

# Statistical Parametric Mapping (SPM)

Finn Årup Nielsen

Neurobiology Research Unit,  
Copenhagen University Hospital Rigshospitalet;  
Informatics and Mathematical Modelling  
Technical University of Denmark

March 3, 2005

# What is SPM?

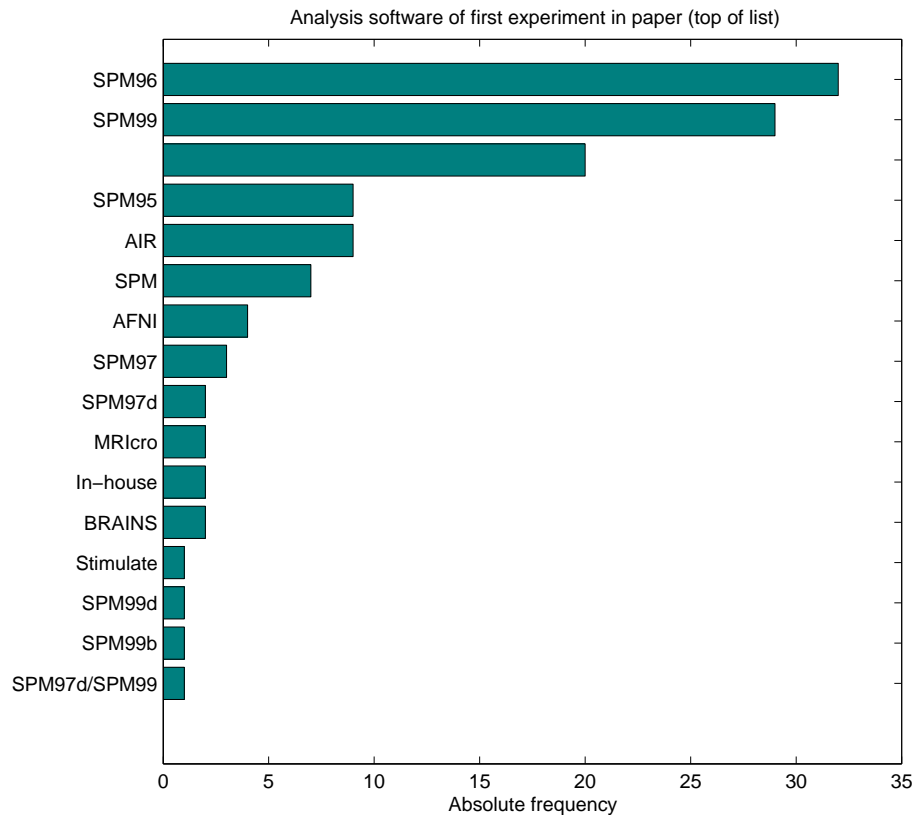


Figure 1: Histogram of used analysis software as recorded in the Brede Database, see original at [http://hendrix.imm.dtu.dk/services/jerne/-brede/index\\_bib\\_stat.html](http://hendrix.imm.dtu.dk/services/jerne/-brede/index_bib_stat.html)

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

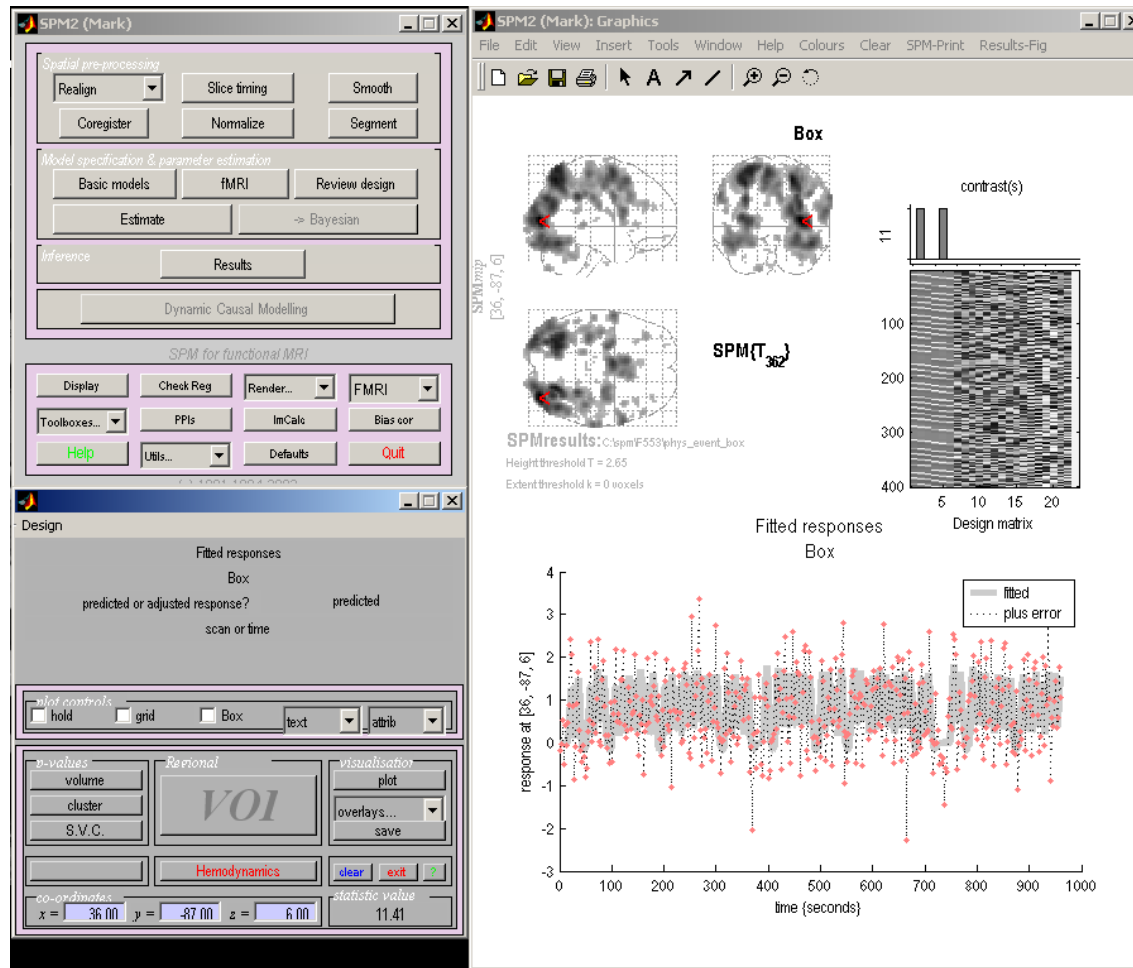


Image registration, segmentation, smoothing, algebraic operations

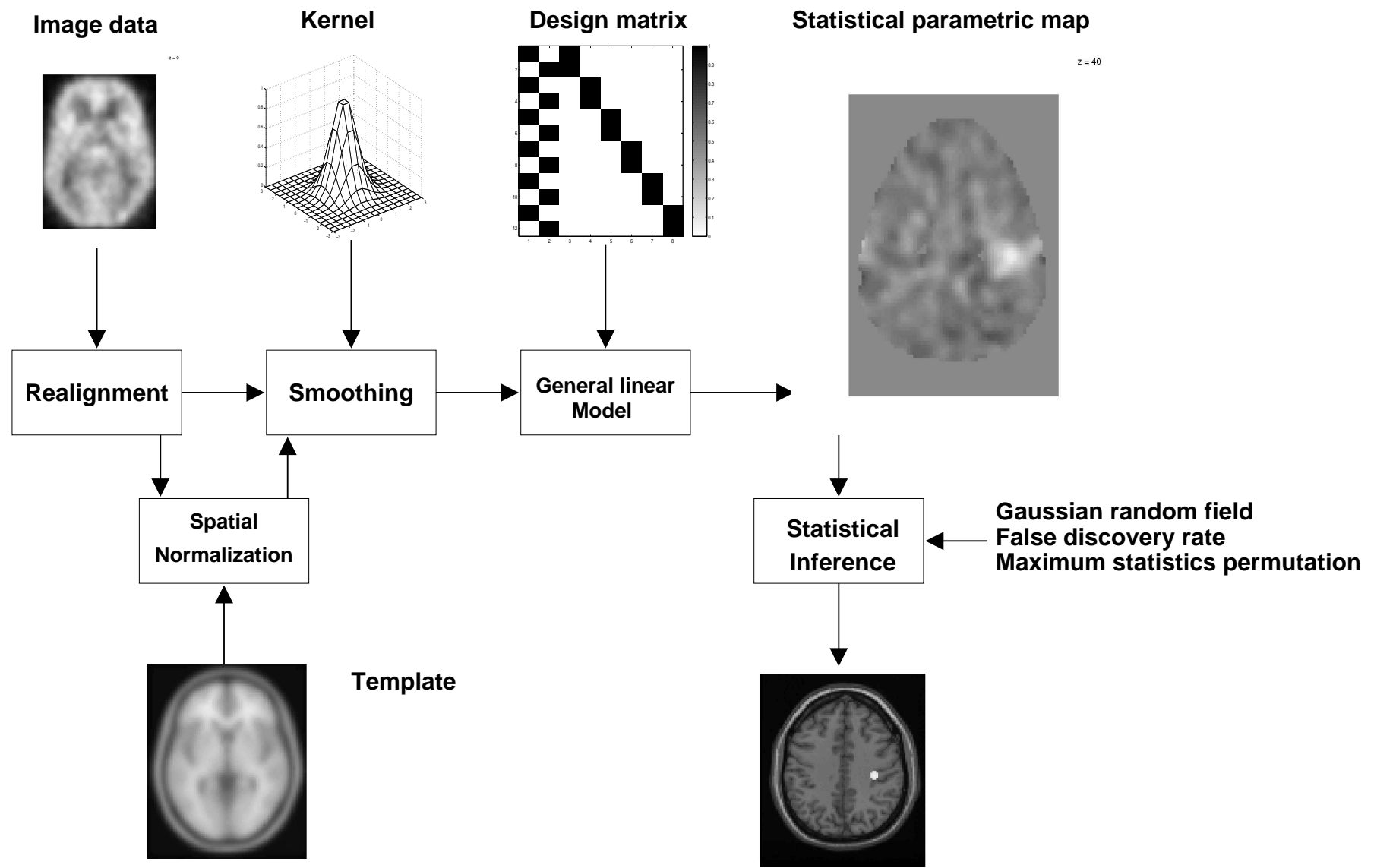
Analysis with general linear model, random field theory, dynamic causal modeling

Visualization

Email list with ~ 2000 subscribers

Figure 2: Image by Mark Schram Christensen.

# Data transformations



# Image registration

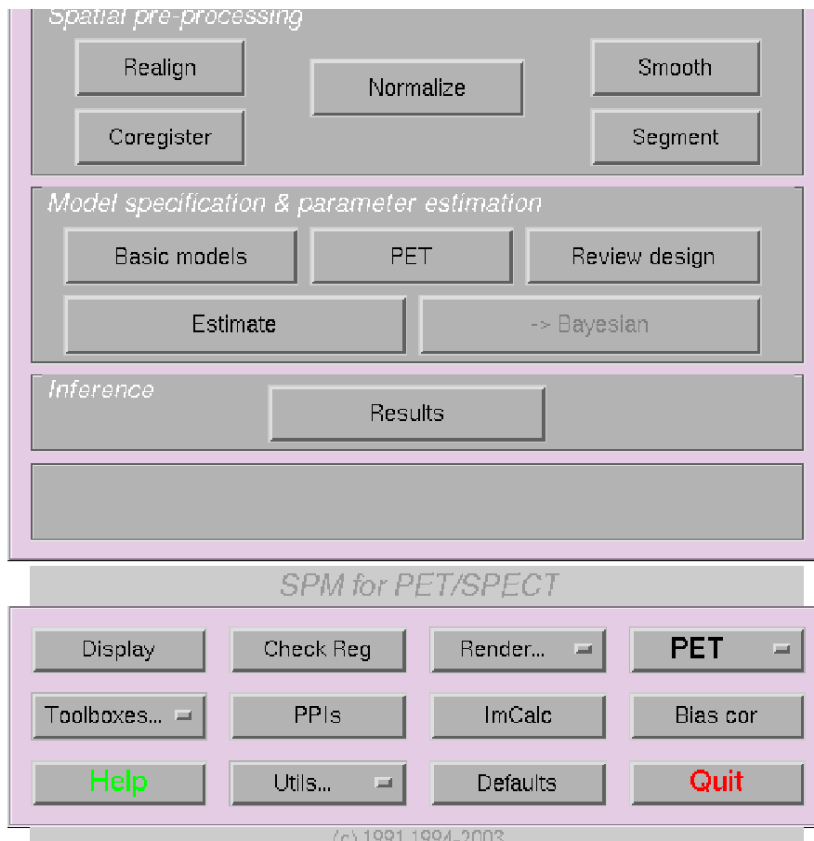


Figure 3: Main window of SPM. Image registration are the three left upmost buttons.

Image registration: Move and warp brain

Motion realignment of consecutive scans (“realign”). Within subject

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

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

# Realignment

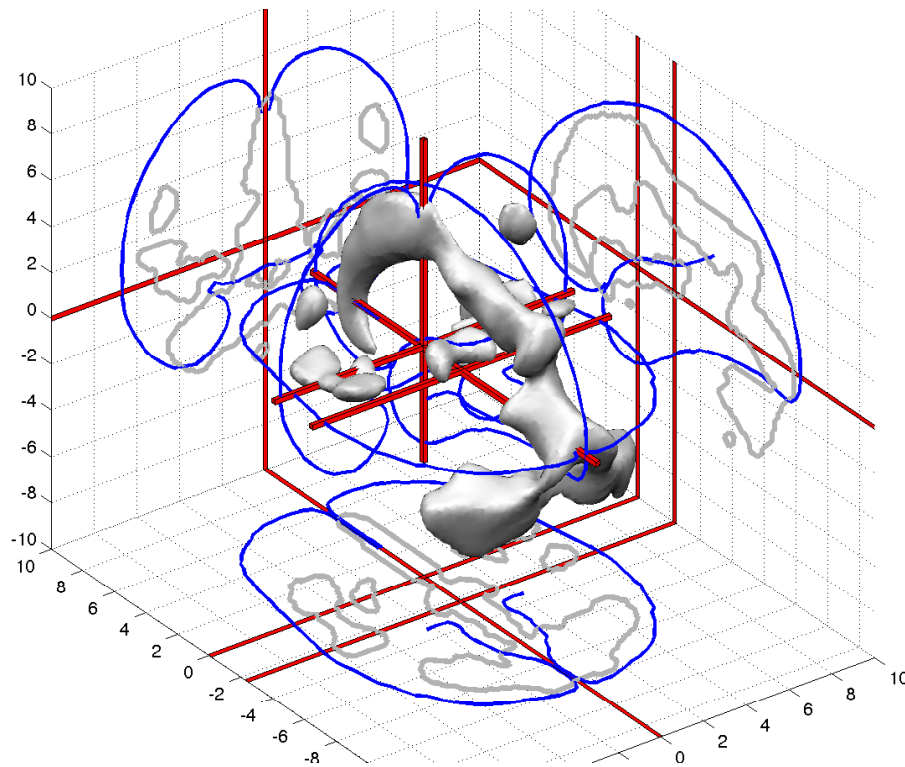
Several images in the same modality from the same subject

Two-stage:

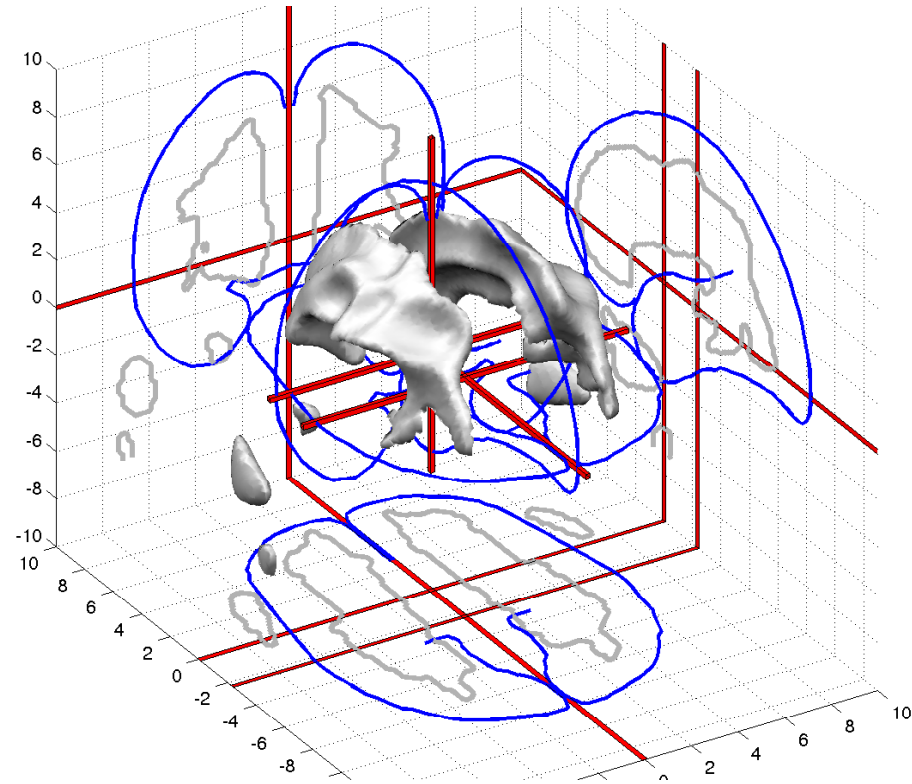
- 1) Estimate movement. SPM: “Determine parameters”
- 2) Resample images based on estimated movement

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

# Coregistration



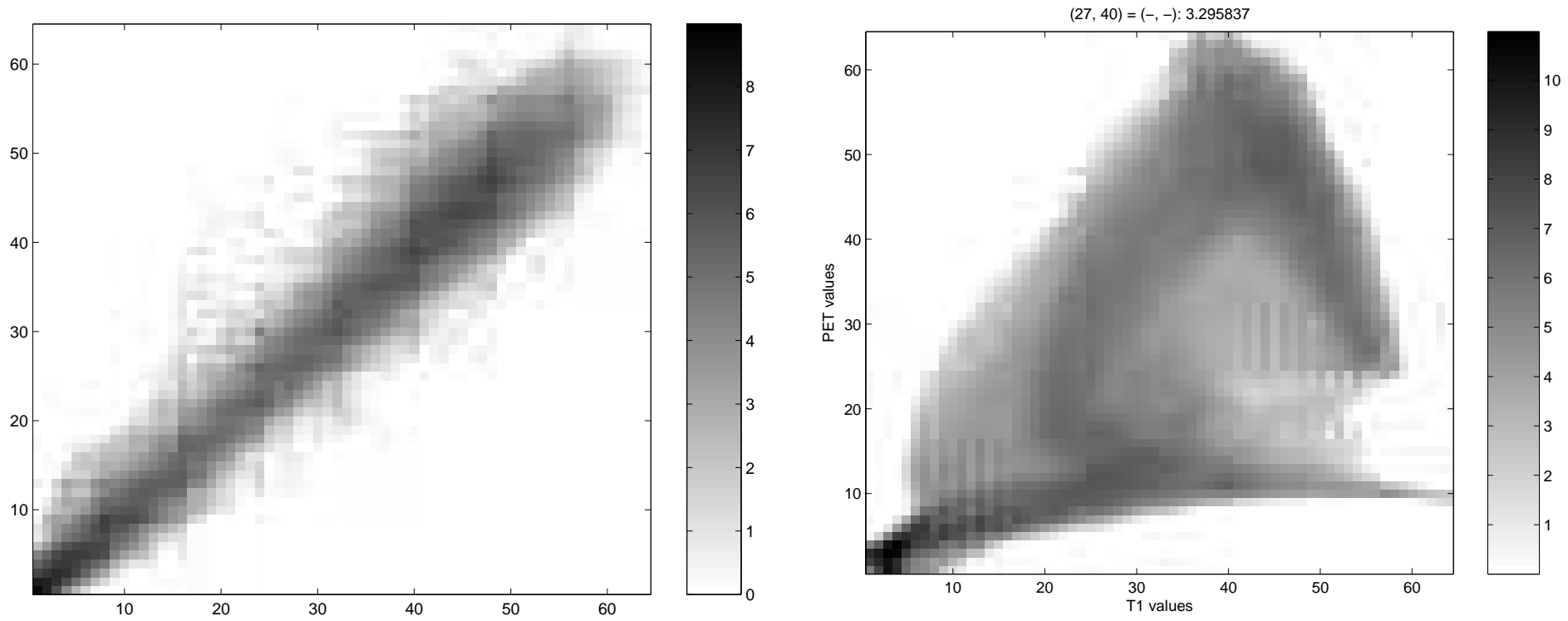
(a) PET template from SPM.



(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!

# Realignment and coregistration



(a) PET/PET.

(b) MRI T1/PET templates from SPM.

Figure 5: Grey level occurrence matrix.



## Spatial normalization

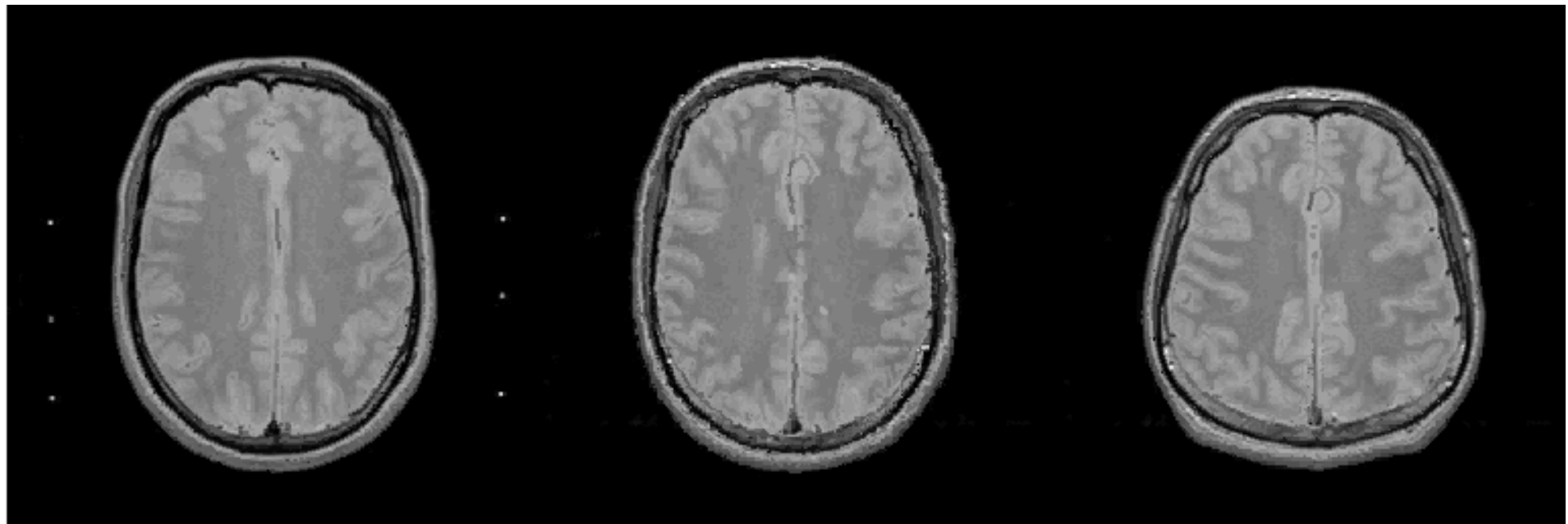


Figure 6: Warp of right subject to left subjects brain. Result in the middle. Image by Ulrik Kjems using MRIwarp.

# Spatial normalization — Batch programming

Spatial normalization: Deform subject brain scans to a template.

Determine warp parameters by matching a subjects anatomical MRI (“Source image”) to a template (“Determine parameters”)

```
params = spm_normalise(Vtemplate, Vmri, matname, '', '', ...  
defaults.normalise.estimate);
```

Apply (“Write normalised”) the warp parameter to warp the functional image (“Images to write”)

```
spm_write_sn(Vpet, params, defaults.normalise.write, msk);
```

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).

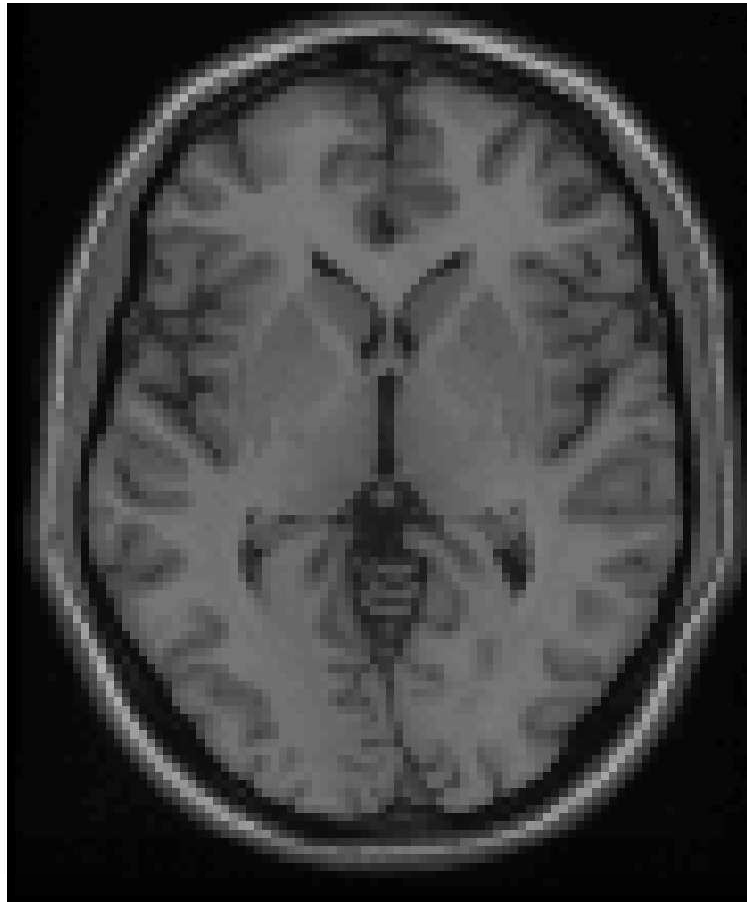
# Spatial normalization batch programming

```
defaults.normalise.estimate.smosrc = 8;
defaults.normalise.estimate.smoref = 0;
defaults.normalise.estimate.regtype = 'mni';
defaults.normalise.estimate.weight = '';
defaults.normalise.estimate.cutoff = 25;
defaults.normalise.estimate.nits = 16;
defaults.normalise.estimate.reg = 1;
defaults.normalise.estimate.wtsrc = 0;
defaults.normalise.write.preserve = 0;
defaults.normalise.write.bb = [[-78 -112 -50]; [78 76 85]];
defaults.normalise.write.vox = [2 2 2];
defaults.normalise.write.interp = 1;
defaults.normalise.write.wrap = [0 0 0];
```

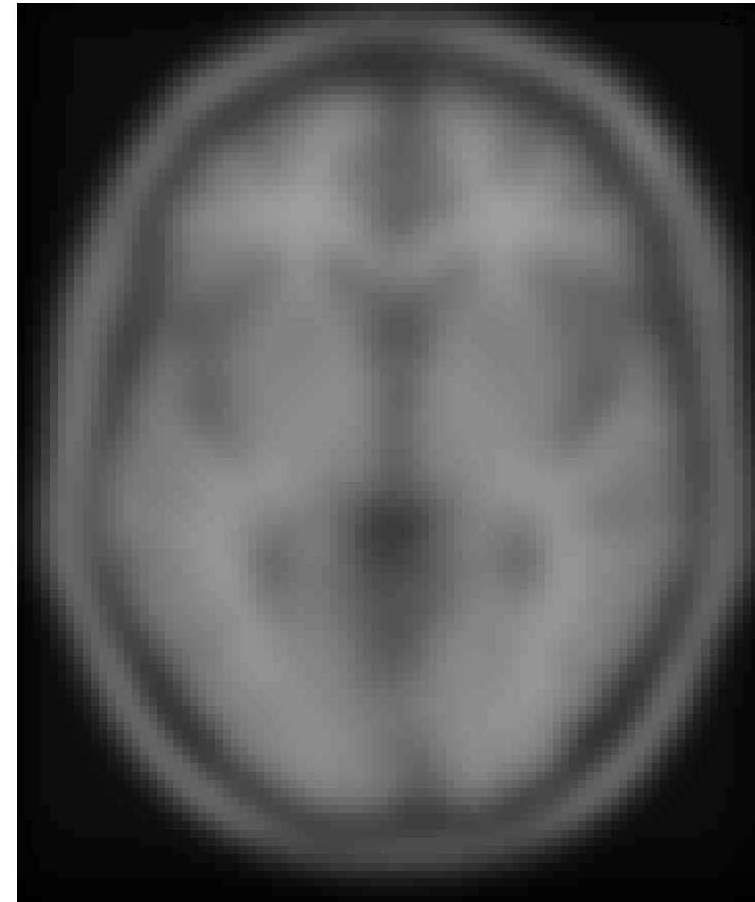
`reg` (regularization) and `cutoff` (cutoff of the discrete cosine basis functions) determine the smoothness of the warp.

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

# Spatial smoothing



(a) Unsmoothed original.



(b) Smoothed. FWHM=10mm.

Figure 7: T1 single subject template from SPM99.

# Spatial smoothing

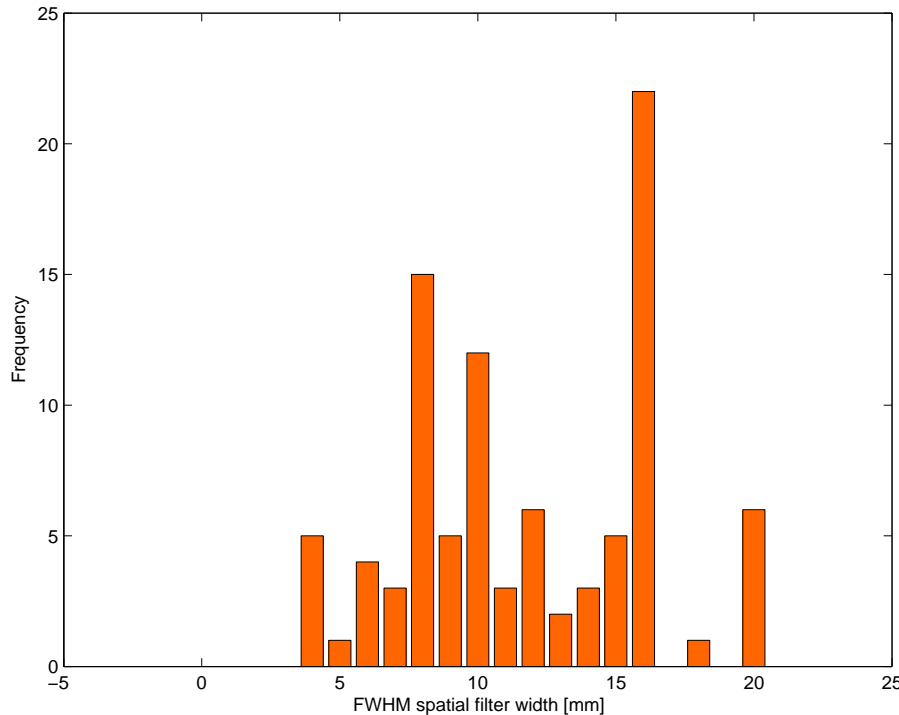


Figure 8: Histogram of smoothing width in the Brede database, see original at [http://hendrix.imm.dtu.dk/services/jerne/-brede/index\\_bib\\_stat.html](http://hendrix.imm.dtu.dk/services/jerne/-brede/index_bib_stat.html)

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

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

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

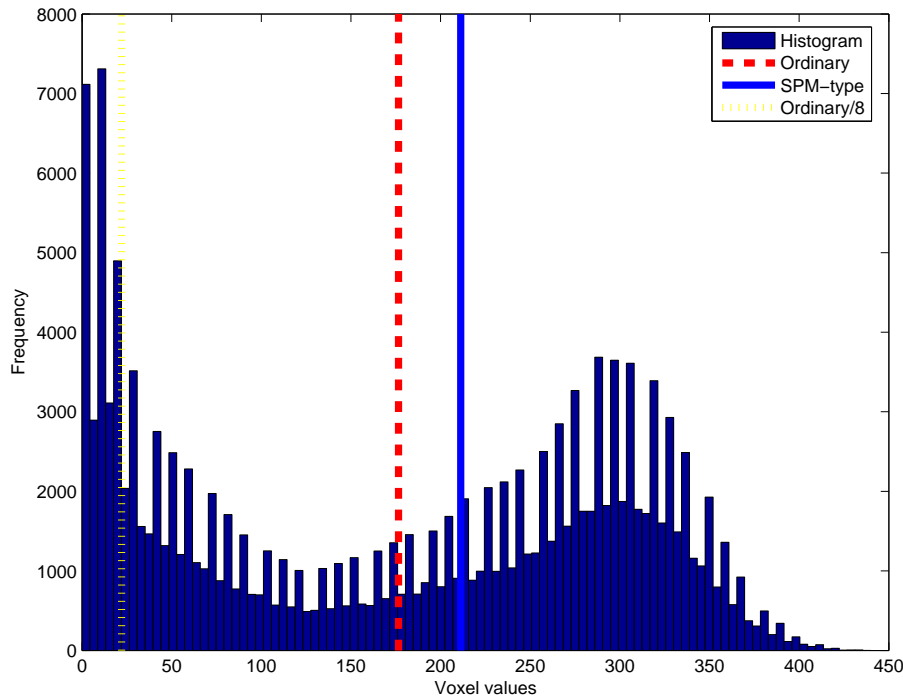


Figure 9: Example of a histogram from a PET volume (Noll et al., 1996).

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  $\text{mean}/8$ . (Computed in `spm_global.m` and `spm_global.c` available at [SPM.xGX.rg](http://SPM.xGX.rg))

The value is used for confounds and masking operations.

# Noll's PET motor SPM masking example

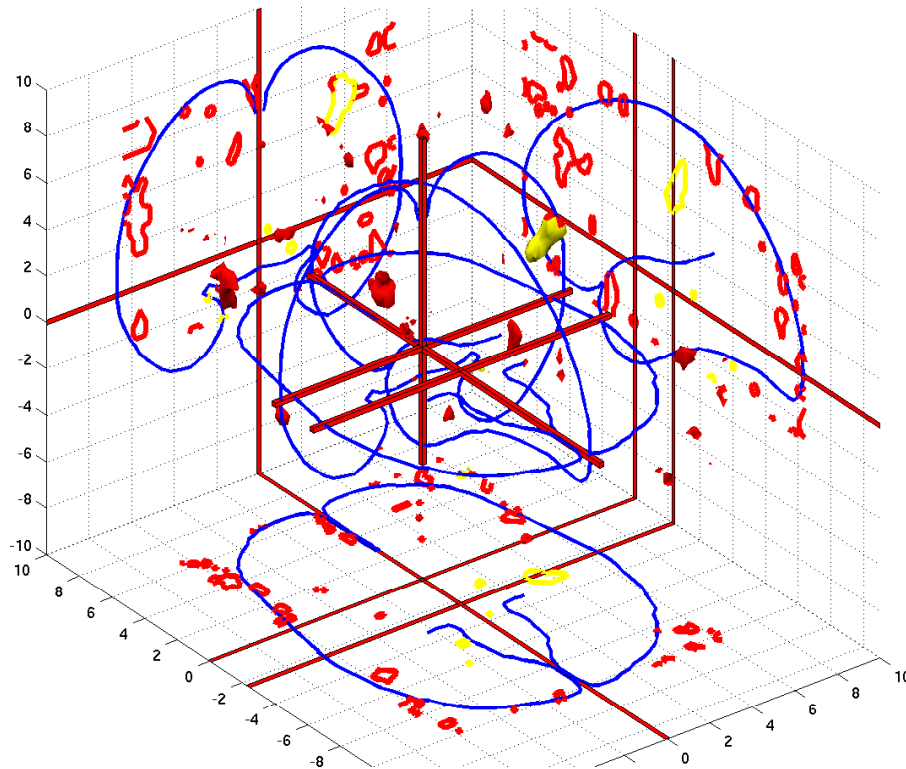


Figure 10: PET motor, left hand finger opposition task, 12 scans: Odd activation, even baseline (Noll et al., 1996). Red is without mask. Yellow with mask. Thresholded at  $t = 2.76$  ( $P < 0.01$ ).

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

“Single-subject: conditions & covariates”, 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)

$$\mathbf{Y} = \mathbf{X}\mathbf{B} + \mathbf{U}, \quad (1)$$

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-univariate setting — in parallel over the columns of  $\mathbf{Y}$  (Friston et al., 1995).

# Process for analysis



Specify design: Set up the design matrix

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

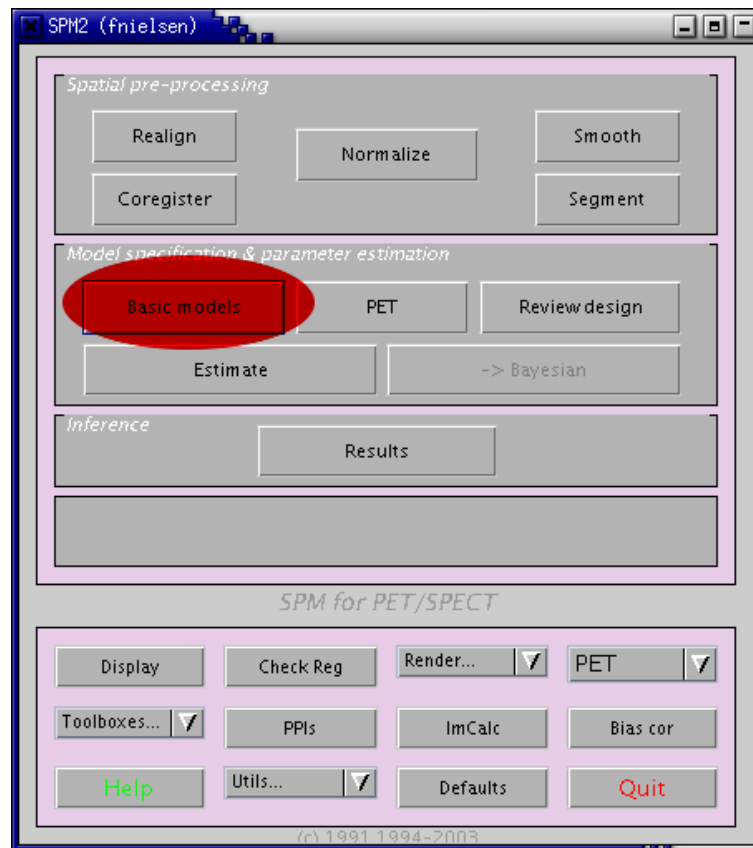


Figure 11: SPM 2 main interface window with “Basic models” button high lighted.

“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.

# Regression model

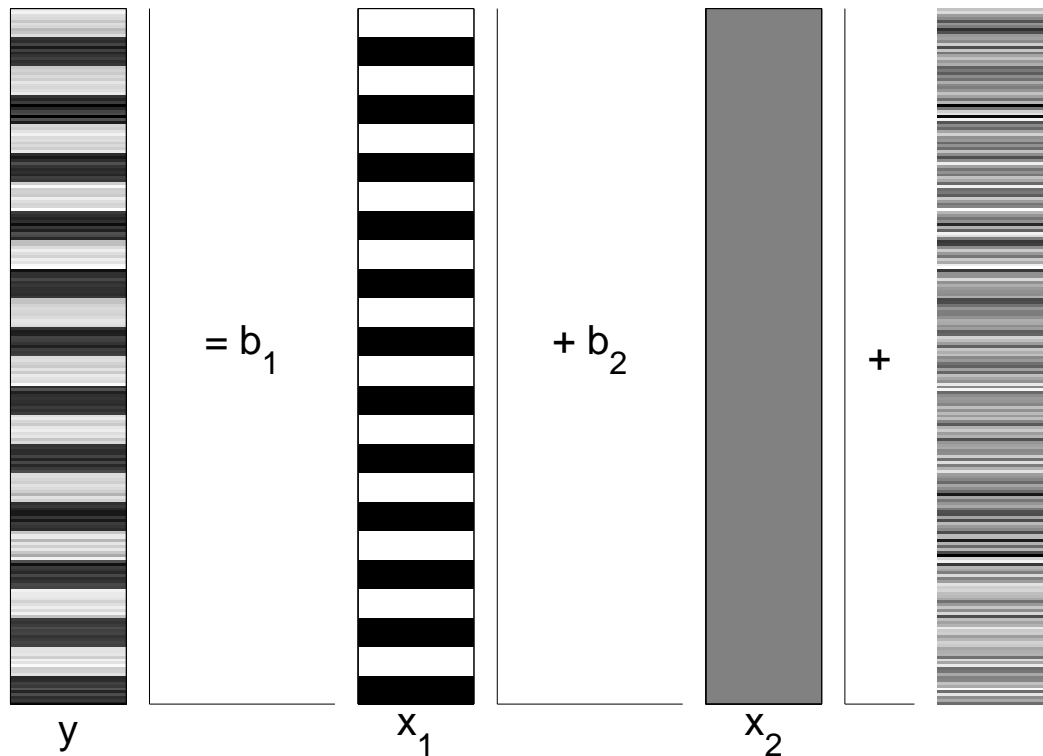


Figure 12: Regression model

Regression model

$$y = b_1x_1 + b_2x_2 + u, \quad (2)$$

where  $y$  contains the values of a specific voxels across scans.

$x_1$  models, e.g., activation/rest or patients/controls.

$x_2$  is the intercept, — a constant value

$u$  the noise

# 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

$$\mathbf{x}_{(1)} = [1, -1, 1, -1, 1, -1, ]^T, \quad (3)$$

that leads to a design matrix with full rank.

“Overparameterized”, where two groups are coded in two design variables

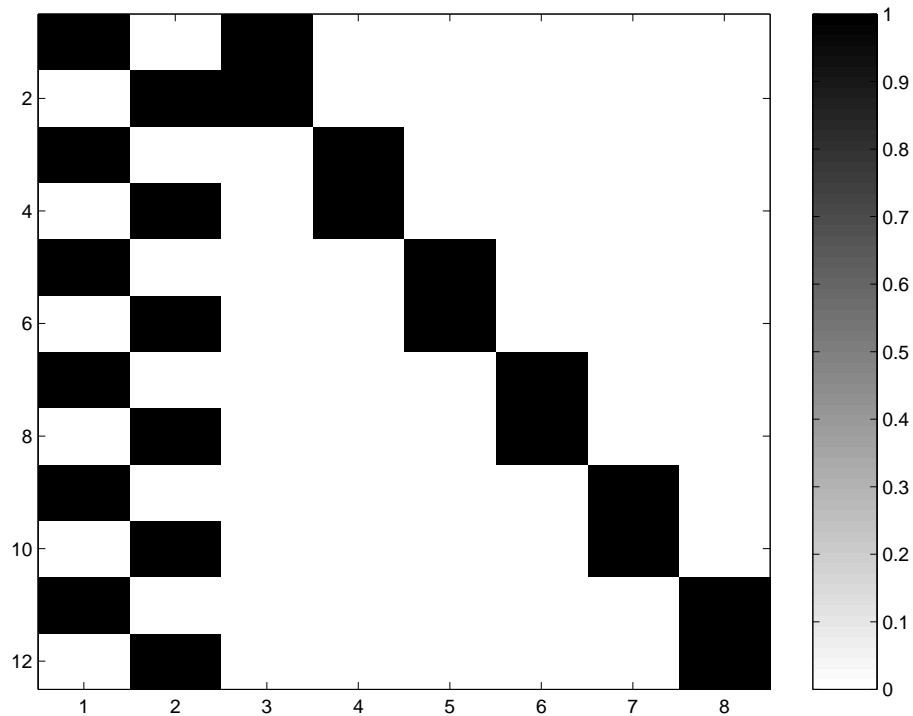
$$\mathbf{X}_{(1:2)} = \begin{bmatrix} 1 & 0 & 1 & 0 & 1 & 0 \\ 0 & 1 & 0 & 1 & 0 & 1 \end{bmatrix}^T, \quad (4)$$

that leads to a design matrix of degenerate rank.

(terminology from [www.statsoftinc.com](http://www.statsoftinc.com))

The overparameterized version is often preferred due to better “ordnung”.

# Design matrix for paired $t$ -test



Paired  $t$ -test example

$$\mathbf{y} = [d_{1,2}, d_{3,4}, \dots, d_{11,12}]^T, \quad (5)$$

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

Degrees of freedom is lost.

New degrees of freedom

$$r = N - \text{rank}(\mathbf{X}) \quad (6)$$

$$= 12 - 7 = 5 \quad (7)$$

Figure 13: Design matrix  $\mathbf{X}$  for paired  $t$ -test with 12 scans.

## Estimation of parameters

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

$$\hat{\mathbf{B}} = (\mathbf{X}^T \mathbf{X})^{-1} \mathbf{X}^T \mathbf{Y}, \quad (8)$$

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

$$\hat{\mathbf{B}} = \mathbf{X} \dagger \mathbf{Y}. \quad (9)$$

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

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

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

## Estimation of error

The “fitted’ error matrix”  $\hat{U}$  (Mardia)

$$\hat{U} = Y - X\hat{B}. \quad (10)$$

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

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

$$s = \text{diag}(\hat{U}^T\hat{U}) \quad (11)$$

With degrees of freedom  $\nu$  normalization

$$r = s/\nu \quad (12)$$

In SPM the volume of residuals is saved in ResMS



# Example contrasts

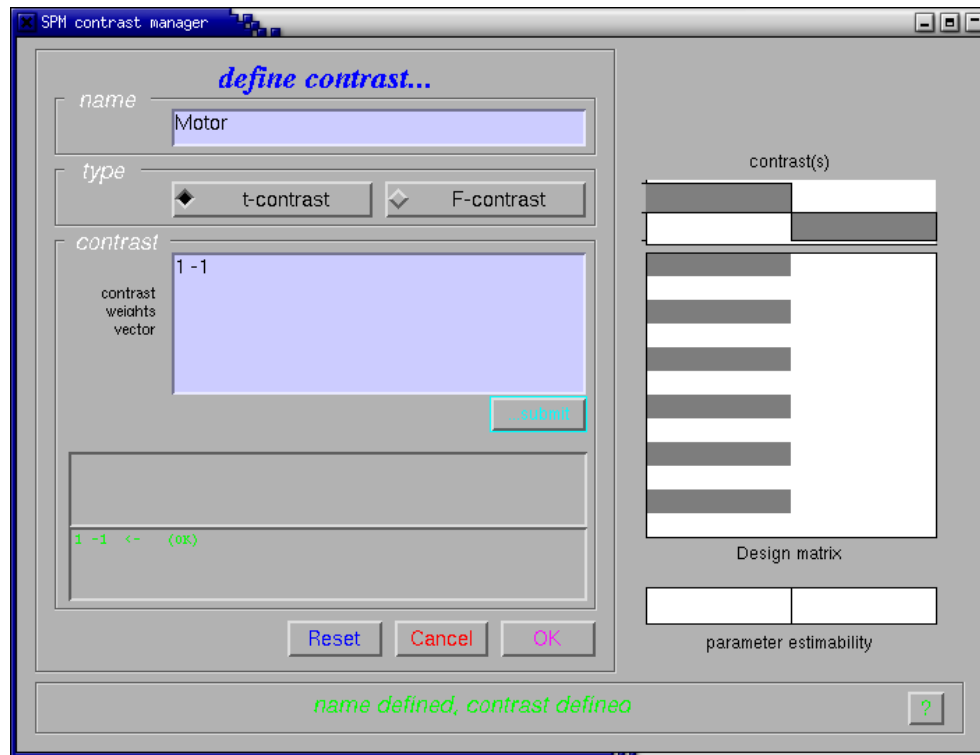


Figure 14: SPM2 contrast manager.

No all testable contrast are appropriate.

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

$$C = \begin{bmatrix} +1 & -1 & 0 & 0 \\ 0 & +1 & -1 & 0 \end{bmatrix} \quad (13)$$

*t*-contrast with 2 groups, one co-variate and one grand mean

$$C = \begin{bmatrix} +1 & -1 & 0 & 0 \end{bmatrix} \quad (14)$$

## “General Linear Hypothesis”

Most general form (Mardia et al., 1979, sec. 6.3)

$$\mathbf{CBM} = \mathbf{D} \quad (15)$$

Usually only a “null” ( $\mathbf{D} = \mathbf{0}$ ) hypothesis is tested and with  $\mathbf{M} = \mathbf{I}$

$$\mathbf{CB} = \mathbf{0} \quad (16)$$

Univariate hypothesis with an  $F$ -test

$$\mathbf{Cb} = 0 \quad (17)$$

A univariate  $t$ -test with  $\mathbf{c}$  as a row vector

$$\mathbf{cb} = 0, \quad (18)$$

Mass-univariate  $t$ -test

$$\mathbf{cB} = \mathbf{0}^T. \quad (19)$$

In SPM the values  $\mathbf{cB}$  are stored in files with `con_` prefix.

## Testable contrasts

For design matrices of degenerate rank not all contrasts are valid: The contrast matrix  $\mathbf{C}$  should be *testable* (Mardia et al., 1979, sec. 6.4).

$\mathbf{C}$  should be in the subspace of  $\mathbf{X}$ :  $\mathcal{C}(\mathbf{C}) \subset \mathcal{C}(\mathbf{X})$  with (Rao, 1962)

$$\mathbf{0} = \mathbf{C} - \mathbf{C}\mathbf{X}^\dagger\mathbf{X}. \quad (20)$$

In practice the difference should be numerically zero.

With rank( $\mathbf{X}$ )-truncated singular value decomposition of  $\mathbf{X}$

$$\mathbf{X} = \mathbf{U}\mathbf{L}\mathbf{V}^\top, \quad (21)$$

the projection can be computed from the eigenvectors  $\mathbf{V}$

$$\mathbf{X}^\dagger\mathbf{X} = \mathbf{V}\mathbf{V}^\top. \quad (22)$$

(SPM2 `spm_sp.m` lines 973–980, 1211–1217; `spm_SpmUtil.m` line 282)

# Hypothesis test example with $t$ -test

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

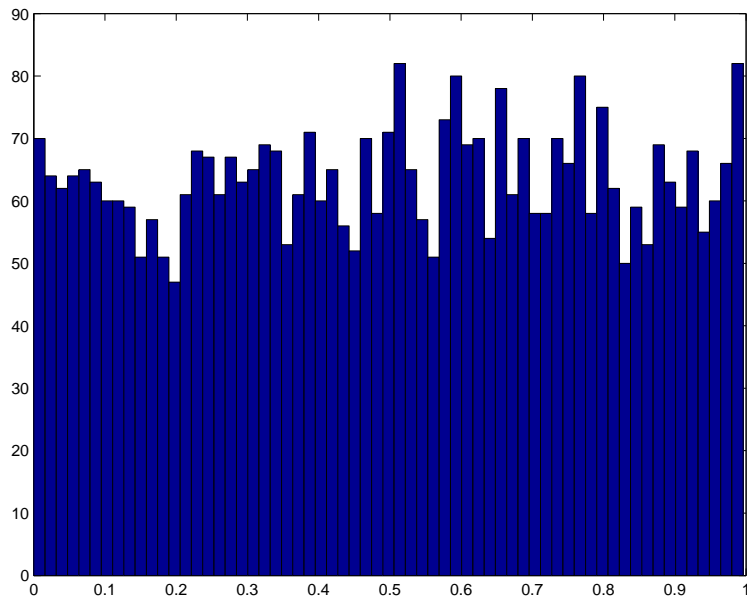


Figure 15: Histogram of the lower tail area of the  $t$ -value:  $1 - p$ -value.

```
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)));
```

# Hypothesis test example with $F$ -test

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

```
X = rand(12, 5);
Y = randn(size(X,1), 1000);
```

```
B = pinv(X) * Y;
dof = size(X,1) - rank(X);
U = Y - X*B;
SSE = sum(U.^2);
MSSE = SSE / dof;
```

```
C = [ 1 0 0 0 0 ; 0 1 0 0 0 ];
F = 1/rank(C) * (diag((C*B)' * pinv(C * ...
    pinv(X'*X) * C') * (C*B))' ./ MSSE);
P = brede_cdf_f(F, rank(C), dof);
```

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

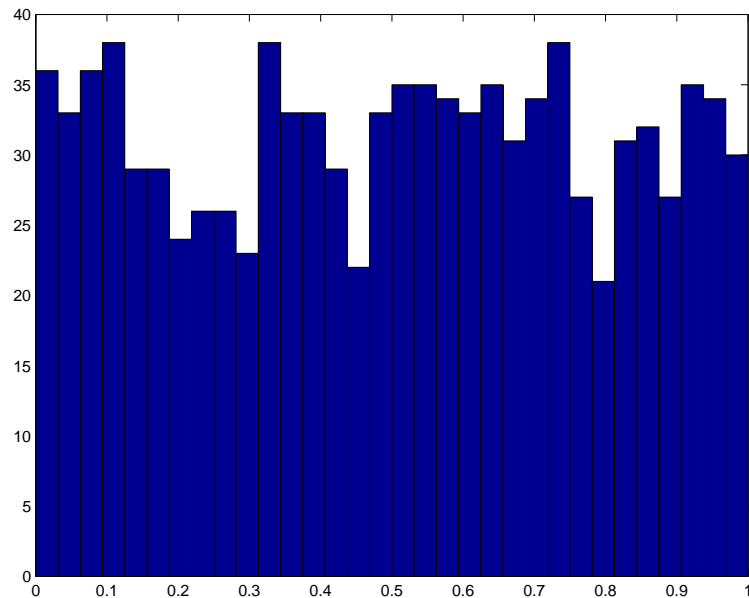


Figure 16: Histogram of the lower tail area of the  $F$ -value:  $1 - p$ -value.

# Multiple testing problem

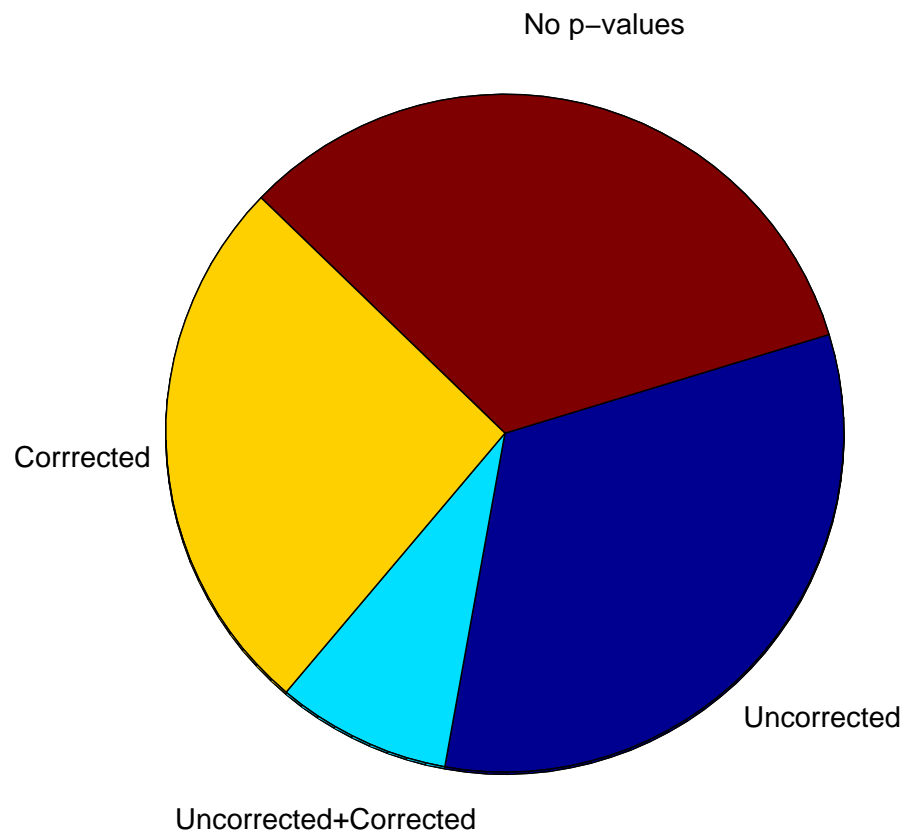


Figure 17: Distribution of coordinates in the Brede database where the “uncorrected” or “corrected”  $P$ -values are given.

If 20.000 voxels are tested and a statistical threshold on 0.05 is used then 1000 will be declared active (significant) if the null hypothesis is true: “uncorrecte  $p$ -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

$$\alpha_{\text{Bonferroni}} = \alpha/N, \quad (23)$$

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

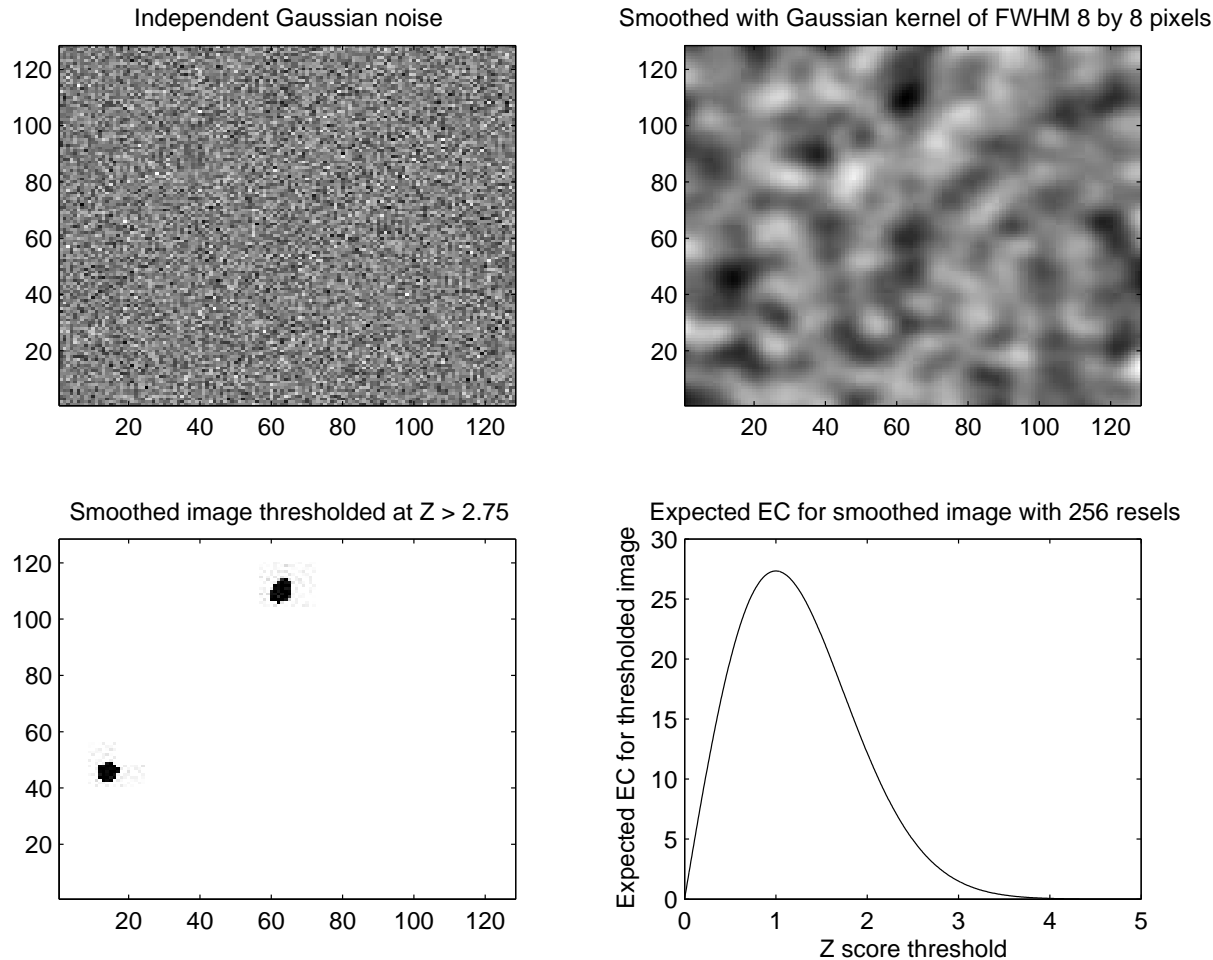


Figure 18: Example from (Brett, 1999b).

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

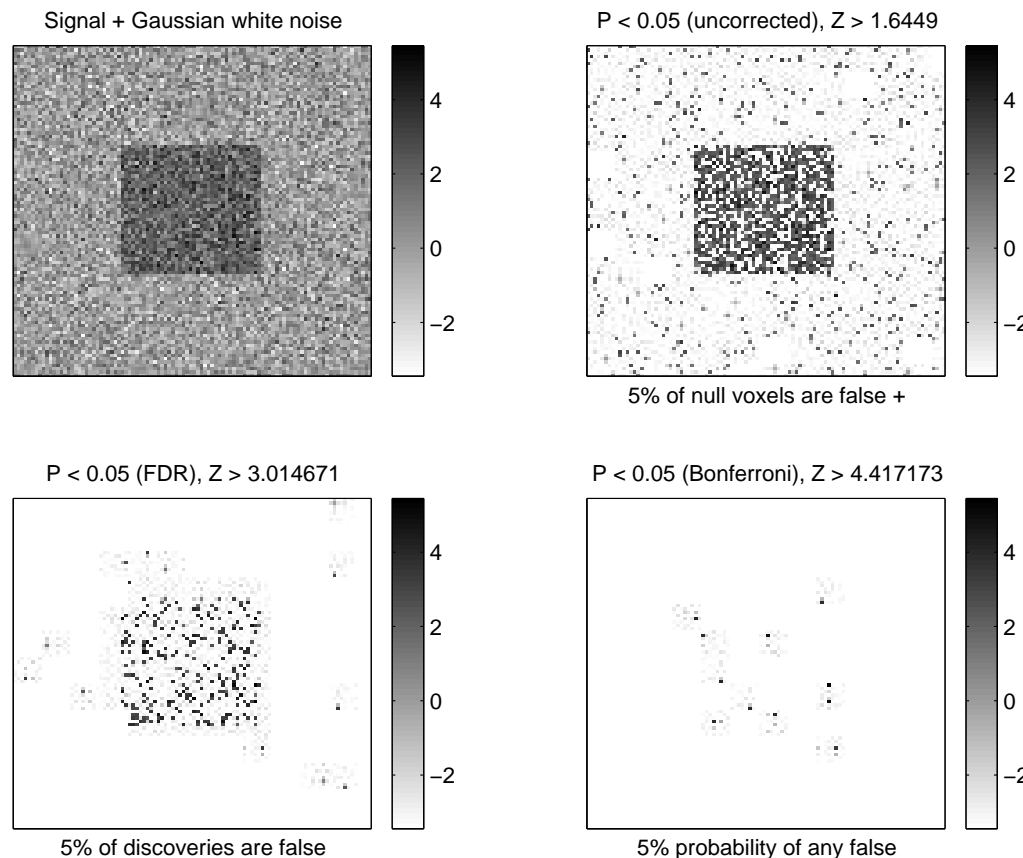
On high threshold there are no holes, i.e.,  $EC = \#blobs$

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

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:  $P_1 \leq P_2 \leq \dots \leq P_N$

$$P_k < \alpha k / N. \quad (24)$$

$P_1 \dots P_k$  declared significant.

Figure 19: Multiple comparison corrections. After (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).

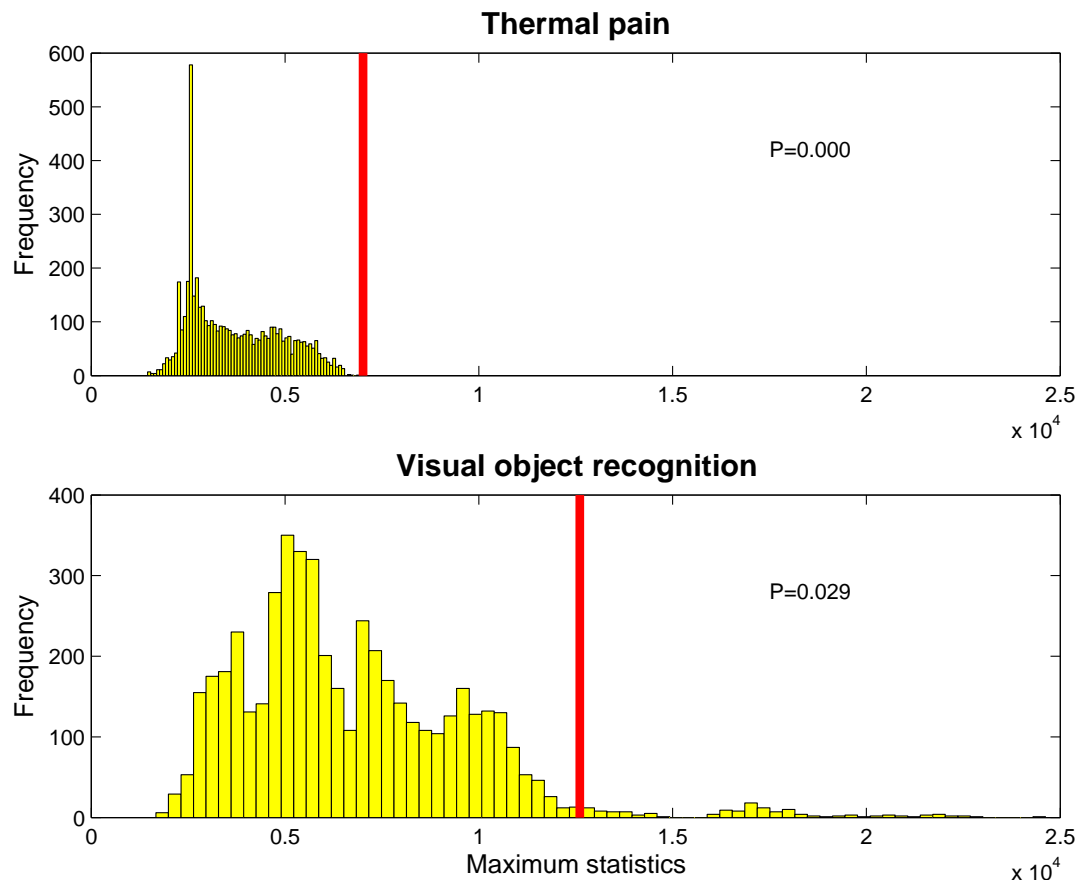
Create a statistics, e.g., a ordinary  $t$ -statistics

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



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

Statistical parametric map:

$$t = (AAAA) - (BBBB)$$

Permutations

$$t_1 = (ABAA) - (BBAB)$$

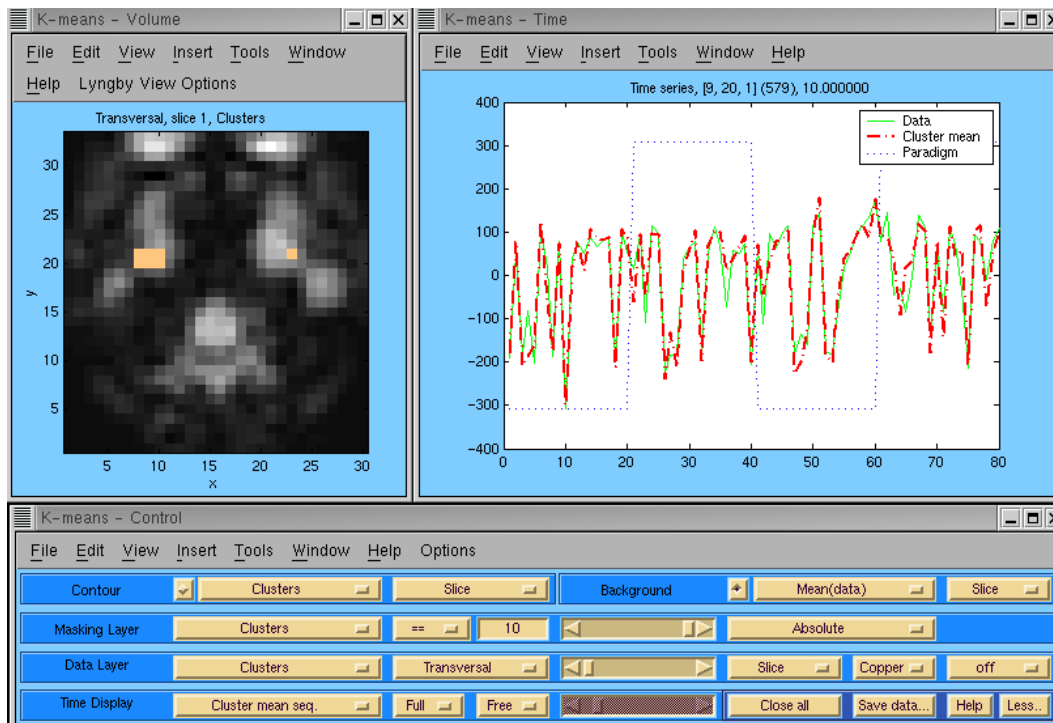
$$t_2 = (BBAA) - (AABB)$$

⋮

P-values is the ratio of  $\max(t_r)$  for  $r = 1 \dots R$  larger than  $t$

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

# Lyngby Toolbox



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

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

Figure 21: One of the windows in the Lyngby toolbox

## SPM plugins — third party software

Batch processing. Programs to construct batch jobs.

INRIAlign. Robust motion alignment.

Diffusion. Functions for DWI MRI

Region of interest modeling (MarsBar, WFUPickAtlas),

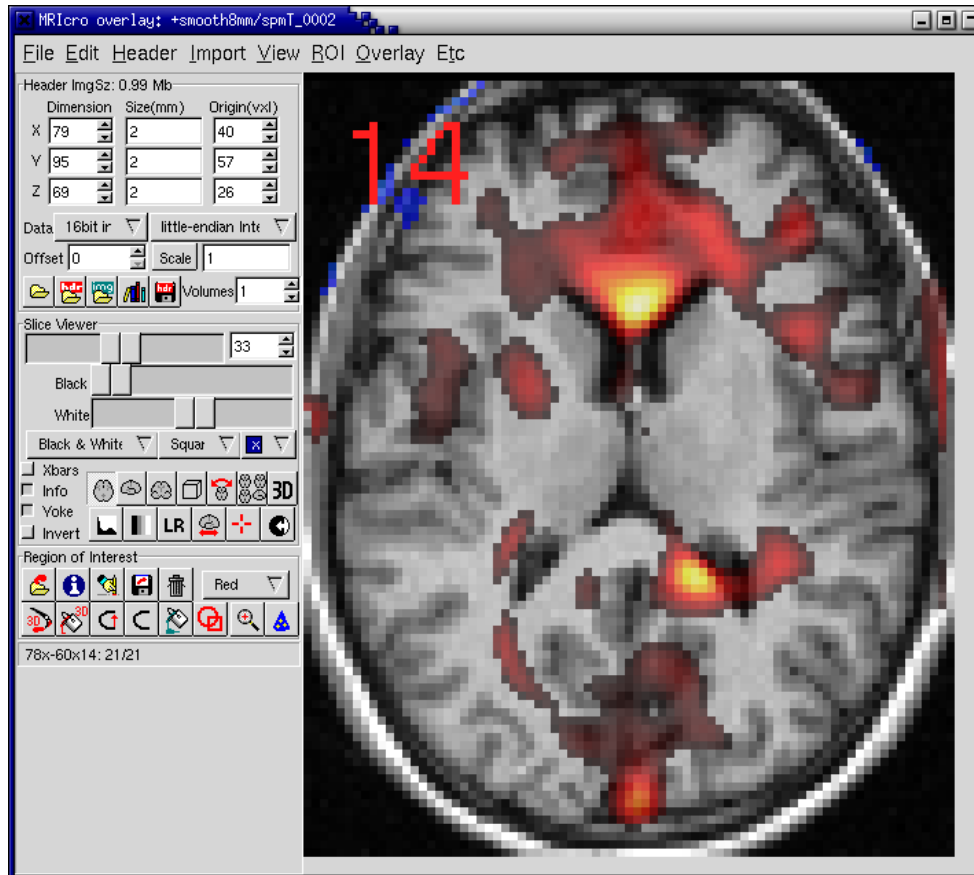
Multivariate analysis (MM Toolbox),

“Statistical Parametric Mapping Diagnosis”

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

...

# MRICro



MRICro programmed by Chris Rorden.

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 skull (ch2) and without skull (ch2bet)

## More information

SPM wiki, <http://en.wikibooks.org/wiki/SPM> and  
[http://en.wikipedia.org/wiki/Statistical\\_parametric\\_mapping](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/>

Jonathan Taylors notes for his “stats191” course: <http://www-stat.stanford.edu/~jtaylo/courses/stats191/spring.2004/>

“General Linear Models” StatSoft, Inc, [http://www.statsoftinc.com-textbook/stglm.html](http://www.statsoftinc.com/textbook/stglm.html)

# References

- Brett, M. (1999a). The MNI brain and the Talairach atlas. <http://www.mrc-cbu.cam.ac.uk/Imaging/mnispace.html>. Accessed 2003 March 17.
- Brett, M. (1999b). Thresholding with random field theory. <http://www.mrc-cbu.cam.ac.uk/Imaging/Common/randomfields.shtml>. Accessed 2005 March 3.
- Friston, K. J., Holmes, A. P., Worsley, K. J., Poline, J.-B., Frith, C. D., and Frackowiak, R. S. J. (1995). Statistical parametric maps in functional imaging: A general linear approach. *Human Brain Mapping*, 2:189–210. [http://www.fil.ion.ucl.ac.uk/spm/papers/SPM\\_3/](http://www.fil.ion.ucl.ac.uk/spm/papers/SPM_3/).
- Genovese, C. R., Lazar, N. A., and Nichols, T. (2002). Thresholding of statistical maps in functional neuroimaging using the false discovery rate. *NeuroImage*, 15(4):870–878.
- Hansen, L. K., Nielsen, F. Å., Toft, P., Liptrot, M. G., Goutte, C., Strother, S. C., Lange, N., Gade, A., Rottenberg, D. A., and Paulson, O. B. (1999). “lyngby” — a modeler’s Matlab toolbox for spatio-temporal analysis of functional neuroimages. In Rosen, B. R., Seitz, R. J., and Volkmann, J., editors, *Fifth International Conference on Functional Mapping of the Human Brain, NeuroImage*, volume 9, page S241. Academic Press. <http://isp.imm.dtu.dk/publications/1999/hansen.hbm99.ps.gz>. ISSN 1053–8119.
- Holmes, A. P., Blair, R. C., Watson, J. D. G., and Ford, I. (1996). Non-parametric analysis of statistic images from functional mapping experiments. *Journal of Cerebral Blood Flow and Metabolism*, 16(1):7–22. PMID: 8530558.
- Mardia, K. V., Kent, J. T., and Bibby, J. M. (1979). *Multivariate Analysis*. Probability and Mathematical Statistics. Academic Press, London. ISBN 0124712525.
- Nichols, T. E. and Holmes, A. P. (2001). Nonparametric permutation tests for PET functional neuroimaging experiments: A primer with examples. *Human Brain Mapping*, 15(1):1–25. PMID: 11747097. <http://www3.interscience.wiley.com/cgi-bin/abstract/86010644/>. ISSN 1065-9471. An reiteration of an older permutation test article by Andrew Holmes. Lengthier and more accessible with three illustrative



examples. An example shows that the permutation test with a pseudo-t statistics detects more “active” voxels than a parametric approach.

Noll, D. C., Kinahan, P. E., Mintun, M. A., Thulborn, K. R., and Townsend, D. W. (1996). Comparison of activation response using functional PET and MRI. *NeuroImage*, 3(3):S34. Second International Conference on Functional Mapping of the Human Brain.

Rao, C. R. (1962). A note on a generalized inverse of a matrix with applications to problems in mathematical statistics. *Journal of the Royal Statistical Society, Series B (Methodological)*, 24(1):152–158.

Talairach, J. and Tournoux, P. (1988). *Co-planar Stereotaxic Atlas of the Human Brain*. Thieme Medical Publisher Inc, New York. ISBN 0865772932.

Tzourio-Mazoyer, N., Landeau, B., Papathanassiou, D., Crivello, F., Etard, O., Delcroix, N., Mazoyer, B., and Joliot, M. (2002). Automated anatomical labeling of activations in SPM using a macroscopic anatomical parcellation of the MNI MRI single-subject brain. *NeuroImage*, 15(1):273–289. <http://www.idealibrary.com/links/doi/10.1006/nimg.2001.0978>.

Worsley, K. J. (2004). Developments in random field theory. In Frackowiak, R. S. J., Friston, K. J., Frith, C. D., Dolan, R. J., Price, C. J., Zeki, S., Ashburner, J., and Penny, W., editors, *Human Brain Function*. Elsevier, Amsterdam, Holland, second edition. <http://www.fil.ion.ucl.ac.uk/spm/doc/books/hbf2/pdfs/Ch15.pdf>.