Inference on SPMs: Random Field Theory & Alternatives

Thomas Nichols, Ph.D.
Oxford Big Data Institute
Li Ka Shing Centre for Health Information and Discovery
Nuffield Department of Population Health
University of Oxford

FIL SPM Course

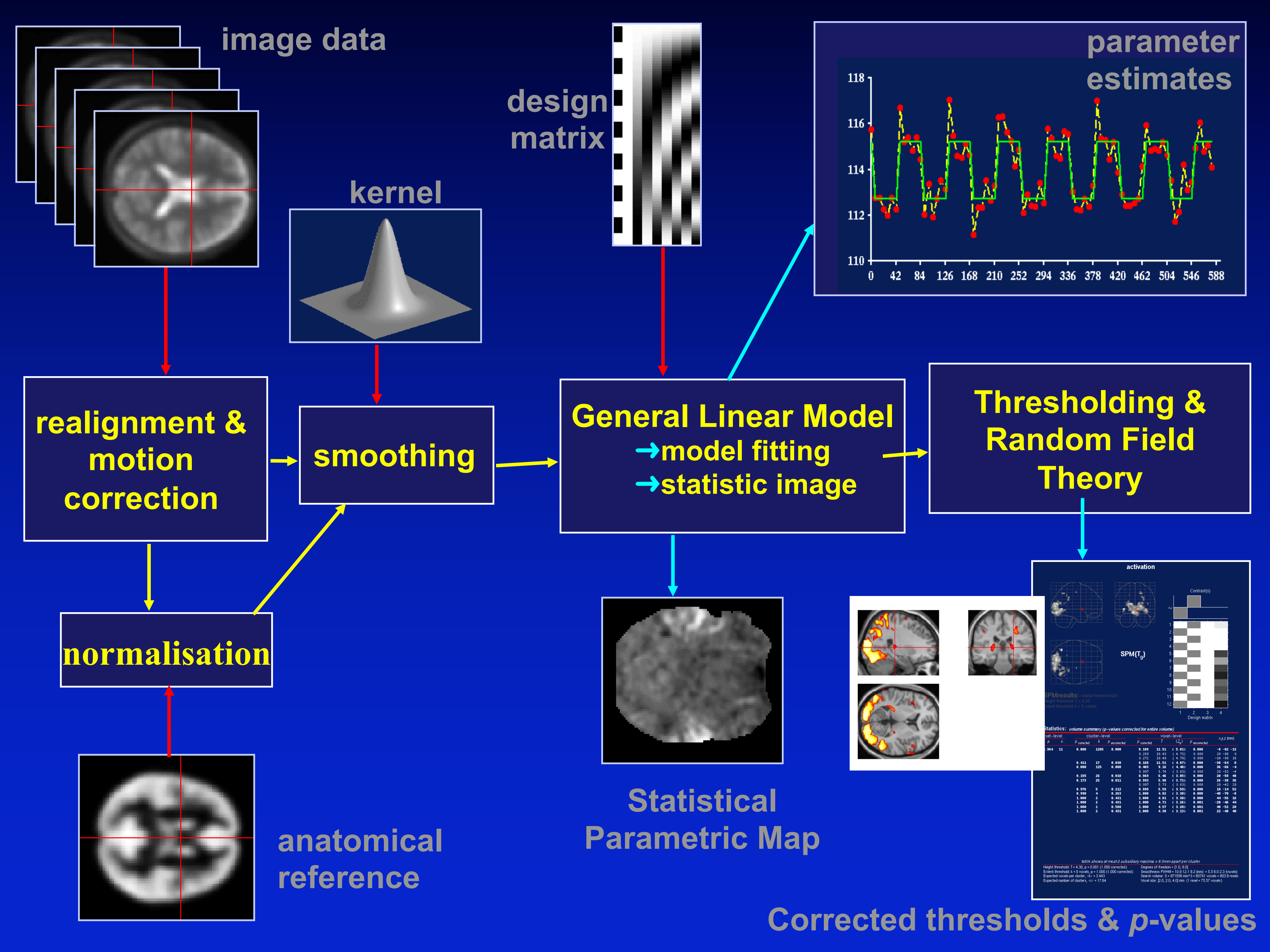
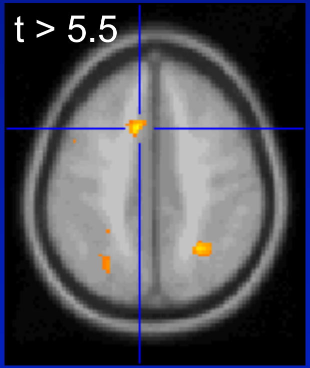
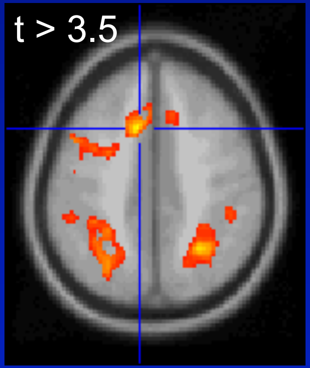
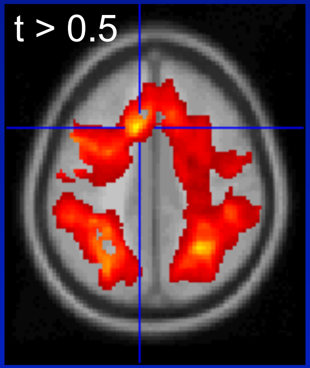


image data
design matrix
parameter estimates
118
116
114
112
110
0 42 84 126 168 210 252 294 336 378 420 462 504 546 588
kernel
realignment & motion correction
smoothing
General Linear Model
→model fitting
→statistic image
Thresholding & Random Field Theory
normalisation
activation
Statistical Parametric Map
anatomical reference
Corrected thresholds & p-values

Assessing Statistic Images…

Assessing Statistic Images

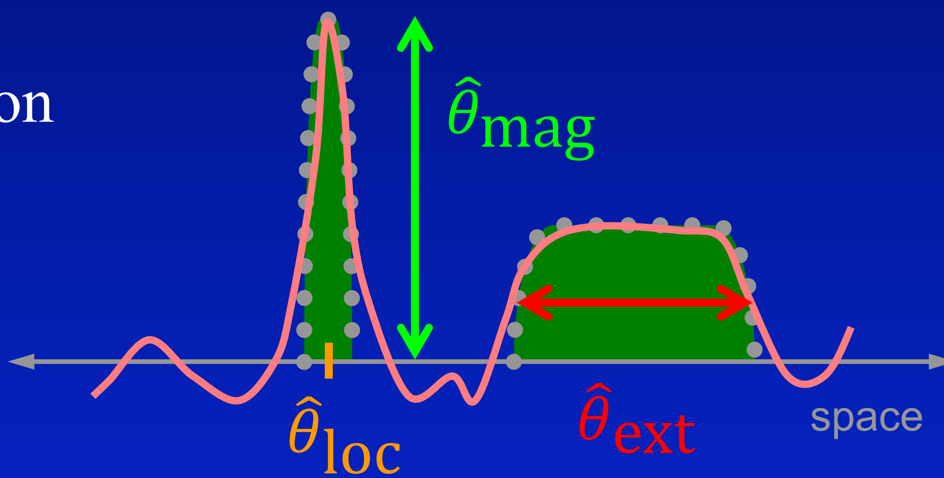
Where's the signal?

High Threshold	Med. Threshold	Low Threshold
		
Good Specificity Poor Power (risk of false negatives)		Poor Specificity (risk of false positives) Good Power

...but why threshold?!

Blue-sky inference: What we' d like

- Don' t threshold, model the signal!
  - Signal location?
    - Estimates and CI' s on (x,y,z) location
  - Signal magnitude?
    - CI' s on % change
  - Spatial extent?
    - Estimates and CI' s on activation volume
    - Robust to choice of cluster definition



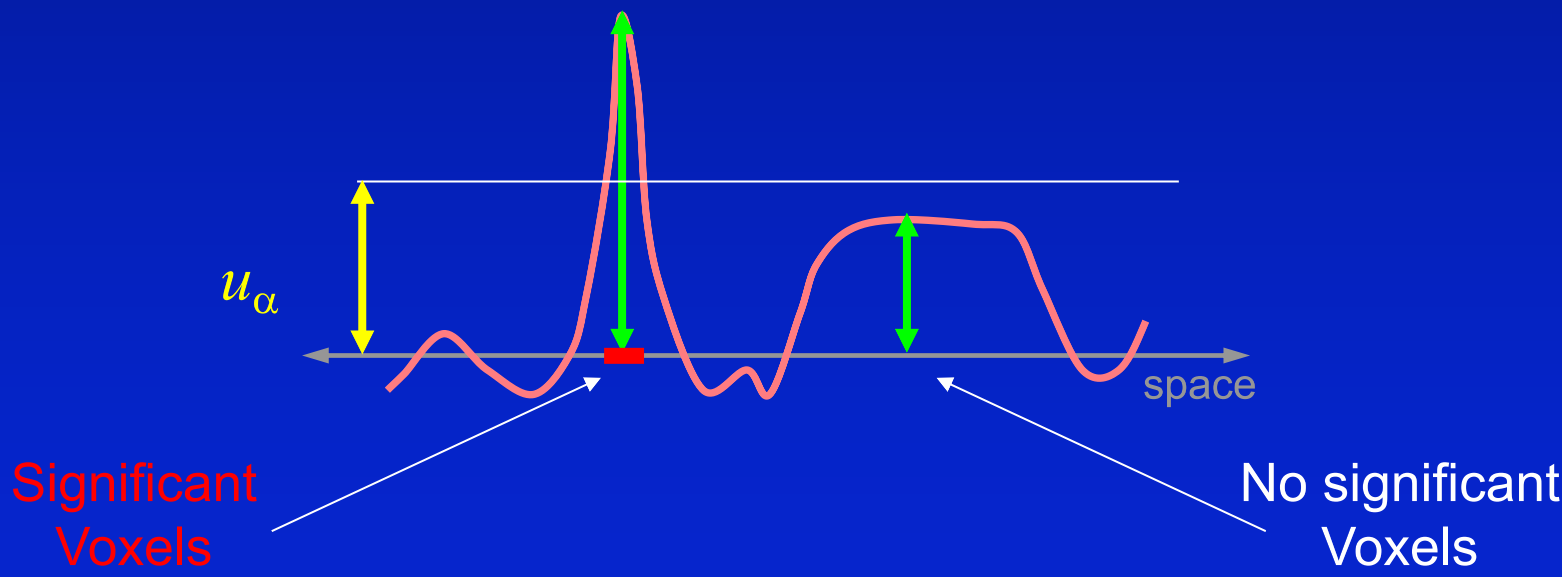
- ...but this requires an explicit spatial model
  - We only have a univariate linear model at each voxel!

Real-life inference: What we get

- Signal location
  - Local maximum – *no inference*
- Signal magnitude
  - Local maximum intensity – P-values (& CI's)
- Spatial extent
  - Cluster volume – P-value, no CI's
    - Sensitive to blob-defining-threshold

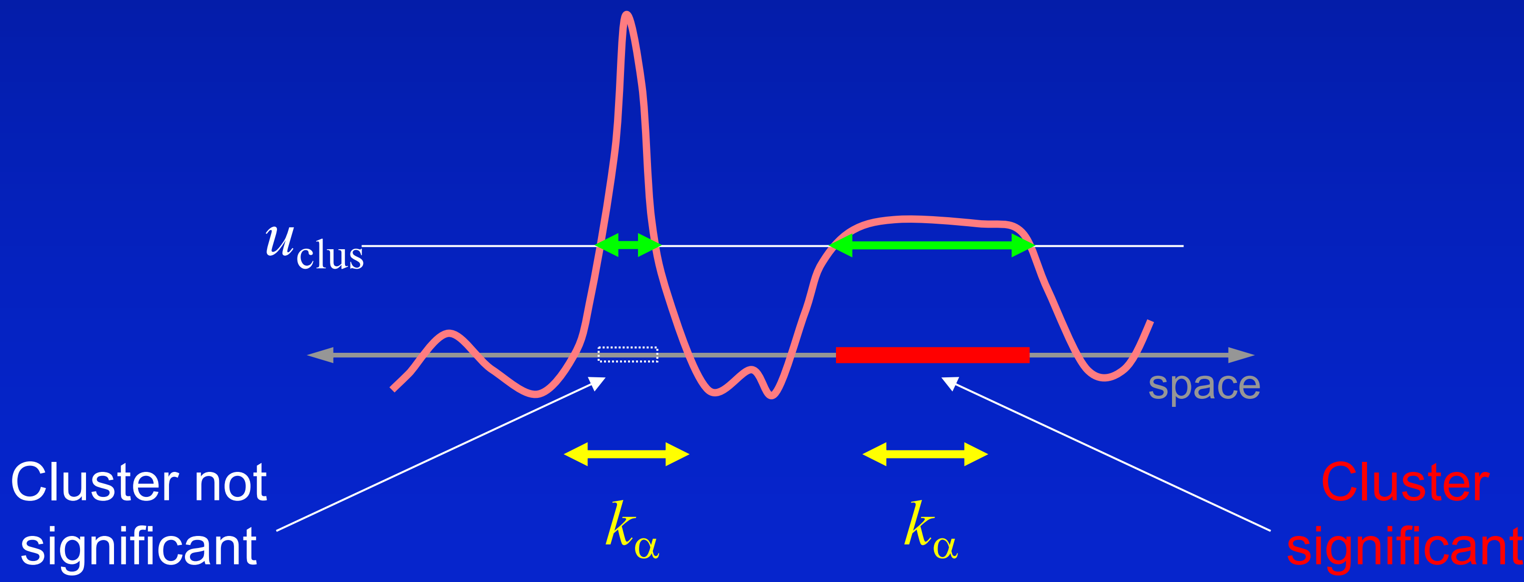
Voxel-level Inference

- Retain voxels above α-level threshold u_α
- Gives best spatial specificity
  - The null hyp. at a single voxel can be rejected



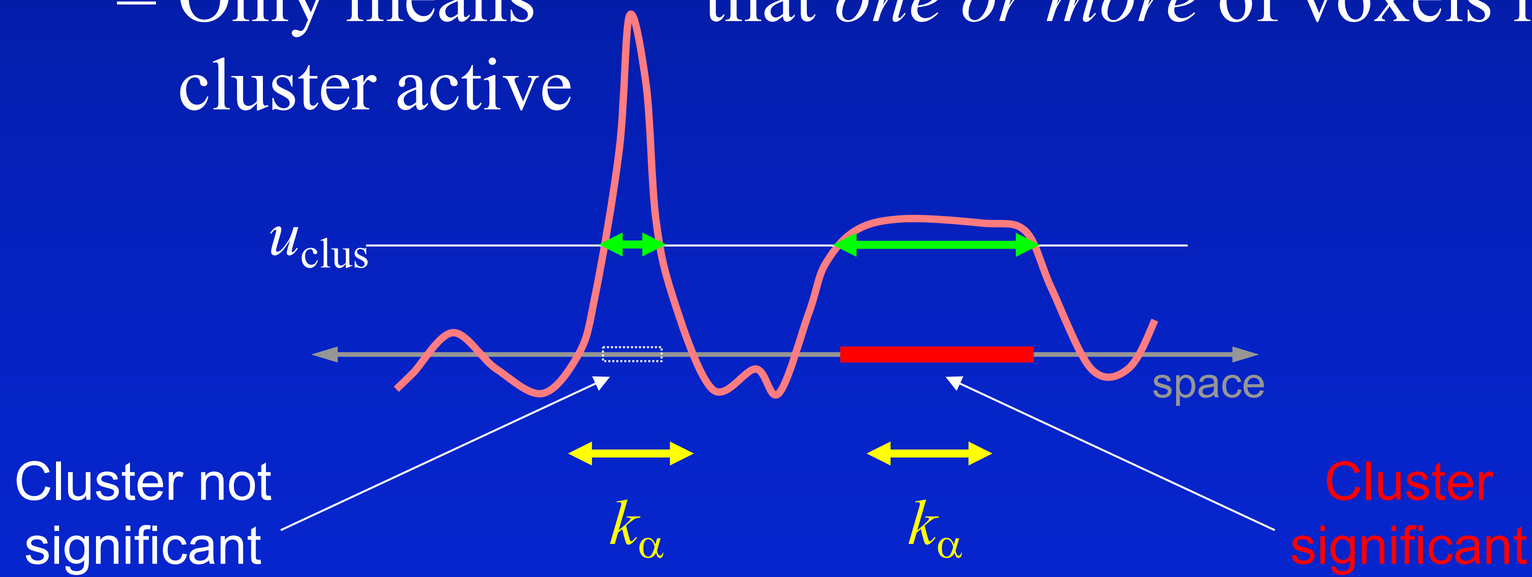
Cluster-level Inference

- Two step-process
  - Define clusters by arbitrary threshold u_{clus}
  - Retain clusters larger than α-level threshold k_α



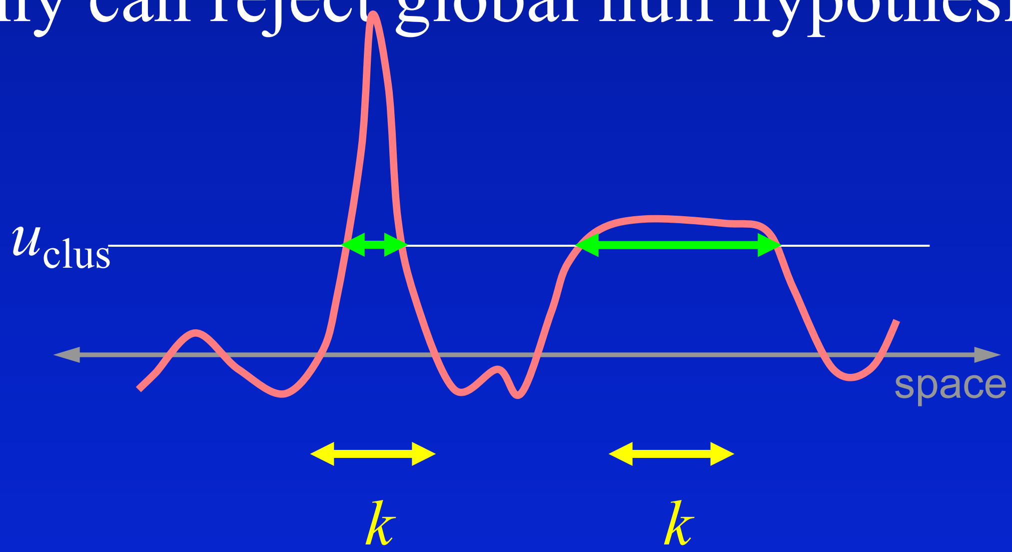
Cluster-level Inference

- Typically better sensitivity
- Worse spatial specificity
  - The null hyp. of entire cluster is rejected
  - Only means that *one or more* of voxels in cluster active



Set-level Inference

- Count number of blobs c
  - Minimum blob size k
- Worst spatial specificity
  - Only can reject global null hypothesis

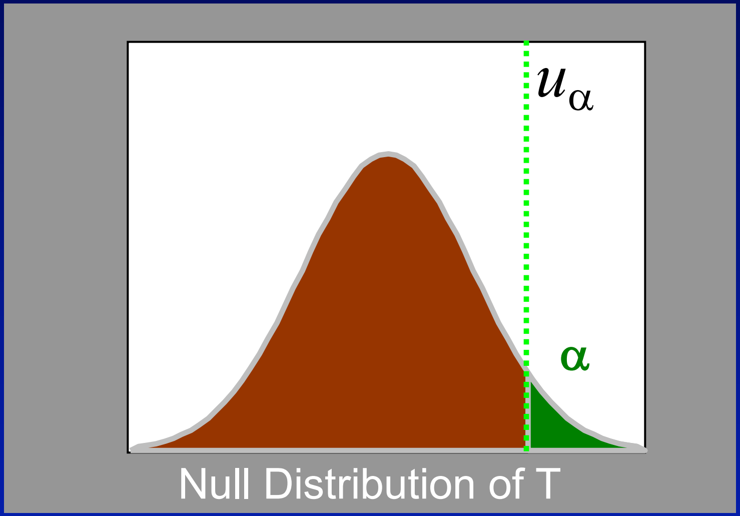


Here $c = 1$; only 1 cluster larger than k

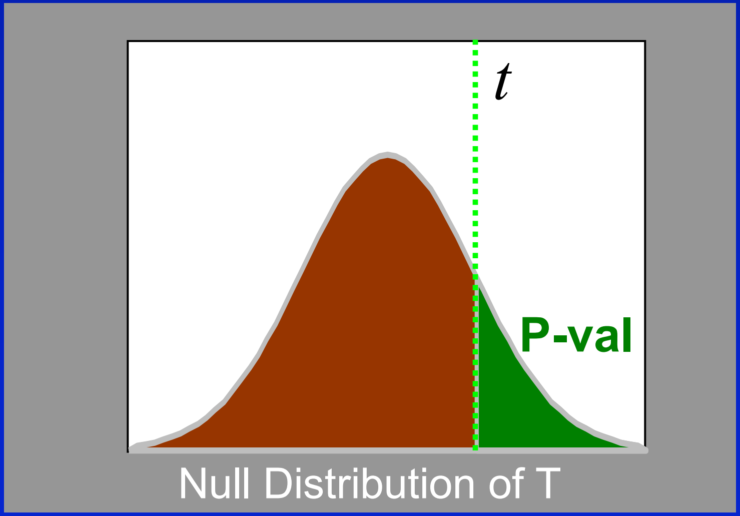
Multiple comparisons…

Hypothesis Testing

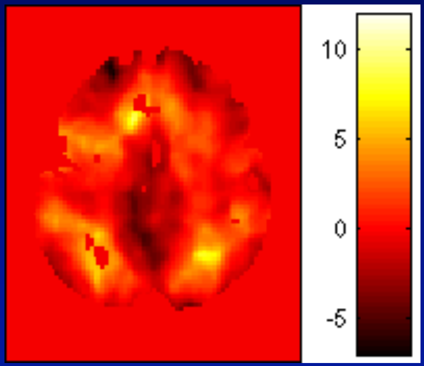
- Null Hypothesis H_0
- Test statistic T
  - t observed realization of T
- α level
  - Acceptable false positive rate
  - Level $\alpha = P(T > u_\alpha \mid H_0)$
  - Threshold u_α controls false positive rate at level α



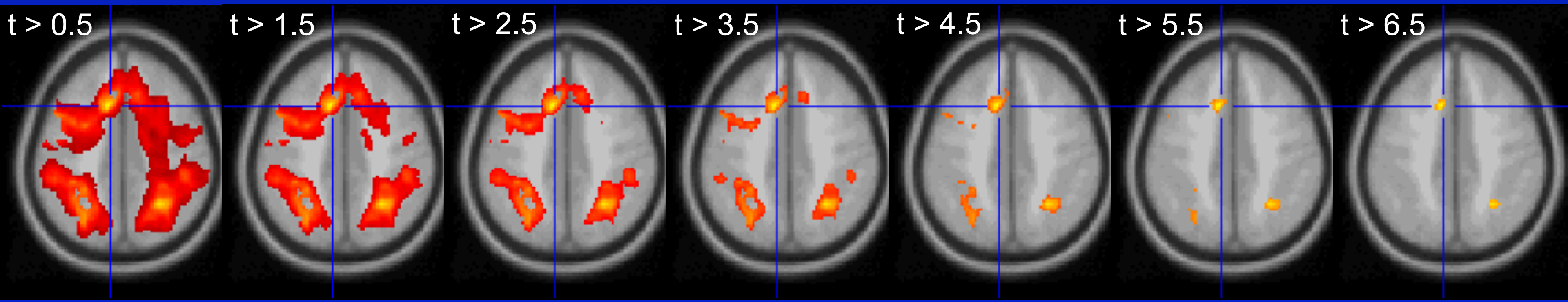
- P-value
  - Assessment of t assuming H_0
  - $P(T > t \mid H_0)$
    - Prob. of obtaining stat. as large or larger in a new experiment
  - P(Data|Null) <u>*not*</u> P(Null|Data)



Multiple Comparisons Problem



- Which of 100,000 voxels are sig.?
  - α=0.05 $\Rightarrow$ 5,000 false positive voxels
- Which of (random number, say) 100 clusters significant?
  - α=0.05 $\Rightarrow$ 5 false positives clusters



MCP Solutions: Measuring False Positives

- Familywise Error Rate (FWER)
  - Familywise Error
    - Existence of one or more false positives
  - FWER is probability of familywise error
- False Discovery Rate (FDR)
  - FDR = E(V/R)
  - R voxels declared active, V falsely so
    - Realized false discovery rate: V/R

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FWE MCP Solutions: Bonferroni

- For a statistic image T...
  - T_i i^{th} voxel of statistic image T
- ...use $\alpha = \alpha_0/V$
  - α_0 FWER level (e.g. 0.05)
  - V number of voxels
  - u_α α-level statistic threshold, $\mathrm{P}(T_i \geq u_\alpha) = \alpha$
- By Bonferroni inequality...

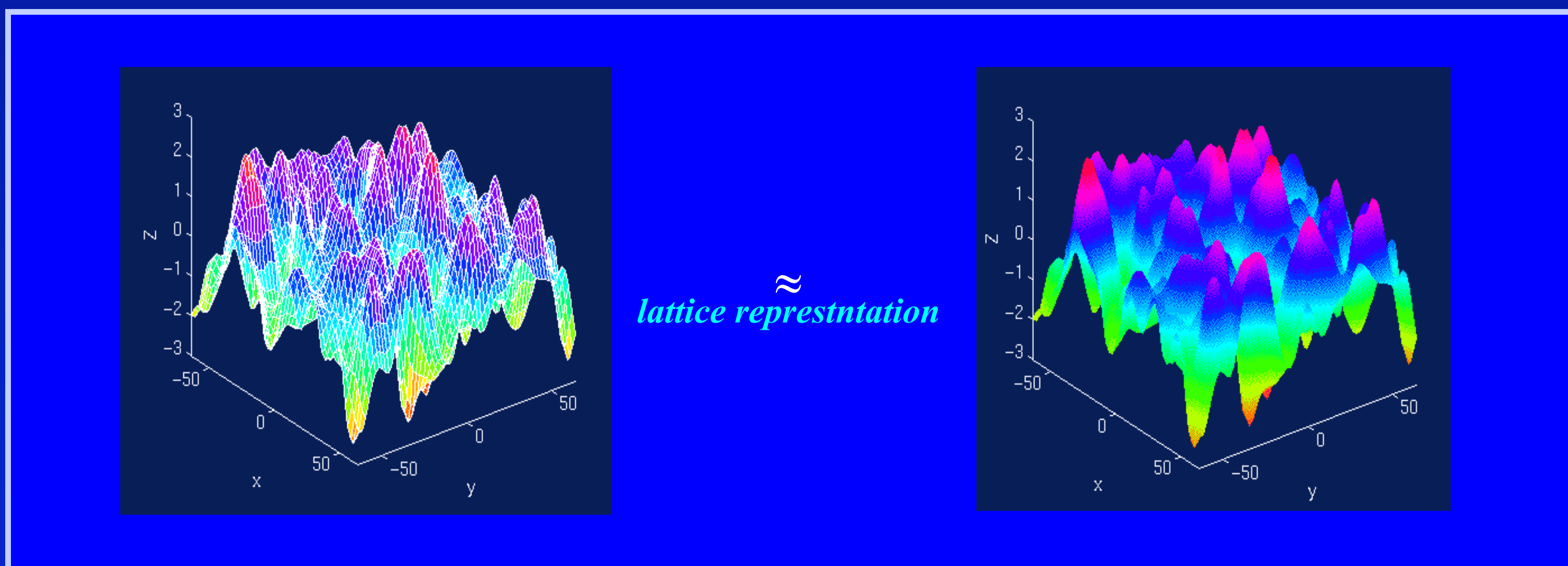
$$
\begin{aligned}
\mathrm{FWER} &= \mathrm{P}(\mathrm{FWE}) \\
&= \mathrm{P}(\cup_i \{T_i \geq u_\alpha\} \mid H_0) \\
&\leq \textstyle\sum_i \mathrm{P}(T_i \geq u_\alpha \mid H_0) \\
&= \textstyle\sum_i \alpha \\
&= \textstyle\sum_i \alpha_0 / V = \alpha_0
\end{aligned}
$$

Conservative under correlation	
Independent:	V tests
Some dep.:	? tests
Total dep.:	1 test

Random field theory…

SPM approach: Random fields…

- Consider statistic image as lattice representation of a continuous random field
- Use results from continuous random field theory



FWER MCP Solutions: Random Field Theory

- Euler Characteristic χ_u
  - Topological Measure
    - #blobs - #holes
  - At high thresholds, just counts blobs
  - FWER = P(Max voxel $\geq u$ | H_o)

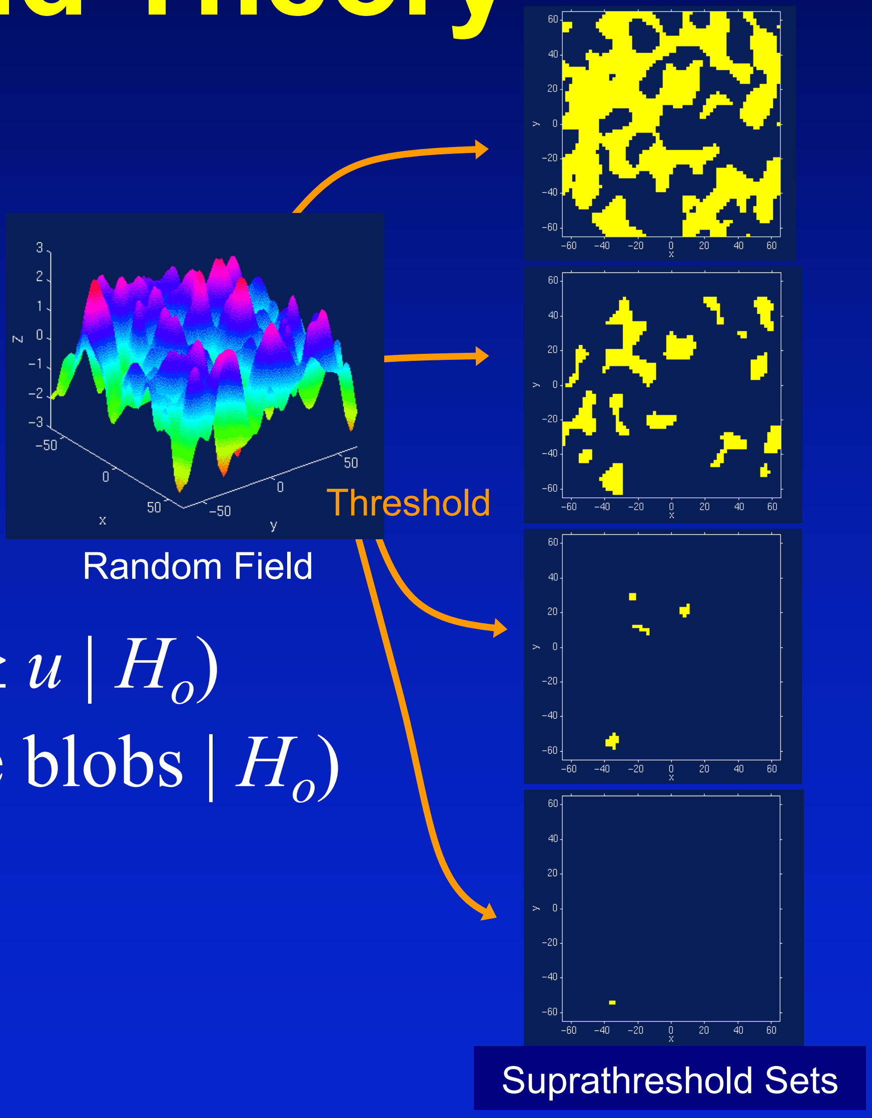
No holes

$$= \text{P(One or more blobs} \mid H_o)$$

$$\approx \text{P}(\chi_u \geq 1 \mid H_o)$$

Never more than 1 blob

$$\approx \text{E}(\chi_u \mid H_o)$$



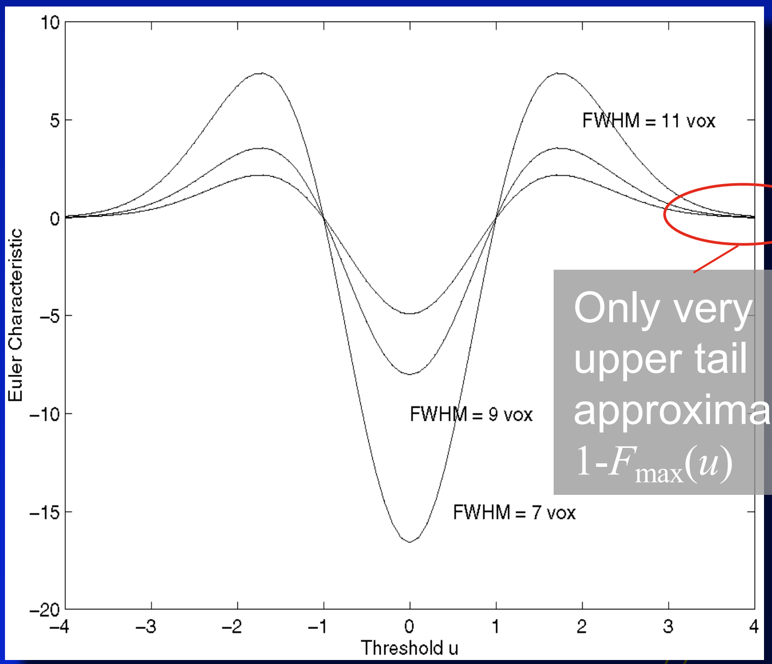
RFT Details: Expected Euler Characteristic

$$E(\chi_u) \approx \lambda(\Omega)\ |\Lambda|^{1/2}\ (u^2 - 1)\ \exp(-u^2/2)\ /\ (2\pi)^2$$

- Ω $\rightarrow$ Search region $\Omega \subset \mathcal{R}^3$
- $\lambda(\Omega)$ $\rightarrow$ volume
- $|\Lambda|^{1/2}$ $\rightarrow$ roughness

- Assumptions
  - Multivariate Normal
  - Stationary*
  - ACF twice differentiable at 0

* Stationary
  - Results valid w/out stationary
  - More accurate when stat. holds



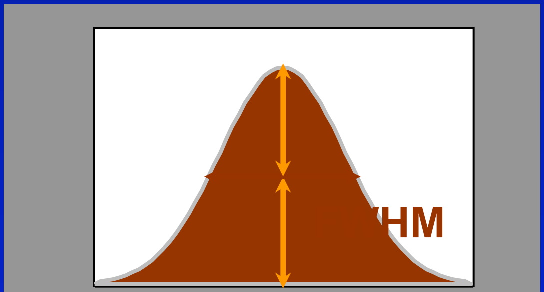
Only very upper tail approximates $1 - F_{max}(u)$

Random Field Theory Smoothness Parameterization

- $E(\chi_u)$ depends on $|\Lambda|^{1/2}$
  - Λ roughness matrix:

$$\Lambda = \textbf{Var}\left(\frac{\partial G}{\partial(x,y,z)}\right) = \begin{pmatrix} \textbf{Var}\left(\frac{\partial G}{\partial x}\right) & \textbf{Cov}\left(\frac{\partial G}{\partial x},\frac{\partial G}{\partial y}\right) & \textbf{Cov}\left(\frac{\partial G}{\partial x},\frac{\partial G}{\partial z}\right) \\ \textbf{Cov}\left(\frac{\partial G}{\partial y},\frac{\partial G}{\partial x}\right) & \textbf{Var}\left(\frac{\partial G}{\partial y}\right) & \textbf{Cov}\left(\frac{\partial G}{\partial y},\frac{\partial G}{\partial z}\right) \\ \textbf{Cov}\left(\frac{\partial G}{\partial z},\frac{\partial G}{\partial x}\right) & \textbf{Cov}\left(\frac{\partial G}{\partial z},\frac{\partial G}{\partial y}\right) & \textbf{Var}\left(\frac{\partial G}{\partial z}\right) \end{pmatrix} = \begin{pmatrix} \lambda_{xx} & \lambda_{xy} & \lambda_{xz} \\ \lambda_{yx} & \lambda_{yy} & \lambda_{yz} \\ \lambda_{zx} & \lambda_{zy} & \lambda_{zz} \end{pmatrix}$$

- Smoothness parameterized as Full Width at Half Maximum
  - FWHM of Gaussian kernel needed to smooth a white noise random field to roughness Λ

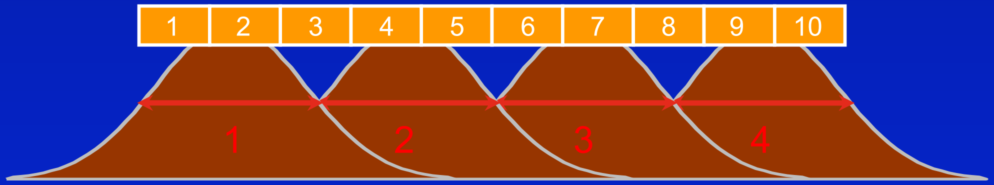


Autocorrelation Function

$$|\Lambda|^{1/2} = \frac{(4\log 2)^{3/2}}{\mathrm{FWHM}_x \mathrm{FWHM}_y \mathrm{FWHM}_z}.$$

Random Field Theory Smoothness Parameterization

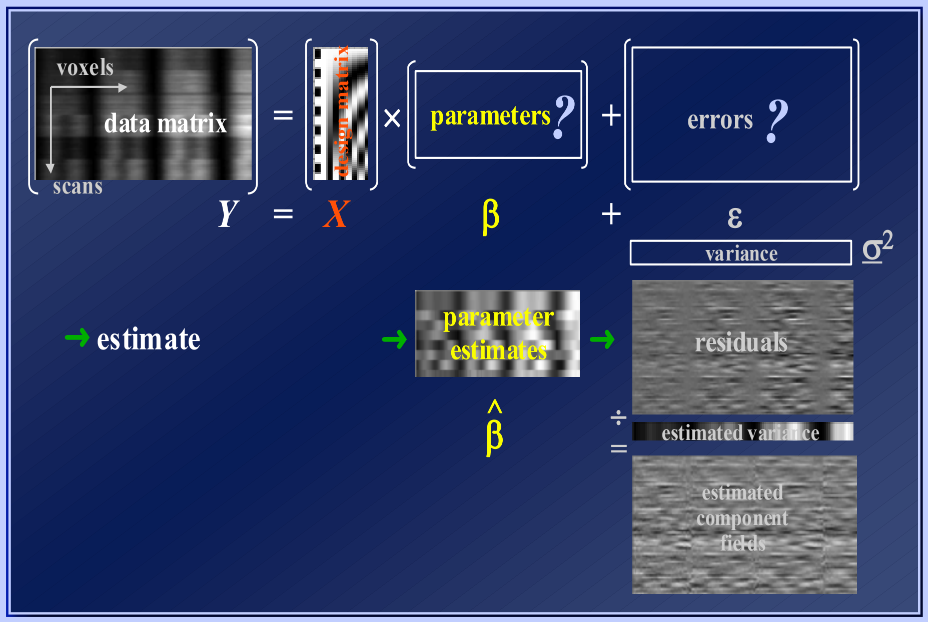
- RESELS
  - Resolution Elements
  - 1 RESEL = $\mathrm{FWHM}_x \times \mathrm{FWHM}_y \times \mathrm{FWHM}_z$
  - RESEL Count R
    - $R = \lambda(\Omega) \sqrt{|\Lambda|} = (4\log 2)^{3/2} \lambda(\Omega) \;/\; (\mathrm{FWHM}_x \times \mathrm{FWHM}_y \times \mathrm{FWHM}_z)$
    - Volume of search region in units of smoothness
    - Eg: 10 voxels, 2.5 FWHM 4 RESELS



- Beware RESEL misinterpretation
  - RESEL *are not* "number of independent 'things' in the image"
    - See Nichols & Hayasaka, 2003, Stat. Meth. in Med. Res.

Random Field Theory Smoothness Estimation

- Smoothness est'd from standardized residuals
  - Variance of gradients
  - Yields resels per voxel (RPV)
- RPV image
  - Local roughness est.
  - Can transform in to local smoothness est.
    - FWHM Img = (RPV Img)$^{-1/D}$
    - Dimension D, e.g. D=2 or 3




```
spm_imcalc_ui('RPV.img', ...
  'FWHM.img','i1.^(-1/3)')
```

Random Field Intuition

- Corrected P-value for voxel value t

$$
\begin{aligned}
P^c &= \mathrm{P}(\max T > t) \\
&\approx \mathrm{E}(\chi_t) \\
&\approx \lambda(\Omega)\, |\Lambda|^{1/2}\, t^2 \exp(-t^2/2)
\end{aligned}
$$

- Statistic value t increases
  - P^c decreases (but only for large t)
- Search volume increases
  - P^c increases (more severe MCP)
- Smoothness increases (roughness $|\Lambda|^{1/2}$ decreases)
  - P^c decreases (less severe MCP)

RFT Details: Unified Formula

- General form for expected Euler characteristic
  - χ^2, F, & t fields • restricted search regions • D dimensions •

$$\mathrm{E}[\chi_u(\Omega)] = \Sigma_d \, \mathrm{R}_d(\Omega) \, \rho_d(u)$$

$\mathrm{R}_d(\Omega)$: d-dimensional Minkowski functional of Ω

– function of dimension, space Ω and smoothness:

$\mathrm{R}_0(\Omega) = \chi(\Omega)$ Euler characteristic of Ω

$\mathrm{R}_1(\Omega)$ = resel diameter

$\mathrm{R}_2(\Omega)$ = resel surface area

$\mathrm{R}_3(\Omega)$ = resel volume

$\rho_d(\Omega)$: d-dimensional EC density of $Z(\underline{x})$

– function of dimension and threshold, specific for RF type:

E.g. Gaussian RF:

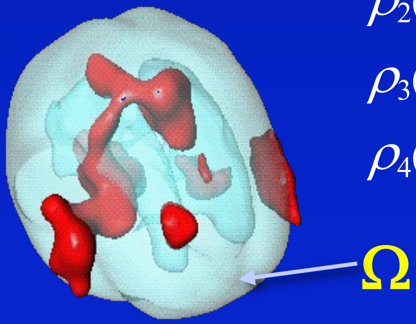
$\rho_0(u) = 1 - \Phi(u)$

$\rho_1(u) = (4 \ln 2)^{1/2} \exp(-u^2/2) / (2\pi)$

$\rho_2(u) = (4 \ln 2) \quad \exp(-u^2/2) / (2\pi)^{3/2}$

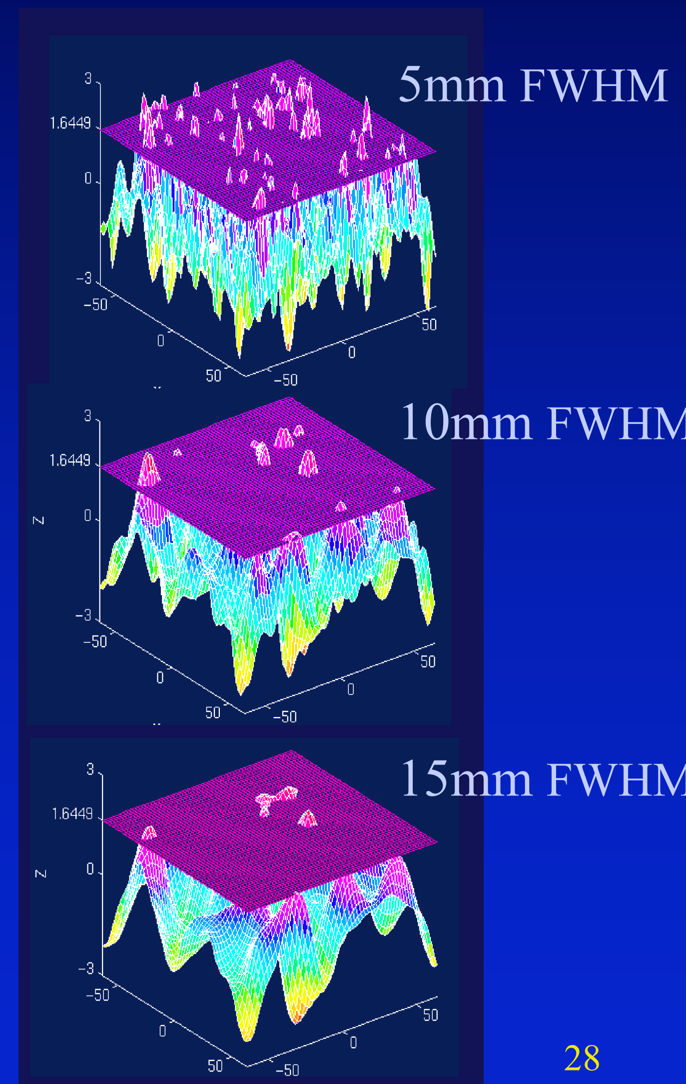
$\rho_3(u) = (4 \ln 2)^{3/2} (u^2 - 1) \quad \exp(-u^2/2) / (2\pi)^2$

$\rho_4(u) = (4 \ln 2)^2 \quad (u^3 - 3u) \exp(-u^2/2) / (2\pi)^{5/2}$



Random Field Theory Cluster Size Tests

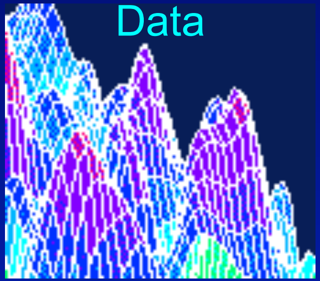
- Expected Cluster Size
  - $E(S) = E(N)/E(L)$
  - S cluster size
  - N suprathreshold volume $\lambda(\{T > u_{\mathrm{clus}}\})$
  - L number of clusters
- $E(N) = \lambda(\Omega)\, P(\, T > u_{clus}\,)$
- $E(L) \approx E(\chi_u)$
  - Assuming no holes



Random Field Theory Limitations

- Sufficient smoothness
  - FWHM smoothness 3-4 × voxel size (Z)
  - More like ~10 × for low-df T images
- Smoothness estimation
  - Estimate is biased when images not sufficiently smooth
- Multivariate normality
  - Virtually impossible to check
- Several layers of approximations
- Stationary required for cluster size results

Lattice Image Data



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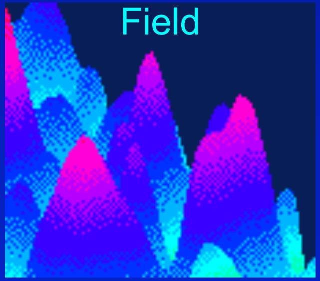
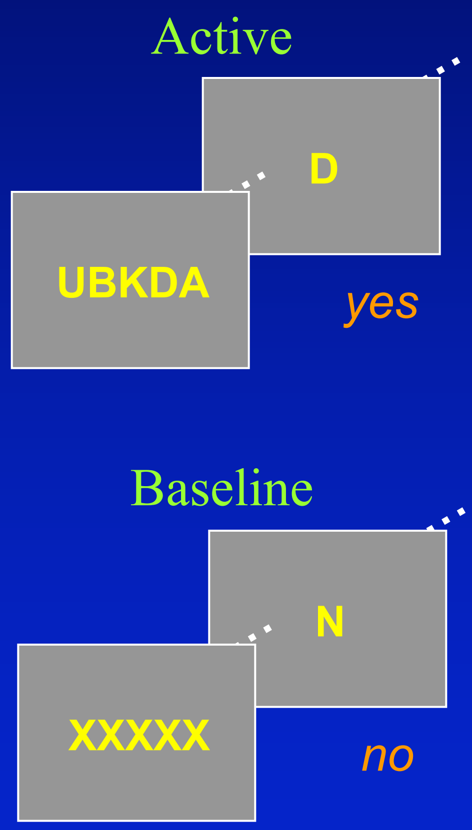
Continuous Random Field



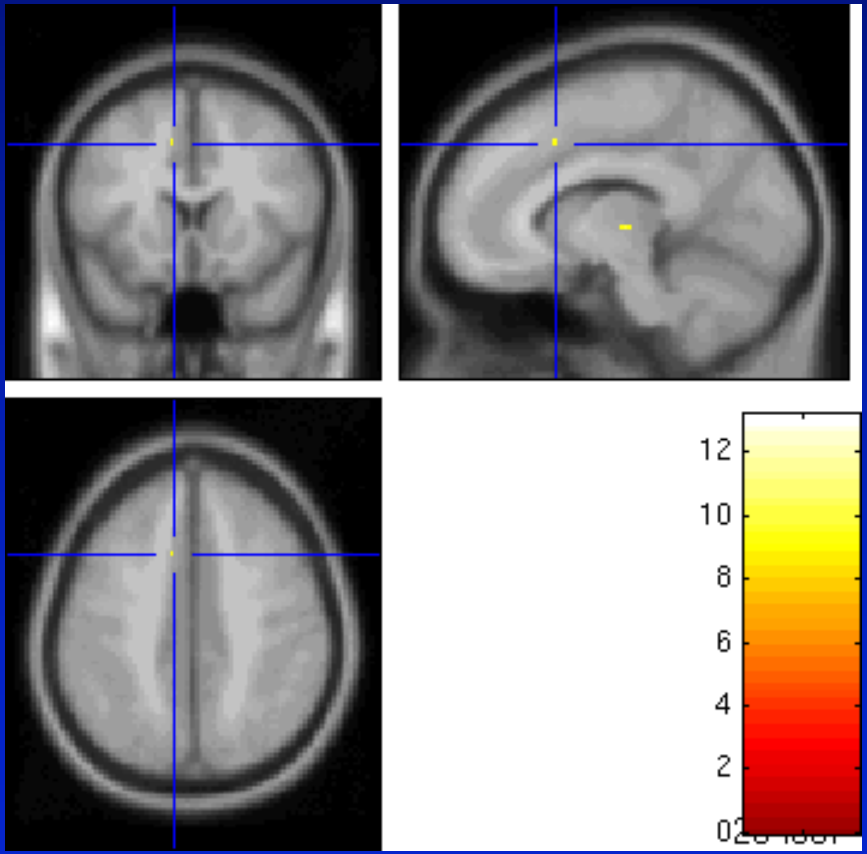
Real Data

- fMRI Study of Working Memory
  - 12 subjects, block design Marshuetz et al (2000)
  - Item Recognition
    - Active:View five letters, 2s pause, view probe letter, respond
    - Baseline: View XXXXX, 2s pause, view Y or N, respond
- Second Level RFX
  - Difference image, A-B constructed for each subject
  - One sample *t* test



Real Data: RFT Result

- Threshold
  - $S = 110{,}776$
  - $2 \times 2 \times 2$ voxels
    $5.1 \times 5.8 \times 6.9$ mm
    FWHM
  - $u = 9.870$
- Result
  - 5 voxels above
     the threshold
  - 0.0063 minimum
    FWE-corrected
    p-value

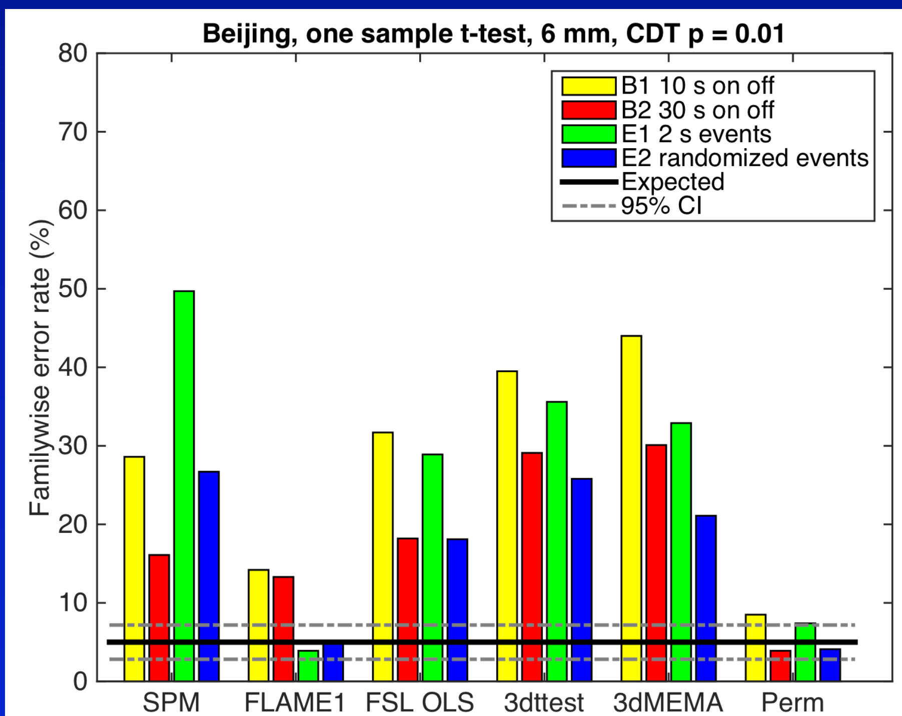


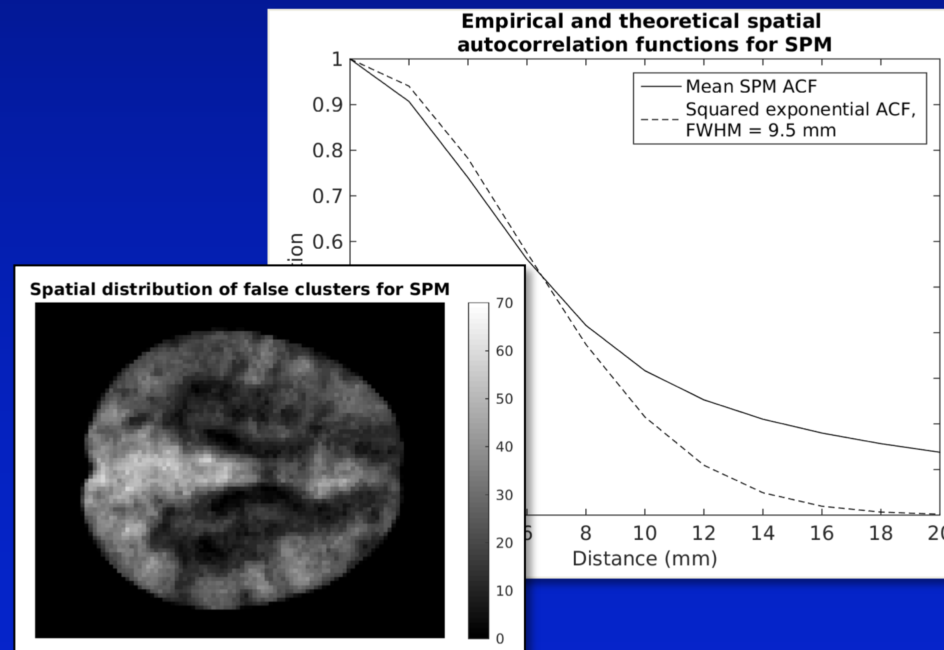
Massive Null (resting-state) fMRI Evaluation

Goal: Evaluate AFNI, FSL & SPM *task* fMRI with *resting-state* fMRI data, using 4 designs, 3 million randomised analyses

Outcome: Voxel FWE ***OK*** (Conservative)
Cluster FWE 0.001 ***OK***
Cluster FWE 0.01 ***Very Bad*** (Liberal)

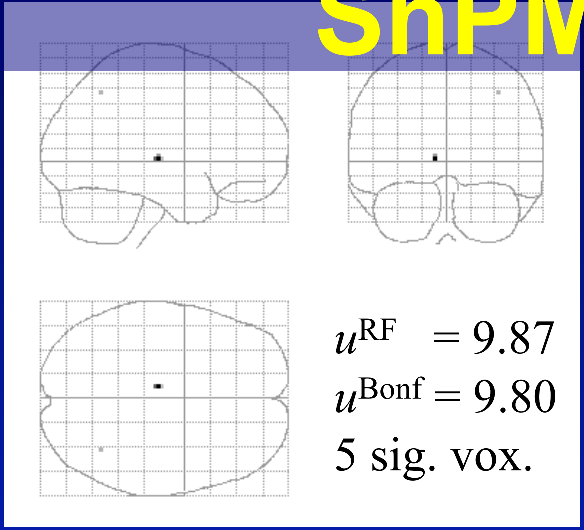
Why? Spatial ACF not Gaussian, Nonstationarity smoothness





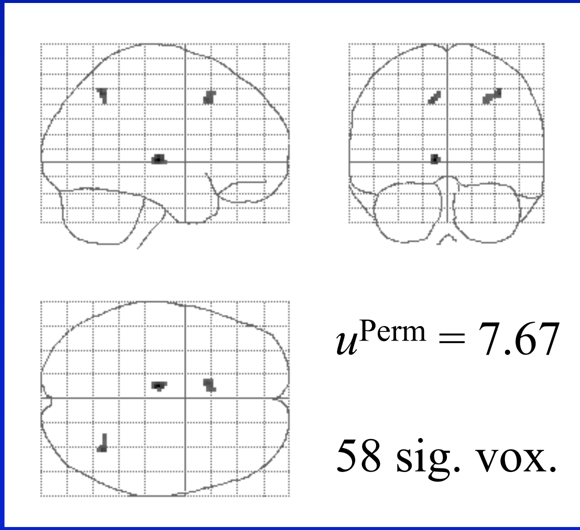
Cluster failure: Why fMRI inferences for spatial extent have inflated false-positive rates (2016). Eklund, TE Nichols, H Knutsson PNAS, 113(28), 7900-5

Real Data: SnPM Promotional

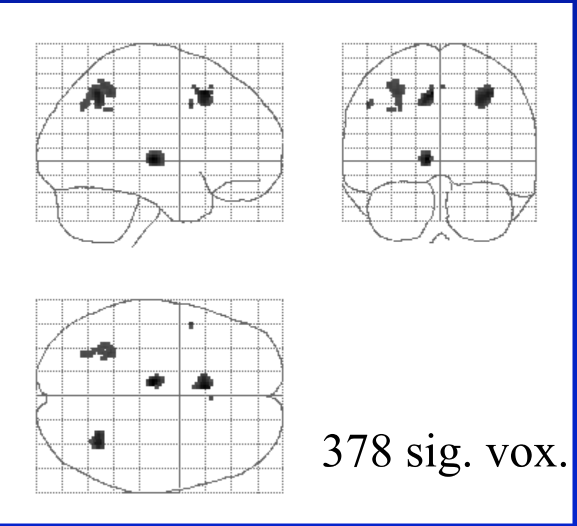


t_{11} Statistic, RF & Bonf. Threshold

- Nonparametric method more powerful than RFT for low DF
- "Variance Smoothing" even more sensitive
- FWE controlled all the while!
- http://nisox.org/Software/SnPM



t_{11} Statistic, Nonparametric Threshold



Smoothed Variance t Statistic, Nonparametric Threshold

False Discovery Rate…

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  - FDR = E(V/R)
  - R voxels declared active, V falsely so
    - Realized false discovery rate: V/R

False Discovery Rate

- For any threshold, all voxels can be cross-classified:

	Accept Null	Reject Null	
Null True	V_{0A}	V_{0R}	m_0
Null False	V_{1A}	V_{1R}	m_1
	N_A	N_R	V

- Realized FDR

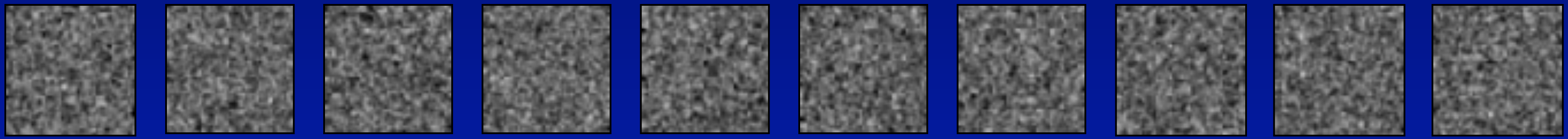
$$rFDR = V_{0R}/(V_{1R}+V_{0R}) = V_{0R}/N_R$$

  - If $N_R = 0$, rFDR = 0
- But only can observe N_R, don't know V_{1R} & V_{0R}
  - We control the *expected* rFDR

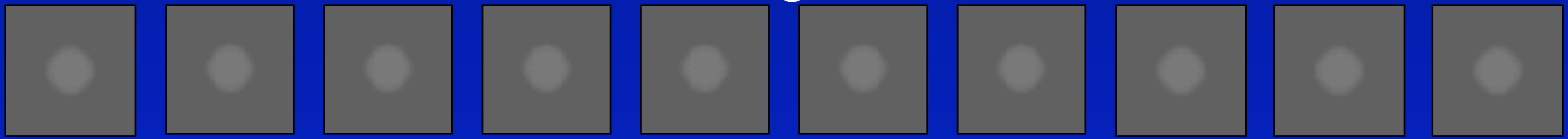
$$FDR = E(rFDR)$$

False Discovery Rate Illustration:

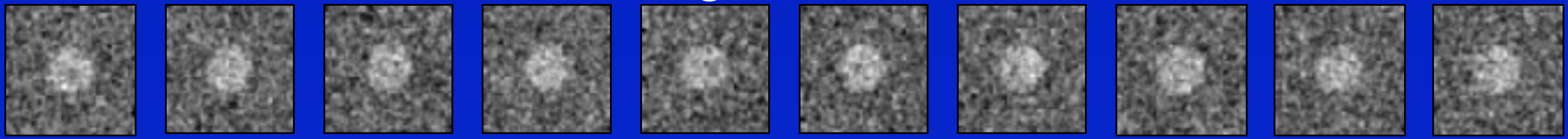
Noise



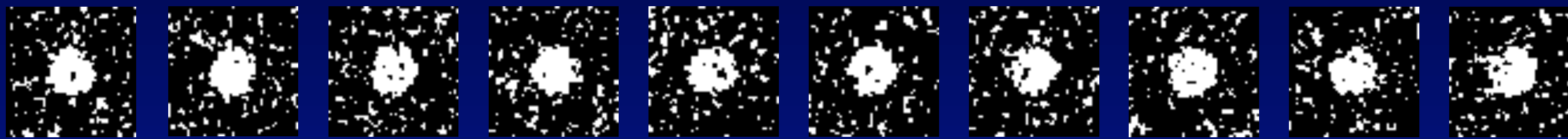
Signal



Signal+Noise



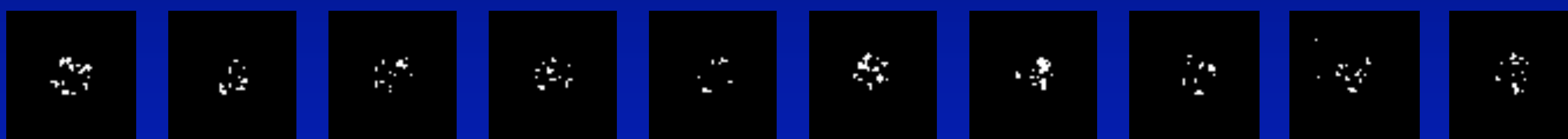
Control of Per Comparison Rate at 10%



11.3% 11.3% 12.5% 10.8% 11.5% 10.0% 10.7% 11.2% 10.2% 9.5%

Percentage of Null Pixels that are False Positives

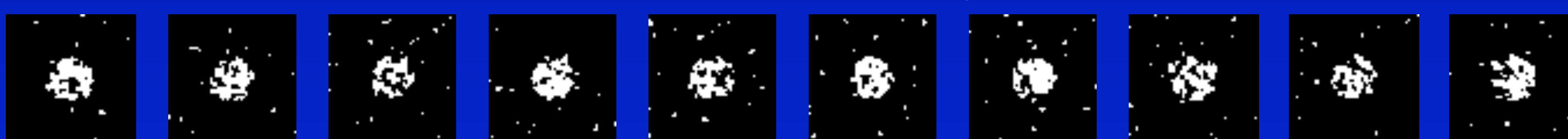
Control of Familywise Error Rate at 10%



FWE

Occurrence of Familywise Error

Control of False Discovery Rate at 10%



6.7% 10.4% 14.9% 9.3% 16.2% 13.8% 14.0% 10.5% 12.2% 8.7%

Percentage of Activated Pixels that are False Positives

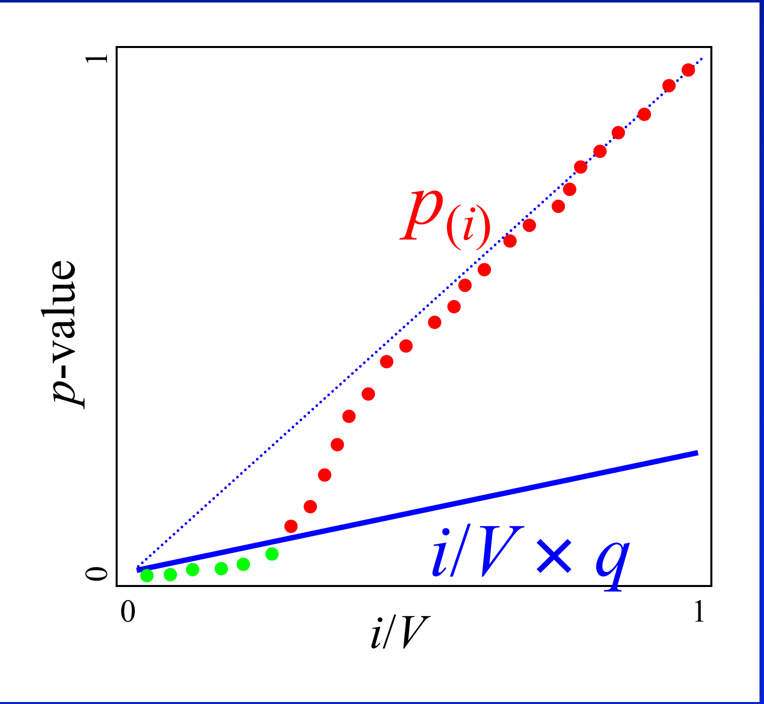
Benjamini & Hochberg Procedure

JRSS-B (1995) 57:289-300

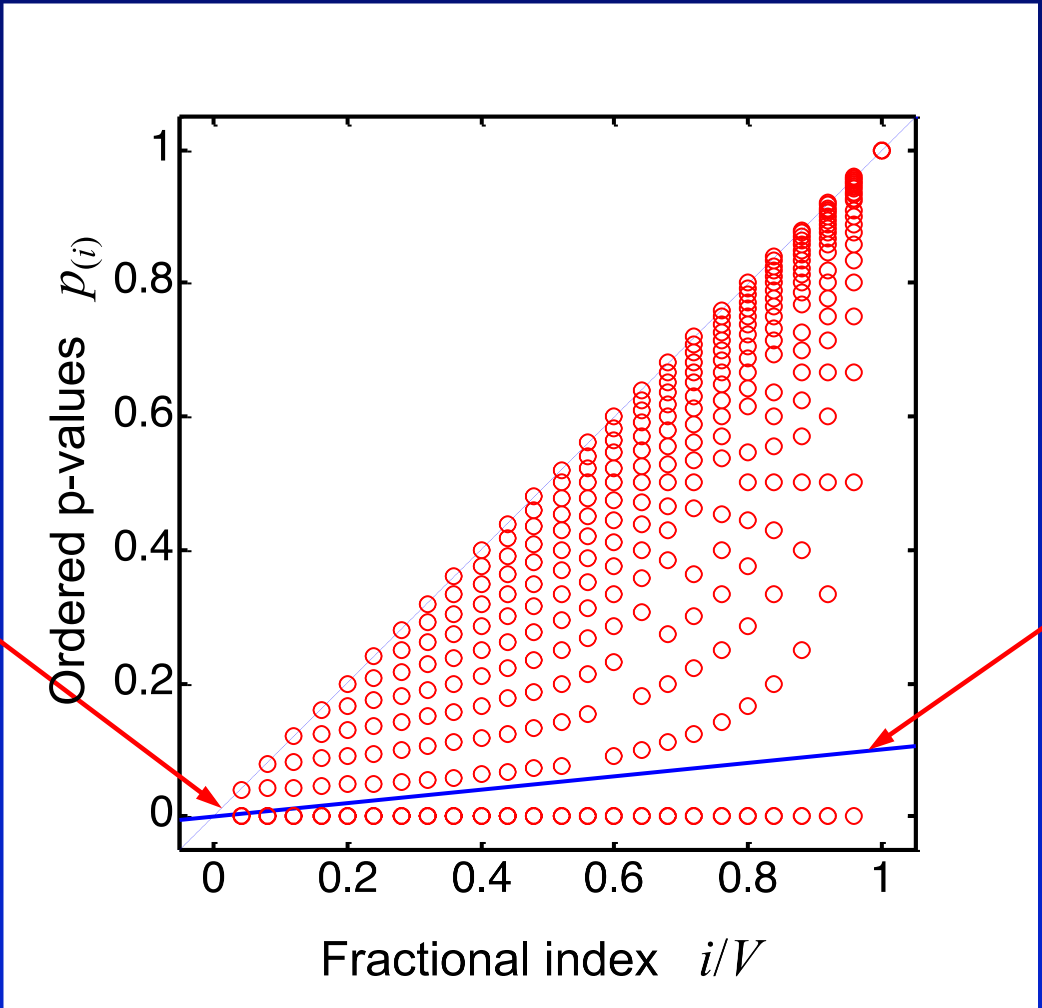
- Select desired limit q on FDR
- Order p-values, $p_{(1)} \leq p_{(2)} \leq \ \ldots \leq p_{(V)}$
- Let r be largest i such that

$$p_{(i)} \leq \ i/V \times q$$

- Reject all hypotheses corresponding to $p_{(1)}, \ldots, p_{(r)}$.



Adaptiveness of Benjamini & Hochberg FDR

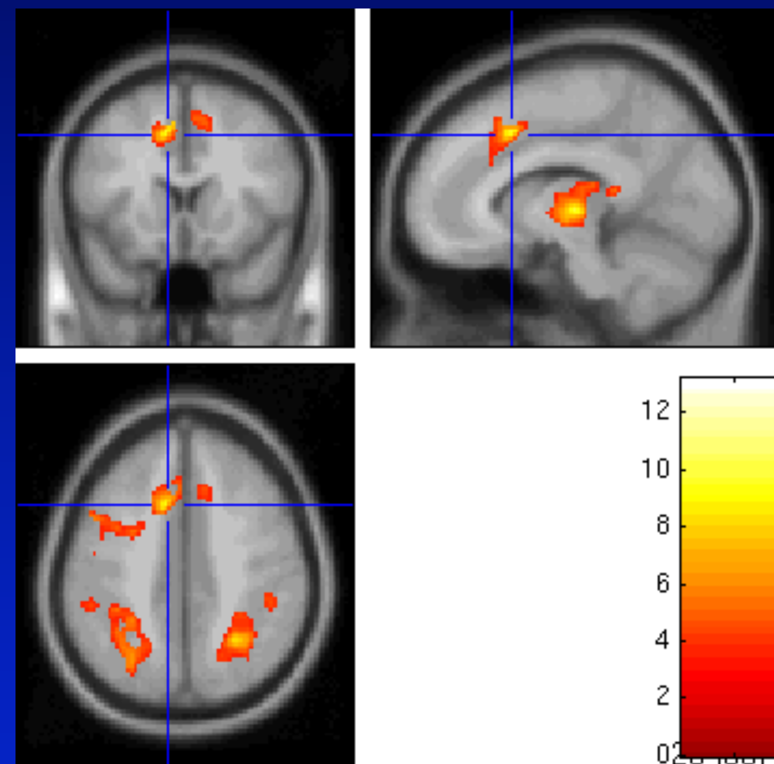


P-value threshold when no signal: α/V

P-value threshold when all signal: α

Real Data: FDR Example

- Threshold
  - $u = 3.83$
- Result
  - 3,073 voxels above u
  - <0.0001 minimum FDR-corrected p-value



FDR Threshold = 3.83
3,073 voxels
FWER Perm. Thresh. = 9.87
7 voxels

FDR Changes

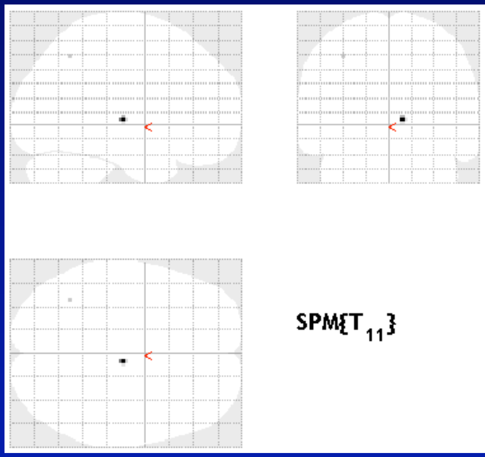
- Before SPM8
  - Only voxel-wise FDR
- SPM8
  - Cluster-wise FDR
  - Peak-wise FDR
  - Voxel-wise available: edit `spm_defaults.m` to read `defaults.stats.topoFDR      = 0;`
  - Note!
    - Both cluster- and peak-wise FDR depends on cluster-forming threshold!

Item Recognition data

Cluster-forming threshold P=0.001
    Peak-wise FDR: t=4.84, P_{FDR} 0.836
Cluster-forming threshold P=0.01
    Peak-wise FDR: t=4.84, P_{FDR} 0.027

Cluster FDR: Example Data

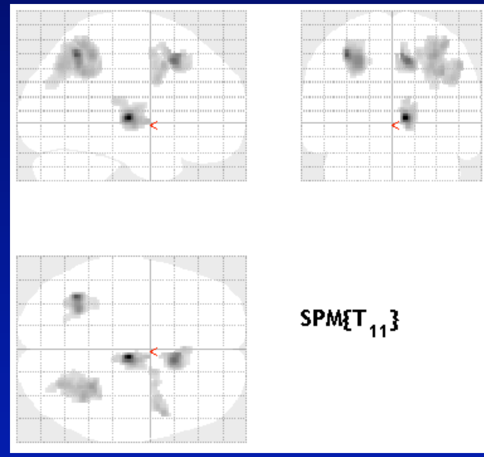
Level 5% **Voxel**-**FWE**



Level 5% **Cluster**-**FWE**

P = 0.001 cluster-forming thresh

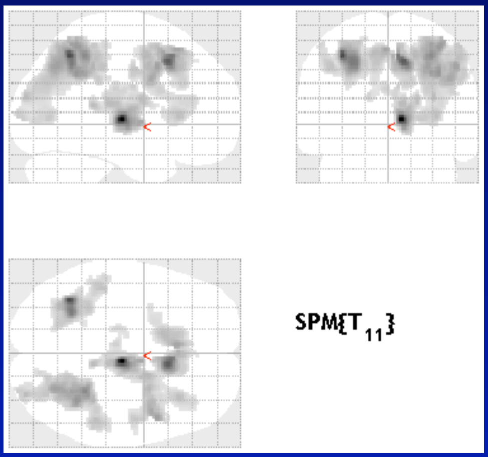
k_{FWE} = 241, 5 clusters



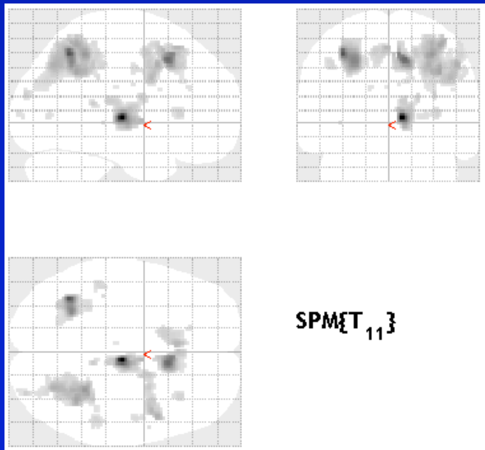
Level 5% **Cluster**-**FWE**

P = 0.01 cluster-forming thresh

k_{FWE} = 1132, 4 clusters



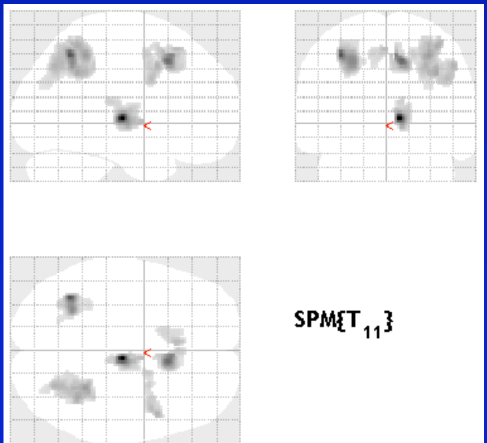
Level 5% **Voxel**-**FDR**



Level 5% **Cluster**-**FDR**,

P = 0.001 cluster-forming thresh

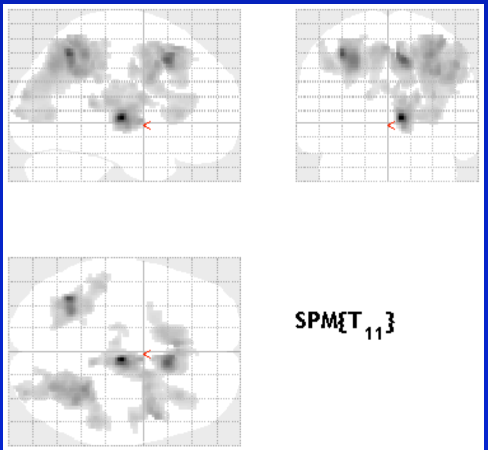
k_{FDR} = 138, 6 clusters



Level 5% **Cluster**-**FDR**

P = 0.01 cluster-forming thresh

k_{FDR} = 1132, 4 clusters



Conclusions

- Must account for multiplicity
  - Otherwise have a fishing expedition
- FWER
  - Very specific, not very sensitive
- FDR
  - Voxel-wise: Less specific, more sensitive
  - Cluster-, Peak-wise: Similar to FWER

References

- TE Nichols & S Hayasaka, Controlling the Familywise Error Rate in Functional Neuroimaging: A Comparative Review. *Statistical Methods in Medical Research*, 12(5): 419-446, 2003.

  TE Nichols & AP Holmes, Nonparametric Permutation Tests for Functional Neuroimaging: A Primer with Examples. *Human Brain Mapping*, 15:1-25, 2001.

  CR Genovese, N Lazar & TE Nichols, Thresholding of Statistical Maps in Functional Neuroimaging Using the False Discovery Rate. *NeuroImage*, 15:870-878, 2002.

  JR Chumbley & KJ Friston. False discovery rate revisited: FDR and topological inference using Gaussian random fields. *NeuroImage*, 44(1), 62-70, 2009