fMRI based on Blood Oxygenation Level Dependence (BOLD) contrast

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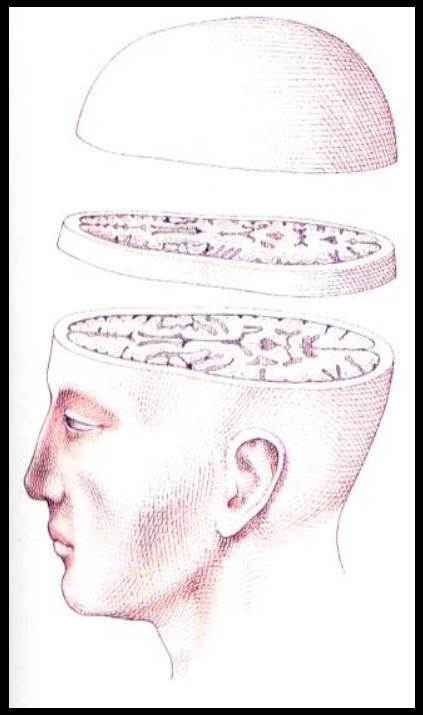
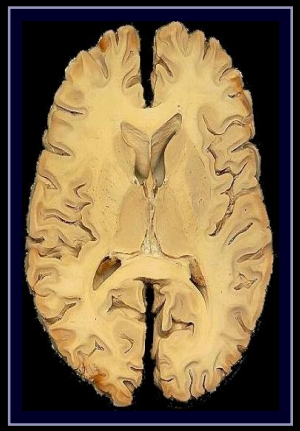
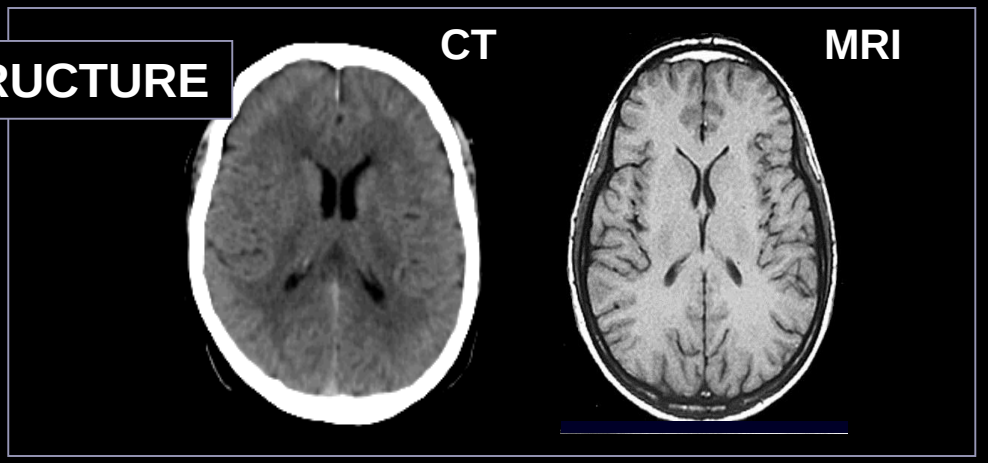
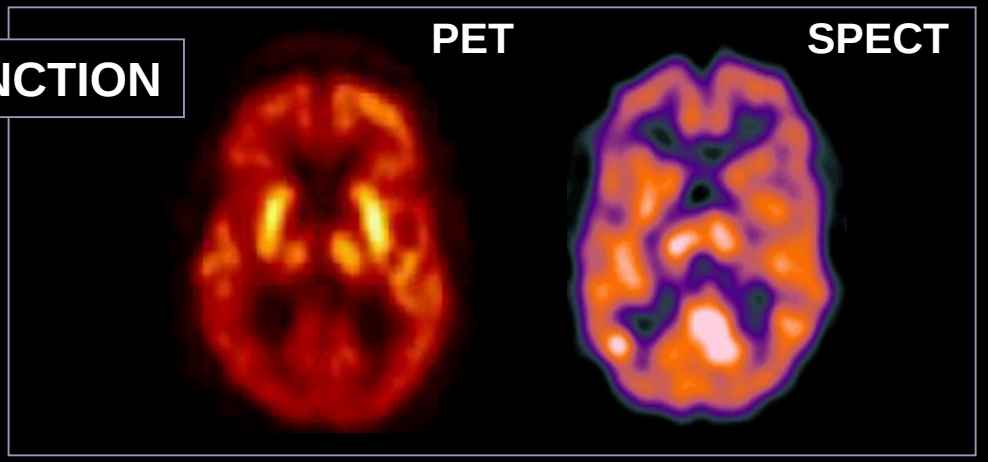
Functional vs Structural Imaging









Nuclear Medicine is to physiology as Radiology is to anatomy

Function vs structure

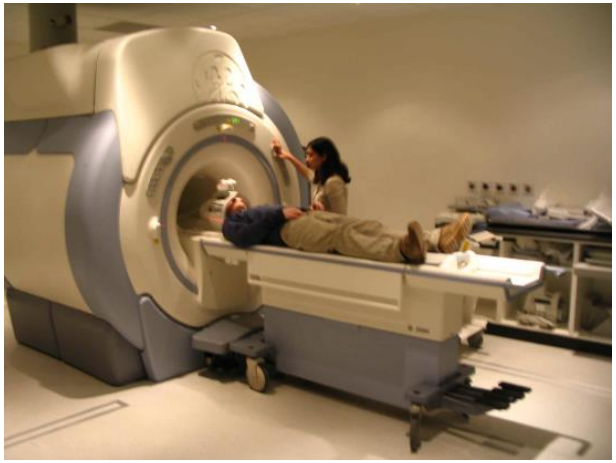
- Structure
  - Anatomical/Morphological imaging
- Function
  - Cell function (Molecular imaging)
    - Metabolic information
  - Tissue/organ function (Physiological imaging)
  - Human Functions (Functional imaging)

What is fMRI?

- Functional Magnetic Resonance Imaging (fMRI): uses MRI to indirectly measure brain activity

- Known for over 100 yrs. that blood flow and blood oxygenation are linked to neural activity– only since the early 1990's was fMRI developed (Ogawa & Kwong)

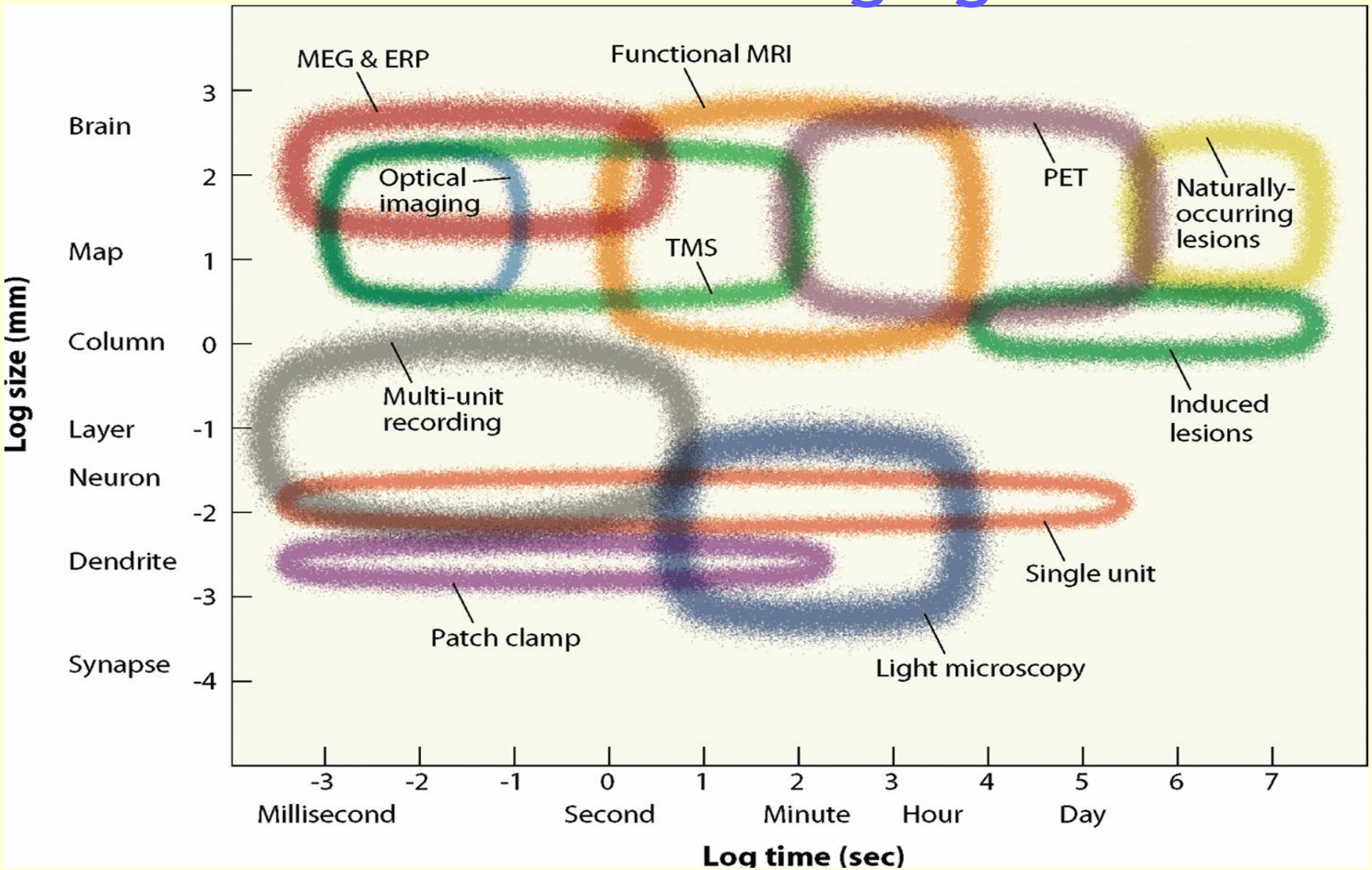
- Based on the assumption that neuronal activity requires O_2 which is carried by the blood; increased blood flow and resulting hemodynamics are foundation to fMRI



fMRI vs. PET

- fMRI does not require exposure to radiation
  - fMRI can be repeated
- fMRI has better spatial and temporal resolution
  - requires less averaging
  - can resolve brief single events
- MRI can obtain anatomical and functional images within same session
- PET can provide more direct measures about metabolic processes

Spatial and Temporal Resolution of Various functional imaging methods

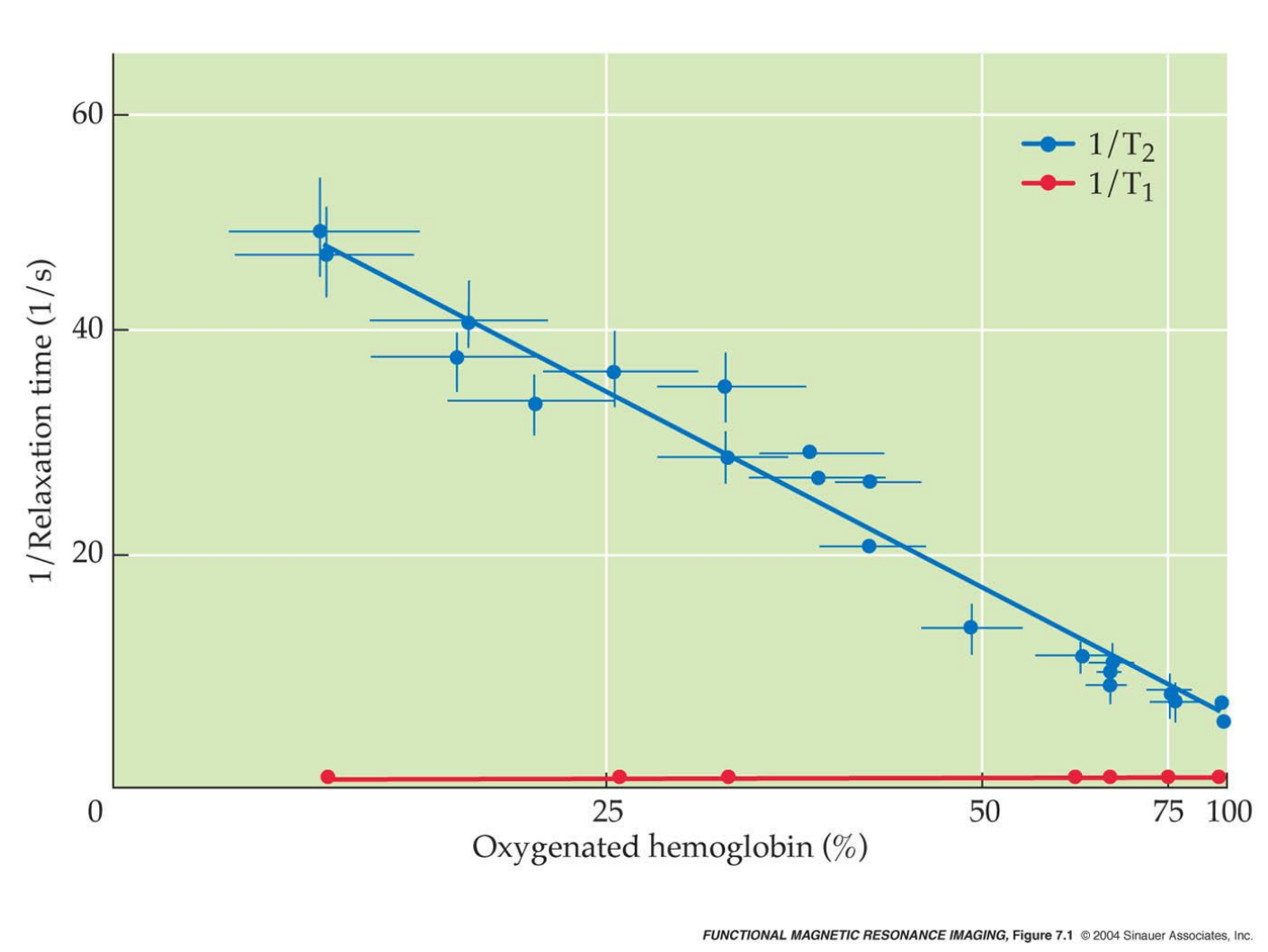


fMRI BOLD imaging is based on inherent Contrast Agents

- Contrast agent is a Substance that alter magnetic susceptibility of tissue, leading to changes in MR signal
  - Affects local magnetic homogeneity: decrease in T1 or T_2^*

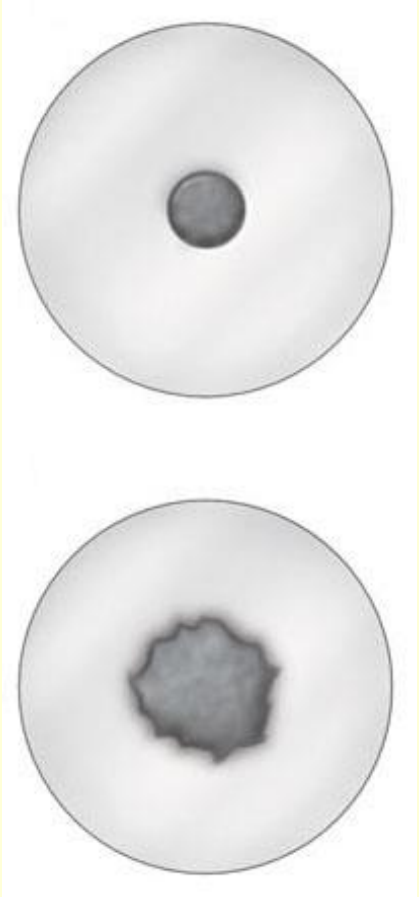
- Two types
  - Exogenous: Externally applied, non-biological compounds (e.g., Gd-DTPA)
  - Endogenous: Internally generated biological compound (e.g., deoxyhemoglobin, dHb)

Blood Deoxygenation affects T_2^* Decay



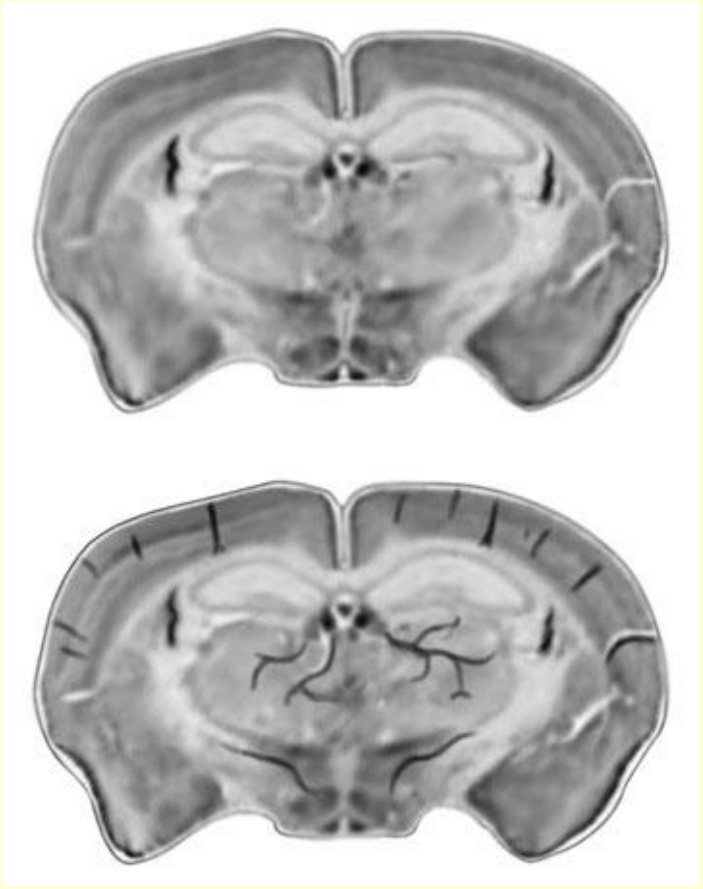
Thulborn et al., 1982

Deoxygenated Blood → Signal Loss



Oxygenated blood?
No signal loss…

Deoxygenated blood?
Signal loss!!!



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

History of fMRI

MRI
-1971: MRI Tumor detection (Damadian)
-1973: Lauterbur suggests NMR could be used to form images
-1977: clinical MRI scanner patented
-1977: Mansfield proposes echo-planar imaging (EPI) to acquire images faster

fMRI
-1990: Ogawa observes BOLD effect with T2*
blood vessels became more visible as blood oxygen decreased
-1991: Belliveau observes first functional images using a contrast agent
-1992: Ogawa et al. and Kwong et al. publish first functional images using BOLD signal

Ogawa

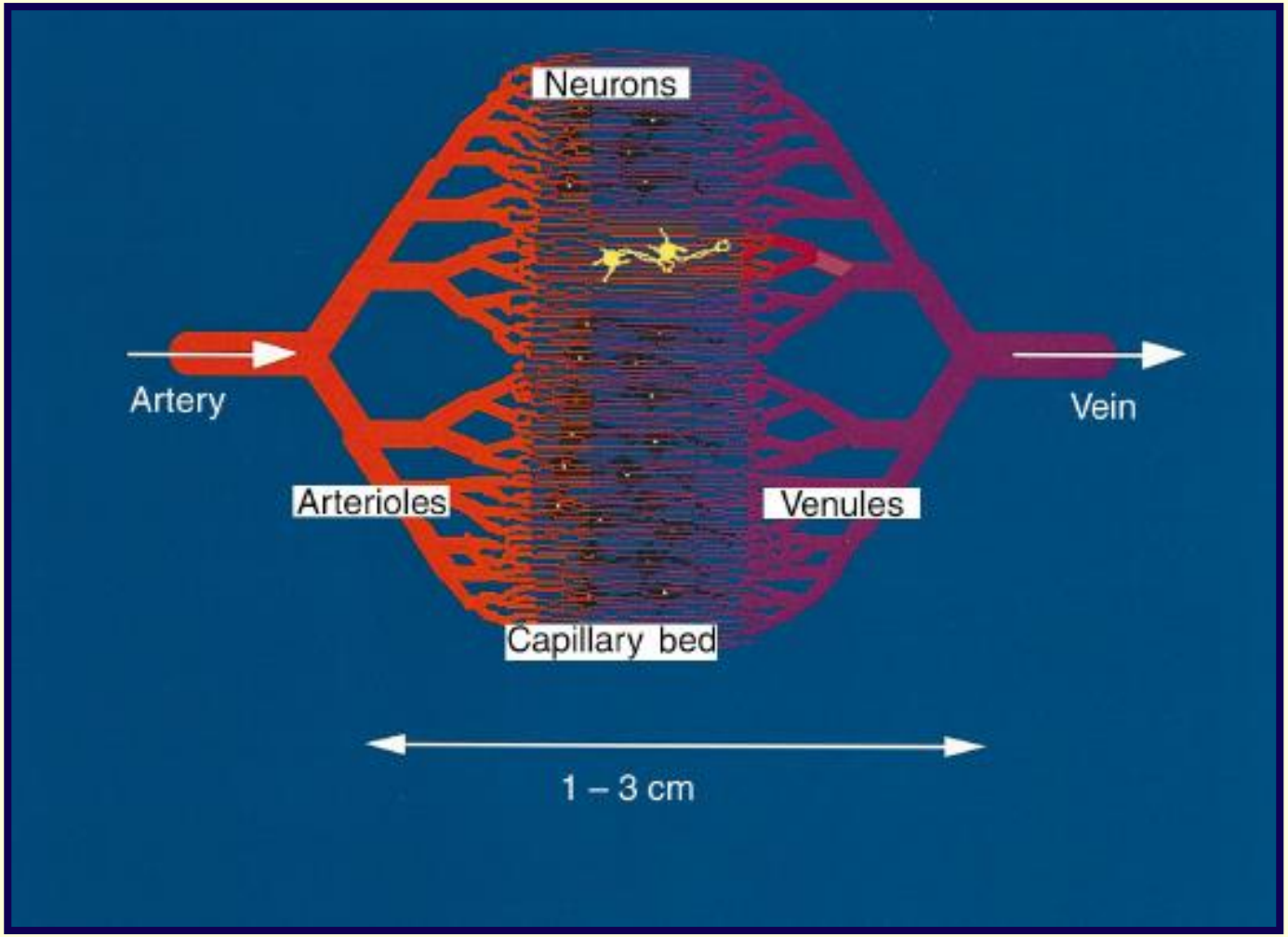
BOLD Endogenous Contrast

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

Measuring Deoxyhemoglobin

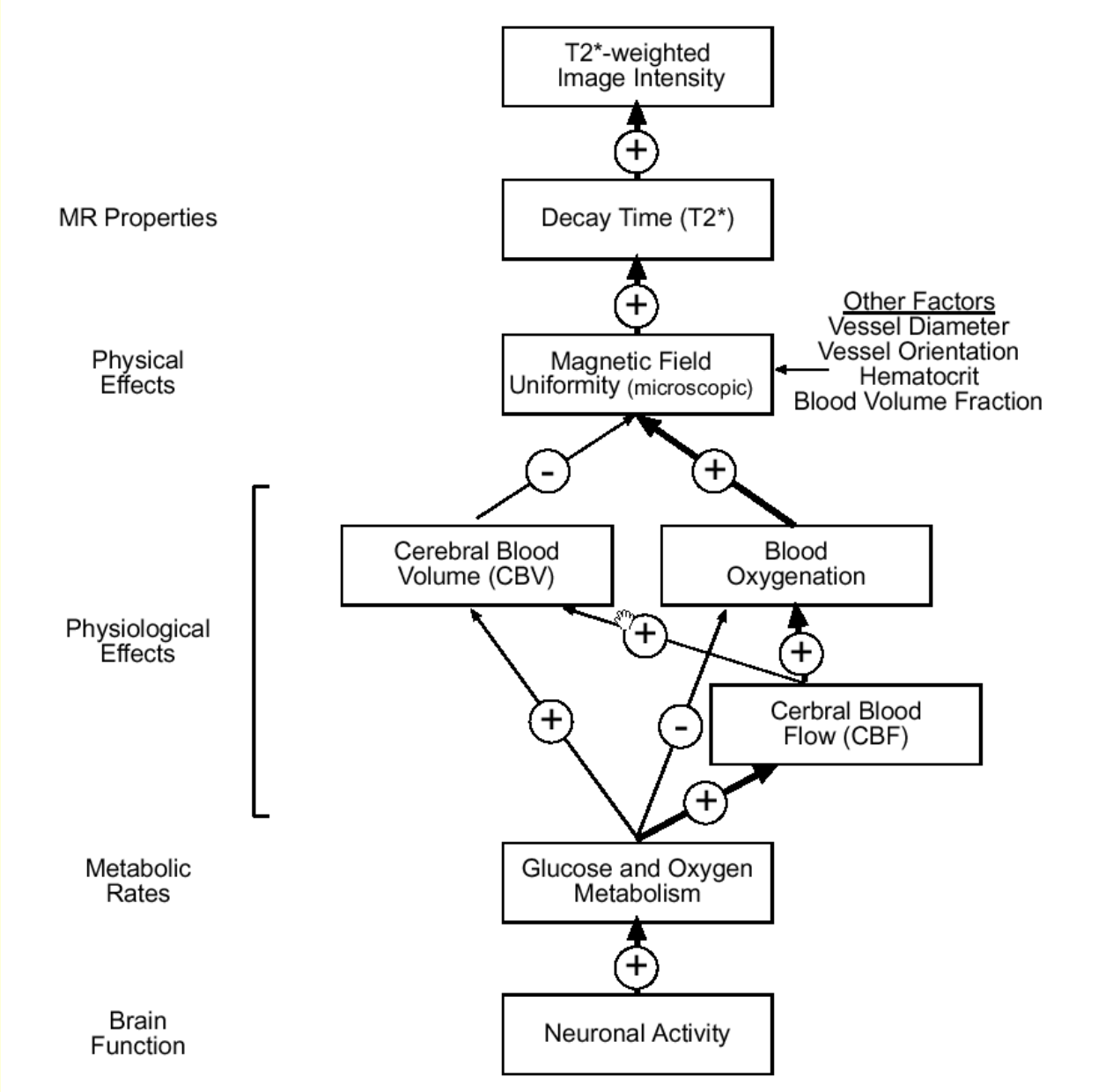
- fMRI measurements are of amount of oxyhemoglobin per voxels in Venus pool
- We assume that amount of oxyhemoglobin in vein is predictive of neuronal activity

Vasculature

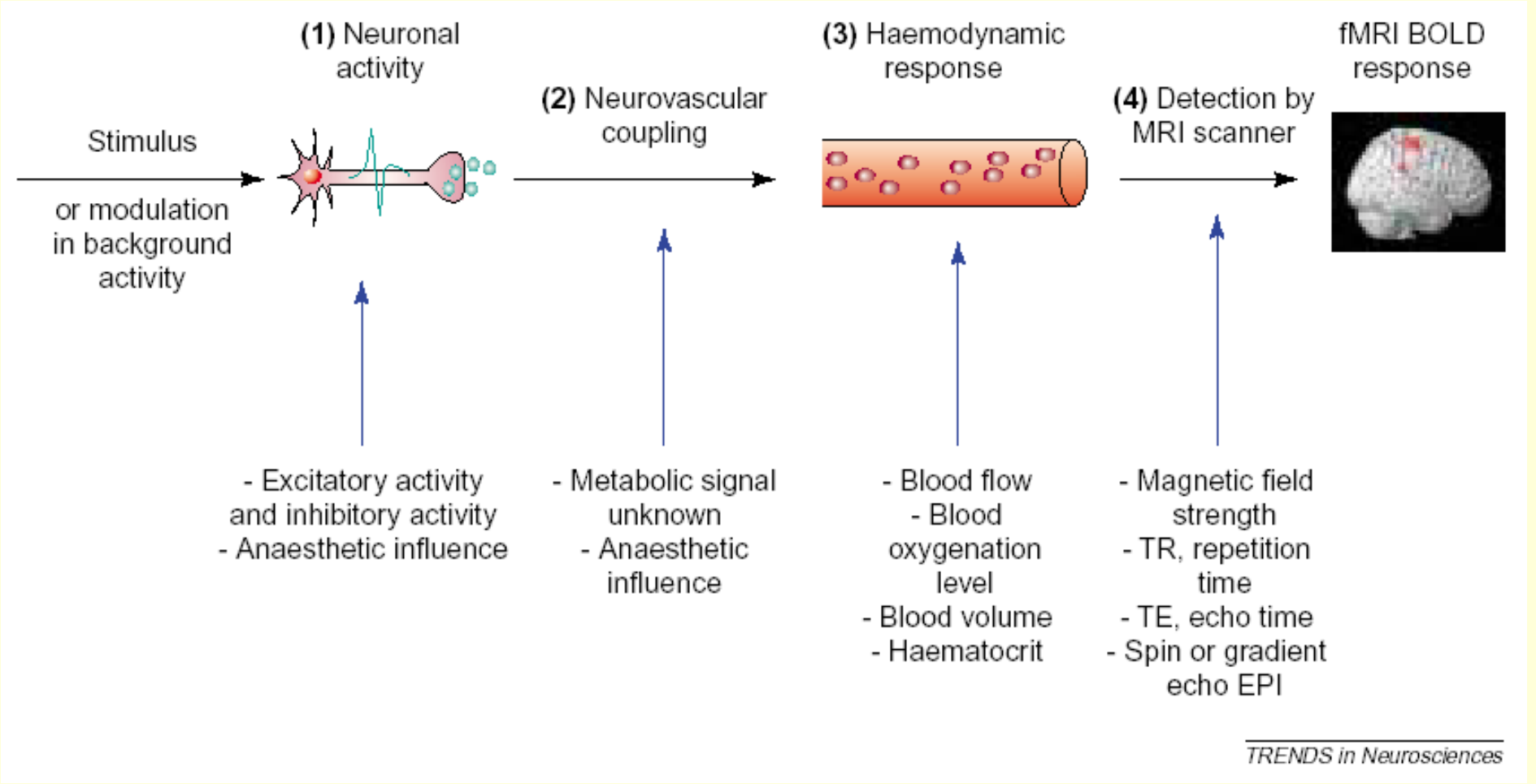


Source: Menon & Kim, TICS

BOLD signal

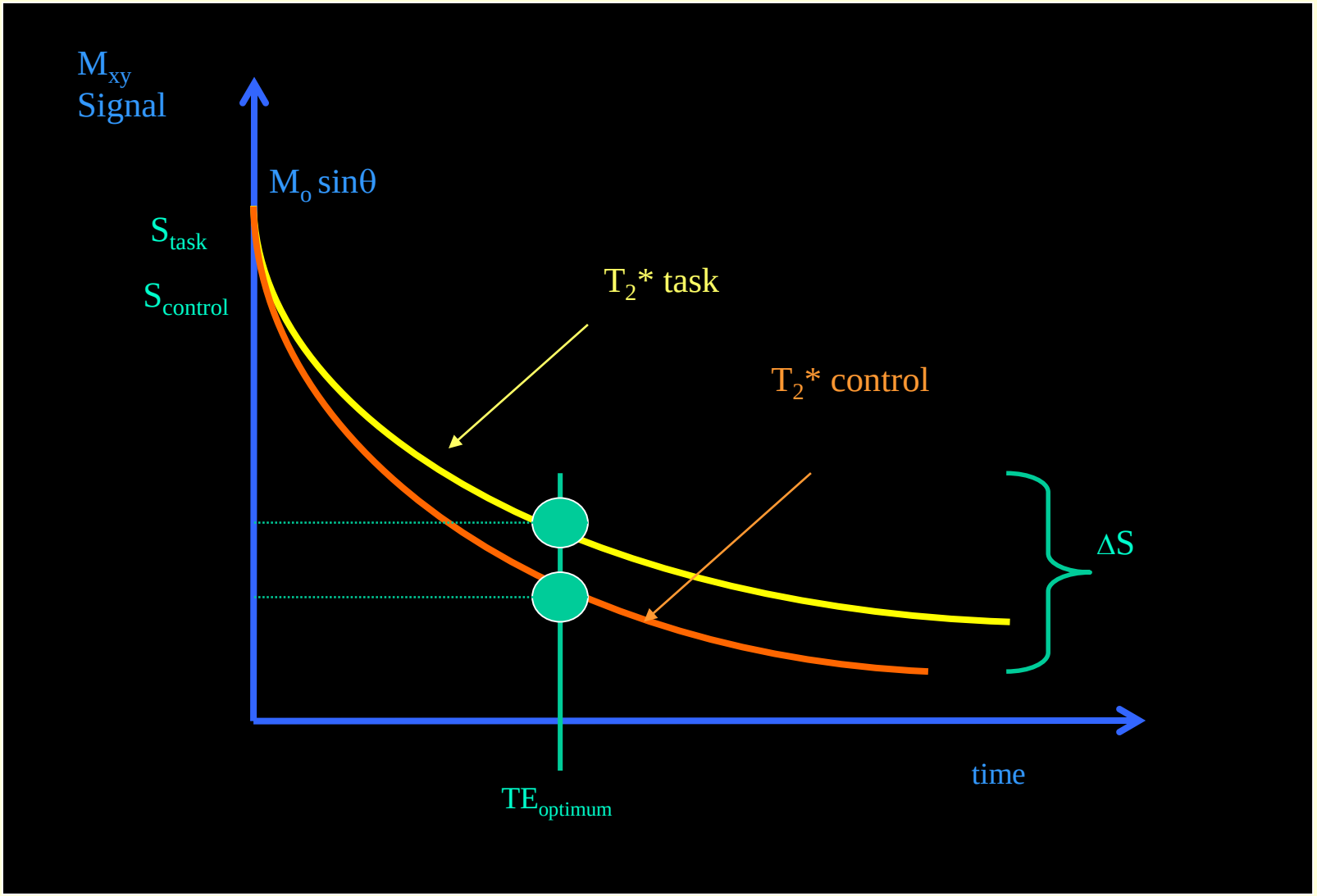

T2*-weighted Image Intensity
MR Properties
Decay Time (T2*)
Other Factors
Vessel Diameter
Vessel Orientation
Hematocrit
Blood Volume Fraction
Physical Effects
Magnetic Field Uniformity (microscopic)
Cerebral Blood Volume (CBV)
Blood Oxygenation
Physiological Effects
Cerbral Blood Flow (CBF)
Metabolic 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
$TE_{optimum}$

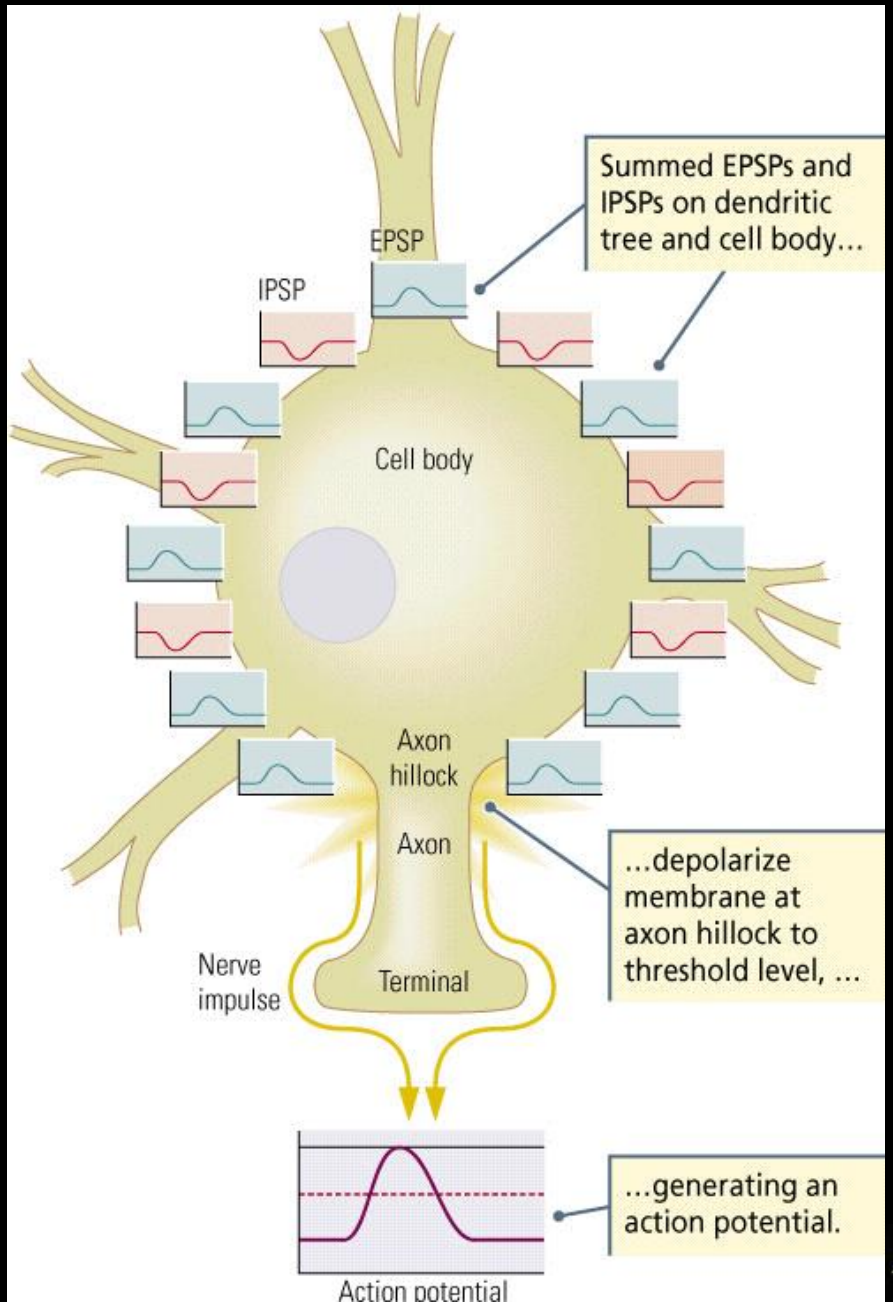
Physiology of BOLD Response

(The Hemodynamic Response)

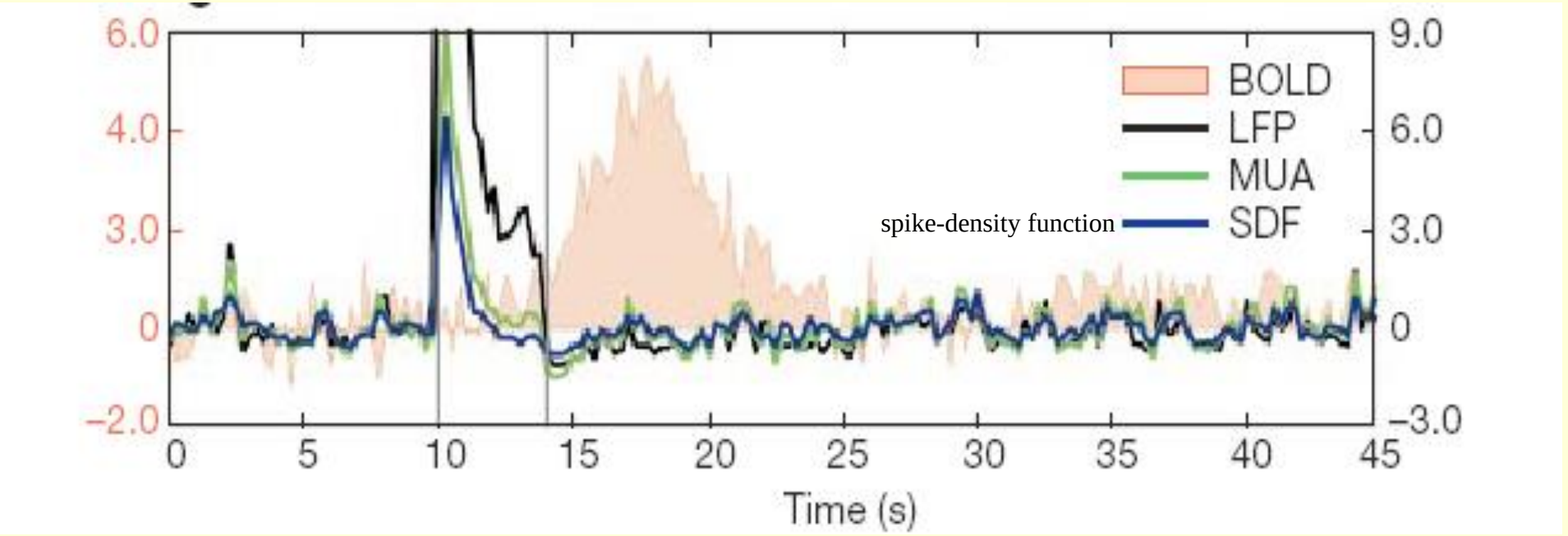
Post-Synaptic Potentials

- 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 temporal Correlations



Local Field Potentials (LFP) reflect post-synaptic potentials

- similar to what EEG (ERPs) and MEG measure

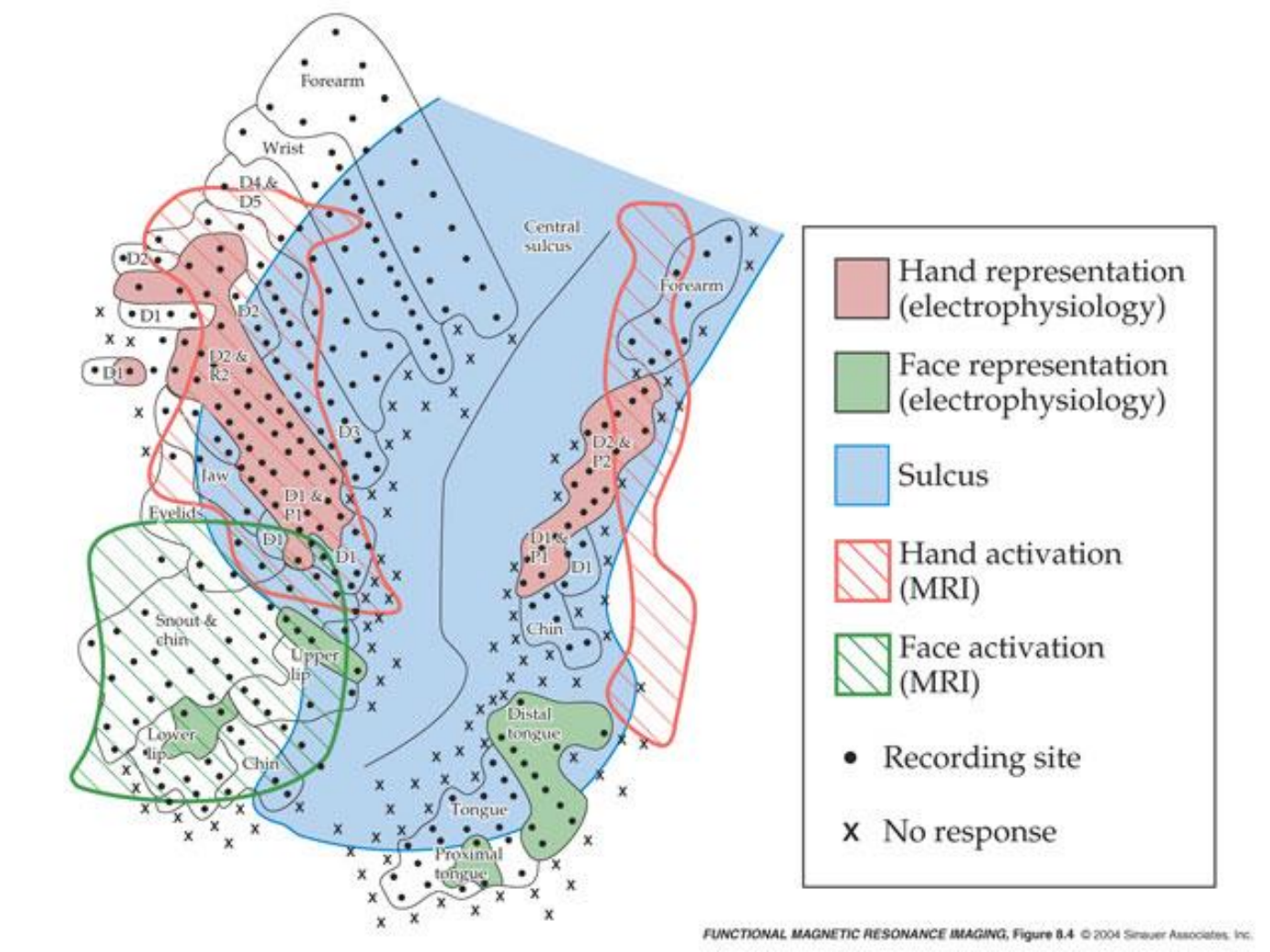
Multi-Unit Activity (MUA) reflects action potentials

- similar to what most electrophysiology measures

- BOLD activity is more closely related to LFPs than MUA

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

BOLD spatial correlation

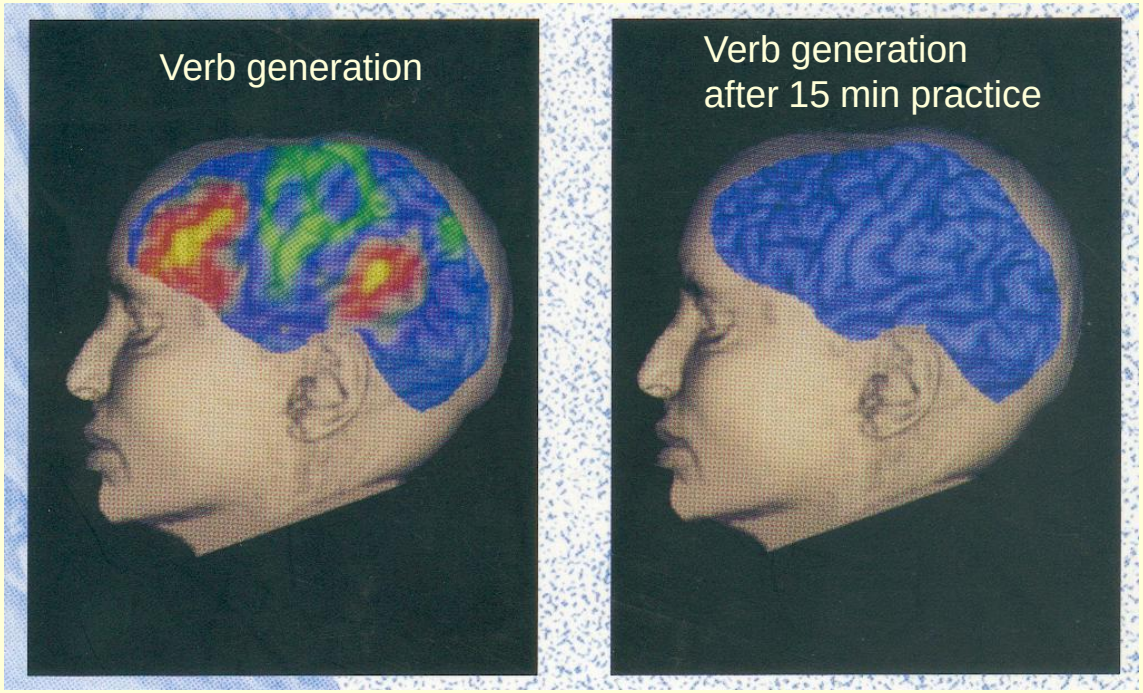


Data Source: Disbrow et al., 2000*, PNAS*
Figure Source, Huettel, Song & McCarthy, *Functional Magnetic Resonance Imaging*

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

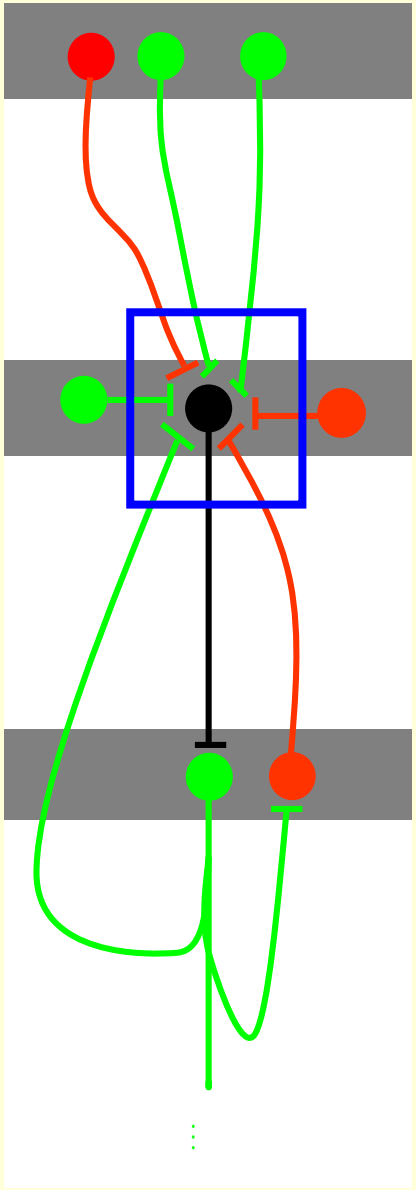


Raichle & Posner, Images of Mind cover image

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

Functional connectivity and networking is important

Lower tier area
(e.g., thalamus)



gray matter
(dendrites, cell bodies
& synapses)

white matter
(axons)

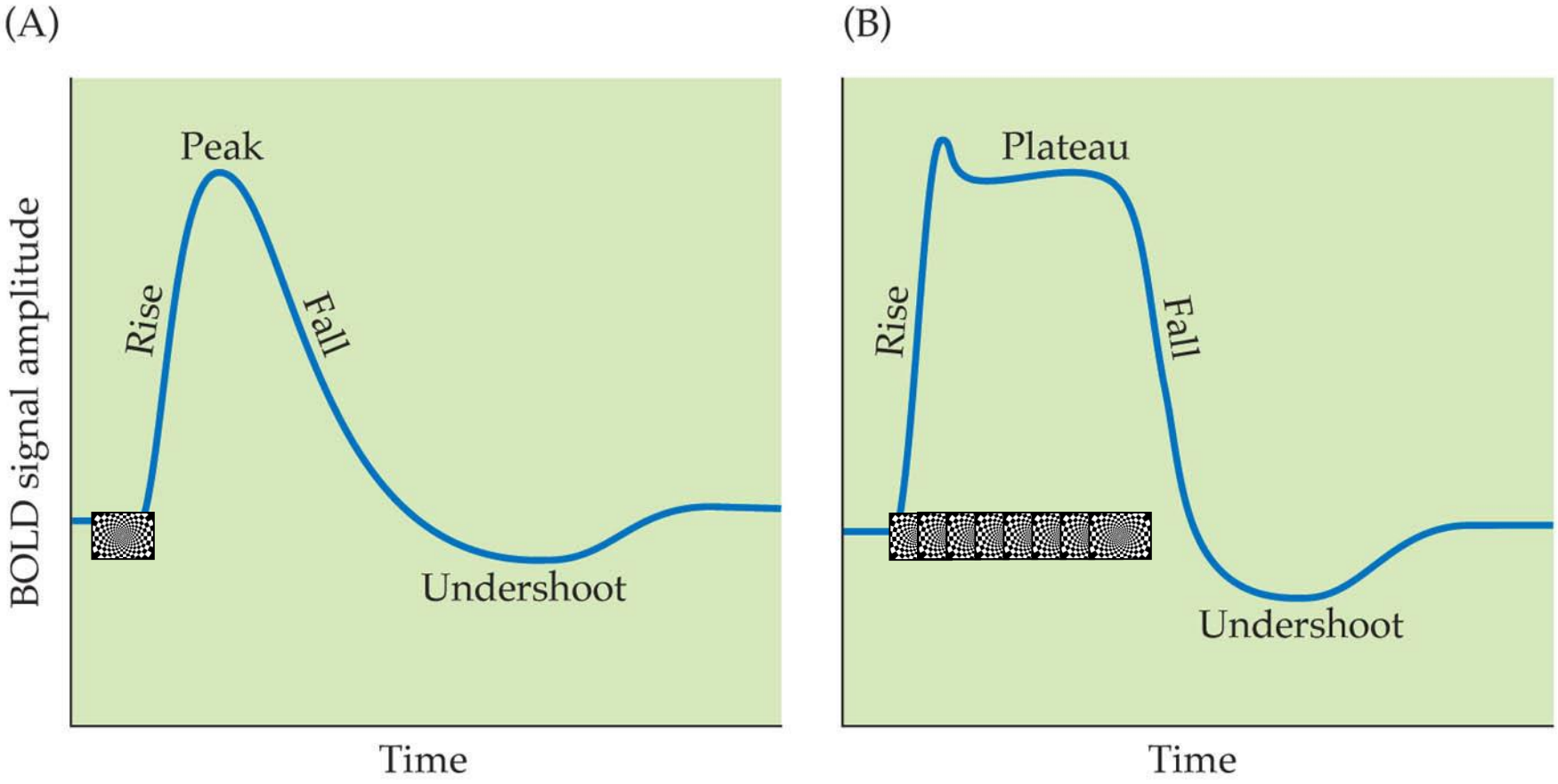
Middle tier area
(e.g., V1, primary visual
cortex)

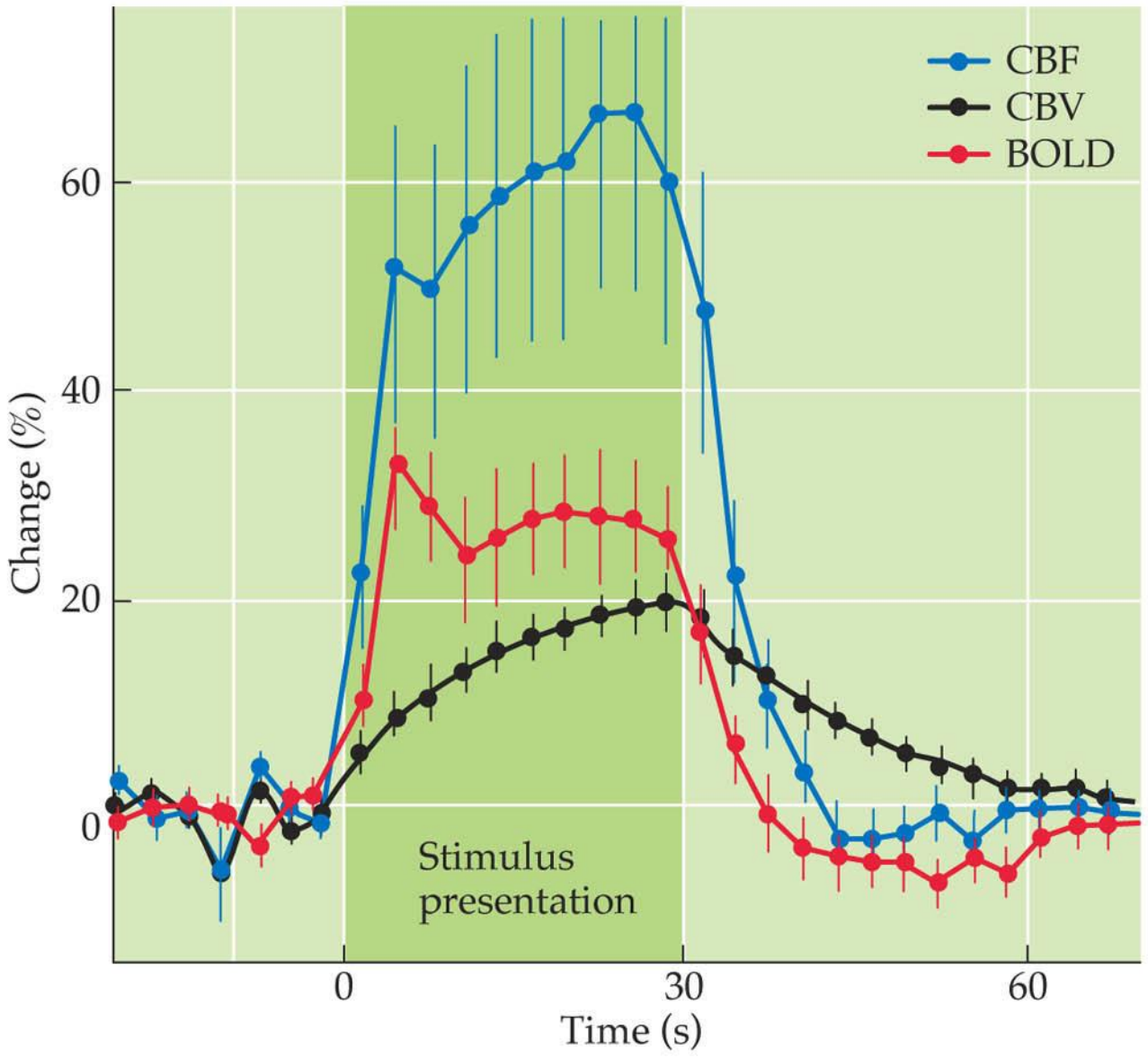
Higher tier area
(e.g., V2, secondary
visual cortex)

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)?*

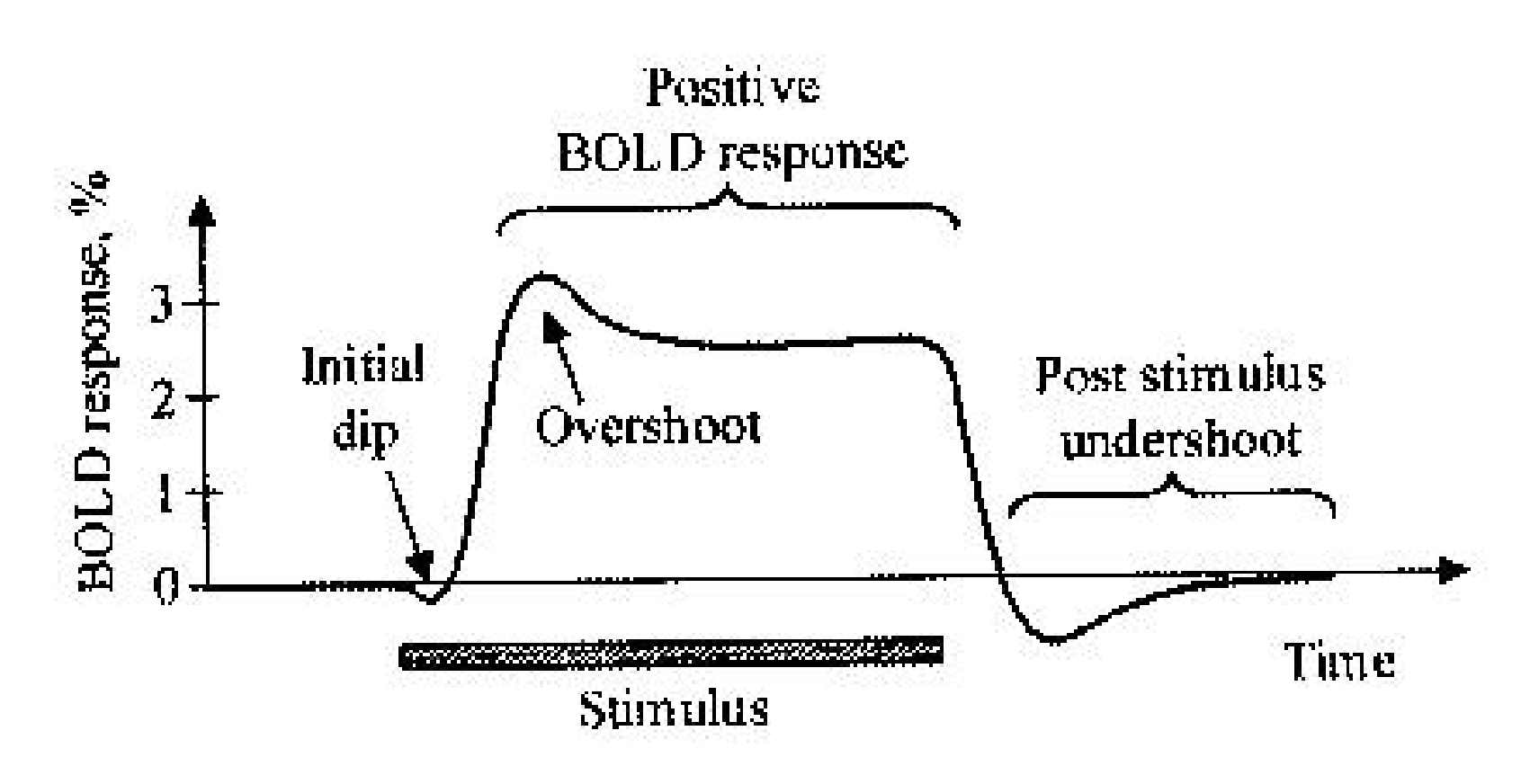
Basic Form of Hemodynamic Response





FUNCTIONAL MAGNETIC RESONANCE IMAGING, **Figure 7.16**

BOLD Time Course



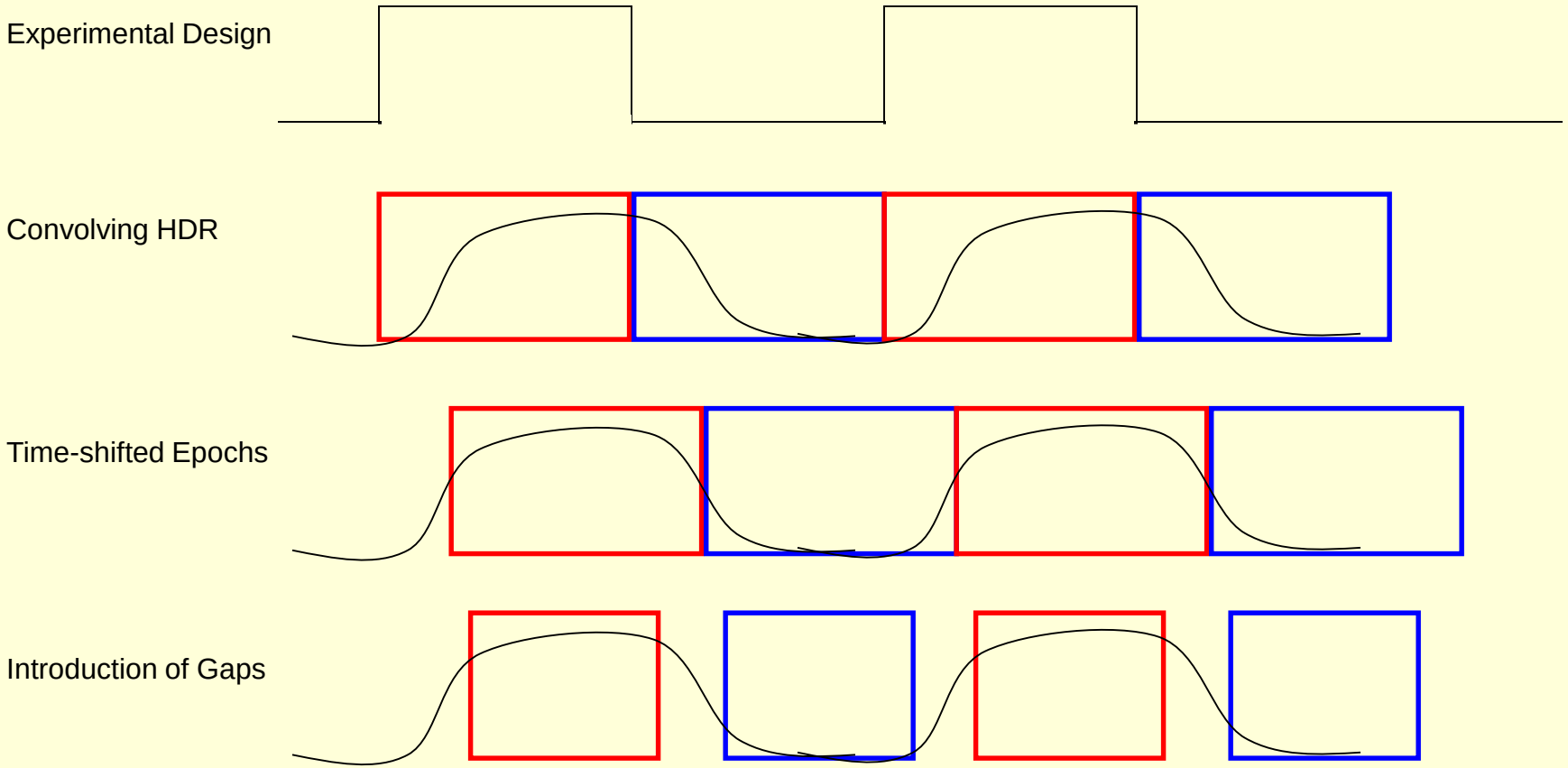
Amplitude of the HDR

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

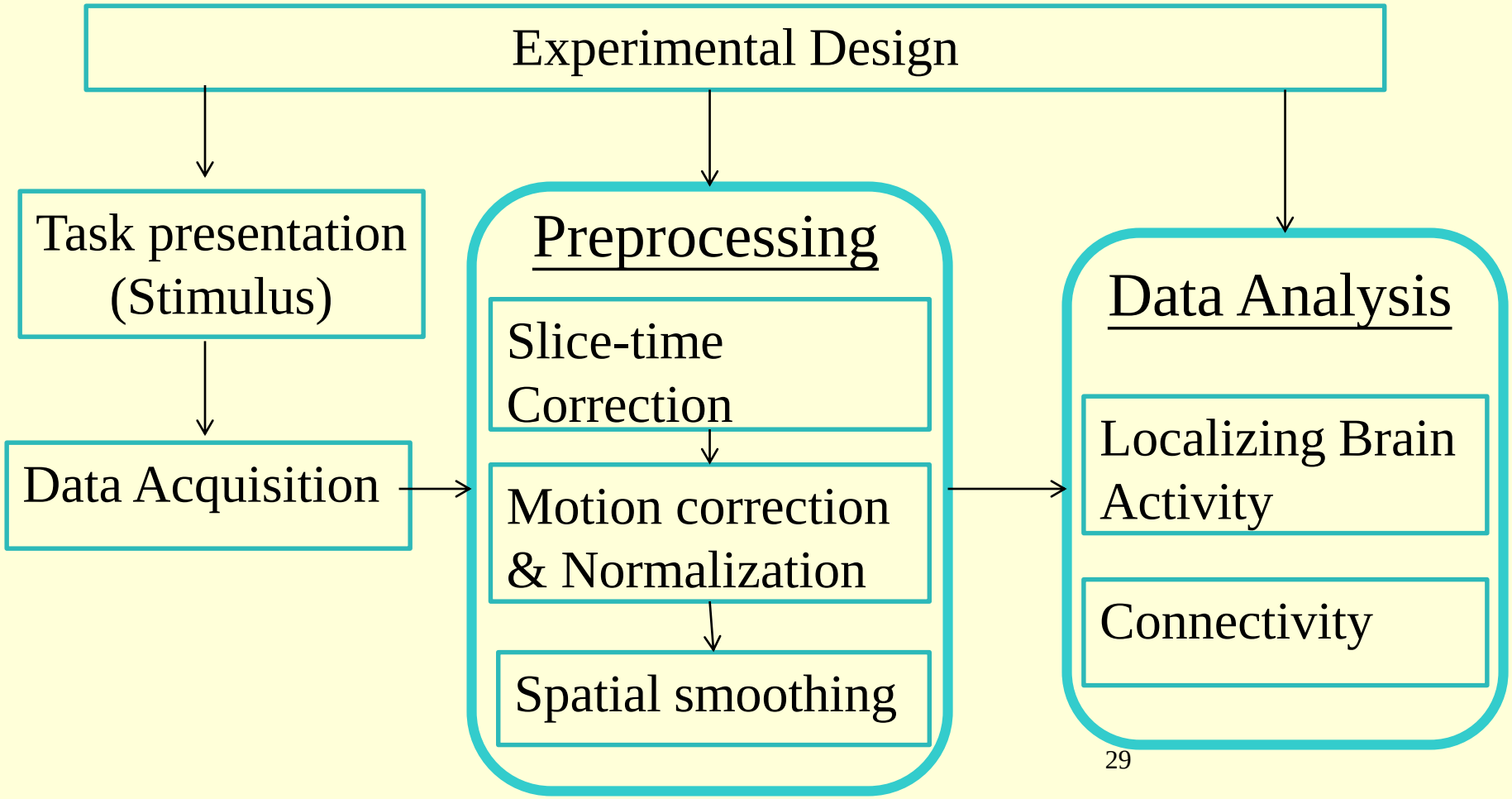
Why does the hemodynamic response matter?

- 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

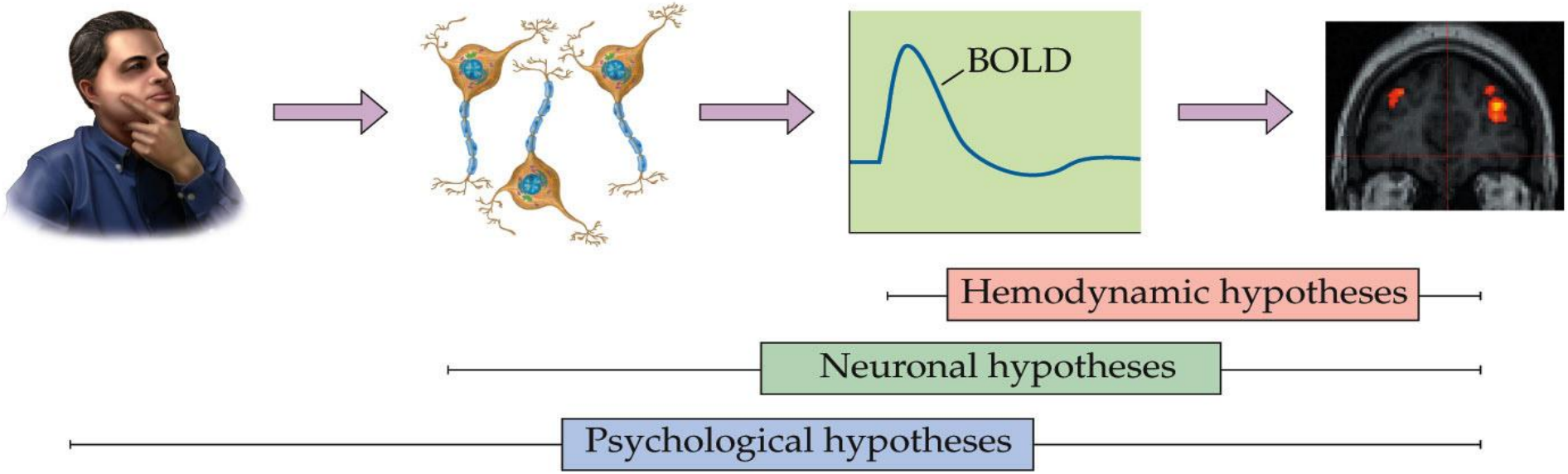
The Hemodynamic Response Lags Neural Activity



How to perform fMRI experiment?

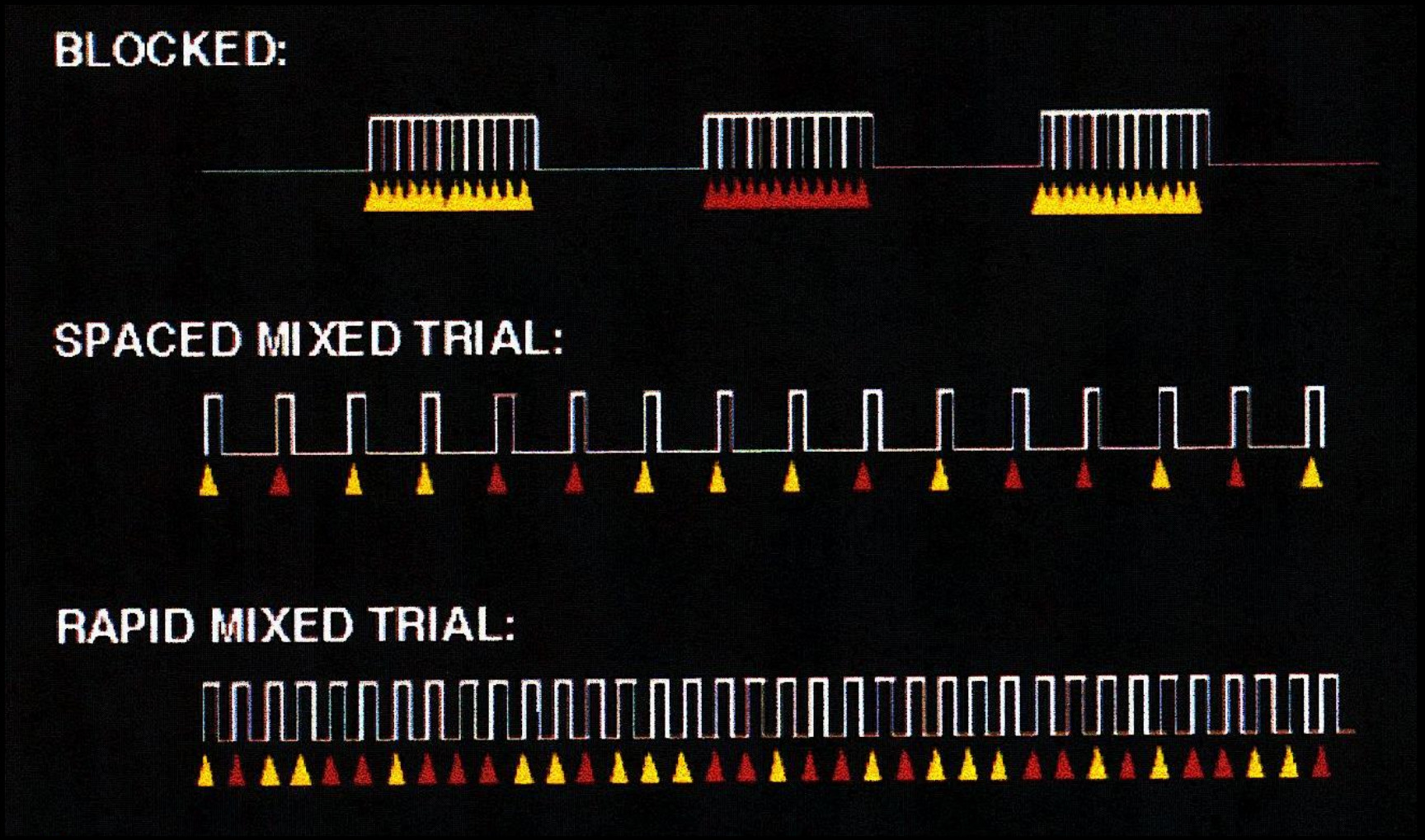


Constructing Research hypotheses



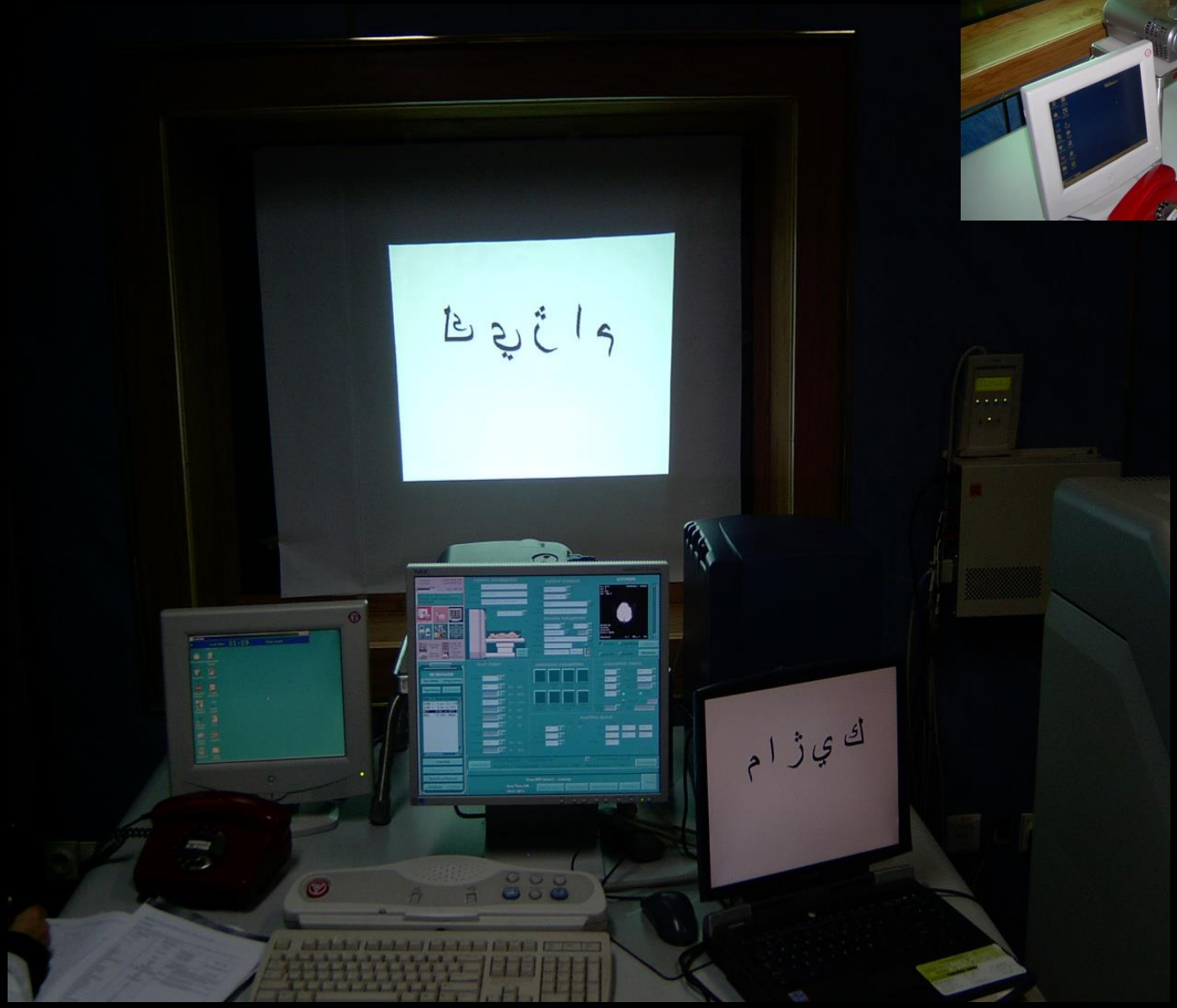
***Functional Magnetic Resonance Imaging 2e*, Figure 9.3**

Blocked vs. Event-related

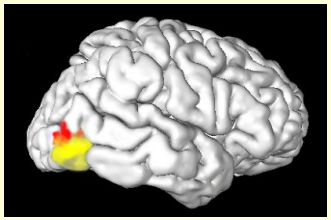


How to perform fMRI experiment?

How to perform fMRI task?

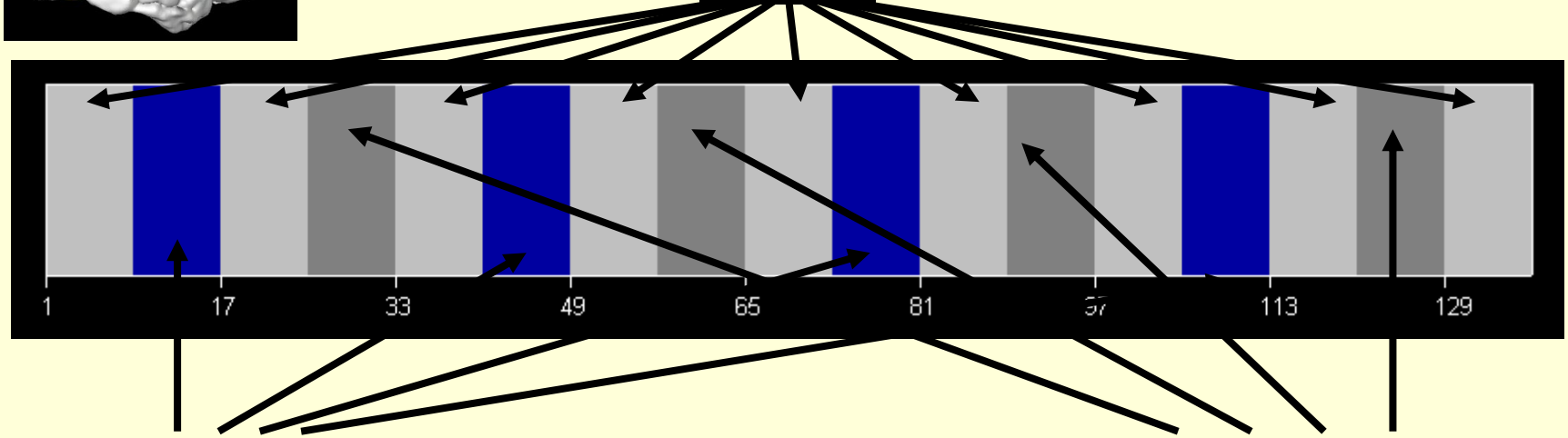


A Simple Experiment

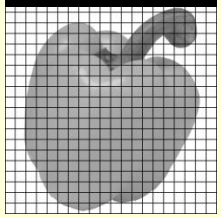


Lateral Occipital Complex
• responds when subject views objects

Blank Screen

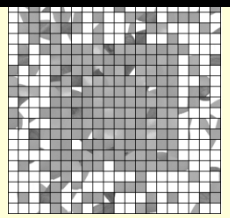


Intact Objects



TIME →

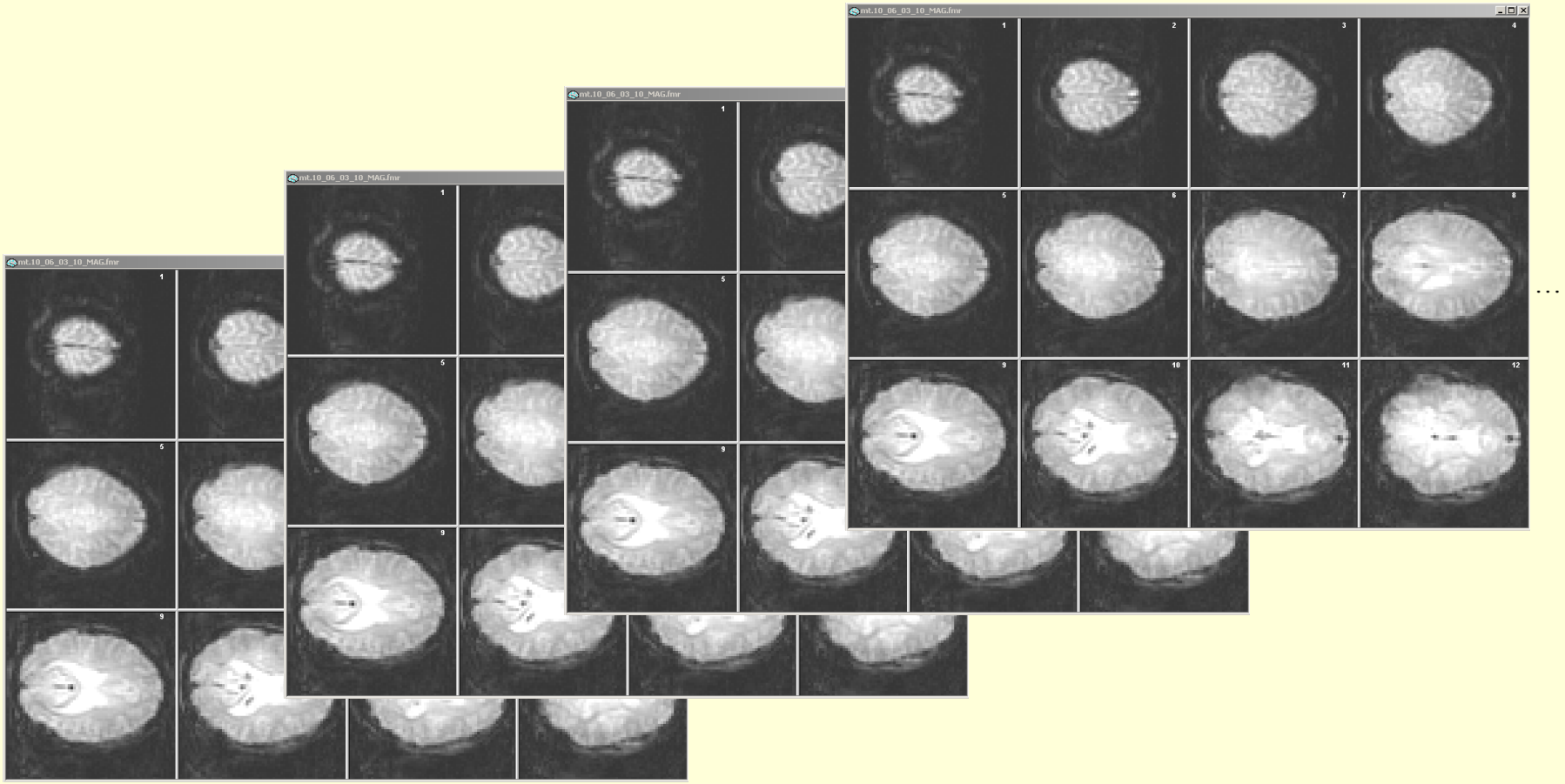
Scrambled Objects



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)

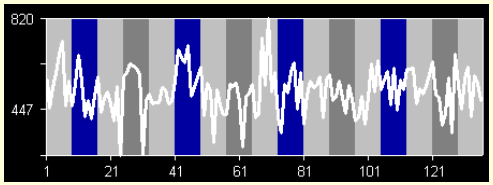
What data do we start with



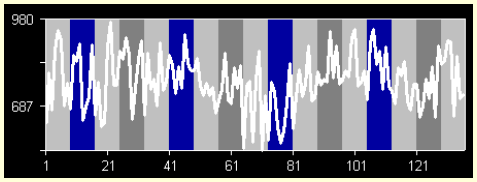
- 12 slices * 64 voxels x 64 voxels = 49,152 voxels
- Each voxel has 136 time points
- Therefore, for each run, we have 6.7 million data points
- We often have several runs for each experiment

Why do we need stats?

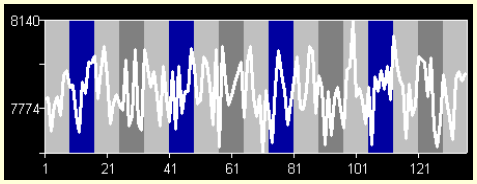
- We could, in principle, analyze data by voxel surfing: move the cursor over different areas and see if any of the time courses look interesting



Slice 9, Voxel 0, 0



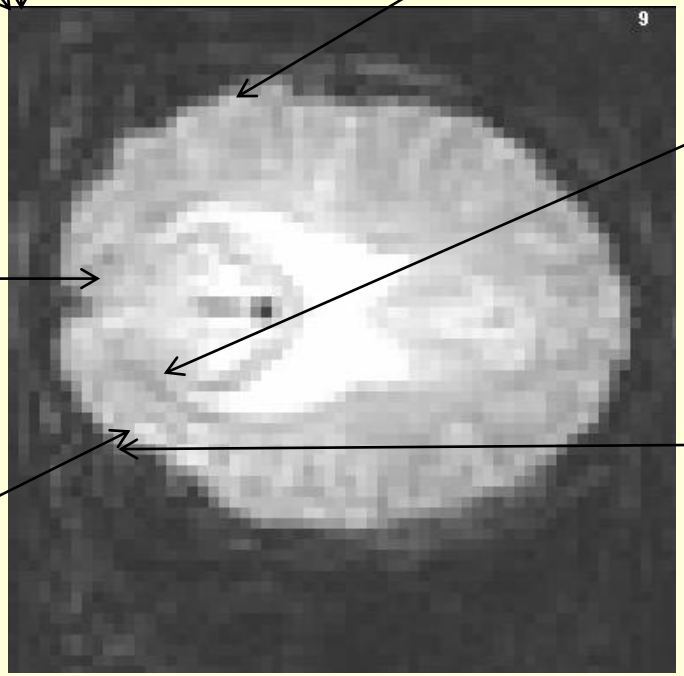
Slice 9, Voxel 1, 0

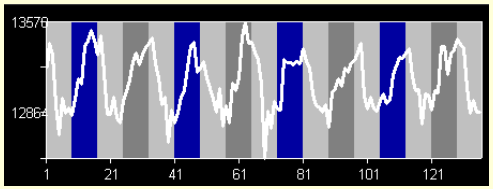


Slice 9, Voxel 22, 7

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

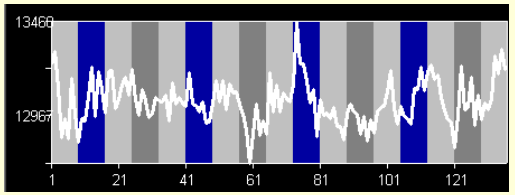
Even where there's no brain, there's noise





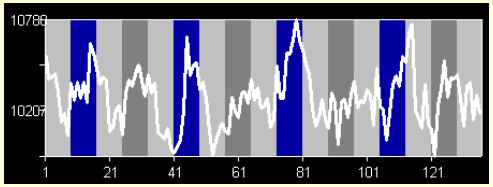
Slice 9, Voxel 9, 27

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



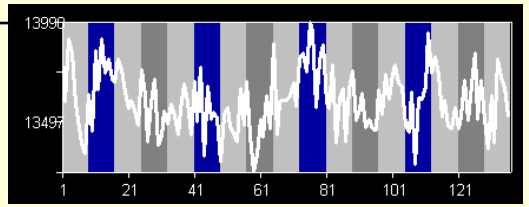
Slice 9, Voxel 18, 36

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?

Does our stat test indicate that the region is active?	Yes	No
Yes	HIT	Type I Error
No	Type II Error	Correct Rejection

p value:
probability of a Type I error

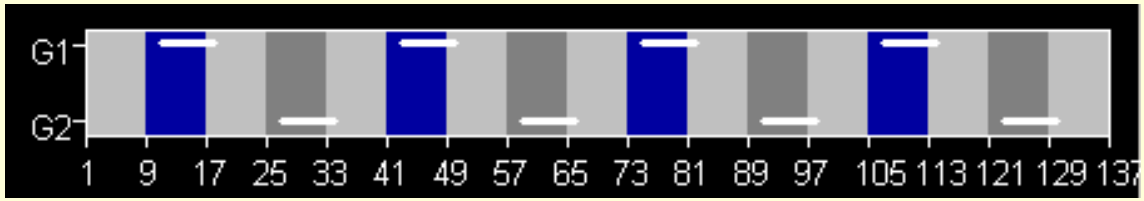
e.g., p <.05

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

Statistical Approaches

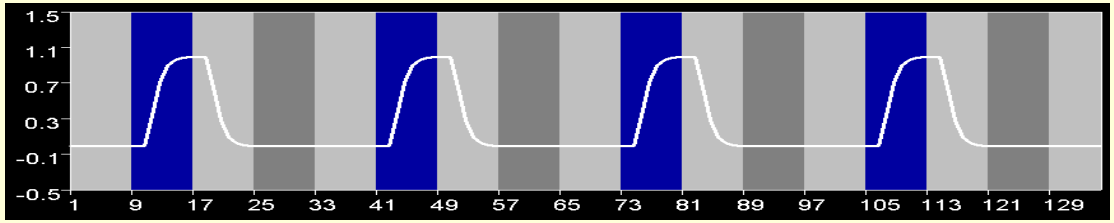
t-tests

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



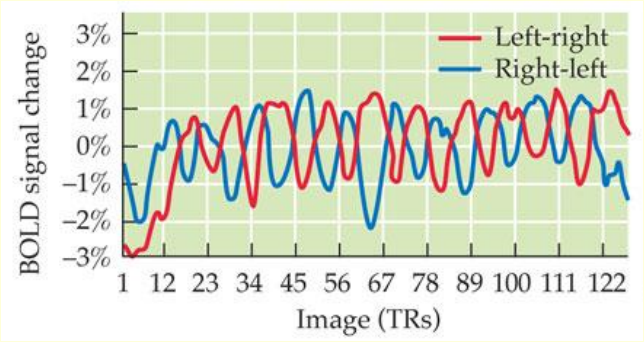
correlations

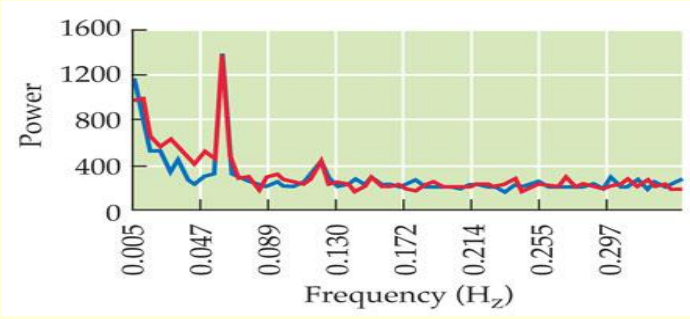
- **model activation and see whether any areas show a similar pattern**



Fourier analysis

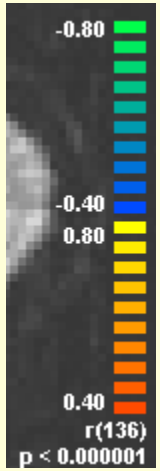
- **Do a Fourier analysis to see if there is energy at your paradigm frequency**

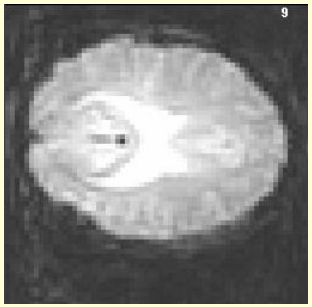




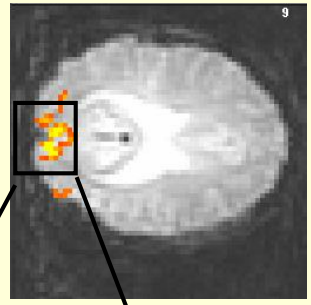
Fourier analysis images

Effect of Thresholds

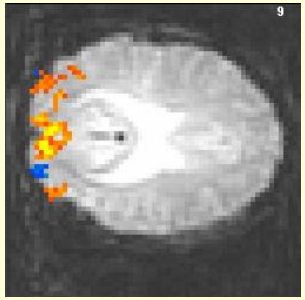




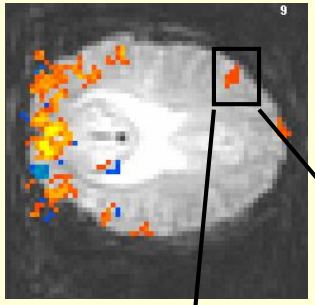
r = .80
64% of variance
$p < 10^{-33}$



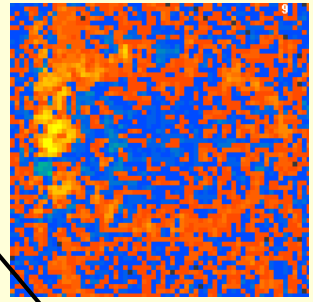
r = .50
25% of variance
p < .000001



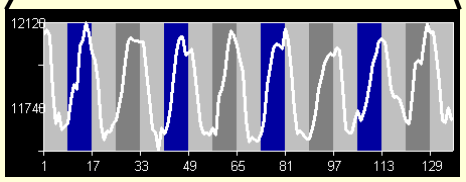
r = .40
16% of variance
p < .000001

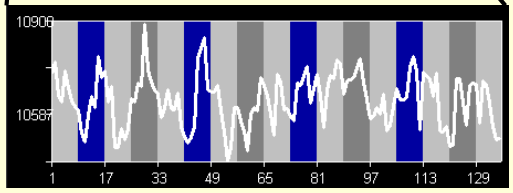


r = .24
6% of variance
p < .05



r = 0
0% of variance
p < 1

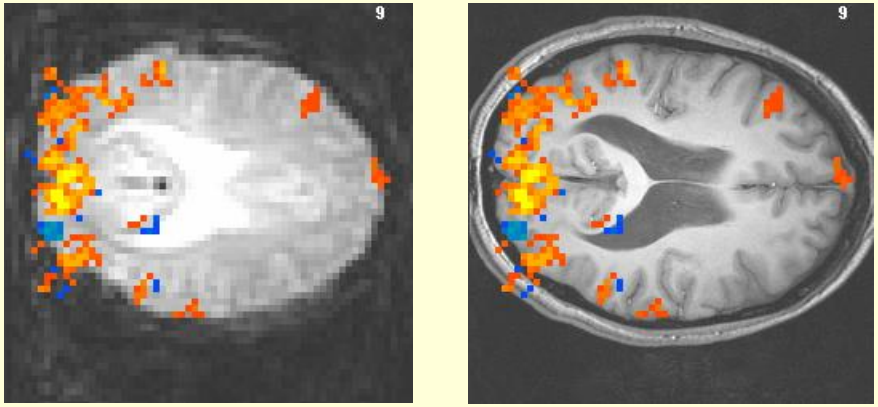




Complications

- There are all sorts of statistical problems:

What's wrong with these data?



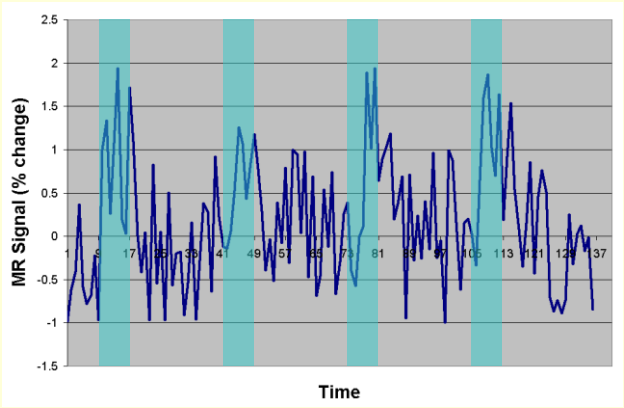
r = .24
6% of variance
p < .05

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)

Source of errors



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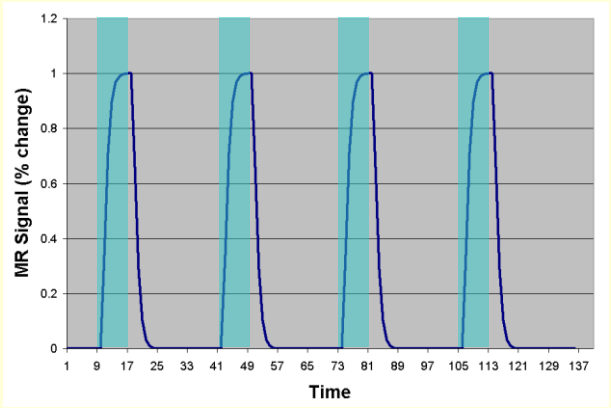
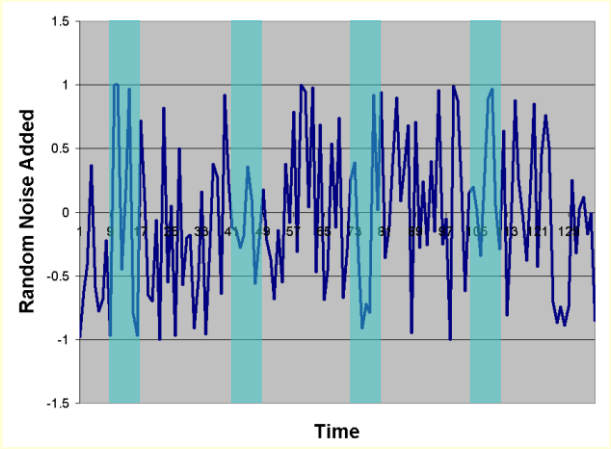


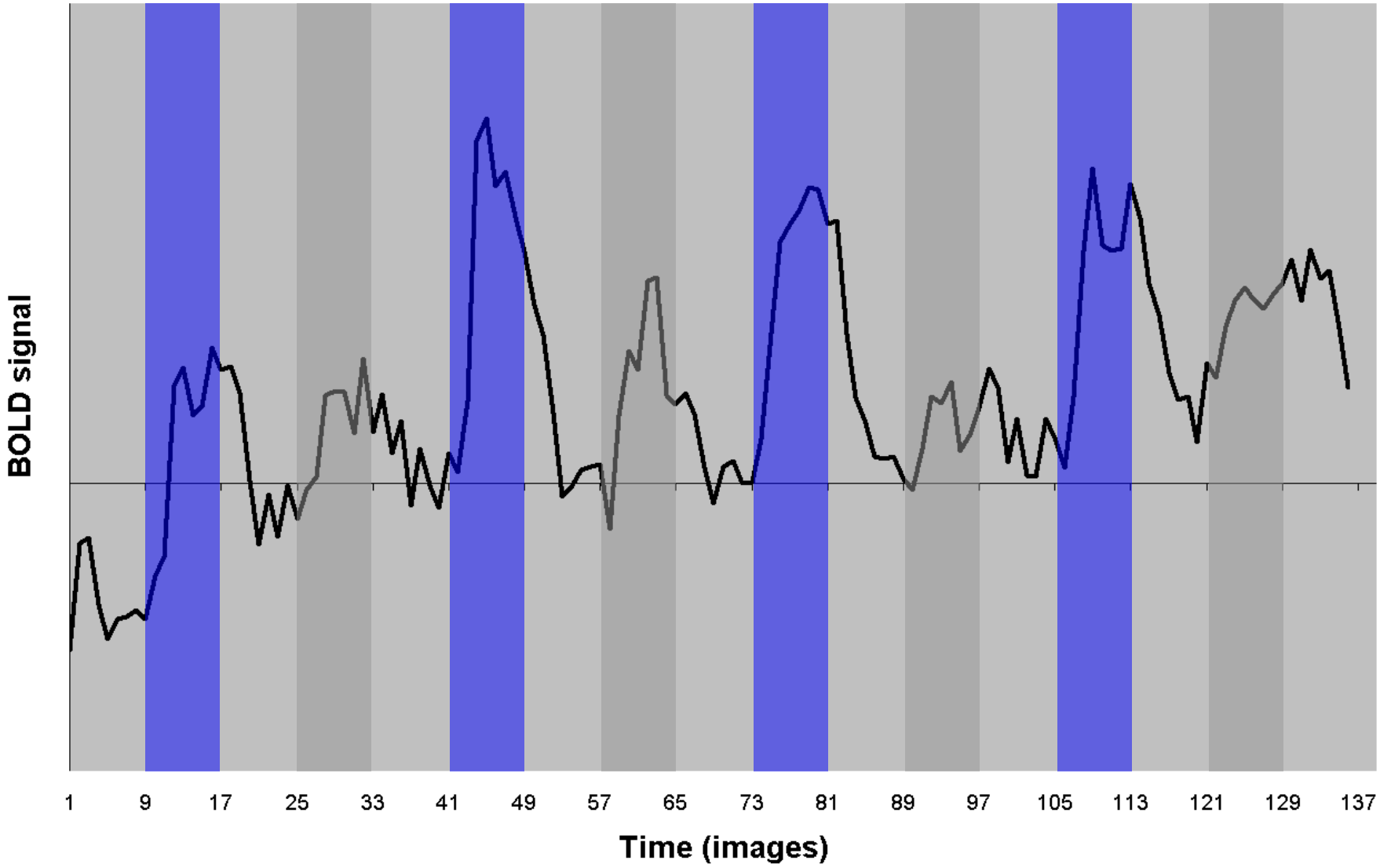
signal

+



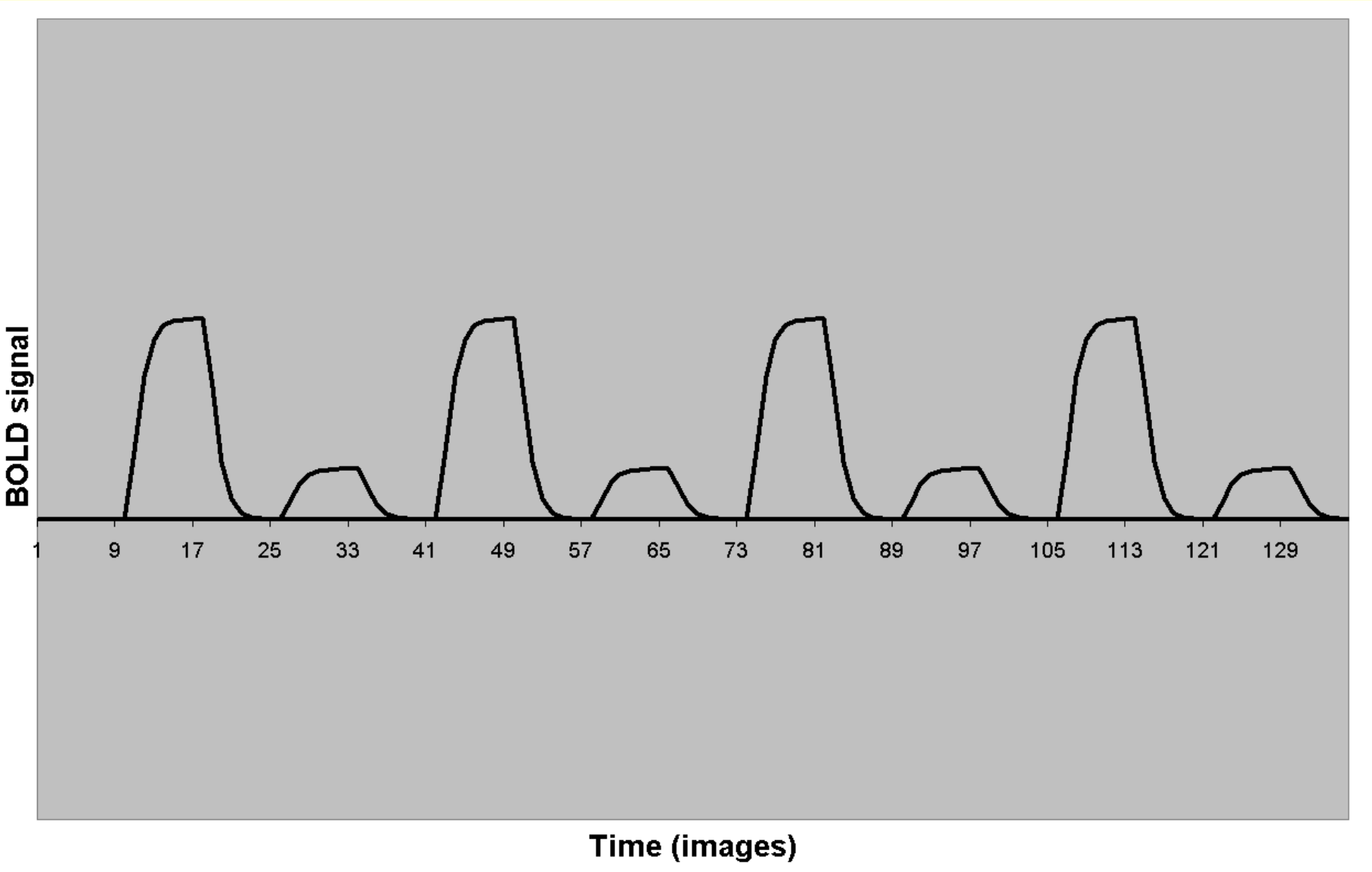
noise

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

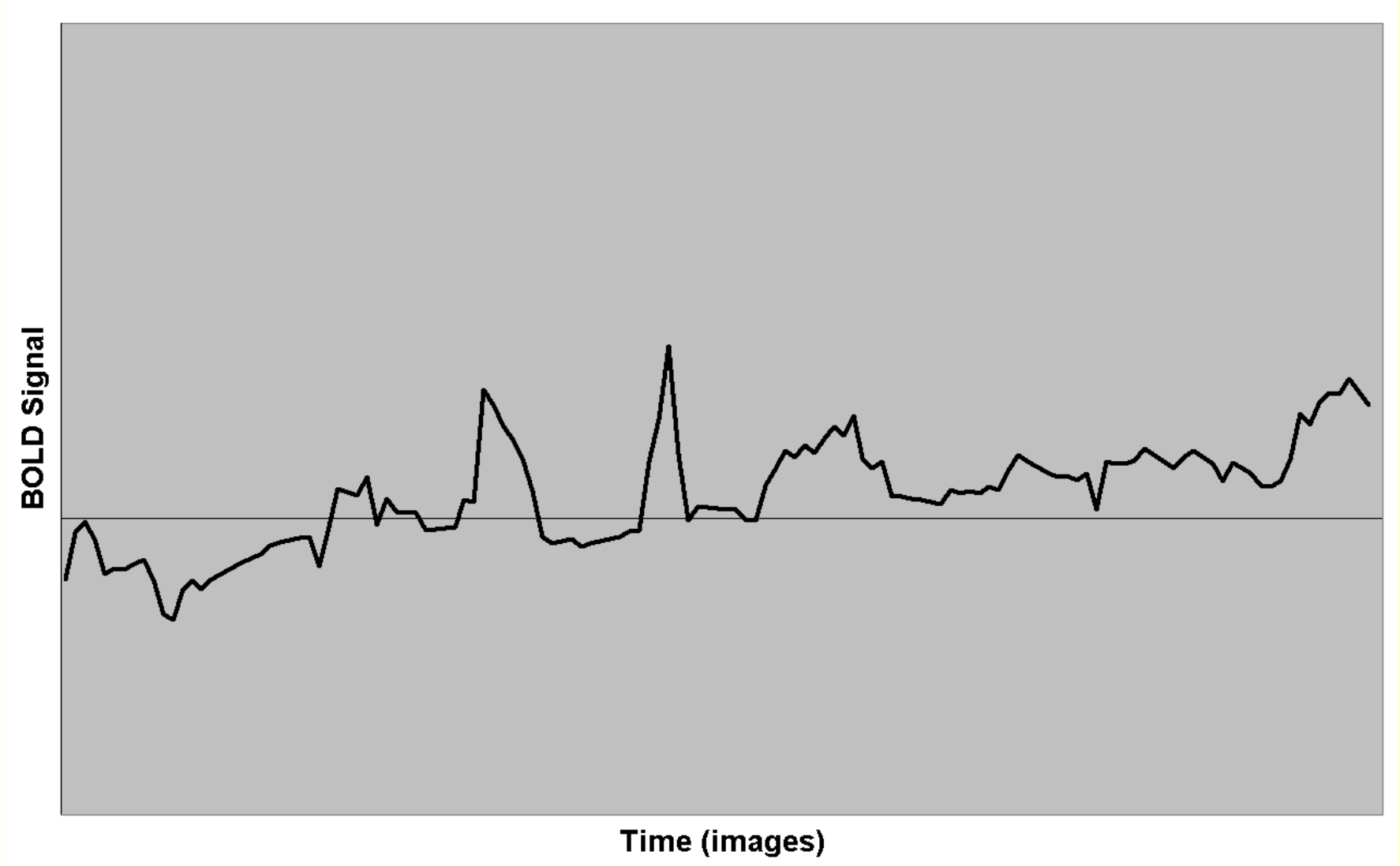


How this signal is build up?

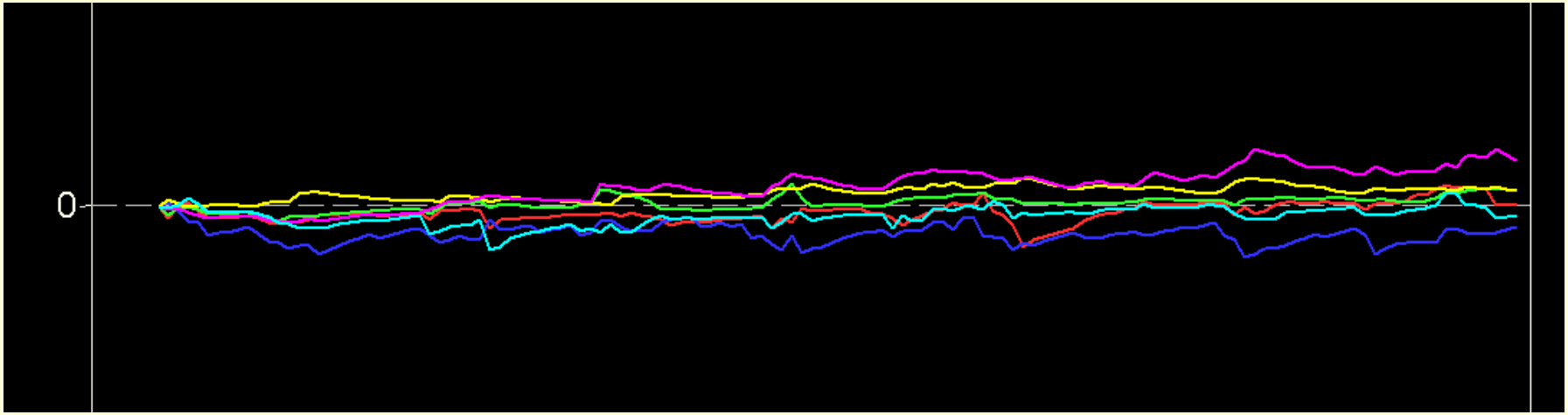
Response to Intact Objects which is 4X greater than Scrambled Objects



Now let's add some variability due to head motion



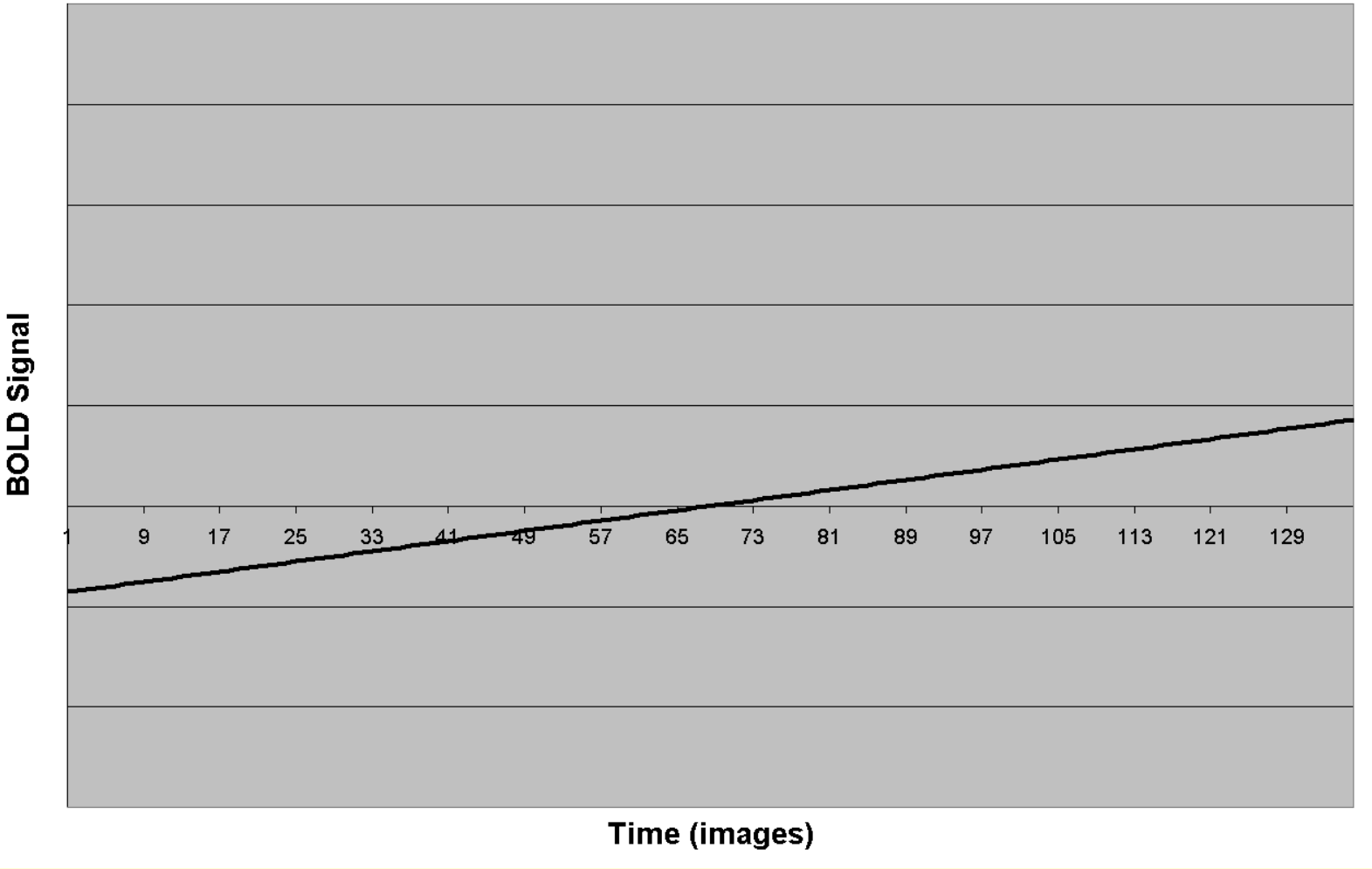
…though really motion is more complex



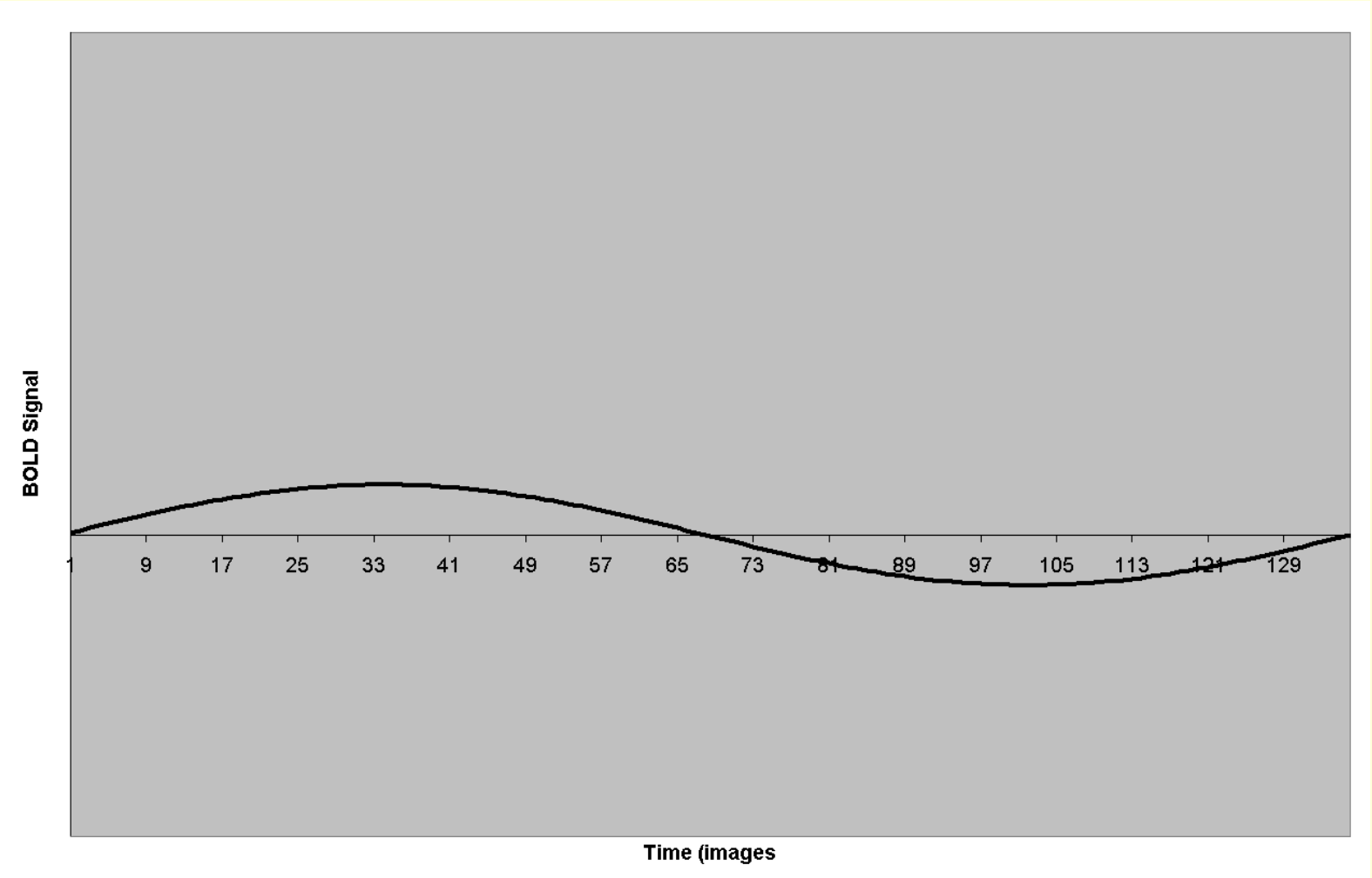
- Head motion can be quantified with 6 parameters given in any motion correction algorithm
  - x translation
  - y translation
  - z translation
  - xy rotation
  - xz rotation
  - yz rotation
- For simplicity, I've only included parameter one in our model

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

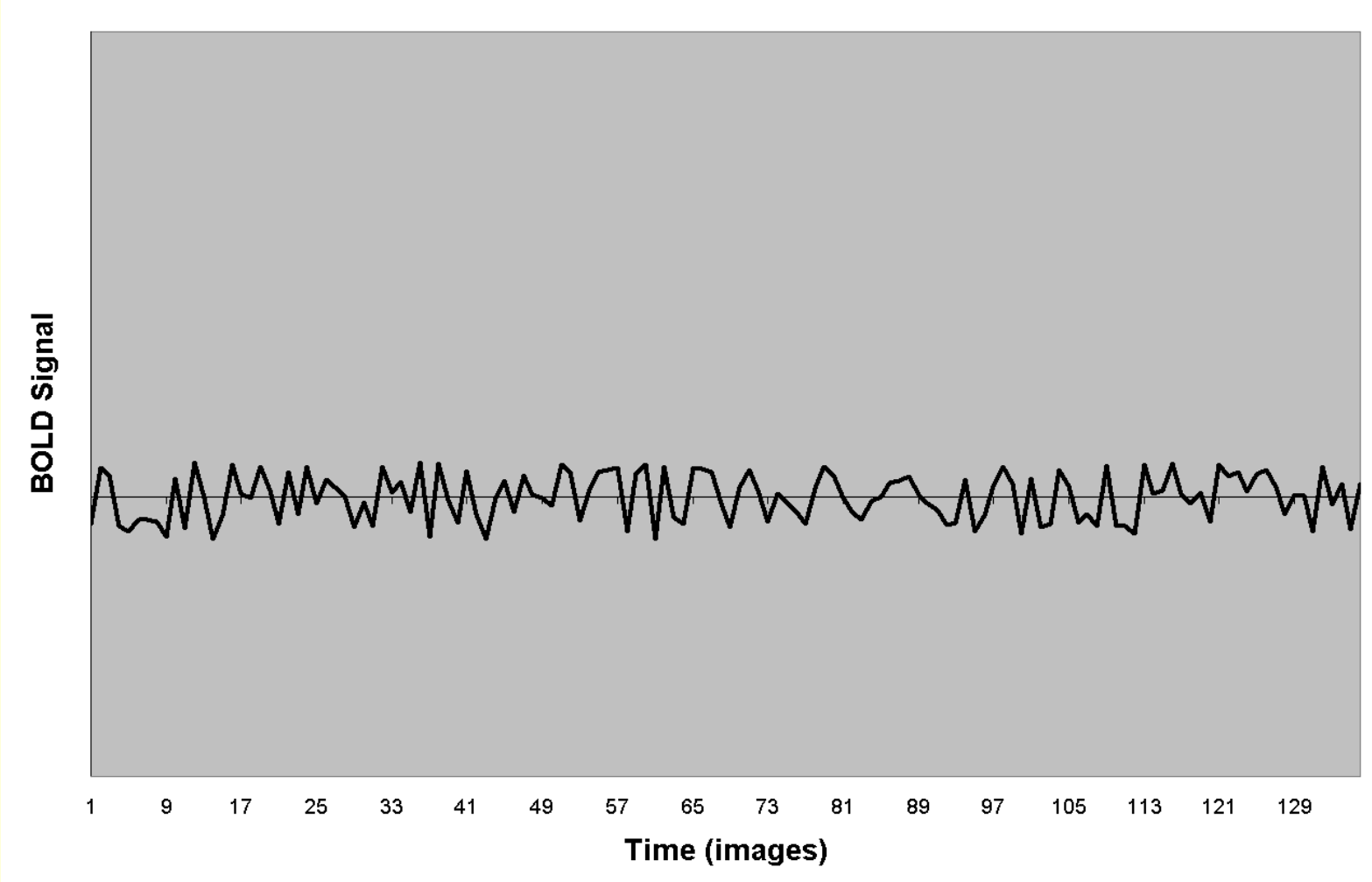
Adding linear drift from magnet noise (e.g., parts warm up) or physiological noise (e.g., subject's head sinks



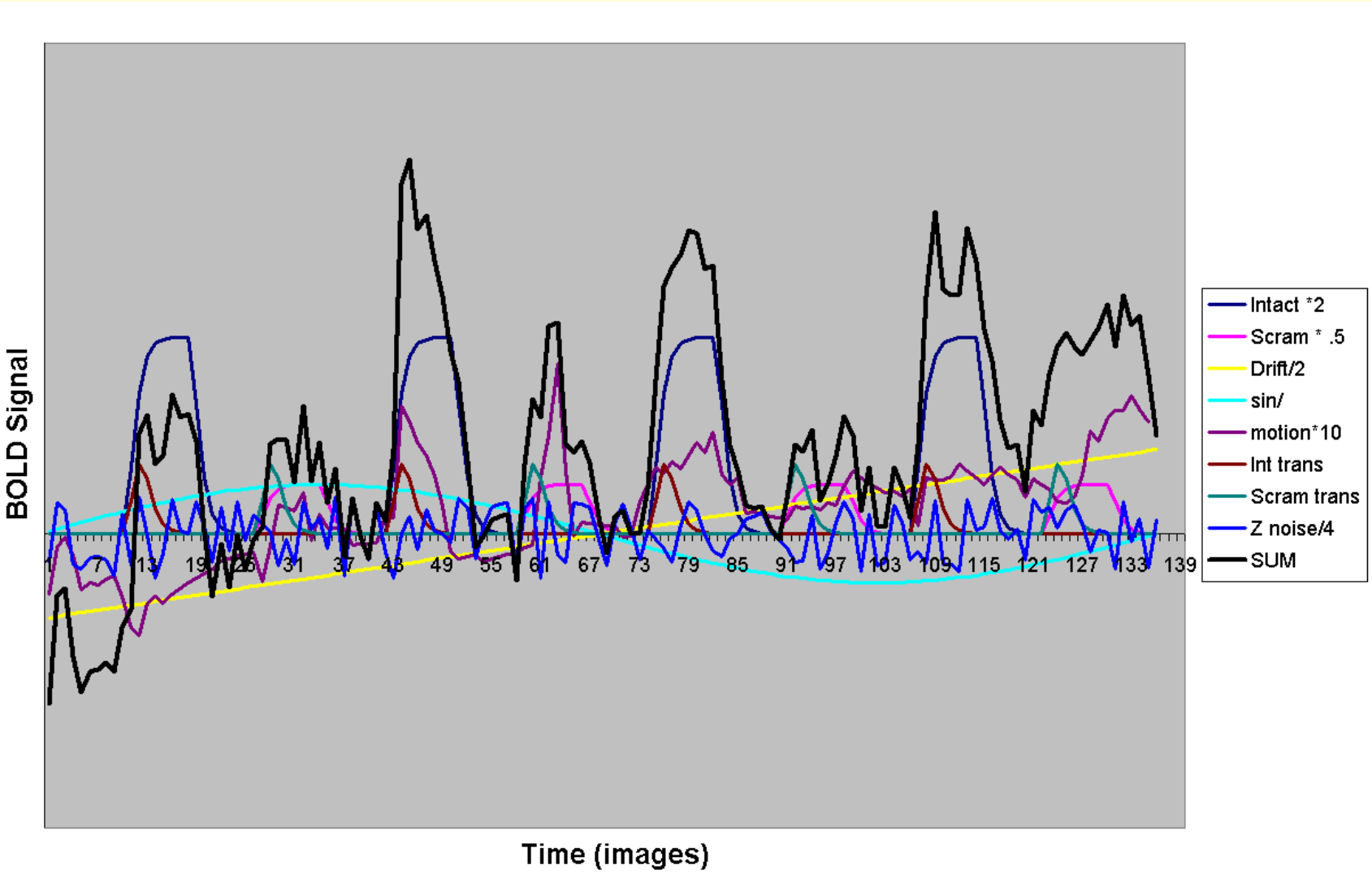
Add a dash of low frequency noise from magnet noise or physiological noise (e.g., subject's cycles of alertness/drowsiness)



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

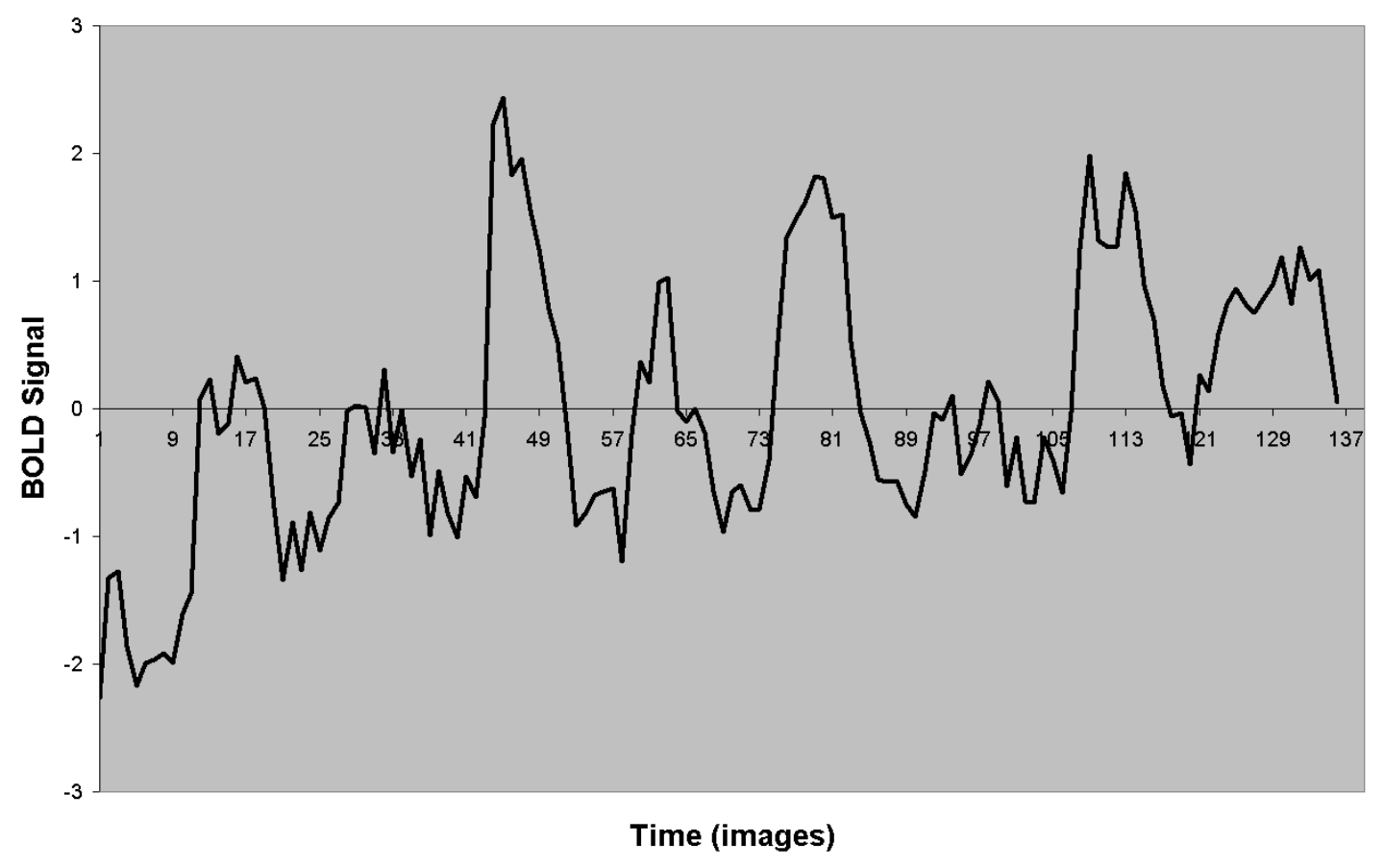


When we add these all together, we get a realistic time course



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



Major components of post-processing and Analysis

1. Quality control (data free from noise and artifacts)
2. Motion correction
3. Slice timing correction
4. Spatial normalization (alignment into common spatial framework)
5. Spatial smoothing
6. Temporal filtering
7. Statistical modeling (GLM & data fitting)
8. Statistical Inference (estimation of statistical significance)
9. Visualization

fMRI Analysis with emphasis on the general linear model (GLM)

Jody Culham niversity of Western Ontario

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?

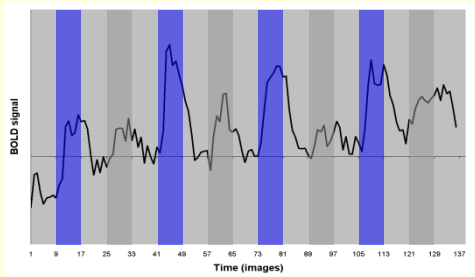
- Any combination of contrasts can be used (e.g., intact - scrambled, scrambled - baseline) with one GLM rather than multiple correlations

- 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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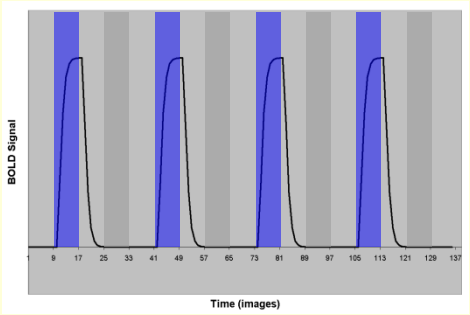
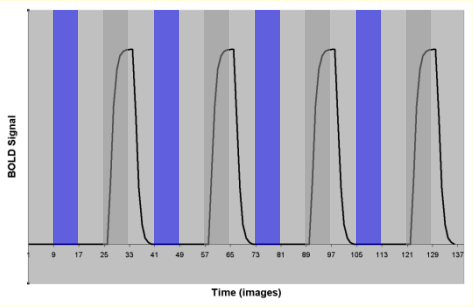


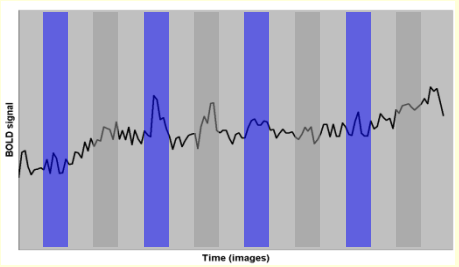
$\times \beta_1$

+



$\times \beta_2$

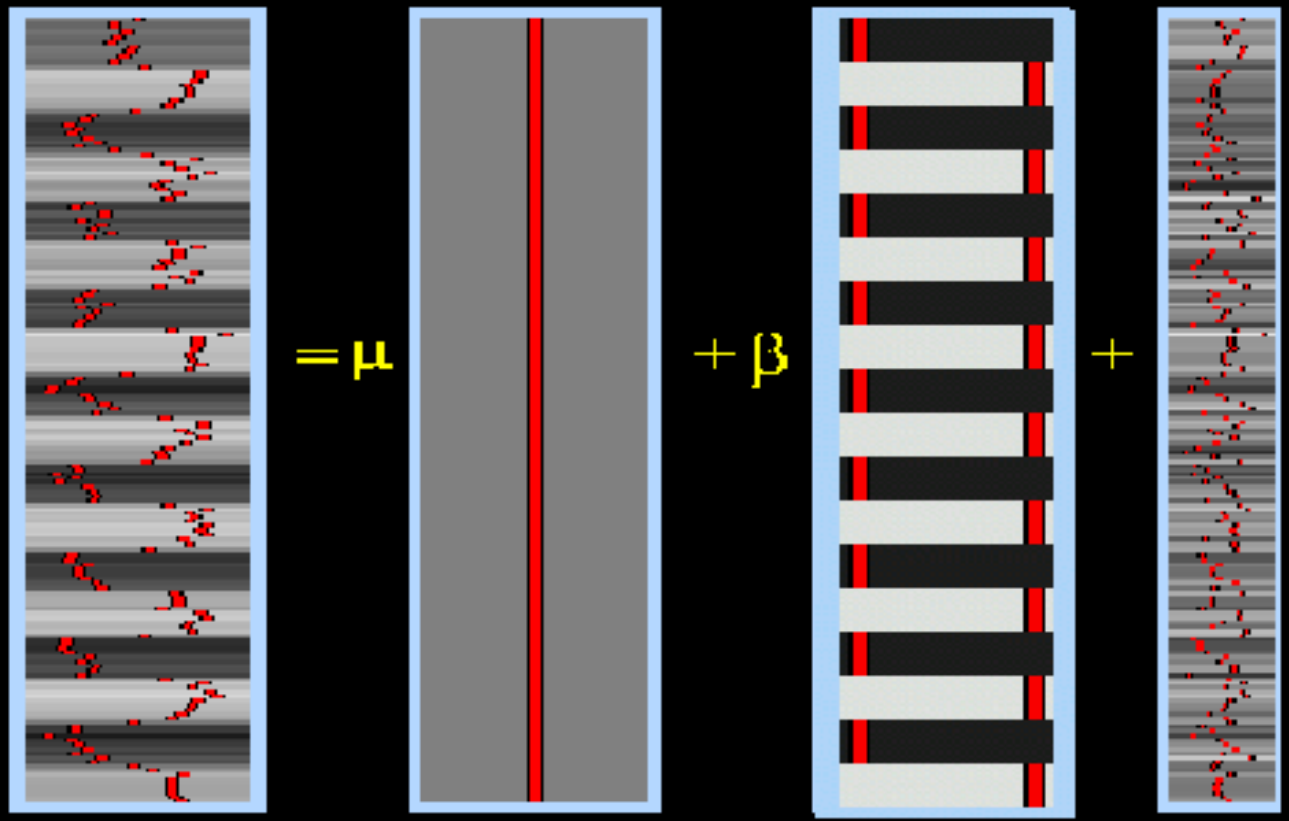
+



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

GLM for an activation



$\underline{Y} = \mu\,\underline{1} + \beta\,\underline{X} + \underline{\varepsilon}$

Data

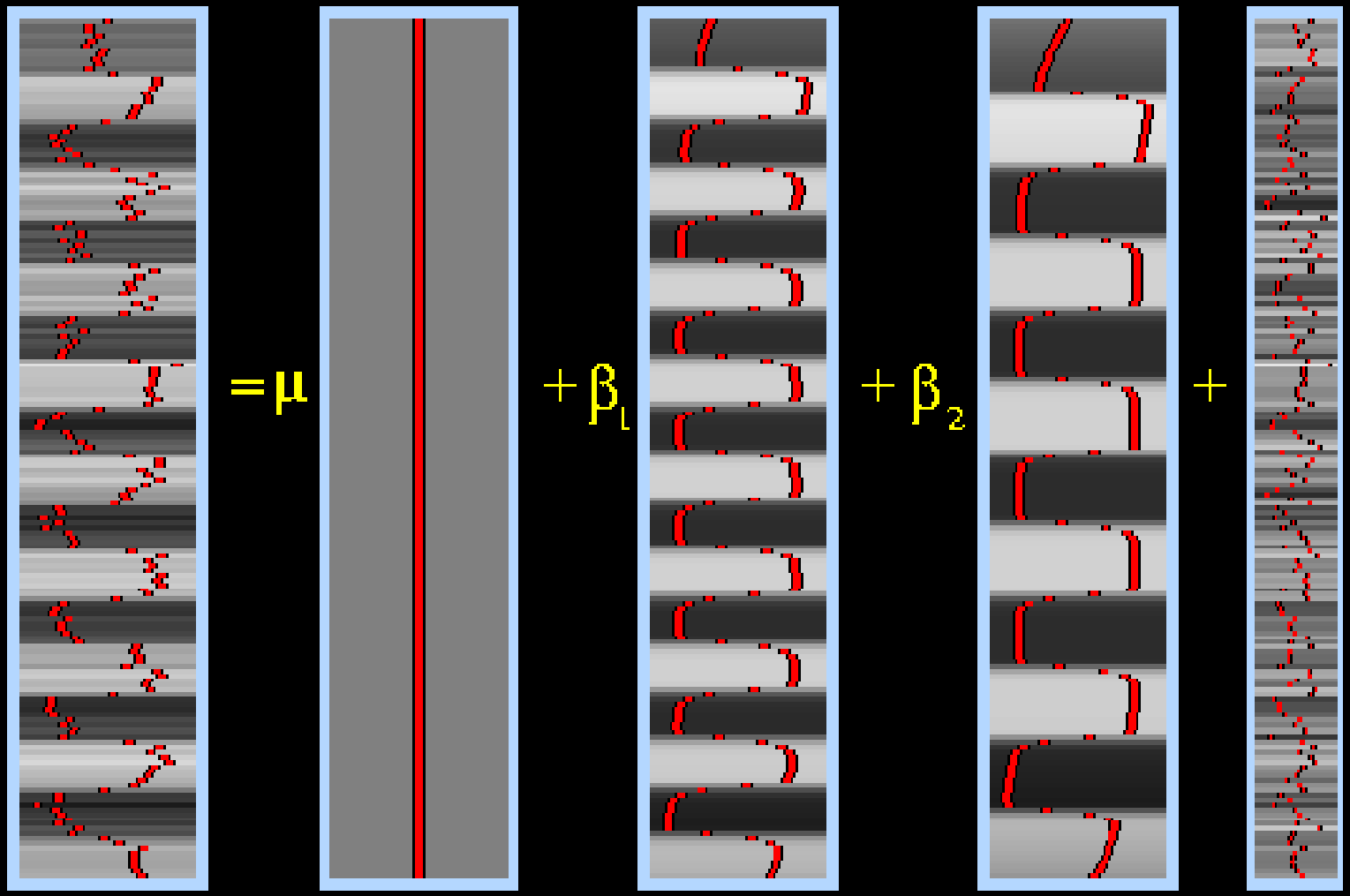
Mean

Parameter estimate (PE)

Explanatory Variable (EV)

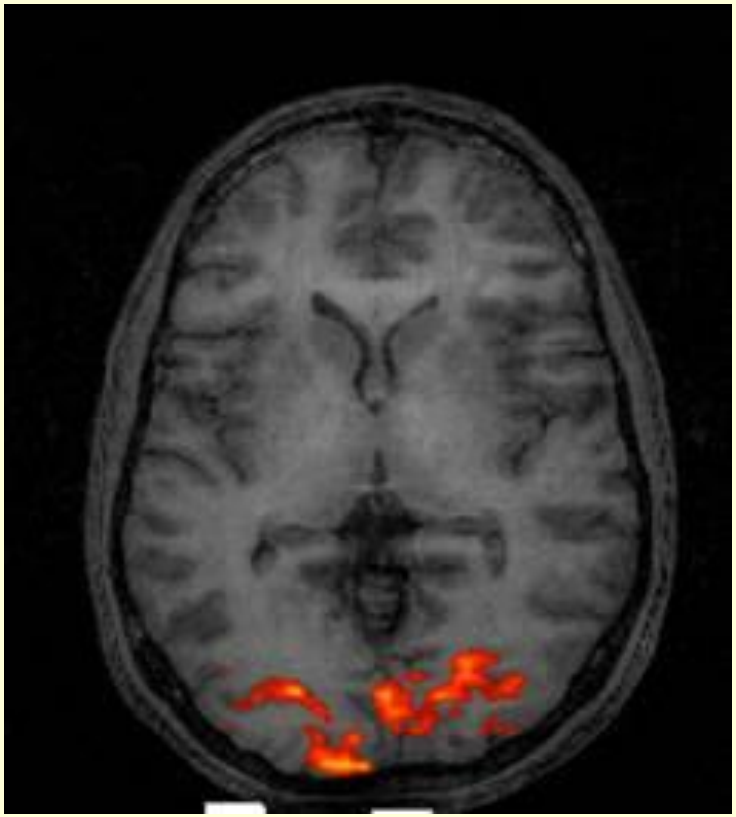
Residuals

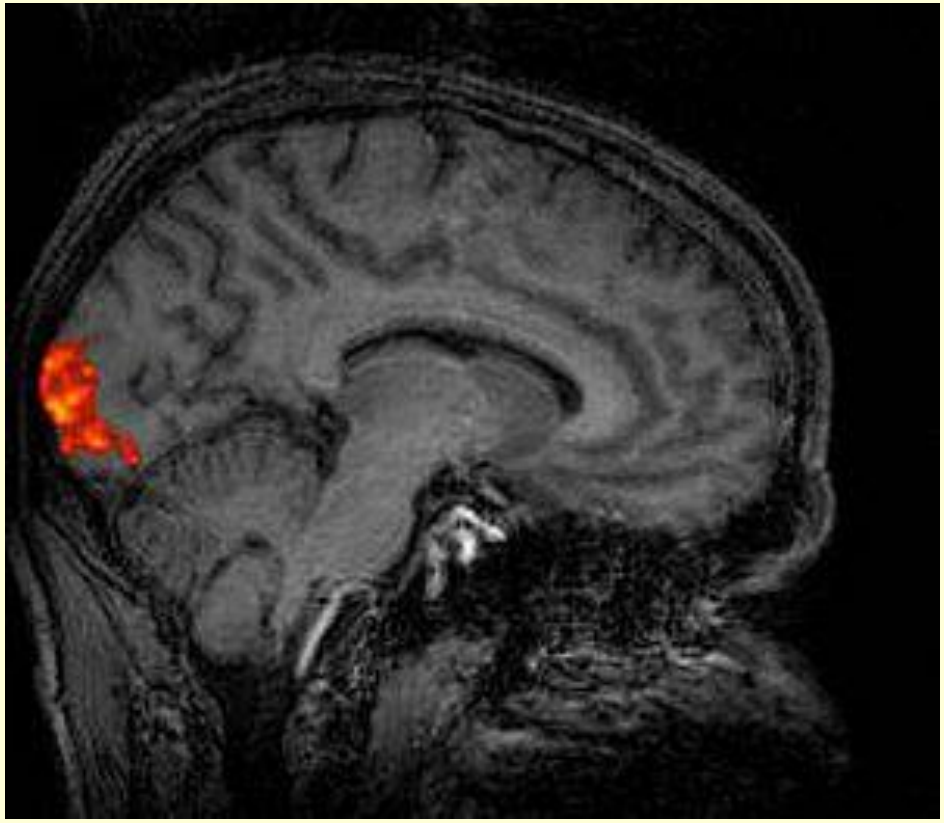
GLM for 2 activations



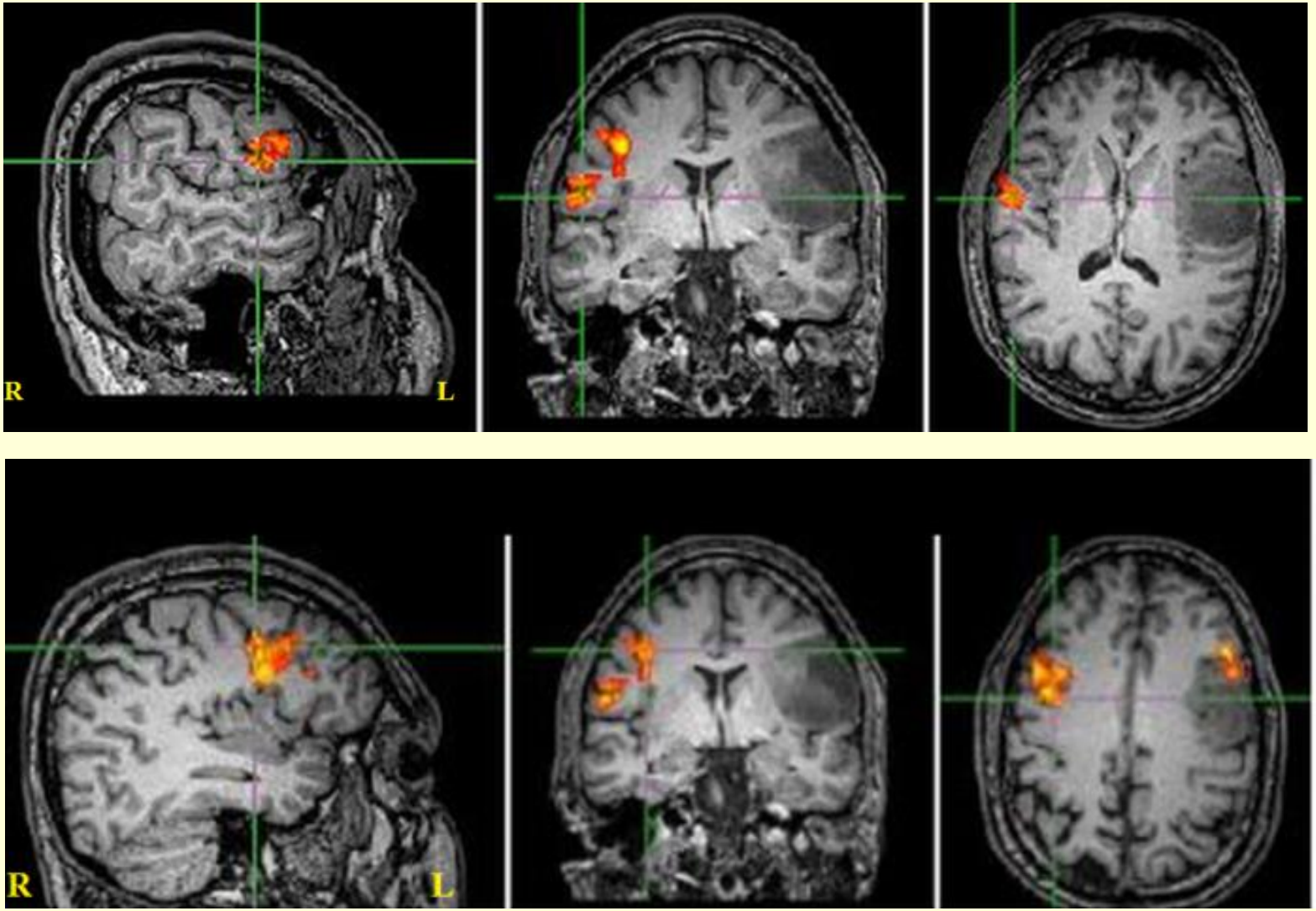
$$\underline{Y} = \mu \underline{1} + \beta_1 \underline{X}_1 + \beta_2 \underline{X}_2 + \underline{\varepsilon}$$

Visual activation area





Language task (WG) on left-handed patient with Temporoparietal mass



Software package for fMRI analysis

Package	Developer	Platforms[a]	Licensing
SPM	University College London	MATLAB	Open-source
FSL	Oxford University	UNIX	Open source
AFNI	NIMH	UNIX	Open source
Brain Voyager	Brain Innovation	Mac OS X, Windows, Linux	Commercial (closed-source)

- SPM: include connectivity modeling tools, psychophysioligical interaction, Dynamic Causal Moleding
- FSL: novel modeling techniques (eg RANDOMISE modules), ICA for resting-state, DTI analysis, FSLview & probabilistic Atlases, enable computing clusters
- AFNI: Powerful visualization abilities, integrating volume and cortical surfaces
- BrainVoyager: commercial on all computing platforms
- Freesurfer: for cortical surfaces and anatomical parcellations; can incorporate fMRI data from SPM/FSL

Pre-requisities for fMRI analysis

- Probability and Statistics
- Computer programming: ATHLAB/python/UNIX shell scripting
- Linear Algebra: GLM/image processing
- MRI: data acquisition/artifacts
- Neurophysiology & biophysics: Neuron activities & blood flow/hemodynamic response
- Signal & Image processing: Fourier analysis based processing

Thank You

M A Oghabian