New and best-practice approaches to thresholding

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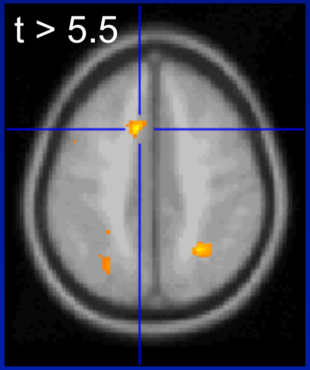
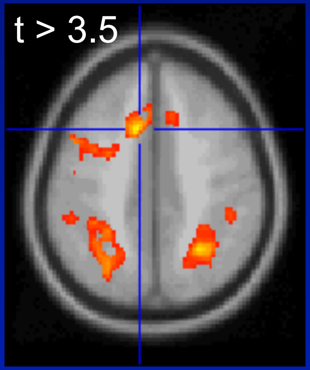
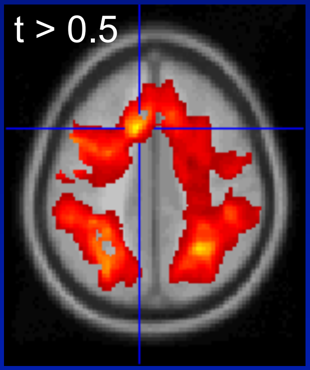
FIL SPM Course
17 May, 2012

Overview

- Why threshold?
- Assessing statistic images
- Measuring false positives
- Practical solutions

Thresholding

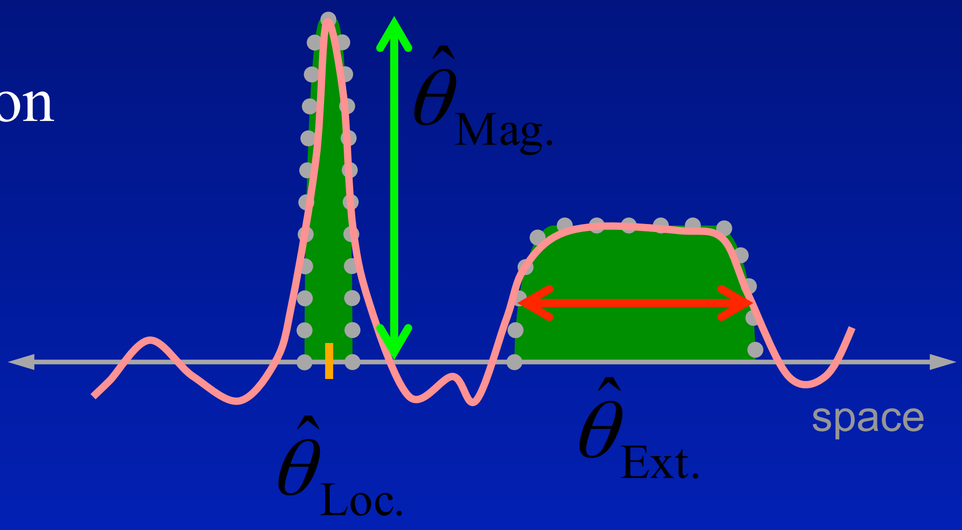
Where's the signal?

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

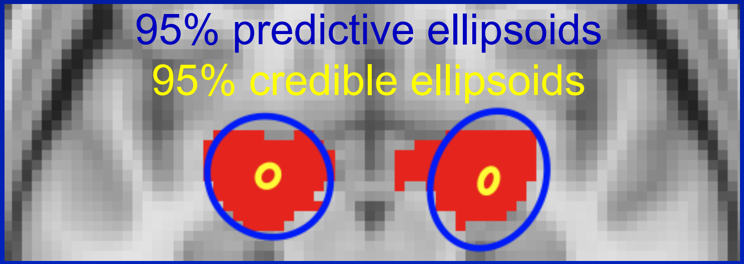
- Don't threshold, model the signal!
  - Signal location?
    - Estimates and CI's on (x,y,z) location
  - Signal magnitude?
    - CI's on % change
  - Spatial extent?
    - Estimates and CI's on activation volume
    - Robust to choice of cluster definition



- ...but this requires an explicit spatial model

Blue-sky inference: What we need

- Explicit spatial models
  - No routine methods exist
    - High-dimensional mixture modeling problem
    - Activations don't look like Gaussian blobs
- Some encouraging initial efforts…



Kang et al. (2011). *JASA* 106:124-134.

Gershman et al. (2011). *NI*, 57(1), 89-100.
Thirion et al. (2010). *MICCAI*, 13(2):241-8.
Kim et al. (2010). *IEEE TMI*, 29:1260-74.
Weeda et al. (2009). *HBM*, 30:2595-605.
Neumann et al. (2008). HBM, 29:177-92.

  - **ADVT:** Thur, 8:30, Ballroom AB, Level 1

    "Where's Your Signal? Explicit Spatial Models to Improve Interpretability and Sensitivity of Neuroimaging Results"

Real-life inference: What we get (typically)

- 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

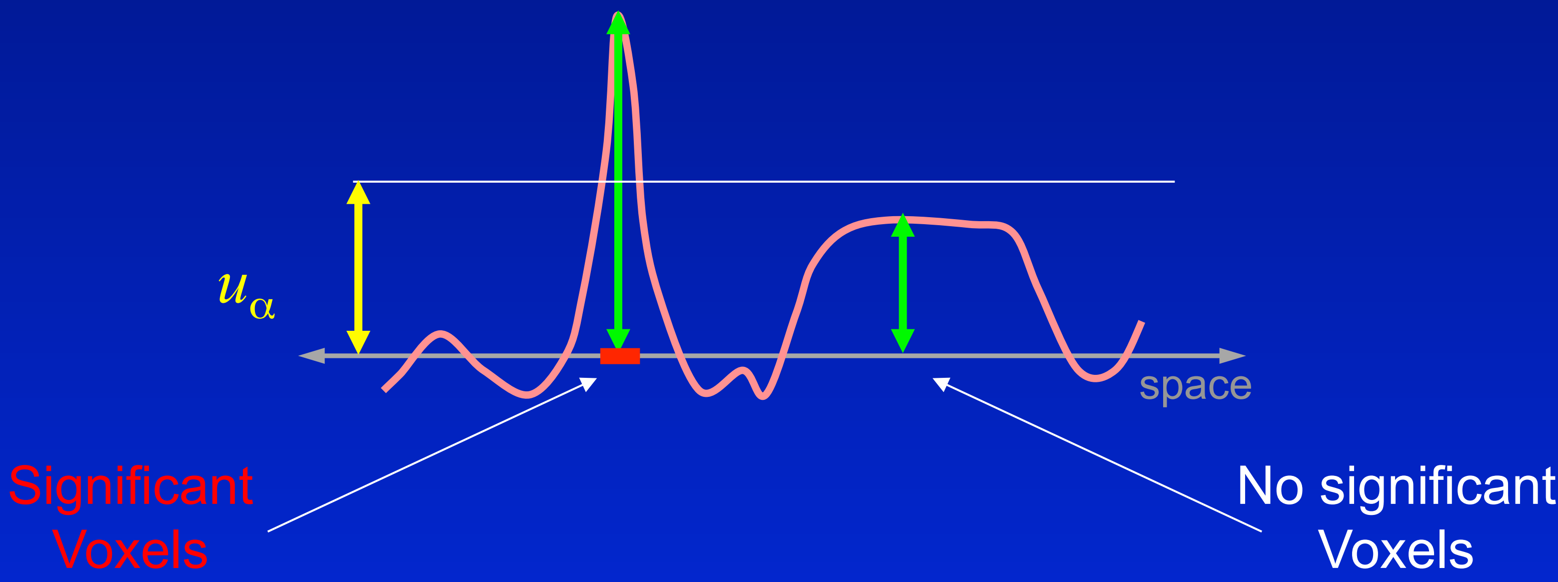
Assessing Statistic Images…

Ways of assessing statistic images

- Standard methods
  - Voxel
  - Cluster
  - Set
  - Peak (new)

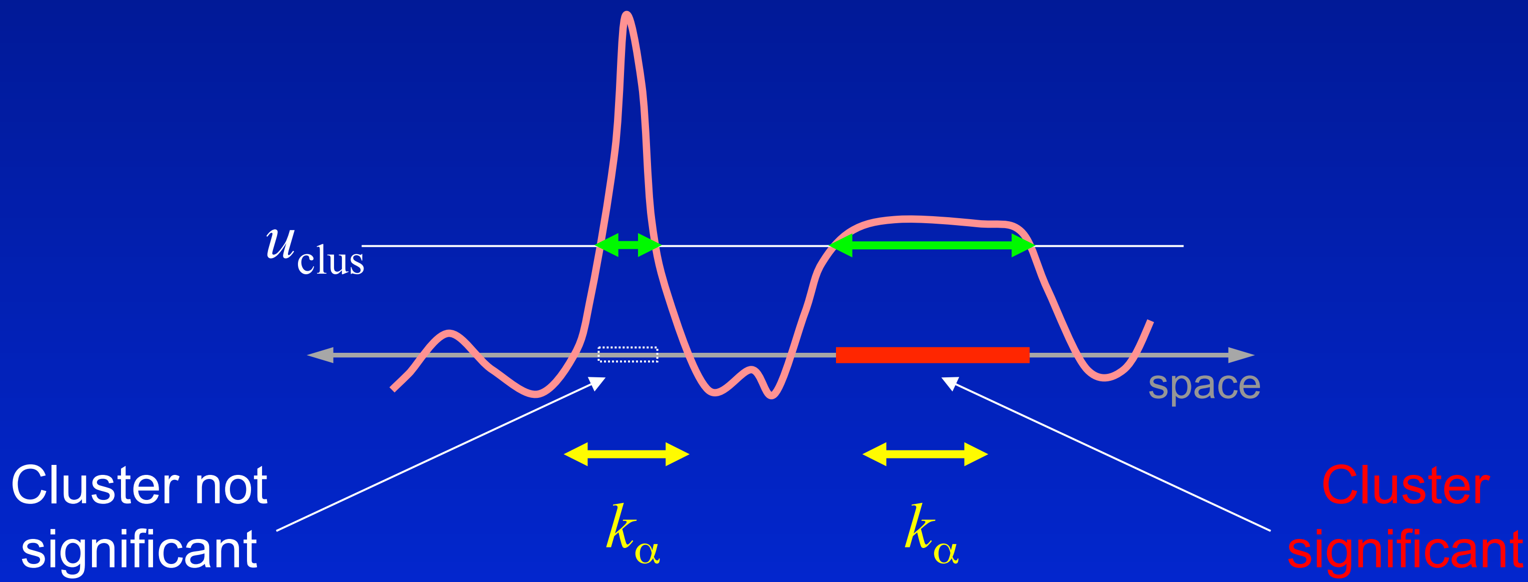
Voxel-level Inference

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



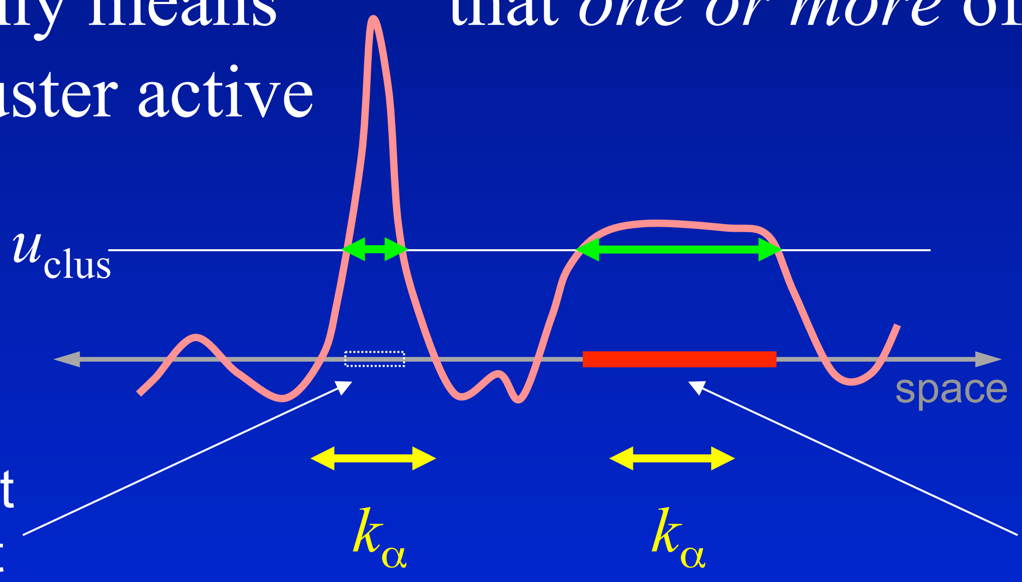
Cluster-level Inference

- 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

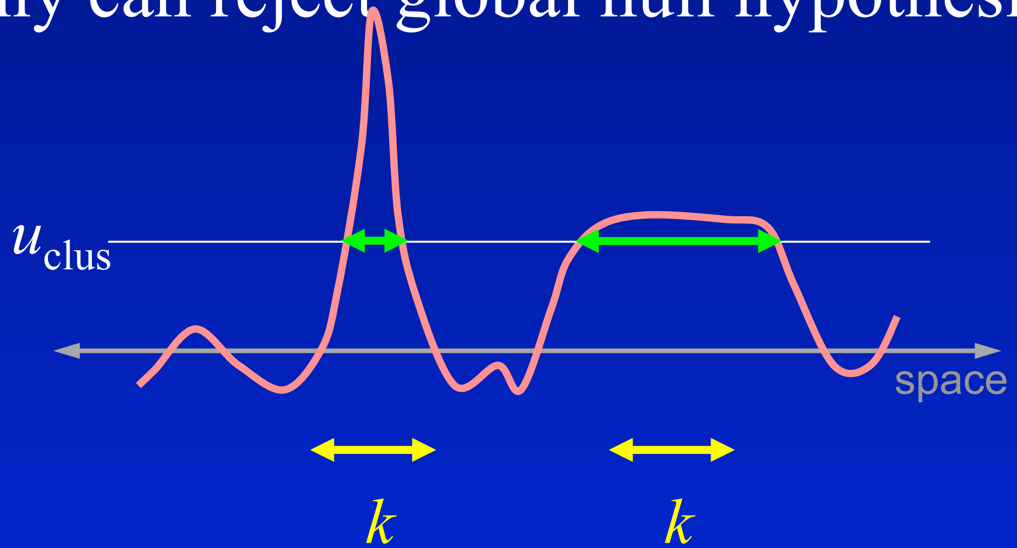


Cluster not significant

Cluster significant

Set-level Inference

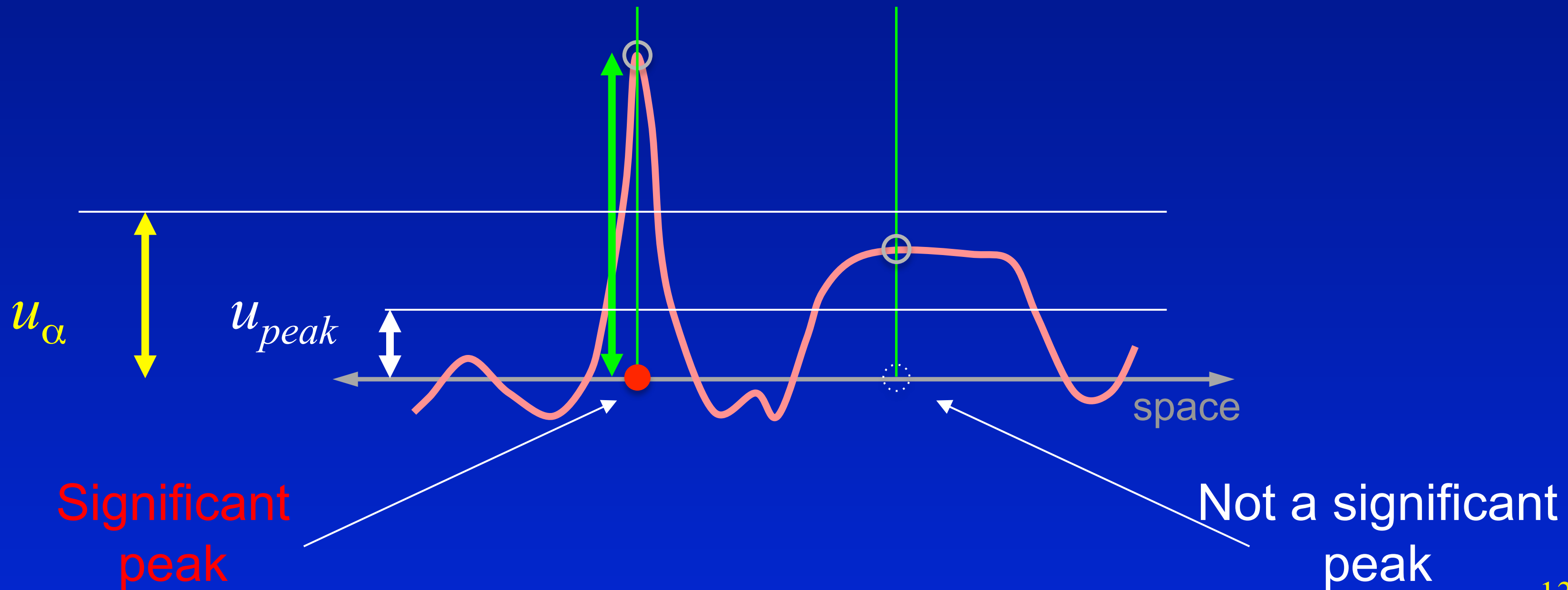
- Count number of blobs c
  - Minimum blob size k
- Worst spatial specificity
  - Only can reject global null hypothesis



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

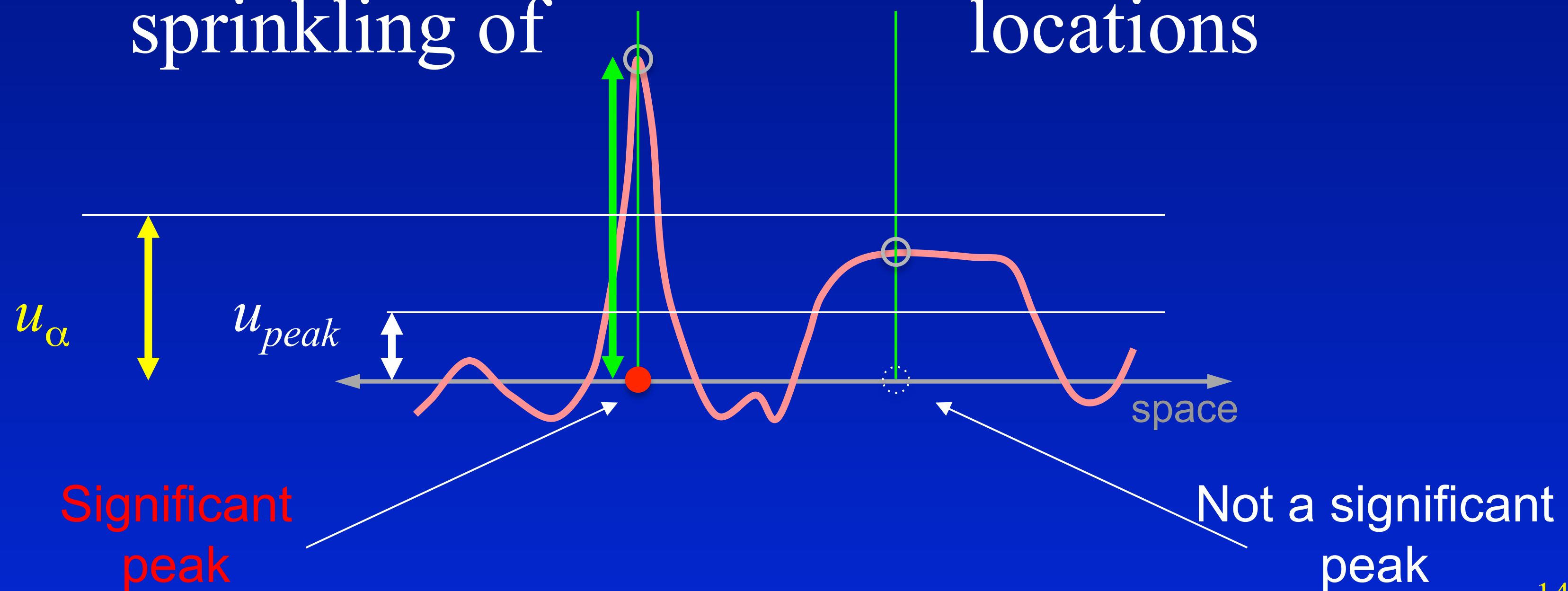
Peak-level Inference

- Identify all the local maxima
  - Ignore all smaller than u_{peak}
- Retain peaks by height



Peak-level Inference

- "Topological inference" – interpretable with boundless Point Spread Function (see Chumbley & Friston, NI, 2009)
- Cumbersome – only making inference at a sprinkling of locations



Test Statistics for Assessing Statistic Images…

Sometimes, Different Possible Ways to Test…

Image Feature	Test Statistic
Voxel	1. Statistic image value
Cluster	1. Cluster size in voxels 2. Cluster size in RESELs 3. Combination, Joint Peak-Cluster 4. Combination, Cluster Mass 5. Combination, Threshold-Free Cluster Enhancement
Set	1. Cluster count
Peak	1. Statistic image value

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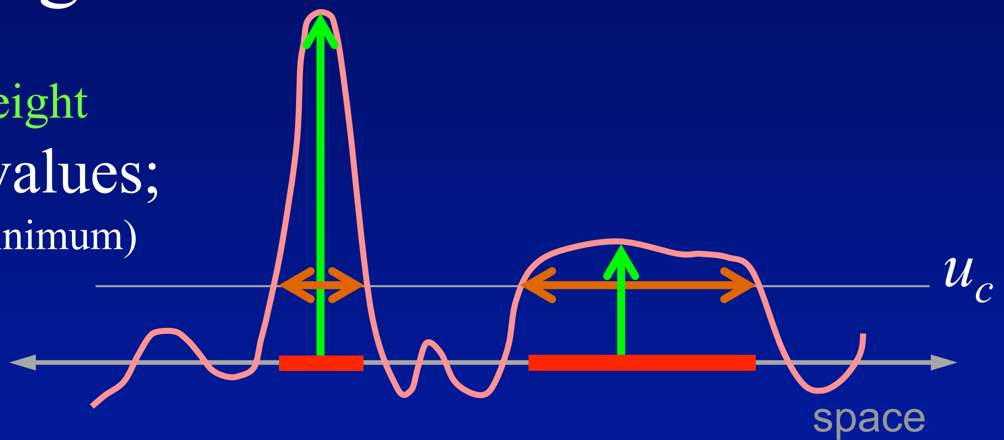
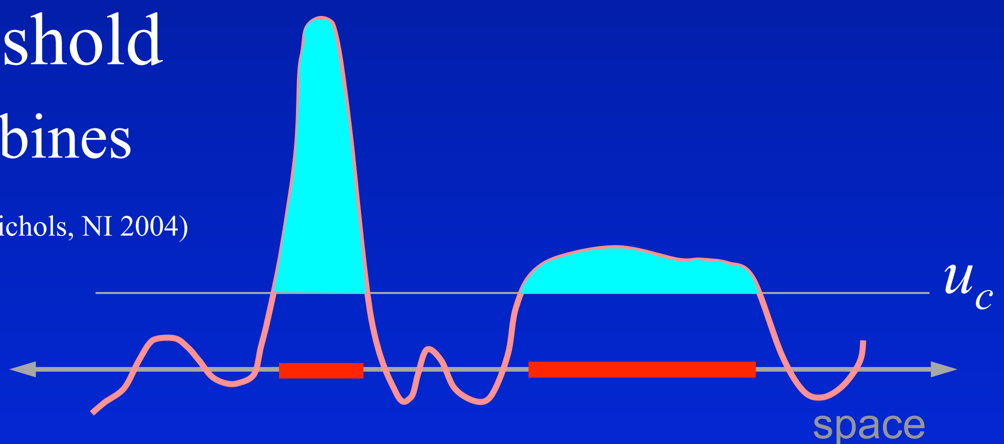
Combining Cluster Size with Intensity Information

- Peak-Height combining Poline *et al.*, NeuroImage 1997
  - Minimum P_{extent} & P_{height}
    - Take better of two P-values; (use RFT to correct for taking minimum)
  - Can catch small, intense clusters



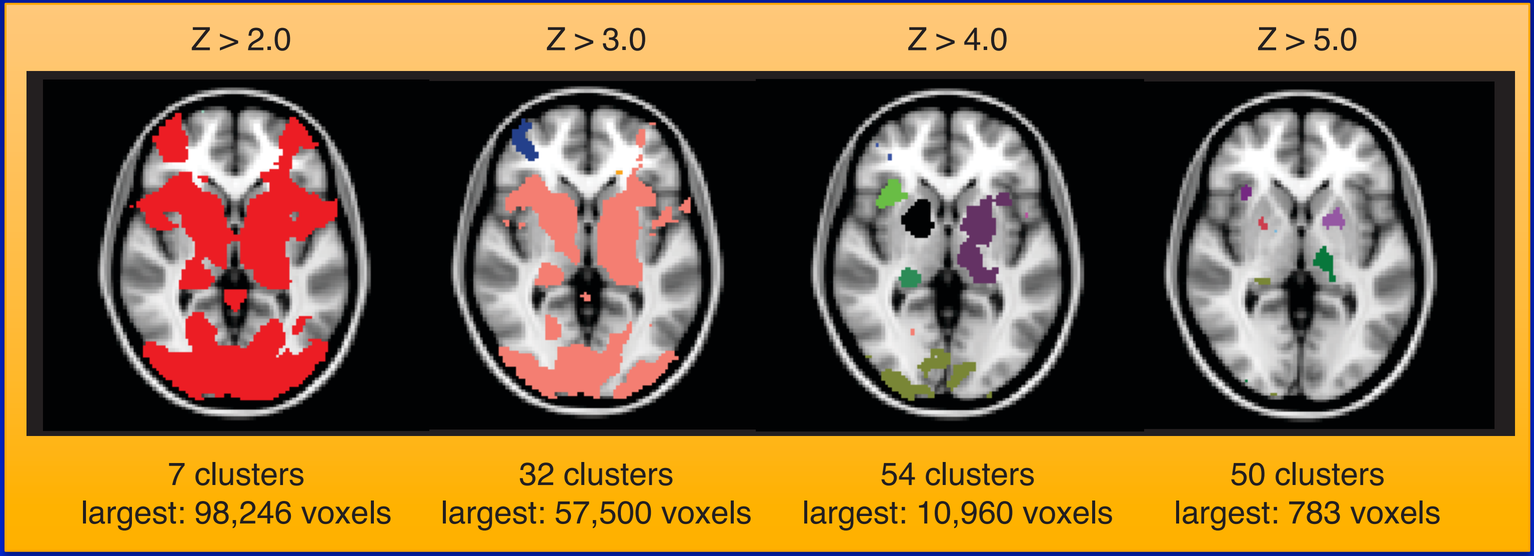
- Cluster mass Bullmore *et al.*, IEEE Trans Med Img 1999
  - Integral M above threshold
    - More powerfully combines peak & height (Hayasaka & Nichols, NI 2004)



- Both are still cluster inference methods!

The Pesky Cluster Forming Threshold u_c

- Cluster inference is highly sensitive to cluster-forming threshold u_c
  - Set too low, one big blob
  - Set too high, miss all the signal

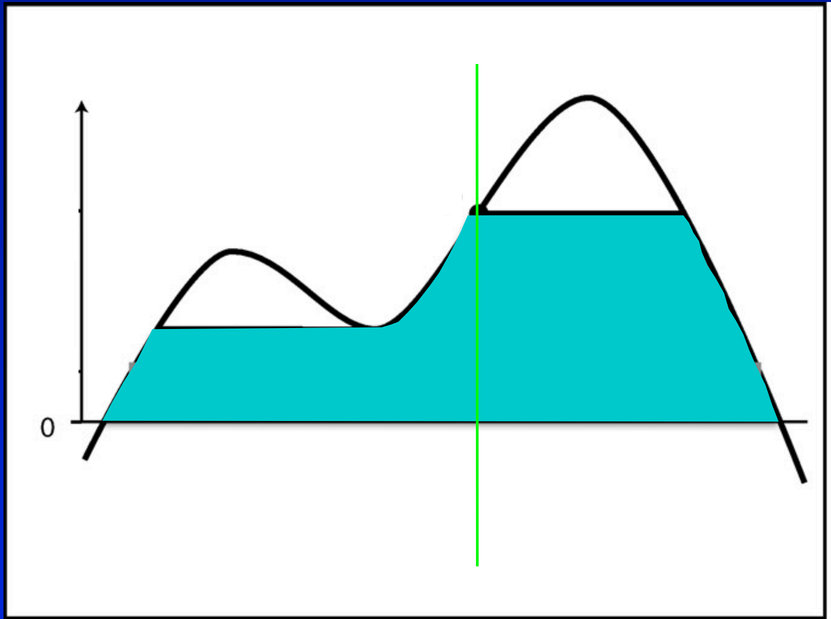


Threshold-Free Cluster Enhancement (TFCE)

- A cluster-informed voxel-wise statistic

Smith & Nichols, NI 2009

- Consider cluster mass voxel-wise, for every u_c!
  - For a given voxel, sum up all clusters 'below'
    - For all possible u_c, add up all clusters that contain that voxel
  - But this would give low u_c's too much weight
    - Low u_c's give big clusters just by chance



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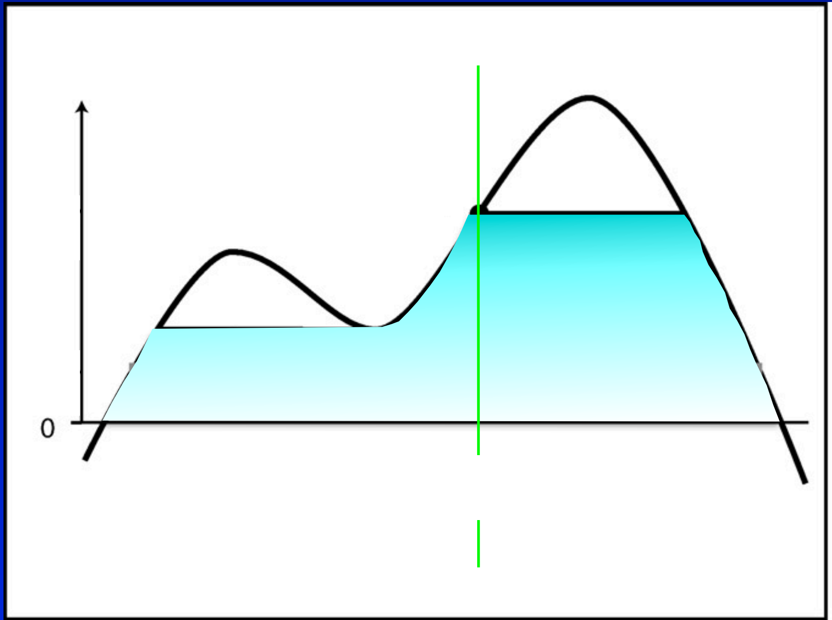
    - Low u_c's give big clusters just by chance
- Solution: Down-weight according to u_c !

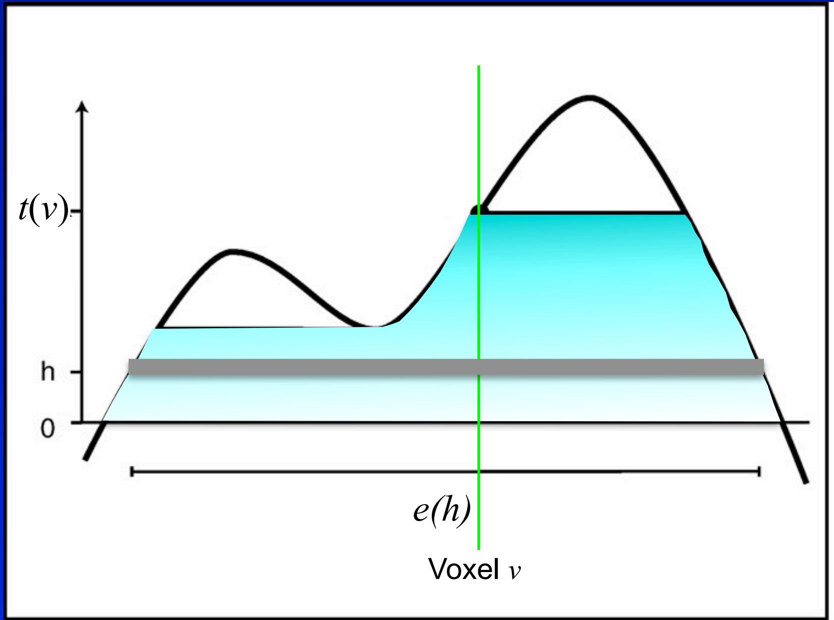


Threshold-Free Cluster Enhancement (TFCE)

- TFCE Statistic for voxel *v*

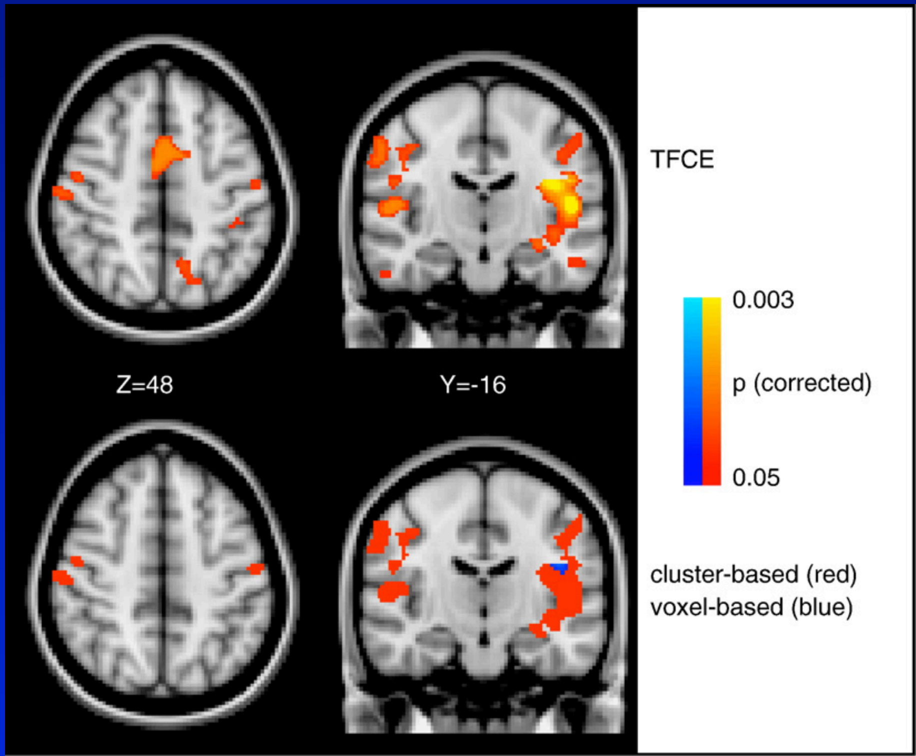
$$TFCE(v) = \int_0^{t(v)} h^H e(h)^E dh \approx \sum_{0,\delta,2\delta,\ldots,t(v)} h^H e(h)^E \delta$$

- Parameters H & E control balance between cluster & height information
  - H=2 & E=1/2 as motivated by theory



TFCE Redux

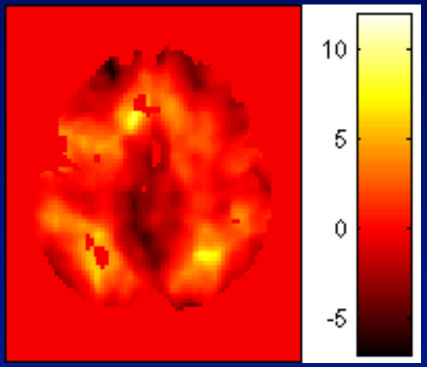
- Avoids choice of cluster-forming threshold u_c
- Generally more sensitive than cluster-wise
- But yet less specific
  - Inference is on some cluster for some u_c
  - "Support" of effect could extend far from significant voxels
- Implementation
  - Currently only FSL's randomise



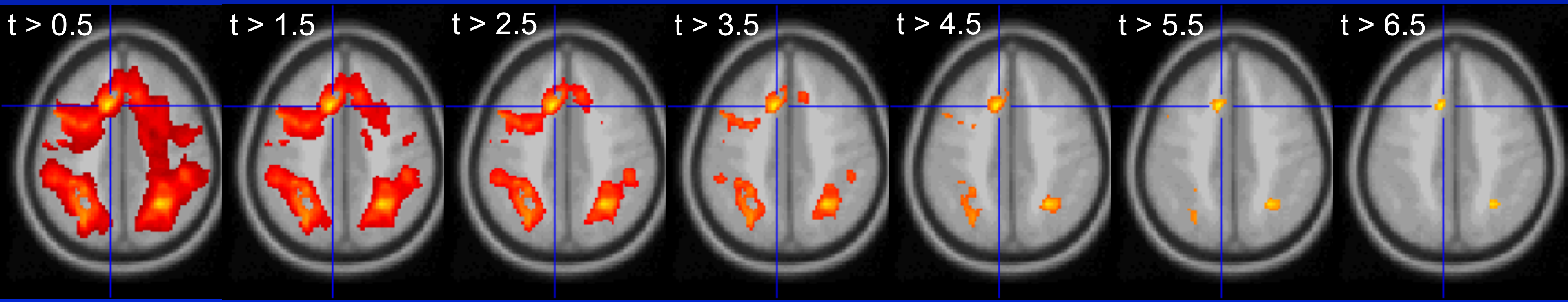
Multiple comparisons…

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

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 ≥ u | H_o)

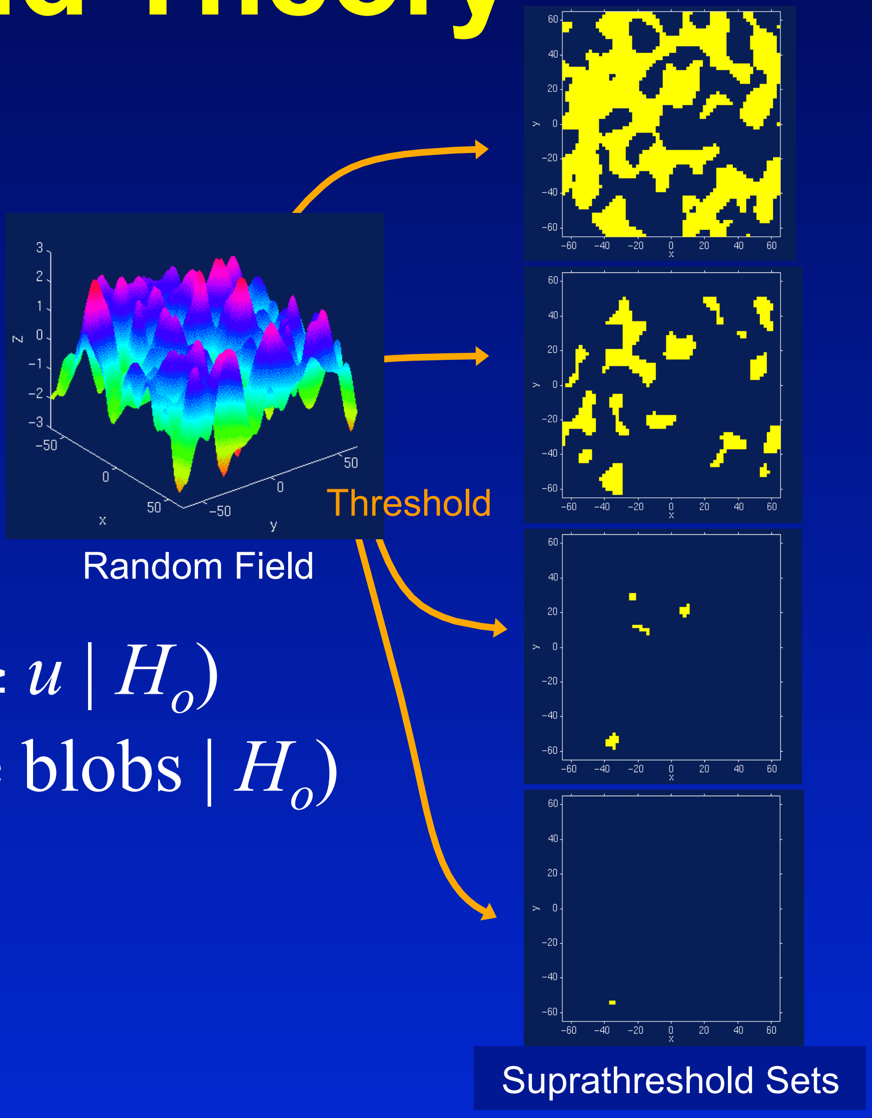
No holes

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

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

Never more than 1 blob

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

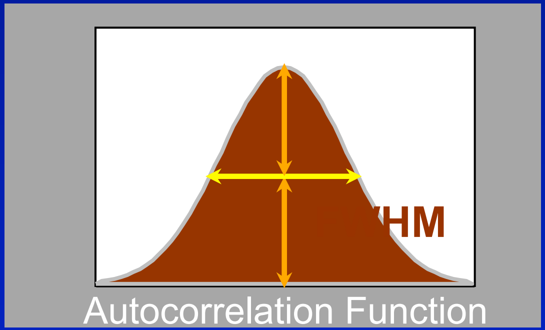


Random Field Theory Smoothness Parameterization

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

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

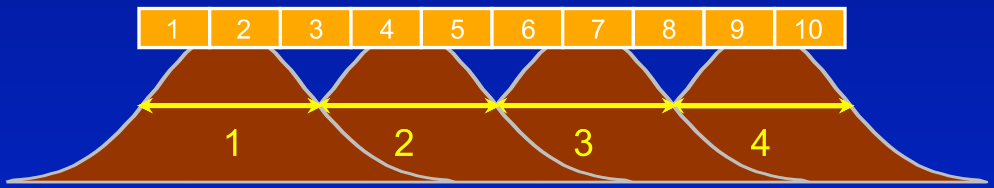
- Smoothness parameterized as **F**ull **W**idth at **H**alf **M**aximum
  - FWHM of Gaussian kernel needed to smooth a white noise random field to roughness Λ



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

Random Field Theory Smoothness Parameterization

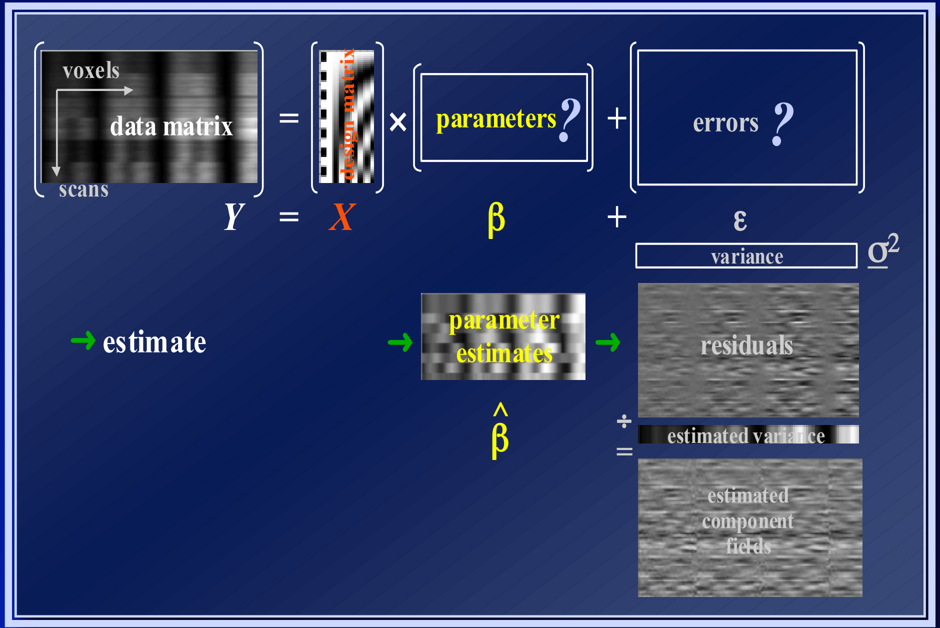
- RESELS
  - **Res**olution **El**ements
  - 1 RESEL = $\text{FWHM}_x \times \text{FWHM}_y \times \text{FWHM}_z$
  - RESEL Count R
    - $R = \lambda(\Omega)\sqrt{|\Lambda|} = (4\log 2)^{3/2}\,\lambda(\Omega) \;/\; (\text{FWHM}_x \times \text{FWHM}_y \times \text{FWHM}_z)$
    - Volume of search region 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

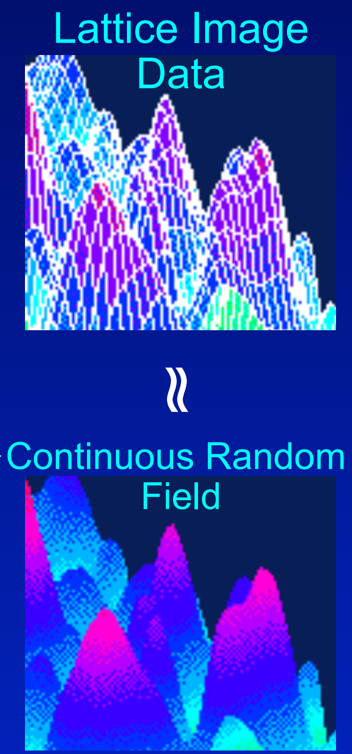
- Smoothness est'd from standardized residuals
  - Variance of gradients
  - Yields resels per voxel (RPV)
- RPV image
  - Local roughness est.
  - Can transform in to local smoothness est.
    - FWHM Img = (RPV Img)$^{-1/D}$
    - Dimension D, e.g. D=2 or 3
- Est. smoothness also needed for AlphaSim




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

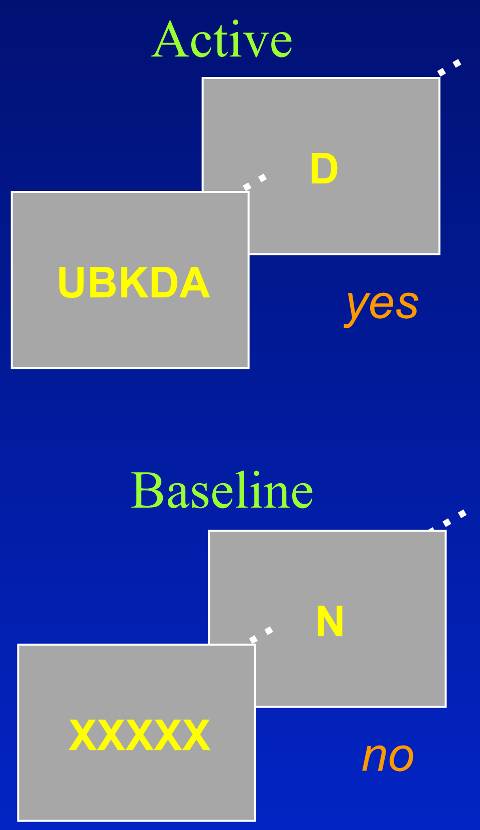
Random Field Theory Limitations

- 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



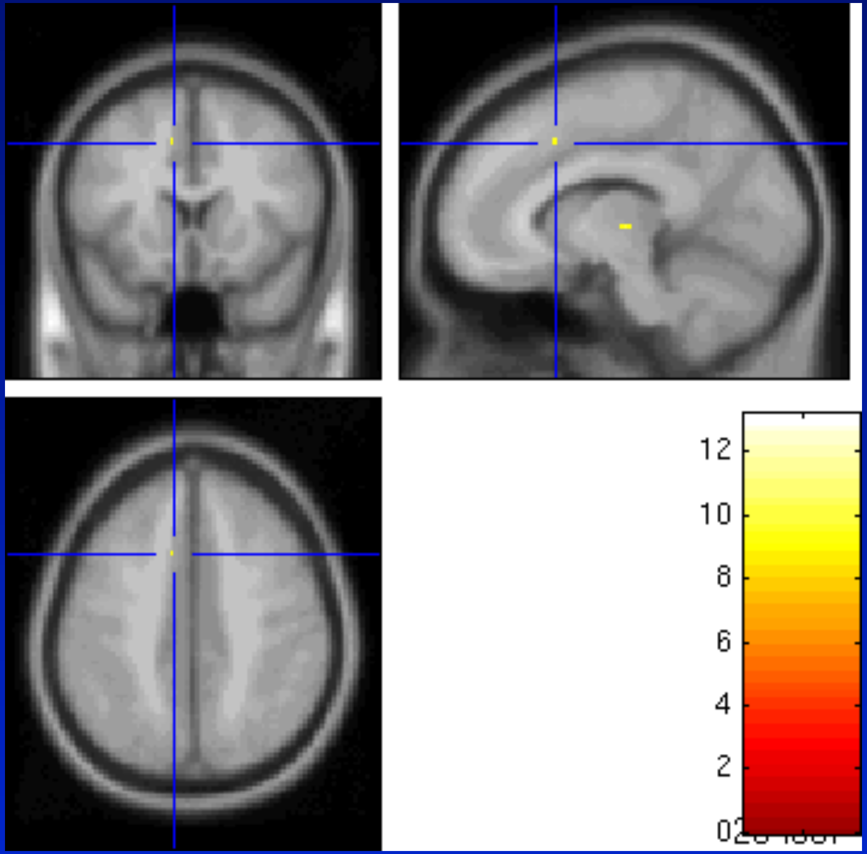
Real Data

- 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

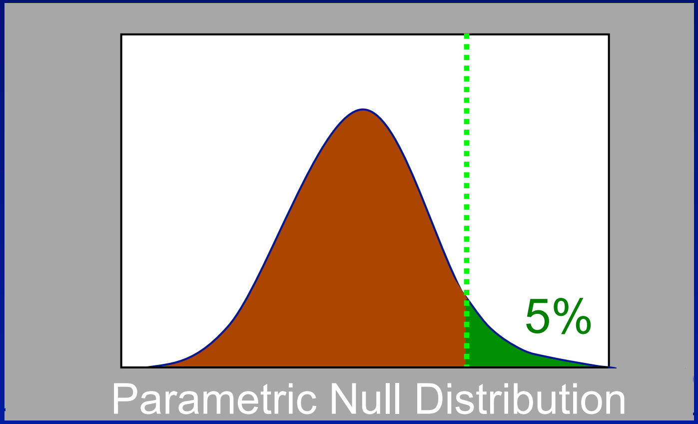
- Threshold
  - $S = 110{,}776$
  - $2 \times 2 \times 2$ voxels
    $5.1 \times 5.8 \times 6.9$ mm
    FWHM
  - $u = 9.870$
- Result
  - 5 voxels above
    the threshold
  - 0.0063 minimum
    FWE-corrected
    p-value

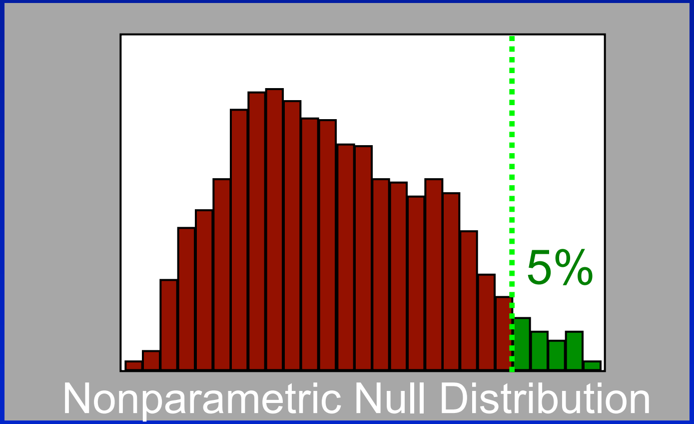


Permutation…

Nonparametric Permutation Test

- Parametric methods
  - Assume distribution of statistic under null hypothesis
- Nonparametric methods
  - Use *data* to find distribution of statistic under null hypothesis
  - Any statistic!



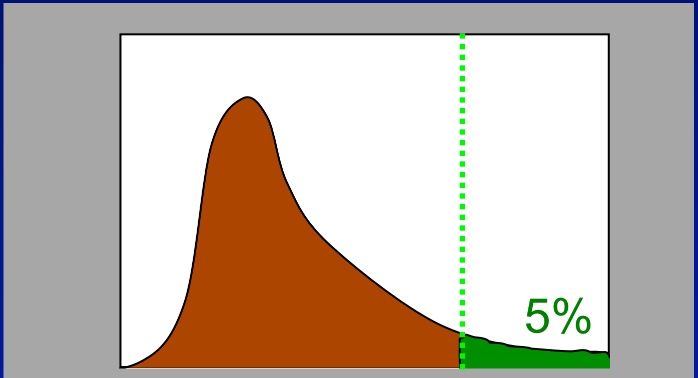


Permutation Test & Exchangeability

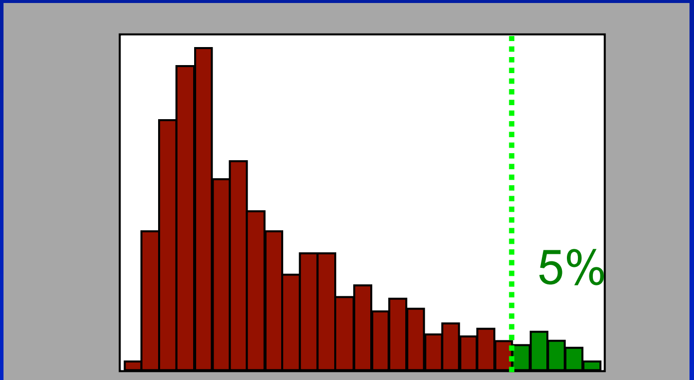
- Exchangeability is fundamental
  - Def: Distribution of the data unperturbed by permutation
  - Under H0, exchangeability justifies permuting data
  - Allows us to build permutation distribution
- fMRI scans not exchangeable over time!
  - Even if no signal, autocorrelation structures data
- Subjects are exchangeable
  - Under Ho, each subject' s "active" "control" labels can be flipped
  - Equivalently, under Ho flip the sign of each subject's contrast images

Controlling FWE: Permutation Test

- Parametric methods
  - Assume distribution of *max* statistic under null hypothesis
- Nonparametric methods
  - Use *data* to find distribution of *max* statistic under null hypothesis
  - Again, any max statistic!



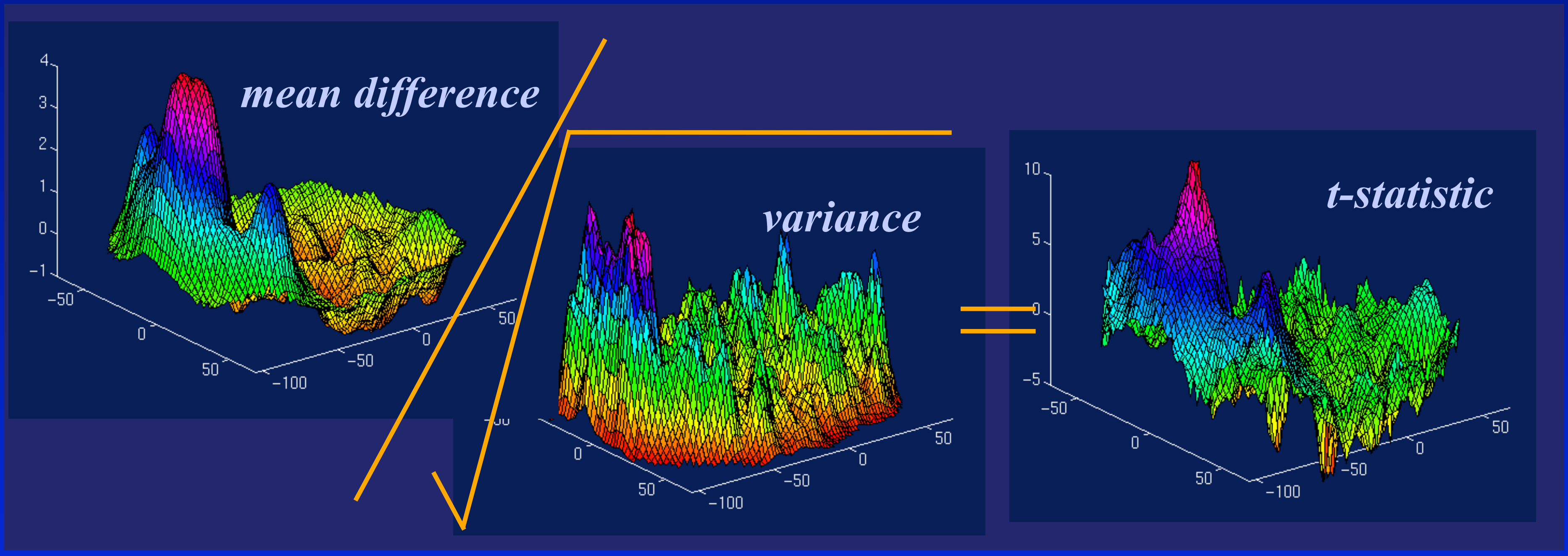
Parametric Null Max Distribution



Nonparametric Null Max Distribution

Permutation Test
Smoothed Variance *t*

- Collect max distribution
  - To find threshold that controls FWER
- Consider smoothed variance *t* statistic



Permutation Test
Smoothed Variance *t*

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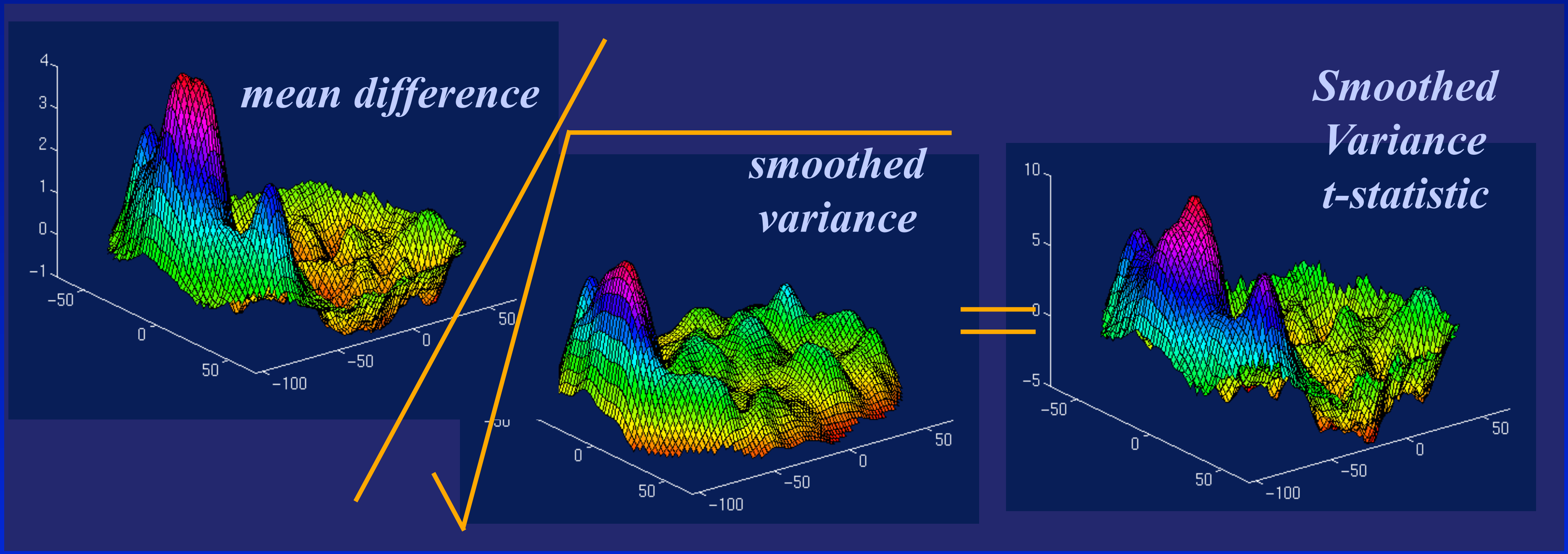
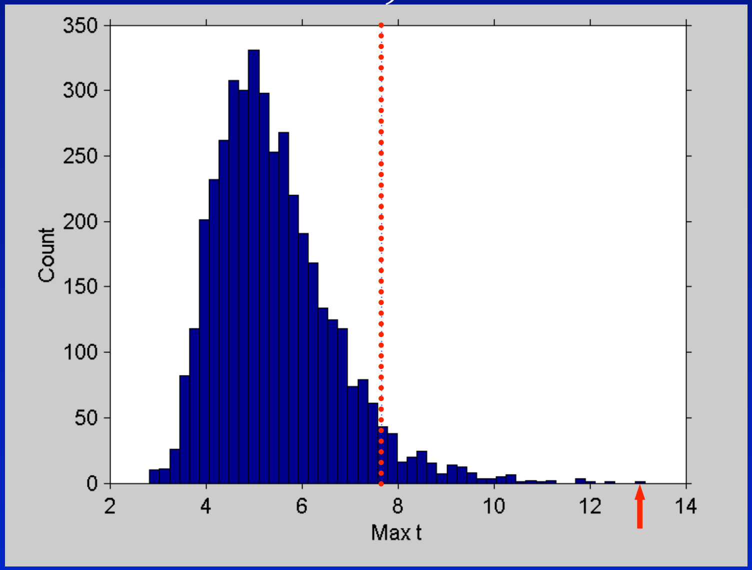
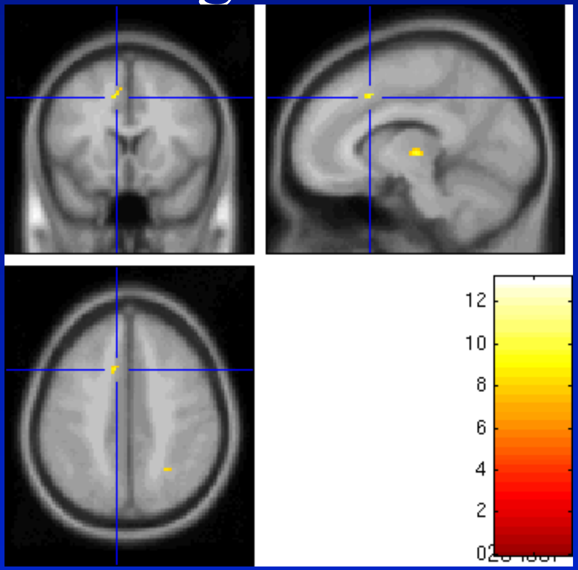


Permutation Test Example

- Permute!
  - $2^{12} = 4{,}096$ ways to flip 12 A/B labels
  - For each, note maximum of t image

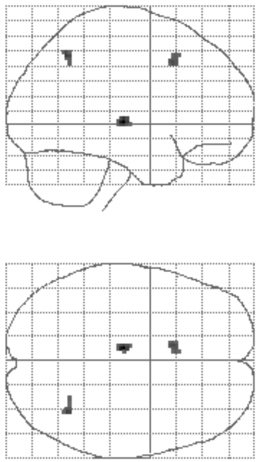


Permutation Distribution
Maximum *t*



Orthogonal Slice Overlay
Thresholded *t*

Permutation

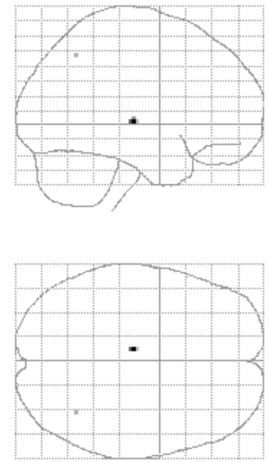


$u^{\text{Perm}} = 7.67$

58 sig. vox.

t_{11} Statistic, Nonparametric Threshold

RFT & Bonferroni

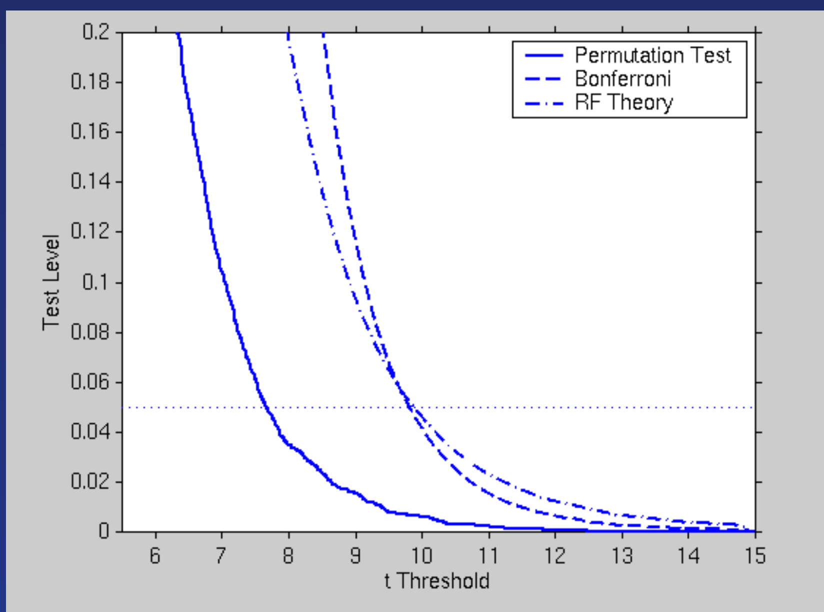


$u^{\text{RF}} = 9.87$
$u^{\text{Bonf}} = 9.80$

5 sig. vox.

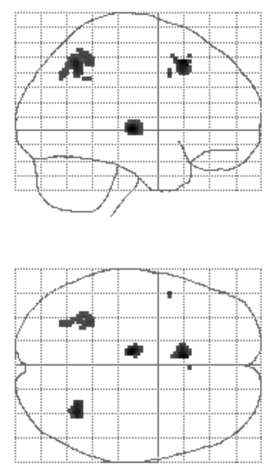
5.1×5.8×6.9 mm FWHM noise smoothness

t_{11} Statistic, RF & Bonf. Threshold



Test Level vs. t_{11} Threshold

Permutation & Sm.Var.



378 sig. vox.

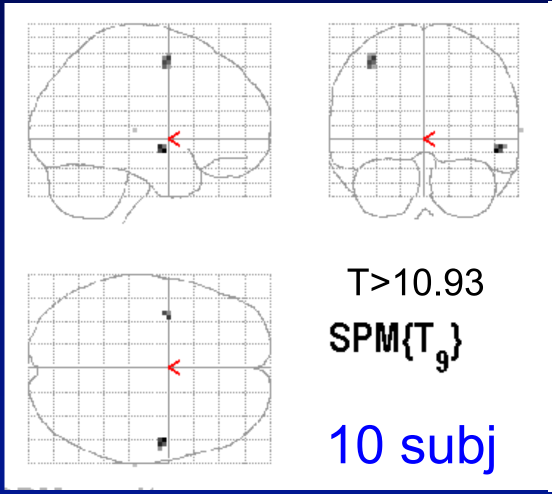
Smoothed Variance t Statistic, Nonparametric Threshold

Reliability with Small Groups

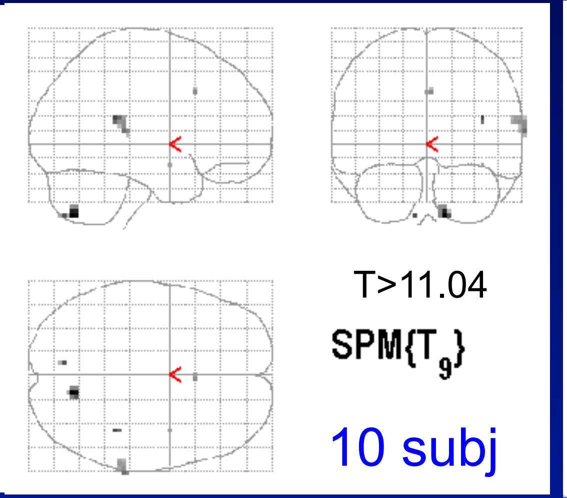
- Consider n=50 group study
  - Event-related Odd-Ball paradigm, Kiehl, et al.
- Analyze all 50
  - Analyze with SPM and SnPM, find FWE thresh.
- Randomly partition into 5 groups 10
  - Analyze each with SPM & SnPM, find FWE thresh
- Compare reliability of small groups with full
  - With and without variance smoothing

.

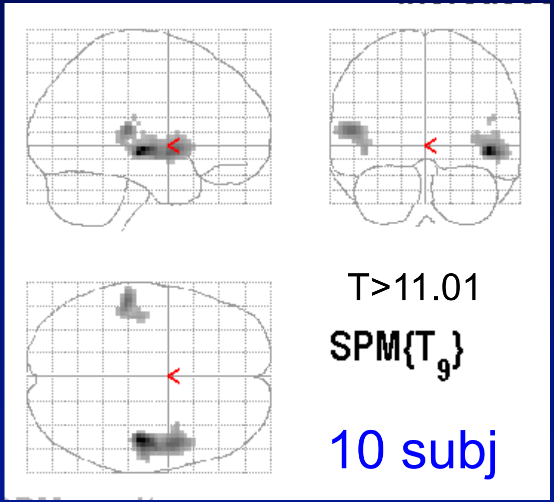
SPM t_{11}: 5 groups of 10 vs all 50
5% FWE Threshold



2 8 11 15 18 35 41 43 44 50



1 3 20 23 24 27 28 32 34 40



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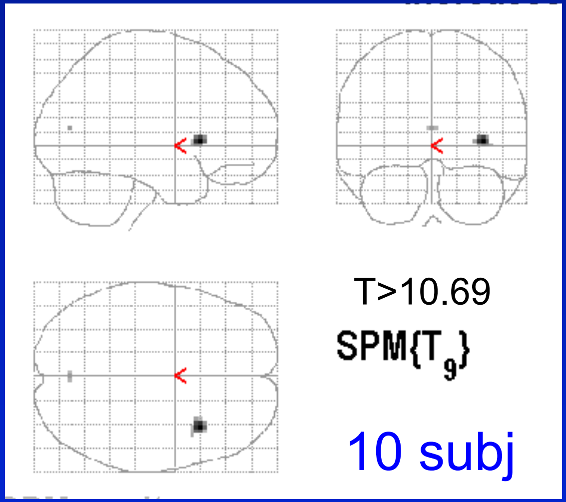

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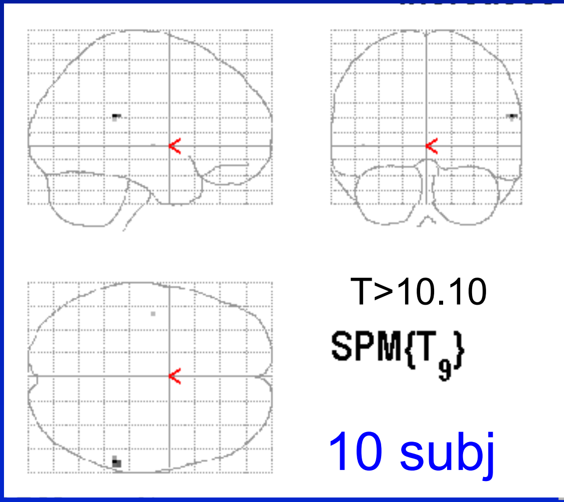
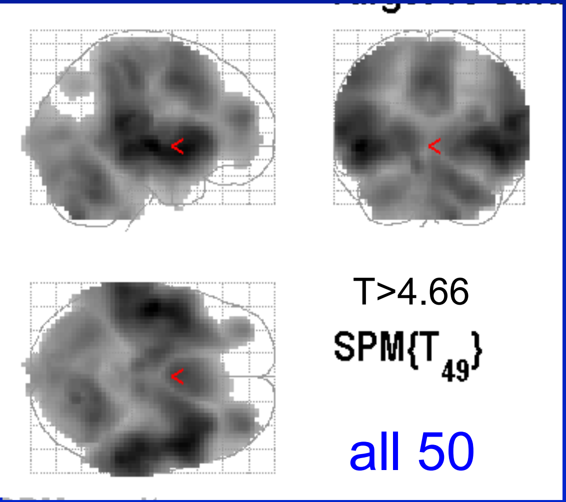
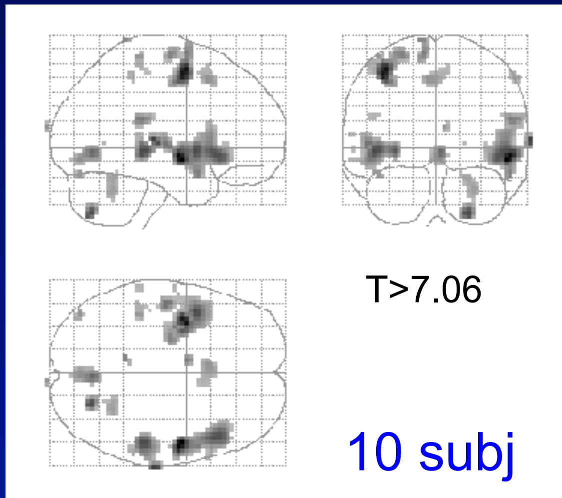


6 7 12 17 26 37 38 46 48 49



SnPM *t*: 5 groups of 10 vs. all 50
5% FWE Threshold



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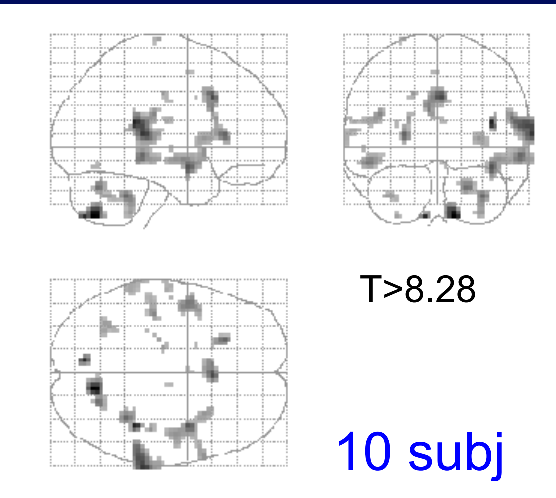

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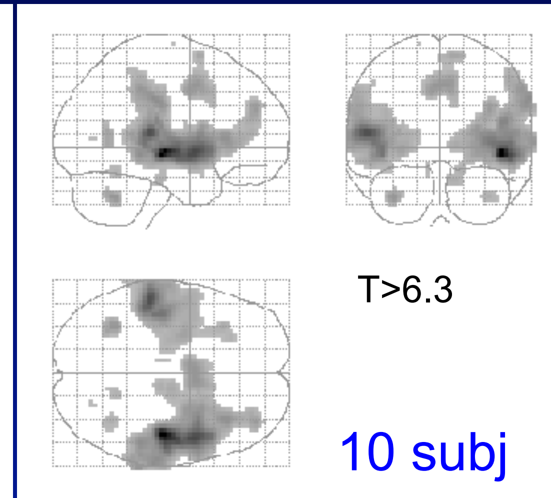

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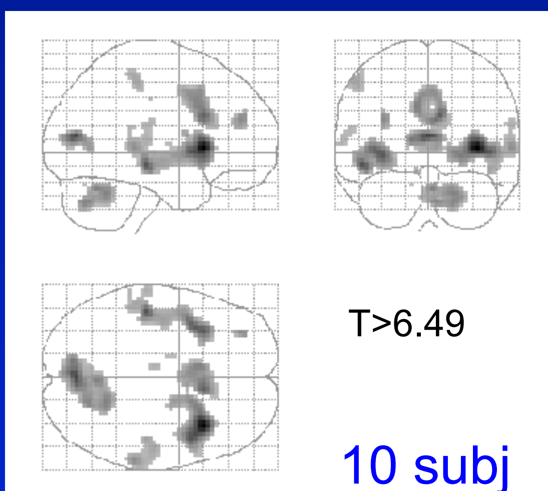

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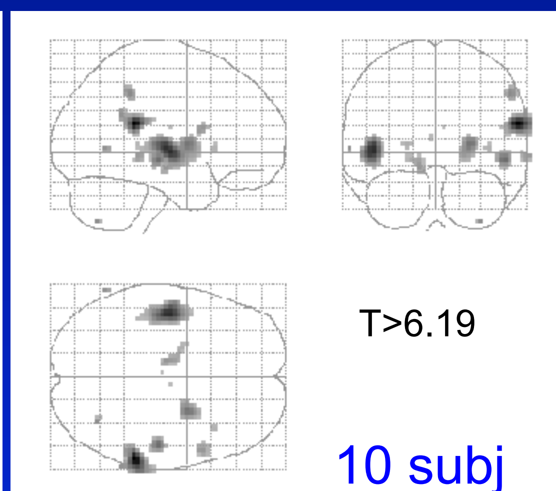

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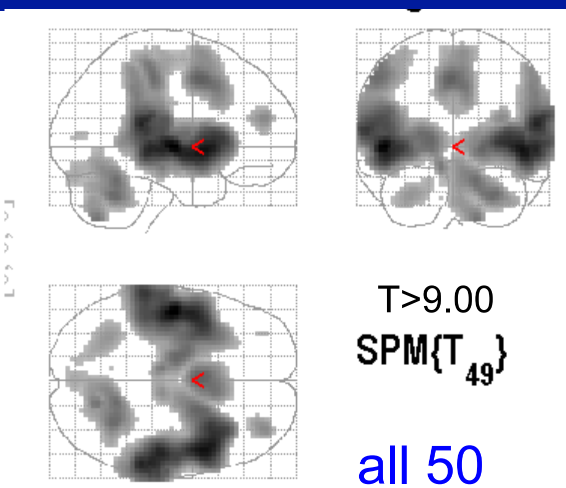
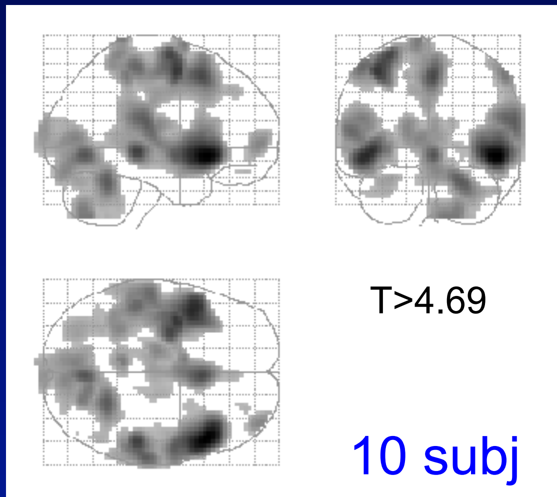


Arbitrary thresh of 9.0

SnPM SmVar *t*: 5 groups of 10 vs. all 50
5% FWE Threshold



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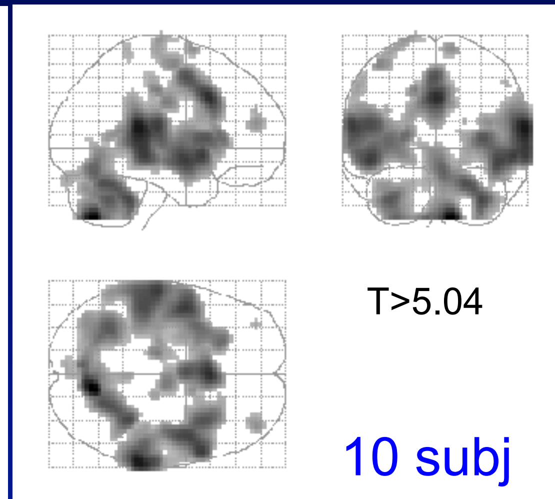

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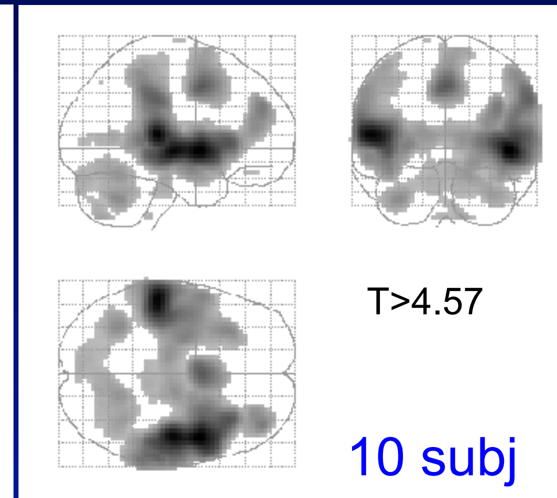

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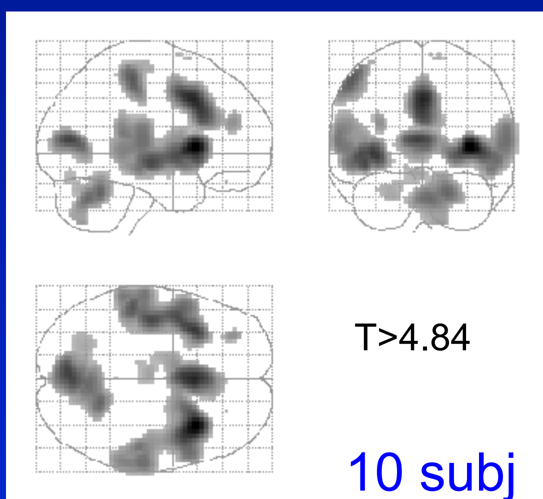

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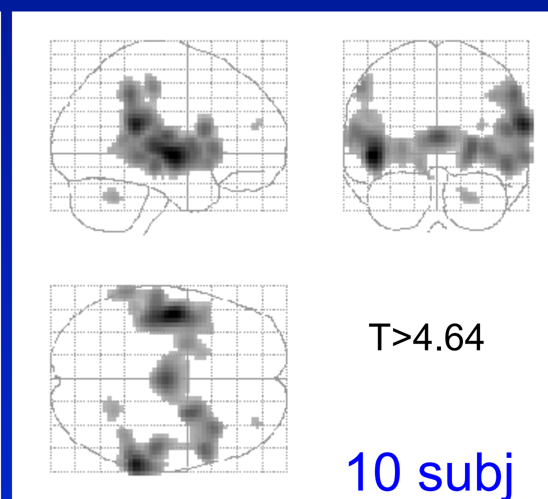

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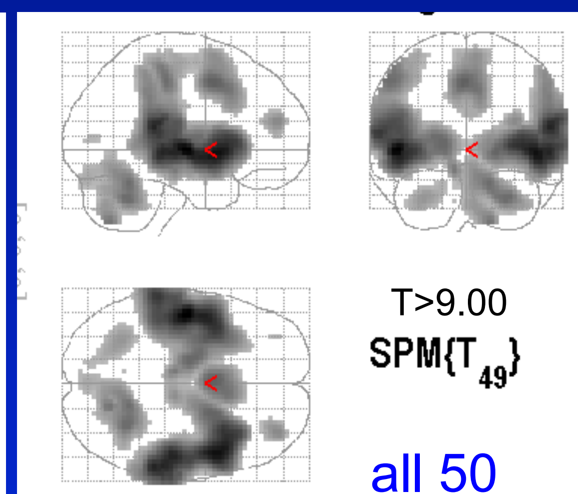


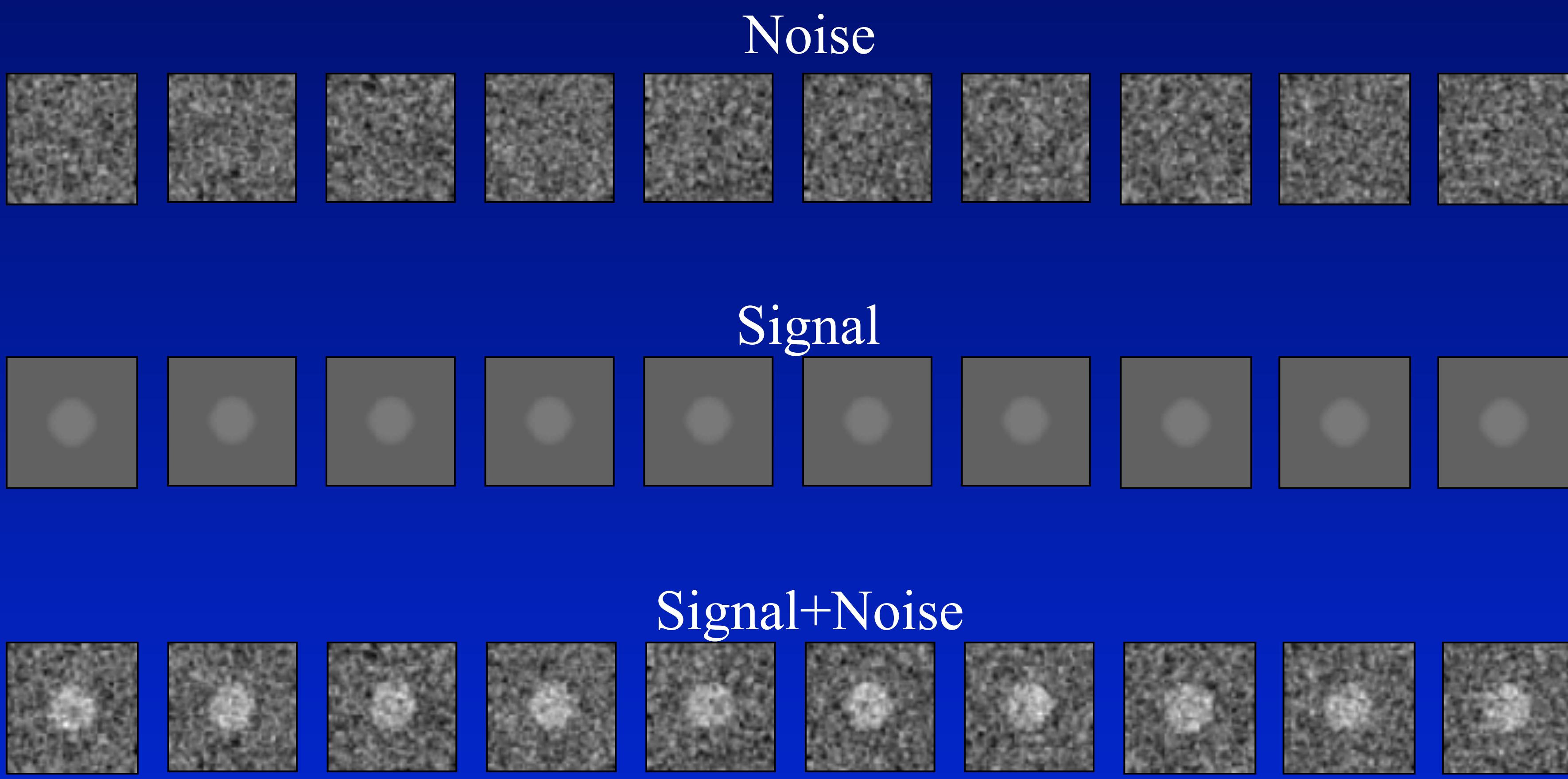
Arbitrary thresh of 9.0

False Discovery Rate…

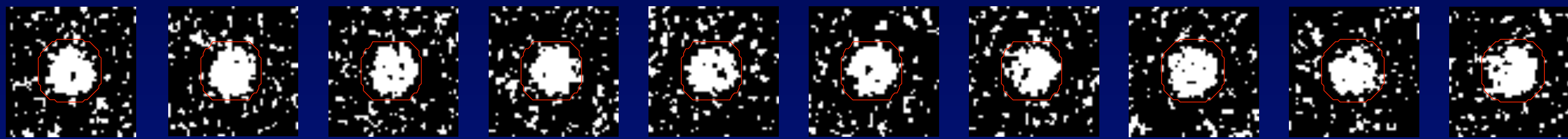
MCP Solutions: Measuring False Positives

- 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 Illustration:



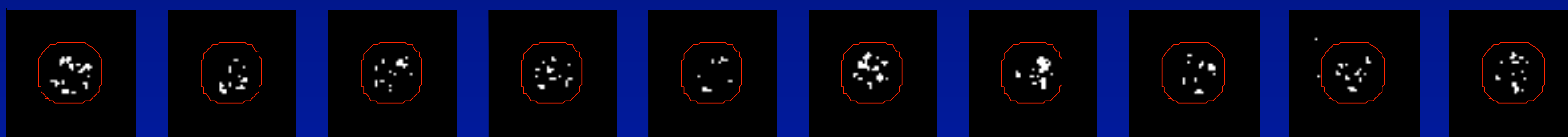
Control of Per Comparison Rate at 10%



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

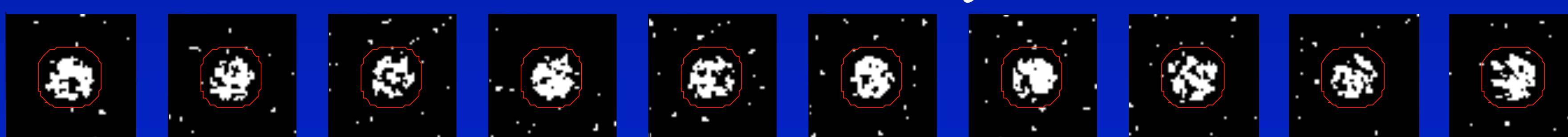
Control of Familywise Error Rate at 10%



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

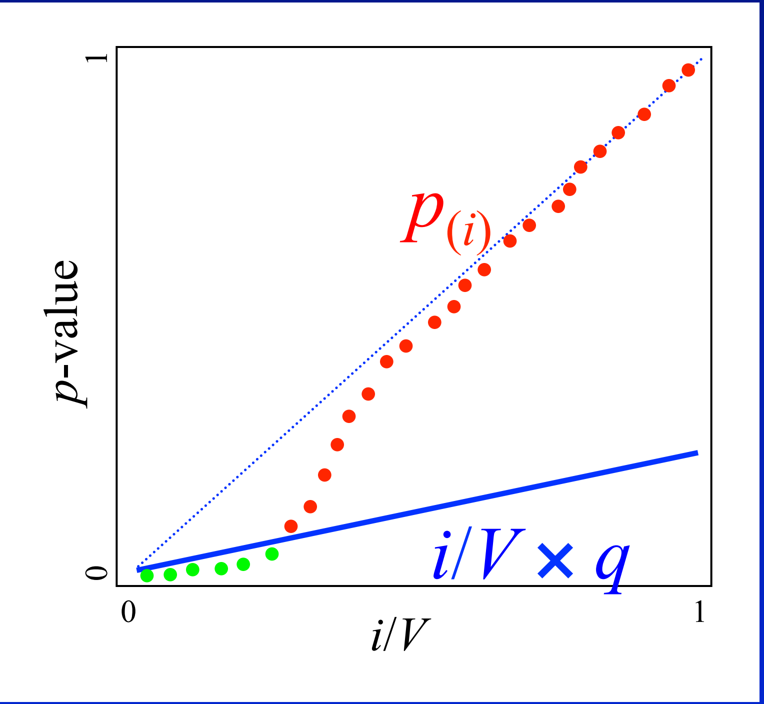
Benjamini & Hochberg Procedure

- 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

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

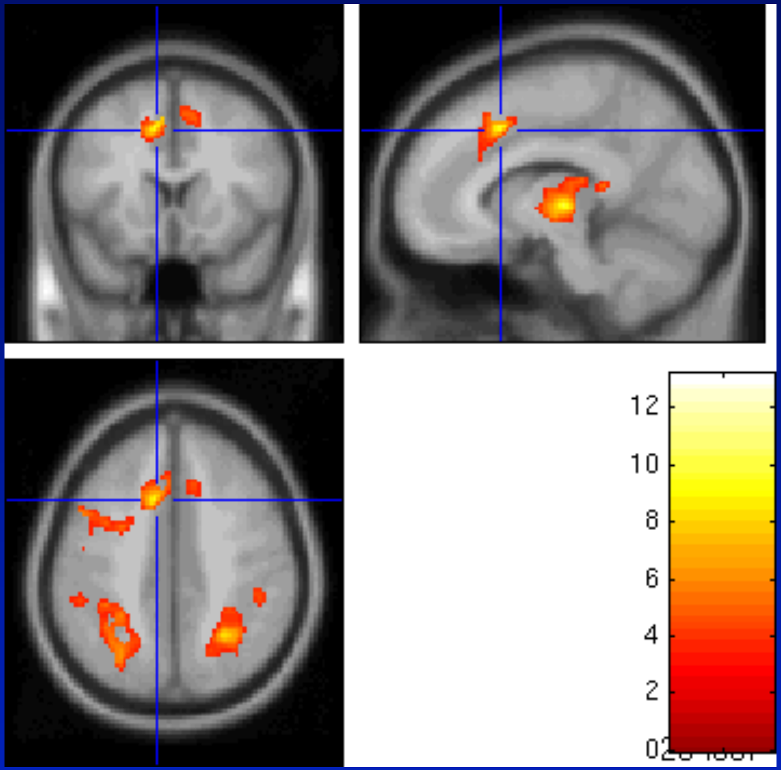
- Reject all hypotheses corresponding to $p_{(1)}, \ldots, p_{(r)}$.
- Threshold is adaptive to signal in the data

JRSS-B (1995) 57:289-300



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

Changes in SPM Inference

Before SPM8

< SPM8	Uncorrected	FDR	FWE
Voxel-wise	×	×	×
Cluster-wise	×		×

SPM8

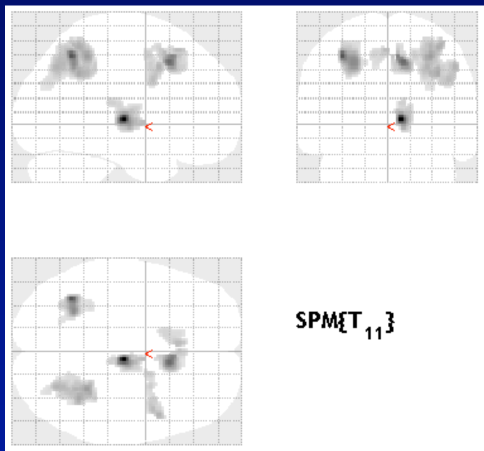
≥ SPM8	Uncorrected	FDR	FWE
Voxel-wise	×		
Cluster-wise	×	×	×
Peak-wise		×	×

- SPM 8 placed new emphasis on peak inference, removed voxel-wise FDR
  - FWE Voxel-wise & Peak-wise equivalent
  - FDR Voxel-wise & Peak-wise not equivalent!
    - To get voxel FDR, edit spm_defaults.m or do

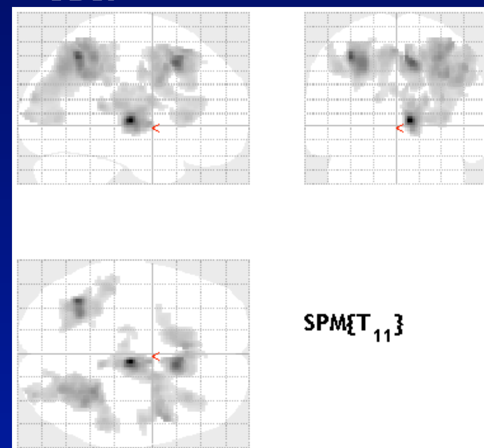
```
global defaults; defaults.stats.topoFDR=0;
```

Cluster FDR: Example Data

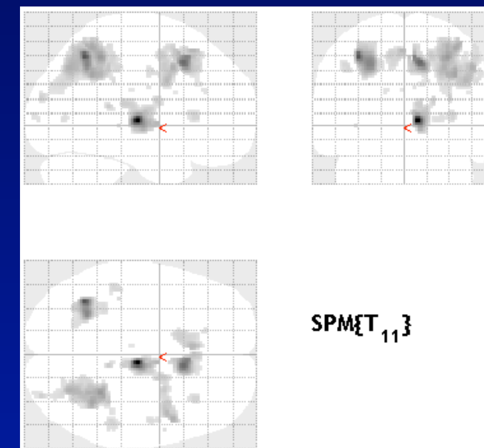
Level 5% Cluster-FDR,
P = 0.001 cluster-forming thresh
k_{FDR} = 138, 6 clusters



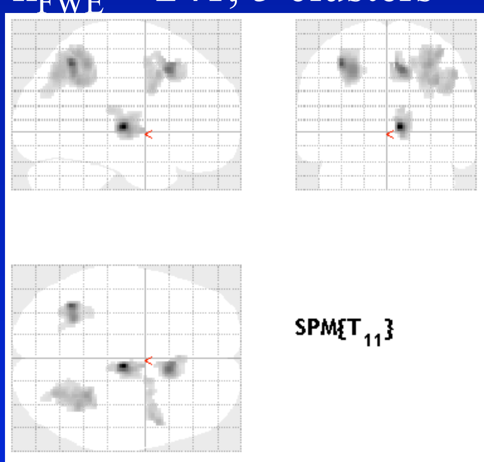
Level 5% Cluster-FDR
P = 0.01 cluster-forming thresh
k_{FDR} = 1132, 4 clusters



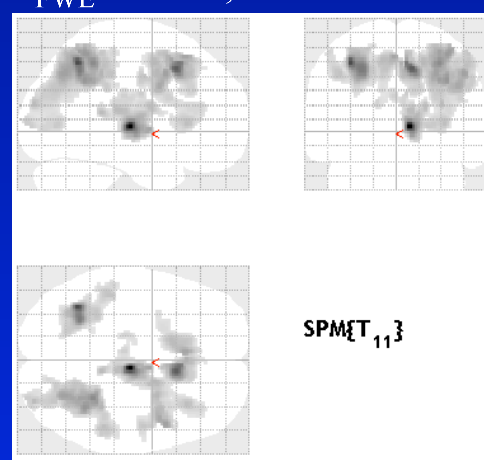
Level 5% Voxel-FDR



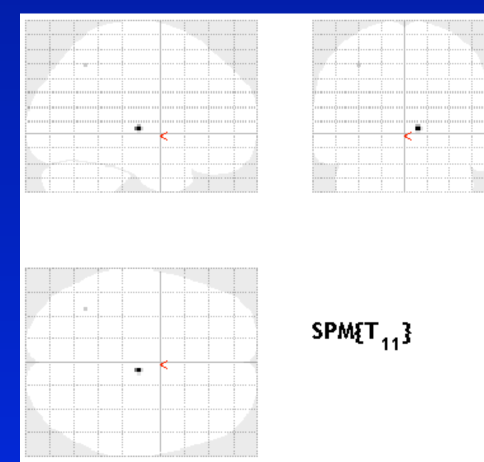
Level 5% Cluster-FWE
P = 0.001 cluster-forming thresh
k_{FWE} = 241, 5 clusters



Level 5% Cluster-FWE
P = 0.01 cluster-forming thresh
k_{FWE} = 1132, 4 clusters



Level 5% Voxel-FWE



Conclusions

- Thresholding is not modeling!
  - Just inference on a feature of a statistic image
- Many features to choose from
  - Voxel-wise, cluster-wise, peak-wise…
- 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. 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.

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