Development of Complex Curricula for Molecular Bionics and Infobionics Programs within a consortial* framework**

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**Molekuláris bionika és Infobionika Szakok tananyagának komplex fejlesztése konzorciumi keretben

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BIOMEDICAL IMAGING

(Orvosbiológiai képalkotás)

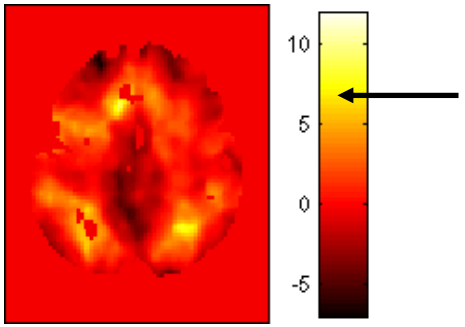
fMRI – Advanced Statistical Analysis

(fMRI – Haladó statisztikai elemzési módszerek)

VIKTOR GÁL, ÉVA BANKÓ

The Multiple Comparison Problem

- doing t-test for every voxel (~100.000) separately will hugely inflate the error-rate (i.e. the number of false positives)
- if α=0.05 $\Rightarrow$ 5,000 false positive!



Where is the significance threshold?

- therefore one needs to correct for this problem of multiple comparison:
  - Bonferroni correction
  - False Discovery Rate (FDR)
  - Familywise Error Rate (FWE)

Bonferroni correction

- if all voxels were independent of each other, than simply:

$$p_{\text{Bonf}} = p_{\text{uncorr}} / \text{N} \qquad \text{where N is the number of voxels}$$

- however, voxels are *not* independent (e.g. neighboring voxels show different pattern, drift affects all of them equally)
- thus, a very conservative correction
- we need to account for the dependency structure between the test statistics

Familywise Error-rate (FWE)

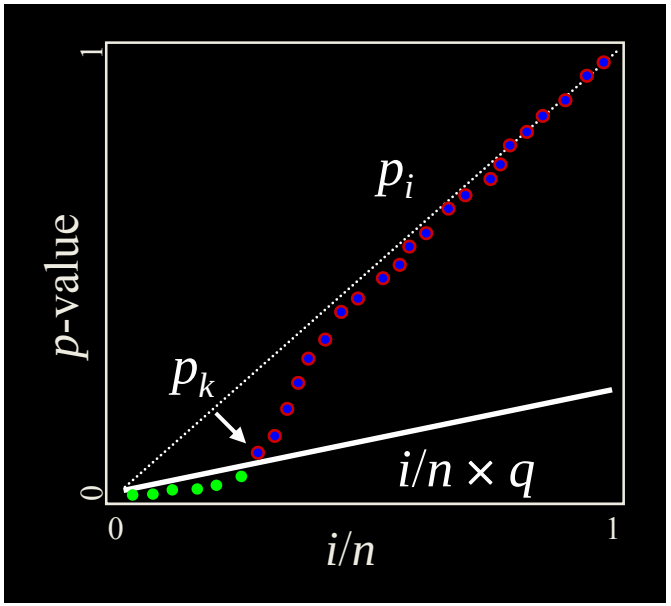
- controls the probability of making even one error (or more)

False Discovery Rate (FDR)

- FDR is the proportion of false discoveries among the discoveries (rejected hypothesis)
- to calculate: order the *p*-values $p_1 \leq p_2 \leq \ldots \leq p_n$
- for a desired FDR level *q*:

  let $$k = \max\{i : p_i \leq (i/n)q\}$$

  reject: $$H^0_{(1)}, H^0_{(2)}, \ldots, H^0_{(k)}$$



- If no such *k* exists reject none (i.e. nothing is significant)

Region-of-Interest (ROI) Analysis

… another way out without statistical tweaks

- limit the analysis to a set of voxels comprising an area (i.e. region of interest) and then average across them to get a parameter estimate
- dimension reduction: the number of predefined ROIs are usually <10
- voxels need to be selected individually, based on an independent contrast (e.g. localizer) to insure there is no manipulation of chosen voxels showing the desired effect
- desirable if the location of the ROI has high individual variance
- how to select voxels (for more details see Tracey et al., 2008, NeuroImage):
  - select all active voxels in a given independent contrast individually (what is active? → ~$p_{uncorrected}<10^{-4}$)
  - select the peak activity (i.e. most active voxel) in the cluster and include all voxels in a volume (sphere, cube) around it

Caveats of classical parametric statistics in fMRI

- fMRI voxels ~ dense 3D matrix of low quality EEG electrodes
- Distribution of error, parameters?
- Time and spatial interdependence -> degrees of freedom (DOF)?
- Correction for multiple univariate stats

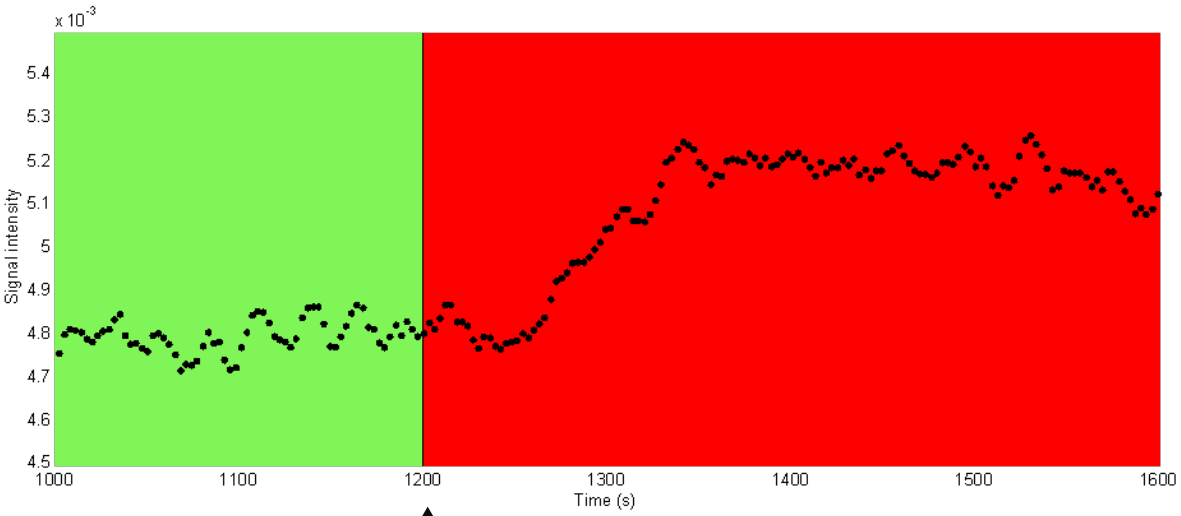
Solution:

- Nonparametric (resampling, bootstrap) methods
- MVPA approach; MVPA & nonparametric analysis

Validation?

Statistical assumptions (fixed-effect analysis):

Acquired datapoints are independent in time



Stimulation

What is our degree of freedom?

- Theoretically: ~ Number of datapoints – Number of predictors
- Can be adjusted by analyzing/modelling of nonsphericity
  - autocorrelation structure
  - AR(1) , ARMA(1,1): AR + white noise
  - drift correction, high pass filtering
  - limited validity

Still it is a question:

- whether an experiment consisting of 1 trial (stimulus) and 1000 data points (very long baseline) is equivalent to an experiment consisting of 500 trials with 2 data points?

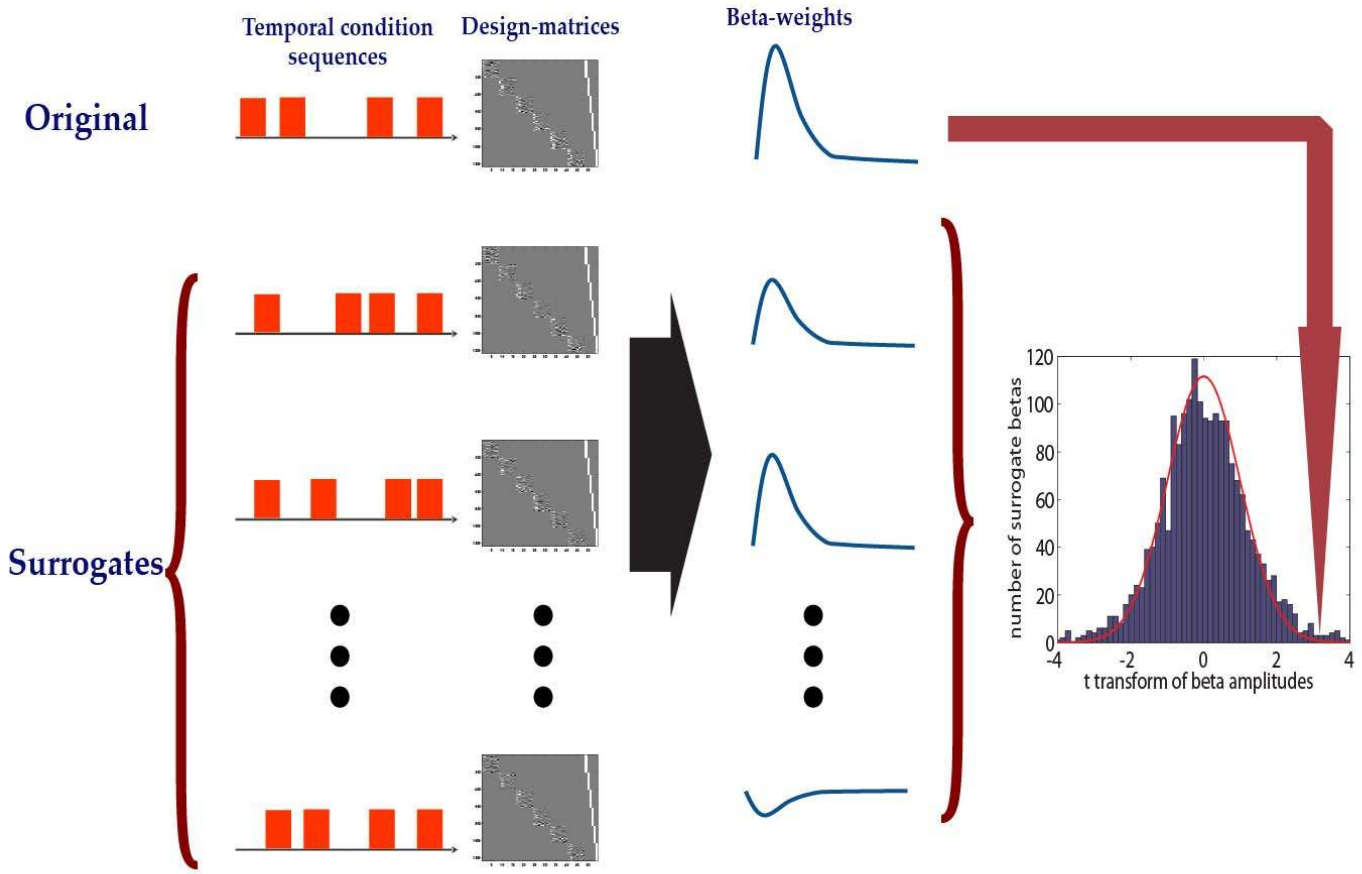
Acquired images of a response to a stimulus are not independent!

Nonparametric methods: sampling statistics

- Generation of surrogate data
  - Surrogates are to be „similar” to the original in any relevant aspect
  - Surrogate stats can be computed via
    - Experiments without stimulation
    - Reshuffling (or decomposing and reshuffling) data points
    - Random predictor time-courses in the design matrix
- Sampling statistics
  - Statistical characterization of the original data and the surrogates
- Decision making
  - Based on rank order of the original

Examples: randomization test, bootstrapping

Biomedical Imaging: fMRI – Advanced Statistical Analysis



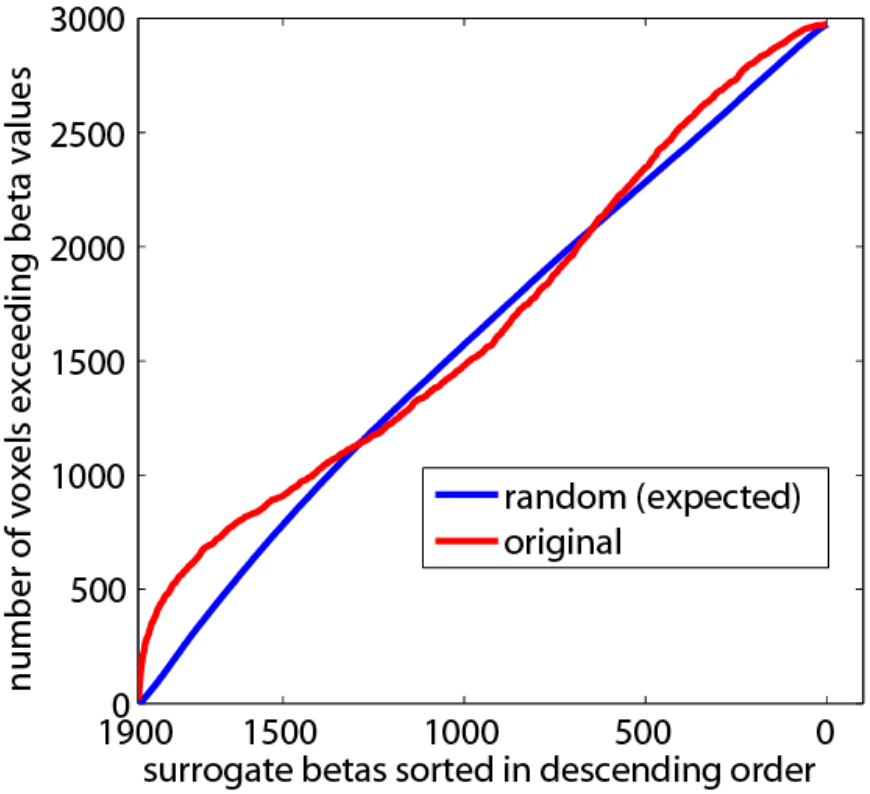
Recipe

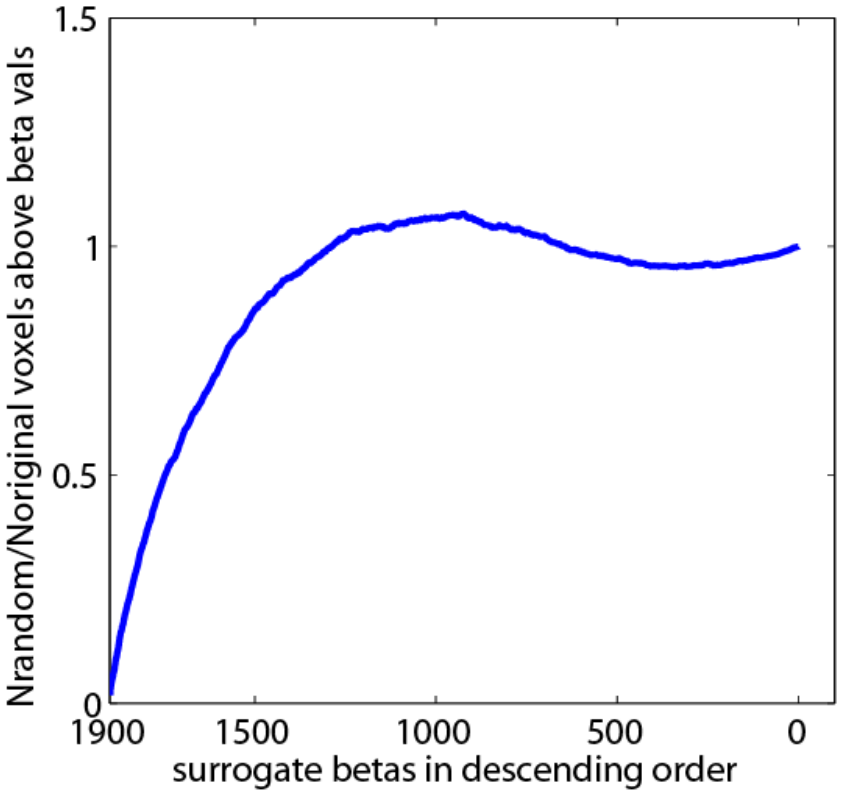
- pseudo-randomize the design matrix (DM)
- estimate parameters from false DM
- repeating these steps we can obtain a parameter distribution centered around 0, which reflect random effects
- compare p estimated from the actual DM to this distribution
- a similar procedure can be used to statistically evaluate the difference between the parameter estimates of two condition
- The same distributions enable an effective correction for multiple comparisons
  - Count the average number of voxels above different threshold with false DM and compare it to the values based on the original DM

„Bootstrap” FDR

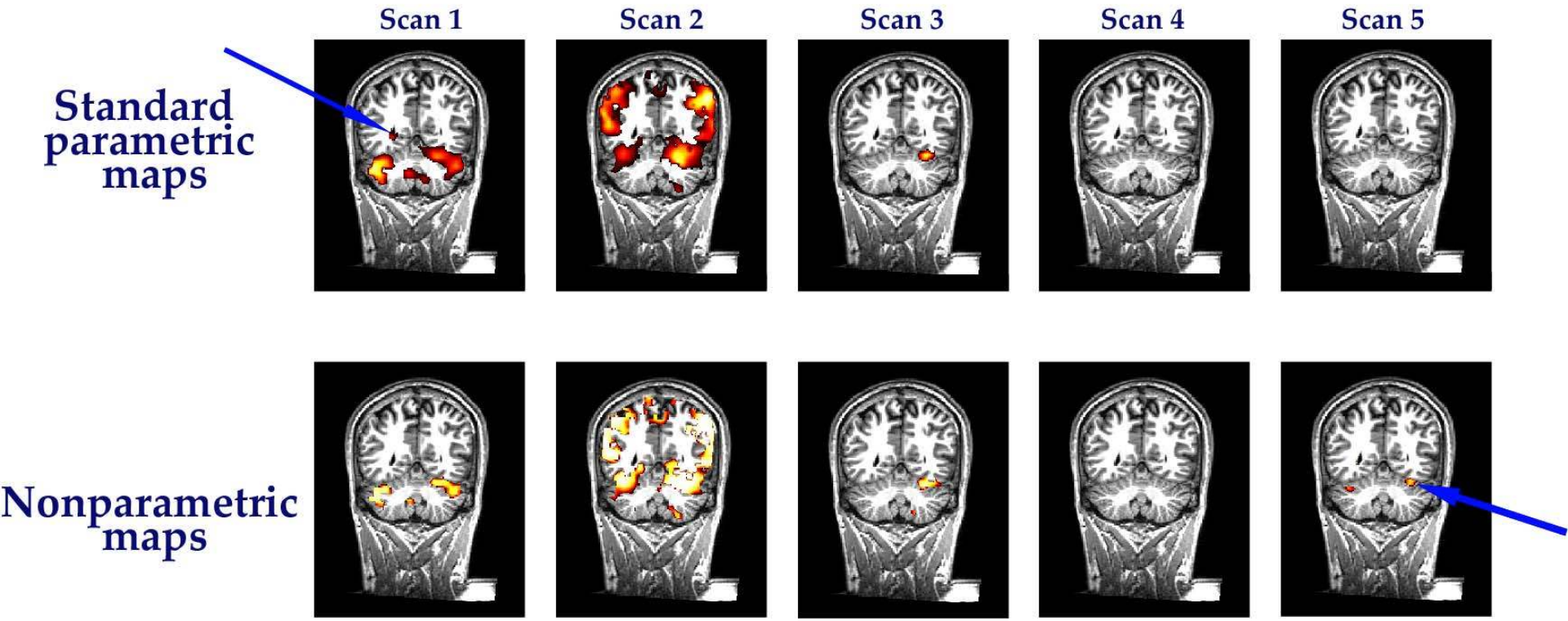
p_voxel	N. active voxels: original	Average n. active voxels: random	FDR:orig/rand ratio
0.0005	241	1.01	0.004190871
0.001	341	2.55	0.007478006
0.0015	408	4.17	0.010220588
0.002	470	6.3	0.013404255
0.0025	527	8.31	0.015768501
0.003	569	10.32	0.018137083
0.0035	610	12.23	0.02004918
0.004	642	14.19	0.022102804
0.0045	660	15.74	0.023848485
0.005	680	17.27	0.025397059
0.0055	712	18.97	0.026643258

„Bootstrap” FDR



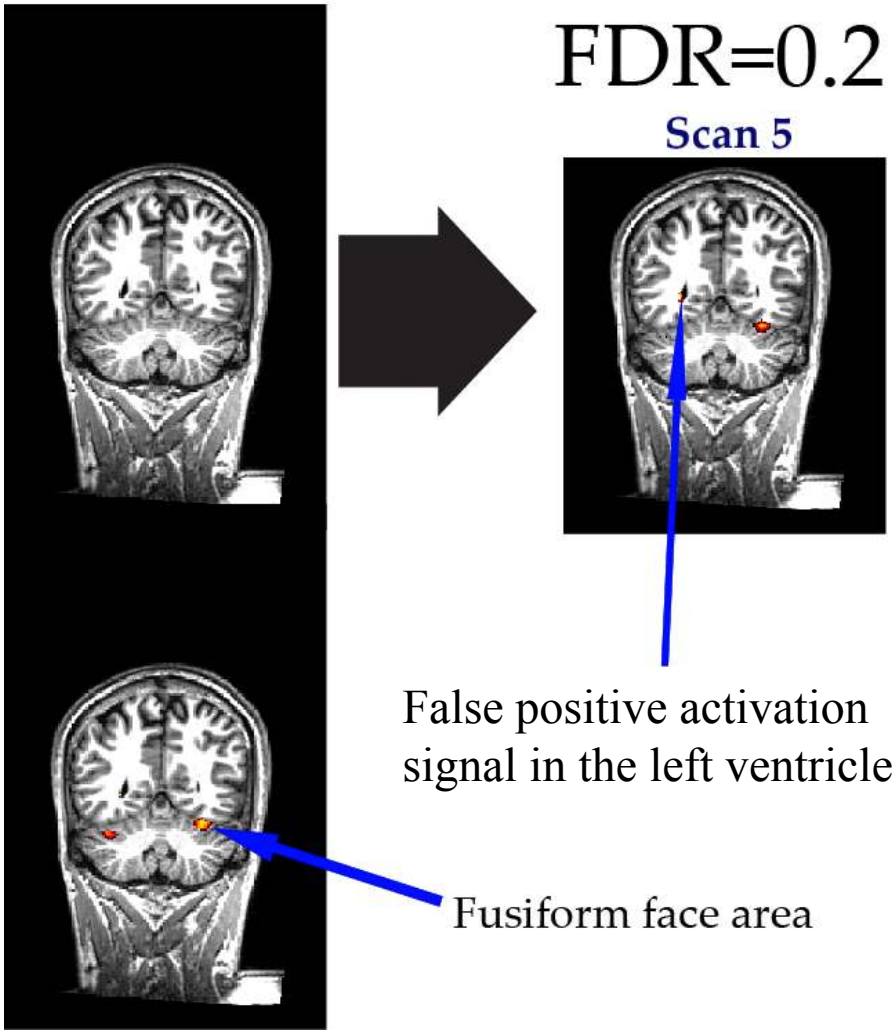


Validation example: activation of the fusiform area (event related design)



Validation example

Standard parametric map



Nonparametric map

Univariant-multivariant analysis in fMRI

Goal

- Is there any effect? Hypothesis testing
- What kind of effect?
- Localization of effect

Complexity of the multi-dimensional signal-processing:

- Separately, one dimension at a time:
  - Traditional: voxelwise, independent
  - Selecting of areas, groups of voxels (ROI: POI, VOI) and averaging
    - S/N may increase
    - correction for multiple univariate comparisons is less important
- Parallel multidimensional:
  - Spatial or spatial-temporal patterns:
    - **Multi-voxel pattern analysis (MVPA)**
    - Multivariate Decomposition: ICA, PICA etc.

Multi-voxel Pattern Analysis (MVPA)
… potentials and requirements

General Purpose:

- ROI based analysis: hypothesis testing
- Search-light: localization

Block design, sparse event-related design

- Training & test based classifiers
  - single event based prediction

Fast event related (& block + sparse ER) design

- Parametric or non-parametric significance estimation of multi-dimensional **distance (**based on standard GLM results)

MVPA details

- Multivariant analysis: decoding („mind reading”)
- Classification of activity patterns:
  - Feature selection
  - Normalization
  - Choosing classification algorithm
  - Optimization-training

•Test, performance estimation

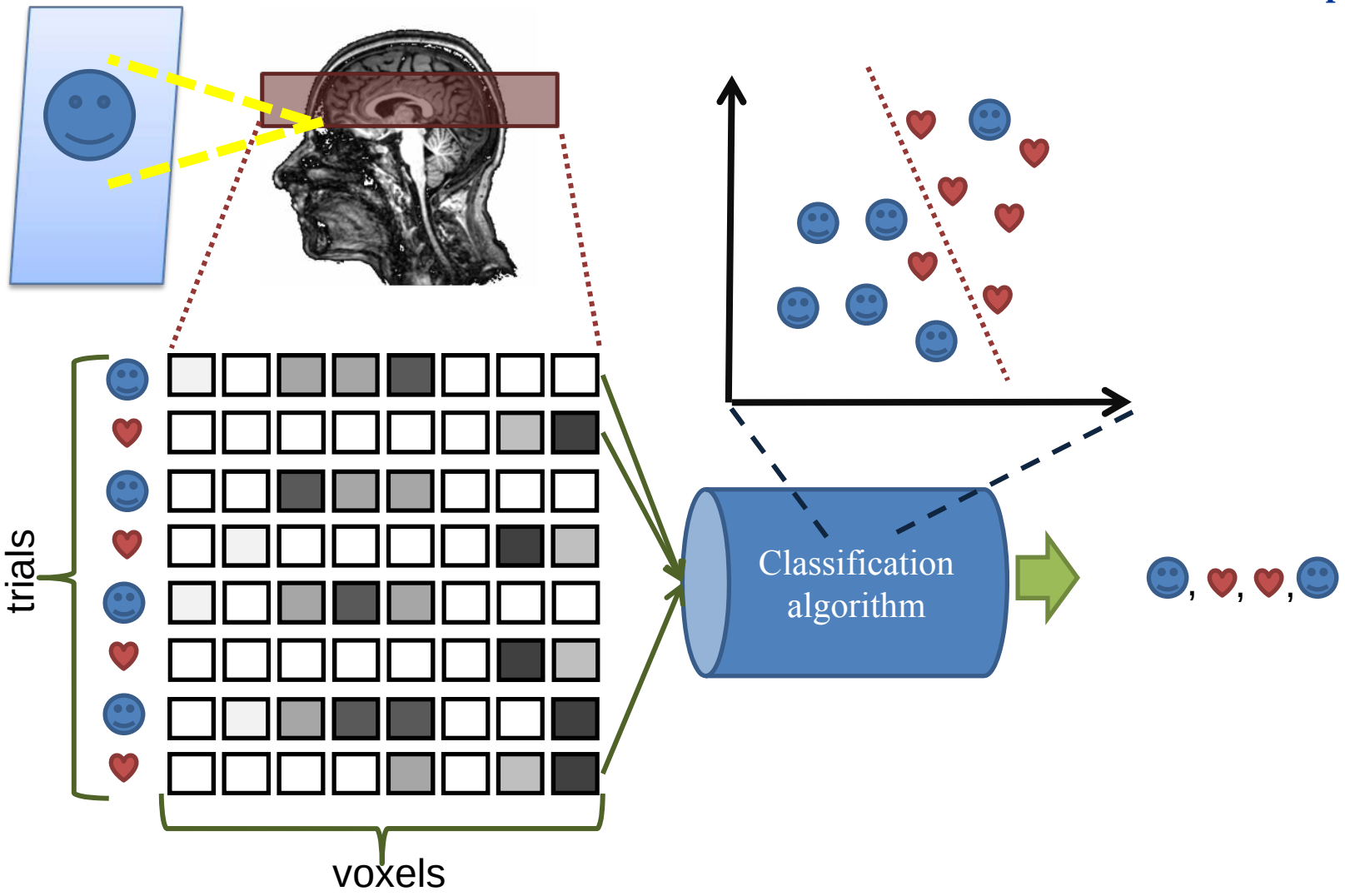
•Validation of efficiency

  •Parametric model

  •Bootstrap, resampling

•Interpretation of results

Biomedical Imaging: fMRI – Advanced Statistical Analysis



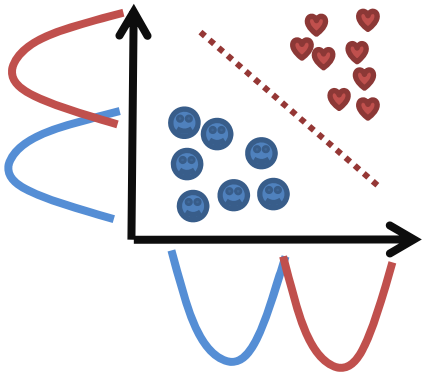
Feature selection

- Dimension (number of voxels) should be reduced
  - To exclude irrelevant and noisy voxels
  - High dimension and small sample size undermines the classification algorithm's
    - Performance
    - Generalization capacity
- Methods:
  - VOI
  - Exlusion of noisy voxels (e.g. (based on variance)
  - Voxelwise univariate statistics (ANOVA, t-test): ordering voxels
- Combinatorial test of MVPA on groups of voxel
  - Full combinatorial, Genetic algorithm etc.

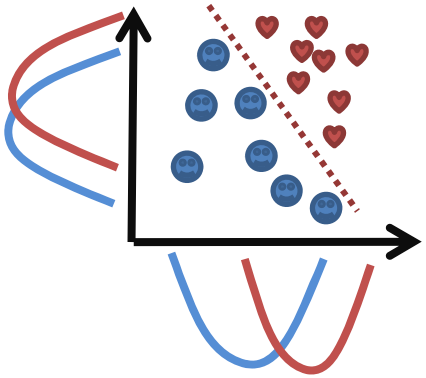
Classifiers (supervised learning)

- Linear
  - Generative models (modeling conditional density functions): fast, non-iterative algorithms
    - Naive Bayes
    - Linear discriminant
    - Mahalanobis distance
  - Discriminative models (slow, iterative optimization)
    - Logistic regression
    - Linear SVM
- Non-linear (interpretation difficulties)
  - SVM
  - Multi-layer neural networks

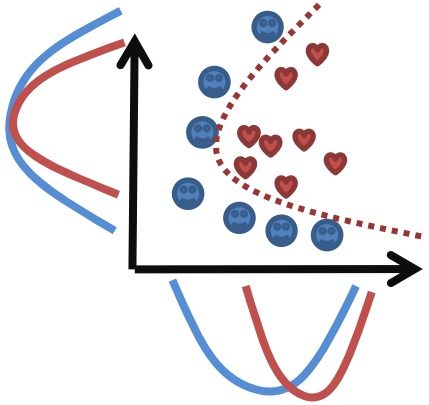
Separability of the activity vectors



Univariate separable

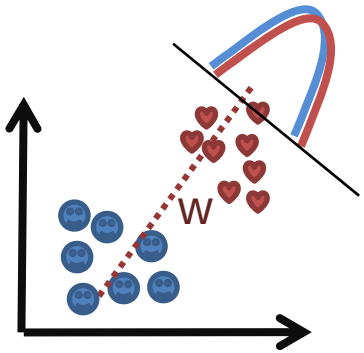


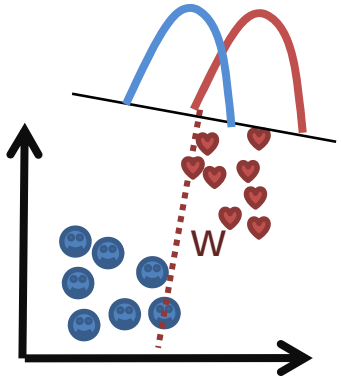
Linearly separable



Linearly not separable

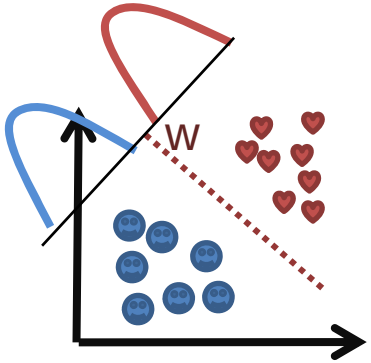
Fisher linear discriminant analysis





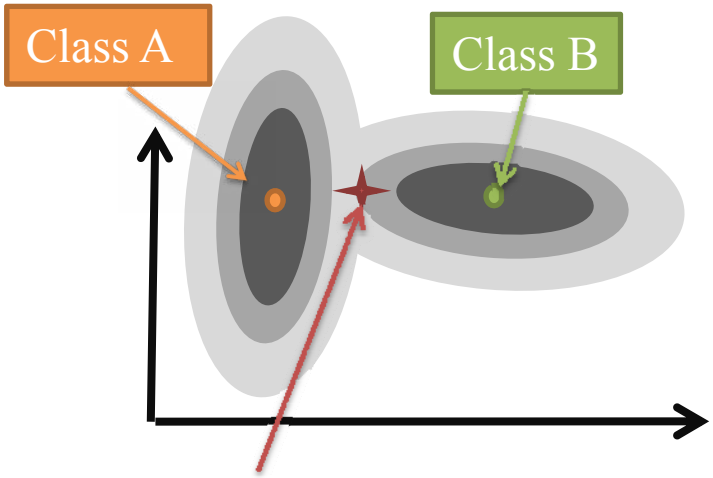
maximize

$$J_{Fisher}(w) = \frac{\text{Between class variance}}{\text{Within class variance}}$$



Mahalanobis distance

- Classify according to distance from class mean
- Takes non-sphericity into account

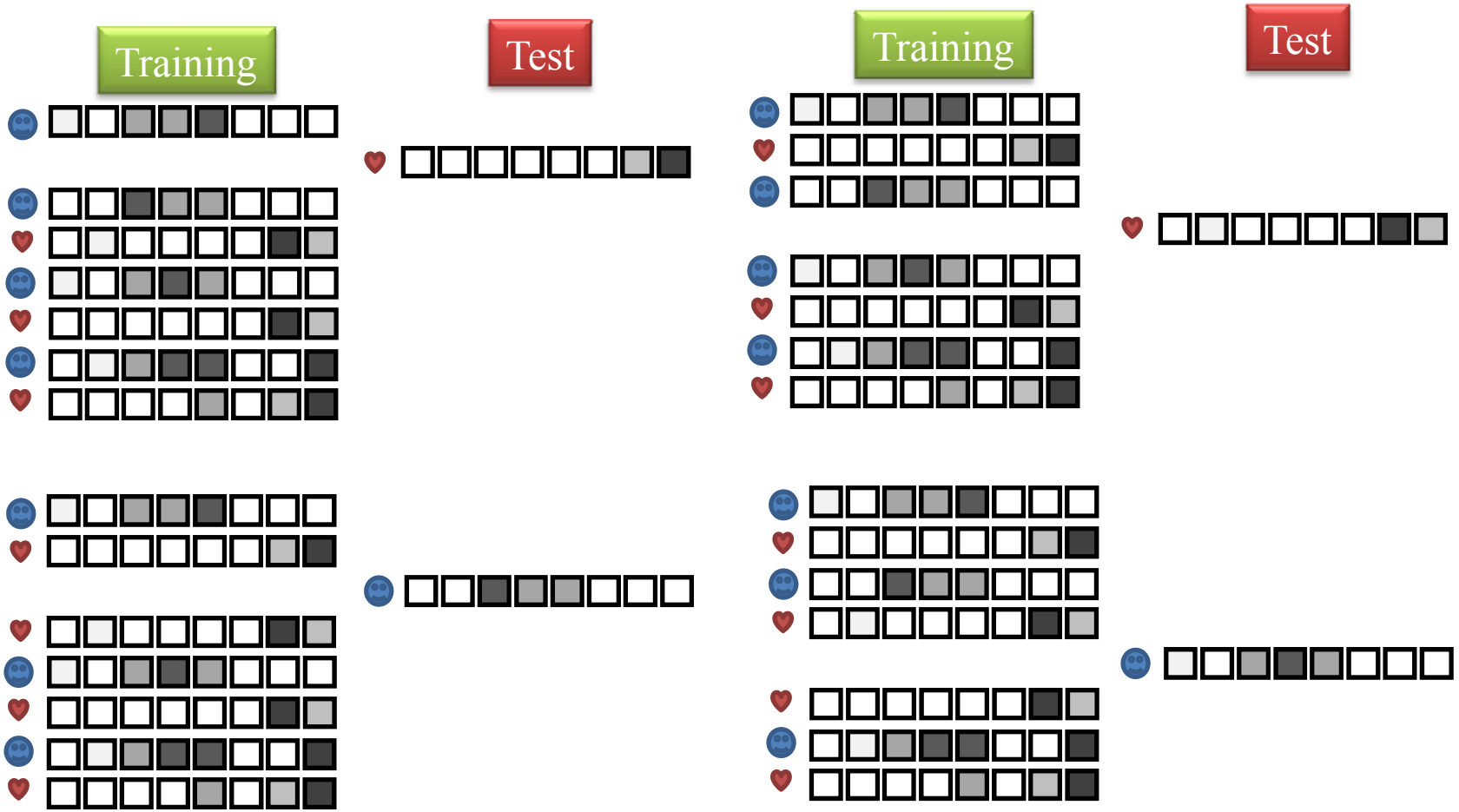


Test vector belongs to
•Class A according to euclidean distance
•Class B according to Mahalanobis distance

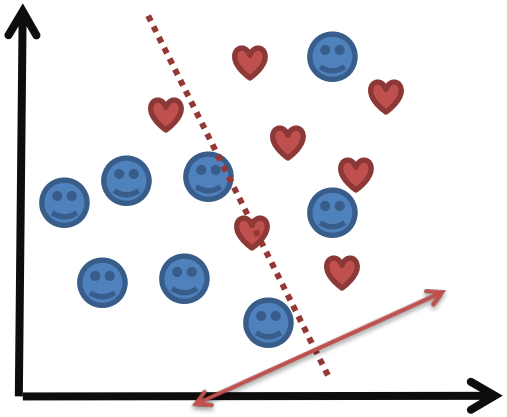
Interpretation of the results

- Linear
  - In scale invariant case, weights of the discriminator can inform about the importance of the voxels separately
  - Patterns can be interpreted and visualized
- Non-linear
  - Difficulties with decoding
  - Different combination of dimensions (voxel subgroups) can be evaluated
- Interpretation of performance
  - Leave-one-out
  - Leave-some out: training-test set
    - Average- variance
  - ROC curve
  - Resampling statistics

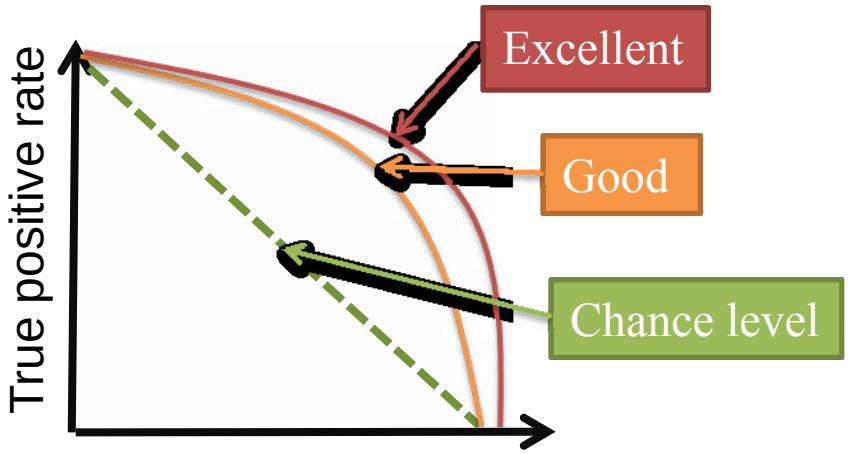
Leave-one-out



ROC curve

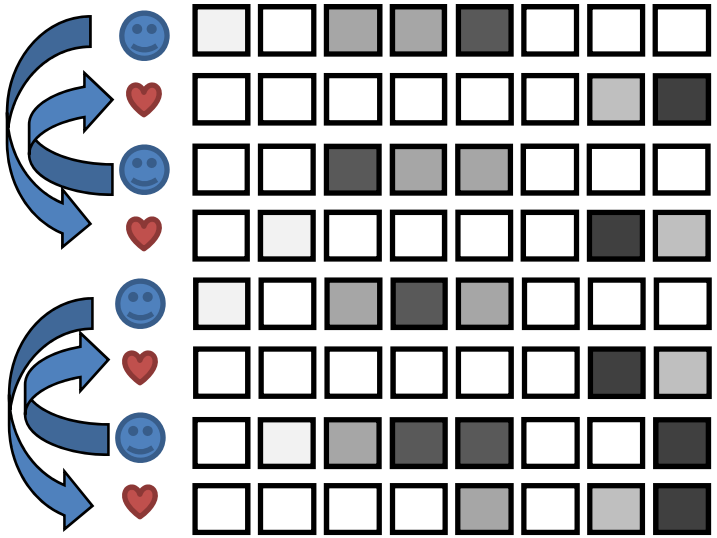


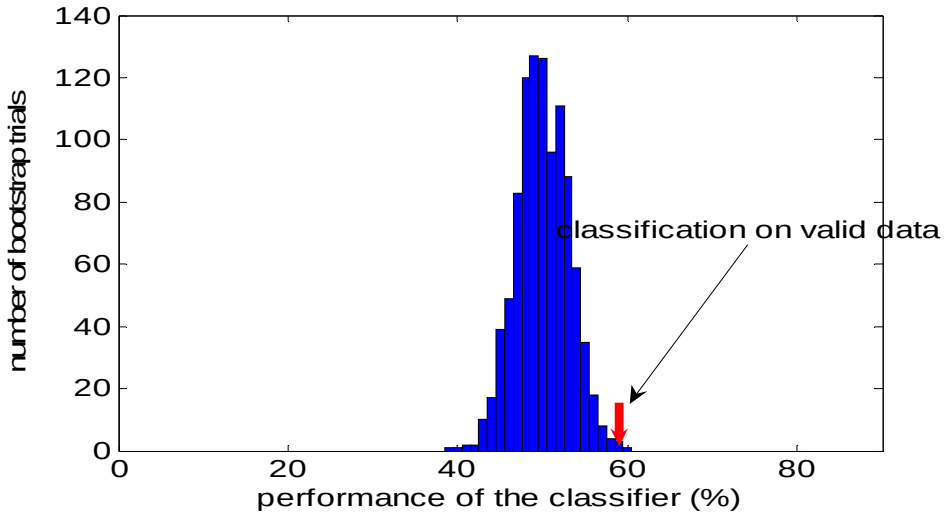
Hyperplane *w* is defined,
Move threshold bias
from min to max



Validation: resampling

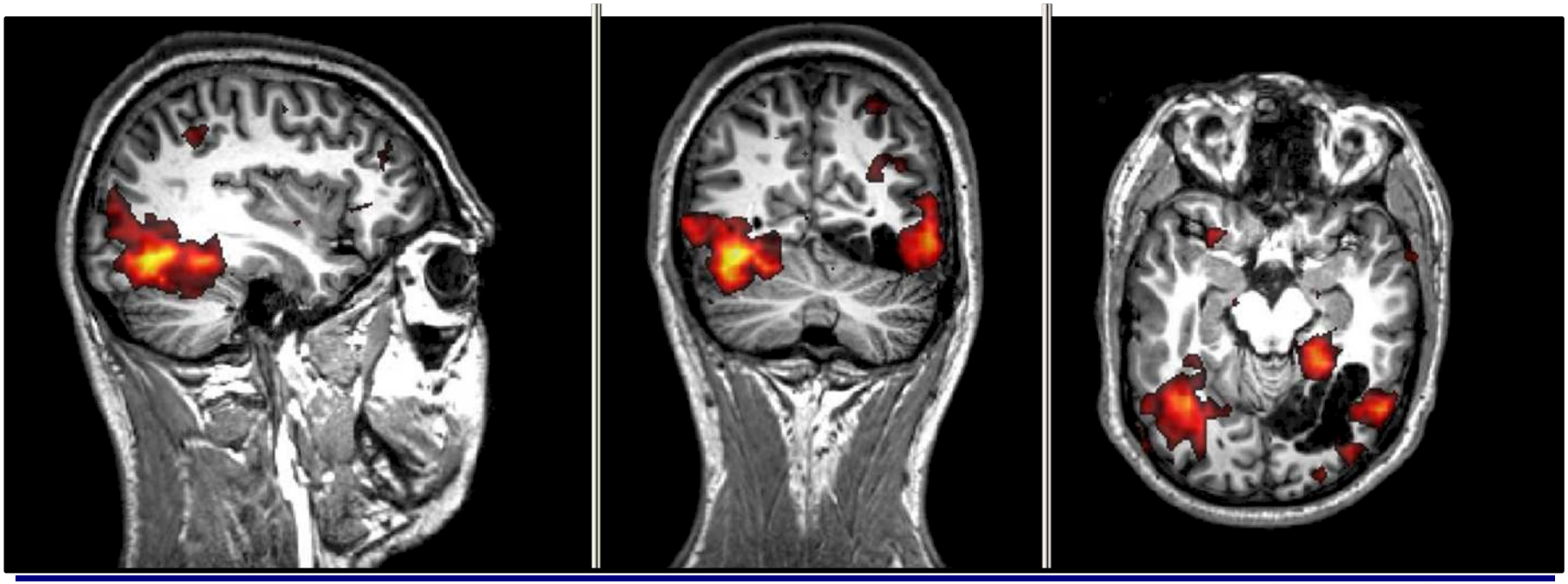
- Shuffling labels on training set
- Measuring performance
- Repetition (~1000) times





Search-light classification, linear discriminant analysis

- At each voxel 3X3 neighbourhood
- Leave-some trials out 10X
- Average performance: 90% at maxima



ROI based SVM: parameter optimization