Outline of Dual Thresholding *plus* ETAC:

Equitable Thresholding And Clustering

Voxel-Wise Group Analysis

- Do *first level* time series analysis on each subject's data separately (**`afni_proc.py`**)
  - Transformed to common template (*e.g.*, MNI)
    - Best with nonlinear transformation (**`3dQwarp`**)
      - Can restrict analysis to dilated gray matter mask
- *Second level* group analysis on voxel β values = % signal change (*not* ROIs)
  - Can be as simple as *t*-tests (**`3dttest++`**)
  - Or a complicated model such as Linear Mixed Effects (**`3dLME`**), *etc.*

Group Spatial Inference - 1

- ***Goal***: control *global* **F**alse **P**ositive **R**ate (FPR) – to 5% level (*e.g.*)
  - **FPR** = **FWE** = **F**amily-**W**ise **E**rror
    - = rate of errors across the family of voxel tests
    - "error" = when *anything* is found in noise-only data *vs* **global null hypothesis** (no "activity")
- Different approach: to control the **F**alse **D**iscovery **R**ate (**FDR**, voxel-wise)
  - = fraction of "discoveries" that are "errors"
  - *Not* what I'm going to talk about at this moment
    - Difficult to allow for inter-voxel correlation in noise

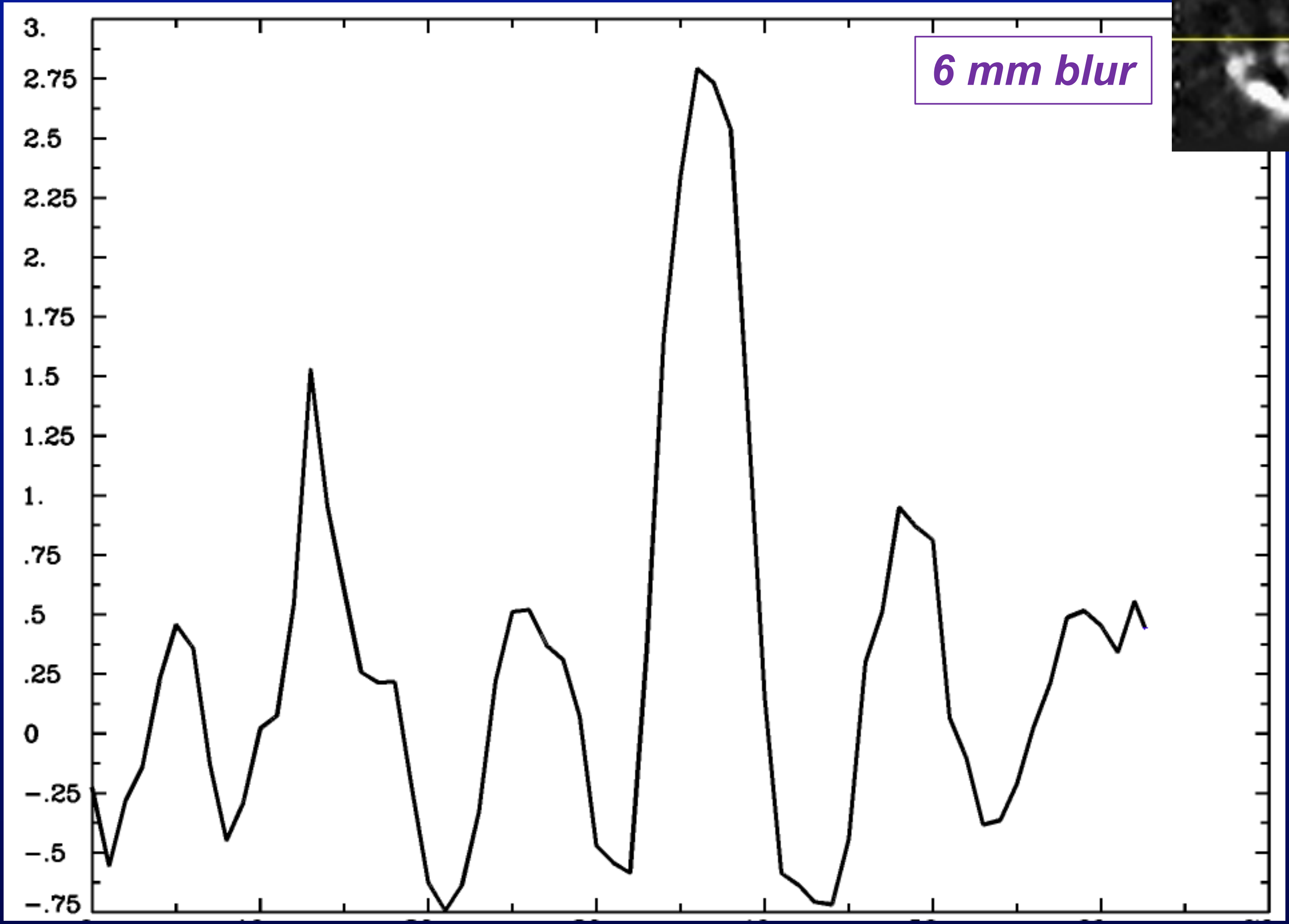
Group Spatial Inference - 2

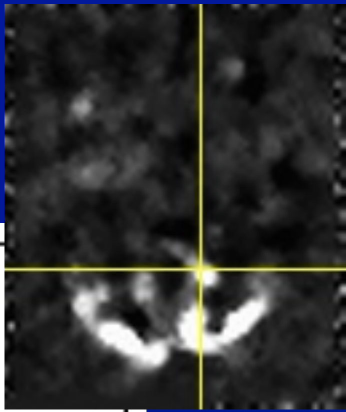
- Voxel-wise thresholding on group *t*-statistic is usually super conservative (to get global FPR≈5%)
- *A Solution*: form *clusters* of neighboring voxels, each above a lower (less strict) voxel-wise *t*-statistic (or *z*-statistic)
  - With a larger voxel-wise *p*-value (=smaller *t*)
- *Then*: threshold on cluster-size as well
  - Given voxel-wise *p*, adjust cluster-FOM threshold to get desired global FPR ⇛⇛⋯

Group Spatial Inference - 3

- Dual threshold method (voxel then cluster) can still be weak (low power to detect)
- *A Solution*: use spatial blurring ≈ average nearby voxel β ("Coef") values together, in each subject, *before* group statistics
  - To reduce noise and reinforce commonality
  - To reduce effective number of independent statistical tests (but lose spatial resolution)
  - To select the *minimum* spatial scale of what we are hunting for

1D Double Thresholding (real data)





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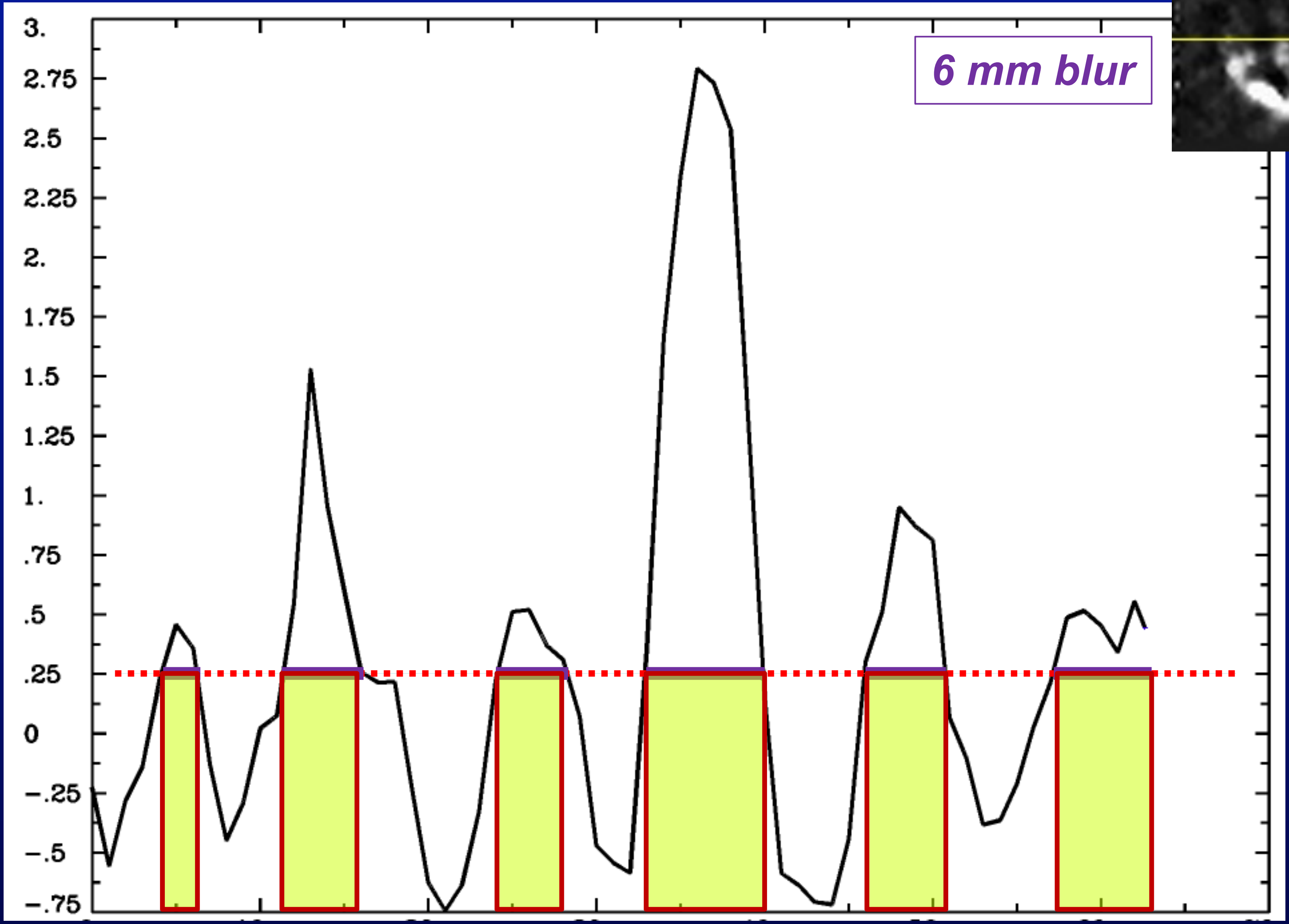

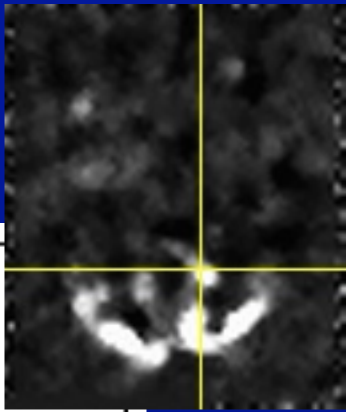

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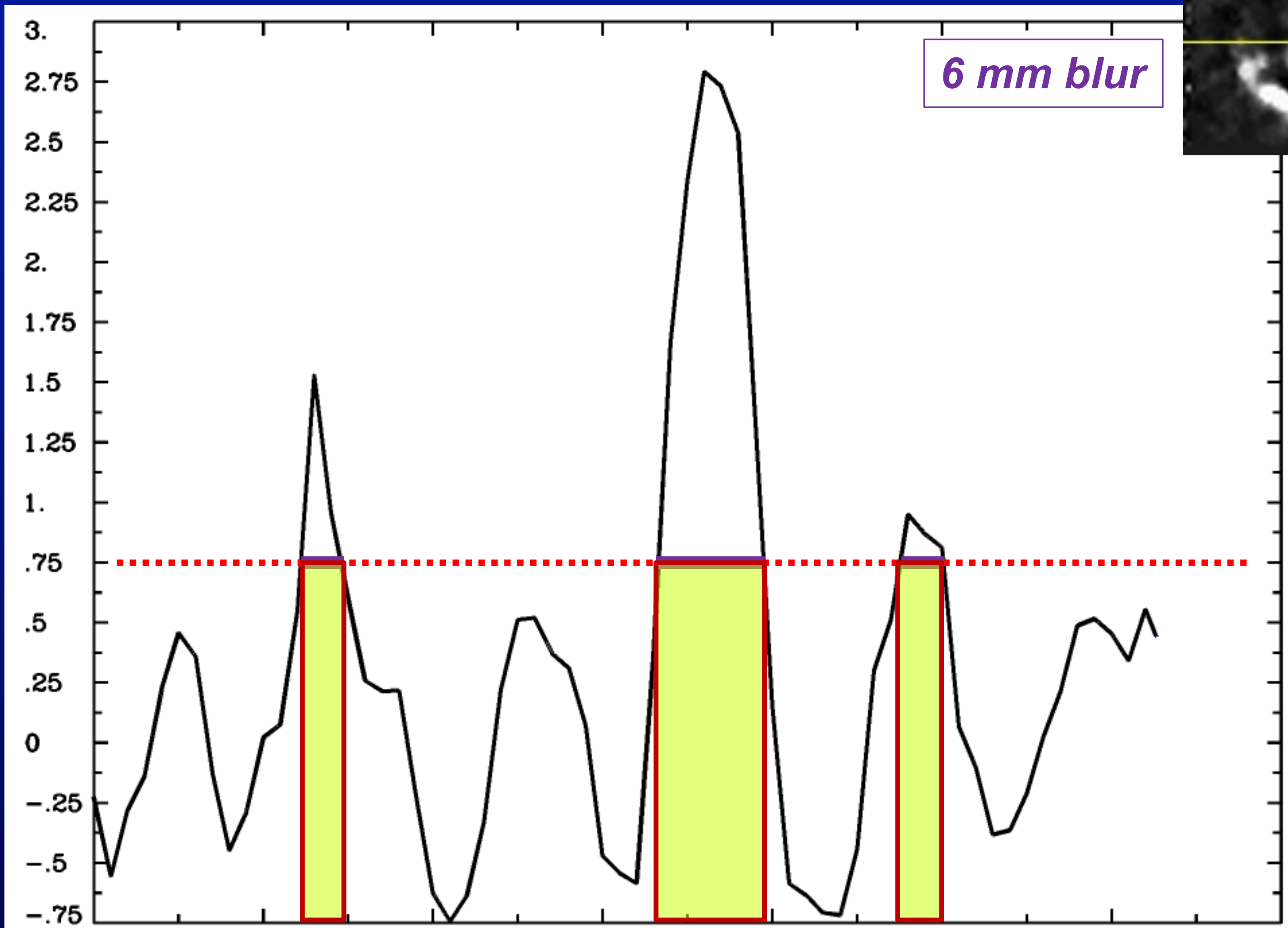

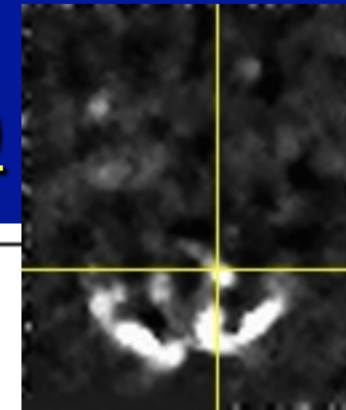

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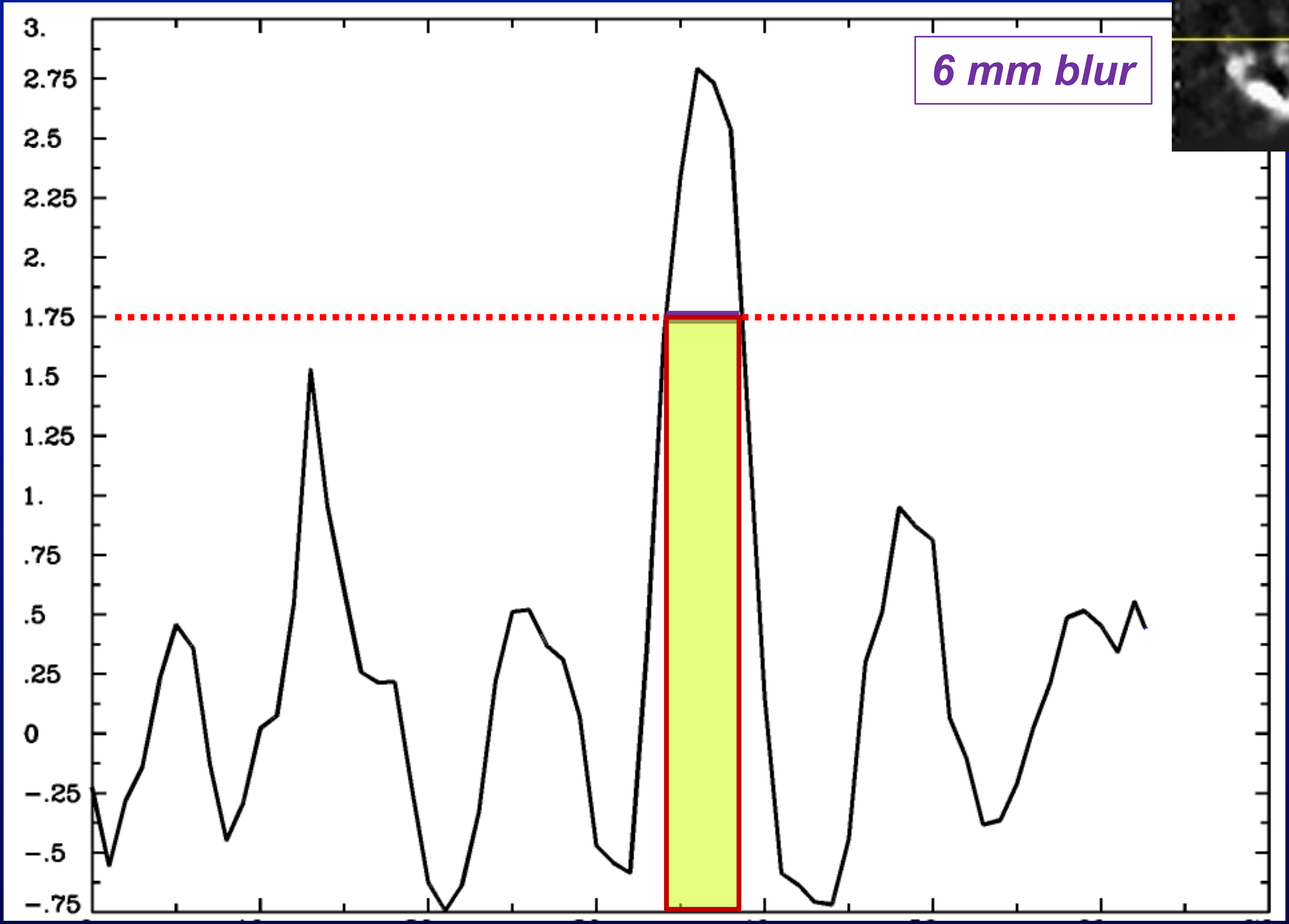
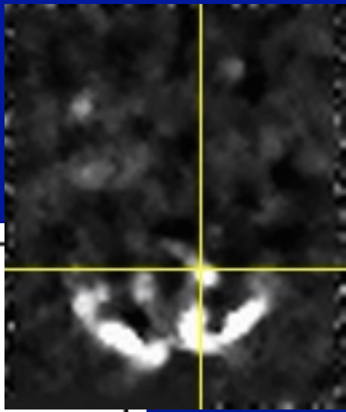
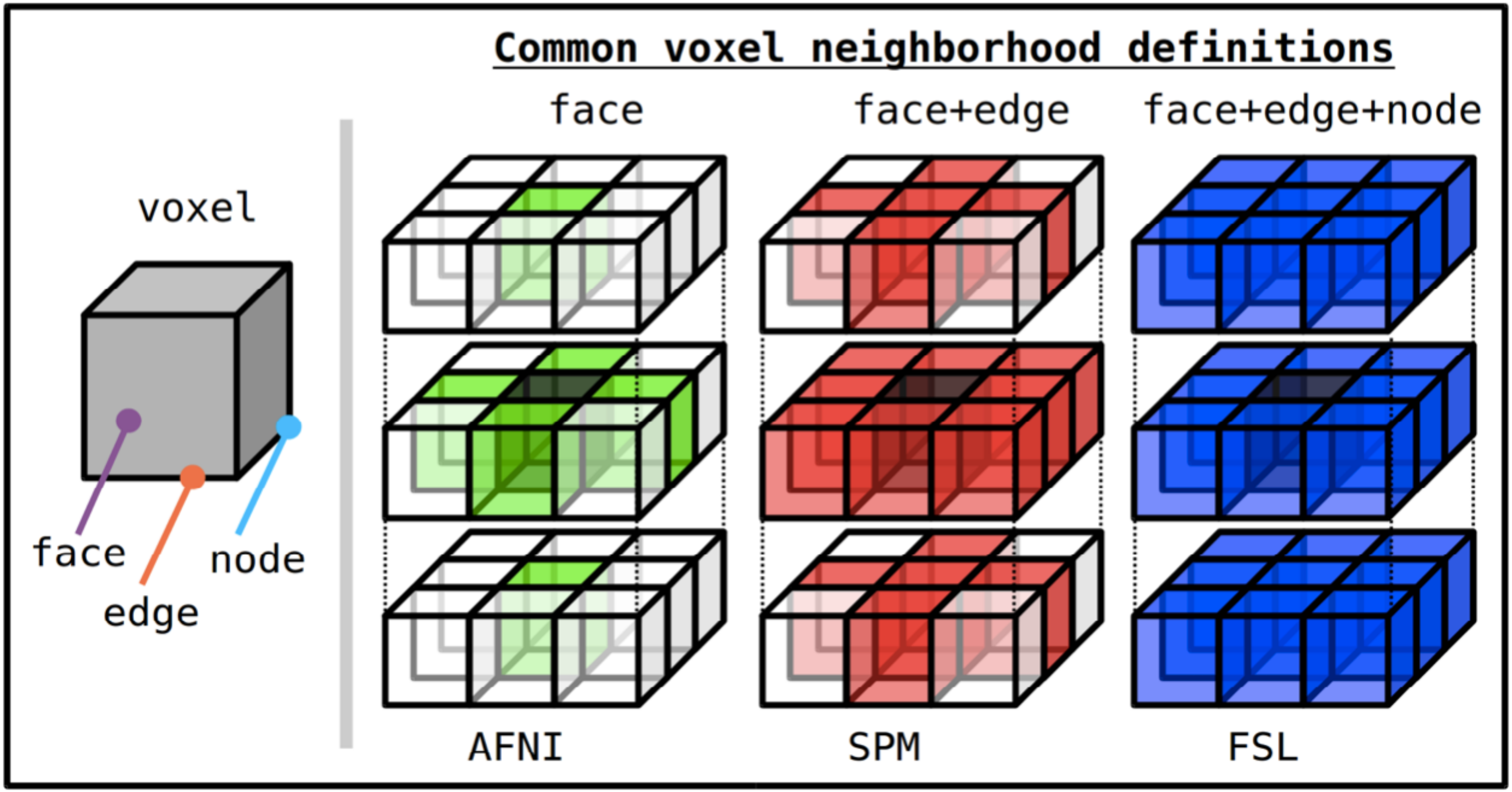




Definitions of "Cluster" in 3D

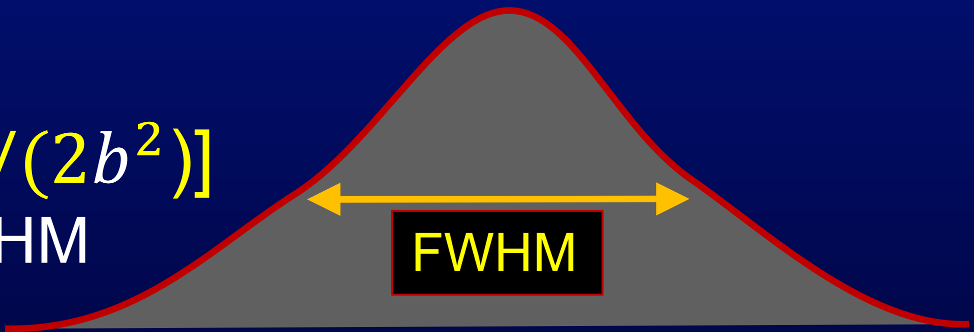


(NN=1) *(NN=2)* *(NN=3)*

Old ClustSim - 1

- Spatial correlation of “noise” in FMRI data means no exact formula for cluster-FOM threshold, for a given *p* threshold
- So: Assume Gaussian-shape for spatial auto-correlation function (ACF) *of noise*
  - Fit Gaussian width parameter (FWHM)
  - Compute cluster-size threshold to get 5% FPR

$$\mathrm{ACF}(r) = \exp[-r^2/(2b^2)]$$
$$b = 0.4246 \cdot \mathrm{FWHM}$$



Old ClustSim - 2

1) Generate *random noise-only* dataset with Gaussian ACF (with chosen FWHM)
2) Threshold at diverse per-voxel *p*-values
3) Find largest cluster *in brain mask*
4) Repeat steps 1-3 10,000+ times
5) For each per-voxel *p*-value, cluster-size threshold is largest cluster size which occurs only in 5% (*e.g.*) of cases

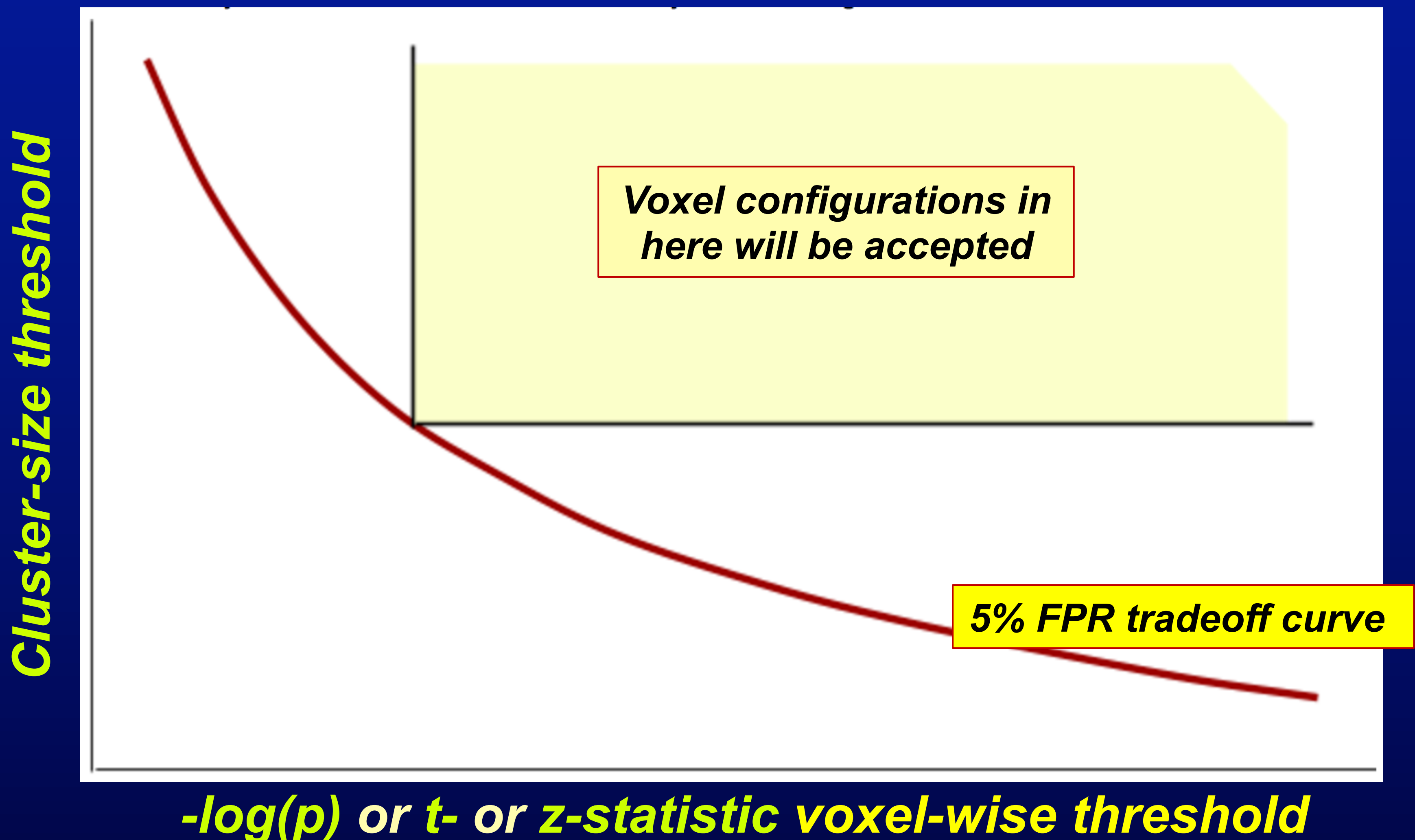
ClustSim - 3

- `3dClustSim` outputs tables like this:

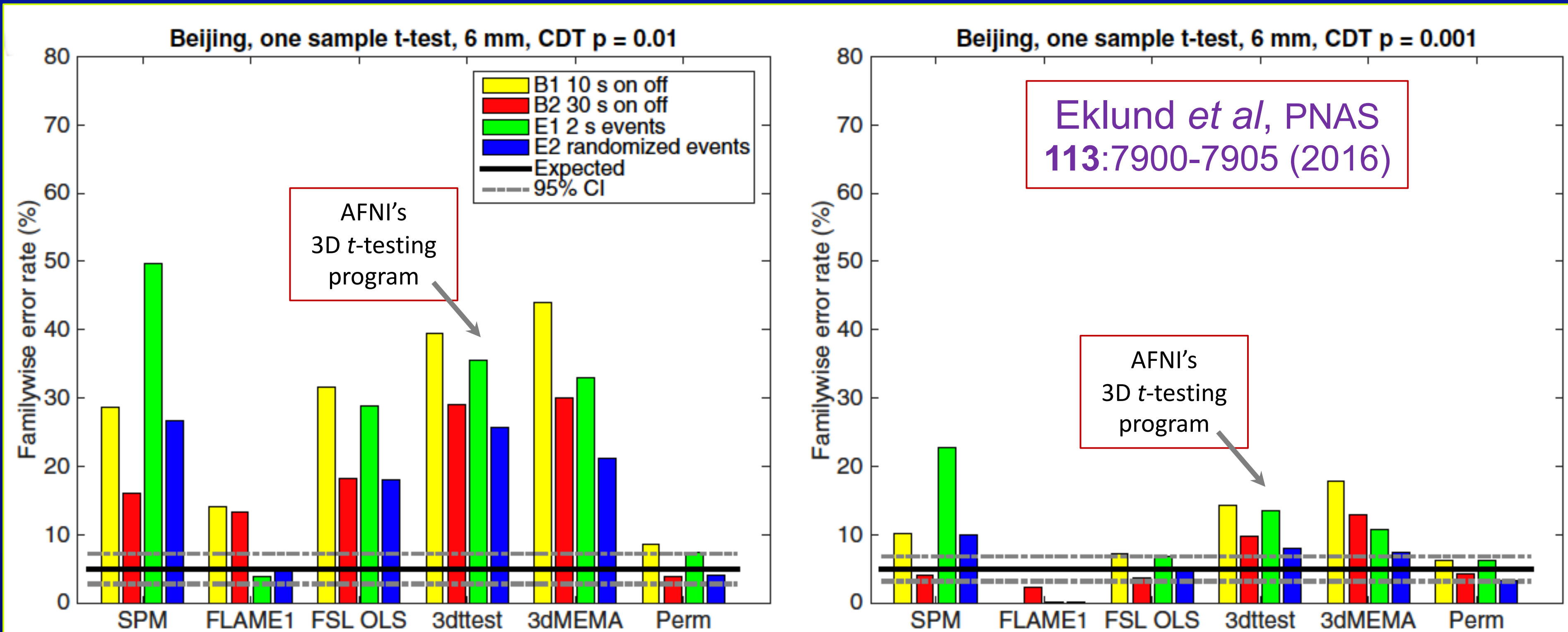
```
# CLUSTER SIZE THRESHOLD(pthr,alpha)
# -NN 2   | alpha=Prob(Cluster > given size)
#  pthr   |.10000 .05000 .02000 .01000
# ------  | ------ ------ ------ ------
0.010000    50.3   57.2   66.3   73.6
0.005000    34.4   39.5   46.3   51.6
0.002000    22.1   25.7   30.4   34.1
0.001000    16.0   19.0   22.8   26.0
0.000500    12.0   14.5   17.4   20.1
0.000200     8.1   10.0   12.6   14.6
0.000100     6.1    7.7    9.9   11.6
```

ClustSim - 4

- High *t* threshold ⇛ small cluster threshold



The Great Cluster Panic - 2016



- FPR ≫ 5%: *notably* for voxel-wise *p*=0.01
- A lot of doom-crying about this in 2016:

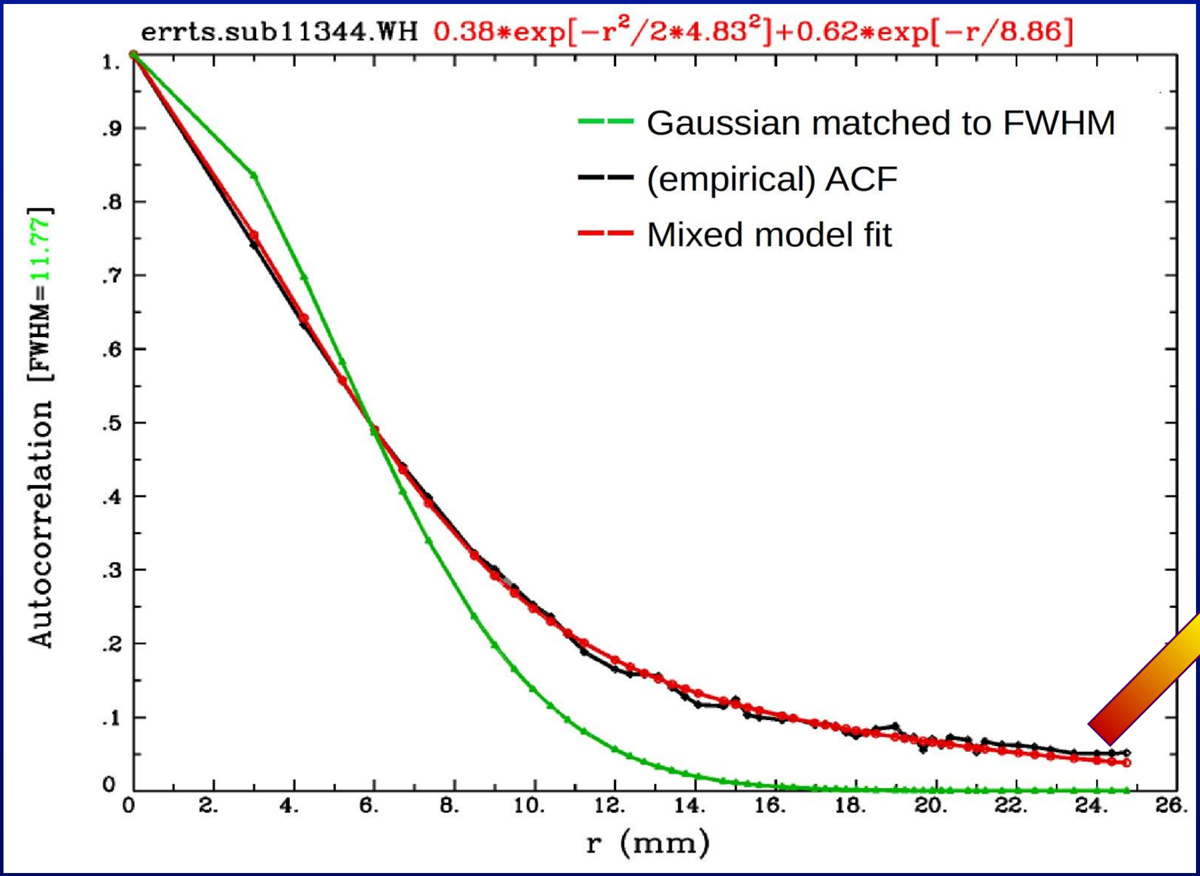
"*Could Invalidate 15 Years of Brain Research*"

3 Solutions in AFNI

1) Extend ACF model in **`3dClustSim`** to be more complicated than a Gaussian shape (the mixed model)
2) Eliminate ACF modeling by extending **`3dClustSim`** to directly use *residuals* from **`3dttest++`** via randomization
3) Generalize cluster-thresholding model in a couple more directions: **ETAC**

1) NonGaussianity in ACF

- ACF from single subject datasets has long tails – nonGaussian shape + 1st difference fail



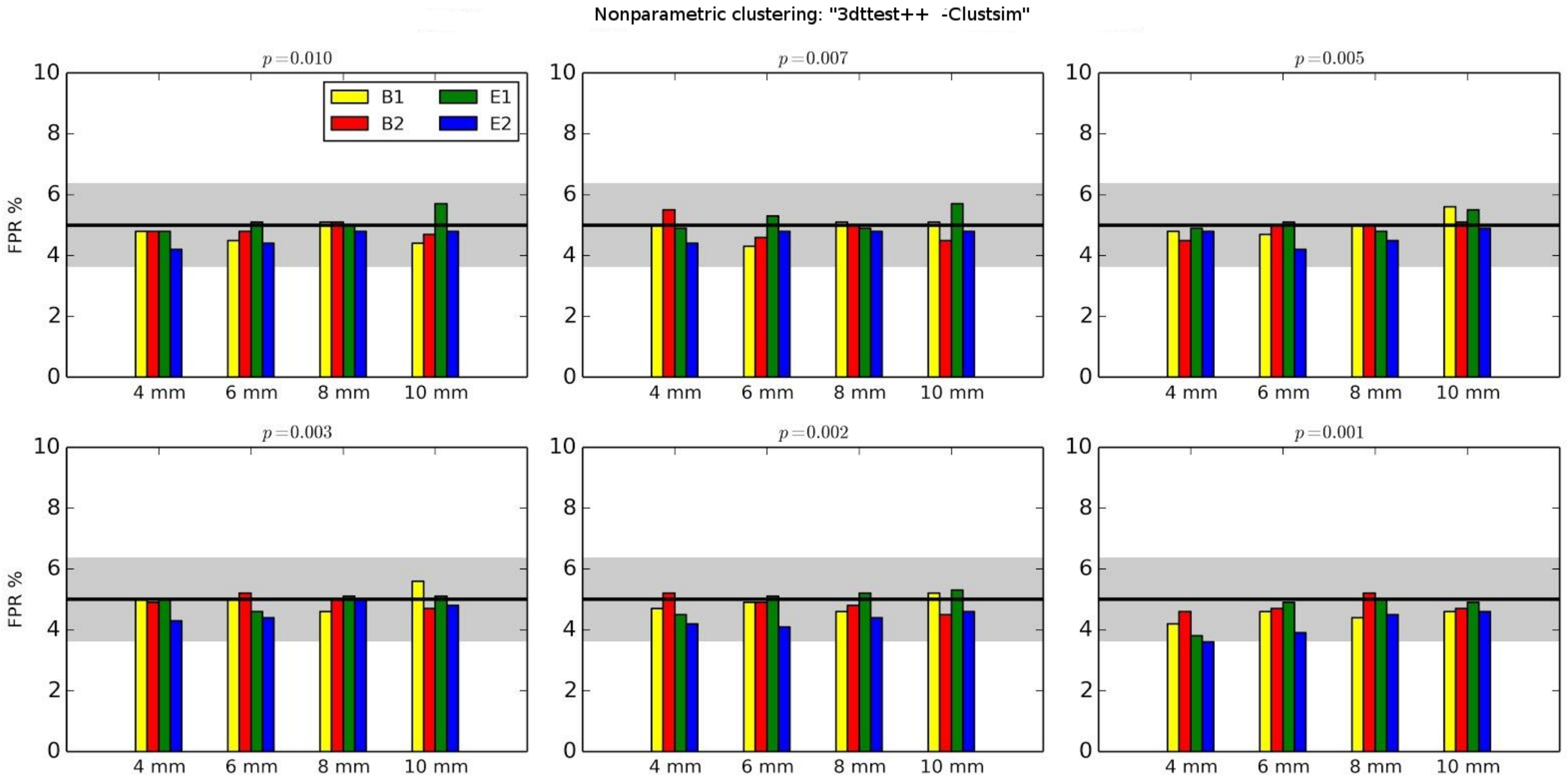
Modify 3dClustSim to use mixed ACF model (Gaussian plus mono-exponential) with 3 parameters (a,b,c) instead of 1 (FWHM)

$$\text{ACF}(r) = a\exp[-r^2/(2b^2)] + (1-a)\exp[-r/c]$$

1) How to: ACF method

- Run **`3dFWHMx`** with '-acf' option to get (*a*,*b*,*c*) for each subject, from residuals dataset errts*+tlrc.HEAD
  - *This calculation is done now in* **`afni_proc.py`**
  - Average each of the 3 ACF parameters across subjects (not automatic)
- Use **`3dClustSim`** with '-acf' option (giving it the 3 averaged parameters) to get cluster size threshold tables for group analysis
  - This method is OK, if per-voxel $p \leq 0.002$

2) A Different Solution:
Nonparametric Clustering in **AFNI**



- *t*-test residuals are permuted/randomized (10000 times)
- 10000 re-*t*-tests computed from residuals fed to **`3dClustSim`**

2) How to: Nonparametric Clustering

- **Only for *t*-tests** (or GLM) **at this time**
  - Re-running many **`3dLME`** cases (*e.g.*) is too slow
- **`3dttest++`** with the **`–Clustsim`** option
- Gives excellent FPR control ☺
- Has fairly large cluster-size thresholds ☹
  - Led me to next set of ideas ⇛⇛ ***ETAC!***

Arbitrary Choices

- I've mentioned two parameters that must be chosen by the researcher in the "usual" methods:
  - Voxel-wise *p*-value for first-level thresholding
    - Typical FMRI values range from 0.001 to 0.01
  - Amount of spatial blurring to add to data
    - Typical FMRI values range from 4 to 10 mm
- But there are no "best" values ☹
  - **ETAC** can rescue you*!* (from these choices) ☺

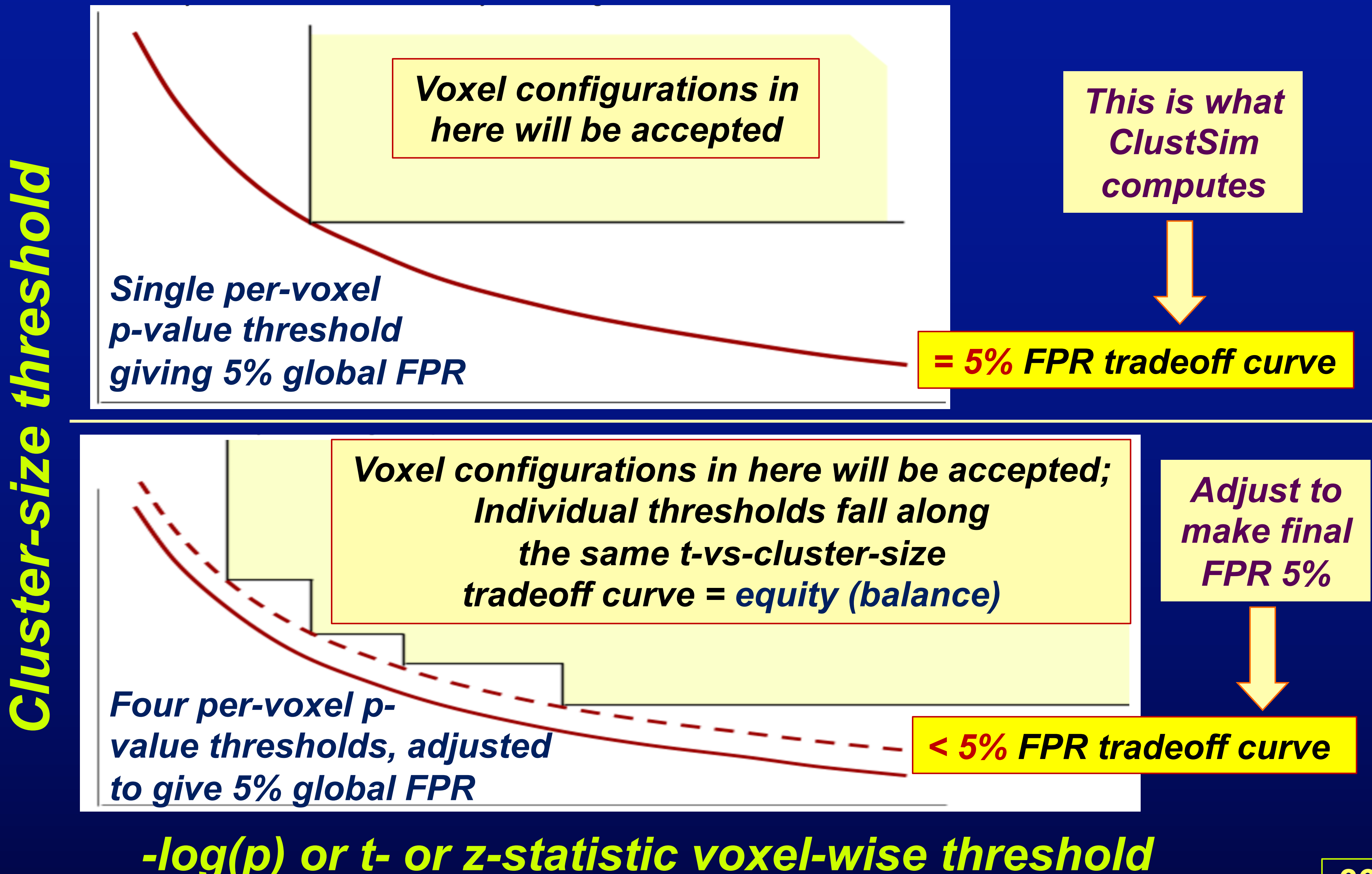
3) ETAC ☺ ☺ ☺ ☺

- **E**quitable **T**hresholding **A**nd **C**lustering
- Uses *multiple* sub-methods at same time
  - **Equity** = **balancing** FPRs of sub-methods

1) Voxel-wise thresholding at *multiple p*-values, then cluster-FOM thresholding
2) *Multiple* cases of spatial blurring

- No model for ACF
  - As before, uses randomization/permutation

Equity: Multi-Thresholding



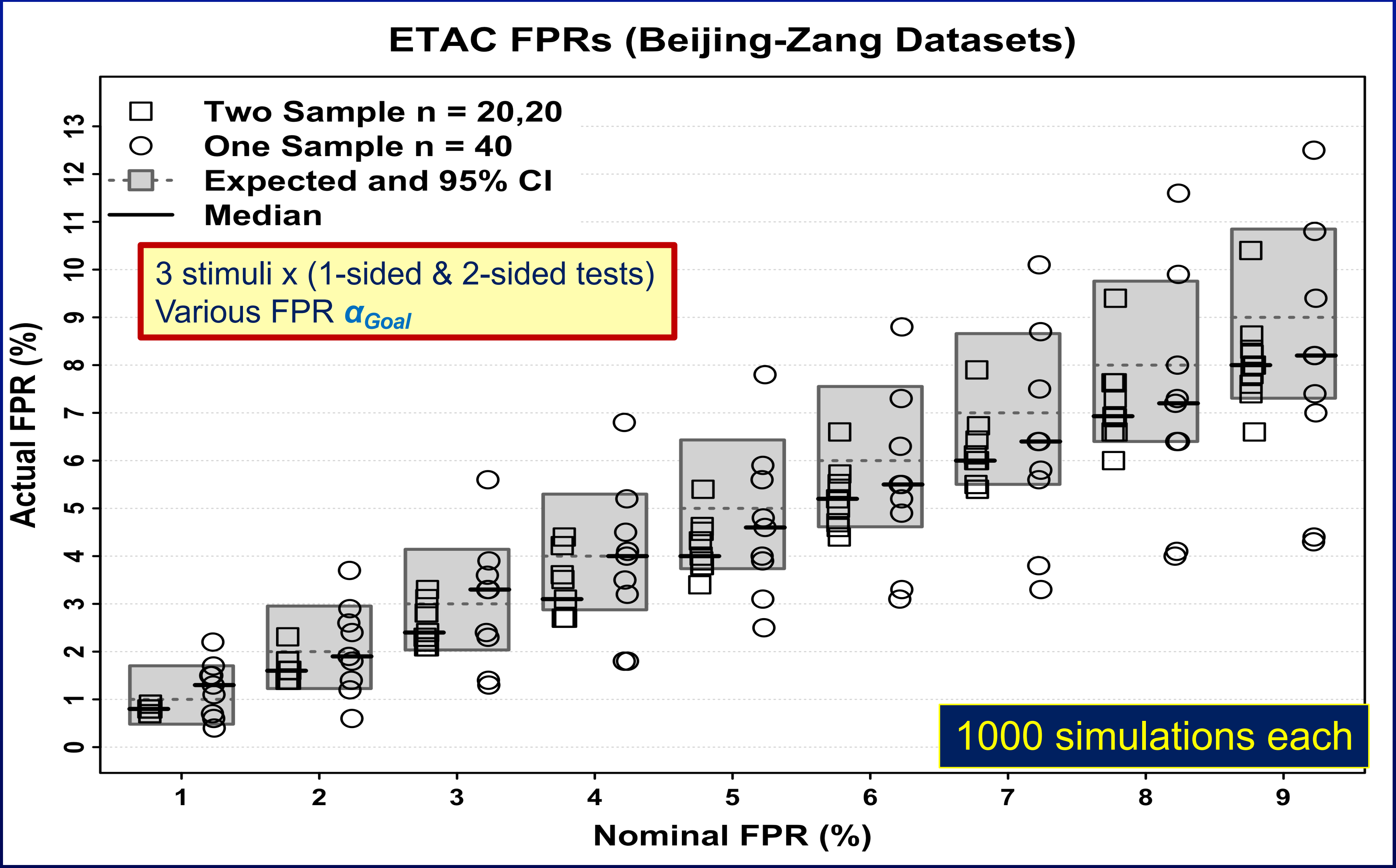
Equity: Across Methods

- Balancing can apply to any multi-choice method for selecting voxel clusters
  - Each sub-method has a cluster-FOM threshold adjustable to get desired FPR
  - Balance = choose each sub-method's cluster-FOM threshold to have the same global FPR $\alpha_0 < \alpha_{Goal}$ (e.g., 5%)
- **ETAC** method (set union): accept a voxel if it survives at least one sub-method
  - Adjust α_0 up or down to get final FPR = α_{Goal}

Equity: Across Blur Cases

- Blurring at (*e.g.*) 4, 6, 8, 10 mm
- Potential to detect both small intense clusters and larger weak clusters
  - Blur = 10 mm might “wash out” small cluster
  - Blur = 4 mm might not reduce noise enough to find larger weak cluster
- Combined with multi-thresholding (different *p*-values), reduces number of arbitrary choices to make in thresholding

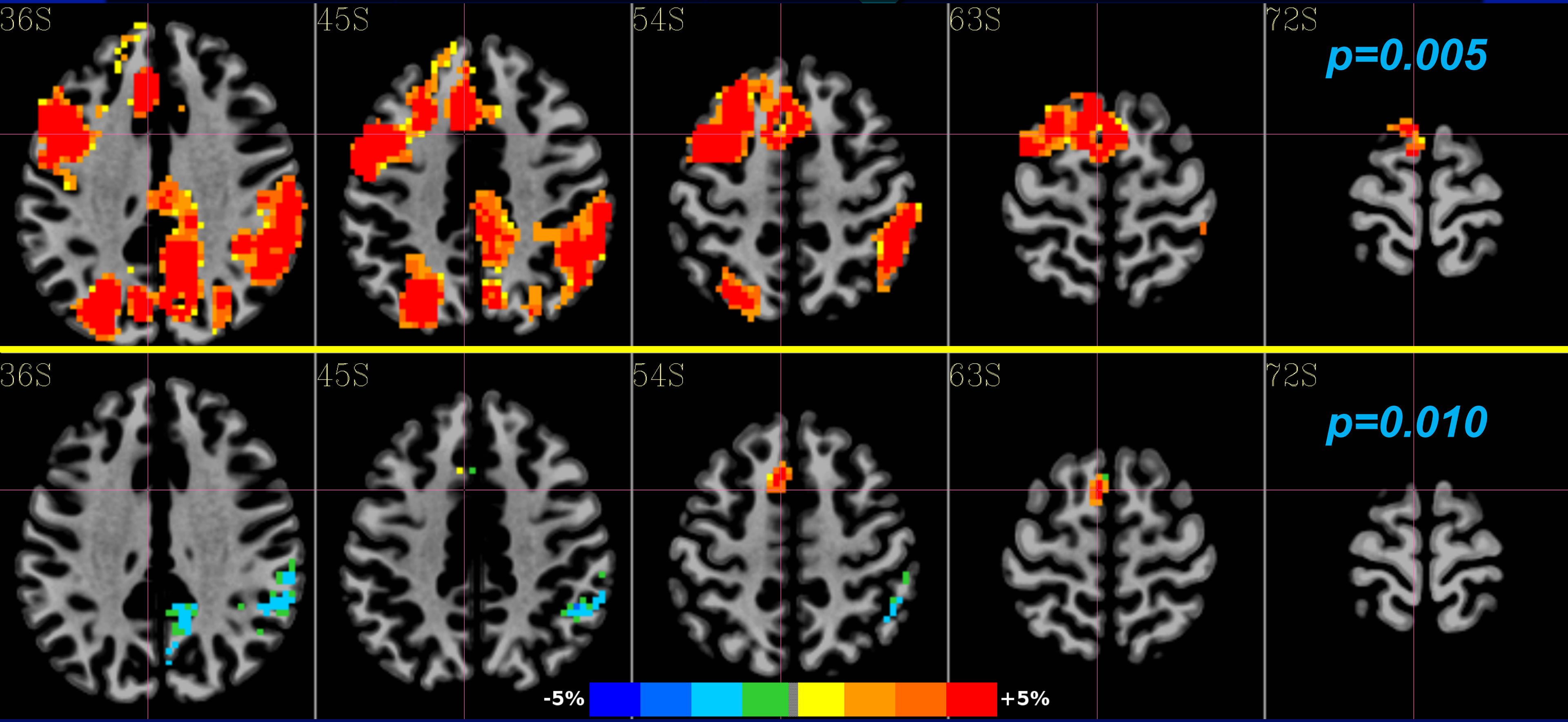
ETAC: FPR Control



p = 0.001,0.002,…,0.010 blurs = 4, 7, 10 mm

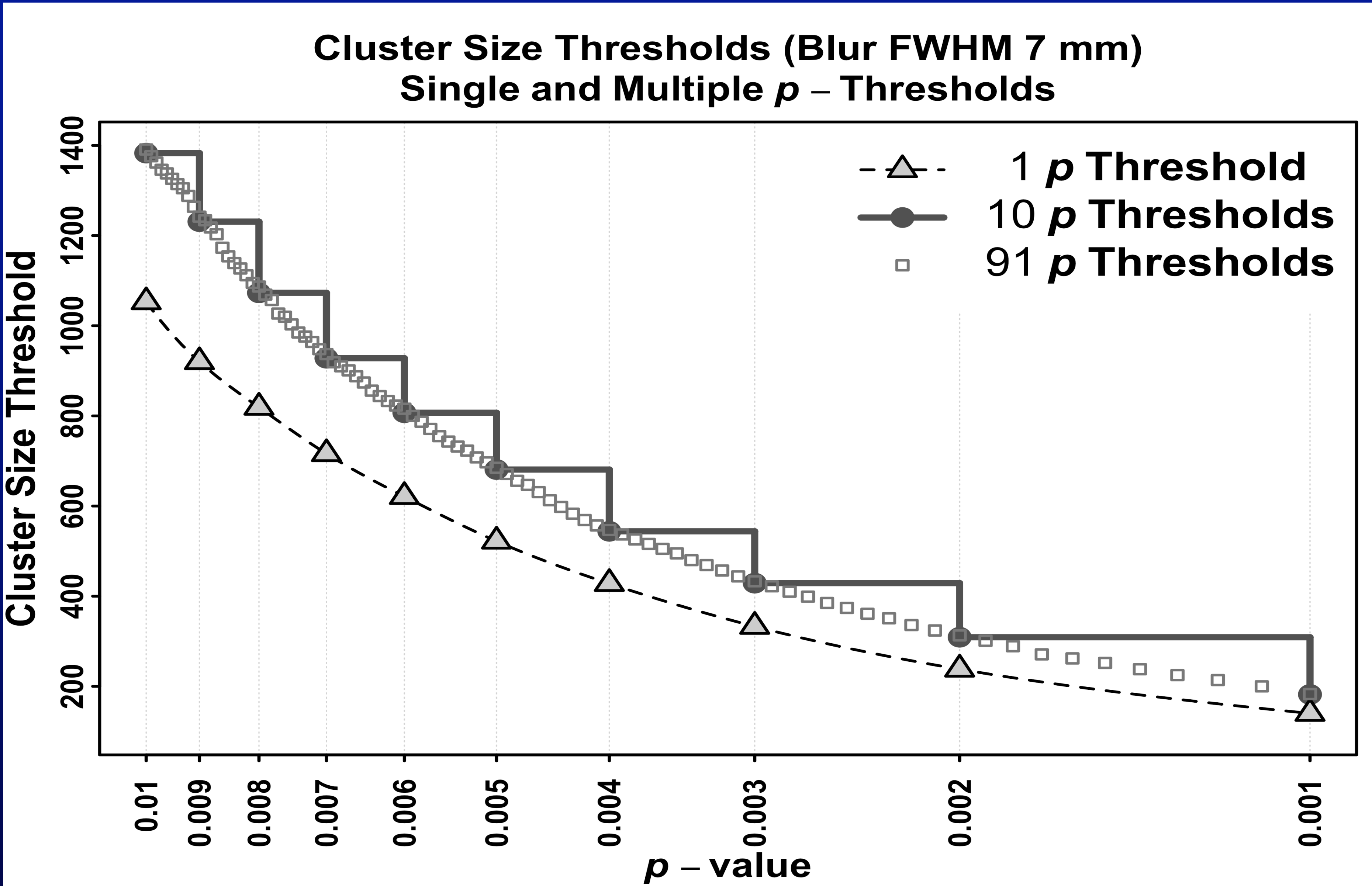
Task Detection Power: ETAC *minus* Single Threshold

1000 simulations



UCLA Phenomics study (*pamenc vs control task*)
20 (out of 81) subjects per test; single blur=7mm, 10 *p*-s
⇛ data from OpenFMRI web site

Cluster Size: ETAC/single *p*



ETAC Sample Command

```
3dttest++
 -setA datasets
 -setB datasets { other options here ... }
 -prefix Gtest.nii
 -prefix_clustsim Gtest
 -ETAC
 -ETAC_blur 4 7
 -ETAC_opt
 sid=2:pthr=0.01/0.001/10:name=TestA
 -ETAC_opt
 sid=2:pthr=0.01/0.001/91:name=TestB
```

Combines with any other blurring (refers to -ETAC_blur 4 7)

Conclusions (At Long Last*!*)

- If `3dttest++` can do your group analysis, **ETAC** might be your new friend
  - Fewer arbitrary thresholding choices ☺
  - Little loss of power, perhaps some gain ☺
  - Publication just accepted (May 2019) ☺
- If you need **`3dLME`**, **`3dMVM`**, *etc.*, then the mixed model ACF method is decent
  - With per-voxel $p \leq 0.002$
  - Publication you can cite ☺

AFNI Clustering Papers

- Accepted in Brain Connectivity – **ETAC** paper
  - https://www.biorxiv.org/content/10.1101/295931v2
- FMRI Clustering and False Positive Rates. PNAS 114: E3370–E3371, 2017.
  - https://arxiv.org/abs/1702.04846
  - https://doi.org/10.1073/pnas.1614961114
- FMRI Clustering in **AFNI**: False Positive Rates Redux. Brain Connectivity 7:152-171, 2017.
  - https://arxiv.org/abs/1702.04845
  - https://doi.org/10.1089/brain.2016.0475

Where It Started