Statistical Parametric Mapping (SPM) 2008

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What is SPM?

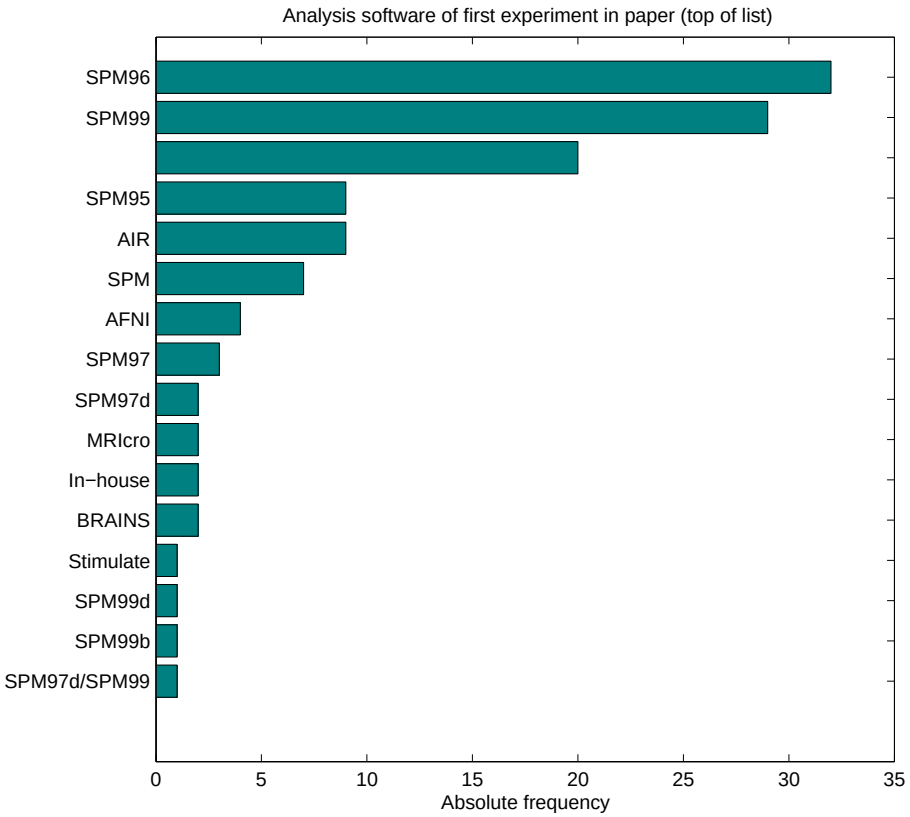


Figure 1: Histogram of used analysis software as recorded in the Brede Database, see original at http://hendrix.imm.dtu.dk/services/jerne/-brede/index_bib_stat.html

A method for processing and analysis of neuroimages.

A method for voxel-based analysis of neuroimages using a 'general linear model'.

The summary images (i.e., result images) from an analysis: Statistical parametric maps.

A Matlab program for processing and analysis of functional neuroimages — and molecular neuroimages. SPM is very dominating in functional neuroimaging

SPM — the program

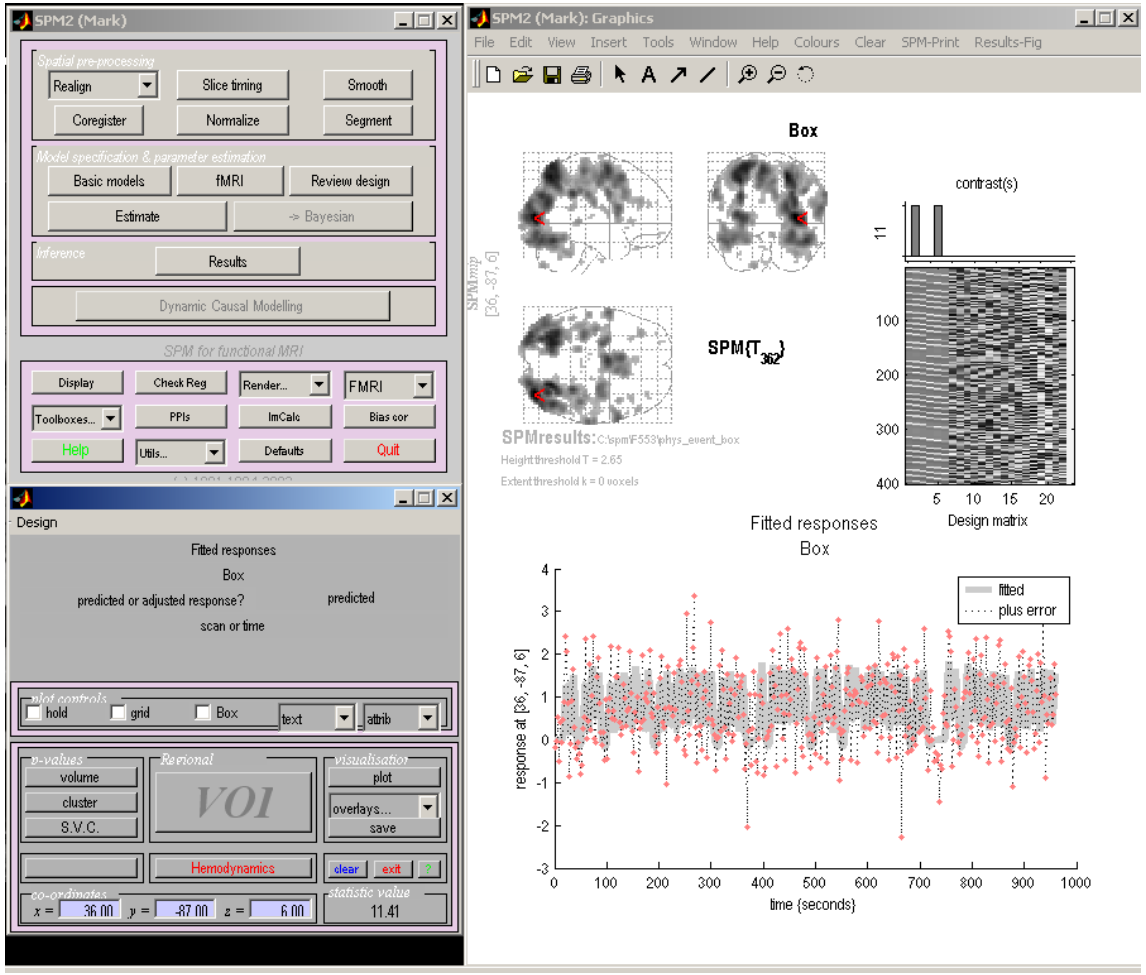


Image registration, segmentation, smoothing, algebraic operations

Analysis with general linear model, random field theory, dynamic causal modeling

Visualization

Email list with $\sim$ 2000 subscribers

Figure 2: Image by Mark Schram Christensen.

Data transformations

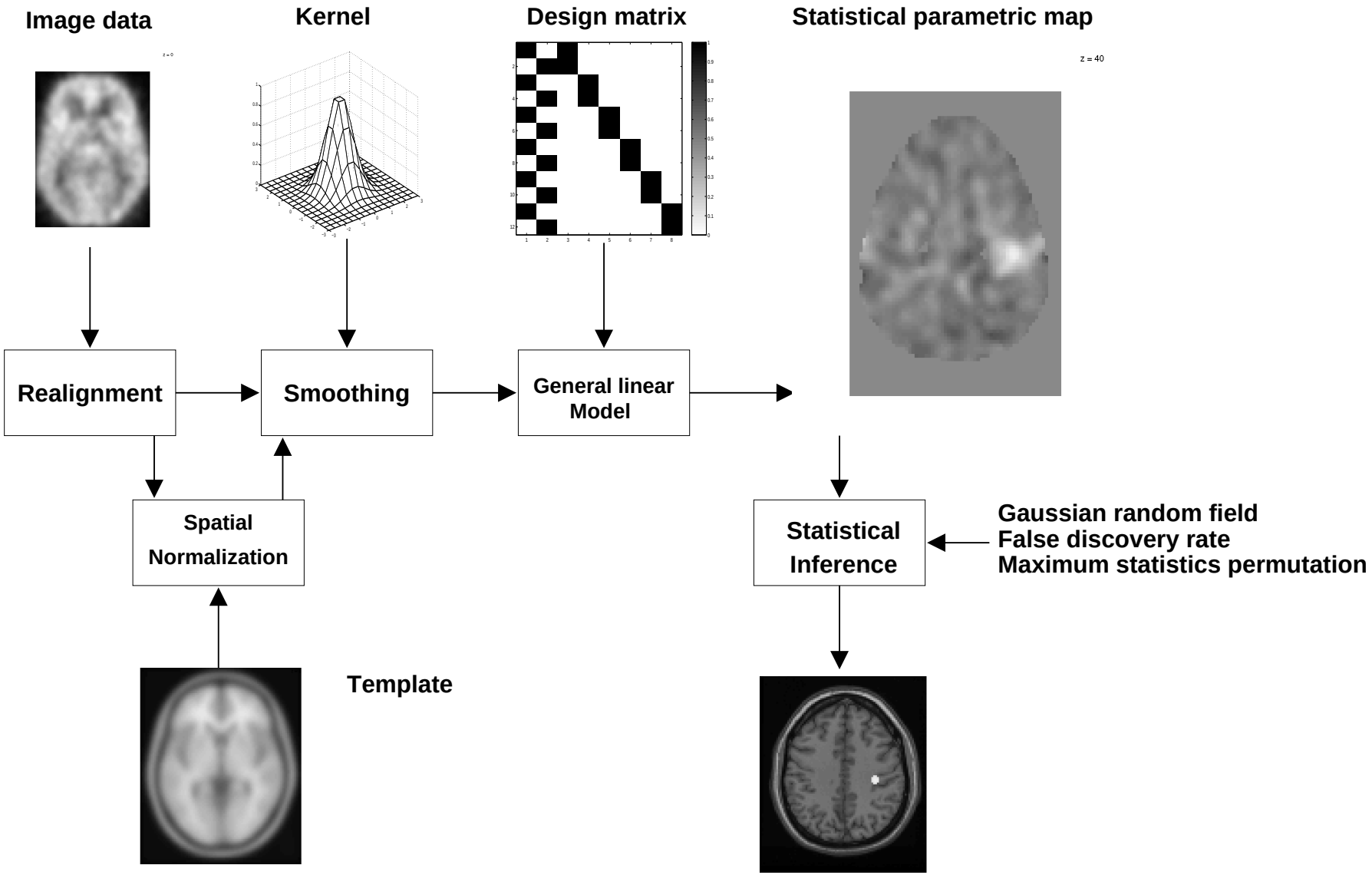


Image registration

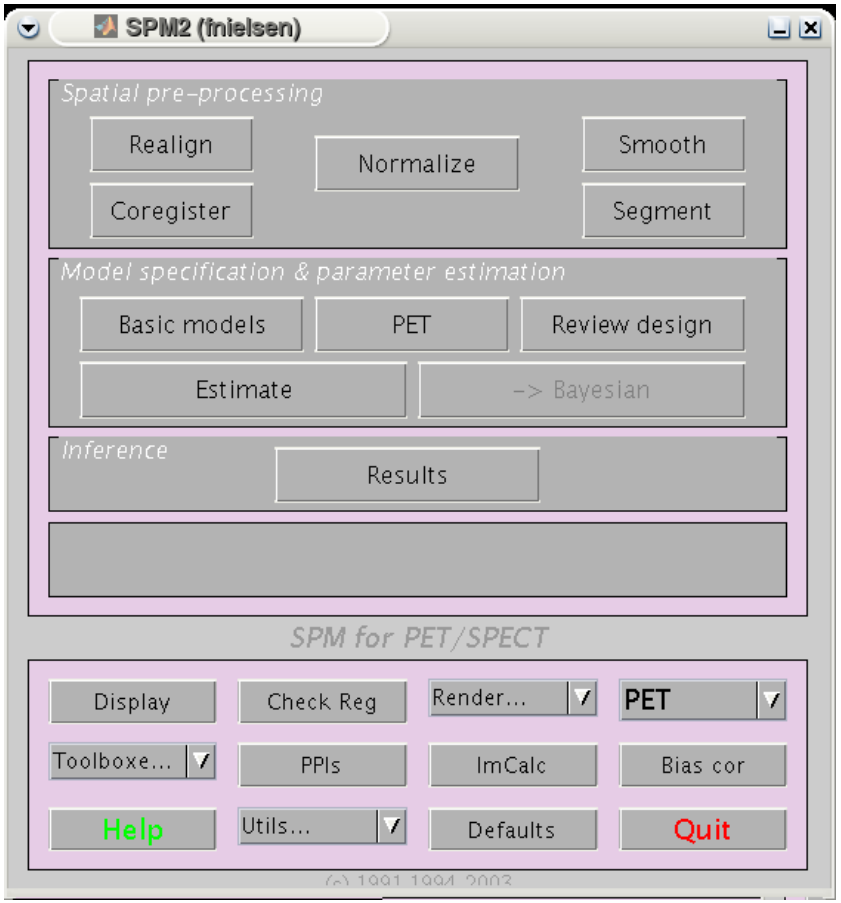


Figure 3: Main window of SPM2. Image registration are the three left upmost buttons.

Image registration: Move and warp brain

Motion realignment of consecutive scans ('realign'). Within subject

Coregistration or intermodality registration, e.g., to registation a PET and an MRI. Wihtin subject.

Spatial normalization: Deform brain to a template. 'MNI' Templates are distributed with SPM. Between subjects.

Realignment

Several images in the same modality from the same subject

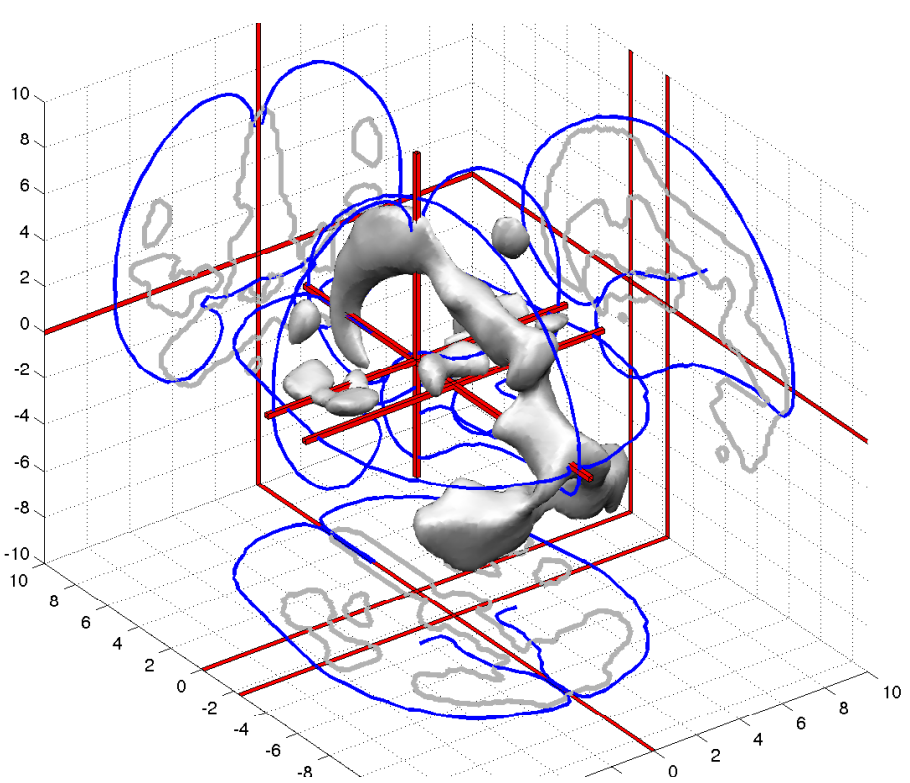
Two-stage procedure:

1. Estimate movement. SPM: 'Determine parameters'

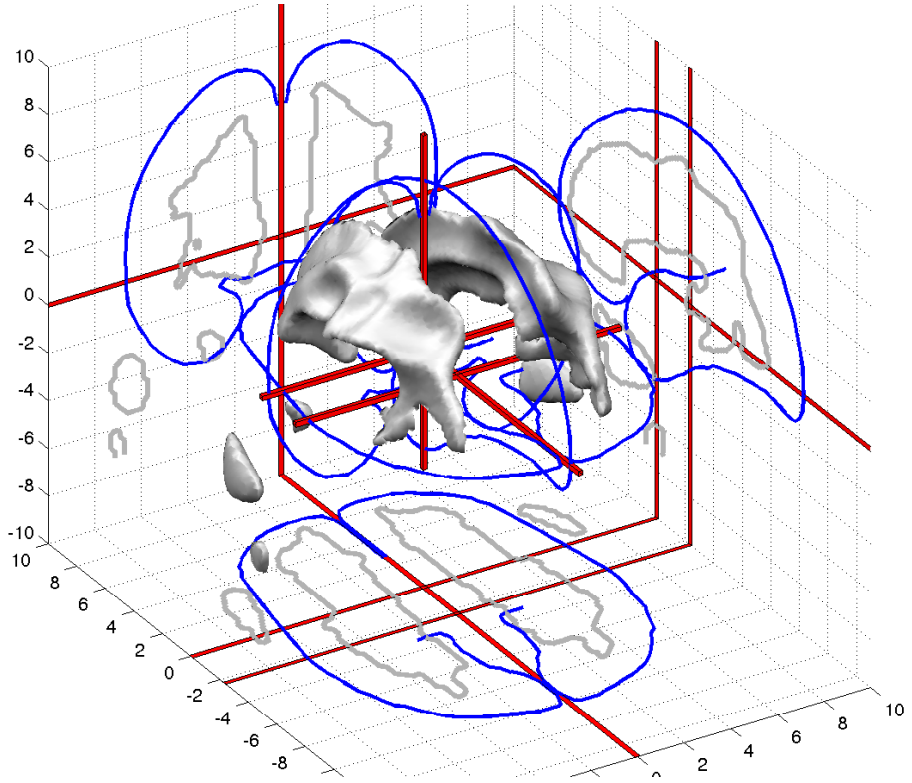
2. Resample images based on estimated movement

In SPM resampling can be postponed and the estimated movement saved in a `.mat` file with the 'transformation matrix'.

Coregistration



(a) PET template from SPM.



(b) MRI T1 template from SPM.

Figure 4: The areas with the highest values in two modalities of PET and MRI brain scans: For registration the problem is that they are different!

Spatial normalization

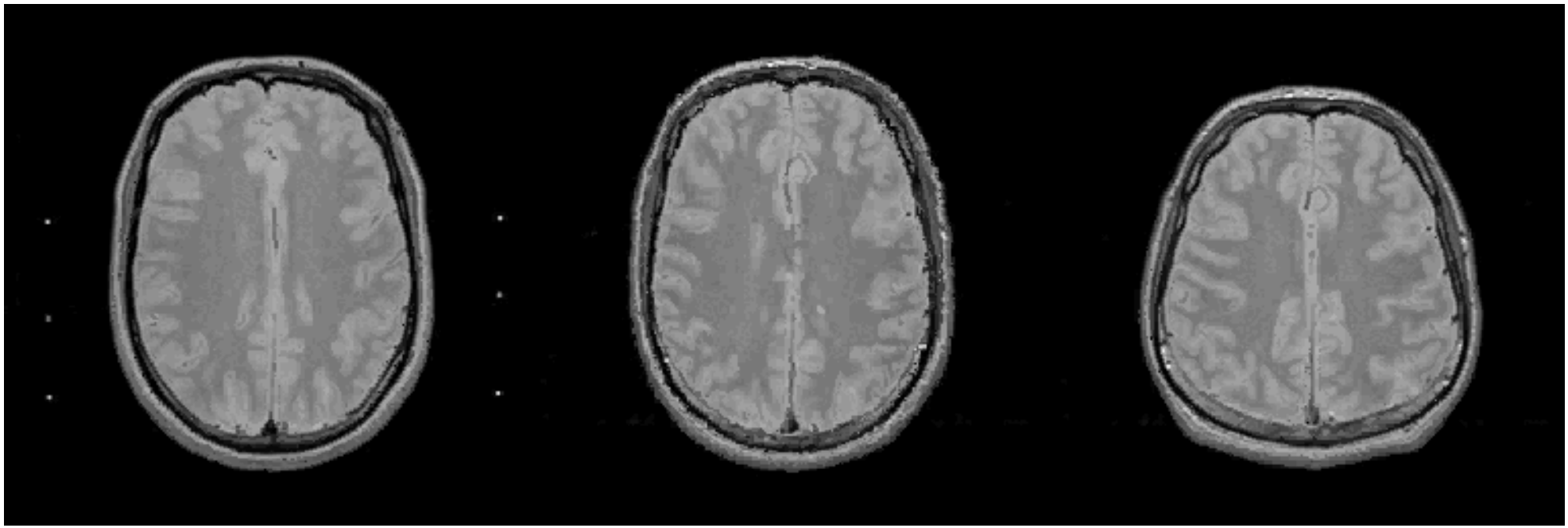


Figure 5: Warp of right subject to left subjects brain. Result in the middle. Image by Ulrik Kjems using MRIwarp (Kjems et al., 1999a; Kjems et al., 1999b).

Spatial normalization in SPM

Two-stage procedure:

1. Determine warp parameters by matching a subjects anatomical MRI ('Source image') to a template ('Determine parameters').

   These parameters are stored in a file with the postfix `_sn.mat`

2. Apply ('Write normalised') the warp parameter to warp the anatomical (T1 MRI) and the functional image (fMRI or PET) ('Images to write')

   The new files have the prefix '`w`' for warp.

By default SPM is normalizing to so-called 'MNI-space' which is slightly different from the original 'Talairach atlas' (Talairach and Tournoux, 1988; Brett, 1999a; Lancaster et al., 2007).

. . . Spatial normalization in SPM

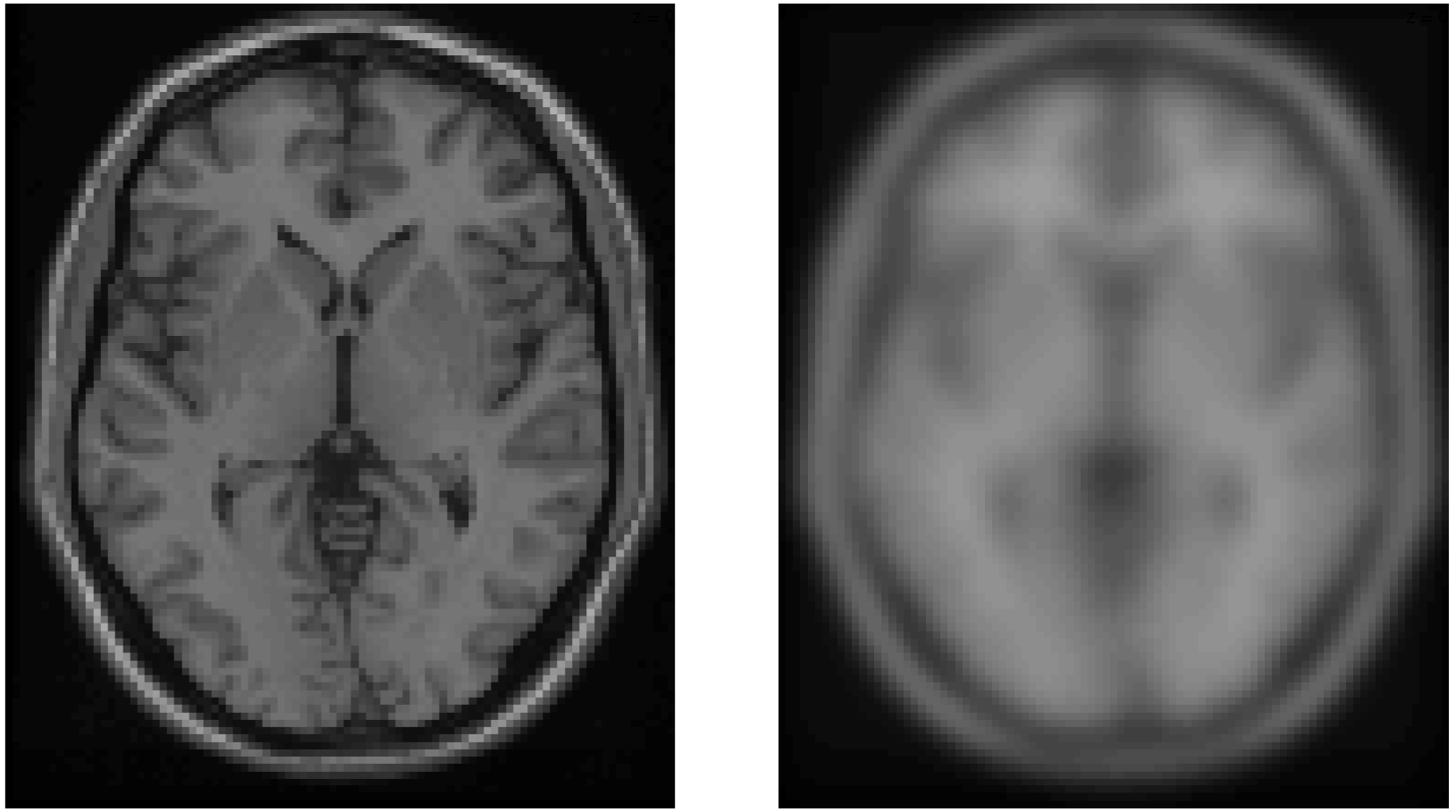
Warping may not work properly: Check the result, e.g., with 'Check Reg.' button in SPM.

There are a number of hidden parameters in SPM: smoothing, regularization, 'cutoff' (how many basis functions), interpolation, bounding box, etc.

> '[. . .] if your normalized images appear distorted, then it may be an idea to increase the amount of regularization' (spm_normalise_ui.m)

If adjusting these parameters does work try to skull strip the volumes.

Spatial smoothing



(a) Unsmoothed original. (b) Smoothed. FWHM=10mm.

Figure 6: T1 single subject template from SPM99.

Spatial smoothing

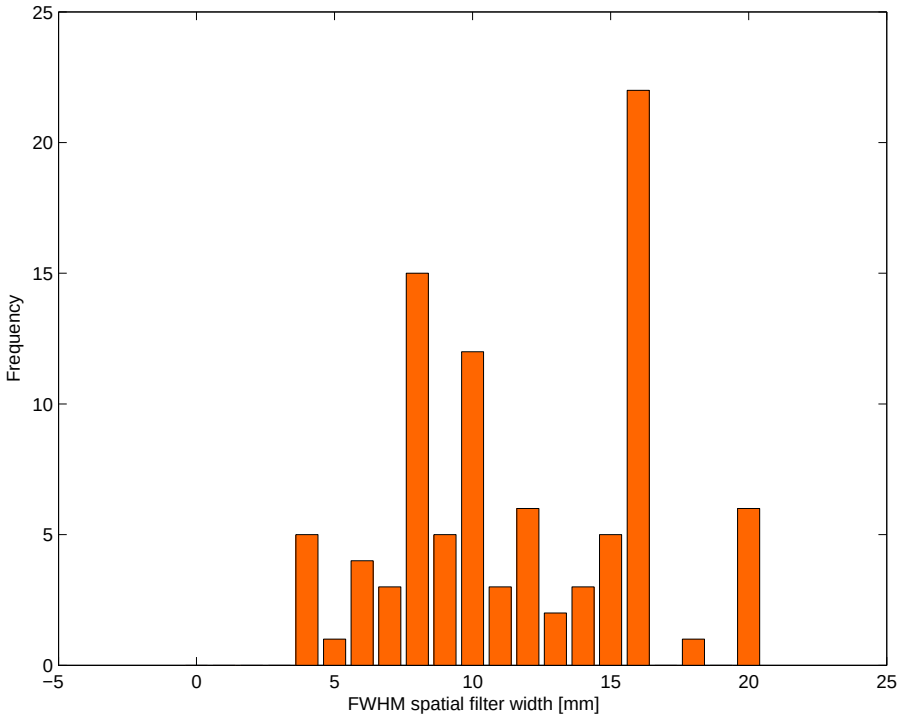


Figure 7: Histogram of smoothing width in the Brede database, see original at http://hendrix.imm.dtu.dk/services/jerne/-brede/index_bib_stat.html

Accounts for anatomical variability. Might increase signal to noise ratio. Increase validity of SPM inference

Usually performed with with an Gaussian kernel.

SPM command line

```
spm_smooth(filenameIn, filenameOut, 16);
```

Here 16 is the 'full width half maximum' in millimeters

$$\mathrm{FWHM} = \sqrt{8 \ln 2}\ \sigma \approx 2.35\sigma.$$

An 's' is prefixed on the filename.

Spatial masks

Spatial mask: Exclude voxels from the statistical analysis, e.g., non-brain voxels and brain voxels not (likely) 'significant'.

SPM terminology

- Threshold, 'absolute', 'relative' ('Grey matter threshold').
- 'Implicit mask': Omit voxels that are zero or NaN.
- 'Explicit mask': A volume file specifying the which voxels to include (ones and zeros).
- So-called 'F-masking' appeared in early versions of SPM: SPM94/5/6.

Spatial mask — Global mean

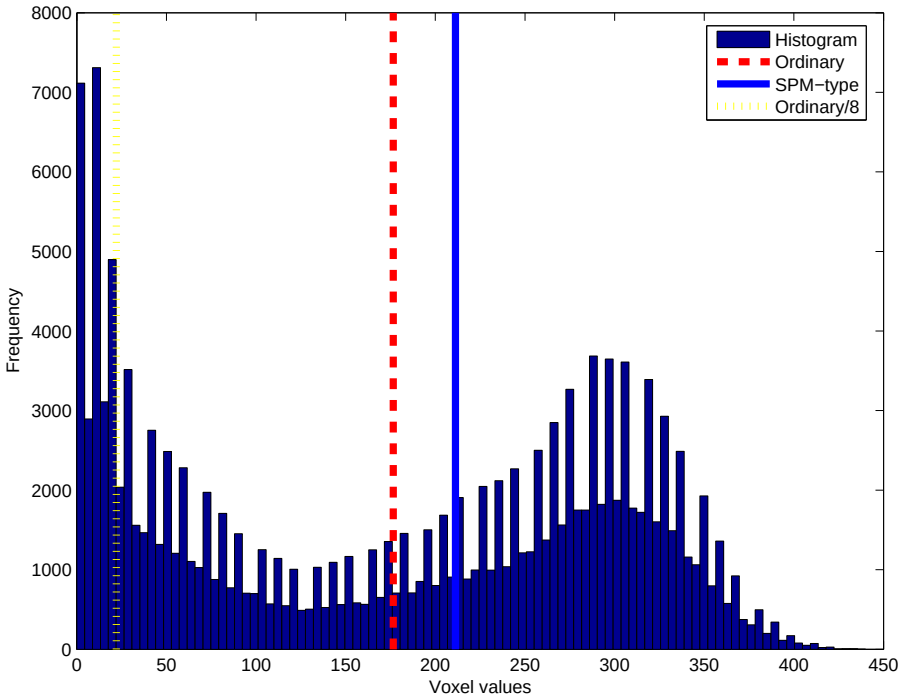


Figure 8: Example of a histogram from a PET volume (Noll et al., 1996).

What is the mean value of a brain scan?

A simple mean will be affected by the number of non-brain voxels. These are around zero.

A more robust 'global mean' can be calculated in two-stages: First the ordinary mean is computed, then the mean of values above mean/8. (Computed in `spm_global.m` and `spm_global.c` available at `SPM.xGX.rg`)

The value is used for confounds and masking operations.

Noll's PET motor SPM masking example

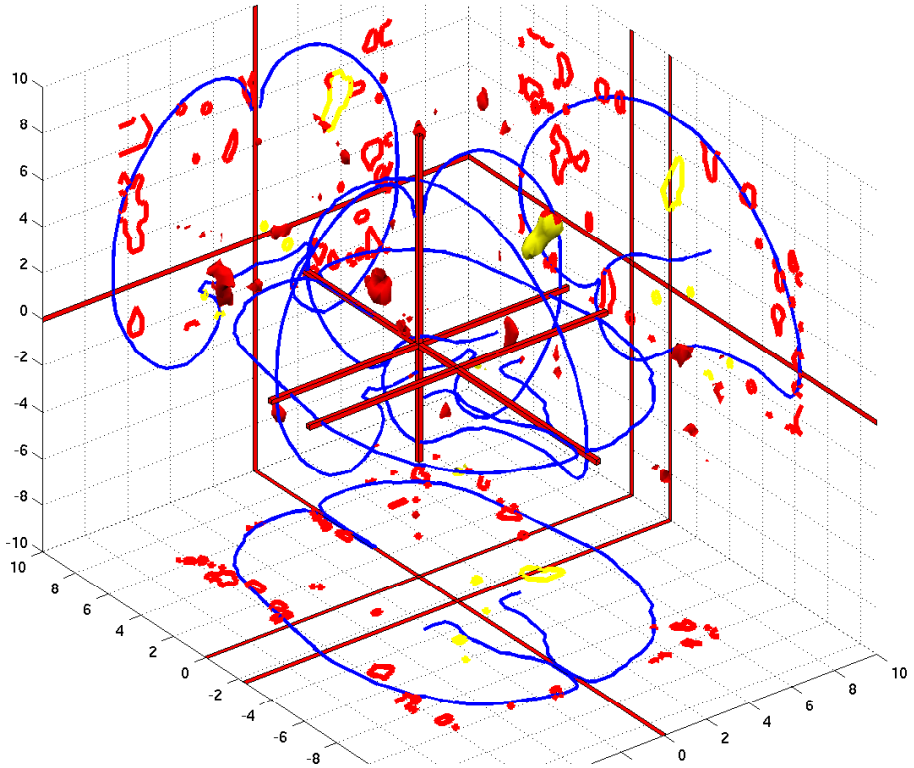


Figure 9: PET motor, left hand finger opposition task, 12 scans: Odd activation, even baseline (Noll et al., 1996). Red is without mask. Yellow with mask. Thresholded at $t = 2.76$ ($P < 0.01$).

SPM analysis: two-sample test, 'no grand mean scaling', 'omit global calculation'.

'Single-subject: conditions & co-variates', 0 covariates and nuisances 'no global normalization', 'no grand mean scaling', mask (fullmean/8 mask).

Without a mask many non-brain voxels appear with high statistics.

Analysis with the general linear model

- The general linear model has the form (Mardia et al., 1979, eq. 6.1.1)

$$\mathbf{Y} = \mathbf{XB} + \mathbf{U},$$

  where $\mathbf{Y}$(scans $\times$ voxels) is the image data, $\mathbf{X}$(scans $\times$ design variables) is the 'design matrix' and $\mathbf{B}$(design variables $\times$ voxels) contains parameters to be estimated and tested. The residuals $\mathbf{U}$ are usually assumed Gaussian.

- Encapsulates many statistical models: t-test (paired, un-paired), F-test, ANOVA (one-way, two-way, main effect, factorial), MANOVA, ANCOVA, MANCOVA, simple regression, linear regression, multiple regression, multivariate regression, ...

- Widely used in functional neuroimaging through the SPM program where it is performed in a mass-univerate setting — in parallel over the columns of $\mathbf{Y}$ (Friston et al., 1995).

Process for analysis

Specify design: Set up the design matrix $\mathbf{X}$

Estimate: Find the parameters $\mathbf{B}$ and the residuals $\mathbf{U}$

Test: Specify a test (a 'contrast') and test-statistic threshold and view the results.

Basic models

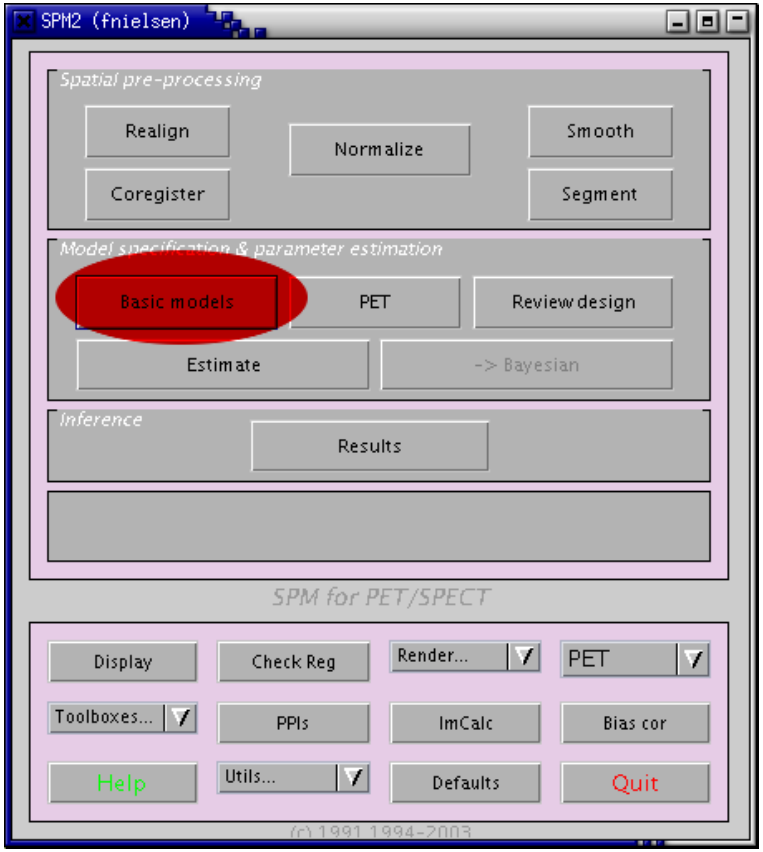


Figure 10: SPM 2 main interface window with 'Basic models' button high lighted.

'Basic models' of SPM:

One-sample t-test, two-sample t-test, paired t-test, one-way ANOVA, one-way ANOVA with constant, one-way ANOVA 'within-subjects', simple regression (correlation), multiple regression, multiple regression with constant, ANCOVA.

The models only vary because of difference in specification of the design matrix.

Simple regression

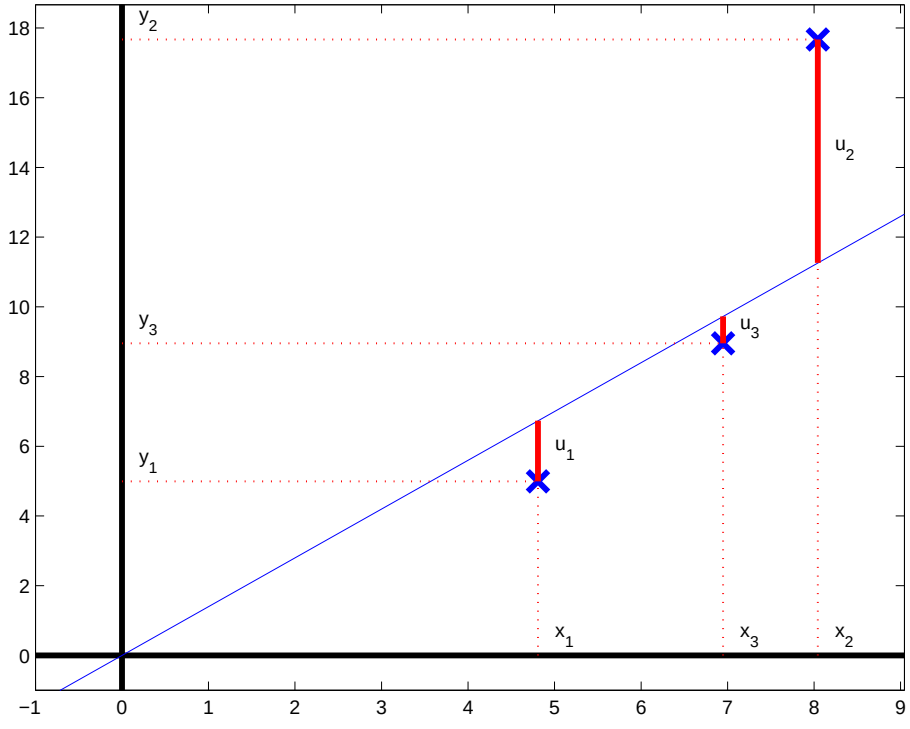


Figure 11: Simple regression.

In simple regression (e.g., one voxel) is univariate and the matrices from the general linear model become vectors or scalars: $\mathbf{Y} \rightarrow \mathbf{y}$, $\mathbf{X} \rightarrow \mathbf{x}$ and $\mathbf{B} \rightarrow b$

$$\mathbf{y} = \mathbf{x}b + \mathbf{u},$$

where $\mathbf{y}$ is the dependent variable (usually measured), $\mathbf{x}$ is the independent variable (design variable) and b is the parameter (regression coefficient).

Regression model

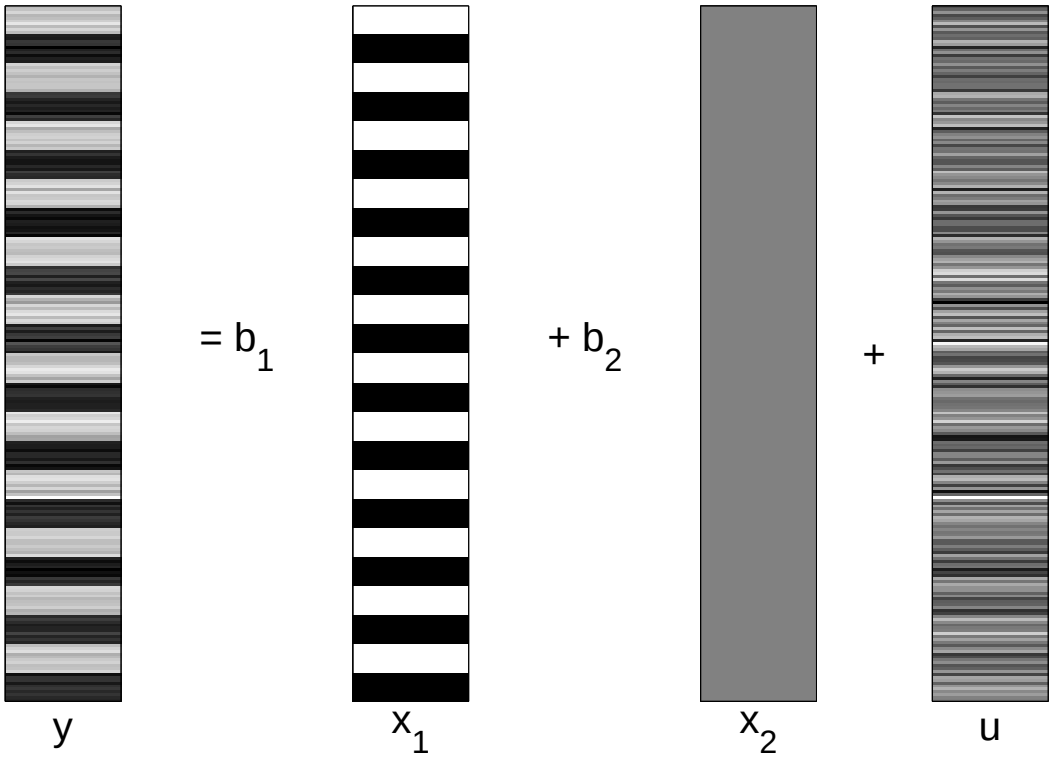


Figure 12: Regression model. One voxel with 120 scans. Gray level indicate the value.

Regression model

$$\mathbf{y} = b_1\mathbf{x}_1 + b_2\mathbf{x}_2 + \mathbf{u},$$

where $\mathbf{y}$ contains the values of a specific voxels across scans.

$\mathbf{x}_1$ models, e.g., activation/rest or patients/controls.

$\mathbf{x}_2$ models, e.g., the intercept, — a constant value

$\mathbf{u}$ the noise/residual/error

Categorical variables in design matrix

Categorical variable can be coded in two different ways:

'Sigma-restricted', where two groups (e.g., male and female) are coded in one design variables, e.g., male $+1$ and female -1

$$\mathbf{x}_{(1)} = \begin{bmatrix} 1, & -1, & 1, & -1, & 1, & -1, \end{bmatrix}^{\mathsf{T}},$$

that leads to a design matrix with full rank.

'Overparameterized', where two groups are coded in two design variables

$$\mathbf{X}_{(1:2)} = \begin{bmatrix} 1 & 0 & 1 & 0 & 1 & 0 \\ 0 & 1 & 0 & 1 & 0 & 1 \end{bmatrix}^{\mathsf{T}},$$

that leads to a design matrix of degenerate rank.

(terminology from www.statsoftinc.com)

The overparameterized version is often preferred due to better 'ordnung'.

ANCOVA — ANalysis of COVAriance

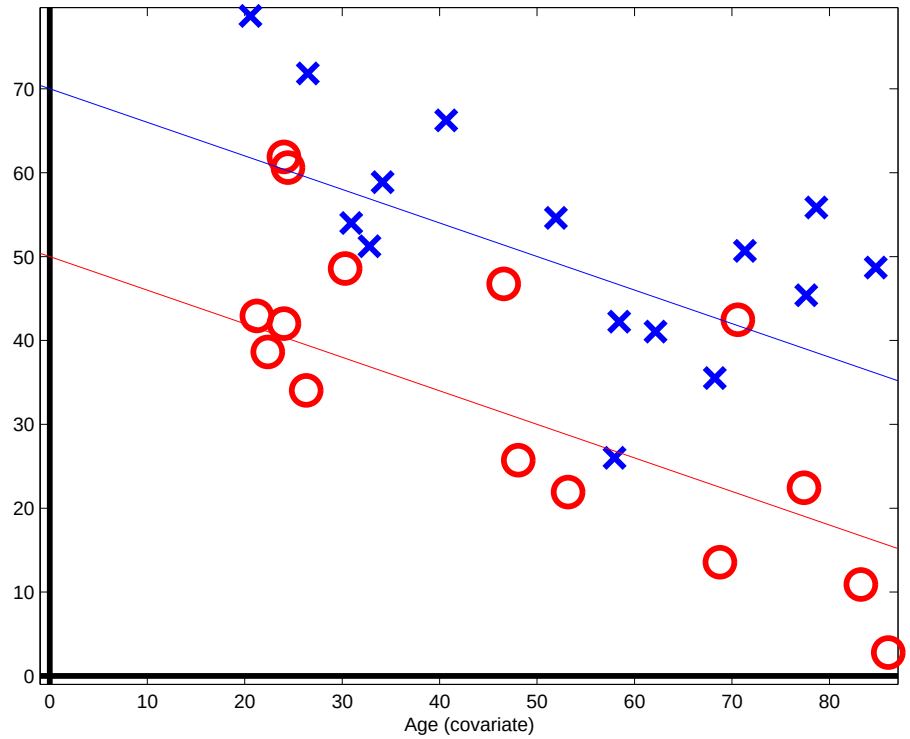


Figure 13: ANCOVA. Two groups (e.g., normals and patients) with and age-effect. Normals/patients indicator variable ($\mathbf{x}_1$), age nuisance variable ($\mathbf{x}_2$) and intercept ($\mathbf{x}_3$).

1) Model with categorical and continuous design variables.

2) Conditions + Nuisances (covariates, e.g., age)

An instance of multiple regression.

Why ANCOVA? Because the variance induced by the covariates might make the test less powerful! t-statistics for the example:

$$t_{\text{ordinary}} = -3.1 \quad (1)$$

$$t_{\text{ANCOVA}} = -5.0 \quad (2)$$

Interactions

With 'linear' interactions (aka moderator effects)

$$\mathbf{y} = \mathbf{x}_1 b_1 + \mathbf{x}_2 b_2 + (\mathbf{x}_1 \odot \mathbf{x}_2) b_3 + + b_4 + \mathbf{u},$$

where $\odot$ is an elementwise multiplication: $\mathbf{x}_3 = \mathbf{x}_1 \odot \mathbf{x}_2$, e.g., for the first scan: $x_{1,3} = x_{1,1} x_{1,2}$.

Design matrix for paired t-test

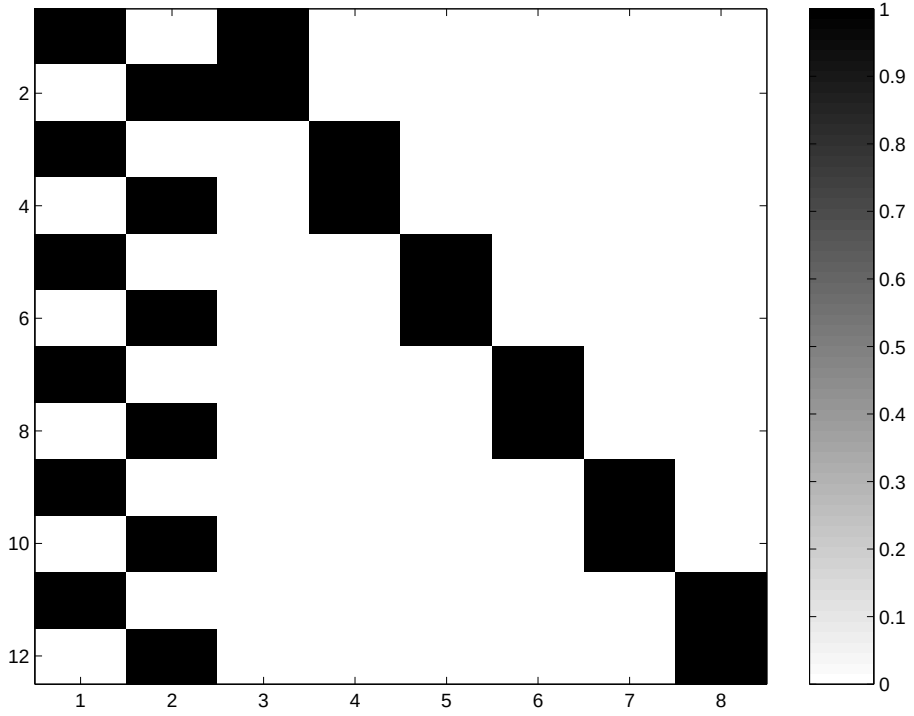


Figure 14: Design matrix $\mathbf{X}$ for paired t-test with 12 scans, i.e., 6 pairs of scans. For each element black indicates a one while white indicates a zero.

Paired t-test example

$$\mathbf{y} = \left[d_{1,2}, d_{3,4}, \ldots, d_{11,12}\right]^{\mathsf{T}},$$

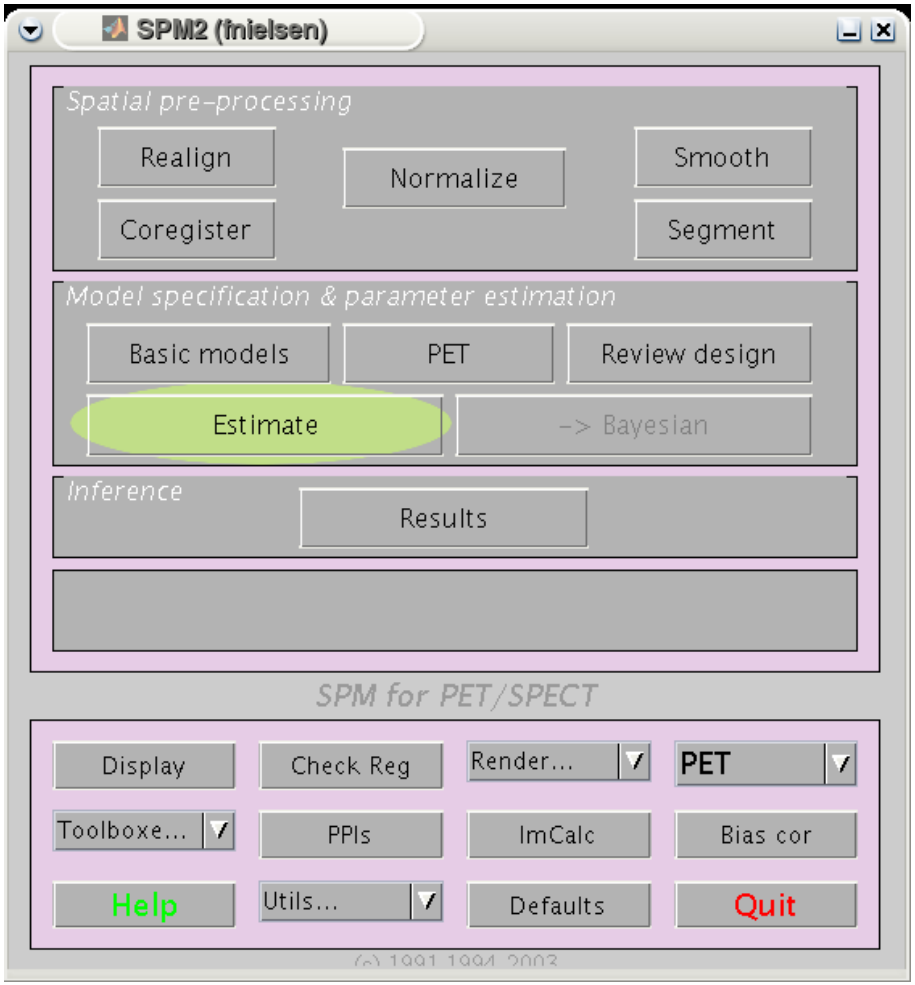
where, e.g., $d_{1,2} = y_1 - y_2$

Degrees of freedom is lost compared to the unpaired t-test.

New degrees of freedom:

$$\begin{aligned} r &= N - \text{rank}(\mathbf{X}) \\ &= 12 - 7 = 5 \end{aligned}$$

Estimation



Estimation requires only the button press of the user.

Estimation of parameters

The 'normal equation' to estimate the parameters in the beta matrix $\mathbf{B}$(design variables $\times$ voxels)

$$\hat{\mathbf{B}} = (\mathbf{X}^\mathsf{T}\mathbf{X})^{-1}\mathbf{X}^\mathsf{T}\mathbf{Y},$$

or with the pseudo-inverse $\dagger$ (`pinv` in Matlab)

$$\hat{\mathbf{B}} = \mathbf{X}^\dagger\mathbf{Y}.$$

The pseudo-inverse will also work for design matrices of degenerate rank.

Each row in $\hat{\mathbf{B}}$ is a volume.

In SPM the parameters are saved in files with the `beta` prefix.

Estimation of error

The "fitted' error matrix' $\hat{\mathbf{U}}$ (Mardia)

$$\hat{\mathbf{U}} = \mathbf{Y} - \mathbf{X}\hat{\mathbf{B}}.$$

The residual sum of squares and products (SSP) matrix $\hat{\mathbf{U}}^{\mathsf{T}}\hat{\mathbf{U}}$ is a (voxels$\times$ voxels)-matrix.

In a mass-univariate test only the diagonal is used $\mathbf{s}$(voxels $\times$ 1)

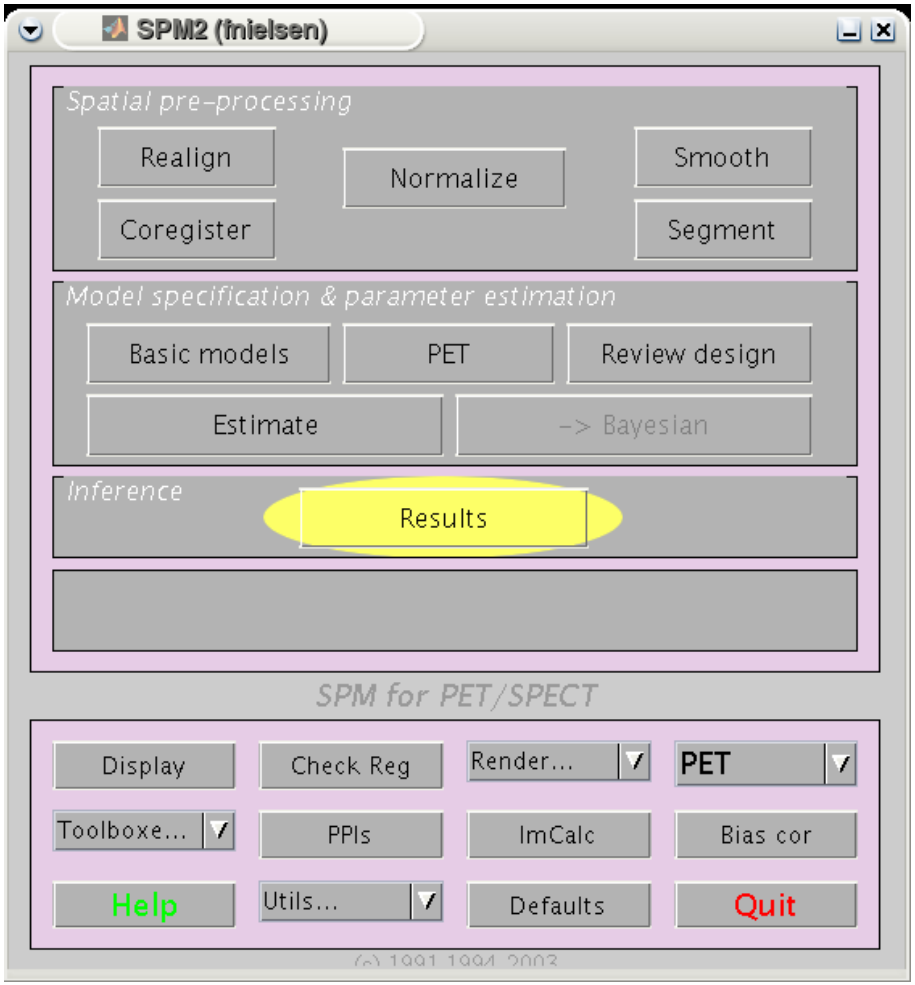
$$\mathbf{s} = \text{diag}(\hat{\mathbf{U}}^{\mathsf{T}}\hat{\mathbf{U}})$$

With degrees of freedom ν normalization

$$\mathbf{r} = \mathbf{s}/\nu$$

In SPM the volume of residuals is saved in `ResMS`

Statistical inference



The statistical inference entails the specification of a so-called 'contrast' and the comparison of the result of the contrast to a statistical distribution.

Example contrasts

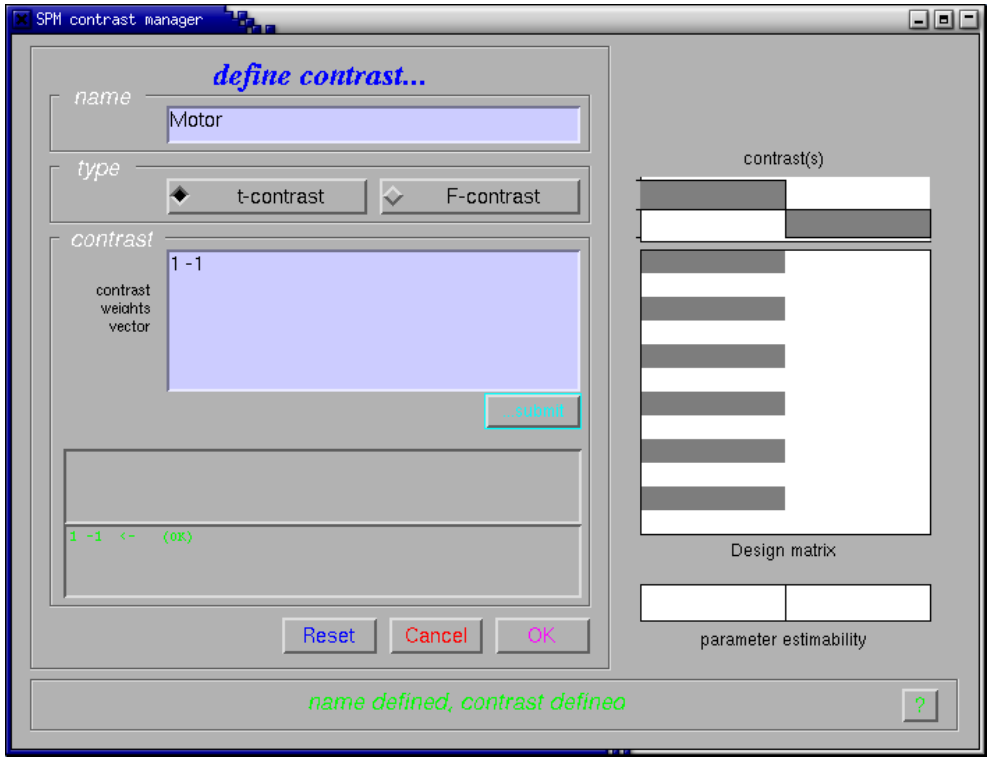


Figure 15: SPM2 contrast manager.

Not all testable contrast are appropriate.

F-contrast for ANOVA with 3 groups encoded in an overparametrized design matrix (cf. SPM2 `spm_conman.m`)

$$\mathbf{C} = \begin{bmatrix} +1 & -1 & 0 & 0 \\ 0 & +1 & -1 & 0 \end{bmatrix}$$

t-contrast with 2 groups, one covariate and one grand mean

$$\mathbf{C} = \begin{bmatrix} +1 & -1 & 0 & 0 \end{bmatrix}$$

'General Linear Hypothesis'

Hypothesis for a univariate t-test with the contrast vector $\mathbf{c}$ as a row vector

$$H_0: \quad \mathbf{cb} = 0.$$

A univariate F-test with the constrast matrix $\mathbf{C}$ as a row vector

$$H_0: \quad \mathbf{Cb} = \mathbf{0}.$$

In SPM the values $\mathbf{c}\hat{\mathbf{B}}$ from a t-test are stored in volume files with `con_` prefix.

The t-test allows one to say something about the direction of the effect. An F-test does not allow it.

Hypothesis test example with t-test

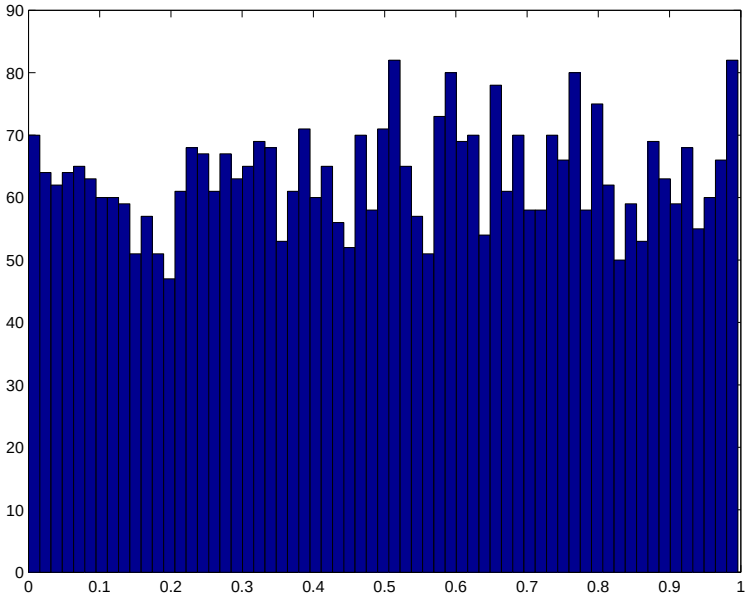


Figure 16: Histogram of the lower tail area of the t-value: $1 - p$-value.

Matlab program with a random design matrix and random image data:

```
X    = rand(12, 5);
Y    = randn(size(X,1), 4000);

B    = pinv(X) * Y;
dof  = size(X,1) - rank(X);
U    = Y - X*B;
SSE  = diag(U'*U)';
MSSE = SSE / dof;
SE   = sqrt(MSSE);

C = [ 1 -1 0 0 0 ];
T = C*B ./ (SE * sqrt(C*pinv(X'*X)*C'));
P = brede_cdf_t(T, dof);

figure
hist(P, sqrt(length(P)));
```

Multiple testing problem

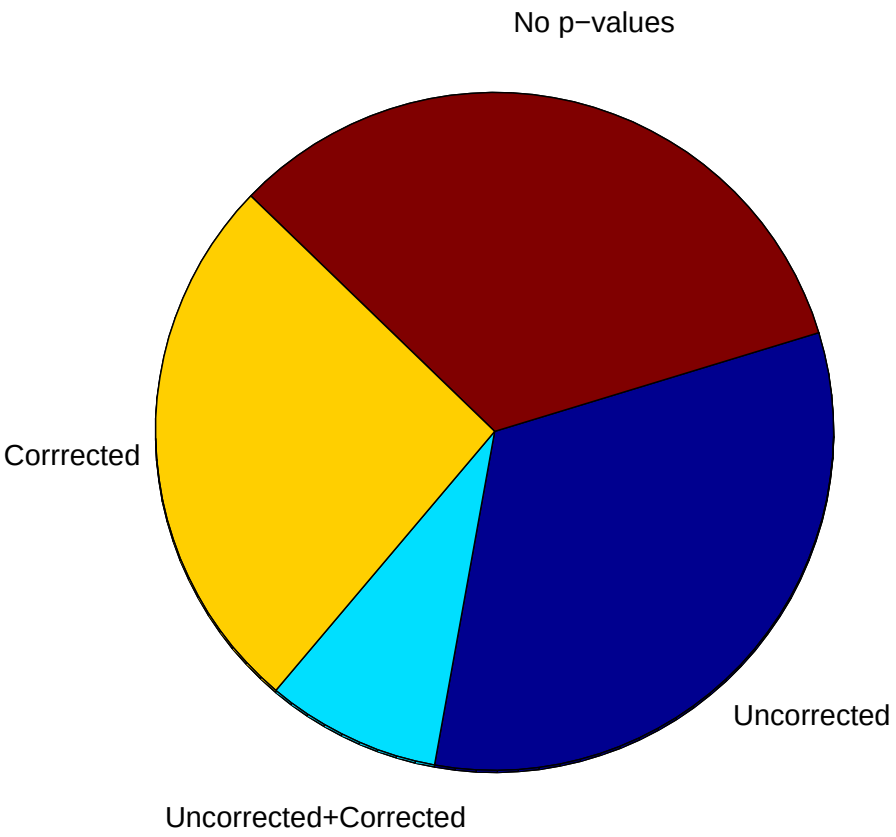


Figure 17: Distribution of coordinates in the Brede database where the 'uncorrected' or 'corrected' P-values are given.

If 20.000 voxels are tested and a statistical threshold on 0.05 is used then around 1000 will be declared active (significant) if the null hypothesis is true: 'uncorrected p-values'.

Usually this is dealt with by using random field theory: 'corrected p-values'.

Not always(!) according to the information in the Brede database.

If multiple contrasts are performed this should also be corrected. This is almost never done!

Multiple testing corrections

Bonferroni correction

$$\alpha_{\text{Bonferroni}} = \alpha/N,$$

where N is the number of voxels, e.g., $0.05/20000 = 0.00000025$

Random field theory

False discovery rate

Maximum statistics permutation testing

Random field theory

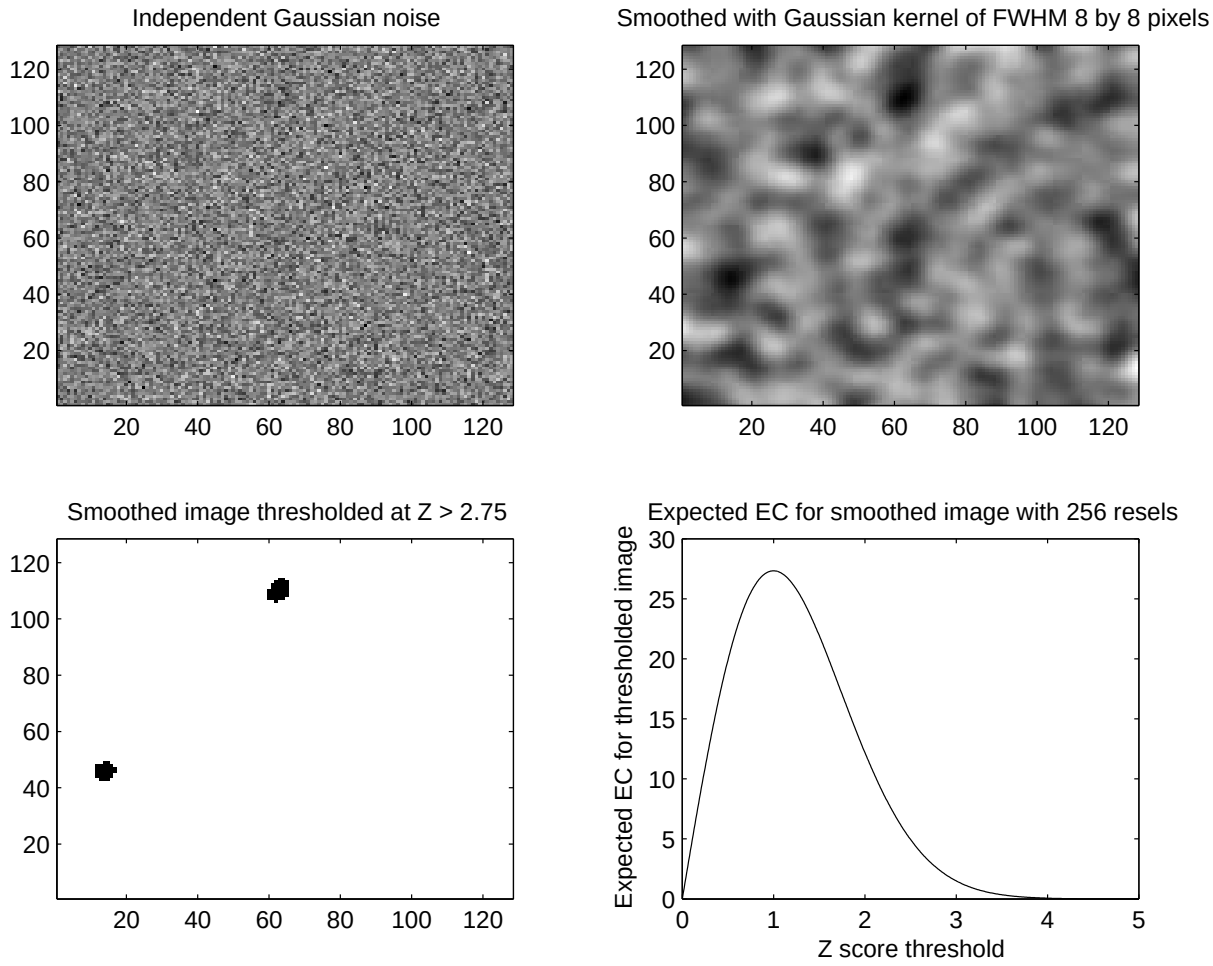


Figure 18: Matthew Brett's example. From (Brett, 1999b).

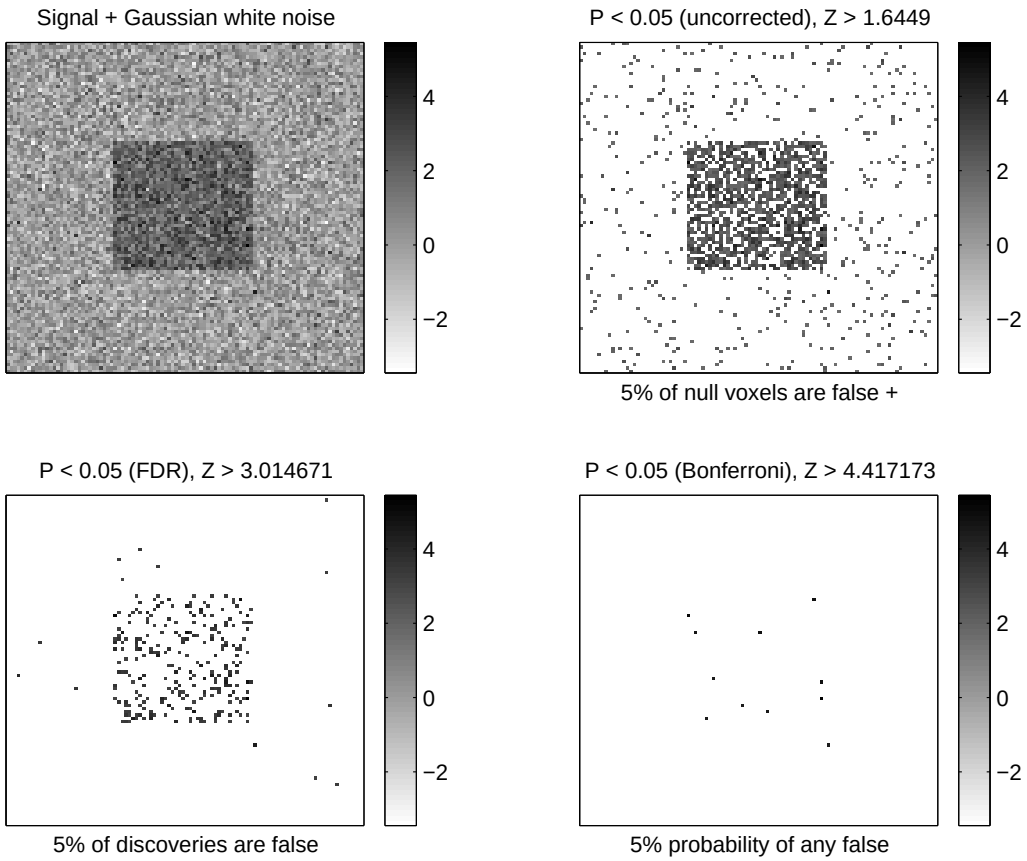
The 'Euler characteristics' (EC) property counts the number of blobs minus the number of holes in a binary image

On high threshold there are no holes, i.e., EC = #blobs

On high threshold: The expected EC $\approx P(\text{EC} = 1) = P(\max > u)$

Formulas for expected EC exist for, e.g., Gaussian random field.

False discovery rate



False discovery rate (Genovese et al., 2002; Worsley, 2004).

Find the largest k in ordered P-values: $P_1 \leq P_2 \leq \ldots \leq P_N$

$$P_k < \alpha k/N.$$

$P_1 \ldots P_k$ declared significant.

Figure 19: Multiple comparison corrections. Example by Keith Worsley (Worsley, 2004, figure 3).

Maximum statistics permutation

Permutation (resampling without replacement) of the labels of the scans (the interesting variables of the design matrix) (Holmes et al., 1996; Nichols and Holmes, 2001).

Create a statistics, e.g., a ordinary t-statistcs

Take the maximum statistics across all voxels.

Iterate many times (several 1000 times) to generate a histogram of maximum values.

The multiple comparison problem can be accounted for — both over voxels and contrasts. 'Non-parametric': No assumption of Gaussianity. But the scans should be 'exchangeable' (not BOLD fMRI).

Maximum statistics permutation

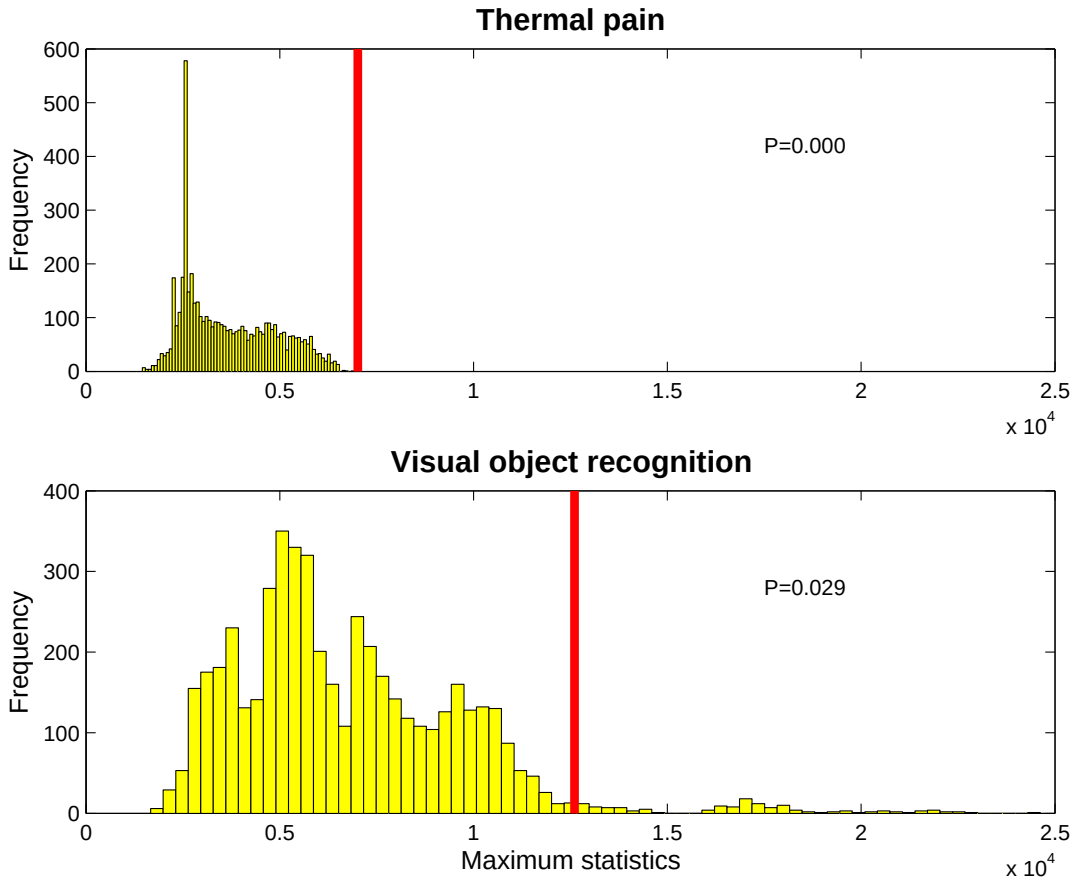


Figure 20: Histogram of resampling distribution. The thick red lines indicate the maxima.

Example data set with 8 scans with two states: ABABABAB.

Statistical parametric map:

$$\mathbf{t} = (AAAA) - (BBBB)$$

Permutations

$$\begin{aligned} \mathbf{t}_1 &= (ABAA) - (BBAB) \\ \mathbf{t}_2 &= (BBAA) - (AABB) \\ &\vdots \end{aligned}$$

The P-values are the ratios of $\max(\mathbf{t}_r)$ for $r = 1 \ldots R$ larger than t

Lyngby Toolbox

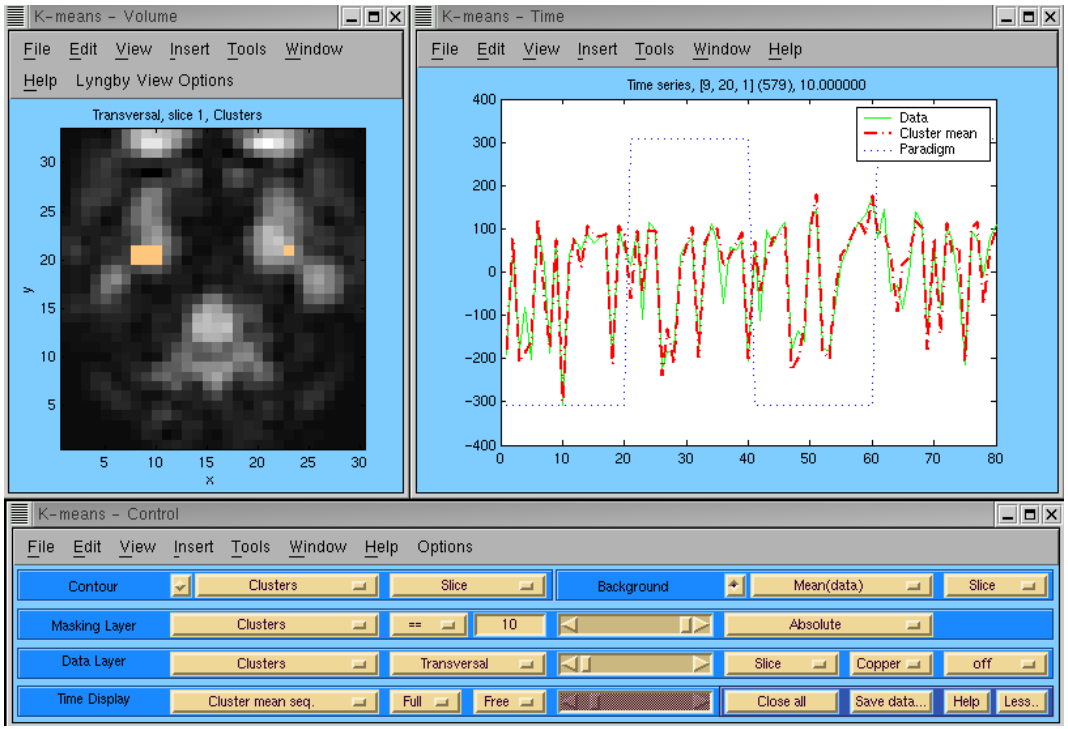
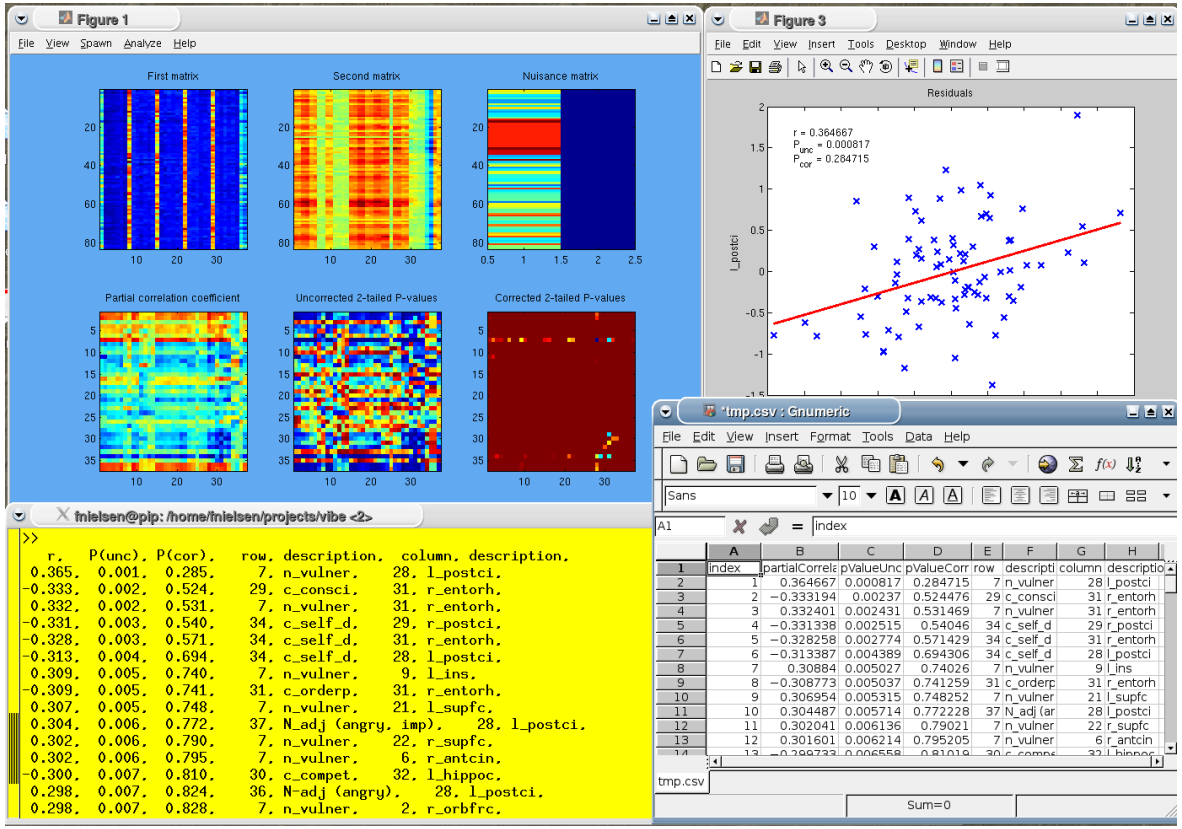


Figure 21: One of the windows in the Lyngby toolbox

Programmed by Matthew Liptrot, Lars Kai Hansen, Finn Årup Nielsen, . . . (Hansen et al., 1999)

Multivariate analyses: Cluster analysis, canonical correlation, independent component analysis

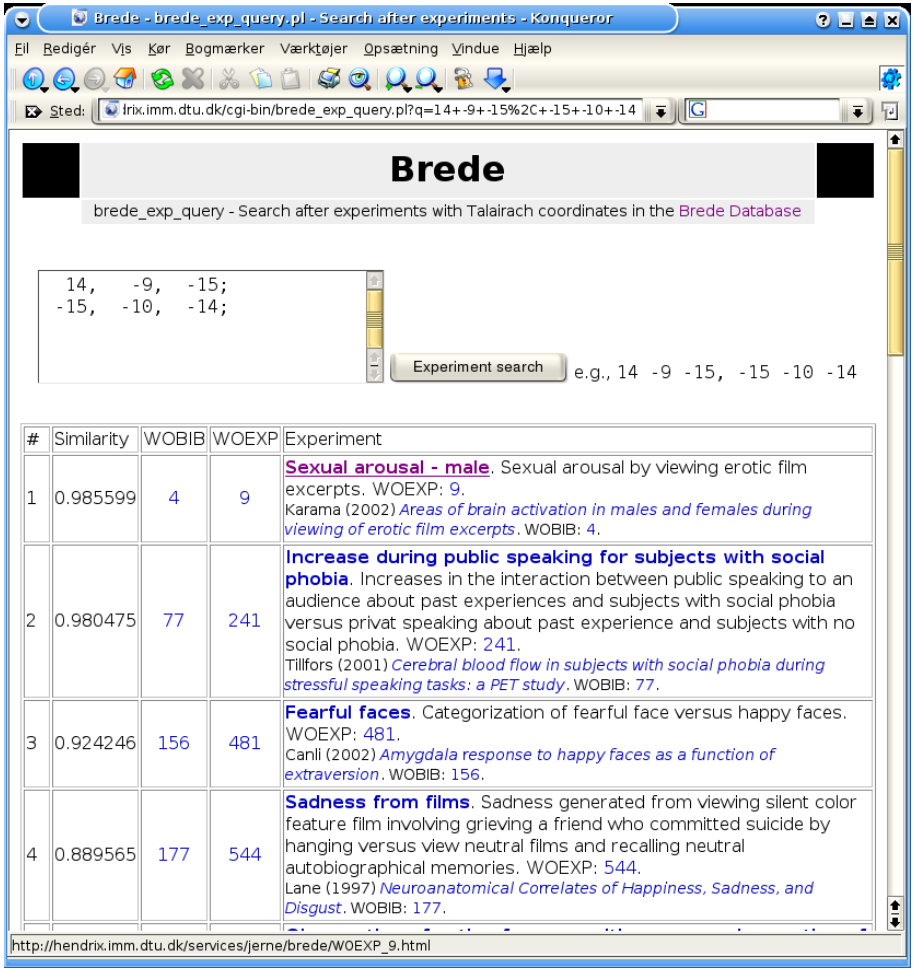
Brede Toolbox



Matlab toolbox with multivariate analysis, meta-analytic modeling, visualizations, . . .

Graphical user interface for partial correlation analysis, suitable for data sets that contain multiple variables that should be tested, e.g., personality scores across many regions. Includes maximum statistics permutation.

Brede database



Brede Database records Talairach/MNI coordinates from experiments.

Online search from http://hendrix.imm.dtu.dk

Example with online search on two coordinates in left and right amygdala in the experiments.

SPM plugins — third party software

Batch processing. Programs to construct batch jobs. Included in SPM5 with spm_jobman.

INRIAlign. Robust motion alignment.

Diffusion. Functions for DWI MRI

Region of interest modeling (MarsBar, WFUPickAtlas),

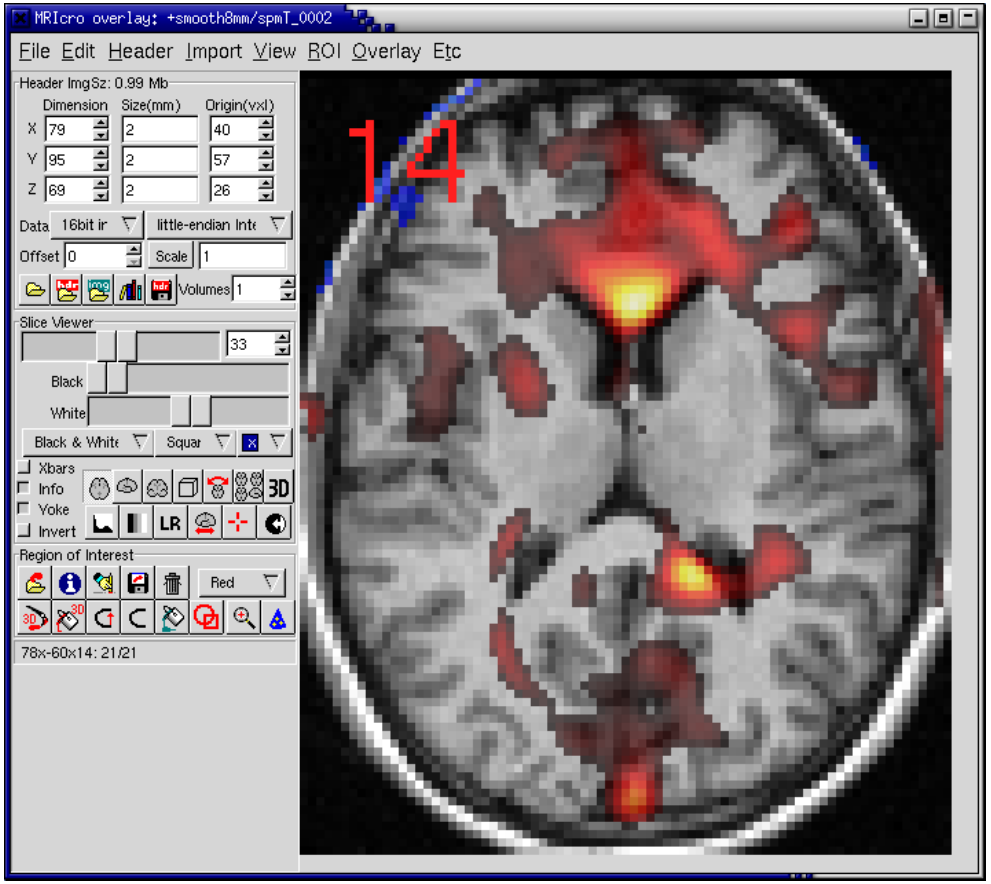
Multivariate analysis (MM Toolbox),

'Statistical Parametric Mapping Diagnosis'

Non-parametric permutation test (SnPM) (Holmes et al., 1996; Nichols and Holmes, 2001)

...

MRIcro



MRIcro programmed by Chris Rorden for PC versions of Linux and Microsoft Windows.

Slice view and volume rendering view. Overlay of functional images on structural, drawing of regions and extraction of the brain

Includes a labeled volume (ALL) based on lobar anatomy (Tzourio-Mazoyer et al., 2002), a labeled volume (brodmann) based on Brodmann areas, and a standard high-resolution single subject MR image with scull (ch2) and without scull (ch2bet)

More information

SPM wiki, http://en.wikibooks.org/wiki/SPM and http://en.wikipedia.org/wiki/Statistical_parametric_mapping

Email list, http://www.jiscmail.ac.uk/lists/SPM.html

Short Course on Statistical Parametric Mapping, ftp://ftp.fil.ion.ucl.ac.uk/spm/course/notes04/slides/london2004.htm

'Human Brain Function' book. The methodological part is available on the Internet, http://www.fil.ion.ucl.ac.uk/spm/doc/books/hbf2/

'fMRI Neuroinformatics' overview article (Nielsen et al., 2006).

Jonathan Taylors notes for his 'stats191' course: http://www-stat.stanford.edu/~jtaylo/courses/stats191/

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