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

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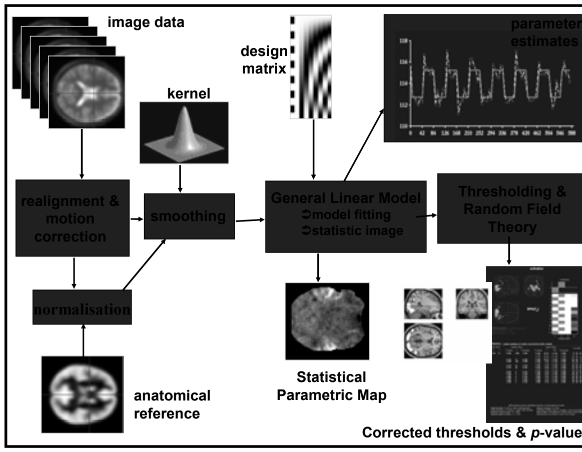
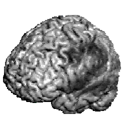


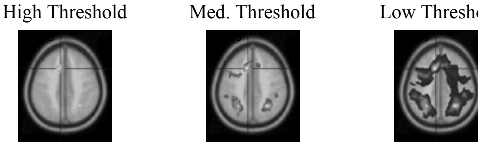
Assessing Statistic Images…



Assessing Statistic Images

Where's the signal?

High Threshold	Med. Threshold	Low Threshold

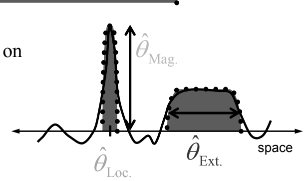


Good Specificity		Poor Specificity (risk of false positives)
Poor Power (risk of false negatives)		Good Power

...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

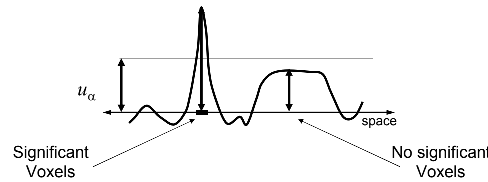
- Need an explicit spatial model
- No routine spatial modeling methods exist
  - High-dimensional mixture modeling problem
  - Activations don't look like Gaussian blobs
  - Need realistic shapes, sparse representation
    - Some work by Hartvig *et al.*, Penny *et al.*

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

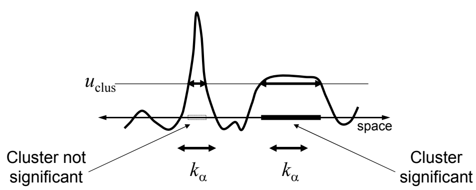
Voxel-level Inference

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



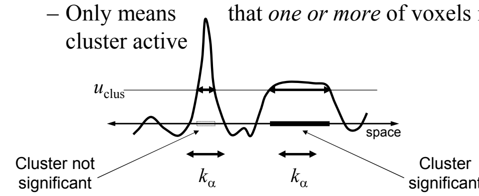
Cluster-level Inference

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



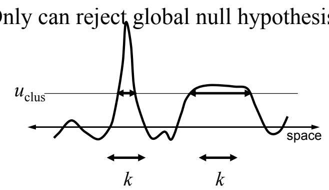
Cluster-level Inference

- 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



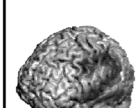
Set-level Inference

- 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

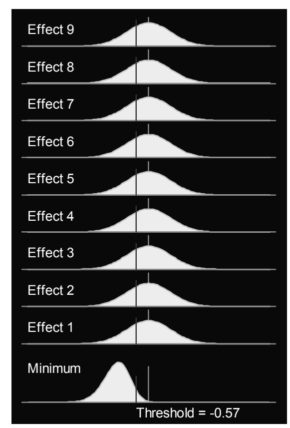
- Use the minimum of the K statistics
  - Idea: Only declare a conjunction if *all* of the statistics are sufficiently large
  - only when for all k
- References
  - SPM99, SPM2 (before patch)
  - Worsley, K.J. and Friston, K.J. (2000). A test for a conjunction. *Statistics and Probability Letters*,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

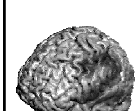
- Consider varying the number of effects tested...
- For K=9, only need all positive responses for this min test to reject!
  - Reason: Easy to reject the "No effects present" null



Valid Conjunction Inference With the Minimum Statistic

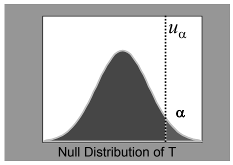
- For valid inference, compare min stat to u_α
  - Assess $\min_k T^k$ image as if it were just T^1
  - E.g. $u_{0.05}$=1.64 (or some corrected threshold)
- Correct Minimum Statistic P-values
  - Compare $\min_k T^k$ to usual, univariate null dist^n

Multiple comparisons…

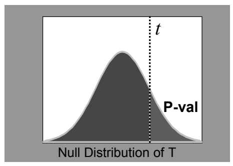


Hypothesis Testing

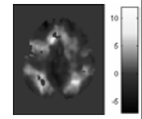
- Null Hypothesis H_0
- Test statistic T
  - t observed realization of T
- α level
  - Acceptable false positive rate
  - Level $\alpha = P(T>u_\alpha \mid H_0)$
  - Threshold u_α controls false positive rate at level α



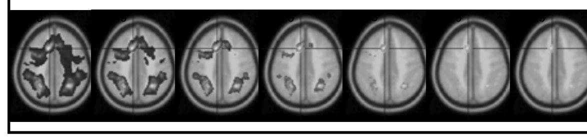
- P-value
  - Assessment of t assuming H_0
  - $P(T > t \mid H_0)$
    - Prob. of obtaining stat. as large or larger in a new experiment
  - P(Data|Null) *not* P(Null|Data)



Multiple Comparisons Problem



- Which of 100,000 voxels are sig.?
  - α=0.05 $\Rightarrow$ 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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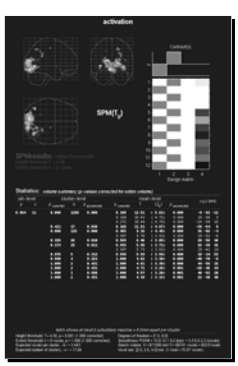
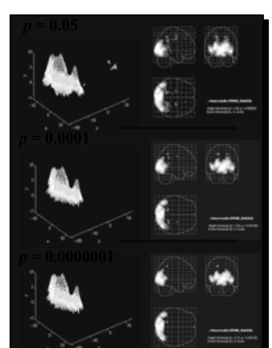
FWE Multiple comparisons terminology…

- *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("reject" $H^\Omega \mid H^\Omega) \le \alpha$
    - *"anything, anywhere" ?*
  - *strong* control – *localising test*
    - Pr("reject" $H^W \mid H^W) \le \alpha$
      $\forall$ 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
    $Pr(T^\Omega_{max} > u_\alpha \mid H^\Omega) \le \alpha$
  - strong control
    since $W \subseteq \Omega$
    $Pr(T^W_{max} > u_\alpha \mid H^W) \le \alpha$
- Adjusted *p* –values
  - $Pr(T^\Omega_{max} > t^k \mid H^\Omega)$

u_α?

FWE MCP Solutions: Bonferroni

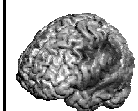
- For a statistic image T...
  - T_i i^{th} voxel of statistic image T
- ...use $\alpha = \alpha_0/V$
  - α_0 FWER level (e.g. 0.05)
  - V number of voxels
  - u_α α-level statistic threshold, $P(T_i \geq u_\alpha) = \alpha$
- By Bonferroni inequality...

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

Conservative under correlation

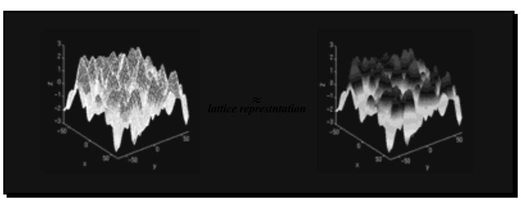
Independent:	V tests
Some dep.:	? tests
Total dep.:	1 test

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: Controlling FWER w/ Max

- FWER & distribution of maximum

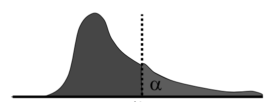
$$\begin{aligned}\text{FWER} &= P(\text{FWE}) \\ &= P(\cup_i \{T_i \geq u\} \mid H_o) \\ &= P(\max_i T_i \geq u \mid H_o)\end{aligned}$$

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

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

  - where

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

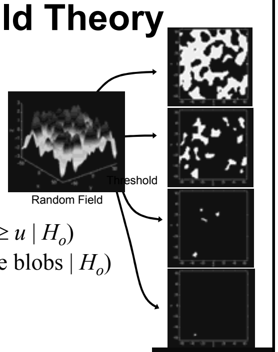


FWER MCP Solutions: Random Field Theory

- Euler Characteristic χ_u
  - Topological Measure
    - #blobs - #holes
  - At high thresholds, just counts blobs
  - FWER = P(Max voxel $\geq u \mid H_o$)
    - = P(One or more blobs $\mid H_o$)
    - $\approx P(\chi_u \geq 1 \mid H_o)$
    - $\approx E(\chi_u \mid H_o)$

No holes

Never more than 1 blob



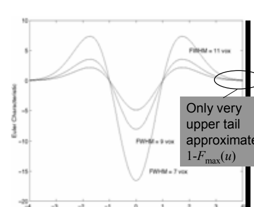
RFT Details: Expected Euler Characteristic

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

- Ω → Search region $\Omega \subset \mathbb{R}^3$
- $\lambda(\Omega)$ → 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

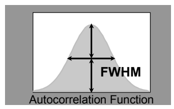


Random Field Theory Smoothness Parameterization

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

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

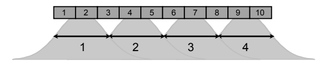
- Smoothness parameterized as Full Width at Half Maximum
  - FWHM of Gaussian kernel needed to smooth a white noise random field to roughness Λ



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

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.

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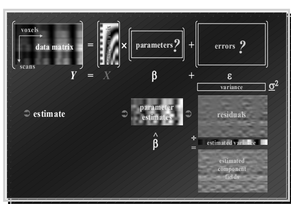
Random Field Theory Smoothness Estimation

- 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 = $(\text{RPV Img})^{-1/D}$
    - Dimension D, e.g. D=2 or 3



Random Field Intuition

- Corrected P-value for voxel value t

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

- 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 •

$$E[\chi_u(\Omega)] = \sum_d R_d(\Omega)\, \rho_d(u)$$

$R_d(\Omega)$: d-dimensional Minkowski functional of Ω

– *function of dimension, space Ω and smoothness:*

$R_0(\Omega) = \chi(\Omega)$ Euler characteristic of Ω
$R_1(\Omega)$ = resel diameter
$R_2(\Omega)$ = resel surface area
$R_3(\Omega)$ = resel volume

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

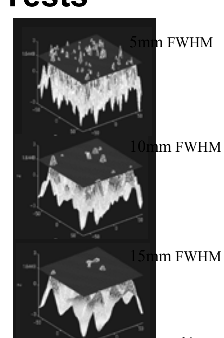
– *function of dimension and threshold, specific for RF type:*

E.g. Gaussian RF:

$\rho_0(u) = 1 - \Phi(u)$
$\rho_1(u) = (4\ln 2)^{1/2} \exp(-u^2/2) / (2\pi)$
$\rho_2(u) = (4\ln 2) \exp(-u^2/2) / (2\pi)^{3/2}$
$\rho_3(u) = (4\ln 2)^{3/2} (u^2 - 1) \exp(-u^2/2) / (2\pi)^2$
$\rho_4(u) = (4\ln 2)^2 (u^3 - 3u) \exp(-u^2/2) / (2\pi)^{5/2}$

Random Field Theory Cluster Size Tests

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



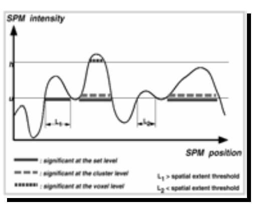
Random Field Theory
Cluster Size Distribution

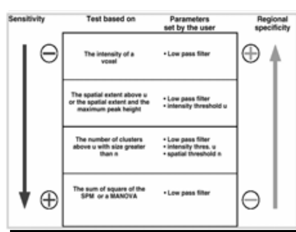
- Gaussian Random Fields (Nosko, 1969)
  - D: Dimension of RF
- t Random Fields (Cao, 1999)
  - *B*: Beta dist^n
  - *U*'s: χ^2's
  - *c* chosen s.t.
    E(*S*) = E(*N*) / E(*L*)

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 $P^c = E(L)\ P^{uncorr}$
  - Poisson Clumping Heuristic (Adler, 1980)
    - Corrected $P^c = 1 - \exp(-E(L)\ P^{uncorr})$

Review:
Levels of inference & power

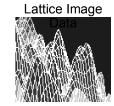




Random Field Theory
Limitations

- 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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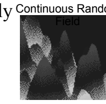
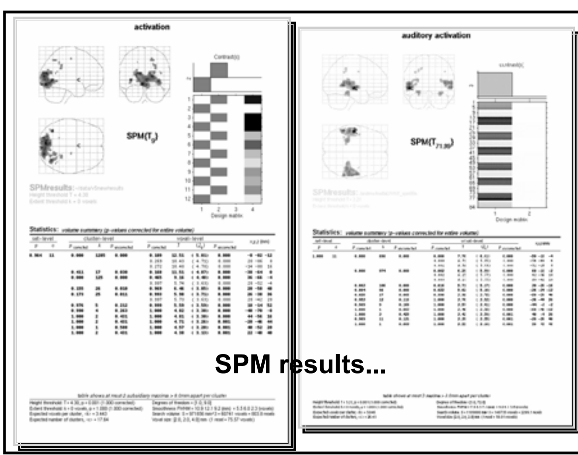
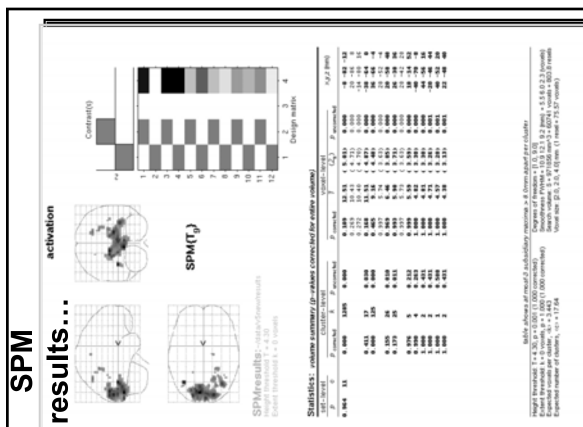
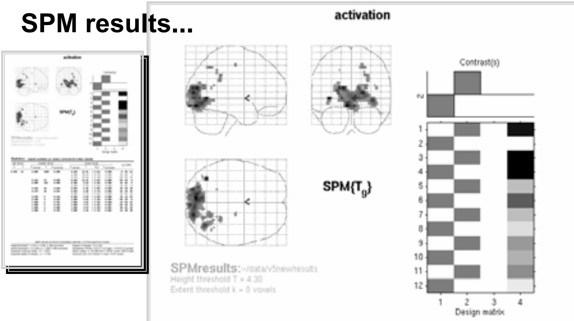
Continuous Random Field





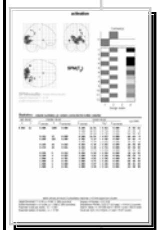


SPM results...



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

set-level p	c	cluster-level $P_{corrected}$	k	$P_{uncorrected}$	voxel-level $P_{corrected}$	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	0.160	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



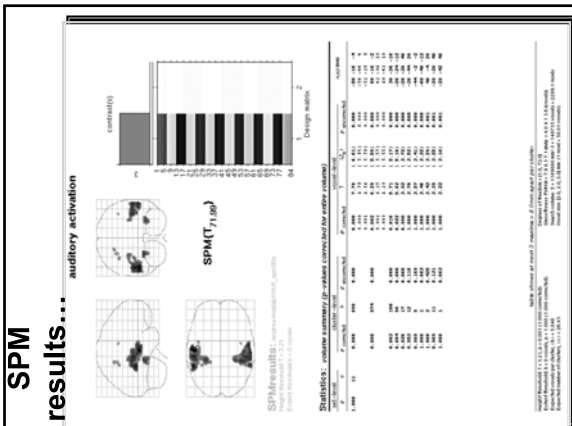
Statistics: *volume summary (p-values corrected for entire volume)*

set-level p	c	cluster-level $P_{corrected}$	k	$P_{uncorrected}$	voxel-level $P_{corrected}$	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	0.160	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	0.363	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

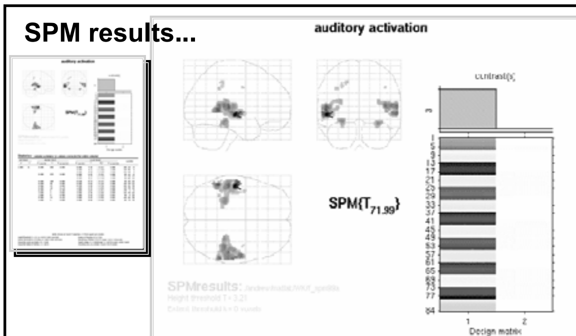
table shows at most 3 subsidiary maxima > 8.0mm apart per cluster

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...



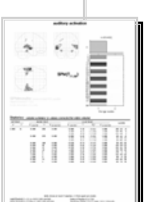
SPM results...



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

set-level p	c	cluster-level $P_{corrected}$	k	$P_{uncorrected}$	voxel-level $P_{corrected}$	T	$(Z_\equiv)$	$P_{uncorrected}$	x,y,z {mm}
1.000	11	0.000	898	0.000	0.000	7.74	(6.61)	0.000	-50 -18 -4
					0.000	6.71	(5.35)	0.000	-54 -41 4
					0.001	6.5?	(5.?)	0.000	-52 -28 8
		0.000	974	0.000	0.002	6.29	(5.59)	0.000	68 -18 -2
					0.002	6.21	(5.17)	0.000	42 -36 18
					0.003	6.01	(5.05)	0.000	60 -42 10

SPM results...



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

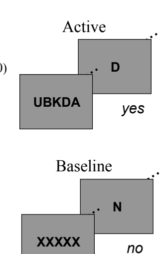
set-level p	c	cluster-level $P_{corrected}$	k	$P_{uncorrected}$	voxel-level $P_{corrected}$	T	$(Z_\equiv)$	$P_{uncorrected}$	x,y,z {mm}
1.000	11	0.000	898	0.000	0.000	7.74	(6.61)	0.000	-50 -18 -4
					0.000	6.71	(5.35)	0.000	-54 -41 4
					0.001	6.57	(5.?3)	0.000	-52 -28 8
		0.000	974	0.000	0.002	6.29	(5.59)	0.000	68 -18 -2
					0.002	6.21	(5.17)	0.000	42 -36 18
					0.003	6.01	(5.?3)	0.000	60 -42 10
		0.002	186	0.000	0.016	5.73	(5.17)	0.000	20 -28 -16
		0.004	58	0.000	0.022	5.65	(5.10)	0.000	-26 -34 -12
		0.020	17	0.000	0.990	3.96	(3.72)	0.000	-20 -20 40
		0.553	12	0.115	1.000	3.74	(3.52)	0.000	-36 -44 38
		0.989	5	0.169	1.000	2.87	(2.41)	0.000	-44 -2 -2
		1.000	1	0.663	1.000	3.44	(3.32)	0.000	-66 -40 -12
		1.000	2	0.429	1.000	2.42	(2.29)	0.001	40 -4 28
		0.565	11	0.131	1.000	3.34	(3.25)	0.001	-28 -28 40
		1.000	1	0.667	1.000	2.25	(2.10)	0.001	28 42 16

table shows at most 3 maxima > 2.0mm 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]
Search volume: S = 1109880 mm^3 = 140735 voxels = 2299.1 resels
Voxel size: [2.0, 2.0, 2.0] mm (1 resel = 58.01 voxels)

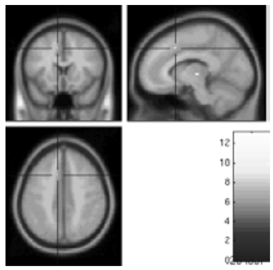
Real Data

- 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

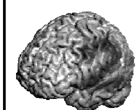


Real Data: RFT Result

- Threshold
  - S = 110,776
  - 2 × 2 × 2 voxels
    5.1 × 5.8 × 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

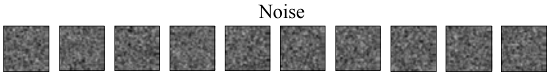
$$rFDR = V_{0R}/(V_{1R}+V_{0R}) = V_{0R}/N_R$$

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

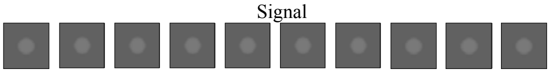
$$FDR = E(rFDR)$$

False Discovery Rate Illustration:

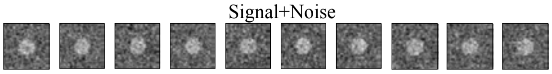
Noise



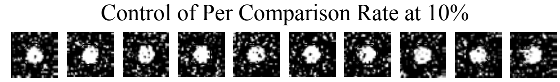
Signal



Signal+Noise



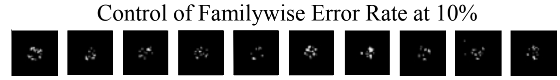
Control of Per Comparison Rate at 10%



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

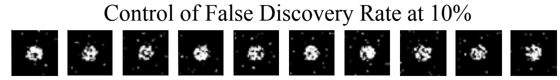
Percentage of Null Pixels that are False Positives

Control of Familywise Error Rate at 10%



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

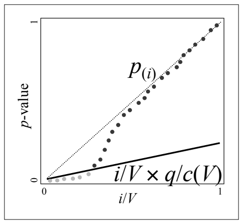
Benjamini & Hochberg Procedure

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

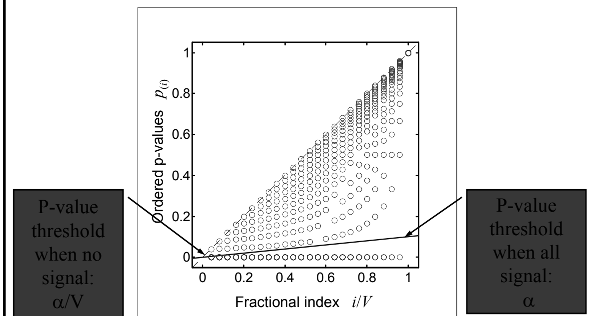
JRSS-B (1995) 57:289-300

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

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



Adaptiveness of Benjamini & Hochberg FDR



Benjamini & Hochberg Procedure Details

- $c(V) = 1$
  - Positive Regression Dependency on Subsets
    $P(X_1 \ge c_1, X_2 \ge c_2, \ldots, X_k \ge c_k \mid X_i = x_i)$ 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

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Benjamini & Hochberg: Key Properties

- FDR is controlled
  $$E(\text{rFDR}) \le q\ m_0/V$$
  - 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 $i/V \times q/c(V)$

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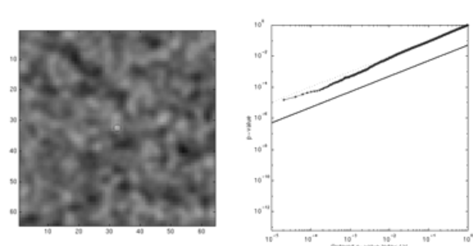
Controlling FDR: Varying Signal Extent

$p =$ $z =$



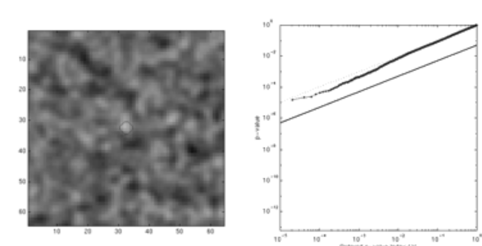
Signal Intensity 3.0 Signal Extent 1.0 Noise Smoothness 3.0

59

1

Controlling FDR: Varying Signal Extent

$p =$ $z =$



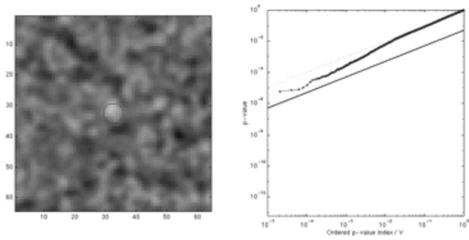
Signal Intensity 3.0 Signal Extent 2.0 Noise Smoothness 3.0

60

2

Controlling FDR: Varying Signal Extent

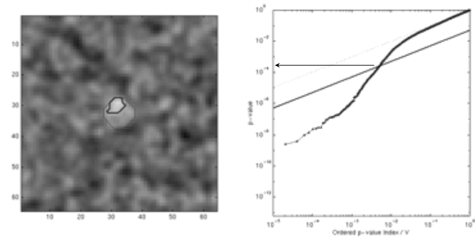
p = *z* =



Signal Intensity 3.0 Signal Extent 3.0 Noise Smoothness 3.0

Controlling FDR: Varying Signal Extent

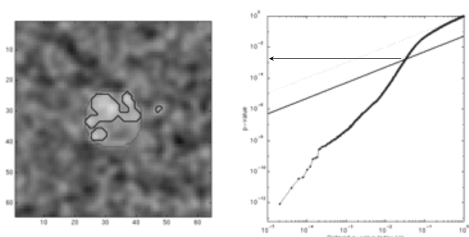
$p = 0.000252$ $z = 3.48$



Signal Intensity 3.0 Signal Extent 5.0 Noise Smoothness 3.0

Controlling FDR: Varying Signal Extent

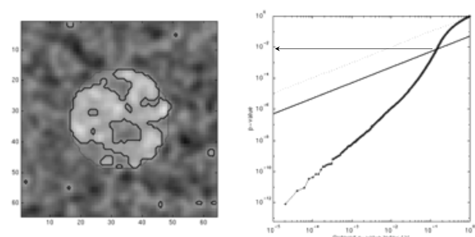
$p = 0.001628$ $z = 2.94$



Signal Intensity 3.0 Signal Extent 9.5 Noise Smoothness 3.0

Controlling FDR: Varying Signal Extent

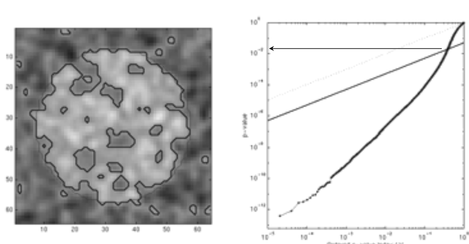
$p = 0.007157$ $z = 2.45$



Signal Intensity 3.0 Signal Extent 16.5 Noise Smoothness 3.0

Controlling FDR: Varying Signal Extent

$p = 0.019274$ $z = 2.07$

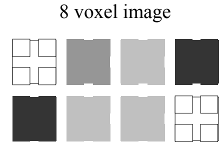


Signal Intensity 3.0 Signal Extent 25.0 Noise Smoothness 3.0

Controlling FDR: Benjamini & Hochberg

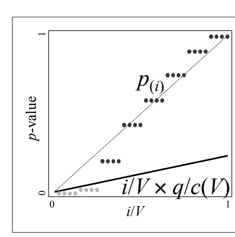
- Illustrating BH under dependence
  - Extreme example of positive dependence

8 voxel image



32 voxel image

(interpolated from 8 voxel image)

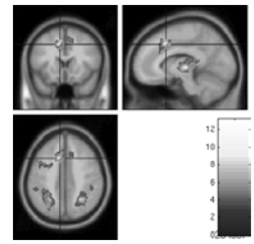


Other FDR Methods

- 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.