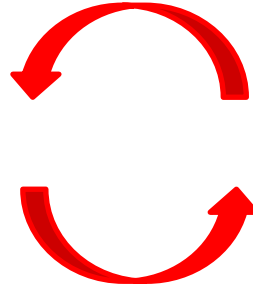
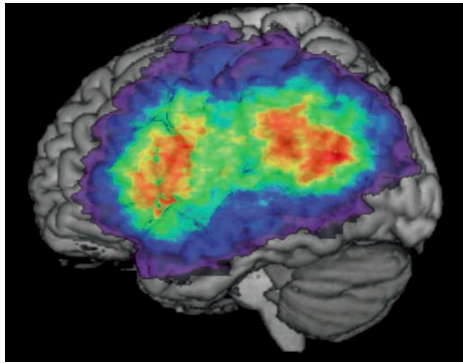




MRRI
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Lesion-Symptom Mapping Workshop



Speakers:

Frank Garcea
Harrison Stoll
Austin Wild

Organizer:

Aaron Wong

Join the discussion

- For those joining us remotely, we have muted incoming audio to reduce background noise
- If you have questions, please use the chat window



Join the discussion

- For those joining us remotely, we have muted incoming audio to reduce background noise
- If you have questions, please use the chat window
- We will also take questions after the session via email or twitter

 wongaaro@einstein.edu
 @WongAaronL

 garceafr@einstein.edu
 @frankgarcea

Lesion-Symptom Mapping Pipeline



Software packages:

- SVR-LSM GUI (Matlab): <https://github.com/atdemarco/svrlsmgui>
- SCCAN (R): <https://github.com/dorianps/LESYMAP/wiki/SCCAN-questions>

Lesion-Symptom Mapping approaches

- VLSM
 - Perform a t-test at each voxel
 - Large number of tests, (incorrectly) assumed to be independent
- SVR-LSM
 - Perform a single multivariate regression, with significance determined using permutation testing
 - P values still determined at the voxel level
 - Unclear how to properly correct for multiple comparisons
 - Unclear how to properly correct for lesion size

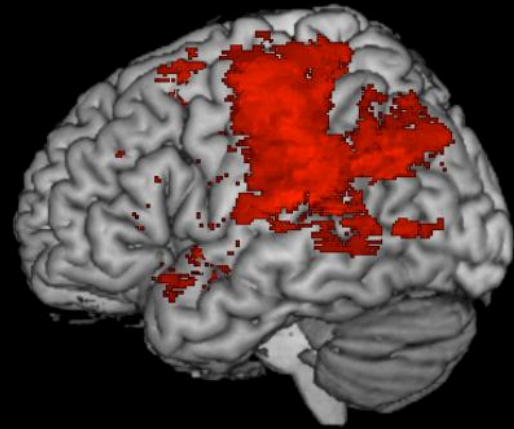
SVR-LSM:

Correcting for lesion volume

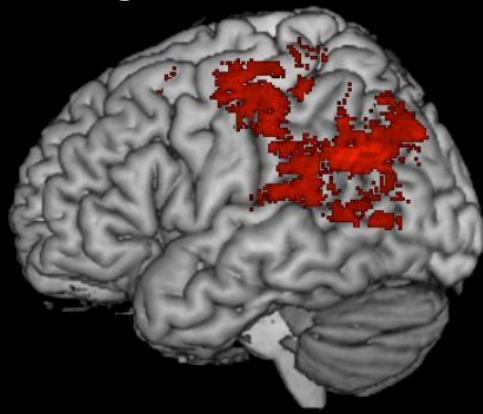
- dTLVC: normalize lesion status by $1/\sqrt{\text{TLV}}$
- Regress on Lesion: Regress lesion status on TLV, use residuals
- Regress on Behavior: Regress behavior on TLV, use residuals
- Regress on Both

#	Method	Corrects behavior	Corrects lesion data
1	No correction	X	X
2	dTLVC (Zhang et al., 2014)	X	Partial
3	Regress on Behavior	✓	X
4	Regress on Lesion	X	✓
5	Regress on Both	✓	✓

dTLVC



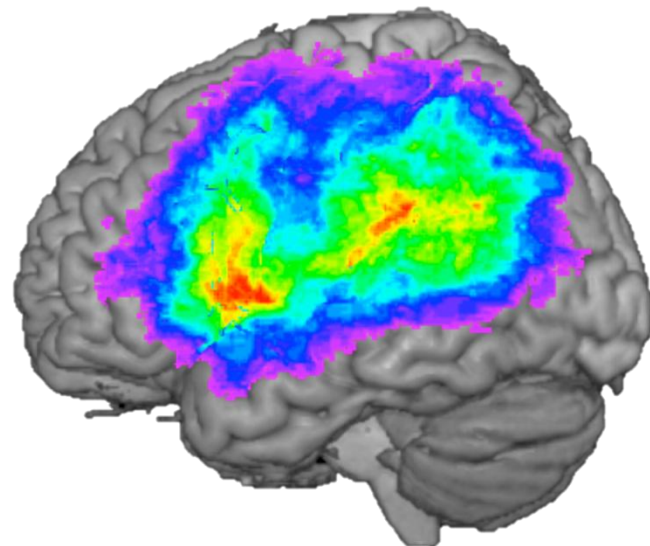
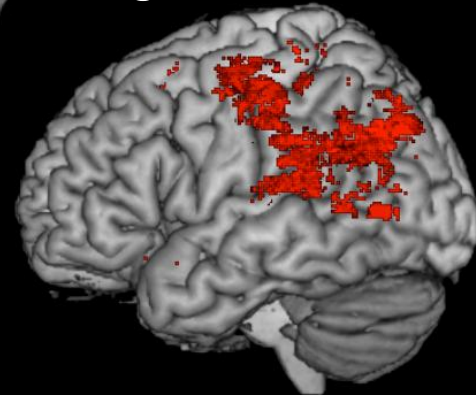
Regress on Lesion



Regress on Behavior



Regress on Both

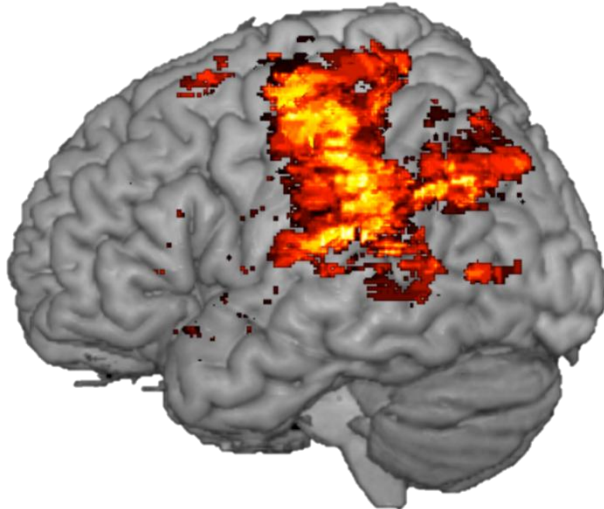


SVR-LSM:

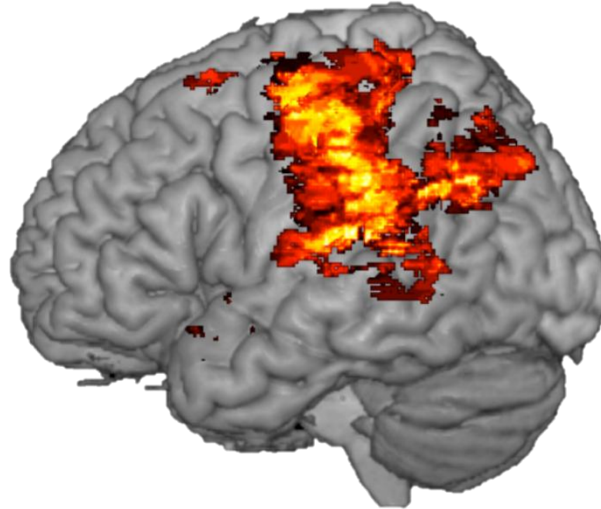
Correcting for multiple comparisons

- Voxel-level correction (FDR, FWER)
- Cluster-size thresholding (minimum contiguous cluster size)
- Cluster-level correction (FDR, FWER)
- Cluster-size correction

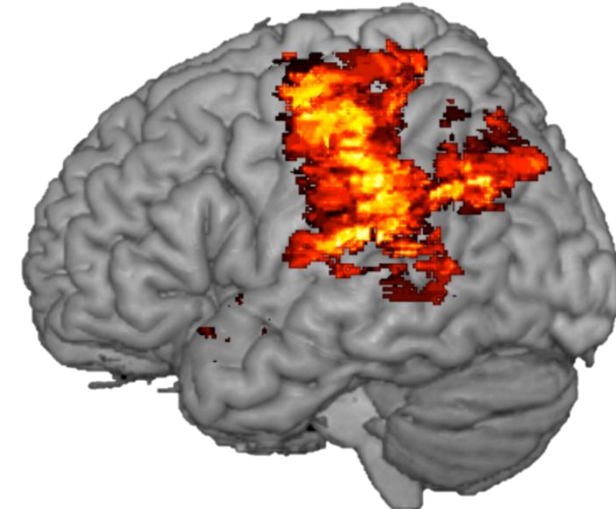
No Correction



Cluster-size threshold



Cluster-size Correction



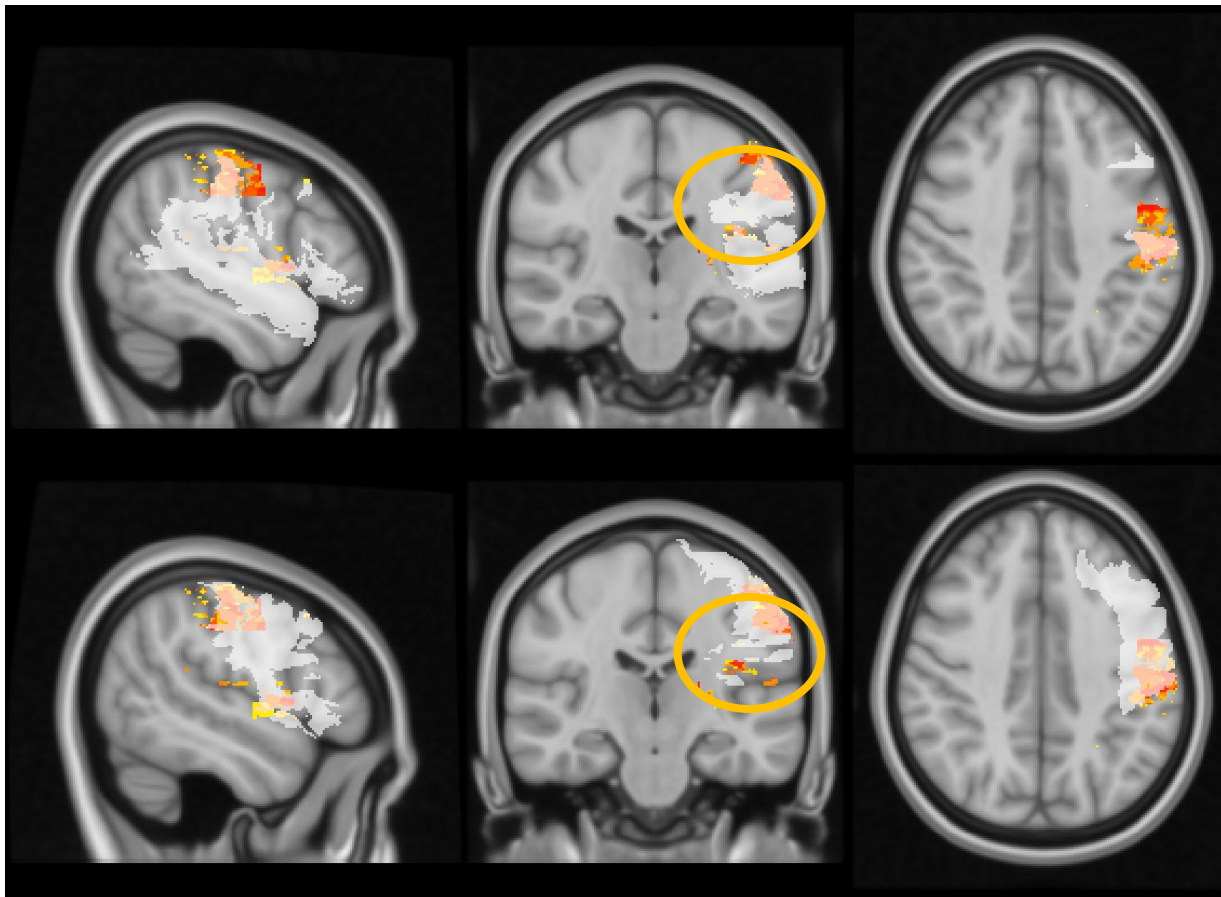
SVR-LSM:

Correcting for multiple comparisons

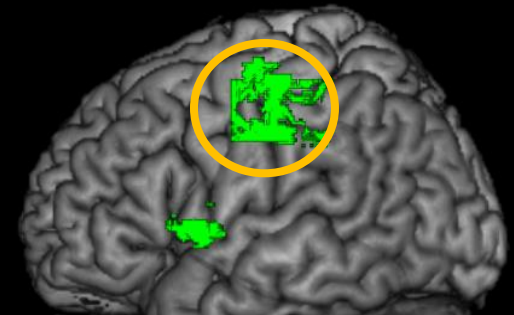
- Voxel level corrections can be anticonservative for small sample sizes and overly conservative at large sample sizes
- Cluster-size thresholding may not prevent spurious clusters
- Very rarely do clusters survive cluster-size correction
 - This approach considers only cluster size, not cluster significance
 - A large cluster with $p = 0.05$ observed by chance will outweigh a small cluster with $p = 0.00001$
 - This will wipe out the smaller clusters that SVR-LSM is supposed to be better at identifying

SVR-LSM: Boundary Effects

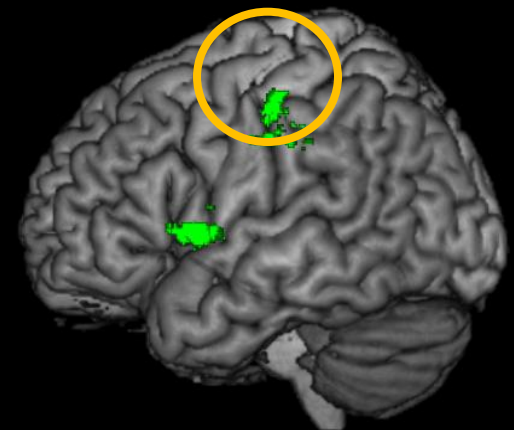
- A few subjects can strongly influence the outcome (e.g., at low N)



$N > 3$



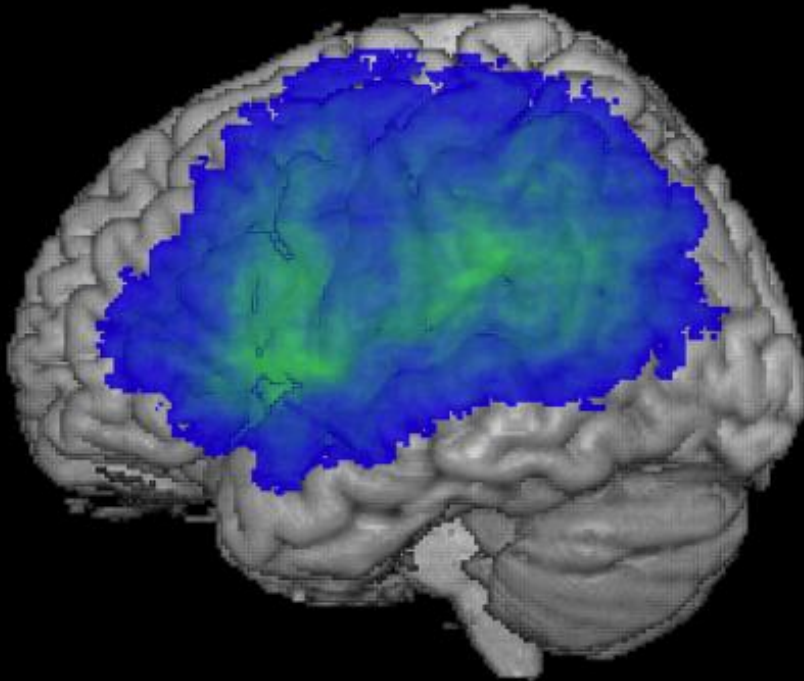
$N > 9$



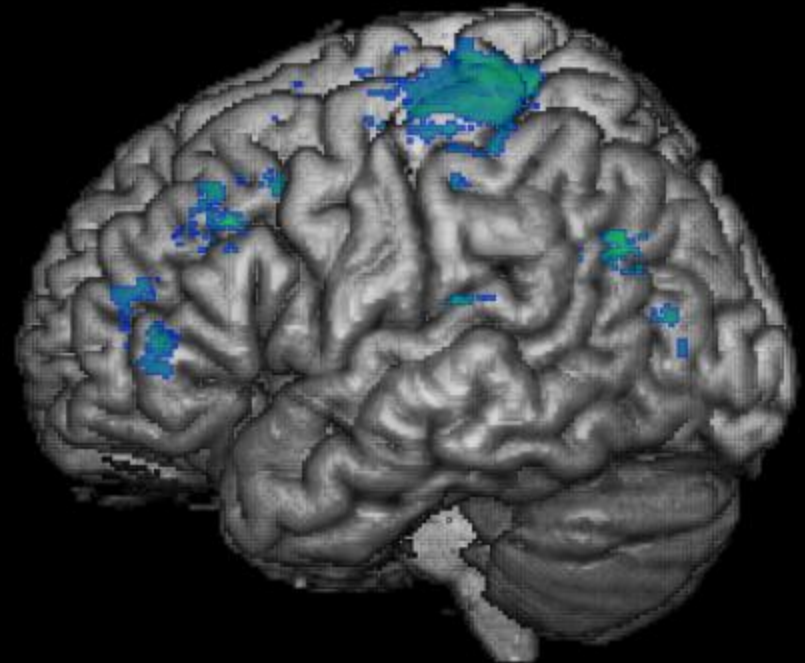
SVR-LSM: Boundary Effects

- Significant regions sometimes follow the edges of the distribution (N = 74)

Overlap: $N > 7$



SVR-LSM (Regress on Both)



SVR-LSM

- Theoretically an improvement over VLSM
- In practice, SVR-LSM is not without its own set of problems
- Is SVR-LSM the right tool for low N?
- We try to look for consistency across analyses/correction techniques (but does this invalidate your stats?)

➤ ***Know your data!***

Multivariate LSM

- SVR-LSM
 - Multivariate beta value calculation, voxel-level significance testing
- SCCAN
 - Multivariate weight calculation, map-level significance testing

Sparse Canonical Correlation Analysis for Neuroimaging (SCCAN)

The screenshot displays the RStudio interface. The main editor shows an R script named 'ScanBD.R' with the following content:

```
1 # SCCAN script
2 # Written by Harrison Stoll on October 2nd 2017
3
4 # Load necessary packages
5
6 library("ITKR", lib.loc="/Library/Frameworks/R.framework/Versions/3.4/Resources/library")
7 library("ANTsRCore", lib.loc="/Library/Frameworks/R.framework/Versions/3.4/Resources/library")
8 library("ANTsR", lib.loc="/Library/Frameworks/R.framework/Versions/3.4/Resources/library")
9 library("LESYMAP", lib.loc="/Library/Frameworks/R.framework/Versions/3.4/Resources/library")
10
11 # Set location where files (i.e., scan and behavioral) will come from.
12
13 Data = file.path("/Users/mrri/Desktop/BodyDot")
14 lesydata = file.path(find.package('LESYMAP'),'extdata')
15
16 # Set location of where lesion and behavioral data will come from. Make sure behavioral data is in a
17 # .txt file (best way to do this is to copy the data from an excel document into a word document, make sure
18 # sure though you paste the data as 'Unformatted Text' via paste special, then save the word document as a
19 # file) and make sure that your lesion files are in .nii.gz format. Finally your lesion files should be in
20 # order as the behavioral data in the .txt file (i.e., first lesion in folder should be first behavioral
21 # in text file).
22 #LESYMAP ASSUMES YOU ARE INTERESTED IN LOWER VALUES...so it uses lower scores to predic lesion locations
23
```

The Environment pane on the right shows the loaded data:

Variable	Value
svr_gs	20 obs. of 11 variables
CA	"/Users/mrri/Desktop/CDA/Behavior/CA_Behavior.txt"
CSG.Gcong	"/Volumes/Data HD/Laurels Group/Users/Stoll.Harrison/data//Beh...
CSG.Lesions	chr [1:131] "/Volumes/Data HD/Laurels Group/Users/Stoll.Harriso...
CSGdata	"/Volumes/Data HD/Laurels Group/Users/Stoll.Harrison/data//"
Data	"/Users/mrri/Desktop/CDA"
Lesions	chr [1:67] "/Users/mrri/Desktop/CDA/Lesions/MR0083.nii.gz" ...
lesydata	"/Library/Frameworks/R.framework/Versions/3.4/Resources/library...
lsm.CA	List of 8
lsm.Gcong	List of 5
reg	List of 12
template	<Object with null pointer>

The bottom pane shows the documentation for the 'LESYMAP' package version 0.0.0.9003, titled 'Leions to Symptom Mapping in R'. It includes links for 'DESCRIPTION file', 'Package NEWS', and 'Help Pages'. The help pages listed are:

- [.createFolds](#) createFolds
- [BM](#) Massive Brunner-Munzel tests
- [BMfast](#) Fast Brunner-Munzel tests (v1)

Canonical Correlation Analysis (CCA)

- Say we have two sets of variables:

$$\mathbf{x} = \{x_1, x_2\}$$

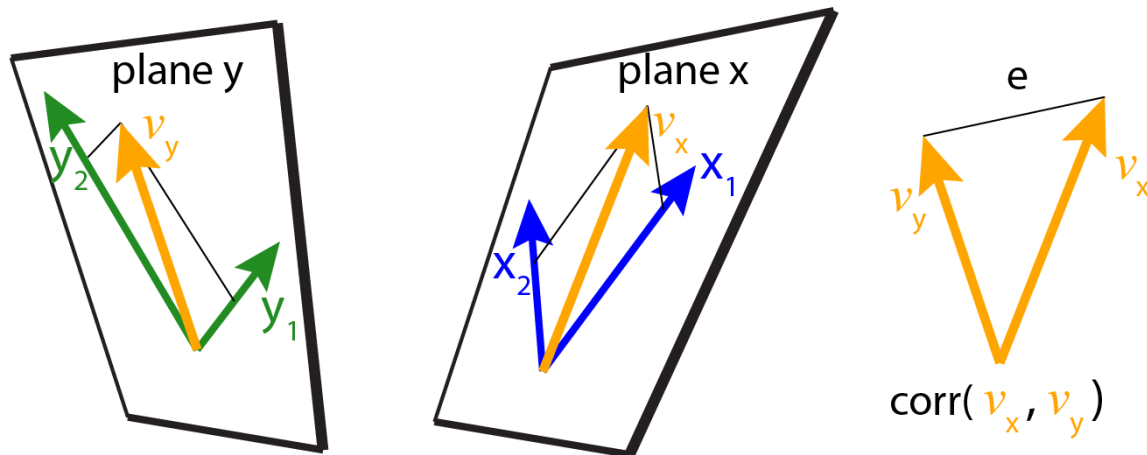
$$\mathbf{y} = \{y_1, y_2\}$$

- We define some \mathbf{a} and \mathbf{b} such that

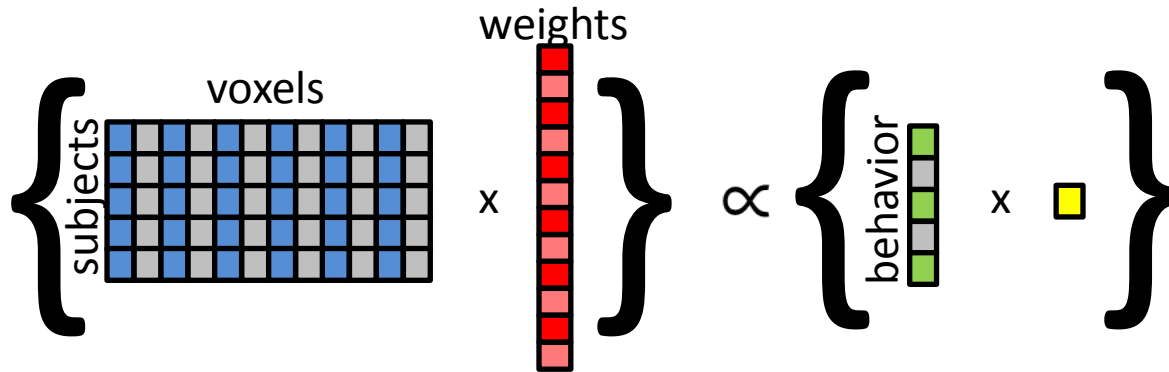
$$v_x = \mathbf{a}^T \mathbf{x}$$

$$v_y = \mathbf{b}^T \mathbf{y}$$

- We will choose \mathbf{a} and \mathbf{b} that maximize the correlation between v_x and v_y



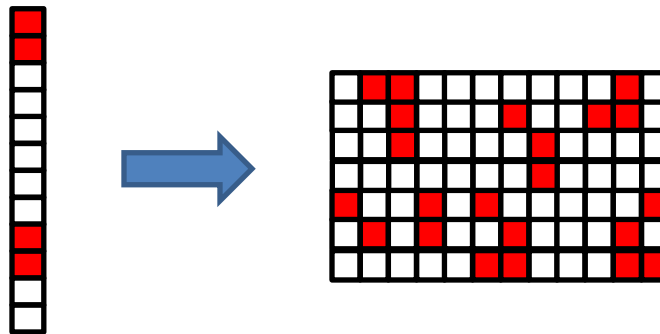
SCCAN: An extension of CCA



- We have a matrix of voxels on one hand, and a vector of behavior on the other
- We look for a [pair of] basis (feature weight) vectors such that the correlation of the projected voxel and behavioral data into that basis set is maximized
 - We require that basis vectors be sparse, i.e. that most of the feature weights are zero
 - Weights are smoothed, and isolated voxels are set back to 0

SCCAN: How it works

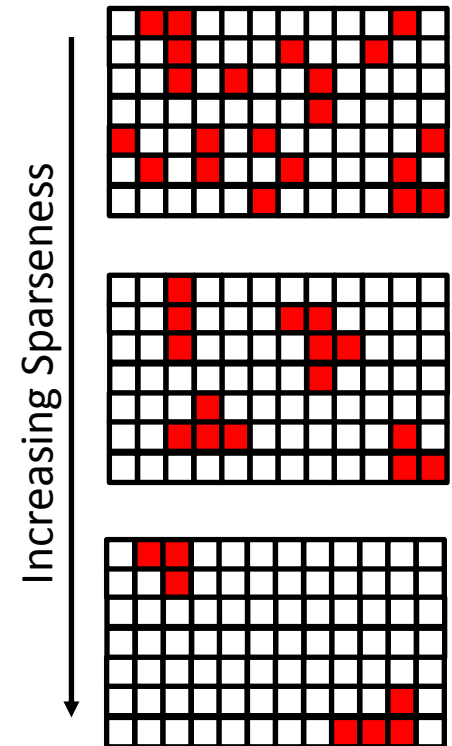
- The basis vector we identified serves as our feature weights (arranged to create a 3D map of voxel weights)
 - Larger weight means a stronger voxel-behavior relationship
 - We do NOT get voxel-level statistical values
- The extent of the map depends on the sparseness value



SCCAN: How it works

Determining sparseness

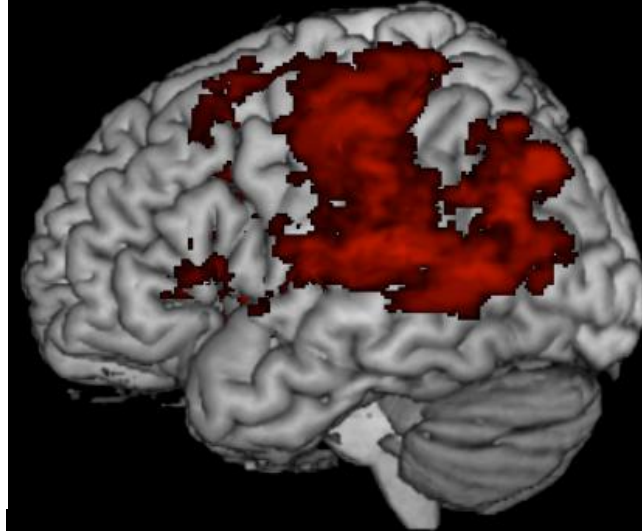
- Iterative cross-validation approach – find the sparseness value that maximizes prediction accuracy in cross-validation
 - Penalty for larger sparseness values (prefer a more sparse feature-weight vector)
 - Sparseness also affects neighboring feature weights (not quite analogous to thresholding a beta map)
- Cross-validation gives us one p value for the entire map
 - This tells us if the map is interpretable or random
- This is the ***opposite*** of SVR-LSM



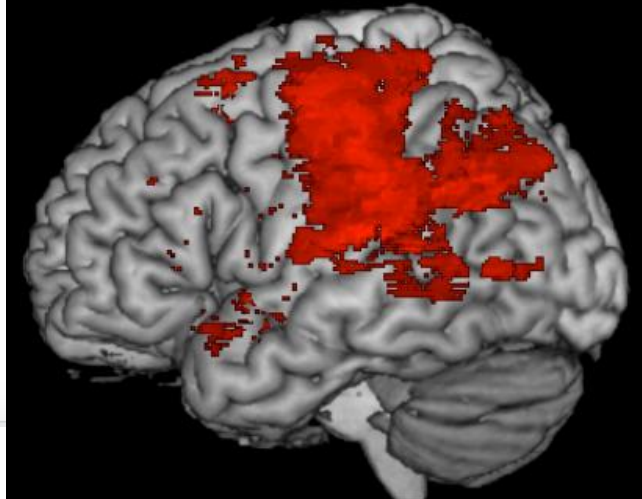
Running SCCAN

```
> lsm.MA = lesymap(Lesions, MA, method = 'sccan',optimizeSparseness=TRUE,sparsenessPenalty = .01)
13:09:01 Running LESYMAP 0.0.0.9221
13:09:01 Checking a few things...
13:09:01 Loading behavioral data... 68 scores found.
13:09:01 Filenames as input, checking lesion values on 1st image...
13:09:01 Detected unusual lesion values, loading files into memory to fix...
13:09:02 Detected lesion value above 1. Rebinarizing 0/1...
13:09:05 SCCAN method: ignoring patch, nperm, and multiple comparison...
13:09:05 Searching voxels lesioned in >= 10% subjects... 296404 found
13:09:06 noPatch true - Patches will not be used...
13:09:06 Computing lesion matrix... 68x296404
13:09:10 Running analysis: sccan ...
  Searching for optimal sparseness:
    lower/upper bound:    -0.9 / 0.9
    cvRepetitions:        3
    nFolds:                4
    sparsenessPenalty:    0.01
    optim tolerance:      0.03
13:09:12    Checking sparseness -0.212 . . . CV correlation 0.0347 (0.684) (cost=0.967)
13:31:10    Checking sparseness 0.212 . . . CV correlation 0.169 (0.571) (cost=0.833)
13:48:40    Checking sparseness 0.475 . . . CV correlation 0.185 (0.522) (cost=0.820)
14:00:40    Checking sparseness 0.413 . . . CV correlation 0.183 (0.537) (cost=0.821)
14:15:31    Checking sparseness 0.523 . . . CV correlation 0.186 (0.513) (cost=0.819)
14:25:34    Checking sparseness 0.667 . . . CV correlation 0.192 (0.484) (cost=0.814)
14:31:25    Checking sparseness 0.756 . . . CV correlation 0.196 (0.469) (cost=0.812)
14:37:13    Checking sparseness 0.811 . . . CV correlation 0.199 (0.463) (cost=0.810)
14:43:00    Checking sparseness 0.845 . . . CV correlation 0.201 (0.457) (cost=0.807)
14:48:50    Checking sparseness 0.866 . . . CV correlation 0.202 (0.452) (cost=0.807)
14:55:51    Checking sparseness 0.879 . . . CV correlation 0.202 (0.451) (cost=0.807)
15:04:02    Checking sparseness 0.856 . . . CV correlation 0.201 (0.453) (cost=0.807)
15:11:00    Checking sparseness 0.866 . . . CV correlation 0.202 (0.452) (cost=0.807)
  Found optimal sparsenes 0.866 (CV corr=0.202 p=0.0983)
  WARNING: Poor cross-validated accuracy, returning NULL result.
15:18:11 Preparing images...
15:18:11 Logging call details...
15:18:11 Done! 2.2 hours
```

SCCAN



SVR-LSM (dTLVC)

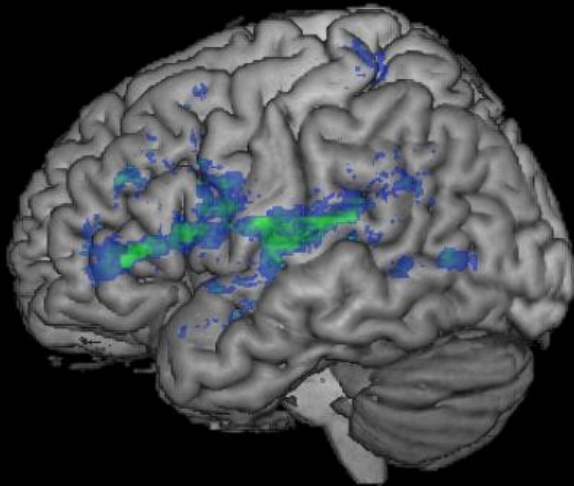


SCCAN versus other methods

- SCCAN often finds similar or more significant voxels compared to other methods

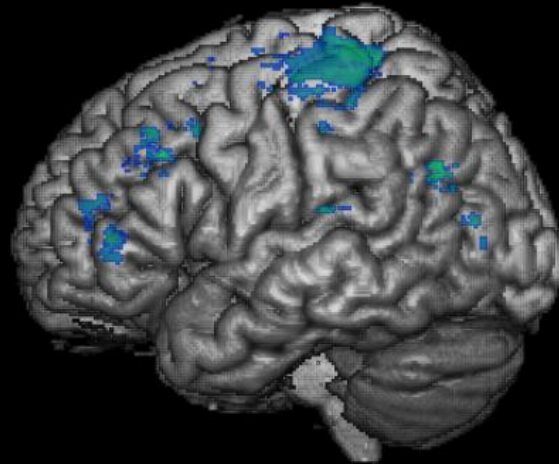
T-test

Lesion Correction: None

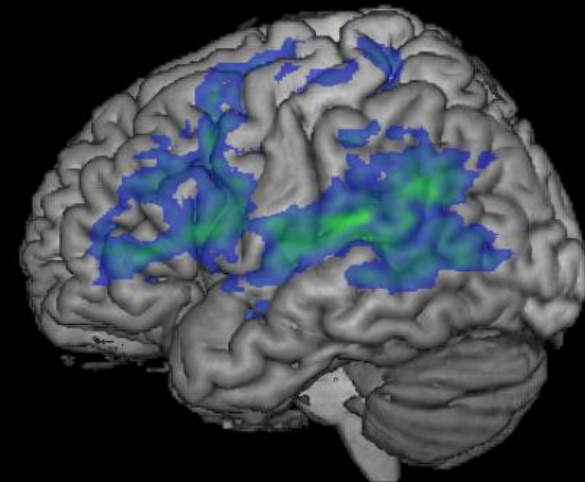


SVR Voxel-Corrected Map

Lesion Correction: Regress on Both



SCCAN



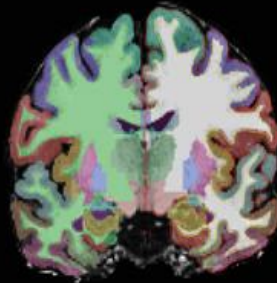
- How do we decide these findings are real and not spurious?
 - No total lesion volume correction by default
 - No voxel-level multiple-comparisons correction necessary
 - Built-in minimum cluster size; should we still threshold post-hoc?

Connectome-based Lesion Symptom Mapping

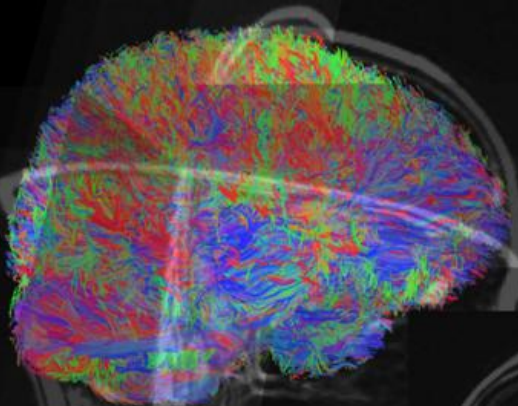
Structural connectivity



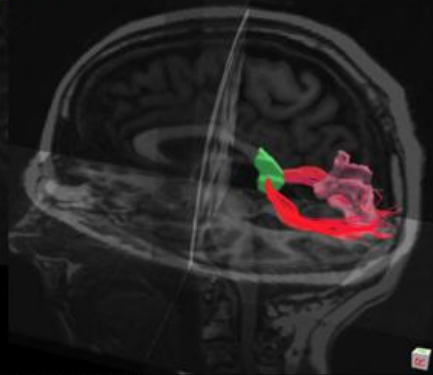
FreeSurfer



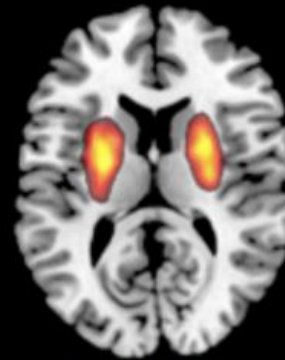
DTI
and
fiber tracking



TrackVis



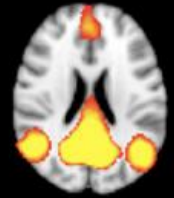
Functional connectivity



Superior Putamen

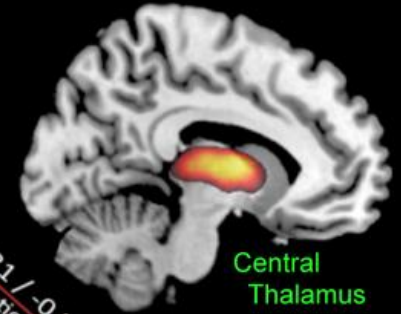
Resting state

fMRI



DMN

FSL



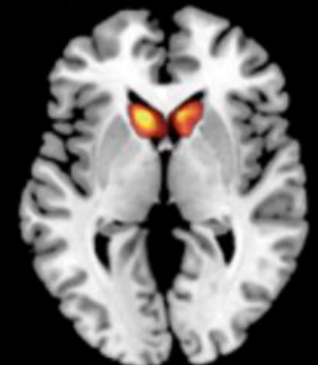
Central
Thalamus

Matlab / GIFT

PC1 = -0.31 / -0.22
Functional Correlation $r = 0.25$

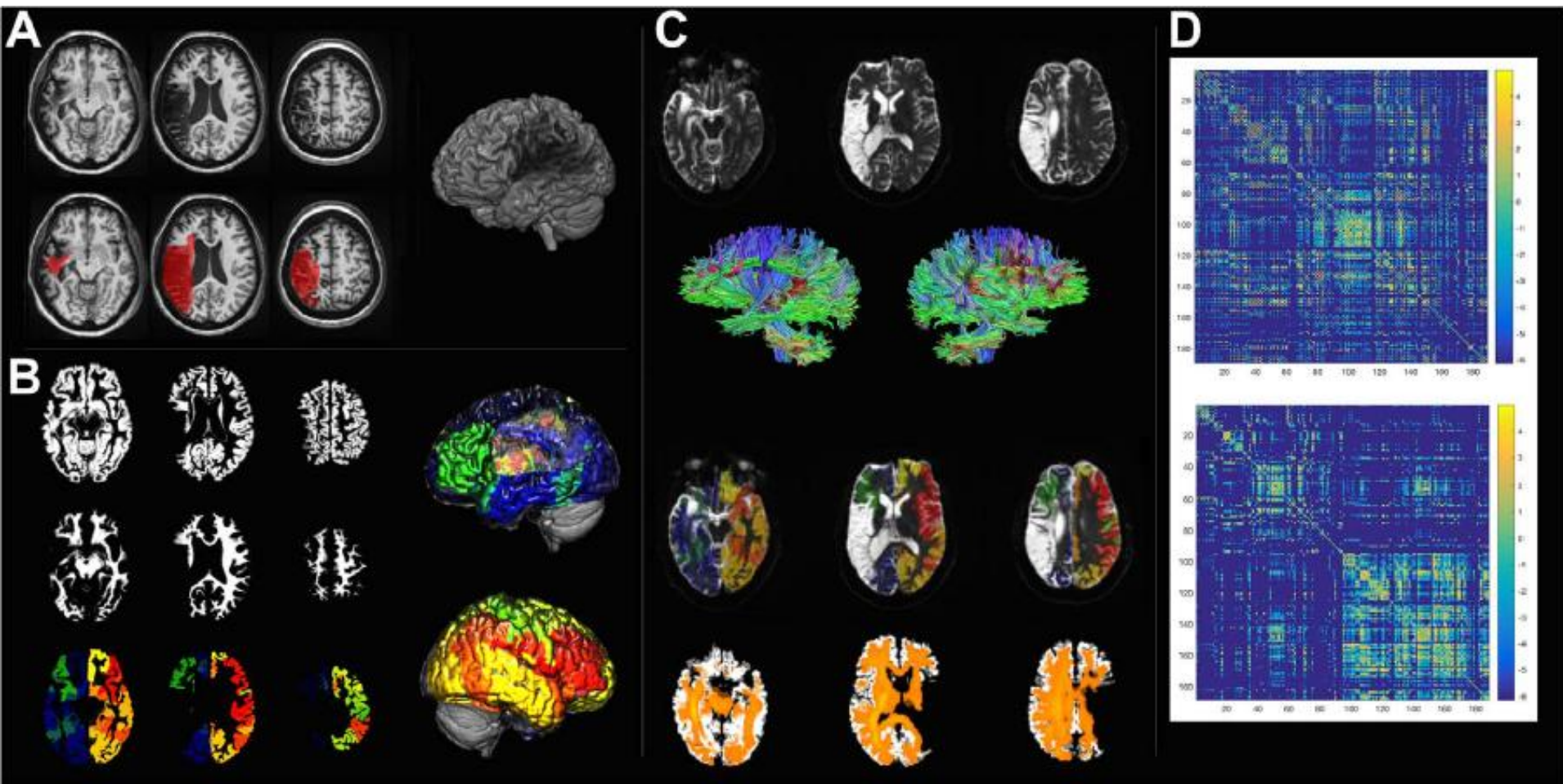


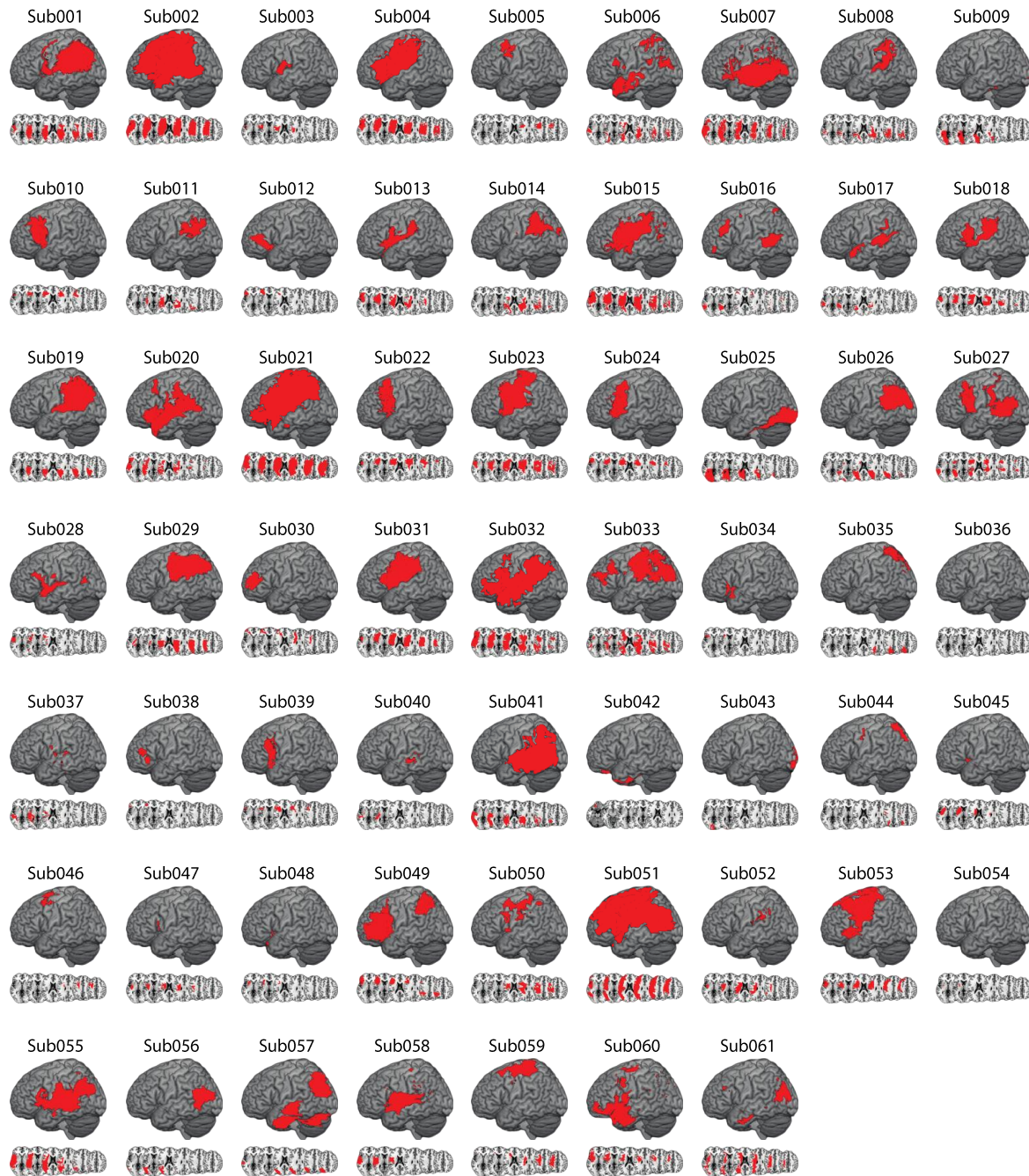
Autopsy

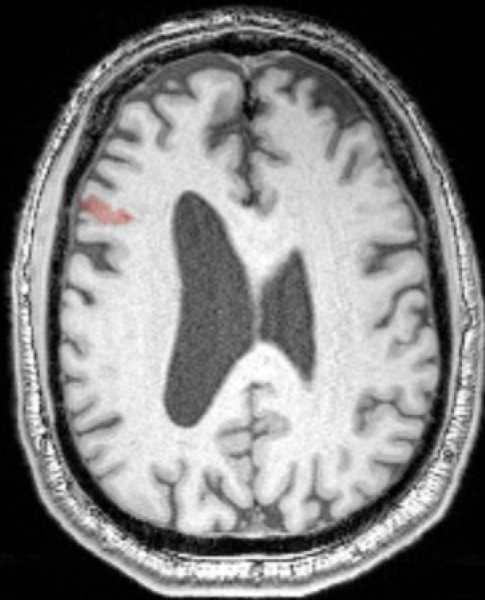
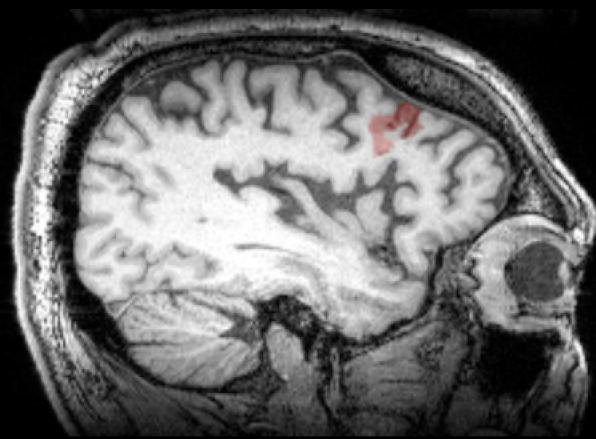
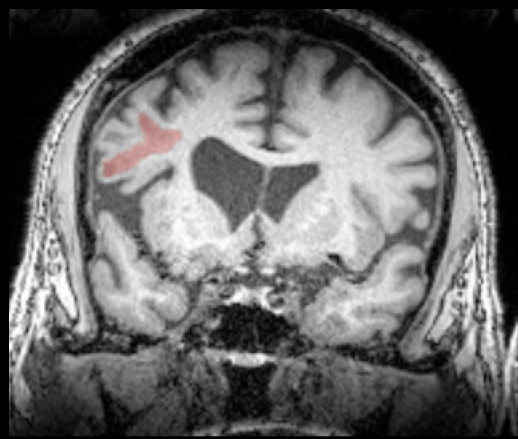


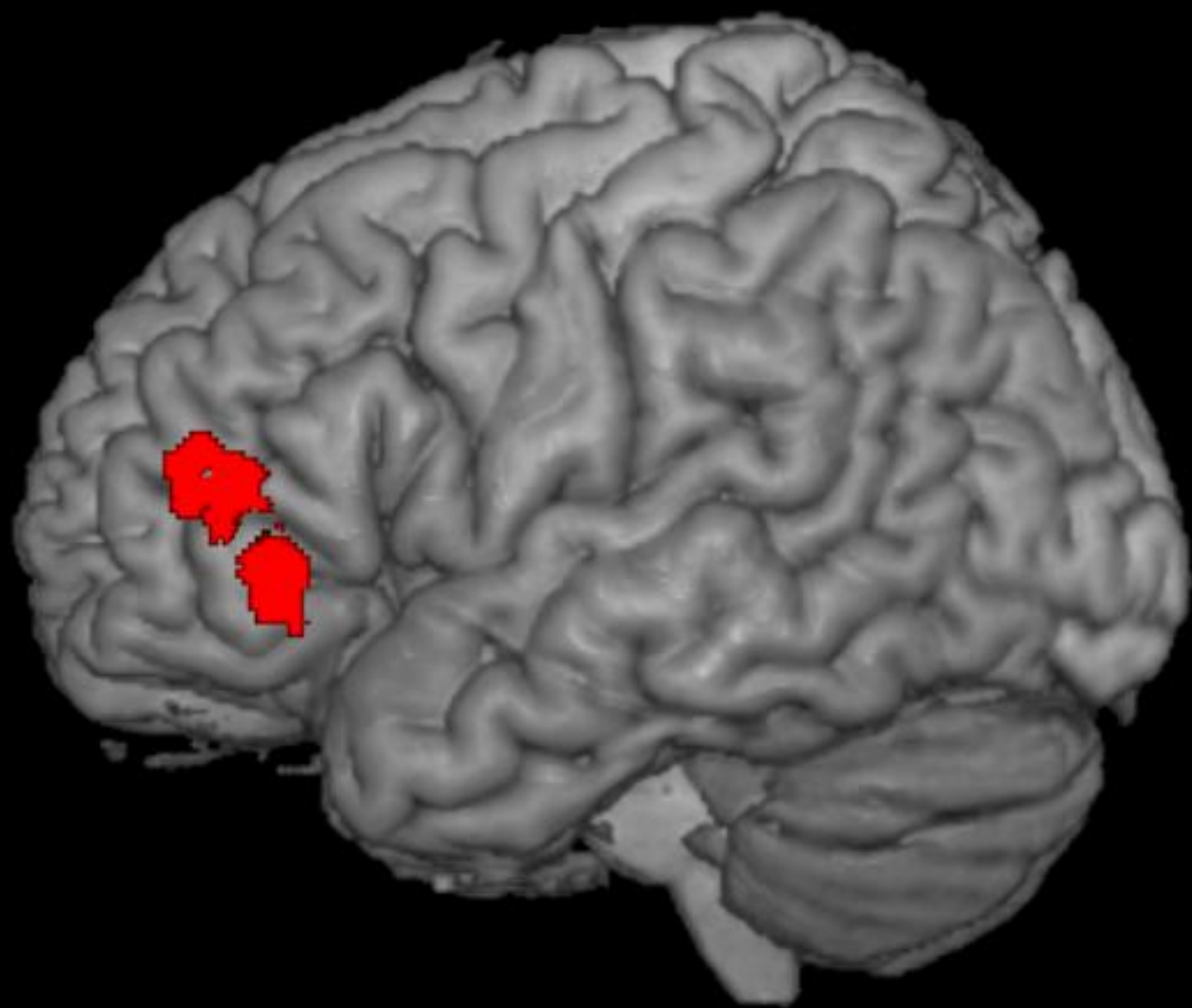
Caudate Nucleus

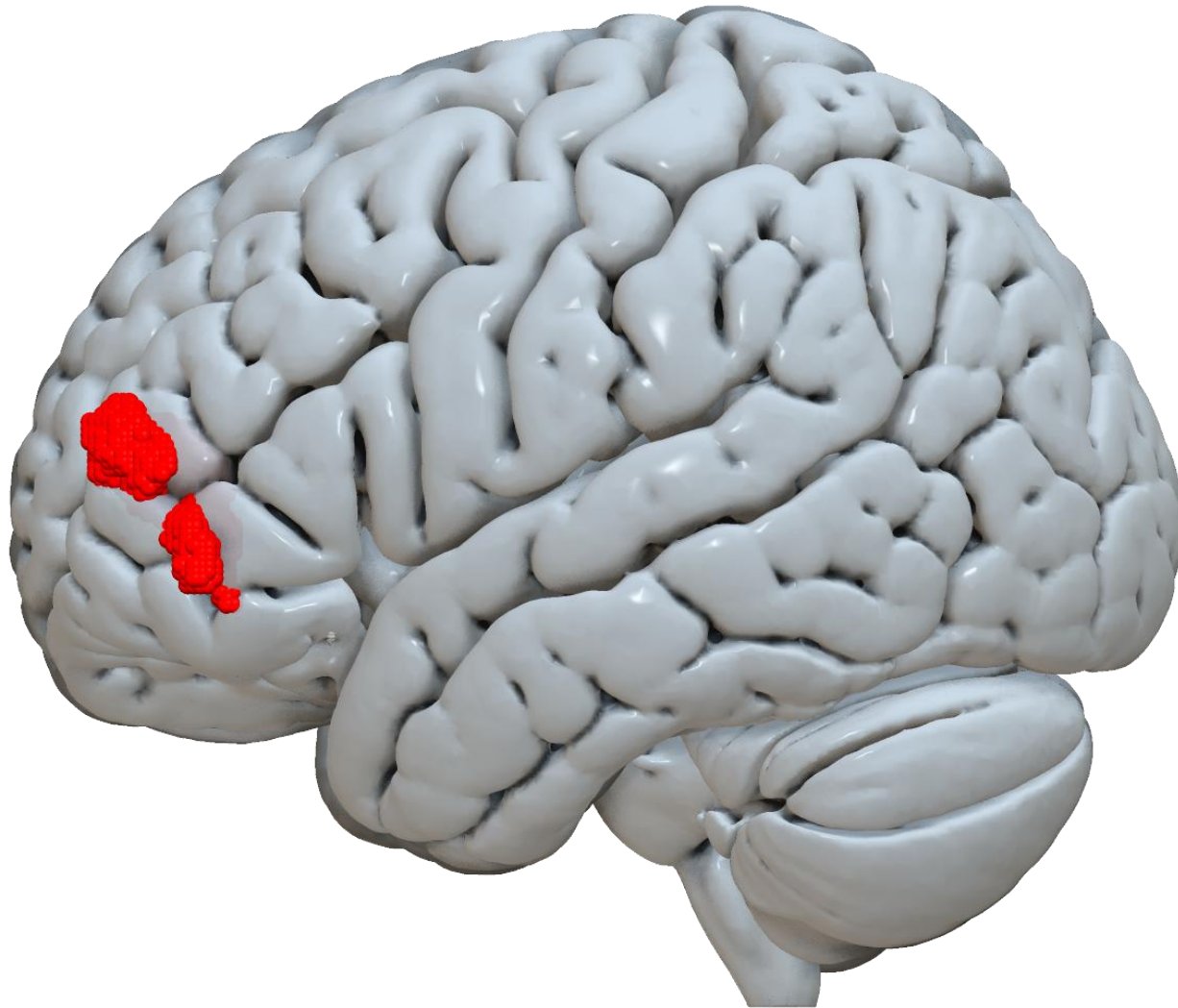
Connectome-based Lesion Symptom Mapping

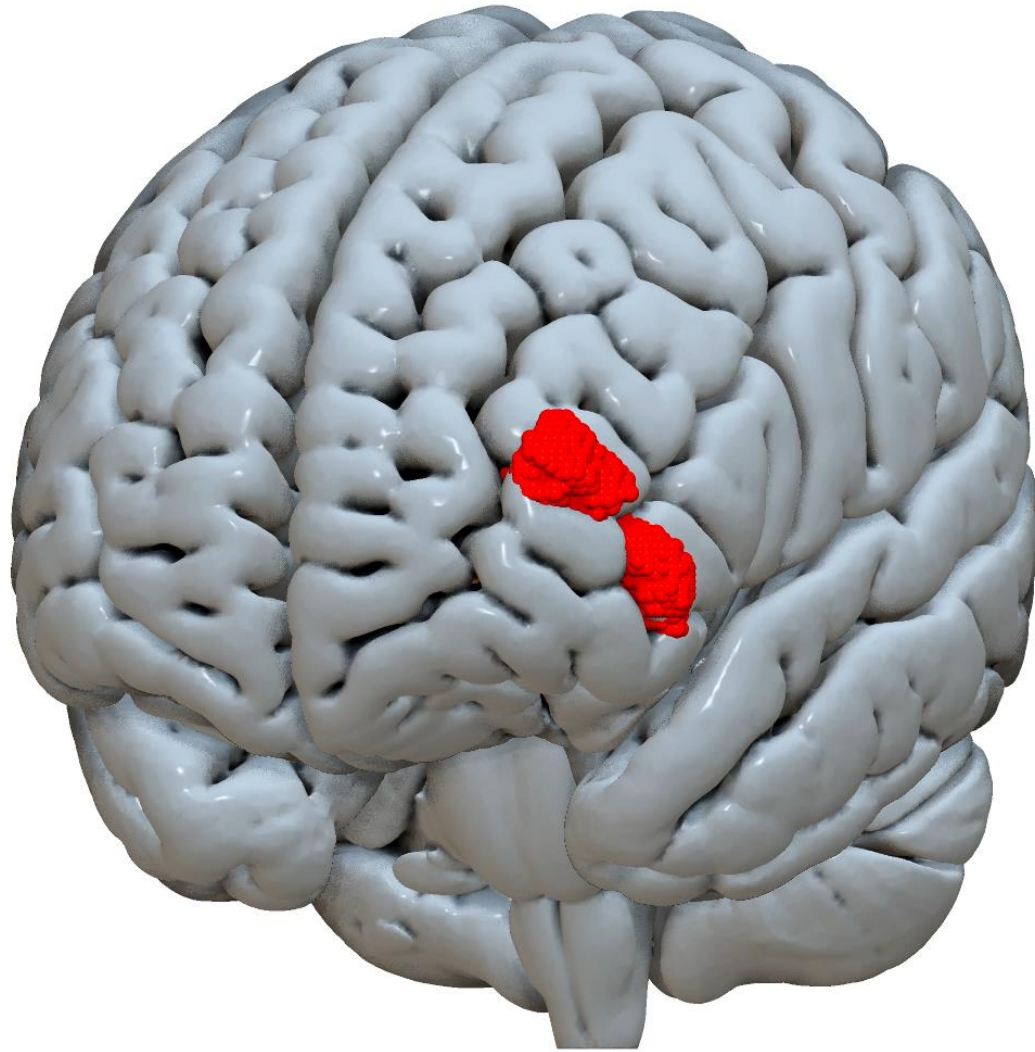


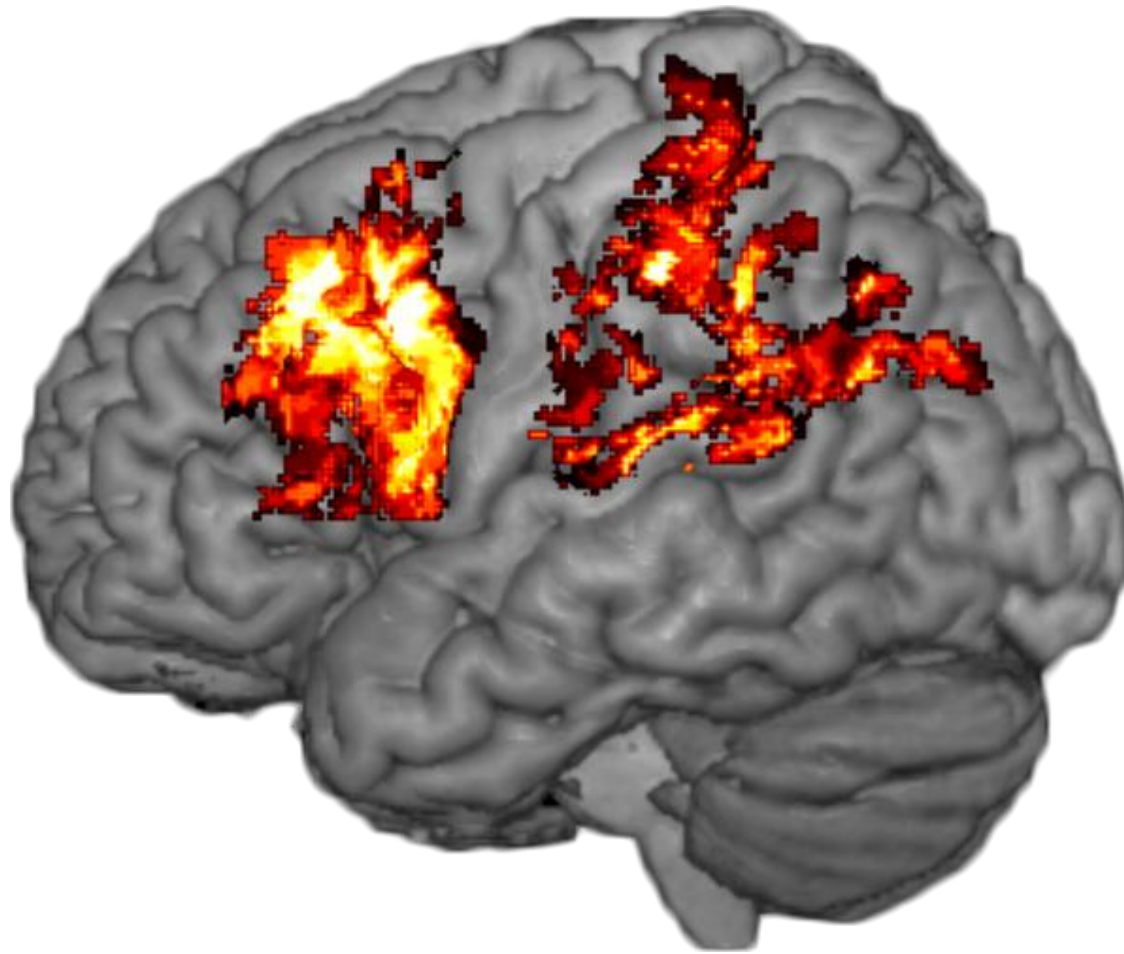


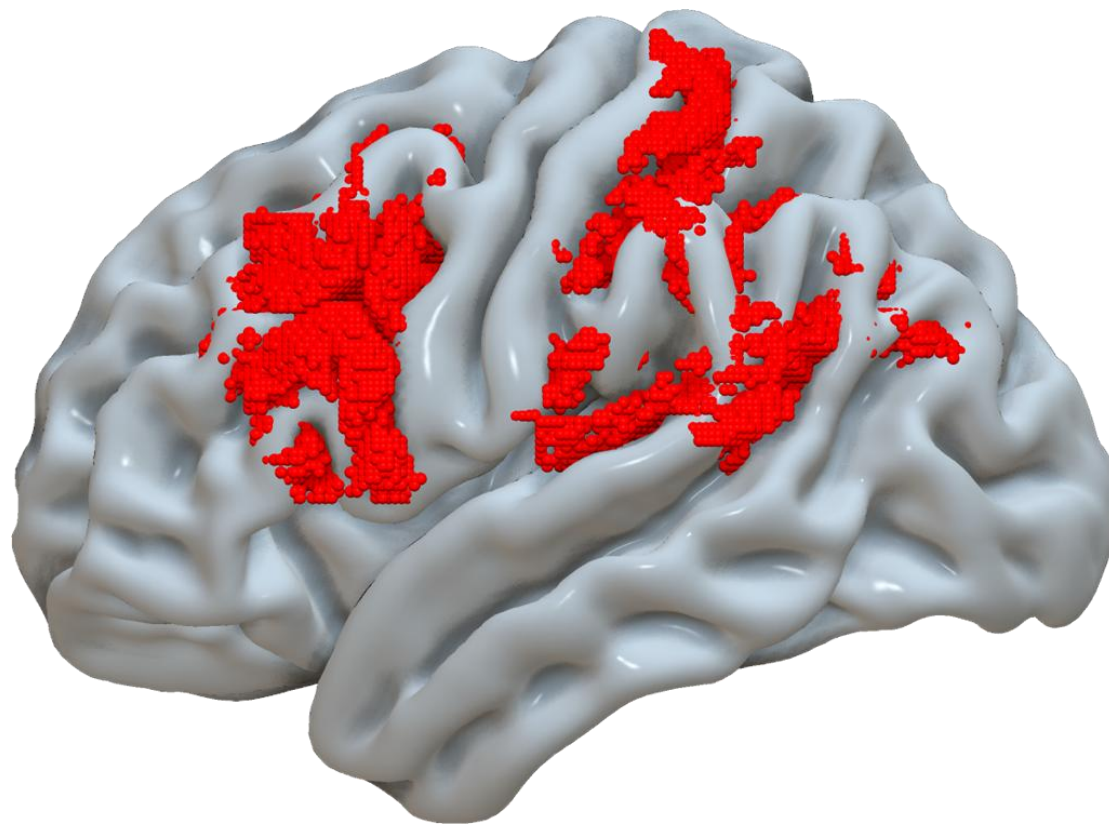


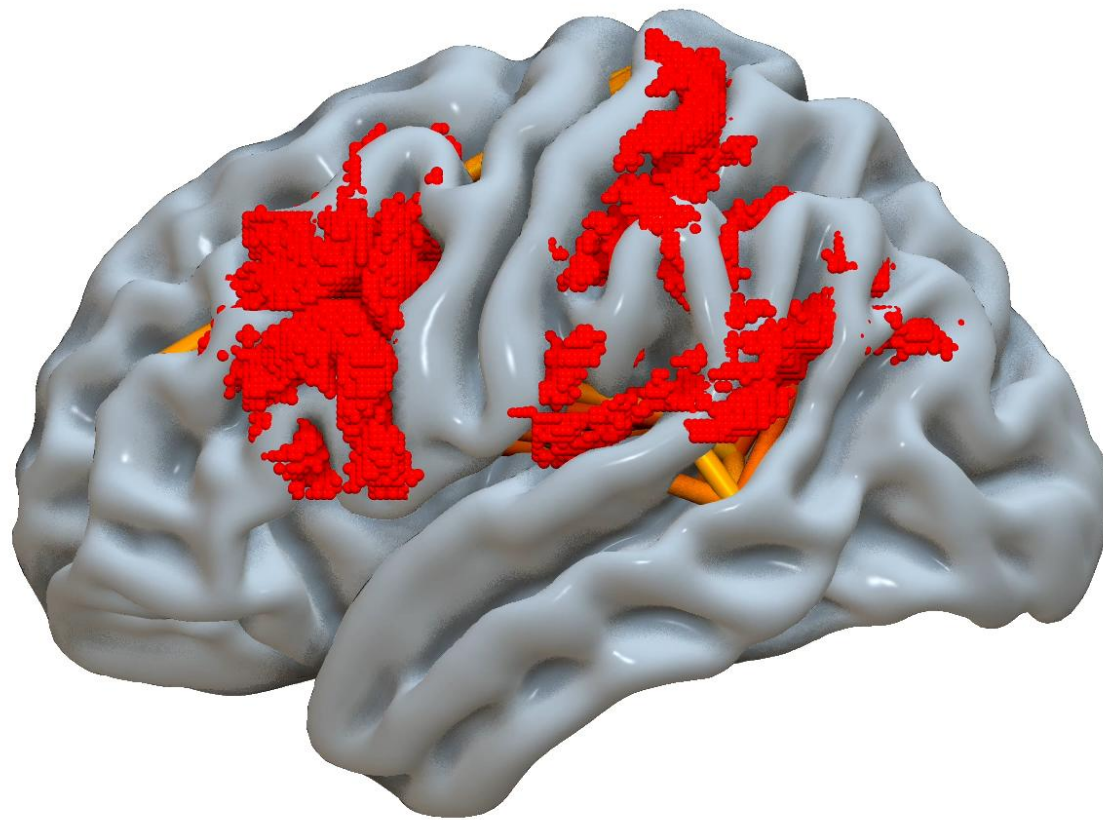












Tool Use Disconnection Network

