The Spatial, Temporal and Interpretive Limits of Functional MRI

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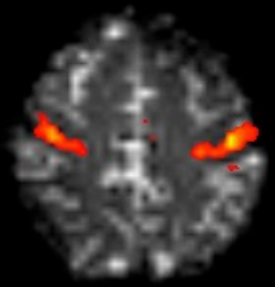
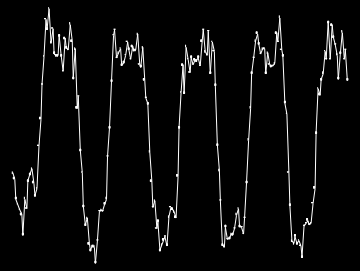
Categories of Questions Asked with fMRI

Where?



When?



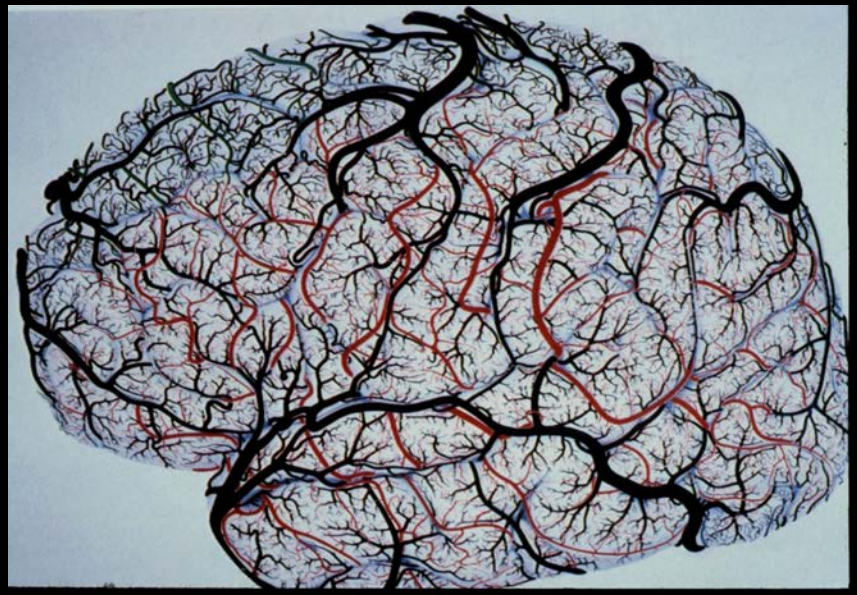
How much?

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:

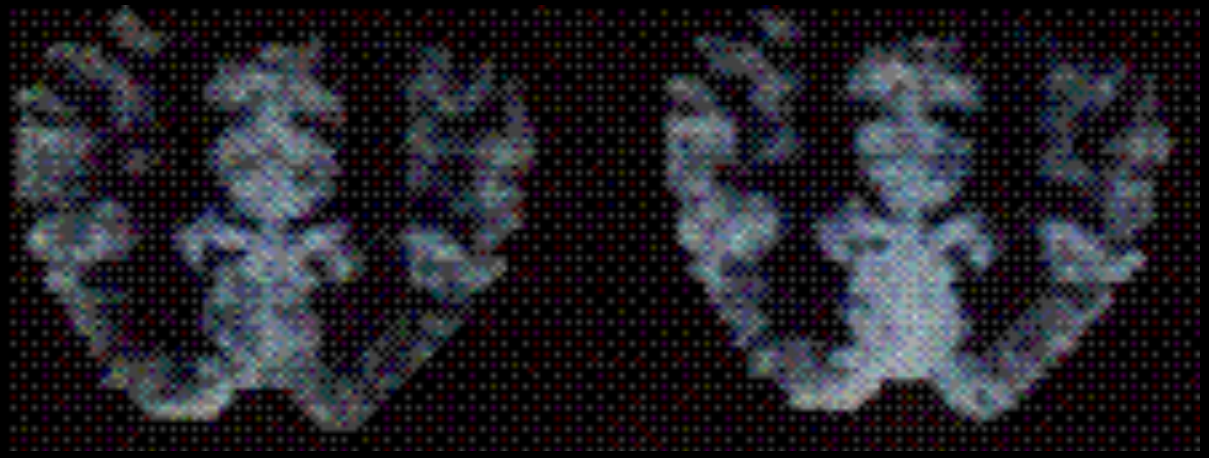
...to make progressively more precise inferences using fMRI without making too many assumptions about non-neuronal physiologic factors.

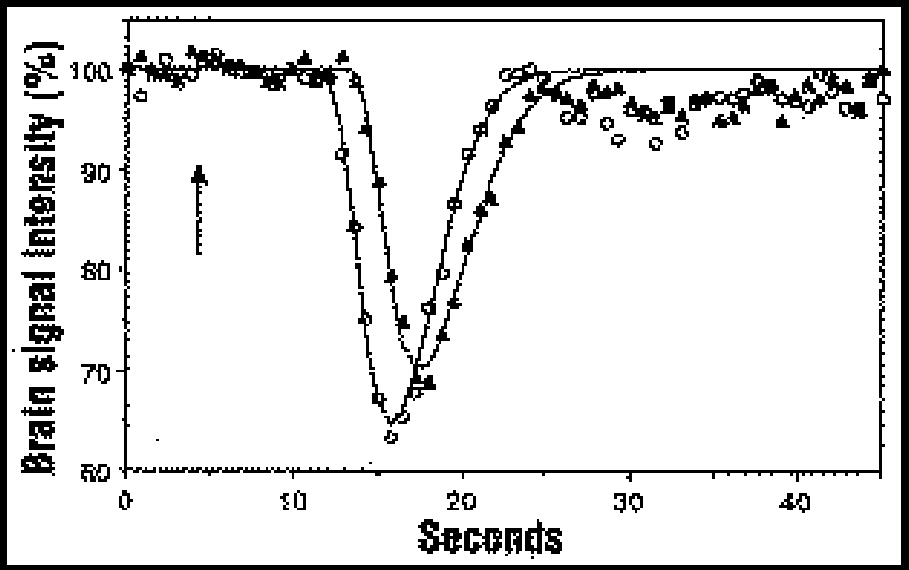


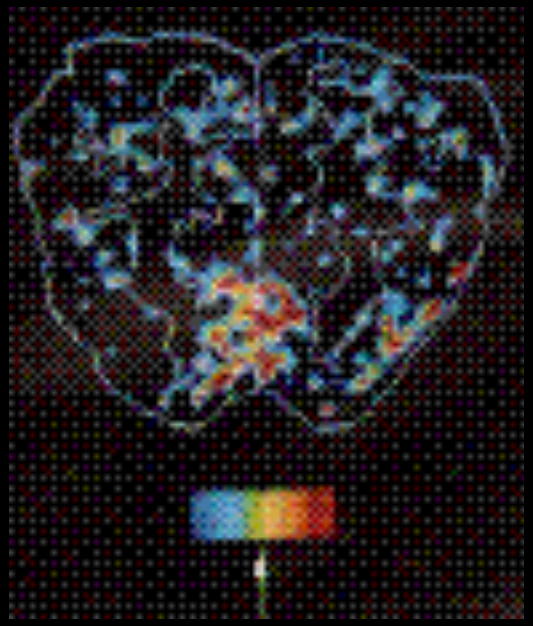
Contrast in Functional MRI

- **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

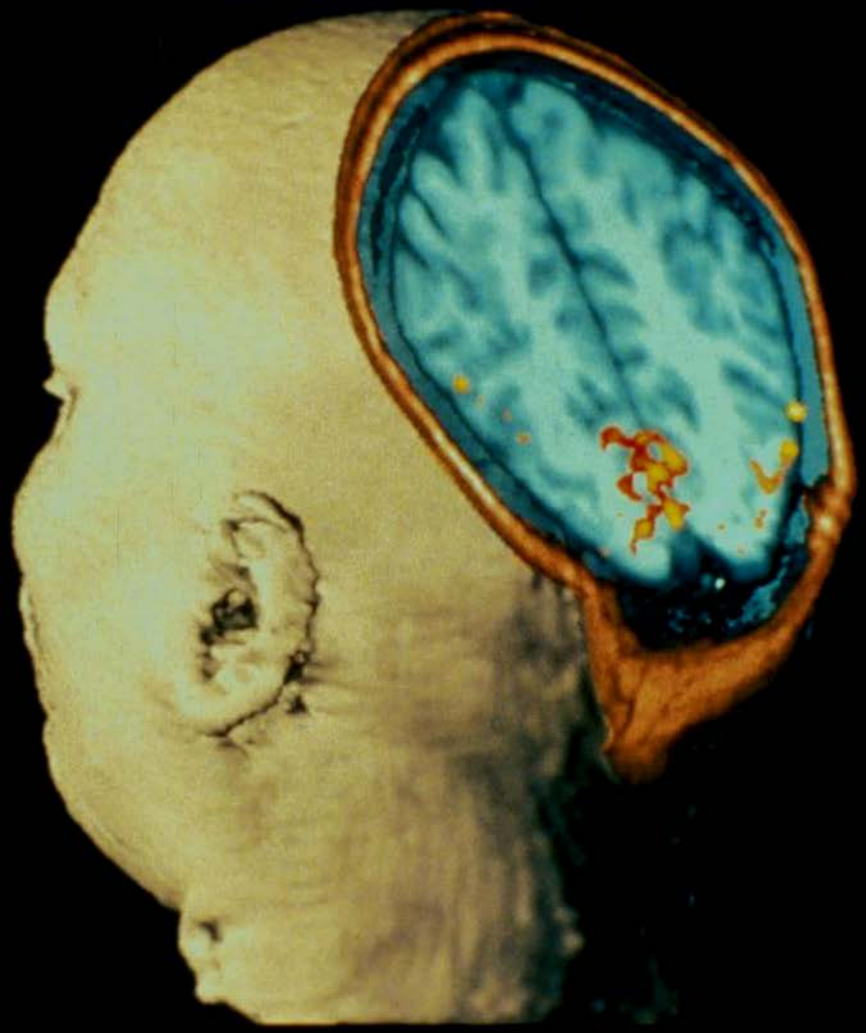
Resting Active







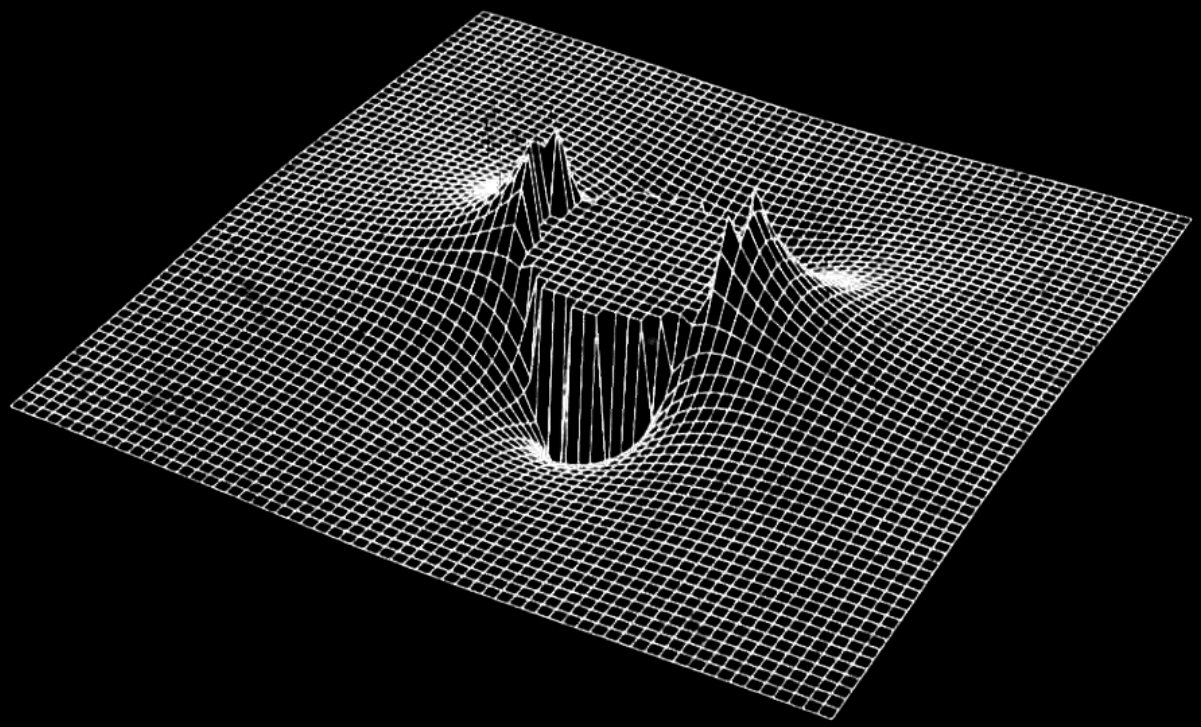
Photic Stimulation



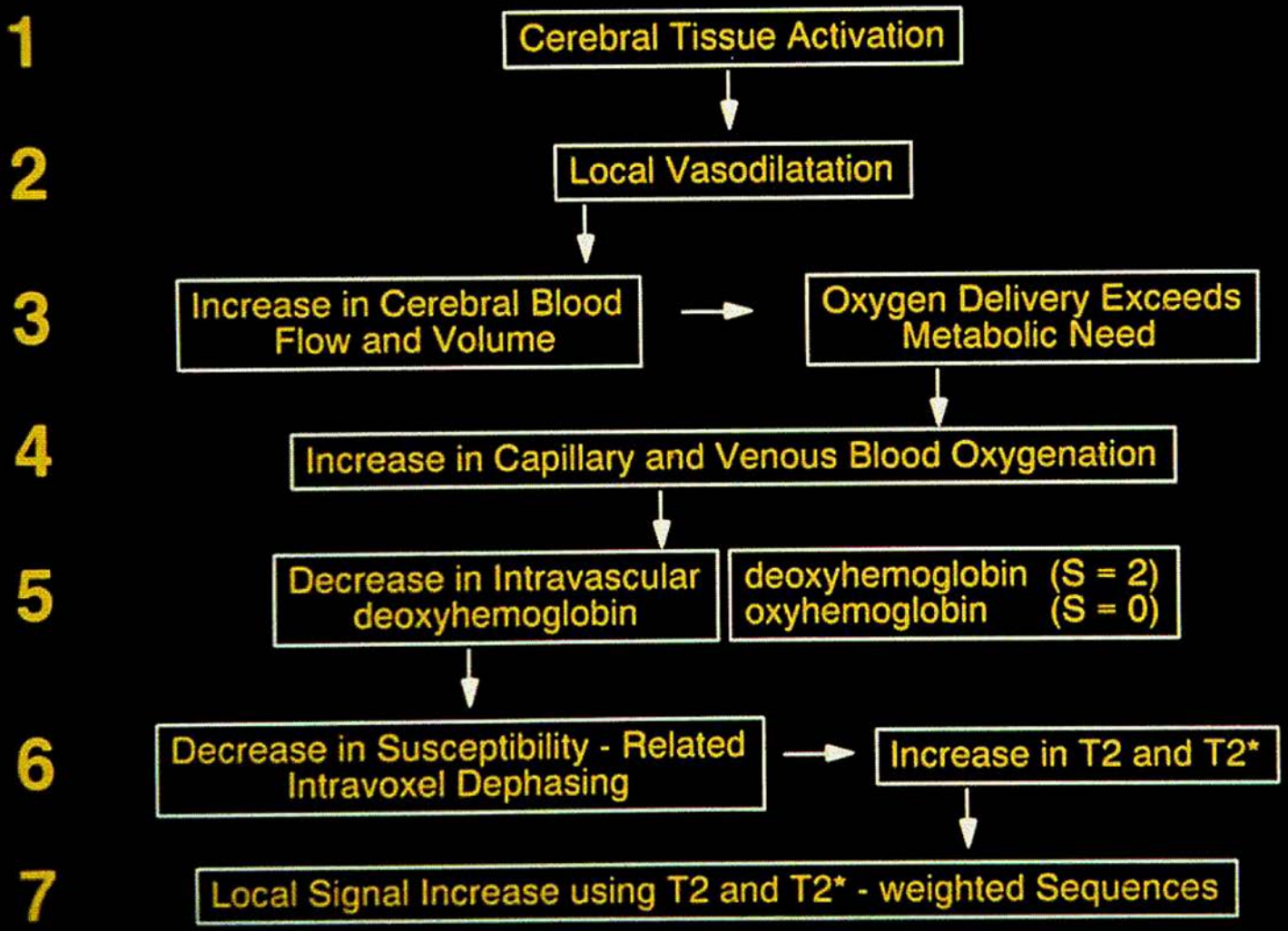
MRI Image showing activation of the Visual Cortex

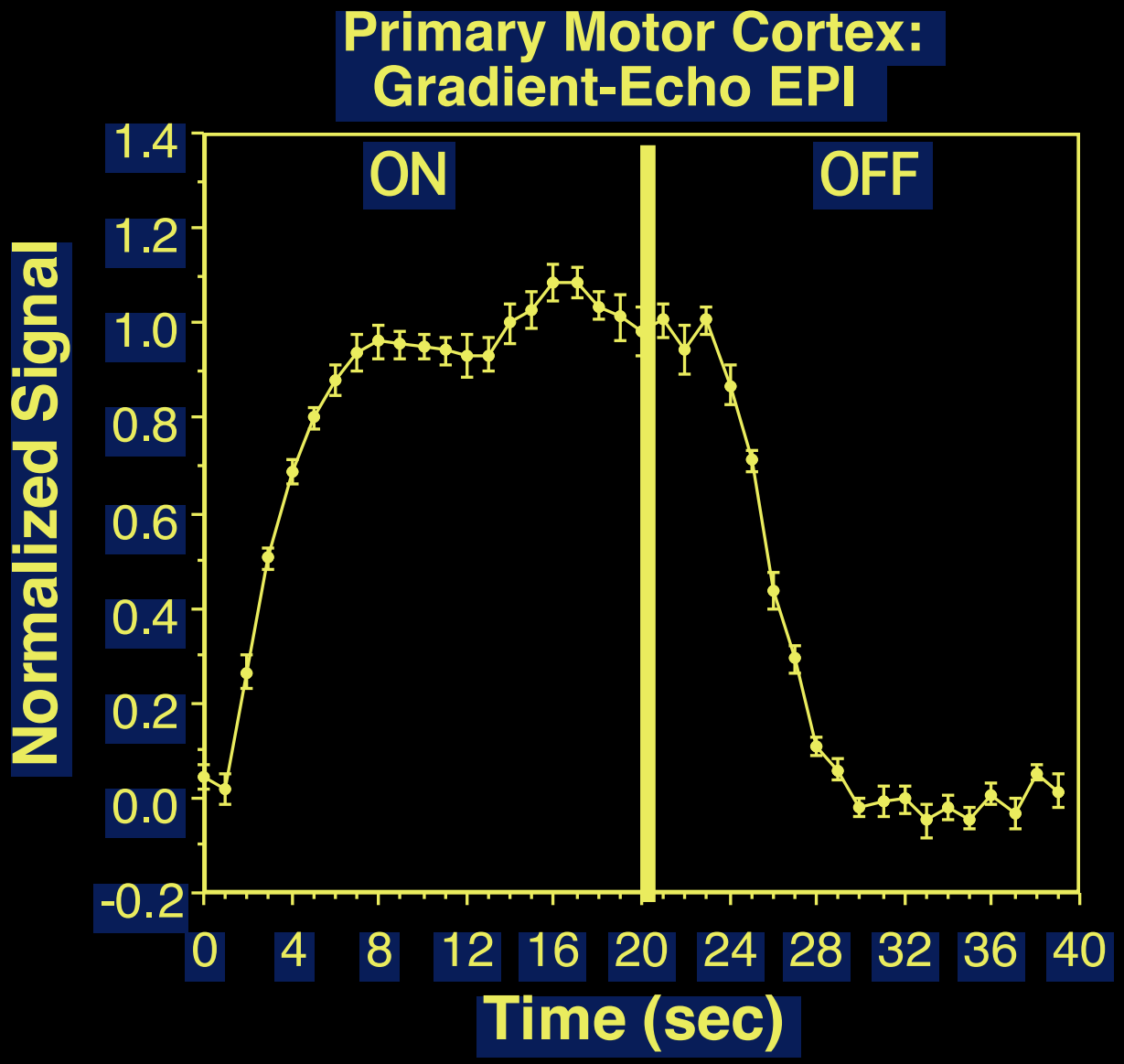
From Belliveau, et al. Science Nov 1991

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

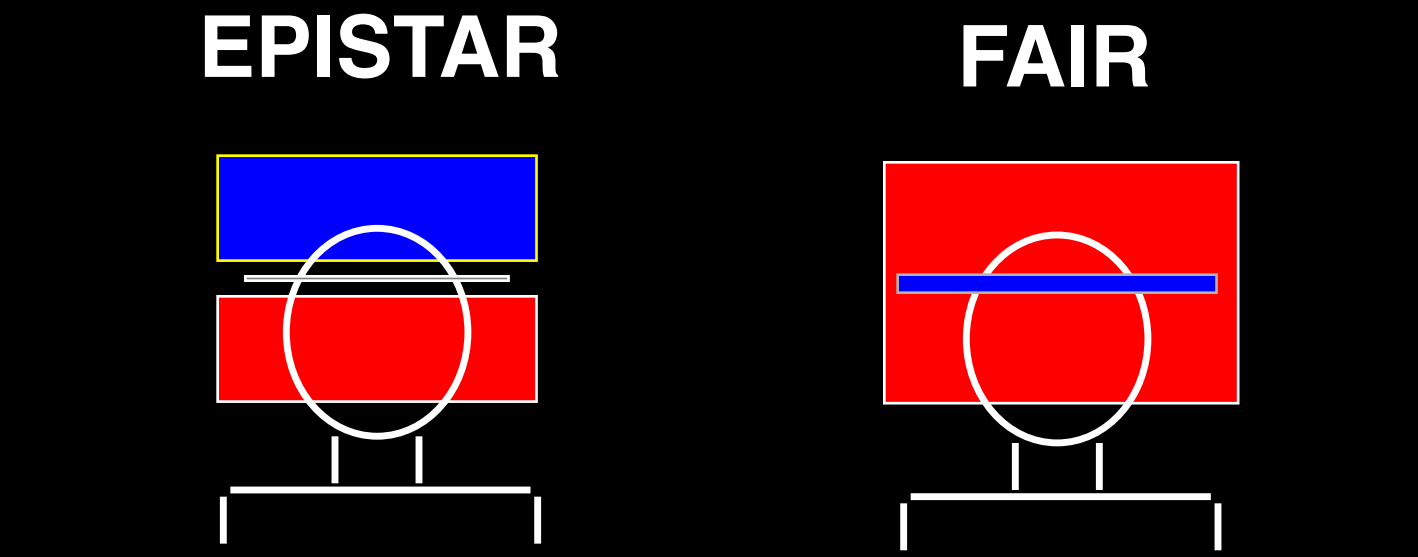


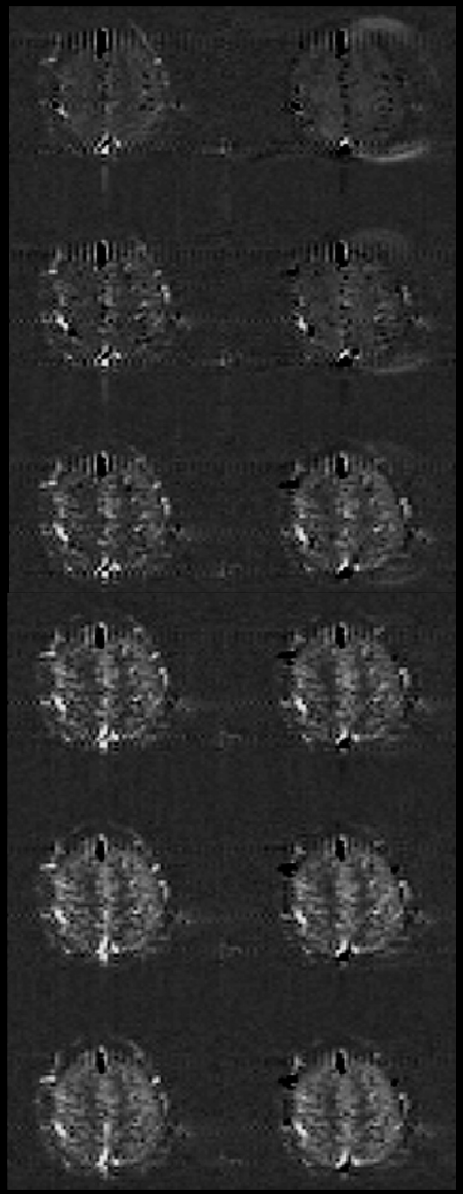
BOLD Contrast in the Detection of Neuronal Activity



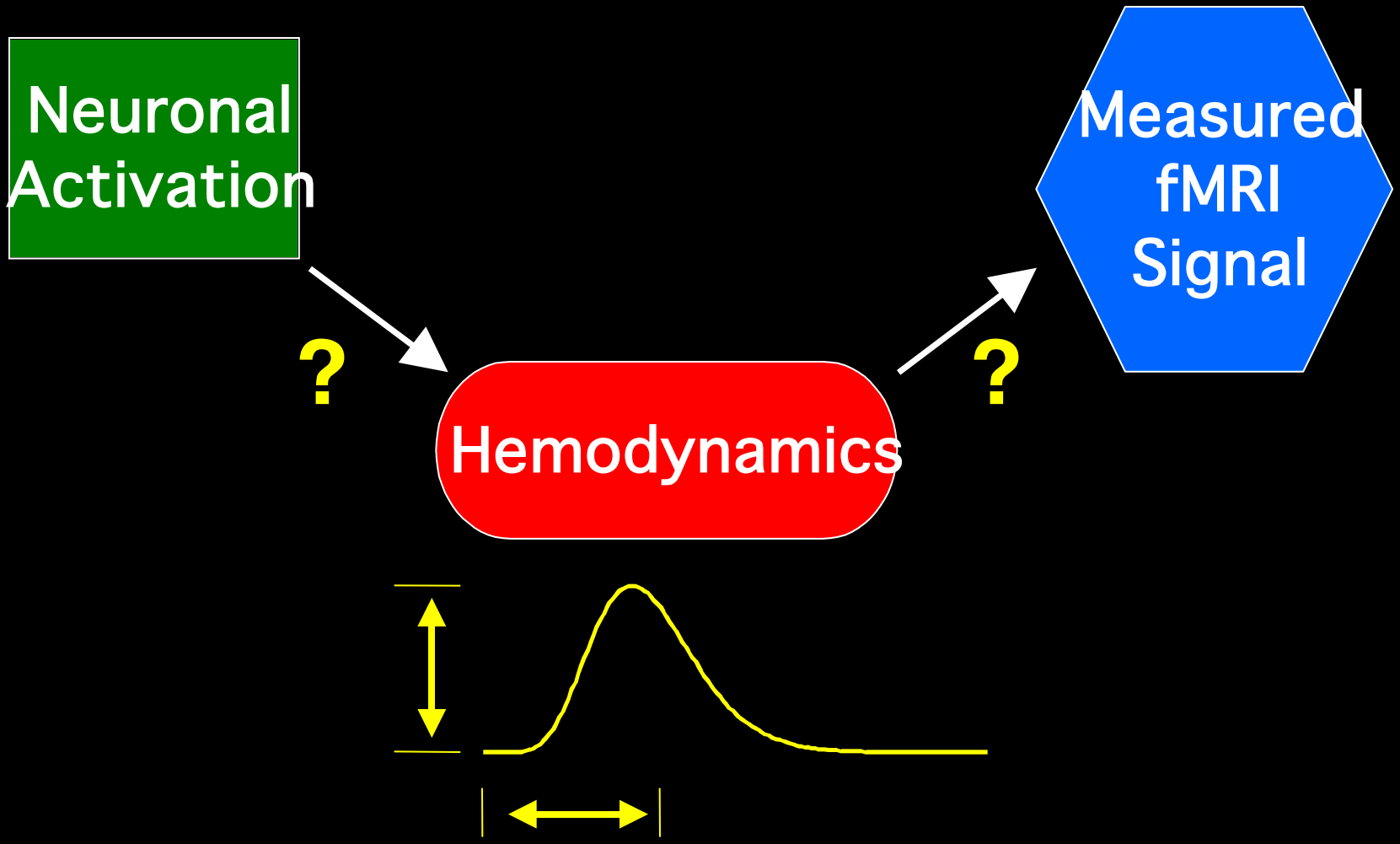

Primary Motor Cortex:
Gradient-Echo EPI
ON
OFF
Normalized Signal
1.4
1.2
1.0
0.8
0.6
0.4
0.2
0.0
-0.2
0
4
8
12
16
20
24
28
32
36
40
Time (sec)

Perfusion / Flow Imaging



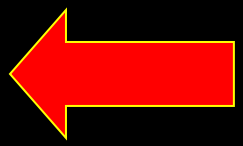
TI (ms)	FAIR	EPISTAR
200		
400		
600		
800		
1000		
1200		

	+	-
Volume	• unique information • baseline information • multislice trivial	• invasive • low C / N for func.
BOLD	• highest C / N • easy to implement • multislice trivial • non invasive • highest temp. res.	• complicated signal • no baseline info.
Perfusion	• unique information • control over ves. size • baseline information • non invasive	• multislice non trivial • lower temp. res. • low C / N

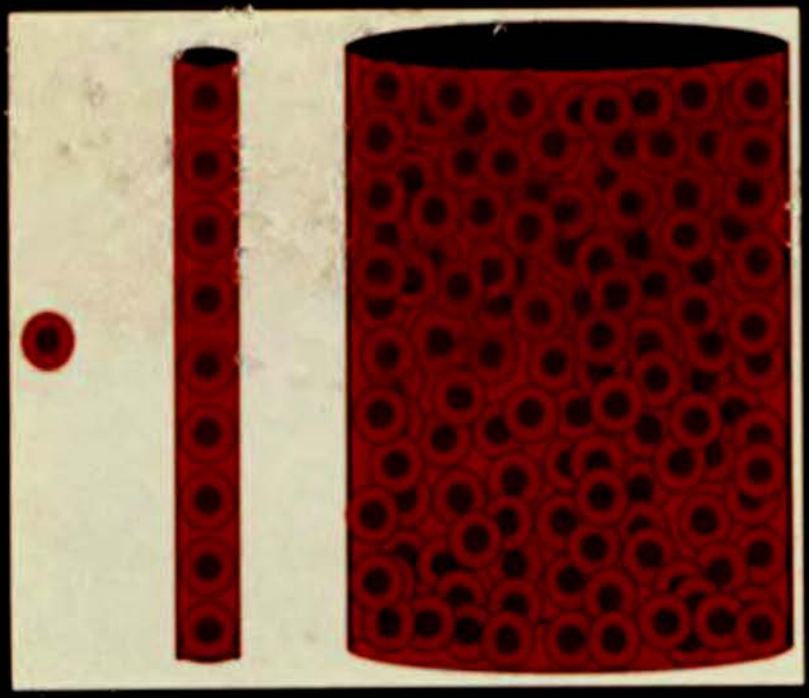

Neuronal Activation
?
Hemodynamics
?
Measured fMRI Signal
Physiologic Factors

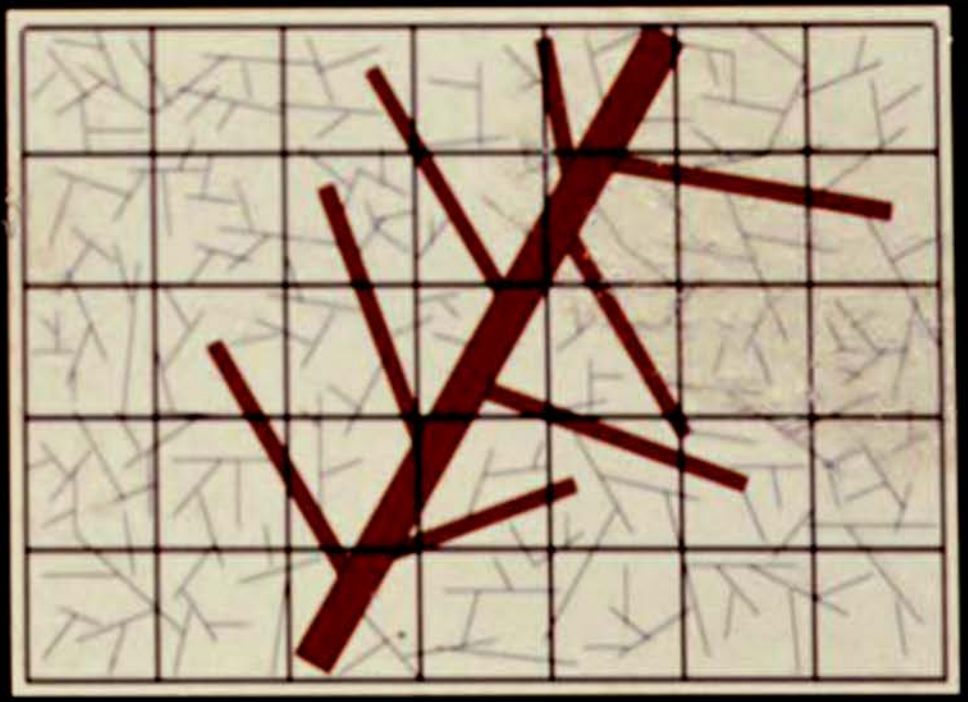
Physiologic Factors that Influence BOLD Contrast

- 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.

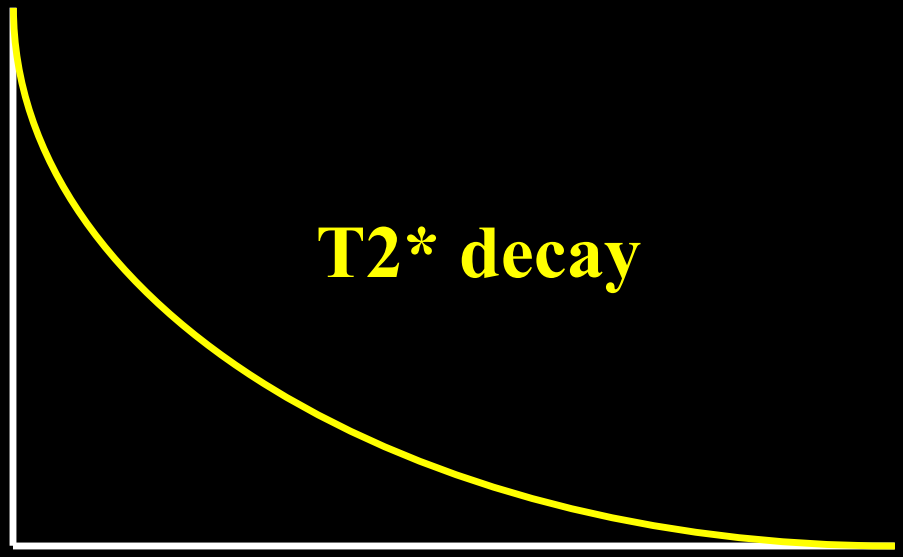
(or)

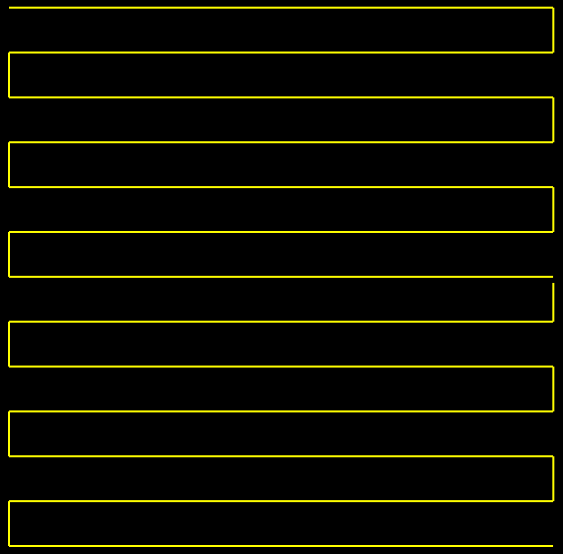
- Normalize to the spatial variation in the vasculature.

(or)

- Make several assumptions.

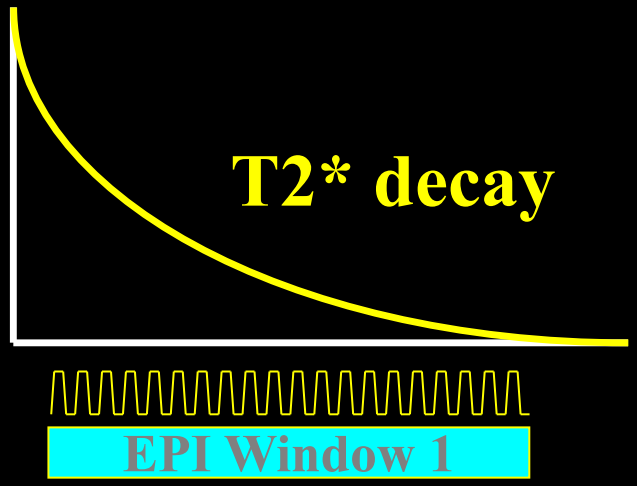
Single Shot Imaging

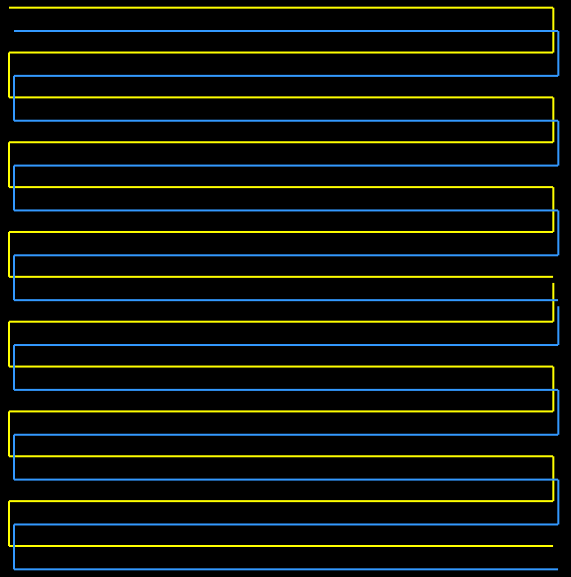


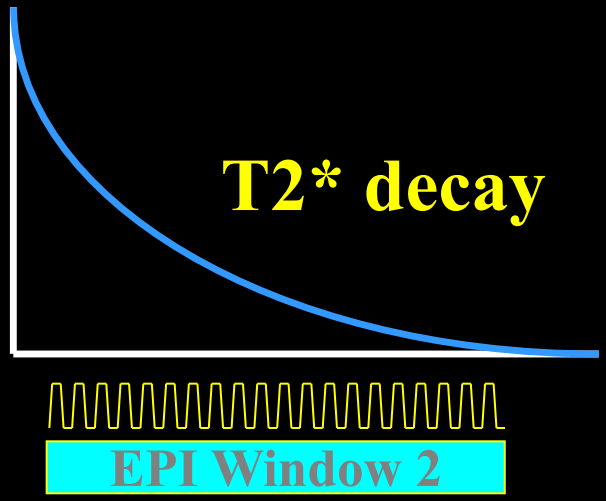


≈ 20 to 40 ms

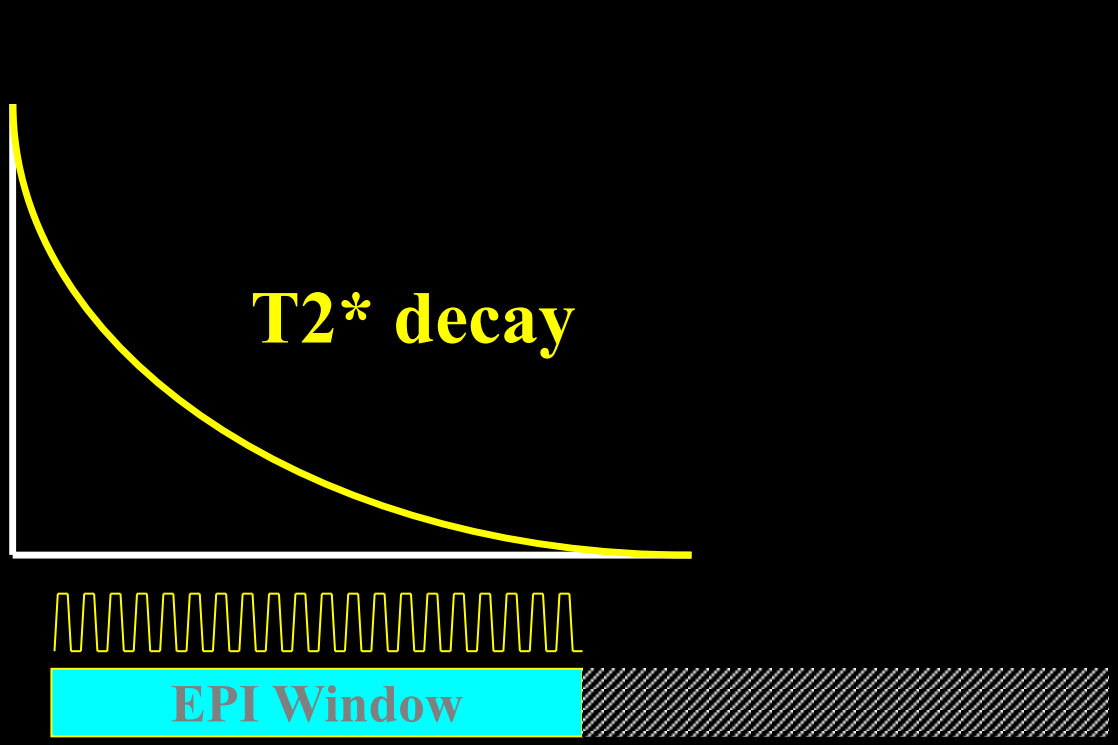
Multishot Imaging

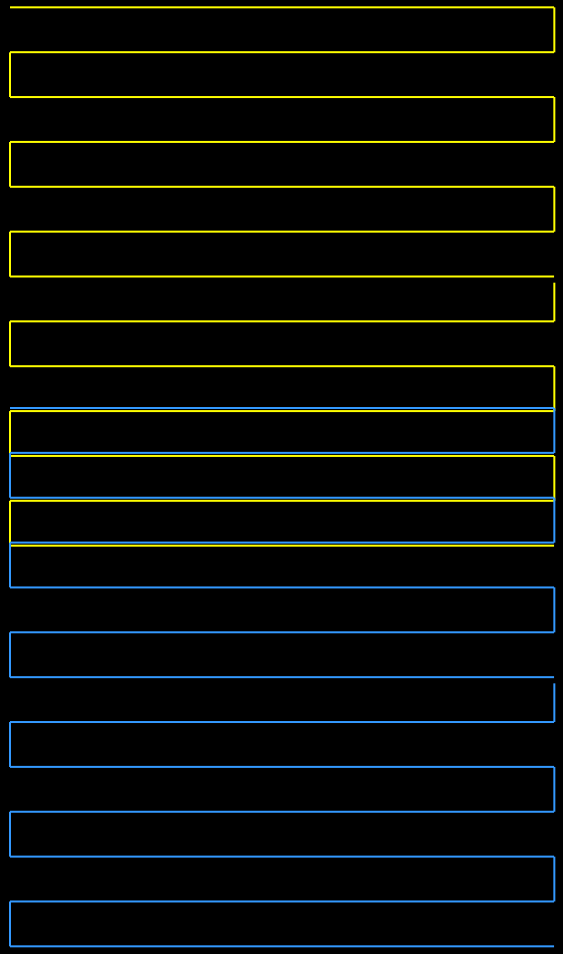




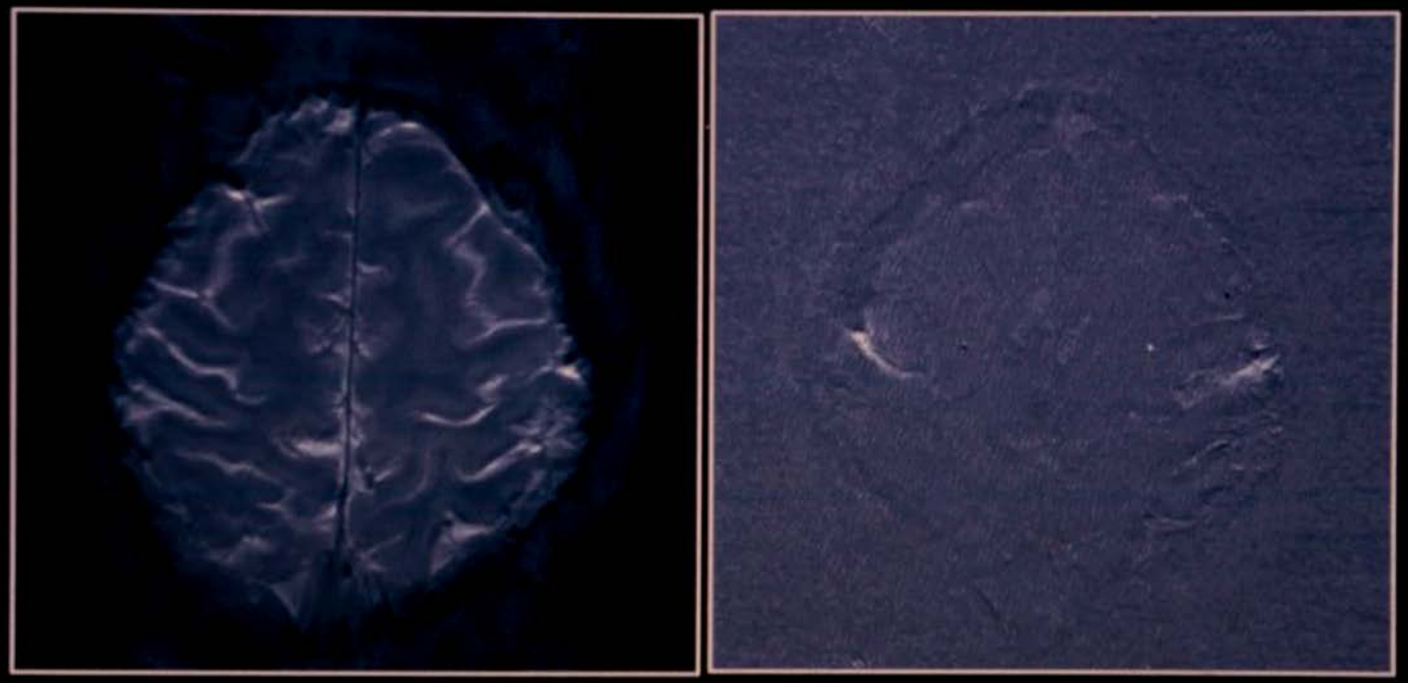


Partial k-space imaging

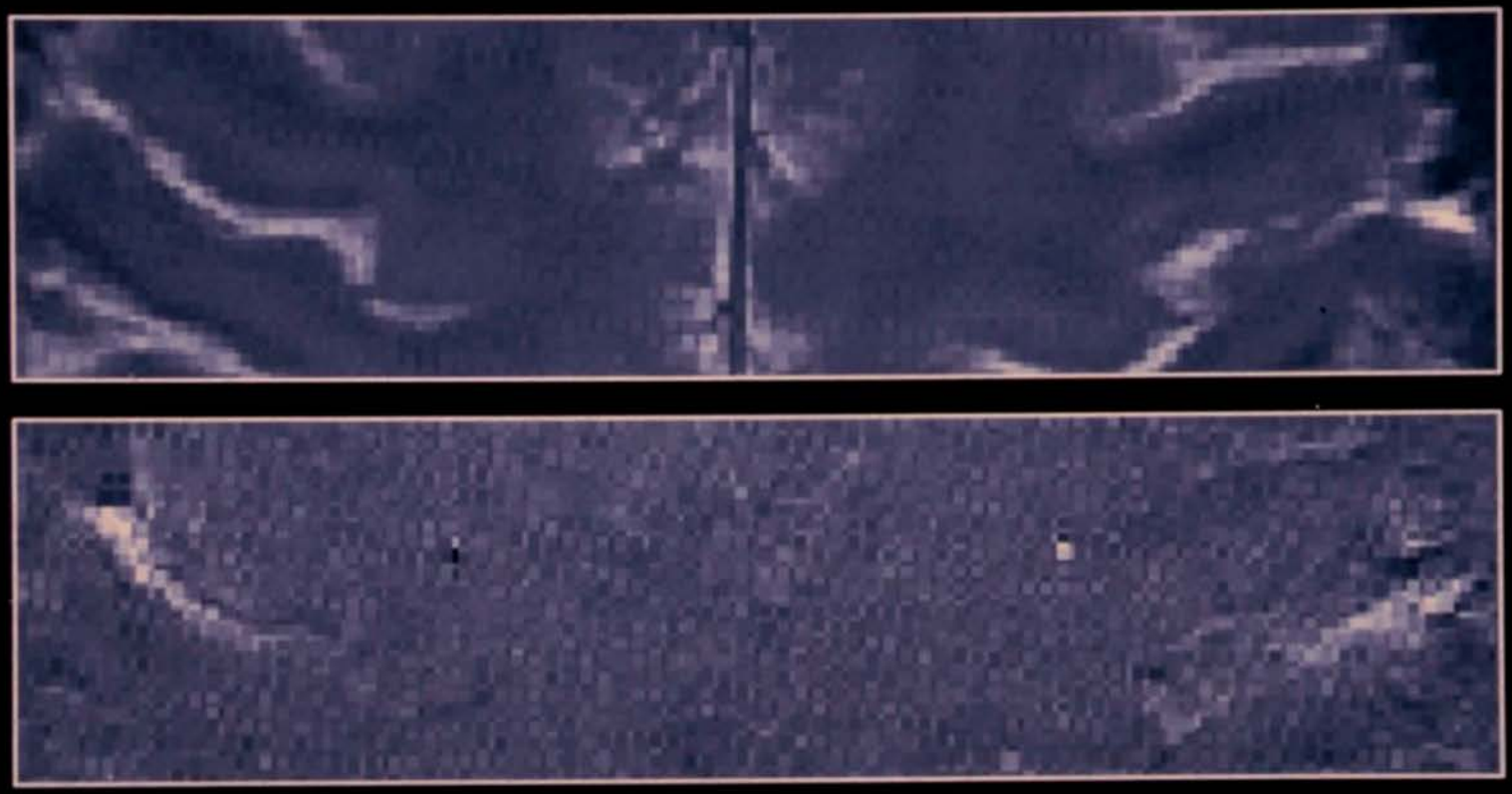


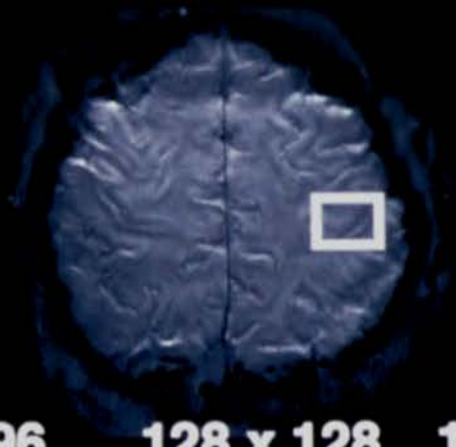


Single - Shot EPI at 3T:
Half NEX, 256 x 256, 16 cm FOV

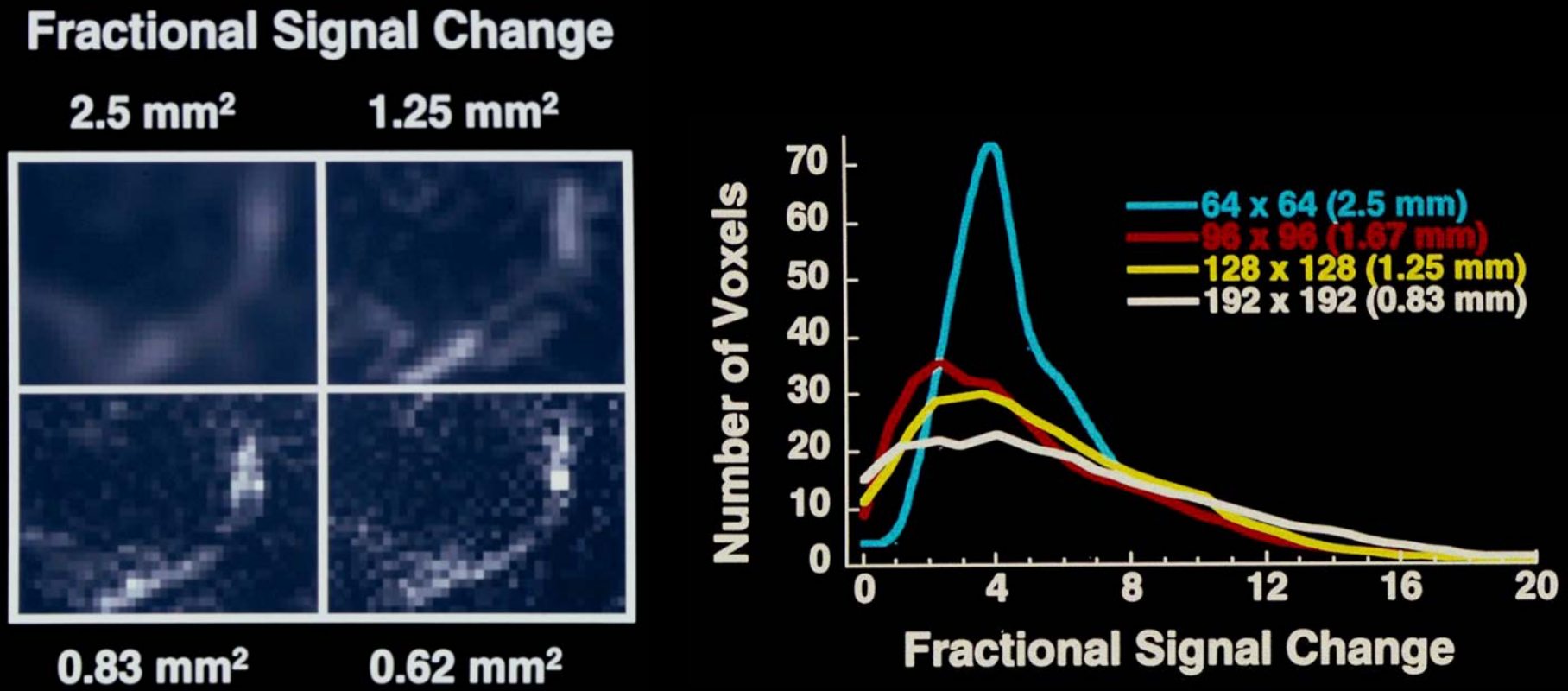


Single - Shot EPI at 3T:
Half NEX 256 x 256, 16 cm FOV



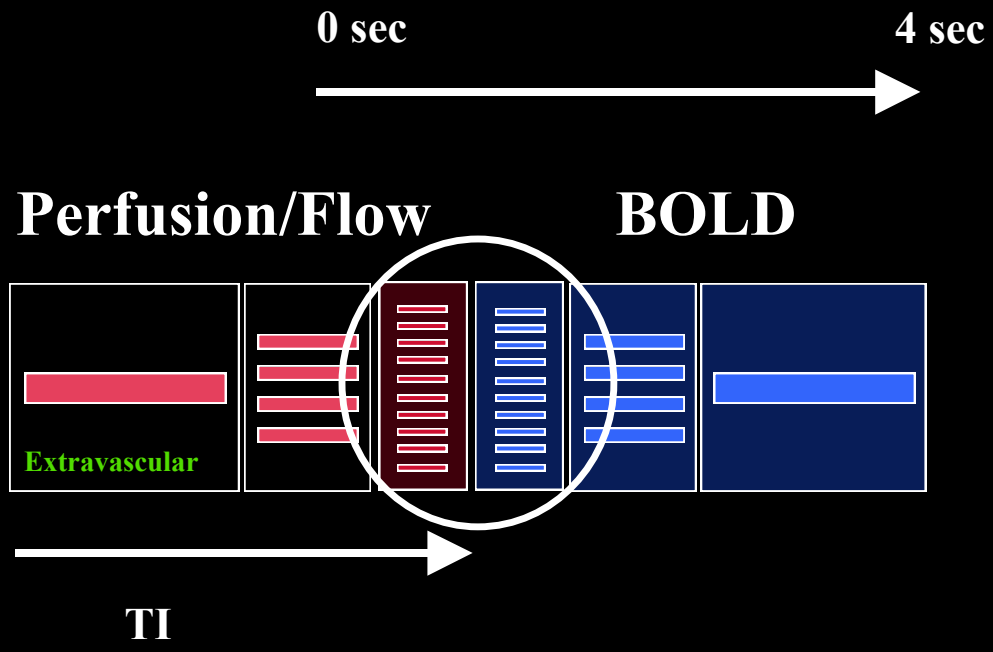


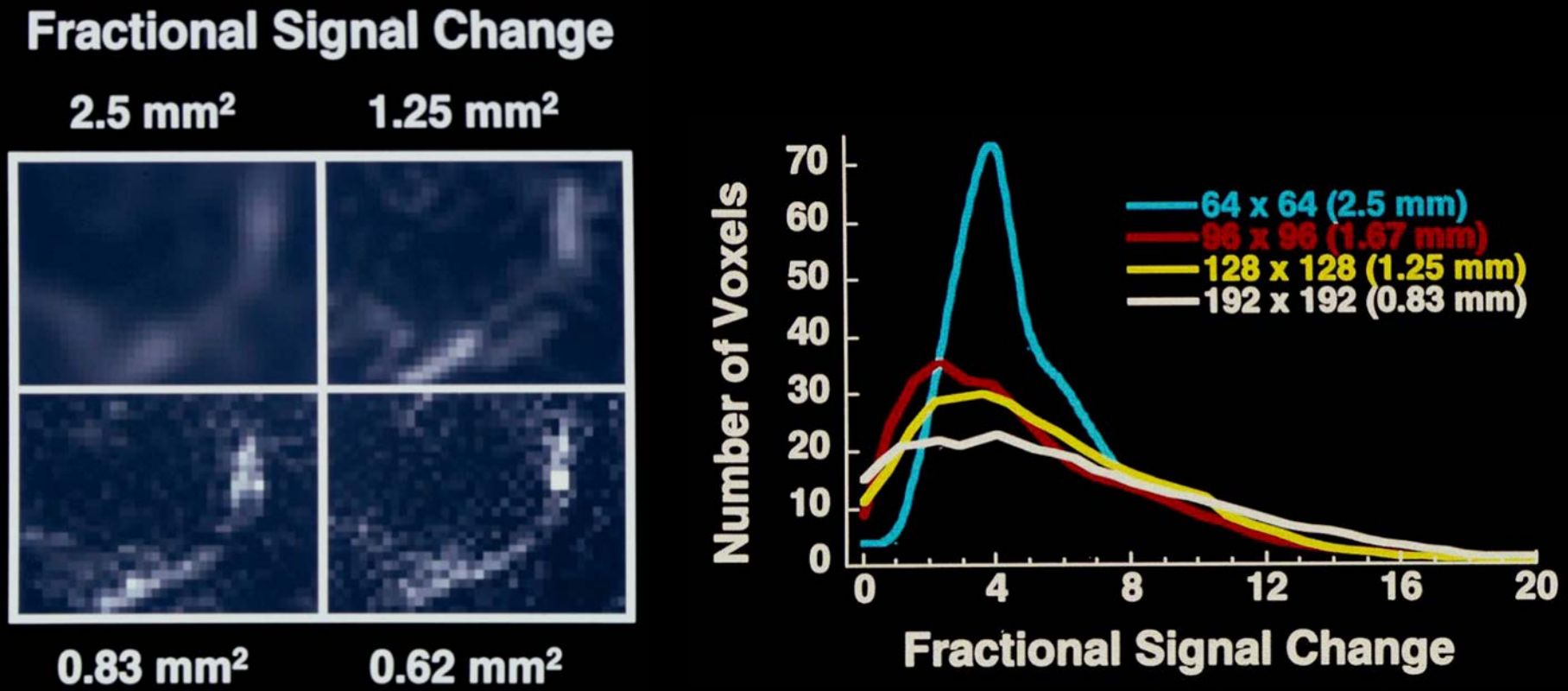
	64 x 64	96 x 96	128 x 128	192 x 192	256 x 256
%					
C/N					
	2.5 mm^2	1.67 mm^2	1.25 mm^2	0.83 mm^2	0.62 mm^2


Fractional Signal Change
2.5 mm²
1.25 mm²
0.83 mm²
0.62 mm²
Number of Voxels
0
10
20
30
40
50
60
70
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)

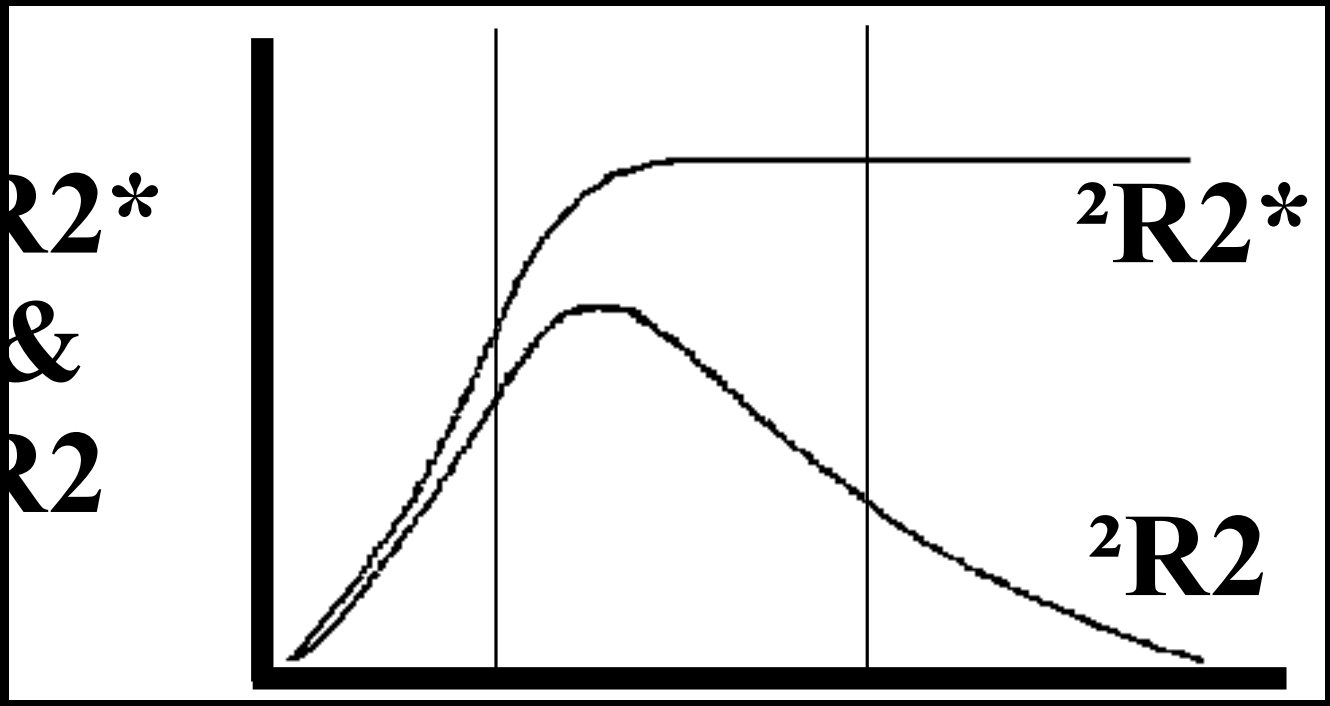
Pulse sequence based methods for increasing spatial and temporal resolution

- Spin-echo
- ASL
- Diffusion weighting
- Threshold based on magnitude




Fractional Signal Change
2.5 mm²
1.25 mm²
0.83 mm²
0.62 mm²
Number of Voxels
0
10
20
30
40
50
60
70
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)

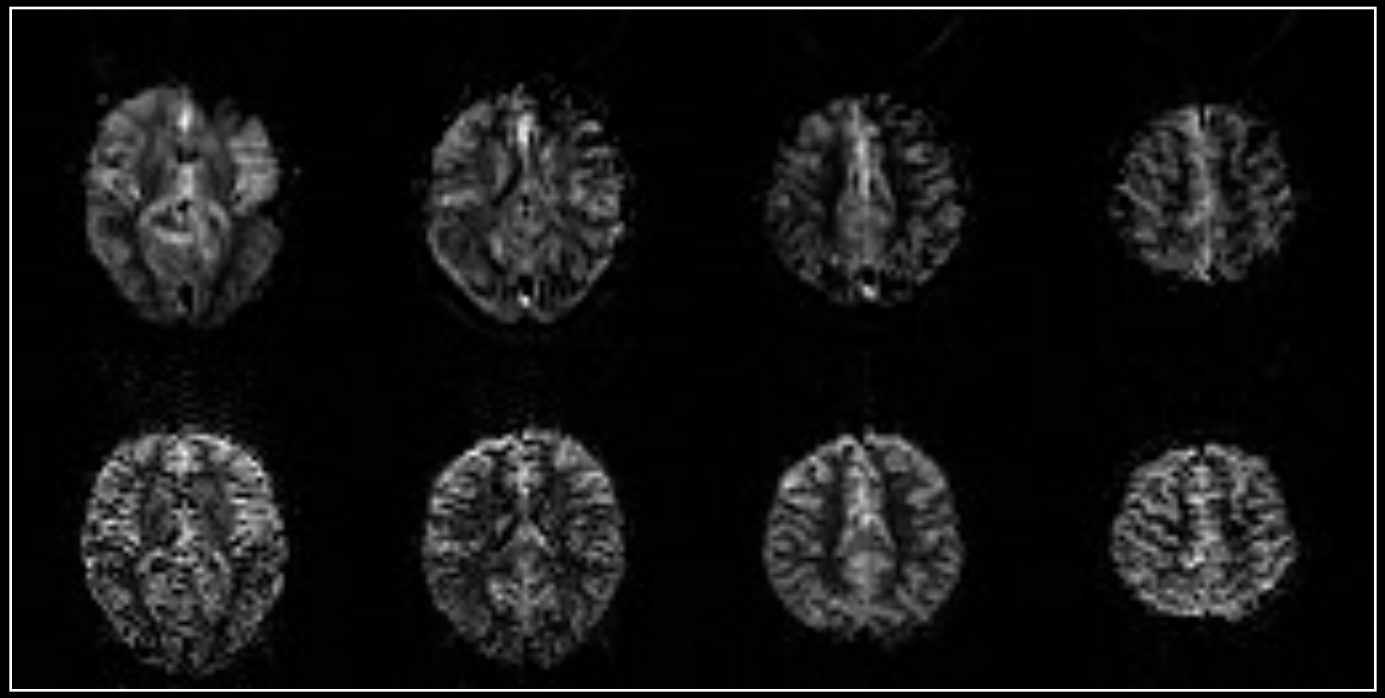
Spin echo vs. Gradient echo



compartment radius:	< 3 µm	3 to 15 µm	> 15 µm

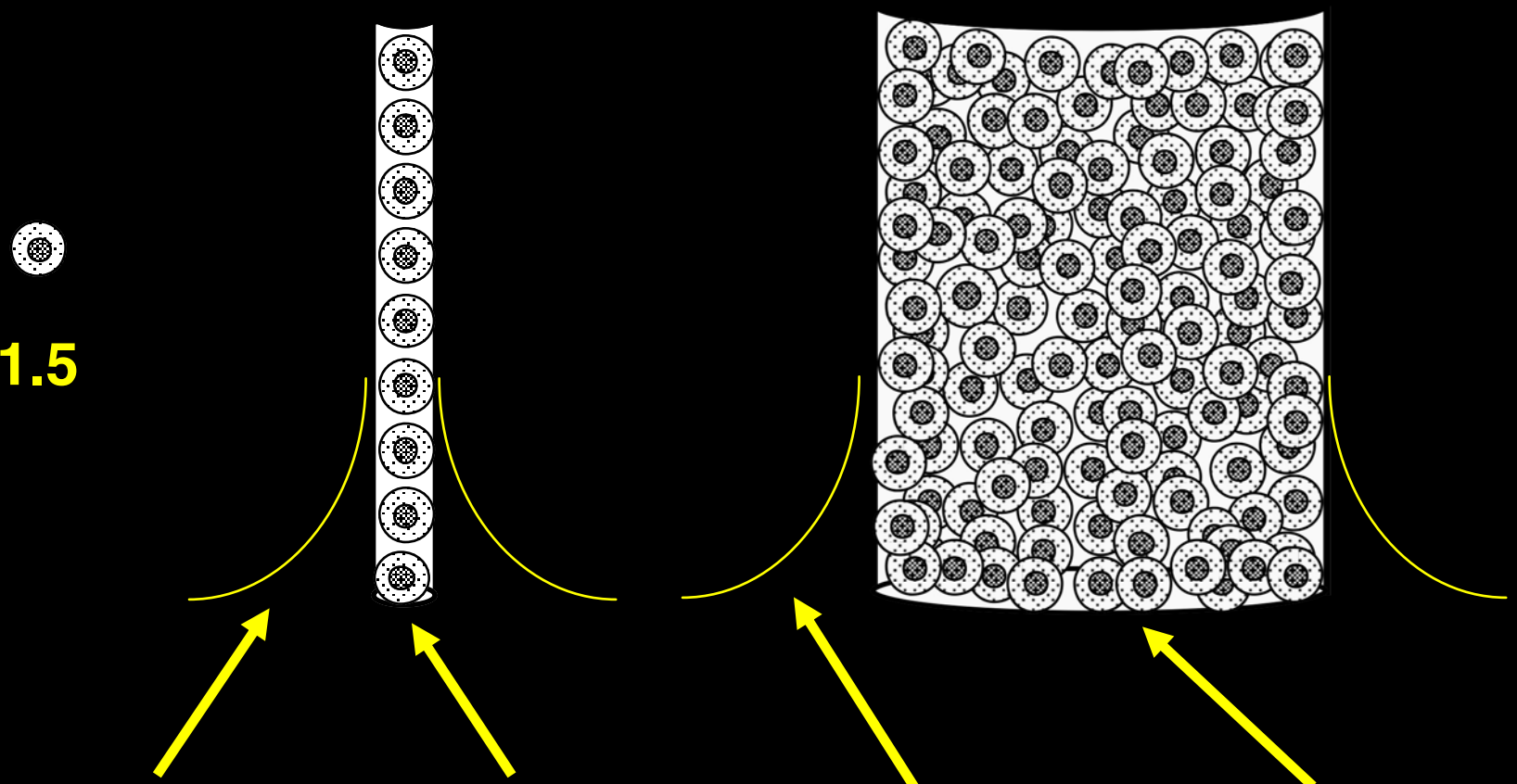
GE
TE = 30 ms

SE
TE = 110 ms

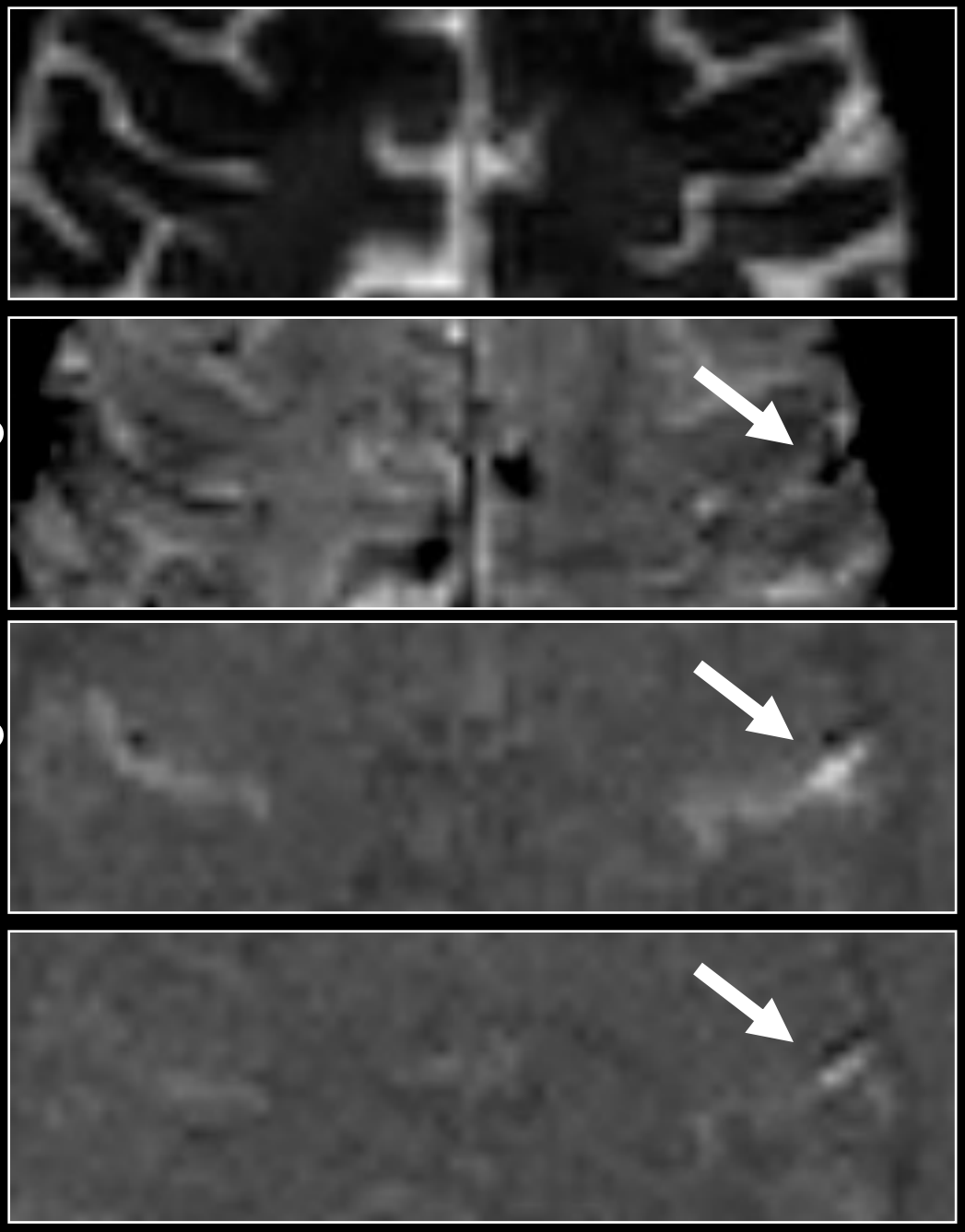


Spin-echo??

ΔR2* /ΔR2

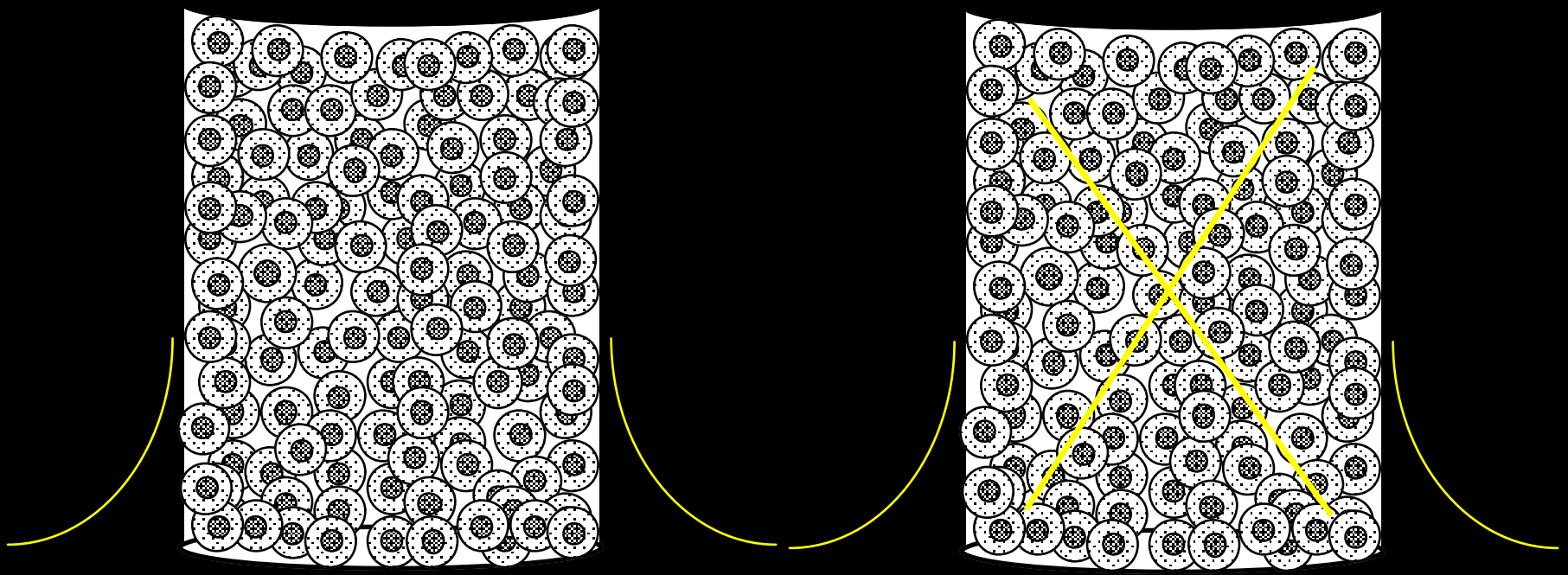


average ΔR2 / ΔR2 ≈ 3 to 4*

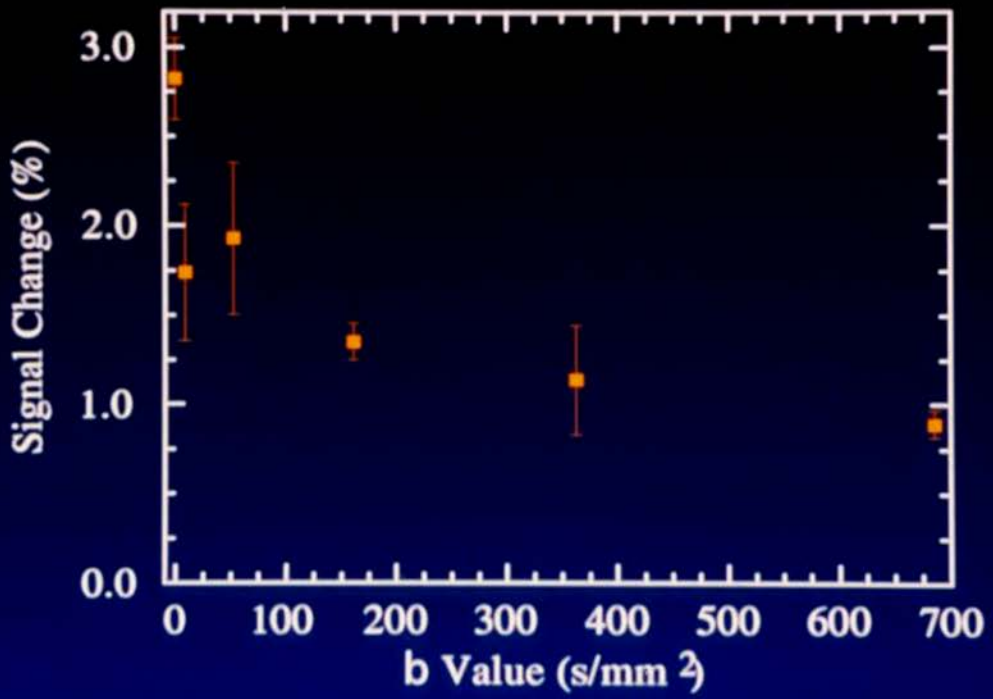

Spin-Echo
TE = 105 ms
TR = ∞
Gradient-Echo
TE = 50 ms
Gradient-Echo
functional
TE = 50 ms
Spin-Echo
functional
TE = 105 ms
3T

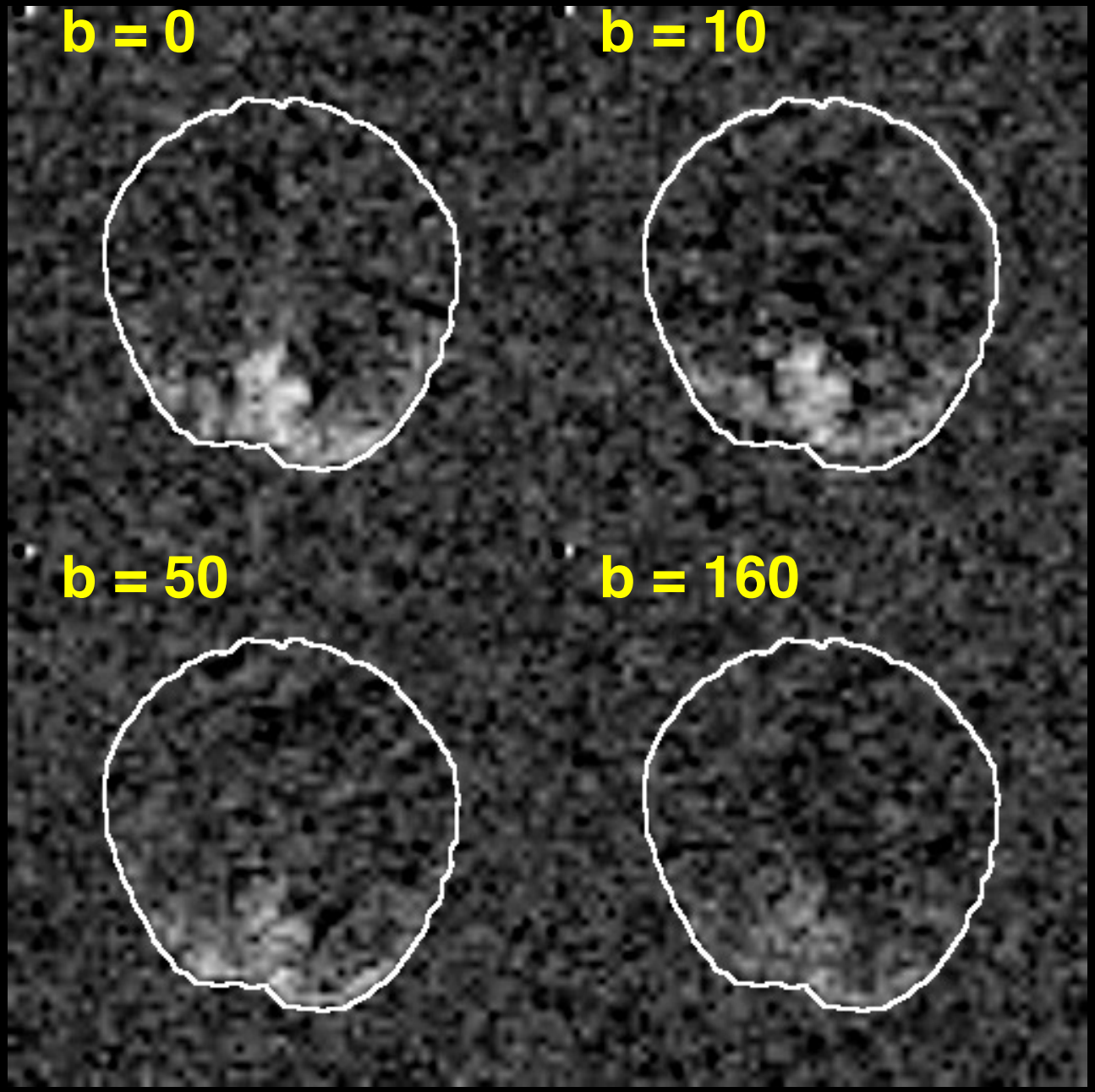
no diffusion weighting

diffusion weighting



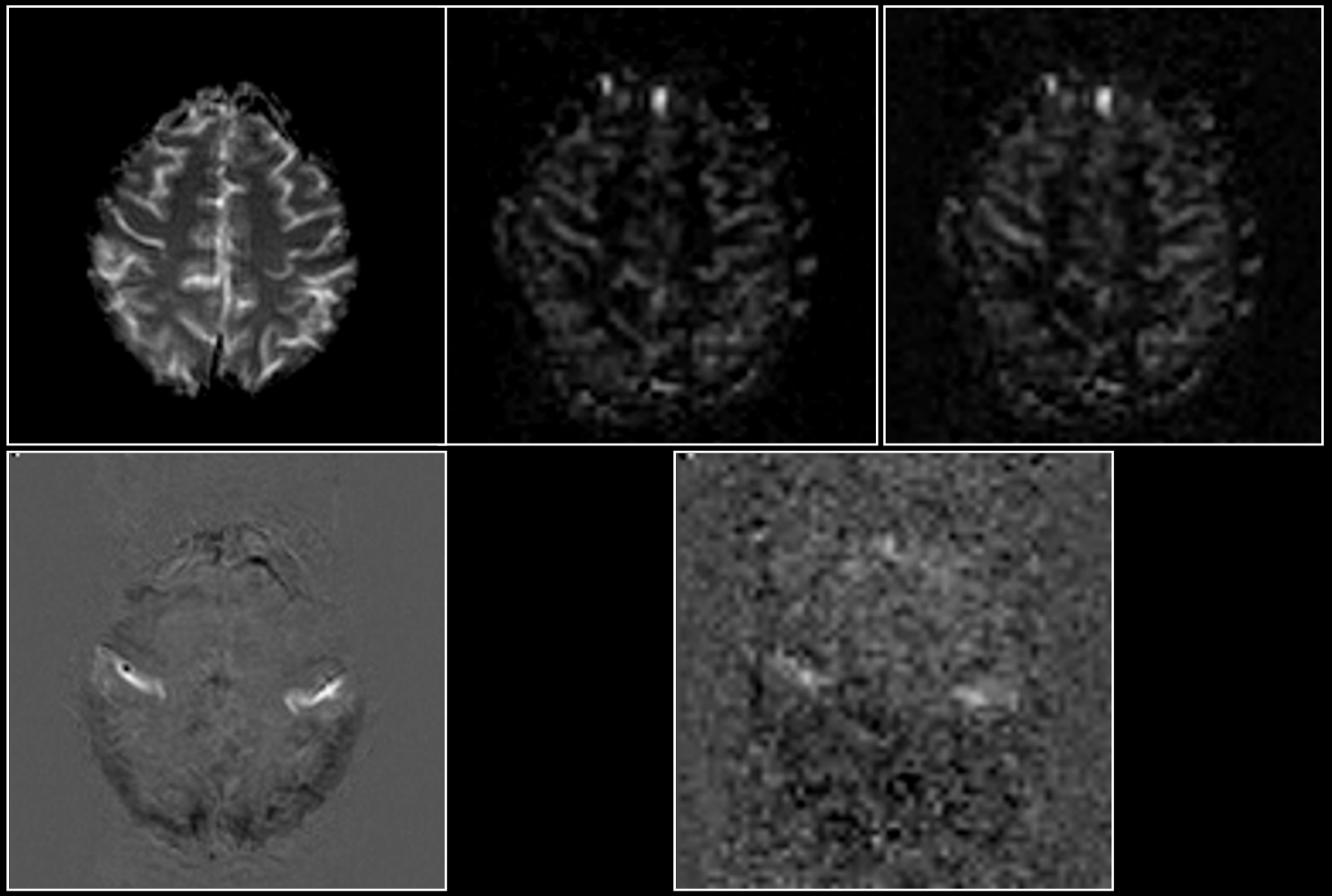
Summary of Diffusion-Weighted fMRI Data




b = 0
b = 10
b = 50
b = 160

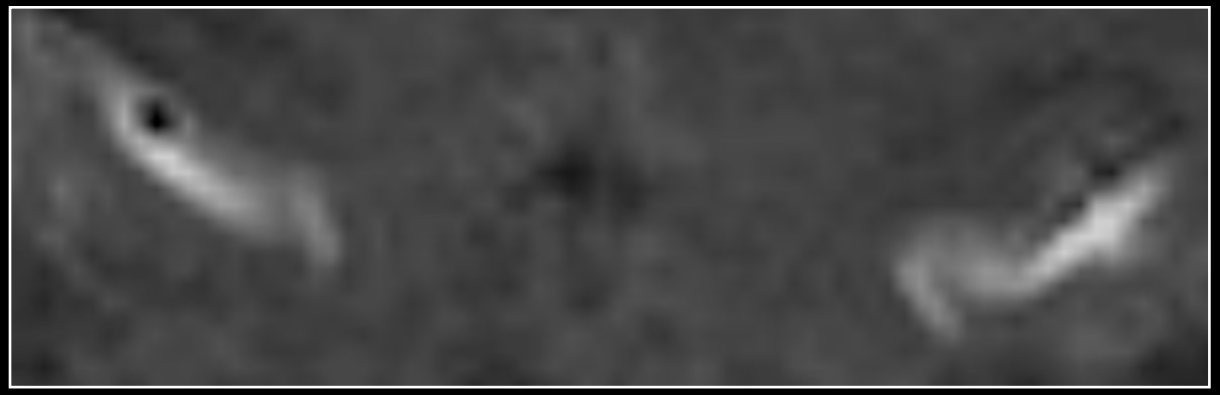
Perfusion

BOLD *Rest* *Activation*



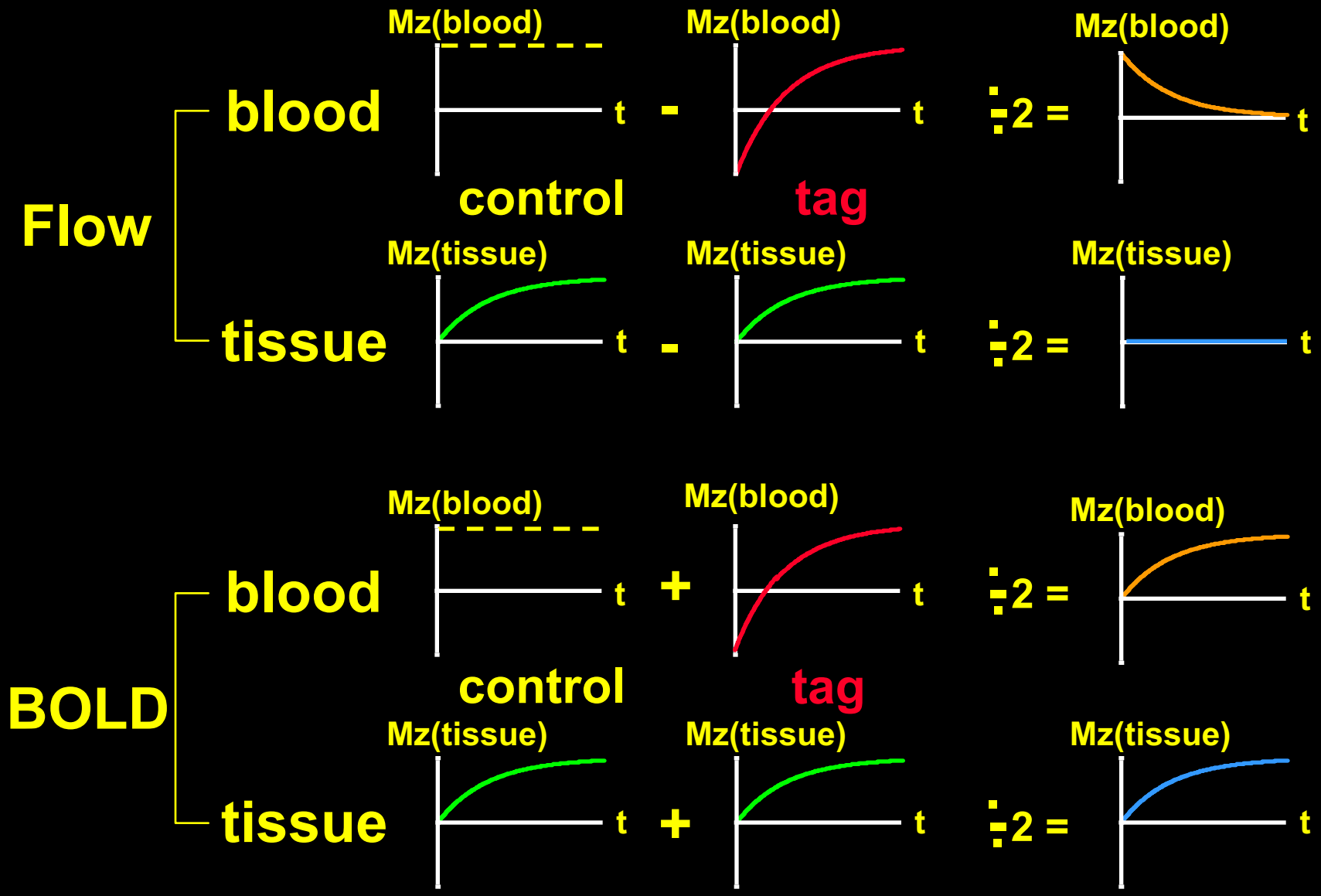
Anatomy

BOLD

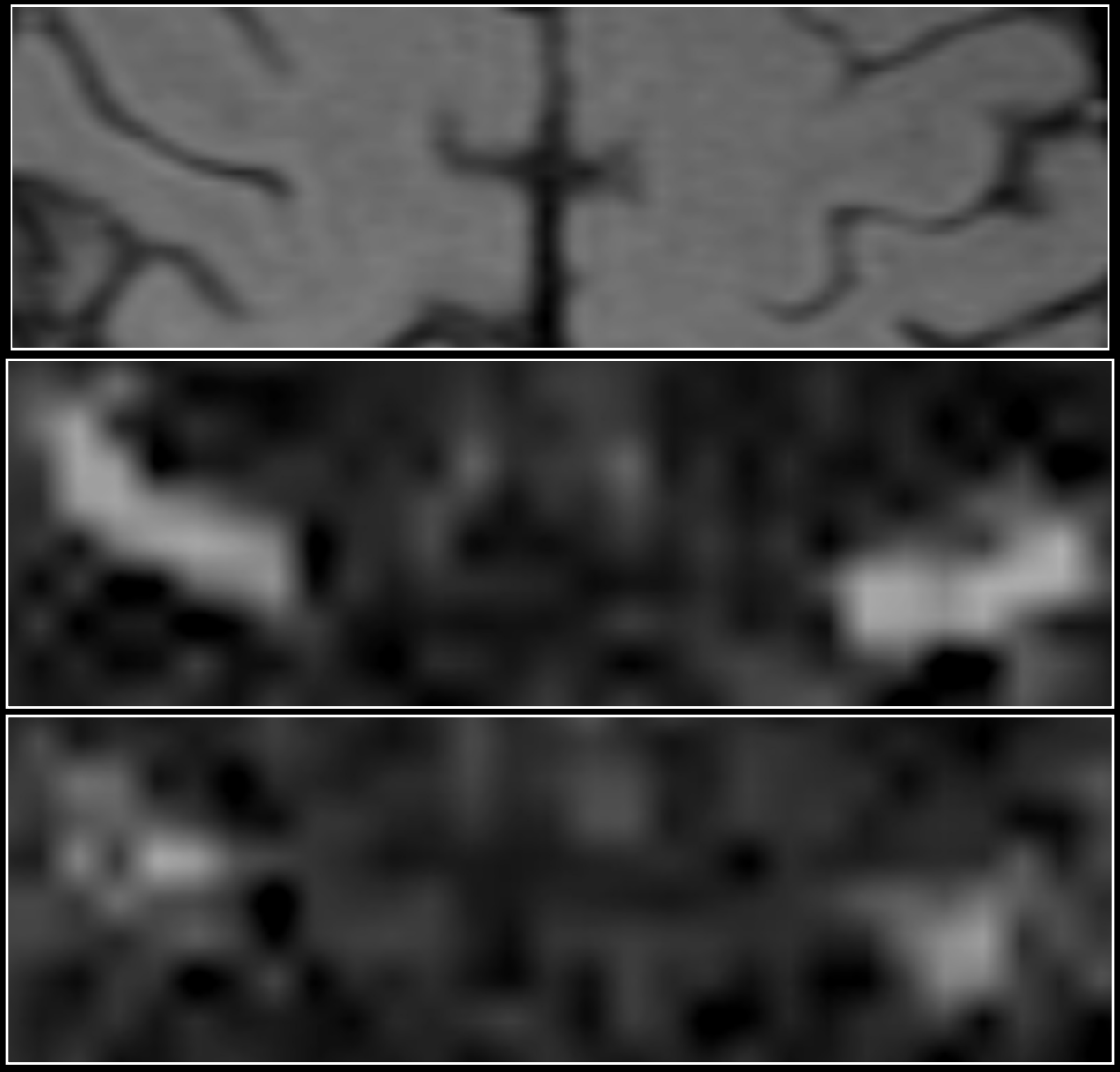


Perfusion

Simultaneous Flow and BOLD



Simultaneous BOLD and Perfusion



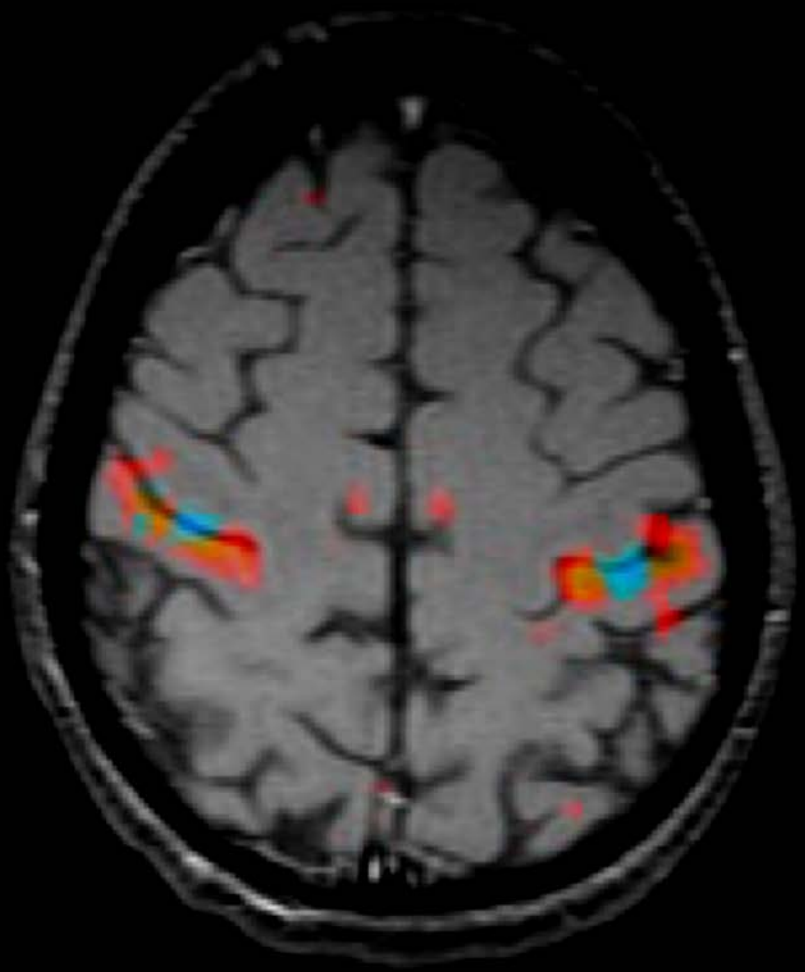
BOLD

Perfusion

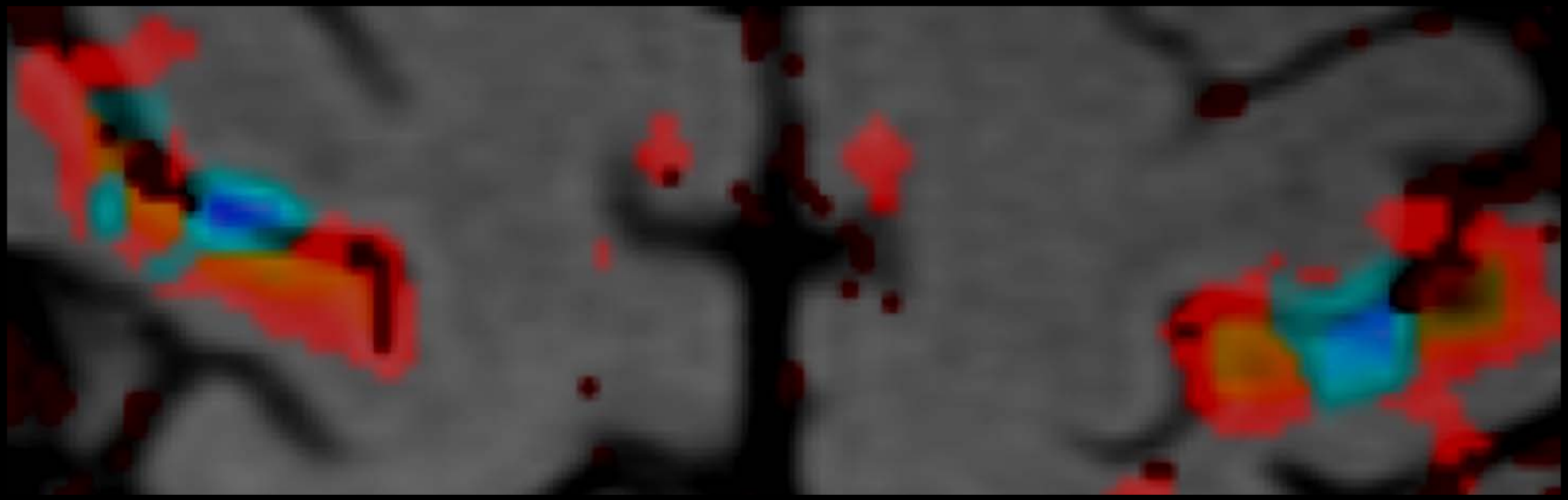
Simultaneous BOLD and Perfusion

perfusion

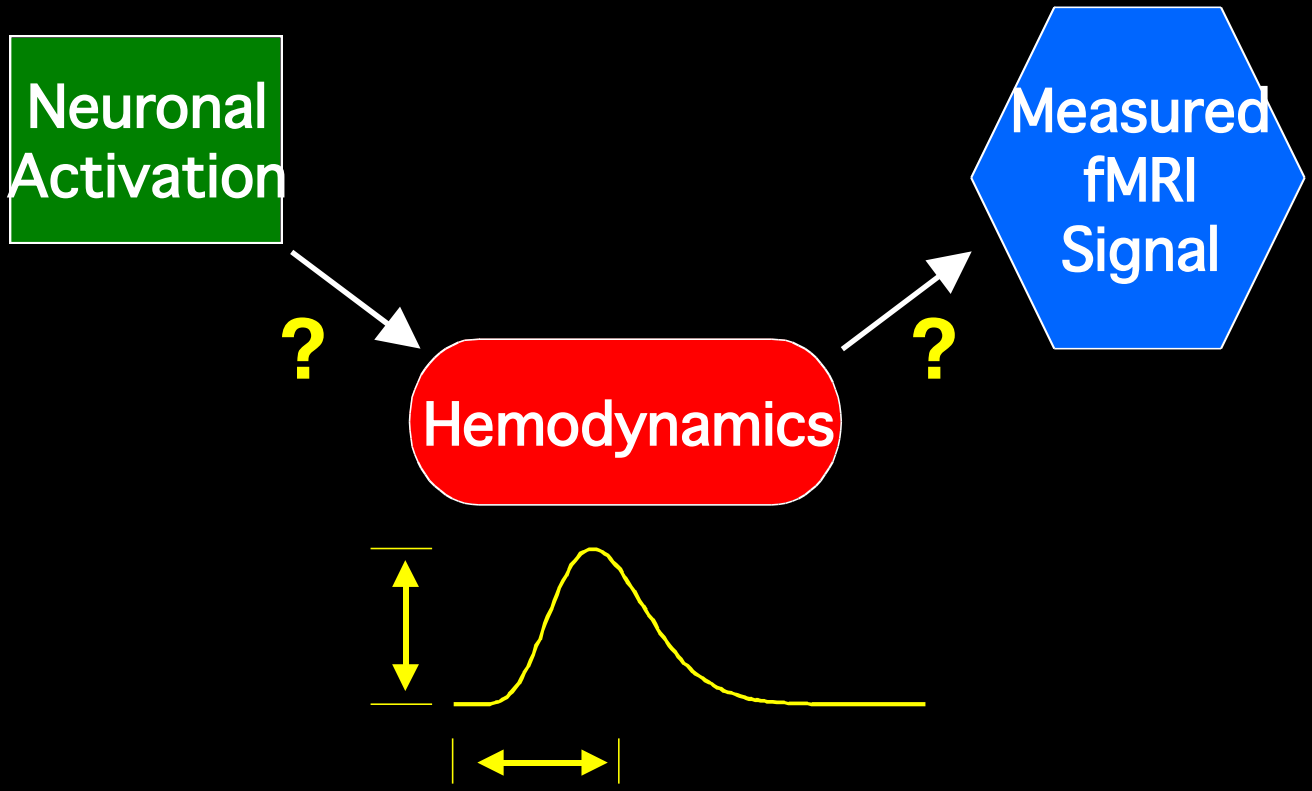
BOLD



Angiogram
Perfusion
BOLD



Spatial Normalization



Physiologic Factors

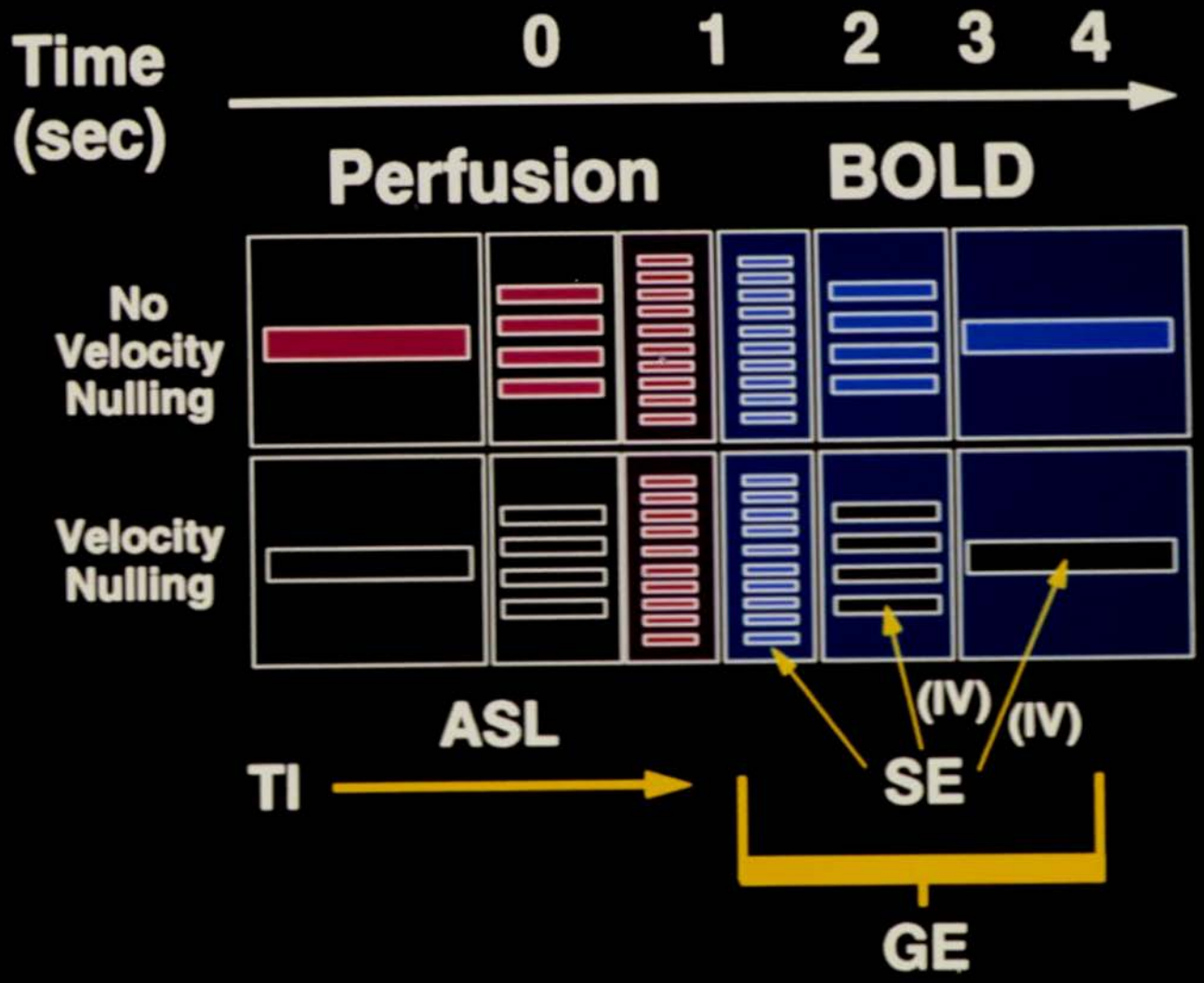
Hypercapnia

T1 - weighted

T2* weighted

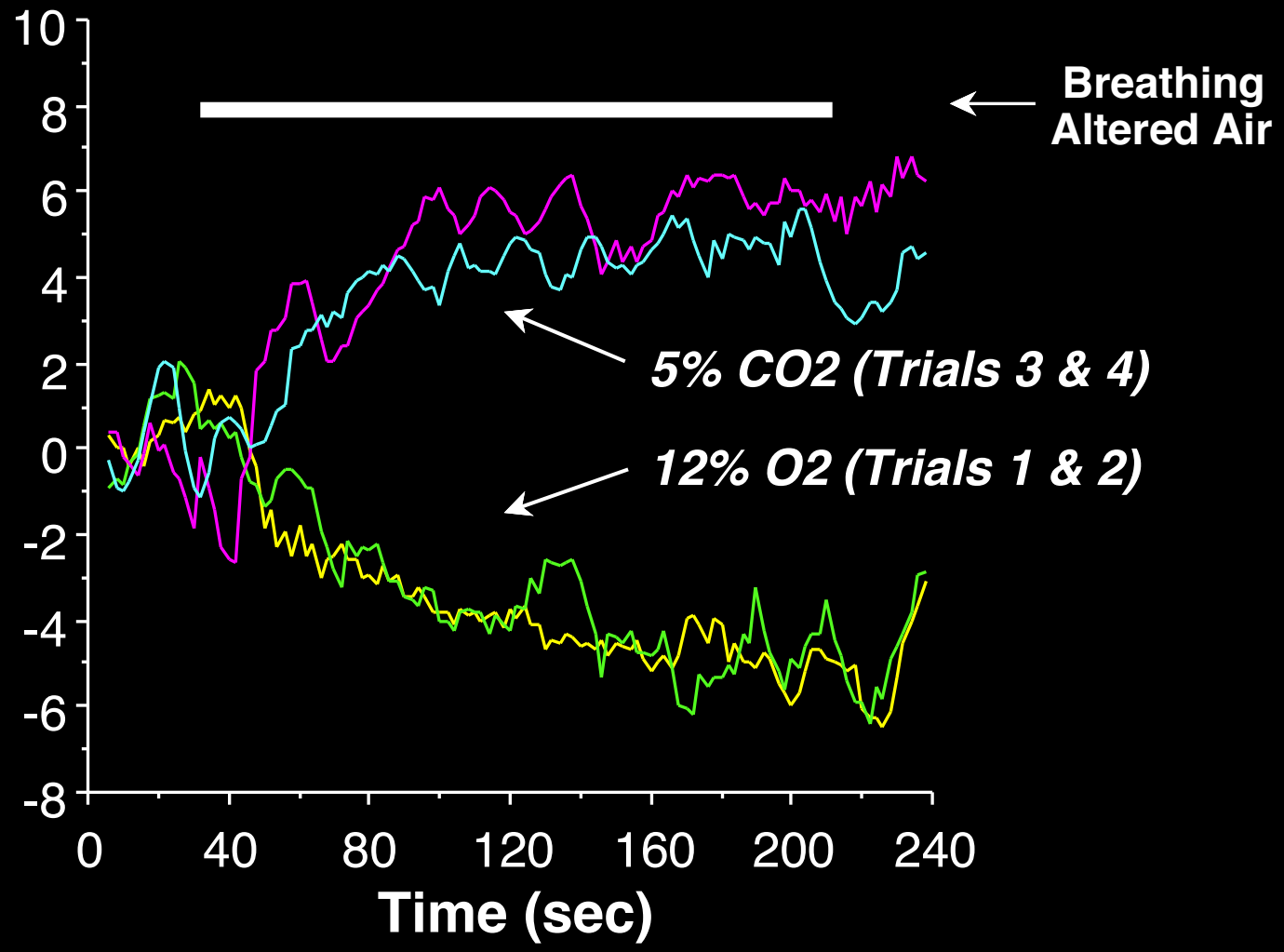
T1 and T2* weighted

Vascular Sensitization



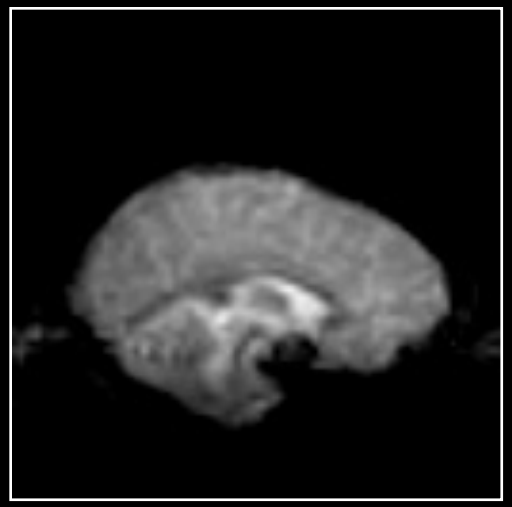
Problems with pulse sequence - based methods for increasing resolution

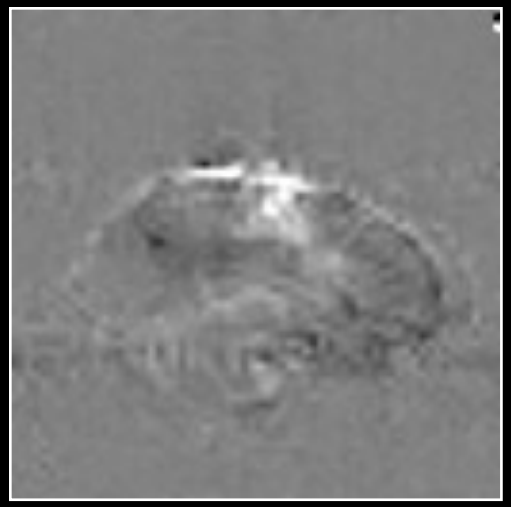
- Spin-echo (sensitivity, specificity)
- Arterial spin-labeling (sensitivity, time, range)
- Diffusion weighting (sensitivity, specificity)
- Threshold based on magnitude (sensitivity, specificity)


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)

,

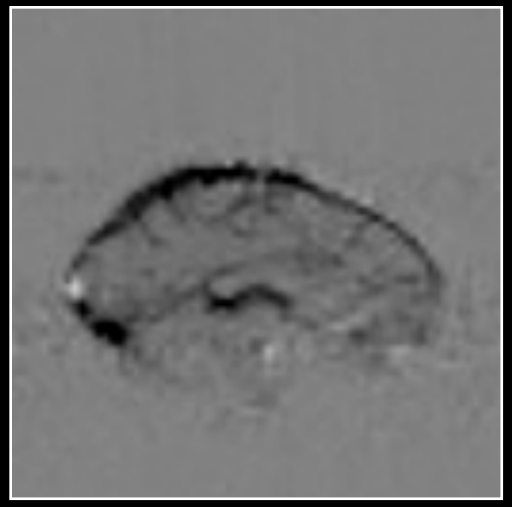
Anatomical

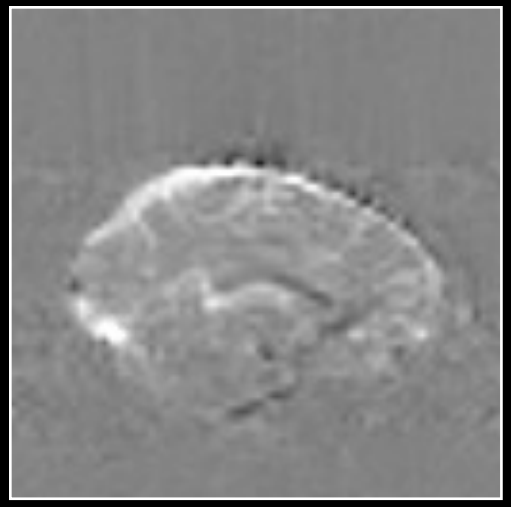




Finger Movement

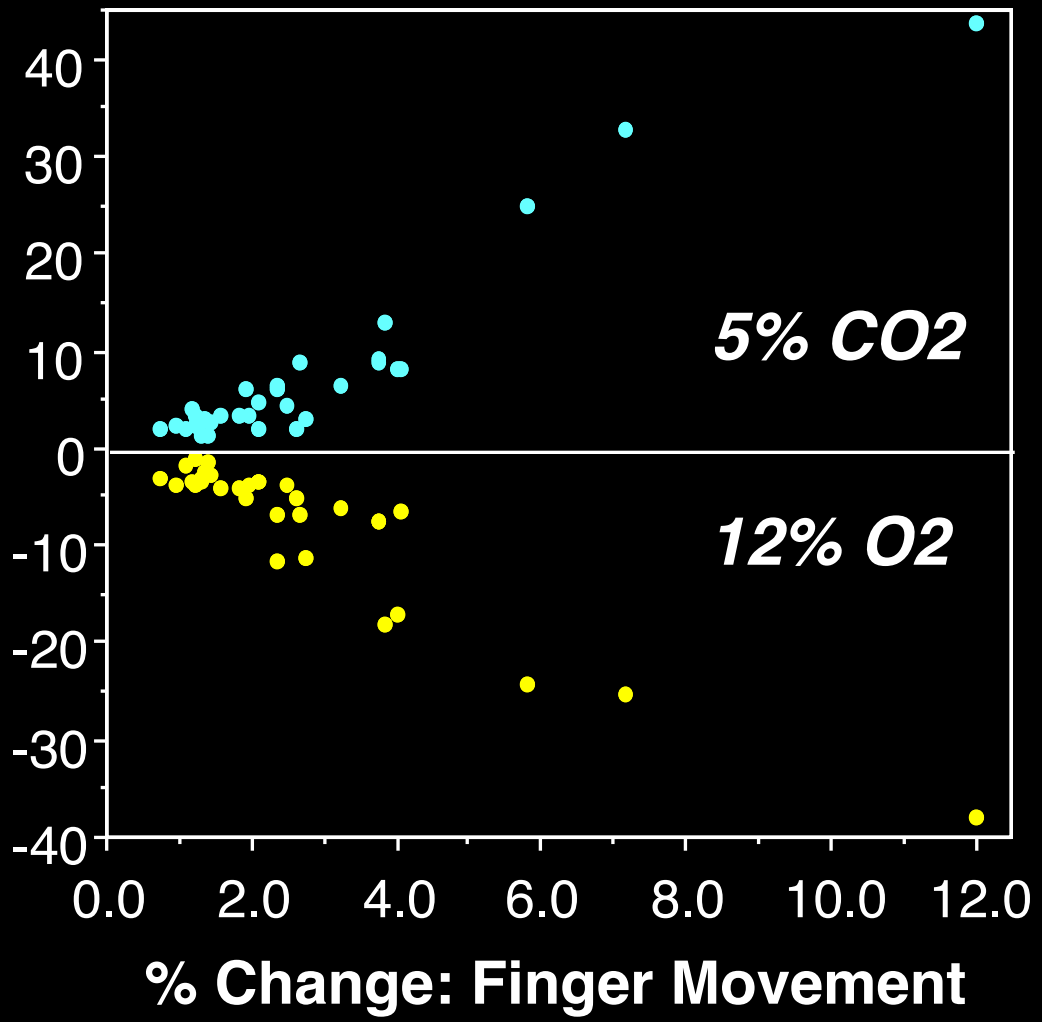
12% O2

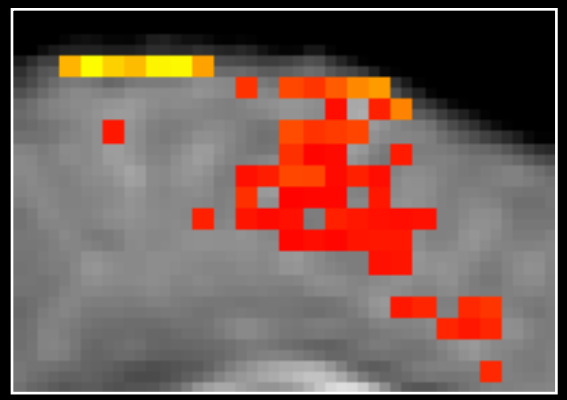




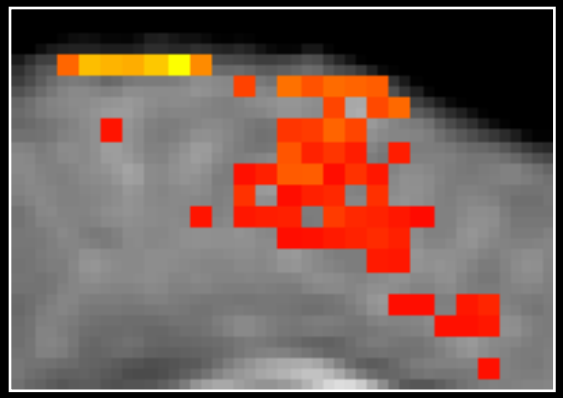
5% CO2

Resting State Blood Volume Weighting





%



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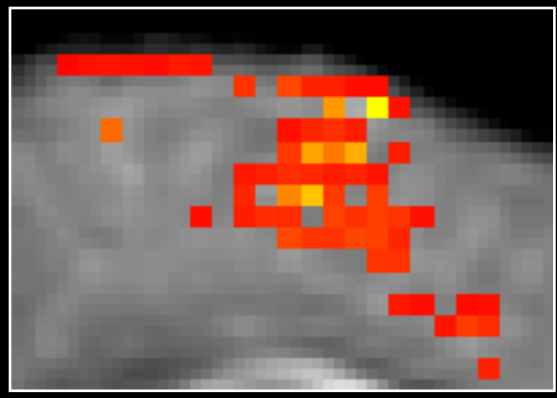
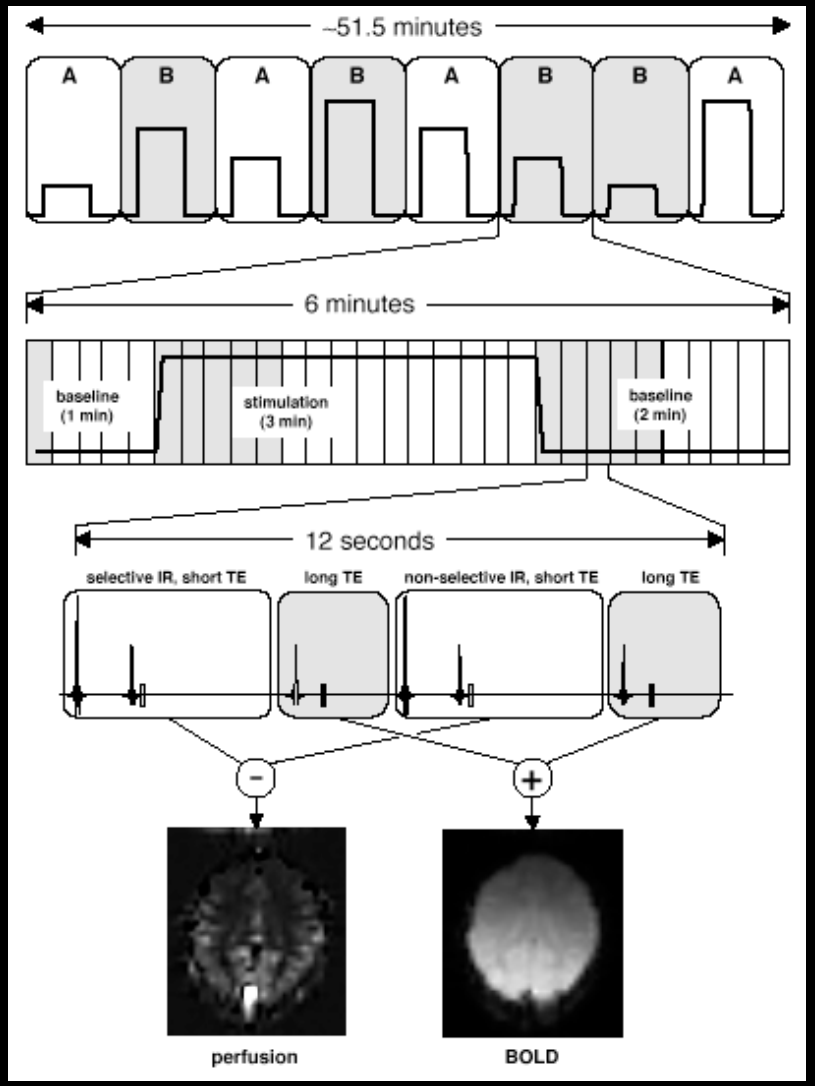
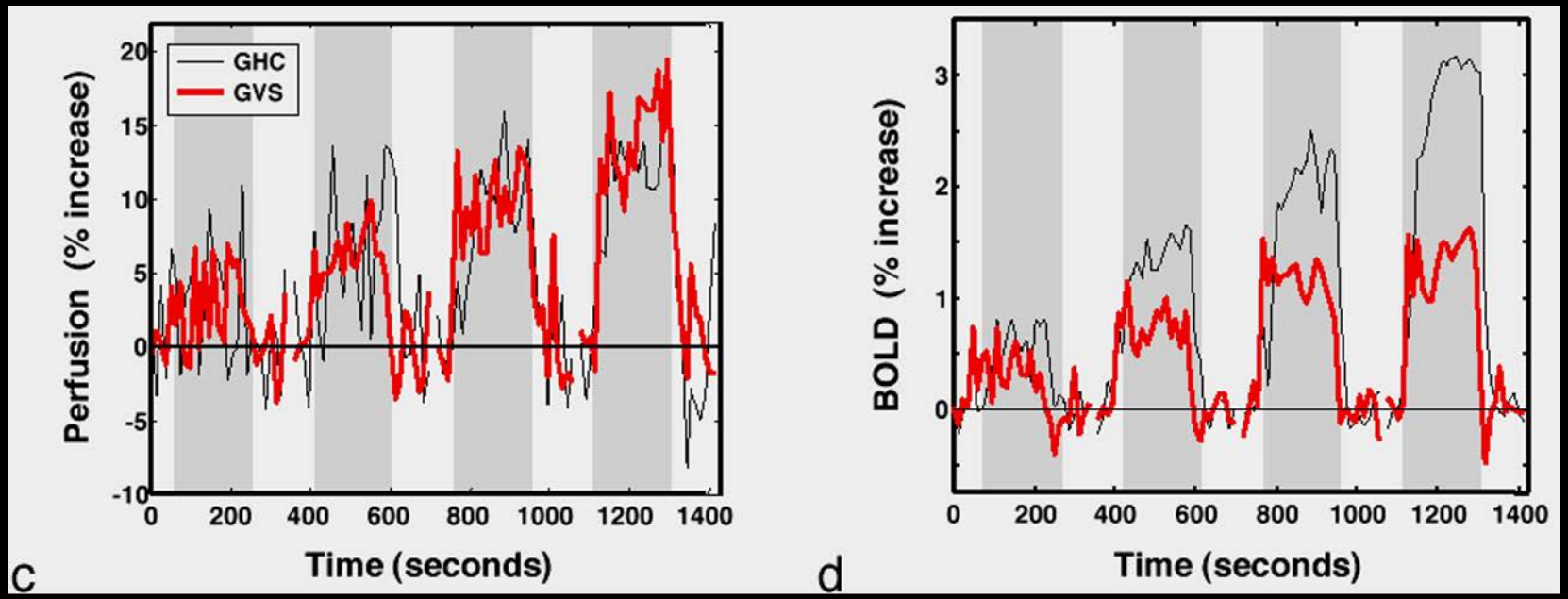


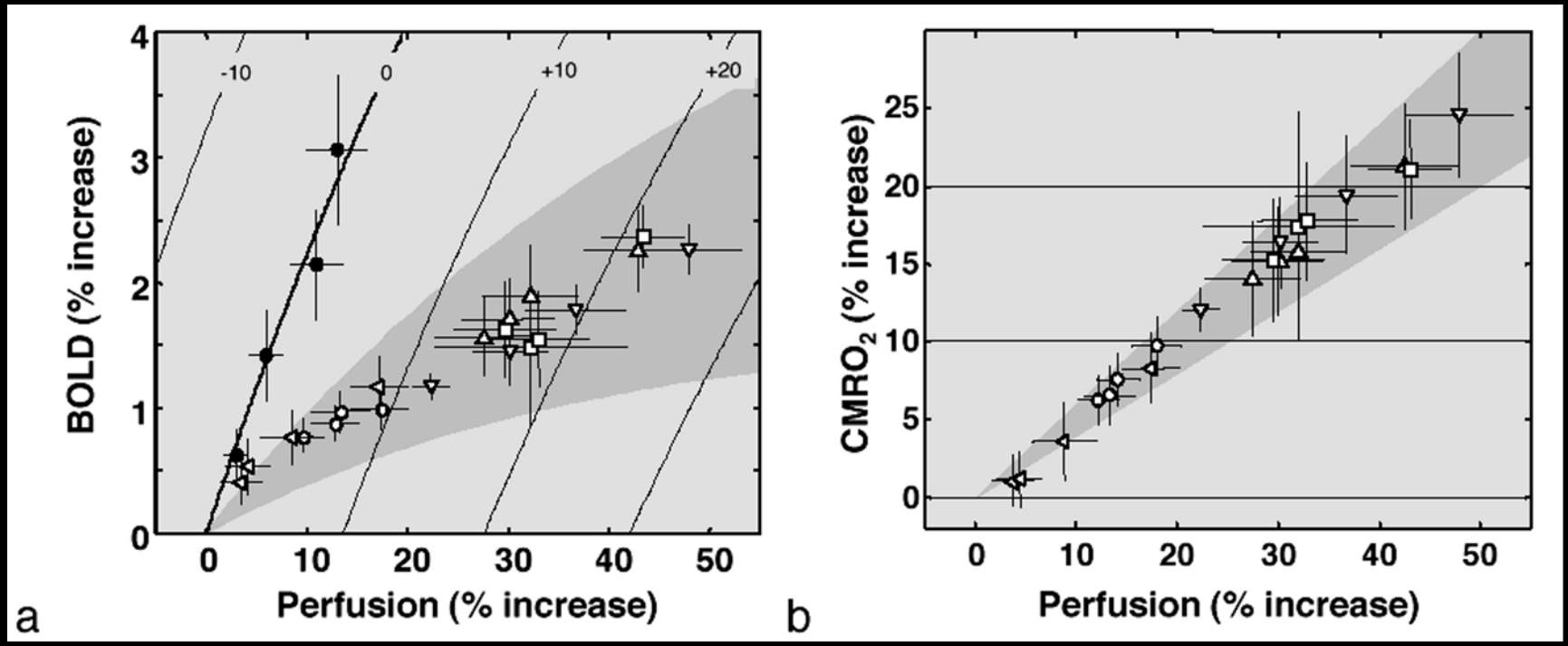

~51.5 minutes
A
B
A
B
A
B
B
A
6 minutes
baseline
(1 min)
stimulation
(3 min)
baseline
(2 min)
12 seconds
selective IR, short TE
long TE
non-selective IR, short TE
long TE
perfusion
BOLD

Hoge et al


GHC
GVS
Perfusion (% increase)
20
15
10
5
0
-5
-10
0
200
400
600
800
1000
1200
1400
Time (seconds)
c
BOLD (% increase)
3
2
1
0
0
200
400
600
800
1000
1200
1400
Time (seconds)
d

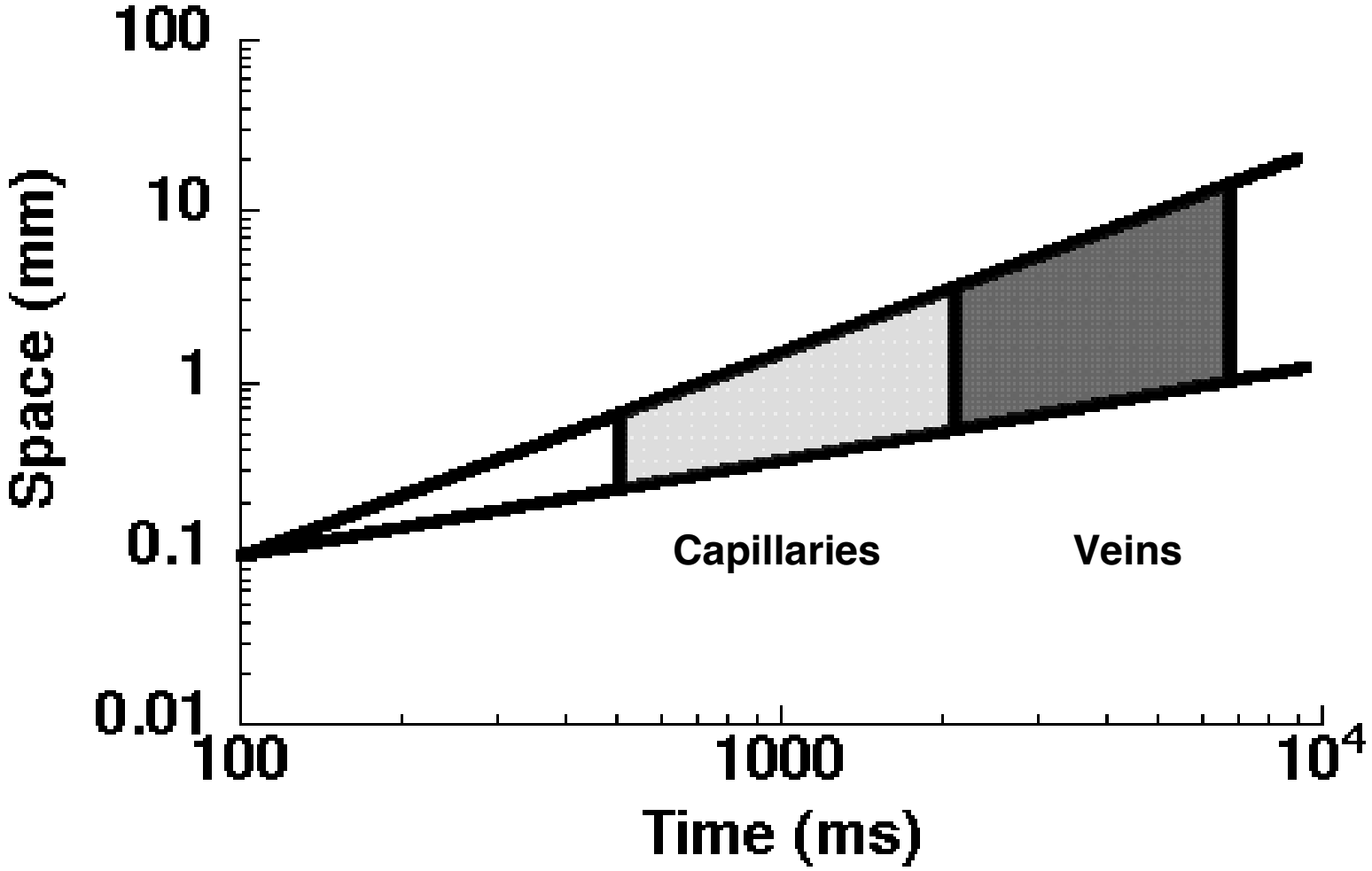
Hoge et al

Mapping $CMRO_2$ using CO_2 Calibration



Hoge et al

Hemodynamic Latency and Variability Following Neuronal Activation



Types of Temporal Resolution

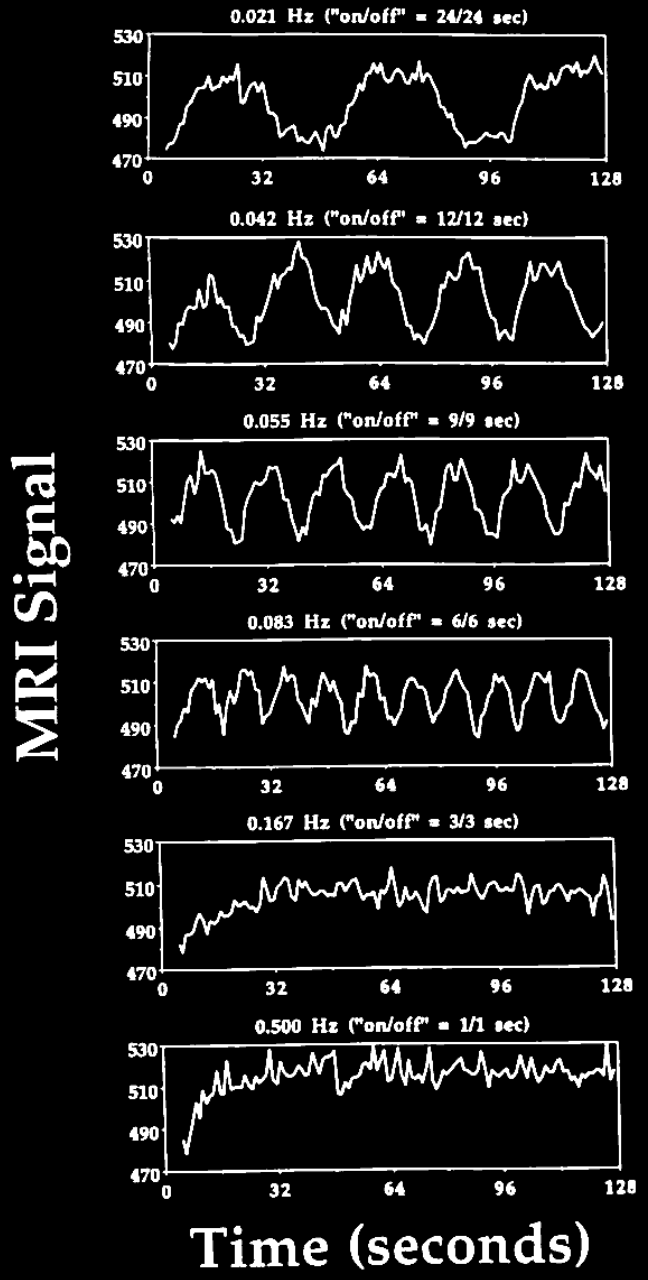
1. Maximum on-off switching rate.

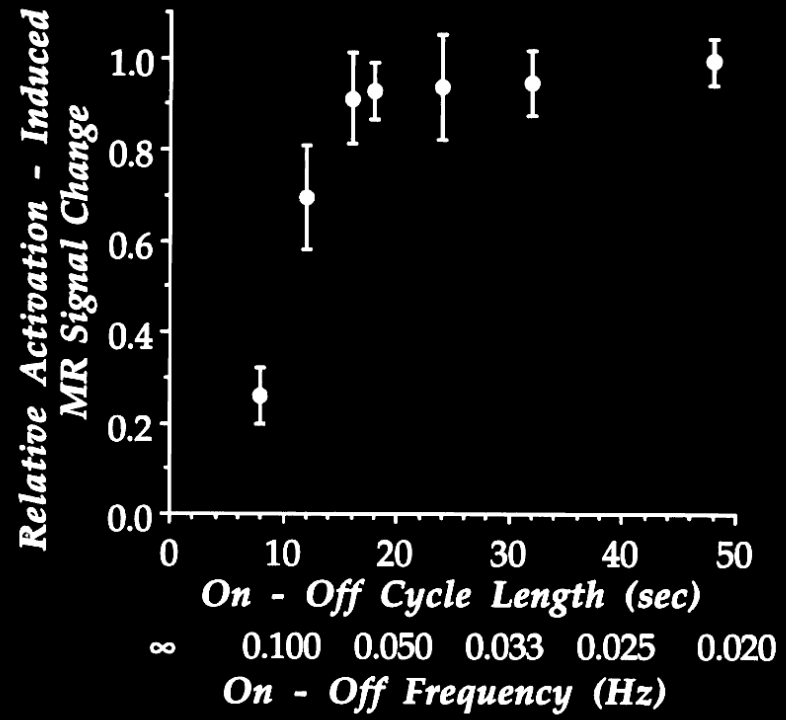
2. Minimum detectable activation duration.

3. Minimum detectable difference in activation duration or onset in same region.

4. Minimum detectable activation interval across separate brain regions.

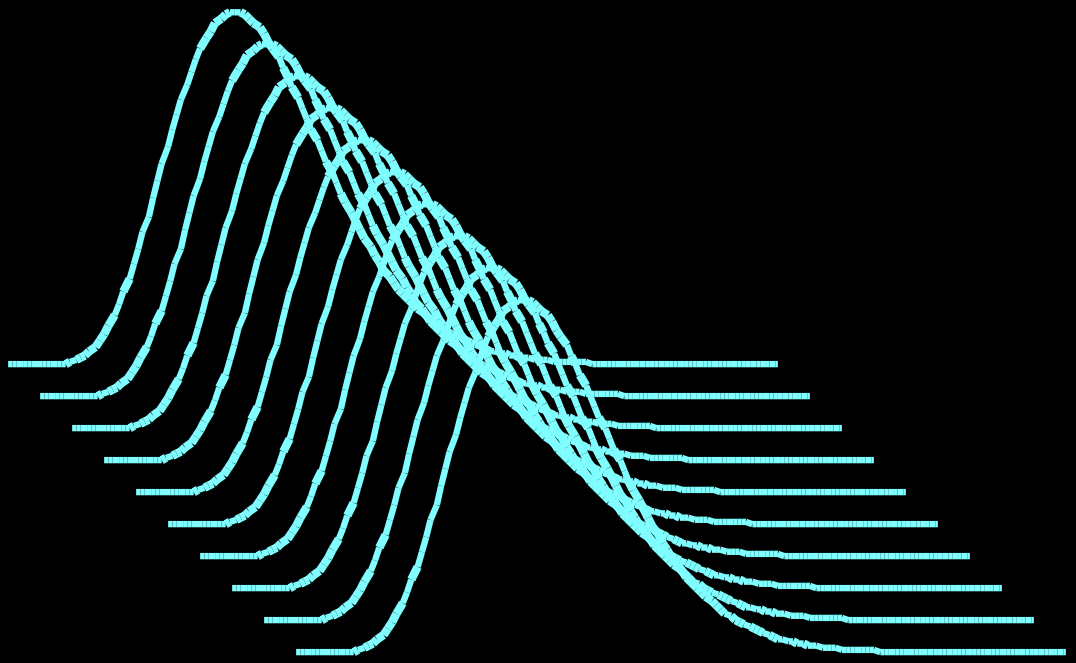
5. Maximum image acquisition rate.


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)

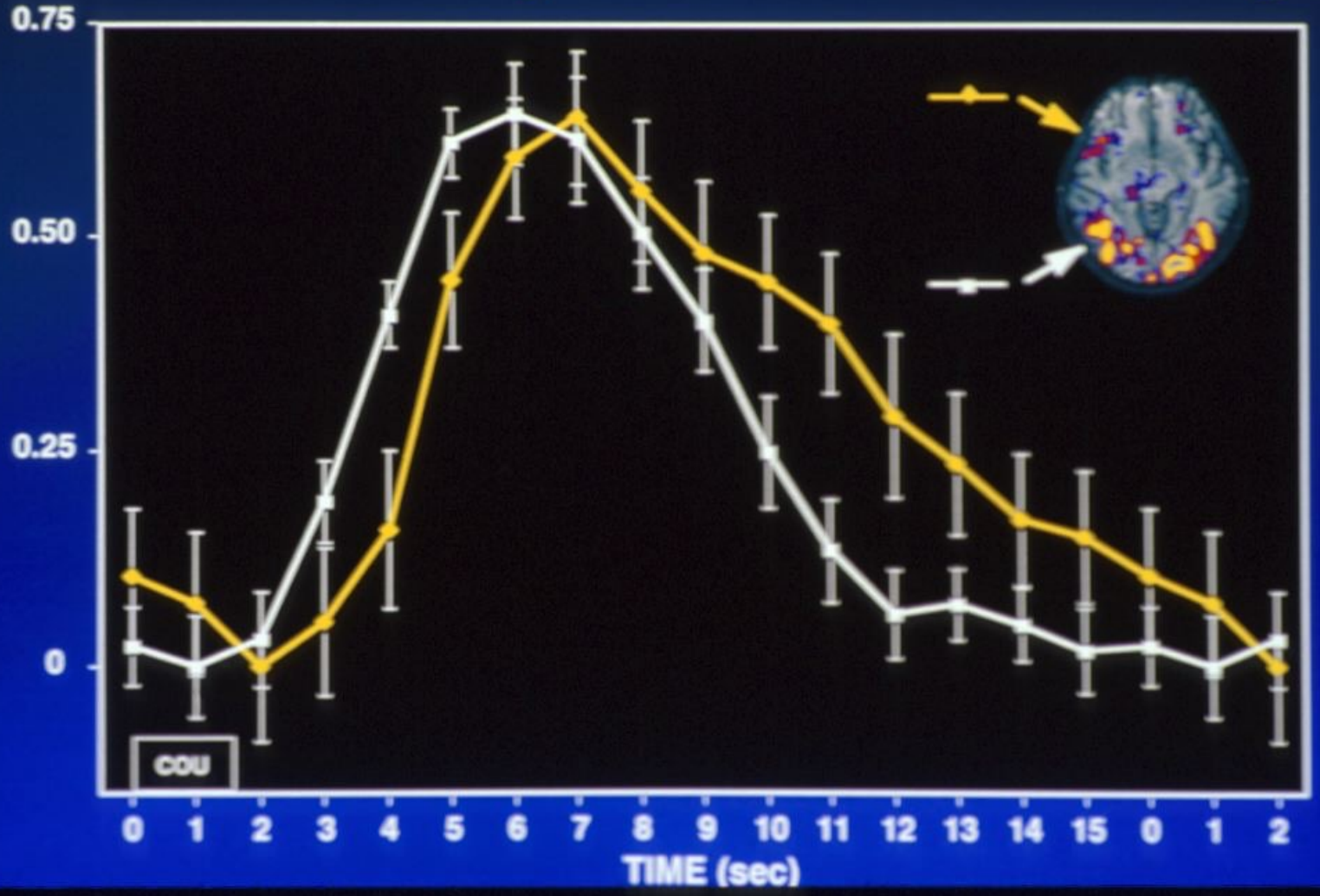

Relative Activation - Induced MR Signal Change
1.0
0.8
0.6
0.4
0.2
0.0
0
10
20
30
40
50
On - Off Cycle Length (sec)
∞
0.100
0.050
0.033
0.025
0.020
On - Off Frequency (Hz)

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

Cohen, Neuroimage 6, 93-103 (1997)

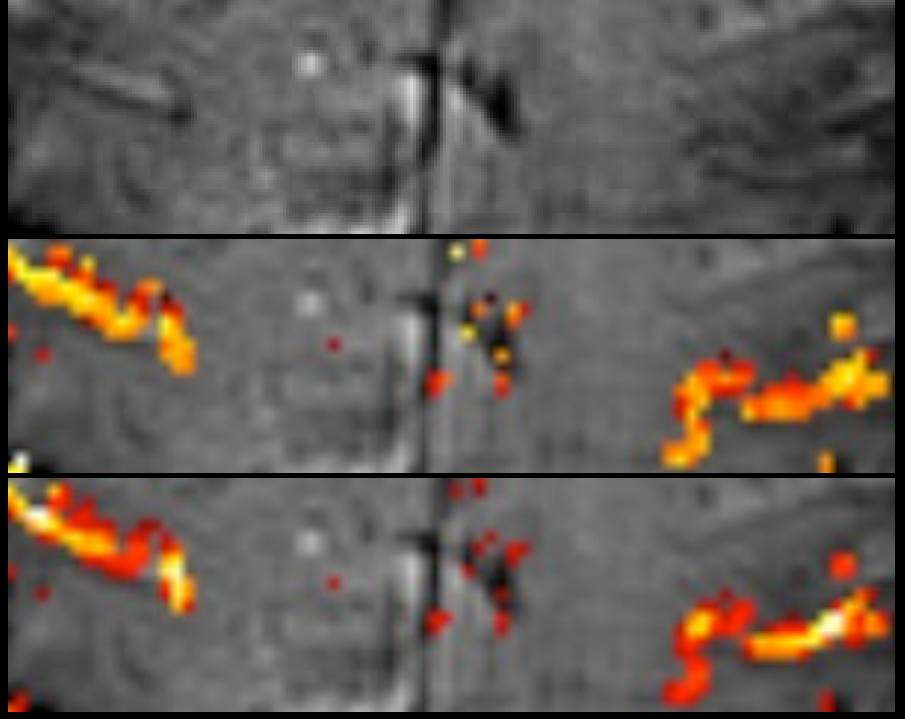


Time Course Comparison Across Brain Regions



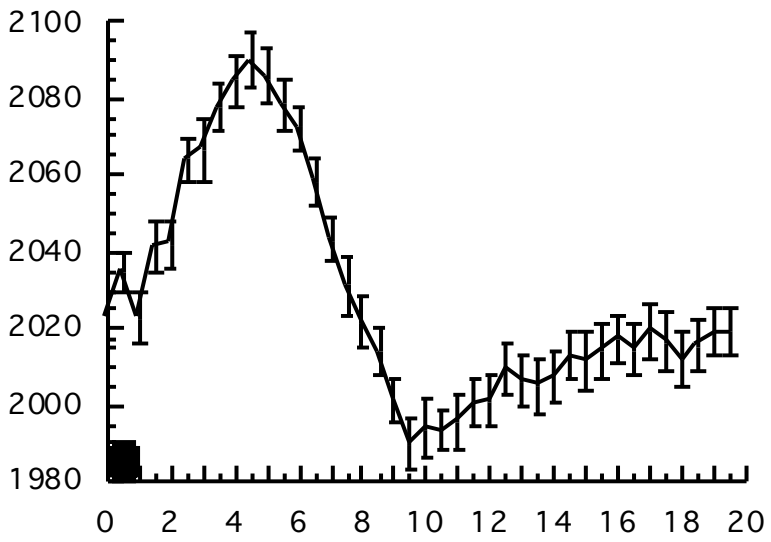
Latency

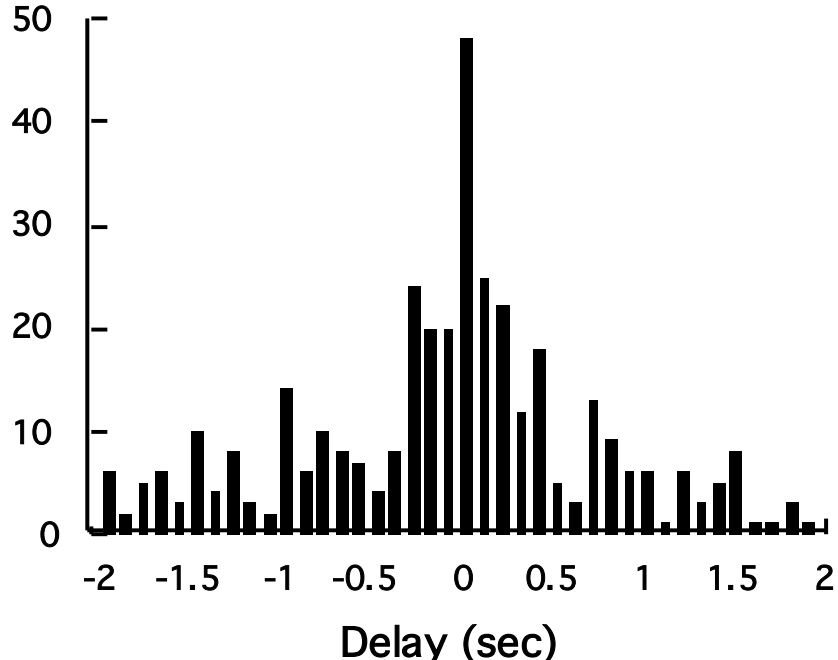
Magnitude



+ 2 sec

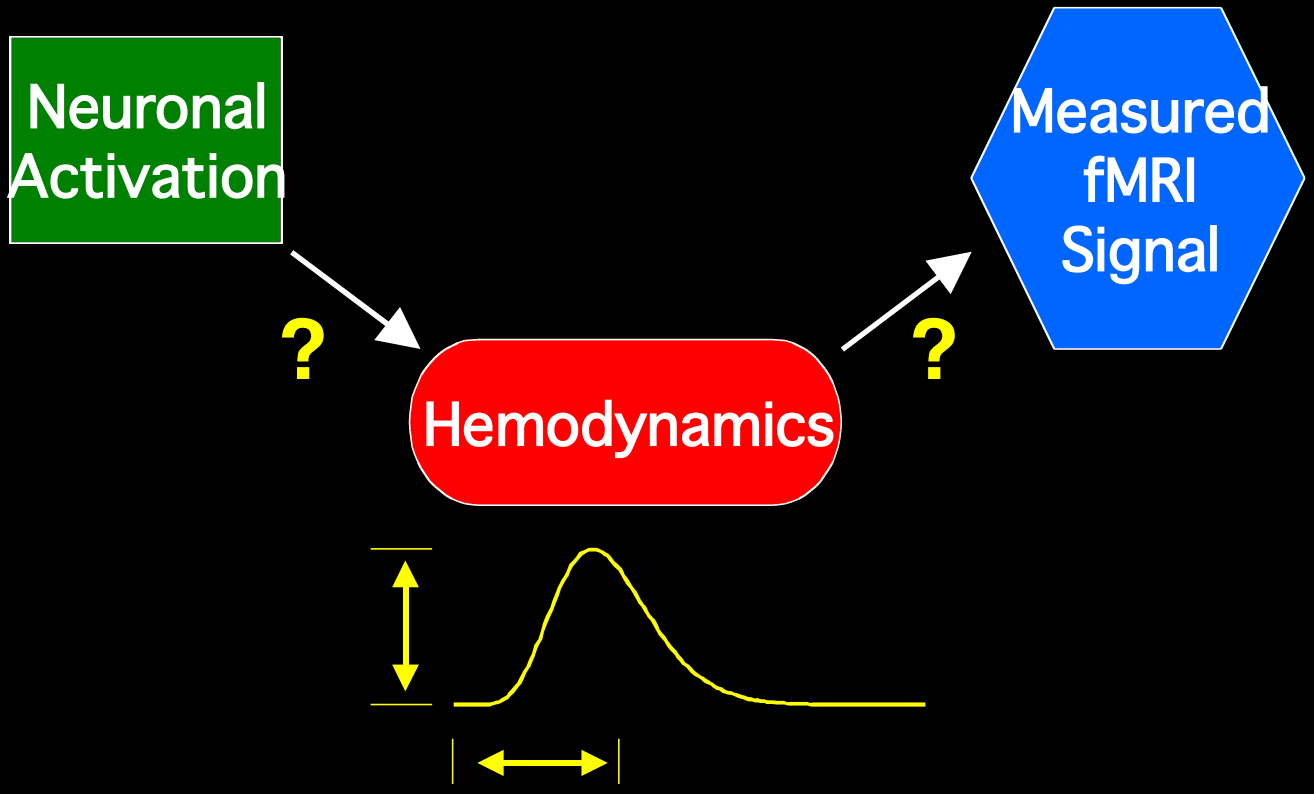
- 2 sec





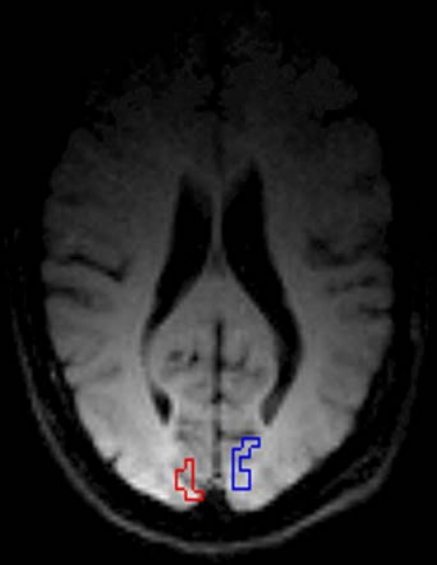
Temporal Normalization

Relative Timing



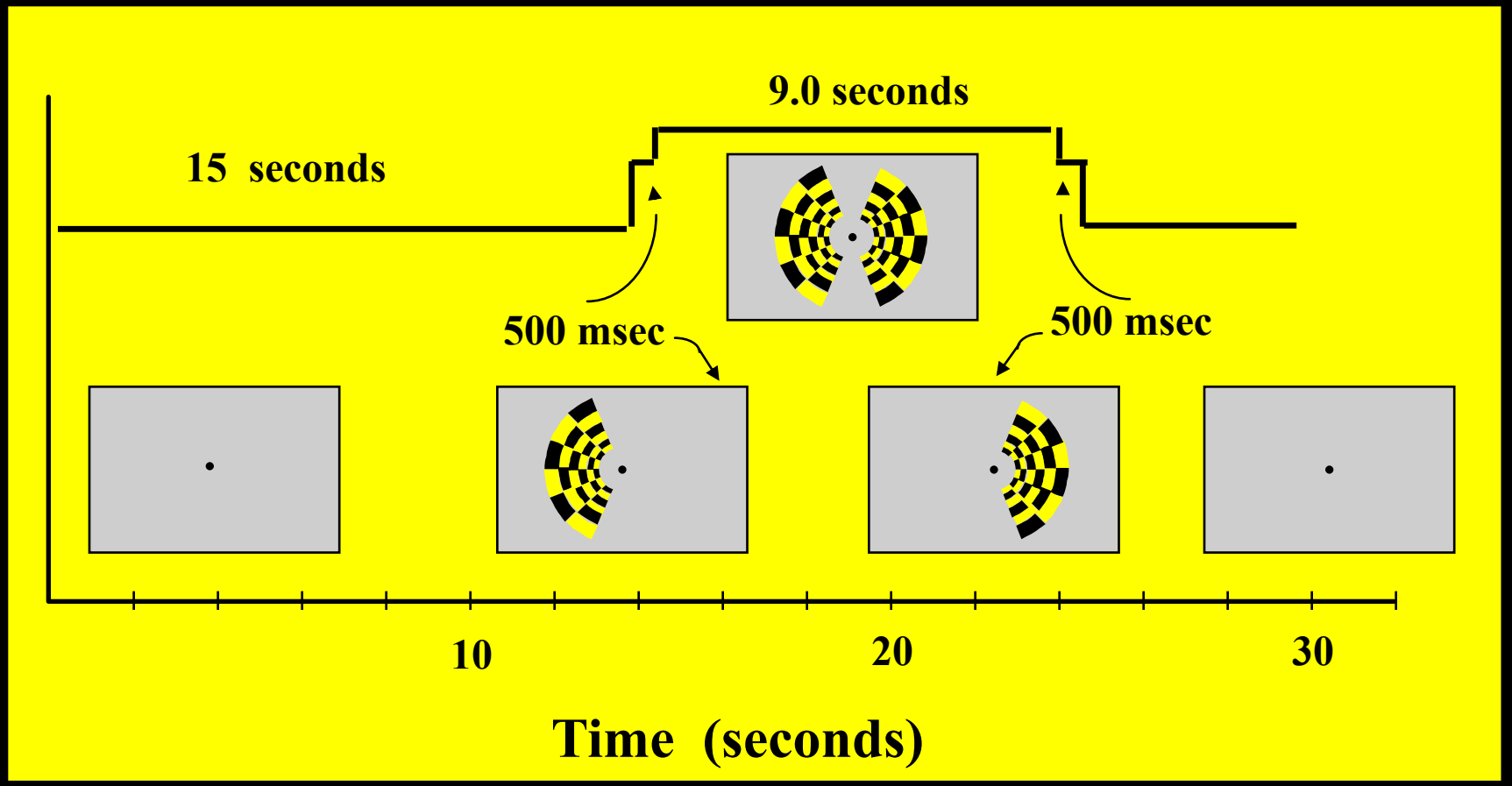
Physiologic Factors

Regions of Interest Used for Hemi-Field Experiment

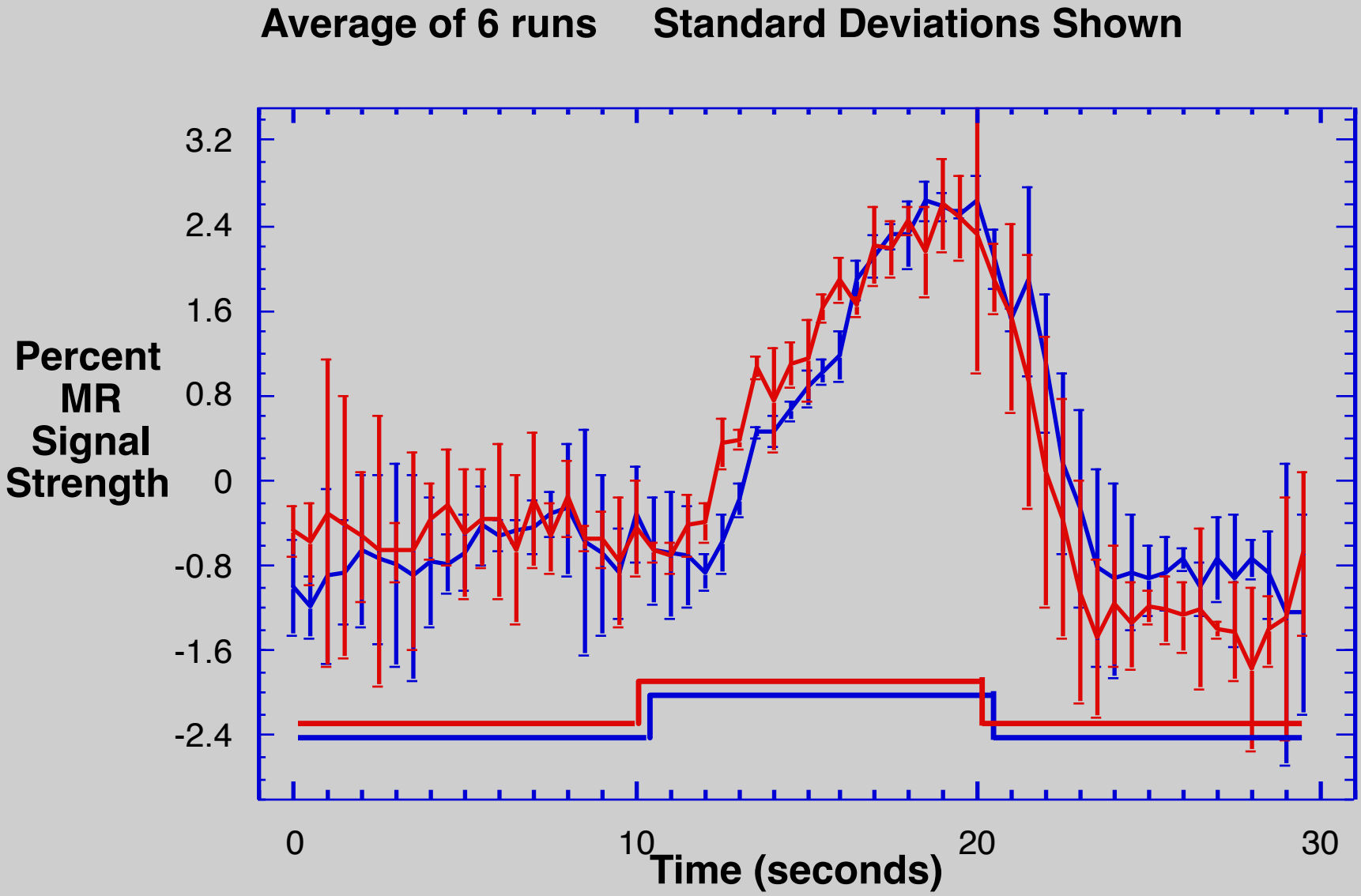


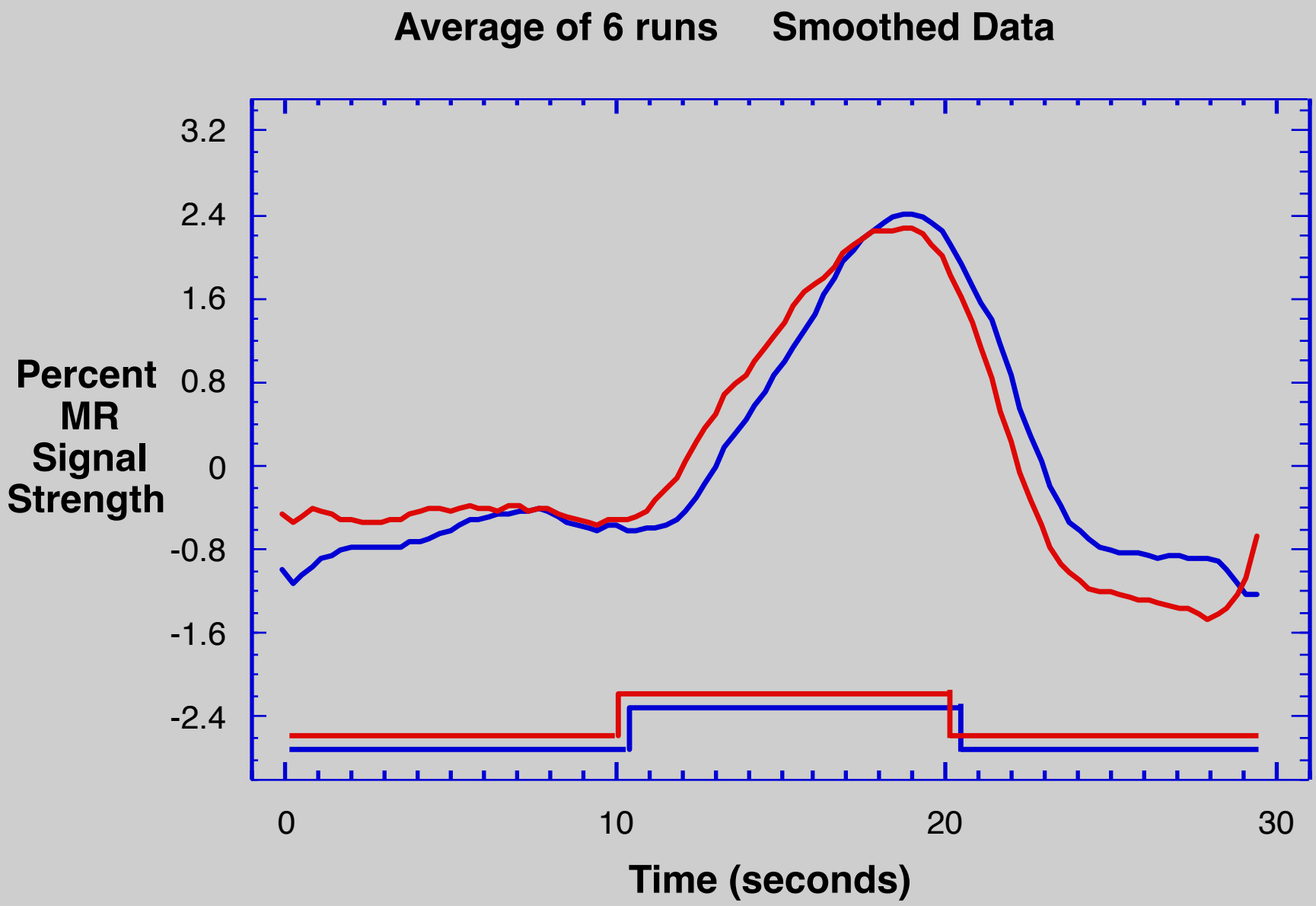
Right Hemisphere

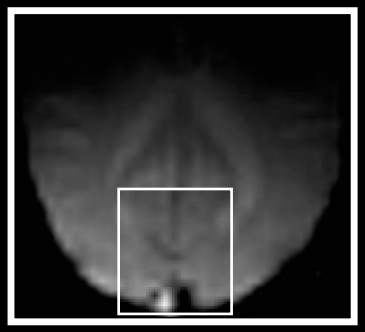
Left Hemisphere


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

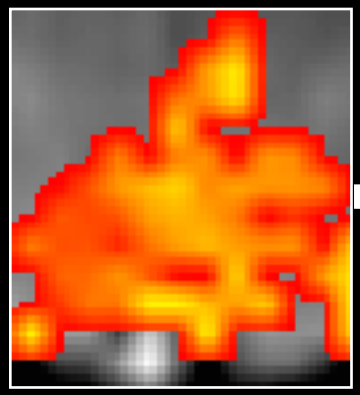
Right Hemifield

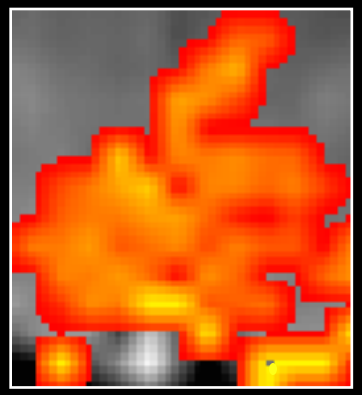
Left Hemifield

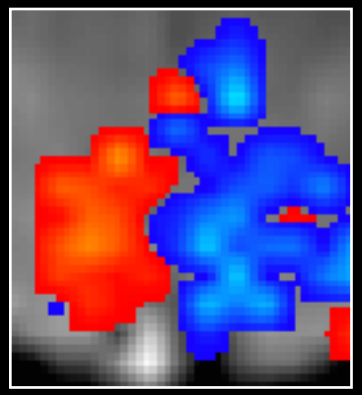
+ 2.5 s

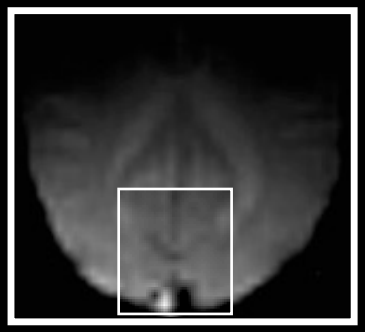
0 s

- 2.5 s





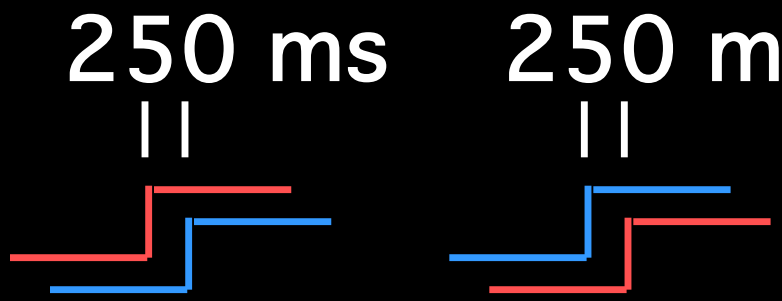




250 ms 250 ms

Right Hemifield

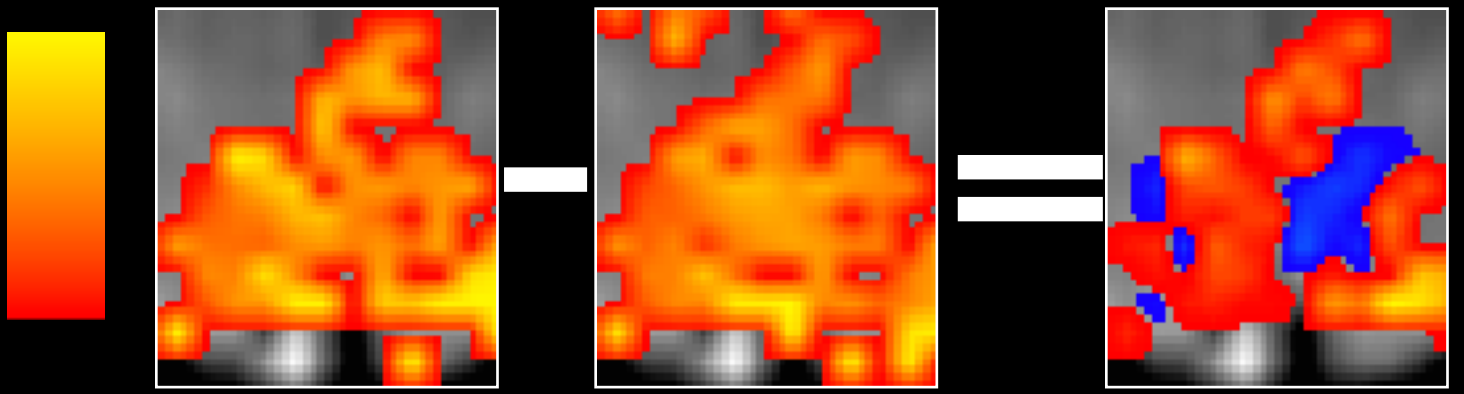
Left Hemifield



+ 2.5 s

0 s

- 2.5 s



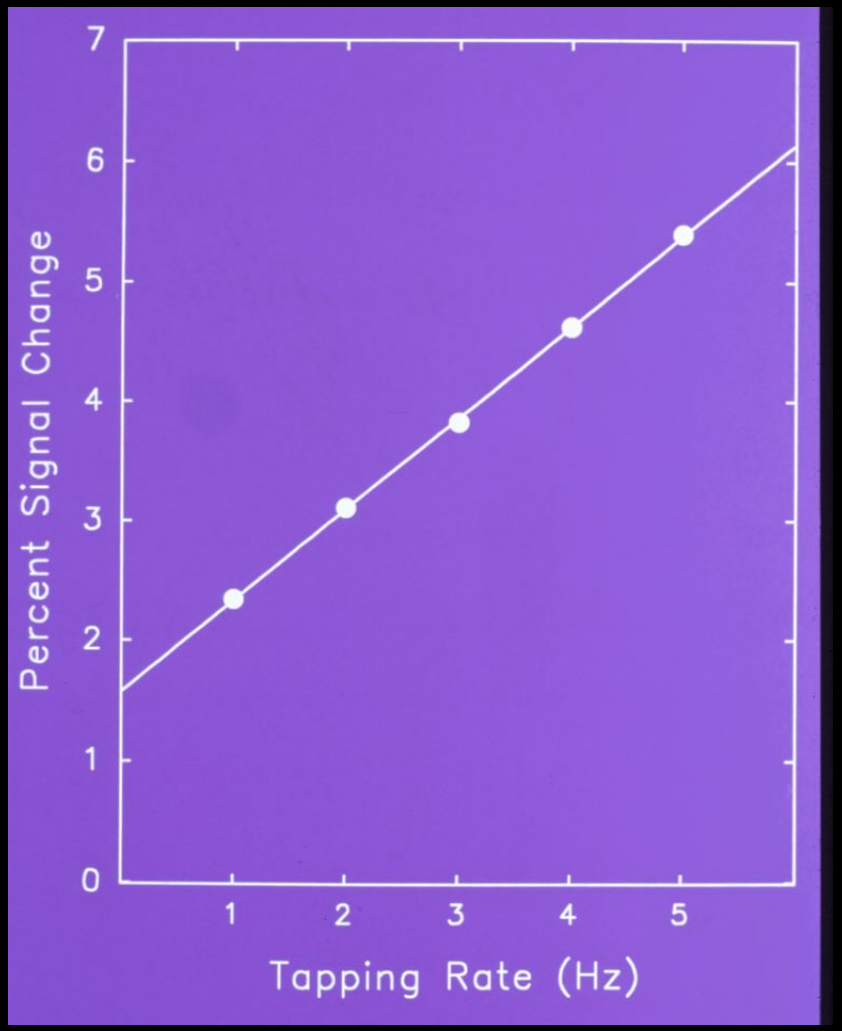
How Much?

Central Issue:

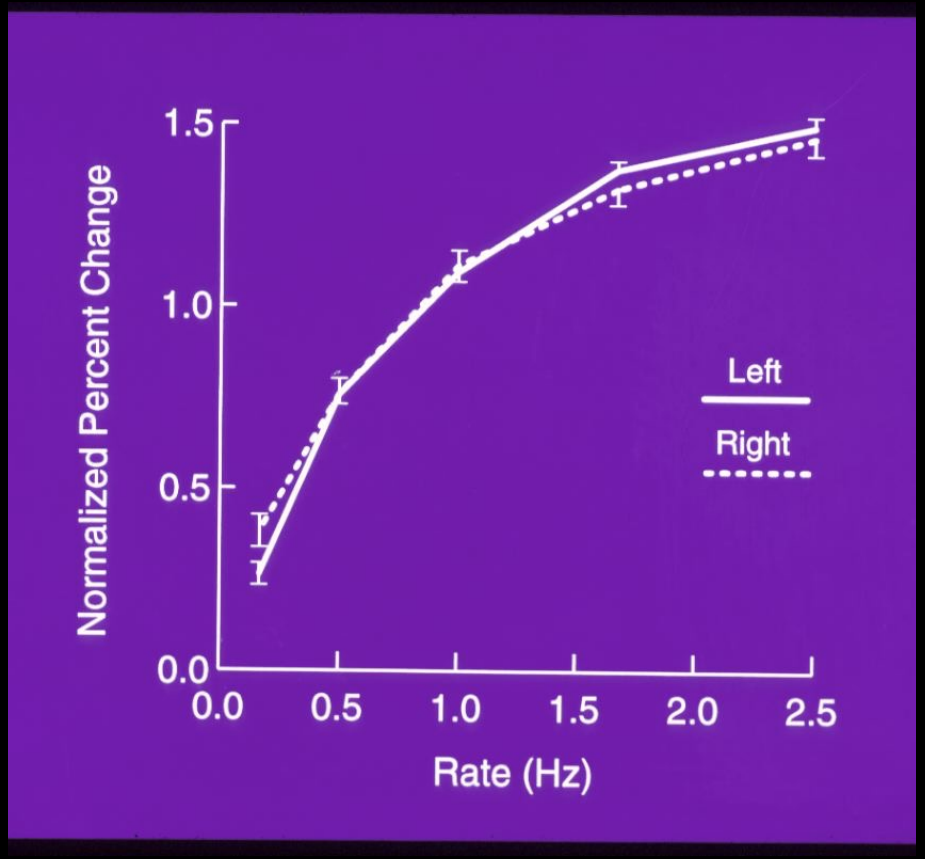
Spatial and temporal neuronal firing integration to create an fMRI signal change.

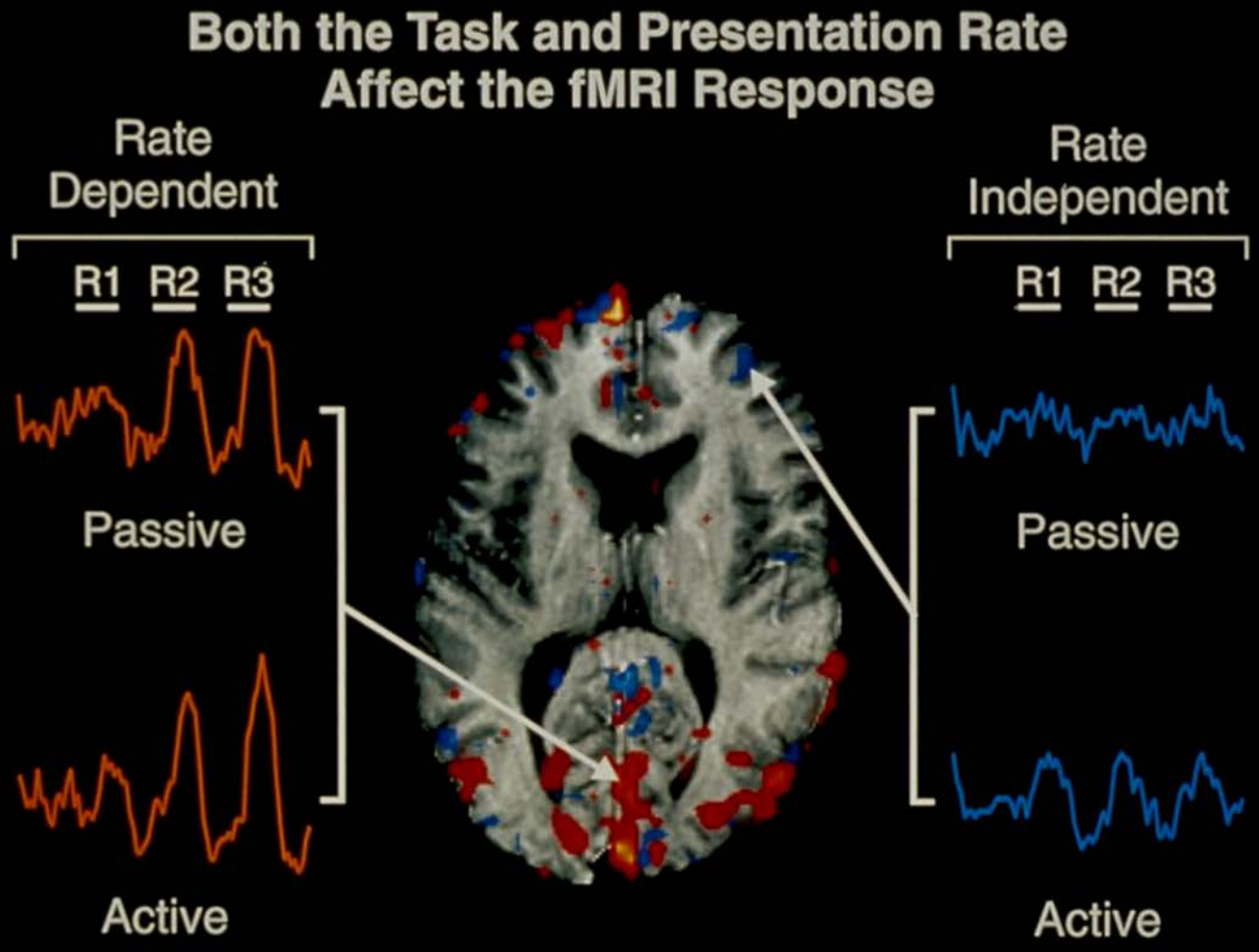
- is the hemodynamic response a linear system?
-what is the dynamic range?

Motor Cortex

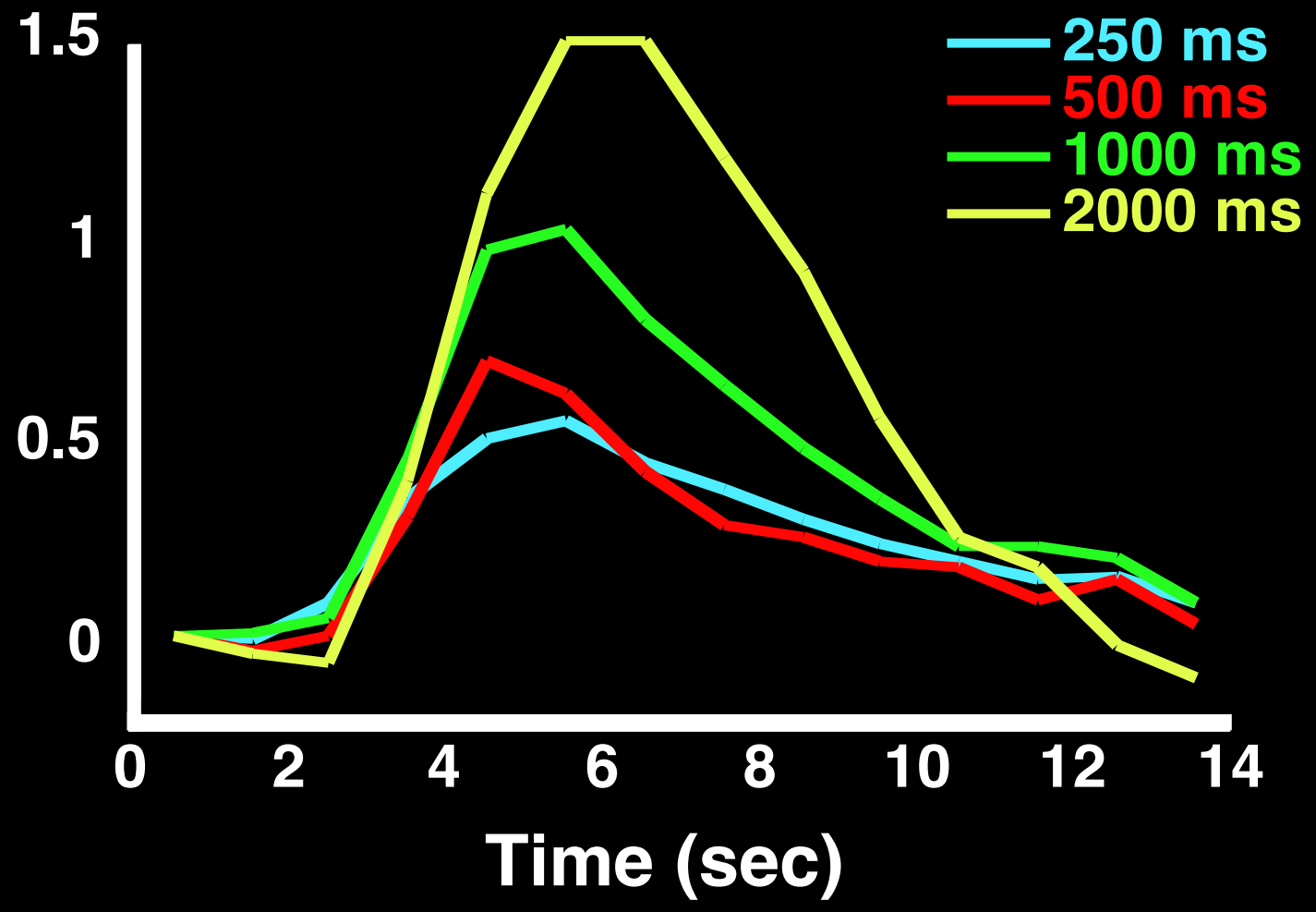


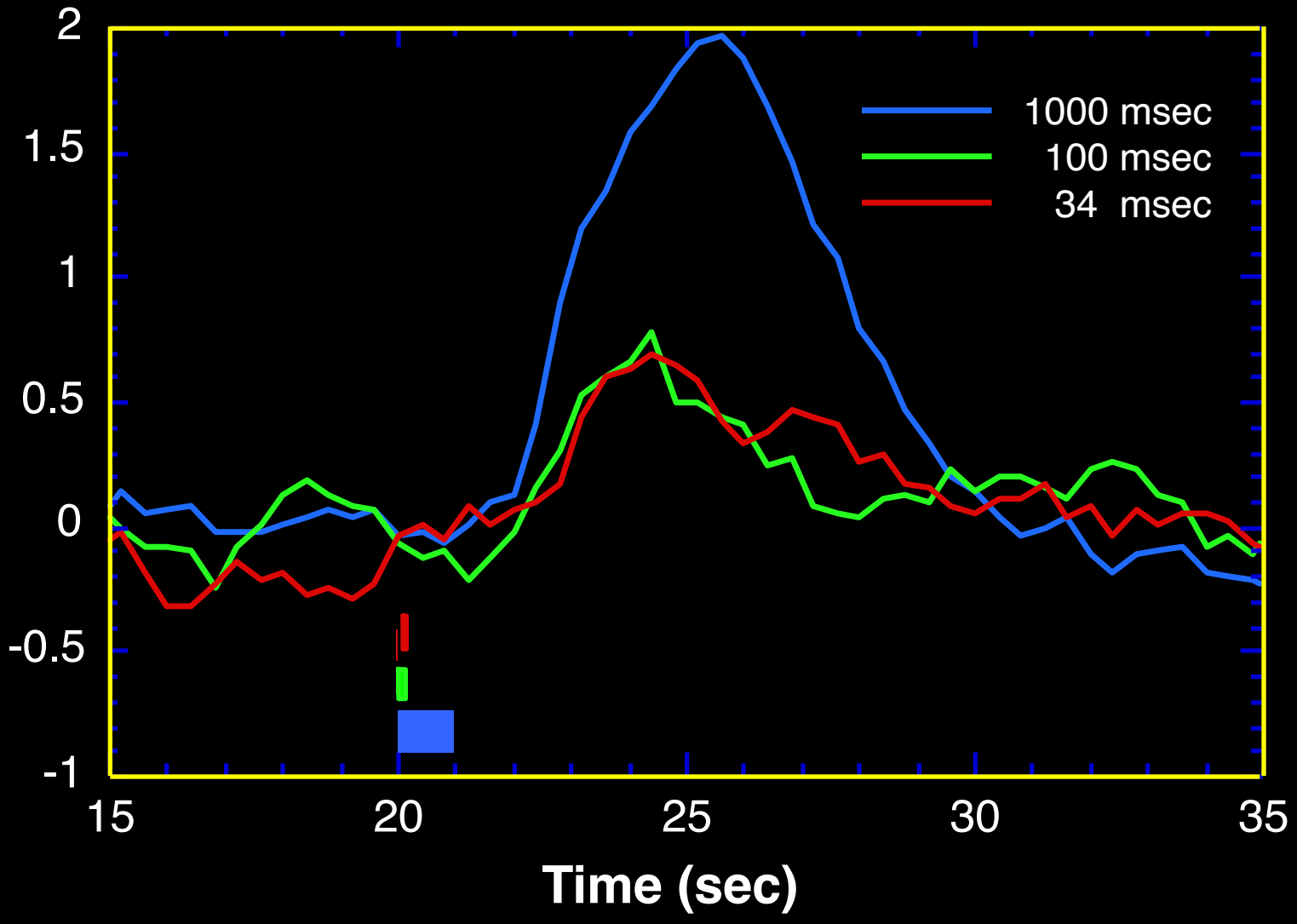
Auditory Cortex

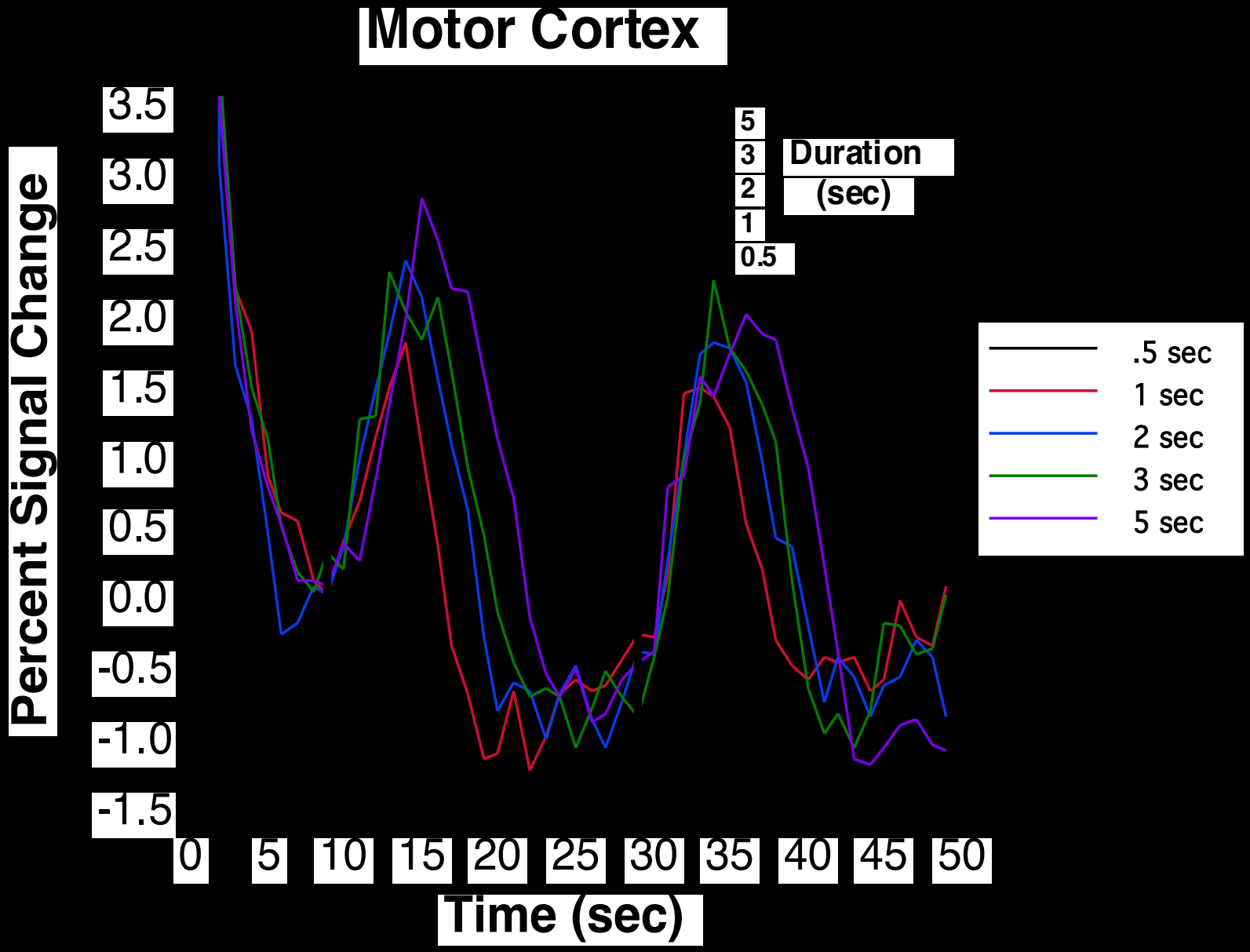



Both the Task and Presentation Rate
Affect the fMRI Response
Rate
Dependent
R1 R2 R3
Passive
Active
Rate
Independent
R1 R2 R3
Passive
Active

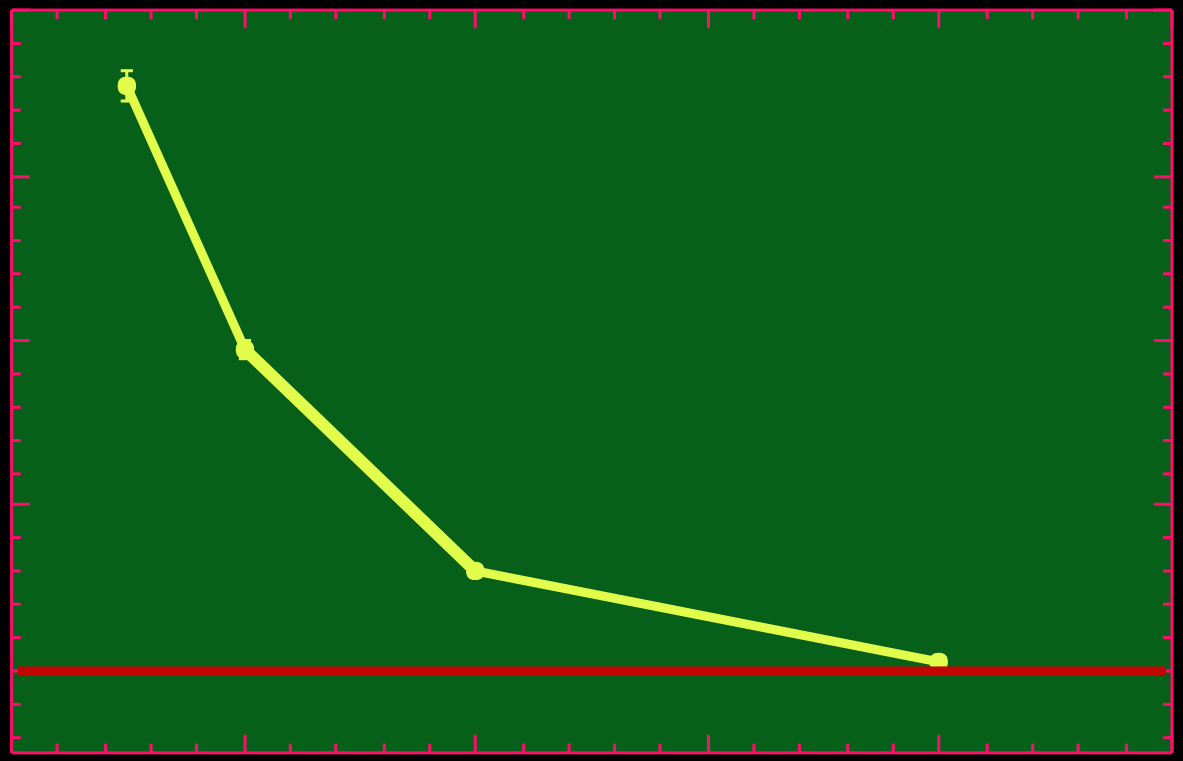
DeYoe et al.


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
Time (sec)
1000 msec
100 msec
34 msec


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

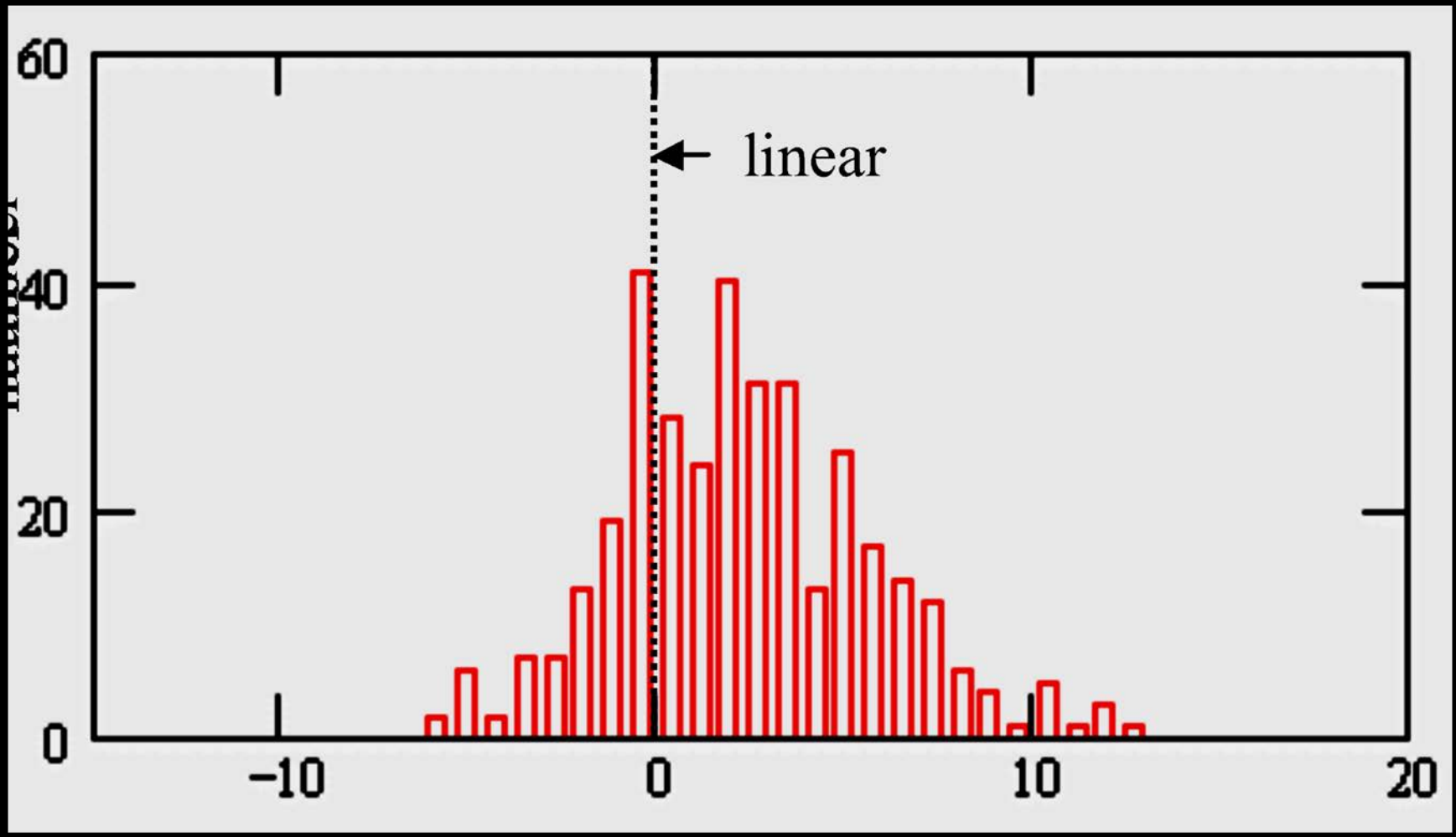
Stimululs - Duration Dependent Deviation from Linearity of the fMRI Response (Hemodynamic or Neuronal?)



>linear

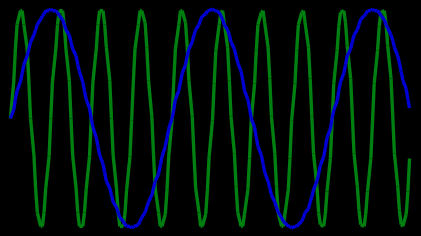
linear

Spatial Distribution of the Hemodynamic Response Linearity

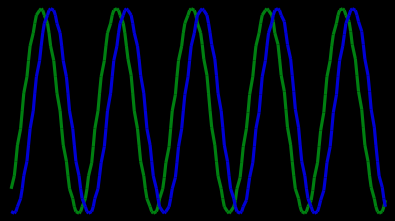


Neuronal Activation Input Strategies

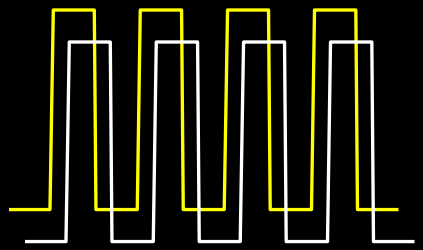
1. Block Design
2. Frequency Encoding



3. Phase Encoding



4. Single Event
5. Orthogonal Block Design



6. Free behavior Design.

Ultimate Limits?

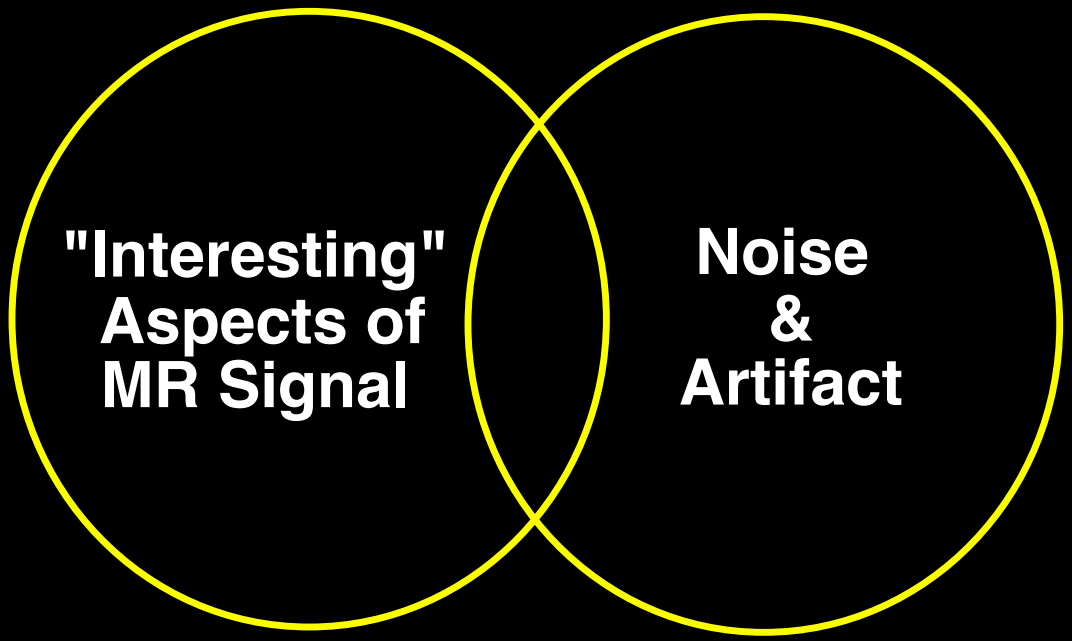
Spatial: 0.5 mm
Temporal: 100 ms
Interpretability…too early to tell, but hopeful

Neuronal Input Strategies

Peter A. Bandettini, Ph.D

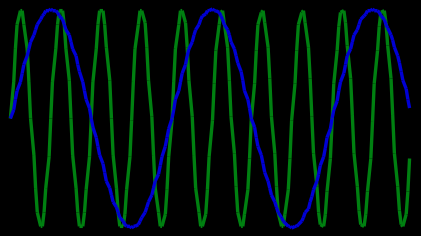
Unit on Functional Imaging Methods
Laboratory of Brain and Cognition
National Institute of Mental Health

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

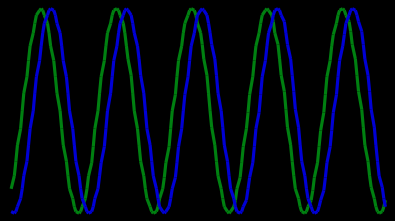


Neuronal Activation Input Strategies

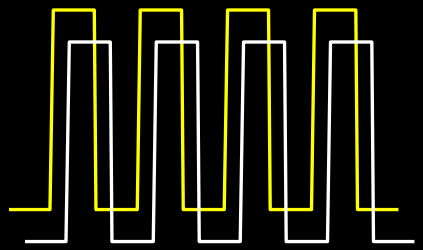
1. Block Design
2. Frequency Encoding



3. Phase Encoding



4. Single Event
5. Orthogonal Block Design

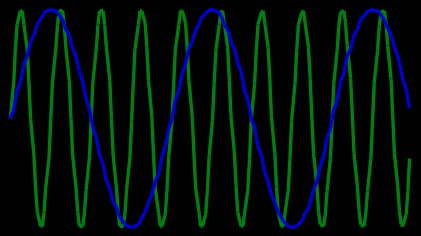


6. Free behavior Design.

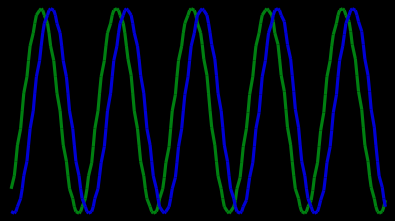
Neuronal Activation Input Strategies

1. Block Design

2. Frequency Encoding

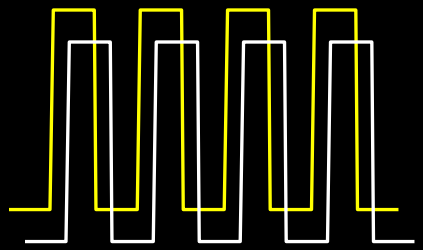


3. Phase Encoding



4. Single Event

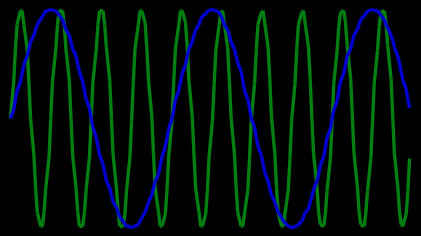
5. Orthogonal Block Design



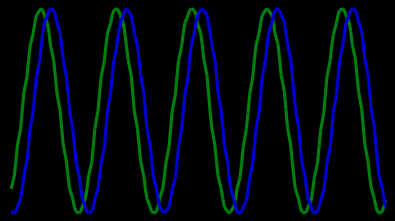
6. Free behavior Design.

Neuronal Activation Input Strategies

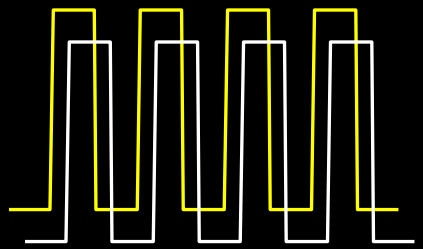
1. Block Design
2. Frequency Encoding



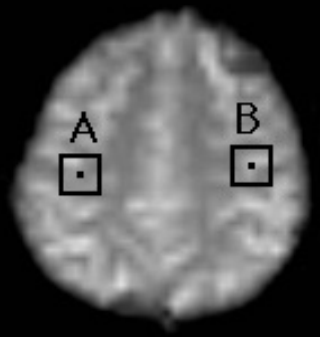
3. Phase Encoding

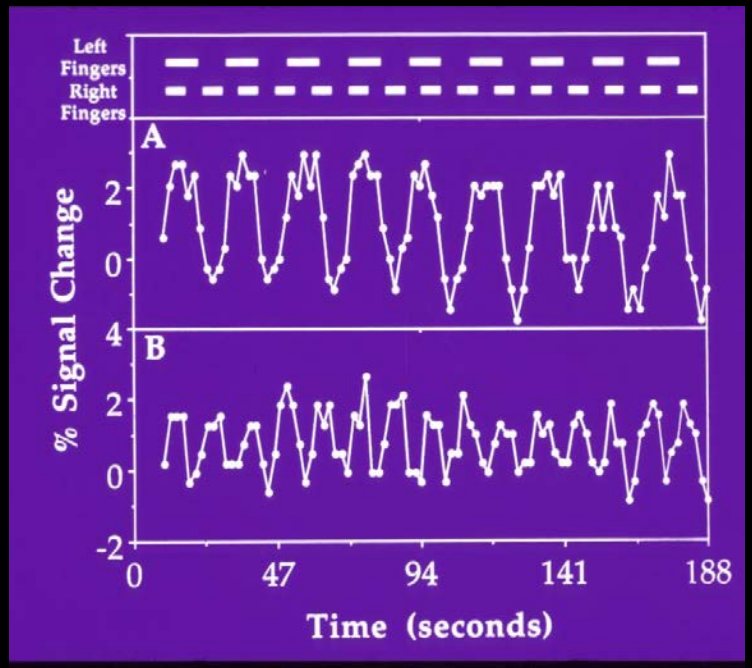


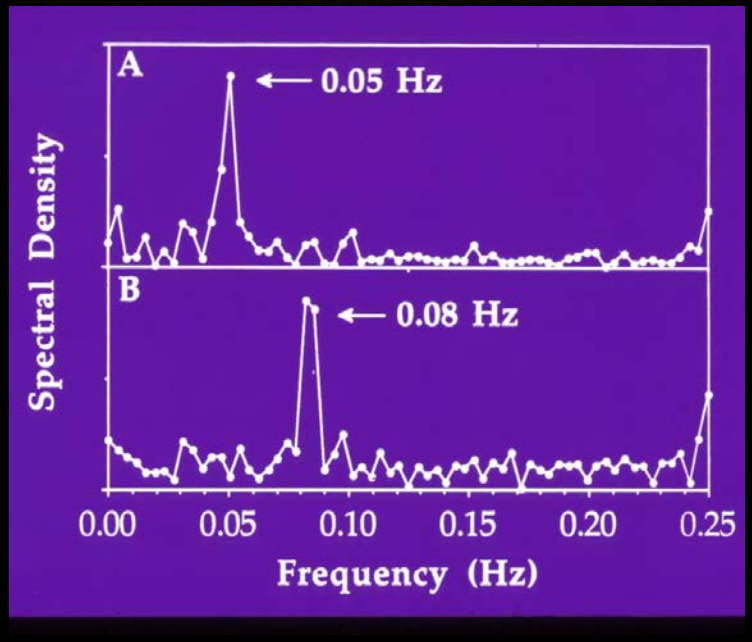
4. Single Event
5. Orthogonal Block Design

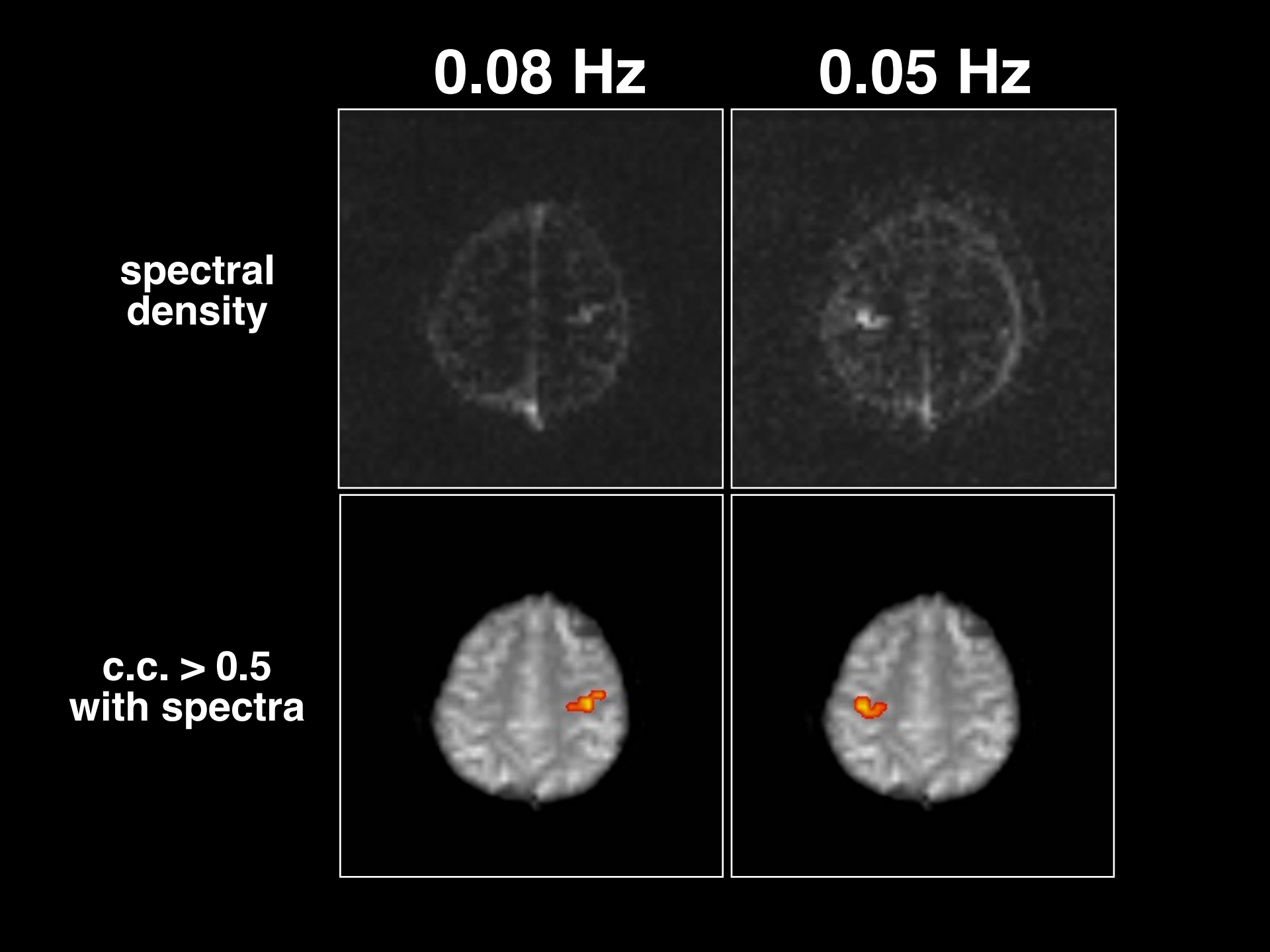


6. Free behavior Design.


A
B

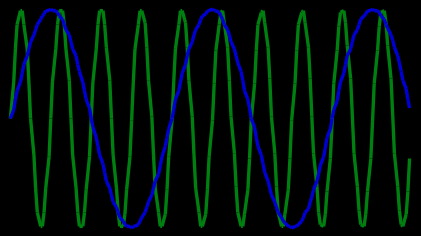

Left Fingers
Right Fingers
A
B
% Signal Change
2
0
4
2
0
-2
0
47
94
141
188
Time (seconds)


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

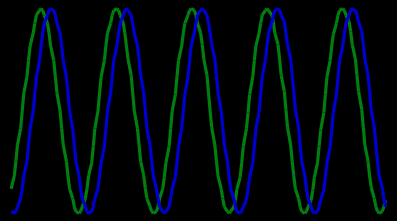

0.08 Hz
0.05 Hz
spectral density
c.c. > 0.5 with spectra

Neuronal Activation Input Strategies

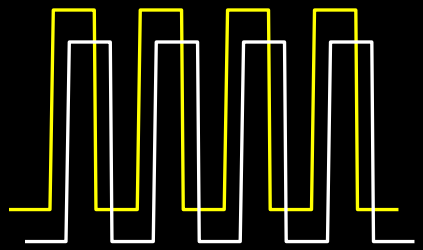
1. Block Design
2. Frequency Encoding



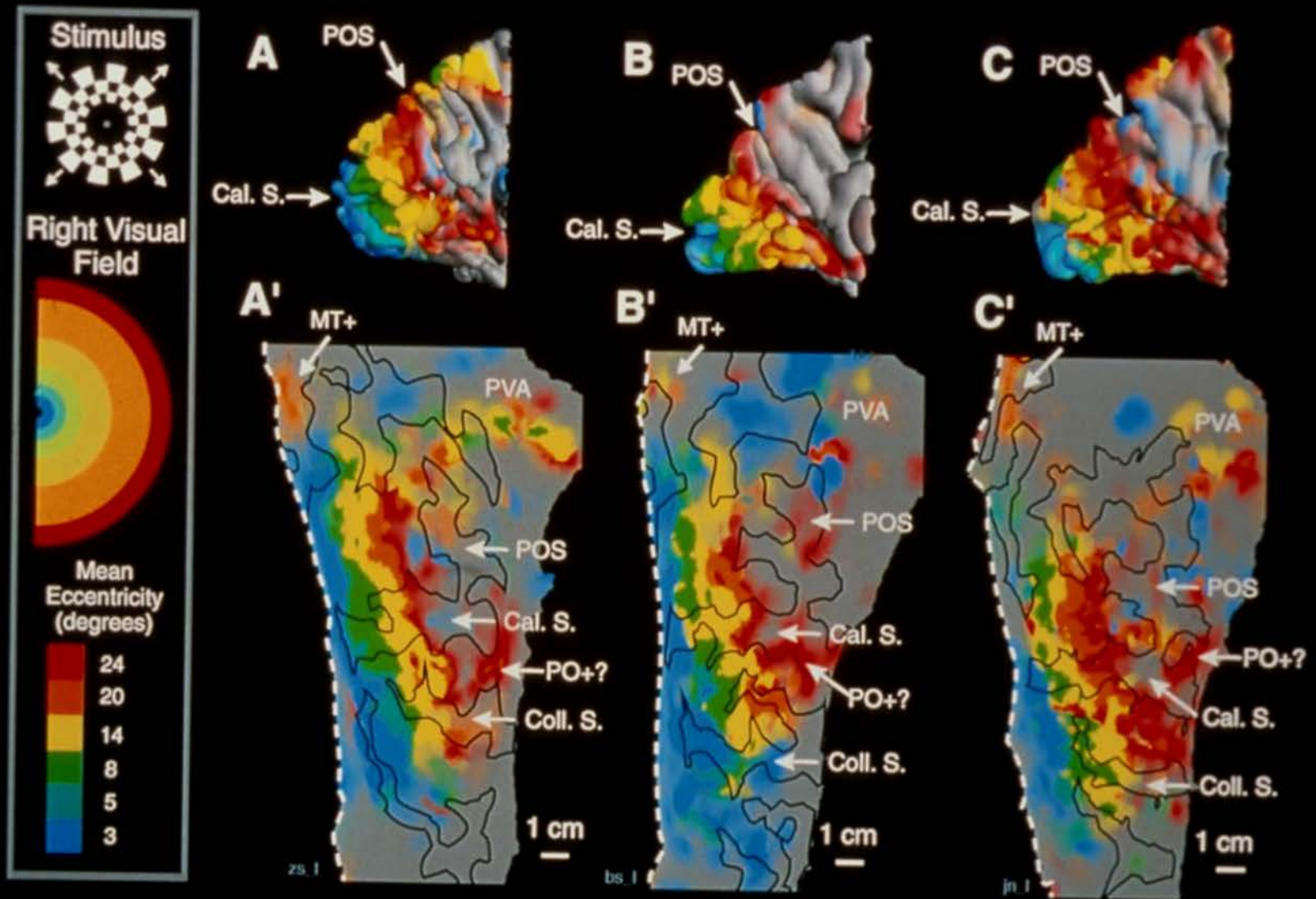
3. Phase Encoding

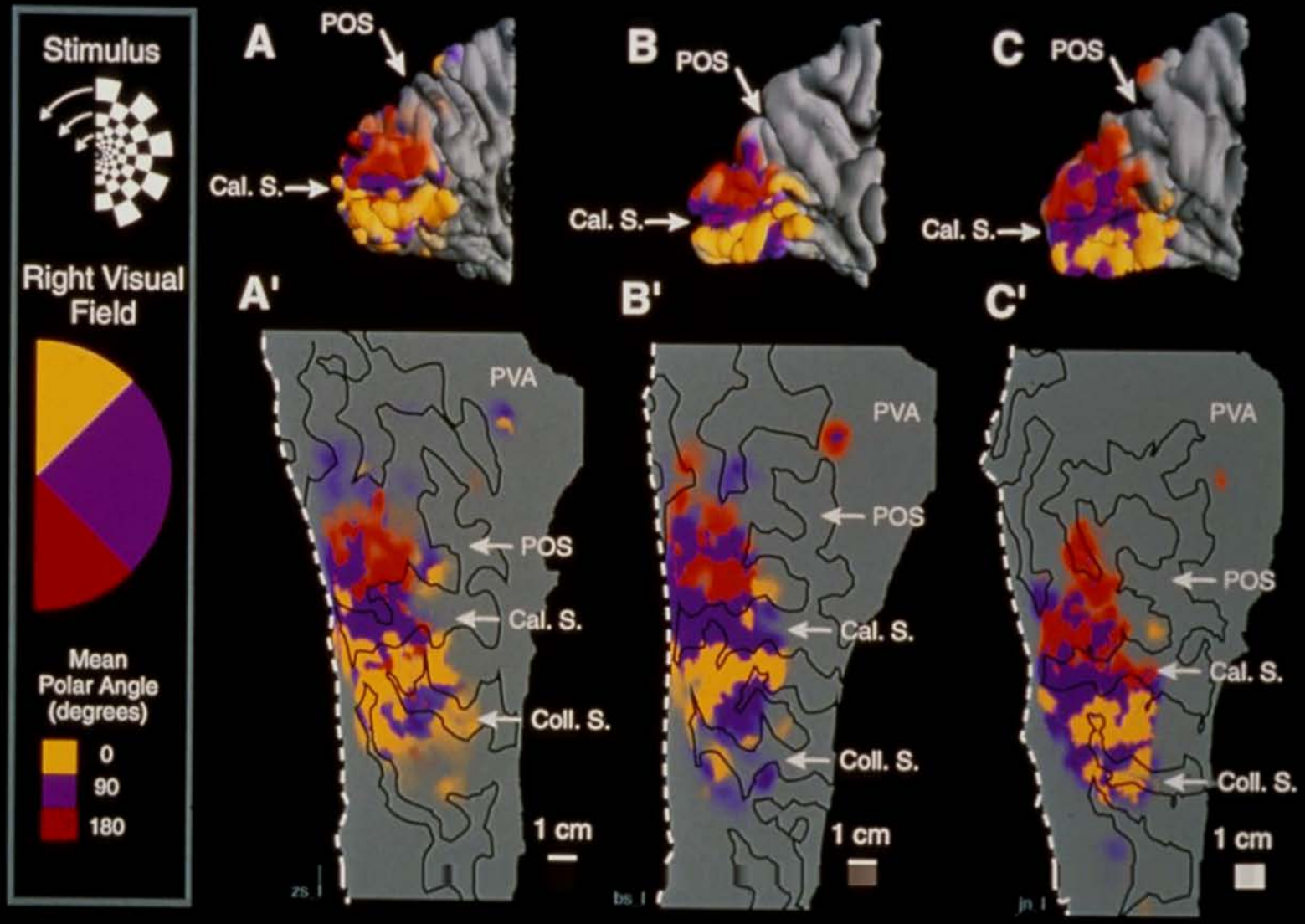


4. Single Event
5. Orthogonal Block Design



6. Free behavior Design.

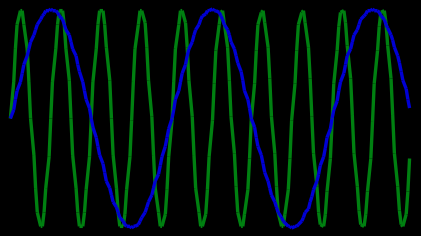

Stimulus
Right Visual Field
Mean Eccentricity (degrees)
24
20
14
8
5
3
A
POS
Cal. S.
B
POS
Cal. S.
C
POS
Cal. S.
A'
MT+
PVA
POS
Cal. S.
PO+?
Coll. S.
1 cm
zs_l
B'
MT+
PVA
POS
Cal. S.
PO+?
Coll. S.
1 cm
bs_l
C'
MT+
PVA
POS
PO+?
Cal. S.
Coll. S.
1 cm
jn_l


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
B'
PVA
POS
Cal. S.
Coll. S.
1 cm
bs
C'
PVA
POS
Cal. S.
Coll. S.
1 cm
jn

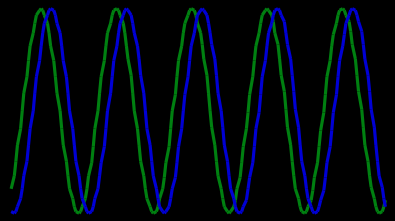
Neuronal Activation Input Strategies

1. Block Design

2. Frequency Encoding

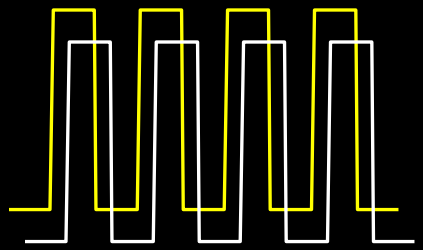


3. Phase Encoding



4. Single Event

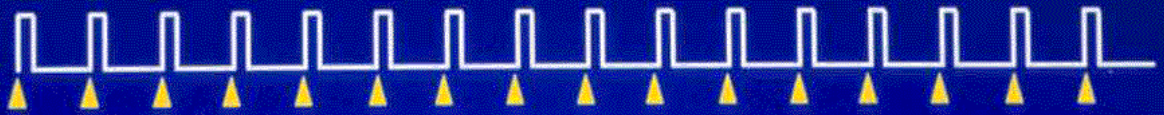
5. Orthogonal Block Design

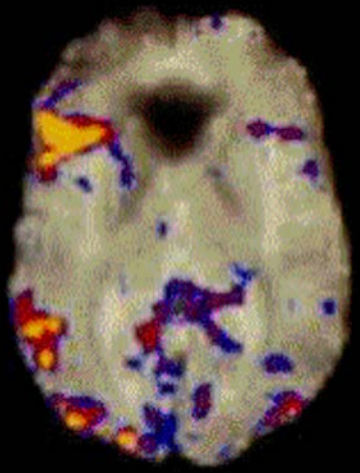


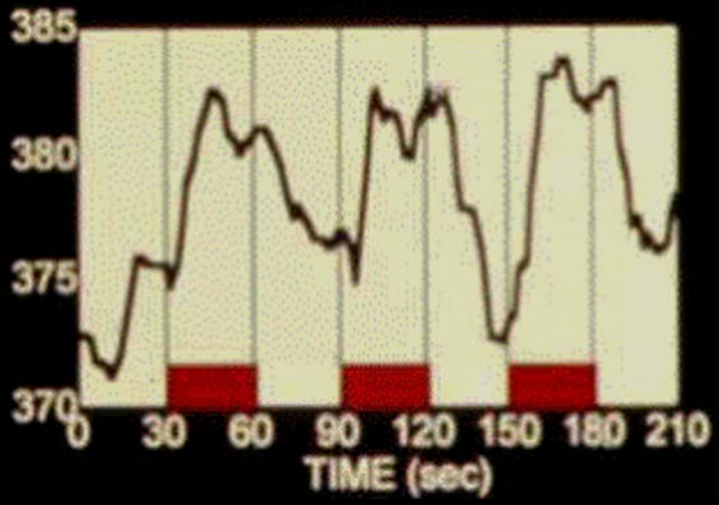
6. Free behavior Design.

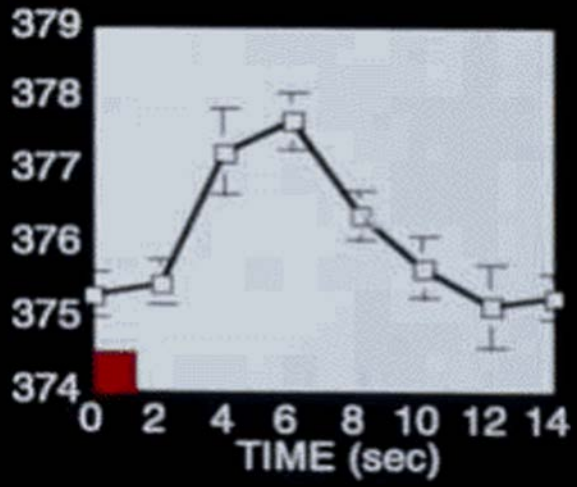
BLOCKED:

SINGLE TRIAL:

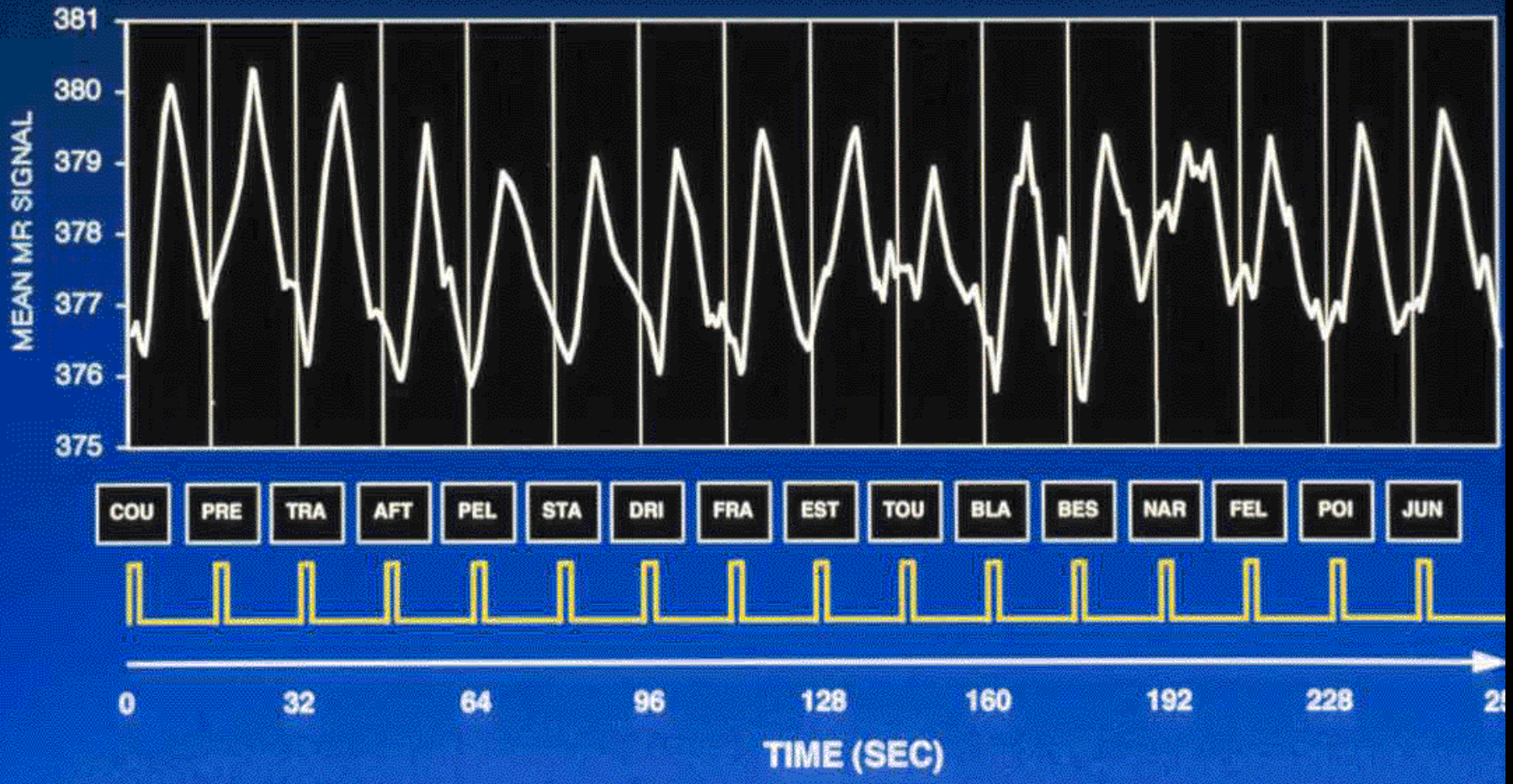




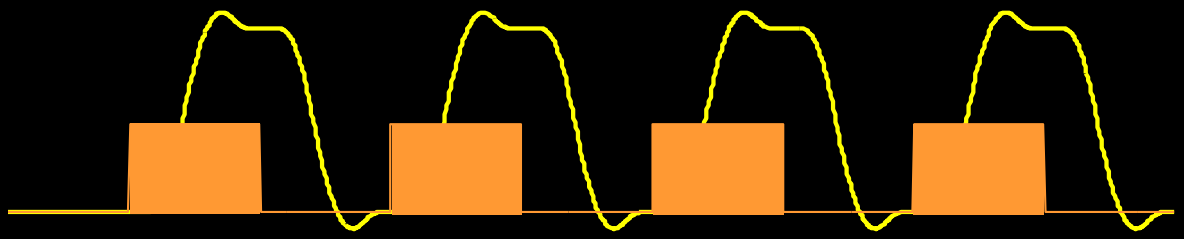


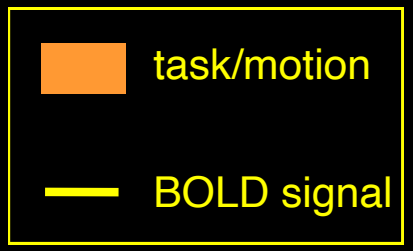


"Single-Trial" Response Across an Averaged Data Set

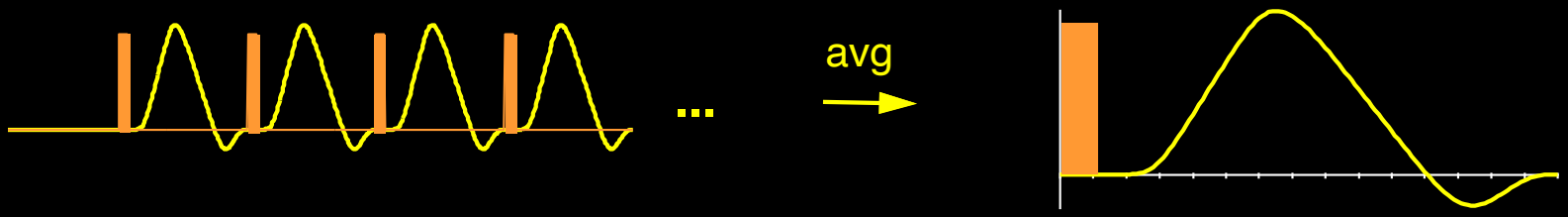


Block-trial

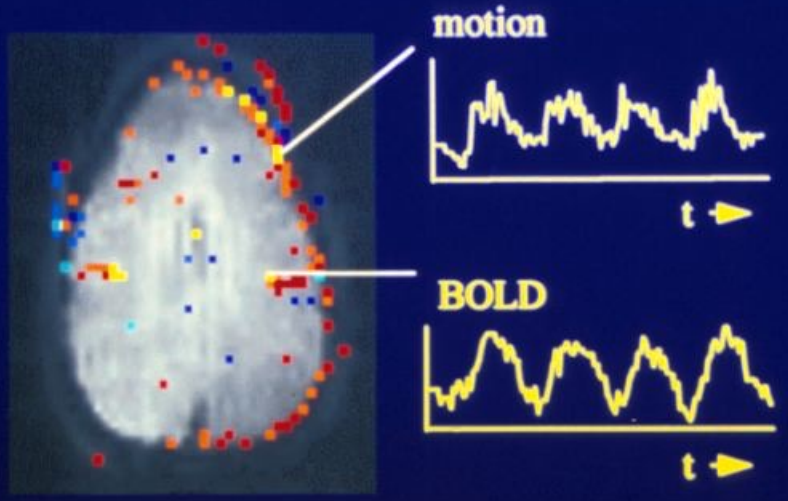


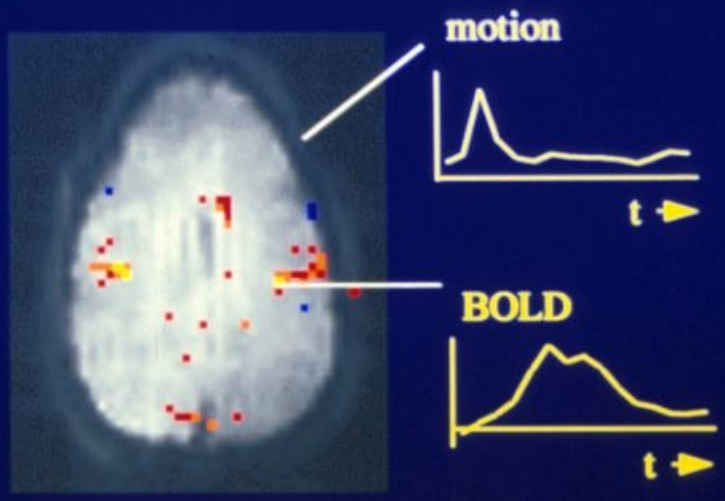


Single-trial (brief stimulus)



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





"block-trial" paradigm

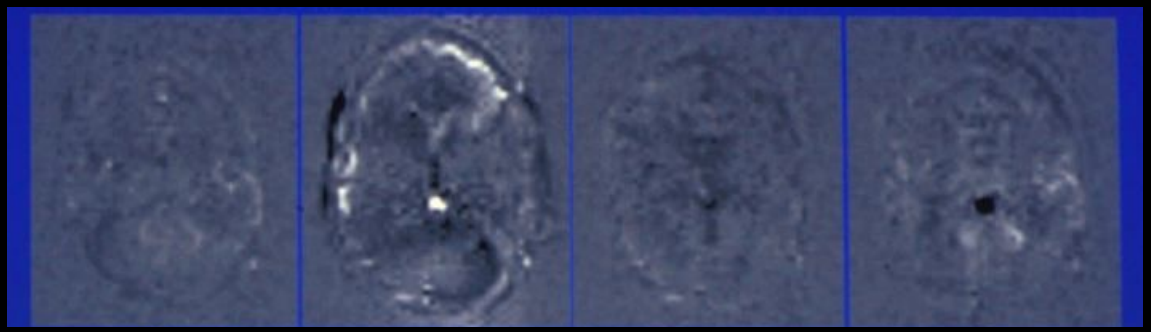
Motion induced signal changes resemble functional (BOLD) signal changes

"single-trial" paradigm

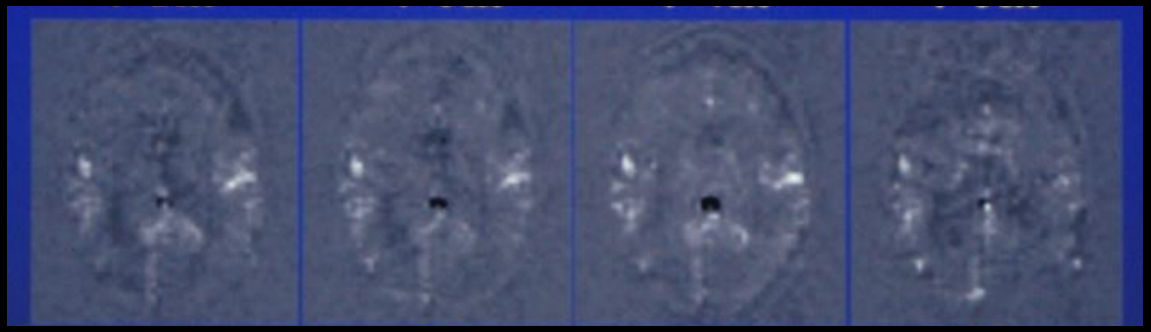
Motion induced and BOLD signal changes are separated in time

R.M. Birn, et al.

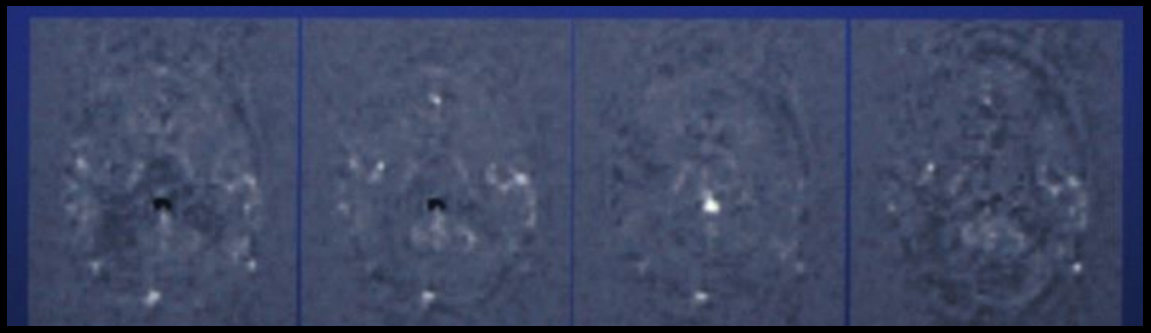
Overt Word Production



2 3 4 5

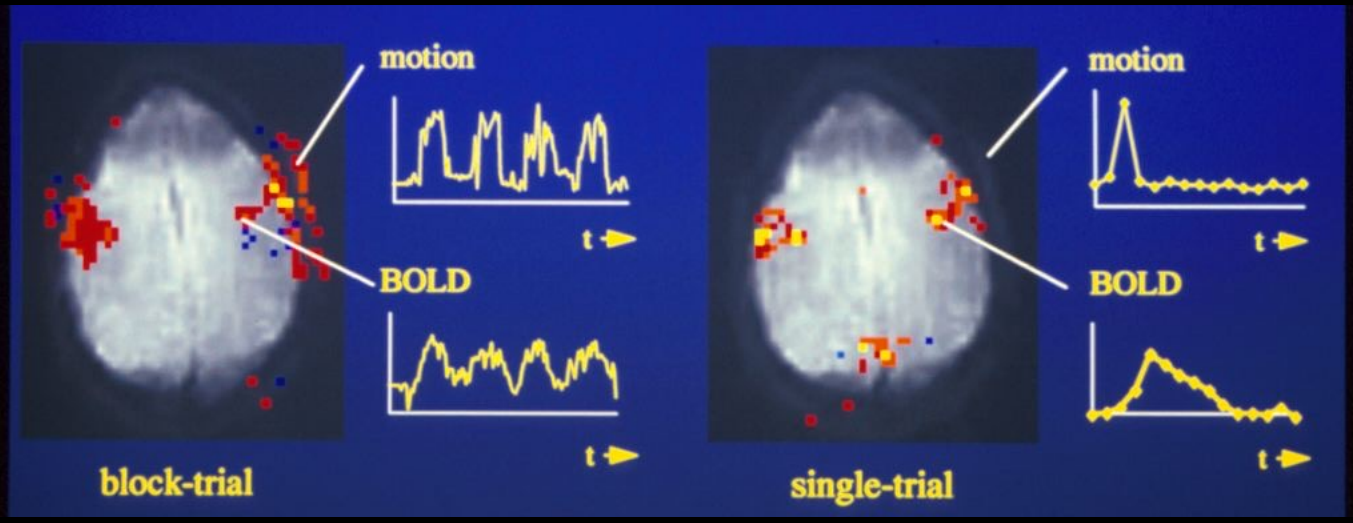


6 7 8 9

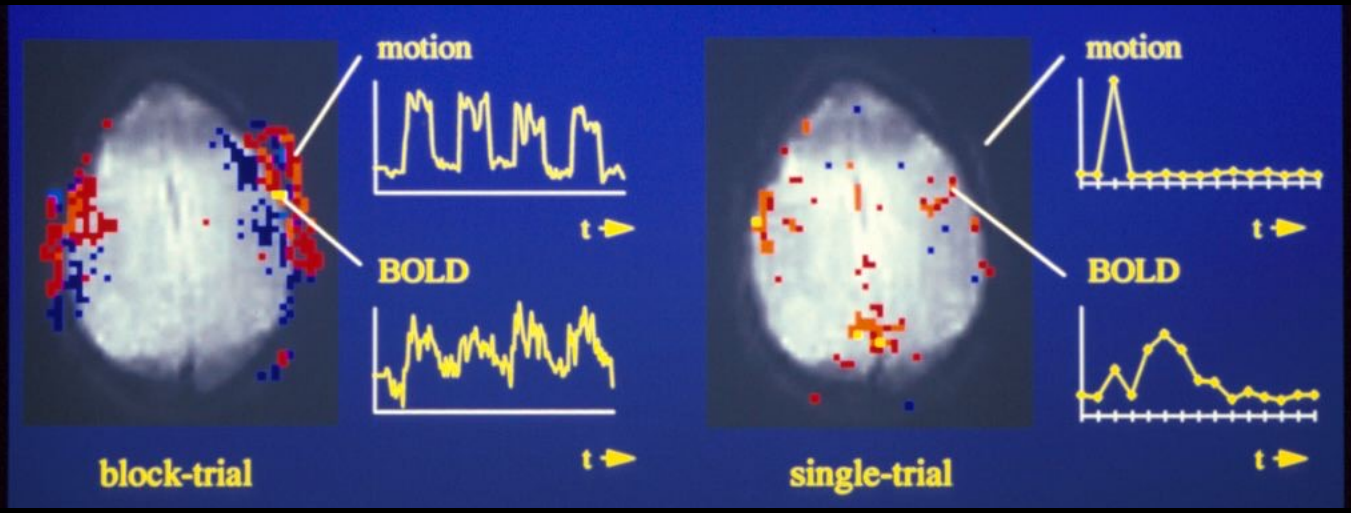


10 11 12 13

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

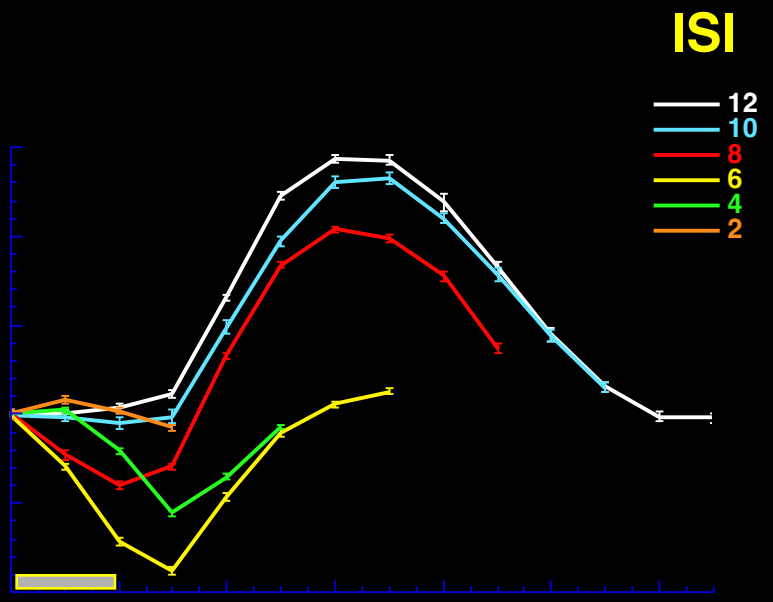
8, 2

6, 2

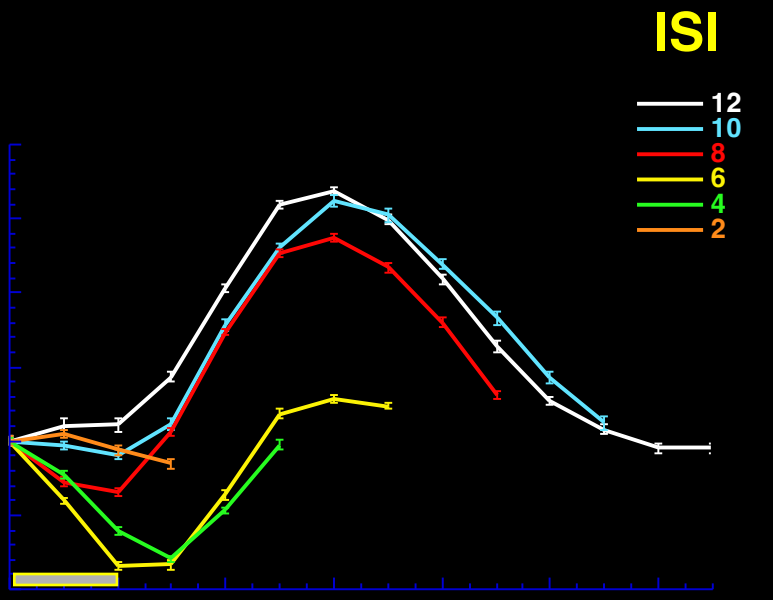
4, 2

2, 2

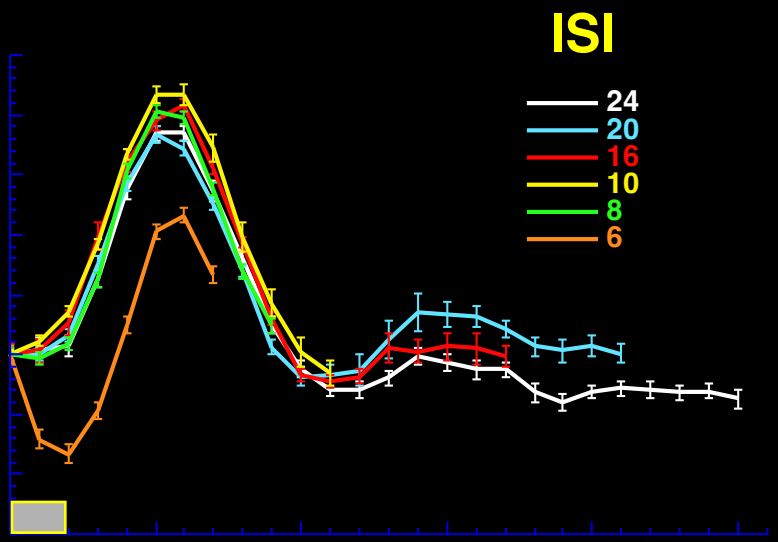
Motor Cortex



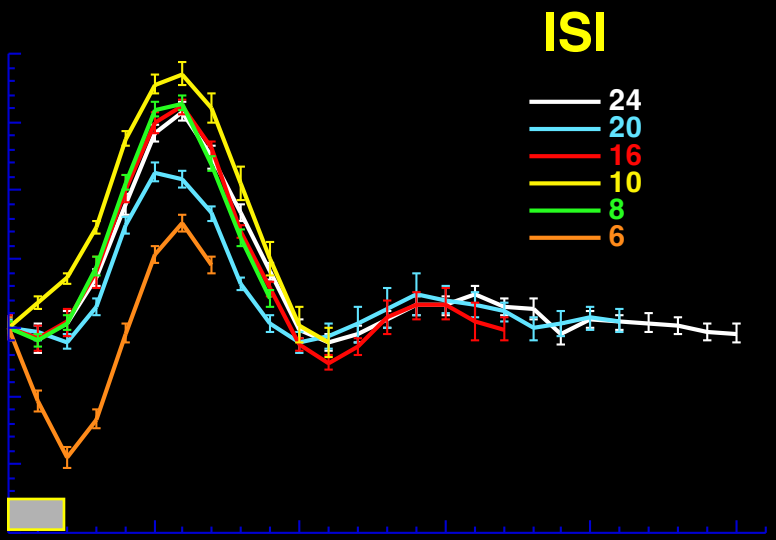
Visual Cortex



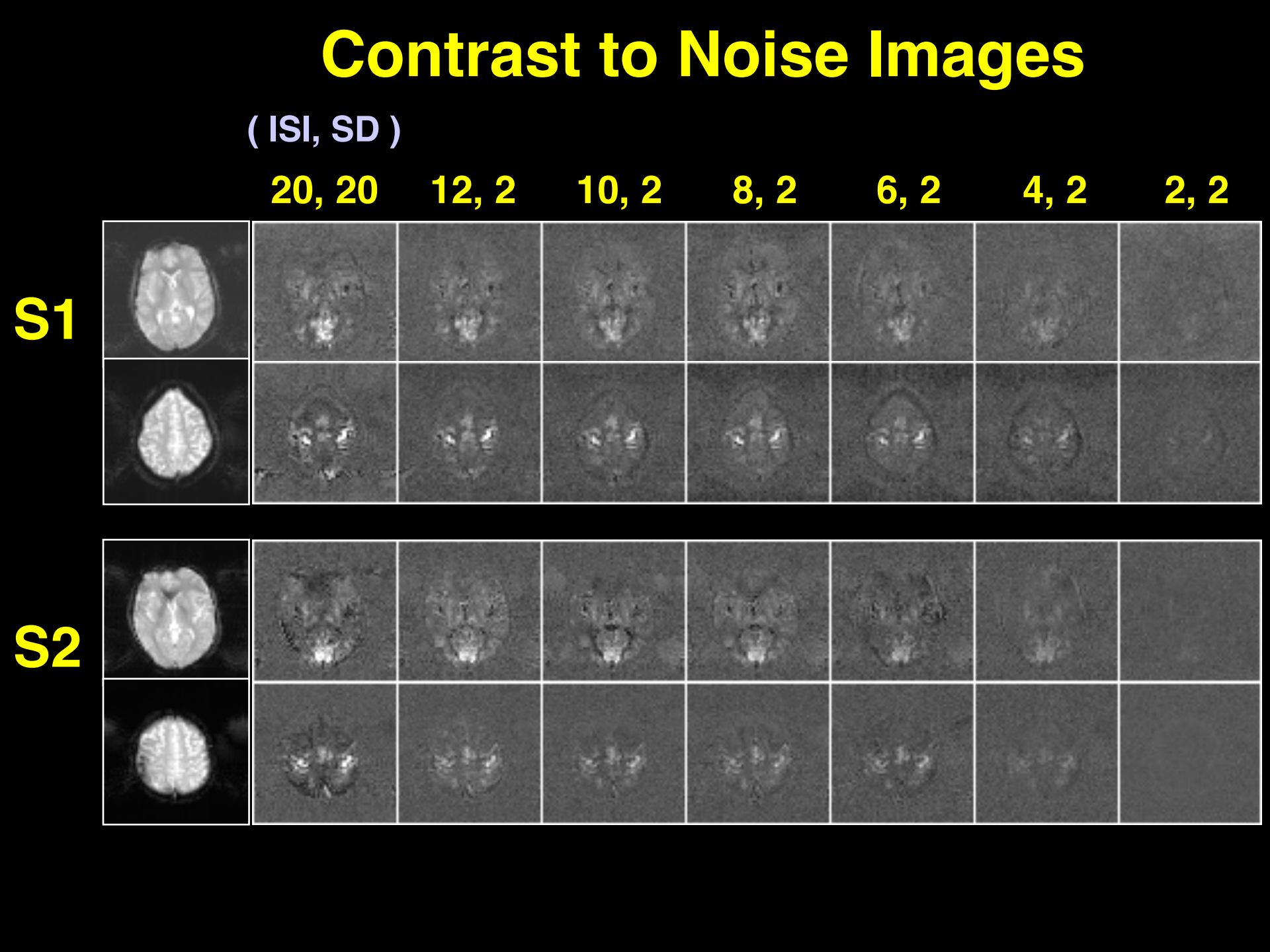
Motor Cortex



Visual Cortex



Contrast to Noise Images

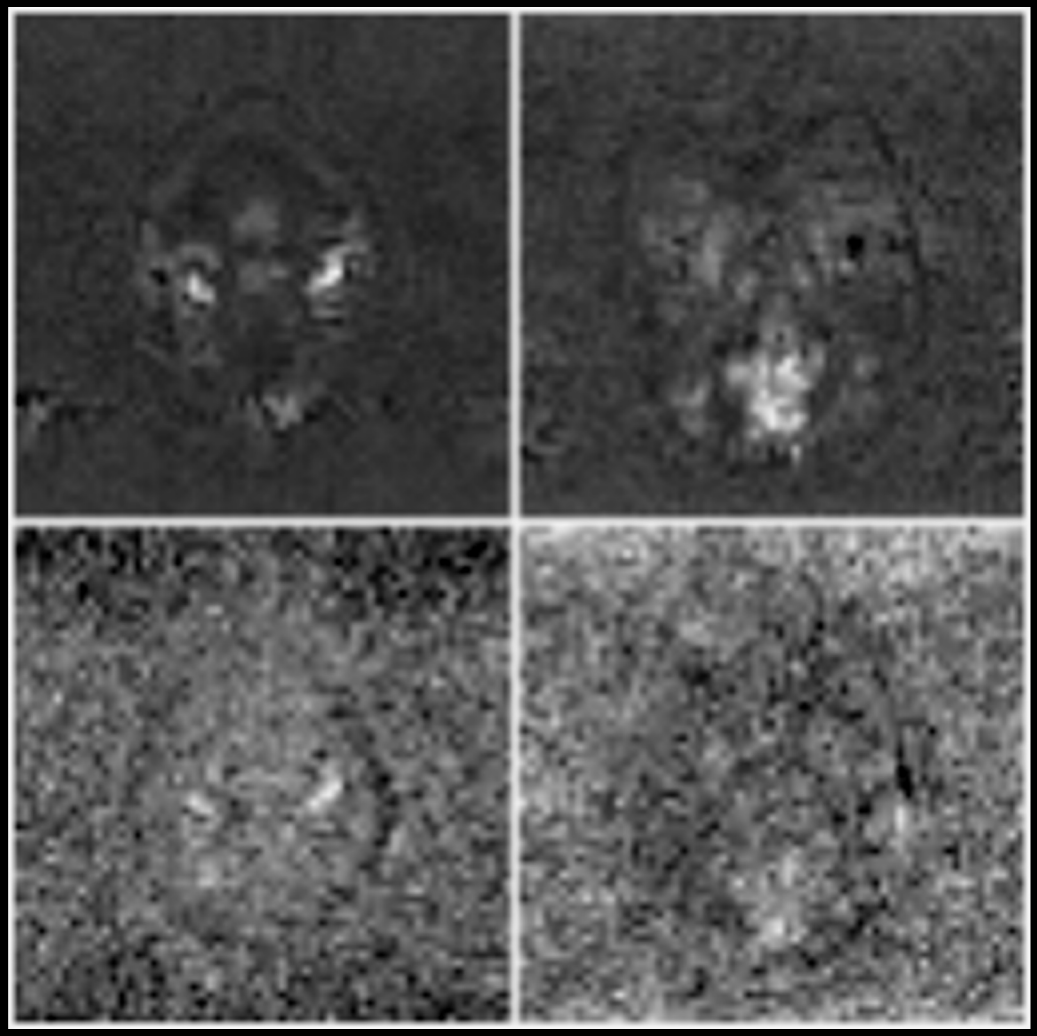


Motor Visual

(ISI, SD)

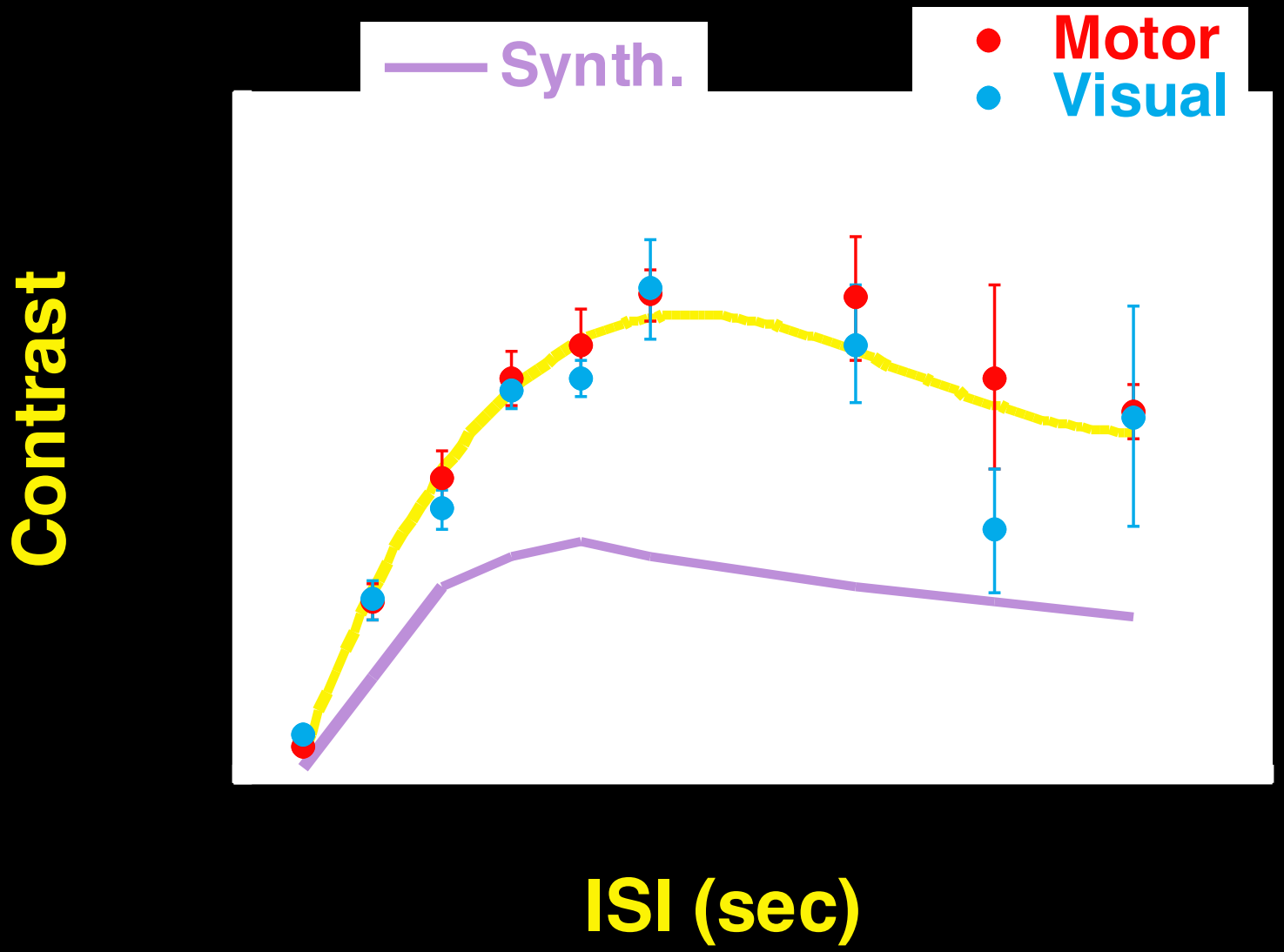
20, 20

2, 2



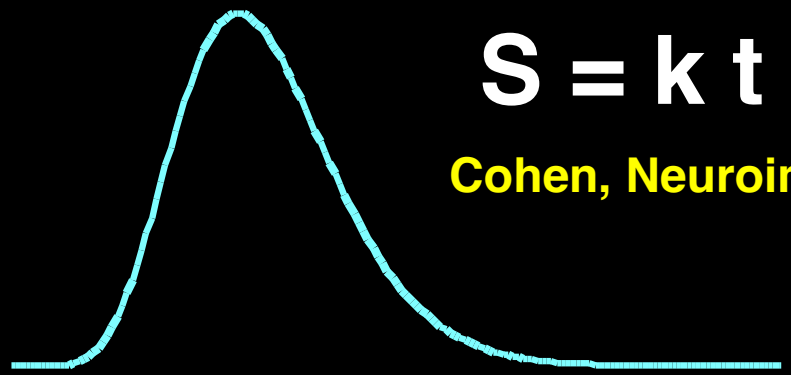
Relative differences in activation intensities may reflect spatial differences in hemodynamic responsivity. (draining veins vs. capillaries).

Functional Contrast



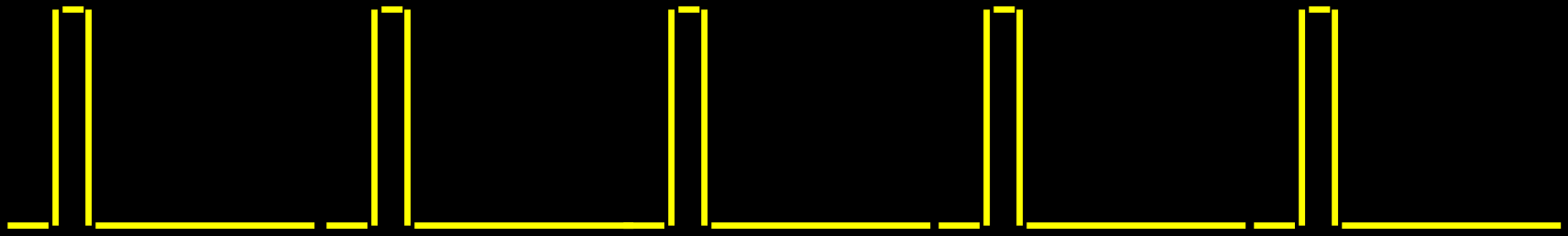
(Block design = 1)

Response Synthesis



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

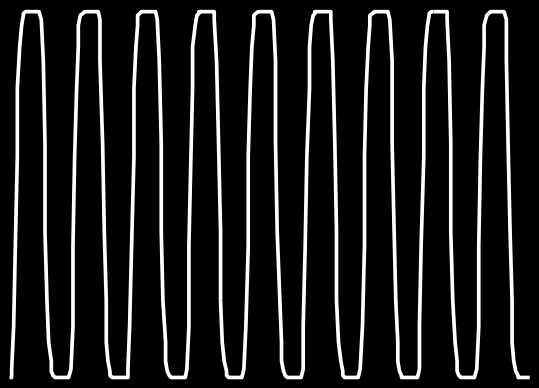
Cohen, Neuroimage 6, 93-103 (1997)



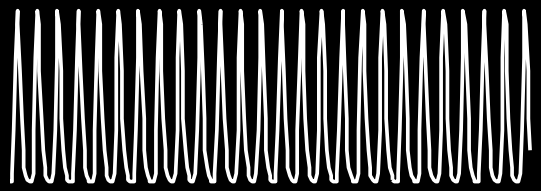
Synthesized Responses

ISI, Dur

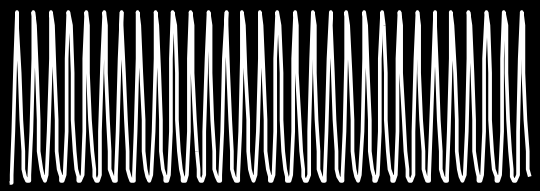
20, 20



12, 2

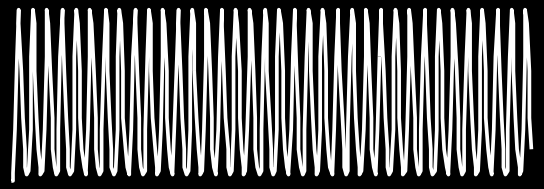


10, 2

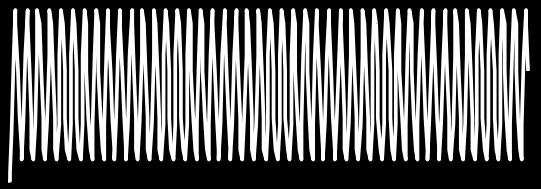


ISI, Dur

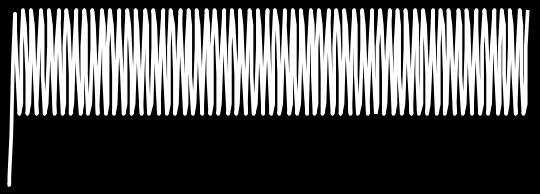
8, 2



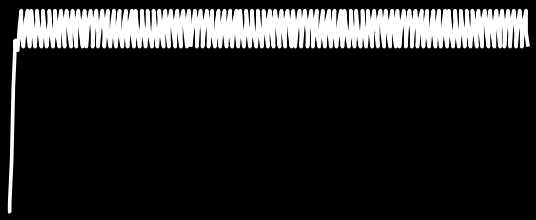
6, 2



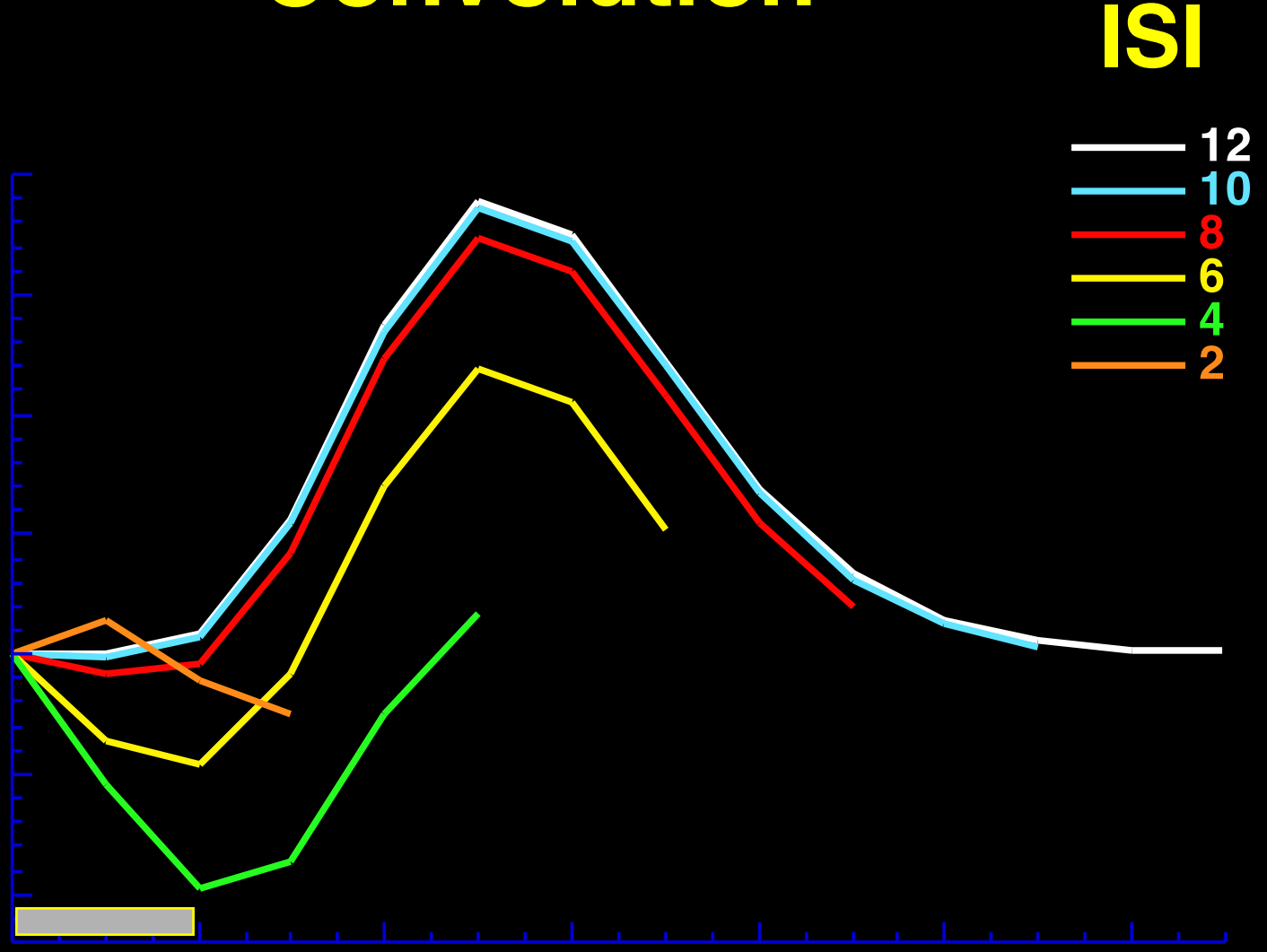
4, 2



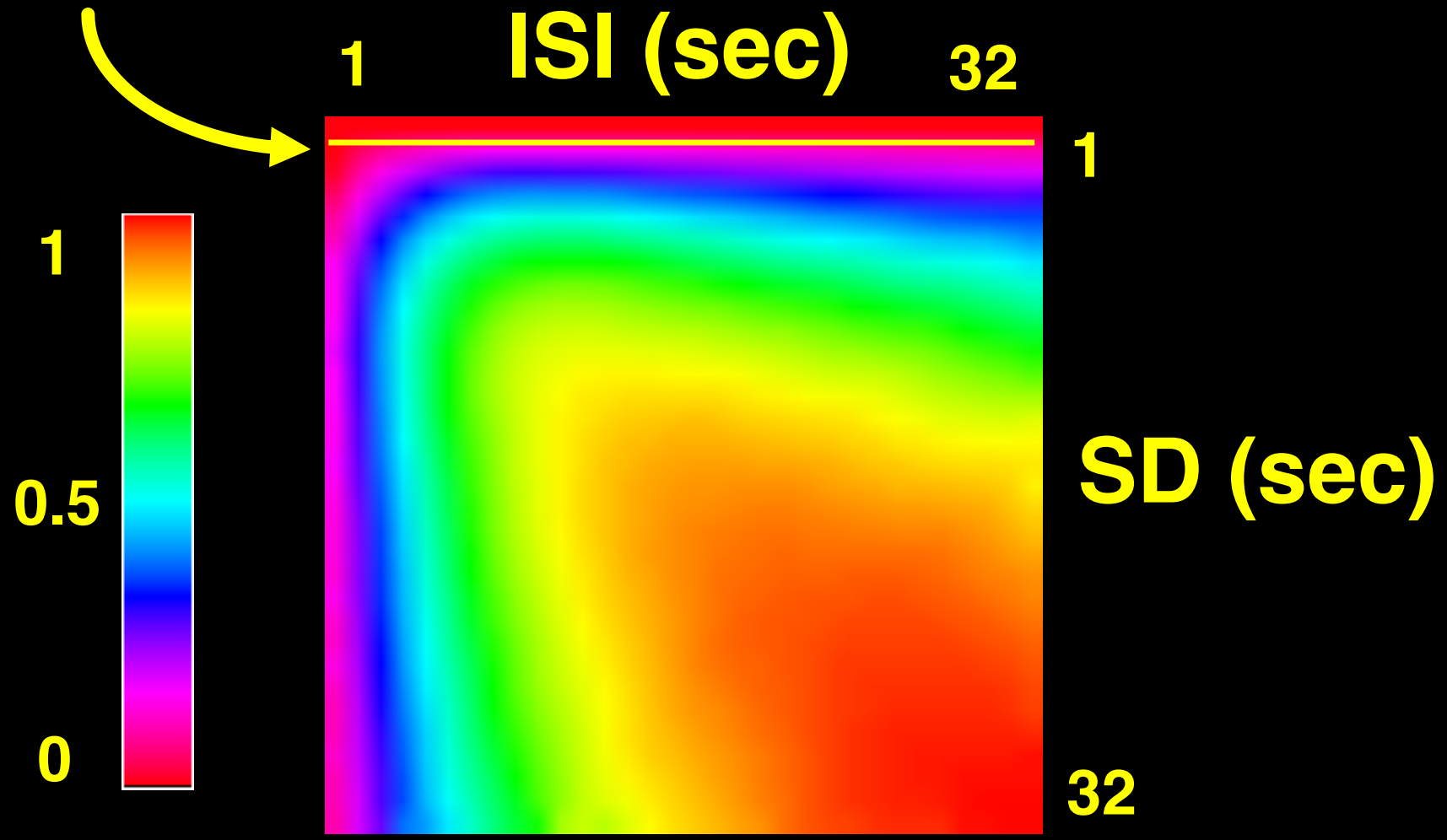
2, 2



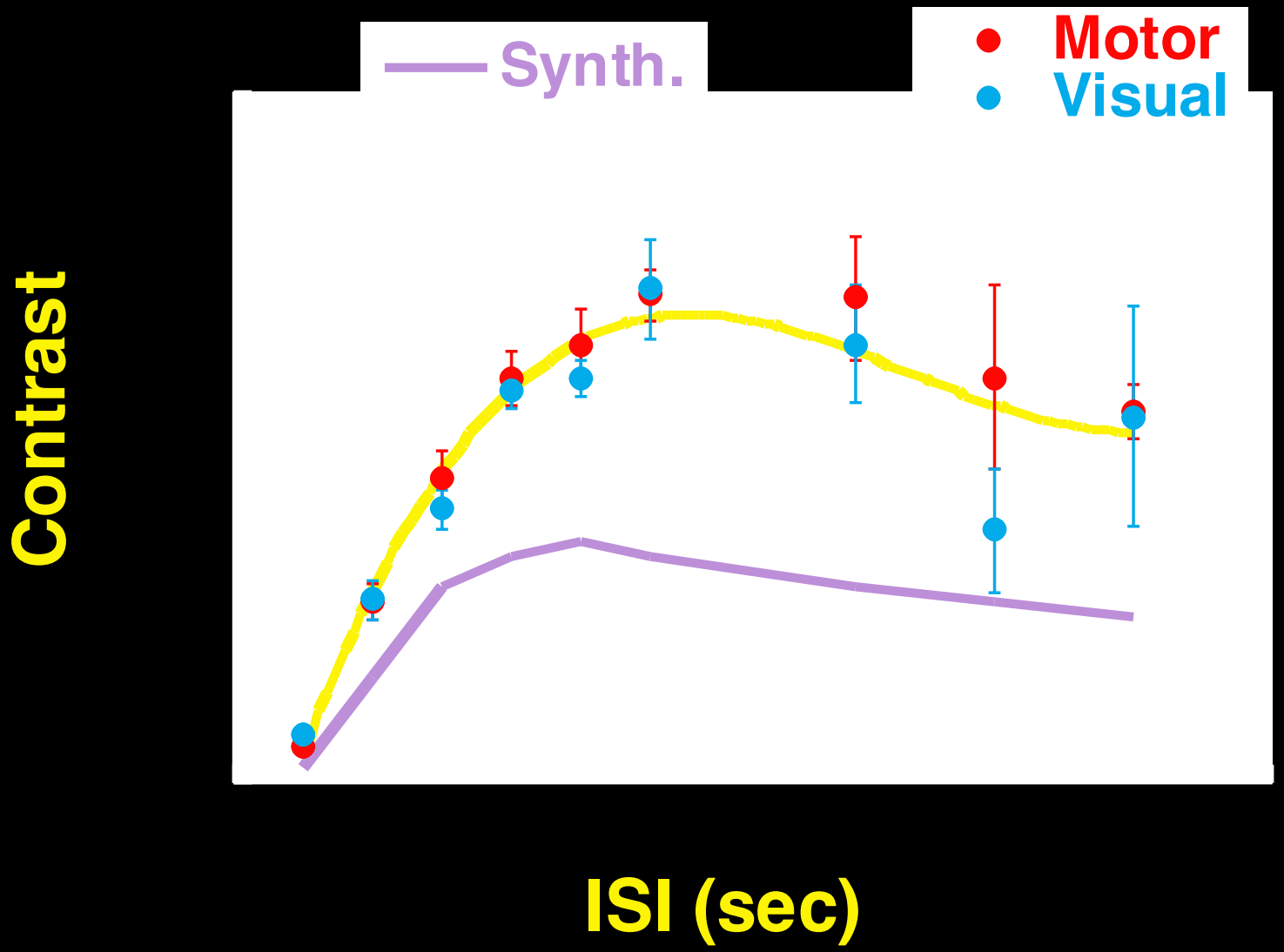
Convolution



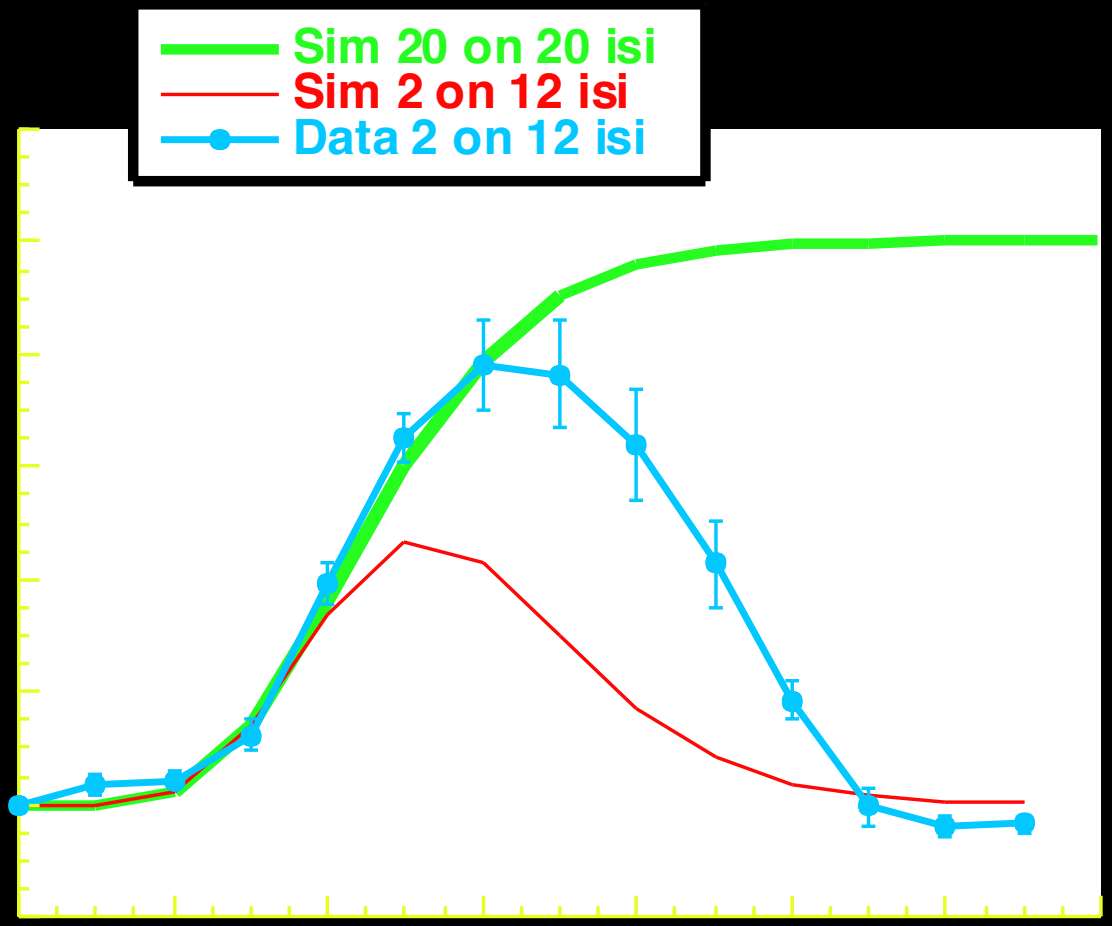
Functional Contrast



Functional Contrast



(Block design = 1)


Sim 20 on 20 isi
Sim 2 on 12 isi
Data 2 on 12 isi

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.

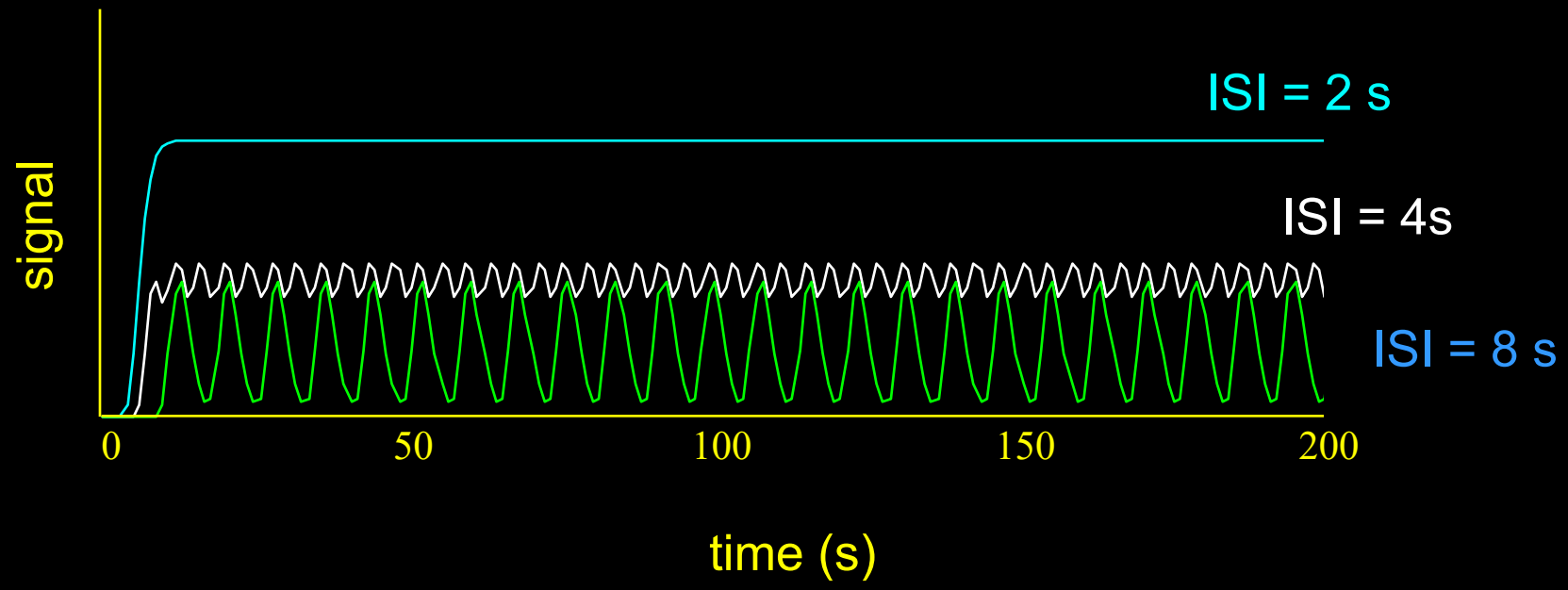
Hemodynamic/Metabolic:

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.

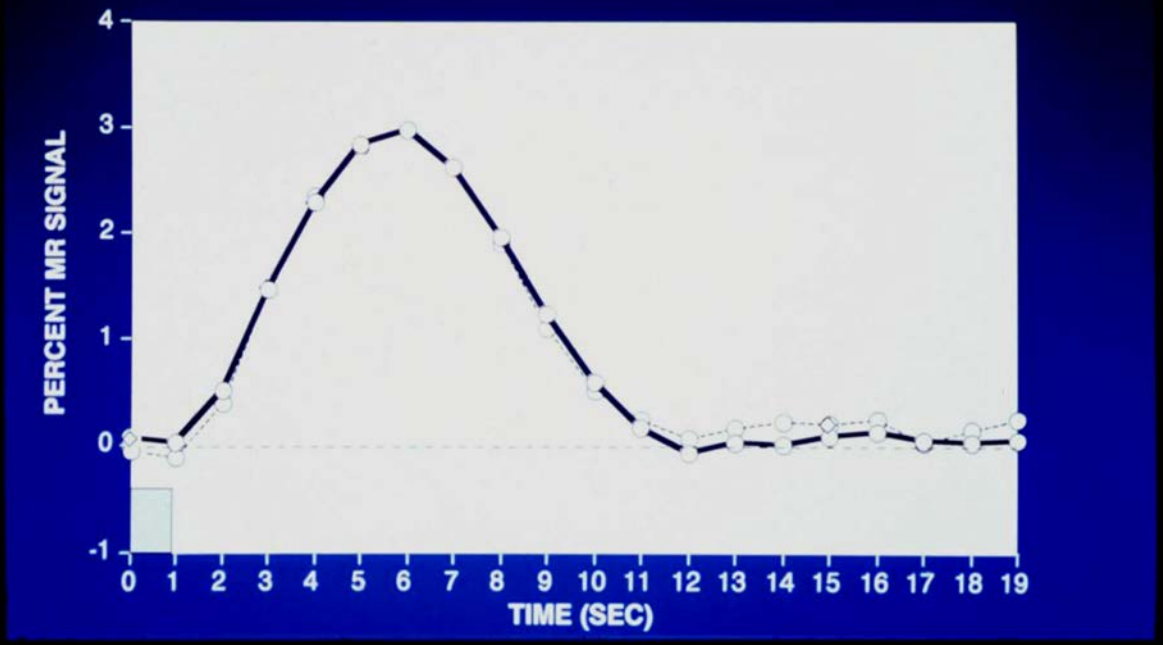
Dale AM, Buckner RL (1997), Human Brain Mapping, 5, 329-340.

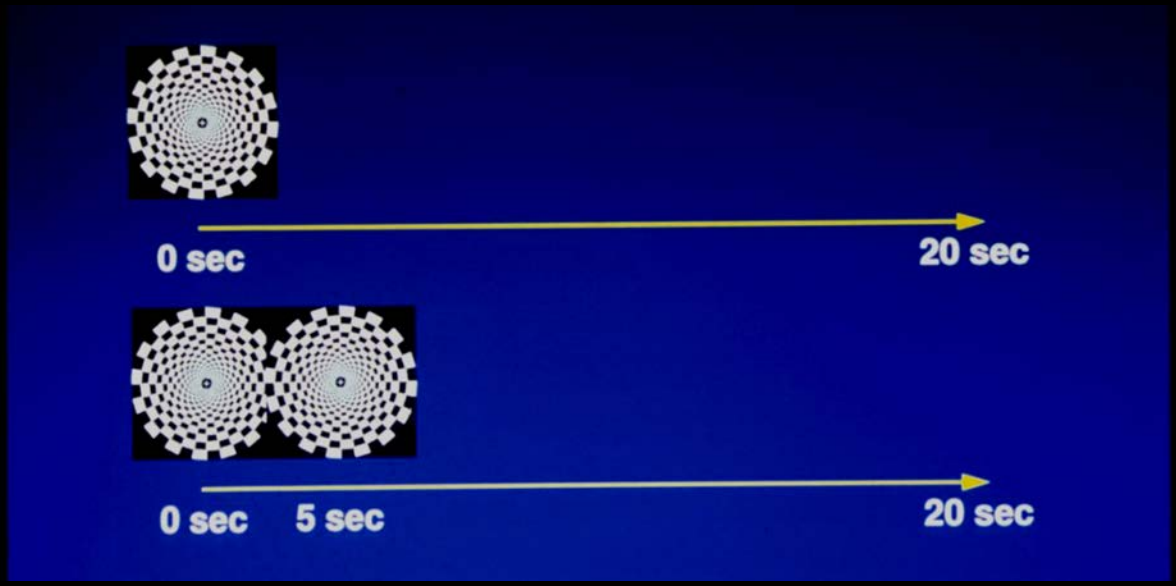
BOLD response - constant ISI



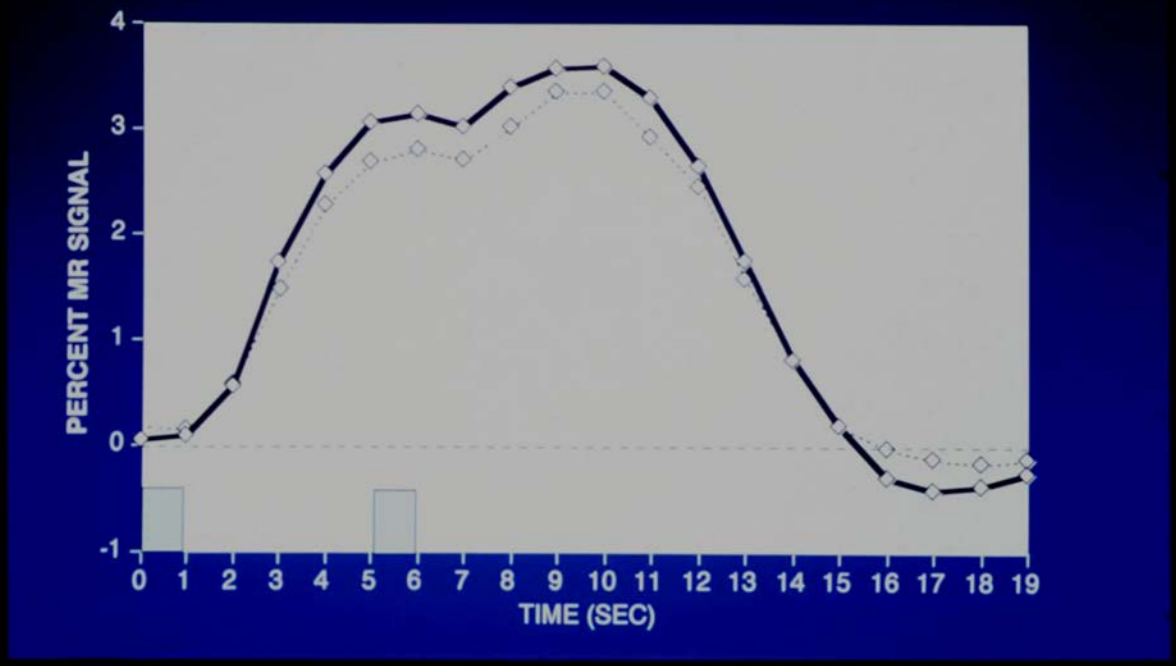
Tasks can be performed faster by varying the ISI

Response to Averaged Single Trials: Subject JM

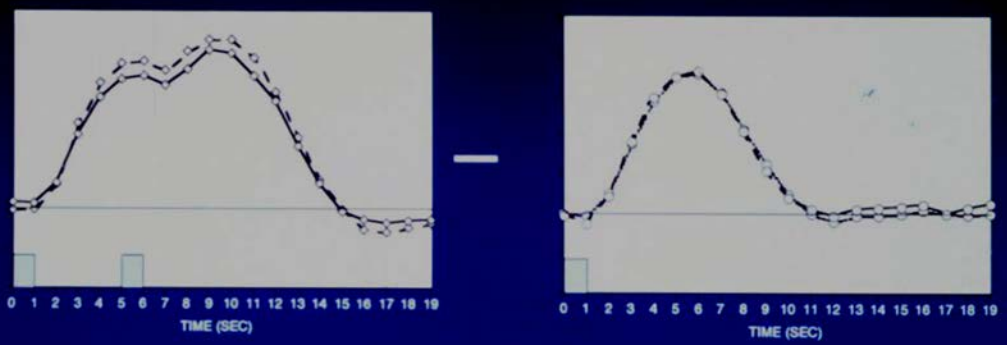




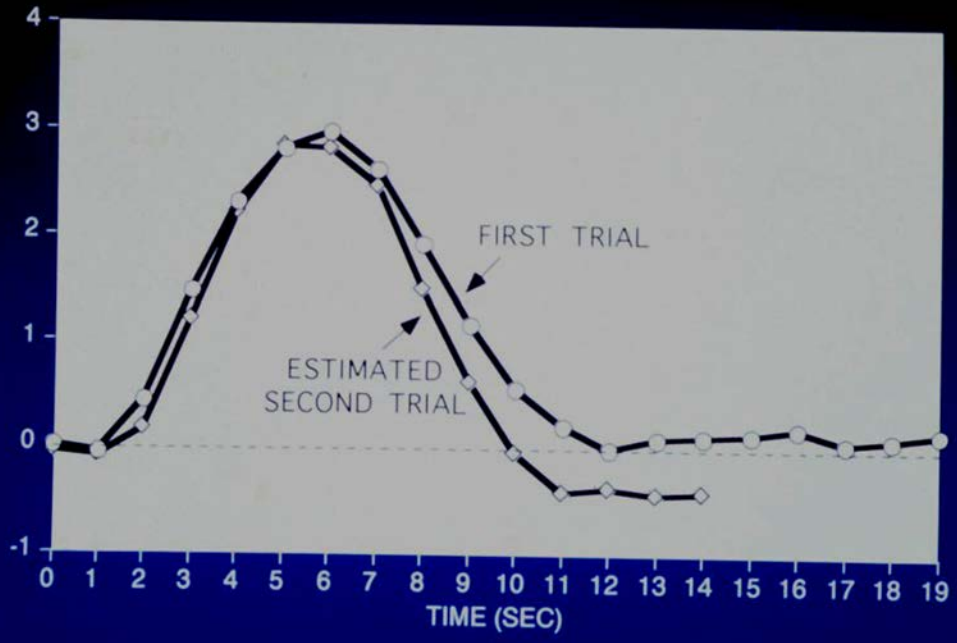
Response to Averaged Double Trials: Subject JM



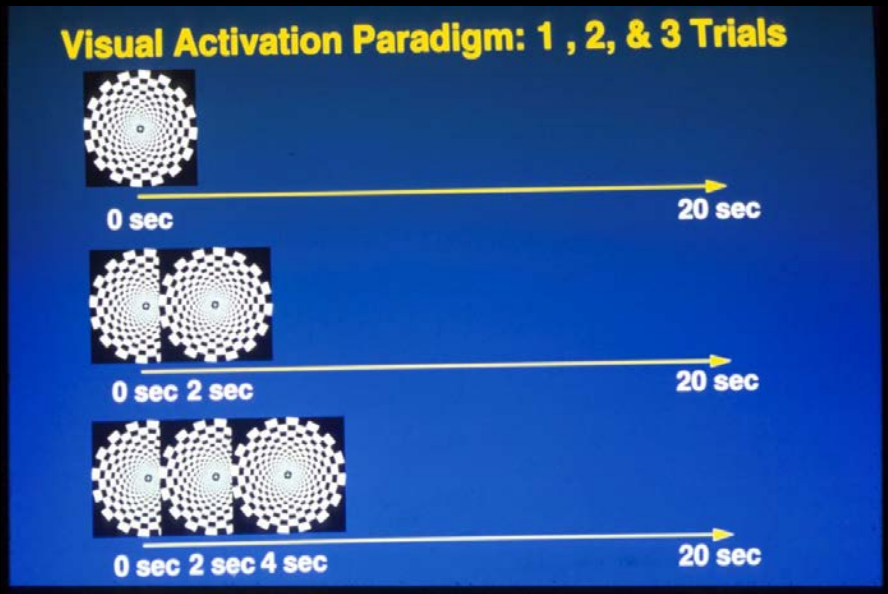
Response to Averaged Double Trials: Subject JM



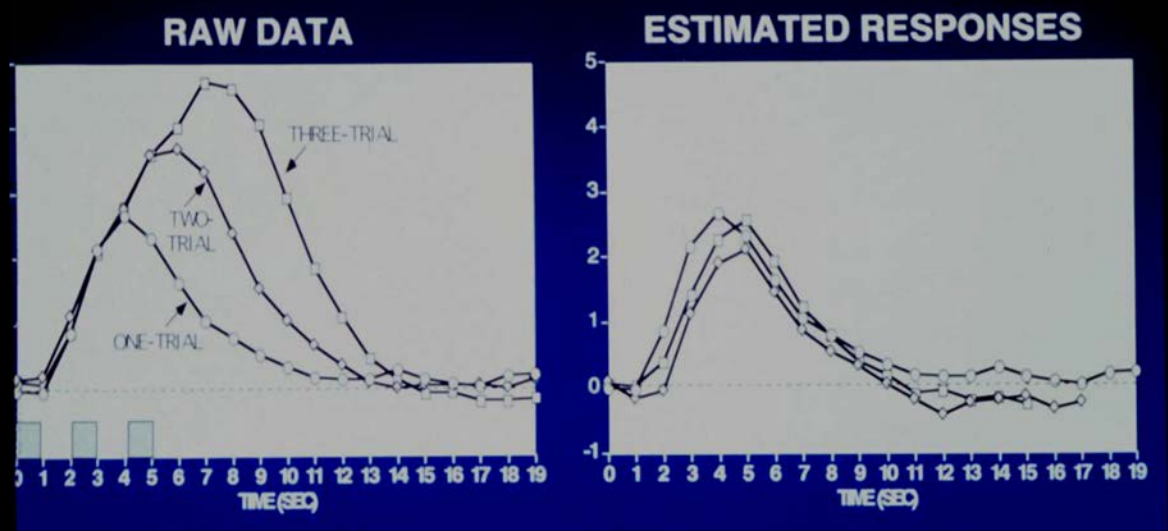
Separation of Responses: Subject JM

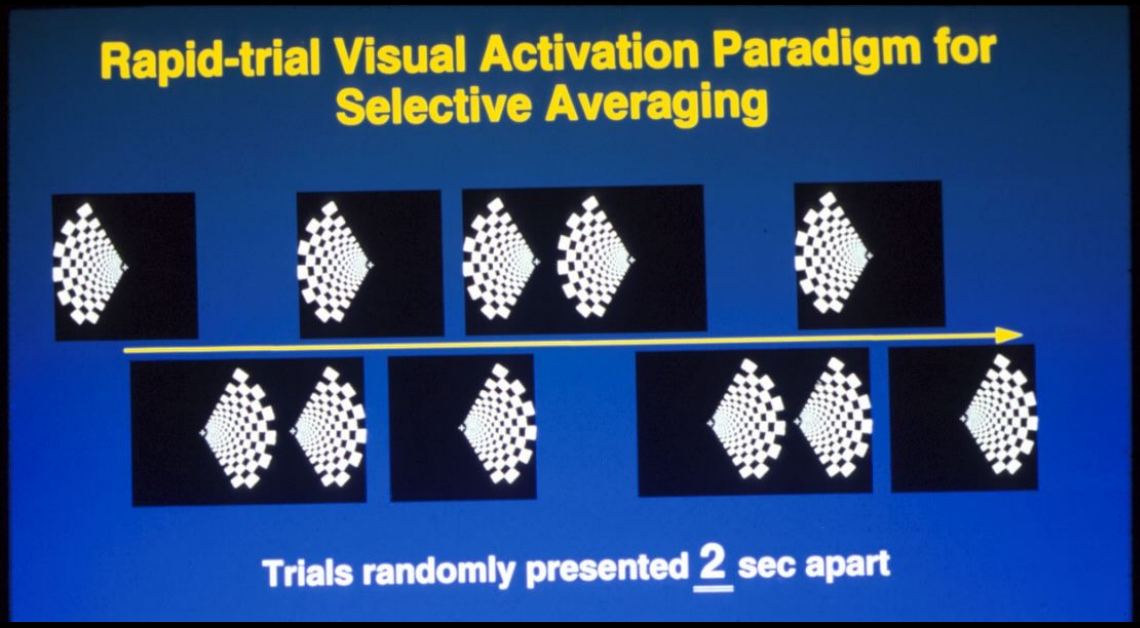


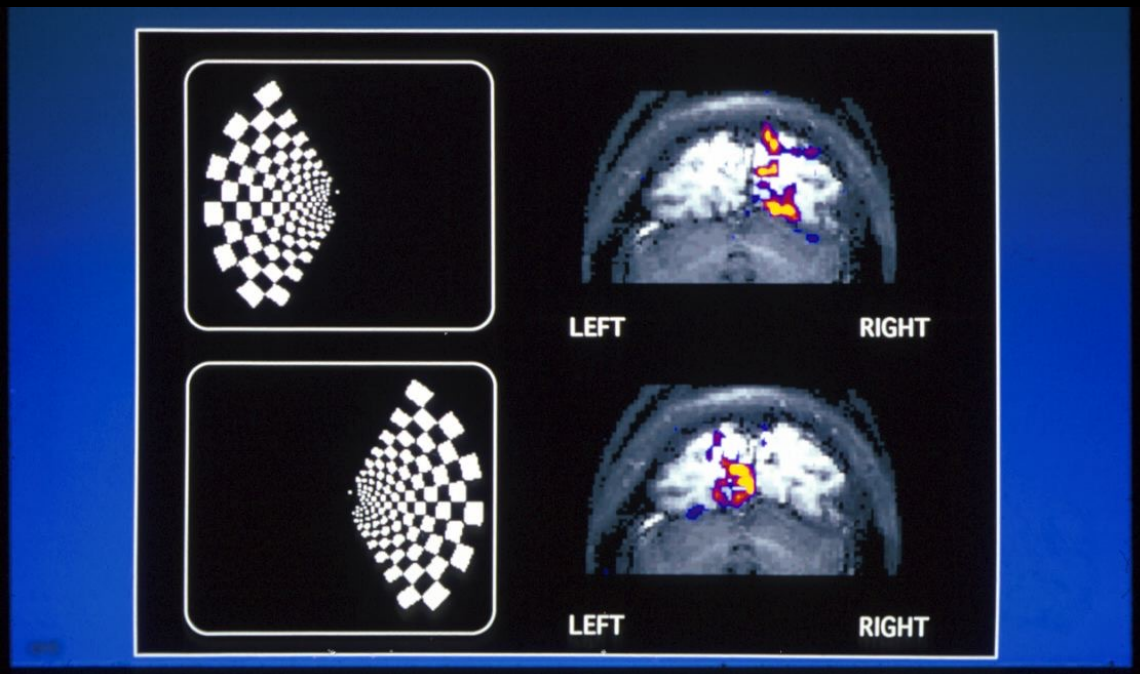
You can go even faster with the assumption of linearity...



Response to Multiple Trials: Subject RW



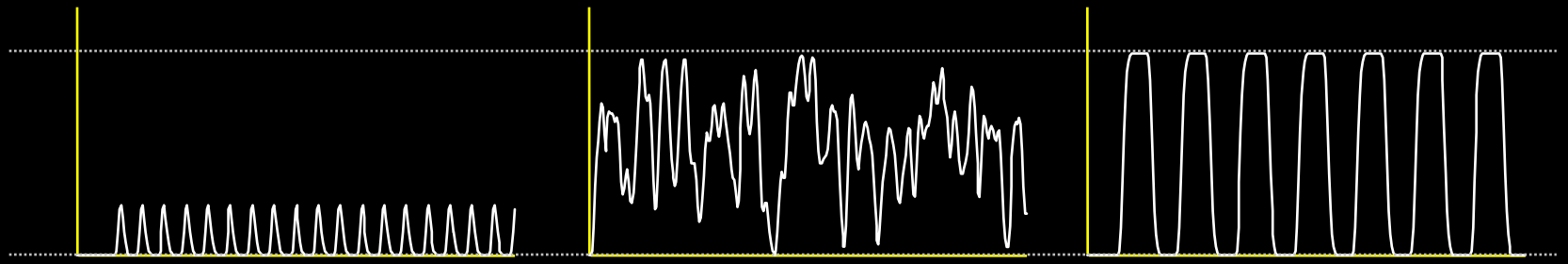




If ISI is randomized, and if ON / OFF distribution is 50%, the optimal average ISI is as short as you can make it.

BOLD response - varying ISI

BOLD response



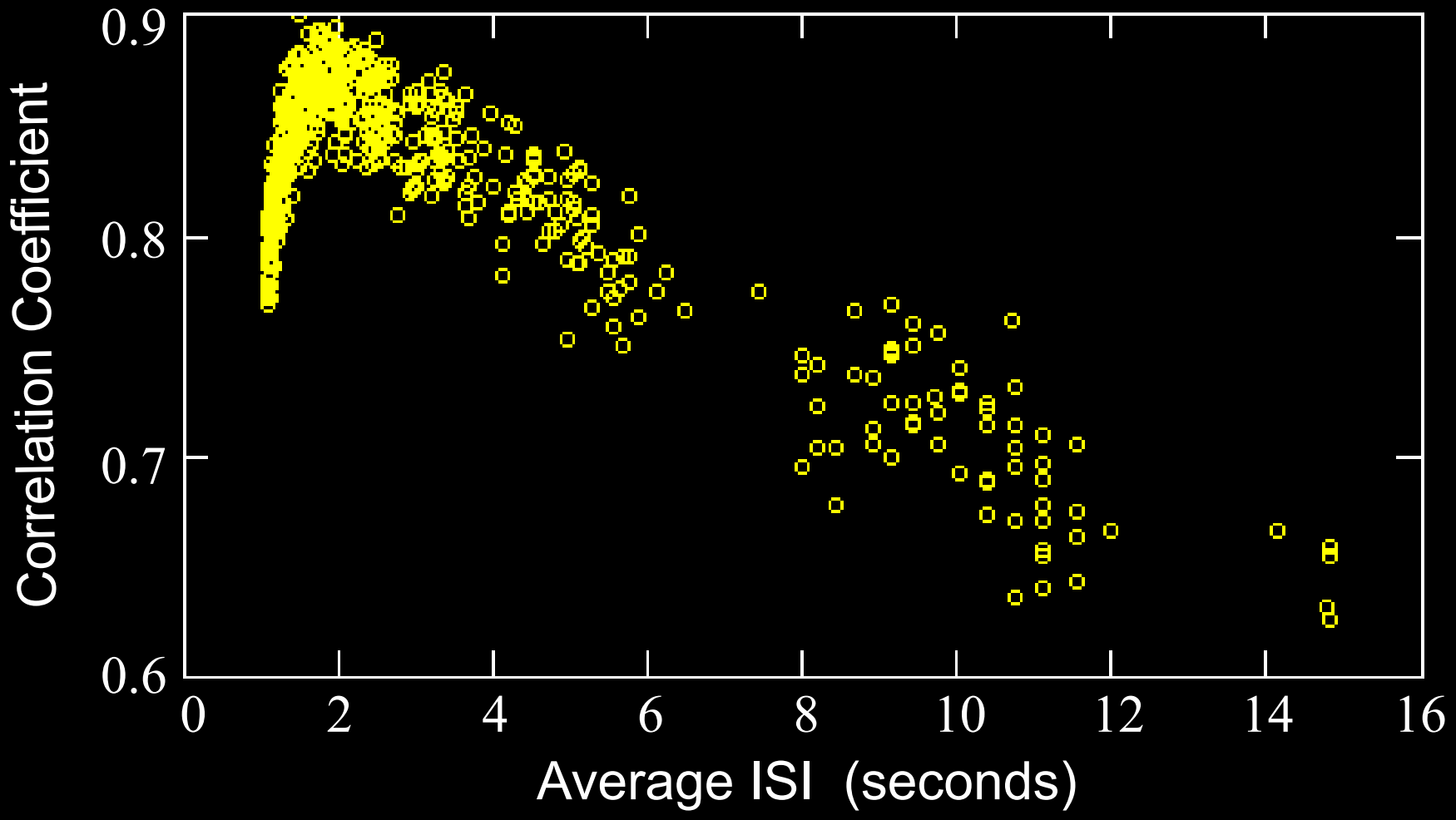
Stimulus

Event-related
constant ISI

Event-related
random ISI

Blocked trial

fCNR vs. Average ISI



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...

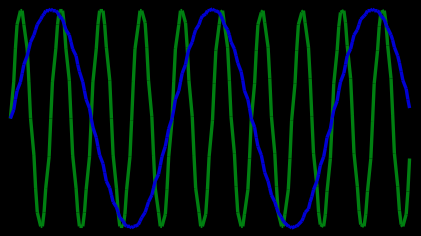
A large amount of additional information exists in the fMRI signal (i.e. fluctuations..).

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.

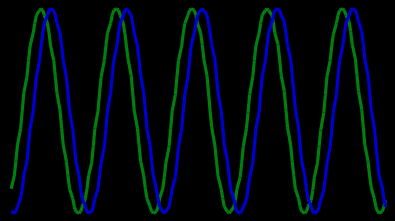
Neuronal Activation Input Strategies

1. Block Design

2. Frequency Encoding

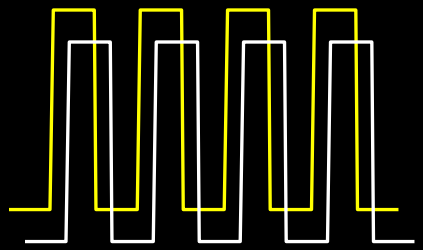


3. Phase Encoding



4. Single Event

5. Orthogonal Block Design

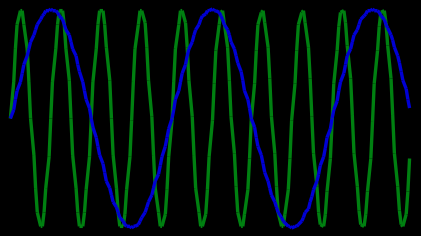


6. Free behavior Design.

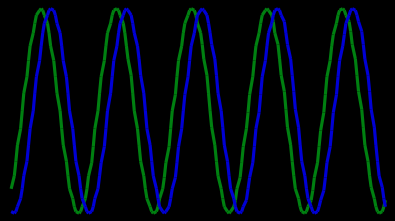
Neuronal Activation Input Strategies

1. Block Design

2. Frequency Encoding



3. Phase Encoding



4. Single Event

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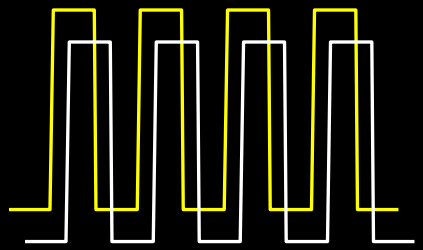
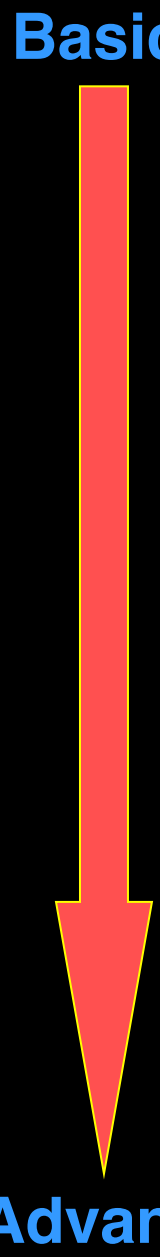


6. Free behavior Design

Free behavior Design:

Use the following as “reference functions”

- Skin Conductance
- EEG
- Eye tracking
- Task performance
- Heart rate
- Respiration rate



Pulse sequences	Processing	Paradigms
		Parametric manipulation
Shimming		Phase and freq. encoding
	Contrast comparisons	
RF coil arrays		Orthogonal multi-task encoding
	Physiologic fluctuations	Physiologic manipulations
	Embedded contrast	
	Motion correction	Event - related fMRI
	Distortion / dropout correction	
	Real time fMRI	
Perfusion quantitation		Effective connectivity mapping
	<- Multi - modal integration ->	
	<- Sub - second resolution ->	
	<- Sub - millimeter resolution ->	
	<- $CMRO_2$ mapping ->	

1991-1992

1992-1999