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？

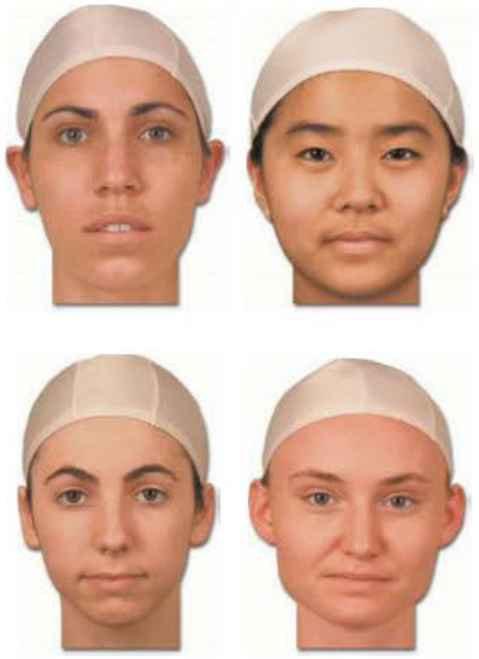
服藥前	服藥	服藥後
發燒、 咳嗽、 流鼻水		症狀消失

什麼是控制良好的實驗？

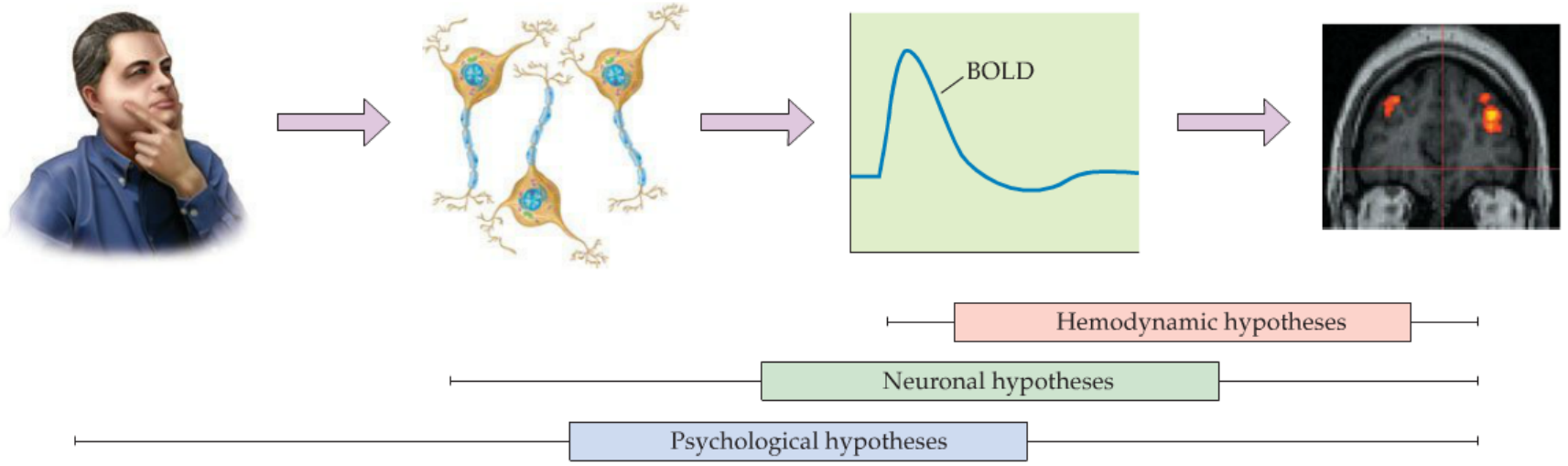
	服藥前	服藥	服藥後
實驗組	發燒、 咳嗽、 流鼻水		症狀消失
對照組	發燒、 咳嗽、 流鼻水	多休息喝水	症狀消失

Experimental vs. Control Conditions

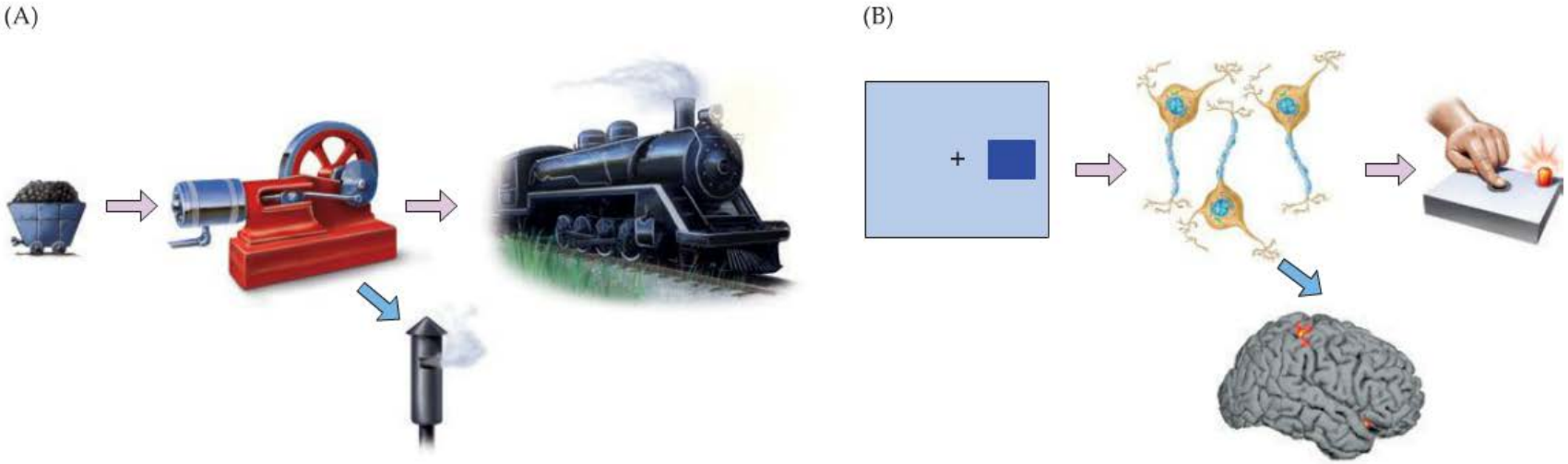
(A)



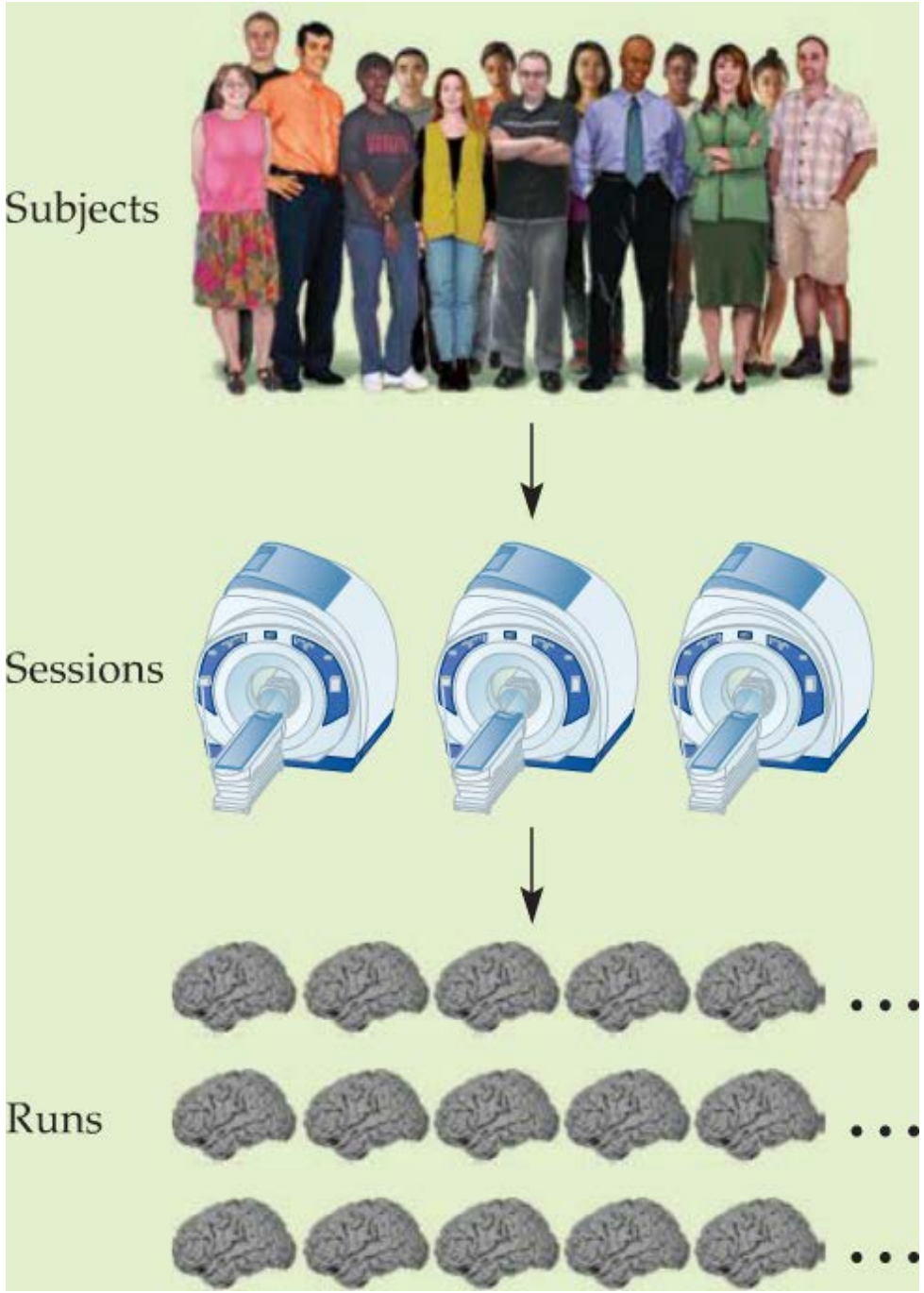
Levels of Research Hypothesis



FMRI is Epiphenomenal?



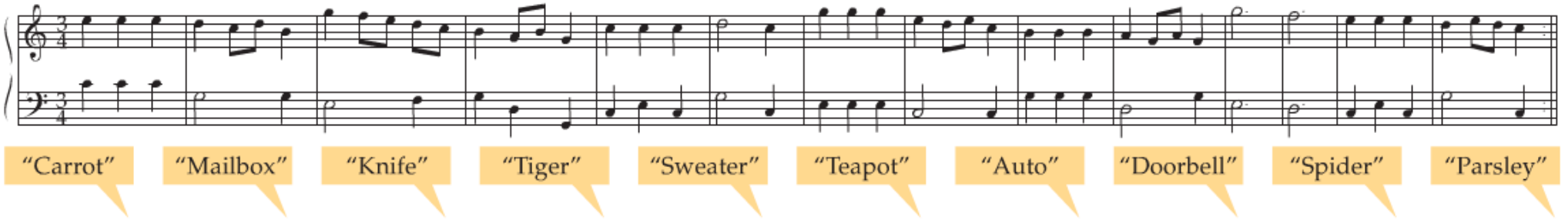
- BOLD changes could be irrelevant to information processing.
- Yet correlational is not equivalent to meaningless.



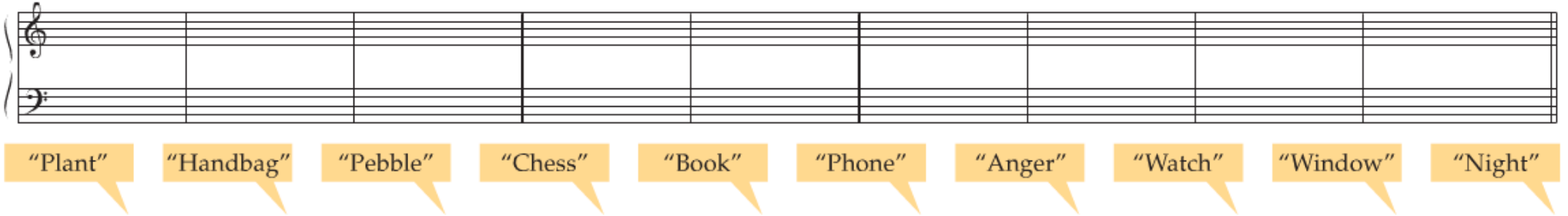
- Blocks
- Conditions
- Trials
- Events

(A)

B1



B2



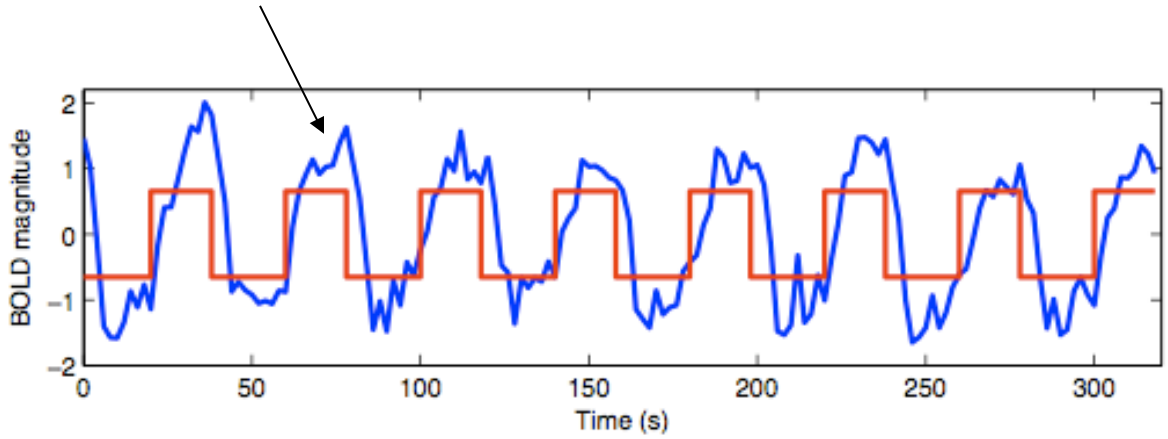
(B) Alternating Design

(C) Interleaving null-task blocks

Time

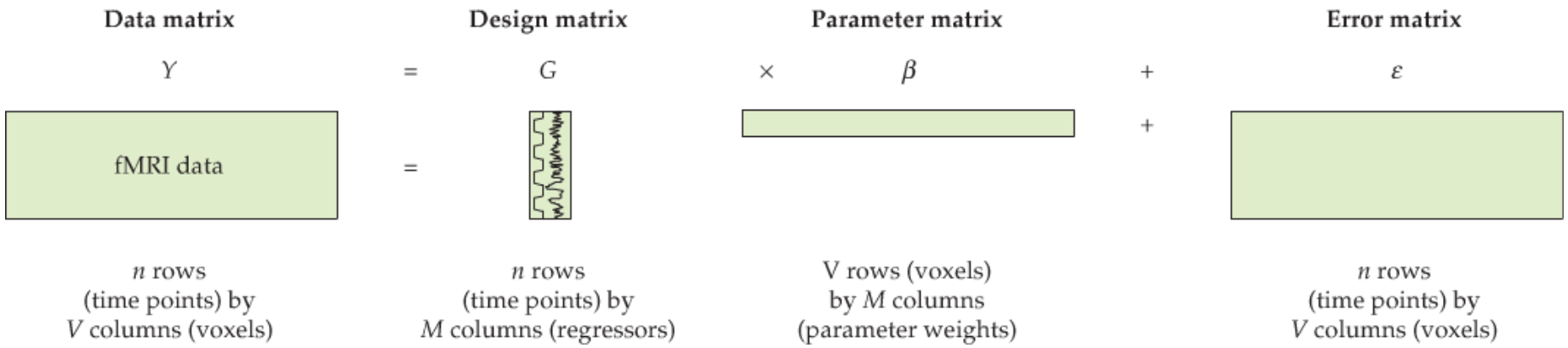
IV and DV from the Perspective of Data Analysis

- Observed BOLD signal (example)



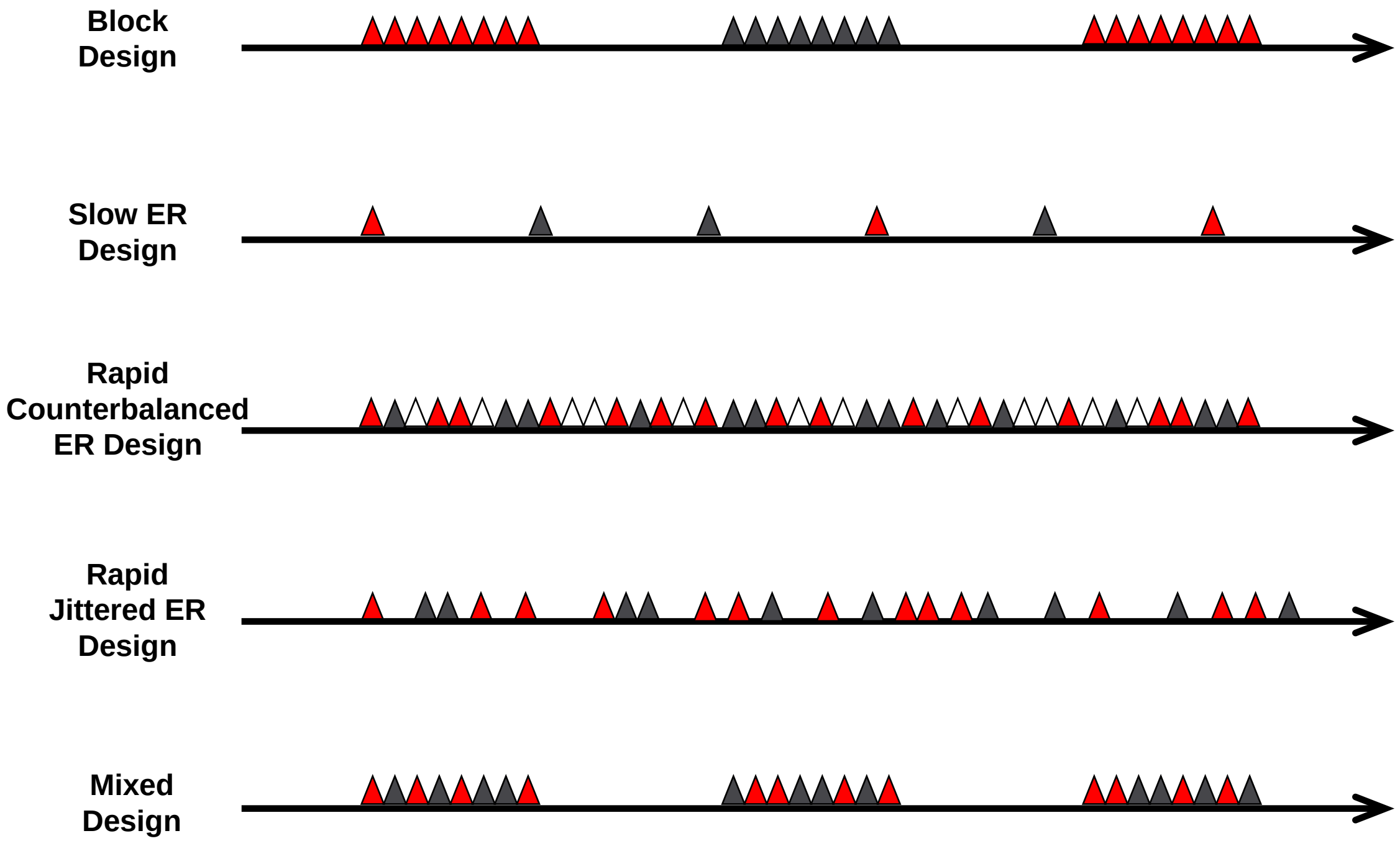
- BOLD signal did not look exactly like the predicted neural activity (in red)

General Linear Model

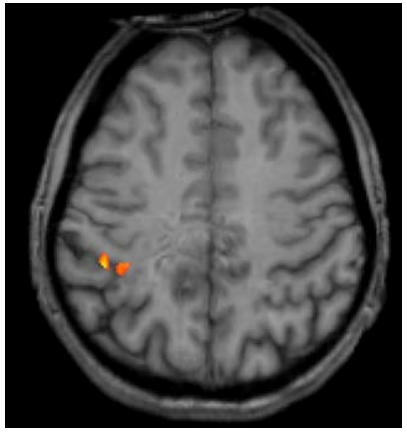


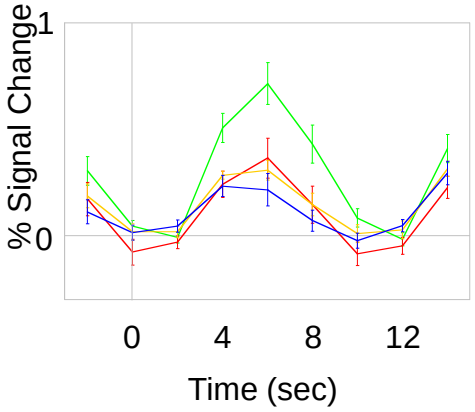
FMRI Experimental Designs

- 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

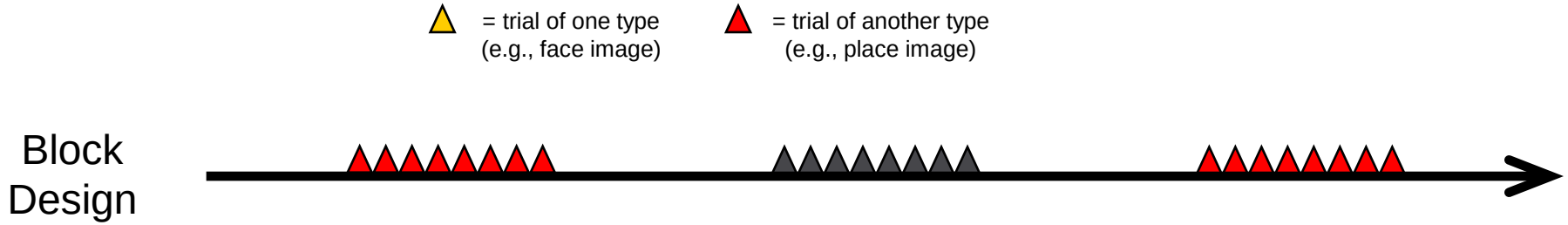




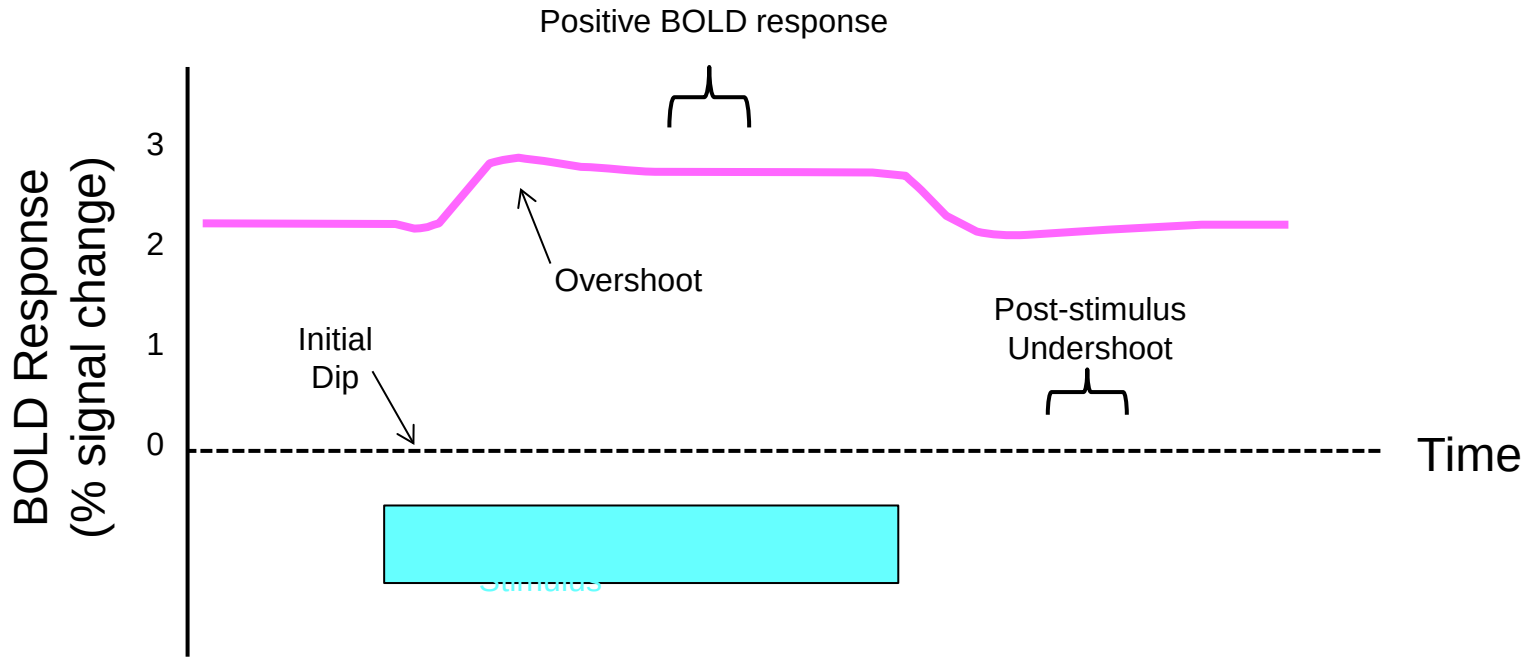
- Detection: determination of whether activity of a given voxel (or region) changes in response to the experimental manipulation
- "which voxel?"
  - Estimation: measurement of the time course within an active voxel in response to the experimental manipulation
  - "How does signal change in a voxel?"

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

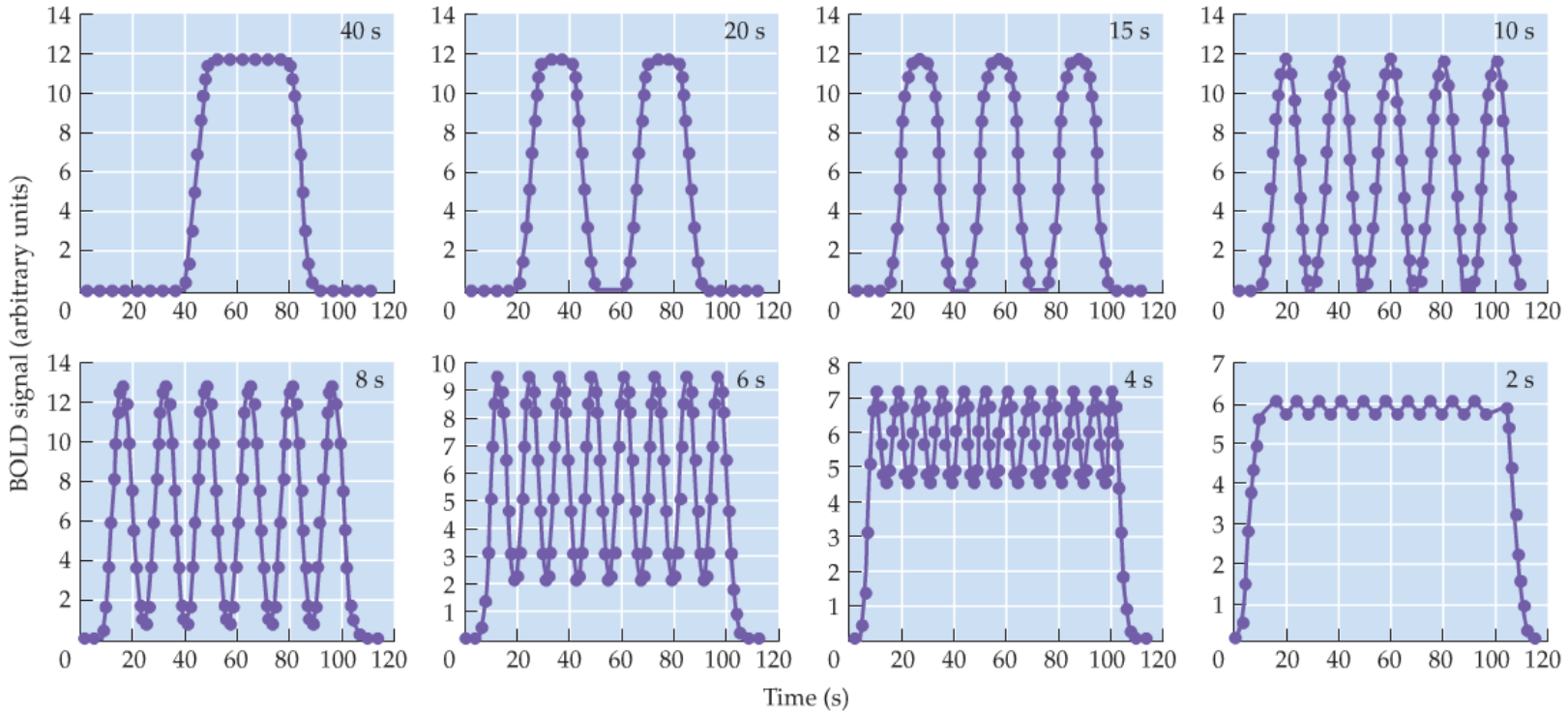
Block Designs



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

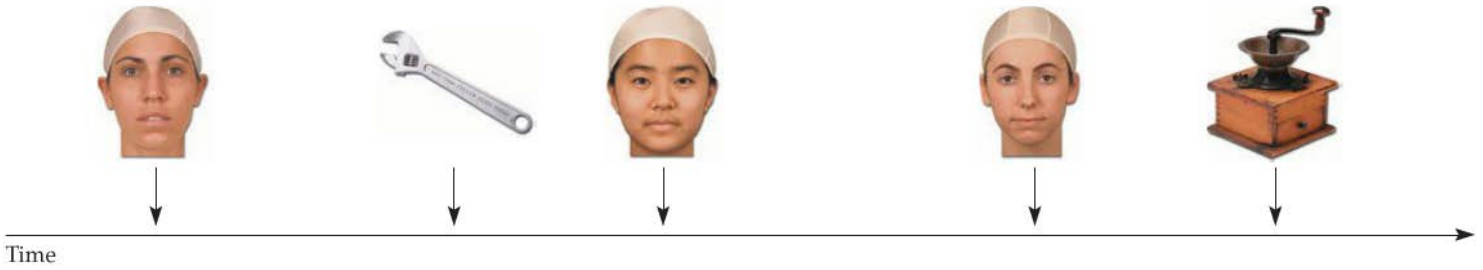
- Length of a block
  - 10s ~ 1 minute
    - Task property
    - Fatigue and practice
  - Equivalent for conditions or combination of conditions to be compared

- 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)

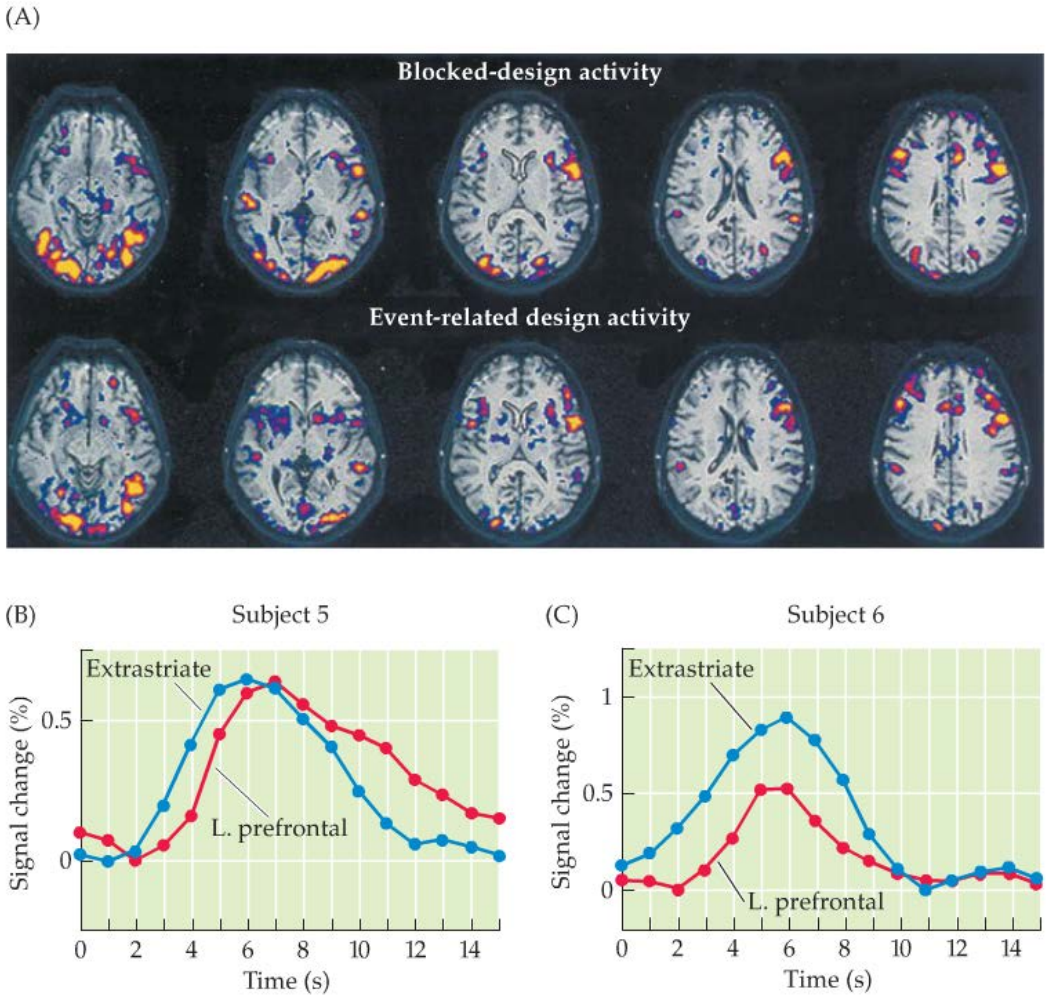
Event-related Designs



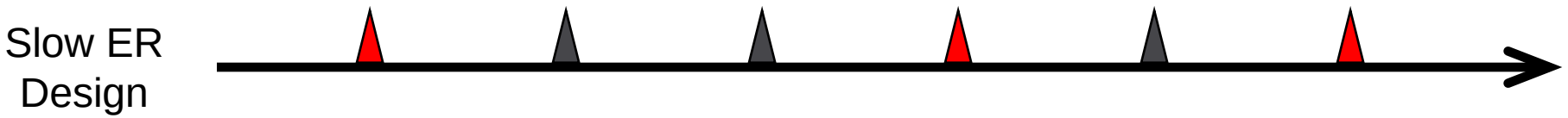
Slow ER Design

Rapid Jittered ER Design

ER-FMRI Showing Timing Differences



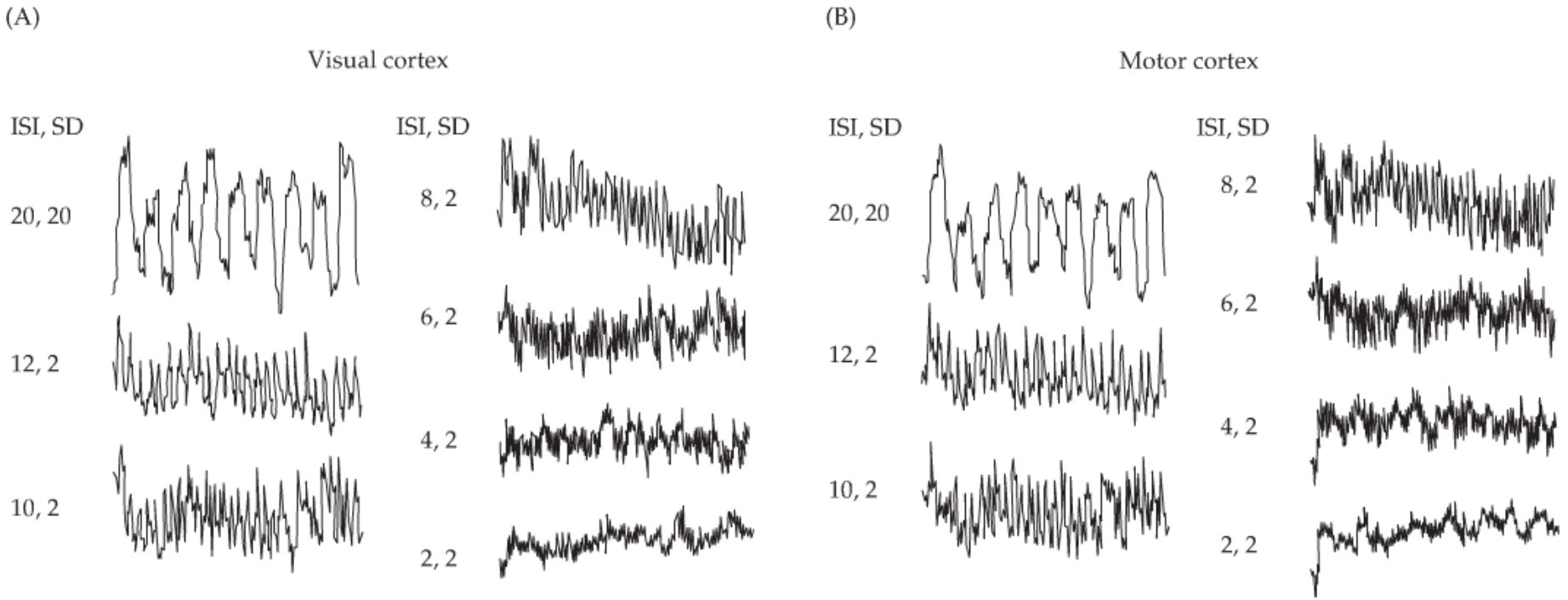
Slow Event-Related Designs



Periodic (Slow) ER Design

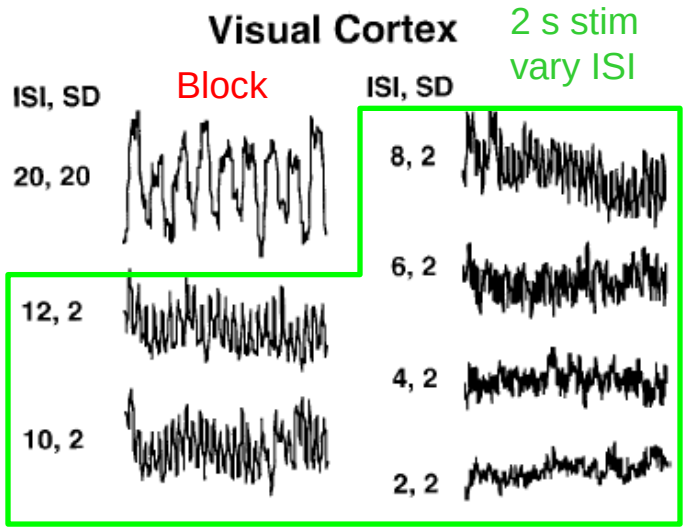
- Fixed and long ISI
  - Usually > 15s
  - Each event evokes a complete HR, and corresponding BOLD are selectively averaged.
  - Inefficient

Effects of ISI on ER-FMRI Activation

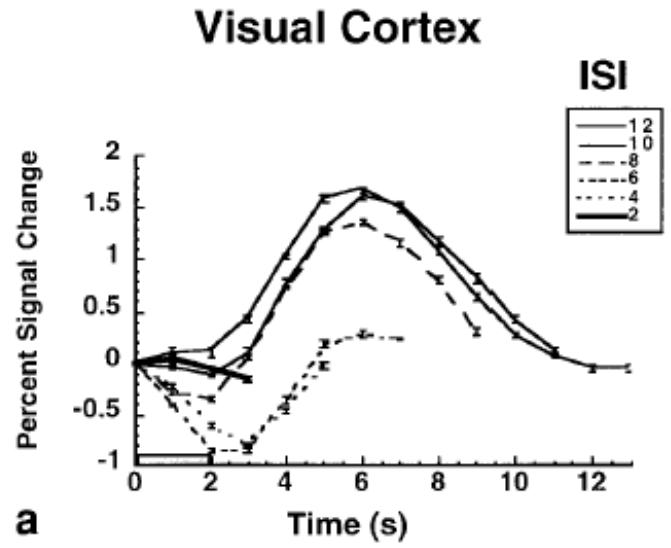


Bandettinni & Cox (2000)

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?



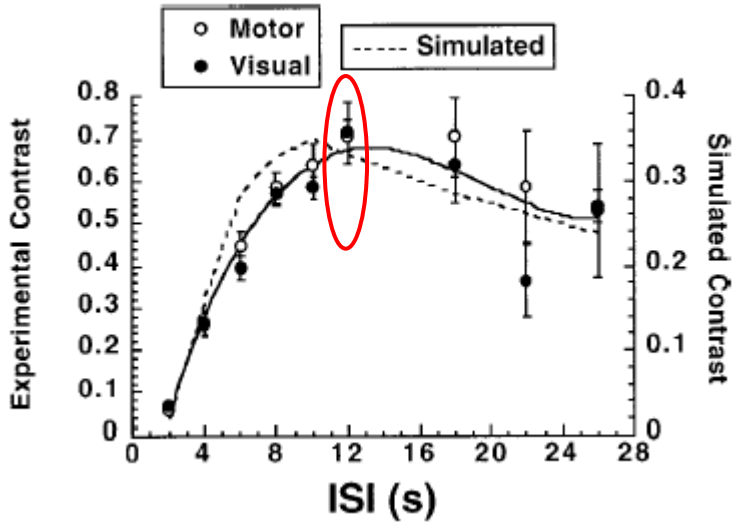
Event-related average

Source: Bandettini et al., 2000

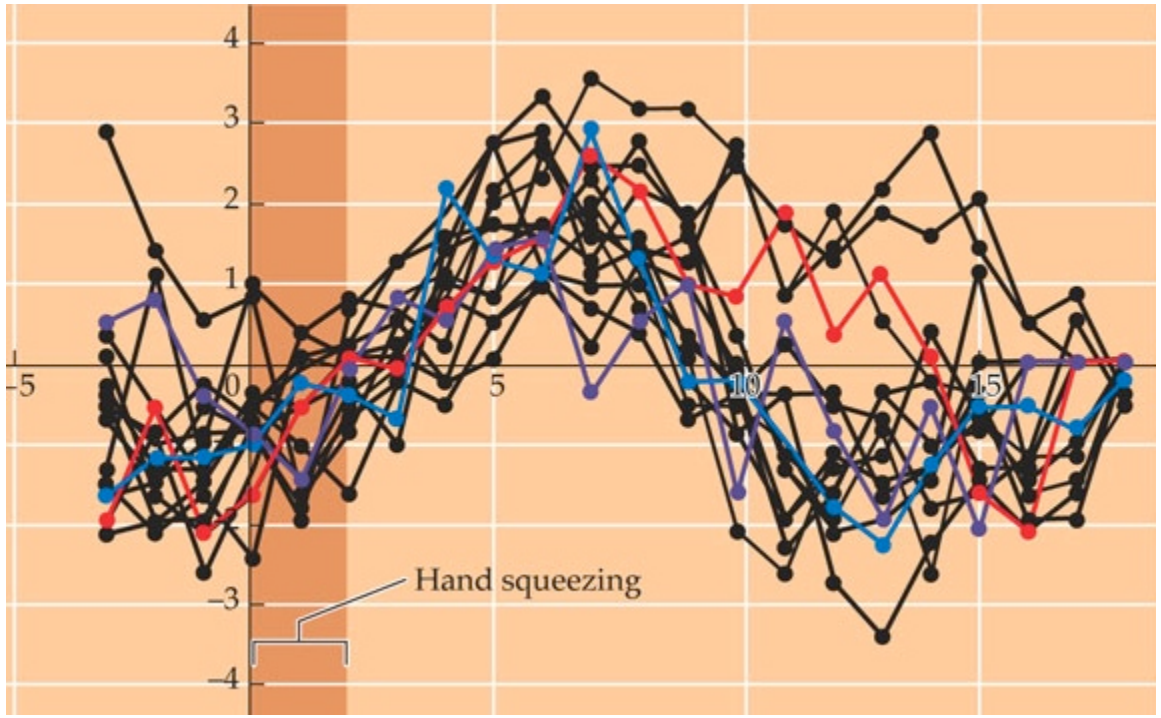
Source: Bandettini et al., 2000

Optimal Constant ITI

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

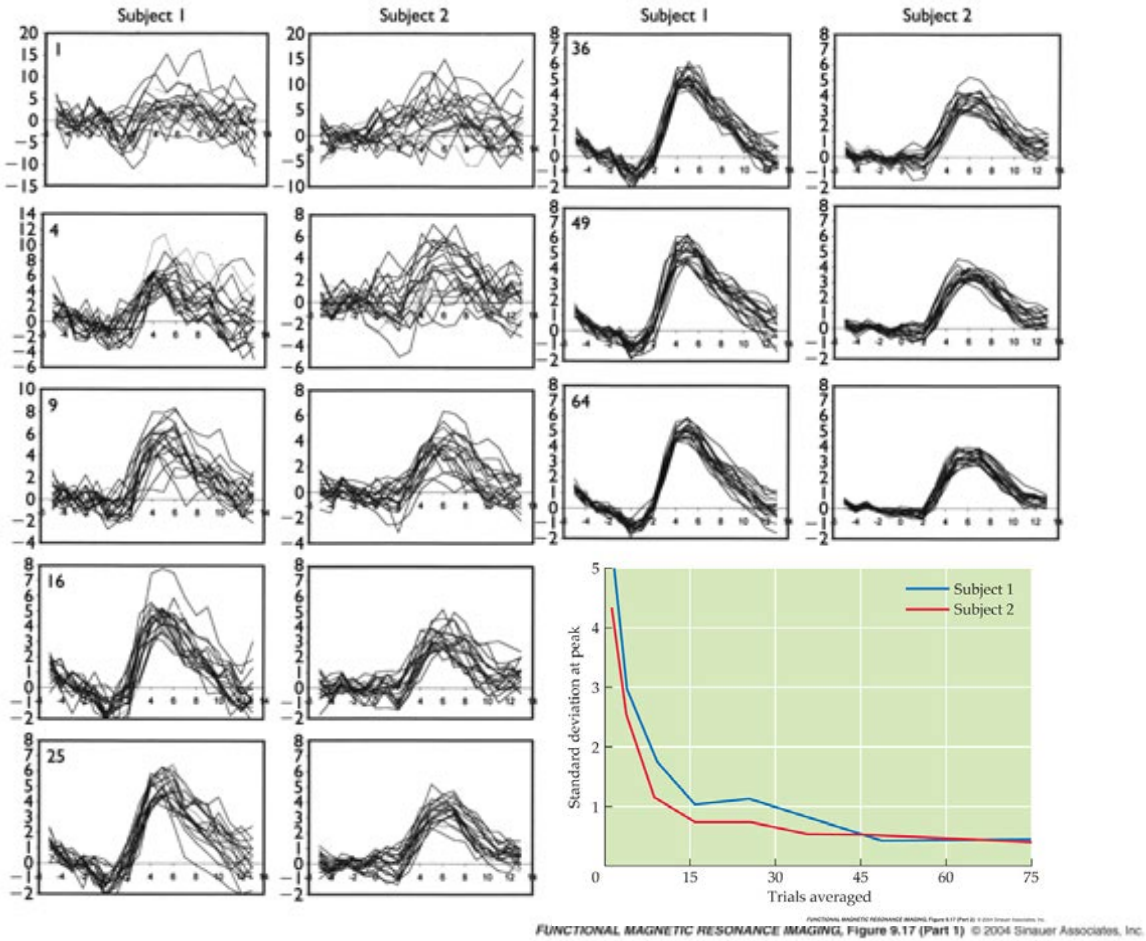


Trial to Trial Variability



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

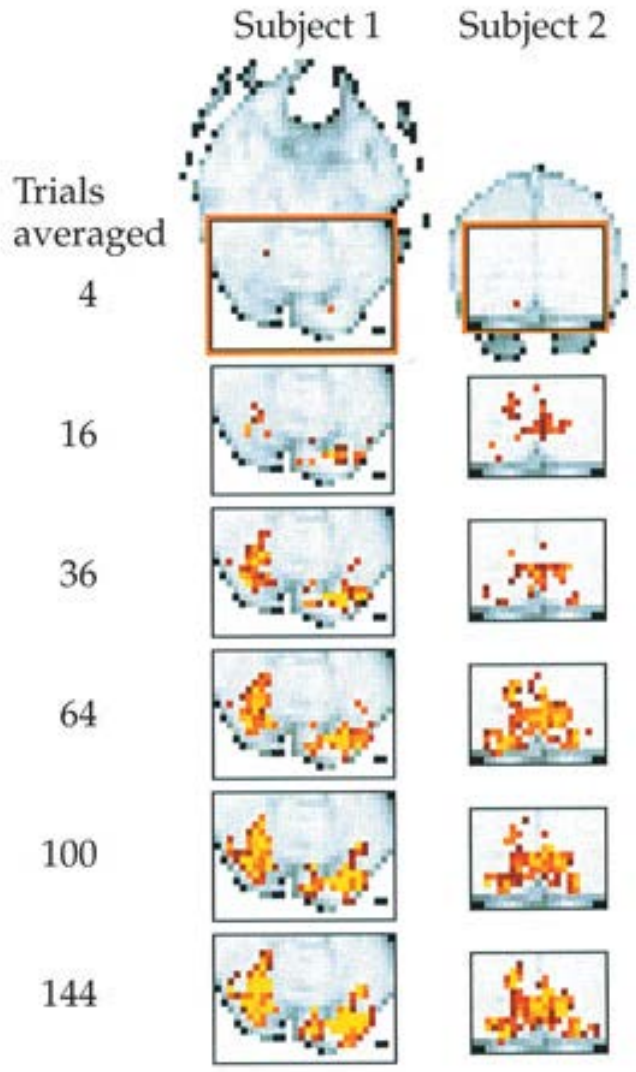
How Many Trials Do You Need?



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



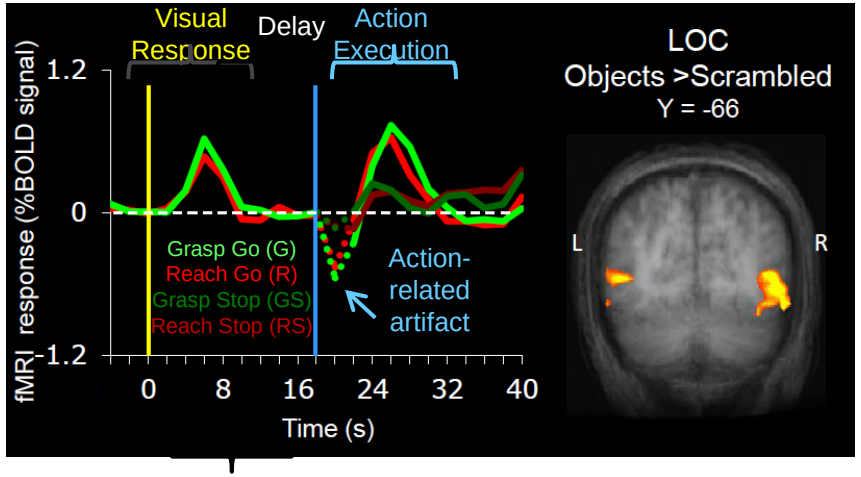
Huettel, Song & McCarthy, 2004, Functional Magnetic Resonance Imaging

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

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



Really long delay:
18 s

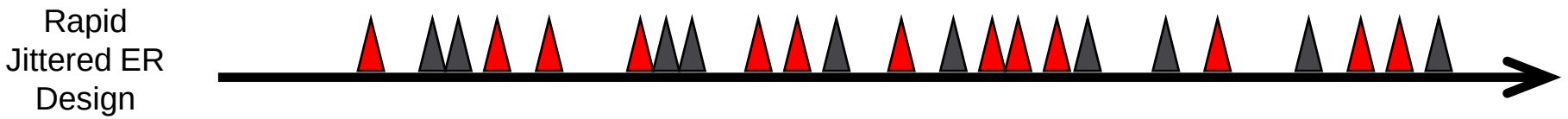
Effect of this design on our subject

Cons

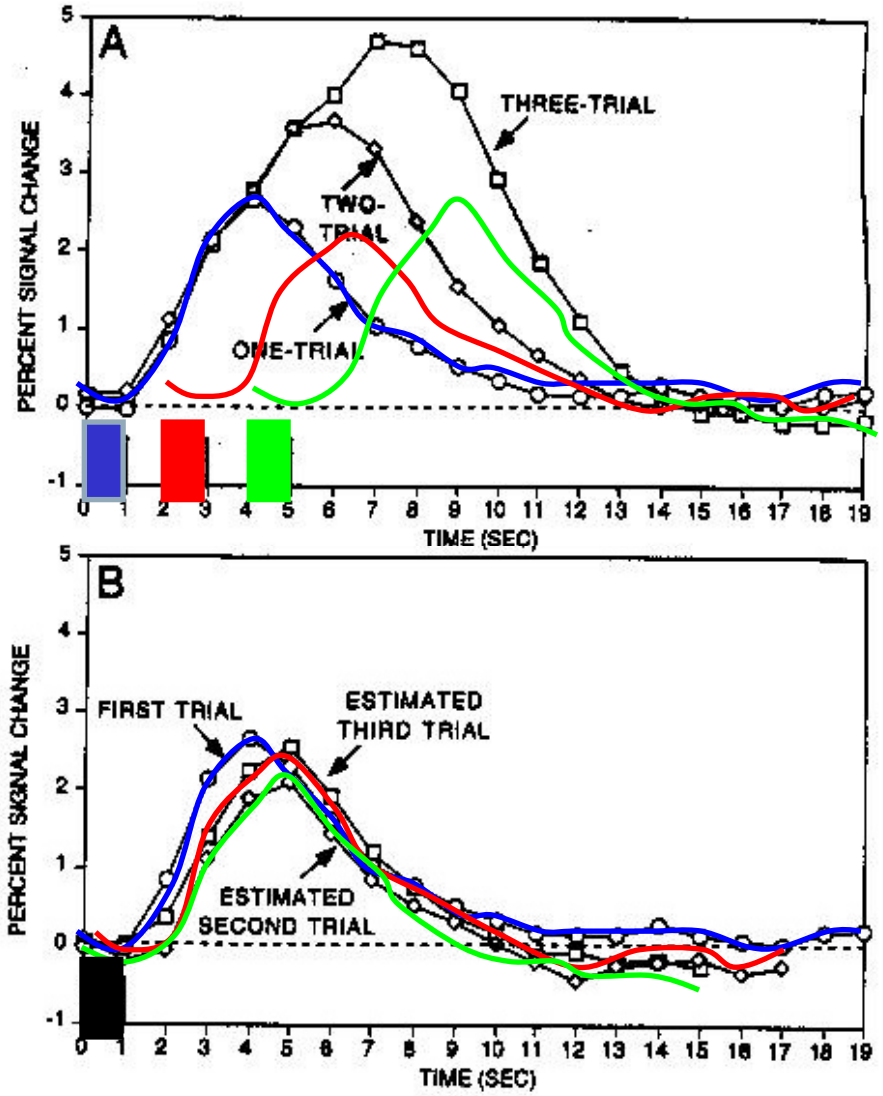
- poor detection power because you get very few trials per condition by spending most of your sampling power on estimating the baseline
- subjects can get VERY bored and sleepy with long inter-trial intervals

"Do You Wanna Go Faster?"

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



Linearity of BOLD response



Source: Dale & Buckner, 1997

Linearity:
"Do things add up?"

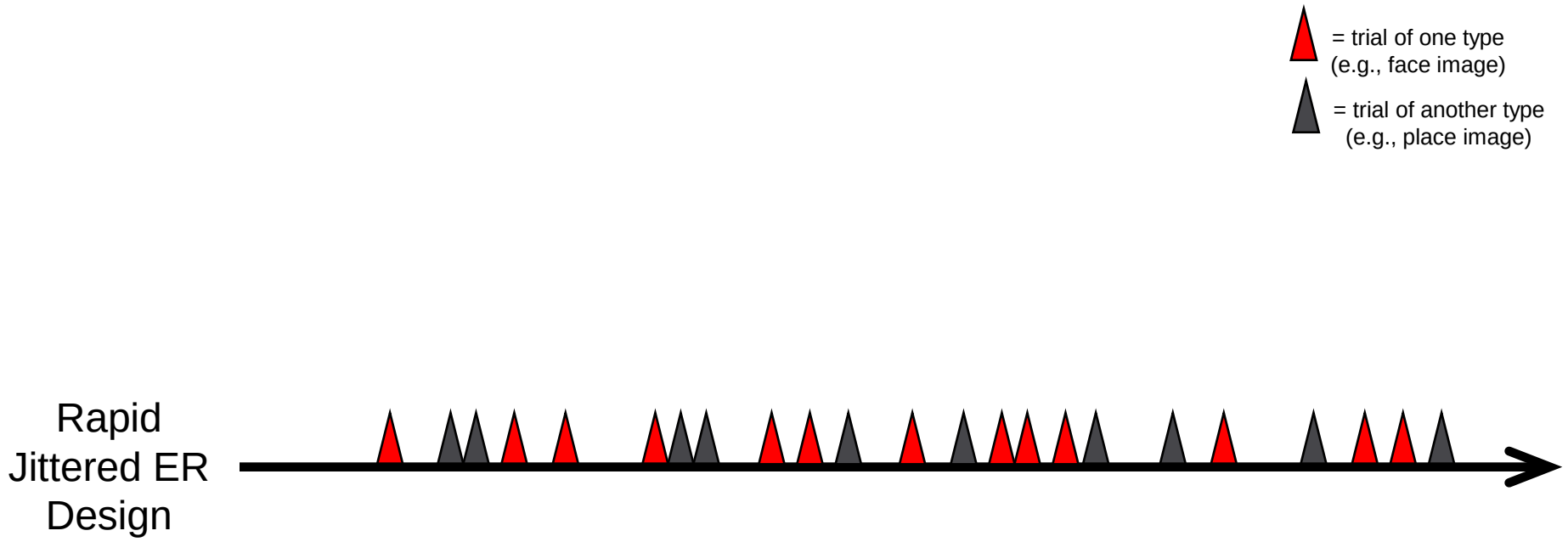
red = 2 - 1

green = 3 - 2

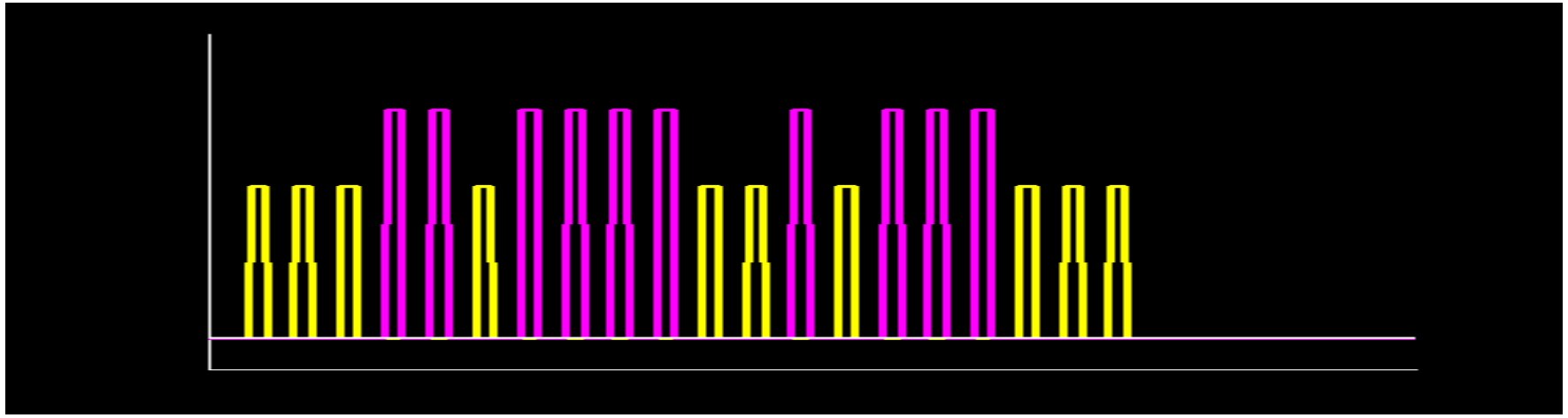
Sync each trial response to start of trial

Not quite linear
but good enough!

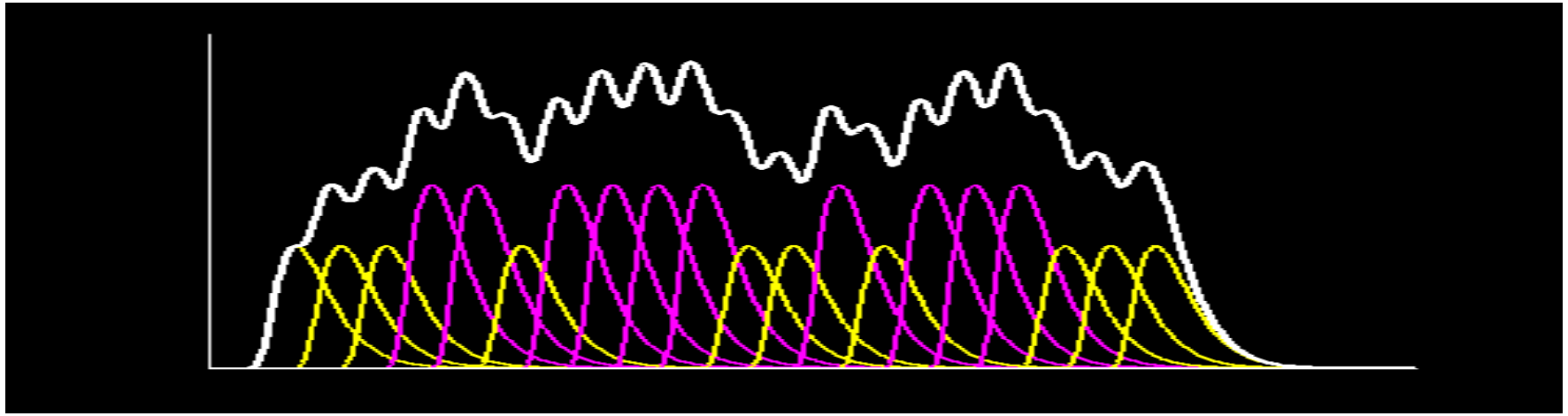
Rapid Jittered ER Design



BOLD Overlap With Regular Trial Spacing



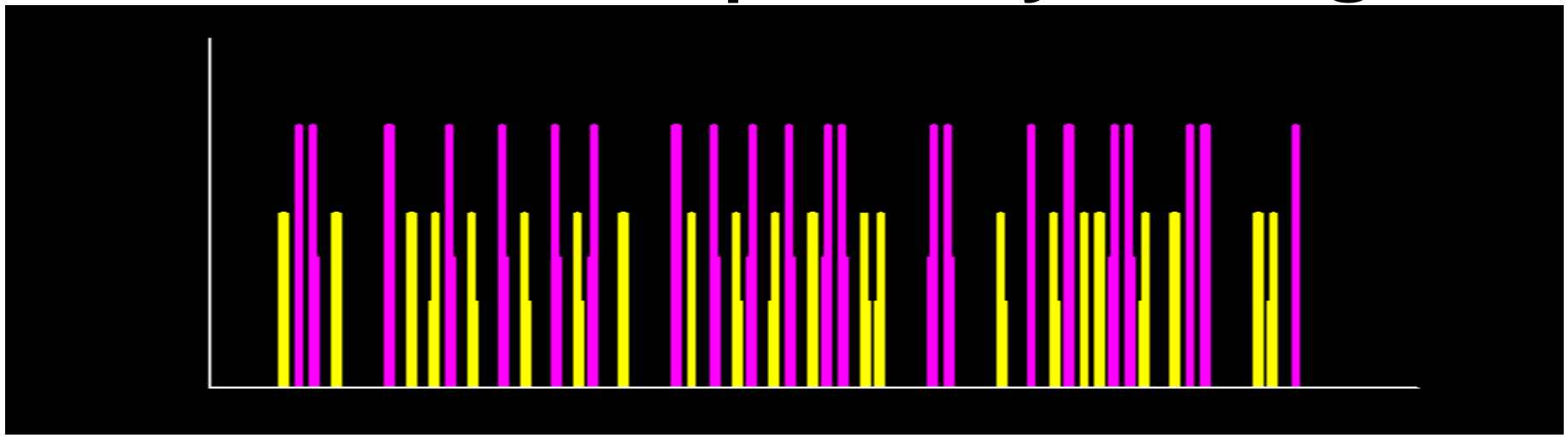
Neuronal activity from **TWO** event types with constant ITI



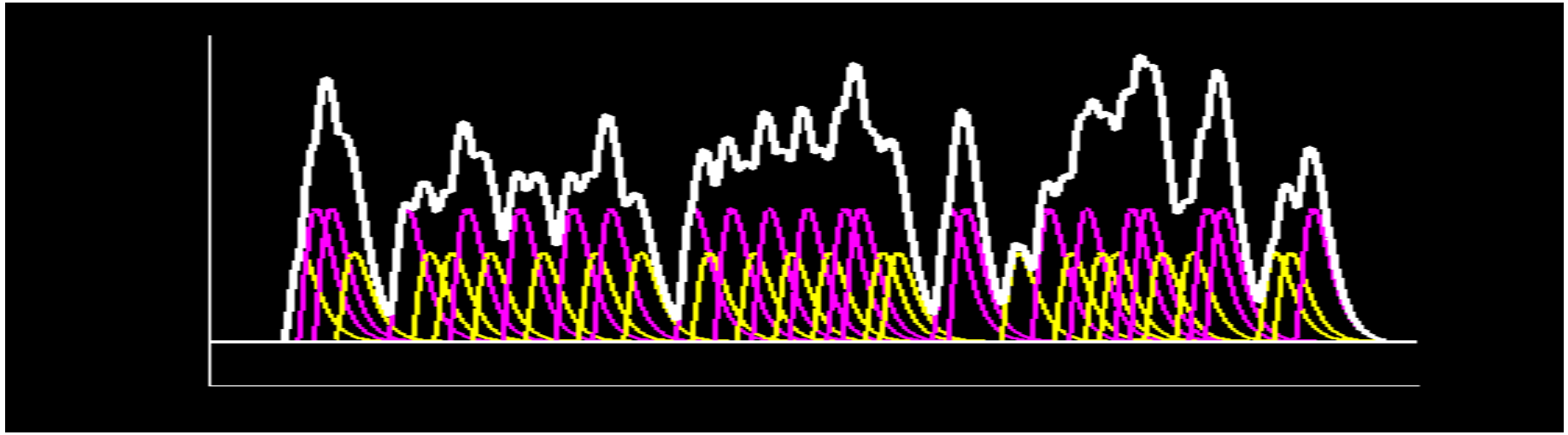
Partial tetanus BOLD activity from two event types

Slide from Matt Brown

BOLD Overlap with Jittering



Neuronal activity from closely-spaced, jittered events

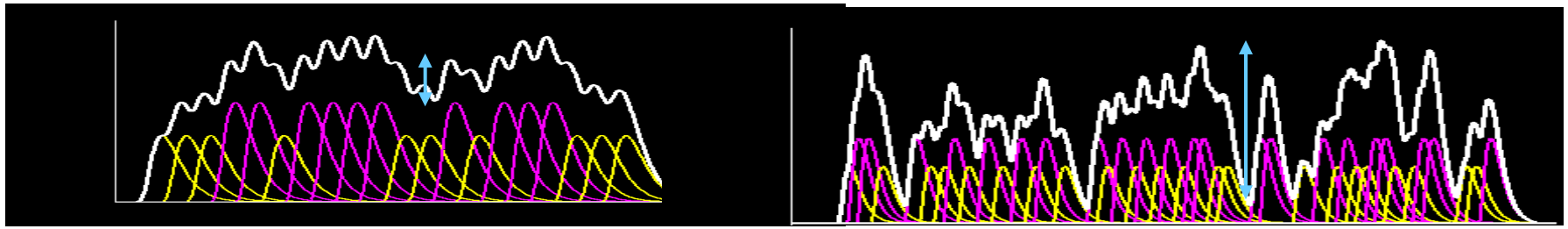


BOLD activity from closely-spaced, jittered events

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:

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

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

$$Y_J = X_{J1}\beta_1 + \ldots + X_{Jl}\beta_l + \ldots + X_{JL}\beta_L + \varepsilon_J$$

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

$$\begin{pmatrix} Y_1 \\ Y_j \\ Y_J \end{pmatrix} = \begin{pmatrix} X_{11} \ldots X_{1l} \ldots X_{1L} \\ X_{j1} \ldots X_{1l} \ldots X_{1L} \\ X_{11} \ldots X_{1l} \ldots X_{1L} \end{pmatrix} \begin{pmatrix} \beta_1 \\ \beta_j \\ \beta_J \end{pmatrix} + \begin{pmatrix} \varepsilon_1 \\ \varepsilon_j \\ \varepsilon_J \end{pmatrix}$$

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

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

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

Assuming this is invertible

Hypothesis Testing: Contrast t-test

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

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

df: $T - (p+1)$

$$H_A : \mathbf{c}\boldsymbol{\beta} > 0$$
$$P(T_{T-(p+1)} \geq t)$$

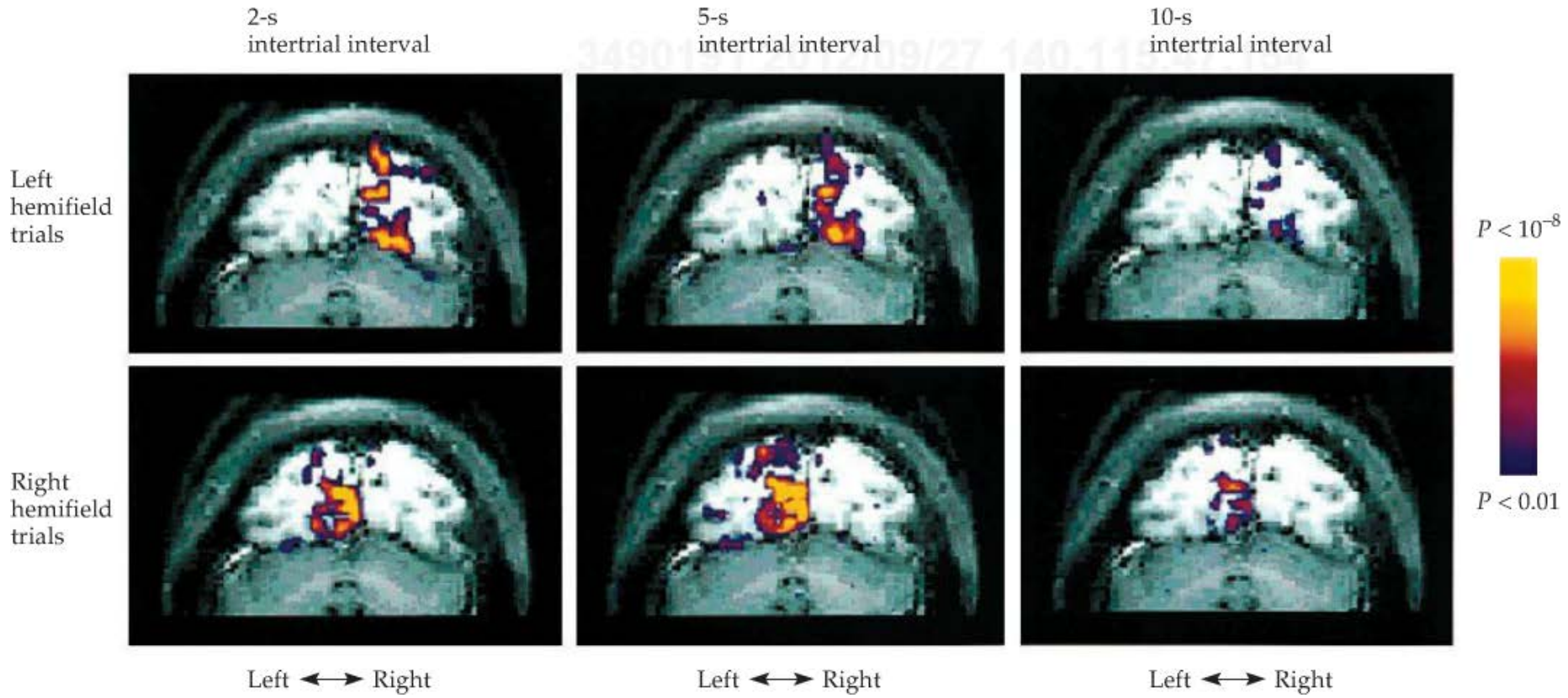
$$H_A : \mathbf{c}\boldsymbol{\beta} \neq 0$$
$$P(T_{T-(p+1)} \geq |t|)$$

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

Design matrix & Contrast Vector; depending on your experimental design

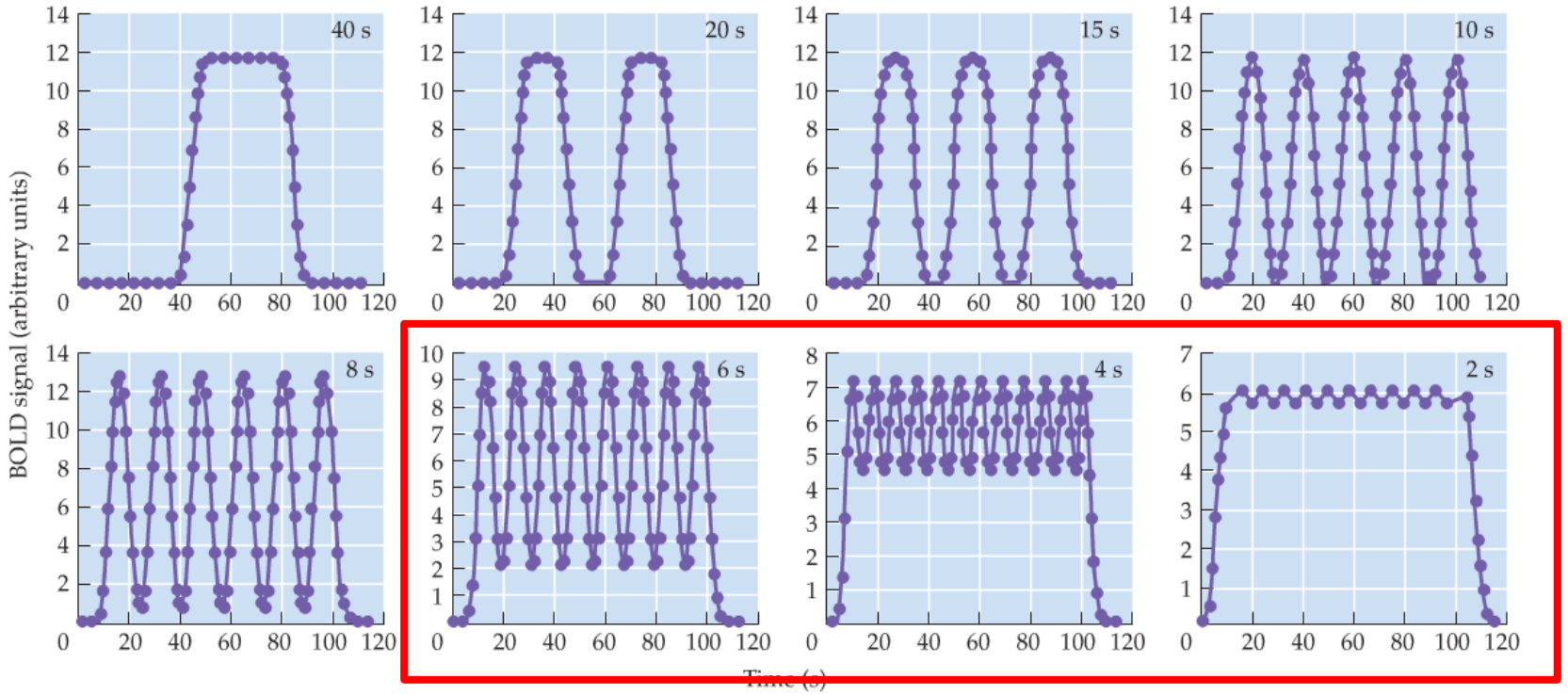
Residual error unaccounted for by your design; depending on the quality of data

Rapid ER-FMRI with Randomized Stimulus Presentation

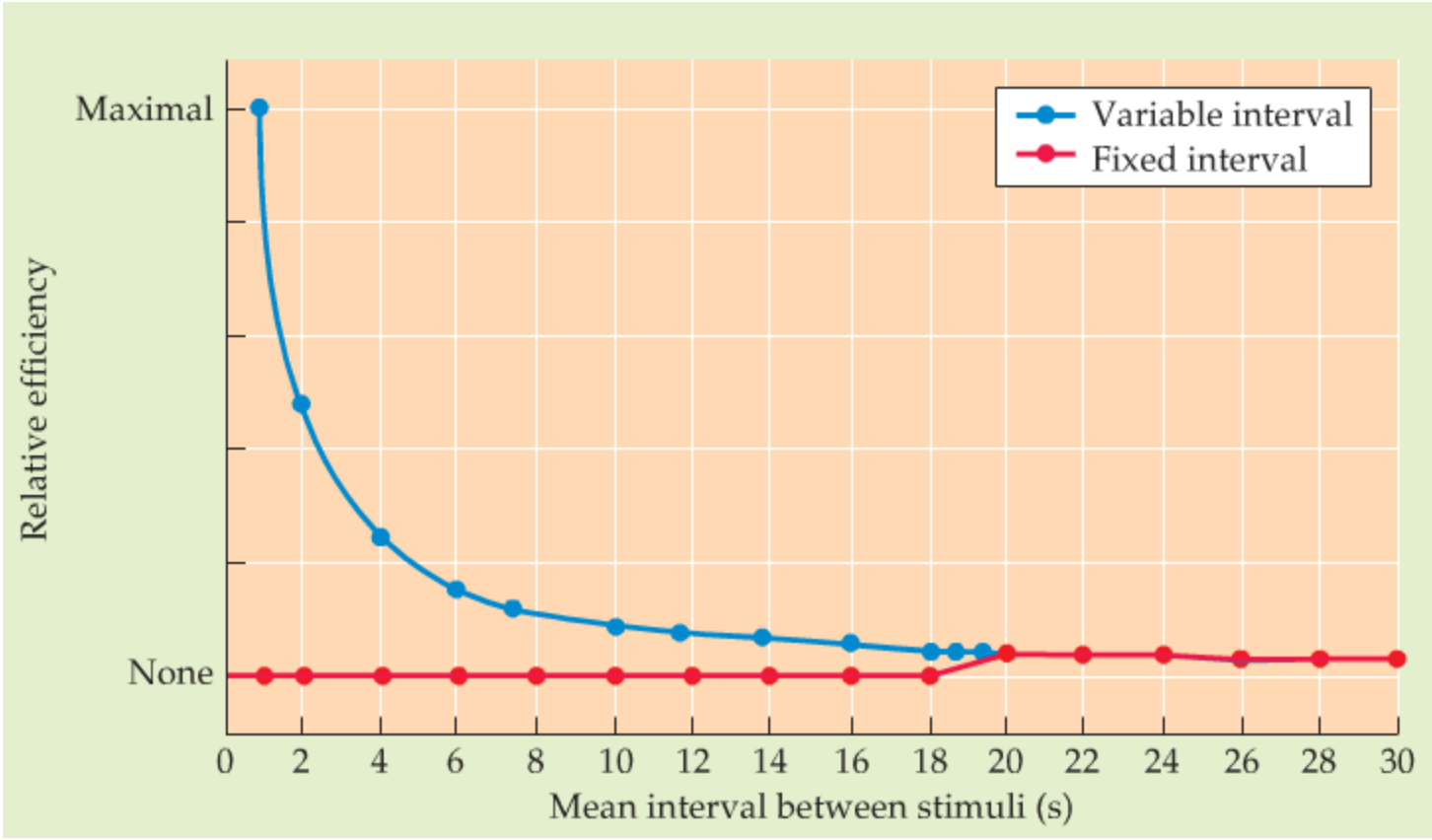


Short randomized ITI enhances detection power.

Note That ITI Has to Be Randomized, Otherwise…



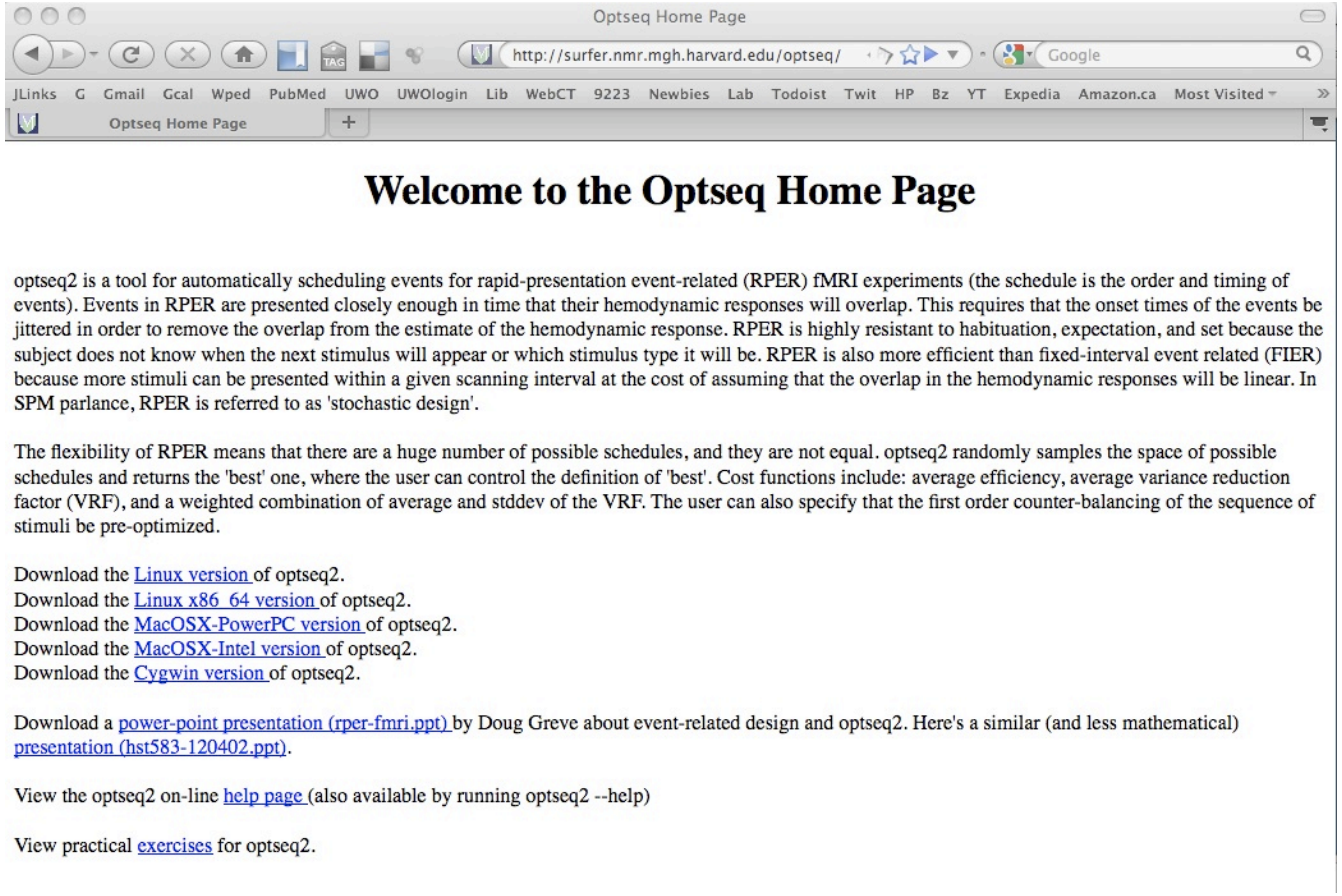
Variable vs. Fixed Intervals



After Dale (1999)

Algorithms for Picking Efficient Designs

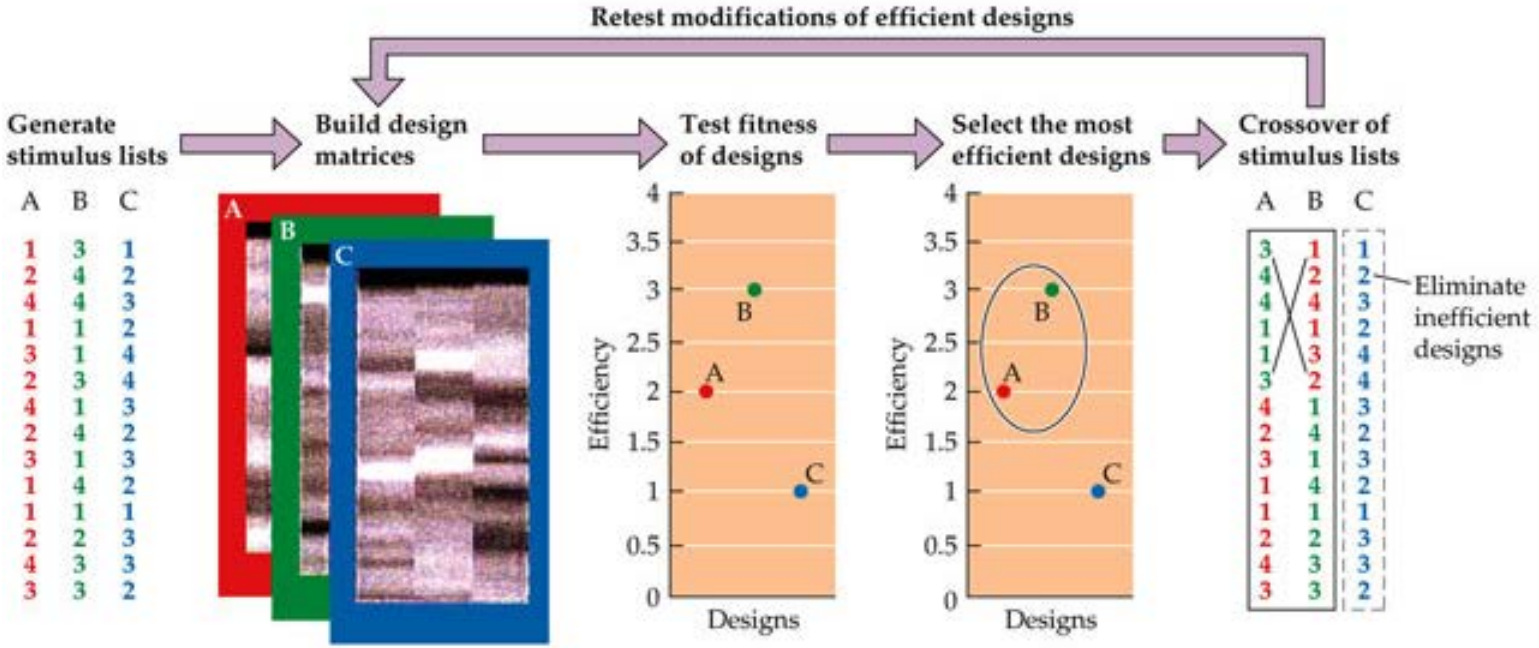
Optseq2



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

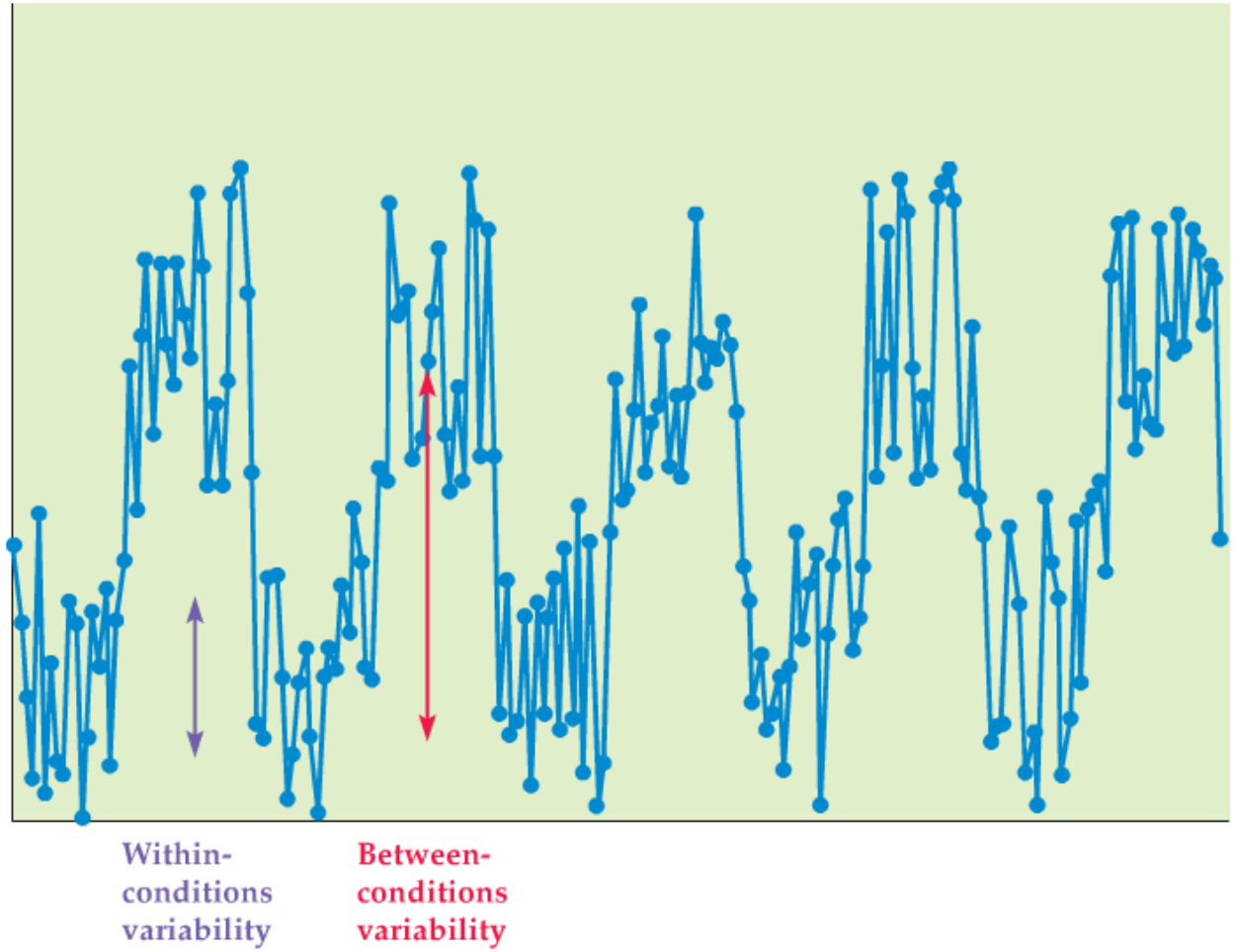
- reduced detection compared to block designs
- requires stronger assumptions about linearity
  - BOLD is non-linear with inter-event intervals < 6 sec.
  - Nonlinearity becomes severe under 2 sec.
- errors in HRF model can introduce errors in activation estimates

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

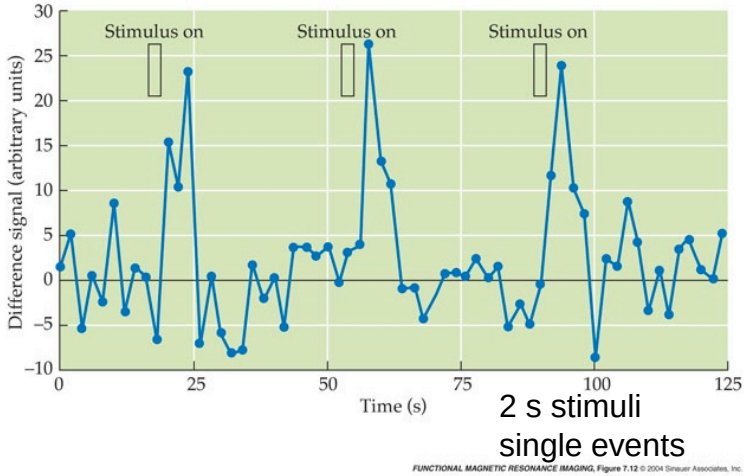
Questions?

Within- vs. Between-condition Variability

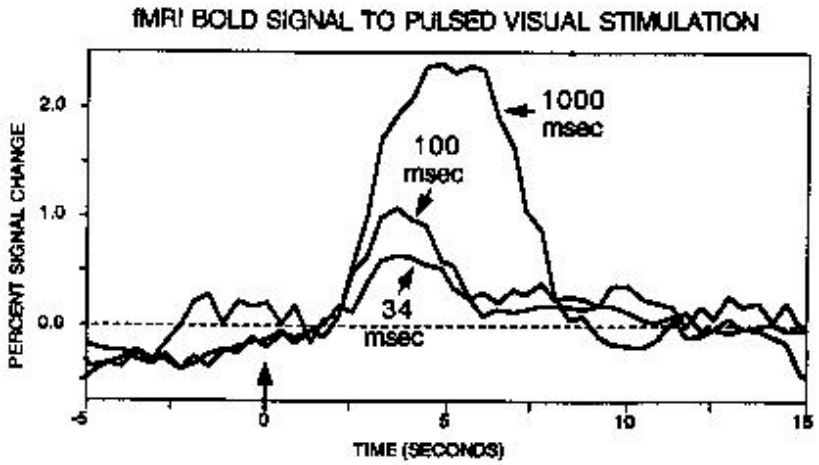


What is the briefest stimulus that FMRI can detect?

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



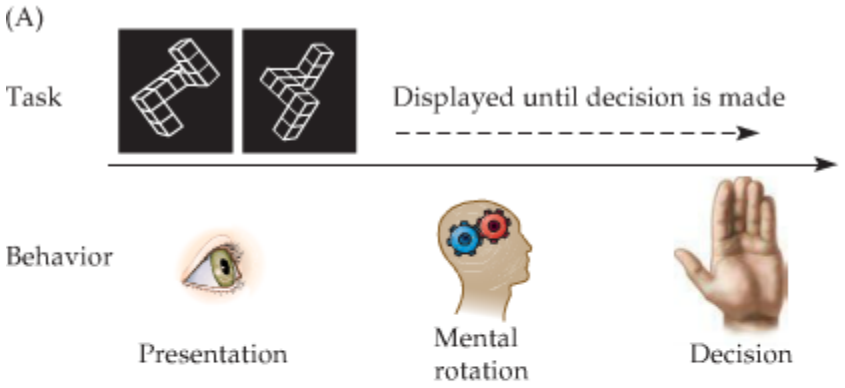
Data: Robert Savoy & Kathy O'Craven
Figure: Rosen et al., 1998, PNAS

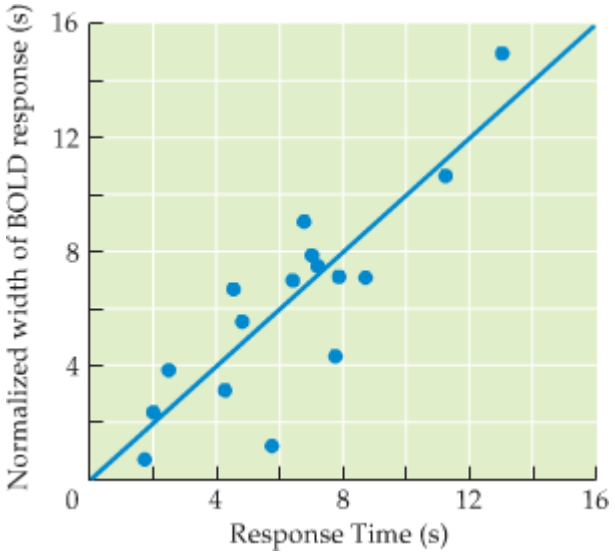
Although the shape of the HRF delayed and blurred, it is predictable.

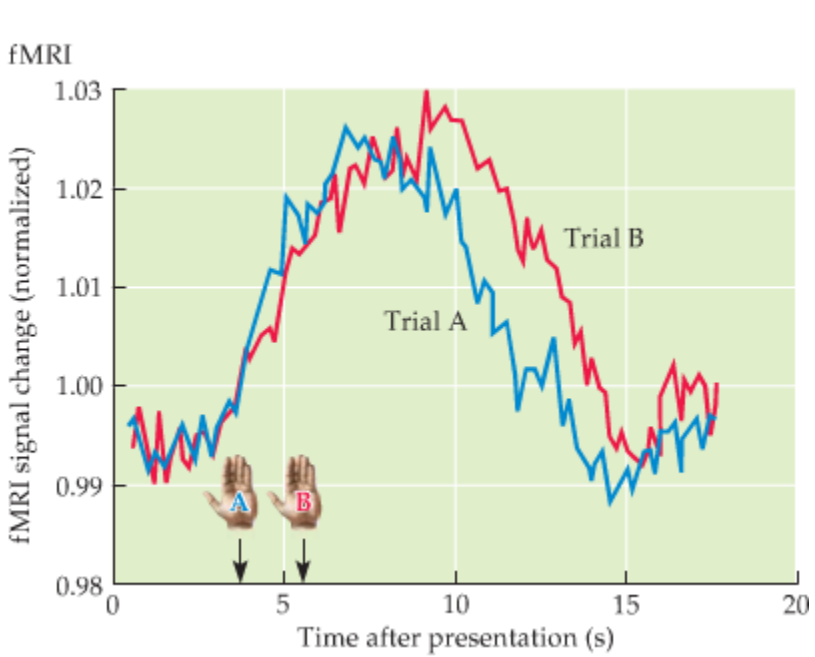
Event-related potentials (ERPs) are based on averaging small responses over many trials.

Can we do the same thing with FMRI?

Reaction Time & BOLD

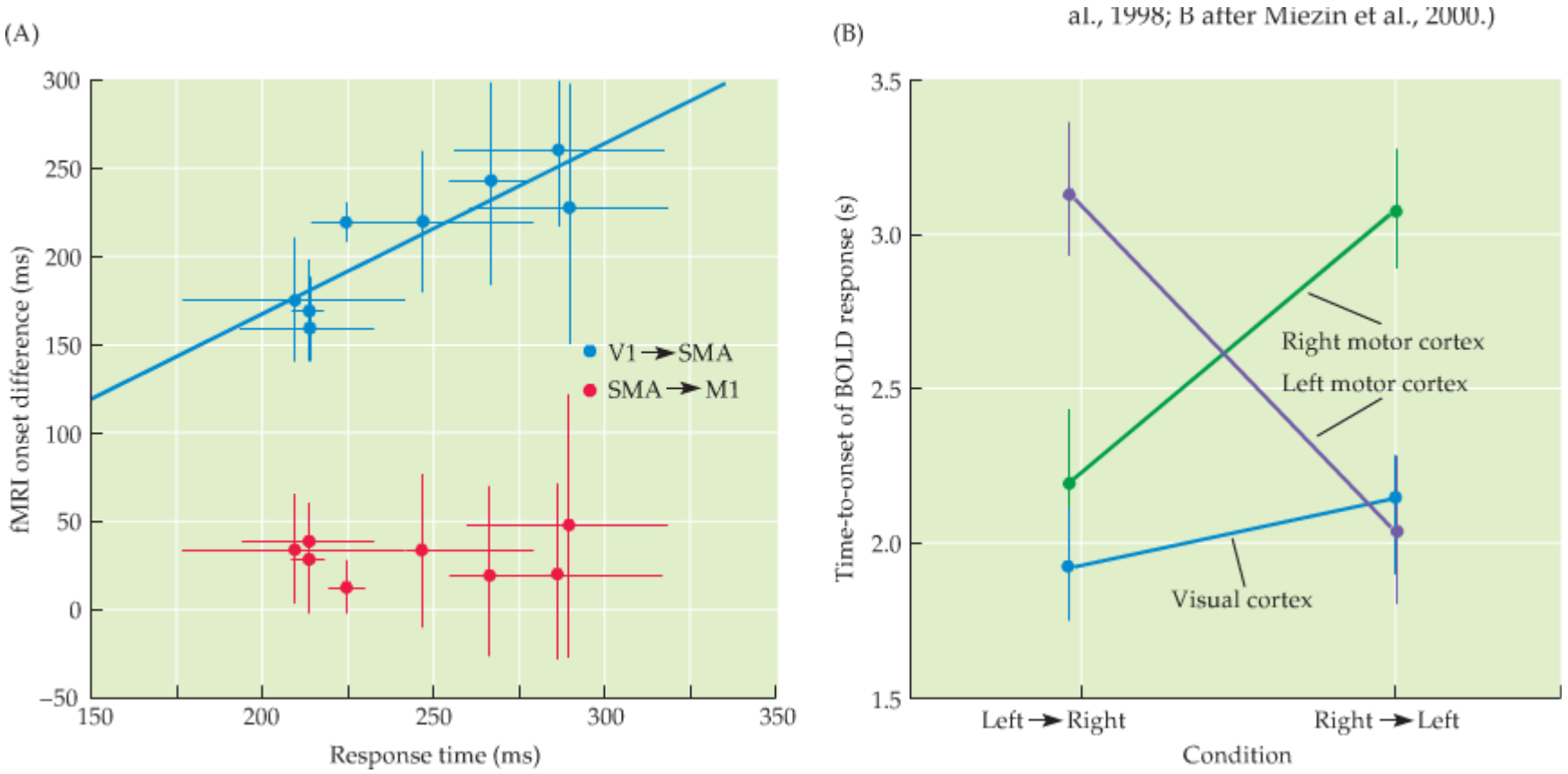






After Menon & Kim (1999); data from Richter et al. (1997)

Relative Timing of BOLD across Brain Regions

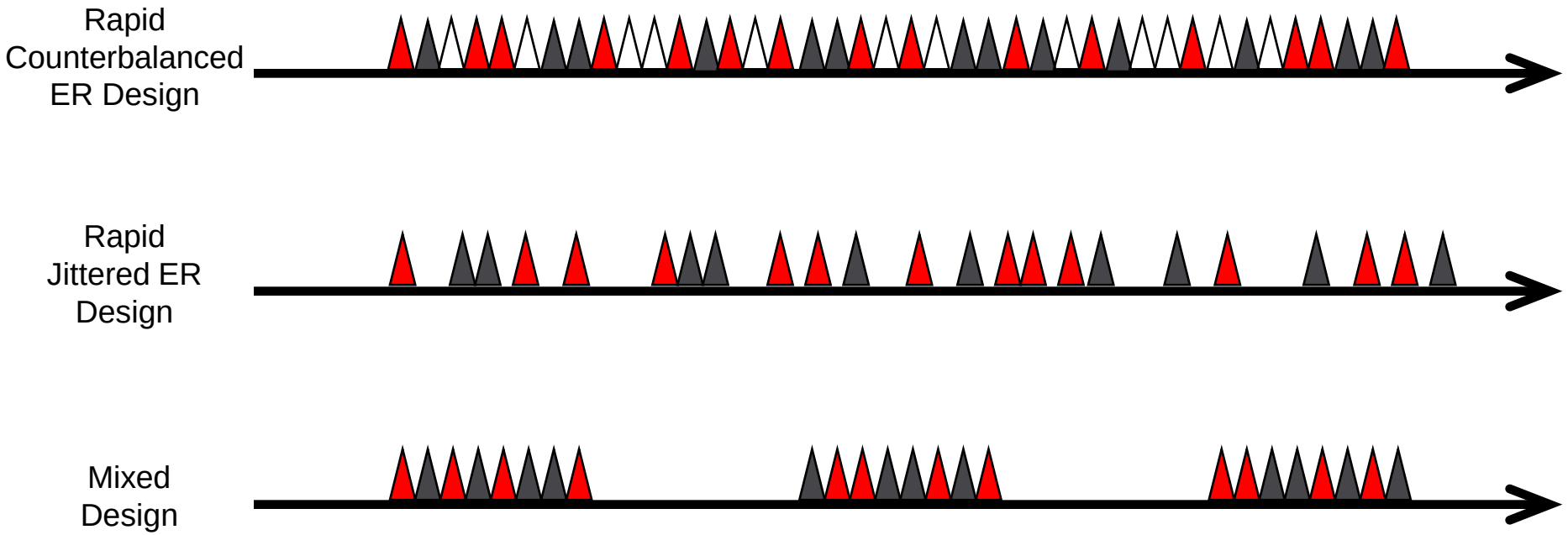


al., 1998; B after Miezin et al., 2000.)

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