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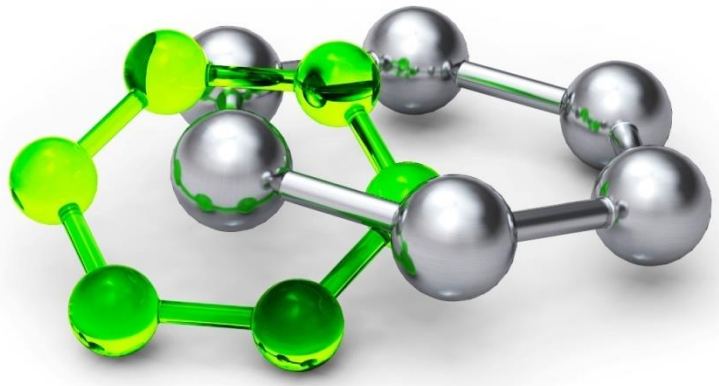
The basics of morphometric methods in neuroscience.

Voxel/Source based morphometry

Radek Mareček

Brno, November 14th 2016



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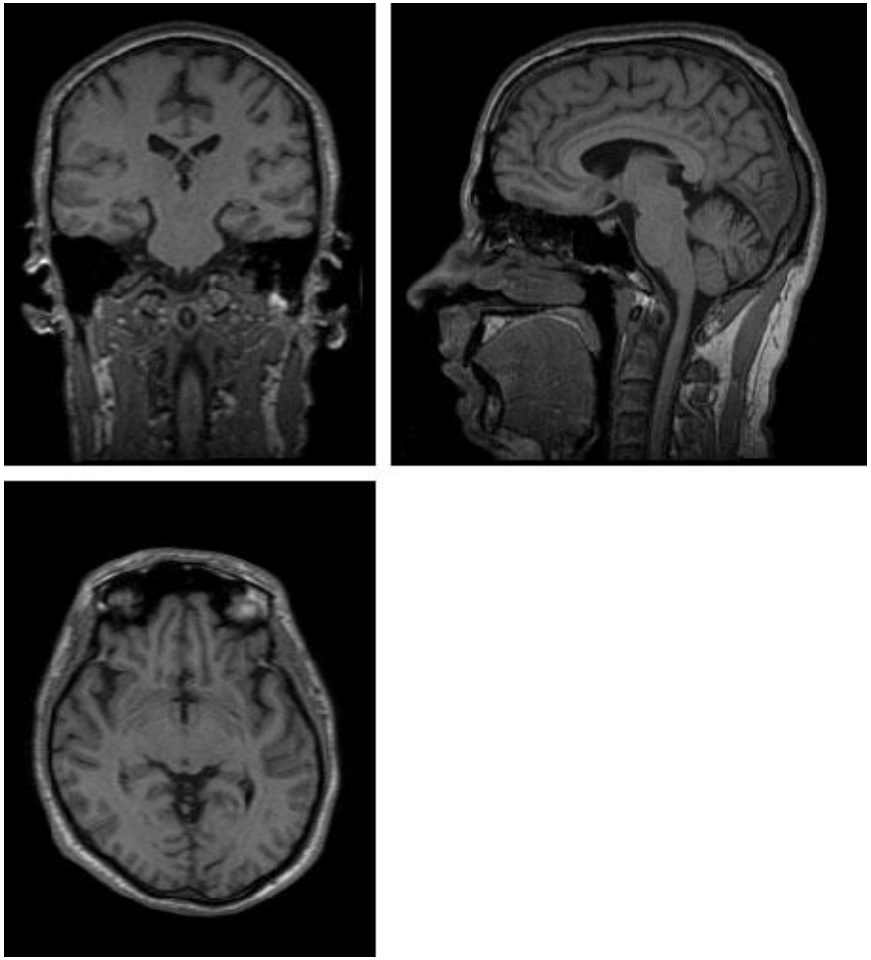
Morphometry



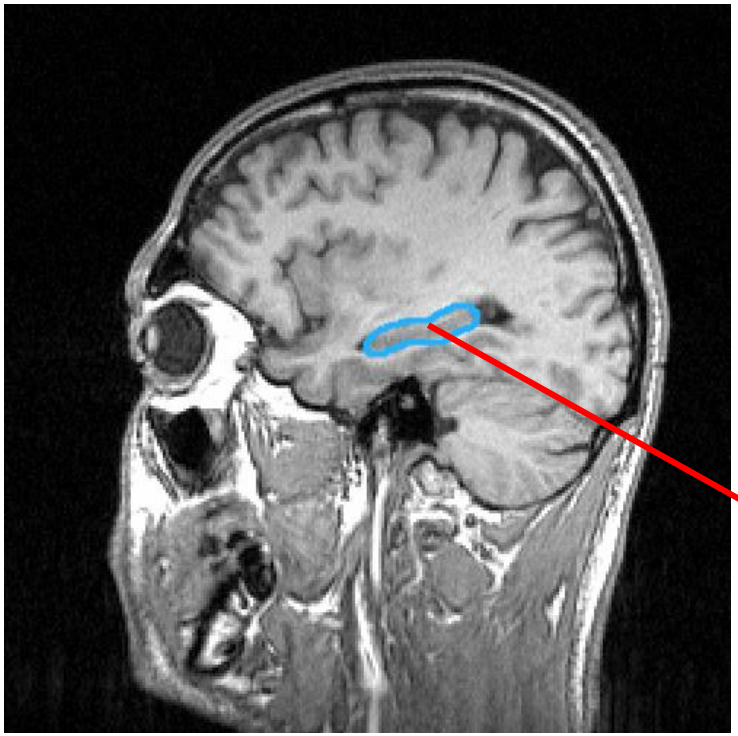
- methods, that identify macroscopic differencies in the (human) brain structure
  - lesion detection
  - local structure changes caused by specific disease
  - local structure changes caused by various behavioral parameters (age, gender, education, etc.)
- outcome
  - statistical comparison among groups of subjects
  - statistic parametric maps

OUTLINE

- overview of morphometry technics/approaches
- data and its preprocessing
- Voxel / Source based morphometry
- Structural covariance
- déjà vu phenomenon viewed by VBM and SBM

Morphometric methods

VOLUMOMETRY

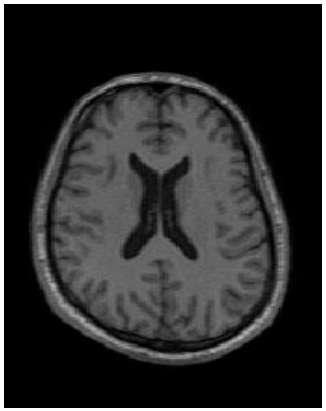


- manual delineation of the region of interest (ROI)
- estimation of the ROI volume
- statistics (e.g. two-sample T test)

ROI volume → statistics

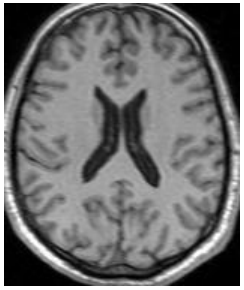
Morphometric methods

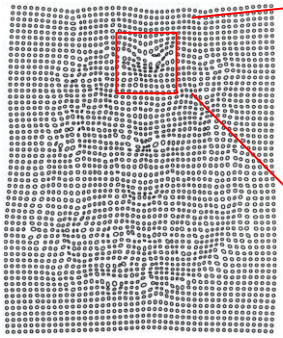
DEFORMATION BASED METHODS

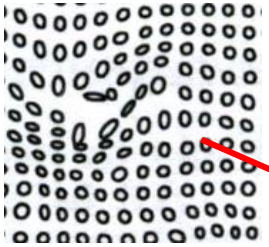


MNI

deformations







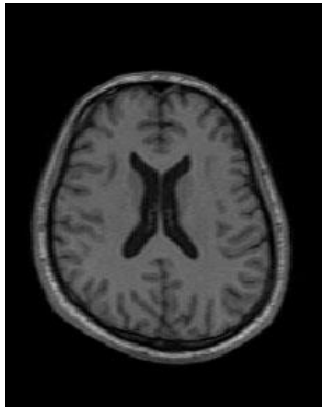
- Deformation Based Morphometry
- Tensor Based Morphometry

- global and local changes in the shape/volume of the brain

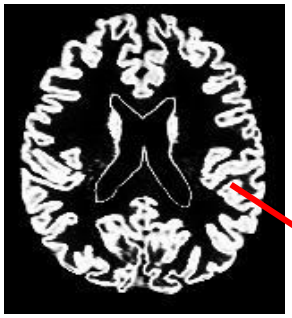
statistics

Morphometric methods

ANALYSES OF LOCAL CHANGES IN THE GRAY/WHITE MATTER CHANGES



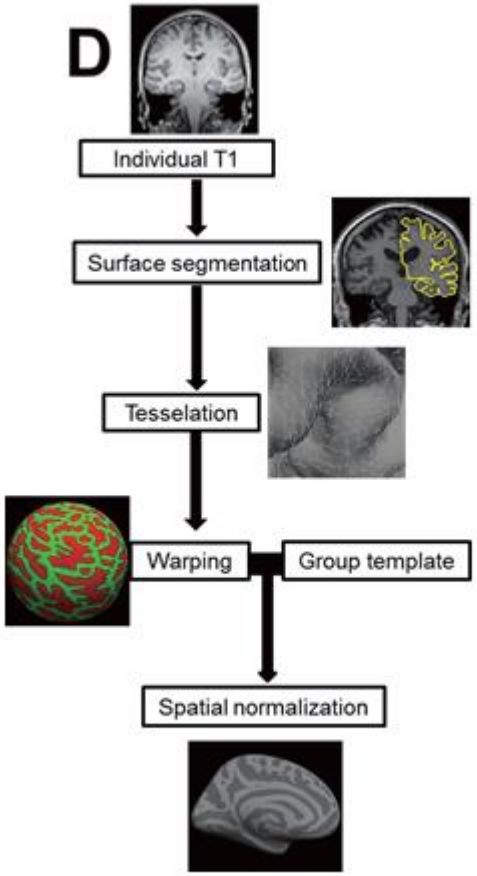
deformations
segmentation



statistics

Voxel Based Morphometry
Source Based Morphometry

Morphometric methods



Martin et al., 2015

SURFACE BASED MORPHOMETRY

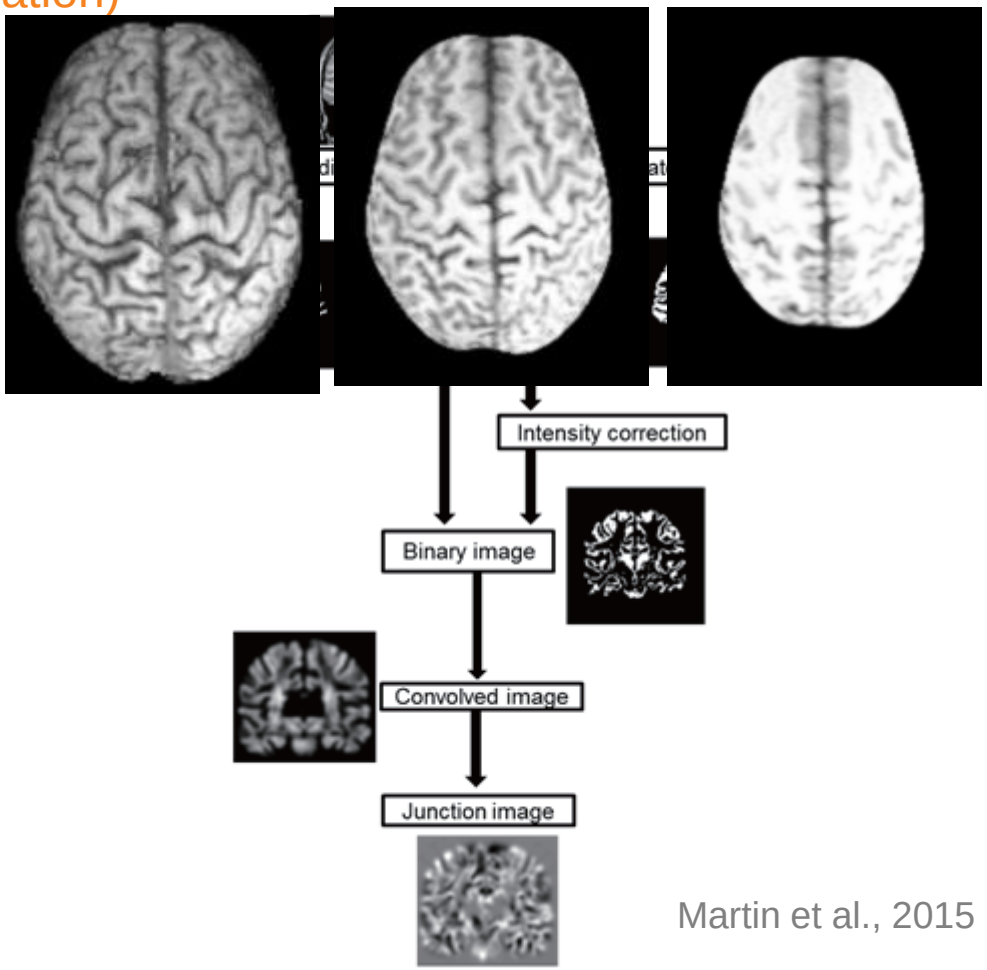
- analysis of the cortical surface geometry
- Nikoleta Szabó

Morphometric methods

OTHER METHODS
(subtle lesion detection; gyrification)

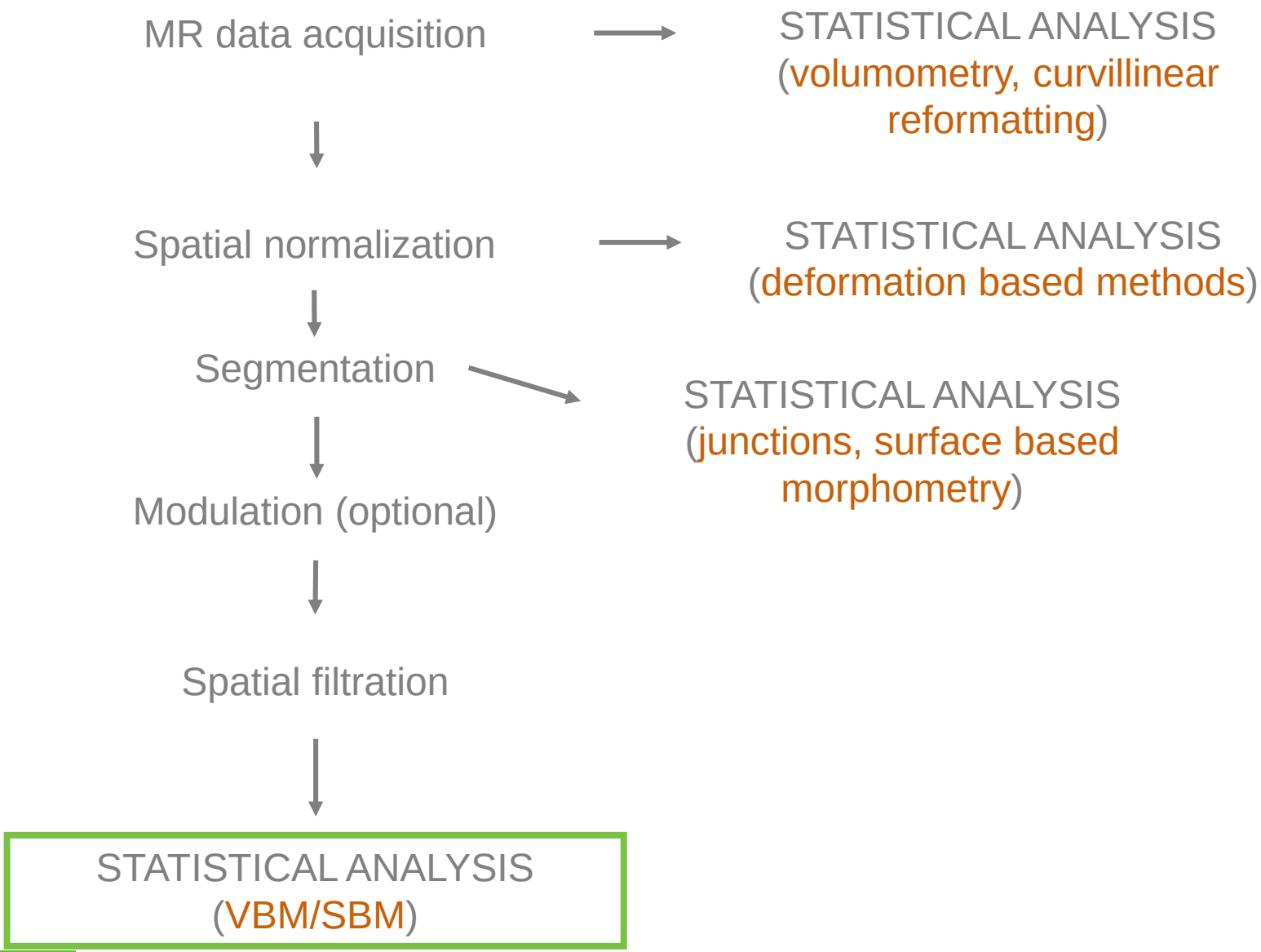
- curvilinear reformatting

- junctions map



Martin et al., 2015

Outline of data processing



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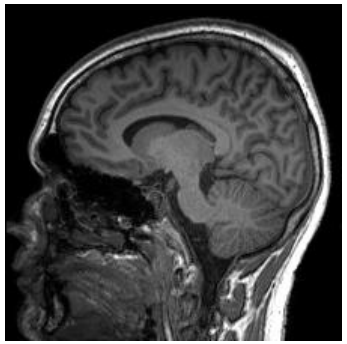
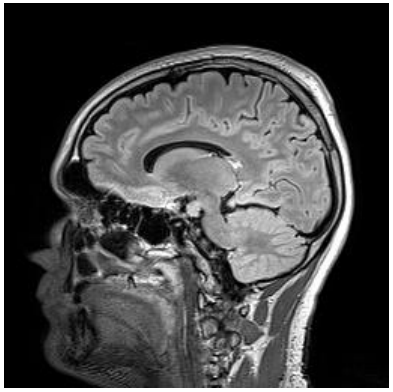
Data

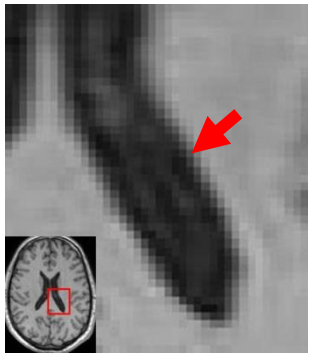
T1 MPRAGE
isotropic resolution 1mm

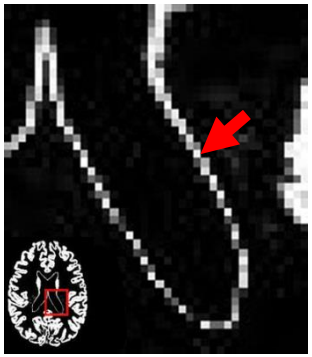


T2 FLAIR
isotropic resolution 1mm



- high MR contrast among different matters
- the more MR channels, the higher accuracy (e.g. T1 MPRGAE + T2 FLAIR)

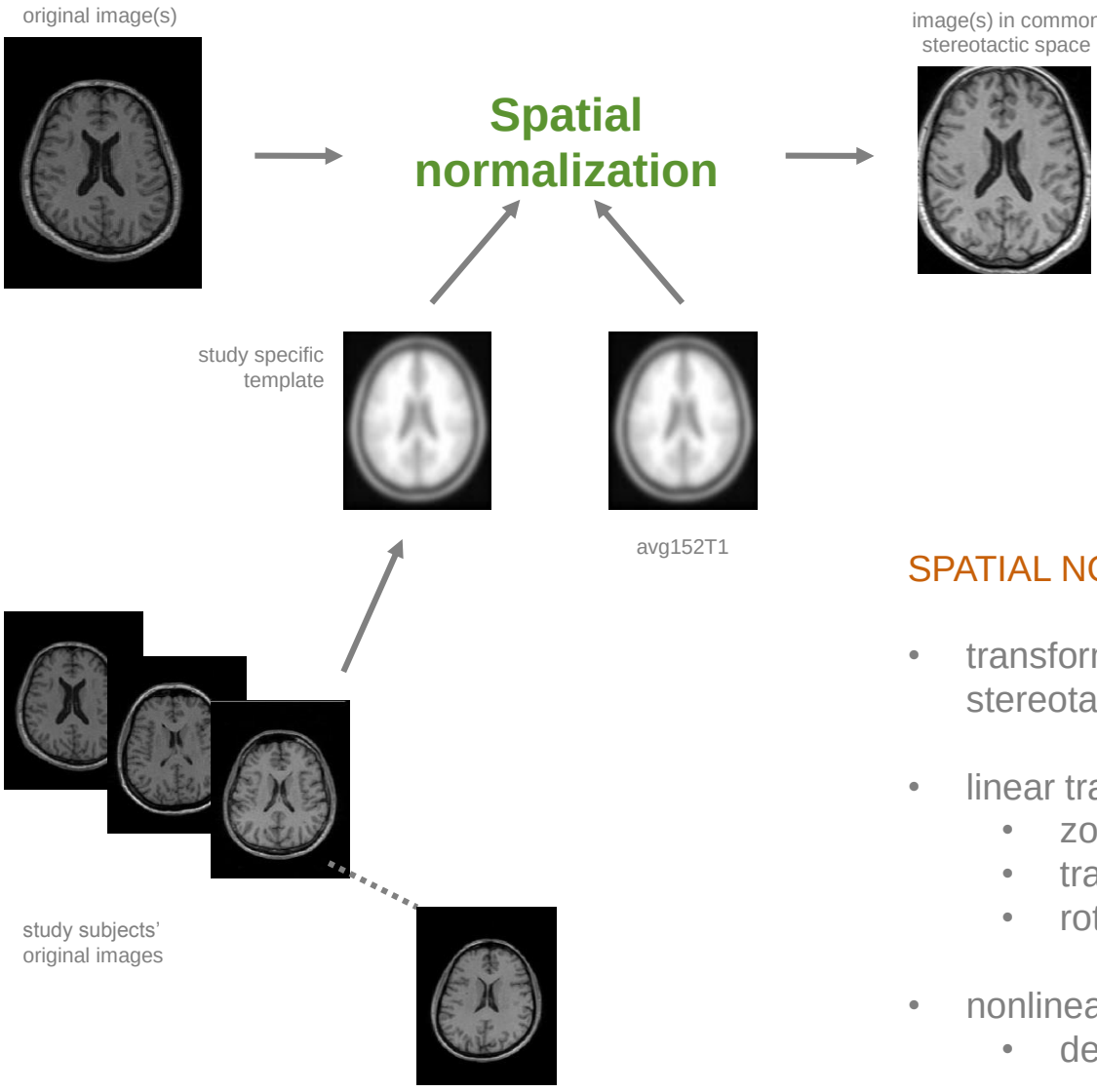




- high spatial resolution
  - isotropic voxels ~1mm
  - minimalization of partial volume artifact
  - localization of results

- data homogeneity
  - data inhomogeneity must not interfere with effect of interest
- enough subjects (20 – 30); depends on the size of the effect of interest

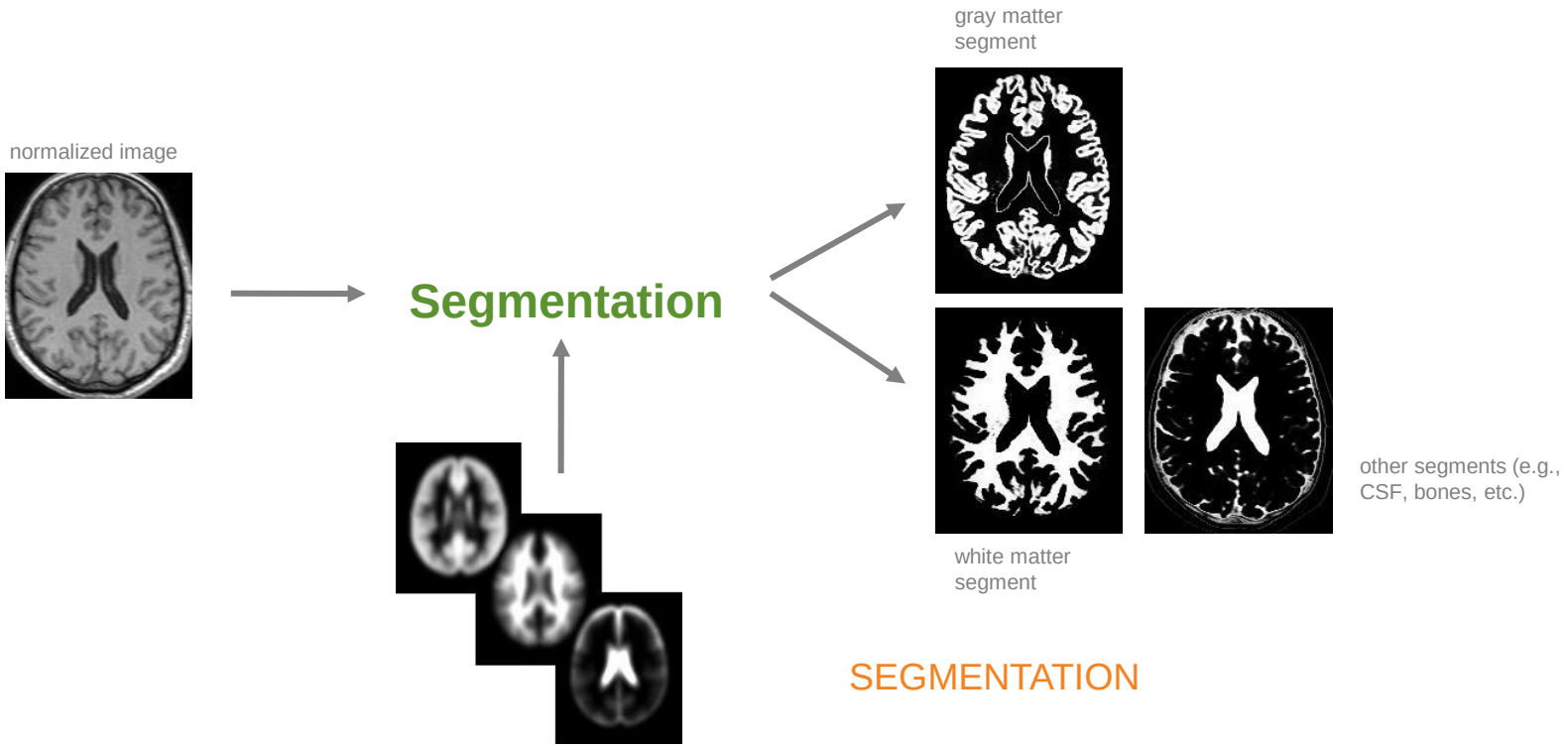
Spatial normalization



SPATIAL NORMALIZATION

- transformation of coordinates into the common stereotactic space
- linear transformation
  - zoom
  - translations
  - rotations
- nonlinear transformation
  - deformations

Segmentation



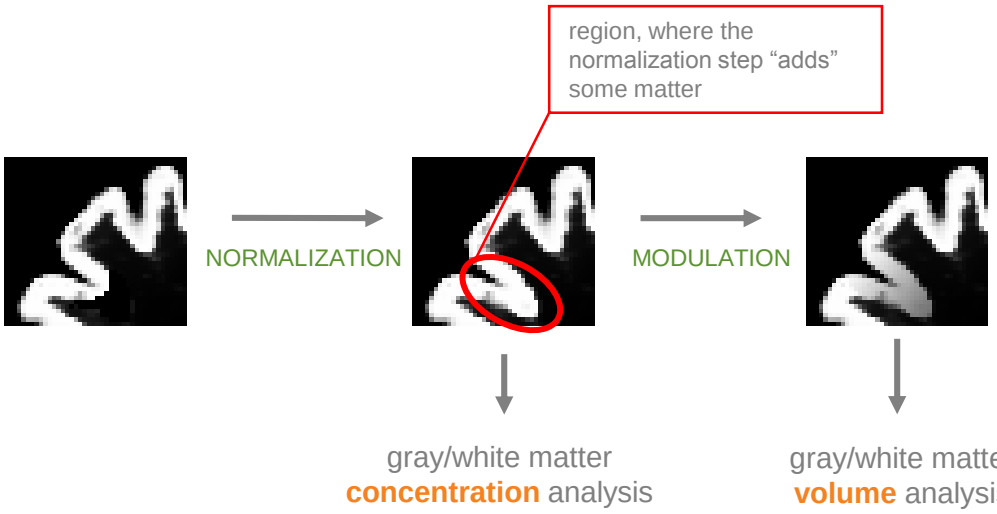
SEGMENTATION

- classification of the voxel
- combines the information hold by the subject's image with the prior knowledge about the matter distribution in the population
- iterative bayesian algorithm
  - the resulting images express the posterior probability that voxel belongs to particular matter

Math

Ashburner J., Friston K., Voxel-Based Morphometry – The Methods, Neuroimage 2000
Ashburner J., Friston K., Unified Segmentation, Neuroimage 2005

Modulation



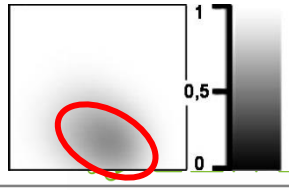
MODULATION

- optional preprocessing step that determines the interpretation of results

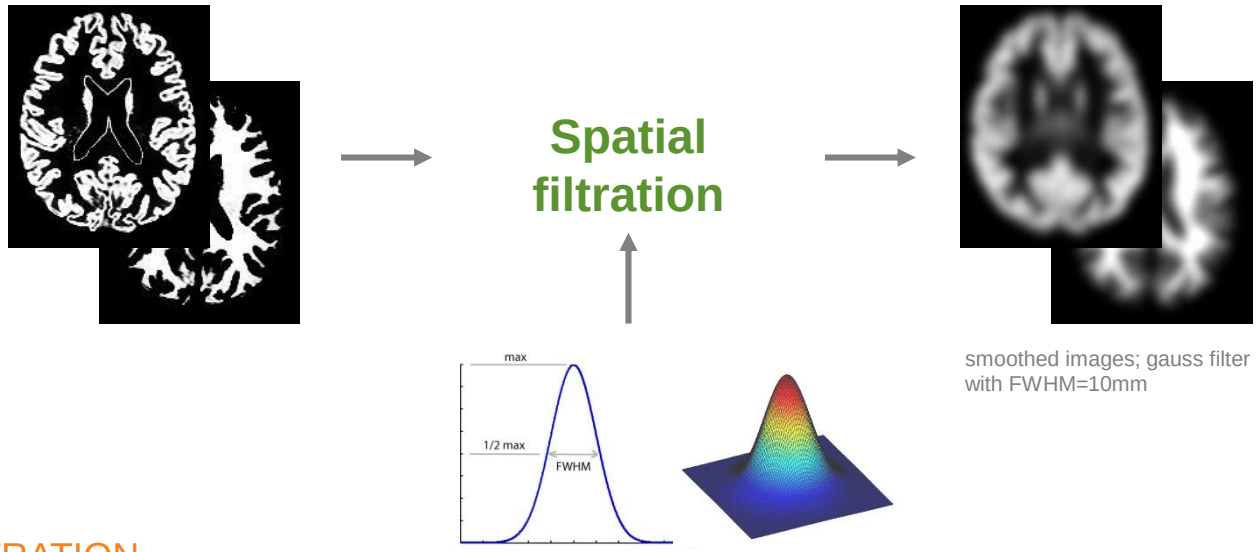
- without modulation – the results show changes in local concentration of gray/white matter
- with modulation – the results show changes in local volume of gray/white matter

Math

the modulation is a result of voxel-by-voxel multiplication between original image g(x) and a scalar function w(x) f(x) = w(x) . g(x) , where w(x) comes from the parameters of non-linear transformation of coordinates during the spatial normalization step



Spatial filtration



smoothed images; gauss filter with FWHM=10mm

SPATIAL FILTRATION

- improves the signal-to-noise ratio
- the data better fits the normal distribution -> important for parametric statistics
- worsen the spatial accuracy of the results

Math

The spatial filtration is a 3D convolution of data matrix g(x,y,z) with filtration kernel h(x,y,z):

$$f(x,y,z) = g(x,y,z) * h(x,y,z) = \sum_{i=-m}^{m} \sum_{j=-m}^{m} \sum_{k=-m}^{m} f(x-i, y-j, z-k) \cdot h(i,j,k)$$

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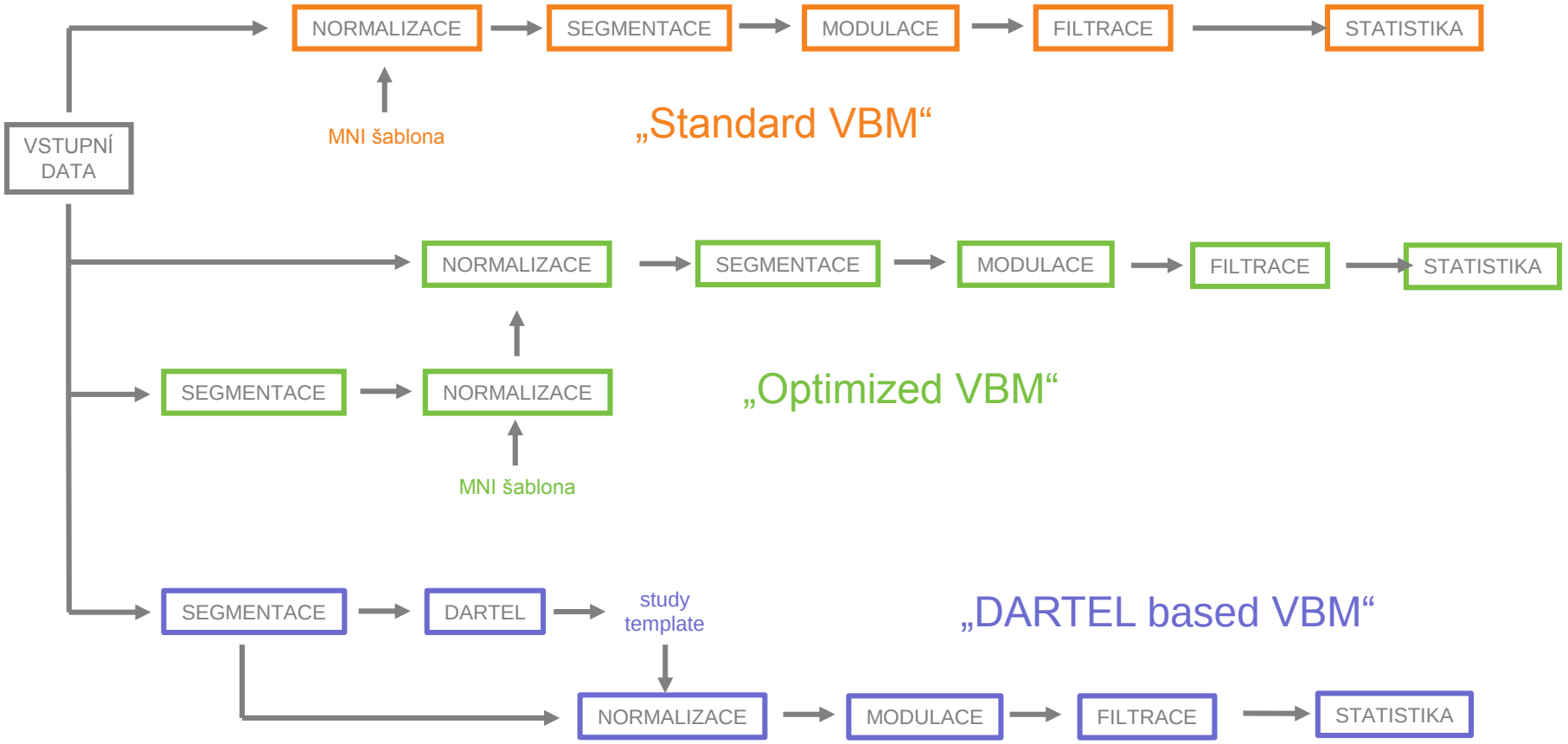
Various preprocessing approaches



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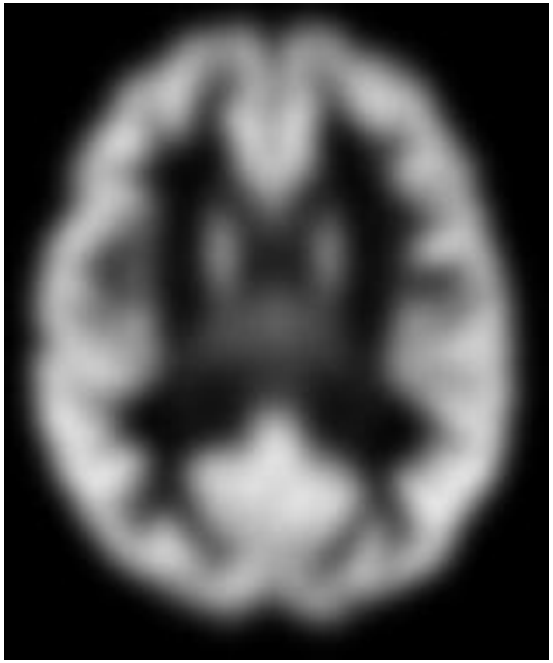
The result of preprocessing

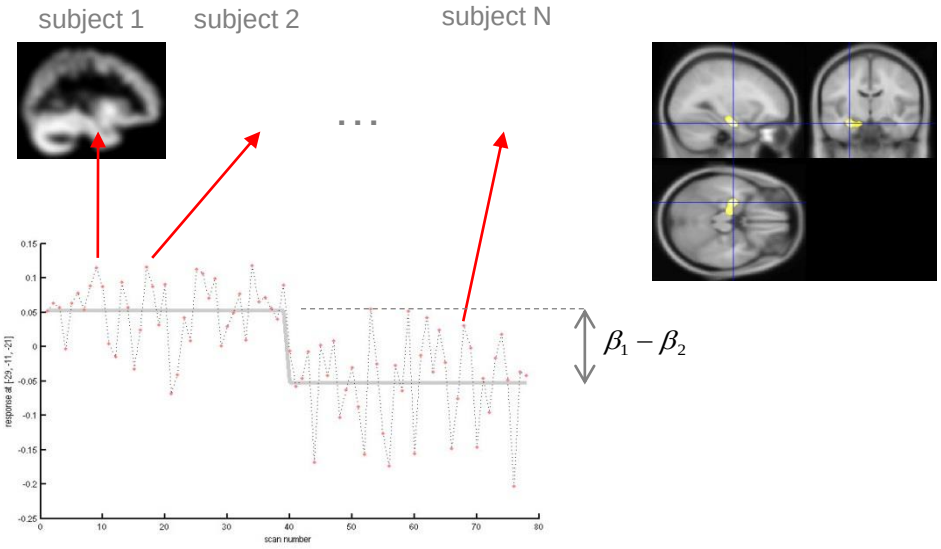


- gray/white matter image for each subject
- images contain values between 0 and 1
- the data has approximately Gauss distribution (in case the spatial filter has gaussian kernel)

VBM

VBM identifies brain regions with significant effect of a-priori set hypothesis.

- comparison between healthy controls and patients (two-sample T-test, ANOVA)
- longitudinal studies - influence of therapy, education etc. (paired test)
- special case – comparison of patient with a group of healthy controls



Parametric testing

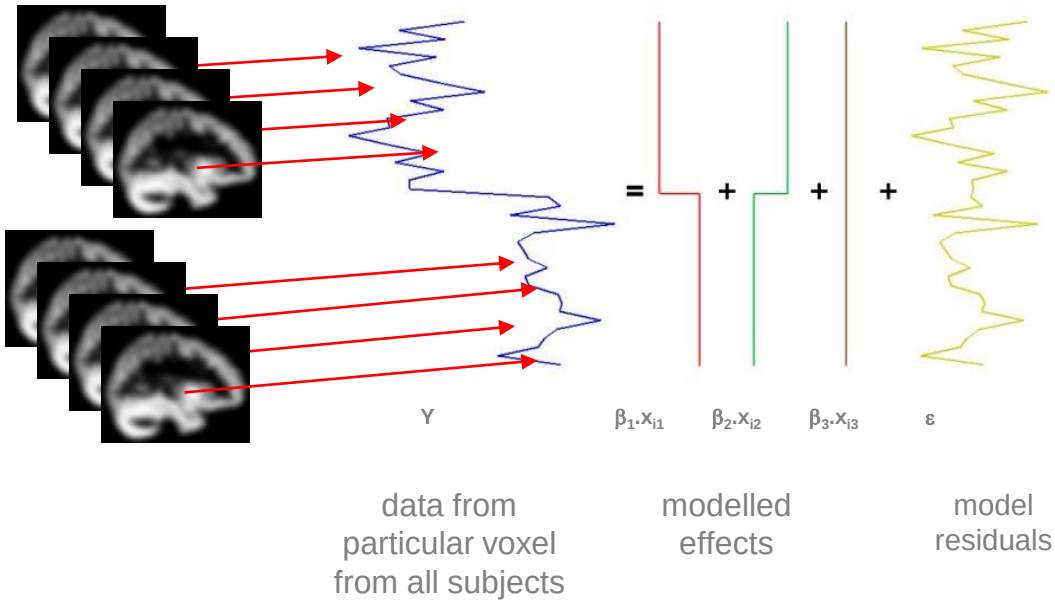
- spatial filtration with gaussian kernel recommended for ensuring the validity of results
  - balanced design … FWHM min 4mm
  - strongly imbalanced design … FWHM min 10mm
    e.g., patient vs controls, (Salmond C., Neuroimaging 2002).

VBM - correlation with behavioral parameters

- exploration the relationship between local structural variance and some behavioral parameter
    - age
    - psychological scale
    - other modalities outcome (e.g. MR Spectroscopy – the concentration of a metabolite)

VBM – implementation with GLM

$$Y = X*b + e$$



data from particular voxel from all subjects

modelled effects

model residuals

The linear model has analytical solution:

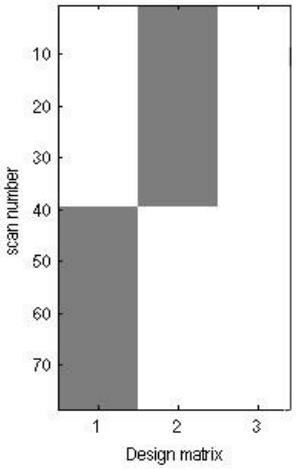
$$\beta = (X^T X)^{-1} X^T Y$$

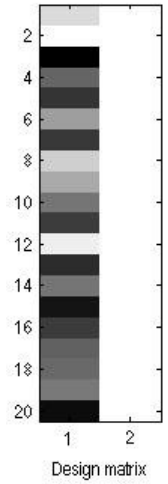
VBM – implementation with GLM

group comparison

correlation with behavioral parameter

design matrix





statistics

$$T \approx \frac{\beta_1 - \beta_2}{\sigma}$$

$$T \approx \frac{\beta_1}{\sigma}$$

estimated effect

residual variance

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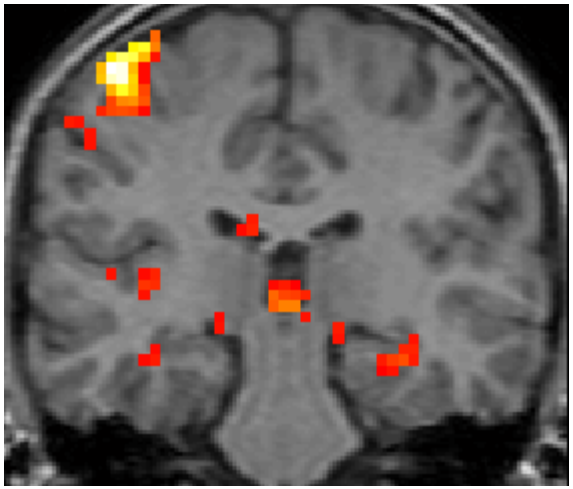
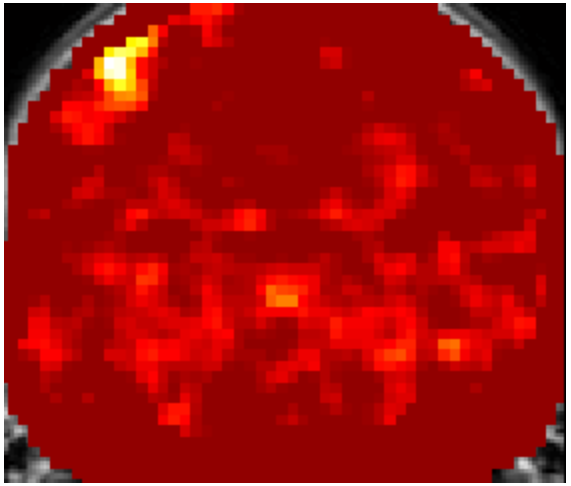
VBM – implementation with GLM

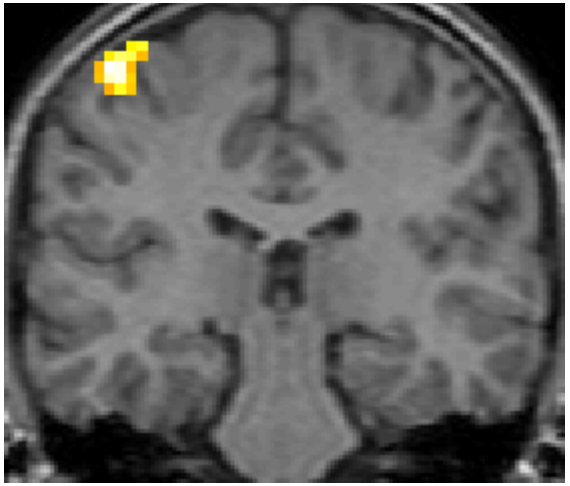
the statistical parametric map



threshold T>2



e.g. map of T-values



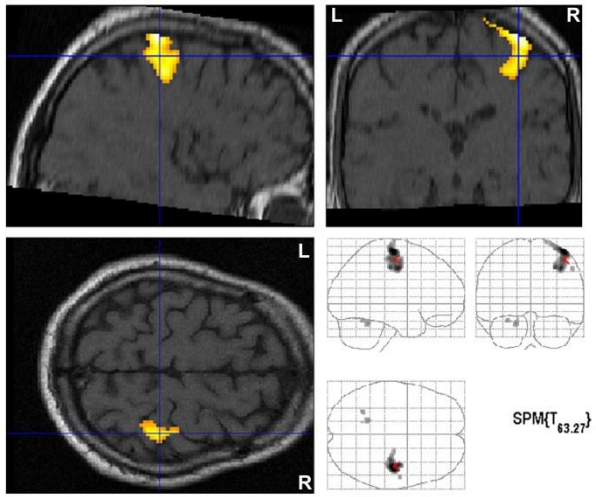
threshold T>5

how to set threshold ??

VBM – implementation with GLM

The threshold is commonly set by the chosen level of statistical significance, i.e. by setting the p-value, we get critical threshold T_{krit}

p – the likelihood of the first-type error – the false positive result



The voxels above threshold show the regions where the tested effect reaches the significance level.

Multiple testing problem

The multiple testing problem

A lot of false positive results, considering hundreds of thousands voxels (i.e. tests) and the standard $p<0.05$.

- FWE correction (family wise error) .. likelihood of obtaining the false positive result anywhere in the volume is less than *p*
  - Bonferoni, RFT theory (SPM)

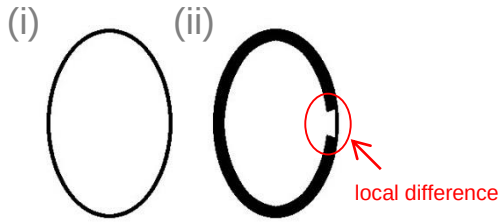
- FDR correction (false discovery rate) .. ratio of false positive results out of all above threshold is less than *p*

Other approaches

- cluster level significance
- small volume correction
- multivariate statistical approach

VBM – confounding effects

Motivation



Mechelli A. et al., Morphometry of the Human Brain: Methods and Applications, Current Medical Imaging Reviews 2005

are we interested in global or local diffferencies?

- we know (or we have strongly suspect) that our data might be affected by confounding effects
- the ways how the confounds affect the data:
  - multiplicative (e.g., total intracranial volume)
  - additive (e.g., age, gender)
  - more complex….

how to handle the data ?

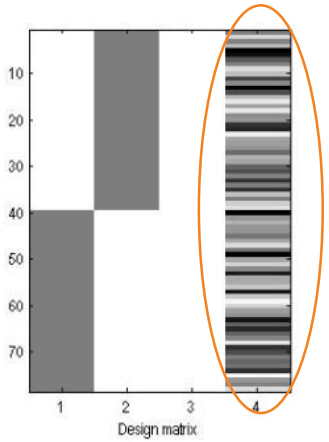
VBM – handling the confounding effects

Multiplicative confounds

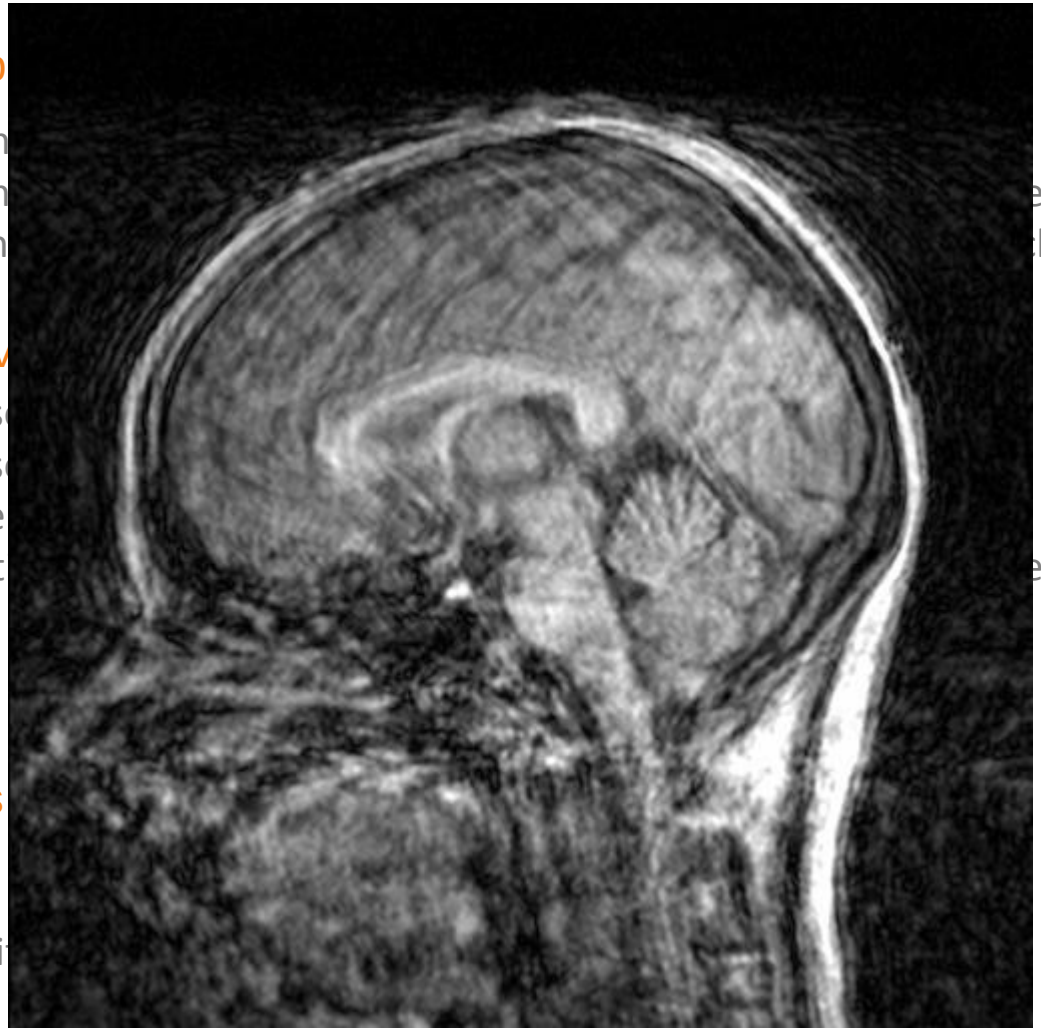
- intensity normalization
- e.g. total intracranial volume computed as a sum of GM, WM and CSF segments

Additive confounds

- additional regressors in GLM design matrix



Notes - VBM



Potential p

- uncertain
- uncertain
- data with

ensive pathologies
h skupin pacientů

Usage of V

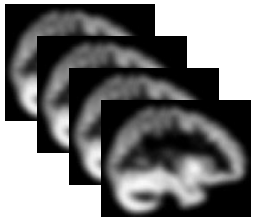
- comparis
- comparis
- influence
- examinat

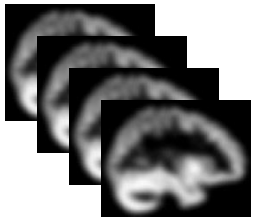
ender, etc.) brain structure variability

Weakness

- uncovers
- low sensi

Source based morphometry

VBM …. → preprocessing →  → voxel-wise statistical analysis

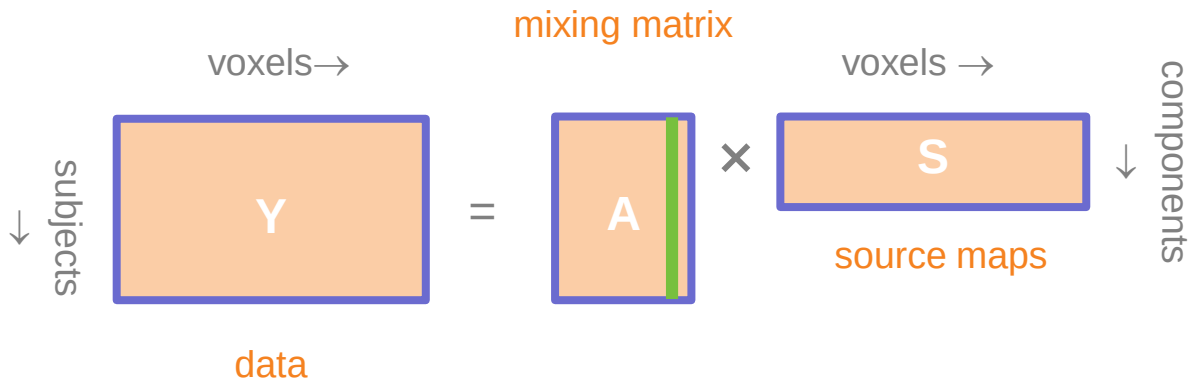
SBM …. → preprocessing →  → ICA decomposition → statistical analysis on components' features

ICA reveals spatially independent sources of local gray matter variability. Voxels within source share the same covariance across subjects.

SBM

ICA model

$$Y = A*S$$



Y — input data, matrix of dimensions **subjects X voxels**

A — mixing matrix, dimensions **subjects X components**, the columns are the subjects' loadings, i.e. how much is the component expressed in each subject

S — source matrix, dimensions **components X voxels**
the rows are spatial maps of components, statistically independent

SBM – data reduction

- data matrix is usually very big – especially in morpho-data (hundreds of thousands of voxels, hundreds of subjects)
- PCA reduction

PCA: $Y \approx R \cdot dwM \qquad R \in \Re^{nV,nC} \quad dwM \in \Re^{nC,nS}$

- matrix R can be evaluated analytically using eigenvectors and eigen values of matrix $Y*Y^T$

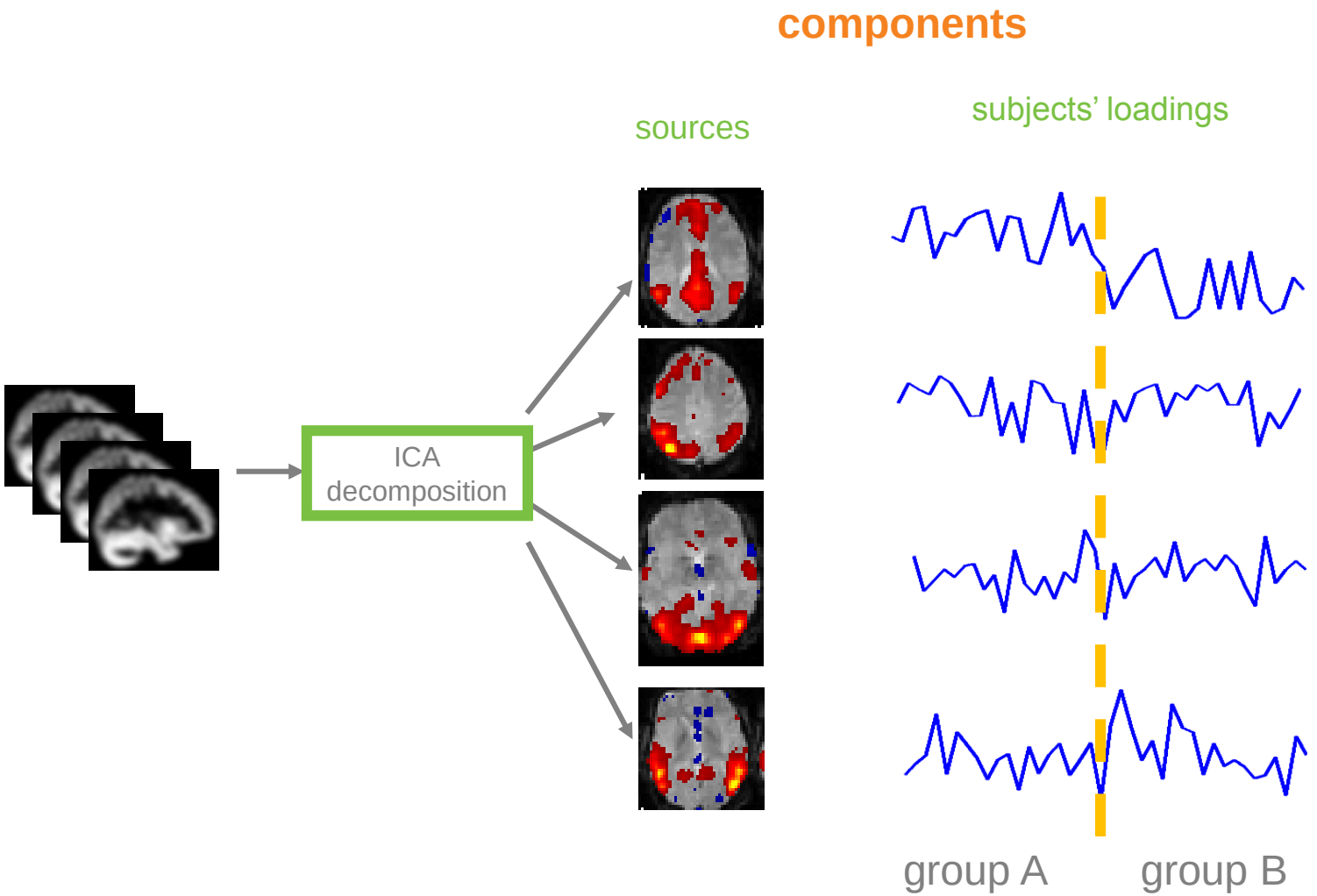
ICA: $S = R \cdot W$

$$Y \approx S \cdot W^{-1} \cdot dwM = S \cdot A$$

subjects' loadings

spatial maps of sources

SBM



The loadings are subjected to the same statistical analysis as voxels in VBM.

SBM – number of components

Number of components… the only input from user

- too many … some components may split
- too few … some component maz merge together

- the problem is how to set an optimal number of components
  - in morphometric studies usually between 8 and 20
  - analytical approaches for optimal number estimation (MDL, AIC, KIC criterions, ….)
  - ICASSO – the ICA estimation is run many times with random initialization, choosing the stable components
  - ratio of variability covered by the retained components

SBM – comparison to VBM

Advantages

- substantially lower number of test – smaller multiple testing problem

Disadvantages

- to set the optimal number of components
  - existing methods, e.g. MDL….

VBM vs SBM

VBM

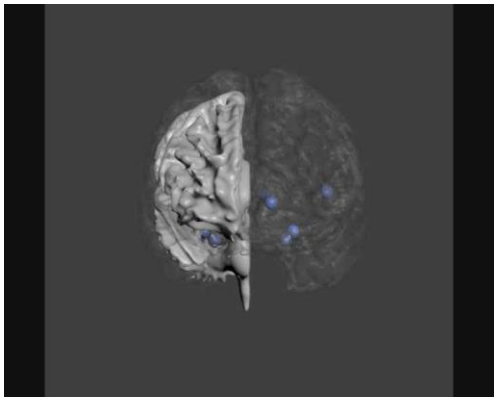
- univariate statistics
- linear model estimated in each voxel independently
- a lot of testing and strict correction for multiple testing
- VBM can reveal strong effects, which may be very discrete in space

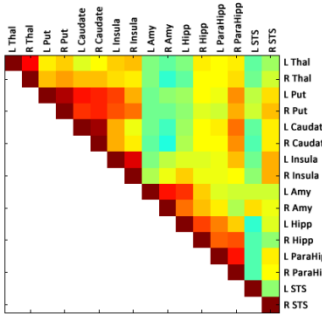
SBM

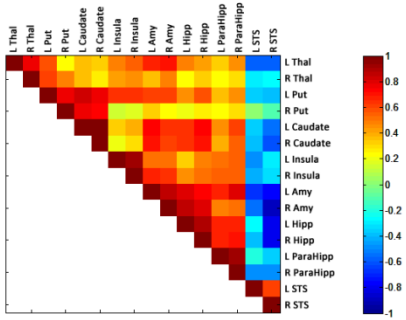
- multivariate statistics
- ICA uncovers spatial relationships in data
- SBM can reveal weak effects which are broadly distributed in space
- the number of components is substantially smaller than number of voxels => „smaller“ problem with correcting for multiple testing

VBM and SBM are complementary methods

Structural covariance







group A **group B**

- variant of structural connectivity
- group-specific cross-correlation matrices of e.g. local gray matter volume
- statistical comparison of the group-specific matrices
  - bootstrapping
  - group – relationship permutation
  - ANOVA, ANcova
  - PLS

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Note

Unveiling the mystery of déjà vu: The structural anatomy of déjà vu

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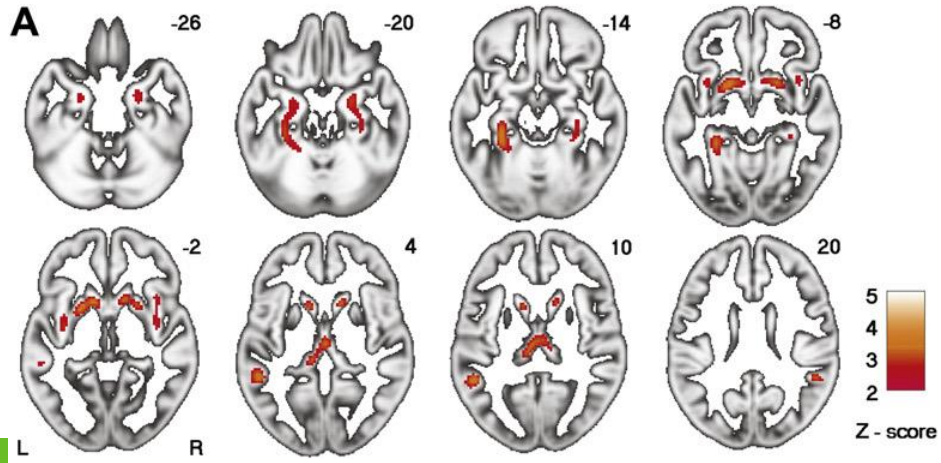
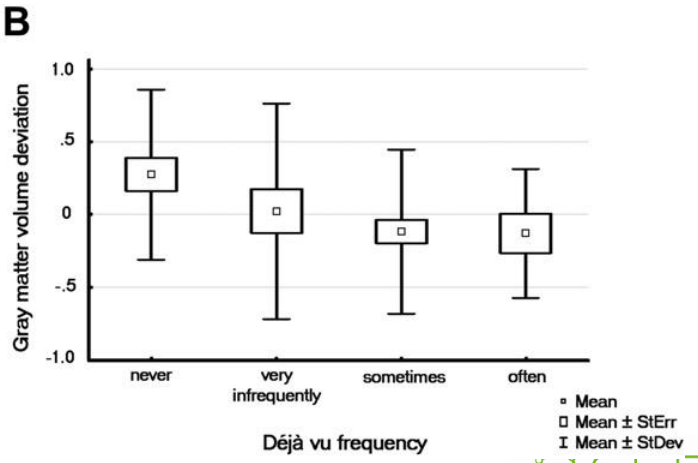




Déjà vu

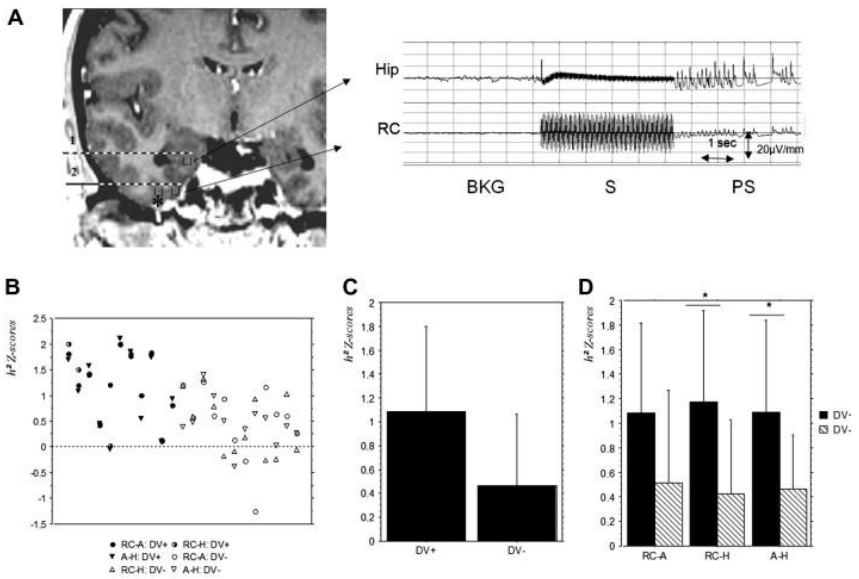
- Illusion déjà vu = feeling of already seen
- first description done by St. Augustine (De Trinitate) – „falsae memoriae“ (false memories)
- We have a feeling that distinct situation is very familiar, though it is experienced for the very first time. Concurrently, we realize that the feeling of familiarity is false…
- very common mental condition phenomenon
- fascinating, disturbing, even mystic experience
- it has been studied by psychologists and neuroscientists for more than one century

Déjà vu in healthy population

- **prevalence of déjà vu is about 60-80% in healthy population**
- it is “normal” condition
- many hypothesis…
- no generally accepted explanation for non-pathological Déjà vu

Déjà vu and temporal lobe epilepsy

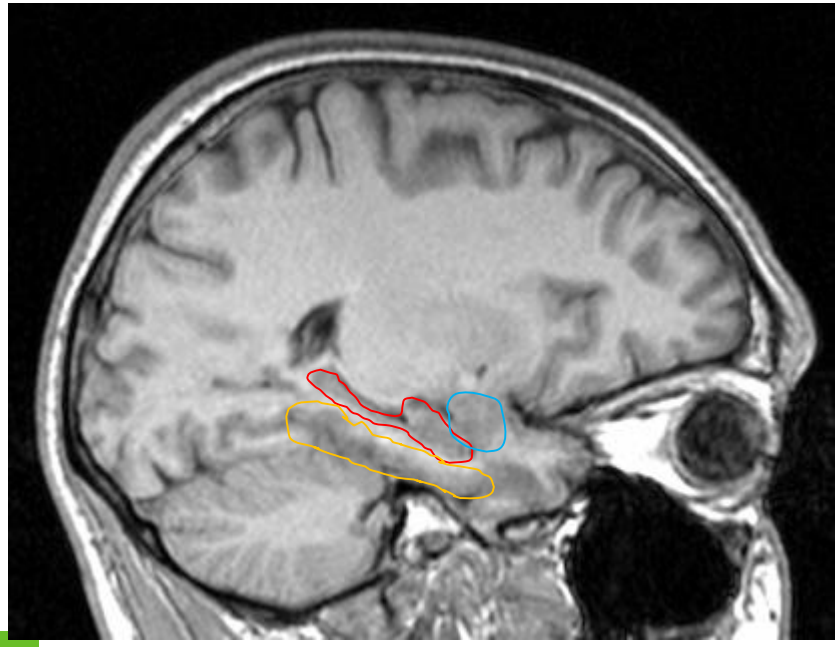
- déjà vu phenomenon is known in the context of temporal lobe epilepsy
- it comes as an “aura”, preceding the seizure (in 30% of cases)
- electrical stimulation of structures belonging to limbic system (amy, hipp and rhinal ctx) repeatedly induced déjà vu in patients



(Mulan and Penfield, 1959; Halgren, 1978; Gloor et al, 1982, Fish et al, 1993; Bartolomei et al, 2004, 2012; Vignal et al, 2007)

Déjà vu and temporal lobe epilepsy

EEG and neuroimaging studies of DV phenomenon showed the involvement of mesiotemporal structures in Déjà vu.



The mesiotemporal structures are involved in memory networks.

(Guedj et al., 2010; Kovacs et al., 2009; Vignal et al., 2007)

Questions and Hypotheses

- **What is the cause of déjà vu in healthy people?**

- DV in healthy population might be ictal (epi) phenomenon, like in epi patients (Penfield, 1955).

- Similar functional networks might play a role in generation of epileptic and non-pathological déjà vu.

- In that case, there might be functional and morphological differencies in these networks between healthy people with and without DV experience.

Participants - questionaires

- retrospective and prospective administration of „Inventory for Déjà Vu Experiences Assessment (IDEA) (Sno et al, 1994)

Měl jste někdy pocit, že jste přesně ten stejný vjem nebo situaci již někdy dříve zažil, přestože jste věděl, že je to poprvé?

- nikdy
- ano, velmi zřídka (méně než 1x za rok)
- ano, občas (několikrát ročně)
- ano, často (několikrát měsíčně)
- ano, více než často (minimálně 1x týdně)
- nevím

Subjects

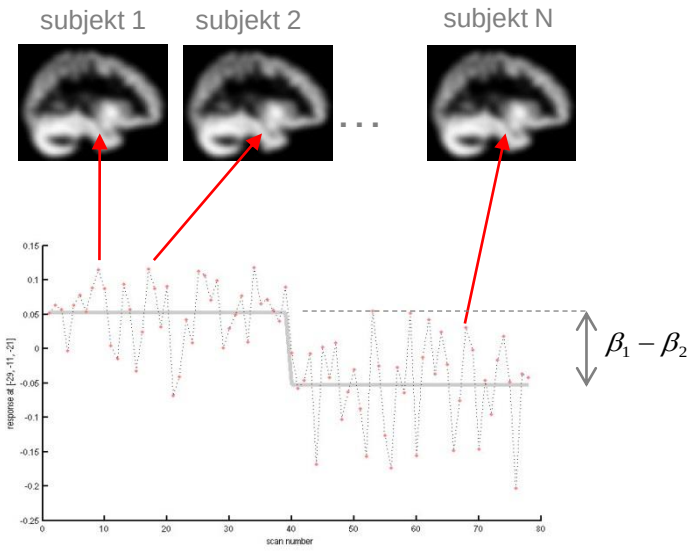
Group (déjà-vu frequency)	N	Age median (range)	Gender males/females
never	26	24 (20 ÷ 50)	13/13
very infrequent	24	24 (20 ÷ 38)	10/14
sometimes	52	24 (19 ÷ 46)	27/25
often	9	24 (21 ÷ 27)	6/3
very often	2	26 (24 ÷ 28)	2/0

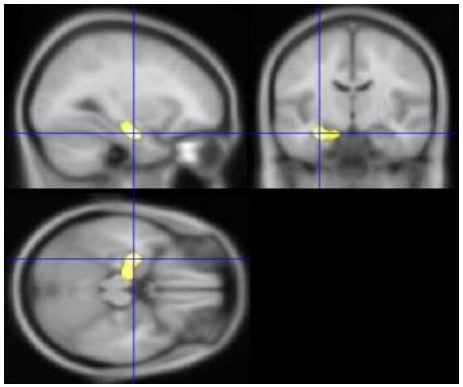
- 113 healthy subjects
- DV group - N=87; 45M; average age 24.8 years
- nonDV group - N=26; 13M; average age 26 years
- DARTEL – based preprocessing, multiplicative correction for TIV

VBM

- our hypothesis

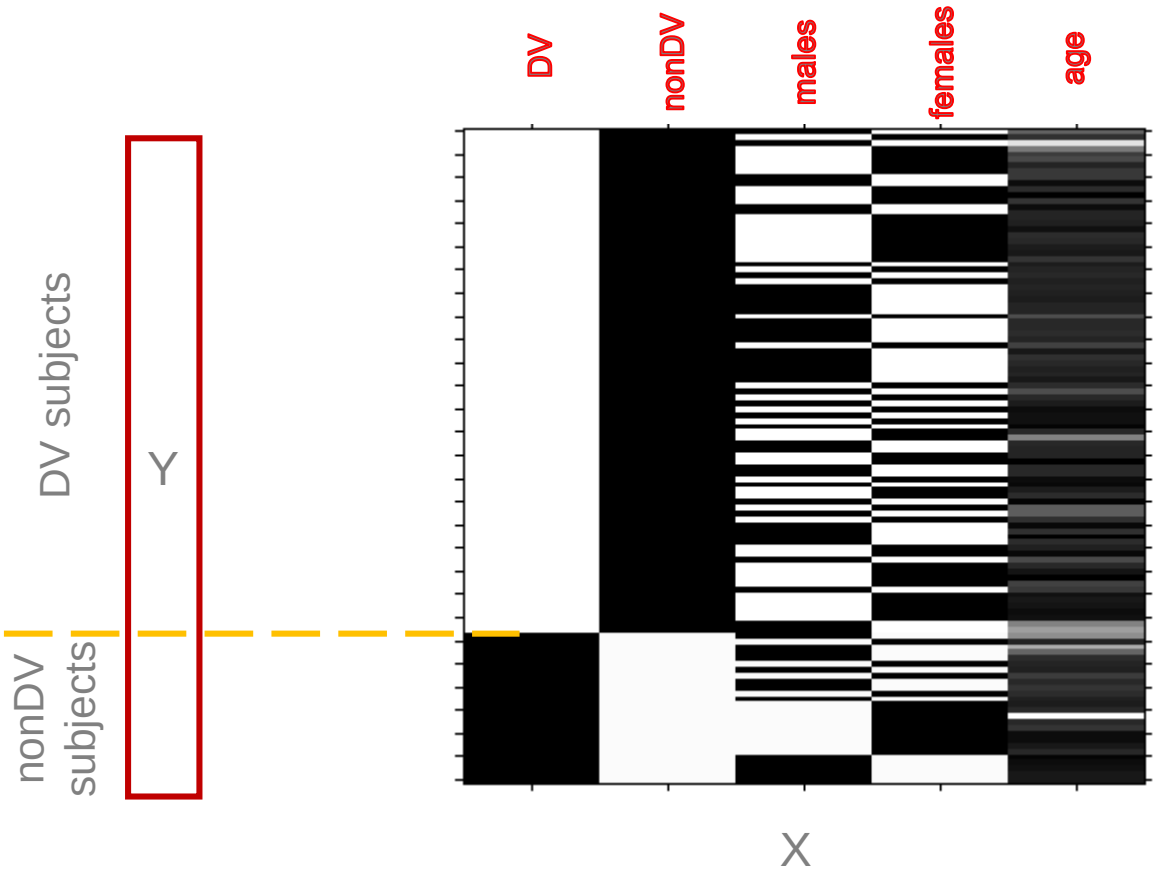
there is a difference in local gray matter volume between DV and nonDV group in some brain regions





VBM – implementation with GLM

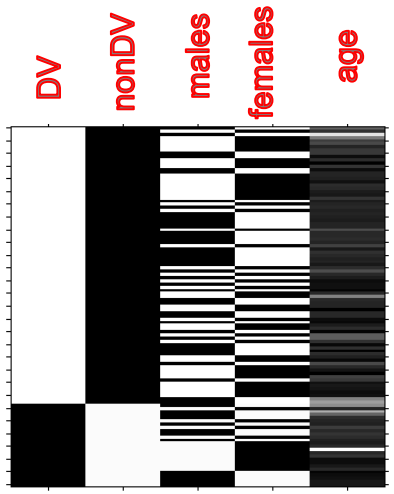
Design matrix:



Regressors:

- DV .. models the average of DV group
- nonDV .. models the average of nonDV group
- males/females .. model the average of male and female subgroups, thus effectively filters an effect of gender on the data
- age .. model an effect of age on the data

VBM – hypothesis testing



- our hypothesis:

there is a difference in local gray matter volume between DV and nonDV group in some brain regions

$$\left|\beta_1 - \beta_2\right| > 0$$

statistics $$T \approx \frac{\beta_1 - \beta_2}{\sigma}$$

error variance

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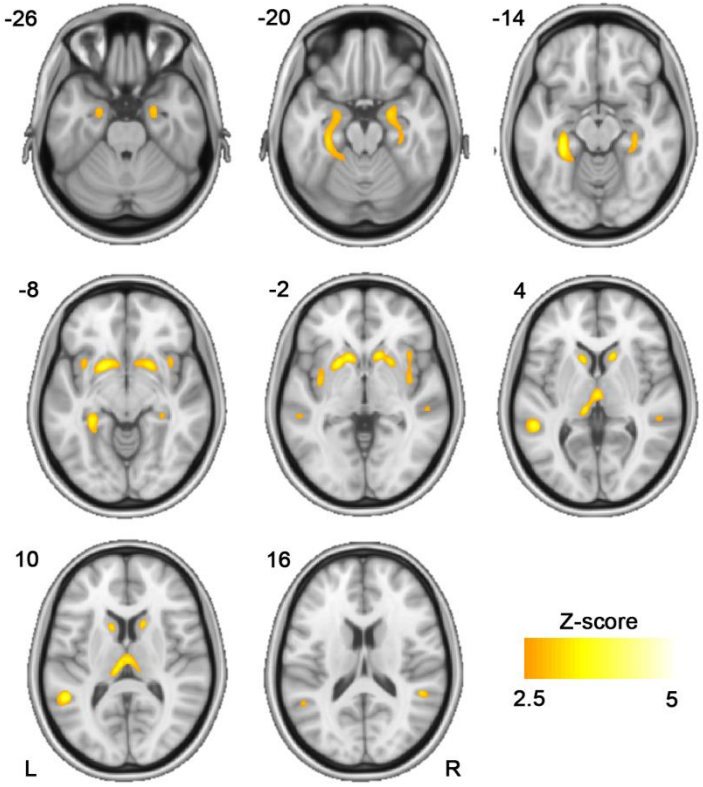
VBM - results

the effect of “group” factor was significant in no voxel at the preselected level of statistical significance ($p < 0.05$ FWE)

SBM and Déjà vu

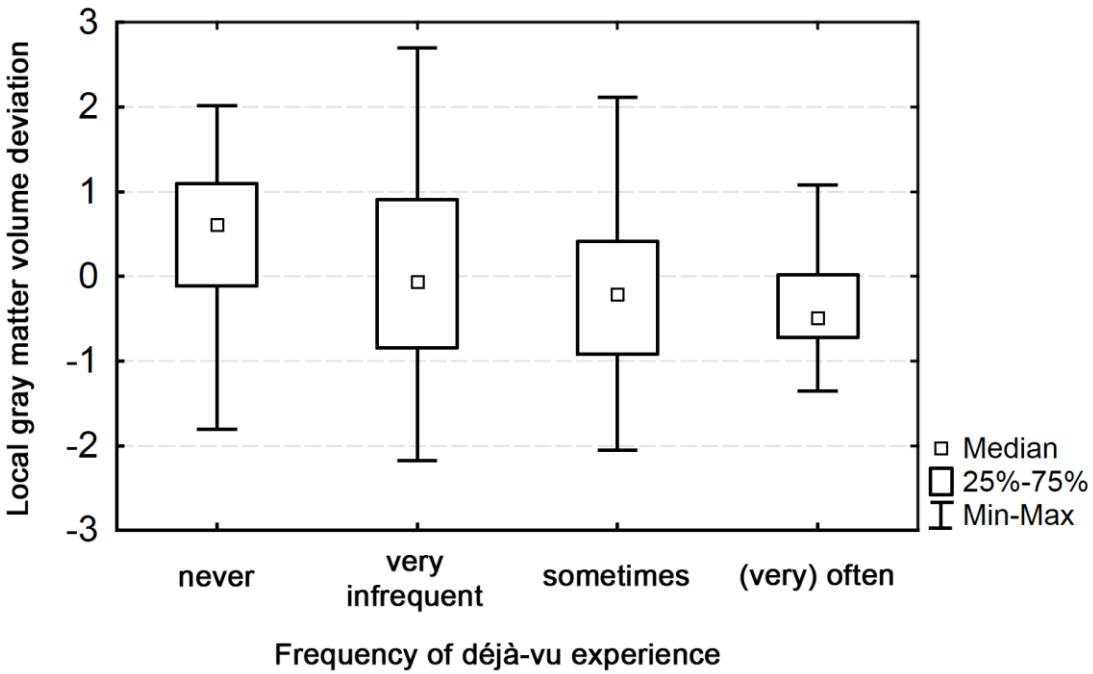
- according to MDL criterion, eight components optimally describe our data
- ICA computed using infomax algorithm
- the components' loadings were corrected for the effects of age and gender (using linear regression)
- the loadings for each component were tested for the group effect (the difference between DV and nonDV), Man-Whitney U test
- one of the components showed significant difference between DV and nonDV, $p<0.05$ FWE corrected (Bonferoni)

SBM - výsledek



R Insula

Kruskal-Wallis ANOVA, H=8.48, p<0.05



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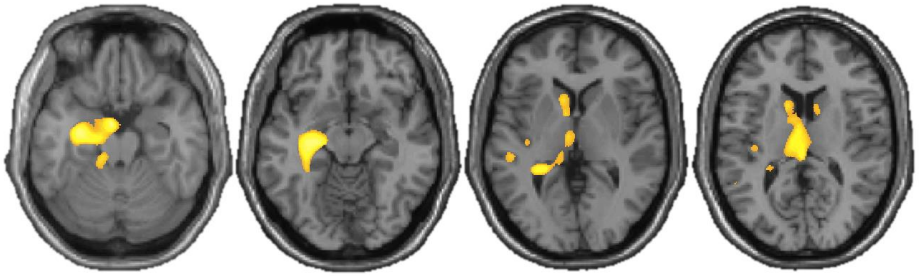
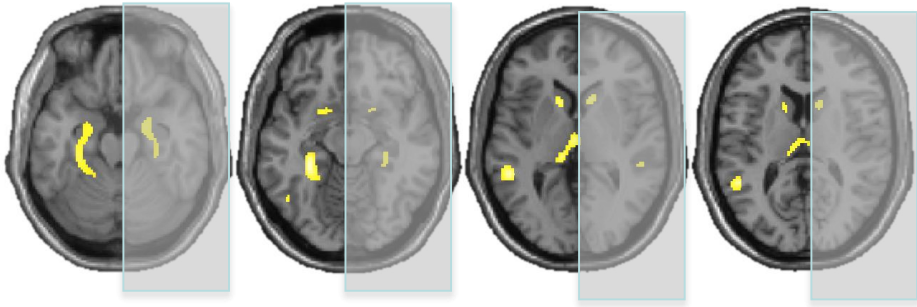
Discussion

- the results resembles recently published distribution of gray matter loss in MTLE patients (Brazdil et al, 2007; Keller and Roberts, 2008; Pail et al, 2010)
- it comprises mesiotemporal structures, temporal neocortex, thalamic and striatal nuclei, cingulum, insula, cerecellum – the structures which belong to limbic-temporal networks



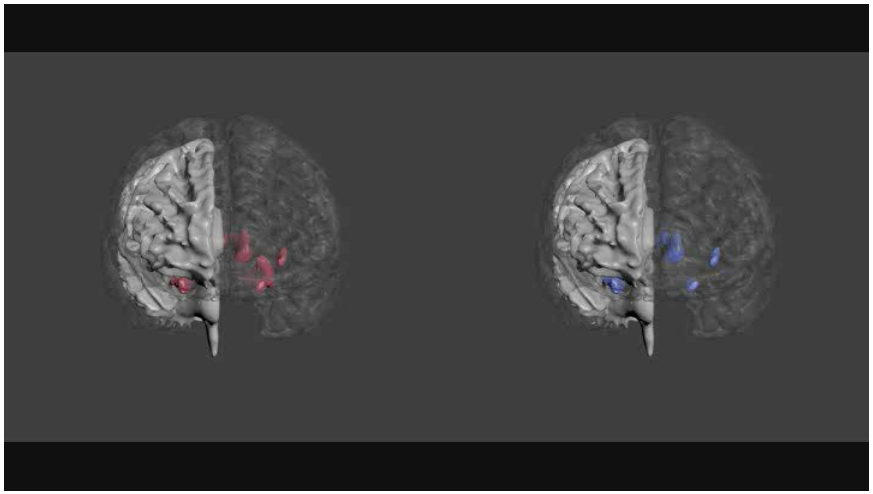
GMV decrease in MTLE patients

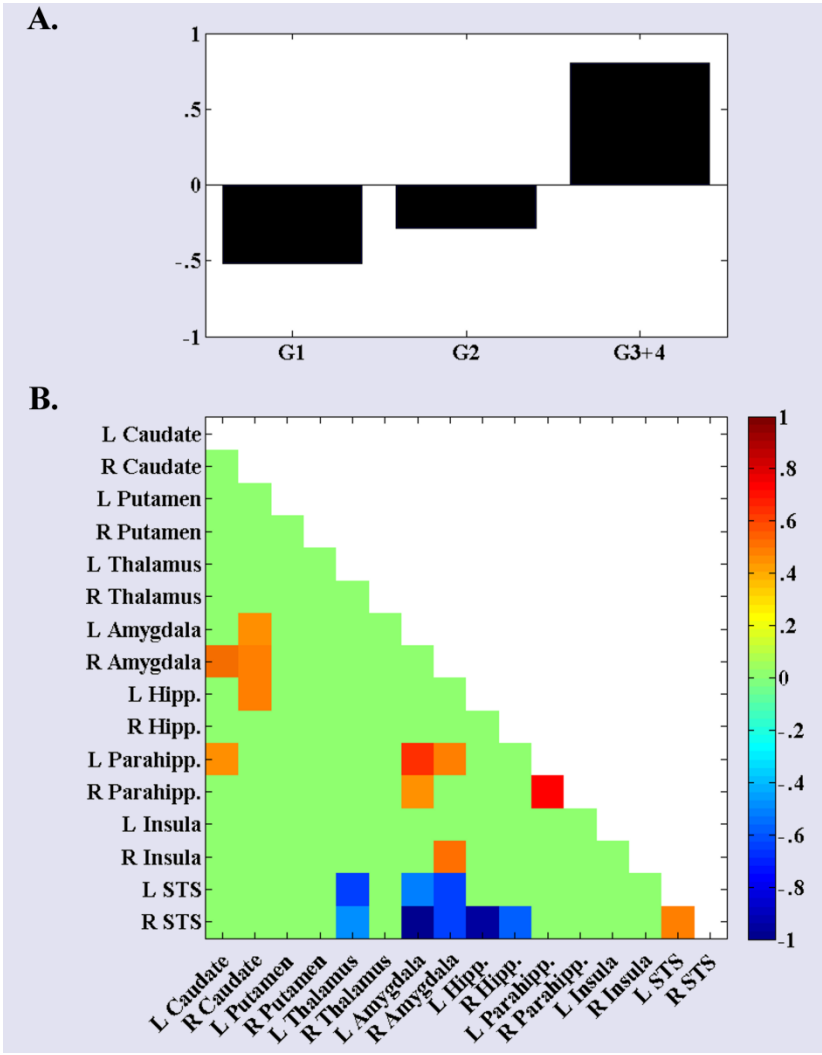


GMV decrease in healthy subjects who experience déjà vu phenomenon

Ensuing studies

- Dr. Daniel Shaw
  - there are two distinct subgroups of regions that have different relationship to déjà vu frequency
  - likely two distinct functional networks





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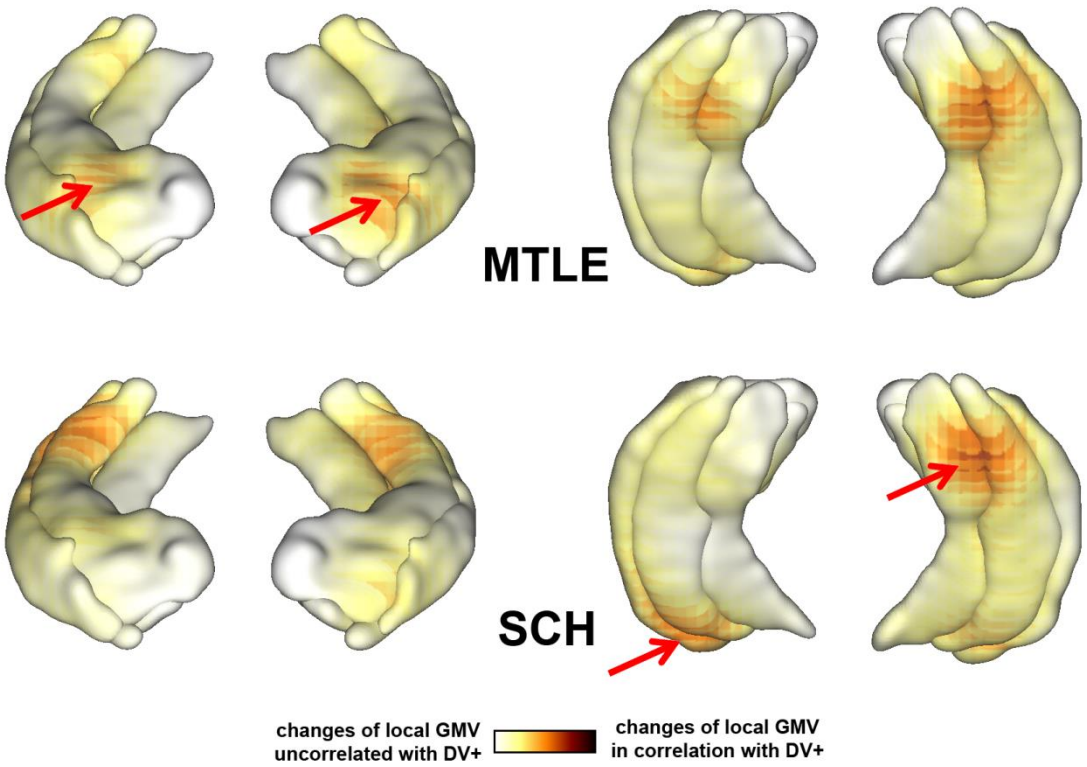
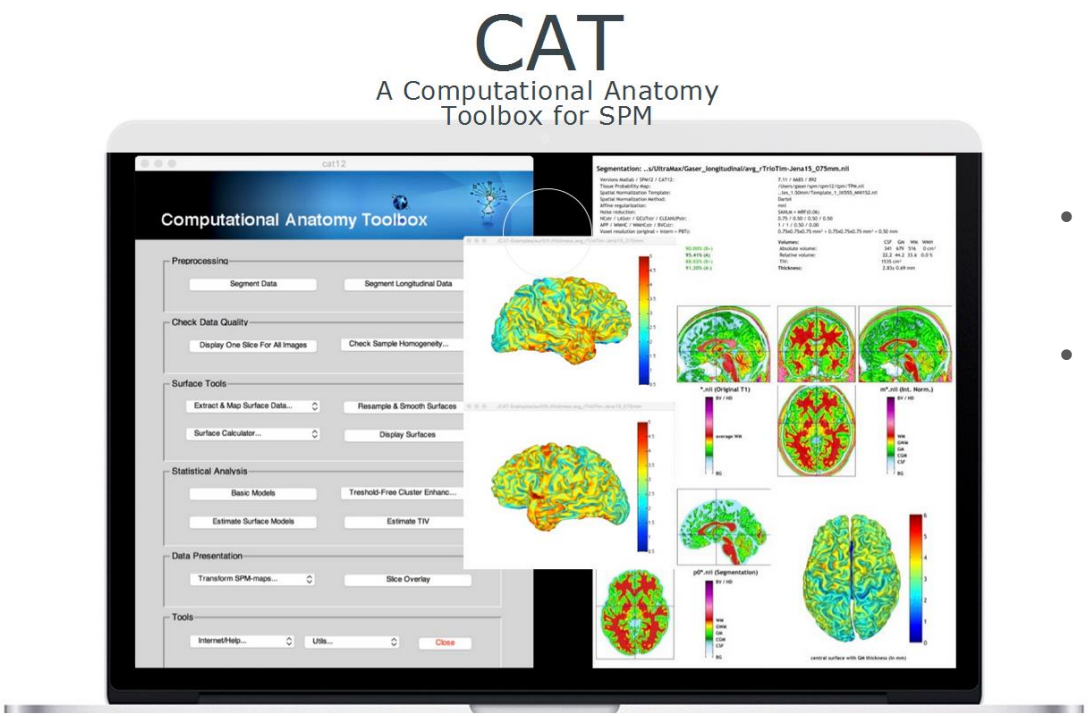
Ensuing studies

- Eva Pešlová (prof. Brázdil)
  - are the morphological changes that go along with Deja Vu close to some neurological/psychic disease? (MTLE or schizophrenia)



Computational Anatomy Toolbox for SPM CAT



- **preprocessing and various statistical analyses**
- **data quality check**

http://dbm.neuro.uni-jena.de/cat/

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Thank you for your attention

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