Methods & Models for fMRI Analysis 2018

GROUP ANALYSIS

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ETH Eidgenössische Technische Hochschule Zürich
Swiss Federal Institute of Technology Zurich

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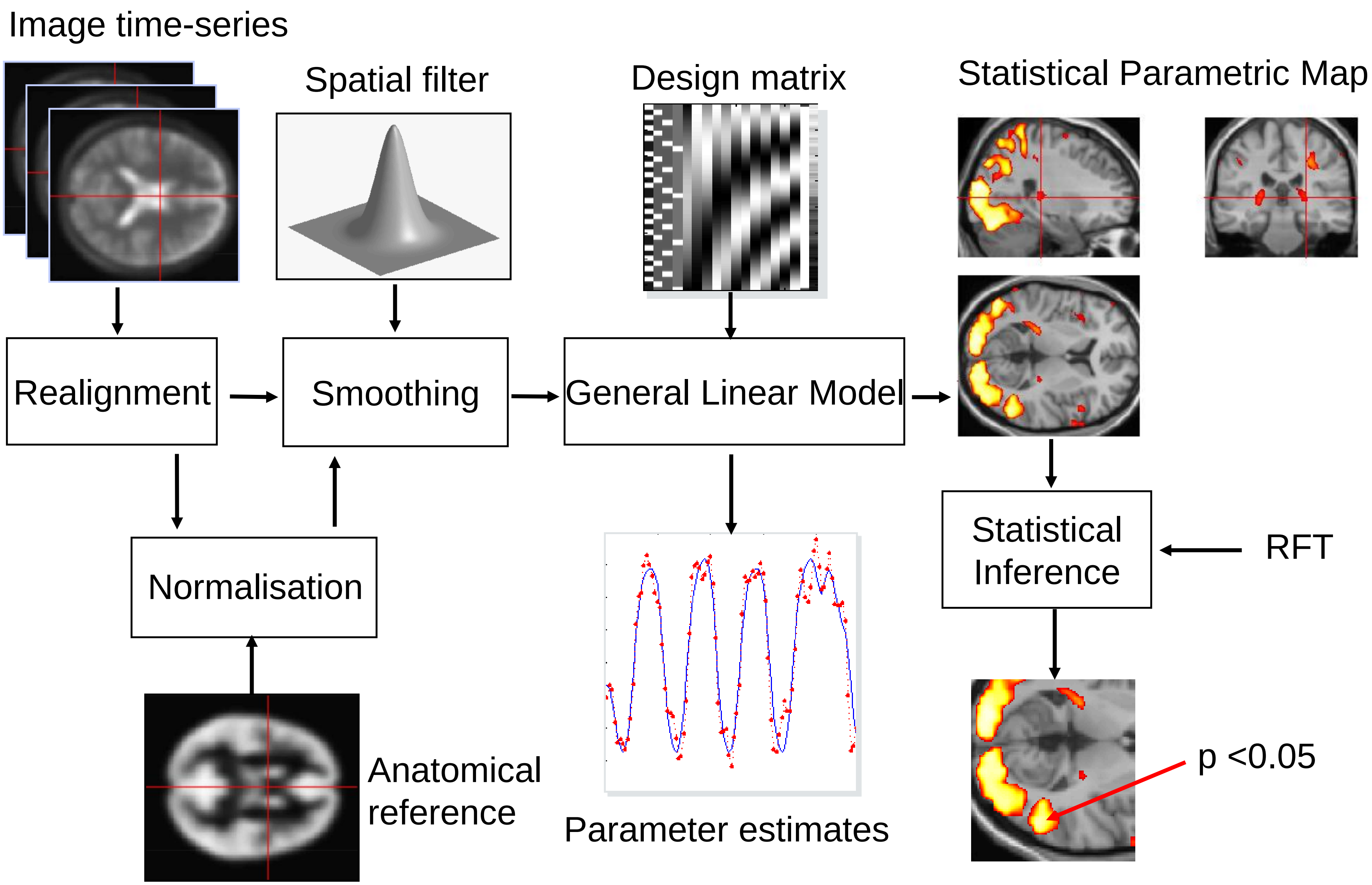
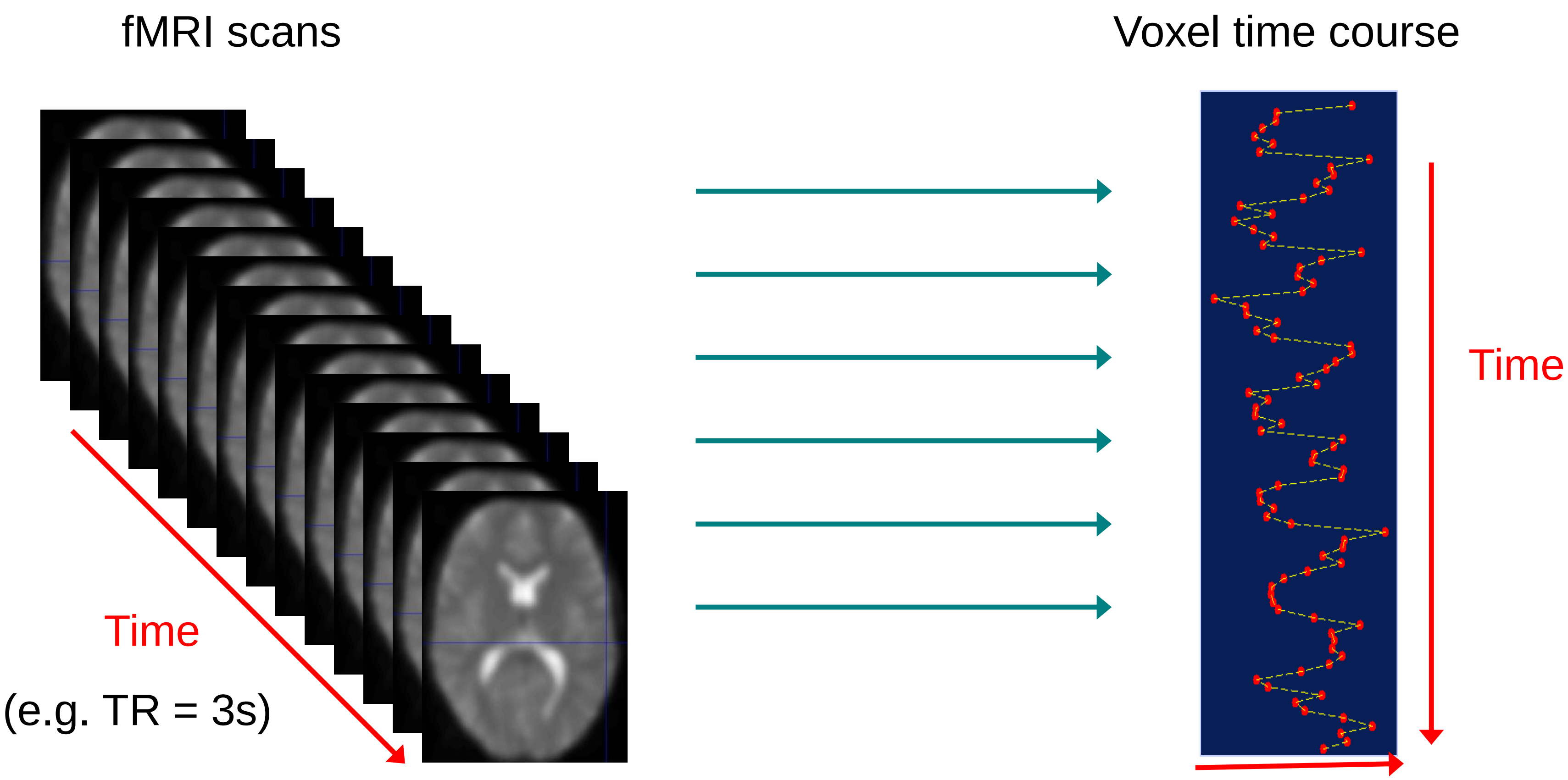
Overview of SPM Steps

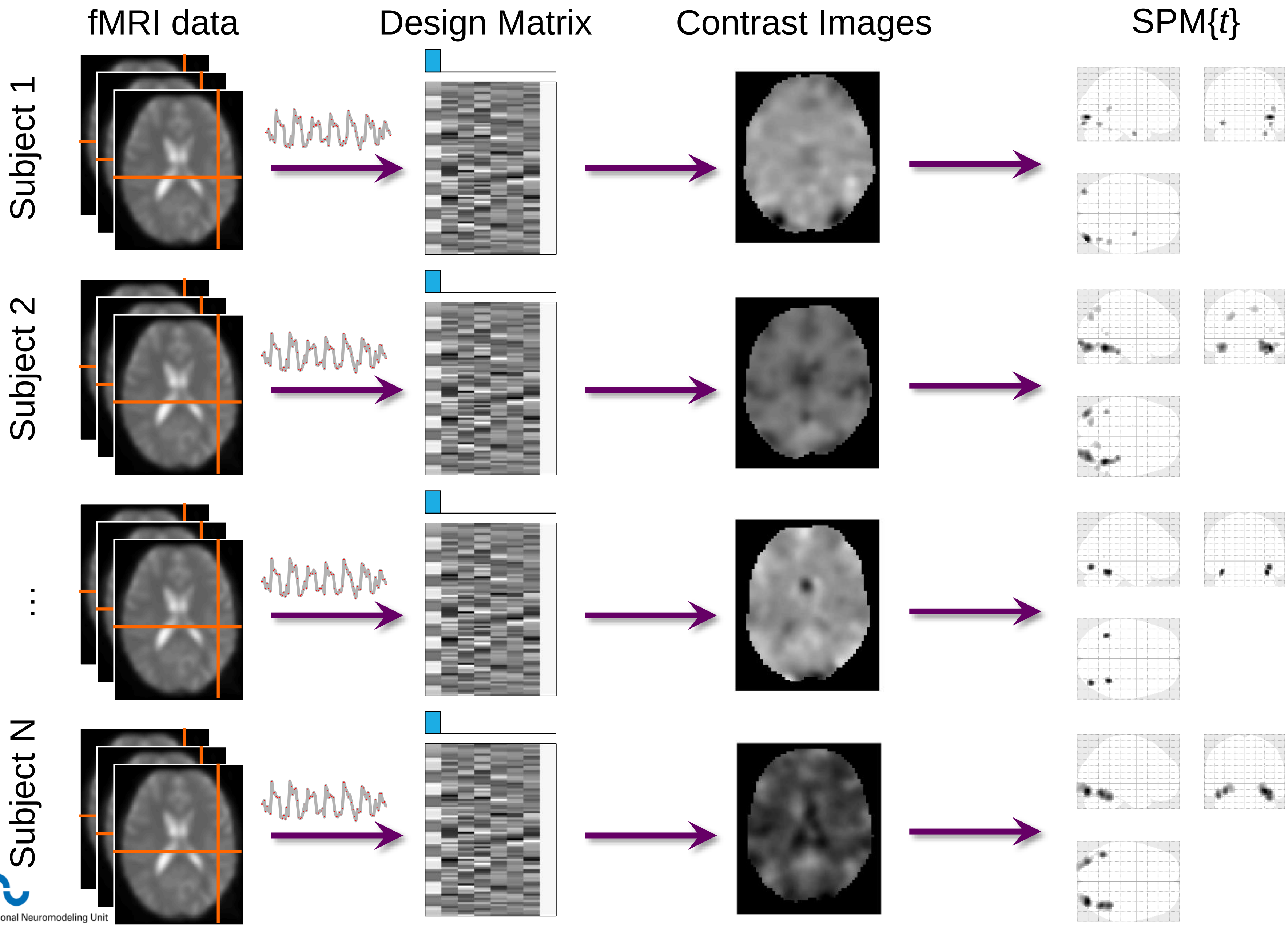


1st Level Analysis is within subject

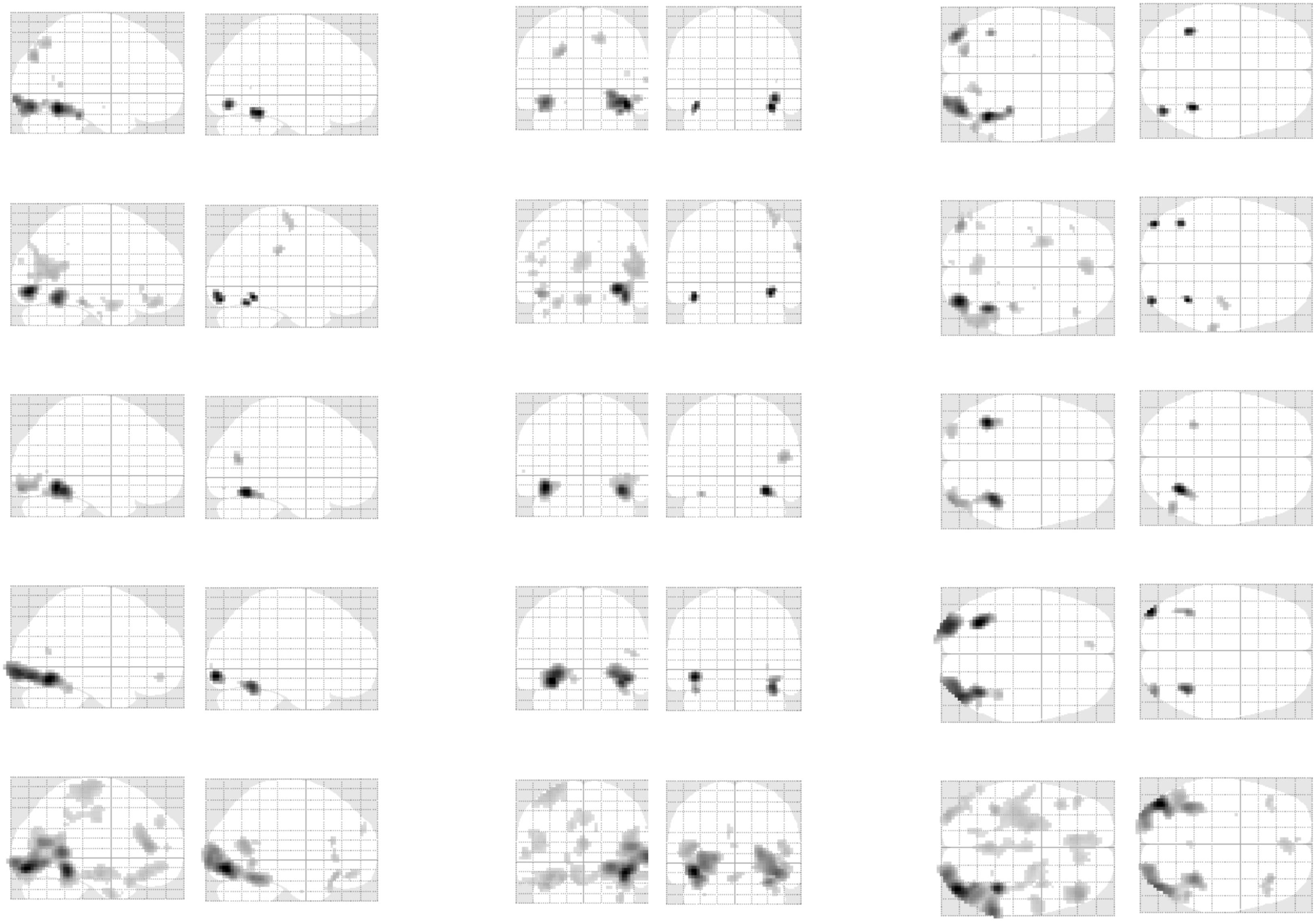
$$y = X\beta + e$$



GLM: repeat over subjects



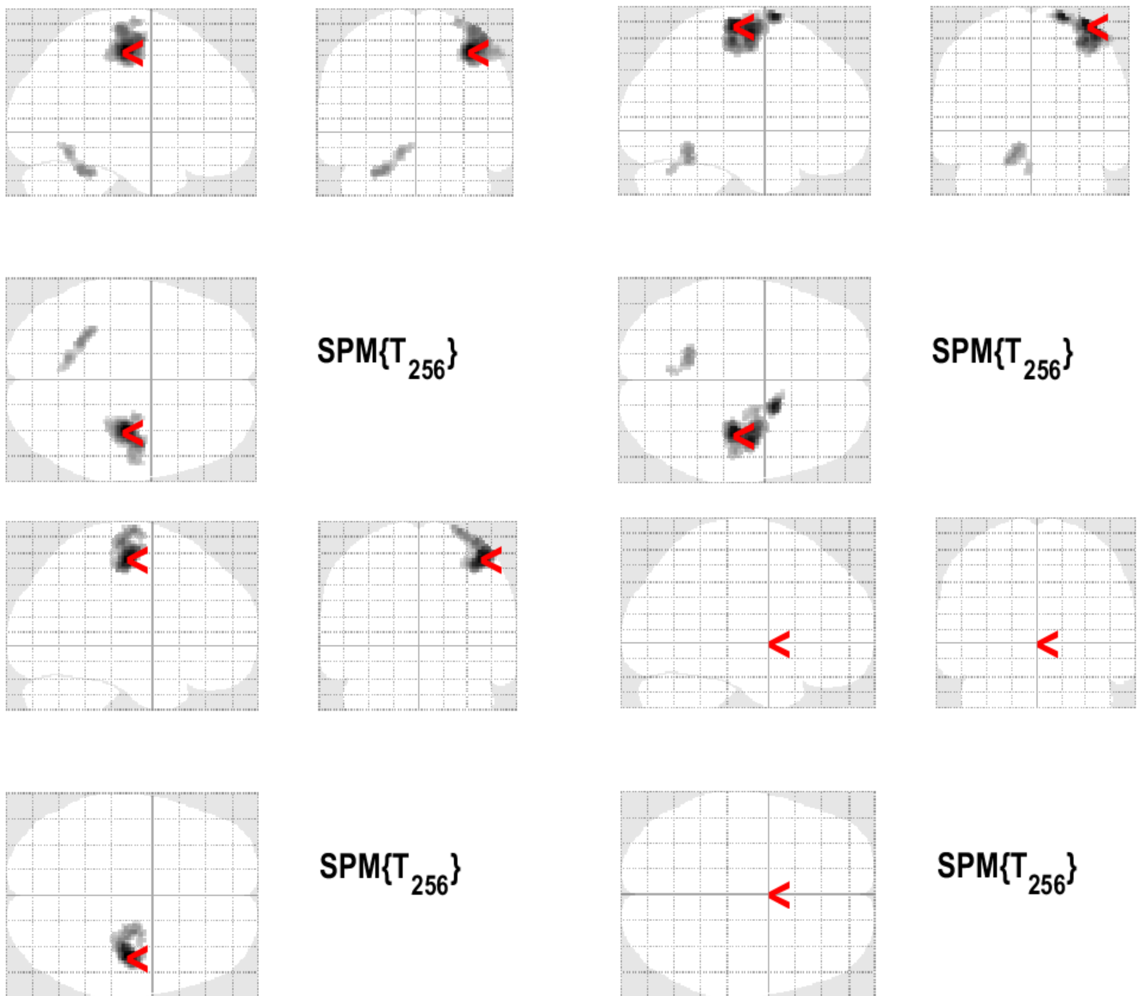
First level analyses (p<0.05 FWE):



Data from R. Henson

First level analyses (p<0.05 FWE at cluster-level, with CDT:p<0.001):

Left Arrow > Right Arrow



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Data from Methods & Models Course 2018

2nd level analysis – across subjects

- It isn't enough to look just at individuals.
- So, we need to look at which voxels are showing a significant activation difference between levels of X consistently <u>within a group.</u>
    1. Average contrast effect across sample
    2. Variation of this contrast effect
    3. T-tests

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Group Analysis: Fixed vs Random

Does the group activate on average?

Group
s1 s2 s3 s4 s5 s6 s7

What group mean are we after?

- The group mean for those exact 7 subjects?
  → Fixed effects analysis (FFX)
- The group mean for the population from which these 7 subjects were drawn?
  → Random effects analysis (RFX)

Fixed effects analysis (FFX)

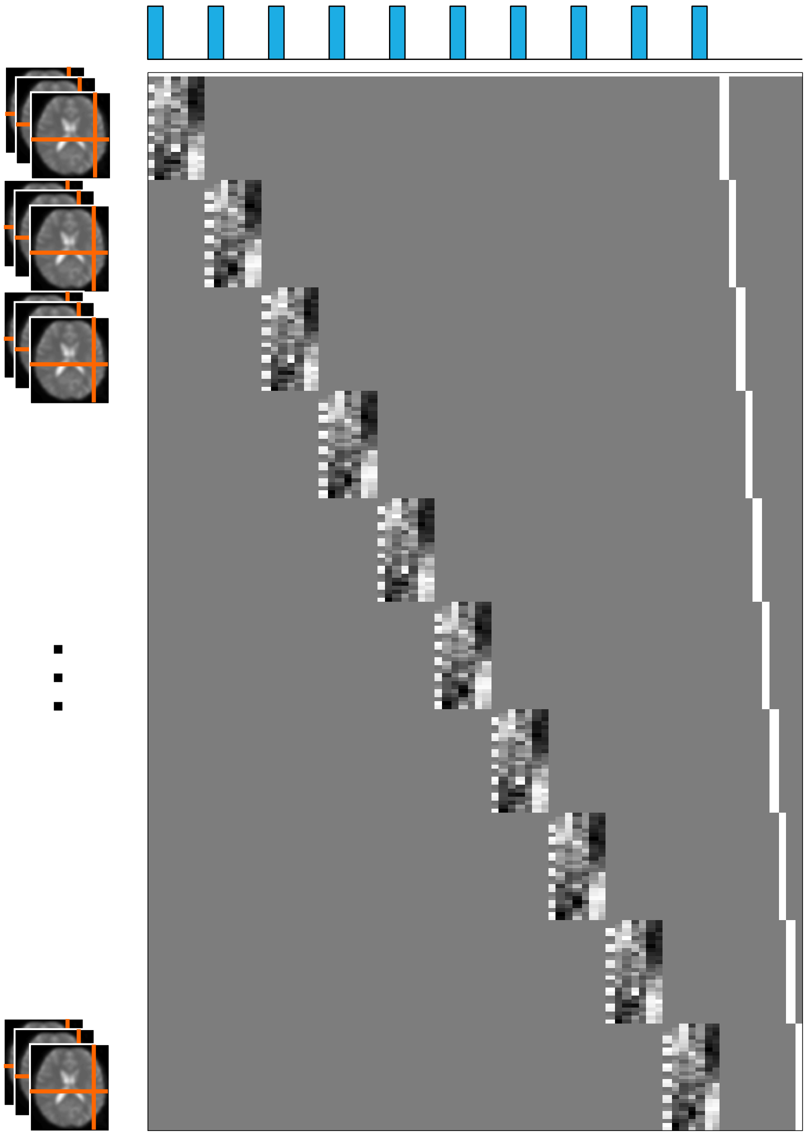
Subject 1

Subject 2

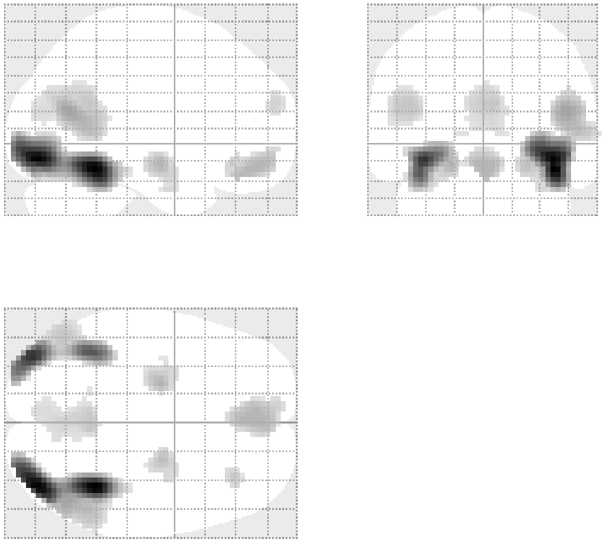
Subject 3

⋮

Subject N



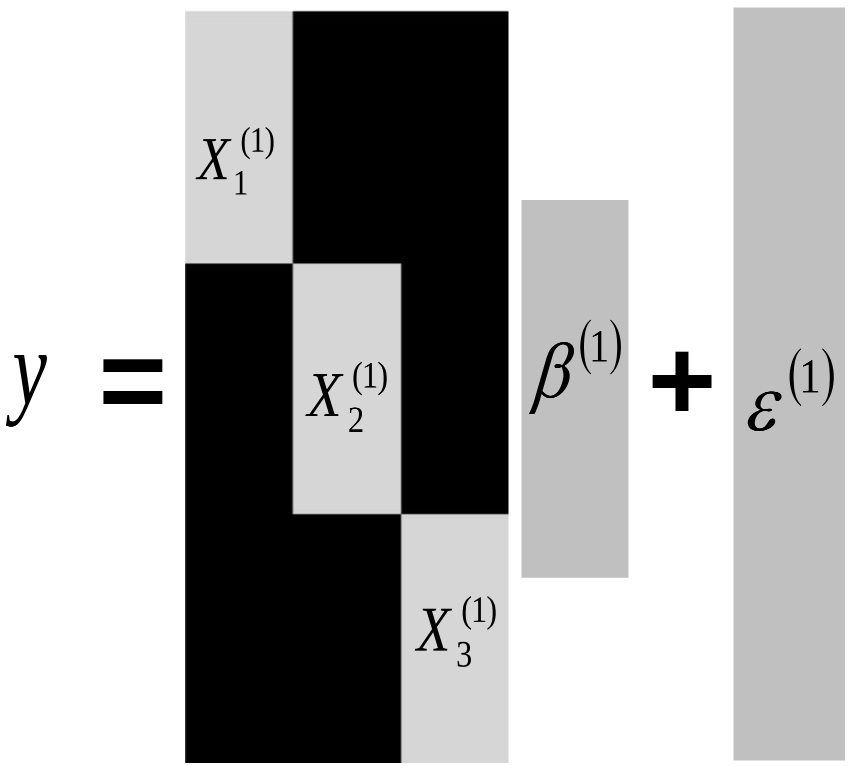
Modelling all subjects at once



variance over subjects at each voxel

Fixed effects analysis (FFX)

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



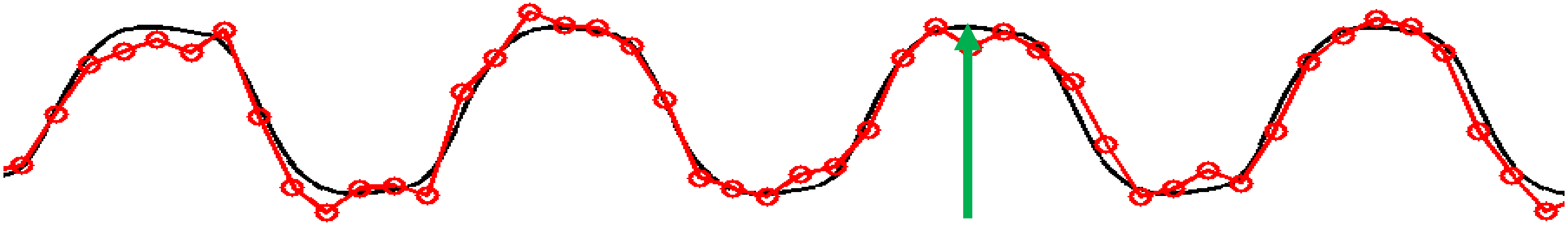
Modelling all subjects at once

- ☑ 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

Within-subject Variance

- True response magnitude is *fixed.*

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Whole Group – FFX calculation

- N subjects = 12 with each 50 scans = 600 scans

c = [4, 3, 2, 1, 1, 2, 3, 3, 3, 2, 4, 4]

Within subject variability:

s_w = [0.9, 1.2, 1.5, 0.5, 0.4, 0.7, 0.8, 2.1, 1.8, 0.8, 0.7, 1.1]

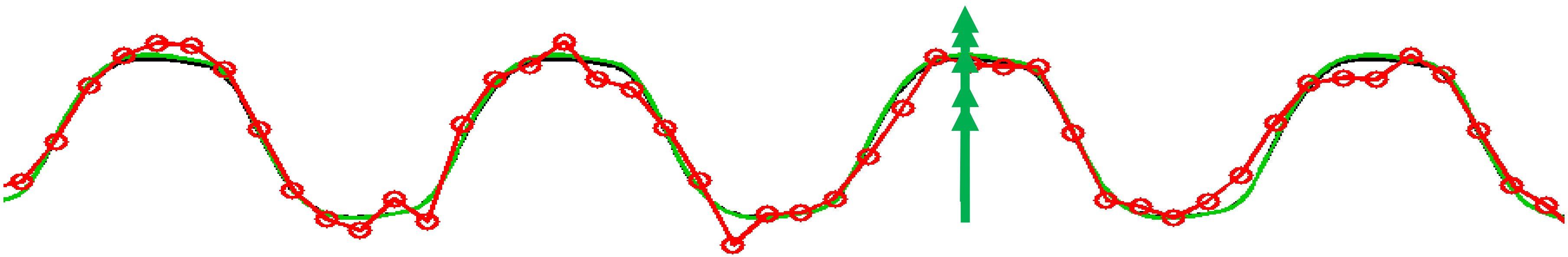
- Mean group effect = 2.67
- Mean s_w = 1.04
- Standard Error Mean (SEM) = s_w /(sqrt(N))=0.04

t=M/SEM = 62.7, $p=10^{-51}$

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)

Within-subject Variance

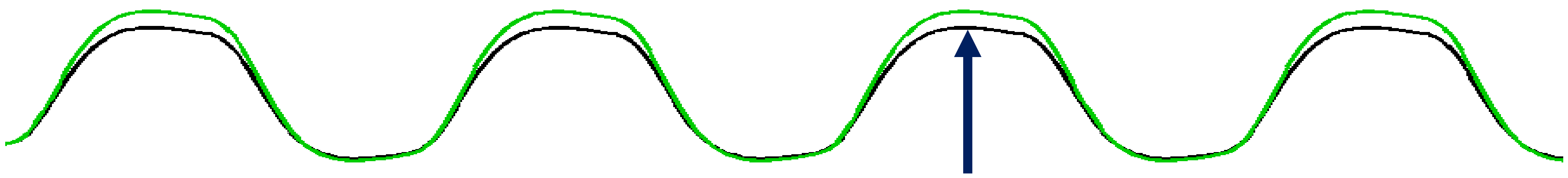
Between-subject Variance

- Response magnitude is *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)

Within-subject Variance

Between-subject Variance

- Response magnitude is *random*
  - → each subject/session has random magnitude
  - → but population mean magnitude is *fixed.*

Whole Group – RFX calculation

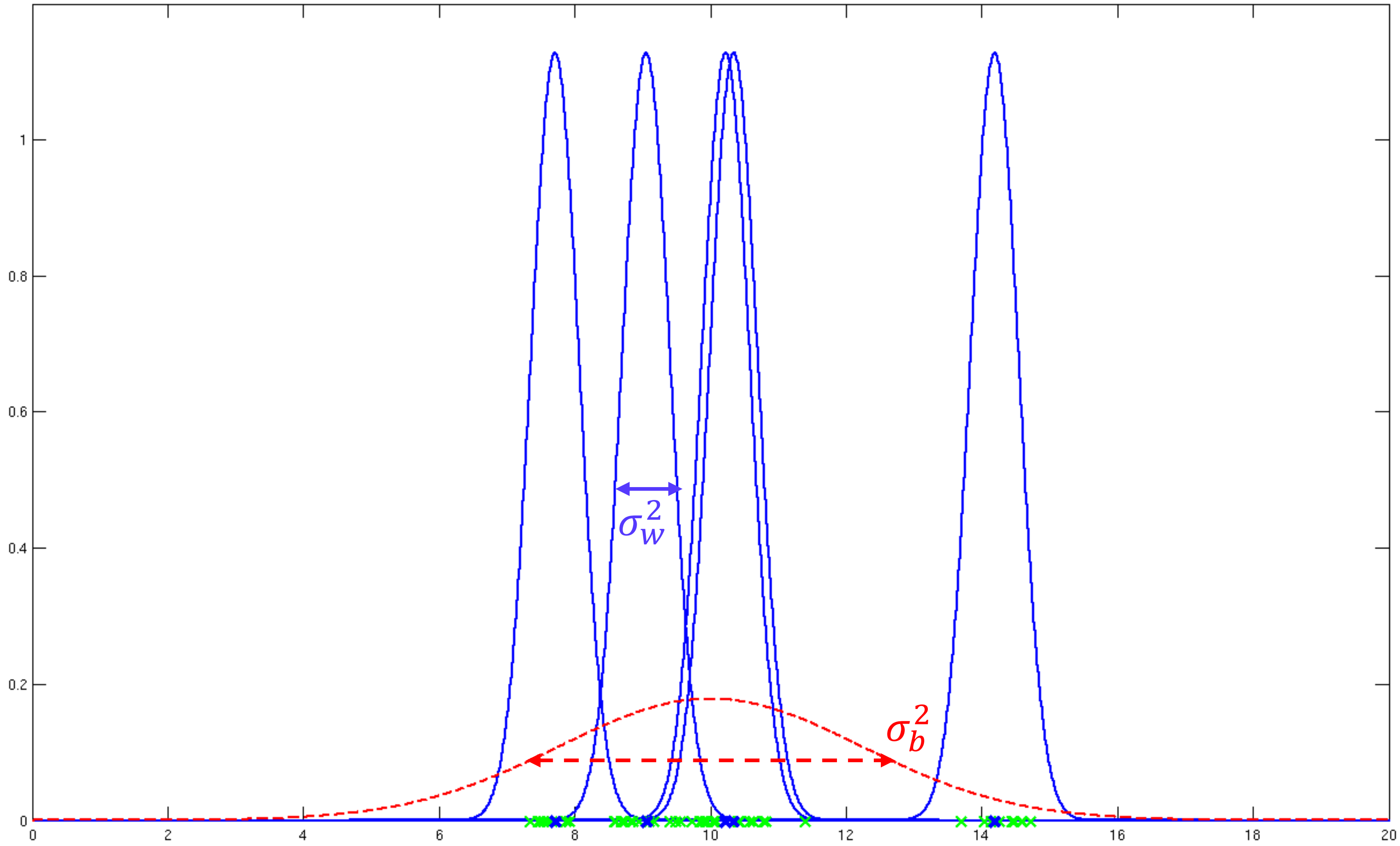
- N subjects = 12

c = [4, 3, 2, 1, 1, 2, 3, 3, 3, 2, 4, 4]

- Mean group effect = 2.67
- Mean s_b (SD) = 1.07
- Standard Error Mean (SEM) = s_b /(sqrt(N))=0.31

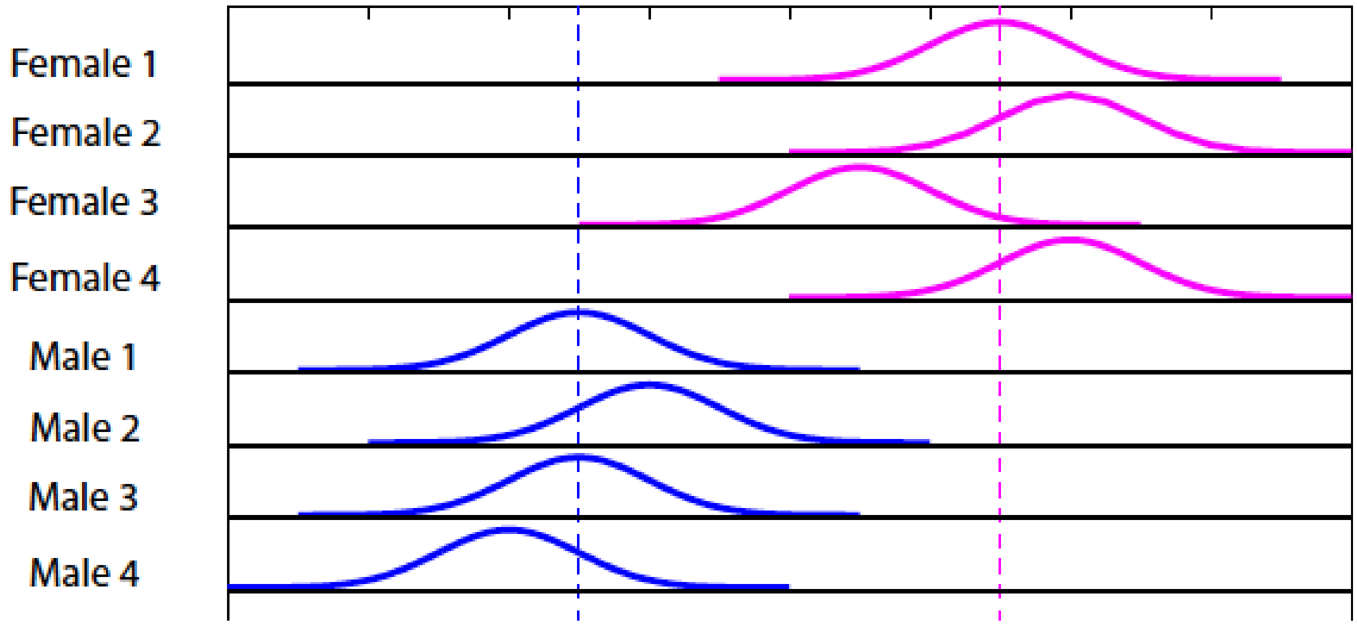
t=M/SEM = 8.61, $p=10^{-6}$

Random effects



Probability model underlying random effects analysis

Fixed vs random effects



Handbook of functional MRI data analysis. Poldrack, R. A., Mumford, J. A., & Nichols, T. E. Cambridge University Press, 2011

Fixed vs random effects

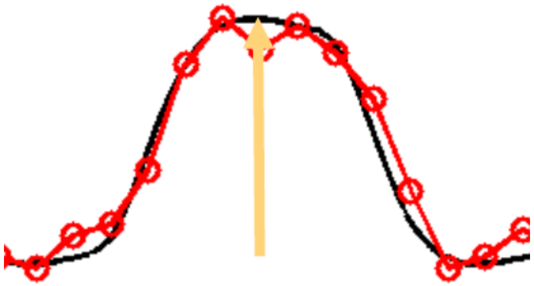
With **Fixed Effects Analysis (FFX)** we compare the group effect to the *within-subject variability*. It is not an inference about the population from which the subjects were drawn.

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

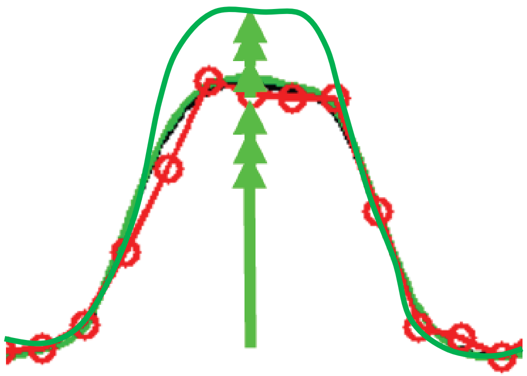
Fixed-effects

- Is not of interest across a population
- Used for a case study
- Only source of variation is measurement error (Response magnitude is **fixed**)



Random-effects

- If I have to take another sample from the population, I would get the same result
- Two sources of variation
  - Measurement error
  - Response magnitude is **random** (population mean magnitude is fixed)



Terminology

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)

Linear hierarchical models

Hierarchical Model

$$y = X^{(1)}\theta^{(1)} + \varepsilon^{(1)}$$

$$\theta^{(1)} = X^{(2)}\theta^{(2)} + \varepsilon^{(2)}$$

$$\vdots$$

$$\theta^{(n-1)} = X^{(n)}\theta^{(n)} + \varepsilon^{(n)}$$

Multiple variance components at each level

$$C_{\varepsilon}^{(i)} = \sum_k \lambda_k^{(i)} Q_k^{(i)}$$

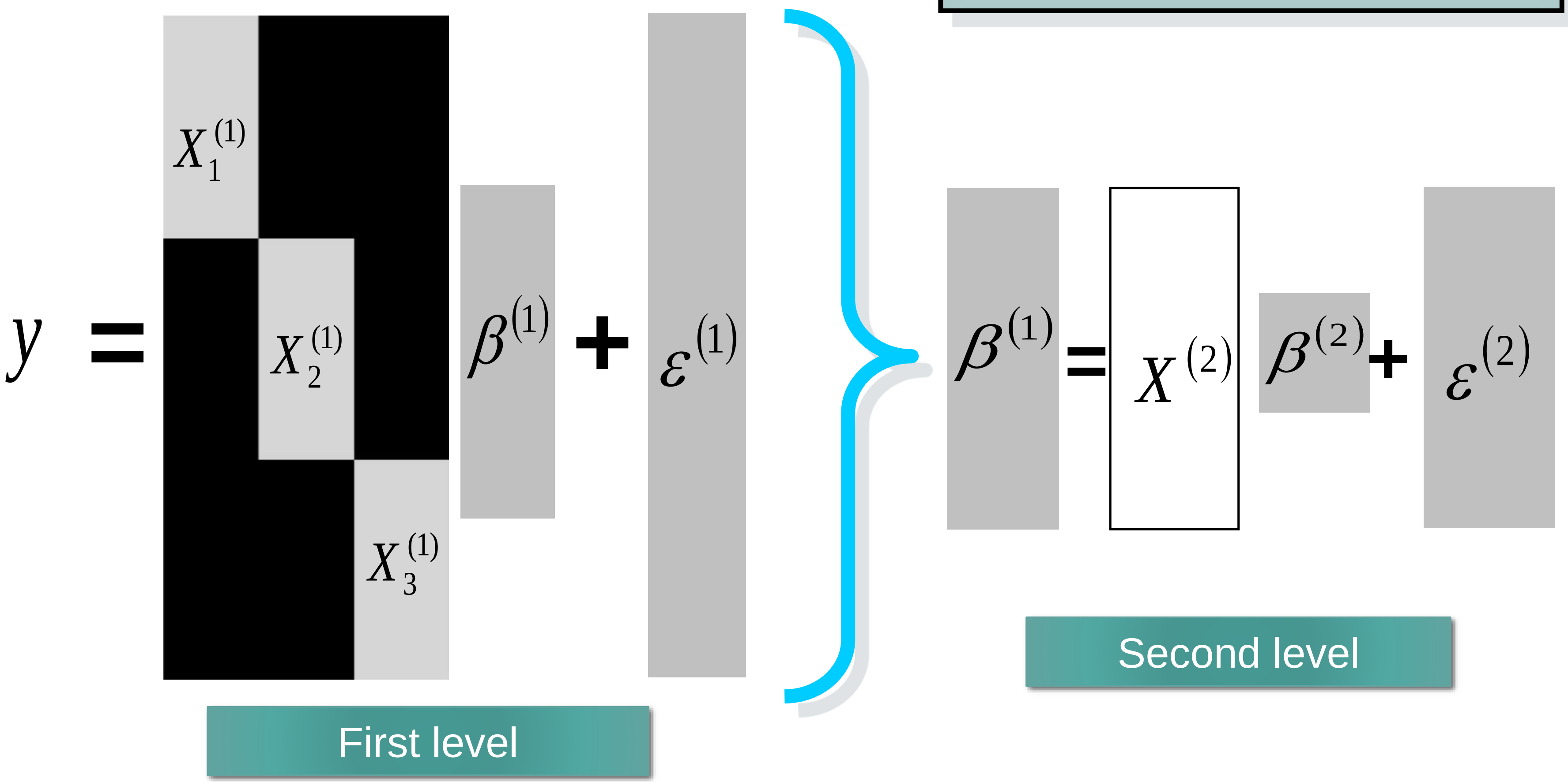
At each level, distribution of parameters is given by level above.

What we don't know: distribution of parameters and variance parameters (hyperparameters).

Hierarchical models

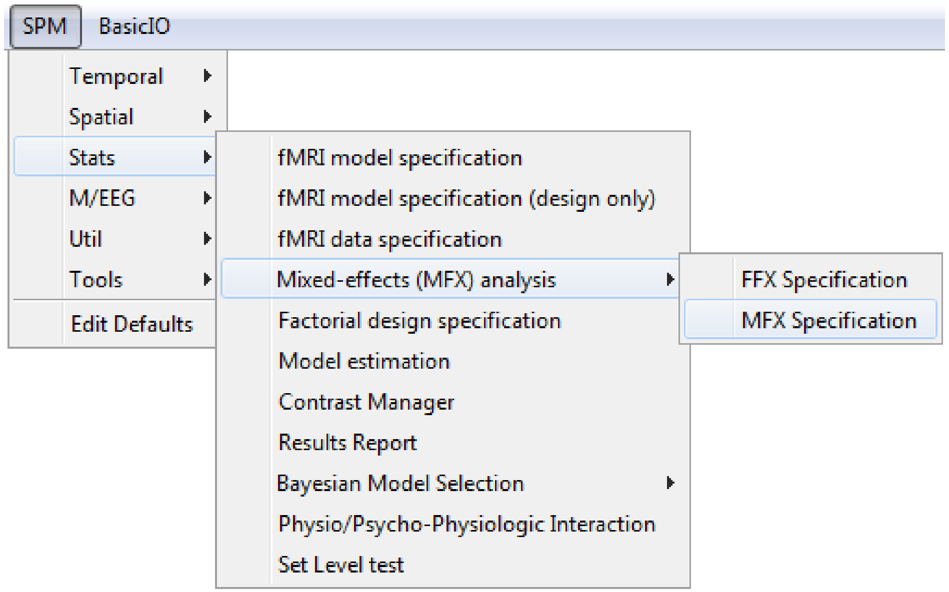
Example: Two level model

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



Hierarchical models

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



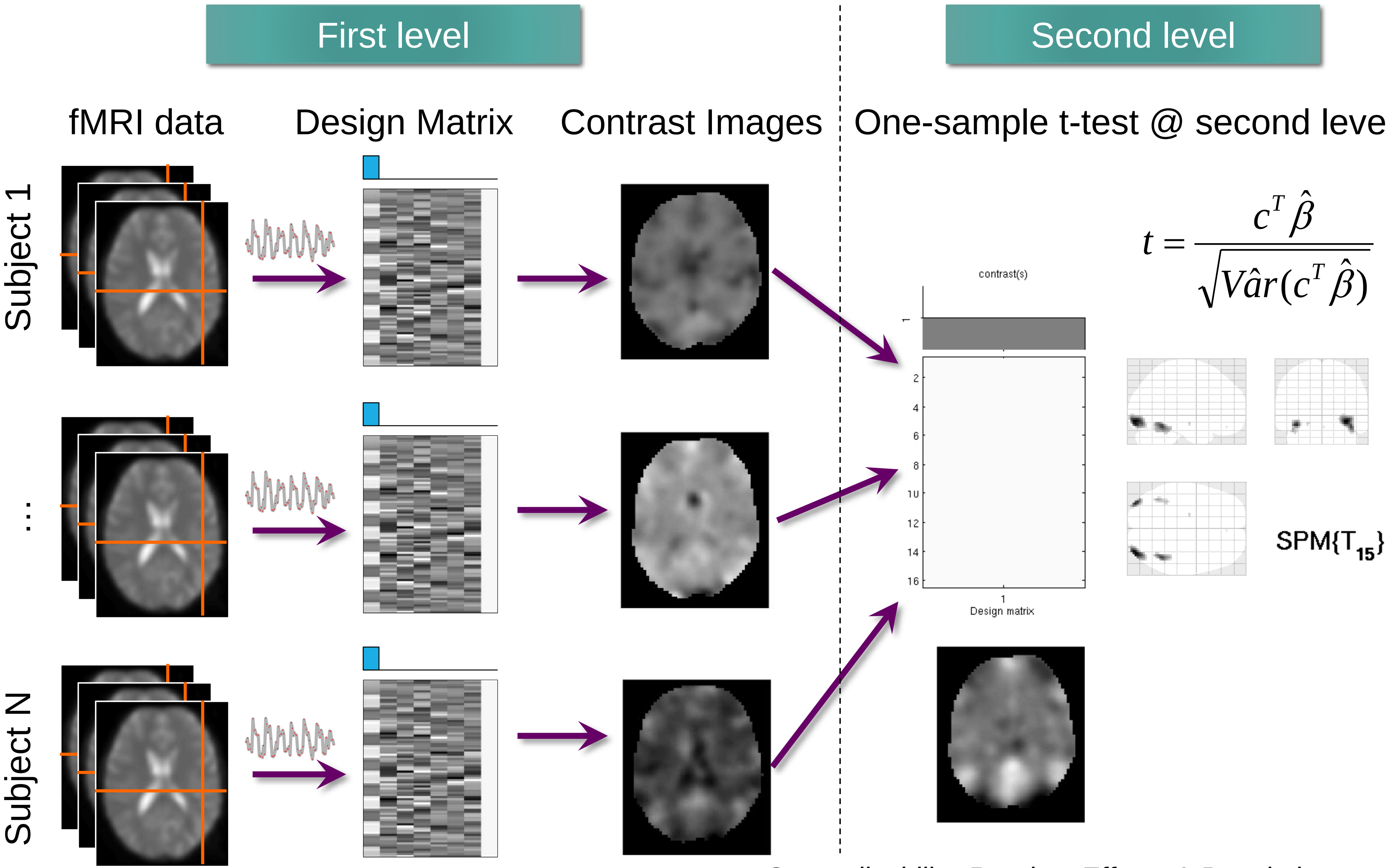
`spm_mfx.m`

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

Practical problems

- Full MFX inference using REML or EM for a whole-brain 2-level model has enormous computational costs
  - for many subjects and scans, covariance matrices become extremely large
  - nonlinear optimisation problem for each voxel
- Moreover, sometimes we are only interested in one specific effect and do not want to model all the data.
- Is there a fast approximation?

Summary Statistics RFX Approach



$$t = \frac{c^T \hat{\beta}}{\sqrt{\hat{Var}(c^T \hat{\beta})}}$$

Generalisability, Random Effects & Population Inference. Holmes & Friston, NeuroImage,1998.

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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)
- However, summary statistics approach is robust against typical violations

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

Statistical Parametric Mapping: The Analysis of Functional Brain Images. Elsevier, 2007.

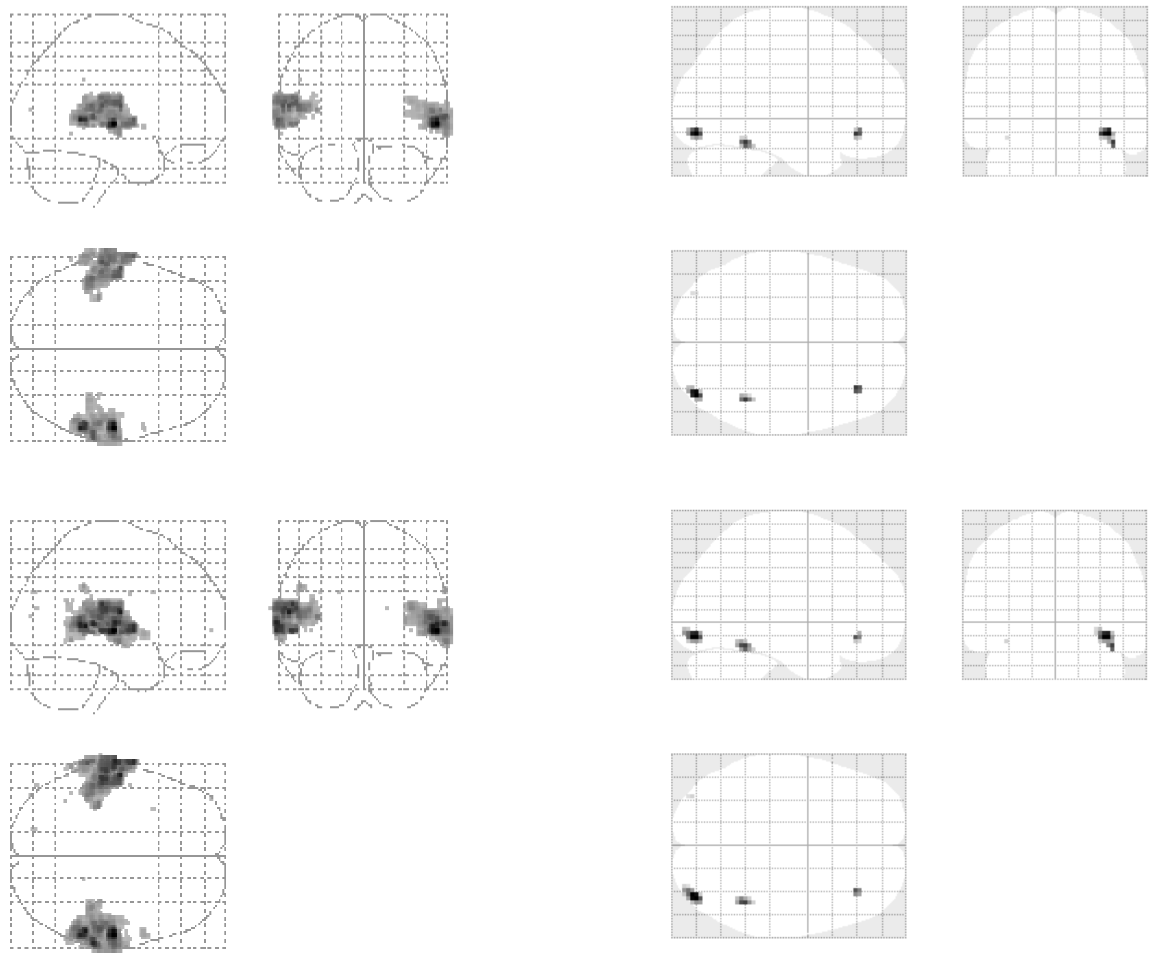
Simple group fMRI modeling and inference. Mumford & Nichols. NeuroImage, 2009.

Robustness

Summary statistics

SPM uses this!

Hierarchical Model



Listening to words

Viewing faces

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

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

Reminder: sphericity

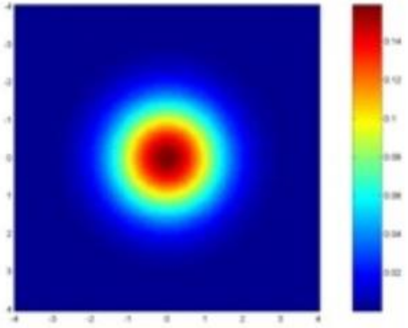
$$y = X\theta + \varepsilon$$

$$C_\varepsilon = Cov(\varepsilon) = E(\varepsilon\varepsilon^T)$$

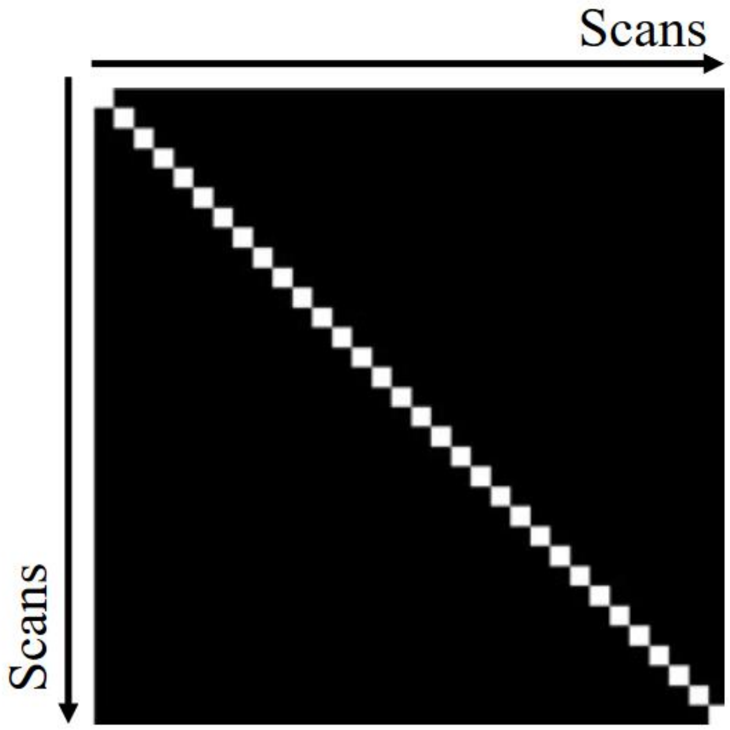
„sphericity“ means:

$$Cov(\varepsilon) = \sigma^2 I$$

i.e. $Var(\varepsilon_i) = \sigma^2$

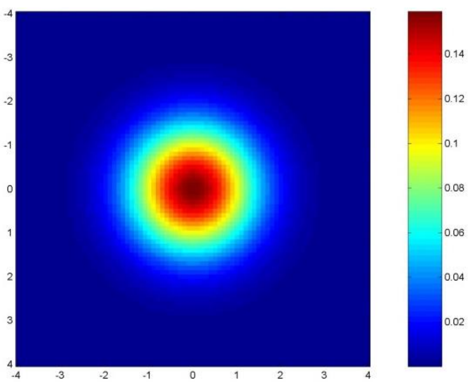


$$Cov(e) = \begin{bmatrix} 1 & 0 \\ 0 & 1 \end{bmatrix}$$



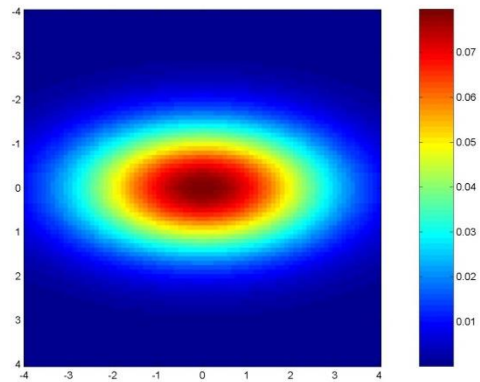
GLM assumes Gaussian "spherical" (i.i.d.) errors

sphericity = iid:
error covariance is scalar multiple of identity matrix:
Cov(e) = σ^2I



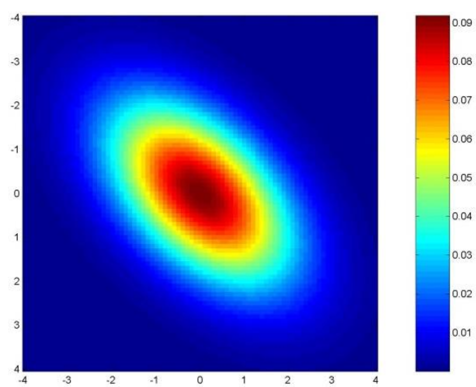
$$Cov(e) = \begin{bmatrix} 1 & 0 \\ 0 & 1 \end{bmatrix}$$

Examples for non-sphericity:



$$Cov(e) = \begin{bmatrix} 4 & 0 \\ 0 & 1 \end{bmatrix}$$

non-identically distributed



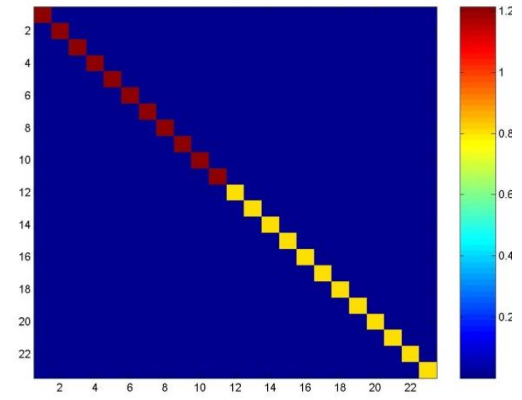
$$Cov(e) = \begin{bmatrix} 2 & 1 \\ 1 & 2 \end{bmatrix}$$

non-independent

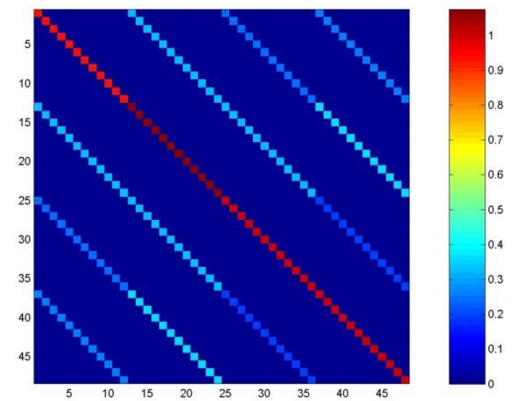
2nd level: Non-sphericity

Error covariance matrix

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.))



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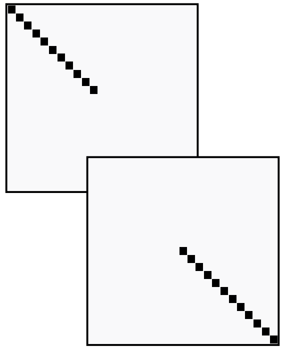
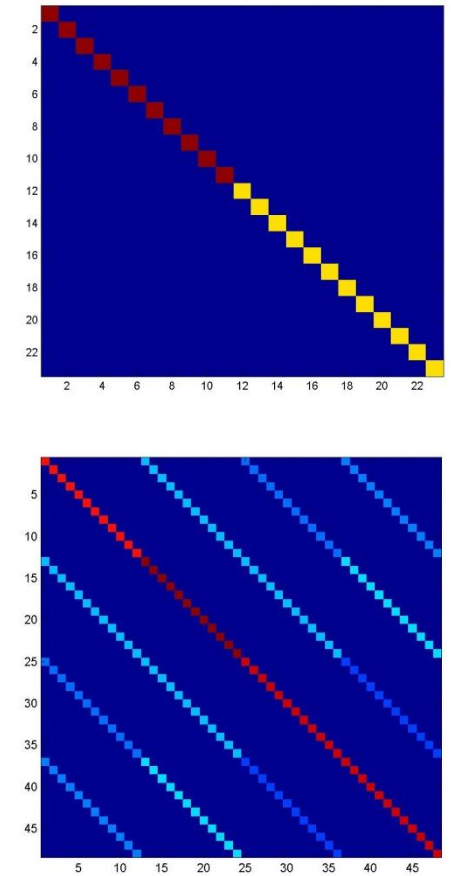
2nd level: Variance components

$$\mathrm{Cov}(\varepsilon) = \sum_k \lambda_k Q_k$$

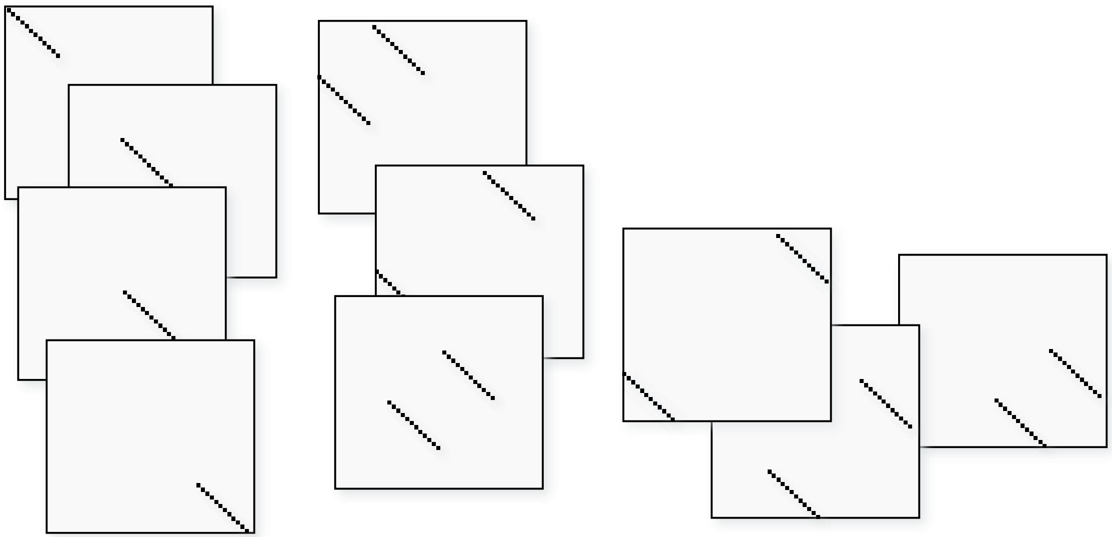
Q_k's:



Error covariance matrix



Q_k's:



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

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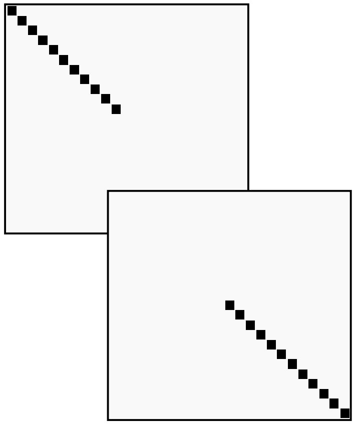
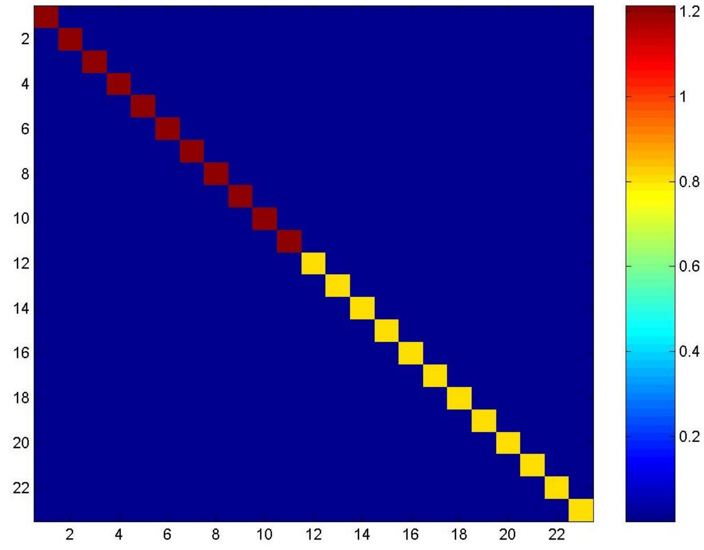
Data from Noppeney et al.

Example 1: Covariance components

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

Q_k's:



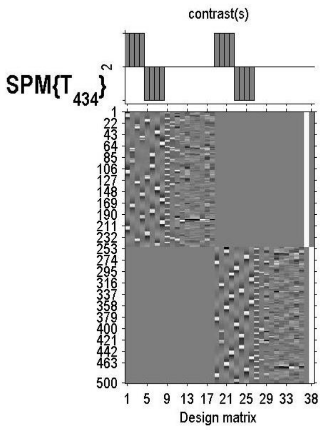


Error covariance matrix

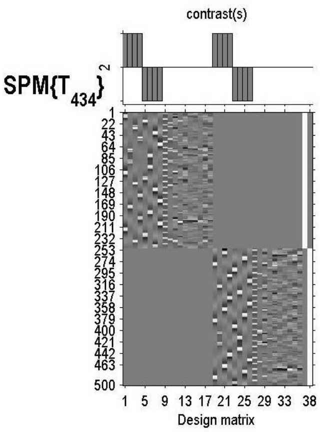
Example 1: Group differences

First Level

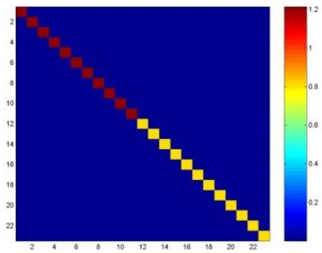
controls



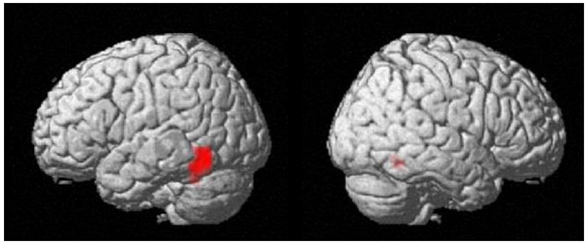
blinds

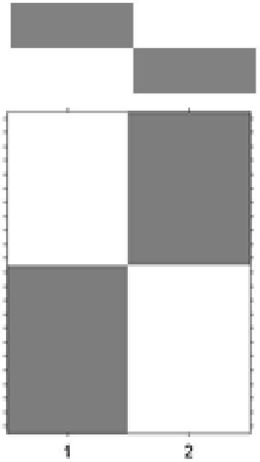


Second Level



$Cov(\varepsilon)$





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

X

design matrix

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”

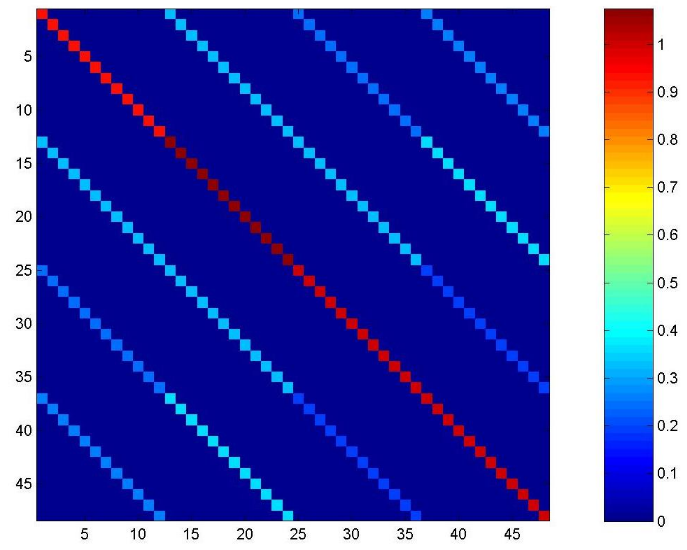
– Subjects:
  - 12 controls

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

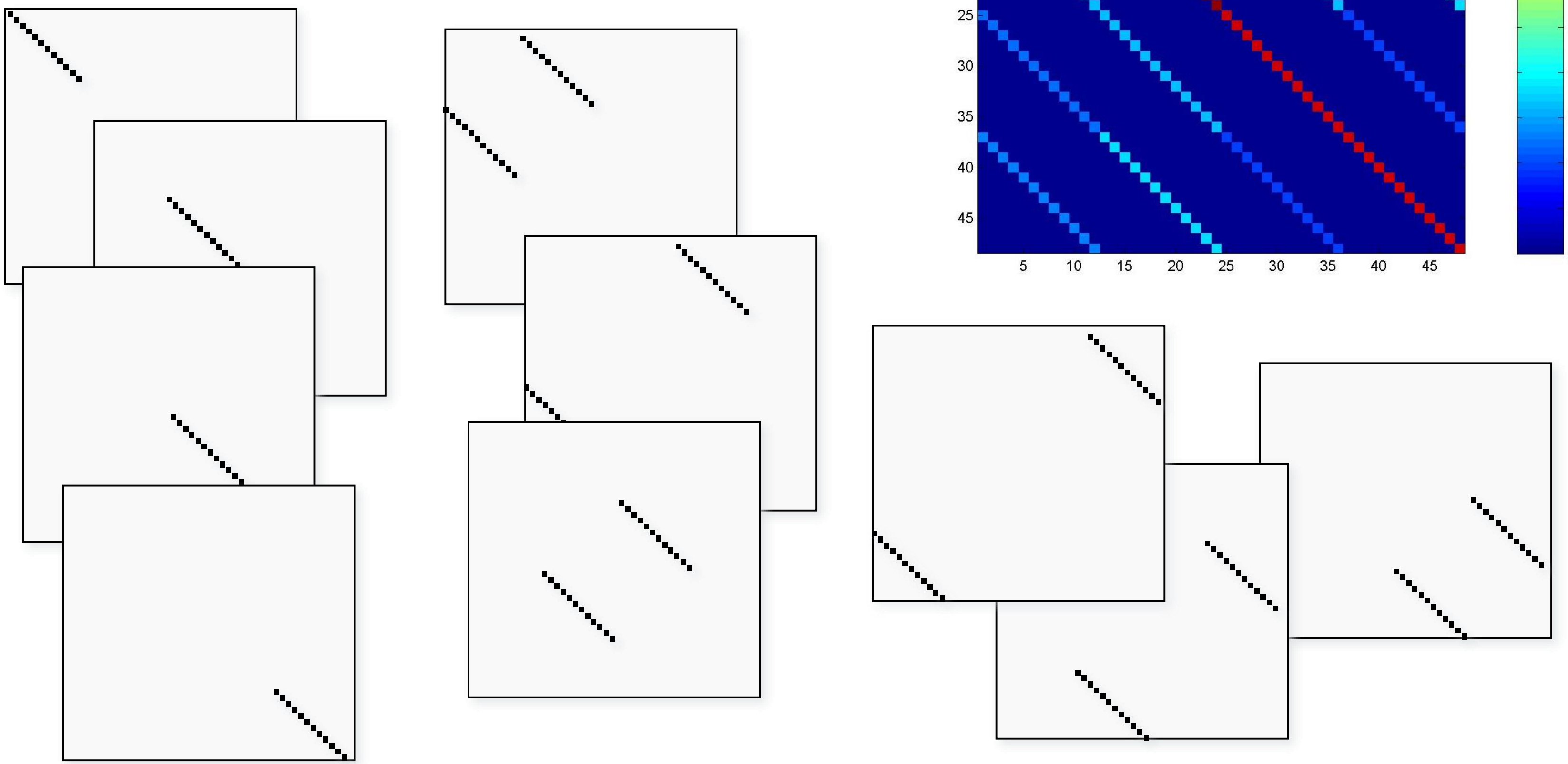
Noppeney et al., Brain, 2003.

Example 2: Covariance components

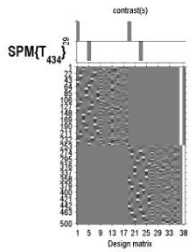
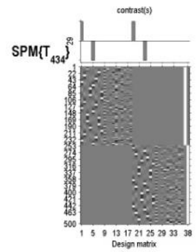
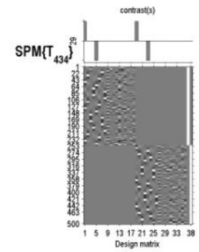
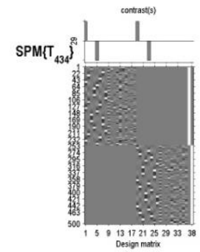
- → Errors are not independent and not identical



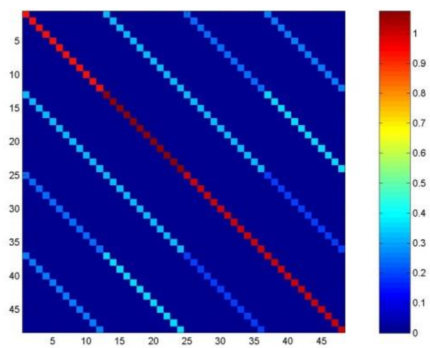
Q_k's:



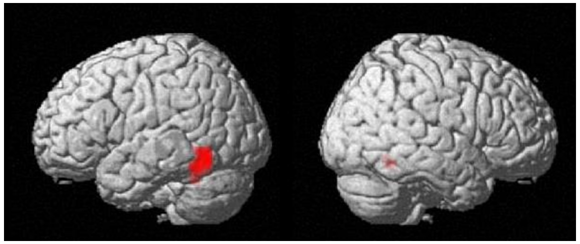
Example 2: Repeated measures ANOVA

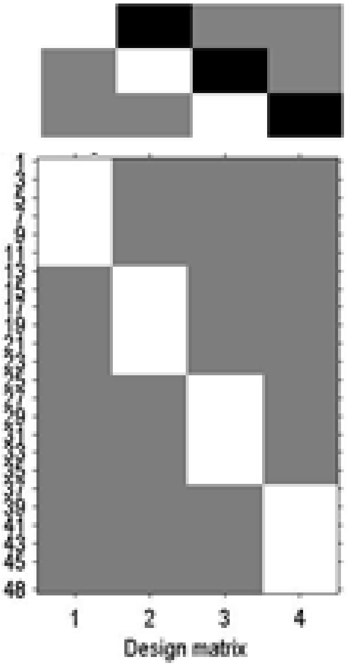
	Motion		Sound		Visual		Action
First Level		$\stackrel{?}{=}$		$\stackrel{?}{=}$		$\stackrel{?}{=}$	

Second Level



$$Cov(\varepsilon)$$

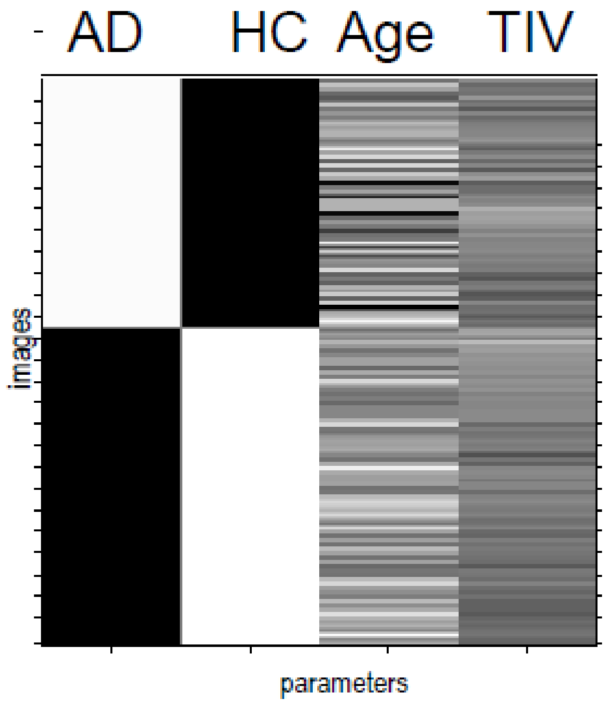


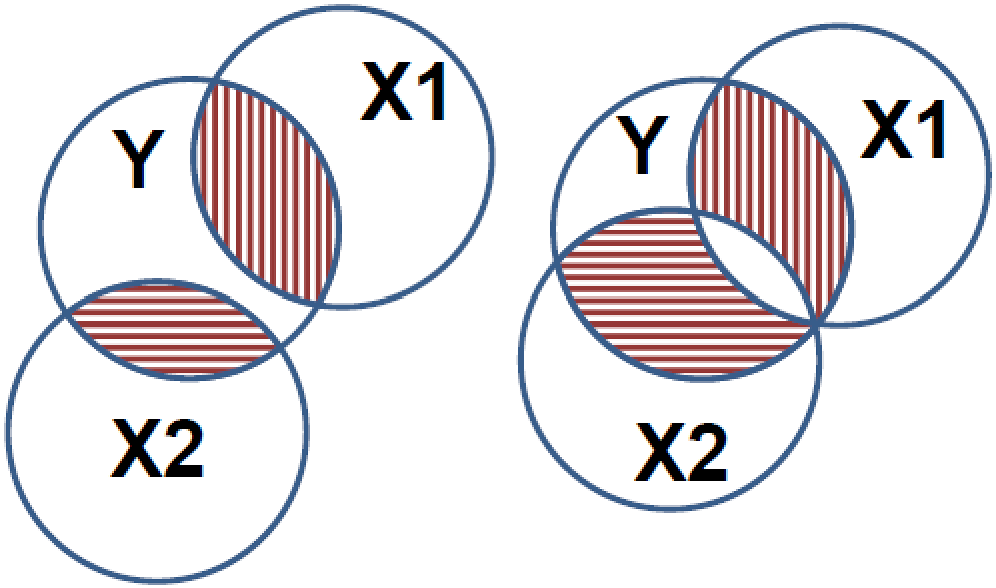


$$c^T = \begin{pmatrix} 1 & -1 & 0 & 0 \\ 0 & 1 & -1 & 0 \\ 0 & 0 & 1 & -1 \end{pmatrix}$$

$$X$$

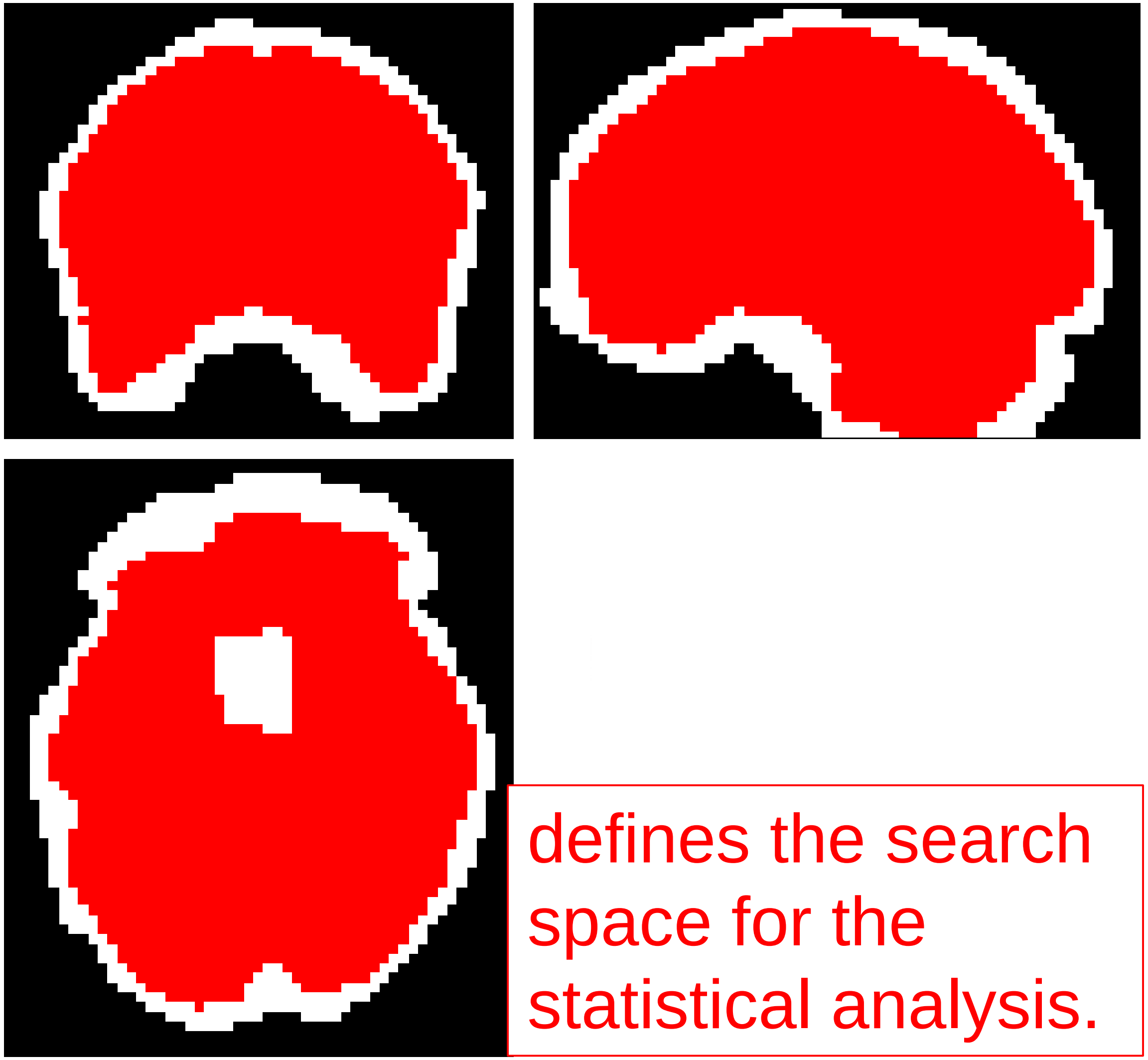
ANCOVA model





Mean centering continuous covariates for a group fMRI analysis, by J. Mumford:
http://mumford.fmripower.org/mean_centering/

Analysis mask: logical AND



defines the search space for the statistical analysis.

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.

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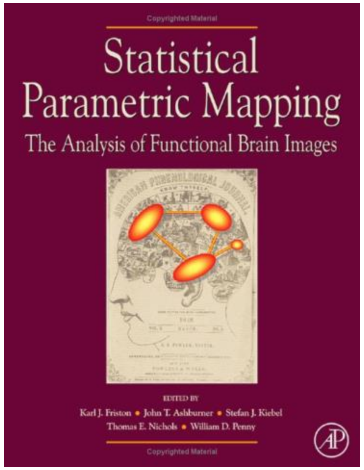

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