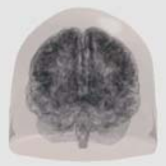
The Wondrous World of fMRI statistics

"FMRI data and Statistics" course, Leiden, 11-3-2008



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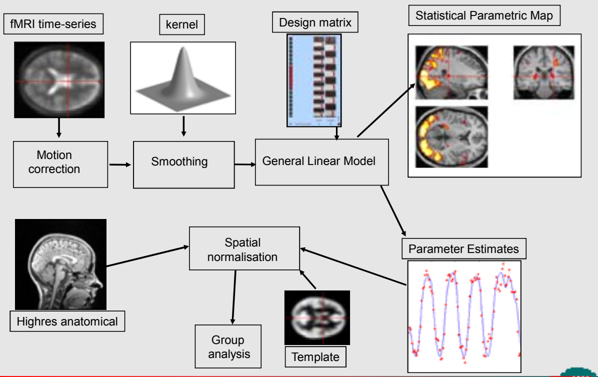
Outline

The General Linear Model
- Overview of fMRI data analysis steps
- fMRI timeseries
- Modeling effects of interest
- Modeling effects of no interest

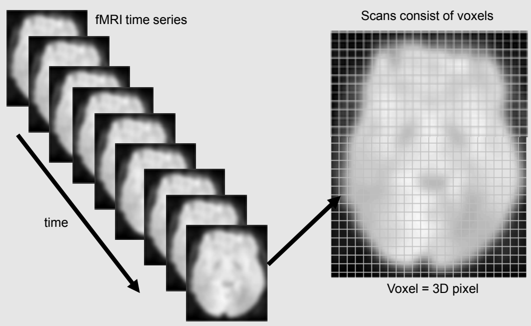
Hypothesis testing
- T contrasts
- F contrasts
- T/F contrasts & significance

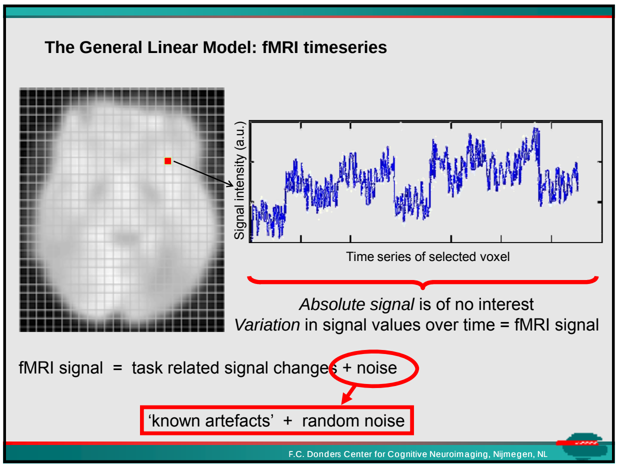
Statistical Inference
- The multiple comparison problem
- Bonferroni correction
- Random field theory based correction
- Regions of interest / small volume corrections
- False discovery rate

The General Linear Model: Overview of data analysis steps



The General Linear Model: fMRI timeseries




The General Linear Model: fMRI timeseries
Signal intensity (a.u.)
Time series of selected voxel
Absolute signal is of no interest
Variation in signal values over time = fMRI signal
fMRI signal = task related signal changes + noise
'known artefacts' + random noise
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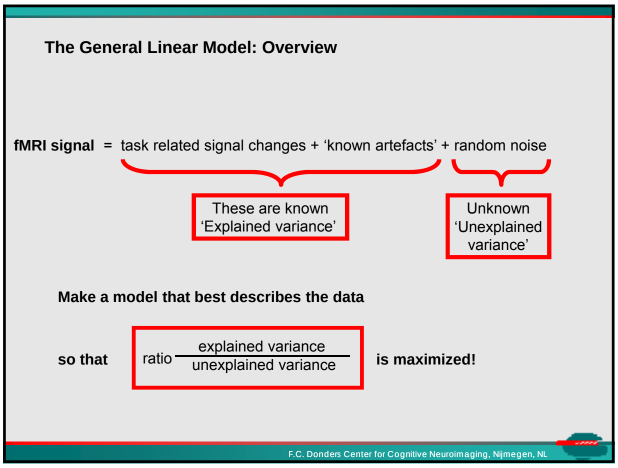
The General Linear Model: Overview
fMRI signal = task related signal changes + 'known artefacts' + random noise
These are known 'Explained variance'
Unknown 'Unexplained variance'
Make a model that best describes the data
so that
ratio explained variance / unexplained variance
is maximized!
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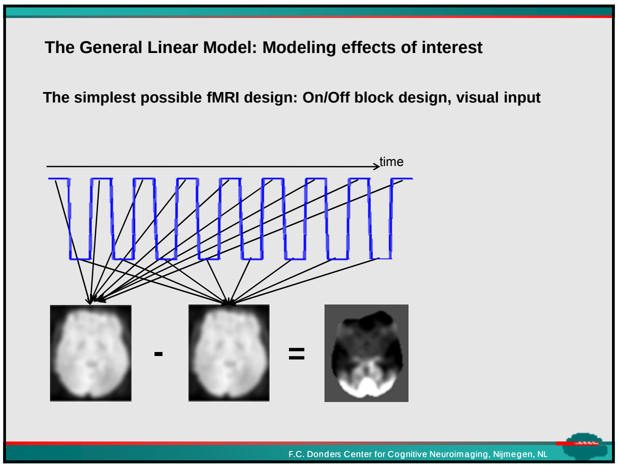
The General Linear Model: Modeling effects of interest
The simplest possible fMRI design: On/Off block design, visual input
time
-
=
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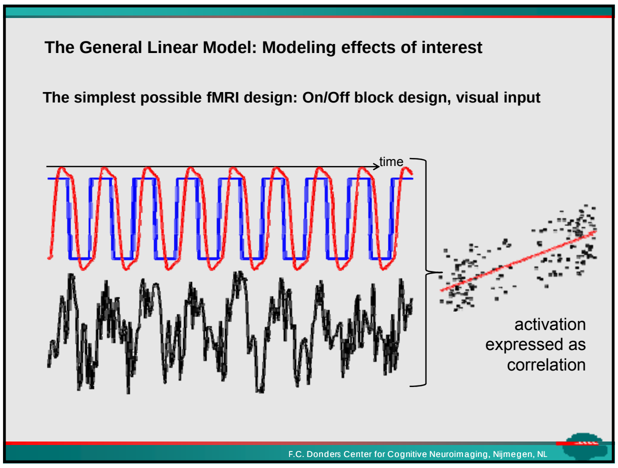
The General Linear Model: Modeling effects of interest
The simplest possible fMRI design: On/Off block design, visual input
time
activation expressed as correlation
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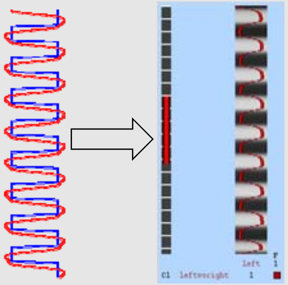
The General Linear Model: Modeling effects of interest

The simplest possible fMRI design: On/Off block design

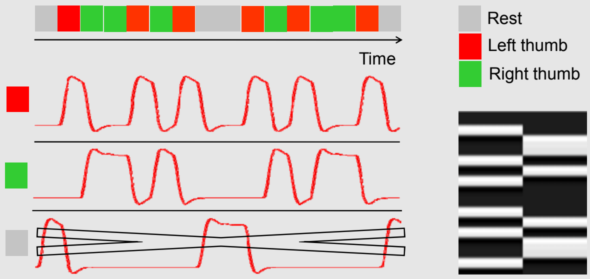


Model usually represented in gray levels

(FSL shows both)

The General Linear Model: Modeling effects of interest

Designs with more than one condition: *multiple regression*



The General Linear Model: Modeling effects of no interest

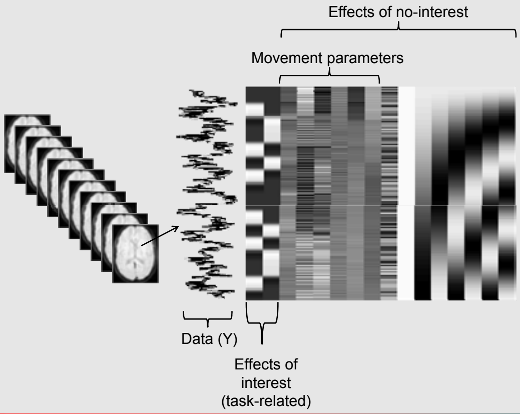
fMRI signal = task related signal changes + 'known artefacts' + random noise

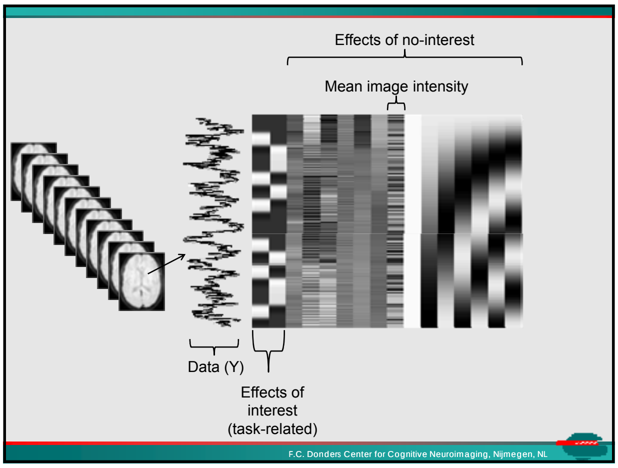
Effects of interest | Effects of NO interest | ?

Effects of **no** interest = Predictable variations in the signal caused by effects other than the task:

- Low-frequency drifts (high-pass filter) and scanner instabilities (model mean intensity of images)
- Movement (obtain from realignment stage)
- Heart beat
- Respiration

These effects can be 'removed' from the data by modeling the signal they generate




Effects of no-interest
Mean image intensity
Data (Y)
Effects of interest (task-related)
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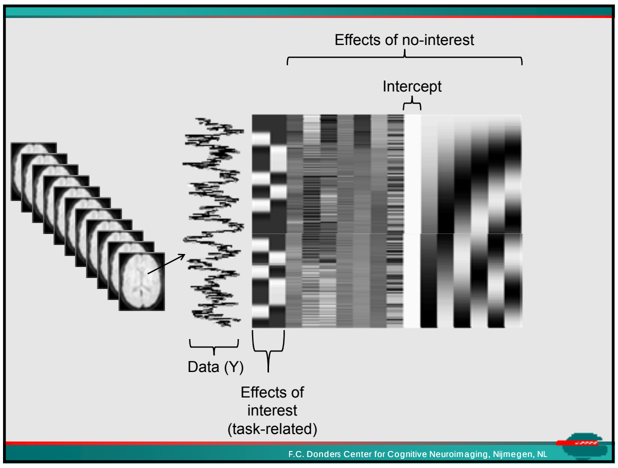
Effects of no-interest
Intercept
Data (Y)
Effects of interest (task-related)
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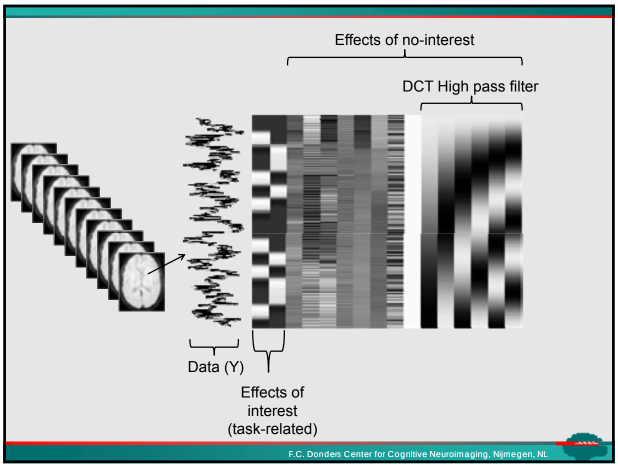
Effects of no-interest
DCT High pass filter
Data (Y)
Effects of interest (task-related)
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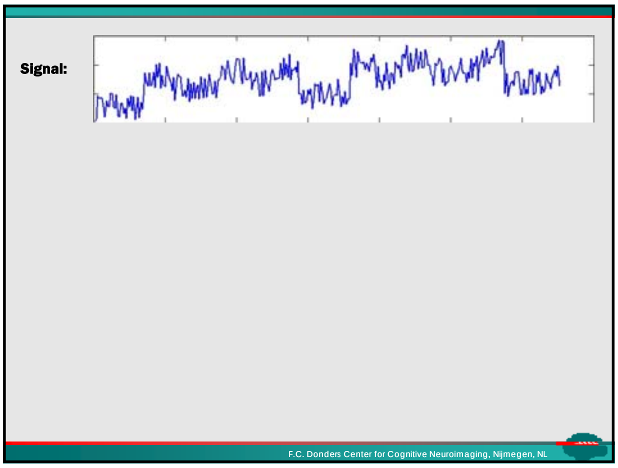
Signal:
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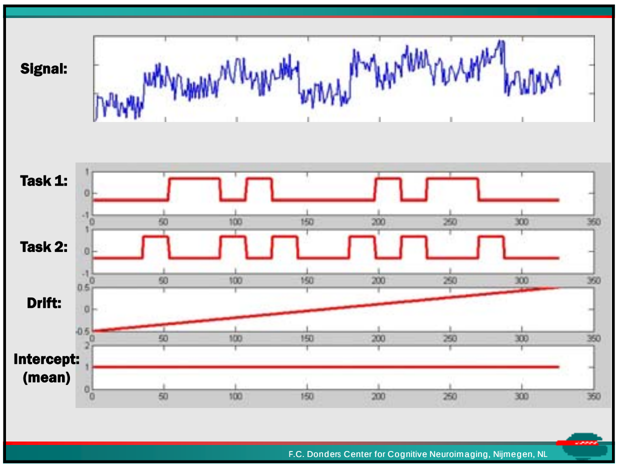
Signal:
Task 1:
Task 2:
Drift:
Intercept:
(mean)
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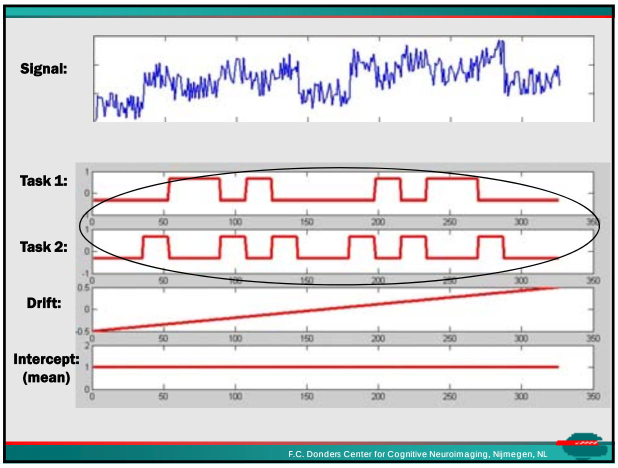
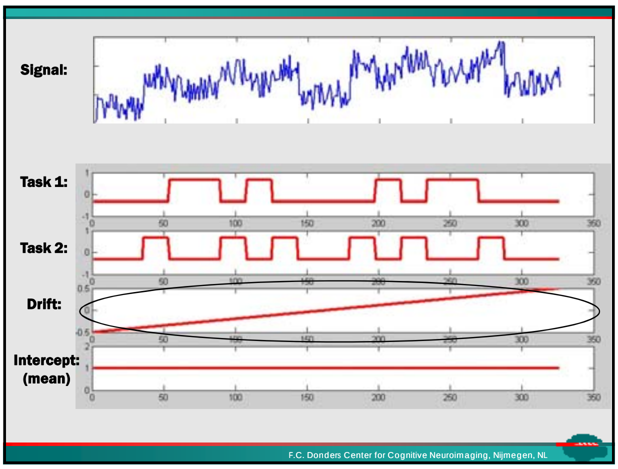
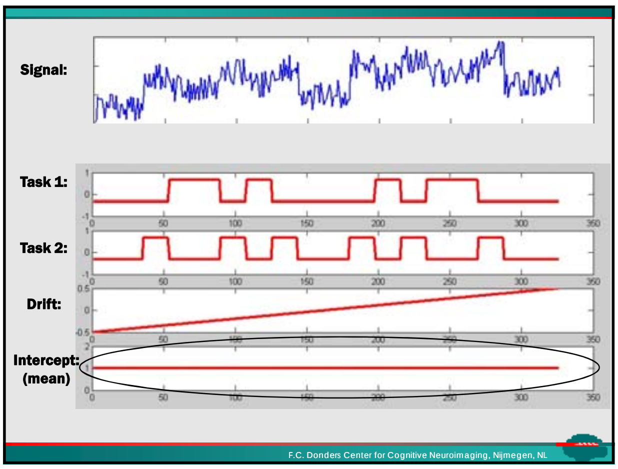

Signal:
Task 1:
Task 2:
Drift:
Intercept:
(mean)
F.C. Donders Center for Cognitive Neuroimaging, Nijmegen, NL


Signal:
Task 1:
Task 2:
Drift:
Intercept:
(mean)
F.C. Donders Center for Cognitive Neuroimaging, Nijmegen, NL


Signal:
Task 1:
Task 2:
Drift:
Intercept:
(mean)
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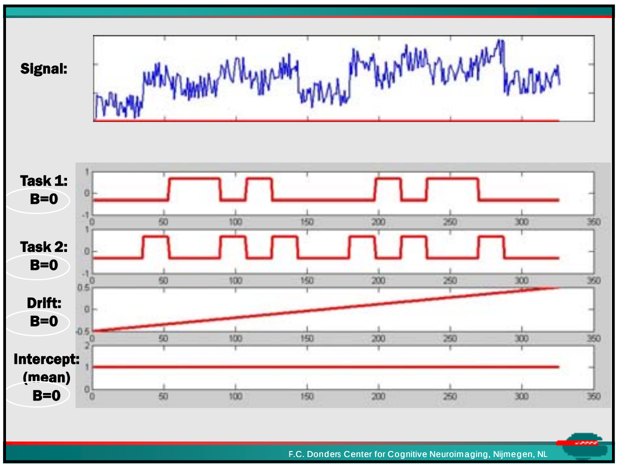
Signal:
Task 1:
B=0
Task 2:
B=0
Drift:
B=0
Intercept:
(mean)
B=0
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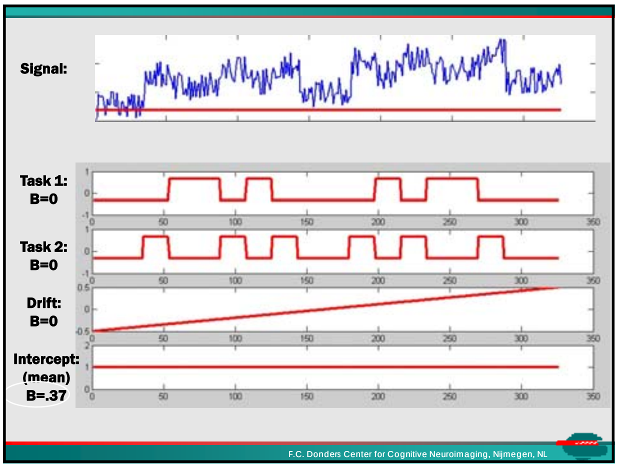
Signal:
Task 1:
B=0
Task 2:
B=0
Drift:
B=0
Intercept:
(mean)
B=.37
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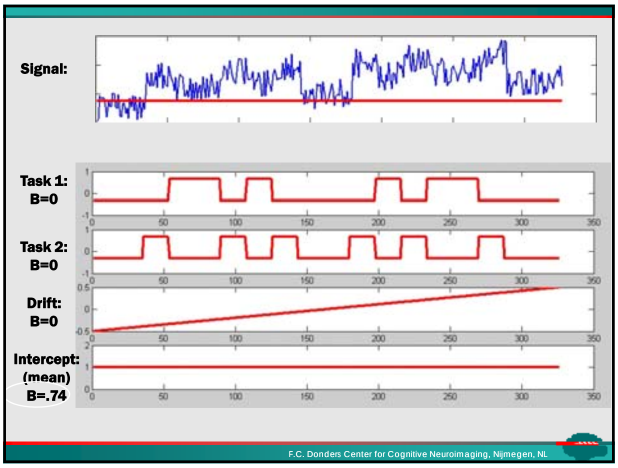
Signal:
Task 1:
B=0
Task 2:
B=0
Drift:
B=0
Intercept:
(mean)
B=.74
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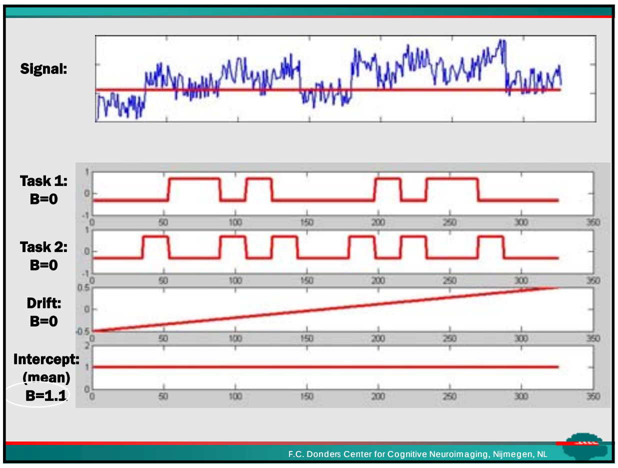
Signal:
Task 1:
B=0
Task 2:
B=0
Drift:
B=0
Intercept:
(mean)
B=1.1
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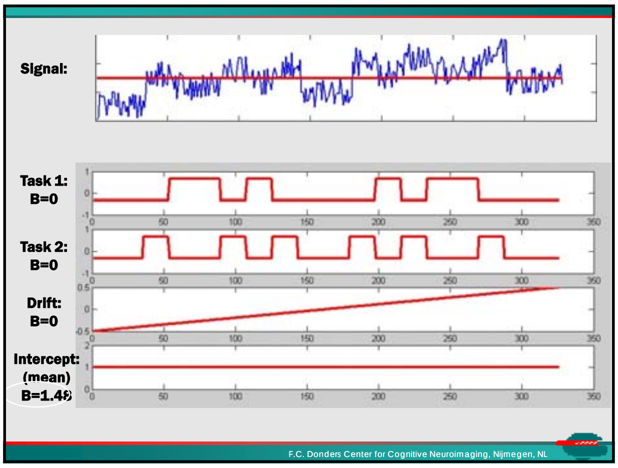
Signal:
Task 1: B=0
Task 2: B=0
Drift: B=0
Intercept: (mean) B=1.48
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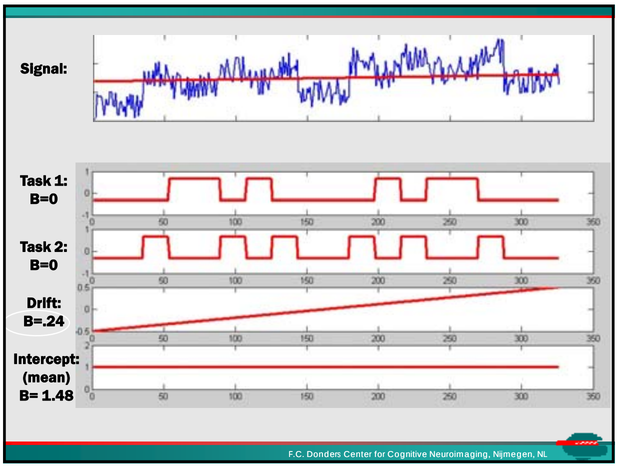
Signal:
Task 1: B=0
Task 2: B=0
Drift: B=.24
Intercept: (mean) B= 1.48
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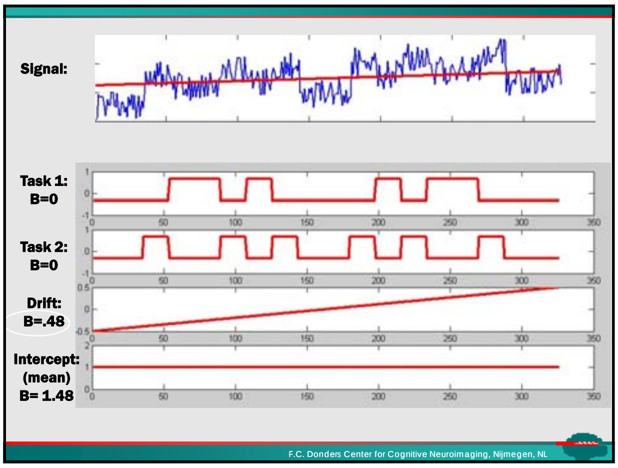
Signal:
Task 1: B=0
Task 2: B=0
Drift: B=.48
Intercept: (mean) B= 1.48
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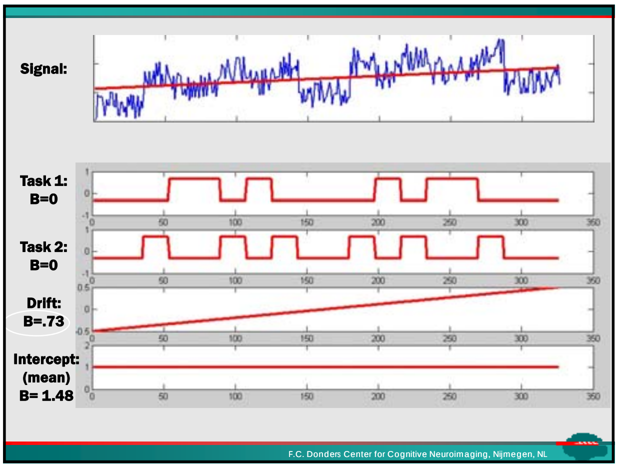
Signal:
Task 1: B=0
Task 2: B=0
Drift: B=.73
Intercept: (mean) B= 1.48
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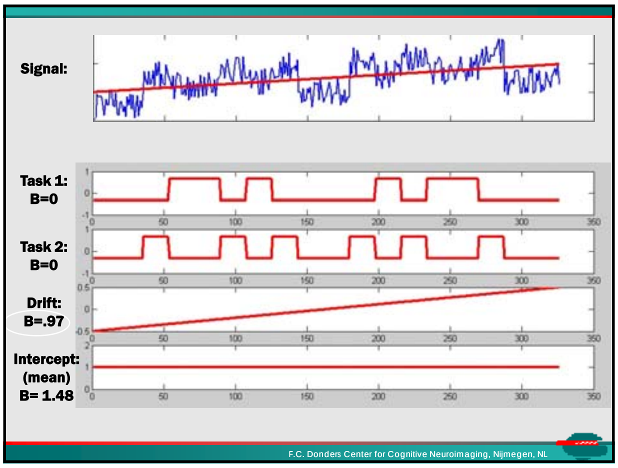
Signal:
Task 1:
B=0
Task 2:
B=0
Drift:
B=.97
Intercept:
(mean)
B= 1.48
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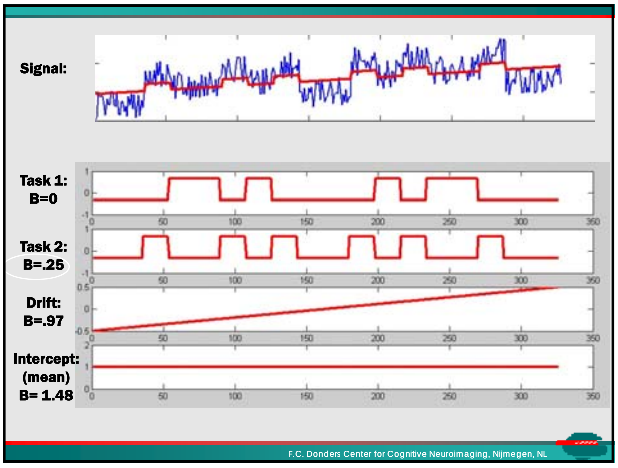
Signal:
Task 1:
B=0
Task 2:
B=.25
Drift:
B=.97
Intercept:
(mean)
B= 1.48
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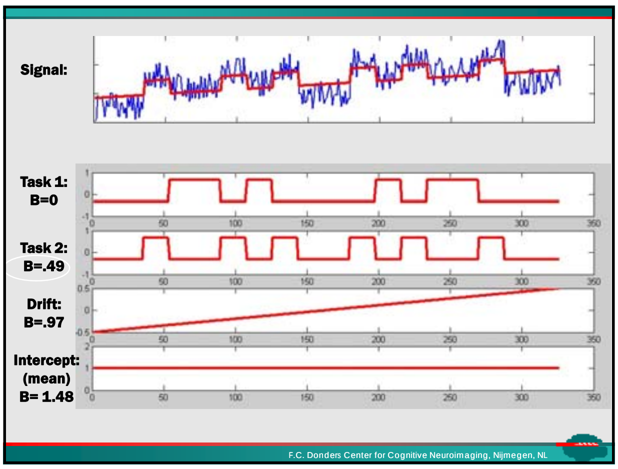
Signal:
Task 1:
B=0
Task 2:
B=.49
Drift:
B=.97
Intercept:
(mean)
B= 1.48
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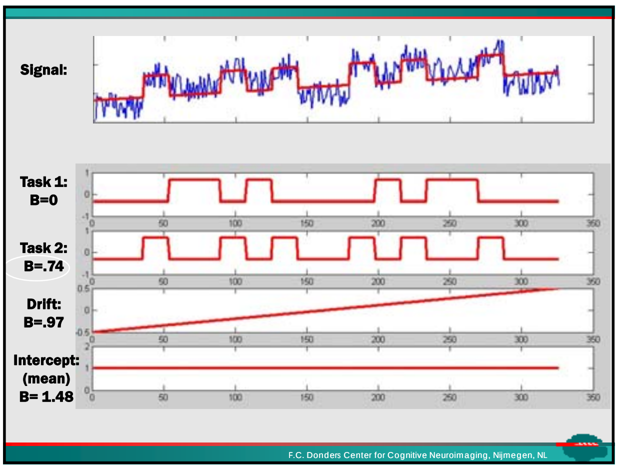
Signal:
Task 1:
B=0
Task 2:
B=.74
Drift:
B=.97
Intercept:
(mean)
B= 1.48
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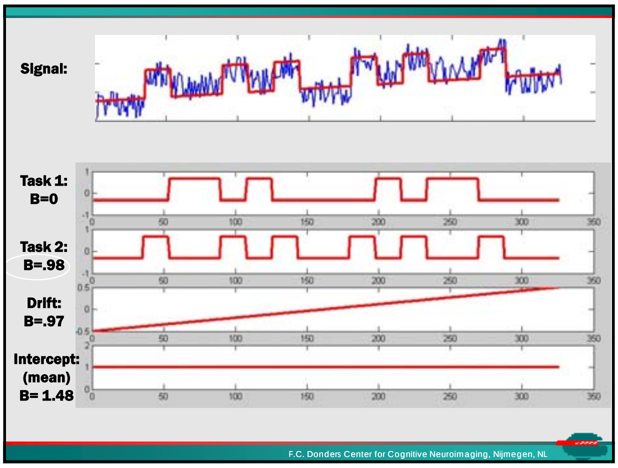
Signal:
Task 1:
B=0
Task 2:
B=.98
Drift:
B=.97
Intercept:
(mean)
B= 1.48
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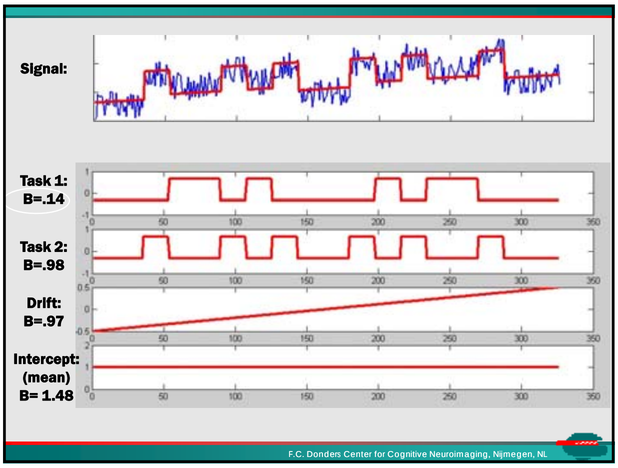
Signal:
Task 1:
B=.14
Task 2:
B=.98
Drift:
B=.97
Intercept:
(mean)
B= 1.48
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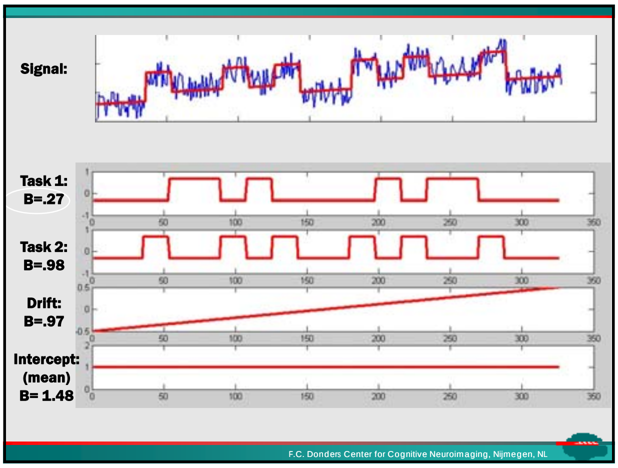
Signal:
Task 1:
B=.27
Task 2:
B=.98
Drift:
B=.97
Intercept:
(mean)
B= 1.48
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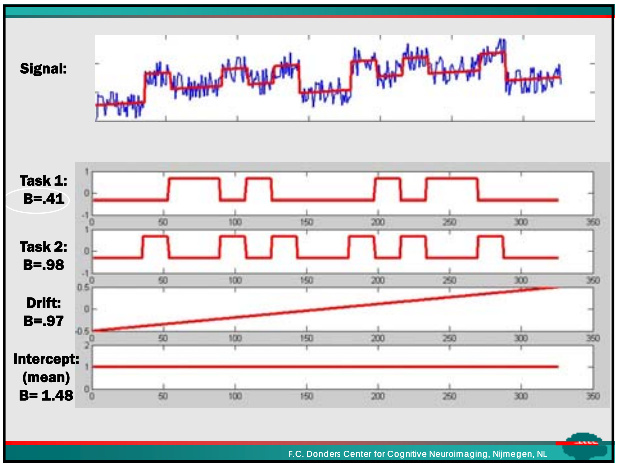
Signal:
Task 1:
B=.41
Task 2:
B=.98
Drift:
B=.97
Intercept:
(mean)
B= 1.48
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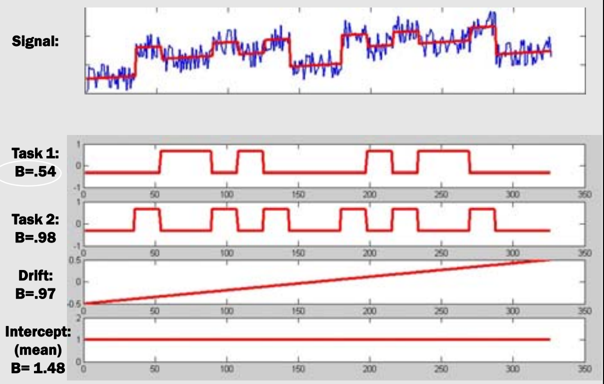
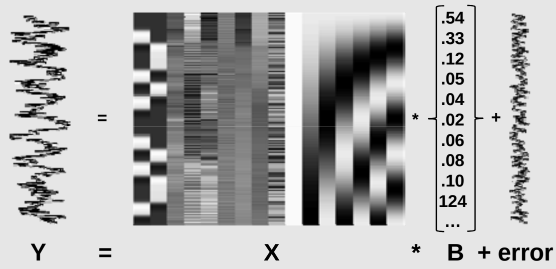


The General Linear Model: Obtaining parameter estimates



The General Linear Model: Obtaining parameter estimates

How are parameter estimates calculated?

- Minimize the amount of residual error
- error = Y – XB
- *Amount of error* summarized as sum of squared errors:

$$\sum(error^2) = (Y - XB)'(Y - XB) = e'e = SS_e$$

- This is solved by:

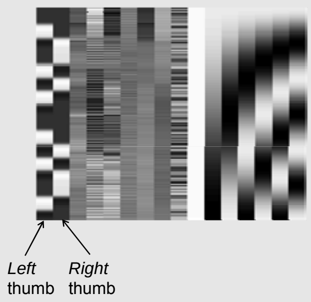
$$B = (X'X)^{-1}X'Y$$

- Error variance is then given by calculated using:

$$MS_e = \frac{SS_e}{df} = \frac{e'e}{N-H}$$

(where N = # of observations and H = # of regressors)

Hypothesis testing: T contrasts



Hypothesis testing: T contrasts

Does my contrast of parameter estimates explain variance?

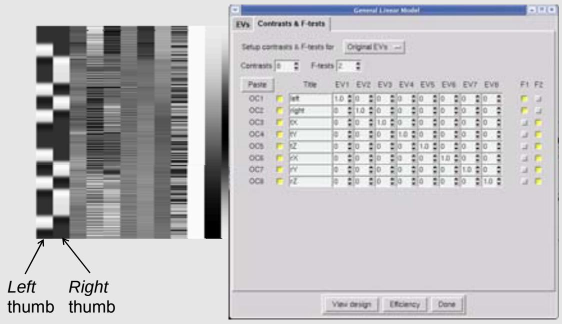
- Contrast of parameter estimates -> mean of the effect
- t-value -> significance of that contrast
  (does that factor explain a significant amount of variance?)

Test significance with a t-statistic:

- Null hypothesis: contrast of parameter estimates (c) = 0
  (i.e., c'B = 0)
- The t-value is given by:

$$t = \frac{\text{explained variance}}{\text{unexplained variance}} \qquad t = \frac{c'B}{\sqrt{MS_e c'(X'X)^{-1}c}}$$

Hypothesis testing: F contrasts



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Hypothesis testing: T/F contrasts & significance

What is the chance of observing this effect under H0?

- Chance (P) depends on t/F statistic and
  degrees of freedom (DF)
- For fMRI timeseries data DF is smaller than # of scans.
- Autoregression correction is applied to account for this.
  (e.g., AR(1) model, pre-colouring, pre-whitening)

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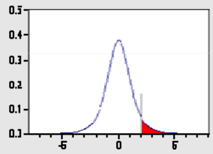
Hypothesis testing: T/F contrasts & significance

What is the chance of observing this effect under H0?

- Should we reject H0?
- Set an acceptable chance of type 1 error (alpha)
- Use the *null distribution:*



DF = 5

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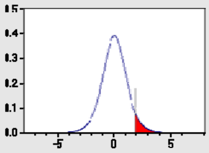
Hypothesis testing: T/F contrasts & significance

What is the chance of observing this effect under H0?
- Should we reject H0?
- Set an acceptable chance of type 1 error (alpha)
- Use the *null distribution:*



DF = 10

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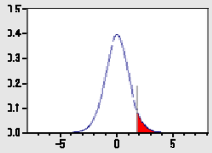
Hypothesis testing: T/F contrasts & significance

What is the chance of observing this effect under H0?
- Should we reject H0?
- Set an acceptable chance of type 1 error (alpha)
- Use the *null distribution:*



DF = 15

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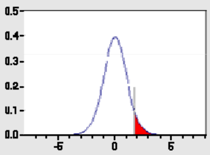
Hypothesis testing: T/F contrasts & significance

What is the chance of observing this effect under H0?
- Should we reject H0?
- Set an acceptable chance of type 1 error (alpha)
- Use the *null distribution:*



DF = 25

At DF = ∞
T=Z

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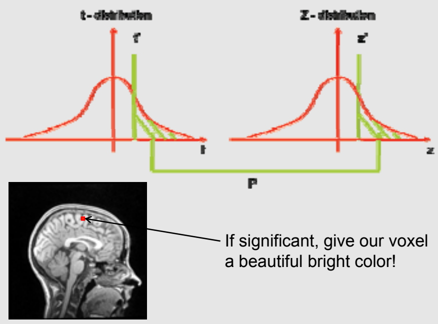
Hypothesis testing: T/F contrasts & significance

t Statistic can be converted to a Z statistic:



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Statistical Inference: The multiple comparison problem

if α = .05, then:

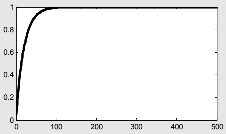
$P^{\text{type I error}}$ = .05

With a *family* of two tests: trouble

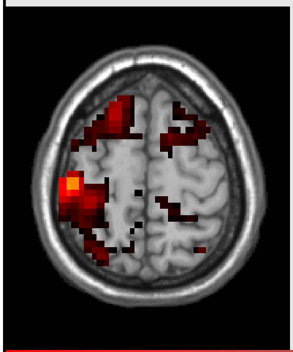
$P^{\text{family wise error}}$ = 1-(1-α)^2 = .095

With a *family* of >20.000 tests: big trouble!

$P^{\text{family wise error}}$ = 1-(1-α)^20000 =~ 1



Statistical Inference: The multiple comparison problem



Alpha=.05

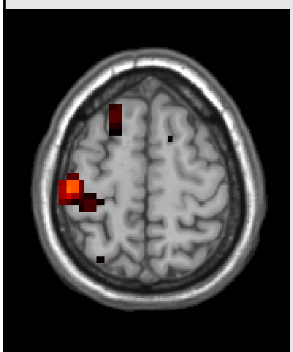
(Z>1.65)

Statistical Inference: The multiple comparison problem

Alpha=.01

(Z>2.33)

Statistical Inference: The multiple comparison problem



Alpha=.001

(Z>3.09)

Statistical Inference: The multiple comparison problem

Alpha=.0001

(Z>3.72)

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Statistical Inference: The multiple comparison problem

Alpha=.00001

(Z>4.26)

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Statistical Inference: Bonferroni correction

If $P^{\text{family wise error}} = 1-(1-\alpha)$^n

And we want: .05 chance of a *single* false positive

Or: $P^{\text{family wise error}} = .05$

$\alpha^{\text{ corrected}} = \alpha / n$

α =.05 / 23914 = .00000209 (pretty small!)

(or Z>4.60)

F.C. Donders Center for Cognitive Neuroimaging, Nijmegen, NL

Statistical Inference: Bonferroni correction

Alpha=.00000209

(Z>4.60)

BUT: Bonferroni assumes that tests are independent

fMRI images are spatially correlated

F.C. Donders Center for Cognitive Neuroimaging, Nijmegen, NL

Statistical Inference: Bonferroni correction

Sources of spatial correlation:

- The spatial resolution of the underlying signal
- Blurring due to resampling during preprocessing
- Smoothing that is often deliberately applied.

So: correct for estimated number of true independent tests instead of number of voxels!

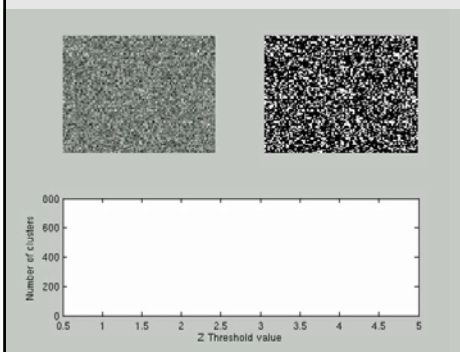
Statistical Inference: Random field theory based correction

Alternative approach to Bonferroni:

1. Control type I error rate by choosing the threshold at which the *expected* number of CLUSTERS is .05.
2. Calculate the expected number of clusters based on the smoothness of the image.

EULER characteristic: number of clusters in an image as a function of threshold and smoothness.

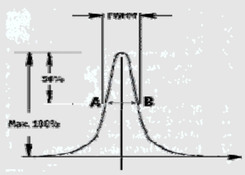
Statistical Inference: Random field theory based correction



<image+ clusters

<Euler char.

Statistical Inference: Random field theory based correction

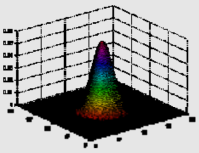


Blur using *Gaussian kernel*

Defined by its

Full Width at Half Maximum (FWHM)

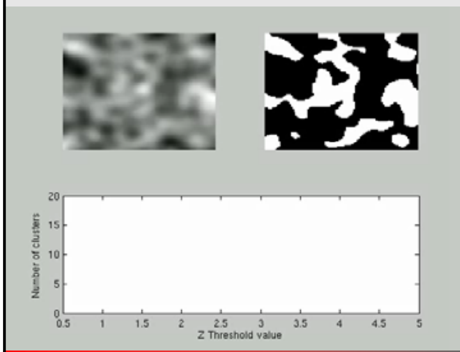
Statistical Inference: Random field theory based correction



2D Gaussian kernel

e.g., single dot

Statistical Inference: Random field theory based correction



<image+
clusters

<Euler char.

Statistical Inference: Random field theory based correction

From (n=1) simulation to:

expected (n=∞) Euler characteristic

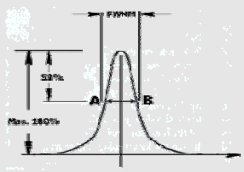
Expected Euler characteristic depends on:

1. Z threshold
2. Smoothness of image

Statistical Inference: Random field theory based correction

How to define smoothness?

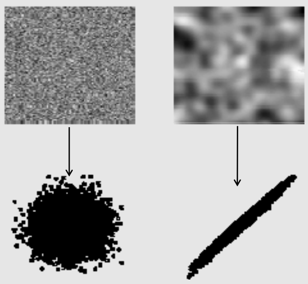
FWHM of smoothing kernel is the *unit* of smoothness



In our example:

- 100*100 pixels
- Smoothed with a 2D FWHM of 10*10 pixels
- 10*10 = 100 *Resolution elements (ResEls)*

Statistical Inference: Random field theory based correction



Statistical Inference: Random field theory based correction

Expected **Euler Characteristic is a function of:**

1. R: Number of ResEls (resolution elements)
2. Z_t: Z threshold

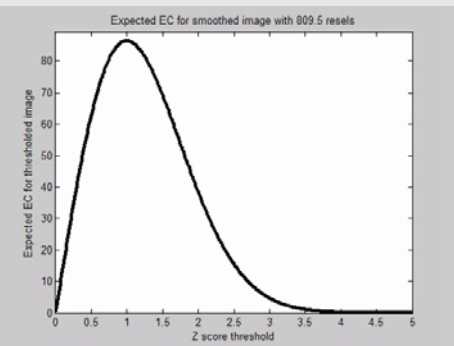
Formula:

$E[EC] = R(4\log_e 2)(2\pi)^{-3/2}\, Z_t e^{-\frac{1}{2}Z_t^2}$

Solve the following equation for alpha=.05:

$.05 = R(4\log_e 2)(2\pi)^{-3/2}\, Z_t e^{-\frac{1}{2}Z_t^2}$

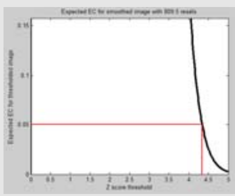
Statistical Inference: Random field theory based correction



Statistical Inference: Random field theory based correction

So, for 809 ResEls, *corrected* alpha of .05:

Z threshold: 4.34



Statistical Inference: Random field theory based correction

Back to example fMRI data:

Smoothness FWHM: 3*3*2.9 voxels

23914 voxels > 809.5 ResEls

T threshold: 4.68; 335 degrees of freedom

P threshold: .00000209

Z threshold: 4.60

Statistical Inference: Random field theory based correction

After smoothing more (15 mm FWHM):

Smoothness FWHM: 5.7*5.9*5.2 voxels

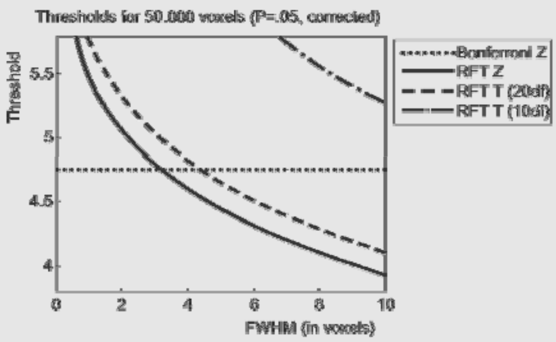
23914 voxels > 124.3 ResEls

T threshold: 4.24; 335 degrees of freedom

P threshold: .0000145

Z threshold: 4.18

Statistical Inference: Random field theory based correction

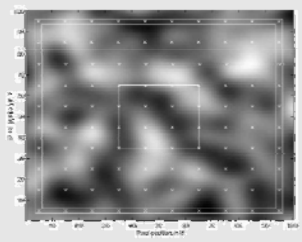


Worsley (2003)

Statistical Inference: Regions of interest / small volume corrections

Regions of interest:

- A priori hypotheses about the search area.
- Correct only for number of independent tests in this area.



Small volume correction :

number of resels may vary with the shape of a small volume:

Statistical Inference: False discovery rate

Instead of voxel level inference: $P^{\text{family wise error}} = .05$

Now control number of *false discoveries:*

Proportion of false positives = .05

Order all P values in the volume:

P1<=P2 <=P3 <= … <=Pn

Cutoff = largest value with:

$P_k < \alpha\, k / n$

Note: this changes the inferences you can make.

Thank you

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Matthijs Vink, Bas Neggers, Matthew Brett
(slides/examples/etc)