Experimental design of fMRI studies

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This book chapter covers the most common experimental designs along with how to efficiently design your experiments such that you maximize your chances of obtaining significant results.

Note the answers to ‘common questions’ at the end of this chapter.
Overview of SPM

Image time-series → Realignement → Smoothing → Normalisation → Template

Kernel

Design matrix → General linear model → Parameter estimates

Statistical parametric map (SPM)

Statistical inference → Gaussian field theory

$p < 0.05$
One voxel = One test (t, F, ...)

Temporal series fMRI

voxel time course

amplitude

General Linear Model → fitting
→ statistical image

Statistical image (SPM)
...revisited: matrix form

\[ Y = \beta_1 \times f(t) + \beta_2 \times 1 + \varepsilon \]
Regression example...

- Voxel time series
- Box-car reference function
- Mean value

\[ \text{voxel time series} = \beta_1 + \beta_2 + \text{Mean value} \]

\[ \beta_1 = 1 \]

\[ \beta_2 = 1 \]

Fit the GLM
Research question:
Which neuronal structures support face recognition?

Hypothesis:
The fusiform gyrus is implicated in face recognition

Experimental design

Parameter estimates

General linear model

Design matrix

Statistical parametric map (SPM)

Statistical inference

Gaussian field theory

$p < 0.05$
Overview

• Categorical designs
  Subtraction - Pure insertion, evoked / differential responses
  Conjunction - Testing multiple hypotheses

• Parametric designs
  Linear - Adaptation, cognitive dimensions
  Nonlinear - Polynomial expansions, neurometric functions

• Factorial designs
  Categorical - Interactions and pure insertion
  Parametric - Linear and nonlinear interactions
  Psychophysiological Interactions
Cognitive subtraction

- **Aim:**
  - Neuronal structures underlying a single process P (e.g., face recognition)?

- **Procedure:**
  - Contrast: [Task with P] – [control task without P] = P
    - the critical assumption of „pure insertion“

- **Example:**
  - [Task with P] – [task without P] = P

![Diagram showing neuronal structures with subtraction](image-url)
Cognitive subtraction

• Aim:
  – Neuronal structures underlying a single process P (e.g., face recognition)?

• Procedure:
  – Contrast: [Task with P] – [control task without P ] = P
    ➔ the critical assumption of „pure insertion“

• Example: [Task with P] – [task without P ] = P

![Diagram showing the subtraction process with neuronal structures.]
Cognitive subtraction: Baseline problems

Which neuronal structures support face recognition?

• „Distant“ stimuli
  ➔ Several components differ!

• „Related“ stimuli
  ➔ P implicit in control condition?

• Same stimuli, different task
  ➔ Interaction of task and stimuli (i.e. do task differences depend on stimuli chosen)?
A categorical analysis

Experimental design

Face viewing  F
Object viewing  O

F - O = Face recognition
O - F = Object recognition

...under assumption of pure insertion

Categorical design
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Conjunctions

• One way to minimize the baseline/pure insertion problem is to isolate the same process by two or more separate comparisons, and inspect the resulting simple effects for commonalities.

• A test for such activation common to several independent contrasts is called “conjunction”.

• Conjunctions can be conducted across a whole variety of different contexts:
  • tasks
  • stimuli
  • senses (vision, audition)
  • etc.

• Note: the contrasts entering a conjunction must be orthogonal (this is ensured automatically by SPM).
Conjunctions

Example: Which neural structures support object recognition, independent of task (naming vs. viewing)?

Task (1/2)

Viewing  Naming

Stimuli (A/B)  Objects  Colours

Objects

Colours

FIG. 3. Illustrations of the stimuli used in the experiment.

FIG. 4 represents a graphic task analysis where we have represented each of the four task pairs in terms of the cognitive components common to both these tasks were early visual analysis and articulation. The differences between these two tasks include orthographic, semantic, and sublexical processing; phonological retrieval. Illustrations of the stimuli were used to identify the brain regions implicated in the activation and baseline tasks and the differences shown in Fig. 3.

For each perceptual category (i.e., words, letters, objects, or colors) there will be a specific set of processes required to retrieve the name. For instance, during object naming phonological retrieval is dependent on the activation of both structural and semantic memories, not dependent on either structural or semantic memories. This task pair comprised (A) reading single familiar letters (task 3) and (B) saying the same prespecified word to single false-font characters (task 4). The cognitive components common to both these tasks were early visual analysis and articulation. The differences between these two tasks include orthographic letter processing, phonological retrieval, and the interaction between these processes.

This task pair comprised (A) reading single familiar monosyllabic words (task 1) and (B) saying the same prespecified word to strings of false font (task 2). The cognitive components common to both these tasks were early visual analysis and articulation. The differences between these two tasks include orthographic letter processing, phonological retrieval, and the interaction between these processes.

This task pair comprised (A) naming visually pre-
<table>
<thead>
<tr>
<th>Stimuli (A/B)</th>
<th>Colours</th>
<th>Viewing</th>
<th>Task (1/2)</th>
<th>Naming</th>
</tr>
</thead>
<tbody>
<tr>
<td>A1</td>
<td>B1</td>
<td>Visual Processing</td>
<td>V</td>
<td>Visual Processing</td>
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<tr>
<td></td>
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<td>Phonological Retrieval</td>
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<td></td>
<td></td>
<td>Object Recognition</td>
<td>R</td>
<td>Object Recognition</td>
</tr>
<tr>
<td>B2</td>
<td>A2</td>
<td>Visual Processing</td>
<td>V</td>
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Which neural structures support object recognition?

\[ (\text{Object - Colour viewing}) \quad [B1 - A1] \]
\&

\[ (\text{Object - Colour naming}) \quad [B2 - A2] \]

\[ [V,R - V] \& [P,V,R - P,V] = R \& R = R \]
Conjunctions
Two types of conjunctions

- Test of global null hypothesis:
  Significant set of consistent effects
  - “Which voxels show effects of similar direction (but not necessarily individual significance) across contrasts?”
  - Null hypothesis: No contrast is significant: $k = 0$
  - does not correspond to a logical AND!

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Main effects and interactions

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- Main effect of task: $(A_1 + B_1) - (A_2 + B_2)$
- Main effect of stimuli: $(A_1 + A_2) - (B_1 + B_2)$
- Interaction of task and stimuli: Can show a failure of pure insertion $(A_1 - B_1) - (A_2 - B_2)$
Factorial design

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Main effect of task:

(A1 + B1) – (A2 + B2)
Factorial design

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Main effect of stimuli: 
\[(A1 + A2) - (B1 + B2)\]
Factorial design

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Interaction of task and stimuli:

$$(A_1 - B_1) - (A_2 - B_2)$$
Main effects and interactions

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- Main effect of stimuli: \((A_1 + A_2) - (B_1 + B_2)\)
- Interaction of task and stimuli: Can show a failure of pure insertion \((A_1 - B_1) - (A_2 - B_2)\)

Is the inferotemporal region implicated in phonological retrieval during object naming?

Interaction effect (Stimuli x Task)
Event-related fMRI
Overview

1. Block/epoch vs. event-related fMRI
2. (Dis)Advantages of efMRI
3. GLM: Convolution
4. BOLD impulse response
5. Temporal Basis Functions
6. Timing Issues
7. Design Optimisation – “Efficiency”
Block/epoch designs examine responses to series of similar stimuli

Event-related designs account for response to each single stimulus

P = Pleasant
U = Unpleasant

~4s
Advantages of event-related fMRI

1. Randomised trial order
Blocked designs may trigger expectations and cognitive sets.

Intermixed designs can minimise this by stimulus randomisation.
Advantages of event-related fMRI

1. Randomised trial order
2. Post-hoc subjective classification of trials
Items with wrong memory of picture ("hat") were associated with more occipital activity at encoding than items with correct rejection ("brain")

Advantages of event-related fMRI

1. Randomised trials order
2. Post-hoc subjective classification of trials
3. Some events can only be indicated by participant
efMRI: Online event definition
Advantages of event-related fMRI

1. Randomised trials order
2. Post-hoc subjective classification of trials
3. Some events can only be indicated by participant
4. Some events cannot be blocked due to stimulus context
efMRI: Stimulus context
Advantages of event-related fMRI

1. Randomised trials order
2. Post-hoc subjective classification of trials
3. Some events can only be indicated by participant
4. Some events cannot be blocked due to stimulus context
5. More accurate model even for epoch/block designs?
“Epoch” model assumes constant neural processes throughout block

“Event” model of block design

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

Data

Model
Models can be blocked or intermixed, BUT models for blocked designs can be epoch- or event-related.

- Epochs are periods of sustained stimulation (e.g., box-car functions);
  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.
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 a parameter that increases with rate, because the parameter reflects response per block
  - An “event” model may estimate a parameter that decreases with rate, because the parameter reflects response per word
Disadvantages of intermixed designs

1. Less efficient for detecting effects than blocked designs

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

Convolution

$u(t)$

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

sampled each scan

Design Matrix
\[ f \otimes g(t) = \int_0^t f(\tau) g(t - \tau) d\tau \]

\text{expected BOLD response} = \text{input function} \otimes \text{impulse response function (HRF)}
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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, $f = 1/33$

Stimulus (“Neural”) $\times$ HRF $=$ Predicted Data

A very “efficient” design!
Blocked, epoch = 20 sec

Stimulus ("Neural") × HRF = Predicted Data

Blocked-epoch (with small SOA) quite “efficient”
Blocked (80s), SOAmin=4s, highpass filter = 1/120s

Stimulus ("Neural") $\otimes$ HRF $\Rightarrow$ Predicted Data

Very ineffective: Don’t have long (>60s) blocks!
Randomised design spreads power over frequencies

Stimulus ("Neural") \times HRF = Predicted Data

Randomised, SOAmin=4s, highpass filter = 1/120s
Design efficiency: Trial spacing

- Design parametrised by:
  - $SOA_{\text{min}}$ Minimum SOA
  - $p(t)$ Probability of event at each $SOA_{\text{min}}$

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

- Stationary stochastic
  $p(t)=\text{constant}$

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

Blocked designs most efficient! (with small SOA_{\text{min}})
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)
Checking your design efficiency
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Parametric designs

- Parametric designs approach the baseline problem by:
  - Varying the stimulus-parameter of interest on a continuum, in multiple (n>2) steps...
  - ... and relating measured BOLD signal to this parameter

- Possible tests for such relations are manifold:
  - Linear
  - Nonlinear: Quadratic/cubic/etc. (polynomial expansion)
  - Model-based (e.g. predictions from learning models)
Parametric modulation of regressors by time

“User-specified” parametric modulation of regressors

Polynomial expansion & orthogonalisation

Büchel et al. 1998, NeuroImage 8:140-148
Investigating neurometric functions
(= relation between a stimulus property and the neuronal response)

P0-P4: Variation of intensity of a laser stimulus applied to the right hand (0, 300, 400, 500, and 600 mJ)

P0: 0 mJ
P1: 300 mJ
P2: 400 mJ
P3: 500 mJ
P4: 600 mJ

Neurometric functions

- Stimulus intensity
- Stimulus presence
- Pain intensity

Model-based regressors

• General idea:
  generate predictions from a computational model, e.g. of learning or decision-making

• Use these predictions to define regressors

• Include these regressors in a GLM and test for significant correlations with voxel-wise BOLD responses
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Thank you