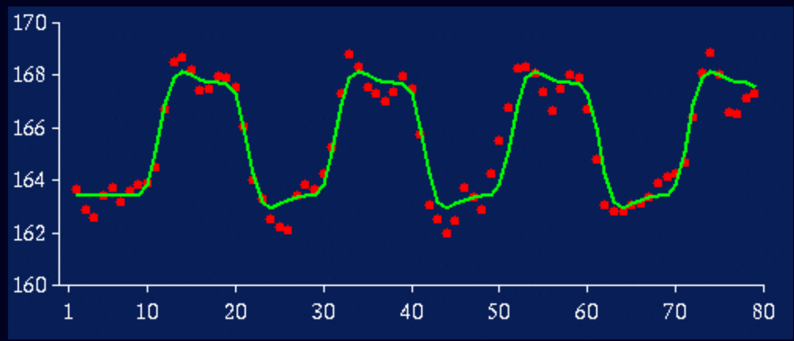
Modelling of hemodynamic timeseries and 2nd-level summary statistics

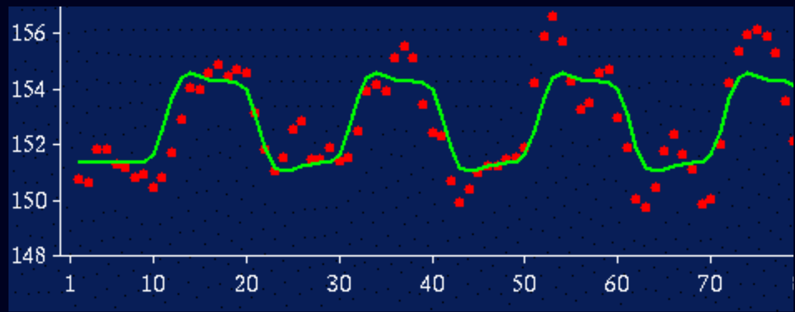
Christian Ruff

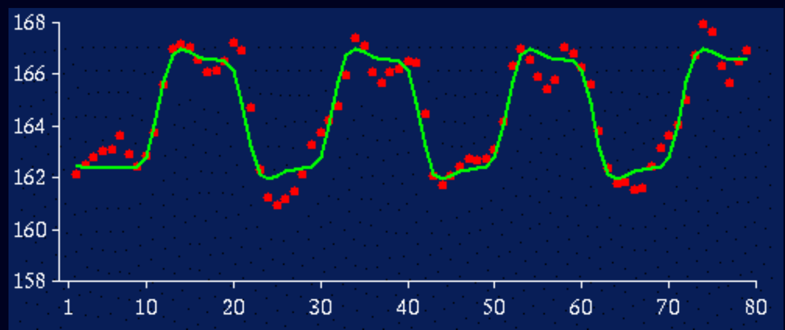
Laboratory for Social and Neural Systems Research
University of Zurich

With thanks to the FIL methods group and Rik Henson

Modelling fMRI timeseries from multiple subjects







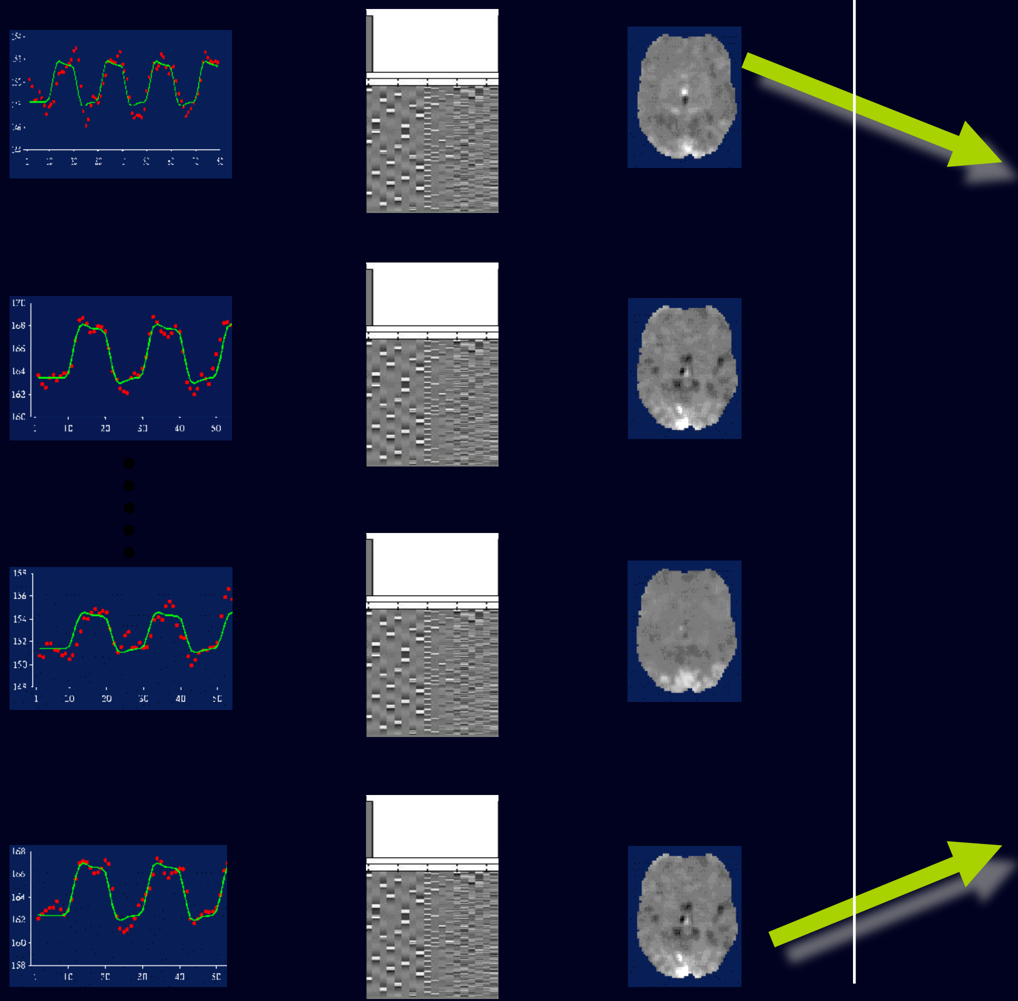
1st Level

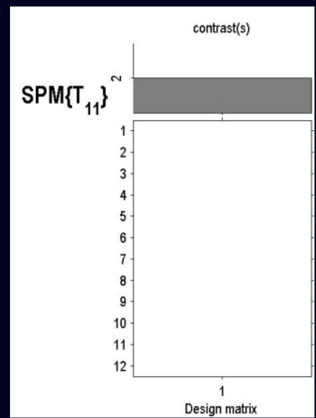
2nd Level

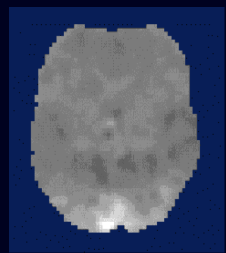
Data

Design matrix

Contrast images

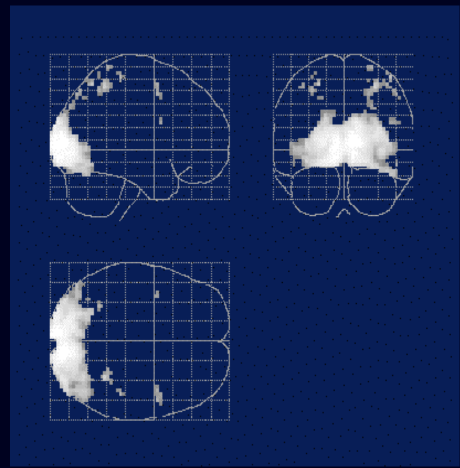






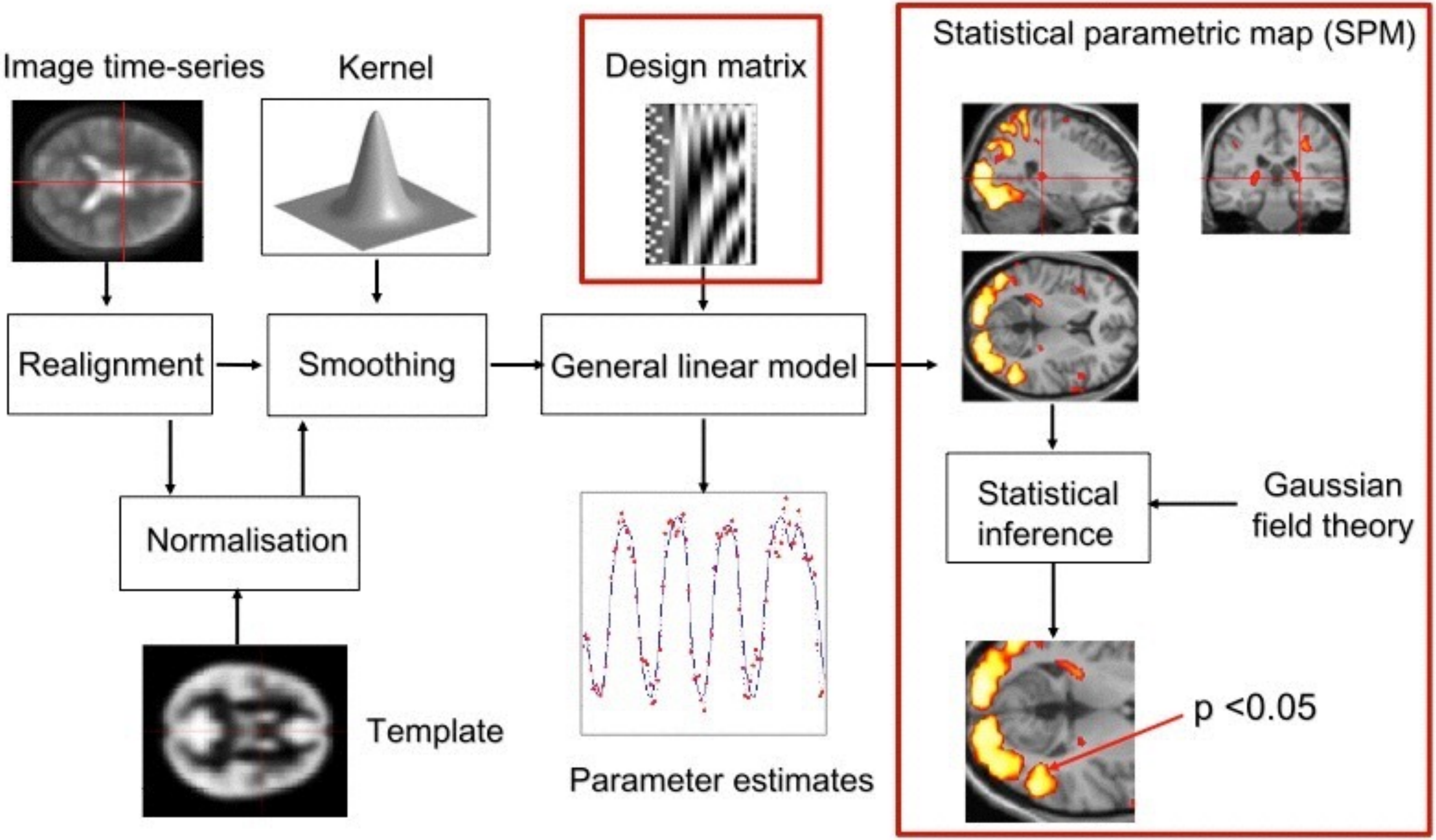
$$t = \frac{c^T \hat{\alpha}}{\sqrt{V\hat{a}r(c^T \hat{\alpha})}}$$

SPM(t)



one-sample t-test
at the second level

Overview of SPM – Event-related fMRI *incl. second level summary statistics*

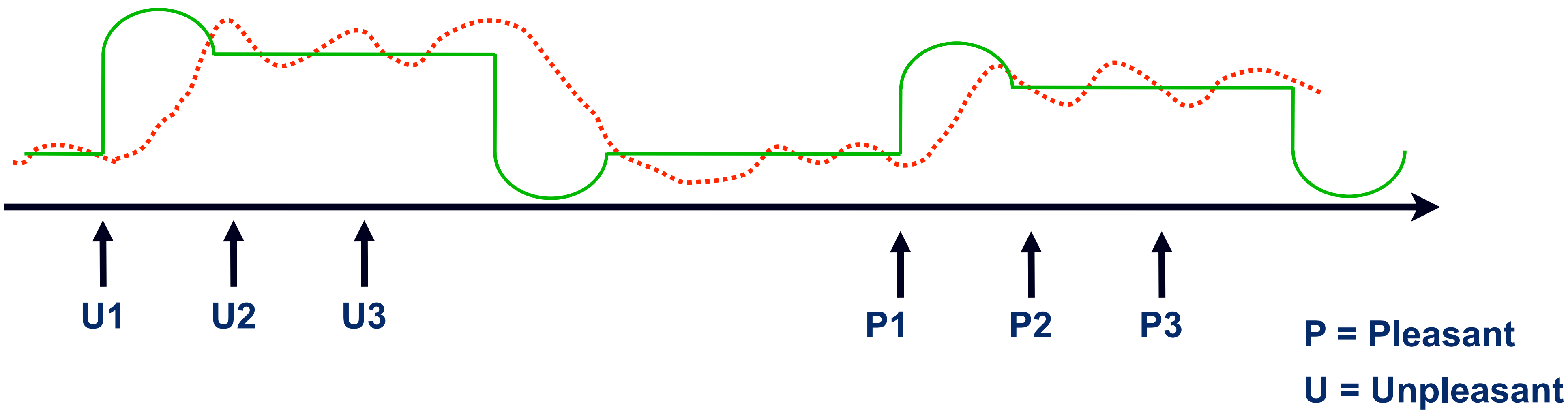


Overview

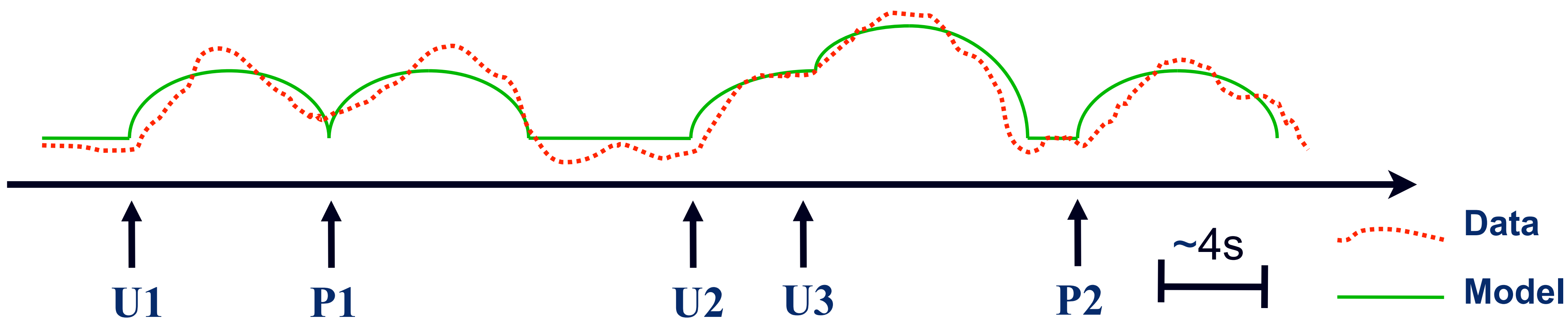
1. 1st level: Blocked vs. event-related designs
2. 1st level GLM: Convolution
3. 1st level GLM: Temporal Basis Functions
4. 1st level GLM: Timing Issues
5. 1st level GLM: Design Optimisation – “Efficiency”
6. 2nd level GLM: Statistical tests

Blocked vs event-related designs

Blocked designs examine responses to series of similar stimuli

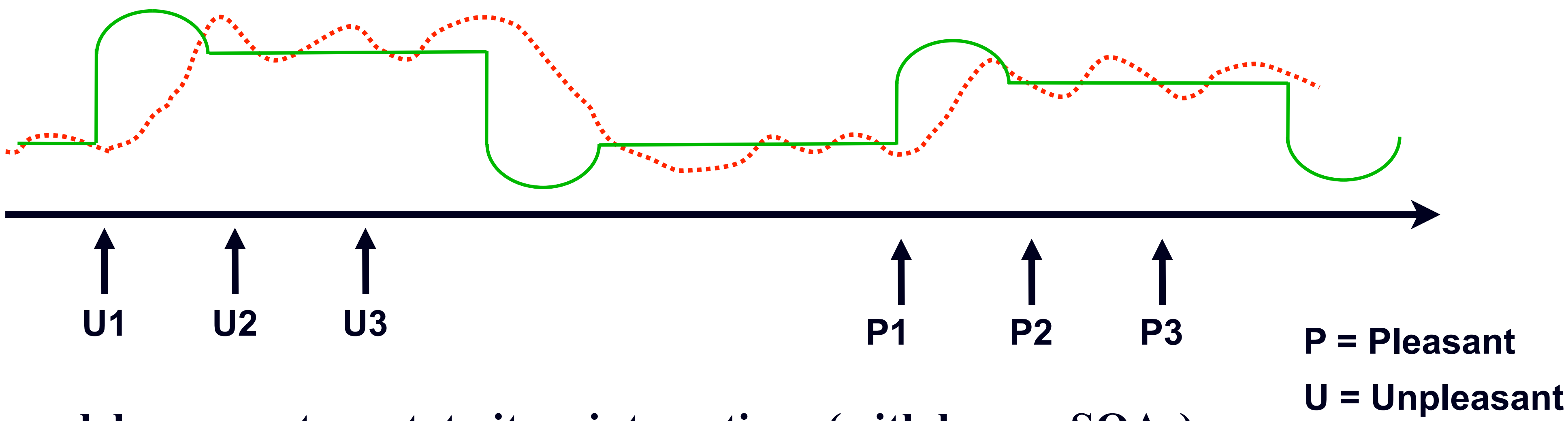


Event-related designs account for response to each single stimulus

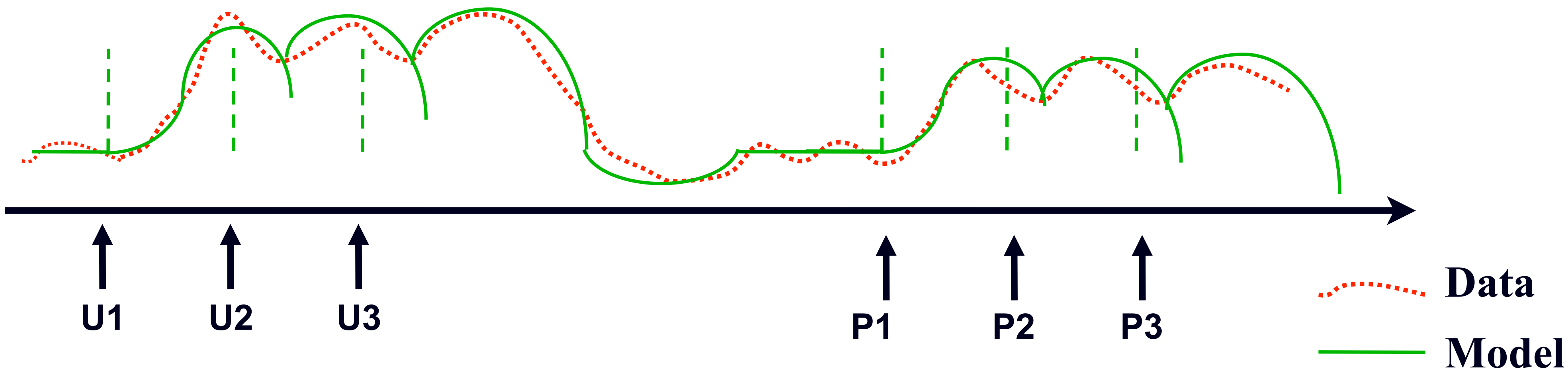


"Epoch" vs "Event" models of blocked designs

"Epoch" model assumes constant neural processes throughout block

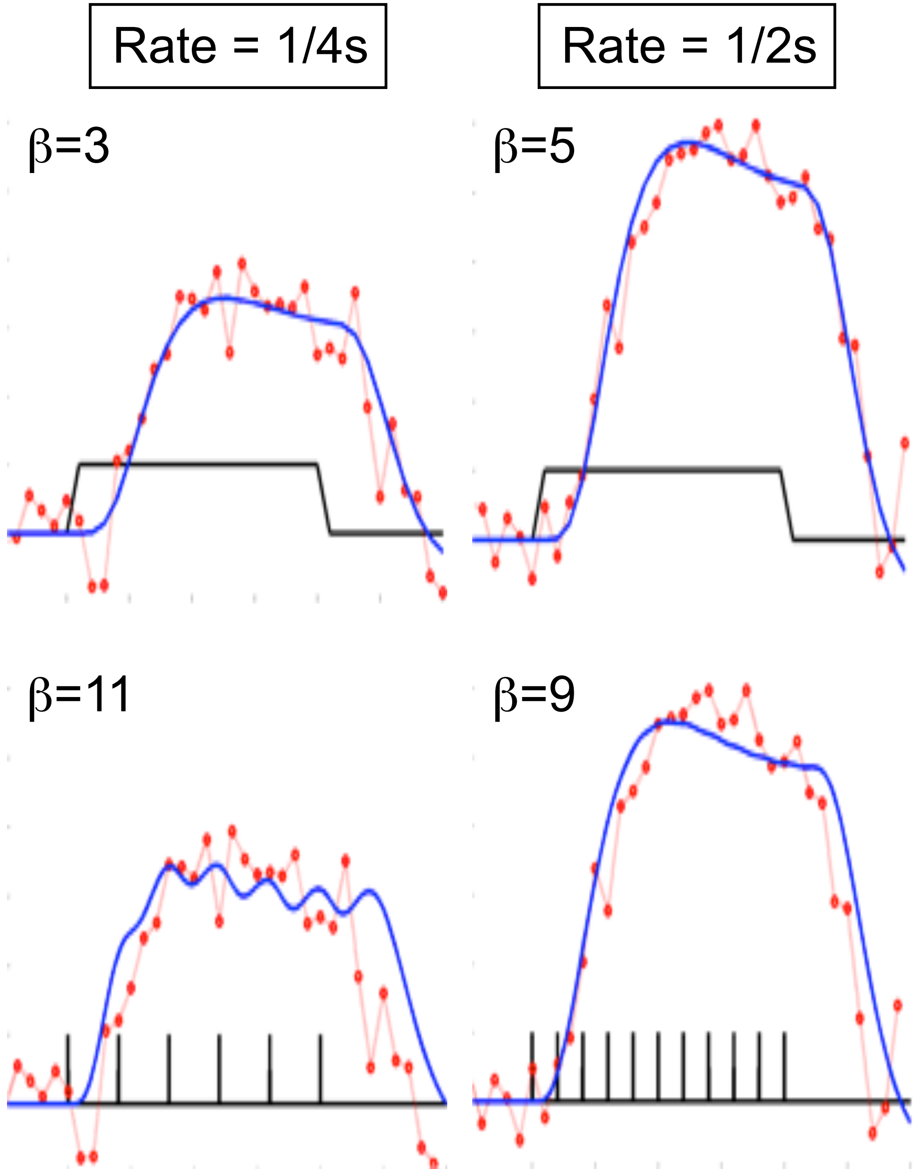


"Event" model may capture state-item interactions (with longer SOAs)



Modeling blocked 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 response per word



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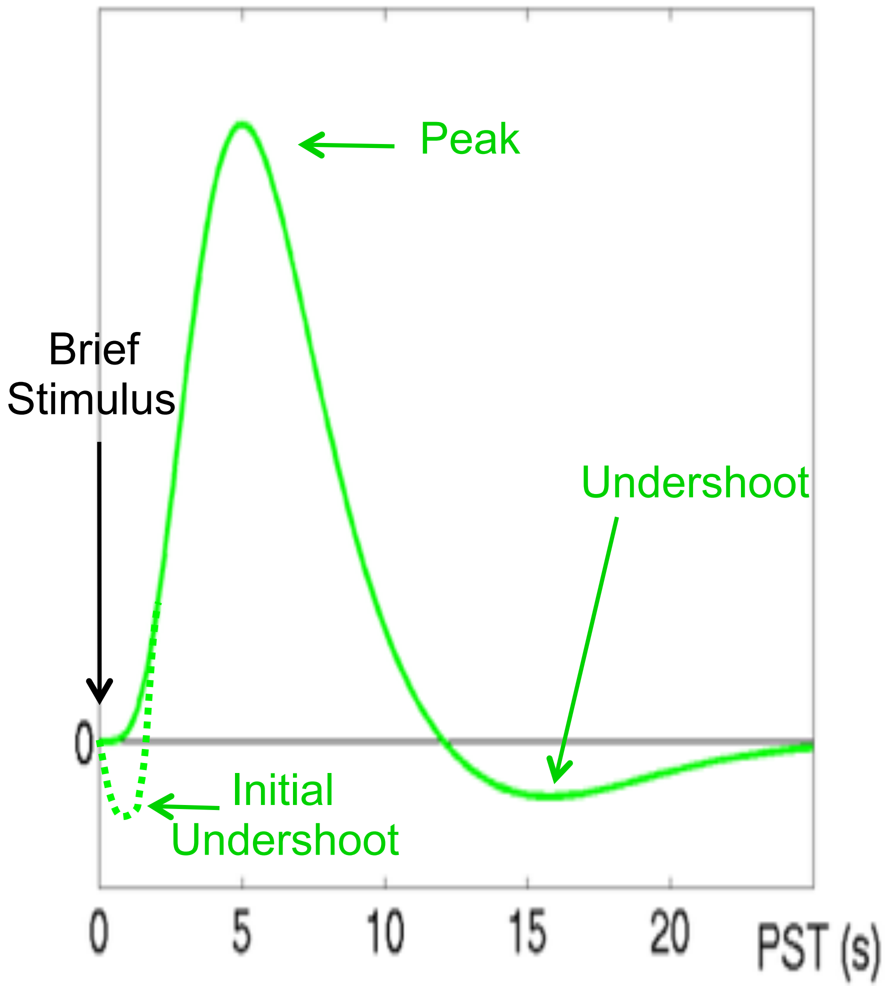
BOLD impulse response

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

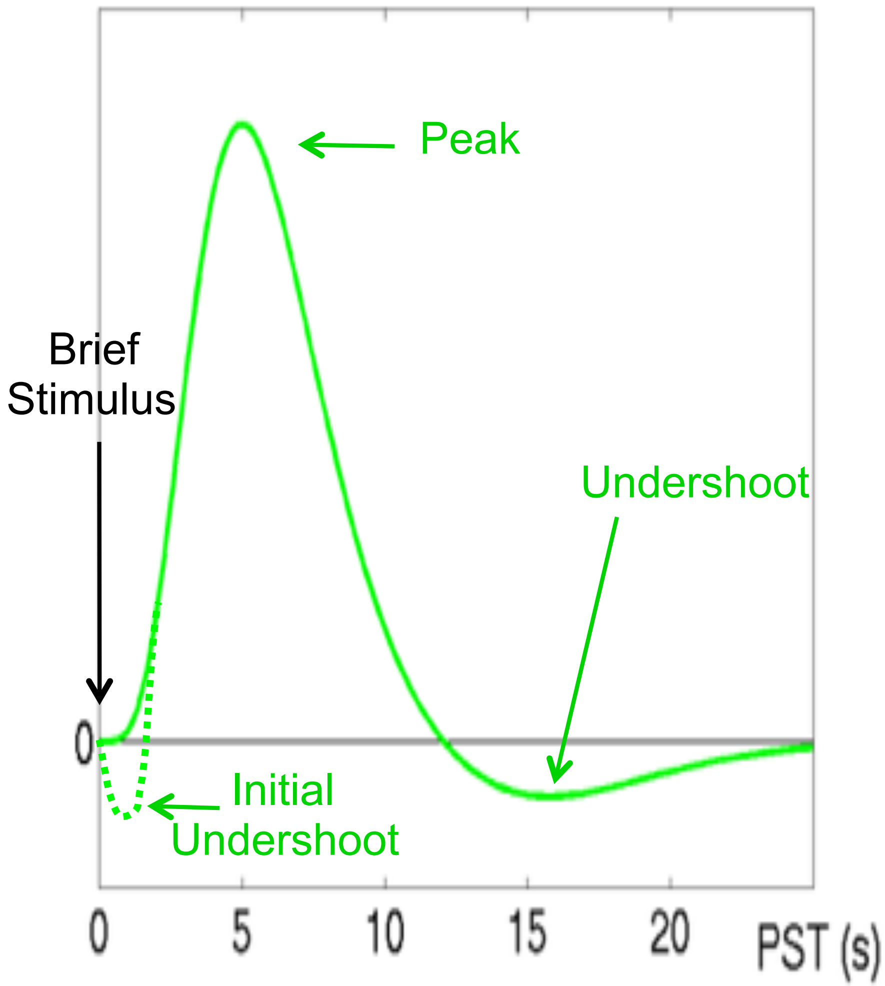


BOLD impulse response

- 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



General Linear (Convolution) Model

GLM for a single voxel:

$$y(t) = u(t) \otimes h(\tau) + \varepsilon(t)$$

$u(t)$ = neural causes (stimulus train)

$$u(t) = \sum \delta\,(t - nT)$$

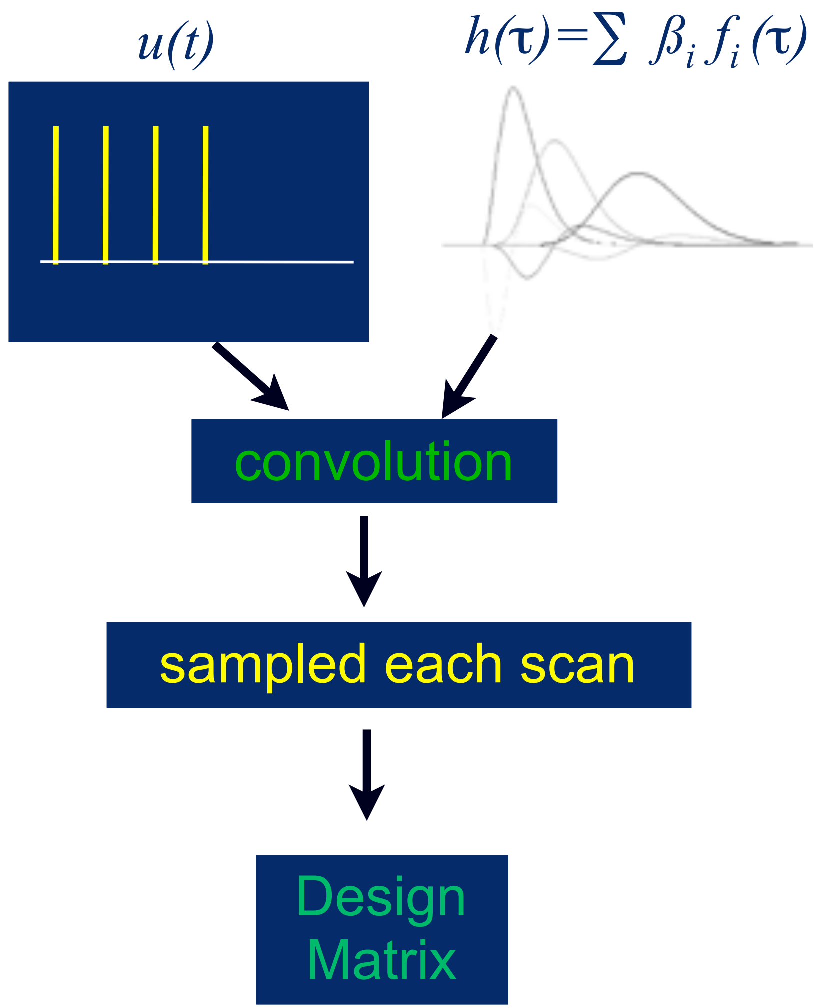
$h(\tau)$ = hemodynamic (BOLD) response

$$h(\tau) = \sum \beta_i\, f_i\,(\tau)$$

$f_i(\tau)$ = temporal basis functions

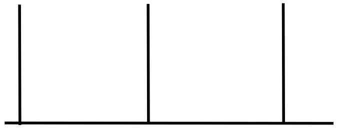
$$y(t) = \sum \sum \beta_i\, f_i\,(t - nT) + \varepsilon(t)$$

$$\boldsymbol{y} = \boldsymbol{X\beta} + \boldsymbol{\varepsilon}$$

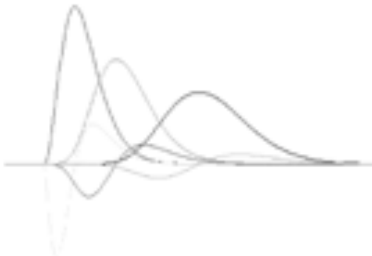


General Linear Model in SPM

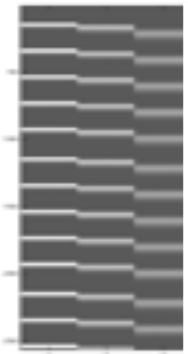
Stimulus
every 20s



Gamma functions $f_i(\tau)$ of
peristimulus time τ
(Orthogonalised)



Sampled every TR = 1.7s
Design matrix, $\mathbf{X}$
$[x(t) \otimes f_1(\tau) \mid x(t) \otimes f_2(\tau) \mid \ldots]$



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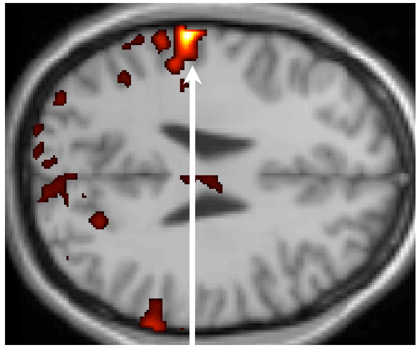

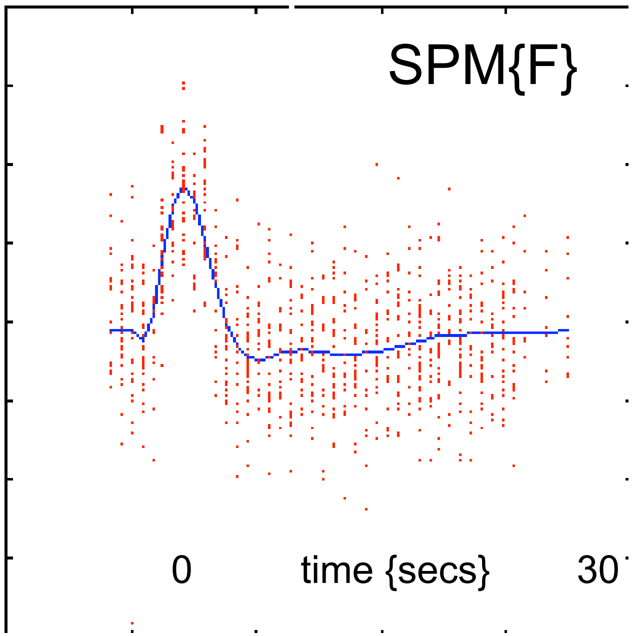

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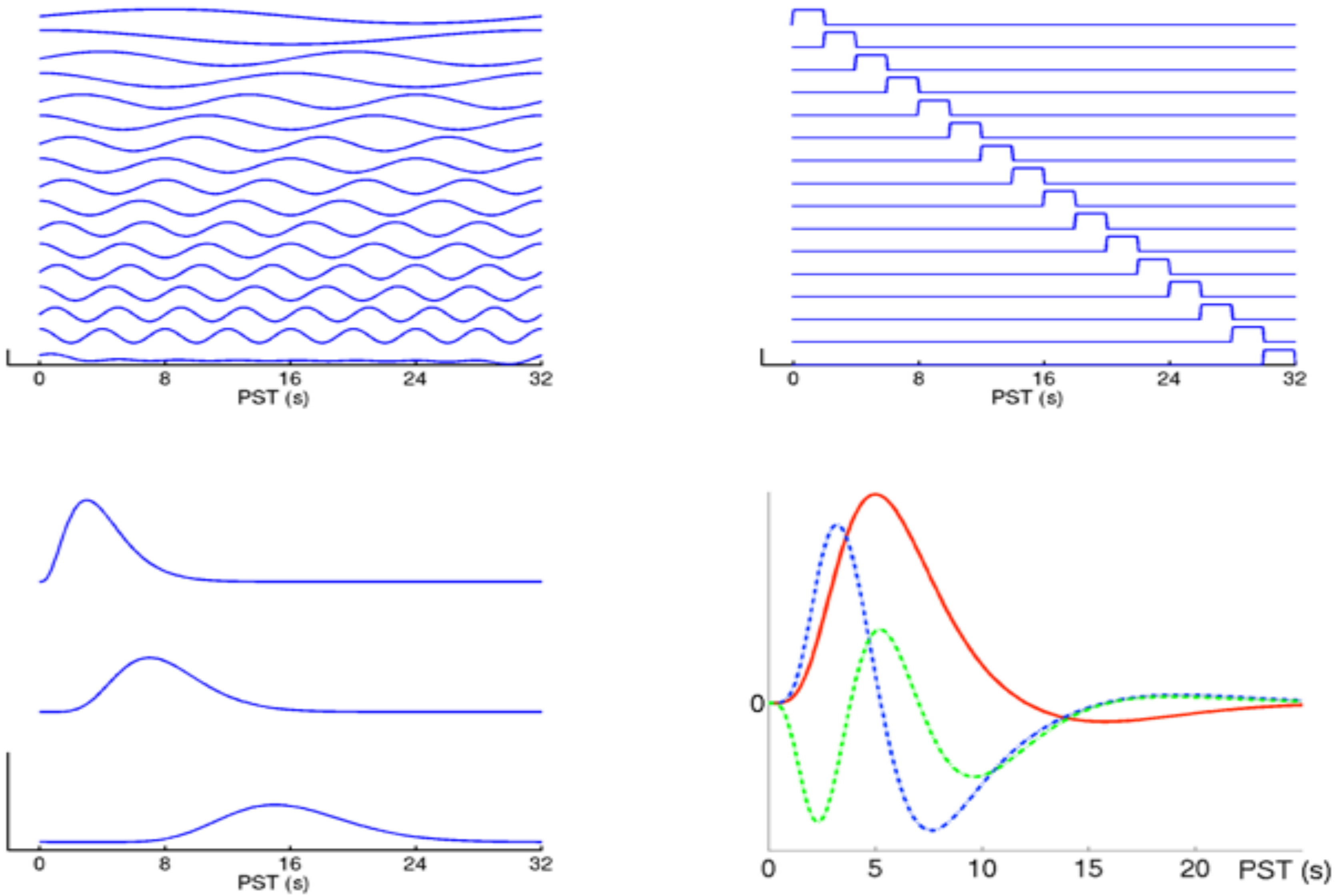
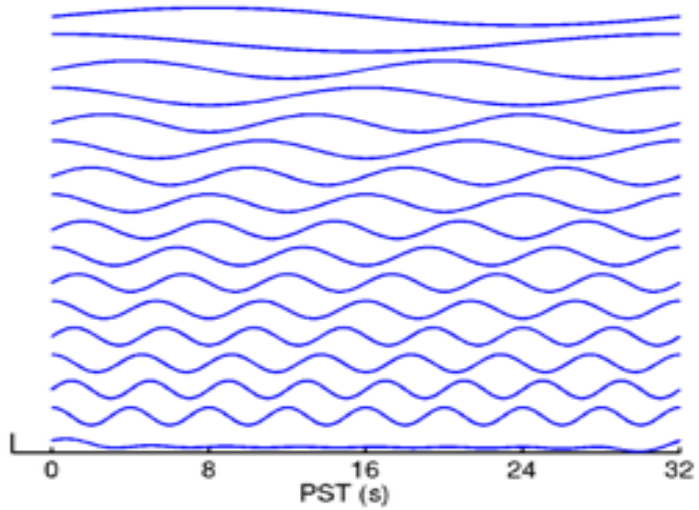
Temporal basis functions

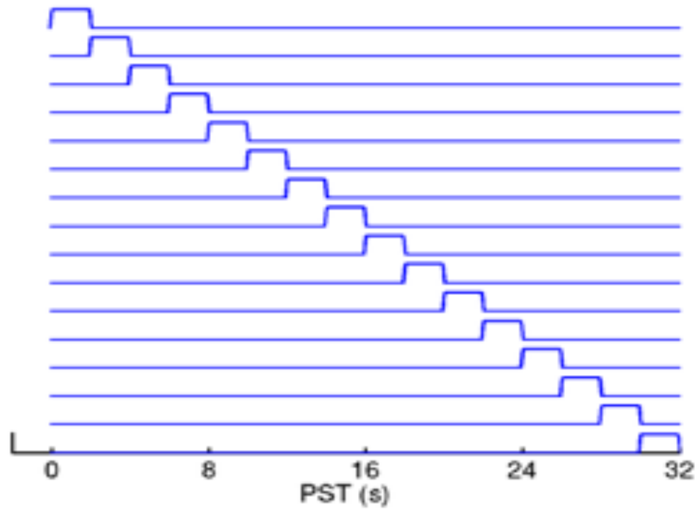


Temporal basis functions

- **Fourier Set**
  - Windowed sines & cosines
  - Any shape (up to frequency limit)
  - Inference via F-test

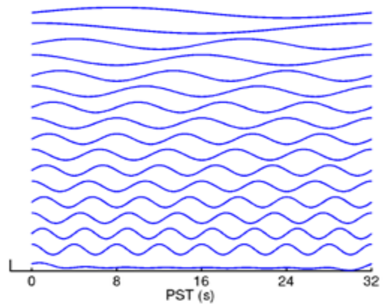


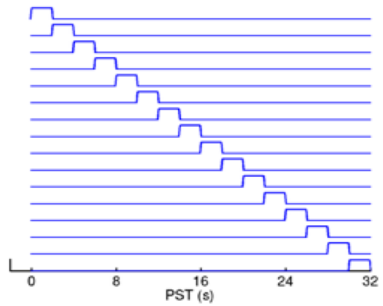
- **Finite Impulse Response**
  - Mini "timebins" (selective averaging)
  - Any shape (up to bin-width)
  - Inference via F-test



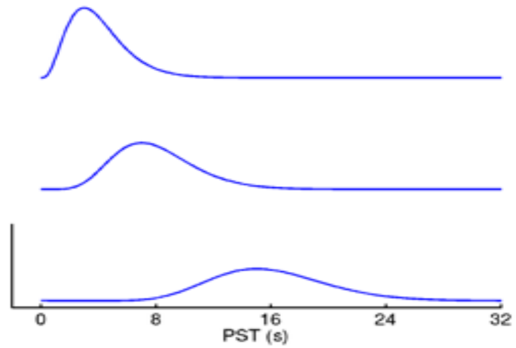
Temporal basis functions

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

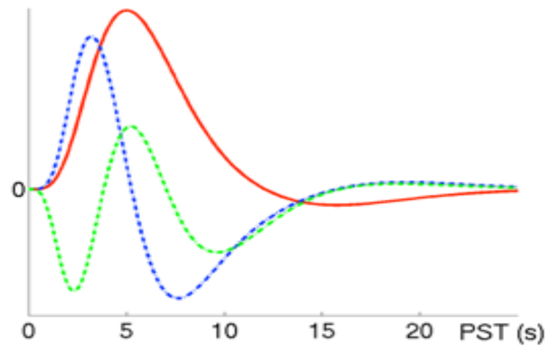




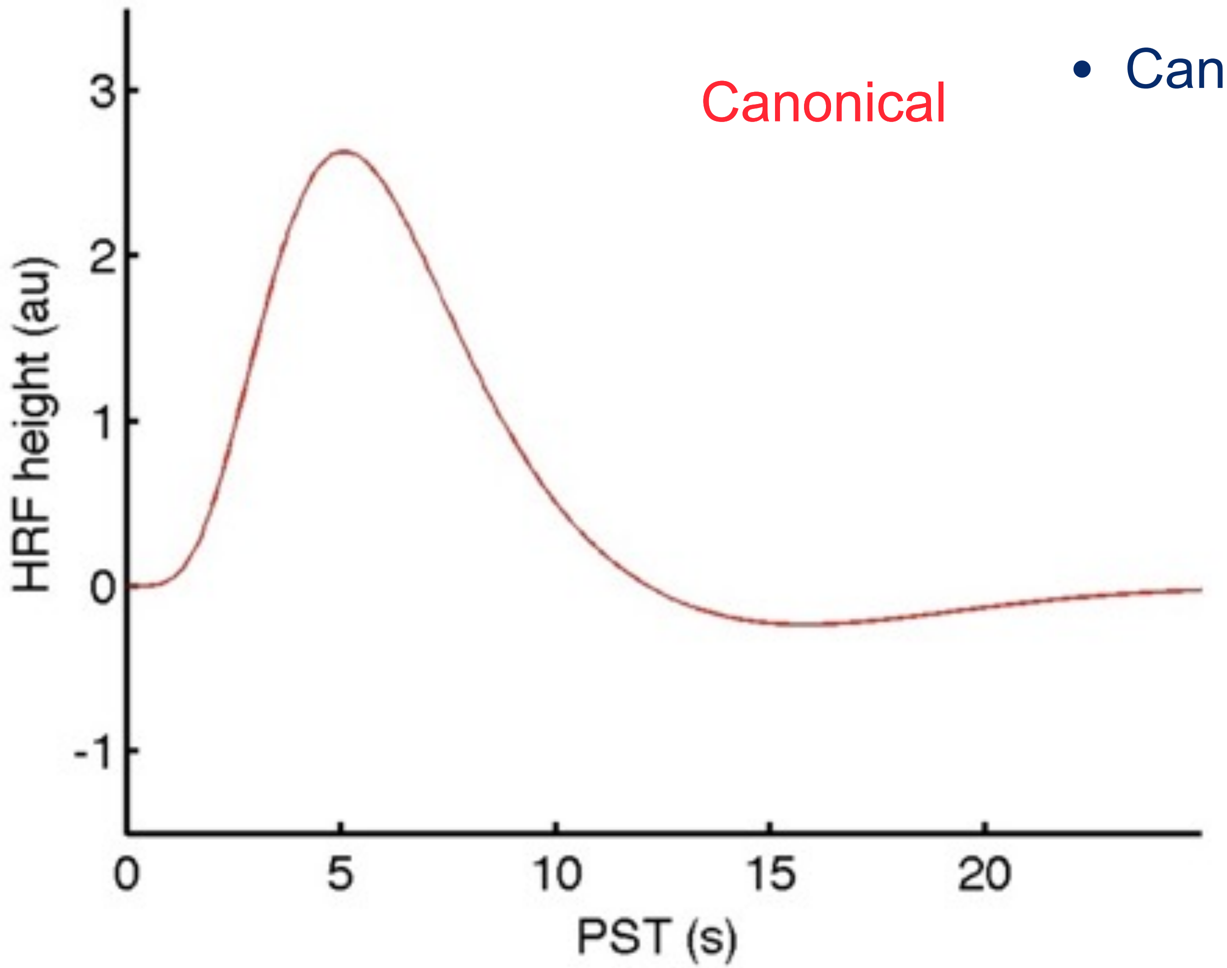
- **Gamma Functions**
  - Bounded, asymmetrical (like BOLD)
  - Set of different lags
  - Inference via F-test



- **"Informed" Basis Set**
  - Best guess of canonical BOLD response
  - Variability captured by Taylor expansion
  - "Magnitude" inferences via t-test…?

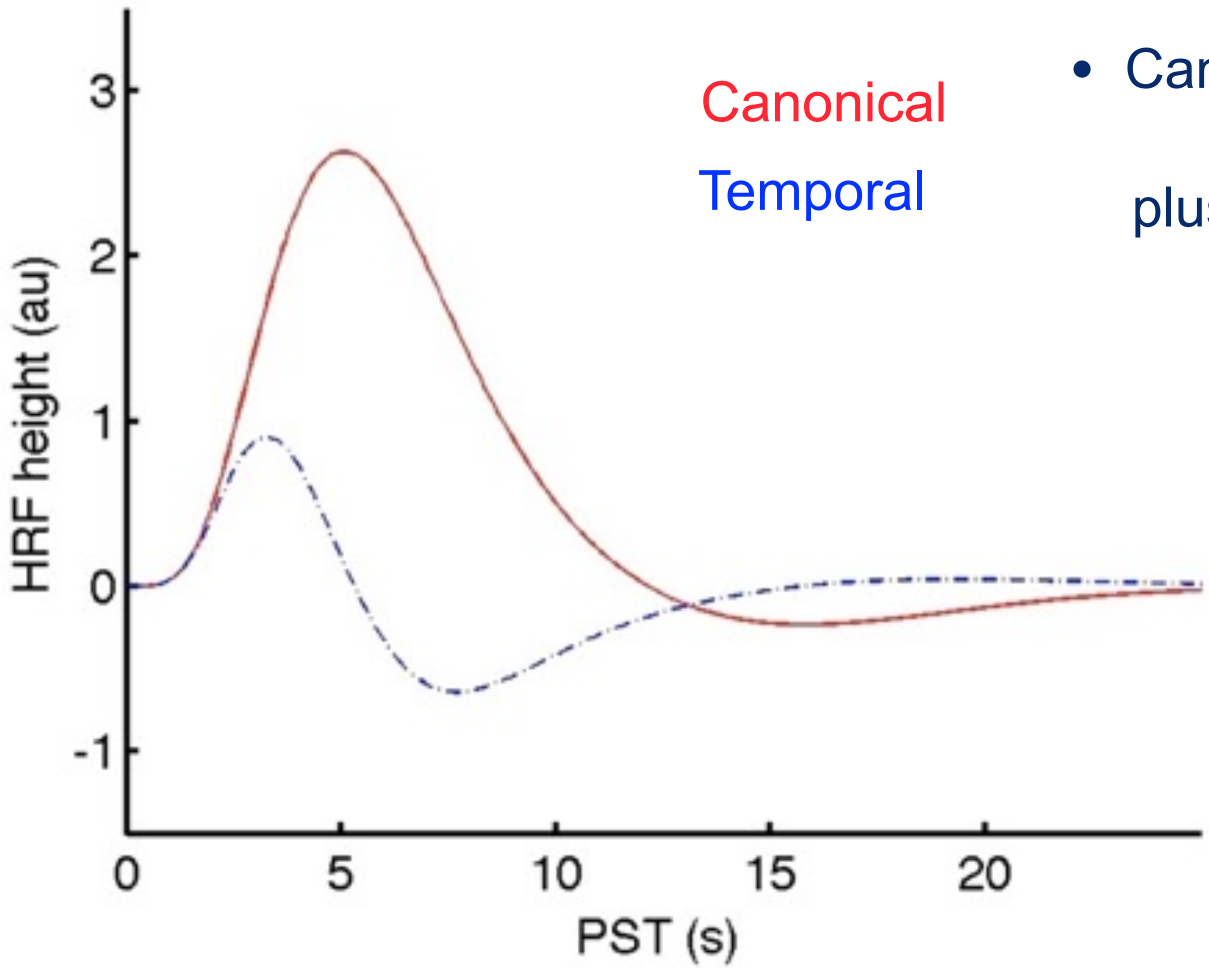


Informed basis set



- Canonical HRF (2 gamma functions)

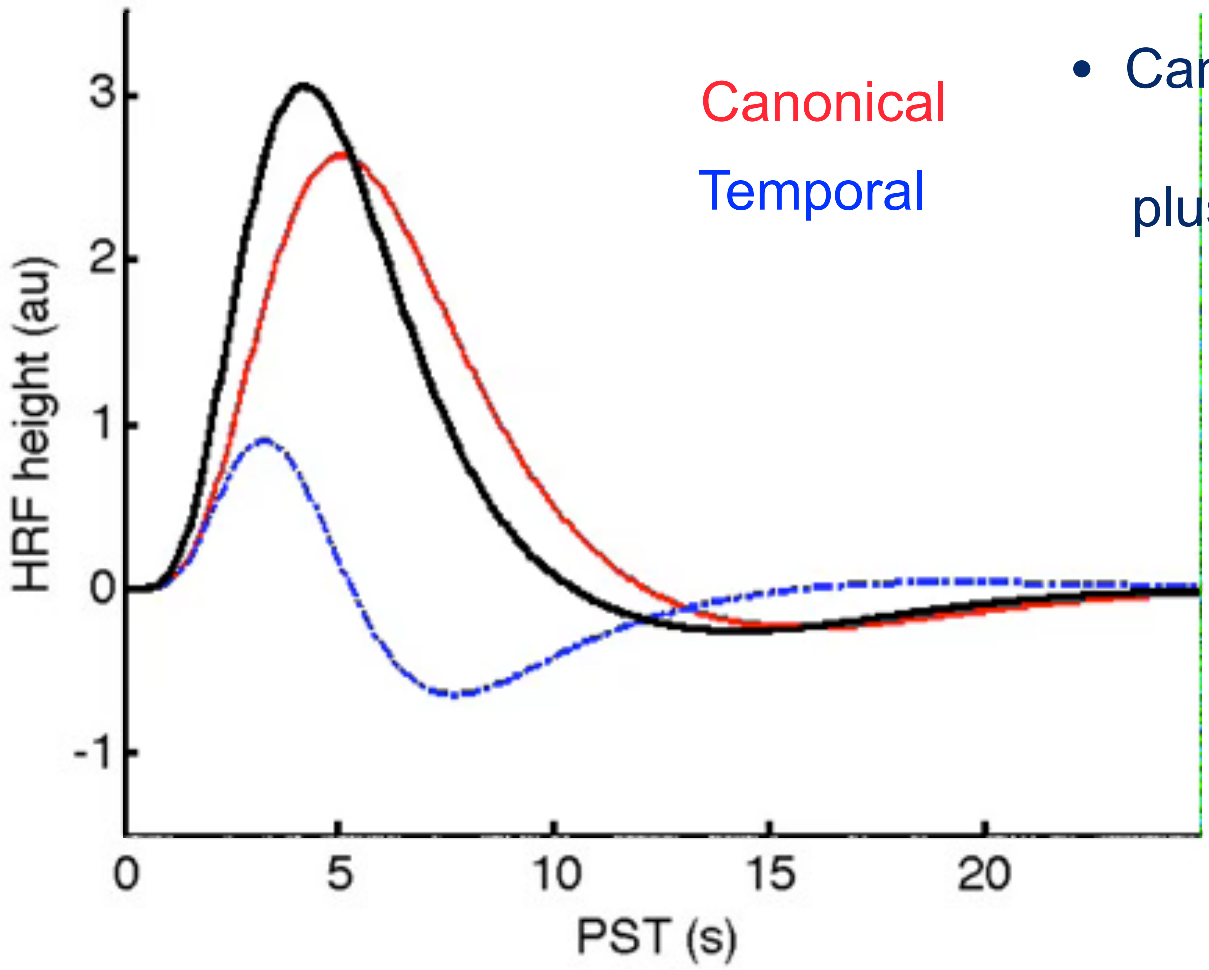
Informed basis set



- Canonical HRF (2 gamma functions)

  plus Multivariate Taylor expansion in:
    - time (Temporal Derivative)

Informed basis set



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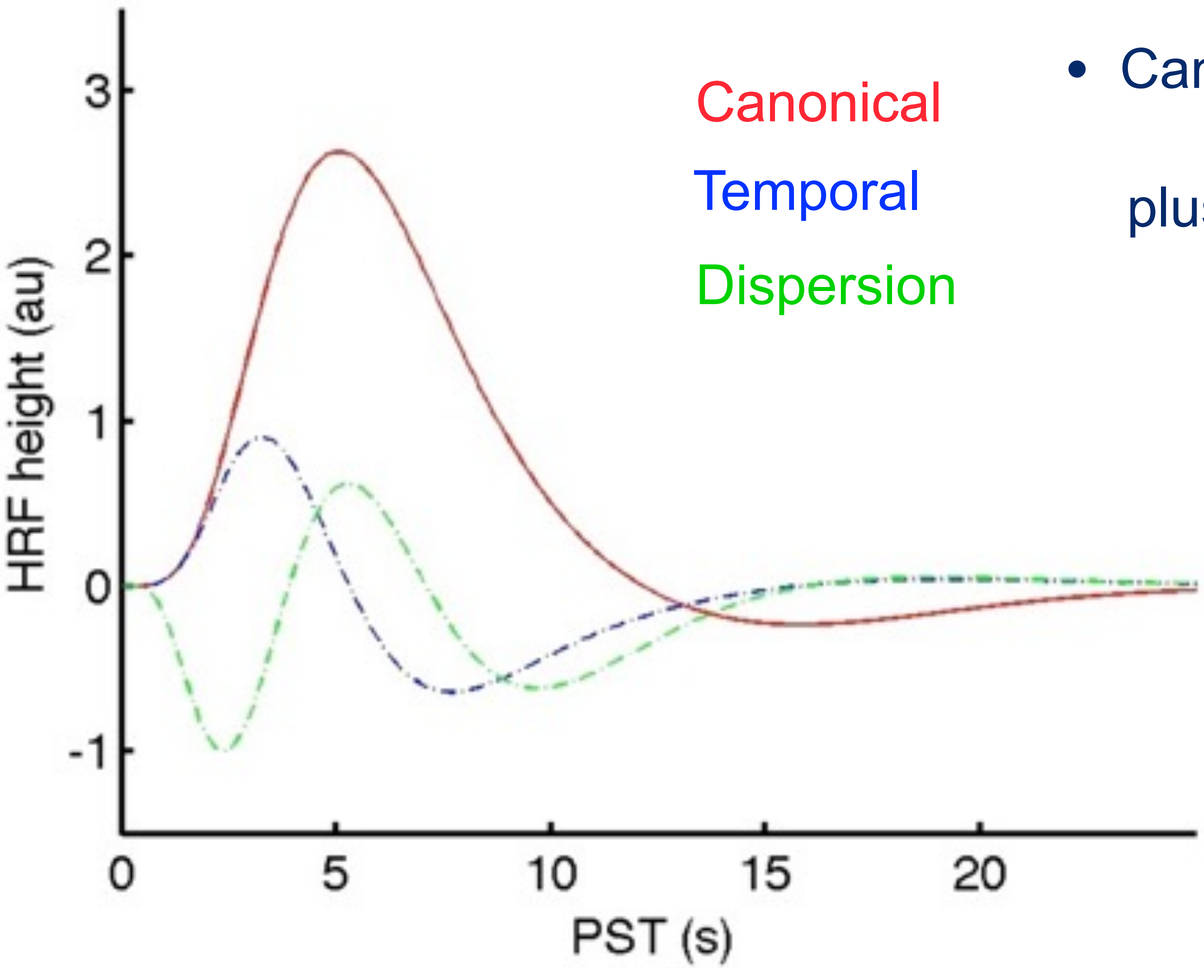
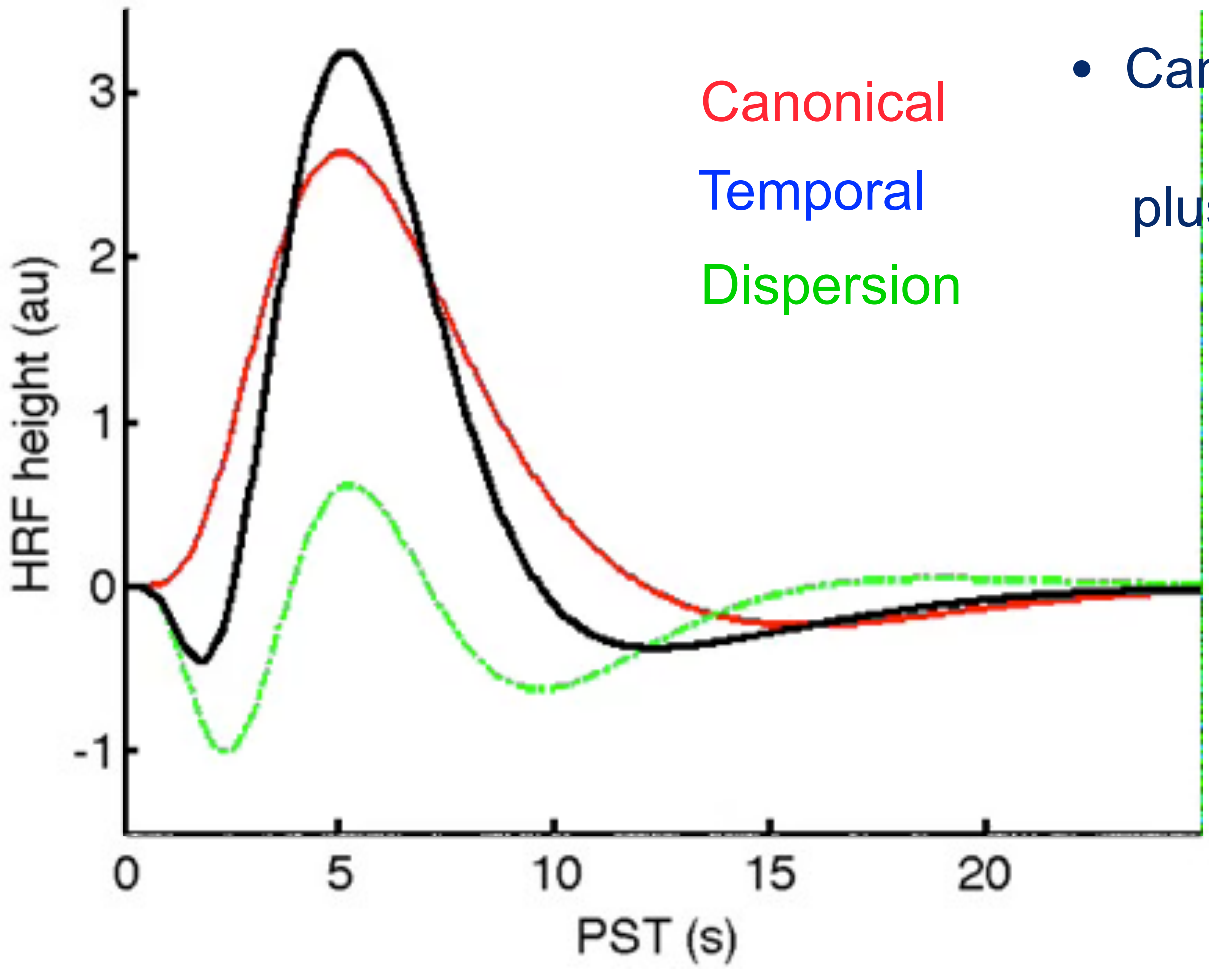
Informed basis set



- Canonical HRF (2 gamma functions)

  plus Multivariate Taylor expansion in:
  - time (Temporal Derivative)
  - width (Dispersion Derivative)

Informed basis set



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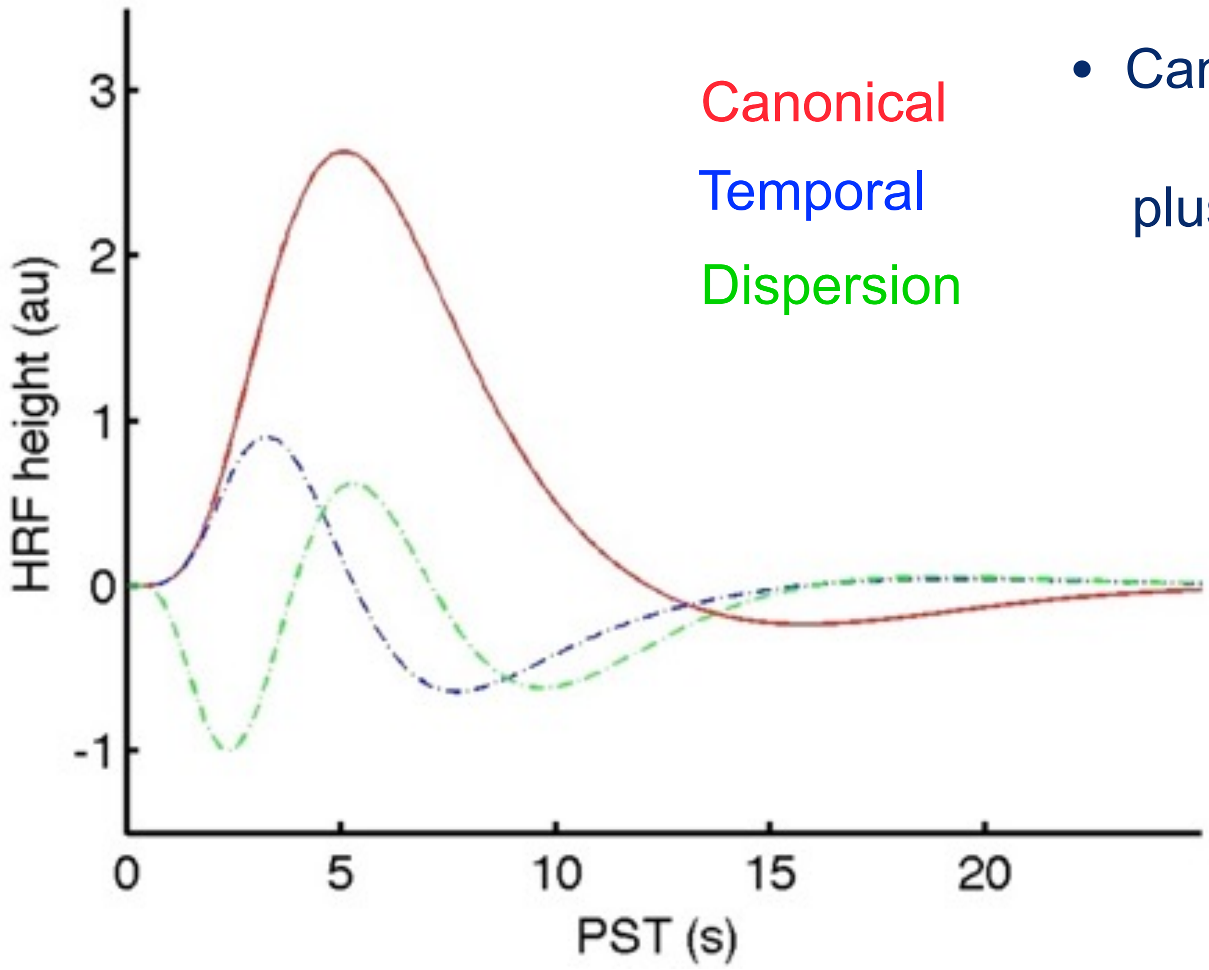


- Canonical HRF (2 gamma functions)

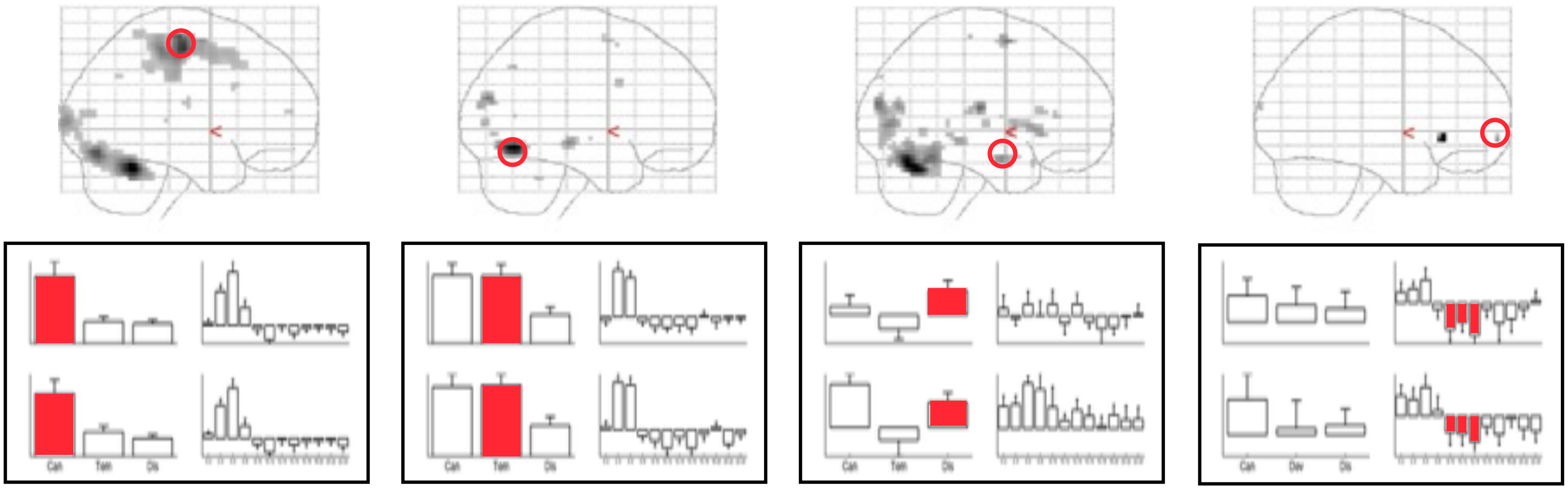
  plus Multivariate Taylor expansion in:
  - time (Temporal Derivative)
  - width (Dispersion Derivative)

- “Magnitude” inferences via t-test on canonical parameters (providing canonical is a reasonable fit)

- “Latency” inferences via tests on ratio of derivative : canonical parameters

Which temporal basis set?

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



Canonical + Temporal + Dispersion + FIR

… 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

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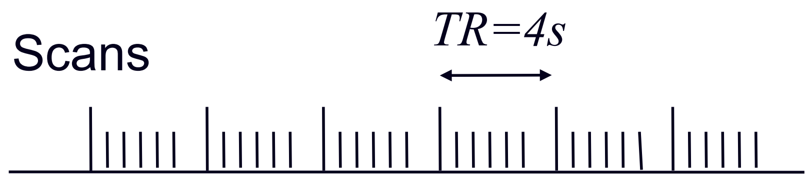
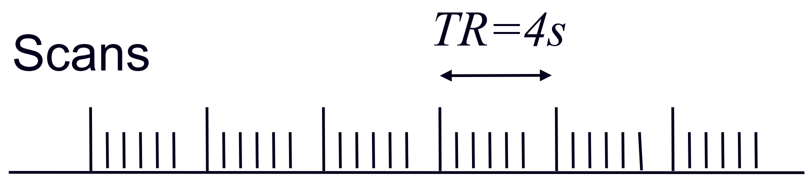
Timing issues: Sampling

- TR for 80 slice EPI at 2 mm spacing is ~ 4s

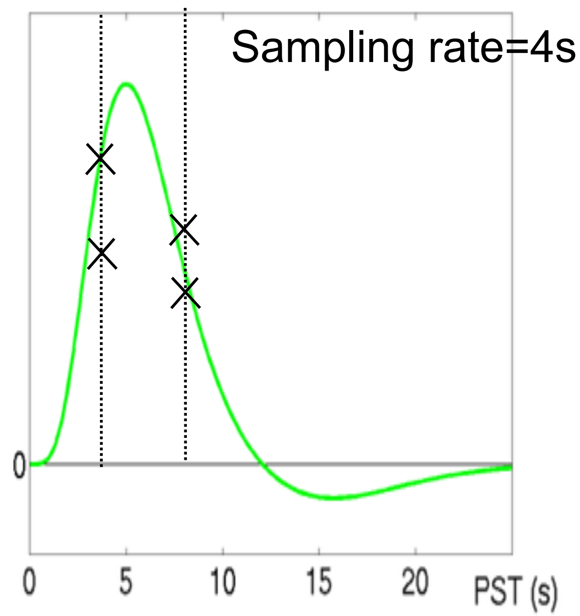


Timing issues: Sampling

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



Stimulus (synchronous)



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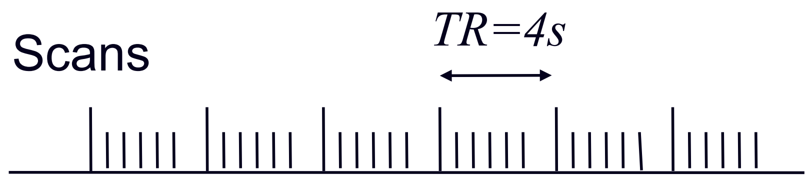
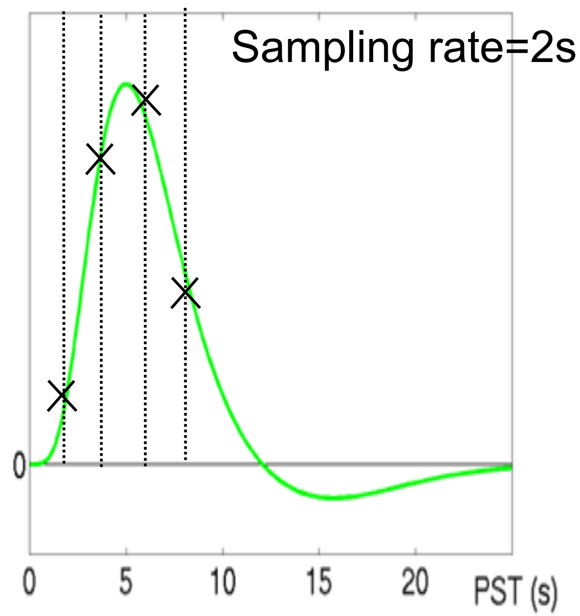
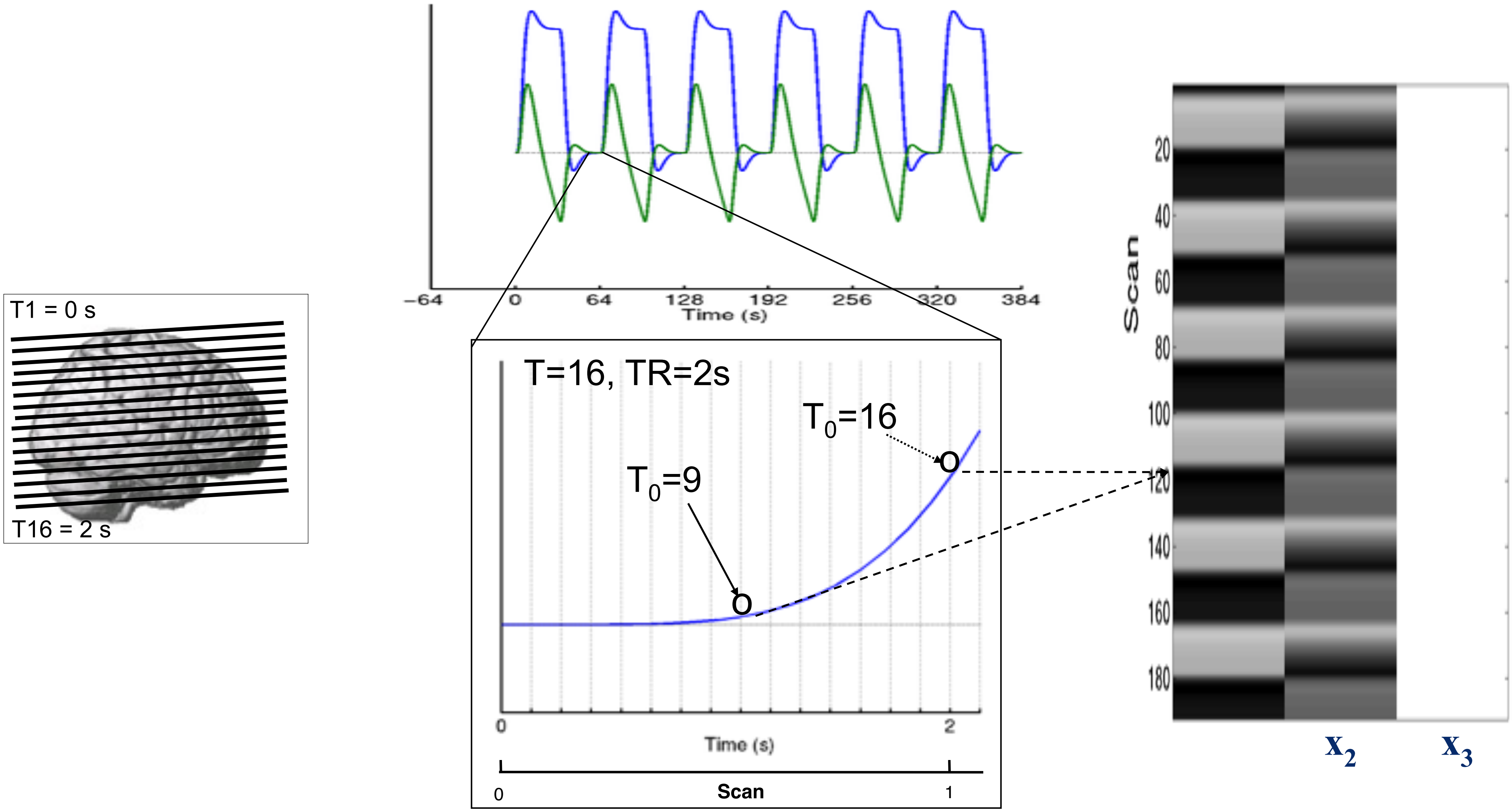


Stimulus (random jitter)

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



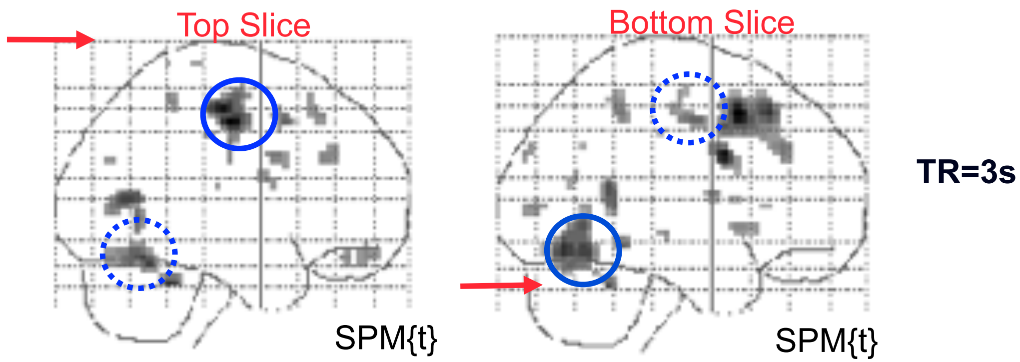
Timing issues: Slice Timing



Timing issues: Slice Timing

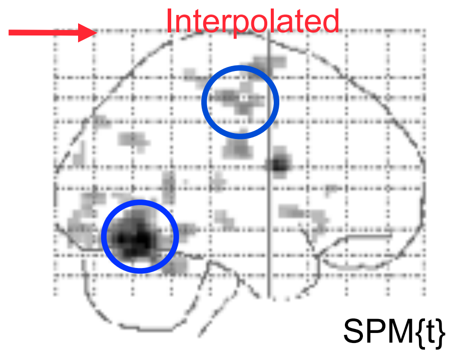
"Slice-timing Problem":

- 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)

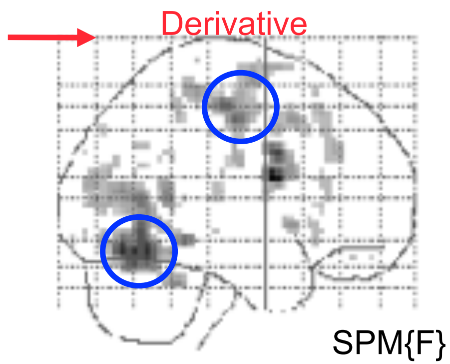


Solutions:

1. Temporal interpolation of data
   … but less good for longer TRs



2. More general basis set (e.g., with temporal derivatives)
   … but inferences via F-test



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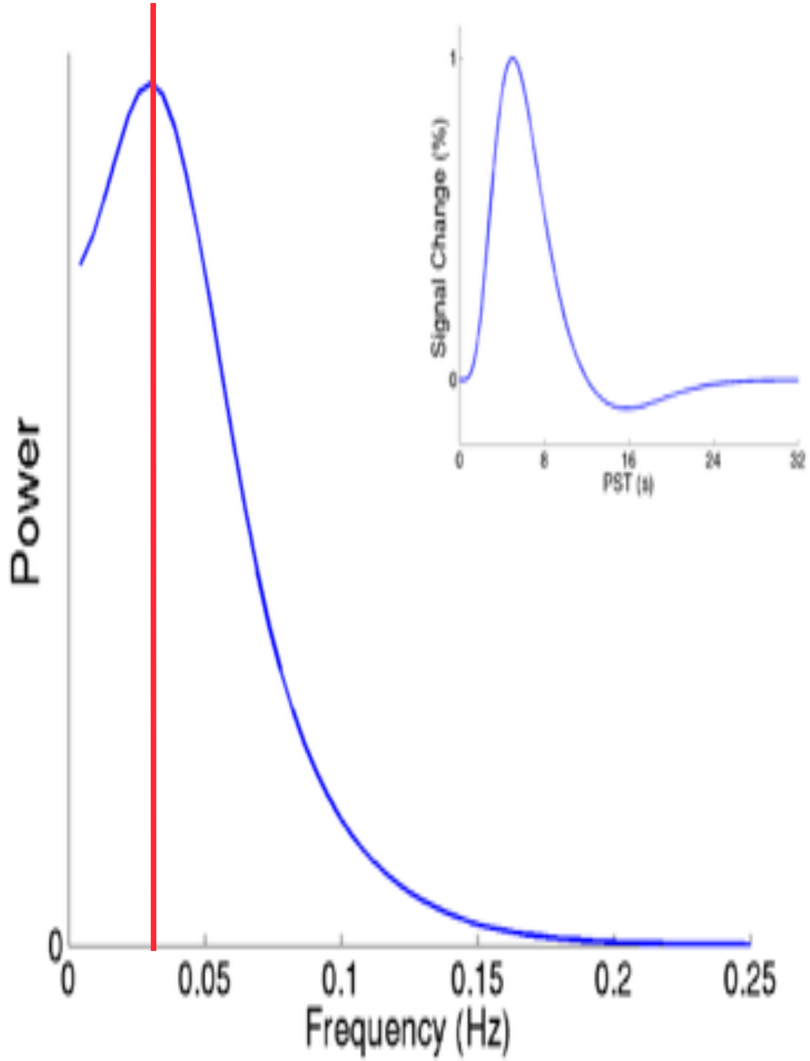
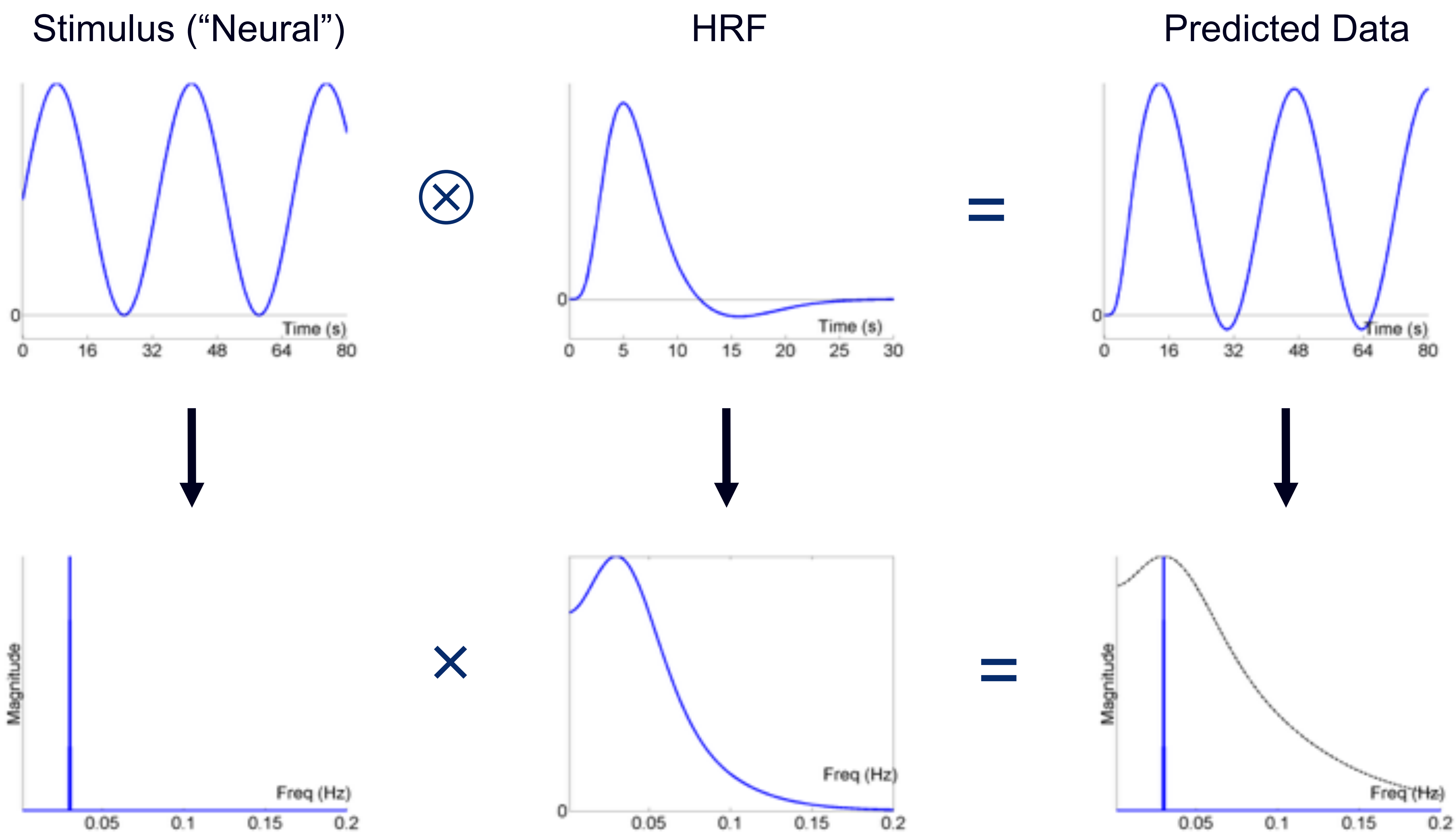
Design efficiency

- HRF can be viewed as a filter (Josephs & Henson, 1999)
- We want to maximise 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)

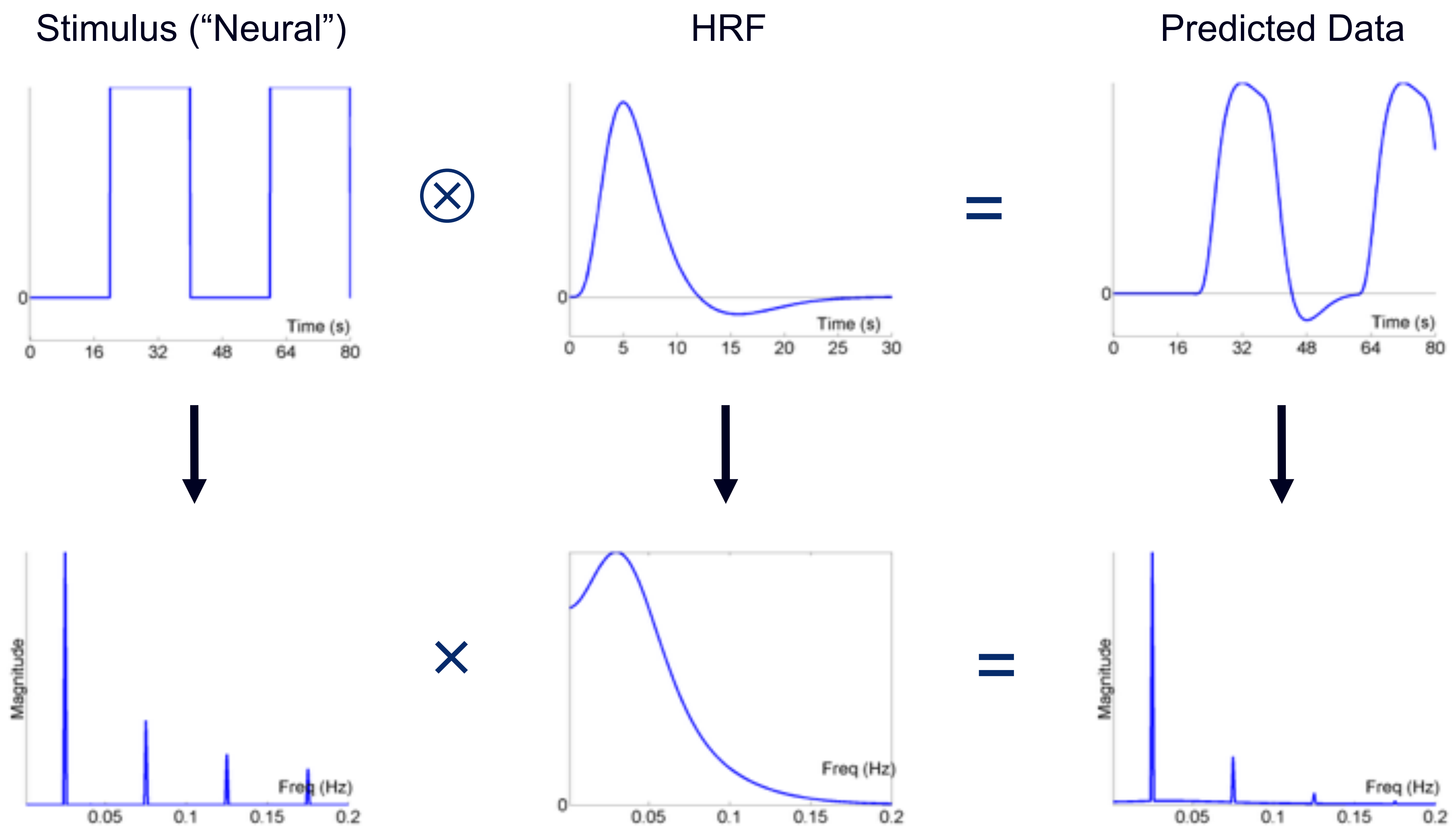


Sinusoidal modulation, f = 1/33



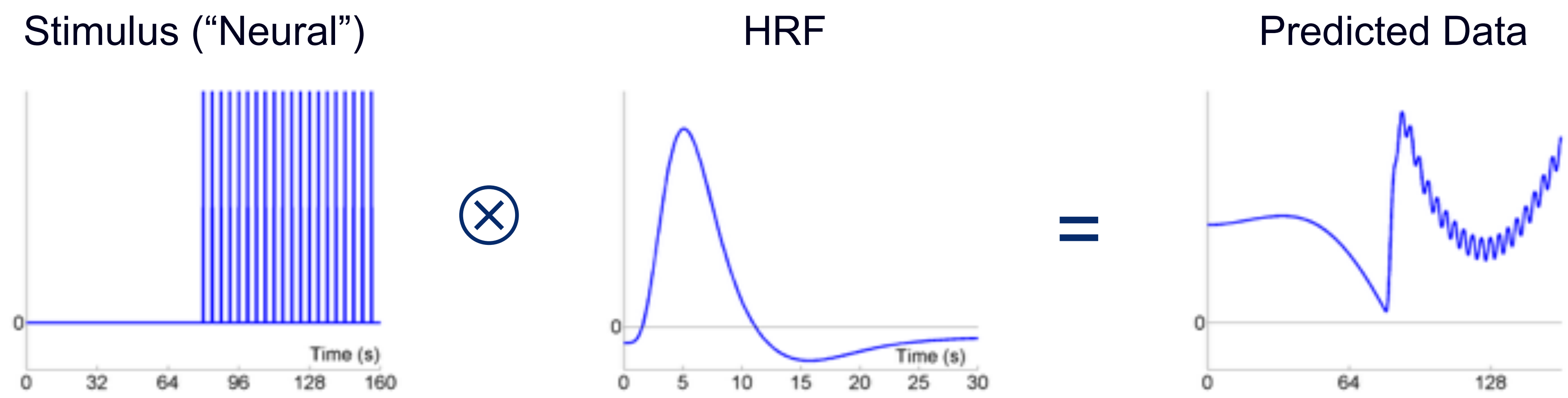
A very "efficient" design!

Blocked, epoch = 20 sec

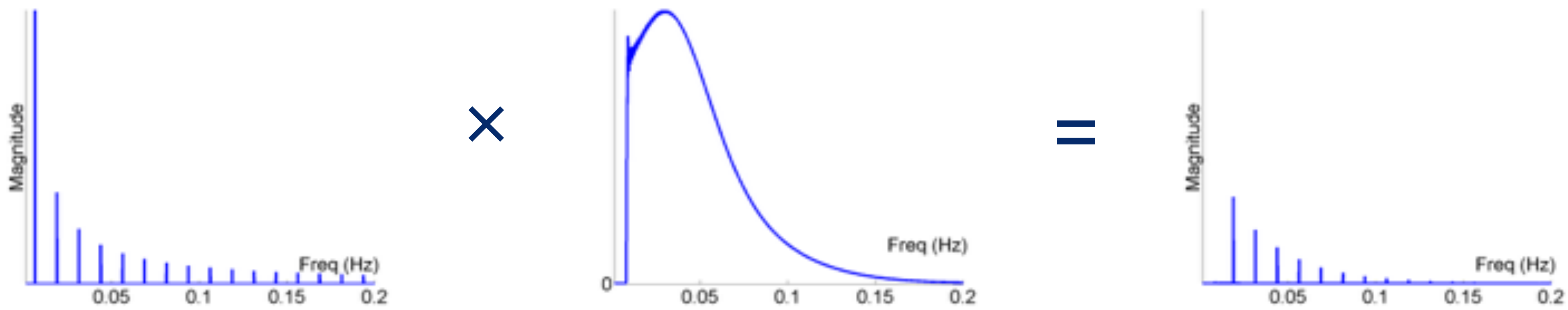


Blocked-epoch (with small SOA) quite “efficient”

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

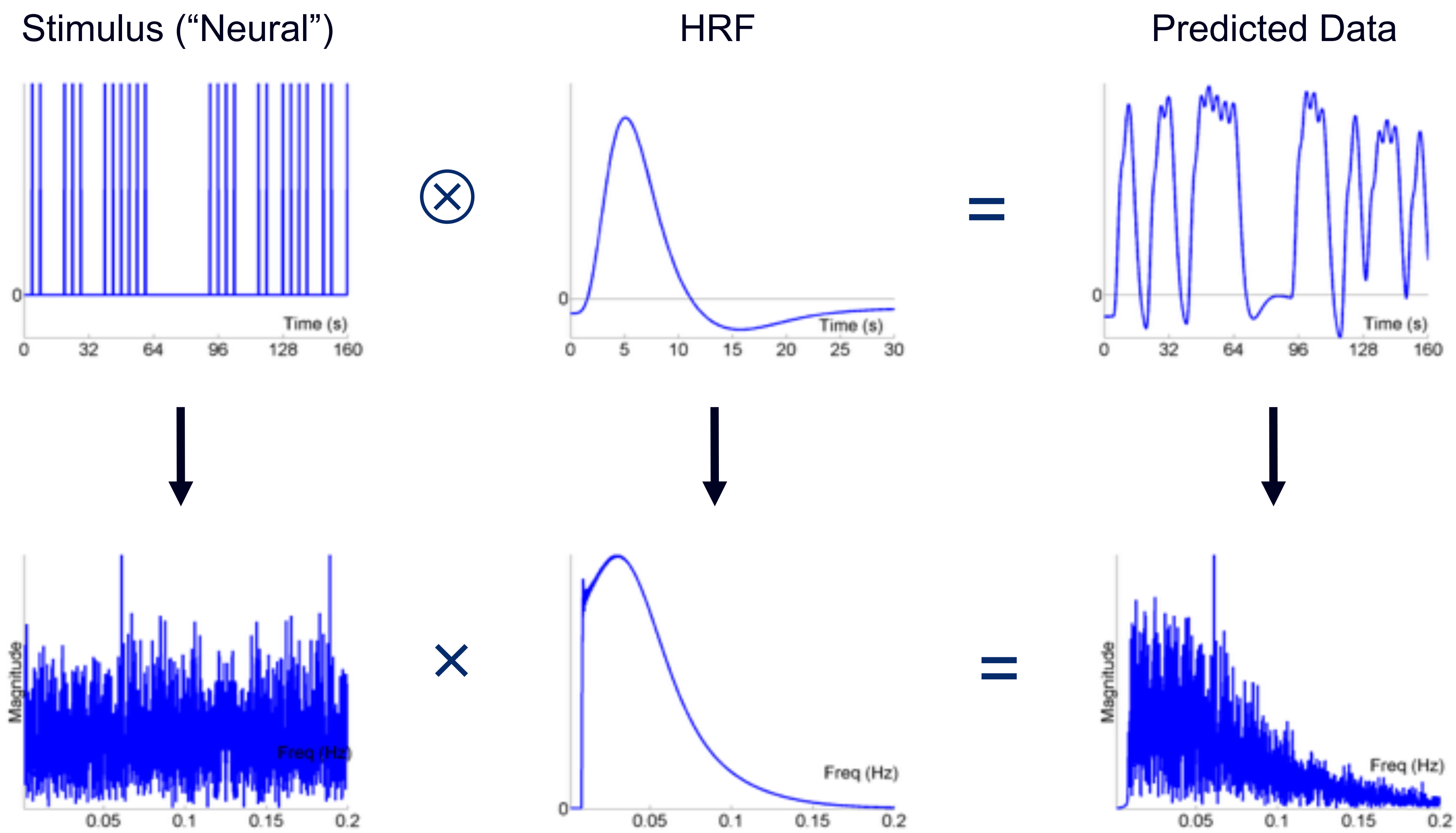


“Effective HRF” (after highpass filtering)
(Josephs & Henson, 1999)



Very ineffective: Don’t have long (>60s) blocks!

Randomised, SOAmin=4s, highpass filter = 1/120s



Randomised design spreads power over frequencies

Design efficiency

- T-statistic for a given contrast: $T = c^Tb / var(c^Tb)$
- For maximum T, we want maximum precision and hence minimum standard error of contrast estimates ($var(c^Tb)$)
- $Var(c^Tb) = sqrt(\sigma^2 c^T(X^TX)^{-1}c)$ (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

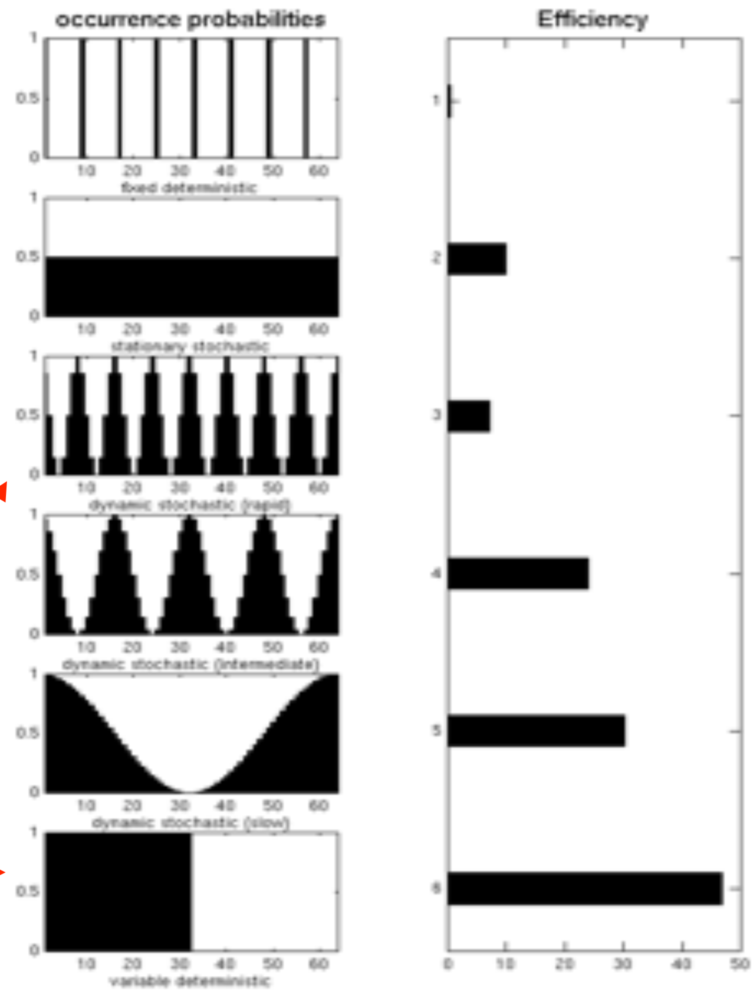
- Design parametrised by:

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

- Deterministic
  $p(t)=1$ iff $t=nSOAmin$

- Stationary stochastic
  $p(t)=constant$

- Dynamic stochastic
  $p(t)$ varies (e.g., blocked)



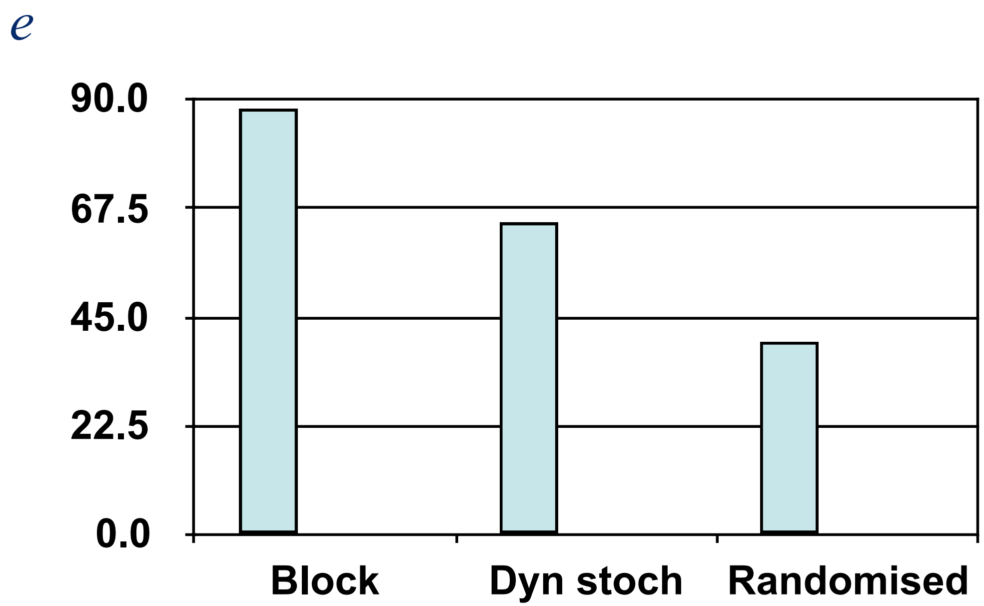
Blocked designs most efficient! (with small SOAmin)

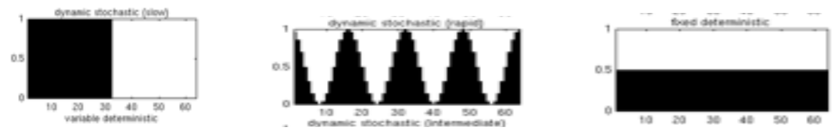
Design efficiency: Trial spacing

- However, block designs are often not advisable due to interpretative difficulties

- Event trains may then be constructed by modulating the event probabilities in a dynamic stochastic fashion

- This can result in intermediate levels of efficiency





3 sessions with 128 scans
Faces, scrambled faces
SOA always 2.97 s
Cycle length 24 s

Design efficiency: Trial sequencing

- Design parametrised by:

SOA_{min} Minimum SOA

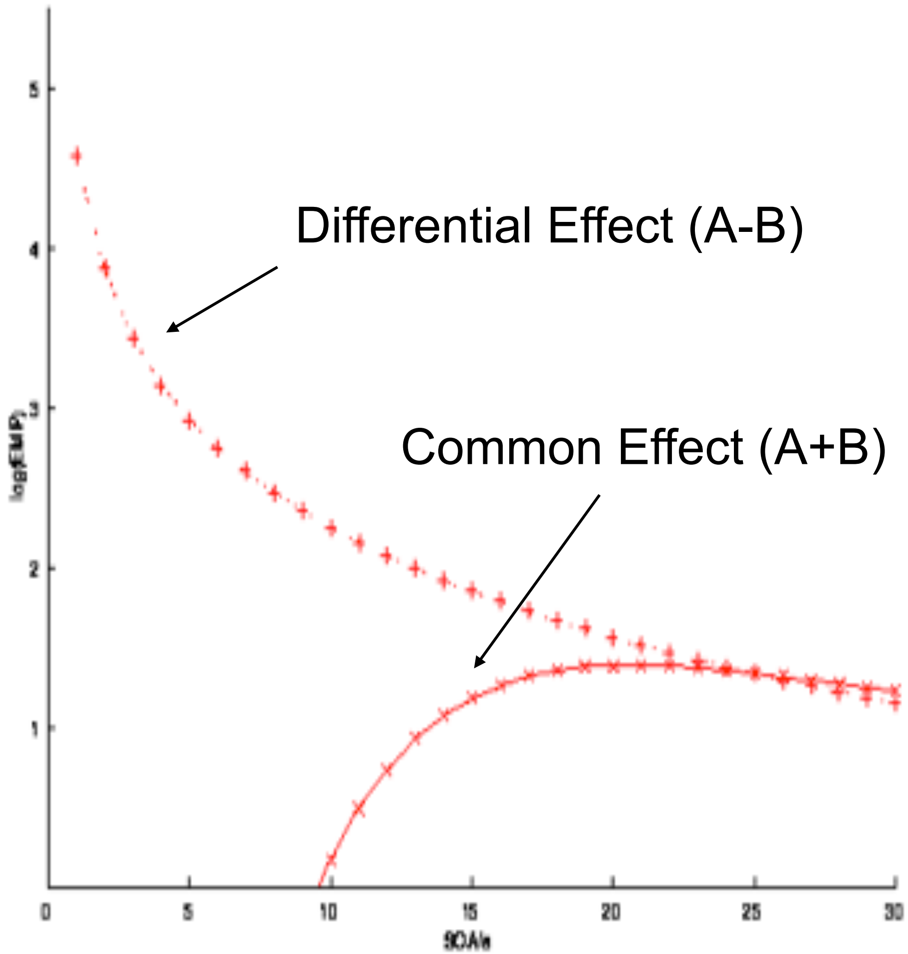
$p_i(\boldsymbol{h})$ Probability of event-type *i* given history ***h*** of last *m* events

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

- Example: Randomised AB

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

=> **ABBBABAABABAAA...**



Design efficiency: Trial sequencing

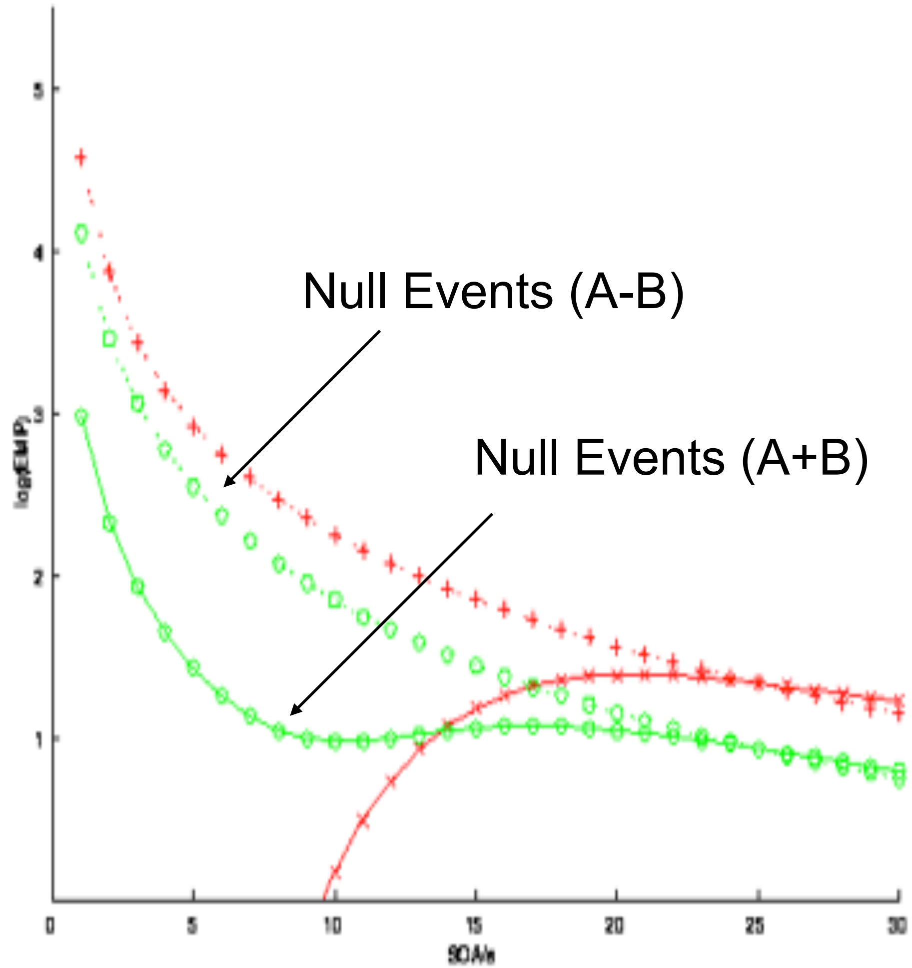
- Example: Null events

	A	**B**
A	0.33	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)



Design efficiency: Trial sequencing

- Example: Alternating AB

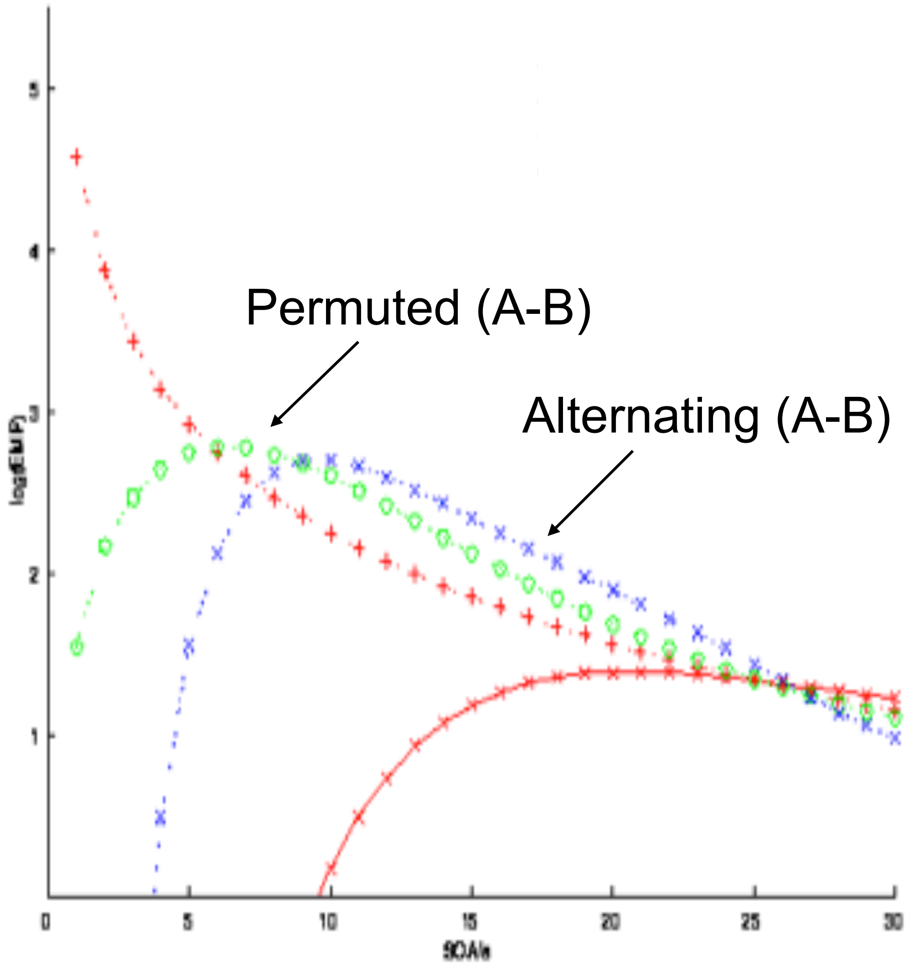
	A	B
A	0	1
B	1	0

=> **ABABABABABAB...**

- Example: Permuted AB

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

=> **ABBAABABABBA...**



Design efficiency: Conclusions

- 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 often also sets limits on SOAs
- With randomised 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 order constrained, intermediate SOAs (5-20s) can be optimal
- If SOA constrained, pseudorandomised designs can be optimal (but may introduce context-sensitivity)

Overview

1. 1st level: Block/epoch vs. event-related fMRI
2. 1st level GLM: Convolution
3. 1st level GLM: Temporal Basis Functions
4. 1st level GLM: Timing Issues
5. 1st level GLM: Design Optimisation – “Efficiency”
6. **2nd level GLM: Statistical tests**

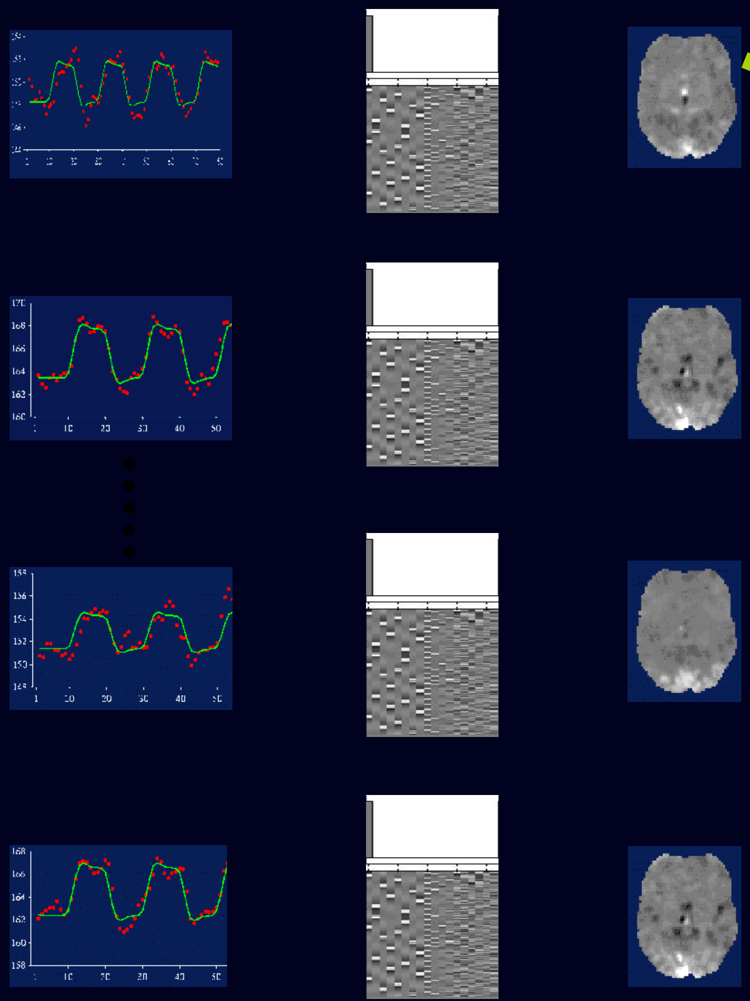
1st Level

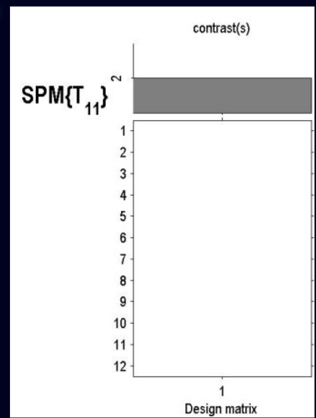
2nd Level

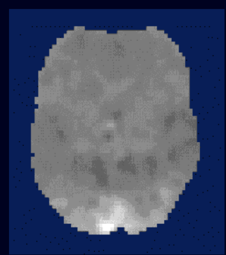
Data

Design matrix

Contrast images

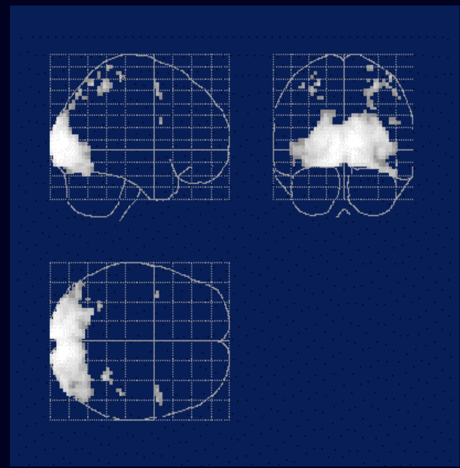






$$t = \frac{c^T \hat{\alpha}}{\sqrt{V\hat{a}r(c^T \hat{\alpha})}}$$

SPM(t)



one-sample t-test
at the second level

Tests with 1 image per subject

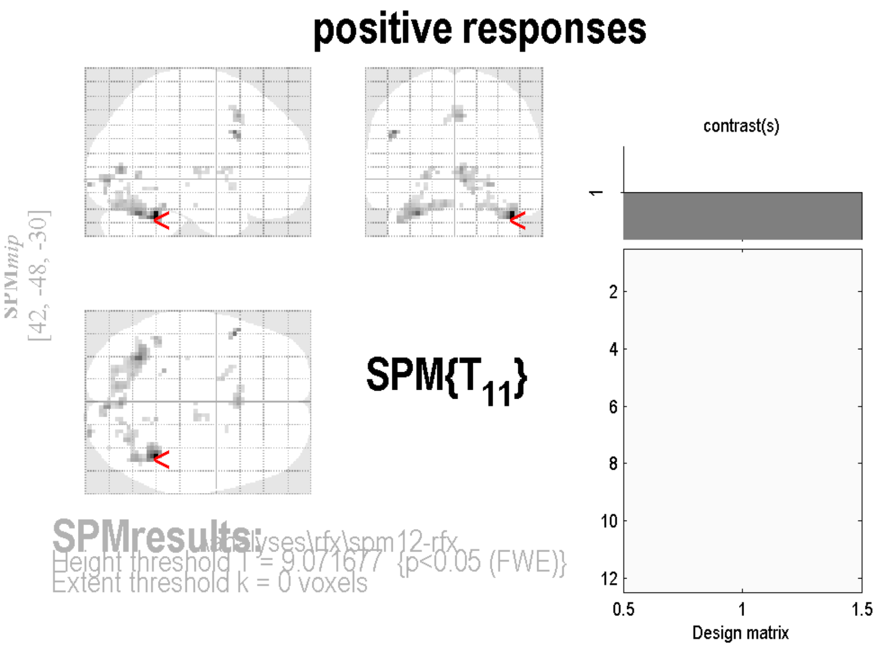
Tests with one contrast image per subject

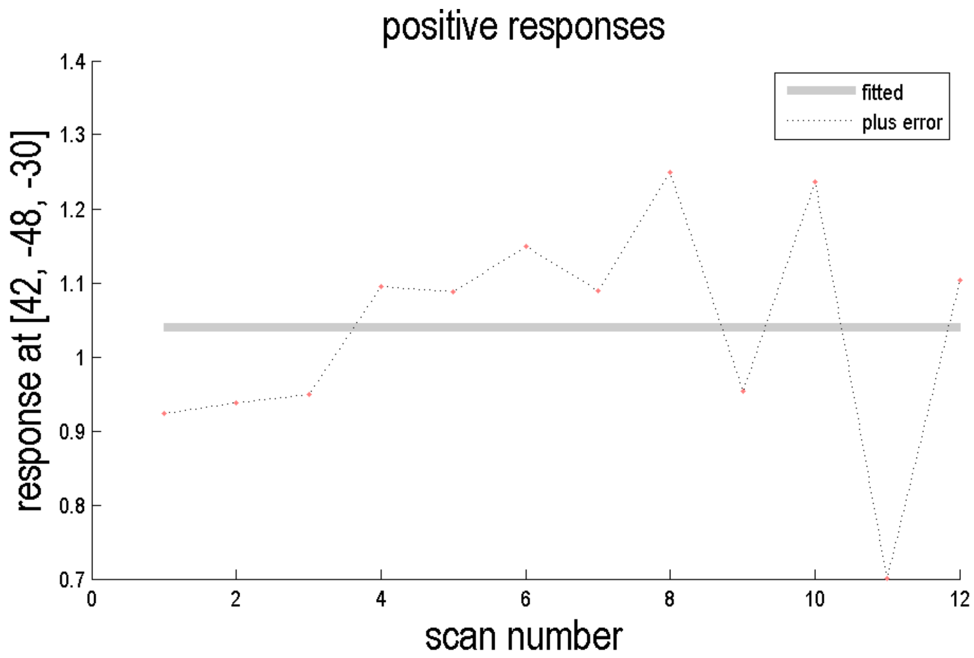
- One-sample t-test
- Multiple regression

=> Straightforward, as only one source of variance in the data (between-subjects)

One-sample t-test

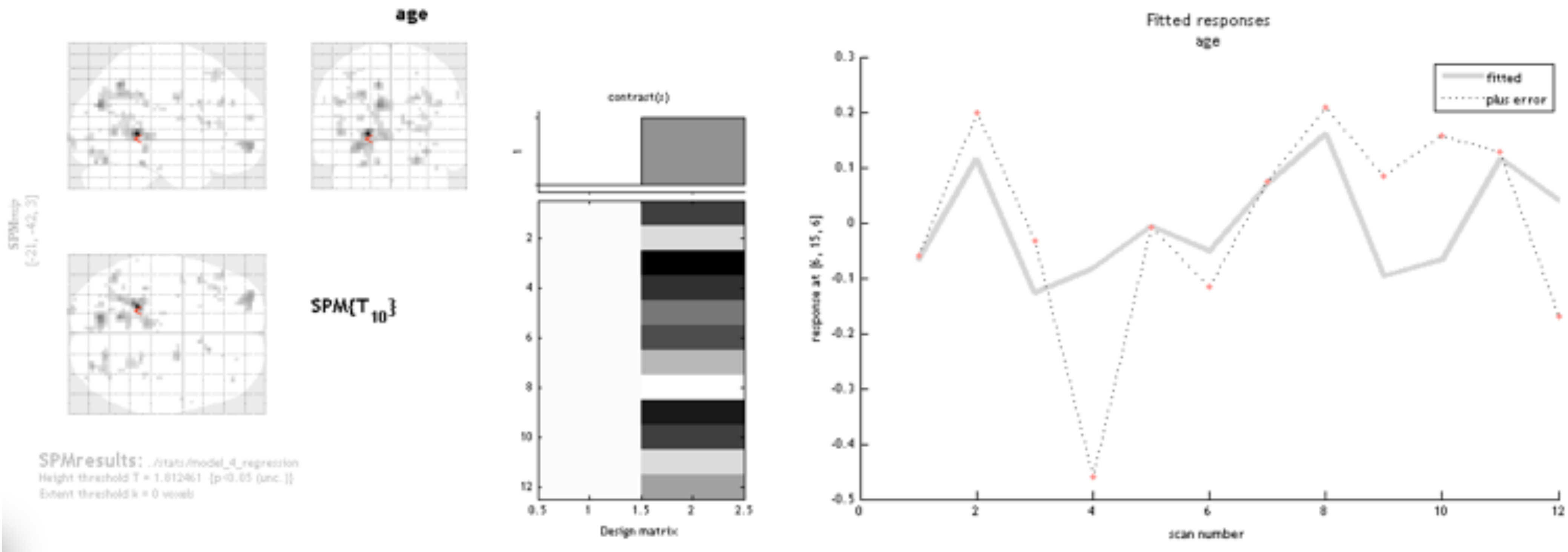
Is the mean of the data different from zero?





Multiple regression

Do the data correspond to numerical predictions for each image?



Tests with multiple groups /images per subject

Tests with one contrast image per subject

- One-sample t-test
- Multiple regression

=> Straightforward, as only one source of variance in the data (between-subjects)

Tests with multiple images per subject, or multiple groups

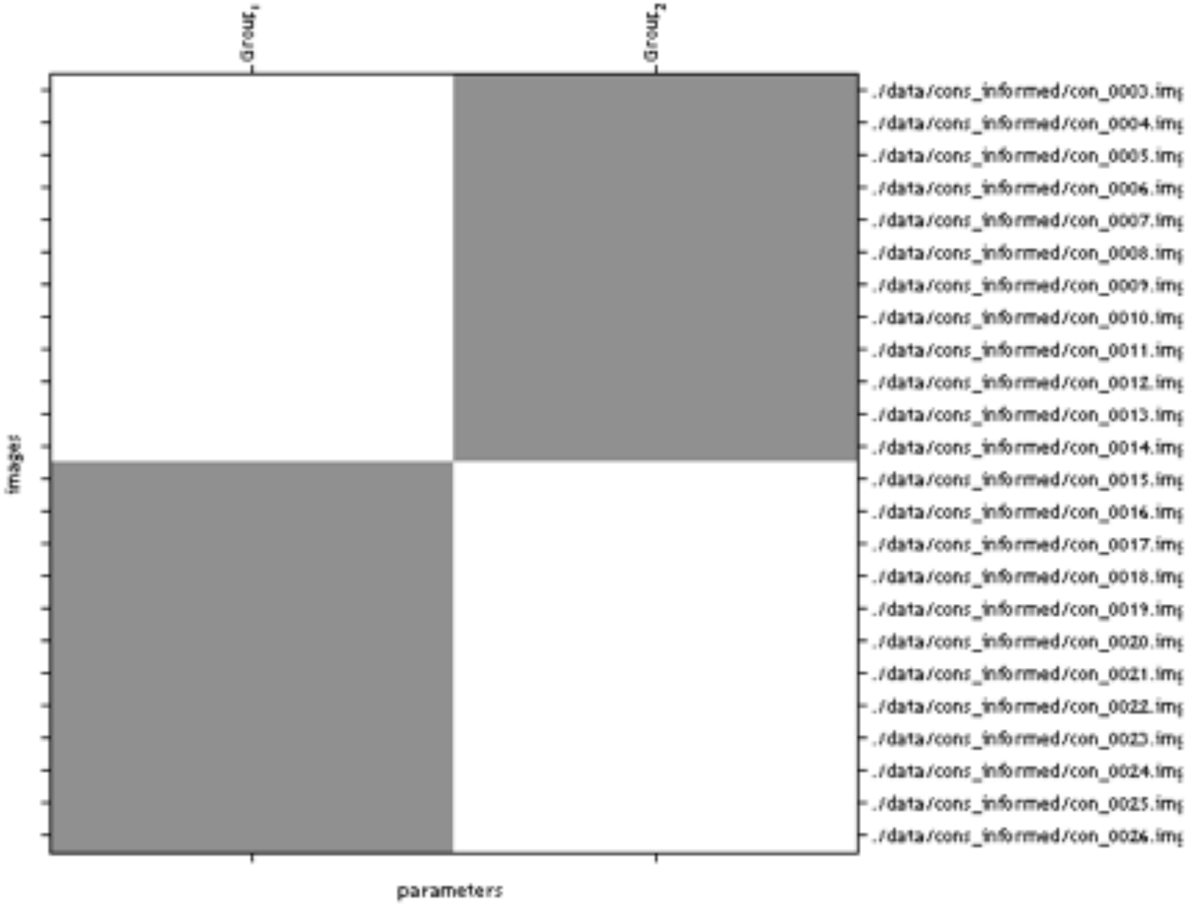
- Two-sample and paired t-test
- n-way ANOVA (between and within)
- Full and flexible factorial

=> More complicated: Several sources of variance and/or correlated values
=> See talk on group analyses

Two-sample t-test

Do the means of two independent sets of data differ?

Example: Comparisons of patients and healthy controls

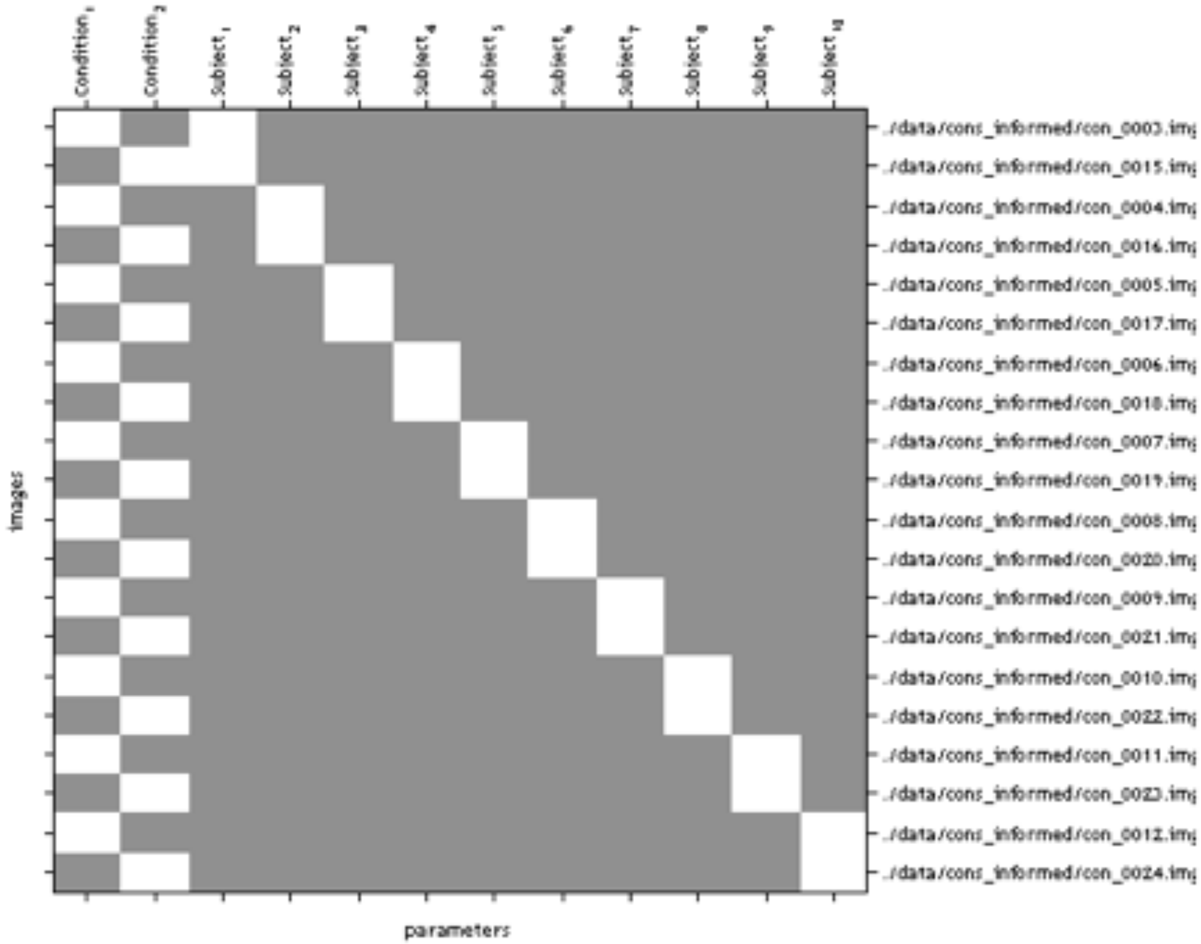


Paired t-test

Do the means of two dependent sets of data differ?

Example: Pre-post designs with TMS or pharmacological interventions

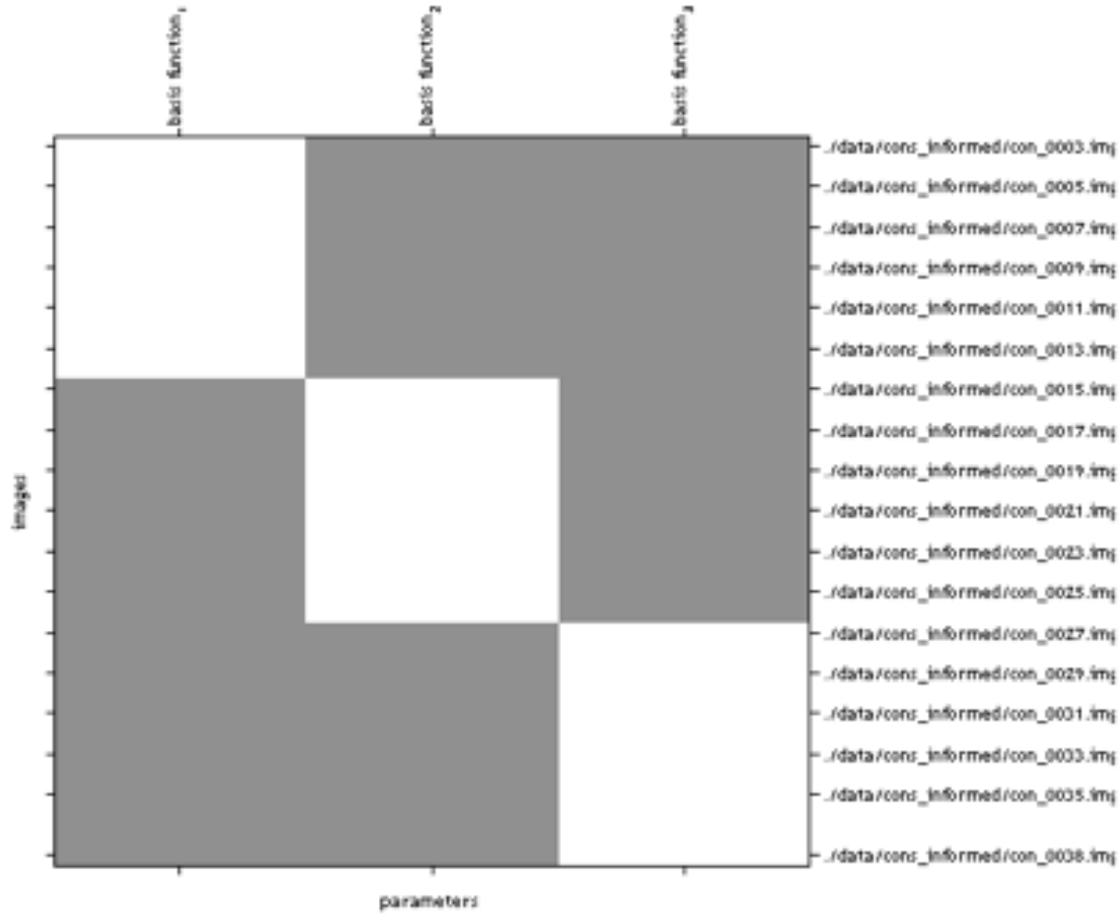
Note: Can also be tested with a one-sample t-test of the difference



One-way ANOVA

Do the means of more than two independent sets of data differ?

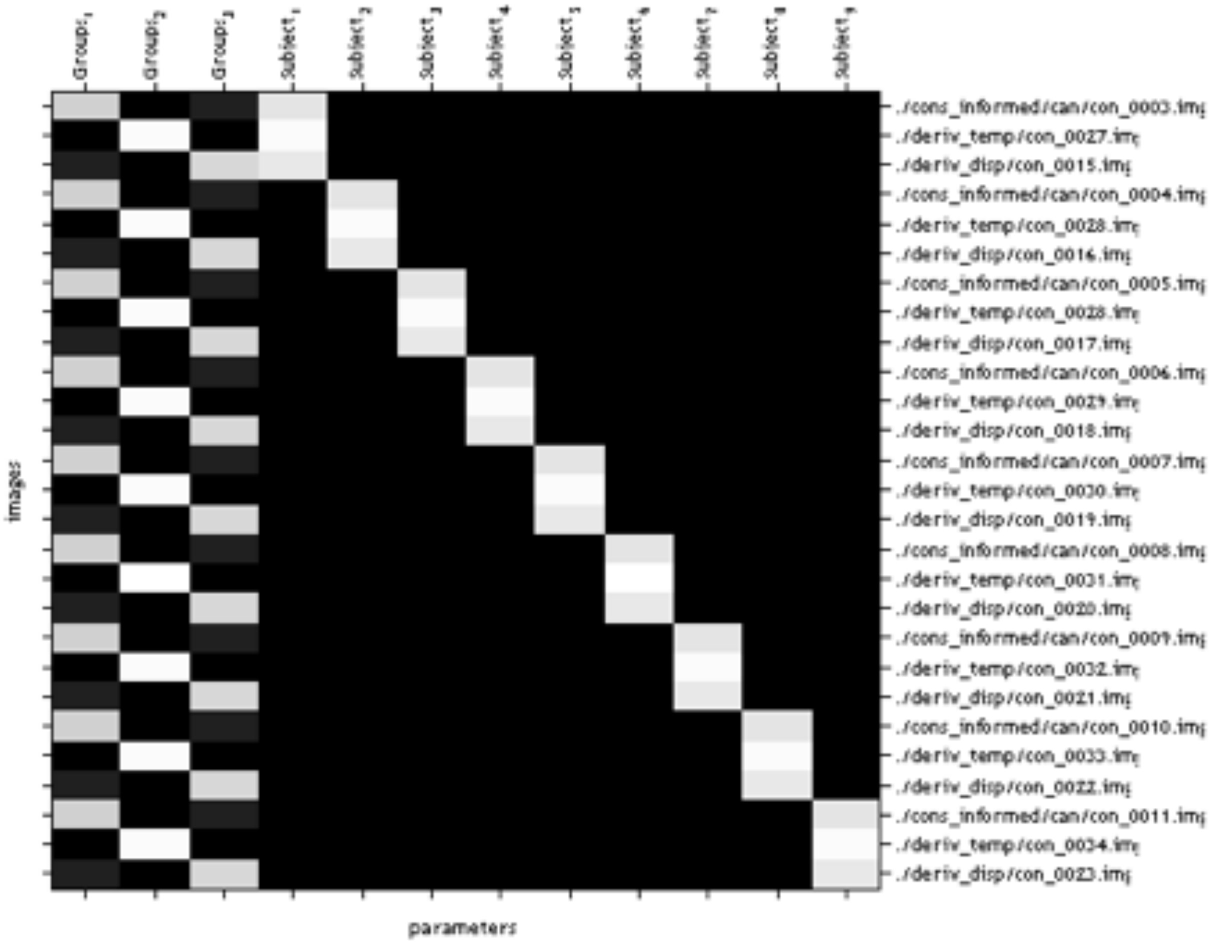
Examples: Multi-group designs (three different age groups)



One-way ANOVA - within subjects

Do the means of more than two dependent sets of data differ?

Examples: Multi-intervention designs (baseline, intervention, baseline)



Factorial ANOVAs

ANOVAS can have several factors reflecting different, interacting experimental effects (e.g., 2x2 ANOVA)

SPM offers factorial designs that specify contrasts for main effects and interactions

These estimate either all (full factorial) or specified (flexible factorial) effects

Note that within-subject main effects and interactions can also be tested with one-sample t-tests of the corresponding first-level contrasts

(this is the “cleanest” way, as only source of variance is between-subject)

But sometimes it may be necessary/helpful to estimate ANOVA effects at 2nd level (e.g., mixed within/between designs, F-tests between any levels of factors)

Examples in the practical session on “group analyses”

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