Experimental design

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With thanks to:

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Rik Henson
The most important slide of this talk

It all starts with a good design!

What process do I want to measure?

How do I need to design my experiment in order to measure that process?

Research question  Experimental design
Why is that?

The BOLD signal does NOT provide you with an absolute measure of neural activity
Therefore, you need to compare activity across conditions

The sensitivity of your design depends on maximizing the relative change between conditions
SPM processing hierarchy

At the very top...

Image time-series → Realignment → Normalisation → Template

Kernel → Smoothing

Design matrix → General linear model → Parameter estimates

Statistical parametric map (SPM) → Statistical inference

Gaussian field theory

p < 0.05

SPM - Experimental design
Overview

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

2. Parametric designs
   - Linear
     - Adaptation, cognitive dimensions
   - Nonlinear
     - Polynomial expansions, neurometric functions
     - Model-based regressors

3. Factorial designs
   - Categorical
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   - Parametric
     - Linear and nonlinear interactions
     - Psychophysiological Interactions (PPI)
Cognitive subtraction

Aim
Neuronal structures underlying a single process P

Procedure
Contrast: [Task with P] – [matched task without P] \( \rightarrow \) P

A good control task is critical!

However…
The critical assumption of pure insertion

*Pure insertion assumption:* Assumption that adding components does not affect other processes

Pretty close to pure insertion…

…this one not…

… the assumption of pure insertion is not realistic for brain processes.
The critical assumption of pure insertion

“Adding” or “removing” a process might change other processes → non-linearity, i.e. interactions
Simple subtraction

**Question:** Which neural structures support face recognition?

Aim: Isolation of a cognitive process

Method: Compare the neural signal for a task that activates the cognitive process of interest (P) and a second task that controls for all but the process of interest (P)
Choosing your baseline

**Problem:** Difficulty of finding baseline tasks that activate all but the process of interest

Different stimuli and task

- **‘Ah, that’s the Queen’** vs. **‘I am so hungry…’**

Different stimulus, same task

- Name: ‘The Queen’
- Name: ‘A burger’

Several components differ (visual-perceptual, cognitive, …) → not good control tasks
Choosing your baseline

**Problem:** Difficulty of finding baseline tasks that activate all but the process of interest

- **Related stimuli, same task**
  - Famous? - yes
  - Famous? – hm, wait, maybe… somewhat familiar…

- **Same stimulus, different tasks**
  - Name the person!
  - Name the gender!

- **Process P implicit in control task?**
  - Difficulty matched?

- **Process P cancelled out (highly specific naming-related activity)?**
  - Interaction of task and stimuli?
Choosing your baseline

Depending on your choice of the control condition, you will answer very different questions!
An example of cognitive subtraction

Experimental design

Face viewing: F
Object viewing: O

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

...under assumption of pure insertion

Kanwisher et al., 1997, J. Neurosci.
Categorical responses

SPM interface

Task 1
Task 2
Session
The problem of cognitive subtraction

Problems:

• Difficulty of finding baseline tasks that activate all but the process of interest (the “baseline problem”)
• Subtraction depends on the assumption of “pure insertion” (an extra cognitive component can be inserted without affecting the pre-existing components)

Friston et al., (1996)
fMRI adaptation as an example of neural interaction

Famous faces: 1st time vs 2nd time

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Tackling the baseline problem

Contrast 1: condition A – condition B

Contrast 2: condition C – condition D
Conjunction

Minimization of “the baseline problem” by isolating the same cognitive process by two or more separate contrasts

**Note:** The contrasts entering a conjunction have to be independent (i.e. they must be orthogonal, which is ensure automatically by SPM)
Question: Which neural structures support **phonological retrieval**, independent of item?
Conjunction analysis

**Question:** Which neural structures support *phonological retrieval*, independent of item?

Phonological retrieval is the only cognitive component common to all task pair differences.

Price & Friston (1996)
Conjunction analysis

SPM

1 task/session
Conjunction analysis

Isolates the process of Phonological retrieval, no interaction with visual processing etc

Overlap of 4 subtractions

Areas are identified in which task-pair effects are **jointly significant** (conjunction)

→ Associated with process of interest (phonological retrieval)

Price & Friston (1996)
Conjunction: two ways of testing for significance

SPM offers two general ways to test the significance 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?”

- **Test of conjunction null hypothesis:**
  Set of consistently significant effects
  “which voxels show, for each specified contrast, effects > threshold $p$?”

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Parametric designs

Does activity vary systematically with a continuously varying parameter?

Varying the stimulus-parameter of interest on a continuum, in multiple (n>2) steps and relating BOLD to this parameter

Possible tests for such relations:
- Linear
- Nonlinear: Quadratic/cubic/etc.
- "Data-driven" (e.g., neurometric functions, computational modelling)

Avoids pure insertion but does assume no qualitative change in processing.
A linear parametric contrast

Is there an adaptation effect if people listen to words multiple times?

Linear effect of time

Non-linear effect of time

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A non-linear parametric design matrix

Polynomial expansion:
\[ f(x) = b_1 x + b_2 x^2 + \ldots \text{up to (N-1)th order for N levels} \]

SPM offers polynomial expansion as option during creation of parametric modulation regressors.

Büchel et al., (1996)
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Parametric design: Model-based regressors

Signals derived from a computational model are correlated against BOLD, to determine brain regions showing a response profile consistent with the model, e.g. Rescorla-Wagner prediction error.
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Factorial design

Highly efficient: Factorial designs allow for testing main effects and interactions!

We can address the “pure insertion” problem!
**Factorial design**

**Question:** Is the inferotemporal cortex sensitive to both object recognition and phonological retrieval of object names?
**SPM - Experimental design**

**Question:** Is the inferiortemporal cortex sensitive to both object recognition and phonological retrieval of object names?

- **A**  Say ‘yes’ when you see an **abstract image**
  - Visual analysis
  - Verbal output

- **B**  Say ‘yes’ when you see an **object**
  - Visual analysis
  - Object recognition
  - Verbal output

- **C**  Name the object
  - Visual analysis
  - Object recognition
  - Phonological retrieval
  - Verbal output
Factorial design

**Question:** Is the inferotemporal cortex sensitive to both object recognition and phonological retrieval of object names?

Say ‘yes’ when you see an abstract image

Say ‘yes’ when you see an object

Name the object

Results in inferotemporal cortex:

Friston et al., (1997)

<table>
<thead>
<tr>
<th>A</th>
<th>B</th>
<th>C</th>
</tr>
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Object recognition

IT not involved in phonological retrieval?!
Addressing interactions in factorial designs

Is the task the sum of its component processes, or does A modulate B?

Let’s test the interaction explicitly!
How?
→ Vary A and B independently!
Factorial designs: Main effects and interaction

**Question:** Is the inferiortemporal cortex sensitive to both **object recognition** and **phonological retrieval** of object names?

- **Non-object**
  - Say ‘yes’
  - Visual analysis
  - Speech

- **Object**
  - Say ‘yes’
  - Visual analysis
  - Object recognition
  - Speech

- **Object name**
  - Visual analysis
  - Object recognition
  - Phonological retrieval
  - Speech

Friston et al., (1997)
Factorial designs: Main effects and interaction

Main effect of task (naming): \((O\text{NAME} + N\text{NAME}) - (O\text{YES} + N\text{YES})\)

Main effect of stimuli (object): \((O\text{YES} + O\text{NAME}) - (N\text{YES} + N\text{NAME})\)

Interaction of task & stimuli: \((O\text{NAME} + N\text{YES}) - (O\text{YES} + N\text{NAME})\)

Can show a failure of pure insertion

Inferotemporal (IT) responses do discriminate between situations where phonological retrieval is present or not. In the absence of object recognition, there is a deactivation in IT cortex, in the presence of phonological retrieval.

Friston et al., (1997)
Interaction in SPM

We can selectively inspect our data for one or the other by masking during inference.

Interactions:
- cross-over
- and
- simple

Definition: 

(define contrast...

(A1 - A2) x (B1 - B2)

contrast(s)

1 -1 -1 1

Design matrix

parameter estimability

name defined, contrast defined

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Psychophysiological Interactions (PPI)
**Question:** Are there different kinds of adaptation for word generation and word repetition as a function of time?

### Linear Parametric Interaction

A (Linear)

Time-by-Condition

Interaction

(“Generation strategy”?)

Contrast:

\[ [5 \ 3 \ 1 \ -1 \ -3 \ -5] \otimes [-1 \ 1] \] (categorical)

\[ = [-5 \ 5 \ -3 \ 3 \ -1 \ 1 \ 1 \ -1 \ 3 \ -3 \ 5 \ -5] \]
Non-Linear Parametric Interaction

F-contrast tests for Generation-by-Time interaction (including both linear and quadratic components)

Factorial Design with 2 factors:
1. Gen/Rep (Categorical, 2 levels)
2. Time (Parametric, 6 levels)

Time effects modelled with both linear and quadratic components…
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     **Psychophysiological Interactions (PPI)**
Psycho-physiological Interaction (PPI)

Question:
Does the activation in one area of the brain predict the activation in another area, depending on whether a contextual factor was present or not.
Psycho-physiological Interaction (PPI)

- Functional connectivity measure
- Can activity in one part of the brain be predicted by an interaction between task and activity in another part of the brain?
- If two areas interact, they will display synchronous activity

Stephan, 2004
Psycho-physiological Interaction (PPI)

Factorial design

<table>
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<th>Learning</th>
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<td>Faces after (Fa)</td>
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Dolan et al., 1997
Psycho-physiological Interaction (PPI)

Main effect of learning

![Image showing brain scans and adjusted response graph]

Dolan et al., 1997

- Learning
  - Objects before (Ob)
  - Objects after (Oa)
  - Faces before (Fb)
  - Faces after (Fa)

- Stimuli
Psycho-physiological Interaction (PPI)

Does learning involve functional connectivity between parietal cortex and stimuli specific areas?

Dolan et al., 1997
Psycho-physiological Interaction (PPI)

Does learning involve functional connectivity between parietal cortex and stimuli specific areas?

Main effect of task (Faces - objects)

Activity in parietal cortex (main effect learning)

PPI regressor = HRF convolved task x seed ROI regressors

Seed region

Whole brain

Anti-correlated for objects correlated for faces

O’Reilly (2012)
Psycho-physiological Interaction (PPI)

Does learning involve functional connectivity between parietal cortex and stimuli specific areas?

Main effect of task (Faces - Objects)

Activity in parietal cortex (main effect of learning)

PPI regressor = HRF convolved task x seed ROI regressors

The interaction term should account for variance over and above what is accounted for by the main effect of task and physiological correlation

O'Reilly (2012)
Psycho-physiological Interaction (PPI)

Coupling between ITC and parietal cortex depends on the stimulus

Coupling between the temporal face area and the medial parietal cortex when, and only when, faces were perceived

Suggests: ITC can differentiate between faces and objects only if parietal activity is high

Dolan et al., 1997
Psycho-physiological interactions (PPI)

A standard PPI analysis does not make inferences about the direction of information flow (causality)
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Questions?