

TMBIC 2015 資料分析助理研習營

# FMRI實驗設計

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# Motivations of Research

- **Question(s)**

- 動作由哪些大腦區域控制？
- 前運動區和主要運動區在伸手抓取物體過程中，活化方式有何差異？

- **Hypothesis**

- 前運動區和主要運動區在伸手抓取物體過程中有活動。
- 在伸手抓取物體過程中，前運動區先活動，再擴展到主要運動區，而且兩者之活動強度有高關聯性。

# Experiments & Experimental Designs

- **Experiments**
  - The controlled test of hypotheses
- **Experimental designs**
  - The organization of an experiment to allow effective testing of the research hypothesis.
- **Well-designed experiments**
  - Test specific hypothesis
  - Can ruled out your hypothesis
  - Minimize costs

# Fundamental Elements of Experiments

- Variables

- Independent variables (IVs)

- Intentionally manipulated by the experimenter
    - Hypothesized to cause changes in DVs
    - Conditions/Levels: Different values of IV

- Dependent variables (DVs)

- Quantities measured for evaluating the effect of IVs
    - Can be multiple
    - Behavioral or physiological
      - RT, accuracy, trajectory, self-report, ratings
      - BOLD, DTI, VBM, MEG, EEG, ERP, ...

# Other Important Aspects

- Within- vs. Between-subjects Designs
- Confounding factors
  - Uncontrolled properties that co-vary with IVs
  - Solutions
    - Randomization
    - counterbalance

# 什麼是控制良好的實驗？

服藥前

---

發燒、  
咳嗽、  
流鼻水

服藥

---




服藥後

---

症狀消失

# 什麼是控制良好的實驗？

	服藥前	服藥	服藥後
<b>實驗組</b>	發燒、 咳嗽、 流鼻水		症狀消失
<b>對照組</b>	發燒、 咳嗽、 流鼻水	多休息喝水	症狀消失

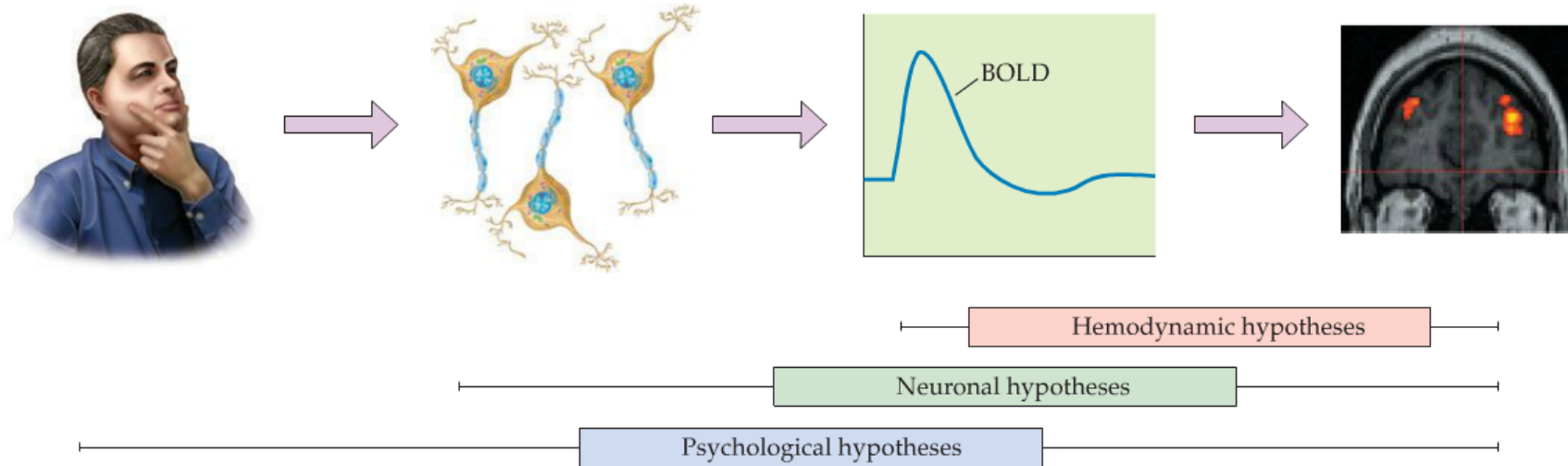
# Experimental vs. Control Conditions

(A)

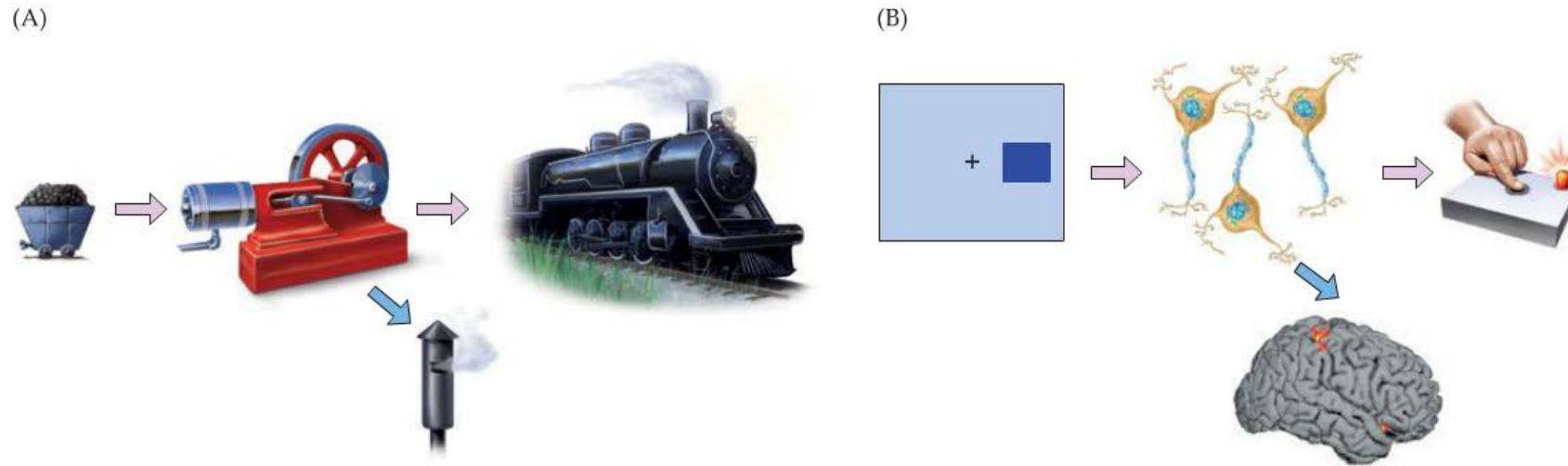




# Levels of Research Hypothesis



# FMRI is Epiphenomenal?

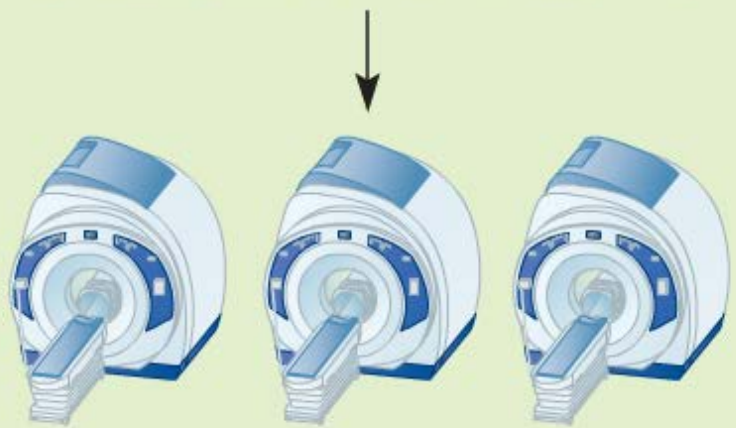


- BOLD changes could be irrelevant to information processing.
- Yet correlational is not equivalent to meaningless.

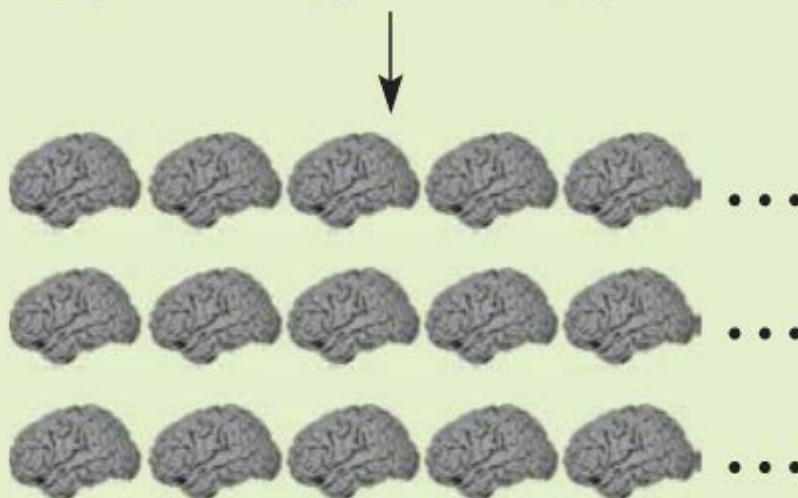
Subjects



Sessions



Runs



- Blocks
- Conditions
- Trials
- Events

(A)

B1

"Carrot" "Mailbox" "Knife" "Tiger" "Sweater" "Teapot" "Auto" "Doorbell" "Spider" "Parsley"

B2

"Plant" "Handbag" "Pebble" "Chess" "Book" "Phone" "Anger" "Watch" "Window" "Night"

(B) **Alternating Design**

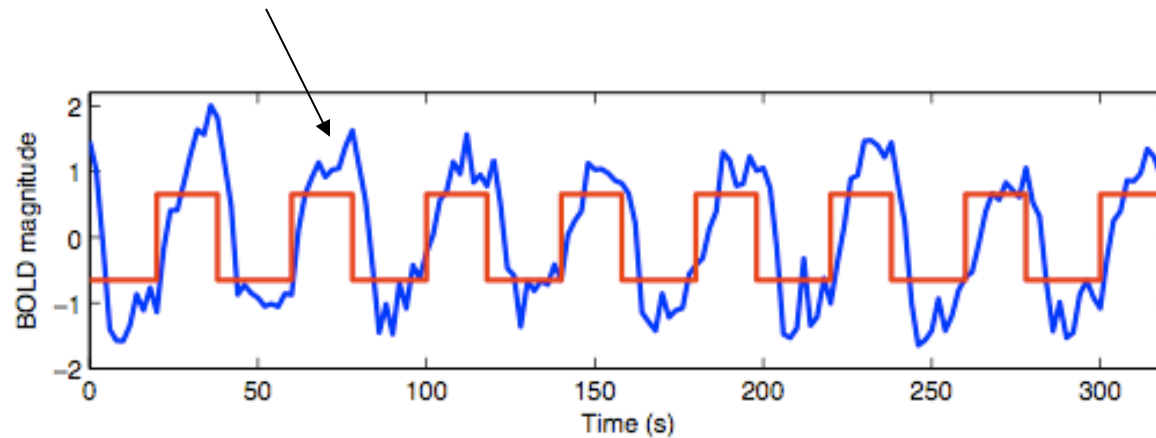


(C) **Interleaving null-task blocks**



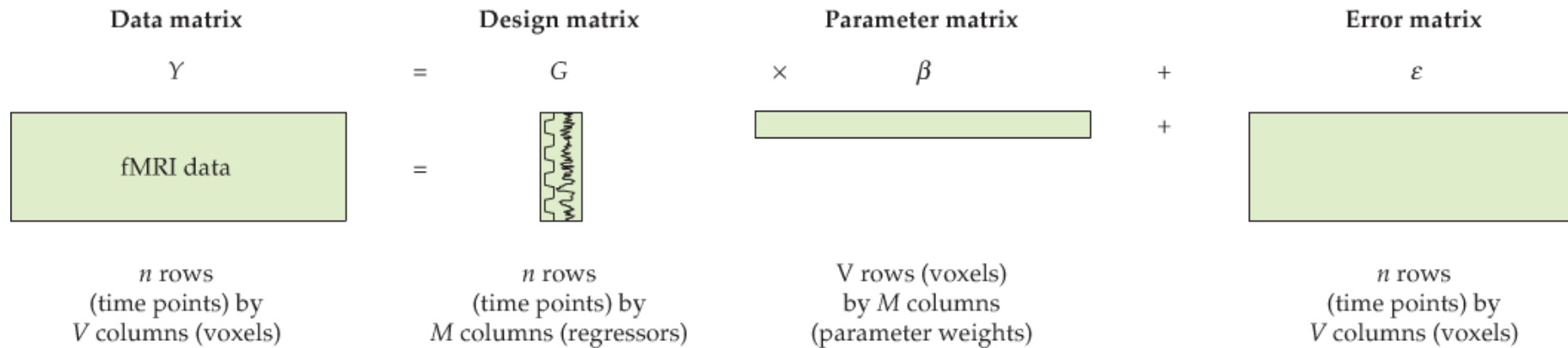
# IV and DV from the Perspective of Data Analysis

- Observed BOLD signal (example)



- BOLD signal did not look exactly like the predicted neural activity (in red)

# General Linear Model



# FMRI Experimental Designs

- Blocked designs
- Event-related designs
- Mixed designs

**Block Design**



**Slow ER Design**



**Rapid Counterbalanced ER Design**



**Rapid Jittered ER Design**

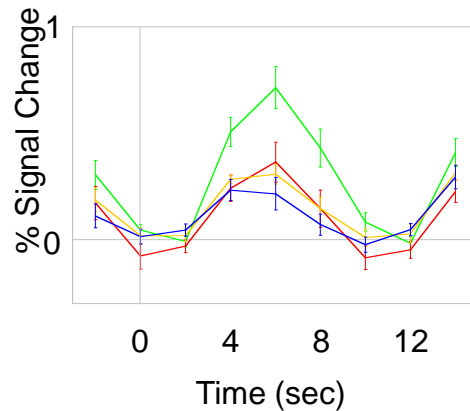
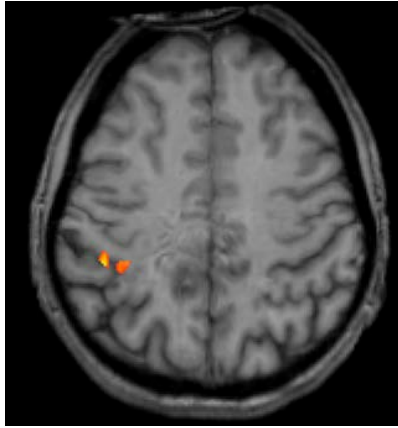


**Mixed Design**





# Detection vs. Estimation



- Detection: determination of whether activity of a given voxel (or region) changes in response to the experimental manipulation
- “which voxel?”
  - Estimation: measurement of the time course within an active voxel in response to the experimental manipulation
  - “How does signal change in a voxel?”

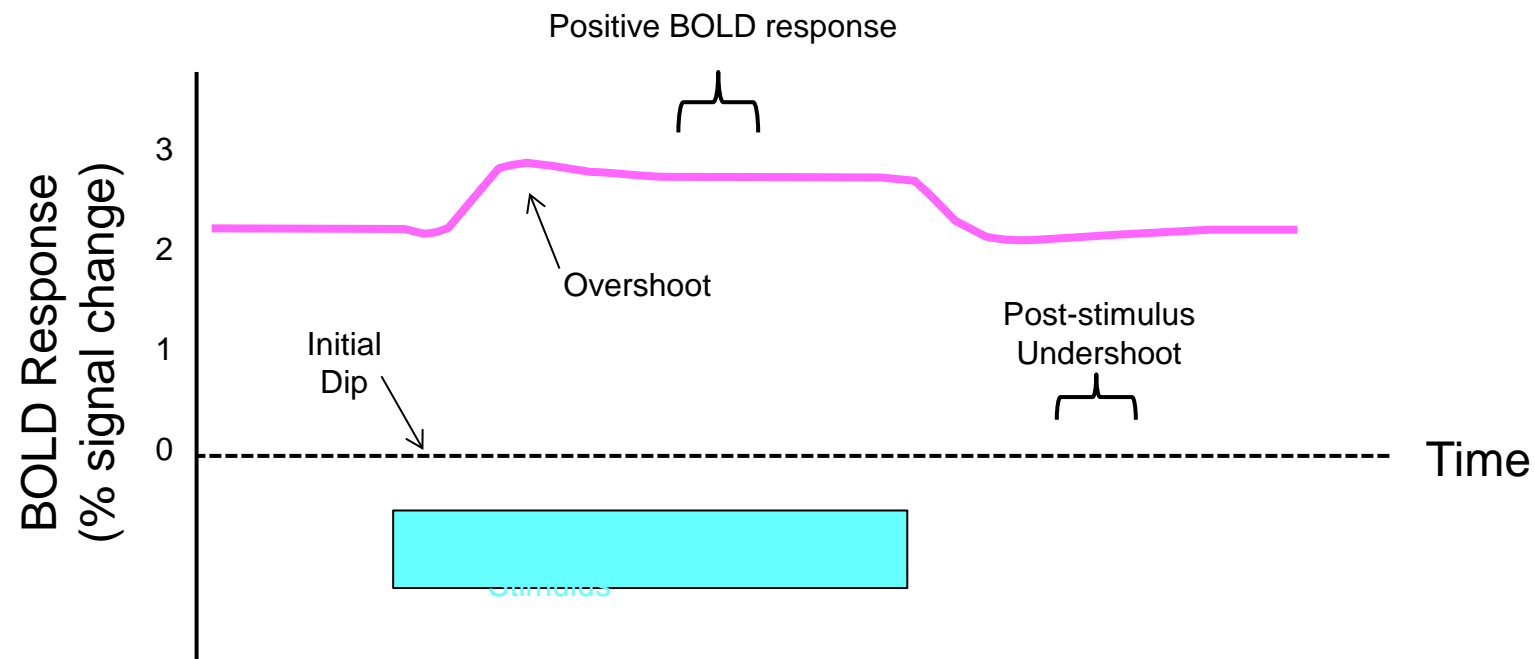
*Definitions modified from: Huettel, Song & McCarthy, 2004, Functional Magnetic Resonance Imaging*

# Block Designs

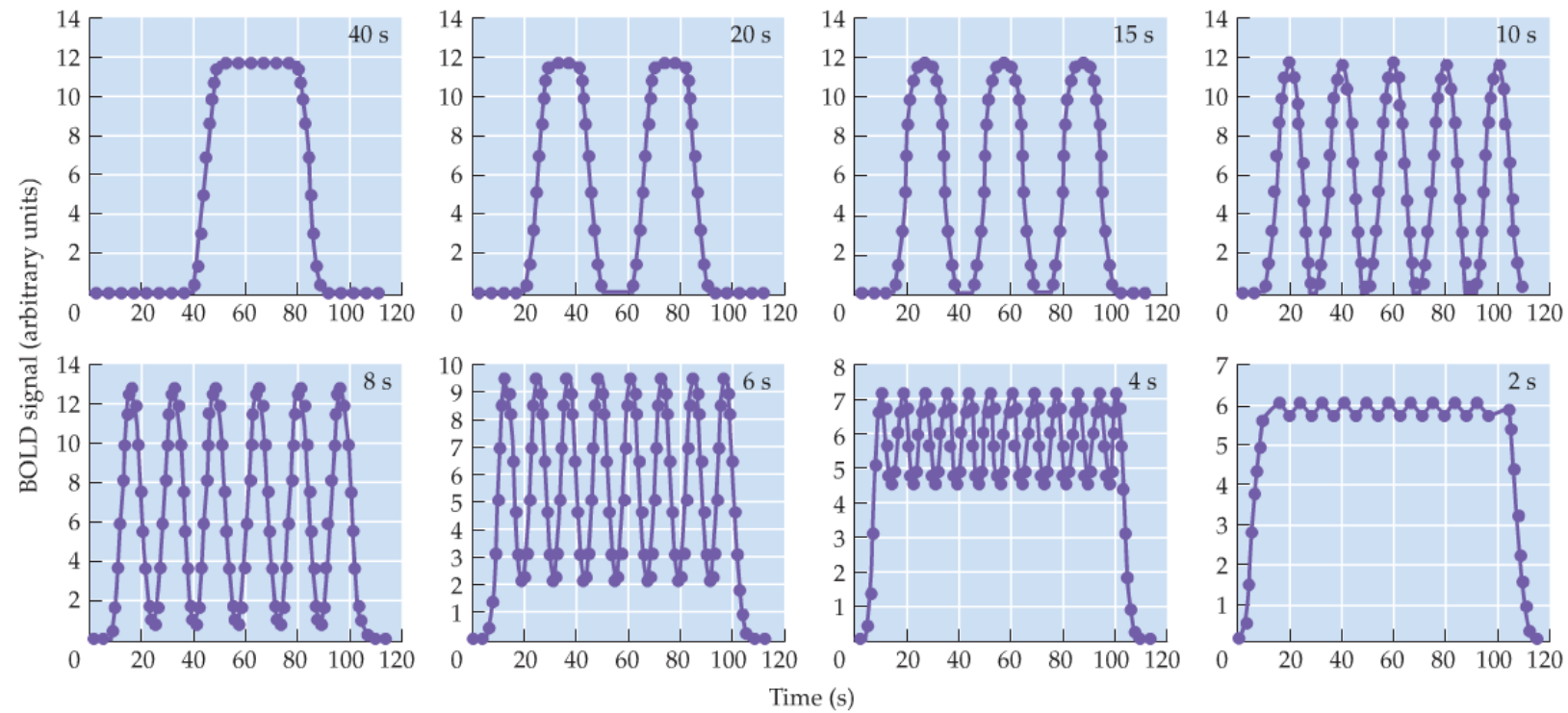
▲ = trial of one type (e.g., face image)    ▲ = trial of another type (e.g., place image)



Early Assumption: Because the hemodynamic response delays and blurs the response to activation, the temporal resolution of fMRI is limited.



# Effect of Block Interval on FMRI HRF



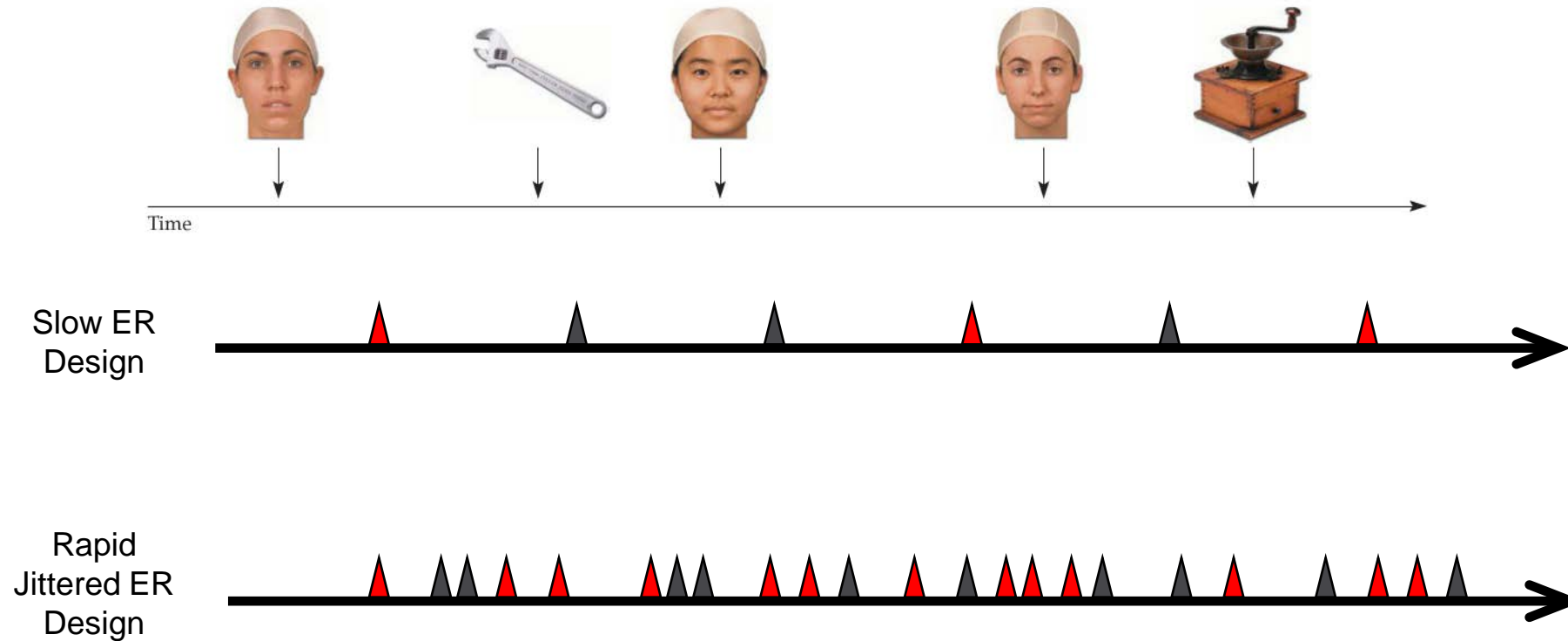
# Recommendations for Using Blocked Design

- Length of a block
  - 10s ~ 1 minute
    - Task property
    - Fatigue and practice
  - Equivalent for conditions or combination of conditions to be compared
- Evoking the same mental process throughout a block

# Advantages and Disadvantages of Blocked Design

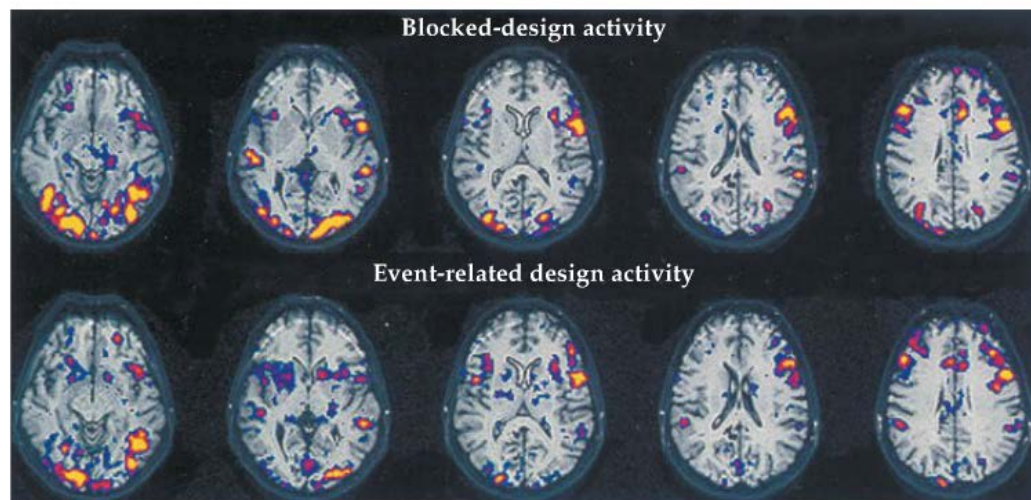
- High detection power
- Trade-off of block length
  - Long block
    - Larger differences between conditions
  - Short block
    - Avoid confounding with low frequency scanner drift
    - Increase SNR at the task frequency
- Rule of thumb
  - Block length at HR duration (10~15 s)

# Event-related Designs

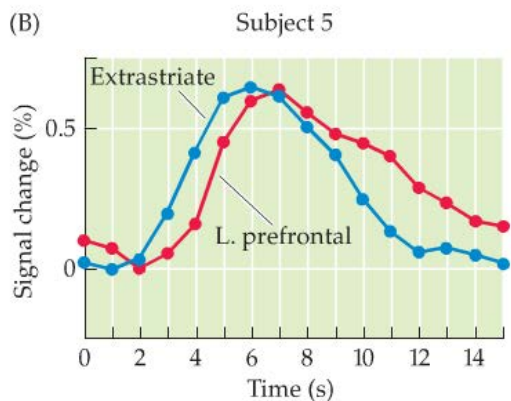


# ER-FMRI Showing Timing Differences

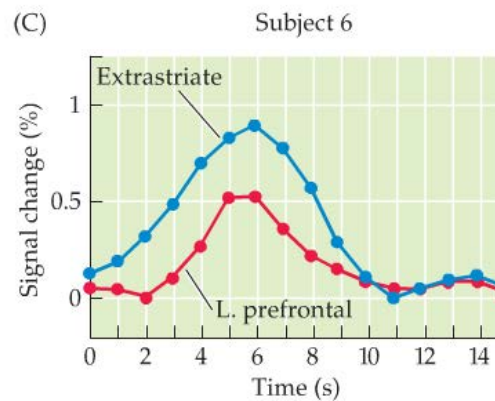
(A)



(B)



(C)



# Slow Event-Related Designs

Slow ER  
Design

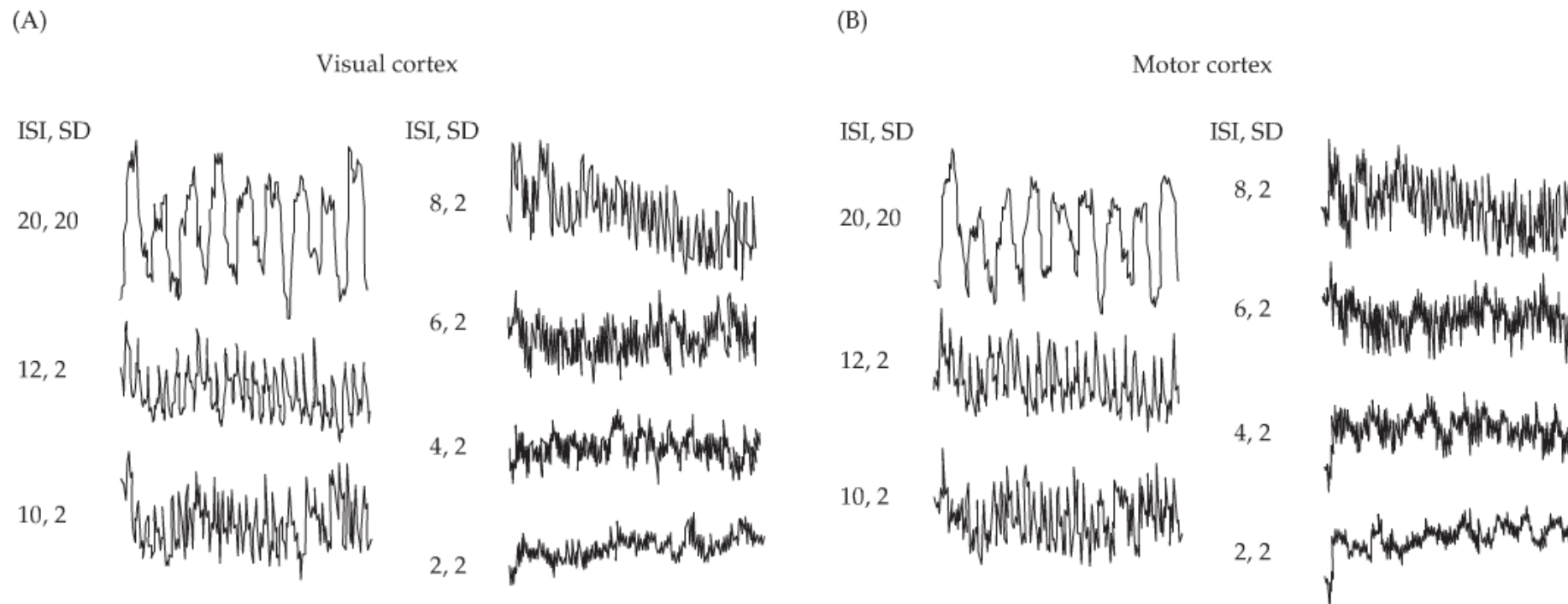




# Periodic (Slow) ER Design

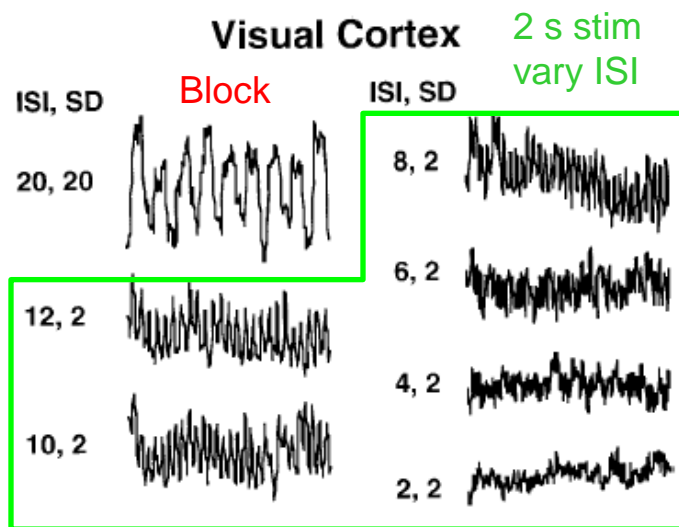
- Fixed and long ISI
  - Usually  $> 15s$
  - Each event evokes a complete HR, and corresponding BOLD are selectively averaged.
  - Inefficient

# Effects of ISI on ER-FMRI Activation



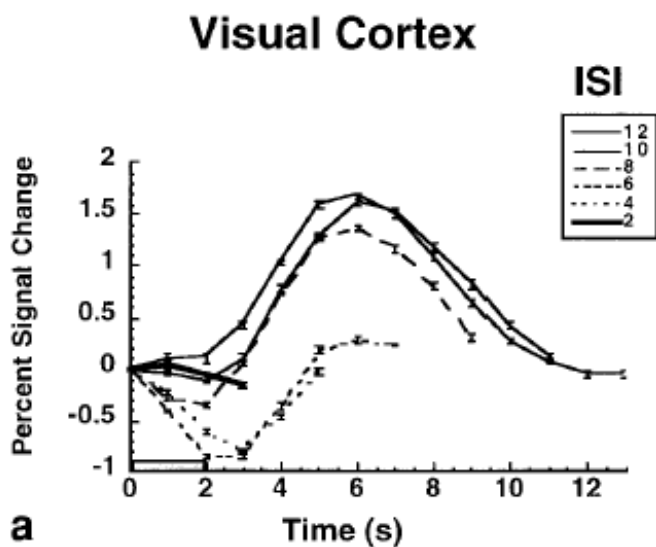
Bandettinni & Cox (2000)

# Slow Event-Related Design: Constant ITI



Bandettini et al. (2000)

What is the optimal trial spacing (duration + intertrial interval, ITI) for a Spaced Mixed Trial design with constant stimulus duration?

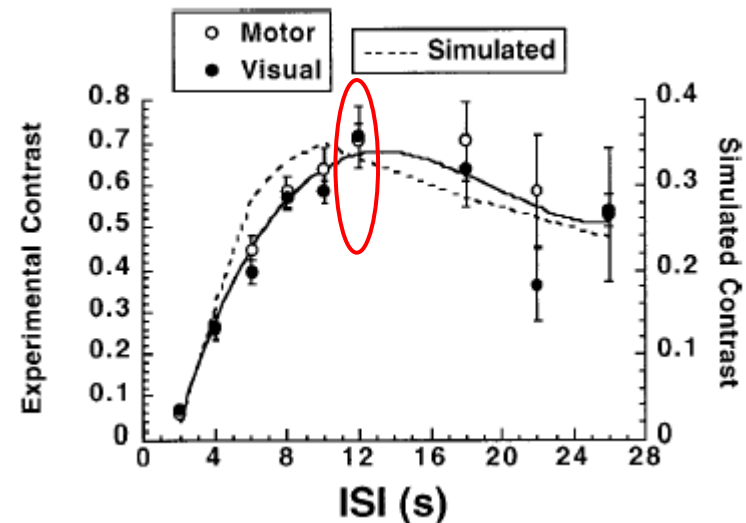


Event-related average

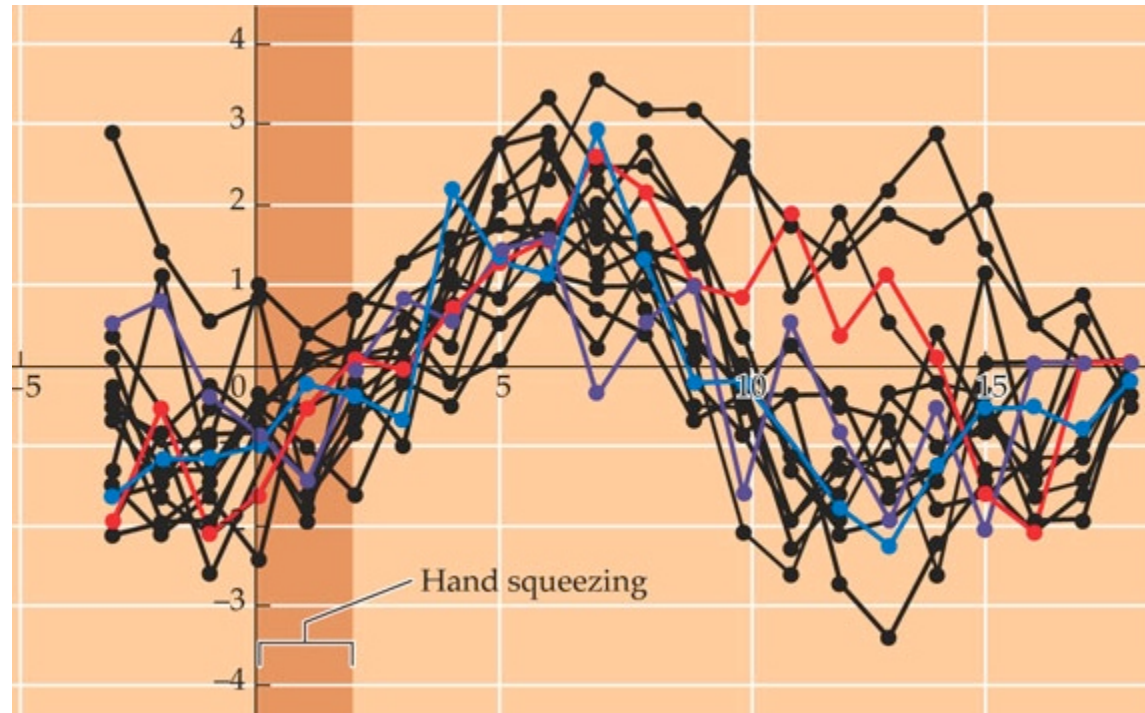
Source: Bandettini et al., 2000

# Optimal Constant ITI

- Brief (< 2 sec) stimuli:
  - optimal trial spacing = 12 sec
- For longer stimuli:
  - optimal trial spacing =  $8 + 2 * \text{stimulus duration}$
- Effective loss in power of event related design:
  - = -35%
  - i.e., for 6 minutes of block design, run ~9 min ER design

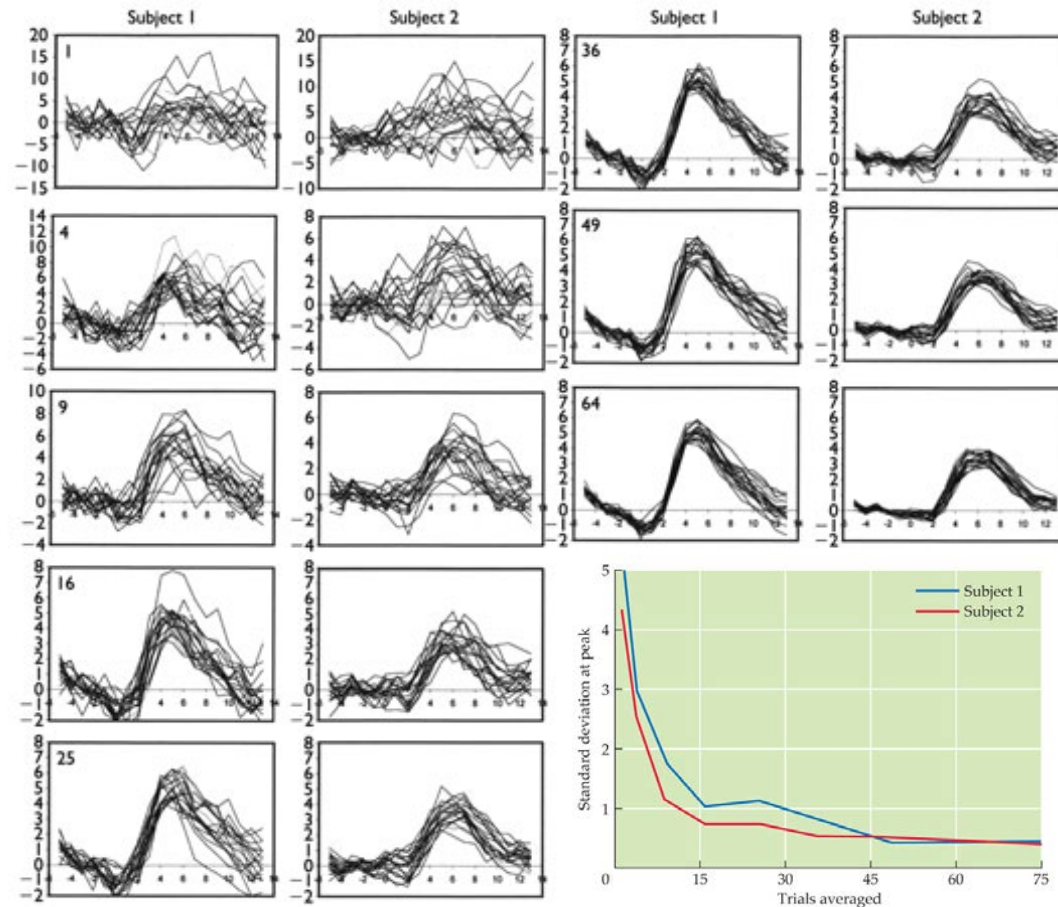


# Trial to Trial Variability



*Huettel, Song & McCarthy, 2004,  
Functional Magnetic Resonance Imaging*

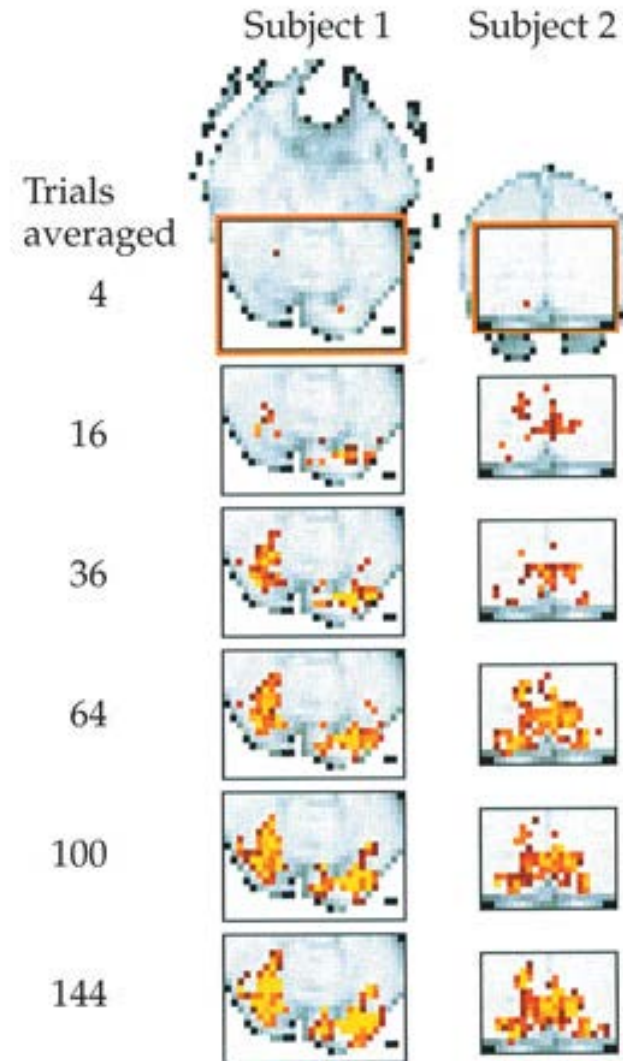
# How Many Trials Do You Need?



*Huettel, Song & McCarthy, 2004, Functional Magnetic Resonance Imaging*

- standard error of the mean varies with square root of number of trials
- Number of trials needed will vary with effect size
- Function begins to asymptote around 15 trials

# Effect of Adding Trials



*Huettel, Song & McCarthy, 2004, Functional Magnetic Resonance Imaging*

# Pros & Cons of Slow ER Designs

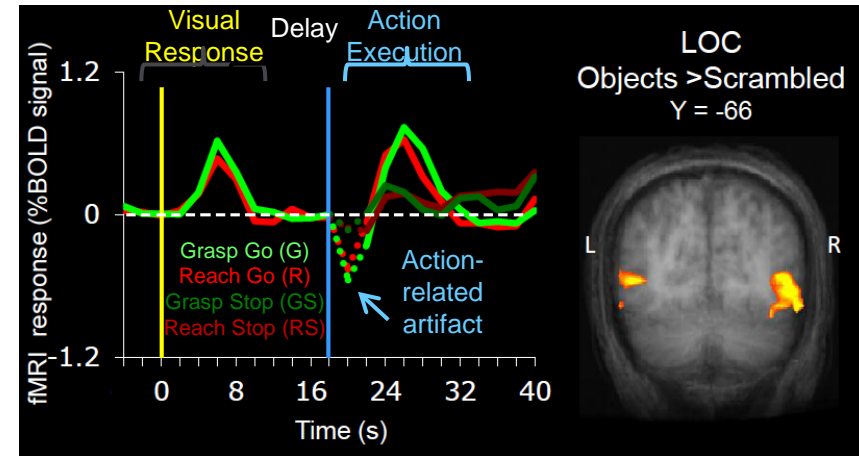
## Pros

- excellent estimation
- useful for studies with delay periods
- very useful for designs with motion artifacts (grasping, swallowing, speech) because you can tease out artifacts
- analysis is straightforward

## Cons

- poor detection power because you get very few trials per condition by spending most of your sampling power on estimating the baseline
- subjects can get VERY bored and sleepy with long inter-trial intervals

Example: Delayed Hand Actions  
(Singhal et al., under revision)



Really long delay:  
18 s



Effect of this design  
on our subject



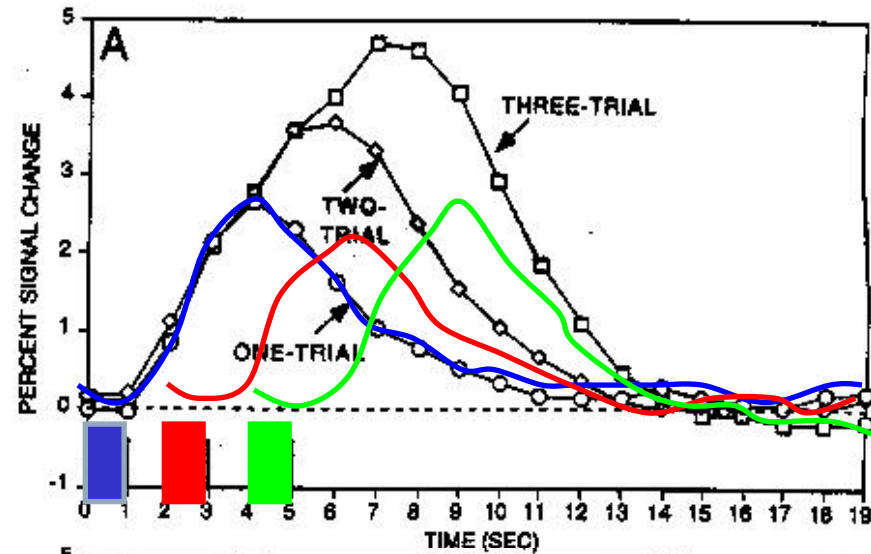
# “Do You Wanna Go Faster?”

- Yes, but we have to test assumptions regarding linearity of BOLD signal first

Rapid  
Jittered ER  
Design



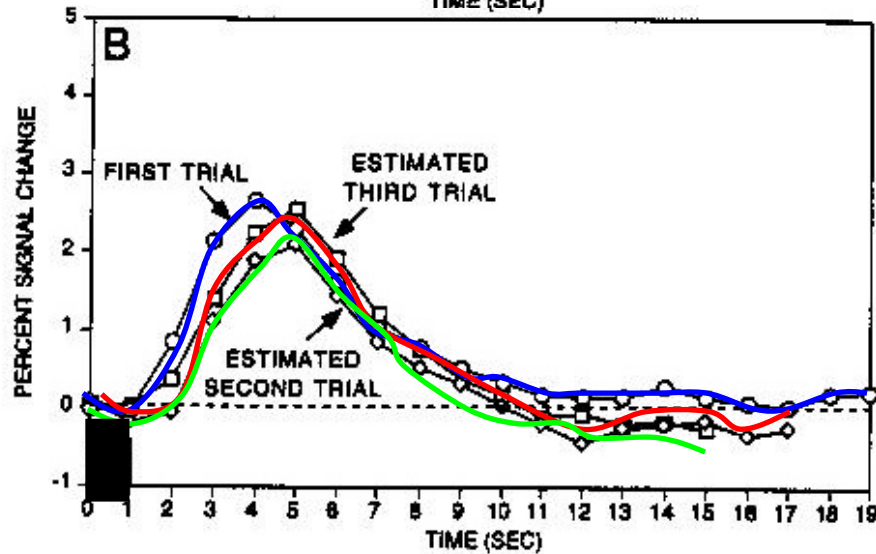
# Linearity of BOLD response



Linearity:  
“Do things add up?”

red = 2 - 1

green = 3 - 2





Sync each trial response  
to start of trial

Not quite linear  
but good enough!

Source: Dale & Buckner, 1997

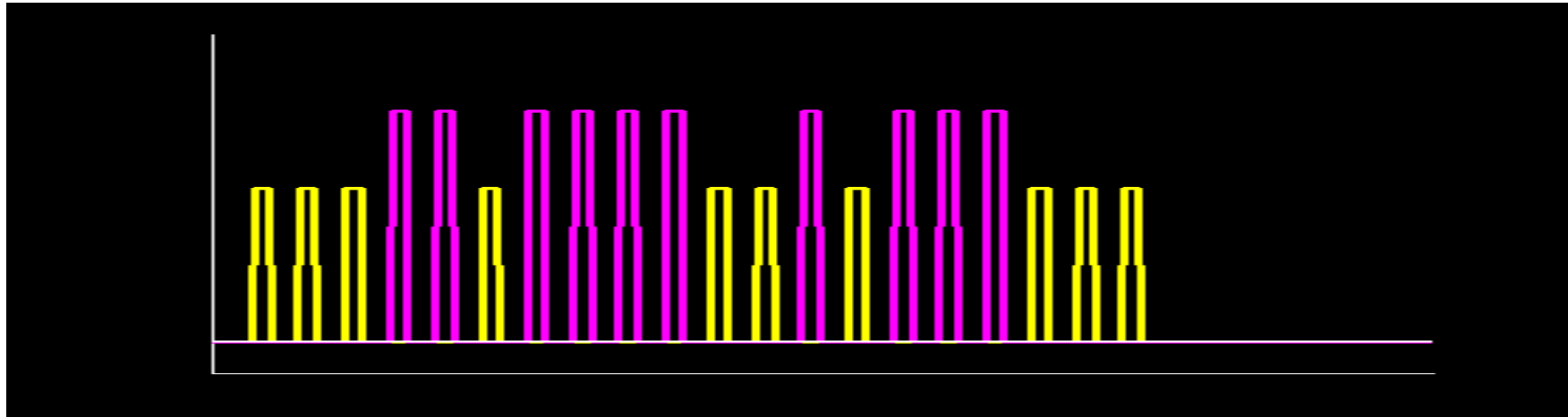
# Rapid Jittered ER Design

-  = trial of one type (e.g., face image)
-  = trial of another type (e.g., place image)

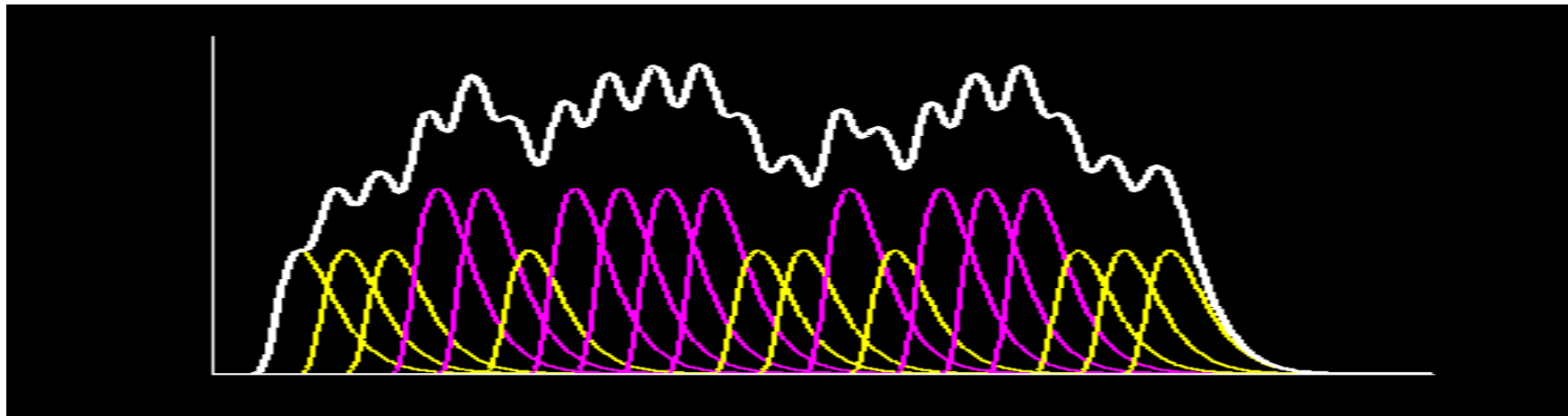
Rapid  
Jittered ER  
Design



# BOLD Overlap With Regular Trial Spacing



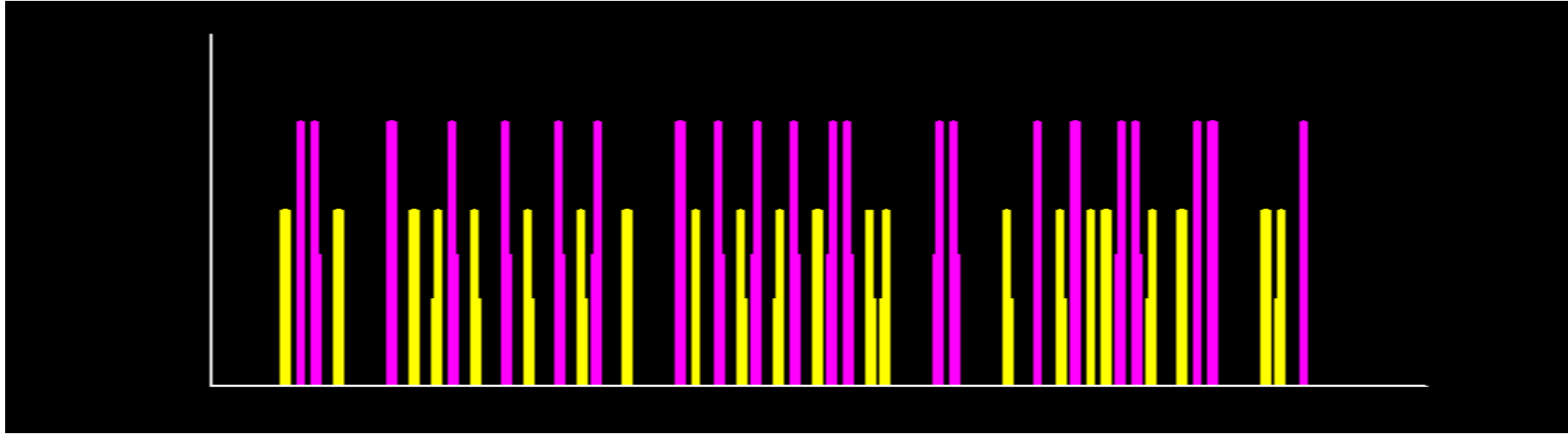
Neuronal activity from TWO event types with constant ITI



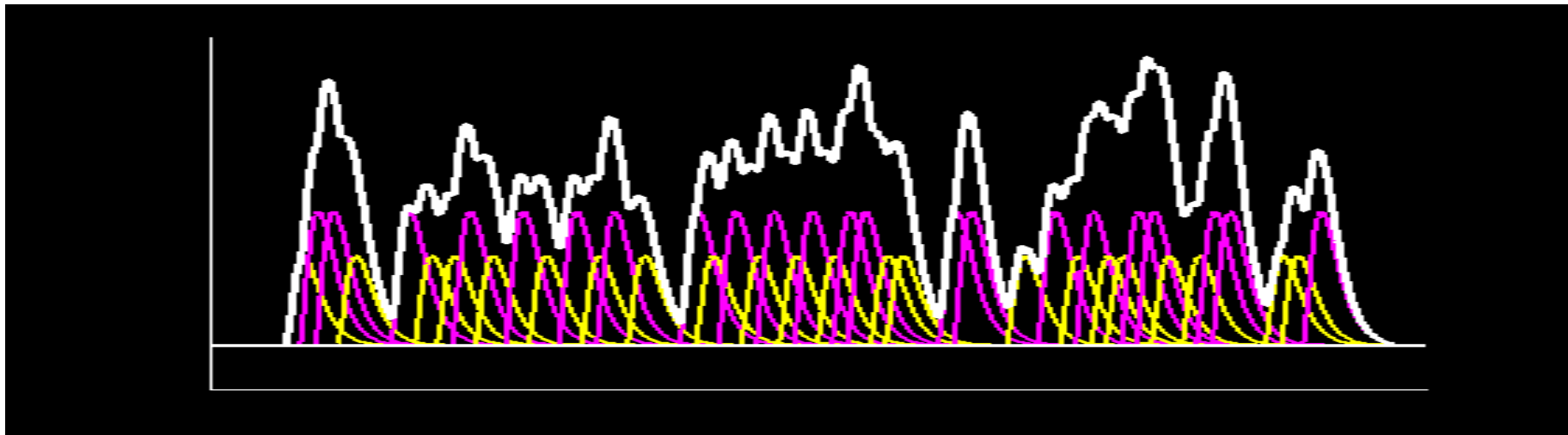
Partial tetanus BOLD activity from two event types

*Slide from Matt Brown*

# BOLD Overlap with Jittering



Neuronal activity from closely-spaced, jittered events

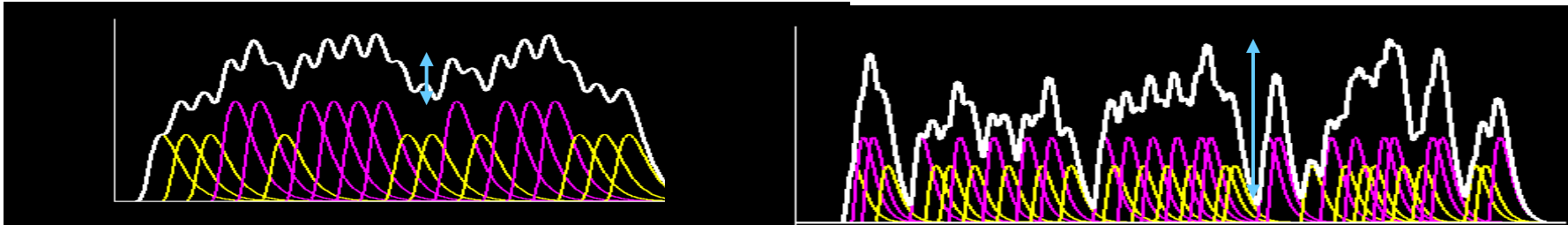


BOLD activity from closely-spaced, jittered events

*Slide from Matt Brown*

# Why jitter?

- Yields larger **fluctuations** in signal



When pink is on, yellow is off  
→ pink and yellow are anticorrelated

Includes cases when both pink and yellow are off  
→ less anticorrelation

- Without jittering predictors from different trial types are strongly **anticorrelated**
  - As we know, the GLM doesn't do so well when predictors are correlated (or anticorrelated)

# Matrix Expression of GLM

$$Y = X \cdot \beta + \varepsilon$$

- Write out equation for each observation of variable Y from 1 to J:

$$Y_1 = X_{11}\beta_1 + \dots + X_{1l}\beta_l + \dots + X_{1L}\beta_L + \varepsilon_1$$

$$Y_j = X_{j1}\beta_1 + \dots + X_{jl}\beta_l + \dots + X_{jL}\beta_L + \varepsilon_j$$

$$Y_j = X_{j1}\beta_1 + \dots + X_{jl}\beta_l + \dots + X_{jL}\beta_L + \varepsilon_j$$

Can turn these simultaneous equations into matrix form to get a single equation:

$$\begin{pmatrix} Y_1 \\ Y_j \\ Y_J \end{pmatrix} = \begin{pmatrix} X_{11} & \dots & X_{1l} & \dots & X_{1L} \\ X_{j1} & \dots & X_{jl} & \dots & X_{jL} \\ X_{J1} & \dots & X_{Jl} & \dots & X_{JL} \end{pmatrix} \begin{pmatrix} \beta_1 \\ \beta_j \\ \beta_J \end{pmatrix} + \begin{pmatrix} \varepsilon_1 \\ \varepsilon_j \\ \varepsilon_J \end{pmatrix}$$

$$Y = X \cdot \beta + \varepsilon$$

Observed data

Design Matrix

Parameters

Residuals/Error

# Solution to the Equation

$$X'Y = X'X\beta \qquad \hat{\sigma}^2 = \frac{e'e}{T-(p+1)}$$

Any  $\beta$  satisfies the normal equation minimizes the sum of the squares of residuals ( $e'e$ )

$$\hat{\beta} = (X'X)^{-1}X'Y$$

 Assuming this is invertible



# Hypothesis Testing: Contrast t-test

$$c\hat{\beta} \sim N(0, c(X'X)^{-1}c'\sigma^2)$$

$$t = \frac{c\hat{\beta}}{\sqrt{c(X'X)^{-1}c'\hat{\sigma}^2}}$$

$$df: T - (p + 1)$$

$$H_A : c\beta > 0$$

$$P(T_{T-(p+1)} \geq t)$$

$$H_A : c\beta \neq 0$$

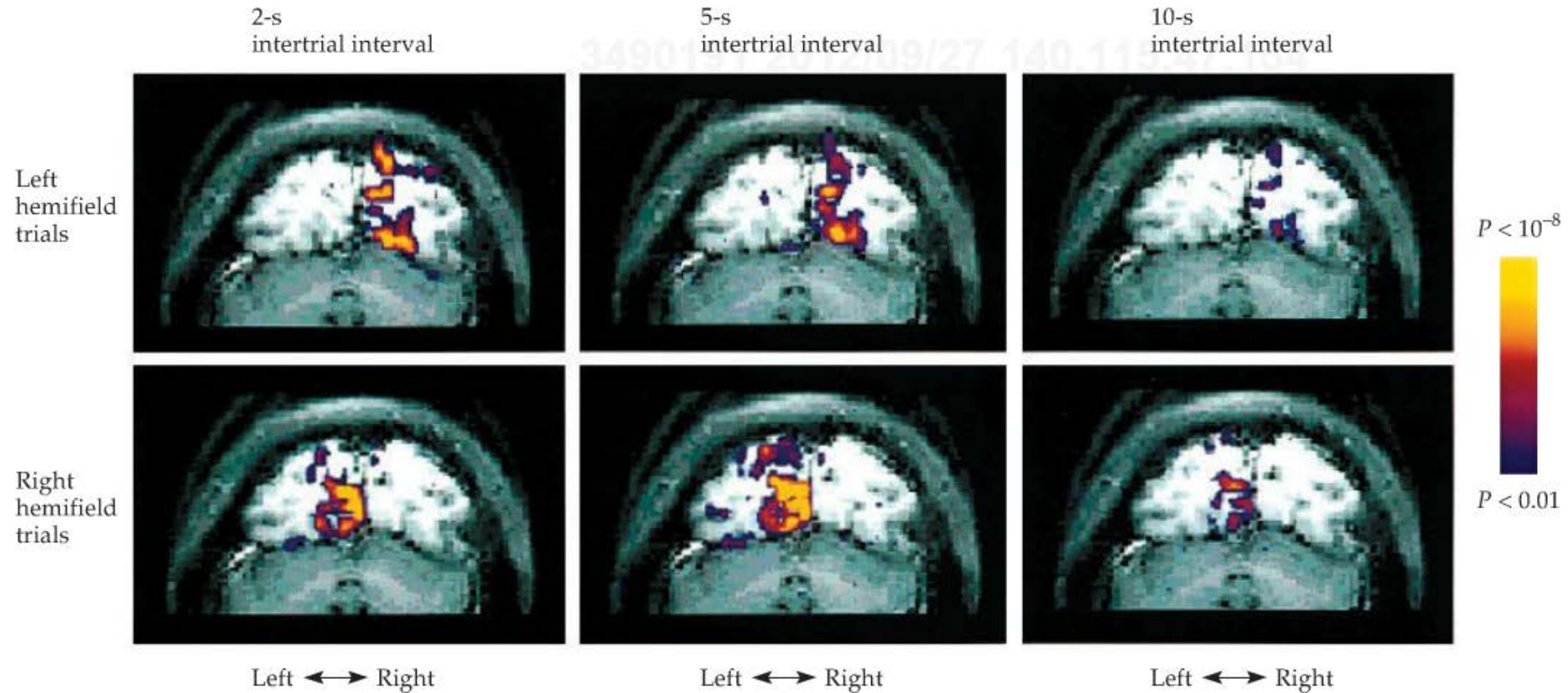
$$P(T_{T-(p+1)} \geq |t|)$$

$$t = \frac{c\hat{\beta}}{\sqrt{c(X'X)^{-1}c'\hat{\sigma}^2}}$$

Design matrix & Contrast Vector;  
depending on your experimental  
design

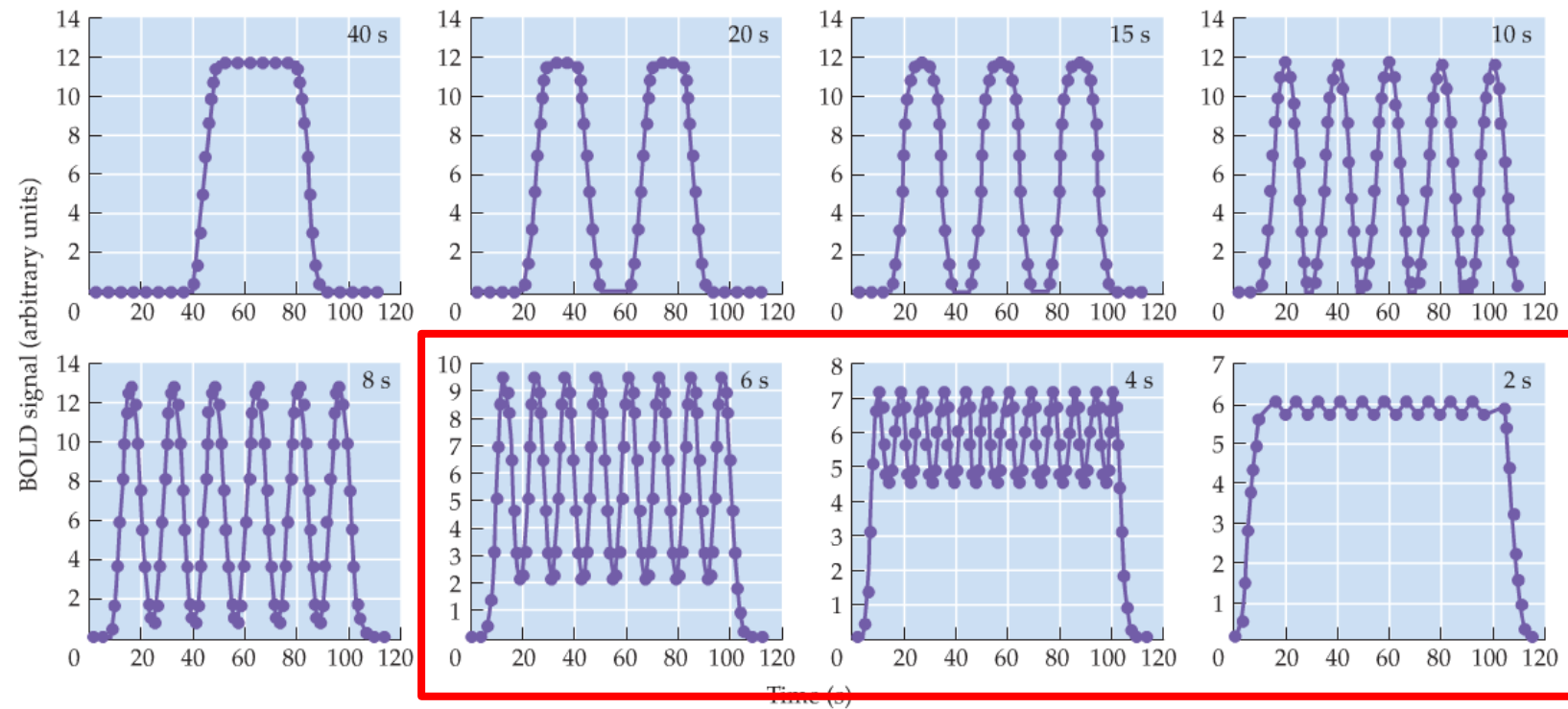
Residual error unaccounted for  
by your design; depending on  
the quality of data

# Rapid ER-FMRI with Randomized Stimulus Presentation

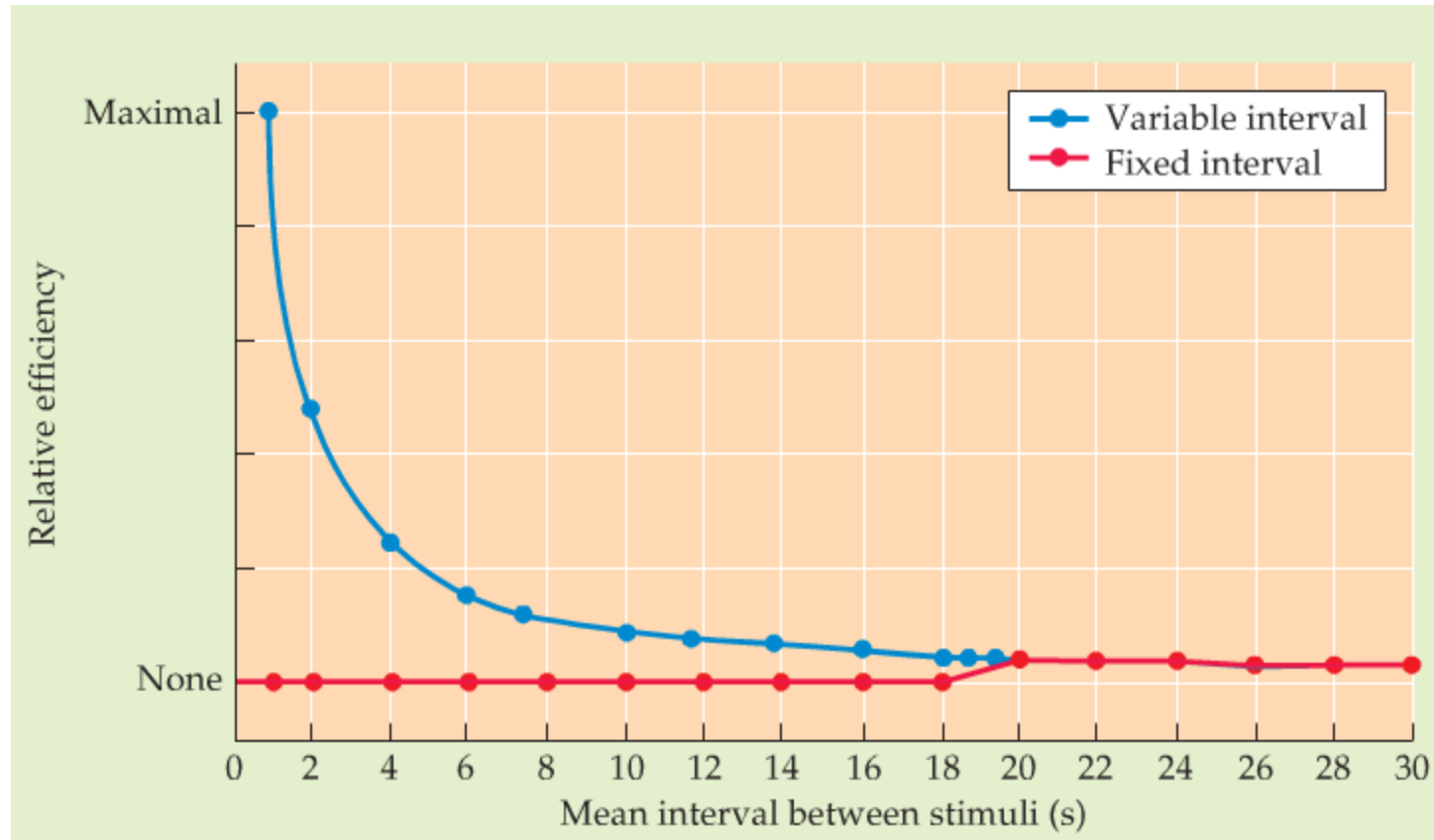


Short randomized ITI enhances detection power.

# Note That ITI Has to Be Randomized, Otherwise...



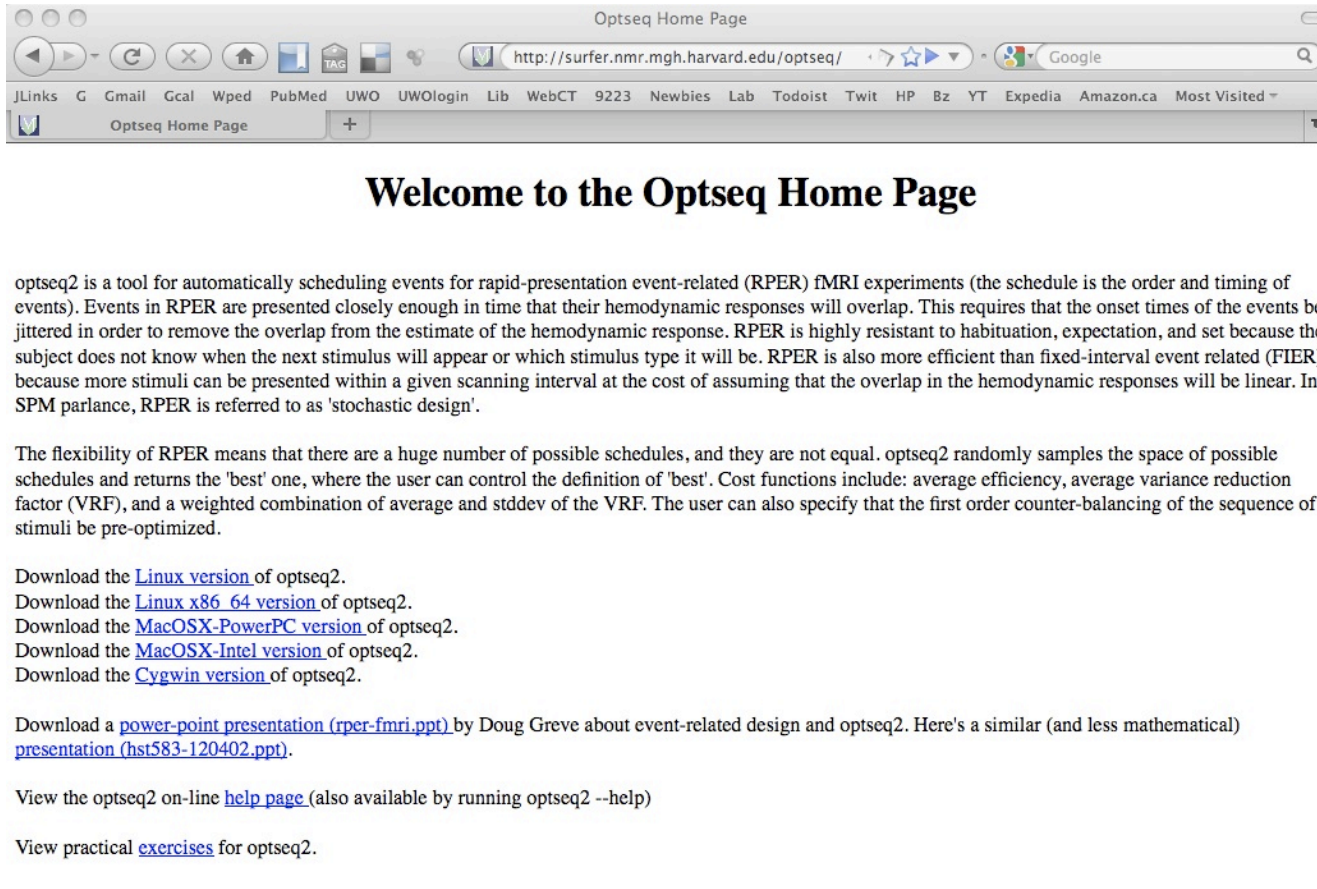
# Variable vs. Fixed Intervals



After Dale (1999)

# Algorithms for Picking Efficient Designs

## Optseq2



The screenshot shows a web browser window titled "Optseq Home Page". The address bar contains the URL "http://surfer.nmr.mgh.harvard.edu/optseq/". The browser's menu bar includes "JLinks", "G", "Gmail", "Gcal", "Wped", "PubMed", "UWO", "UWOlogin", "Lib", "WebCT", "9223", "Newbies", "Lab", "Todoist", "Twit", "HP", "Bz", "YT", "Expedia", "Amazon.ca", and "Most Visited". The main content of the page is as follows:

### Welcome to the Optseq Home Page

optseq2 is a tool for automatically scheduling events for rapid-presentation event-related (RPER) fMRI experiments (the schedule is the order and timing of events). Events in RPER are presented closely enough in time that their hemodynamic responses will overlap. This requires that the onset times of the events be jittered in order to remove the overlap from the estimate of the hemodynamic response. RPER is highly resistant to habituation, expectation, and set because the subject does not know when the next stimulus will appear or which stimulus type it will be. RPER is also more efficient than fixed-interval event related (FIER) because more stimuli can be presented within a given scanning interval at the cost of assuming that the overlap in the hemodynamic responses will be linear. In SPM parlance, RPER is referred to as 'stochastic design'.

The flexibility of RPER means that there are a huge number of possible schedules, and they are not equal. optseq2 randomly samples the space of possible schedules and returns the 'best' one, where the user can control the definition of 'best'. Cost functions include: average efficiency, average variance reduction factor (VRF), and a weighted combination of average and stddev of the VRF. The user can also specify that the first order counter-balancing of the sequence of stimuli be pre-optimized.

Download the [Linux version](#) of optseq2.  
Download the [Linux x86\\_64 version](#) of optseq2.  
Download the [MacOSX-PowerPC version](#) of optseq2.  
Download the [MacOSX-Intel version](#) of optseq2.  
Download the [Cygwin version](#) of optseq2.

Download a [power-point presentation \(rper-fmri.ppt\)](#) by Doug Greve about event-related design and optseq2. Here's a similar (and less mathematical) [presentation \(hst583-120402.ppt\)](#).

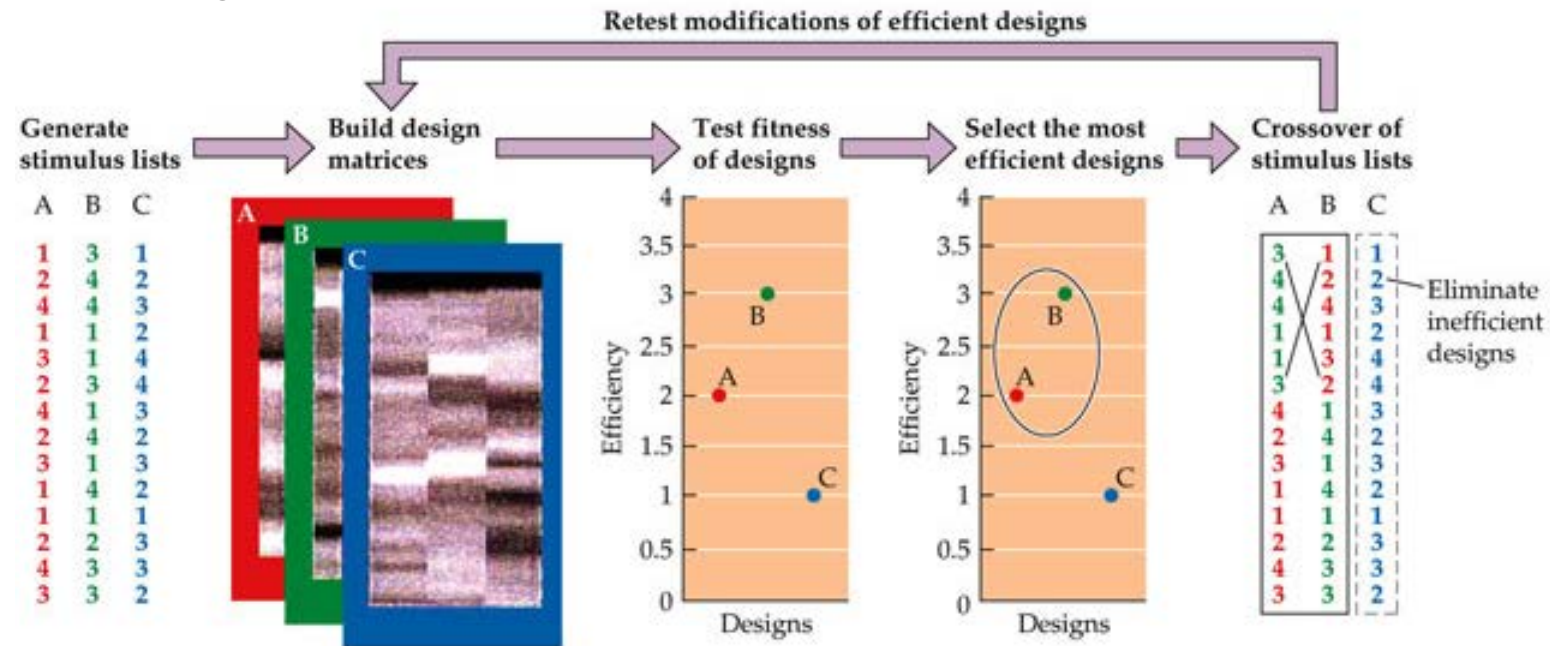
View the optseq2 on-line [help page](#) (also available by running `optseq2 --help`)

View practical [exercises](#) for optseq2.

<http://surfer.nmr.mgh.harvard.edu/optseq/>

# Algorithms for Picking Efficient Designs

## Genetic Algorithms



<http://wagerlab.colorado.edu/tools>

# Pros & Cons of Applying Standard GLM to Rapid-ER Designs

## Pros

- Acceptable detection power
- trials can be put in unpredictable order
- subjects don't get so bored

## Cons and Caveats

- reduced detection compared to block designs
- requires stronger assumptions about linearity
  - BOLD is non-linear with inter-event intervals  $< 6$  sec.
  - Nonlinearity becomes severe under 2 sec.
- errors in HRF model can introduce errors in activation estimates

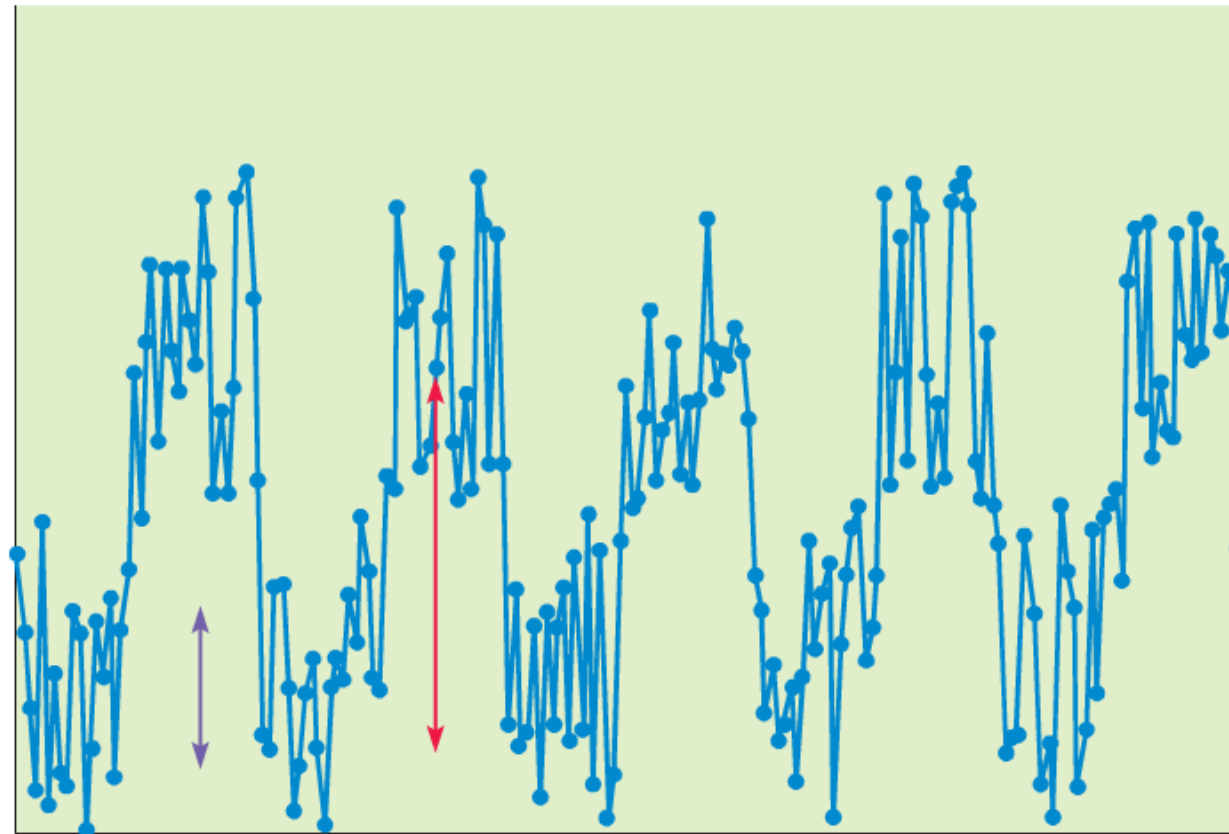


# Good Practices in fMRI

- Evoke the cognitive processes of interest
- Maximize data collection from each subject
- Maximize sample size
- Choose conditions and timings that maximize evoked changes in the process of interests
- Minimize correlation between BOLDs of successive events
- Compute correlation between behavioral performance and activation

# Questions?

# Within- vs. Between-condition Variability



Within-conditions variability

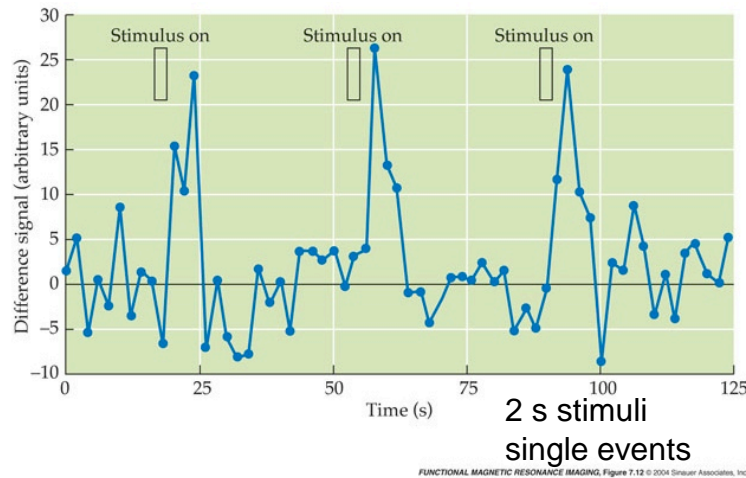
Between-conditions variability

# What is the briefest stimulus that fMRI can detect?

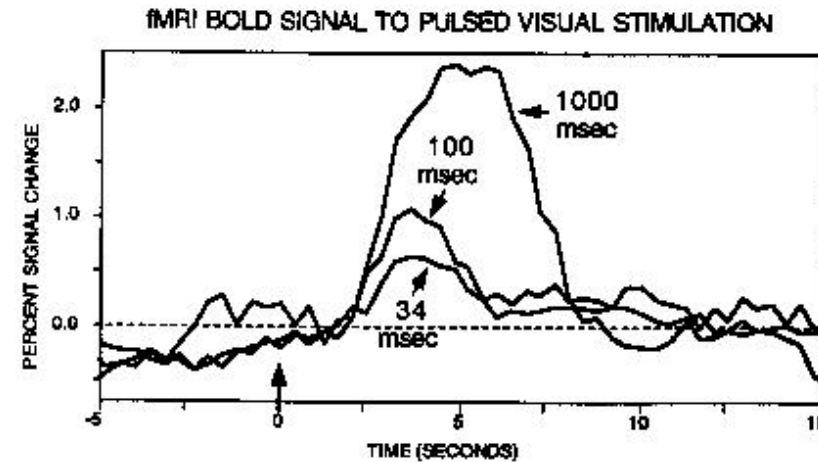
Blamire et al. (1992): 2 sec

Bandettini (1993): 0.5 sec

Savoy et al (1995): 34 msec



Data: Blamire et al., 1992, PNAS  
Figure: Huettel, Song & McCarthy, 2004



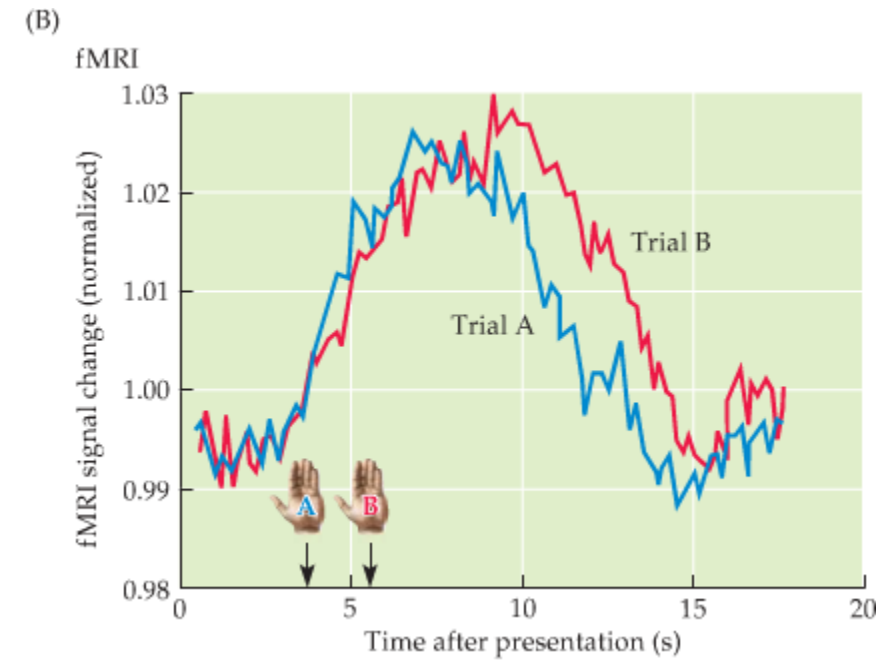
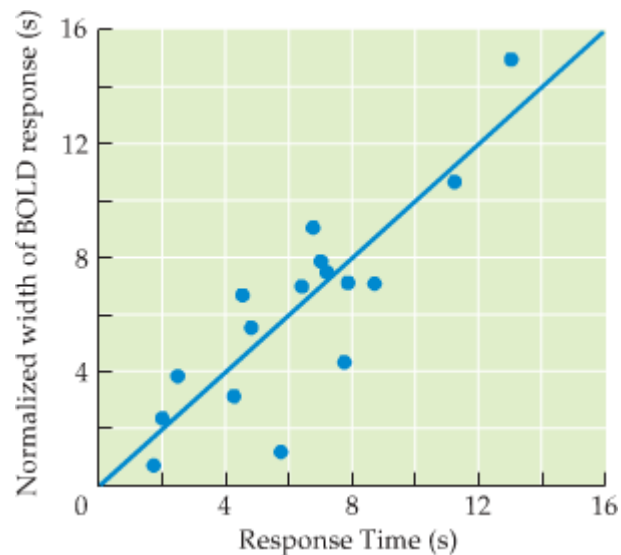
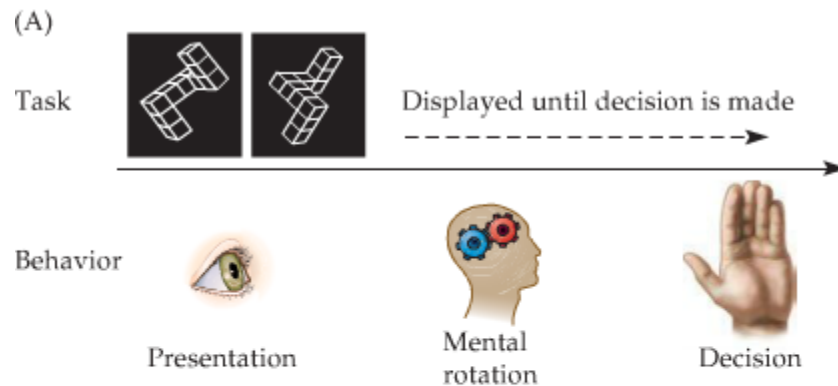
Data: Robert Savoy & Kathy O'Craven  
Figure: Rosen et al., 1998, PNAS

Although the shape of the HRF delayed and blurred, it is predictable.

Event-related potentials (ERPs) are based on averaging small responses over many trials.

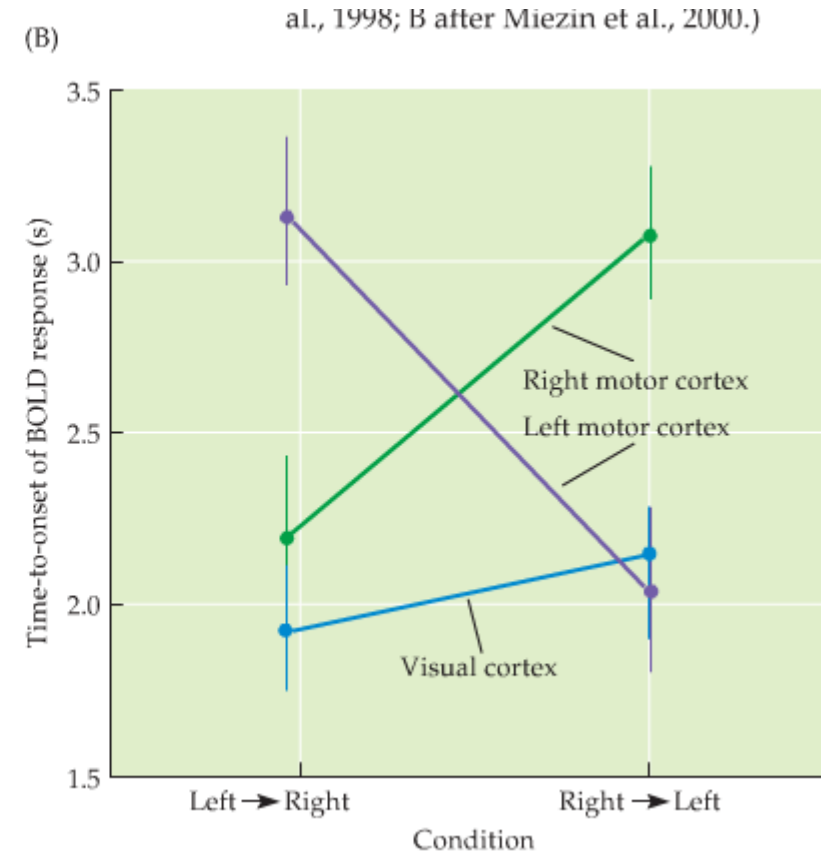
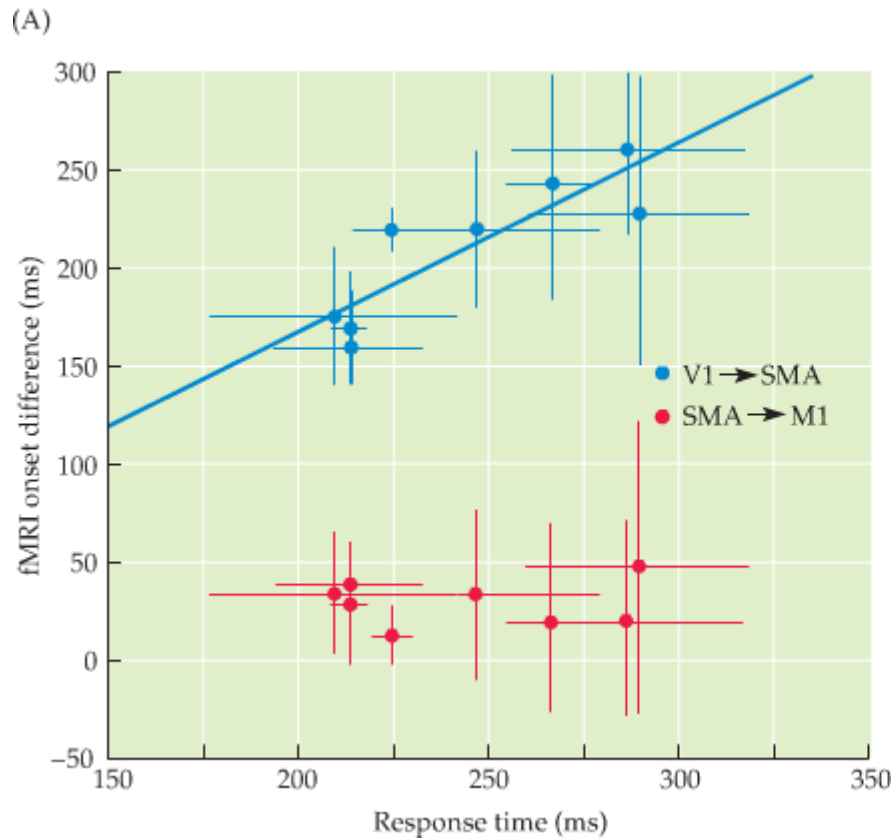
Can we do the same thing with fMRI?

# Reaction Time & BOLD



After Menon & Kim (1999); data from Richter et al. (1997)

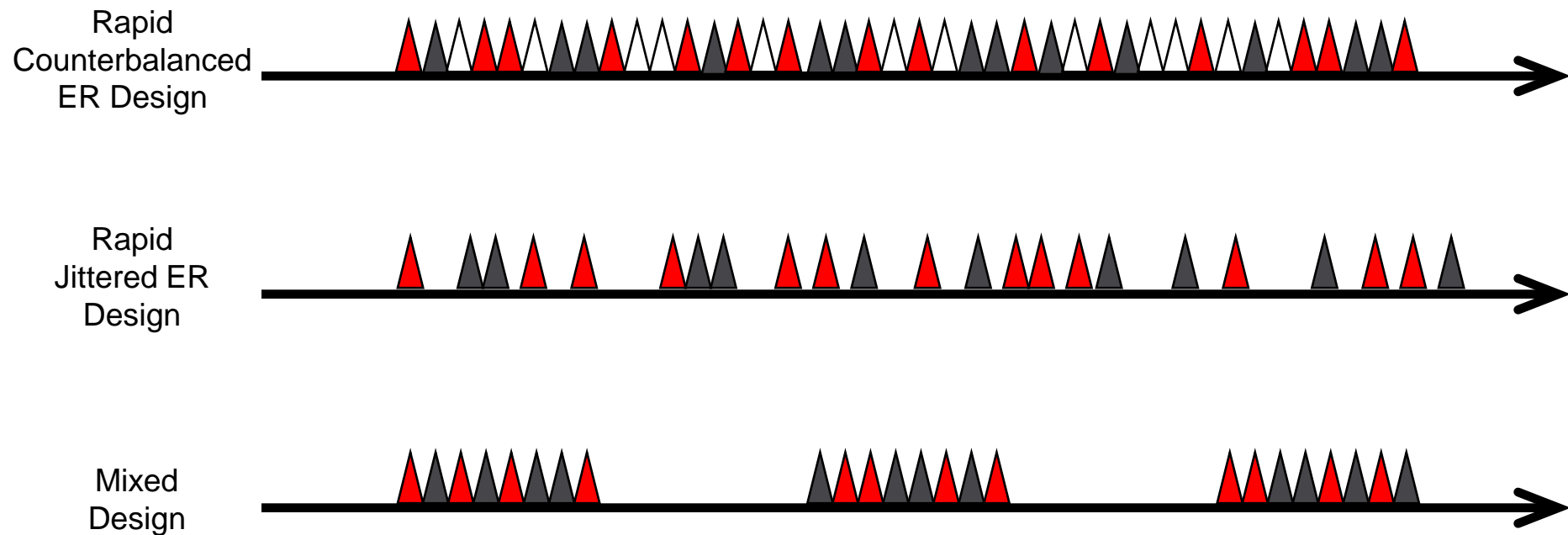
# Relative Timing of BOLD across Brain Regions





A) Menon et al. (1998); B) Miezin et al. (2000)

# “Do You Wanna Go Faster?”

- Yes, but we have to test assumptions regarding linearity of BOLD signal first



# Rapid Counterbalanced ER Design

-  = trial of one type (e.g., face image)
-  = trial of another type (e.g., place image)

