Spatial, Temporal, and Interpretive Limits of Functional MRI

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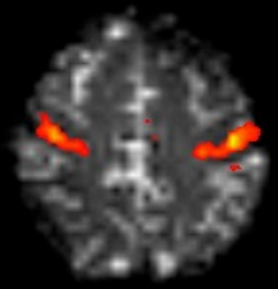
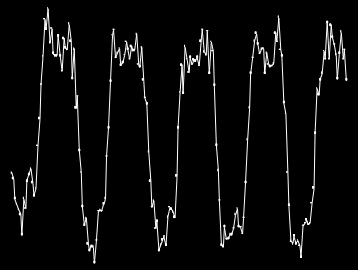
The use of fMRI to Investigate Brain Function

Where?



When?

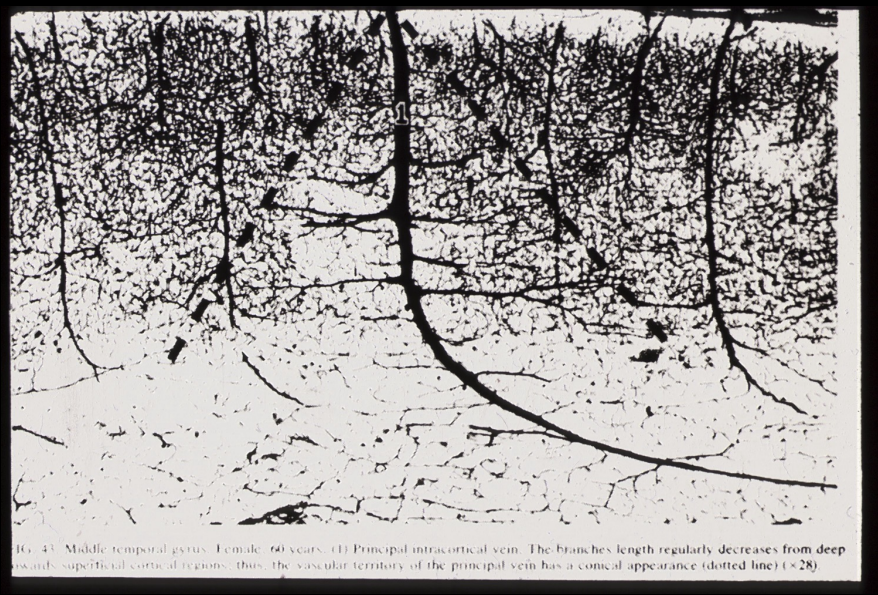


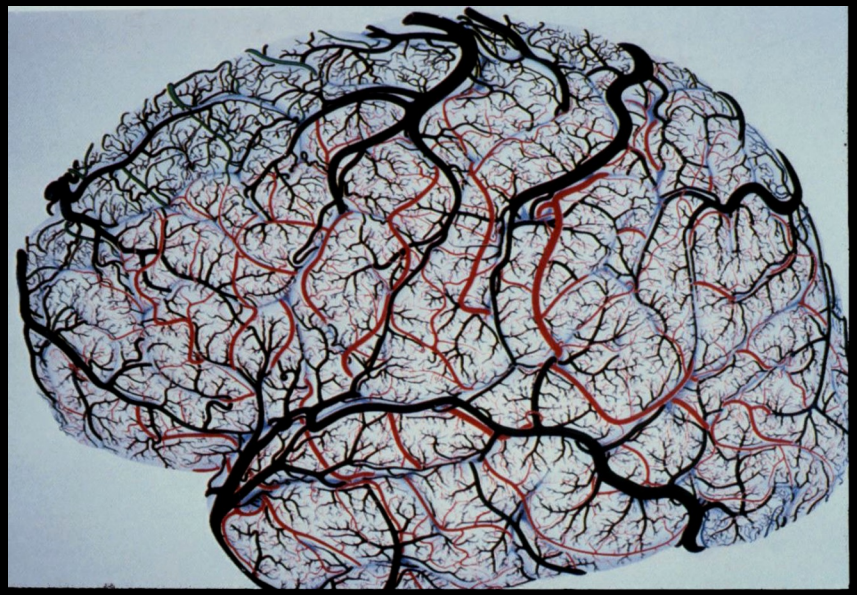
How much?

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

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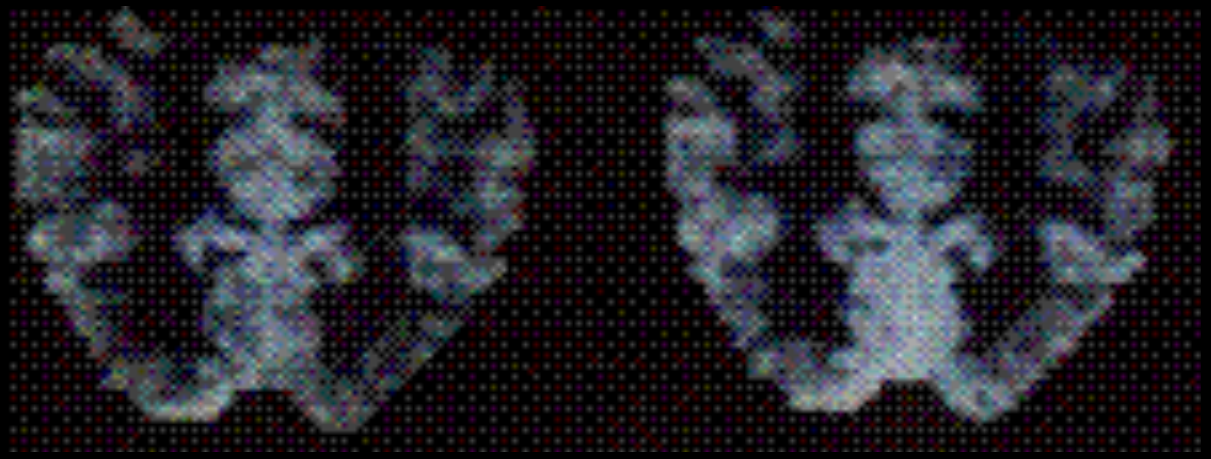
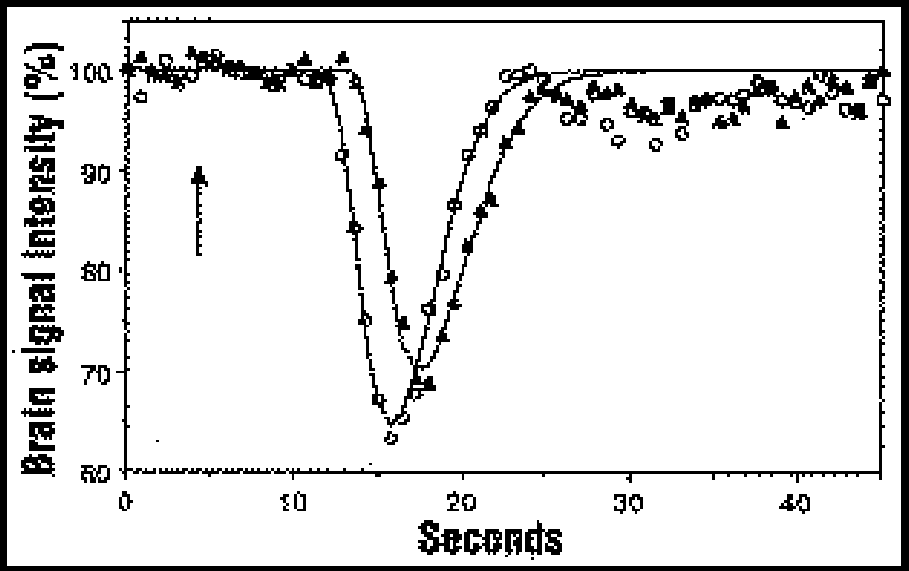
Contrast in Functional MRI

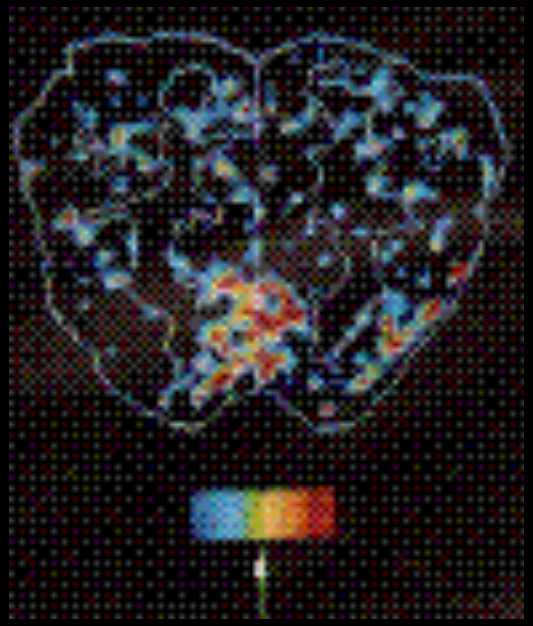
- **Blood Volume**
  - Contrast agent injection and time series collection of T2* or T2 - weighted images
- **BOLD**
  - Time series collection of T2* or T2 - weighted images
- **Perfusion**
  - T1 weighting
  - Arterial spin labeling
- **$CMRO_2$**
  - BOLD and Perfusion w/

  Normalization to Global Perfusion Change

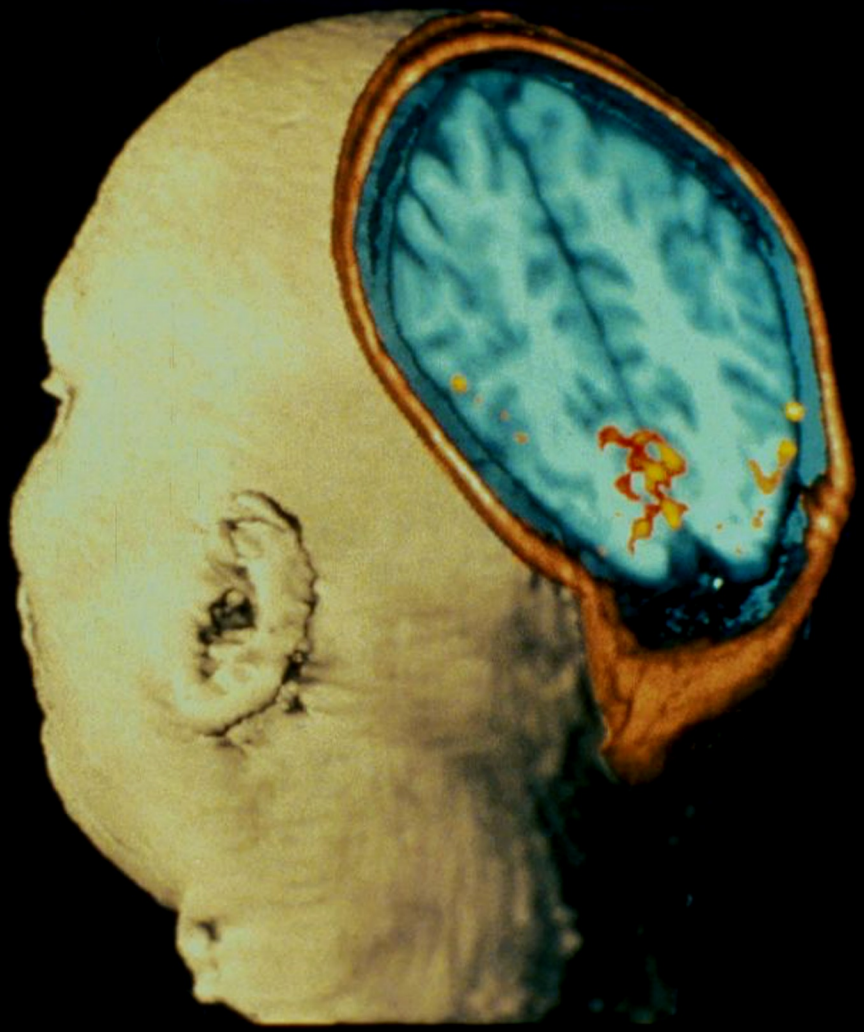
Resting Active







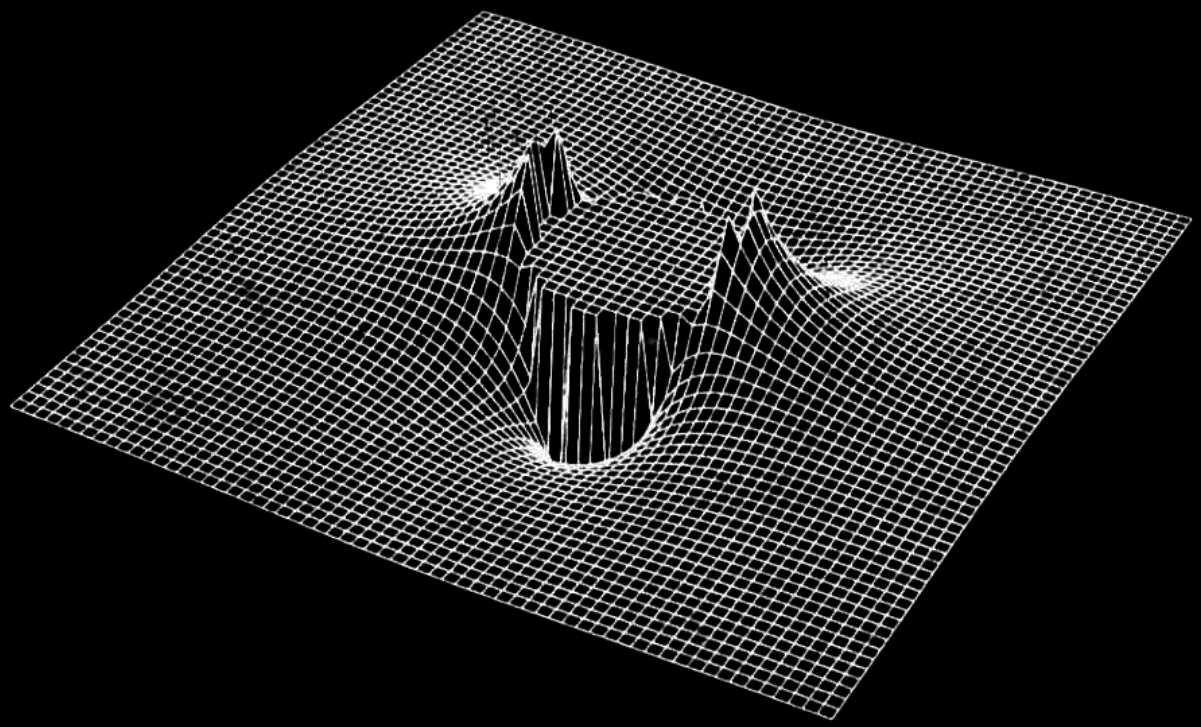
Photic Stimulation



MRI Image showing activation of the Visual Cortex

From Belliveau, et al. Science Nov 1991

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



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

↓

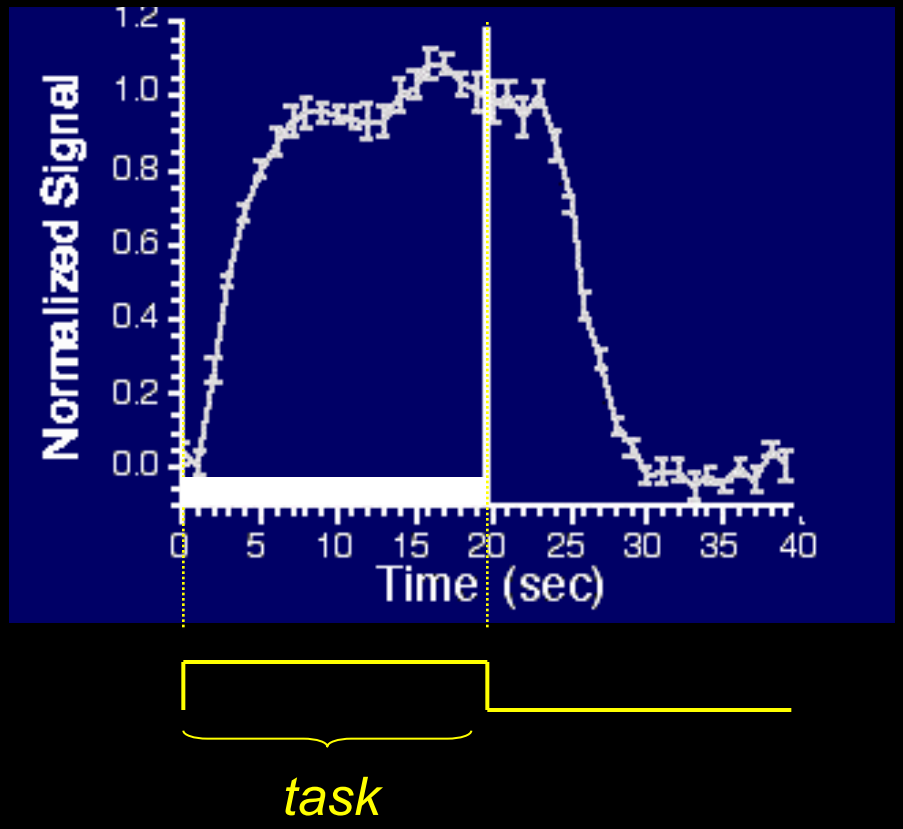
Decrease in susceptibility-related intravoxel dephasing → Increase in T2 and T2*

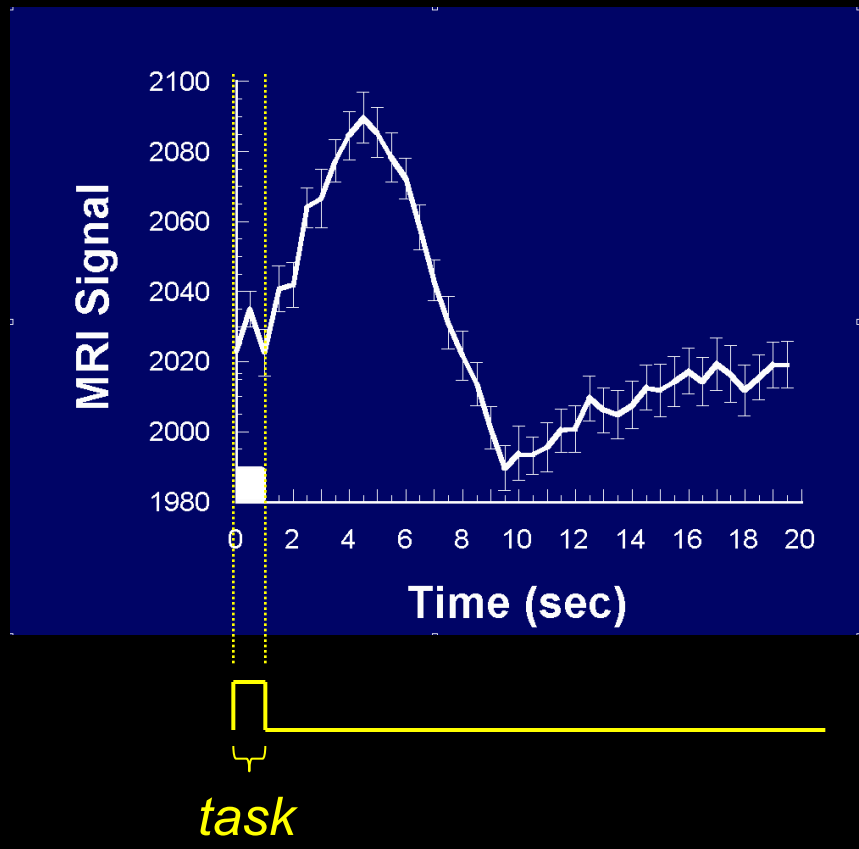
↓

Local Signal Increase in T2 and T2* - weighted sequences

The BOLD Signal

Blood Oxygenation Level Dependent (BOLD) signal changes

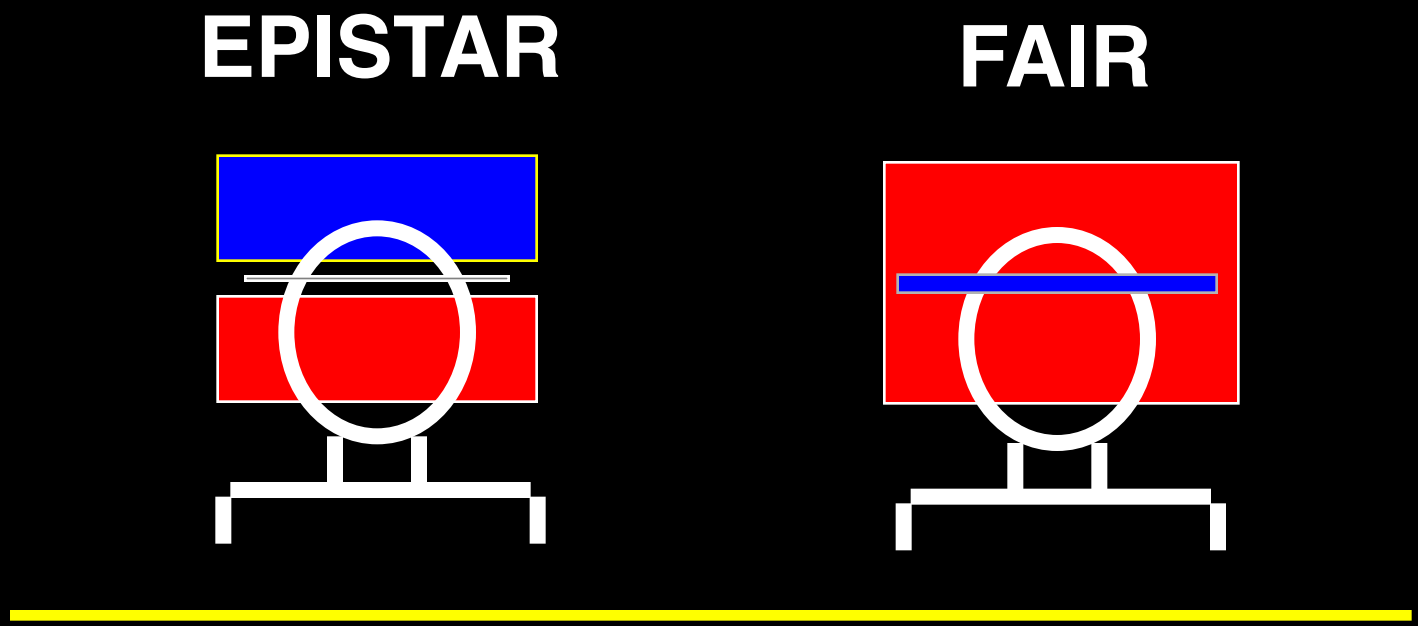


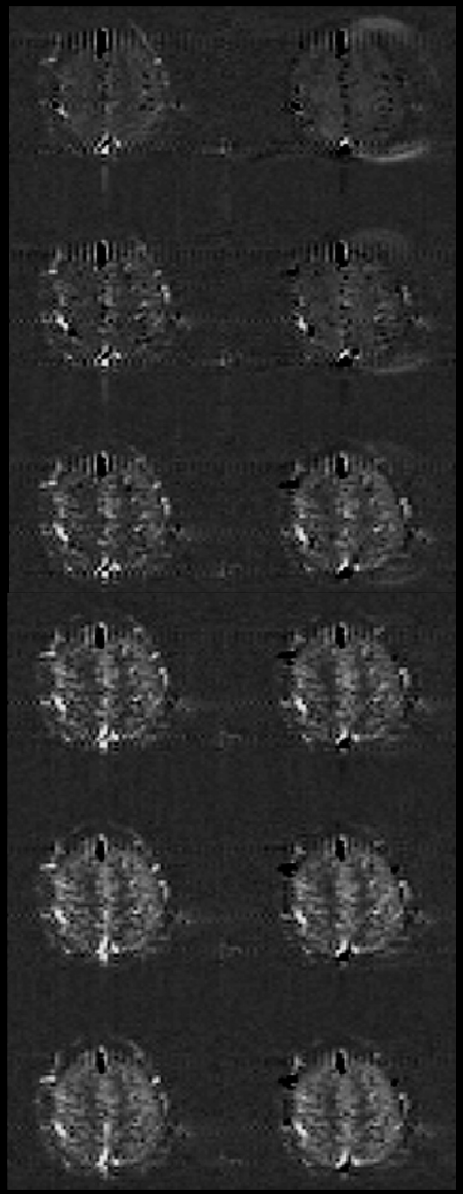


Alternating Left and Right Finger Tapping

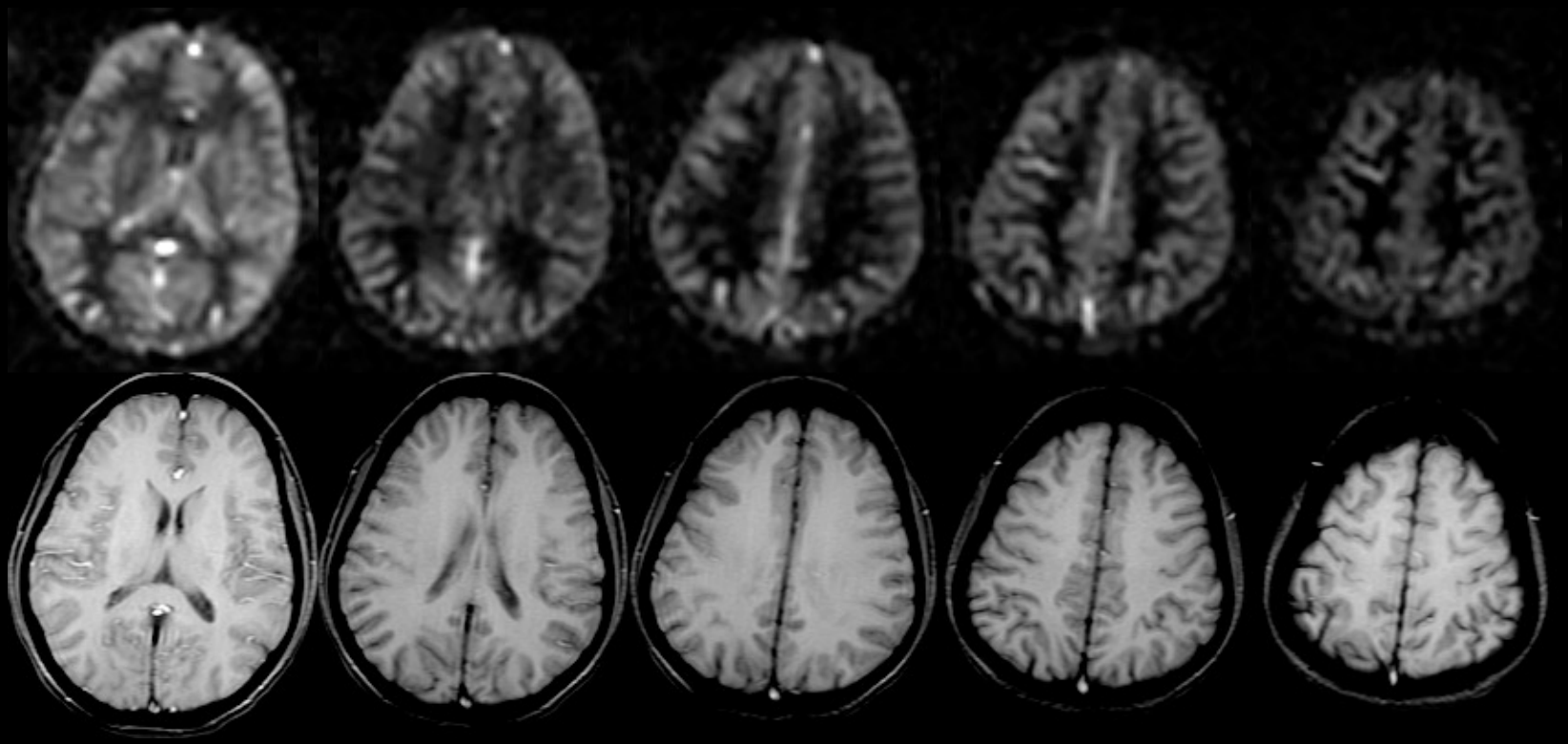
~ 1992

Perfusion / Flow Imaging

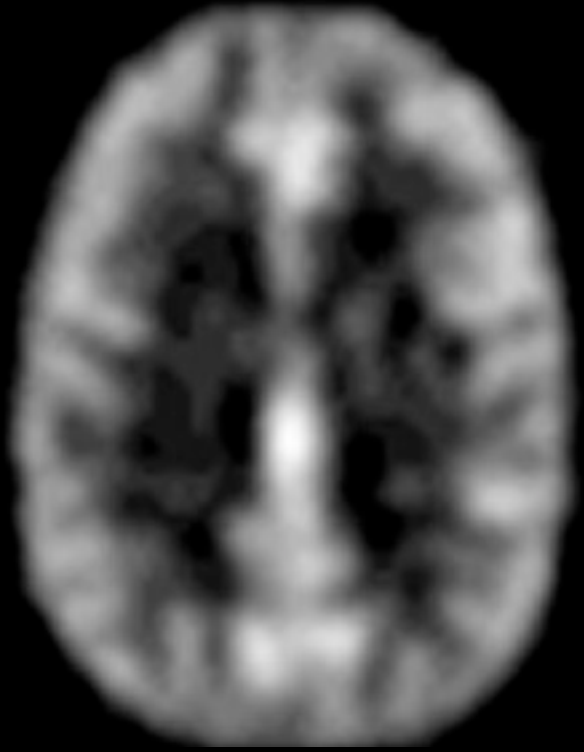


TI (ms)	FAIR	EPISTAR
200		
400		
600		
800		
1000		
1200		

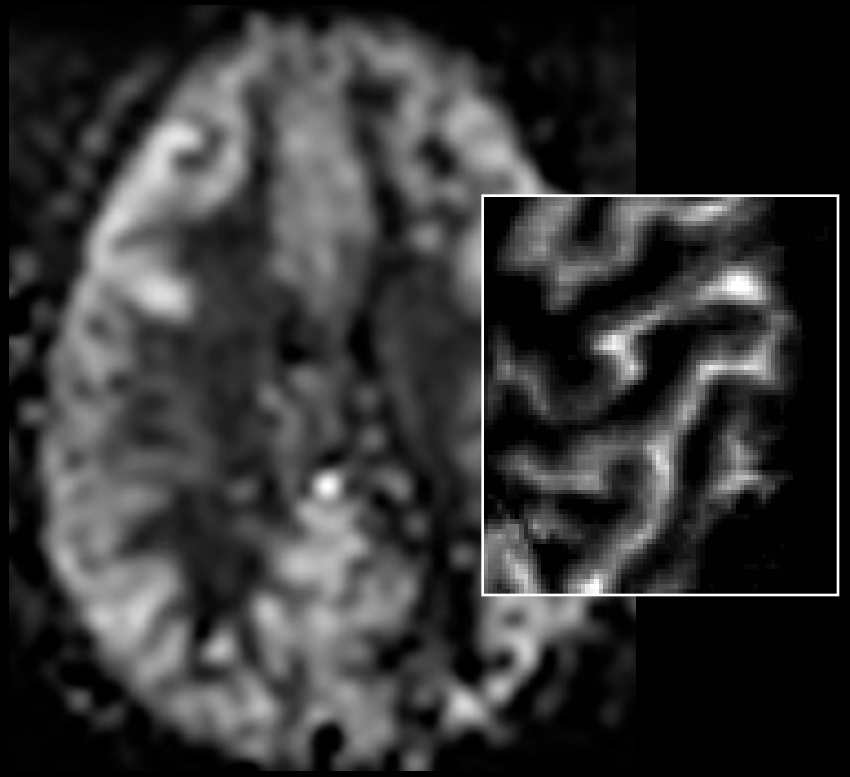
Resting ASL Signal



Comparison with Positron Emission Tomography



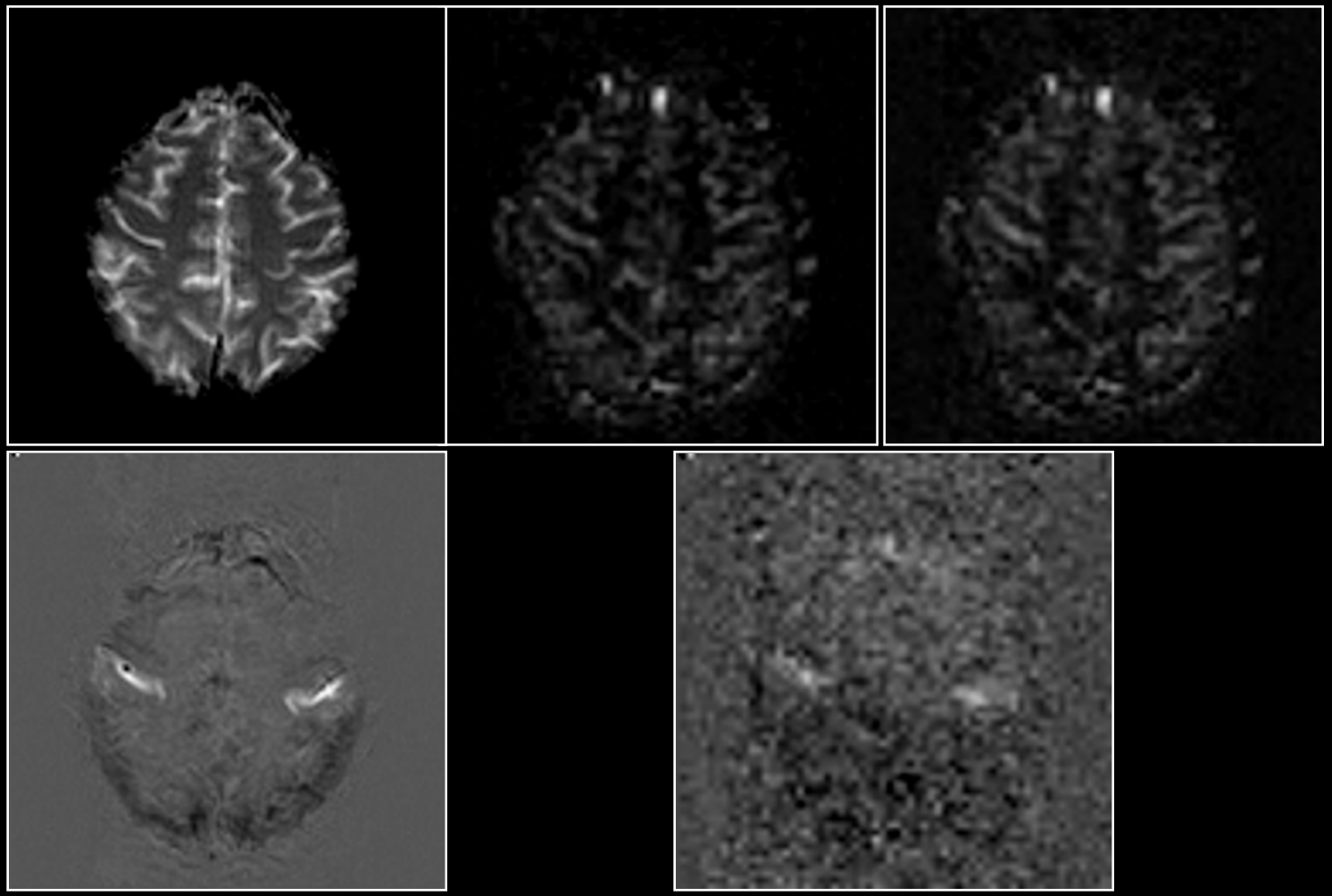
PET: $H_2{}^{15}O$



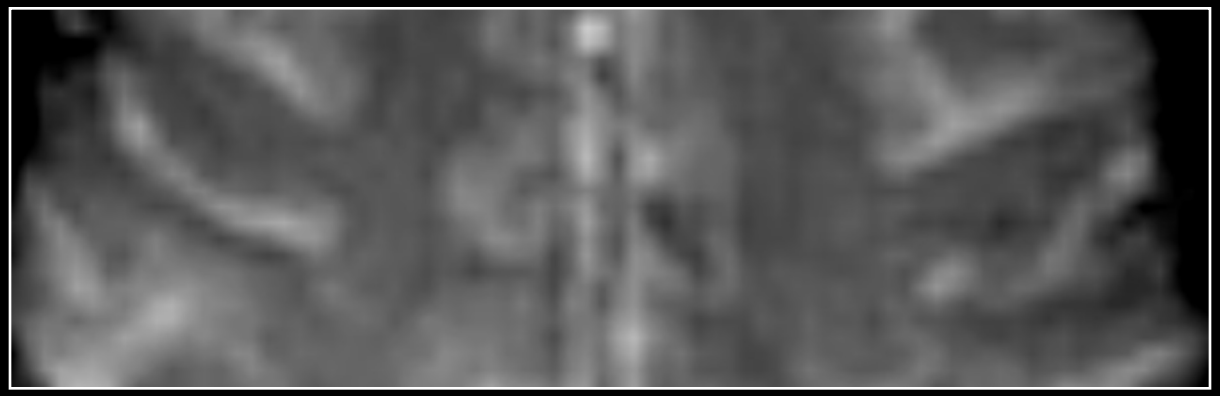
MRI: ASL

Perfusion

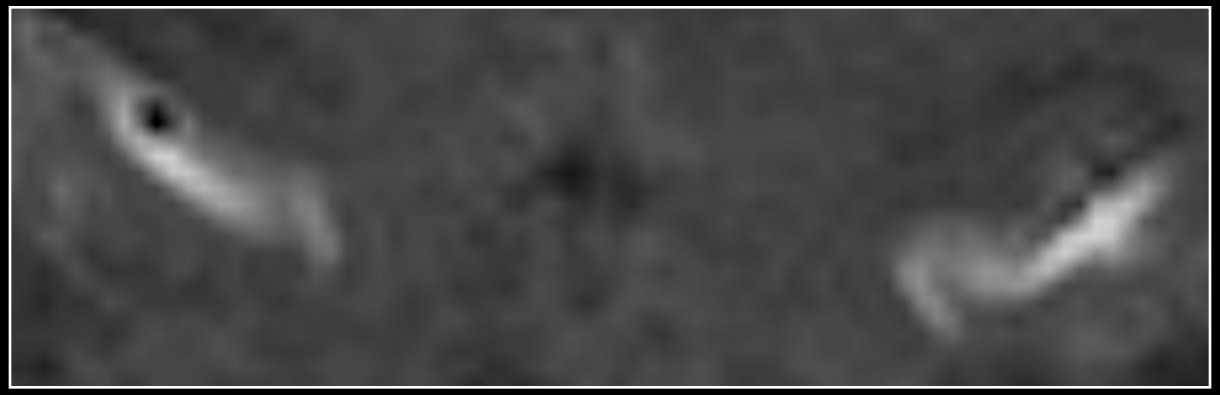
BOLD *Rest* *Activation*



Anatomy

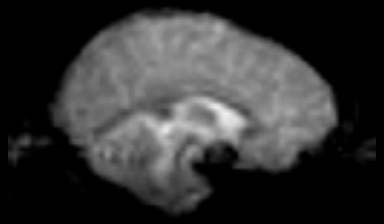


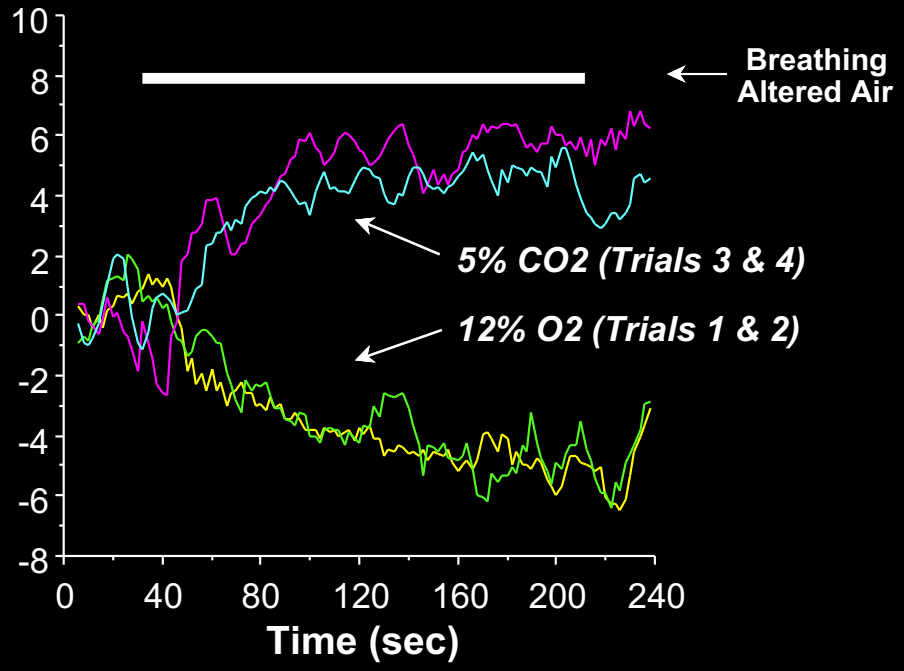
BOLD



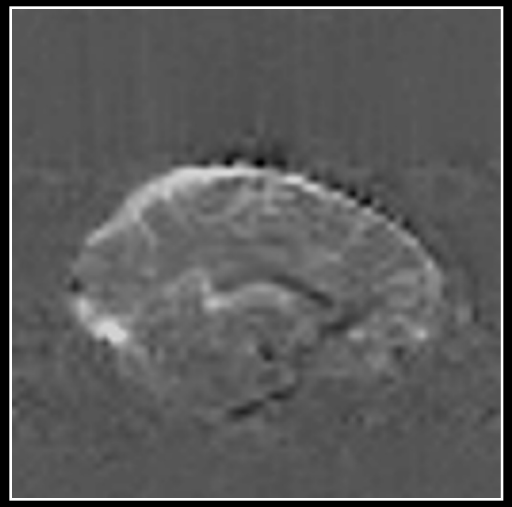
Perfusion

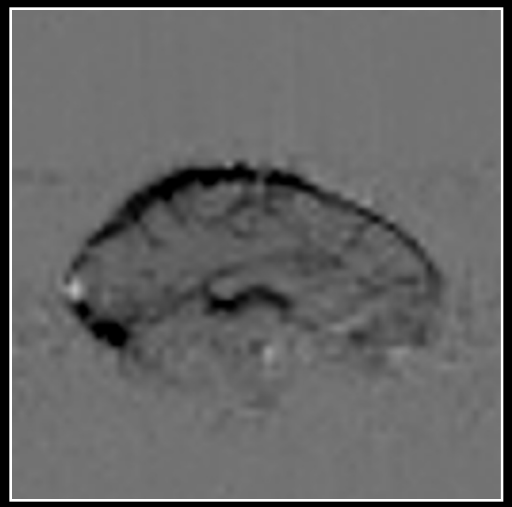
Hemdodynamic Stress Calibration





5% CO2

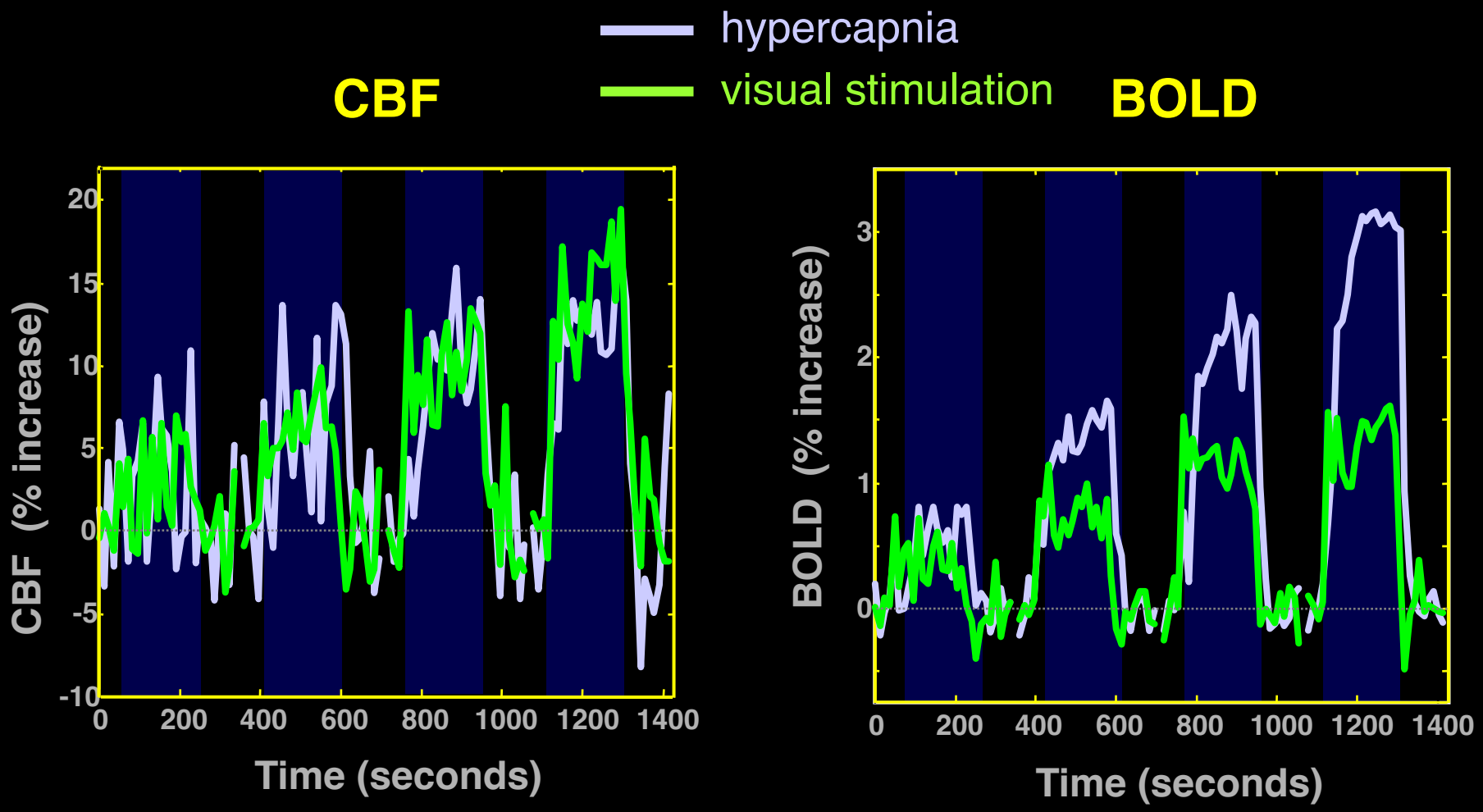




12% O2

$CMRO_2$-related BOLD signal deficit:

Hoge, et al.

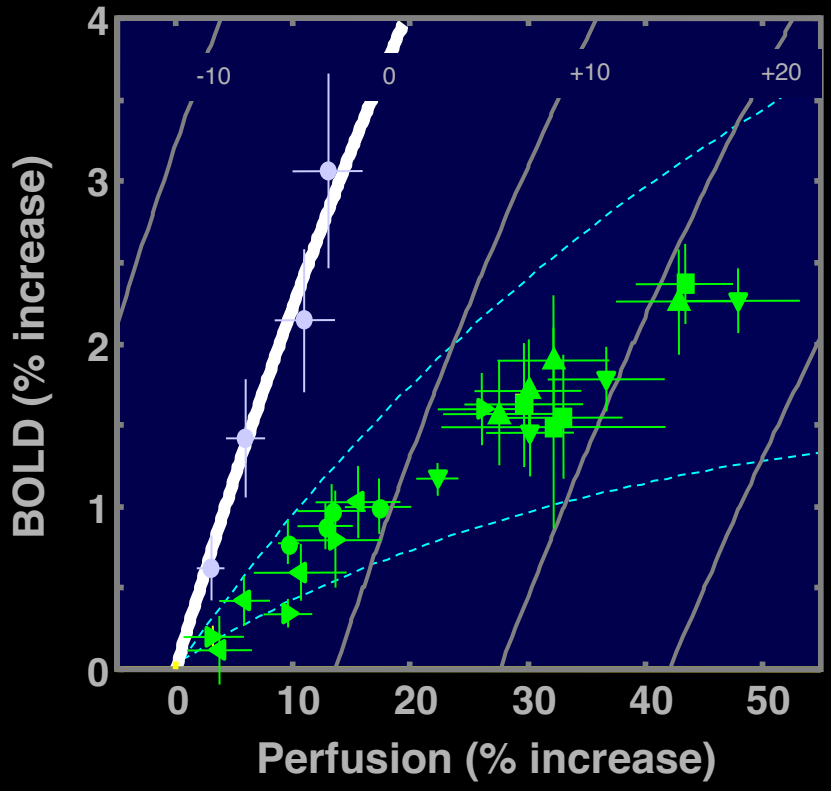


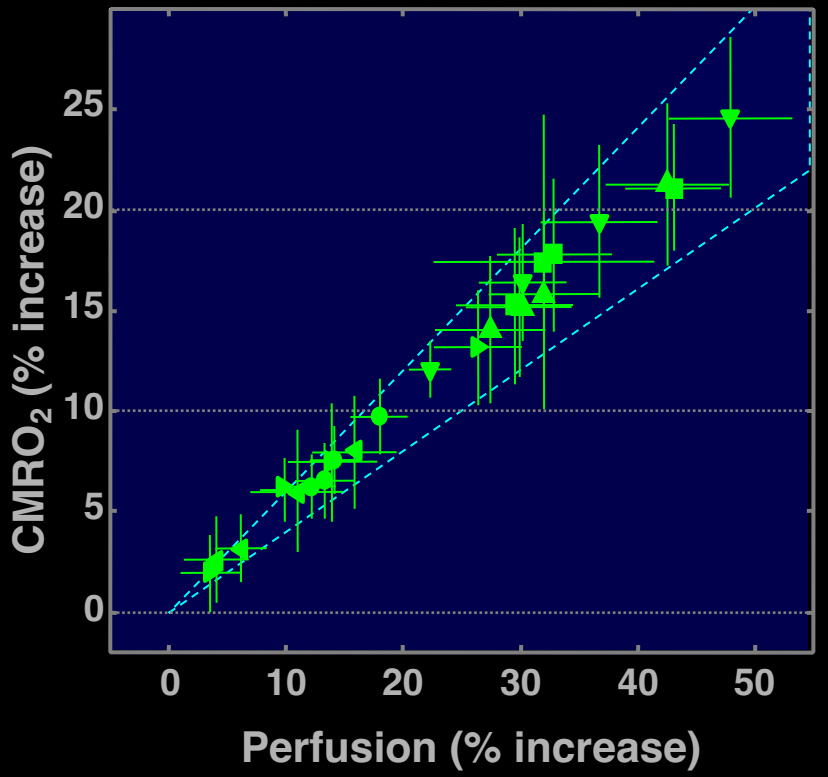
Simultaneous Perfusion and BOLD imaging during graded visual activation and hypercapnia

N=12

CBF-$CMRO_2$ coupling

Hoge, et al.

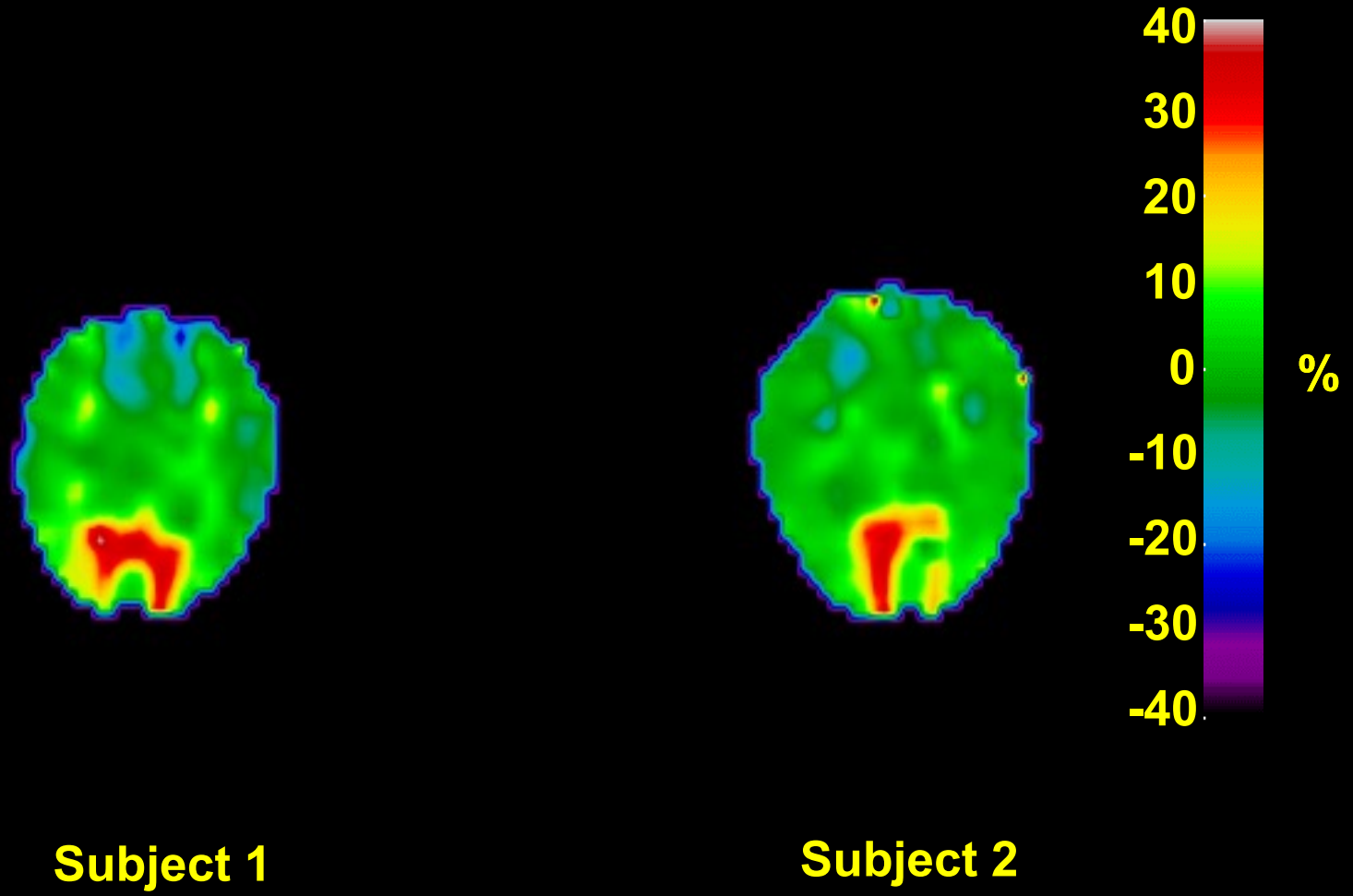




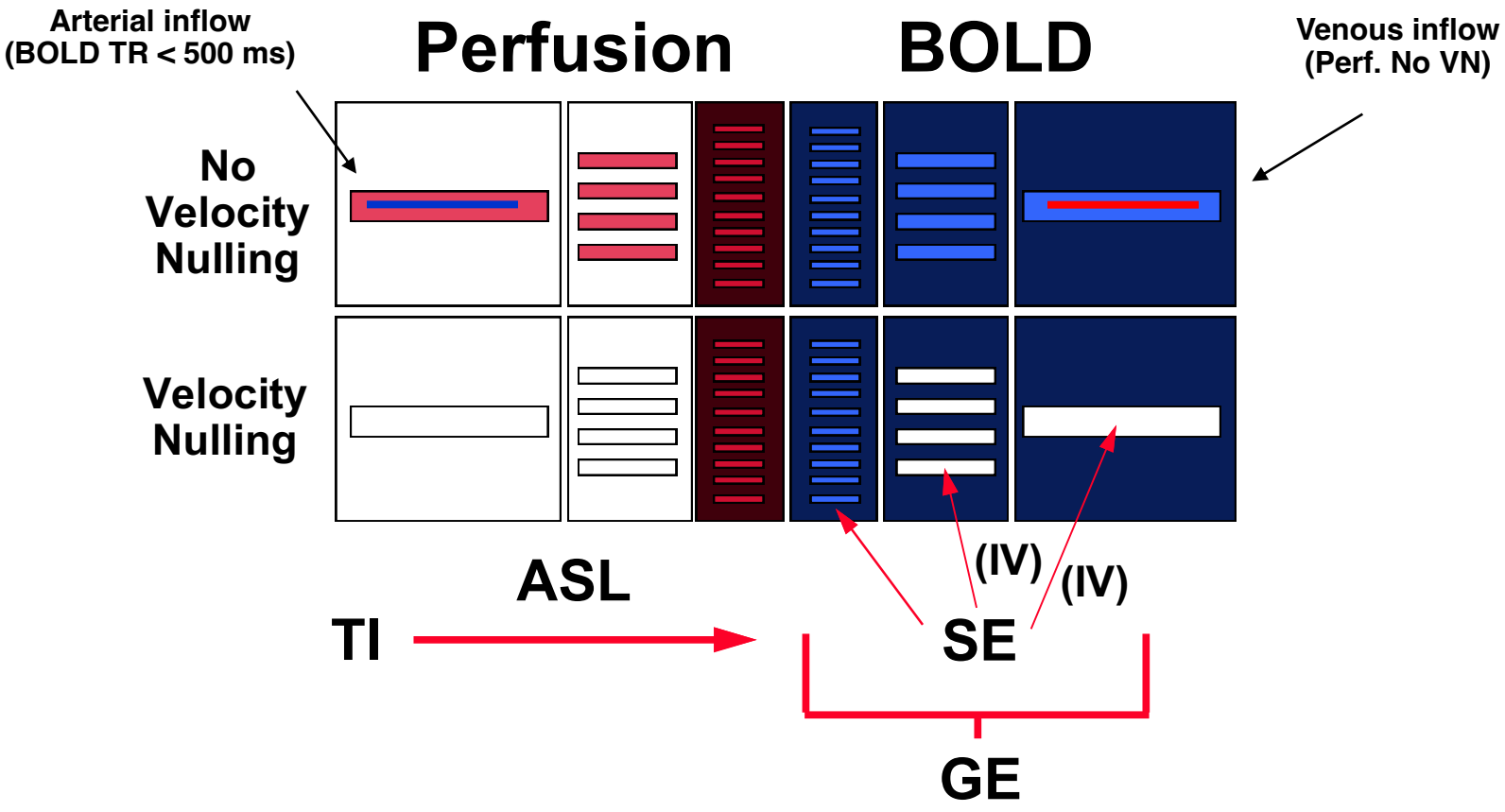
Characterizing Activation-induced $CMRO_2$ changes using calibration with hypercapnia

Hoge, et al.

Computed $CMRO_2$ changes



Hemodynamic Specificity



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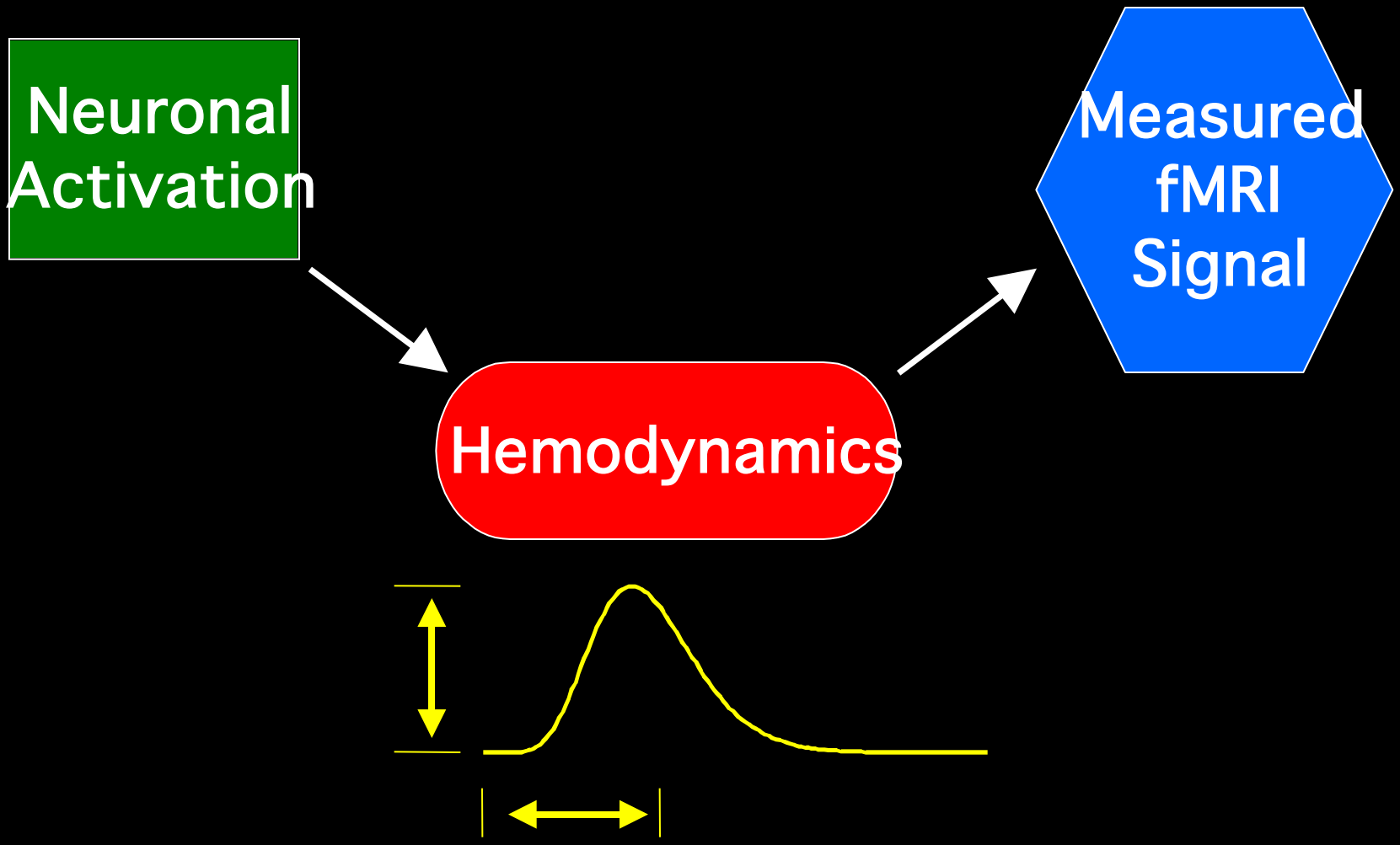
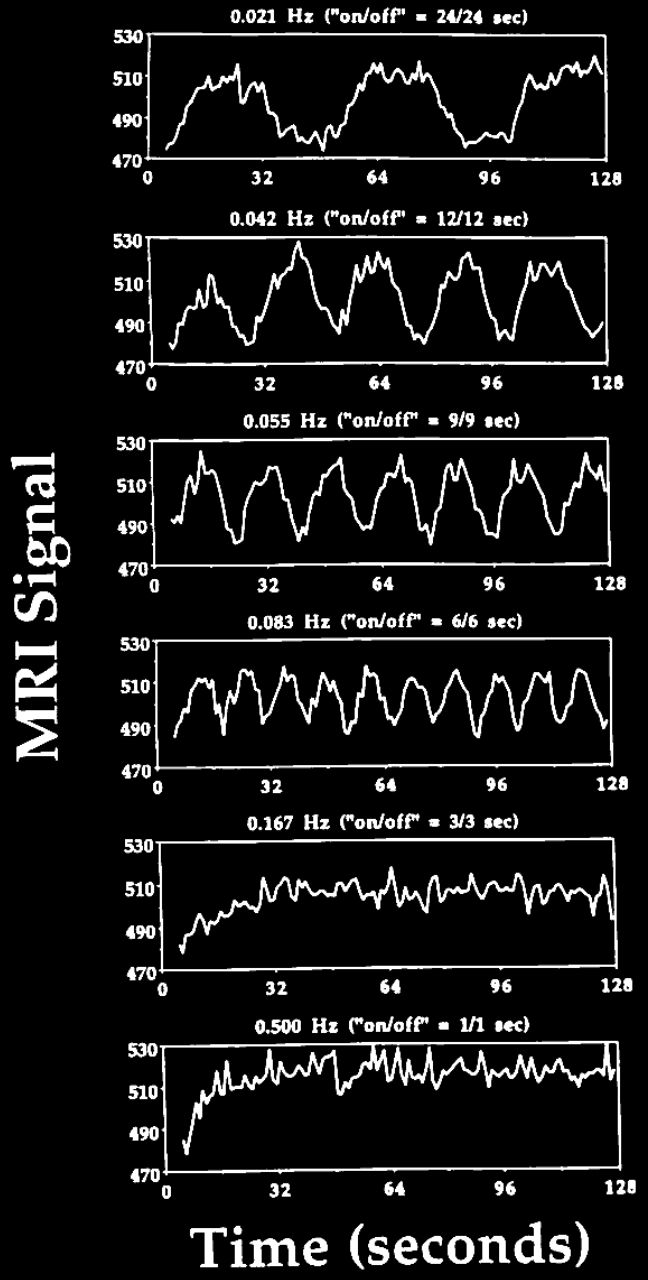
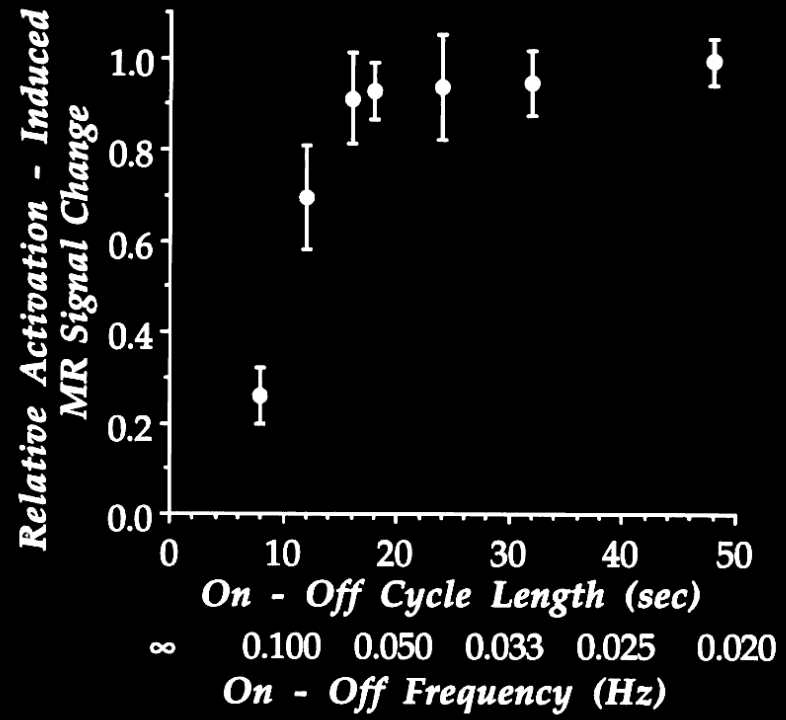
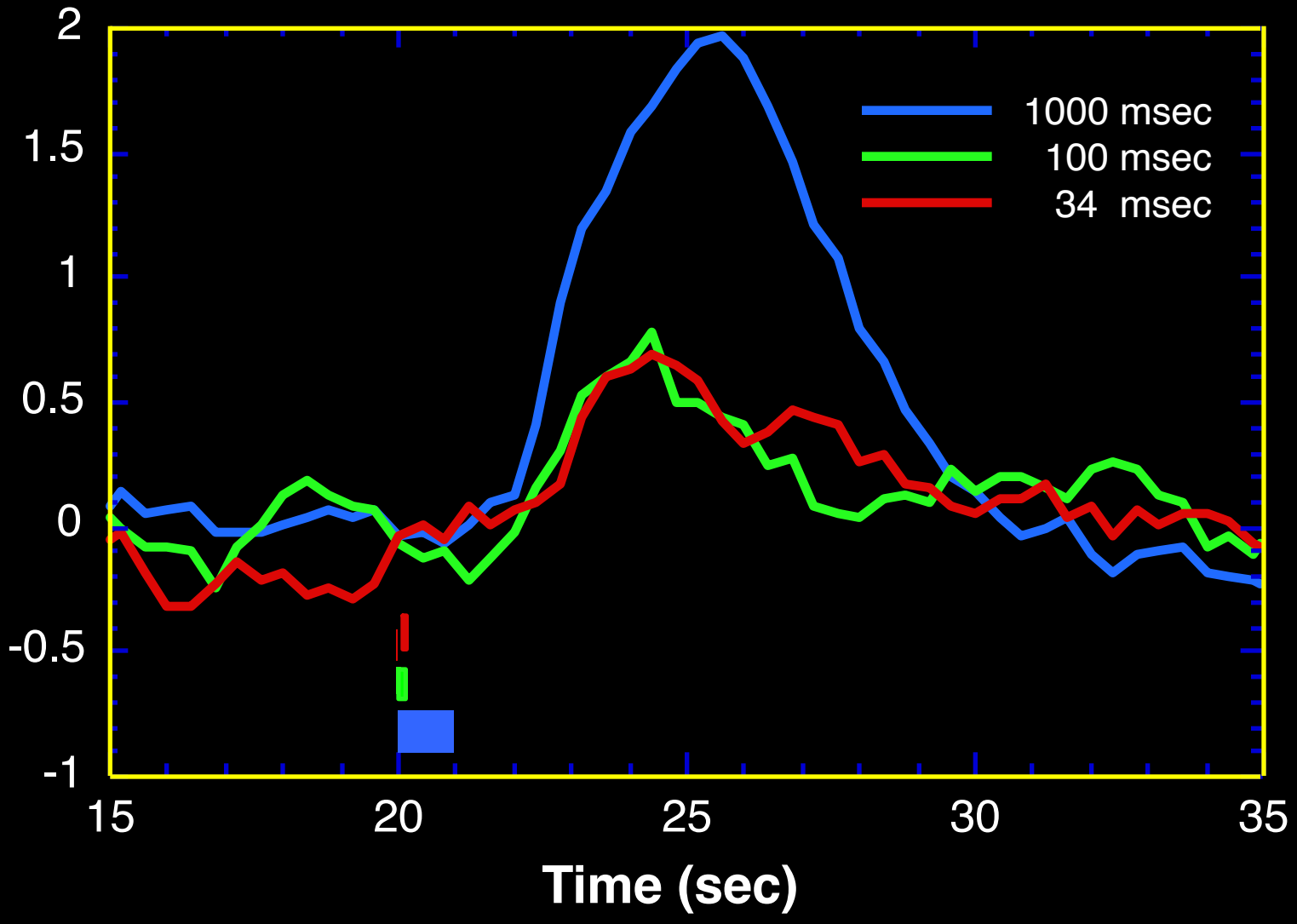
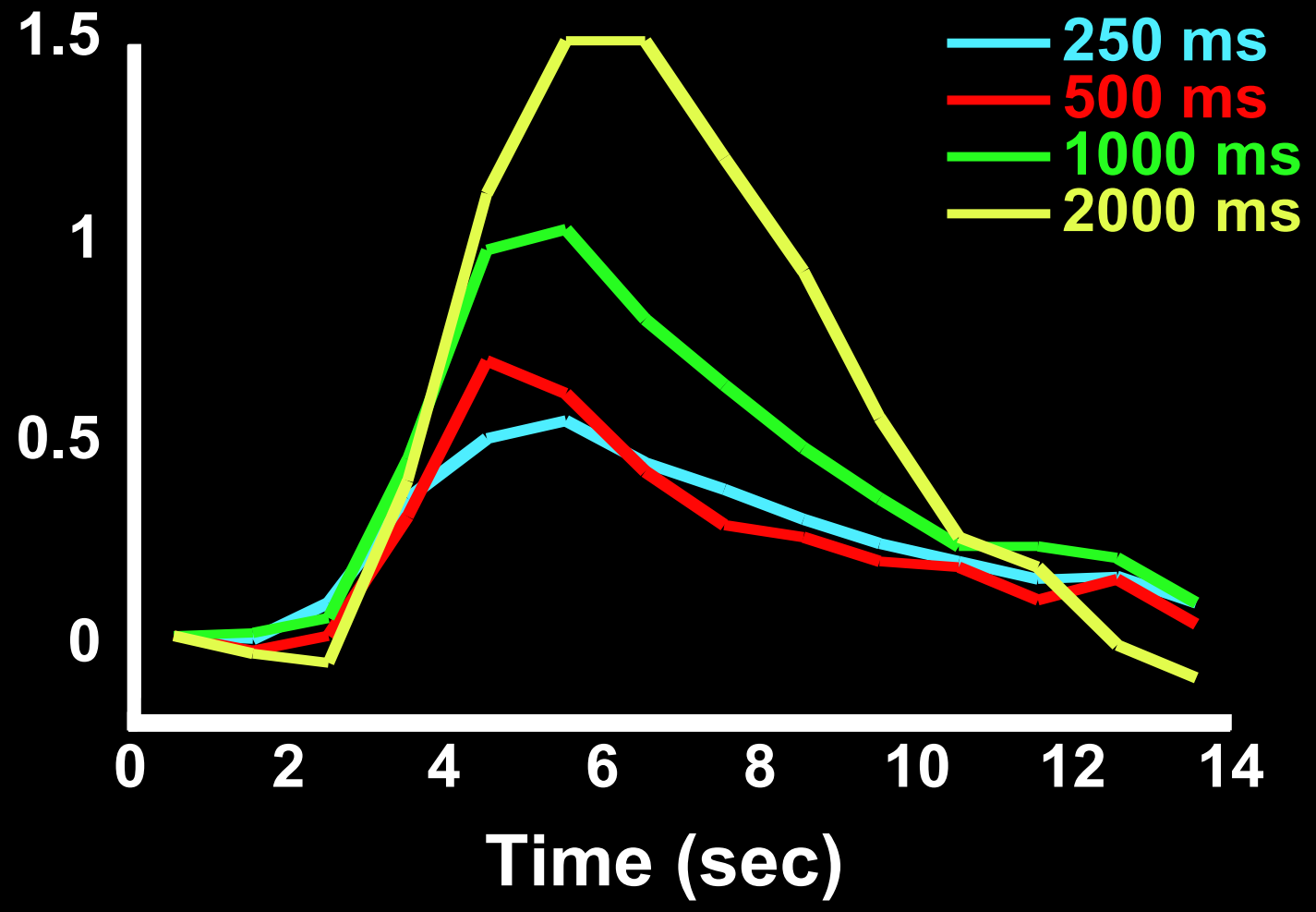
Hemodynamic Transfer Function




0.021 Hz ("on/off" = 24/24 sec)
0.042 Hz ("on/off" = 12/12 sec)
0.055 Hz ("on/off" = 9/9 sec)
0.083 Hz ("on/off" = 6/6 sec)
0.167 Hz ("on/off" = 3/3 sec)
0.500 Hz ("on/off" = 1/1 sec)
530
510
490
470
0
32
64
96
128
MRI Signal
Time (seconds)

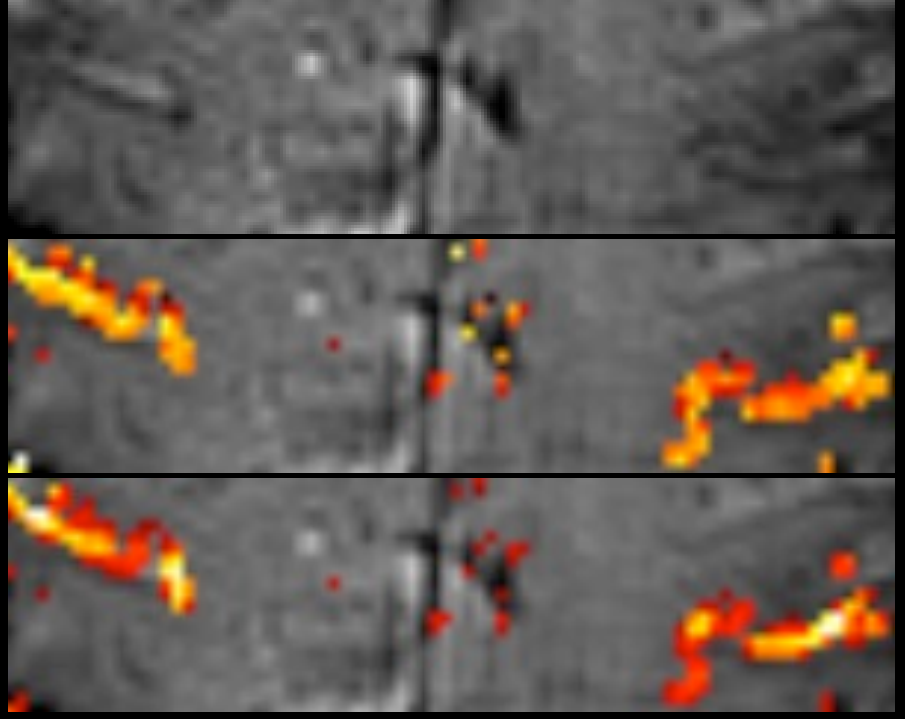

Relative Activation - Induced MR Signal Change
1.0
0.8
0.6
0.4
0.2
0.0
0
10
20
30
40
50
On - Off Cycle Length (sec)
∞
0.100
0.050
0.033
0.025
0.020
On - Off Frequency (Hz)

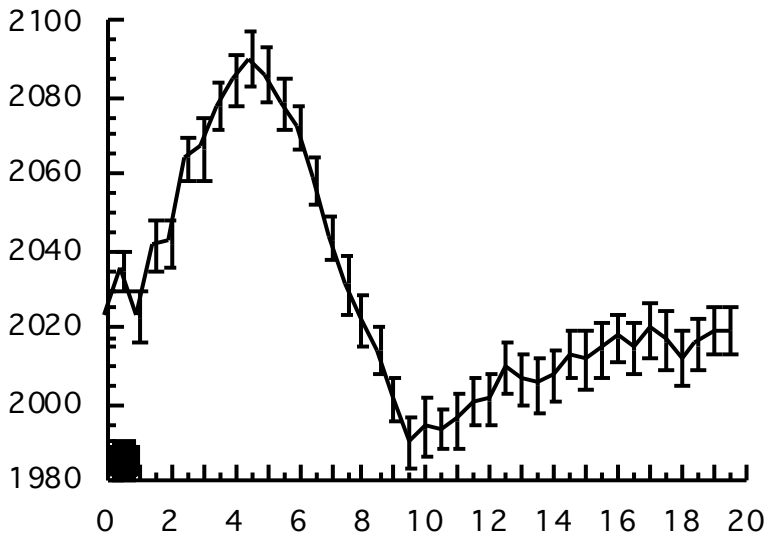

2
1.5
1
0.5
0
-0.5
-1
15
20
25
30
35
1000 msec
100 msec
34 msec
Time (sec)

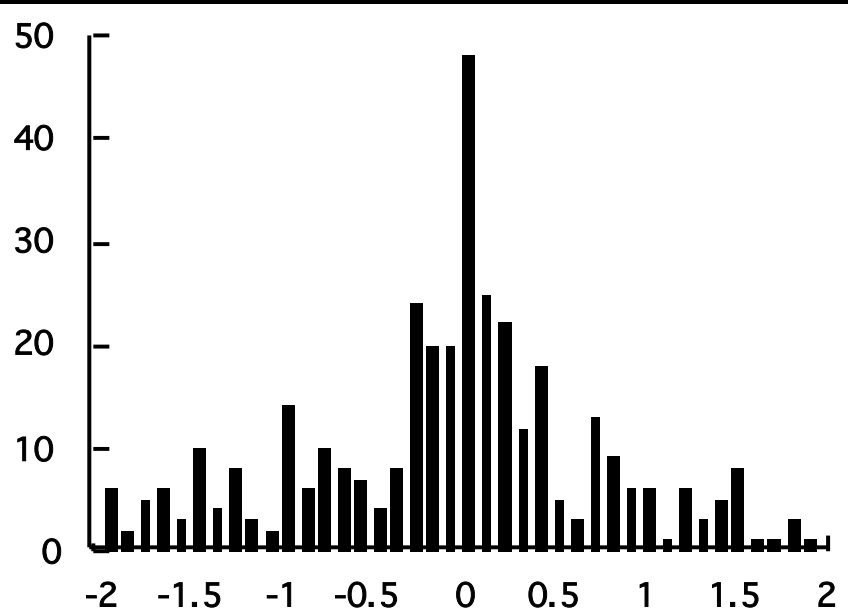

1.5
1
0.5
0
0
2
4
6
8
10
12
14
Time (sec)
250 ms
500 ms
1000 ms
2000 ms

Latency

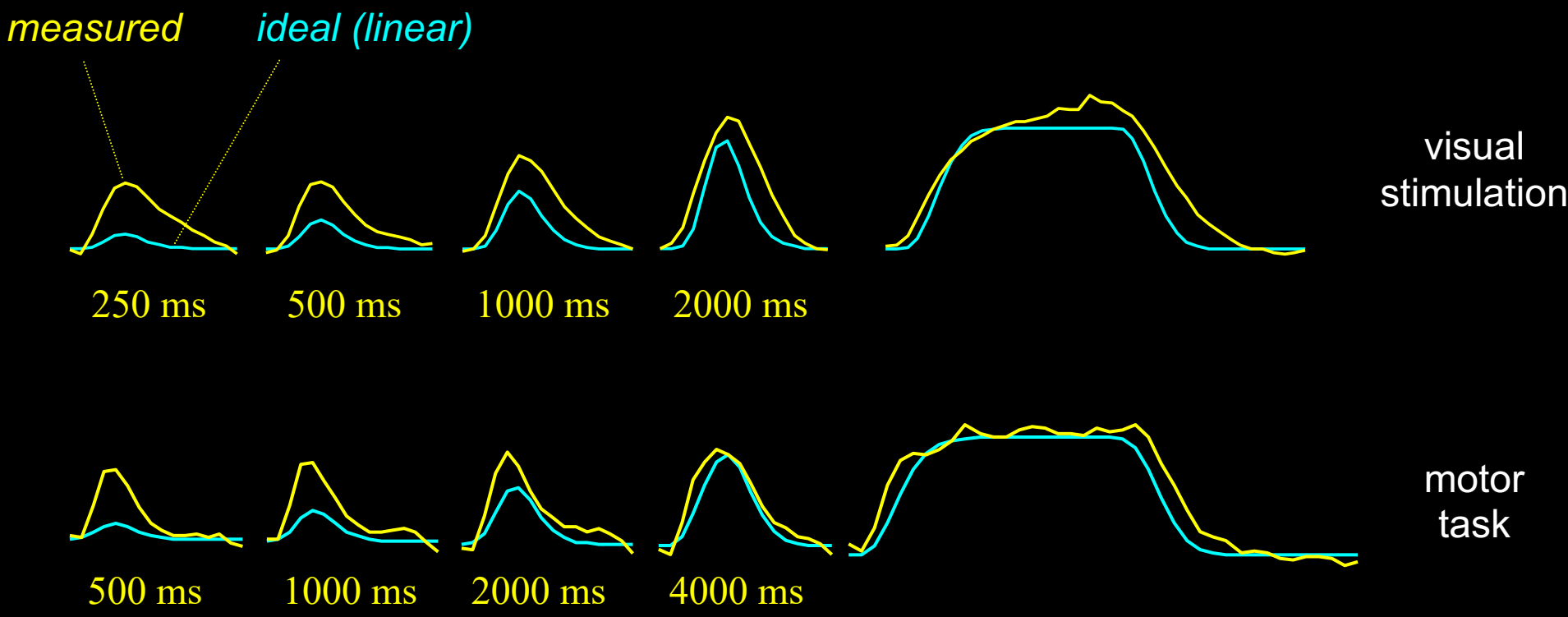
Magnitude



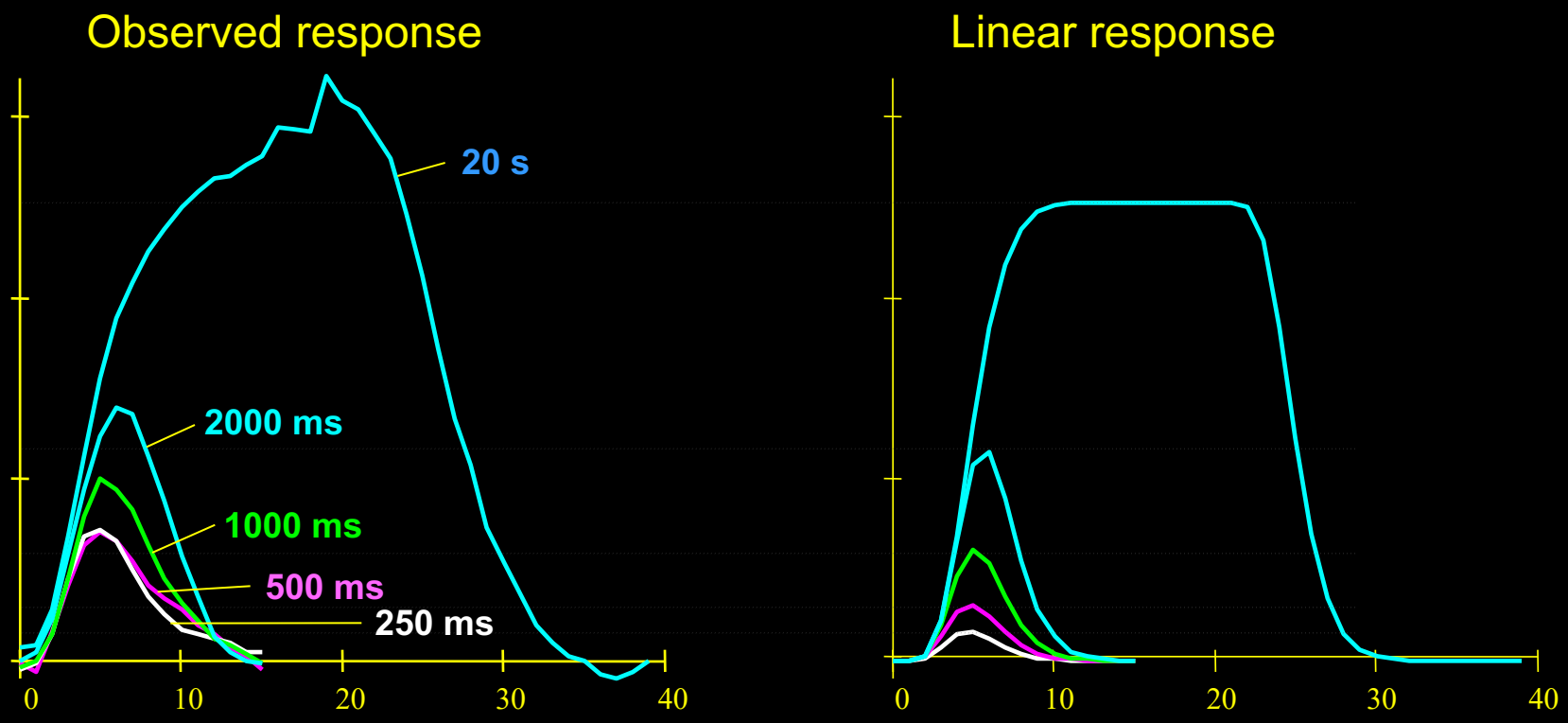




Observed Responses

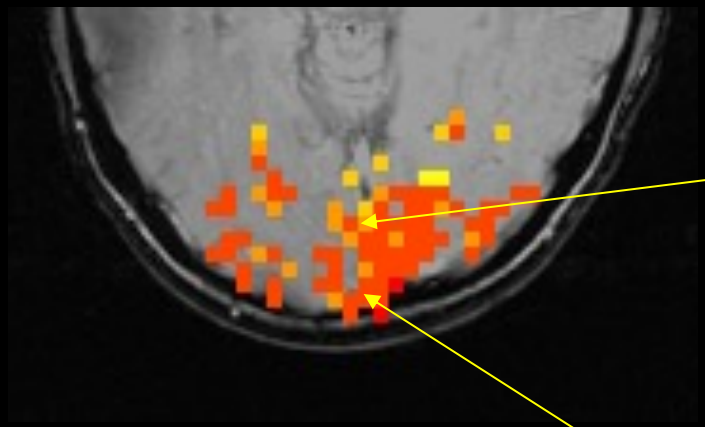


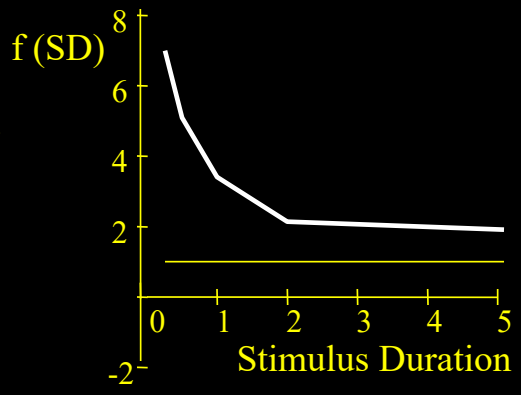
BOLD response is nonlinear

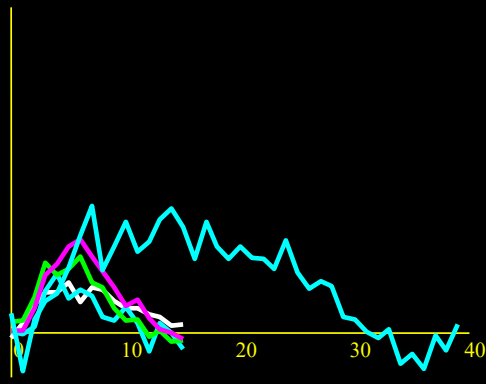


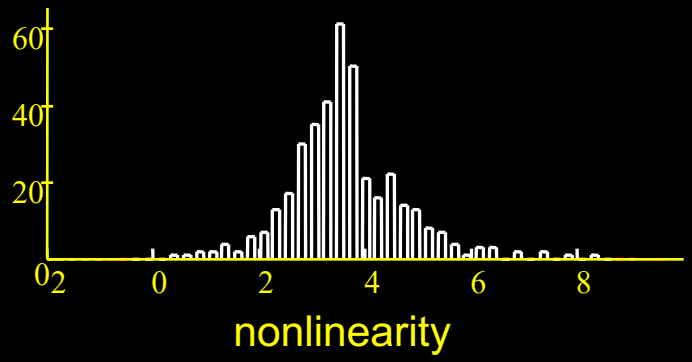
Short duration stimuli produce larger responses than expected

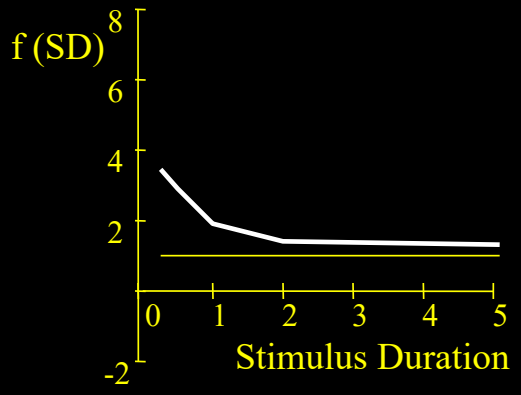
Results – visual task

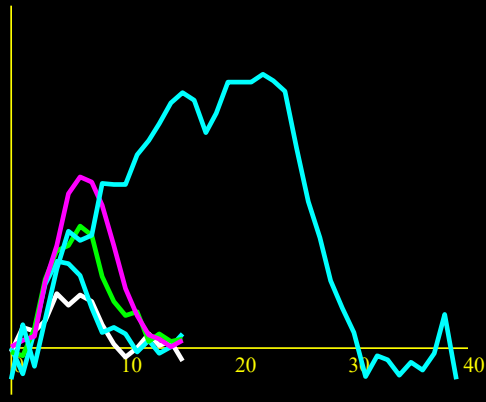










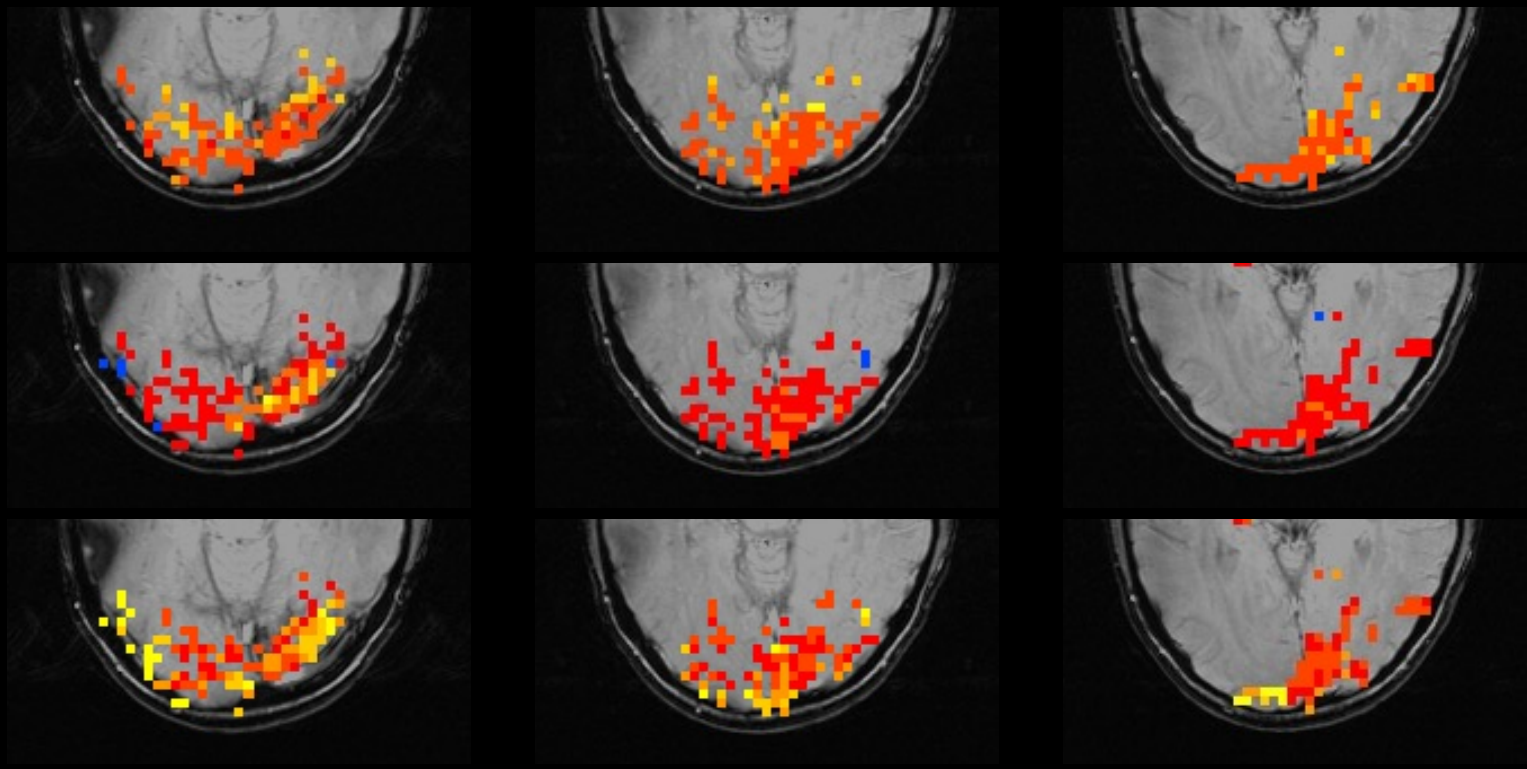


Results – visual task

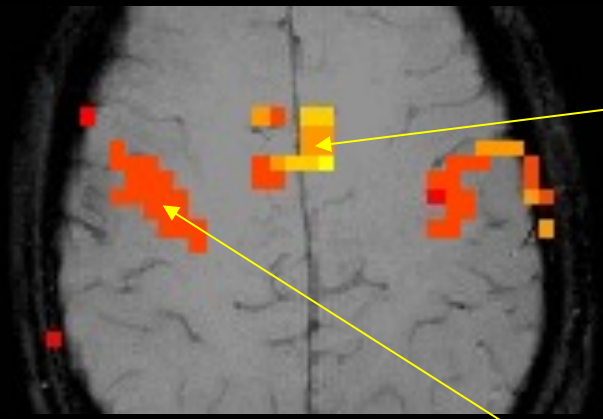
Nonlinearity

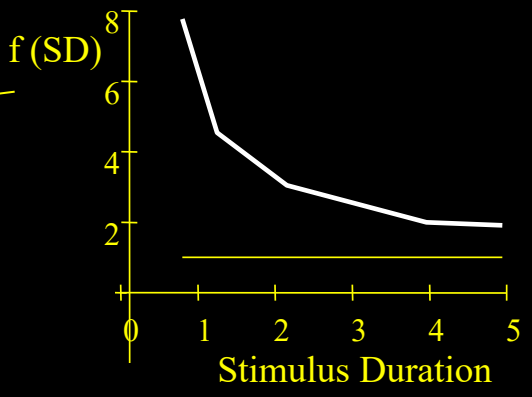
Magnitude

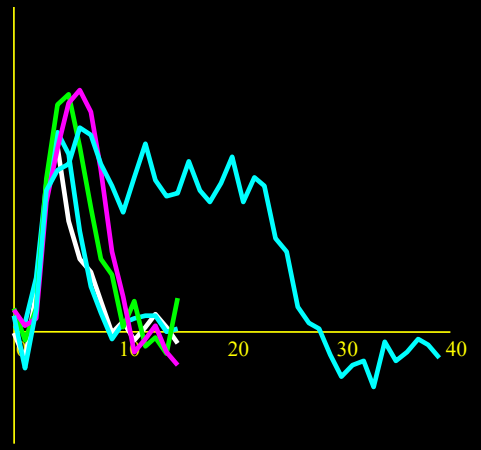
Latency

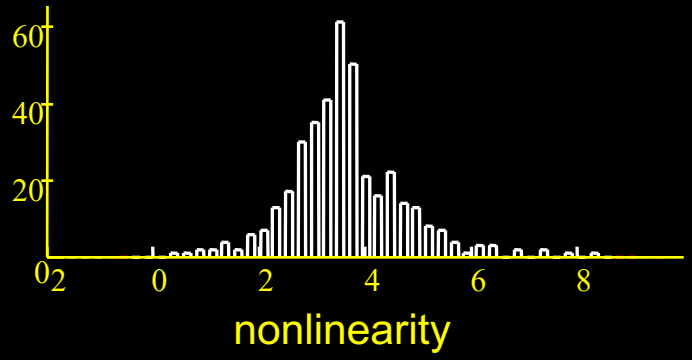


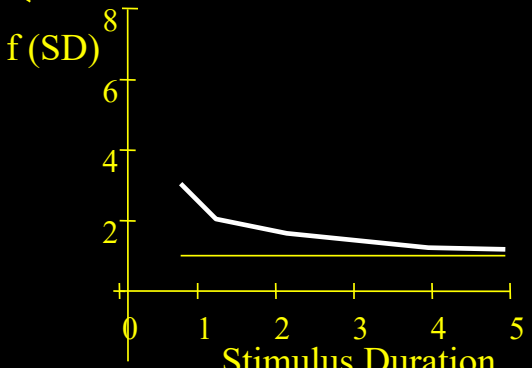
Results – motor task

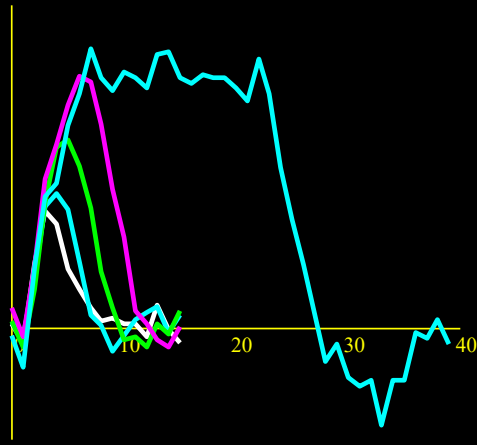










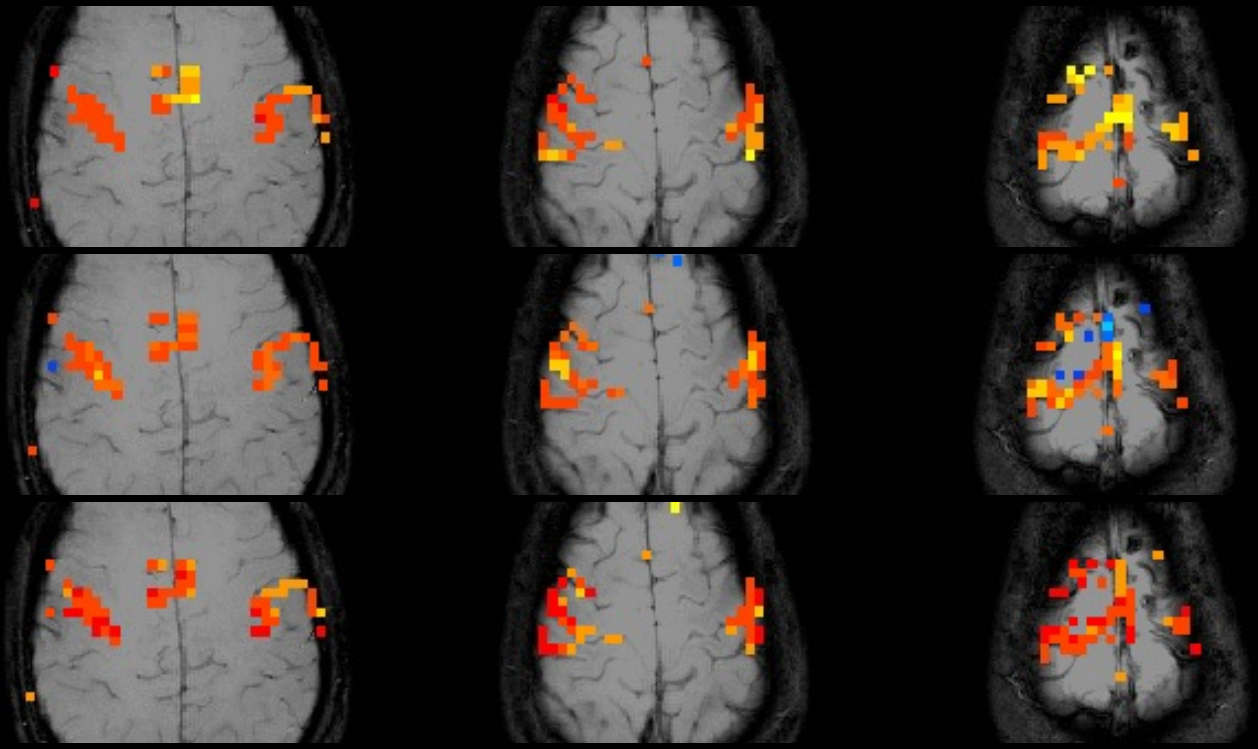


Results – motor task

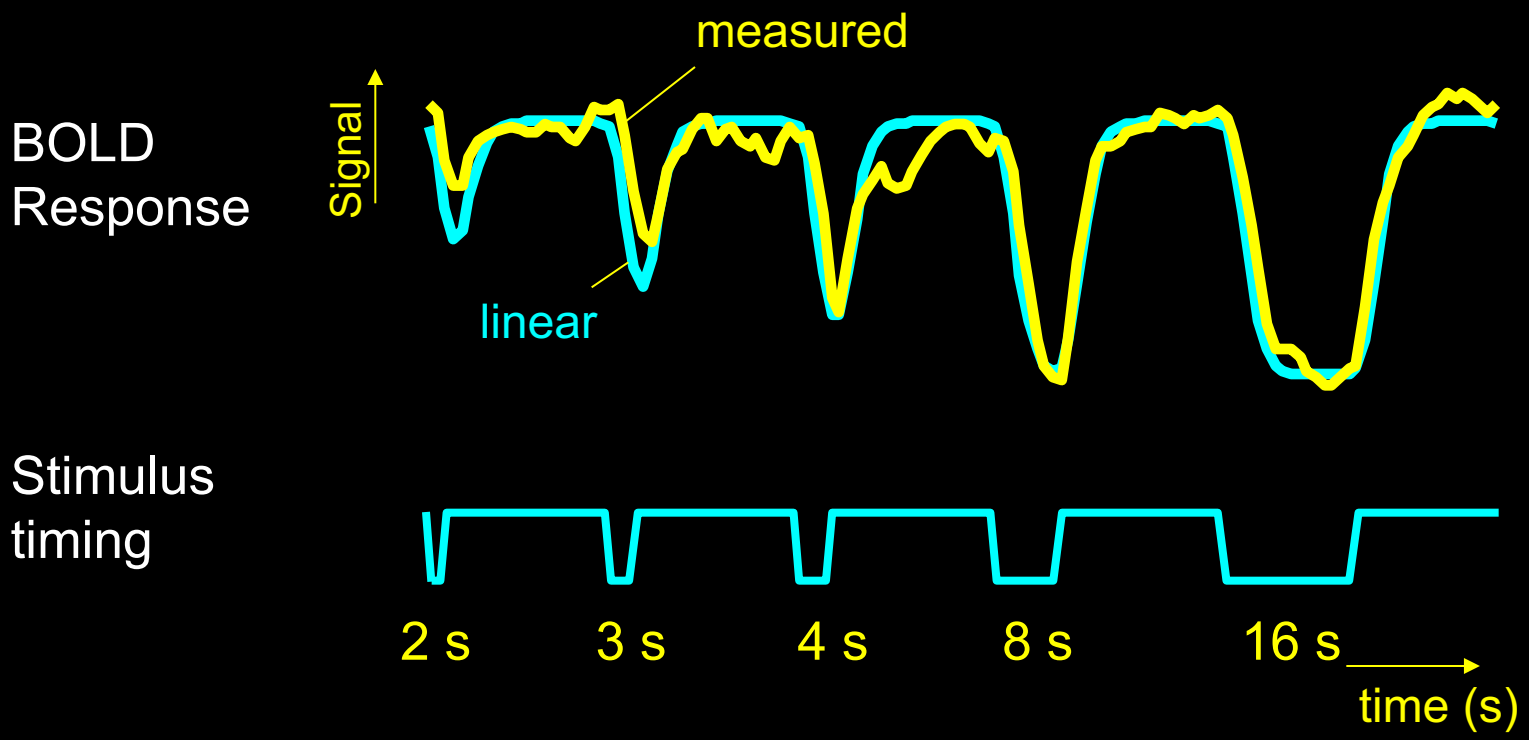
Nonlinearity

Magnitude

Latency



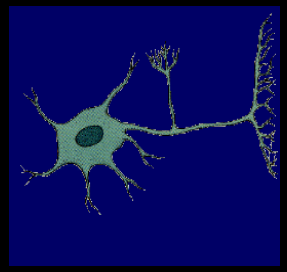
Different stimulus “ON” periods

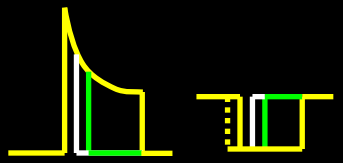


Brief stimulus OFF periods produce smaller decreases than expecte

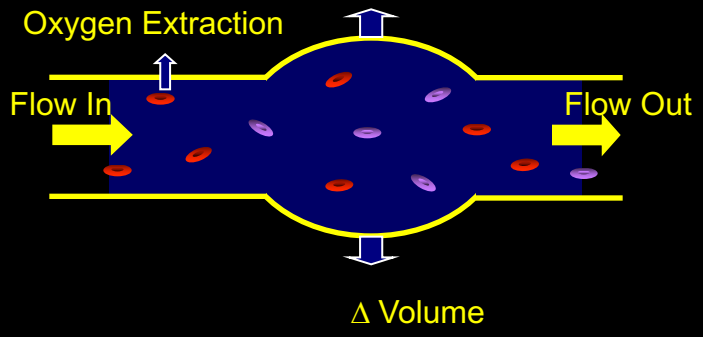
Sources of this Nonlinearity

- Neuronal

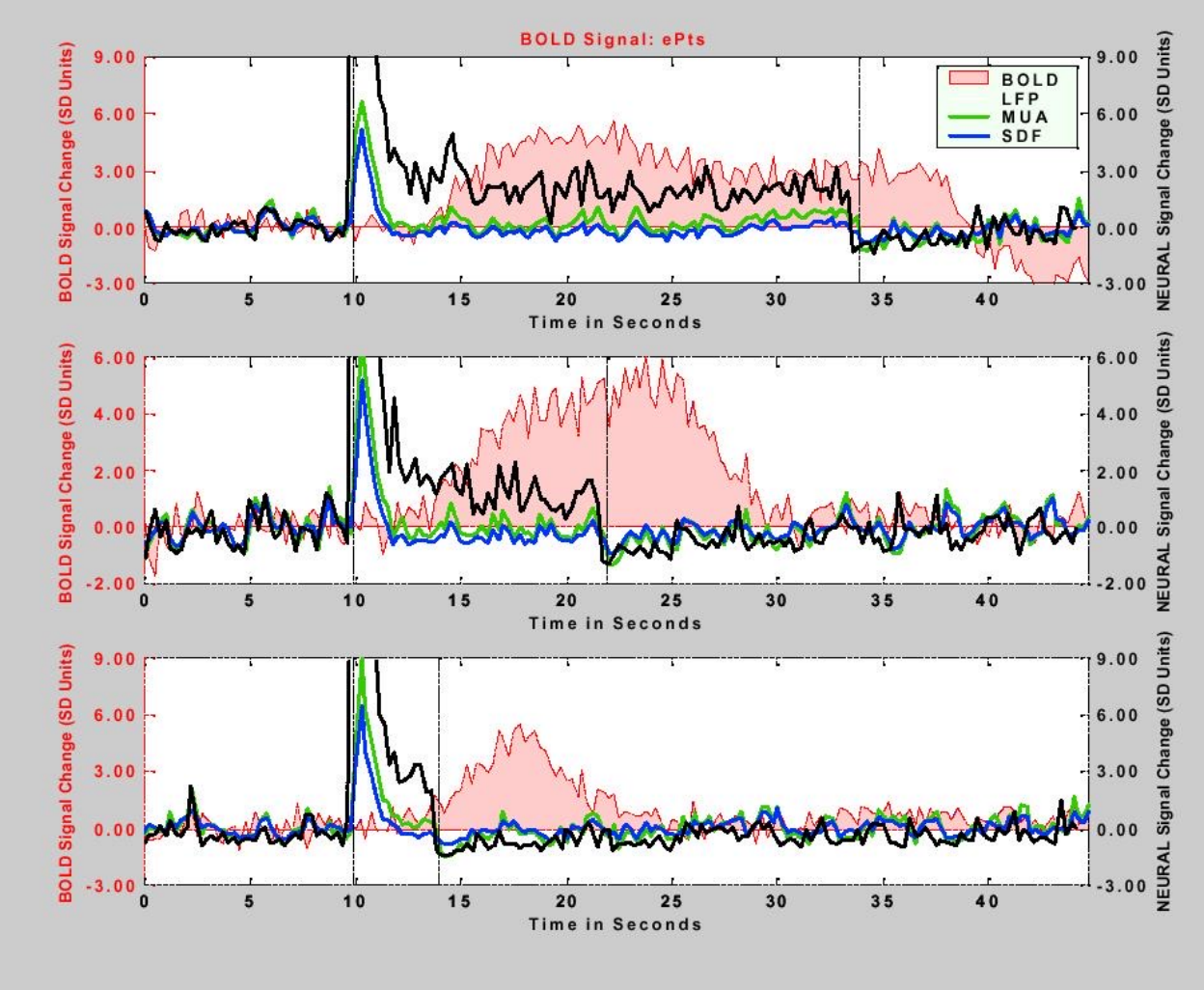




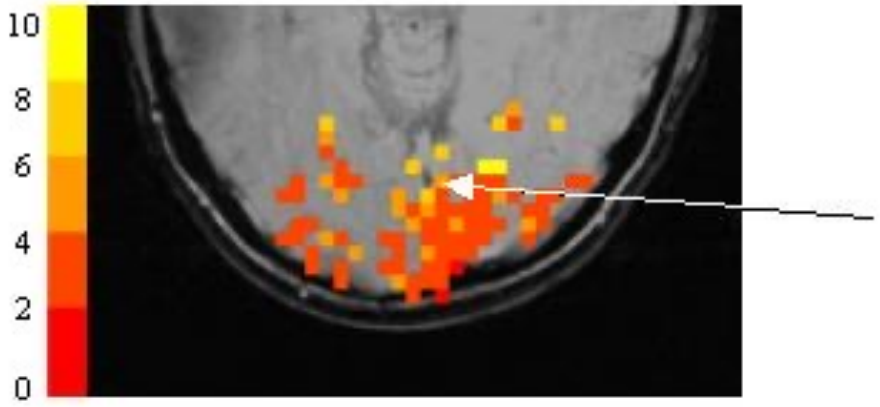
- Hemodynamic
  - Oxygen extraction
  - Blood volume dynamics

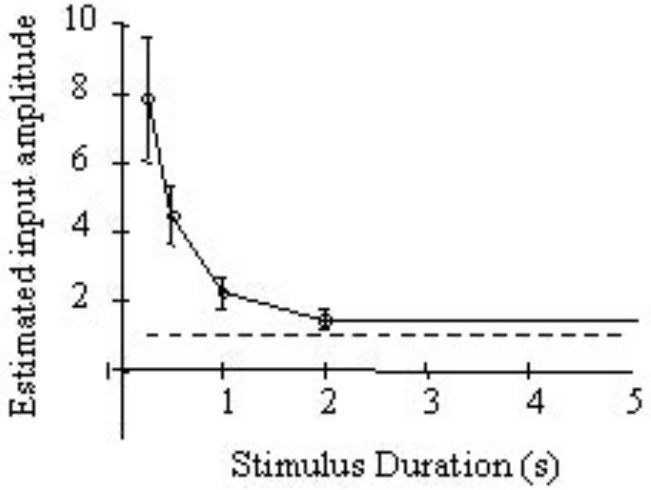


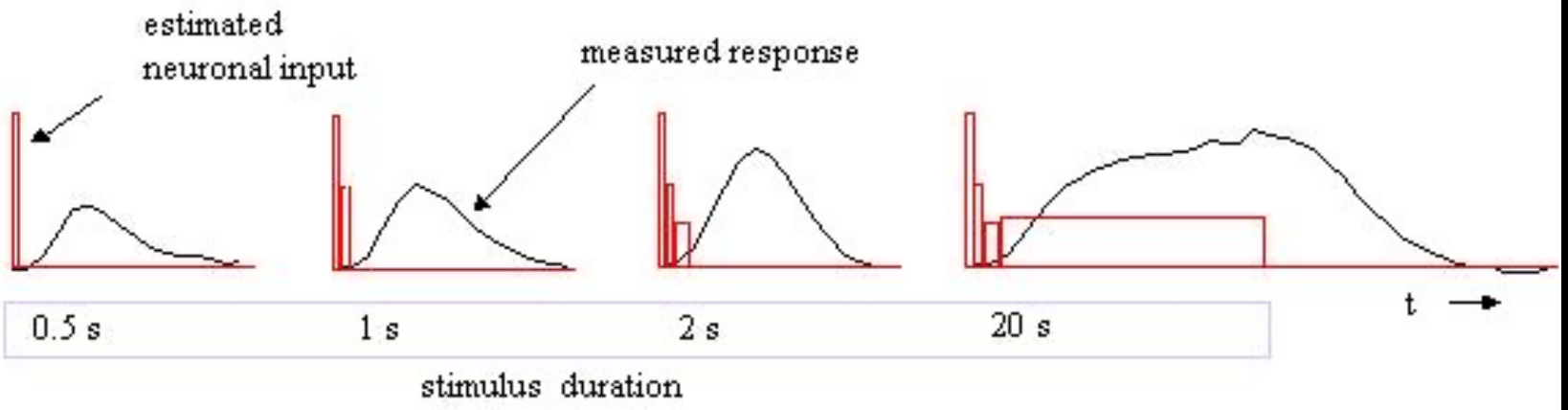
BOLD Correlation with Neuronal Activity



Logothetis et al. Nature, 412, 150-157

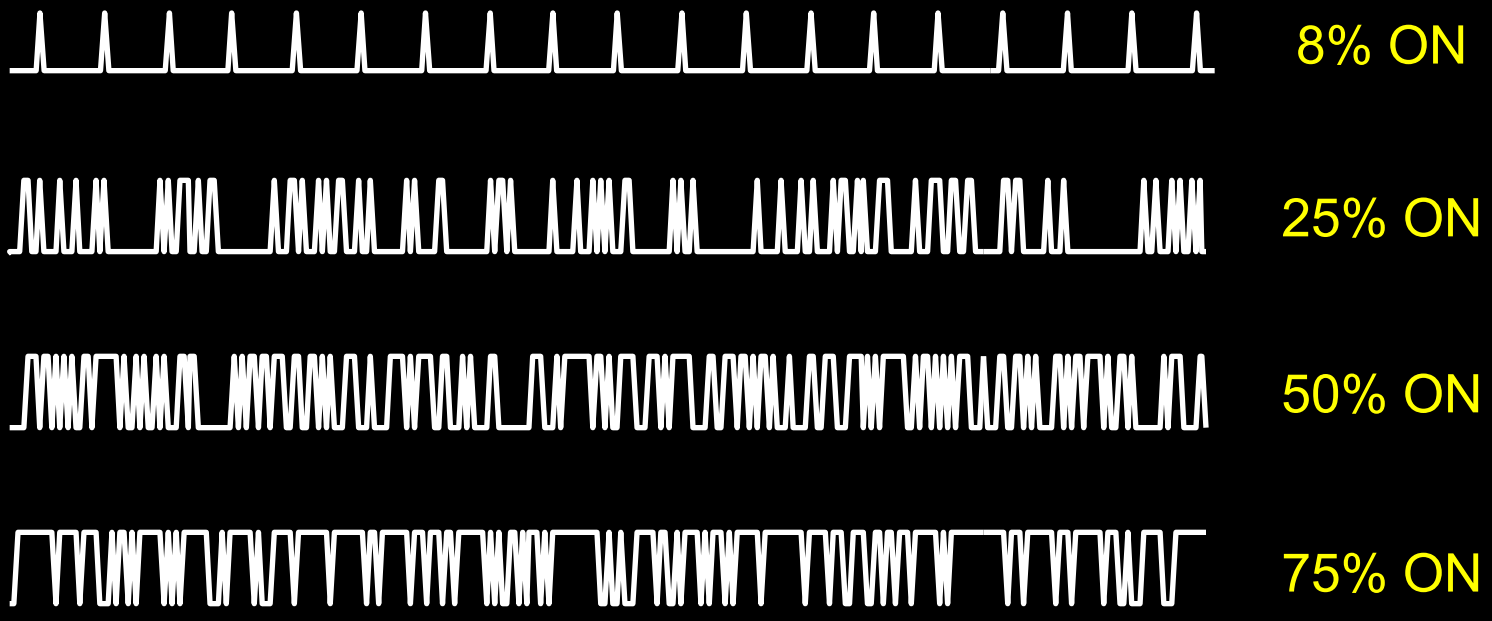

10
8
6
4
2
0


Estimated input amplitude
10
8
6
4
2
1
1
2
3
4
5
Stimulus Duration (s)


estimated
neuronal input
measured response
t
0.5 s
1 s
2 s
20 s
stimulus duration

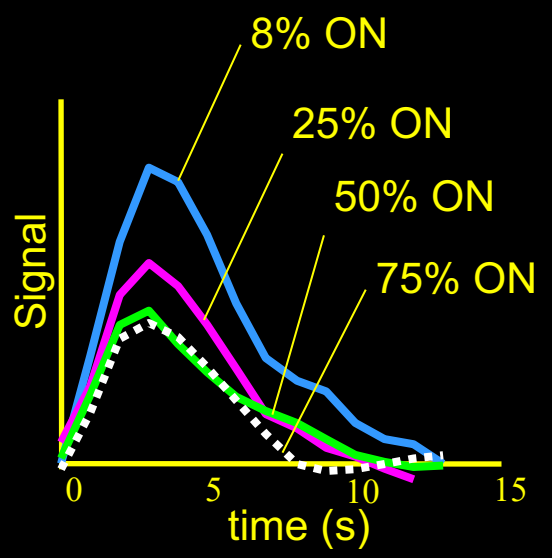
Varying “ON” and “OFF” periods

- *Rapid event-related design with varying ISI*

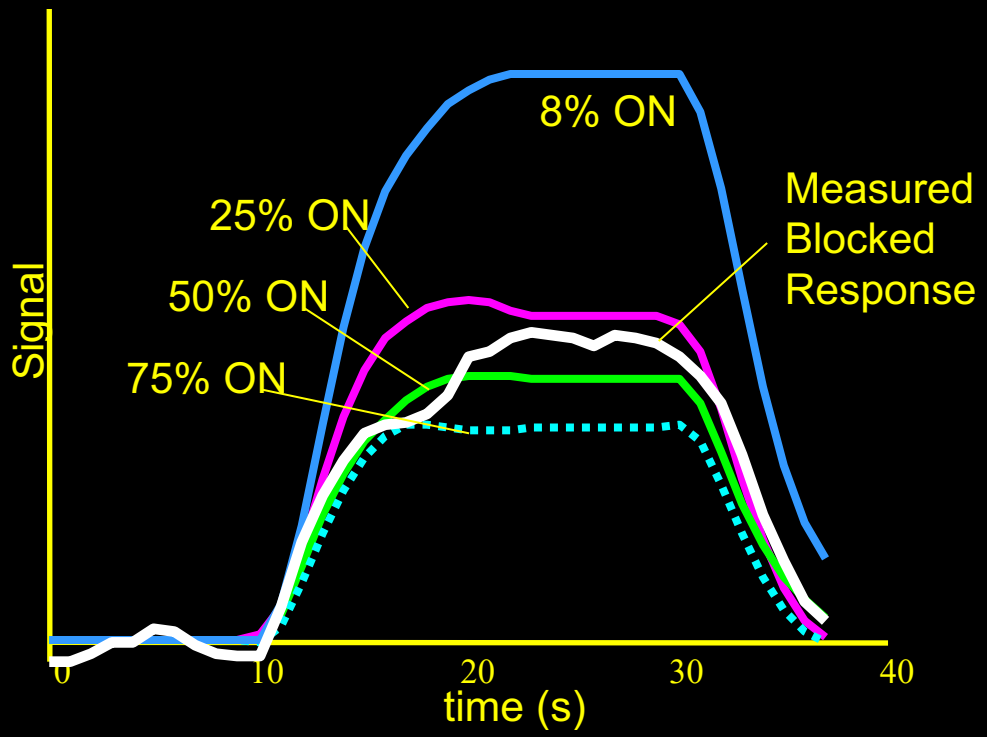


Varying “ON” and “OFF” periods

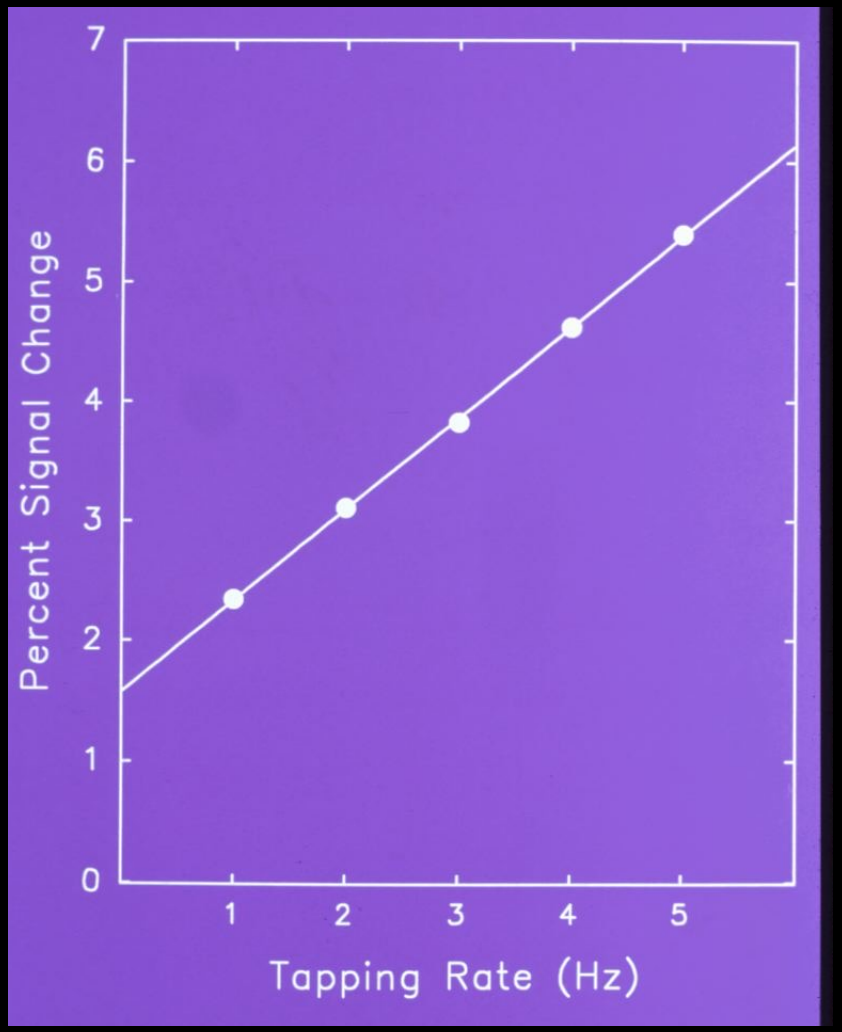
Estimated Impulse Response



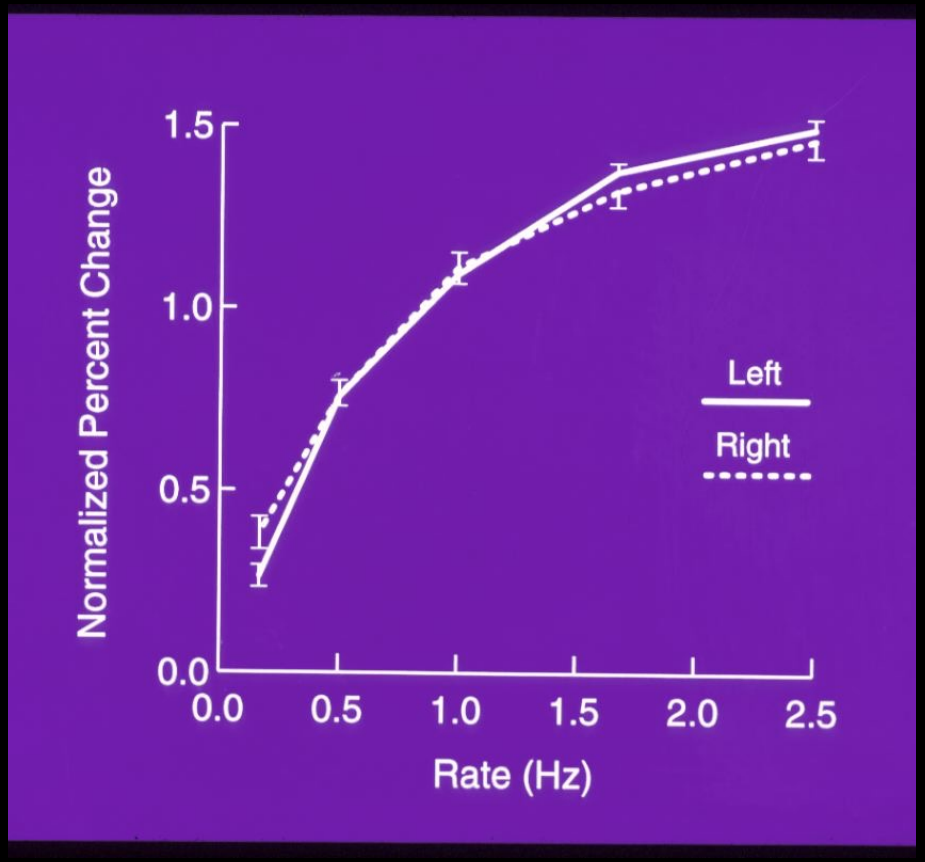
Predicted Responses to 20 s stimulation

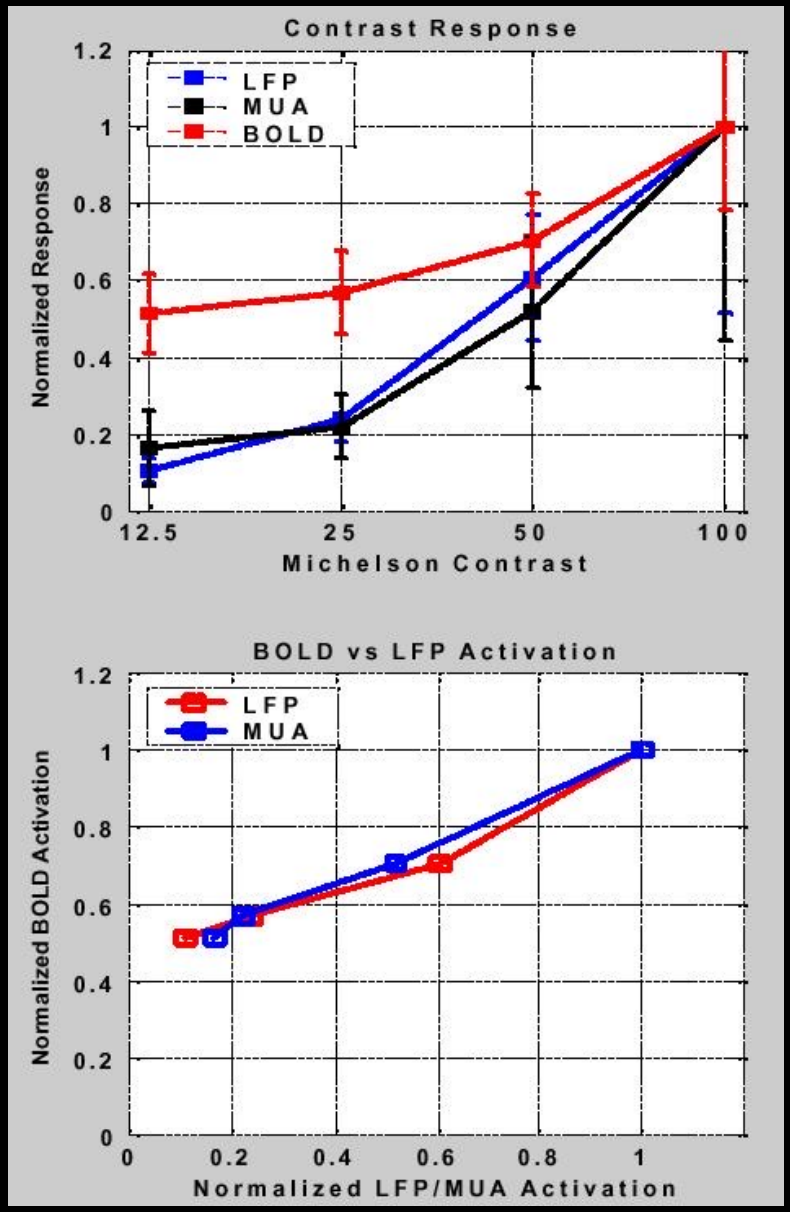


Motor Cortex



Auditory Cortex





Logothetis et al. Nature, 412, 150-157

- Contrast in FMRI

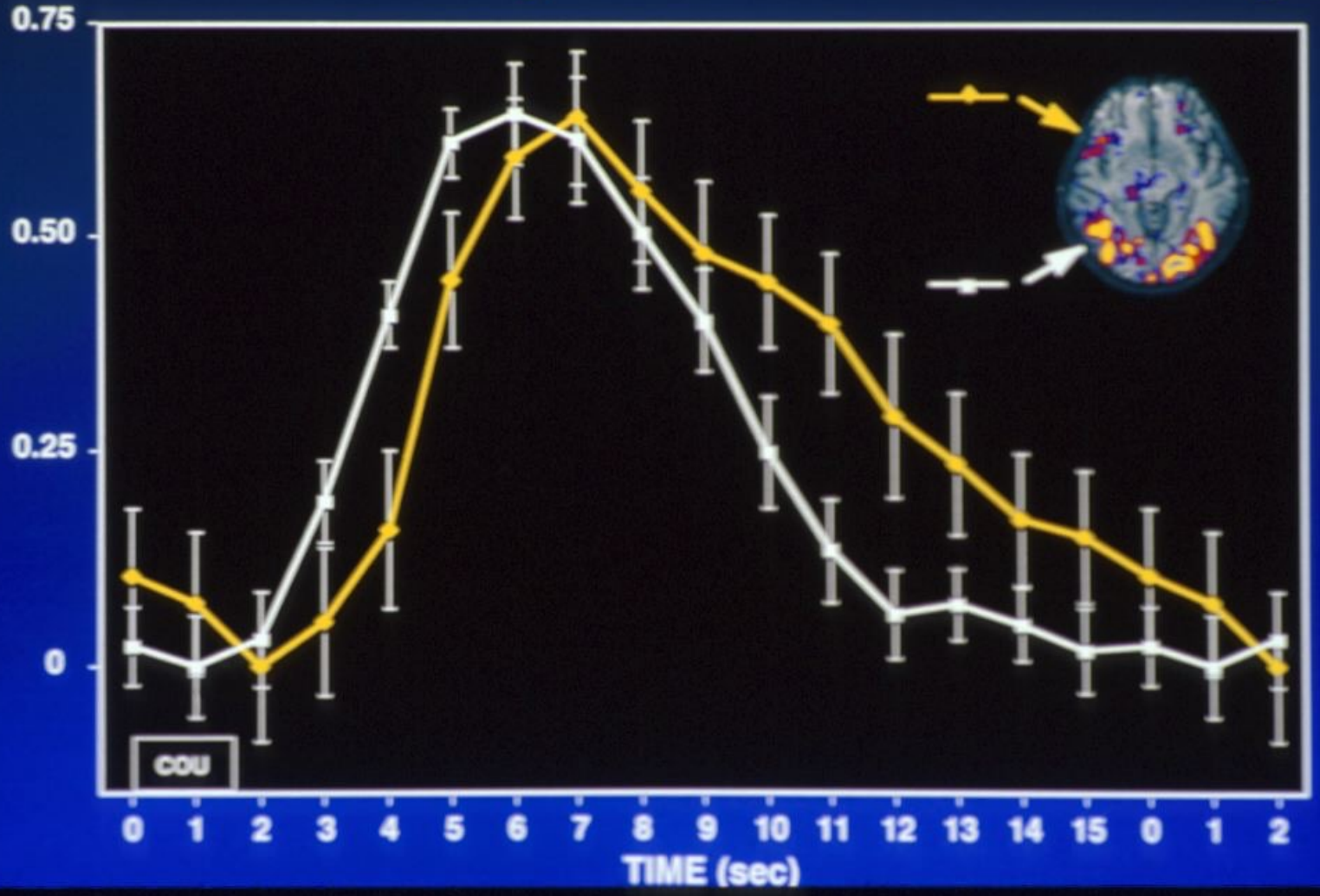
  Hemodynamic Specificity
- The Hemodynamic Transfer Function

  Location, Latency, Magnitude
- Best Results So Far

  Temporal Resolution, Spatial Resolution
- Neuronal Activation Input Strategies

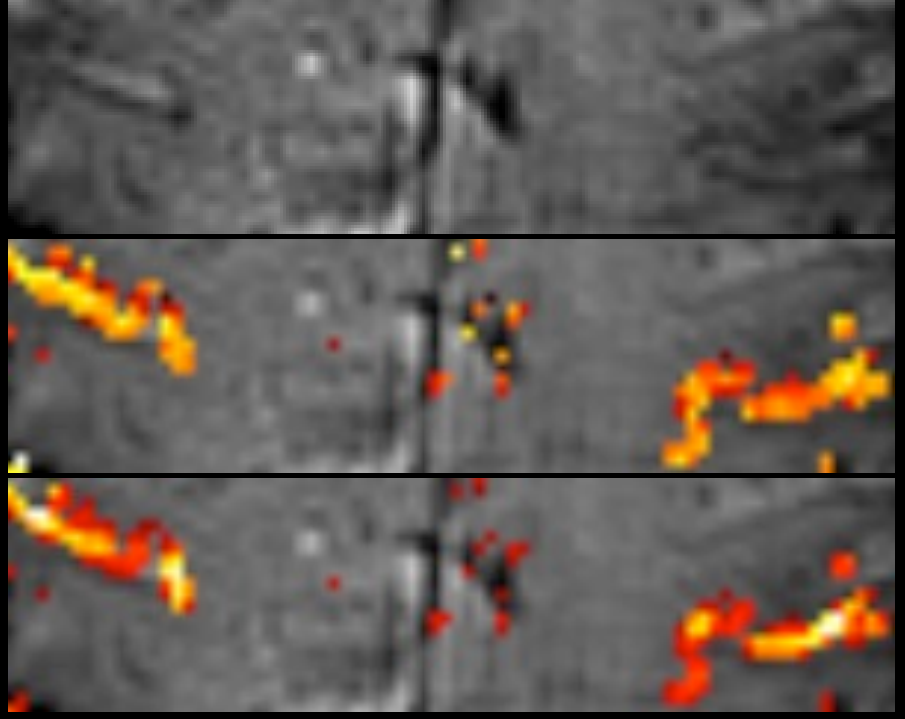
  Block Design
  Phase and Frequency Encoding
  Orthogonal Designs
  Parametric Designs
  Event-Related Designs
  Free Behavior Designs

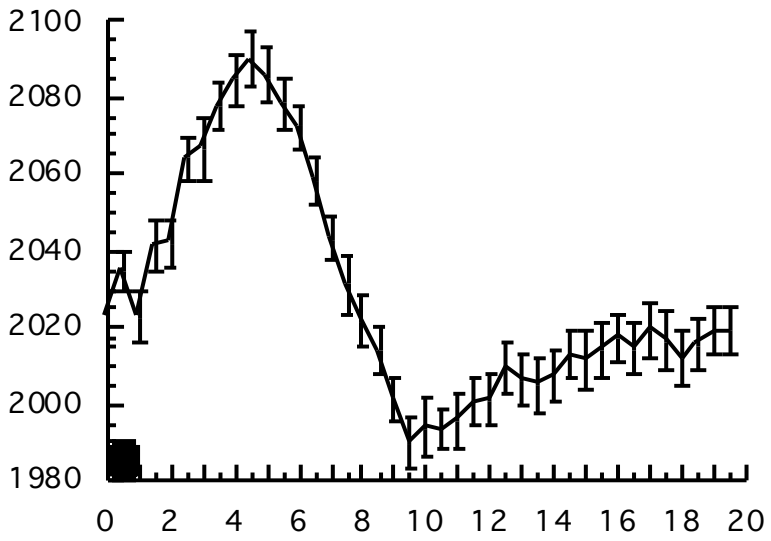
Time Course Comparison Across Brain Regions

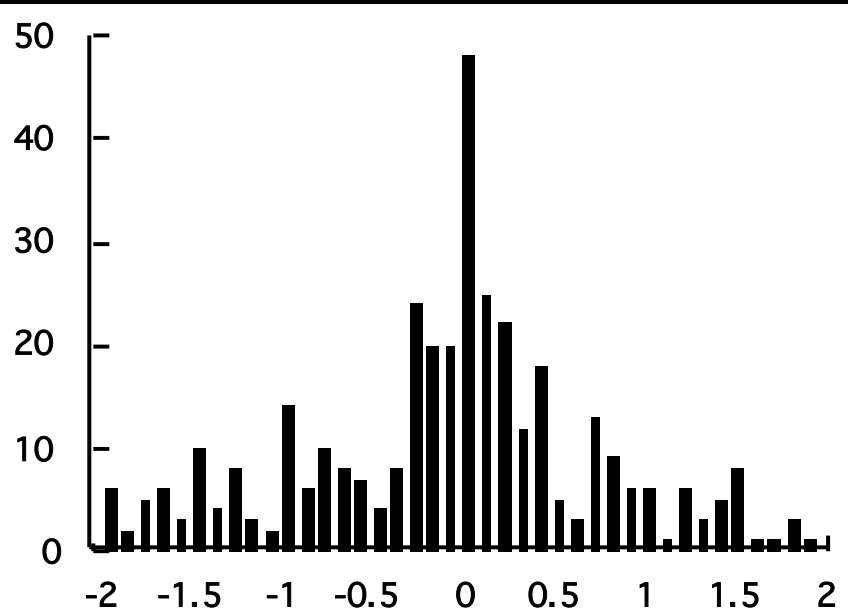


Latency

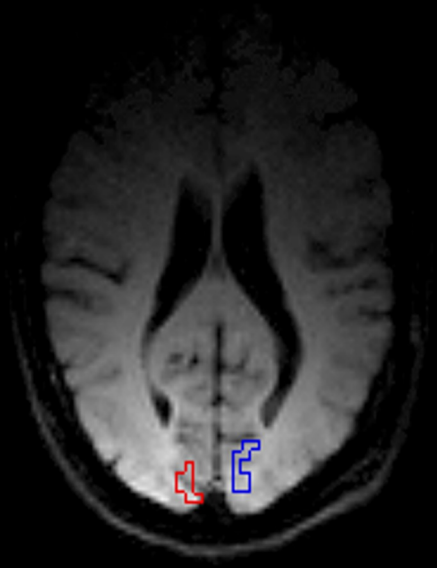
Magnitude





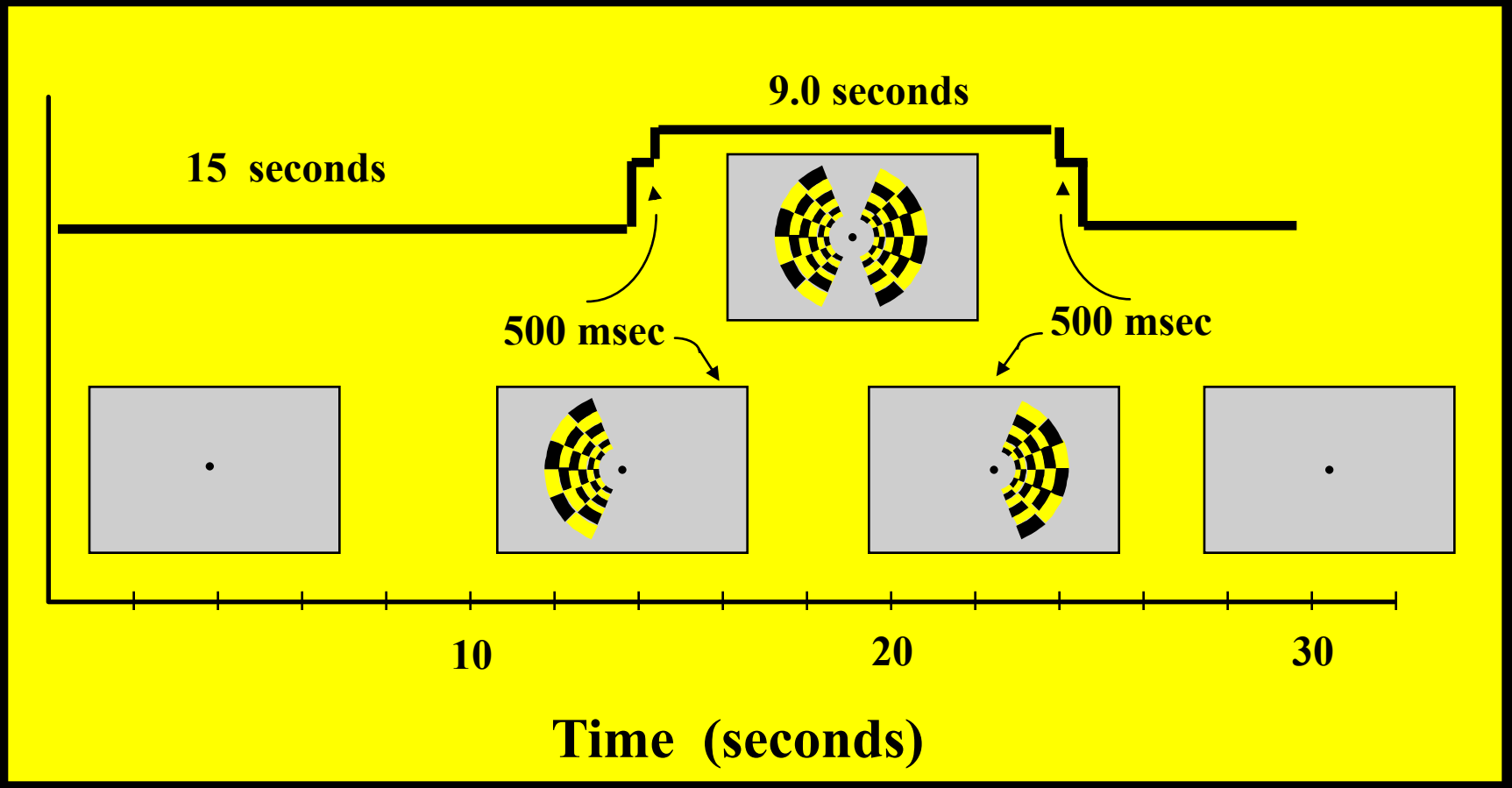


Regions of Interest Used for Hemi-Field Experiment

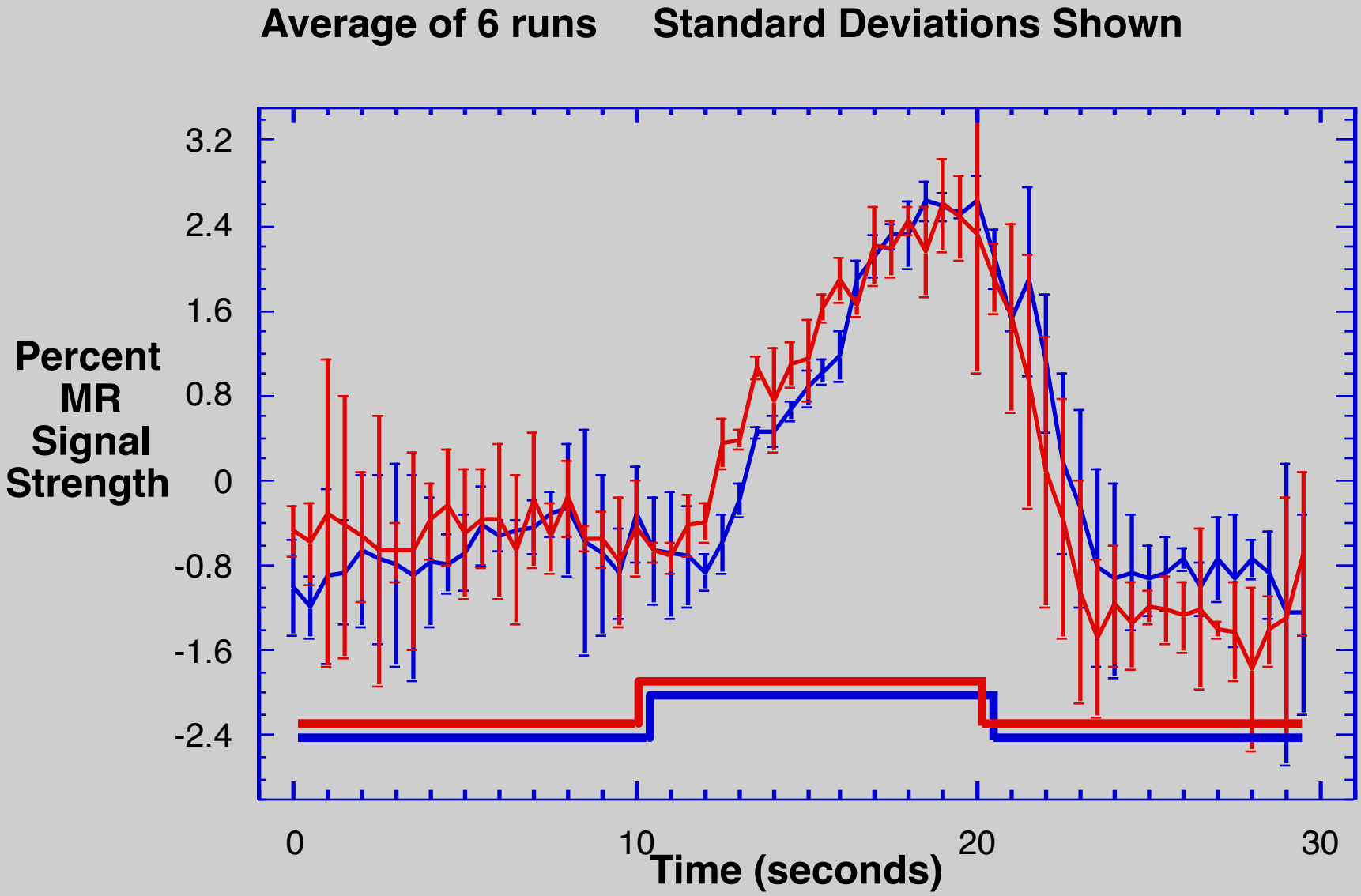


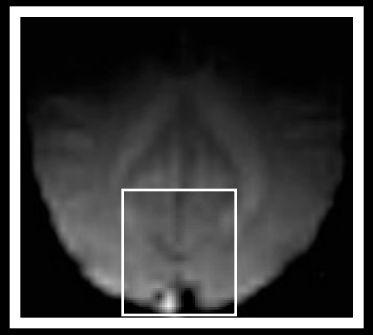
Right Hemisphere

Left Hemisphere


9.0 seconds
15 seconds
500 msec
500 msec
10
20
30
Time (seconds)

Hemi-field with 500 msec asynchrony





500 ms

500 ms

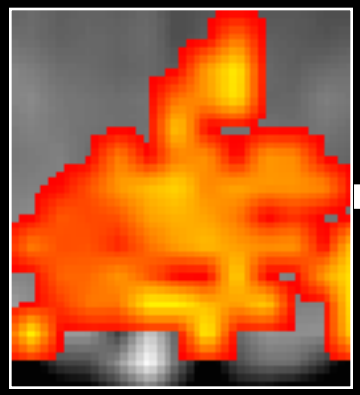
Right Hemifield

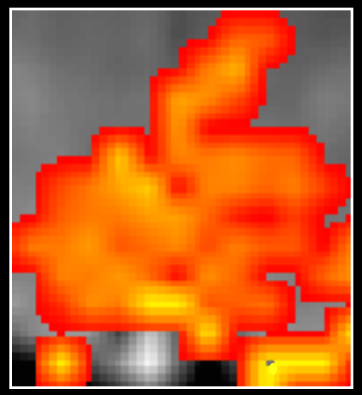
Left Hemifield

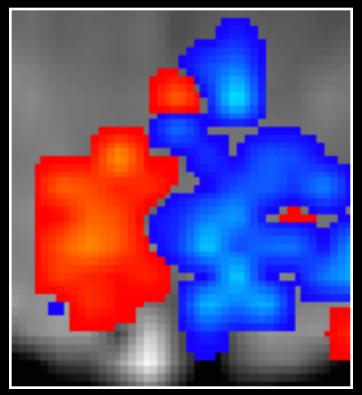
+ 2.5 s

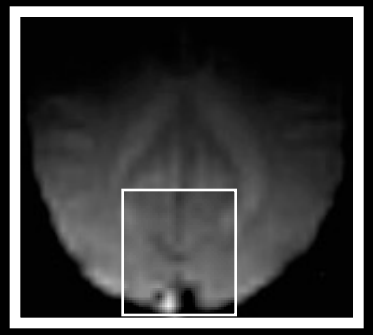
0 s

- 2.5 s





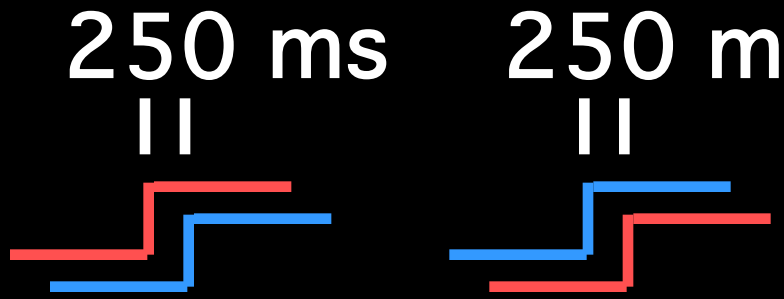




250 ms 250 ms

Right Hemifield

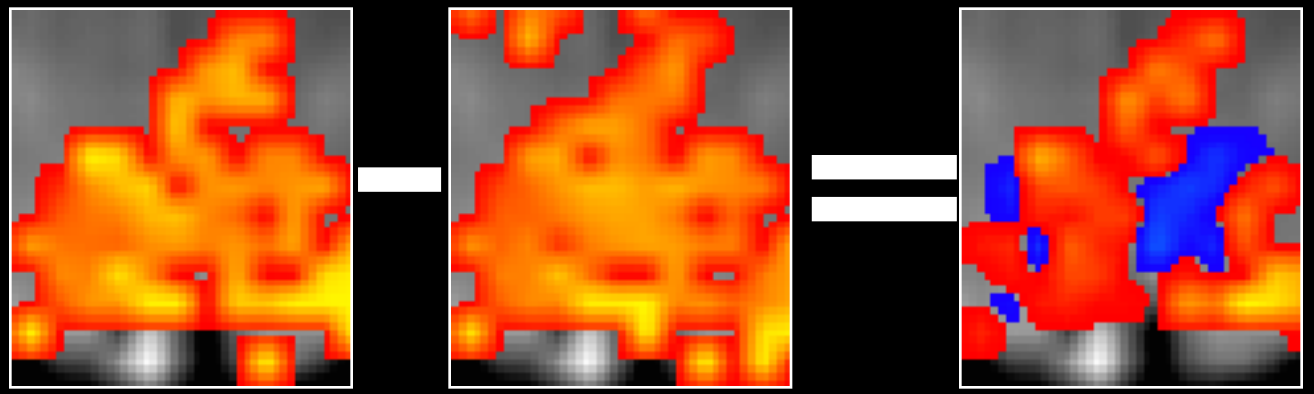
Left Hemifield



+ 2.5 s

0 s

- 2.5 s



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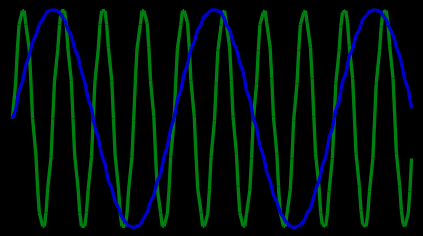
  Parametric Designs

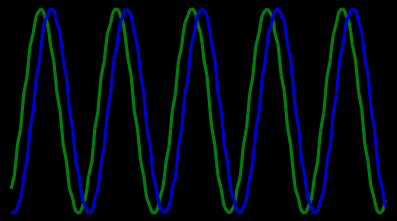
  Event-Related Designs

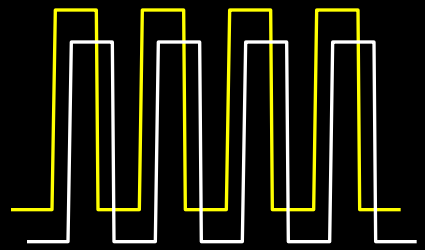
  Free Behavior Designs

Neuronal Activation Input Strategies

1. Block Design
2. Frequency Encoding
3. Phase Encoding
4. Single Event
5. Orthogonal Block Design
6. Free Behavior Design.



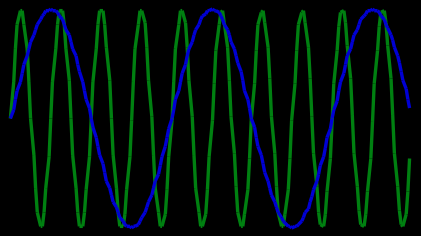




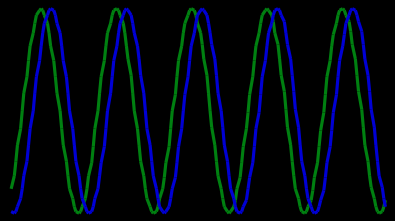
Neuronal Activation Input Strategies

1. Block Design

2. Frequency Encoding

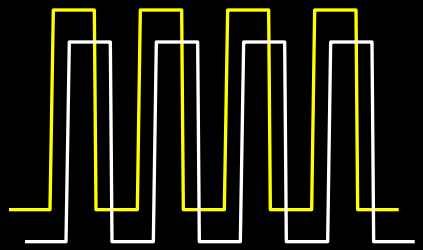


3. Phase Encoding

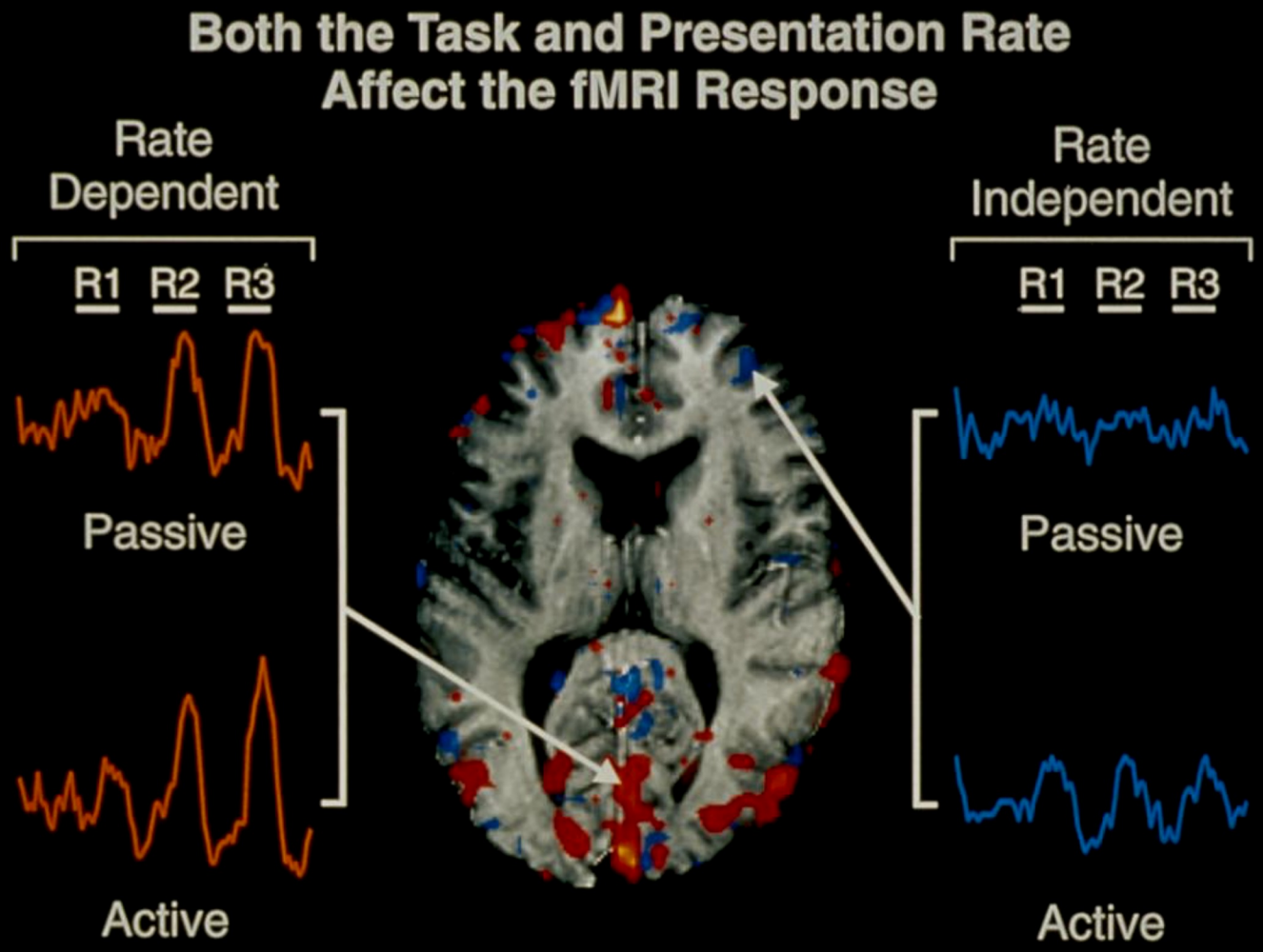


4. Single Event

5. Orthogonal Block Design



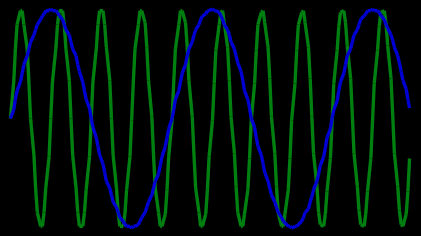
6. Free Behavior Design.


Both the Task and Presentation Rate
Affect the fMRI Response
Rate
Dependent
R1 R2 R3
Passive
Active
Rate
Independent
R1 R2 R3
Passive
Active

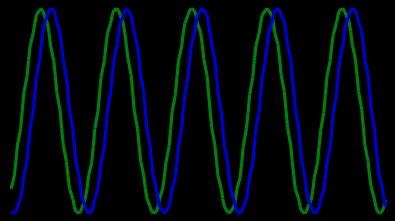
DeYoe et al.

Neuronal Activation Input Strategies

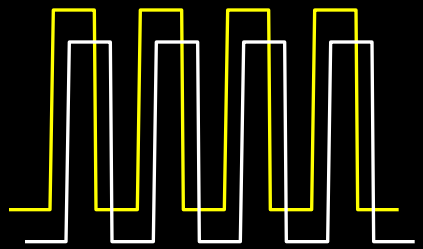
1. Block Design
2. Frequency Encoding



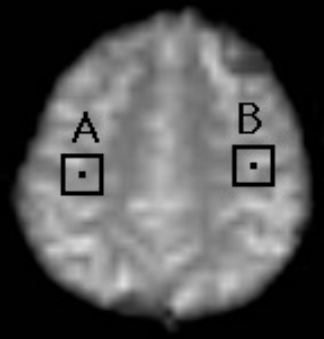
3. Phase Encoding

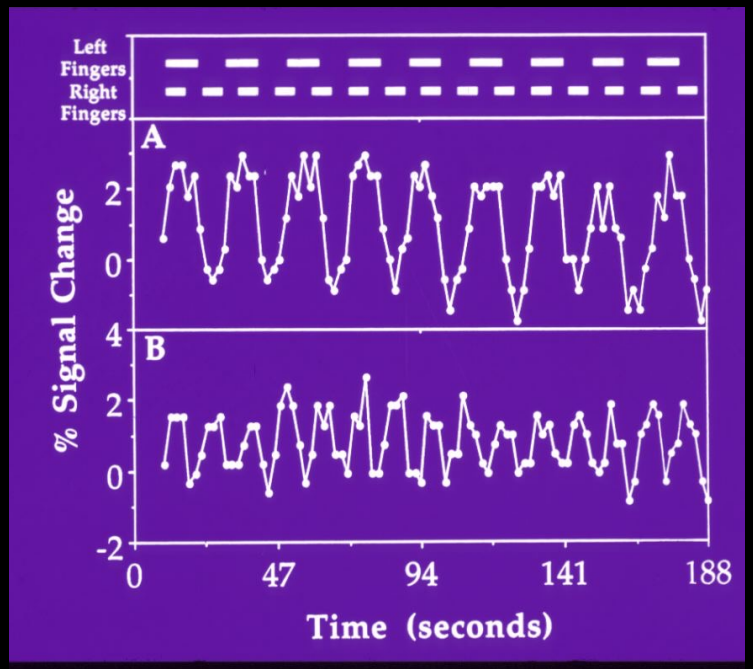


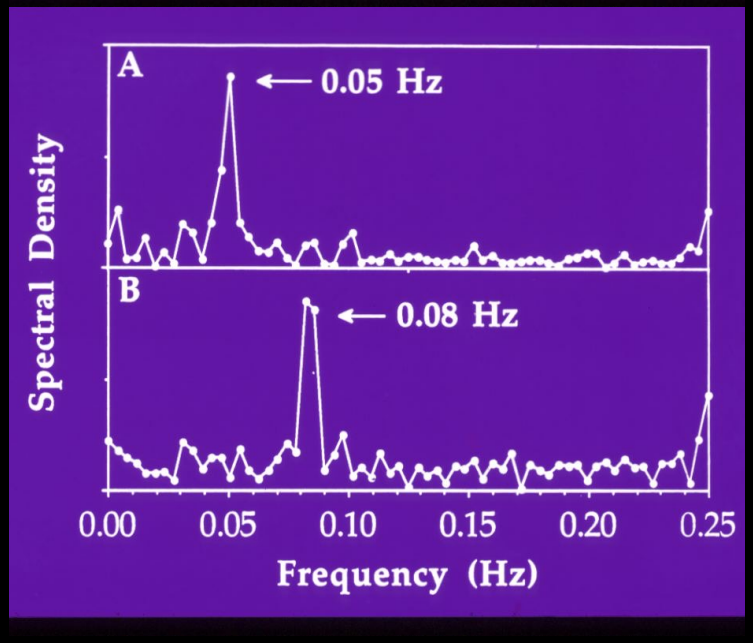
4. Single Event
5. Orthogonal Block Design

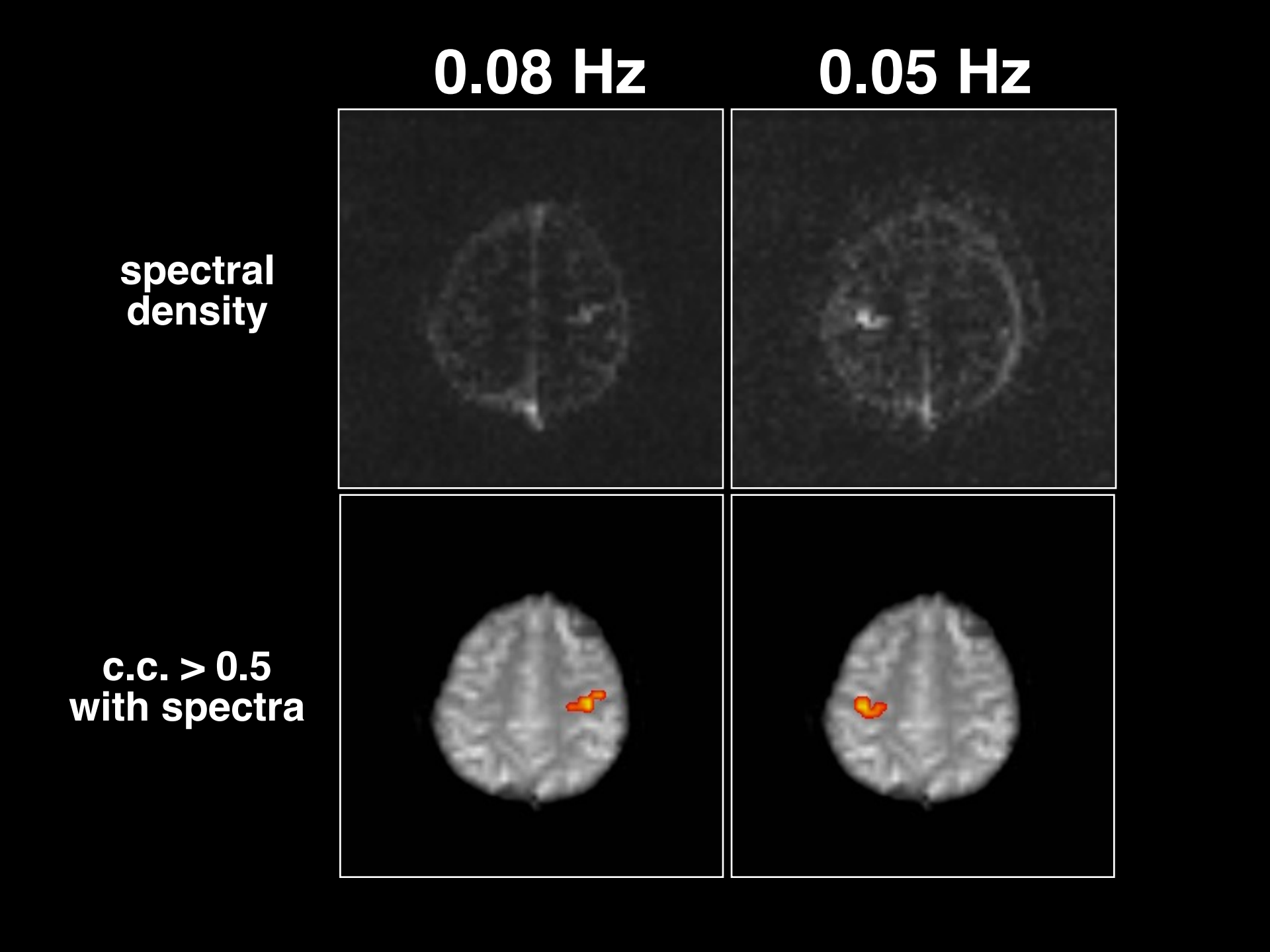


6. Free Behavior Design.


A
B


Left Fingers
Right Fingers
A
B
% Signal Change
2
0
4
2
0
-2
0
47
94
141
188
Time (seconds)

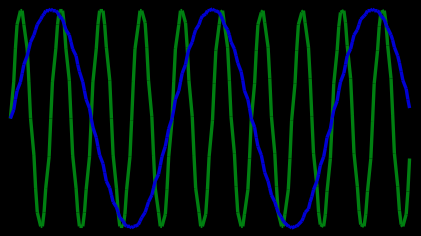

A
0.05 Hz
B
0.08 Hz
Spectral Density
0.00
0.05
0.10
0.15
0.20
0.25
Frequency (Hz)


0.08 Hz
0.05 Hz
spectral density
c.c. > 0.5 with spectra

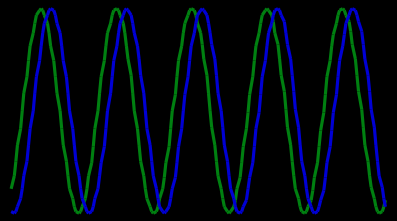
Neuronal Activation Input Strategies

1. Block Design

2. Frequency Encoding

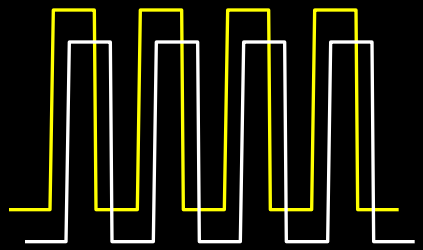


3. Phase Encoding

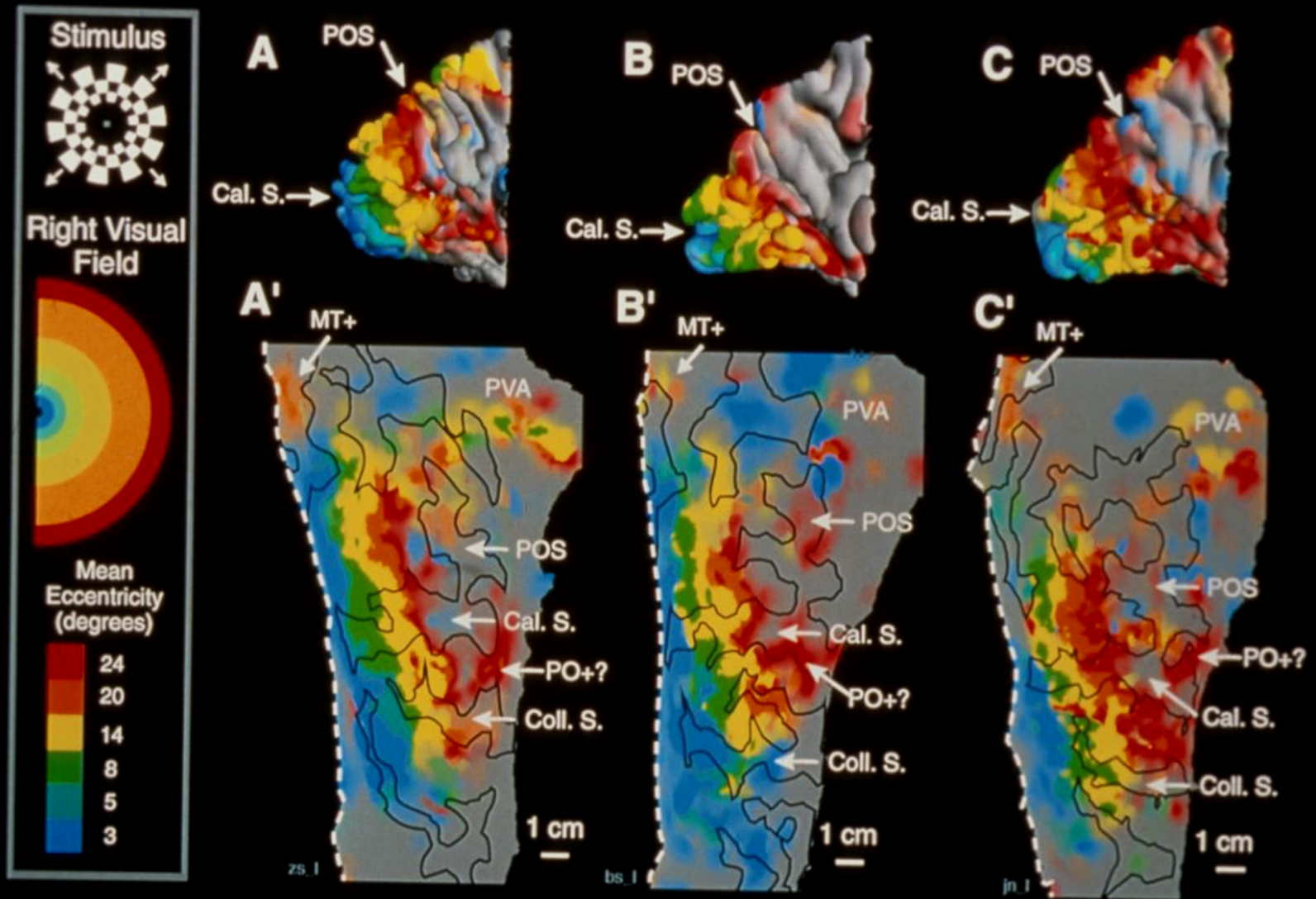


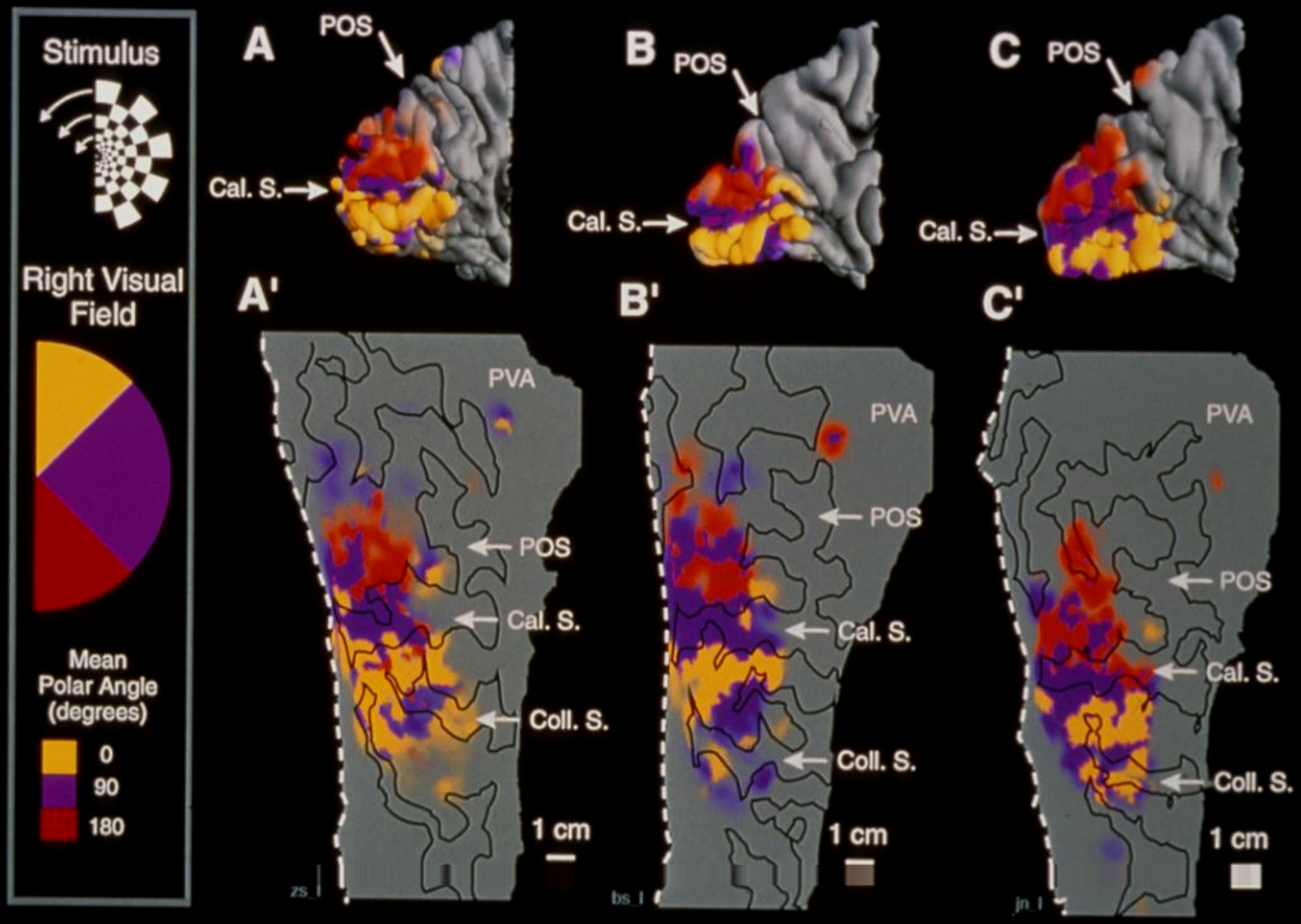
4. Single Event

5. Orthogonal Block Design



6. Free Behavior Design.

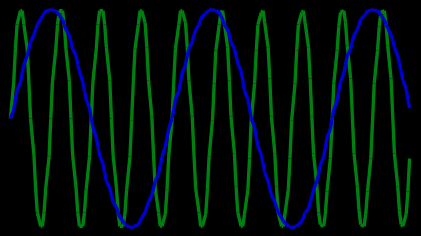

Stimulus
Right Visual Field
Mean Eccentricity (degrees)
24
20
14
8
5
3
A
POS
Cal. S.
B
POS
Cal. S.
C
POS
Cal. S.
A'
MT+
PVA
POS
Cal. S.
PO+?
Coll. S.
1 cm
zs_l
B'
MT+
PVA
POS
Cal. S.
PO+?
Coll. S.
1 cm
bs_l
C'
MT+
PVA
POS
PO+?
Cal. S.
Coll. S.
1 cm
jn_l


Stimulus
Right Visual Field
Mean Polar Angle (degrees)
0
90
180
A
POS
Cal. S.
B
POS
Cal. S.
C
POS
Cal. S.
A'
PVA
POS
Cal. S.
Coll. S.
1 cm
zs_l
B'
PVA
POS
Cal. S.
Coll. S.
1 cm
bs_l
C'
PVA
POS
Cal. S.
Coll. S.
1 cm
jn_l

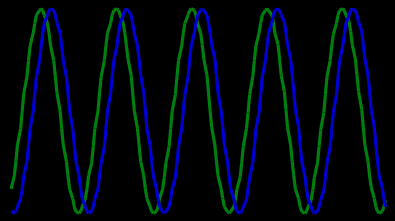
Neuronal Activation Input Strategies

1. Block Design

2. Frequency Encoding

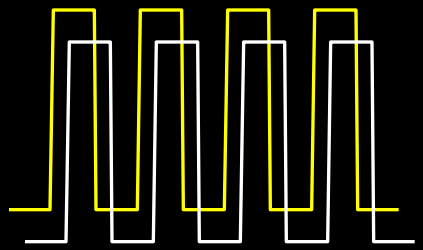


3. Phase Encoding



4. Single Event

5. Orthogonal Block Design

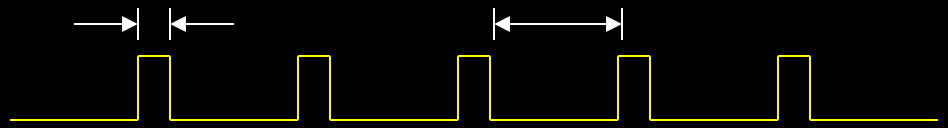


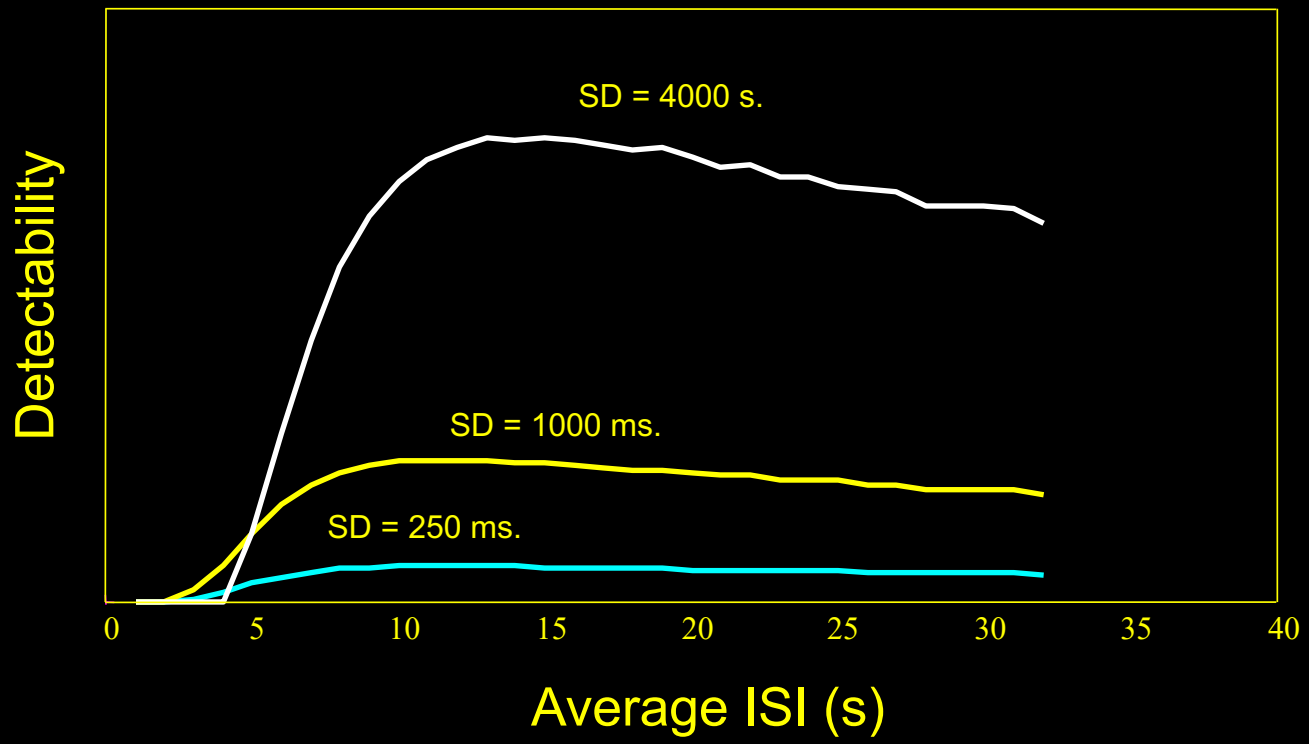
6. Free Behavior Design.

Detectability – constant ISI

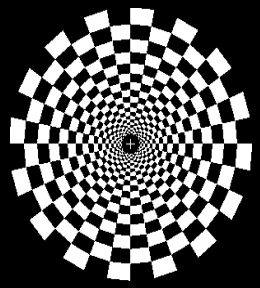
SD – stimulus duration

ISI – inter-stimulus interval

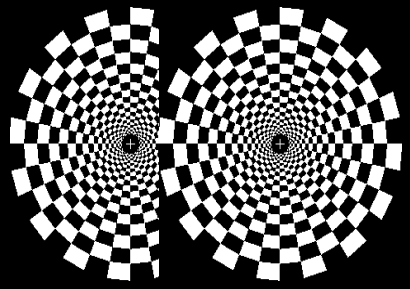




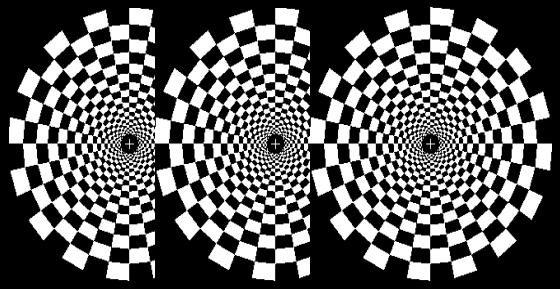
Visual Activation Paradigm: 1 , 2, & 3 Trials



0 sec 20 sec



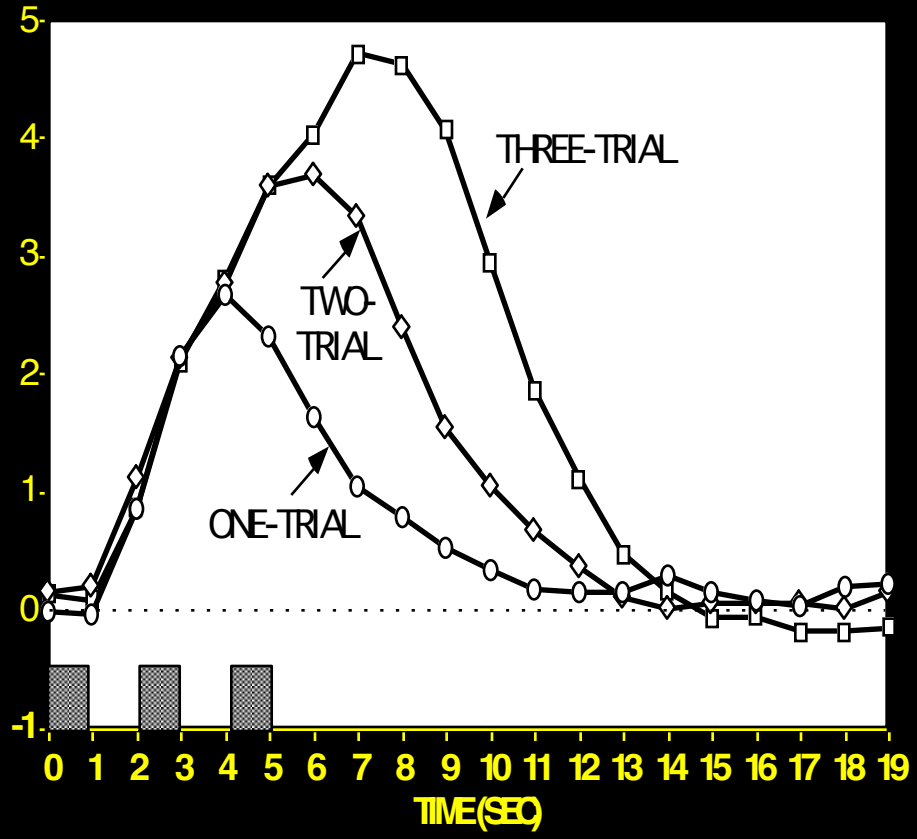
0 sec2 sec 20 sec



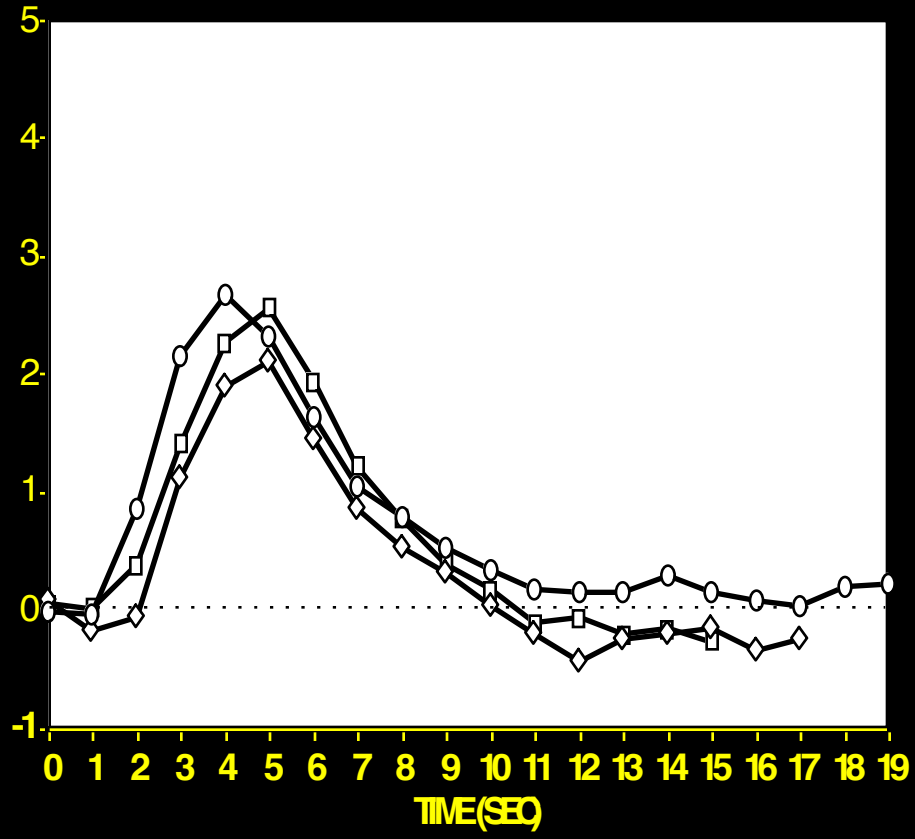
0 sec2 sec4 sec 20 sec

Response to Multiple Trials: Subject RW

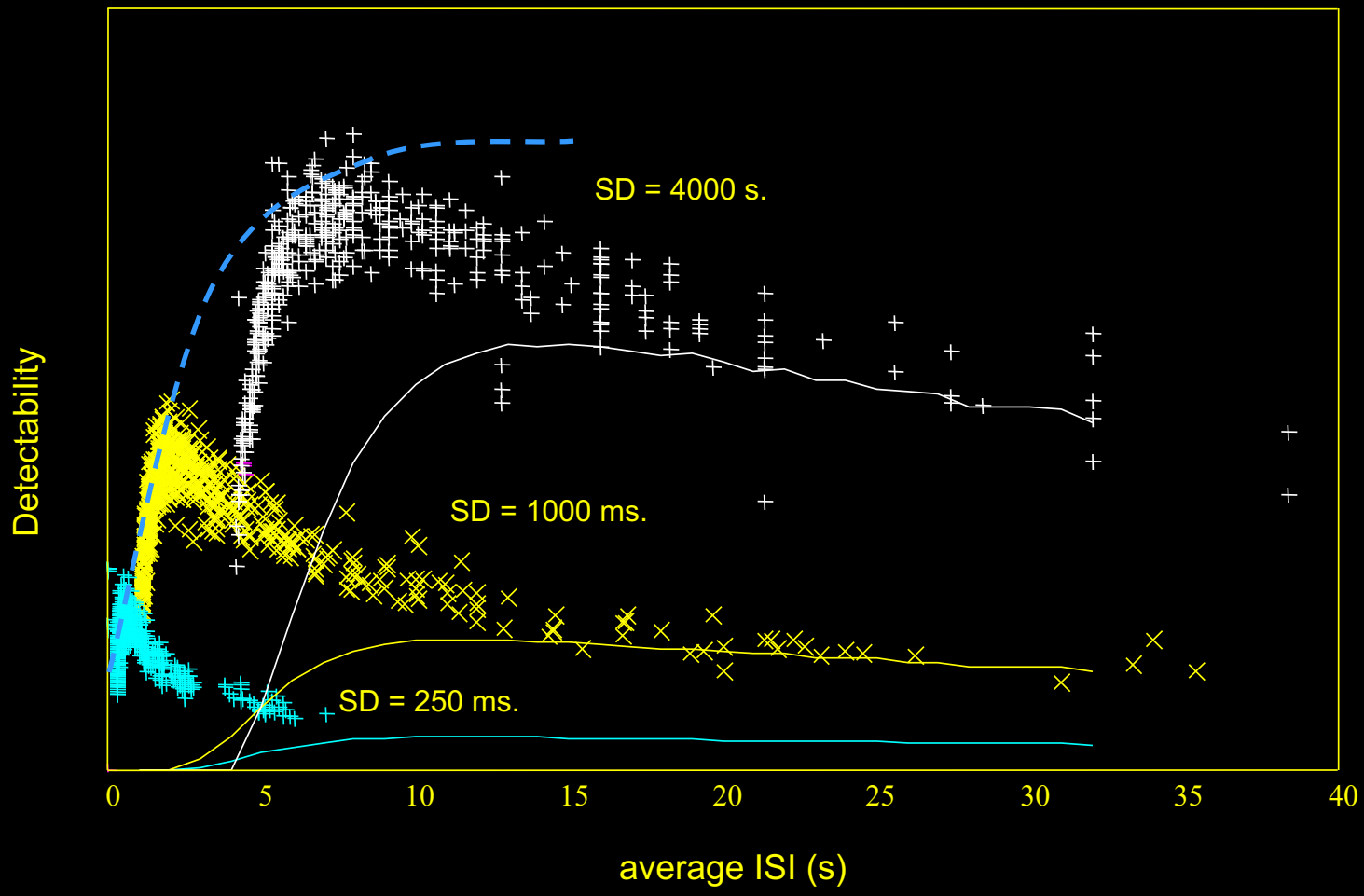
RAW DATA



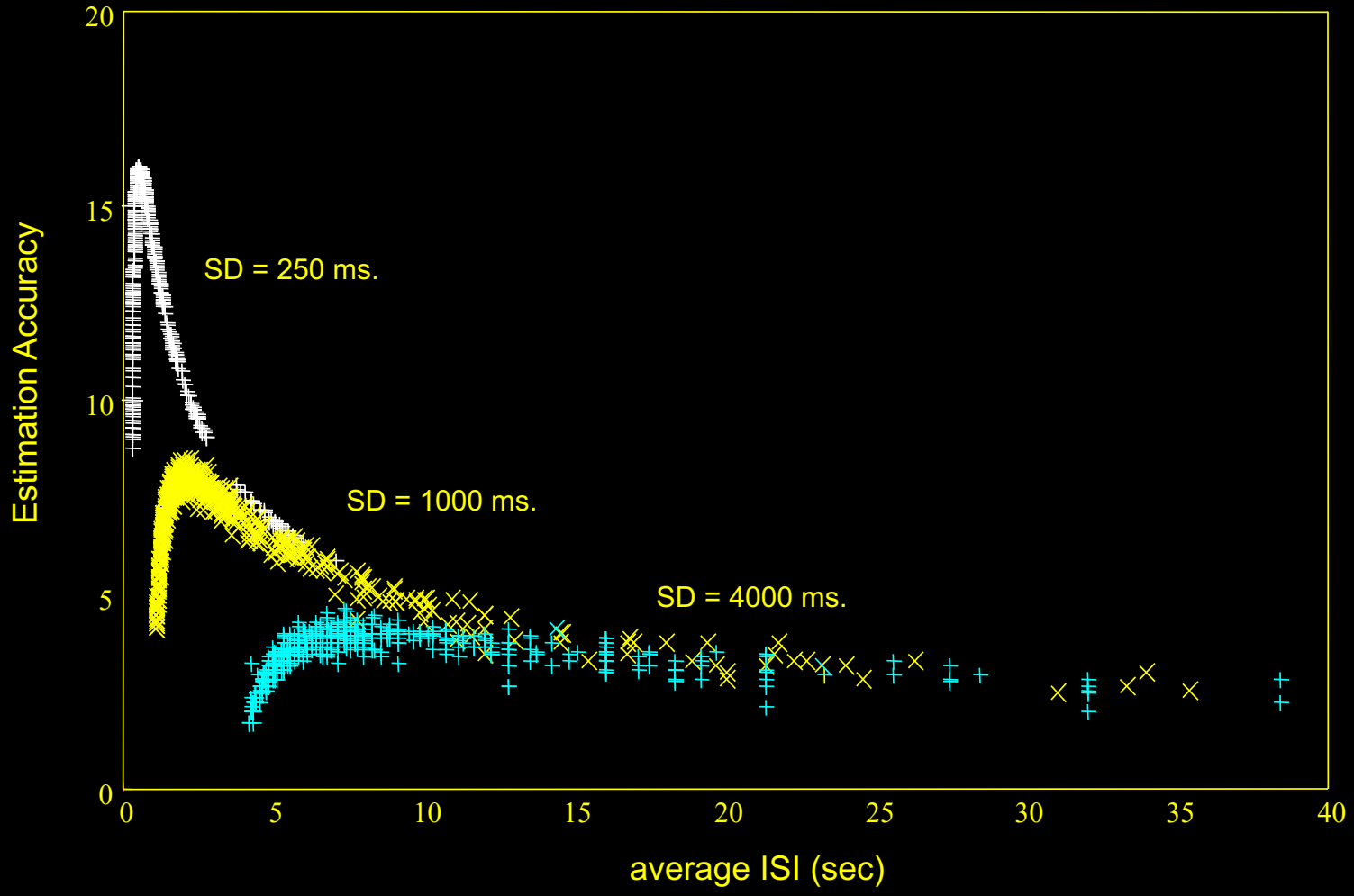
ESTIMATED RESPONSES



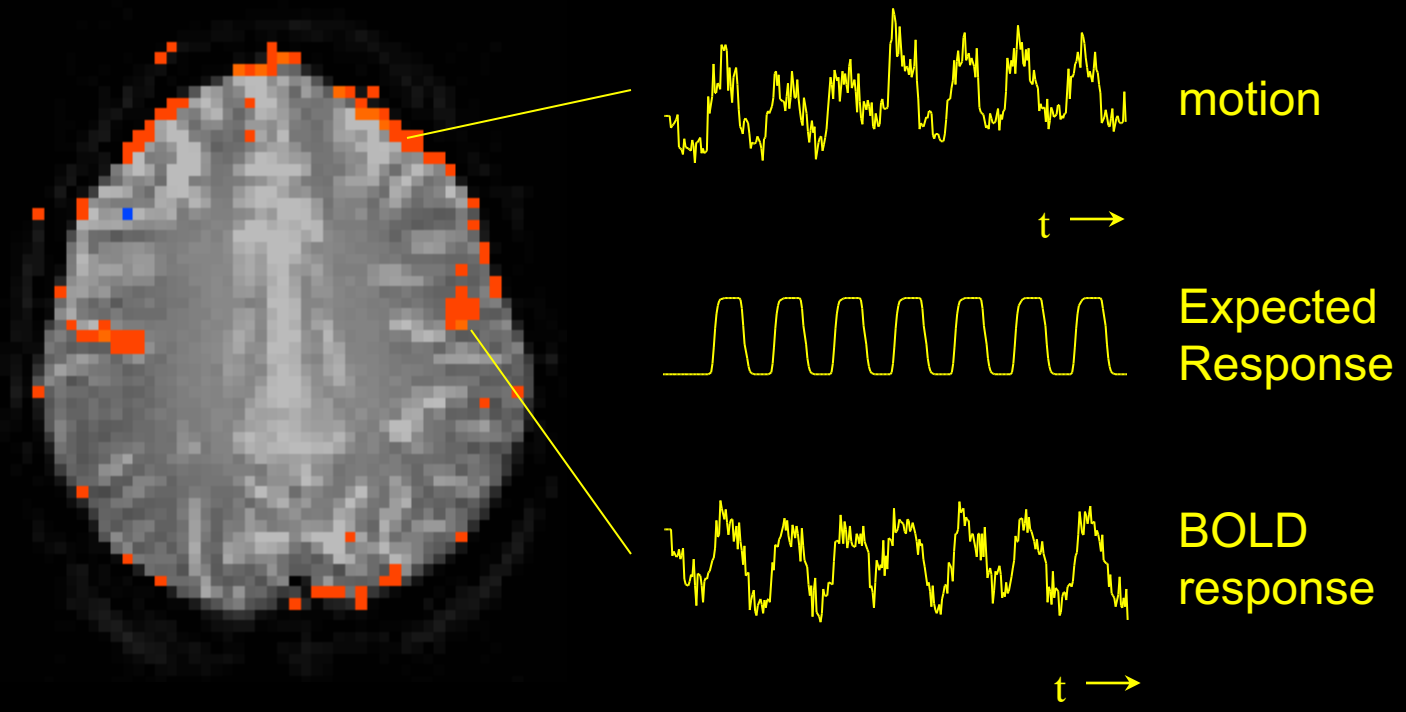
Detectability vs. Average ISI



Estimation accuracy vs. average ISI

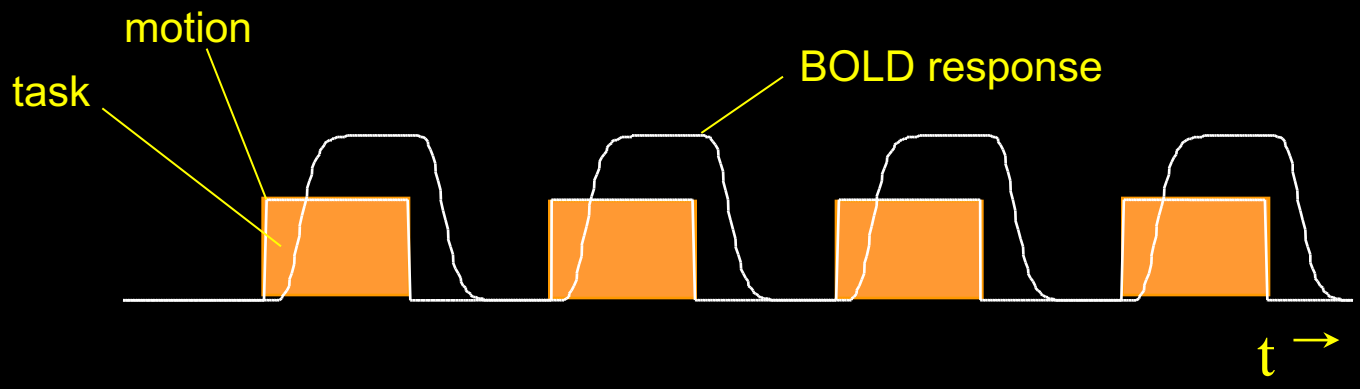


Speaking - Blocked Trial

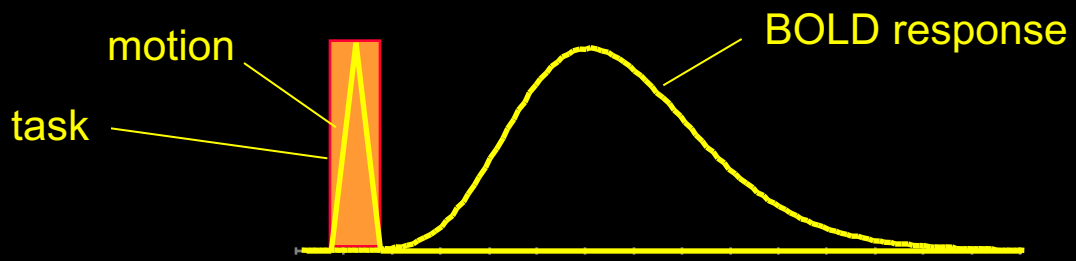


fMRI during tasks that involve brief motion

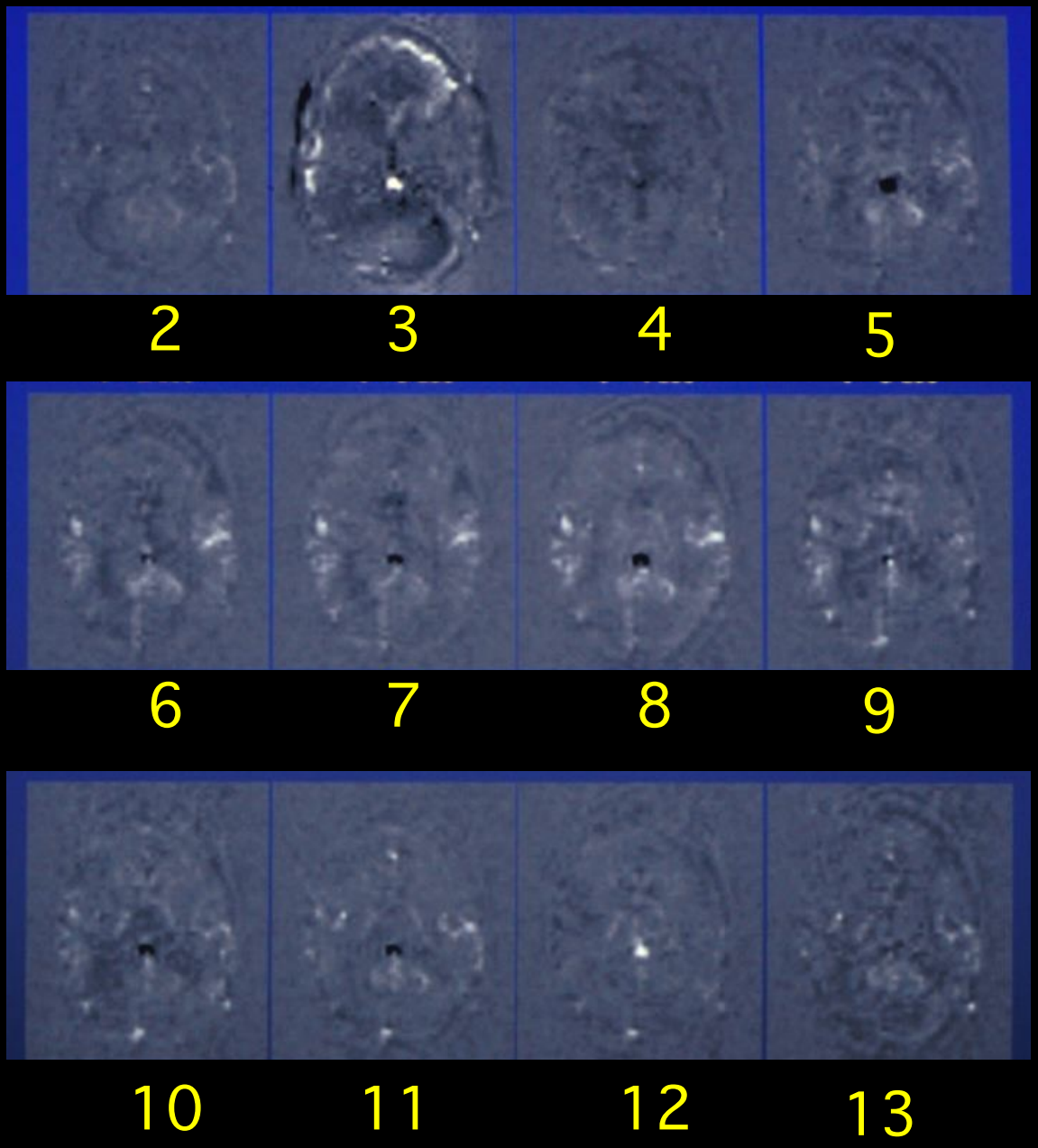
Blocked Design



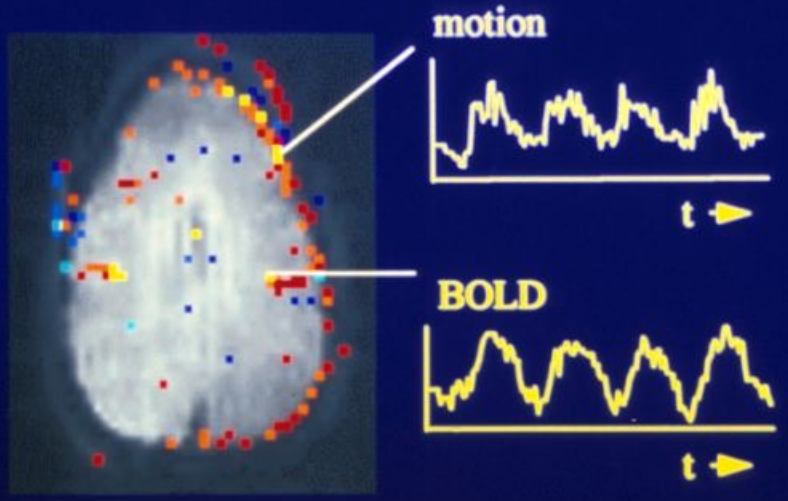
Event-Related Design

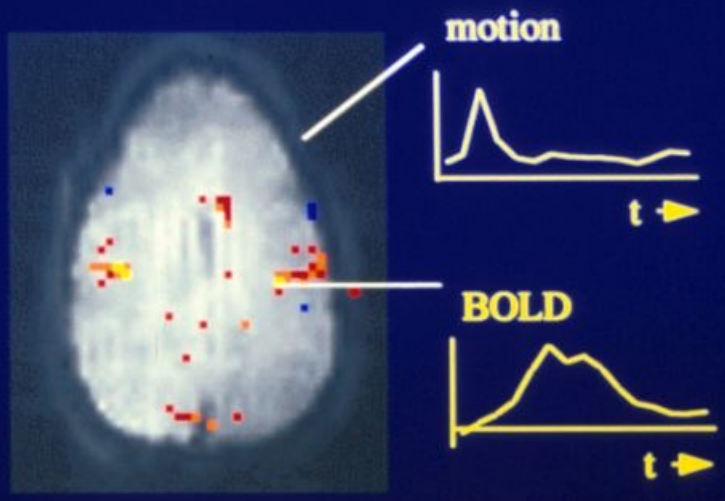


Overt Word Production



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





"block-trial" paradigm

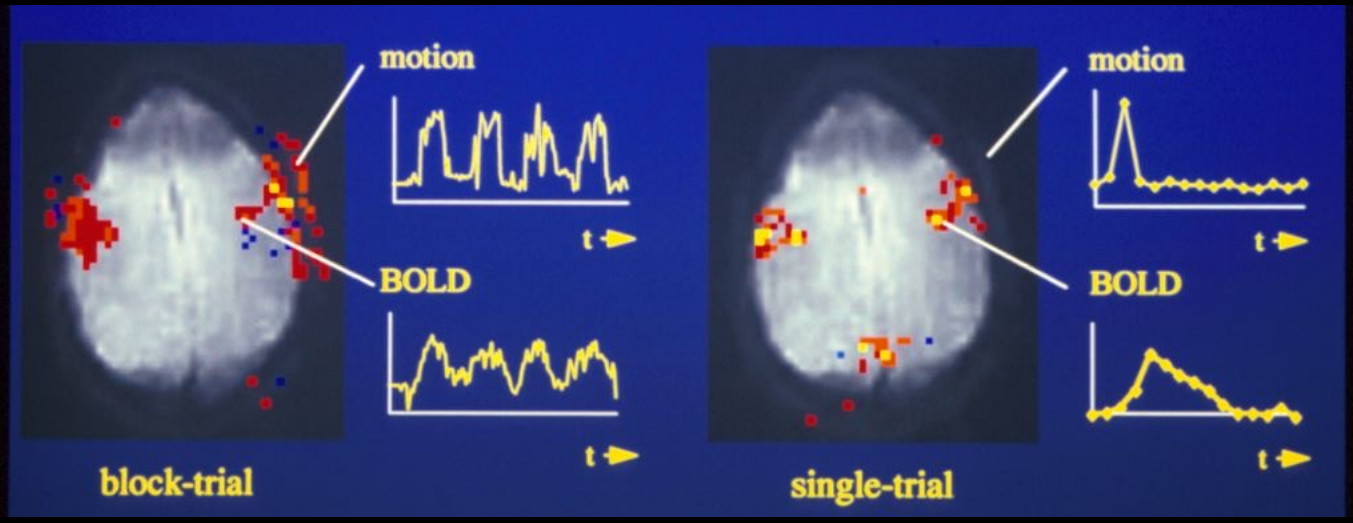
Motion induced signal changes resemble functional (BOLD) signal changes

"single-trial" paradigm

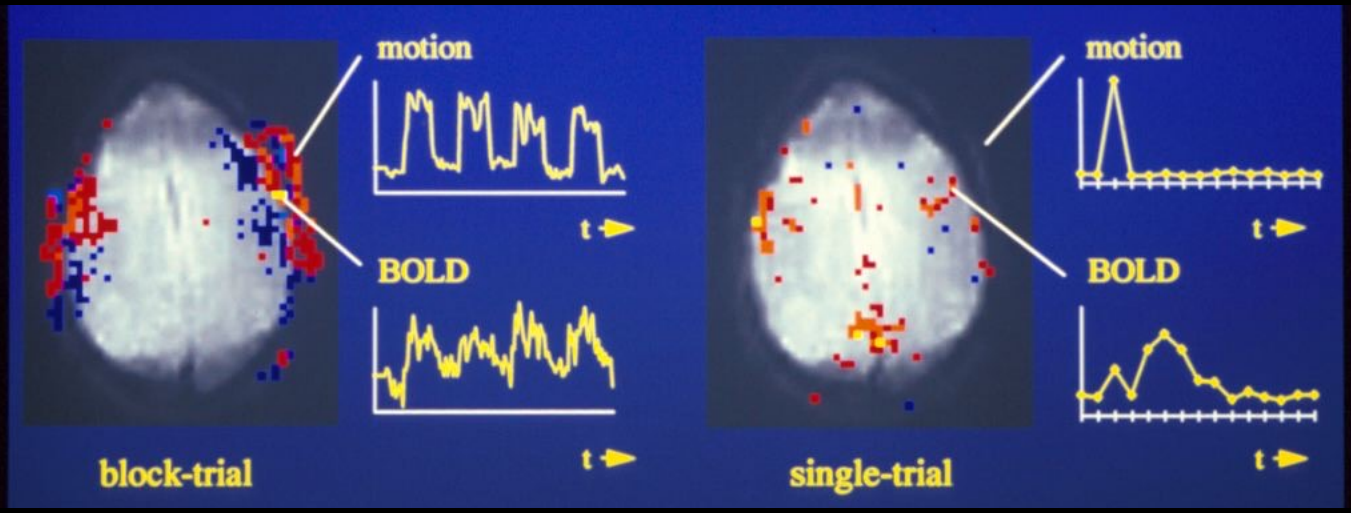
Motion induced and BOLD signal changes are separated in time

R.M. Birn, et al.

Tongue Movement

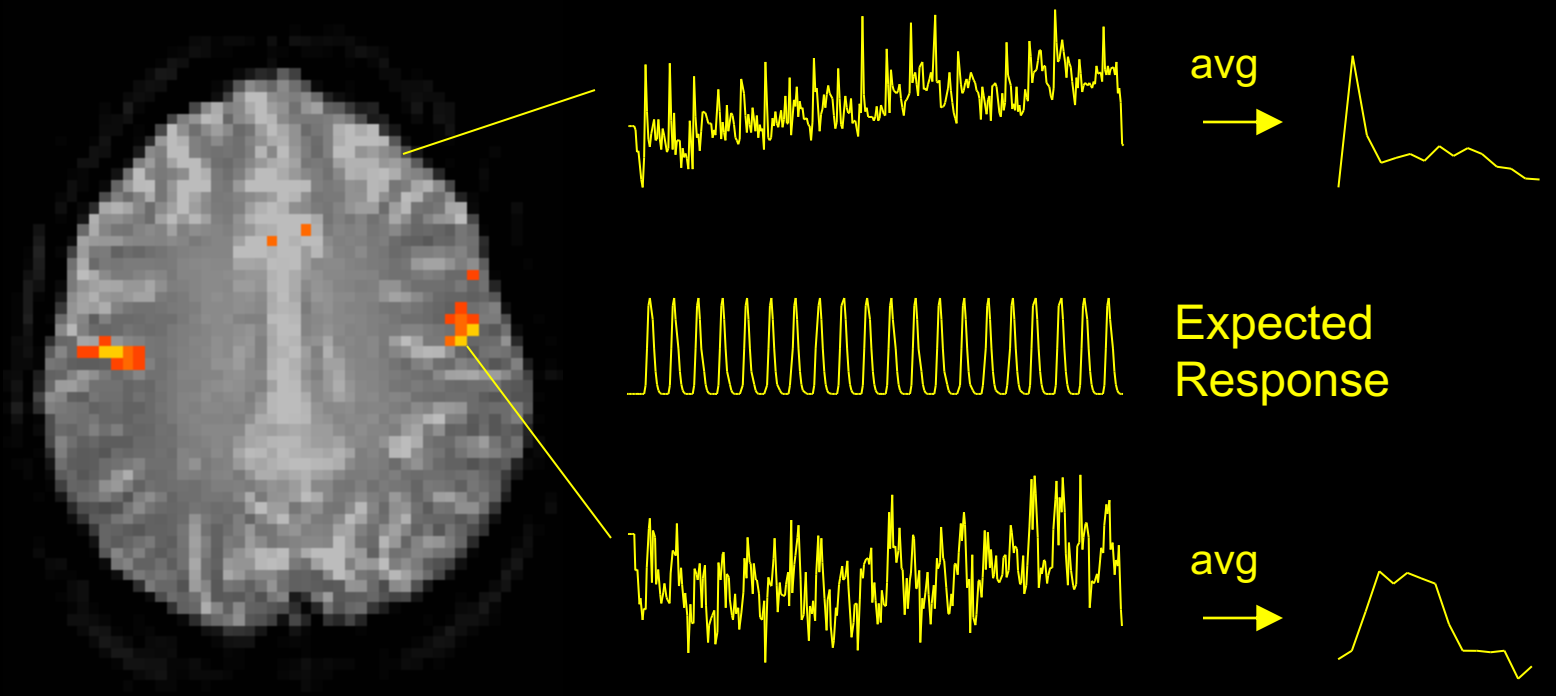


Jaw Clenching

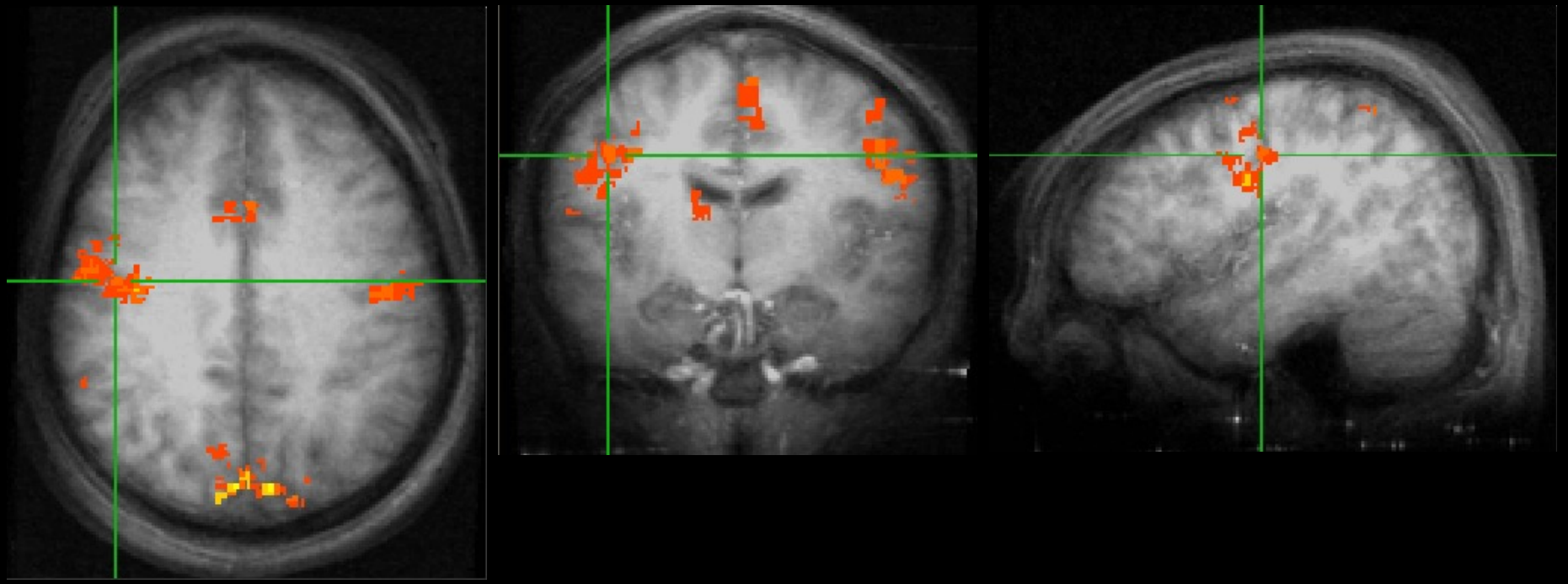


Constant ISI

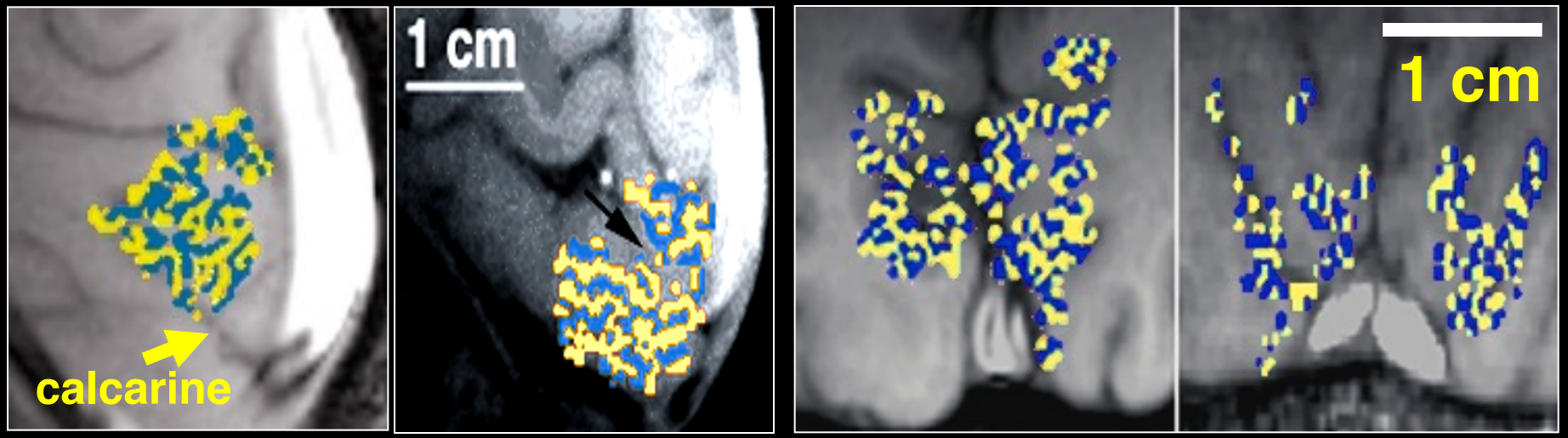
Speaking - ER-fMRI



Swallowing - Event-Related



ODC Maps using fMRI

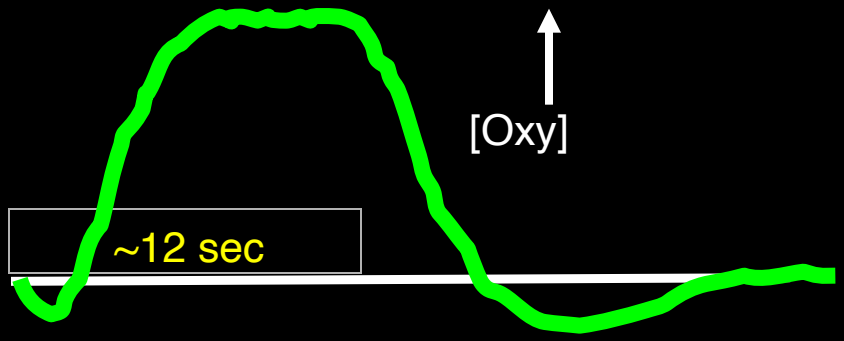


- Identical in size, orientation, and appearance to those obtained by optical imaging[1] and histology[3,4].

[1]Malonek D, Grinvald A. *Science* 272, 551-4 (1996).
[3]Horton JC, Hocking DR. *J Neurosci* 16, 7228-39 (1996).
[4]Horton JC, et al. *Arch Ophthalmol* 108, 1025-31 (1990).

Why short is better than long

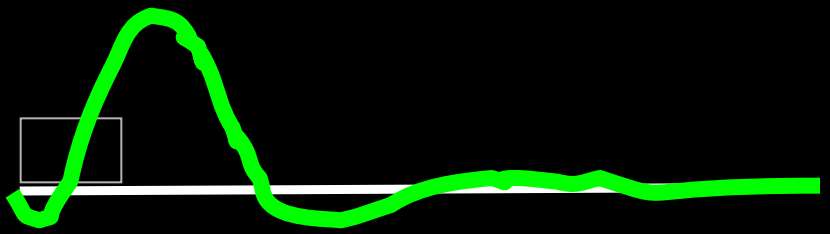
The vascular response to prolonged neural stimulation



It is argued that fMRI cannot achieve submillimeter functional resolution because a saturated hyperoxic vascular response to neural activity spreads over many millimeters[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

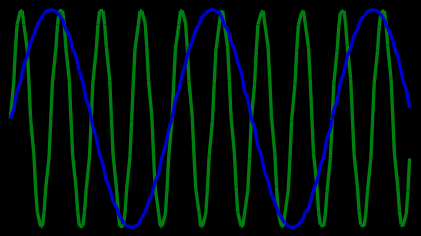


[1]Malonek D, Grinvald A. Science 272, 551-4 (1996).
[2]Kim D-S, Duong T, Kim S-G. Nat Neurosci 3, 164-9 (2000).

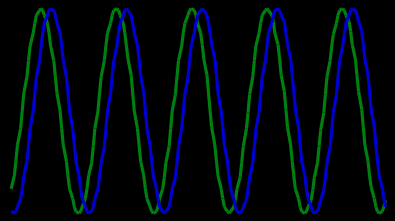
Neuronal Activation Input Strategies

1. Block Design

2. Frequency Encoding

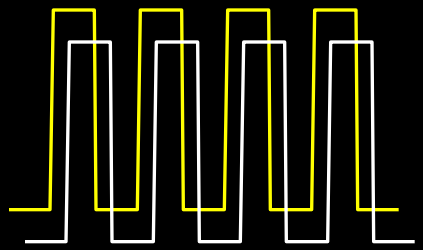


3. Phase Encoding



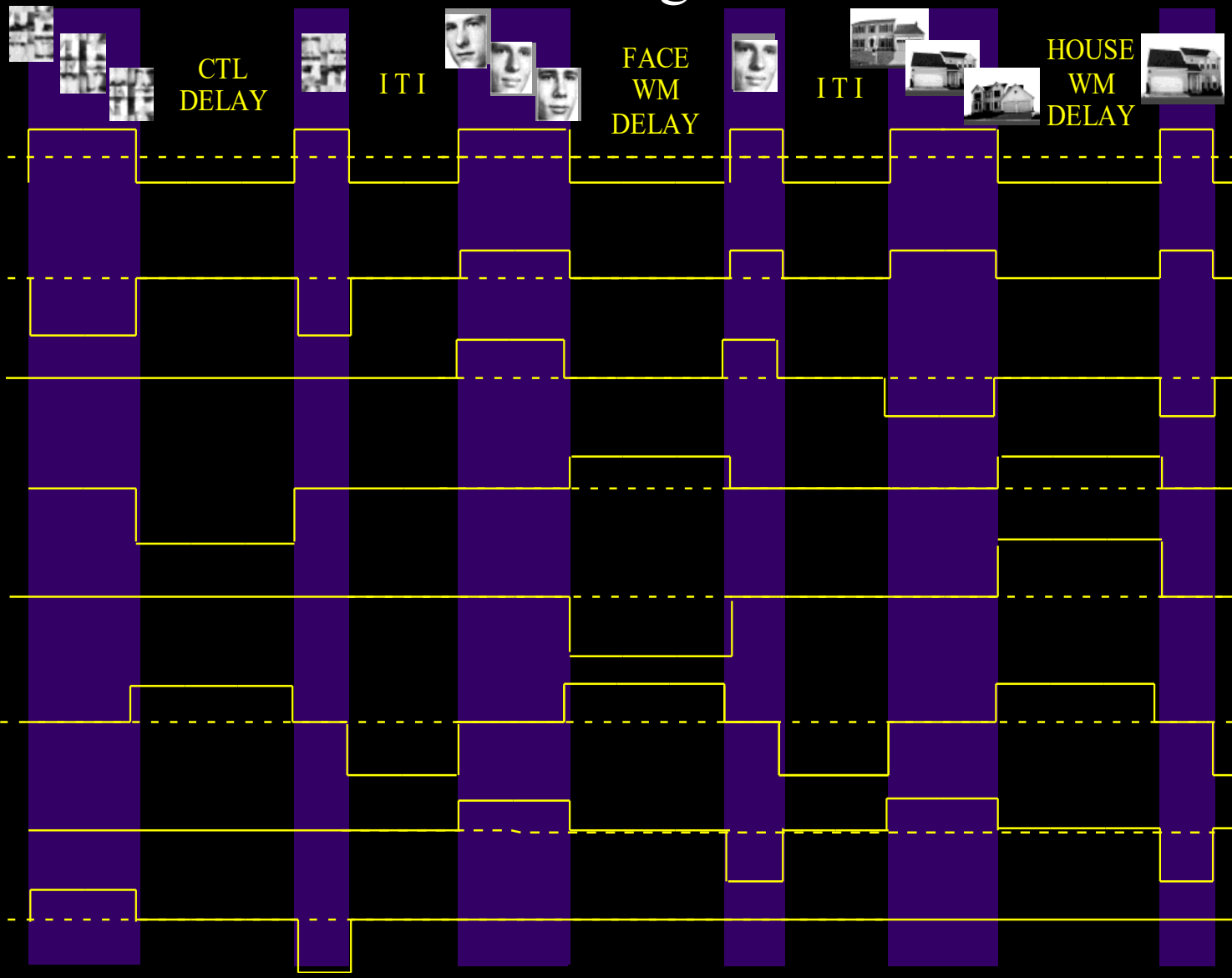
4. Single Event

5. Orthogonal Block Design



6. Free Behavior Design.

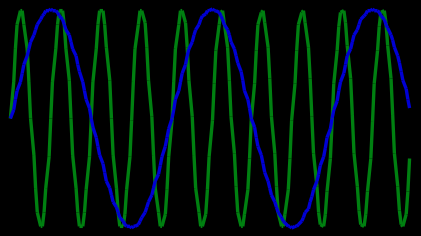
Example of a Set of Orthogonal Contrasts for Multiple Regression



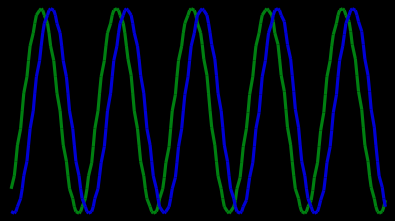
Neuronal Activation Input Strategies

1. Block Design

2. Frequency Encoding



3. Phase Encoding



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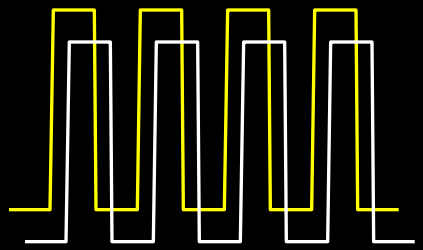


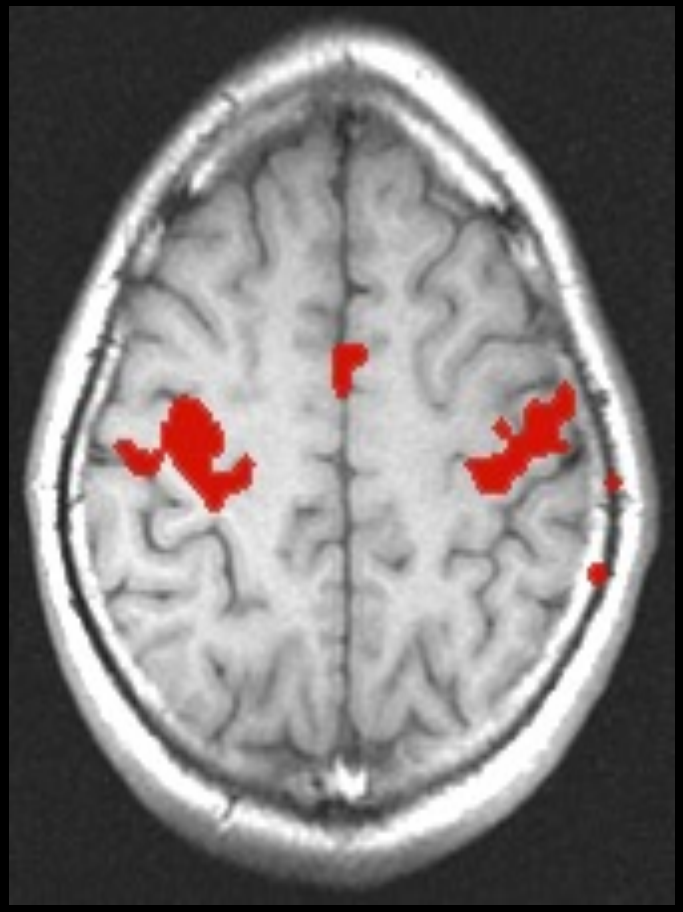
6. Free Behavior Design.

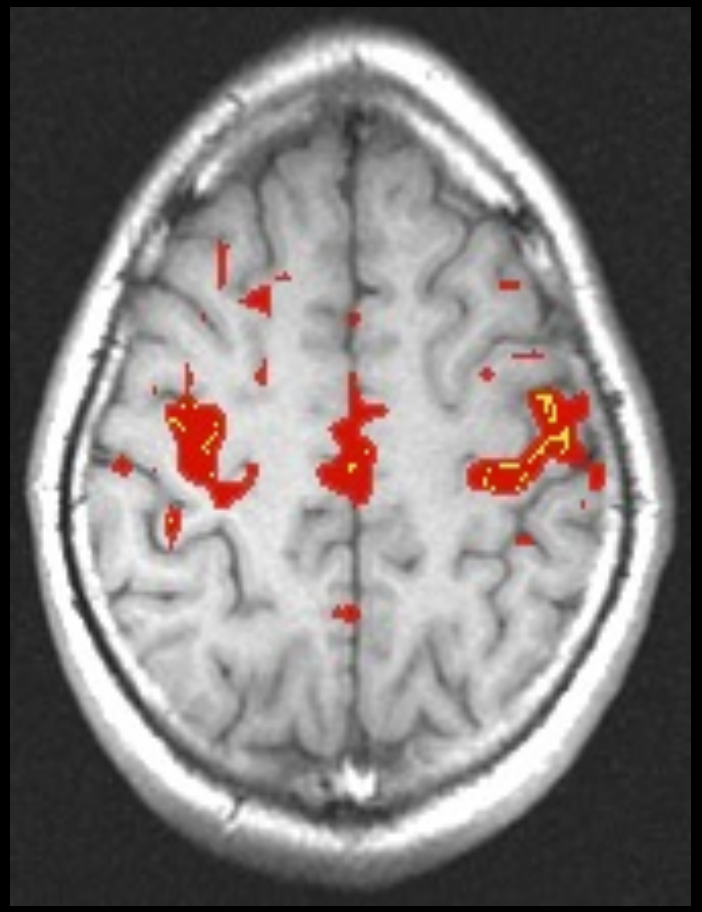
Free Behavior Design

Use a continuous measure as a reference function:

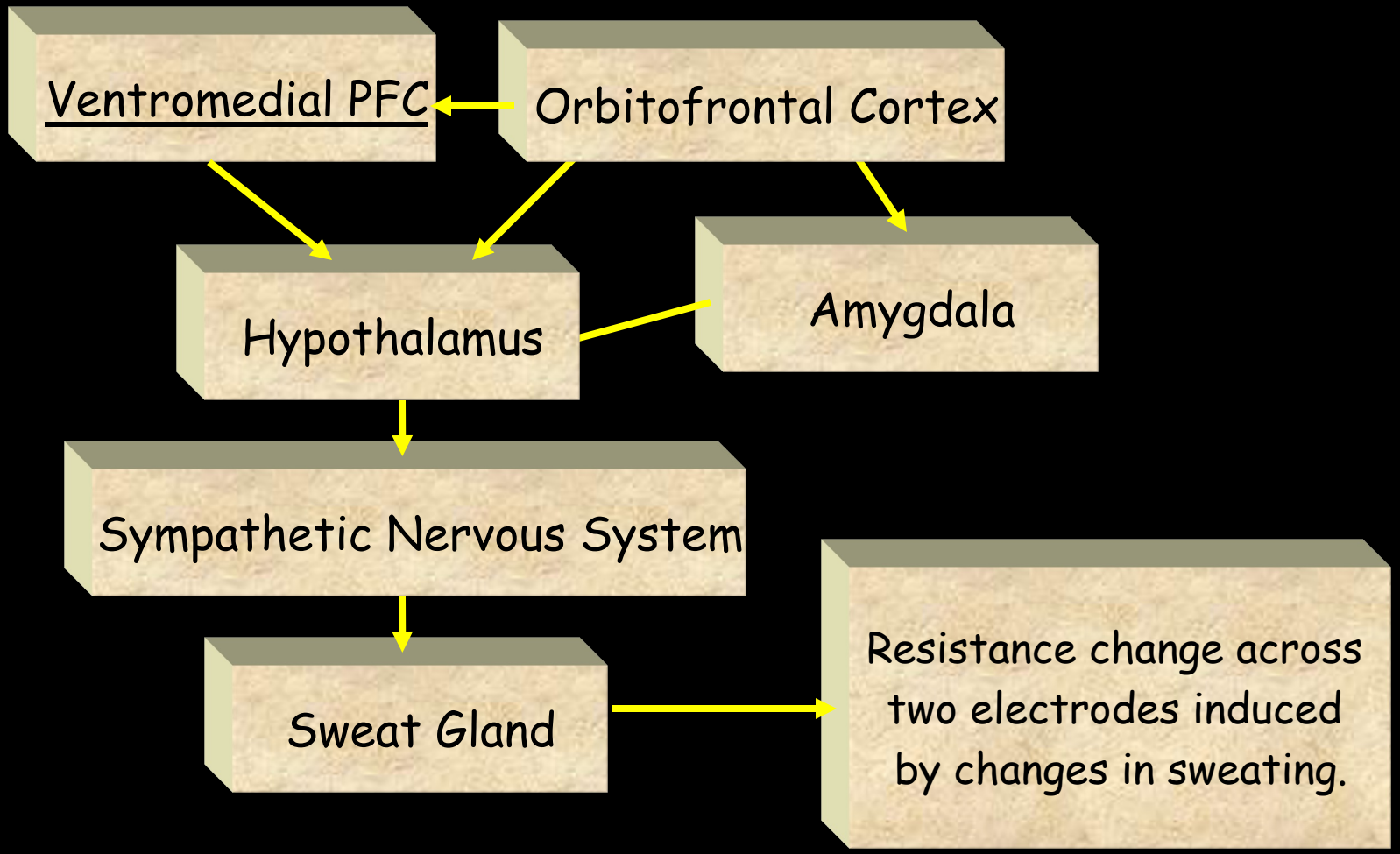
- Task performance
- Skin Conductance
- Heart, respiration rate..
- Eye position
- EEG

Resting Hemodynamic Autocorrelations





The Skin Conductance Response (SCR)



Skin Conductance Dynamics

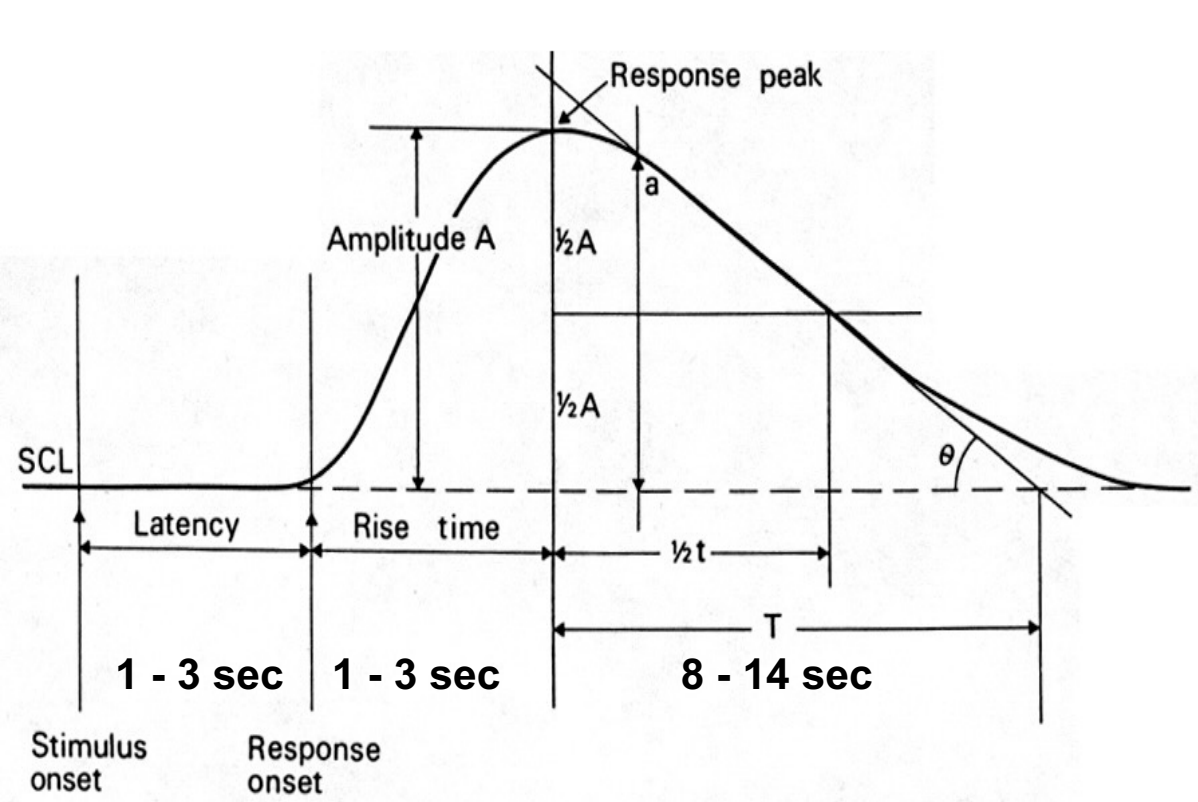
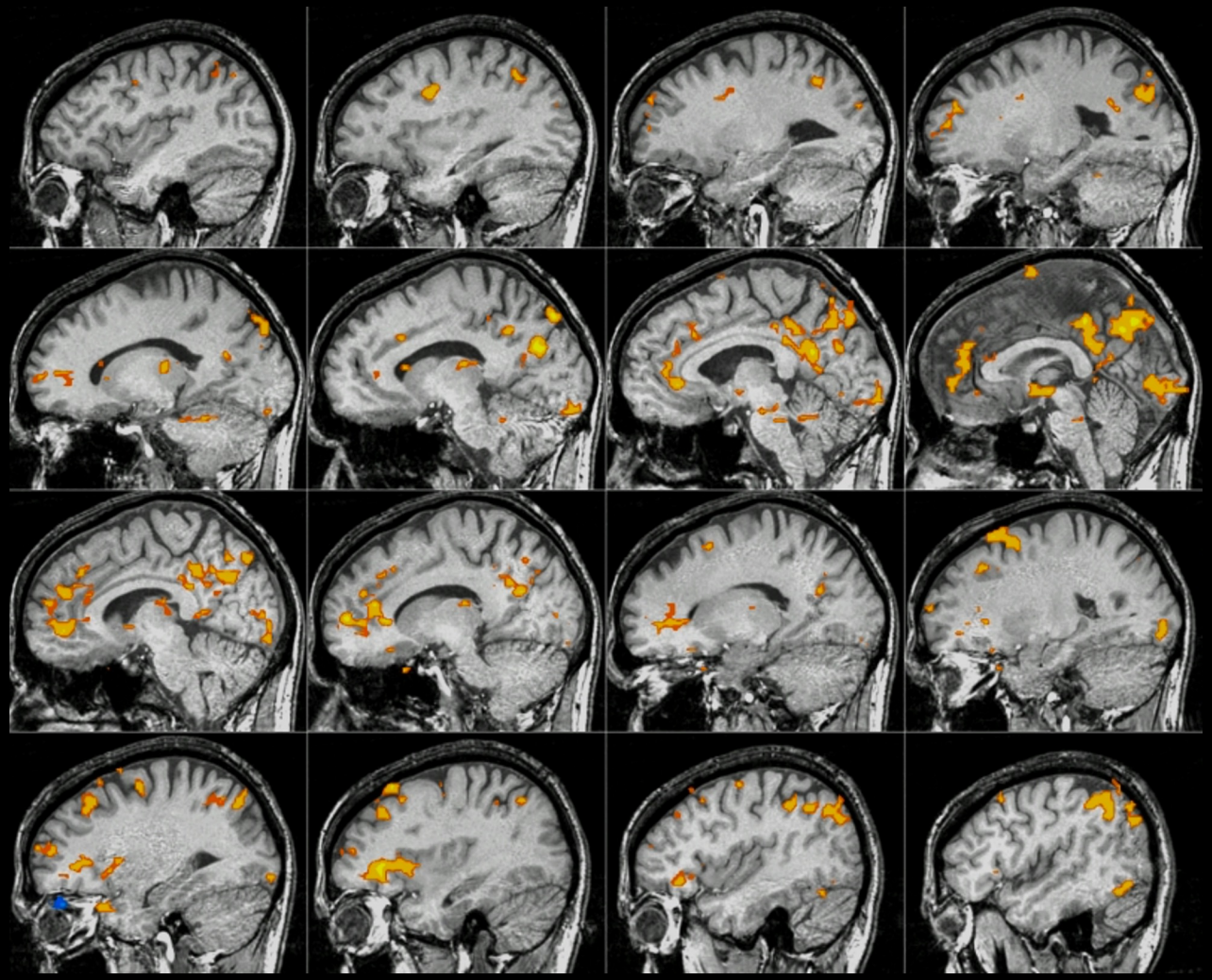


FIGURE 1. Diagrammatic skin conductance response.

•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

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Patrick Bellgowan, NIH