Pushing the Spatial, Temporal and Interpretive Limits of Functional MRI

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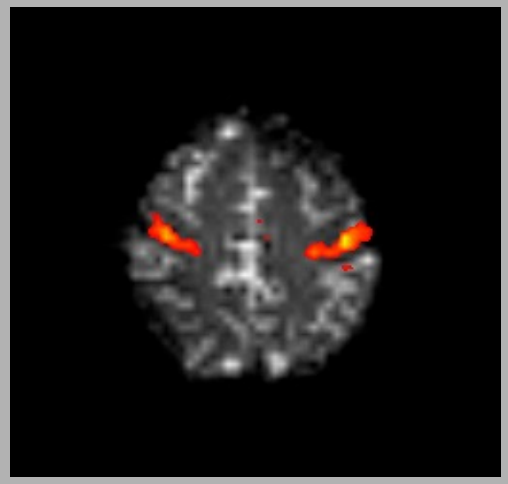
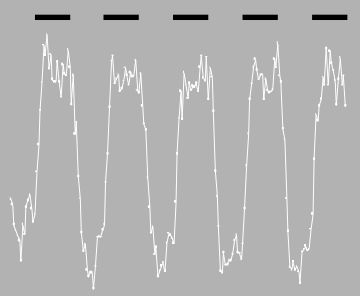
Categories of Questions Asked with fMRI

Where?

When?

How much?



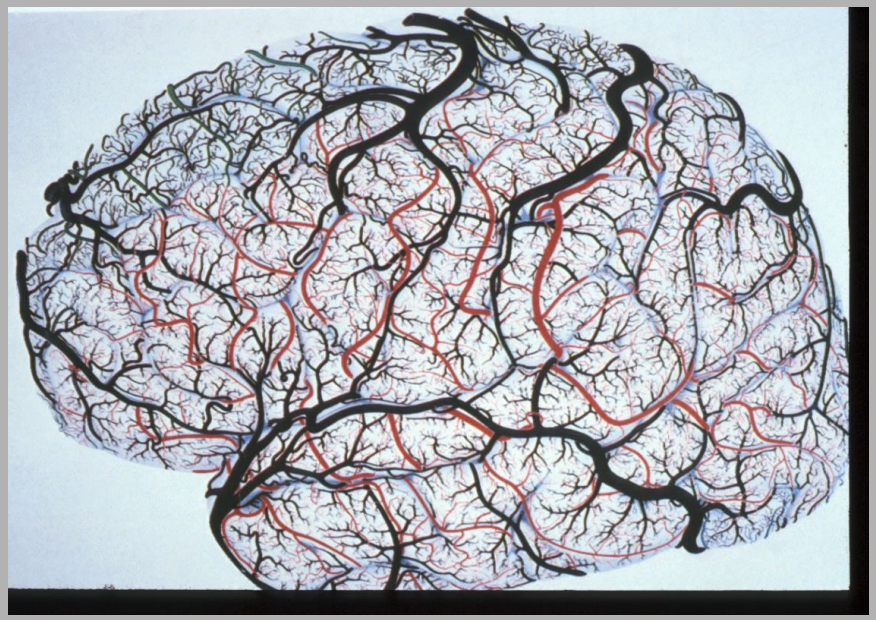


How to get the brain to do what we want it to do in the context of an fMRI experiment?

(***limitations***: time, motion, acoustic noise)

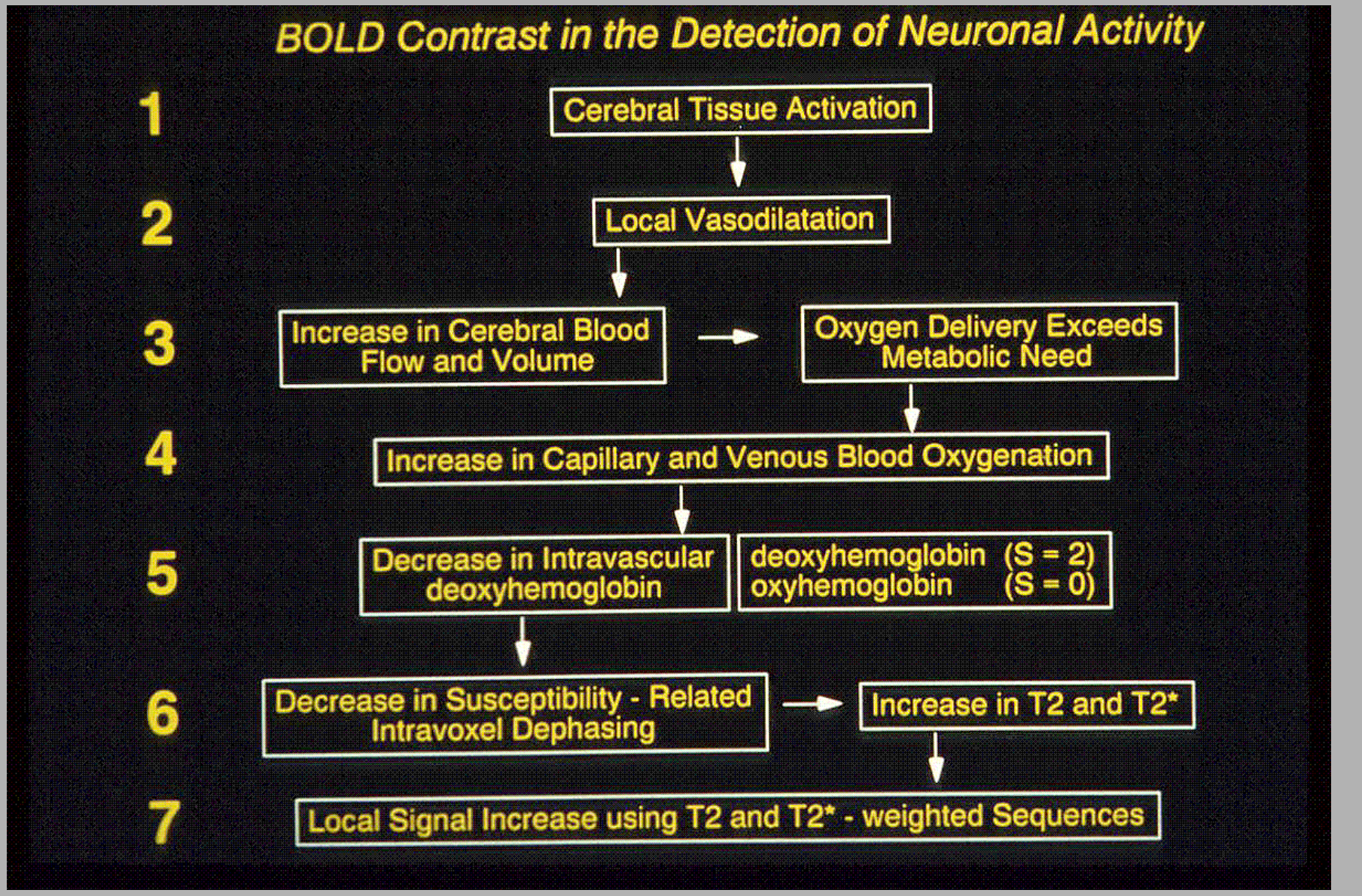
A Primary Challenge:

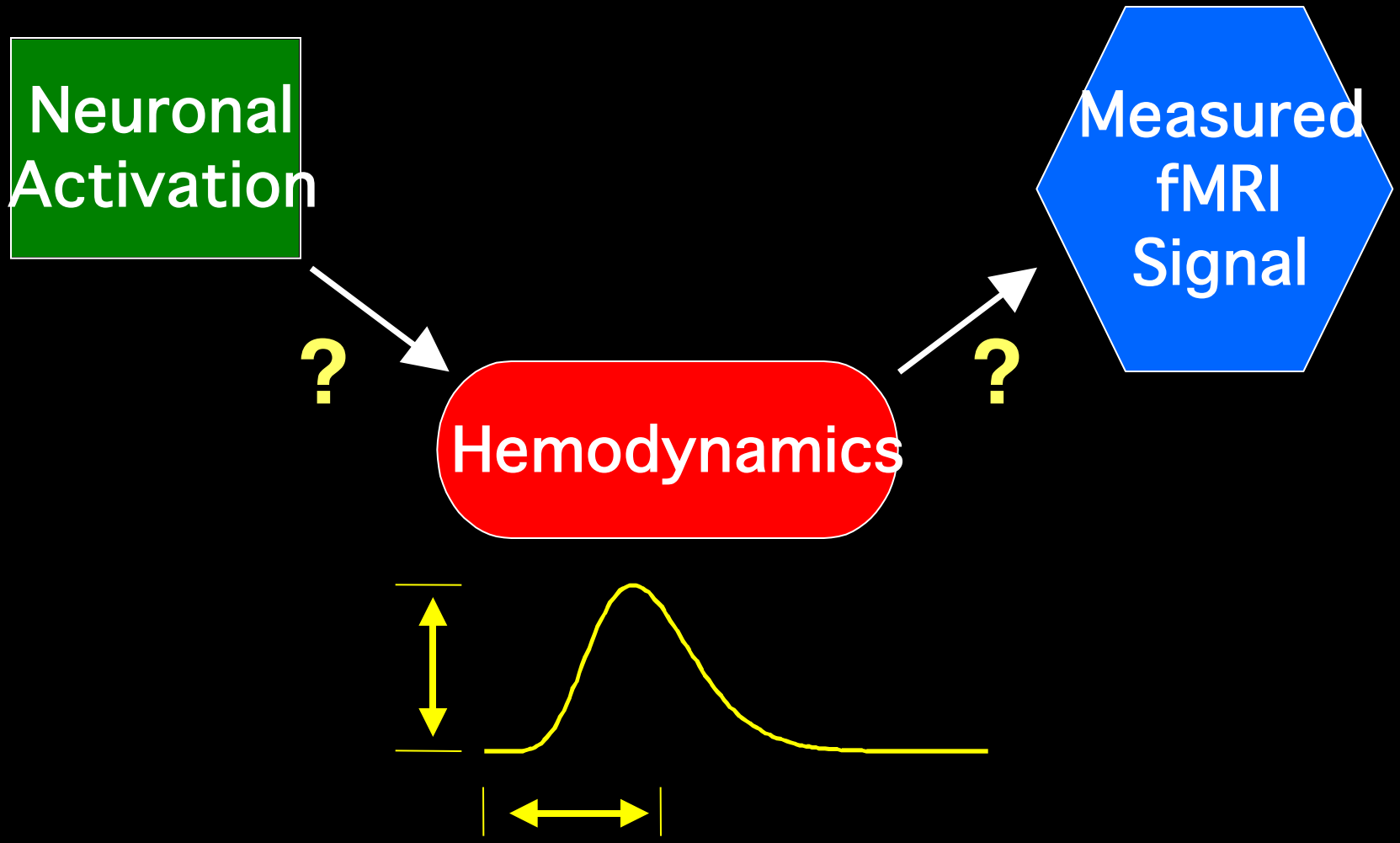
...to make progressively more precise inferences using fMRI without making too many assumptions about non-neuronal physiologic factors.



Contrast in Functional MRI

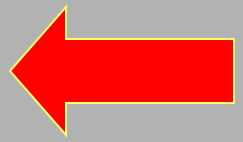
- **Blood Volume**
  - **Contrast agent injection and time series collection of T2* or T2 - weighted images**
- **BOLD**
  - **Time series collection of T2* or T2 - weighted images**
- **Perfusion**
  - **T1 weighting**
  - **Arterial spin labeling**


BOLD Contrast in the Detection of Neuronal Activity
1
Cerebral Tissue Activation
2
Local Vasodilatation
3
Increase in Cerebral Blood Flow and Volume
Oxygen Delivery Exceeds Metabolic Need
4
Increase in Capillary and Venous Blood Oxygenation
5
Decrease in Intravascular deoxyhemoglobin
deoxyhemoglobin (S = 2)
oxyhemoglobin (S = 0)
6
Decrease in Susceptibility - Related Intravoxel Dephasing
Increase in T2 and T2*
7
Local Signal Increase using T2 and T2* - weighted Sequences


Neuronal Activation
?
Hemodynamics
?
Measured fMRI Signal
Physiologic Factors

Physiologic Factors that Influence BOLD Contrast

- Blood oxygenation
- Blood volume
- Blood pressure
- Hematocrit
- Vessel size



Coupling: Flow & $CMRO_2$

Where and When?

The resolution is determined by the cerebral hemodynamics.

- **Know the vasculature at which you are looking.**

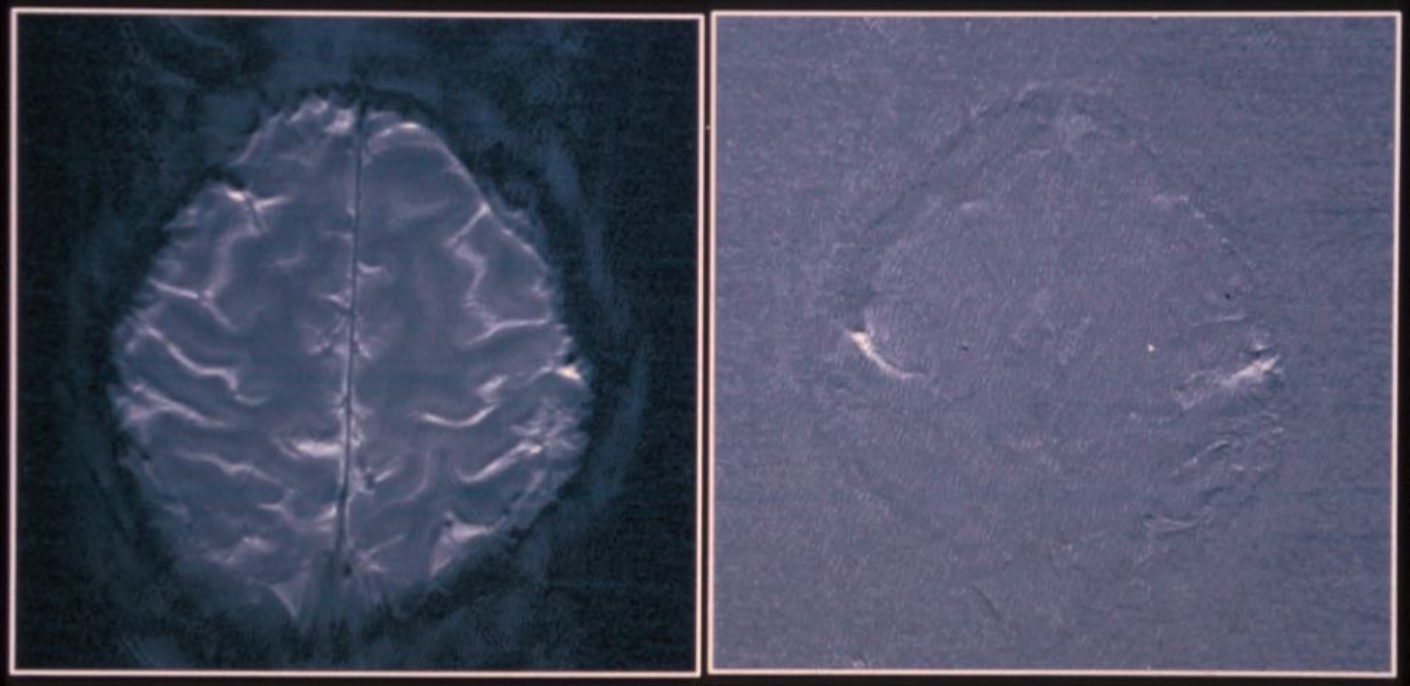
(or)

- **Normalize to the spatial variation in the vasculature.**

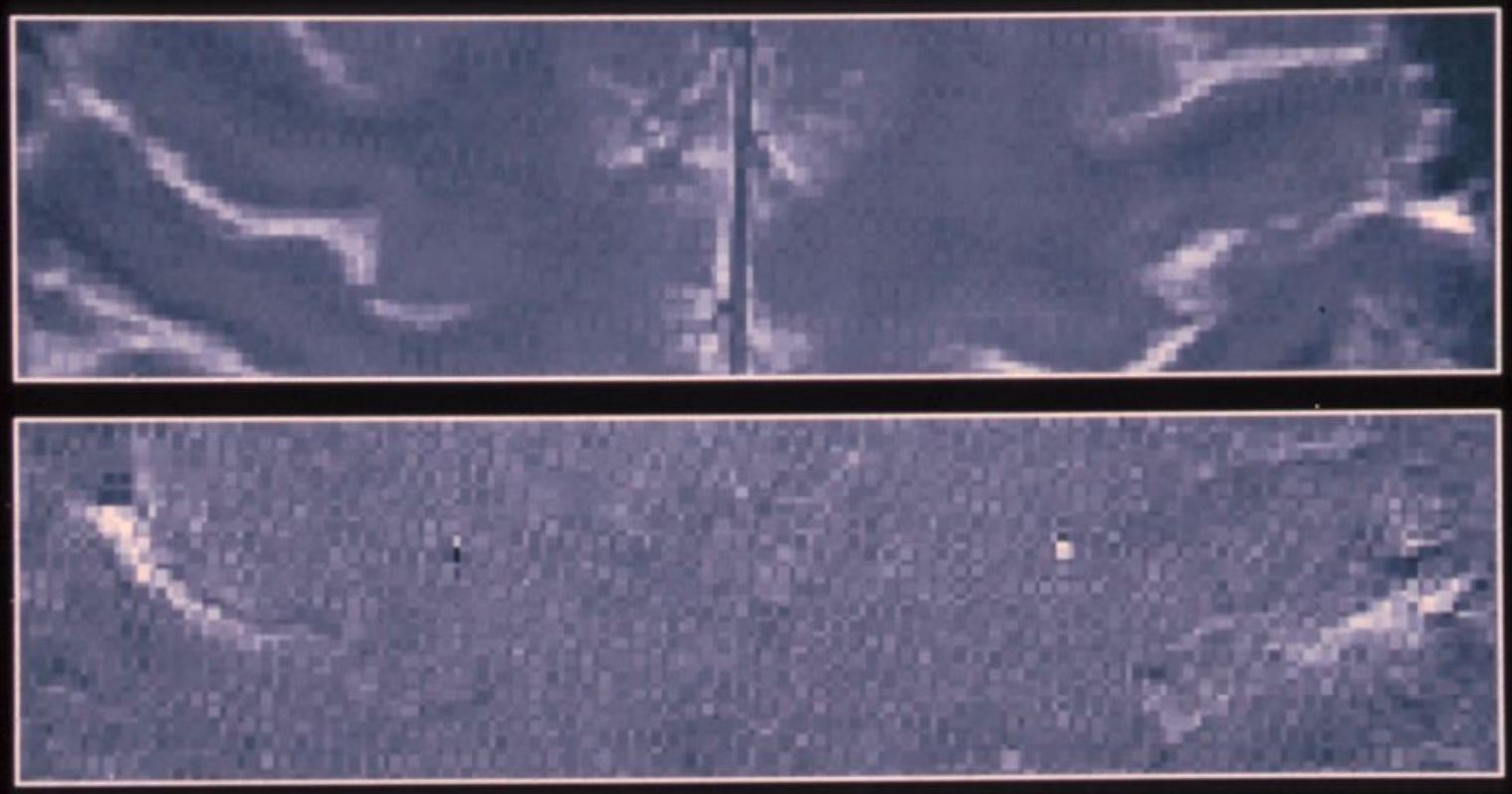
(or)

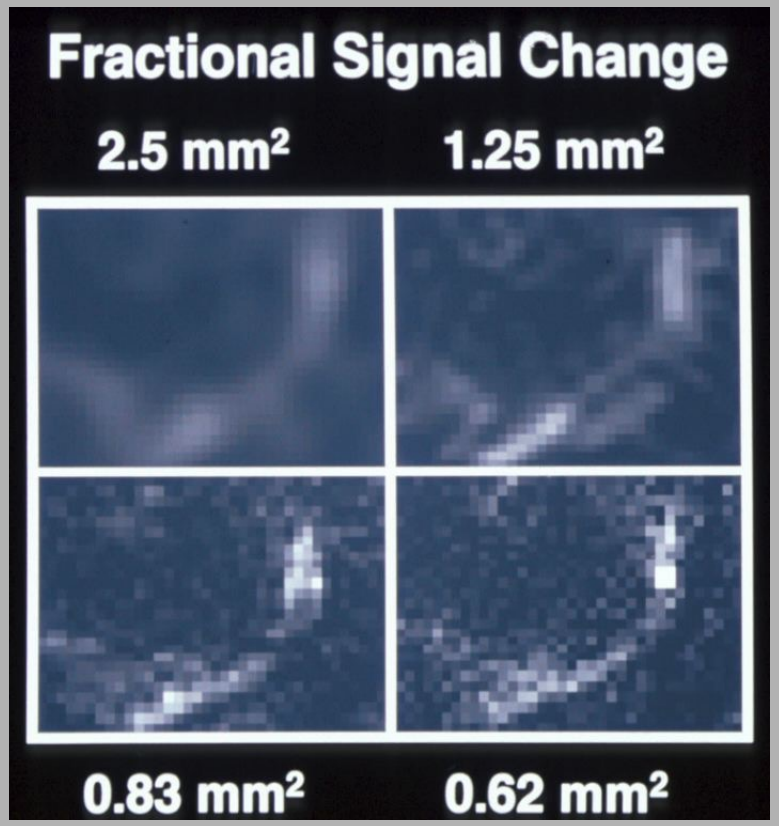
- **Make several assumptions.**

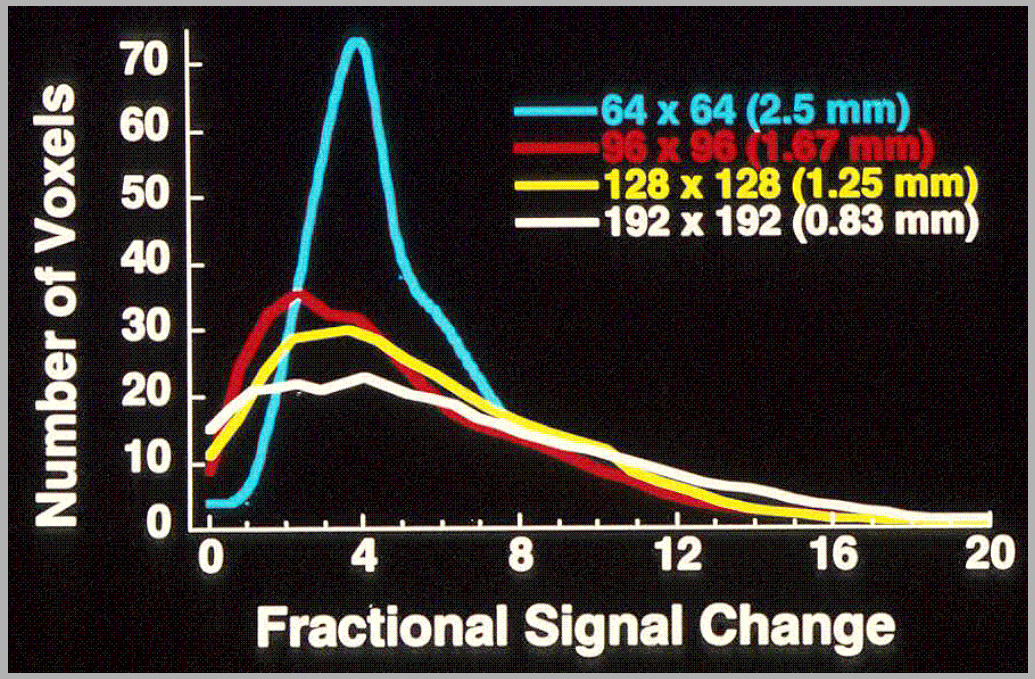
Single - Shot EPI at 3T:
Half NEX, 256 x 256, 16 cm FOV



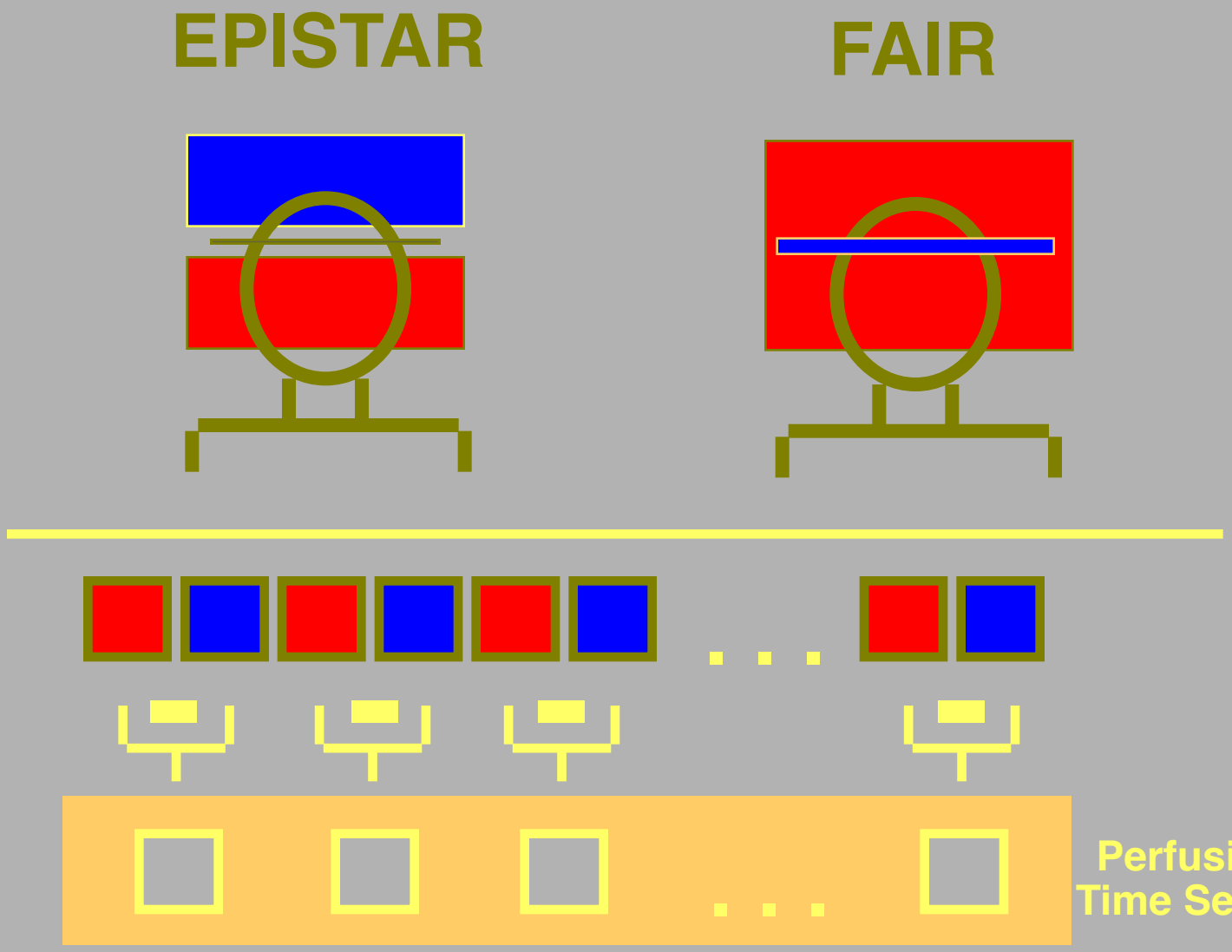
Single - Shot EPI at 3T:
Half NEX 256 x 256, 16 cm FOV

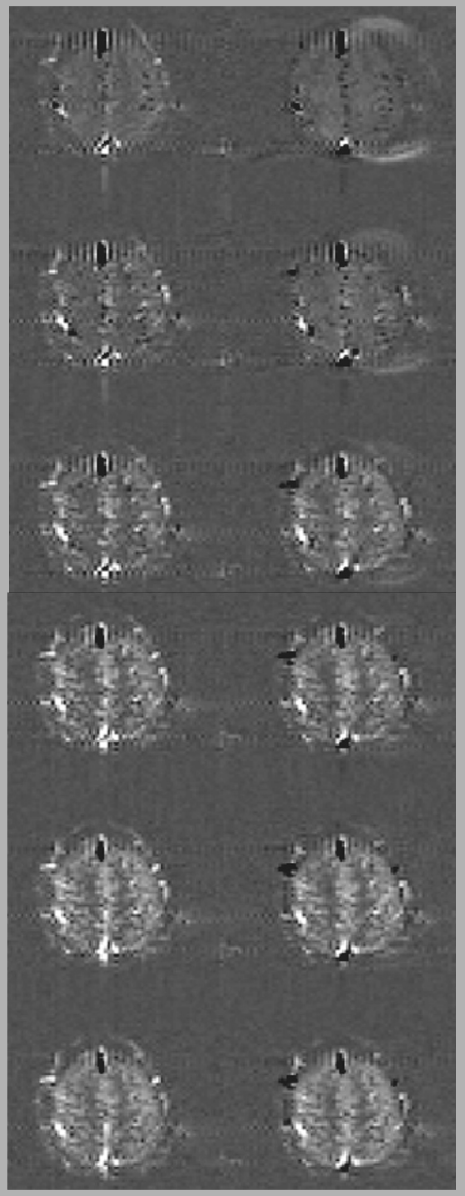



Fractional Signal Change
2.5 mm²
1.25 mm²
0.83 mm²
0.62 mm²


Number of Voxels
70
60
50
40
30
20
10
0
0
4
8
12
16
20
Fractional Signal Change
64 x 64 (2.5 mm)
96 x 96 (1.67 mm)
128 x 128 (1.25 mm)
192 x 192 (0.83 mm)

Perfusion / Flow Imaging



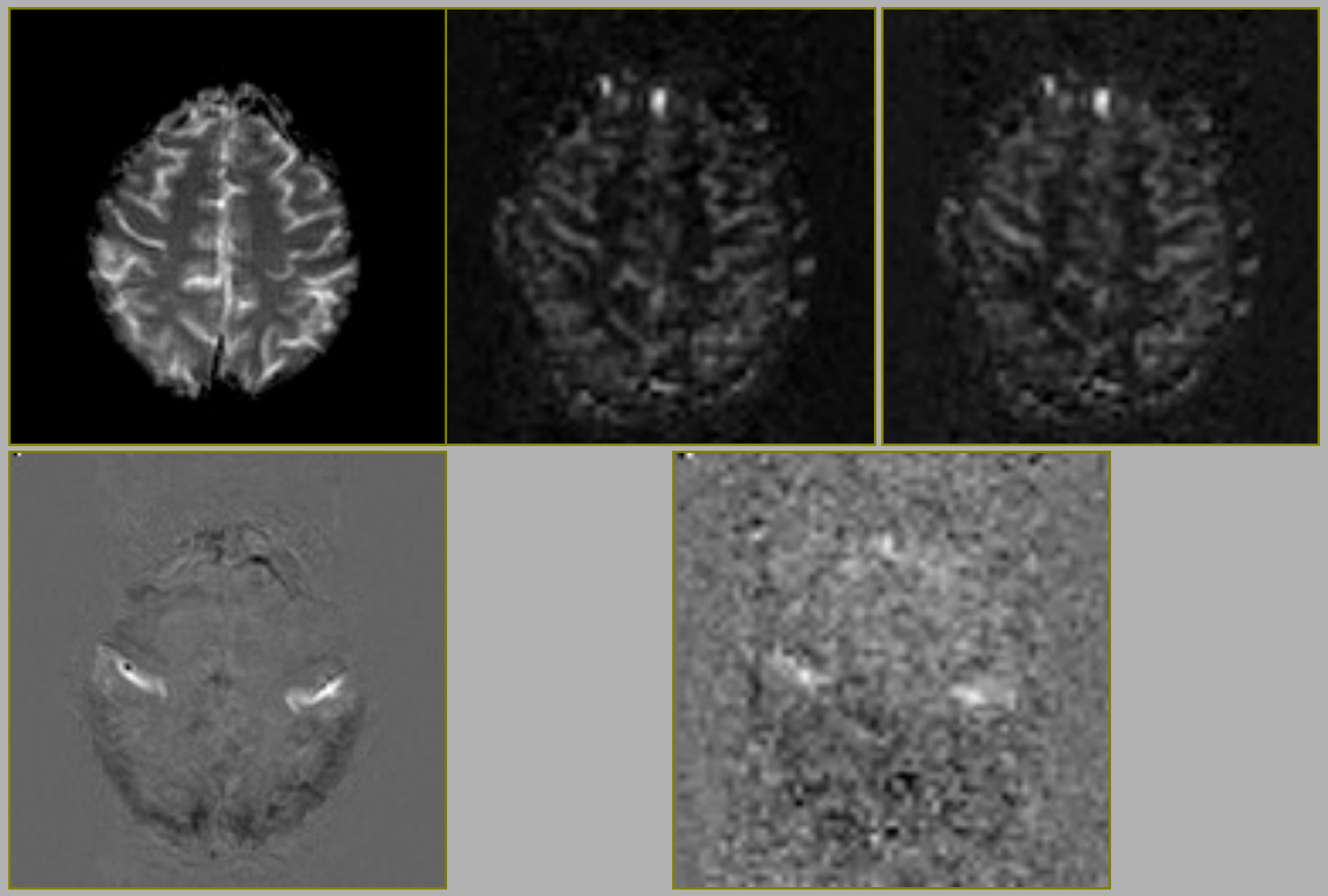
TI (ms)	FAIR	EPISTAR
200		
400		
600		
800		
1000		
1200		

Perfusion

BOLD

Rest

Activation

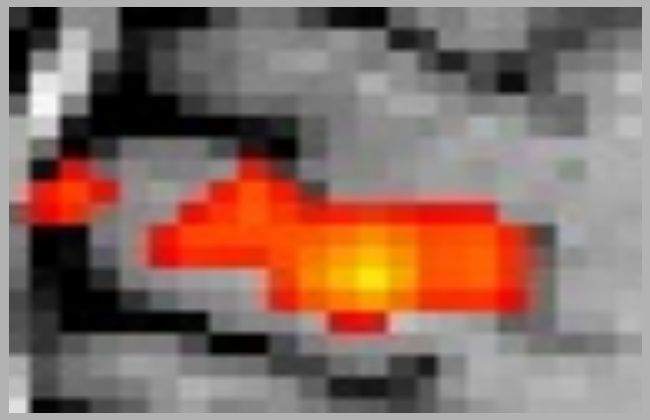


Anatomy

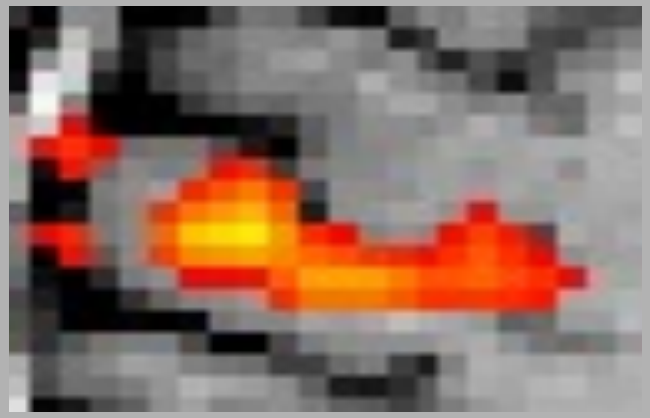
BOLD

Perfusion

T1 - weighted

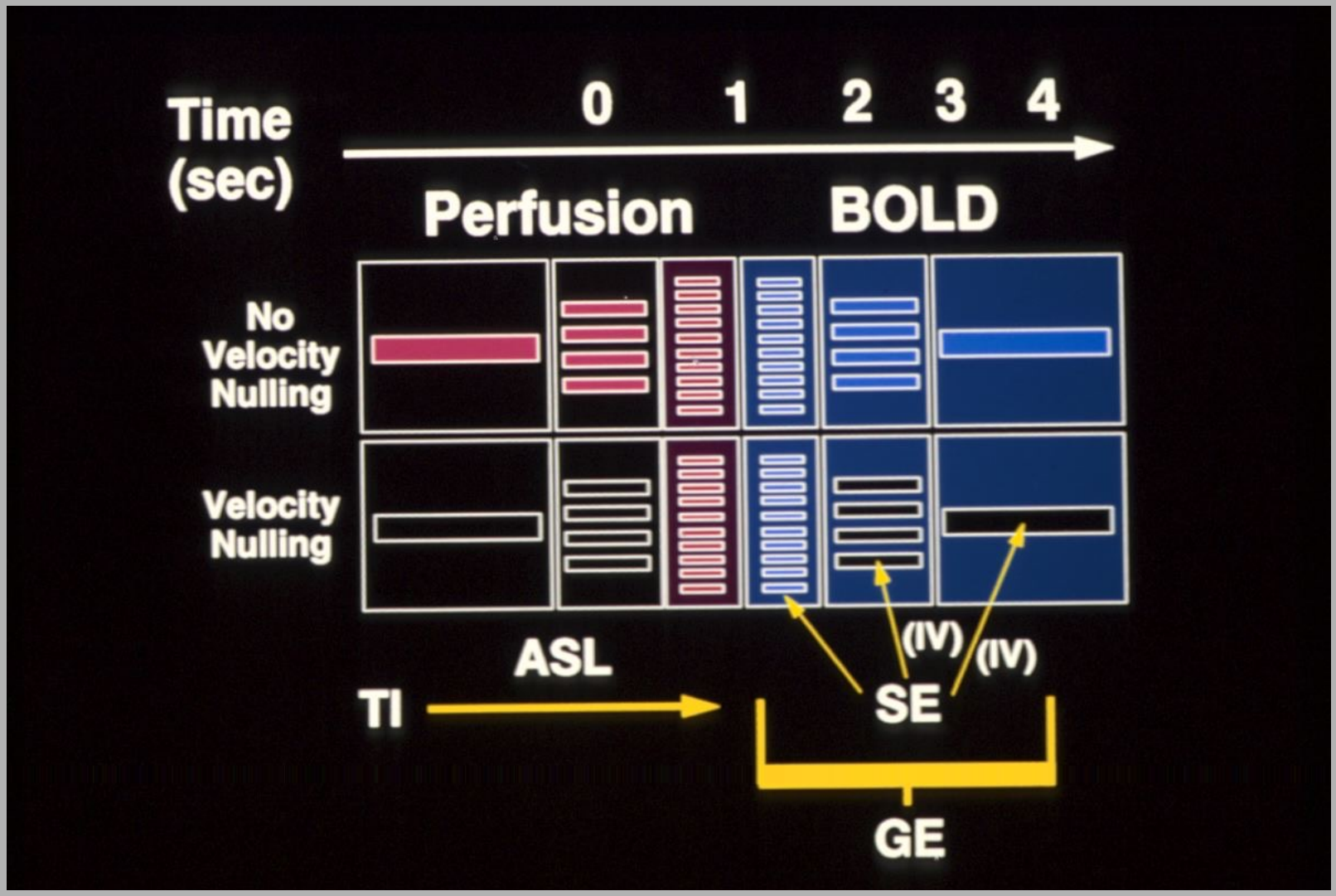


T2* weighted

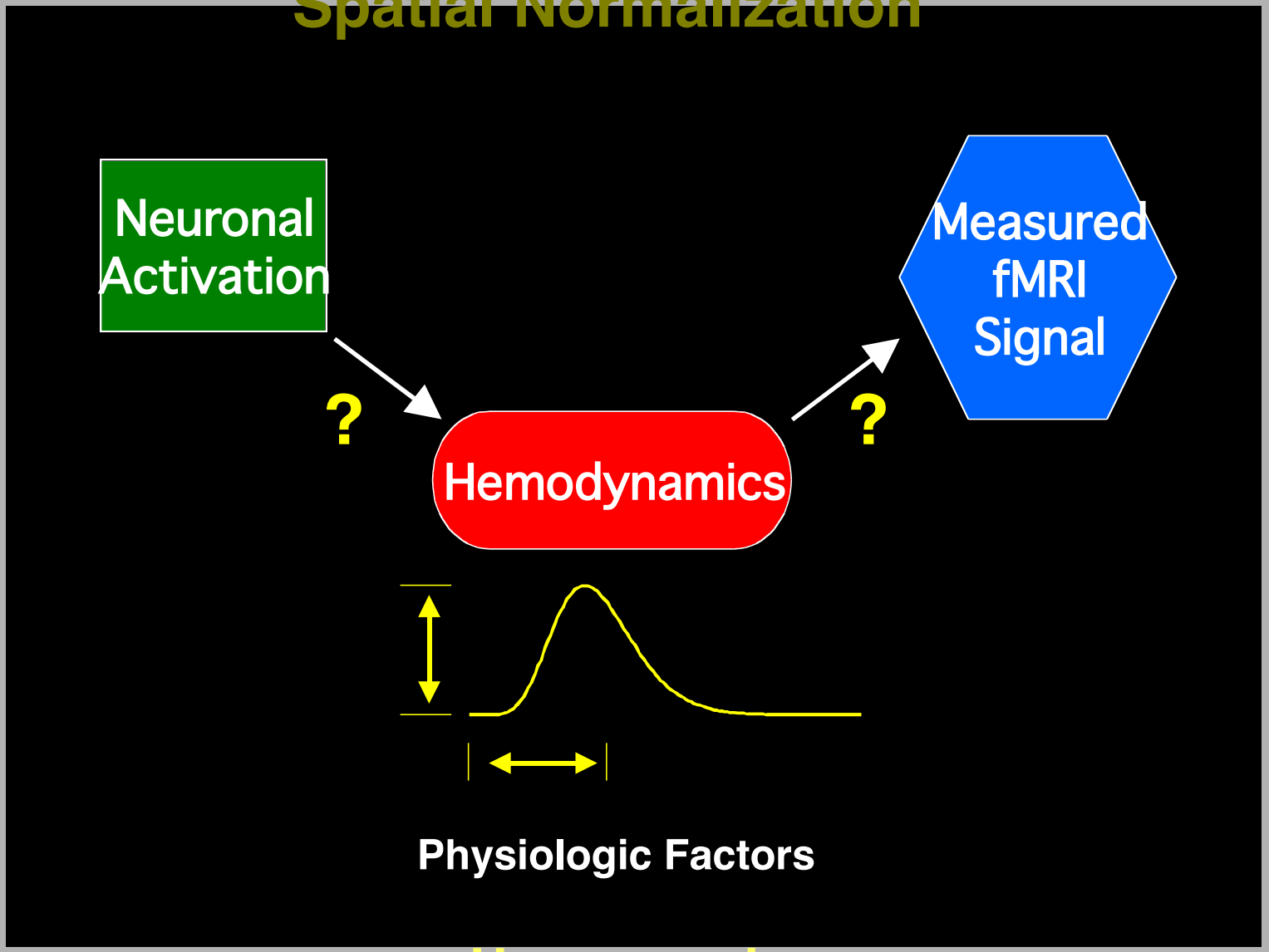


T2* and T1* weighted

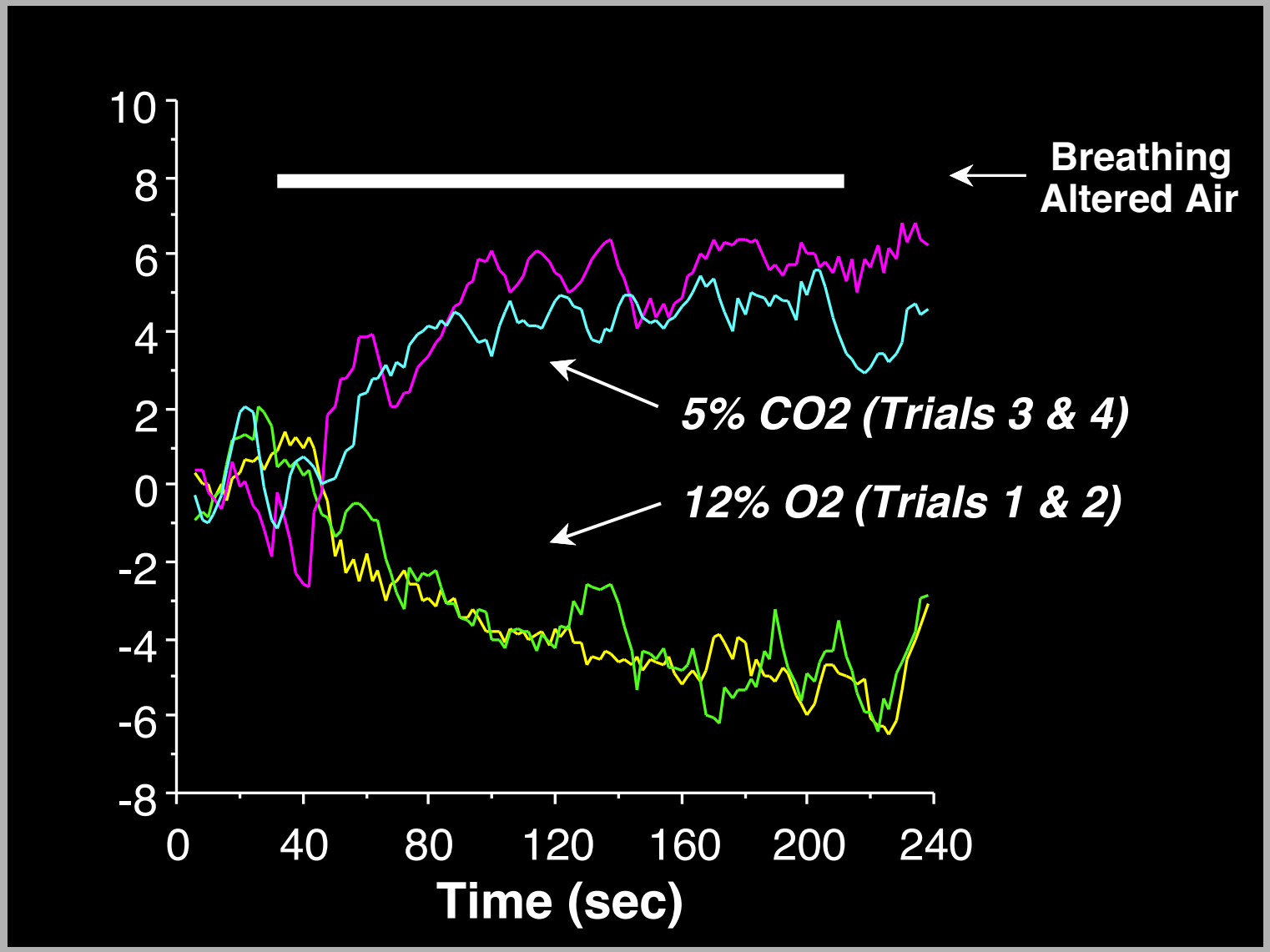
Vascular Sensitization



Spatial Normalization

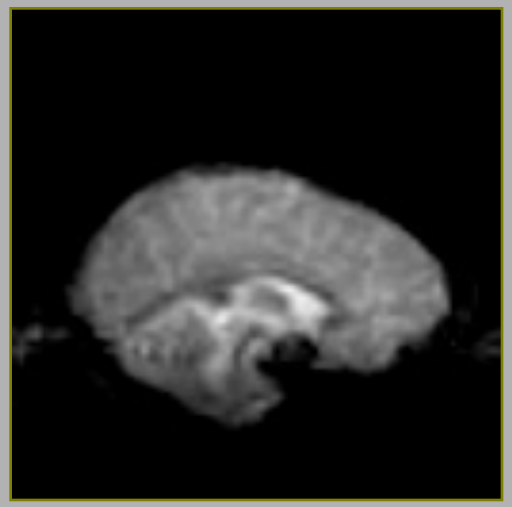


Hypercapnia


10
8
6
4
2
0
-2
-4
-6
-8
0
40
80
120
160
200
240
Time (sec)
Breathing
Altered Air
5% CO2 (Trials 3 & 4)
12% O2 (Trials 1 & 2)

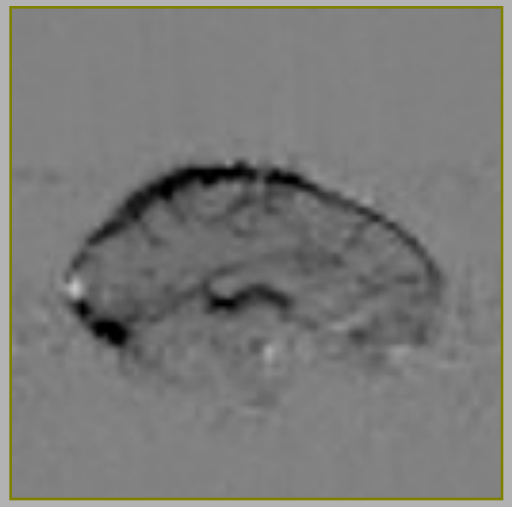
,

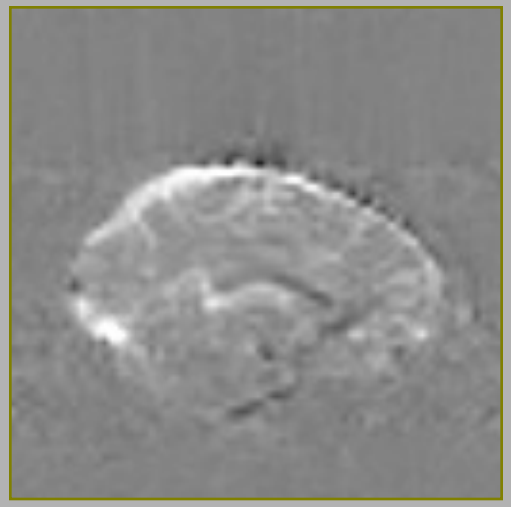
Anatomical



Finger Movement

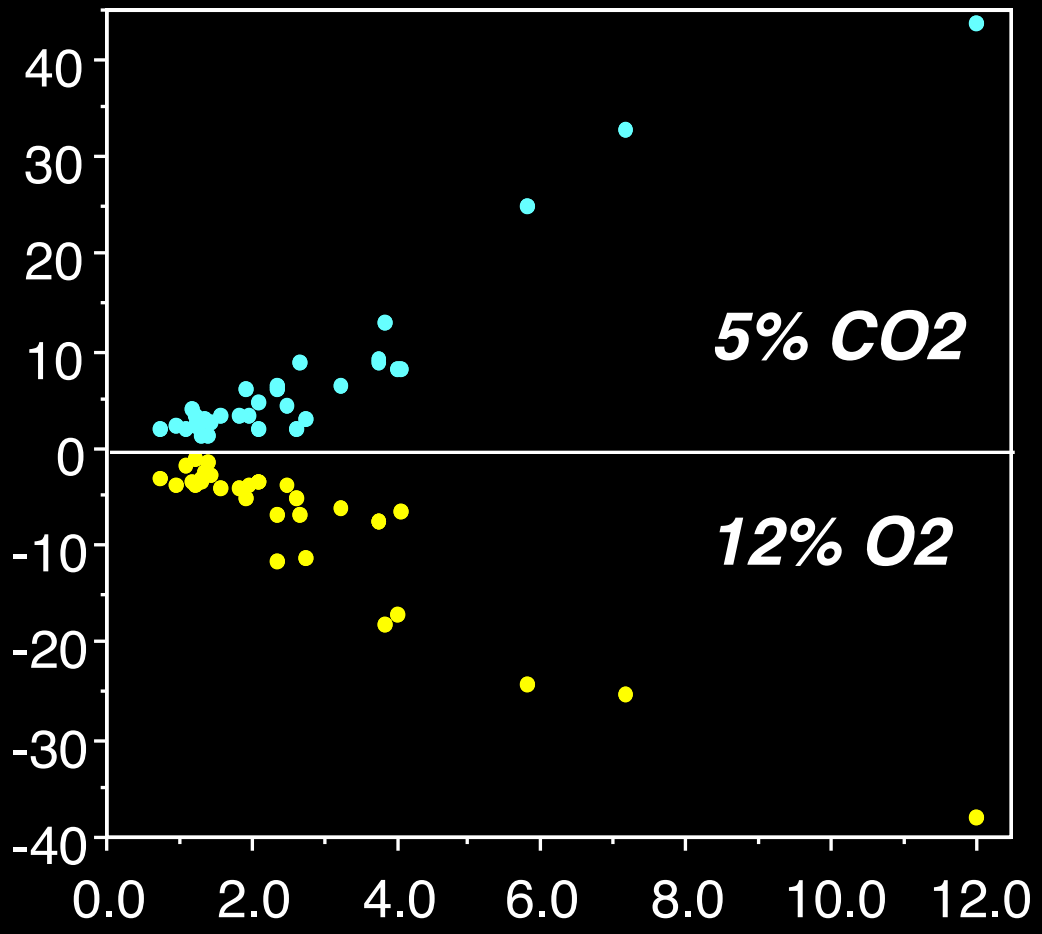
12% O2



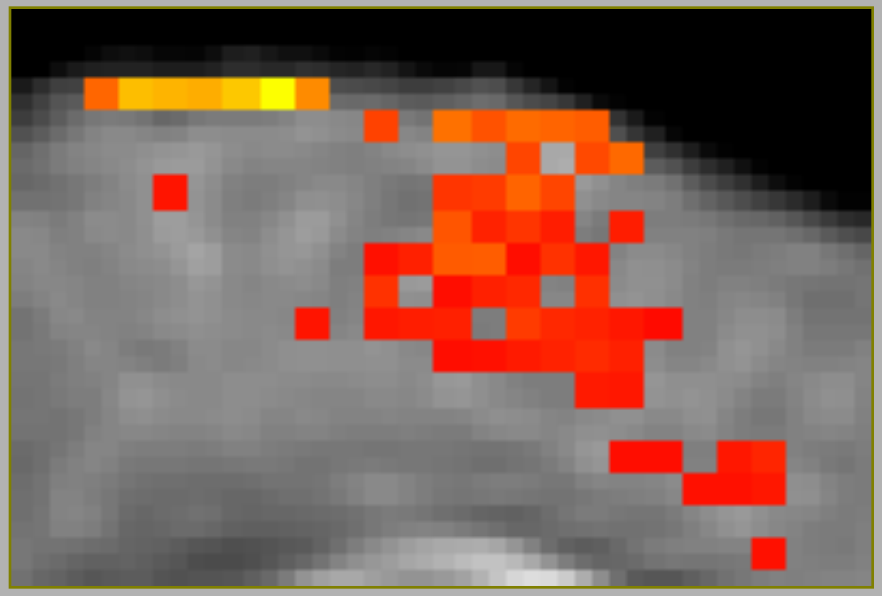


5% CO2

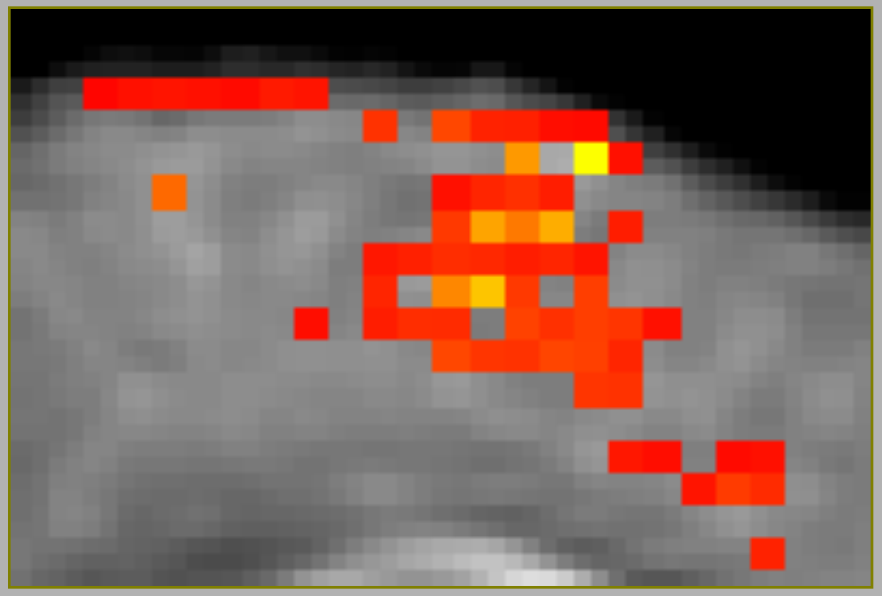
Resting State Blood Volume Weighting

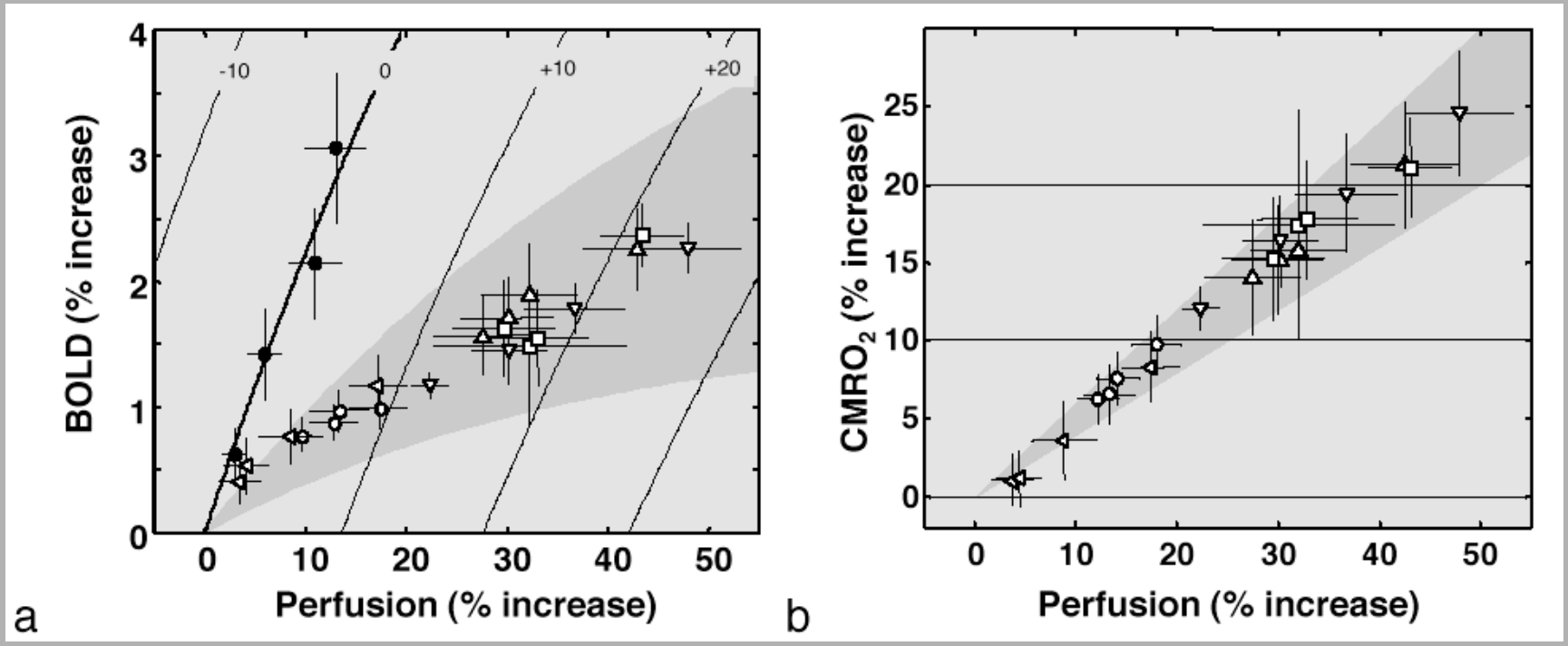


Finger Movement

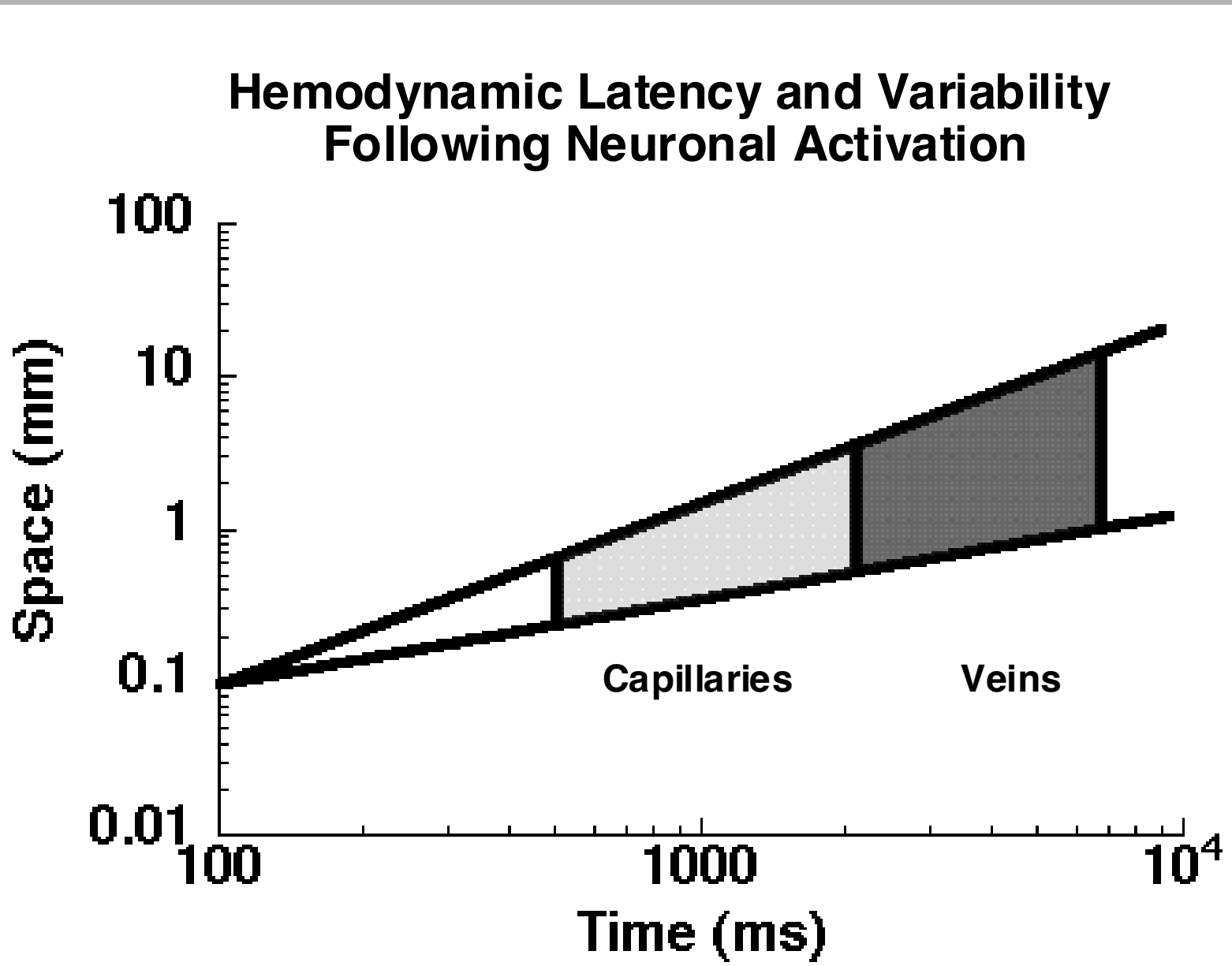


Finger Movement / 5% CO2

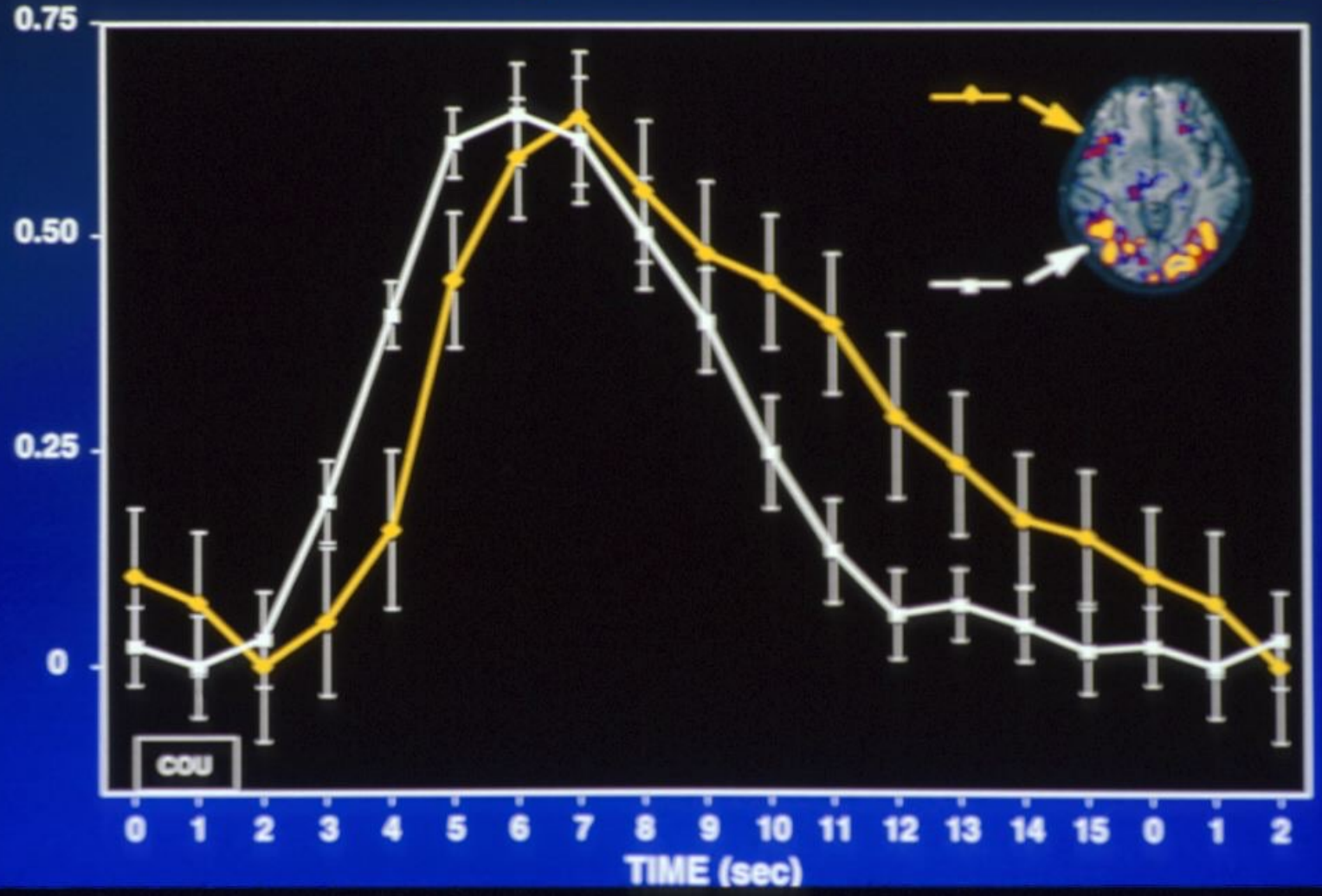


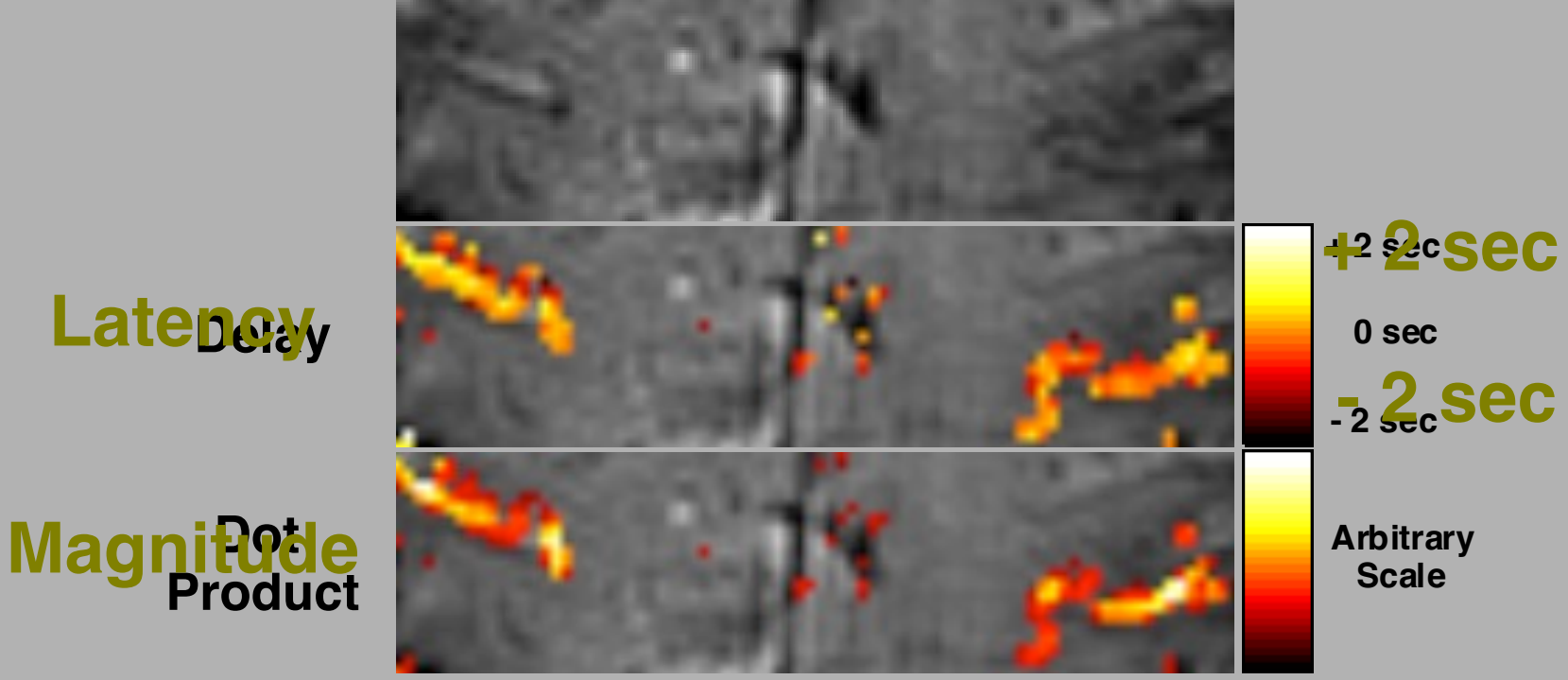

BOLD (% increase)
-10
0
+10
+20
Perfusion (% increase)
a
CMRO2 (% increase)
Perfusion (% increase)
b

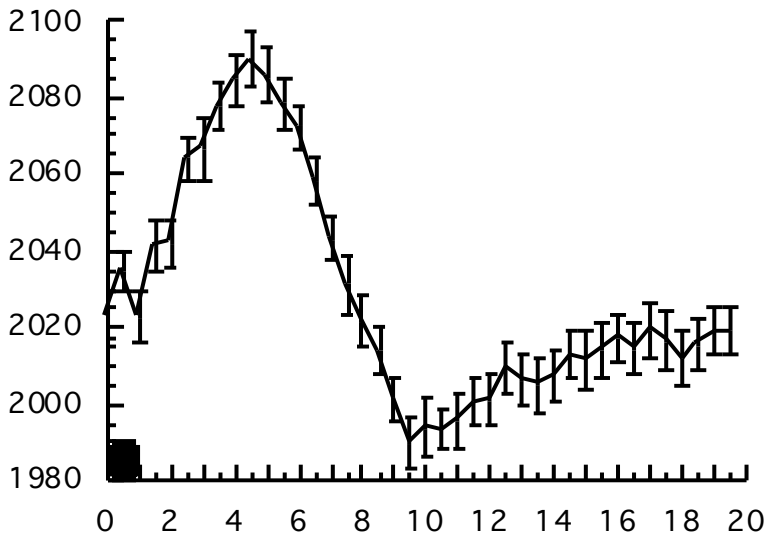
Hoge et al

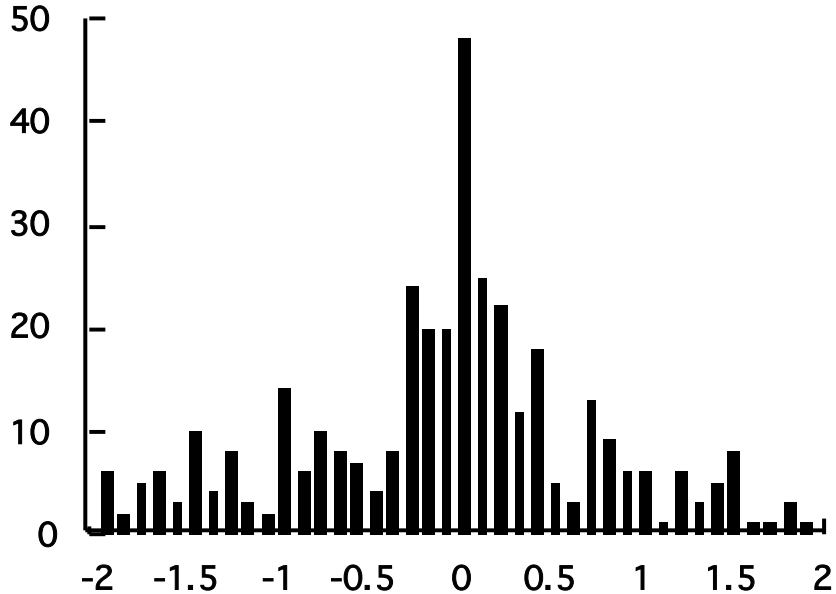

Hemodynamic Latency and Variability
Following Neuronal Activation
100
10
1
0.1
0.01
Space (mm)
Capillaries
Veins
100
1000
10^4
Time (ms)

Time Course Comparison Across Brain Regions

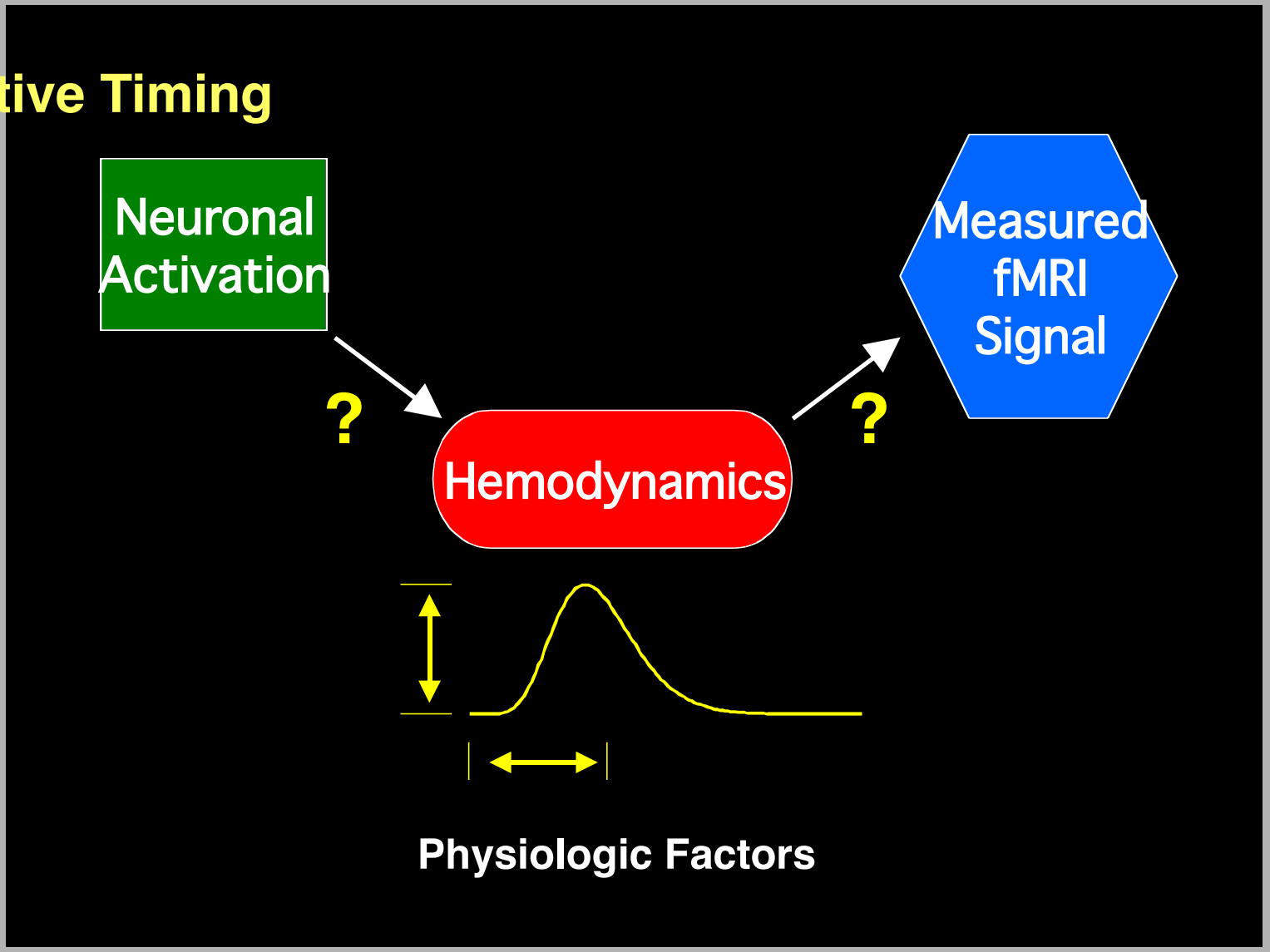



Latency
Delay
Magnitude
Dot Product
+2 sec
0 sec
-2 sec
+2 sec
-2 sec
Arbitrary Scale


2100
2080
2060
2040
2020
2000
1980
0 2 4 6 8 10 12 14 16 18 20
Time (sec)

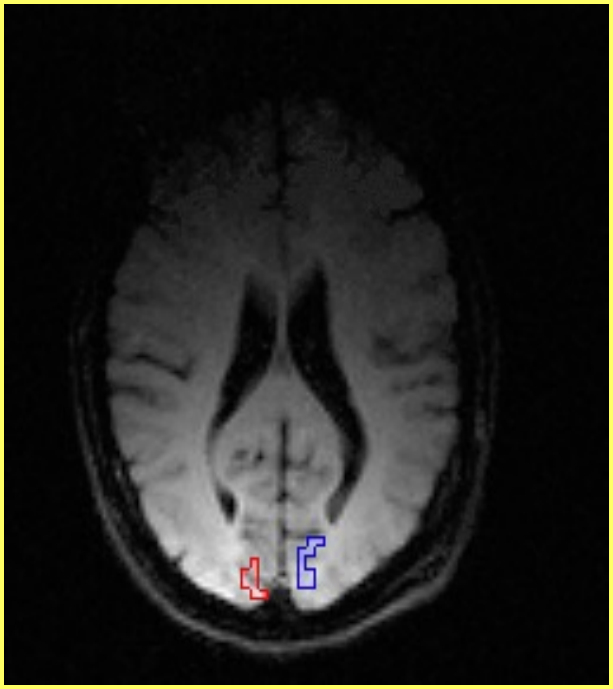

50
40
30
20
10
0
-2 -1.5 -1 -0.5 0 0.5 1 1.5 2
Delay (sec)

Temporal Normalization

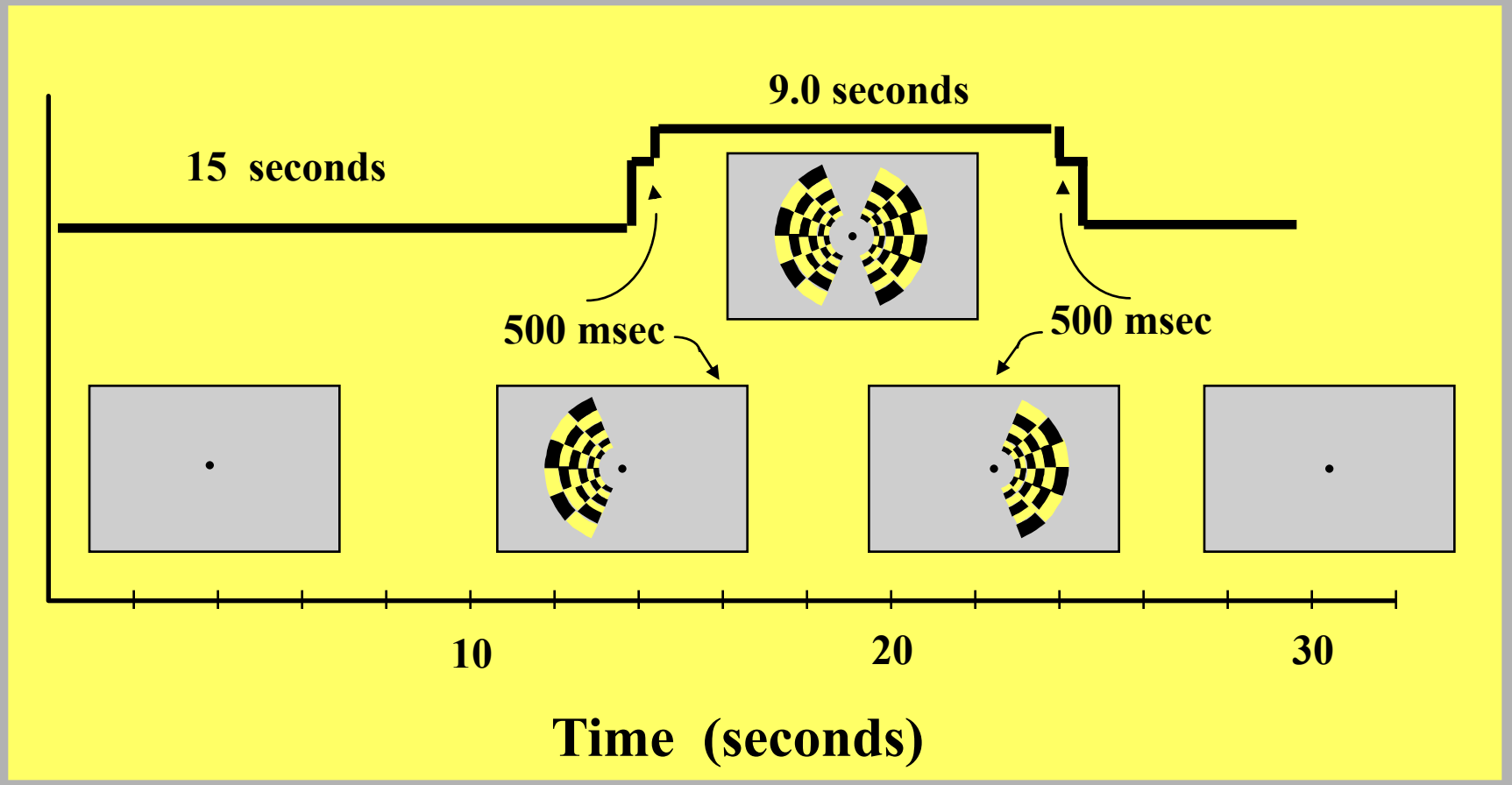


Regions of Interest Used for Hemi-Field Experiment

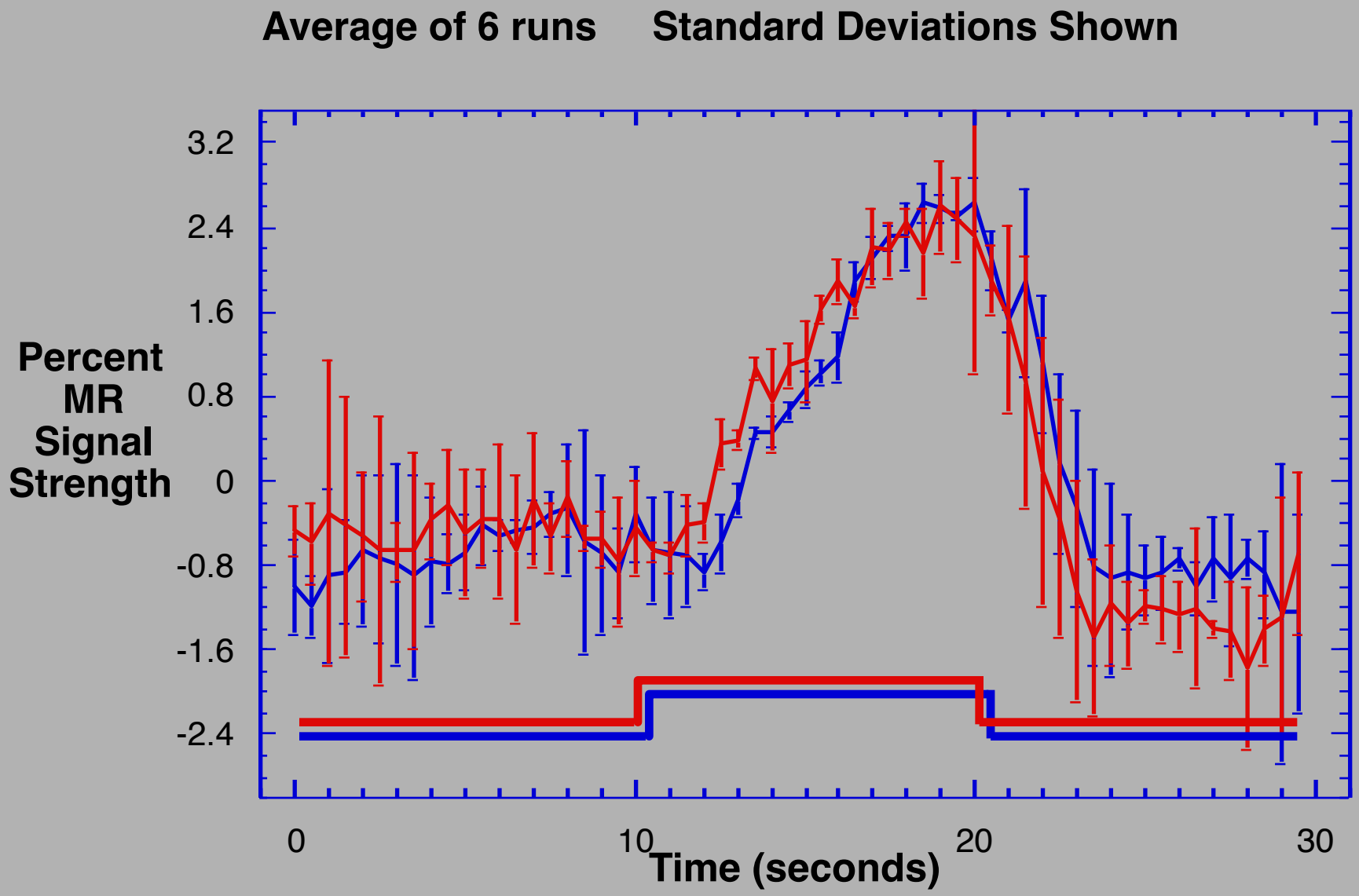
Right Hemisphere

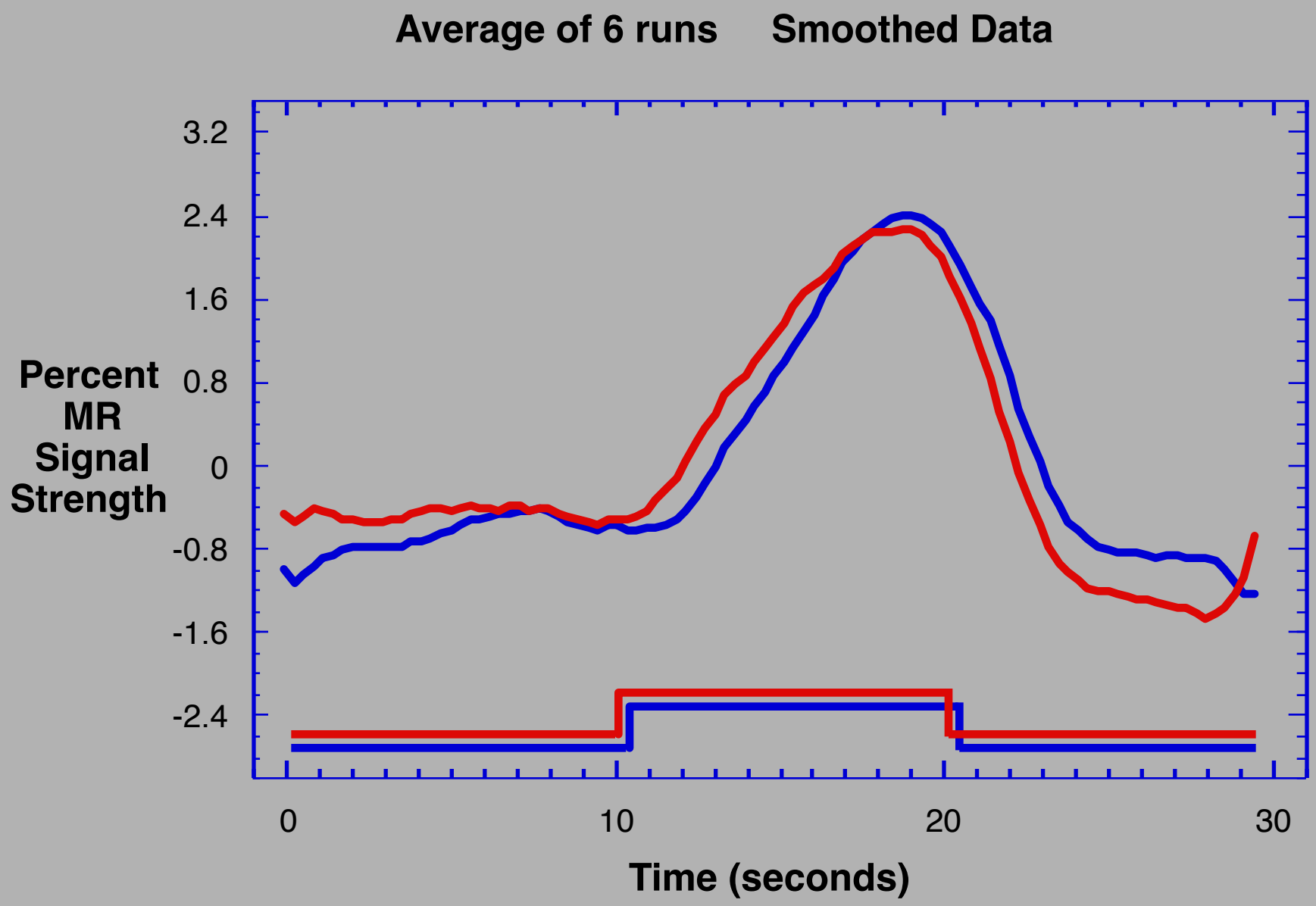


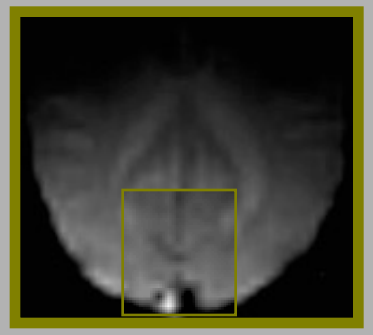
Left Hemisphere


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

Hemi-field with 500 msec asynchrony




Average of 6 runs
Smoothed Data
Percent MR Signal Strength
3.2
2.4
1.6
0.8
0
-0.8
-1.6
-2.4
0
10
20
30
Time (seconds)

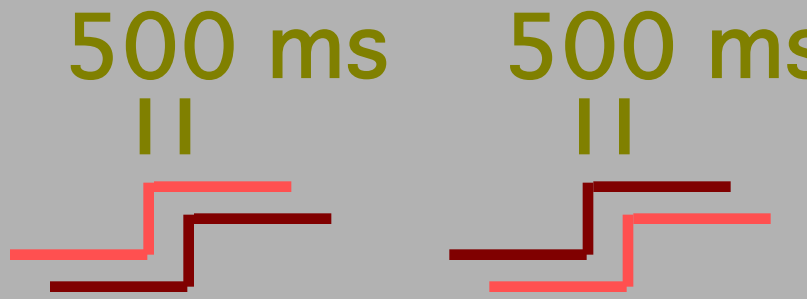


500 ms

500 ms

Right Hemifield

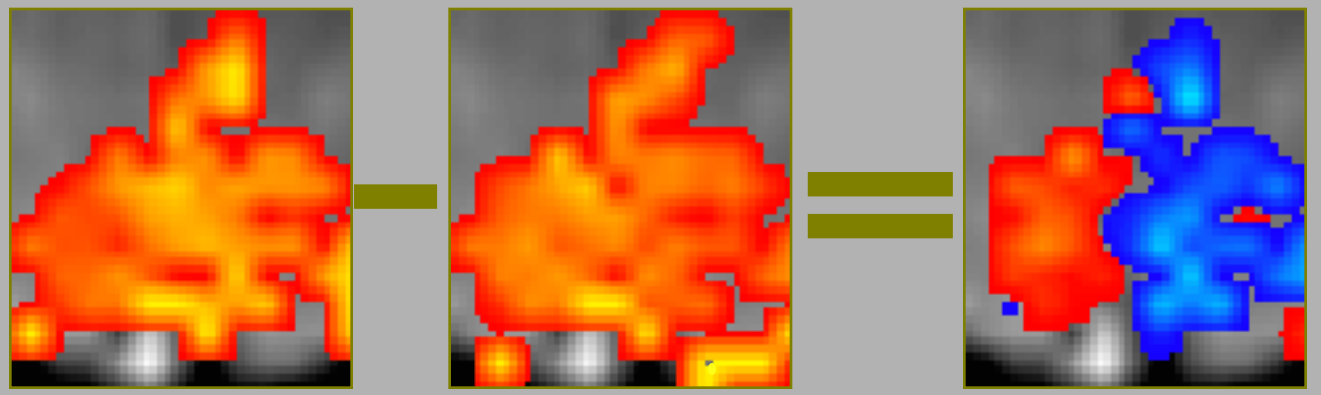
Left Hemifield

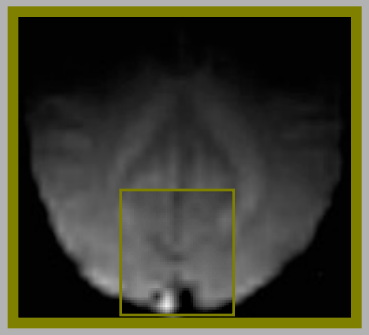


+ 2.5 s

0 s

- 2.5 s





250 ms

250 ms

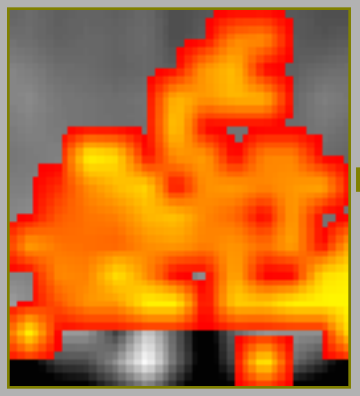
Right Hemifield

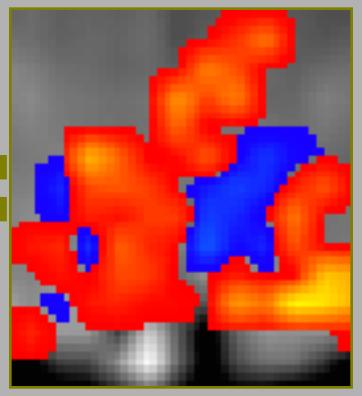
Left Hemifield

+ 2.5 s

0 s

- 2.5 s





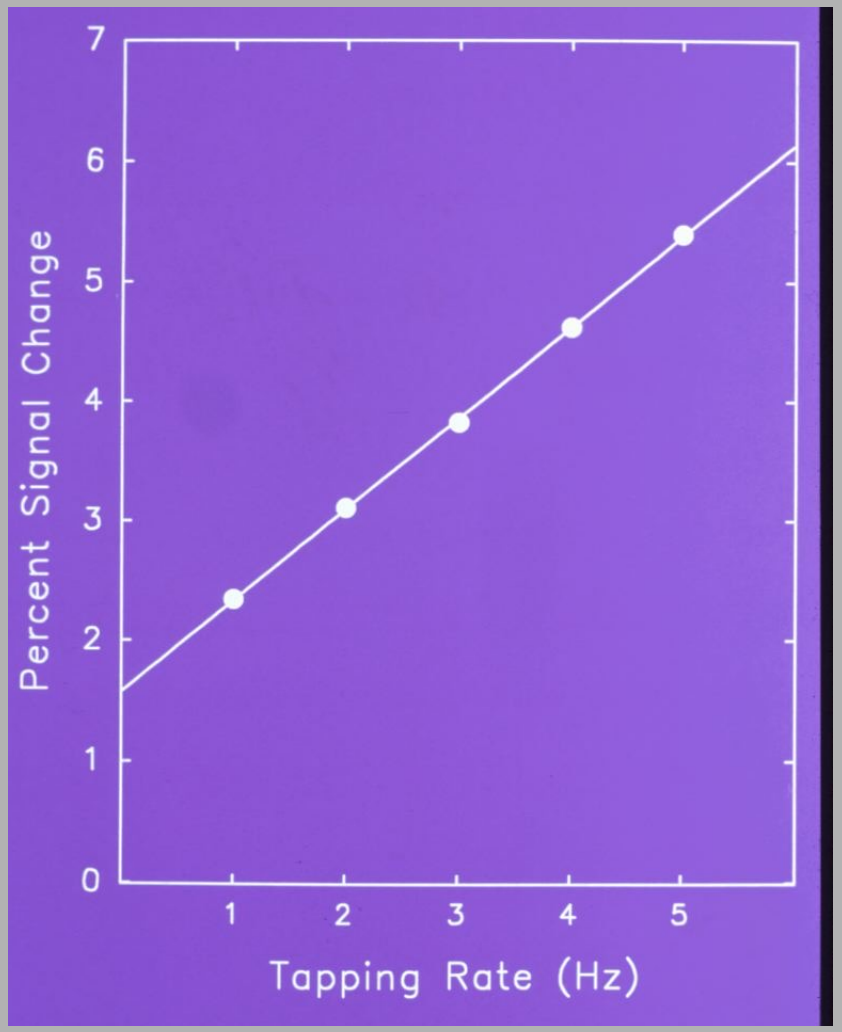
How Much?

Central Issue:

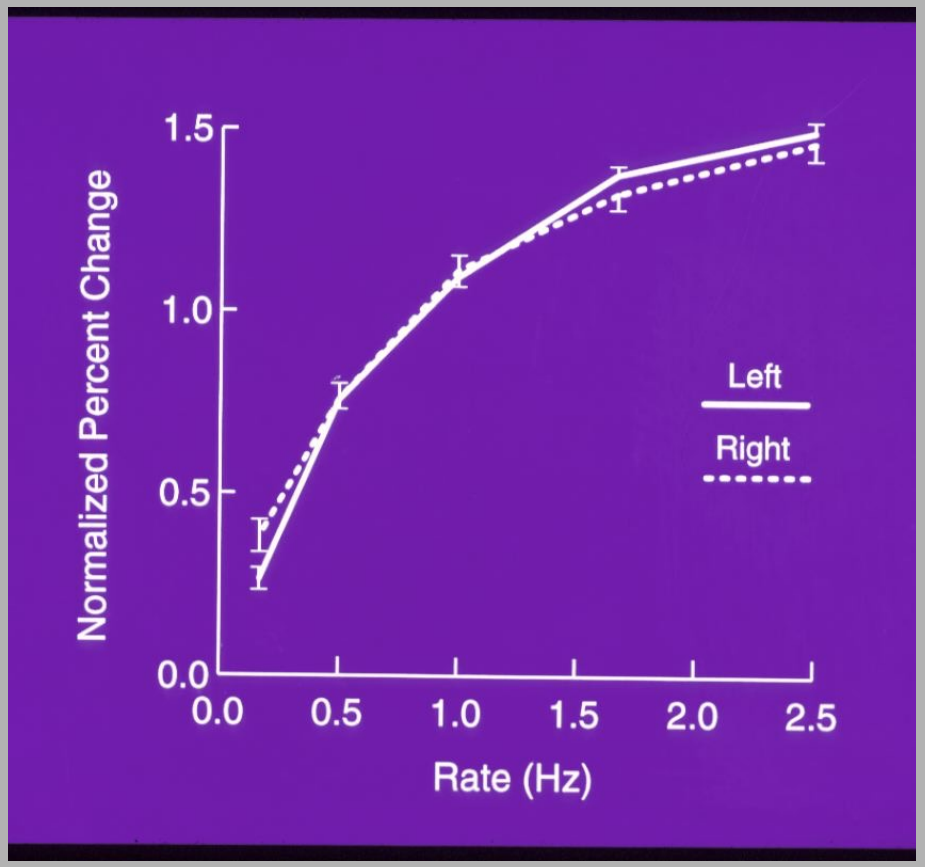
Spatial and temporal neuronal firing integration to create an fMRI signal change.

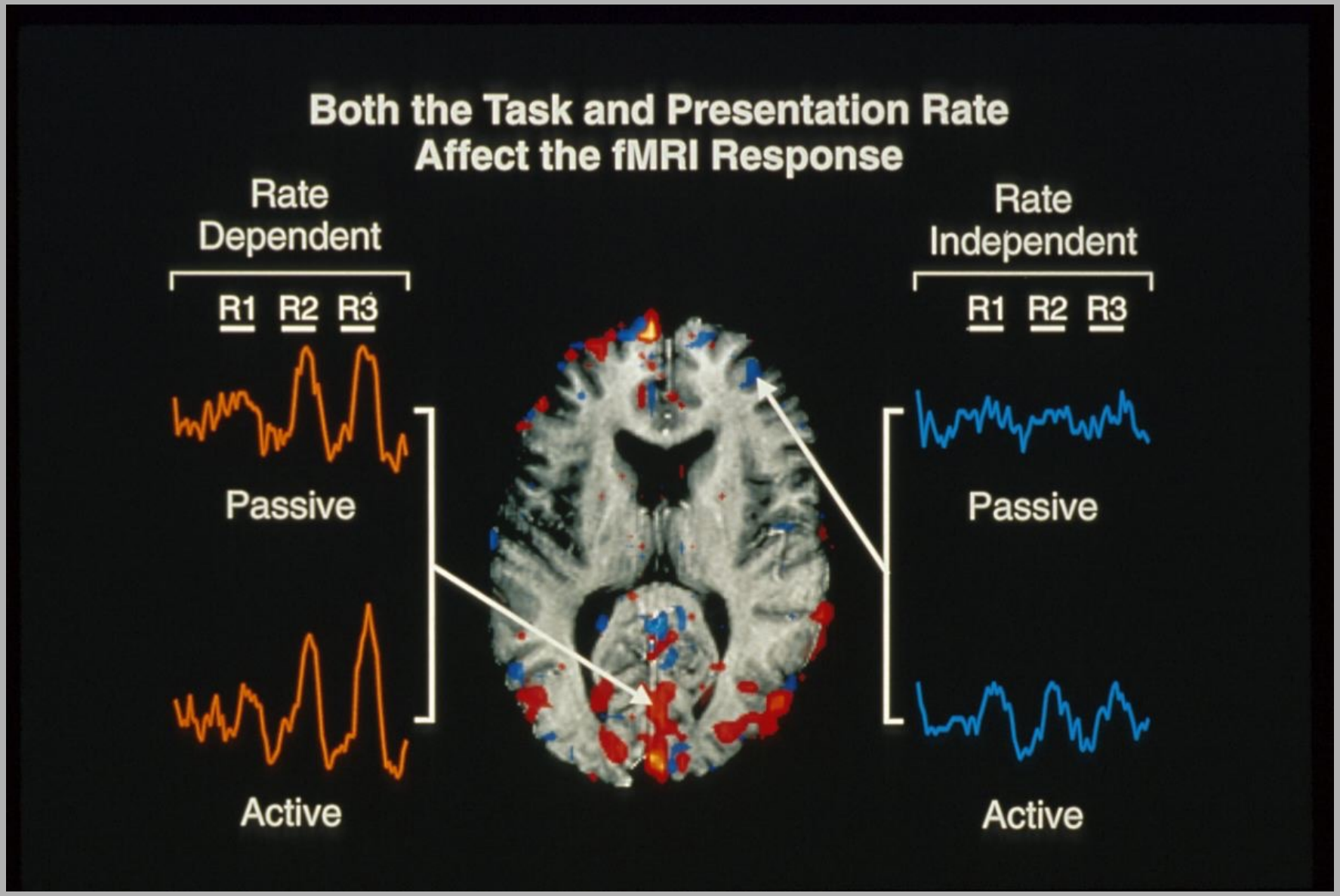
- is the hemodynamic response a linear system?
-what is the dynamic range?

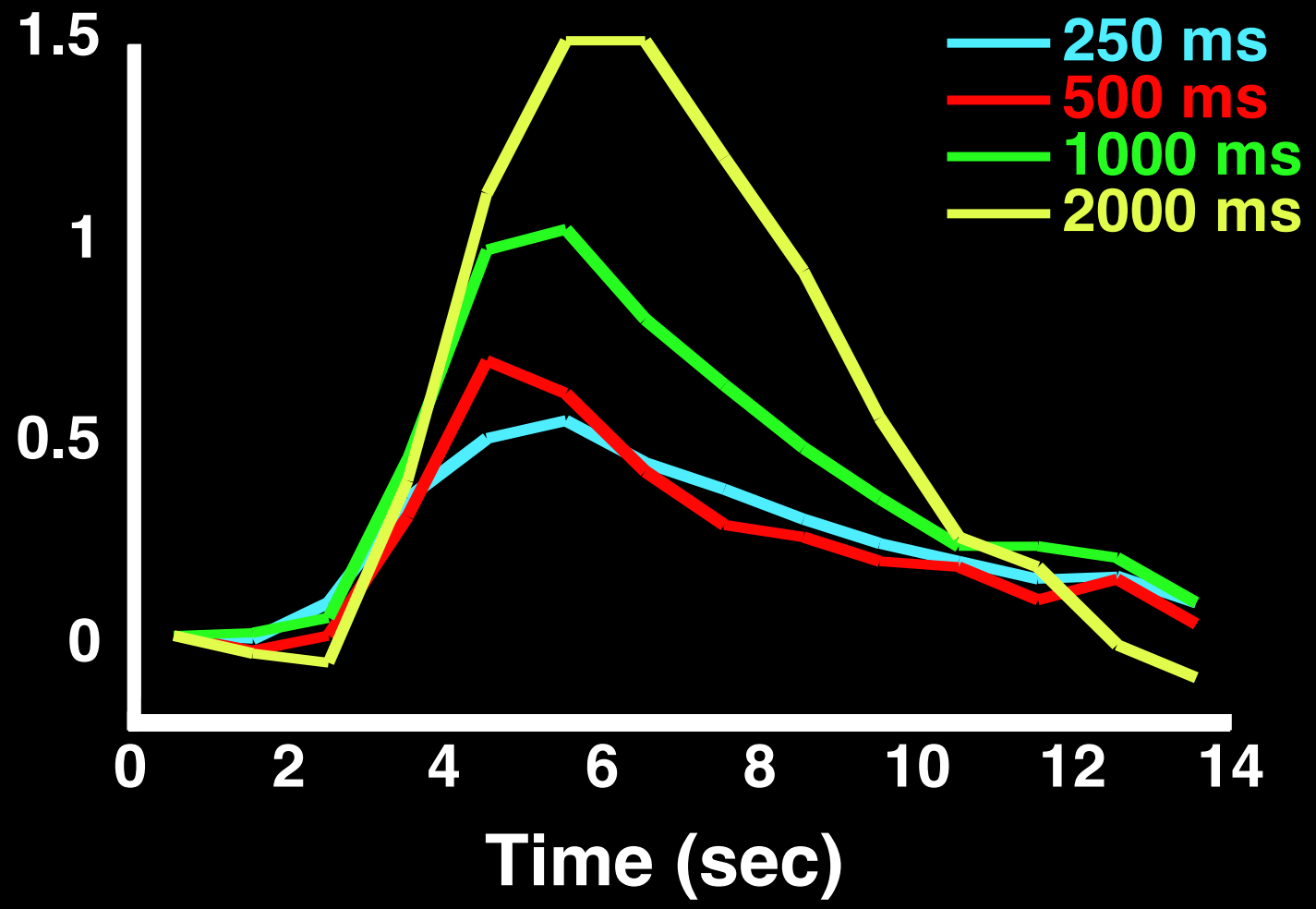
Motor Cortex

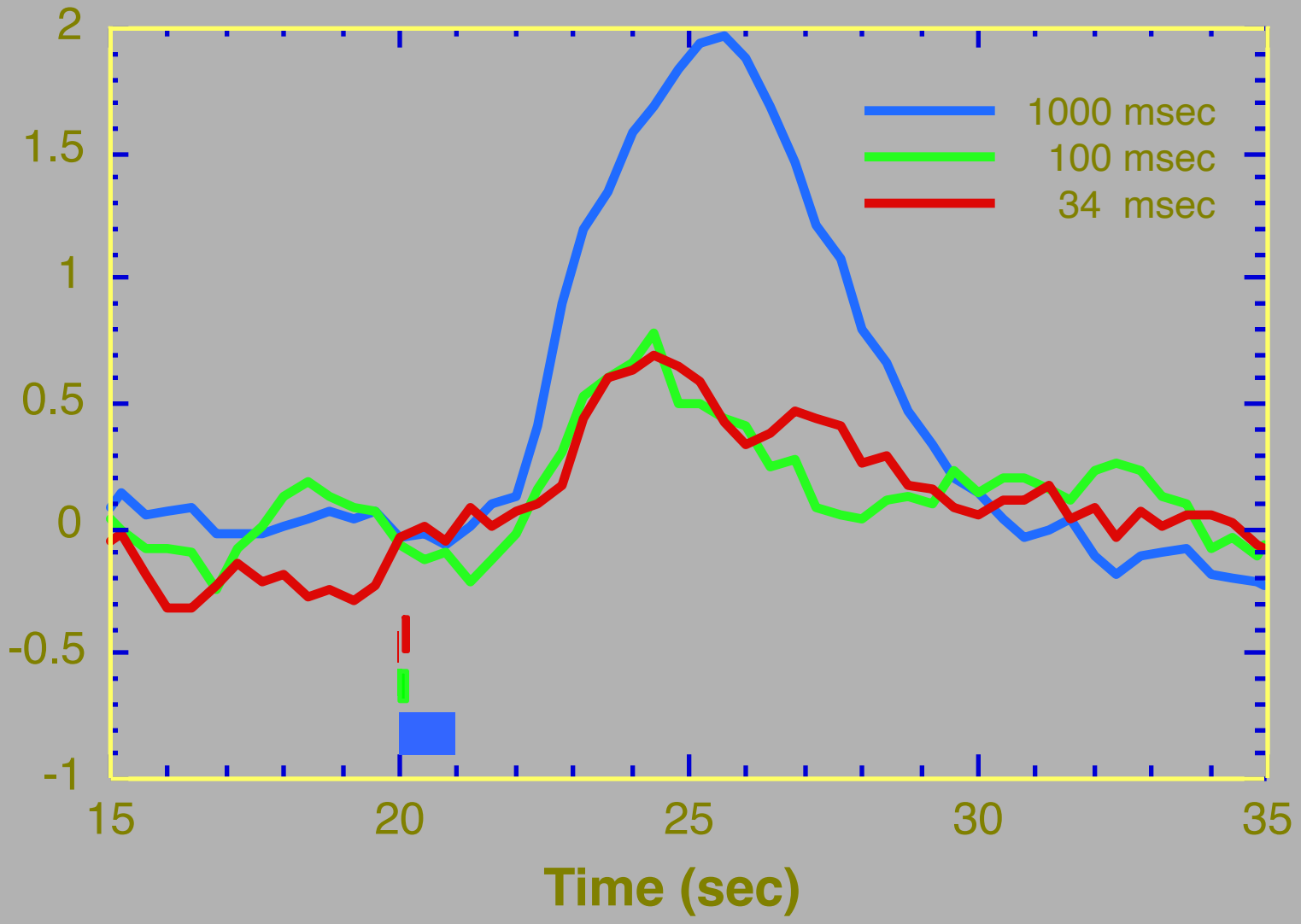


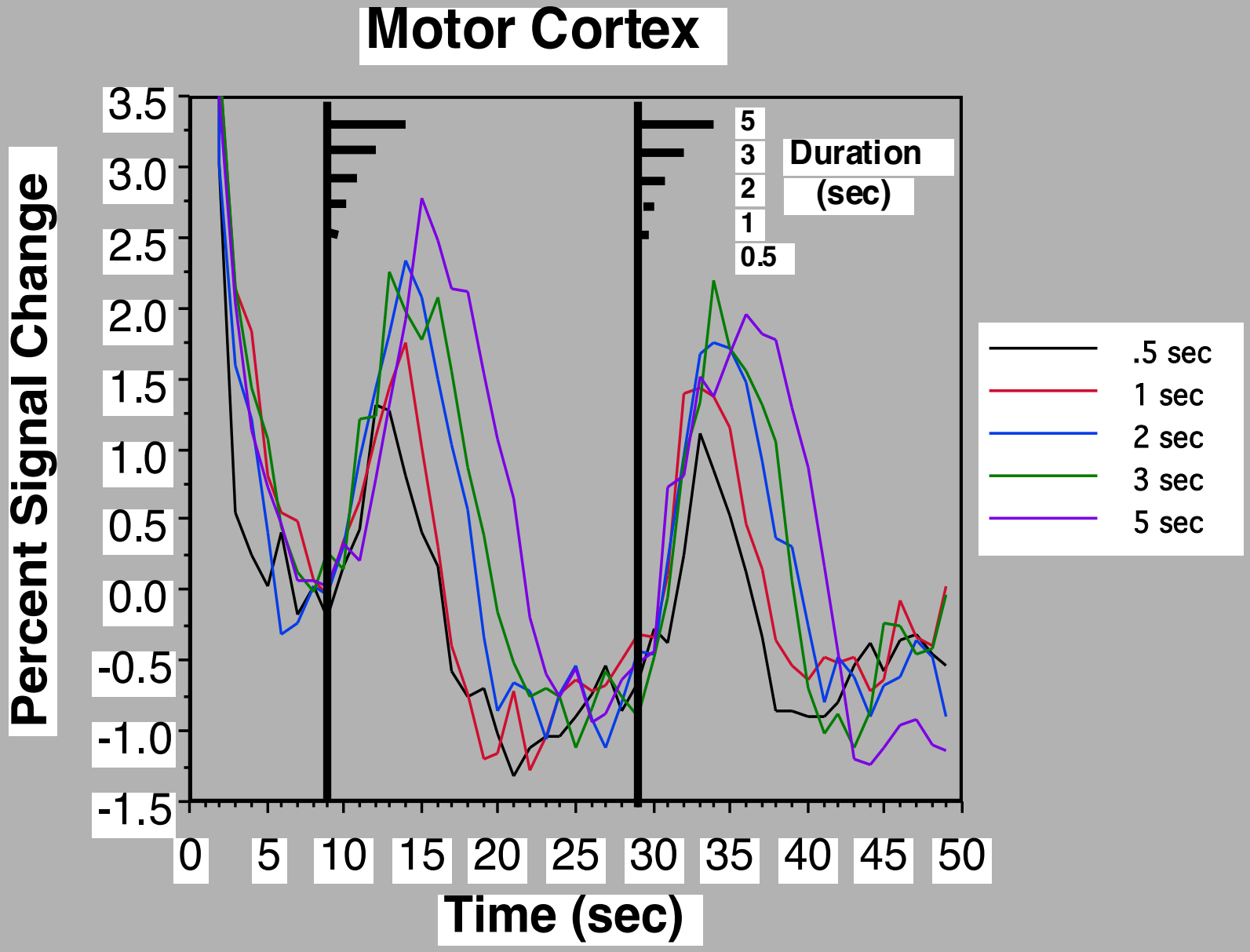
Auditory Cortex



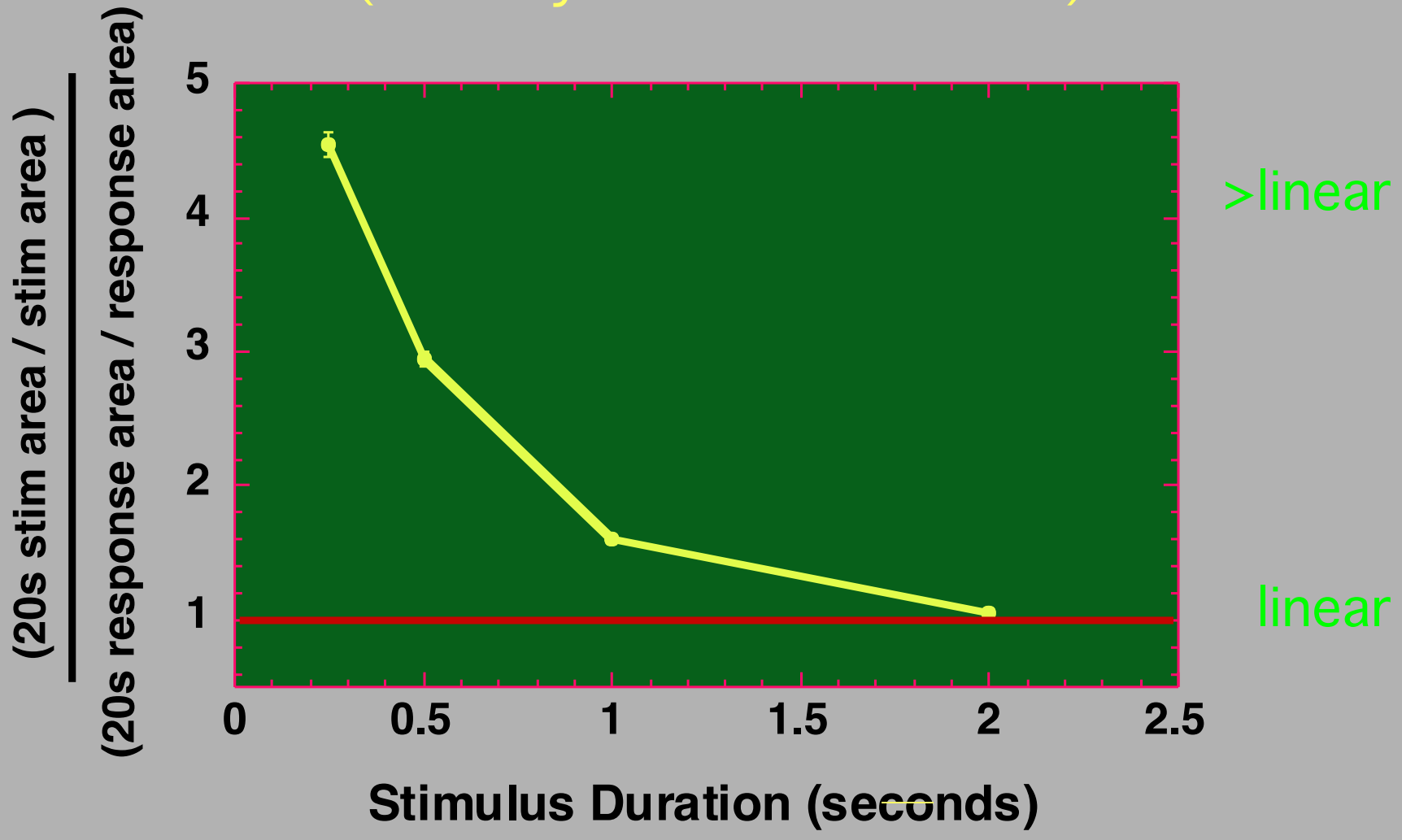

Both the Task and Presentation Rate
Affect the fMRI Response
Rate
Dependent
R1 R2 R3
Passive
Active
Rate
Independent
R1 R2 R3
Passive
Active


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

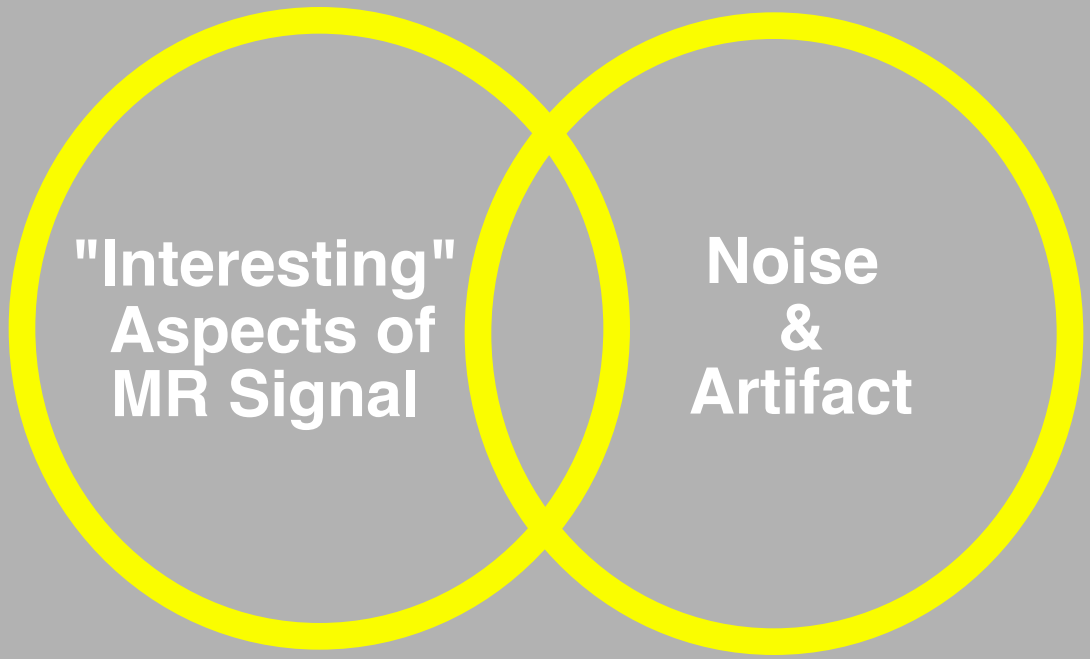

2
1.5
1
0.5
0
-0.5
-1
15
20
25
30
35
1000 msec
100 msec
34 msec
Time (sec)


Motor Cortex
Percent Signal Change
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
-1.0
-1.5
0
5
10
15
20
25
30
35
40
45
50
Time (sec)
5
3
2
1
0.5
Duration
(sec)
.5 sec
1 sec
2 sec
3 sec
5 sec

Stimululs - Duration Dependent Deviation from Linearity of the fMRI Response (Hemodynamic or Neuronal?)

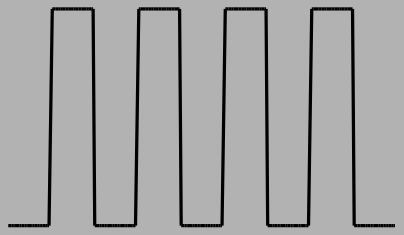


How to get the brain to do what we want it to do in the context of an fMRI experiment?

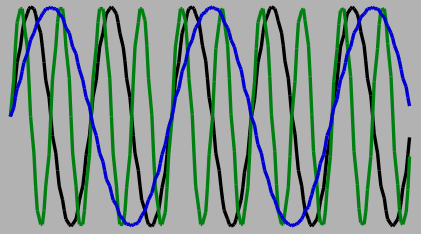


Neuronal Activation Input Strategies

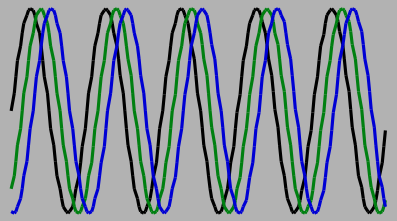
1. Block Design



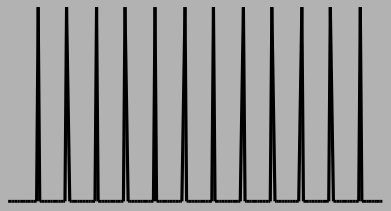
2. Frequency Encoding



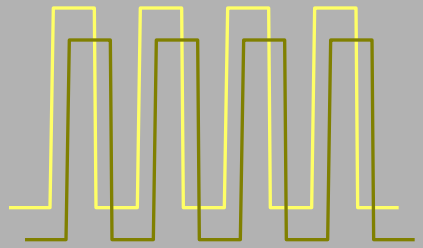
3. Phase Encoding



4. Single Event

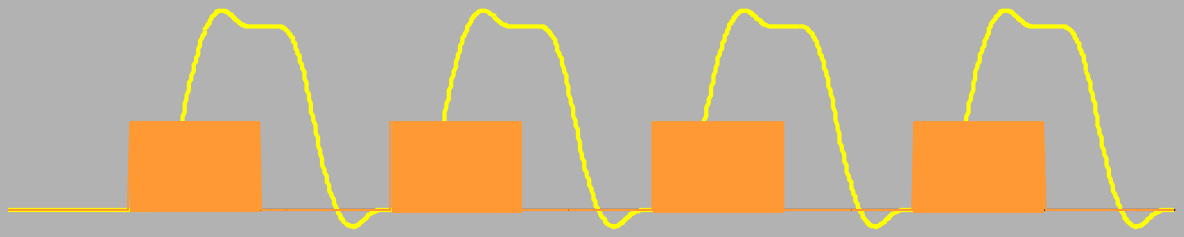


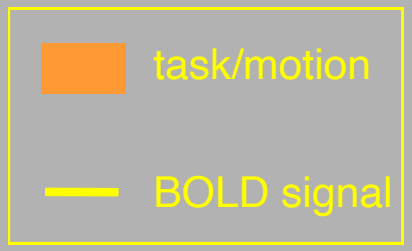
5. Orthogonal Block Design



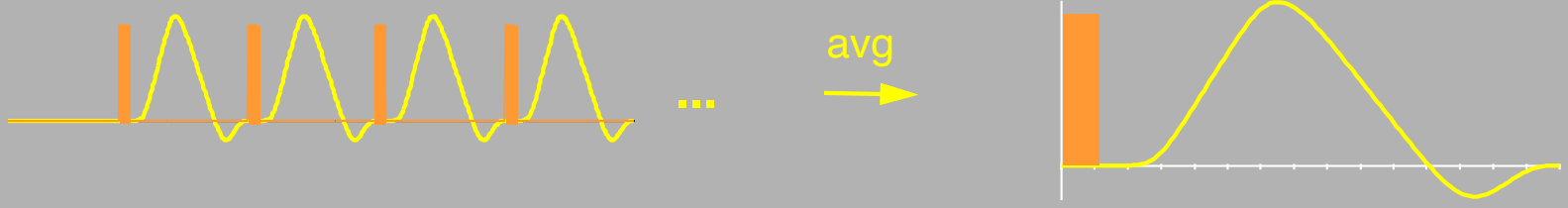
6. Free behavior Design.

Block-trial

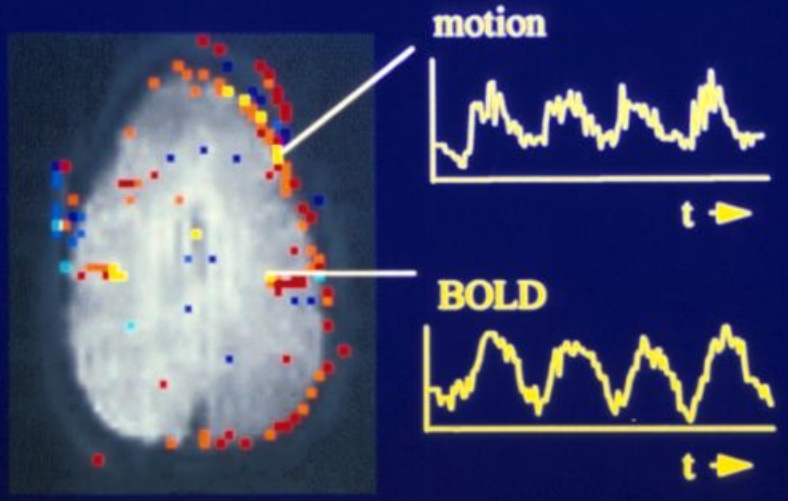




Single-trial (brief stimulus)

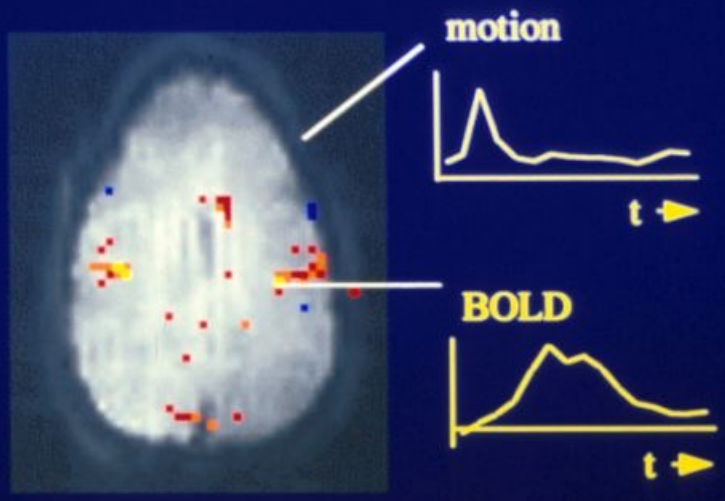


Motion-Decoupled fMRI:
Functional MRI during of overt word production



"block-trial" paradigm

Motion induced signal changes resemble functional (BOLD) signal changes

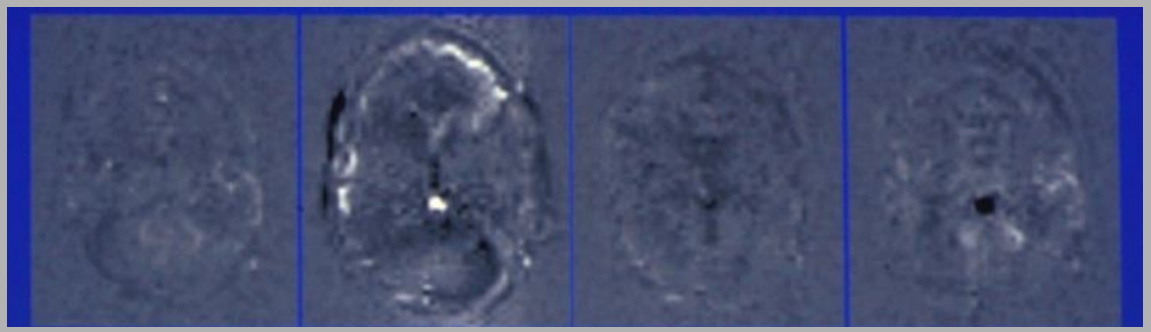


"single-trial" paradigm

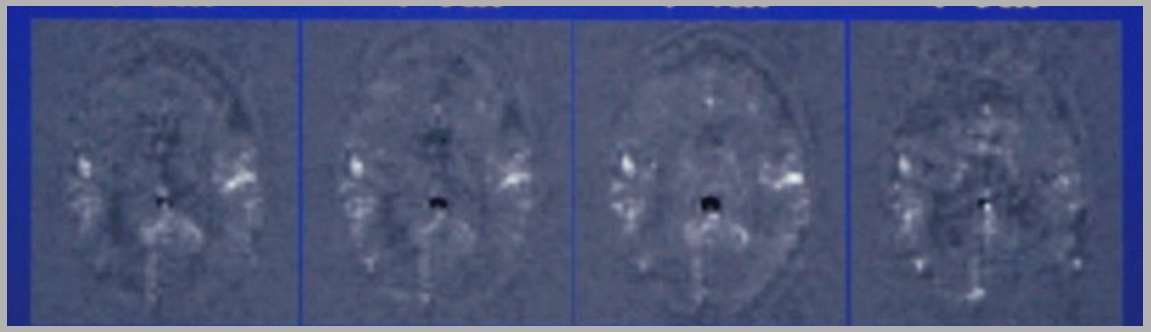
Motion induced and BOLD signal changes are separated in time

R.M. Birn, et al.

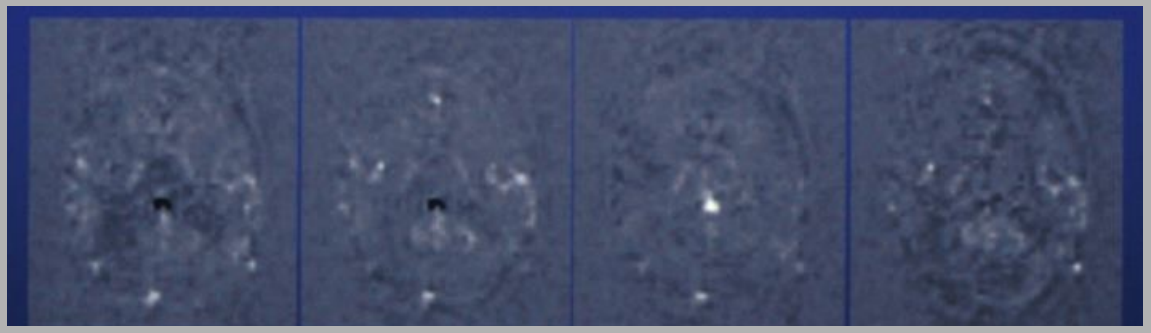
Overt Word Production



2 3 4 5

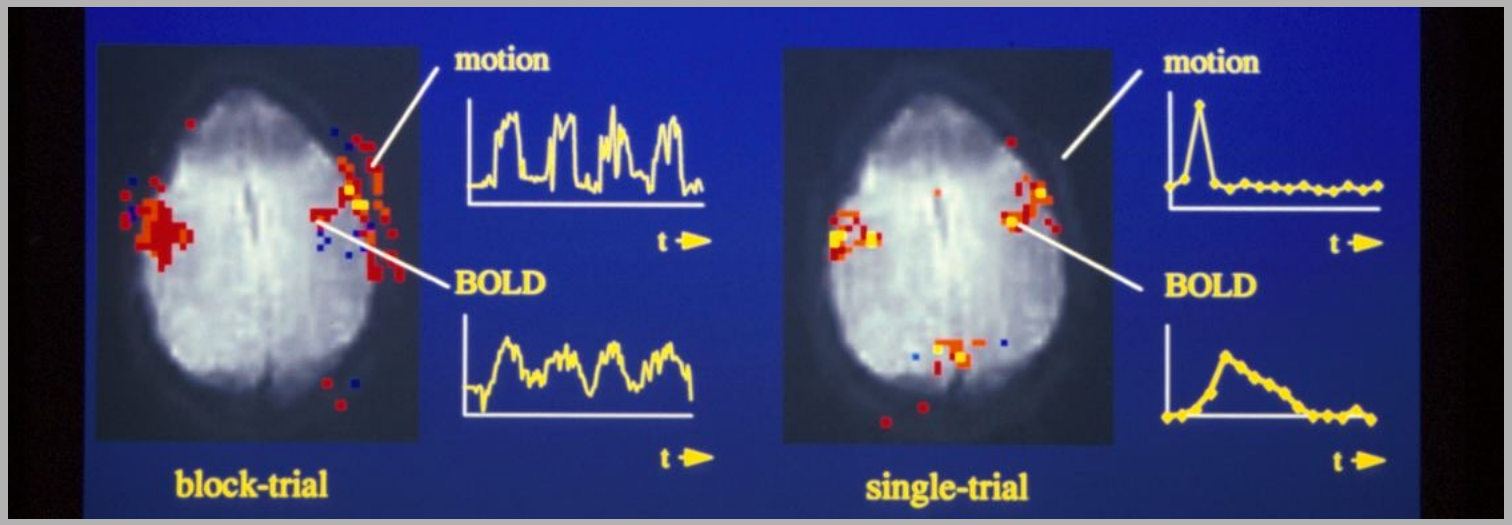


6 7 8 9

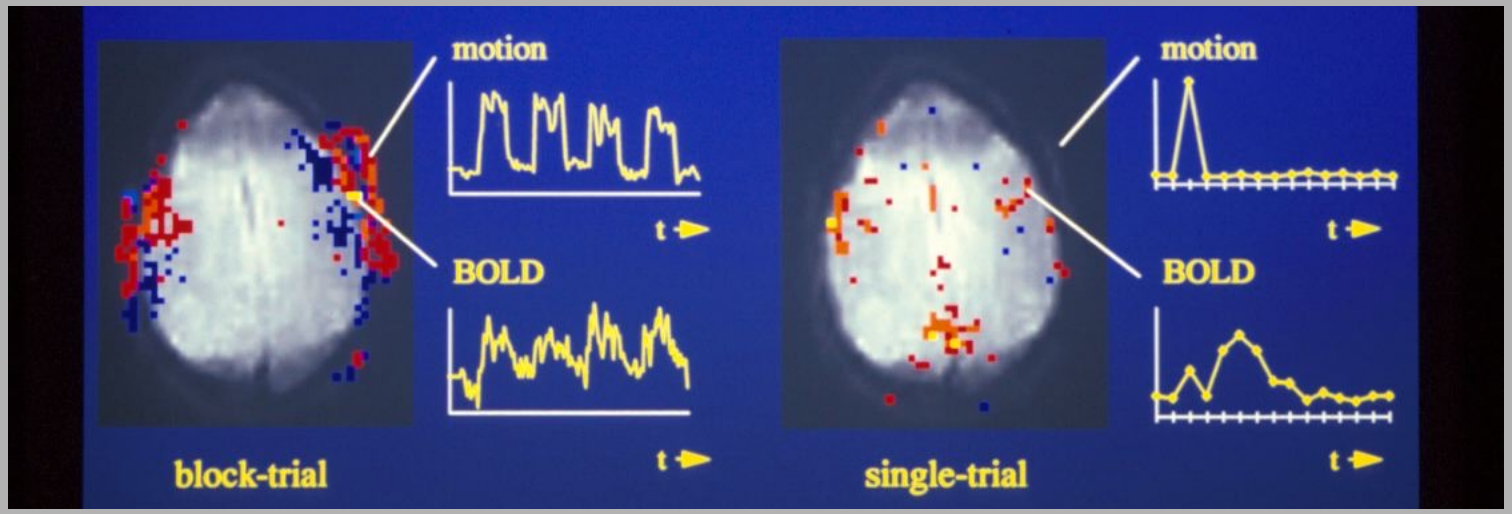


10 11 12 13

Tongue Movement



Jaw Clenching



Event-Related fMRI Questions:

1. What is the optimal ISI?

2. How does functional contrast compare with “blocked” timing?

(Is the hemodynamic response a linear system?)

Contrast in Event Related fMRI

Dependency on:

- Inter-stimulus Interval (ISI)
- Stimulus Duration (SD)

Comparison with:

- Blocked strategies
- Synthesized responses created using convolution

Issues:

1. ISI Issue

- Shorter ISI provides more trials per unit time.
- Shorter ISI causes overlap in hemodynamic response, reducing dynamic range.

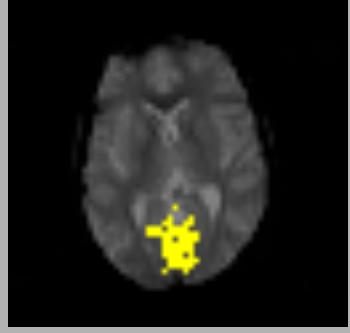
2. Contrast Issue

- Does signal behave like a linear system with brief SD?

Experimental Methods

- Two imaging planes containing motor and visual cortex.
- EPI, 3.75 x 3.75 x 7 mm, TE = 40 ms, TR = 1 sec.
- Time series duration = 360 images (6 minutes).
- 10 series compared:
  - **Single Trial:** SD = 2, ISI = 24, 20, 16, 12, 10, 8, 6, 4, 2.
  - **Blocked:** SD = 20, ISI = 20.
- Subjects instructed to tap fingers when GRASS goggles were on.

Visual Cortex



ISI, SD

20, 20

12, 2

10, 2

ISI, SD

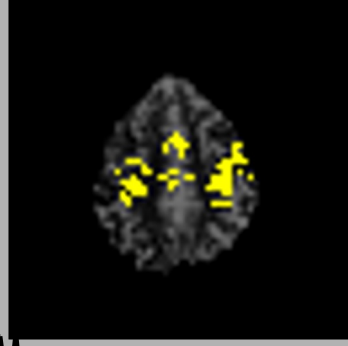
8, 2

6, 2

4, 2

2, 2

Motor Cortex



ISI, SD

20, 20

12, 2

10, 2

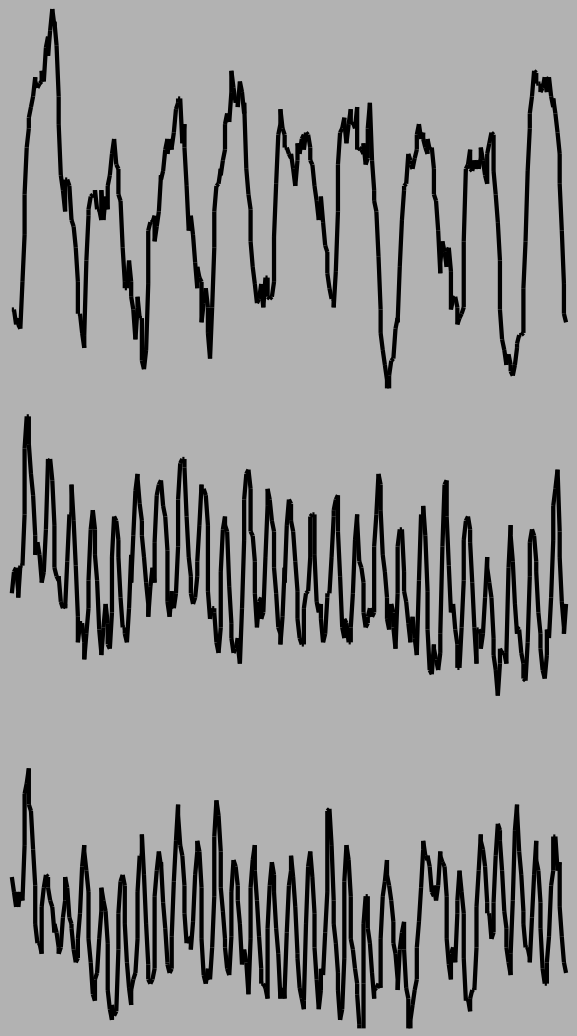
ISI, SD

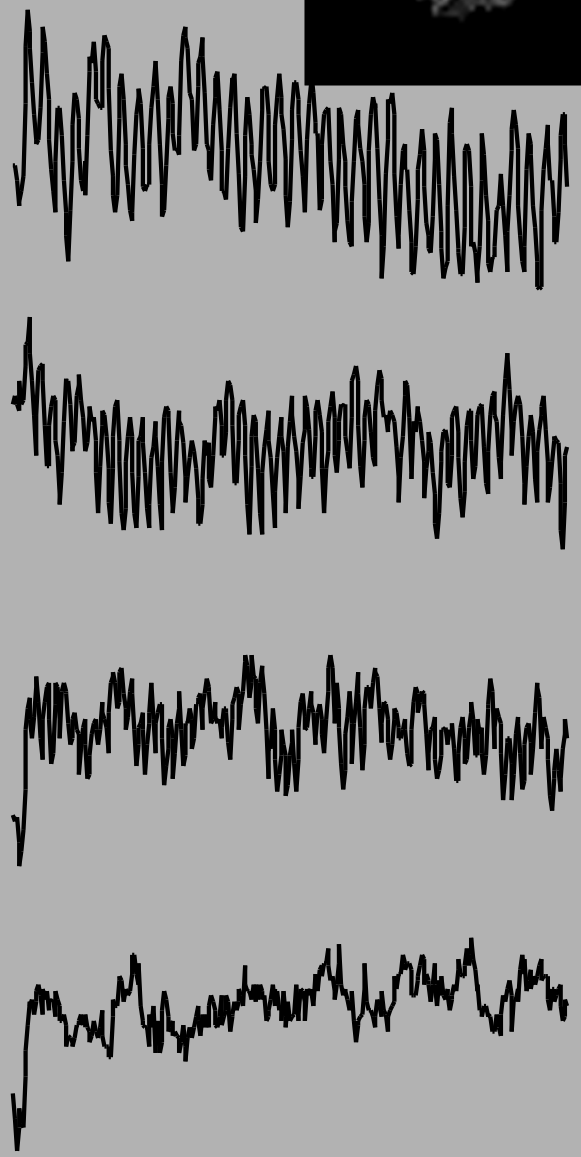
8, 2

6, 2

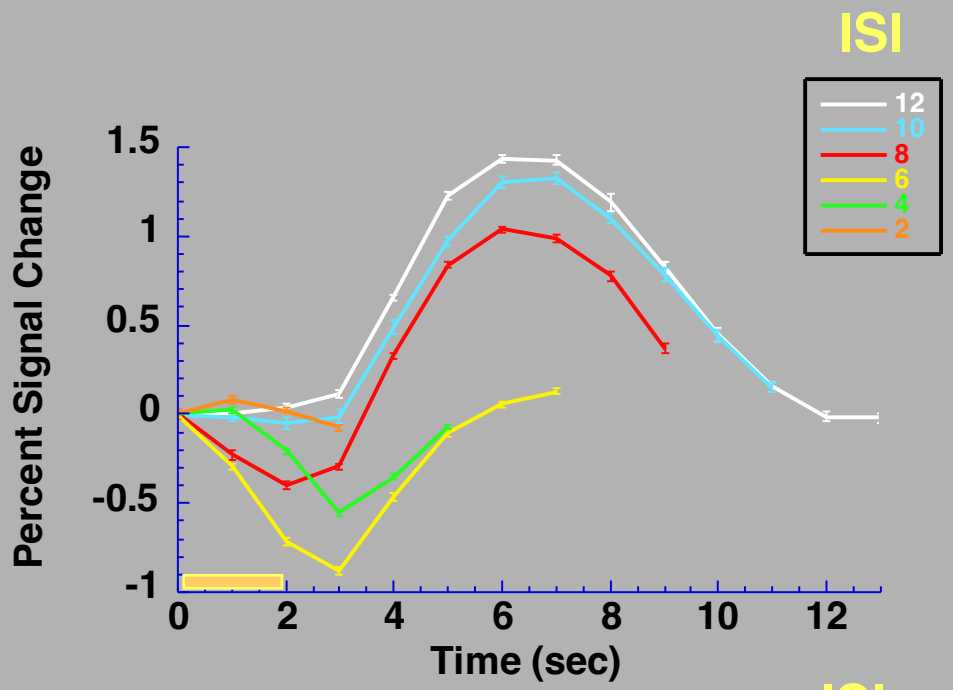
4, 2

2, 2

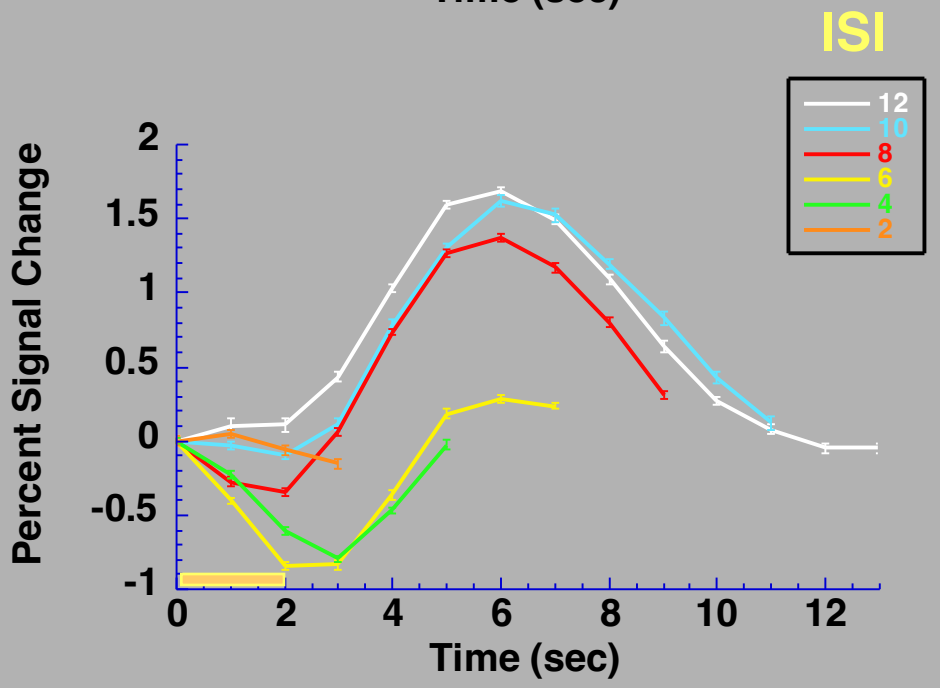




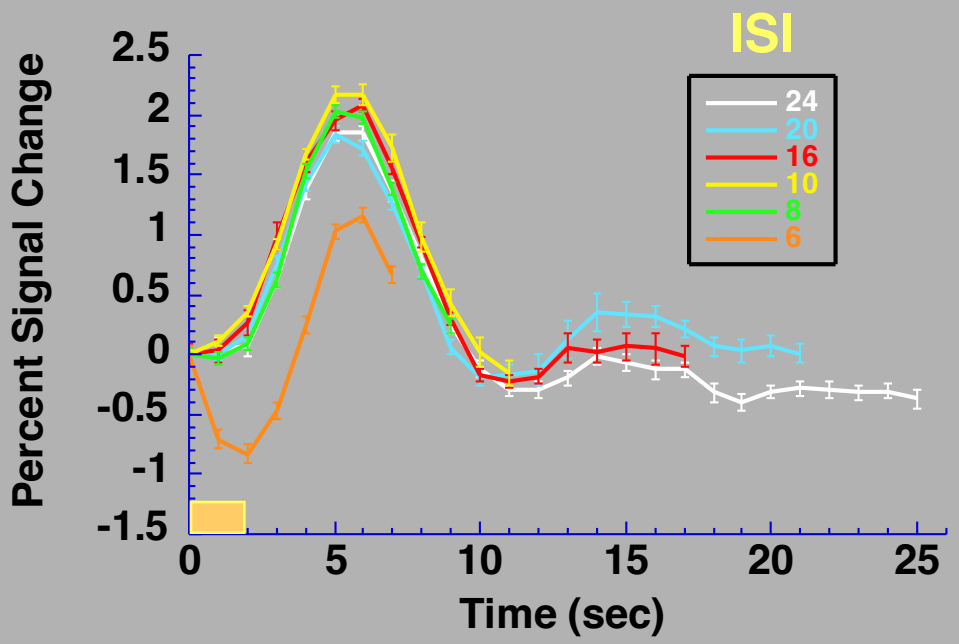
Motor Cortex



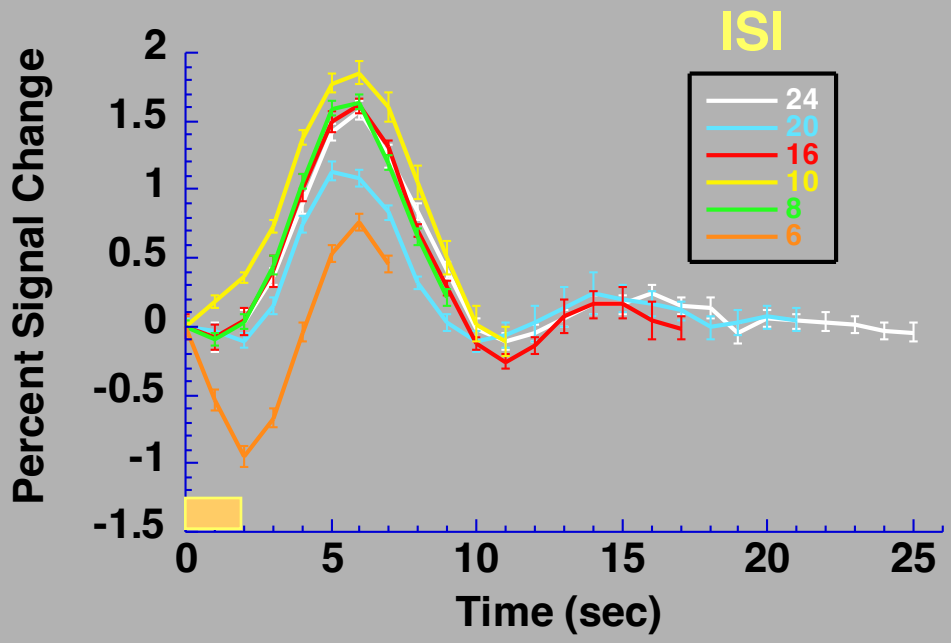
Visual Cortex



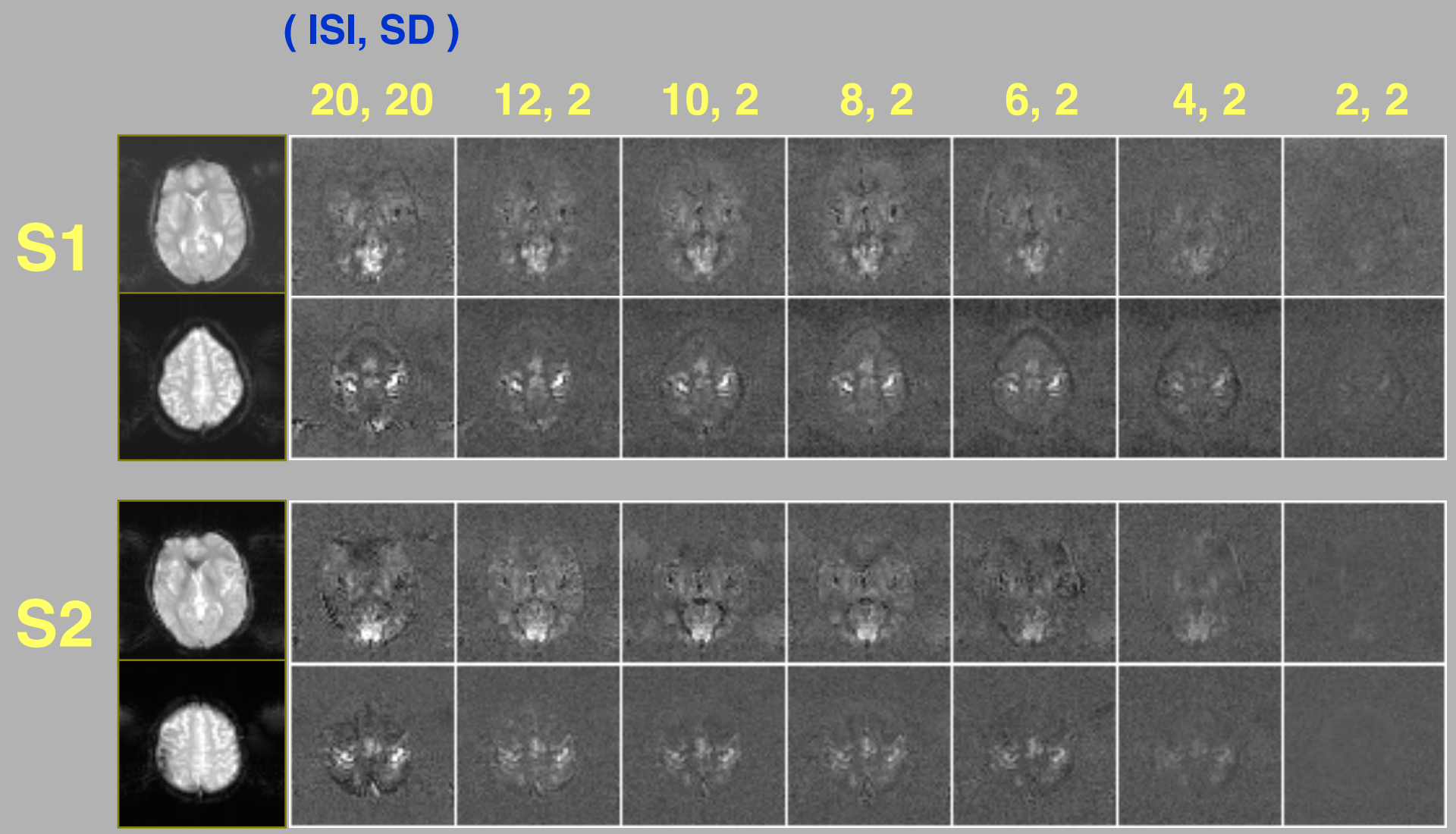
Motor Cortex



Visual Cortex



Contrast to Noise Images

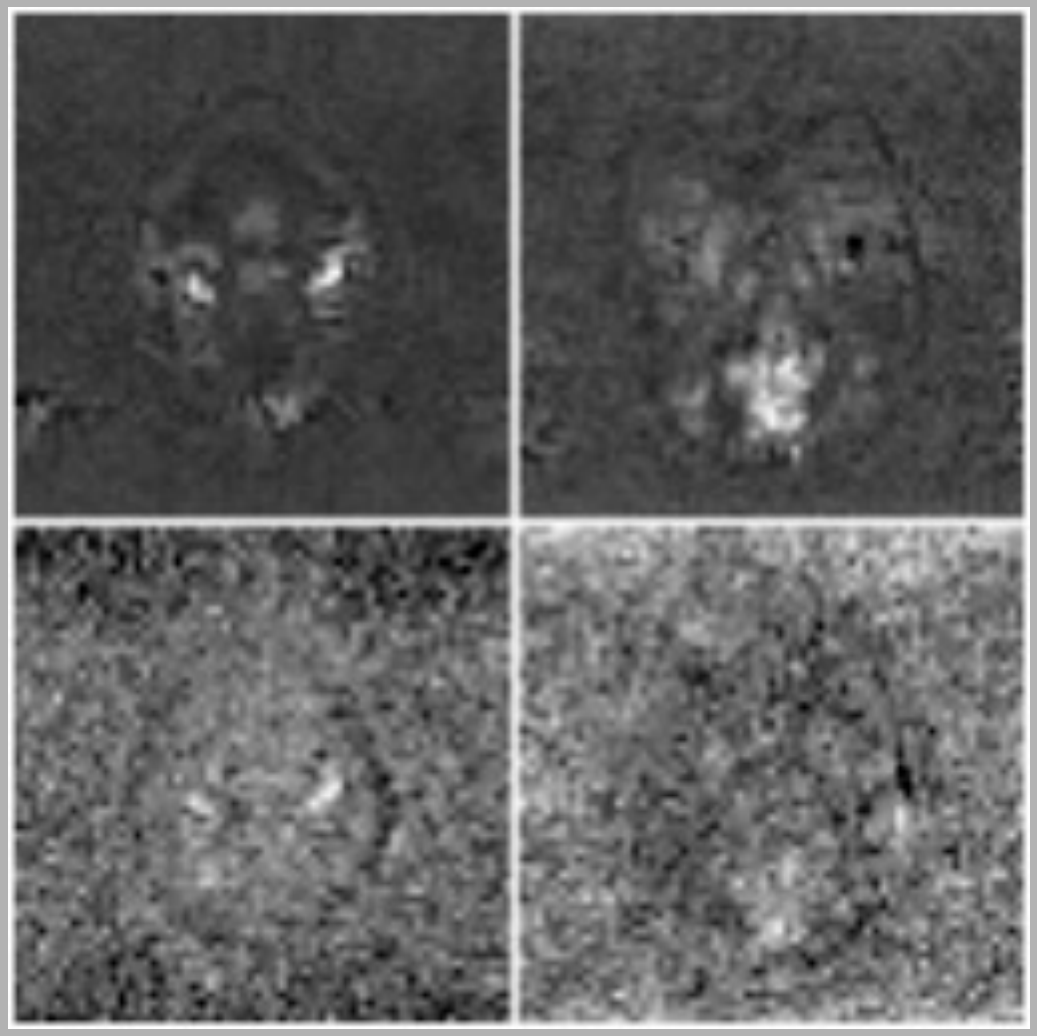


Motor Visual

(ISI, SD)

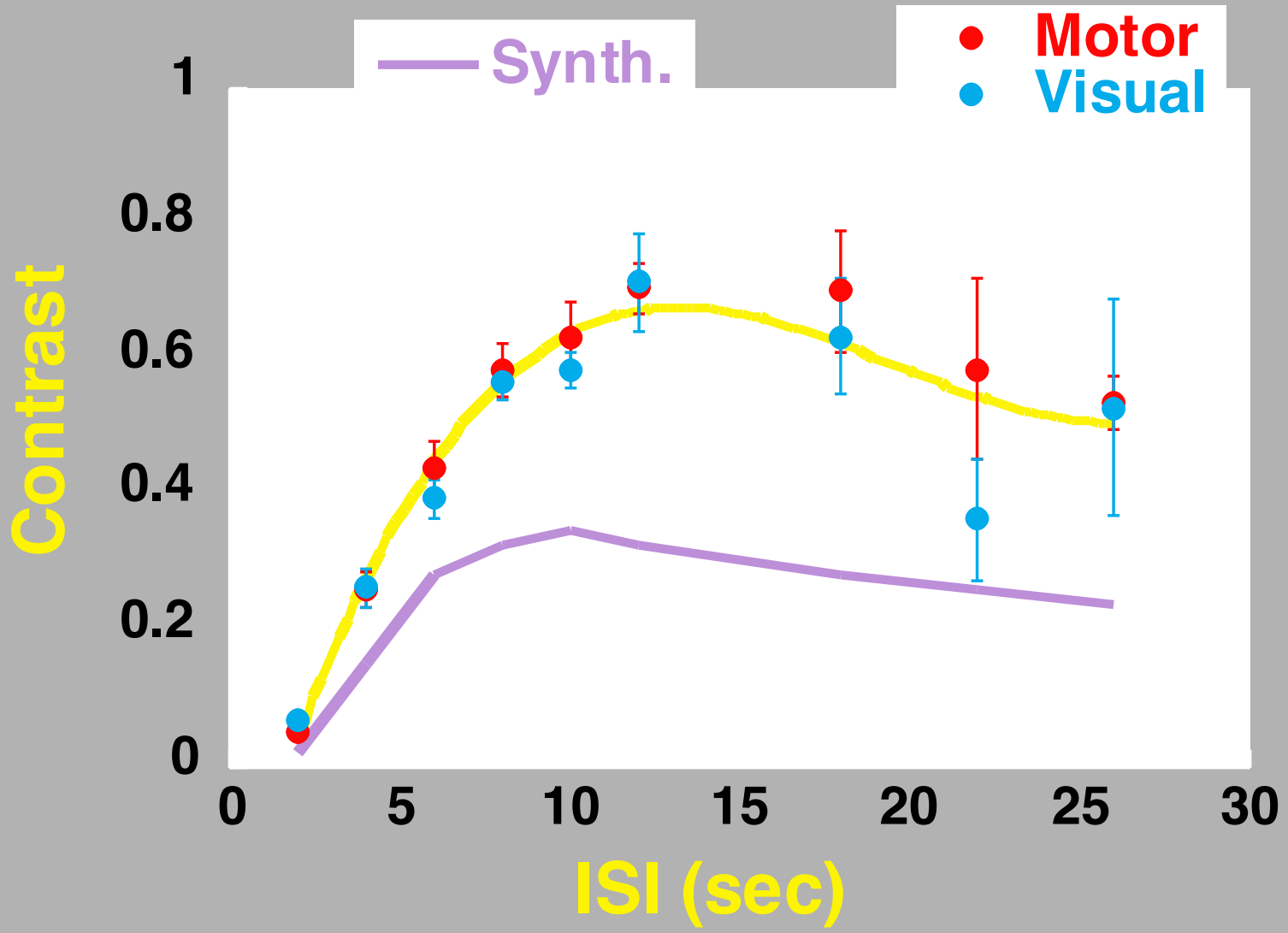
20, 20

2, 2



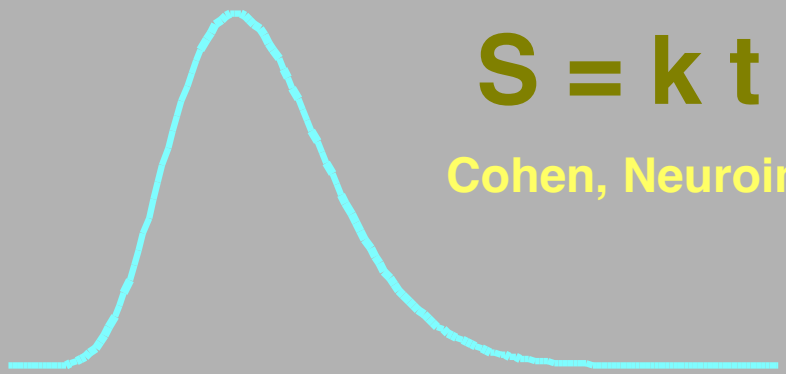
Relative differences in activation intensities may reflect spatial differences in hemodynamic responsivity. (draining veins vs. capillaries).

Functional Contrast



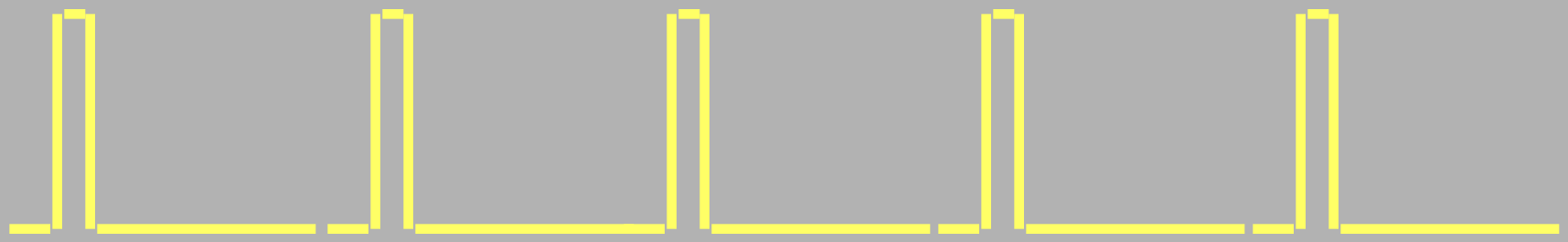
(Block design = 1)

Response Synthesis



$$S = k\, t^{8.6}\, e^{-t / 0.547}$$

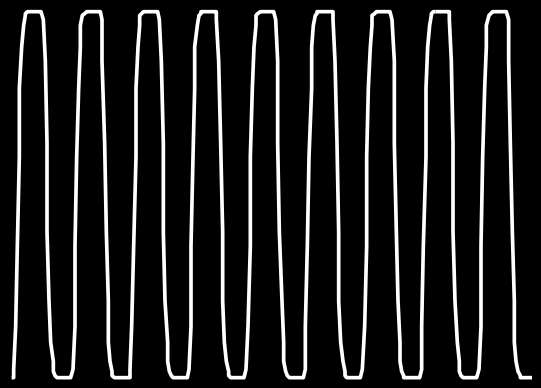
Cohen, Neuroimage 6, 93-103 (1997)



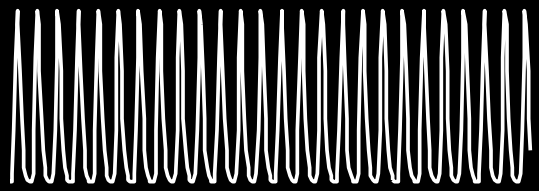
Synthesized Responses

ISI, Dur

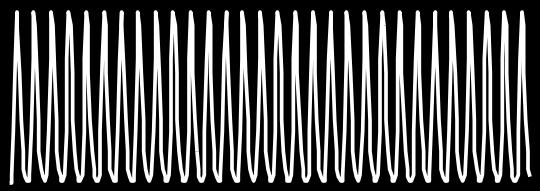
20, 20



12, 2

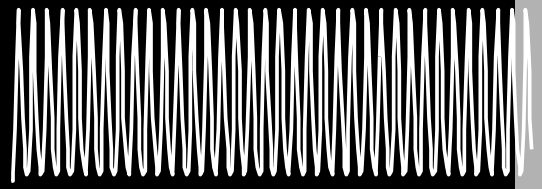


10, 2

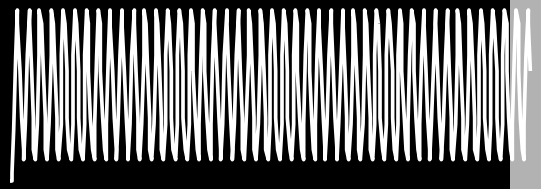


ISI, Dur

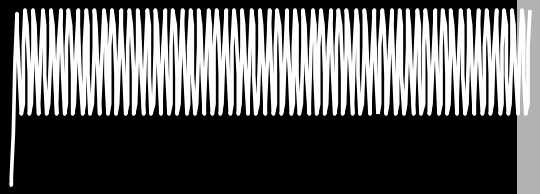
8, 2



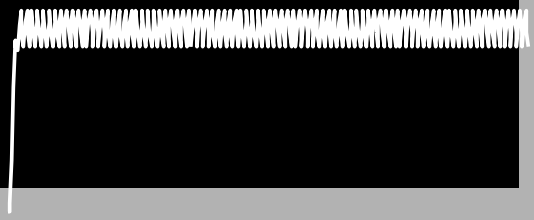
6, 2

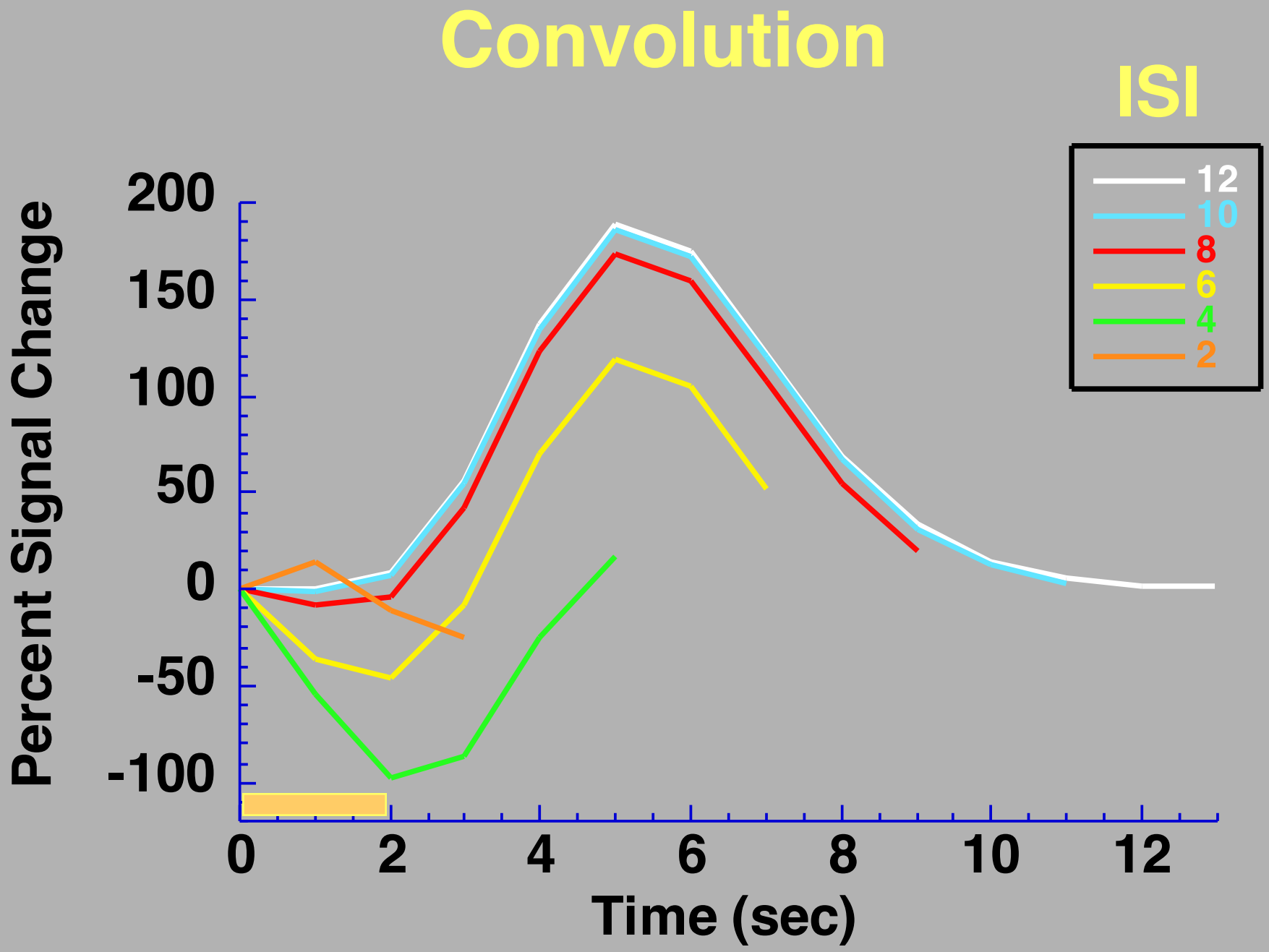


4, 2

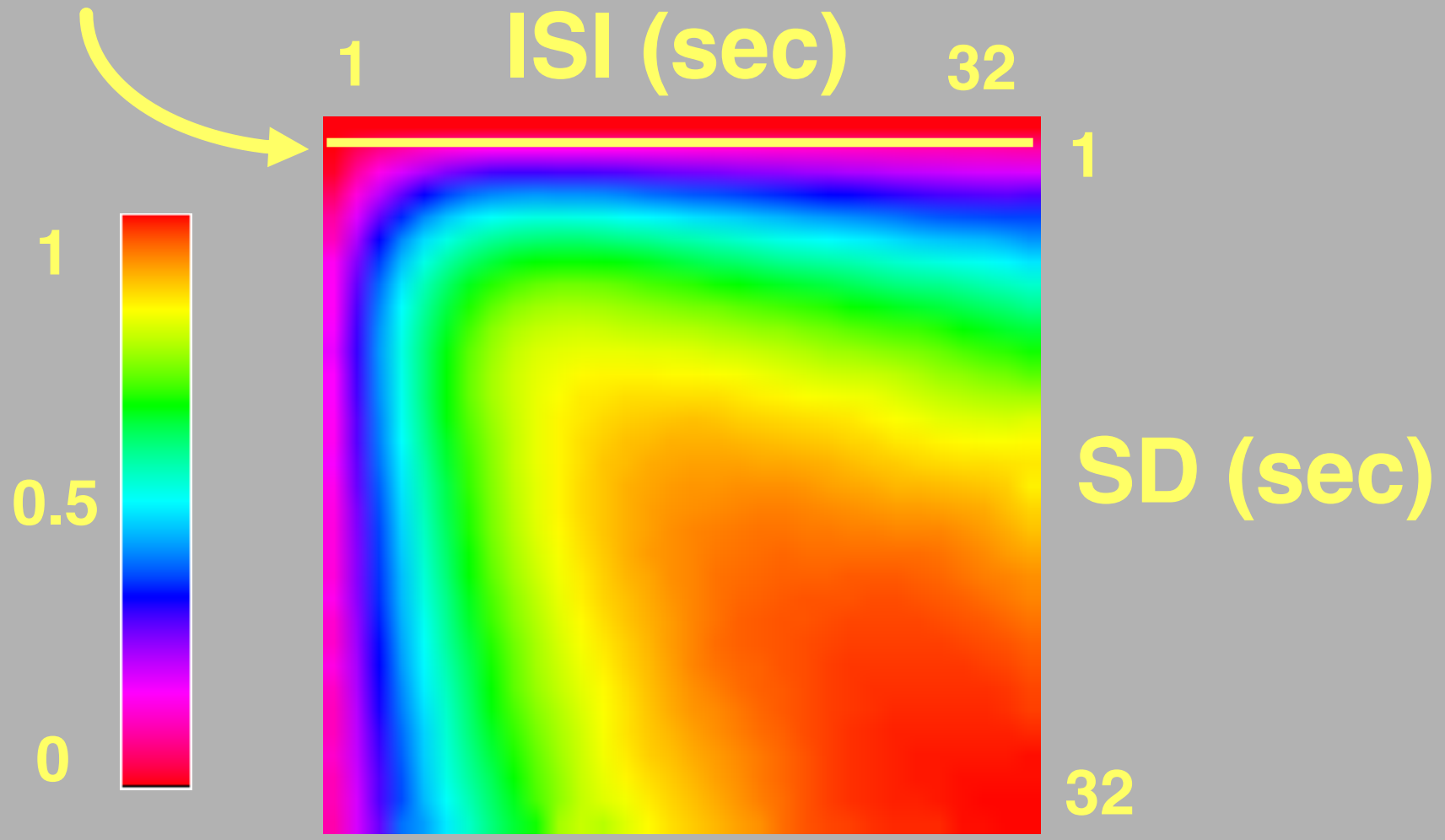


2, 2

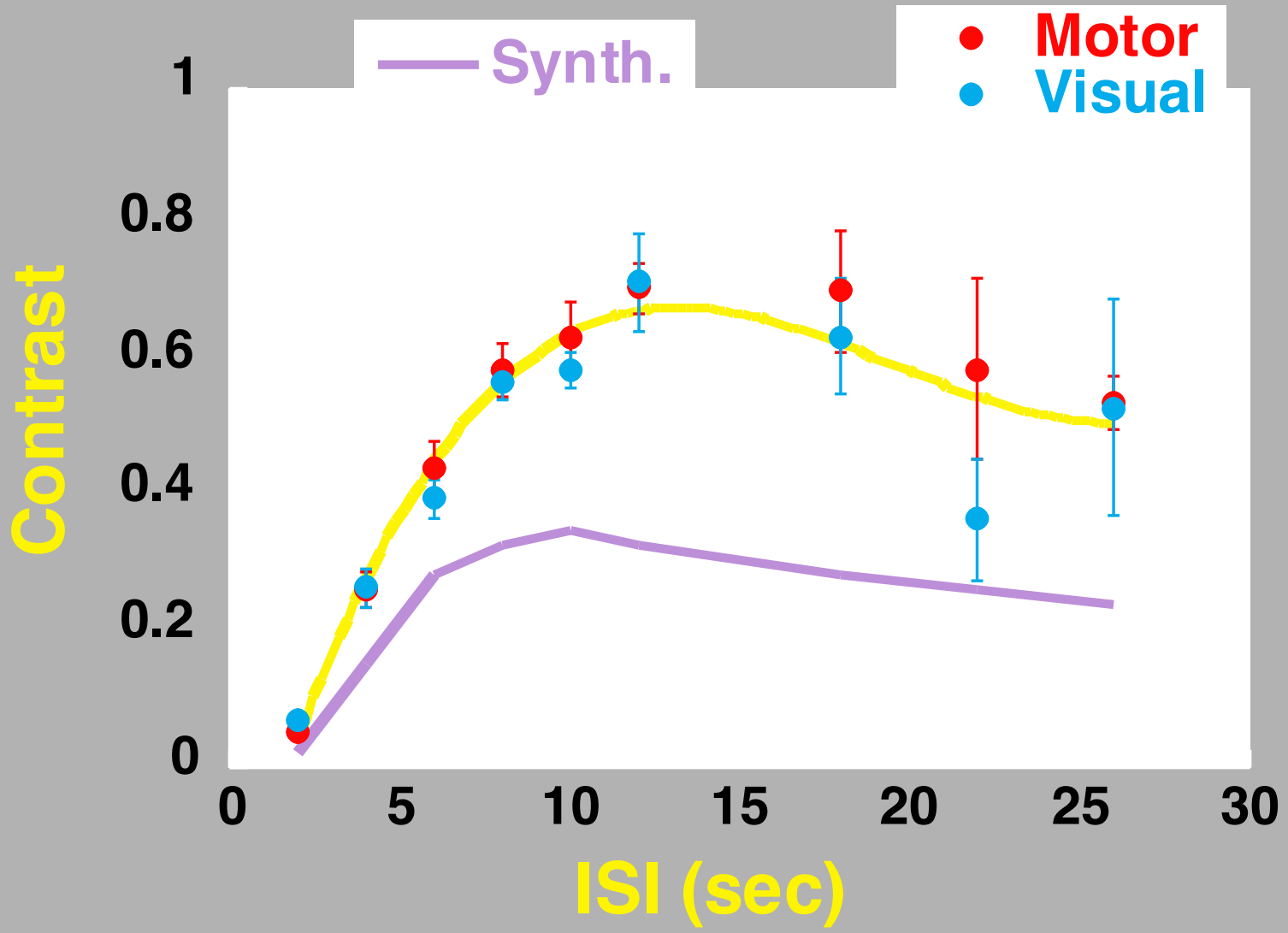



Convolution
ISI
12
10
8
6
4
2
Percent Signal Change
200
150
100
50
0
-50
-100
0
2
4
6
8
10
12
Time (sec)

Functional Contrast



Functional Contrast



(Block design = 1)

Conclusions

- **Experimental:**

  For SD = 2 sec, Optimal ISI ≈ 12 sec.
  Contrast = 0.65 x blocked contrast

- **Simulation using convolution:**

  For SD = 2 sec, Optimlal ISI ≈ 10 sec.
  Contrast = 0.35 x blocked contrast

Possible reasons for greater than linear response.

Neuronal:

"Bursting" during first 100 ms.

Hemodynamic/Metabolic:

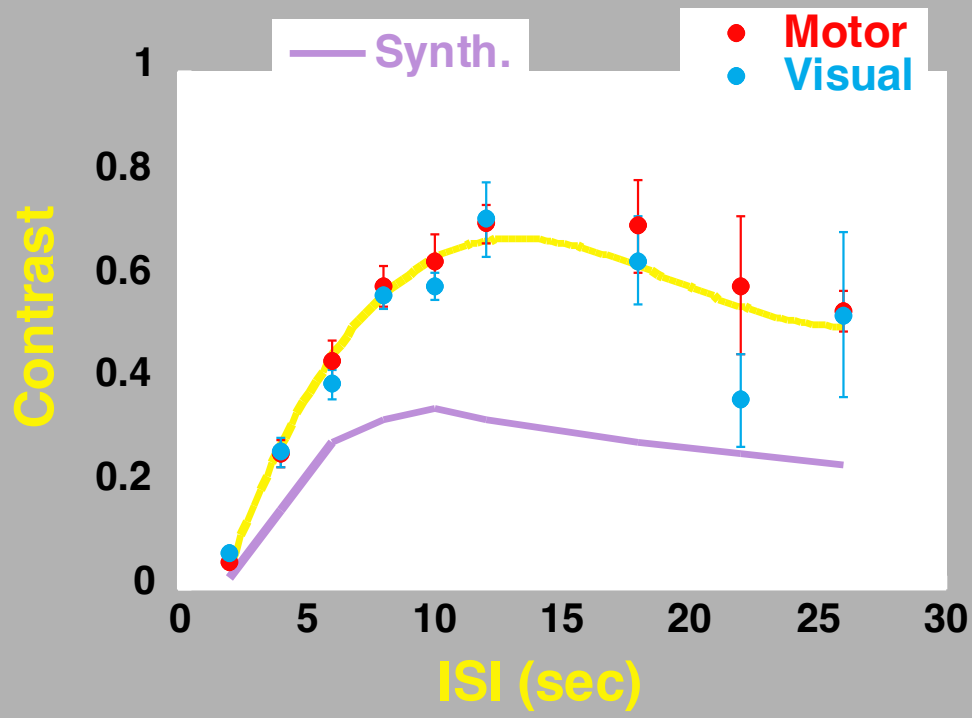
ΔBV and/or $\Delta CMRO_2$ time constants slower than ΔFlow during initial seconds of activation.

Possible implications for interpretation of event-related data using short, randomized ISI w/ deconvolution.

Dale AM, Buckner RL (1997), Human Brain Mapping, 5, 329-340.

Event - Related Functional Contrast

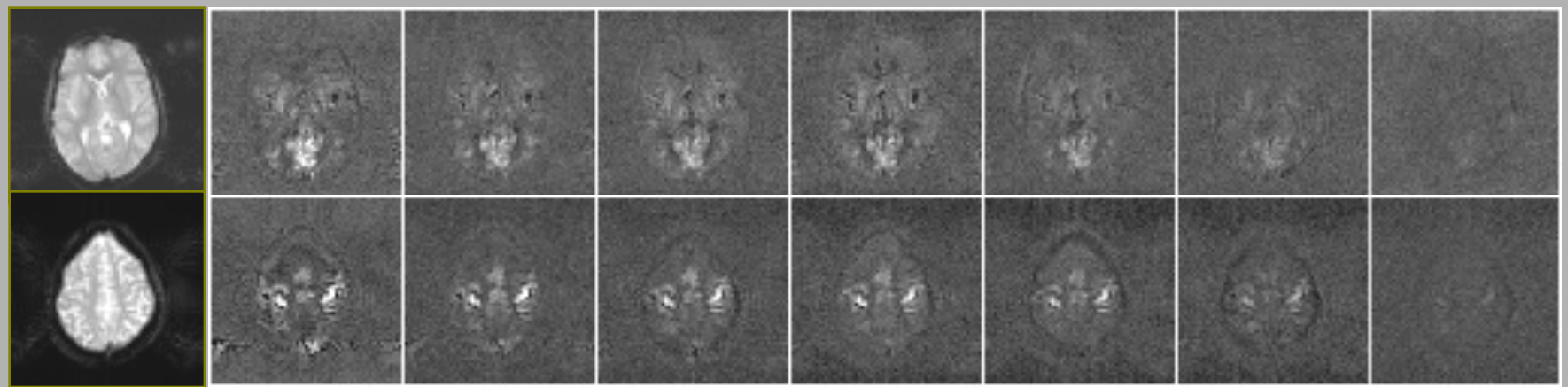
(Block design = 1)



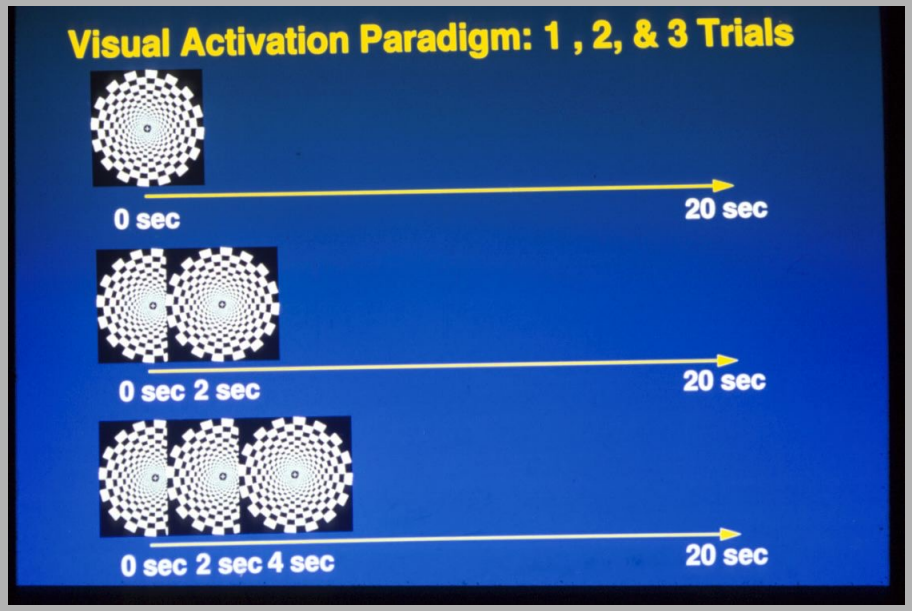
Contrast to Noise Images

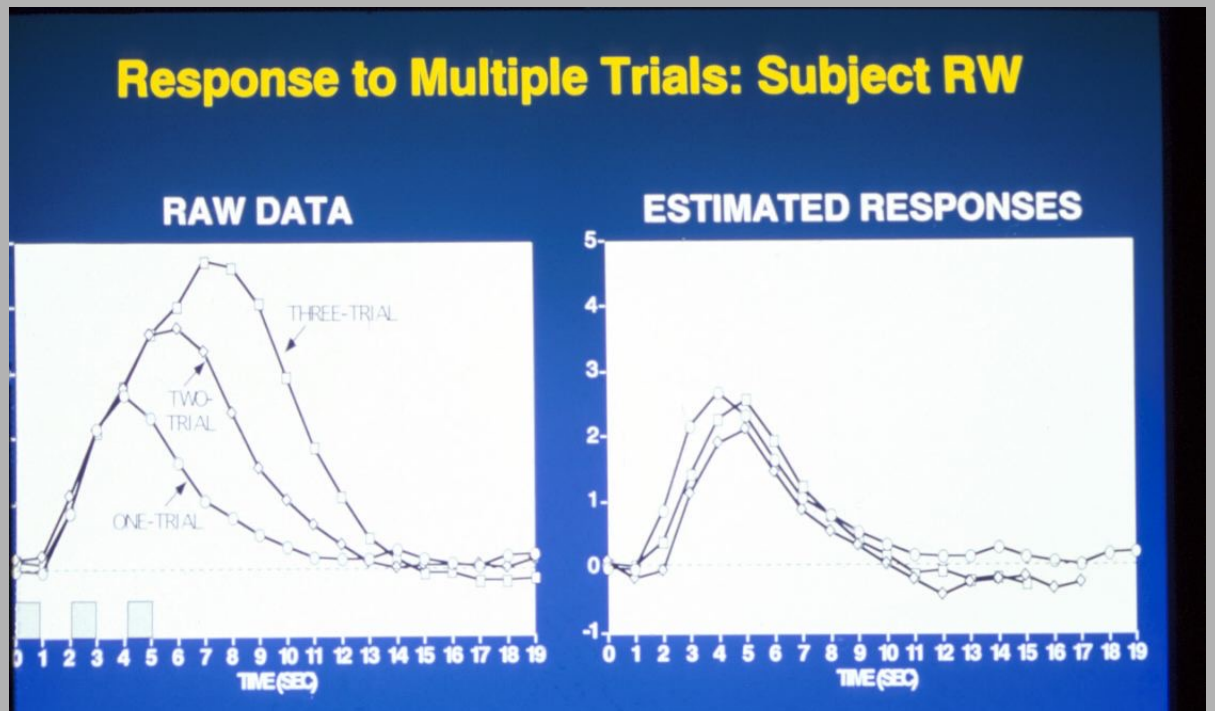
(ISI, SD)

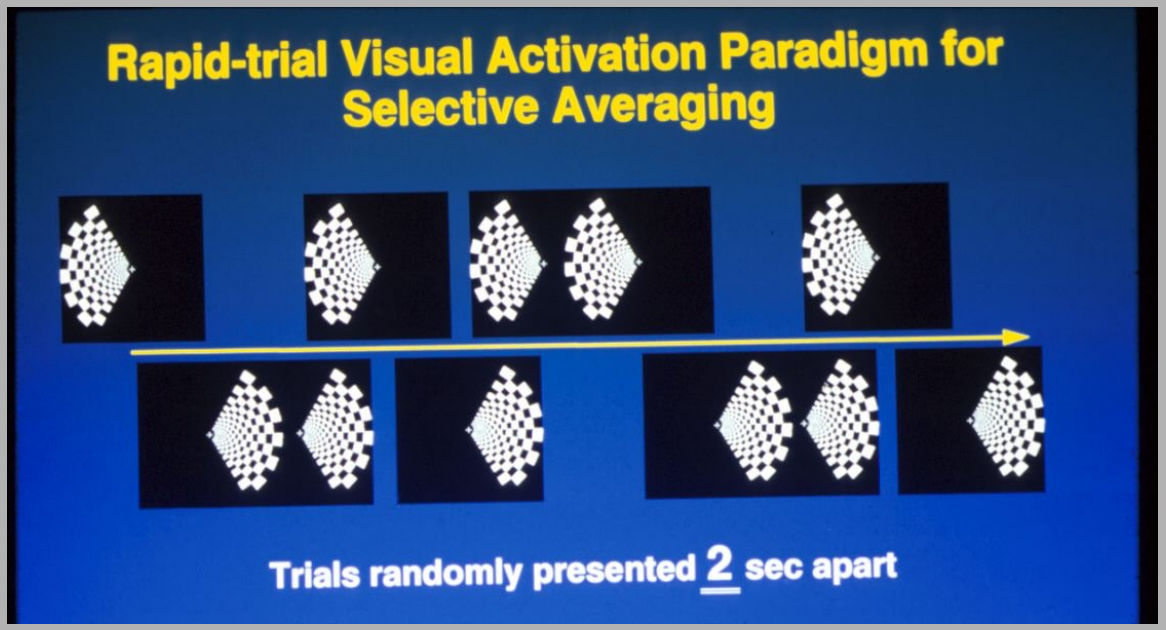
20, 20 12, 2 10, 2 8, 2 6, 2 4, 2 2, 2

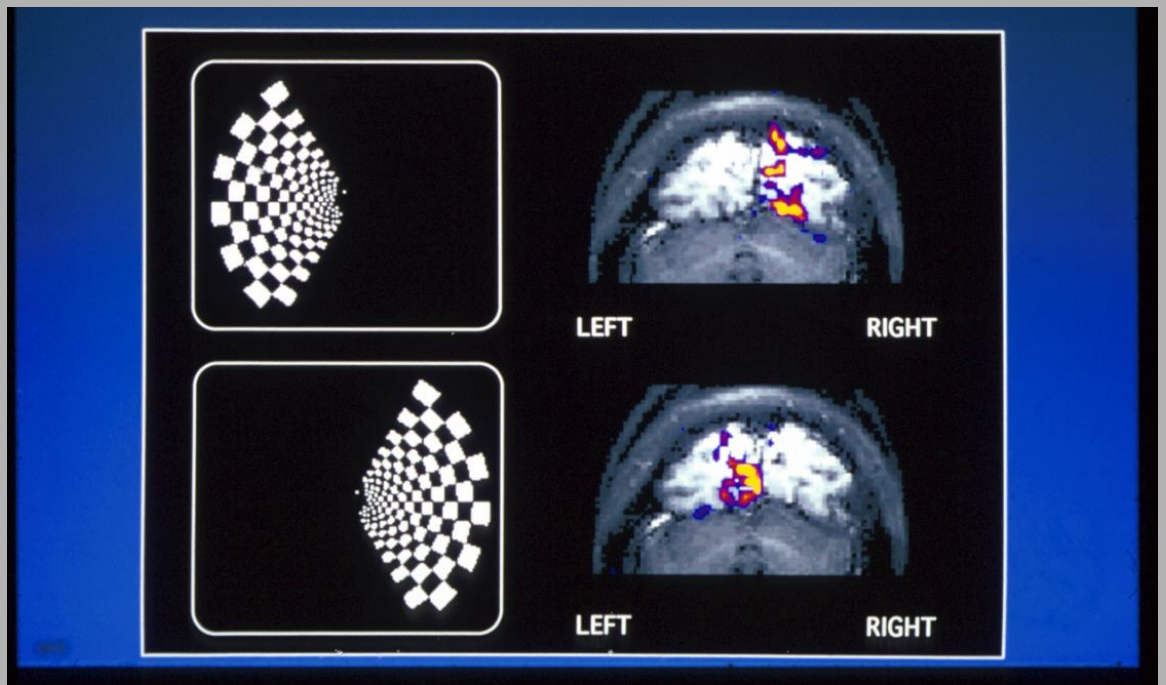


You can go even faster with the assumption of linearity...









If ISI is randomized, and if ON / OFF distribution is 50%, the optimal average ISI is as short as you can make it.

Conclusions

The fMRI signal is able to be calibrated. Physiologic, neuronal, and pulse sequence calibration techniques are just starting to develop to complement pulse sequence advances.

-spatial resolution < 0.5 mm
-temporal resolution < 100 ms
-information content: quantitative flow, CMRO2...

A large amount of additional information exists in the fMRI signal (i.e. fluctuations..).

To aid the development of calibration, more work needs to be done using extremely well understood neuronal activation (across several temporal, spatial, and intensity scales) to better characterize of the fMRI signal.