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CZECH BIOIMAGING
Imaging principles of life

Statistical analysis of fMRI data
General linear model

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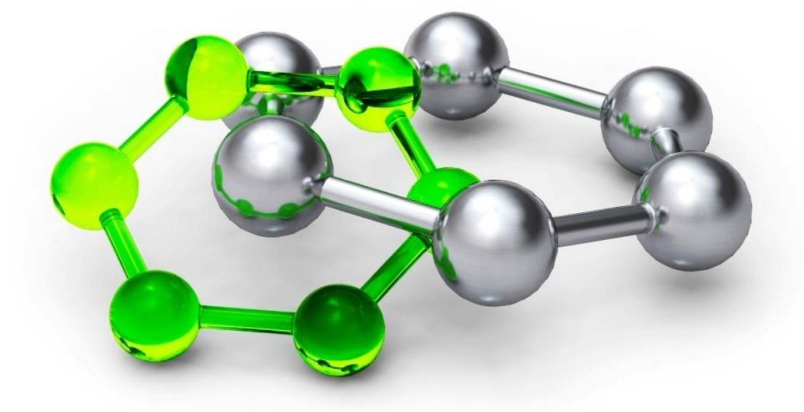

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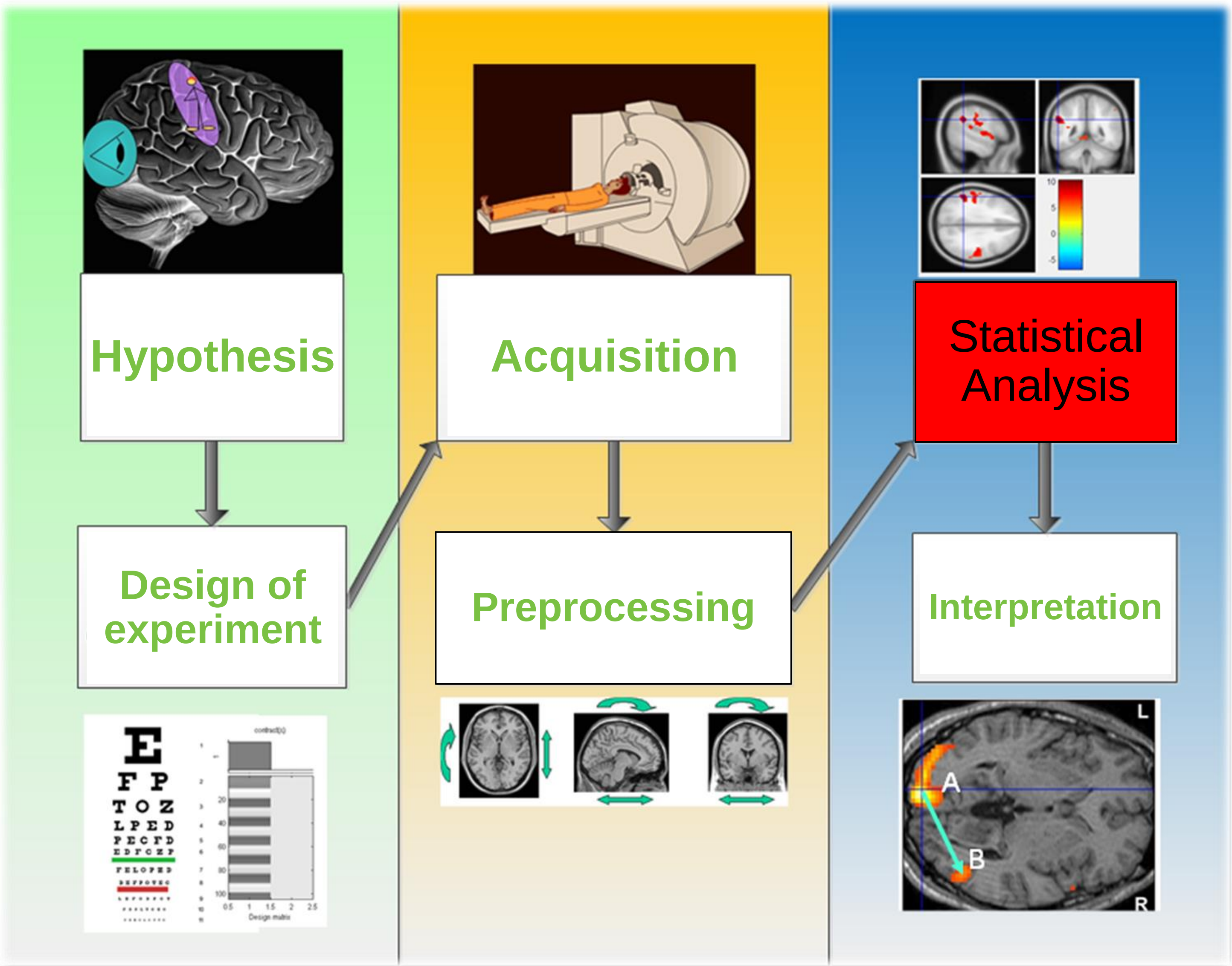
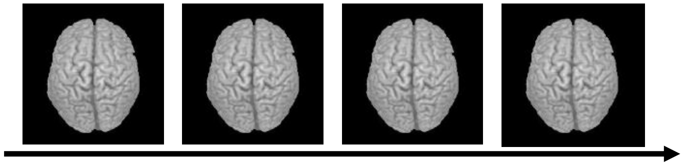
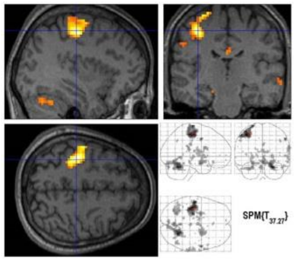

Hypothesis
Design of experiment
Acquisition
Preprocessing
Statistical Analysis
Interpretation

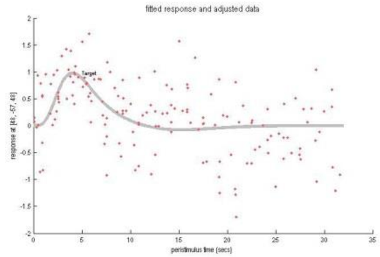
Statistical analysis

- Dataset is prepared



- Interests: Activations and context
  - Activation map
  - Table of activated areas
  - Connectivity
  - Shape of hemodynamic response

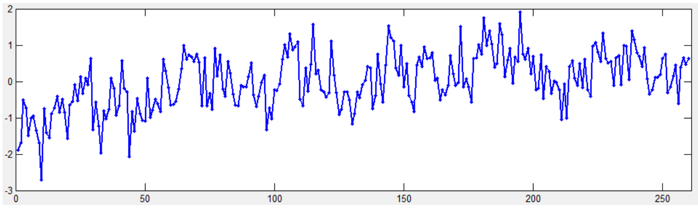




Statistics: ***p-values adjusted for search volume***

set-level		cluster-level			voxel-level					
p	c	$p_{corrected}$	k_E	$p_{uncorrected}$	$p_{FWE-corr}$	$p_{FDR-corr}$	T	$(Z_{\equiv})$	$p_{uncorrected}$	mm mm mm
0.000	**20**	**0.000**	**4225**	**0.000**	**0.000**	**0.000**	**8.44**	**Inf**	**0.000**	**-6 -6 6**
					0.000	0.000	8.34	Inf	0.000	45 27 -12
					0.000	0.000	8.02	Inf	0.000	0 -18 9
		0.000	**724**	**0.000**	**0.000**	**0.000**	**8.18**	**Inf**	**0.000**	**51 -54 48**
					0.000	0.000	7.70	7.58	0.000	57 -48 21
					0.038	0.000	4.68	4.65	0.000	33 -66 60
		0.000	**776**	**0.000**	**0.000**	**0.000**	**7.16**	**7.06**	**0.000**	**-57 -51 15**
					0.000	0.000	7.04	6.95	0.000	-54 -45 51

- Limitations
  - Baseline of the signal is unknown
  - Change (magnitude) of the signal caused by stimulation/activation is low



Statistical detection

- Model free methods
  - ICA/PCA

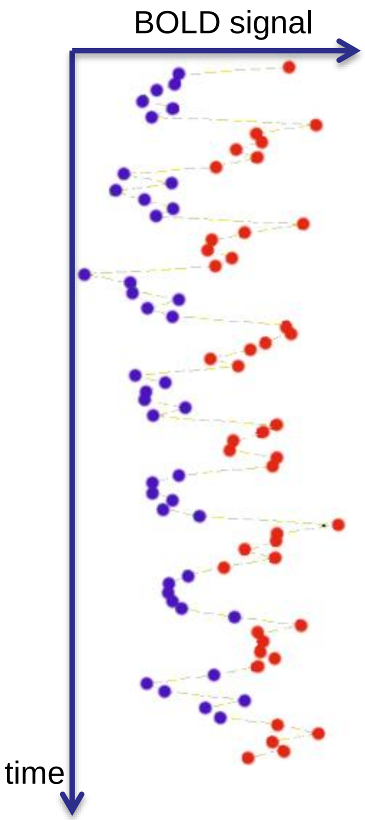
- Model based methods
  (assumption of defined shape of measured signal)
  - Correlation
  - t-test
  - ANOVA
  - AnCova
  - Linear regression
  - Multiple regression
  - F-test
  - etc…

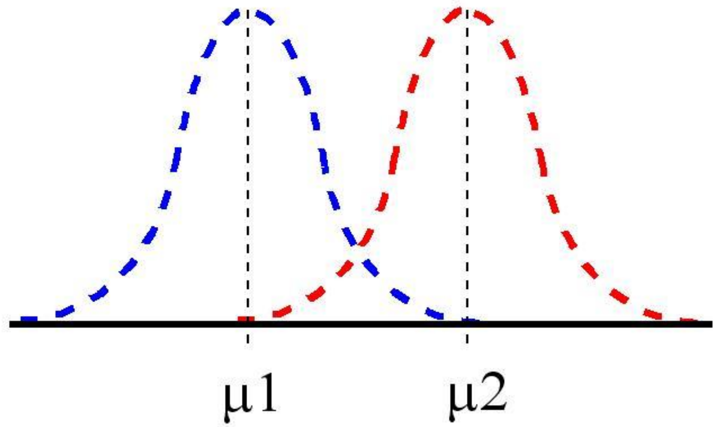
All single cases

GLM

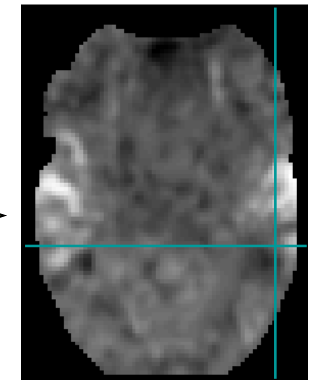
(General linear model)

Two-sample t-test



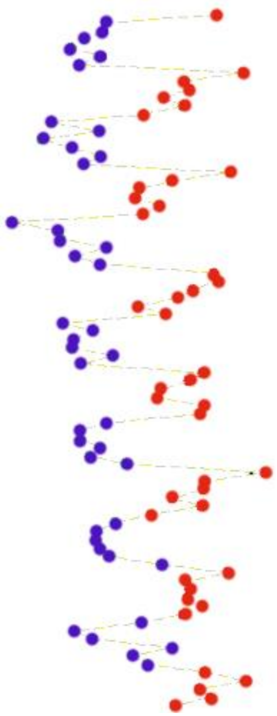


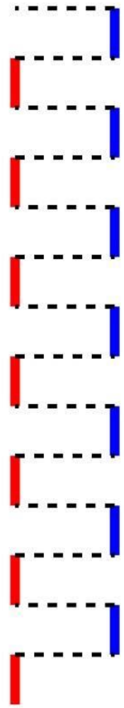
$$t = \frac{\overline{\mu_1} - \overline{\mu_2}}{\sqrt{\frac{s_f^2}{n_1} + \frac{s_f^2}{n_2}}}$$

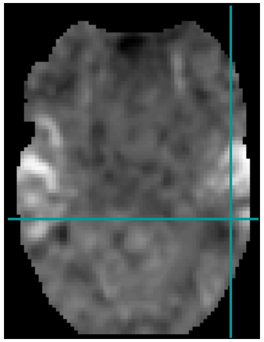


- Compares effect size to their standard deviation
- Basic t-test assumes independence in the data, therefore autocorrelation in time domain remains ignored

Linear regression

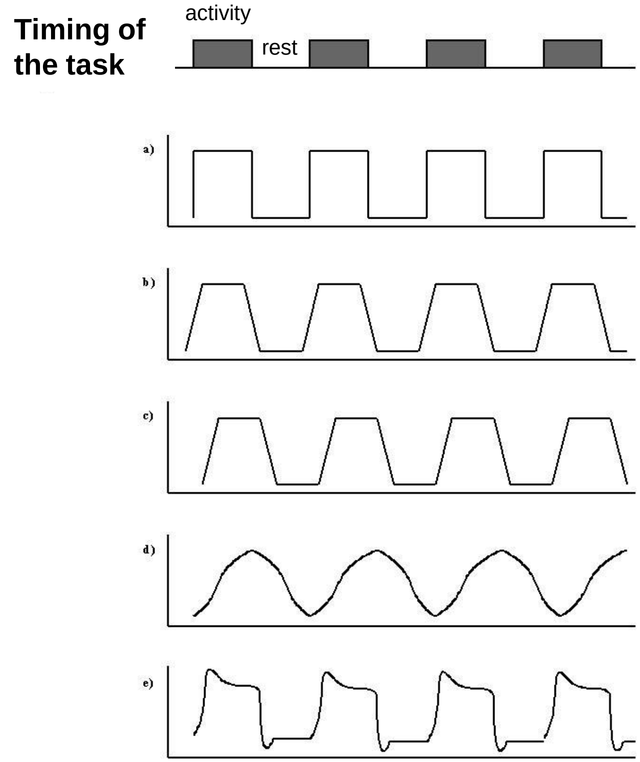


$= \mu + \alpha$  $+ \varepsilon$



t-statistics

$H_0: \alpha = 0$



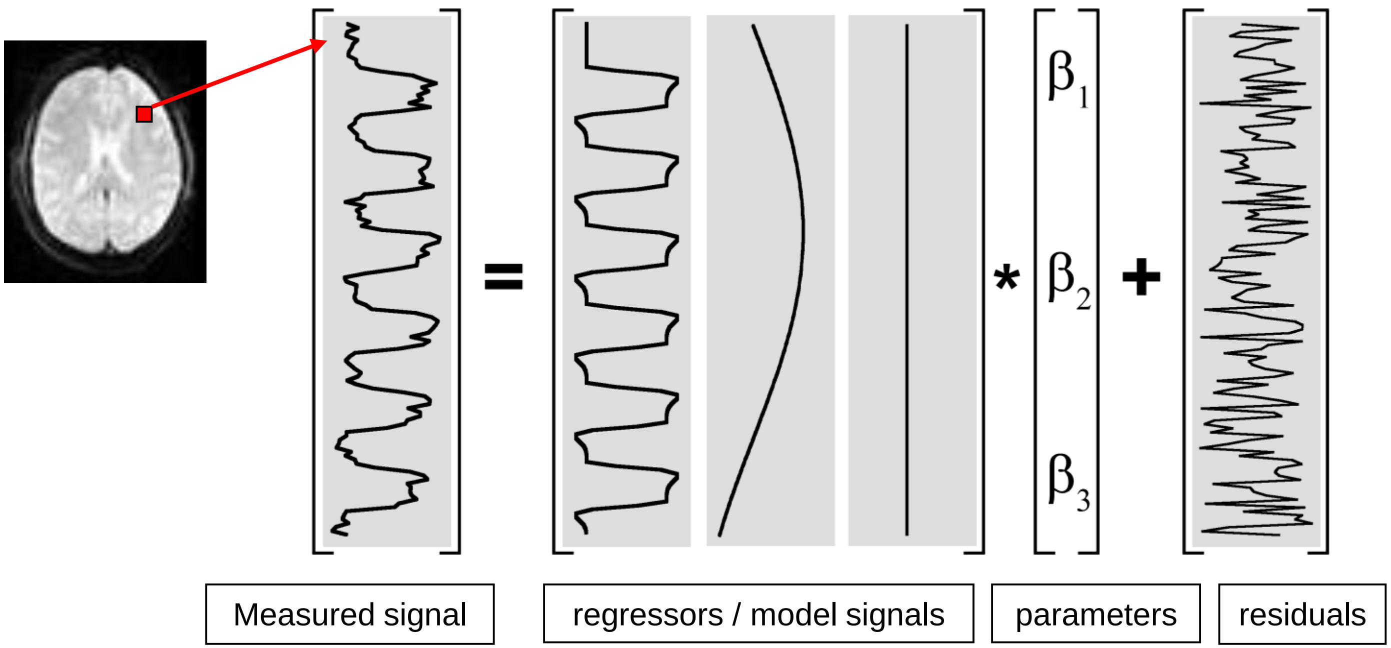
Different basis functions can be used for regression/correlation

General linear model (GLM)

- Flexible tool, incorporates several statistical techniques for exploration of relations between dependent and independent variables
- GLM assumes, that BOLD signal in defined element of the brain is linear combination of model signals

$$\mathbf{Y} = \mathbf{X}\boldsymbol{\beta} + \boldsymbol{\varepsilon}$$

$$\mathbf{Y}_i = \mathbf{x}_1 \cdot \beta_{1i} + \mathbf{x}_2 \cdot \beta_{2i} + \ldots\ldots + \mathbf{x}_n \cdot \beta_{ni} + \mathbf{e}_i$$

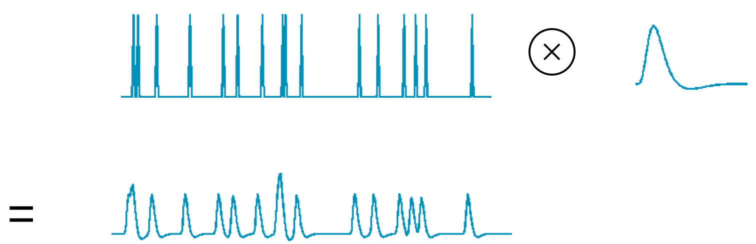


Regressors for fMRI GLM

- Signals $\mathbf{x}_i$ forms the columns of the design matrix

regressors modelling stimulation

Convolution of stimulation with HRF



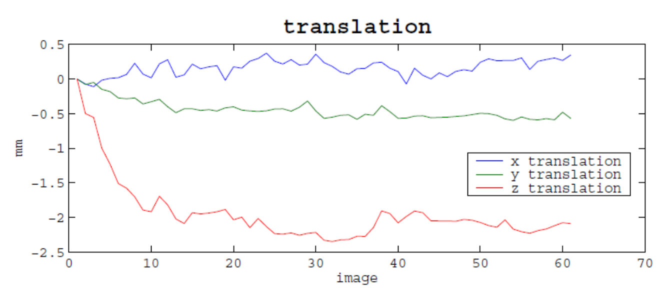
- variability of HRF shape

=> different HRF model

- time/disperse derivation of canonical HRF
- FIR
- Fourier expansion

regressors modelling artificial components of the signal

- e.g. artificial signal caused by movements (movements parameters estimated in ‚Realign‘ step)



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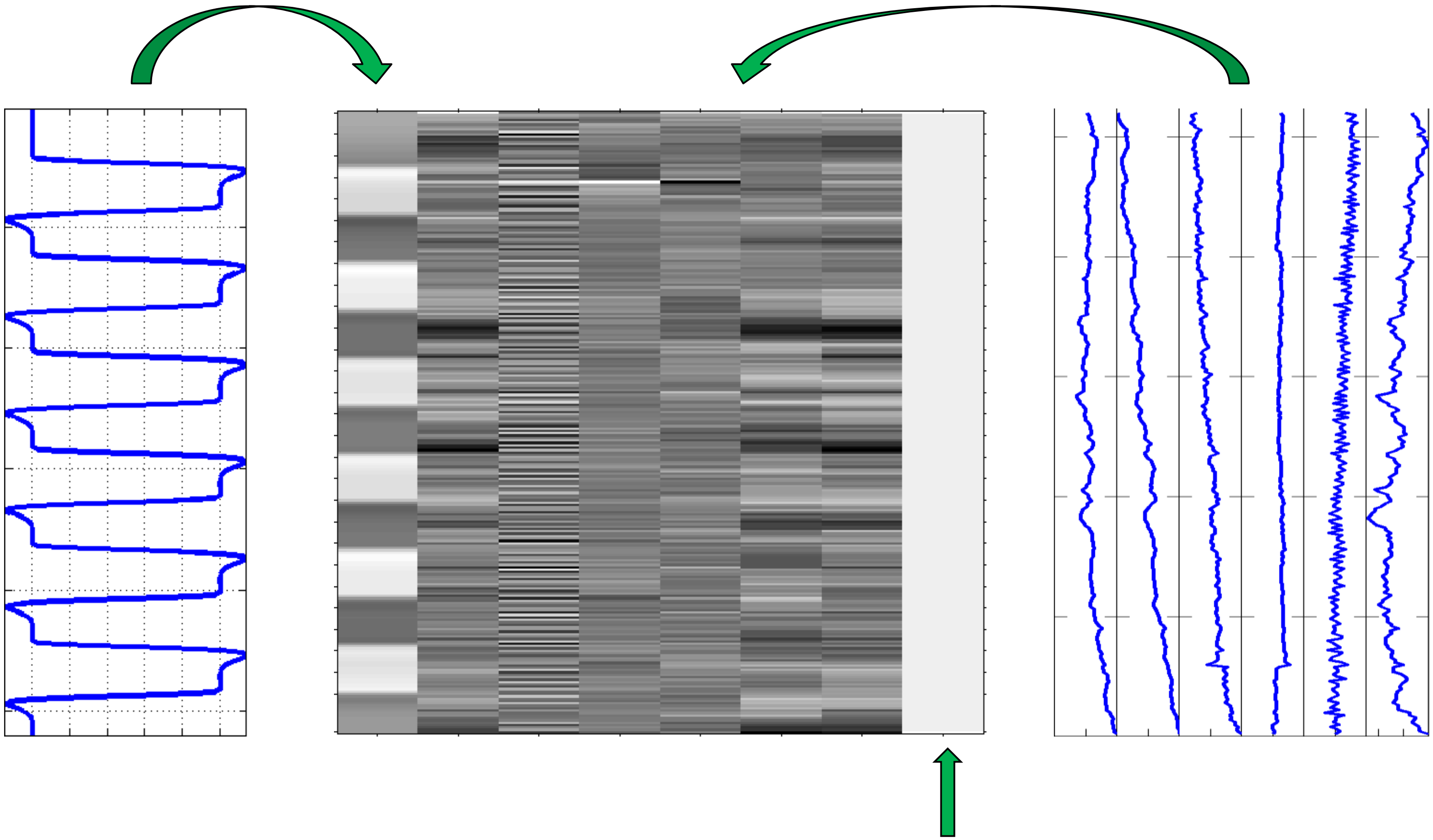
Design matrix in SPM tool

Model of response on stimulation

Models of artifacts– movement parameters



constant
(estimation of mean signal value)

GLM estimation

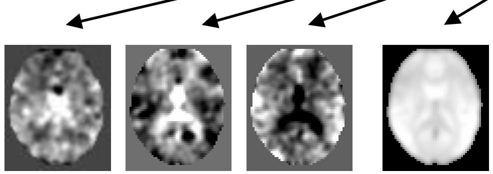
- GLM equation

$$Y = X^*\beta + \varepsilon$$

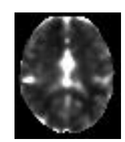
- Solution of the GLM equation is set of optimally estimated β weights, by minimisation of the residual signal ε

- Analytical solution using least squares method

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



Spatial maps of effects of particular regressors



Spatial map of standard deviations of the residual signal

Hypotheses

- Simplest case: **subject stimulated by single condition**

$$\mathbf{Y} = \mathbf{x}_1 \,.\, \beta_1 + \mathbf{e}$$

Null hypothesis: $\beta_1 = 0$

Alternative hypothesis: $|\beta_1| > 0$

- More complicated case: **subject stimulated by more conditions**

$$\mathbf{Y} = \mathbf{x}_1 \,.\, \beta_1 + \ldots + \mathbf{x}_n \,.\, \beta_n + \mathbf{e}$$

Null hypothesis: $c^T\beta_1 = 0$

Alternative hypothesis: $|c^T\beta_1| > 0$

- Possible to compare responses on particular stimulation conditions

Testing of hypotheses

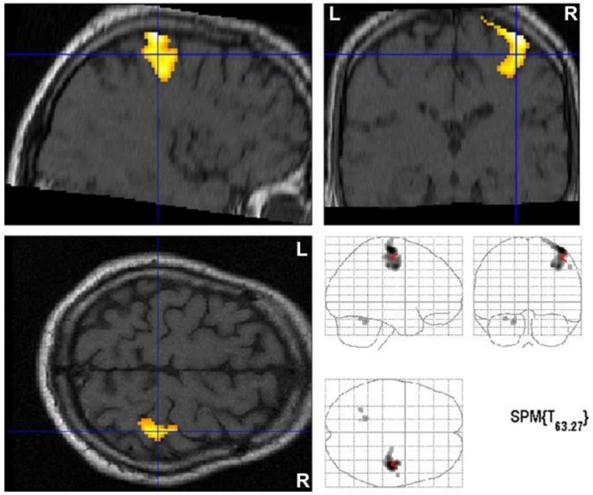
- Most common: T-test with β parameters

$$t = \frac{\mathbf{c}^{\mathrm{T}}\hat{\boldsymbol{\beta}}}{SE\left(\mathbf{c}^{\mathrm{T}}\hat{\boldsymbol{\beta}}\right)} = \frac{\mathbf{c}^{\mathrm{T}}\hat{\boldsymbol{\beta}}}{\sqrt{\sigma_R^2 \cdot \mathbf{c}^{\mathrm{T}}\left(\mathbf{X}^{\mathrm{T}}\mathbf{X}\right)^{-1}\mathbf{c}}}$$

- T is **directly** proportional to the size of tested effect
- T is **inversely** proportional to the standard deviation of residuals
- T – test is performed in every voxel in the brain
- T statistics has Student distribution, for df > 30 is nearing the normal distribution

Choice of the threshold of statistical significance *p* results to the threshold t-value T_{krit}.

Suprathreshold voxels labels parts of the brain, where is tested effect significant on defined significance level.



Right hand movement

$p < 0.001 \sim T_{krit} = 3.1$

Hypotheses testing

- F – test - comparison of two variants of the models as implemented in SPM
  - Model f .. full model, considers whole design matrix
  - Model c .. reduced model considering tested contrast

$$F \approx \frac{RSSc}{RSSf}$$

RSSf .. Standard deviation of residuals from full model

RSSc .. Standard deviation of residuals from tested part of the model

F statistics - chi-square distribution

- It can test, if reduced (contrast tested) model is able to explain significant part of variability in the data. E.g.:
  - If movement regressors explain significant part of the signal variability
  - Testing the effect of the stimulation, if we use more basis functions for HRF modeling

SPM option for contrasts

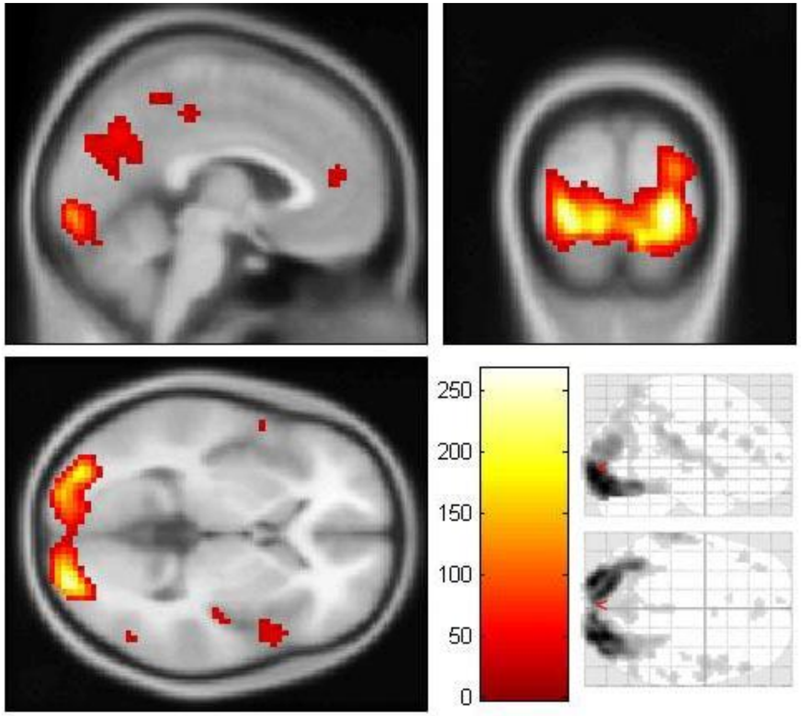
- **t-contrast**
  - Simple hypothesis – used to test linear combination of estimated parameters
  - In SPM one-sided test
  - SPM{t} as a result of t-contrast

- **F-contrast**
  - To test some set of hypotheses
  - In case of simple hypothesis $F = t^2$
  - Test is always one-sided (based on distribution), we are not able to recognize sign of effect
  - Suitable for overall effect of interest, for multiple basis function set (e.g.. FIR, hrf + derivatives)
  - SPM{F} as a result of F-contrast

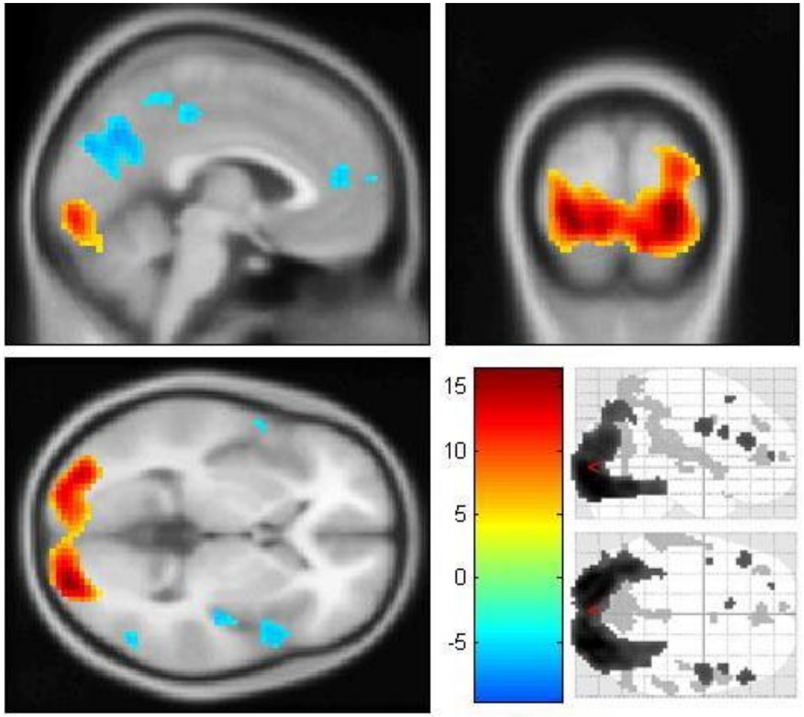
SPM{z} – statistical parametric map with z-values (Normal/Gauss distribution). It is possible to calculate z-values from t-values

SPM option for contrasts

F-contrast, $p < 0.05$ FWE corr.



t-contrast $p < 0.05$ FWE corr.



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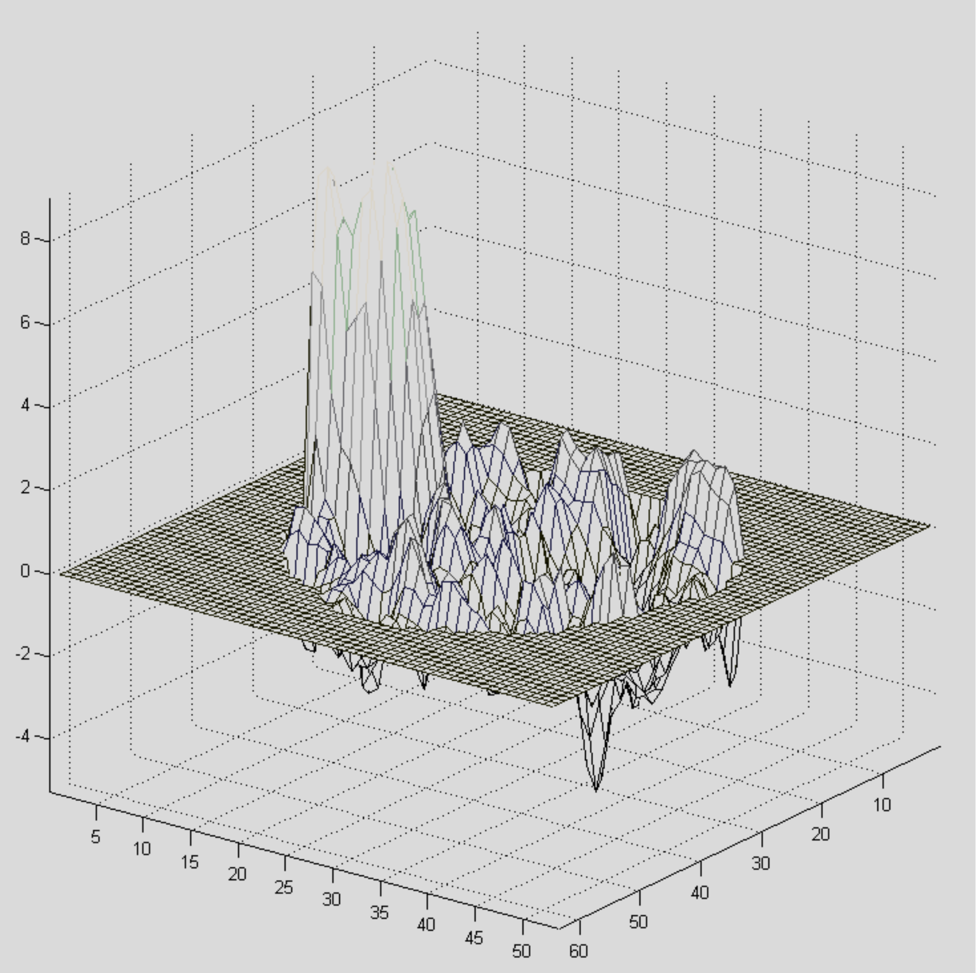
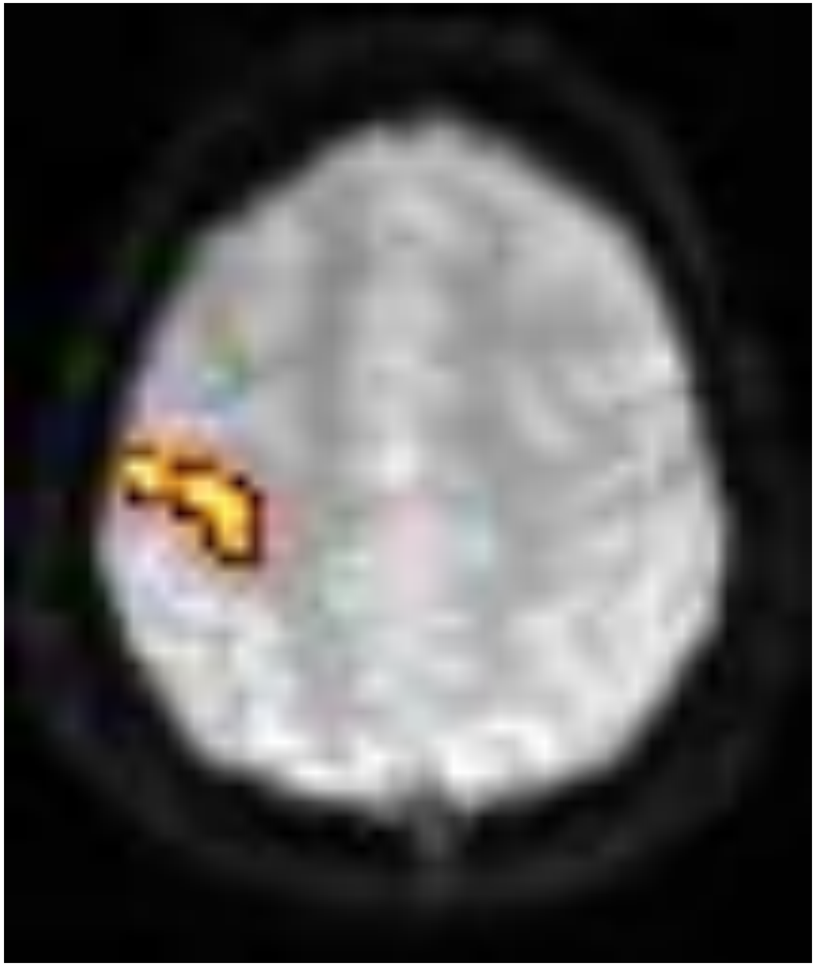
Thresholding of the SPM





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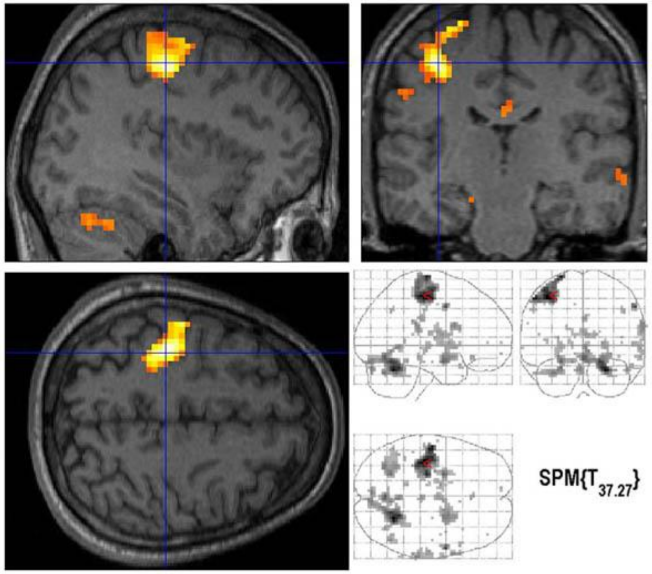
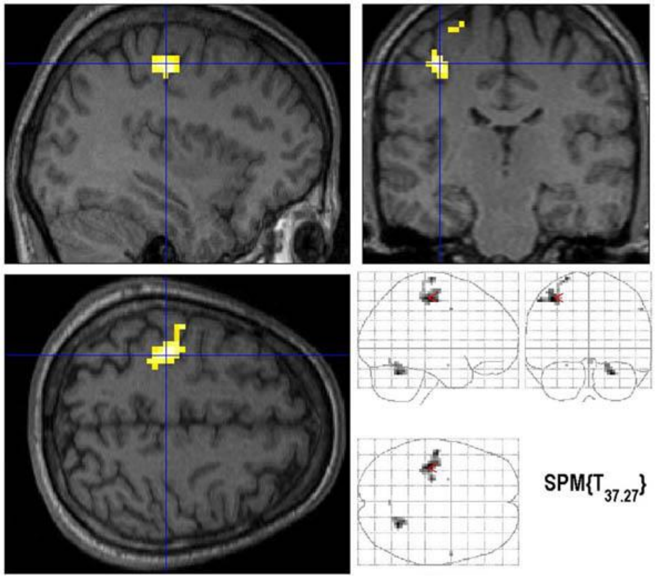
Multiple comparisons correction

- **Uncorrected** (significance level suitable for one vx)
  - Displaying *n* results, probability of false positive result i *n* times higher
  - Usually p < 0,001



- **Corrected** (significance level suitable for whole dataset)
  - **FWE** (family wise error)
    - Bonferroni correction (independence in data)
    - Theory of Gauss random fields (smoothness of data assumed)
  - **FDR** (false discovery rate)
    - Usually p < 0,05



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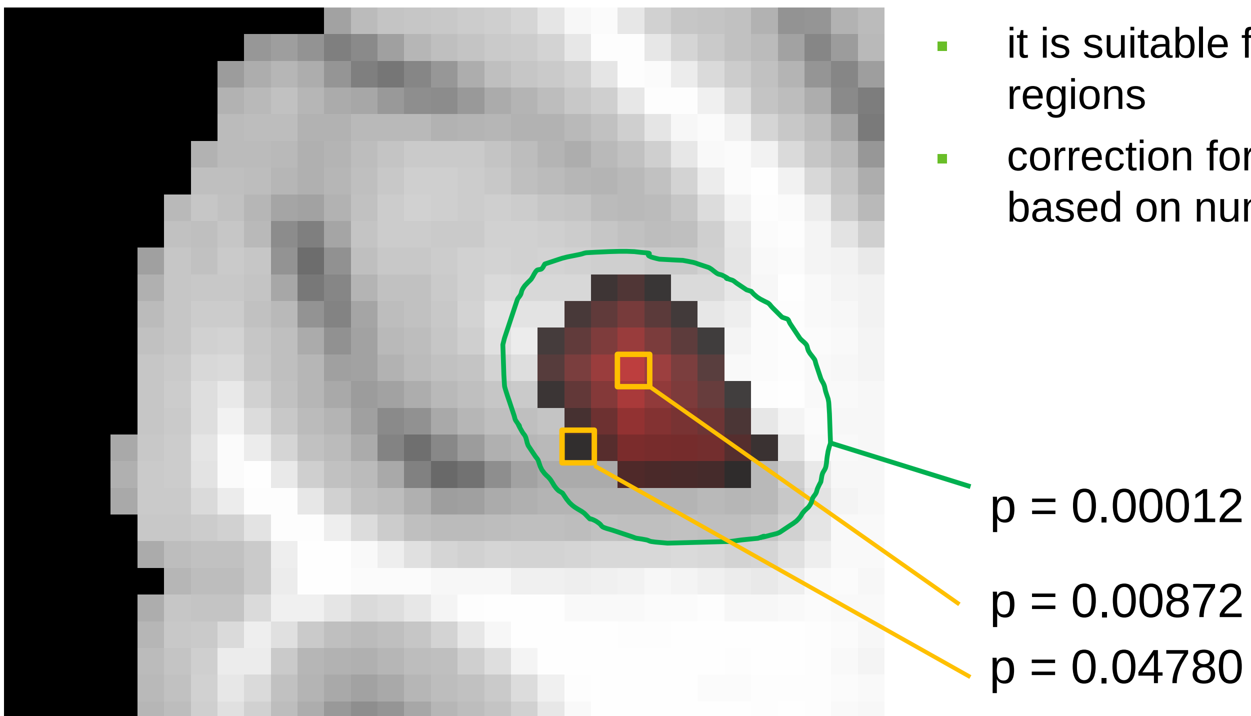
Statistical inference

Voxel-level inference

- p-values for each voxel
- these p-values are corrected for multiple testing
- more significant results are required to reach corrected threshold

Cluster level inference

- p-values for individual clusters
- it is necessary to define „initial cut“ (voxel-level threshold) to define clusters
- cluster p-value depends on number of voxels within specific cluster
- it is suitable for data with large active regions
- correction for multiple comparison is based on number of clusters



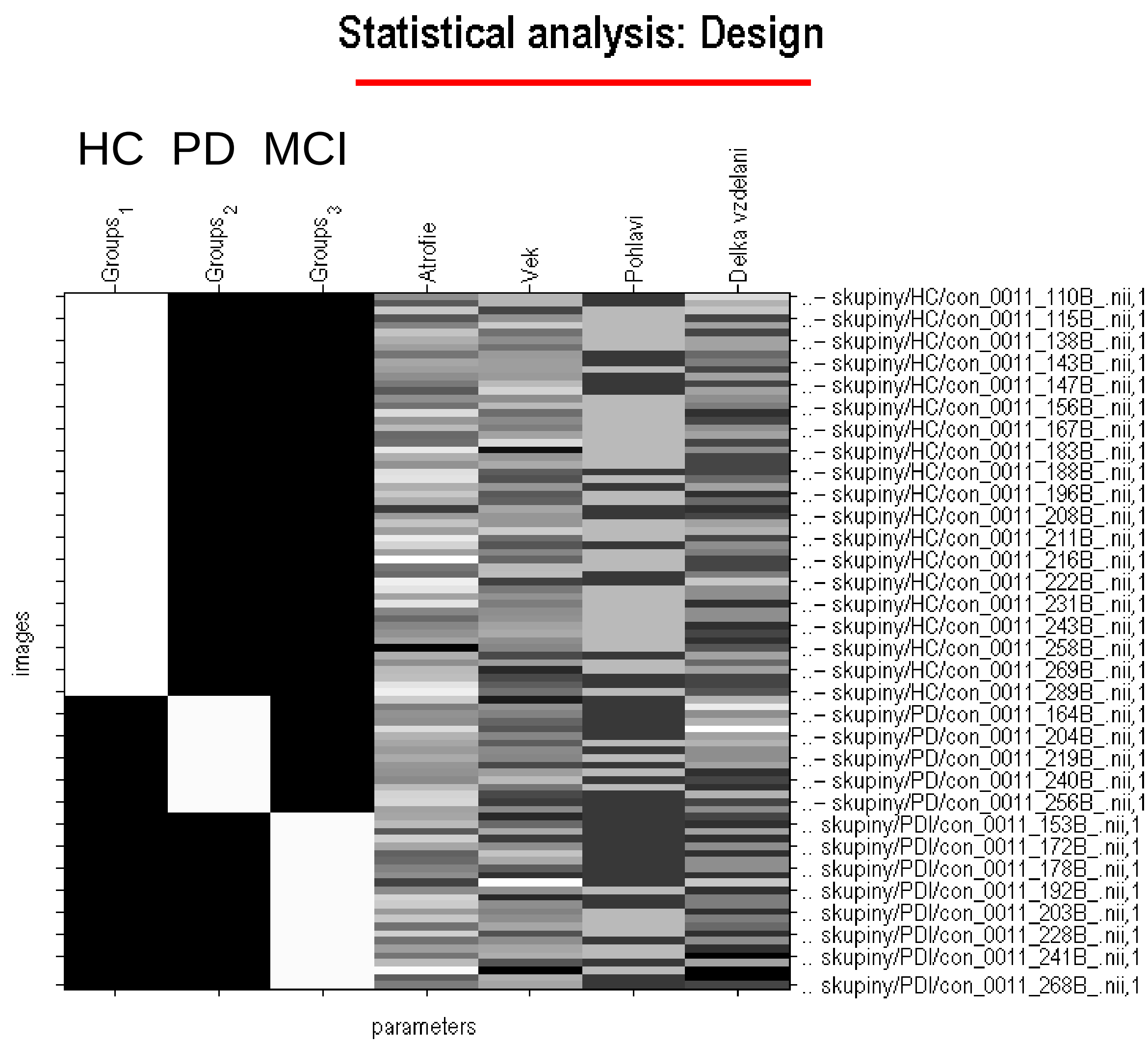
Group comparisons

- Mean activation in the group
- Difference of activations between two groups
- Difference of activations before and after treatment

- Attitudes:
  - **„Fixed effects“ analysis**
    - Compares only variability between scans of all subjects in group
    - Results cannot be generalized on whole population
    - Small amount of subjects is sufficient (3 to 8)
  - **„Random effects“ analysis**
    - Compares variability between particular subjects
    - Requests results of the single subjects analyses
    - Results can be generalized on target population
    - Suitable for larger amounts of subjects (10 and more)

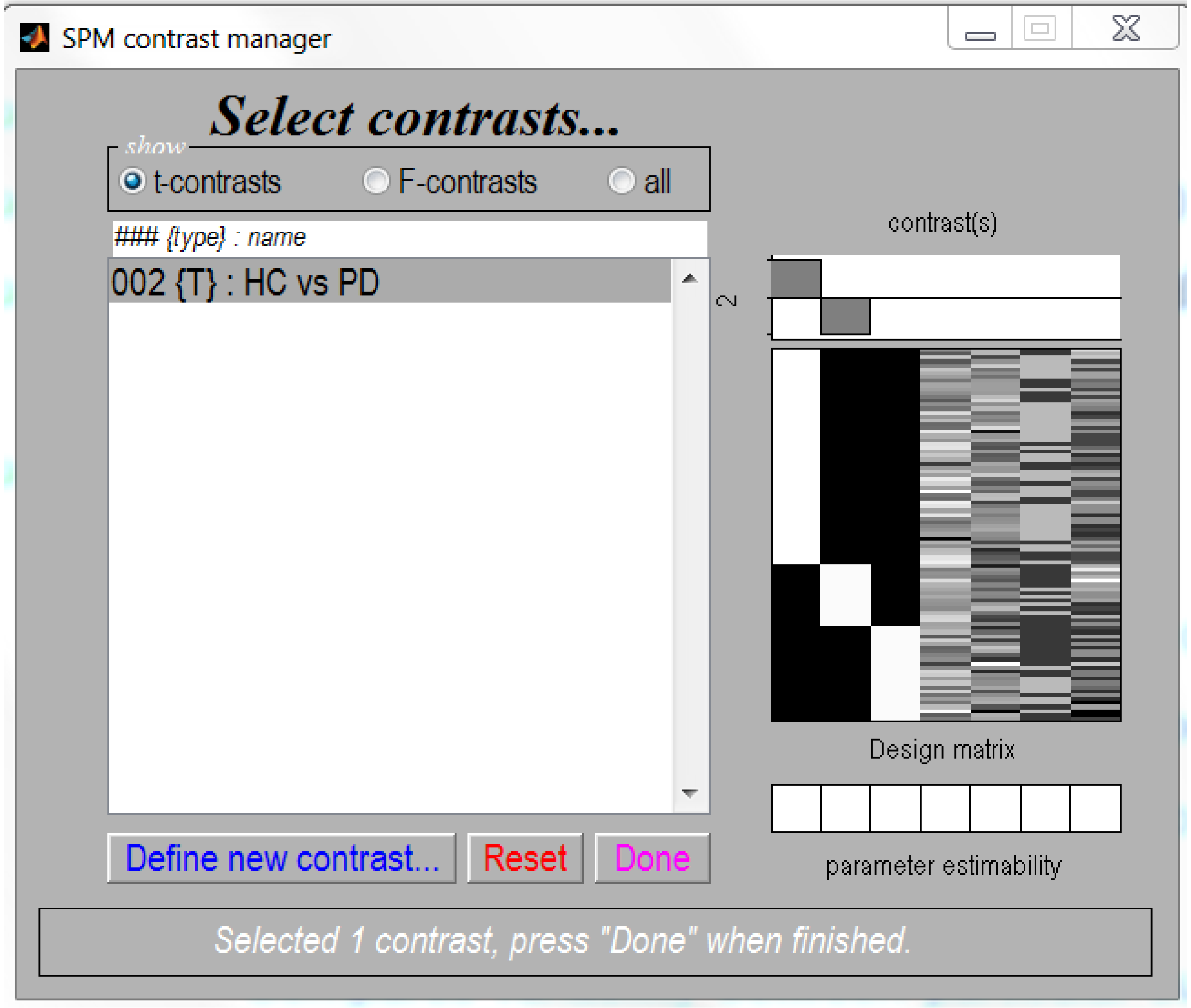
Group comparisons – SPM example

- Example: Difference of activations between two groups



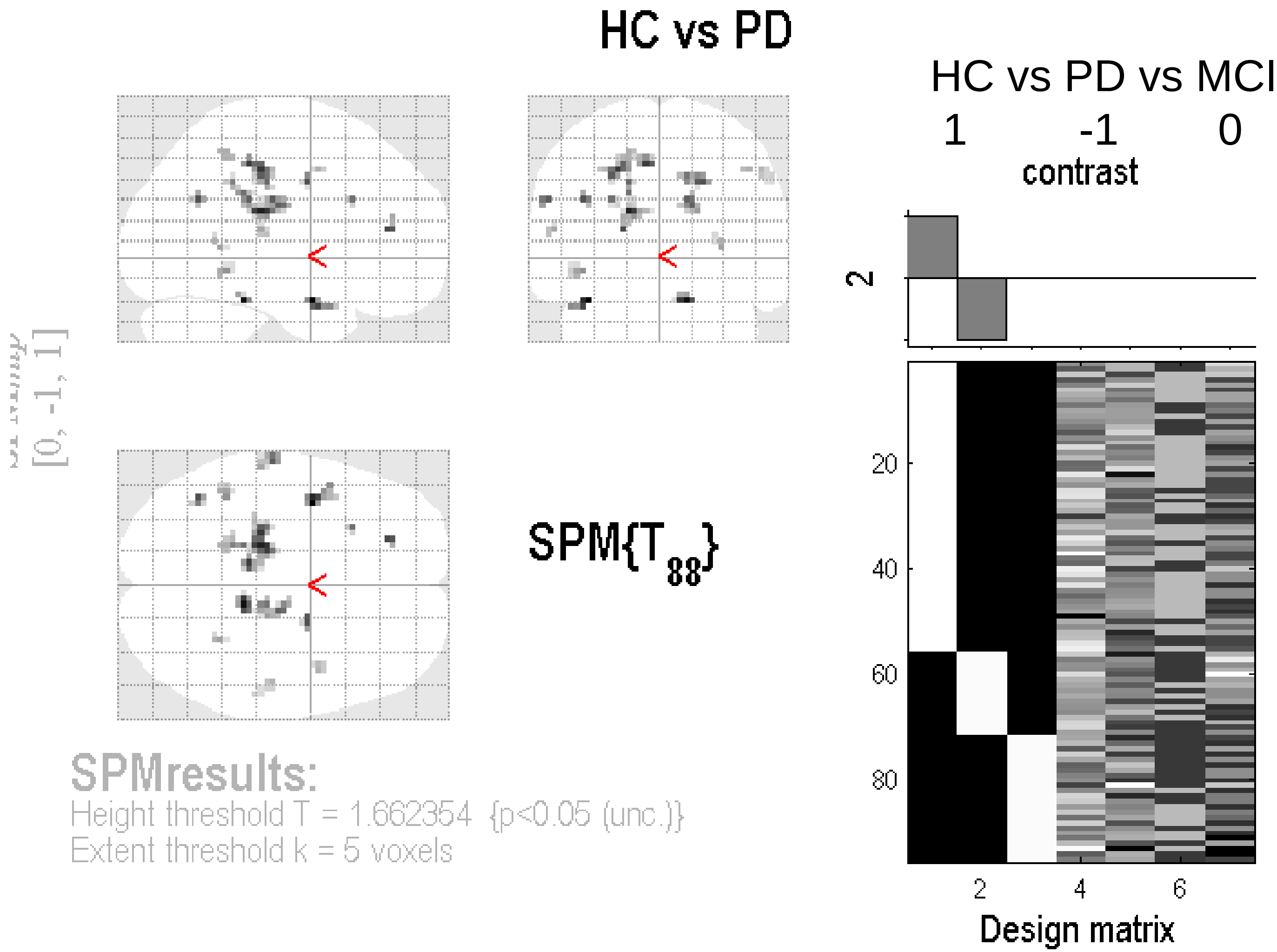
Group comparisons – SPM example

- Example: Difference of activations between two groups



Group comparisons – SPM example

- Example: Difference of activations between two groups



Group comparisons – SPM example

- Example: Difference of activations between two groups

Statistical values for cluster-level inference

voxel-level inference

Statistics: ***p-values adjusted for search volume***

set-level		cluster-level			voxel-level					mm mm mm		
p	c	$p_{corrected}$	k_E	$p_{uncorrected}$	$p_{FWE-corr}$	$p_{FDR-corr}$	T	$(Z_{\equiv})$	$p_{uncorrected}$			
0.000	**20**	**0.000**	**4225**	**0.000**	**0.000**	**0.000**	**8.44**	**Inf**	**0.000**	**-6**	**-6**	**6**
					0.000	0.000	8.34	Inf	0.000	45	27	-12
					0.000	0.000	8.02	Inf	0.000	0	-18	9
		0.000	**724**	**0.000**	**0.000**	**0.000**	**8.18**	**Inf**	**0.000**	**51**	**-54**	**48**
					0.000	0.000	7.70	7.58	0.000	57	-48	21
					0.038	0.000	4.68	4.65	0.000	33	-66	60
		0.000	**776**	**0.000**	**0.000**	**0.000**	**7.16**	**7.06**	**0.000**	**-57**	**-51**	**15**
					0.000	0.000	7.04	6.95	0.000	-54	-45	51
					0.000	0.000	6.70	6.62	0.000	-51	-54	33
		0.000	**198**	**0.000**	**0.000**	**0.000**	**6.48**	**6.41**	**0.000**	**0**	**-27**	**36**
					0.080	0.000	4.50	4.47	0.000	0	-42	18
		0.023	**91**	**0.003**	**0.000**	**0.000**	**6.23**	**6.17**	**0.000**	**-15**	**-60**	**36**
					0.983	0.004	3.33	3.32	0.000	0	-54	30
		0.015	**102**	**0.002**	**0.000**	**0.000**	**6.18**	**6.12**	**0.000**	**57**	**-27**	**-9**
					0.512	0.001	3.91	3.89	0.000	60	-36	-18
		0.024	**90**	**0.003**	**0.000**	**0.000**	**5.97**	**5.92**	**0.000**	**-30**	**63**	**-3**
		0.125	**53**	**0.018**	**0.000**	**0.000**	**5.80**	**5.75**	**0.000**	**-36**	**51**	**15**
		0.035	**81**	**0.005**	**0.000**	**0.000**	**5.76**	**5.71**	**0.000**	**18**	**-60**	**39**
		0.000	**226**	**0.000**	**0.023**	**0.000**	**4.80**	**4.77**	**0.000**	**0**	**-69**	**-15**
					0.066	0.000	4.55	4.52	0.000	0	-51	-18

table shows 3 local maxima more than 8.0mm apart

Height threshold: T = 3.10, p = 0.001 (0.999) {p<0.001 (unc.)}
Extent threshold: k = 0 voxels, p = 1.000 (0.999)
Expected voxels per cluster, <k> = 8.741
Expected number of clusters, <c> = 7.42
Expected false discovery rate, <= 0.01

Degrees of freedom = [1.0, 936.0]
FWHM = 12.4 12.6 12.7 mm mm mm; 4.1 4.2 4.2 {voxels};
Volume: 1533735 = 56805 voxels = 684.4 resels
Voxel size: 3.0 3.0 3.0 mm mm mm; (resel = 74.33 voxels)
Page 1

Coordinates of local maxima in cluster

Coordinates of other local maxima in cluster

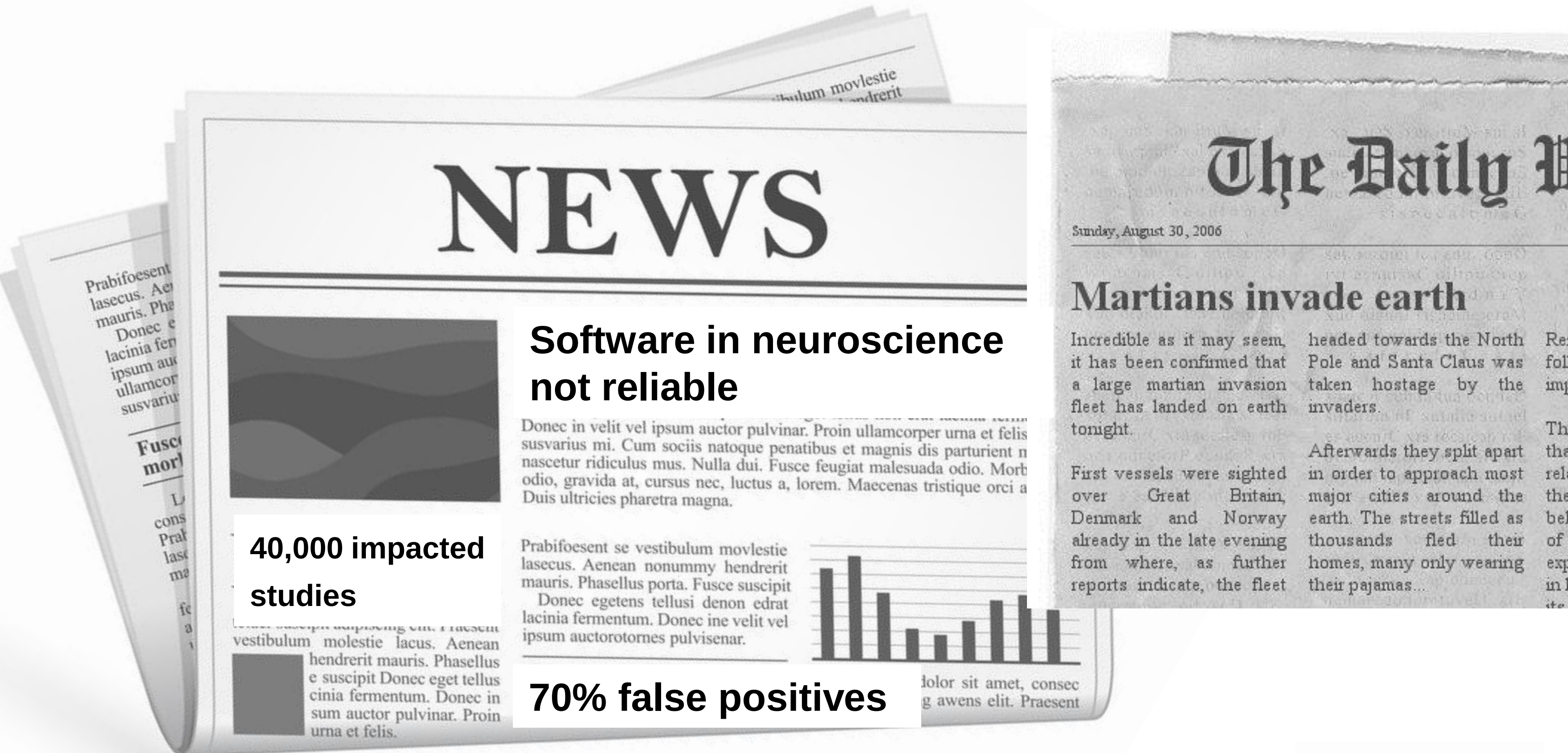
Additional information – degrees of freedom, resolution, resels, etc.

Cluster failure: Why fMRI inferences for spatial extent have inflated false-positive rates (Eklund, 2016)

- Focus on multiple comparisons problem, resting state data
  - FWE for voxelwise approach– safe
  - FWE Clusterwise approach – sometimes invalid, depends on method and tool
- Cluster-defining threshold of p=0.001 has better control of FWE than p=0.01 for SPM, FSL and AFNI
- Problem in AFNI - version of 3dClustSim has a flaw that increases the FWE
- http://www.ohbmbrainmappingblog.com/blog/keep-calm-and-scan-on

Cluster failure: Why fMRI inferences for spatial extent have inflated false-positive rates (Eklund, 2016)

- Media attention has been based on a misunderstanding and an ‘inflated’ interpretation of the results:



Cluster failure: Why fMRI inferences for spatial extent have inflated false-positive rates (Eklund, 2016)

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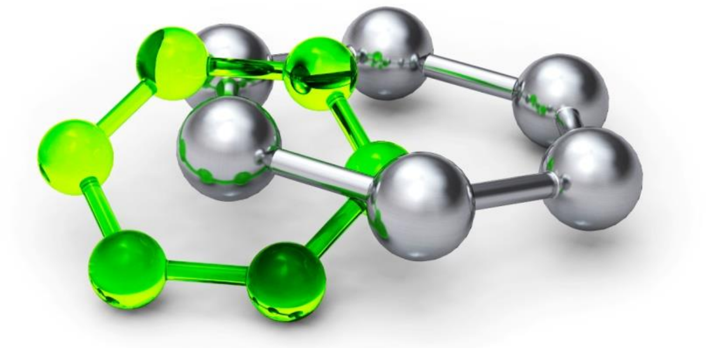

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