

**Outline of Dual
Thresholding and
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 = Family-Wise Error**
 - = 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

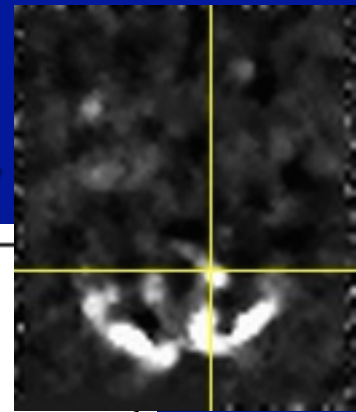
Group Spatial Inference - 2

- Voxel-wise thresholding on group t -statistic is usually super conservative (to get global FPR $\approx 5\%$)
- ***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 $\Rightarrow \Rightarrow \dots$

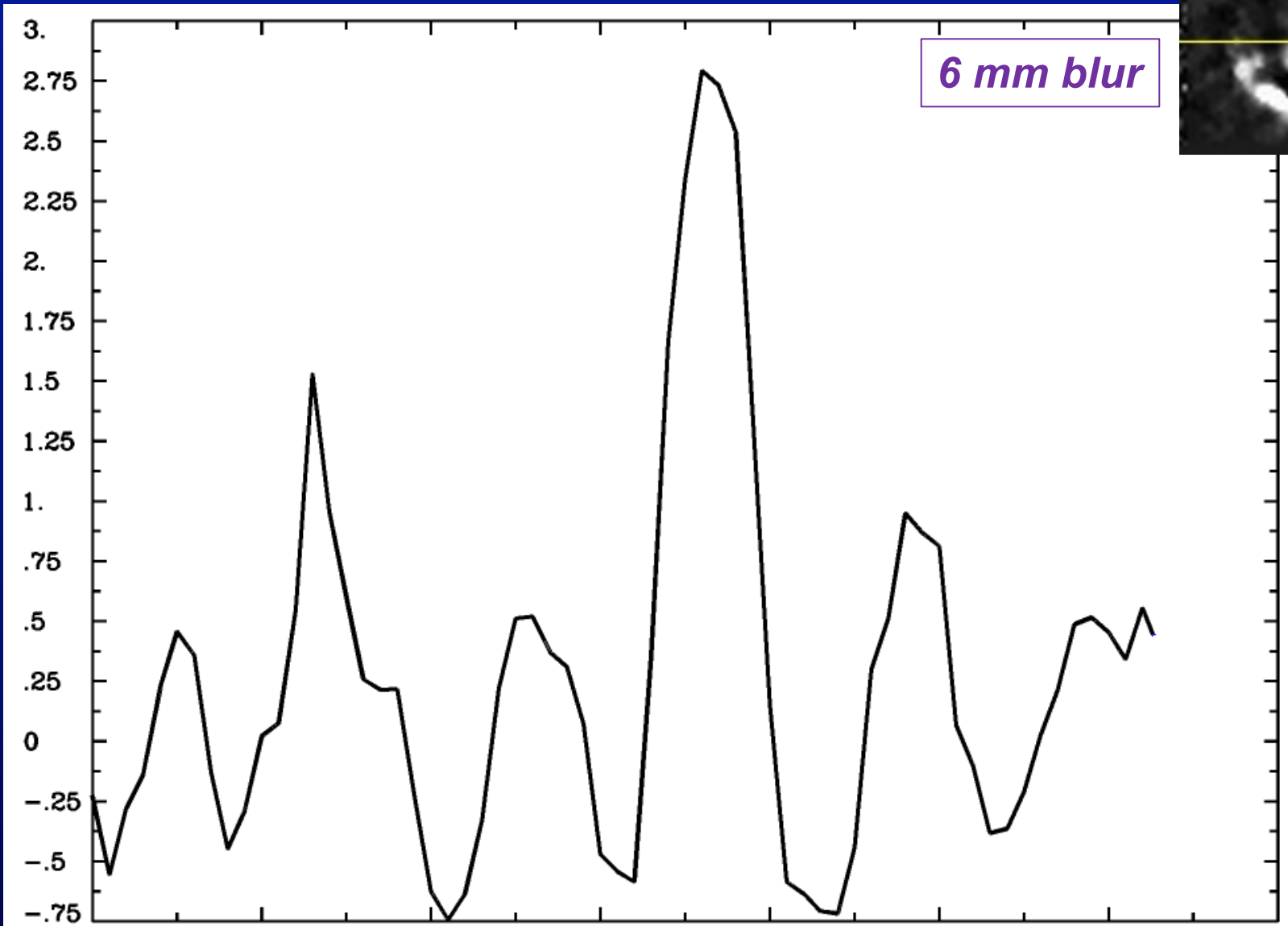
Group Spatial Inference - 3

- Dual threshold method (voxel then cluster) can still be weak (low power to detect)
- ***A Solution***: use spatial blurring \approx 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

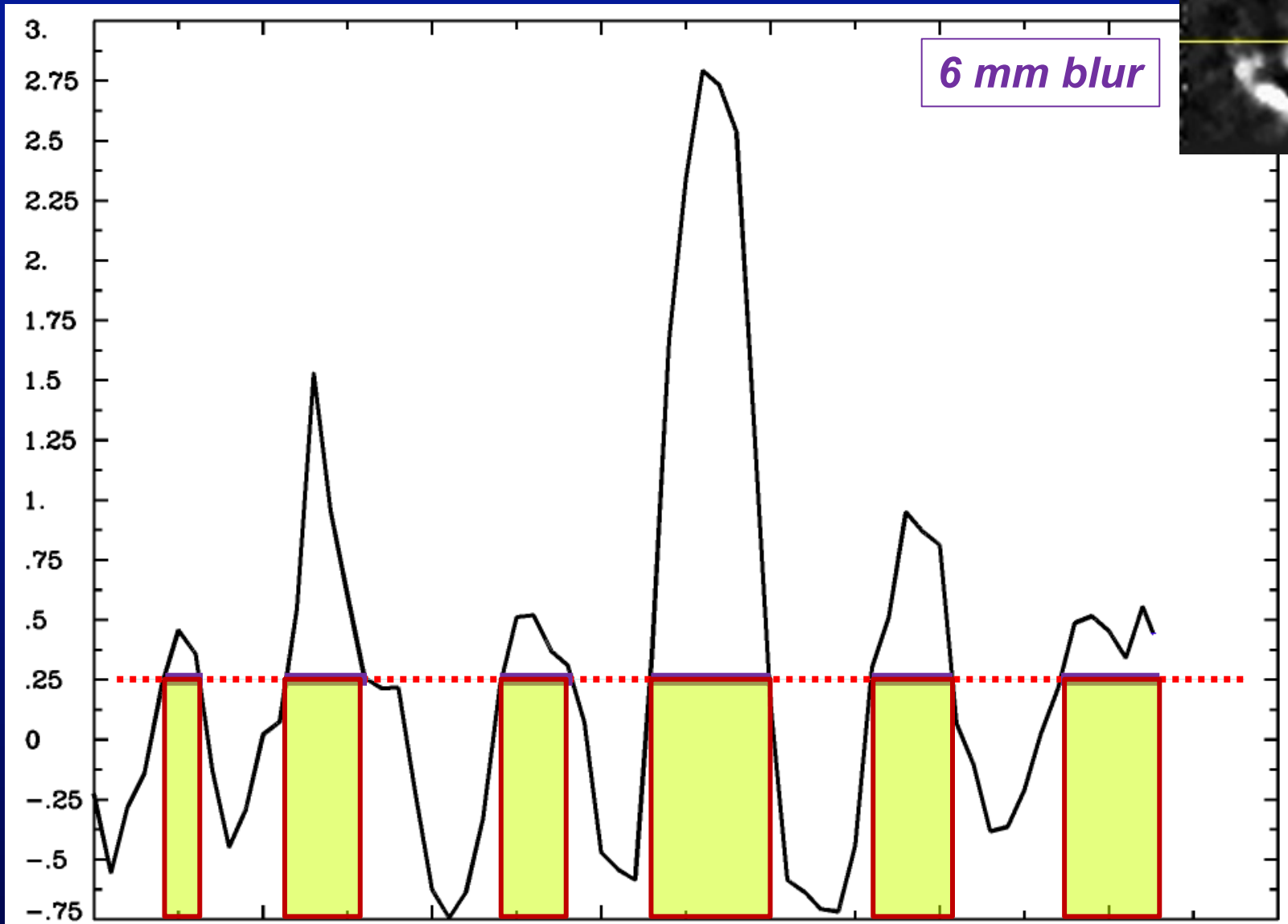
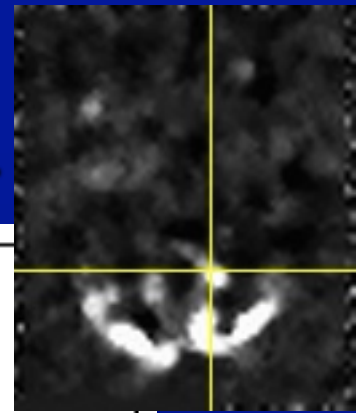
1D Double Thresholding (real data)



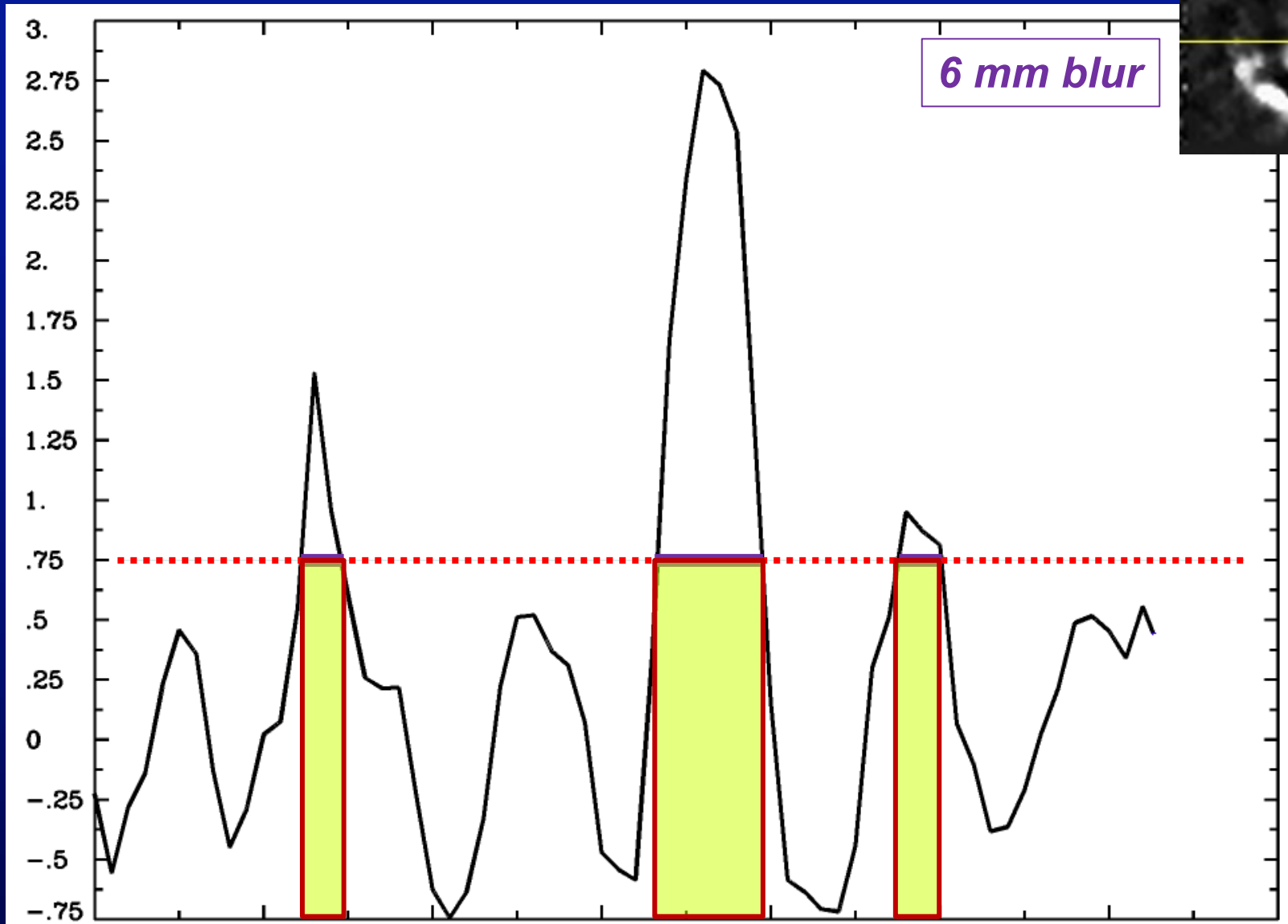
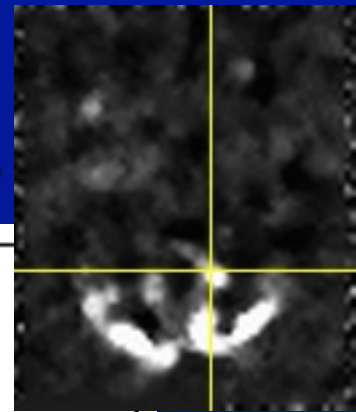
6 mm blur



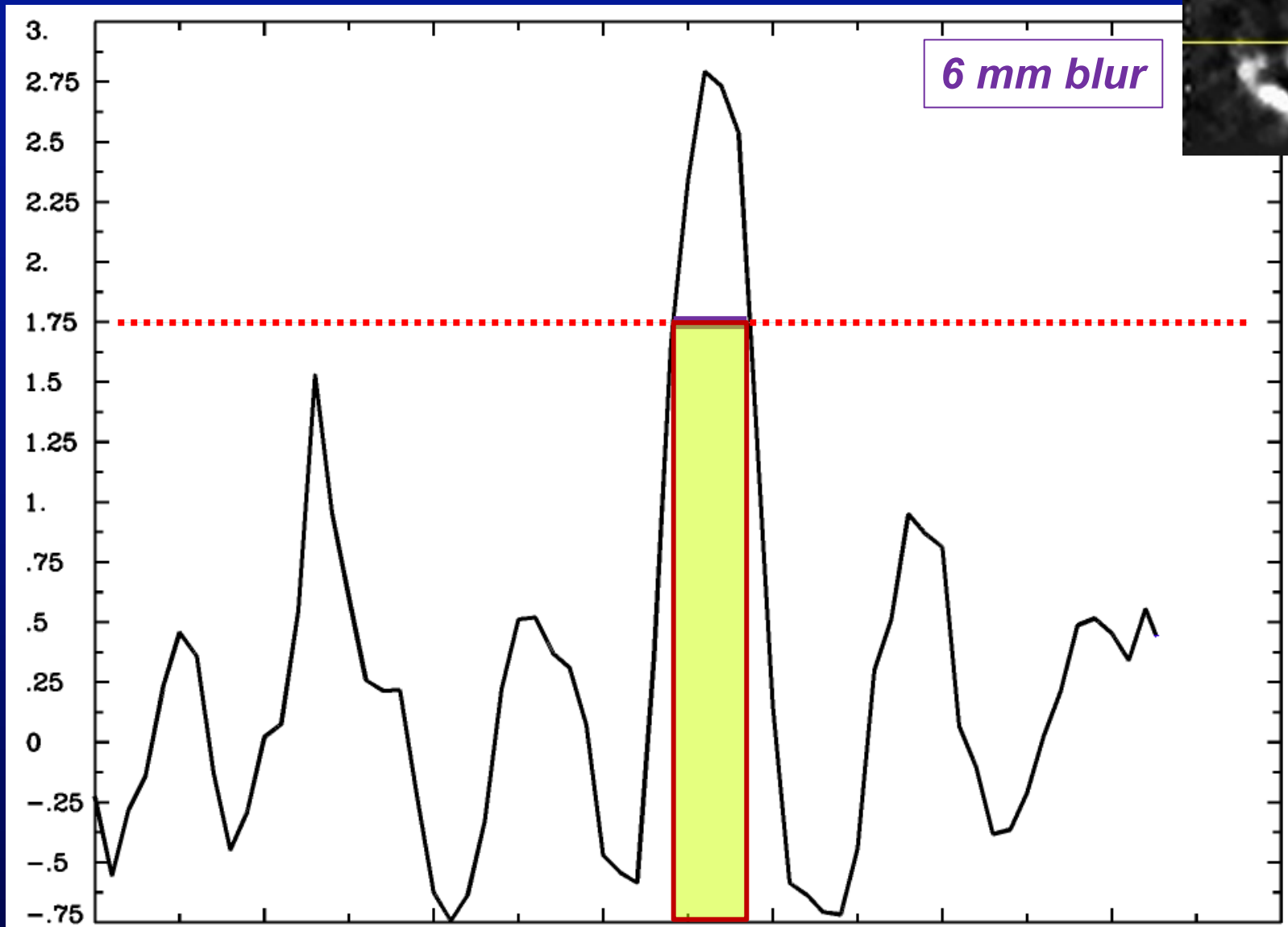
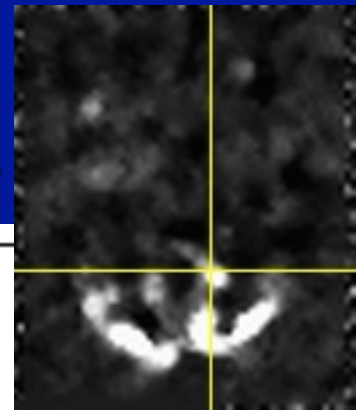
1D Double Thresholding (real data)



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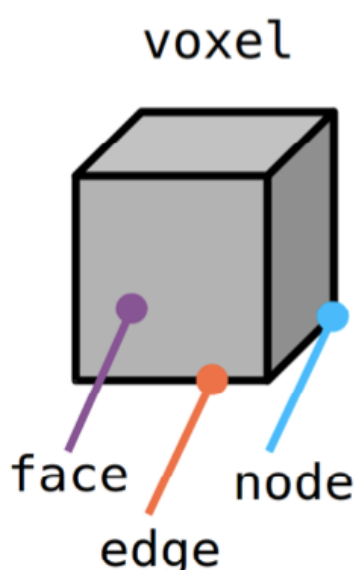


1D Double Thresholding (real data)

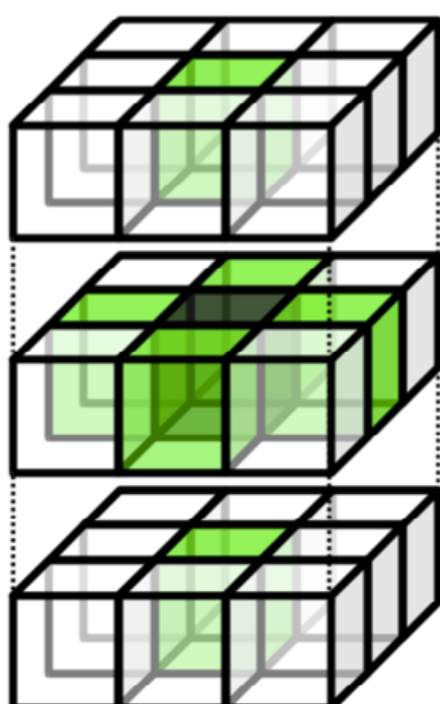


Definitions of “Cluster” in 3D

Common voxel neighborhood definitions



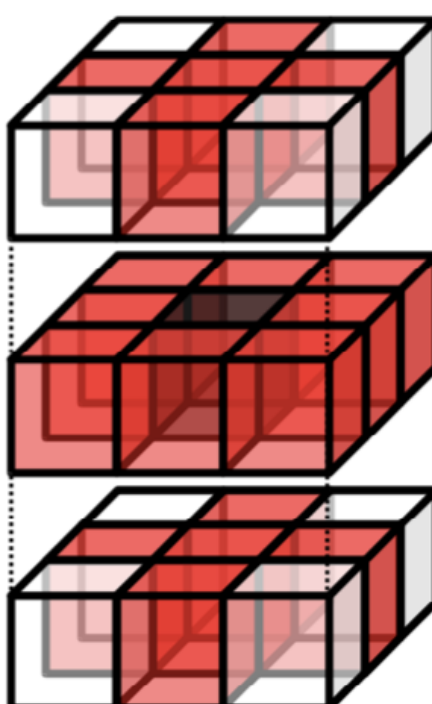
face



AFNI

(NN=1)

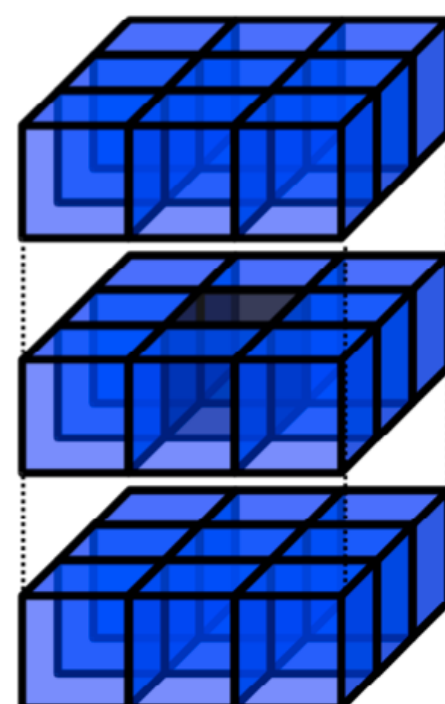
face+edge



SPM

(NN=2)

face+edge+node



FSL

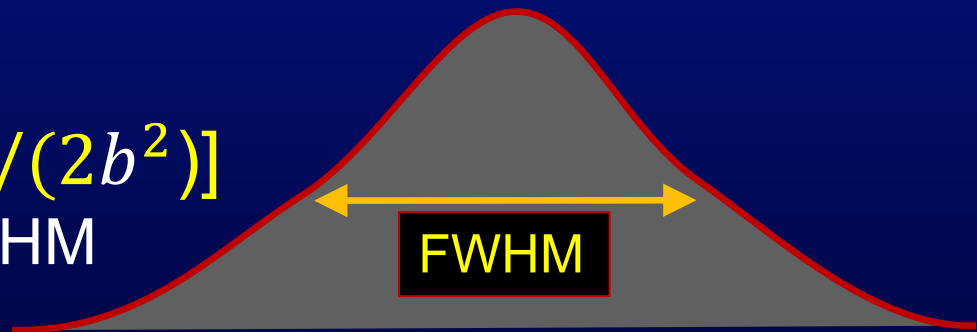
(NN=3)

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

$$ACF(r) = \exp[-r^2 / (2b^2)]$$

$$b = 0.4246 \cdot \text{FWHM}$$



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

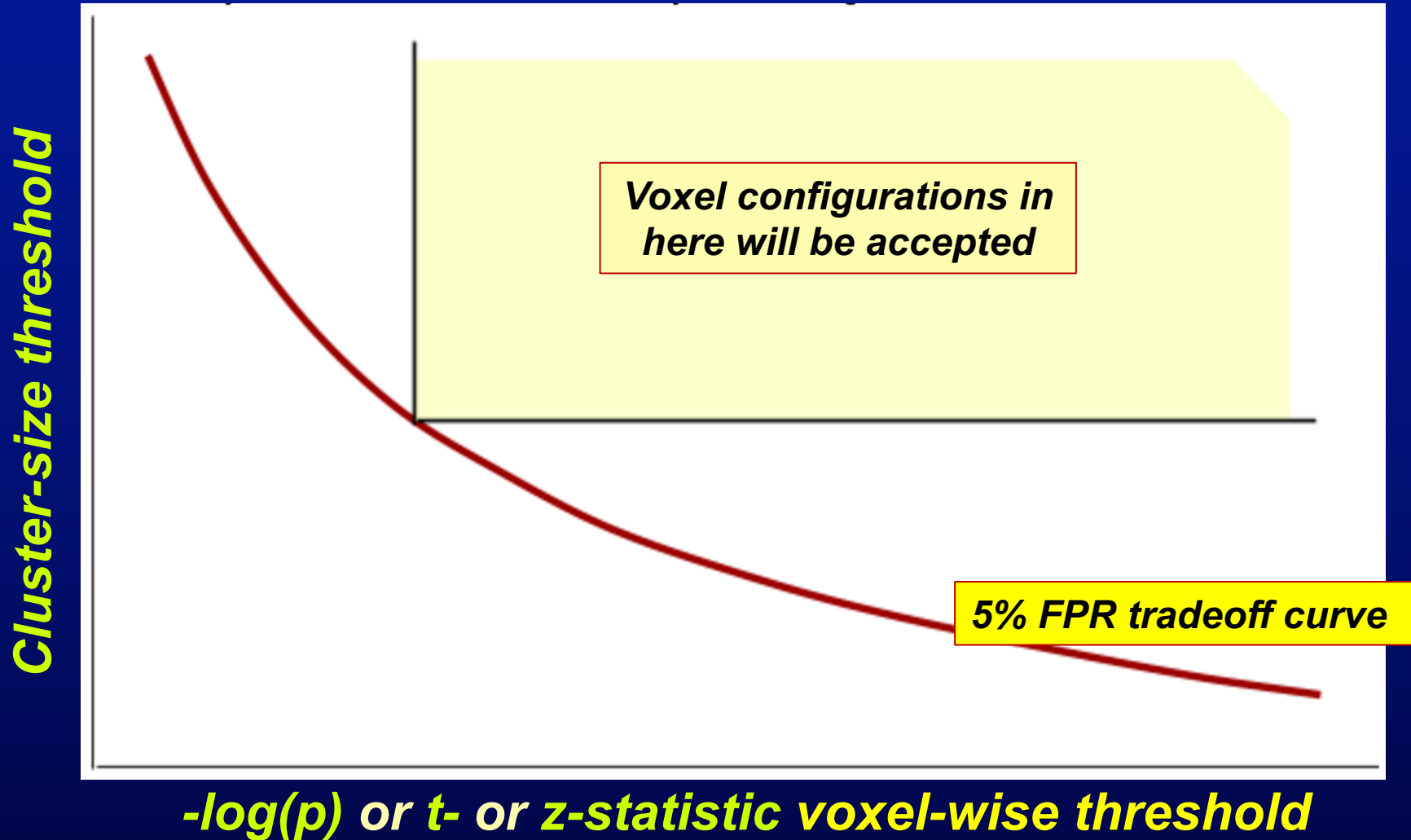
ClustSim - 3

- **3dClustSim** outputs tables like this:

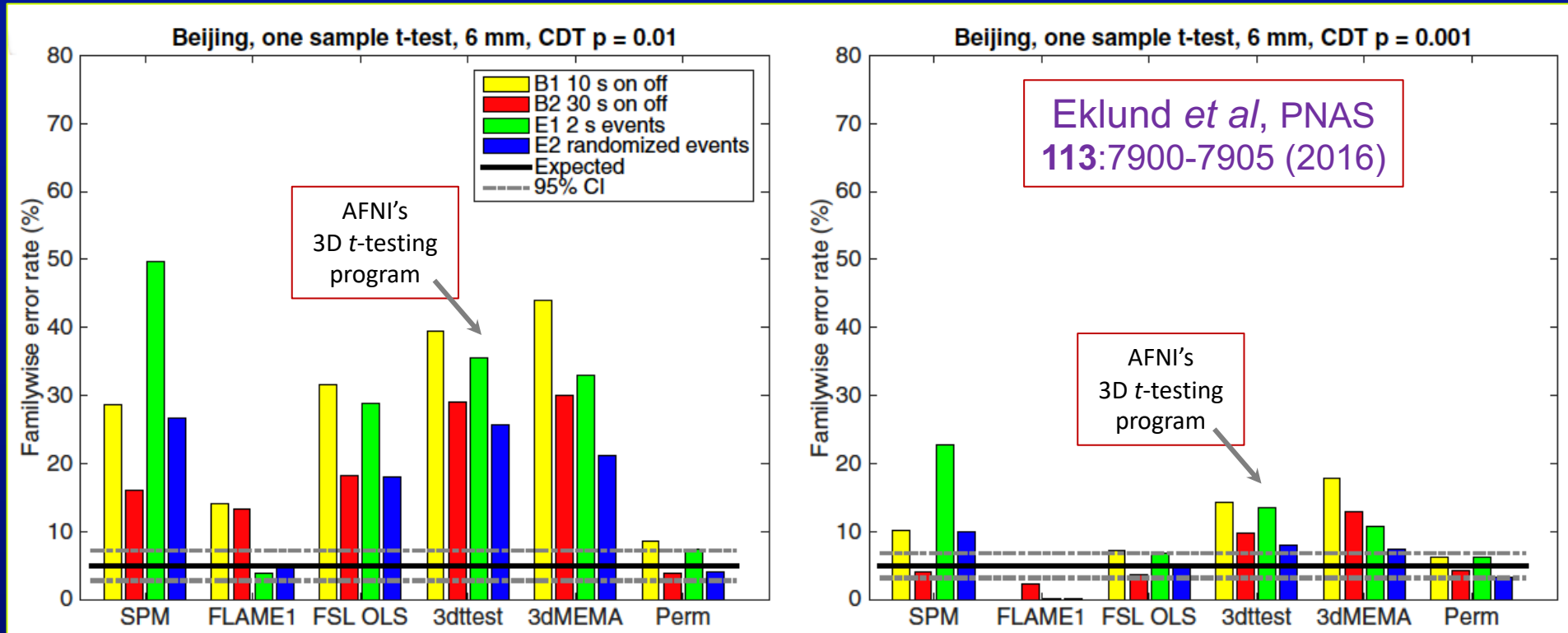
```
# CLUSTER SIZE THRESHOLD (pthr, alpha)
# -NN 2 | alpha=Prob(Cluster > given size)
# pthr | .10000 .05000 .02000 .01000
# ----- | -----
0.010000 50.3 57.2 66.3 73.6
0.005000 34.4 39.5 46.3 51.6
⇒ 0.002000 22.1 25.7 30.4 34.1
0.001000 16.0 19.0 22.8 26.0
0.000500 12.0 14.5 17.4 20.1
0.000200 8.1 10.0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

ClustSim - 4

- High t threshold \Rightarrow small cluster threshold



The Great Cluster Panic - 2016



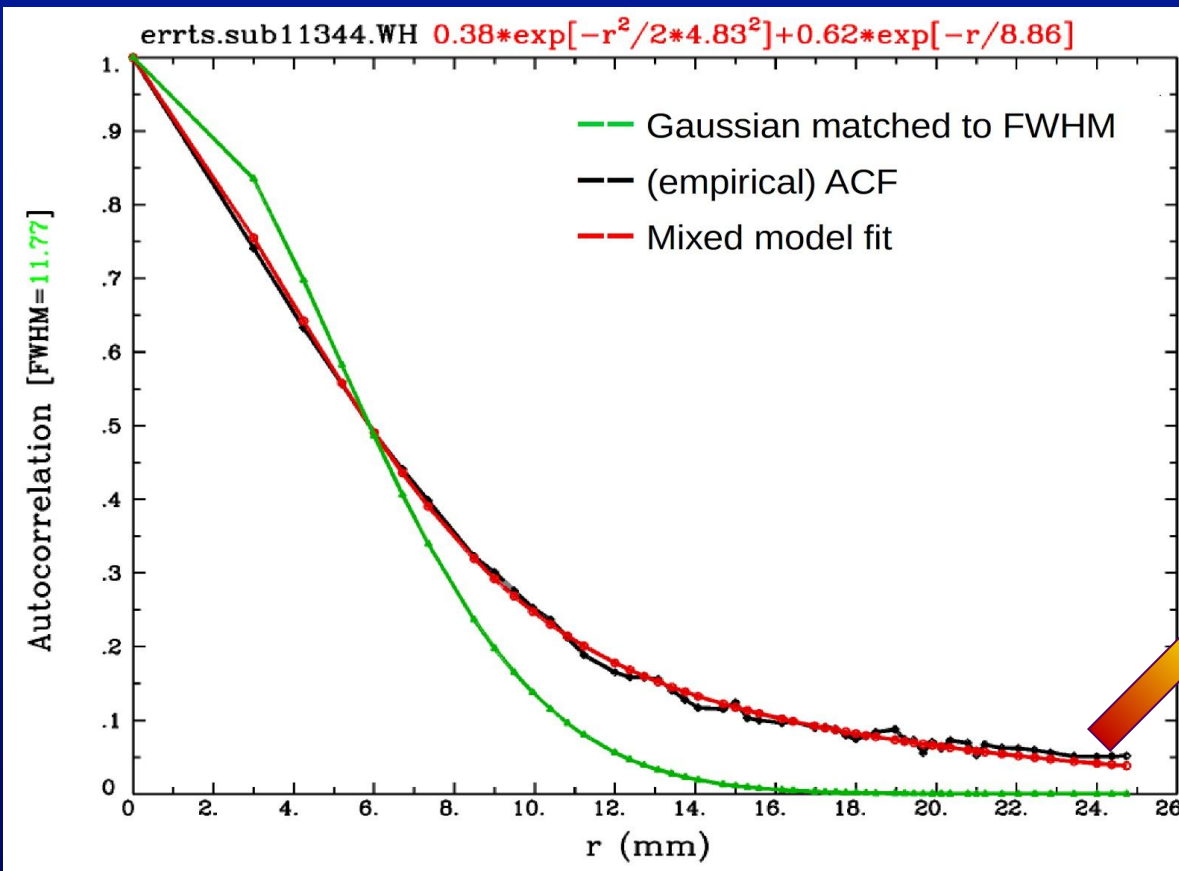
- **FPR \gg 5%**: notably for voxel-wise $p=0.01$
- A lot of doom-crying about this in 2016:
“*Could Invalidate 15 Years of Brain Research*”

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)

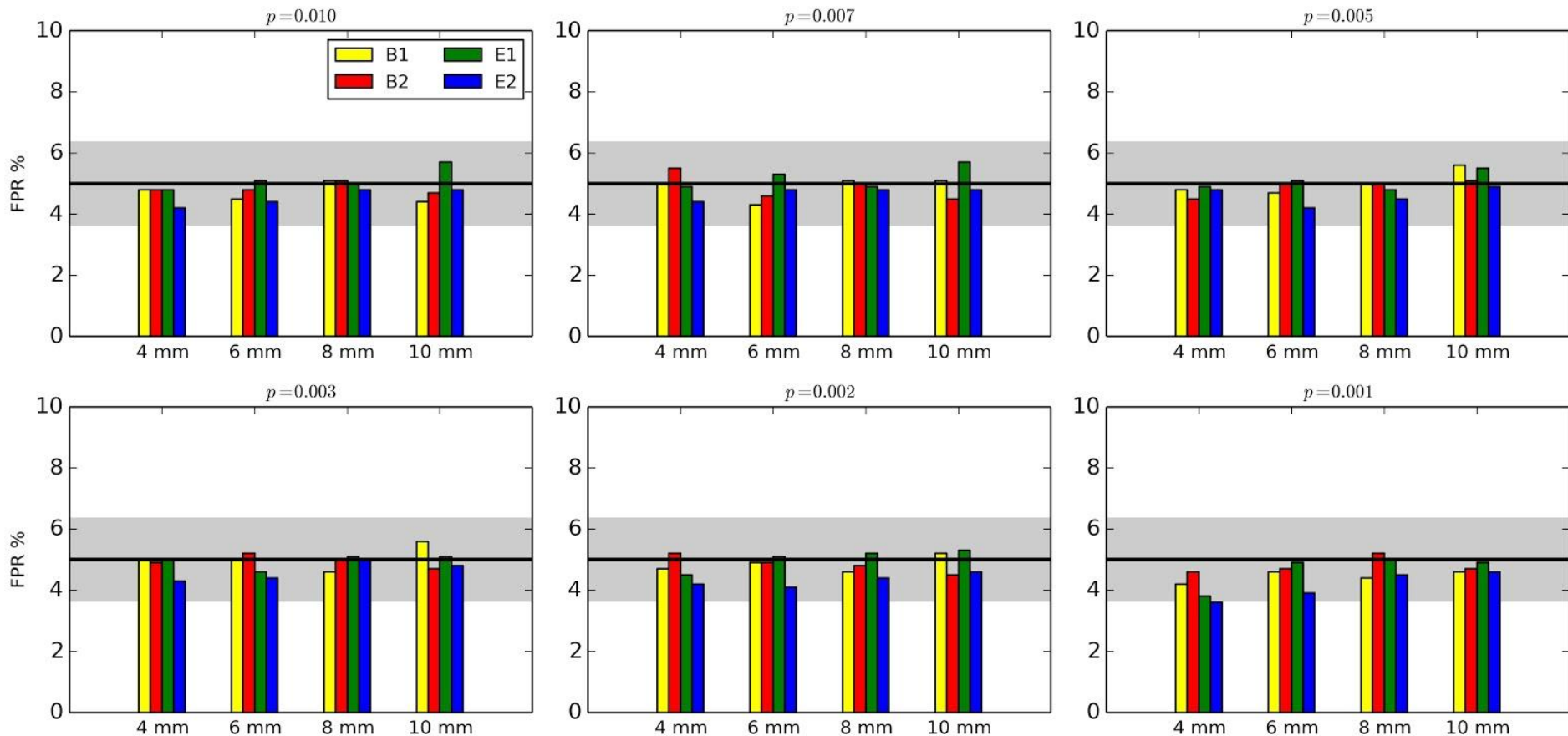
$$ACF(r) = a \exp[-r^2 / (2b^2)] + (1 - a) \exp[-r/c]$$

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*

Nonparametric clustering: "3dttest++ -Clustsim"



- *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 at this time
 - Re-running many **3dLME** cases (*e.g.*) is too slow
- **3dtttest++** with the **-Clustsim** option
- Gives excellent FPR control 😊
- Has fairly large cluster-size thresholds 😞
 - Led me to next set of ideas ⇒⇒⇒ **ETAC!**

Arbitrary Choices

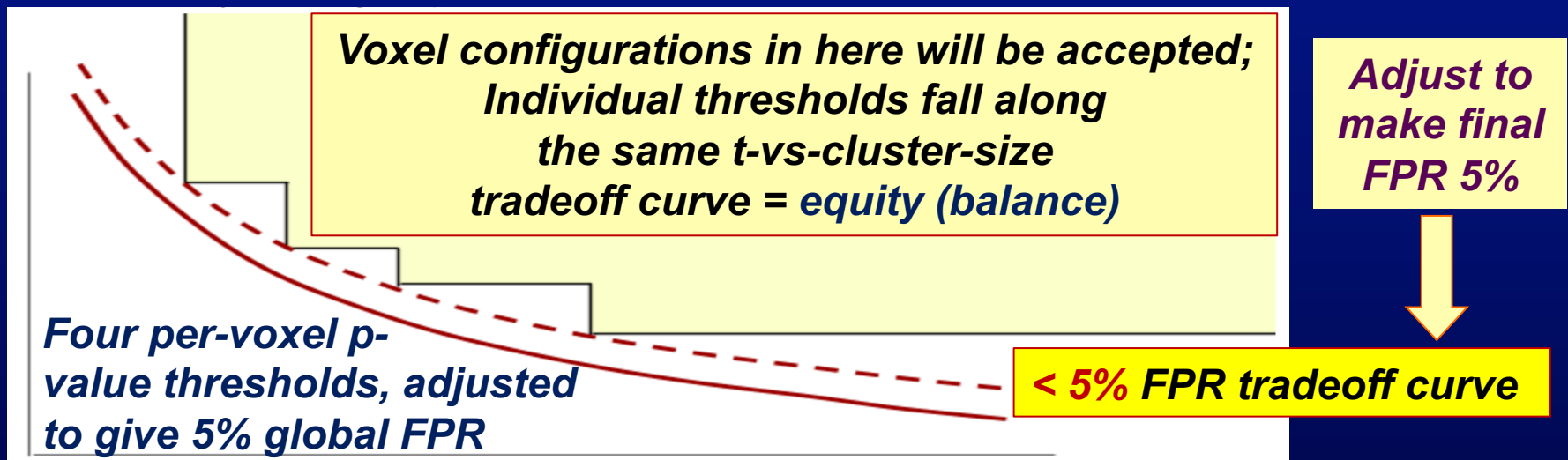
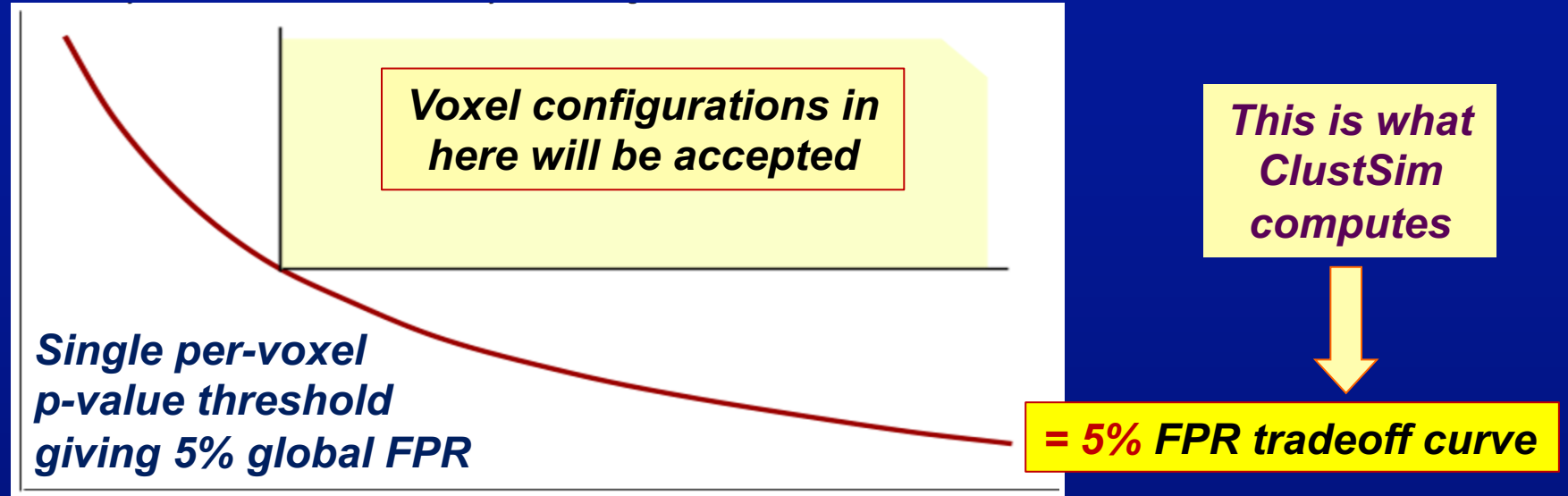
- I've mentioned two parameters that must be chosen by the researcher in the “usual” methods:
 - Voxel-wise p -value for first-level thresholding
 - Typical fMRI values range from 0.001 to 0.01
 - Amount of spatial blurring to add to data
 - Typical fMRI values range from 4 to 10 mm
- But there are no “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: uses **randomization**

Equity: Multi-Thresholding

Cluster-size threshold



$-\log(p)$ or t- or z-statistic voxel-wise threshold

Equity: Across Methods

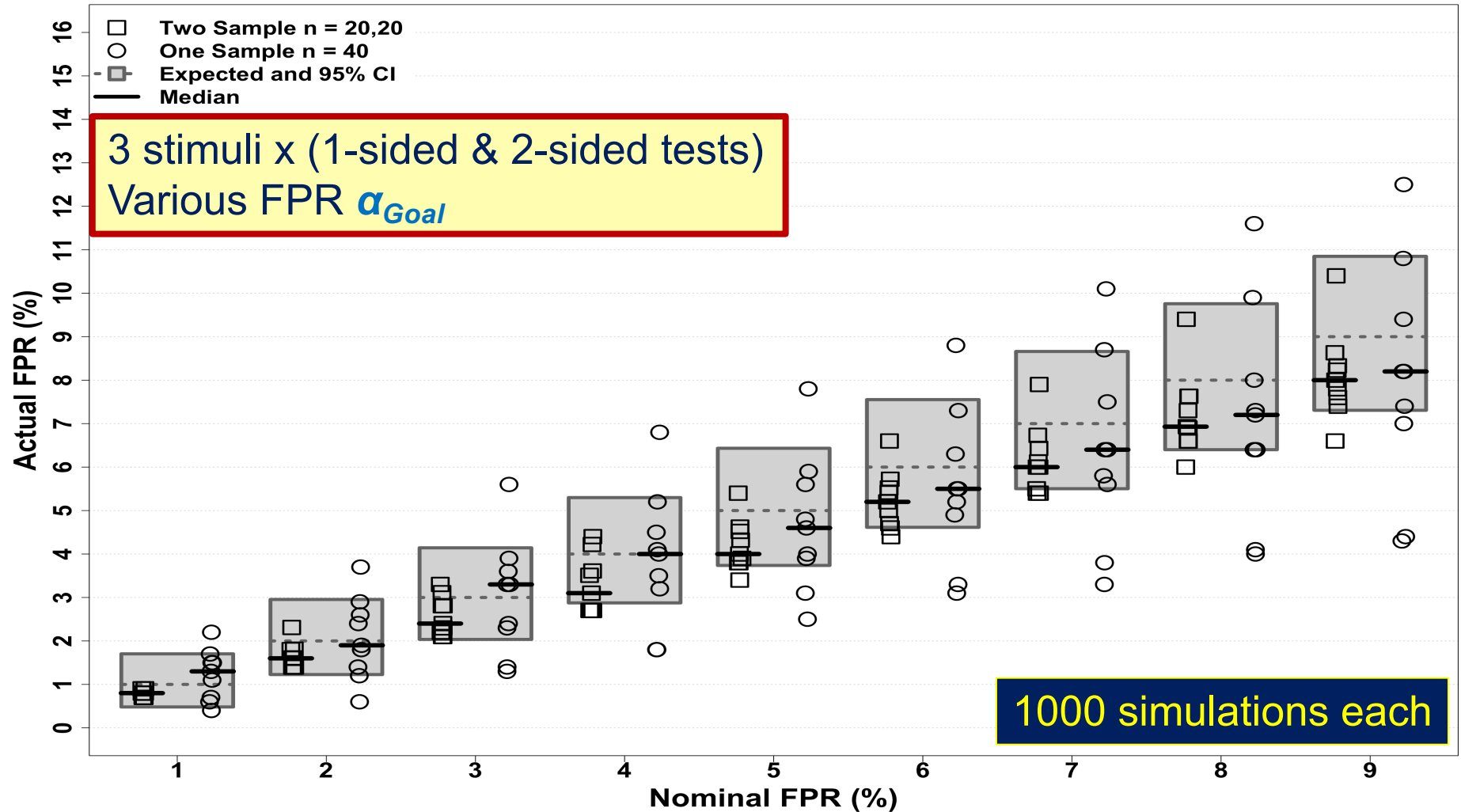
- Balancing can apply to any multi-choice method for selecting voxel clusters
 - Each sub-method has a cluster-FOM threshold adjustable to get desired FPR
 - **Balance** = choose each sub-method's cluster-FOM threshold to have the same global FPR $\alpha_0 < \alpha_{\text{Goal}}$ (e.g., 5%)
- **ETAC 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

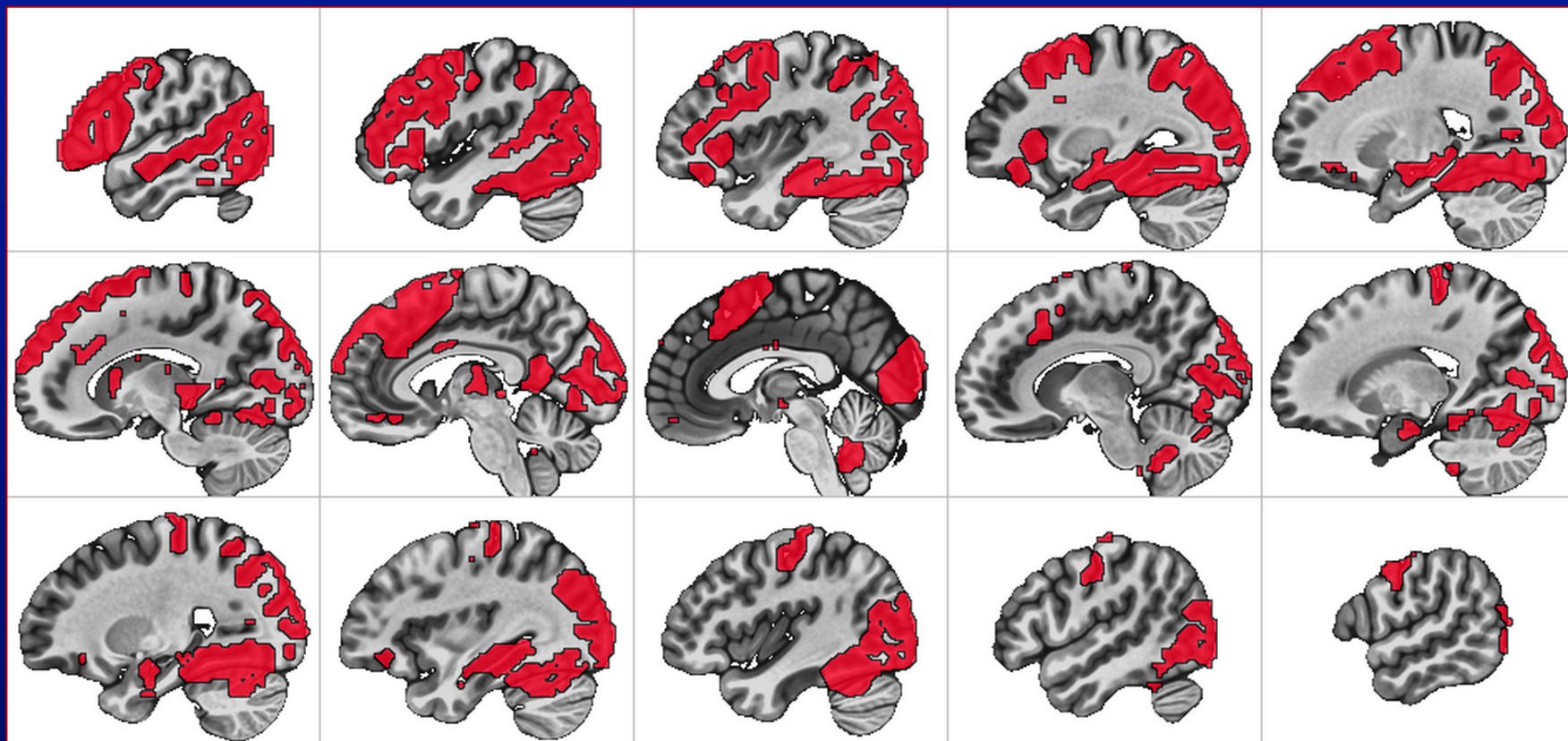
ETAC: FPR Control

ETAC FPRs (Beijing-Zang Datasets)
Global Cluster Thresholds



$p = 0.01, 0.005, 0.002, 0.001$ blur = 4, 7, 10

ETAC activation mask (2% FPR, all 81 subjects)



UCLA Phenomics study (*pamenc vs control task*)

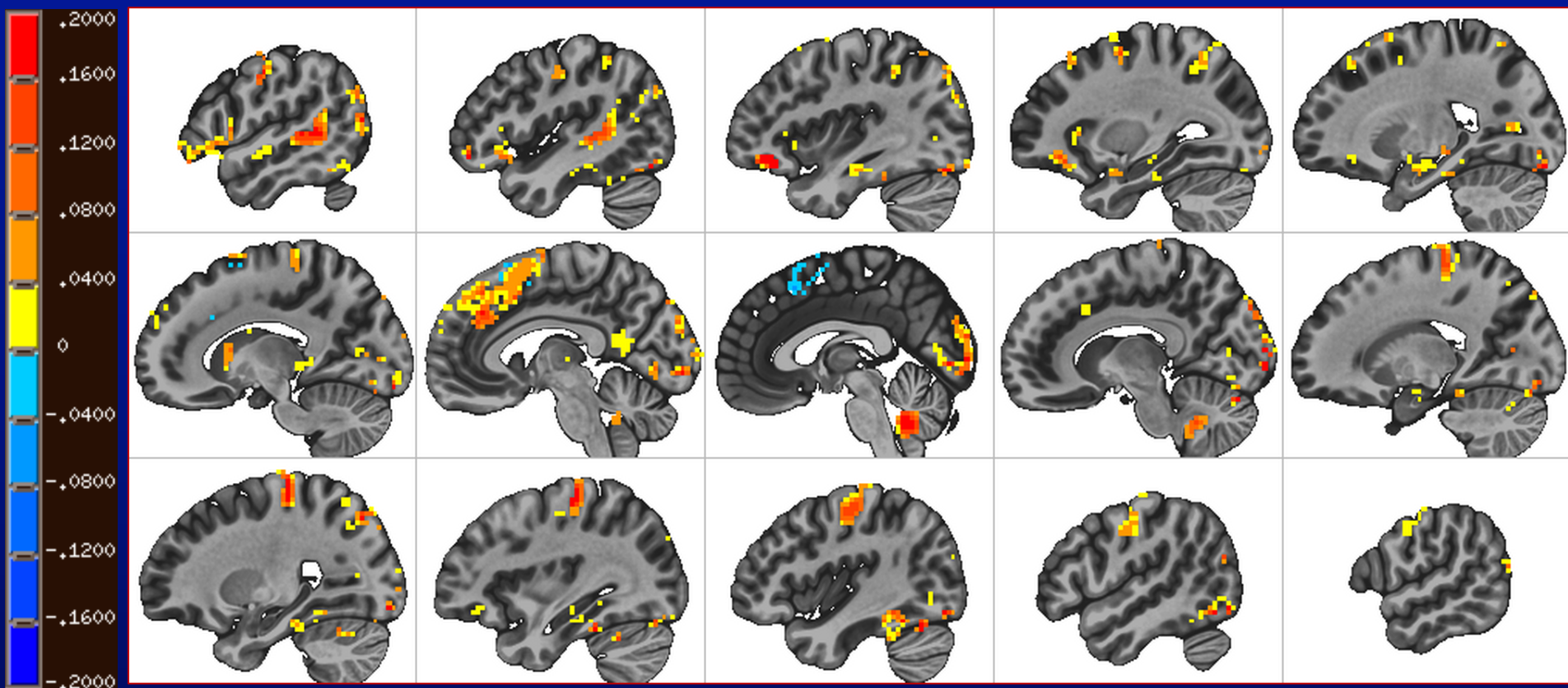
20 (out of 81) subjects per test

⇒ data from OpenfMRI web site

Task Detection Power:

500 simulations

ETAC *minus* Single Threshold



UCLA Phenomics study (*pamenc vs control task*)

20 (out of 81) subjects per test

⇒ data from OpenfMRI web site

ETAC Sample Command

```
3dtttest++
```

```
-setA datasets
```

```
-setB datasets { other options here ... }
```

```
-prefix Gtest.nii
```

```
-prefix_clustsim GtestX
```

```
-ETAC
```

```
-ETAC_blur 6 12 ← Combines with any other blurring
```

```
-ETAC_opt
```

```
sid=2:pthr=0.01,0.003,0.001:name=TestA
```

```
-ETAC_opt
```

```
sid=1:pthr=0.01,0.003,0.001:name=TestB
```

Conclusions (At Long Last!)

- If **3dttest++** can do your group analysis, **ETAC** might be your new friend
 - Fewer arbitrary thresholding choices 😊
 - No loss of power 😊
 - No publication to cite yet 😞
- 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

- Somewhere over the rainbow – ETAC paper
 - <https://www.biorxiv.org/content/early/2018/04/05/295931>
- 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

Clear Creek trail, Grand Canyon

