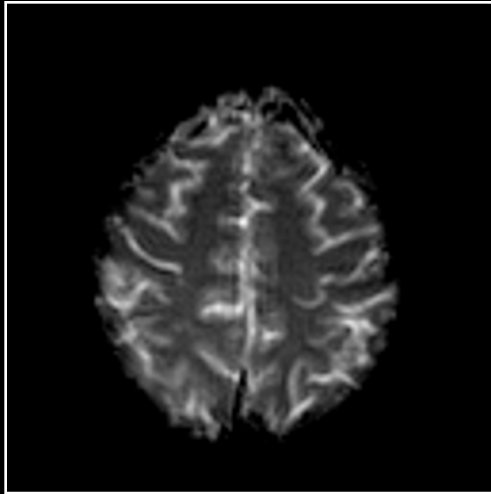
MRI: ASL

Perfusion

BOLD

Rest

Activation



Anatomy



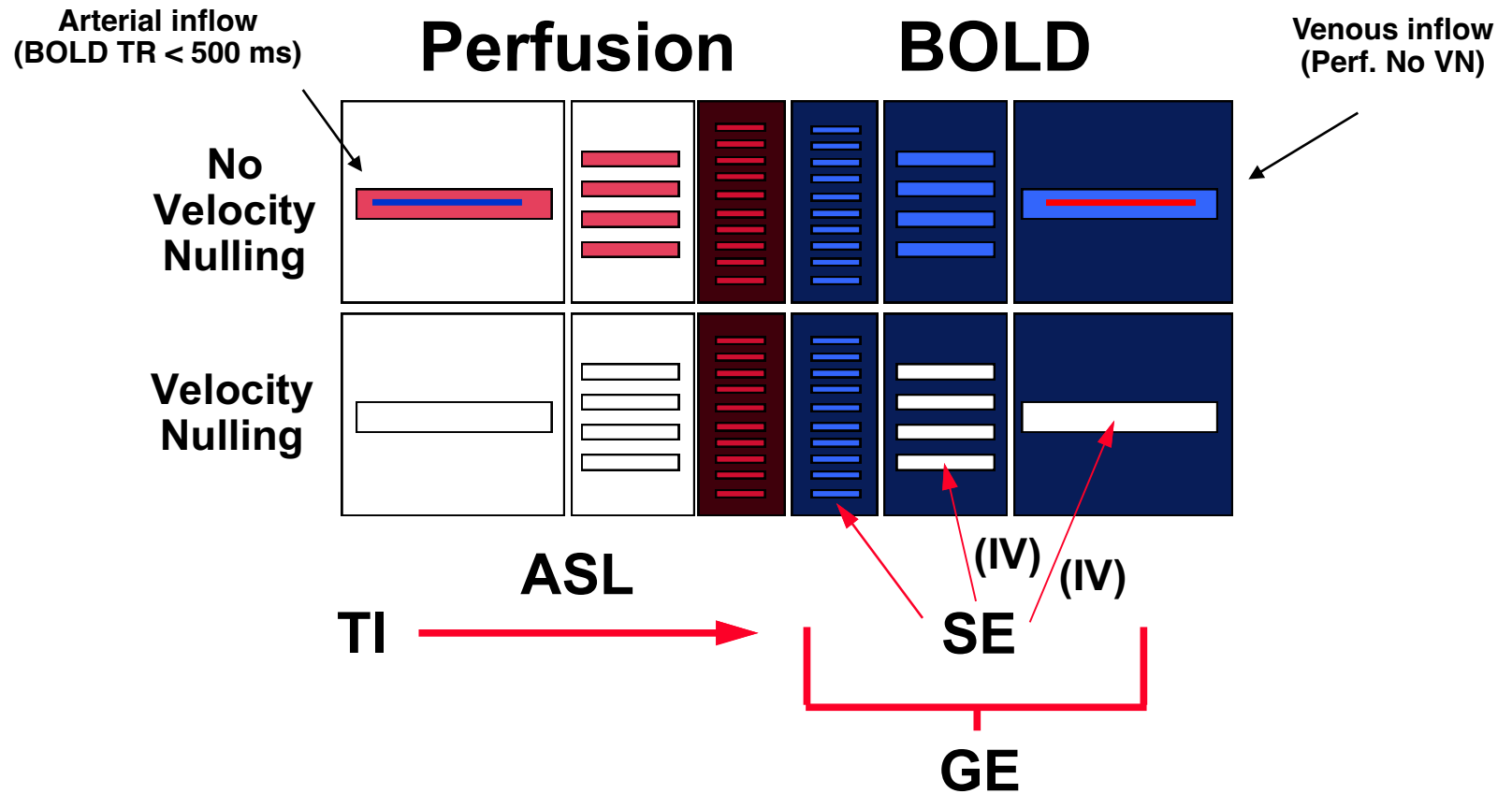
BOLD



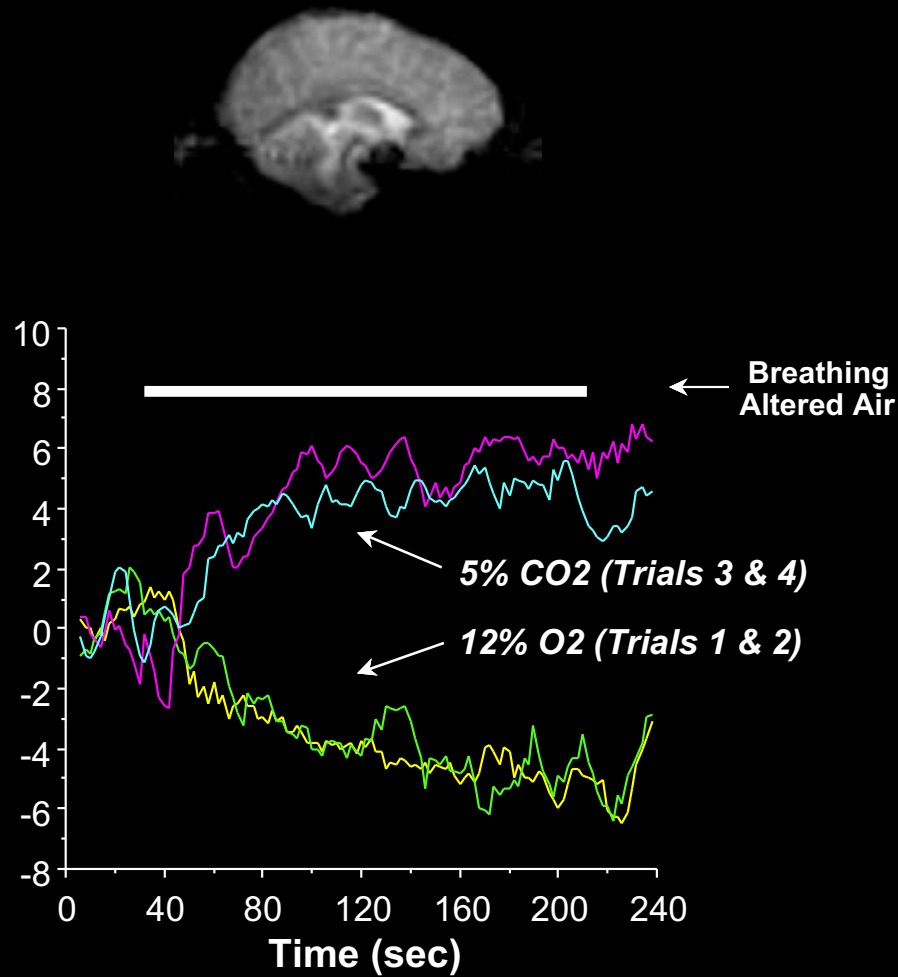
Perfusion



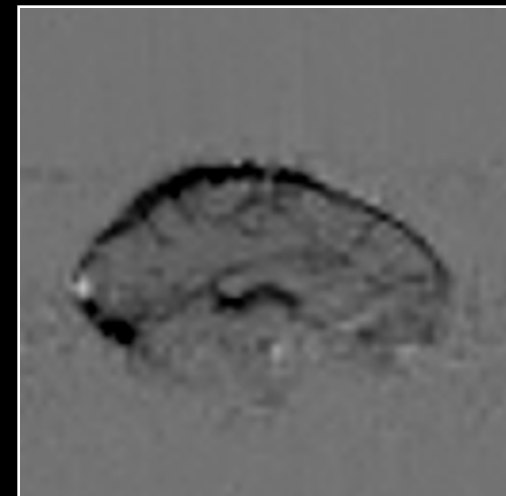
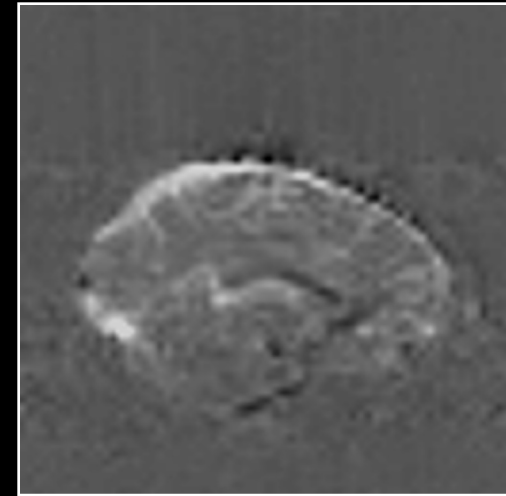
Hemodynamic Specificity



Hemodynamic Stress Calibration

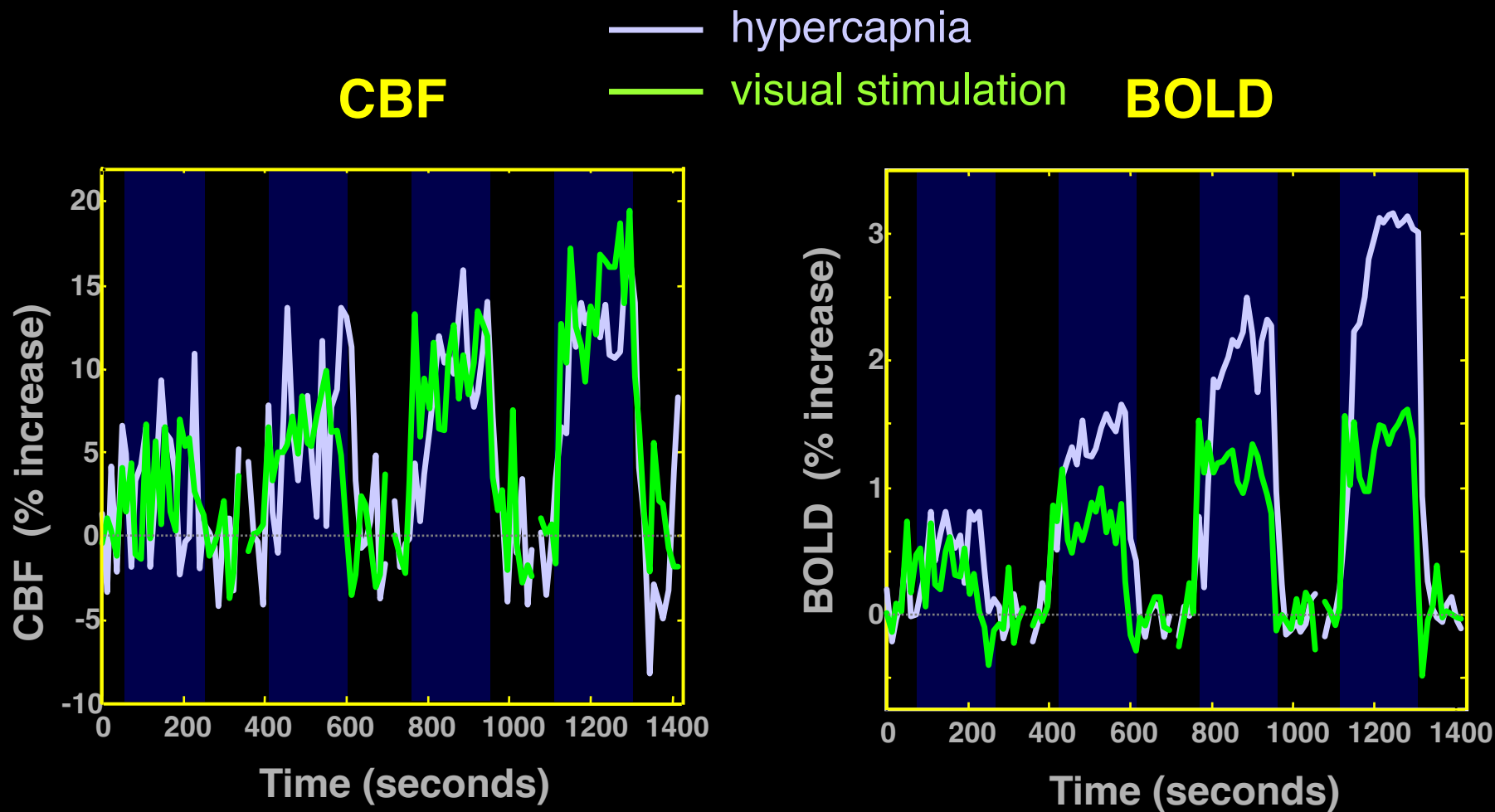


5% CO2



12% O2

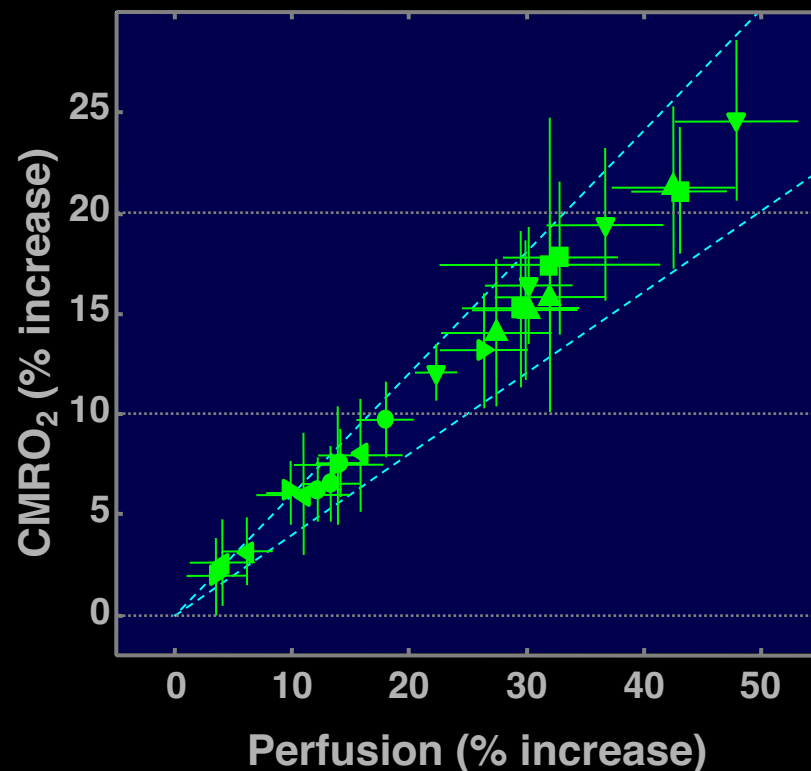
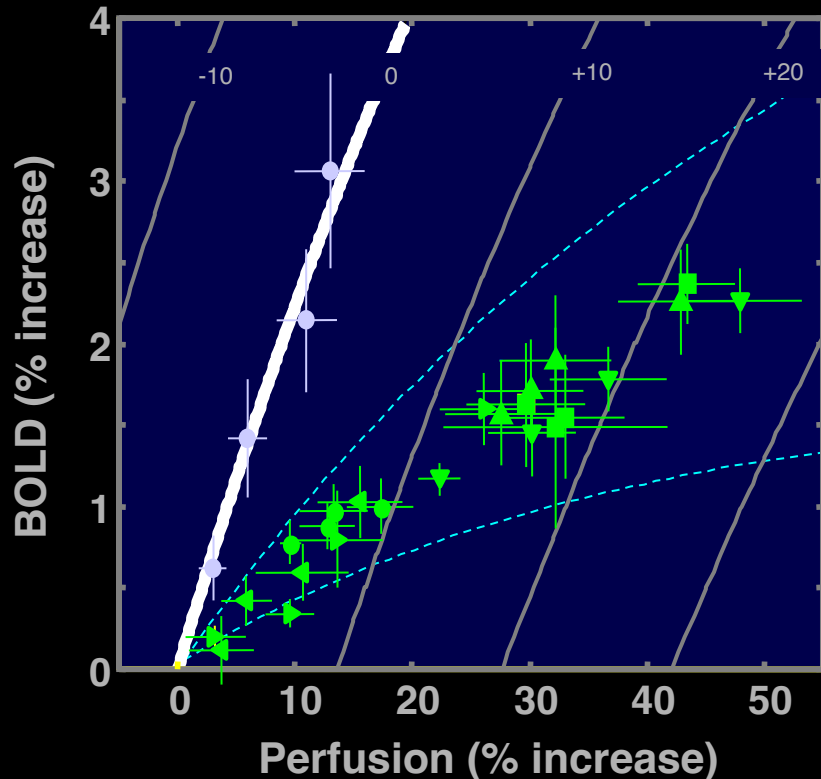
CMRO₂-related BOLD signal deficit:



Simultaneous Perfusion and BOLD imaging during graded visual activation and hypercapnia

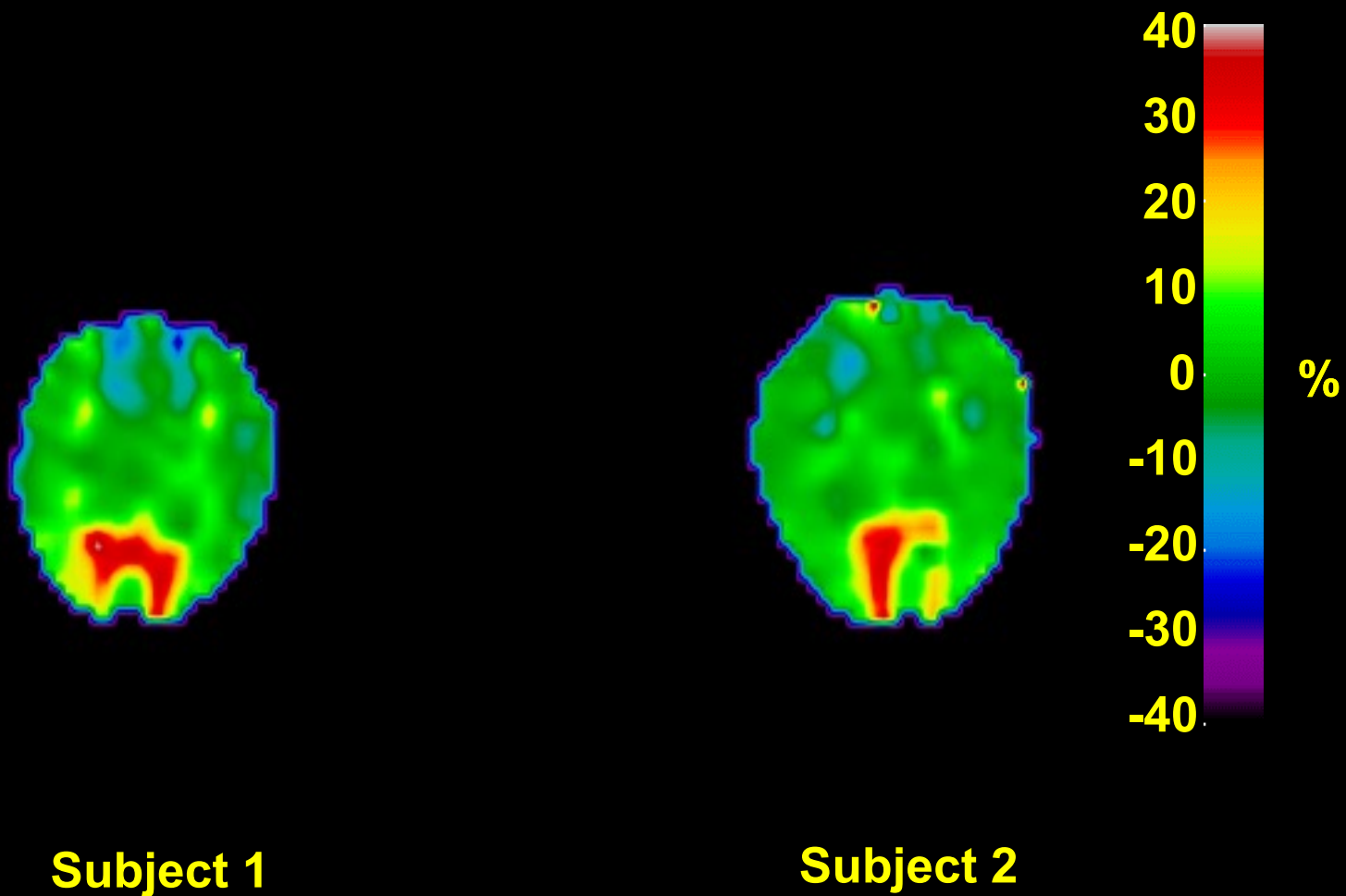
CBF-CMRO₂ coupling

Hoge, et al.



Characterizing Activation-induced CMRO₂ changes using calibration with hypercapnia

Computed CMRO₂ changes



Quantitative Measurements of Cerebral Metabolic Rate of Oxygen (CMRO₂) Using MRI: A Volunteer Study

Hongyu AN¹, Weili LIN², Azim CELIK³, Yueh Z. LEE⁴

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

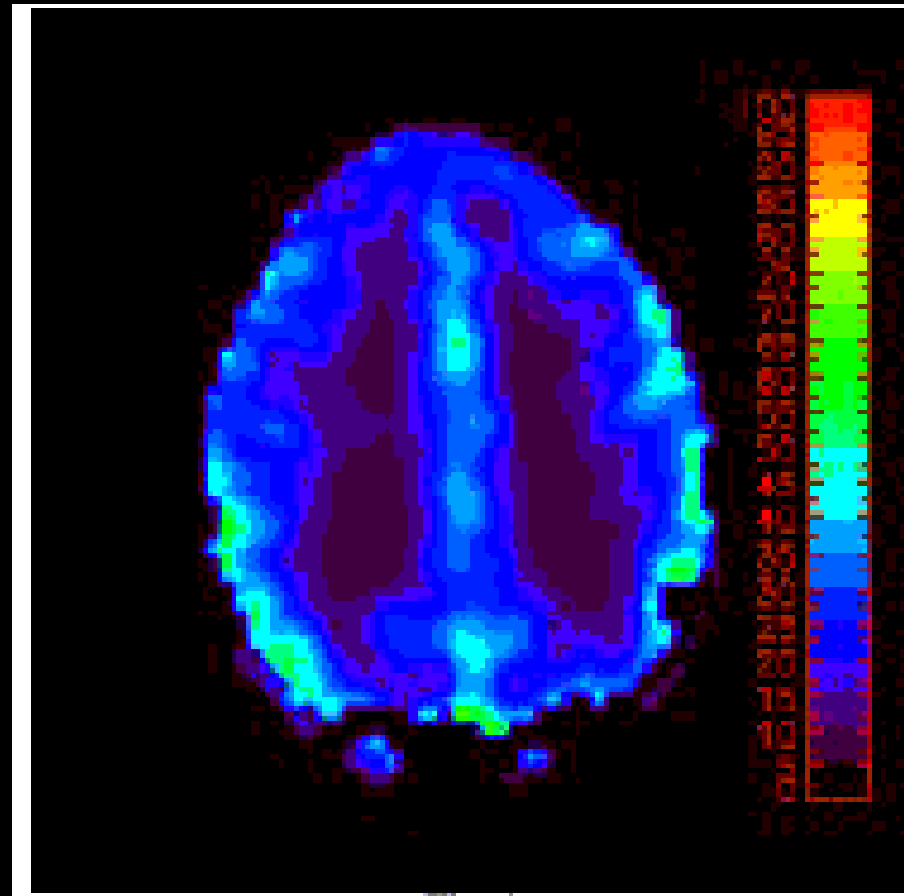
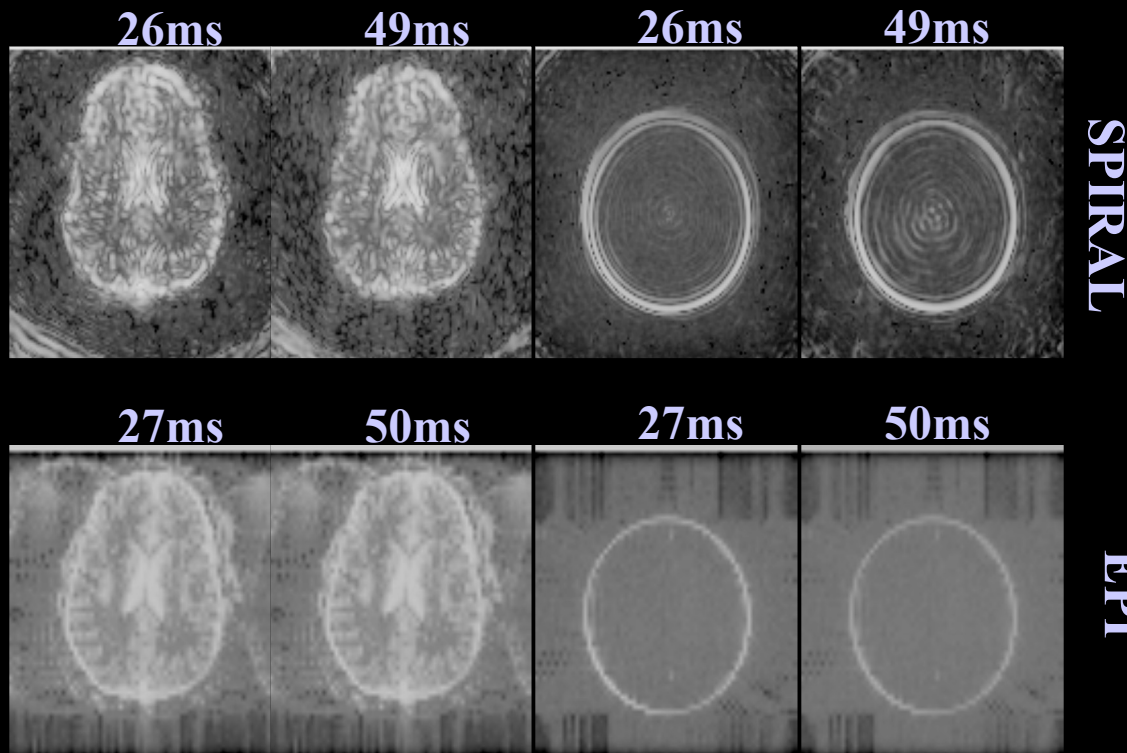


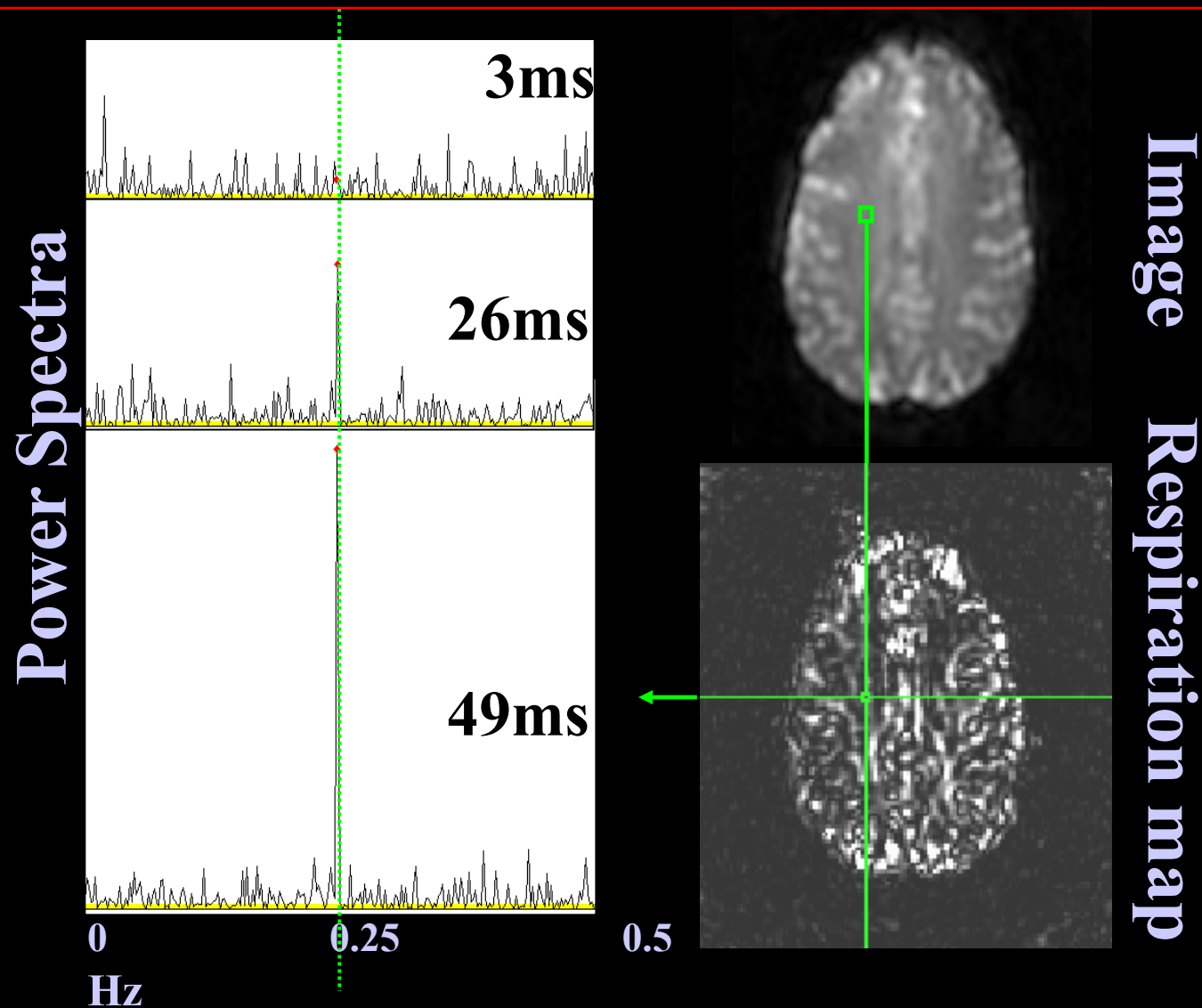
Figure 1

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

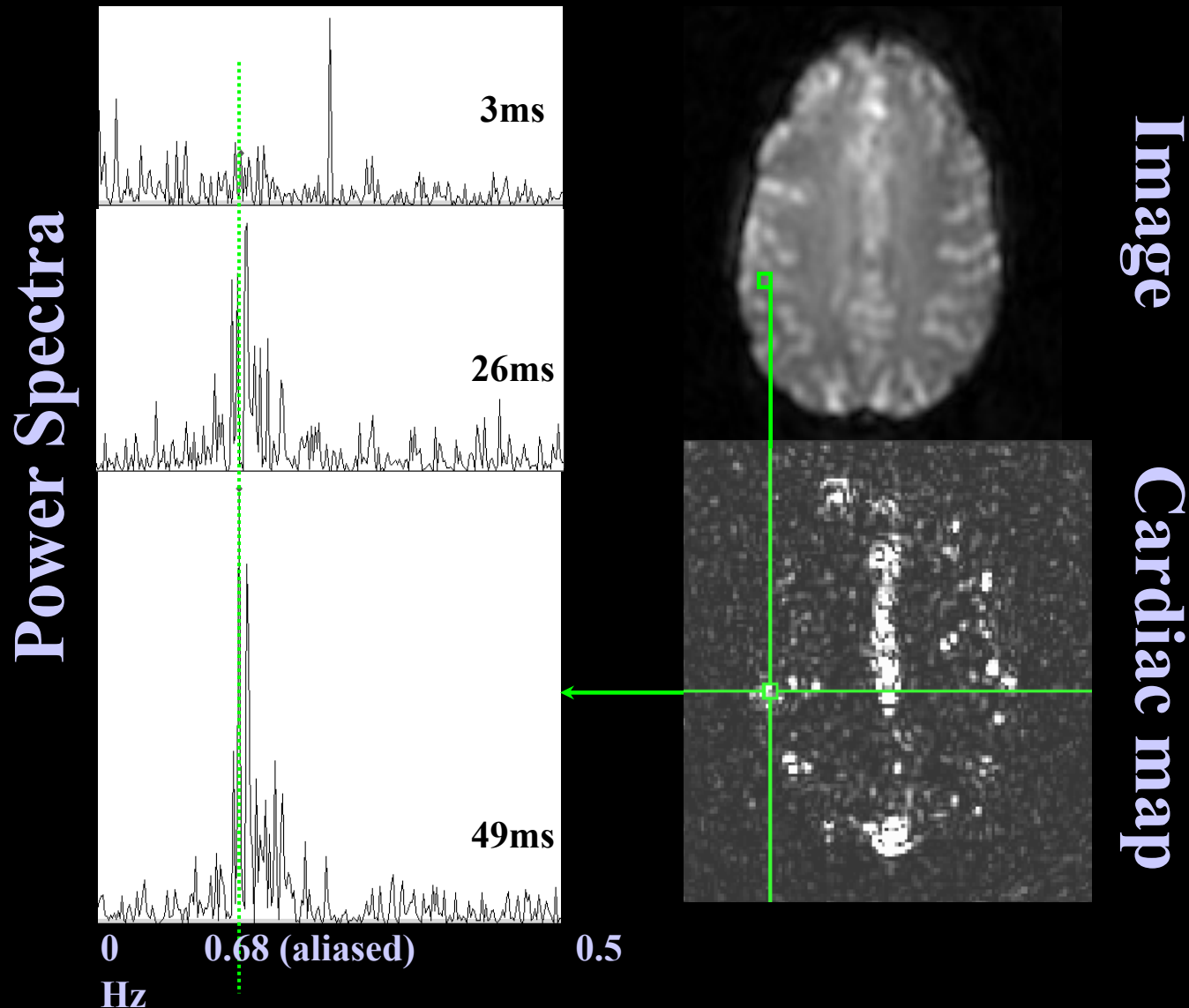
Temporal vs. Spatial SNR- 3T



0.25 Hz Breathing at 3T

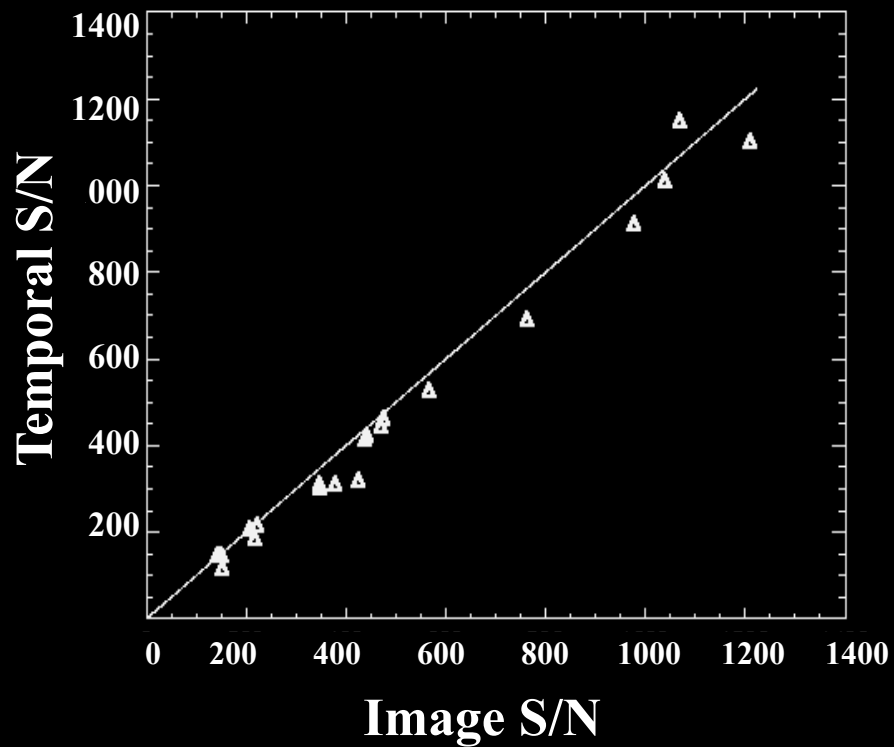


0.68 Hz Cardiac rate at 3T

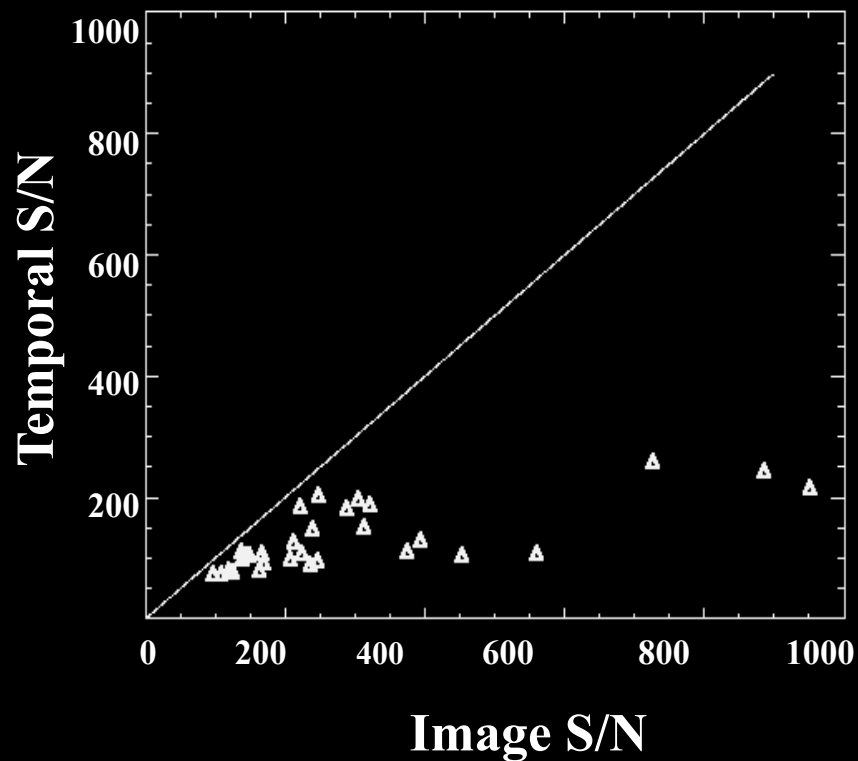


Temporal S/N vs. Image S/N

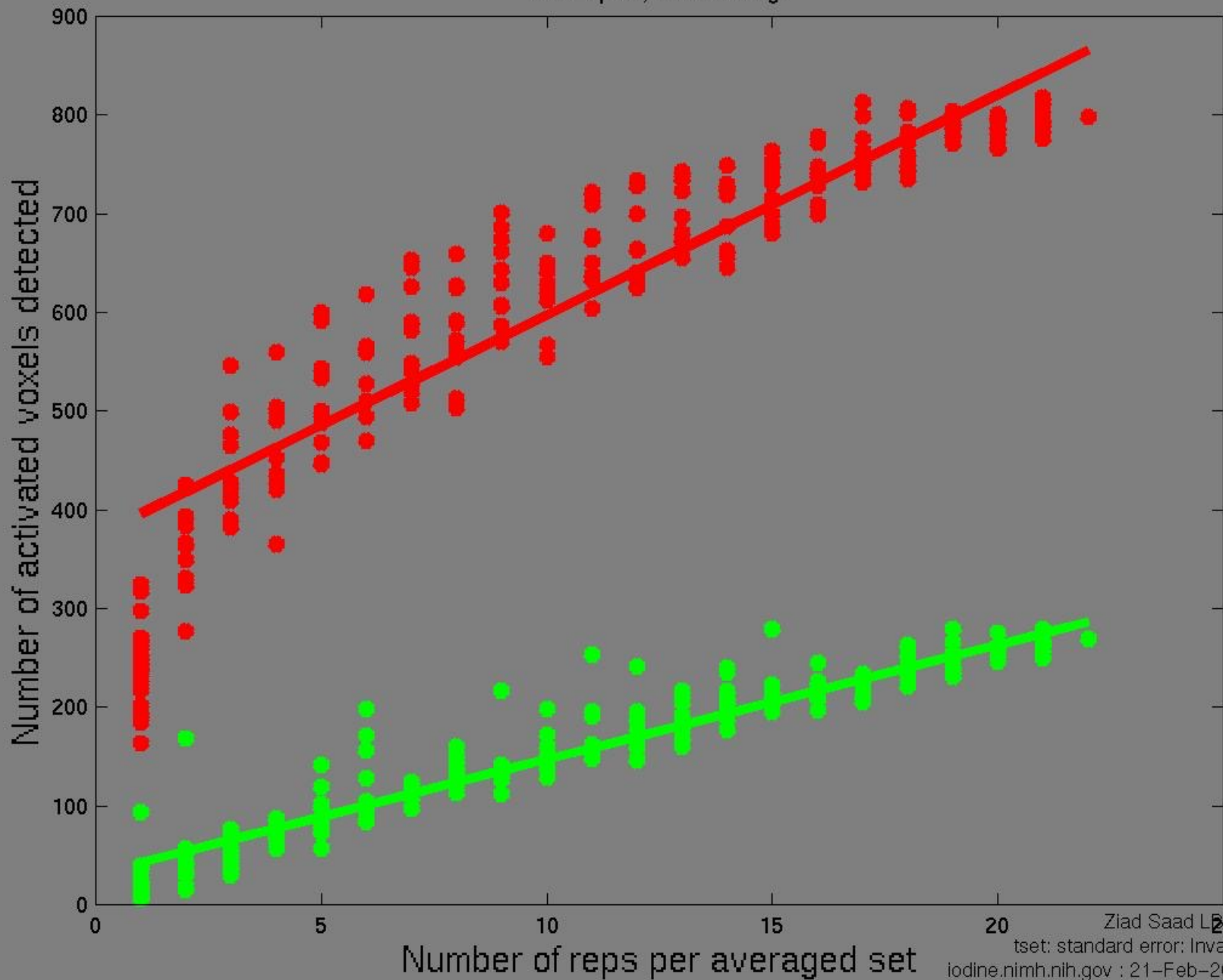
PHANTOMS

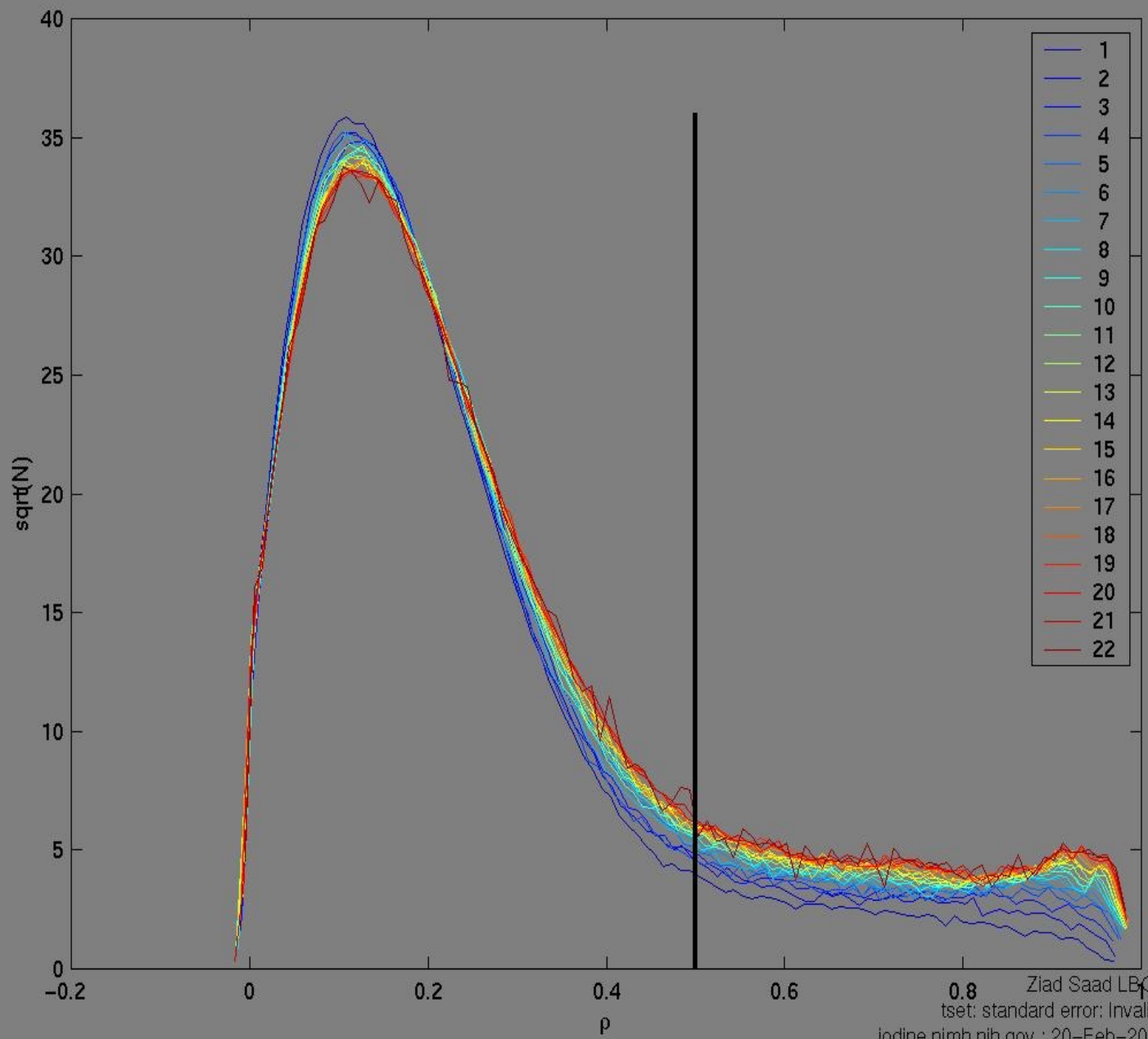


SUBJECTS



Fit curve: Pos: $22.3478 \text{ Nrep} + 373.782$ --- Neg: $11.6126 \text{ Nrep} + 30.8055$
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

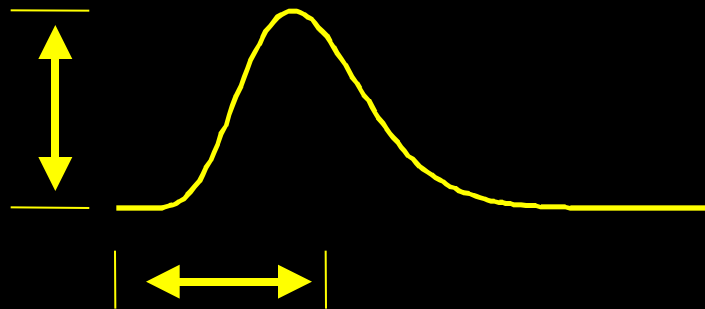
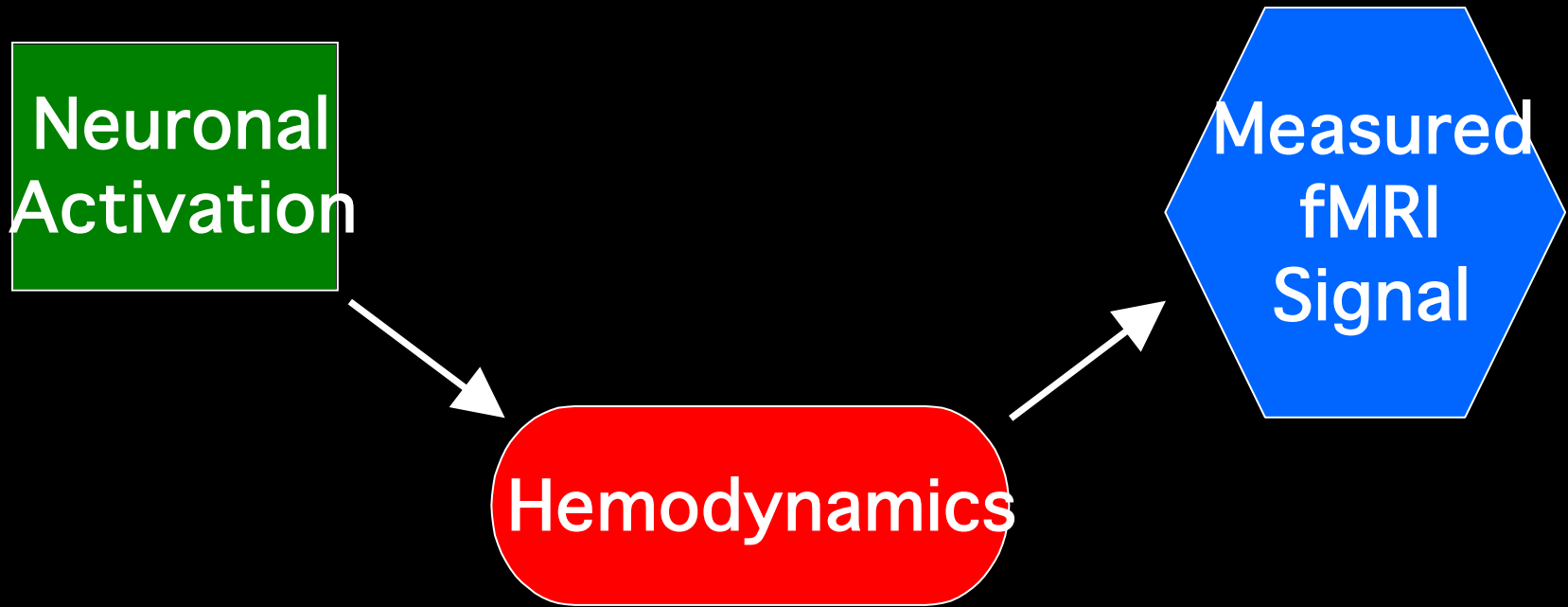
Orthogonal Designs

Parametric Designs

Event-Related Designs

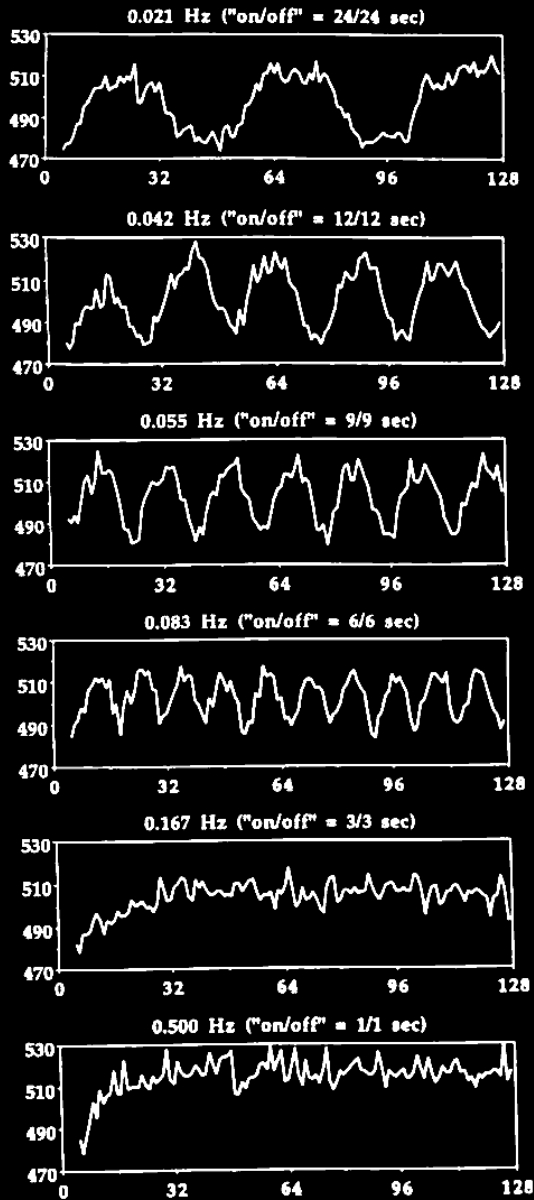
Free Behavior Designs

Hemodynamic Transfer Function



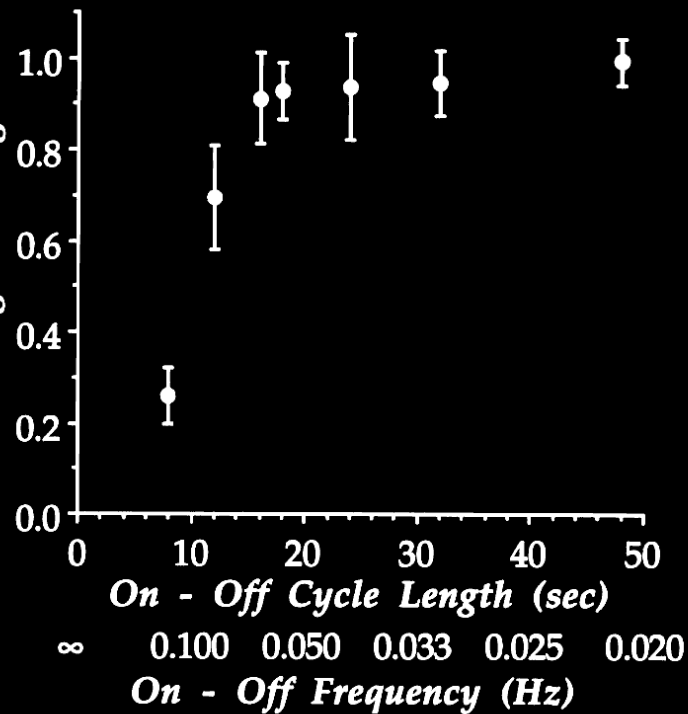
Physiologic Factors

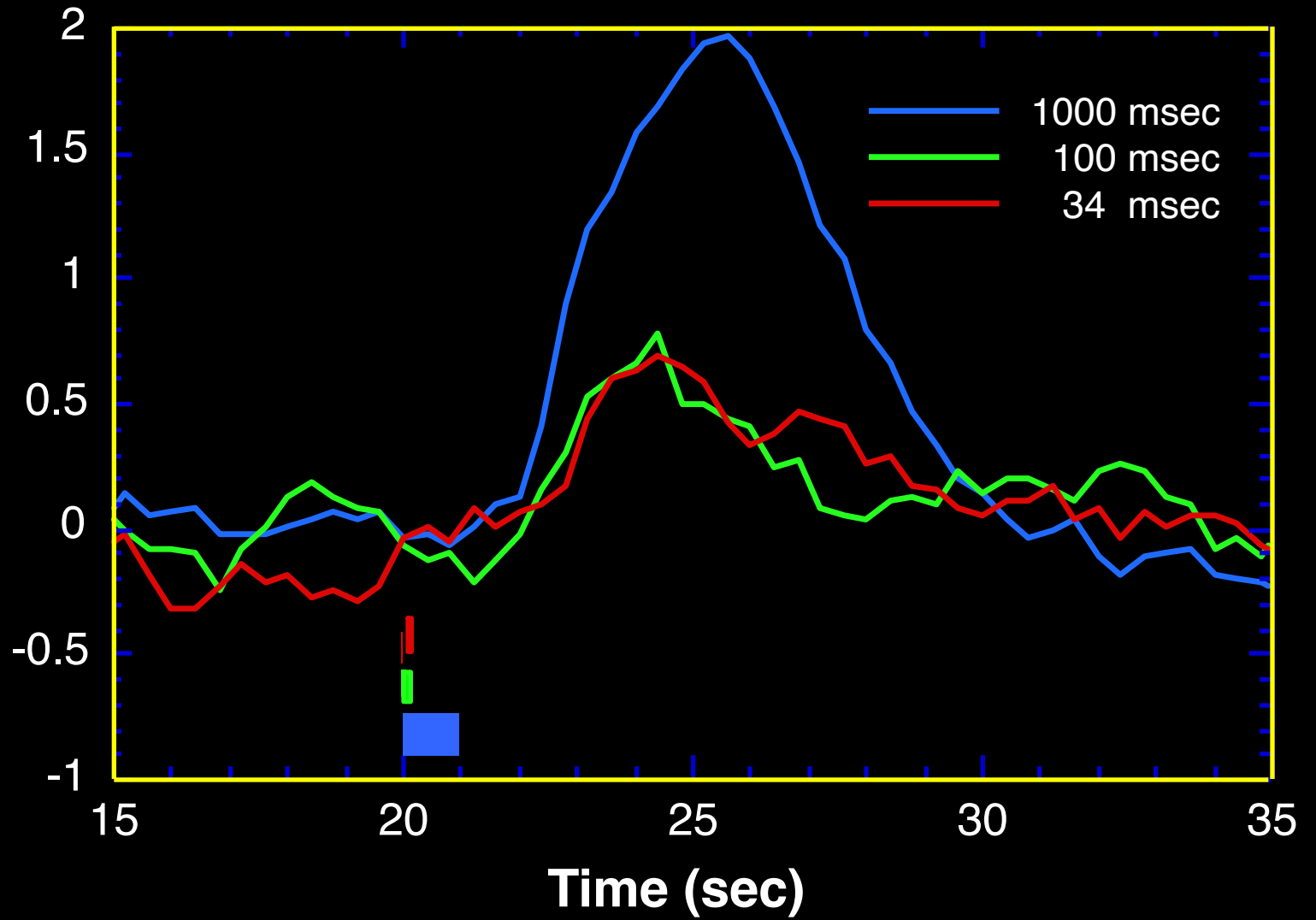
MRI Signal

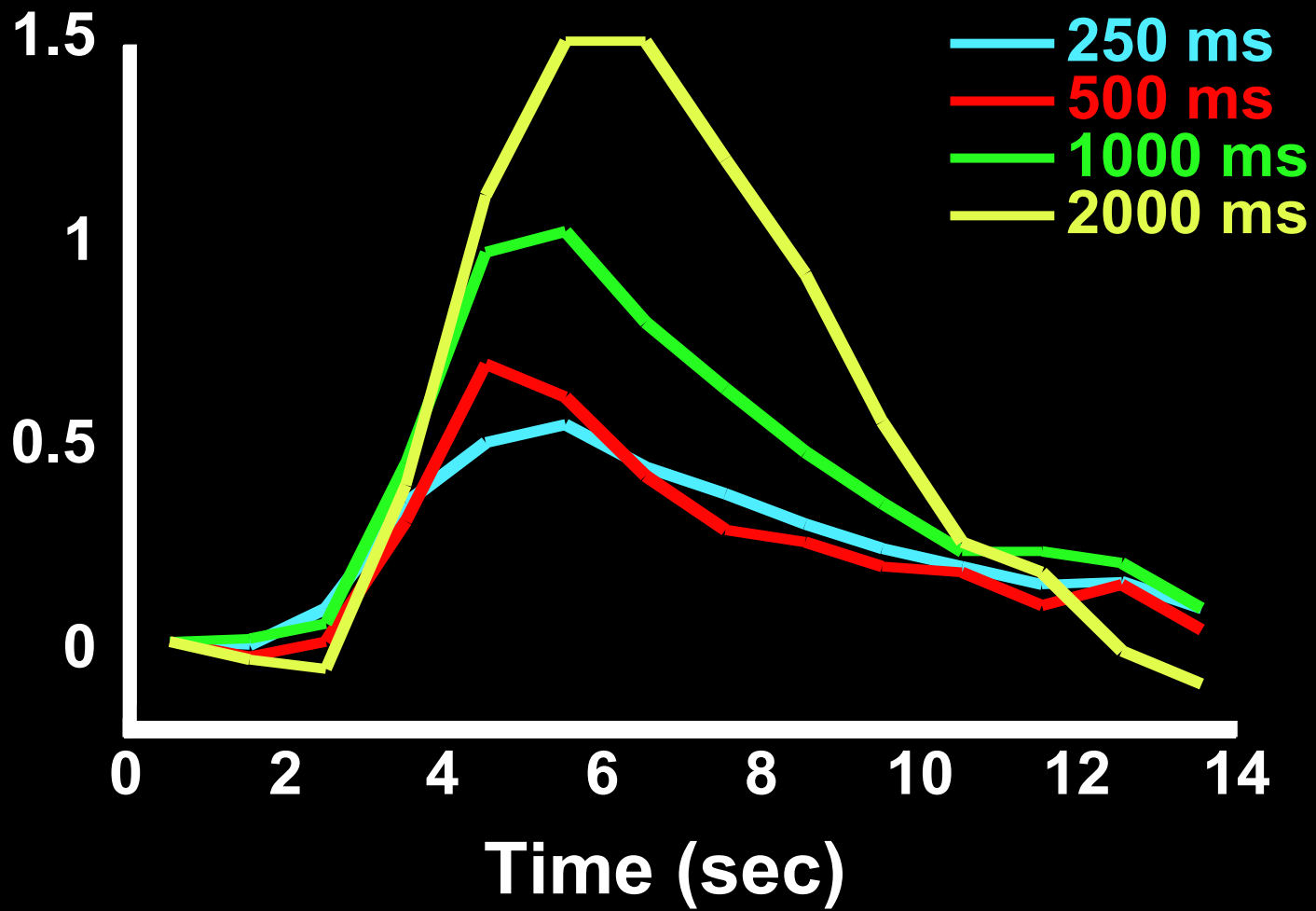


Time (seconds)

Relative Activation - Induced
MR Signal Change

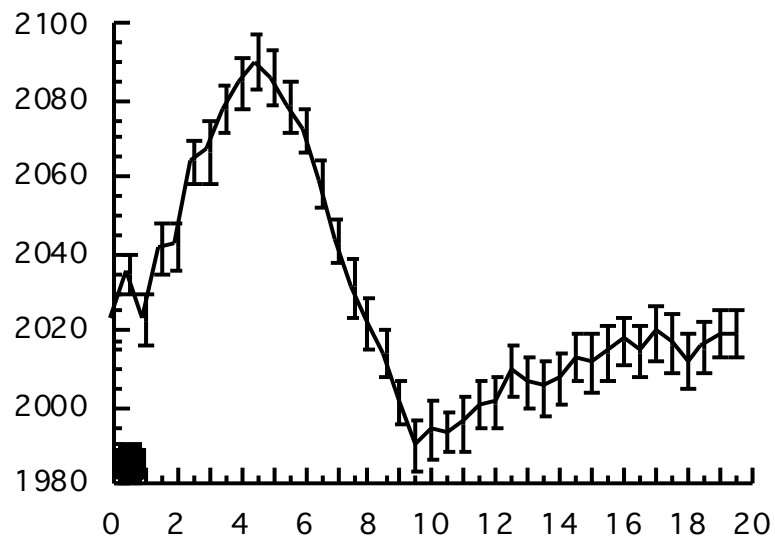
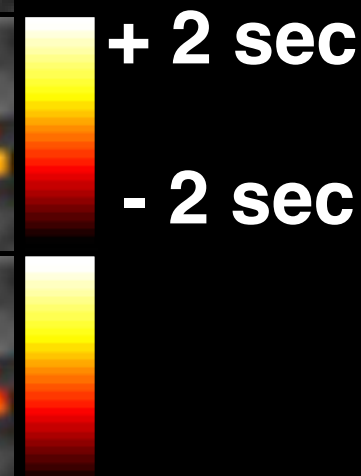
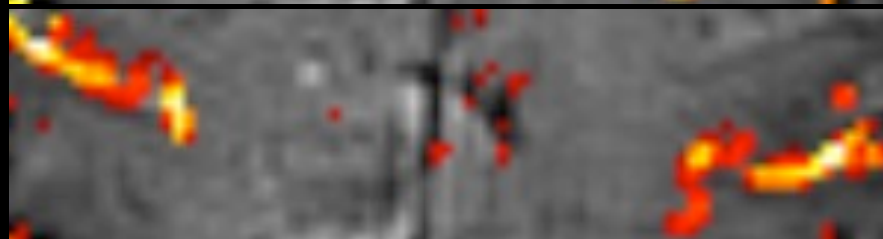
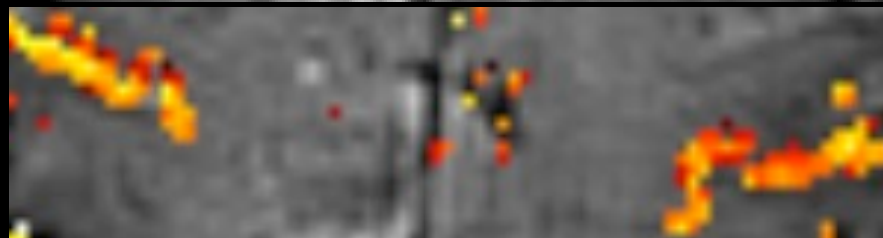




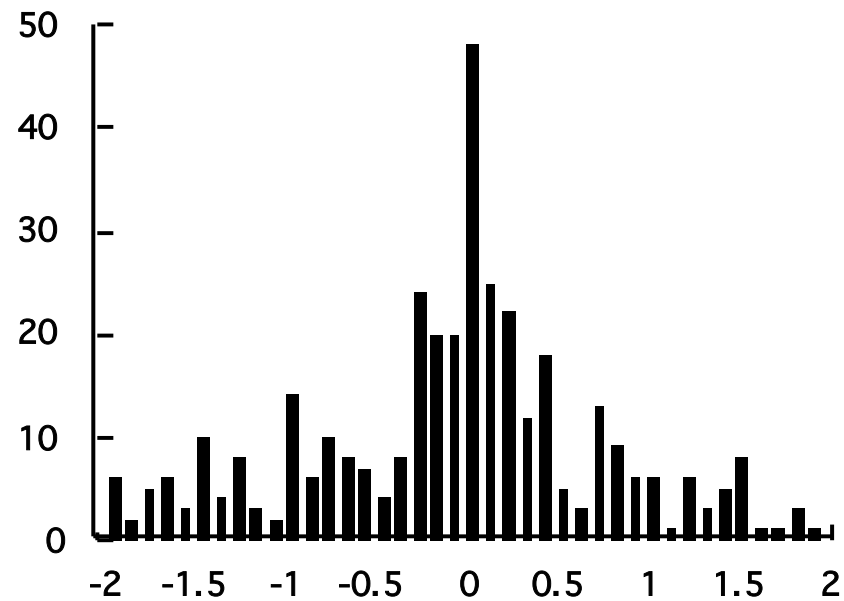


Latency

Magnitude



Time (sec)

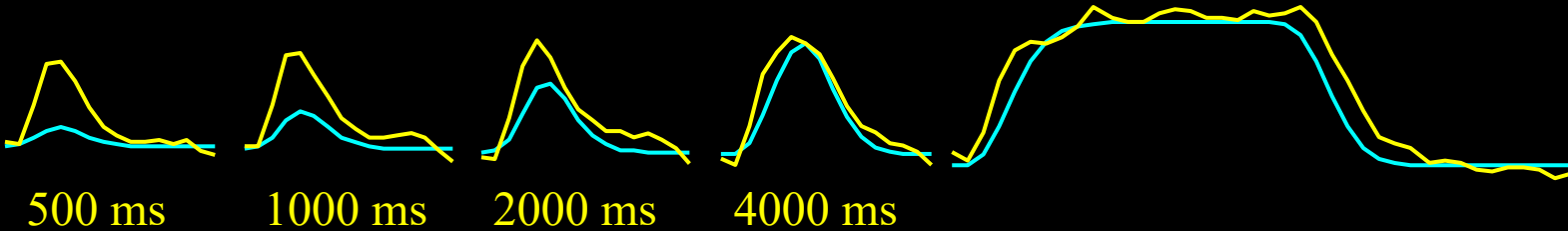
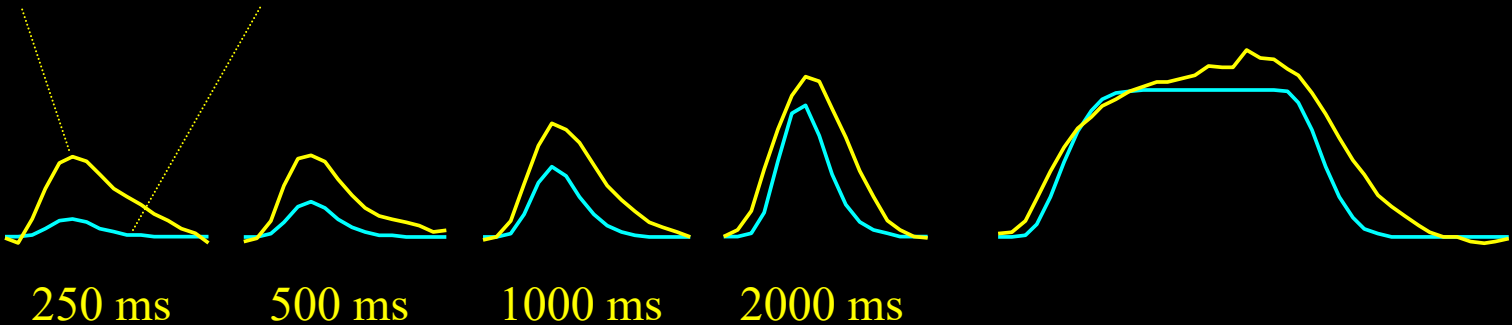


Delay (sec)

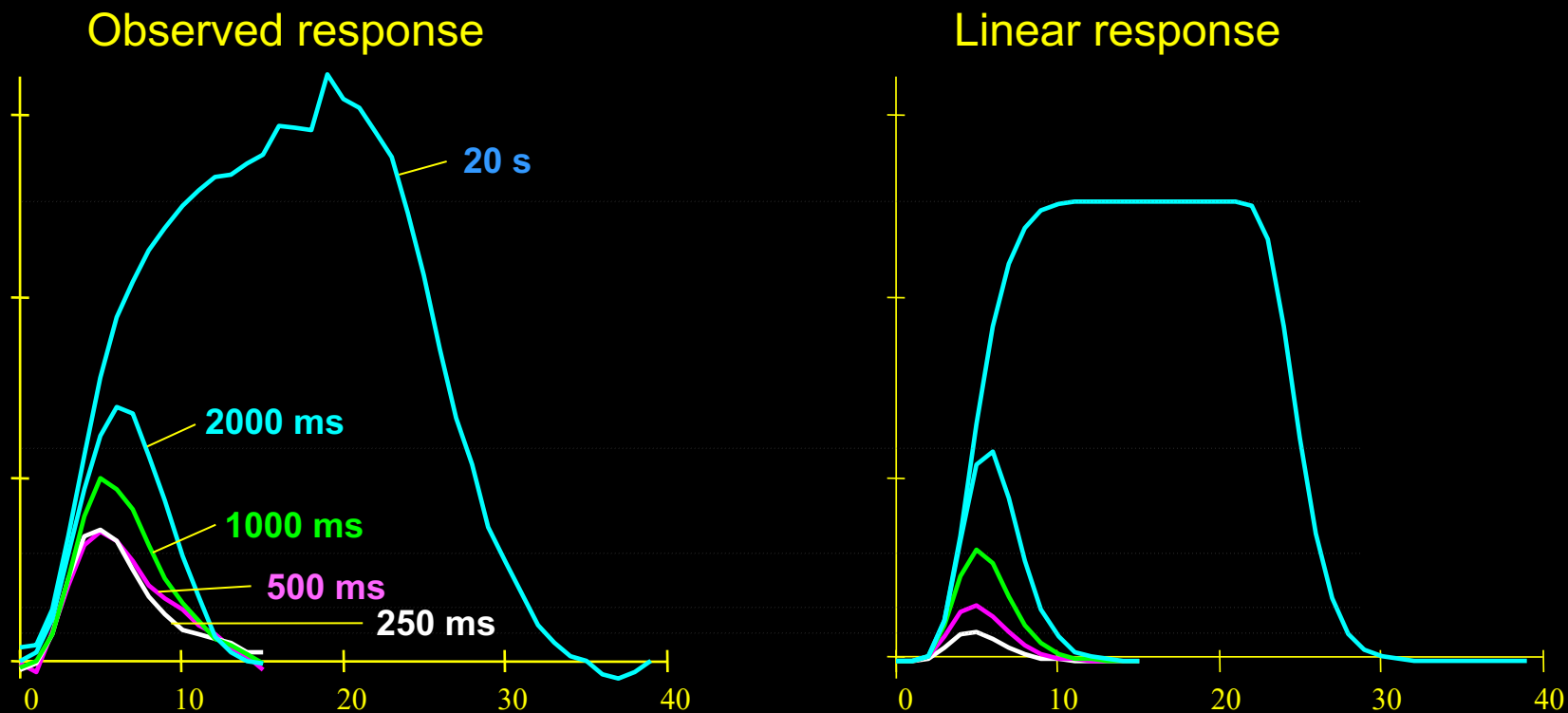
Observed Responses

measured

ideal (linear)

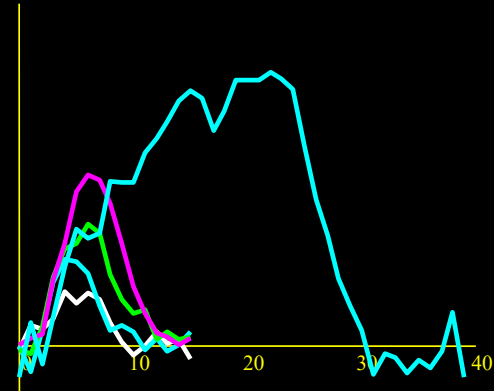
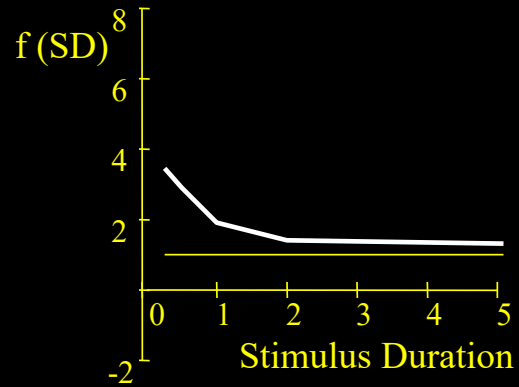
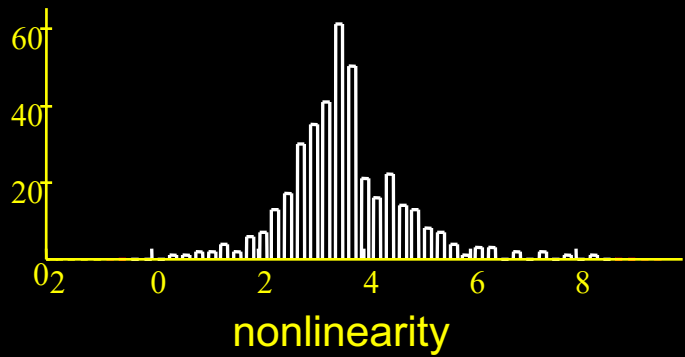
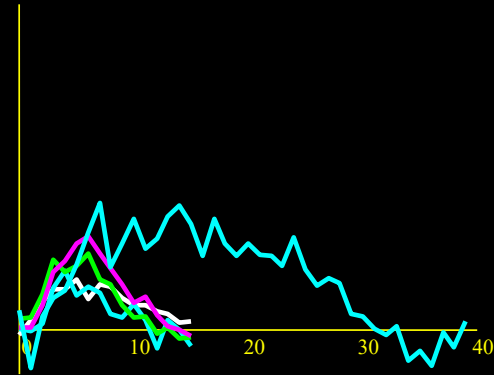
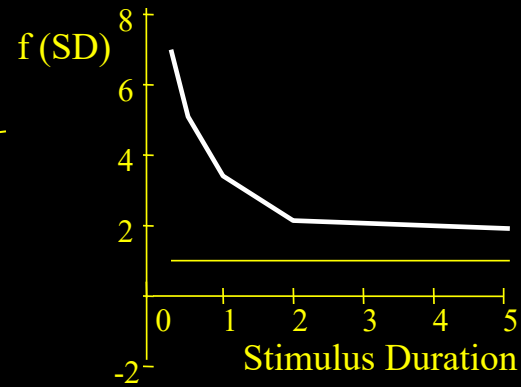
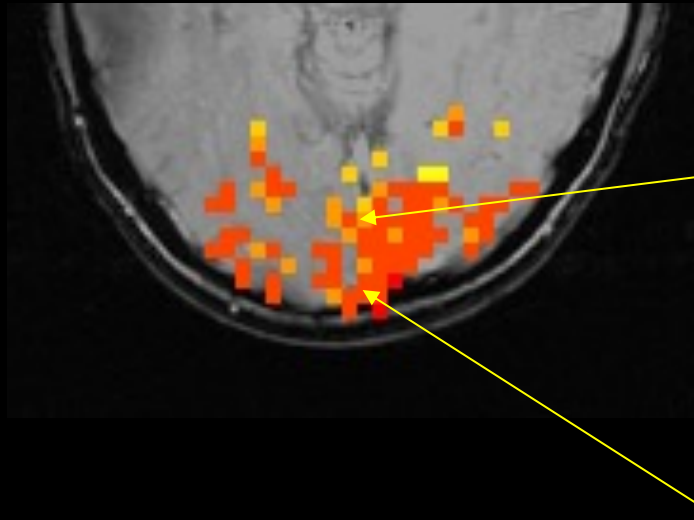


BOLD response is nonlinear



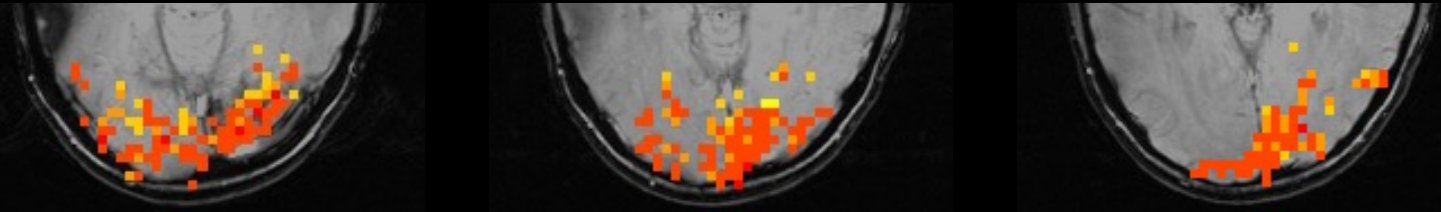
Short duration stimuli produce larger responses than expected

Results — visual task

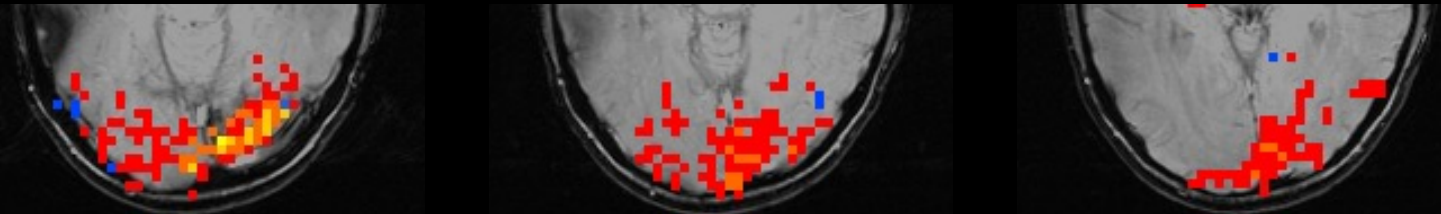


Results — visual task

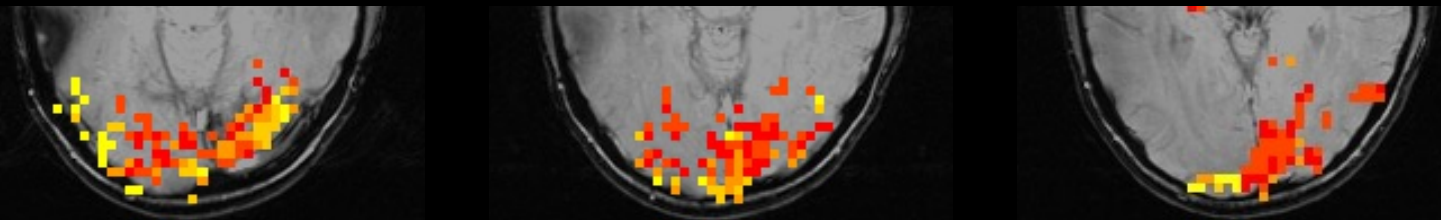
Nonlinearity



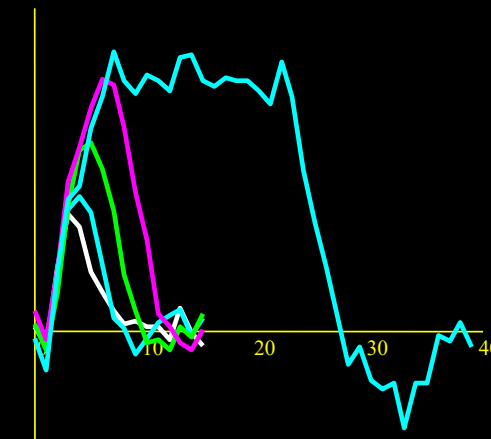
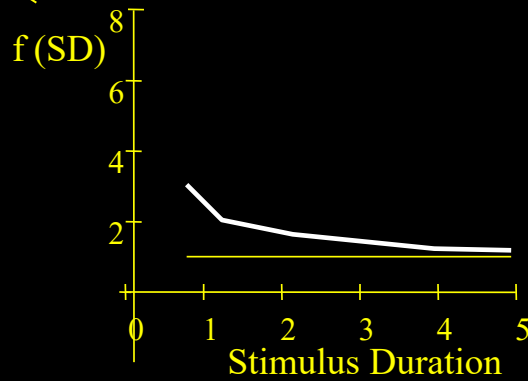
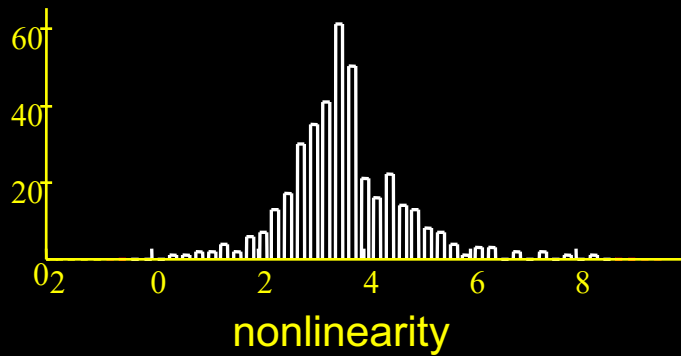
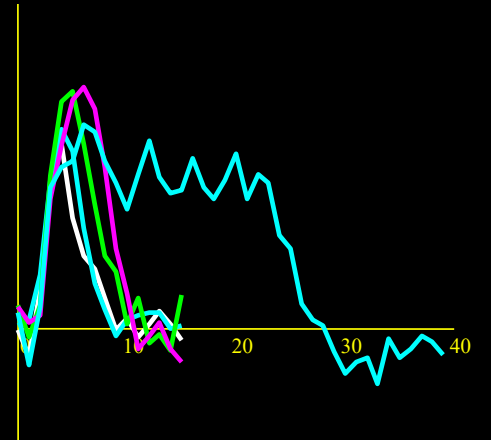
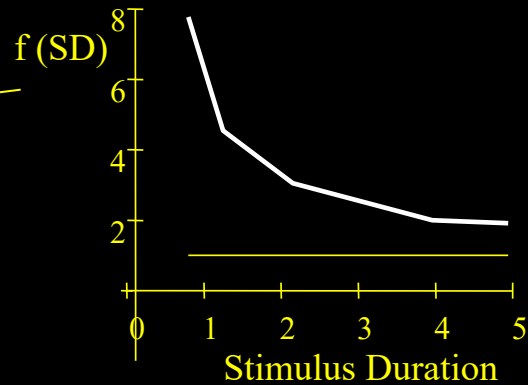
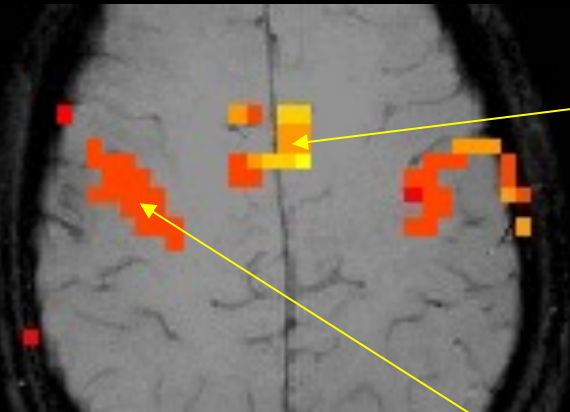
Magnitude



Latency

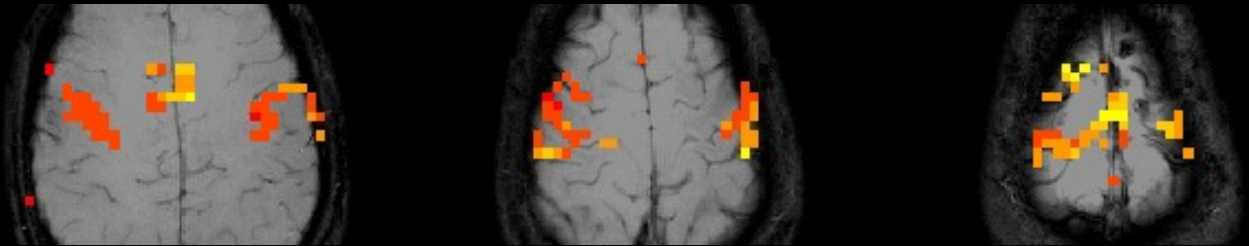


Results — motor task

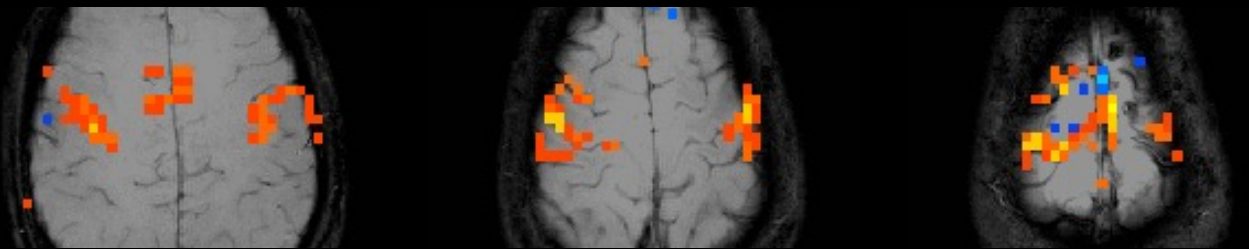


Results — motor task

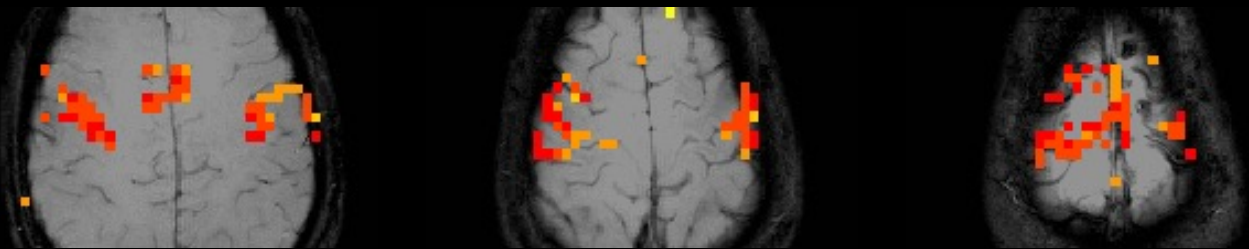
Nonlinearity



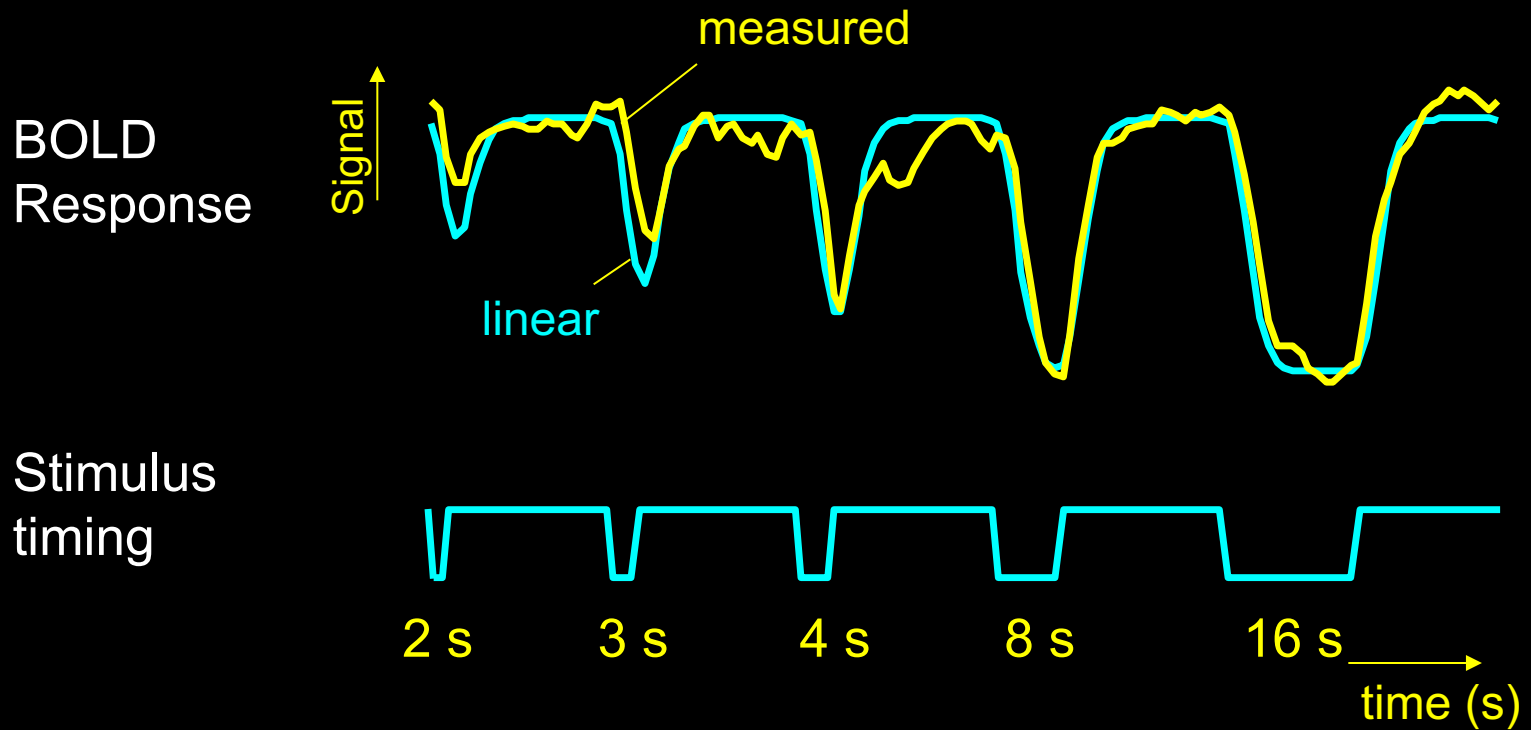
Magnitude



Latency



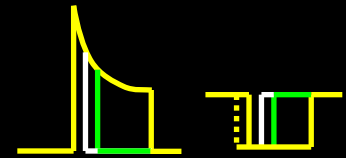
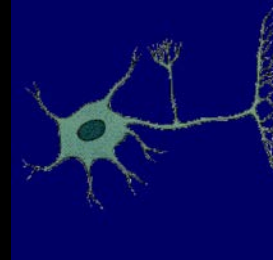
Different stimulus “ON” periods



Brief stimulus OFF periods produce smaller decreases than expected

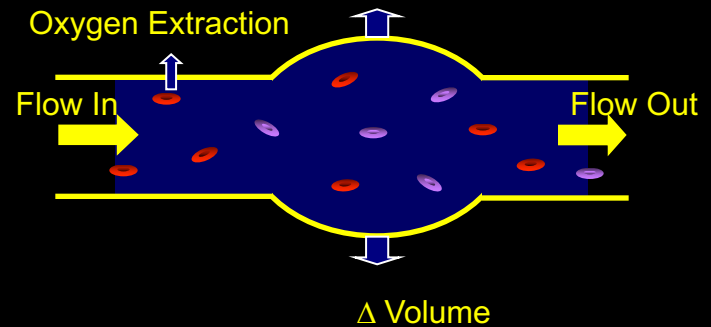
Sources of this Nonlinearity

- Neuronal

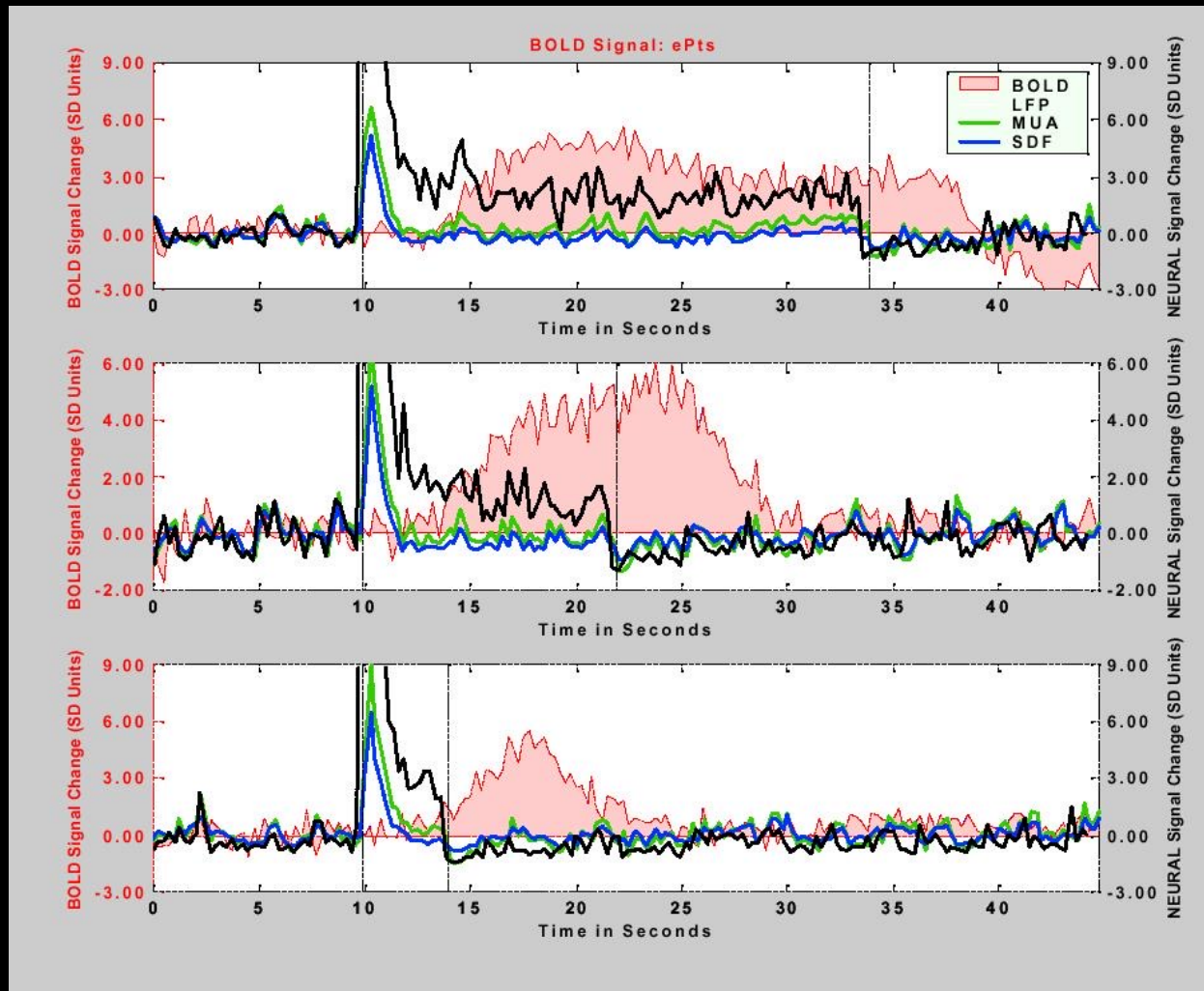


- Hemodynamic

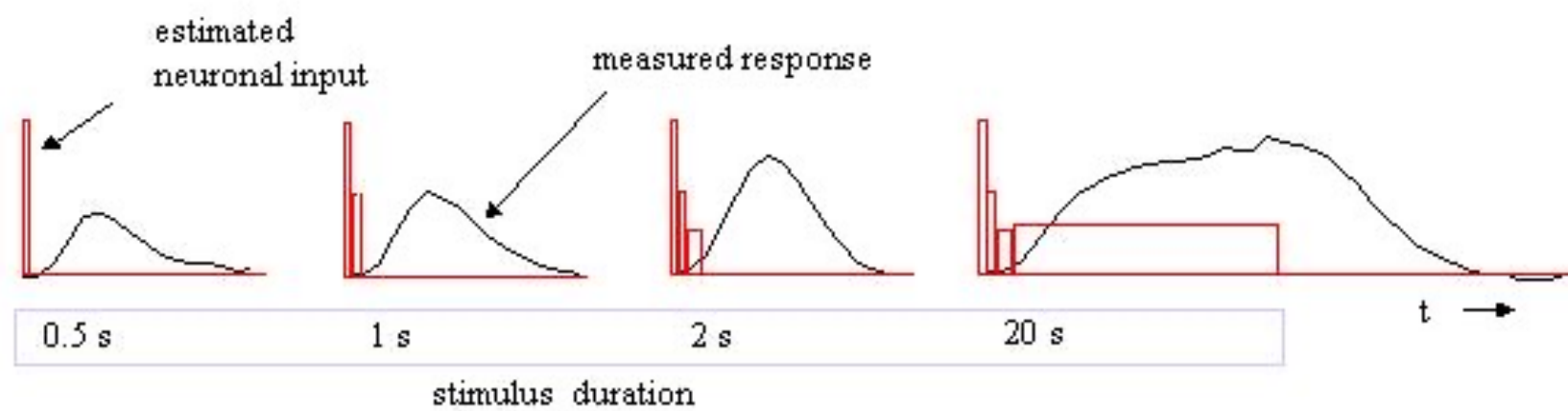
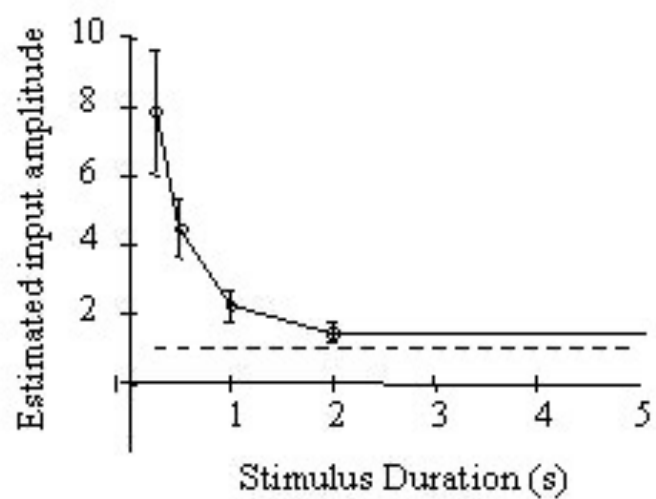
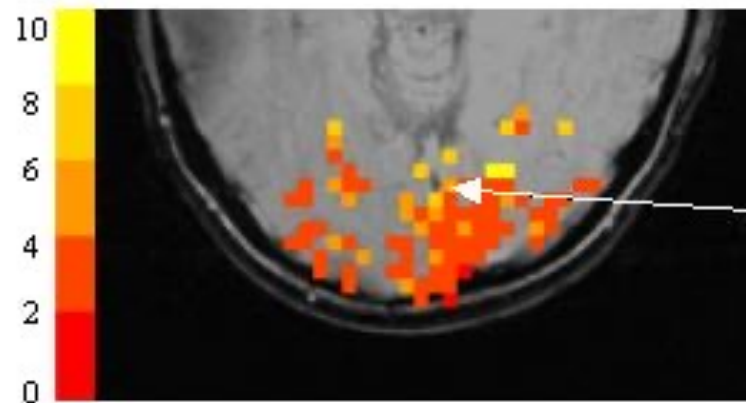
- Oxygen extraction
- Blood volume dynamics



BOLD Correlation with Neuronal Activity



Logothetis et al. Nature, 412, 150-157



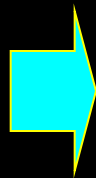
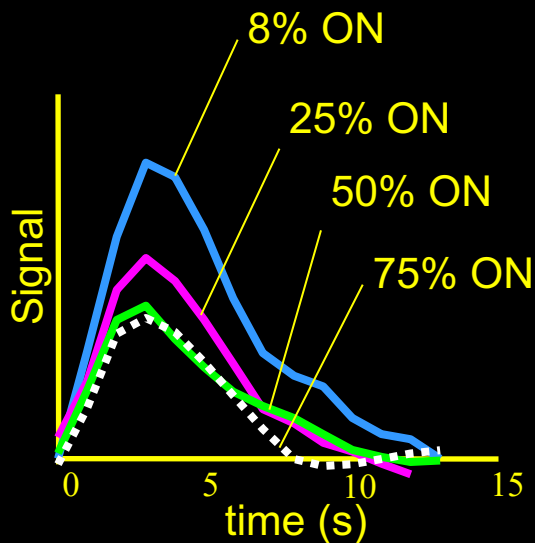
Varying “ON” and “OFF” periods

- *Rapid event-related design with varying ISI*

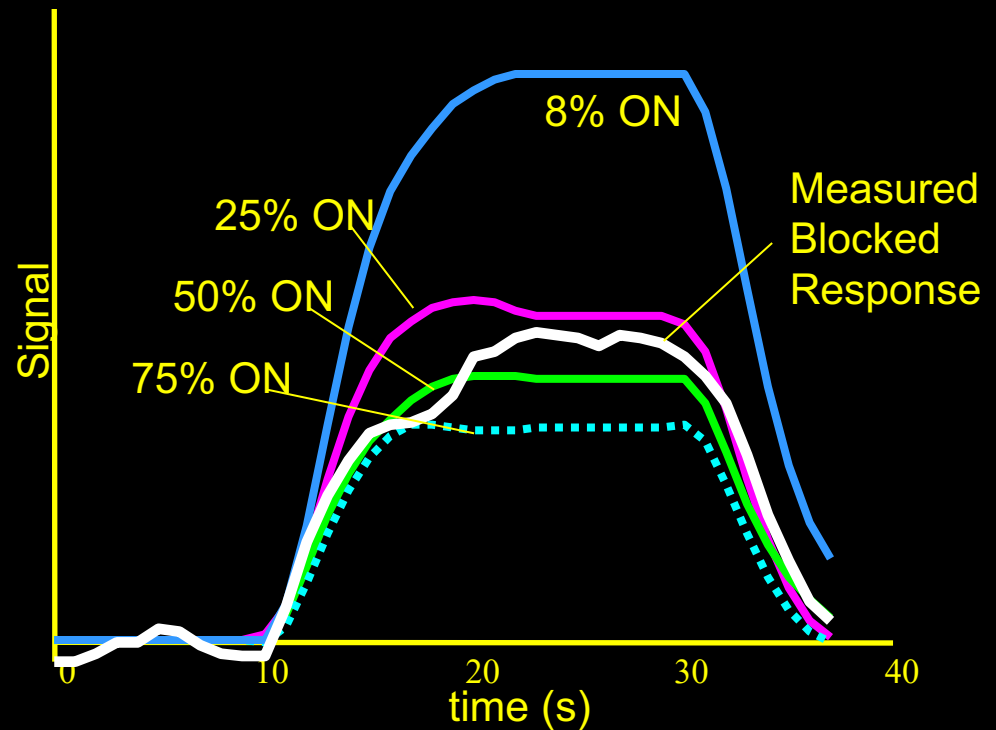


Varying “ON” and “OFF” periods

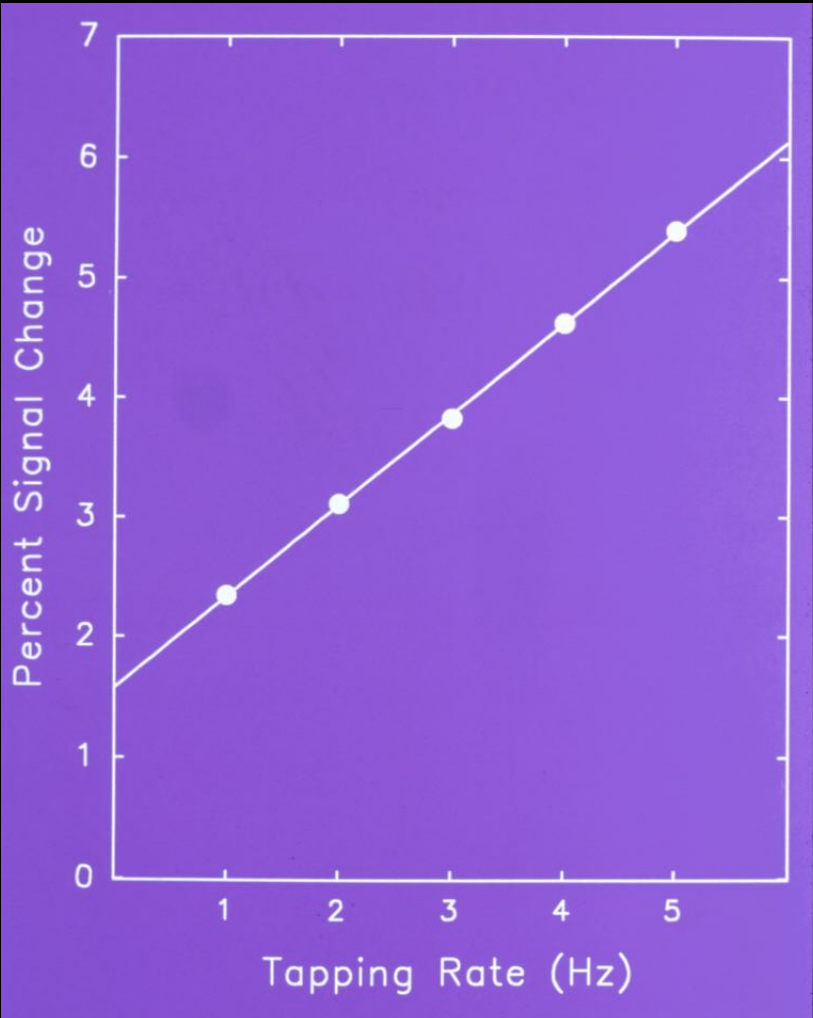
Estimated Impulse Response



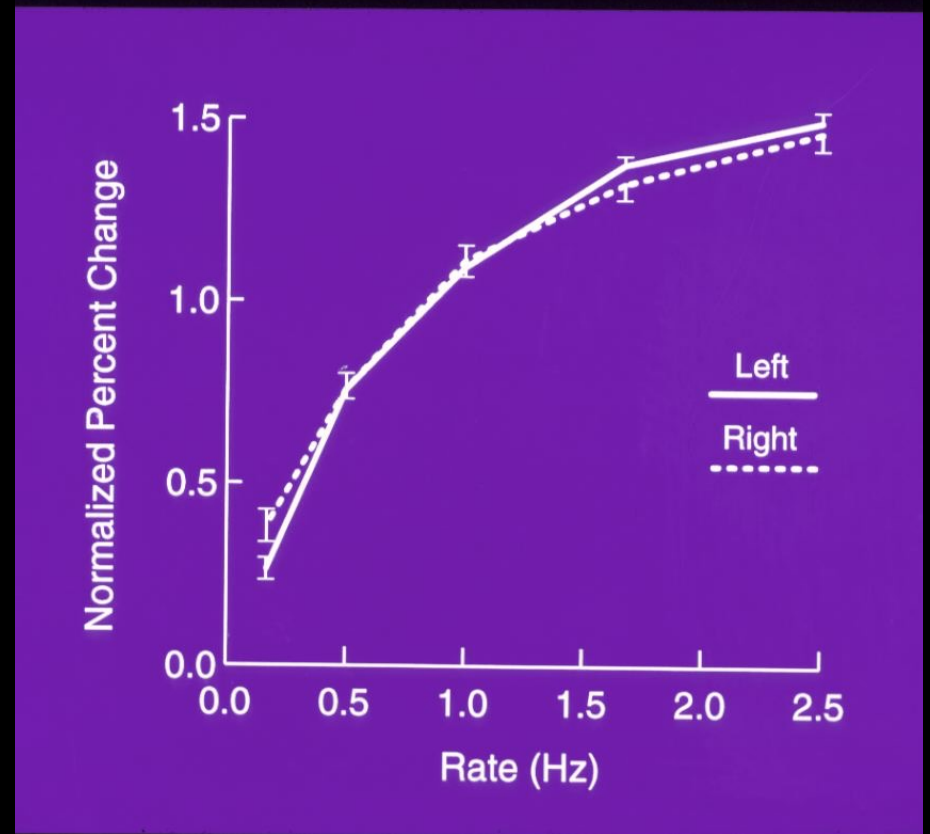
Predicted Responses to 20 s stimulation

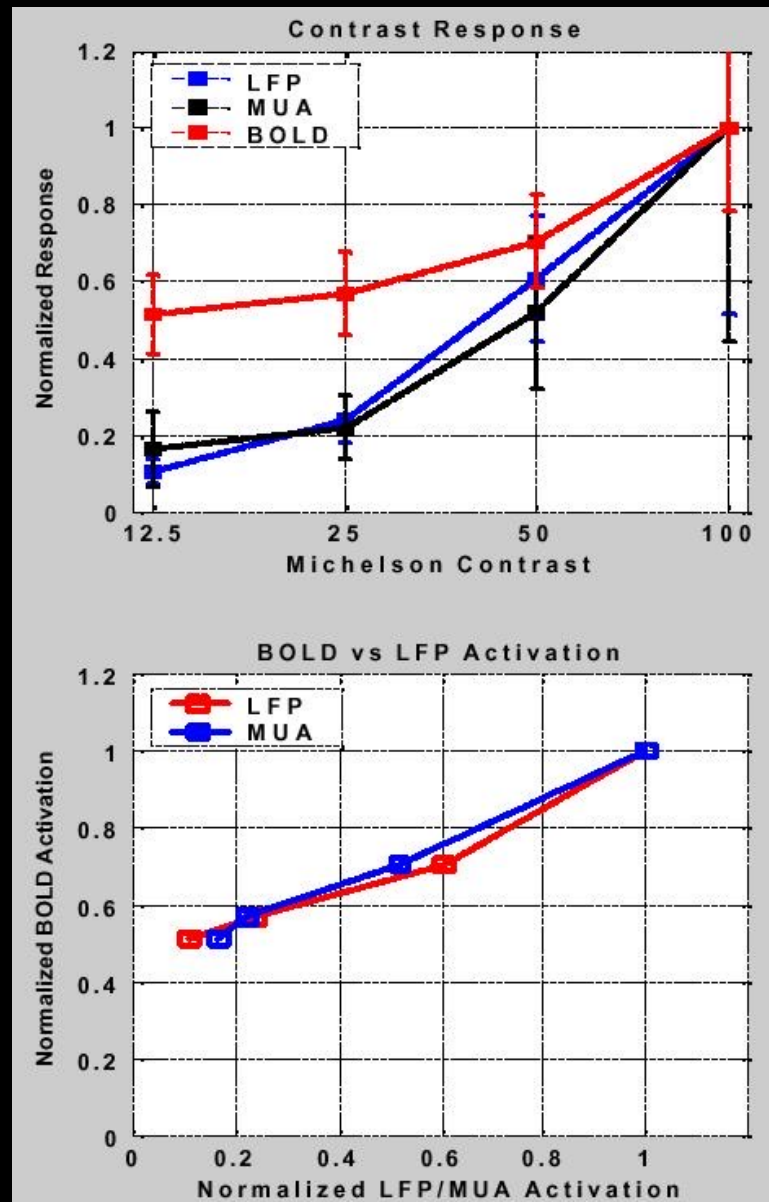


Motor Cortex



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

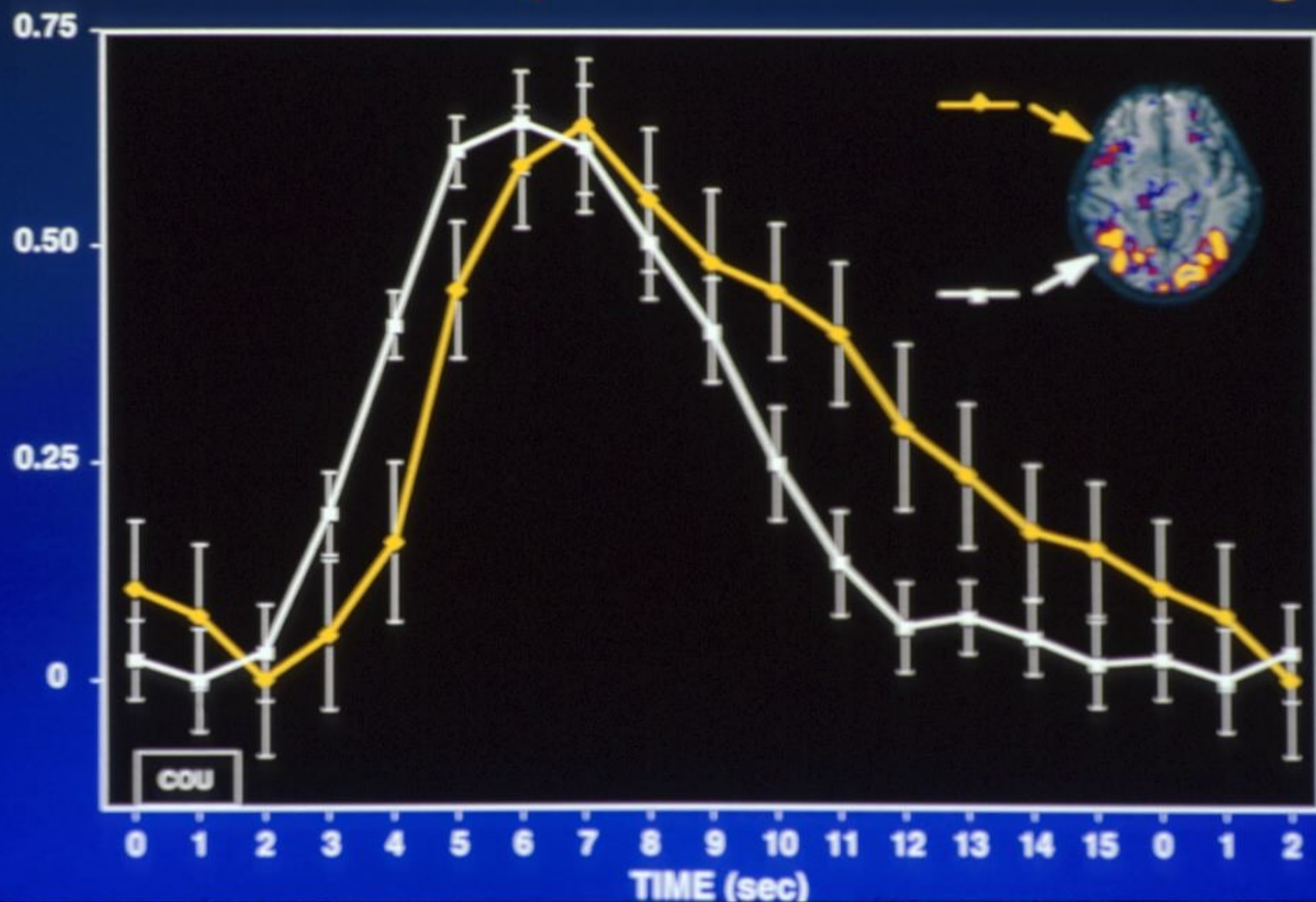
Orthogonal Designs

Parametric Designs

Event-Related Designs

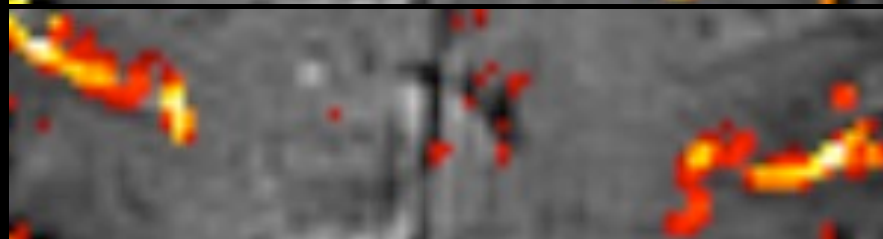
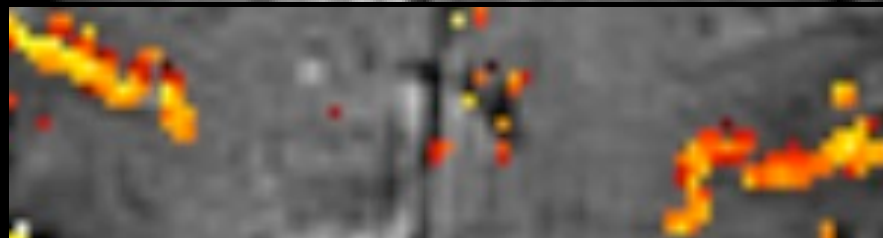
Free Behavior Designs

Time Course Comparison Across Brain Regions



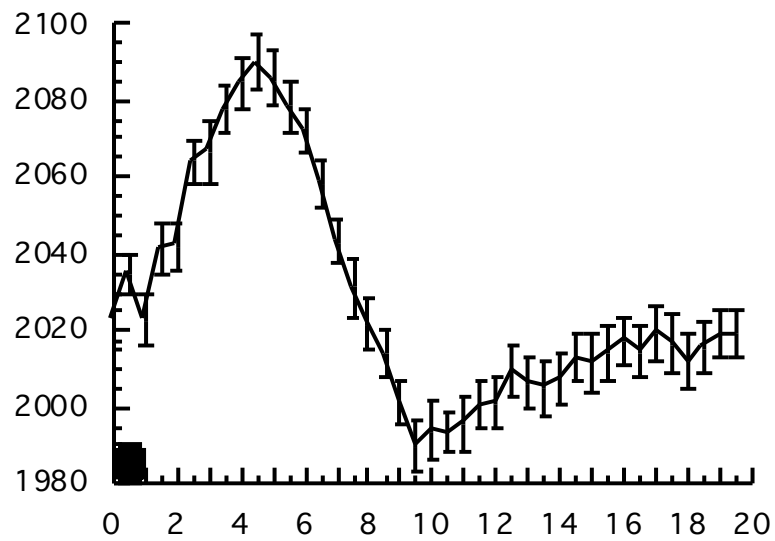
Latency

Magnitude

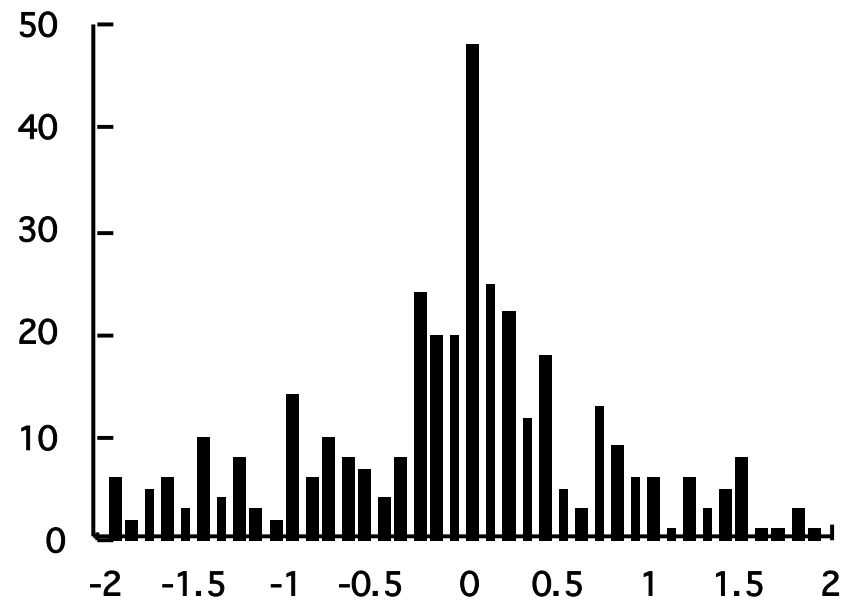


+ 2 sec

- 2 sec



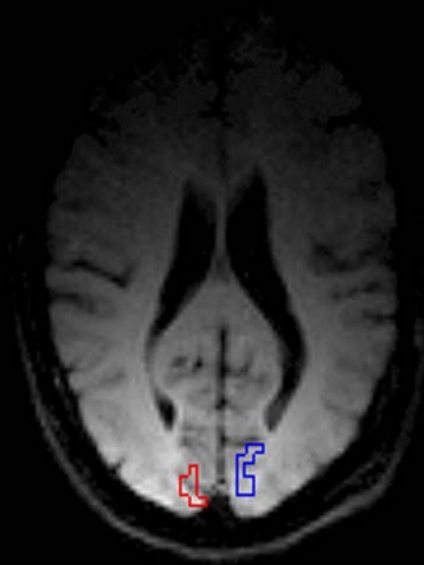
Time (sec)



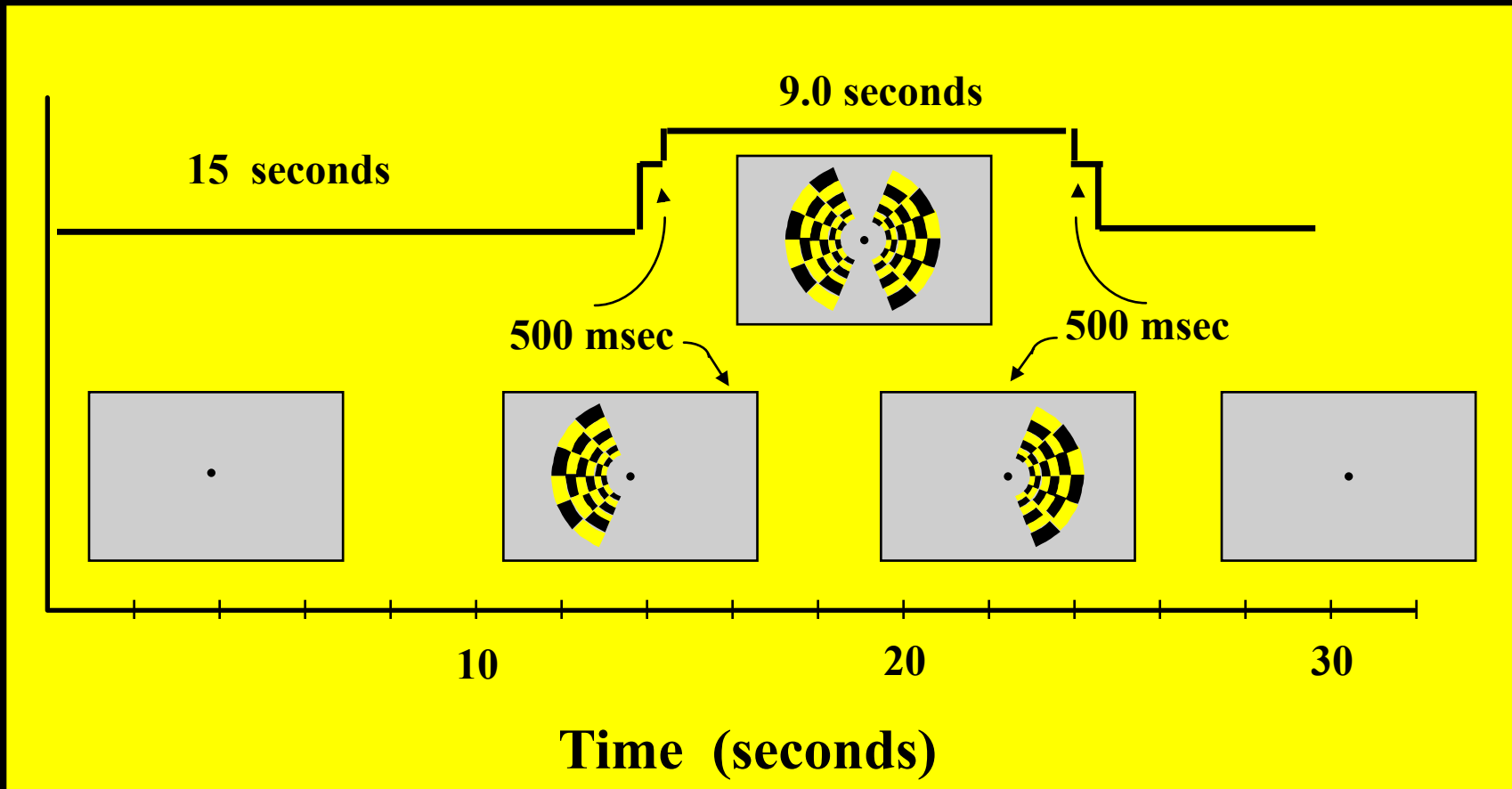
Delay (sec)

Regions of Interest Used for Hemi-Field Experiment

**Right
Hemisphere**

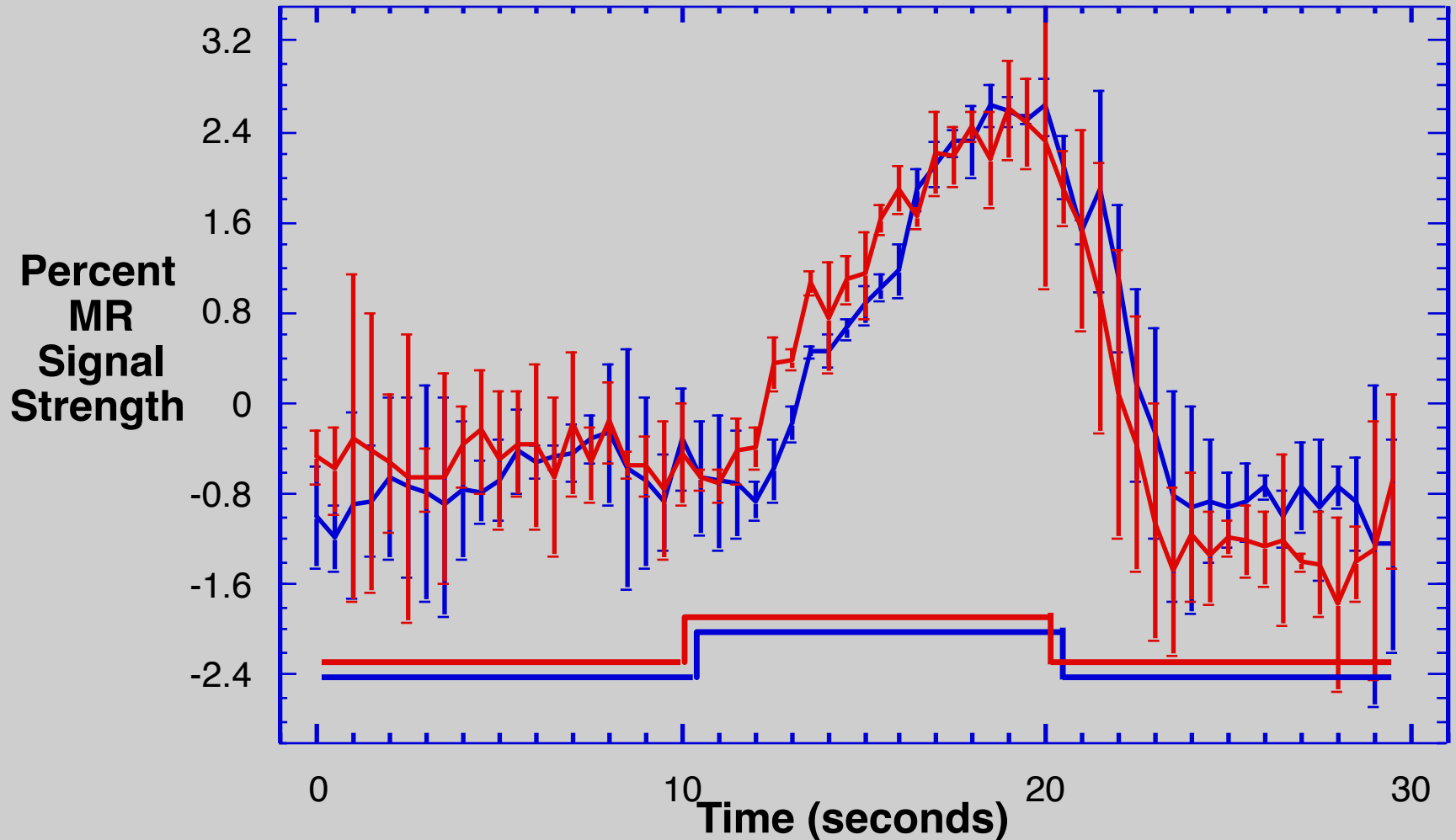


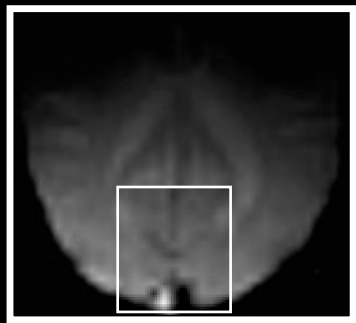
**Left
Hemisphere**



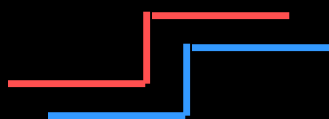
Hemi-field with 500 msec asynchrony

Average of 6 runs Standard Deviations Shown





500 ms



500 ms



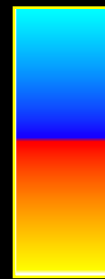
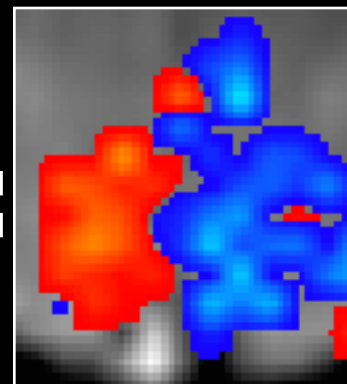
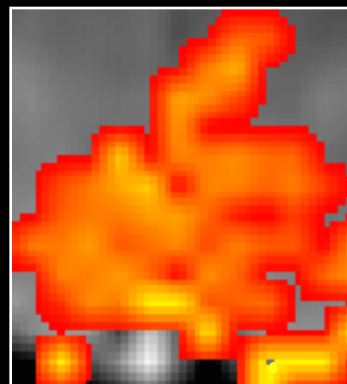
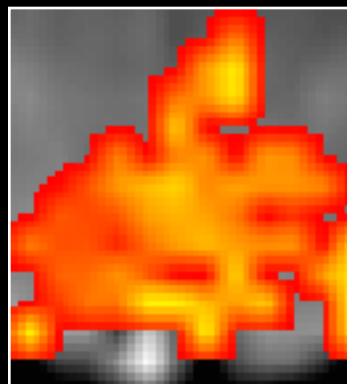
Right Hemifield

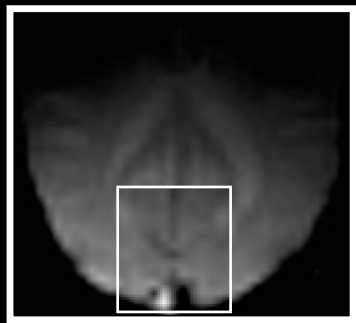
Left Hemifield

+ 2.5 s

0 s

- 2.5 s





250 ms



250 ms



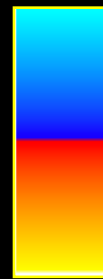
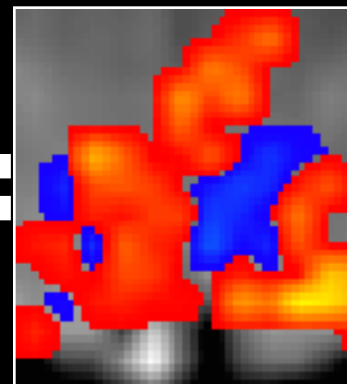
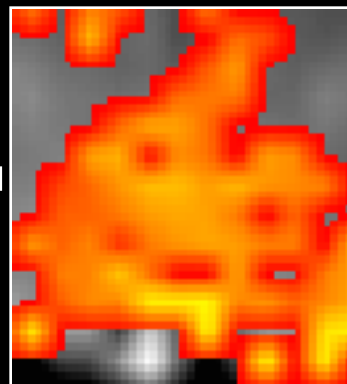
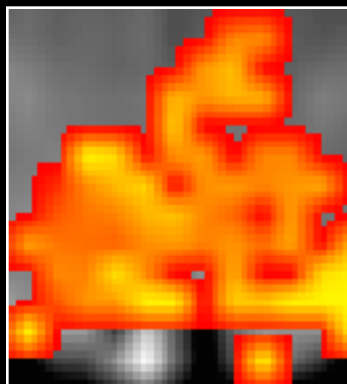
Right Hemifield

Left Hemifield

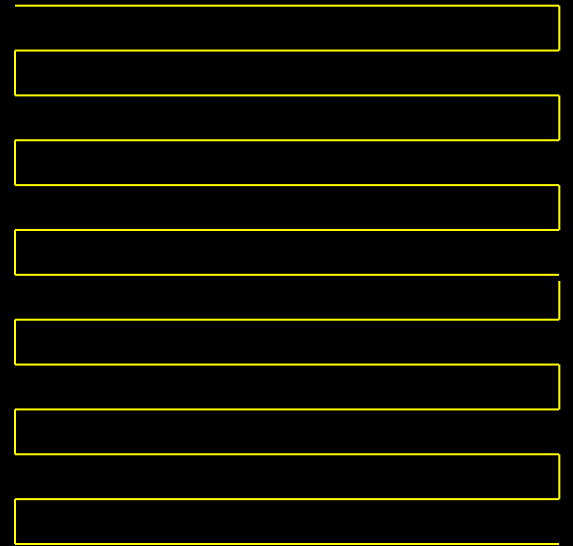
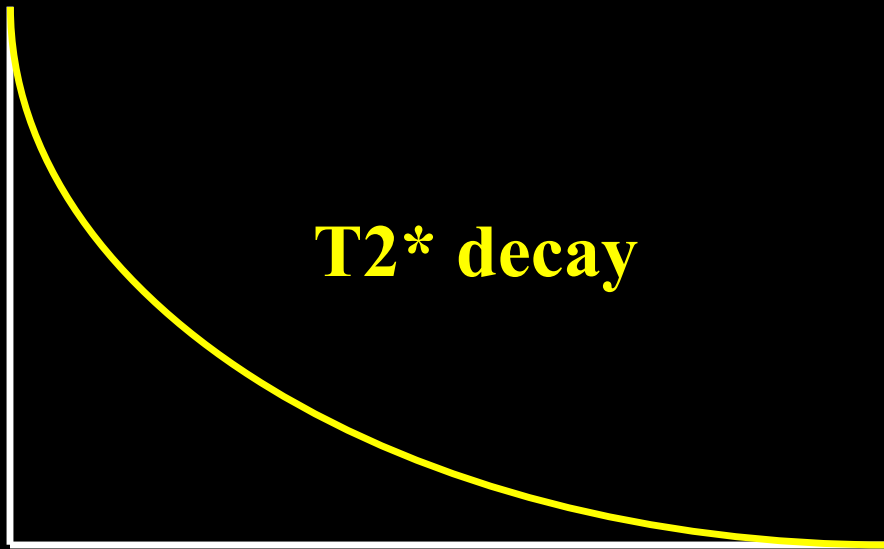
+ 2.5 s

0 s

- 2.5 s



Single Shot Imaging



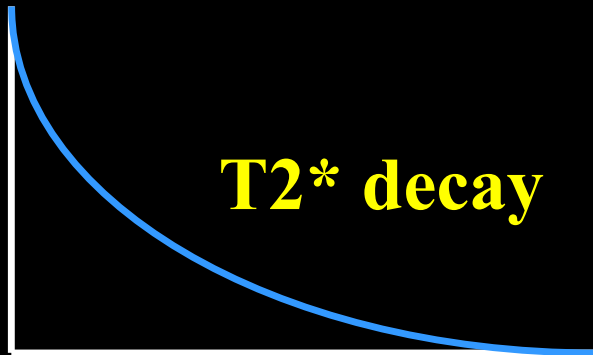
EPI Readout Window

≈ 20 to 40 ms

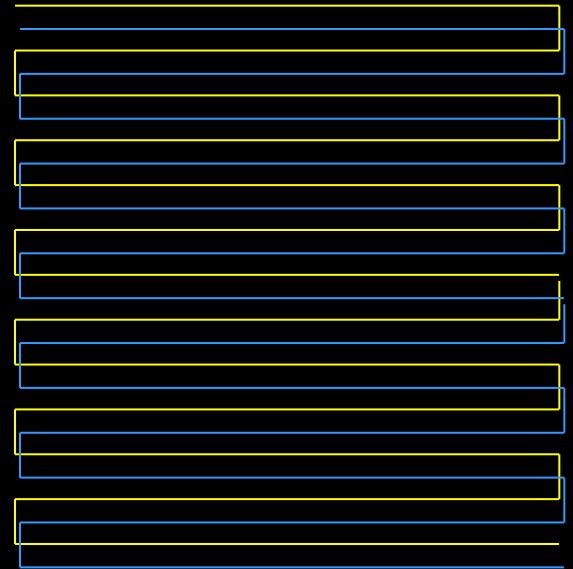
Multishot Imaging



EPI Window 1



EPI Window 2



Multi Shot EPI

Excitations
Matrix Size

1

64 x 64

2

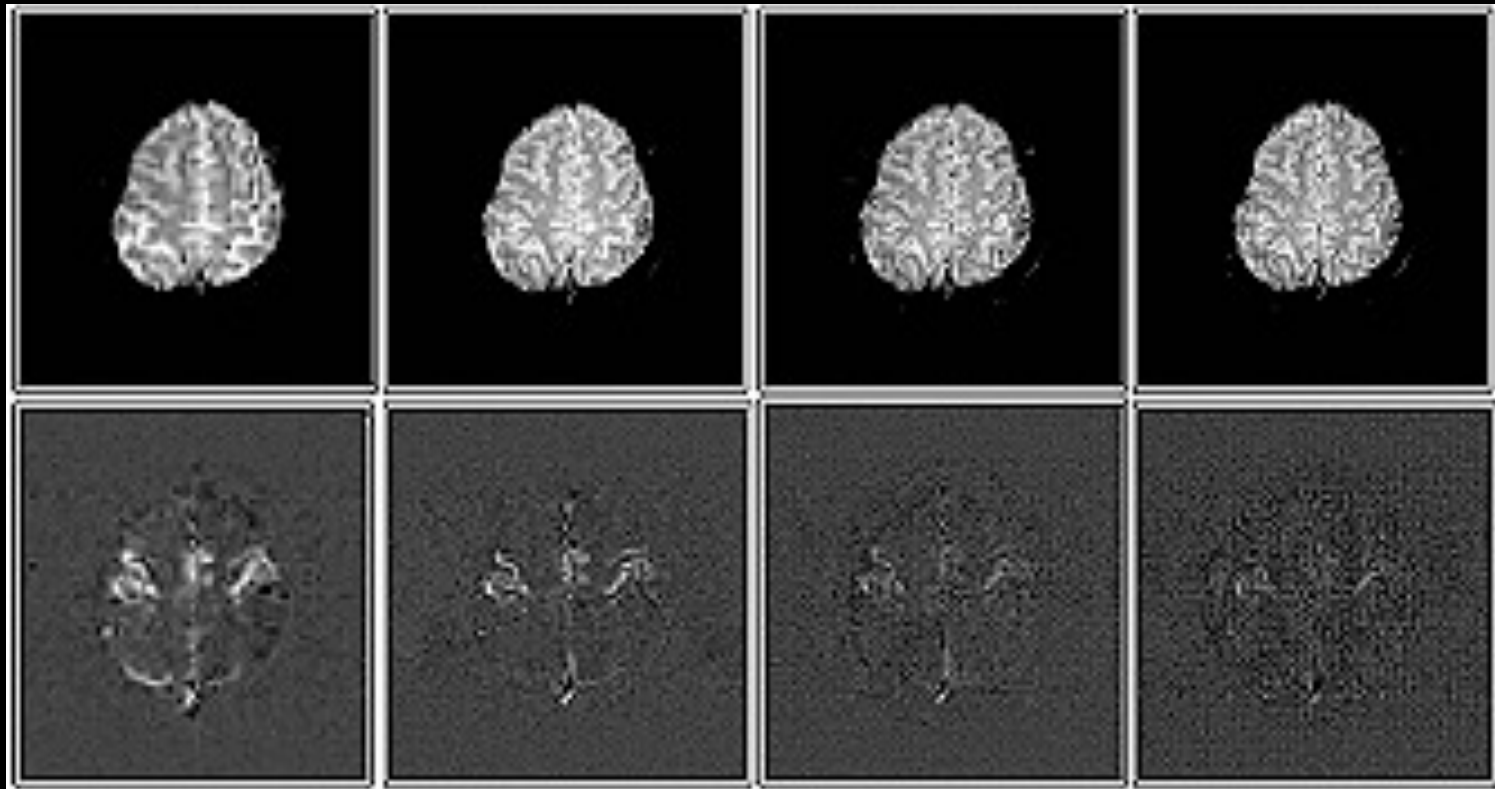
128 x 128

4

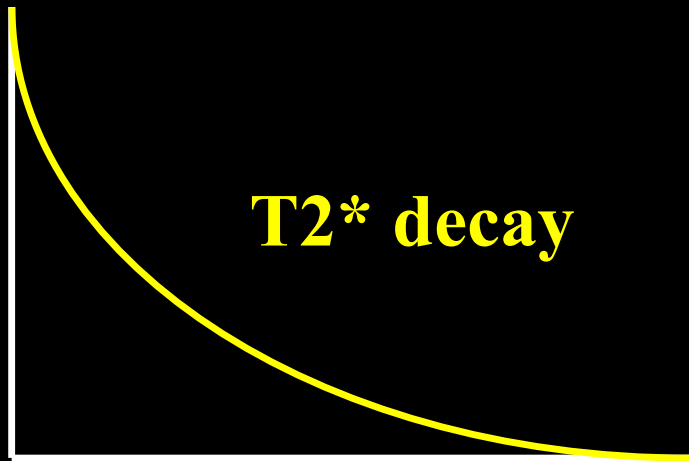
256 x 128

8

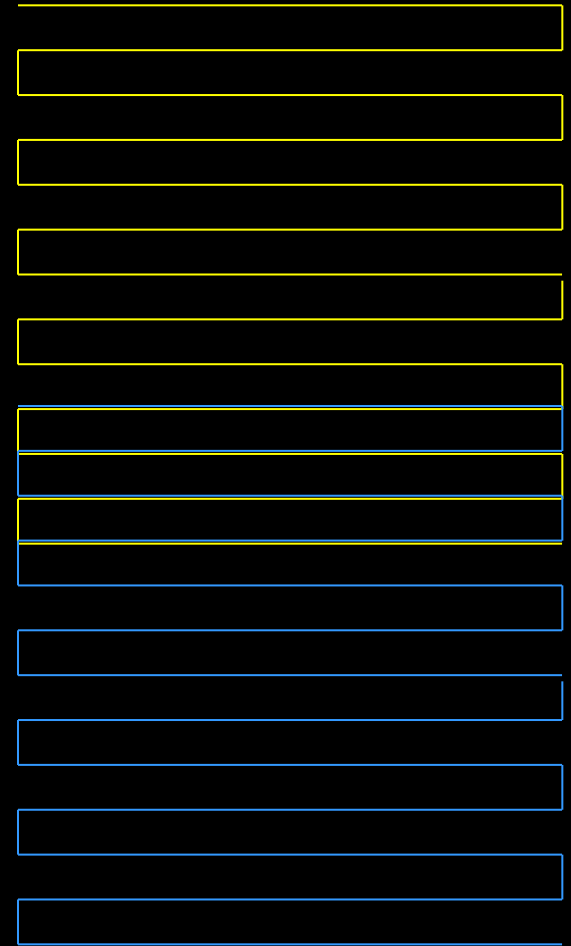
256



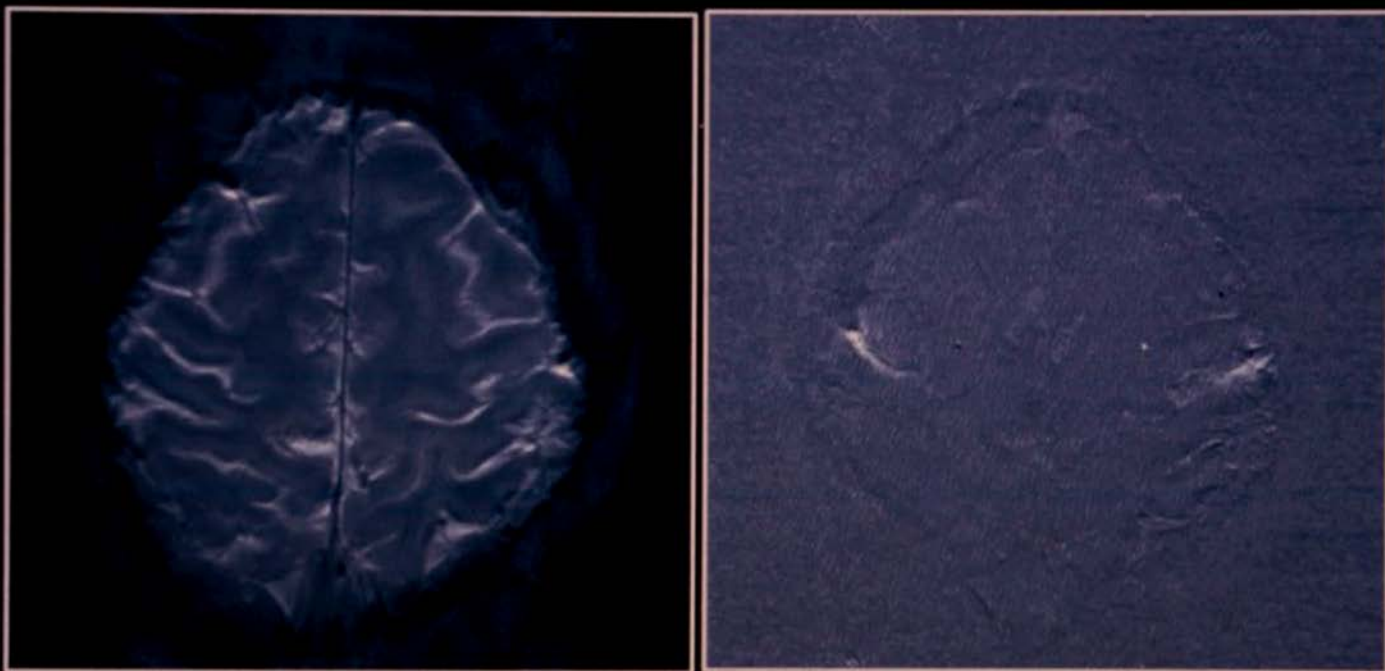
Partial k-space imaging



EPI Window



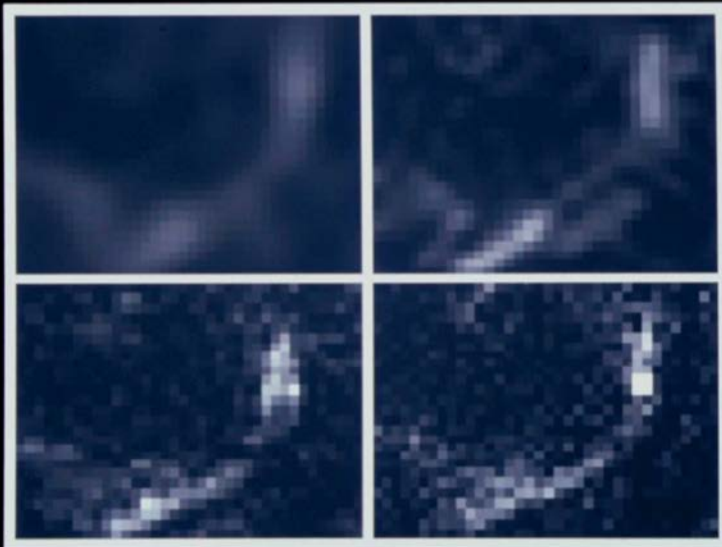
**Single - Shot EPI at 3T:
Half NEX, 256 x 256, 16 cm FOV**



Fractional Signal Change

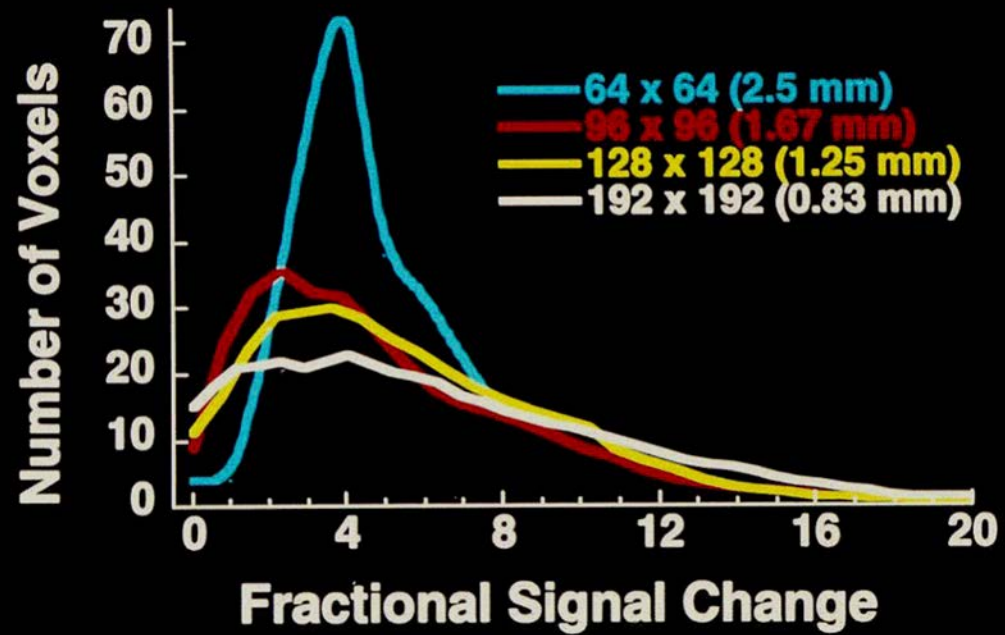
2.5 mm²

1.25 mm²

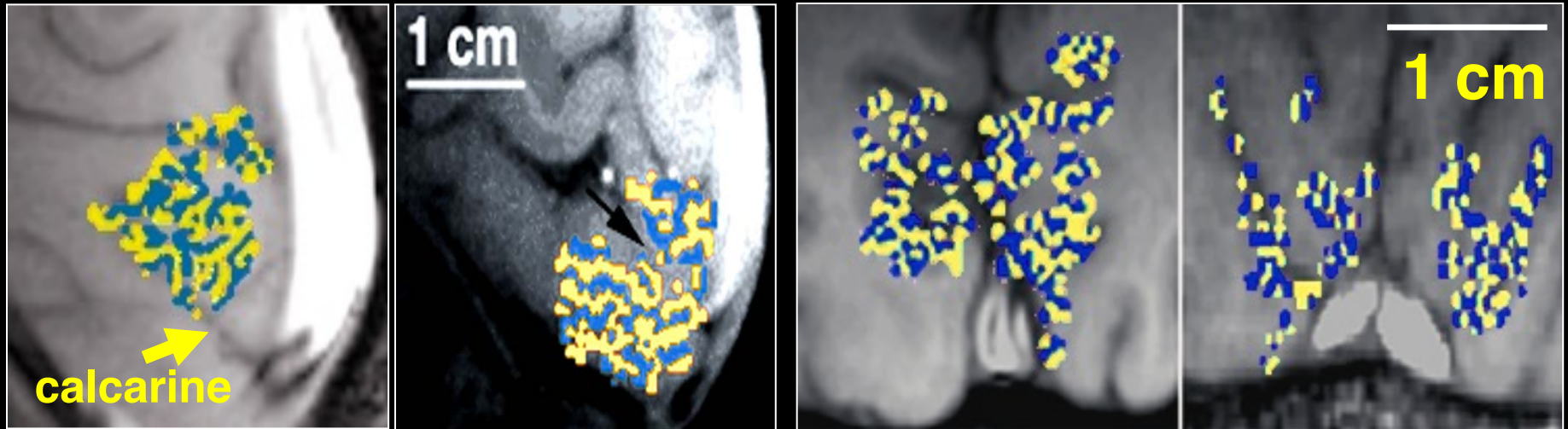


0.83 mm²

0.62 mm²



ODC Maps using fMRI



• Identical in size, orientation, and appearance to those obtained by optical imaging¹ and histology^{3,4}.

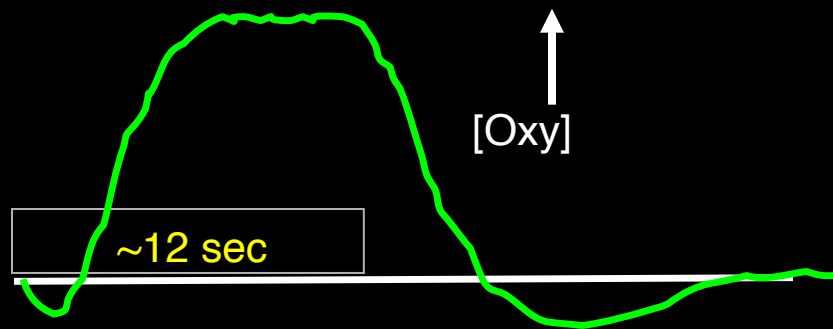
¹Malonek D, Grinvald A. *Science* 272, 551-4 (1996).

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

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

Why short is better than long

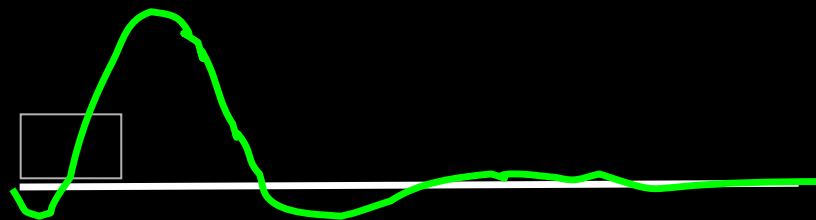
The vascular response to prolonged neural stimulation



It is argued that fMRI cannot achieve submillimeter functional resolution because a saturated hyperoxic vascular response to neural activity spreads over many millimeters^{1,2}.

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

The vascular response to brief neural stimulation



¹Malonek D, Grinvald A. Science 272, 551-4 (1996).

²Kim 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

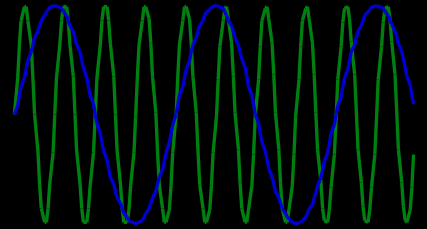
Event-Related Designs

Free Behavior Designs

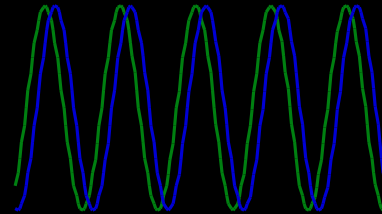
Neuronal Activation Input Strategies

1. Block Design

2. Frequency Encoding

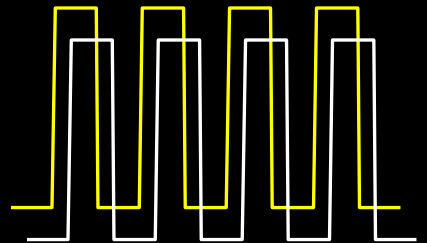


3. Phase Encoding



4. Single Event

5. Orthogonal Block Design

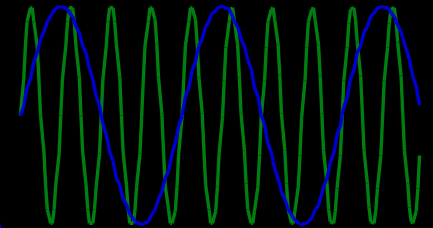


6. Free Behavior Design.

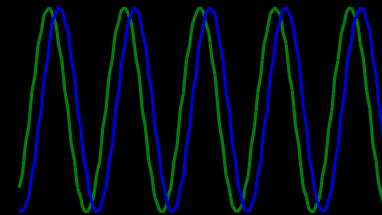
Neuronal Activation Input Strategies

1. Block Design

2. Frequency Encoding

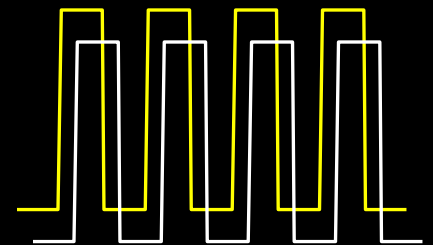


3. Phase Encoding



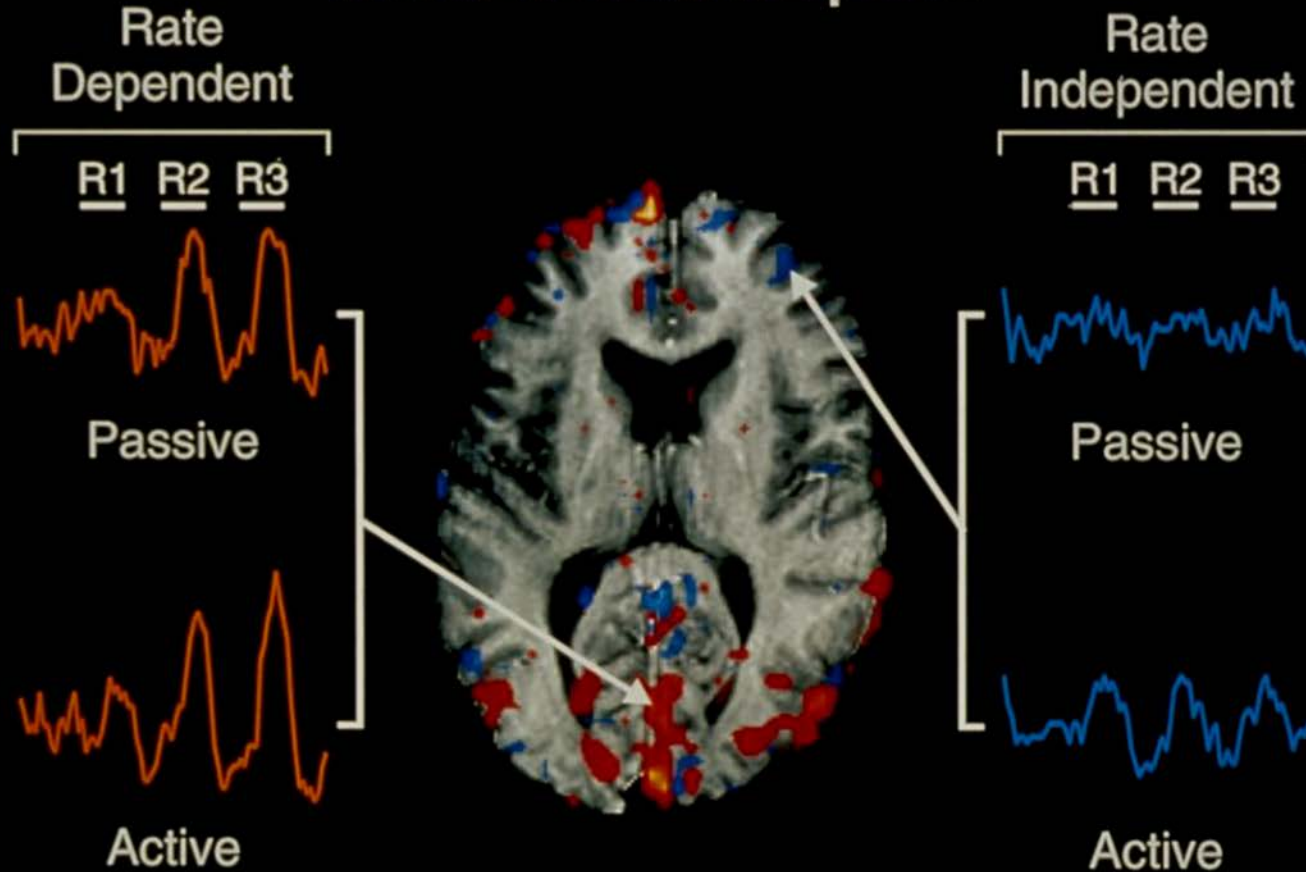
4. Single Event

5. Orthogonal Block Design



6. Free Behavior Design.

Both the Task and Presentation Rate Affect the fMRI Response

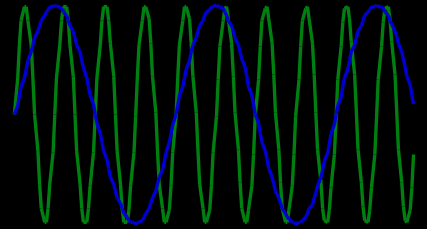


DeYoe et al.

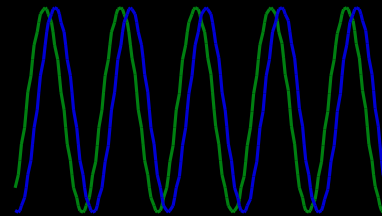
Neuronal Activation Input Strategies

1. Block Design

2. Frequency Encoding

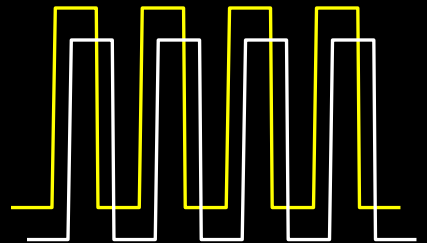


3. Phase Encoding

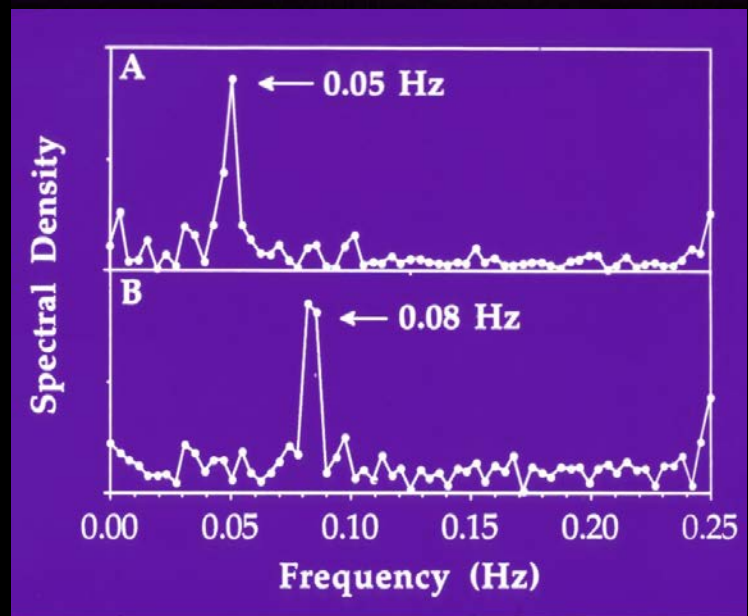
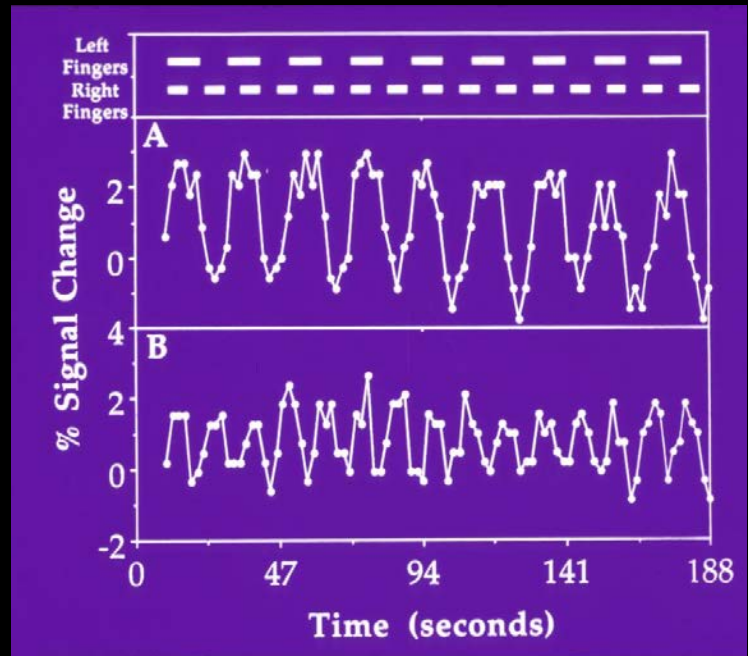
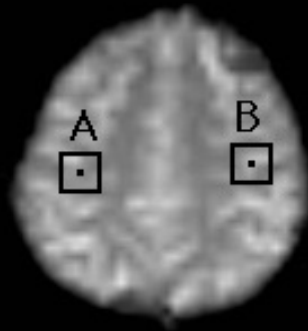


4. Single Event

5. Orthogonal Block Design



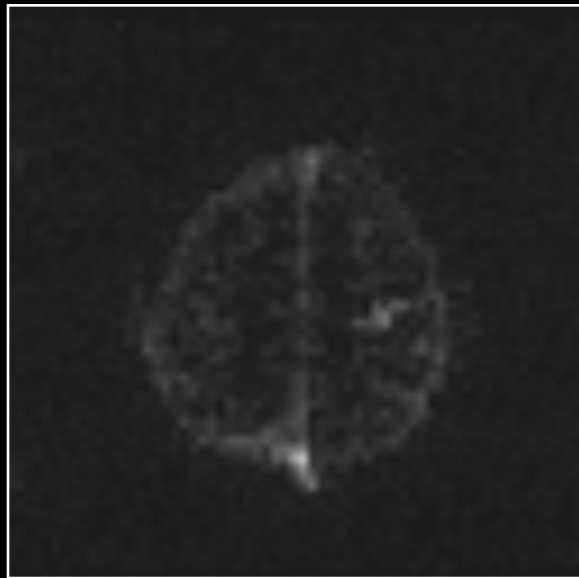
6. Free Behavior Design.



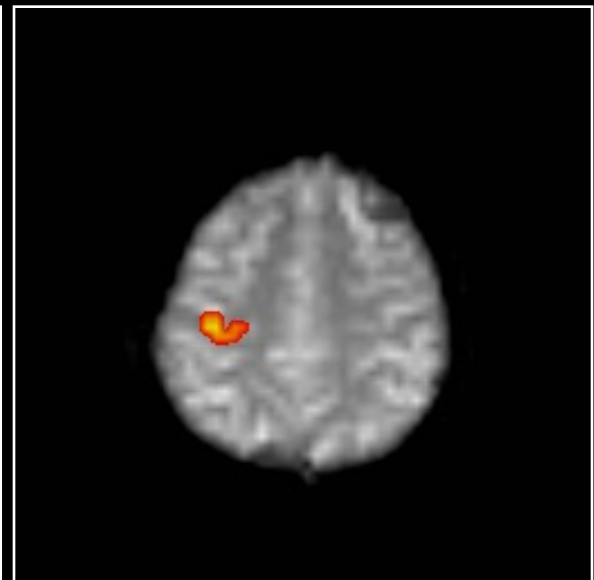
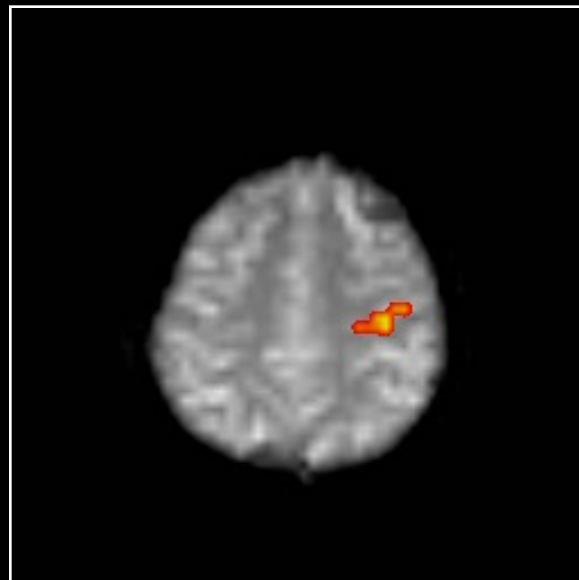
0.08 Hz

0.05 Hz

**spectral
density**



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



Neuronal Activation Input Strategies

1. Block Design

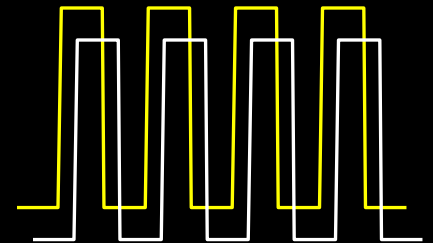
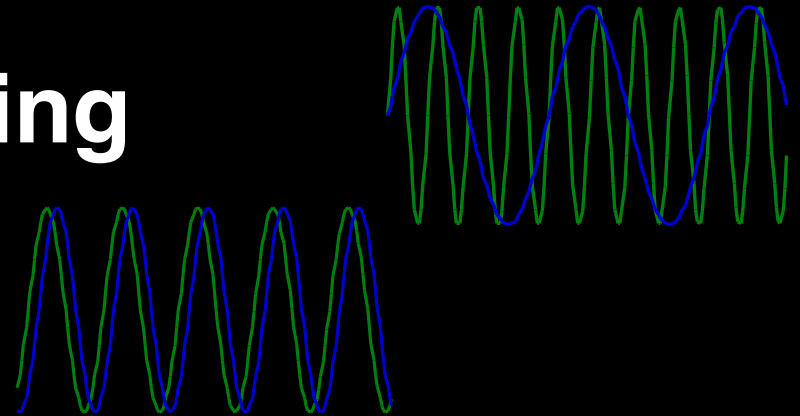
2. Frequency Encoding

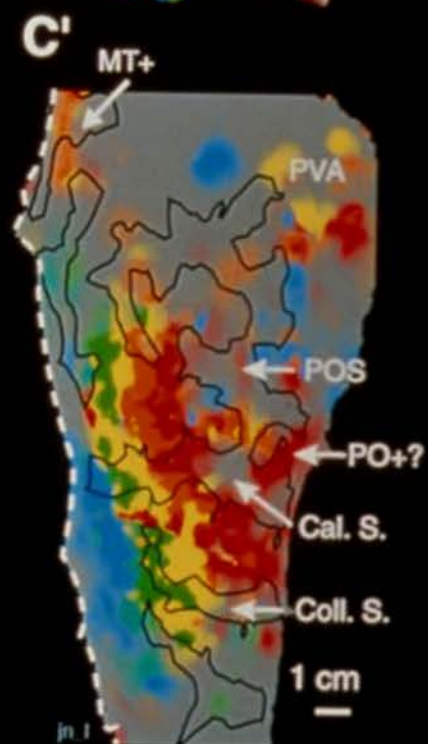
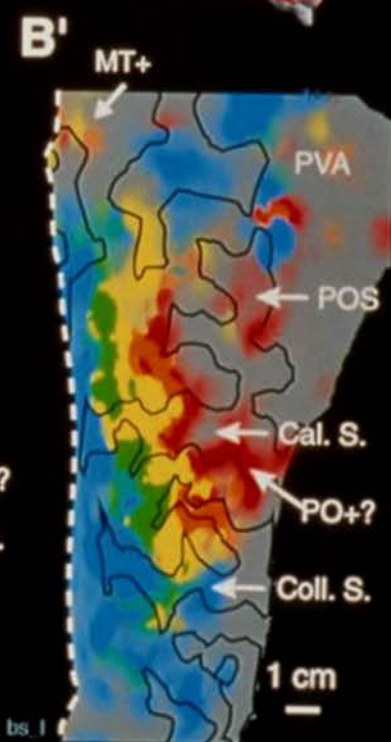
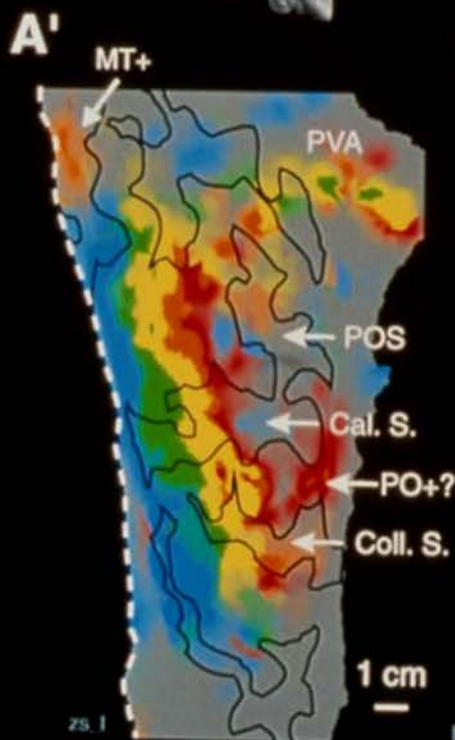
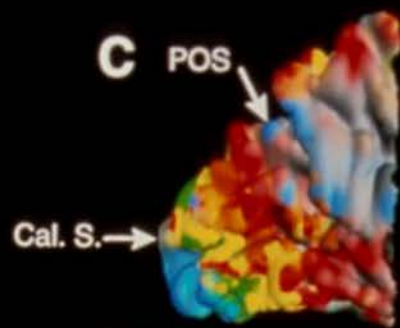
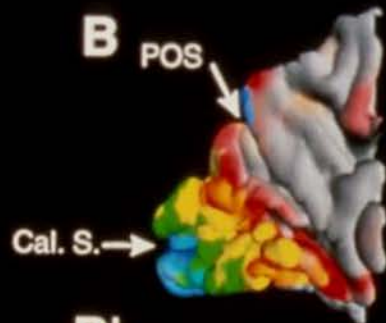
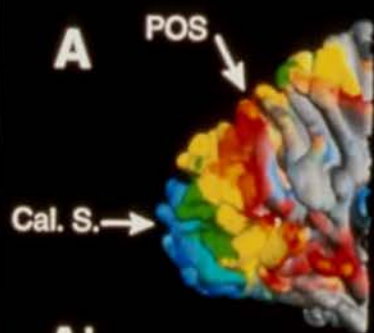
3. Phase Encoding

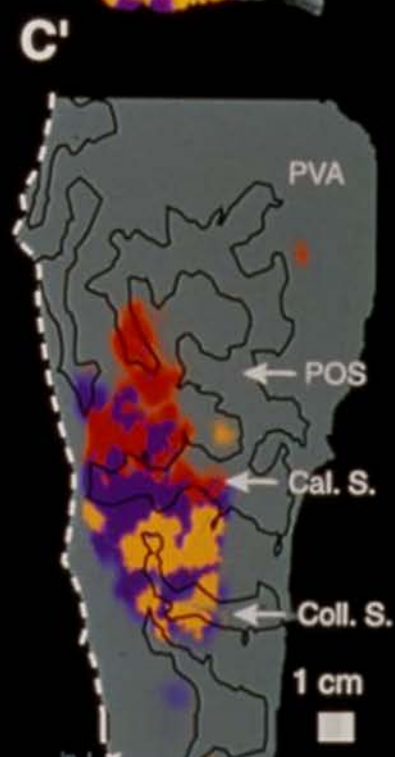
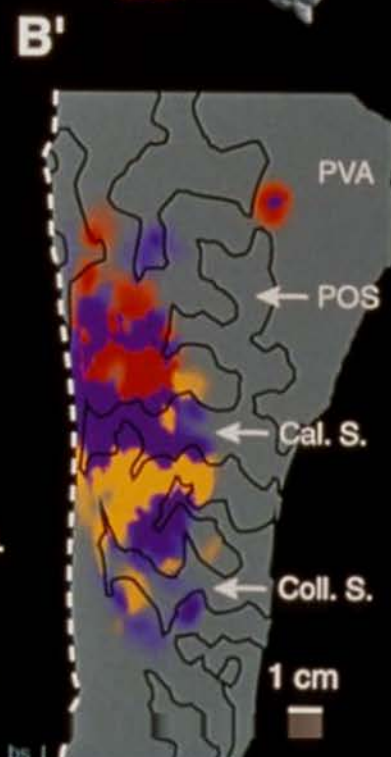
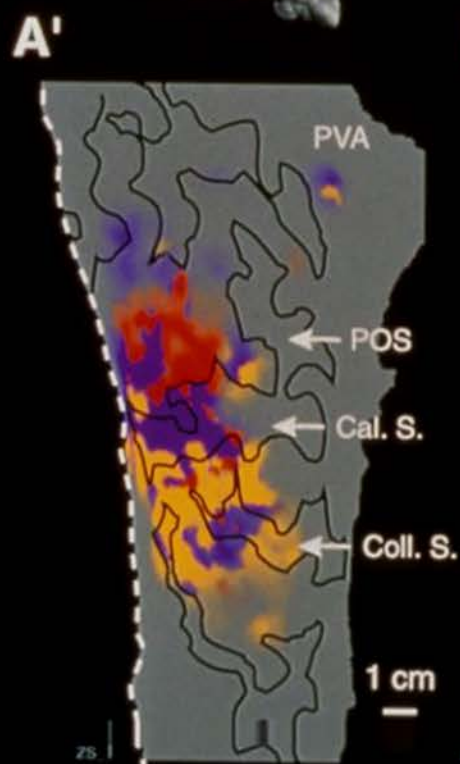
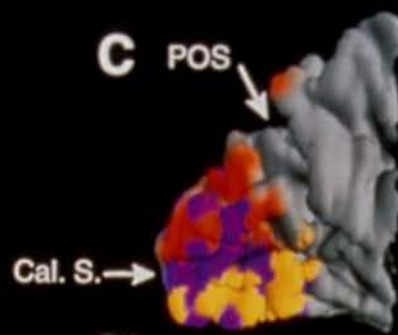
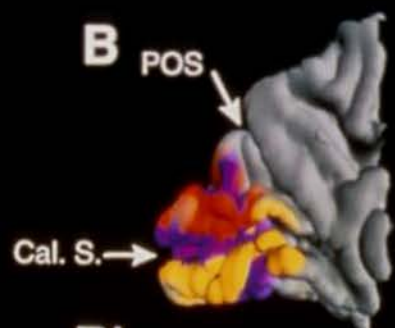
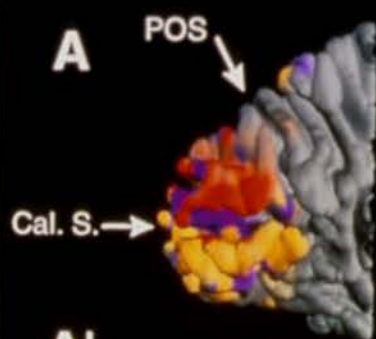
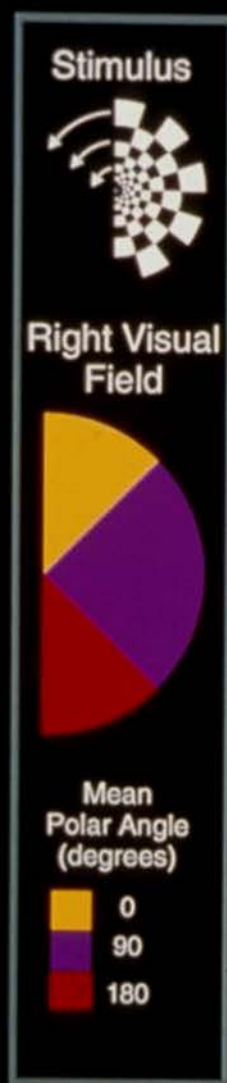
4. Single Event

5. Orthogonal Block Design

6. Free Behavior Design.



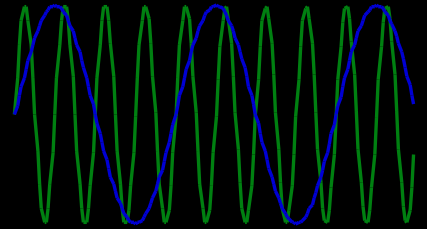




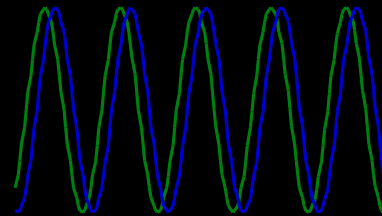
Neuronal Activation Input Strategies

1. Block Design

2. Frequency Encoding

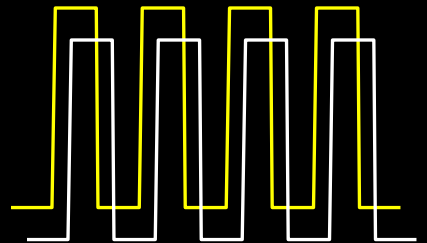


3. Phase Encoding



4. Single Event

5. Orthogonal Block Design

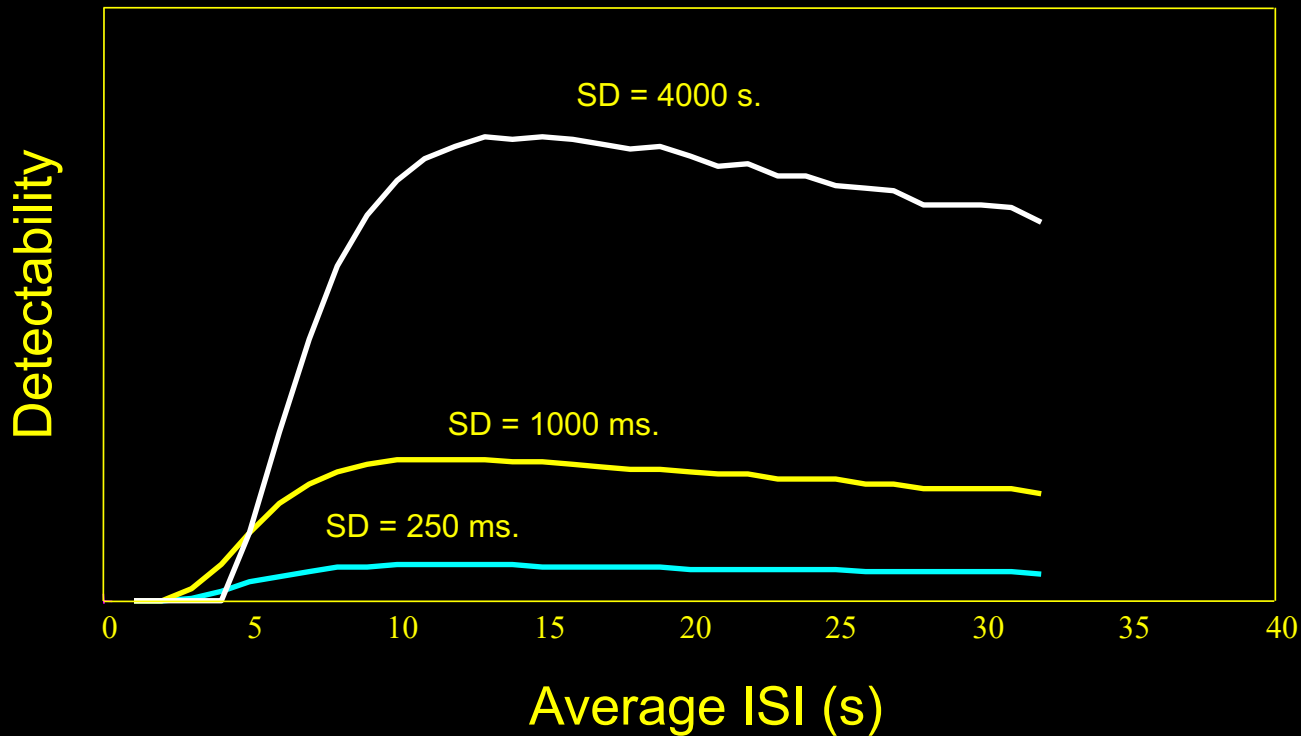
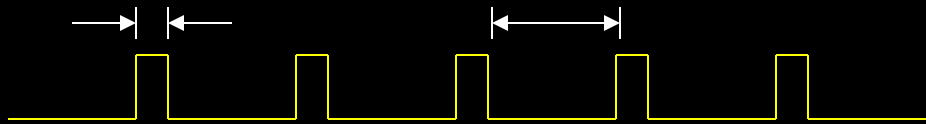


6. Free Behavior Design.

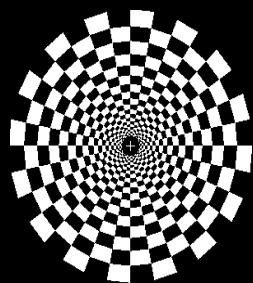
Detectability – constant ISI

SD – stimulus duration

ISI – inter-stimulus interval

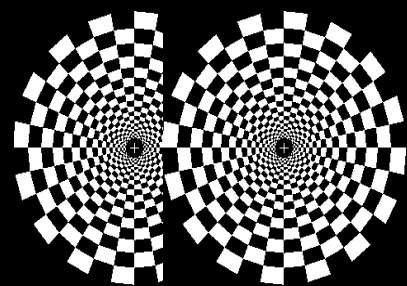


Visual Activation Paradigm: 1 , 2, & 3 Trials



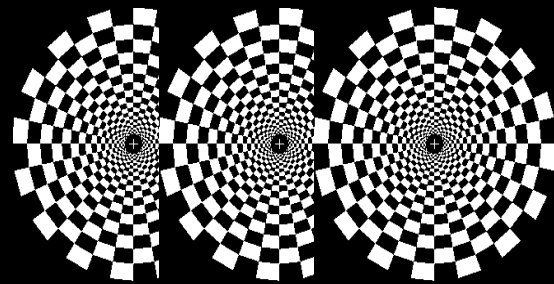
0 sec

20 sec



0 sec 2 sec

20 sec

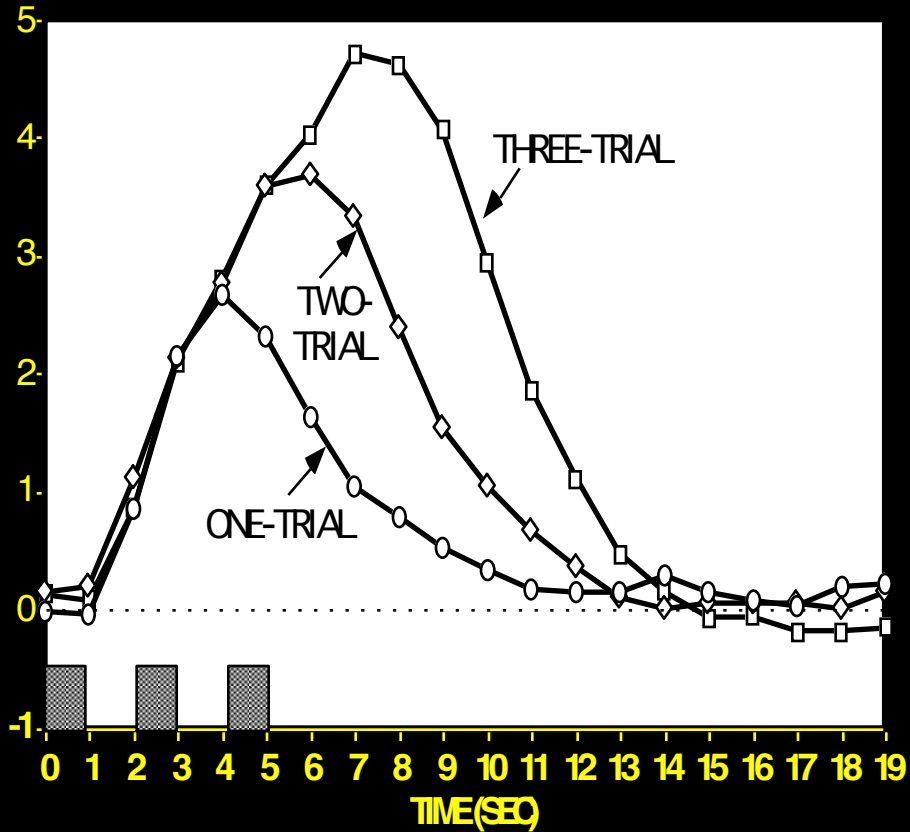


0 sec 2 sec 4 sec

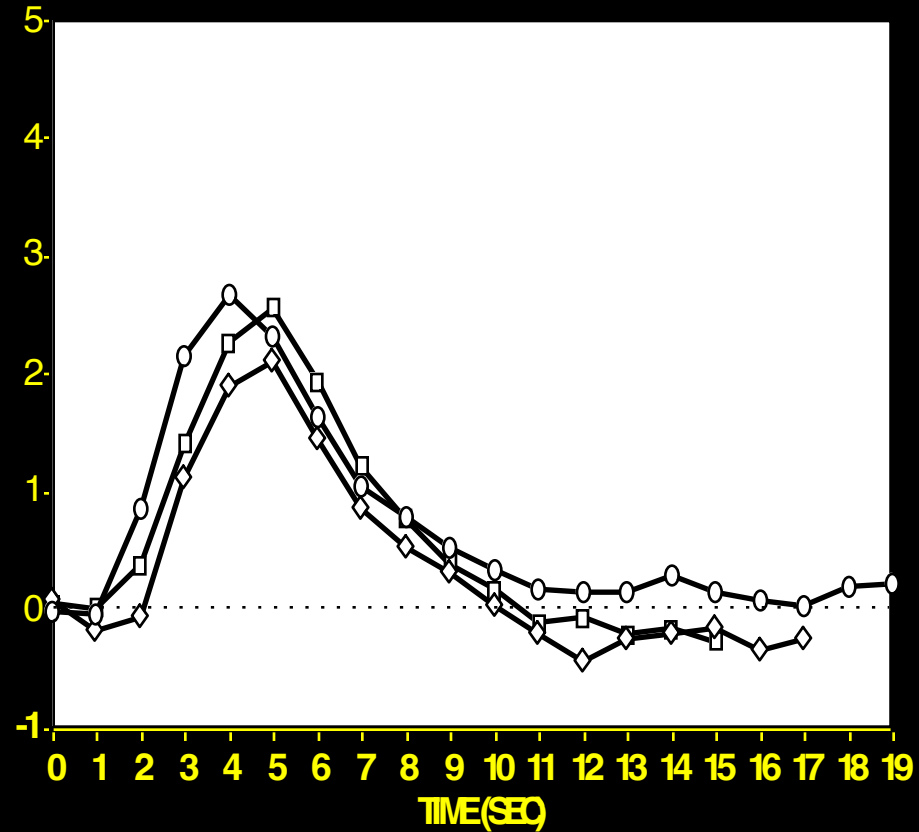
20 sec

Response to Multiple Trials: Subject RW

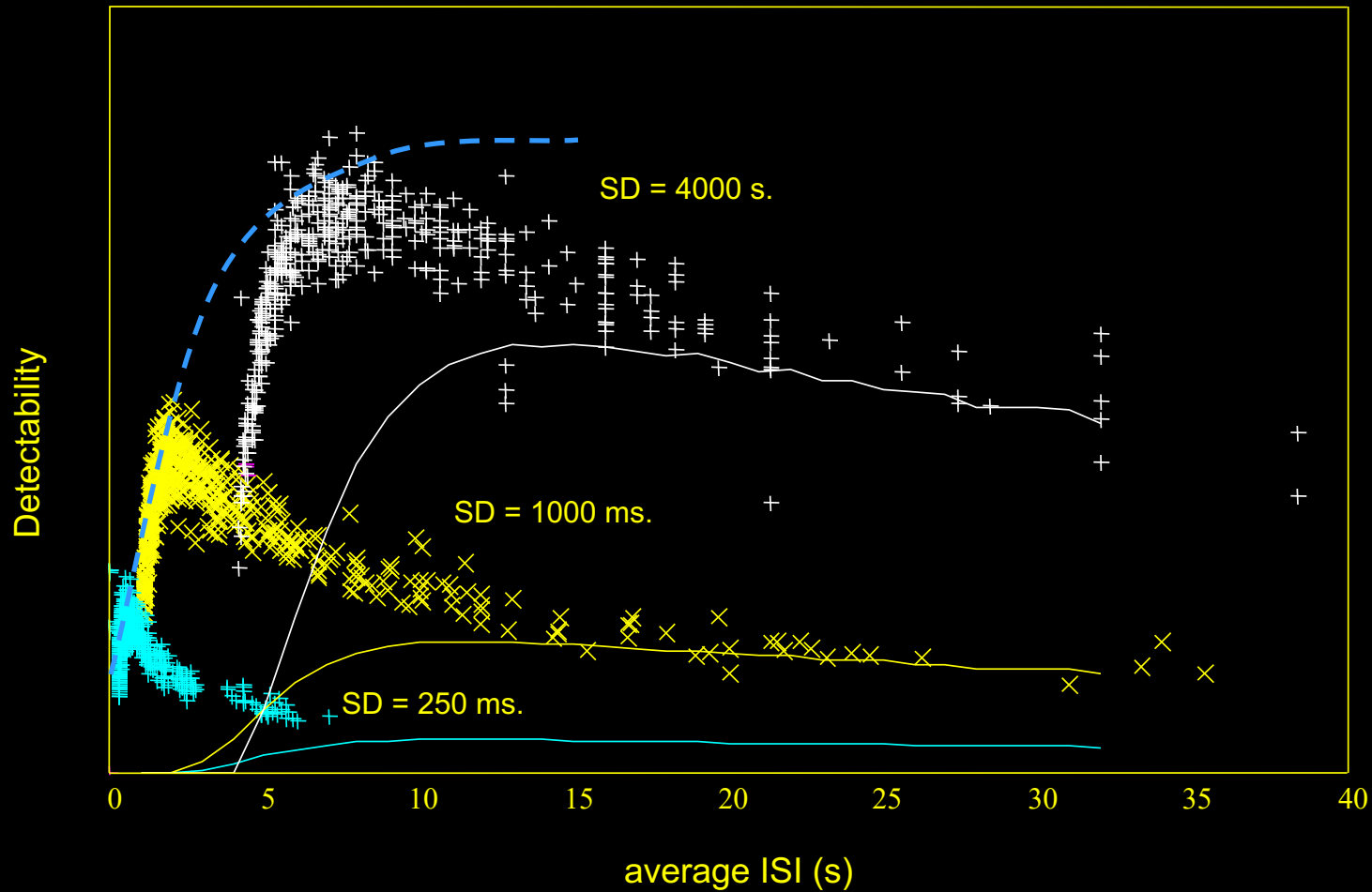
RAW DATA



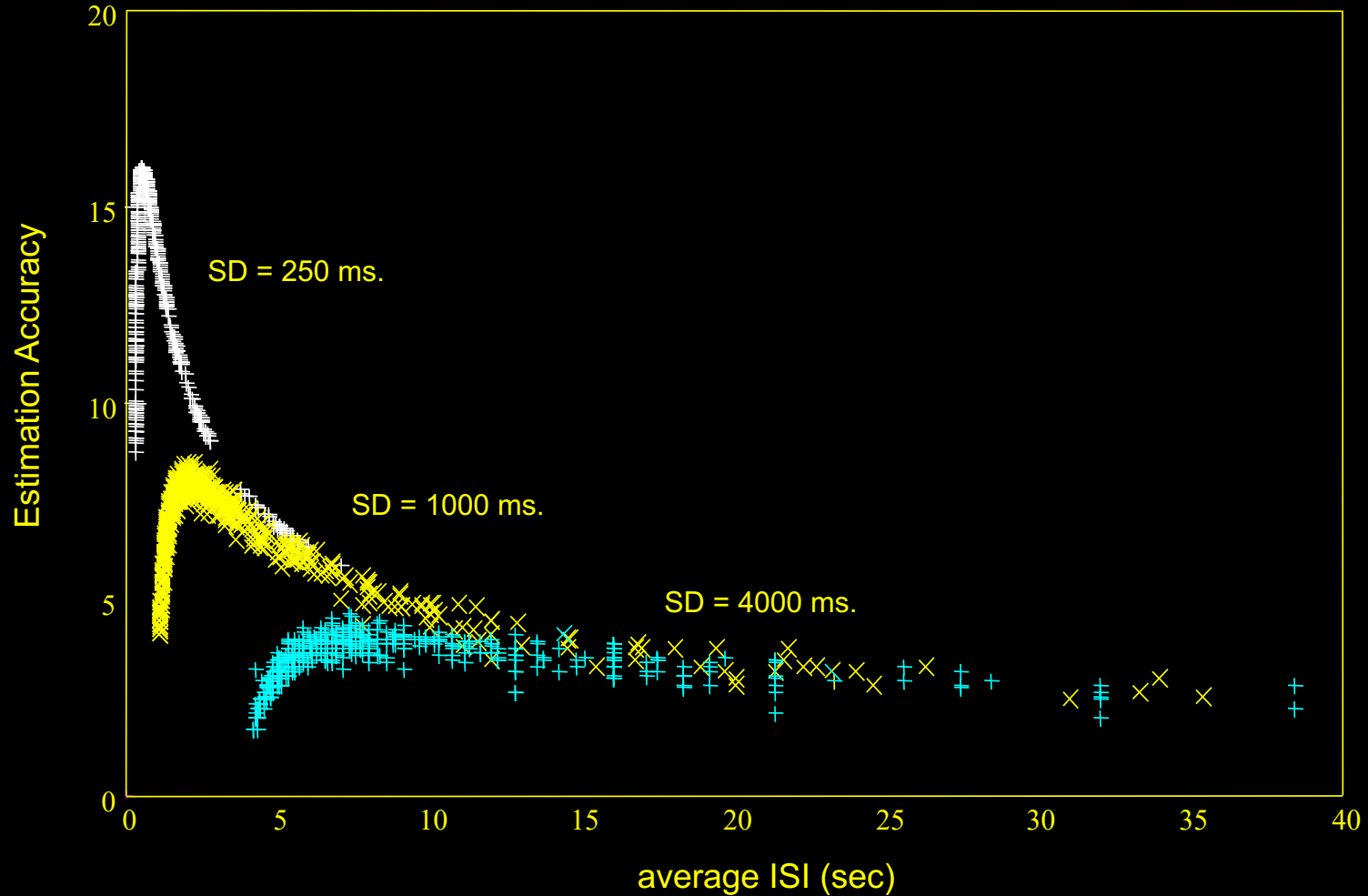
ESTIMATED RESPONSES



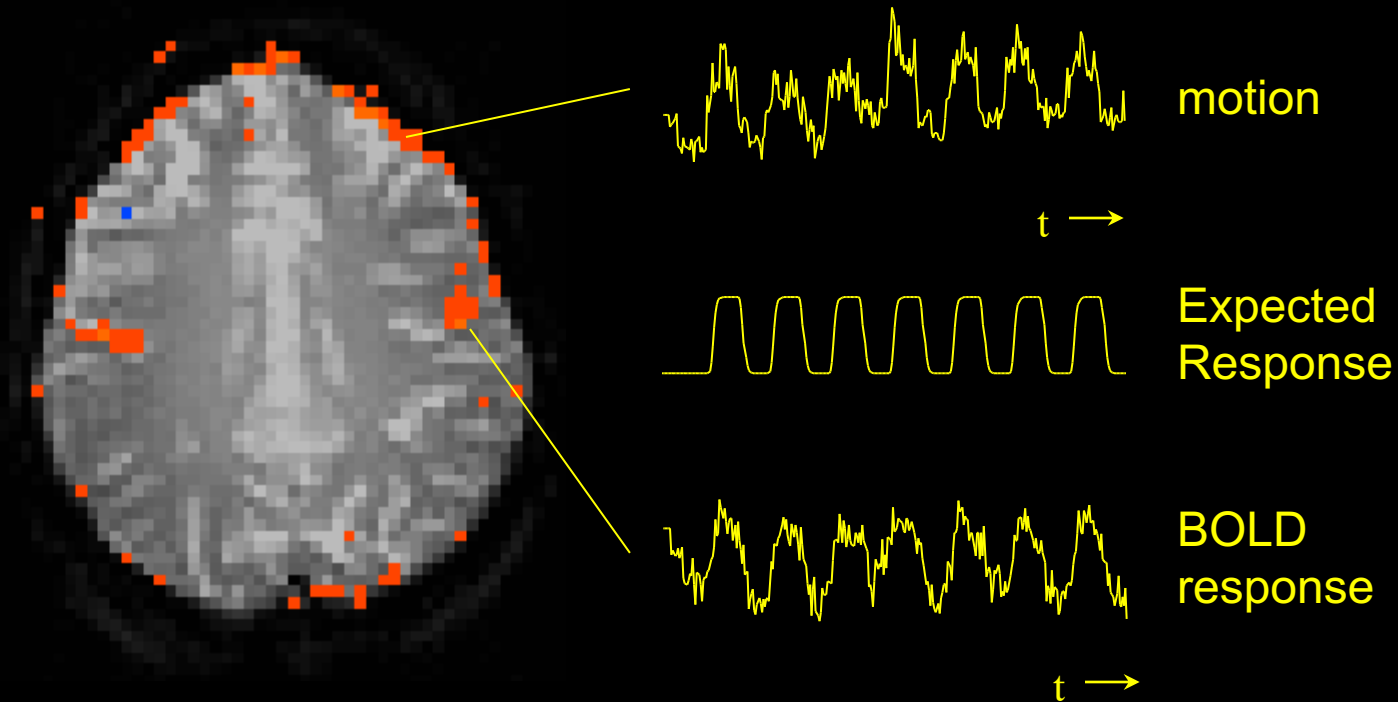
Detectability vs. Average ISI



Estimation accuracy vs. average ISI

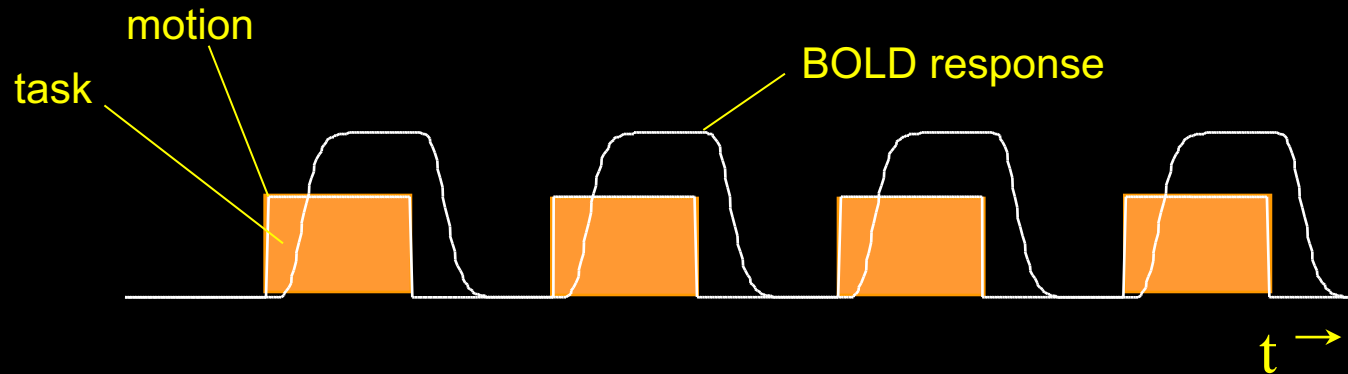


Speaking - Blocked Trial

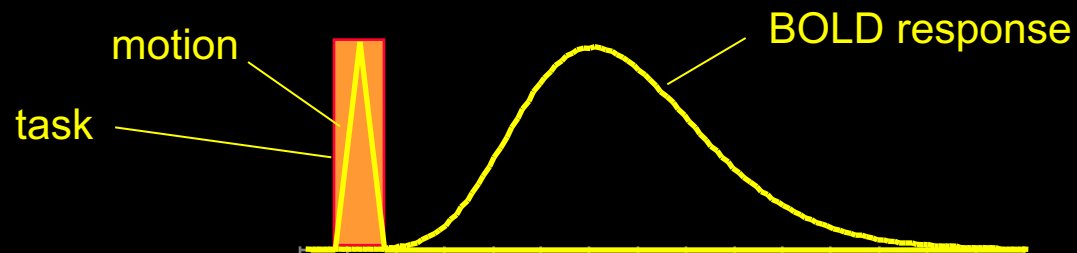


fMRI during tasks that involve brief motion

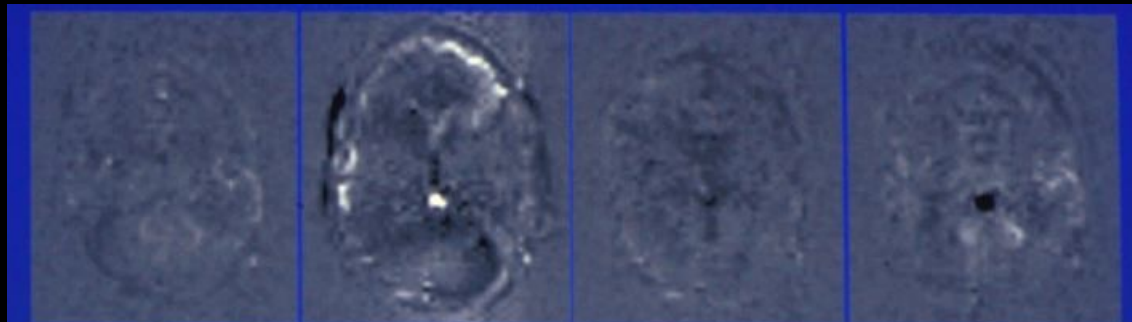
Blocked Design



Event-Related Design



Overt Word Production



2

3

4

5

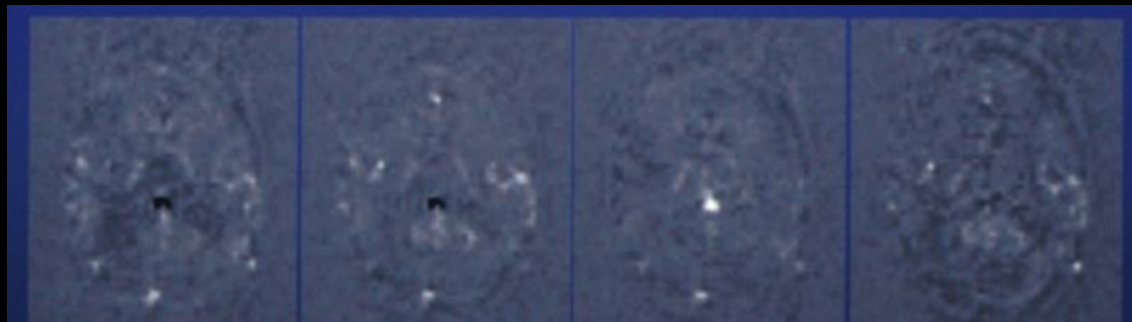


6

7

8

9



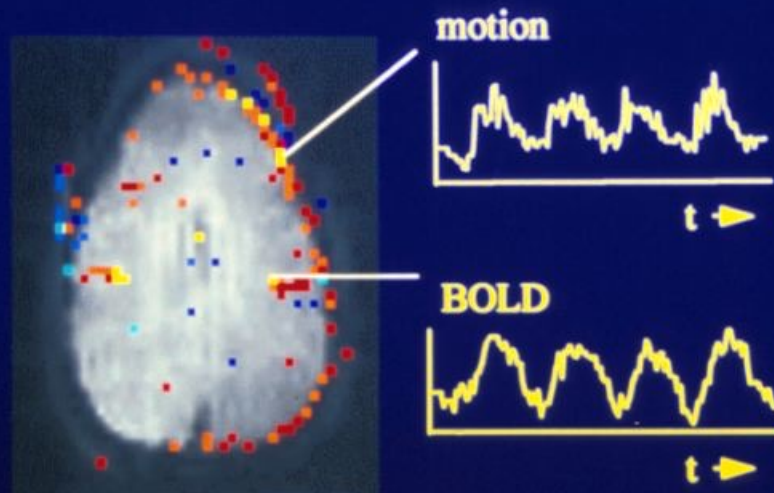
10

11

12

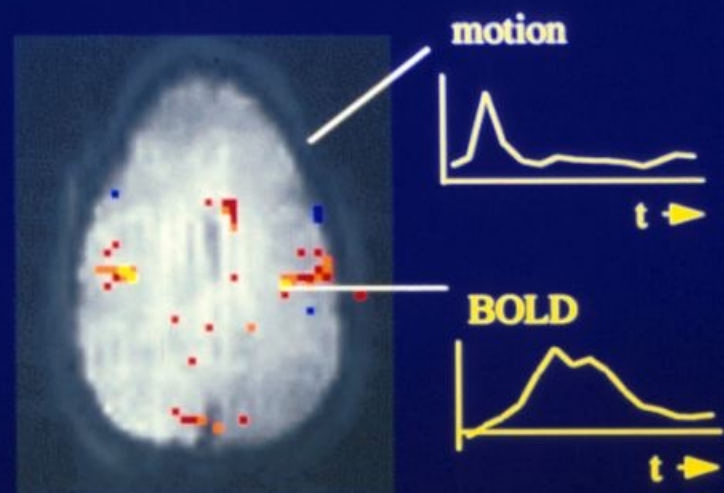
13

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



“block-trial” paradigm

Motion induced signal changes resemble functional (BOLD) signal changes

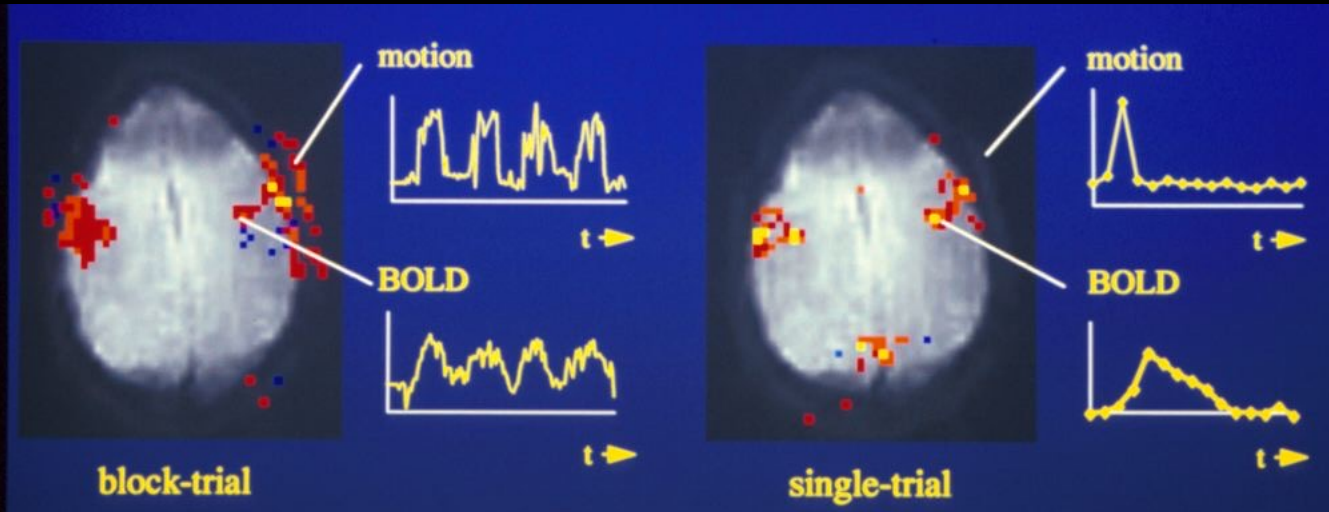


“single-trial” paradigm

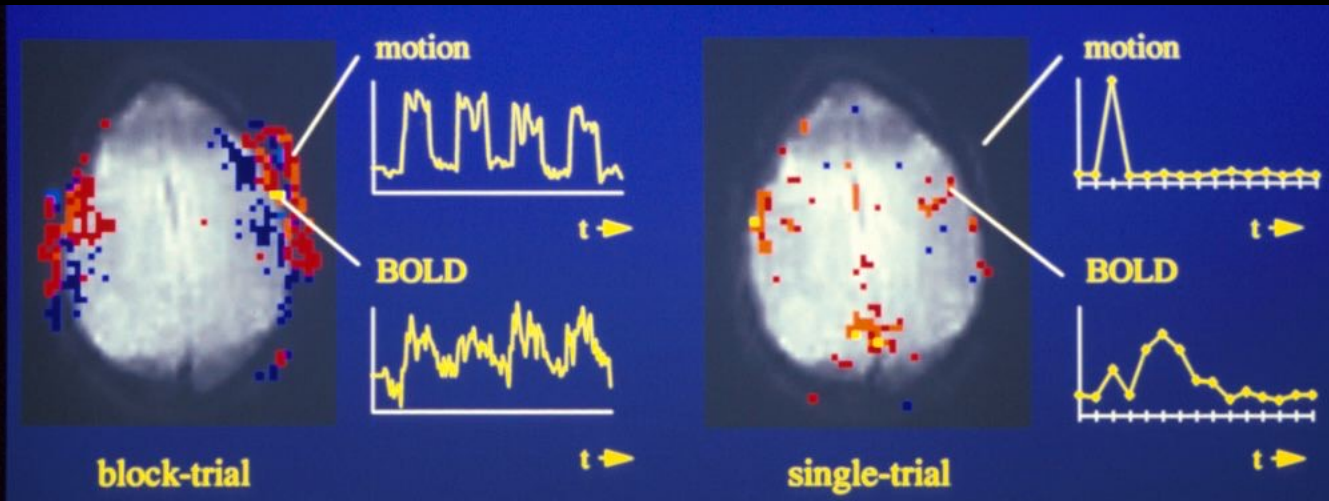
Motion induced and BOLD signal changes are separated in time

R.M. Birn, et al.

Tongue Movement

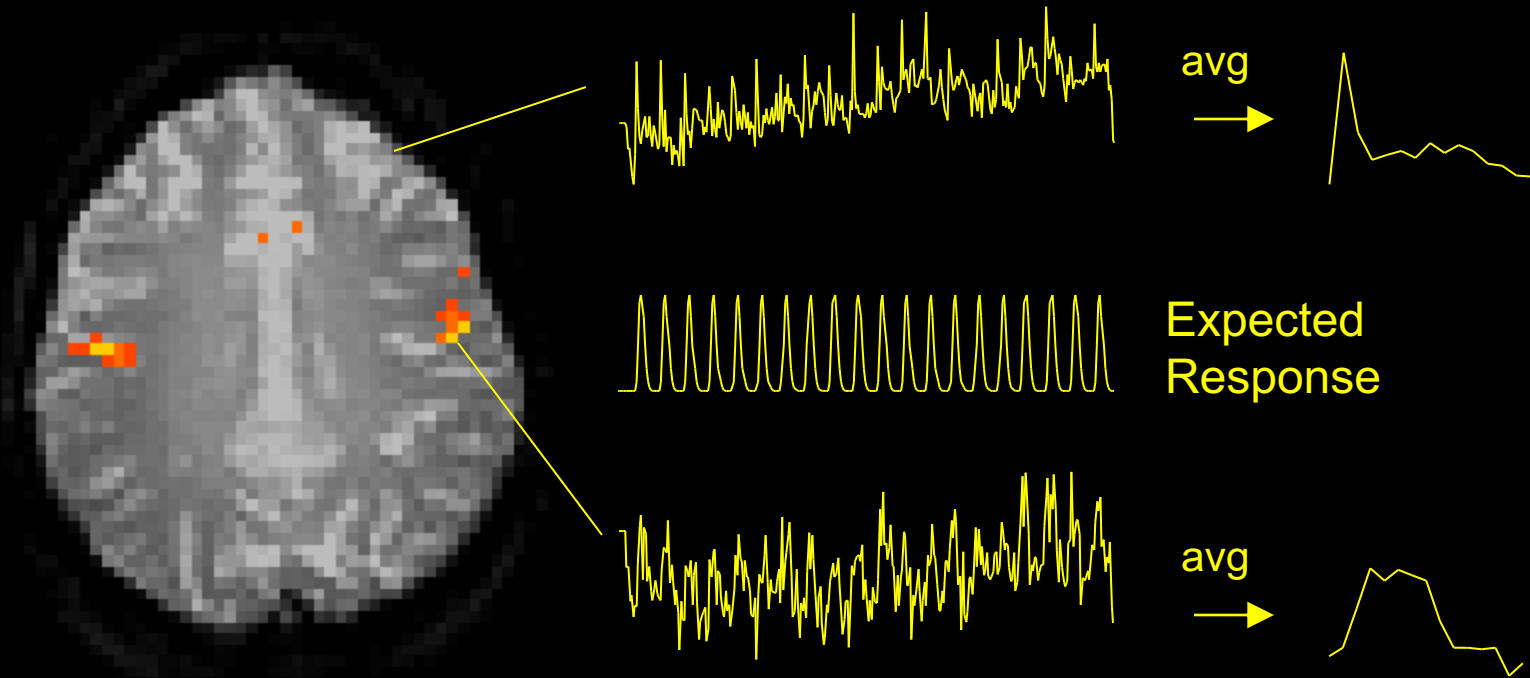


Jaw Clenching

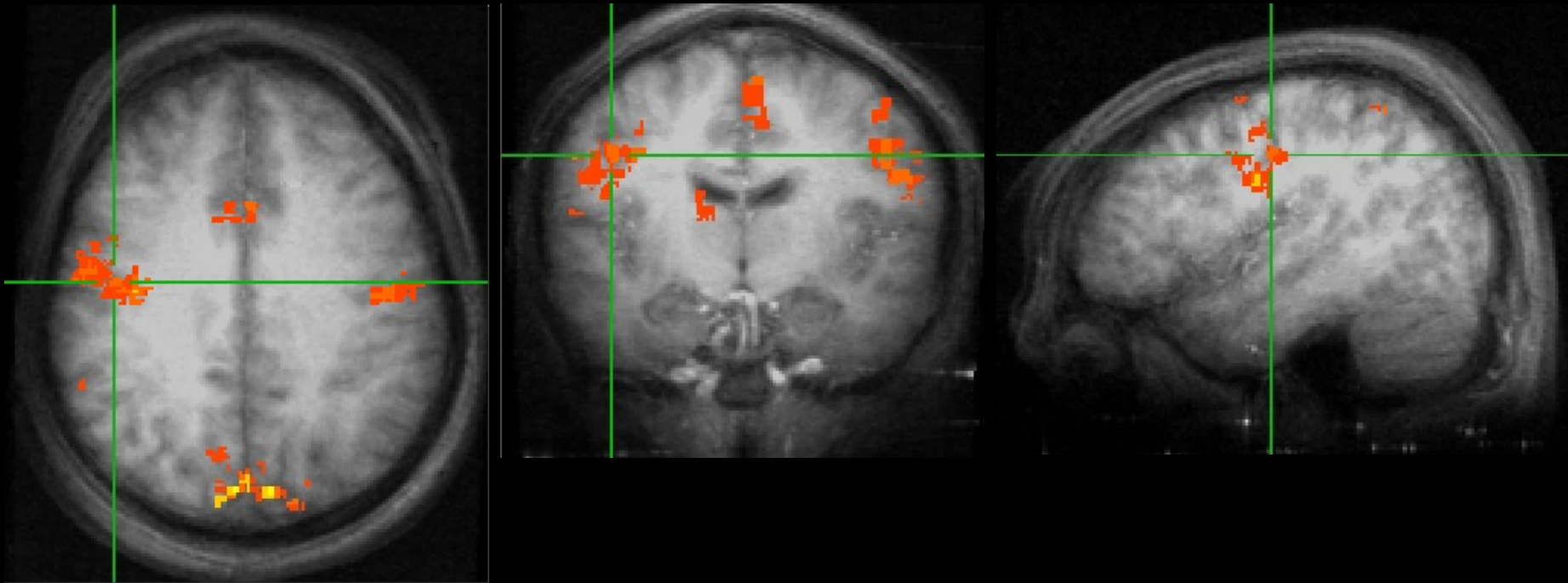


Constant ISI

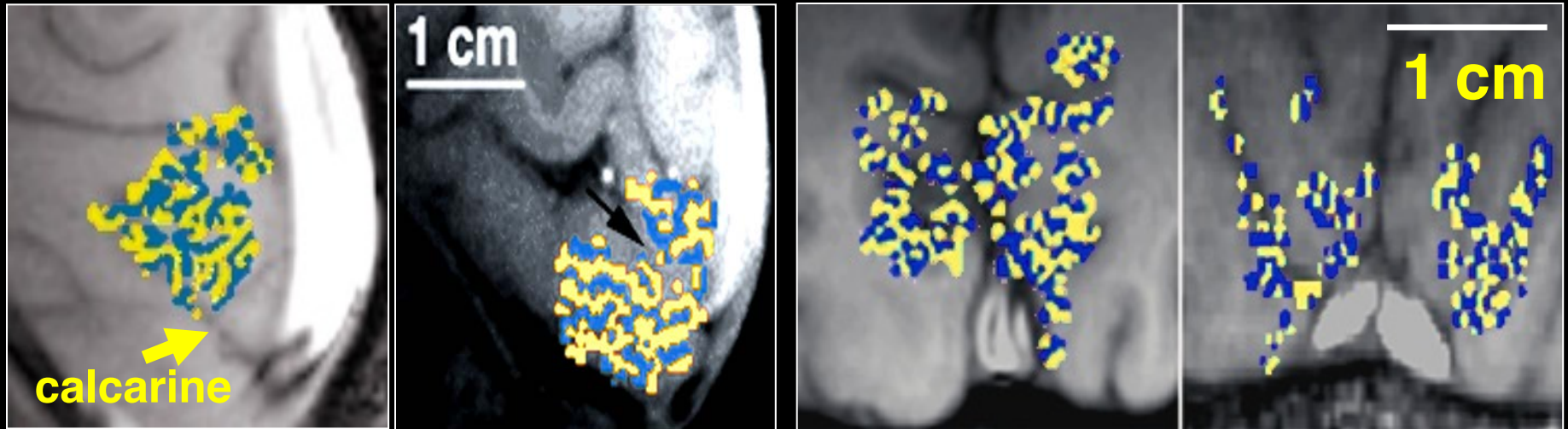
Speaking - ER-fMRI



Swallowing - Event-Related



ODC Maps using fMRI



- Identical in size, orientation, and appearance to those obtained by optical imaging¹ and histology^{3,4}.

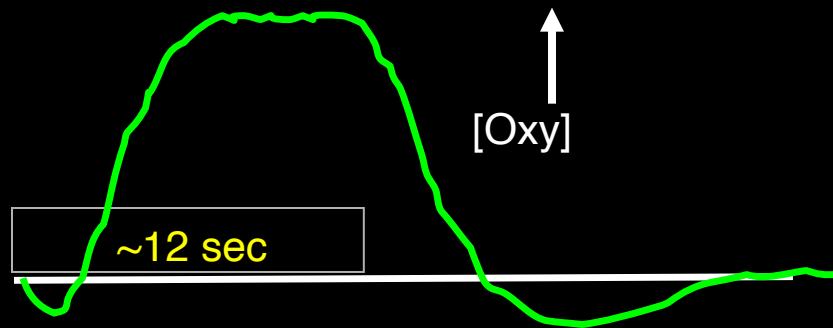
¹Malonek D, Grinvald A. *Science* 272, 551-4 (1996).

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

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

Why short is better than long

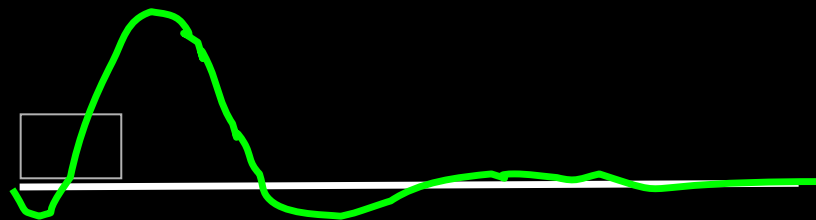
The vascular response to prolonged neural stimulation



It is argued that fMRI cannot achieve submillimeter functional resolution because a saturated hyperoxic vascular response to neural activity spreads over many millimeters^{1,2}.

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

The vascular response to brief neural stimulation



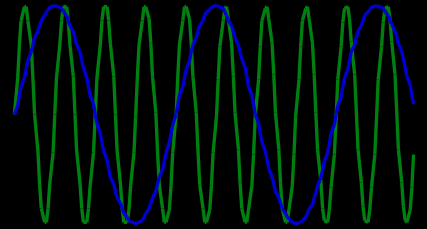
¹Malonek D, Grinvald A. Science 272, 551-4 (1996).

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

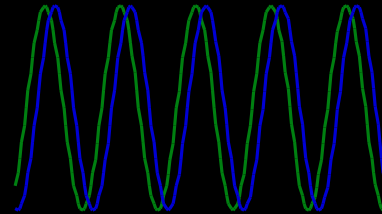
Neuronal Activation Input Strategies

1. Block Design

2. Frequency Encoding

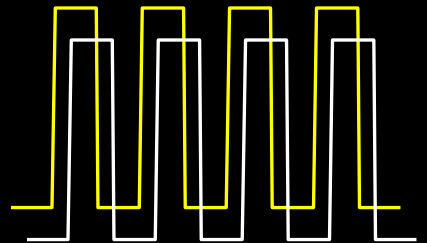


3. Phase Encoding



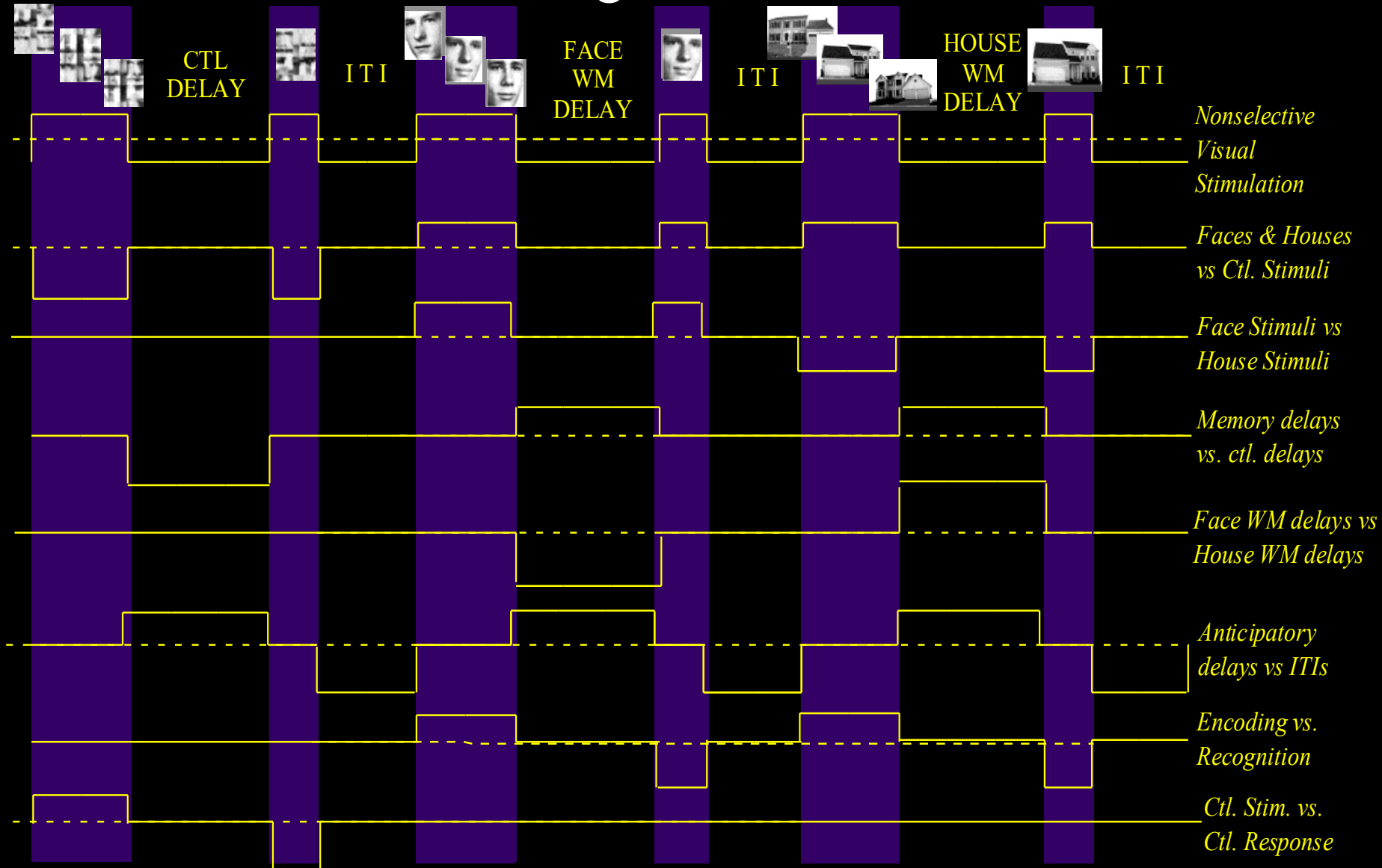
4. Single Event

5. Orthogonal Block Design



6. Free Behavior Design.

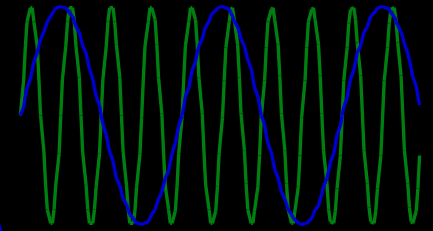
Example of a Set of Orthogonal Contrasts for Multiple Regression



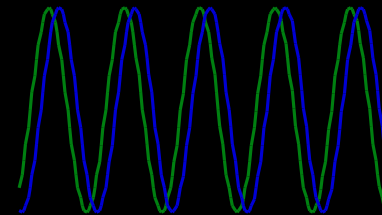
Neuronal Activation Input Strategies

1. Block Design

2. Frequency Encoding

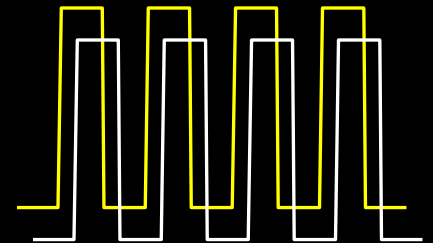


3. Phase Encoding



4. Single Event

5. Orthogonal Block Design



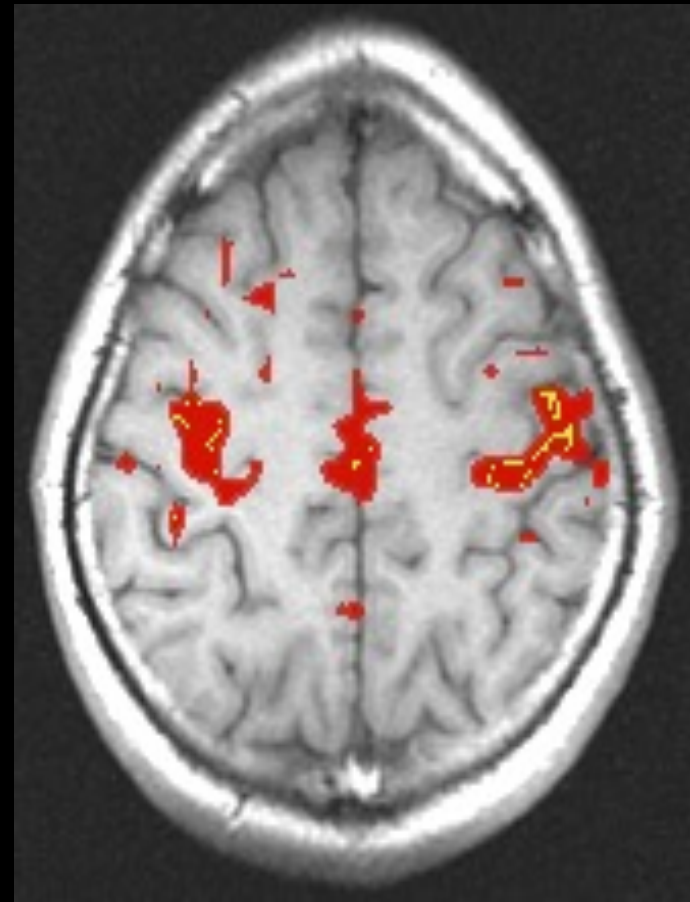
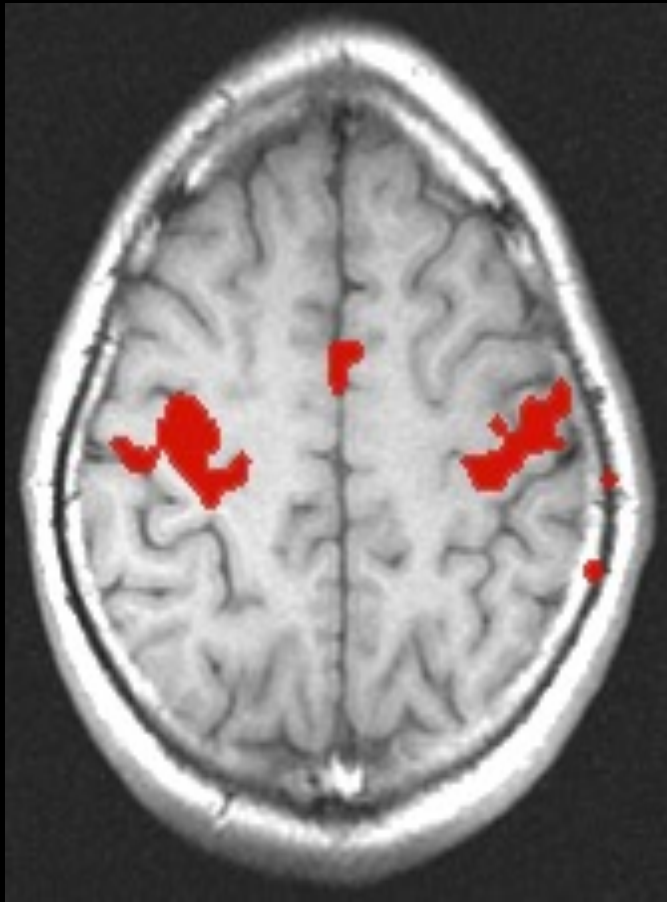
6. Free Behavior Design.

Free Behavior Design

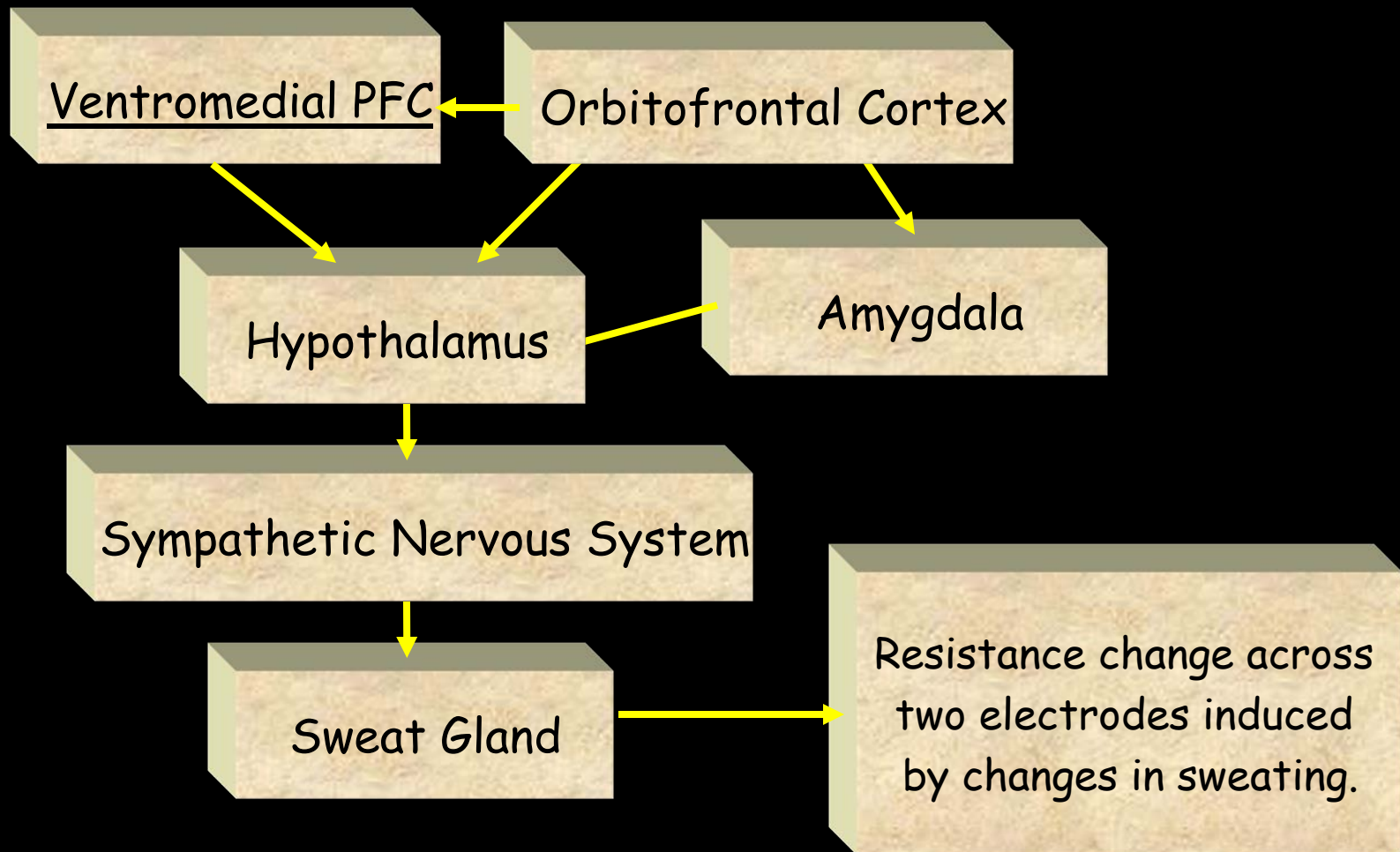
Use a continuous measure as a reference function:

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

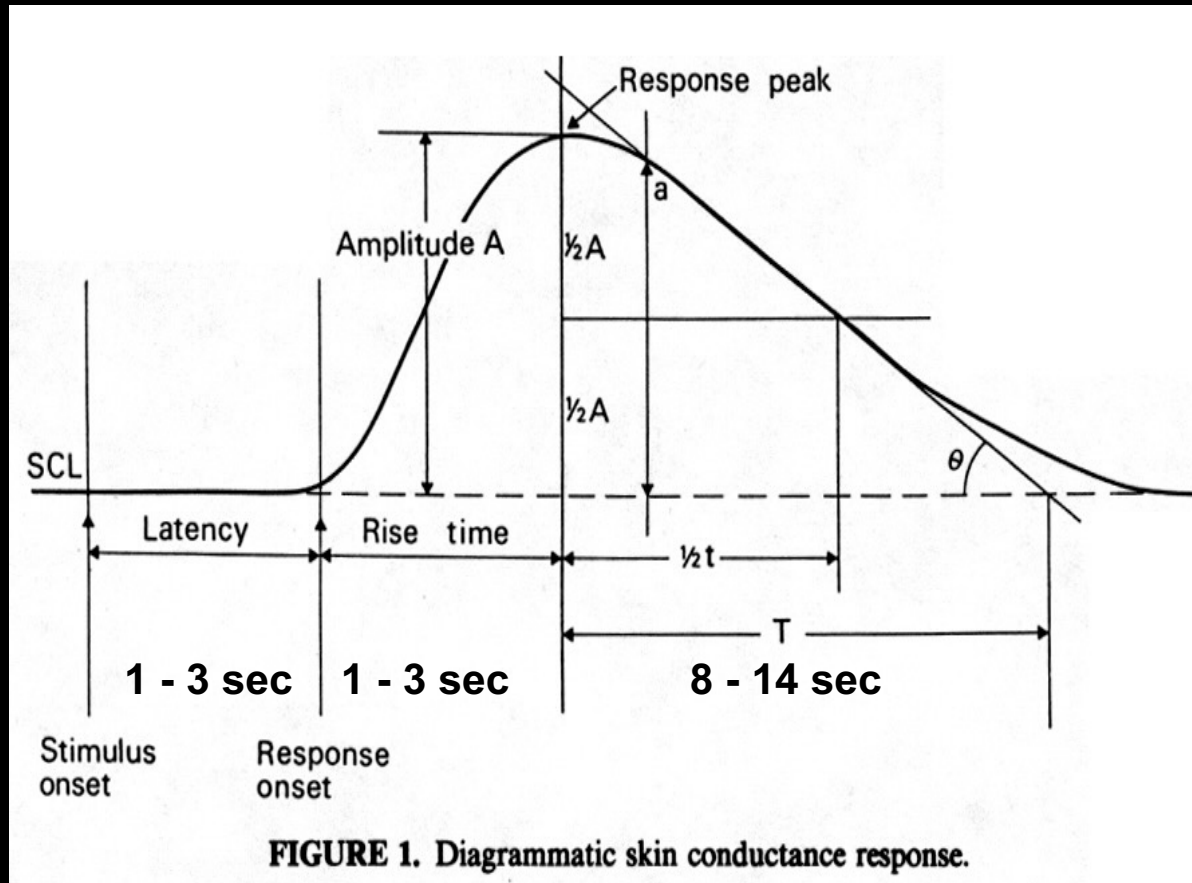
Resting Hemodynamic Autocorrelations



The Skin Conductance Response (SCR)

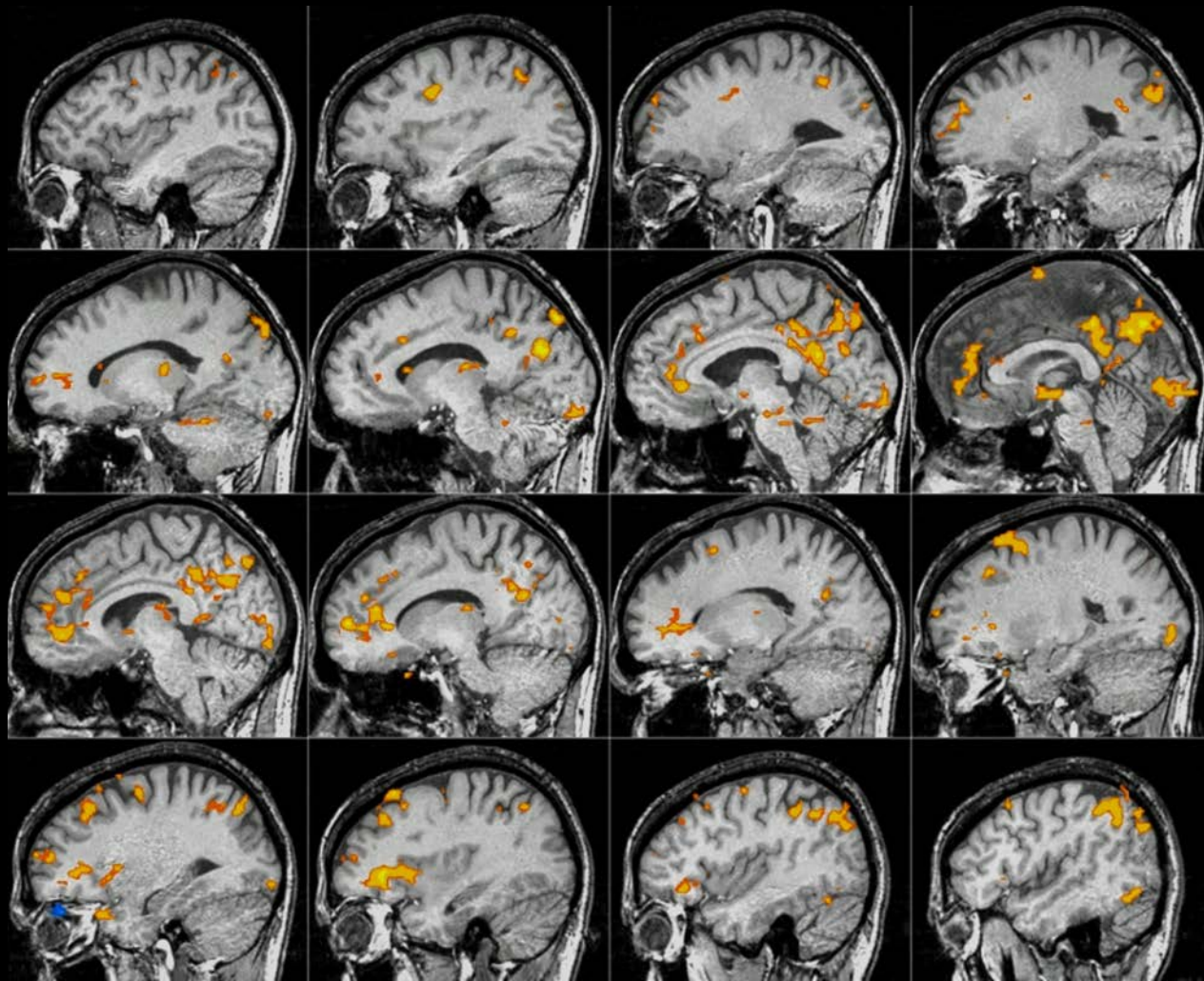


Skin Conductance Dynamics



- 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...

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