Classical Inference (Thresholding with Random Field Theory & False Discovery Rate methods)

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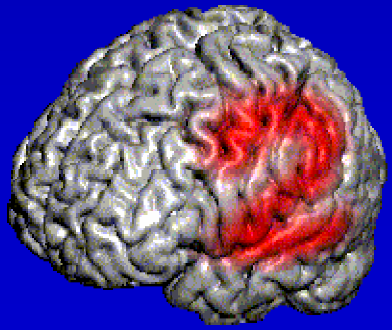
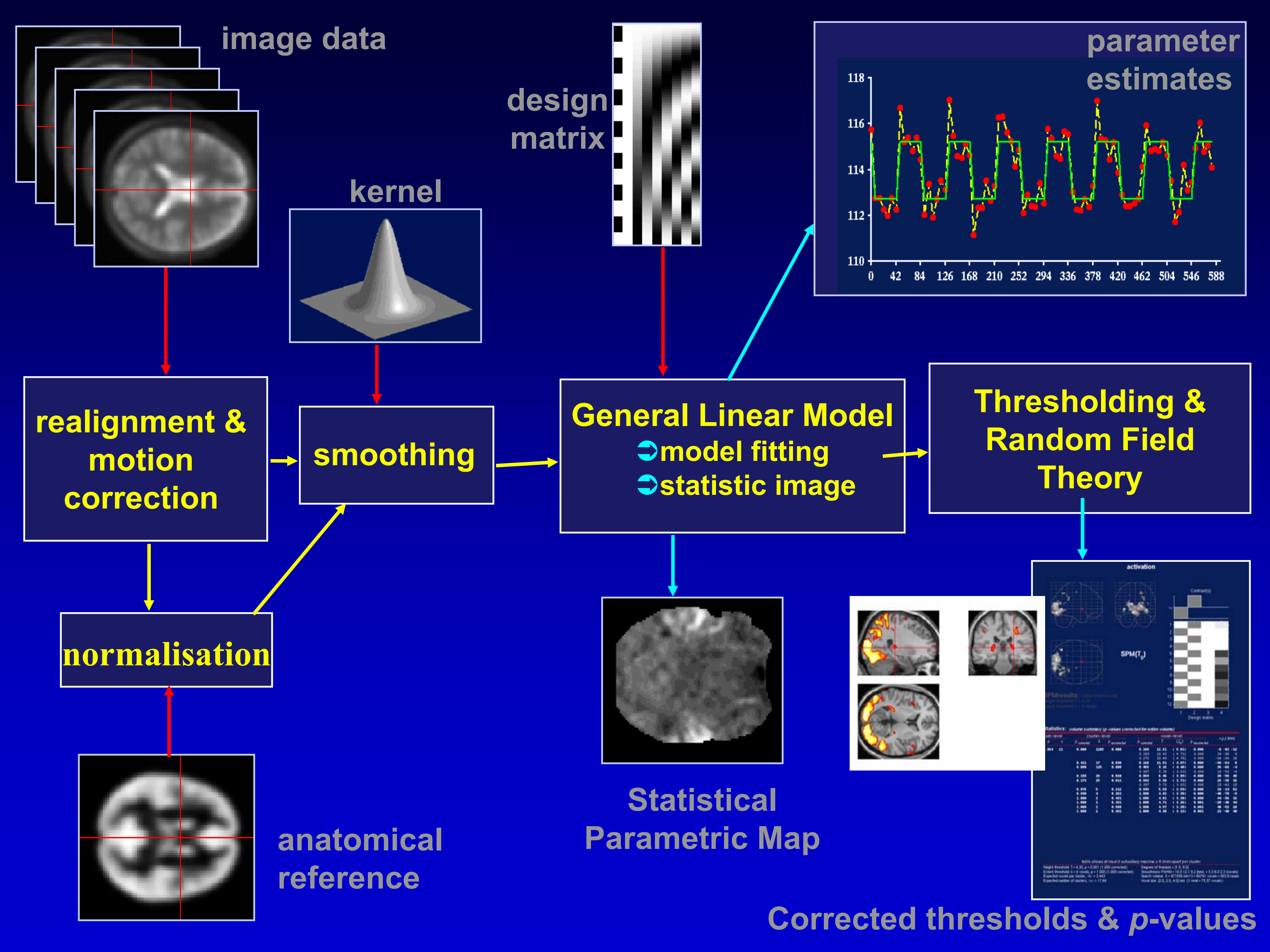


USA SPM Course
April 7, 2005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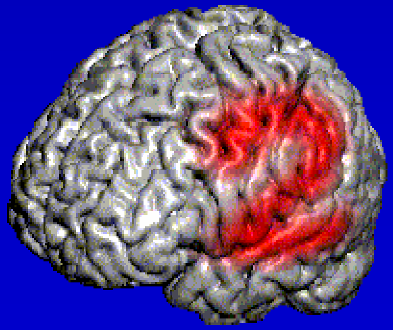
kernel
realignment &
motion
correction
smoothing
General Linear Model
➲model fitting
➲statistic image
Thresholding &
Random Field
Theory
normalisation
activation
SPM(T)
Statistical
Parametric Map
anatomical
reference
Corrected thresholds & p-values

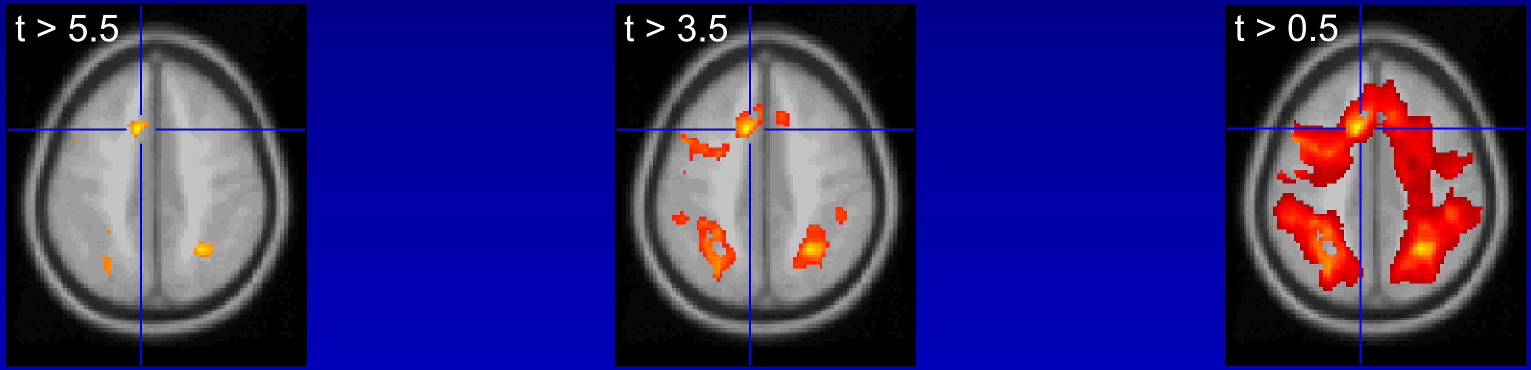
Assessing Statistic Images…



Assessing Statistic Images

Where's the signal?

High Threshold | Med. Threshold | Low Threshold



Good Specificity

Poor Power
(risk of false negatives)

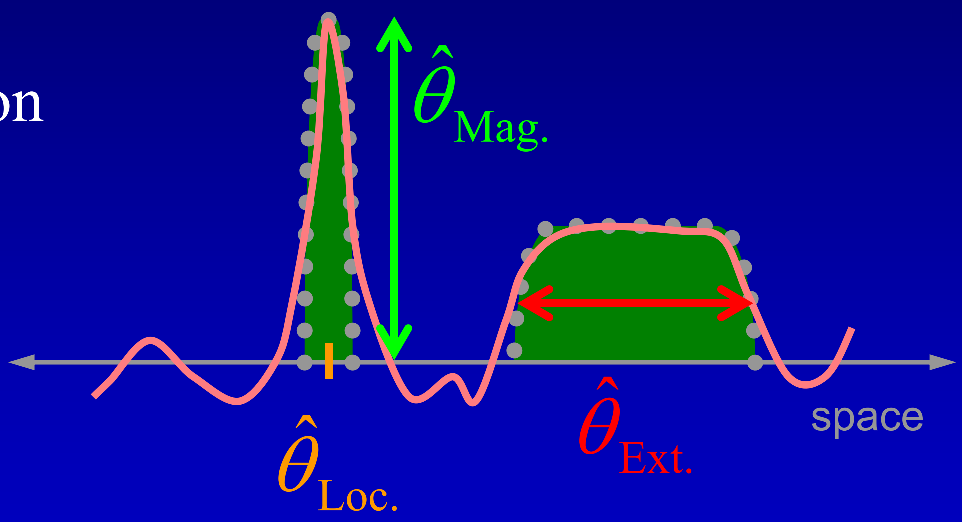
Poor Specificity
(risk of false positives)

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

Blue-sky inference: What we need

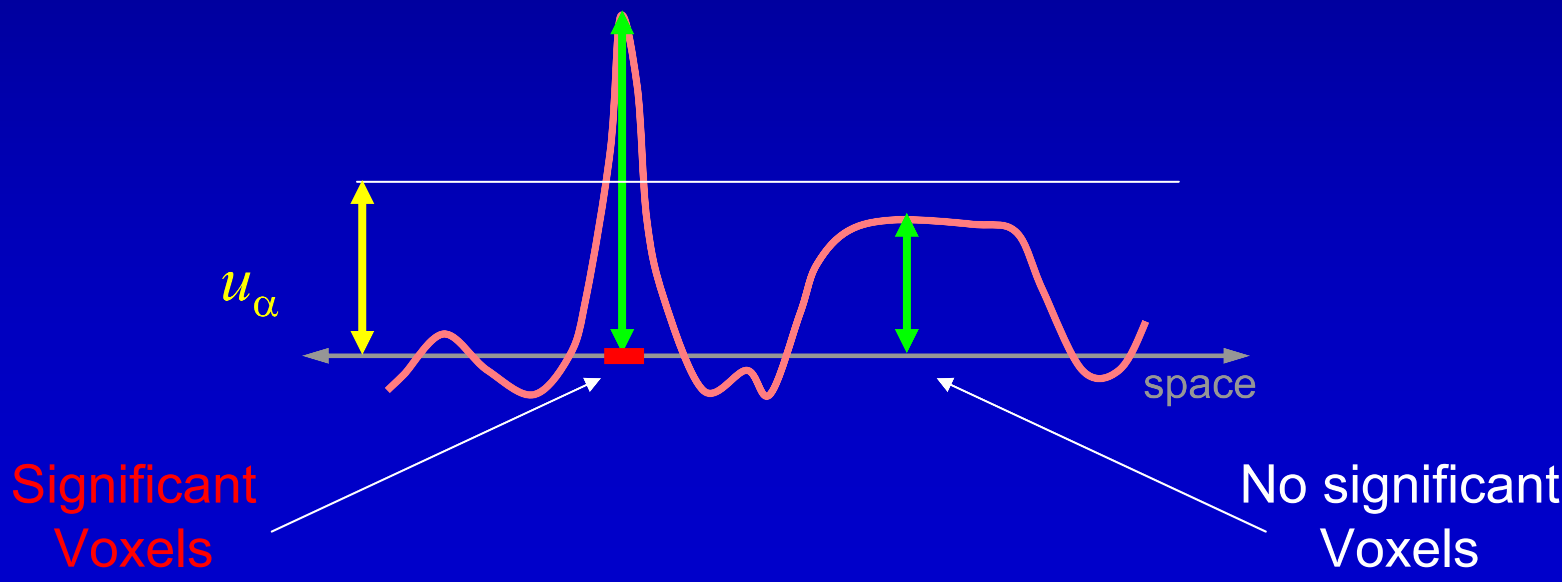
- Need an explicit spatial model
- No routine spatial modeling methods exist
  - High-dimensional mixture modeling problem
  - Activations don't look like Gaussian blobs
  - Need realistic shapes, sparse representation
    - Some work by Hartvig *et al.*, Penny *et al.*

Real-life inference: What we get

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

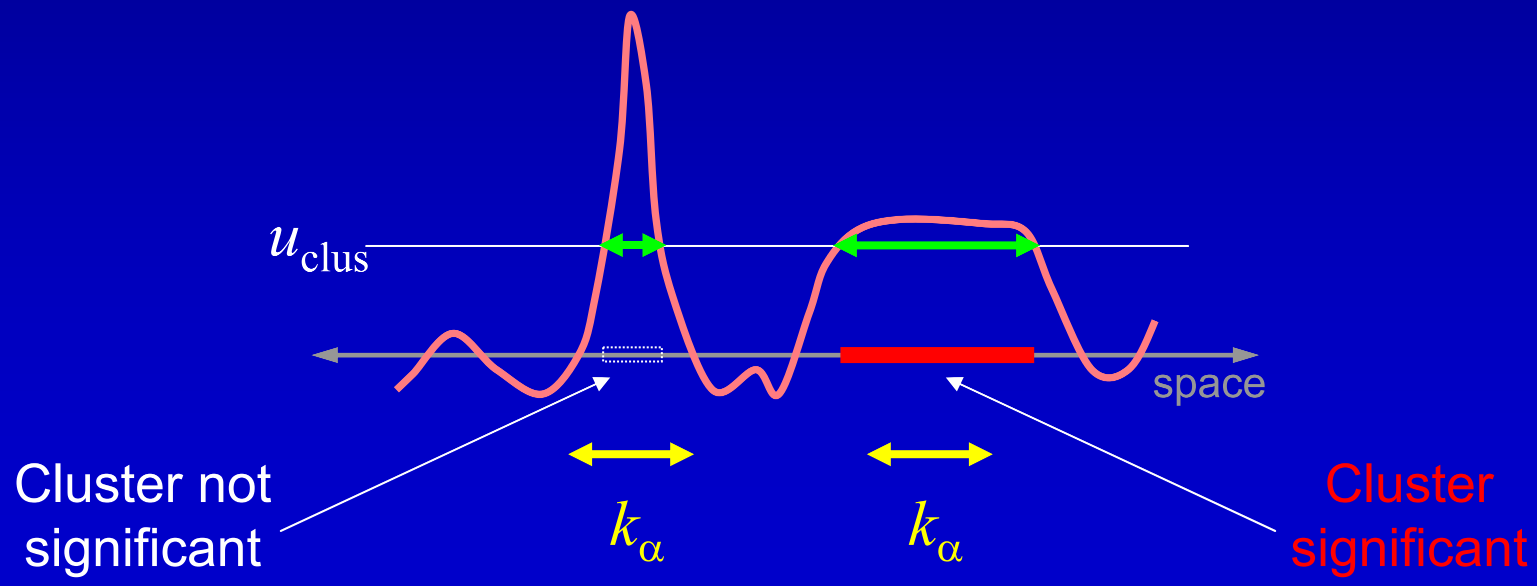
Voxel-level Inference

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



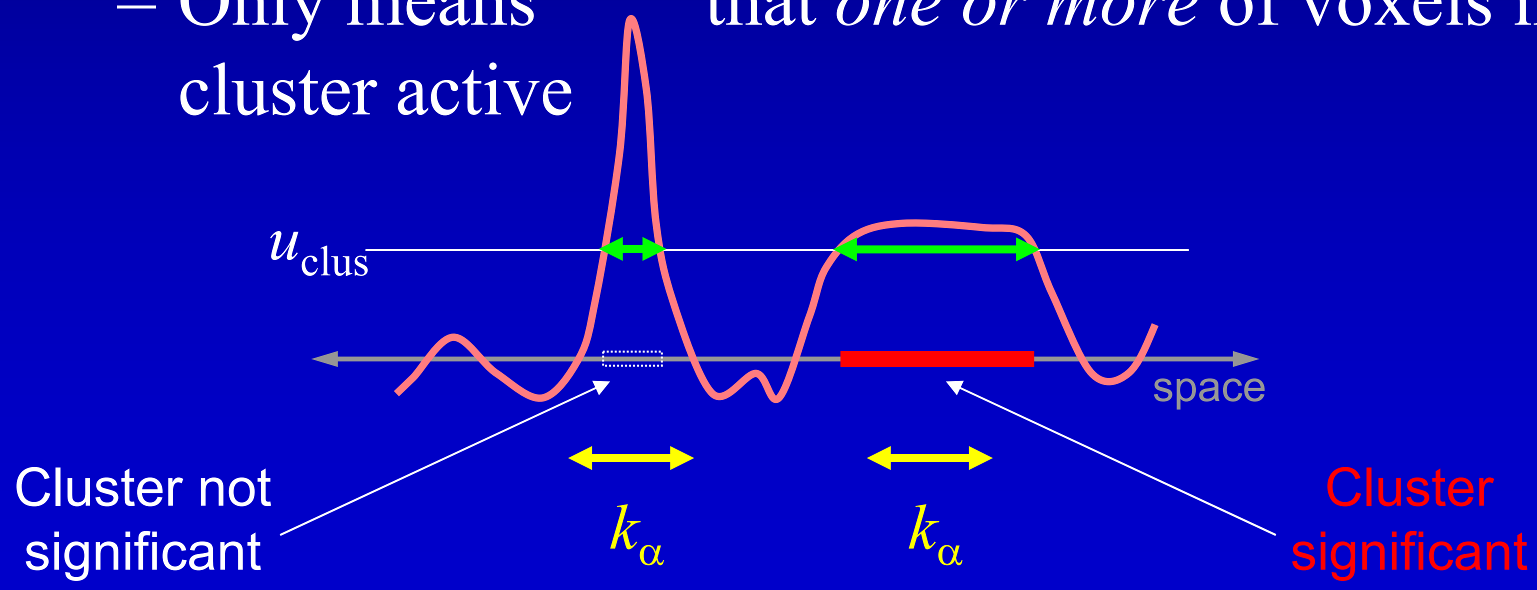
Cluster-level Inference

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



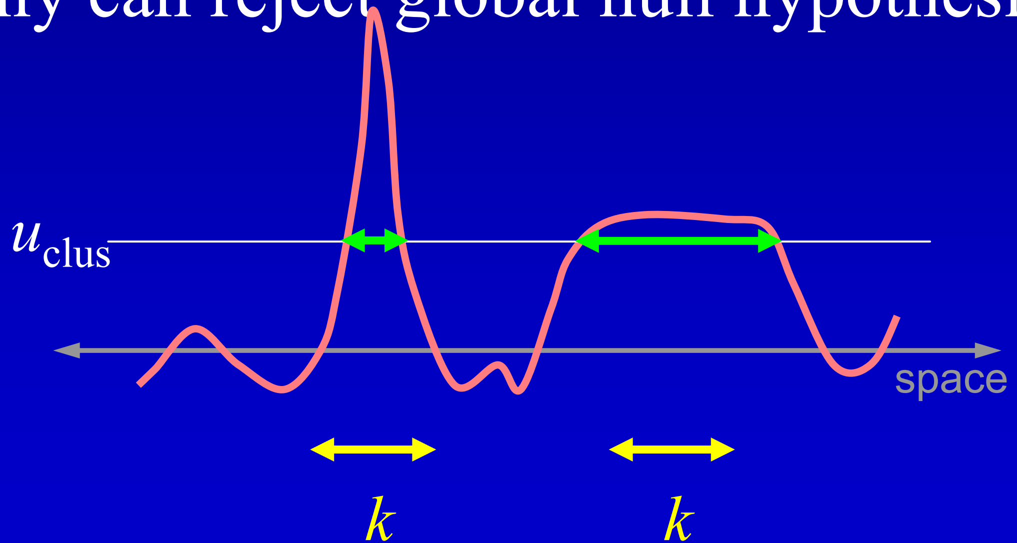
Cluster-level Inference

- 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



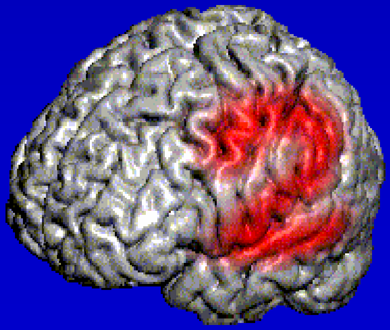
Set-level Inference

- 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

Conjunctions…



Conjunction Inference

- Consider several working memory tasks
  - N-Back tasks with different stimuli
  - Letter memory: D J P F D R A T F M R I B K
  - Number memory: 4 2 8 4 4 2 3 9 2 3 5 8 9 3 1 4
  - Shape memory: ♣ ⊂ ♥ ♣ × ♠ ♦ ∩ ♠ ⊗ ∪ •
- Interested in stimuli-generic response
  - What areas of the brain respond to *all* 3 tasks?
  - Don't want areas that only respond in 1 or 2 tasks

Conjunction Inference Methods: Friston et al

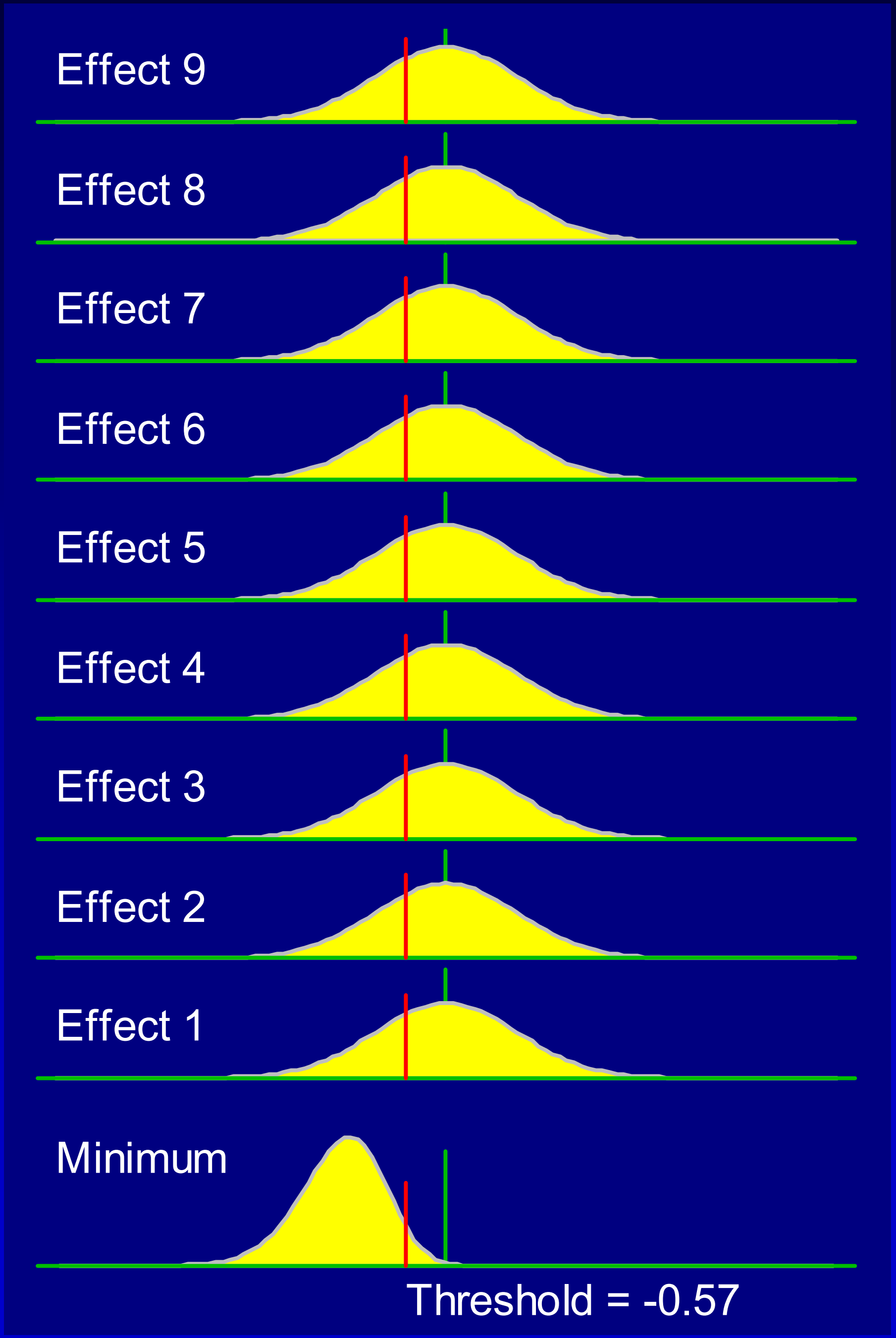
- Use the minimum of the K statistics
  - Idea: Only declare a conjunction if *all* of the statistics are sufficiently large
  - $\min_k T_k \geq u$ only when $T_k \geq u$ for all k
- References
  - SPM99, SPM2 (before patch)
  - Worsley, K.J. and Friston, K.J. (2000). A test for a conjunction. *Statistics and Probability Letters*, **47**, 135-140.

Conjunction Inference Methods: Friston et al

- Strengths
  - P-values easy to find
    - Distribution of $\min_k T^k$ is trivial...
      ...assuming all K nulls true
- Problems
  - Needs K independent statistics
  - Inference assumes all K nulls are true!
    - Wrong P-value!

Impact of Using the Wrong Null Hypothesis

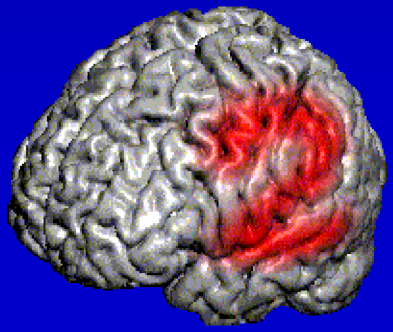
- Consider varying the number of effects tested...
- For K=9, only need all positive responses for this min test to reject!
  - Reason: Easy to reject the "No effects present" null



Valid Conjunction Inference With the Minimum Statistic

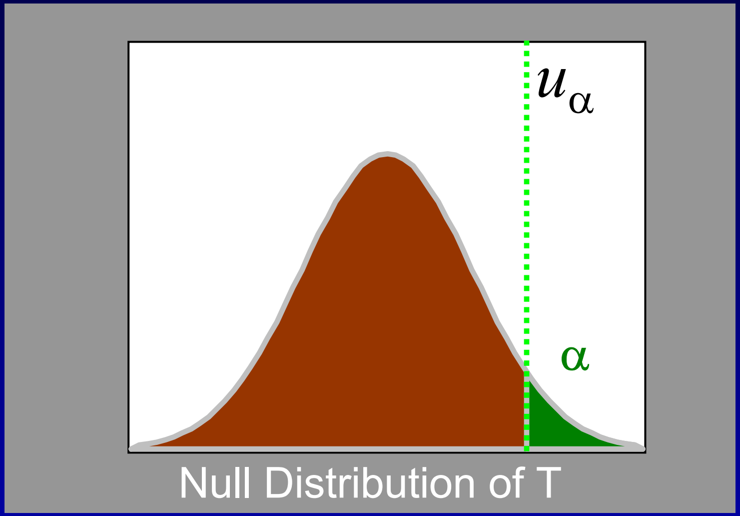
- For valid inference, compare min stat to u_α
  - Assess $\min_k T^k$ image as if it were just T^1
  - E.g. $u_{0.05}$=1.64 (or some corrected threshold)
- Correct Minimum Statistic P-values
  - Compare $\min_k T^k$ to usual, univariate null dist^n

Multiple comparisons…

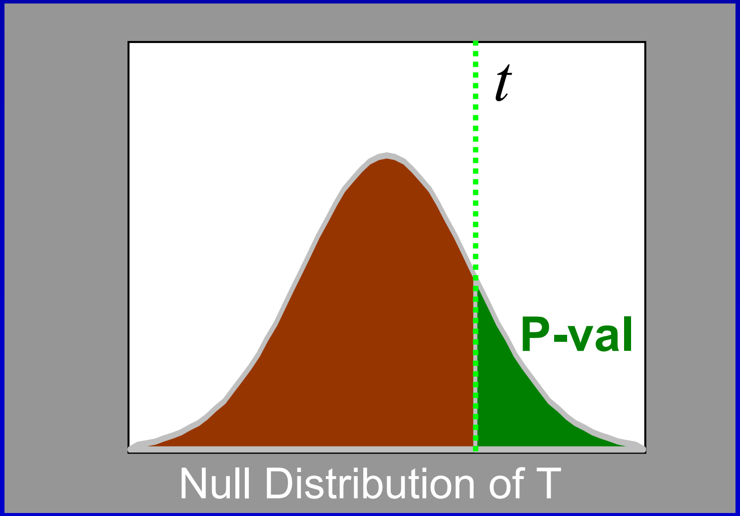


Hypothesis Testing

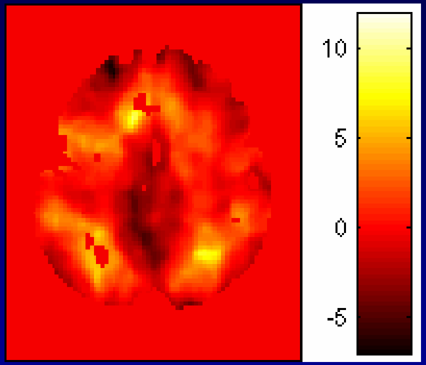
- Null Hypothesis H_0
- Test statistic T
  - t observed realization of T
- α level
  - Acceptable false positive rate
  - Level $\alpha = P(T > u_\alpha \mid H_0)$
  - Threshold u_α controls false positive rate at level α



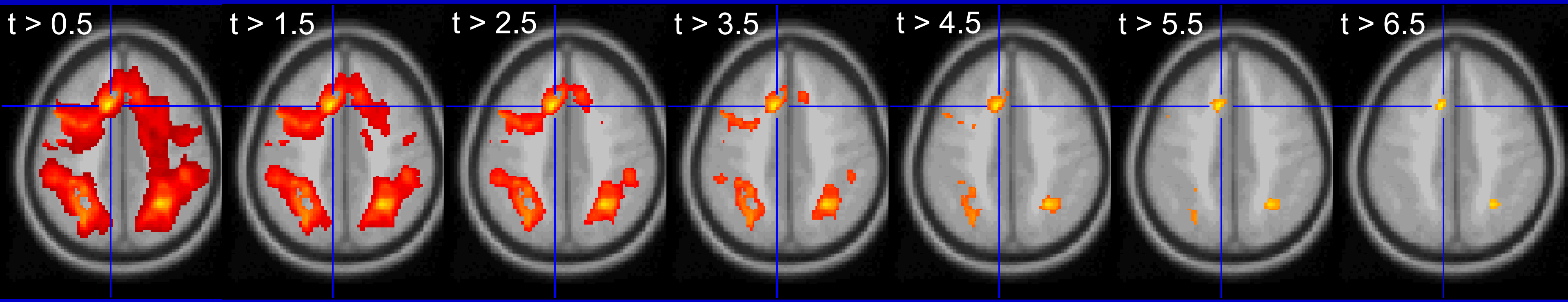
- P-value
  - Assessment of t assuming H_0
  - $P(T > t \mid H_0)$
    - Prob. of obtaining stat. as large or larger in a new experiment
  - P(Data|Null) *not* P(Null|Data)



Multiple Comparisons Problem



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

MCP Solutions: Measuring False Positives

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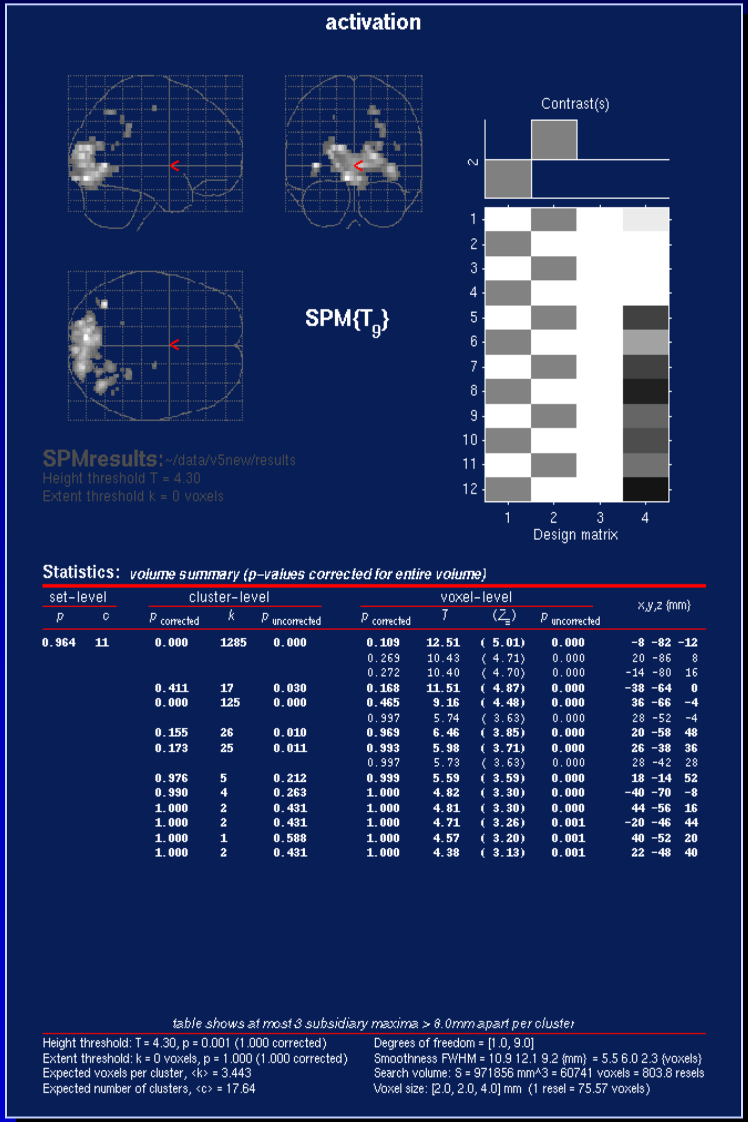
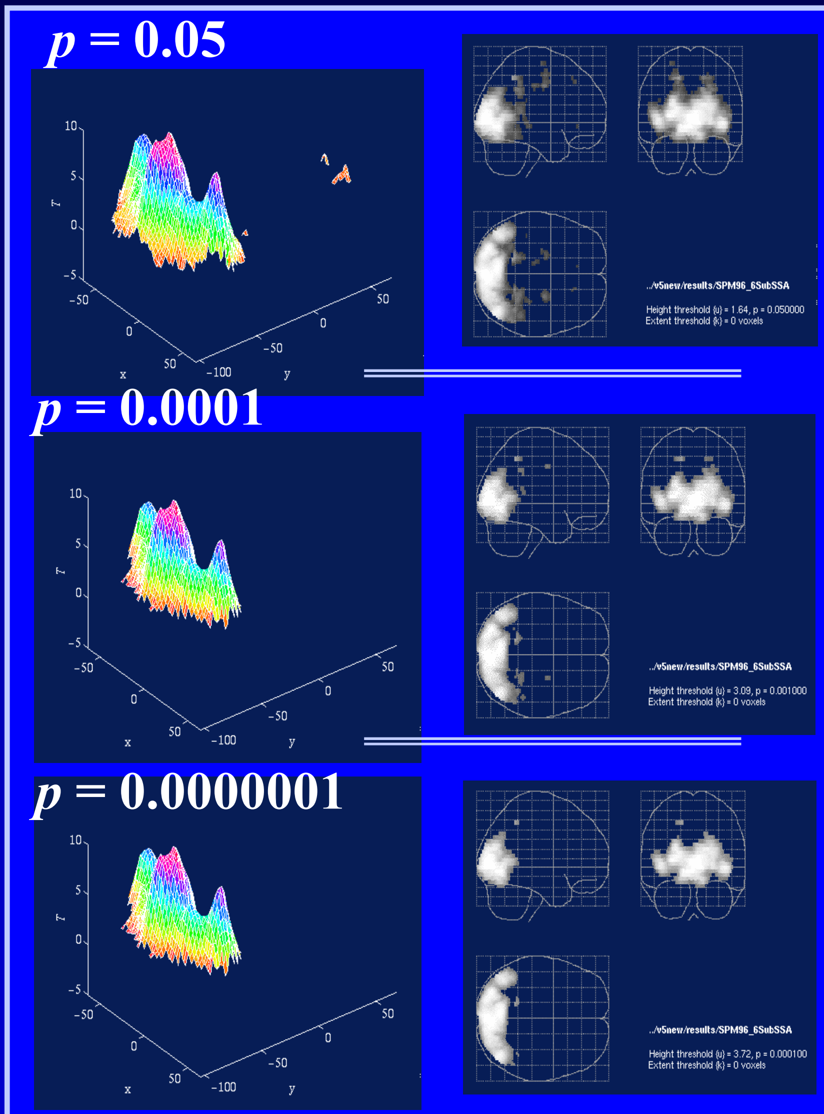
FWE Multiple comparisons terminology…

- *Family* of hypotheses
  - $H^k \; k \in \Omega = \{1,\ldots,K\}$
  - $H^\Omega = \cap \, H^k$
- *Familywise* Type I error
  - *weak* control – *omnibus test*
    - $\Pr(\text{“reject”} \; H^\Omega \mid H^\Omega) \leq \alpha$
    - *“anything, anywhere” ?*
  - *strong* control – *localising test*
    - $\Pr(\text{“reject”} \; H^W \mid H^W) \leq \alpha$
      $\forall \;\; W\!: W \subseteq \Omega \;\&\; H^W$
    - *“anything, & where” ?*
- Adjusted *p*–values
  - test level at which reject H^k



Voxel-level test…



- Threshold u_α
  - $t^k > u_\alpha \Rightarrow$ reject H^k
  - reject any $H^k \Rightarrow$ reject H^Ω

  $\Rightarrow$reject H^Ω if $t^\Omega_{max} > u_\alpha$
- Valid test
  - weak control

    $\Pr(T^\Omega_{max} > u_\alpha \mid H^\Omega) \leq \alpha$
  - strong control

    since $W \subseteq \Omega$

    $\Pr(T^W_{max} > u_\alpha \mid H^W) \leq \alpha$
- Adjusted p –values
  - $\Pr(T^\Omega_{max} > t^k \mid H^\Omega)$

u_α?

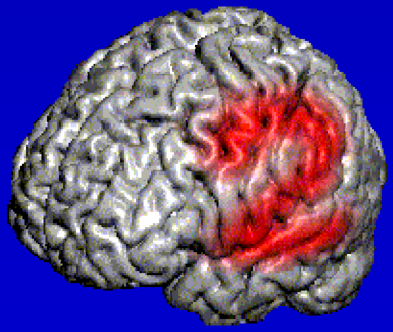
FWE MCP Solutions: Bonferroni

- 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, $P(T_i \geq u_\alpha) = \alpha$
- By Bonferroni inequality...

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

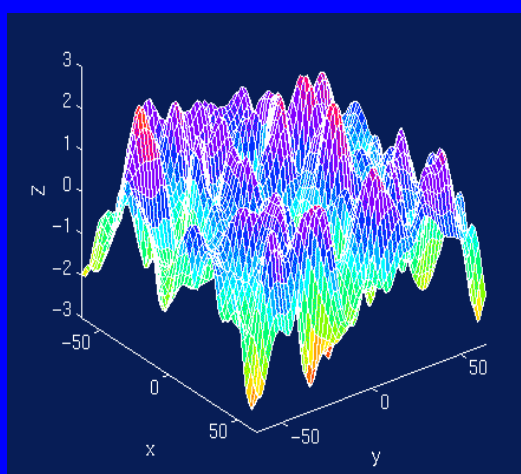
Conservative under correlation	
Independent:	V tests
Some dep.:	? tests
Total dep.:	1 test

Random field theory…

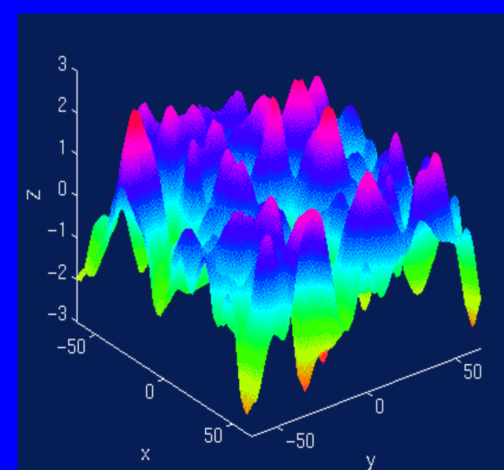


SPM approach: Random fields…

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



≈
lattice represtntation



FWER MCP Solutions: Controlling FWER w/ Max

- FWER & distribution of maximum

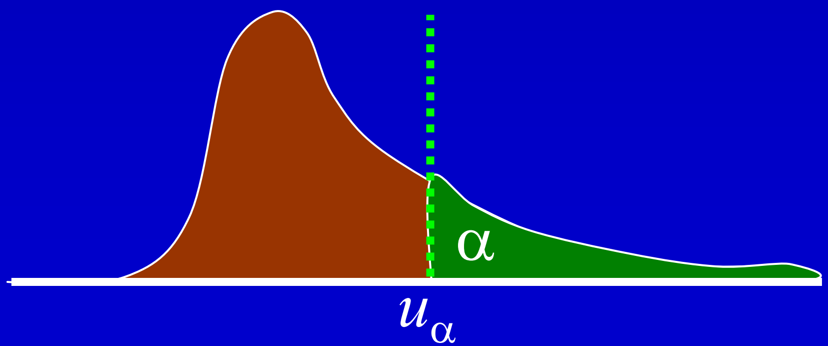
$$\begin{aligned} \text{FWER} &= \text{P(FWE)} \\ &= \text{P}(\cup_i \{T_i \geq u\} \mid H_o) \\ &= \text{P}(\max_i T_i \geq u \mid H_o) \end{aligned}$$

- 100(1-α)%ile of max dist^n controls FWER

$$\text{FWER} = \text{P}(\max_i T_i \geq u_\alpha \mid H_o) = \alpha$$

  - where

$$u_\alpha = F^{-1}_{\max}(1-\alpha)$$



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)

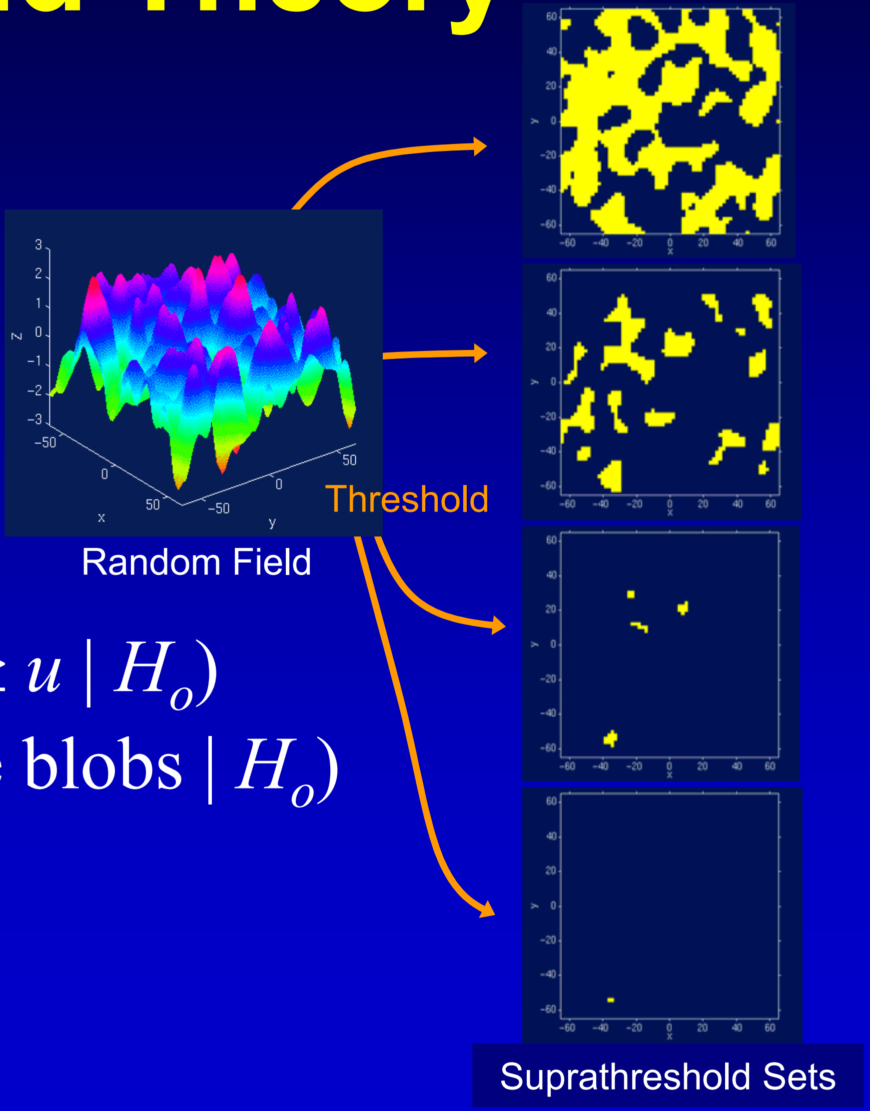
    = P(One or more blobs | H_o)

    $\approx P(\chi_u \geq 1 \mid H_o)$

    $\approx E(\chi_u \mid H_o)$

No holes

Never more than 1 blob



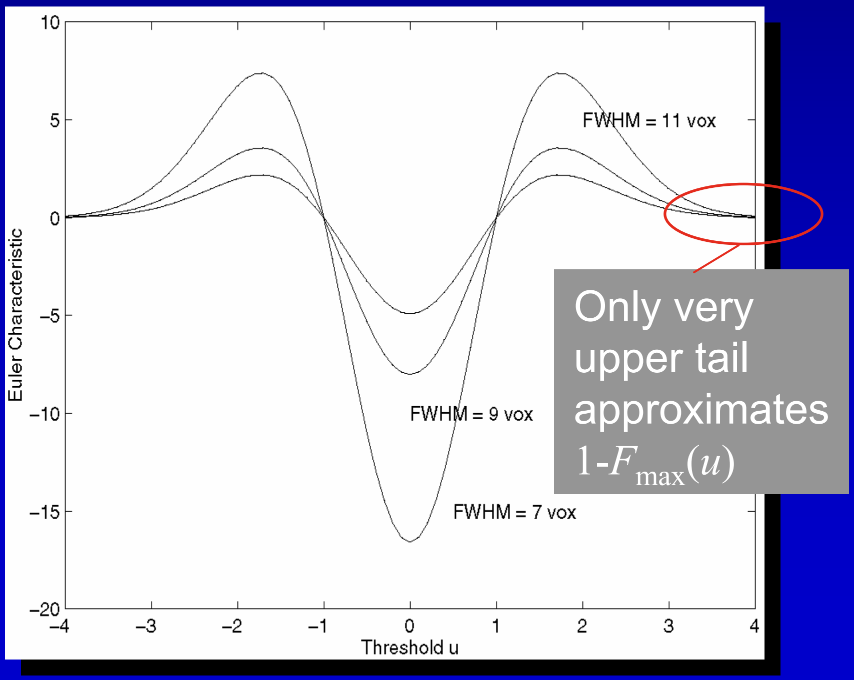
RFT Details:
Expected Euler Characteristic

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

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

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

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



Random Field Theory Smoothness Parameterization

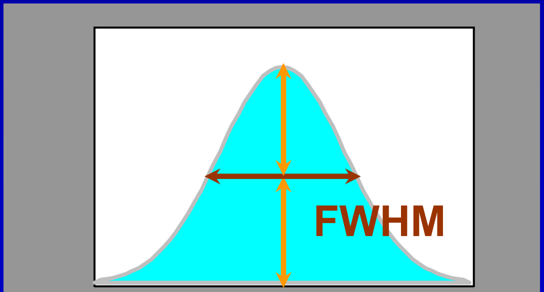
- $E(\chi_u)$ depends on $|\Lambda|^{1/2}$
  - Λ roughness matrix:

$$\Lambda = \mathbf{Var}\left(\frac{\partial G}{\partial(x,y,z)}\right)$$

$$= \begin{pmatrix} \mathbf{Var}\left(\frac{\partial G}{\partial x}\right) & \mathbf{Cov}\left(\frac{\partial G}{\partial x}, \frac{\partial G}{\partial y}\right) & \mathbf{Cov}\left(\frac{\partial G}{\partial x}, \frac{\partial G}{\partial z}\right) \\ \mathbf{Cov}\left(\frac{\partial G}{\partial y}, \frac{\partial G}{\partial x}\right) & \mathbf{Var}\left(\frac{\partial G}{\partial y}\right) & \mathbf{Cov}\left(\frac{\partial G}{\partial y}, \frac{\partial G}{\partial z}\right) \\ \mathbf{Cov}\left(\frac{\partial G}{\partial z}, \frac{\partial G}{\partial x}\right) & \mathbf{Cov}\left(\frac{\partial G}{\partial z}, \frac{\partial G}{\partial y}\right) & \mathbf{Var}\left(\frac{\partial G}{\partial z}\right) \end{pmatrix}$$

$$= \begin{pmatrix} \lambda_{xx} & \lambda_{xy} & \lambda_{xz} \\ \lambda_{yx} & \lambda_{yy} & \lambda_{yz} \\ \lambda_{zx} & \lambda_{zy} & \lambda_{zz} \end{pmatrix}$$

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

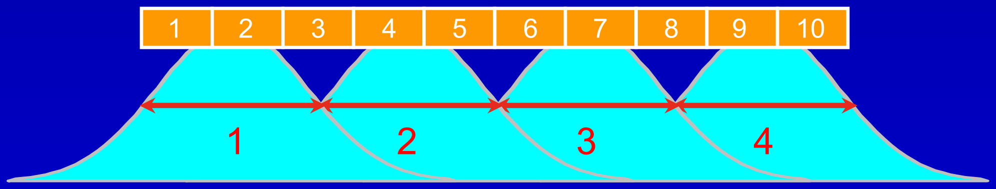


Autocorrelation Function

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

Random Field Theory Smoothness Parameterization

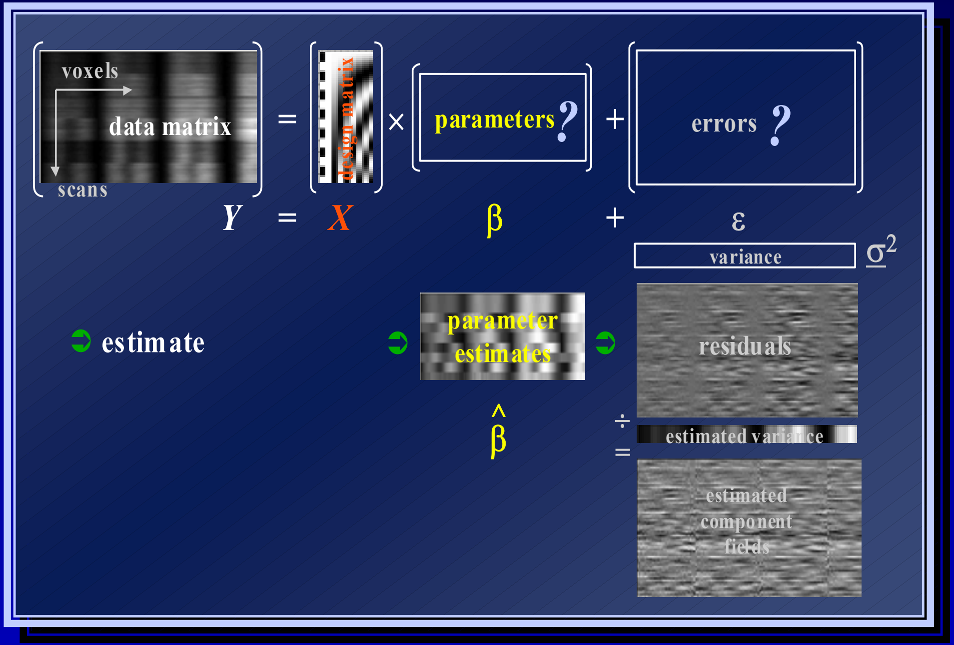
- RESELS
  - Resolution Elements
  - 1 RESEL = $FWHM_x \times FWHM_y \times FWHM_z$
  - RESEL Count R
    - $R = \lambda(\Omega) \sqrt{|\Lambda|} = (4\log 2)^{3/2} \lambda(\Omega) \; / \; (FWHM_x \times FWHM_y \times FWHM_z)$
    - Volume of search region in units of smoothness
    - Eg: 10 voxels, 2.5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



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)
- Roughness increases (Smoothness decreases)
  - P^c increases (more 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:

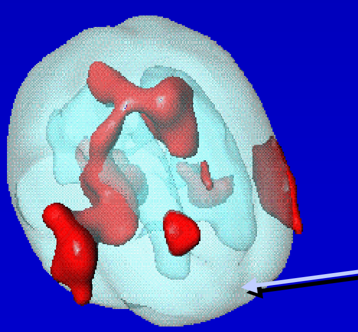
$\rho_0(u) = 1 - \Phi(u)$

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

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

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

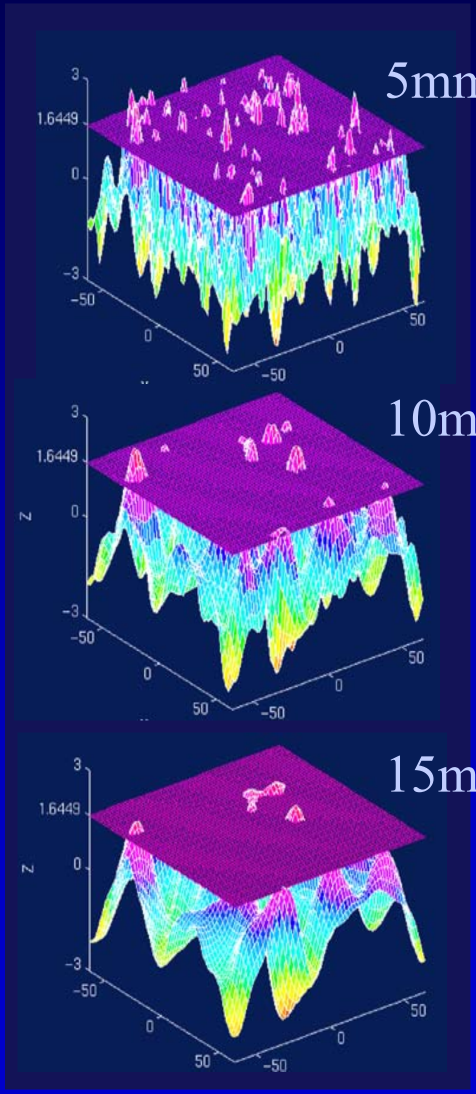
$\rho_4(u) = (4 \ln 2)^2 \quad (u^3 - 3u) \exp(-u^2/2) / (2\pi)^{5/2}$



Ω

Random Field Theory
Cluster Size Tests

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



5mm FWHM

10mm FWHM

15mm FWHM

Random Field Theory
Cluster Size Distribution

- Gaussian Random Fields (Nosko, 1969)

$$S^{2/D} \sim Exp\left(\left[\frac{E(N)}{\Gamma(D/2+1)E(L)}\right]^{-2/D}\right)$$

  - D: Dimension of RF

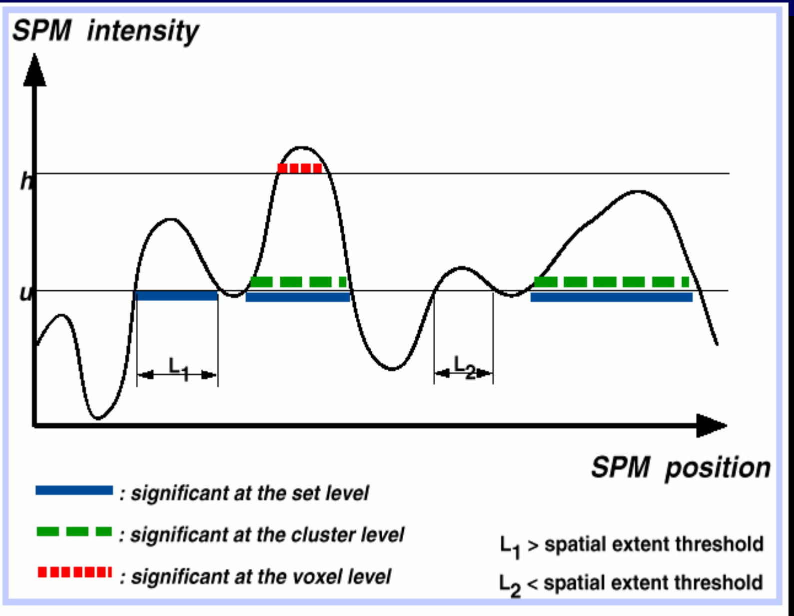
- t Random Fields (Cao, 1999)
  - B: Beta dist^n
  - U's: χ^2's
  - c chosen s.t. E(S) = E(N) / E(L)

$$S \sim cB^{1/2}\left[\frac{U_0^D}{\Pi_{b=0}^D U_b}\right]^{2/D}$$

Random Field Theory Cluster Size Corrected P-Values

- Previous results give uncorrected P-value
- Corrected P-value
  - Bonferroni
    - Correct for expected number of clusters
    - Corrected $P^c = \mathrm{E}(L)\, P^{\mathrm{uncorr}}$
  - Poisson Clumping Heuristic (Adler, 1980)
    - Corrected $P^c = 1 - \exp(\, -\mathrm{E}(L)\, P^{\mathrm{uncorr}}\,)$

Review:
Levels of inference & power

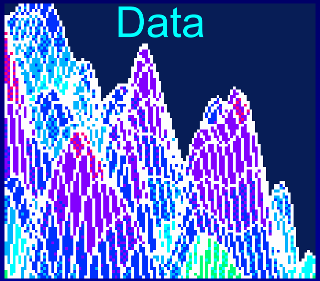


Sensitivity	Test based on	Parameters set by the user	Regional specificity
−	The intensity of a voxel	• Low pass filter	+
	The spatial extent above u or the spatial extent and the maximum peak height	• Low pass filter • intensity threshold u	
	The number of clusters above u with size greater than n	• Low pass filter • intensity thres. u • spatial threshold n	
+	The sum of square of the SPM or a MANOVA	• Low pass filter	−

Random Field Theory Limitations

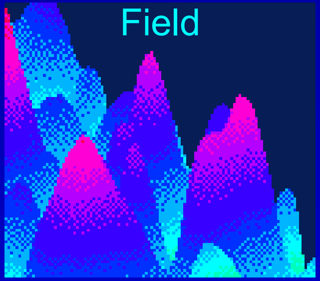
- Sufficient smoothness
  - FWHM smoothness 3-4× voxel size (Z)
  - More like ~10× for low-df T images
- Smoothness estimation
  - Estimate is biased when images not sufficiently smooth
- Multivariate normality
  - Virtually impossible to check
- Several layers of approximations
- Stationary required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

Lattice Image Data



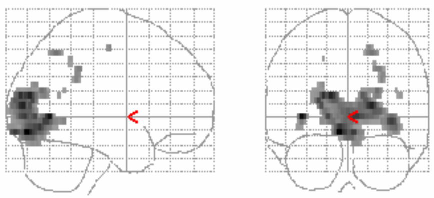
≈

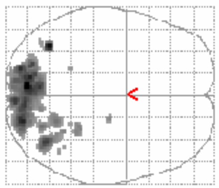
Continuous Random Field



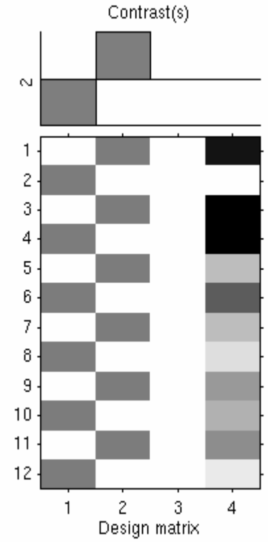
SPM results...

activation





SPM{T_9}



SPMresults: ~/data/v5new/results
Height threshold T = 4.30
Extent threshold k = 0 voxels

Statistics: *volume summary (p-values corrected for entire volume)*

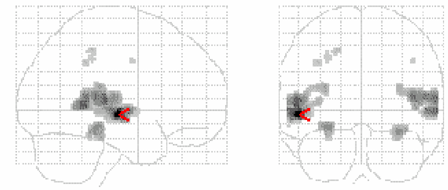
set-level p	set-level c	cluster-level $p_{corrected}$	cluster-level k	cluster-level $p_{uncorrected}$	voxel-level $p_{corrected}$	voxel-level T	voxel-level ($Z_{\equiv}$)	voxel-level $p_{uncorrected}$	x,y,z {mm}
0.964	11	0.000	1285	0.000	0.109	12.51	(5.01)	0.000	-8 -82 -12
					0.269	10.43	(4.71)	0.000	20 -86 8
					0.272	10.40	(4.70)	0.000	-14 -80 16
		0.411	17	0.030	0.168	11.51	(4.87)	0.000	-38 -64 0
		0.000	125	0.000	0.465	9.16	(4.48)	0.000	36 -66 -4
					0.997	5.74	(3.63)	0.000	28 -52 -4
		0.155	26	0.010	0.969	6.46	(3.85)	0.000	20 -58 48
		0.173	25	0.011	0.993	5.98	(3.71)	0.000	26 -38 36
					0.997	5.73	(3.63)	0.000	28 -42 28
		0.976	5	0.212	0.999	5.59	(3.59)	0.000	18 -14 52
		0.990	4	0.263	1.000	4.82	(3.30)	0.000	-40 -70 -8
		1.000	2	0.431	1.000	4.81	(3.30)	0.000	44 -56 16
		1.000	2	0.431	1.000	4.71	(3.26)	0.001	-20 -46 44
		1.000	1	0.588	1.000	4.57	(3.20)	0.001	40 -52 20
		1.000	2	0.431	1.000	4.38	(3.13)	0.001	22 -48 40

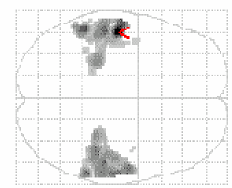
table shows at most 3 subsidiary maxima > 8.0mm apart per cluster

Height threshold: T = 4.30, p = 0.001 (1.000 corrected)
Extent threshold: k = 0 voxels, p = 1.000 (1.000 corrected)
Expected voxels per cluster, <k> = 3.443
Expected number of clusters, <c> = 17.64

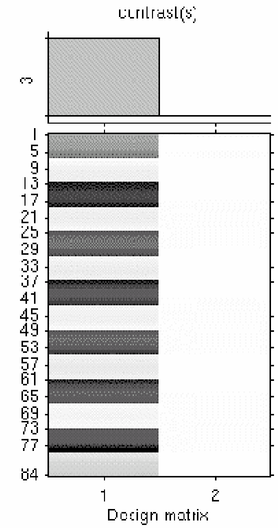
Degrees of freedom = [1.0, 9.0]
Smoothness FWHM = 10.9 12.1 9.2 {mm} = 5.5 6.0 2.3 {voxels}
Search volume: S = 971856 mm^3 = 60741 voxels = 803.8 resels
Voxel size: [2.0, 2.0, 4.0] mm (1 resel = 75.57 voxels)

auditory activation





SPM{$T_{71.99}$}



SPMresults: /andrew/matlab/WK/f_spm99a
Height threshold T = 3.21
Extent threshold k = 0 voxels

Statistics: *volume summary (p-values corrected for entire volume)*

set-level p	set-level c	cluster-level $p_{corrected}$	cluster-level k	cluster-level $p_{uncorrected}$	voxel-level $p_{corrected}$	voxel-level T	voxel-level ($Z_{\equiv}$)	voxel-level $p_{uncorrected}$	x,y,z {mm}
1.000	11	0.000	898	0.000	0.000	7.7E	(6.61)	C.000	-50 -16 -4
					0.000	6.79	(5.35)	C.000	-54 -44 4
					0.001	6.56	(5.73)	C.000	-52 -28 8
		0.000	974	0.000	0.002	6.29	(5.59)	C.000	60 -16 -2
					0.002	6.25	(5.57)	C.000	42 -36 10
					0.003	6.23	(5.35)	C.000	60 -42 10
		0.003	106	0.000	0.016	5.71	(5.17)	C.000	30 -36 -16
		0.004	98	0.000	0.022	5.62	(5.10)	C.000	-26 -34 -12
		0.026	17	0.060	0.990	3.92	(3.72)	C.000	-20 -30 40
		0.953	12	0.116	1.000	3.70	(3.52)	C.000	-36 -44 38
		0.989	9	0.169	1.000	3.57	(3.41)	C.000	-44 -2 -2
		1.000	1	0.663	1.000	3.40	(3.32)	C.000	-60 -40 -12
		1.000	3	0.425	1.000	3.43	(3.29)	C.001	40 -4 38
		0.969	11	0.131	1.000	3.39	(3.25)	C.001	-28 -38 40
		1.000	1	0.663	1.000	3.22	(3.10)	C.001	28 42 46

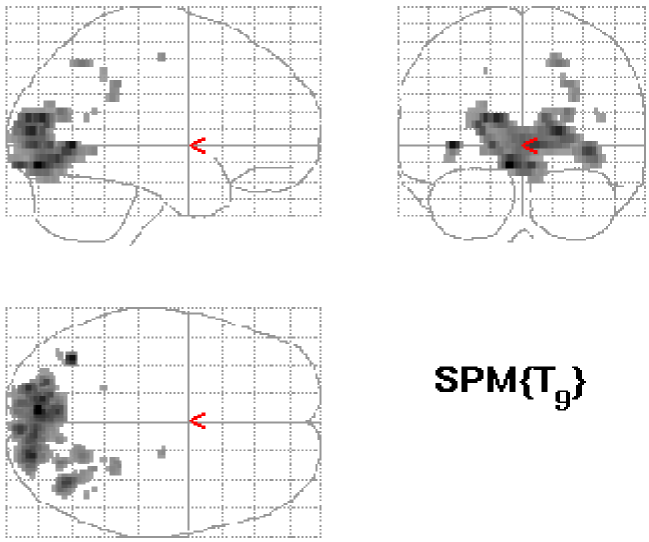
table shows at most 3 maxima > 8.0mm apart per cluster

Height threshold: T = 3.21, p = 0.001 (1.000 corrected)
Extent threshold: k = 0 voxels, p = 1.000 (1.000 corrected)
Expected voxels per cluster, <k> = 5.046
Expected number of clusters, <c> = 26.43

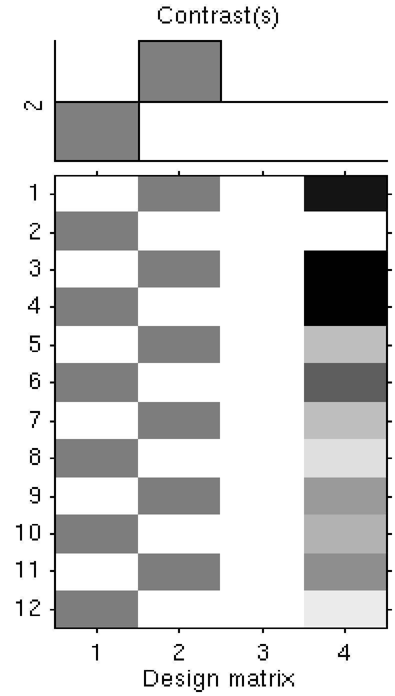
Degrees of freedom = [1.0, 72.0]
Smoothness FWHM = 7.9 8.5 7.1 {mm} = 4.0 4.1 3.6 {voxels}
Search volume: S = 1189880 mm^3 = 148735 voxels = 2299.1 resels
Voxel size: [2.0, 2.0, 2.0] mm (1 resel = 58.01 voxels)

SPM results…

activation



SPM{T_9}



SPMresults: ~/data/v5new/results
Height threshold T = 4.30
Extent threshold k = 0 voxels

Statistics: *volume summary (p-values corrected for entire volume)*

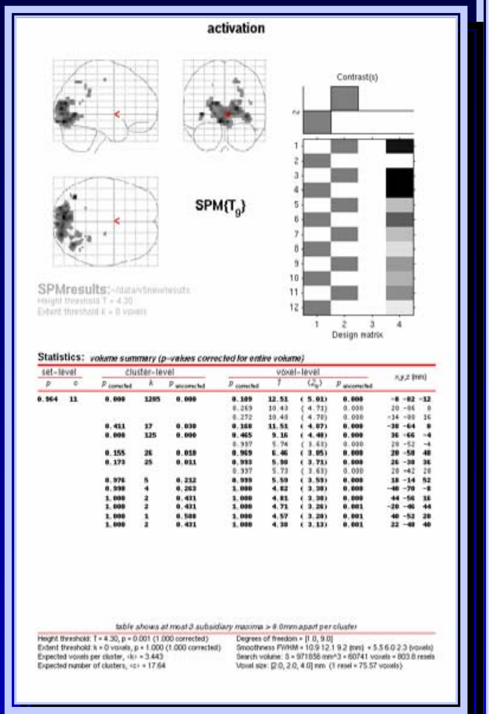
set-level		cluster-level			voxel-level				
p	c	$p_{corrected}$	k	$p_{uncorrected}$	$p_{corrected}$	T	($Z_{\equiv}$)	$p_{uncorrected}$	x,y,z {mm}
0.964	11	0.000	1285	0.000	0.109	12.51	(5.01)	0.000	-8 -82 -12
					0.269	10.43	(4.71)	0.000	20 -86 8
					0.272	10.40	(4.70)	0.000	-14 -80 16
		0.411	17	0.030	0.168	11.51	(4.87)	0.000	-38 -64 0
		0.000	125	0.000	0.465	9.16	(4.48)	0.000	36 -66 -4
					0.997	5.74	(3.63)	0.000	28 -52 -4
		0.155	26	0.010	0.969	6.46	(3.85)	0.000	20 -58 48
		0.173	25	0.011	0.993	5.98	(3.71)	0.000	26 -38 36
					0.997	5.73	(3.63)	0.000	28 -42 28
		0.976	5	0.212	0.999	5.59	(3.59)	0.000	18 -14 52
		0.990	4	0.263	1.000	4.82	(3.30)	0.000	-40 -70 -8
		1.000	2	0.431	1.000	4.81	(3.30)	0.000	44 -56 16
		1.000	2	0.431	1.000	4.71	(3.26)	0.001	-20 -46 44
		1.000	1	0.588	1.000	4.57	(3.20)	0.001	40 -52 20
		1.000	2	0.431	1.000	4.38	(3.13)	0.001	22 -48 40

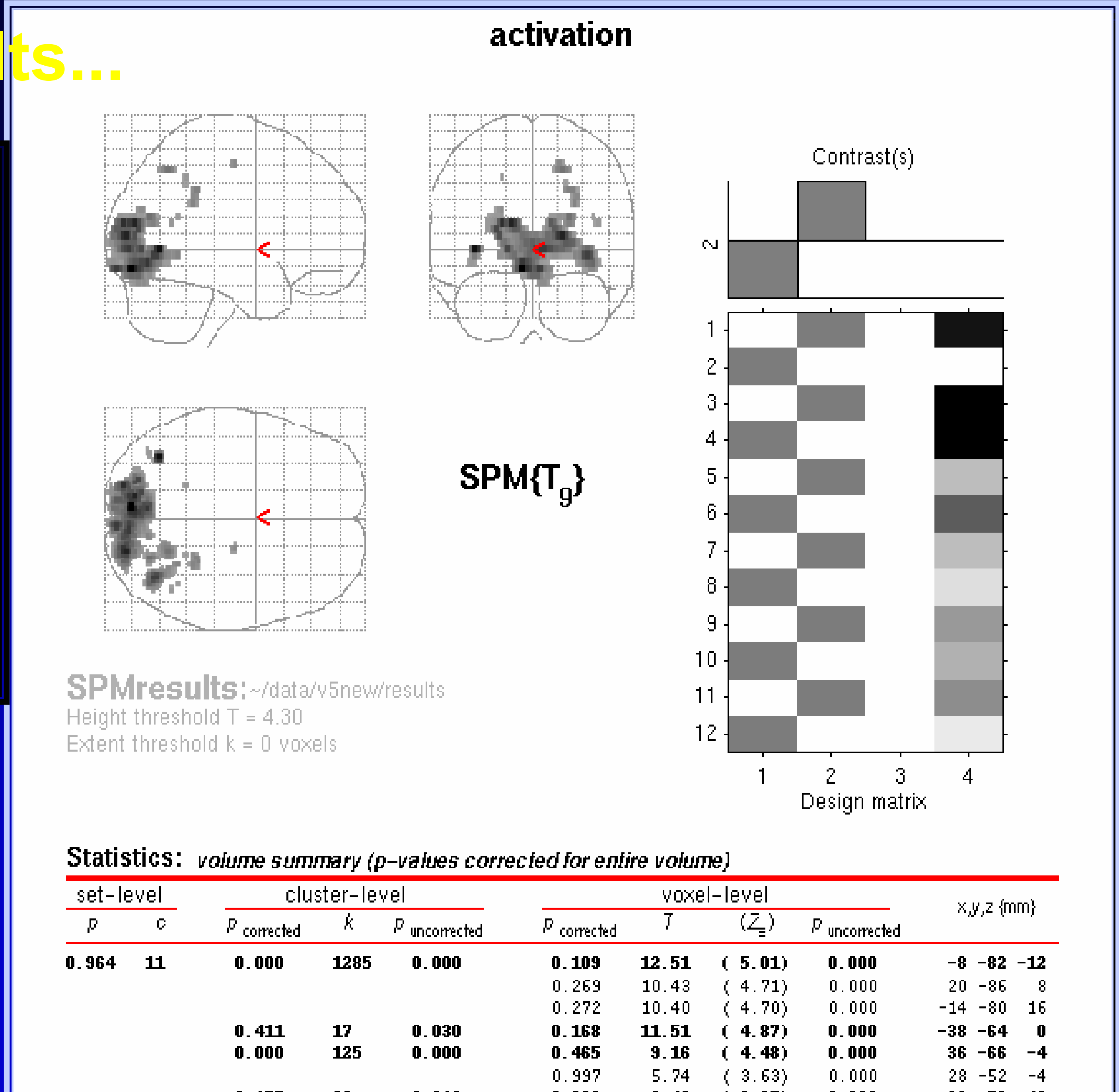
table shows at most 3 subsidiary maxima > 8.0mm apart per cluster

Height threshold: T = 4.30, p = 0.001 (1.000 corrected)
Extent threshold: k = 0 voxels, p = 1.000 (1.000 corrected)
Expected voxels per cluster, <k> = 3.443
Expected number of clusters, <c> = 17.64

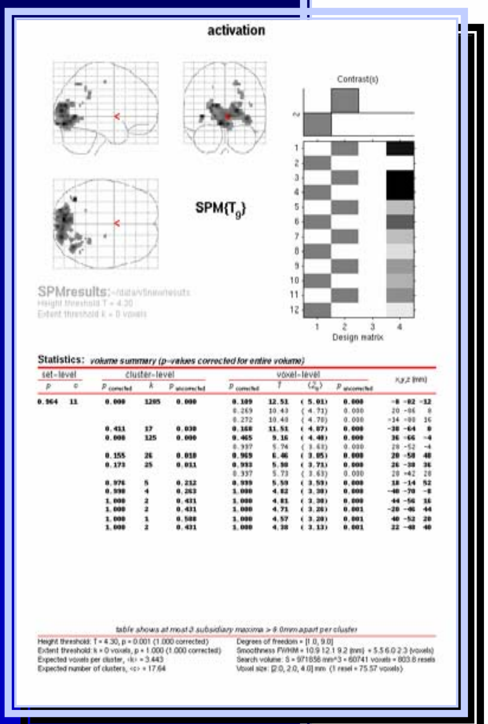
Degrees of freedom = [1.0, 9.0]
Smoothness FWHM = 10.9 12.1 9.2 {mm} = 5.5 6.0 2.3 {voxels}
Search volume: S = 971856 mm^3 = 60741 voxels = 803.8 resels
Voxel size: [2.0, 2.0, 4.0] mm (1 resel = 75.57 voxels)

SPM results...





set-level		cluster-level			voxel-level				x,y,z {mm}
p	c	p corrected	k	p uncorrected	p corrected	T	(Z≡)	p uncorrected	
0.964	11	0.000	1285	0.000	0.109	12.51	(5.01)	0.000	-8 -82 -12
					0.269	10.43	(4.71)	0.000	20 -86 8
					0.272	10.40	(4.70)	0.000	-14 -80 16
		0.411	17	0.030	0.168	11.51	(4.87)	0.000	-38 -64 0
		0.000	125	0.000	0.465	9.16	(4.48)	0.000	36 -66 -4
					0.997	5.74	(3.63)	0.000	28 -52 -4



Statistics: *volume summary (p-values corrected for entire volume)*

set-level		cluster-level			voxel-level				x,y,z {mm}
p	c	p corrected	k	p uncorrected	p corrected	T	($Z_{\equiv}$)	p uncorrected	
0.964	**11**	**0.000**	**1285**	**0.000**	**0.109**	**12.51**	**(5.01)**	**0.000**	**-8 -82 -12**
					0.269	10.43	(4.71)	0.000	20 -86 8
					0.272	10.40	(4.70)	0.000	-14 -80 16
		0.411	**17**	**0.030**	**0.168**	**11.51**	**(4.87)**	**0.000**	**-38 -64 0**
		0.000	**125**	**0.000**	**0.465**	**9.16**	**(4.48)**	**0.000**	**36 -66 -4**
					0.997	5.74	(3.63)	0.000	28 -52 -4
		0.155	**26**	**0.010**	**0.969**	**6.46**	**(3.85)**	**0.000**	**20 -58 48**
		0.173	**25**	**0.011**	**0.993**	**5.98**	**(3.71)**	**0.000**	**26 -38 36**
					0.997	5.73	(3.63)	0.000	28 -42 28
		0.976	**5**	**0.212**	**0.999**	**5.59**	**(3.59)**	**0.000**	**18 -14 52**
		0.990	**4**	**0.263**	**1.000**	**4.82**	**(3.30)**	**0.000**	**-40 -70 -8**
		1.000	**2**	**0.431**	**1.000**	**4.81**	**(3.30)**	**0.000**	**44 -56 16**
		1.000	**2**	**0.431**	**1.000**	**4.71**	**(3.26)**	**0.001**	**-20 -46 44**
		1.000	**1**	**0.588**	**1.000**	**4.57**	**(3.20)**	**0.001**	**40 -52 20**
		1.000	**2**	**0.431**	**1.000**	**4.38**	**(3.13)**	**0.001**	**22 -48 40**

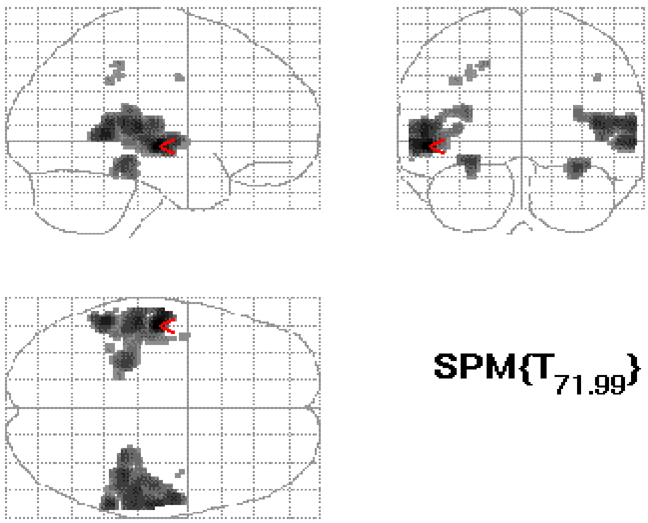
table shows at most 3 subsidiary maxima > 8.0mm apart per cluster

Height threshold: T = 4.30, p = 0.001 (1.000 corrected)
Extent threshold: k = 0 voxels, p = 1.000 (1.000 corrected)
Expected voxels per cluster, <k> = 3.443
Expected number of clusters, <c> = 17.64

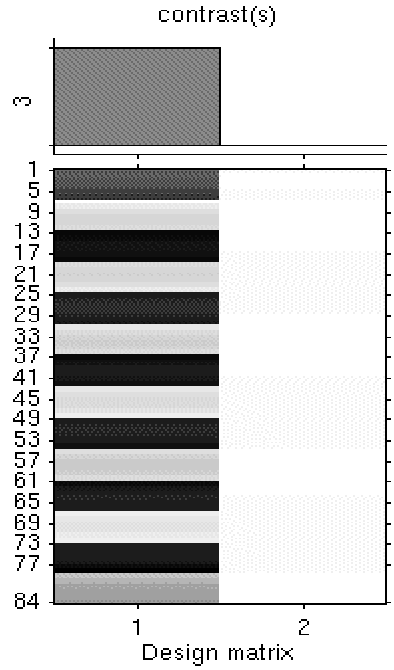
Degrees of freedom = [1.0, 9.0]
Smoothness FWHM = 10.9 12.1 9.2 {mm} = 5.5 6.0 2.3 {voxels}
Search volume: S = 971856 mm^3 = 60741 voxels = 803.8 resels
Voxel size: [2.0, 2.0, 4.0] mm (1 resel = 75.57 voxels)

SPM results…

auditory activation



SPM{$T_{71.99}$}



SPMresults: ./andrew/matlab/WK/f_spm99a
Height threshold T = 3.21
Extent threshold k = 0 voxels

Statistics: *volume summary (p-values corrected for entire volume)*

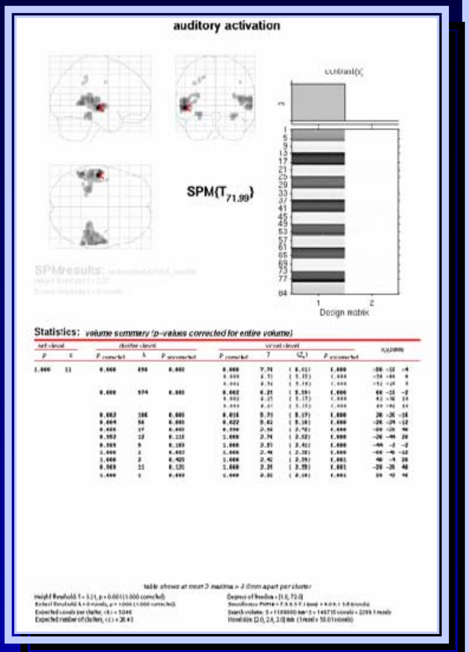
set-level		cluster-level			voxel-level				x,y,z (mm)
p	c	p corrected	k	p uncorrected	p corrected	T	($Z_{\equiv}$)	p uncorrected	
1.000	11	0.000	898	0.000	0.000	7.78	(6.61)	0.000	-50 -16 -4
					0.000	6.79	(5.95)	0.000	-54 -44 4
					0.001	6.56	(5.79)	0.000	-52 -28 8
		0.000	974	0.000	0.002	6.29	(5.59)	0.000	60 -16 -2
					0.002	6.25	(5.57)	0.000	42 -36 10
					0.003	6.23	(5.55)	0.000	60 -42 10
		0.003	106	0.000	0.016	5.71	(5.17)	0.000	30 -36 -16
		0.004	98	0.000	0.022	5.62	(5.10)	0.000	-26 -34 -12
		0.826	17	0.066	0.990	3.92	(3.72)	0.000	-20 -38 48
		0.953	12	0.116	1.000	3.70	(3.52)	0.000	-36 -44 38
		0.989	9	0.169	1.000	3.57	(3.41)	0.000	-44 -2 -2
		1.000	1	0.663	1.000	3.46	(3.32)	0.000	-60 -40 -12
		1.000	3	0.425	1.000	3.43	(3.29)	0.001	40 -4 38
		0.969	11	0.131	1.000	3.39	(3.25)	0.001	-28 -38 40
		1.000	1	0.663	1.000	3.22	(3.10)	0.001	-28 -42 46

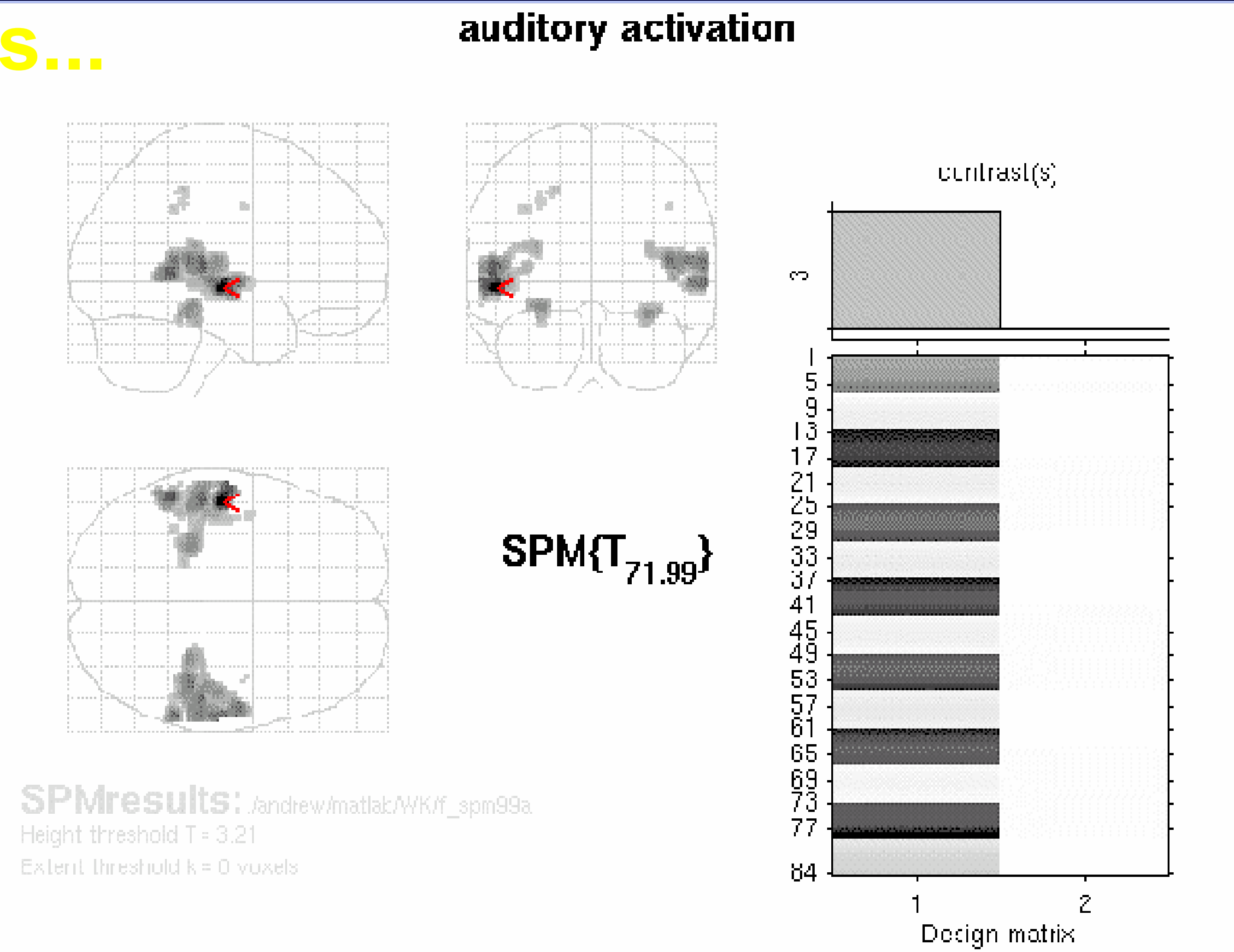
table shows at most 3 maxima > 8.0mm apart per cluster

Height threshold: T = 3.21, p = 0.001 (1.000 corrected)
Extent threshold: k = 0 voxels, p = 1.000 (1.000 corrected)
Expected voxels per cluster, <k> = 5.046
Expected number of clusters, <c> = 26.43

Degrees of freedom = [1.0, 72.0]
Smoothness FWHM = 7.9 8.3 7.1 (mm) = 4.0 4.1 3.6 (voxels)
Search volume: S = 1189880 mm^3 = 148735 voxels = 2299.1 resels
Voxel size: [2.0, 2.0, 2.0] mm (1 resel = 58.01 voxels)

SPM results...

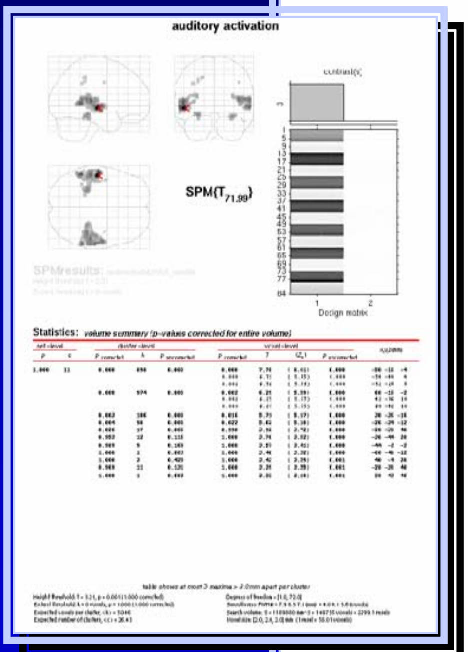




Statistics: *volume summary (p-values corrected for entire volume)*

set-level		cluster-level			voxel-level				x,y,z (mm)
P	c	P corrected	k	P uncorrected	P corrected	T	($Z_=$)	P uncorrected	
1.000	11	0.000	898	0.000	0.000	7.78	(6.61)	0.000	-50 -16 -4
					0.000	6.79	(5.95)	0.000	-54 -44 4
					0.001	6.56	(5.79)	0.000	-52 -28 8
		0.000	974	0.000	0.002	6.29	(5.59)	0.000	60 -16 -2
					0.002	6.25	(5.57)	0.000	42 -36 10
					0.003	6.23	(5.55)	0.000	60 -42 10

SPM results...



Statistics: *volume summary (p-values corrected for entire volume)*

set-level		cluster-level			voxel-level				x,y,z (mm)		
p	c	P corrected	k	P uncorrected	P corrected	T	($Z_\equiv$)	P uncorrected			
1.000	11	0.000	898	0.000	0.000	7.78	(6.61)	0.000	-50	-16	-4
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					0.001	6.56	(5.79)	0.000	-52	-28	8
		0.000	974	0.000	0.002	6.29	(5.59)	0.000	60	-16	-2
					0.002	6.25	(5.57)	0.000	42	-36	10
					0.003	6.23	(5.55)	0.000	60	-42	10
		0.003	106	0.000	0.016	5.71	(5.17)	0.000	30	-36	-16
		0.004	98	0.000	0.022	5.62	(5.10)	0.000	-26	-34	-12
		0.026	17	0.066	0.990	3.98	(3.72)	0.000	-20	-30	40
		0.953	12	0.116	1.000	3.70	(3.52)	0.000	-36	-44	38
		0.989	9	0.169	1.000	3.57	(3.41)	0.000	-44	-2	-2
		1.000	1	0.663	1.000	3.40	(3.32)	0.000	-60	-40	-12
		1.000	3	0.425	1.000	3.42	(3.29)	0.001	40	-4	38
		0.969	11	0.131	1.000	3.39	(3.25)	0.001	-28	-38	40
		1.000	1	0.663	1.000	3.22	(3.10)	0.001	28	42	46

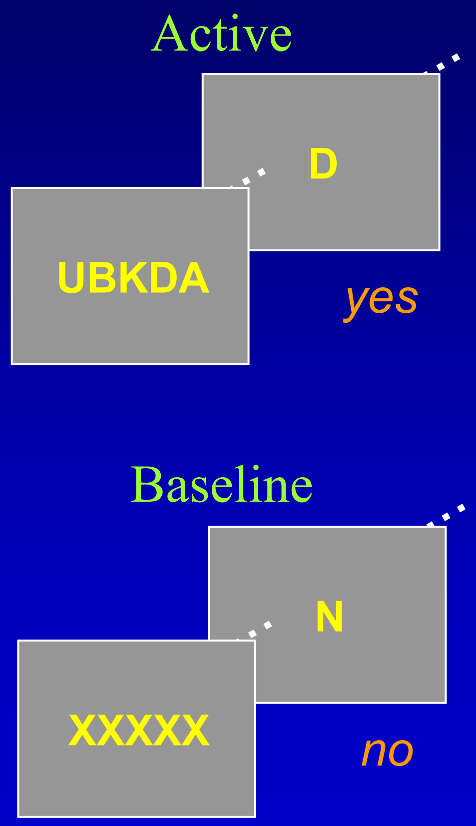
table shows at most 3 maxima > 8.0mm apart per cluster

Height threshold: T = 3.21, p = 0.001 (1.000 corrected)
Extent threshold: k = 0 voxels, p = 1.000 (1.000 corrected)
Expected voxels per cluster, <k> = 5.046
Expected number of clusters, <c> = 26.43

Degrees of freedom = [1.0, 72.0]
Smoothness FWHM = 7.9 8.5 7.1 (mm) = 4.0 4.1 3.6 (voxels)
Search volume: S = 1189880 mm^3 = 148735 voxels = 2299.1 resels
Voxel size: [2.0, 2.0, 2.0] mm (1 resel = 58.01 voxels)

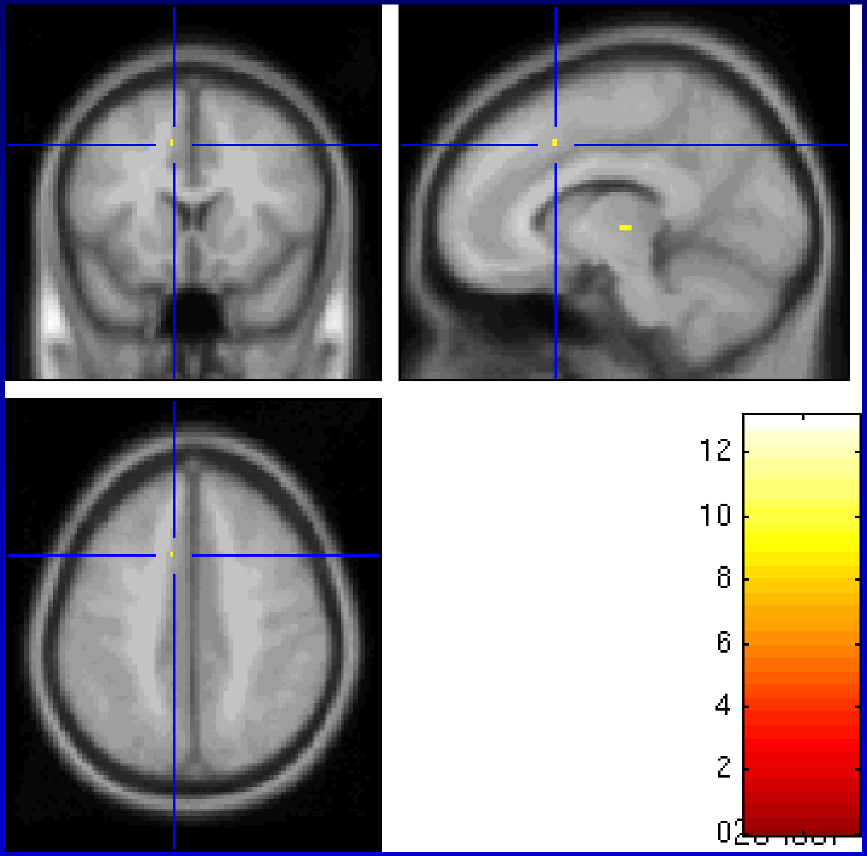
Real Data

- 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

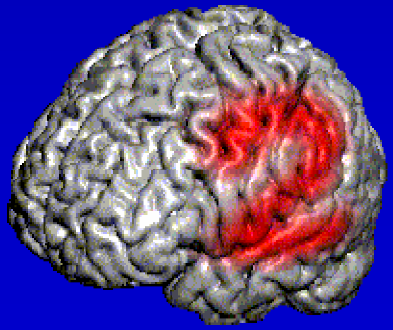


Real Data:
RFT Result

- 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



False Discovery Rate…



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

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

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

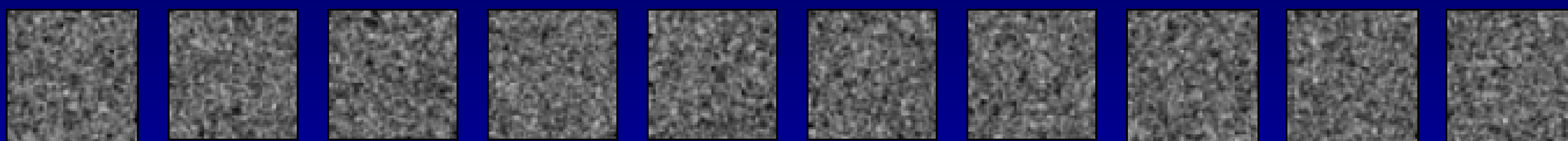
  – If $N_R = 0$, rFDR = 0

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

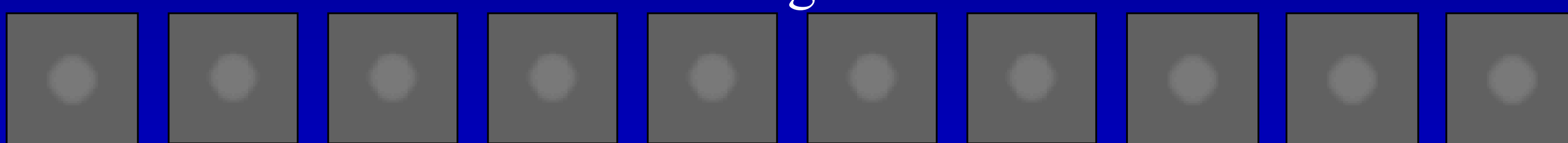
$$FDR = E(rFDR)$$

False Discovery Rate Illustration:

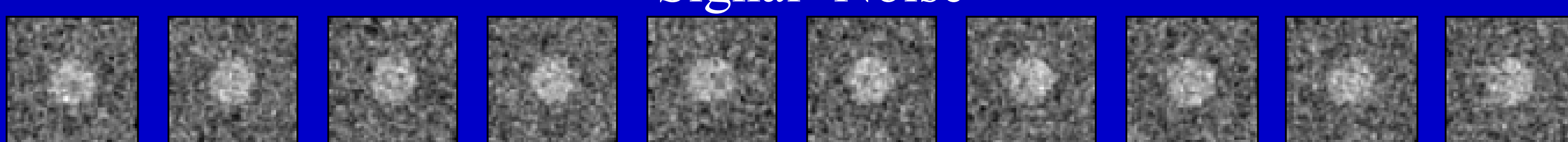
Noise



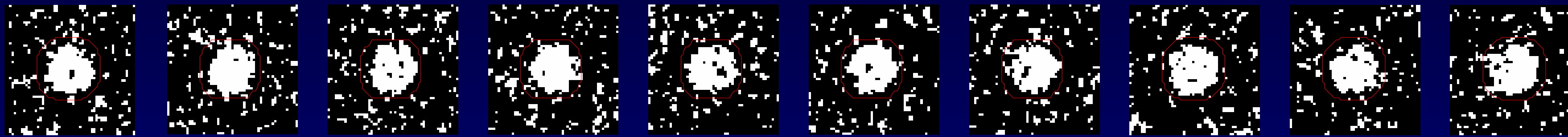
Signal



Signal+Noise



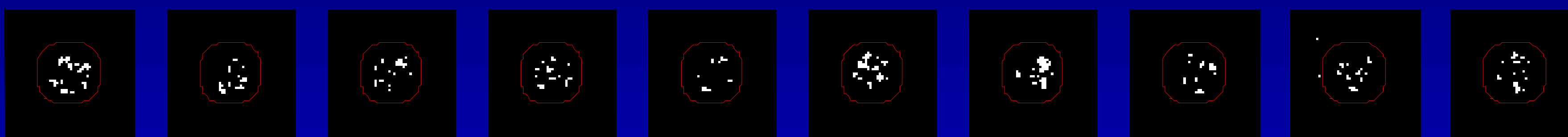
Control of Per Comparison Rate at 10%



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

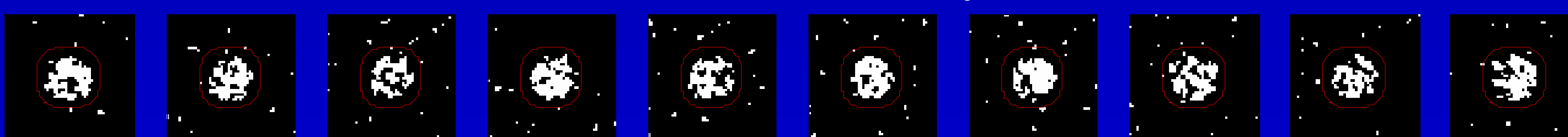
Control of Familywise Error Rate at 10%



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

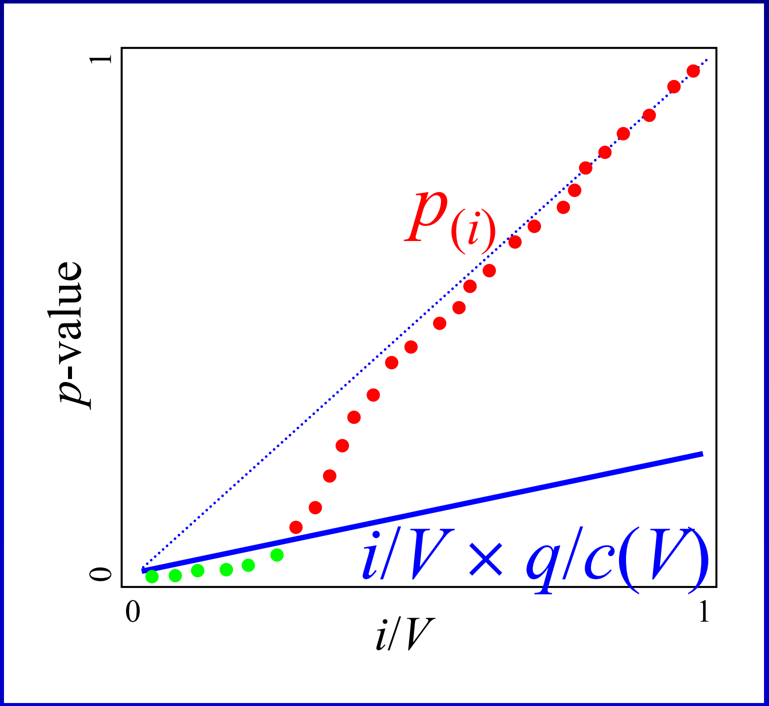
Benjamini & Hochberg Procedure

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

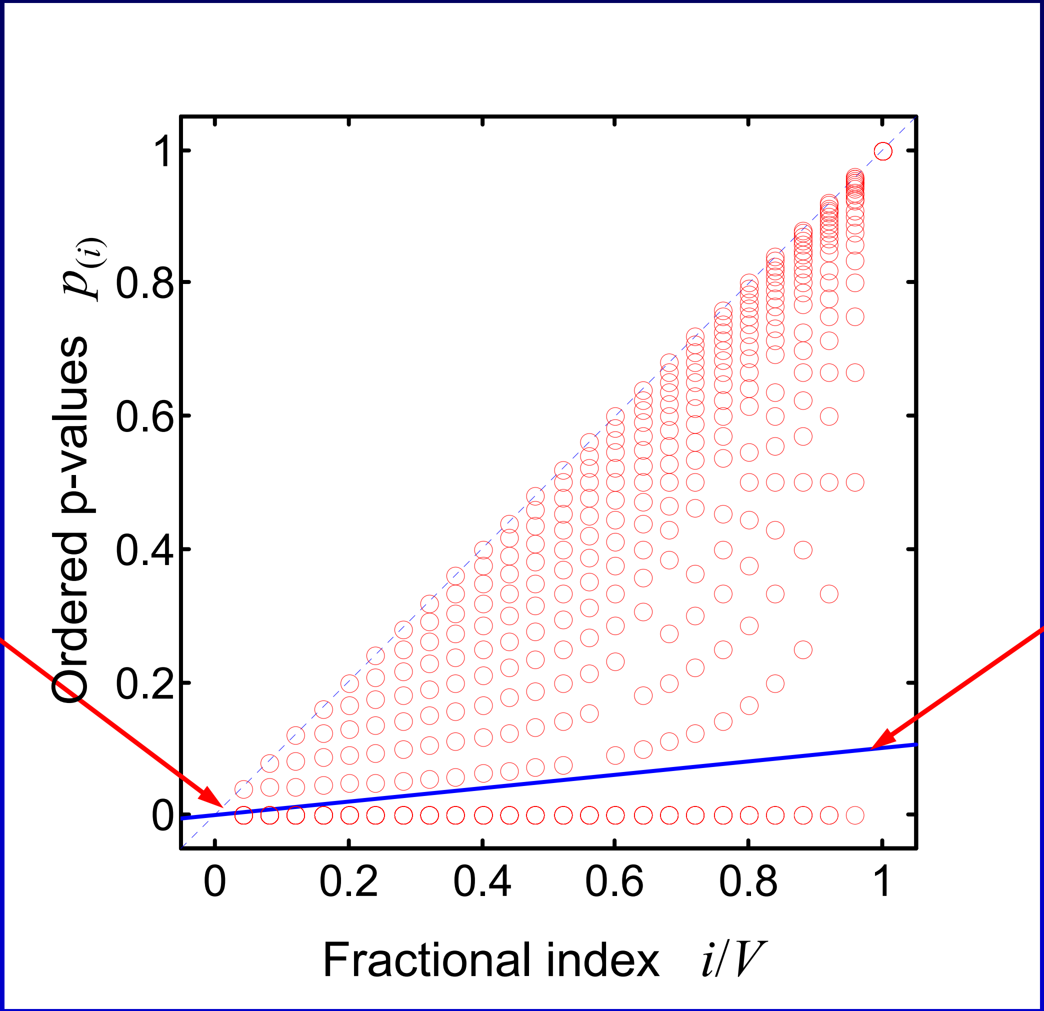
$$p_{(i)} \leq \ i/V \times q/c(V)$$

- 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

Benjamini & Hochberg Procedure Details

- $c(V) = 1$
  - Positive Regression Dependency on Subsets

    P($X_1 \geq c_1$, $X_2 \geq c_2$, ..., $X_k \geq c_k$ | $X_i = x_i$) is non-decreasing in x_i

    - Only required of test statistics for which null true
    - Special cases include
      - Independence
      - Multivariate Normal with all positive correlations
      - Same, but studentized with common std. err.
- $c(V) = \Sigma_{i=1,\ldots,V} 1/i \approx \log(V) + 0.5772$
  - Arbitrary covariance structure

Benjamini & Yekutieli (2001). *Ann. Stat.* 29:1165-1188

Benjamini & Hochberg: Key Properties

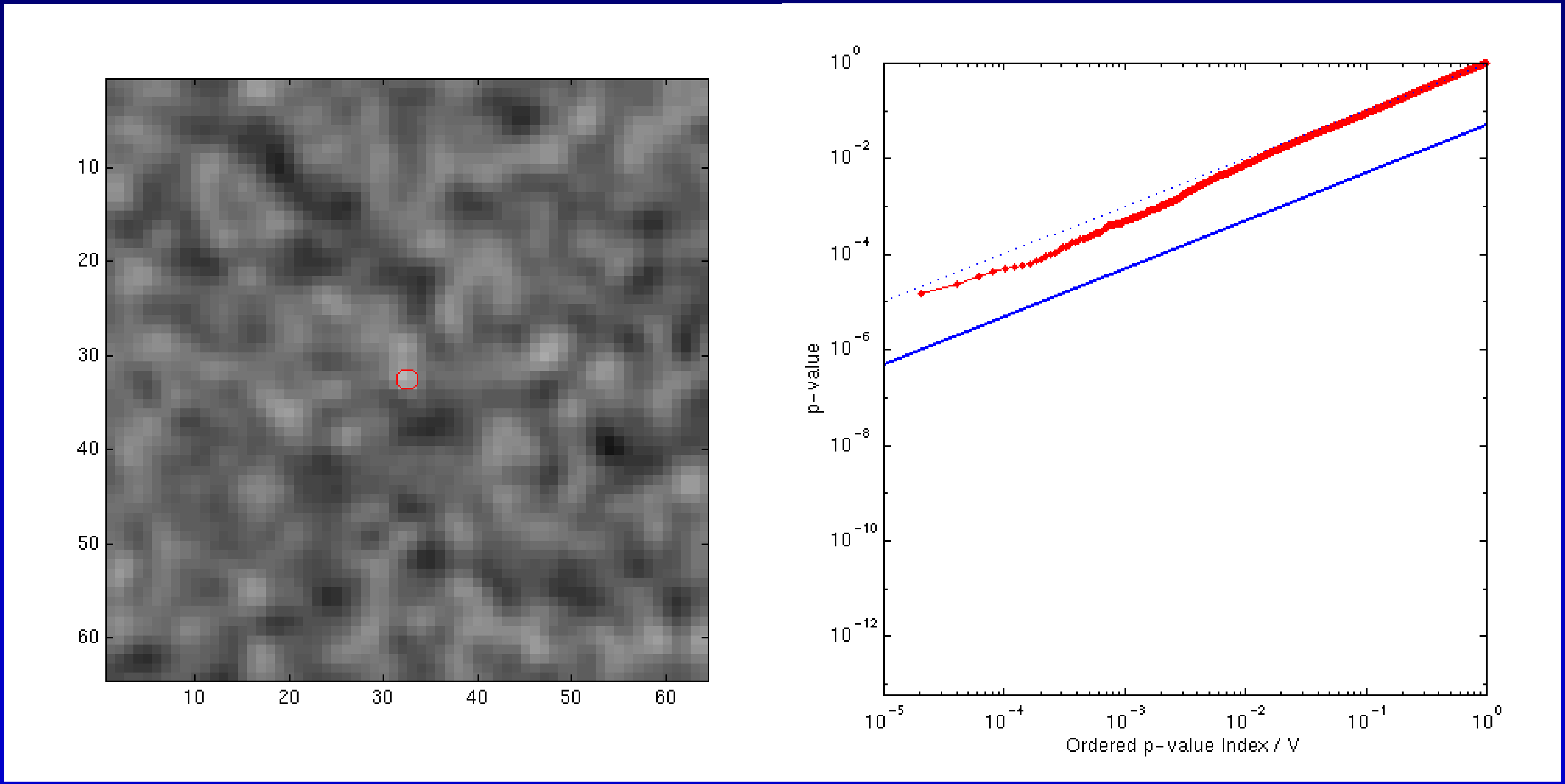
- FDR is controlled

$$E(\mathrm{rFDR}) \le q\, m_0 / V$$

  - Conservative, if large fraction of nulls false
- Adaptive
  - Threshold depends on amount of signal
    - More signal, More small p-values, More $p_{(i)}$ less than $i/V \times q/c(V)$

Controlling FDR: Varying Signal Extent

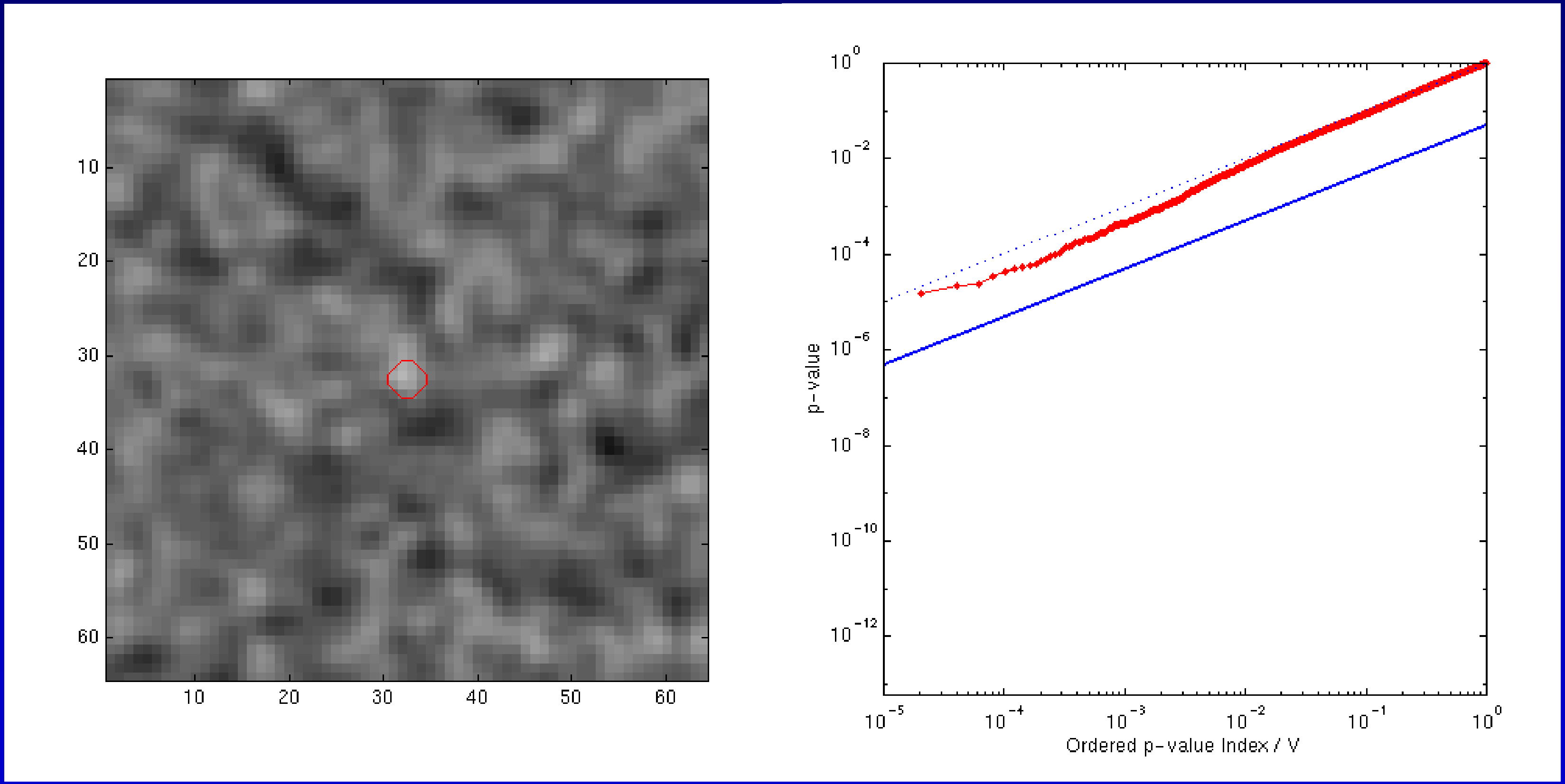
$p =$ $z =$



Signal Intensity 3.0 Signal Extent 1.0 Noise Smoothness 3.0

Controlling FDR: Varying Signal Extent

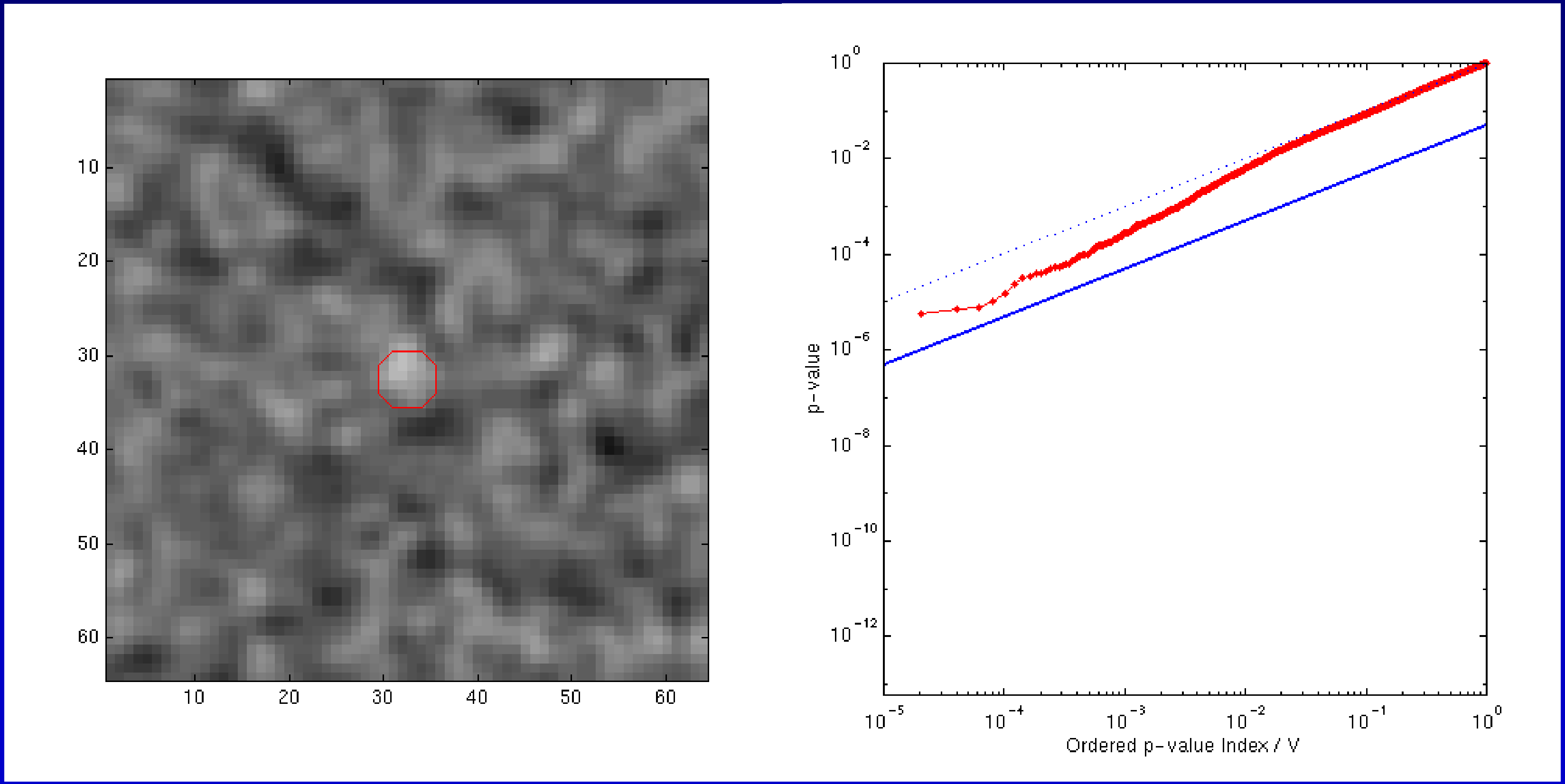
$p =$ $z =$



Signal Intensity 3.0 Signal Extent 2.0 Noise Smoothness 3.0

Controlling FDR: Varying Signal Extent

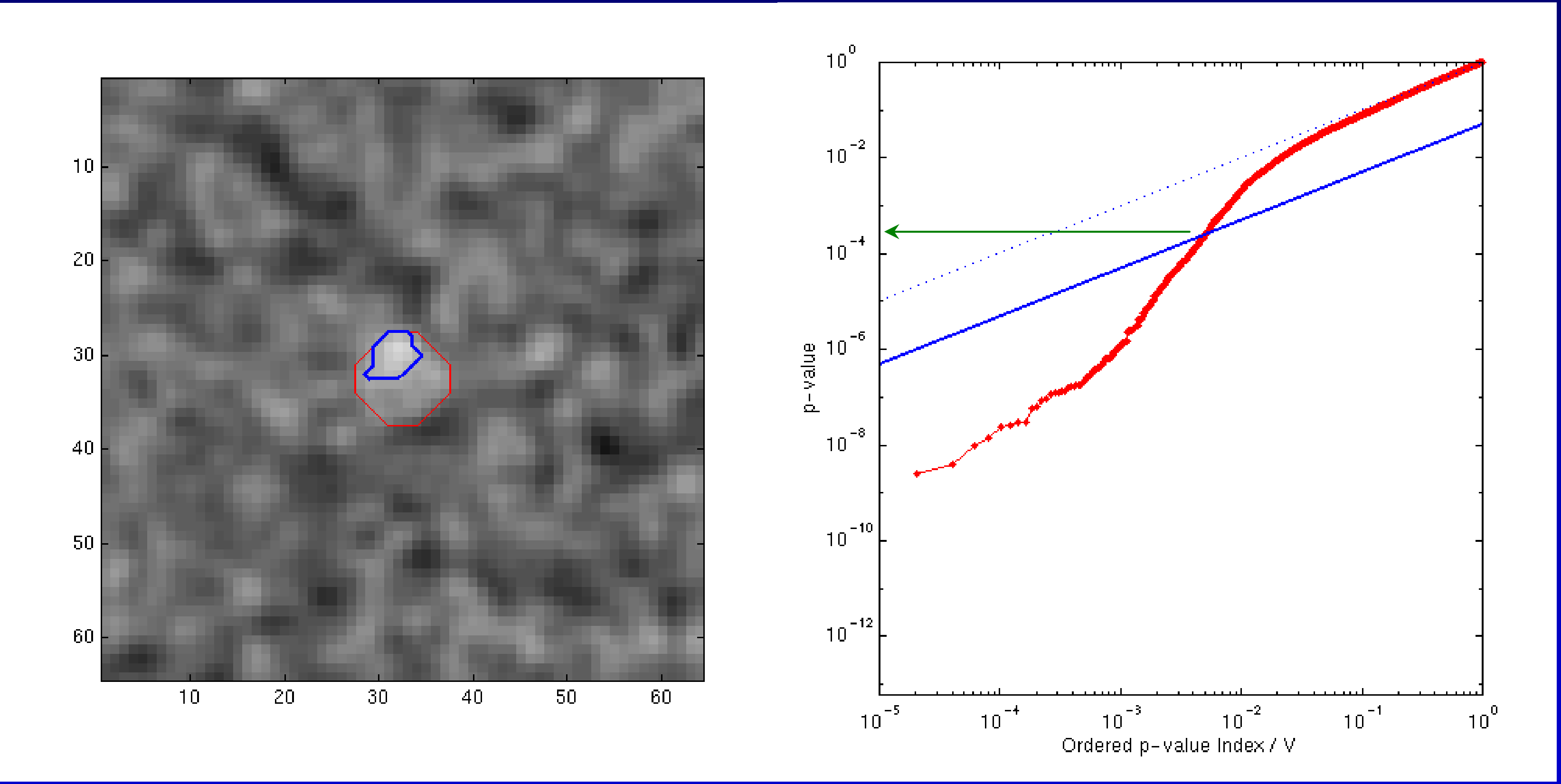
$p =$ $z =$



Signal Intensity 3.0 Signal Extent 3.0 Noise Smoothness 3.0

Controlling FDR: Varying Signal Extent

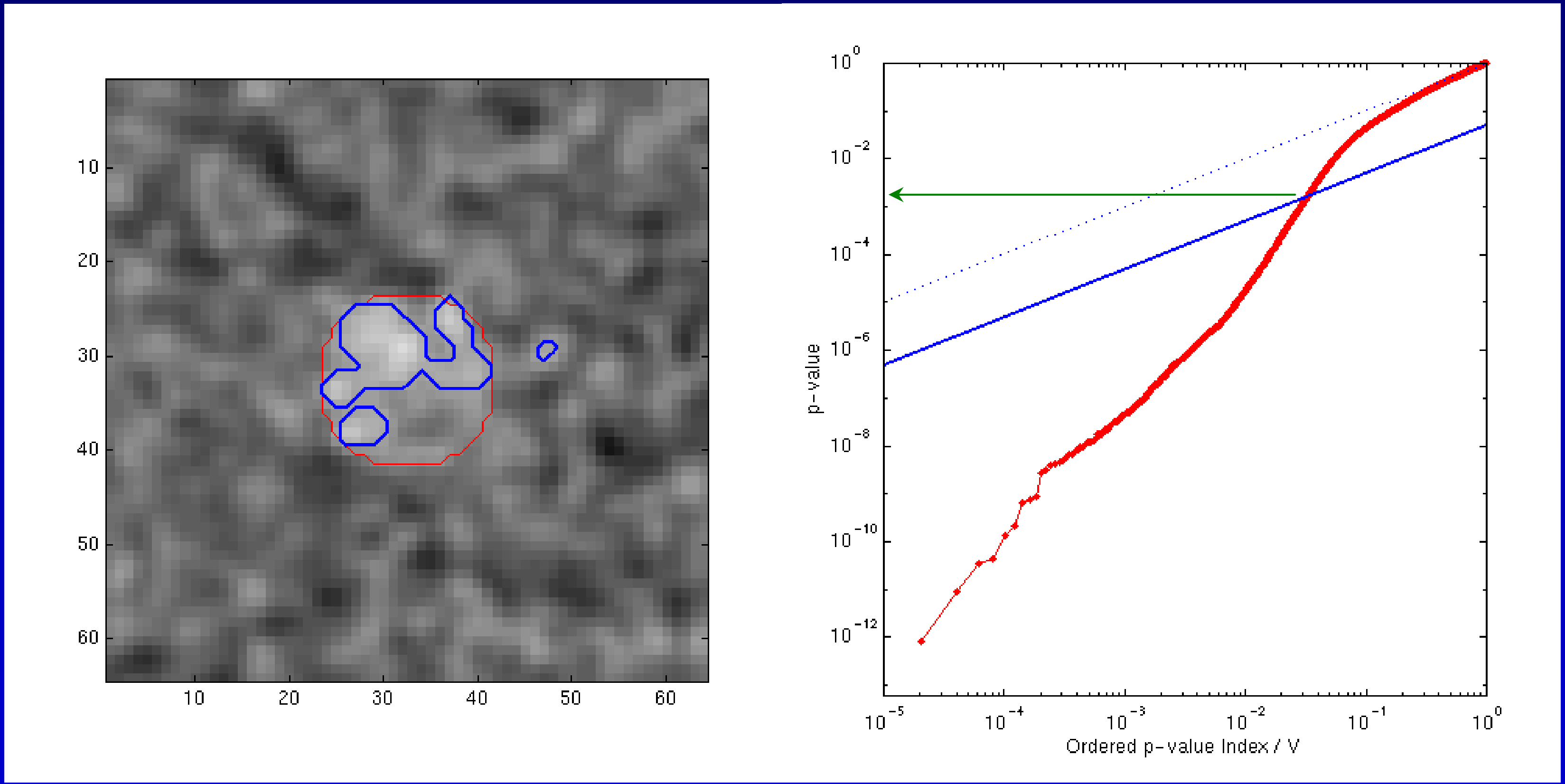
$p = 0.000252$ $z = 3.48$



Signal Intensity 3.0 Signal Extent 5.0 Noise Smoothness 3.0

Controlling FDR: Varying Signal Extent

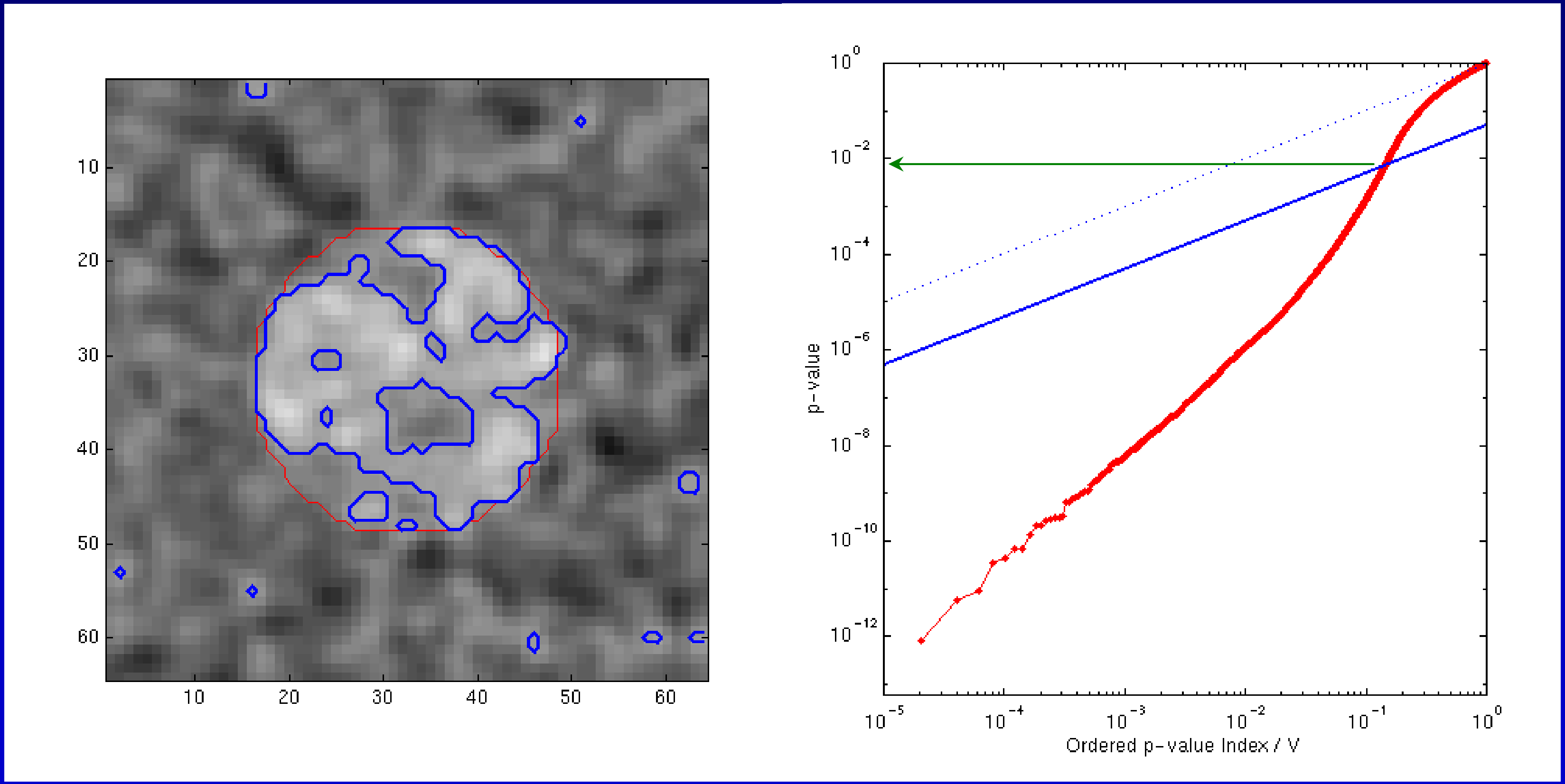
$p = 0.001628 \qquad z = 2.94$



Signal Intensity 3.0 Signal Extent 9.5 Noise Smoothness 3.0

Controlling FDR: Varying Signal Extent

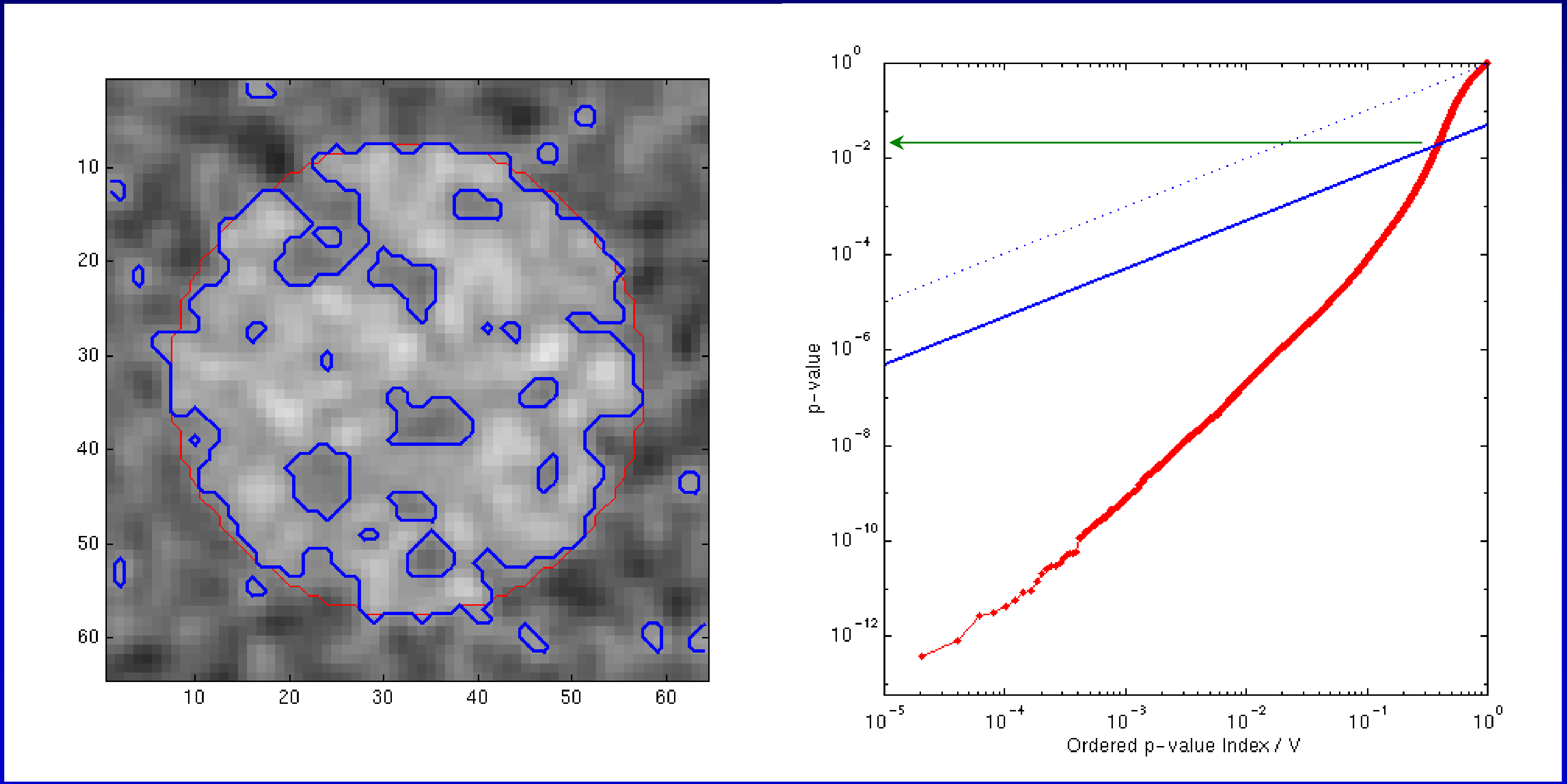
$p = 0.007157$ $z = 2.45$



Signal Intensity 3.0 Signal Extent 16.5 Noise Smoothness 3.0

Controlling FDR: Varying Signal Extent

$p = 0.019274 \qquad z = 2.07$

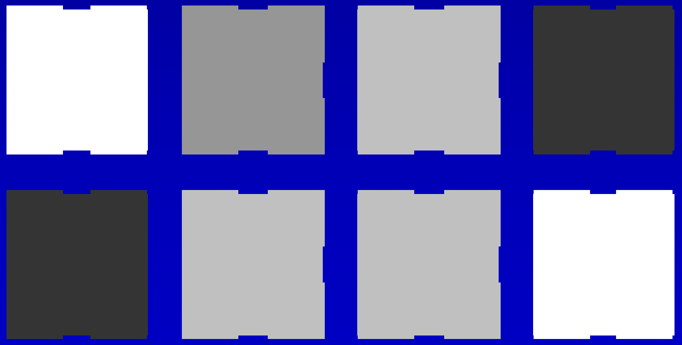


Signal Intensity 3.0 Signal Extent 25.0 Noise Smoothness 3.0

Controlling FDR: Benjamini & Hochberg

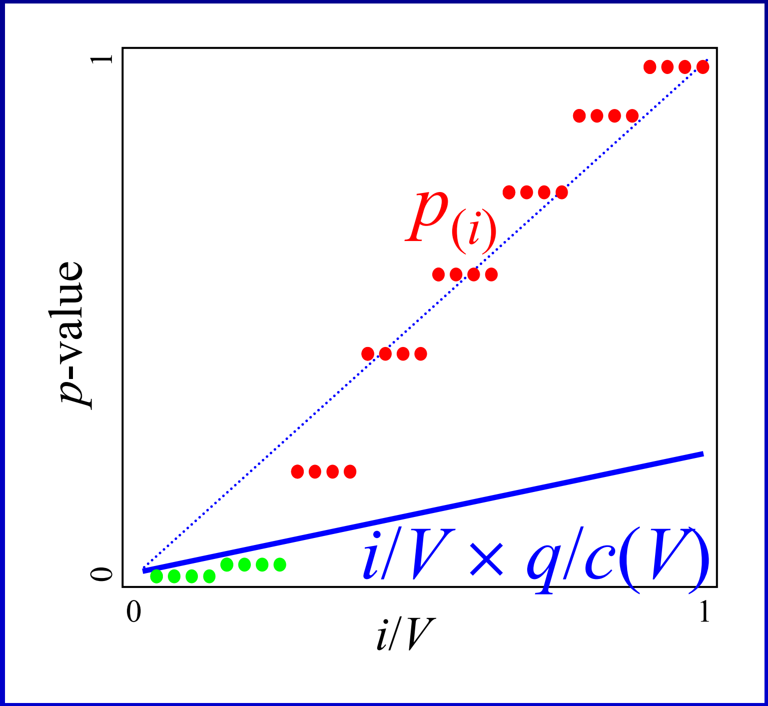
- Illustrating BH under dependence
  - Extreme example of positive dependence

8 voxel image



32 voxel image

(interpolated from 8 voxel image)

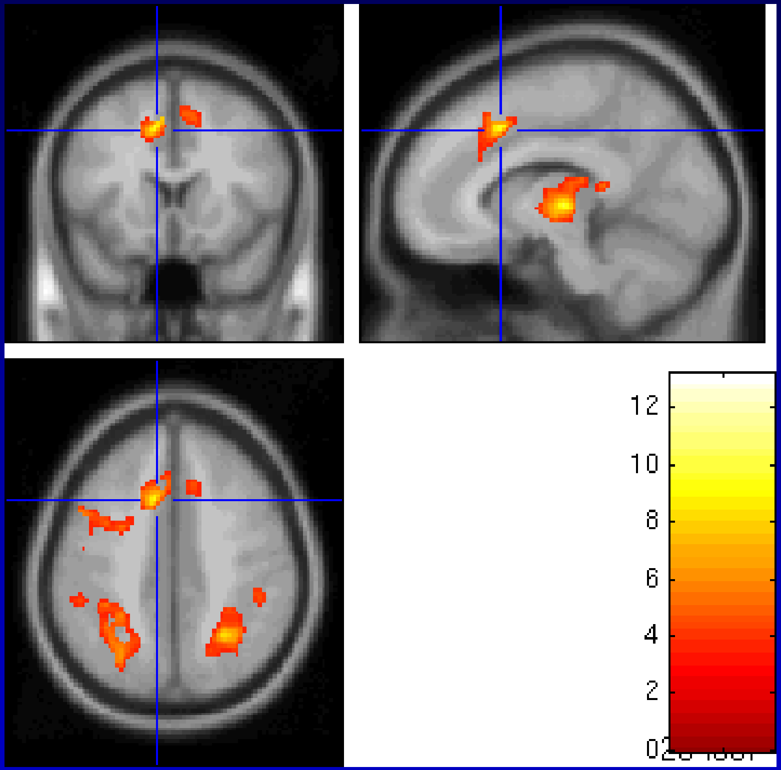


Other FDR Methods

- James Troendle *JSPI* (2000) 84:139-158
  - Normal theory FDR
    - More powerful than BH FDR
    - Requires numerical integration to obtain thresholds
  - Exactly valid if whole correlation matrix known
- John Storey *JRSS-B* (2002) 64:479-498
  - pFDR "Positive FDR"
    - FDR conditional on one or more rejections
    - Critical threshold is fixed, not estimated
    - pFDR and Emperical Bayes
  - Asymptotically valid under "clumpy" dependence

Real Data: FDR Example

- Threshold
  - Indep/PosDep
    $u = 3.83$
  - Arb Cov
    $u = 13.15$
- Result
  - 3,073 voxels above Indep/PosDep u
  - <0.0001 minimum FDR-corrected p-value



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

Conclusions

- Must account for multiplicity
  - Otherwise have a fishing expedition
- FWER
  - Very specific, not very sensitive
- FDR
  - Less specific, more sensitive
  - Sociological calibration still underway

References

- Most of this talk covered in these papers

TE Nichols & S Hayasaka, Controlling the Familywise Error Rate in Functional Neuroimaging: A Comparative Review. S*tatistical 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.