FMRI based on Blood Oxygenation Level Dependence (BOLD) contrast

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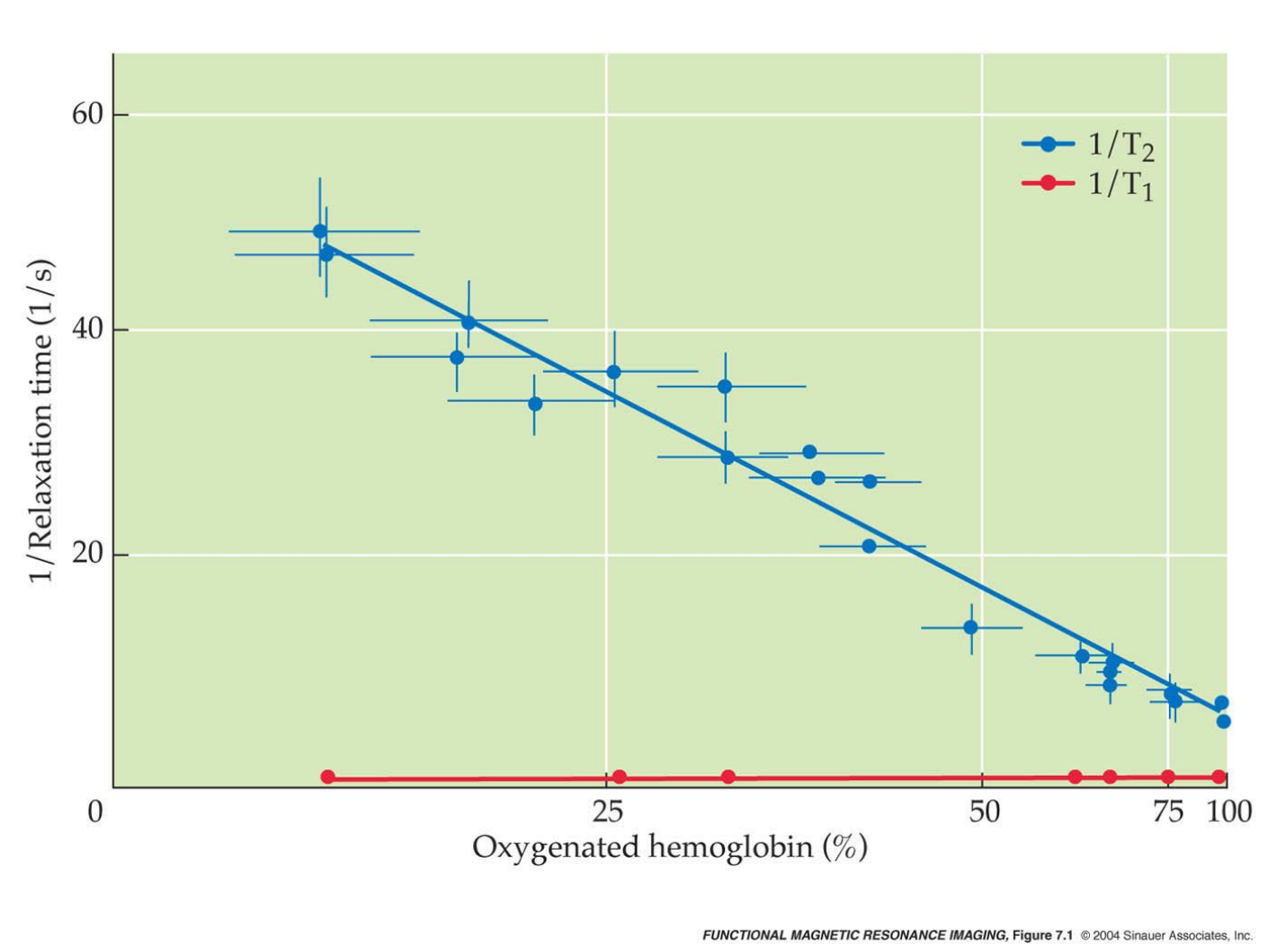
Contrast Agents in MRI

- Definition: Substances that alter magnetic susceptibility of tissue or blood, leading to changes in MR signal
  - Affects local magnetic homogeneity: decrease in T_2^*

- Two types
  - Exogenous: Externally applied, non-biological compounds (e.g., Gd-DTPA)
  - Endogenous: Internally generated biological compound (e.g., deoxyhemoglobin, dHb)

Blood Deoxygenation affects T_2^* Decay



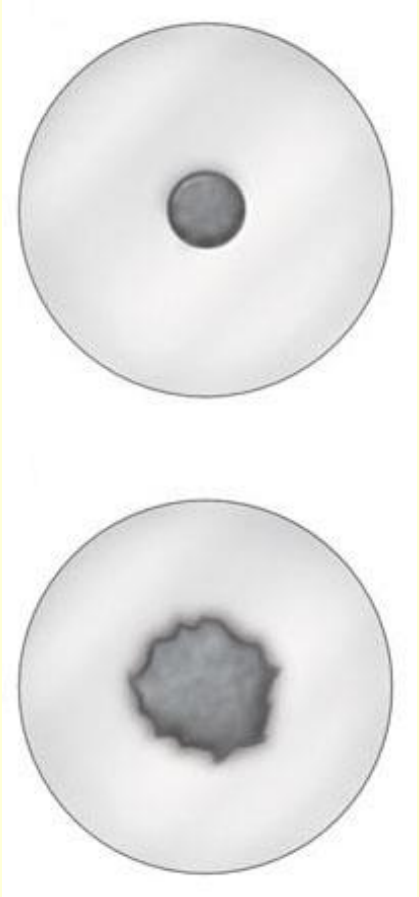
Thulborn et al., 1982

BOLD Endogenous Contrast

- Blood Oxyenation Level Dependent Contrast
  - Deoxyhemoglobin is paramagnetic
  - Magnetic susceptibility of blood increases linearly with increasing Deoxygenation

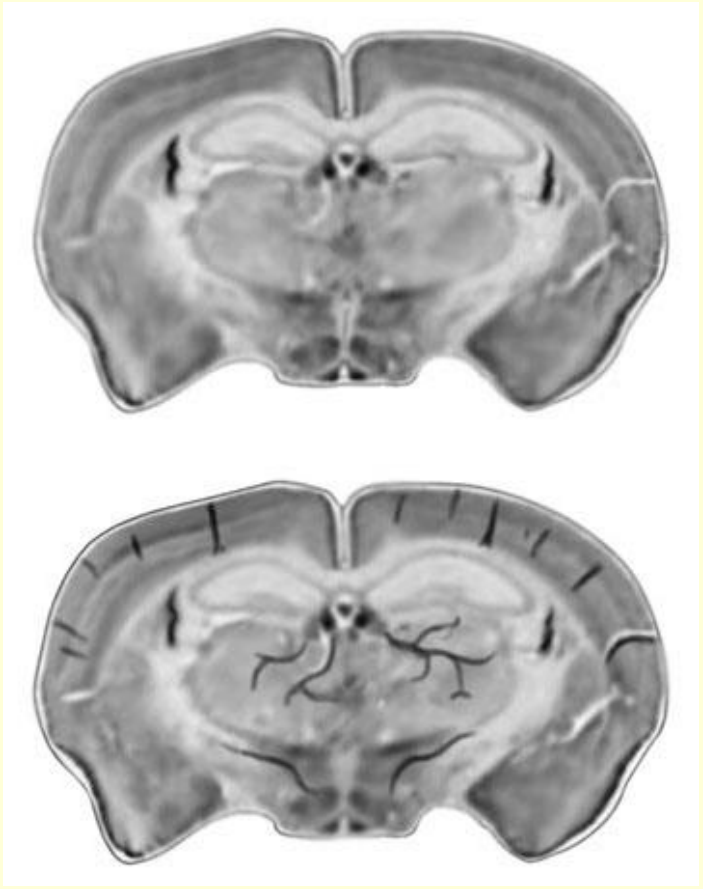
- Oxygen is extracted during passage through capillary bed
  - Brain arteries are fully oxygenated
  - During activation Venous (and capillary) blood has increased proportion of Doxyhemoglobin
  - Then oxygen is compensated in veins
  - Difference between oxy and deoxy states becomes greater for veins → BOLD sensitive to venous changes

Deoxygenated Blood → Signal Loss



Oxygenated blood?
No signal loss…

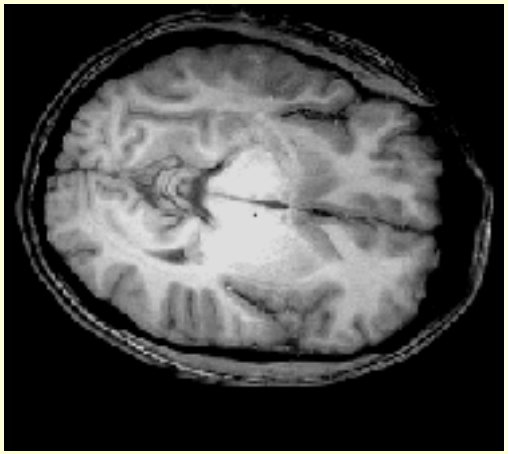
Deoxygenated blood?
Signal loss!!!



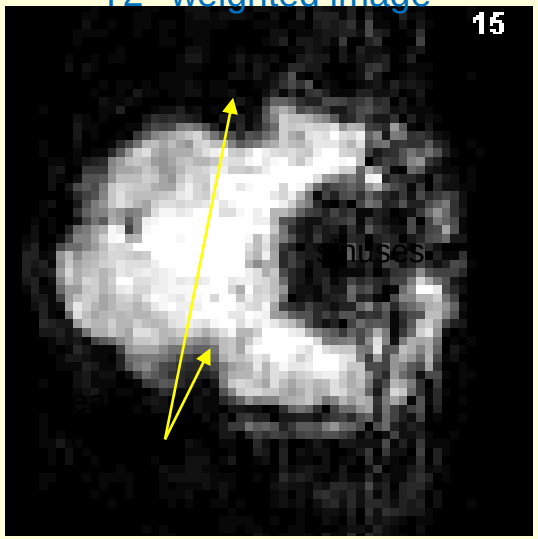
Images from Huettel, Song & McCarthy, 2004, Functional Magnetic Resonance Imaging

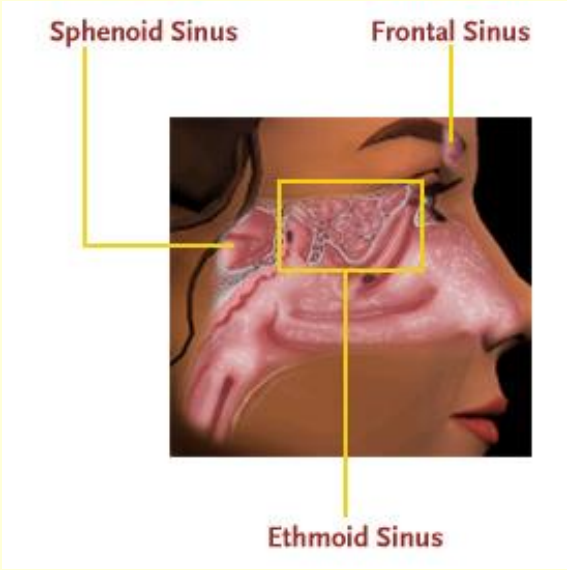
Susceptibility Artifacts

T1-weighted image



T2*-weighted image





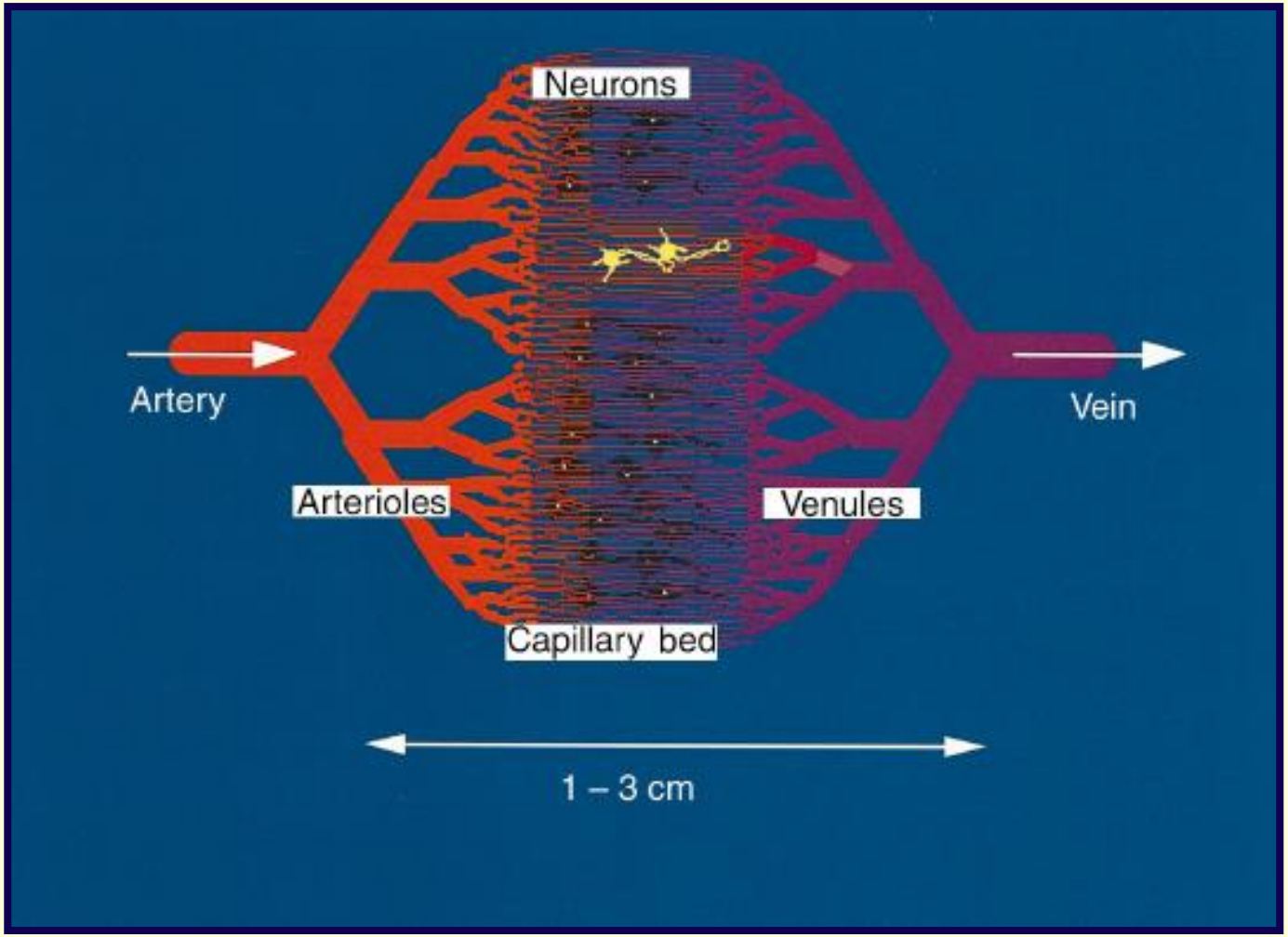
-In T2* images, artifacts occur near junctions between air (sinuses, ear canals) and tissue

Measuring Deoxyhemoglobin

- fMRI measurements are of amount of oxyhemoglobin per voxels in Venus pool

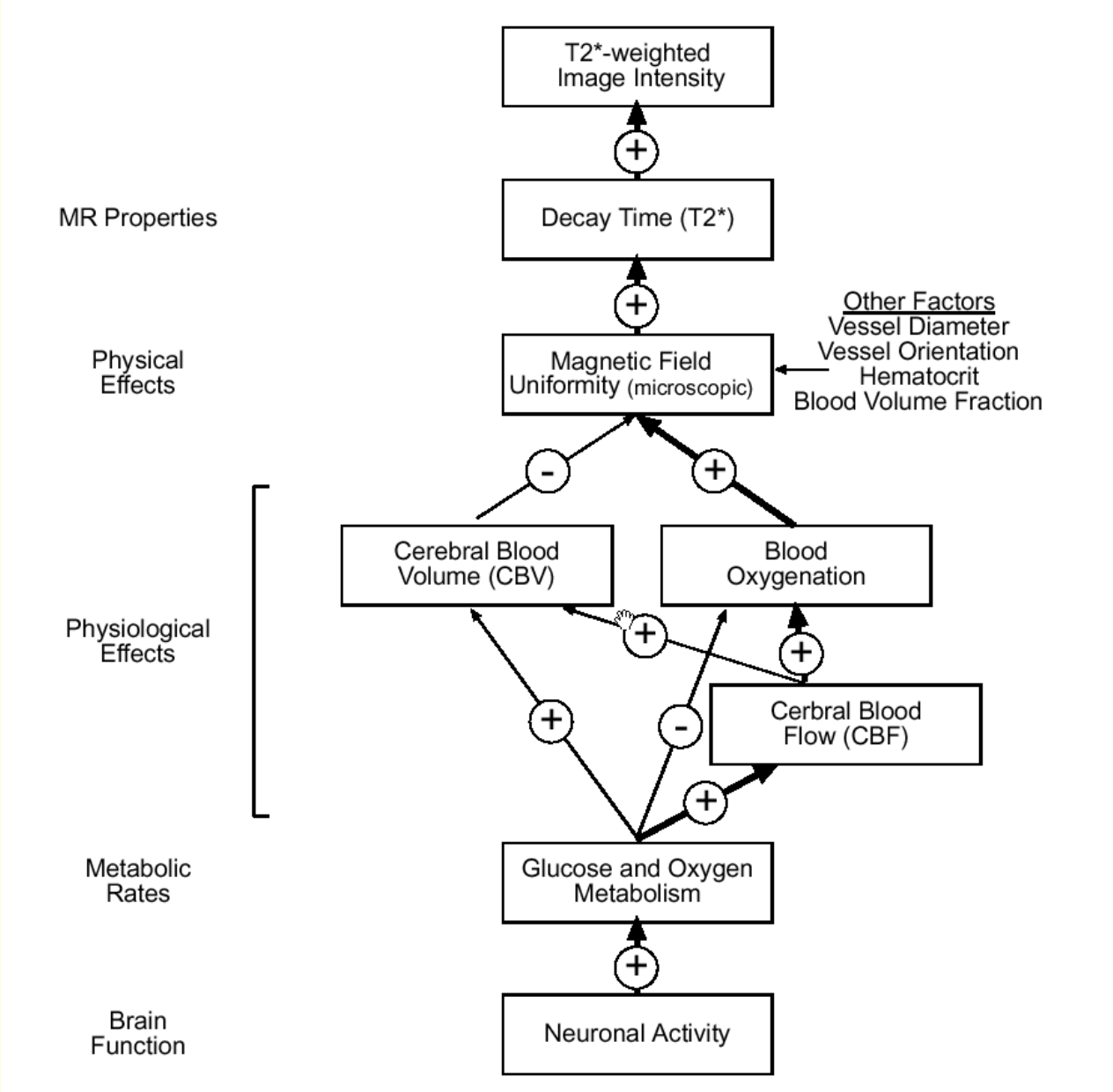
- We assume that amount of deoxygenated hemoglobin in vein (and oxyhemoglobin in later stage) is predictive of neuronal activity

Vasculature

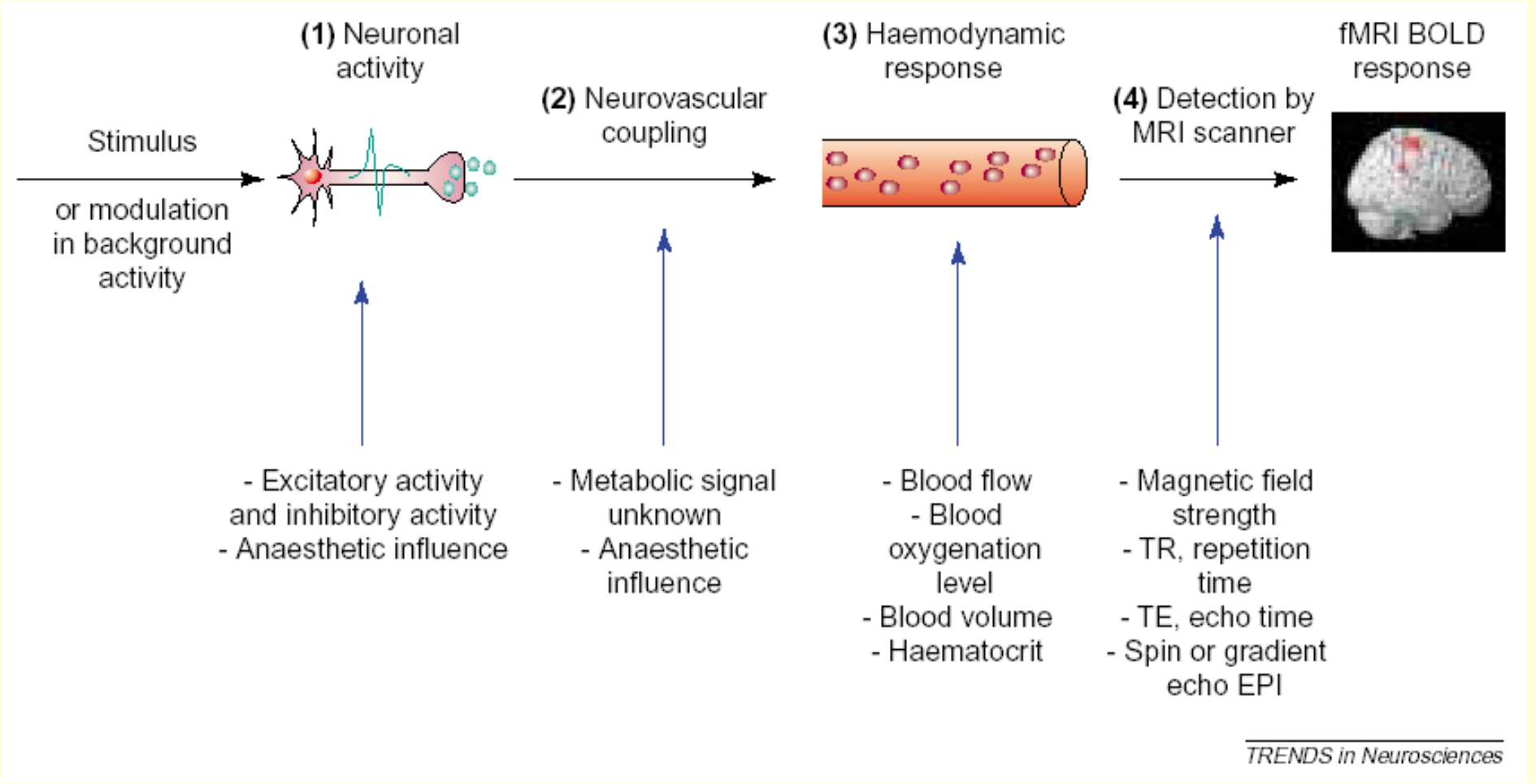


Source: Menon & Kim, TICS

BOLD signal

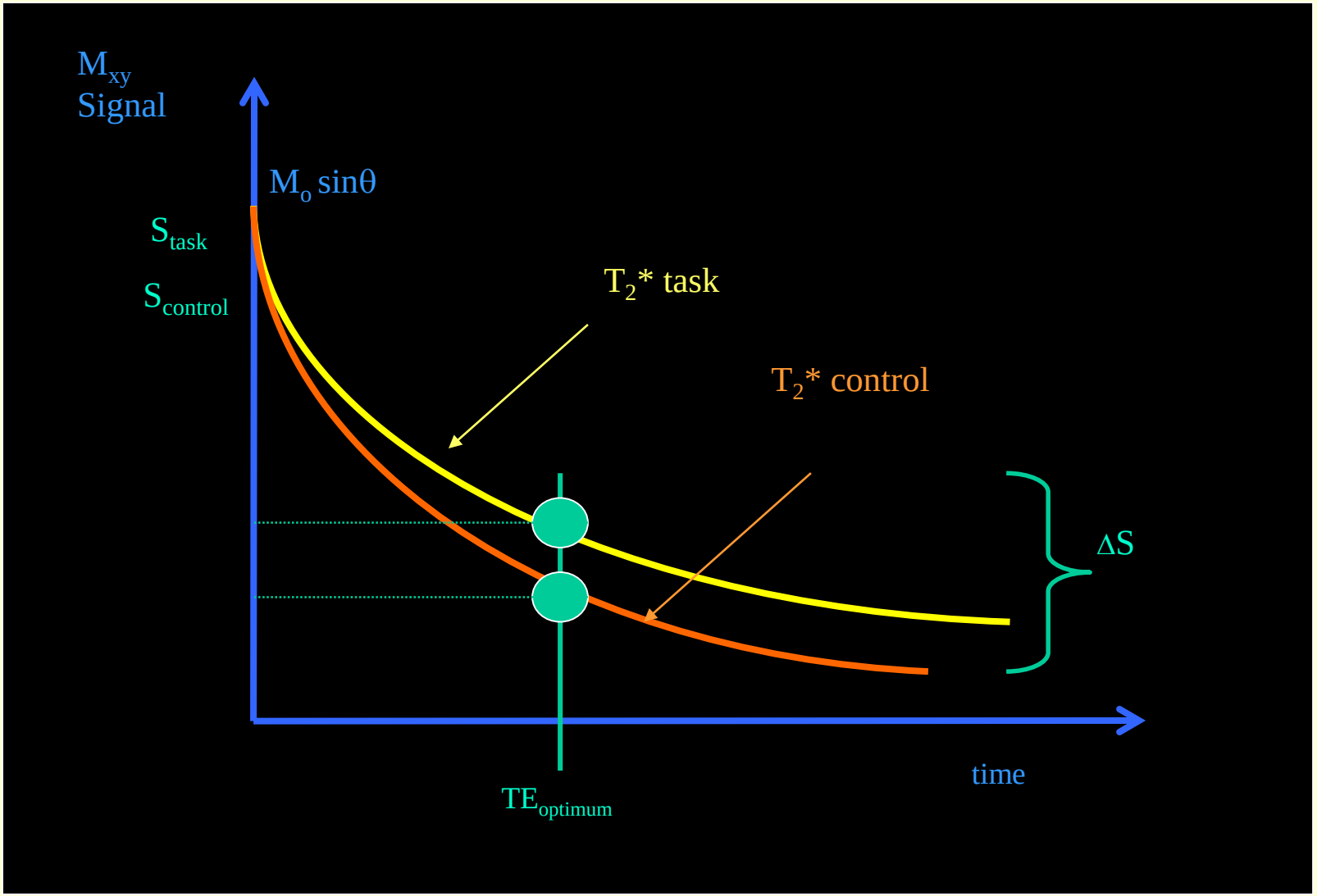

T2*-weighted Image Intensity
MR Properties
Decay Time (T2*)
Other Factors
Vessel Diameter
Vessel Orientation
Hematocrit
Blood Volume Fraction
Physical Effects
Magnetic Field Uniformity (microscopic)
Cerebral Blood Volume (CBV)
Blood Oxygenation
Physiological Effects
Cerbral Blood Flow (CBF)
Metabolic Rates
Glucose and Oxygen Metabolism
Brain Function
Neuronal Activity

Stimulus to BOLD



Source: Arthurs & Boniface, 2002, *Trends in Neurosciences*

BOLD signal


M_{xy} Signal
$M_o \sin\theta$
S_{task}
$S_{control}$
T_2* task
T_2* control
ΔS
time
$TE_{optimum}$

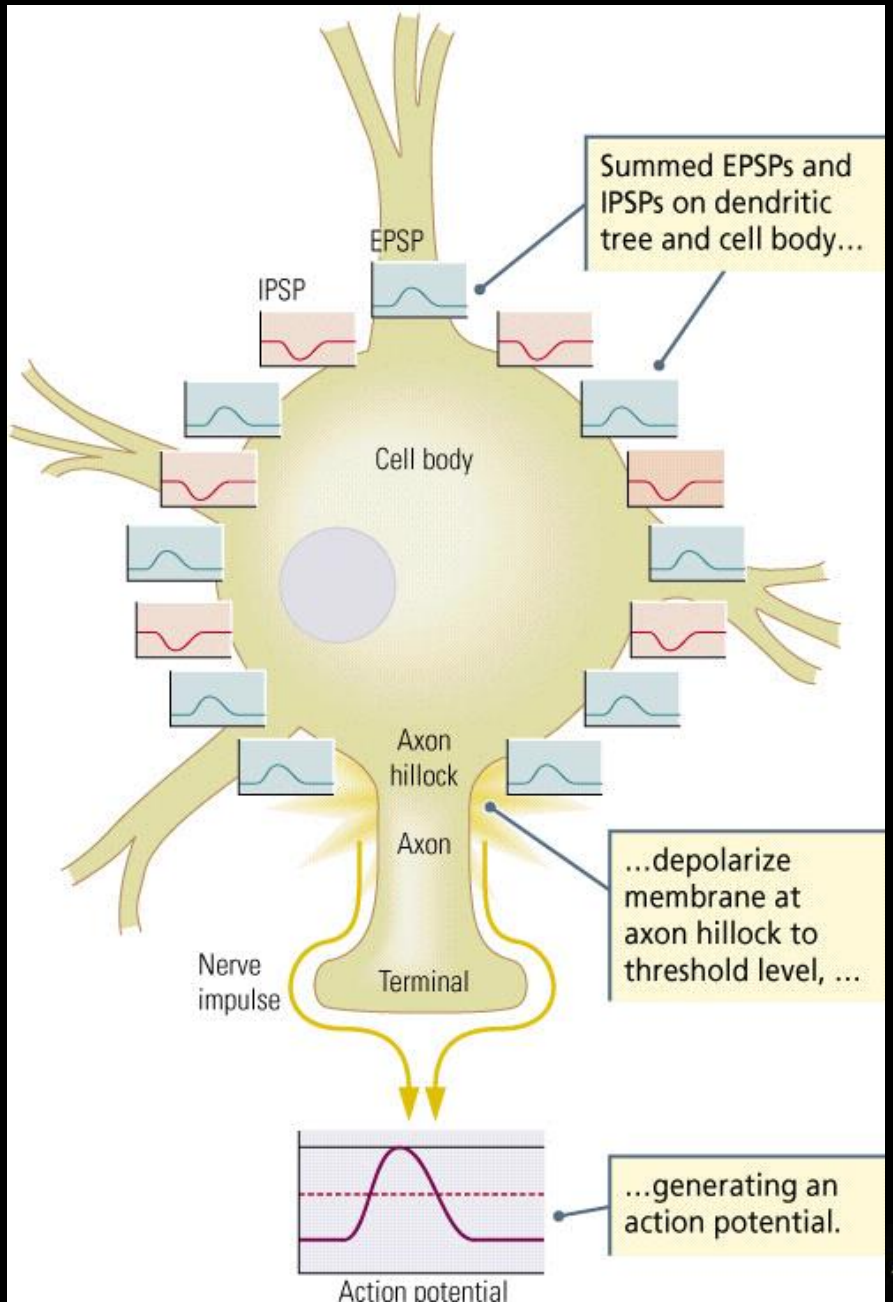
Physiology of BOLD Response

(The Hemodynamic Response)

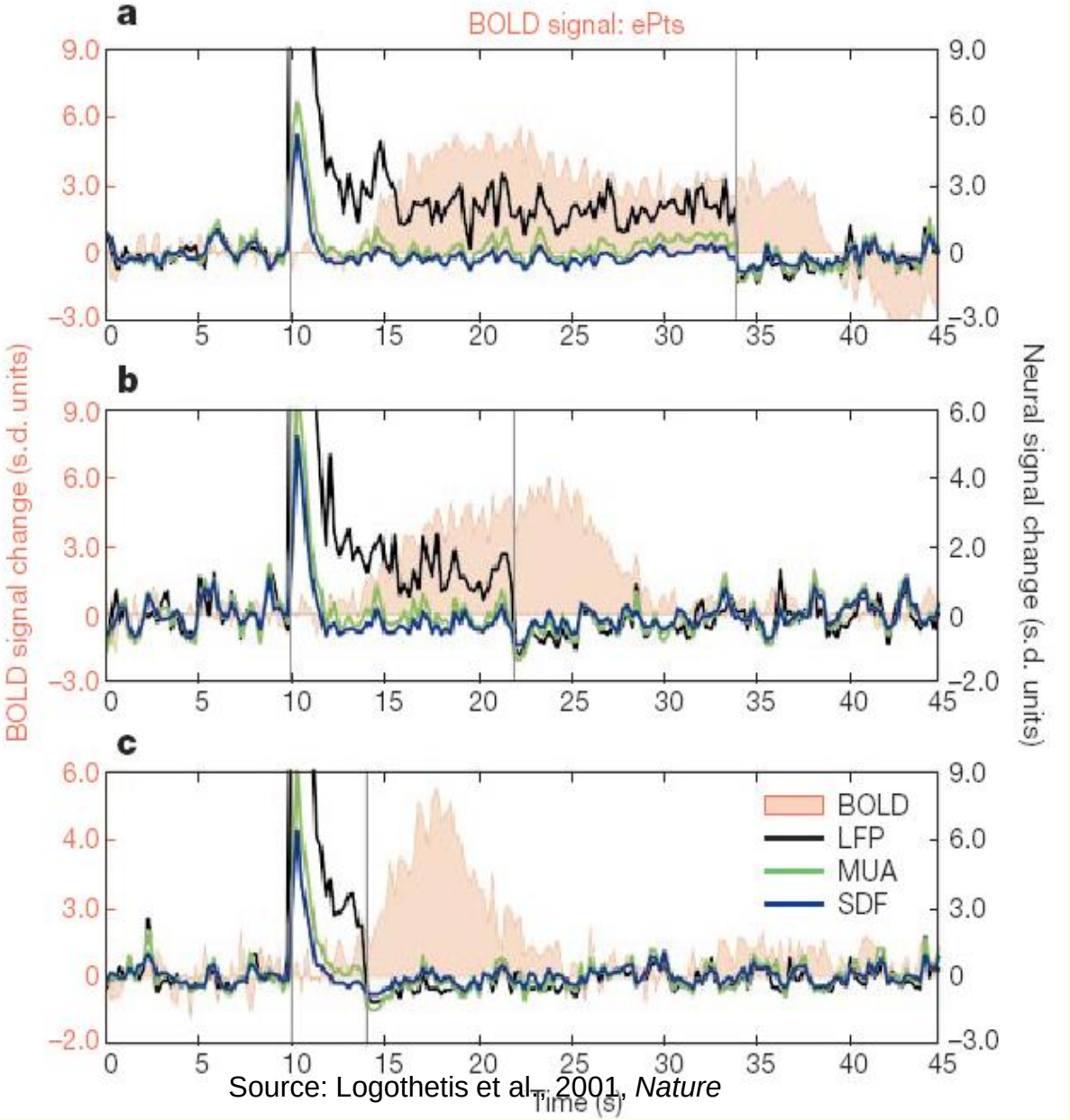
Post-Synaptic Potentials

- The inputs to a neuron (post-synaptic potentials) increase (excitatory PSPs) or decrease (inhibitory PSPs) the membrane voltage

- If the summed PSPs at the axon hillock push the voltage above the threshold, the neuron will fire an action potential



BOLD Correlations



Source: Logothetis et al., 2001, *Nature*

Local Field Potentials (LFP)

- reflect post-synaptic potentials
- similar to what EEG (ERPs) and MEG measure

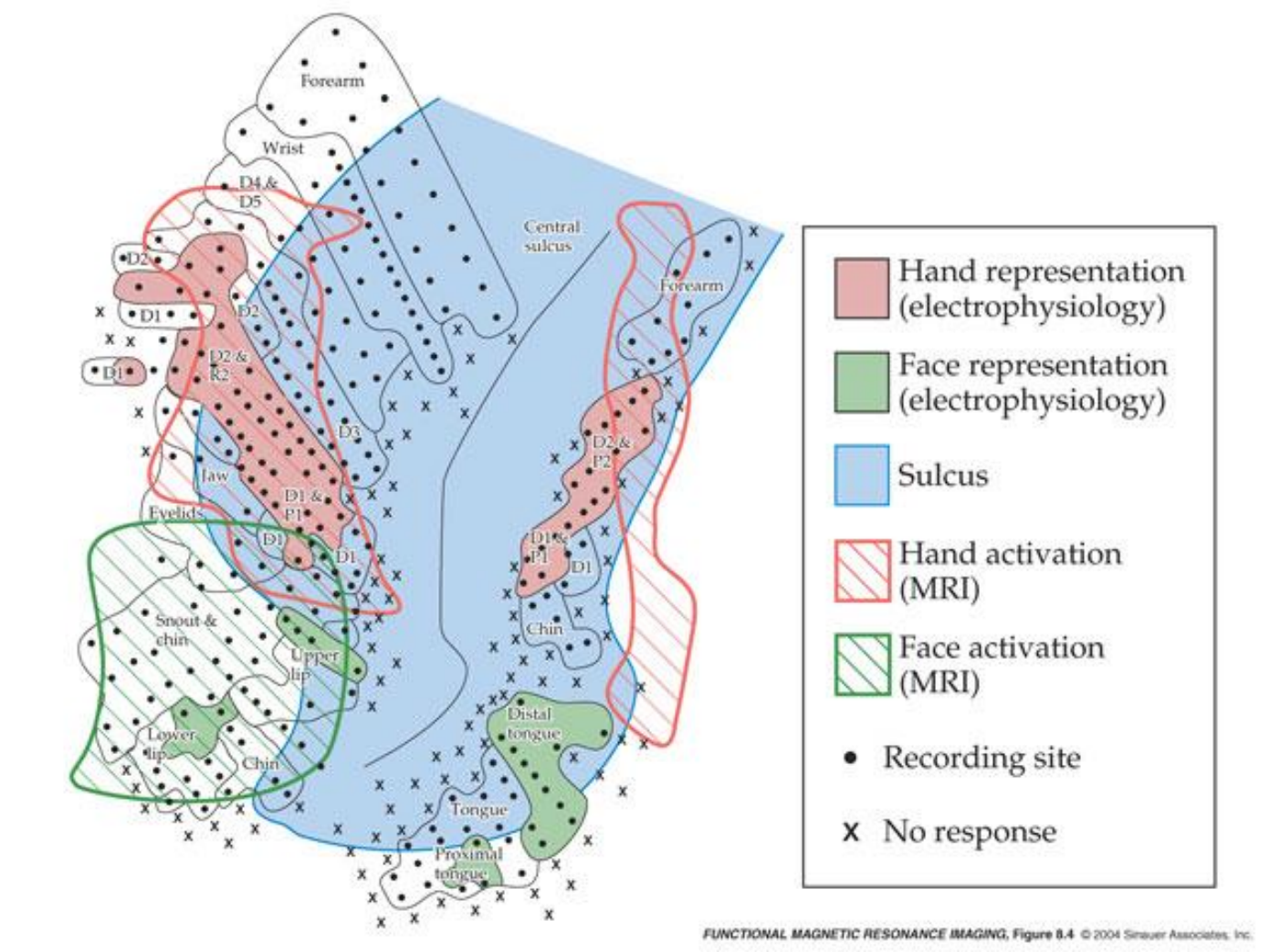
Multi-Unit Activity (MUA)

- reflects action potentials
- similar to what most electrophysiology measures

- BOLD activity
- is more closely related to LFPs than MUA

- SDF= spike-density function

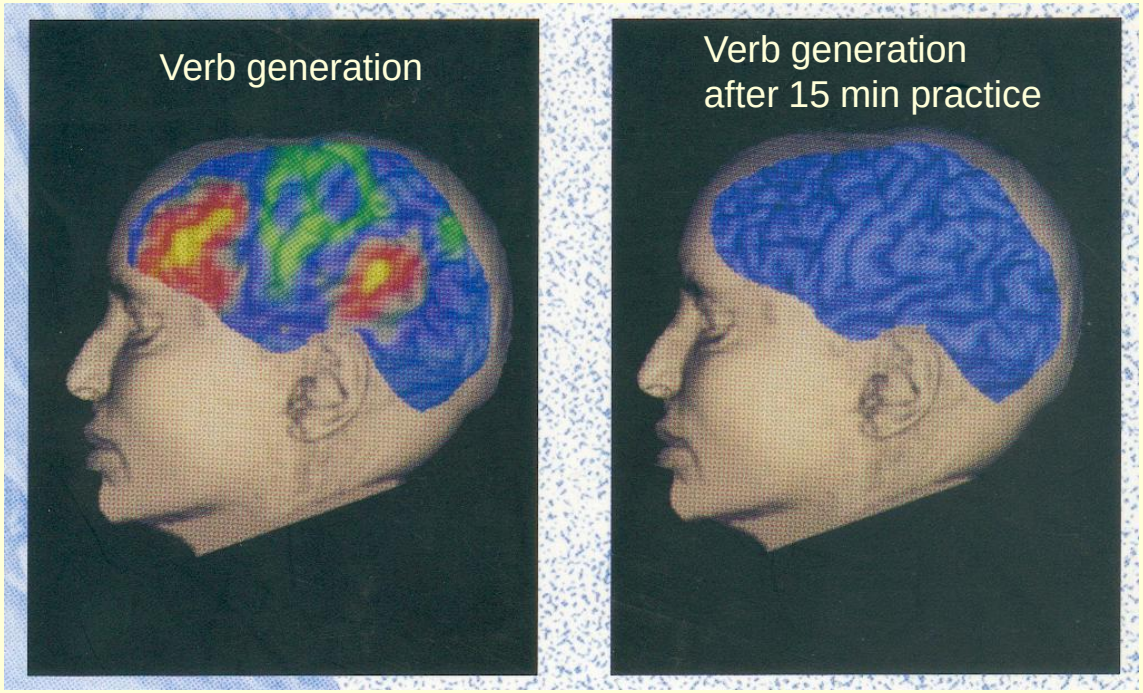
Comparing Electrophysiolgy and BOLD



Data Source: Disbrow et al., 2000*, PNAS*
Figure Source, Huettel, Song & McCarthy, *Functional Magnetic Resonance Imaging*

fMRI Measures the Population Activity

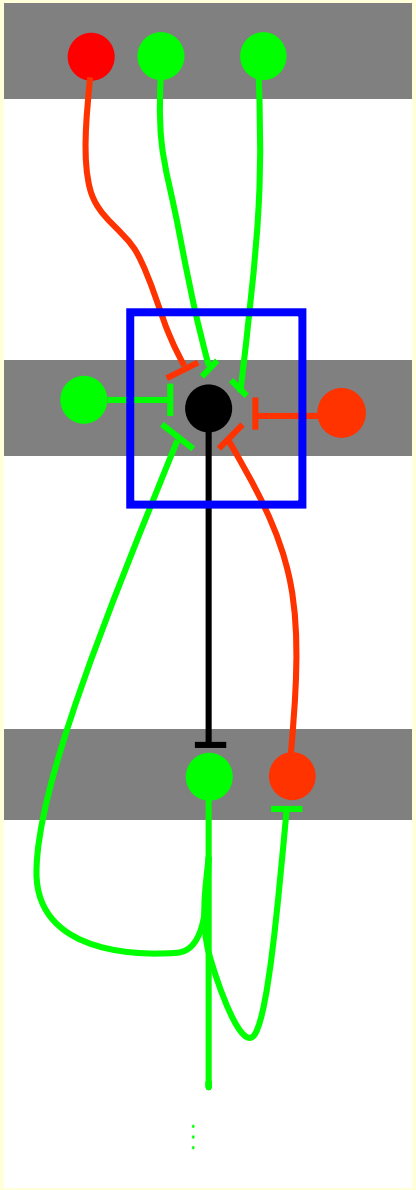
- fMRI may not match single neuron physiology results
- population activity depends on
  - how active the neurons are
  - how many neurons are active



Raichle & Posner, Images of Mind cover image

Ideas from: Scannell & Young, 1999, Proc Biol Sci

Lower tier area
(e.g., thalamus)



gray matter
(dendrites, cell bodies
& synapses)

white matter
(axons)

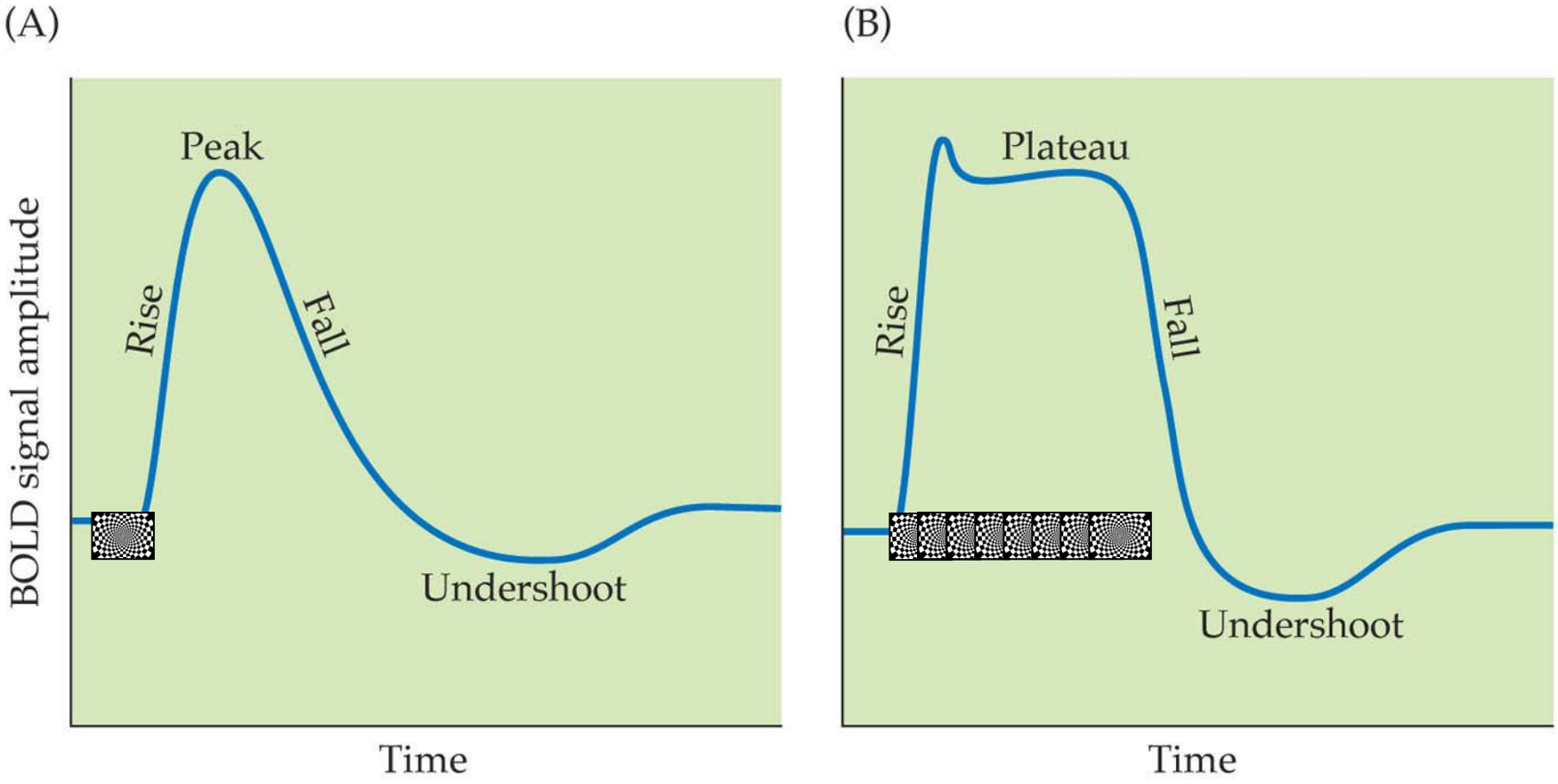
Middle tier area
(e.g., V1, primary visual
cortex)

Higher tier area
(e.g., V2, secondary
visual cortex)

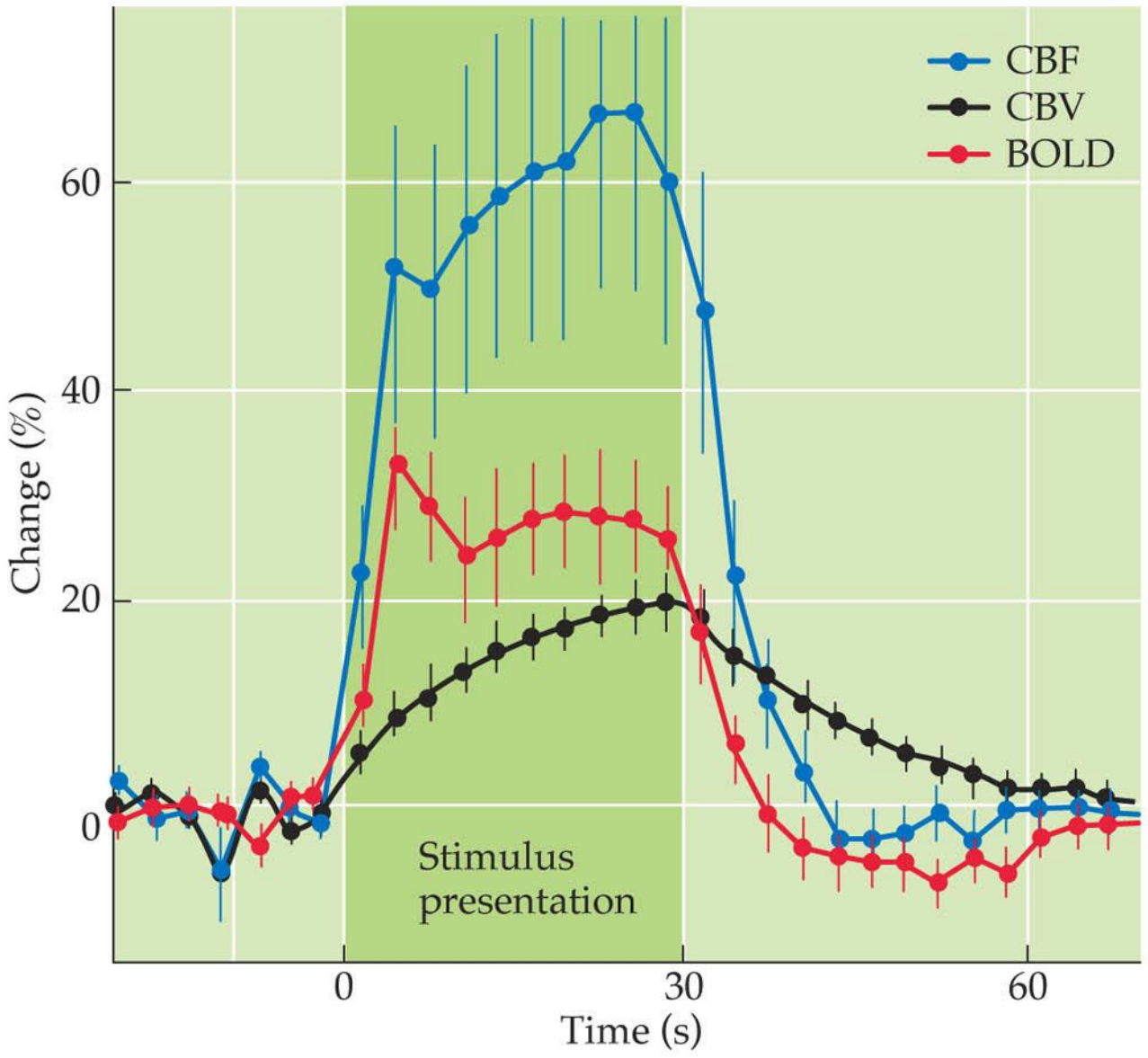
Will BOLD activation from the blue voxel reflect:

- *output of the black neuron (action potentials)?*
- *excitatory input (green synapses)?*
- *inhibitory input (red synapses)?*
- *inputs from the same layer?*
- *feedforward projections (from lower-tier areas)?*
- *feedback projections (from higher-tier areas)?*

Basic Form of Hemodynamic Response

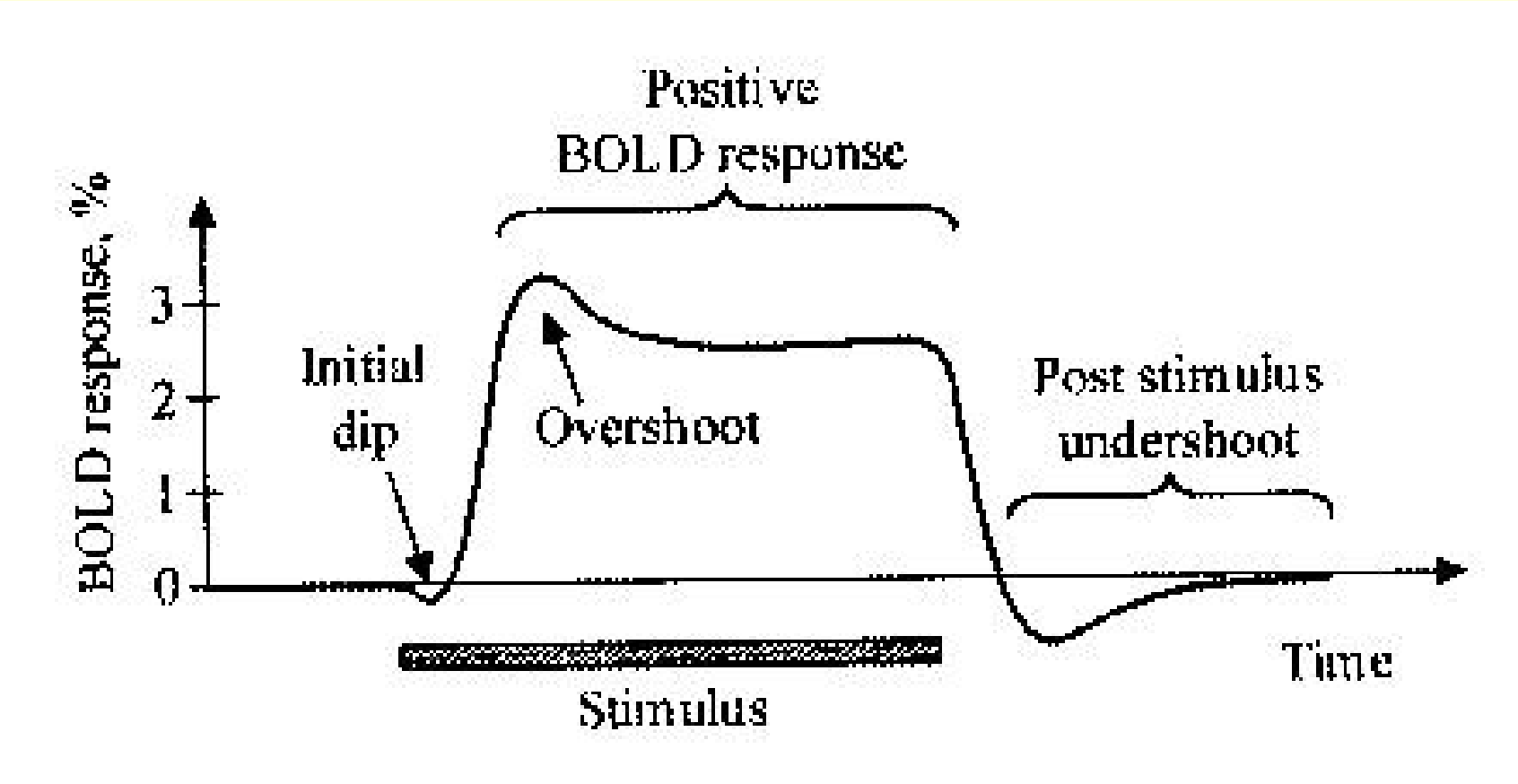


FUNCTIONAL MAGNETIC RESONANCE IMAGING, **Figure 7.15** © 2004 Sinauer Associates, Inc.



FUNCTIONAL MAGNETIC RESONANCE IMAGING, **Figure 7.16** © 2004 Sinauer Associates, Inc.

BOLD Time Course



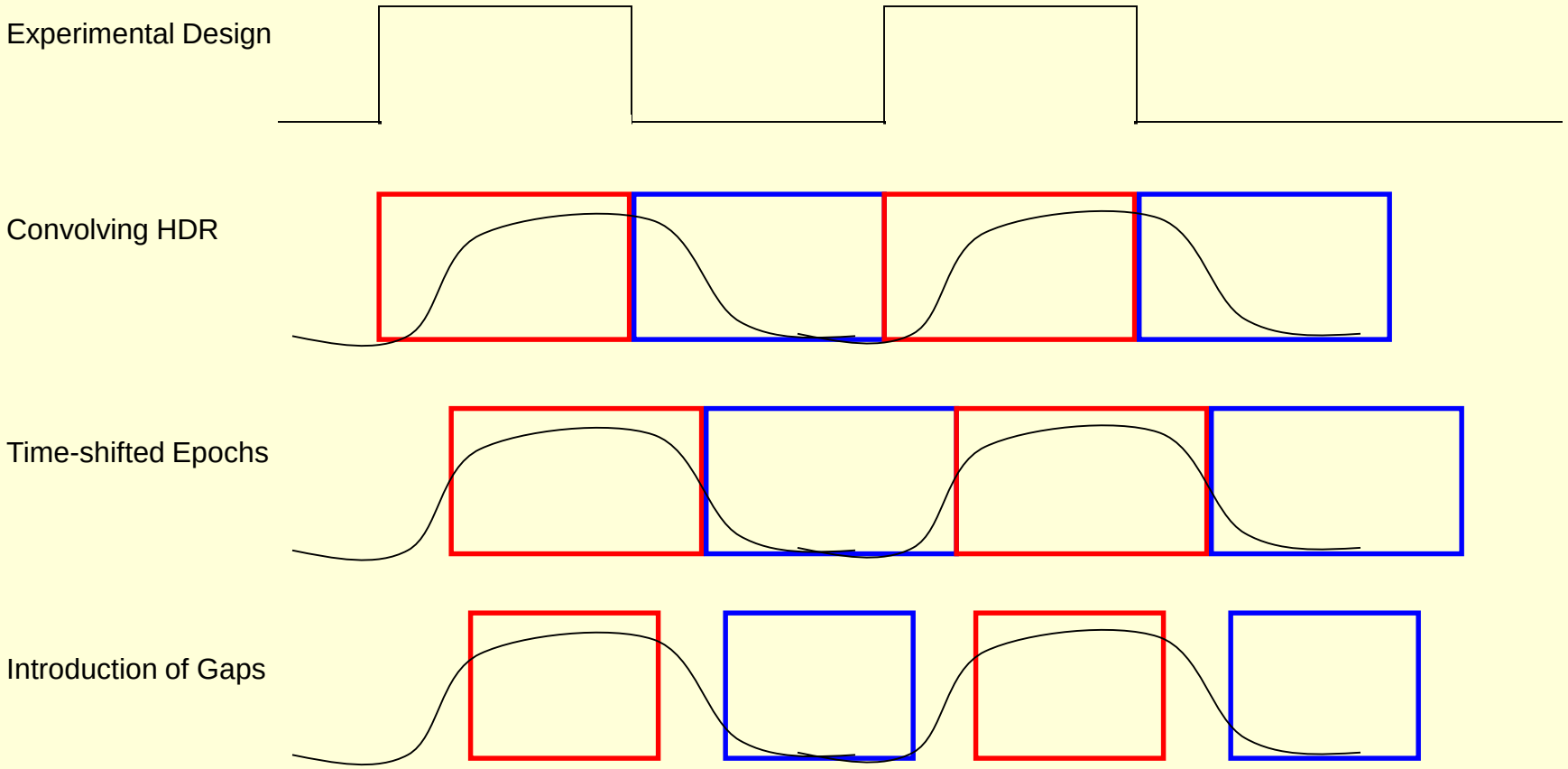
Amplitude of the HDR

- Peak signal change dependent on:
  - Brain region
  - Task parameters
  - Voxel size
  - Field Strength

Why does the hemodynamic response matter?

- Delay in the hemodynamic response (HDR)
  - Hemodynamic activity lags neuronal activity
- Amplitude of the HDR
- Variability in the HDR
- Linearity of the HDR
- HDR as a relative measure

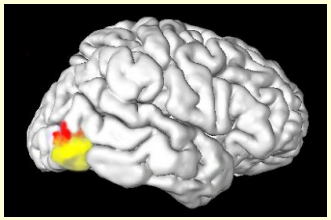
The Hemodynamic Response Lags Neural Activity



fMRI Analysis with emphasis on the general linear model

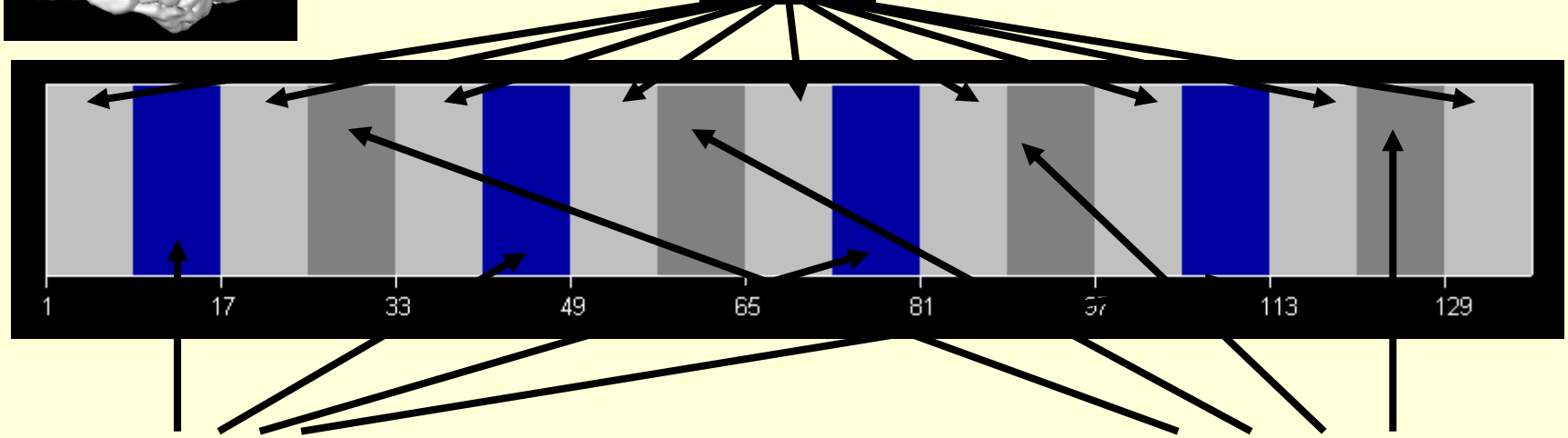
Jody Culham niversity of Western Ontario

A Simple Experiment

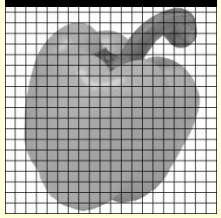


Lateral Occipital Complex
• responds when subject views objects

Blank Screen

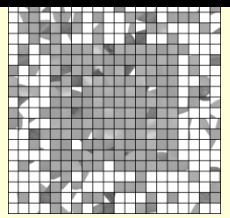


Intact Objects



TIME →

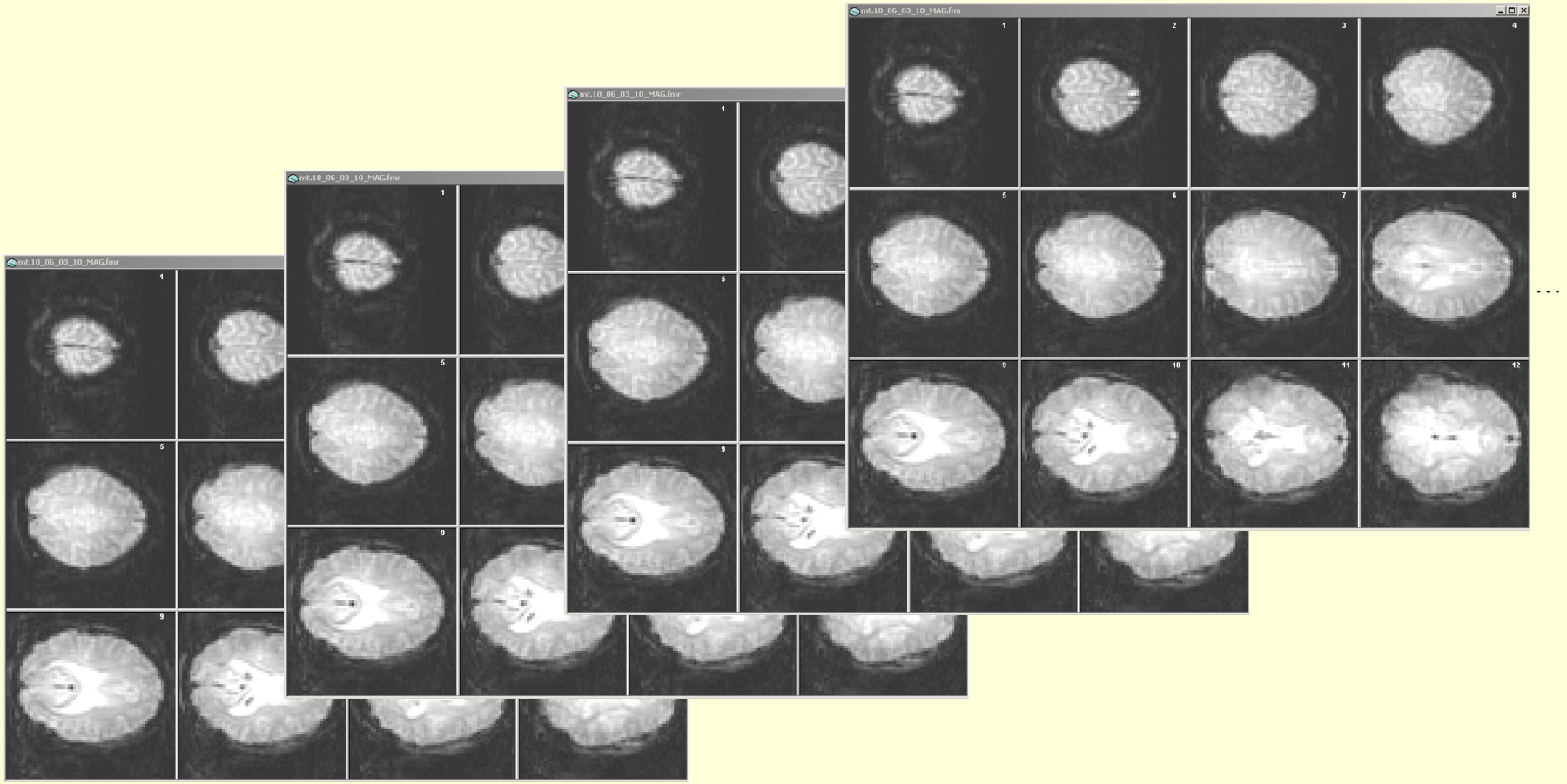
Scrambled Objects



Condition changes every 16 seconds (8 volumes per Block), 17 block
One volume (12 slices) every 2 seconds

for 272 seconds (4 minutes, 32 seconds)

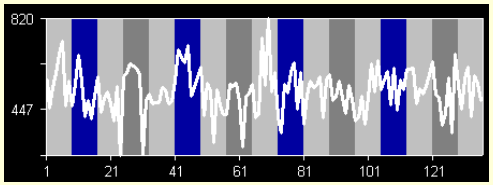
What data do we start with



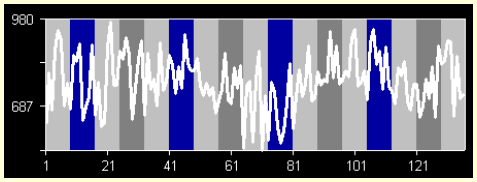
- 12 slices * 64 voxels x 64 voxels = 49,152 voxels
- Each voxel has 136 time points
- Therefore, for each run, we have 6.7 million data points
- We often have several runs for each experiment

Why do we need stats?

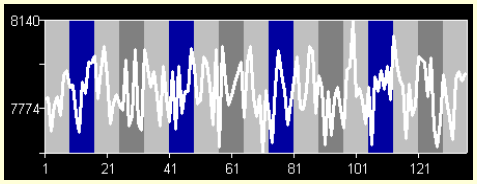
- We could, in principle, analyze data by voxel surfing: move the cursor over different areas and see if any of the time courses look interesting



Slice 9, Voxel 0, 0



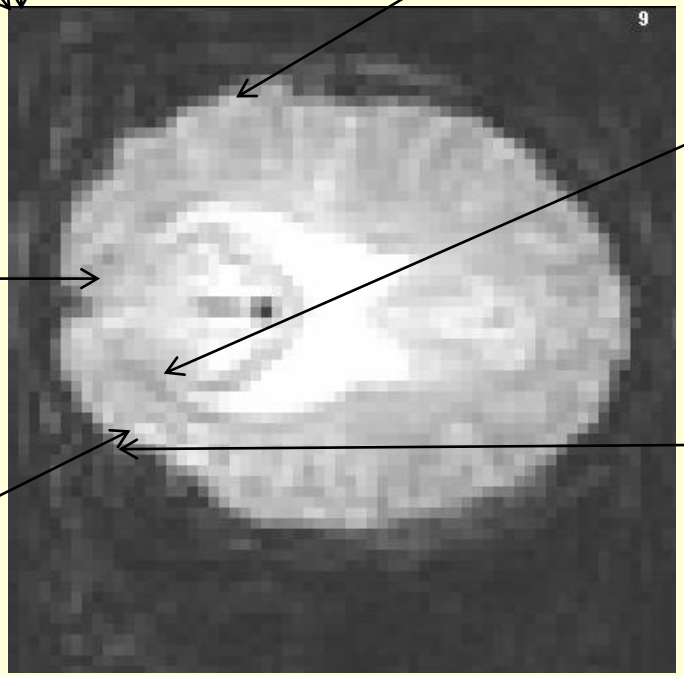
Slice 9, Voxel 1, 0

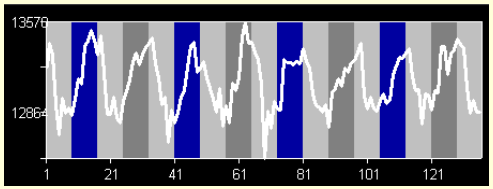


Slice 9, Voxel 22, 7

The signal is much higher where there is brain, but there's still noise

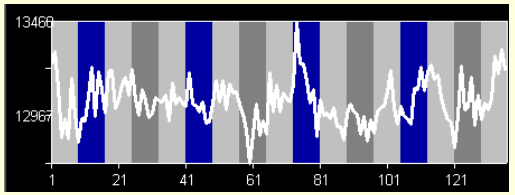
Even where there's no brain, there's noise





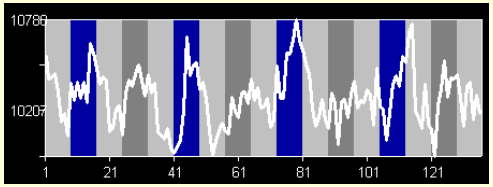
Slice 9, Voxel 9, 27

Here's a voxel that responds well whenever there's visual stimulation



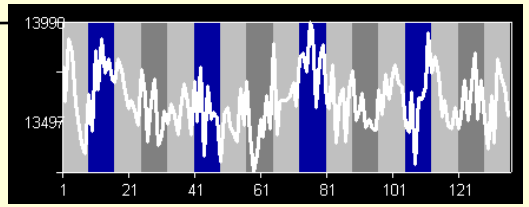
Slice 9, Voxel 18, 36

Here's a couple that sort of show the right pattern but is it "real"?



Slice 9, Voxel 13, 41

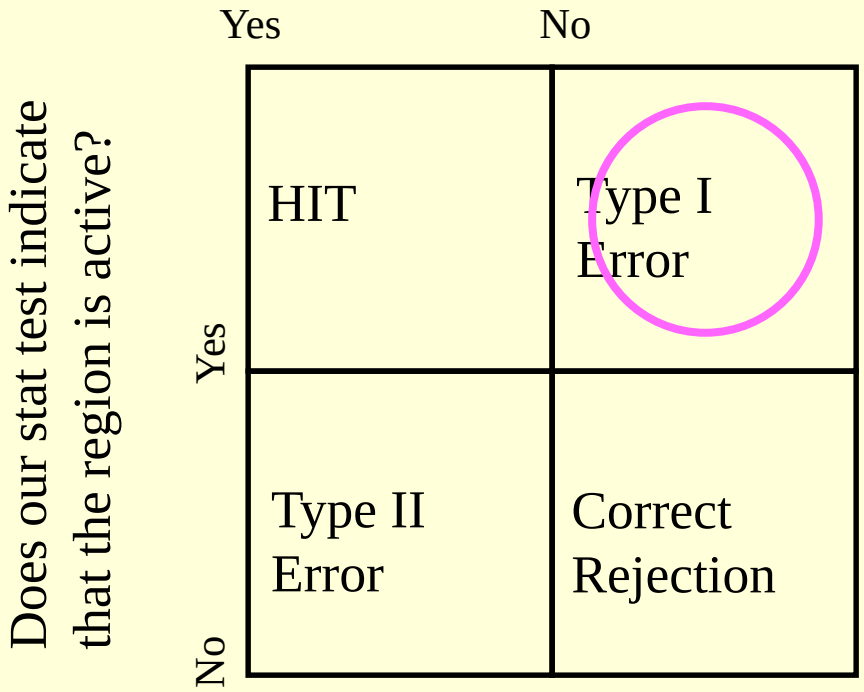
Here's one that responds well whenever there's intact objects



Slice 9, Voxel 14, 42

Types of Errors

Is the region truly active?



p value:
probability of a Type I error

e.g., p <.05

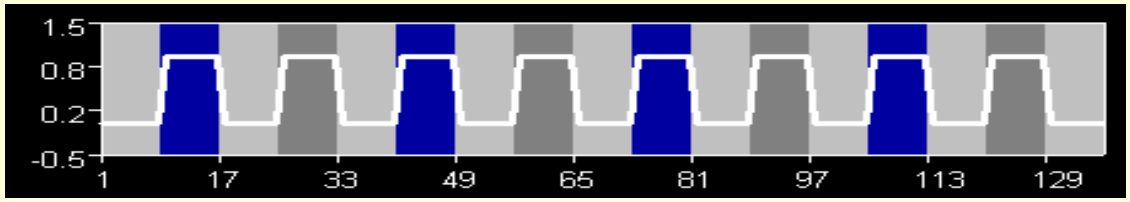
"There is less than a 5% probability that a voxel our stats have declared as "active" is in reality NOT active

Modeling the Predicted activation

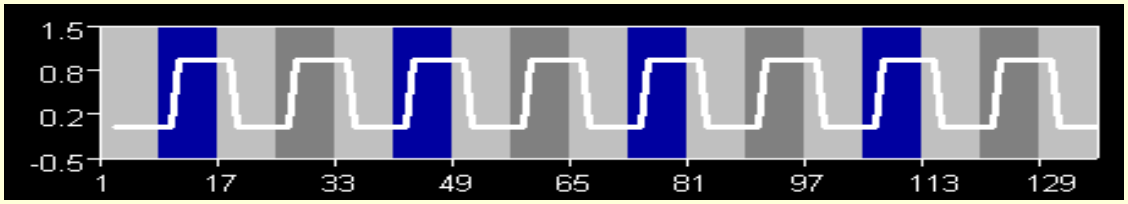
- It takes about 5 sec for the blood to catch up with the brain, therefore we can model the predicted activation in one of two ways:
  1. shift the boxcar by approximately 5 seconds (2 images x 2 seconds/image = 4 sec, close enough)
  2. convolve the boxcar with the hemodynamic response to model the shape of the true function as well as the delay

PREDICTED ACTIVATION IN VISUAL AREA

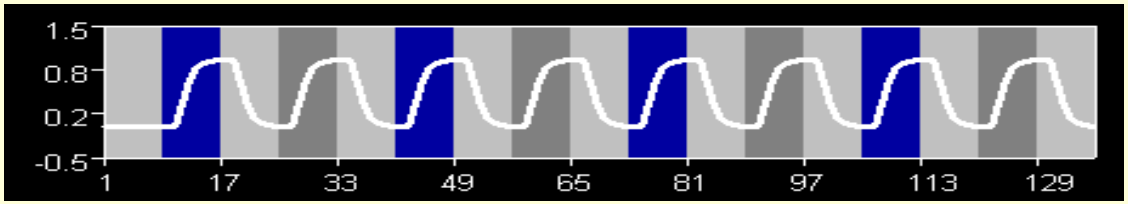
BOXCAR



SHIFTED



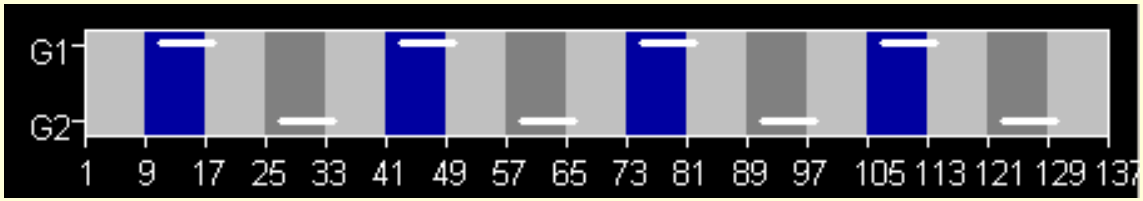
CONVOLVED WITH HRF



Statistical Approaches

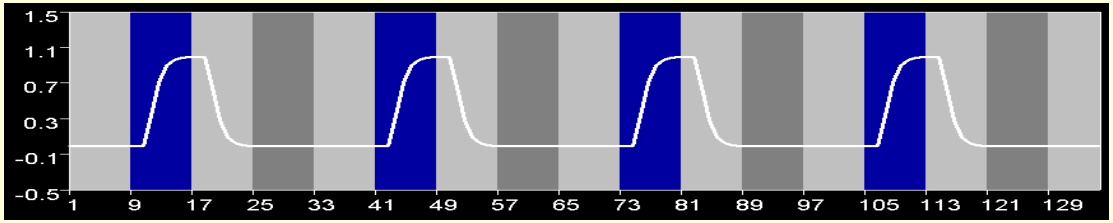
t-tests

- **compare activation levels between two conditions (eg. Activation and Rest)**



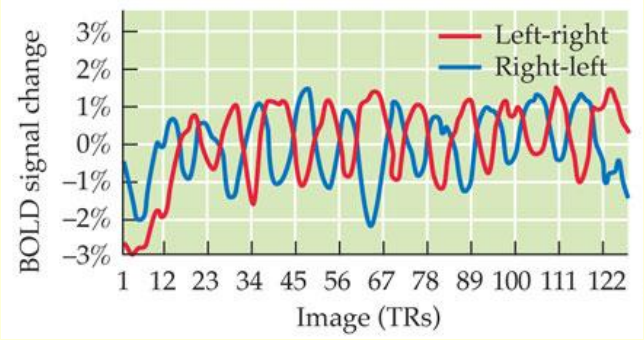
correlations

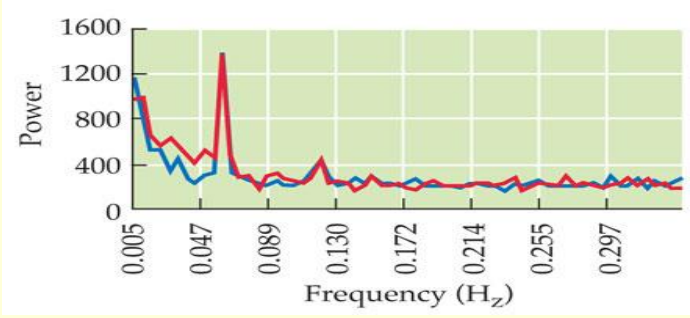
- **model activation and see whether any areas show a similar pattern**



Fourier analysis

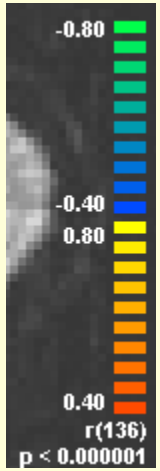
- **Do a Fourier analysis to see if there is energy at your paradigm frequency**

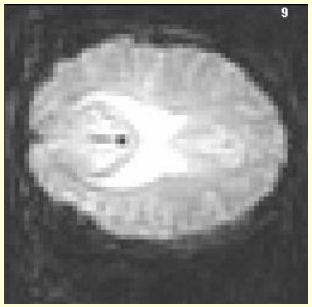




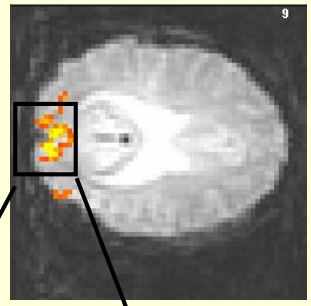
Fourier analysis images

Effect of Thresholds

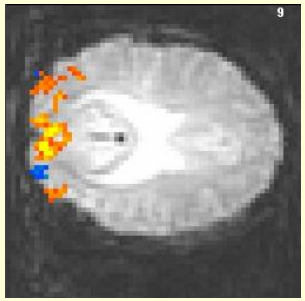




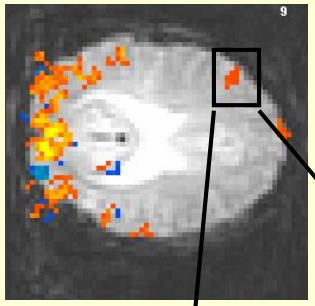
r = .80
64% of variance
$p < 10^{-33}$



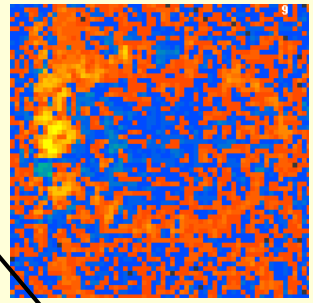
r = .50
25% of variance
p < .000001



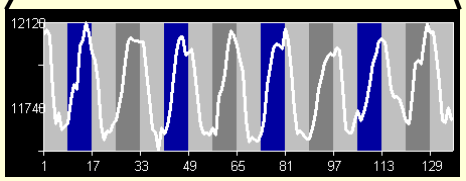
r = .40
16% of variance
p < .000001

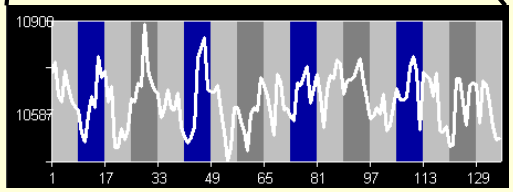


r = .24
6% of variance
p < .05



r = 0
0% of variance
p < 1

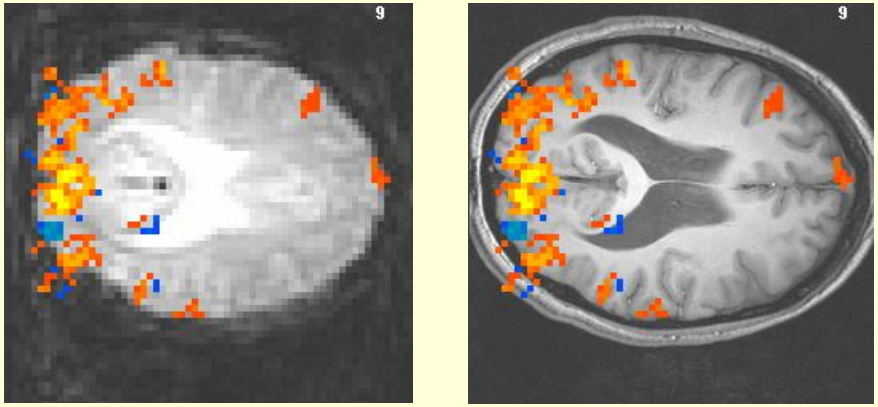




Complications

- There are all sorts of statistical problems:

What's wrong with these data?



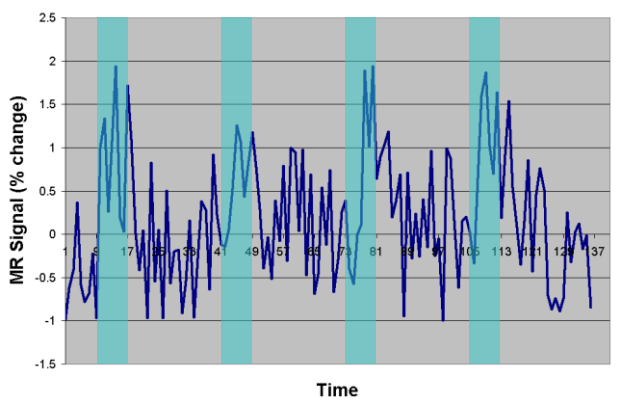
r = .24
6% of variance
p < .05

1. data may be contaminated by artifacts (e.g., head motion, breathing artifacts)

2. "significant" voxels by chance alone. (P=05) * 49,152 = 2457 voxels

3. many assumptions of statistics are false. (e.g. adjacent voxels uncorrelated with each other; adjacent time points uncorrelated with one another)

What's real?



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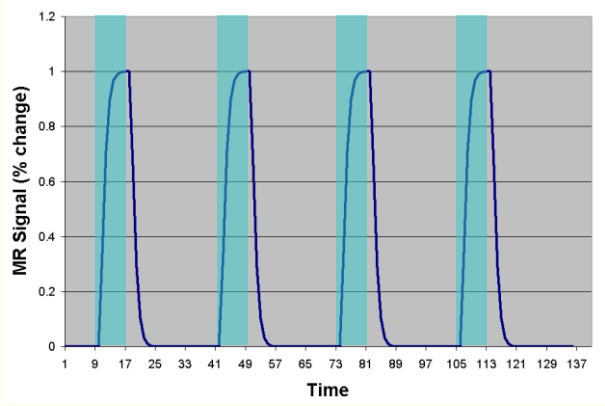
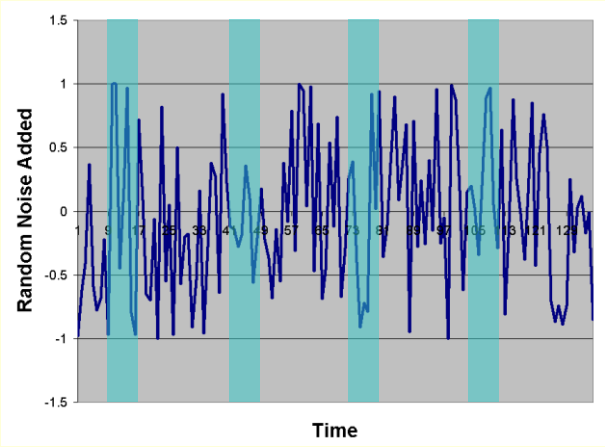


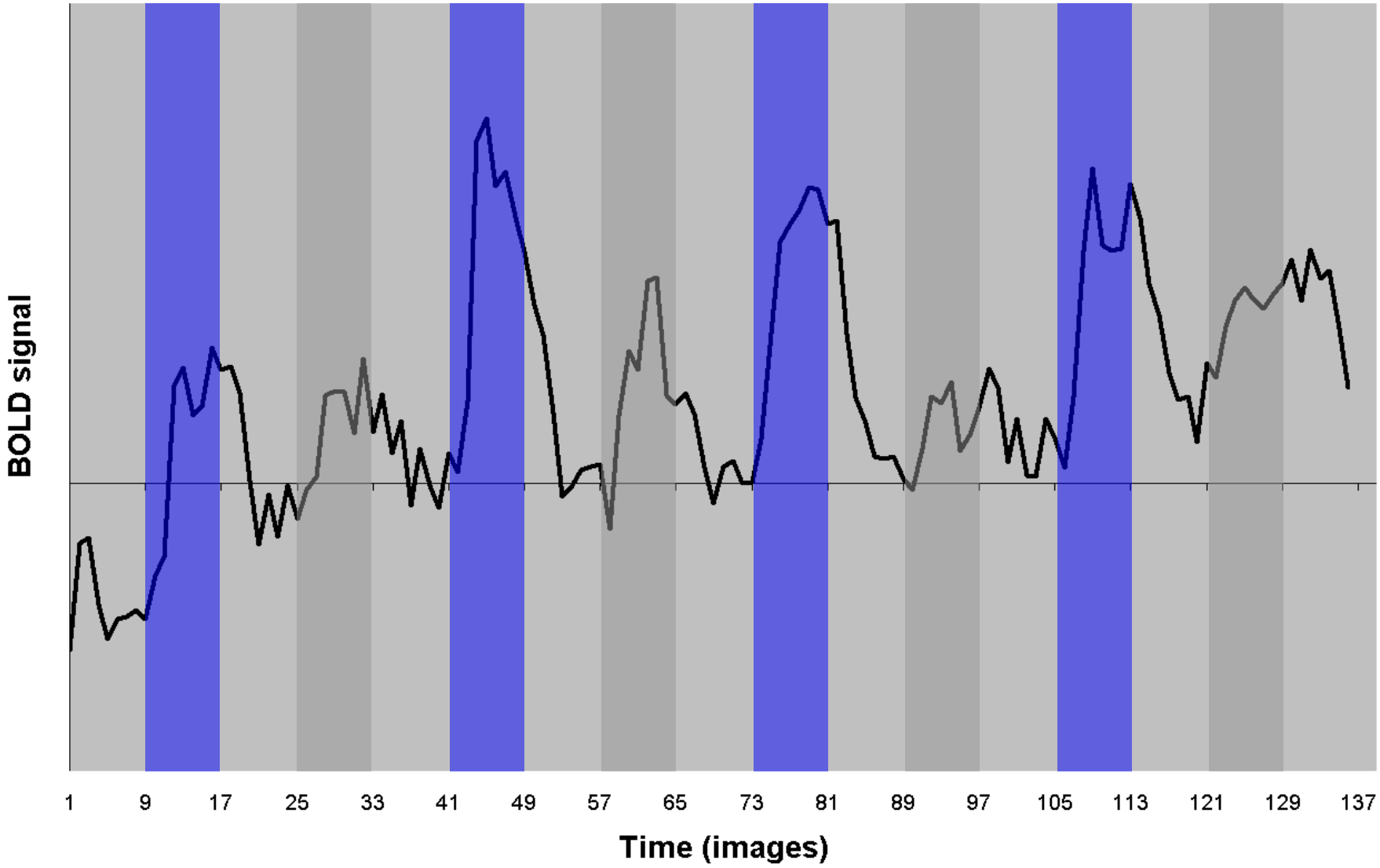
signal

+



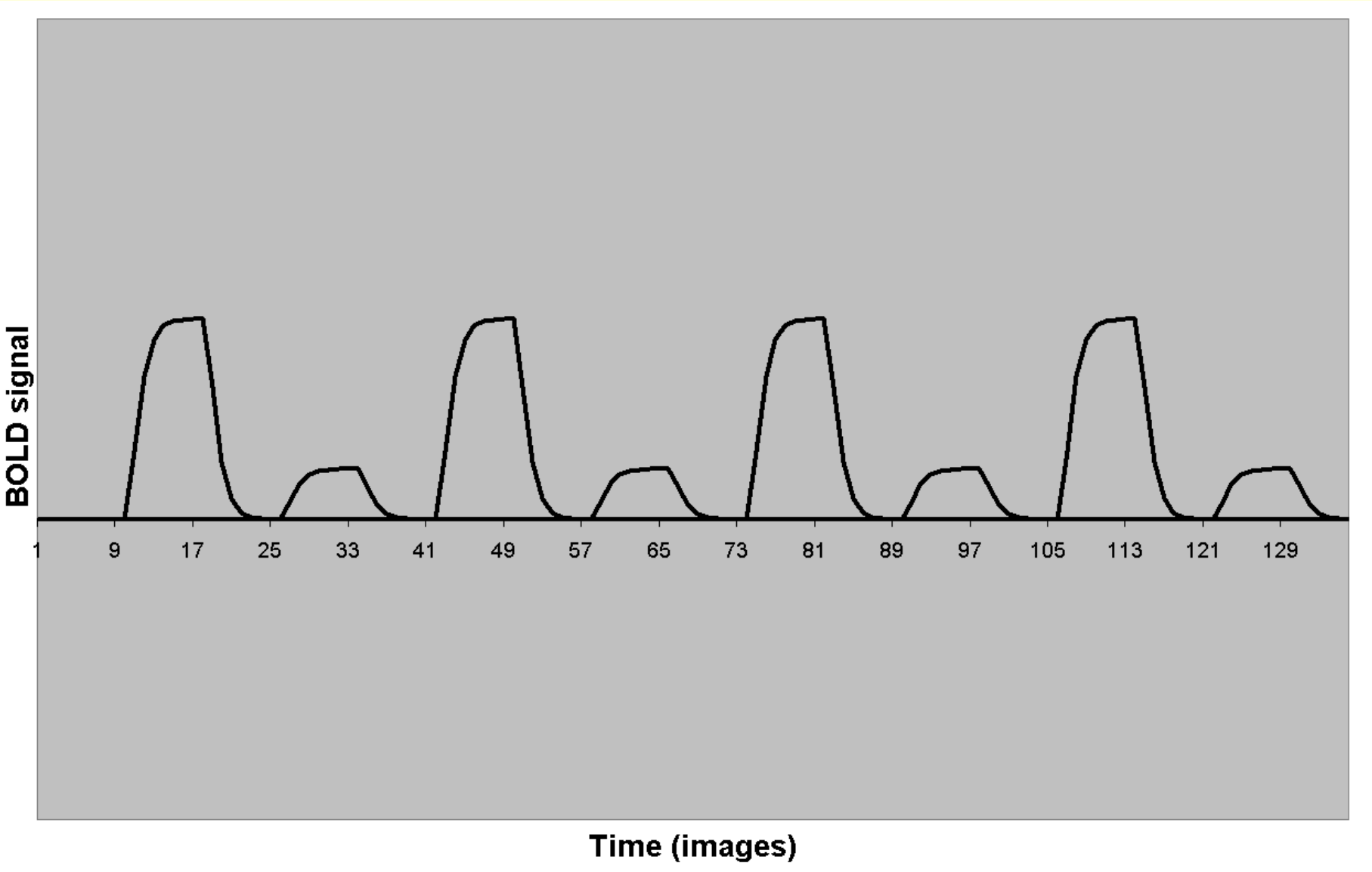
noise

Let's create a time course for one voxel
Intact Objects is greater than Scrambled

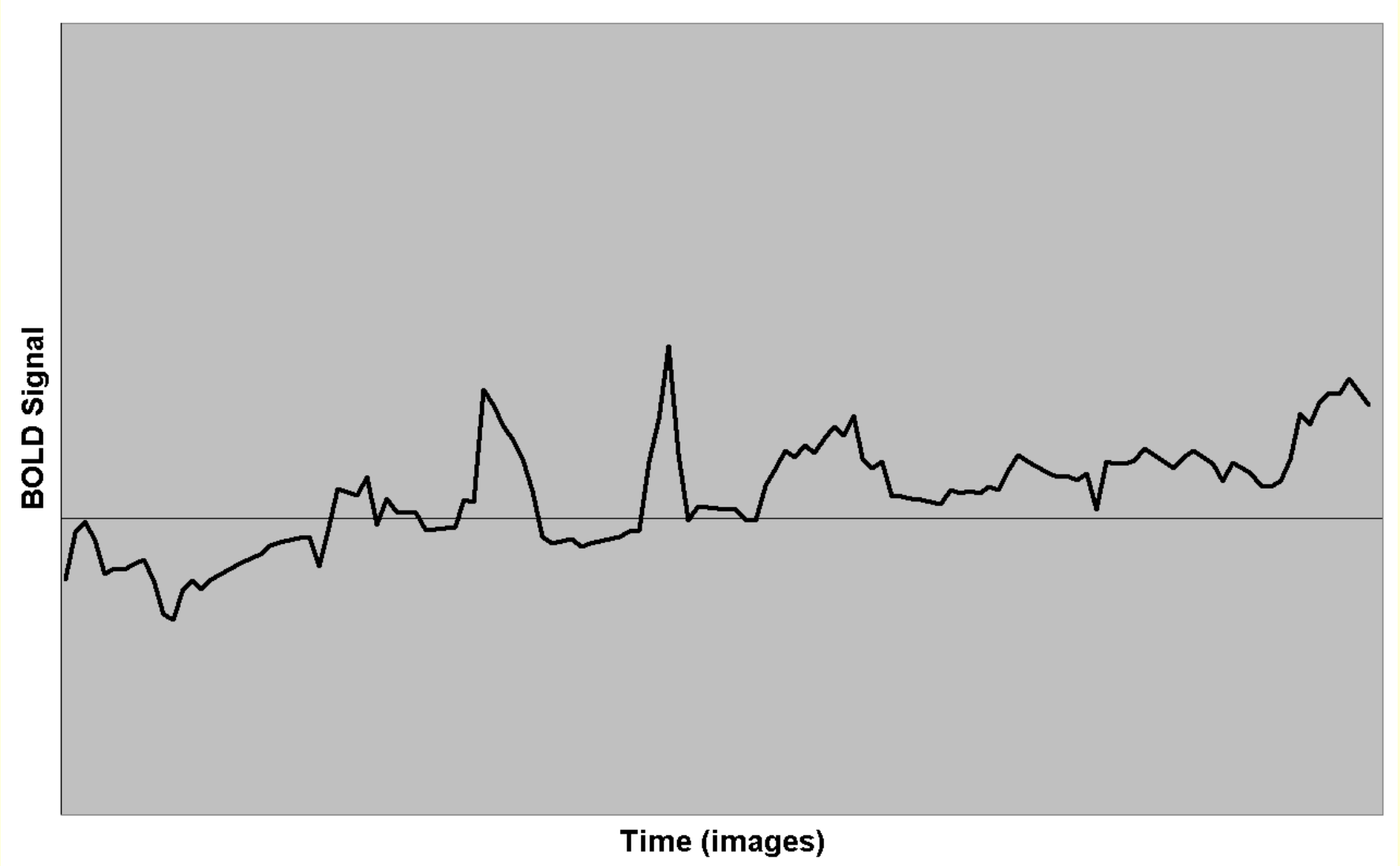


How this signal is build up?

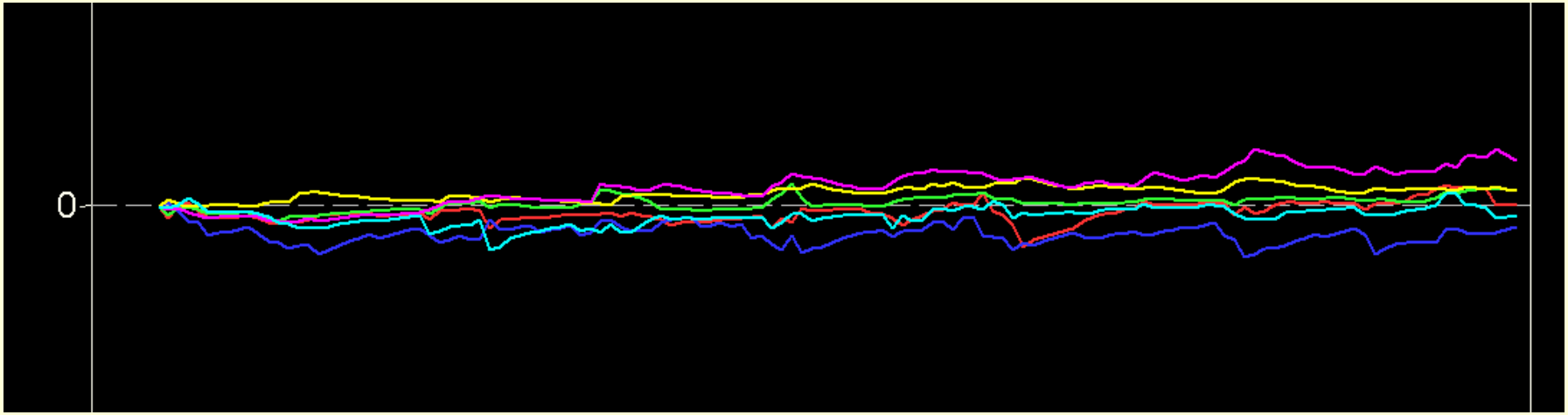
Response to Intact Objects which is 4X greater than Scrambled Objects



Now let's add some variability due to head motion



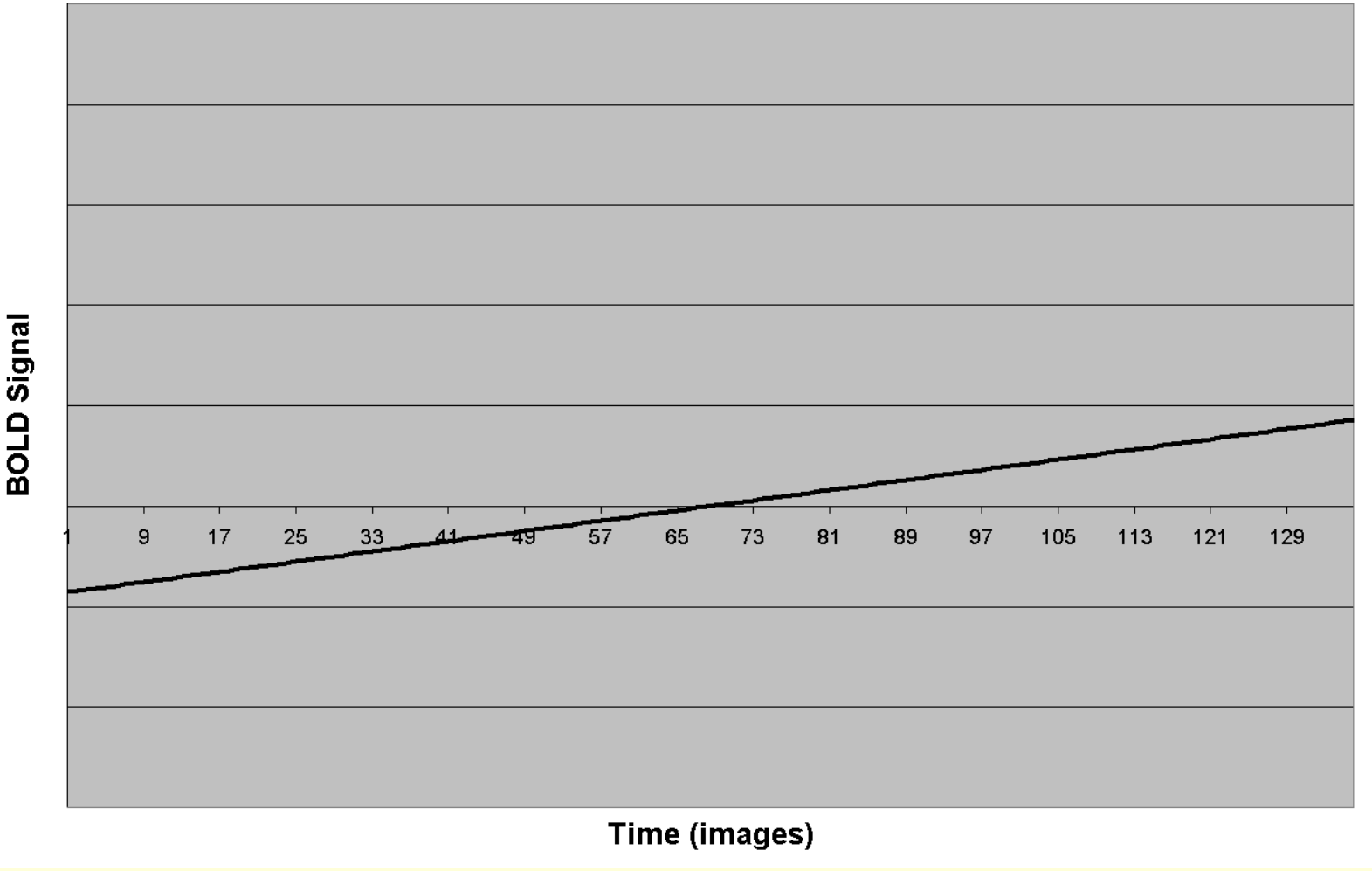
…though really motion is more complex



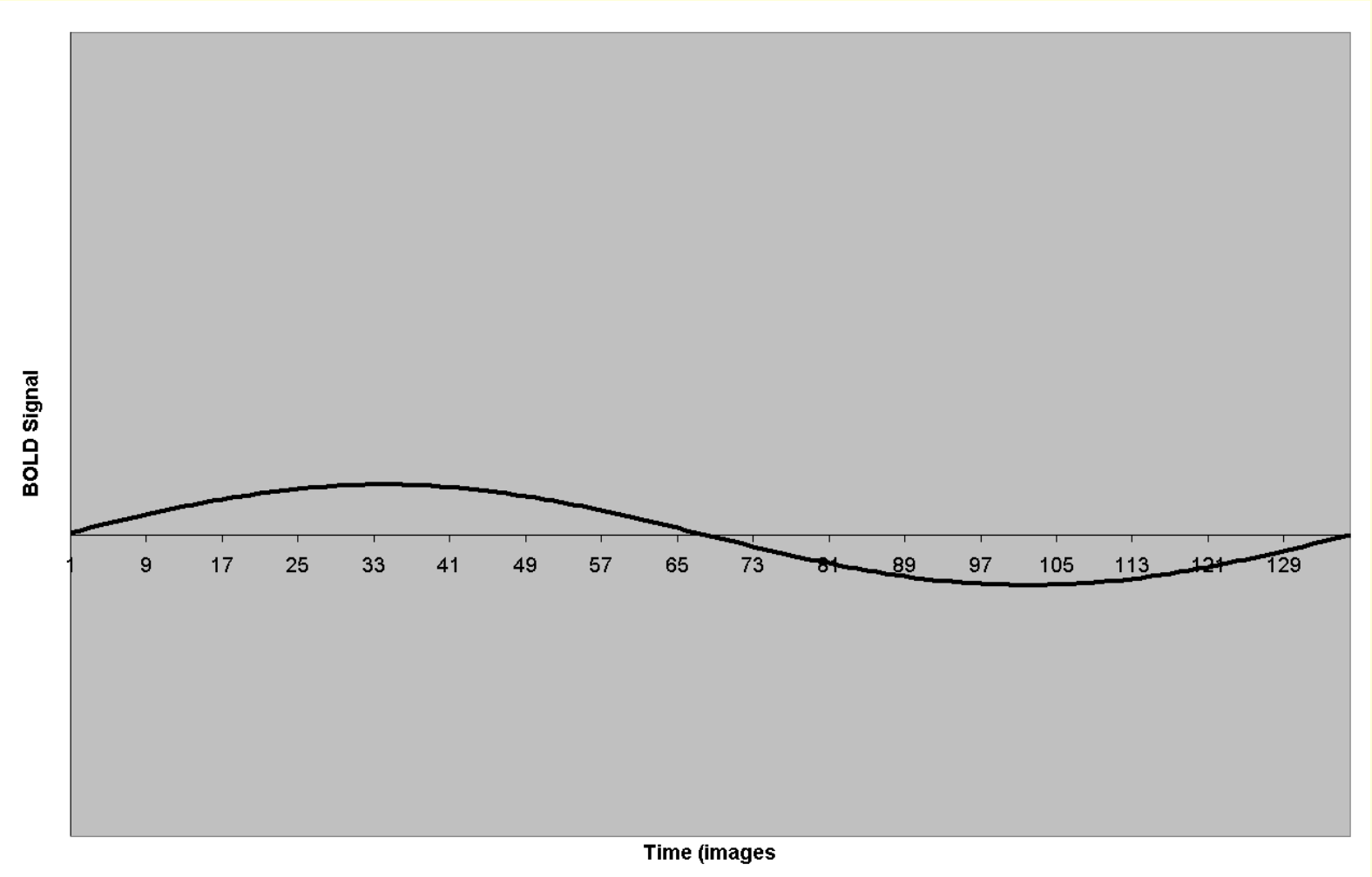
- Head motion can be quantified with 6 parameters given in any motion correction algorithm
  - x translation
  - y translation
  - z translation
  - xy rotation
  - xz rotation
  - yz rotation
- For simplicity, I've only included parameter one in our model

- Head motion can lead to other problems not predictable by these parameters

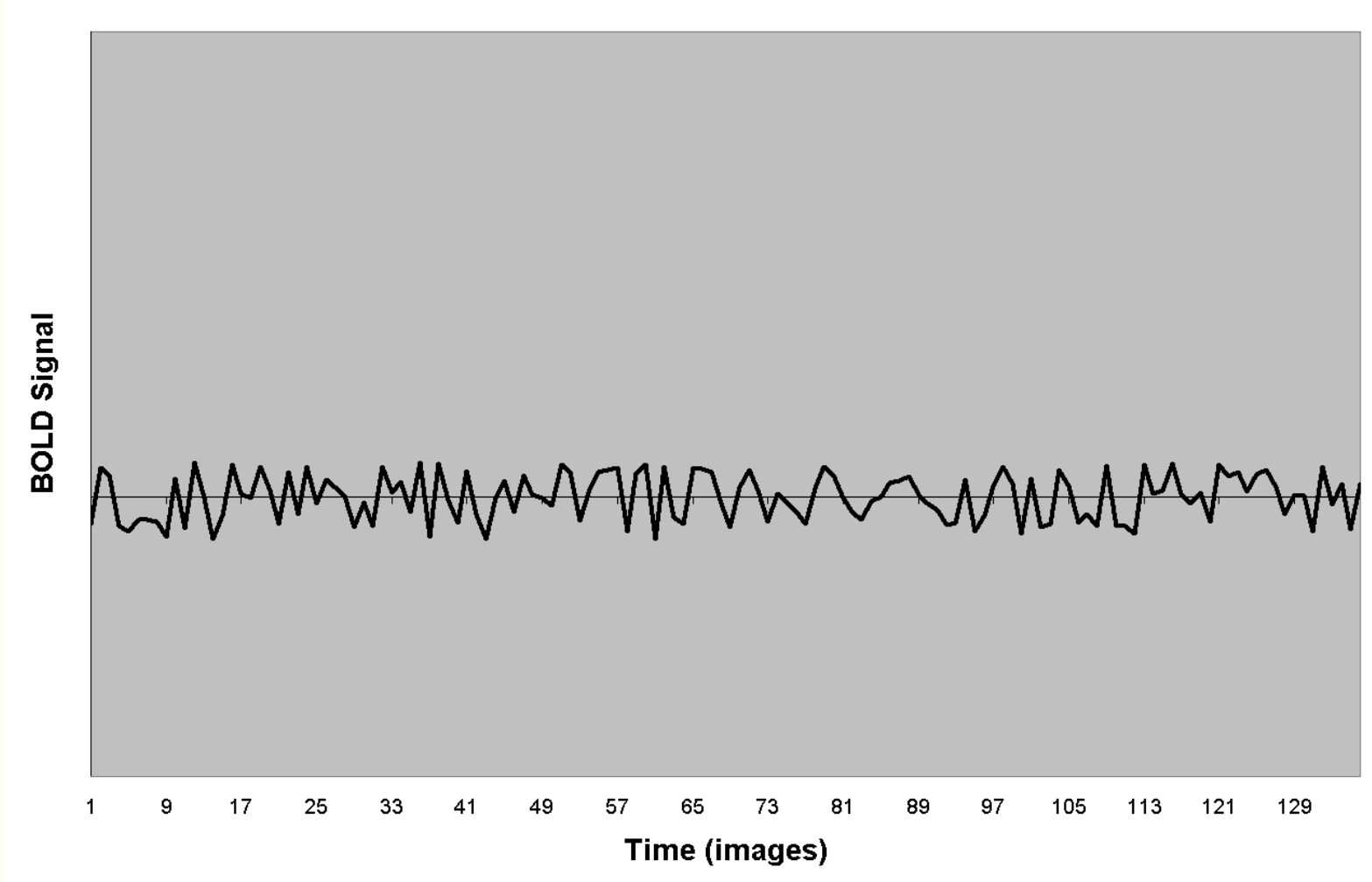
Adding linear drift from magnet noise (e.g., parts warm up) or physiological noise (e.g., subject's head sinks



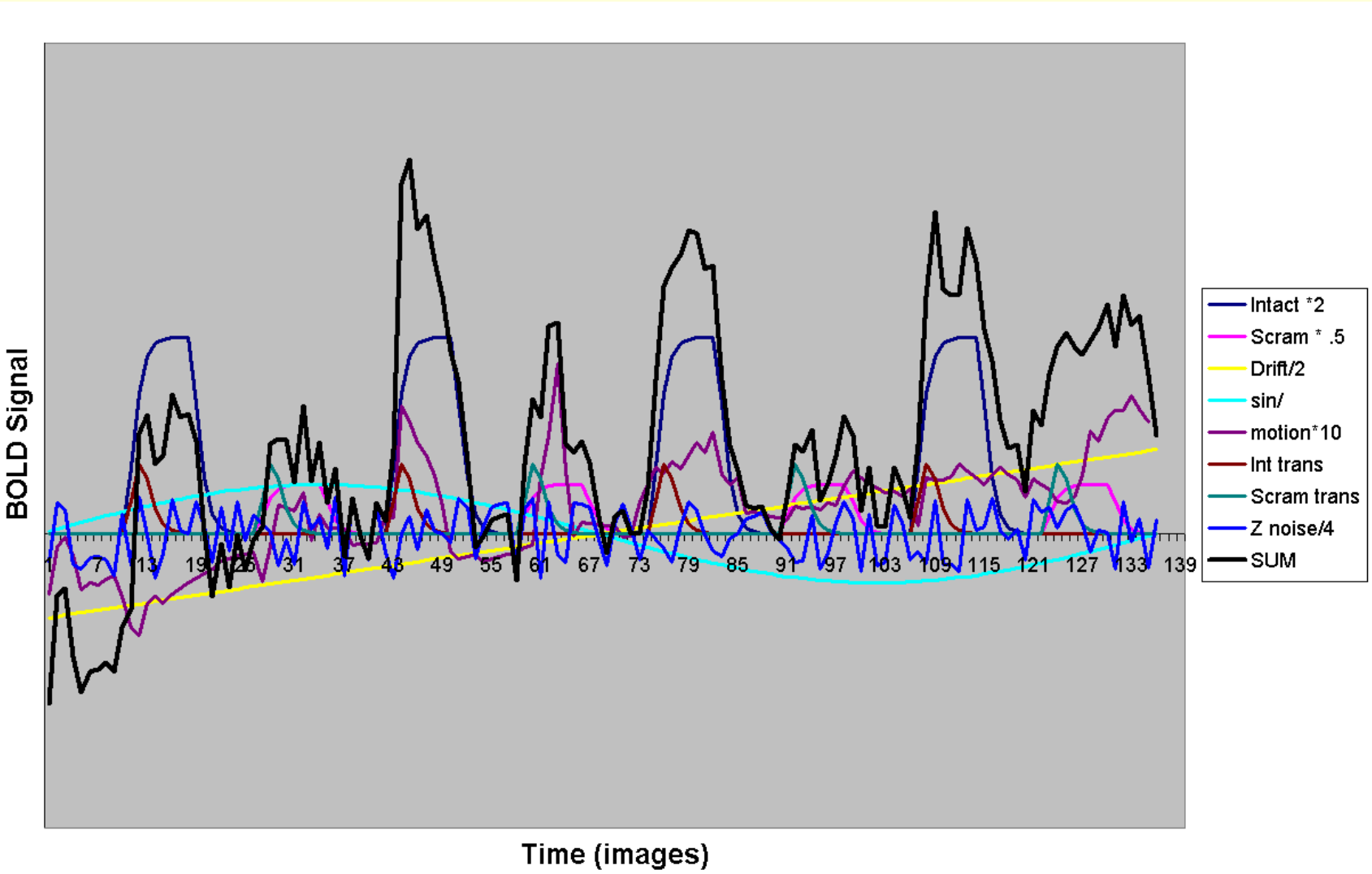
Add a dash of low frequency noise from magnet noise or physiological noise (e.g., subject's cycles of alertness/drowsiness)



Adding some high frequency noise from magnet noise or physiological noise (e.g., subject's breathing rate and heartrate

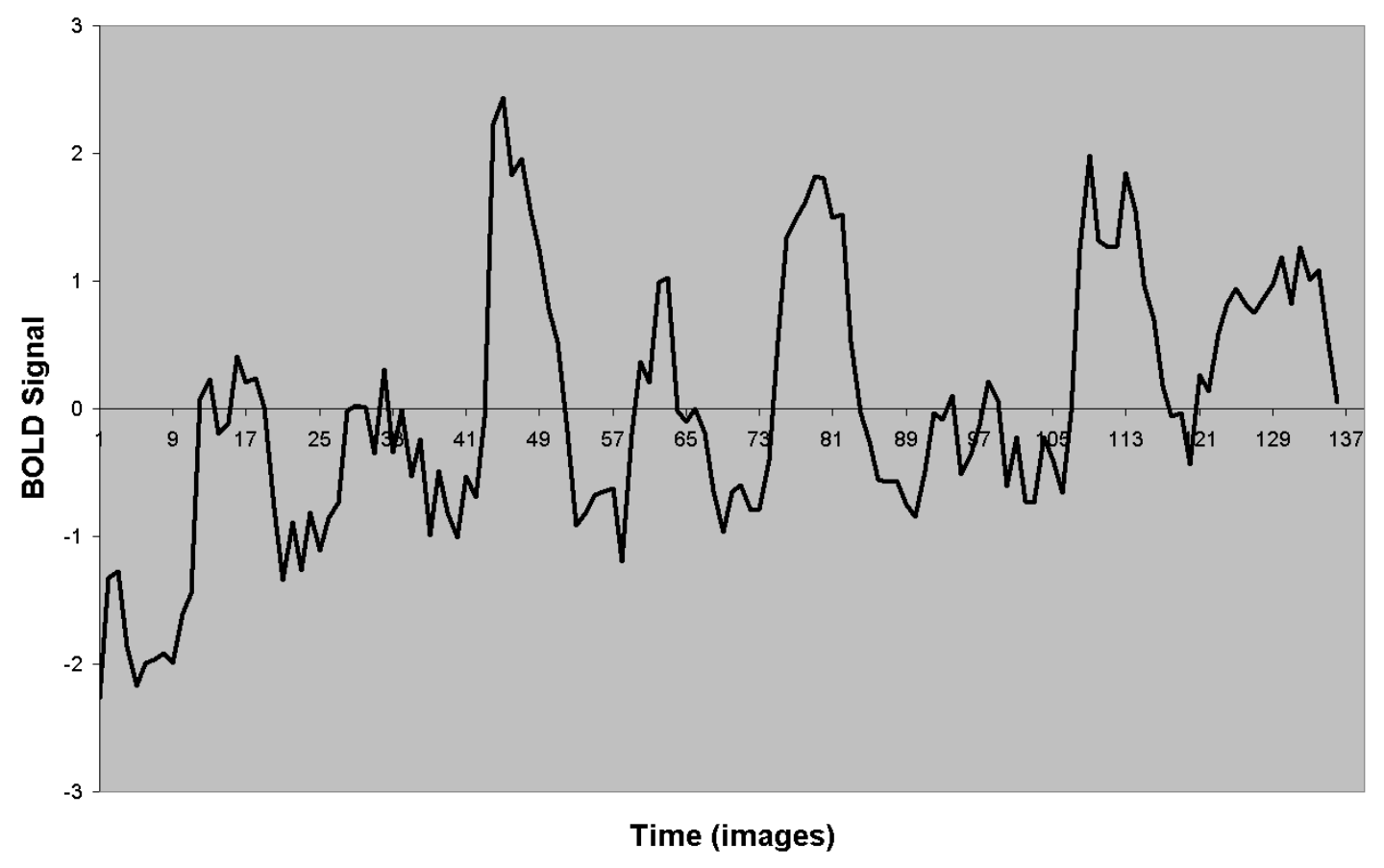


When we add these all together, we get a realistic time course



Now let's be the experimenter

- First, we take our time course and normalize it using z scores
- z = (x - mean)/SD
- normalization leads to data where: mean = zero SD = 1



Using General Linear Model

- T-tests, correlations and Fourier analysis work for simple designs.
- The General Linear Model (GLM) can be used

Why is the GLM so great?

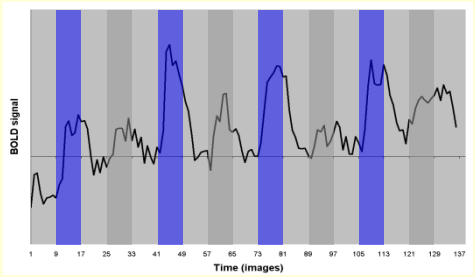
- Any combination of contrasts can be used (e.g., intact - scrambled, scrambled - baseline) with one GLM rather than multiple correlations

- the GLM allows for combining data within subjects and between subjects

- the GLM allows you to model things that may account for variability in the data (e.g., head motion)

- GLM allows using more complex designs (e.g., factorial designs)

We create a GLM with 2 predictors



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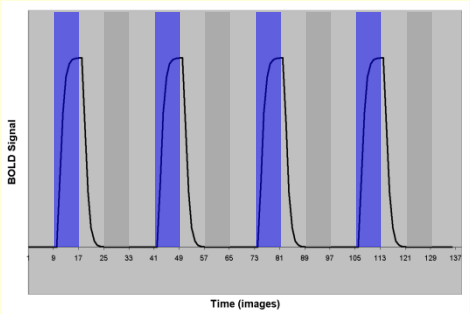
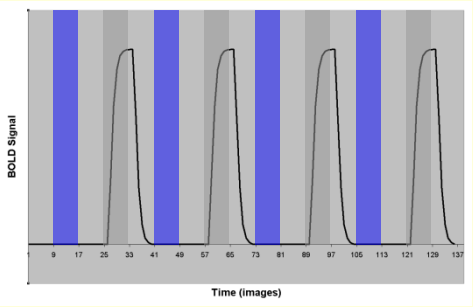


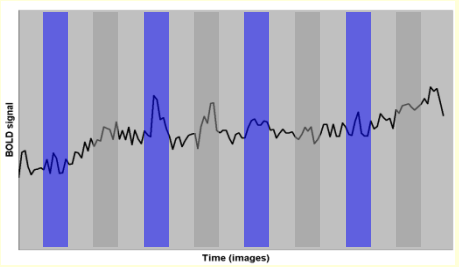
$\times \beta_1$

+



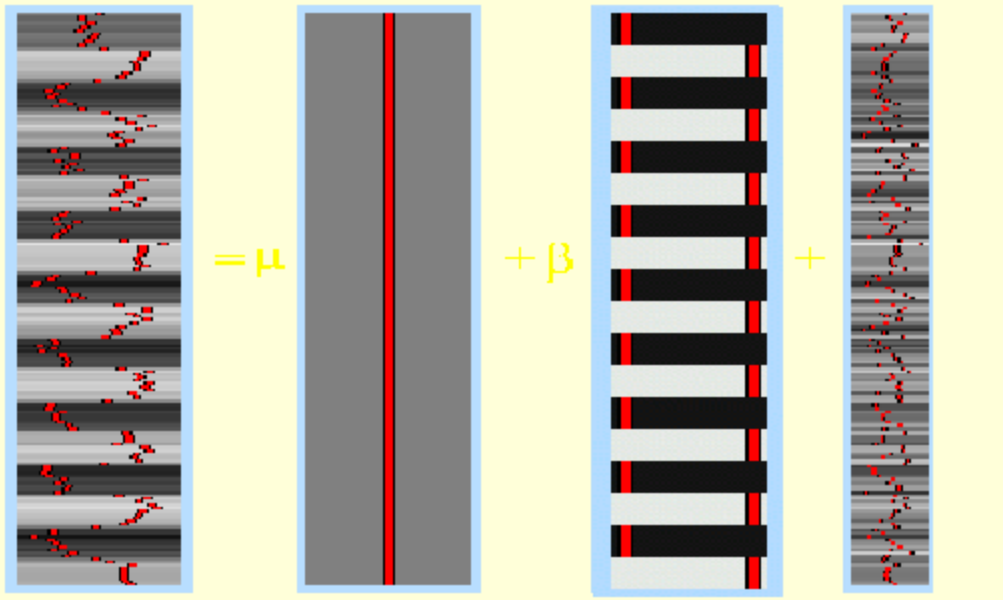
$\times \beta_2$

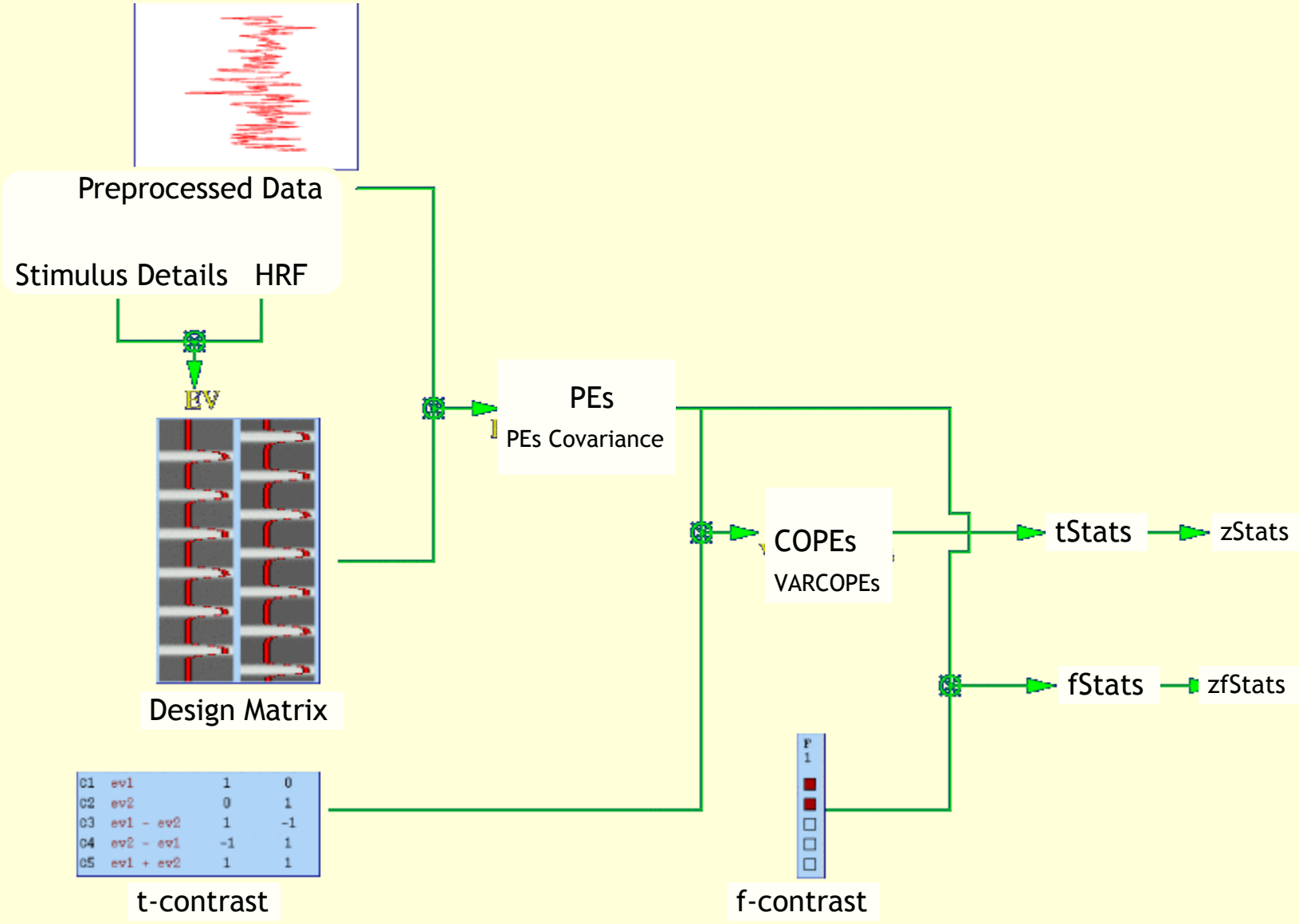
+



fMRI Signal	=	Design Matrix	x	Betas	+	Residuals
"our data"	=	*"what we CAN explain"*	x	*"how much of it we CAN explain"*	+	*"what we CANNOT explain"*

Statistical significance is basically a ratio of explained to unexplained variance


= μ
+ β
+
Y
= μ 1
+ β X
+ ε
Data
Mean
Parameter estimate (PE)
Explanatory Variable (EV)
Residuals


Preprocessed Data
Stimulus Details
HRF
EV
Design Matrix
PEs
PEs Covariance
COPEs
VARCOPEs
tStats
zStats
fStats
zfStats
t-contrast
f-contrast