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CRC In vivo Imaging

SPM

fnrs
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Group Analyses

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Slides from G. Flandin, W. Penny, S. Kiebel, T. Nichols, R. Henson, J.-B. Poline, F. Kherif, T.Hauser

SPM Course
Woluwe, 28 November 2019

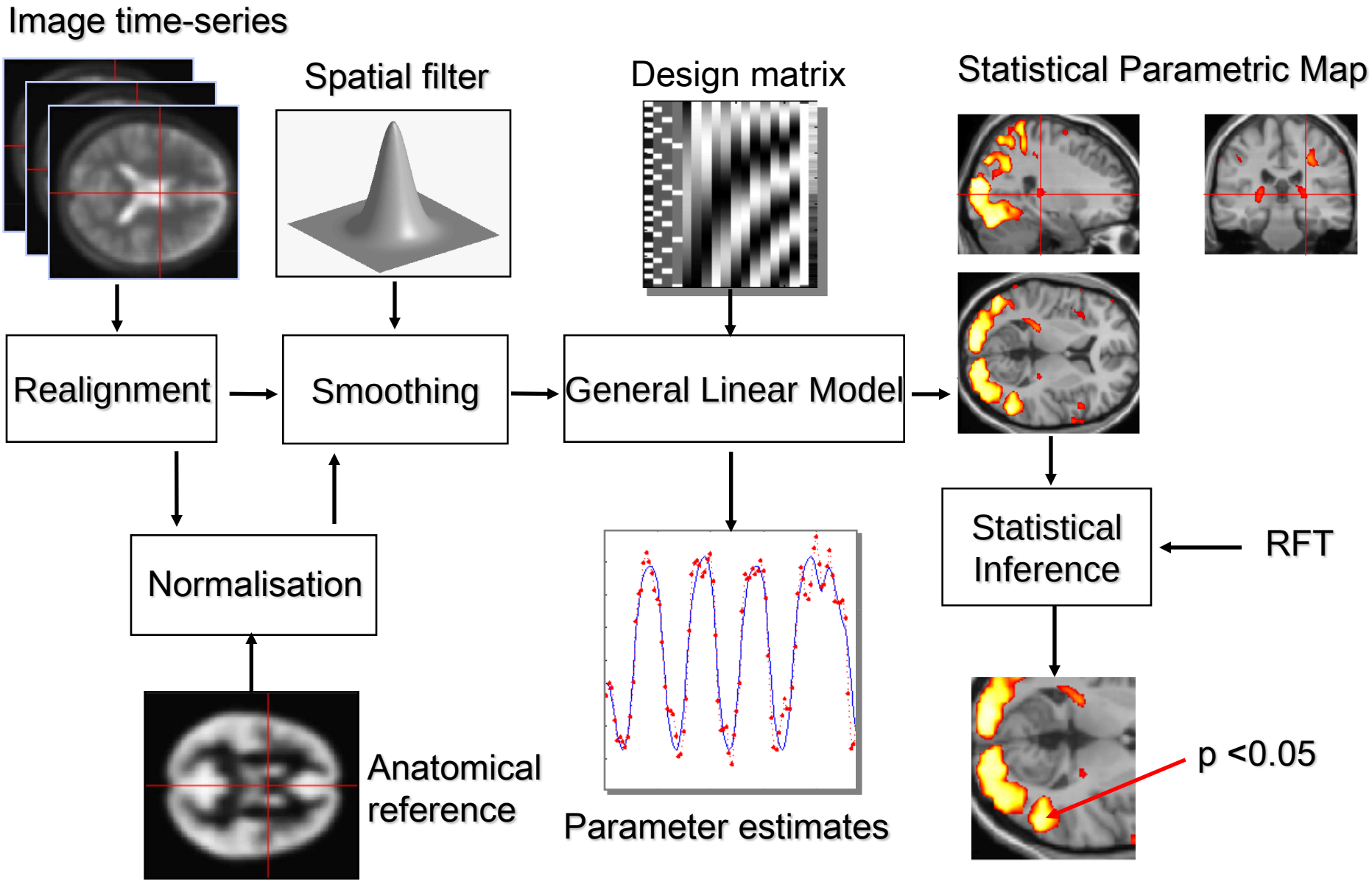
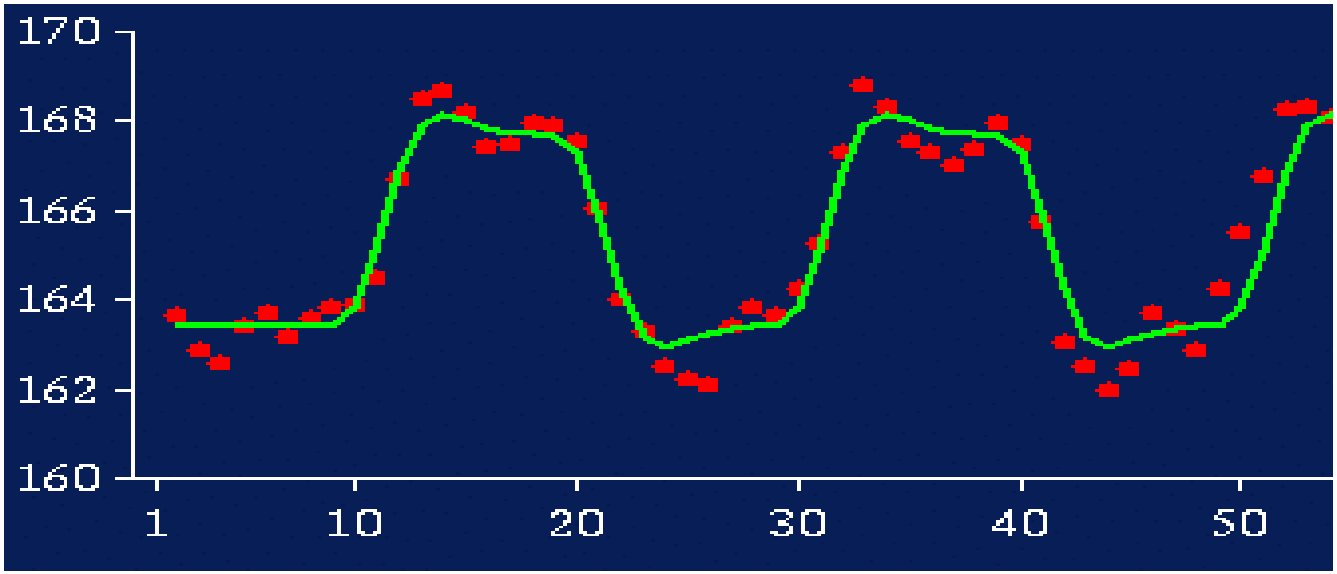


Image time-series
Spatial filter
Design matrix
Statistical Parametric Map
Realignment
Smoothing
General Linear Model
Normalisation
Statistical Inference
RFT
Anatomical reference
Parameter estimates
p <0.05

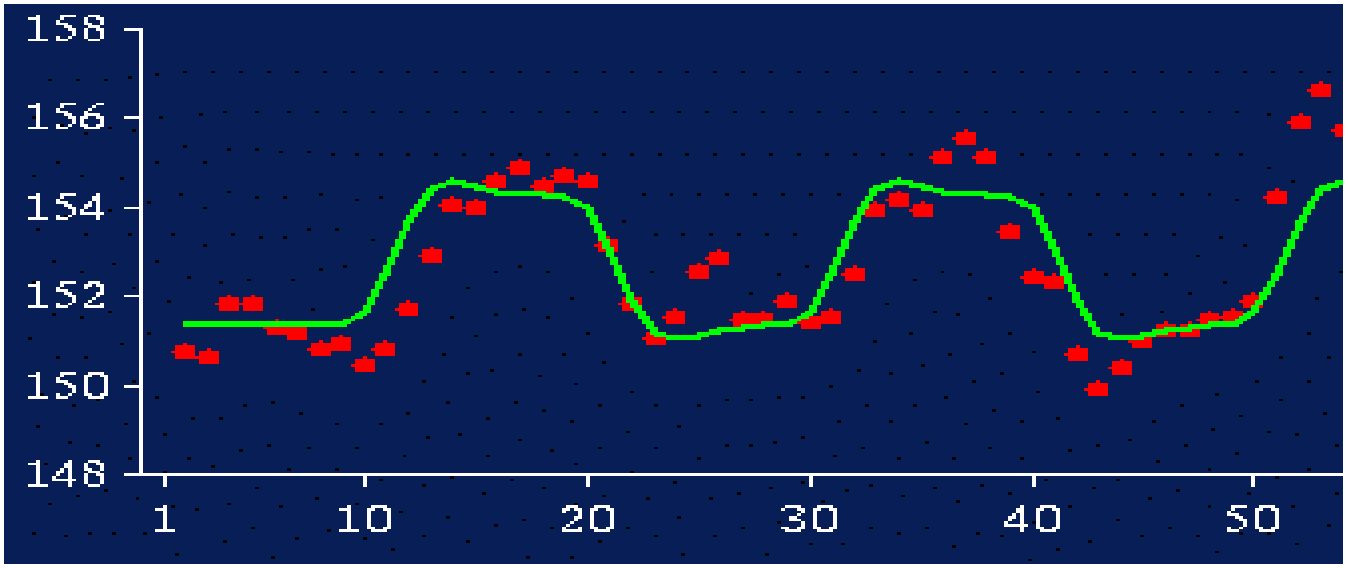
Subject 1



Effect size, c ~ 4

Within subject variability, s_w~0.9

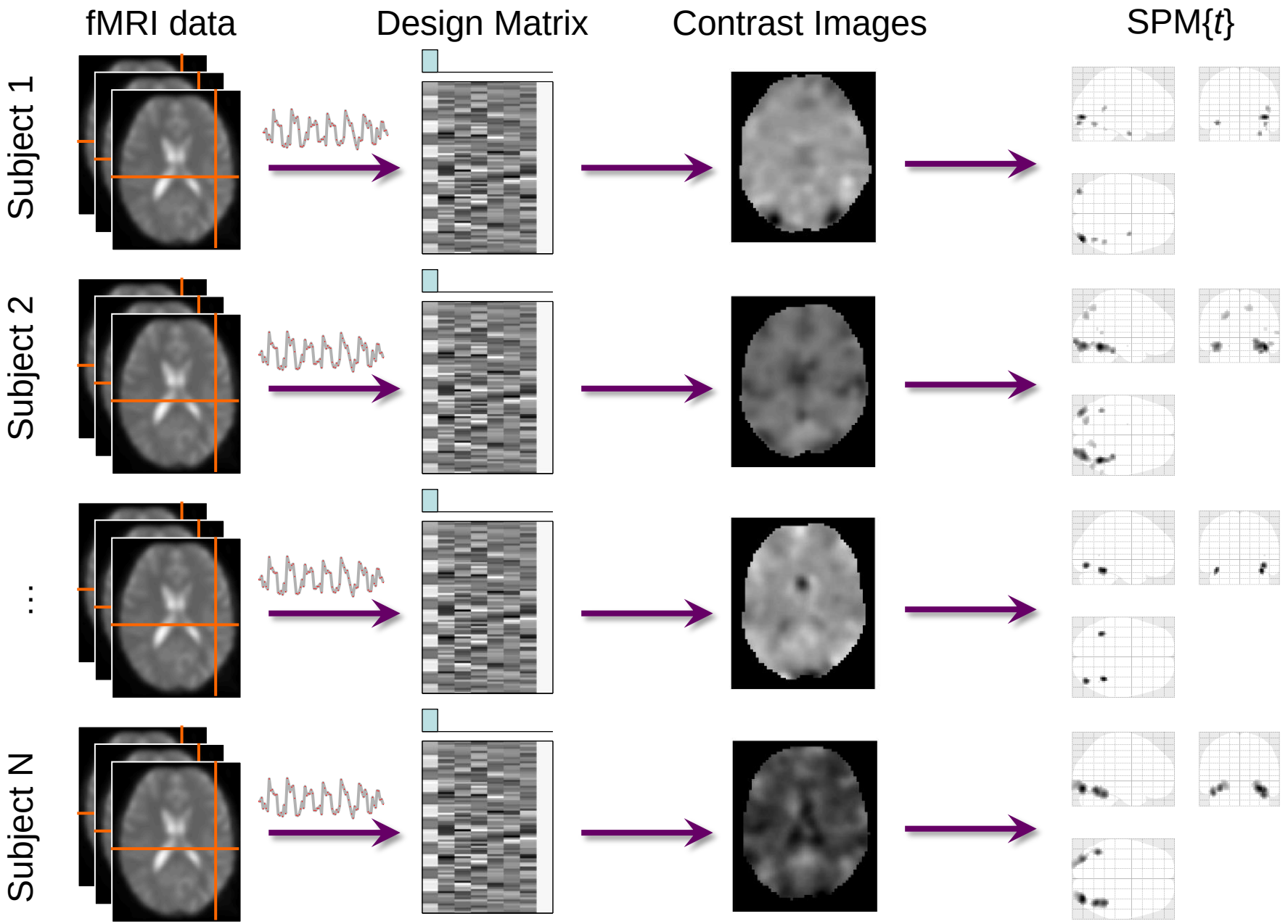
Subject N



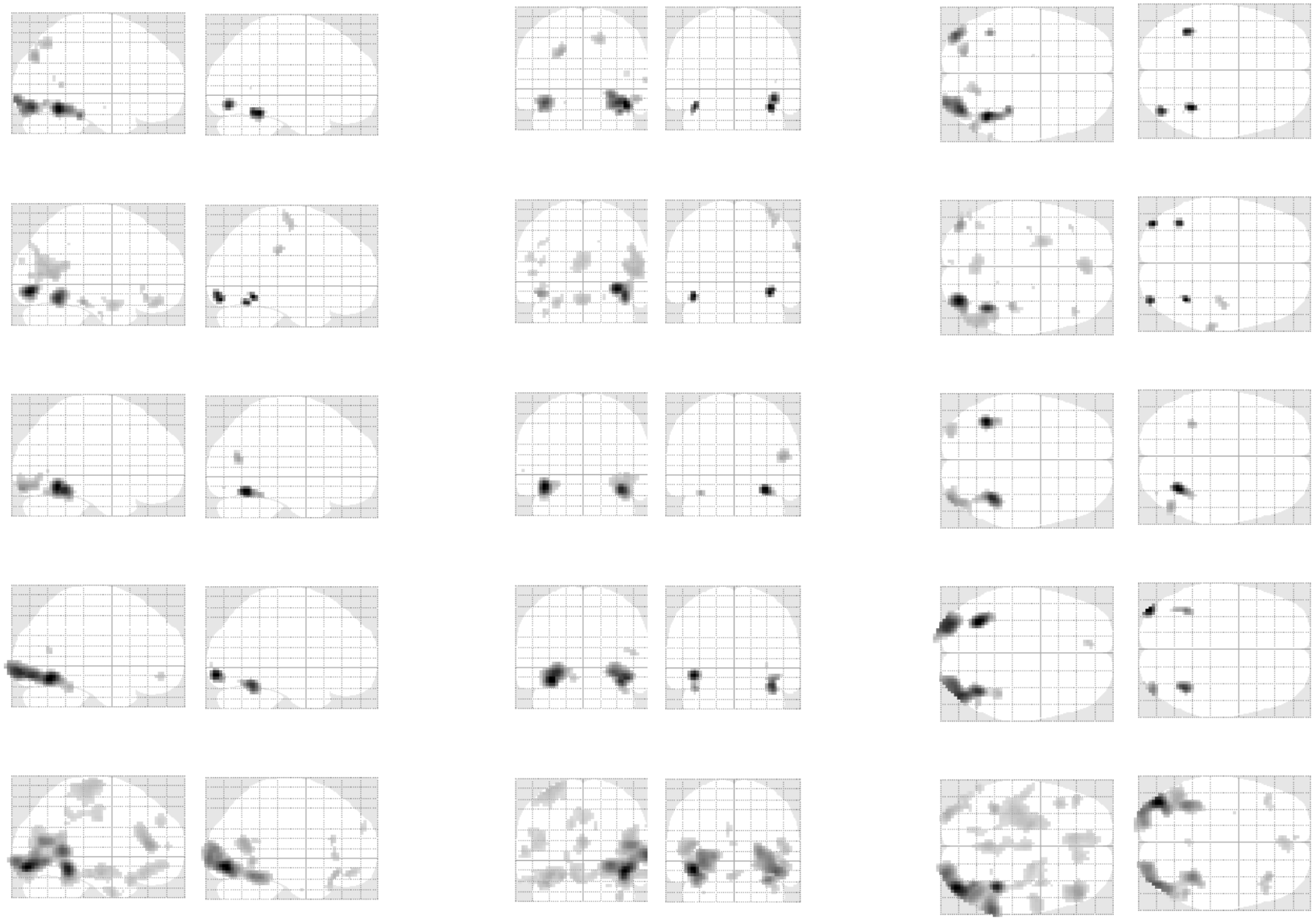
Effect size, c ~ 2

Within subject variability, s_w~1.5

GLM: repeat over subjects



First level analyses (p<0.05 FWE):

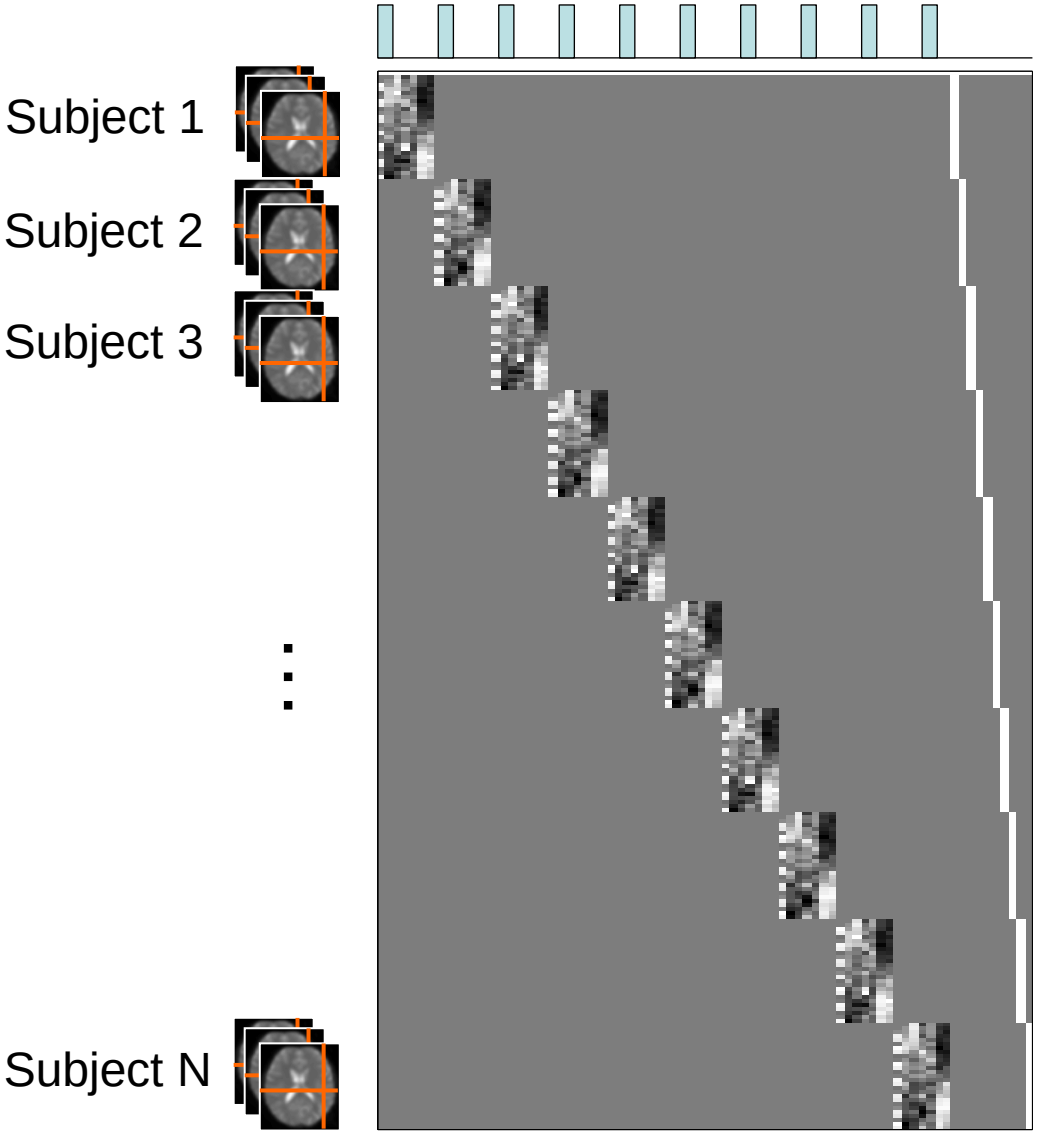


Data from R. Henson

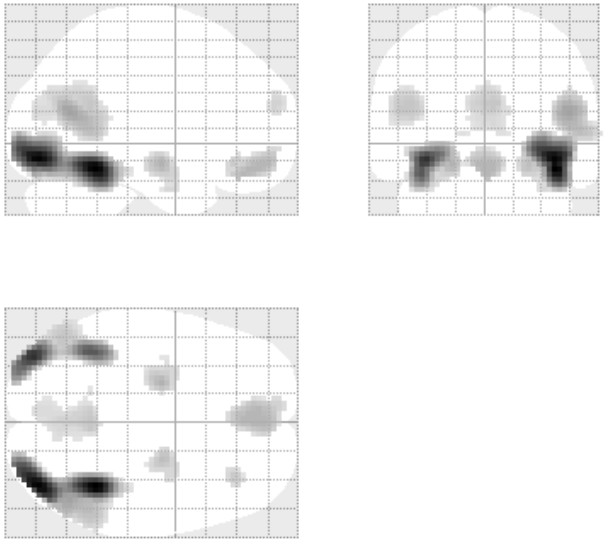
How to assess these different subjects?

- Fixed Effects Analysis (FFX)
- Random Effects Analysis (RFX)
  - Summary Statistics approach
  - Mixed Effects Analysis (MFX)

Fixed effects analysis (FFX)



Modelling all subjects at once



Fixed Effects Analysis (FFX)

Time series are effectively concatenated –
as though we had one subject with N=50x12=600 scans.

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 effect, $m=2.67$
Average within subject variability (std), $s_w = 1.04$

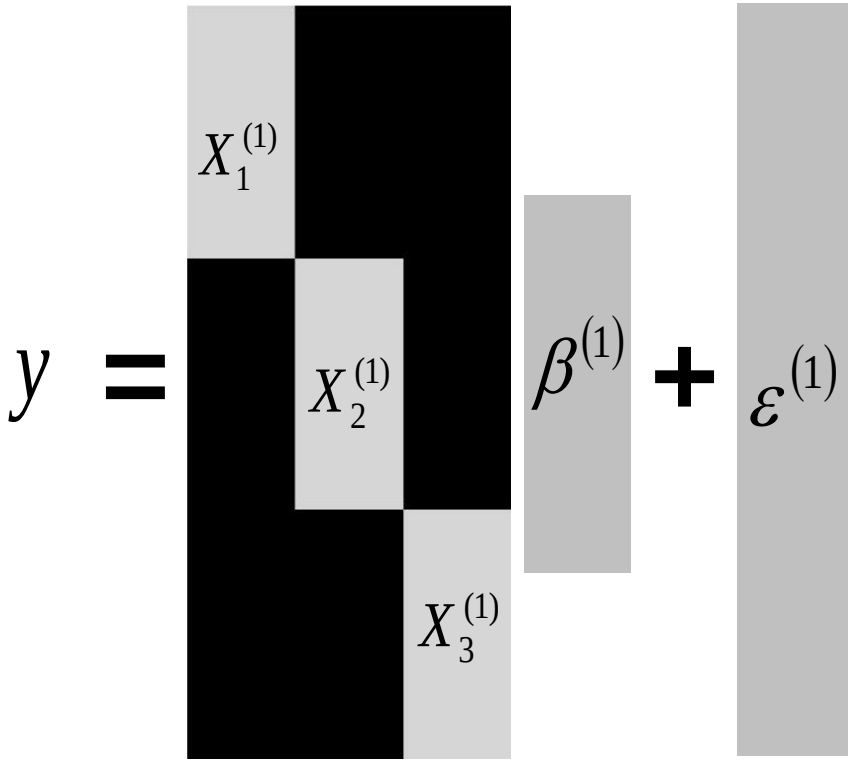
Standard Error Mean (SEM_W) = $s_w / sqrt(N) = 0.04$

Is effect significant at voxel v?

$t=m/SEM_W=62.7$ and $p=10^{-51}$

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

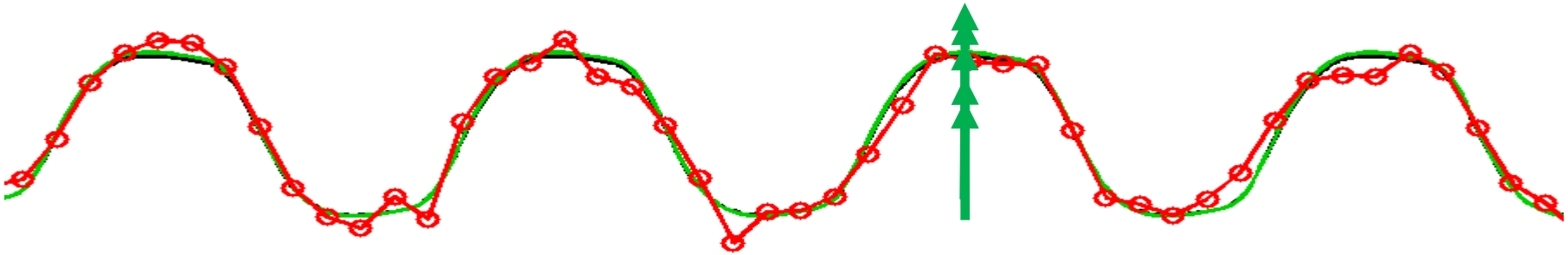
- True response magnitude is *fixed.*

➔ **How consistent is the response within this group of people, no inference about the population**

Random effects

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

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

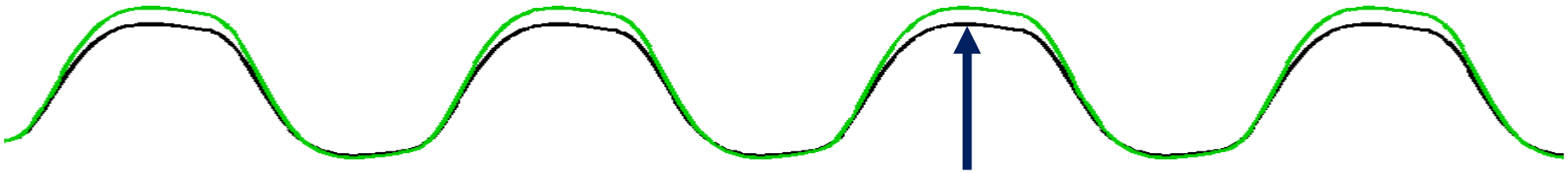


- Two sources of random variation:
  - measurement errors — Within-subject Variance
  - response magnitude (over subjects) — Between-subject Variance
- Response magnitude is *random*
  - each subject/session has random magnitude

Random effects

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

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



- Two sources of random variation:
  - measurement errors — Within-subject Variance
  - response magnitude (over subjects) — Between-subject Variance
- Response magnitude is *random*
  - each subject/session has random magnitude
  - but population mean magnitude is *fixed.*

Random Effects Analysis (RFX)

For group of N=12 subjects effect sizes are

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

Group effect (mean), $m=2.67$
Between subject variability (stand dev), $s_b = 1.07$
Standard Error Mean (SEM) = s_b /sqrt(N)=0.31

Is effect significant at voxel v?

$t=m/SEM=8.61$ and $p=10^{-6}$

Random Effects Analysis (RFX)

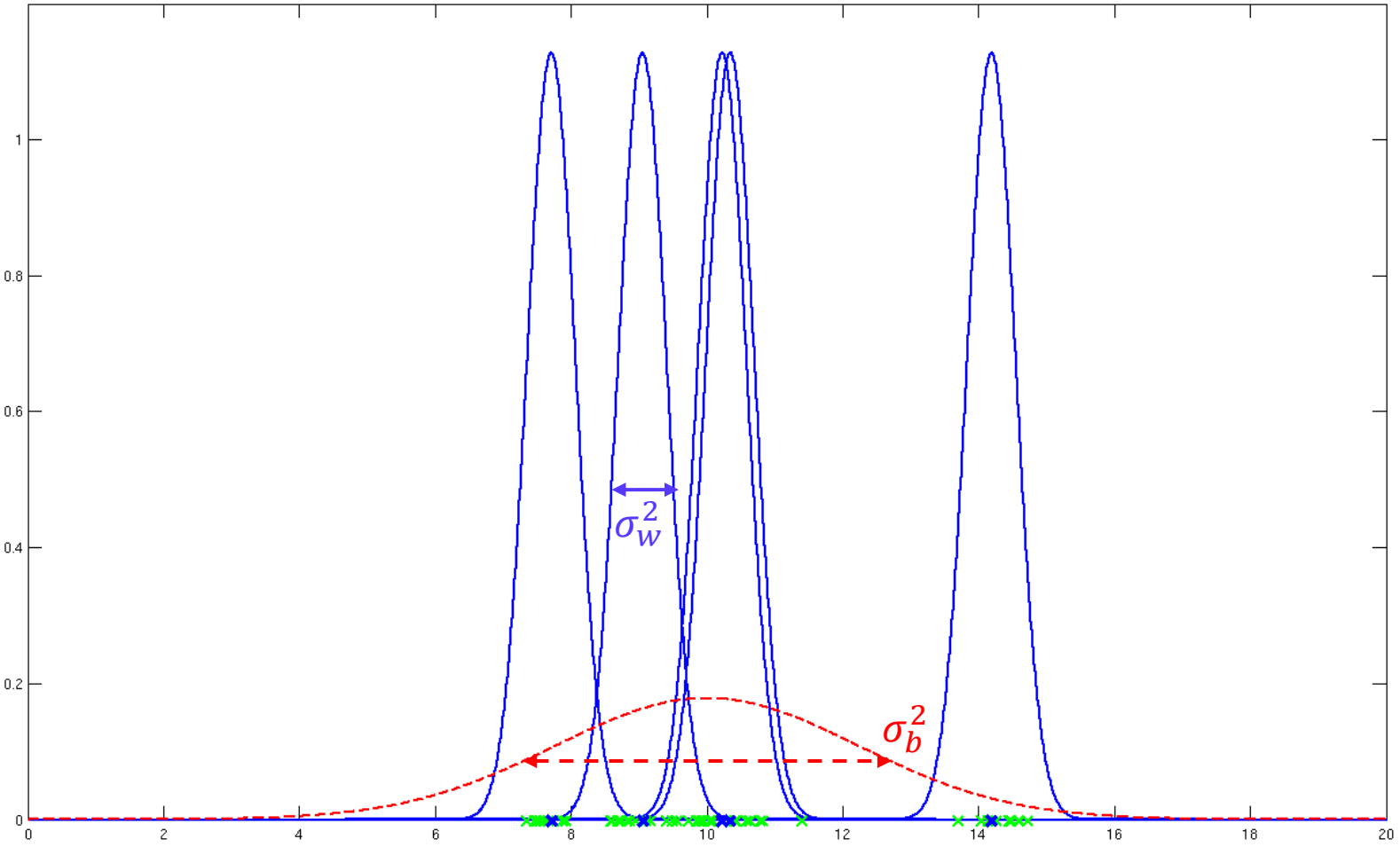
For group of N=12 subjects effect sizes are

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

Group effect (mean), $m=2.67$
Between subject variability (stand dev), $s_b = 1.07$

This is called a Random Effects Analysis because we are comparing the group effect to the between-subject variability.

Random effects



Probability model underlying random effects analysis

Fixed vs Random effects

Fixed Effects Analysis (FFX):

- compare the group effect to the *within-subject variability*.
- **no inference about the population** from which the subjects were drawn.

Random Effects Analysis (RFX):

- compare the group effect to the *between-subject variability*.
- **inference about the population** from which the subjects were drawn.
- a new subject from that population
  → confidence of observing the same 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"

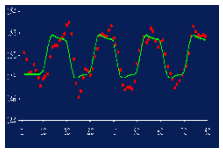
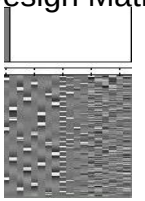
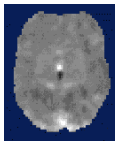
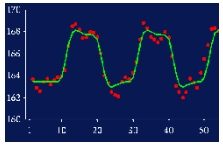
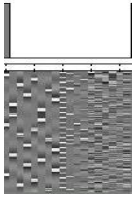
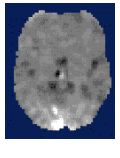
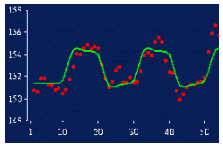
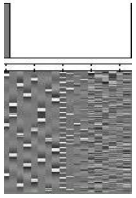
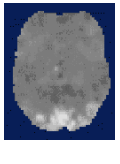
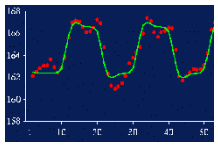
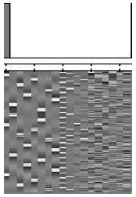
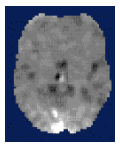
How to assess these different subjects?

- Fixed Effects Analysis (FFX)
- Random Effects Analysis (RFX)
  - **Summary Statistics approach**
  - Mixed Effects Analysis (MFX)

Summary Statistics Approach

First level

Data | Design Matrix | Contrast Images

Summary Statistics Approach

First level

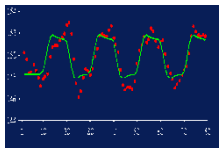
Second level

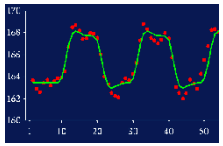
$$t = \frac{c^T \hat{\alpha}}{\sqrt{V\hat{a}r(c^T \hat{\alpha})}}$$

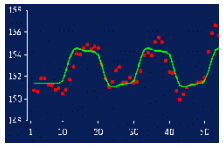
Data

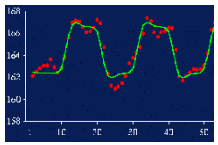
Design Matrix

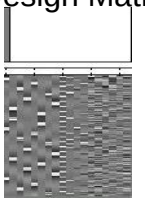
Contrast Images

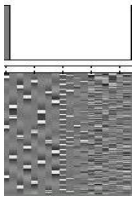


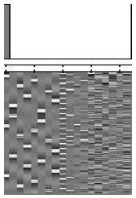


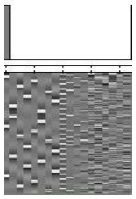


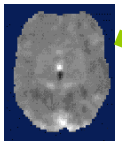


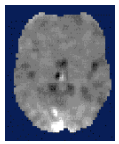


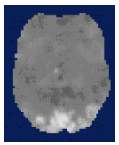


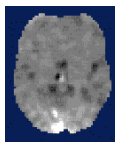


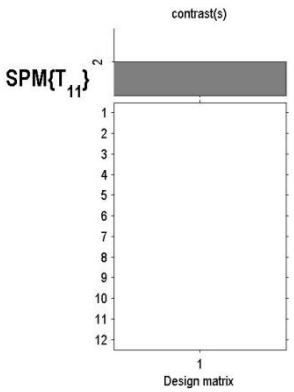


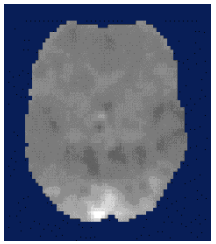




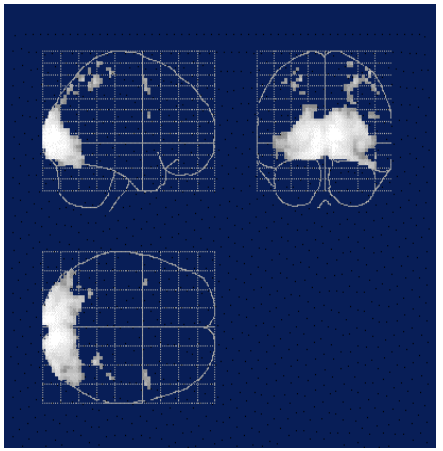






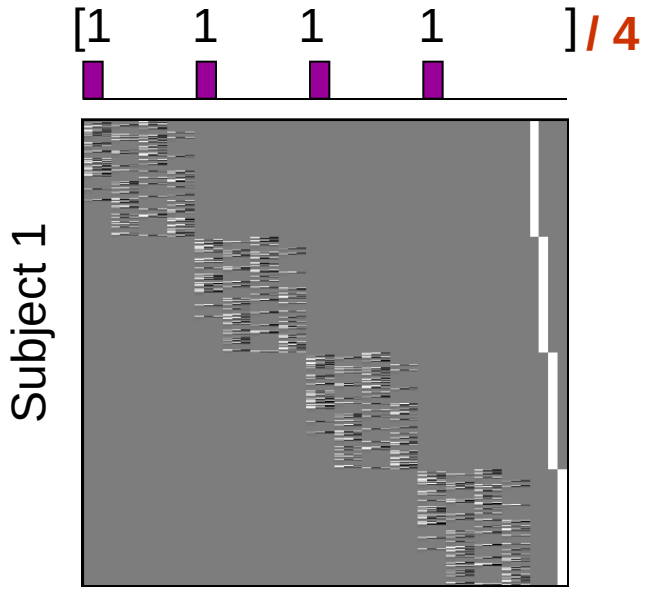


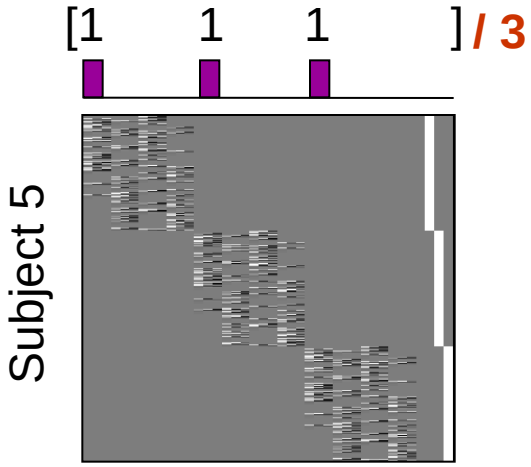
SPM(t)



One-sample
t-test @ 2nd level

Scaling issue





$$T = \frac{c^T \hat{\beta}}{\sqrt{\mathrm{var}(c^T \hat{\beta})}} = \frac{c^T \hat{\beta}}{\sqrt{\hat{\sigma}^2 c^T (X^T X)^{-1} c}}$$

- The *T*-statistic does not depend on the scaling of the regressors.
- The *T*-statistic does not depend on the scaling of the contrast.
- Contrast $c^T \hat{\beta}$ depends on scaling.

➢ Be careful of the interpretation of the contrasts $c^T \hat{\beta}$ themselves (eg, for a second level analysis):

sum ≠ average

Assumptions for SS-RFX approach

- 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.

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

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

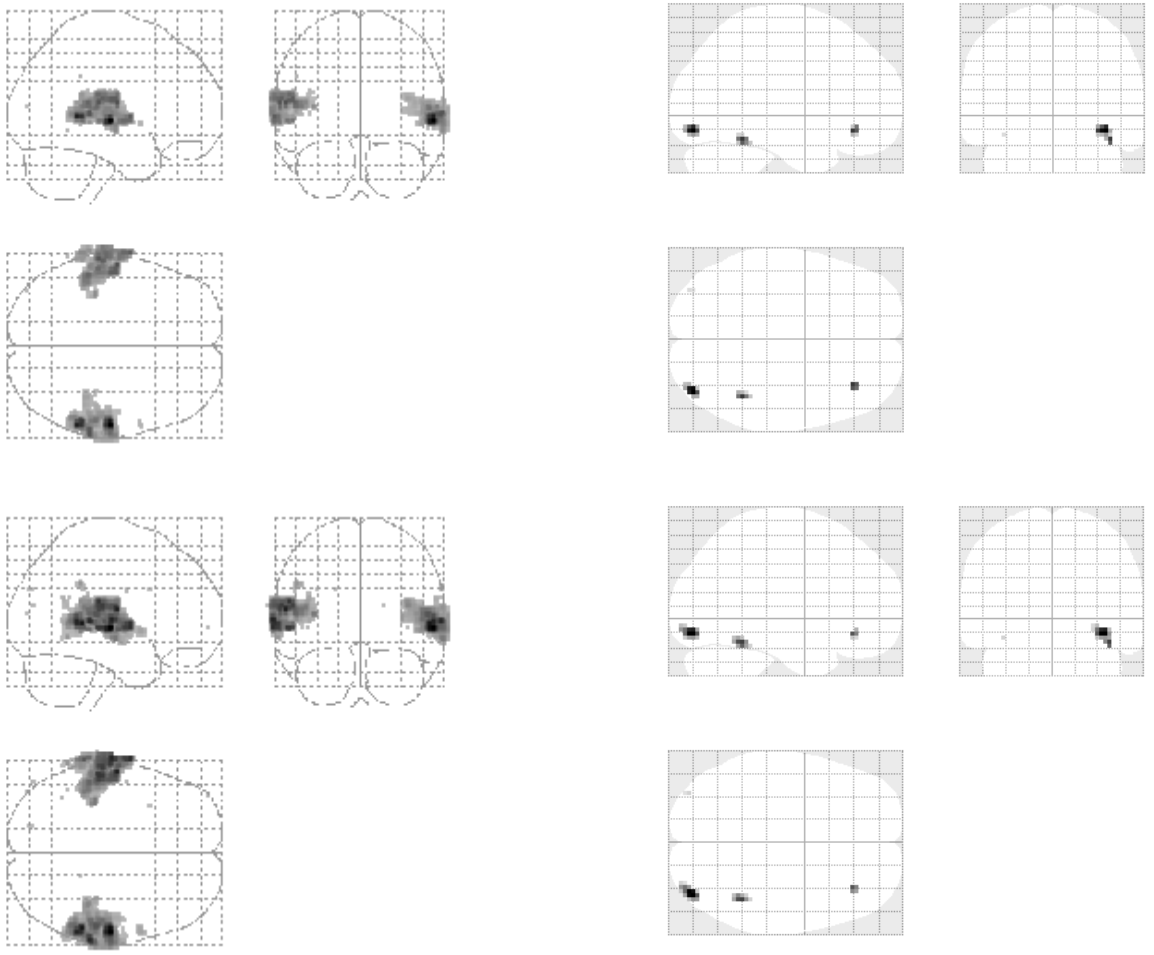
Simple group fMRI modeling and inference. Mumford & Nichols. NeuroImage, 2009.

Summary Statistics RFX Approach

Robustness

Summary statistics

Hierarchical Model



Listening to words

Viewing faces

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

Terminology

Hierarchical linear models:

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

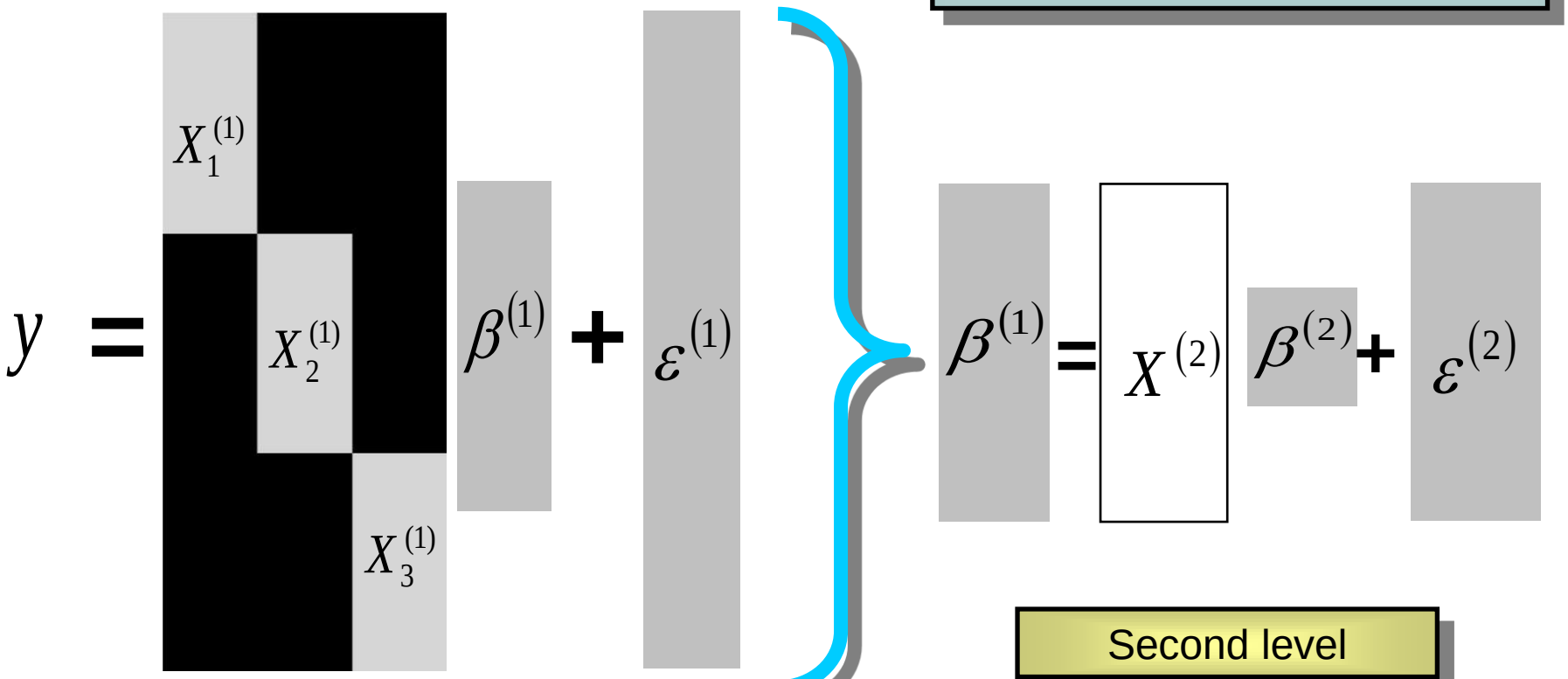
… all the same

… all alluding to multiple sources of variation (in contrast to fixed effects)

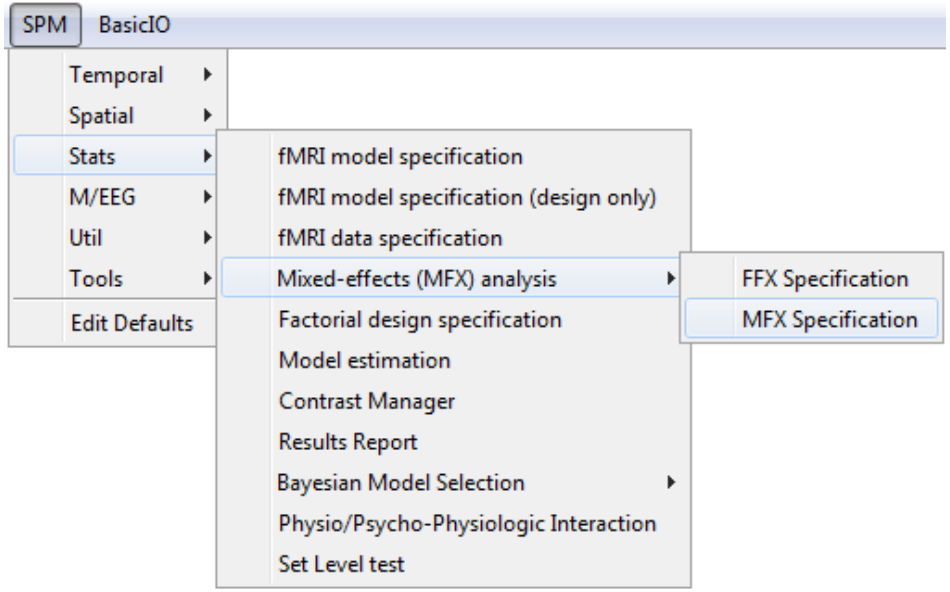
Hierarchical models

Example: Two level model

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



Hierarchical models



`spm_mfx.m`

But:

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

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

Do MFX models when…

- ...Summary statistics assumptions are violated
  - Largely different subject-level designs
  - Within-subject variances are different

(in practice:

- … you don’t trust your results
- … benefit from more precise variance estimates
- … you have a lot of computing power and time)

How to assess these different subjects?

- Fixed Effects Analysis (FFX)
- Random Effects Analysis (RFX)
  - Summary Statistics approach
  - Mixed Effects Analysis (MFX)
- Beyond one-sample t-tests
  - Paired t-tests
  - ANOVAs

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

ANOVA

Condition 1	Condition 2	Condition3
Sub1	Sub13	Sub25
Sub2	Sub14	Sub26
...	...	...
Sub12	Sub24	Sub36

ANOVA at second level (e.g. clinical populations).
If you have two conditions this is a two-sample t-test.

ANOVA within subject

Condition 1	Condition 2	Condition3
Sub1	Sub1	Sub1
Sub2	Sub2	Sub2
...	...	...
Sub12	Sub12	Sub12

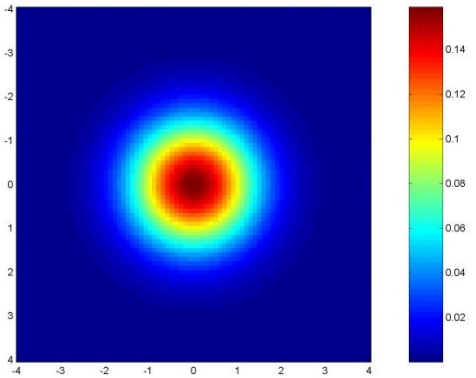
ANOVA within subjects at second level (e.g. same subjects on placebo, drug1, drug2). This is an ANOVA but with subject effects removed.
If you have two conditions this is a paired t-test.

SPM interface: factorial design specification

- Many 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

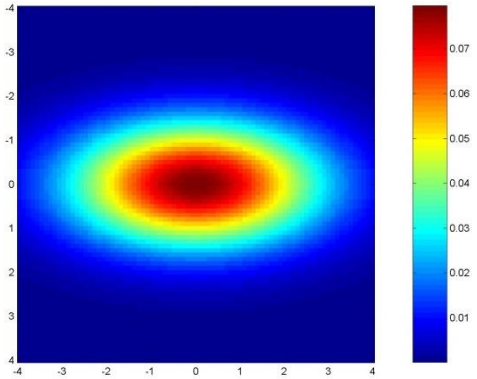
GLM assumes Gaussian "spherical" (i.i.d.) errors

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



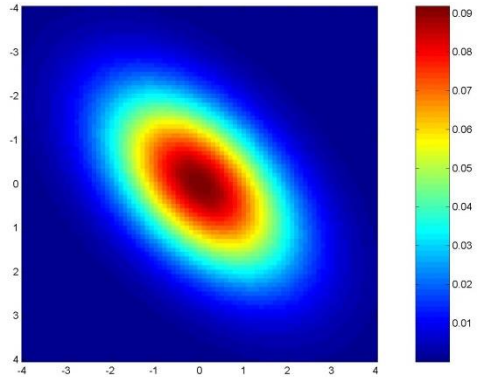
$$Cov(e) = \begin{bmatrix} 1 & 0 \\ 0 & 1 \end{bmatrix}$$

Examples for non-sphericity:



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

non-identically distributed

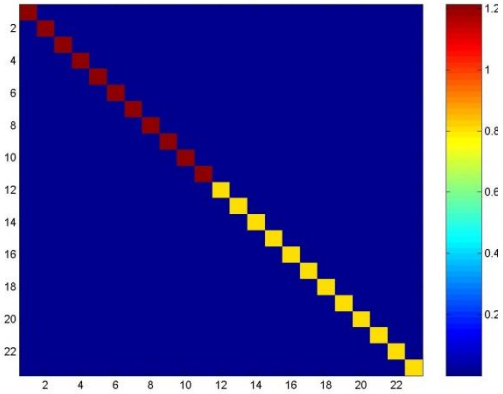


$$Cov(e) = \begin{bmatrix} 2 & 1 \\ 1 & 2 \end{bmatrix}$$

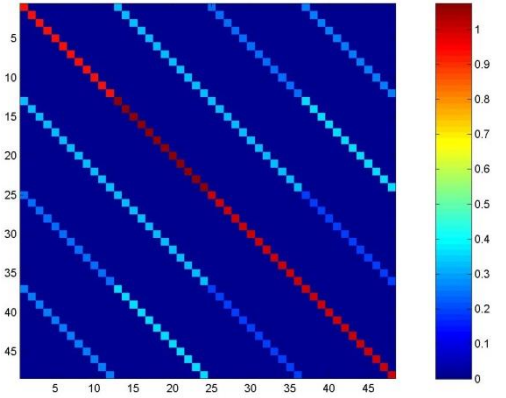
non-independent

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.))

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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