Event-related fMRI

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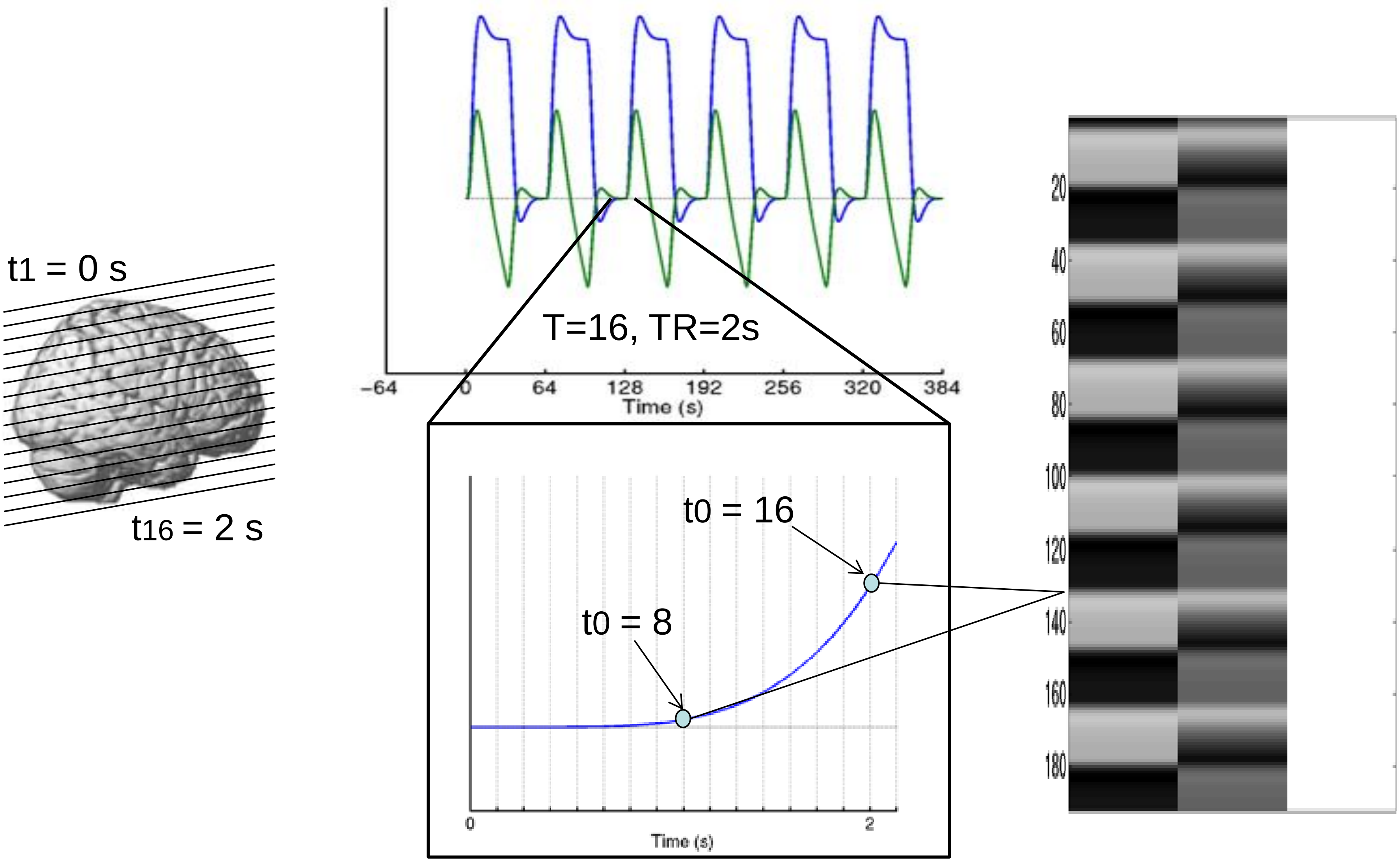
Slice Timing issue



Slice Timing issue

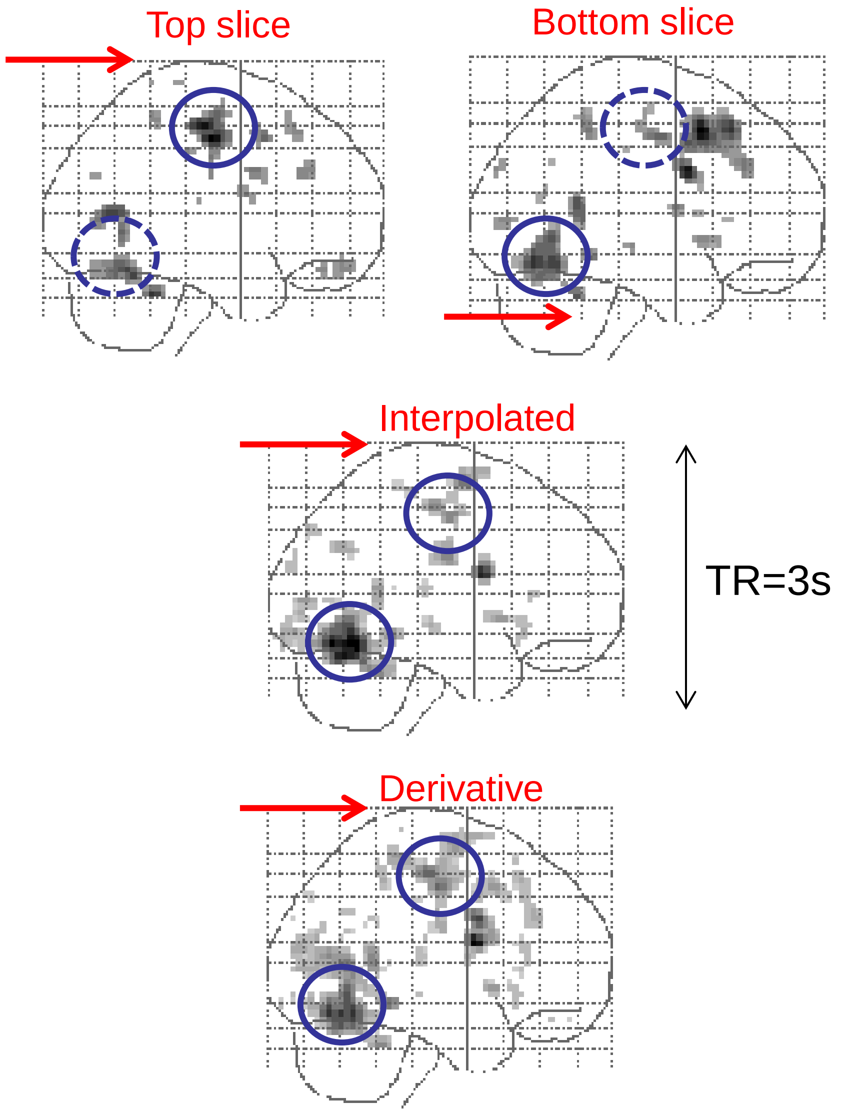
“Slice-timing Problem”:

- Slices acquired at different times, yet model is the same for all slices
- different results (using canonical HRF) for different reference slices
- (slightly less problematic if middle slice is selected as reference, and with short TRs)

Solutions:

1. Temporal interpolation of data “Slice timing correction”
2. More general basis set (e.g., with temporal derivatives)

See Sladky et al, NeuroImage, 2012.



Timing issues: Sampling

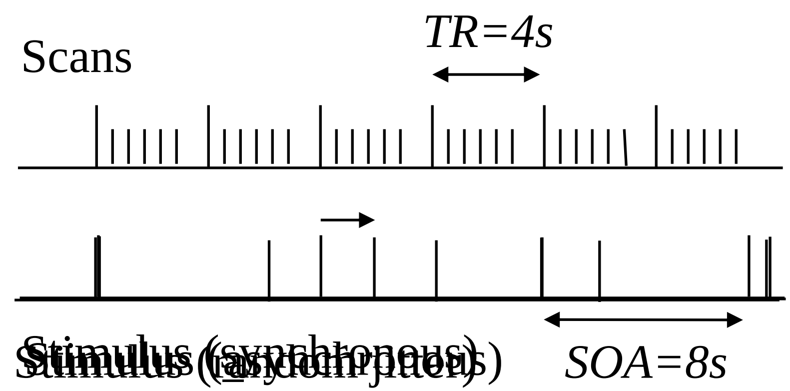
Typical TR for 48 slice EPI at 3mm spacing is ~ 4s

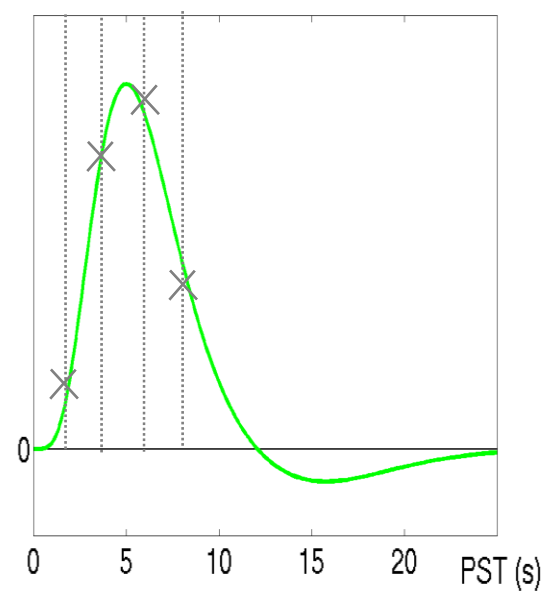
Sampling at [0,4,8,12…] post-stimulus may miss peak signal.

Higher effective sampling by:

1. Asynchrony
   eg SOA=1.5TR

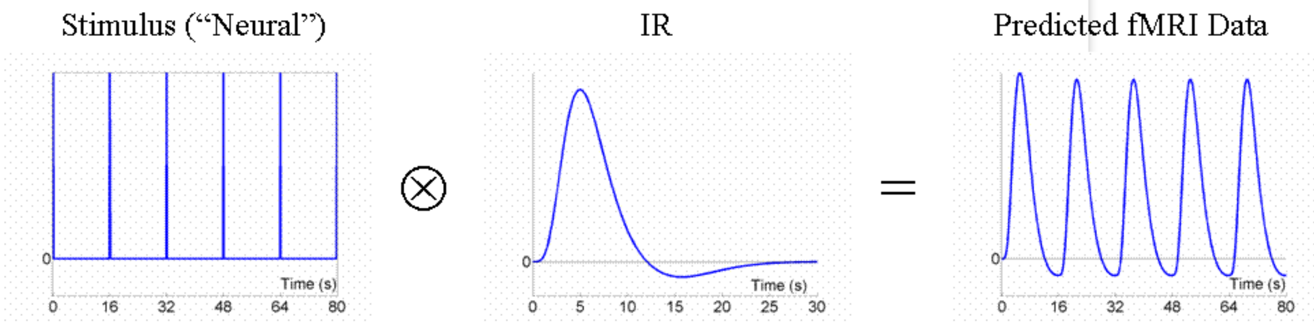
2. Random Jitter
   eg SOA=(2±0.5)TR





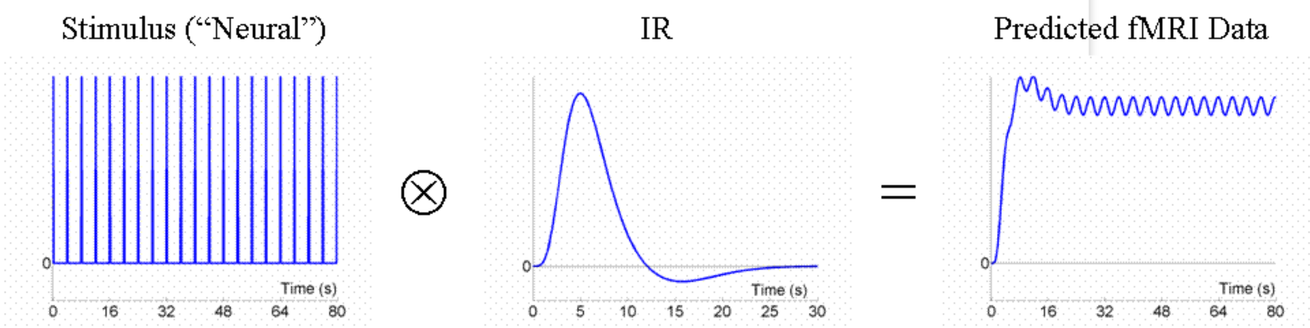
Optimal SOA?

16s SOA



Not very efficient…

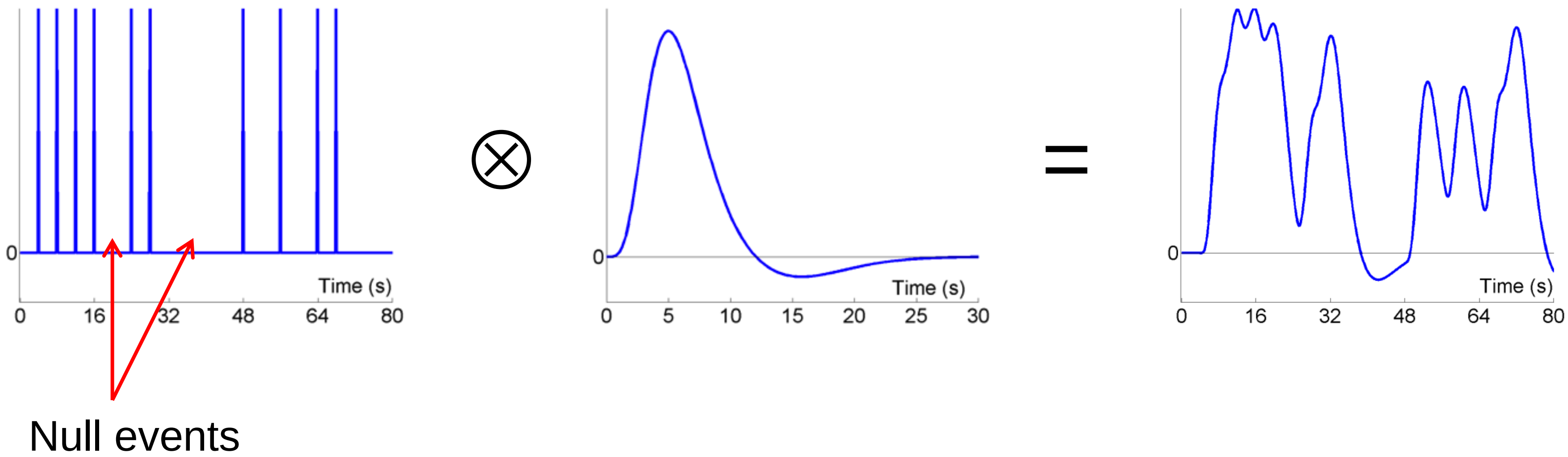
4s SOA



Very inefficient…

Short randomised SOA

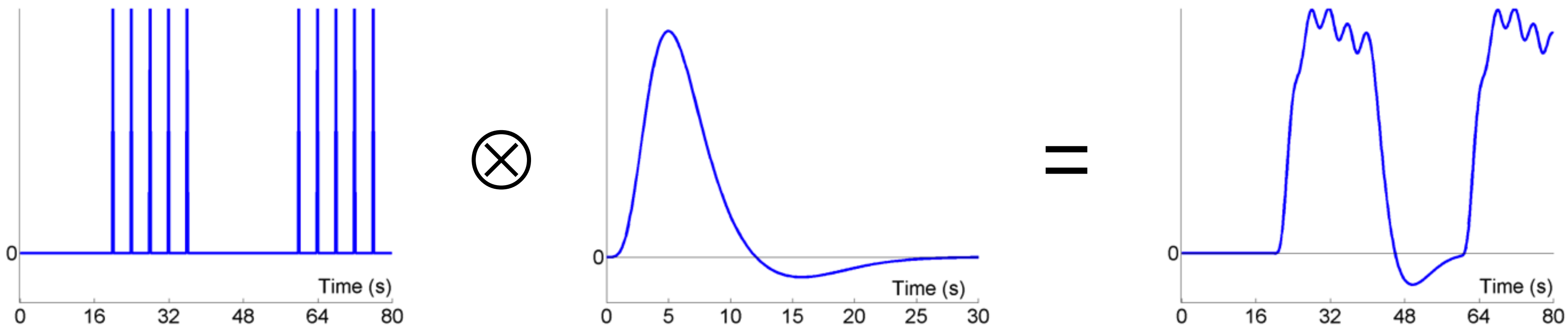
Stimulus ("Neural") HRF Predicted Data



More efficient!

Block design SOA

Stimulus ("Neural") HRF Predicted Data

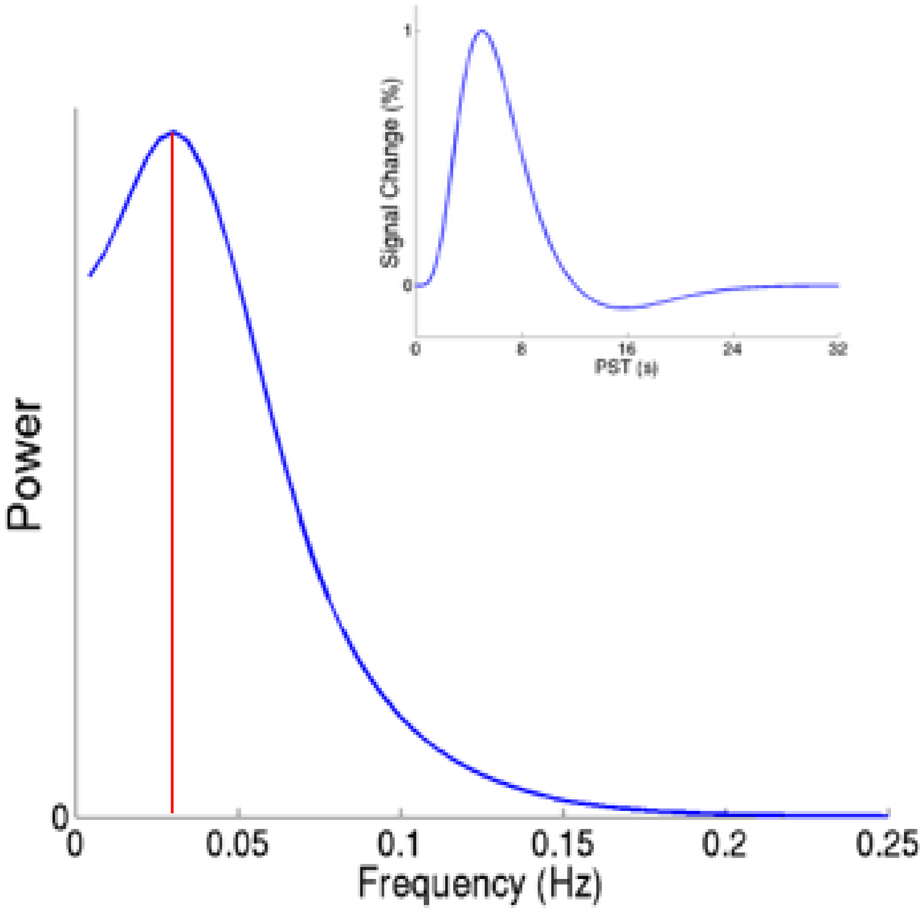


Even more efficient!

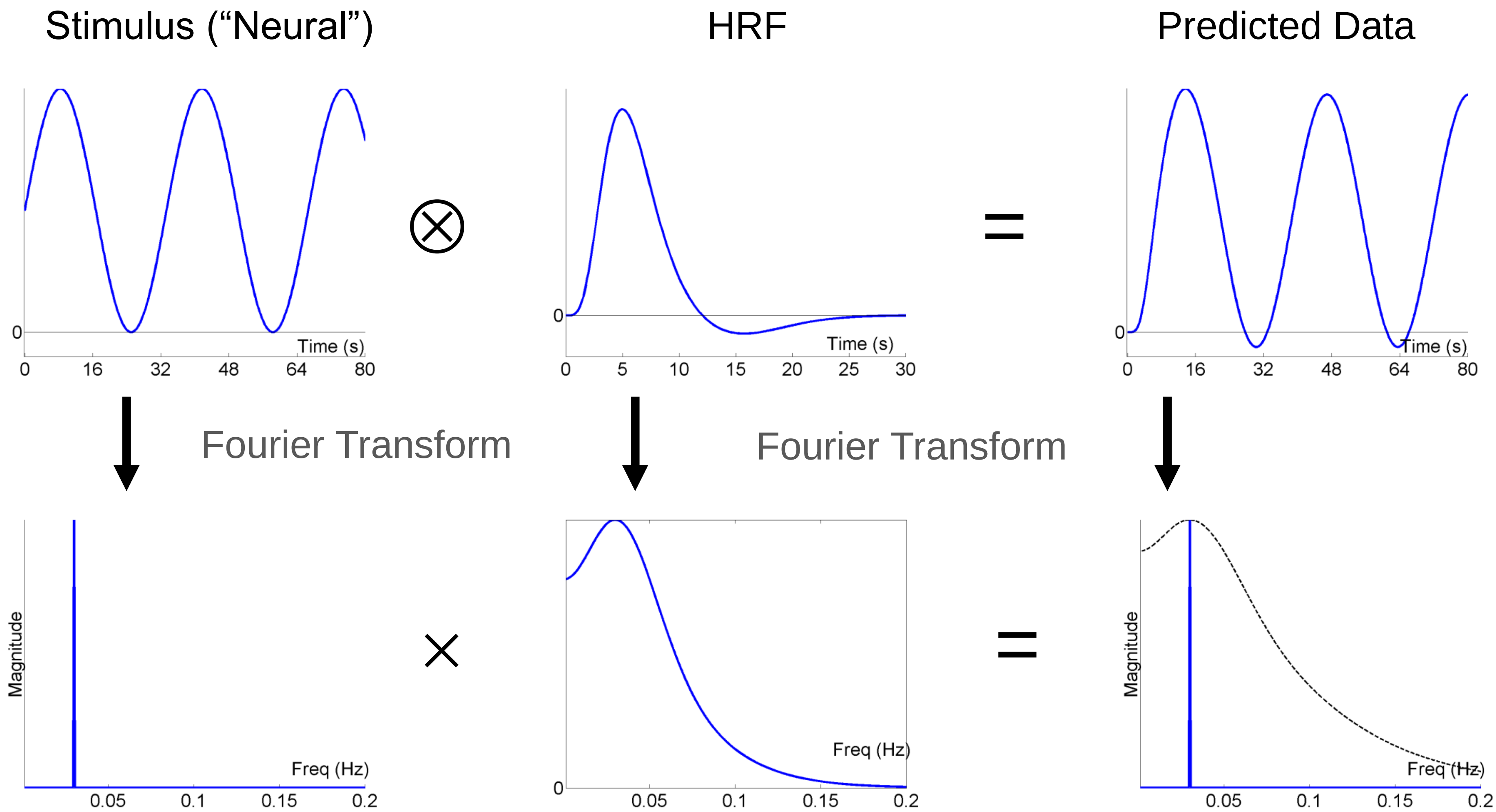
Design efficiency

- HRF can be viewed as a filter.
- We want to maximise the signal passed by this filter.
- Dominant frequency of canonical HRF is ~0.03 Hz.

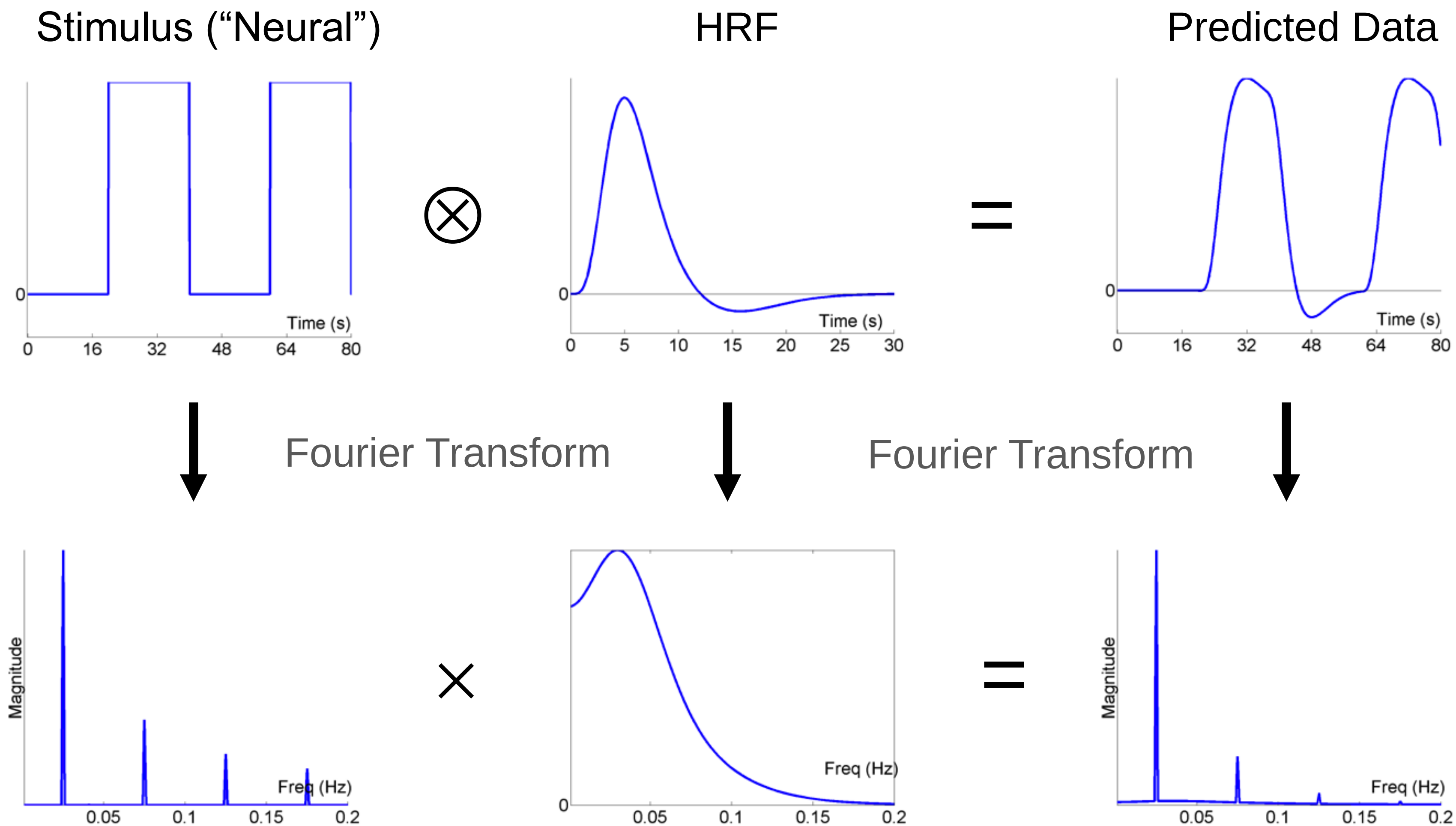
➢ The most efficient design is a sinusoidal modulation of neuronal activity with period ~32s



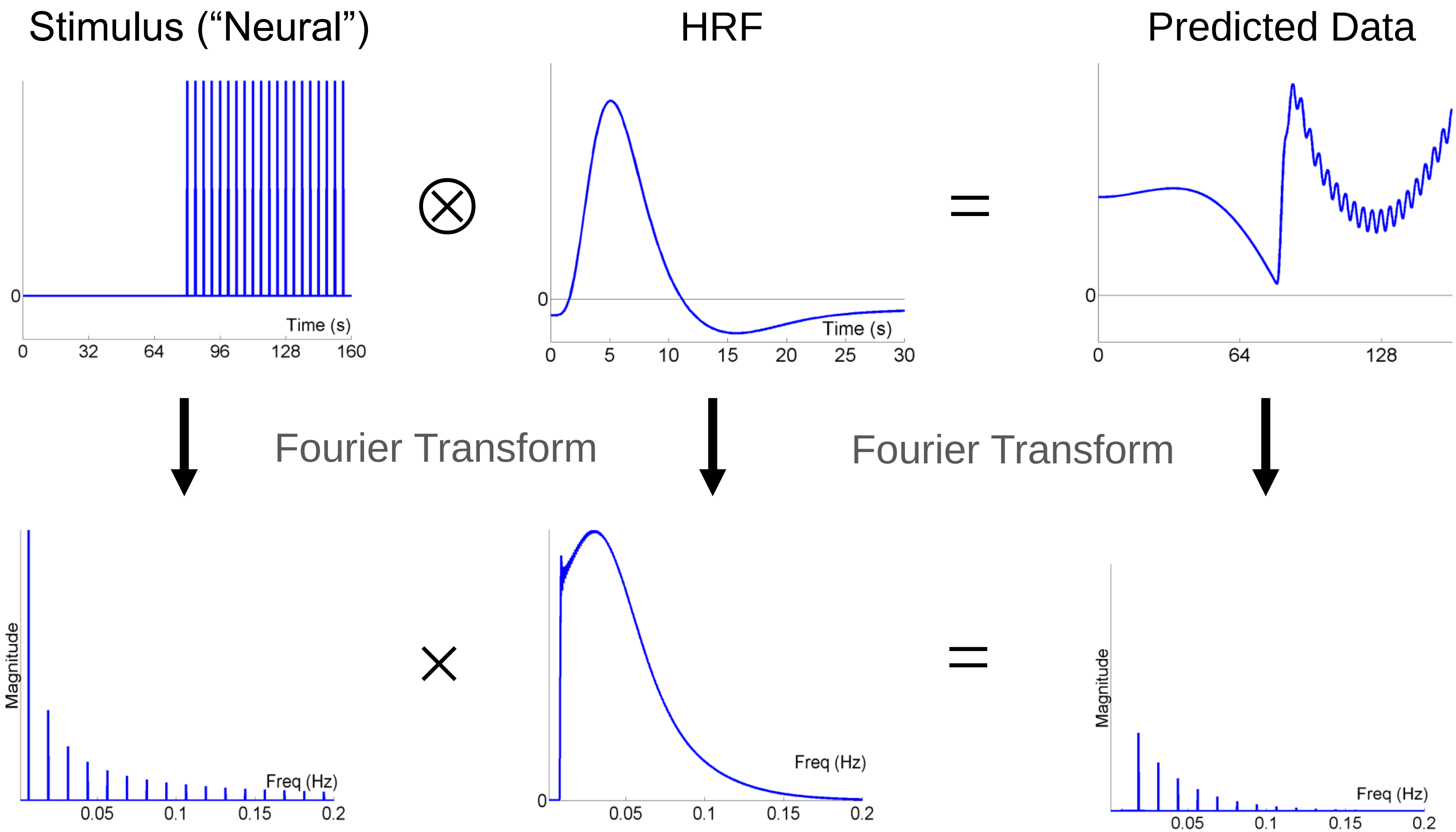
Sinusoidal modulation, f=1/32



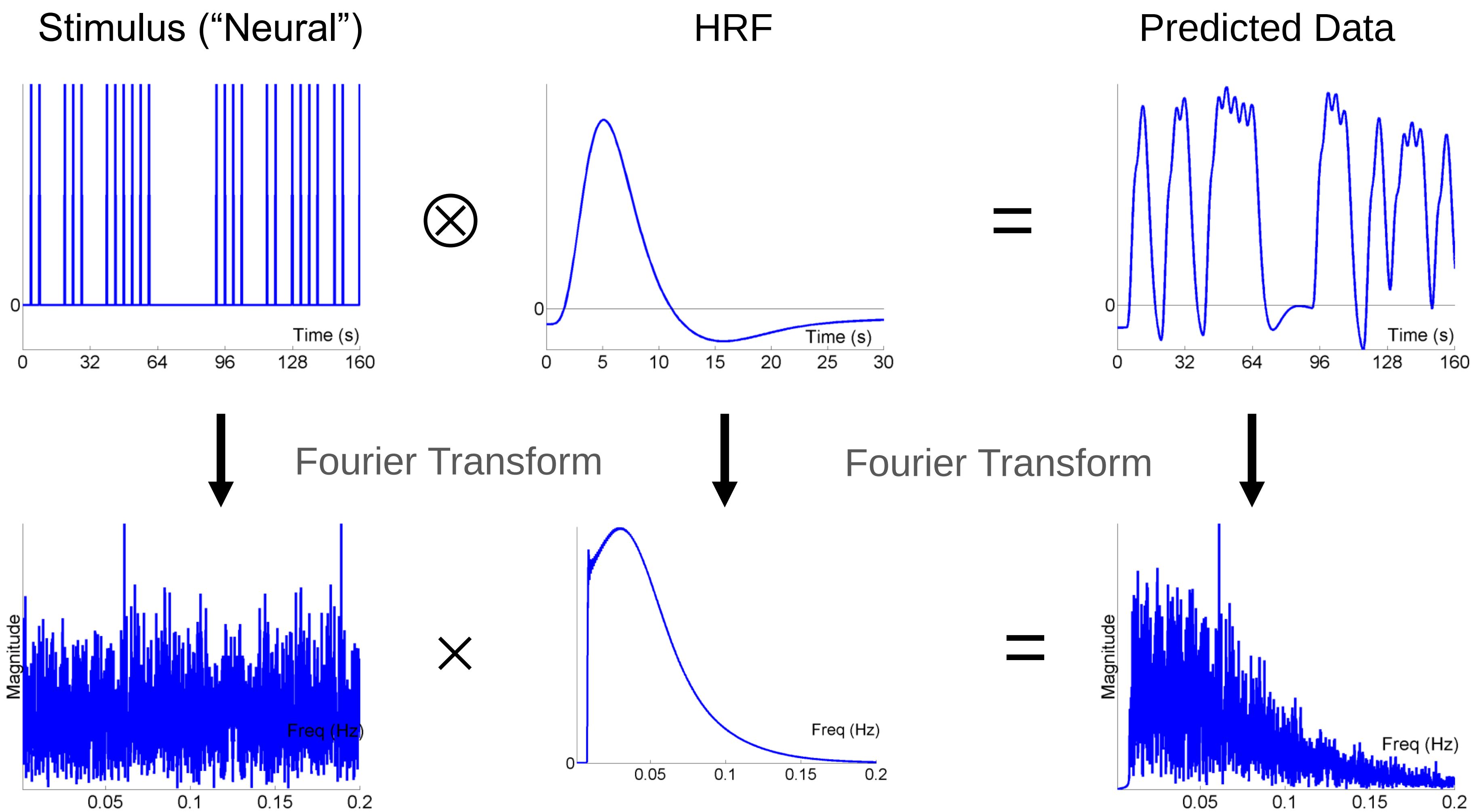
Blocked: epoch = 20s



Blocked: epoch = 80s, high-pass filter = 1/120s



Randomised Design, SOA_{min} = 4s, high pass filter = 1/120s



Randomised design spreads power over frequencies

Design efficiency

Block designs:

- Generally efficient but often not appropriate.
- Optimal block length 16s with short SOA (beware of high-pass filter).

Event-related designs:

- Efficiency depends on the contrast of interest
- With short SOAs ‘null events’ (jittered ITI) can optimise efficiency across multiple contrasts.
- Non-linear effects start to become problematic at SOA<2s

http://imaging.mrc-cbu.cam.ac.uk/imaging/DesignEfficiency

Multiple testing

(random field theory)

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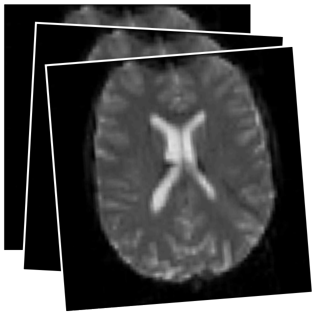
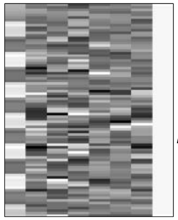
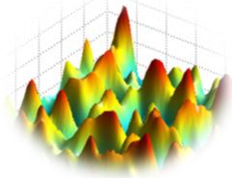


$y =$  $\beta + \varepsilon$

Contrast c

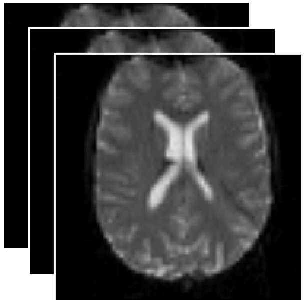
Random Field Theory



Pre-processings

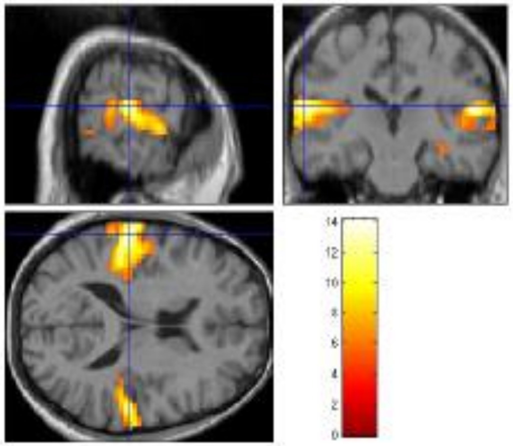
General Linear Model

Statistical Inference

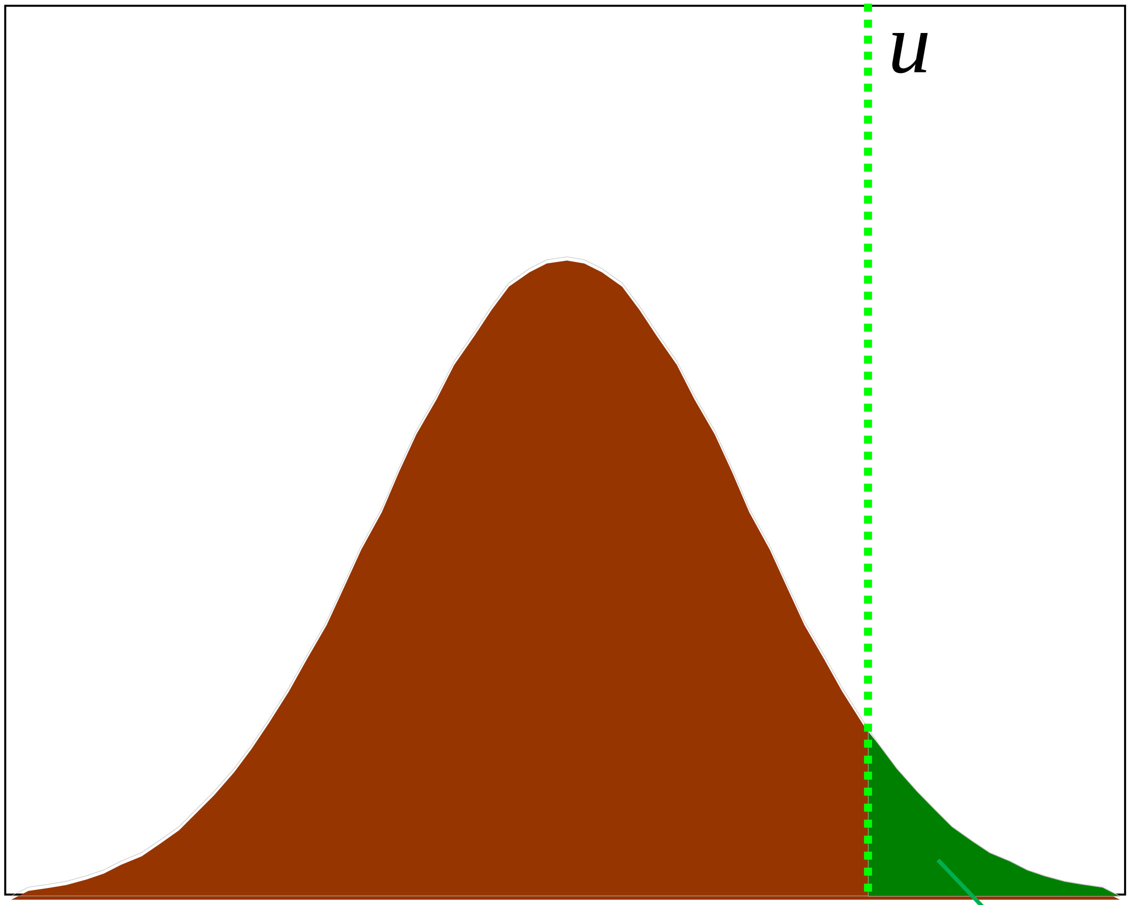


$$\hat{\beta} = (X^T X)^{-1} X^T y$$

$$\hat{\sigma}^2 = \frac{\hat{\varepsilon}^T \hat{\varepsilon}}{rank(X)}$$



Inference at a single voxel



Null distribution of test statistic T

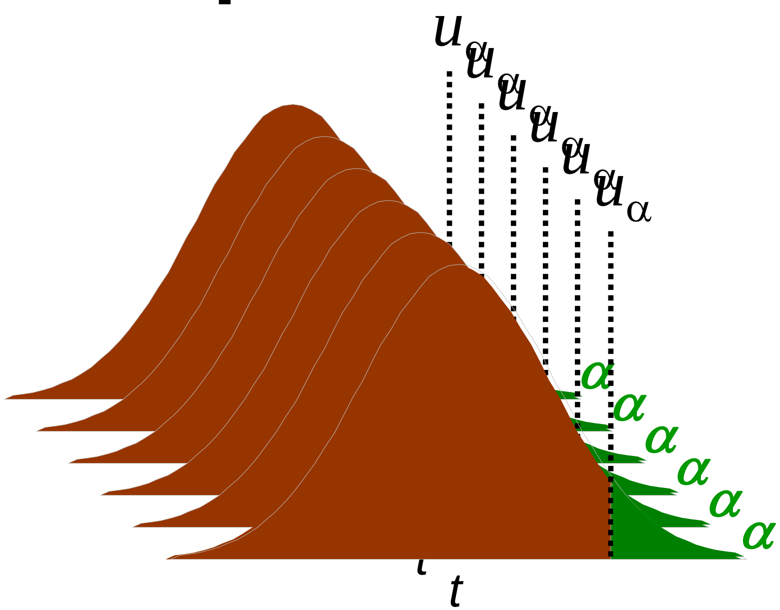
Null Hypothesis H_0:
zero activation

Decision rule (threshold) u:
determines false positive rate α

$\Rightarrow$ Choose u to give acceptable α under H_0

$$\alpha = p(t > u | H_0)$$

Multiple tests

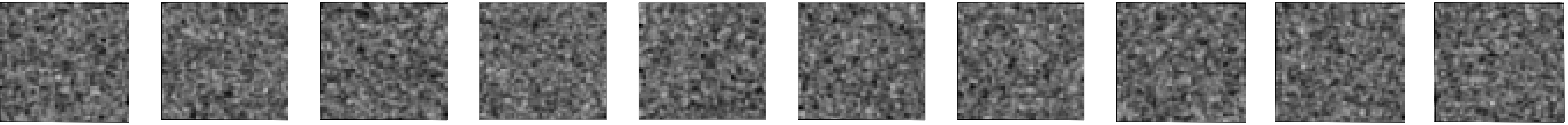


If we have 100,000 voxels,

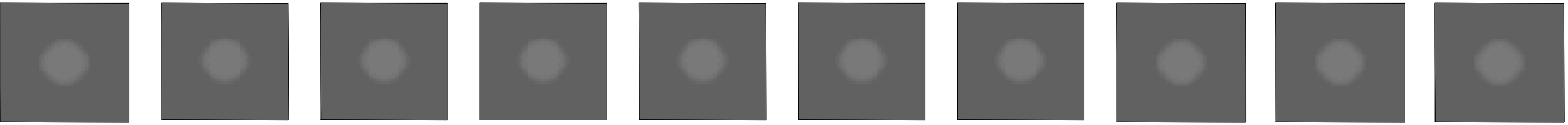
α=0.05 $\Rightarrow$ 5,000 false positive voxels.

This is clearly undesirable; to correct for this we can define a null hypothesis for a collection of tests.

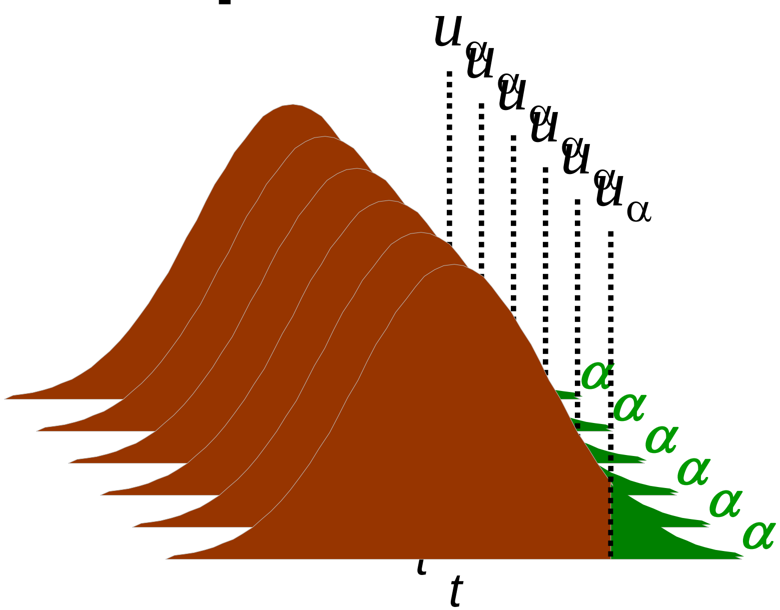
Noise



Signal



Multiple tests



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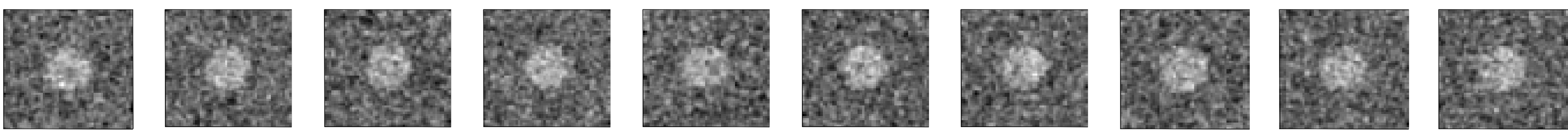
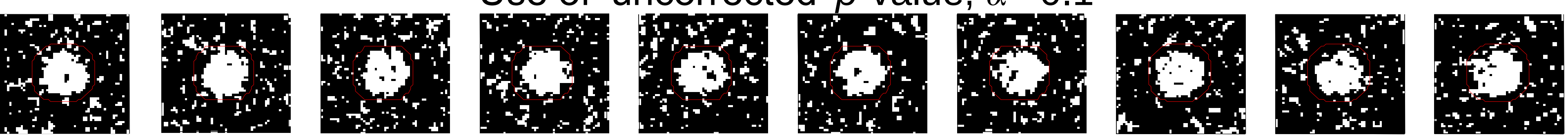


Use of 'uncorrected' *p*-value, α =0.1



11.3% 11.3% 12.5% 10.8% 11.5% 10.0% 10.7% 11.2% 10.2% 9.5%

Percentage of Null Pixels that are False Positives

Family-Wise Null Hypothesis

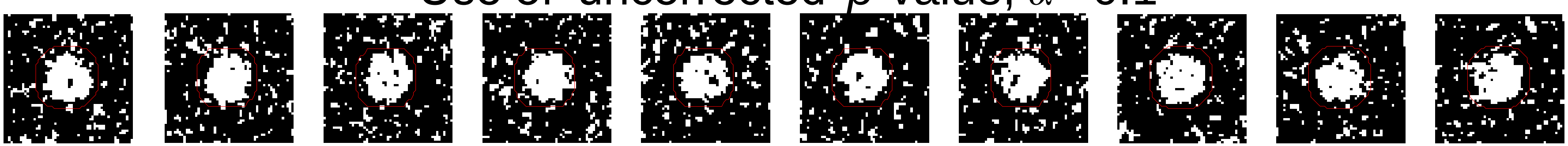
Family-Wise Null Hypothesis:
Activation is zero everywhere

If we reject a voxel null hypothesis at *any* voxel,
we reject the family-wise Null hypothesis

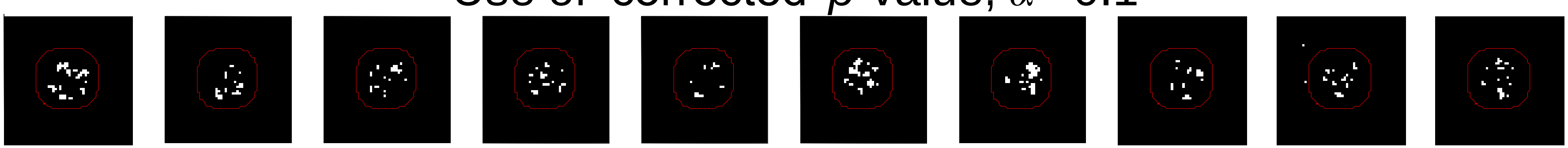
A FP ***anywhere*** in the image gives a **Family Wise Error** (FWE)

Family-Wise Error rate (FWER) = ‘*corrected*’ *p*-value

Use of ‘uncorrected’ *p*-value, α =0.1



Use of ‘corrected’ *p*-value, α =0.1



FWE

Bonferroni correction

The Family-Wise Error rate (FWER), α_{FWE}, for a family of N tests follows the inequality:

$$\alpha_{FWE} \leq N\alpha$$

where α is the test-wise error rate.

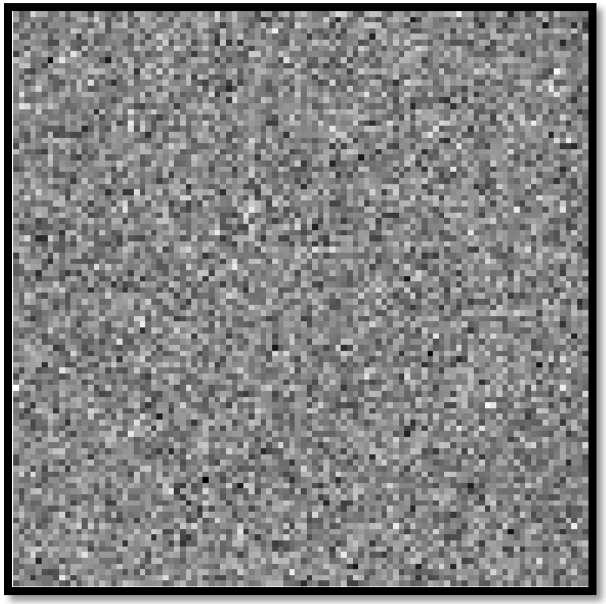
Therefore, to ensure a particular FWER choose:

$$\alpha = \frac{\alpha_{FWE}}{N}$$

This correction does not require the tests to be independent but becomes very stringent if dependence.

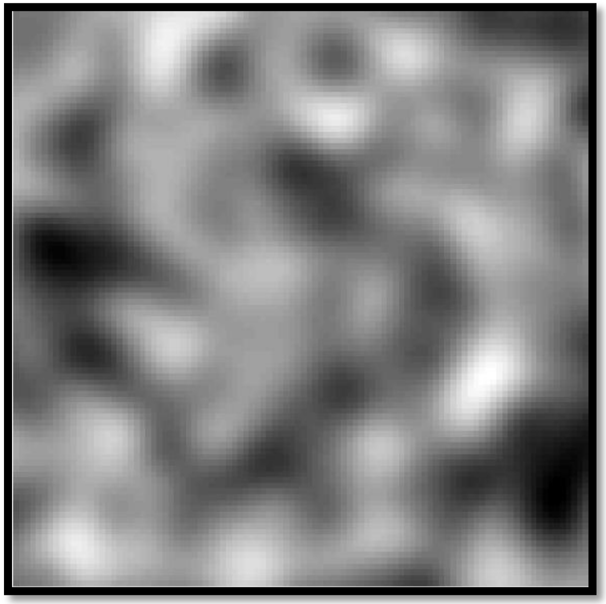
Spatial correlations

100 x 100 independent tests



Discrete data

Spatially correlated tests (FWHM=10)



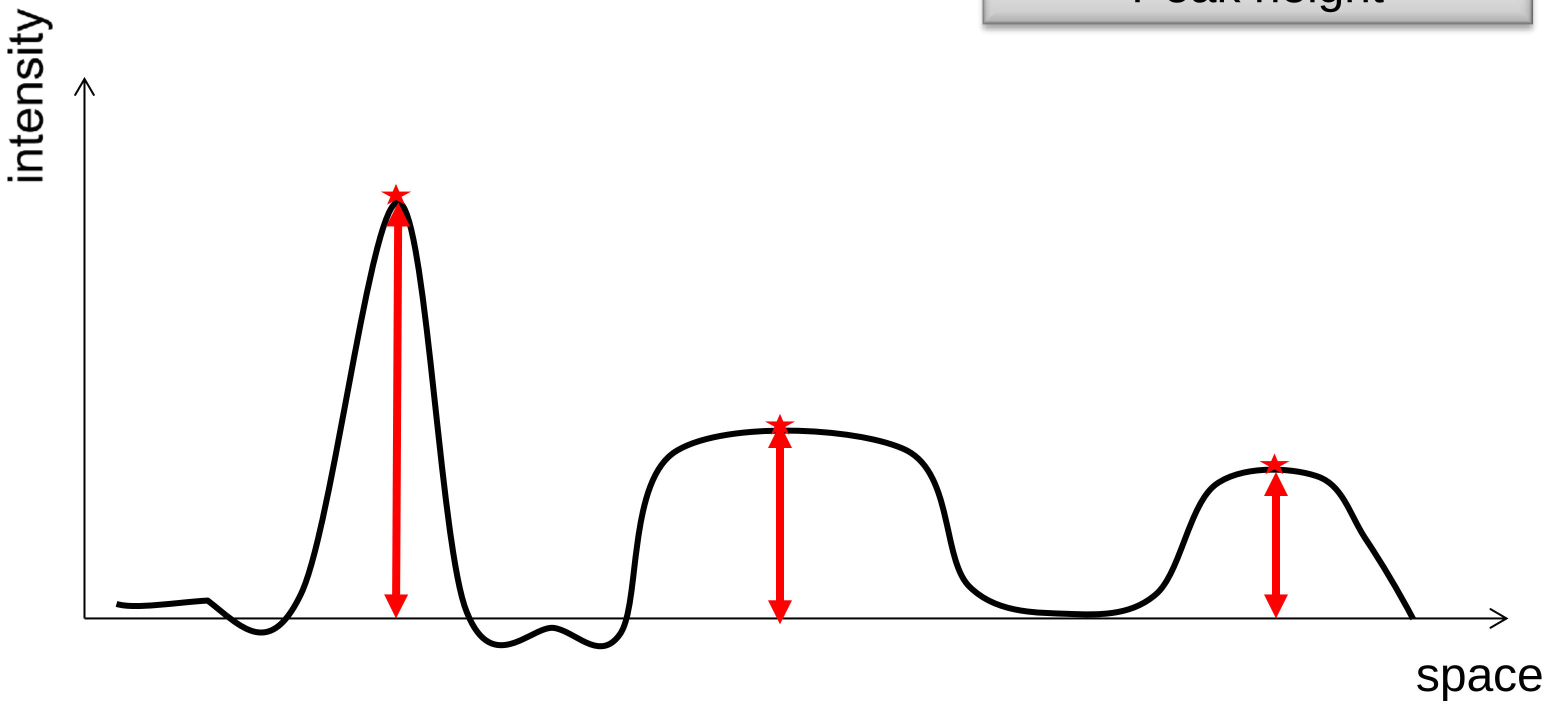
Spatially extended data

Bonferroni is too conservative for spatially correlated data.

Topological inference

Peak level inference

Topological feature:
Peak height

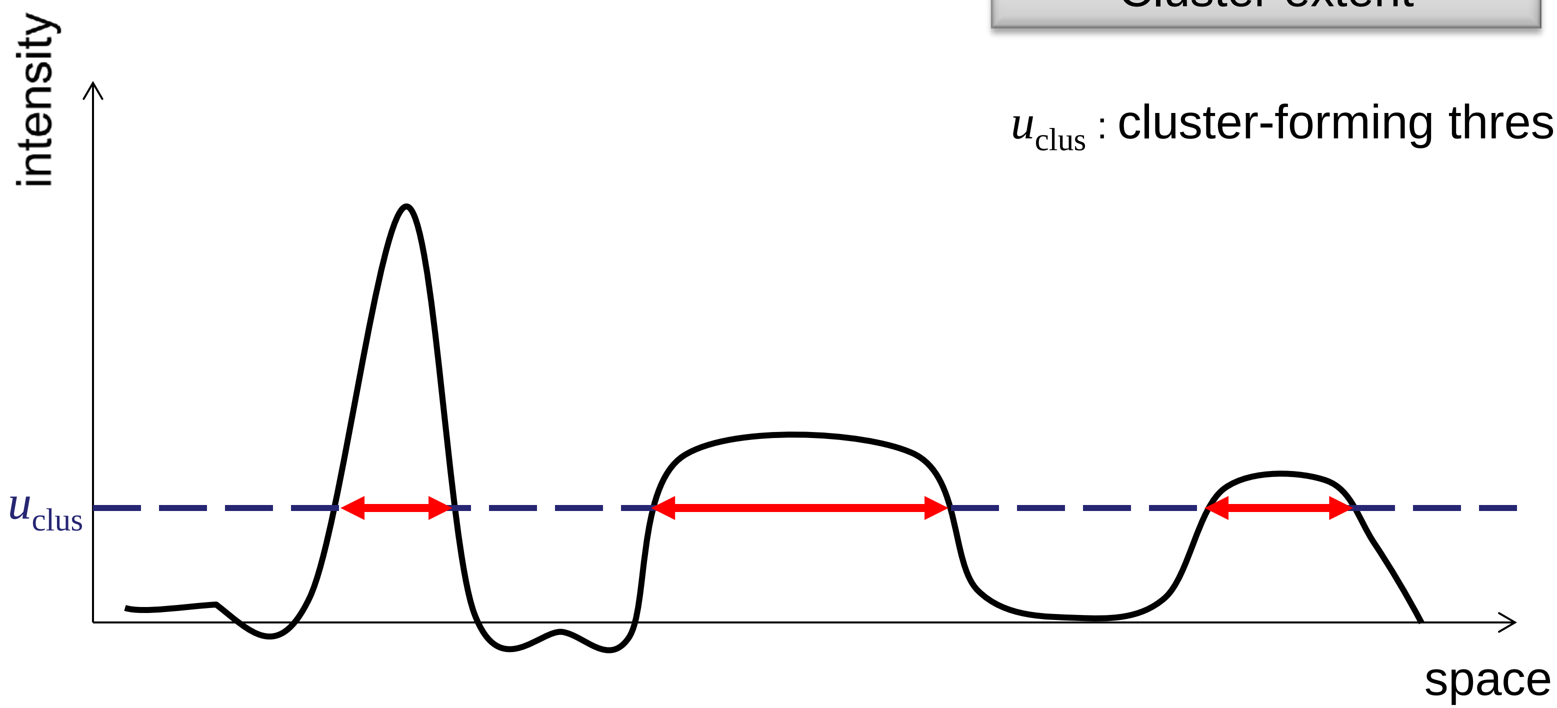


Topological inference

Cluster level inference

Topological feature:
Cluster extent

u_{clus} : cluster-forming threshold

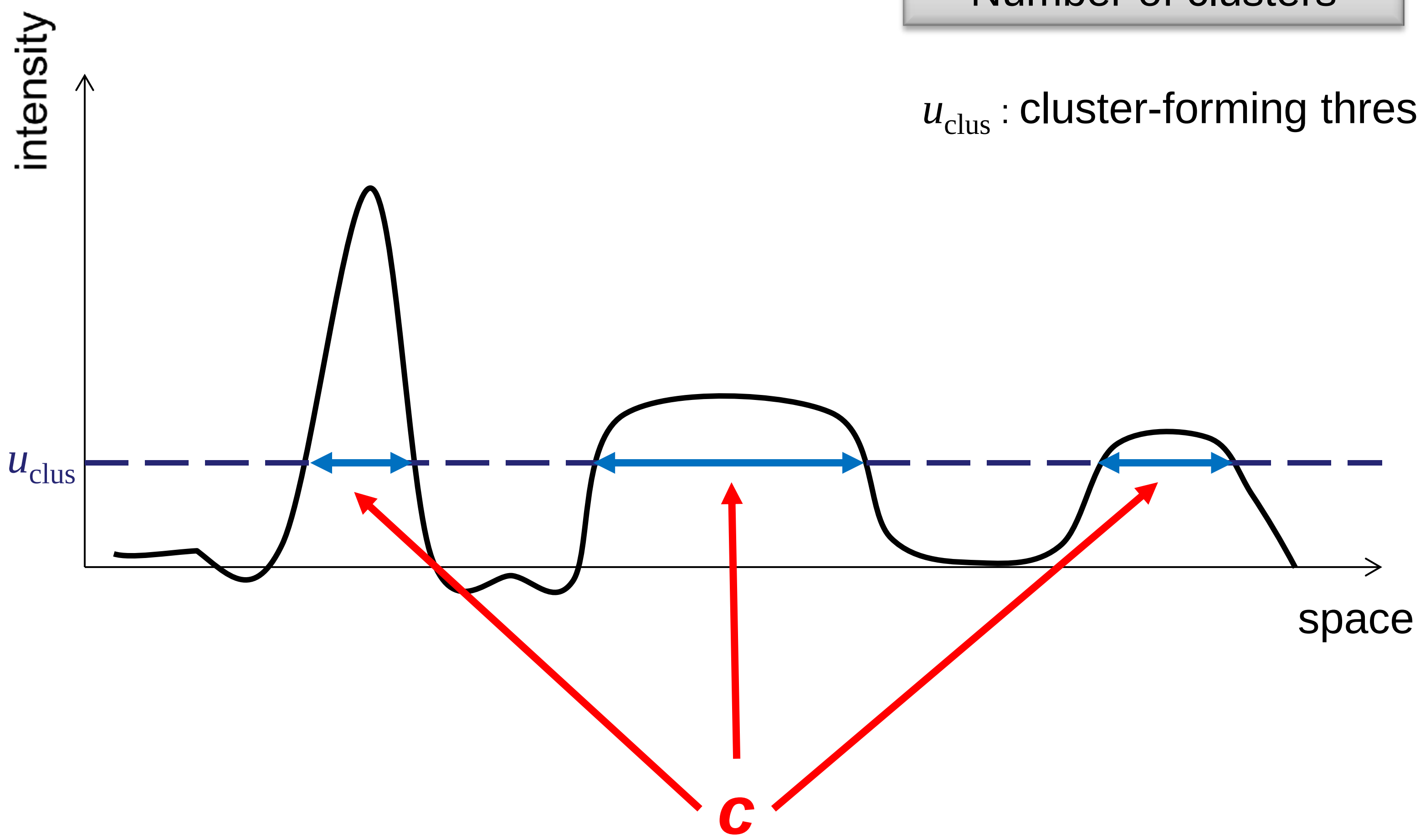


Topological inference

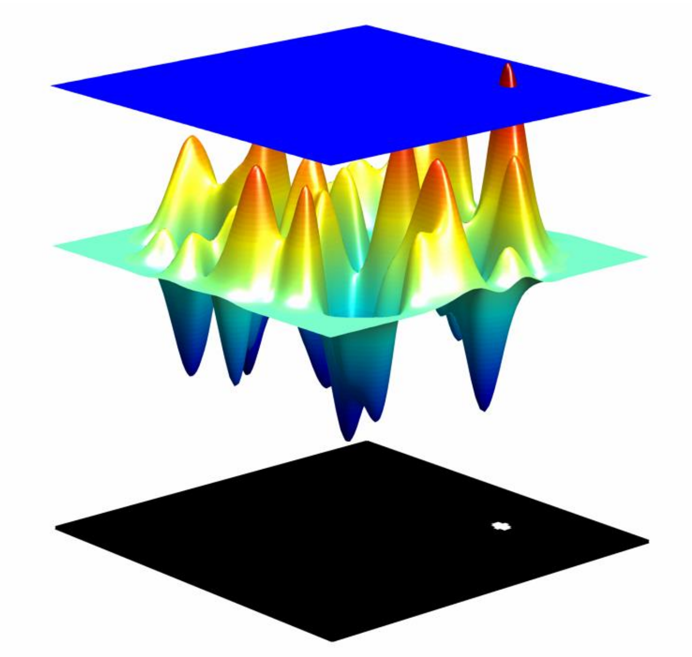
Set level inference

Topological feature:
Number of clusters

u_{clus} : cluster-forming threshold



RFT and Euler Characteristic



$$FWER = p(FWE)$$
$$\approx E[\chi_u]$$
$$\propto \lambda(\Omega)|\Lambda|^{1/2}\, u \exp(-u^2/2)/(2\pi)^{3/2}$$

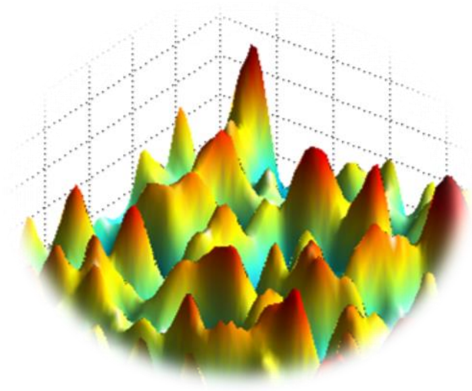
Search volume

Roughness (1/smoothness)

Threshold

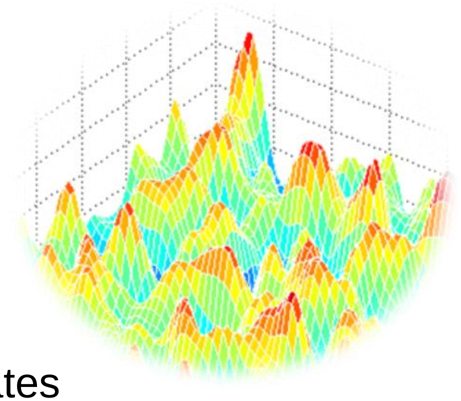
Random Field Theory

- The statistic image is assumed to be a good lattice representation of an underlying continuous stationary random field.
  Typically, FWHM > 3 voxels
  (combination of intrinsic and extrinsic smoothing)



- Smoothness of the data is unknown and estimated:
  very precise estimate by pooling over voxels ⇒ stationarity assumptions (esp. relevant for cluster size results).

- *A priori* hypothesis about where an activation should be, reduce search volume ⇒ Small Volume Correction:
  - mask defined by (probabilistic) anatomical atlases
  - mask defined by separate "functional localisers"
  - mask defined by orthogonal contrasts
  - (spherical) search volume around previously reported coordinates



Conclusion

- There is a ***multiple testing problem*** and *corrections* have to be applied on *p*-values (for the volume of interest only (see Small Volume Correction)).

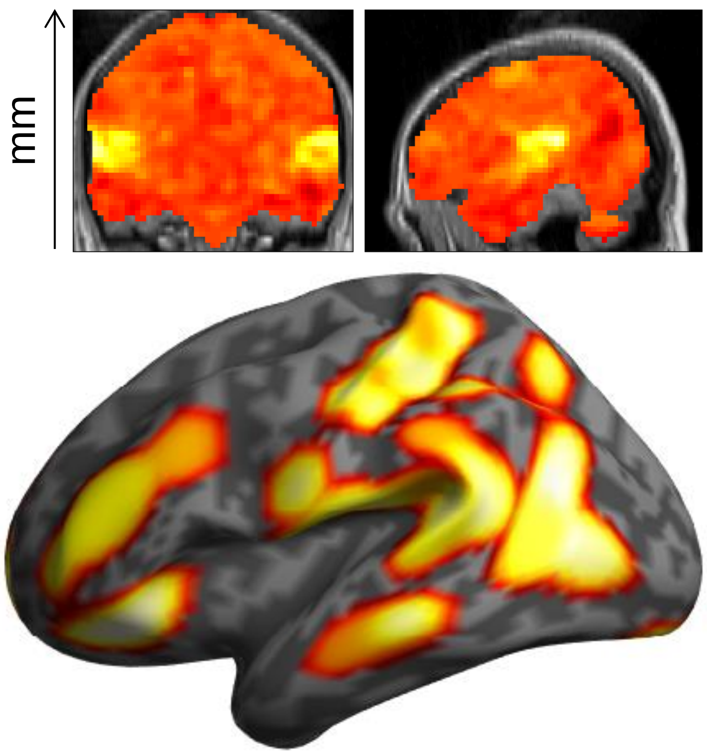
- Inference is made about ***topological features*** (peak height, spatial extent, number of clusters).
  Use results from the ***Random Field Theory***.

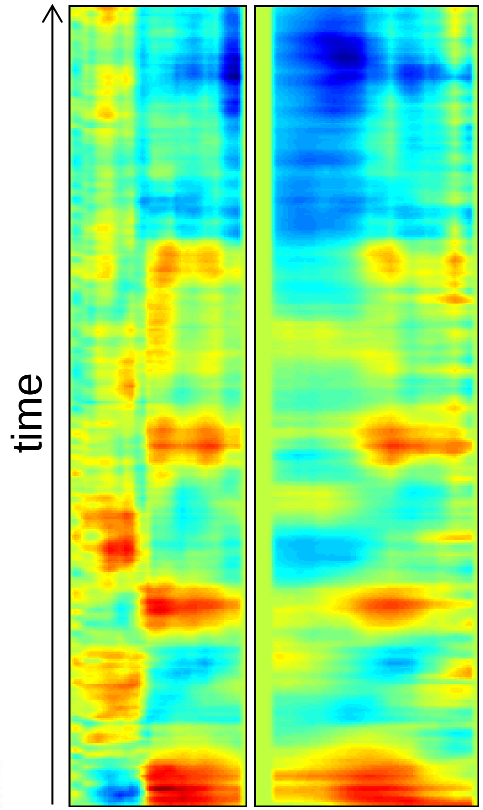
- **Control of *FWER*** (probability of a false positive anywhere in the image): very specific, not so sensitive.

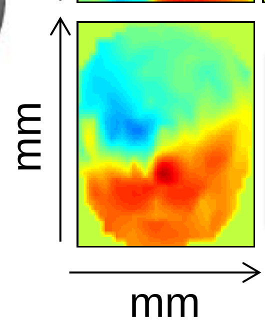
- ***Control of FDR*** (expected proportion of false positives amongst those features declared positive (the *discoveries*)): less specific, more sensitive.

Statistical Parametric Maps

fMRI, VBM,
M/EEG source reconstruction

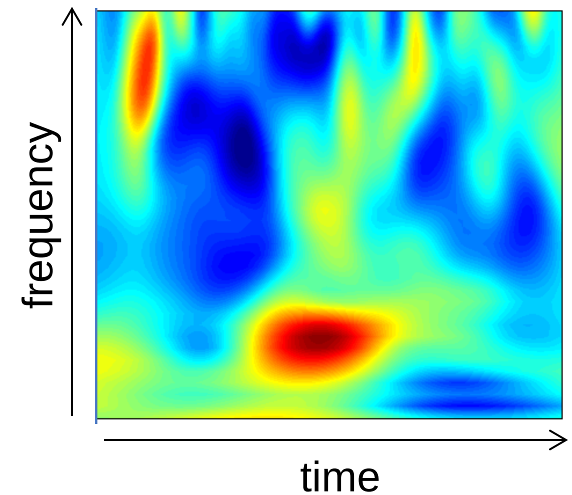




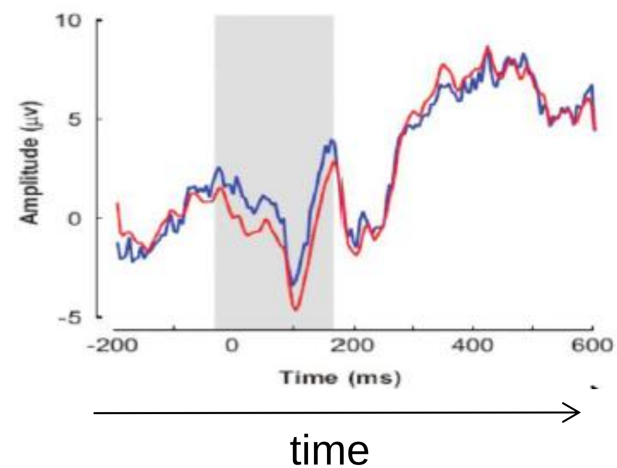


M/EEG
2D+t
scalp-time

M/EEG 2D time-frequency



M/EEG 1D channel-time



Group Analyses

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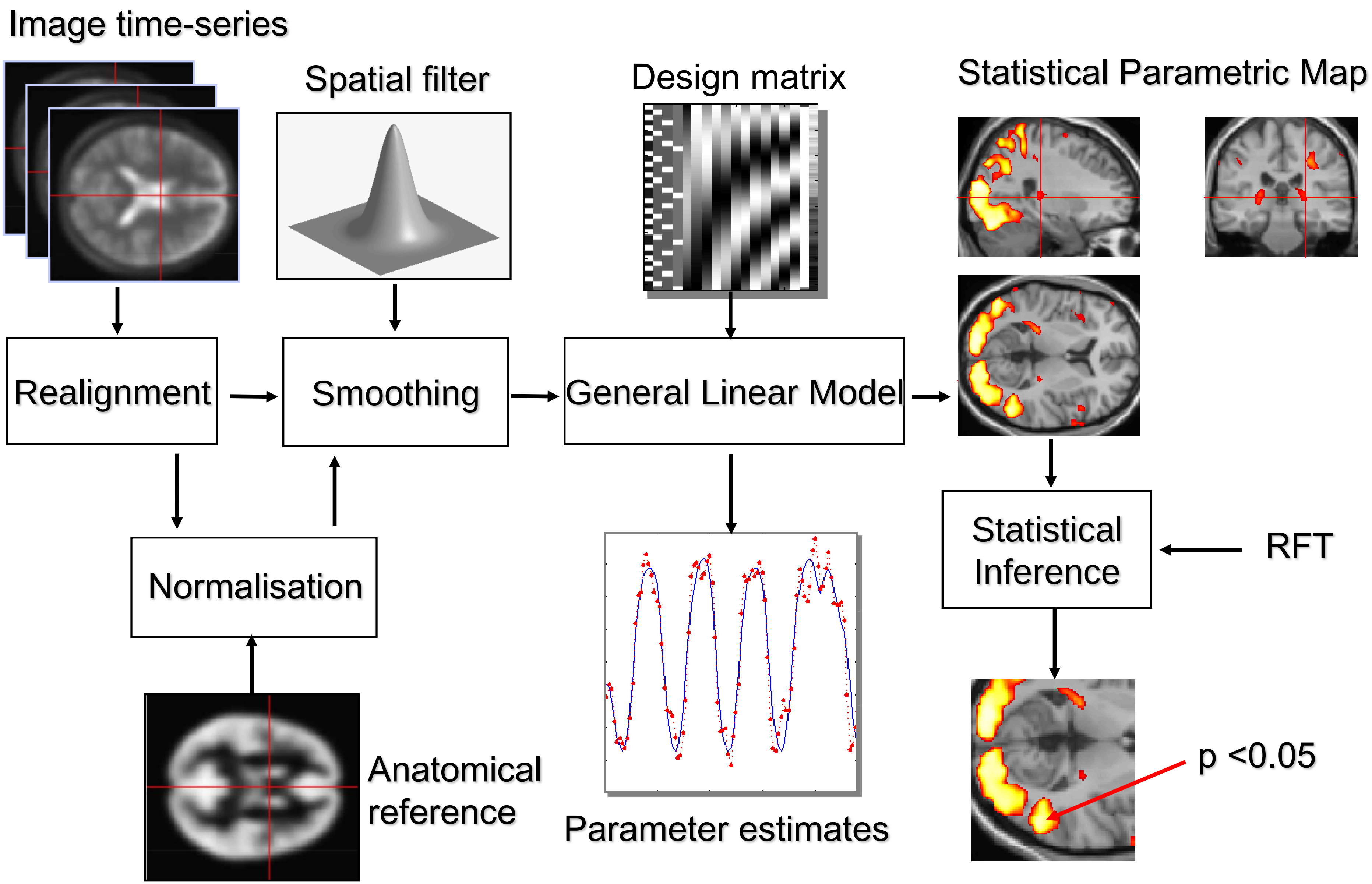
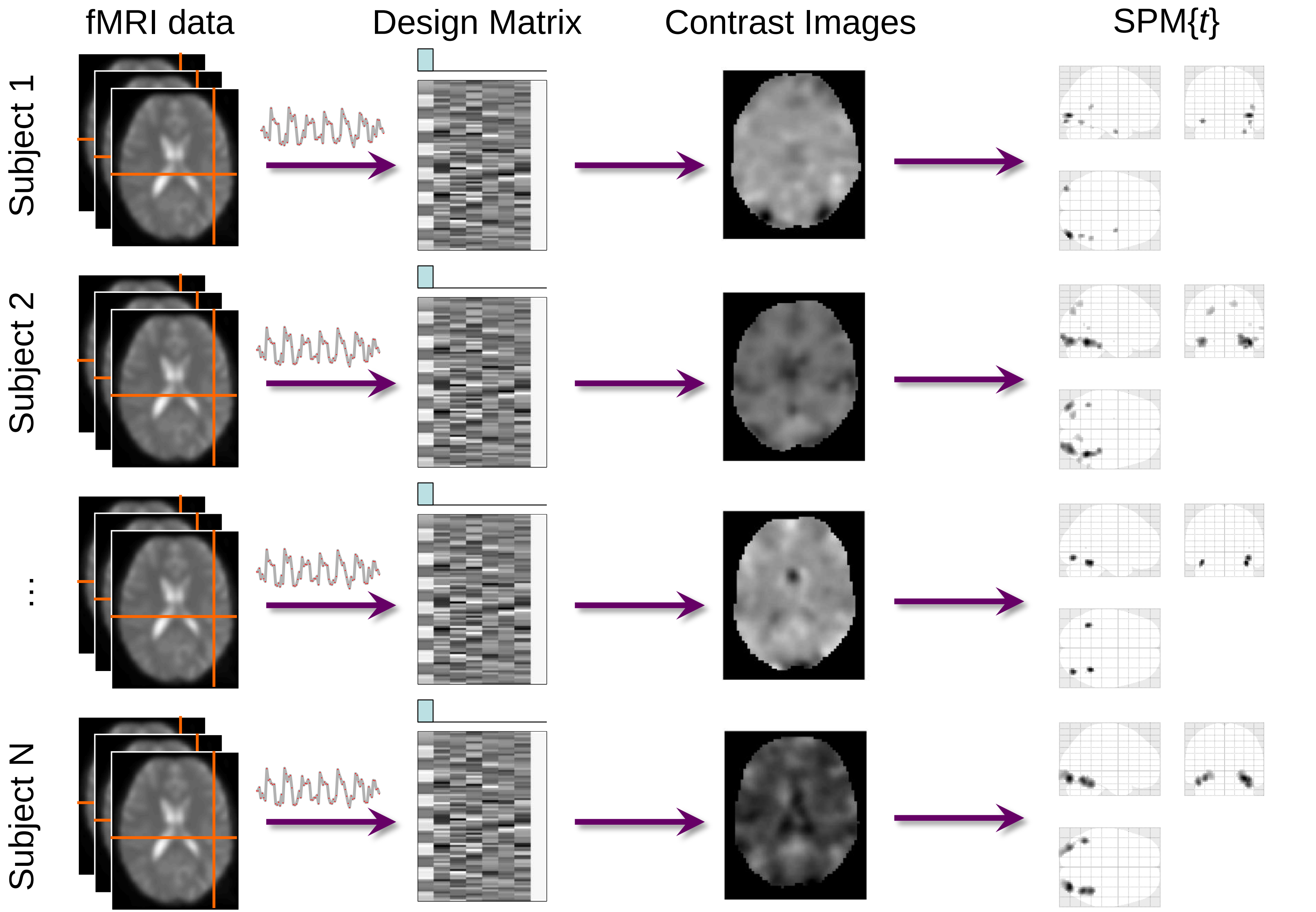
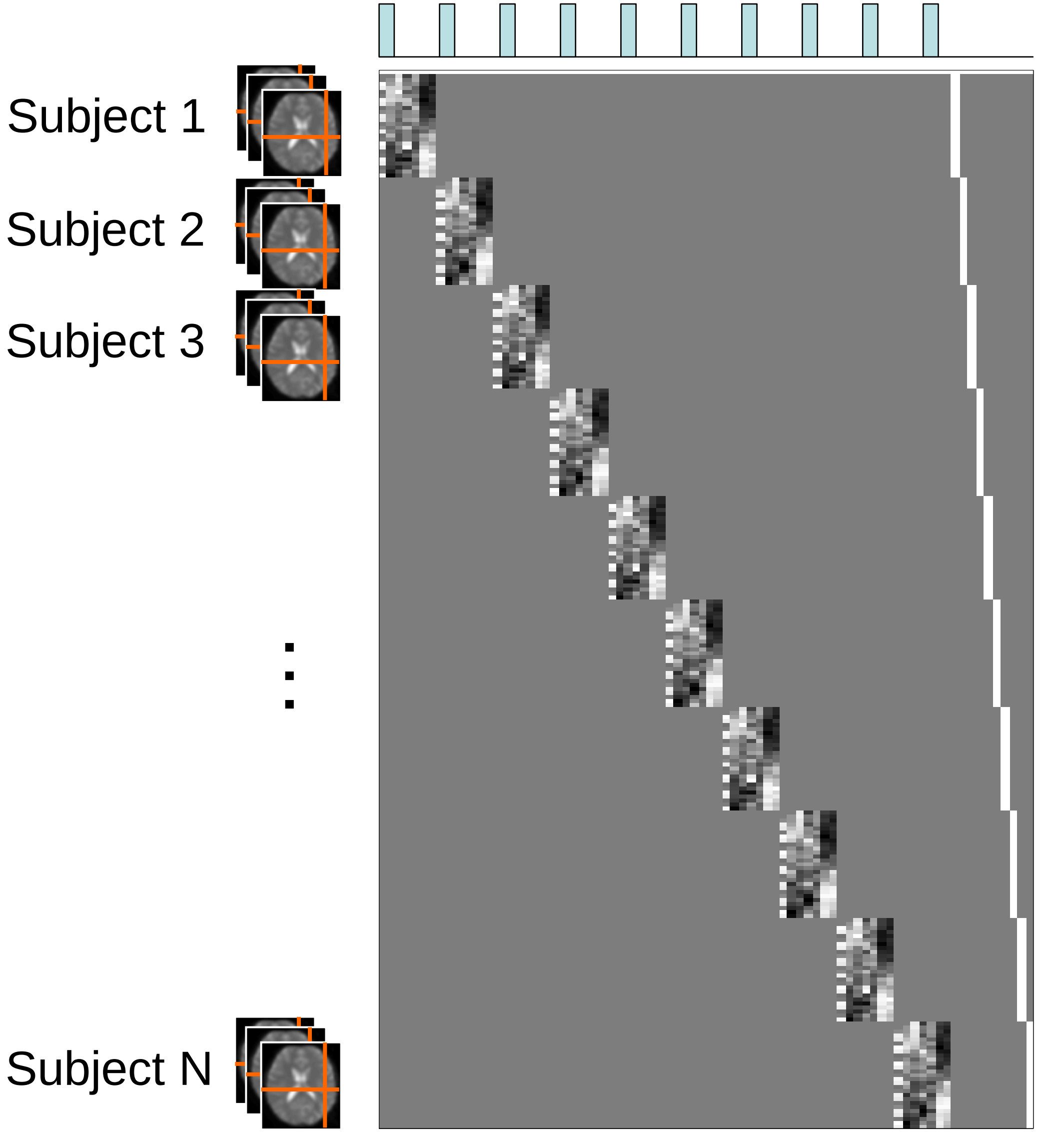


SPM
Image time-series
Spatial filter
Design matrix
Statistical Parametric Map
Realignment
Smoothing
General Linear Model
Statistical Inference
RFT
Normalisation
Anatomical reference
Parameter estimates
p <0.05

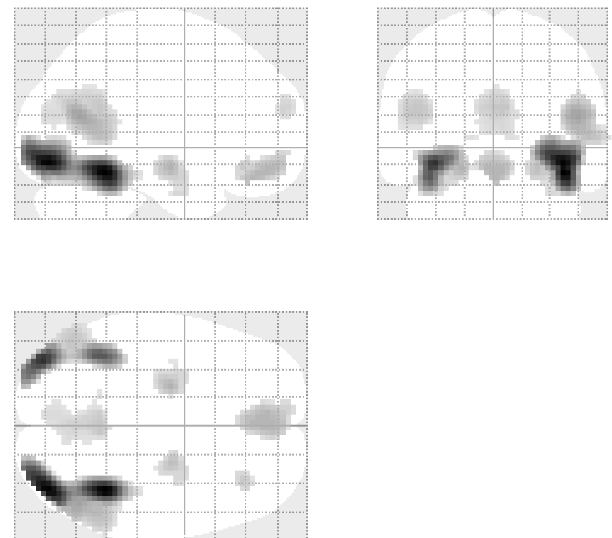
GLM: repeat over subjects



Fixed effects analysis (FFX)



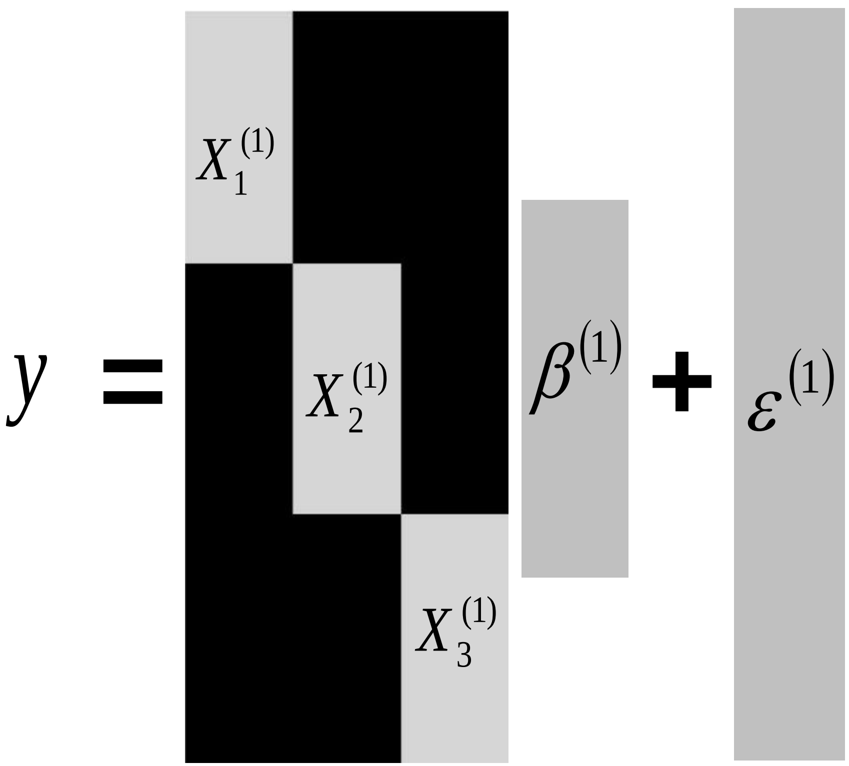
Modelling all subjects at once



variance over subjects at each voxel

Fixed effects analysis (FFX)

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

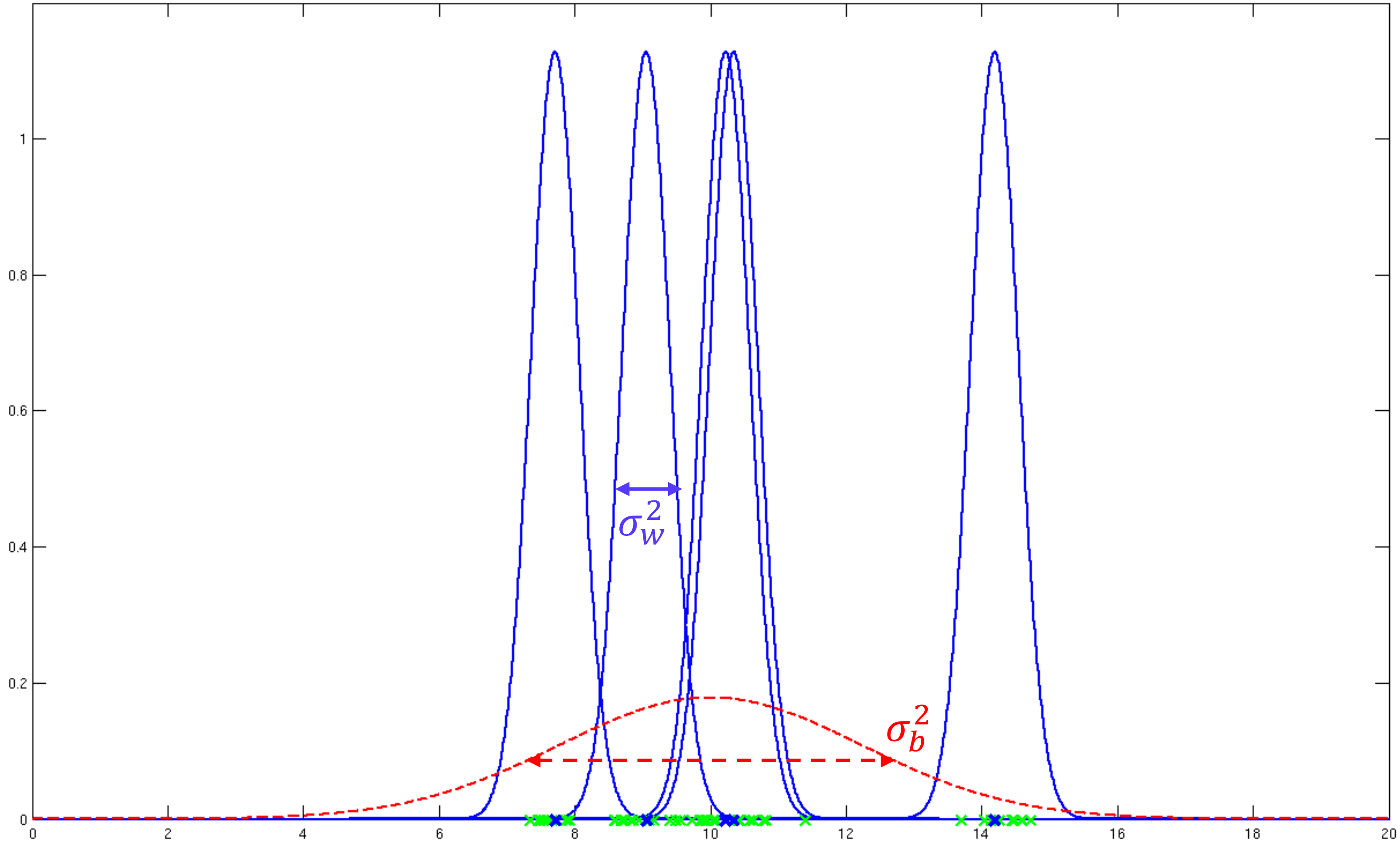


Modelling all subjects at once

- ☑ Simple model
- ☑ Lots of degrees of freedom

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

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"

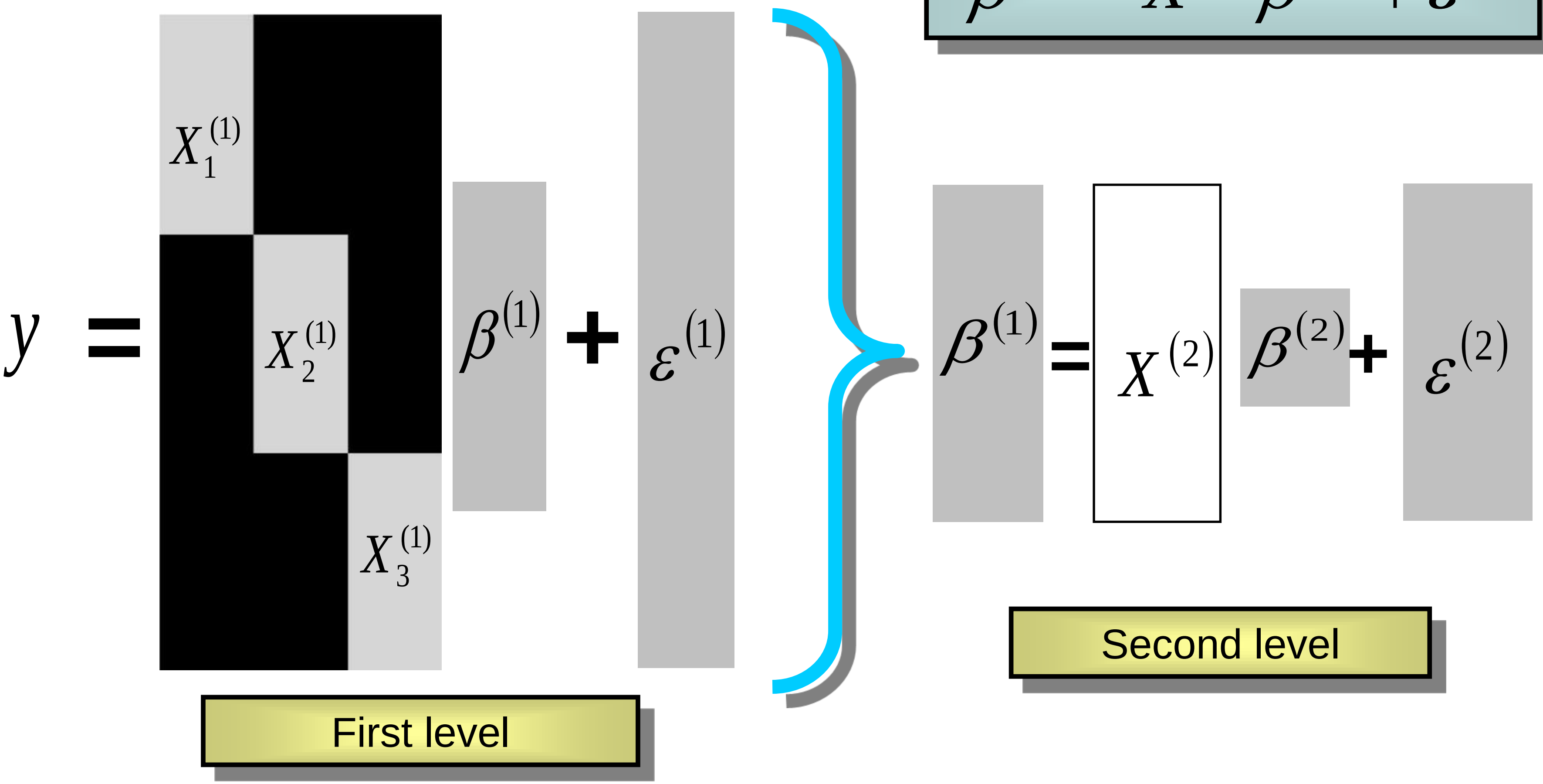
  - **Random effects inference**:

    "If I were to sample a new cohort from the same population I would get the same result"

Hierarchical models

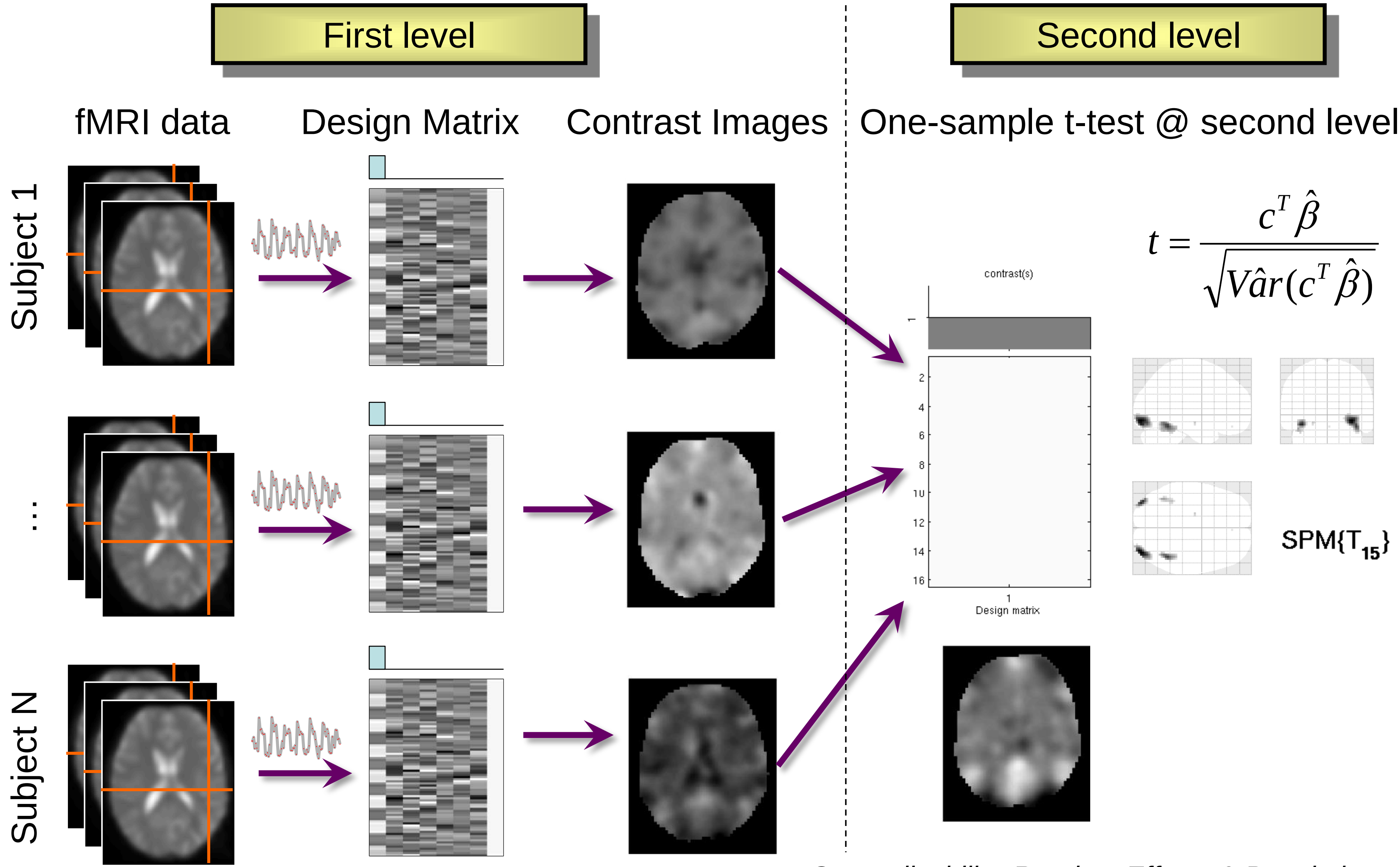
Example: Two level model

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



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

Summary Statistics RFX Approach



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

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.

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.

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

Summary

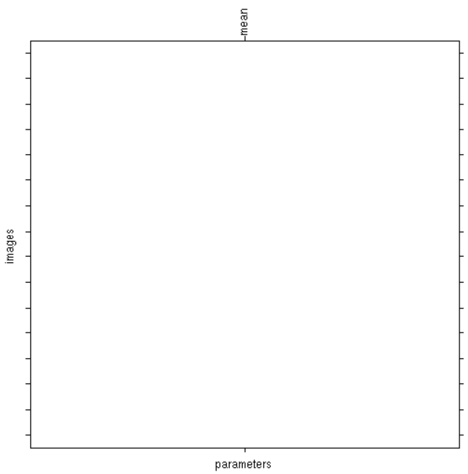
- Group Inference usually proceeds with **RFX analysis**, not FFX. Group effects are compared to between rather than within subject variability.

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

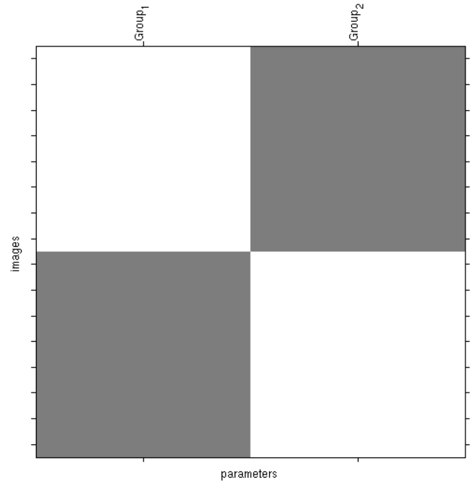
- **Summary statistics** approach is a robust method for RFX group analysis.

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

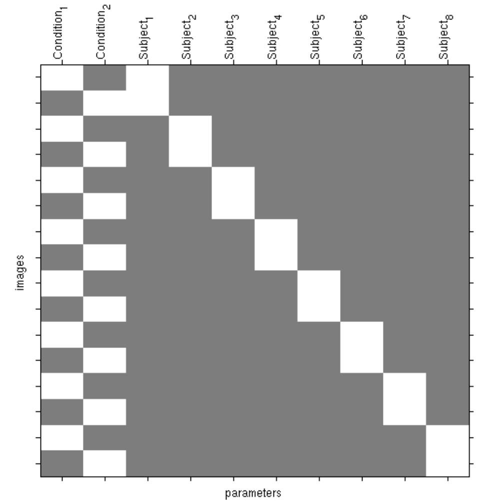
One-sample t-test



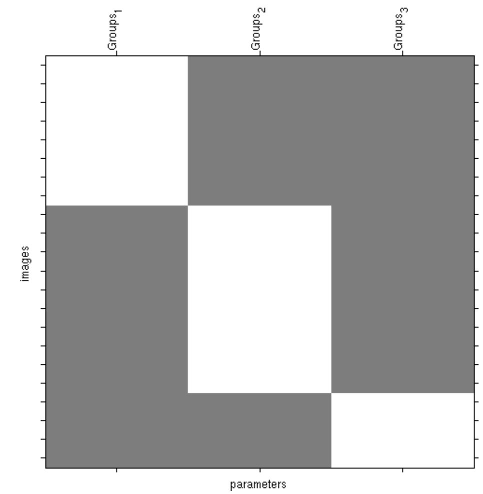
Two-sample t-test



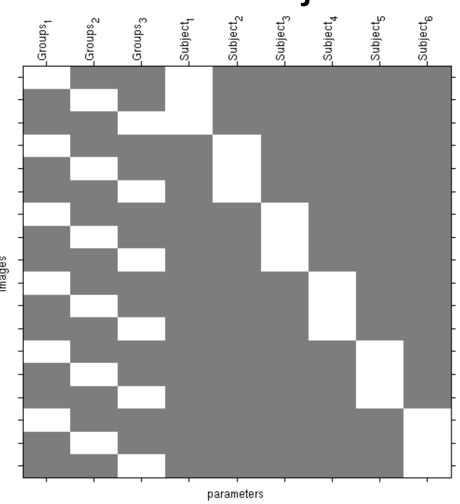
Paired t-test



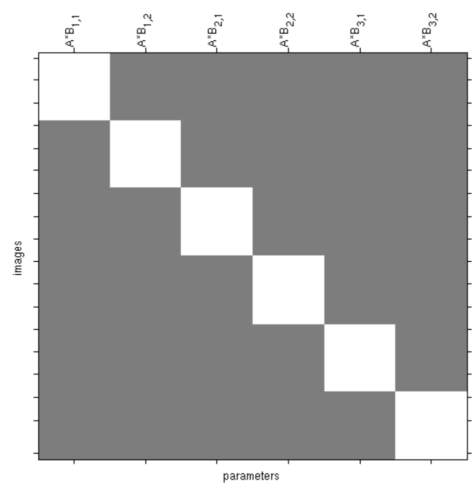
One-way ANOVA



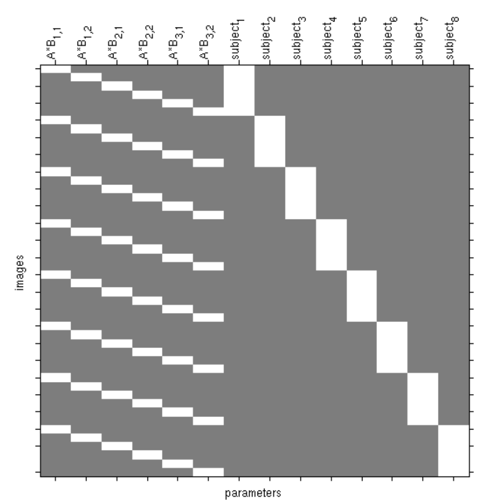
One-way ANOVA within-subject



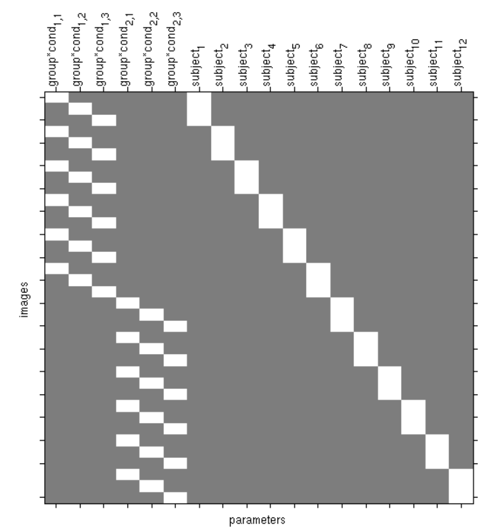
Full Factorial



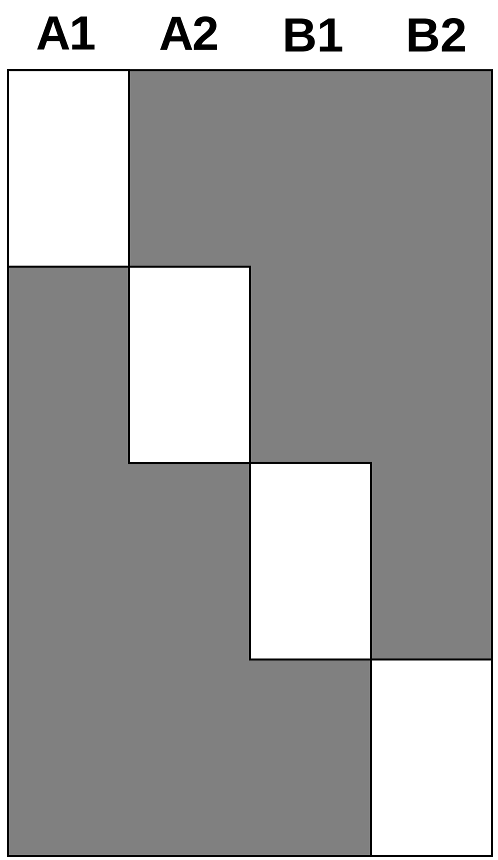
Flexible Factorial

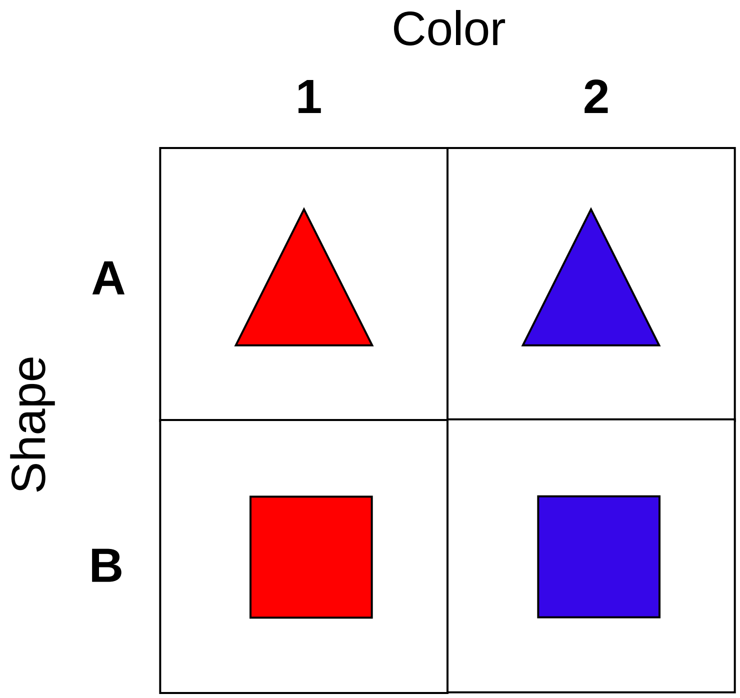


Flexible Factorial



2x2 factorial design





Main effect of Shape:

(A1+A2) – (B1+B2) : 1 1 -1 -1

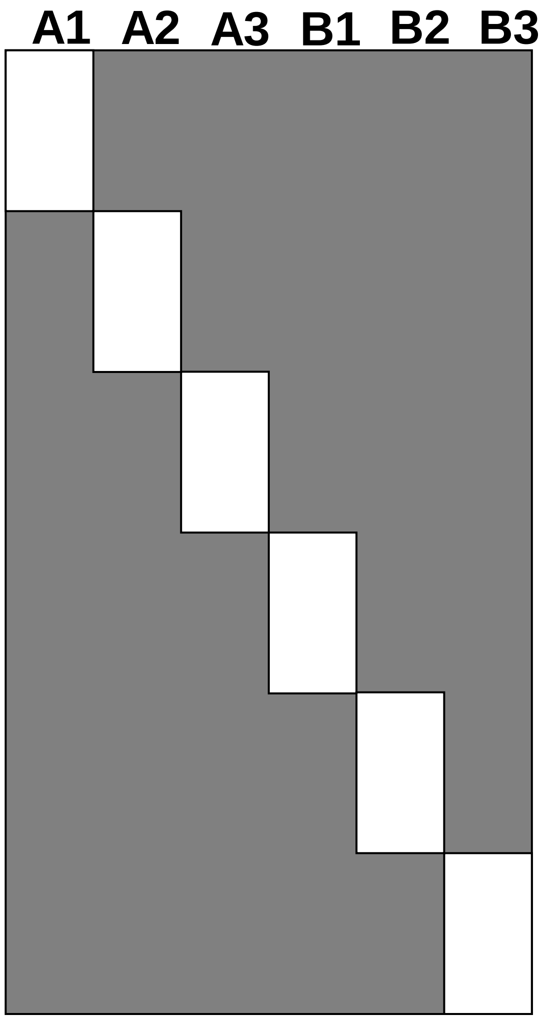
Main effect of Color:

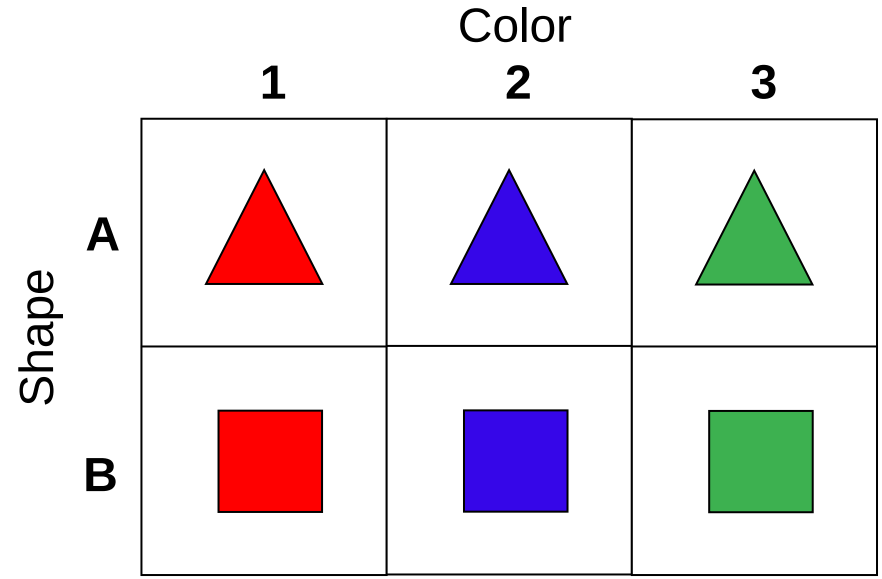
(A1+B1) – (A2+B2) : 1 -1 1 -1

Interaction Shape x Color:

(A1-B1) – (A2-B2) : 1 -1 -1 1

2x3 factorial design





Main effect of Shape:

(A1+A2+A3) – (B1+B2+B3) : 1 1 1 -1 -1 -1

Main effect of Color:

(A1+B1) – (A2+B2) : 1 -1 0 1 -1 0
(A2+B2) – (A3+B3) : 0 1 -1 0 1 -1
(A1+B1) – (A3+B3) : 1 0 -1 1 0 -1

Interaction Shape x Color:

(A1-B1) – (A2-B2) : 1 -1 0 -1 1 0
(A2-B2) – (A3-B3) : 0 1 -1 0 -1 1
(A1-B1) – (A3-B3) : 1 0 -1 -1 0 1