fMRI Course, Day 9

Pitfalls of fMRI Analysis

Tuesday, August 9th, 2022

Before We Begin

Questions about either 1st- or 2nd-level analysis?

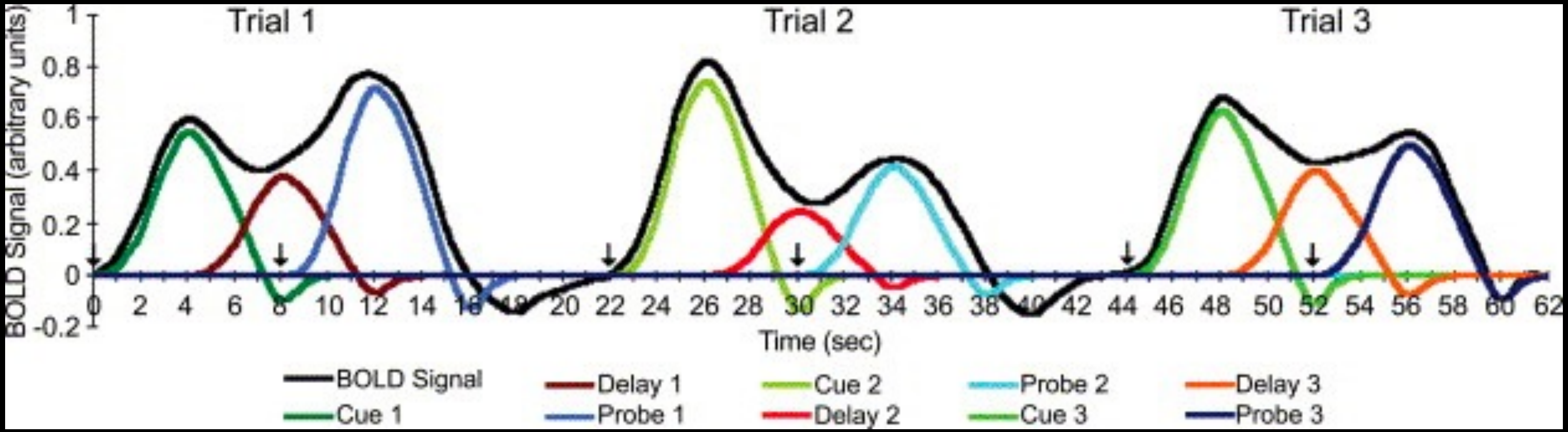
Questions about anything else?

Extra Slides from Previous Lectures

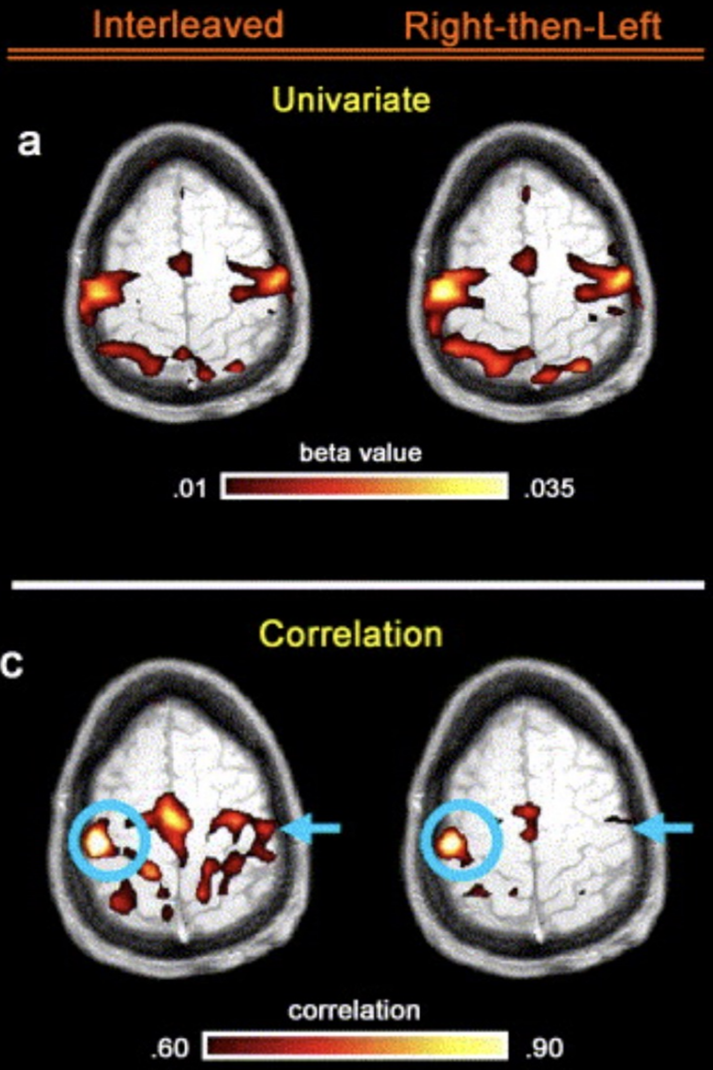
Applying the GLM to fMRI Data

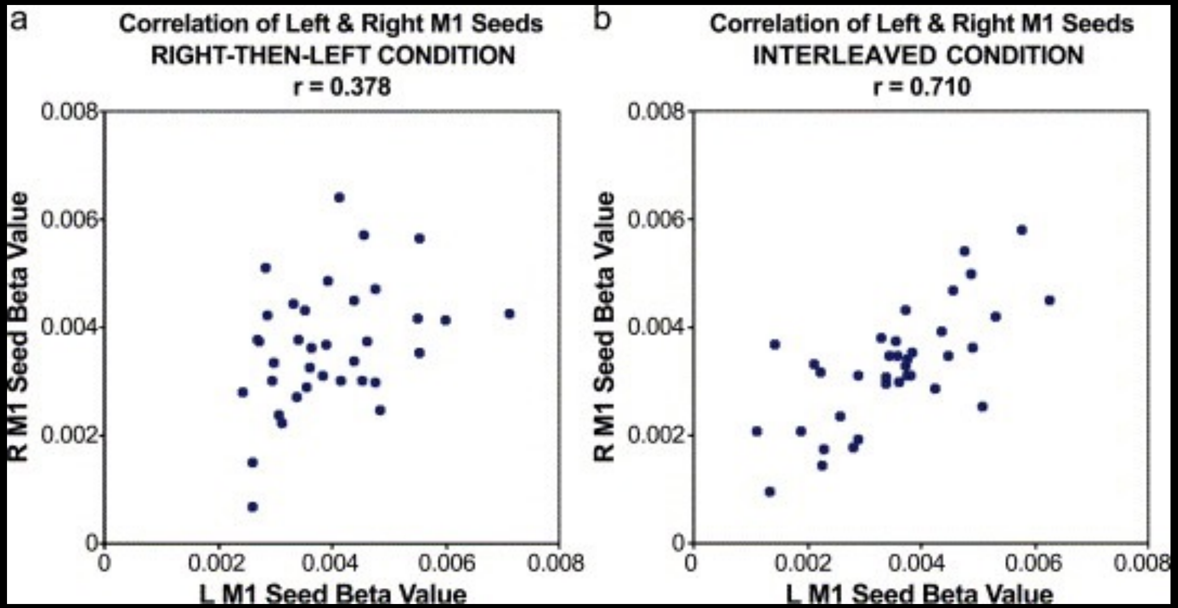
Other options: Individual Modulation

Useful for beta-series correlation, MVPA classification

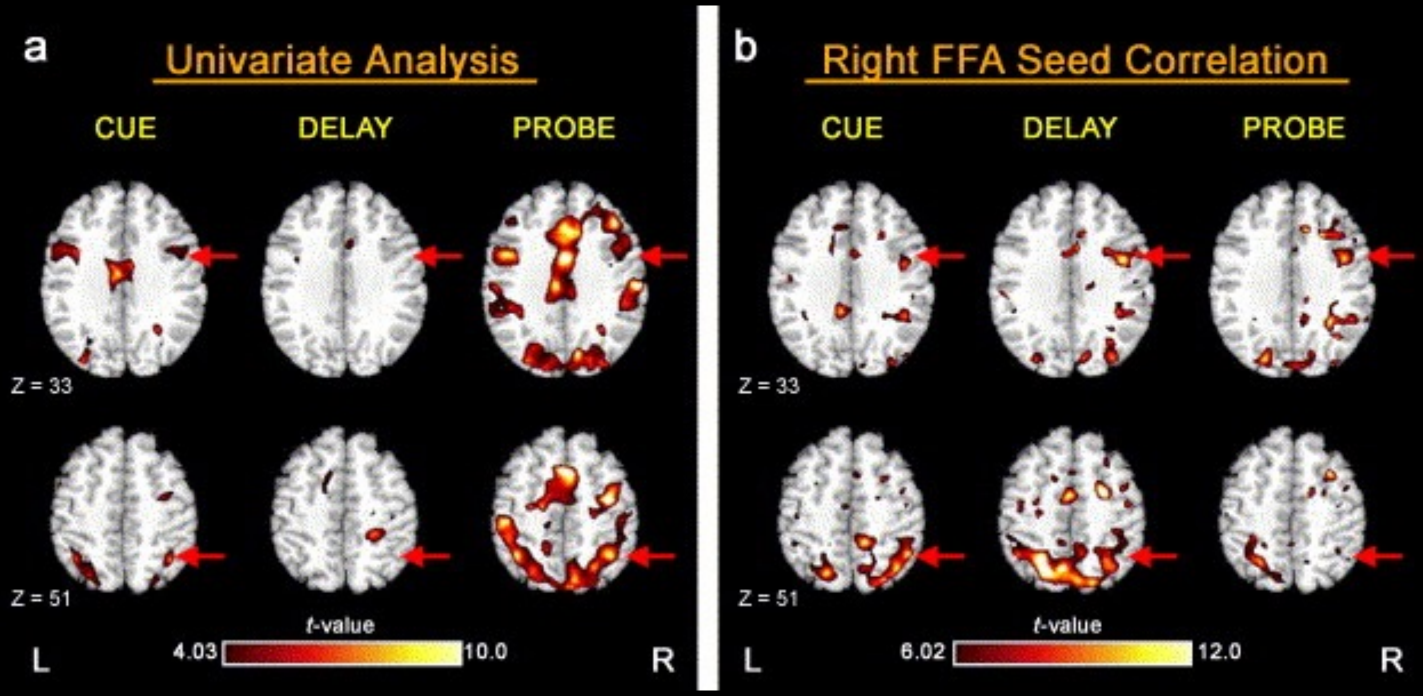


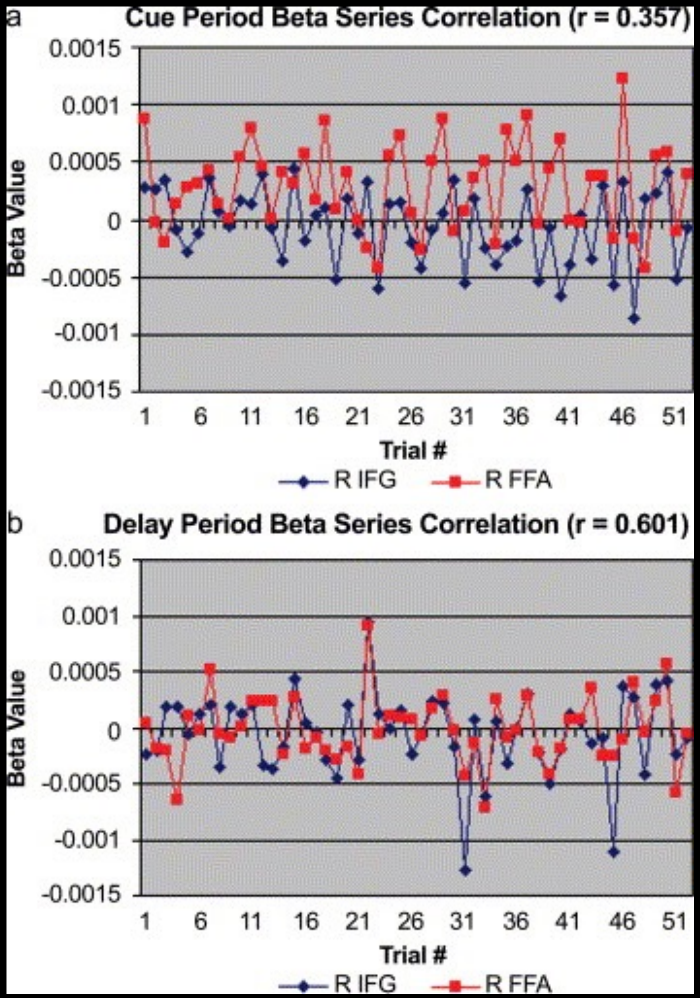
Applying the GLM to fMRI Data





Applying the GLM to fMRI Data





Applying the GLM to fMRI Data

Drawback: Very tedious to implement without scripting!

For AFNI users: Can use ‘IM’ basis function in 3dDeconvolve

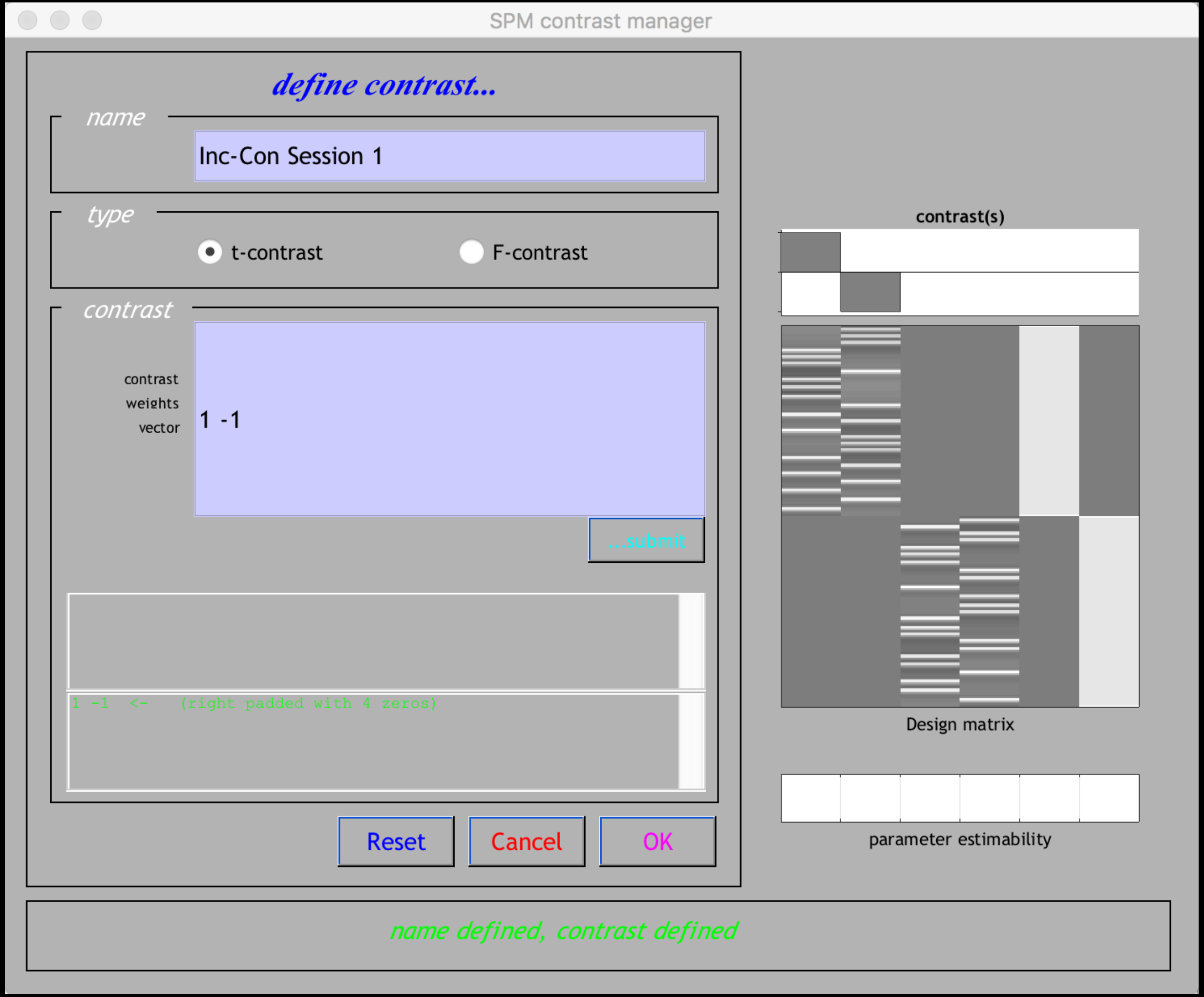
ImCalc: The Image Calculator

One of the most versatile tools is the image calculator

Every package has one (AFNI, FSL, MRtrix, etc.)

Simple to do basic arithmetic on a 3D image

ImCalc: The Image Calculator



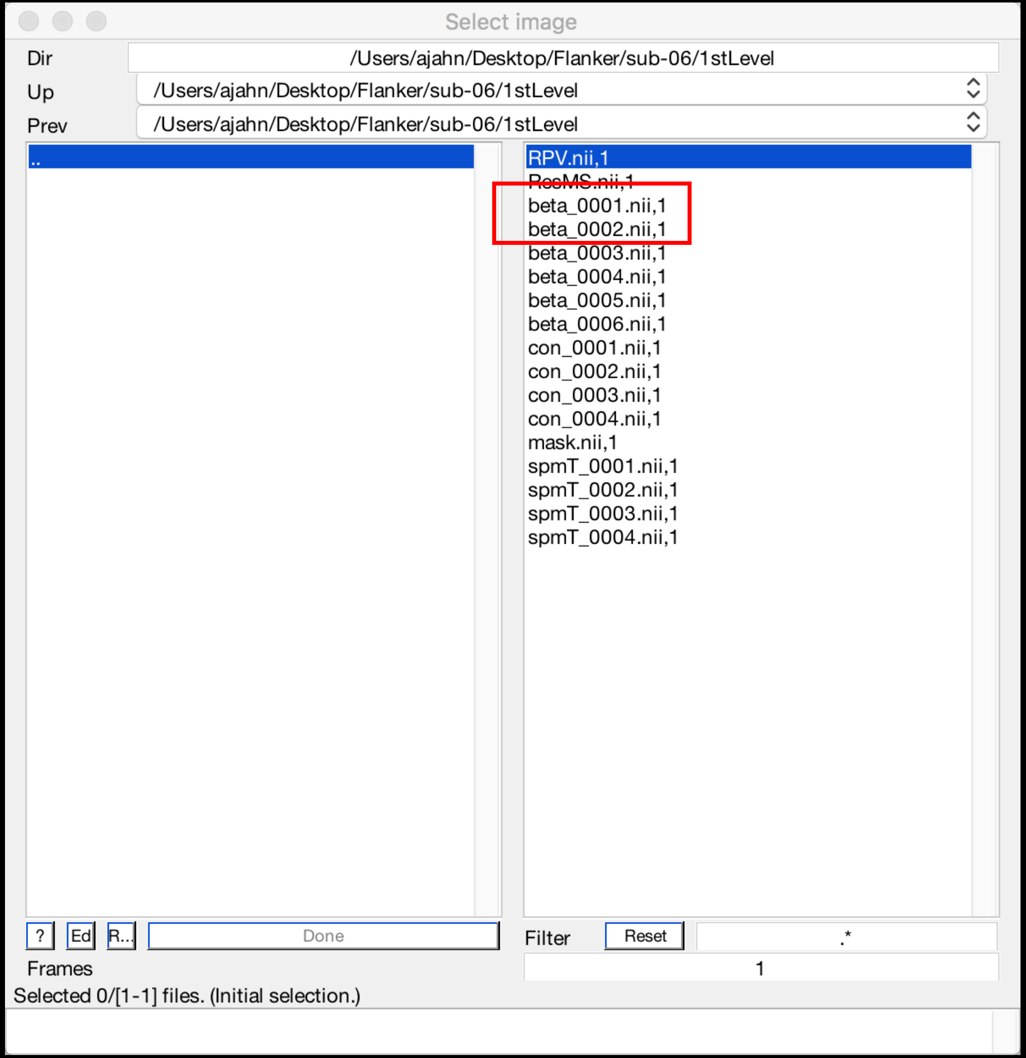
name: Inc-Con Session 1

type: ● t-contrast ○ F-contrast

contrast weights vector: 1 -1

```
1 -1  <-   (right padded with 4 zeros)
```

name defined, contrast defined



Dir /Users/ajahn/Desktop/Flanker/sub-06/1stLevel

Up /Users/ajahn/Desktop/Flanker/sub-06/1stLevel

Prev /Users/ajahn/Desktop/Flanker/sub-06/1stLevel

..

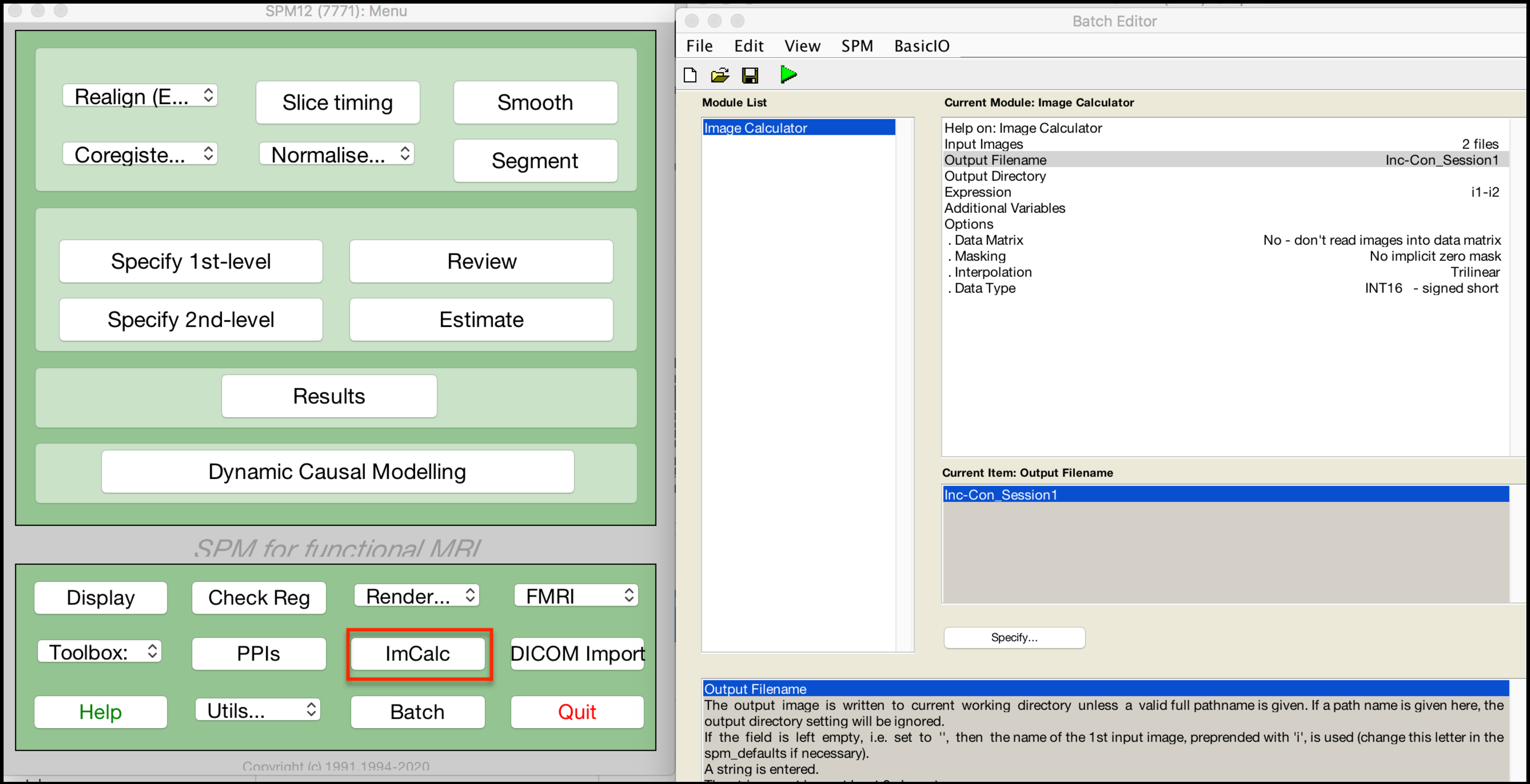
RPV.nii,1
ResMS.nii,1
beta_0001.nii,1
beta_0002.nii,1
beta_0003.nii,1
beta_0004.nii,1
beta_0005.nii,1
beta_0006.nii,1
con_0001.nii,1
con_0002.nii,1
con_0003.nii,1
con_0004.nii,1
mask.nii,1
spmT_0001.nii,1
spmT_0002.nii,1
spmT_0003.nii,1
spmT_0004.nii,1

Filter .*

Frames 1

Selected 0/[1-1] files. (Initial selection.)

ImCalc: The Image Calculator



Current Module: Image Calculator

Help on: Image Calculator	
Input Images	2 files
Output Filename	Inc-Con_Session1
Output Directory	
Expression	i1-i2
Additional Variables	
Options	
. Data Matrix	No - don't read images into data matrix
. Masking	No implicit zero mask
. Interpolation	Trilinear
. Data Type	INT16 - signed short

Current Item: Output Filename

Inc-Con_Session1

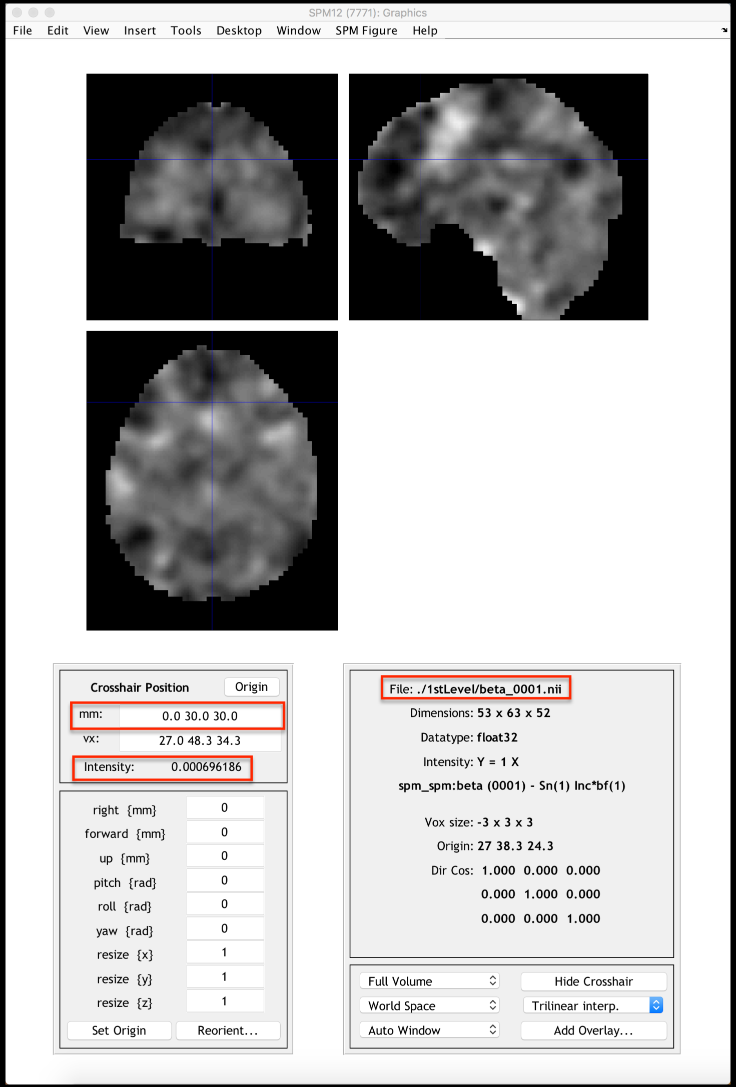
Output Filename

The output image is written to current working directory unless a valid full pathname is given. If a path name is given here, the output directory setting will be ignored.

If the field is left empty, i.e. set to '', then the name of the 1st input image, preprended with 'i', is used (change this letter in the spm_defaults if necessary).

A string is entered.

ImCalc: The Image Calculator



Crosshair Position

mm: 0.0 30.0 30.0

vx: 27.0 48.3 34.3

Intensity: 0.000696186

right {mm}	0
forward {mm}	0
up {mm}	0
pitch {rad}	0
roll {rad}	0
yaw {rad}	0
resize {x}	1
resize {y}	1
resize {z}	1

File: ./1stLevel/beta_0001.nii

Dimensions: **53 x 63 x 52**

Datatype: **float32**

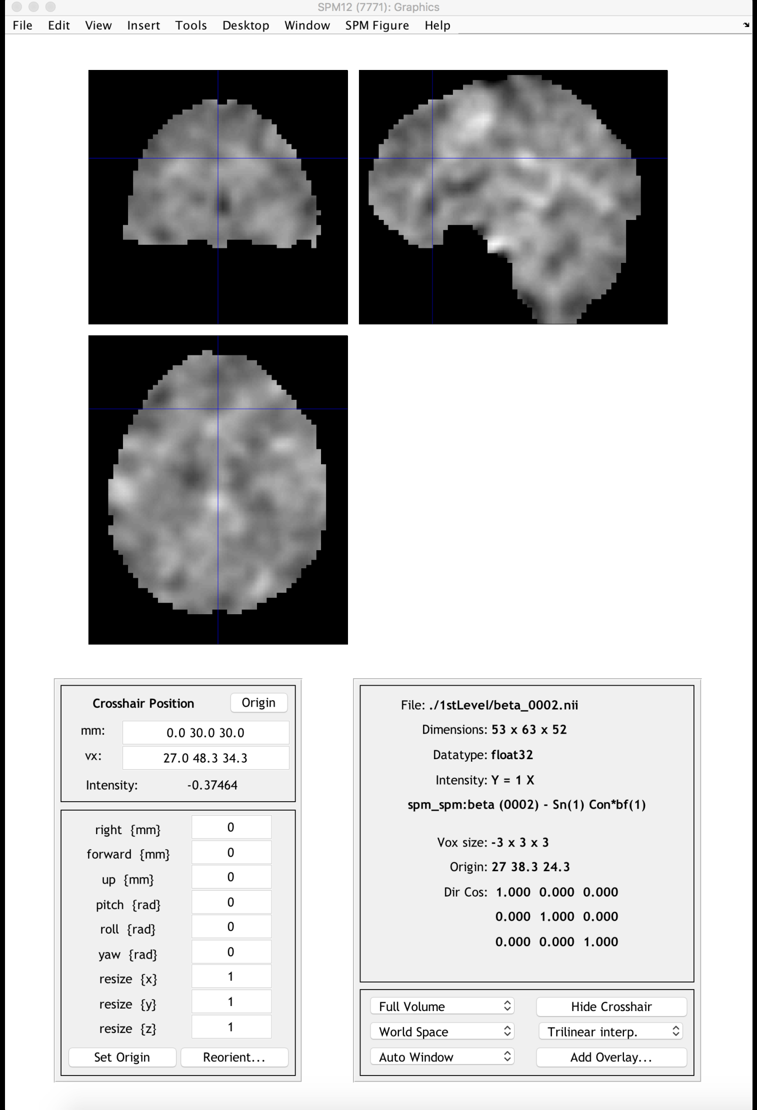
Intensity: **Y = 1 X**

spm_spm:beta (0001) - Sn(1) Inc*bf(1)

Vox size: **-3 x 3 x 3**

Origin: **27 38.3 24.3**

Dir Cos: **1.000 0.000 0.000**
0.000 1.000 0.000
0.000 0.000 1.000



Crosshair Position

mm: 0.0 30.0 30.0

vx: 27.0 48.3 34.3

Intensity: -0.37464

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forward {mm}	0
up {mm}	0
pitch {rad}	0
roll {rad}	0
yaw {rad}	0
resize {x}	1
resize {y}	1
resize {z}	1

File: ./1stLevel/beta_0002.nii

Dimensions: **53 x 63 x 52**

Datatype: **float32**

Intensity: **Y = 1 X**

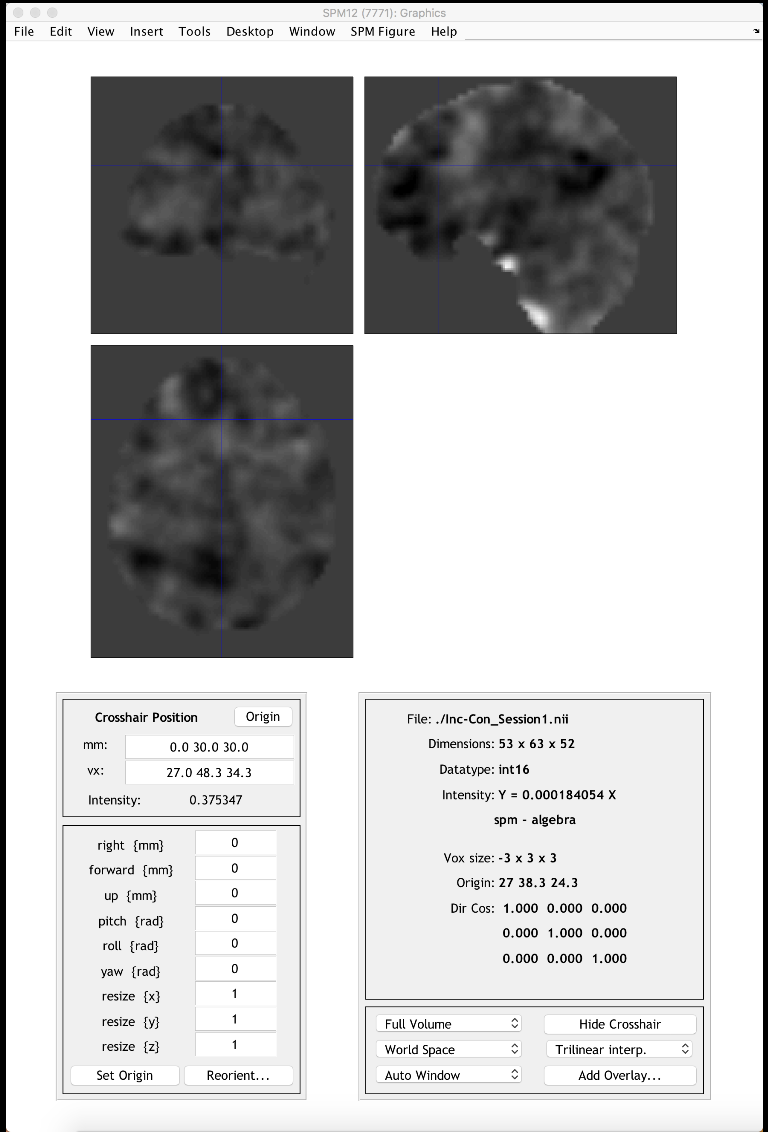
spm_spm:beta (0002) - Sn(1) Con*bf(1)

Vox size: **-3 x 3 x 3**

Origin: **27 38.3 24.3**

Dir Cos: **1.000 0.000 0.000**
0.000 1.000 0.000
0.000 0.000 1.000

ImCalc: The Image Calculator



Crosshair Position

mm: 0.0 30.0 30.0

vx: 27.0 48.3 34.3

Intensity: 0.375347

right {mm}	0
forward {mm}	0
up {mm}	0
pitch {rad}	0
roll {rad}	0
yaw {rad}	0
resize {x}	1
resize {y}	1
resize {z}	1

File: ./Inc-Con_Session1.nii

Dimensions: 53 x 63 x 52

Datatype: int16

Intensity: Y = 0.000184054 X

spm - algebra

Vox size: -3 x 3 x 3

Origin: 27 38.3 24.3

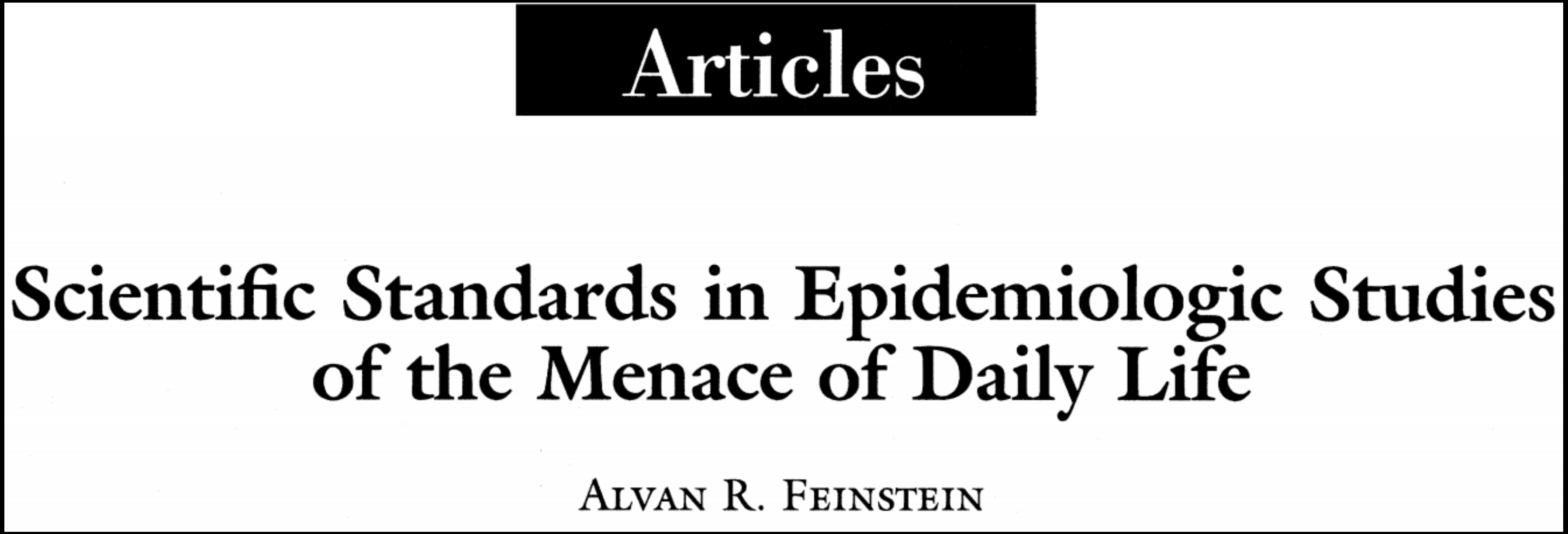
Dir Cos: 1.000 0.000 0.000
0.000 1.000 0.000
0.000 0.000 1.000

Outline

Today: Pitfalls of fMRI Analysis

Specifically, non-independence and cluster failure

Ways to avoid these pitfalls



Articles

Scientific Standards in Epidemiologic Studies of the Menace of Daily Life

ALVAN R. FEINSTEIN

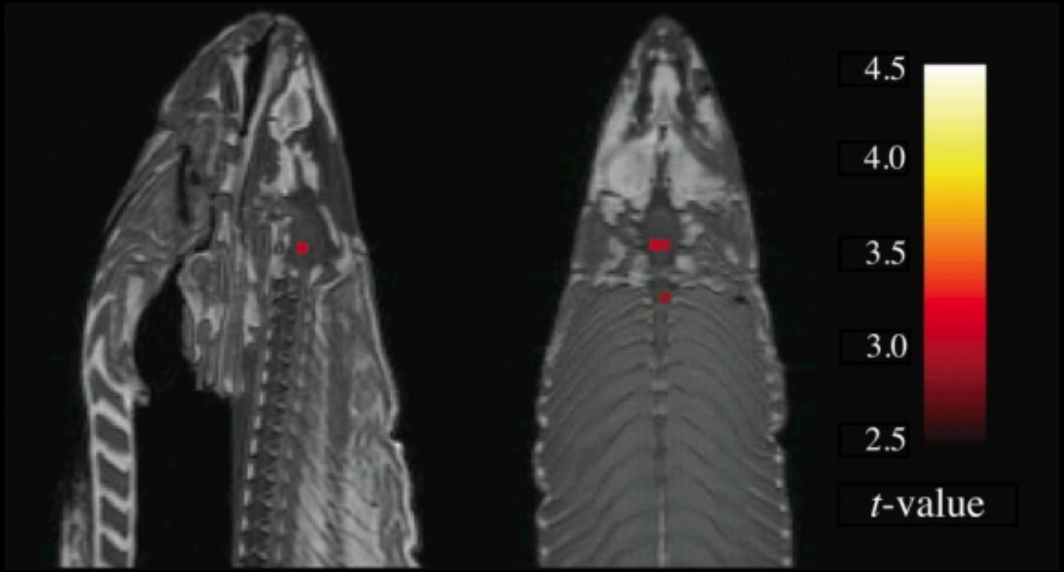
Focused on methods of epidemiological studies

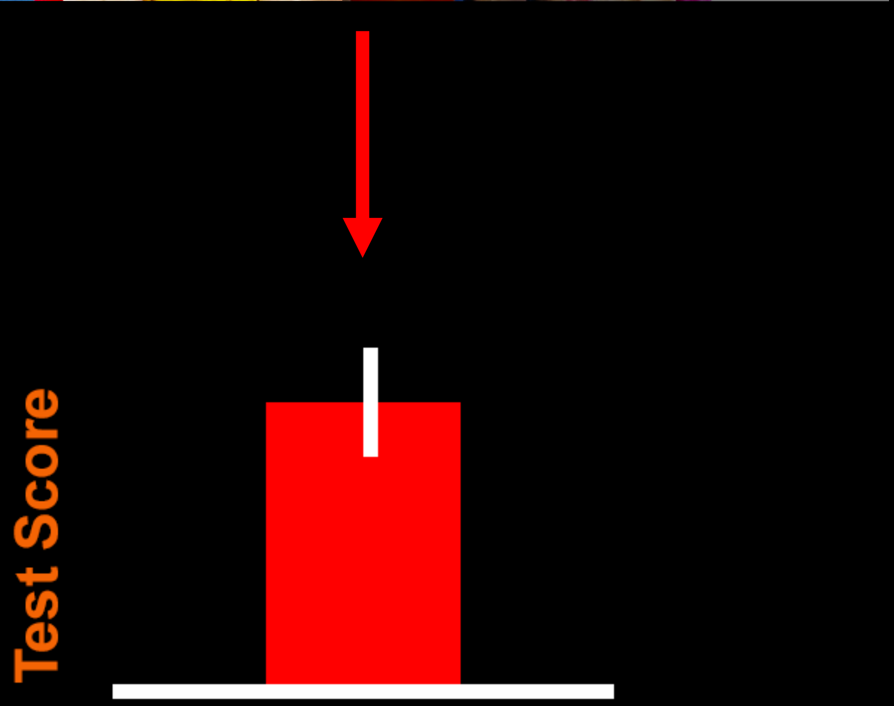
Hypothesizing after the fact

Uncorrected for multiple comparisons

Back in 2009…

Bennet et al.: Illustration of the Multiple Comparisons Problem





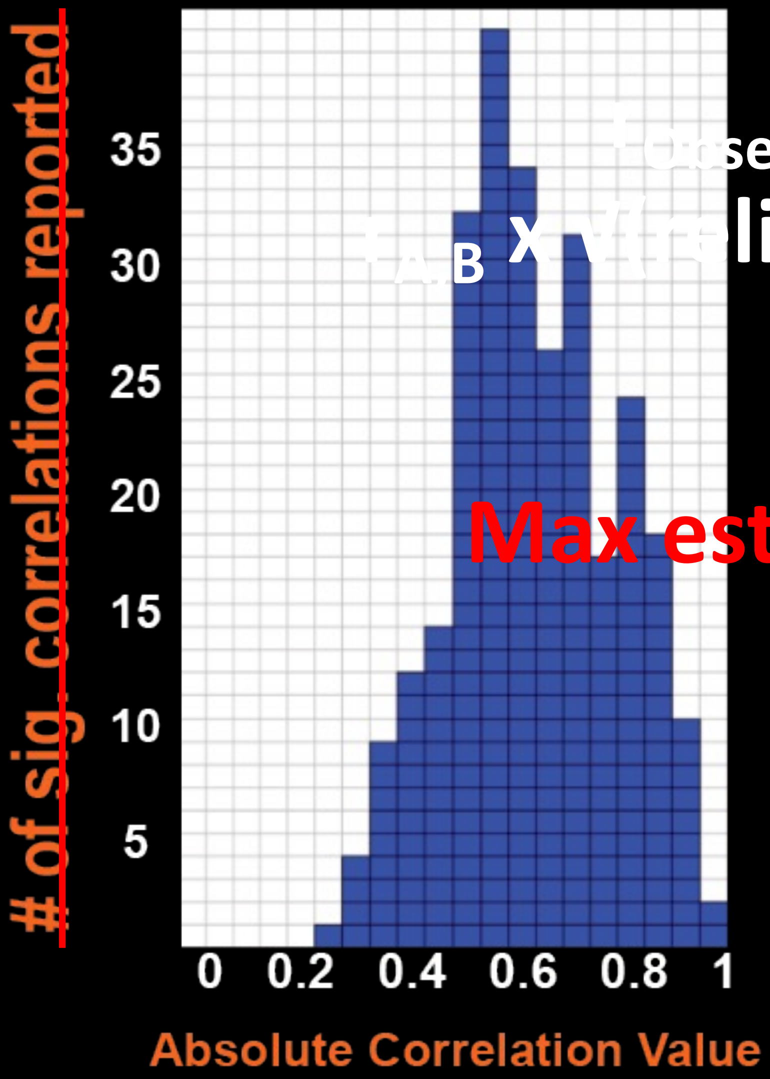
Biased Analysis

Circular Analysis

Nonindependent

Double Dipping

Back in 2009…



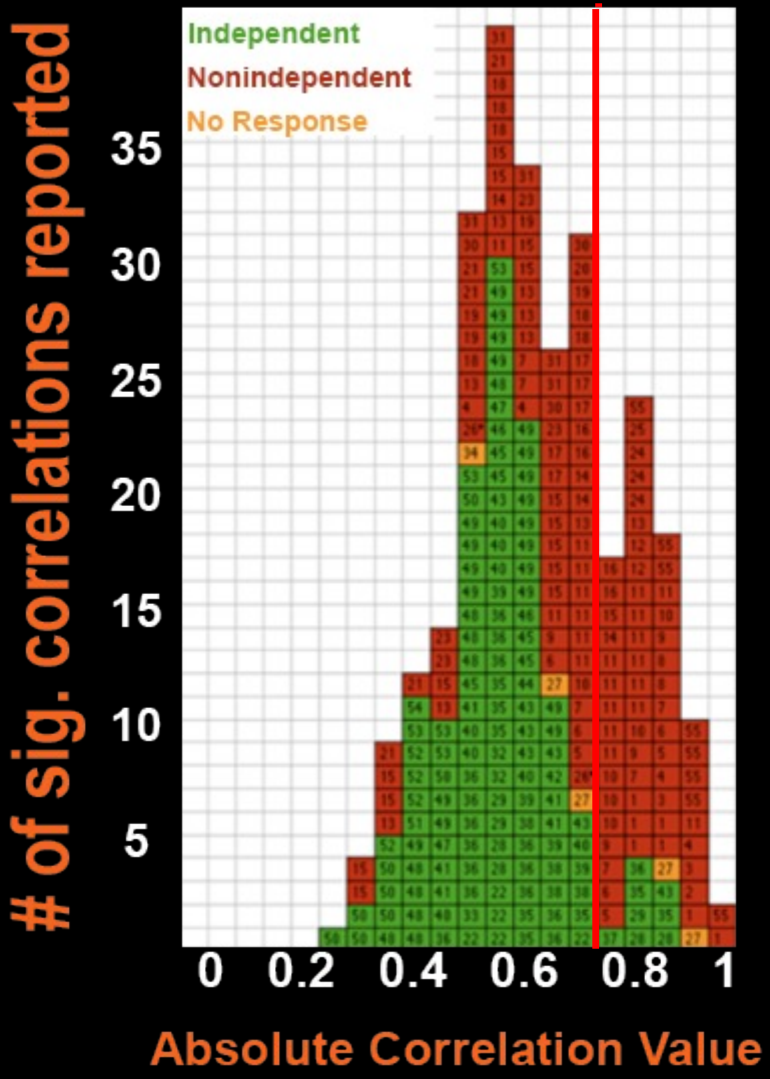
$r_{ObservedA, ObservedB} =$

$r_{A,B} \times \sqrt{(reliability_A \times reliability_B)}$

Max estimate for r = 0.74

From Vul et al., 2009

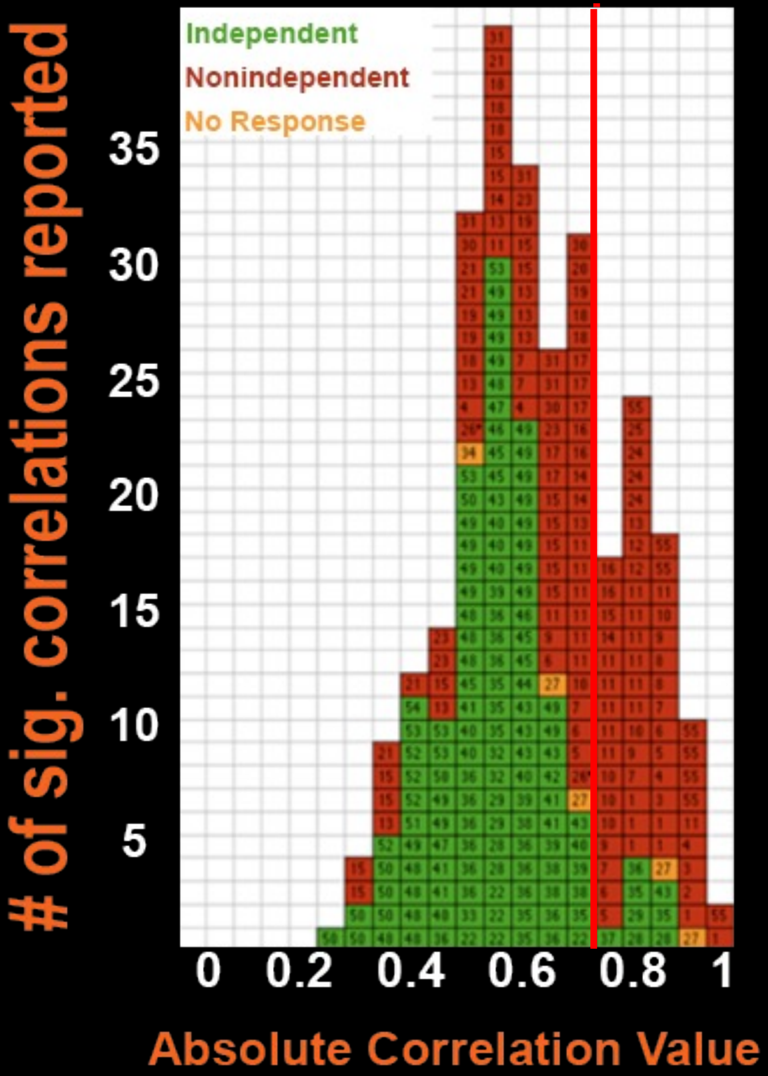
Back in 2009…



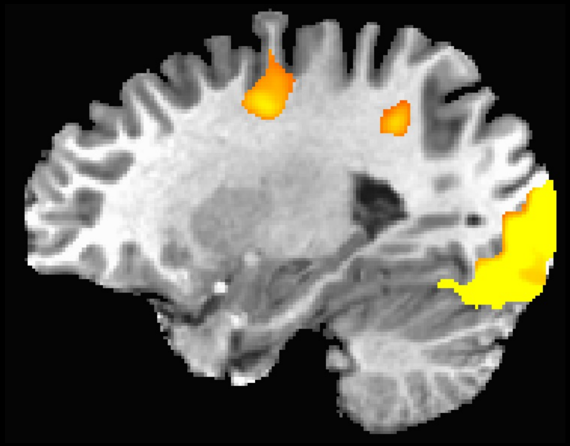
$$r_{ObservedA,\ ObservedB} = r_{A,B} \times \sqrt{(reliability_A \times reliability_B)}$$

Max estimate for r = 0.74

Vul’s Interpretation



Significant voxels more likely to benefit from noise



Leads to inflated effect sizes

Objections

What if I just want to see what’s going on?

My recommendation: Look, but don’t publish

If included, explain how it was done,
and do *not* include error bars

Objections

But doesn’t the correlation (or effect) actually exist?

Assuming multiple comparisons correction, yes

But, magnitude is also important,
and is misleading with biased analyses

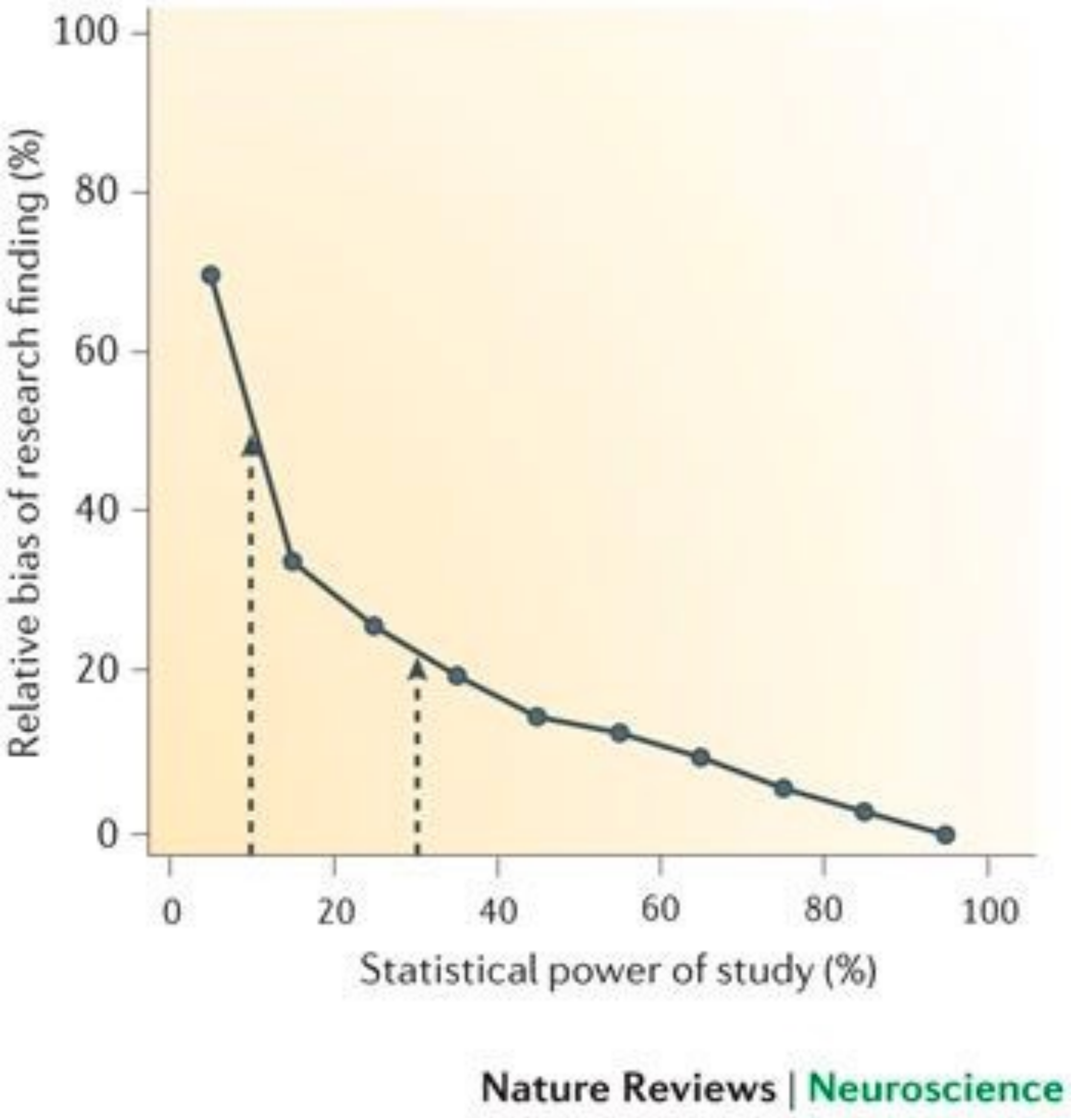
Problems with Sample Size

Only high correlations are reported

Power drops, effect size inflates

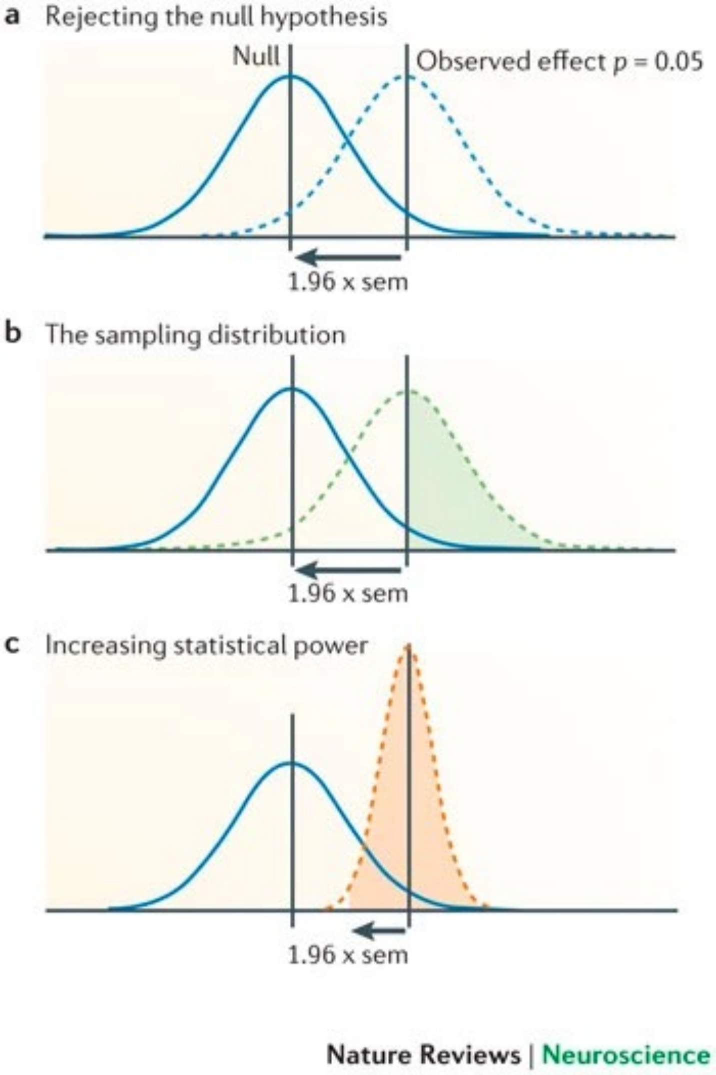
“Winner’s Curse”

Problems with Sample Size



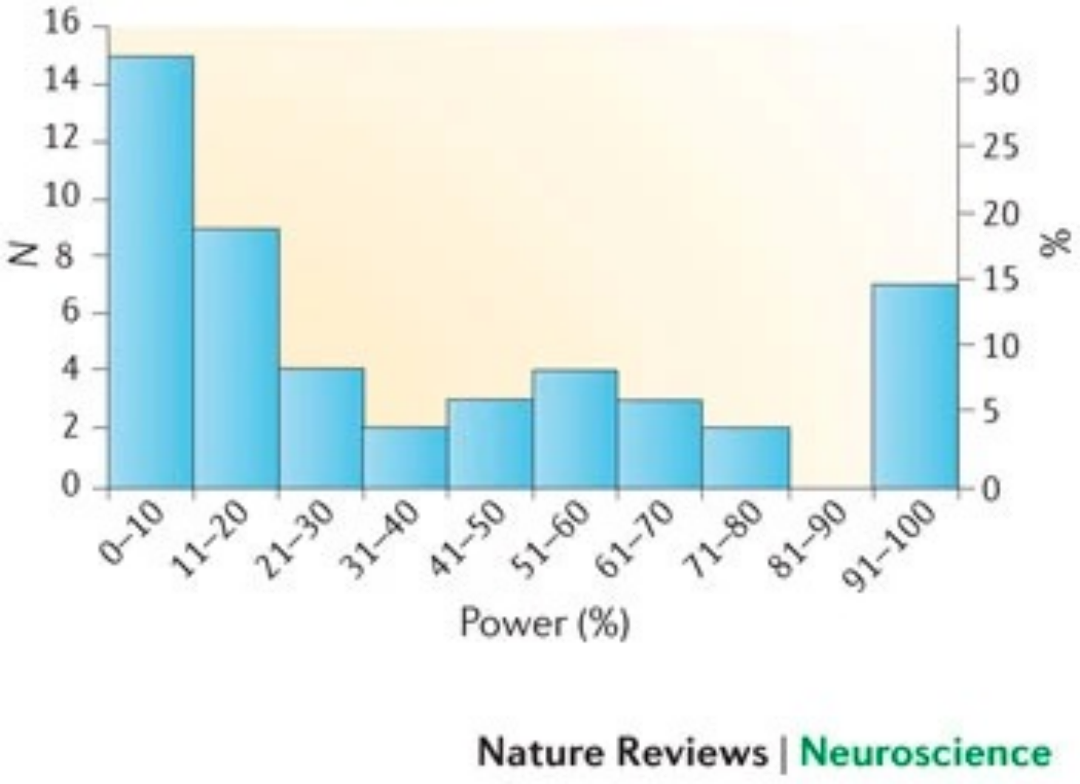
Button et al., 2013

Problems with Sample Size



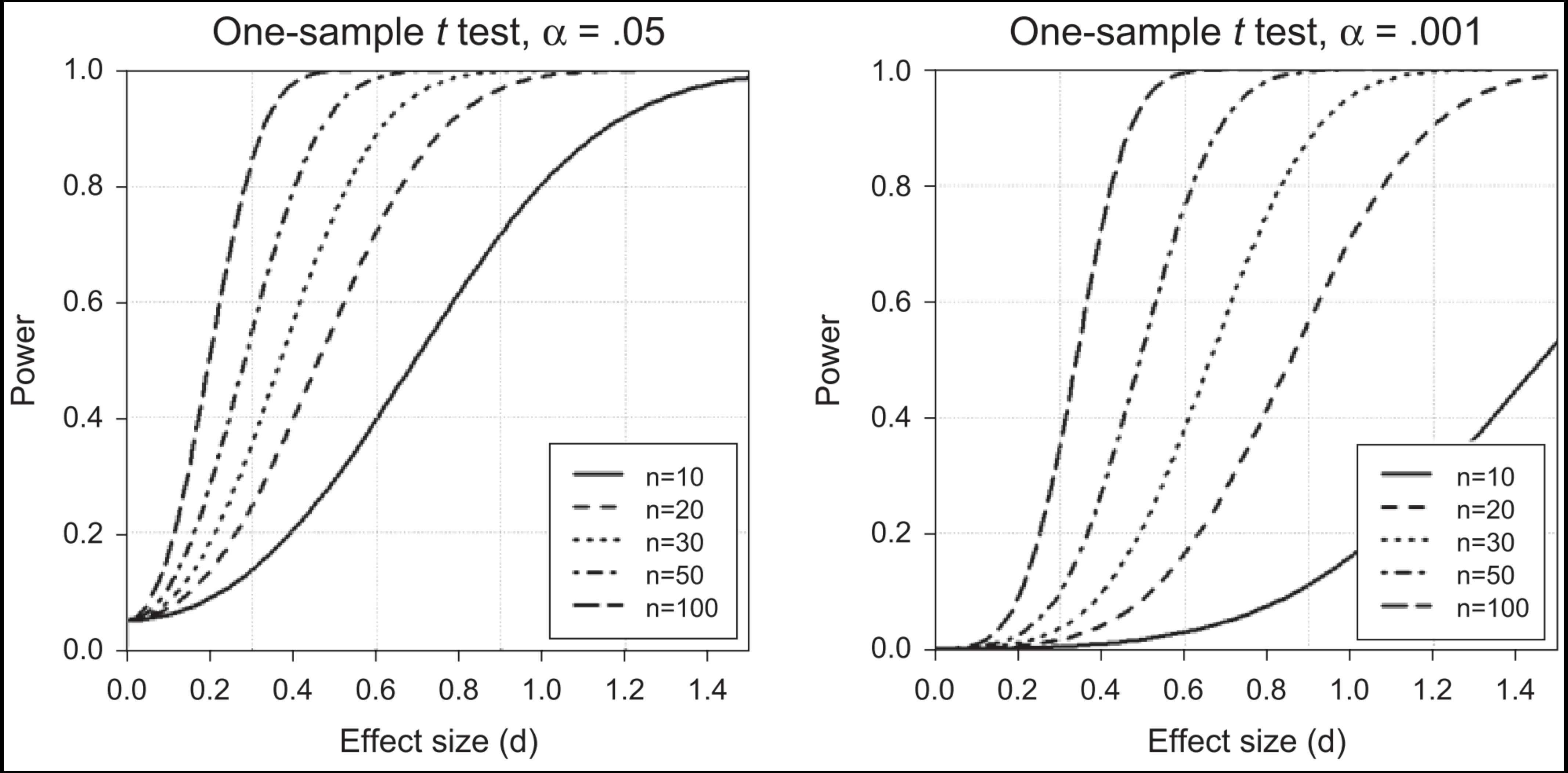
Button et al., 2013

Problems with Sample Size



Button et al., 2013

Problems with Sample Size

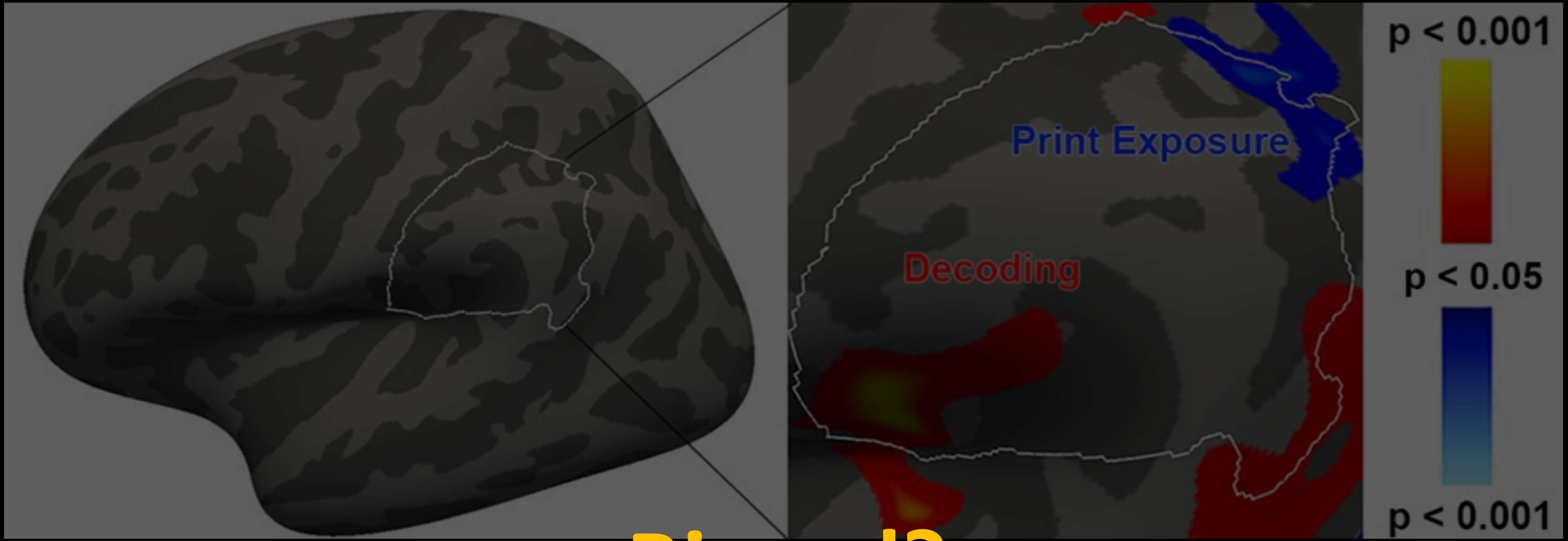


What to do?

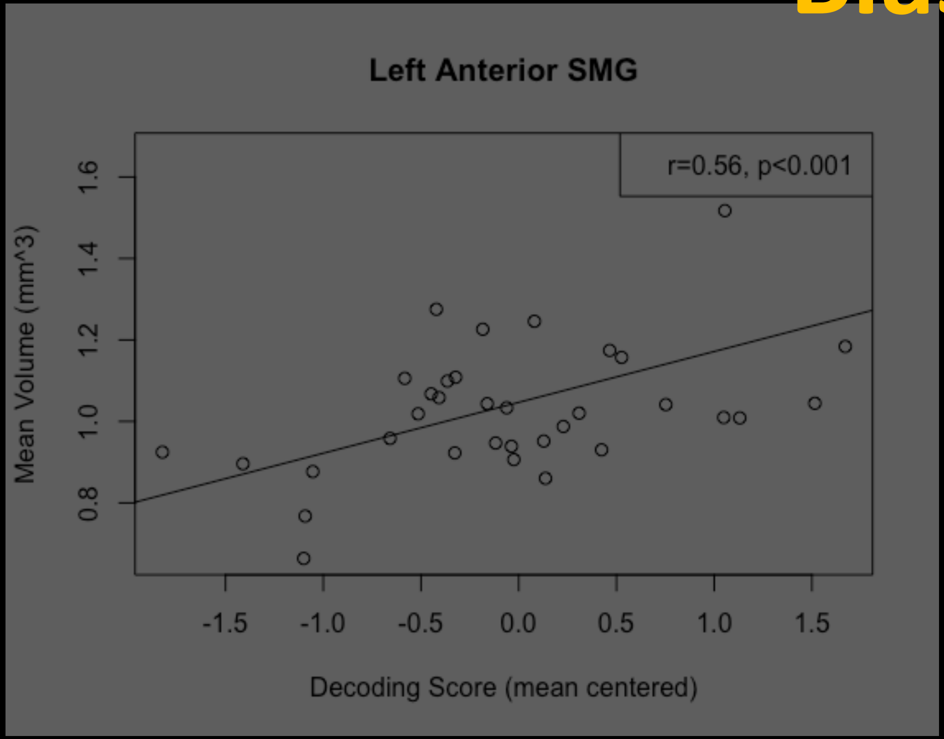
Increase N

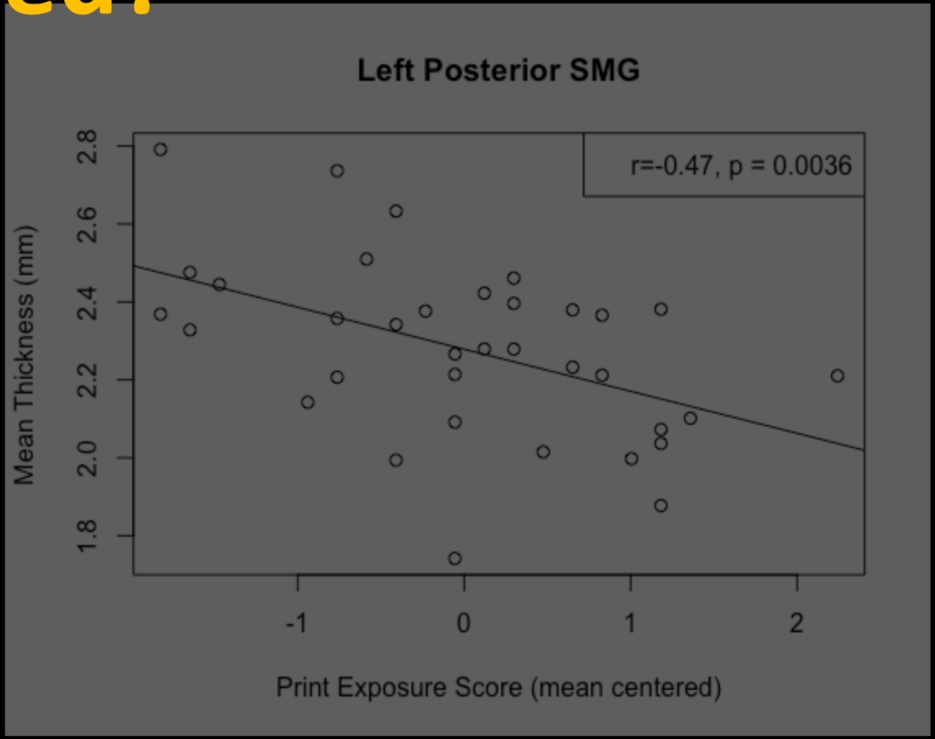
Power analyses to estimate effect size

Pre-registered reports

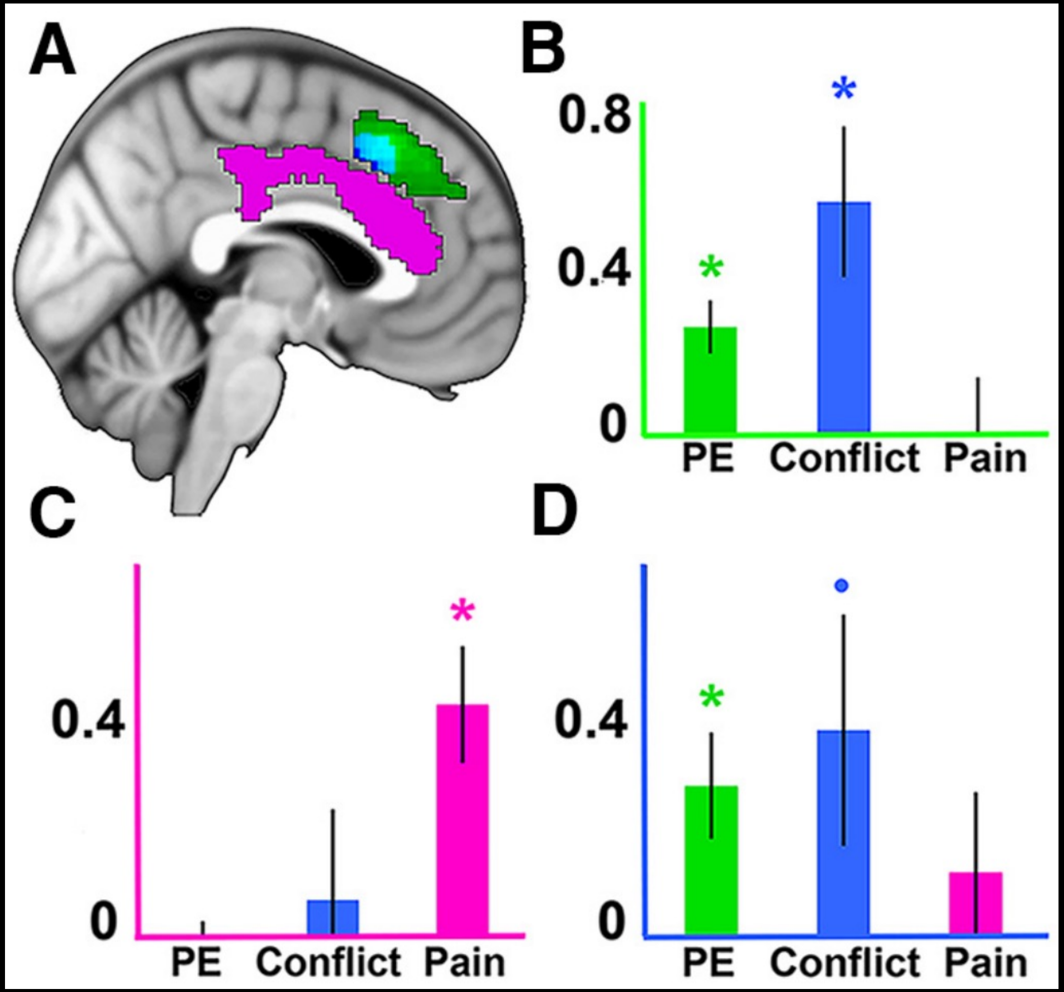

Print Exposure
Decoding
p < 0.001
p < 0.05
p < 0.001

Biased?


Left Anterior SMG
r=0.56, p<0.001
Mean Volume (mm^3)
0.8
1.0
1.2
1.4
1.6
-1.5
-1.0
-0.5
0.0
0.5
1.0
1.5
Decoding Score (mean centered)


Left Posterior SMG
r=-0.47, p = 0.0036
Mean Thickness (mm)
1.8
2.0
2.2
2.4
2.6
2.8
-1
0
1
2
Print Exposure Score (mean centered)

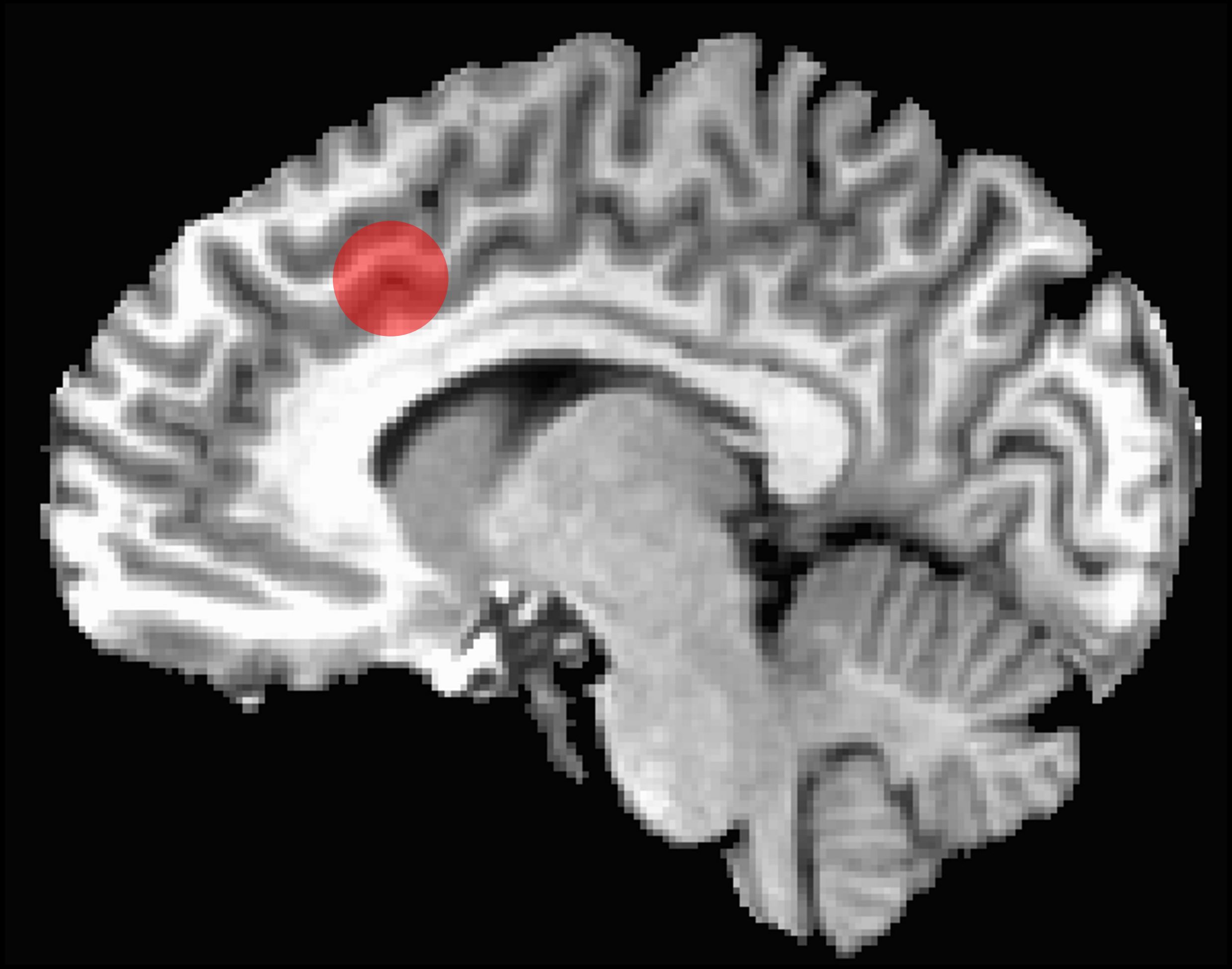
What about this?



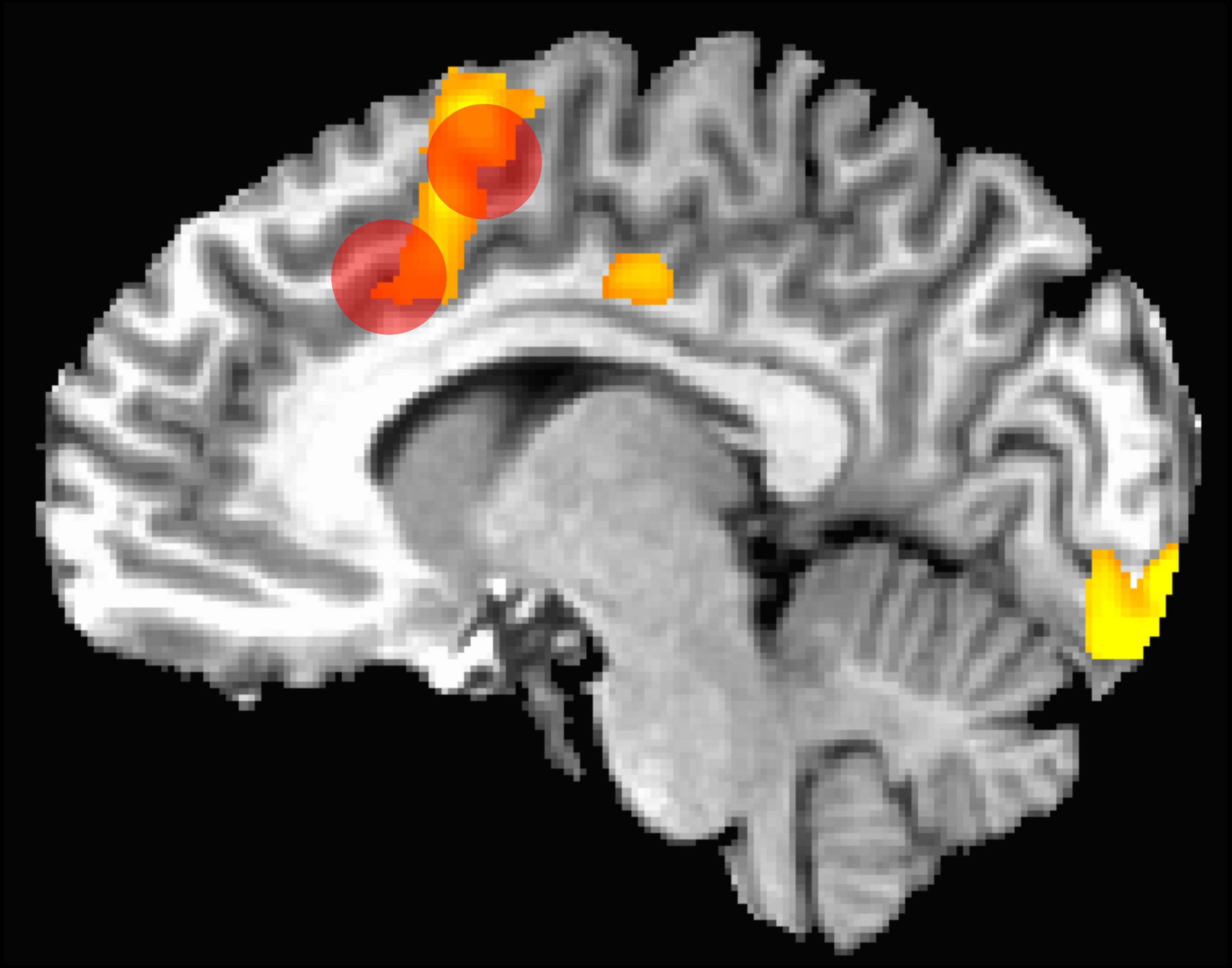
"In this approach, second-level analyses are run for each contrast, consecutively leaving out each subject from the GLM and extracting that subject's contrast estimates from the resulting ROI."

Jahn et al., 2016

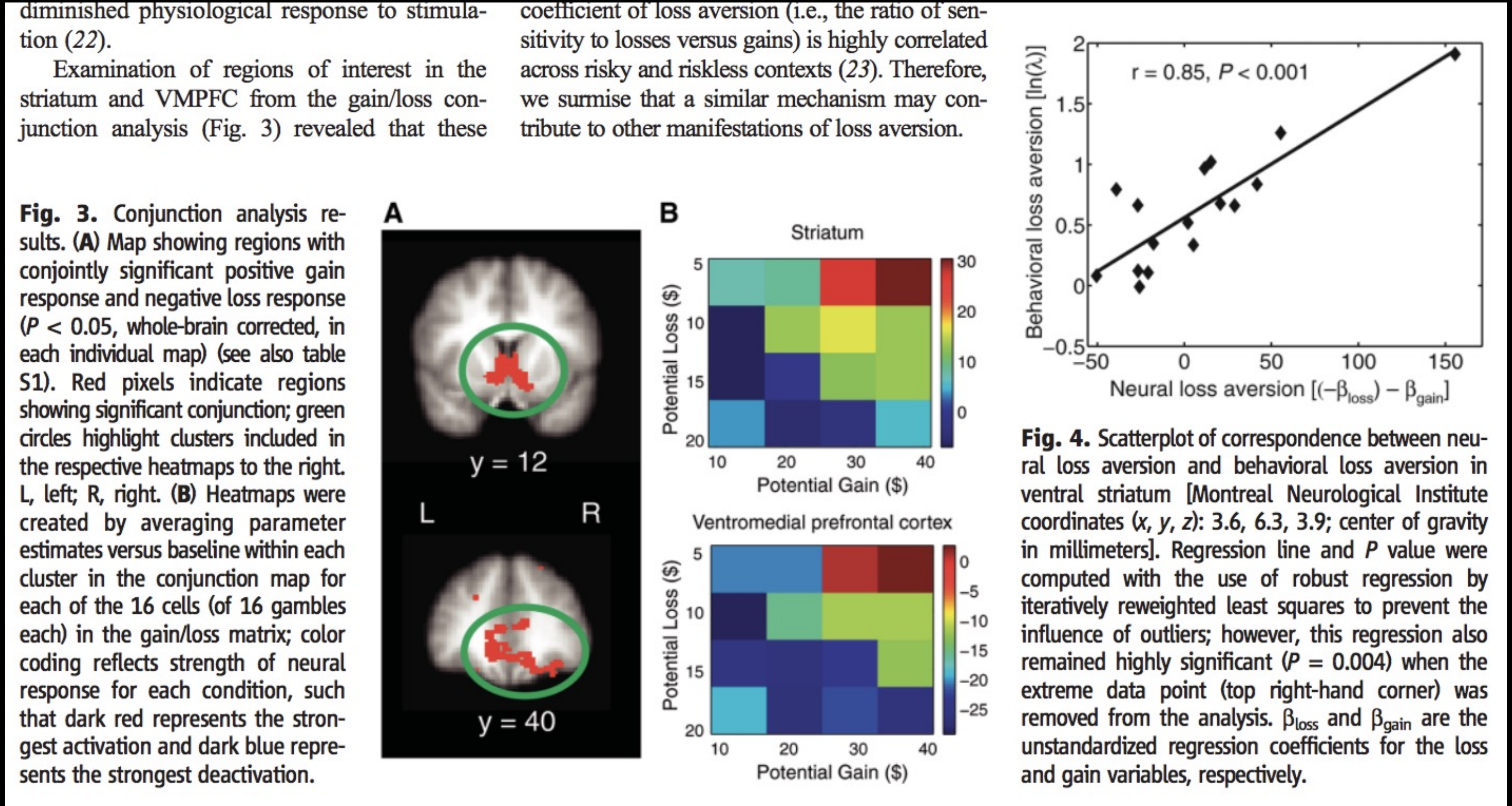
What about this?



What about this?



Remember This?



diminished physiological response to stimulation (*22*).

Examination of regions of interest in the striatum and VMPFC from the gain/loss conjunction analysis (Fig. 3) revealed that these

coefficient of loss aversion (i.e., the ratio of sensitivity to losses versus gains) is highly correlated across risky and riskless contexts (*23*). Therefore, we surmise that a similar mechanism may contribute to other manifestations of loss aversion.

Fig. 3. Conjunction analysis results. (**A**) Map showing regions with conjointly significant positive gain response and negative loss response ($P < 0.05$, whole-brain corrected, in each individual map) (see also table S1). Red pixels indicate regions showing significant conjunction; green circles highlight clusters included in the respective heatmaps to the right. L, left; R, right. (**B**) Heatmaps were created by averaging parameter estimates versus baseline within each cluster in the conjunction map for each of the 16 cells (of 16 gambles each) in the gain/loss matrix; color coding reflects strength of neural response for each condition, such that dark red represents the strongest activation and dark blue represents the strongest deactivation.

Fig. 4. Scatterplot of correspondence between neural loss aversion and behavioral loss aversion in ventral striatum [Montreal Neurological Institute coordinates (*x*, *y*, *z*): 3.6, 6.3, 3.9; center of gravity in millimeters]. Regression line and *P* value were computed with the use of robust regression by iteratively reweighted least squares to prevent the influence of outliers; however, this regression also remained highly significant ($P = 0.004$) when the extreme data point (top right-hand corner) was removed from the analysis. β_{loss} and β_{gain} are the unstandardized regression coefficients for the loss and gain variables, respectively.

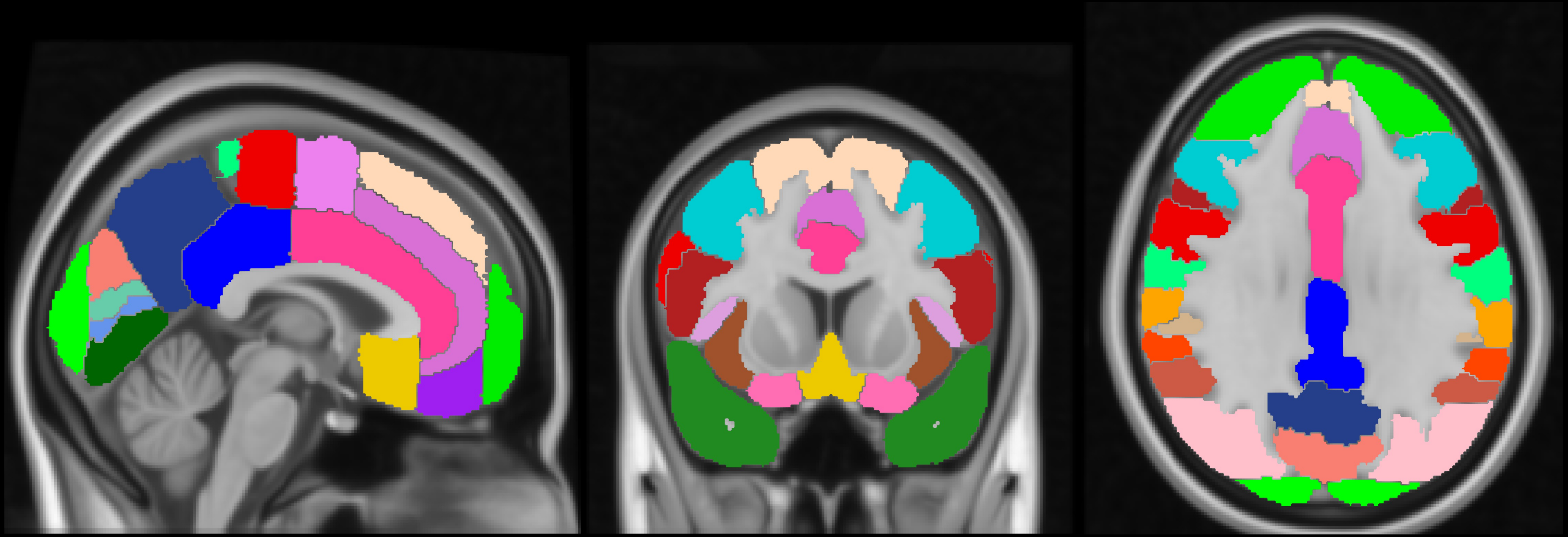
Let’s try it!

Demonstration

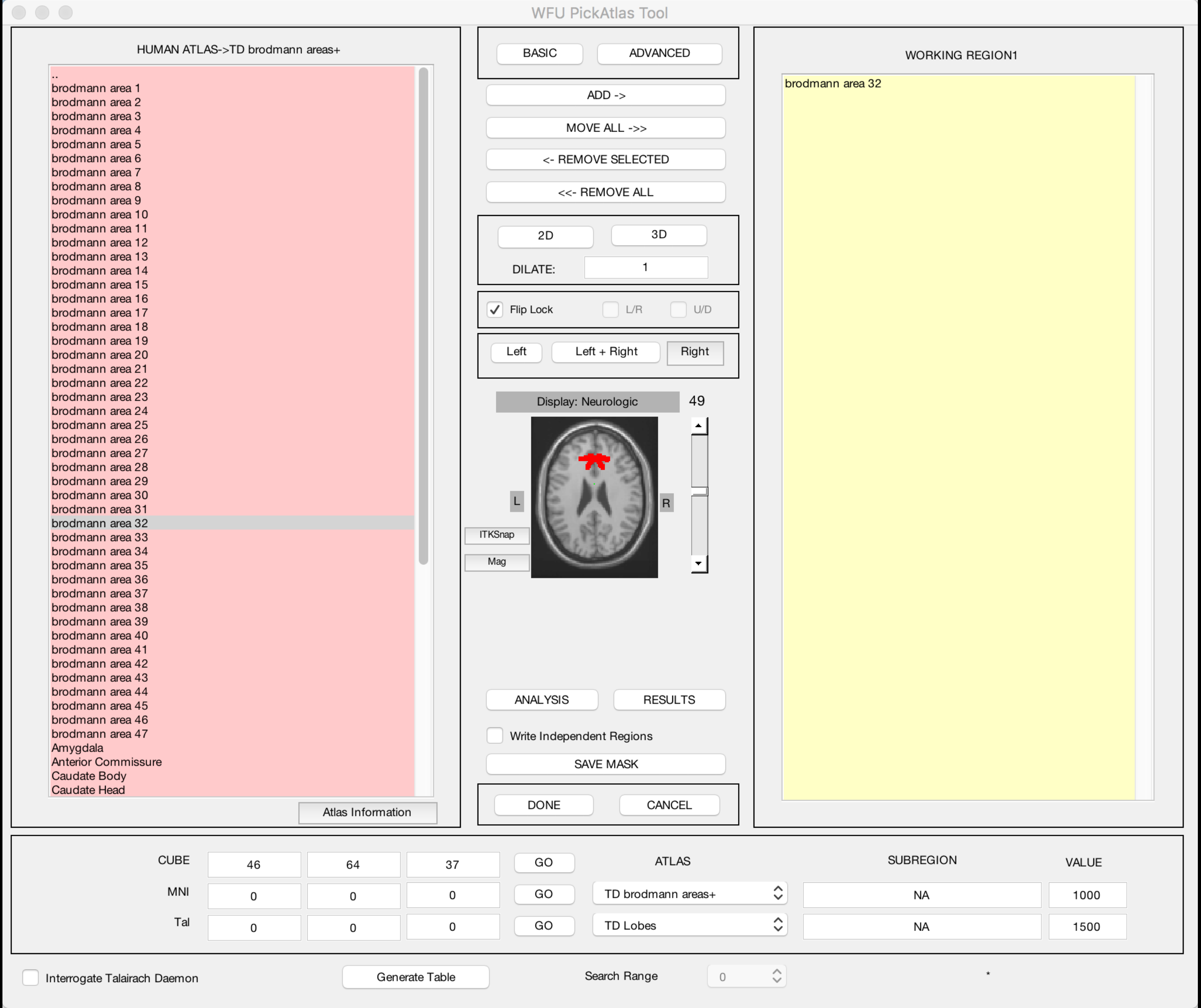
Resources for Independent Analysis

Atlases

Popular: Harvard-Oxford Atlas, WFU PickAtlas



WFU PickAtlas is a toolbox that needs to be installed



WFU PickAtlas Tool

HUMAN ATLAS->TD brodmann areas+

..
brodmann area 1
brodmann area 2
brodmann area 3
brodmann area 4
brodmann area 5
brodmann area 6
brodmann area 7
brodmann area 8
brodmann area 9
brodmann area 10
brodmann area 11
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brodmann area 36
brodmann area 37
brodmann area 38
brodmann area 39
brodmann area 40
brodmann area 41
brodmann area 42
brodmann area 43
brodmann area 44
brodmann area 45
brodmann area 46
brodmann area 47
Amygdala
Anterior Commissure
Caudate Body
Caudate Head

WORKING REGION1

brodmann area 32

DILATE: 1

☑ Flip Lock ☐ L/R ☐ U/D

Display: Neurologic 49

☐ Write Independent Regions

				ATLAS	SUBREGION	VALUE
CUBE	46	64	37			
MNI	0	0	0	TD brodmann areas+	NA	1000
Tal	0	0	0	TD Lobes	NA	1500

☐ Interrogate Talairach Daemon

Search Range 0

Extracting Data from Sphere

Based on coordinates of another study

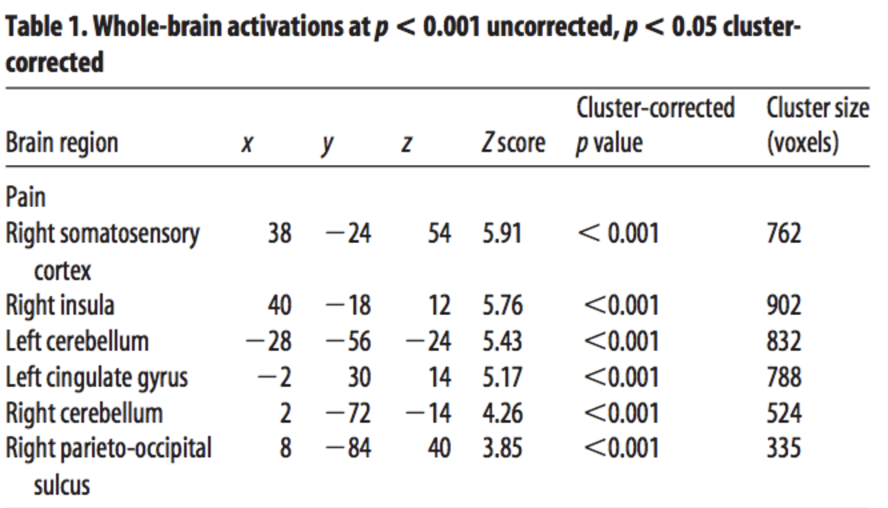
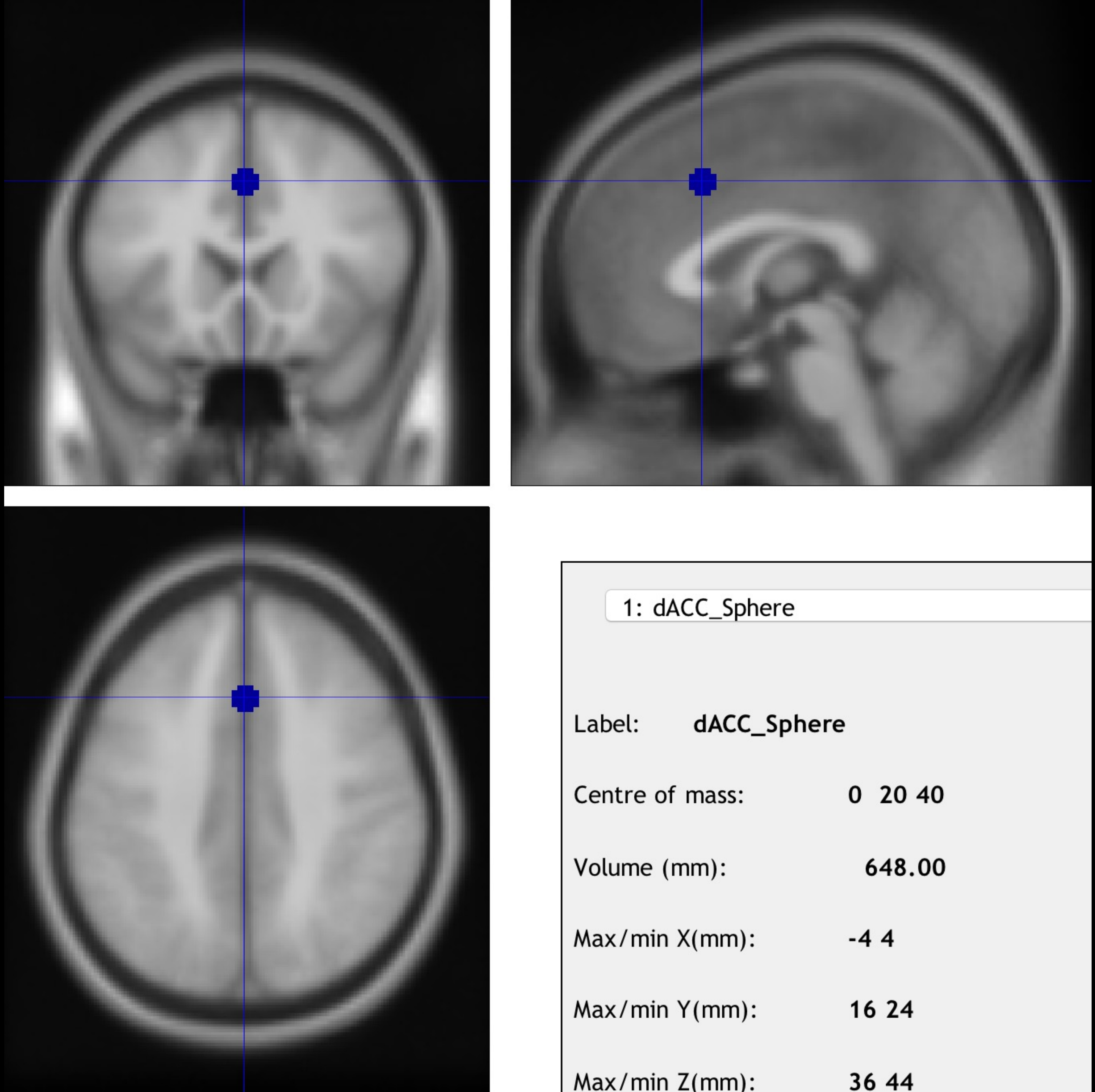


Table 1. Whole-brain activations at $p < 0.001$ uncorrected, $p < 0.05$ cluster-corrected

Brain region	*x*	*y*	*z*	*Z* score	Cluster-corrected *p* value	Cluster size (voxels)
Pain						
Right somatosensory cortex	38	−24	54	5.91	< 0.001	762
Right insula	40	−18	12	5.76	<0.001	902
Left cerebellum	−28	−56	−24	5.43	<0.001	832
Left cingulate gyrus	−2	30	14	5.17	<0.001	788
Right cerebellum	2	−72	−14	4.26	<0.001	524
Right parieto-occipital sulcus	8	−84	40	3.85	<0.001	335

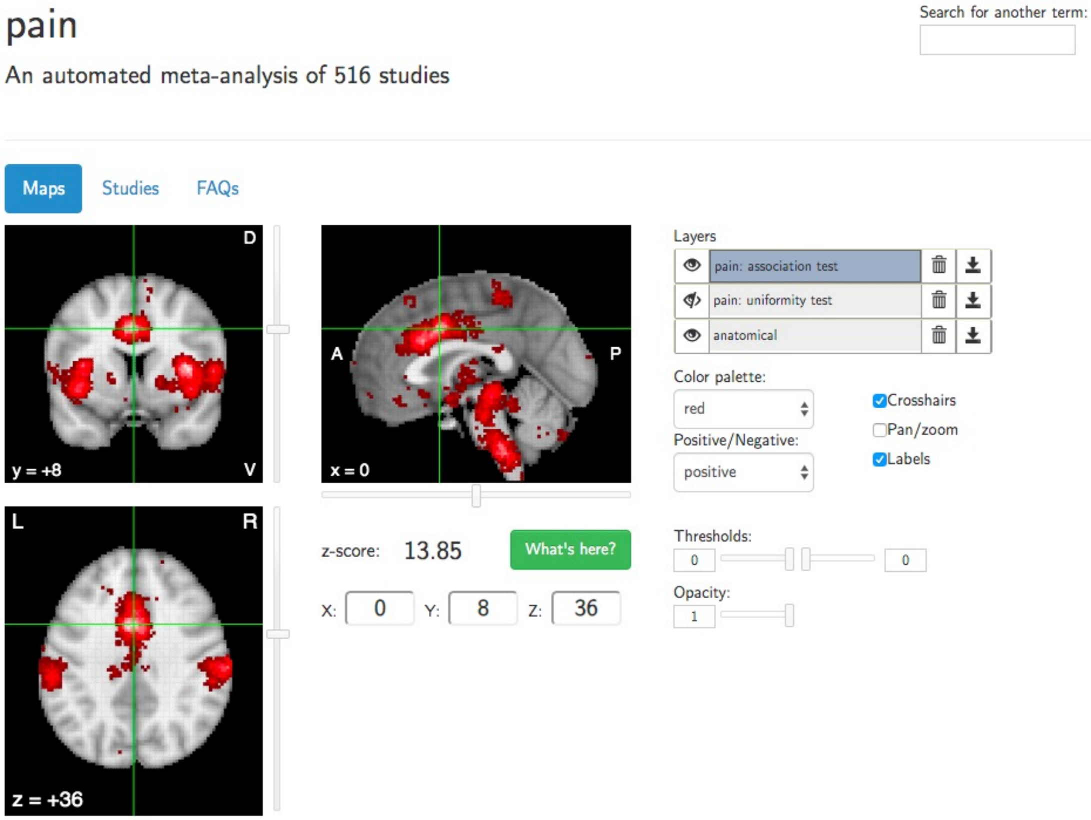


1: dACC_Sphere

Label:	**dACC_Sphere**
Centre of mass:	**0 20 40**
Volume (mm):	**648.00**
Max/min X(mm):	**-4 4**
Max/min Y(mm):	**16 24**
Max/min Z(mm):	**36 44**

Neurosynth

How it works: Search Terms



pain

An automated meta-analysis of 516 studies

Search for another term:

z-score: 13.85

X: 0 Y: 8 Z: 36

Layers
- pain: association test
- pain: uniformity test
- anatomical

Color palette: red

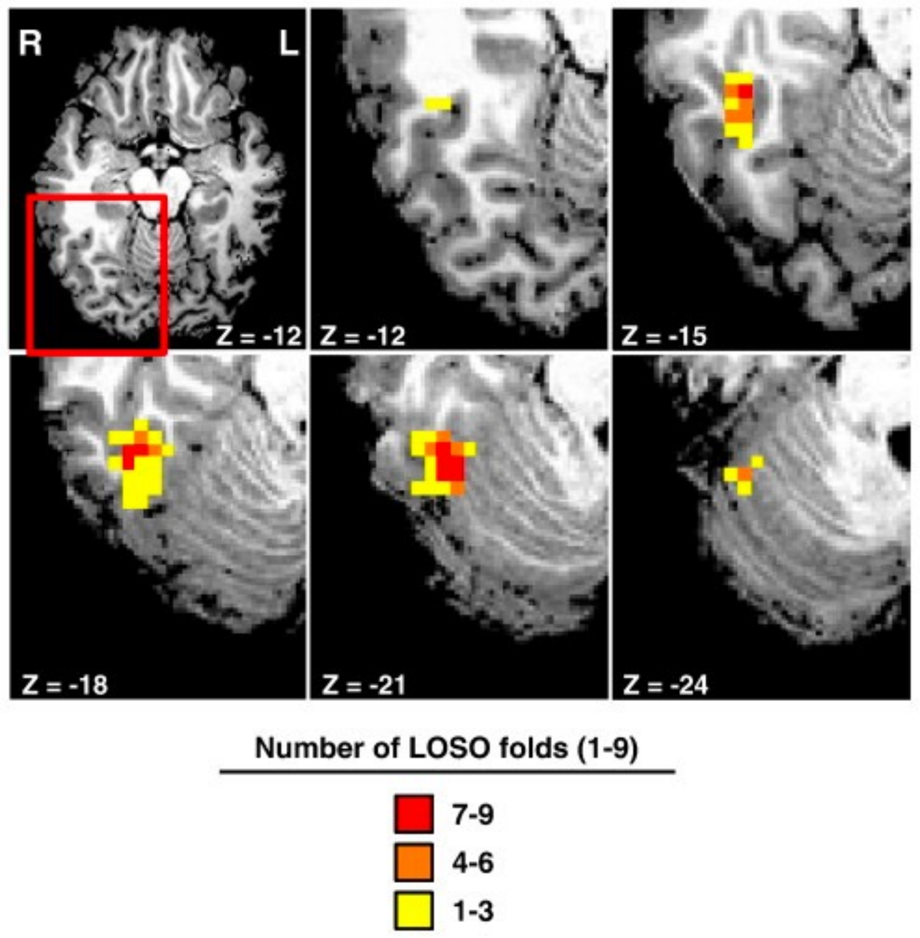
Positive/Negative: positive

☑ Crosshairs
☐ Pan/zoom
☑ Labels

Thresholds: 0 0

Opacity: 1

Cross-Validation



Esterman et al., 2010

Demonstration

Biased Analyses: What to do about it?

Choose an independent analysis

Know the reasons behind choosing it

An “independent” analysis does not guarantee non-biased results!

Cluster Failure: A Discussion of Eklund et al. (2016)

PNAS

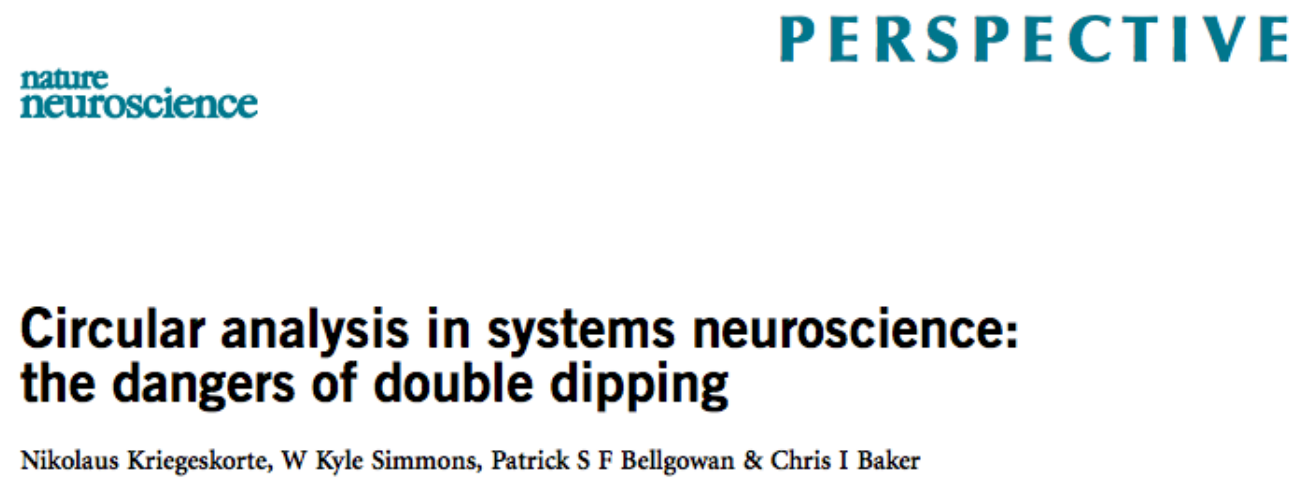
…we found that the most common software packages for fMRI…can result in false-positive rates of up to 70%. These results question the validity of some *40,000 fMRI studies.* [Emphasis added.]

The Economist

When science goes wrong (I)

Computer says: oops

Two studies, one on neuroscience and one on palaeoclimatology, cast doubt on established results. First, neuroscience and the reliability of brain scanning


PERSPECTIVE

nature neuroscience

Circular analysis in systems neuroscience: the dangers of double dipping

Nikolaus Kriegeskorte, W Kyle Simmons, Patrick S F Bellgowan & Chris I Baker

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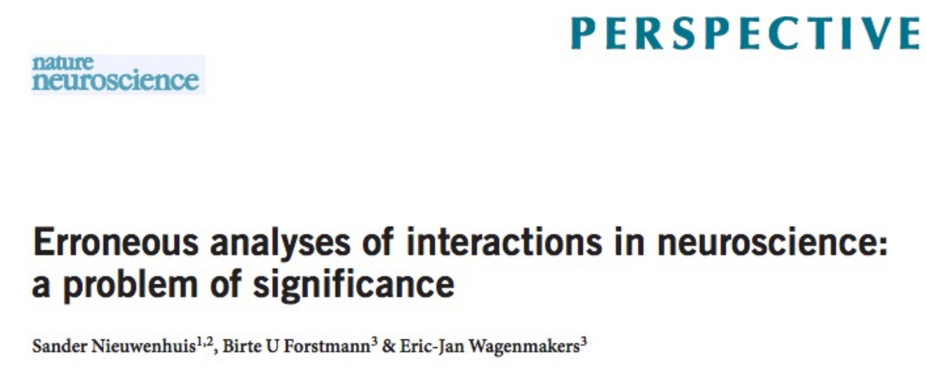
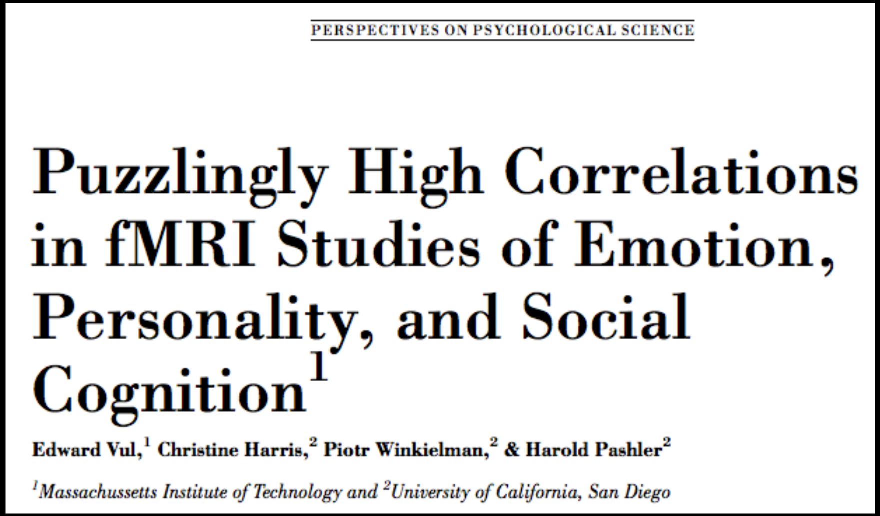

PERSPECTIVE

nature neuroscience

Erroneous analyses of interactions in neuroscience: a problem of significance

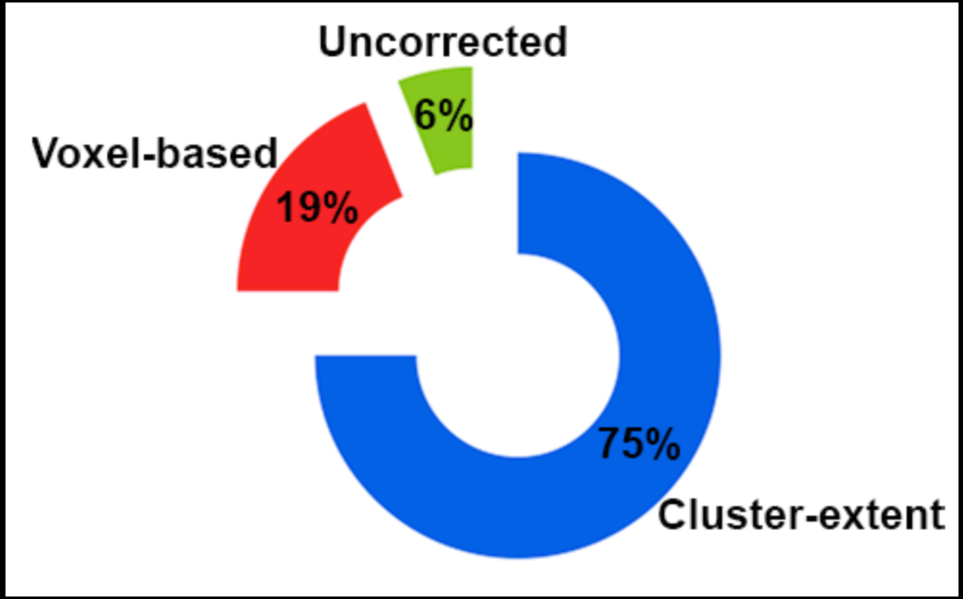
Sander Nieuwenhuis[1,2], Birte U Forstmann[3] & Eric-Jan Wagenmakers[3]


PERSPECTIVES ON PSYCHOLOGICAL SCIENCE

Puzzlingly High Correlations in fMRI Studies of Emotion, Personality, and Social Cognition[1]

Edward Vul,[1] Christine Harris,[2] Piotr Winkielman,[2] & Harold Pashler[2]

[1]*Massachussetts Institute of Technology and* [2]*University of California, San Diego*



Adapted from Woo et al. (2014)

Is this true?

How big of a problem is this?

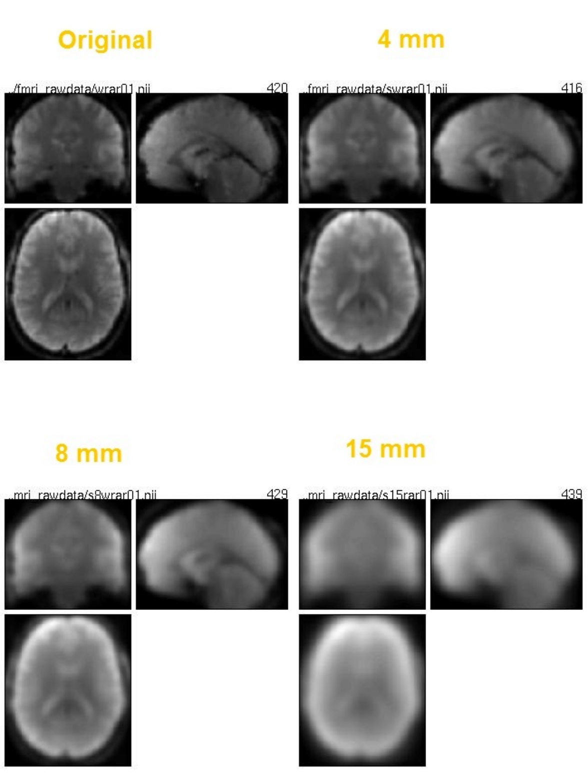
What should we do about it?

1. Review of cluster thresholding

2. Problems with cluster thresholding

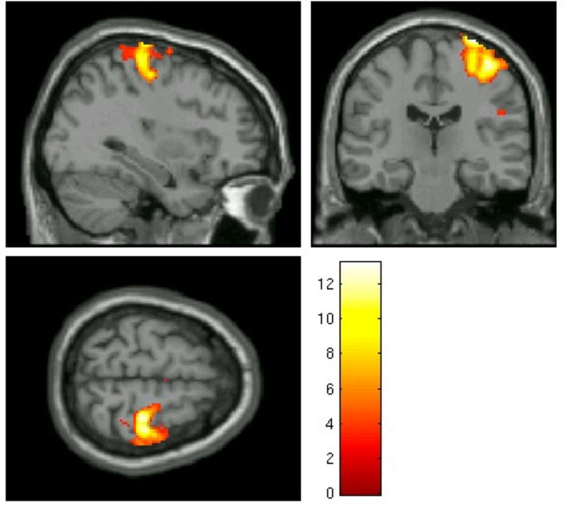
3. How to address these problems

Smoothing increases spatial correlation

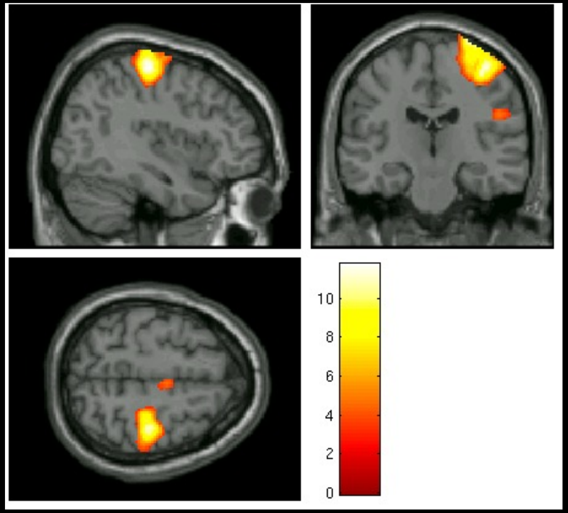


Smoothing increases cluster size

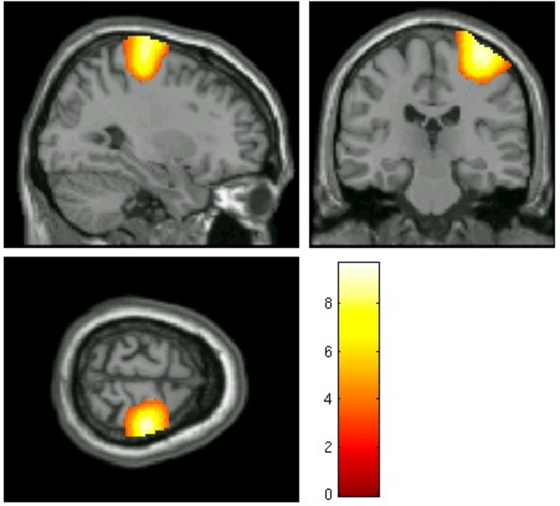
4mm



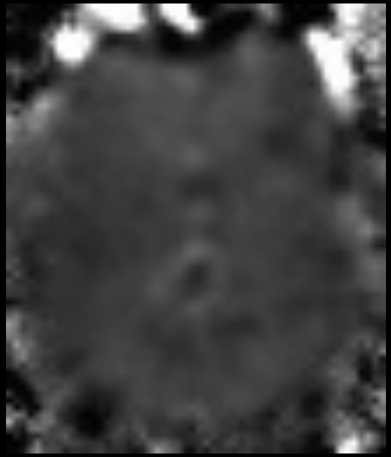
8mm



15mm



Smoothness is estimated from the residuals



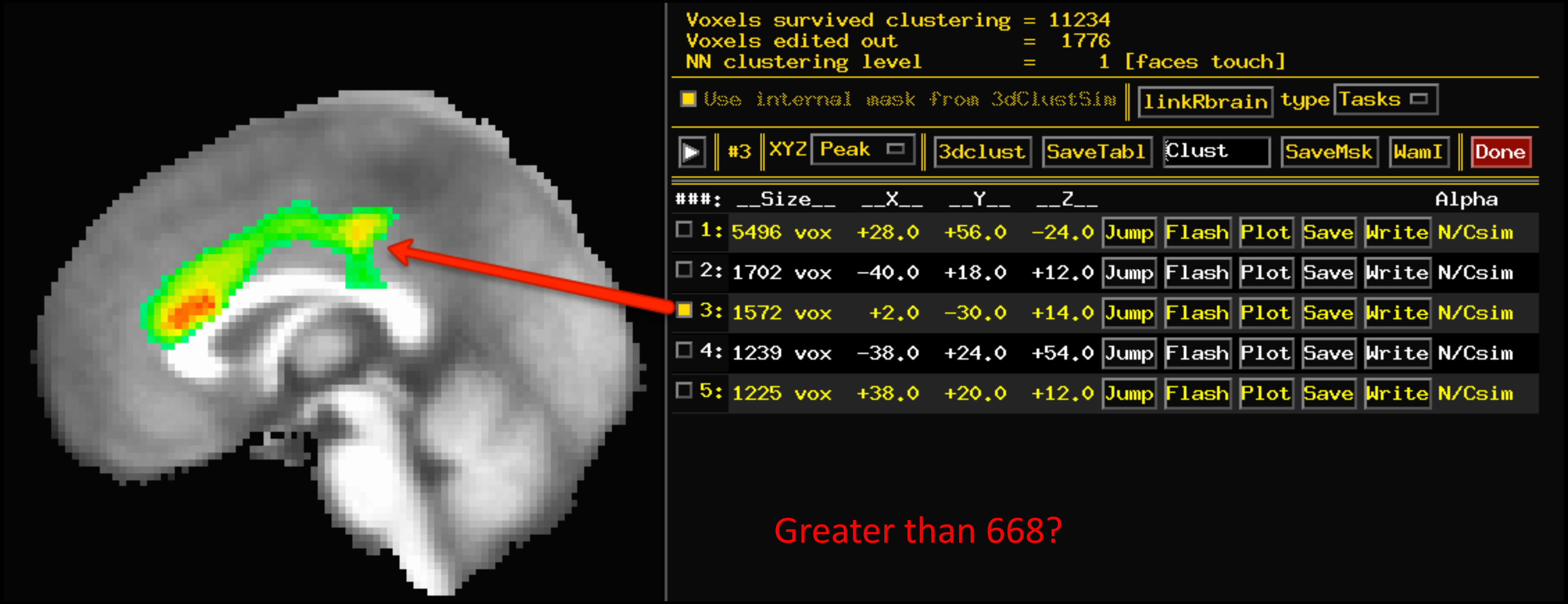
```
3dFWHMx -mask mask.hdr ResMS.hdr
++ 3dFWHMx: AFNI version=AFNI_16.1.28 (Jun 30 2016) [64-bit]
++ Authored by: The Bob
++ Number of voxels in mask = 174611
++ start FWHM calculations
 + FWHM done (0.00 CPU s thus far)
 11.8179  12.9726  12.9531
```

These smoothness estimates form cluster thresholds

```
3dClustSim -mask mask.hdr -fwhm 12.5 -athr 0.05 -pthr 0.01
++ 3dClustSim: AFNI version=AFNI_16.1.28 (Jun 30 2016) [64-bit]
++ 174611 voxels in mask (19.34% of total)
++ Padding by 10 x 10 x 10 slices to allow for edge effects of blurring
++ Startup clock time = 0.0 s
++ Using 8 OpenMP threads
# CLUSTER SIZE THRESHOLD(pthr,alpha) in Voxels
# -NN 3  | alpha = Prob(Cluster >= given size)

#  pthr  | .05000
# ------ | ------
 0.010000   667.8
```

i.e., A cluster size of 668 voxels or more is significant

Determine whether clusters pass threshold



```
Voxels survived clustering = 11234
Voxels edited out          =  1776
NN clustering level        =     1 [faces touch]
```

☐ Use internal mask from 3dClustSim

```
###: __Size__  __X__  __Y__  __Z__                                  Alpha
☐ 1: 5496 vox  +28.0  +56.0  -24.0  Jump Flash Plot Save Write N/Csim
☐ 2: 1702 vox  -40.0  +18.0  +12.0  Jump Flash Plot Save Write N/Csim
☐ 3: 1572 vox   +2.0  -30.0  +14.0  Jump Flash Plot Save Write N/Csim
☐ 4: 1239 vox  -38.0  +24.0  +54.0  Jump Flash Plot Save Write N/Csim
☐ 5: 1225 vox  +38.0  +20.0  +12.0  Jump Flash Plot Save Write N/Csim
```

Greater than 668?

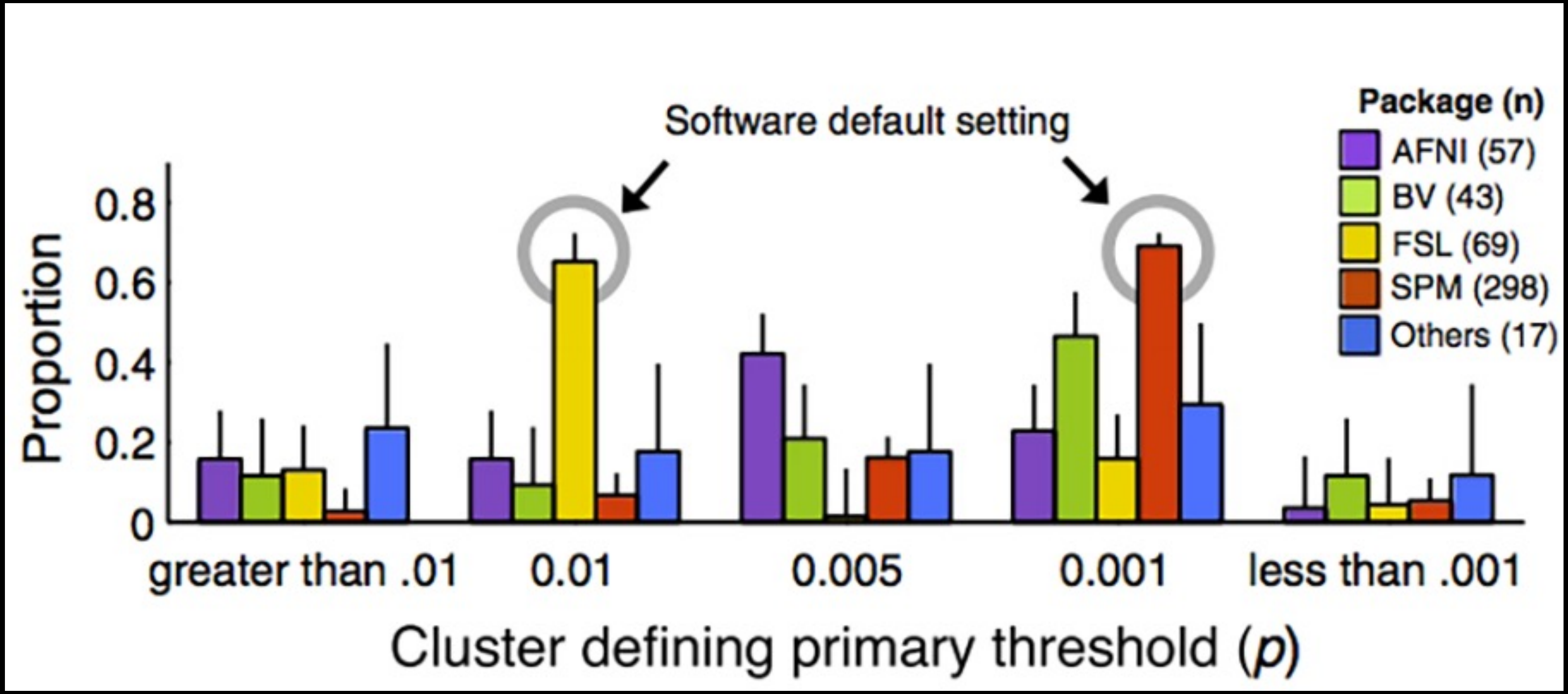
Problems with Cluster Thresholding

1. **Using default thresholds**

2. **Clusters span multiple areas**

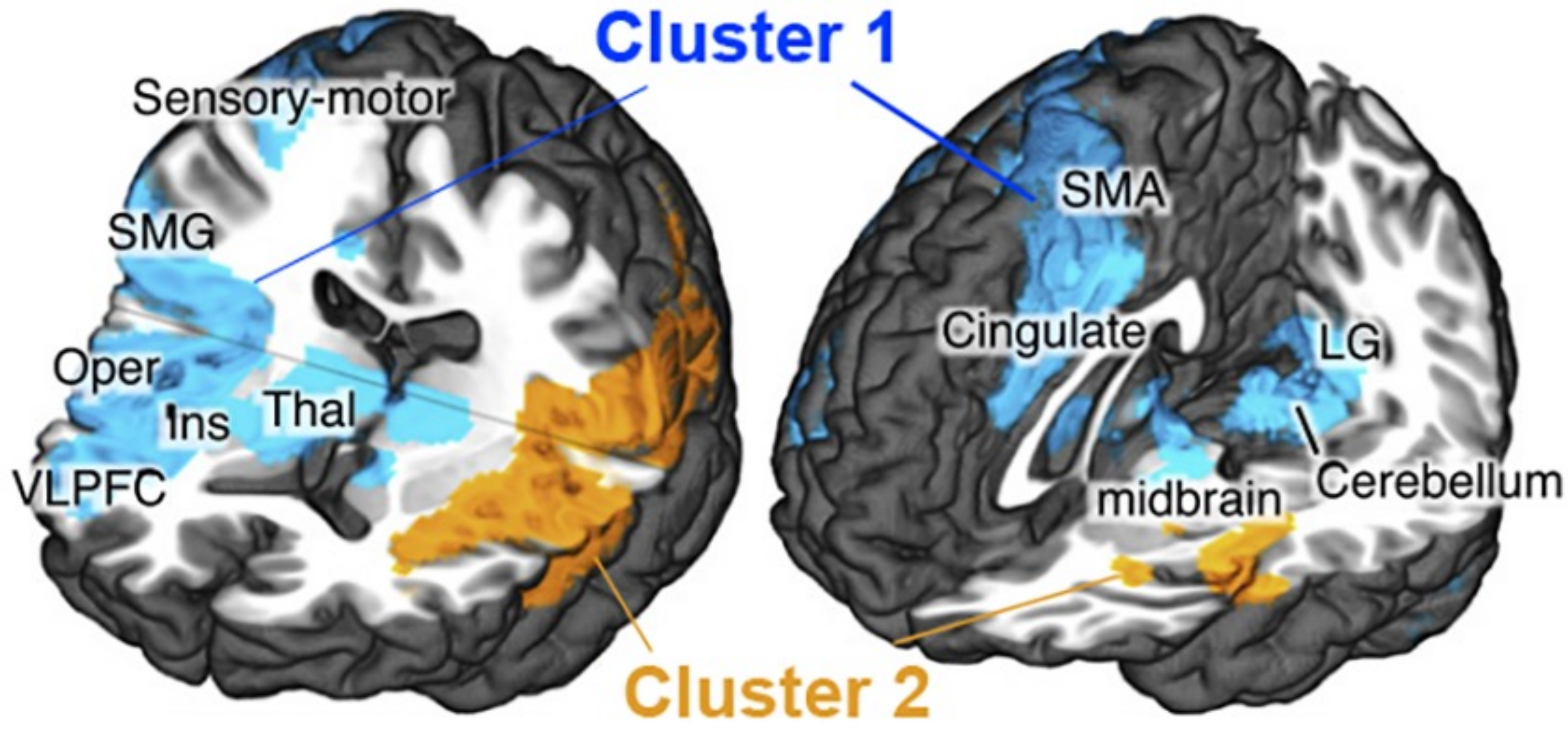
3. **Cluster simulations violate parametric assumptions**

Problem #1
Using default thresholds



Adapted from Woo et al. (2014)

Problem #2
Clusters span multiple areas



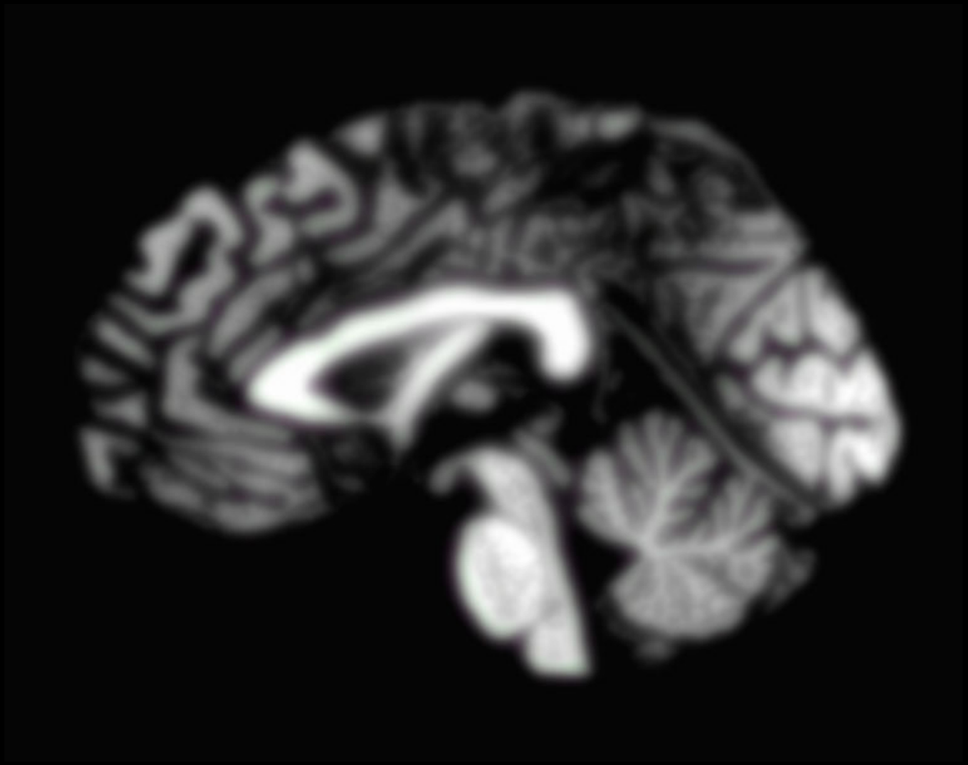
Adapted from Woo et al. (2014)

Problem #3
Violation of assumptions

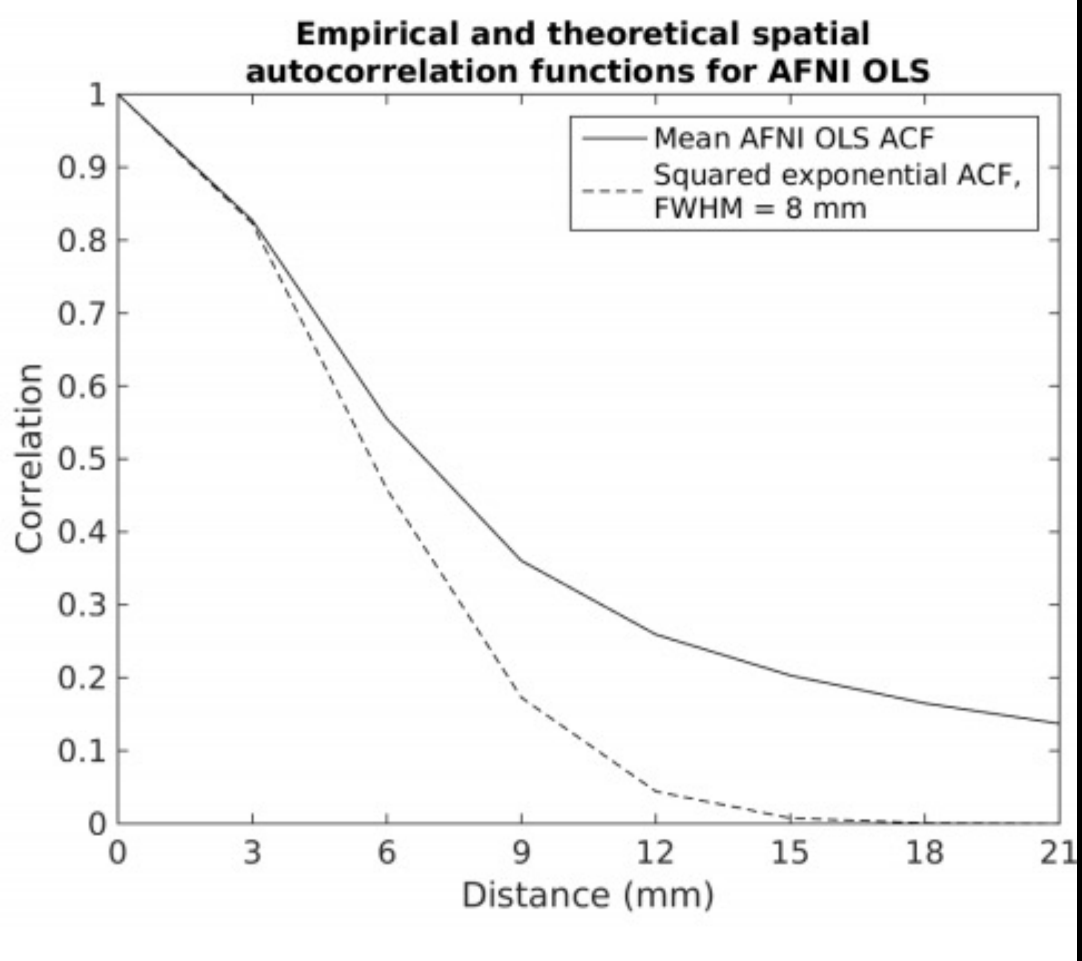
Cluster thresholding methods assume that:

1) Spatial smoothness is constant over the entire brain; and
2) Spatial autocorrelation is normally distributed

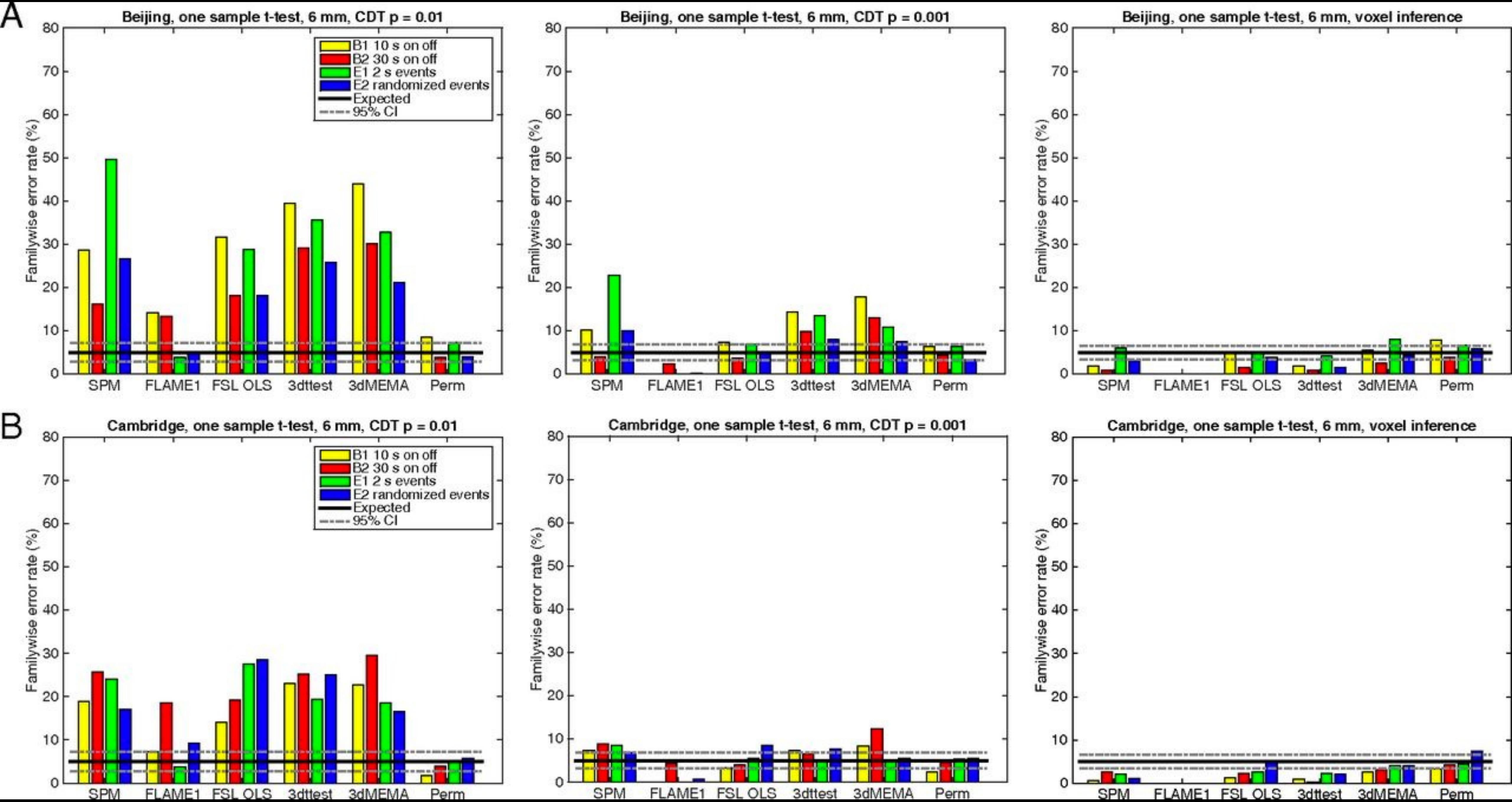
1. Smoothness varies over the brain



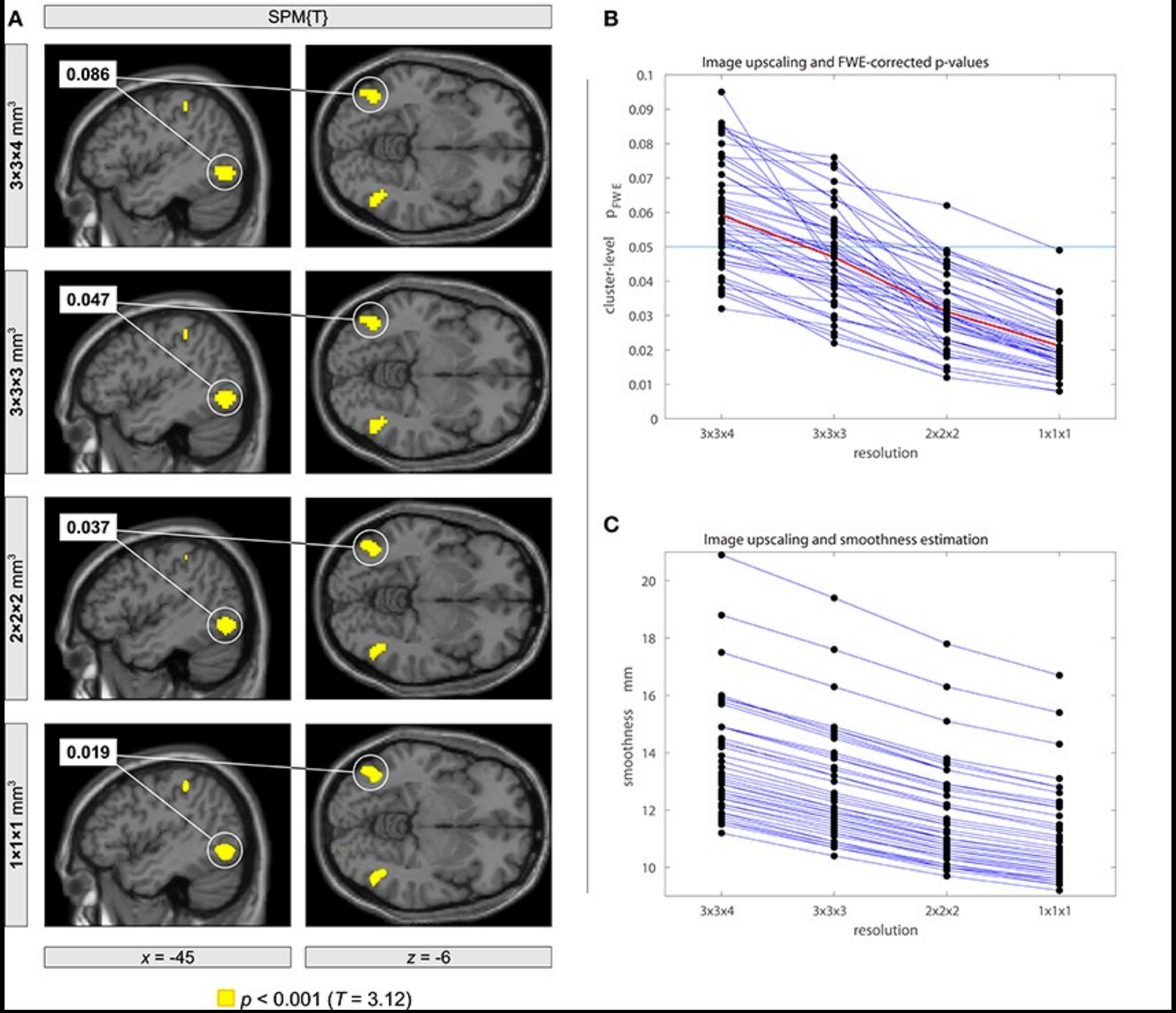
2. Spatial autocorrelation is best modeled as a mixture of Gaussian and exponential distributions



Eklund et al., 2016


A
Beijing, one sample t-test, 6 mm, CDT p = 0.01
Beijing, one sample t-test, 6 mm, CDT p = 0.001
Beijing, one sample t-test, 6 mm, voxel inference
B
Cambridge, one sample t-test, 6 mm, CDT p = 0.01
Cambridge, one sample t-test, 6 mm, CDT p = 0.001
Cambridge, one sample t-test, 6 mm, voxel inference
B1 10 s on off
B2 30 s on off
E1 2 s events
E2 randomized events
Expected
95% CI
Familywise error rate (%)
0
10
20
30
40
50
60
70
80
SPM
FLAME1
FSL OLS
3dttest
3dMEMA
Perm

Aside: Does Voxel Size affect FPR?



Should we trust cluster corrected results from SPM?

Unclear how SPM has addressed this in latest updates

FSL seems unaffected with default settings

AFNI has made attempts to address this, as we will see

Pre-bug fix

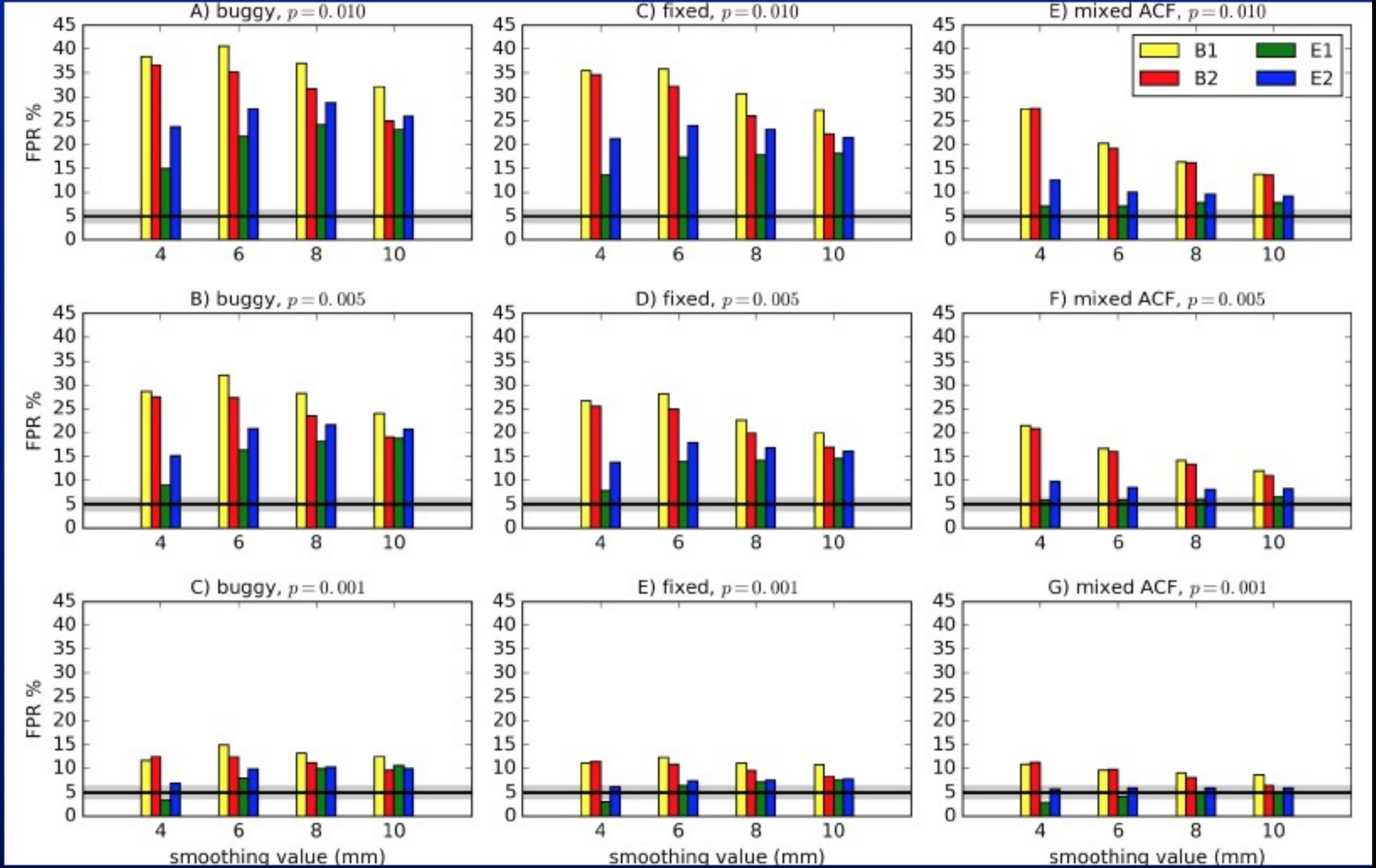
Post-bug fix

Mixed-model ACF

p=0.010

p=0.005

p=0.001



Eklund et al., 2016

Solutions

1) Use voxel-wise thresholds;

2) Use more conservative cluster thresholds; or

3) Use nonparametric methods (e.g., permutations)

Non-parametric tests

FSL’s randomise (requires creating a design matrix)

SPM’s SnPM (separate toolbox)

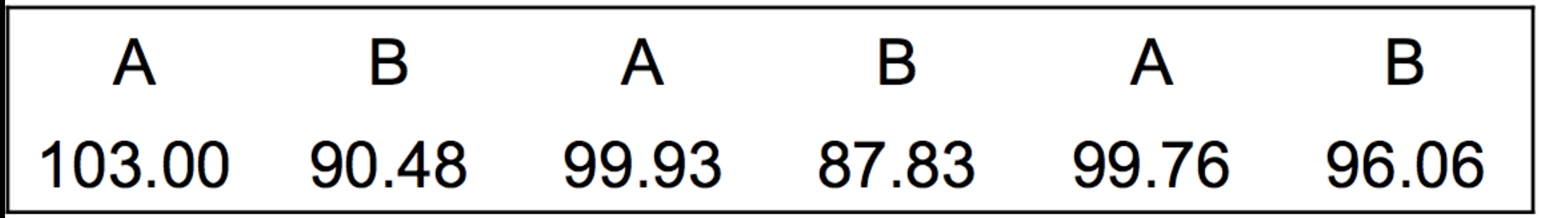
Non-parametric tests

No assumption of the distribution the data were drawn from

The data itself is used to construct a new distribution

Example: We have a positively-skewed distribution,
and still want to use p-values

Non-parametric tests



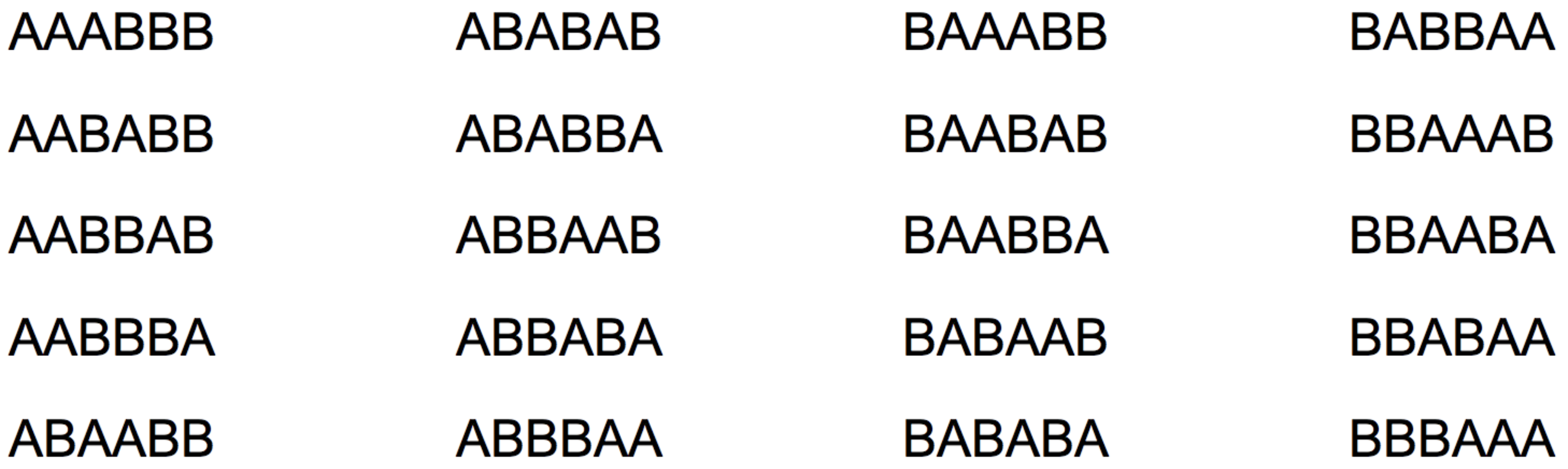
A	B	A	B	A	B
103.00	90.48	99.93	87.83	99.76	96.06

Experiment with two conditions: A=StimOn, B=StimOff

Null Hypothesis: Labels are arbitrary

Non-parametric tests

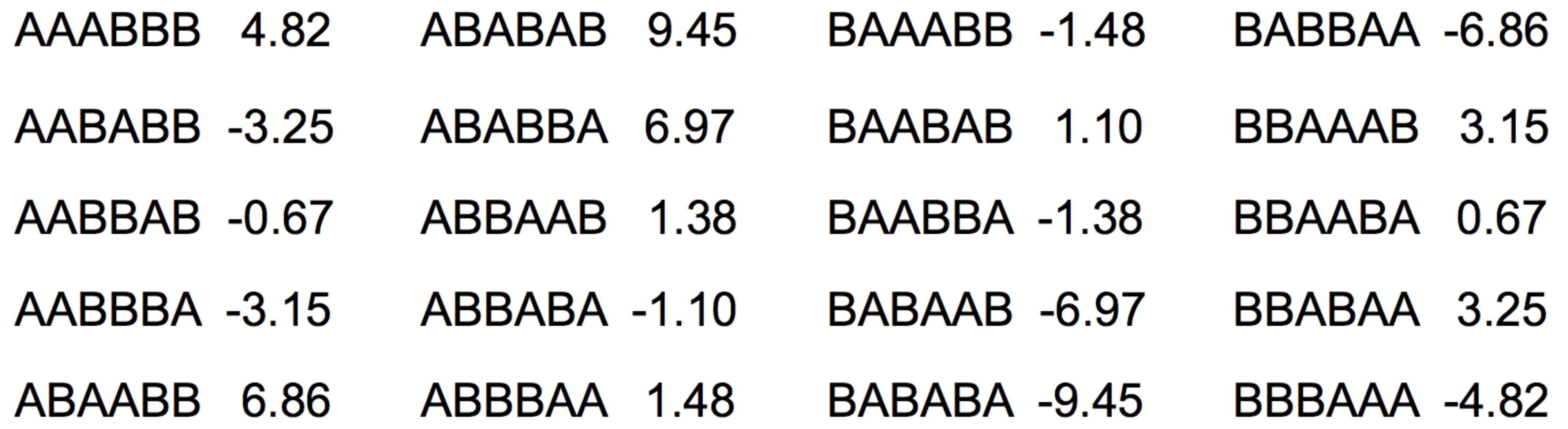
Construct a set of all possible relabelings



AAABBB
AABABB
AABBAB
AABBBA
ABAABB
ABABAB
ABABBA
ABBAAB
ABBABA
ABBBAA
BAAABB
BAABAB
BAABBA
BABAAB
BABABA
BABBAA
BBAAAB
BBAABA
BBABAA
BBBAAA

Non-parametric tests

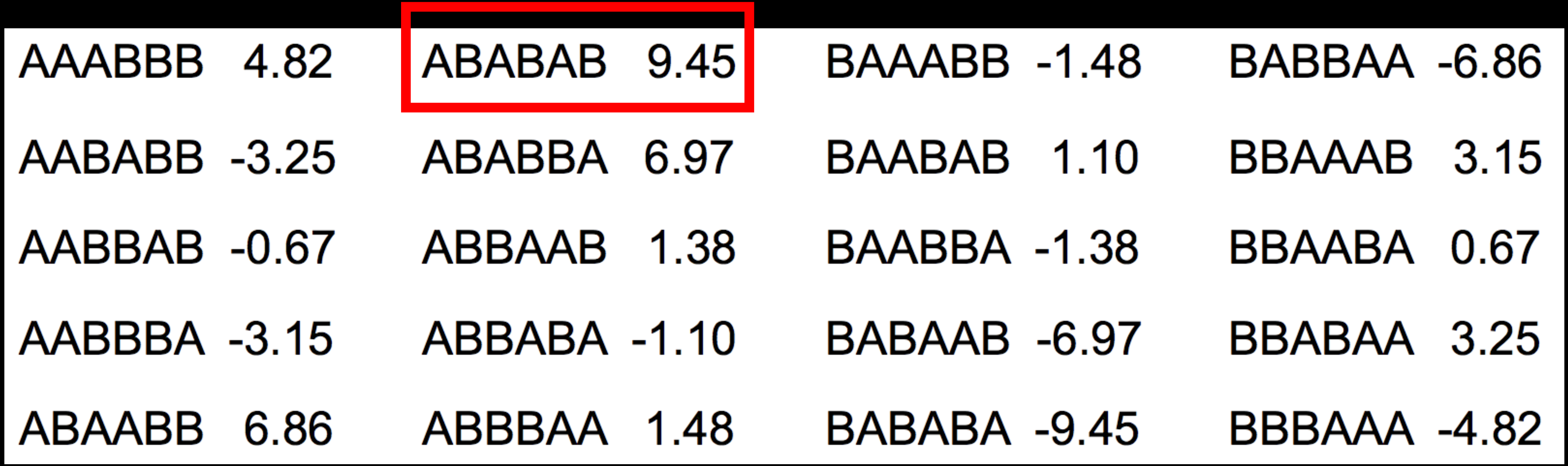
Construct a set of all possible relabelings



AAABBB	4.82	ABABAB	9.45	BAAABB	-1.48	BABBAA	-6.86
AABABB	-3.25	ABABBA	6.97	BAABAB	1.10	BBAAAB	3.15
AABBAB	-0.67	ABBAAB	1.38	BAABBA	-1.38	BBAABA	0.67
AABBBA	-3.15	ABBABA	-1.10	BABAAB	-6.97	BBABAA	3.25
ABAABB	6.86	ABBBAA	1.48	BABABA	-9.45	BBBAAA	-4.82

Non-parametric tests

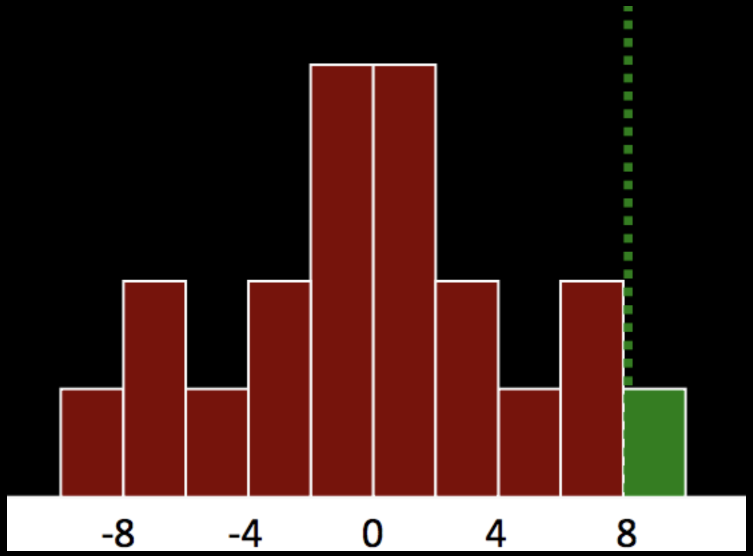
Construct a set of all possible relabelings



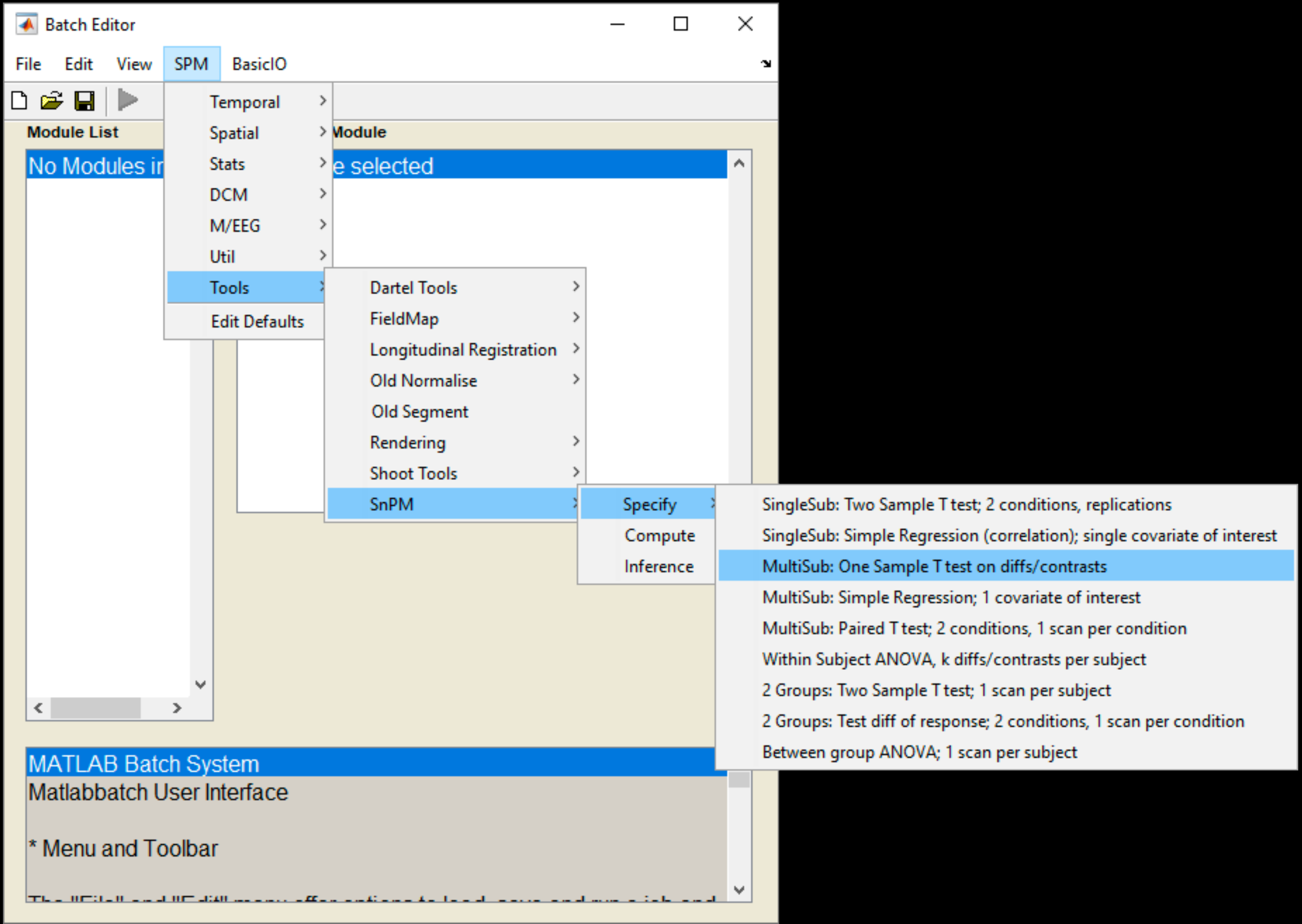
AAABBB	4.82	ABABAB	9.45	BAAABB	-1.48	BABBAA	-6.86
AABABB	-3.25	ABABBA	6.97	BAABAB	1.10	BBAAAB	3.15
AABBAB	-0.67	ABBAAB	1.38	BAABBA	-1.38	BBAABA	0.67
AABBBA	-3.15	ABBABA	-1.10	BABAAB	-6.97	BBABAA	3.25
ABAABB	6.86	ABBBAA	1.48	BABABA	-9.45	BBBAAA	-4.82

Non-parametric tests

Construct a set of all possible relabelings



SnPM

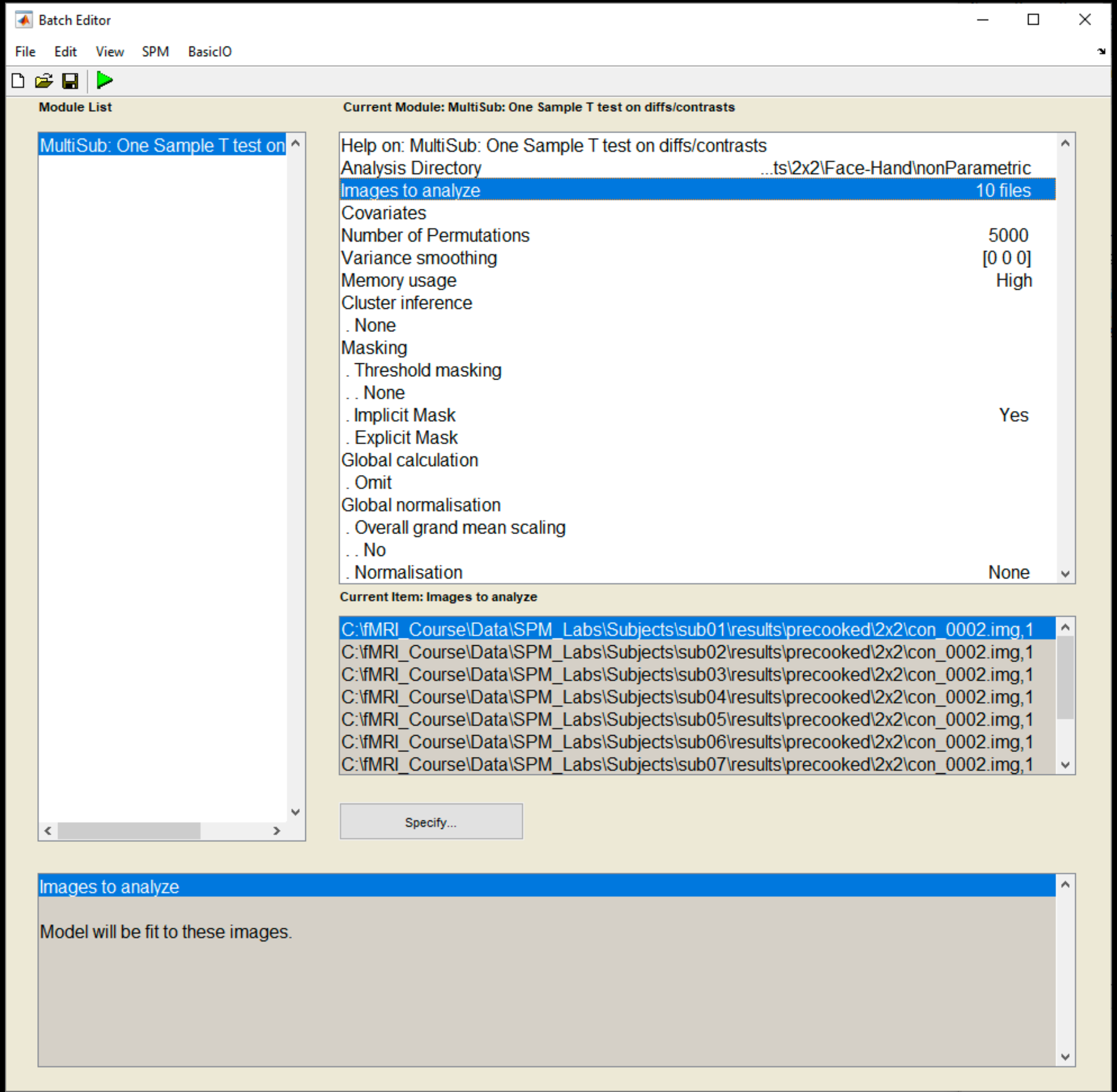


MATLAB Batch System

Matlabbatch User Interface

* Menu and Toolbar

SnPM



MultiSub: One Sample T test on

Current Module: MultiSub: One Sample T test on diffs/contrasts

Help on: MultiSub: One Sample T test on diffs/contrasts
Analysis Directory ...ts\2x2\Face-Hand\nonParametric
Images to analyze 10 files
Covariates
Number of Permutations 5000
Variance smoothing [0 0 0]
Memory usage High
Cluster inference
. None
Masking
. Threshold masking
. . None
. Implicit Mask Yes
. Explicit Mask
Global calculation
. Omit
Global normalisation
. Overall grand mean scaling
. . No
. Normalisation None

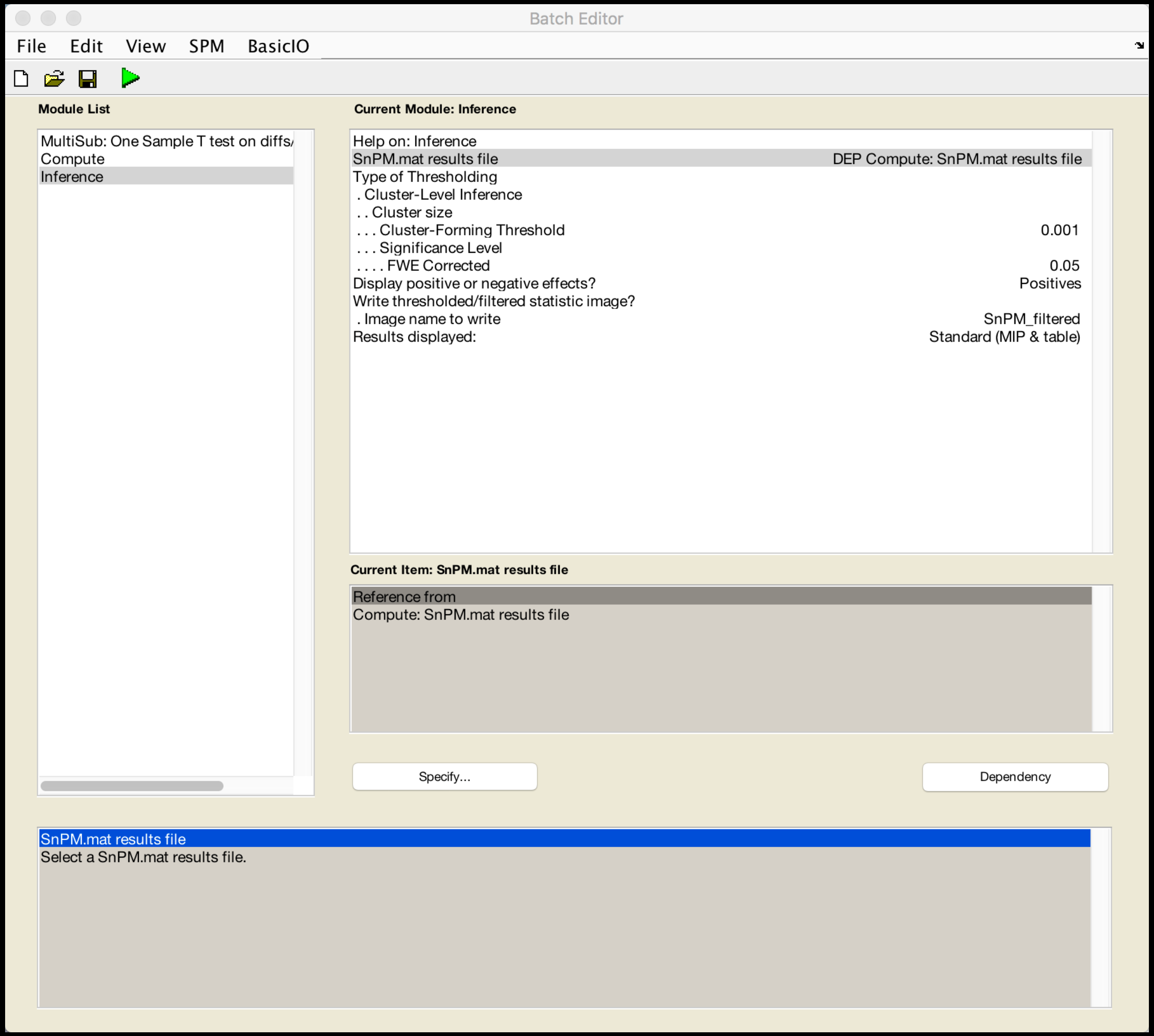
Current Item: Images to analyze

C:\fMRI_Course\Data\SPM_Labs\Subjects\sub01\results\precooked\2x2\con_0002.img,1
C:\fMRI_Course\Data\SPM_Labs\Subjects\sub02\results\precooked\2x2\con_0002.img,1
C:\fMRI_Course\Data\SPM_Labs\Subjects\sub03\results\precooked\2x2\con_0002.img,1
C:\fMRI_Course\Data\SPM_Labs\Subjects\sub04\results\precooked\2x2\con_0002.img,1
C:\fMRI_Course\Data\SPM_Labs\Subjects\sub05\results\precooked\2x2\con_0002.img,1
C:\fMRI_Course\Data\SPM_Labs\Subjects\sub06\results\precooked\2x2\con_0002.img,1
C:\fMRI_Course\Data\SPM_Labs\Subjects\sub07\results\precooked\2x2\con_0002.img,1

Images to analyze

Model will be fit to these images.

SnPM



MultiSub: One Sample T test on diffs/
Compute
Inference

Help on: Inference
SnPM.mat results file DEP Compute: SnPM.mat results file
Type of Thresholding
. Cluster-Level Inference
. . Cluster size
. . . Cluster-Forming Threshold 0.001
. . . Significance Level
. . . . FWE Corrected 0.05
Display positive or negative effects? Positives
Write thresholded/filtered statistic image?
. Image name to write SnPM_filtered
Results displayed: Standard (MIP & table)

Current Item: SnPM.mat results file

Reference from
Compute: SnPM.mat results file

SnPM.mat results file
Select a SnPM.mat results file.

Non-Parametric Analyses: Pros and Cons

Pros: Tends to be accurate for multiple comparisons

No assumption about the shape of the distribution

Cons: Conservative for small sample sizes

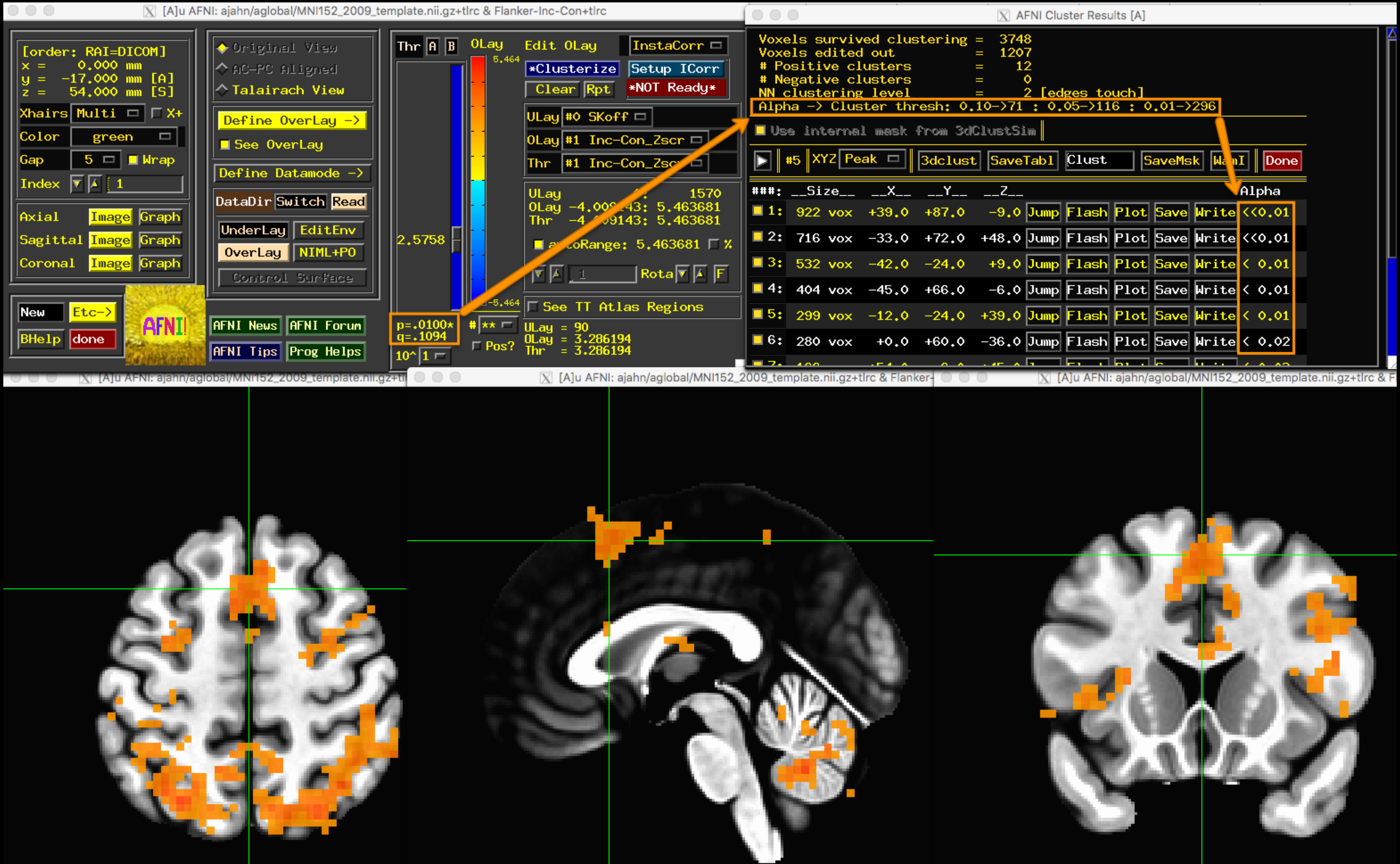
Assumes exchangeability of data

3dttest++

Using the –Clustsim option will generate a table for each cluster-wise p-threshold

Which threshold you use is up to you;
there is nothing taboo about using 0.01 or 0.05

AFNI Distributions since 2019 will use mixed ACF



```
[order: RAI=DICOM]
x =      0.000 mm
y =    -17.000 mm [A]
z =     54.000 mm [S]
```

```
ULay  #0 SKoff
OLay  #1 Inc-Con_Zscr
Thr   #1 Inc-Con_Zscr
```

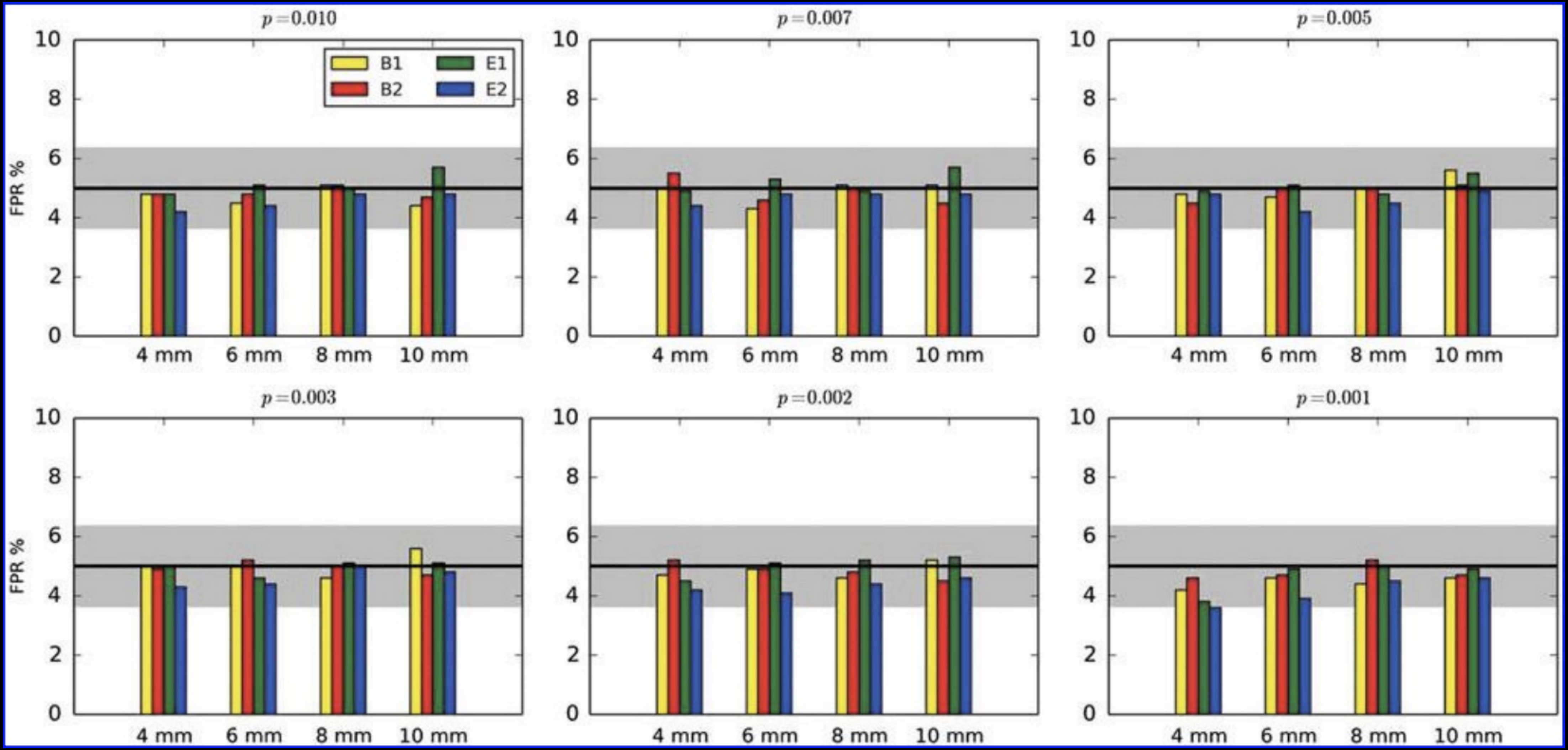
```
ULay                    1570
OLay  -4.009143:  5.463681
Thr   -4.009143:  5.463681
```

```
p=.0100*
q=.1094
```

```
ULay = 90
OLay = 3.286194
Thr  = 3.286194
```

```
Voxels survived clustering =  3748
Voxels edited out          =  1207
# Positive clusters        =    12
# Negative clusters        =     0
NN clustering level        =     2 [edges touch]
Alpha -> Cluster thresh: 0.10->71 : 0.05->116 : 0.01->296
```

```
###: __Size__  __X__  __Y__  __Z__                                Alpha
  1:  922 vox  +39.0  +87.0   -9.0 Jump Flash Plot Save Write <<0.01
  2:  716 vox  -33.0  +72.0  +48.0 Jump Flash Plot Save Write <<0.01
  3:  532 vox  -42.0  -24.0   +9.0 Jump Flash Plot Save Write < 0.01
  4:  404 vox  -45.0  +66.0   -6.0 Jump Flash Plot Save Write < 0.01
  5:  299 vox  -12.0  -24.0  +39.0 Jump Flash Plot Save Write < 0.01
  6:  280 vox   +0.0  +60.0  -36.0 Jump Flash Plot Save Write < 0.02
```



Cox et al., 2017

3dClustSim Demo

Problems with 3dClustSim

Still a risk of false negatives

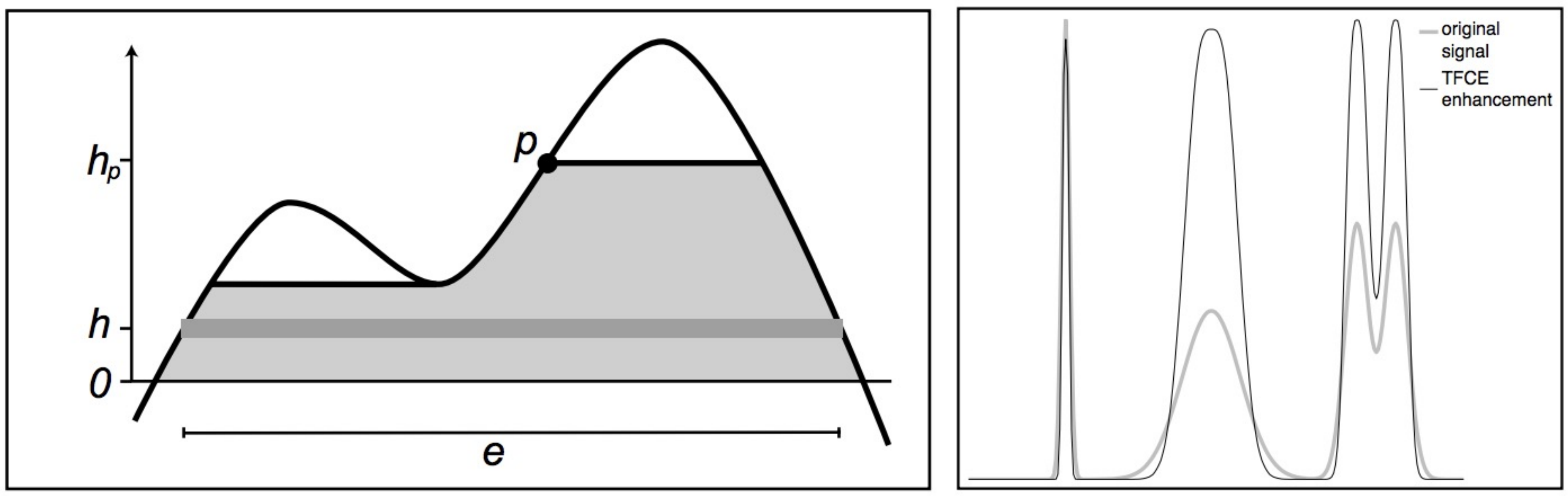
Uses arbitrary threshold set by user

Threshold-Free Cluster Enhancement (TFCE)

What if we didn't have to set a cluster-forming threshold?

Calculate the area under the curve

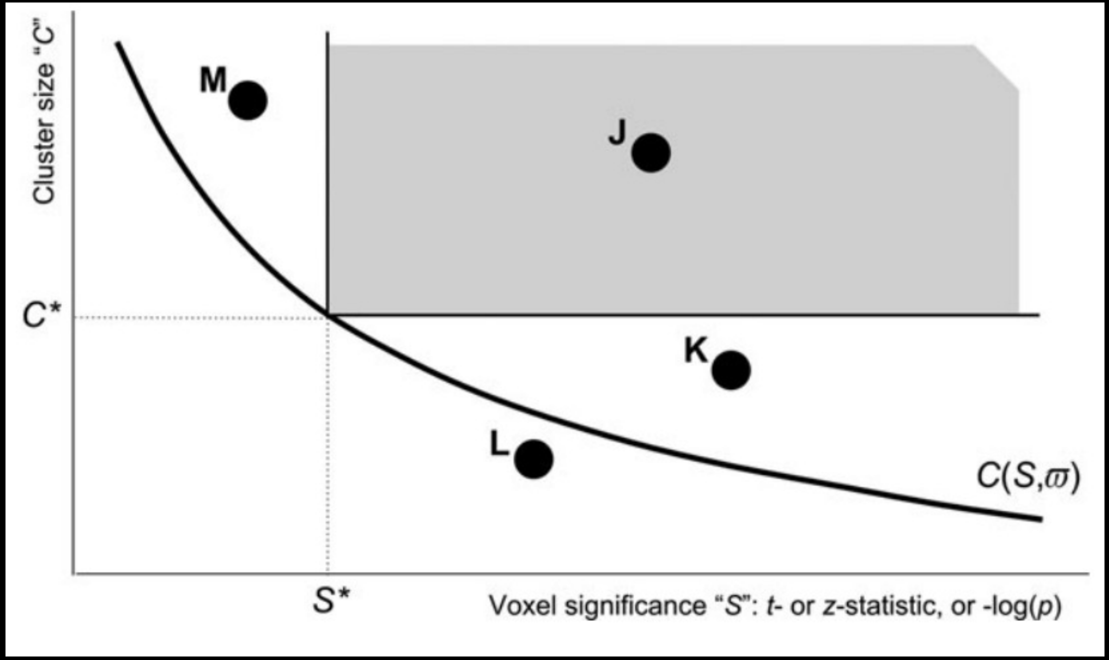
Similar to AFNI's Equitable Thresholding and Clustering (ETAC)

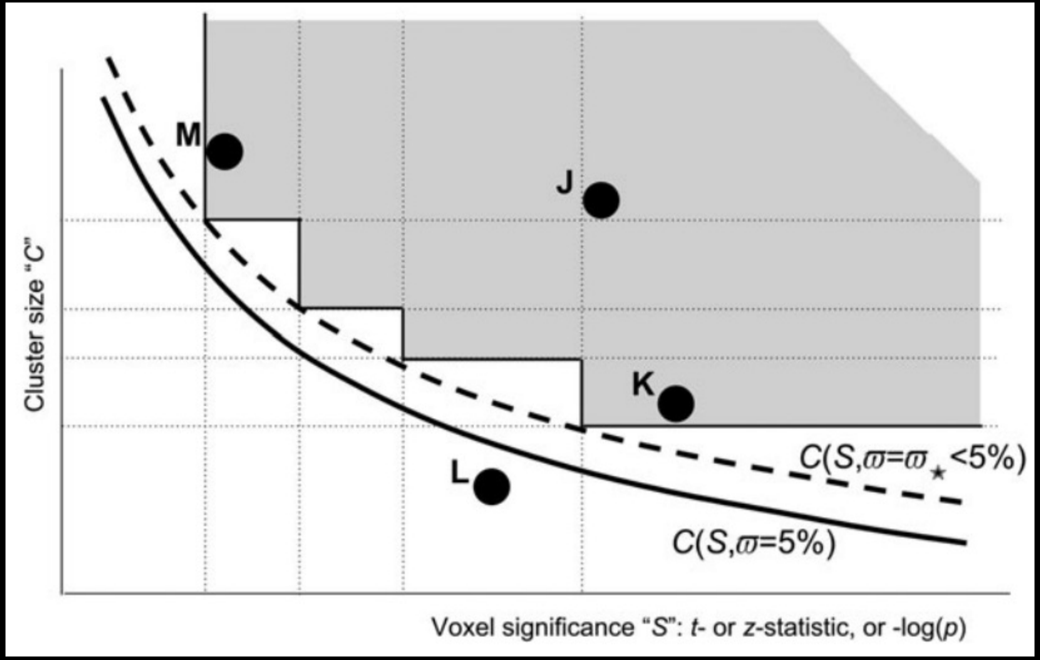


Threshold-Free Cluster Enhancement (TFCE)

No parametric assumptions about shaped of smoothness

Balances the extent and height thresholds at constant FPR



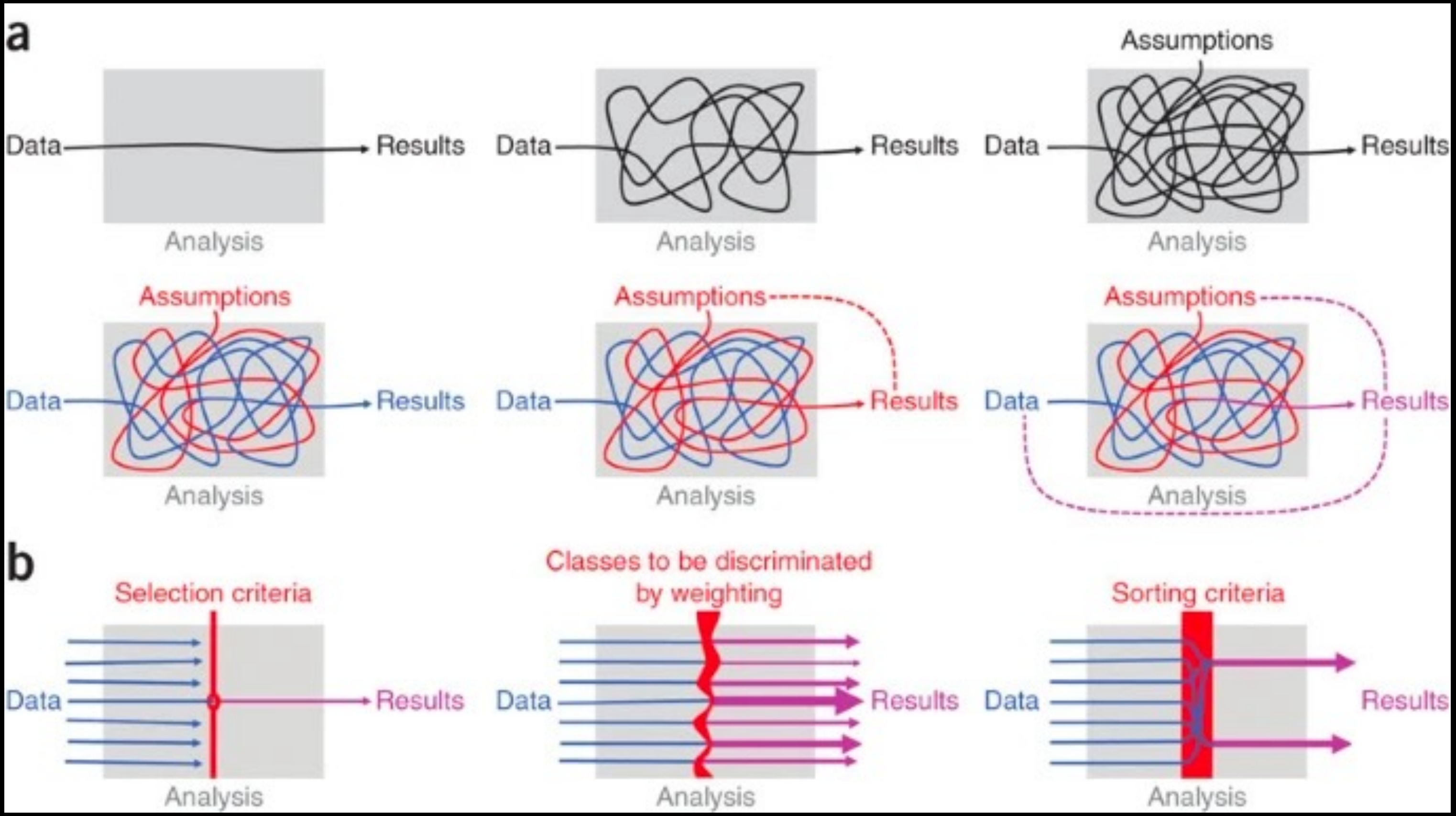


Cox, 2019

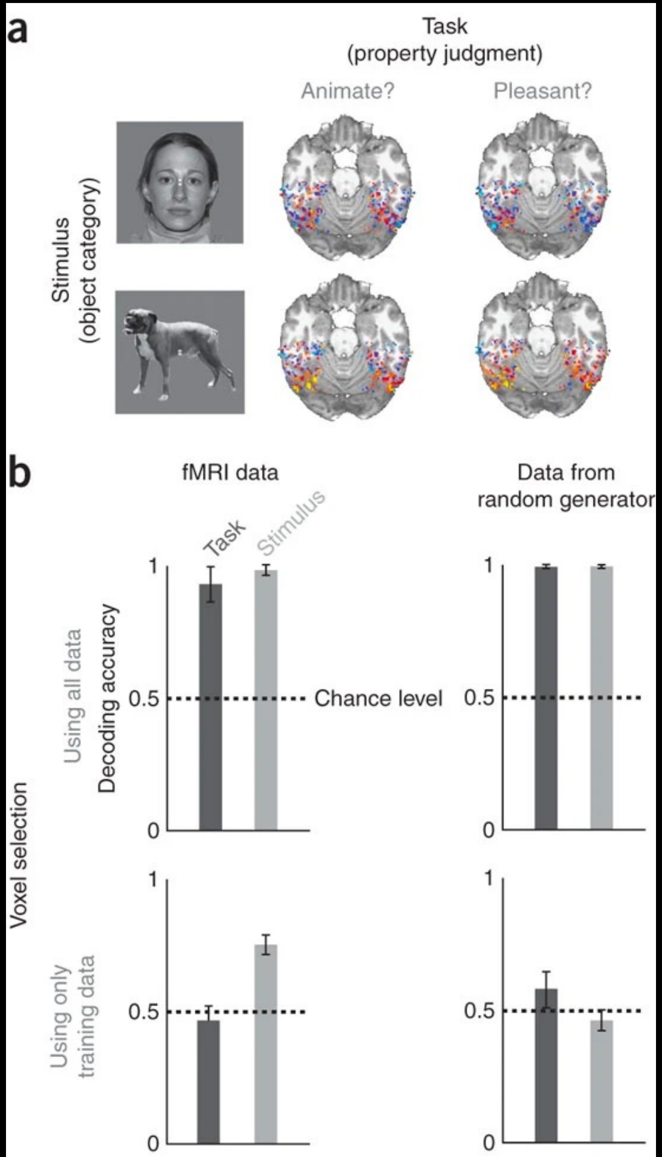
Demonstration

Kriegeskorte et al., 2010

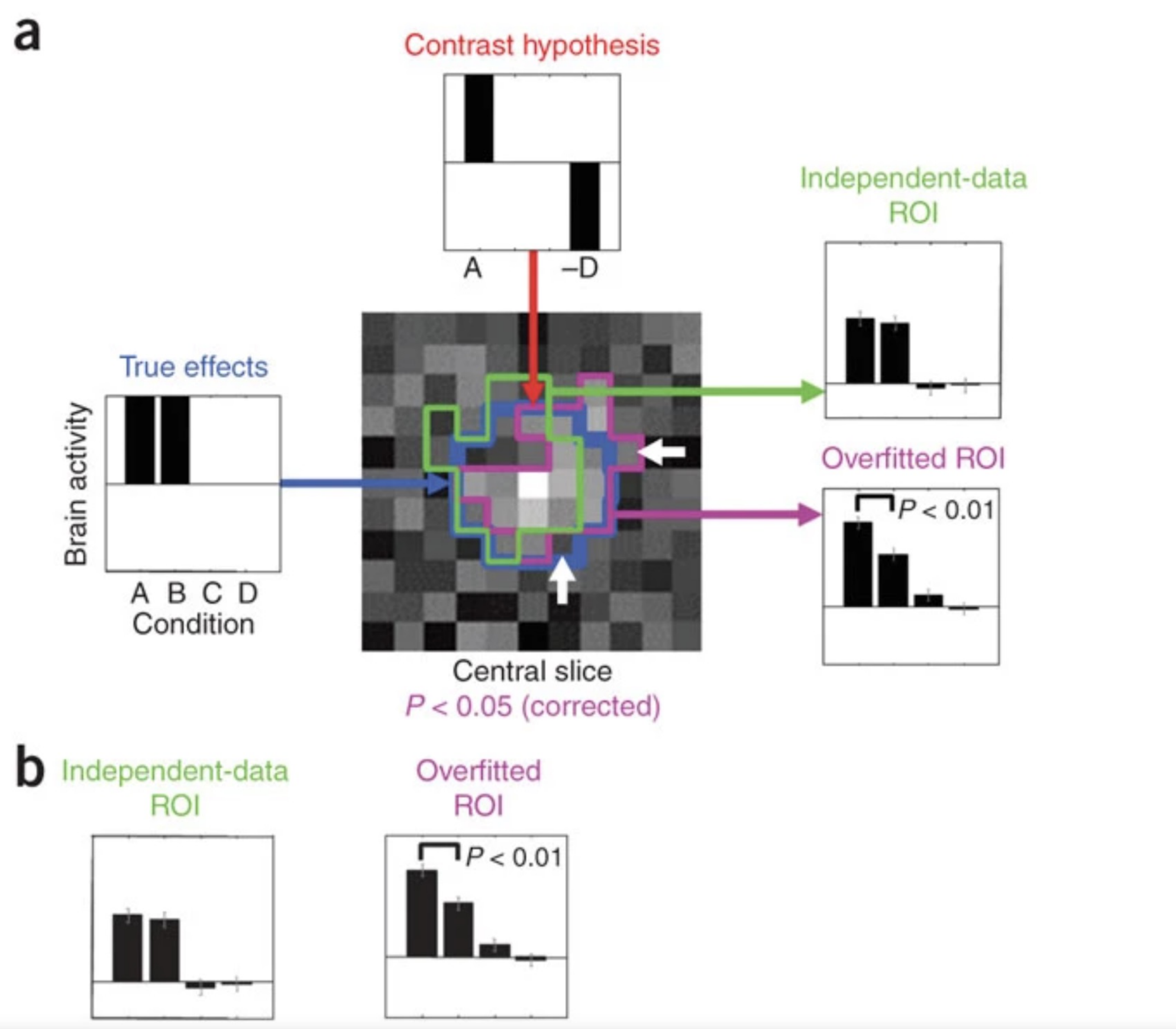
Recommendations for how to avoid non-independence



Kriegeskorte et al., 2010

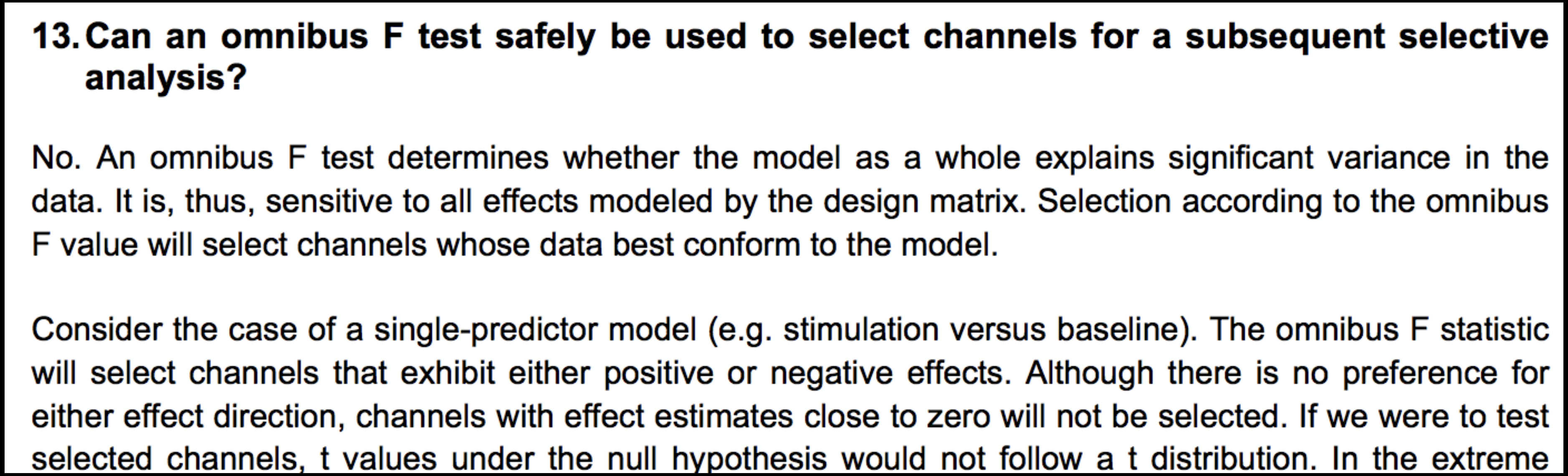


Kriegeskorte et al., 2010



Kriegeskorte et al., 2010

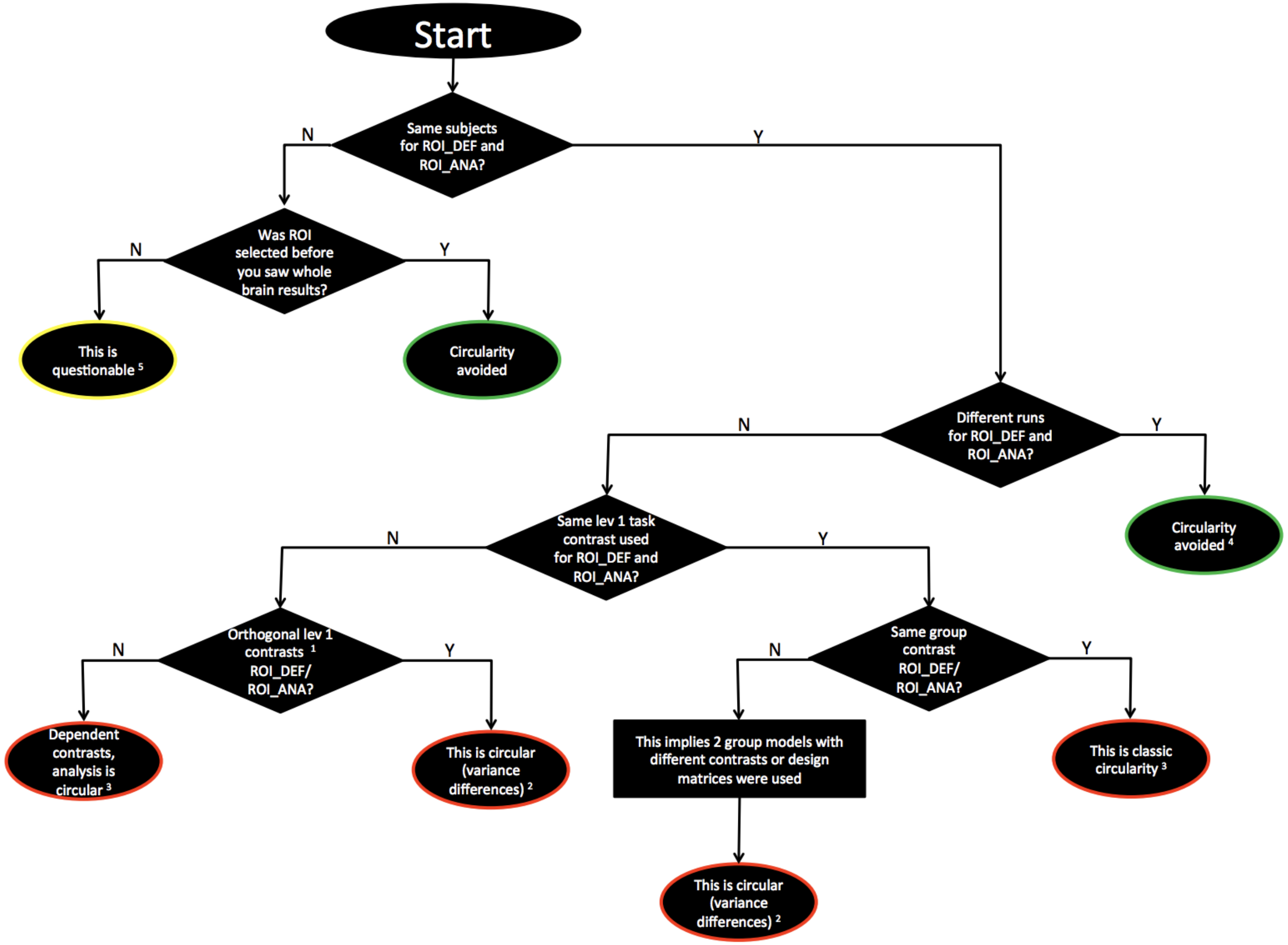
The supplementary material reviews different scenarios



13. Can an omnibus F test safely be used to select channels for a subsequent selective analysis?

No. An omnibus F test determines whether the model as a whole explains significant variance in the data. It is, thus, sensitive to all effects modeled by the design matrix. Selection according to the omnibus F value will select channels whose data best conform to the model.

Consider the case of a single-predictor model (e.g. stimulation versus baseline). The omnibus F statistic will select channels that exhibit either positive or negative effects. Although there is no preference for either effect direction, channels with effect estimates close to zero will not be selected. If we were to test selected channels, t values under the null hypothesis would not follow a t distribution. In the extreme



Start

Same subjects for ROI_DEF and ROI_ANA?

N

Was ROI selected before you saw whole brain results?

N

This is questionable [5]

Y

Circularity avoided

Y

Different runs for ROI_DEF and ROI_ANA?

Y

Circularity avoided [4]

N

Same lev 1 task contrast used for ROI_DEF and ROI_ANA?

N

Orthogonal lev 1 contrasts [1] ROI_DEF/ ROI_ANA?

N

Dependent contrasts, analysis is circular [3]

Y

This is circular (variance differences) [2]

Y

Same group contrast ROI_DEF/ ROI_ANA?

N

This implies 2 group models with different contrasts or design matrices were used

This is circular (variance differences) [2]

Y

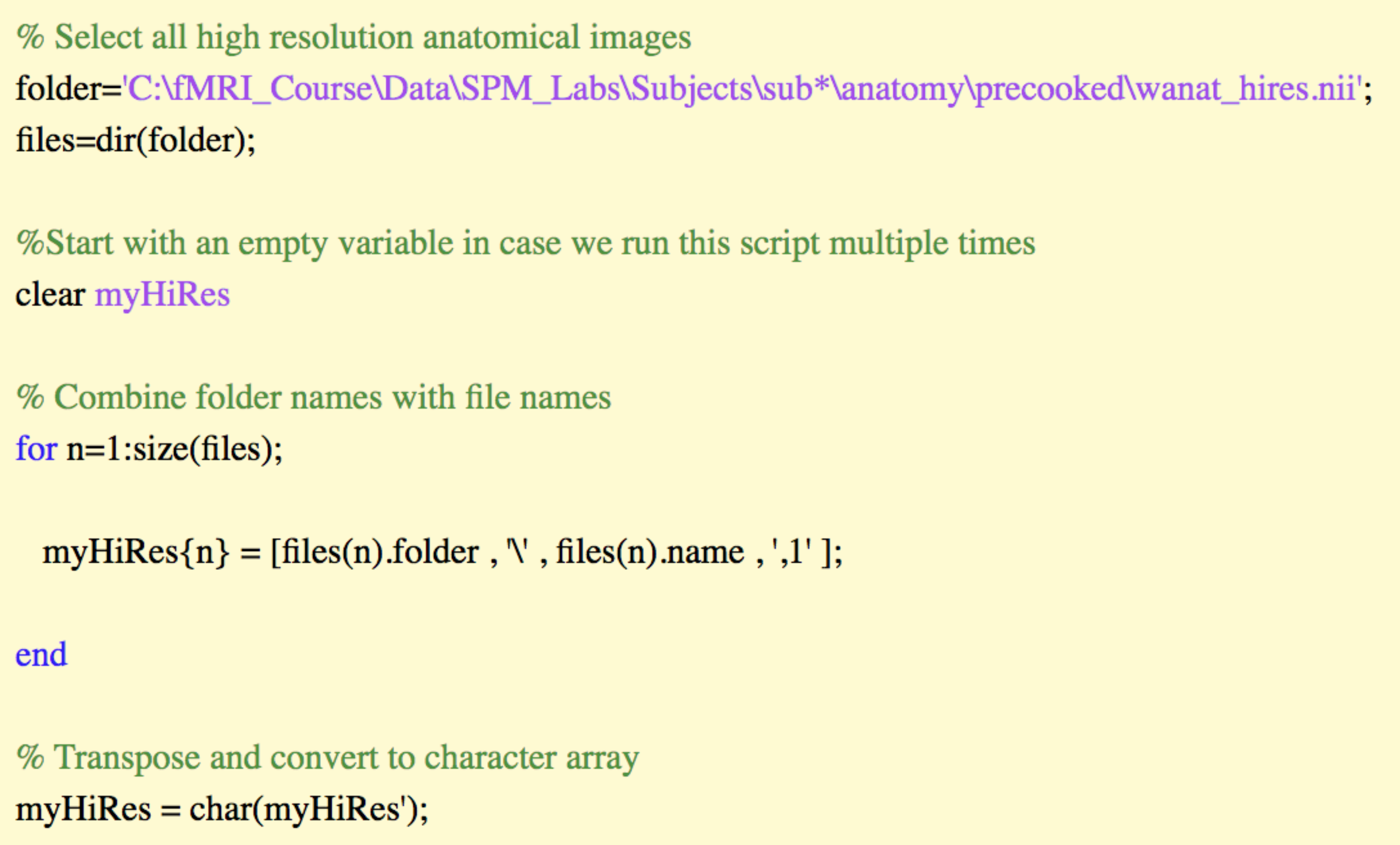
This is classic circularity [3]

ROI_DEF = ROI defining analysis; ROI_ANA = ROI analysis

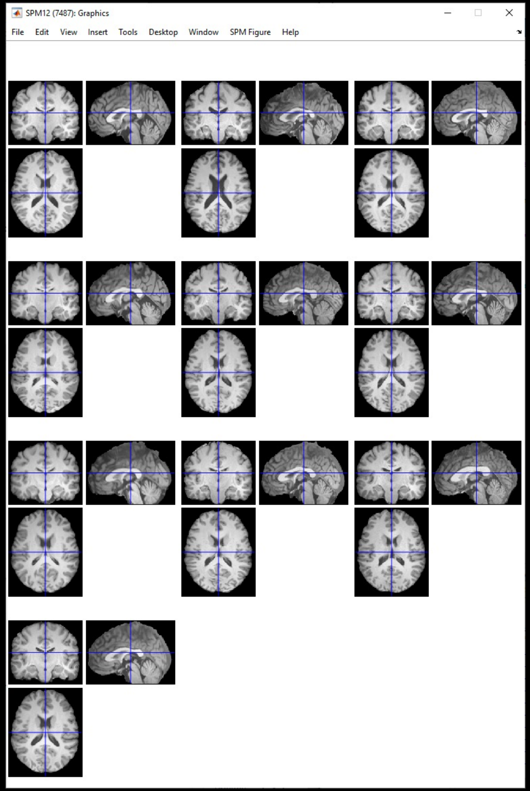
1. Orthogonal contrasts may refer to first level contrast vectors that are orthogonal (e.g. face+house and face-house) or orthogonal second level contrasts (group mean used for ROI_DEF where ROI_ANA is group comparison).
2. See supplement of Kriegeskorte *et al.* (2009), bottom of p1 for orthogonal contrast and http://mumfordbrainstats.tumblr.com/post/126904300281/less-obvious-double-dipping. Typical practices are using a 1-sample t-test for ROI_DEF and a different ROI_ANA. For the example of using a group mean for ROI_DEF and 2-sample t for ROI_ANA, the contrasts are A-B and A+B, and Cov(A-B, A+B)=Var(A)-Var(B), which is only 0 if the variances are equal. Thus orthogonality of the contrasts does not imply independence of the tests, unless the variances are equal. FYI, adding in a test of equal variances will not get you out of this jam, since it has its own false positive rate and those tests don't tend to work well.
3. Kriegeskorte *et al.* (2009) or Vul *et al.* (2009).
4. This assumes you either had 2 sets of runs with the same task or 2 sets of runs with different tasks, such as a localizer and task of interest. The latter is clearly independent and for the former, see page 2 of the supplement for Kriegeskorte *et al.* (2009) for a set of guidelines for splitting up runs for ROI_DEF and ROI_ANA.
5. If you looked at the whole brain results that mirror what you'll do for ROI_ANA, even at uncorrected thresholds, it will now be difficult to choose an ROI from independent data without bias leaking in.

Lab Preview

Checking Data Quality

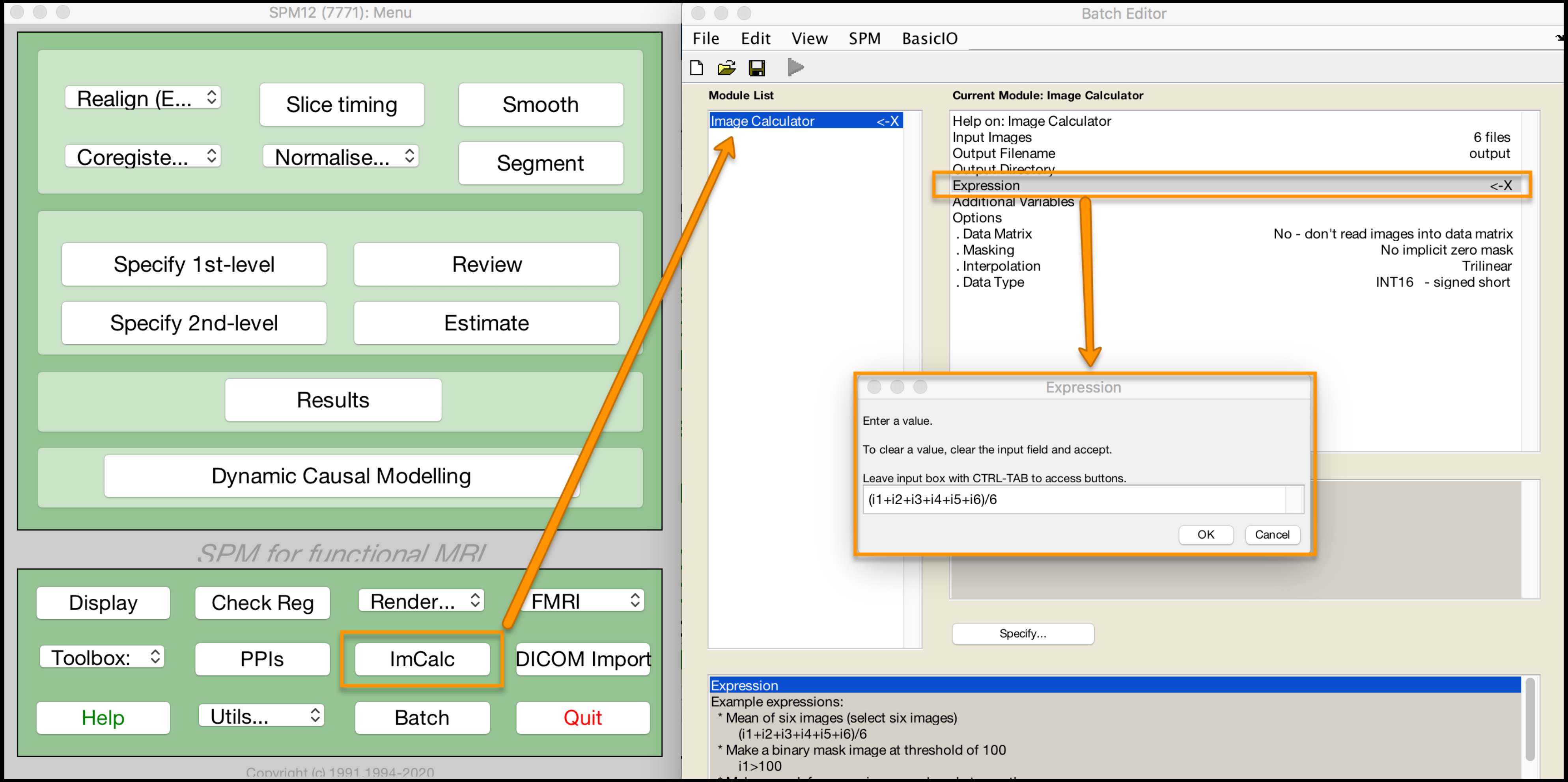


```
% Select all high resolution anatomical images
folder='C:\fMRI_Course\Data\SPM_Labs\Subjects\sub*\anatomy\precooked\wanat_hires.nii';
files=dir(folder);

%Start with an empty variable in case we run this script multiple times
clear myHiRes

% Combine folder names with file names
for n=1:size(files);

  myHiRes{n} = [files(n).folder , '\' , files(n).name , ',1' ];

end

% Transpose and convert to character array
myHiRes = char(myHiRes');
```



Lab Preview

Create Mean Anatomical



Current Module: Image Calculator

Help on: Image Calculator
Input Images — 6 files
Output Filename — output
Output Directory
Expression <-X
Additional Variables
Options
. Data Matrix — No - don't read images into data matrix
. Masking — No implicit zero mask
. Interpolation — Trilinear
. Data Type — INT16 - signed short

Expression

Enter a value.

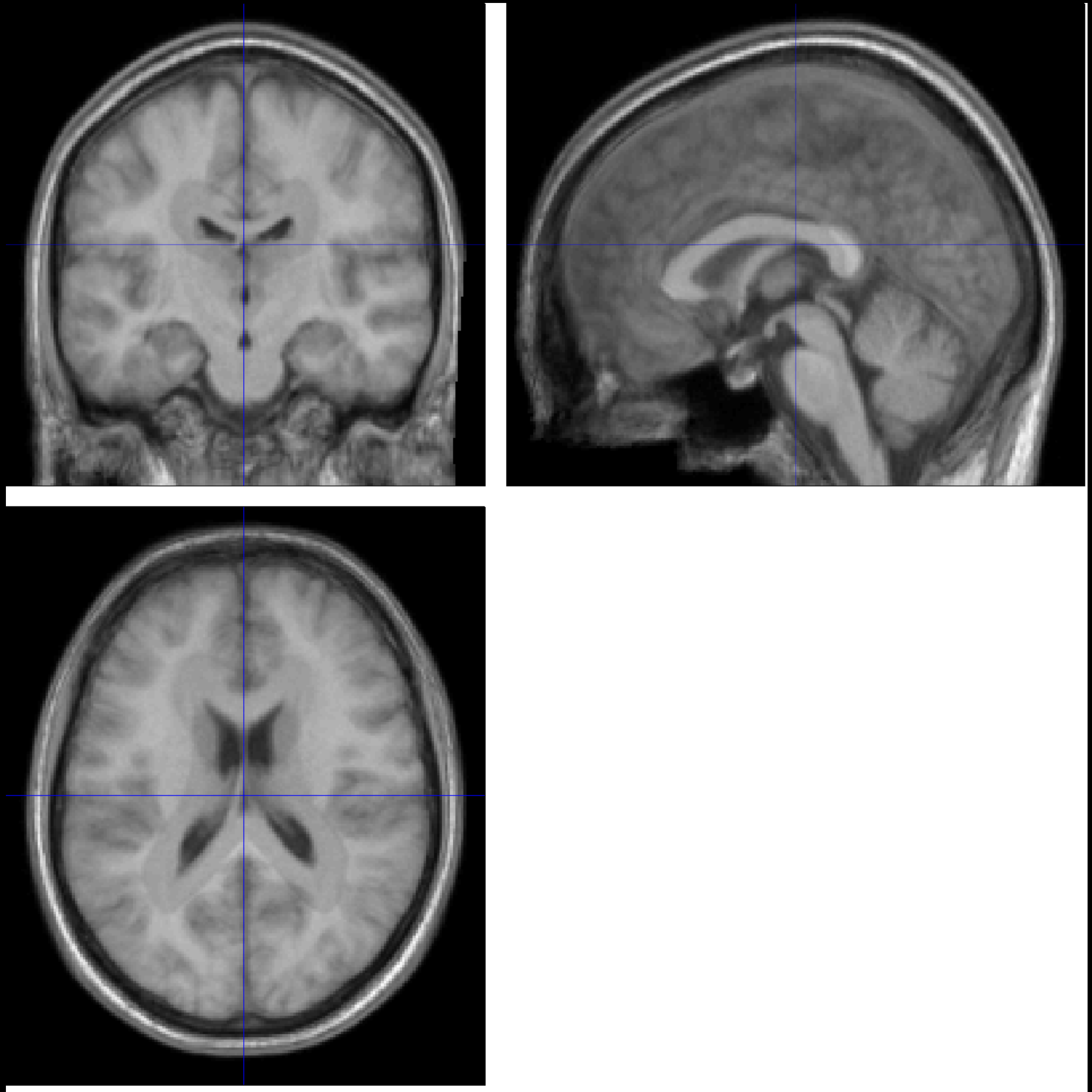
To clear a value, clear the input field and accept.

Leave input box with CTRL-TAB to access buttons.

(i1+i2+i3+i4+i5+i6)/6

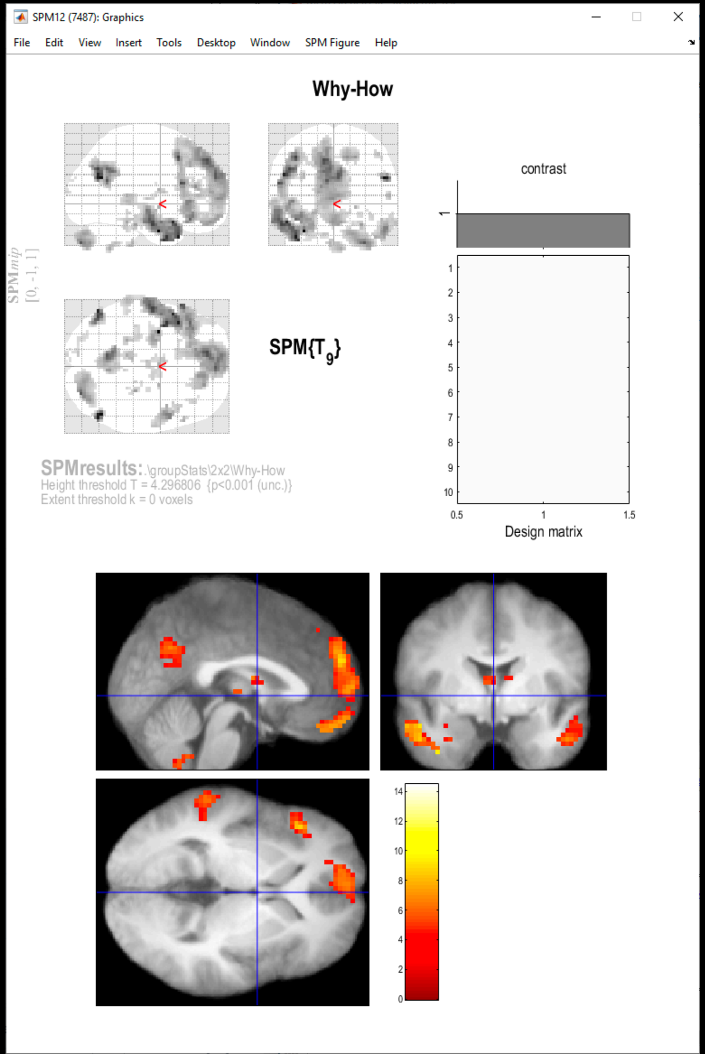
Expression
Example expressions:
 * Mean of six images (select six images)
   (i1+i2+i3+i4+i5+i6)/6
 * Make a binary mask image at threshold of 100
   i1>100

Lab Preview

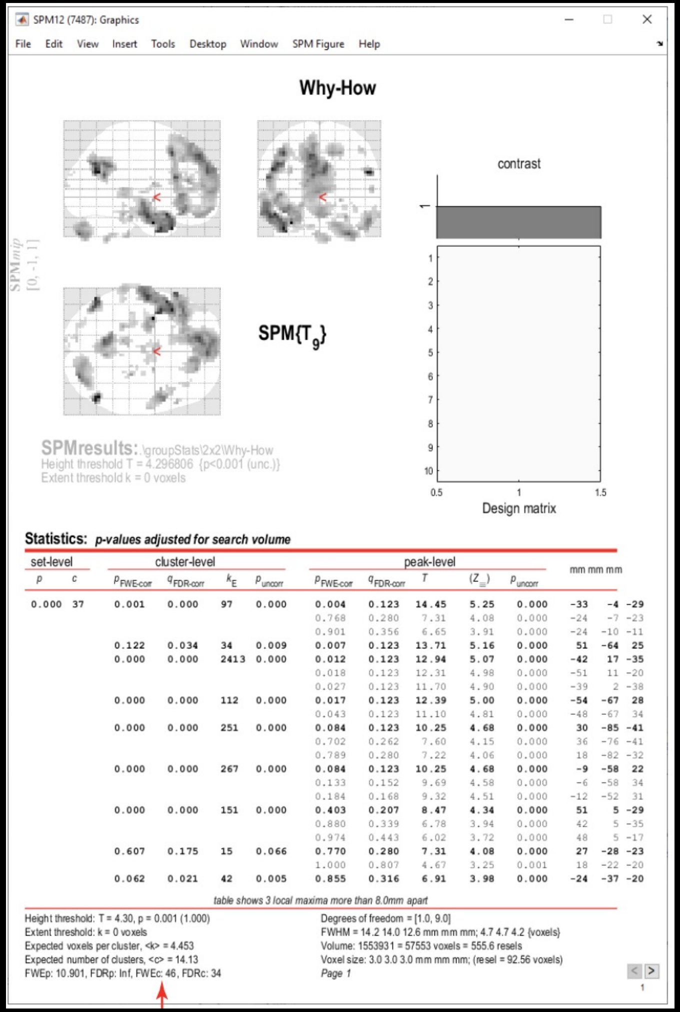


Lab Preview

Examine Results



SPMresults: .\groupStats\2x2\Why-How
Height threshold T = 4.296806 {p<0.001 (unc.)}
Extent threshold k = 0 voxels



SPMresults: .\groupStats\2x2\Why-How
Height threshold T = 4.296806 {p<0.001 (unc.)}
Extent threshold k = 0 voxels

Statistics: ***p-values adjusted for search volume***

set-level		cluster-level				peak-level					mm mm mm		
p	c	$p_{FWE-corr}$	$q_{FDR-corr}$	k_E	p_{uncorr}	$p_{FWE-corr}$	$q_{FDR-corr}$	T	$(Z_\equiv)$	p_{uncorr}			
0.000	37	0.001	0.000	97	0.000	0.004	0.123	14.45	5.25	0.000	-33	-4	-29
						0.768	0.280	7.31	4.08	0.000	-24	-7	-23
						0.901	0.356	6.65	3.91	0.000	-24	-10	-11
		0.122	0.034	34	0.009	0.007	0.123	13.71	5.16	0.000	51	-64	25
		0.000	0.000	2413	0.000	0.012	0.123	12.94	5.07	0.000	-42	17	-35
						0.018	0.123	12.31	4.98	0.000	-51	11	-20
						0.027	0.123	11.70	4.90	0.000	-39	2	-38
		0.000	0.000	112	0.000	0.017	0.123	12.39	5.00	0.000	-54	-67	28
						0.043	0.123	11.10	4.81	0.000	-48	-67	34
		0.000	0.000	251	0.000	0.084	0.123	10.25	4.68	0.000	30	-85	-41
						0.702	0.262	7.60	4.15	0.000	36	-76	-41
						0.789	0.280	7.22	4.06	0.000	18	-82	-32
		0.000	0.000	267	0.000	0.084	0.123	10.25	4.68	0.000	-9	-58	22
						0.133	0.152	9.69	4.58	0.000	-6	-58	34
						0.184	0.168	9.32	4.51	0.000	-12	-52	31
		0.000	0.000	151	0.000	0.403	0.207	8.47	4.34	0.000	51	5	-29
						0.880	0.339	6.78	3.94	0.000	42	5	-35
						0.974	0.443	6.02	3.72	0.000	48	5	-17
		0.607	0.175	15	0.066	0.770	0.280	7.31	4.08	0.000	27	-28	-23
						1.000	0.807	4.67	3.25	0.001	18	-22	-20
		0.062	0.021	42	0.005	0.855	0.316	6.91	3.98	0.000	-24	-37	-20

table shows 3 local maxima more than 8.0mm apart

Height threshold: T = 4.30, p = 0.001 (1.000)
Extent threshold: k = 0 voxels
Expected voxels per cluster, <k> = 4.453
Expected number of clusters, <c> = 14.13
FWEp: 10.901, FDRp: Inf, FWEc: 46, FDRc: 34

Degrees of freedom = [1.0, 9.0]
FWHM = 14.2 14.0 12.6 mm mm mm; 4.7 4.7 4.2 {voxels}
Volume: 1553931 = 57553 voxels = 555.6 resels
Voxel size: 3.0 3.0 3.0 mm mm mm; (resel = 92.56 voxels)
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