

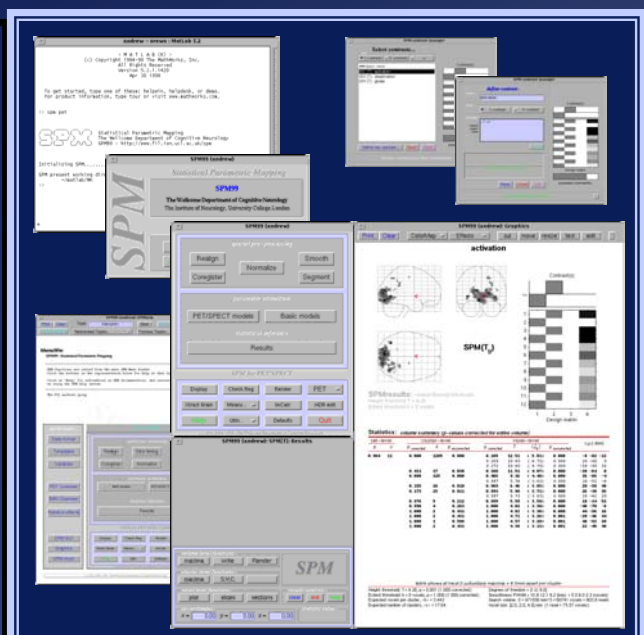
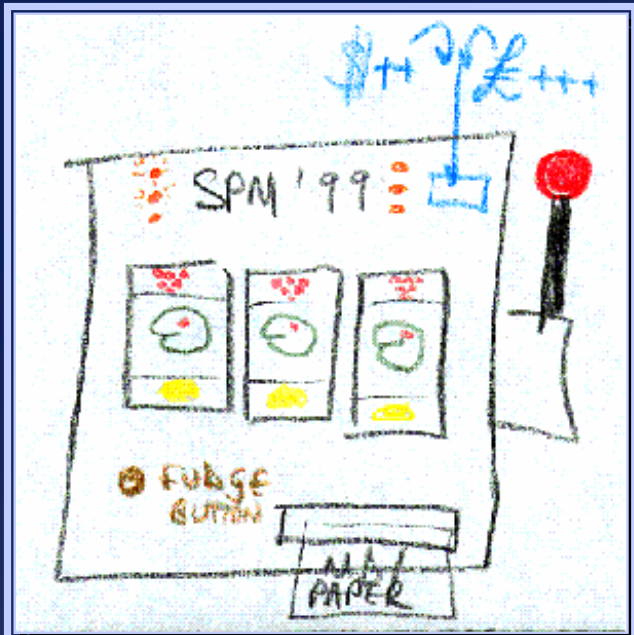
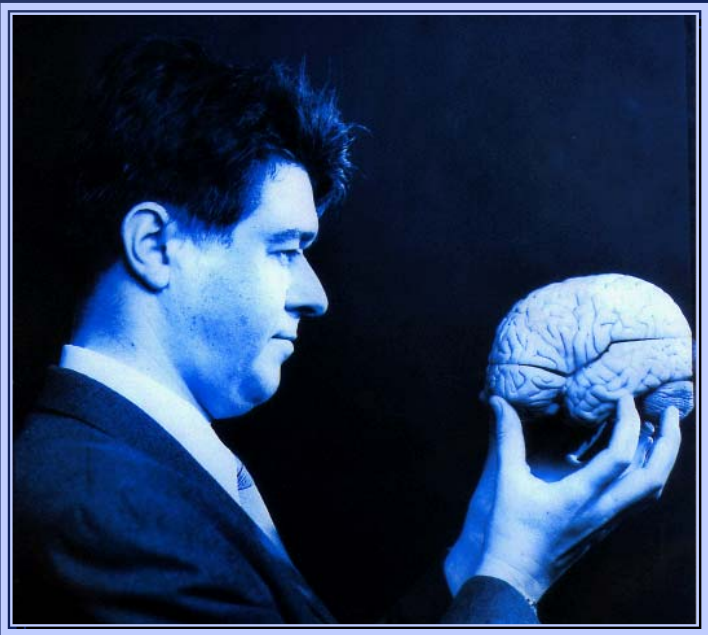


Event-related fMRI



Rik Henson

With thanks to:
Karl Friston, Oliver Josephs

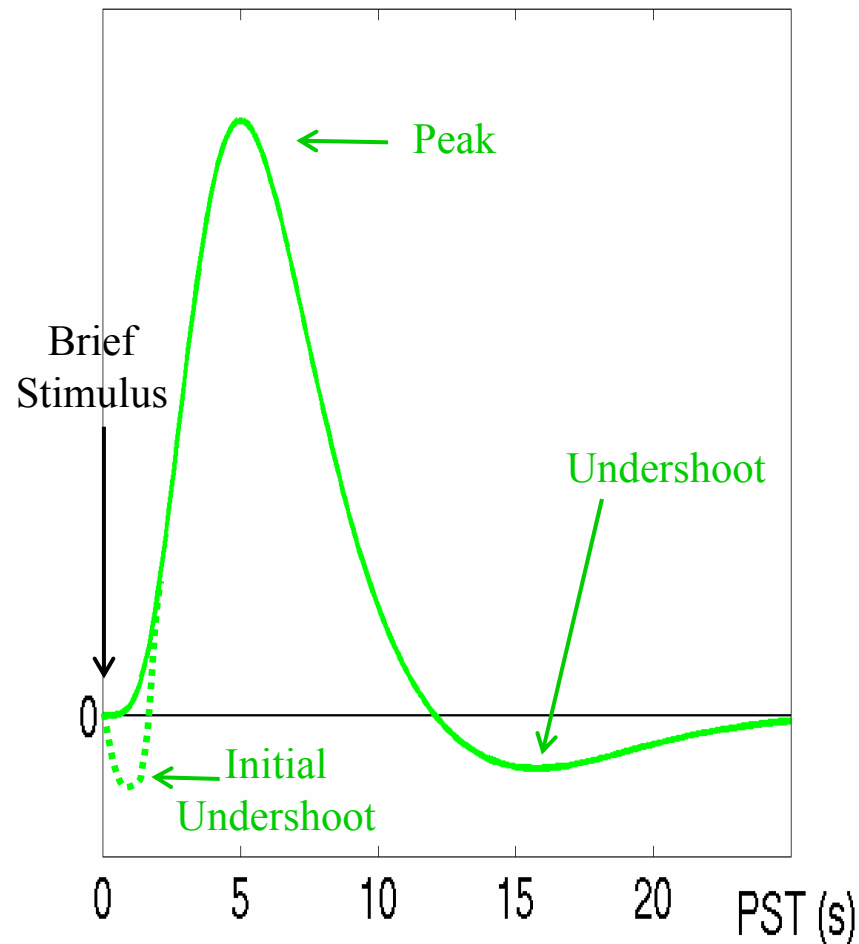


Overview

1. BOLD impulse response
2. General Linear Model
3. Temporal Basis Functions
4. Timing Issues
5. Design Optimisation
6. Nonlinear Models
7. Example Applications

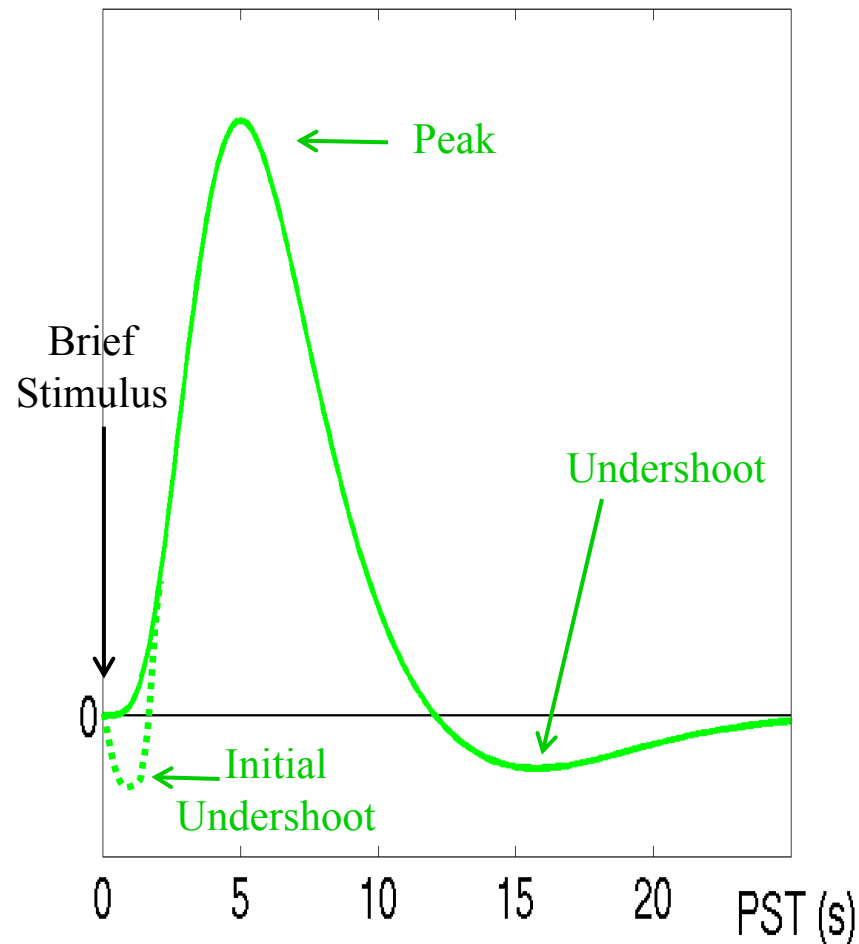
BOLD Impulse Response

- Function of blood oxygenation, flow, volume (Buxton et al, 1998)
- Peak (max. oxygenation) 4-6s poststimulus; baseline after 20-30s
- Initial undershoot can be observed (Malonek & Grinvald, 1996)
- Similar across V1, A1, S1...
- ... but differences across:
other regions (Schacter et al 1997)
individuals (Aguirre et al, 1998)



BOLD Impulse Response

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



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General Linear (Convolution) Model

GLM for a single voxel:

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

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

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

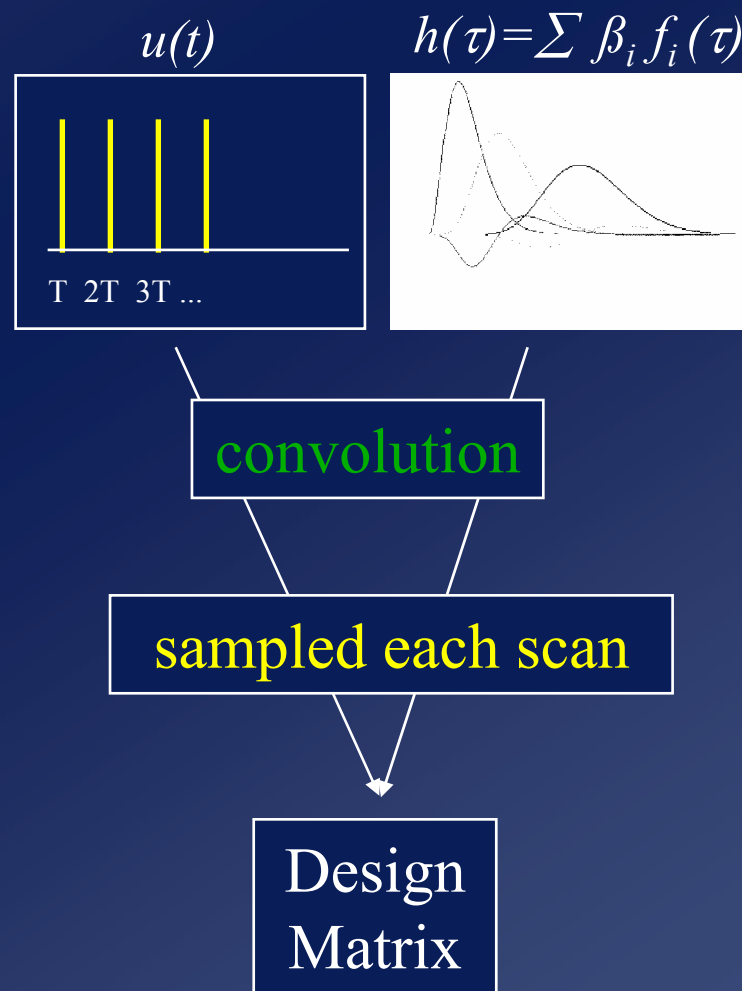
$h(\tau)$ = hemodynamic (BOLD) response

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

$f_i(\tau)$ = temporal basis functions

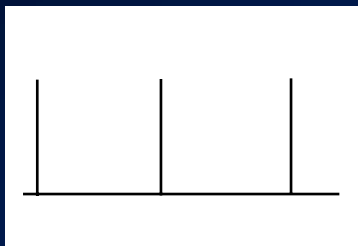
$$y(t) = \sum \sum \beta_i f_i(t - nT) + \varepsilon(t)$$

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

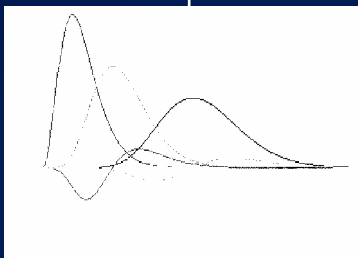


General Linear Model (in SPM)

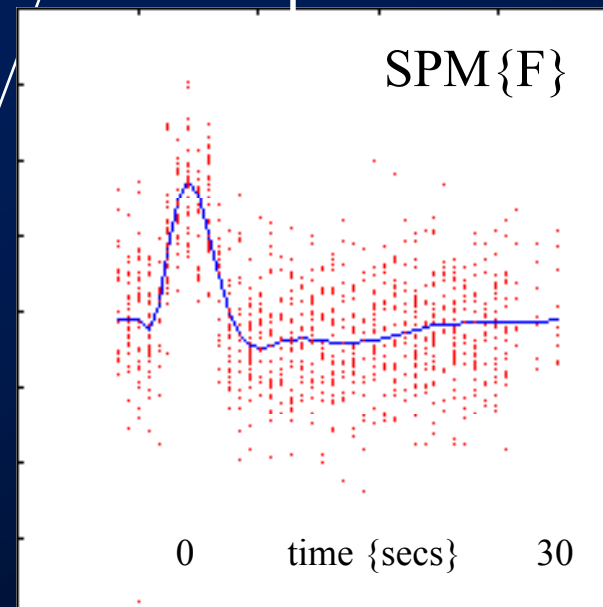
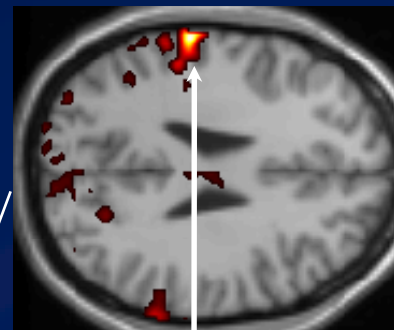
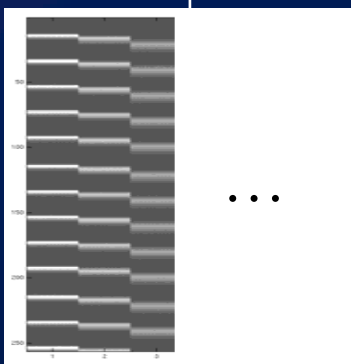
Auditory words
every 20s



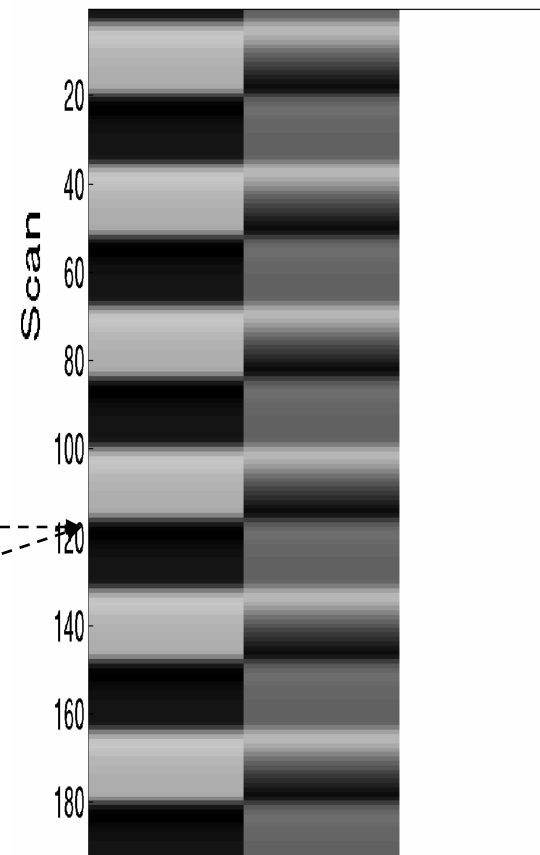
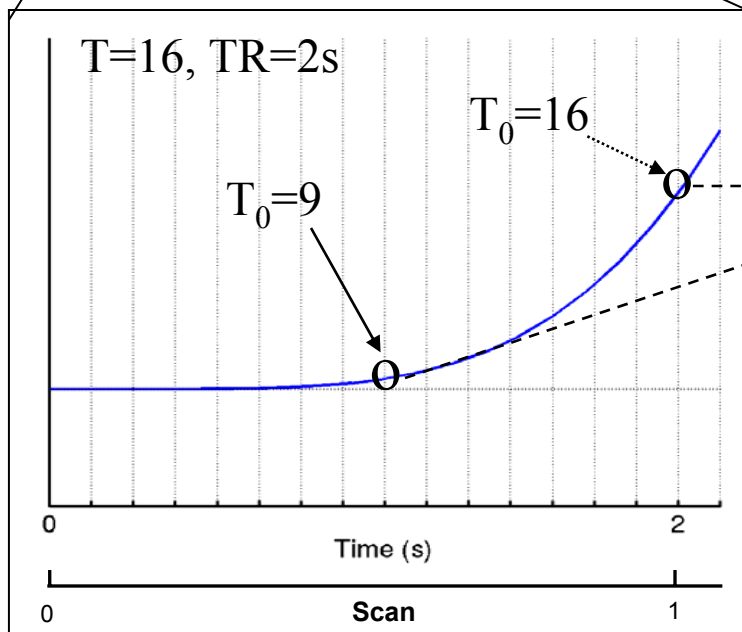
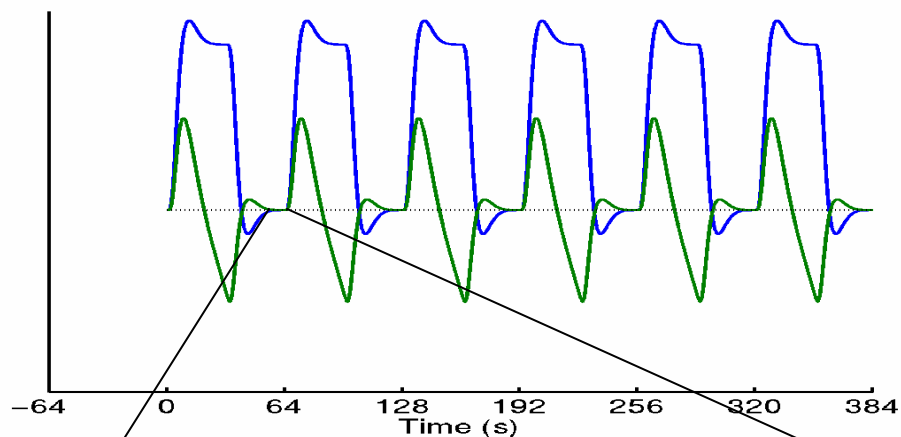
Gamma functions $f_i(\tau)$ of
peristimulus time τ
(Orthogonalised)



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



A word about down-sampling



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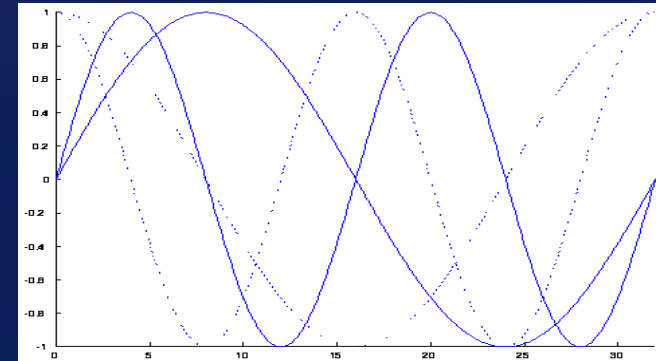
Temporal Basis Functions

- **Fourier Set**

Windowed sines & cosines

Any shape (up to frequency limit)

Inference via F-test



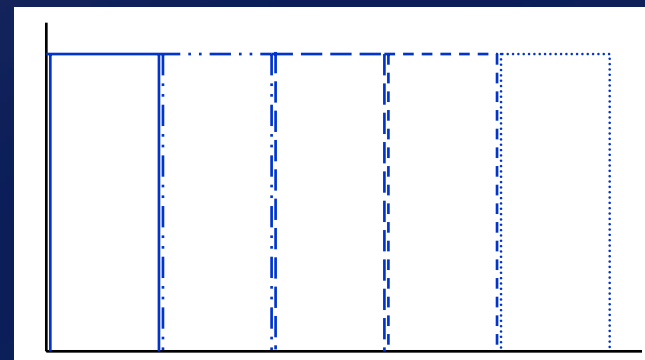
Temporal Basis Functions

- **Finite Impulse Response**

Mini “timebins” (selective averaging)

Any shape (up to bin-width)

Inference via F-test



Temporal Basis Functions

- **Fourier Set**

Windowed sines & cosines

Any shape (up to frequency limit)

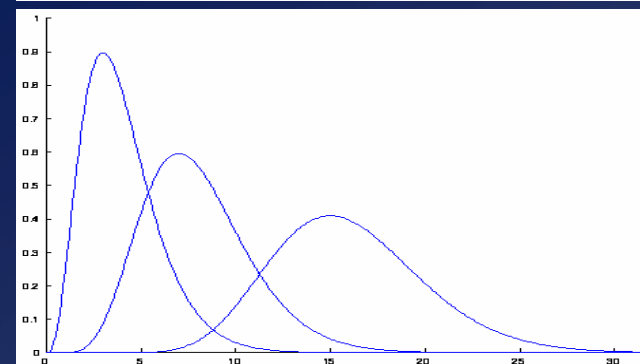
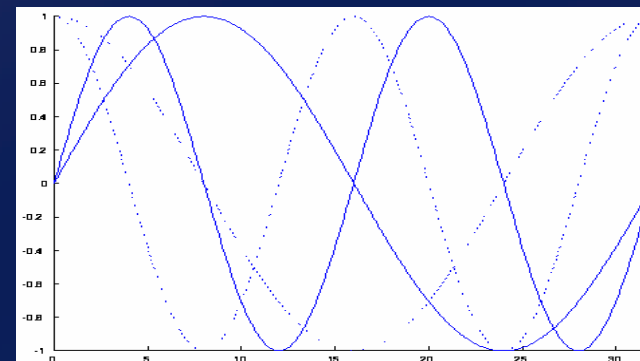
Inference via F-test

- **Gamma Functions**

Bounded, asymmetrical (like BOLD)

Set of different lags

Inference via F-test



Temporal Basis Functions

- **Fourier Set**

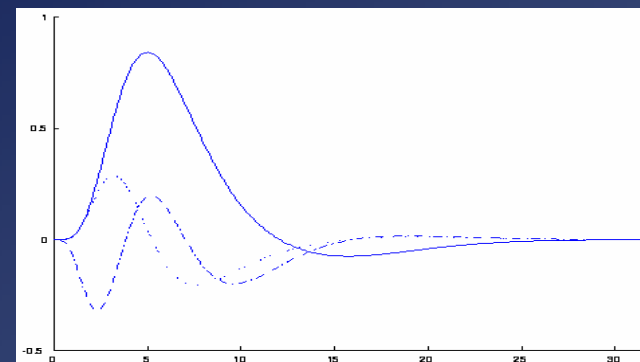
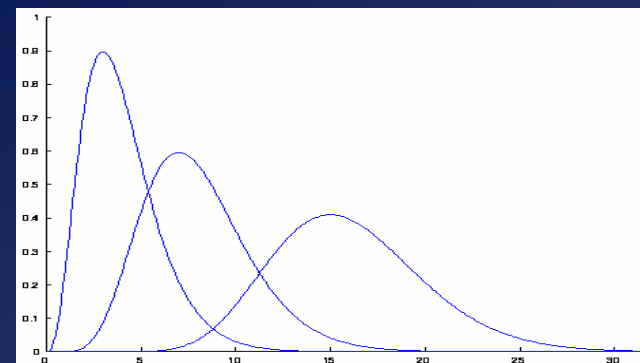
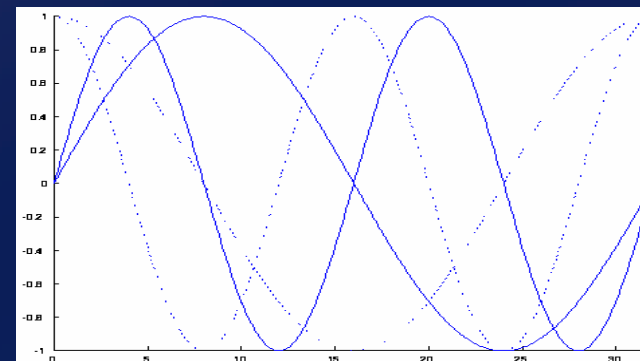
Windowed sines & cosines
Any shape (up to frequency limit)
Inference via F-test

- **Gamma Functions**

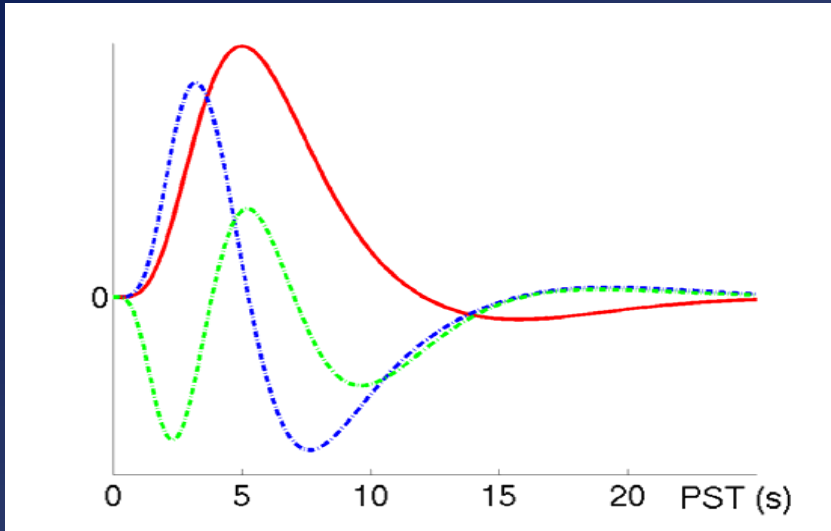
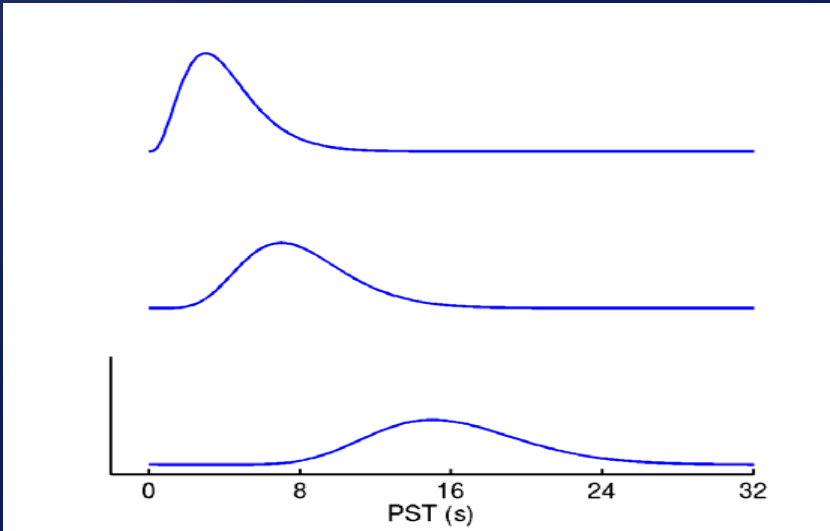
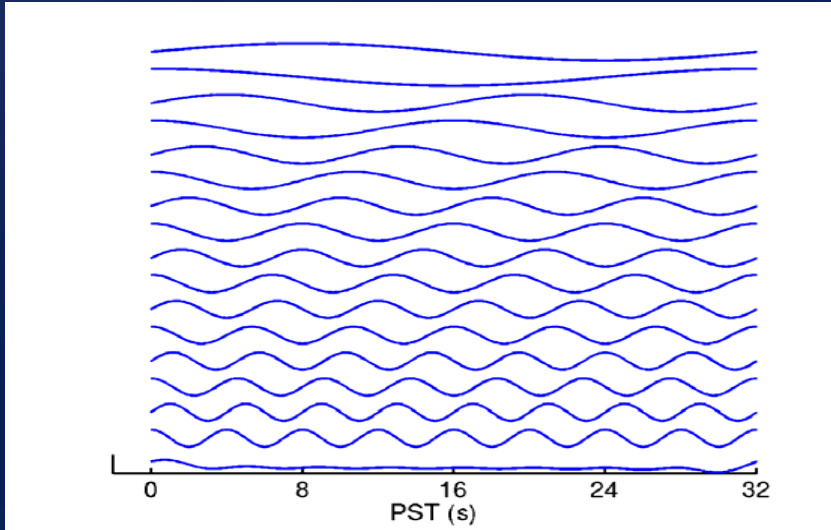
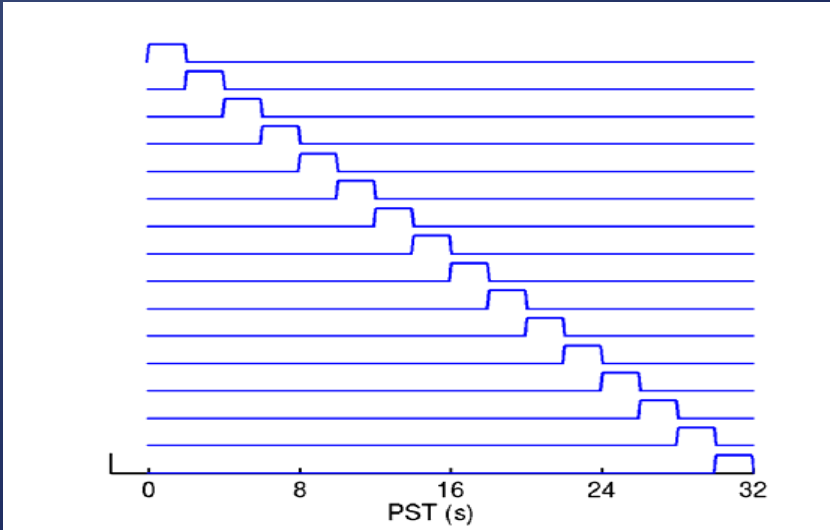
Bounded, asymmetrical (like BOLD)
Set of different lags
Inference via F-test

- **“Informed” Basis Set**

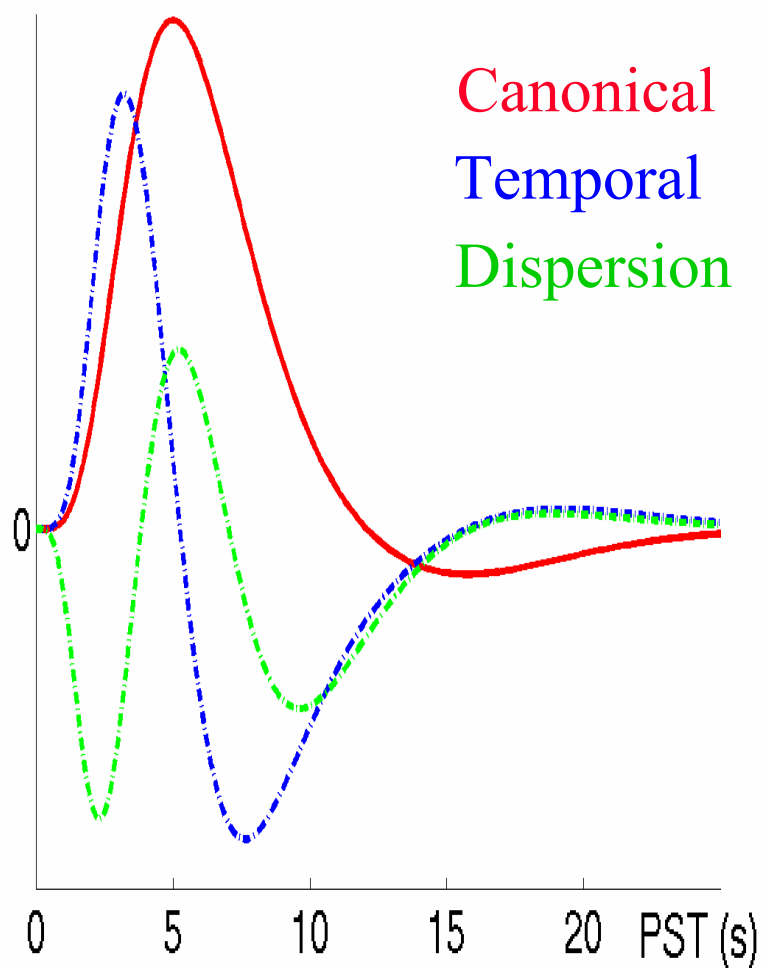
Best guess of canonical BOLD response
Variability captured by Taylor expansion
“Magnitude” inferences via t-test...?



Temporal Basis Functions



Temporal Basis Functions



“Informed” Basis Set (Friston et al. 1998)

- 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 good fit...more later)
- “Latency” inferences via tests on *ratio of derivative : canonical parameters* (more later...)

(Other Approaches)

- **Long Stimulus Onset Asynchrony (SOA)**

Can ignore overlap between responses (Cohen et al 1997)

... but long SOAs are less sensitive

- **Fully counterbalanced designs**

Assume response overlap cancels (Saykin et al 1999)

Include fixation trials to “selectively average” response even at short SOA (Dale & Buckner, 1997)

... but unbalanced when events defined by subject

- **Define HRF from pilot scan on each subject**

May capture intersubject variability (Zarahn et al, 1997)

... but not interregional variability

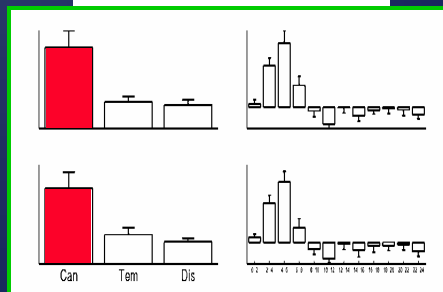
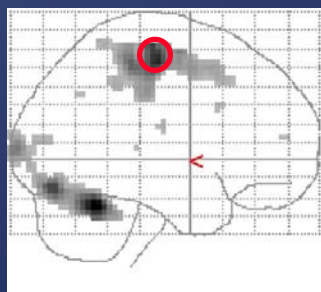
- **Numerical fitting of highly parametrised response functions**

Separate estimate of magnitude, latency, duration (Kruggel et al 1999)

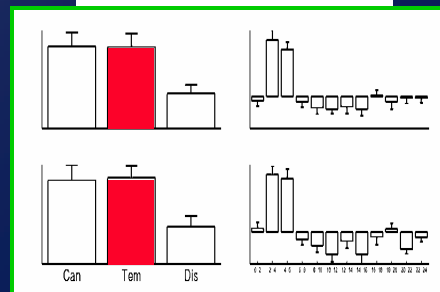
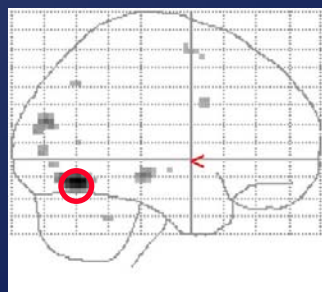
... but computationally expensive for every voxel

Temporal Basis Sets: Which One?

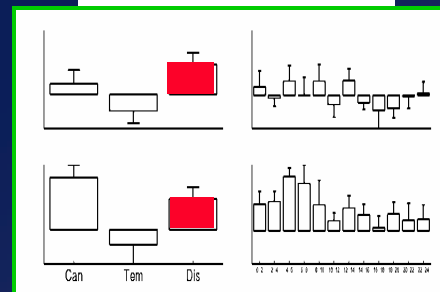
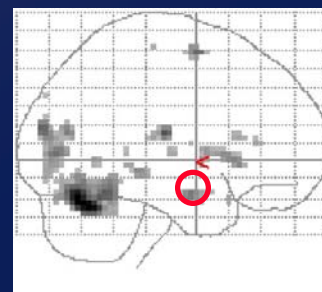
In this example (rapid motor response to faces, *Henson et al, 2001*)...



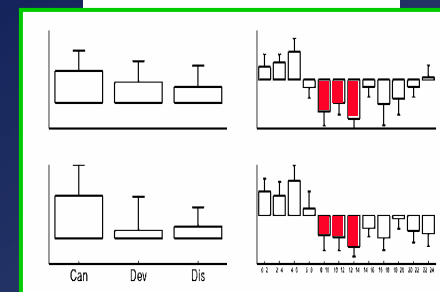
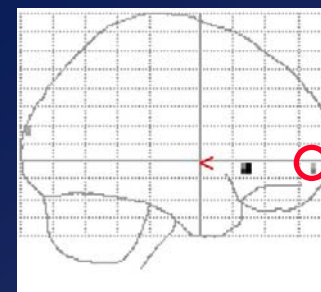
Canonical



+ Temporal



+ Dispersion



+ FIR

...canonical + temporal + dispersion derivatives appear sufficient

...may not be for more complex trials (eg stimulus-delay-response)

...but then such trials better modelled with separate neural components

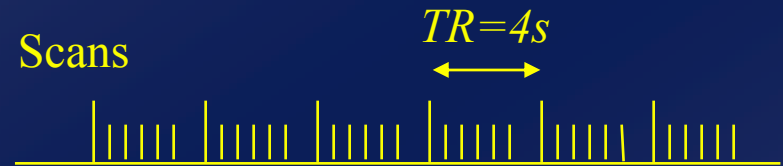
(ie activity no longer delta function) + constrained HRF (Zarahn, 1999)

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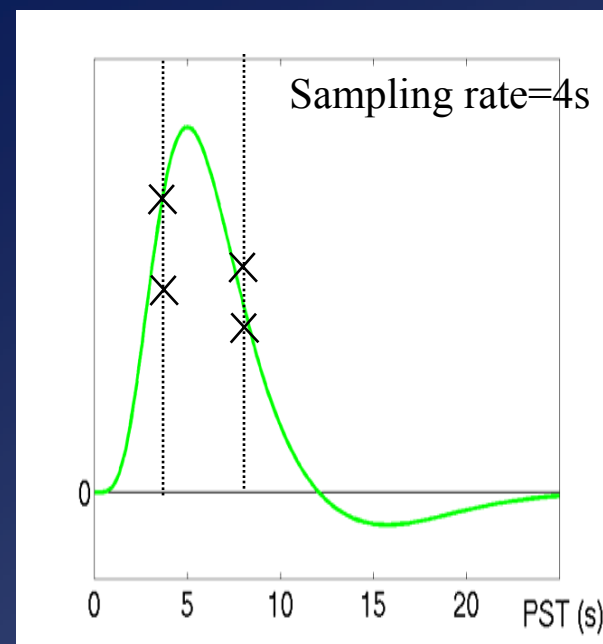
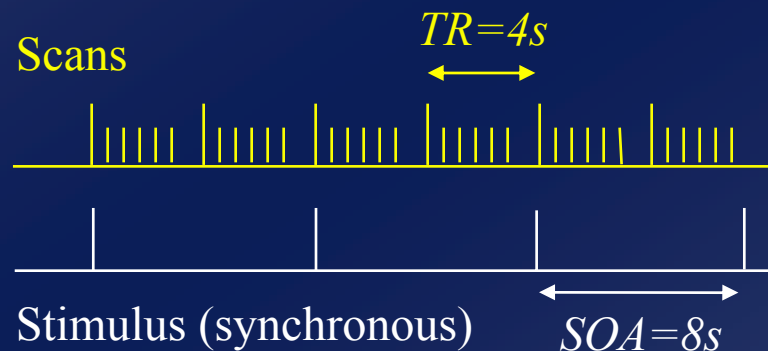
Timing Issues : Practical

- Typical TR for 48 slice EPI at 3mm spacing is $\sim 4s$



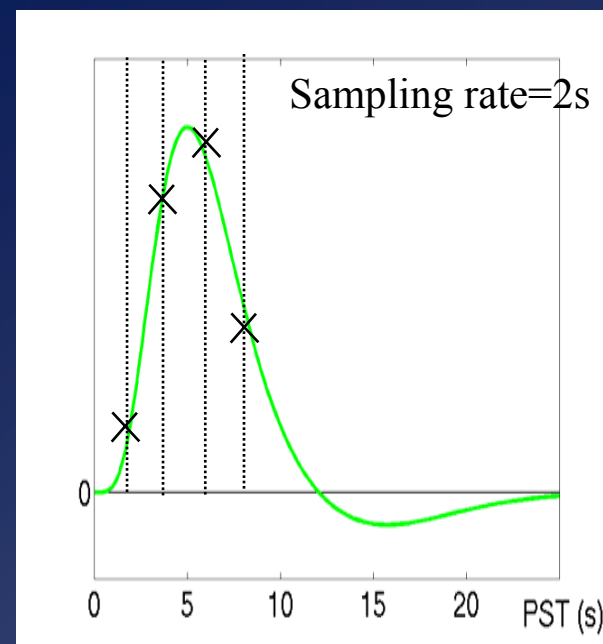
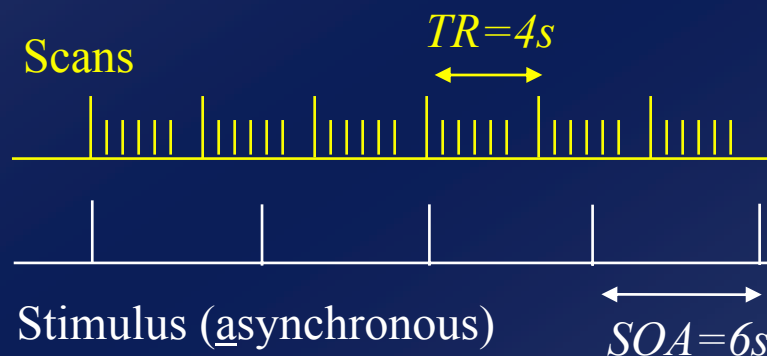
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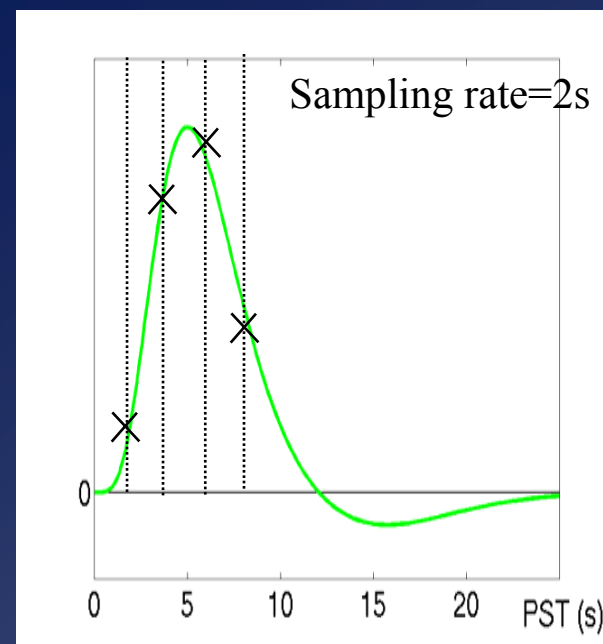
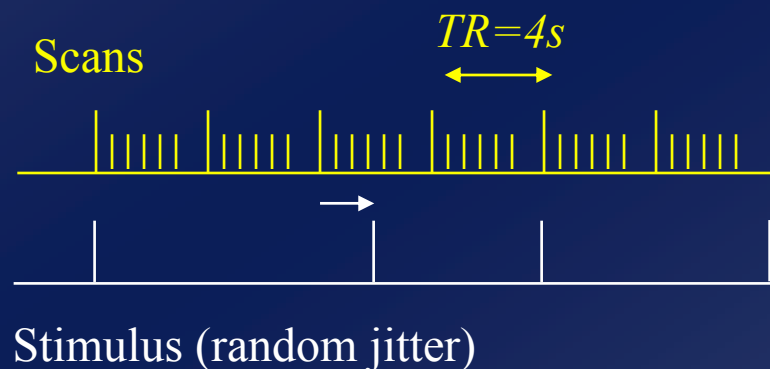
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- Higher effective sampling by:
 1. Asynchrony
eg SOA=1.5TR



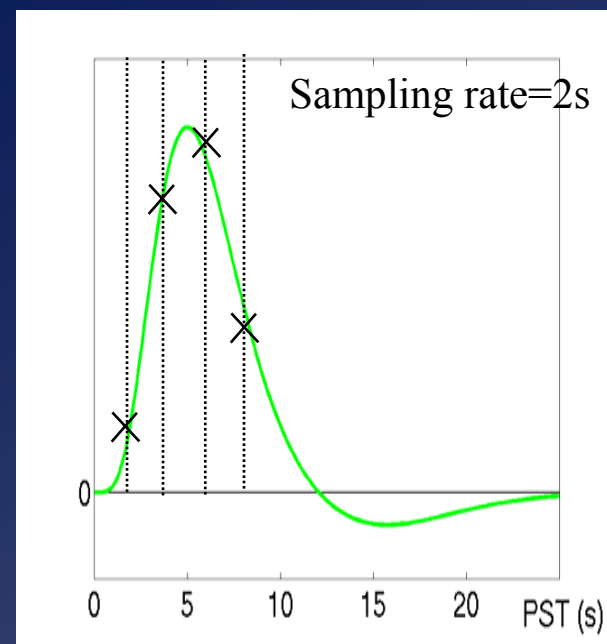
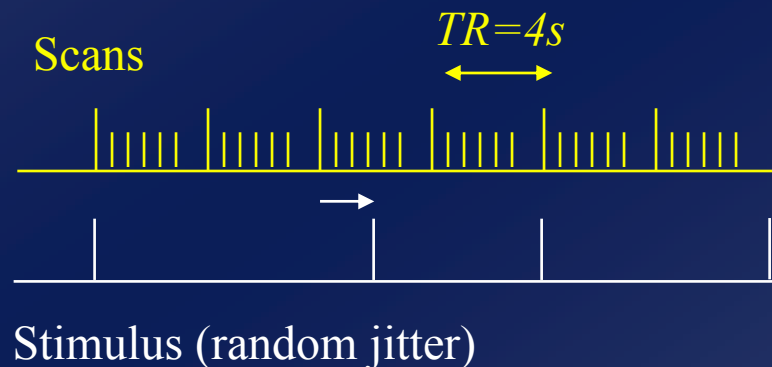
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 2. Random Jitter
eg $SOA=(2\pm 0.5)TR$



Timing Issues : Practical

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- Higher effective sampling by:
 1. Asynchrony
eg $SOA=1.5TR$
 2. Random Jitter
eg $SOA=(2\pm 0.5)TR$
- **Better response characterisation (Miezin et al, 2000)**



Timing Issues : Practical

- ...but “Slice-timing Problem”

(Henson et al, 1999)

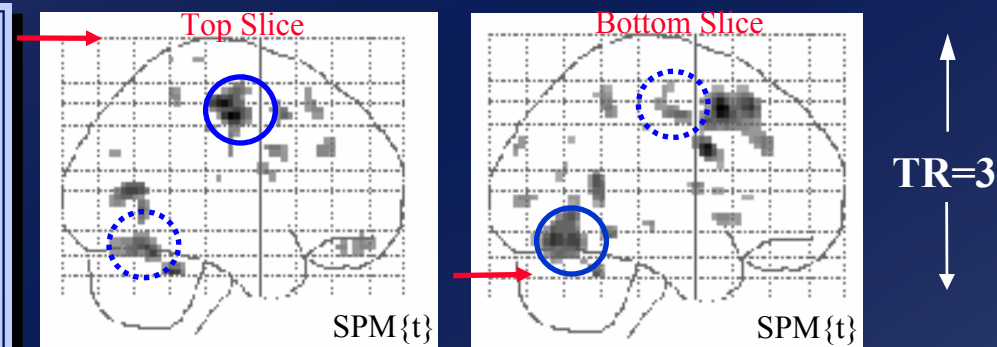
Slices acquired at different times,
yet model is the same for all slices

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=> *different results (using canonical HRF) for different reference slices*



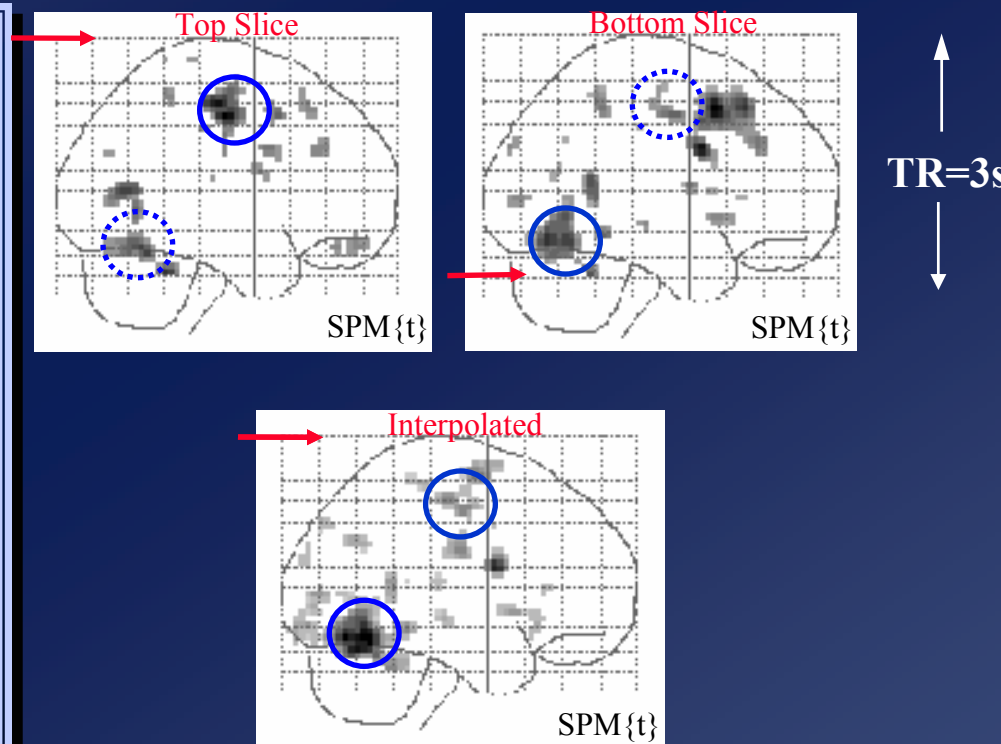
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- Solutions:

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



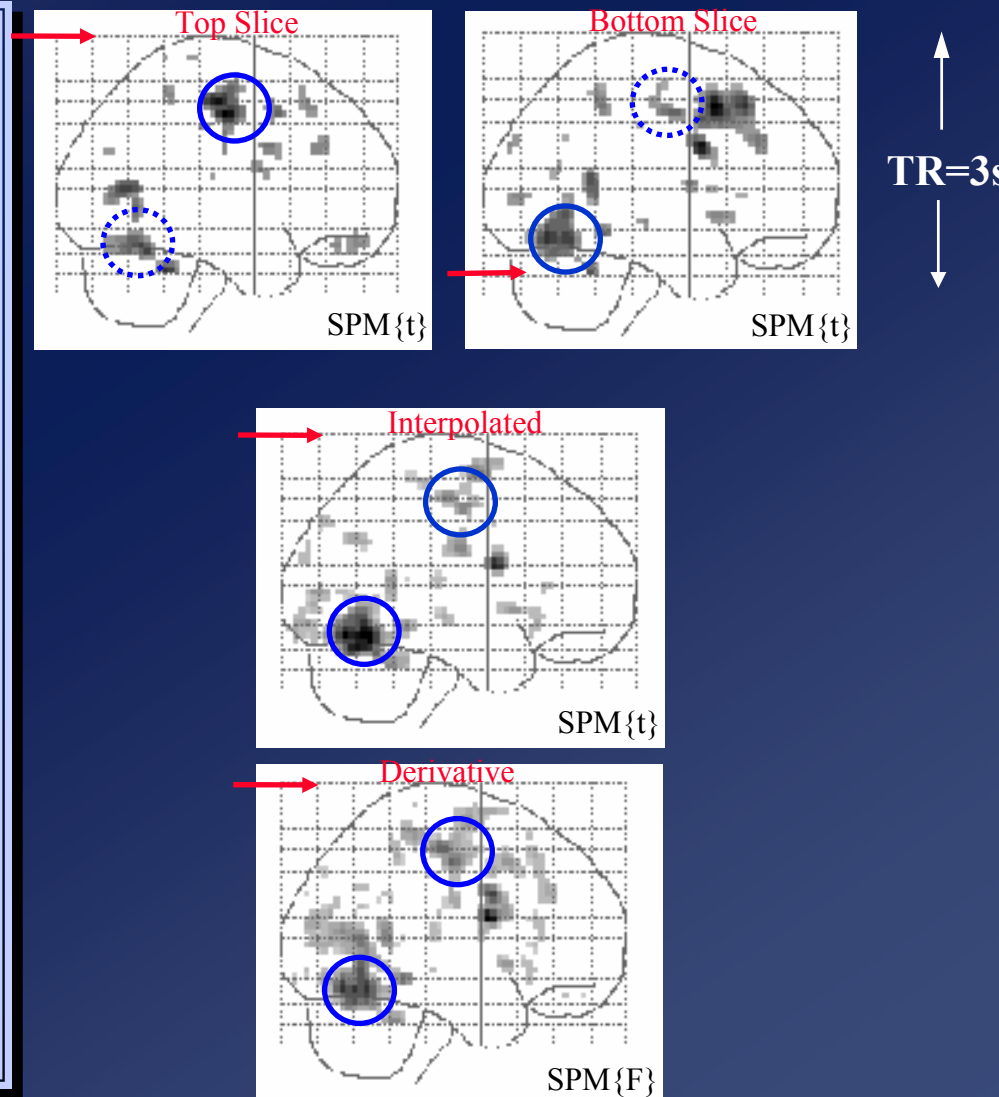
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Slices acquired at different times,
yet model is the same for all slices
=> *different results (using canonical HRF) for different reference slices*

- 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

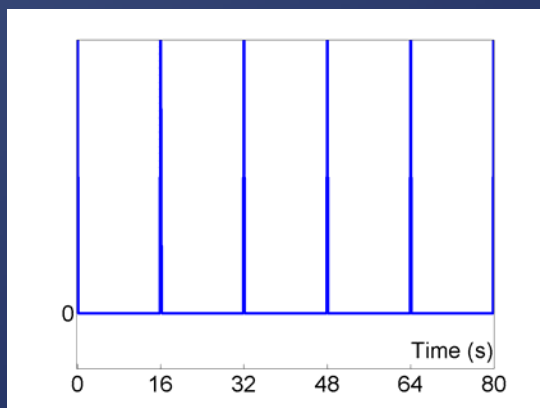


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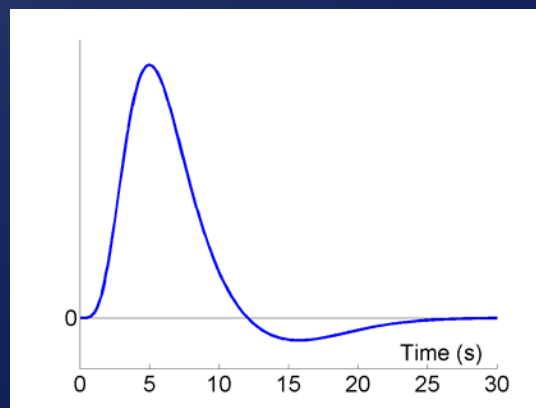
1. BOLD impulse response
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Fixed SOA = 16s

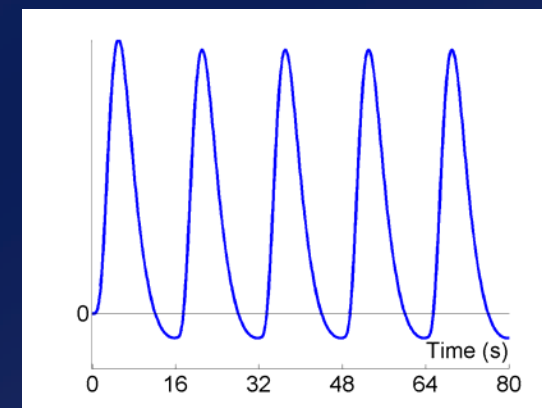
Stimulus ("Neural")



HRF



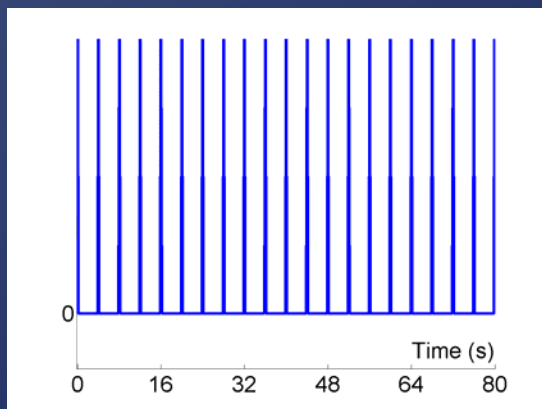
Predicted Data



Not particularly efficient...

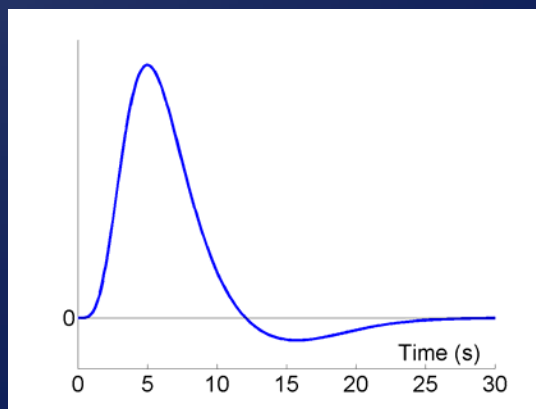
Fixed SOA = 4s

Stimulus ("Neural")



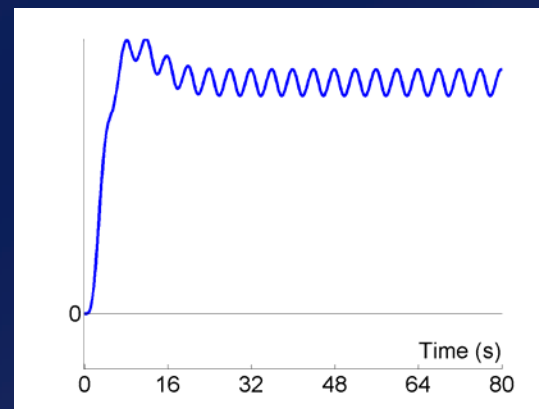
⊗

HRF



=

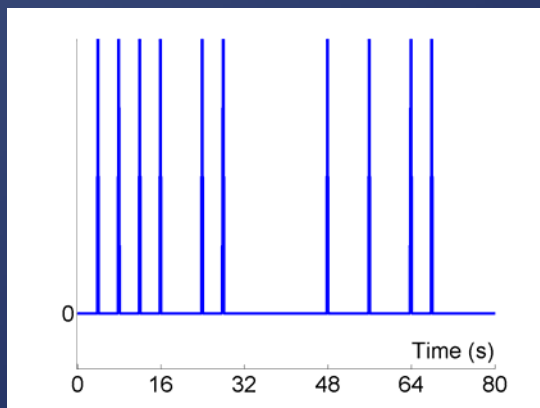
Predicted Data



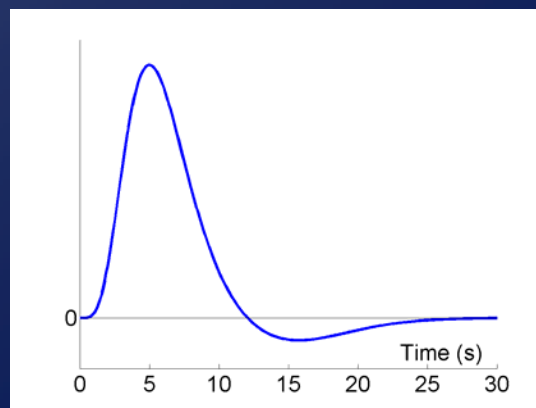
Very Inefficient...

Randomised, $SOA_{\min} = 4s$

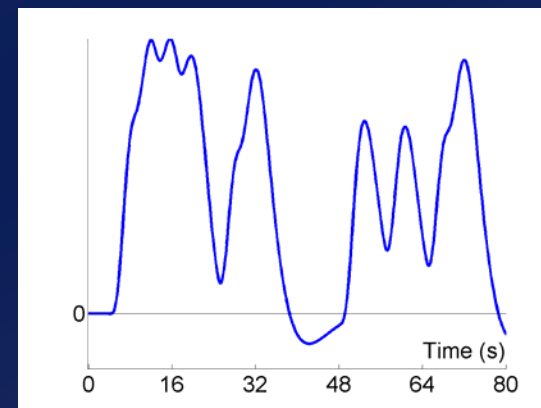
Stimulus ("Neural")



HRF



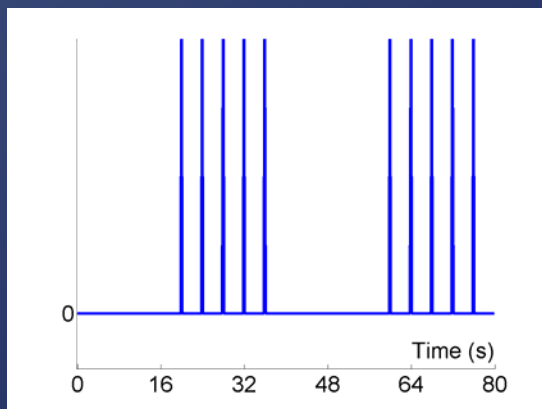
Predicted Data



More Efficient...

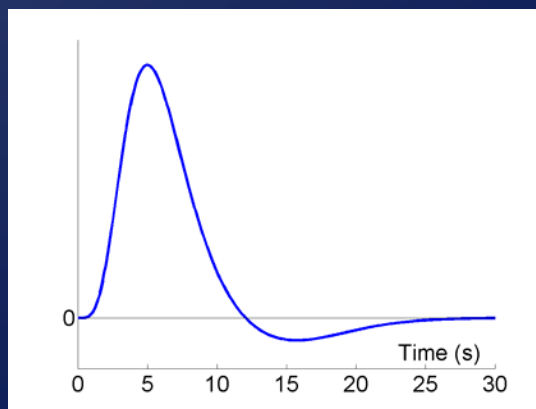
Blocked, $SOA_{min} = 4s$

Stimulus ("Neural")



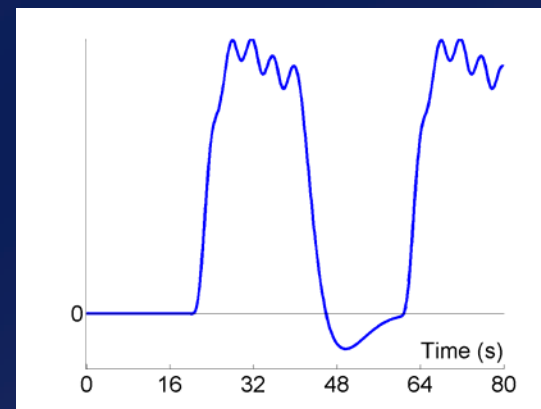
⊗

HRF



=

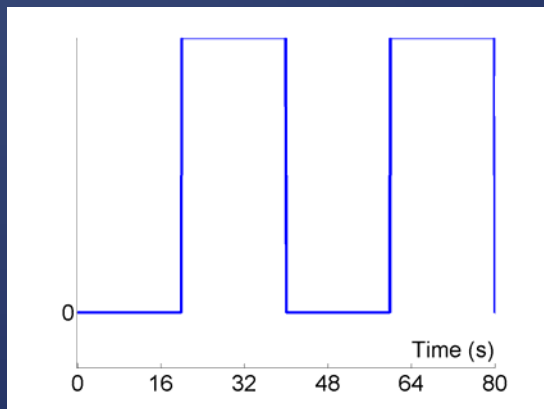
Predicted Data



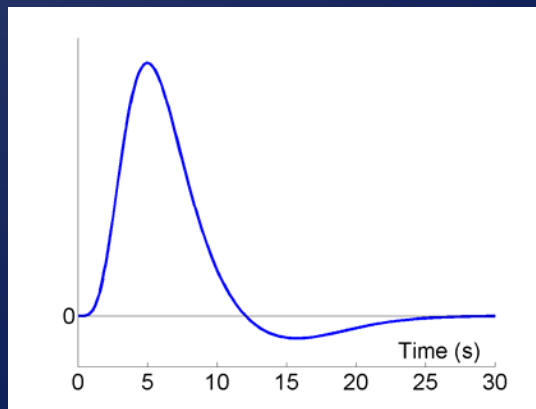
Even more Efficient...

Blocked, epoch = 20s

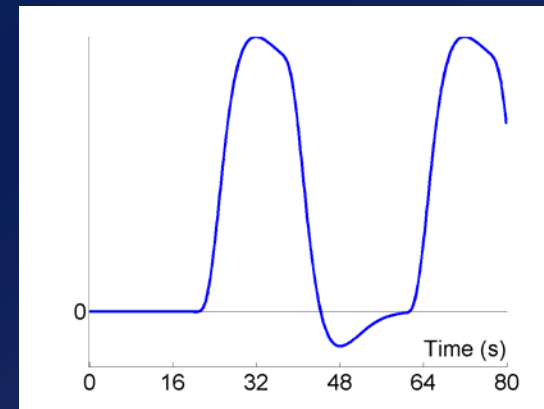
Stimulus ("Neural")



HRF

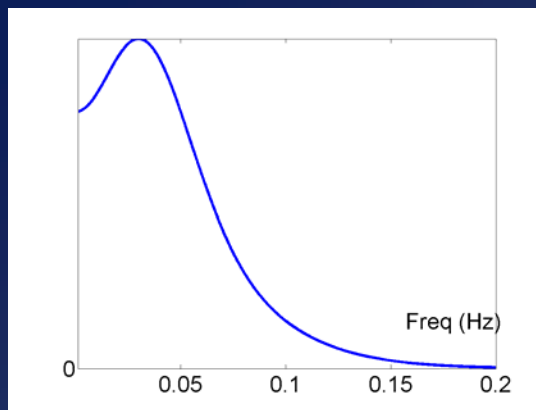
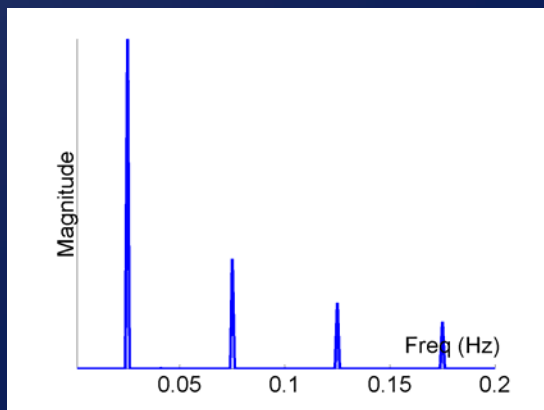


Predicted Data



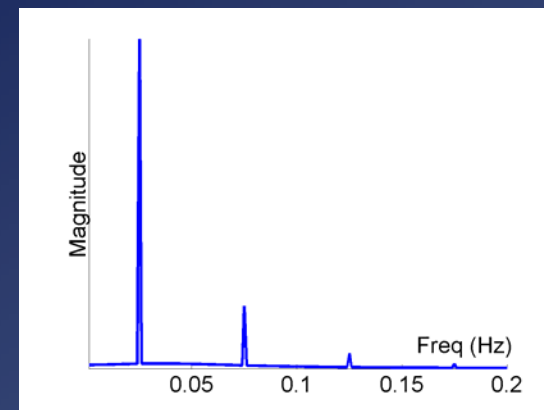
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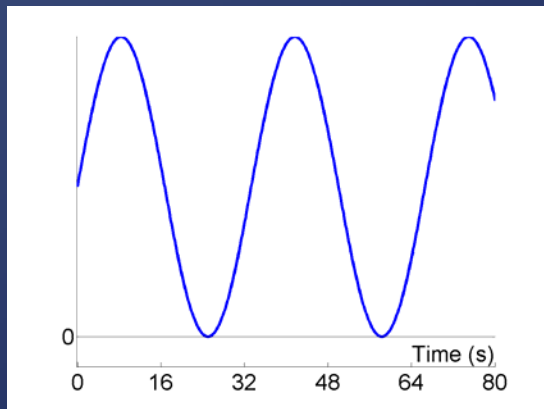
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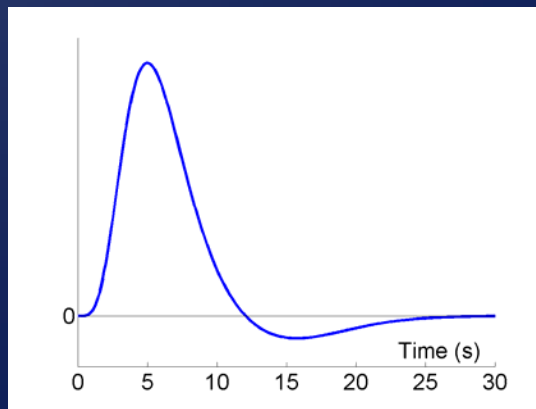
Blocked-epoch (with small SOA) and Time-Freq equivalences

Sinusoidal modulation, $f = 1/33s$

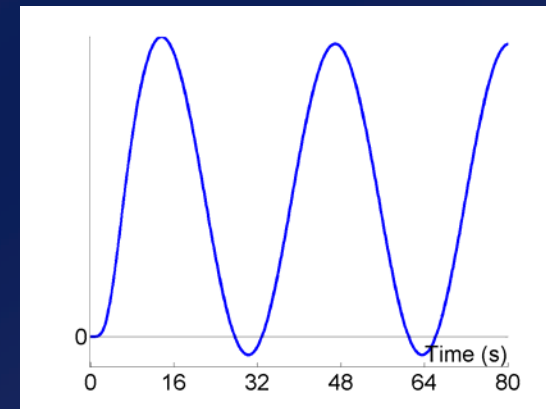
Stimulus ("Neural")



HRF

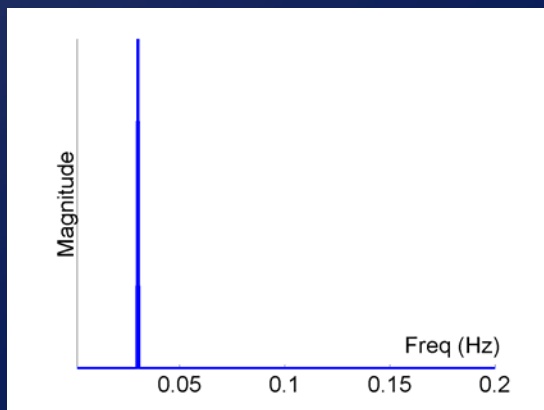


Predicted Data



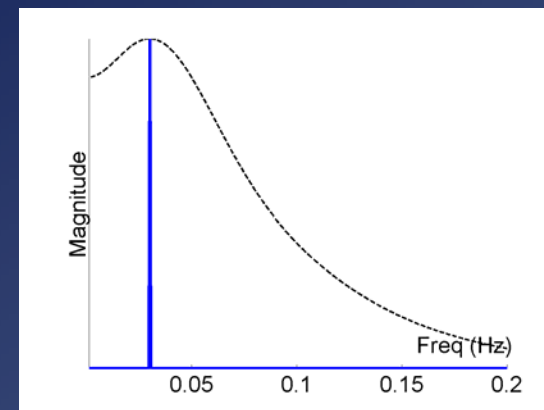
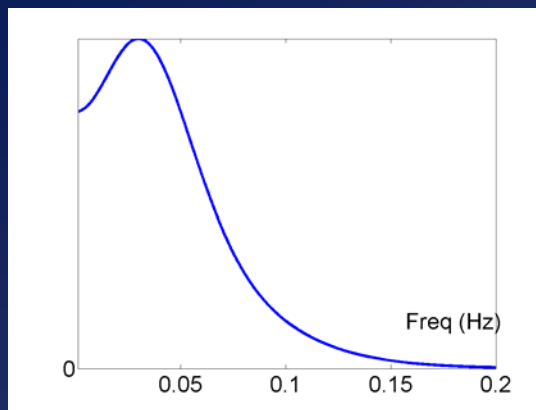
⊗

≡



×

≡



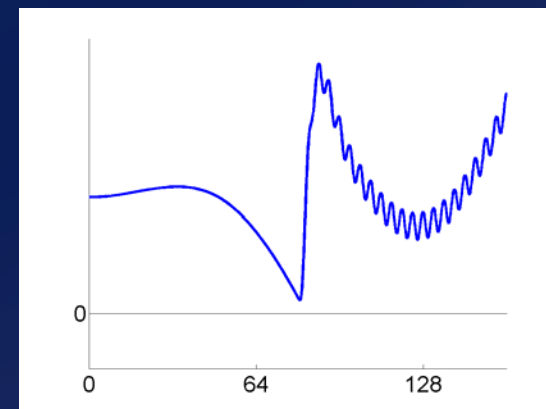
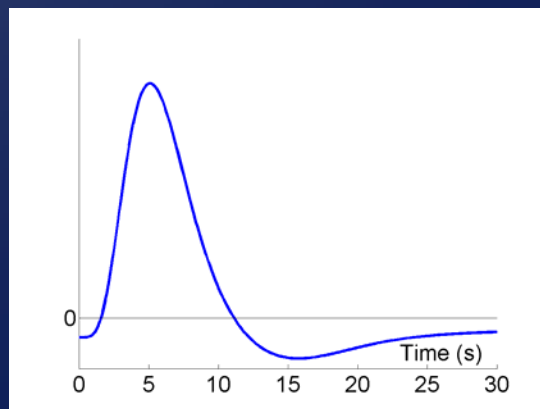
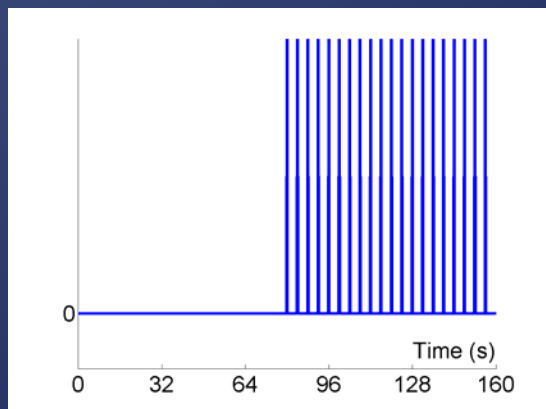
The most efficient design of all!

Blocked (80s), $SOA_{min}=4s$, highpass filter = $1/120s$

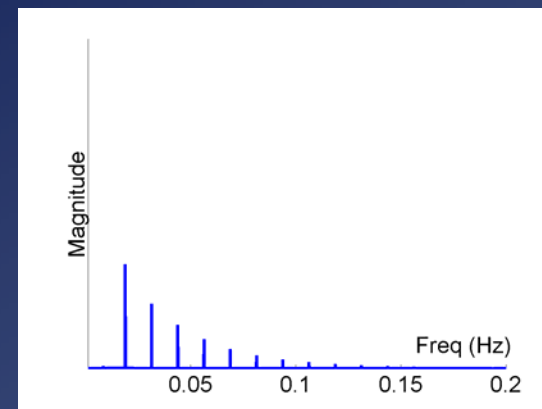
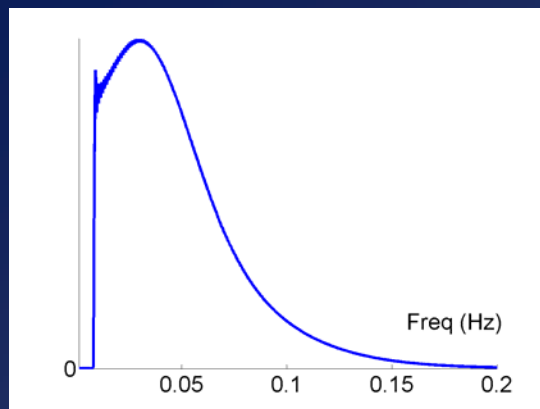
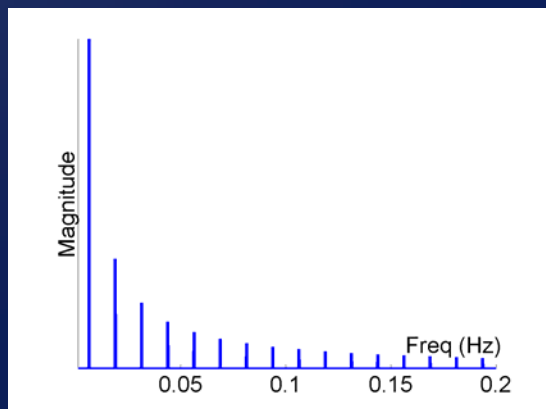
Stimulus (“Neural”)

HRF

Predicted Data



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



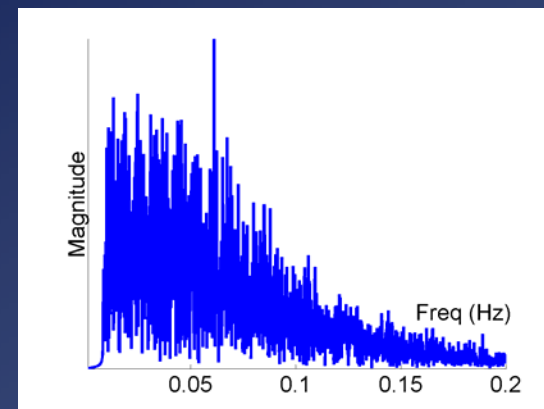
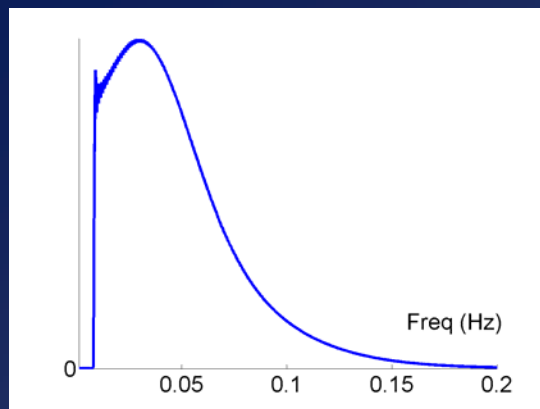
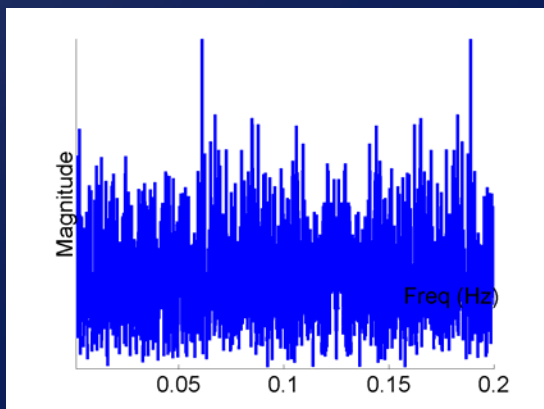
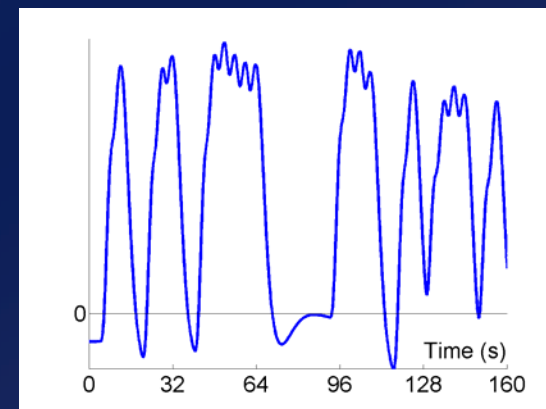
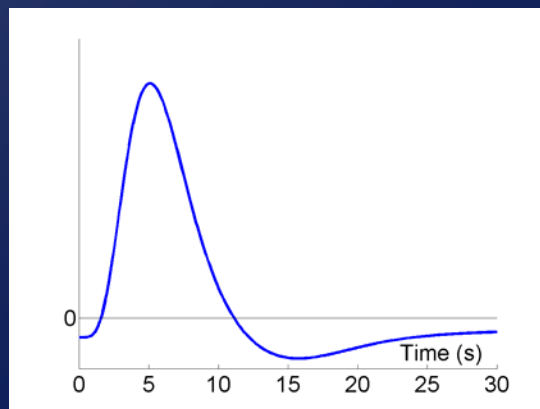
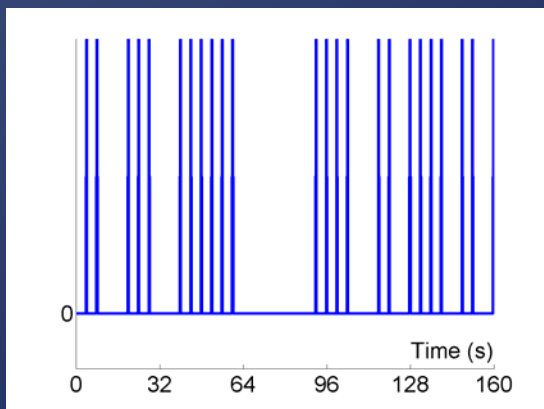
Don't have long (>60s) blocks!

Randomised, $SOA_{min}=4s$, highpass filter = $1/120s$

Stimulus (“Neural”)

HRF

Predicted Data



(Randomised design spreads power over frequencies)

Design Efficiency

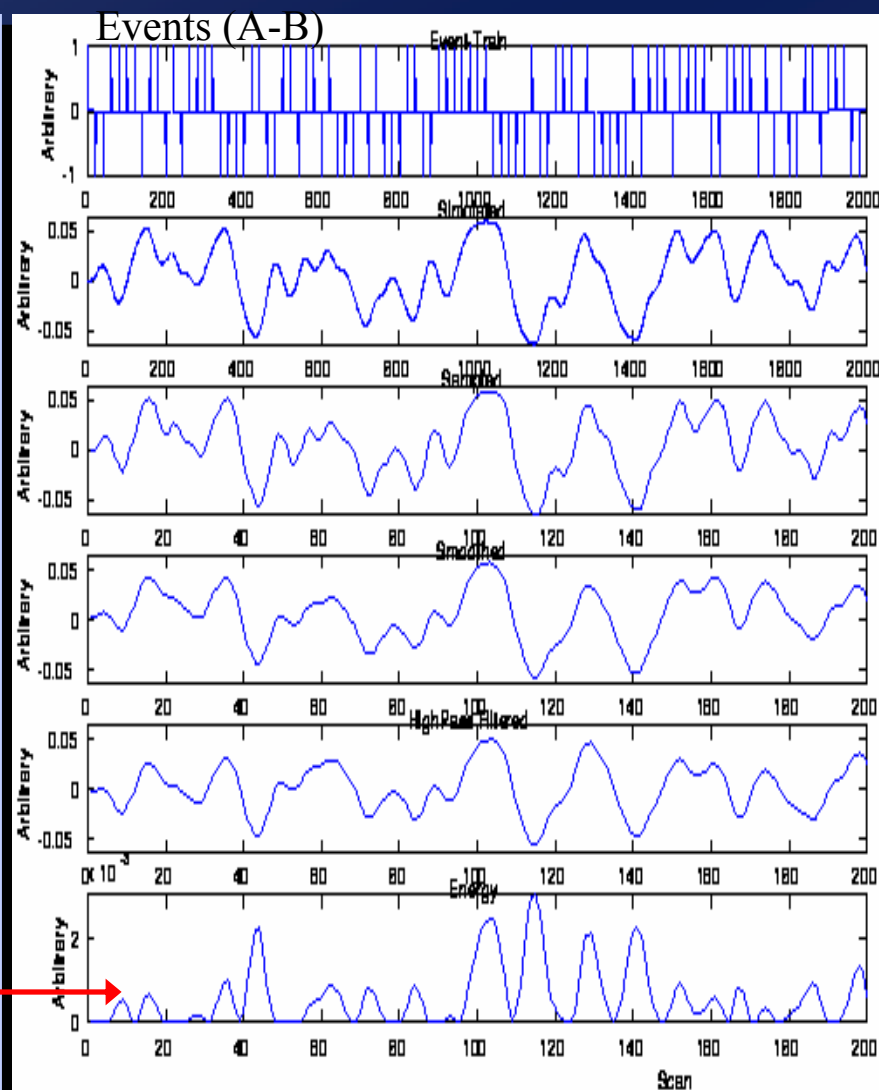
$$T = \mathbf{c}^T \boldsymbol{\beta} / \text{var}(\mathbf{c}^T \boldsymbol{\beta})$$

$$\text{Var}(\mathbf{c}^T \boldsymbol{\beta}) = \text{sqrt}(\sigma^2 \mathbf{c}^T (\mathbf{X}^T \mathbf{X})^{-1} \mathbf{c}) \quad (\text{i.i.d})$$

- For max. T , want min. contrast variability (Friston et al, 1999)
- If assume that noise variance (σ^2) is unaffected by changes in X ...
- ...then want maximal efficiency, e :

$$e(\mathbf{c}, X) = \{ \mathbf{c}^T (\mathbf{X}^T \mathbf{X})^{-1} \mathbf{c} \}^{-1}$$

- = maximal bandpassed signal energy (Josephs & Henson, 1999)



Efficiency - Single Event-type

- Design parametrised by:

SOA_{min} Minimum SOA

Efficiency - Single Event-type

- Design parametrised by:

SOA_{min} Minimum SOA

$p(t)$ Probability of event
at each SOA_{min}

Efficiency - Single Event-type

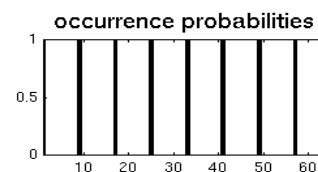
- Design parametrised by:

SOA_{min} Minimum SOA

$p(t)$ Probability of event
at each SOA_{min}

- **Deterministic**

$$p(t)=1 \text{ iff } t=nT$$



Efficiency - Single Event-type

- Design parametrised by:

SOA_{min} Minimum SOA

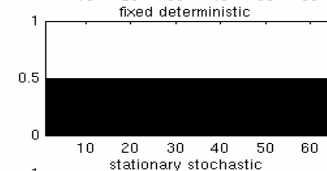
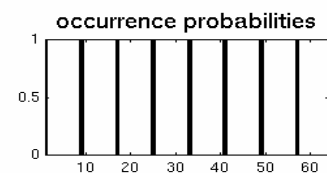
$p(t)$ Probability of event
at each SOA_{min}

- Deterministic

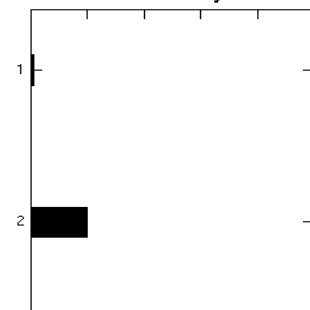
$$p(t) = 1 \text{ iff } t = nSOA_{min}$$

- Stationary stochastic**

$$p(t) = \text{constant} < 1$$



Efficiency



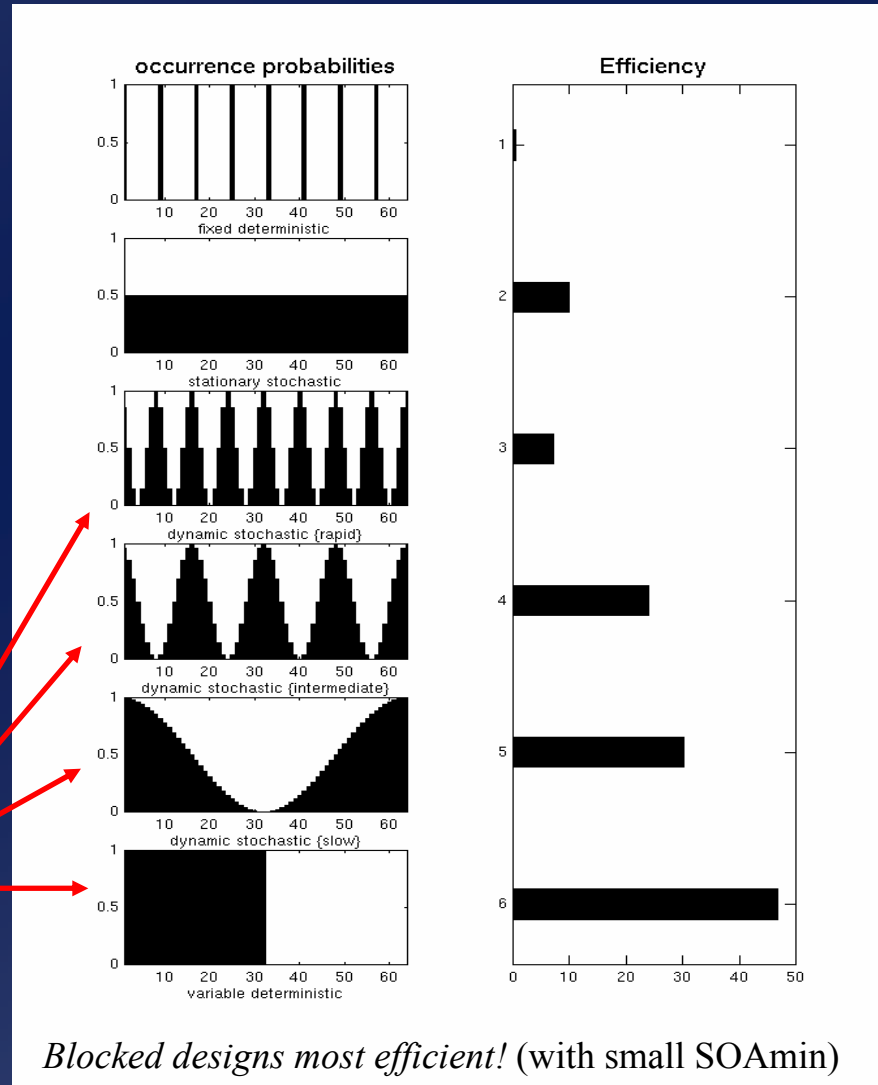
Efficiency - Single Event-type

- Design parametrised by:

SOA_{min} Minimum SOA

$p(t)$ Probability of event
at each SOA_{min}

- Deterministic
 $p(t) = 1 \text{ iff } t = nT$
- Stationary stochastic
 $p(t) = \text{constant}$
- Dynamic stochastic**
 $p(t)$ varies (eg blocked)



Efficiency - Multiple Event-types

- Design parametrised by:

SOA_{min} Minimum SOA

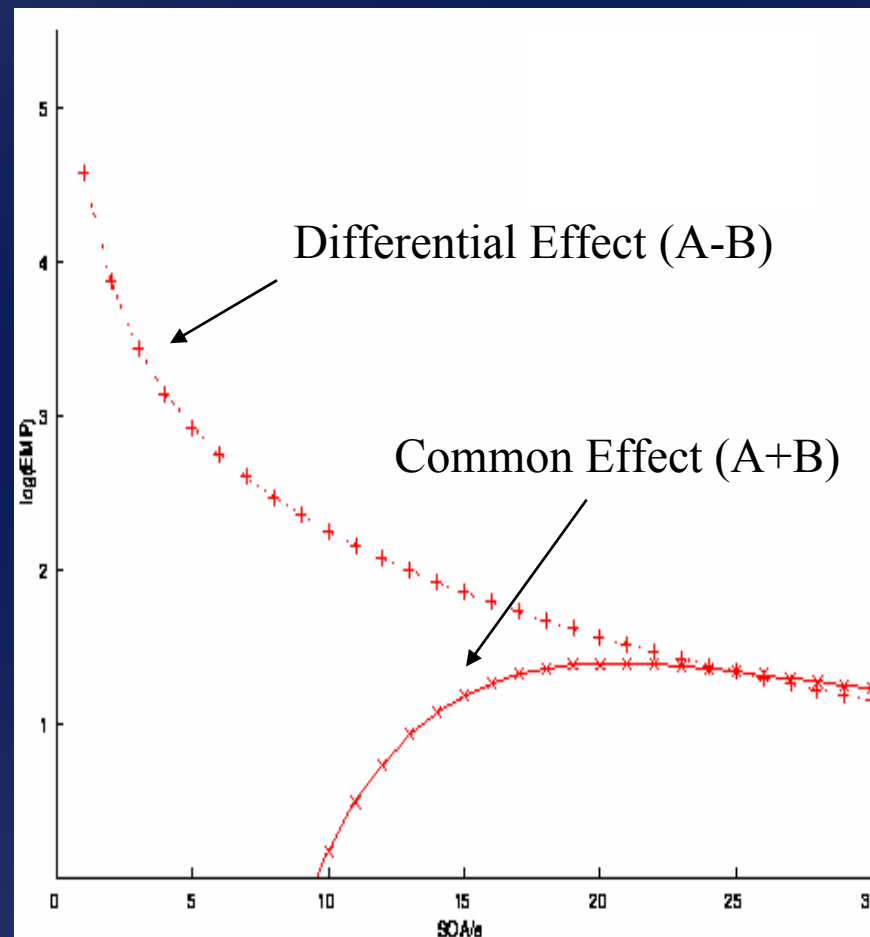
$p_i(\mathbf{h})$ Probability of event-type i given history \mathbf{h} of last m events

- With n event-types $p_i(\mathbf{h})$ is a $n^m \times n$ Transition Matrix

- Example: Randomised AB

	A	B
A	0.5	0.5
B	0.5	0.5

=> **ABBBABAABABAAA...**



4s smoothing; 1/60s highpass filtering

Efficiency - Multiple Event-types

- Example: Alternating AB

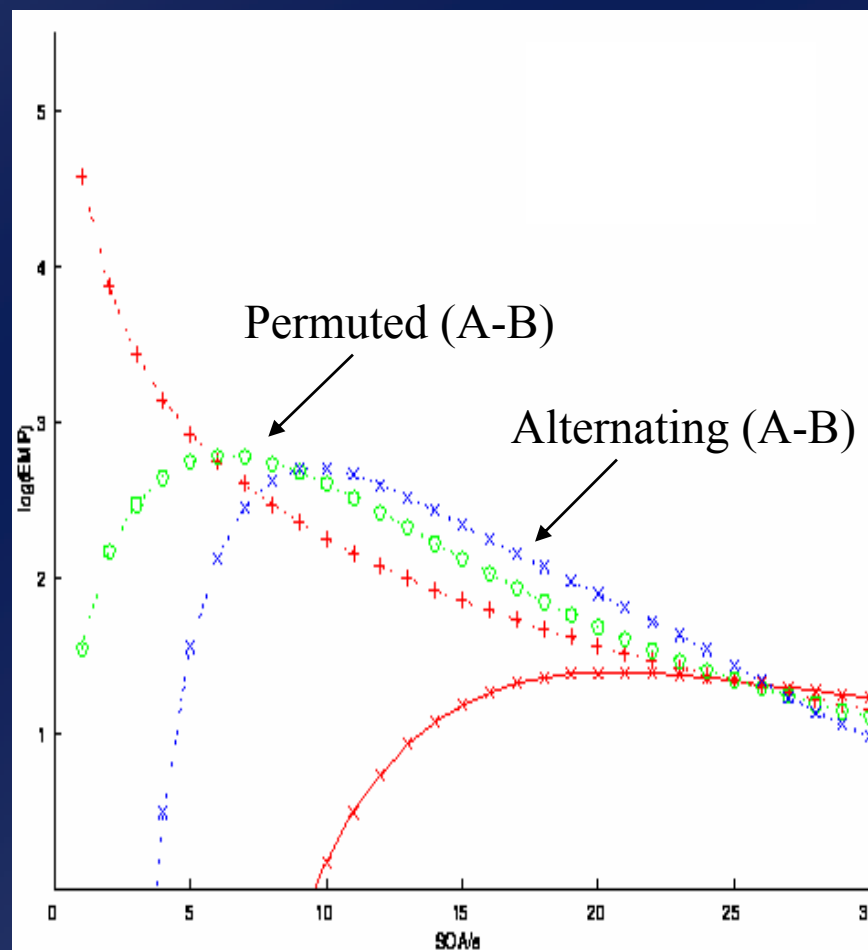
	A	B
A	0	1
B	1	0

=> **ABABABABABAB...**

- Example: Permuted AB

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

=> **ABBAABABABBA...**



4s smoothing; 1/60s highpass filtering

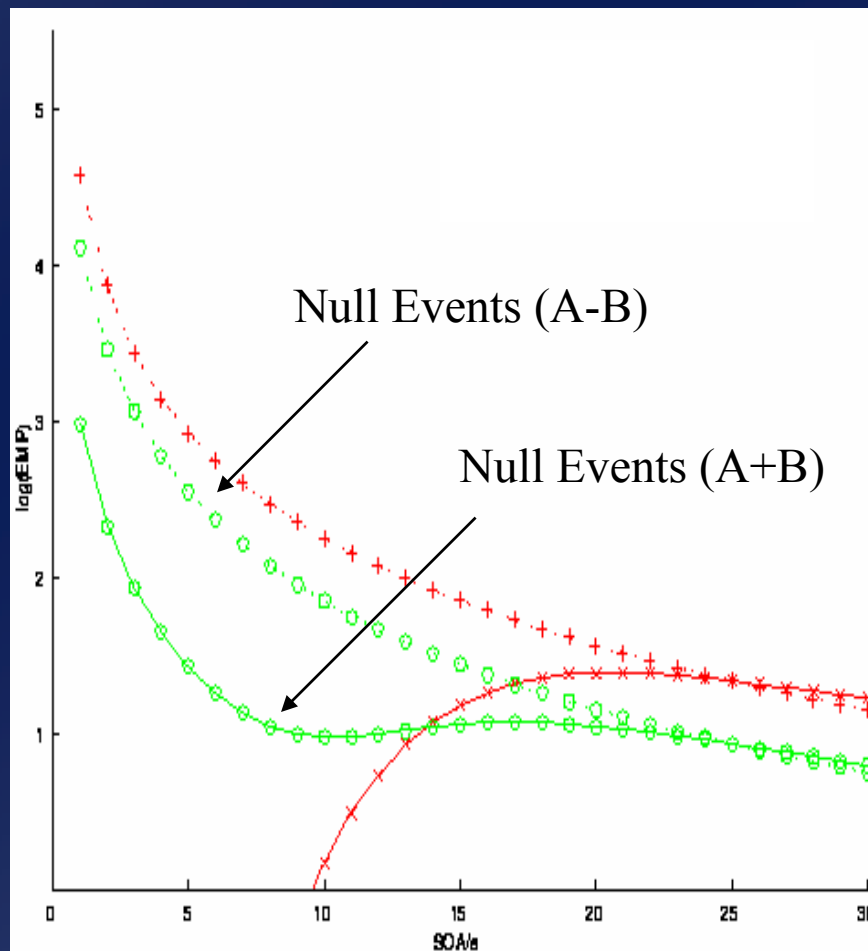
Efficiency - Multiple Event-types

- 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)
- Selective averaging of data (Dale & Buckner 1997)



4s smoothing; 1/60s highpass filtering

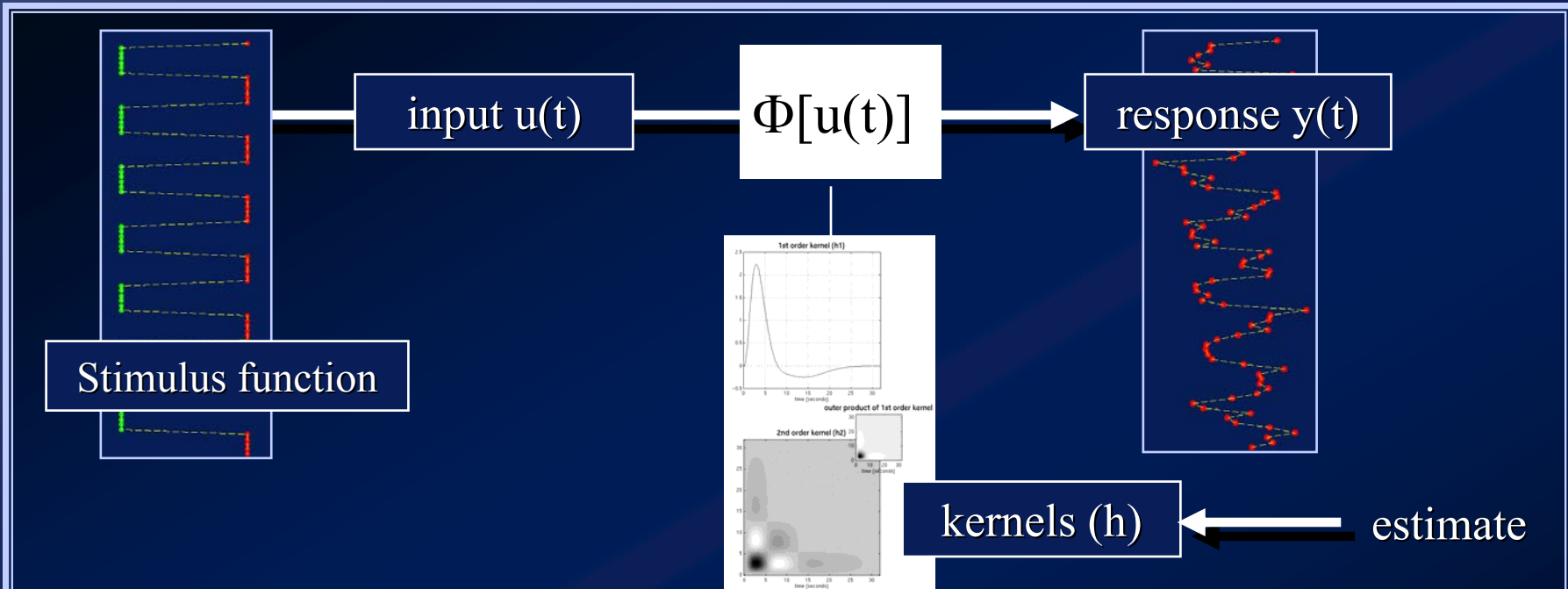
Efficiency - Conclusions

- Optimal design for one contrast may not be optimal for another
- Blocked designs generally most efficient with short SOAs (but earlier restrictions and problems of interpretation...)
- With randomised designs, optimal SOA for differential effect (A-B) is minimal SOA (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. BOLD impulse response
2. General Linear Model
3. Temporal Basis Functions
4. Timing Issues
5. Design Optimisation
6. **Nonlinear Models**
7. Example Applications

Nonlinear Model



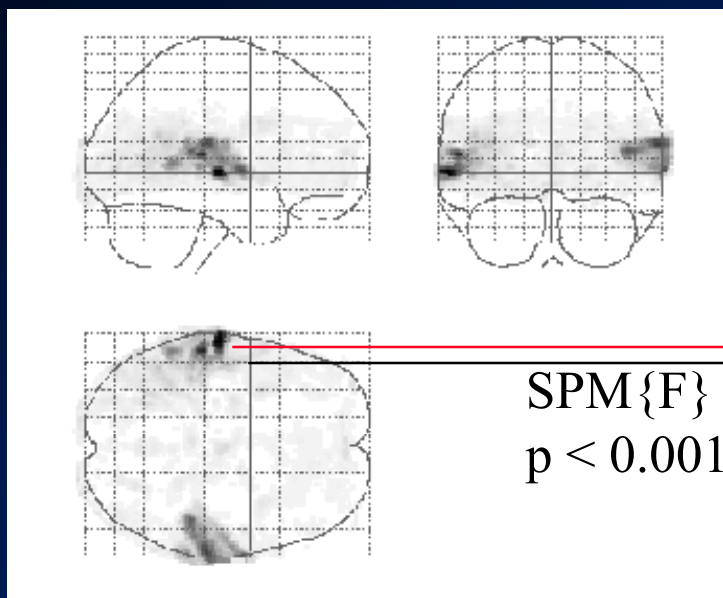
Volterra series - a general nonlinear input-output model

$$y(t) = \Phi_1[u(t)] + \Phi_2[u(t)] + \dots + \Phi_n[u(t)] + \dots$$

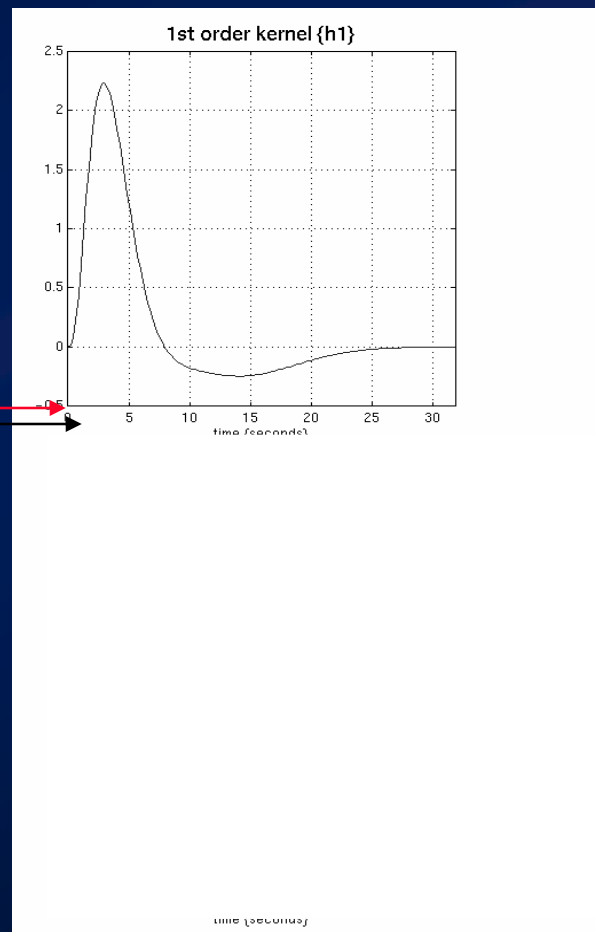
$$\Phi_n[u(t)] = \sum \dots \sum h_n(t_1, \dots, t_n) u(t - t_1) \dots u(t - t_n) dt_1 \dots dt_n$$

Nonlinear Model

Friston et al (1997)



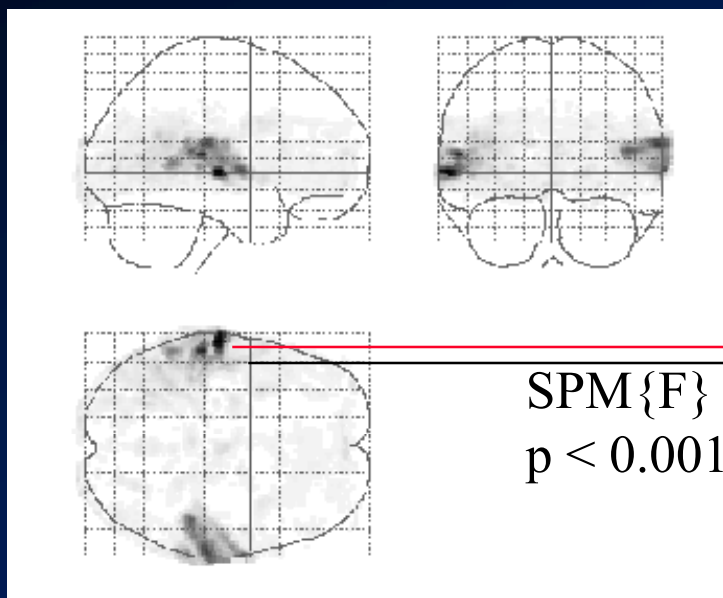
kernel coefficients - h



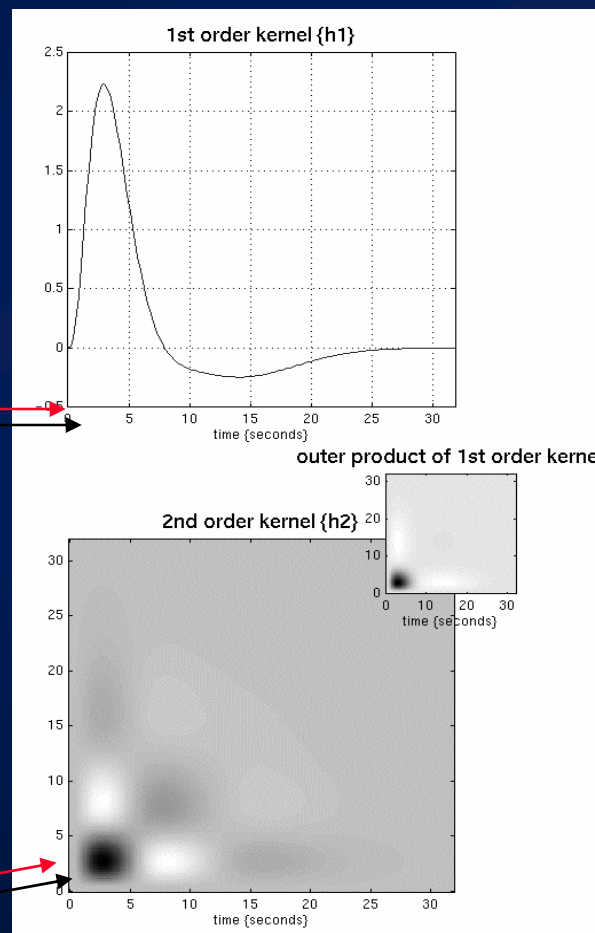
SPM{F} testing H_0 : kernel coefficients, $h = 0$

Nonlinear Model

Friston et al (1997)



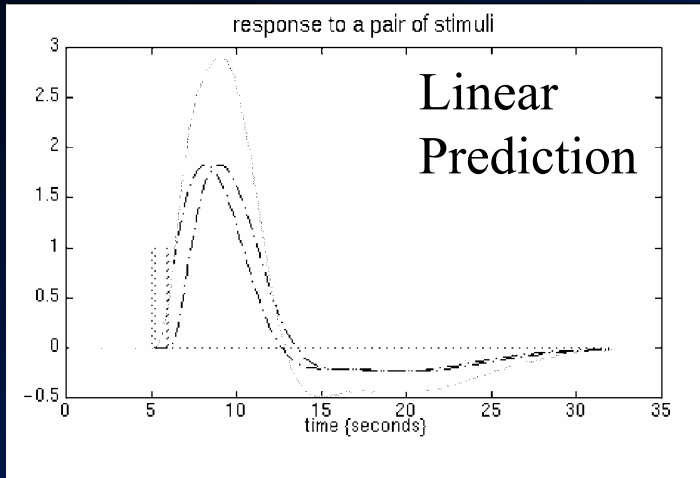
kernel coefficients - h



SPM{F} testing H_0 : kernel coefficients, $h = 0$

Significant nonlinearities at SOAs 0-10s:
(e.g., underadditivity from 0-5s)

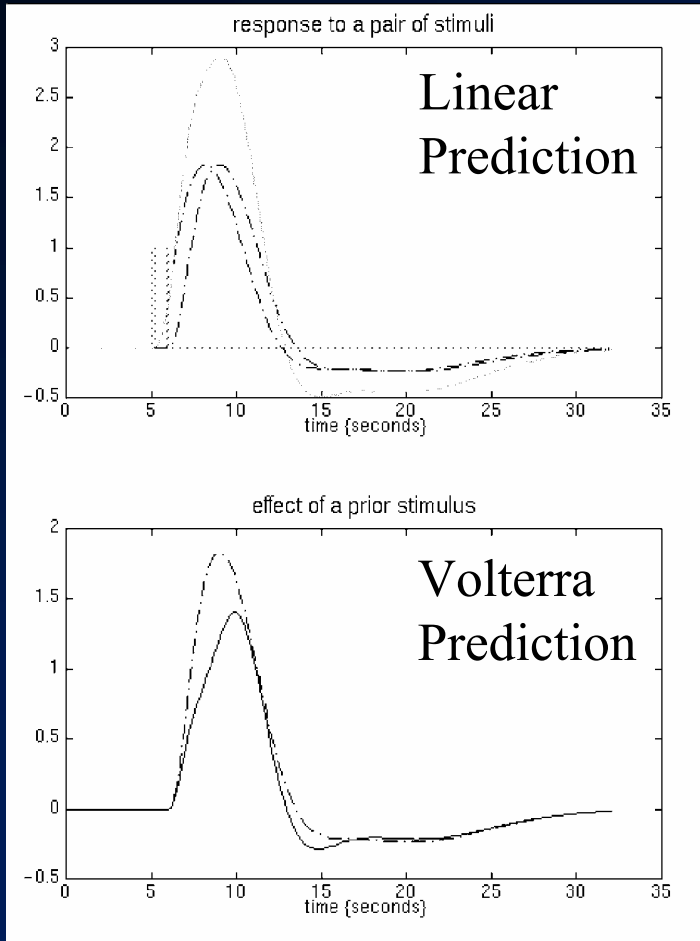
Nonlinear Effects



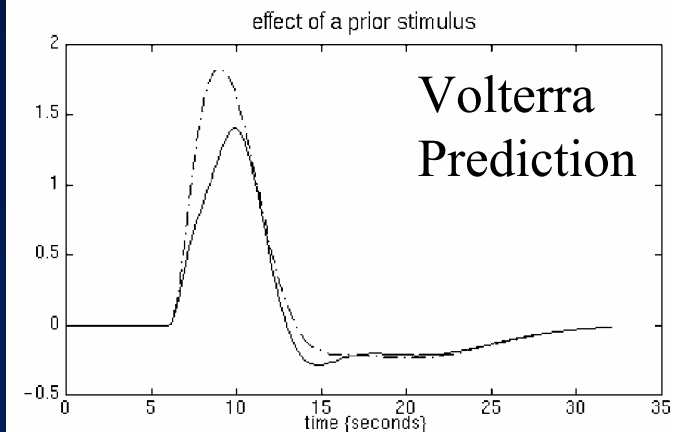
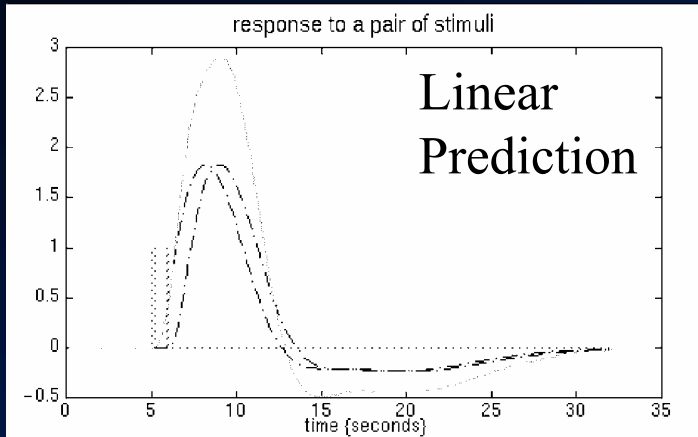
Underadditivity at short SOAs

Nonlinear Effects

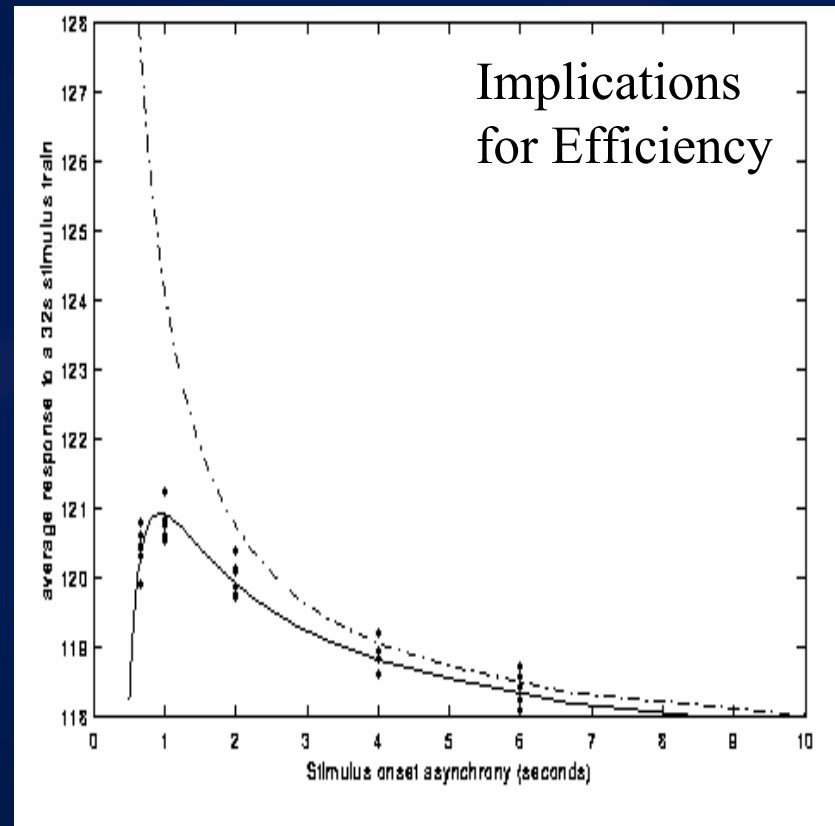
Underadditivity at short SOAs



Nonlinear Effects



Underadditivity at short SOAs

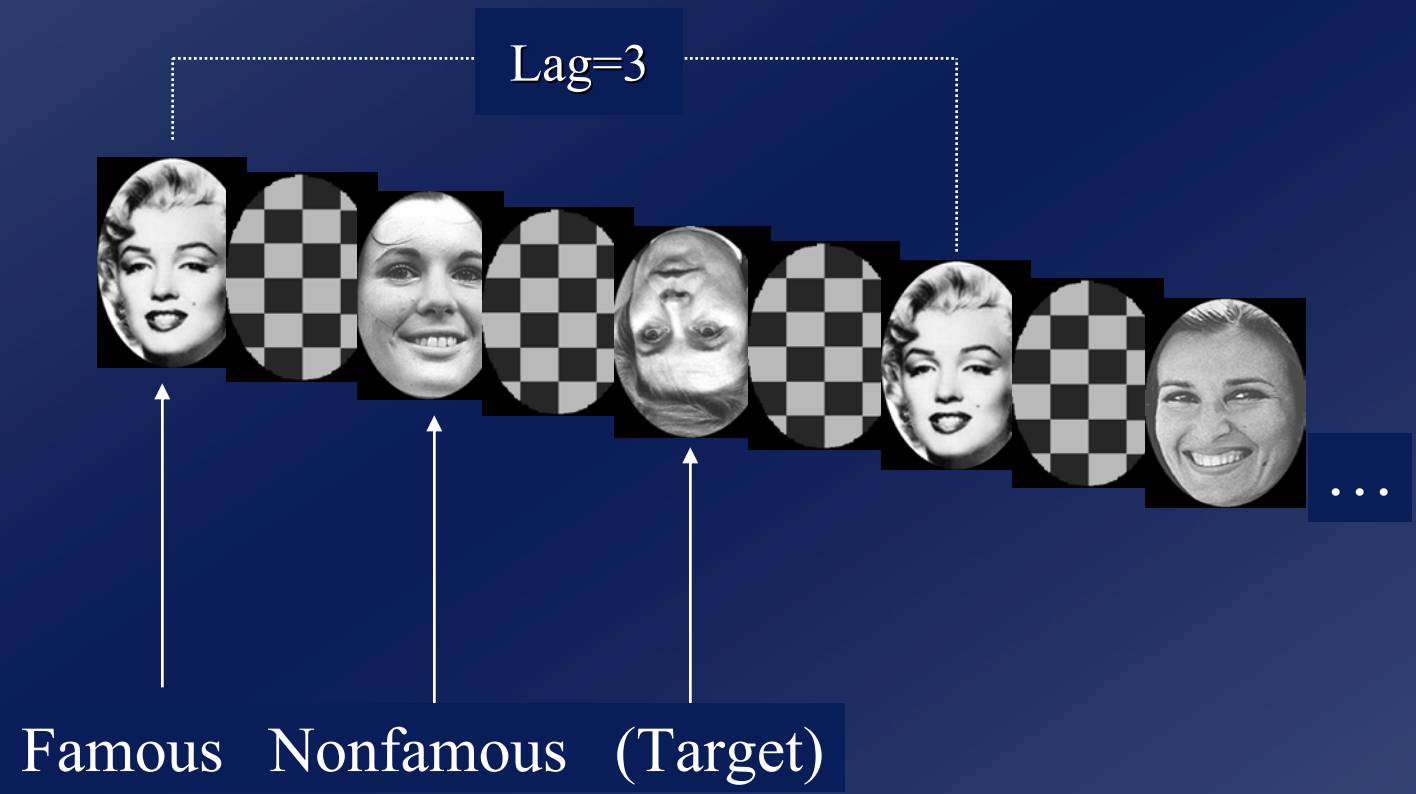


Overview

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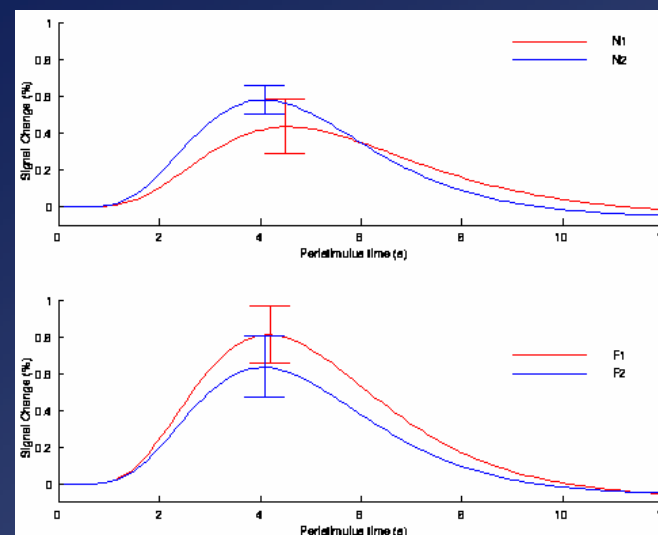
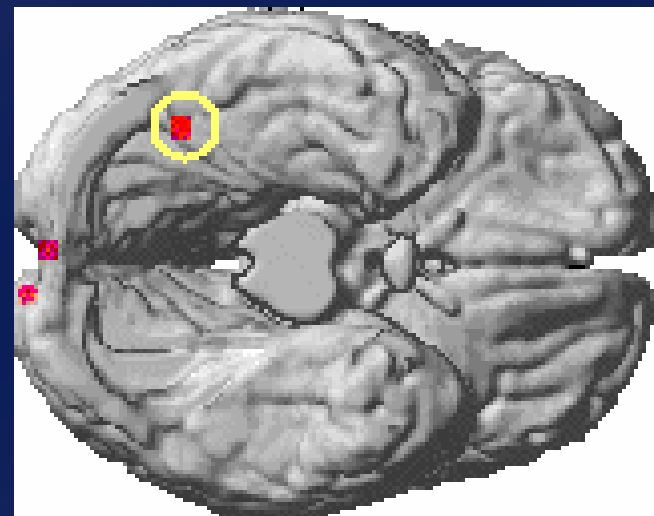
Example 1: Intermixed Trials (Henson et al 2000)

- Short SOA, fully randomised, with 1/3 null events
- Faces presented for 0.5s against chequerboard baseline, SOA=(2 ± 0.5)s, TR=1.4s
- Factorial event-types:
 1. Famous/Nonfamous (F/N)
 2. 1st/2nd Presentation (1/2)



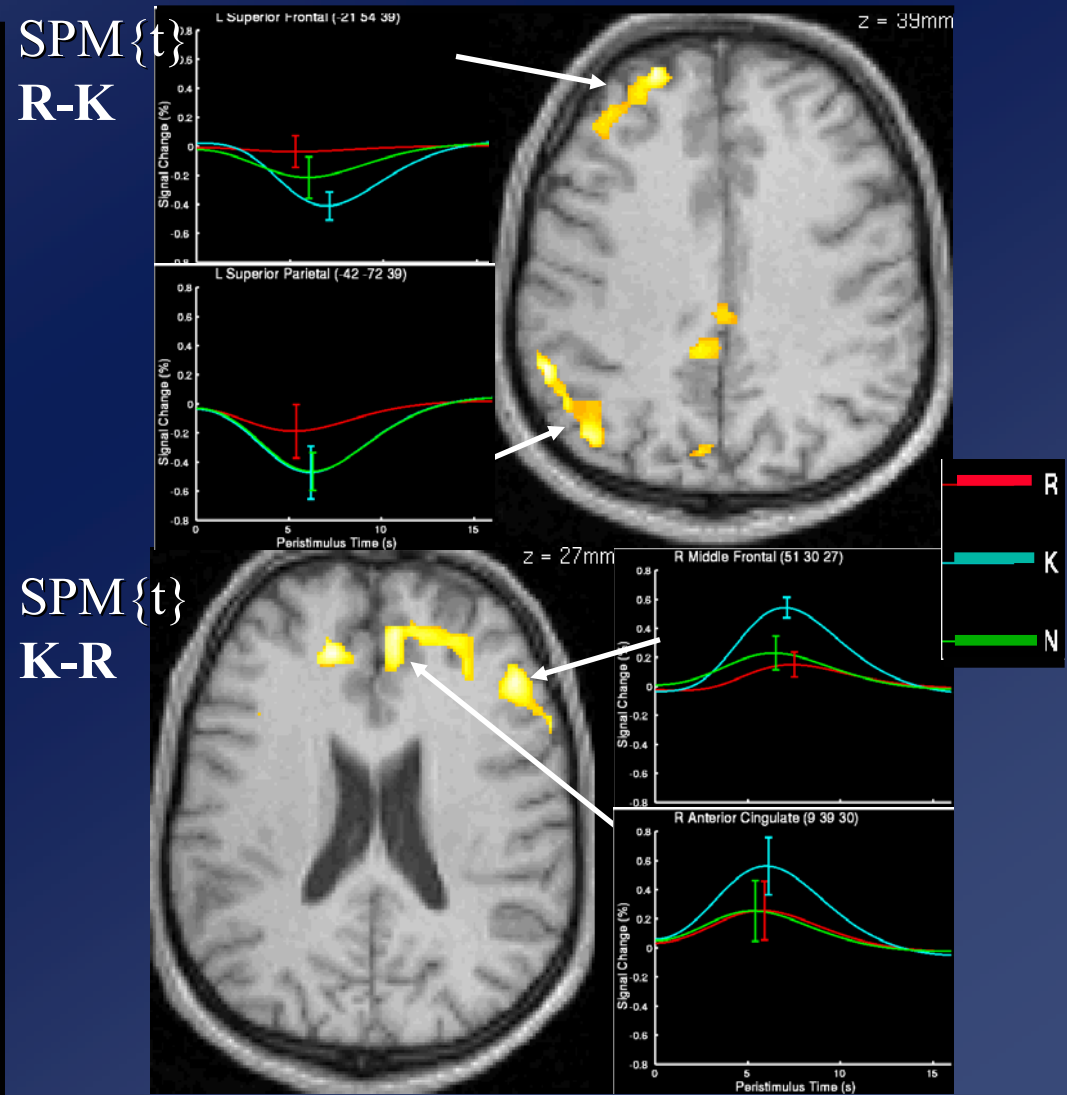
Example 1: Intermixed Trials (Henson et al 2000)

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- Faces presented for 0.5s against checkerboard baseline, $SOA=(2 \pm 0.5)s$, $TR=1.4s$
- Factorial event-types:
 1. Famous/Nonfamous (F/N)
 2. 1st/2nd Presentation (1/2)
- Interaction (F1-F2)-(N1-N2) masked by main effect (F+N)
- Right fusiform interaction of repetition priming and familiarity



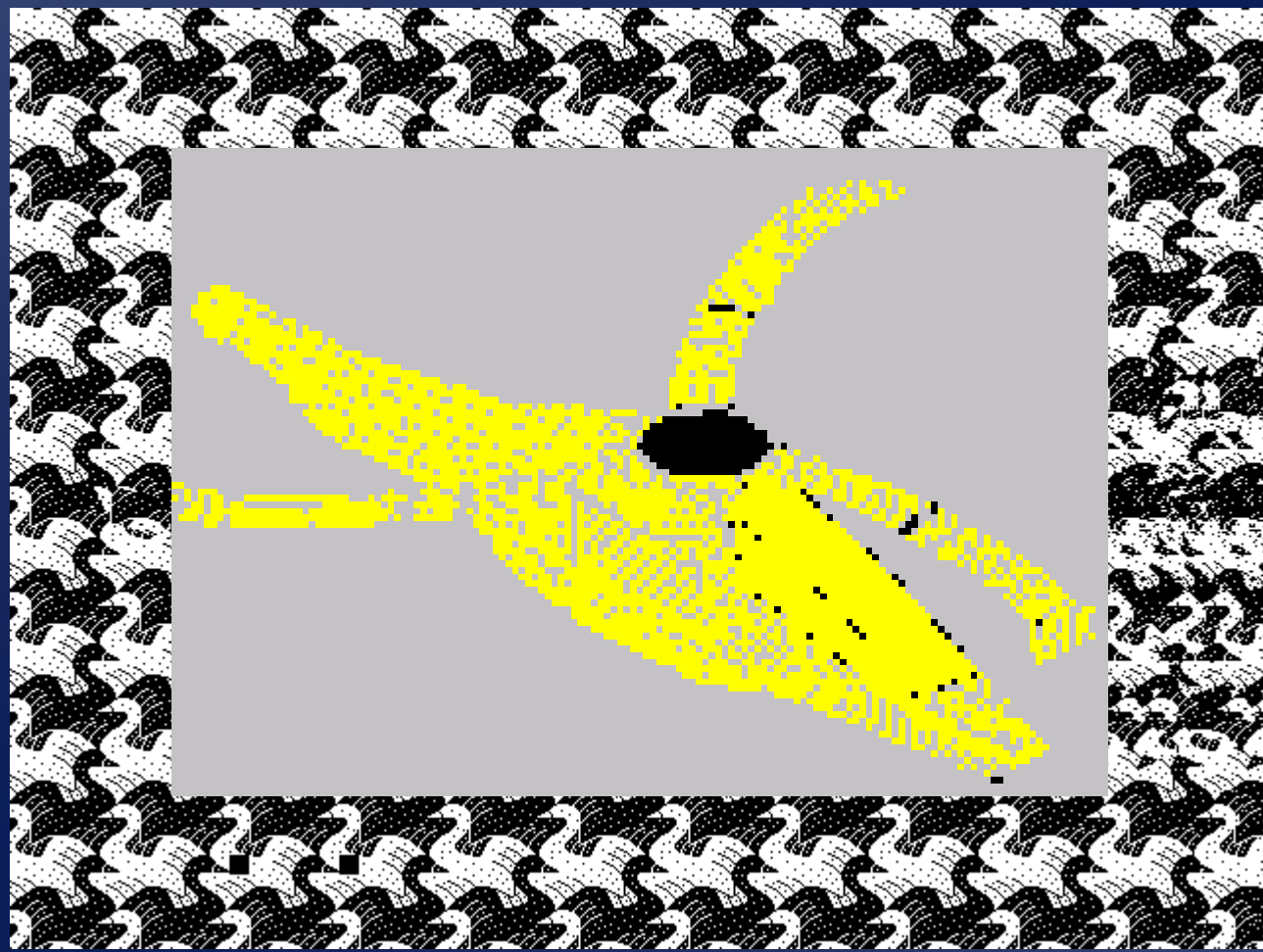
Example 2: Post hoc classification (Henson et al 1999)

- Subjects indicate whether studied (Old) words:
 - i) evoke recollection of prior occurrence (R)
 - ii) feeling of familiarity without recollection (K)
 - iii) no memory (N)
- Random Effects analysis on canonical parameter estimate for event-types
- Fixed SOA of 8s => sensitive to differential but not main effect (de/activations arbitrary)



Example 3: Subject-defined events (Portas et al 1999)

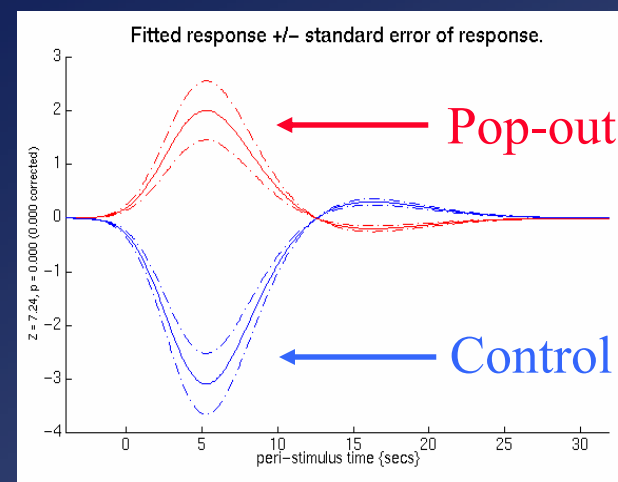
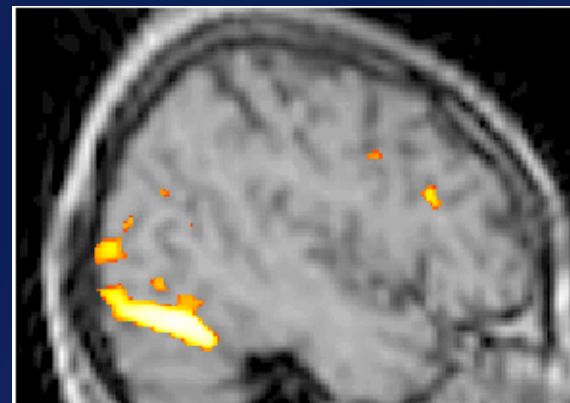
- Subjects respond when “pop-out” of 3D percept from 2D stereogram



Example 3: Subject-defined events (Portas et al 1999)

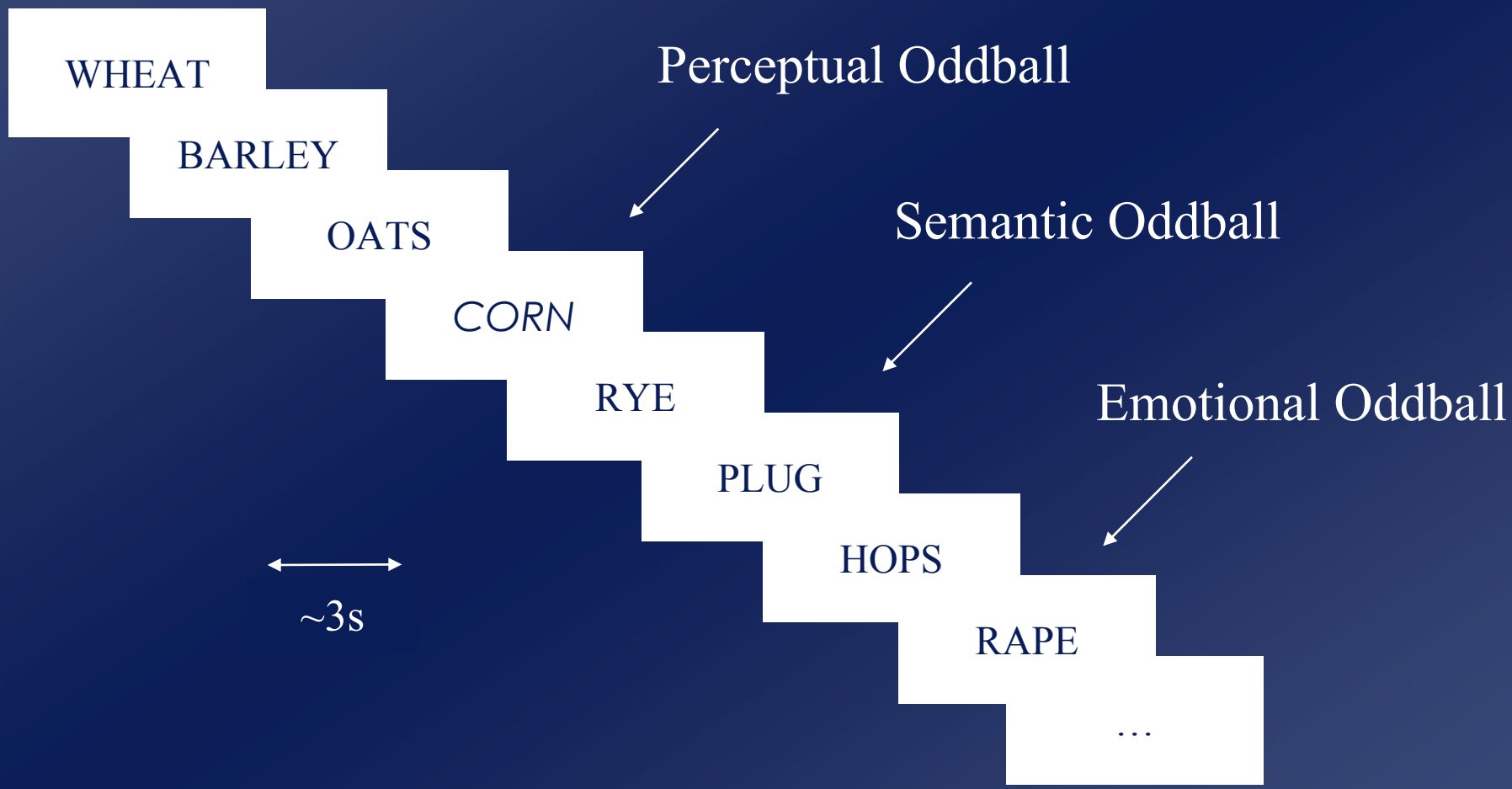
- Subjects respond when “pop-out” of 3D percept from 2D stereogram
- Popout response also produces tone
- Control event is response to tone during 3D percept

Temporo-occipital differential activation



Example 4: Oddball Paradigm (Strange et al, 2000)

- 16 same-category words every 3 secs, plus ...
- ... 1 perceptual, 1 semantic, and 1 emotional oddball



WHEAT

BARLEY

OATS

CORN

RYE

PLUG

HOPS

RAPE

...

Perceptual Oddball

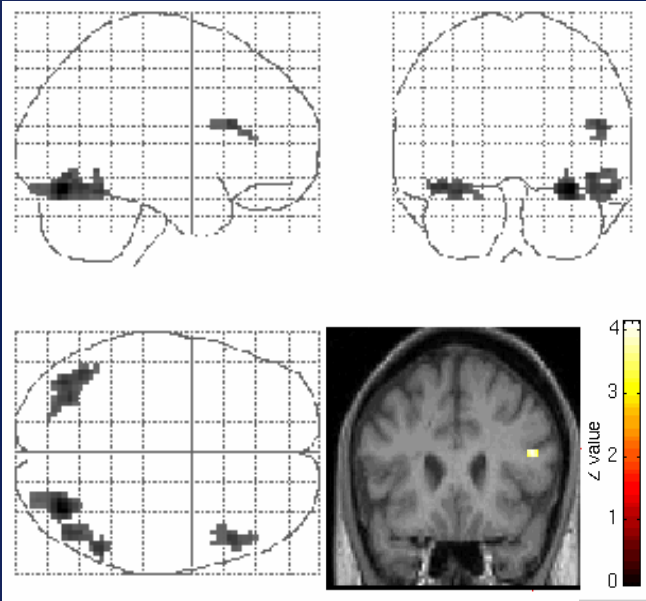
Semantic Oddball

Emotional Oddball

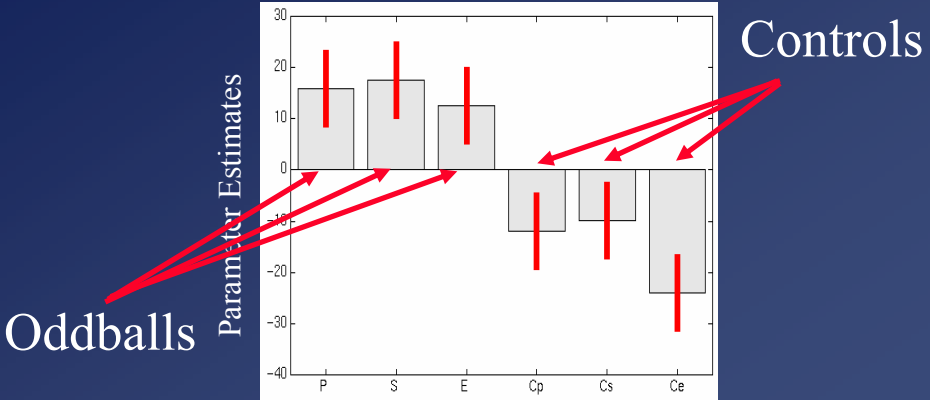
~3s

Example 4: Oddball Paradigm (Strange et al, 2000)

- 16 same-category words every 3 secs, plus ...
- ... 1 perceptual, 1 semantic, and 1 emotional oddball
- 3 nonoddballs randomly matched as controls
- Conjunction of oddball vs. control contrast images: generic deviance detector



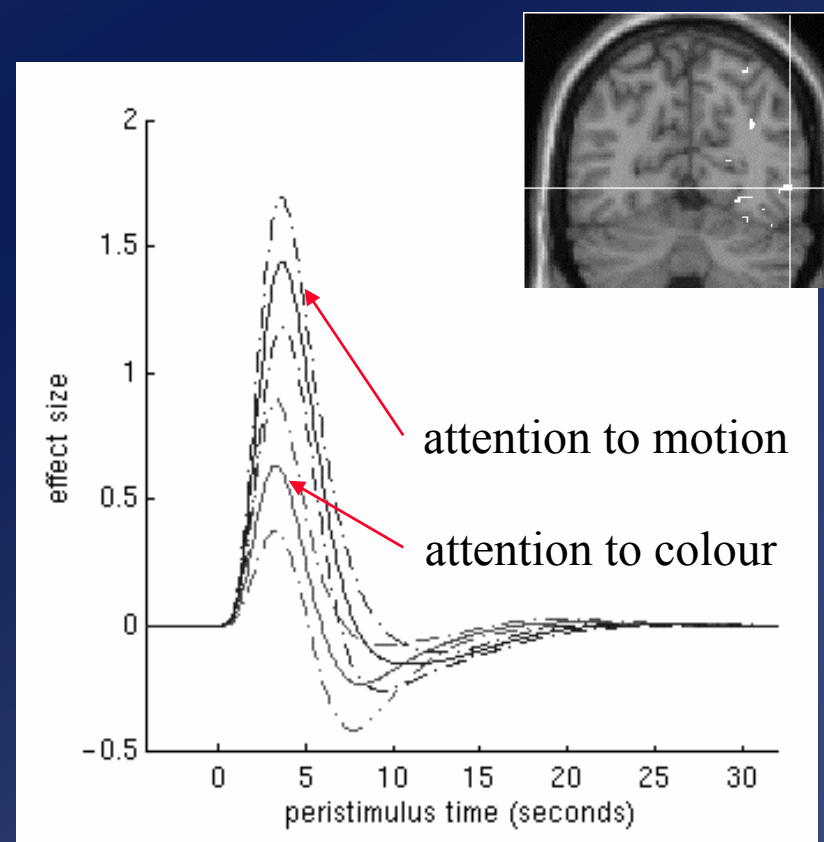
Right Prefrontal Cortex



Example 5: Epoch/Event Interactions (Chawla et al 1999)

- Epochs of attention to:
1) motion, or 2) colour
- Events are target stimuli differing in motion or colour
- Randomised, long SOAs to decorrelate epoch and event-related covariates
- Interaction between epoch (attention) and event (stimulus) in V4 and V5

Interaction between attention and stimulus motion change in V5



Efficiency – Detection vs Estimation

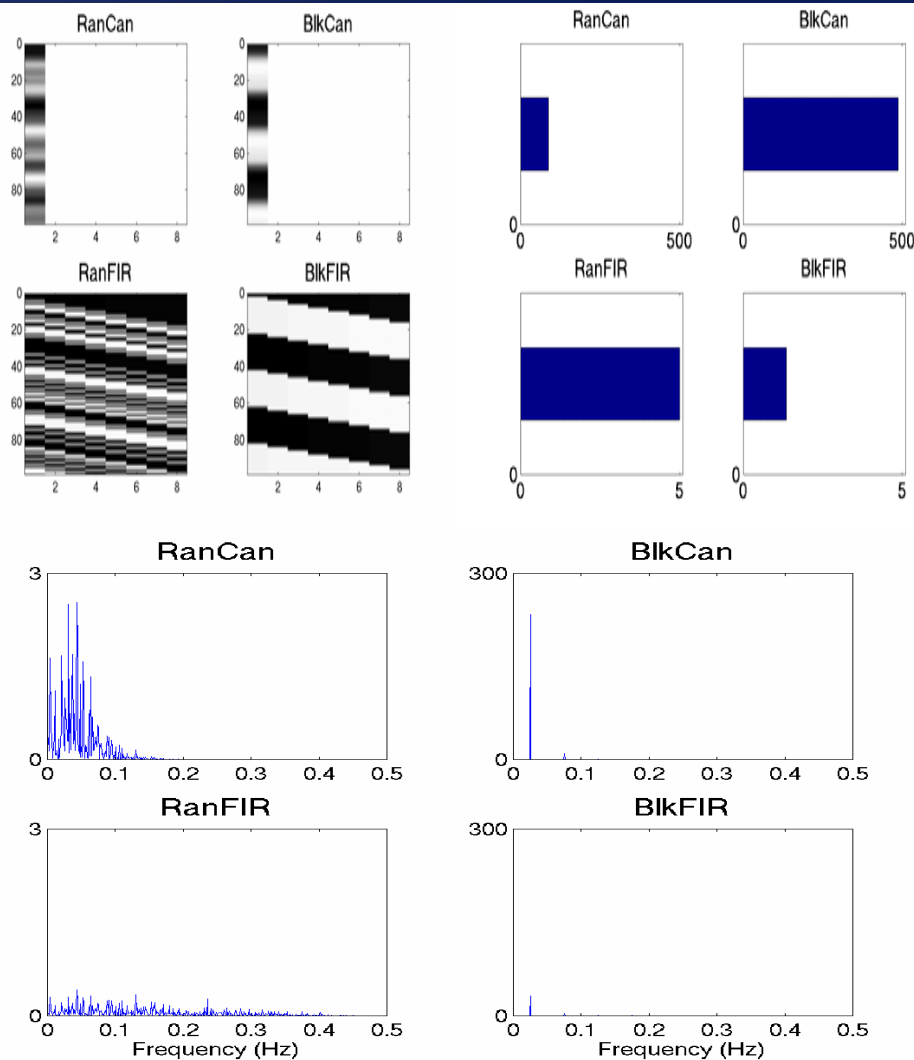
- “Detection power” vs “Estimation efficiency” (Liu et al, 2001)

- Detect response, or characterise shape of response?

- Maximal detection power in blocked designs;
Maximal estimation efficiency in randomised designs

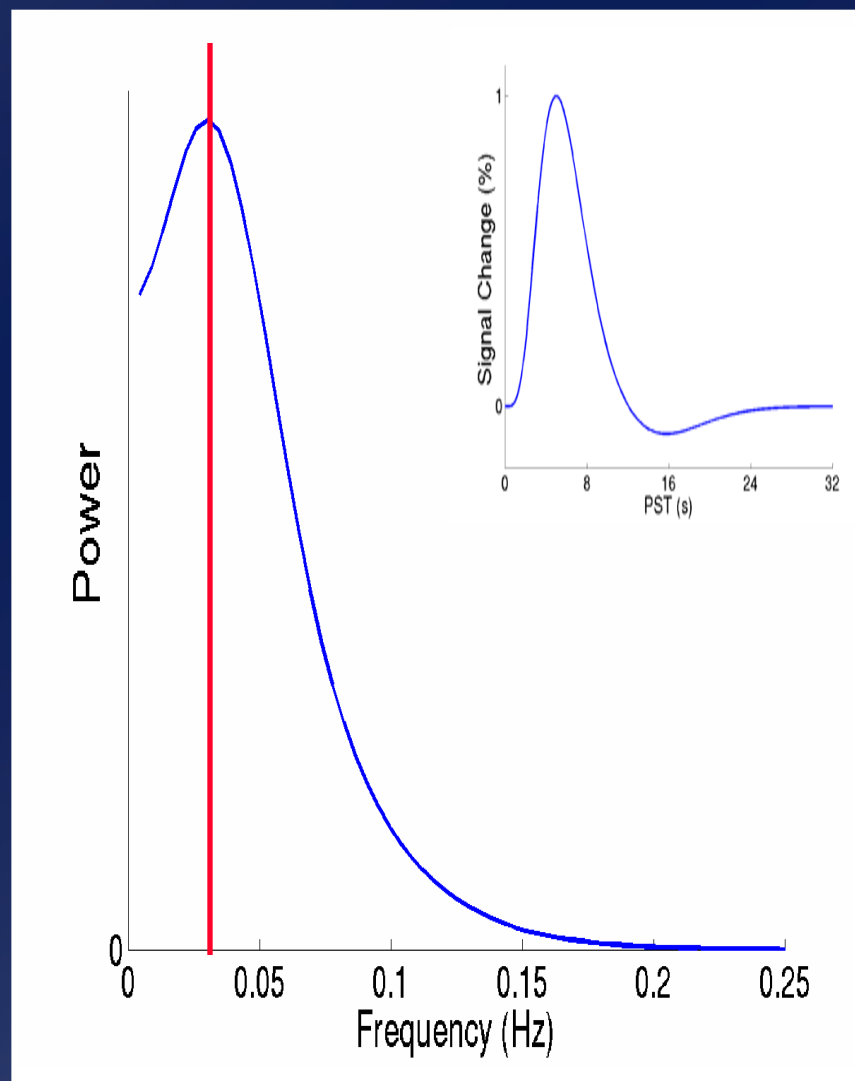
=> simply corresponds to choice of basis functions:

detection = canonical HRF
estimation = FIR



Design Efficiency

- HRF can be viewed as a filter (Josephs & Henson, 1999)
- Want to maximise the signal passed by this filter
- Dominant frequency of canonical HRF is ~ 0.04 Hz
- So most efficient design is a sinusoidal modulation of neural activity with period ~ 24 s
- (eg, boxcar with 12s on/ 12s off)



Timing Issues : Latency

- Assume the real response, $r(t)$, is a scaled (by α) version of the canonical, $f(t)$, but delayed by a small amount dt :

$$r(t) = \alpha f(t+dt) \sim \alpha f(t) + \alpha f'(t) dt \quad \text{1st-order Taylor}$$

- If the fitted response, $R(t)$, is modelled by the canonical + temporal derivative:

$$R(t) = \beta_1 f(t) + \beta_2 f'(t) \quad \text{GLM fit}$$

- Then canonical and derivative parameter estimates, β_1 and β_2 , are such that :

$$\Rightarrow \quad \alpha = \beta_1 \quad dt = \beta_2 / \beta_1 \quad \begin{array}{l} \text{(Henson et al, 2002)} \\ \text{(Liao et al, 2002)} \end{array}$$

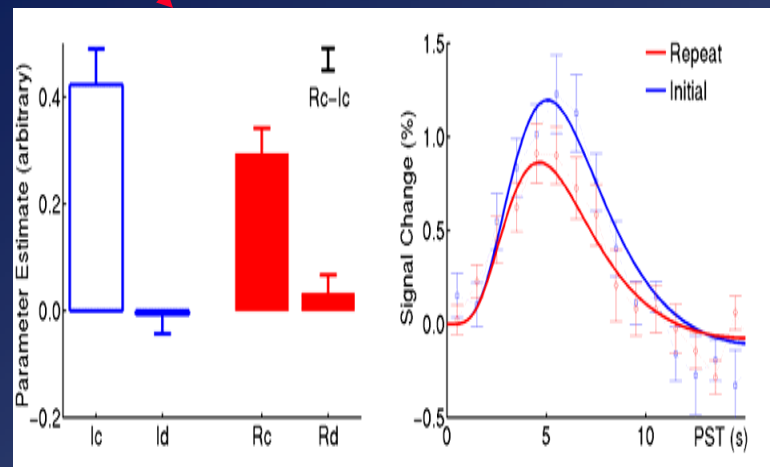
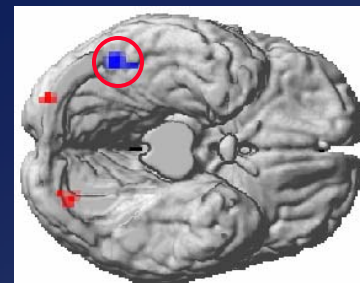
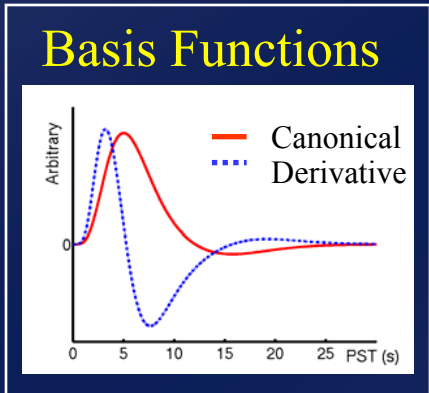
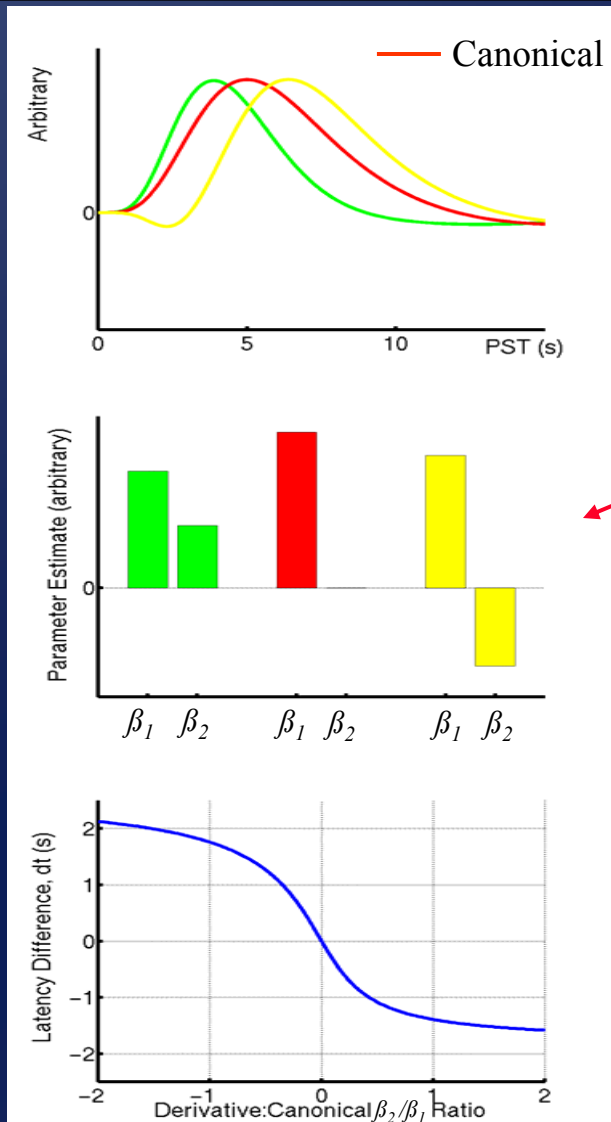
ie, Latency can be approximated by the ratio of derivative-to-canonical parameter estimates (within limits of first-order approximation, +/-1s)

Timing Issues : Latency

Delayed Responses (green/ yellow)

Parameter Estimates

Actual latency, dt , vs. β_2 / β_1



Face repetition reduces latency as well as magnitude of fusiform response

Timing Issues : Latency

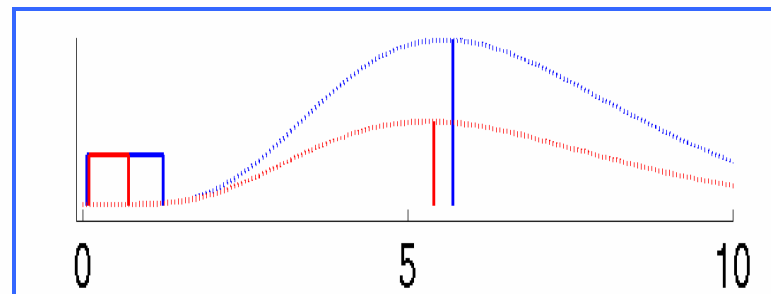
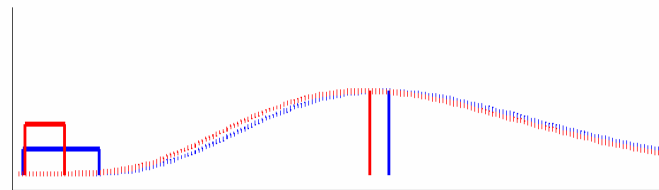
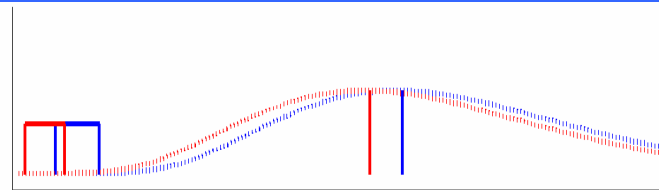
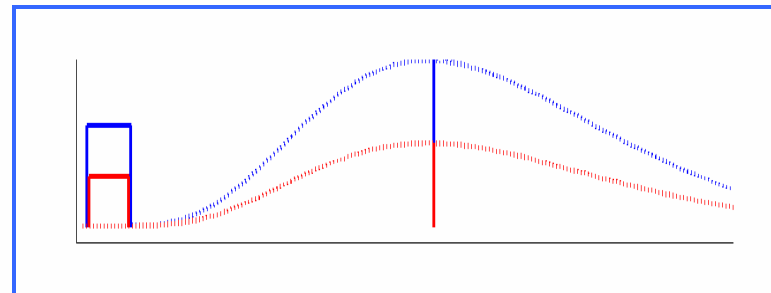
Neural

A. Decreased

B. Advanced

C. Shortened
(same integrated)

D. Shortened
(same maximum)



BOLD

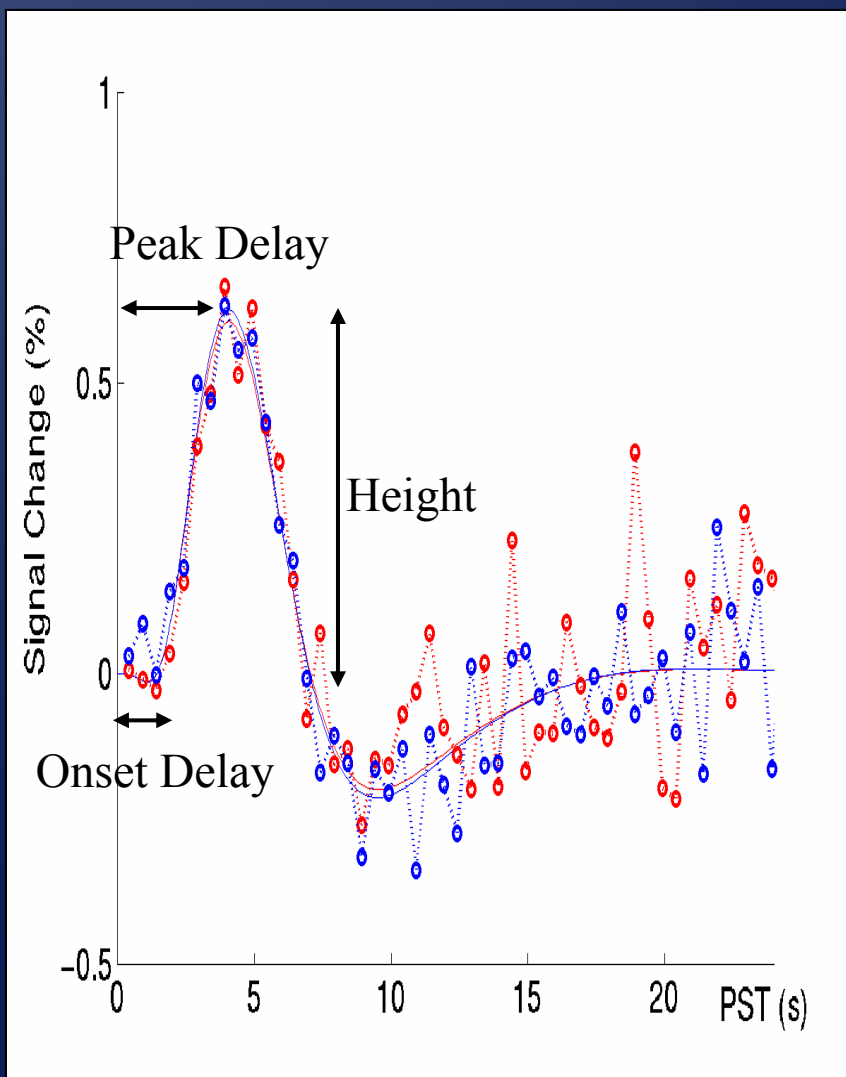
A. Smaller Peak

B. Earlier Onset

C. Earlier Peak

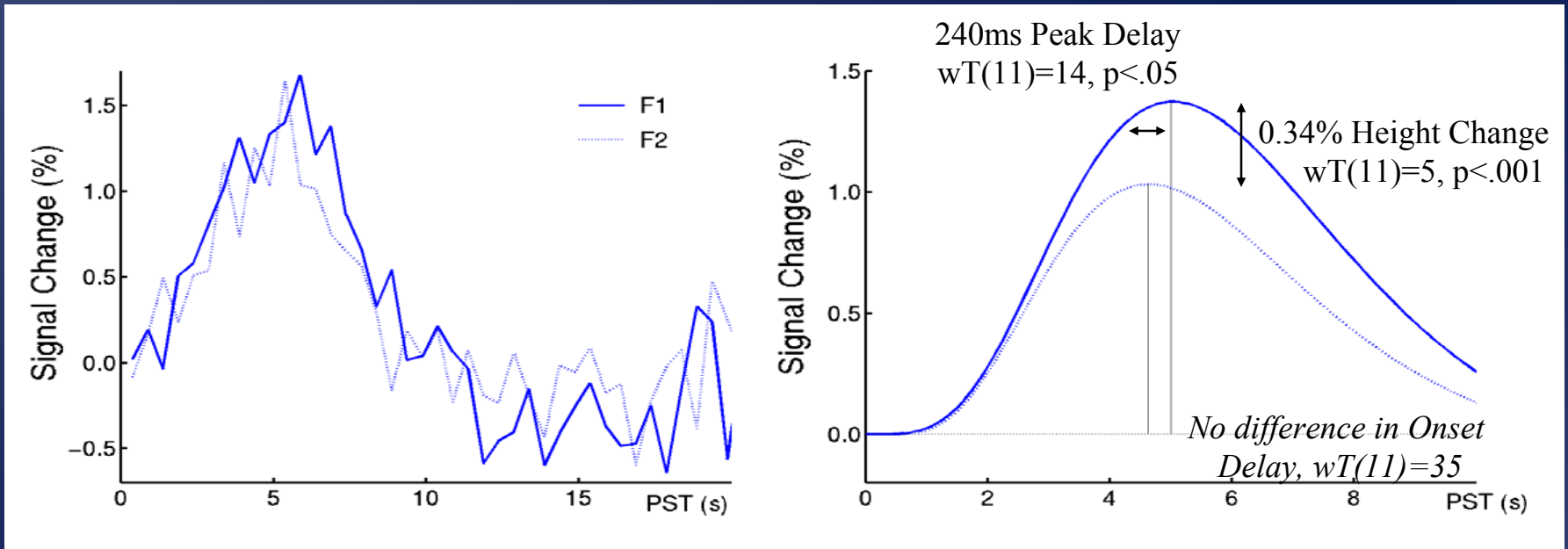
D. Smaller Peak
and earlier Peak

BOLD Response Latency (Iterative)



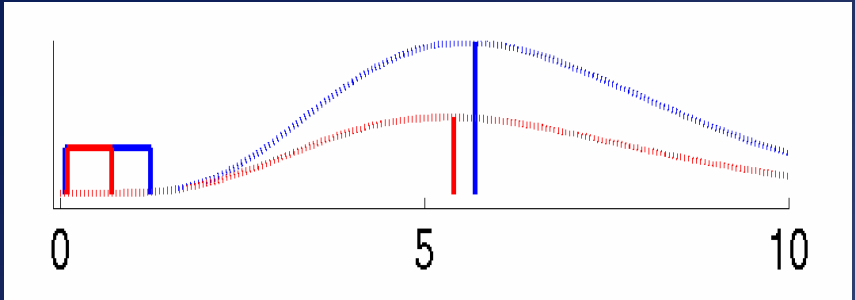
- Numerical fitting of explicitly parameterised canonical HRF (*Henson et al, 2001*)
- Distinguishes between *Onset* and *Peak* latency...
 - ...unlike temporal derivative...
 - ...and which may be important for interpreting neural changes (see previous slide)
- Distribution of parameters tested nonparametrically (Wilcoxon's T over subjects)

BOLD Response Latency (Iterative)



Neural

D. Shortened
 (same maximum)

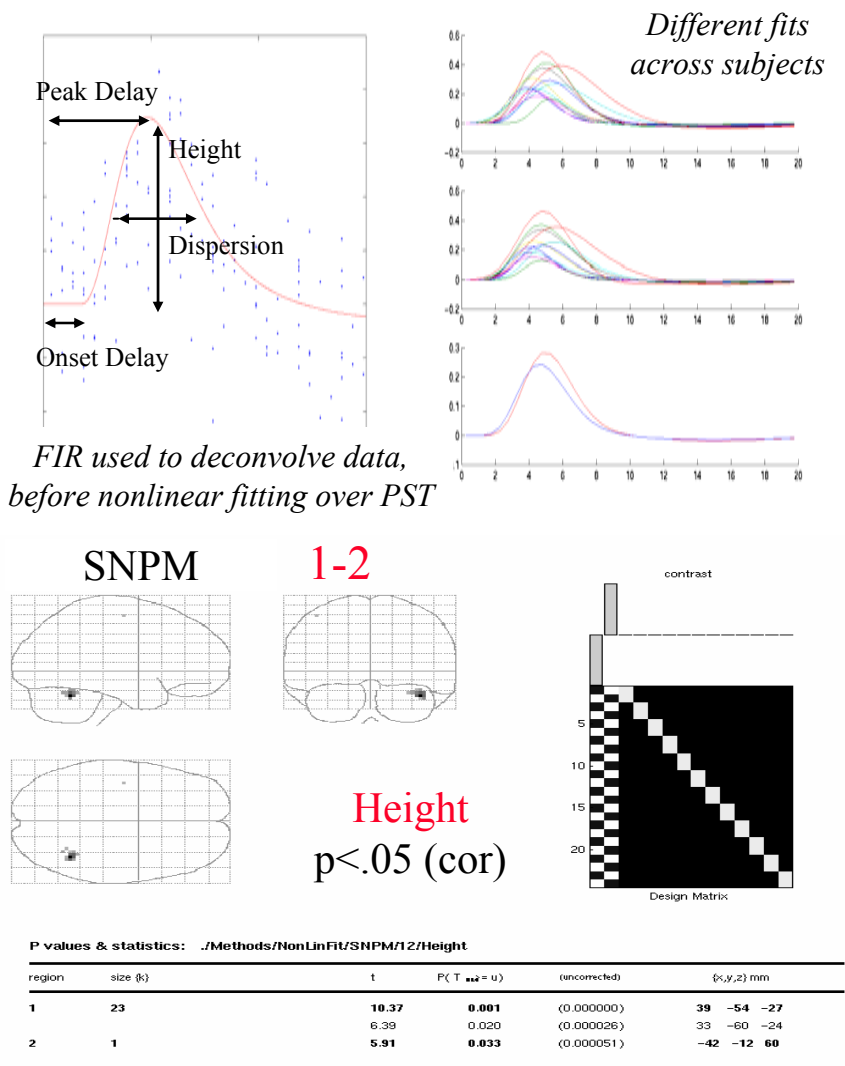


BOLD

D. Smaller Peak and earlier Peak

*Most parsimonious account is that repetition reduces **duration** of neural activity...*

BOLD Response Latency (Iterative)



- **Four-parameter HRF, nonparametric Random Effects (SNPM99)**
- **Advantages of iterative vs linear:**
 1. Height “independent” of shape
Canonical “height” confounded by latency (e.g, different shapes across subjects); no slice-timing error
 2. Distinction of onset/peak latency
Allowing better neural inferences?
- **Disadvantages of iterative:**
 1. Unreasonable fits (onset/peak tension)
Priors on parameter distributions? (Bayesian estimation)
 2. Local minima, failure of convergence?
 3. CPU time (~3 days for above)

Temporal Basis Sets: Inferences

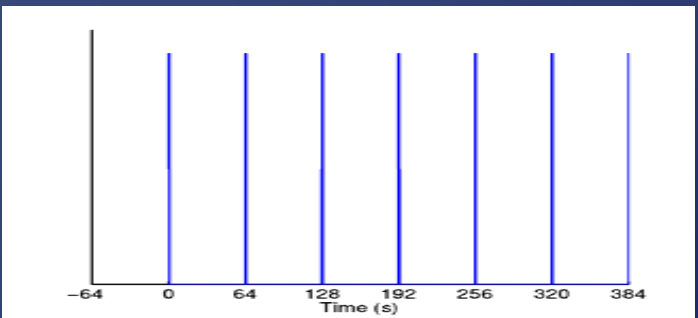
- How can inferences be made in hierarchical models (eg, “Random Effects” analyses over, for example, subjects)?
 - 1. Univariate T-tests on canonical parameter alone?**

may miss significant experimental variability
canonical parameter estimate not appropriate index of “magnitude”
if real responses are non-canonical (see later)
 - 2. Univariate F-tests on parameters from multiple basis functions?**

need appropriate corrections for nonsphericity (Glaser et al, 2001)
 - 3. Multivariate tests (eg Wilks Lambda, Henson et al, 2000)**

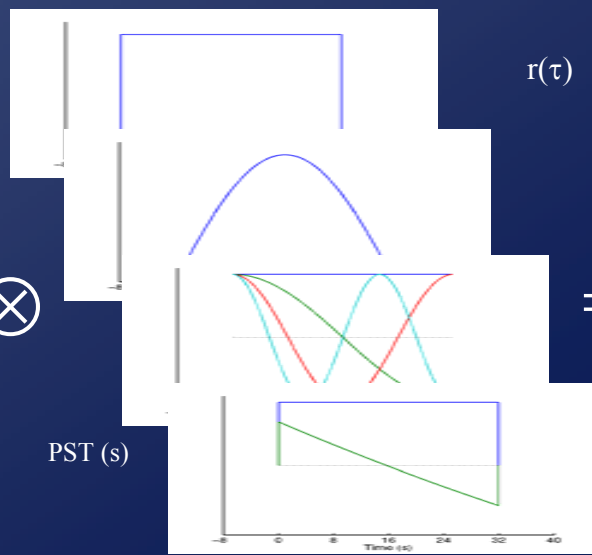
not powerful unless ~10 times as many subjects as parameters

$s(t)$



Time (s)

\otimes

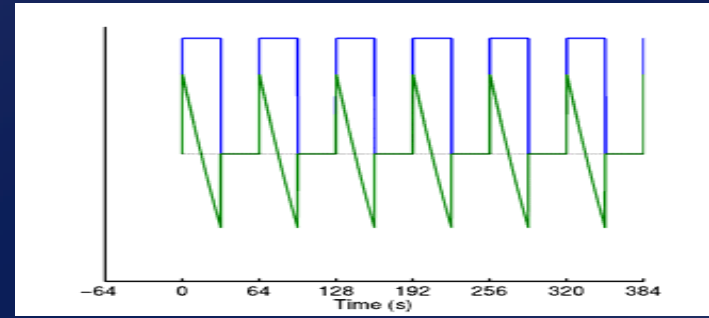


PST (s)

$r(\tau)$

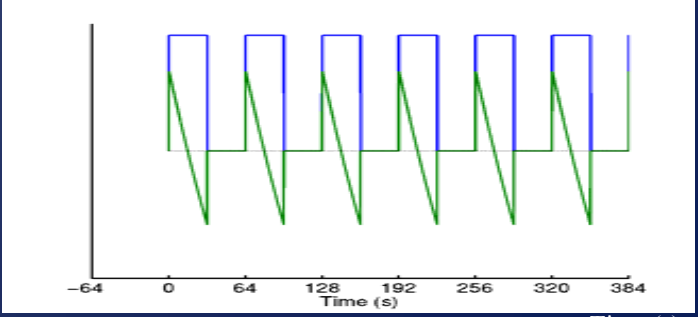
$=$

$u(t)$



Time (s)

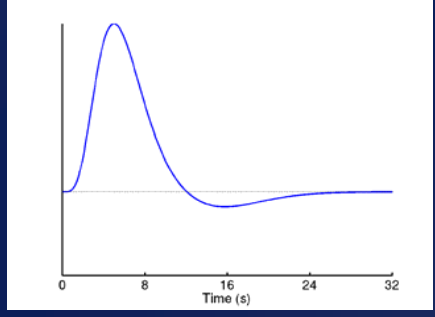
$u(t)$



Time (s)

\otimes

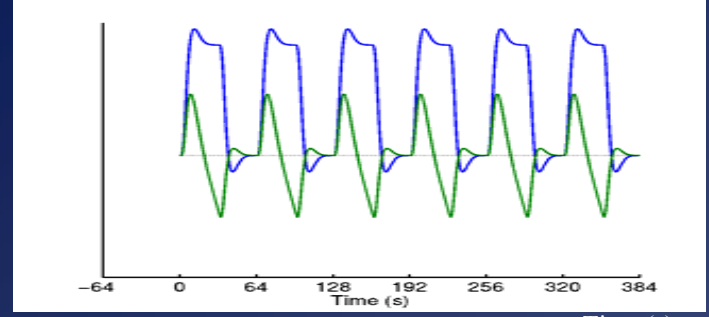
$h(\tau)$



PST (s)

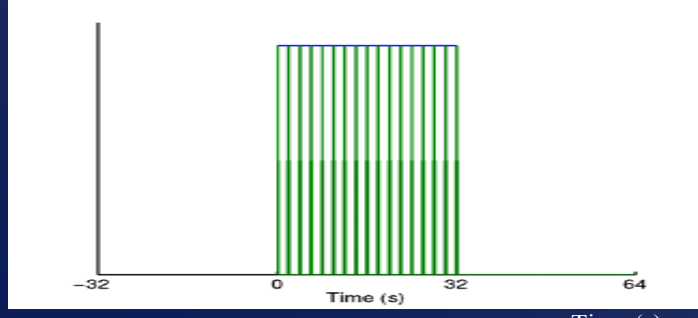
$=$

$x(t)$



Time (s)

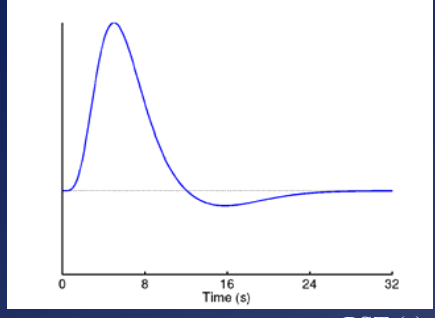
$u(t)$



Time (s)

\otimes

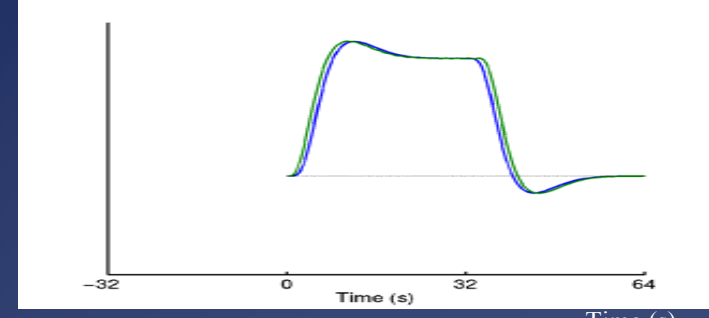
$h(\tau)$



PST (s)

$=$

$x(t)$



Time (s)

