

MGH/HST Athinoula A. Martinos Center for Biomedical Imaging



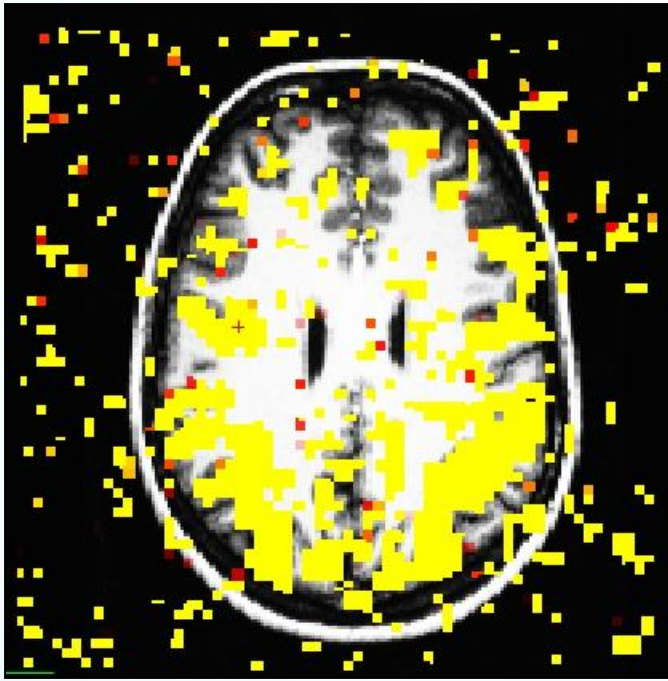
MASSACHUSETTS
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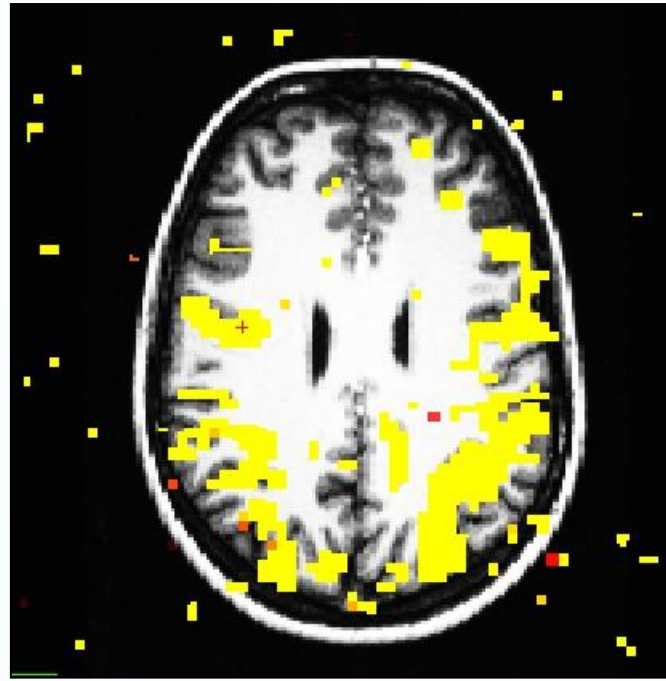
Harvard-MIT
Health Sciences & Technology

Correction for multiple comparisons in FreeSurfer

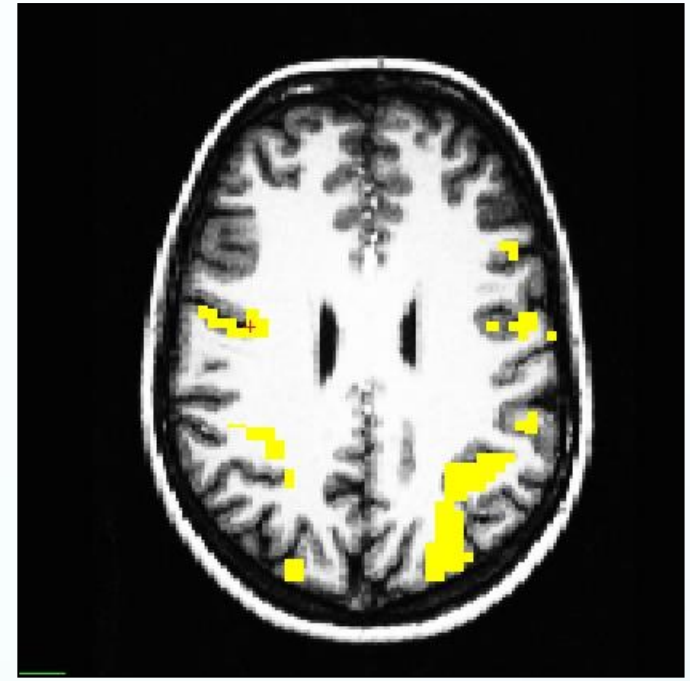
Problem of Multiple Comparisons



$p < 0.10$



$p < 0.01$

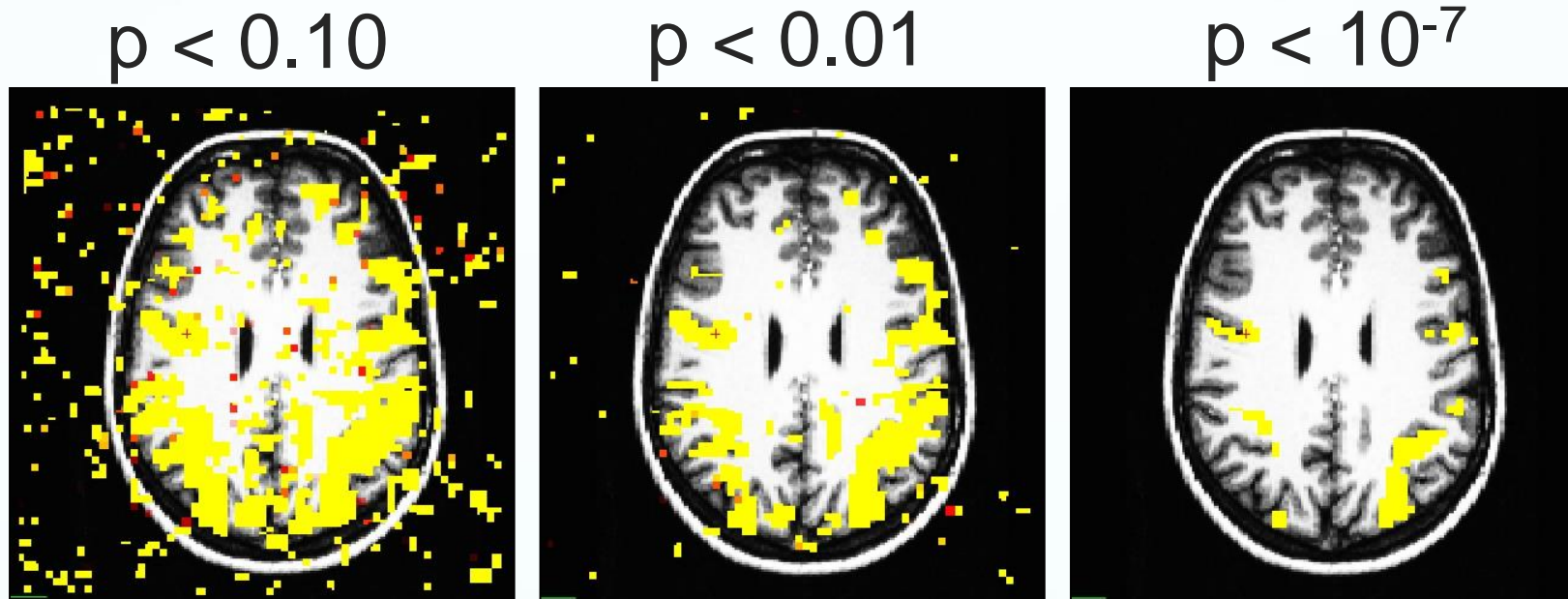


$p < 10^{-7}$

p value is probability that a voxel is falsely activated

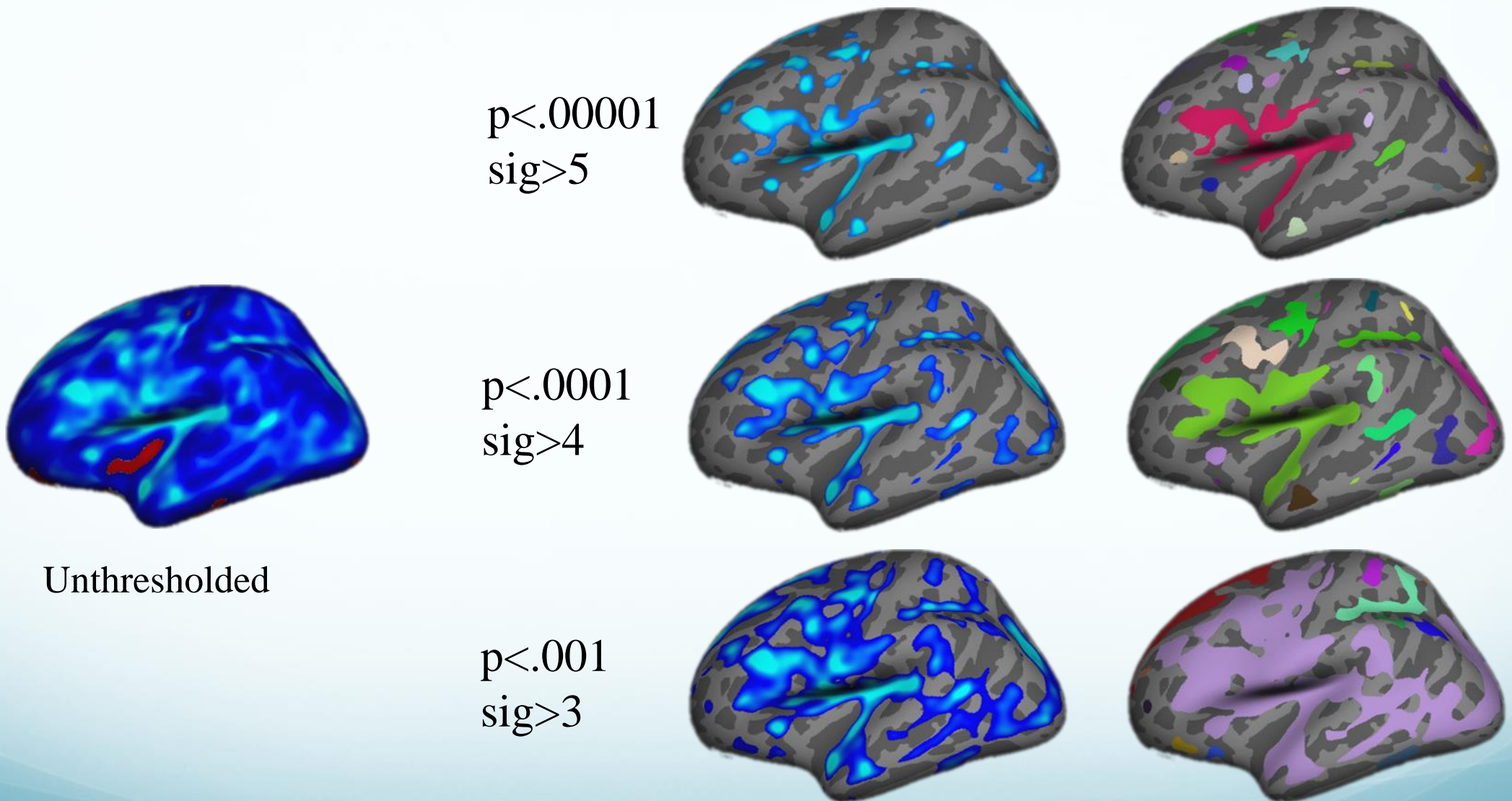
- Threshold too liberal: many false positives
- Threshold too restrictive: lose activation (false negatives)

Clusters



- True signal tends to be clustered
- False Positives tend to be randomly distributed in space
- Cluster – set of spatially contiguous voxels that are above a given threshold.

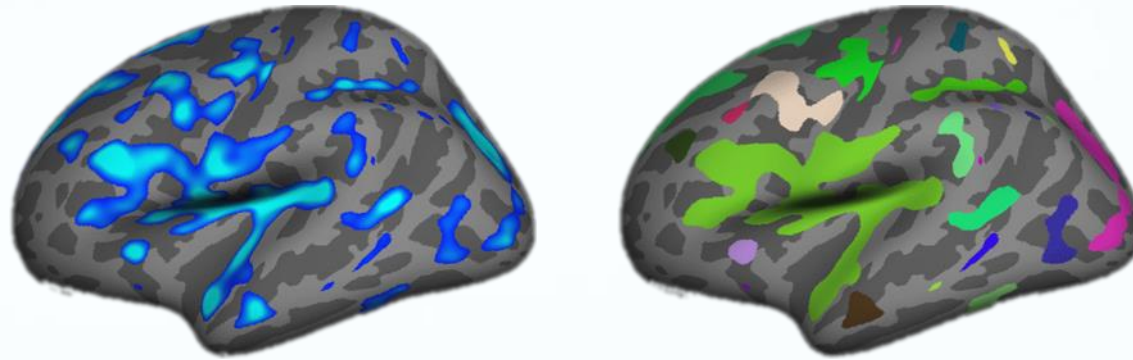
Cluster-forming Threshold



As threshold lowers, clusters may expand or merge and new clusters can form. There is no way to say what the threshold is best.

Cluster Table, Uncorrected

$p < .0001$
 $\text{sig} > 4$



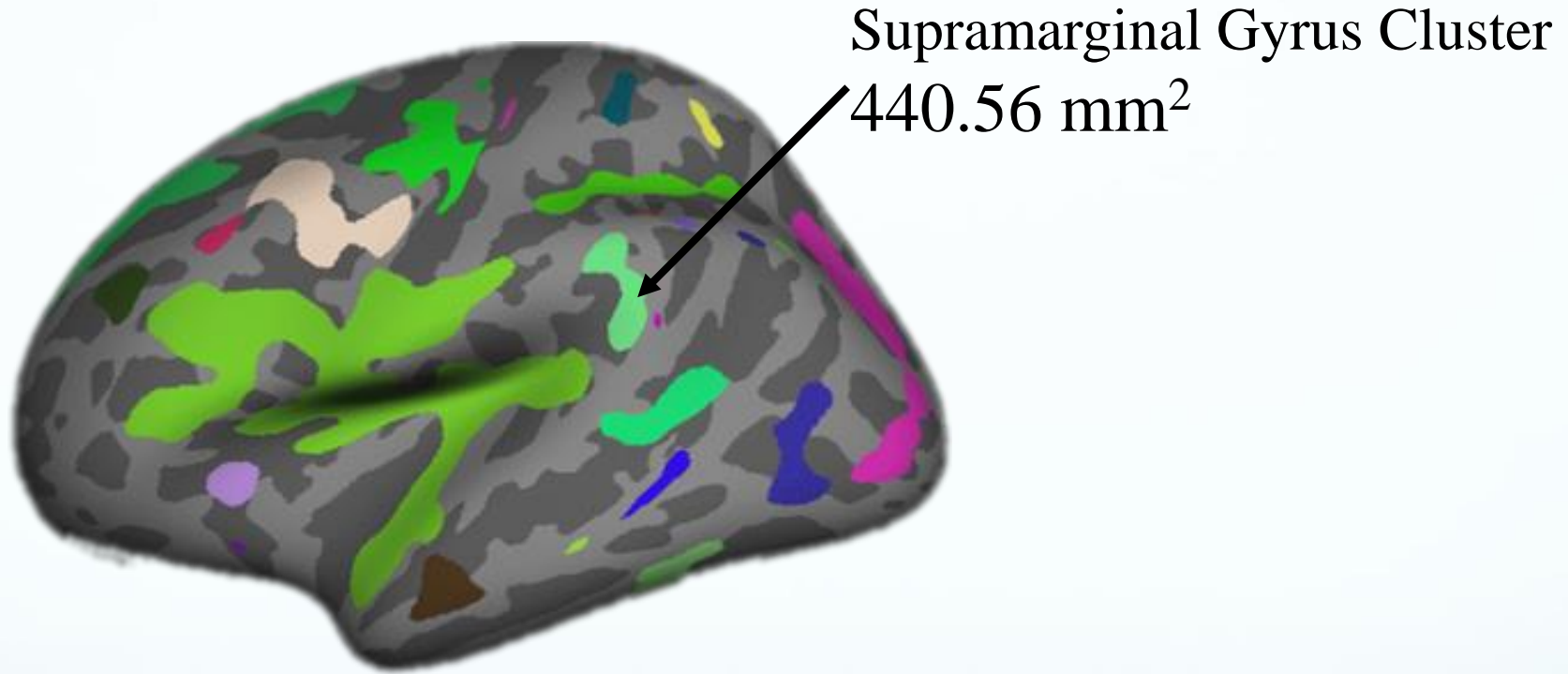
38 clusters

ClusterNo	Area(mm ²)	X	Y	Z	Structure
Cluster 1	3738.82	-11.1	34.5	27.2	superiorfrontal
Cluster 2	5194.19	-32.4	-23.3	15.7	insula
Cluster 3	1271.30	-25.9	-75.0	19.0	superiorparietal
Cluster 4	775.38	-44.4	-9.7	51.3	precentral
Cluster 5	440.56	-33.0	-36.8	37.5	supramarginal

...

How likely is it to get a cluster of a certain size under the null hypothesis?

Clusterwise Correction

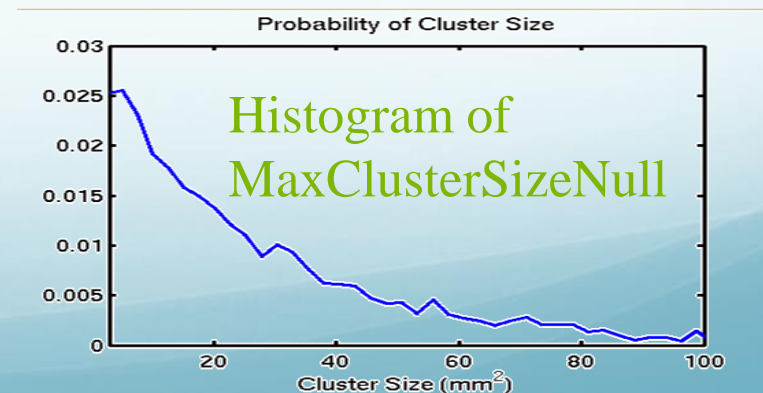


How likely is it to get a cluster 440.56mm² or bigger by chance?

How likely is it to get a cluster of a certain size under the null hypothesis?

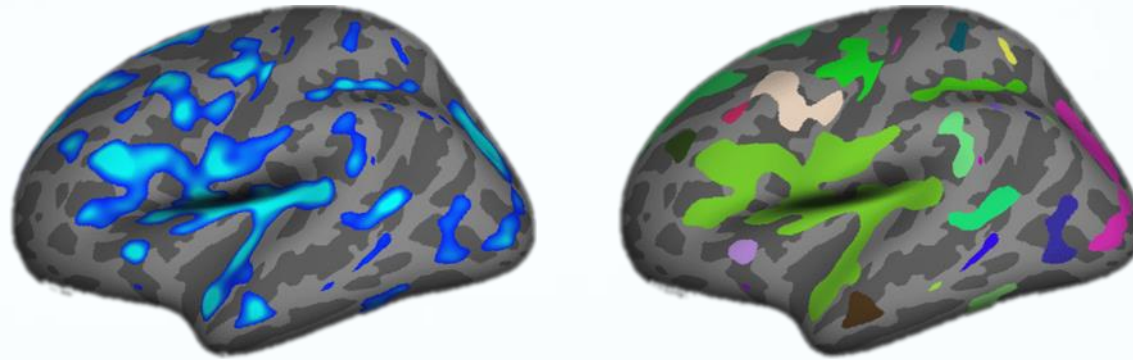
Cluster-based Correction for Multiple Comparisons

1. Simulate data under Null Hypothesis:
 - Synthesize Gaussian noise and then smooth (Monte Carlo)
 - Permute rows of design matrix (Permutation, orthog.)
 2. Analyze, threshold, cluster, get **MaxClusterSizeNull**
 3. Repeat 10,000 times – gives a list of 10000 **MaxClusterSizeNulls** under the null
 4. Analyze real data, get **ClusterSize** (eg, 440.56 mm²)
 5. Count number of times **MaxClusterSizeNull** > **ClusterSize**
- $P(\text{cluster}) = \#(\text{MaxClusterSizeNull} > \text{ClusterSize}) / 10000$



Cluster Table, Corrected

$p < .0001$
 $\text{sig} > 4$



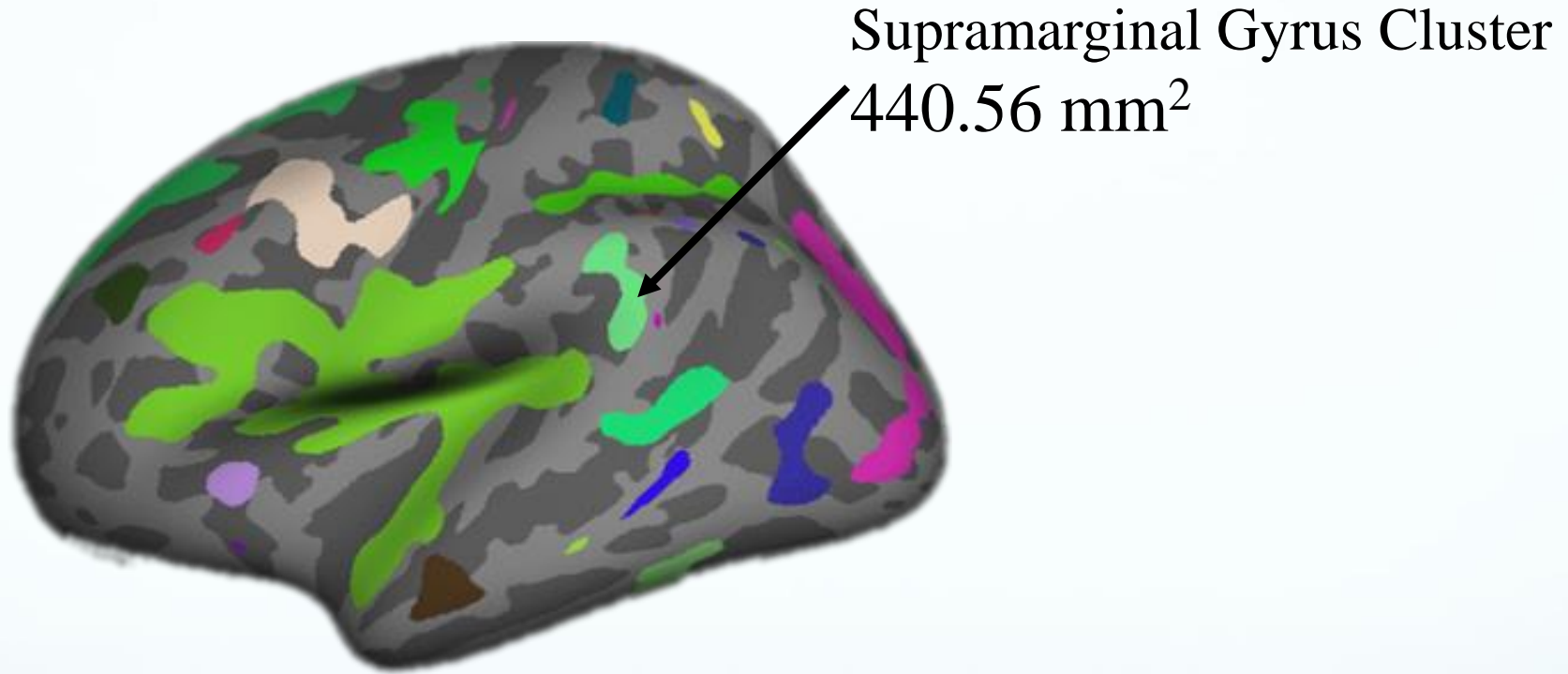
22 clusters out of 38 have cluster p-value $< .05$

ClusterNo	Area(mm ²)	X	Y	Z	Structure	Cluster P
Cluster 1	3738.82	-11.1	34.5	27.2	superiorfrontal	.0001
Cluster 2	5194.19	-32.4	-23.3	15.7	insula	.0003
Cluster 3	1271.30	-25.9	-75.0	19.0	superiorparietal	.0050
Cluster 4	775.38	-44.4	-9.7	51.3	precentral	.0100
Cluster 5	440.56	-33.0	-36.8	37.5	supramarginal	.0400

...

Note the difference between the Cluster Forming Threshold ($p < .0001$) and the Clusterwise p-value (.05).

Clusterwise Correction



Probability of getting a cluster 440.56mm² or bigger by chance is $p=.04$
This is the clusterwise p-value.

Surface-based Correction for Multiple Comparisons

- 2D Cluster-based Correction at $p < .05$

```
mri_glmfit-sim  
--glmdir lh.gender_age.glm  
--cache pos 2  
--2spaces  
--cwpvalthresh .05
```

Surface-based Correction for Multiple Comparisons

- 2D Cluster-based Correction at $p < .05$

mri_glmfit-sim

```
--glmdir lh.gender_age.glmdir  
--cache pos 2  
--2spaces  
--cwpvalthresh .05
```

Original mri_glmfit command:

```
mri_glmfit  
--y lh.thickness.sm10.mgh  
--fsgd gender_age.txt  
--C age.mtx --C gender.mtx  
--surf fsaverage lh  
--cortex
```

```
--glmdir lh.gender_age.glmdir
```

```
lh.gender_age.glmdir/  
beta.mgh – parameter estimates  
rvar.mgh – residual error variance  
age/  
sig.mgh – -log10(p), uncorrected  
gamma.mgh, F.mgh  
gender/  
sig.mgh – -log10(p), uncorrected  
gamma.mgh, F.mgh
```

Surface-based Correction for Multiple Comparisons

- 2D Cluster-based Correction at $p < .05$

mri_glmfit-sim

--glmdir lh.gender_age.glmdir

--cache pos 2

--2spaces

--cwpvalthresh .05

- Use pre-computed simulation results
- positive contrast
- voxelwise threshold $\text{thres} = 2$ ($p < .01$)
- Can do another simulation or permutation
- Not related to recon-all -qcache

Surface-based Correction for Multiple Comparisons

- 2D Cluster-based Correction at $p < .05$

```
mri_glmfit-sim  
  --glmdir lh.gender_age.glm  
  --cache pos 2  
  --cwpvalthresh .05  
  --2spaces
```

Cluster-wise threshold $p < .05$
cw = cluster-wise
pval = p value
thresh = threshold



Surface-based Correction for Multiple Comparisons

- 2D Cluster-based Correction at $p < .05$

```
mri_glmfit-sim  
--glmdir lh.gender_age.glmdir  
--cache pos 2  
--cwpvalthresh .05  
--2spaces
```

Doing analysis with left hemi but right hemi will be done separately. Need to correct for full search space.

Correction for Multiple Comparisons Output

```
mri_glmfit-sim  
--glmdir lh.gender_age.glmmdir  
--cache pos 2  
--cwpvalthresh .05  
--2spaces
```

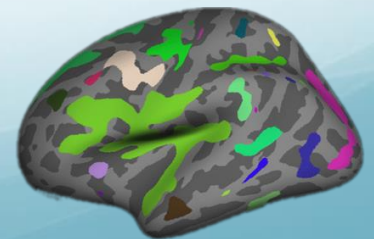
lh.gender_age.glmmdir

age

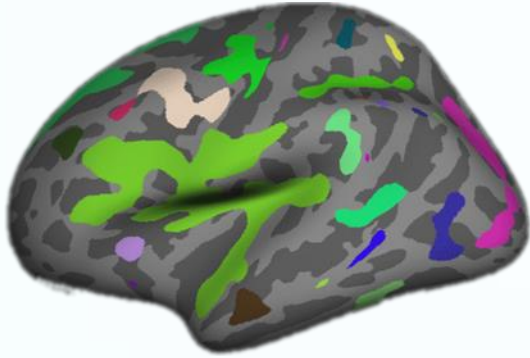
gender

sig.mgh – pre-existing uncorrected p-values
cache.th20.pos.sig.cluster.mgh – map of significance of clusters
cache.th20.pos.sig.ocn.annot – annotation of significant clusters
cache.th20.pos.sig.cluster.summary – text file of cluster table
(clusters, sizes, MNI305 XYZ, and their significances)

- Only shows clusters $p < .05$, change `--cwpvalthresh` to a larger value to get more (ie, less sig) clusters



Corrected Outputs



cache.th20.pos.sig.ocn.annot – annotation of significant clusters

cache.th20.pos.sig.cluster.summary -- text file of cluster table

ClusterNo	Area(mm ²)	X	Y	Z	Structure	Cluster P
Cluster 1	3738.82	-11.1	34.5	27.2	superiorfrontal	.0001
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...

False Discover Correction Possible

- False Discovery Rate (FDR) – built into tksurfer and QDEC. (Genovese, et al, NI 2002)

Tutorial

1. Command-line Stream

- Create an FSGD File for a thickness study
- Age and Gender
- Run
 - `mris_preproc`
 - `mri_surf2surf`
 - `mri_glmfit`
 - `mri_glmfit-sim`
 - `tksurfer`

2. QDEC – same data set

QDEC – An Interactive Statistical Engine GUI

Query – Select subjects based on Match Criteria

Design – Specify discrete and continuous factors

Estimate – Fit Model

Contrast – Automatically Generate Contrast Matrices

Interactive – Makes easy things easy (that used to be hard)

...a work in progress

- No Query yet
- Two Discrete Factors (Two Levels)
- Two Continuous Factors
- Surface only

QDEC – Spreadsheet

qdec.table.dat – spreadsheet with subject information – can be huge!

fsid	gender	age	diagnosis	Left-Cerebral-White-Matter-Vol
011121_vc8048	Female	70	Demented	202291
021121_62313-2	Female	71	Demented	210188
010607_vc7017	Female	73	Nondemented	170653
021121_vc10557	Male	75	Demented	142029
020718_62545	Male	76	Demented	186087
020322_vc8817	Male	77	Nondemented	149810

gender.levels

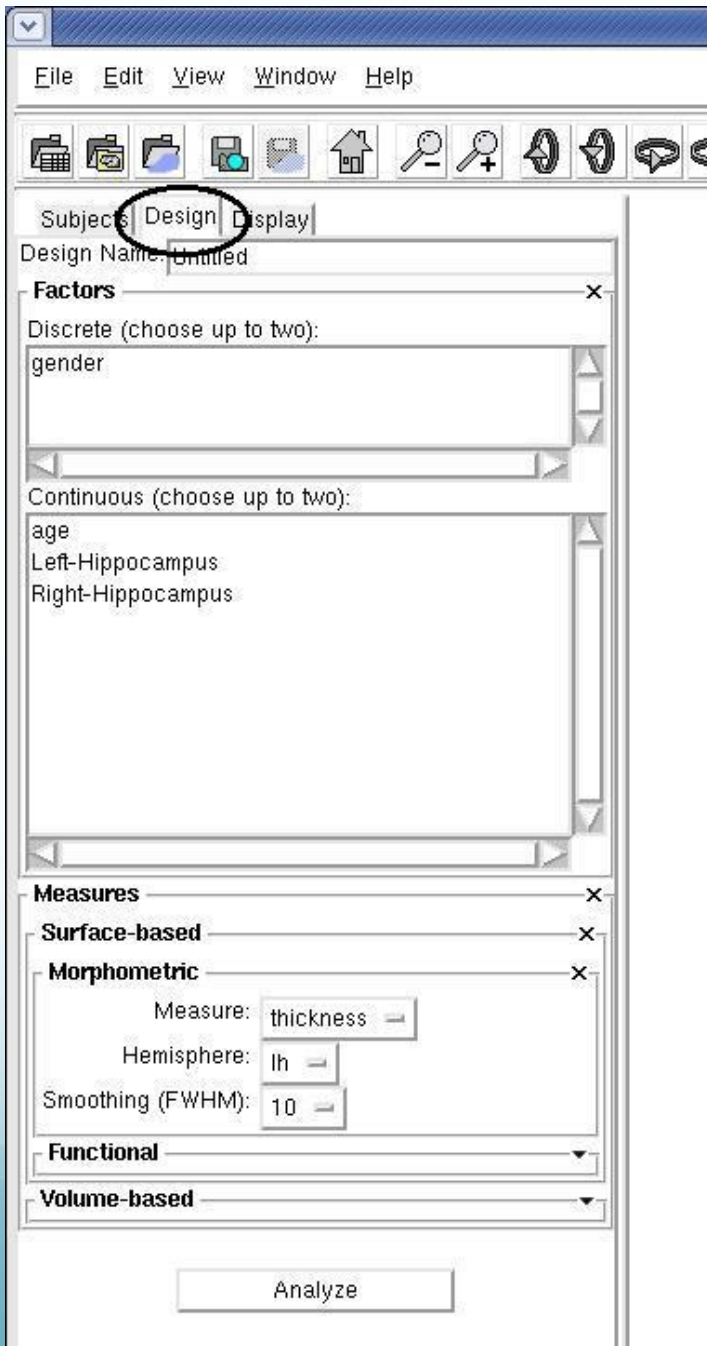
Female
Male

diagnosis.levels

Demented
Nondemented

Discrete Factors need a
factorname.level file

QDEC GUI



- Load QDEC Table File
 - List of Subjects
 - List of Factors (Discrete and Cont)
- Choose Factors
- Choose Input (cached):
 - Hemisphere
 - Measure (eg, thickness)
 - Smoothing Level
- “Analyze”
 - Builds Design Matrix
 - Builds Contrast Matrices
 - Constructs Human-Readable Questions
 - Analyzes
 - Displays Results