Group Analyses

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With many thanks to W. Penny, S. Kiebel, T. Nichols, R. Henson, J.-B. Poline, F. Kherif
**Image time-series**

- **Realignment**
  - **Spatial filter**
  - **Normalisation**
  - **Anatomical reference**

- **Smoothing**

- **Design matrix**

- **General Linear Model**

- **Parameter estimates**

- **Statistical Inference**

- **Statistical Parametric Map**

  - **RFT**

  - $p < 0.05$
GLM: repeat over subjects

fMRI data → Design Matrix → Contrast Images → SPM{t}

Subject 1
Subject 2
...
Subject N
First level analyses ($p<0.05$ FWE):

Data from R. Henson
Fixed effects analysis (FFX)

Modelling all subjects at once

- Simple model
- Large amount of data
- Assumes common variance over subjects at each voxel

Subject 1
Subject 2
Subject 3
Subject N
Fixed effects analysis (FFX)

\[ y = X^{(1)} \beta^{(1)} + \varepsilon^{(1)} \]

- Modelling all subjects at once
- Simple model
- Lots of degrees of freedom
- Large amount of data
- Assumes common variance over subjects at each voxel
Fixed effects

\[ y = X^{(1)} \beta^{(1)} + \varepsilon^{(1)} \]

- Only one source of random variation (over sessions):
  - measurement error

- True response magnitude is fixed.
Random effects

\[ y = X^{(1)} \beta^{(1)} + \varepsilon^{(1)} \]

\[ \beta^{(1)} = X^{(2)} \beta^{(2)} + \varepsilon^{(2)} \]

- Two sources of random variation:
  - measurement errors
  - response magnitude (over subjects)

- Response magnitude is \textit{random}
  - each subject/session has random magnitude
Random effects

\[ y = X^{(1)} \beta^{(1)} + \varepsilon^{(1)} \]
\[ \beta^{(1)} = X^{(2)} \beta^{(2)} + \varepsilon^{(2)} \]

- Two sources of random variation:
  - measurement errors
  - response magnitude (over subjects)

- Response magnitude is random
  - each subject/session has random magnitude
  - but population mean magnitude is fixed.
Random effects

Probability model underlying random effects analysis
Fixed vs random effects

With **Fixed Effects Analysis (FFX)** we compare the group effect to the *within-subject variability*. It is not an inference about the population from which the subjects were drawn.

With **Random Effects Analysis (RFX)** we compare the group effect to the *between-subject variability*. It is an inference about the population from which the subjects were drawn. If you had a new subject from that population, you could be confident they would also show the effect.
Fixed vs random effects

- Fixed isn’t “wrong”, just usually isn’t of interest.

- Summary:
  - Fixed effects inference:
    “I can see this effect in this cohort”
  - Random effects inference:
    “If I were to sample a new cohort from the same population I would get the same result”
Hierarchical linear models:

- Random effects models
- Mixed effects models
- Nested models
- Variance components models

... all the same

... all alluding to multiple sources of variation

(in contrast to fixed effects)
Hierarchical models

Example: Two level model

\[ y = X^{(1)} \beta^{(1)} + \epsilon^{(1)} \]
\[ \beta^{(1)} = X^{(2)} \beta^{(2)} + \epsilon^{(2)} \]
Hierarchical models

- Restricted Maximum Likelihood (ReML)
- Parametric Empirical Bayes
- Expectation-Maximisation Algorithm

But:

- Many two level models are just too big to compute.
- And even if, it takes a long time!
- Any approximation?

Summary Statistics RFX Approach

First level

fMRI data → Design Matrix → Contrast Images

Second level

One-sample t-test @ second level

\[ t = \frac{c^T \hat{\beta}}{\sqrt{\text{Var}(c^T \hat{\beta})}} \]

Subject 1 → Contrast Images → One-sample t-test @ second level

... → Contrast Images → One-sample t-test @ second level

Subject N → Contrast Images → One-sample t-test @ second level

Summary Statistics RFX Approach

Assumptions

- The summary statistics approach is exact if for each session/subject:
  - Within-subjects variances the same
  - First level design the same (e.g. number of trials)

- Other cases: summary statistics approach is robust against typical violations.


Robustness

Summary statistics

Hierarchical Model

Listening to words

Viewing faces

ANOVA & non-sphericity

- One effect per subject:
  - Summary statistics approach
  - One-sample t-test at the second level

- More than one effect per subject or multiple groups:
  - Non-sphericity modelling
  - Covariance components and ReML
GLM assumes Gaussian “spherical” (i.i.d.) errors

**sphericity = iid:** error covariance is scalar multiple of identity matrix: $\text{Cov}(e) = \sigma^2 I$

**Examples for non-sphericity:**

- $\text{Cov}(e) = \begin{bmatrix} 4 & 0 \\ 0 & 1 \end{bmatrix}$ non-identically distributed
- $\text{Cov}(e) = \begin{bmatrix} 2 & 1 \\ 1 & 2 \end{bmatrix}$ non-independent

\[
\text{Cov}(e) = \begin{bmatrix} 1 & 0 \\ 0 & 1 \end{bmatrix}
\]
Errors are independent but not identical (e.g. different groups (patients, controls))

Errors are not independent and not identical (e.g. repeated measures for each subject (multiple basis functions, multiple conditions, etc.))
2nd level: Variance components

\[
\text{Cov}(\varepsilon) = \sum_k \lambda_k Q_k
\]
Example 1: between-subjects ANOVA

- **Stimuli:**
  - Auditory presentation (SOA = 4 sec)
  - 250 scans per subject, block design
  - 2 conditions
    - Words, e.g. “book”
    - Words spoken backwards, e.g. “koob”

- **Subjects:**
  - 12 controls
  - 11 blind people

Data from Noppeney et al.
Example 1: Covariance components

- Two-sample t-test:
  - Errors are independent but not identical.
  - 2 covariance components

Errors covariance matrix

$Q_k$'s:
Example 1: Group differences

First Level

Second Level

\[ c^T = [1 \quad -1] \]

\[ X \]
Example 2: within-subjects ANOVA

- Stimuli:
  - Auditory presentation (SOA = 4 sec)
  - 250 scans per subject, block design
  - Words:
    - Motion
    - Sound
    - Visual
    - Action
    - “jump”
    - “click”
    - “pink”
    - “turn”

- Subjects:
  - 12 controls

- Question:
  - What regions are generally affected by the semantic content of the words?

Noppeney et al., Brain, 2003.
Example 2: Covariance components

- Errors are not independent and not identical

$Q_k$'s:
Example 2: Repeated measures ANOVA

First Level

Second Level

\[
Cov(\varepsilon) = \begin{pmatrix}
1 & -1 & 0 & 0 \\
-1 & 1 & -1 & 0 \\
0 & 0 & 1 & -1 \\
0 & 0 & -1 & 1
\end{pmatrix}
\]

\[
c^T = \begin{pmatrix}
1 \\
-1 \\
0 \\
0
\end{pmatrix}
\]

\[
X
\]
ANCOVA model

Mean centering continuous covariates for a group fMRI analysis, by J. Mumford: http://mumford.fmripower.org/mean_centering/
Analysis mask: logical AND
SPM interface: factorial design specification

- Options:
  - One-sample t-test
  - Two-sample t-test
  - Paired t-test
  - Multiple regression
  - One-way ANOVA
  - One-way ANOVA – within subject
  - Full factorial
  - Flexible factorial
Summary

- Group Inference usually proceeds with **RFX analysis**, not FFX. Group effects are compared to between rather than within subject variability.

- **Hierarchical models** provide a gold-standard for RFX analysis but are computationally intensive.

- **Summary statistics** approach is a robust method for RFX group analysis.

- Can also use ‘**ANOVA**’ or ‘**ANOVA within subject**’ at second level for inference about multiple experimental conditions or multiple groups.
Bibliography:


- **Classical and Bayesian inference in neuroimaging: theory.** Friston et al., NeuroImage, 2002.

- **Classical and Bayesian inference in neuroimaging: variance component estimation in fMRI.** Friston et al., NeuroImage, 2002.

- **Mixed-effects and fMRI studies.** Friston et al., NeuroImage, 2005.

- **Simple group fMRI modeling and inference.** Mumford & Nichols, NeuroImage, 2009.