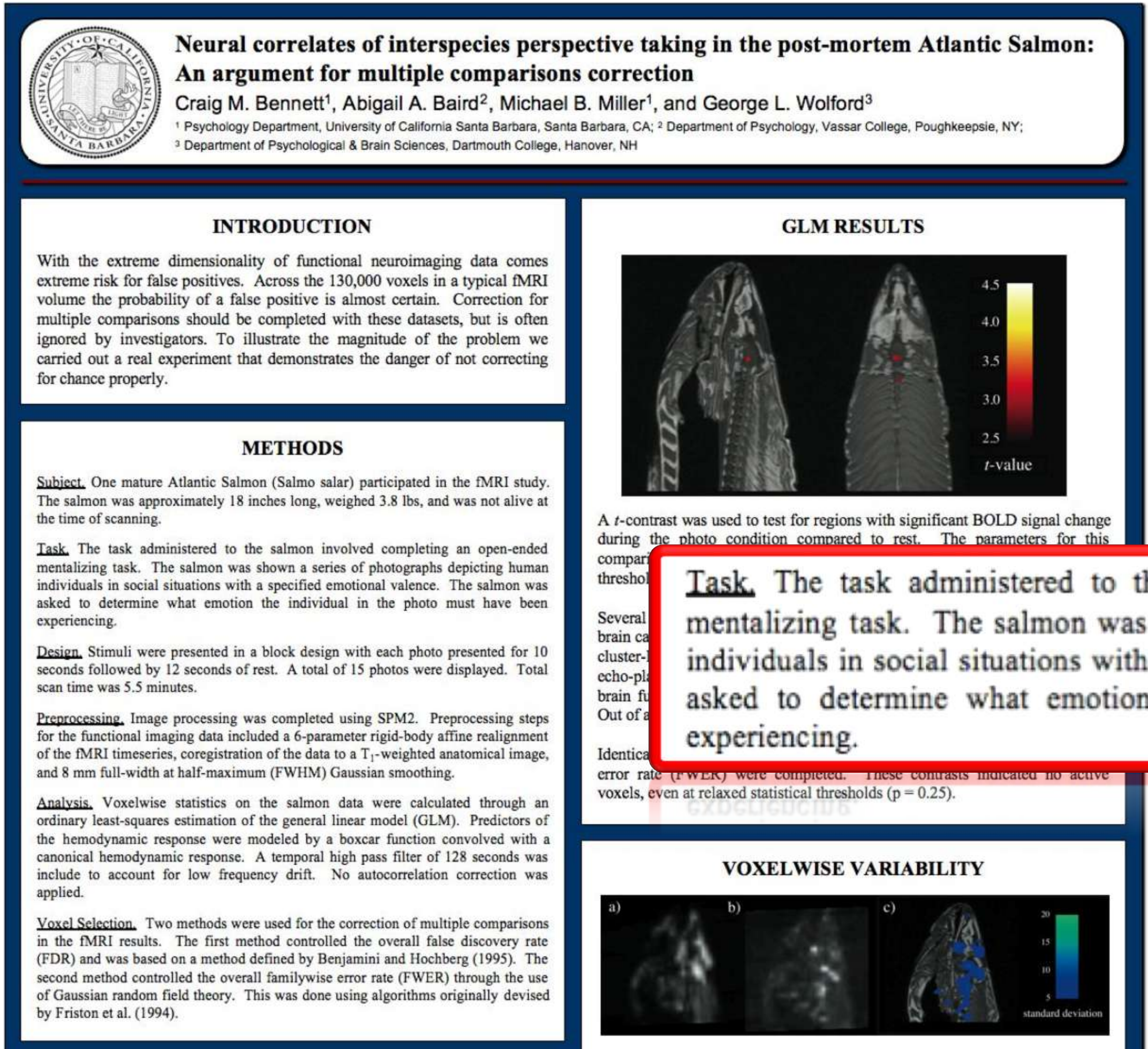
Equitable Thresholding and Clustering

Robert W. Cox
Scientific and Statistical Computing Core, NIMH/NIH/DHHS, Bethesda, MD, USA

June 11th, 2018
NKI



Neural correlates of interspecies perspective taking in the post-mortem Atlantic Salmon: An argument for multiple comparisons correction

Craig M. Bennett[1], Abigail A. Baird[2], Michael B. Miller[1], and George L. Wolford[3]
[1] Psychology Department, University of California Santa Barbara, Santa Barbara, CA; [2] Department of Psychology, Vassar College, Poughkeepsie, NY;
[3] Department of Psychological & Brain Sciences, Dartmouth College, Hanover, NH

INTRODUCTION

With the extreme dimensionality of functional neuroimaging data comes extreme risk for false positives. Across the 130,000 voxels in a typical fMRI volume the probability of a false positive is almost certain. Correction for multiple comparisons should be completed with these datasets, but is often ignored by investigators. To illustrate the magnitude of the problem we carried out a real experiment that demonstrates the danger of not correcting for chance properly.

METHODS

Subject. One mature Atlantic Salmon (Salmo salar) participated in the fMRI study. The salmon was approximately 18 inches long, weighed 3.8 lbs, and was not alive at the time of scanning.

Task. The task administered to the salmon involved completing an open-ended mentalizing task. The salmon was shown a series of photographs depicting human individuals in social situations with a specified emotional valence. The salmon was asked to determine what emotion the individual in the photo must have been experiencing.

Design. Stimuli were presented in a block design with each photo presented for 10 seconds followed by 12 seconds of rest. A total of 15 photos were displayed. Total scan time was 5.5 minutes.

Preprocessing. Image processing was completed using SPM2. Preprocessing steps for the functional imaging data included a 6-parameter rigid-body affine realignment of the fMRI timeseries, coregistration of the data to a T_1-weighted anatomical image, and 8 mm full-width at half-maximum (FWHM) Gaussian smoothing.

Analysis. Voxelwise statistics on the salmon data were calculated through an ordinary least-squares estimation of the general linear model (GLM). Predictors of the hemodynamic response were modeled by a boxcar function convolved with a canonical hemodynamic response. A temporal high pass filter of 128 seconds was include to account for low frequency drift. No autocorrelation correction was applied.

Voxel Selection. Two methods were used for the correction of multiple comparisons in the fMRI results. The first method controlled the overall false discovery rate (FDR) and was based on a method defined by Benjamini and Hochberg (1995). The second method controlled the overall familywise error rate (FWER) through the use of Gaussian random field theory. This was done using algorithms originally devised by Friston et al. (1994).

GLM RESULTS

A t-contrast was used to test for regions with significant BOLD signal change during the photo condition compared to rest. The parameters for this compari
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error rate (FWER) were completed. These contrasts indicated no active voxels, even at relaxed statistical thresholds (p = 0.25).

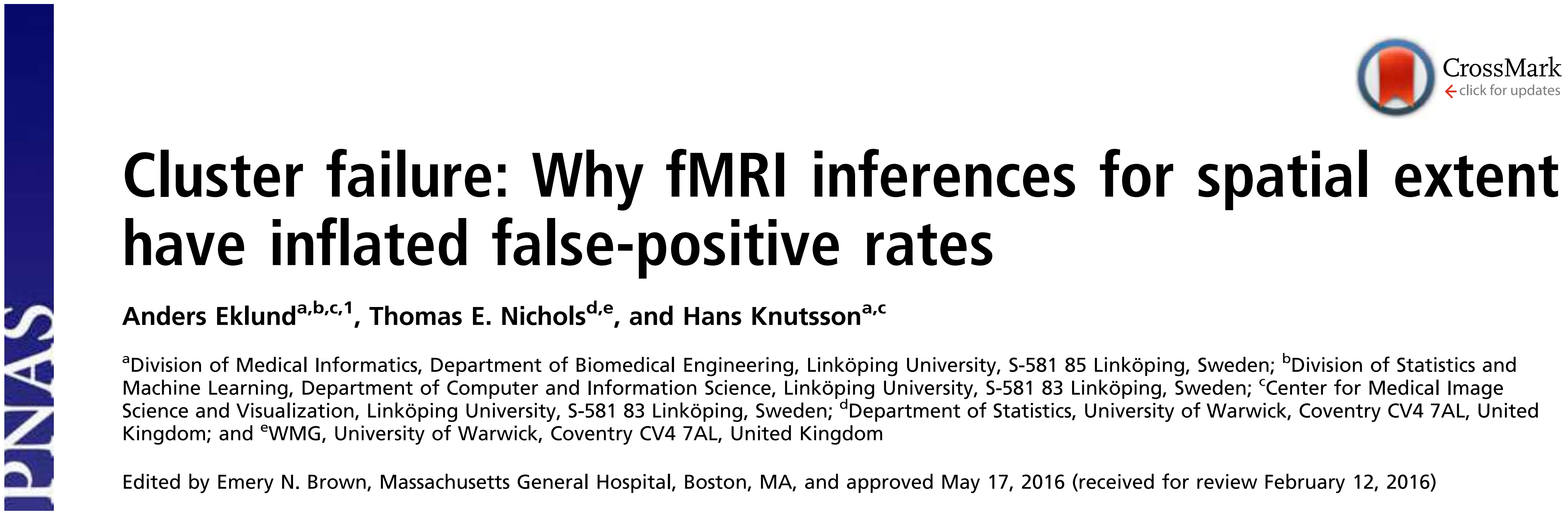
VOXELWISE VARIABILITY

OHBM 2010

Ig Nobel Neuroscience 2012

Task. The task administered to the salmon involved completing an open-ended mentalizing task. The salmon was shown a series of photographs depicting human individuals in social situations with a specified emotional valence. The salmon was asked to determine what emotion the individual in the photo must have been experiencing.

And then in 2016, this paper came out…



Cluster failure: Why fMRI inferences for spatial extent have inflated false-positive rates

Anders Eklund[a,b,c,1], **Thomas E. Nichols**[d,e], **and Hans Knutsson**[a,c]

[a]Division of Medical Informatics, Department of Biomedical Engineering, Linköping University, S-581 85 Linköping, Sweden; [b]Division of Statistics and Machine Learning, Department of Computer and Information Science, Linköping University, S-581 83 Linköping, Sweden; [c]Center for Medical Image Science and Visualization, Linköping University, S-581 83 Linköping, Sweden; [d]Department of Statistics, University of Warwick, Coventry CV4 7AL, United Kingdom; and [e]WMG, University of Warwick, Coventry CV4 7AL, United Kingdom

Edited by Emery N. Brown, Massachusetts General Hospital, Boston, MA, and approved May 17, 2016 (received for review February 12, 2016)

Which had the following statement in the Highlights section of the paper …

"These results question the validity of some 40,000 fMRI studies and may have a large impact on the interpretation of neuroimaging results"

Which generated …

Technology

15 years of br
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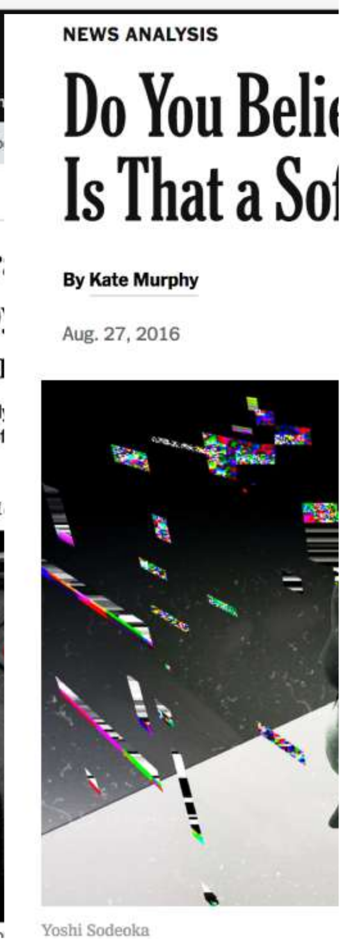
Swedish scie

Up to 70% of fMRI anal
challenging the validity o

By Mary-Ann Russon
Updated July 13, 201

Scientists claim to have found serio

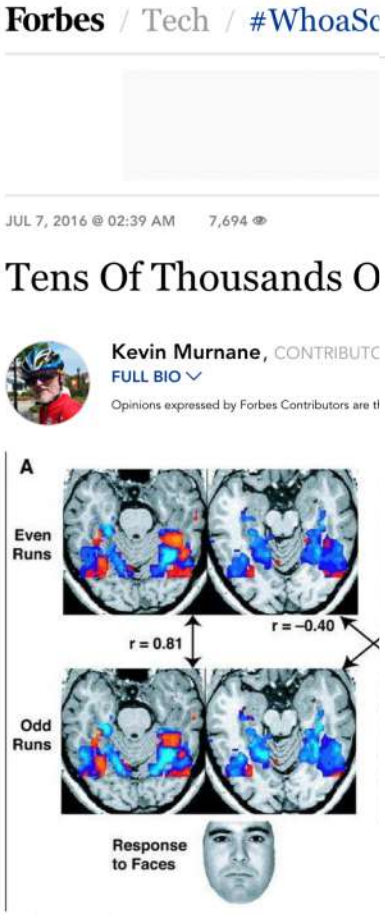

NEWS ANALYSIS

Do You Beli
Is That a So

By Kate Murphy

Aug. 27, 2016

Yoshi Sodeoka



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Kevin Murnane, CONTRIBUTC
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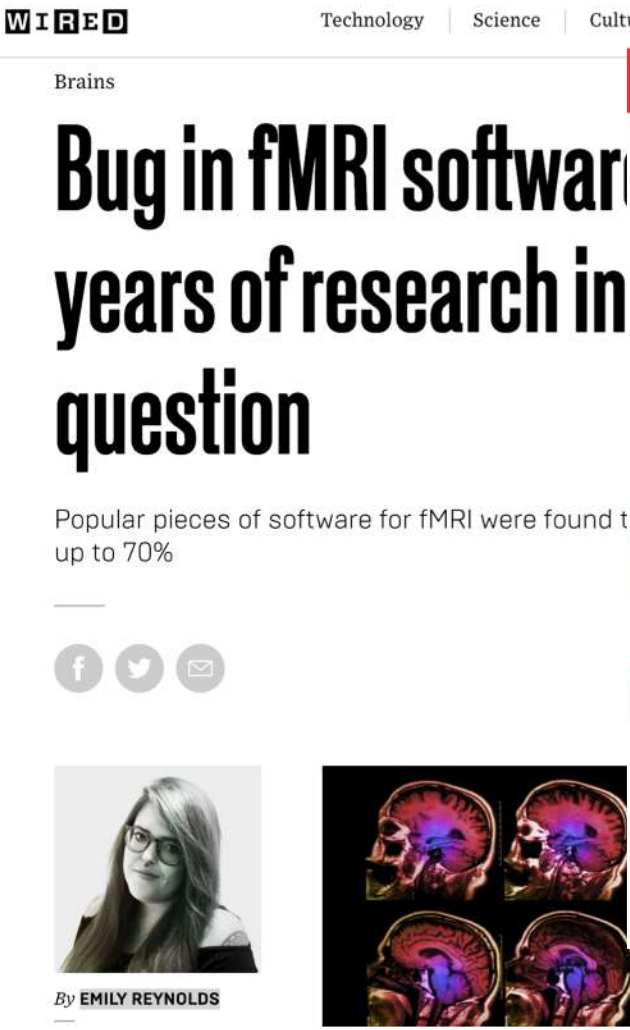
Opinions expressed by Forbes Contributors are t



Brains

Bug in fMRI softwar
years of research in
question

Popular pieces of software for fMRI were found t
up to 70%

By **EMILY REYNOLDS**

Ciência

Bug em software de ressonância magnética pode invalidar 15 anos de pesquisas sobre o cérebro

Cientistas descobrem problema no método usado para medir atividade cerebral. Se eles estiverem certos, mais de 40 mil pesquisas sobre o funcionamento do cérebro podem ser perdidas.

Por **Denis Russo Burgierman**
31 out 2016, 19h01 - Publicado em 6 jul 2016, 20h00

And in the Scientific community...

Reevaluating “clust
nonparametric cont
rate

Daniel Kessler, Mike Angstadt, and Cha

PNAS April 25, 2017. 114 (17) E3372-E3373; pub
https://doi.org/10.1073/pnas.1614502114

This article has letters. Please see:
Relationship between Letter and Rep
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In a substantial contribution to the fM
to demonstrate that random field the
cluster inference does not control er
pronounced for lenient cluster-defini
of RFT assumptions as the culprit fo

Controversy in
functional mag

Emery N. Brown and Marlene

PNAS April 25, 2017. 114 (17) E3368-
https://doi.org/10.1073/pnas.170551

This article has letters. Please
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To test the validity of statis
the first time, large-scale e
fMRI measurements to rep
authors compare familywis

fMRI clustering

Robert W. Cox, Gang Chen, D

PNAS April 25, 2017. 114 (17) E3370
https://doi.org/10.1073/pnas.161496

This article has letters. Pleas
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Recently, Eklund et al. (1) a
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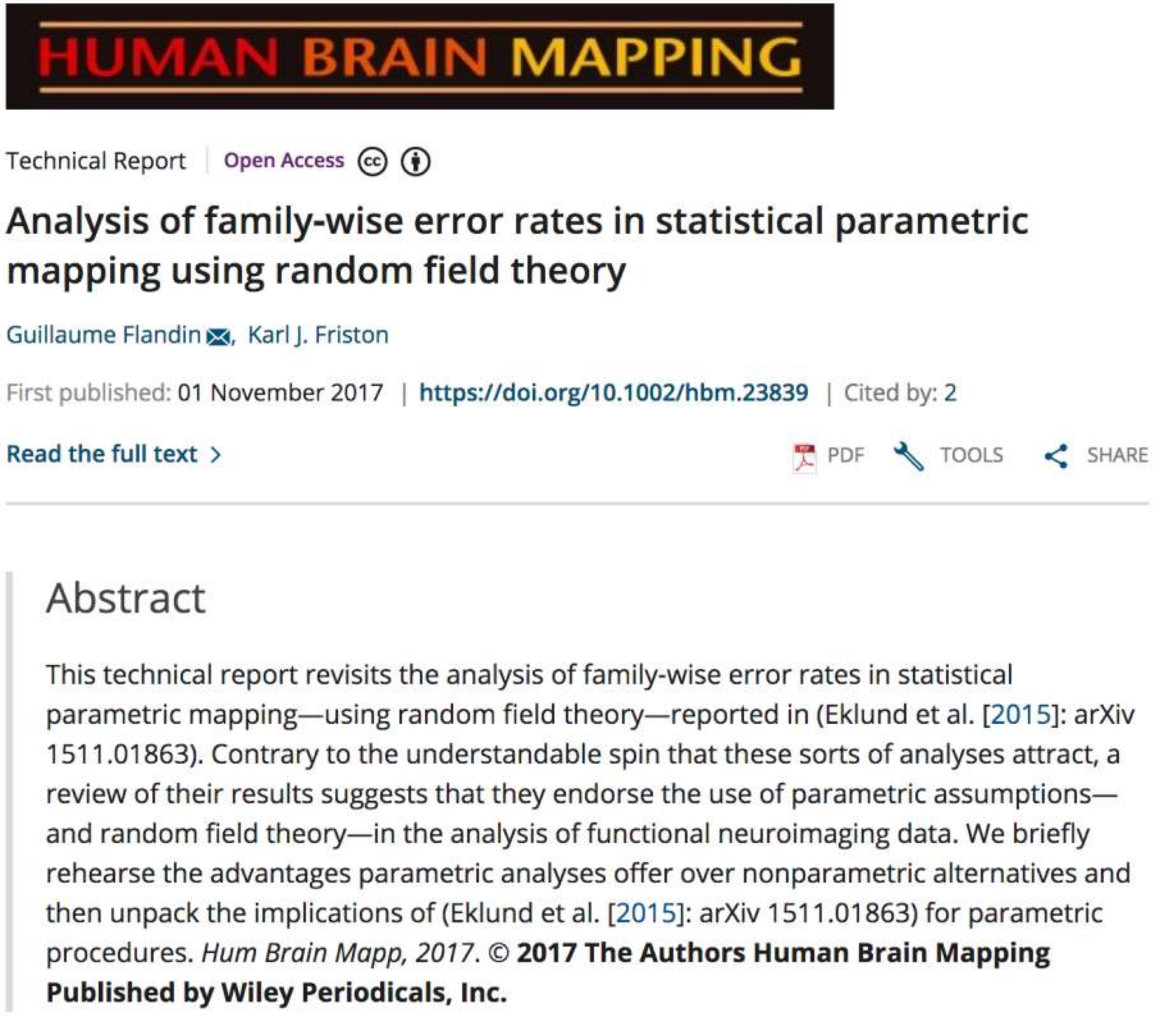


HUMAN BRAIN MAPPING

Technical Report | Open Access

Analysis of family-wise error rates in statistical parametric mapping using random field theory

Guillaume Flandin, Karl J. Friston

First published: 01 November 2017 | https://doi.org/10.1002/hbm.23839 | Cited by: 2

Abstract

This technical report revisits the analysis of family-wise error rates in statistical parametric mapping—using random field theory—reported in (Eklund et al. [2015]: arXiv 1511.01863). Contrary to the understandable spin that these sorts of analyses attract, a review of their results suggests that they endorse the use of parametric assumptions—and random field theory—in the analysis of functional neuroimaging data. We briefly rehearse the advantages parametric analyses offer over nonparametric alternatives and then unpack the implications of (Eklund et al. [2015]: arXiv 1511.01863) for parametric procedures. *Hum Brain Mapp, 2017*. © **2017 The Authors Human Brain Mapping Published by Wiley Periodicals, Inc.**

Later the Highlights where changed…

From:

“These results question the validity of some 40,000 fMRI studies and may have a large impact on the interpretation of neuroimaging results”

To:

“These results question the validity of a number of fMRI studies and may have a large impact on the interpretation of weakly significant neuroimaging results.”

Brain Connectivity, VOL. 7, NO. 3 |

FMRI Clustering in AFNI: False-Positive Rates Redux

Cox Robert W., Chen Gang, Glen Daniel R., Reynolds Richard C., and Taylor Paul A.

Published Online: 1 Apr 2017 | https://doi.org/10.1089/brain.2016.0475

Abstract

AbstractRecent reports of inflated false-positive rates (FPRs) in FMRI group analysis tools by Eklund and associates in 2016 have become a large topic within (and outside) neuroimaging. They concluded that
existing parametric metho
to 70%," mainly due to the f
shaped and stationary), ca
nonparametric methods, su
that AFNI showed "particul

GENERAL COMMENTARY ARTICLE

Front. Hum. Neurosci., 28 June 2017 | https://doi.org/10.3389/fnhum.2017.00345

Commentary: Cluster failure: Why fMRI inferences for spatial extent have inflated false-positive rates

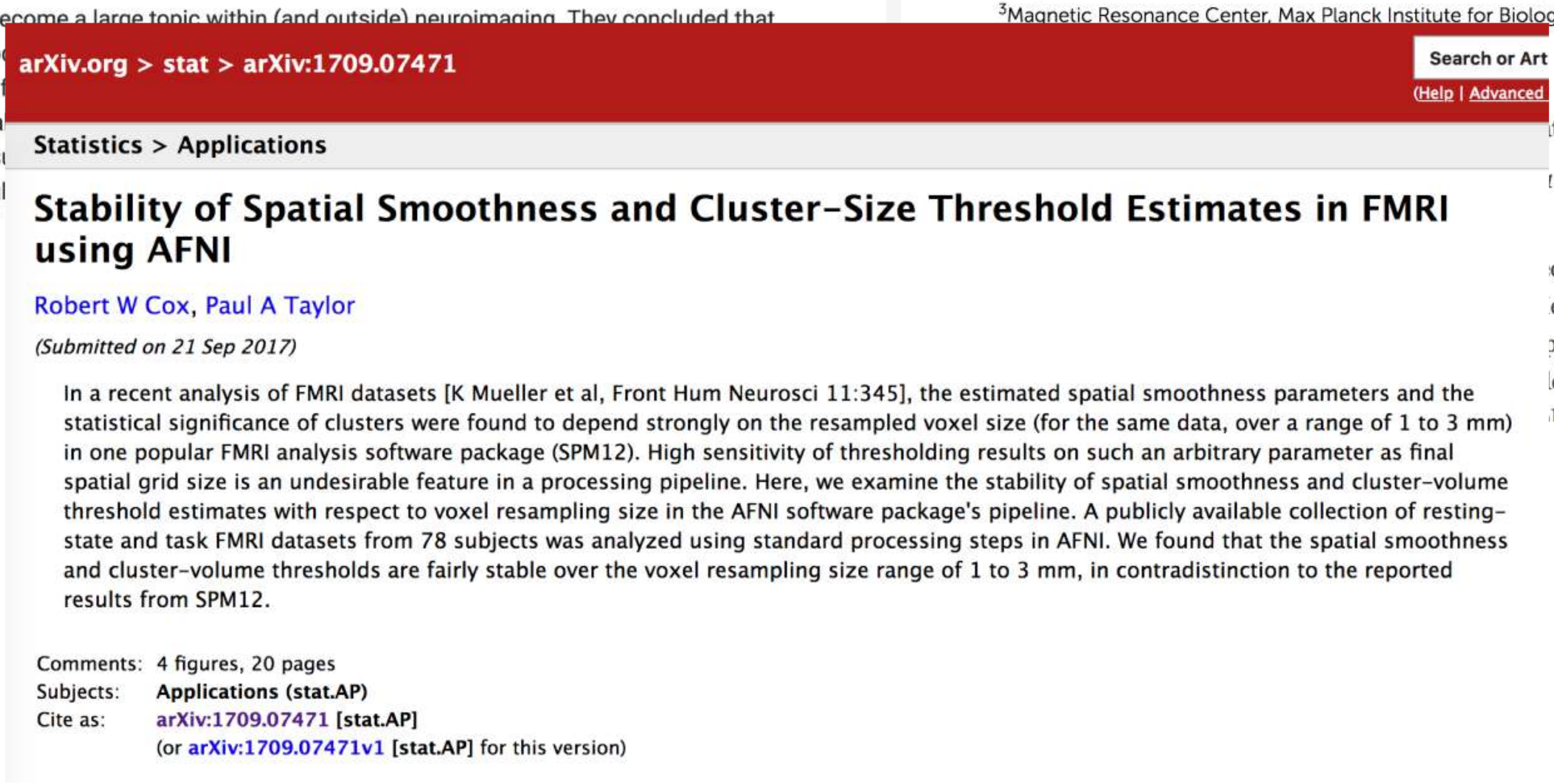
Karsten Mueller[1*], **Jöran Lepsien**[1], **Harald E. Möller**[1] **and** **Gabriele Lohmann**[2,3]

[1]Nuclear Magnetic Resonance Unit, Max Planck Institute for Human Cognitive and Brain Sciences, Leipzig, Germany
[2]Department of Biomedical Magnetic Resonance, University Hospital Tuebingen, Tuebingen, Germany
[3]Magnetic Resonance Center, Max Planck Institute for Biological Cybernetics, Tuebingen, Tuebingen, Germany

tial extent have inflated false-positive rates

6). Proc. Natl. Acad. Sci. U.S.A. 113, 7900–7905.

d inflated false positive rates in functional MRI
ere we would like to draw attention to an important
pecifically, we would like to note that statistical
epend heavily on a preprocessing parameter not
l resolution to which the data sets are resampled



Statistics > Applications

Stability of Spatial Smoothness and Cluster-Size Threshold Estimates in FMRI using AFNI

Robert W Cox, Paul A Taylor

(Submitted on 21 Sep 2017)

In a recent analysis of FMRI datasets [K Mueller et al, Front Hum Neurosci 11:345], the estimated spatial smoothness parameters and the statistical significance of clusters were found to depend strongly on the resampled voxel size (for the same data, over a range of 1 to 3 mm) in one popular FMRI analysis software package (SPM12). High sensitivity of thresholding results on such an arbitrary parameter as final spatial grid size is an undesirable feature in a processing pipeline. Here, we examine the stability of spatial smoothness and cluster-volume threshold estimates with respect to voxel resampling size in the AFNI software package's pipeline. A publicly available collection of resting-state and task FMRI datasets from 78 subjects was analyzed using standard processing steps in AFNI. We found that the spatial smoothness and cluster-volume thresholds are fairly stable over the voxel resampling size range of 1 to 3 mm, in contradistinction to the reported results from SPM12.

Comments: 4 figures, 20 pages
Subjects: **Applications (stat.AP)**
Cite as: arXiv:1709.07471 **[stat.AP]**
(or arXiv:1709.07471v1 **[stat.AP]** for this version)

Eklund is still at it...

arXiv.org > stat > arXiv:1804.03185

Statistics > Applications

Cluster Failure Revisited: Impact of First Level Design and Data Quality on Cluster False Positive Rates

Anders Eklund, Hans Knutsson, Thomas E Nichols

(Submitted on 9 Apr 2018)

Methodological research rarely generates a broad interest, yet our work on the validity of cluster inference methods for functional magnetic resonance imaging (fMRI) created intense discussion on both the minutia of our approach and its implications for the discipline. In the present work, we take on various critiques of our work and further explore the limitations of our original work. We address issues about the particular event-related designs we used, considering multiple event types and randomisation of events between subjects. We consider the lack of validity found with one-sample permutation (sign flipping) tests, investigating a number of approaches to improve the false positive control of this widely used procedure. We also discuss the implications of our work on the fMRI literature as a whole, estimating that at least 10% of the fMRI studies have used the most problematic cluster inference method (P = 0.01 cluster defining threshold), and how individual studies can be interpreted in light of our findings. These additional results underscore our original conclusions, on the importance of data sharing and thorough evaluation of statistical methods on realistic null data.

How do you solve the Multiple Comparison problem?

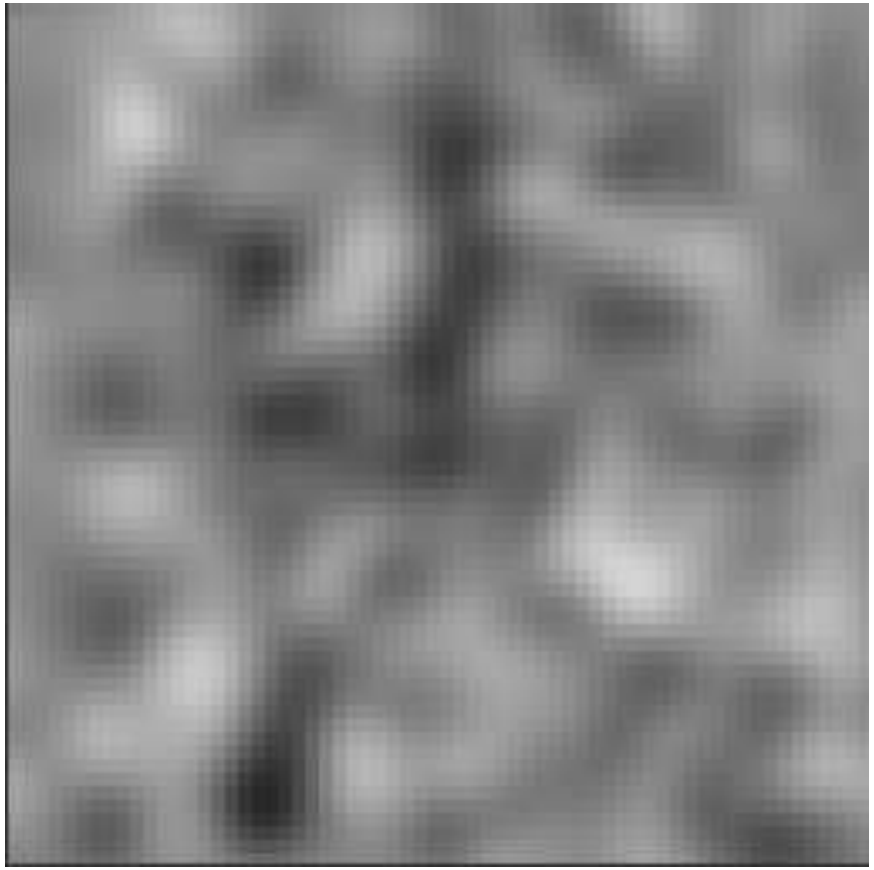
Family-wise error rate (FWER):defined as the probability of obtaining at least one false positive in a family of tests

Bonferroni
Random Field Theory

False discovery rate (FDR): defined as the proportion of false positives among all rejected tests.

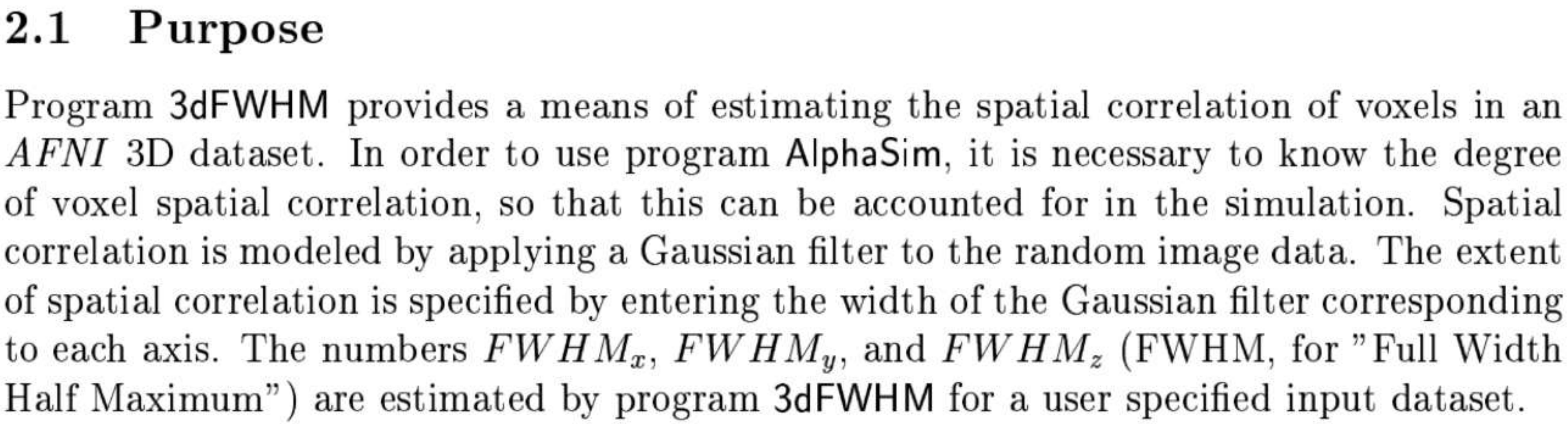
Random Field Theory (RFT)

- Random field theory provides a method to determine statistical threshold while controlling FWE rate
- t-maps (or Z, F and X^2) modeled as realizations of a random process
- Takes into account smoothness AND number of activated voxels



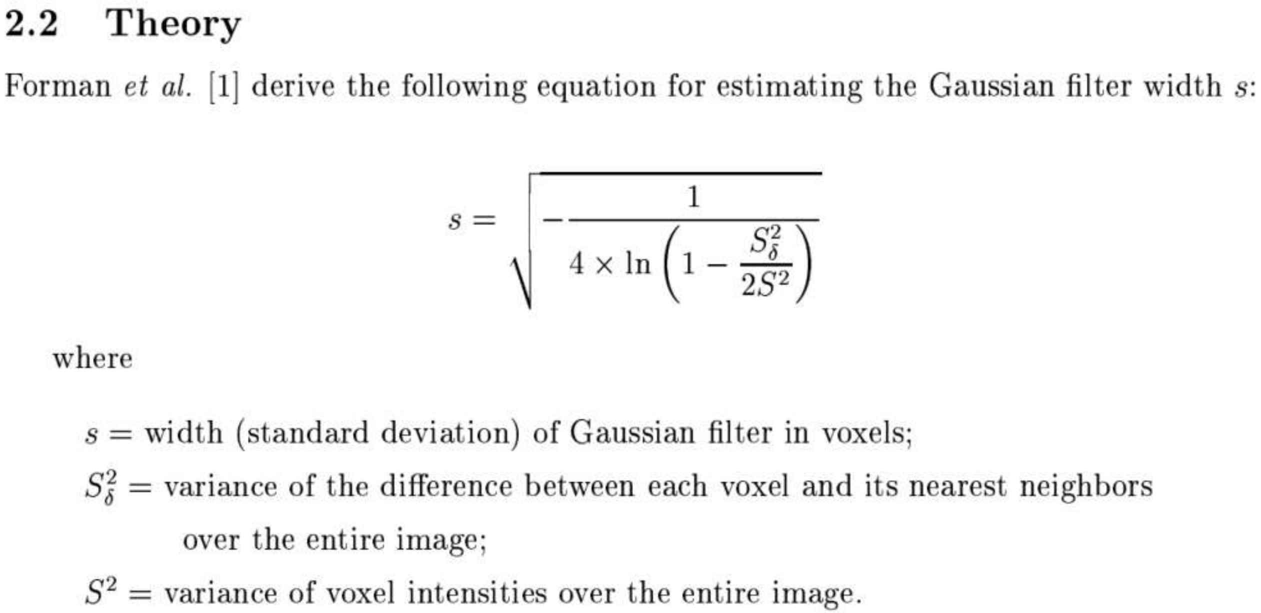
How to measure smoothness

- AFNI – 3dFWHMx



2.1 Purpose

Program 3dFWHM provides a means of estimating the spatial correlation of voxels in an *AFNI* 3D dataset. In order to use program AlphaSim, it is necessary to know the degree of voxel spatial correlation, so that this can be accounted for in the simulation. Spatial correlation is modeled by applying a Gaussian filter to the random image data. The extent of spatial correlation is specified by entering the width of the Gaussian filter corresponding to each axis. The numbers $FWHM_x$, $FWHM_y$, and $FWHM_z$ (FWHM, for "Full Width Half Maximum") are estimated by program 3dFWHM for a user specified input dataset.



2.2 Theory

Forman *et al.* [1] derive the following equation for estimating the Gaussian filter width s:

$$s = \sqrt{-\frac{1}{4 \times \ln\left(1 - \frac{S_\delta^2}{2S^2}\right)}}$$

where

s = width (standard deviation) of Gaussian filter in voxels;

S_δ^2 = variance of the difference between each voxel and its nearest neighbors over the entire image;

S^2 = variance of voxel intensities over the entire image.

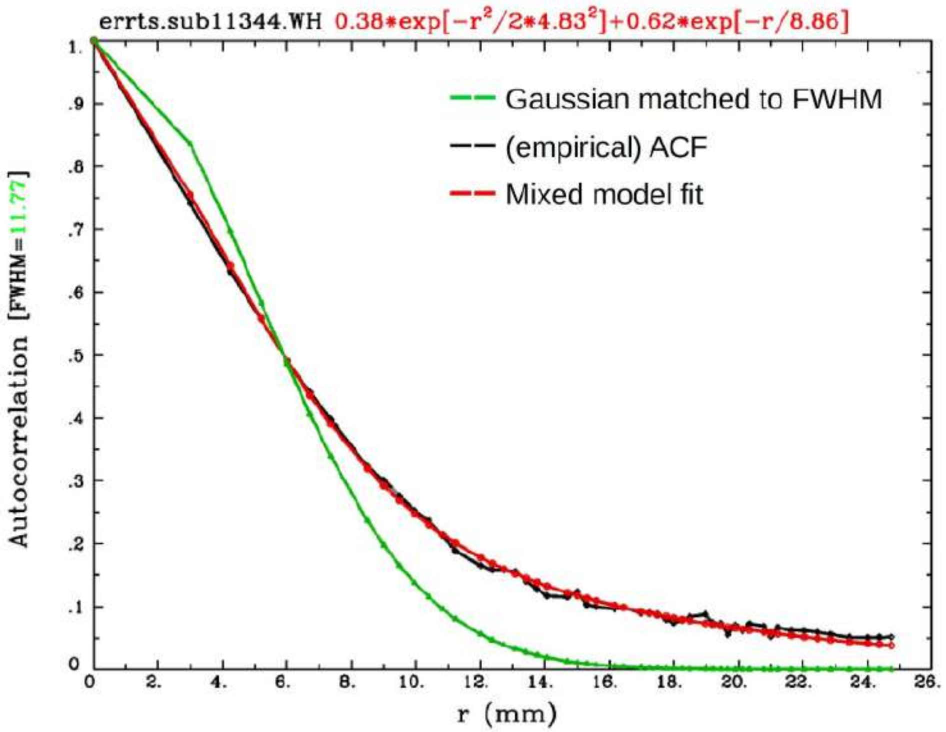


Figure 3. An example comparison of the original Gaussian fit (green) and the globally estimated empirical ACF values (black) from a single subject, which have large differences (importantly, in the tail drop-off above *r* ~ 8 mm). The proposed mixed model (red) after fitting parameters as described in Eq. (3) provides a much better fit of the data in this case (and in all cases in the datasets used herein). This plot is automatically generated in program 3dFWHMx.

Source: Cox et al. FMRI Clustering in AFNI: False-Positive Rates Redux, Brian Connectivity (2017)

```
Usage: 3dFWHMx [options] dataset

**** NOTICE ****
 You should use the '-acf' option (which is what afni_proc.py uses now).
 The 'Classic' method giving just a Gaussian FWHM can no longer be
 considered reliable for FMRI statistical analyses!
****************

 >>>>> 20 July 2017: Results from the 'Classic' method are no longer output!
 >>>>>               If you want to see these values, you must give the
 >>>>>               command line option '-ShowMeClassicFWHM'.
 >>>>>               You no longer need to give the '-acf' option, as it
 >>>>>               is now the default method of calculation (and
 >>>>>               cannot be turned off). Note that if you need the
 >>>>>               FWHM estimate, the '-acf' method gives a value
 >>>>>               for that as its fourth output.
 >>>>> Options and comments that only apply to the 'Classic' FWHM estimation
 >>>>> method are now marked below with this '>>>>>' marker, to indicate that
 >>>>> they are obsolete, archaic, and endangered (as well as fattening).

>>>>> Unlike the older 3dFWHM, this program computes FWHMs for all sub-bricks
>>>>> in the input dataset, each one separately.  The output for each one is
>>>>> written to the file specified by '-out'.  The mean (arithmetic or geometric)
>>>>> of all the FWHMs along each axis is written to stdout.  (A non-positive
>>>>> output value indicates something bad happened; e.g., FWHM in z is meaningless
>>>>> for a 2D dataset; the estimation method computed incoherent intermediate results.)

(Classic) METHOD: <<<<< NO LONGER OUTPUT -- SEE ABOVE >>>>>
 - Calculate ratio of variance of first differences to data variance.
 - Should be the same as 3dFWHM for a 1-brick dataset.
   (But the output format is simpler to use in a script.
```

--
************* IMPORTANT NOTE [Dec 2015] **
--

A completely new method for estimating and using noise smoothness values is now available in 3dFWHMx and 3dClustSim. This method is implemented in the **'-acf'** options to both programs. **'ACF' stands for (spatial) AutoCorrelation Function**, and it is estimated by calculating moments of differences out to a larger radius than before.

Notably, **real FMRI data does not actually have a Gaussian-shaped ACF**, so the estimated ACF is then fit (in 3dFWHMx) to a mixed model (**Gaussian plus mono-exponential**) of the form

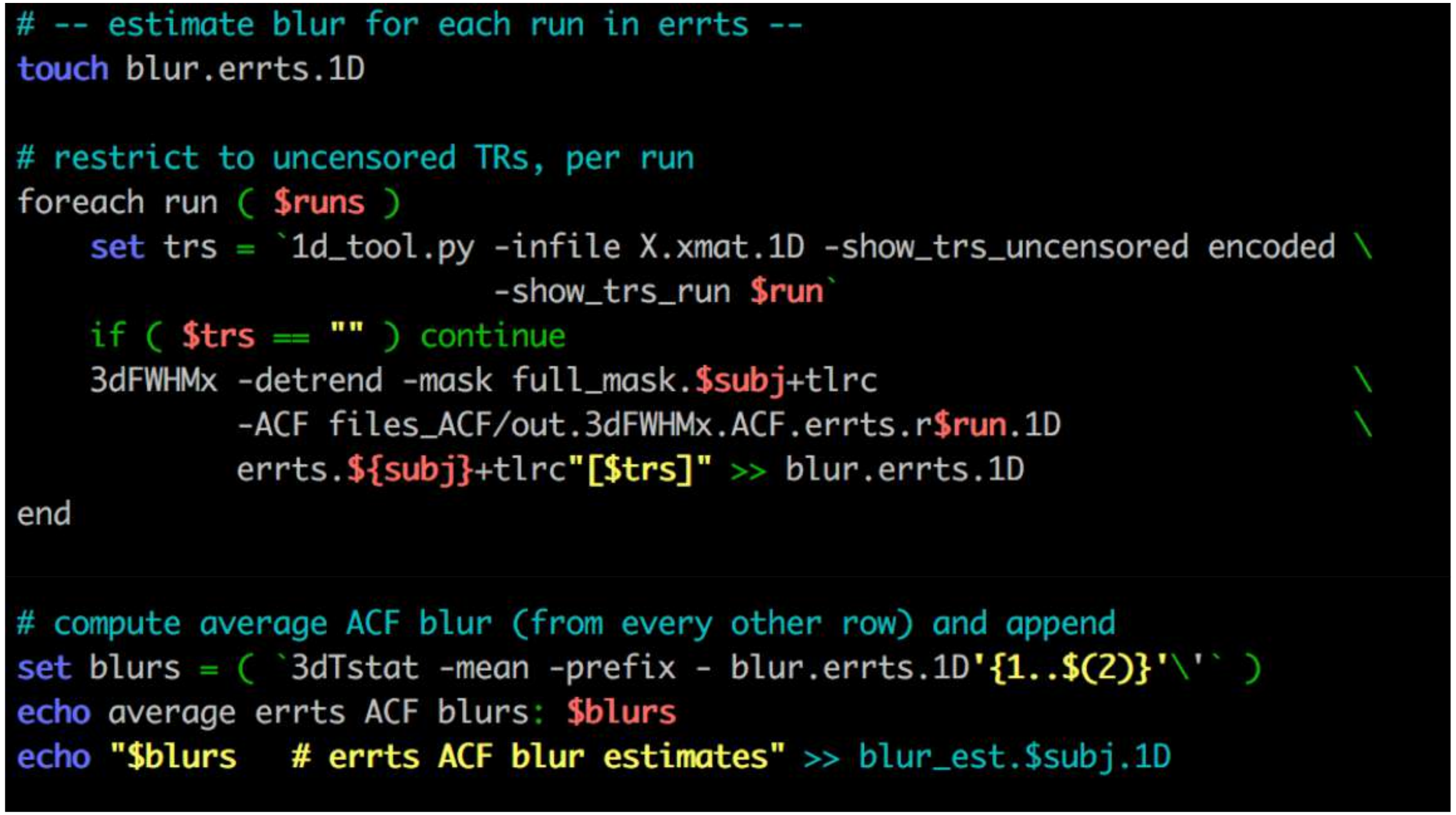
ACF(r) = a * exp(-r*r/(2*b*b)) + (1-a)*exp(-r/c)

where 'r' is the radius, and 'a', 'b', 'c' are the fitted parameters. The apparent FWHM from this model is usually somewhat larger in real data than the FWHM estimated from just the nearest-neighbor differences used in the 'classic' analysis.

The longer tails provided by the mono-exponential are also significant. 3dClustSim has also been modified to use the ACF model given above to generate noise random fields.

--
** The take-away (TL;DR or summary) message is that the 'classic' 3dFWHMx and **
** 3dClustSim analysis, **using a pure Gaussian ACF, is not very correct for** **
** **FMRI data** -- I cannot speak for PET or MEG data. **
--

Code:



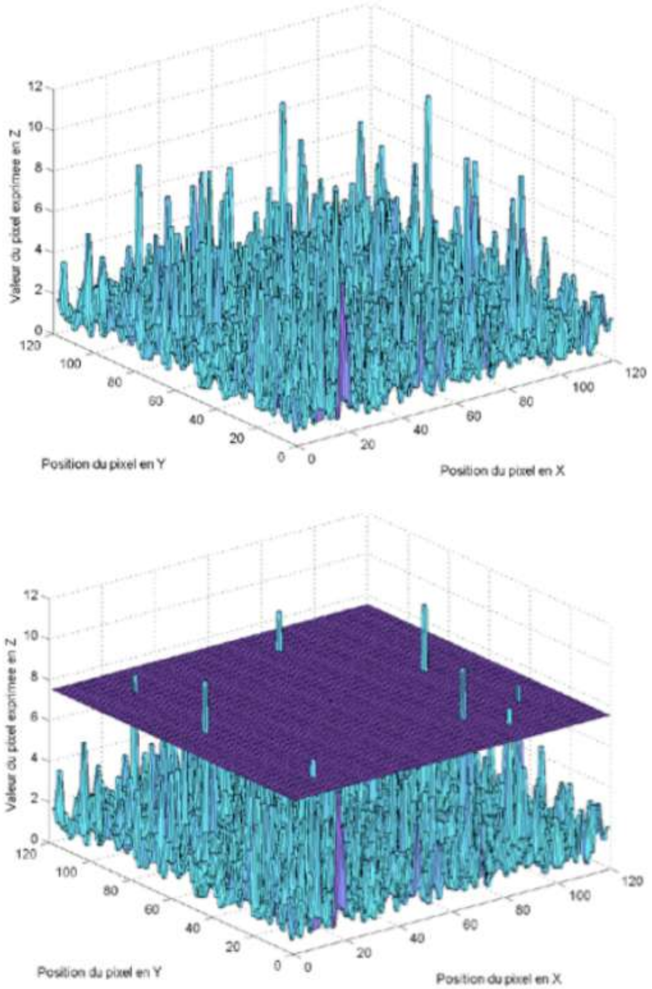
```
# -- estimate blur for each run in errts --
touch blur.errts.1D

# restrict to uncensored TRs, per run
foreach run ( $runs )
    set trs = `1d_tool.py -infile X.xmat.1D -show_trs_uncensored encoded \
                          -show_trs_run $run`
    if ( $trs == "" ) continue
    3dFWHMx -detrend -mask full_mask.$subj+tlrc                          \
            -ACF files_ACF/out.3dFWHMx.ACF.errts.r$run.1D                \
            errts.${subj}+tlrc"[$trs]" >> blur.errts.1D
end

# compute average ACF blur (from every other row) and append
set blurs = ( `3dTstat -mean -prefix - blur.errts.1D'{1..$(2)}'\'` )
echo average errts ACF blurs: $blurs
echo "$blurs   # errts ACF blur estimates" >> blur_est.$subj.1D
```

Output:

```
afranco@inscer:~/DATA/VIVA/VIVA023/visit1/PROC.RMET$ more blur_est.VIVA023.1D
10.4453 10.364 9.00825 9.91638   # epits FWHM blur estimates
0.437901 5.89822 13.1252 15.3785   # epits ACF blur estimates
10.3545 10.2873 8.93106 9.83491   # errts FWHM blur estimates
0.452279 5.90349 12.7922 15.195   # errts ACF blur estimates
```

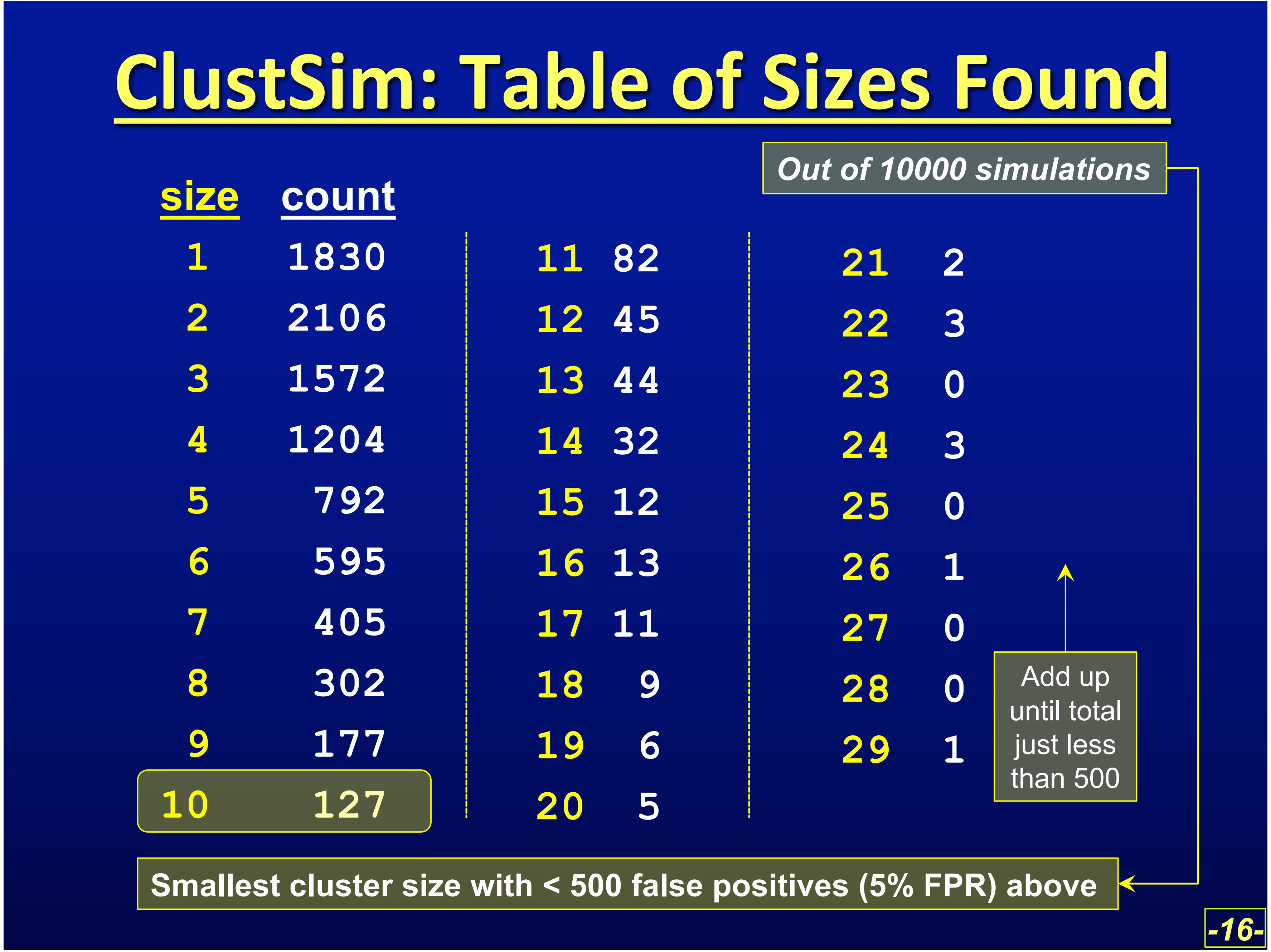
Topology of Random Fields

- Euler Characteristic (EC) is a measure of the ‘roughness’ of a random field
- In neuroimaging number of blobs (aka clusters) that remain after thresholding at a particular p-value defines EC (minus holes/hollows)



3dClustSim

```
Usage: 3dClustSim [options]

Program to estimate the probability of false positive (noise-only) clusters.
An adaptation of Doug Ward's AlphaSim, streamlined for various purposes.

-----------------------------------------------------------------------------
This program has several different modes of operation, each one involving
simulating noise-only random volumes, thresholding and clustering them,
and counting statistics of how often data 'survives' these processes at
various threshold combinations (per-voxel and cluster-size).

OLDEST method = simulate noise volume assuming the spatial auto-correlation
                function (ACF) is given by a Gaussian-shaped function, where
                this shape is specified using the FWHM parameter. The FWHM
                parameter can be estimated by program 3dFWHMx.
          ** THIS METHOD IS NO LONGER RECOMMENDED **

NEWER method  = simulate noise volume assuming the ACF is given by a mixed-model
                of the form a*exp(-r*r/(2*b*b))+(1-a)*exp(-r/c), where a,b,c
                are 3 parameters giving the shape, and can also be estimated
                by program 3dFWHMx.
          ** THIS METHOD IS ACCEPTABLE **

NEWEST method = program 3dttest++ simulates the noise volumes by randomizing
                and permuting input datasets, and sending those volumes into
                3dClustSim directly. There is no built-in math model for the
                spatial ACF.
          ** THIS METHOD IS MOST ACCURATE AT CONTROLLING FALSE POSITIVE RATE **
          ** You invoke this method with the '-Clustsim' option in 3dttest++ **
```



ClustSim: Table of Sizes Found

Out of 10000 simulations

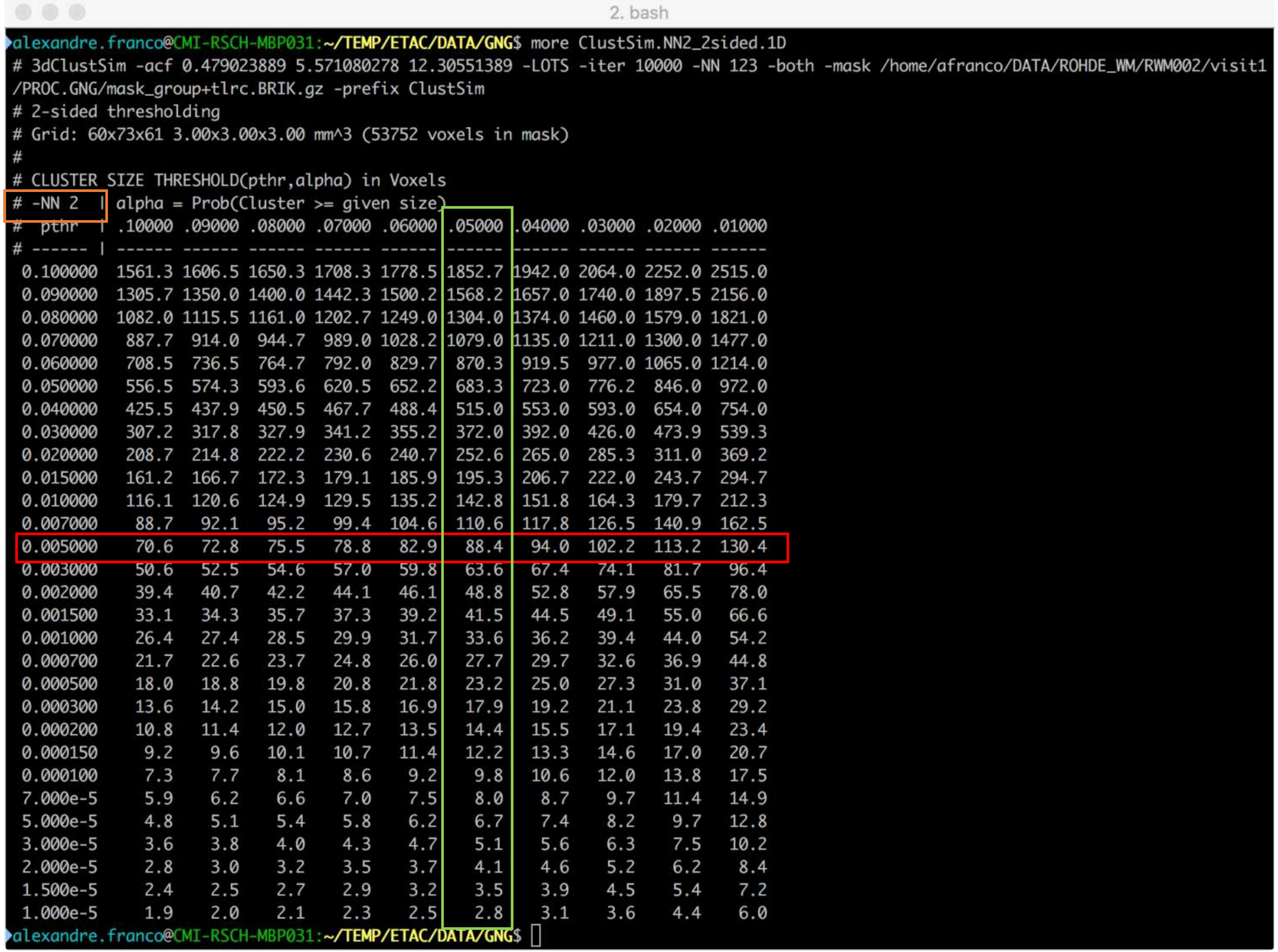
size	count
1	1830
2	2106
3	1572
4	1204
5	792
6	595
7	405
8	302
9	177
10	127
11	82
12	45
13	44
14	32
15	12
16	13
17	11
18	9
19	6
20	5
21	2
22	3
23	0
24	3
25	0
26	1
27	0
28	0
29	1

Add up until total just less than 500

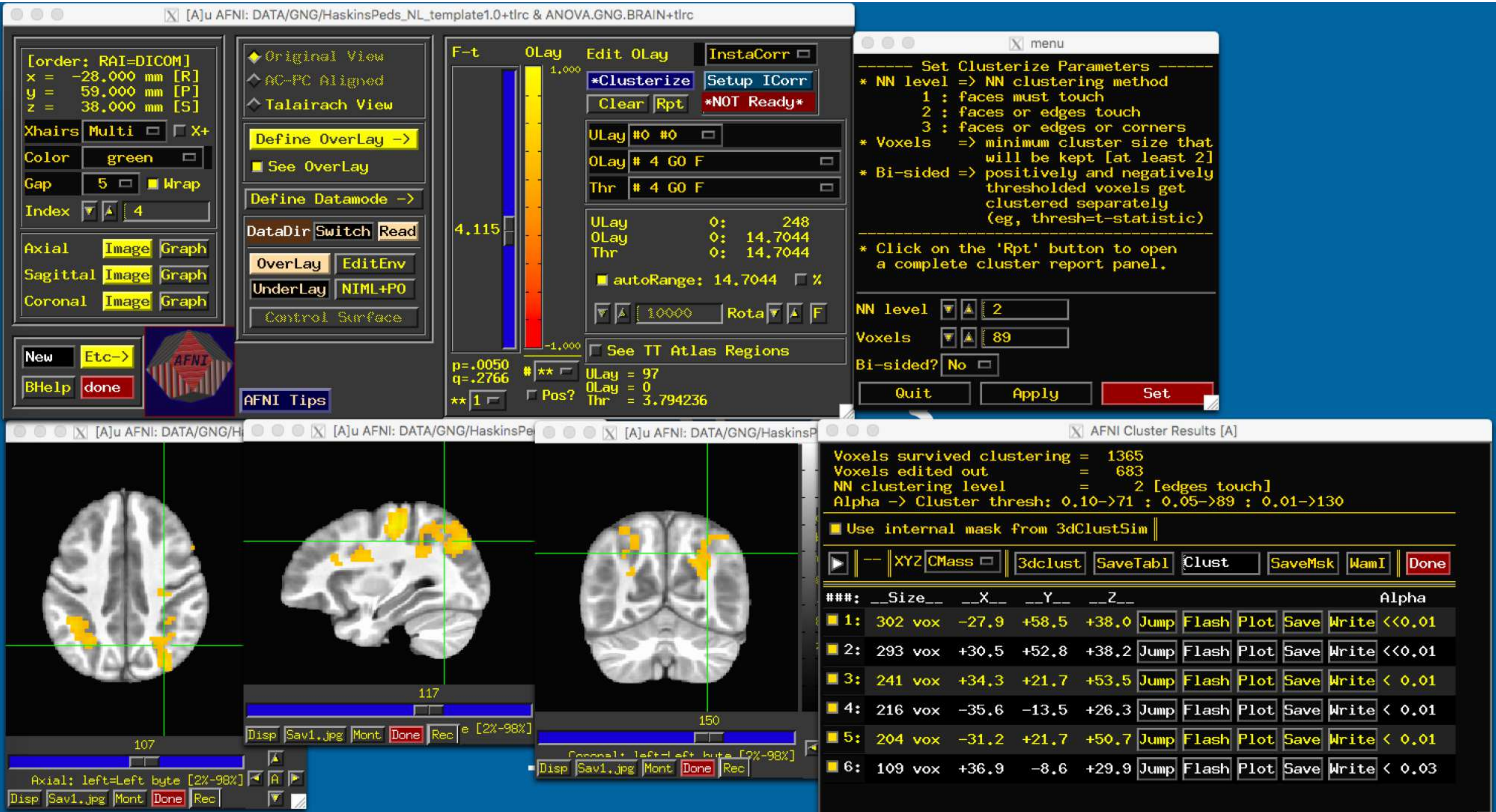
Smallest cluster size with < 500 false positives (5% FPR) above

Figure stolen from Bob Cox’s ETAC slides

Output from ClustSim



```
alexandre.franco@CMI-RSCH-MBP031:~/TEMP/ETAC/DATA/GNG$ more ClustSim.NN2_2sided.1D
# 3dClustSim -acf 0.479023889 5.571080278 12.30551389 -LOTS -iter 10000 -NN 123 -both -mask /home/afranco/DATA/ROHDE_WM/RWM002/visit1
/PROC.GNG/mask_group+tlrc.BRIK.gz -prefix ClustSim
# 2-sided thresholding
# Grid: 60x73x61 3.00x3.00x3.00 mm^3 (53752 voxels in mask)
#
# CLUSTER SIZE THRESHOLD(pthr,alpha) in Voxels
# -NN 2  | alpha = Prob(Cluster >= given size)
#  pthr  | .10000 .09000 .08000 .07000 .06000 .05000 .04000 .03000 .02000 .01000
# ------ | ------ ------ ------ ------ ------ ------ ------ ------ ------ ------
 0.100000  1561.3 1606.5 1650.3 1708.3 1778.5 1852.7 1942.0 2064.0 2252.0 2515.0
 0.090000  1305.7 1350.0 1400.0 1442.3 1500.2 1568.2 1657.0 1740.0 1897.5 2156.0
 0.080000  1082.0 1115.5 1161.0 1202.7 1249.0 1304.0 1374.0 1460.0 1579.0 1821.0
 0.070000   887.7  914.0  944.7  989.0 1028.2 1079.0 1135.0 1211.0 1300.0 1477.0
 0.060000   708.5  736.5  764.7  792.0  829.7  870.3  919.5  977.0 1065.0 1214.0
 0.050000   556.5  574.3  593.6  620.5  652.2  683.3  723.0  776.2  846.0  972.0
 0.040000   425.5  437.9  450.5  467.7  488.4  515.0  553.0  593.0  654.0  754.0
 0.030000   307.2  317.8  327.9  341.2  355.2  372.0  392.0  426.0  473.9  539.3
 0.020000   208.7  214.8  222.2  230.6  240.7  252.6  265.0  285.3  311.0  369.2
 0.015000   161.2  166.7  172.3  179.1  185.9  195.3  206.7  222.0  243.7  294.7
 0.010000   116.1  120.6  124.9  129.5  135.2  142.8  151.8  164.3  179.7  212.3
 0.007000    88.7   92.1   95.2   99.4  104.6  110.6  117.8  126.5  140.9  162.5
 0.005000    70.6   72.8   75.5   78.8   82.9   88.4   94.0  102.2  113.2  130.4
 0.003000    50.6   52.5   54.6   57.0   59.8   63.6   67.4   74.1   81.7   96.4
 0.002000    39.4   40.7   42.2   44.1   46.1   48.8   52.8   57.9   65.5   78.0
 0.001500    33.1   34.3   35.7   37.3   39.2   41.5   44.5   49.1   55.0   66.6
 0.001000    26.4   27.4   28.5   29.9   31.7   33.6   36.2   39.4   44.0   54.2
 0.000700    21.7   22.6   23.7   24.8   26.0   27.7   29.7   32.6   36.9   44.8
 0.000500    18.0   18.8   19.8   20.8   21.8   23.2   25.0   27.3   31.0   37.1
 0.000300    13.6   14.2   15.0   15.8   16.9   17.9   19.2   21.1   23.8   29.2
 0.000200    10.8   11.4   12.0   12.7   13.5   14.4   15.5   17.1   19.4   23.4
 0.000150     9.2    9.6   10.1   10.7   11.4   12.2   13.3   14.6   17.0   20.7
 0.000100     7.3    7.7    8.1    8.6    9.2    9.8   10.6   12.0   13.8   17.5
 7.000e-5     5.9    6.2    6.6    7.0    7.5    8.0    8.7    9.7   11.4   14.9
 5.000e-5     4.8    5.1    5.4    5.8    6.2    6.7    7.4    8.2    9.7   12.8
 3.000e-5     3.6    3.8    4.0    4.3    4.7    5.1    5.6    6.3    7.5   10.2
 2.000e-5     2.8    3.0    3.2    3.5    3.7    4.1    4.6    5.2    6.2    8.4
 1.500e-5     2.4    2.5    2.7    2.9    3.2    3.5    3.9    4.5    5.4    7.2
 1.000e-5     1.9    2.0    2.1    2.3    2.5    2.8    3.1    3.6    4.4    6.0
alexandre.franco@CMI-RSCH-MBP031:~/TEMP/ETAC/DATA/GNG$
```



[A]u AFNI: DATA/GNG/HaskinsPeds_NL_template1.0+tlrc & ANOVA.GNG.BRAIN+tlrc

```
[order: RAI=DICOM]
x =  -28.000 mm [R]
y =   59.000 mm [P]
z =   38.000 mm [S]
```

Xhairs Multi ☐ X+
Color green
Gap 5 ■ Wrap
Index 4

ULay #0 #0
OLay # 4 GO F
Thr # 4 GO F

```
ULay     0:     248
OLay     0:  14.7044
Thr      0:  14.7044
```

■ autoRange: 14.7044 ☐ %

4.115
p=.0050
q=.2766

ULay = 97
OLay = 0
Thr = 3.794236

menu

```
------ Set Clusterize Parameters ------
* NN level => NN clustering method
        1 : faces must touch
        2 : faces or edges touch
        3 : faces or edges or corners
* Voxels   => minimum cluster size that
              will be kept [at least 2]
* Bi-sided => positively and negatively
              thresholded voxels get
              clustered separately
              (eg, thresh=t-statistic)
----------------------------------------
* Click on the 'Rpt' button to open
  a complete cluster report panel.
```

NN level 2
Voxels 89
Bi-sided? No

AFNI Cluster Results [A]

```
Voxels survived clustering =  1365
Voxels edited out          =   683
NN clustering level        =     2 [edges touch]
Alpha -> Cluster thresh: 0.10->71 : 0.05->89 : 0.01->130
```

■ Use internal mask from 3dClustSim

###:	__Size__	__X__	__Y__	__Z__						Alpha
■ 1:	302 vox	-27.9	+58.5	+38.0	Jump	Flash	Plot	Save	Write	<<0.01
■ 2:	293 vox	+30.5	+52.8	+38.2	Jump	Flash	Plot	Save	Write	<<0.01
■ 3:	241 vox	+34.3	+21.7	+53.5	Jump	Flash	Plot	Save	Write	< 0.01
■ 4:	216 vox	-35.6	-13.5	+26.3	Jump	Flash	Plot	Save	Write	< 0.01
■ 5:	204 vox	-31.2	+21.7	+50.7	Jump	Flash	Plot	Save	Write	< 0.01
■ 6:	109 vox	+36.9	-8.6	+29.9	Jump	Flash	Plot	Save	Write	< 0.03

3dttest++

* The new-ish options '-Clustsim' and '-ETAC' will use randomization and permutation simulation to produce cluster-level threshold values that can be used to control the false positive rate (FPR) globally. These options are slow, since they will run 1000s of simulated 3D t-tests in order to get cluster-level statistics about the 1 actual test.

-Clustsim = With this option, after the commanded t-tests are done, then:

(a) the residuals from '-resid' are used with '-randomsign' to simulate about 10000 null 3D results, and then
(b) 3dClustSim is run with those to generate cluster-threshold tables, and then
(c) 3drefit is used to pack those tables into the main output dataset, and then
(d) the temporary files created in this process are deleted.

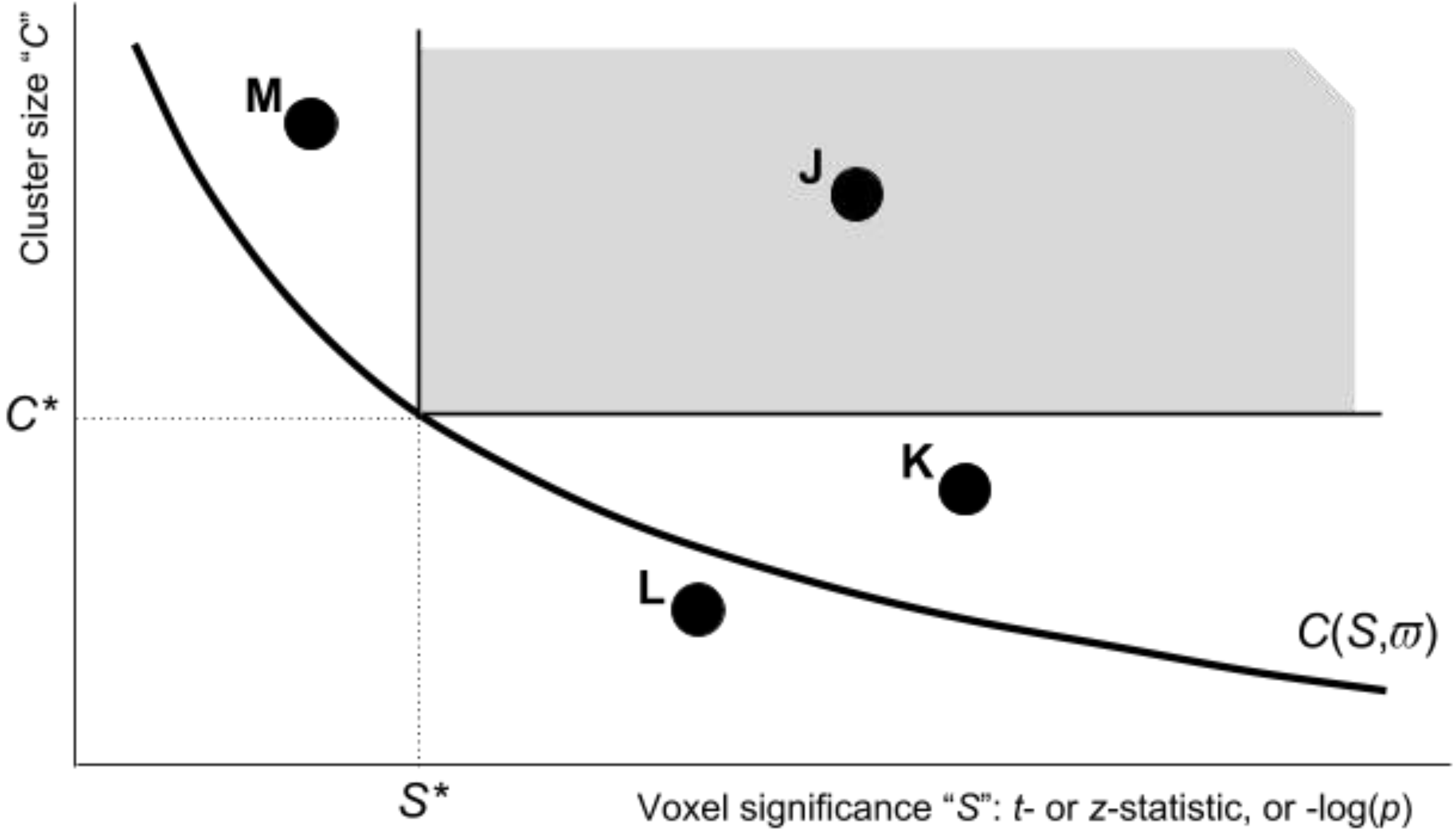
```
-resid q   = Output the residuals into a dataset with prefix 'q'.
               ++ The residuals are the difference between the data values
                  and their prediction from the set mean (and set covariates).
```

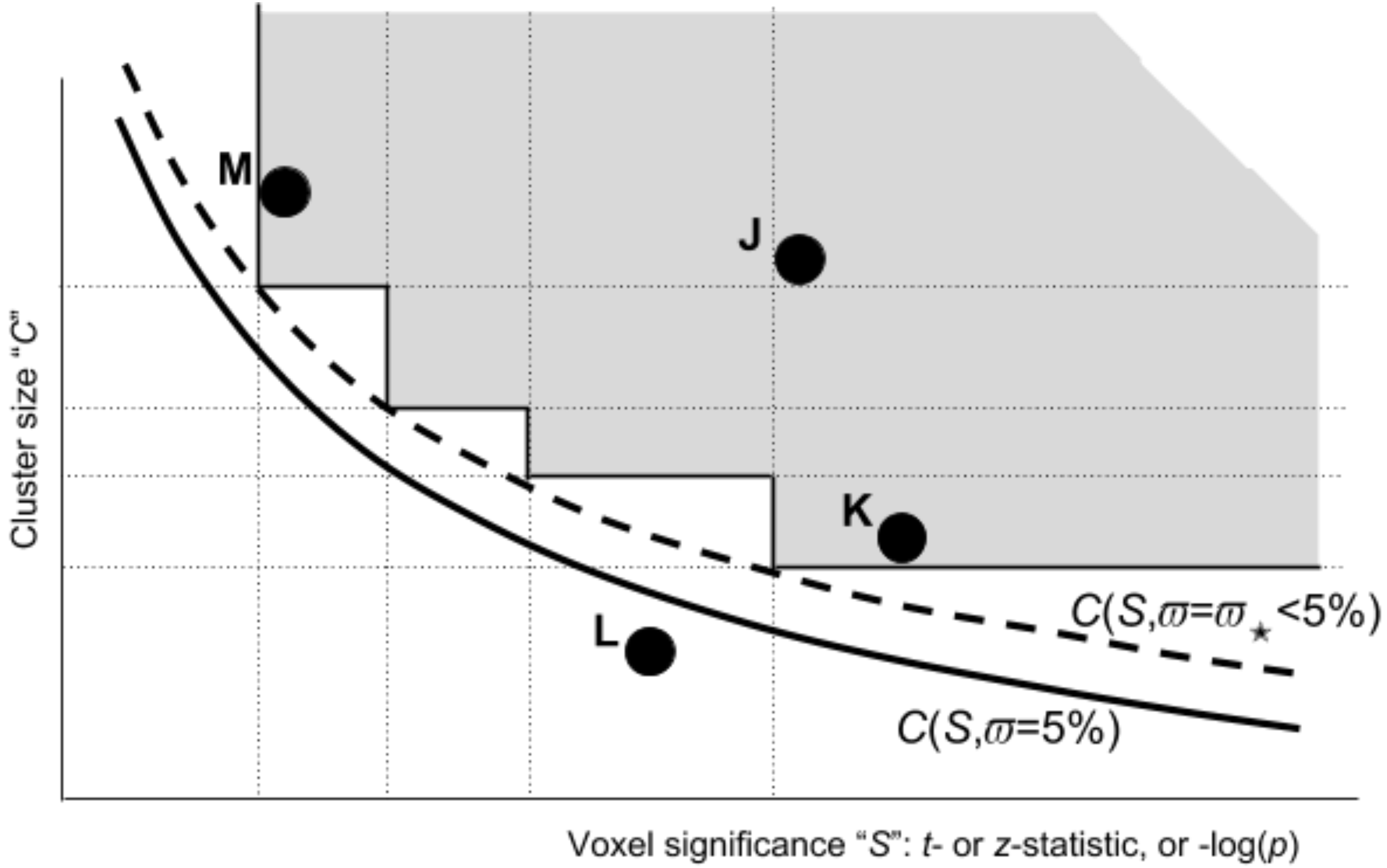
Equitable Thresholding and Clustering - ETAC

ETAC approach is grounded in two ideas:

(i) reducing the dependence of clustering results on **arbitrary parameter values** by using multiple sub-tests—each equivalent to a “standard” FMRI clustering analysis—to make decisions about which groups of voxels are potentially “significant”, then combining the results of each sub-test to decide which voxels are "accepted" ;

(ii) **adjusting the cluster-thresholding parameters** of each sub-test from (i) in an equitable way—so that the individual false positive rates (FPRs) are balanced across sub-tests and voxels—to achieve a desired global FPR (e.g., 5%).


Cluster size "C"
M
J
C*
K
L
$C(S,\varpi)$
S*
Voxel significance "S": t- or z-statistic, or -log(p)


M
J
K
L
$C(S,\varpi=\varpi_{\star}<5\%)$
$C(S,\varpi=5\%)$
Cluster size "C"
Voxel significance "S": t- or z-statistic, or -log(p)

Simulation

Paired t-test

Go x NoGo

N = 36

Average ate = 12

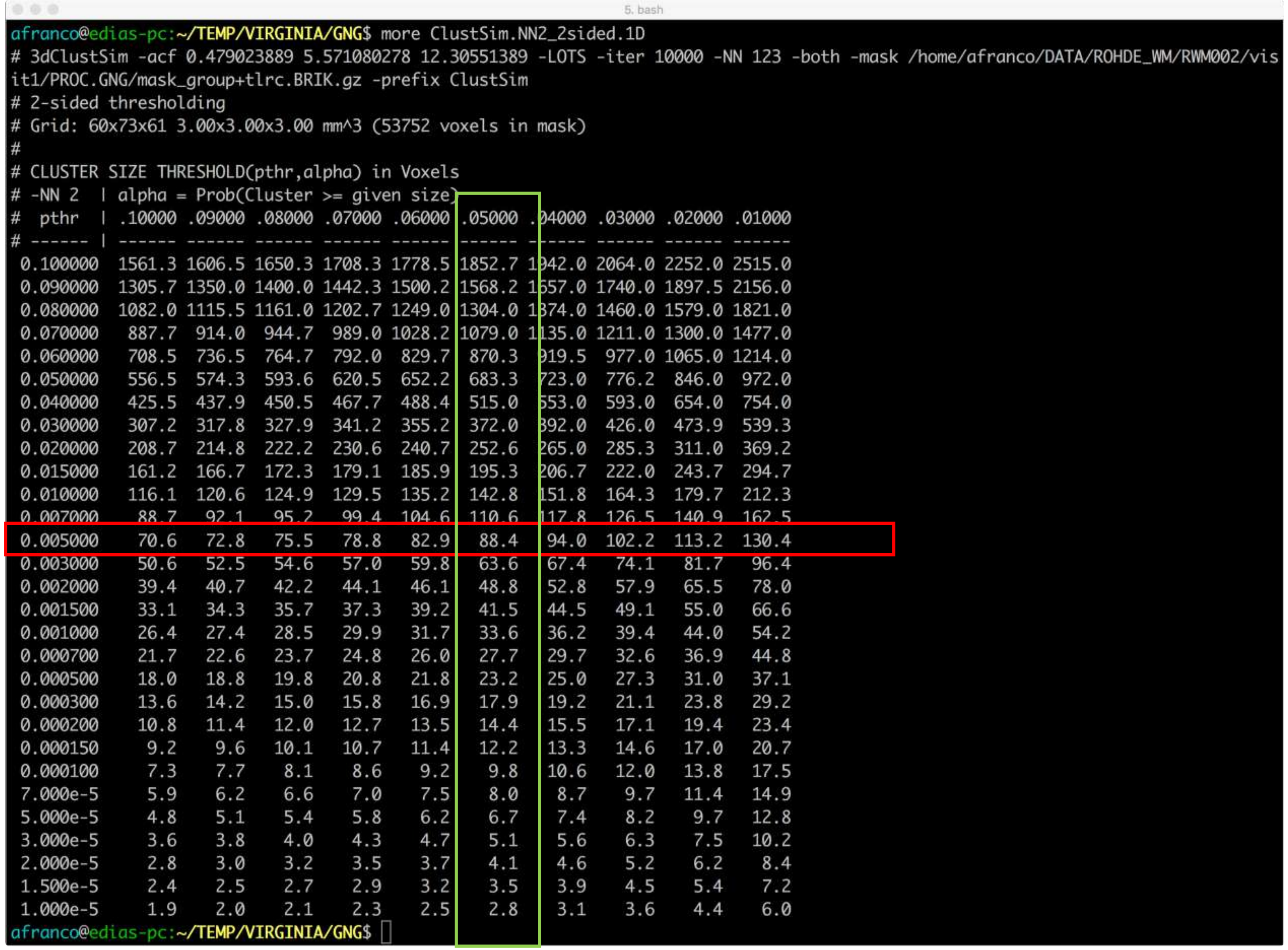
ADHD

Script for simulations

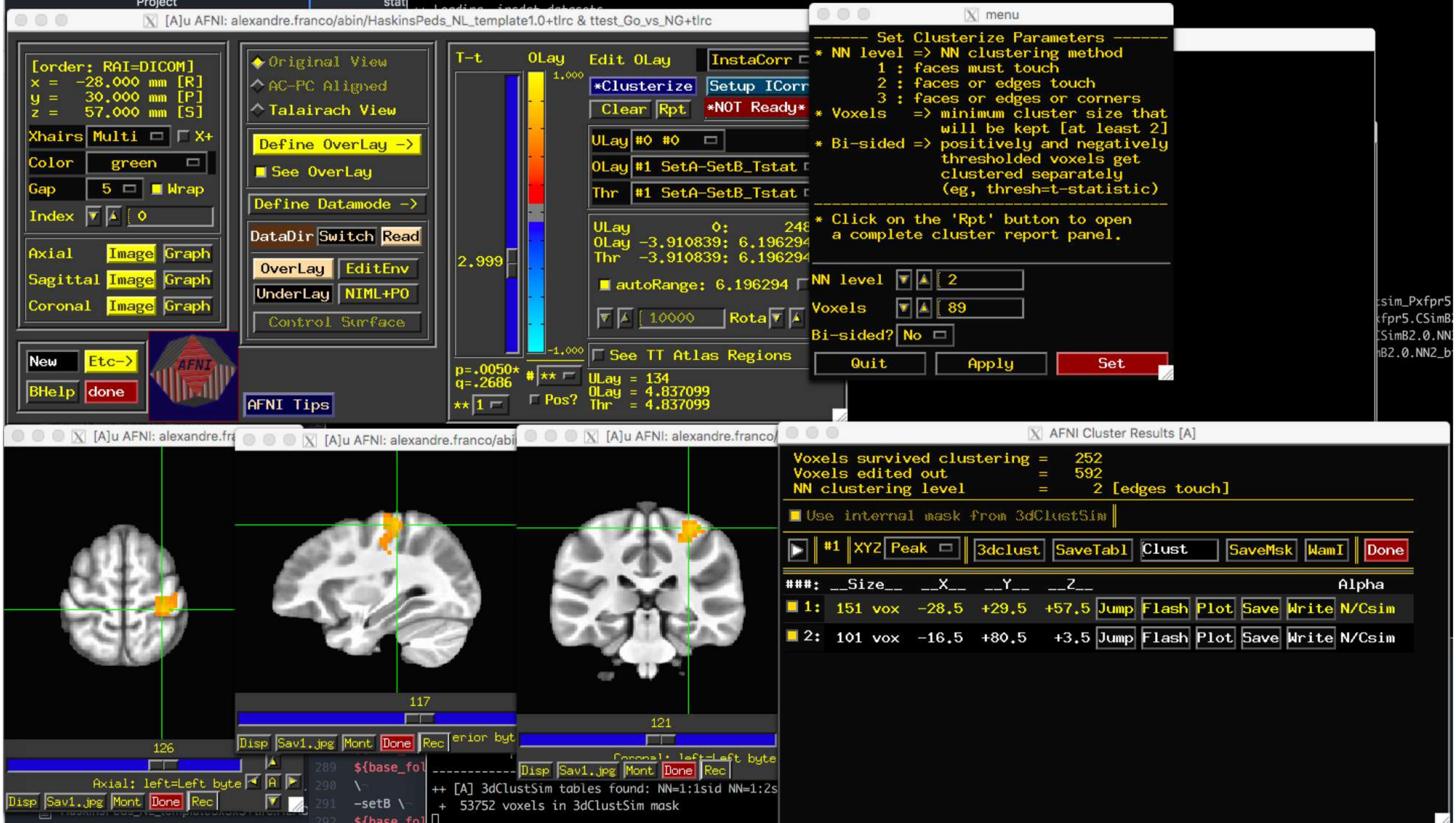
```
3dttest++ -paired \
-mask $mask \
-Clustsim \
-ETAC \
-ETAC_blur 2 4 \
-ETAC_opt sid=2:pthr=0.01,0.005,0.002,0.01:fpr=5:name=FPR5 \
-prefix ttest_Go_vs_NG_ClustSim \
-prefix_clustsim Clustsim_Pxfpr5 \
-setA \
${base_folder}/visit1/stats.RWM002.GO+tlrc \
${base_folder}/visit1/stats.RWM003.GO+tlrc \
${base_folder}/visit1/stats.RWM005.GO+tlrc \
${base_folder}/visit1/stats.RWM008.GO+tlrc \
${base_folder}/visit1/stats.RWM012.GO+tlrc \
```

Generated 8.1 GB of data in the process
Took 2 hours to process on this laptop: 2.3GHz i5, 8GB ram

3dClustSim – output



```
afranco@edias-pc:~/TEMP/VIRGINIA/GNG$ more ClustSim.NN2_2sided.1D
# 3dClustSim -acf 0.479023889 5.571080278 12.30551389 -LOTS -iter 10000 -NN 123 -both -mask /home/afranco/DATA/ROHDE_WM/RWM002/vis
it1/PROC.GNG/mask_group+tlrc.BRIK.gz -prefix ClustSim
# 2-sided thresholding
# Grid: 60x73x61 3.00x3.00x3.00 mm^3 (53752 voxels in mask)
#
# CLUSTER SIZE THRESHOLD(pthr,alpha) in Voxels
# -NN 2  | alpha = Prob(Cluster >= given size)
#  pthr  | .10000 .09000 .08000 .07000 .06000 .05000 .04000 .03000 .02000 .01000
# ------ | ------ ------ ------ ------ ------ ------ ------ ------ ------ ------
 0.100000  1561.3 1606.5 1650.3 1708.3 1778.5 1852.7 1942.0 2064.0 2252.0 2515.0
 0.090000  1305.7 1350.0 1400.0 1442.3 1500.2 1568.2 1657.0 1740.0 1897.5 2156.0
 0.080000  1082.0 1115.5 1161.0 1202.7 1249.0 1304.0 1374.0 1460.0 1579.0 1821.0
 0.070000   887.7  914.0  944.7  989.0 1028.2 1079.0 1135.0 1211.0 1300.0 1477.0
 0.060000   708.5  736.5  764.7  792.0  829.7  870.3  919.5  977.0 1065.0 1214.0
 0.050000   556.5  574.3  593.6  620.5  652.2  683.3  723.0  776.2  846.0  972.0
 0.040000   425.5  437.9  450.5  467.7  488.4  515.0  553.0  593.0  654.0  754.0
 0.030000   307.2  317.8  327.9  341.2  355.2  372.0  392.0  426.0  473.9  539.3
 0.020000   208.7  214.8  222.2  230.6  240.7  252.6  265.0  285.3  311.0  369.2
 0.015000   161.2  166.7  172.3  179.1  185.9  195.3  206.7  222.0  243.7  294.7
 0.010000   116.1  120.6  124.9  129.5  135.2  142.8  151.8  164.3  179.7  212.3
 0.007000    88.7   92.1   95.2   99.4  104.6  110.6  117.8  126.5  140.9  162.5
 0.005000    70.6   72.8   75.5   78.8   82.9   88.4   94.0  102.2  113.2  130.4
 0.003000    50.6   52.5   54.6   57.0   59.8   63.6   67.4   74.1   81.7   96.4
 0.002000    39.4   40.7   42.2   44.1   46.1   48.8   52.8   57.9   65.5   78.0
 0.001500    33.1   34.3   35.7   37.3   39.2   41.5   44.5   49.1   55.0   66.6
 0.001000    26.4   27.4   28.5   29.9   31.7   33.6   36.2   39.4   44.0   54.2
 0.000700    21.7   22.6   23.7   24.8   26.0   27.7   29.7   32.6   36.9   44.8
 0.000500    18.0   18.8   19.8   20.8   21.8   23.2   25.0   27.3   31.0   37.1
 0.000300    13.6   14.2   15.0   15.8   16.9   17.9   19.2   21.1   23.8   29.2
 0.000200    10.8   11.4   12.0   12.7   13.5   14.4   15.5   17.1   19.4   23.4
 0.000150     9.2    9.6   10.1   10.7   11.4   12.2   13.3   14.6   17.0   20.7
 0.000100     7.3    7.7    8.1    8.6    9.2    9.8   10.6   12.0   13.8   17.5
 7.000e-5     5.9    6.2    6.6    7.0    7.5    8.0    8.7    9.7   11.4   14.9
 5.000e-5     4.8    5.1    5.4    5.8    6.2    6.7    7.4    8.2    9.7   12.8
 3.000e-5     3.6    3.8    4.0    4.3    4.7    5.1    5.6    6.3    7.5   10.2
 2.000e-5     2.8    3.0    3.2    3.5    3.7    4.1    4.6    5.2    6.2    8.4
 1.500e-5     2.4    2.5    2.7    2.9    3.2    3.5    3.9    4.5    5.4    7.2
 1.000e-5     1.9    2.0    2.1    2.3    2.5    2.8    3.1    3.6    4.4    6.0
afranco@edias-pc:~/TEMP/VIRGINIA/GNG$
```



[A]u AFNI: alexandre.franco/abin/HaskinsPeds_NL_template1.0+tlrc & ttest_Go_vs_NG+tlrc

```
[order: RAI=DICOM]
x =  -28.000 mm [R]
y =   30.000 mm [P]
z =   57.000 mm [S]
```

Xhairs: Multi
Color: green
Gap: 5
Index: 0

ULay #0 #0
OLay #1 SetA-SetB_Tstat
Thr #1 SetA-SetB_Tstat

```
ULay        0:         248
OLay -3.910839: 6.196294
Thr  -3.910839: 6.196294
```

autoRange: 6.196294

p=.0050*
q=.2686

```
ULay = 134
OLay = 4.837099
Thr  = 4.837099
```

```
------- Set Clusterize Parameters -------
* NN level => NN clustering method
       1 : faces must touch
       2 : faces or edges touch
       3 : faces or edges or corners
* Voxels   => minimum cluster size that
              will be kept [at least 2]
* Bi-sided => positively and negatively
              thresholded voxels get
              clustered separately
              (eg, thresh=t-statistic)
-----------------------------------------
* Click on the 'Rpt' button to open
  a complete cluster report panel.
```

NN level: 2
Voxels: 89
Bi-sided?: No

AFNI Cluster Results [A]

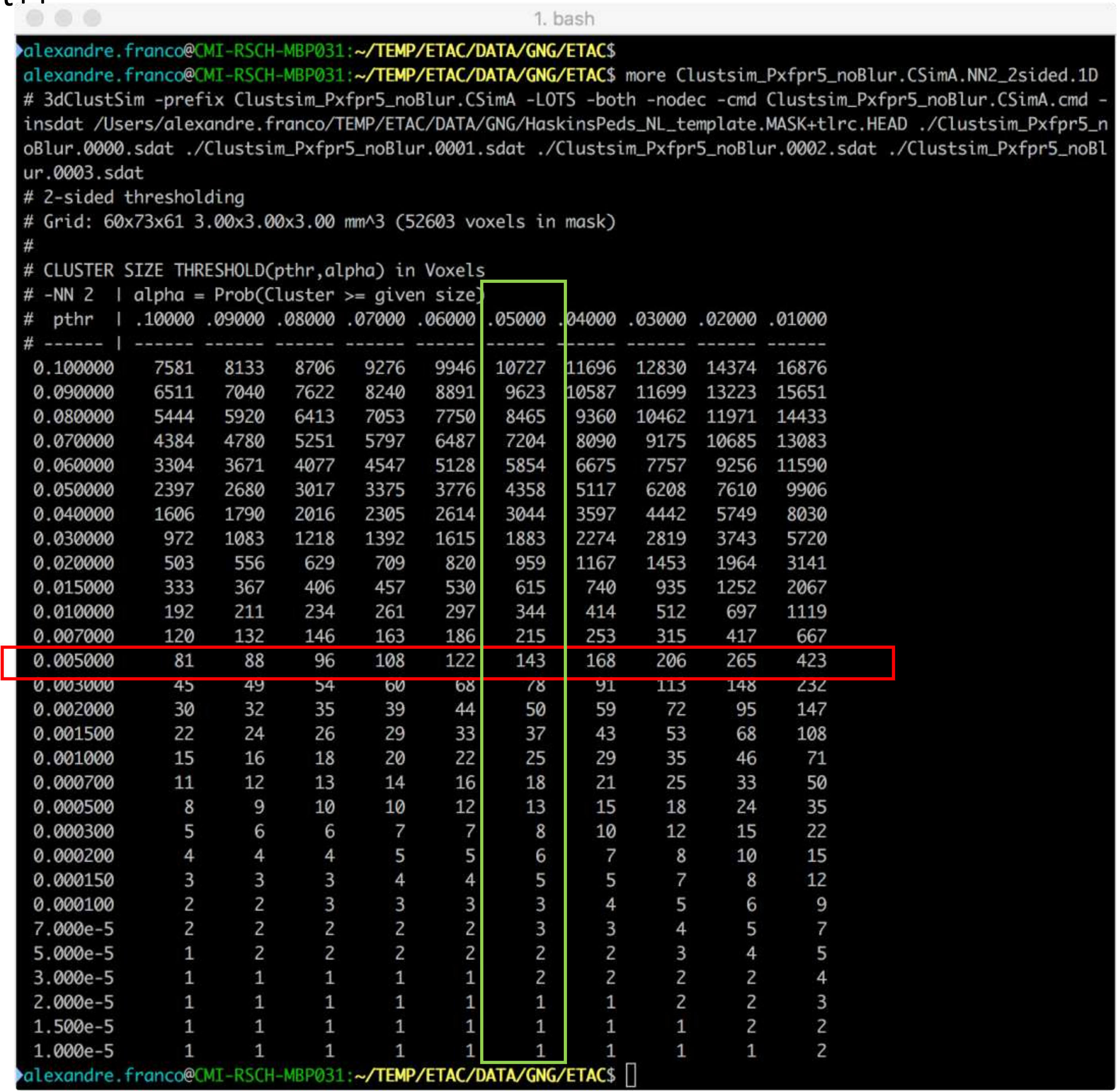
```
Voxels survived clustering =    252
Voxels edited out          =    592
NN clustering level        =      2 [edges touch]
```

```
###: __Size__   __X__   __Y__   __Z__                                  Alpha
 1:  151 vox   -28.5   +29.5   +57.5  Jump Flash Plot Save Write N/Csim
 2:  101 vox   -16.5   +80.5    +3.5  Jump Flash Plot Save Write N/Csim
```

```
${base_fol
\
-setB \
${base_fol
```

```
++ [A] 3dClustSim tables found: NN=1:1sid NN=1:2s
 + 53752 voxels in 3dClustSim mask
```

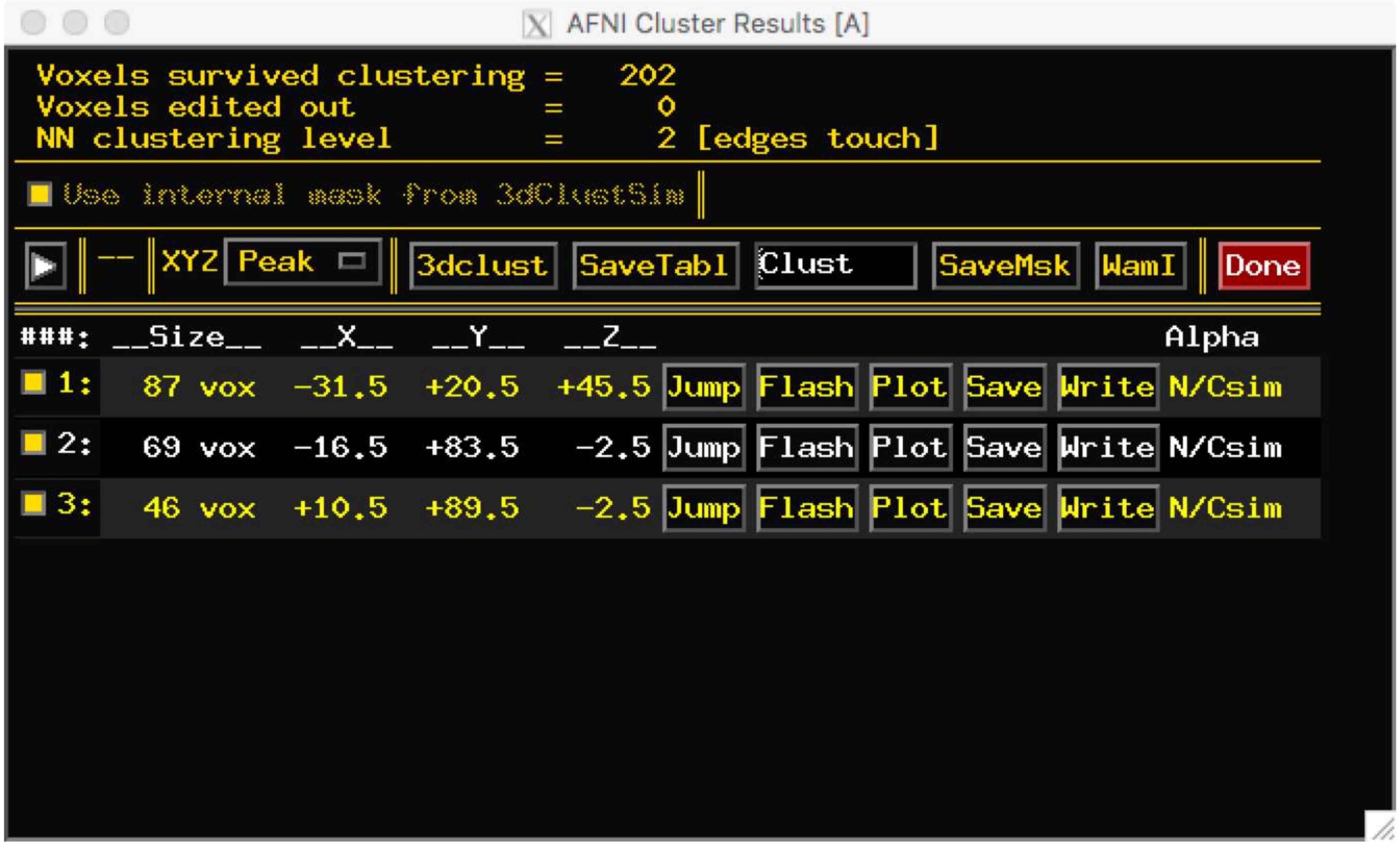
ClustSim from 3dttest++



```
alexandre.franco@CMI-RSCH-MBP031:~/TEMP/ETAC/DATA/GNG/ETAC$
alexandre.franco@CMI-RSCH-MBP031:~/TEMP/ETAC/DATA/GNG/ETAC$ more Clustsim_Pxfpr5_noBlur.CSimA.NN2_2sided.1D
# 3dClustSim -prefix Clustsim_Pxfpr5_noBlur.CSimA -LOTS -both -nodec -cmd Clustsim_Pxfpr5_noBlur.CSimA.cmd -
insdat /Users/alexandre.franco/TEMP/ETAC/DATA/GNG/HaskinsPeds_NL_template.MASK+tlrc.HEAD ./Clustsim_Pxfpr5_n
oBlur.0000.sdat ./Clustsim_Pxfpr5_noBlur.0001.sdat ./Clustsim_Pxfpr5_noBlur.0002.sdat ./Clustsim_Pxfpr5_noBl
ur.0003.sdat
# 2-sided thresholding
# Grid: 60x73x61 3.00x3.00x3.00 mm^3 (52603 voxels in mask)
#
# CLUSTER SIZE THRESHOLD(pthr,alpha) in Voxels
# -NN 2  | alpha = Prob(Cluster >= given size)
#  pthr  | .10000 .09000 .08000 .07000 .06000 .05000 .04000 .03000 .02000 .01000
# ------ | ------ ------ ------ ------ ------ ------ ------ ------ ------ ------
 0.100000   7581   8133   8706   9276   9946  10727  11696  12830  14374  16876
 0.090000   6511   7040   7622   8240   8891   9623  10587  11699  13223  15651
 0.080000   5444   5920   6413   7053   7750   8465   9360  10462  11971  14433
 0.070000   4384   4780   5251   5797   6487   7204   8090   9175  10685  13083
 0.060000   3304   3671   4077   4547   5128   5854   6675   7757   9256  11590
 0.050000   2397   2680   3017   3375   3776   4358   5117   6208   7610   9906
 0.040000   1606   1790   2016   2305   2614   3044   3597   4442   5749   8030
 0.030000    972   1083   1218   1392   1615   1883   2274   2819   3743   5720
 0.020000    503    556    629    709    820    959   1167   1453   1964   3141
 0.015000    333    367    406    457    530    615    740    935   1252   2067
 0.010000    192    211    234    261    297    344    414    512    697   1119
 0.007000    120    132    146    163    186    215    253    315    417    667
 0.005000     81     88     96    108    122    143    168    206    265    423
 0.003000     45     49     54     60     68     78     91    113    148    232
 0.002000     30     32     35     39     44     50     59     72     95    147
 0.001500     22     24     26     29     33     37     43     53     68    108
 0.001000     15     16     18     20     22     25     29     35     46     71
 0.000700     11     12     13     14     16     18     21     25     33     50
 0.000500      8      9     10     10     12     13     15     18     24     35
 0.000300      5      6      6      7      7      8     10     12     15     22
 0.000200      4      4      4      5      5      6      7      8     10     15
 0.000150      3      3      3      4      4      5      5      7      8     12
 0.000100      2      2      3      3      3      3      4      5      6      9
 7.000e-5      2      2      2      2      2      3      3      4      5      7
 5.000e-5      1      2      2      2      2      2      2      3      4      5
 3.000e-5      1      1      1      1      1      2      2      2      2      4
 2.000e-5      1      1      1      1      1      1      1      2      2      3
 1.500e-5      1      1      1      1      1      1      1      1      2      2
 1.000e-5      1      1      1      1      1      1      1      1      1      2
alexandre.franco@CMI-RSCH-MBP031:~/TEMP/ETAC/DATA/GNG/ETAC$
```

ETAC Output

[A]u AFNI: alexandre.franco/abin/HaskinsPeds_NL_template1.0+tlrc & Clustsim_Pxfpr5_noBlur.FPR5.ETACmask.2sid.5perc.nii.gz+tlrc



```
Voxels survived clustering =   202
Voxels edited out          =     0
NN clustering level        =     2 [edges touch]
```

```
###: __Size__  __X__  __Y__  __Z__                                        Alpha
■ 1:  87 vox  -31.5  +20.5  +45.5 Jump Flash Plot Save Write N/Csim
■ 2:  69 vox  -16.5  +83.5   -2.5 Jump Flash Plot Save Write N/Csim
■ 3:  46 vox  +10.5  +89.5   -2.5 Jump Flash Plot Save Write N/Csim
```

Acknowledgments

Cox:

“The ideas for equitable application of multiple sub-tests came to RWC while hiking in Grand Canyon National Park and in Gunnison National Forest; thanks go to the US National Park Service and US Forest Service for maintaining these inspirational public treasures.”