Experimental Design

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With thanks to:
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Joe Devlin

Outline

- Choices for experimental paradigm
  - Subtraction / hierarchical
  - Factorial
  - Parametric
  - Conjunction
  - Adaptation
- Choices for FMRI protocol
  - Blocked vs. Event-related
    - Efficiency and sampling
  - Mixed designs
  - Sparse-sampling

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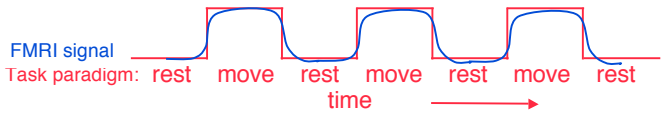
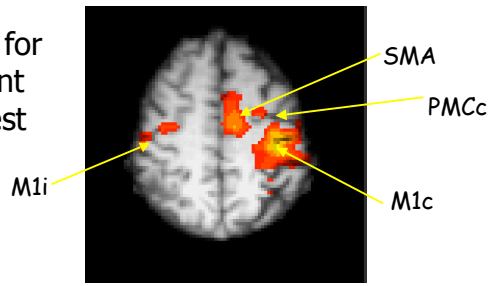
A very simple experiment

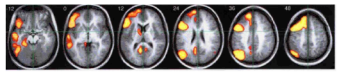


Activation for movement versus rest

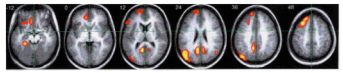


Choosing Baselines

- Rest may not be truly rest
- Need to control as much as possible to isolate component of interest
- Multiple baselines may be a good idea
- Even if a task does not explicitly involve a particular component, subjects may engage in it anyway
  - E.g. rehearsing previous stimuli



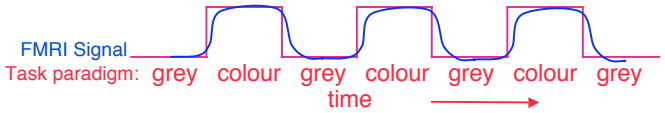
Rest vs tones

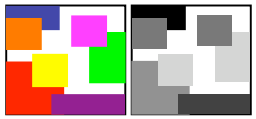


Semantic processing vs tones

Binder et al, 1999

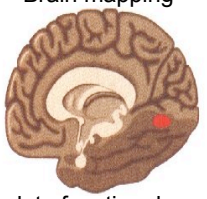
Simple experiment: subtraction





Colour > No colour
Luminance = Luminance
Contrast = Contrast
Shape = Shape

Brain mapping



Isolate functional area

Hierarchical processing

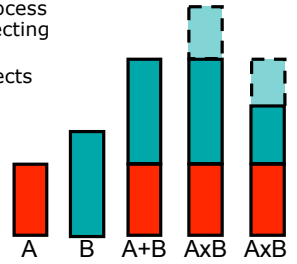
Single-Word processing

Subtraction	Control	Task	Hypothetical Cognitive Operations
Sensory	Fixation	Passive words	Passive sensory processing
Production	Passive words	Repeat words	Motor programming and output
Association	Repeat words	Generate words	Semantic association, selection

Petersen et al., Nature 1998

Problems with subtractive designs

- Depends on the assumption of 'Pure Insertion'
  - i.e. the idea that you can insert a single component process into a task without affecting other processes
  - Can get interactive effects
- Alternatives
  - Parametric designs
  - Factorial designs
  - Cognitive conjunction



Friston et al., (1996) *Neuroimage* 4: 97

Factorial designs

	No Vision	Vision
No Touch		
Touch		

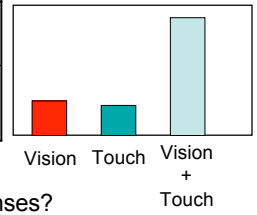
Main effect of Touch

Main effect of Vision

Allows you to characterise interactions between component processes – i.e., effect that one component has on another (does not make assumption of pure insertion)

Positive Interactions

	No Vision	Vision
No Touch		
Touch		

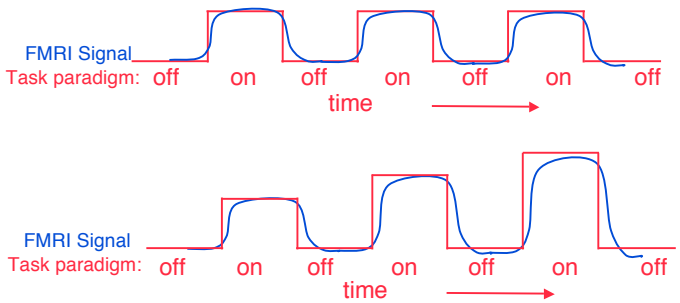


Does touch modulate vision responses?

Does vision modulate touch responses?

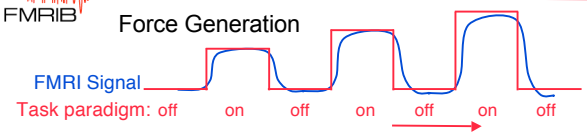
Is there a multisensory integration area?

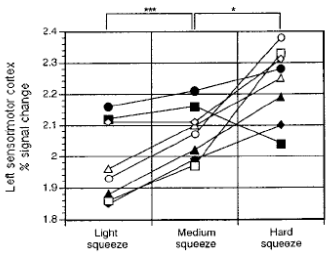
Parametric designs

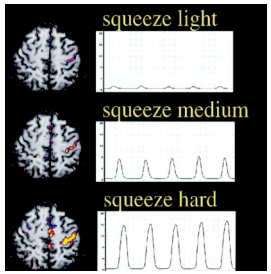


Parametric designs

Force Generation



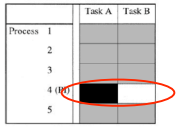




Cramer et al., 2002

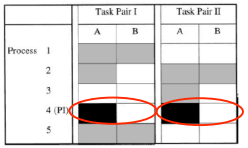
Conjunction analyses

Cognitive subtraction



Activation vs baseline
= component of interest

Cognitive conjunction

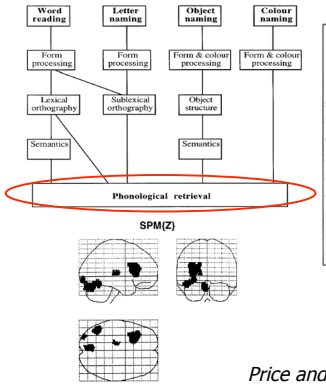


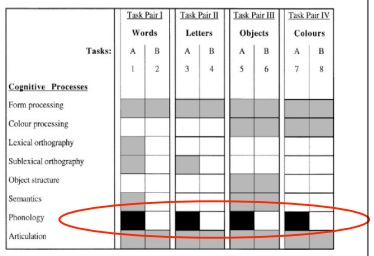
Commonalities in
activation vs baseline
across task pairs
= component of interest

- Does not assume pure insertion
- Does not depend on perfect baseline

Price and Friston, 1997, NeuroImage 5, 261-170

Phonological Retrieval

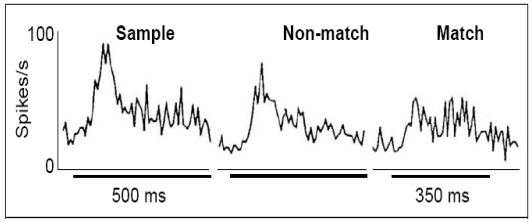




Price and Friston, 1997, NeuroImage 5, 261-170

fMRI adaptation

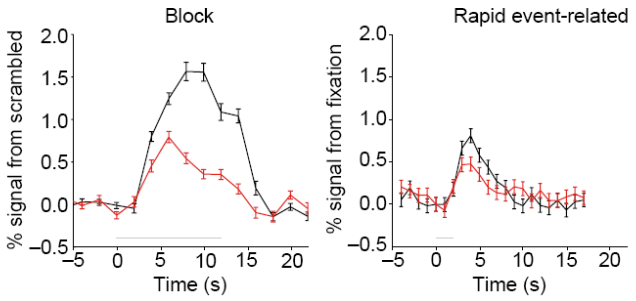
- Based on neural repetition suppression



Averaged neuronal response (spike/s)

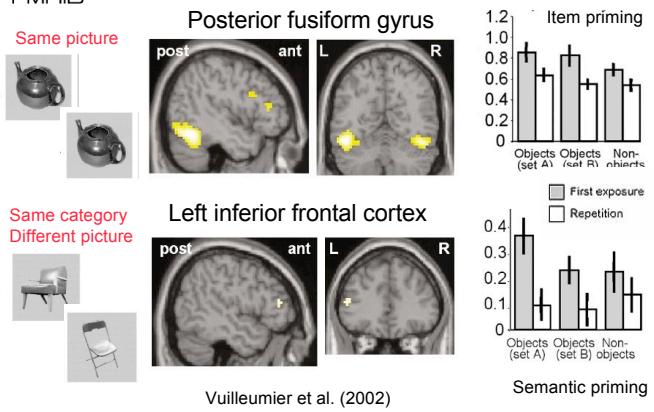
Desimone (1996)

BOLD decrease for repetition



Grill-Spector et al. (2006)

Repetition Priming



Vuilleumier et al. (2002)

Other considerations

- Is your subject doing what you think they are doing?
  - Consider practice session
- Collect behavioural data
  - Can use for post-hoc sorting of data
  - Correlation with FMRI signal (within or between scans)
- Task/scan/condition order effects
  - Counter-balance
  - Match stimuli for difficulty
  - Learning and attention effects

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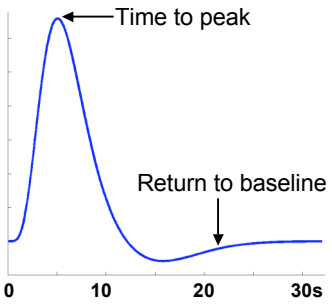
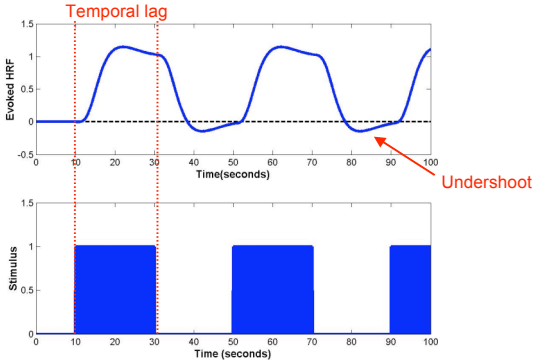
Haemodynamic response

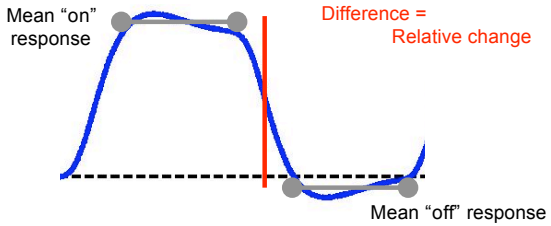
- HRF is slow to peak
- Peak response comes 4-6s after stimulus onset
- Can vary in time-to-peak across brain areas and across subjects
- Returns to baseline about 21s after stimulus ends



Convolving with HRF



BOLD is a relative measure

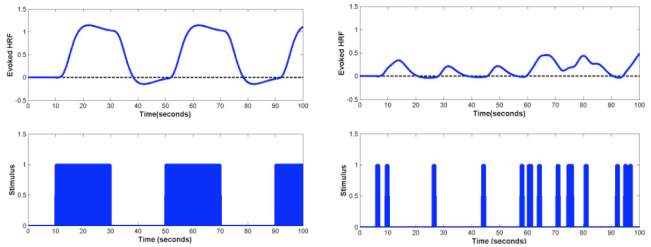


Sensitivity depends on maximizing relative change

Basic designs

Blocked

Event related



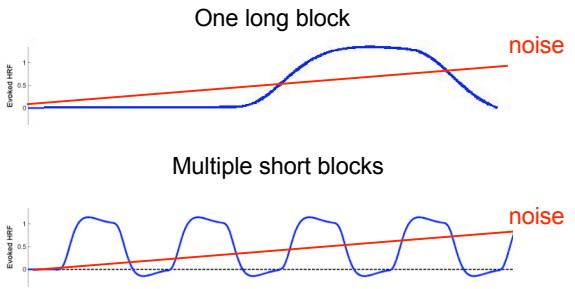
Blocked design

- Advantages
  - Simple (for you and for subject)
  - Minimise task switching
  - Maximum efficiency
  - Does not depend on accurate HRF model
  - Robust to uncertainty in timing
  - Straightforward analysis
- Disadvantages
  - Not all tasks can be blocked
  - Subjects can anticipate conditions - order and duration
  - Does not allow separation of response to individual trials
  - No timing information

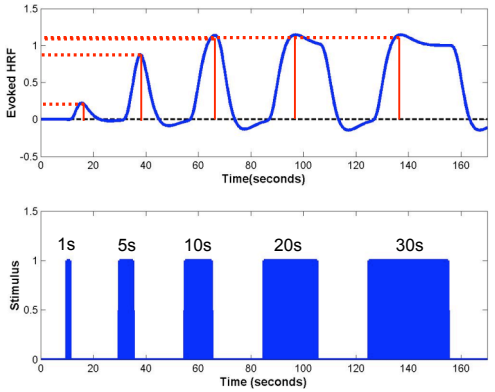
Event-related designs

- Advantages
  - Flexible – removes anticipation, allows for surprises
  - Good estimate of time course of HRF
  - Post hoc sorting of trial types, e.g. correct vs. incorrect; remembered vs. forgotten stimuli
  - Can separate our response to task components – e.g., cue, target, response
  - High temporal resolution
- Disadvantages
  - More things can go wrong
  - Reduced efficiency
  - Typically results in longer experiments
  - More dependent on accurate HRF modelling
  - Increased task switching

Noise interferes with long blocks

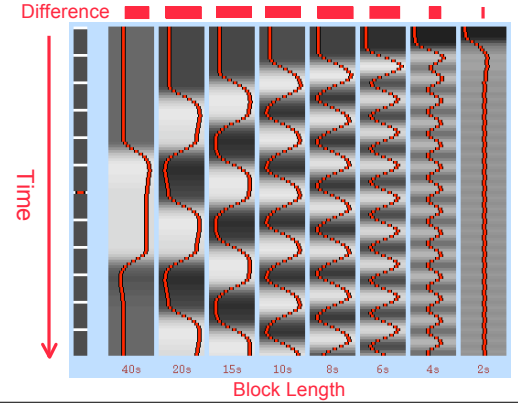


Blocked designs: efficiency

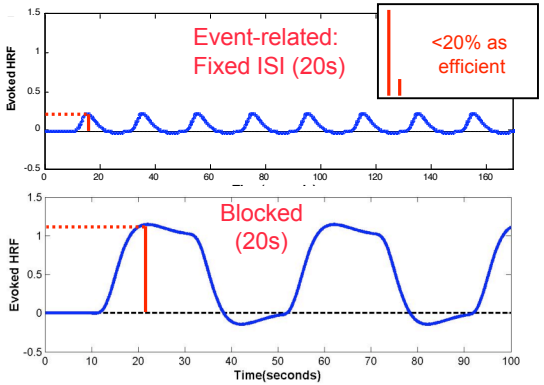


Blocked designs: how long?

16-45s recommended



Event-related designs: efficiency

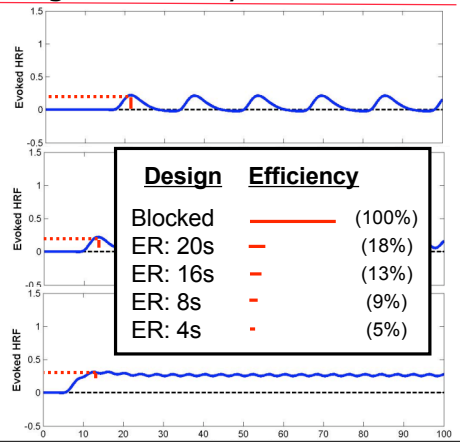


ER design efficiency: fixed ISI

Fixed ISI (16s)

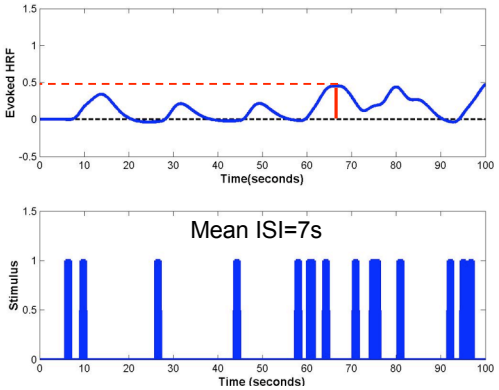
Fixed ISI (8s)

Fixed ISI (4s)

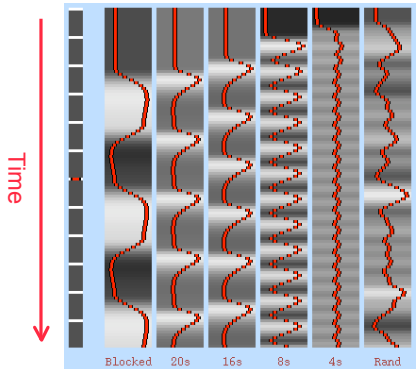


Design	Efficiency
Blocked	(100%)
ER: 20s	(18%)
ER: 16s	(13%)
ER: 8s	(9%)
ER: 4s	(5%)

ER design efficiency: random ISI



ER designs: ISI?

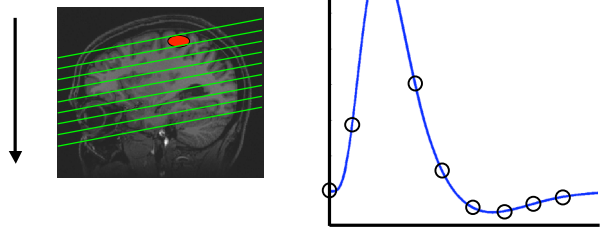


Short (2≤ ISI ≤ 6s), random ISIs best for simple ER

More interesting contrasts

- To detect differences between conditions, 4-8s mean ISI is most efficient
- Programs for optimising random presentation
  - OptSeq: Greve
  - Genetic algorithm: Wager & Nichols
- Optimise designs *before* scanning

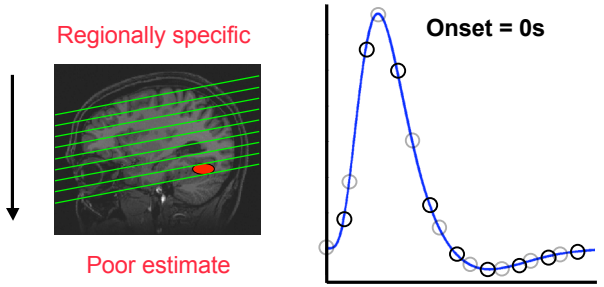
Sampling bias



Only sample the HRF once per TR (3s)

Sampling bias

Regionally specific

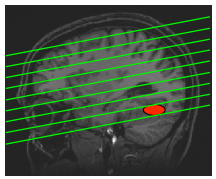


Poor estimate

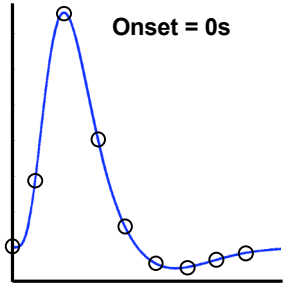
Can underestimate effect sizes

Sampling bias

Depends on acquisition

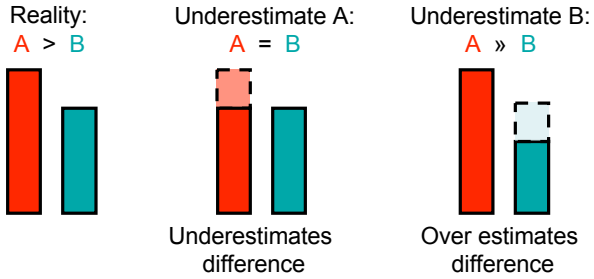


Good estimate



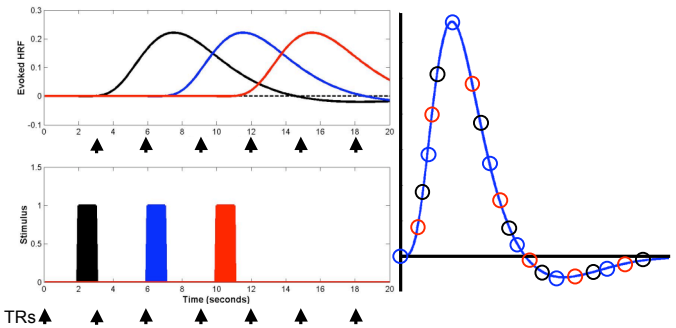
Effects of sampling bias

Contrasts can over- or under-estimate effects

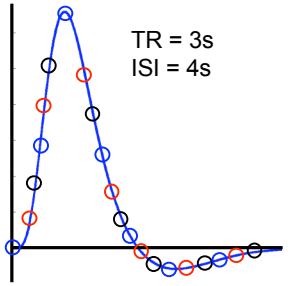


Oversampling

TR = 3s ISI = 4s



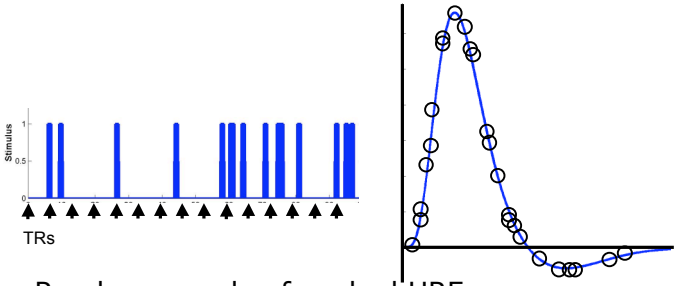
Effect of oversampling



- Effective sampling rate of 1s
- Requires a fixed, non-integer relation between ISI and TR
- Best for blocked designs where *fixed ISI* is still efficient

Jittering the ISI

Choosing ISI from a random distribution



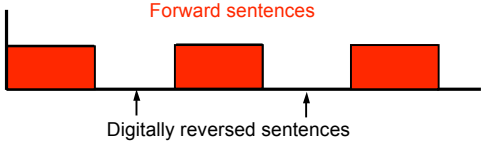
Random sample of evoked HRF

Sampling bias summary

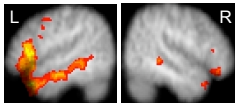
- For both blocked and event-related designs:
  - Avoid TR = integer multiple of ISI
  - Oversampling uses *fixed* ISIs (therefore best for blocked)
  - Jitter uses *random* ISI (therefore best with event-related)

Mixed design

- Example: Brain mapping paradigm

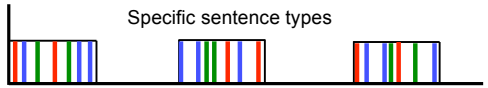


- Forward > Reversed sentences identifies regions engaged in auditory sentence processing



Cardillo et al. (2004)

Mixing blocks and events



Congruent: "The boy bounced the BALL"
Neutral: "The next item is DREAM"
Incongruent: "I like coffee with milk and HEMLOCK"

- Congruent > Incongruent = Facilitation effects
- Masking limits priming effects to areas engaged by sentence processing
- Mixed designs also used to evaluate both short and long period responses (specific events vs. attentional set)

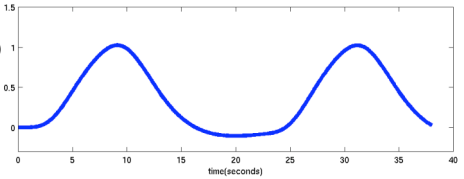
Sparse sampling

- Useful for studying auditory processes without scanner noise by presenting auditory stimuli during silence
- Also for allowing subjects to speak in the scanner without introducing further distortions in the image
- Acquire one volume at peak BOLD response
- Wait until BOLD evoked by scanner noise returns to baseline levels

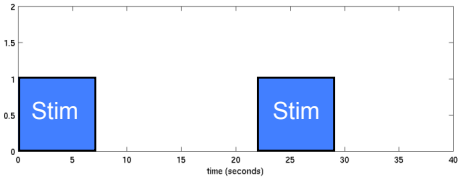
Hall et al. (1999)

Sparse sampling

Evoked BOLD response

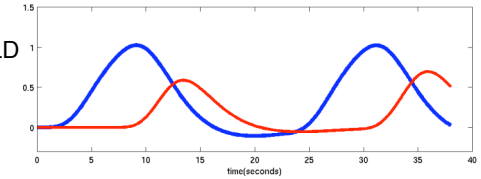


Stimulus paradigm

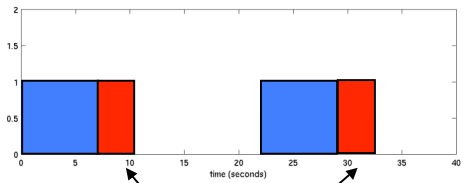


Sparse sampling

Evoked BOLD response



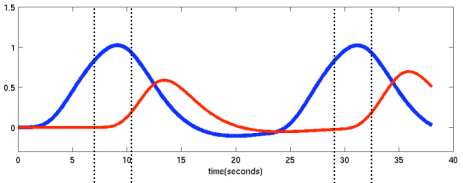
Stimulus paradigm



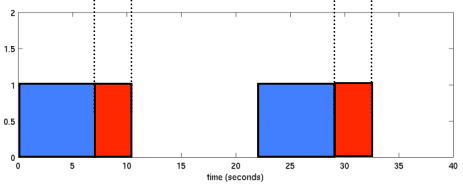
Scanner noise

Sparse sampling

Evoked BOLD response



Stimulus paradigm

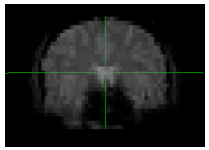


Requires knowledge of HRF timing

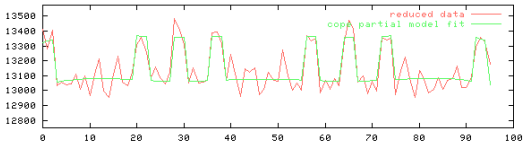
Sparse sampling: analysis

- Only a single volume is collected

Volume 2

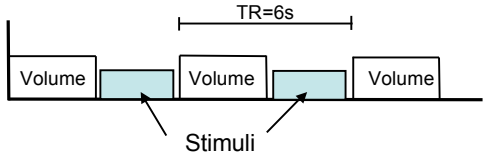


- Not a time series (more like PET data)



Interleaved acquisition

- Uses a delay in TR measurement so that stimuli can be presented when the gradients are off



- Good for auditory stimuli or TMS
- Requires careful jittering or oversampling to avoid potentially strong biased sampling effects

Questions before you start

- What is your question?
- What is the best way to evaluate it?
  - Subtraction, parametric, factorial, conjunction, adaptation
  - Blocked, event-related, mixed?
- How long is your experiment?
  - One run or many?
  - Movement and attention considerations
- How many blocks/events?
- TR? Sampling in time vs. space trade-off
  - Whole brain? Resolution?
  - If partial coverage - think about group average
- How many subjects?
  - Collect behavioural responses
  - Counter-balance order
  - Make sure your subjects know what they are doing