Experimental design of fMRI task

Optimization and efficiency of contrast

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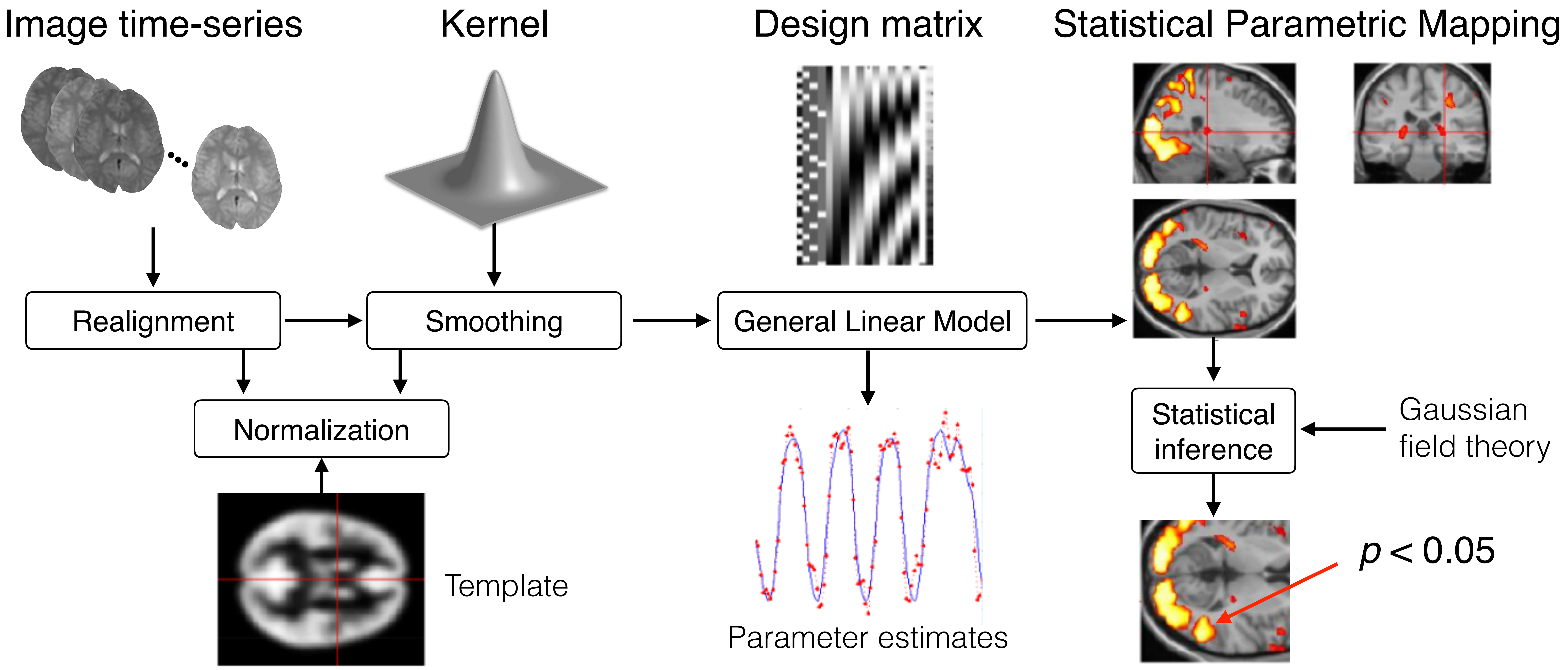
Repository for Lectures

https://github.com/skyeong/Lectures_on_Neuroimaging

Contents

- Overview of SPM
- Block design vs. event related design
- BOLD impulse responses
- Temporal basis functions
- Timing issues
- Design optimization (“efficiency”)
- Rapid-Presentation Event-Related Design for fMRI
- Optseq2 and efficiency

Overview of SPM



Research Flow in fMRI study

Research question

Which neuronal structures
support
face recognition?

Hypothesis

The fusiform gyrus
is implicated
in face recognition.

Experimental design


Face

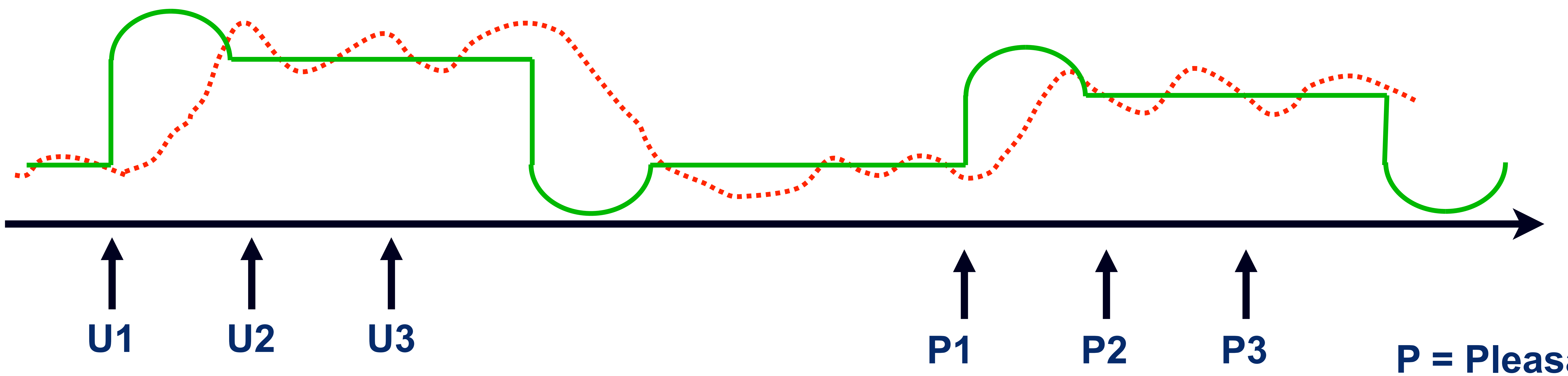

Object

Block vs. Event Related Design

Reference) Event-related fMRI: Modeling of hemodynamic time-series — Christian Ruff (UZH)

Block/epoch designs vs event-related design

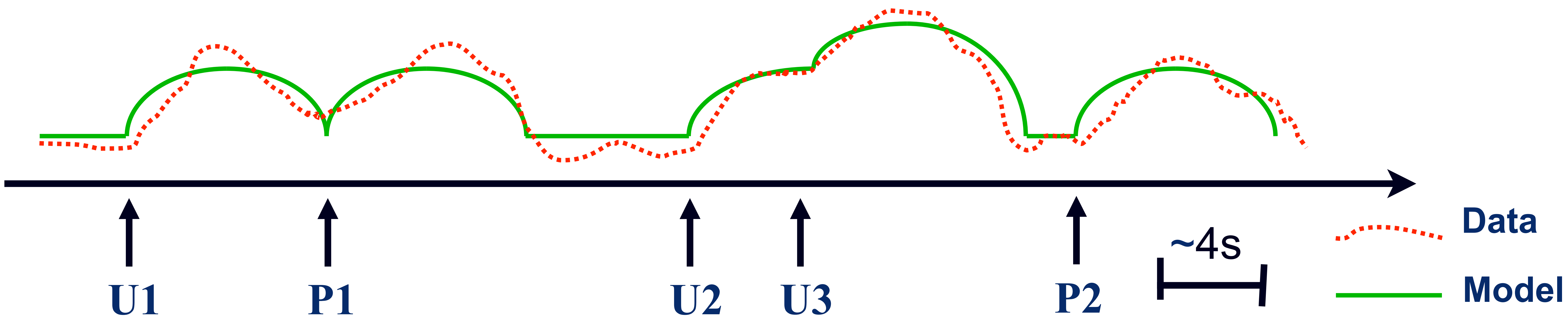
Block/epoch designs examine responses to series of similar stimuli



P = Pleasant

U = Unpleasant

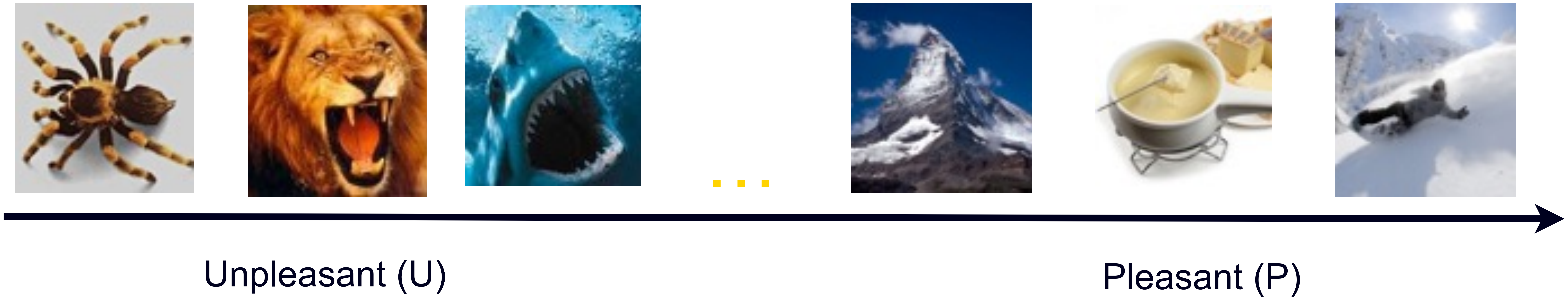
Event-related designs account for response to each single stimulus



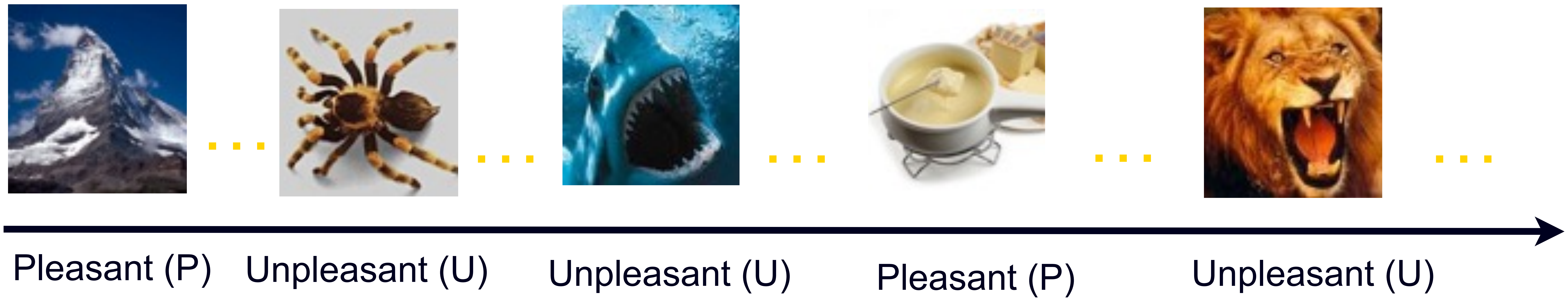
Advantages of event-related fMRI

1. Randomized trial order

Blocked designs may trigger expectations and cognitive sets



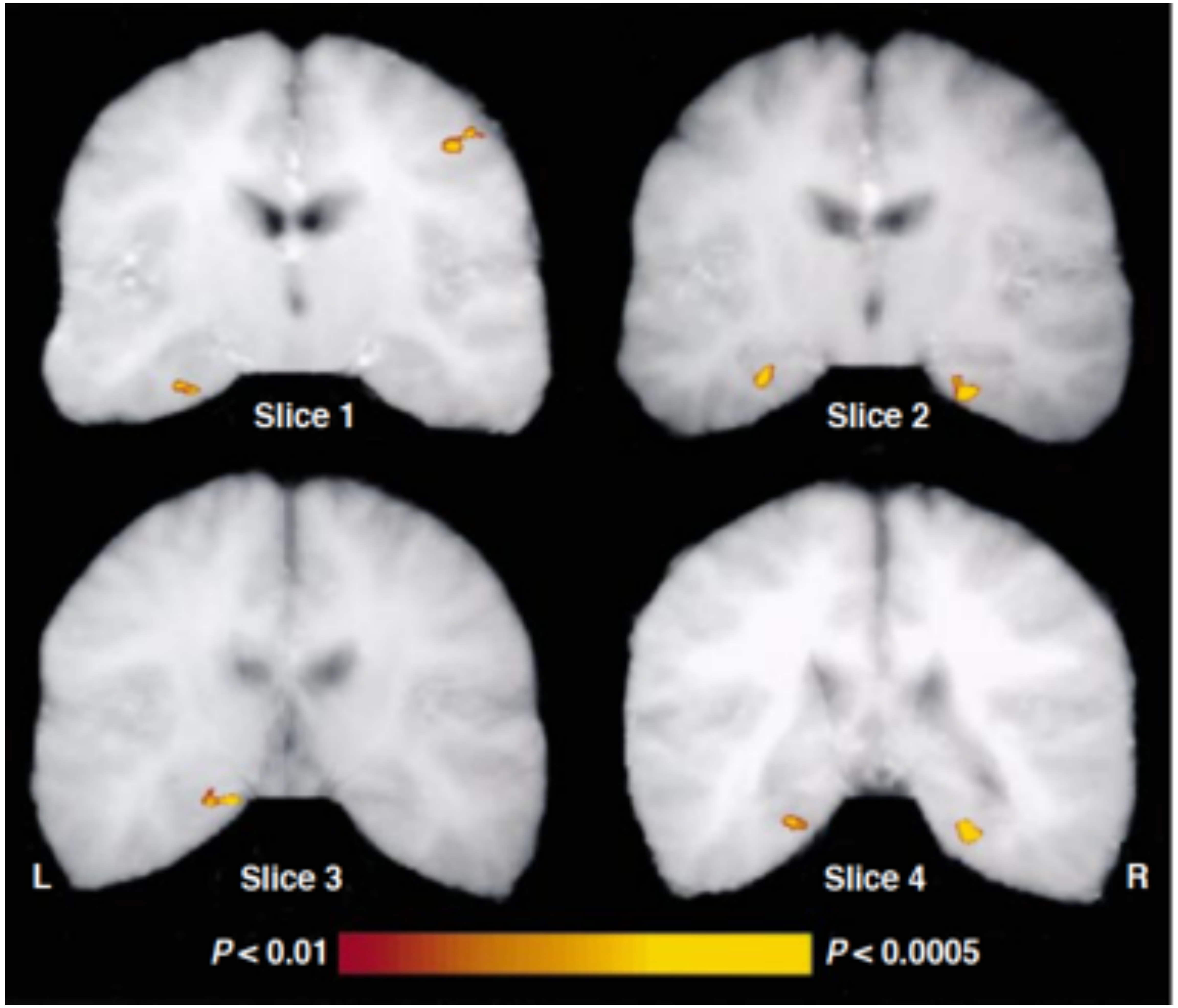
Intermixed designs can minimise this by stimulus randomisation

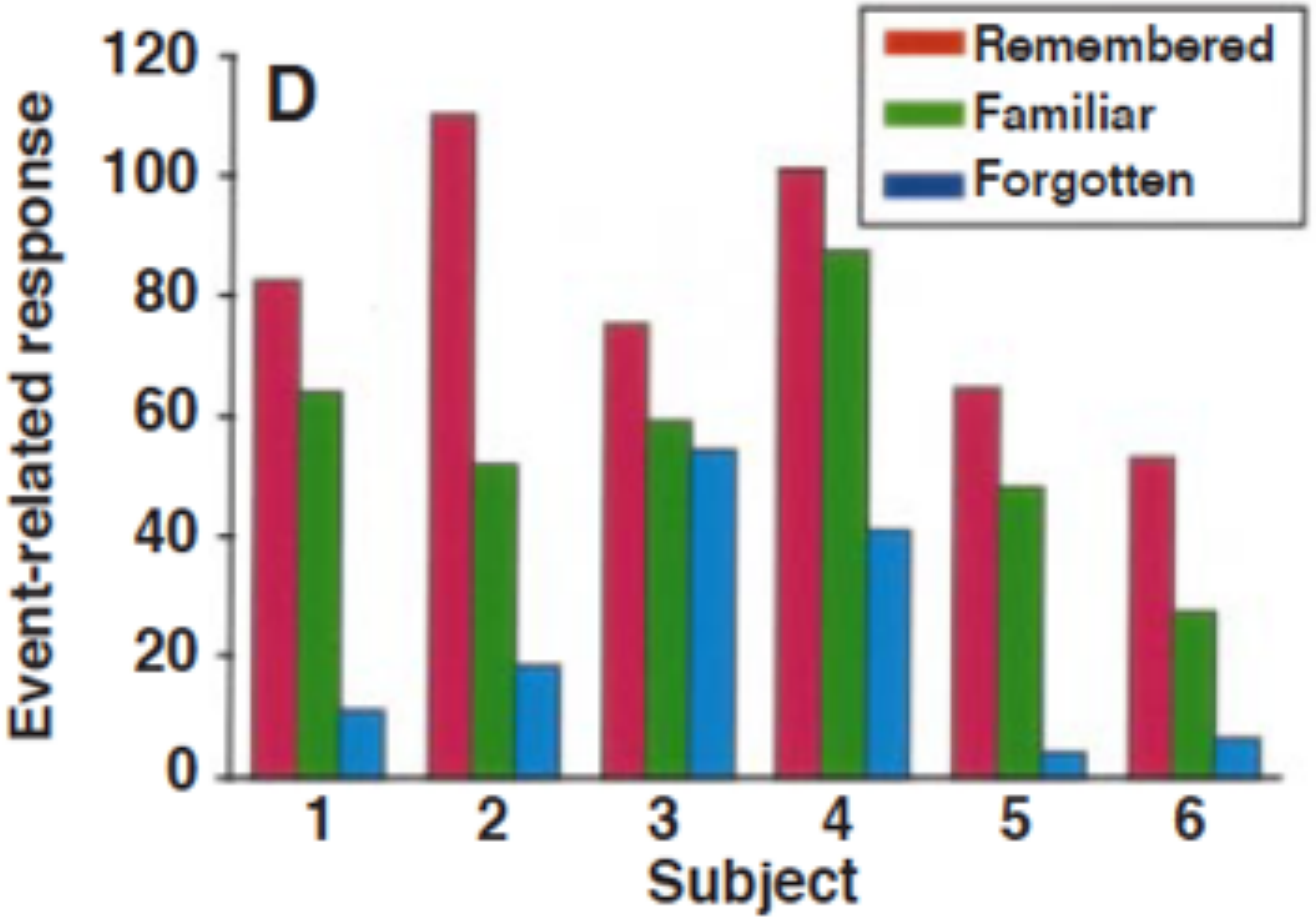


Advantages of event-related fMRI

1. Randomized trial order
2. Post-hoc subjective classification of trials

Brewer *et al.* (1999) Science



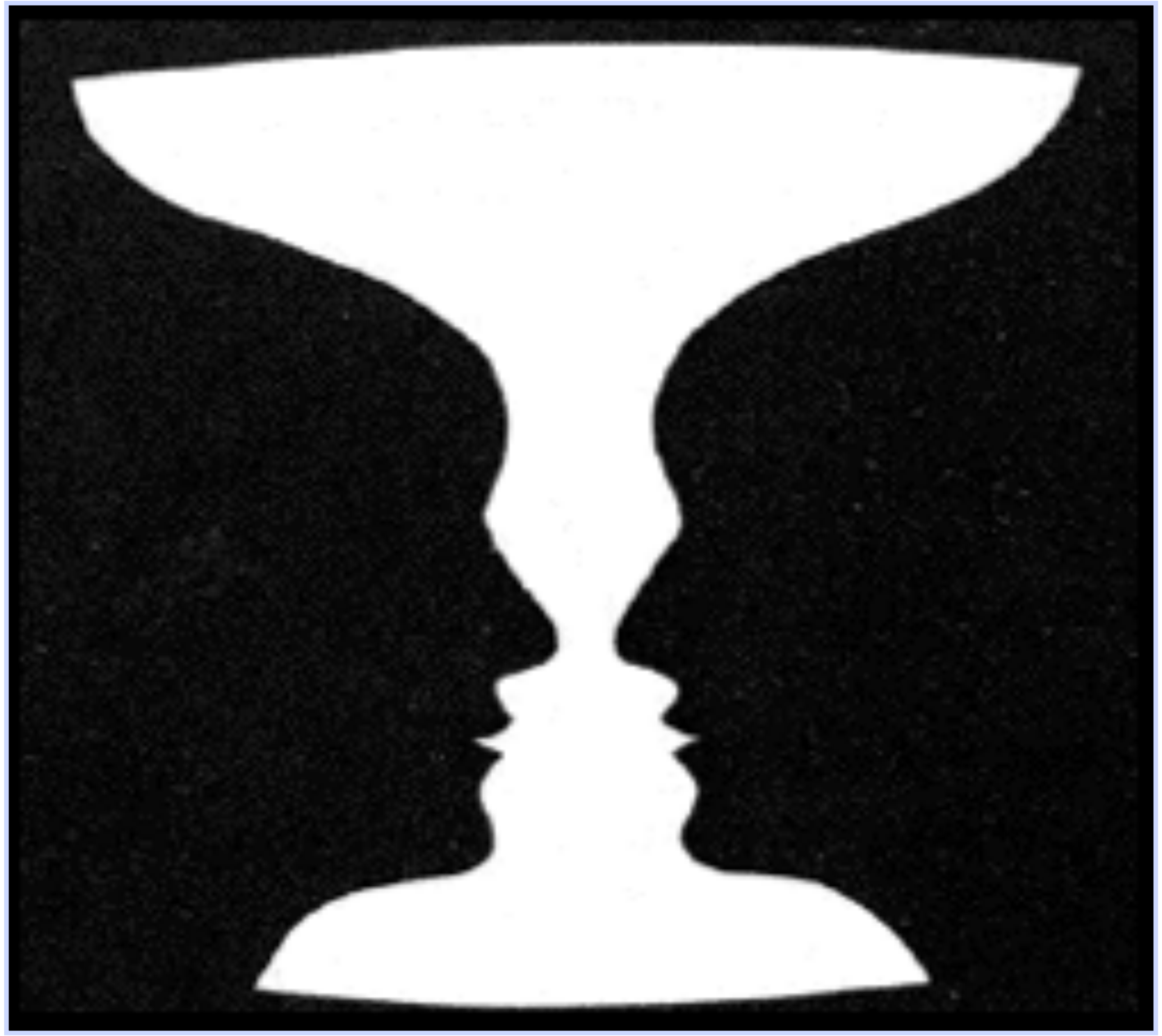


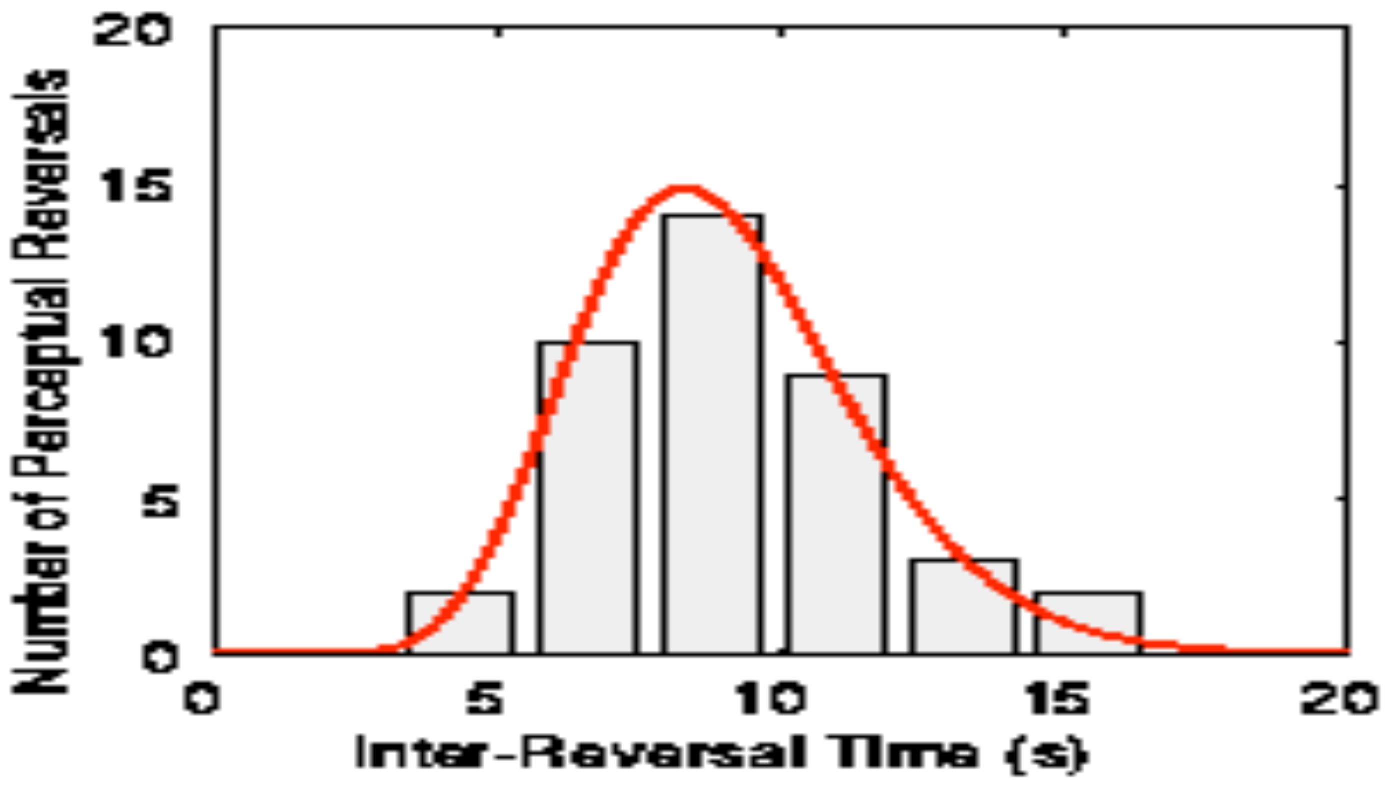
각각의 자극에 대한 뇌반응과 연구 참가자가 개발 자극에 대해 반응한 행동데이터를 연구에 활용할 수 있음.

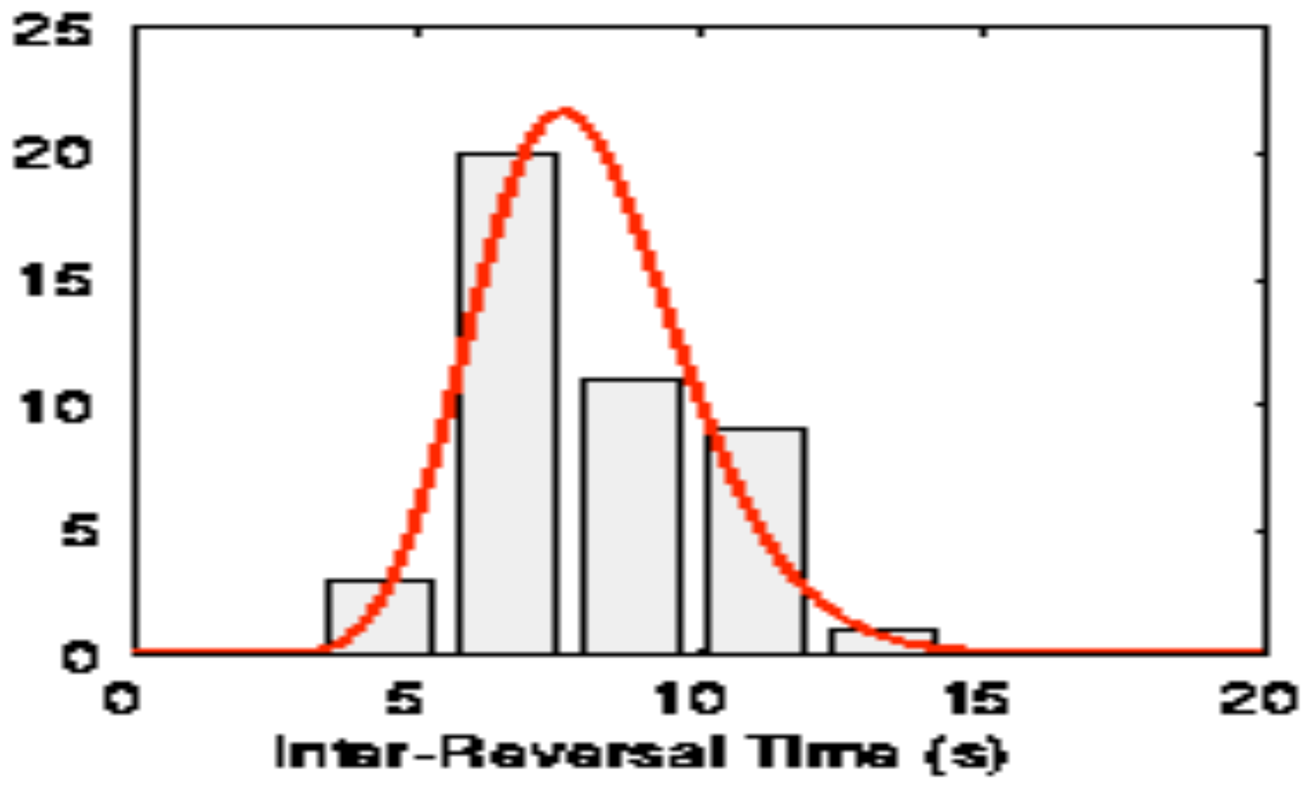
Advantages of event-related fMRI

1. Randomized trial order
2. Post-hoc subjective classification of trials
3. Some events can only be indicated by participant

Online event definition





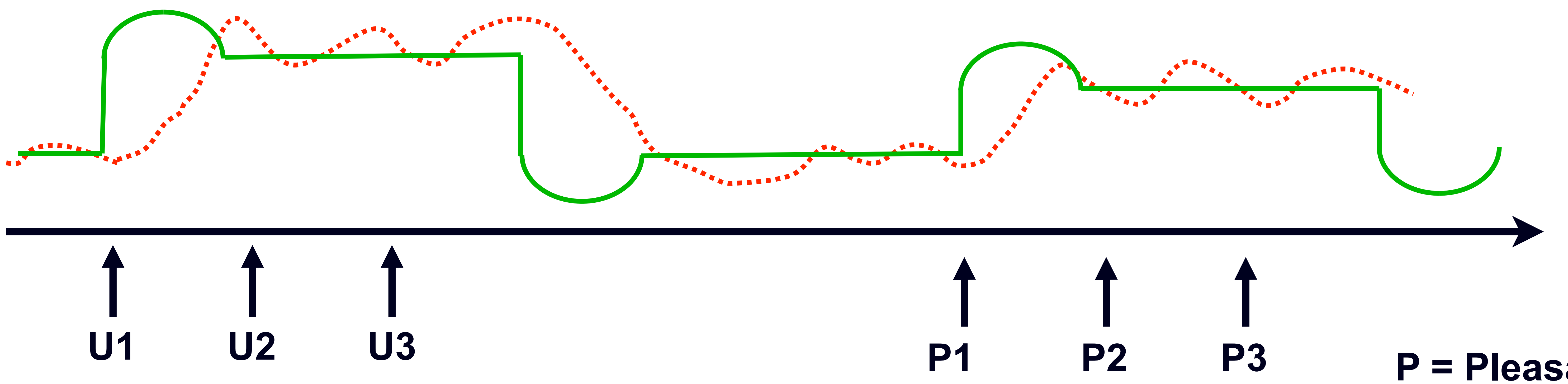


Advantages of event-related fMRI

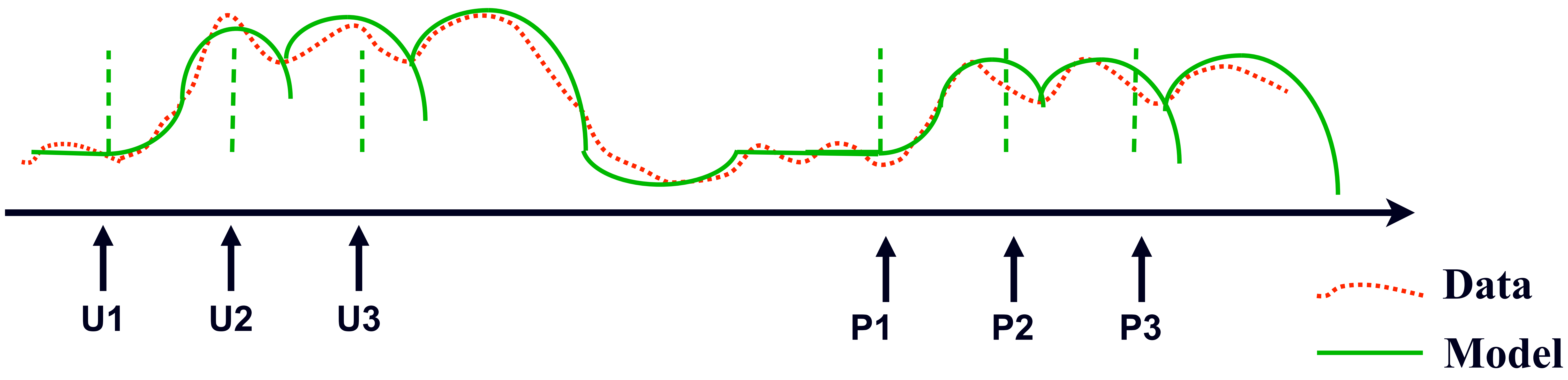
1. Randomized trial order
2. Post-hoc subjective classification of trials
3. Some events can only be indicated by participant
4. More accurate model event for epoch/block design?

“Event” model of block design

“Epoch” model assumes constant neural processes throughout block



“Event” model may capture state-item interactions (with longer SOAs)



Modeling block designs: Epochs vs events

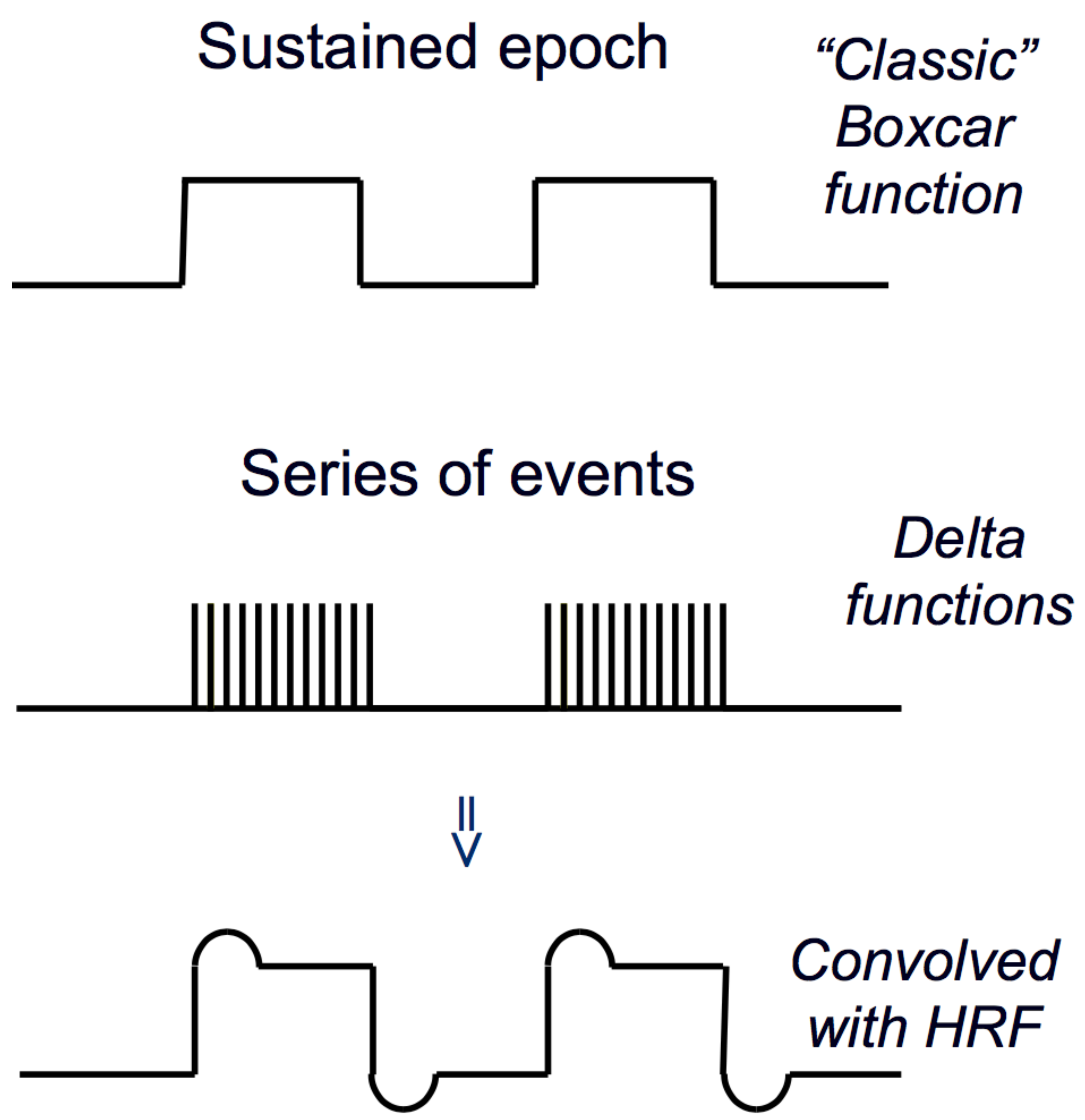
Designs can be blocked or intermixed, BUT models for blocked designs can be epoch- or event-related

Epochs are periods of sustained stimulus (e.g., box-car functions) or Events are impulses (delta_functions)

Near-identical regressors can be created by 1) sustained epochs, 2) rapid series of events (SOAs<~3s)

In SPM12, all conditions are specified in terms of their 1) onsets and 2) durations
… epochs: variable or constant duration
… events: zero duration

SOA: stimulus onset asynchrony



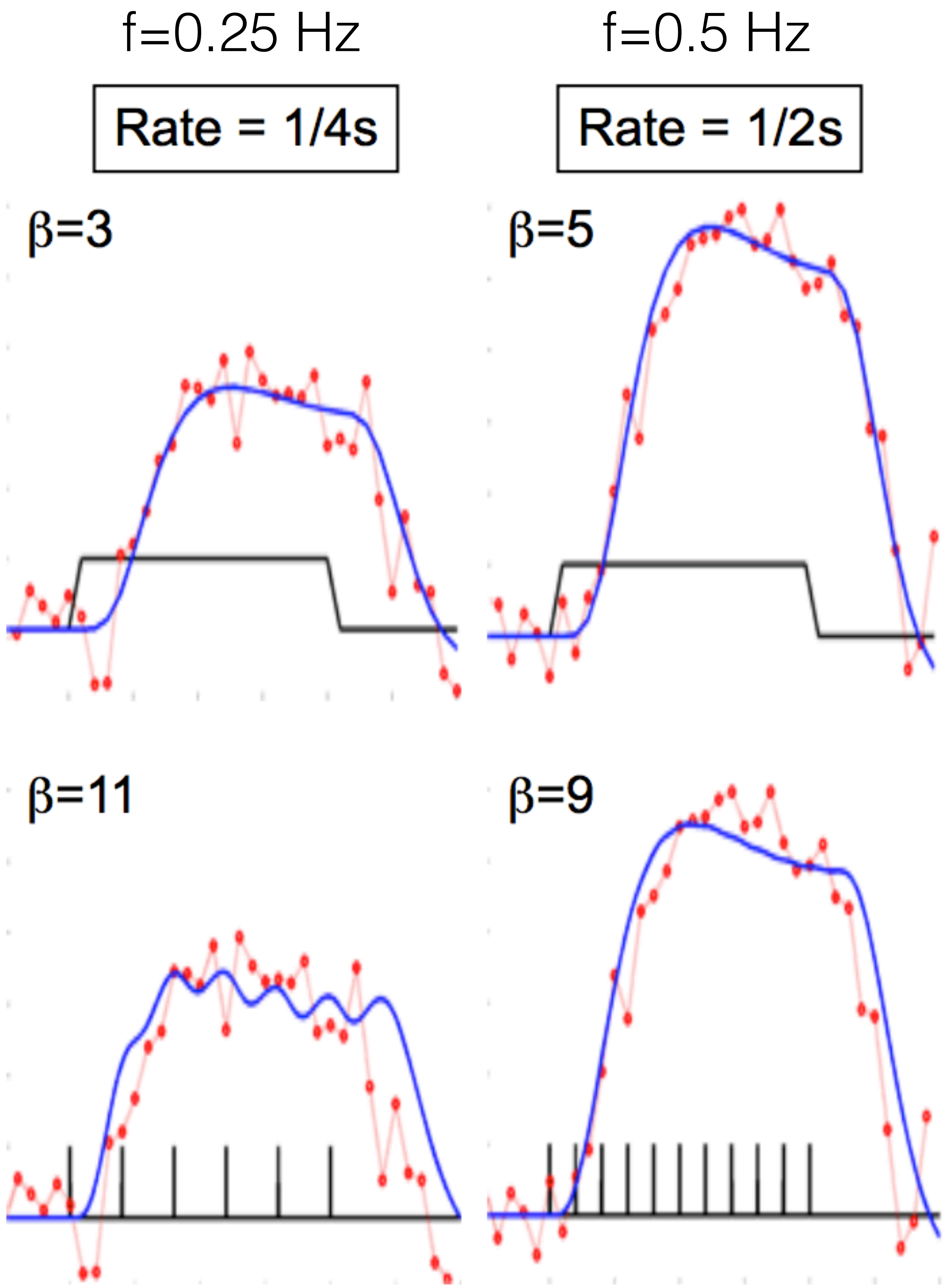
Modeling block designs: Epochs vs events

Blocks of trials can be modeled as boxcars or runs of events

BUT: interpretation of the parameter estimates may differ

Consider an experiment presenting words at different rates in different blocks:

- An “epoch” model will estimate parameter that increases with rate, because the parameter reflects response per block
- An “event” model may estimate parameter that decreases with rate, because the parameter reflects responses per word



Disadvantages of intermixed designs

1. Less efficient for detecting effects than blocked designs
   (see later …)

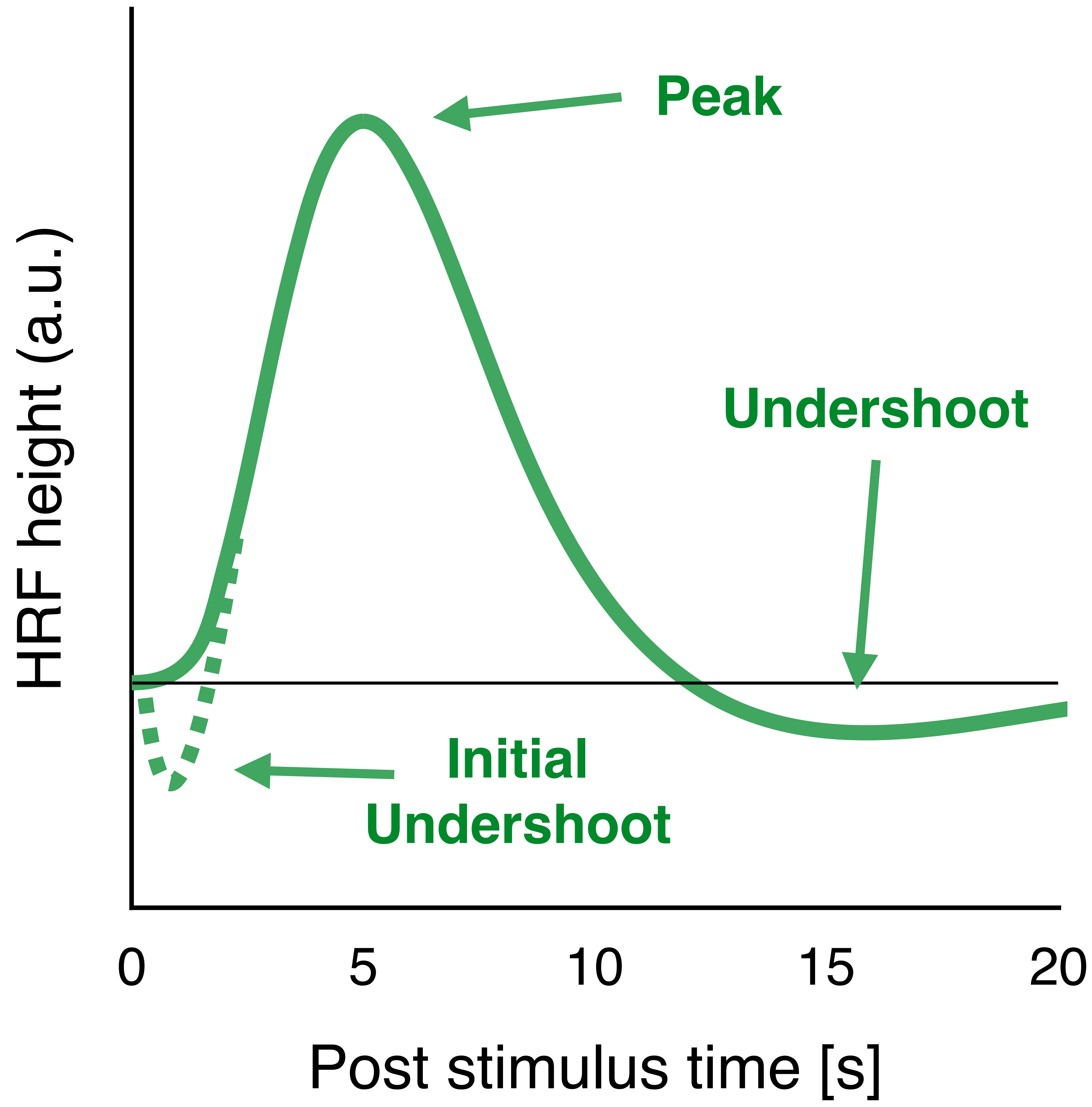
2. Some psychological processes have to/may be better blocked
   (e.g., if difficult to switch between states, or to reduce surprise
   (salience) effects)

BOLD impulse response

Reference) Event-related fMRI: Modeling of hemodynamic time-series — Christian Ruff (UZH)

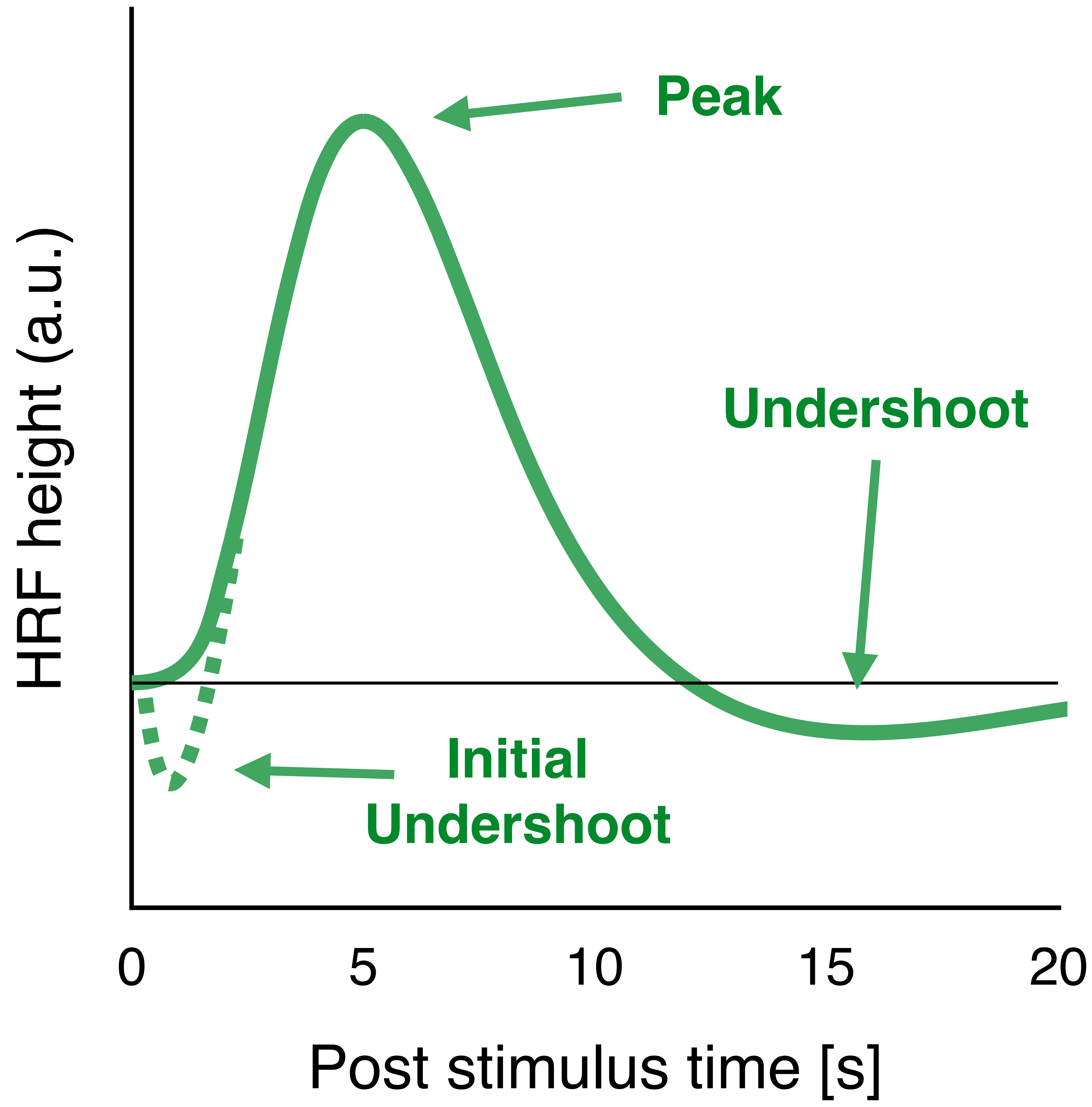
BOLD impulse response

- Function of blood oxygenation, flow, volume
- Peak (max. oxygenation) 4-6s post stimulus; baseline after 20-30s
- Initial undershoot can be observed
- Similar across V1, A1, S1...
- ... but possible differences across:
  - other regions
  - individuals

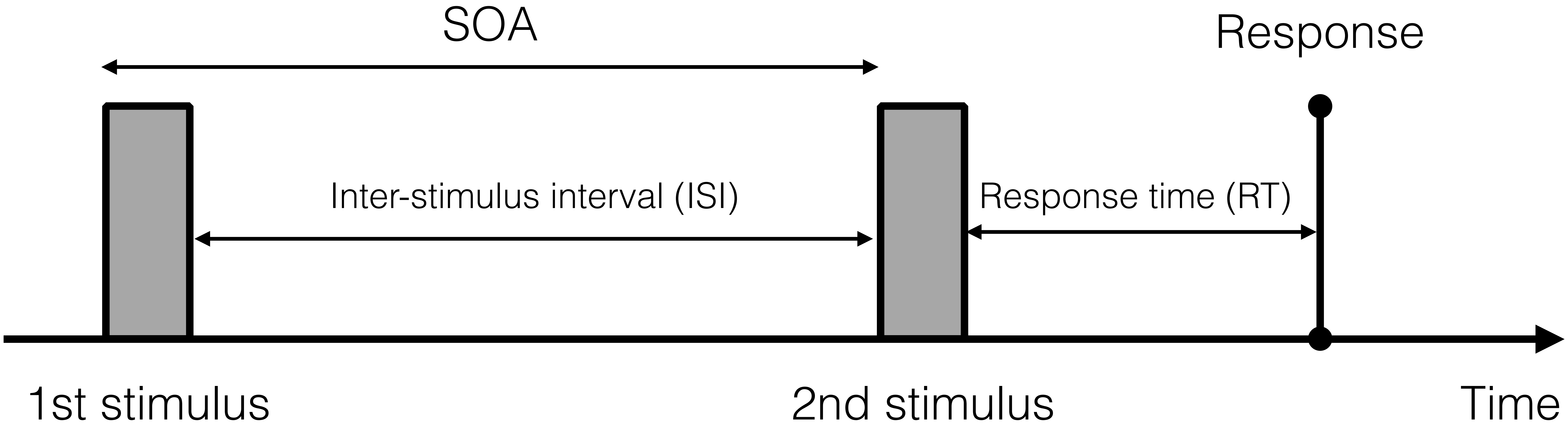


BOLD impulse response

- Early event-related fMRI studies used a long Stimulus Onset Asynchrony (SOA) to allow BOLD response to return to baseline
- However, overlap between successive responses at short SOAs can be accommodated if the BOLD response is explicitly modeled, particularly if responses are assumed to superpose linearly
- Short SOAs are more sensitive; see later



Stimulus Onset Asynchrony (SOA)



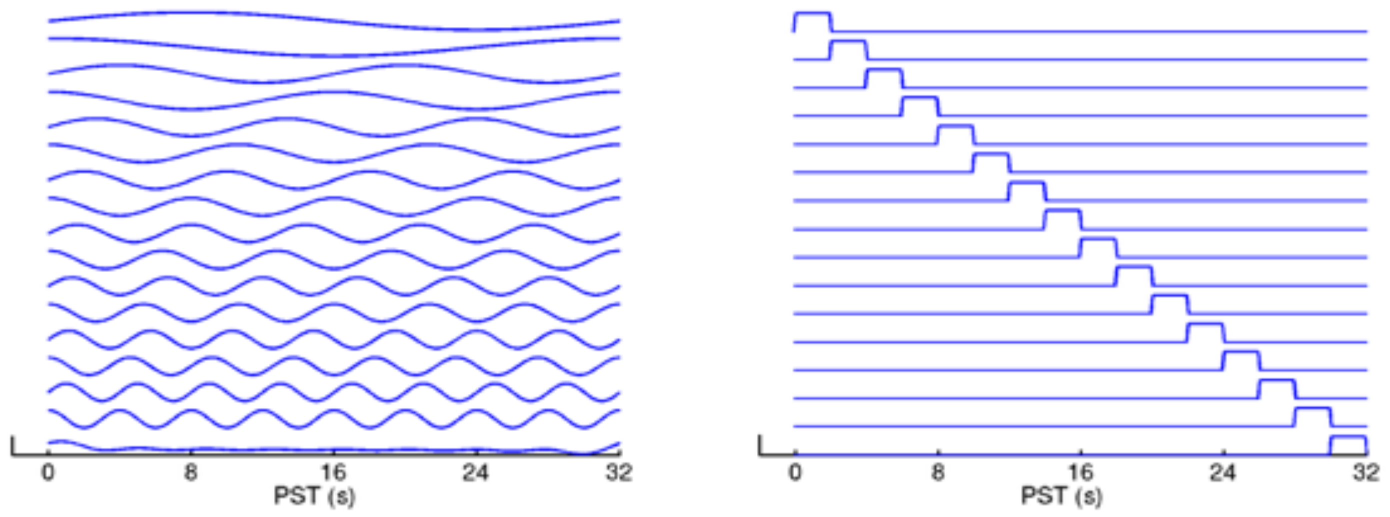
Temporal basis functions

Reference) Event-related fMRI: Modeling of hemodynamic time-series — Christian Ruff (UZH)

Temporal basis functions

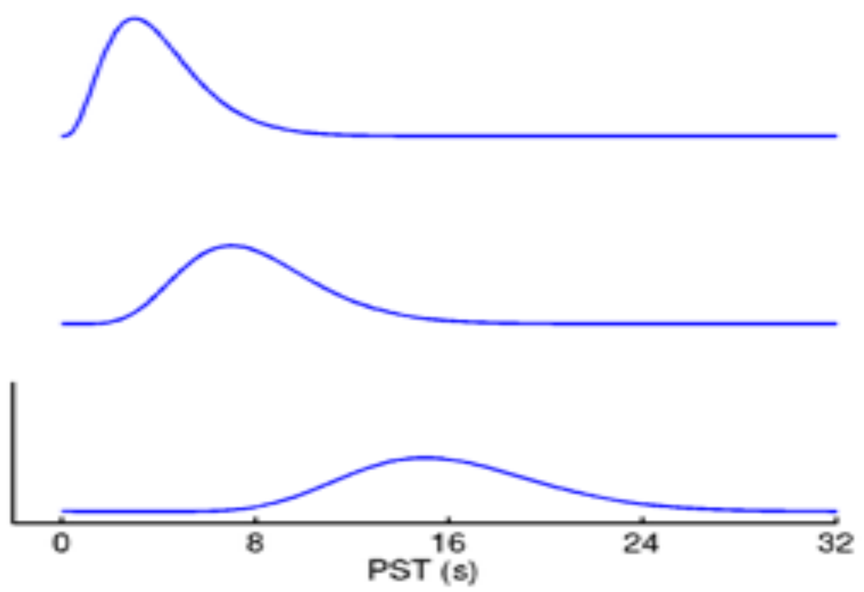
Fourer Set / FIR

- Any shape (up to frequency limit / bin width)
- Inference via F-test



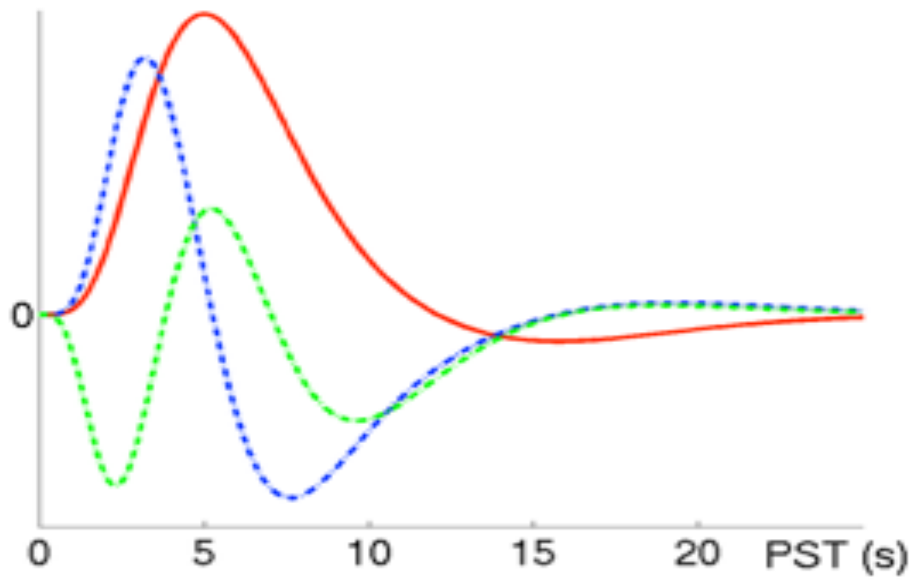
Gamma Functions

- Bounded, asymmetrical (line BOLD)
- Set of different lags
- Inference via F-test

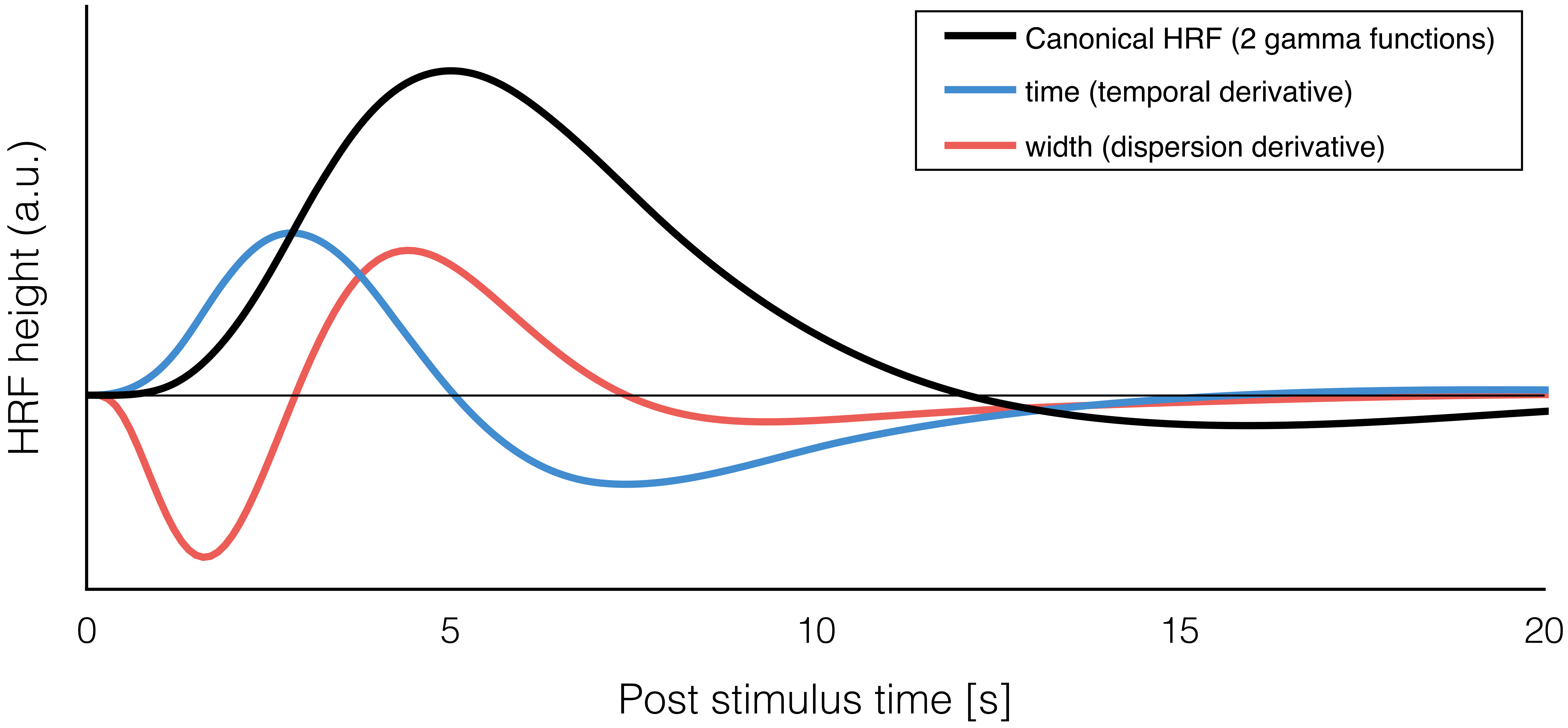


"Informed" Basis Set

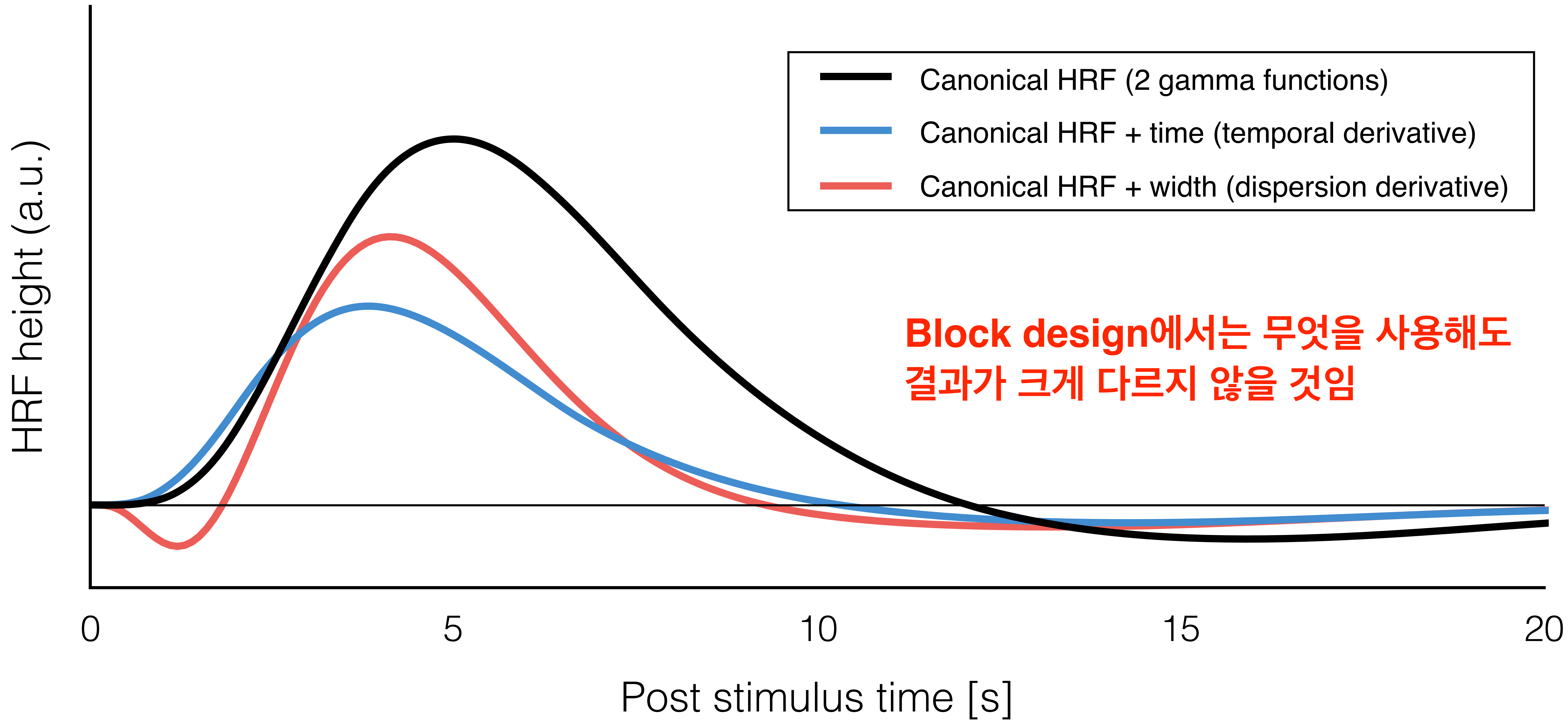
- Best guess of canonical BOLD response
- Variability captured by Taylor expansion
- "Magnitude" inference via t-test?



What are HRFs?



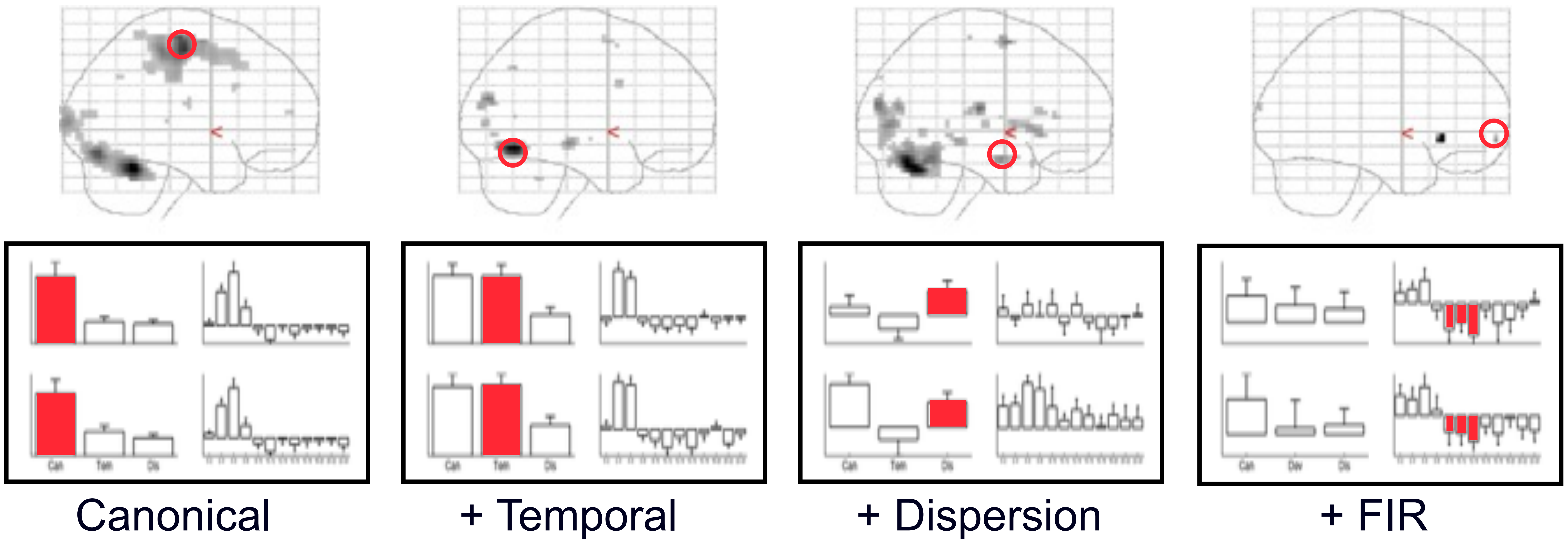
Variants of Canonical HRF



Block design에서는 무엇을 사용해도 결과가 크게 다르지 않을 것임

Which temporal basis set

In this example (rapid motor response to faces, *Henson et al, 2001*)…



... canonical + temporal + dispersion derivatives appear sufficient to capture most activity

... may not be true for more complex trials (e.g. stimulus-prolonged delay (>~2 s)-response)

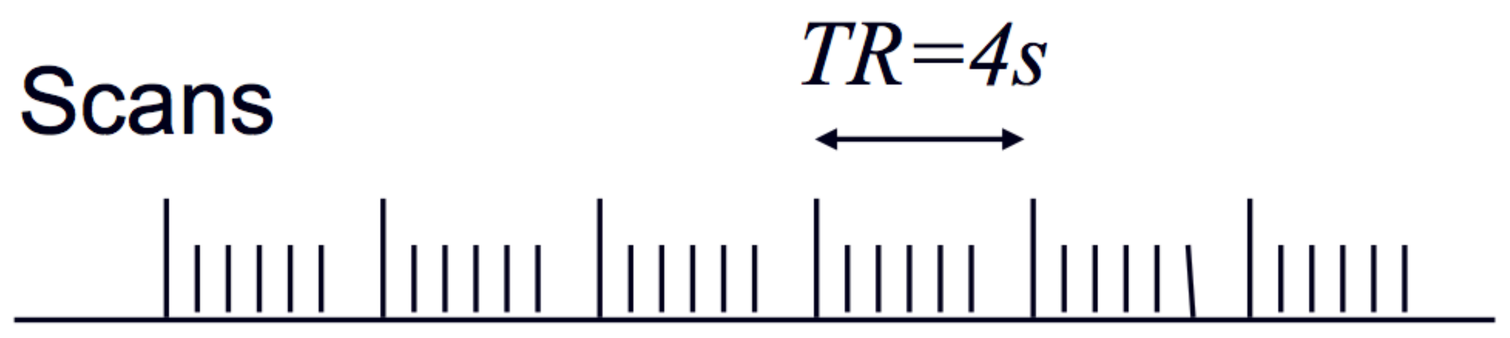
... but then such trials better modelled with separate neural components (i.e., activity no longer delta function) + constrained HRF

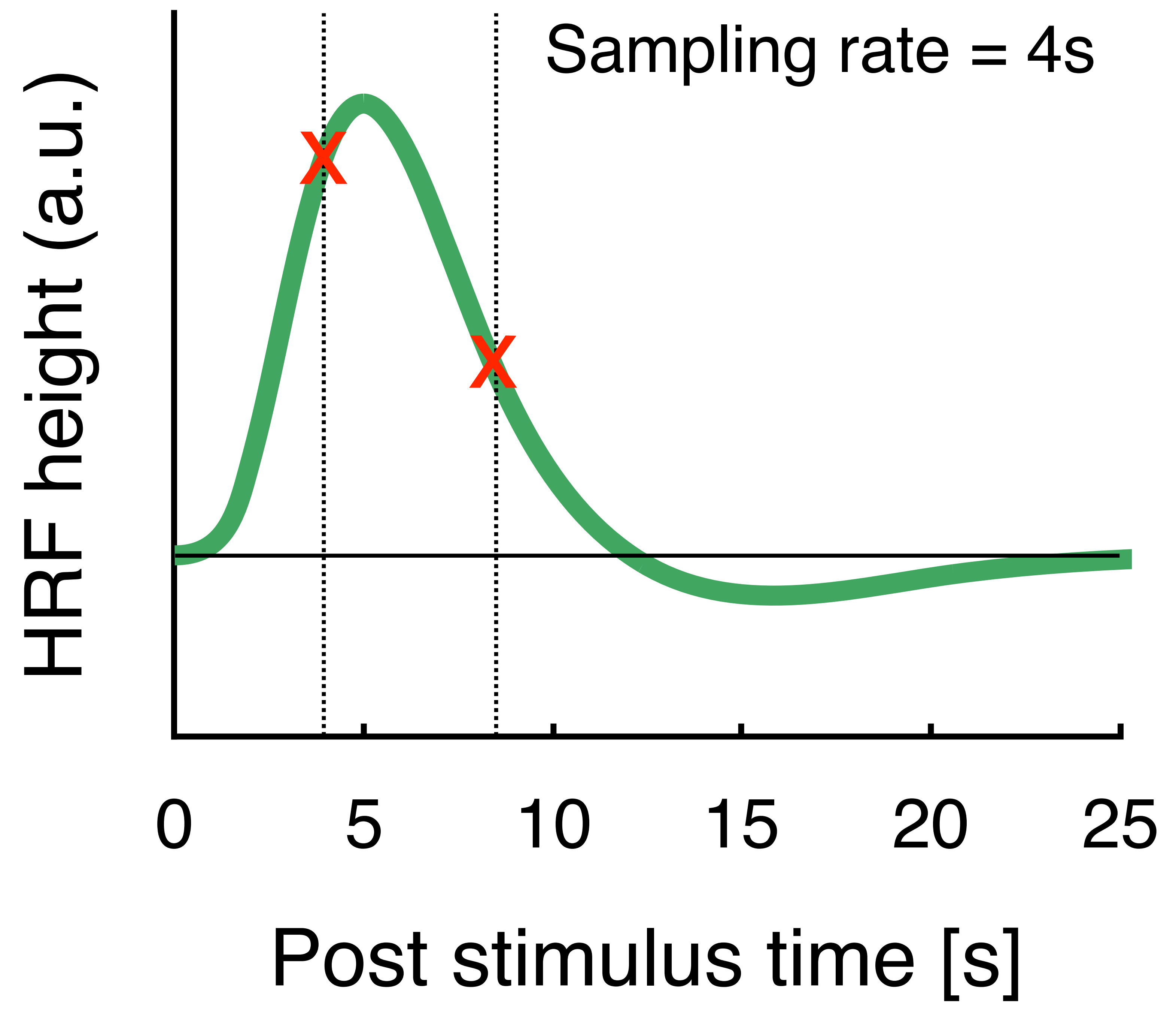
Timing Issues

Reference) Event-related fMRI: Modeling of hemodynamic time-series — Christian Ruff (UZH)

Timing issue: sampling

- TR for 80 slice EPI at 2 mm spacing is ~ 4s
- Sampling at [0,4,8,12...] post- stimulus may miss peak signal





Timing issue: sampling

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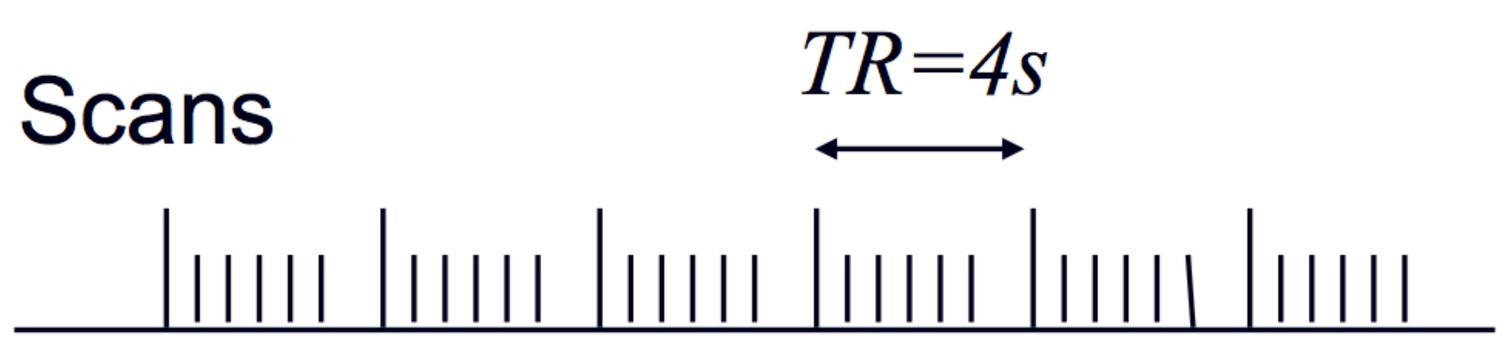
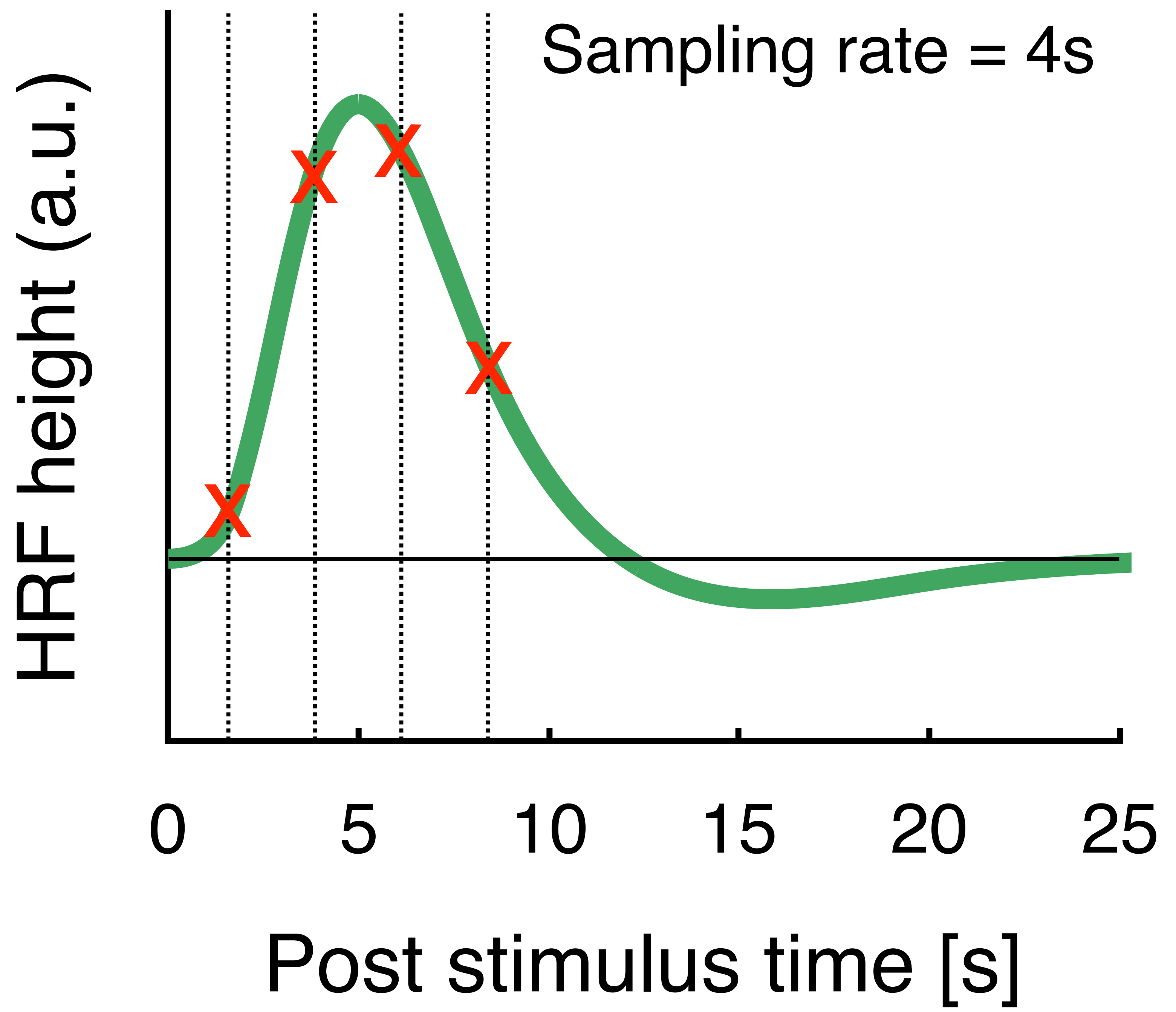


- Higher effective sampling by:
  1. Asynchrony; e.g., SOA=1.5TR
  2. Random Jitter; e.g., SOA=(2±0.5)TR

- Better response characterization



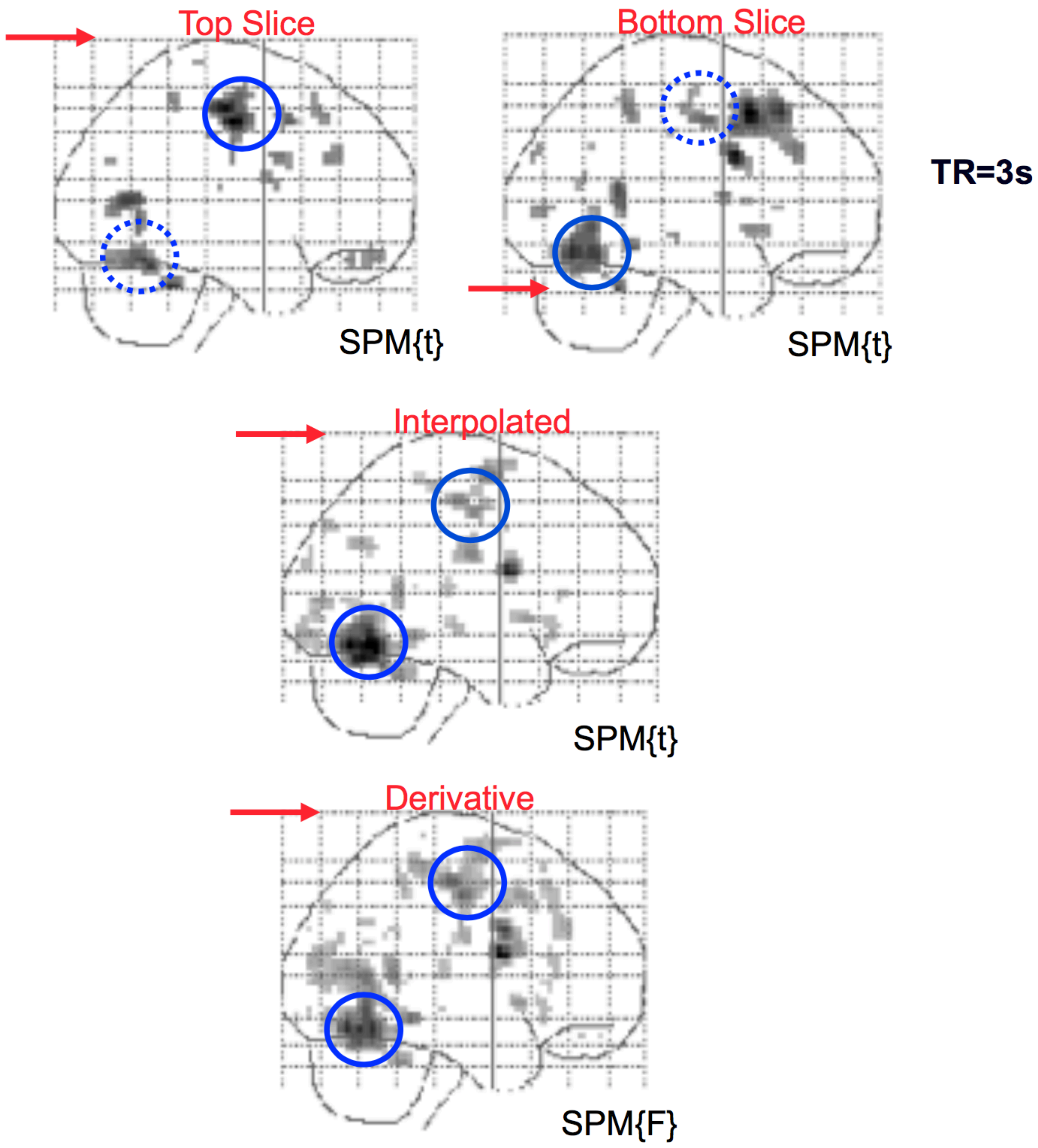
Timing issues: slice timing

"Slice-timing Problem":

- Slices acquired at different times, yet model is the same for all slices
- different results (using canonical HRF) for different reference slices
- (slightly less problematic if middle slice is selected as reference, and with short TRs)

Solutions:

1. Temporal interpolation of data (at specify 1st-level) ... but less good for longer TRs
2. More general basis set (e.g., with temporal derivatives) ... but inferences via F-test



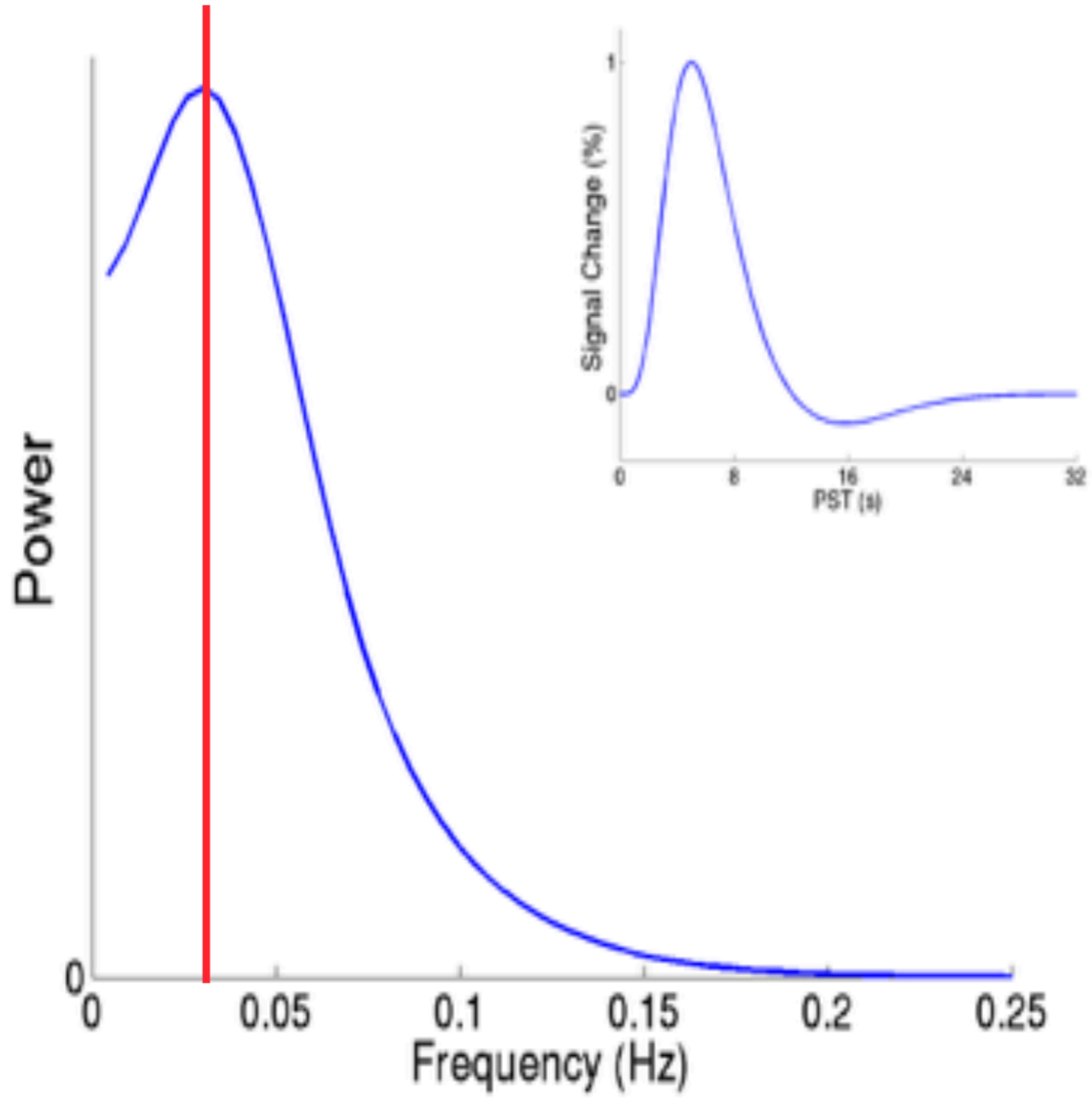
Design Optimization
“Efficiency”

Reference) Event-related fMRI: Modeling of hemodynamic time-series — Christian Ruff (UZH)

Design efficiency

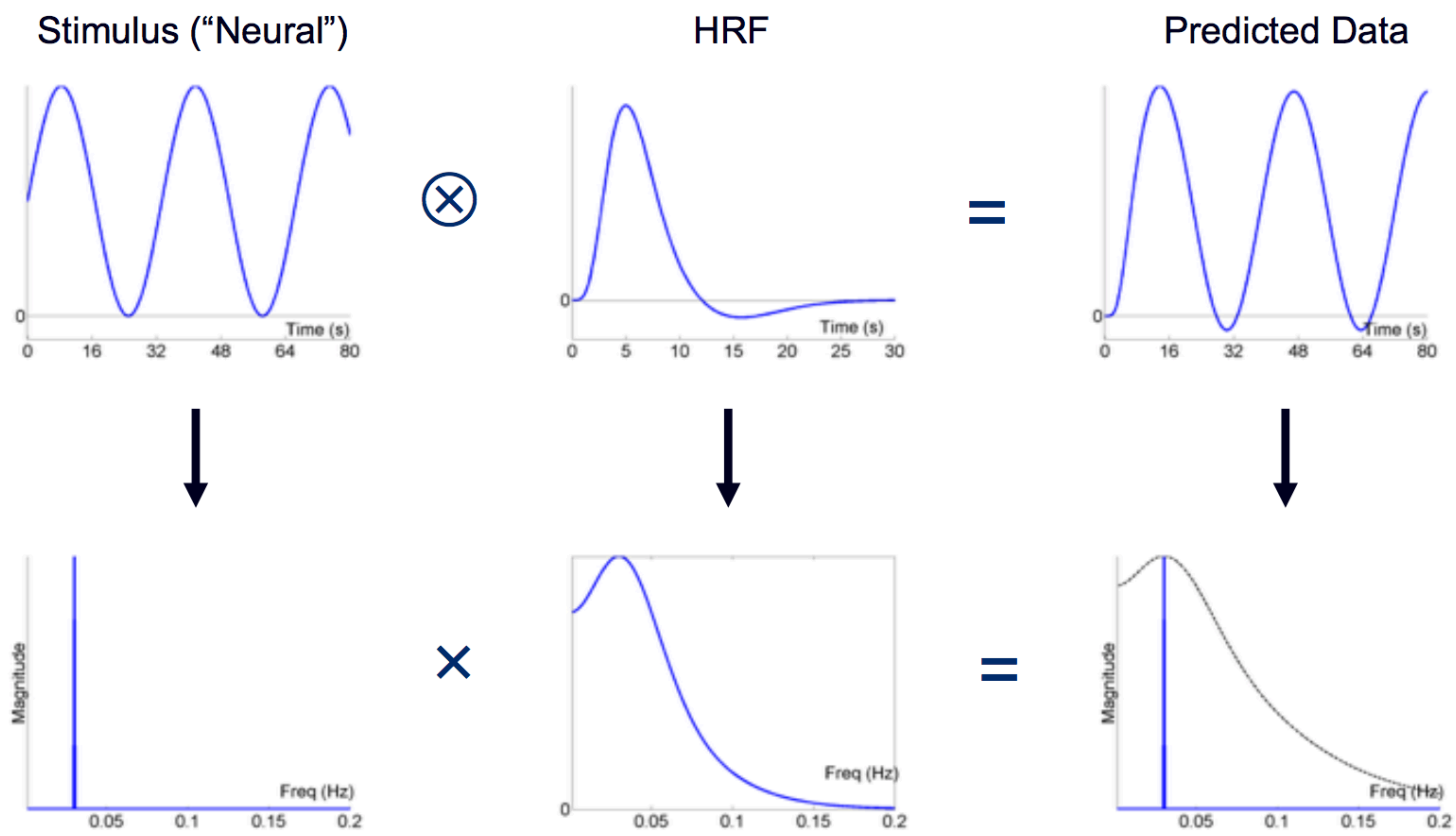
- HRF can be viewed as a filter (Josephs & Henson, 1999)
- We want to maximize the signal passed by this filter
- Dominant frequency of canonical HRF is ~0.04 Hz

➡ The most efficient design is a sinusoidal modulation of neural activity with period ~24s
(e.g., boxcar with 12s on/ 12s off)



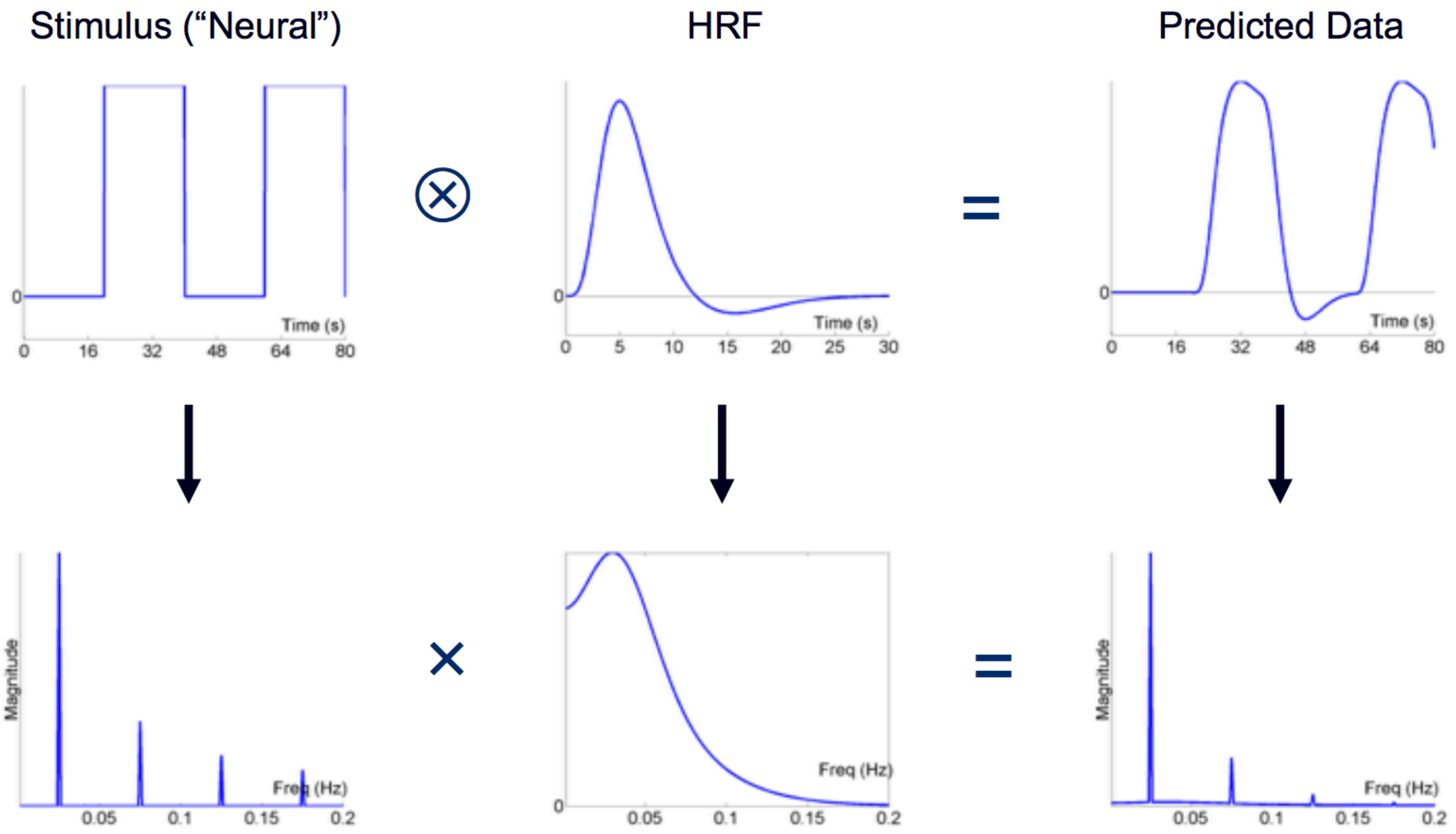
Sinusoidal modulation, f=1/33

A very
“efficient” design!



Blocked, epoch = 20s

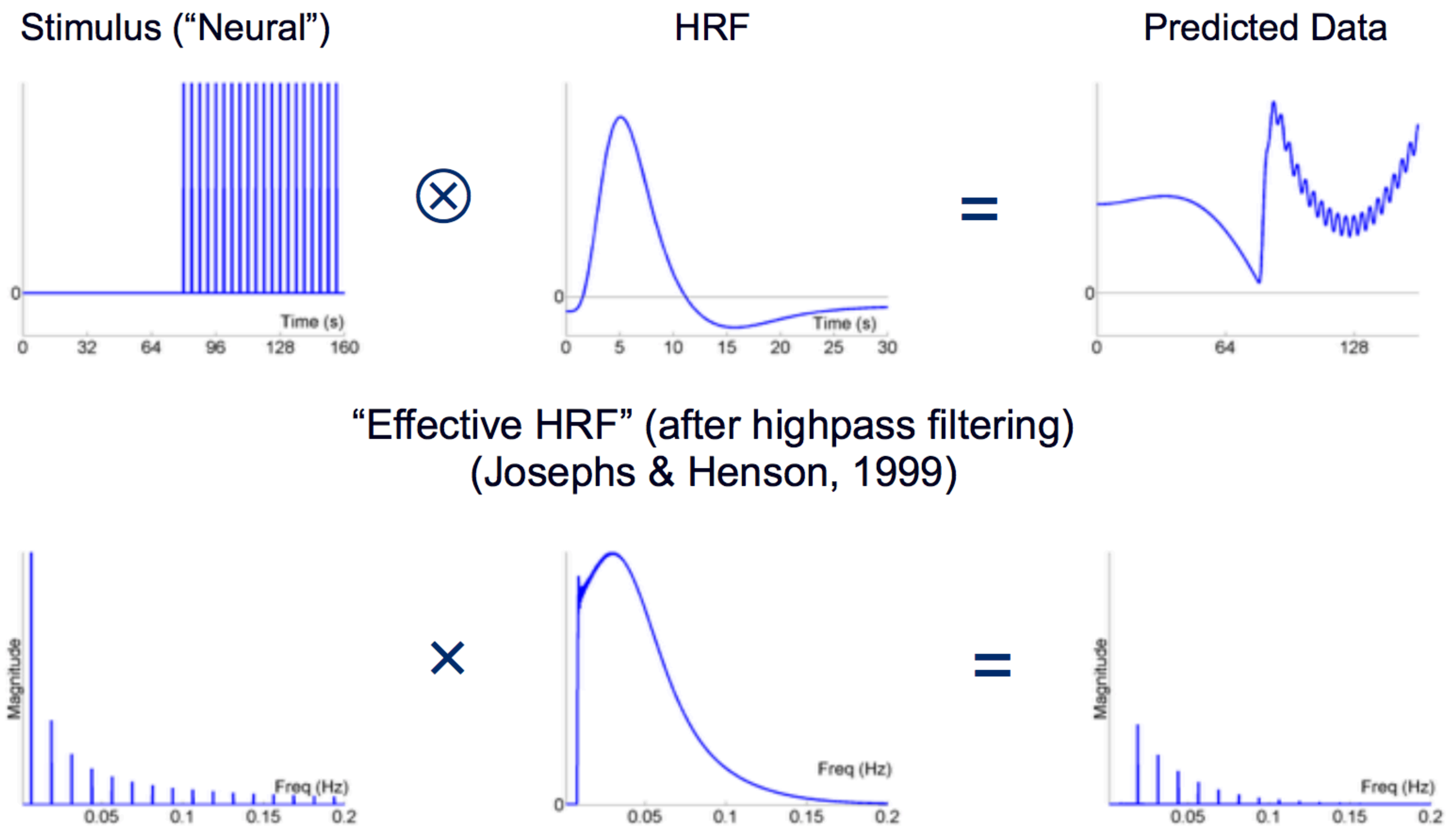
Blocked-epoch (with small SOA) quite "efficient"



Blocked (80s), SOAmin=4s, hipass filter = 1/120s

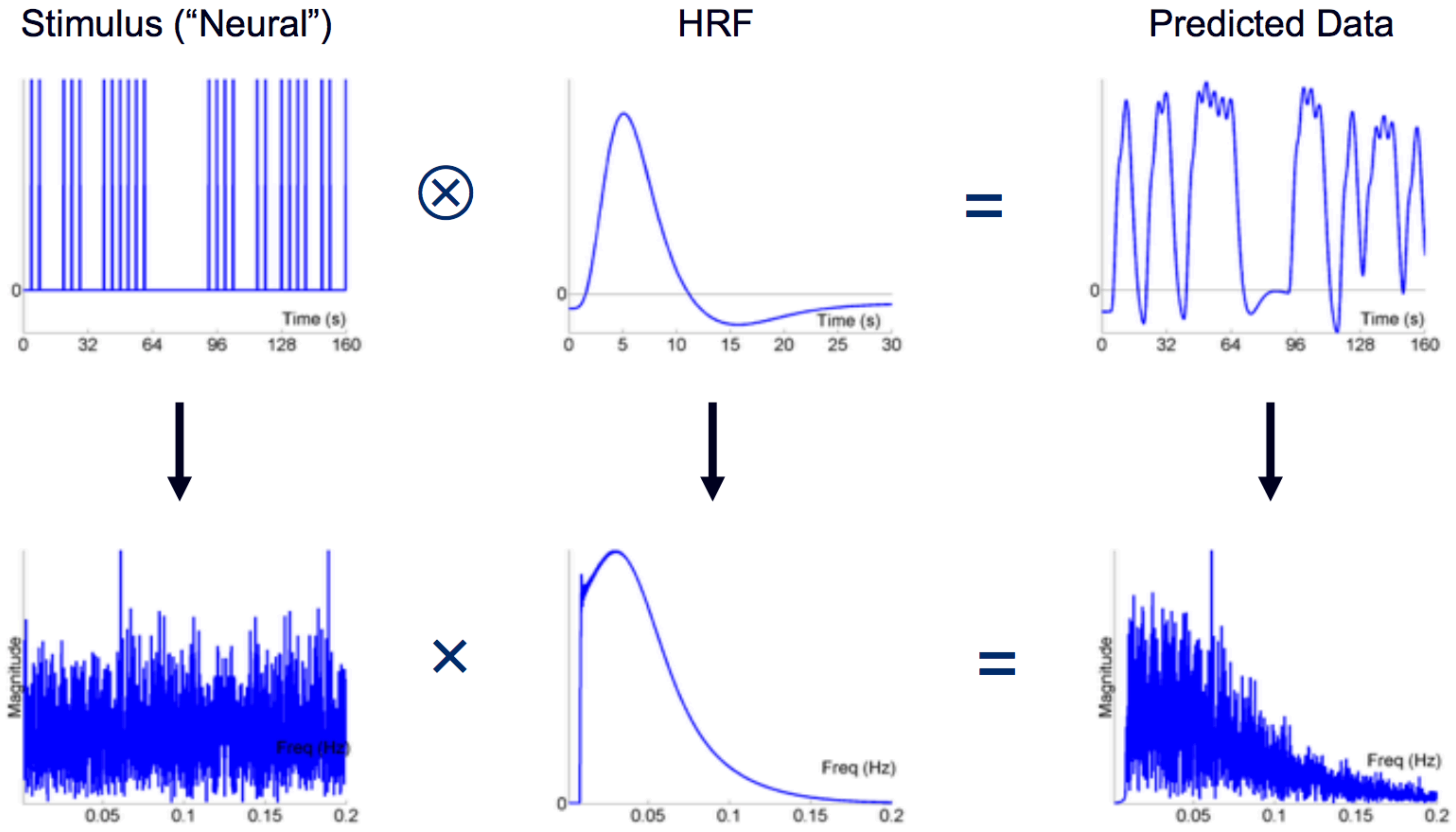
Very ineffective:

Don’t have long (>60s) blocks!



Randomized, SOAmin=4s, highness filter = 1/120s

Randomised design spreads power over frequencies



Design efficiency

- T-statistic for a given contrast: $T = c^T b / var(c^T b)$
- For maximum T, we want maximum precision and hence minimum standard error of contrast estimates ($var(c^T b)$)
- $Var(c^T b) = sqrt(\sigma^2 c^T (X^T X)^{-1} c)$ (i.i.d)
- If we assume that noise variance (σ^2) is unaffected by changes in X, then our precision for given parameters is proportional to the *design efficiency:* $e(c,X) = \{ \mathbf{c}^T (\mathbf{X}^T\mathbf{X})^{-1} \mathbf{c} \}^{-1}$

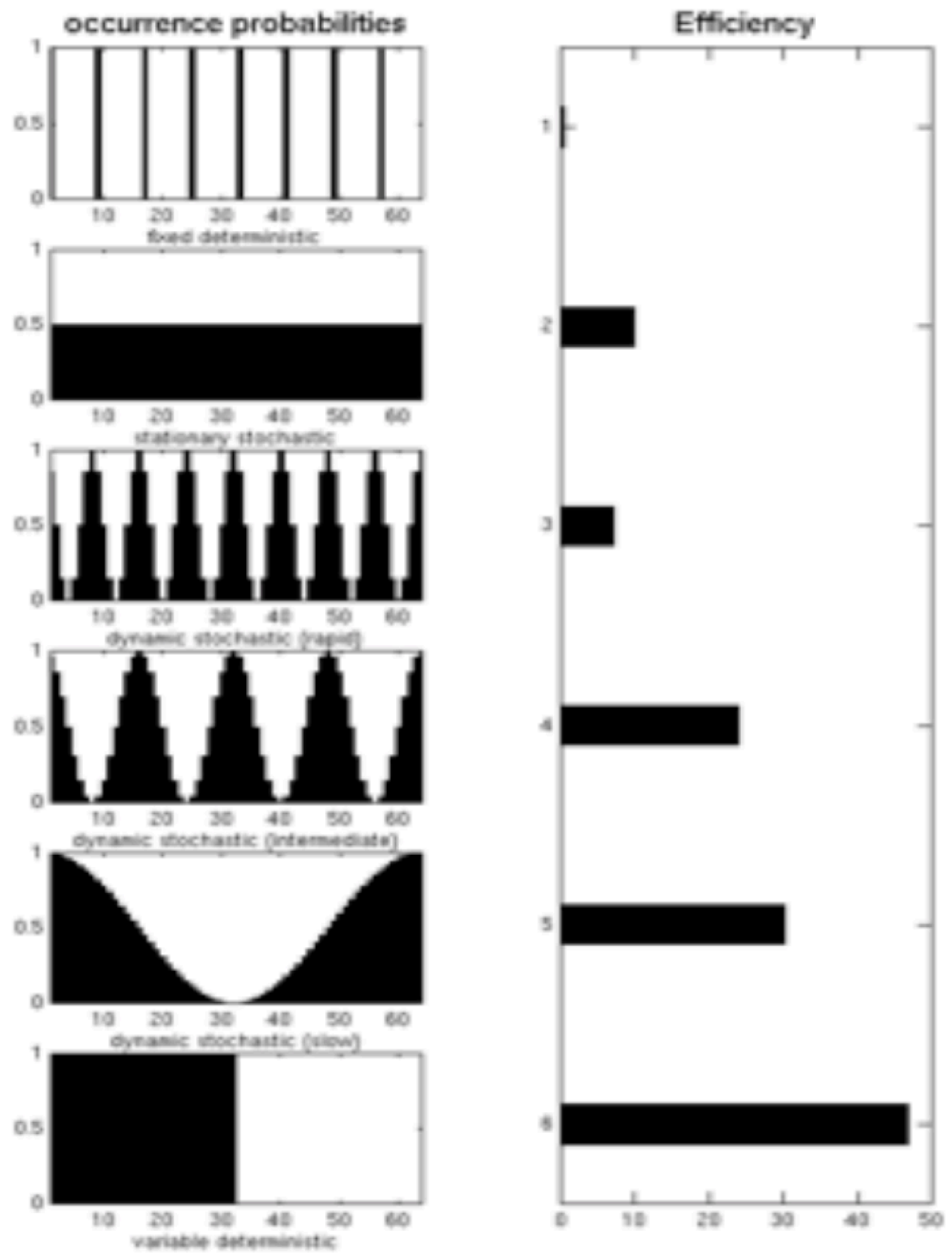
➡ We can influence *e* (a priori) by the spacing and sequencing of epochs/events in our design matrix

➡ *e* is specific for a given contrast!

Design efficiency: Trial spacing

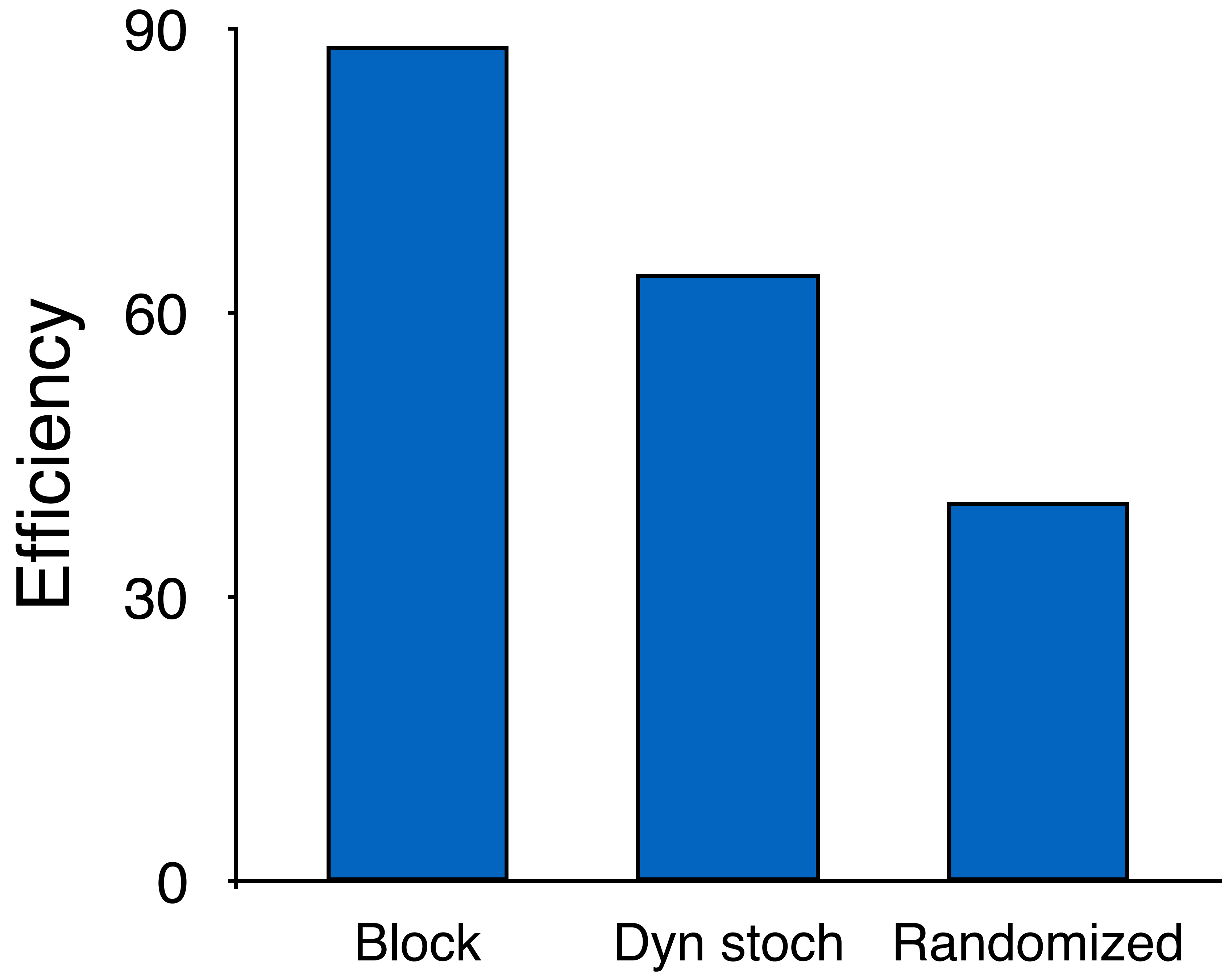
- Design parametrized by:

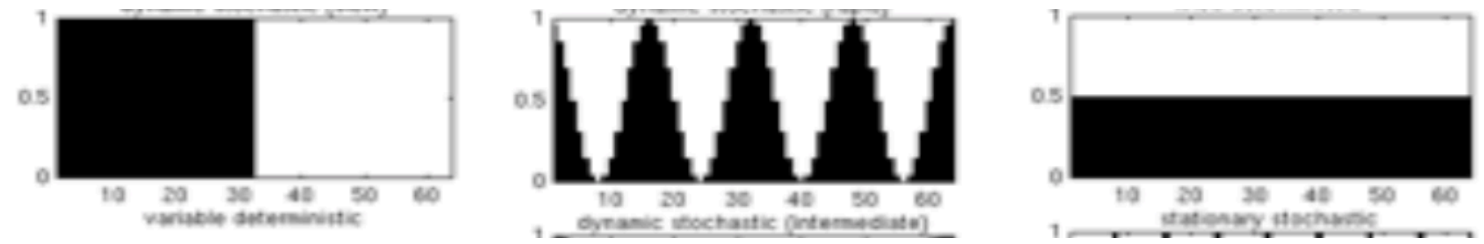
  - SOA_{min} Minimum SOA
  - *p(t)* Probability of event at each SOA_{min}
- Deterministic
  p(t) = 1 iif $t = nSOA_{min}$
- Stationary stochastic
  p(t) = constant
- Dynamic stochastic
  p(t) varies (e.g., blocked)



Design efficiency: Trial spacing

- However, block designs are often not advisable due to interpretative difficulties (see before)
- Event trains may then be constructed by modulating the event probabilities in a dynamic stochastic fashion
- This can result in intermediate levels of efficiency





Design efficiency: Trial sequencing

- Design parametrized by:

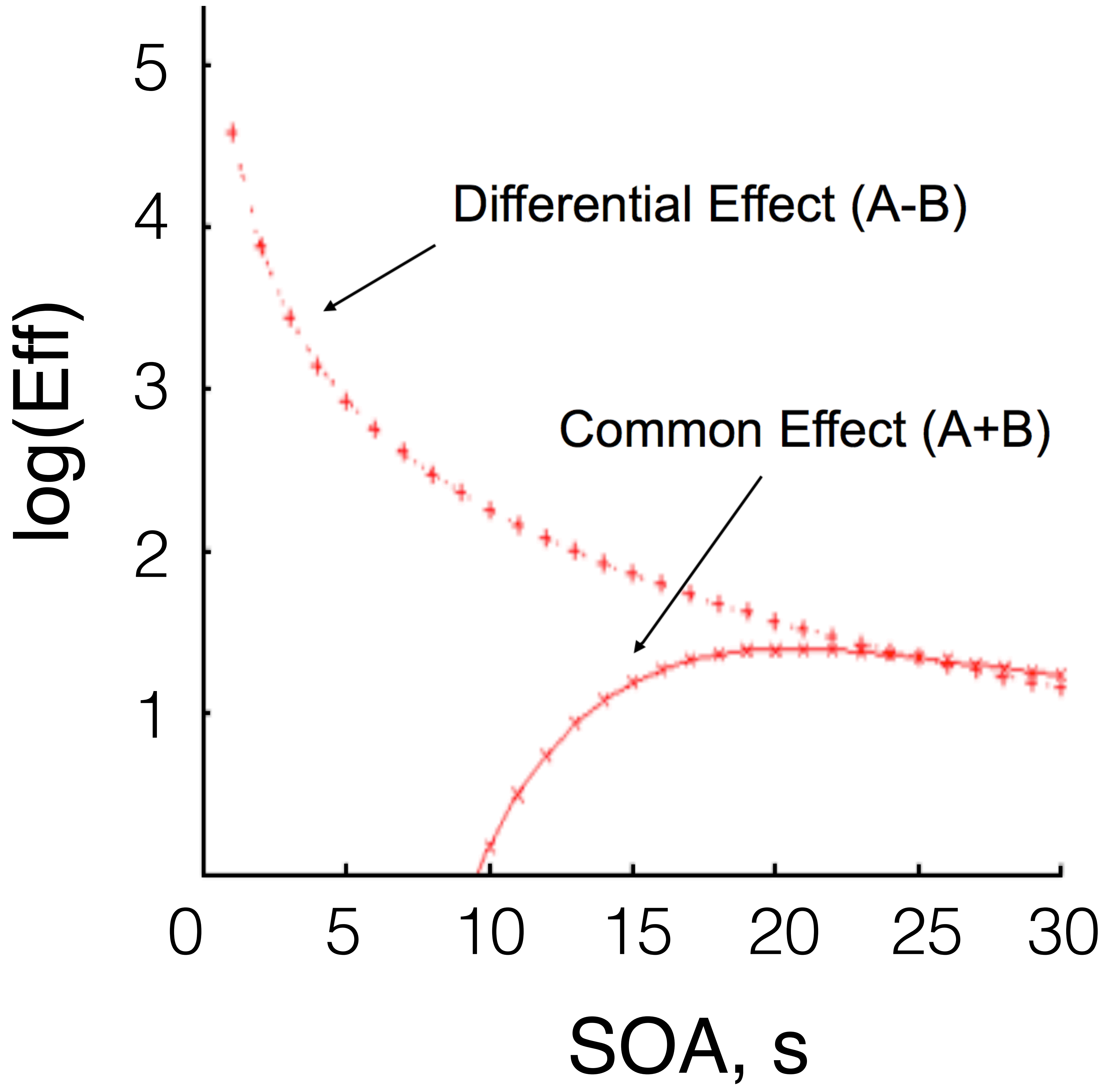
  - SOA_{min} Minimum SOA
  - *p(t)* Probability of event at each SOA_{min}

- With *n* event-types $p_i(\boldsymbol{h})$ is a *n* x n Transition Matrix

- Example: Randomized AB

	A	B
A	**0.5**	**0.5**
B	**0.5**	**0.5**

=> ABBBABAABABAAA…



Design efficiency: Trial sequencing

- Example: Null events

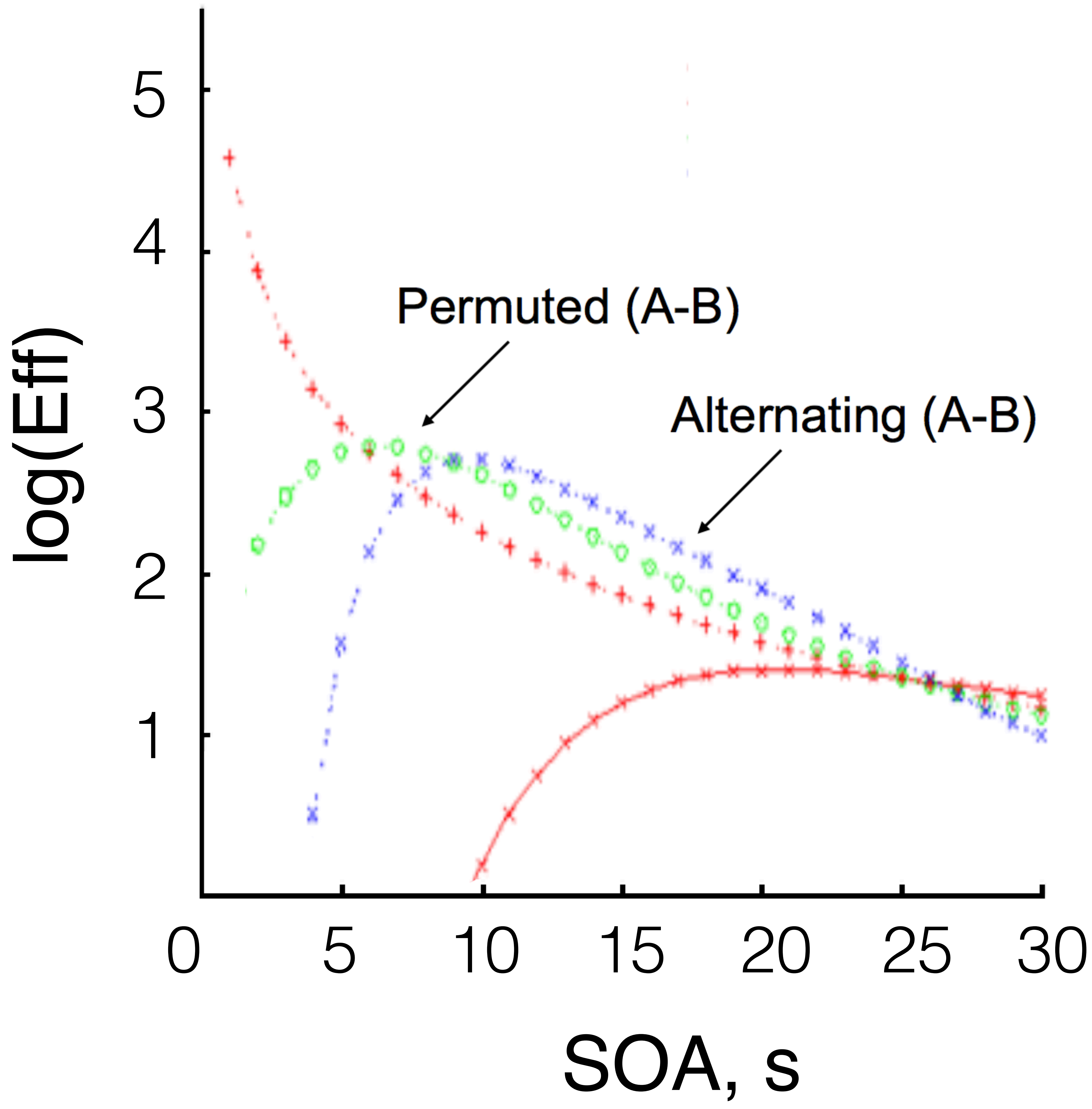
	A	B
A	**0**	**1**
B	**1**	**0**

=> ABABABABABABAB…

- Example: Permuted AB

	A	B
AA	**0**	**1**
AB	**0.5**	**0.5**
BA	**0.5**	**0.5**
BB	**1**	**0**

=> ABBAABABABBA…



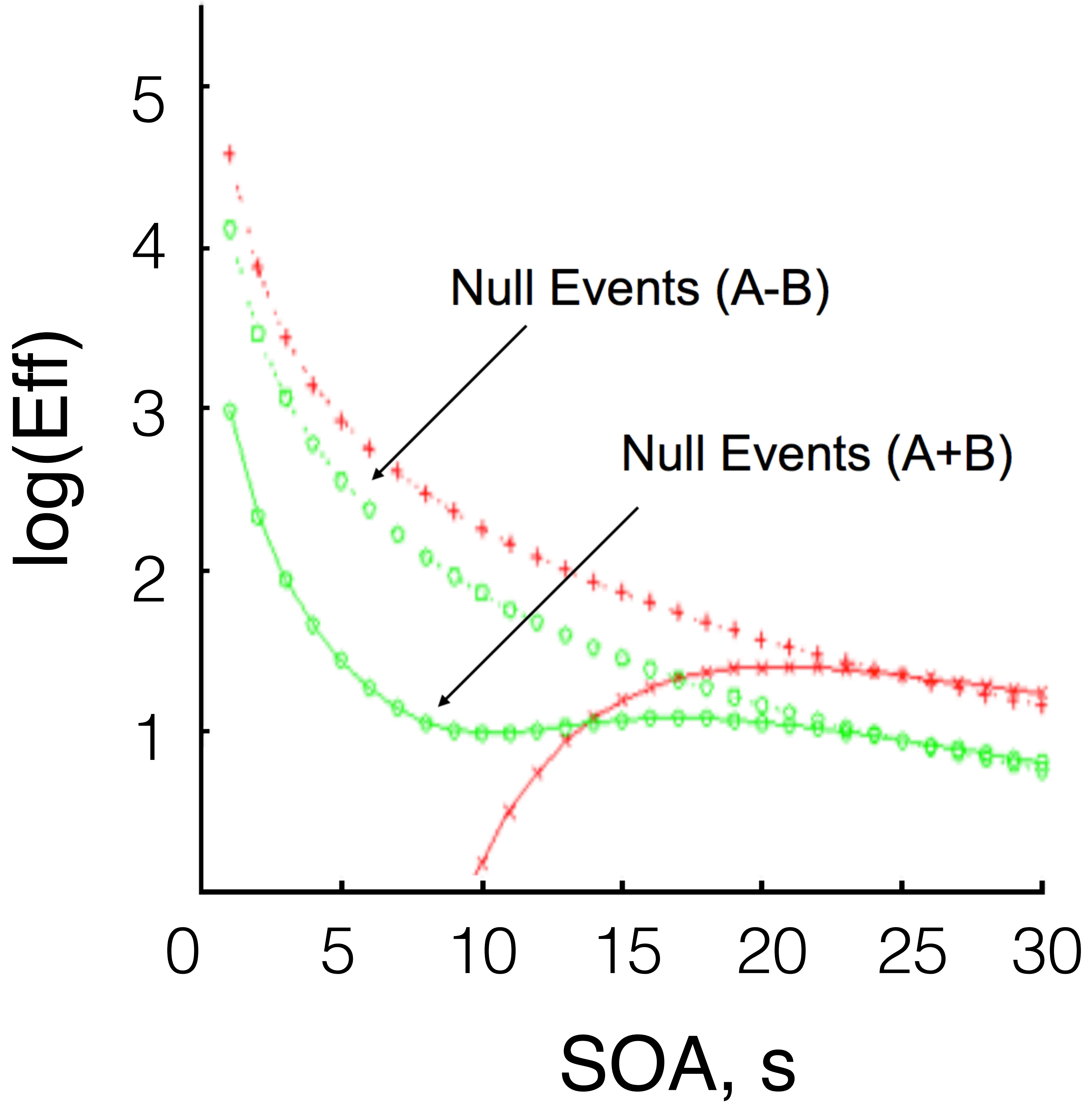
Design efficiency: Trial sequencing

- Example: Null events

	A	B
A	**0.33**	**0.33**
B	**0.33**	**0.33**

=> AB–BAA––B–––ABB…

- Efficient for differential and main effects at short SOA
- Equivalent to stochastic SOA (Null Event like third unmodelled event-type)



◆ Human Brain Mapping 8:109–114(1999) ◆

Optimal Experimental Design for Event-Related fMRI

Anders M. Dale*

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This analysis shows that statistical efficiency falls off dramatically as the ISI gets sufficiently short, if the ISI is kept fixed for all trials.

However, if the ISI is properly jittered or randomized from trial to trial, the efficiency improves monotonically with decreasing mean ISI.

Importantly, the efficiency afforded by such variable ISI designs can be more than 10 times greater than that which can be achieved by fixed ISI designs.

NeuroImage **14,** 1193–1205 (2001)
doi:10.1006/nimg.2001.0880, available online at http://www.idealibrary.com on IDEAL®

Improved Detection of Event-Related Functional MRI Signals Using Probability Functions

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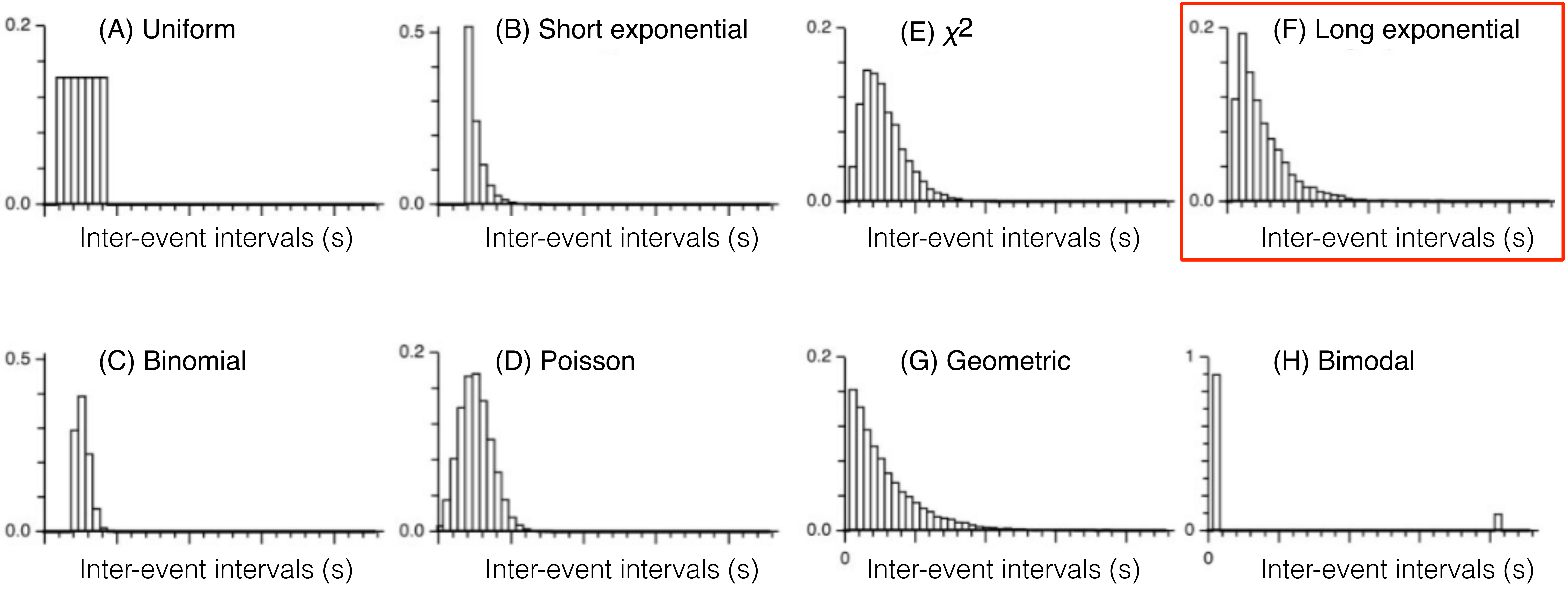
Received September 15, 2000



Probability density functions used for the selection of IEI. (A) Uniform; (B) short-decay exponential; (C) binomial; (D) Poisson; (E) χ^2; (F) long-decay exponential; (G) Geometric; and (H) bimodal distribution. Besides these distributions, IEI were selected by uniform permutation and according to a Latin square design.

Event sequences from the bimodal distribution, like **block designs**, had **the best performance for detection** and the poorest for estimation,

while **high estimation and detectability** occurred for the **long-decay exponential distribution.**

※ Efficiency indicates a measure of the expected accuracy of the estimator.

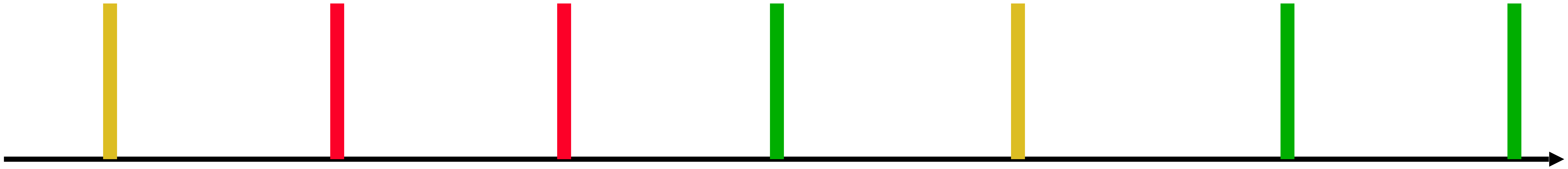
Design efficiency: Conclusion

- Optimal design for one contrast may not be optimal for another
- Blocked designs generally most efficient (with short SOAs, given optimal block length is not exceeded)
- However, psychological efficiency often dictates intermixed designs, and ofter also sets limits on SOAs
- With randomized designs, optimal SOA for differential effect (A-B) is minimal SOA (>2 seconds, and assuming no saturation), whereas optimal SOA for main effect (A+B) is 16-20s
- Inclusion of null events improves efficiency for main effect at short SOAs (at cost of efficiency for differential effects)
- If ordered constrained, intermediate SOAs (5-20s) can be optimal
- If SOA constrained, pseudo randomized designs can be optimal (but may introduce context-sensitivity)

Rapid-Presentation Event-Related Design for fMRI

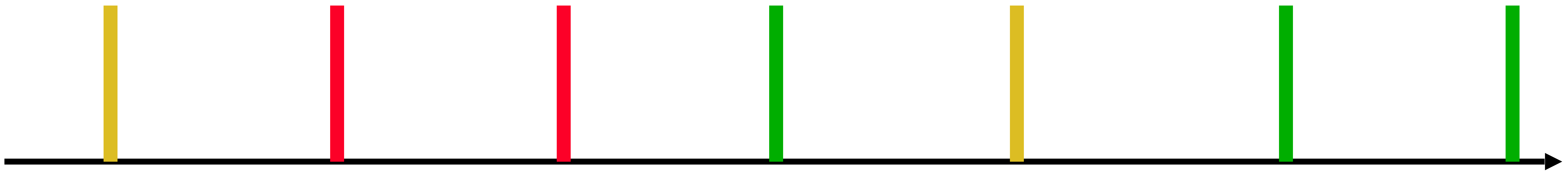
Reference) Rapid-Presentation Event-related Design for fMRI — Douglas N. Greve

Event vs Event Type



- Three Event Types (yellow, red, green)
- Number of Events (Repetitions) per Event Type (Yellow: 1, Red: 2, Green: 3)
- Two events belong to the same *Event Type* if, by hypothesis, they have the same response (violations are treated as noise).
- Event Type = Condition = Trial Type = Explanatory Variable
- Event = Stimulus = Trial

Event Schedule

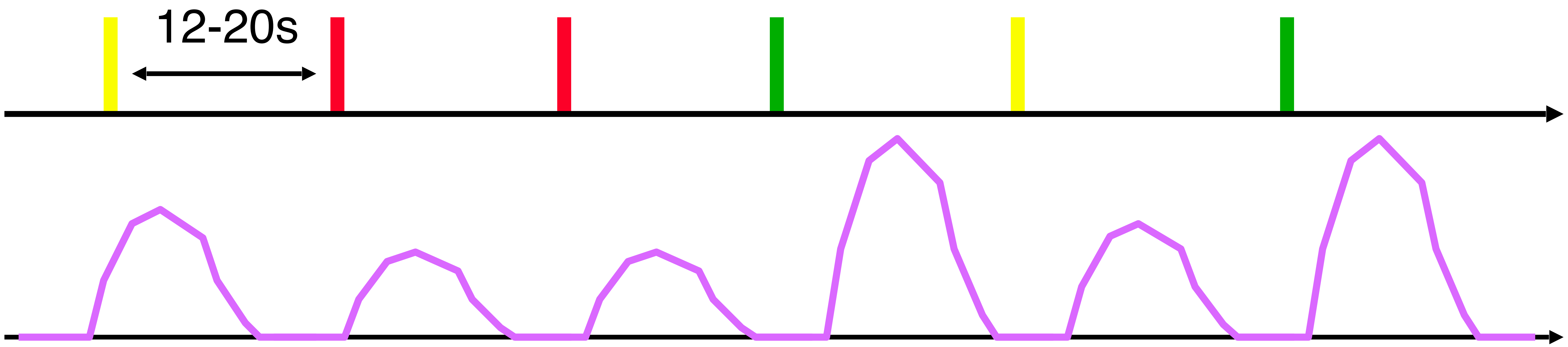


- Description of which event is presented when

time	code	duration	label
4.0	2	4	yellow
20.0	1	2	red
36.0	1	2	red
52.0	3	6	green

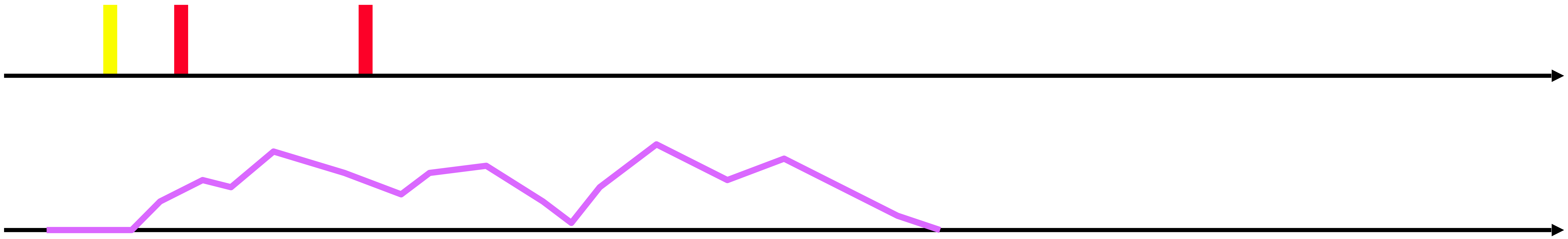
- Time is the accumulated time since onset of scanning run
- Code unique numeric id
- Output of optseq

Fixed-Interval Event-Related



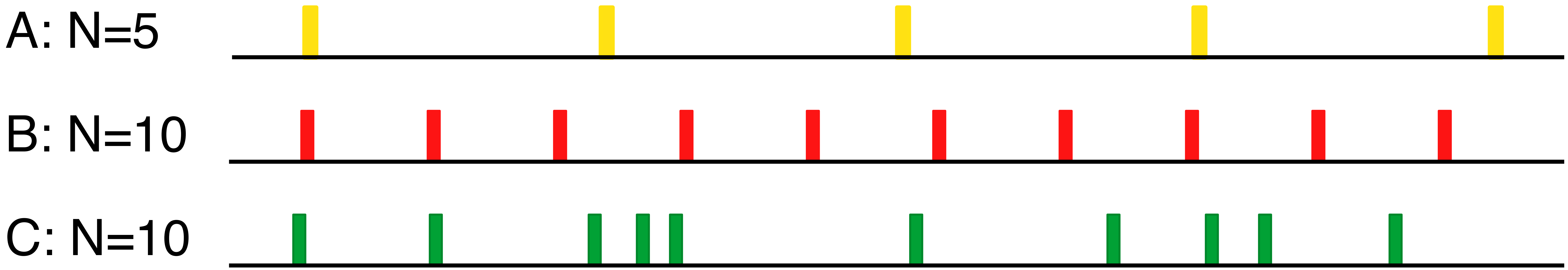
- Push trials apart enough to prevent overlap.
- Interval fixed at minimum is most efficient.
- Random Sequence (Counter-balanced)
- Allows Post-Hoc Stimulus Definition
- Mitigates Habituation, Expectation (?), and Set
- Inflexible/Inefficient/Boring
- Good if limited by number of stimuli (not scanning time)

Rapid-Presentation Event-Related



- Closely Spaced Trials (Overlap!)
- Raw signal uninterpretable
- Random Sequence and Schedule
- Highly resistant to habituation, set, and expectation
- Jitter = "Random" Inter-Stimulus Interval (ISI/SOA)

Scheduling and Efficiency



- Efficiency is statistical power/SNR/CNR per acquisition
- Efficiency increases with N (number of observations)
- Efficiency decreases with overlap
- Efficiency increases with differential overlap
- Choose schedule with optimum efficiency ***before*** scanning

Mathematical Concepts

$$y = X\beta + n$$

Forward Model
(X = design matrix)

$$\hat{\beta} = \left(X^T X\right)^{-1} X y$$

Inverse Model

$$\varepsilon = y - \hat{y} = y - X\hat{\beta}$$

Residual Error

$$\gamma = C\hat{\beta}$$

Contrast, Contrast Vector

$$t_{DOF} = \frac{\gamma}{\sigma_{\varepsilon}^{2}(C(X^{T}X)^{-1}C^{T})}$$

t-statistics

$$\text{eff} = \frac{1}{\text{trace}(C(X^{T}X)^{-1}C^{T})}$$

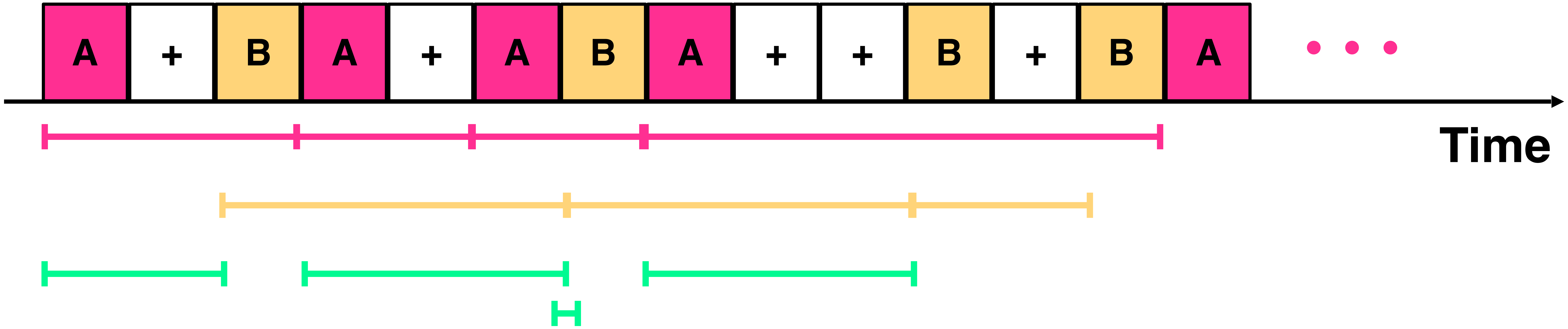
Efficiency

$$VRF_i = \frac{1}{d_i}, \ d = \text{diag}(C(X^{T}X)^{-1}C^{T})$$

Variance Reduction Factor

Where does jitter come from?

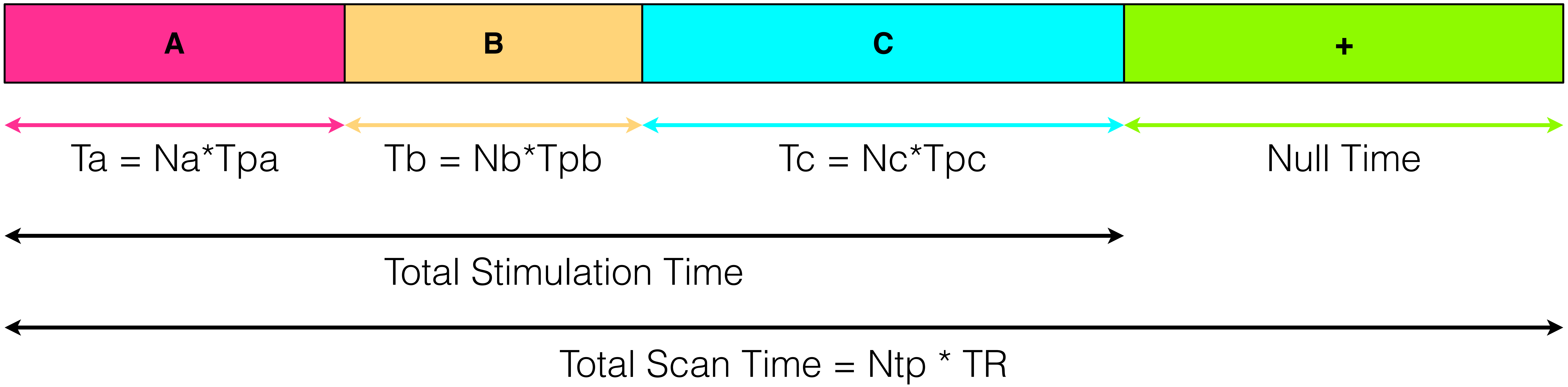
- “Null” condition — fixation cross or dot
- By hypothesis, no response to null
- Insert random amounts of null between task conditions
- Differential ISI = Differential Overlap



Design Parameters (optseq2)

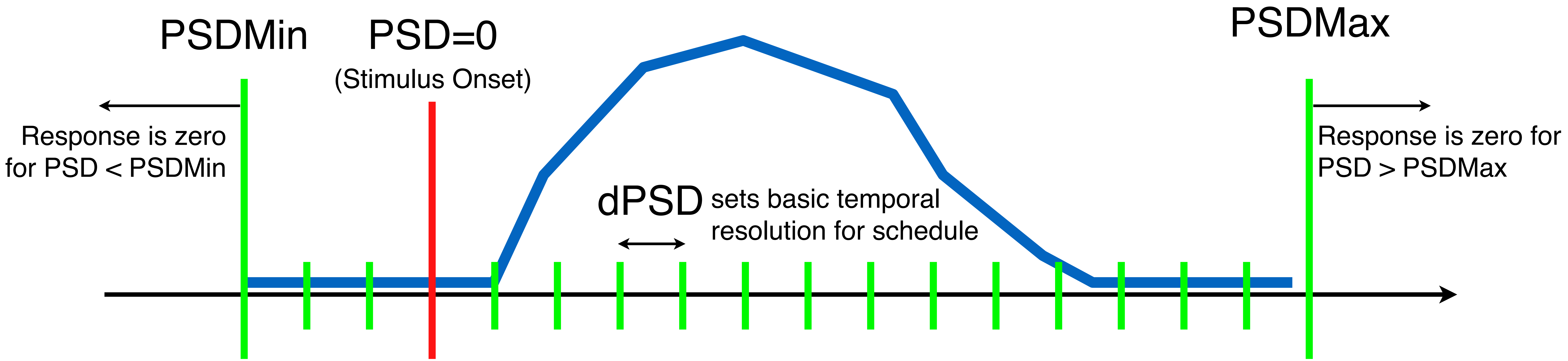
- TR – time between volume acquisition (temporal resolution).
- Ntp – number of time points (TRs, frames, volumes, …)
- Nc – number of event types (conditions)
- Npc – number of events/repetitions of each event type (can vary across event types)
- Tpc – duration of each event type (can vary across event types)
- Schedule – event onset time and identity
- Event Response Model – FIR Post-Stimulus Delay Window (needed for optimization)

Time Constraints



- Total Stimulation Time Cannot Exceed Total Scan Time
- How much Null Time is needed? Rule of thumb: same as any other task condition (or the average of the task conditions).

Event Response Model (FIR)



- PSD: Post-Stimulus Delay
- PSD Window should be long enough to capture response
- Response can be anything in between (FIR model)
- DOF Constraint: Nbeta = nPSD*Nc < Ntp

Optseq2 Parameters

- Getting help: optseq2 --help
- Search termination criteria: nsearch/tsearch
- Output files (and format)
- Optimizing over number of repetitions
- Nuisance variables (polynomial drift terms)
- Cost Functions
- First-Order Counter-Balancing Pre-optimization
- http://surfer.nmr.mgh.harvard.edu/optseq
- To come: contrasts and non-FIR

Rapid-Presentation Properties

- Efficient (not as efficient as blocked)
- Can distinguish responses despite overlap
- Highly resistant to habituation, set, and expectation
- Flexible timing (Behavioral, EEG, MEG)
- Linear overlap assumption
- Analysis: Selective Averaging/Deconvolution (GLM)
- Schedule Optimization Tool (optseq)

Optseq2 실습

Welcome to the Optseq Home Page

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

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'.

Download the Linux version of optseq2. ← 리눅스용
Download the Linux x86_64 version of optseq2.
Download the MacOSX-PowerPC version of optseq2.
Download the MacOSX-Intel version of optseq2. ← 맥용
Download the Cygwin version of optseq2. ← 윈도우 32비트 전용?

Optseq 실행하기 (MacOX)

- 맥에서는 optseq를 다운로드 받고 optseq 파일에 실행 권한을 줘야 함.
  만약 다운로드 받은 optseq 파일이 Downloads 폴더에 있다면, 터미널에서 다음과 같은 명령어를 통해서 optseq 파일에 실행 권한을 부여할 수 있음.

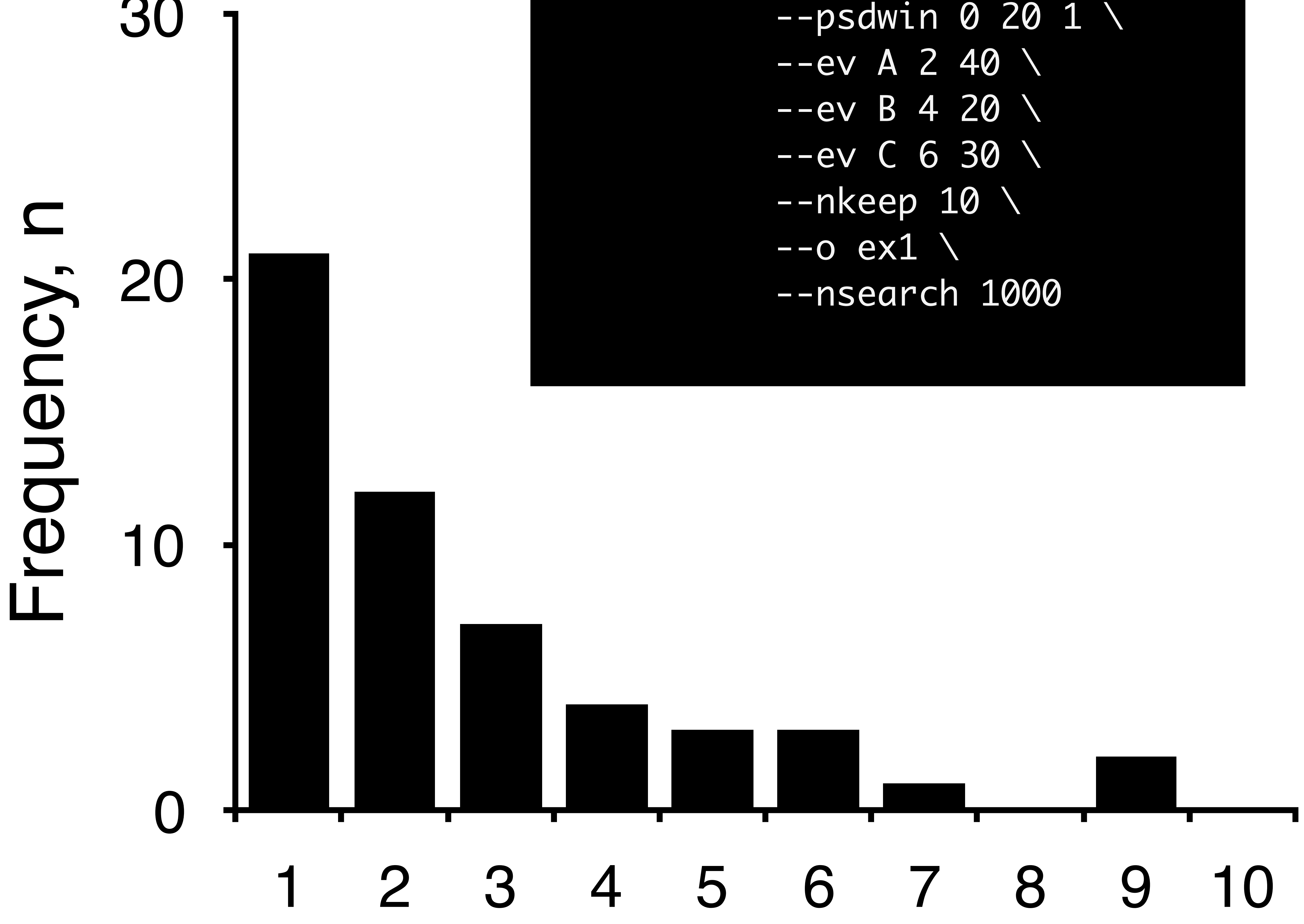
실행 권한이 없는 상태

```
skyeong@MacbookPro ~/Downloads>ls -al ~/Downloads/optseq2
-rw-r--r--@ 1 skyeong  staff   1.4M Apr  6 14:13 optseq2
```

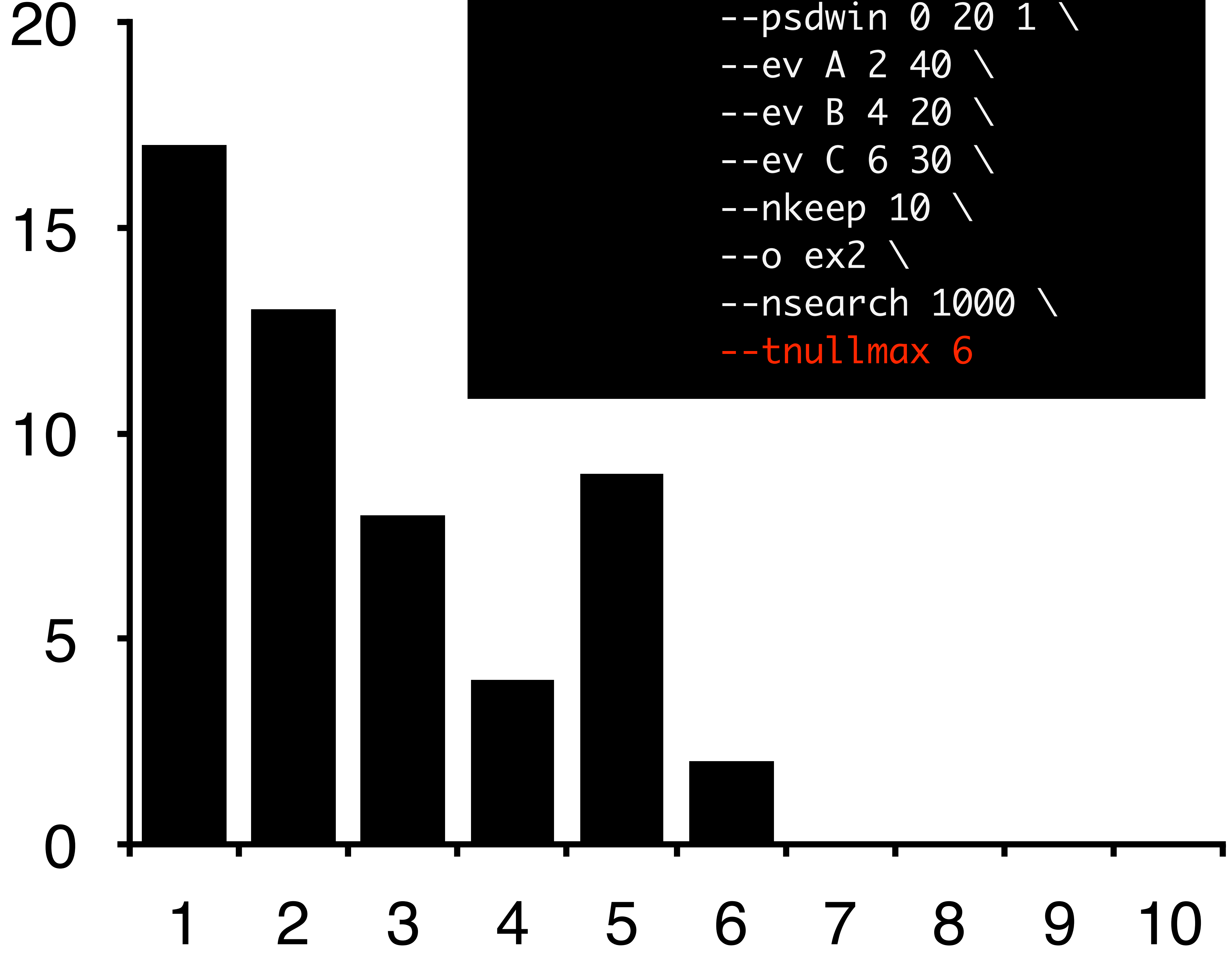
실행 권한이 **있는** 상태

```
skyeong@MacbookPro ~/Downloads>chmod +x ~/Downloads/optseq2
skyeong@MacbookPro ~/Downloads>ls -al ~/Downloads/optseq2
-rwxr-xr-x@ 1 skyeong  staff   1.4M Apr  6 14:13 optseq2
```

Examples of optseq2




```
./optseq2 --ntp 240 --tr 2 \
          --psdwin 0 20 1 \
          --ev A 2 40 \
          --ev B 4 20 \
          --ev C 6 30 \
          --nkeep 10 \
          --o ex1 \
          --nsearch 1000
```



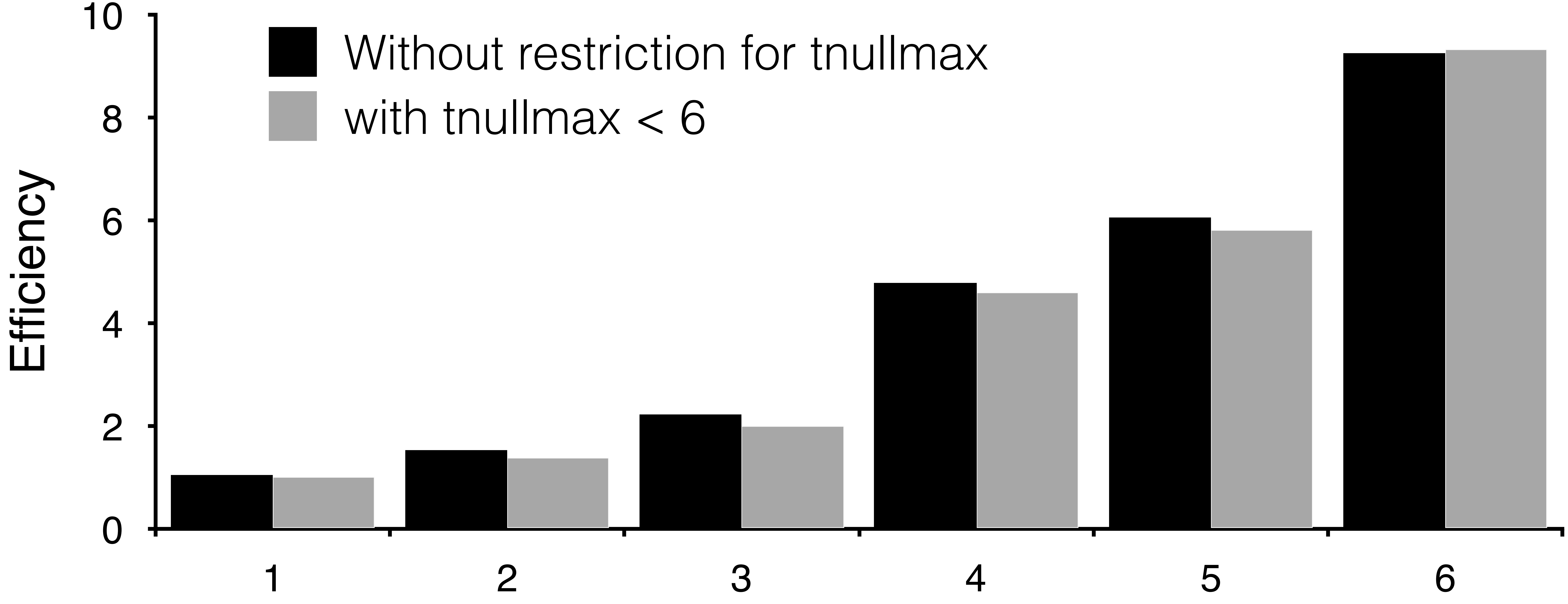

```
./optseq2 --ntp 240 --tr 2 \
          --psdwin 0 20 1 \
          --ev A 2 40 \
          --ev B 4 20 \
          --ev C 6 30 \
          --nkeep 10 \
          --o ex2 \
          --nsearch 1000 \
          --tnullmax 6
```

Examples of optseq2

```
skyeong$optseq2 --ntp 240 --tr 2 \
                --psdwin 0 20 2 \
                --ev A 2 40 \
                --ev B 4 20 \
                --ev C 6 30 \
                --nkeep 10 \
                --o ex2 \
                --nsearch 1000
```

```
skyeong$optseq2 --ntp 240 --tr 2 \
                --psdwin 0 20 2 \
                --ev A 2 40 \
                --ev B 4 20 \
                --ev C 6 30 \
                --nkeep 10 \
                --o ex3 \
                --nsearch 1000 \
                --tnullmax 6
```

Long tail vs. tnullmax<6



Computate Efficiency

- **SPM을 연동하지 않고 계산하는 방법**
  간단하고 빠르다.
  Parametric modulation 등에 대한 efficiency 계산은 안됨

- **SPM과 연동하여 계산하는 방법**
  1st-level 에 모델을 넣어서 계산하기 때문에 (fake) fMRI 데이터가 필요함
  Parametric modulation 에 대한 contrast에 대해서도 efficiency를 계산할 수 있음. 하지만, 프로그램이 조금 복잡하고 시간이 오래 걸림

Design efficiency: Conclusion

- Optimal design for one contrast may not be optimal for another
- Blocked designs generally most efficient (with short SOAs, given optimal block length is not exceeded)
- However, psychological efficiency often dictates intermixed designs, and ofter also sets limits on SOAs
- With randomized designs, optimal SOA for differential effect (A-B) is minimal SOA (>2 seconds, and assuming no saturation), whereas optimal SOA for main effect (A+B) is 16-20s
- Inclusion of null events improves efficiency for main effect at short SOAs (at cost of efficiency for differential effects)
- If ordered constrained, intermediate SOAs (5-20s) can be optimal
- If SOA constrained, pseudo randomized designs can be optimal (but may introduce context-sensitivity)

Efficiency 계산 실습

실습 자료 디렉토리 설명

- **optseq2**
  맥용 optseq2 프로그램이 있는 폴더
- **optseq2_output**
  optseq2를 이용하여 만든 event sequences
- **eff_without_spm**
  SPM 없이 efficiency를 계산하는 Matlab 프로그램. 비교적 빠르고 단간하게 contrast 별로 efficiency를 계산할 수 있음.
- **eff_with_spm**
  SPM을 이용하여 efficiency를 계산하는 Matlab 프로그램. Parametric modulation contrast에 대한 efficiency 계산도 가능함. 시간이 오래걸리는 단점이 있음.
- **utils**
  실습을 위해서 필요한 utilities를 모아둔 폴더

Remaining Topics

Group-level statistical inference (2nd-level) in SPM12

Analyzing fMRI time-courses in SPM12

Psychophysiological interaction in SPM12

Voxel-based morphometry (VBM) in SPM12