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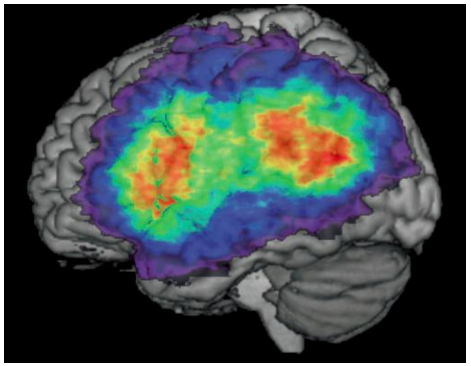
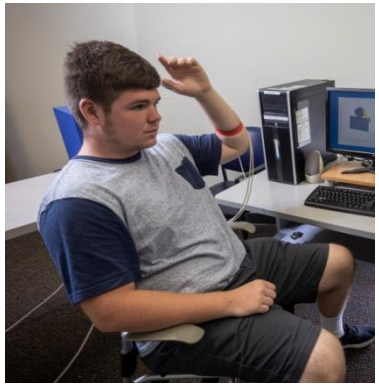
Lesion-Symptom Mapping Workshop



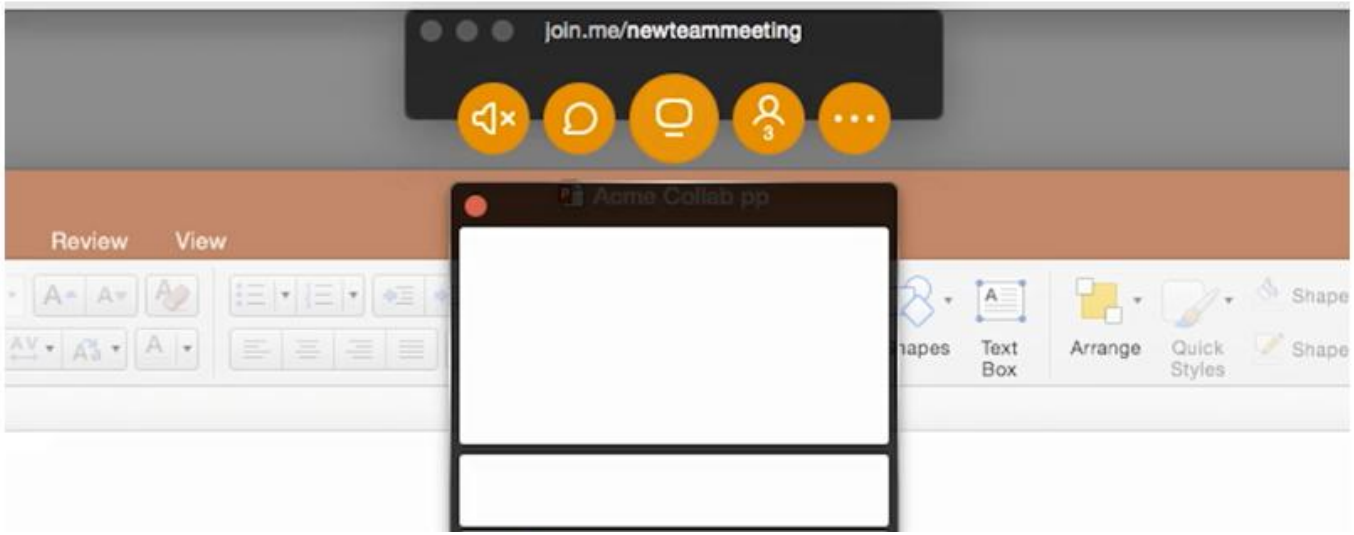


Speakers:
Frank Garcea
Harrison Stoll
Austin Wild

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

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- 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

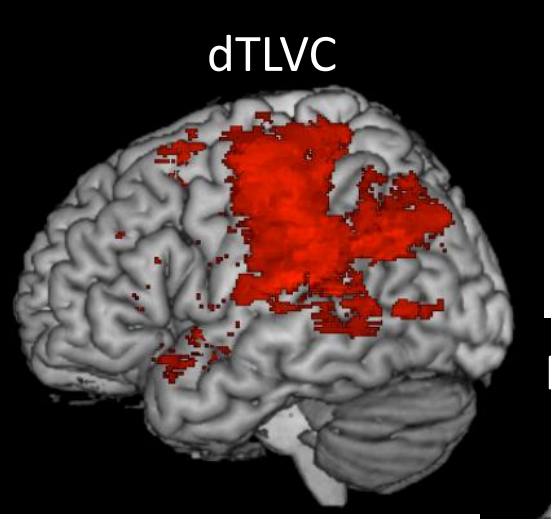
- VLSM
  - Perform a t-test at each voxel
  - Large number of tests, (incorrectly) assumed to be independent
- SVR-LSM
  - Perform a single multivariate regression, with significance determined using permutation testing
  - P values still determined at the voxel level
  - Unclear how to properly correct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

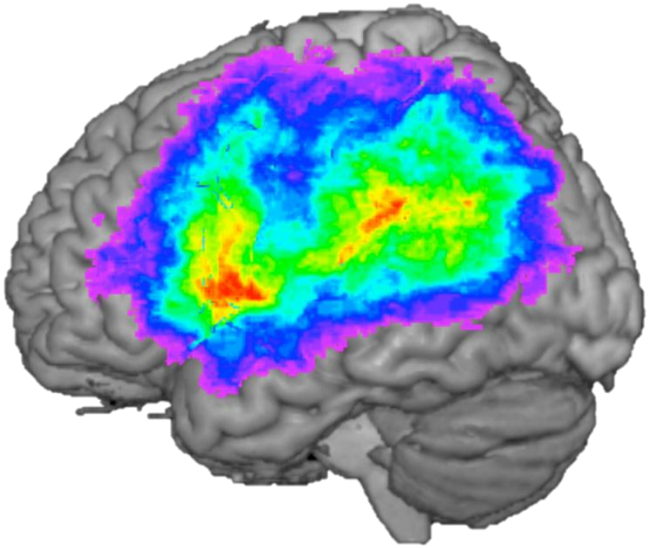
SVR-LSM: Correcting for lesion volume

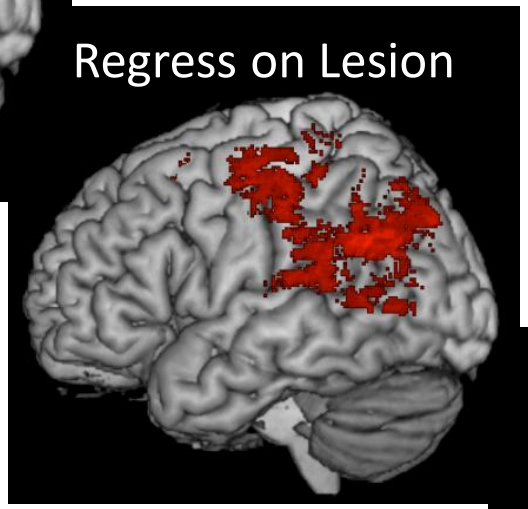
- dTLVC: normalize lesion status by 1/sqrt(TLV)
- Regress on Lesion: Regress lesion status on TLV, use residuals
- Regress on Behavior: Regress behavior on TLV, use residuals
- Regress on Both

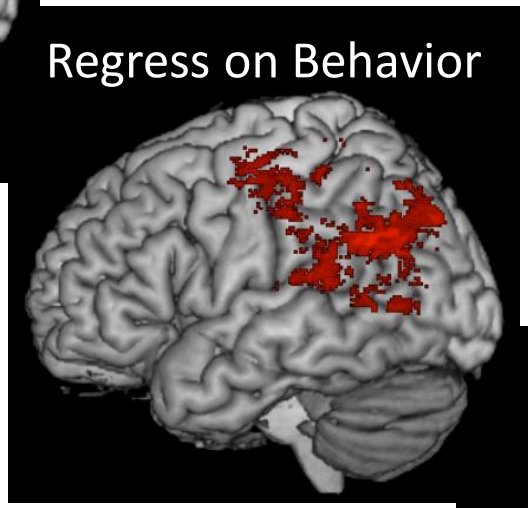
#	Method	Corrects behavior	Corrects lesion data
1	No correction	✗	✗
2	dTLVC (Zhang et al., 2014)	✗	Partial
3	Regress on Behavior	✓	✗
4	Regress on Lesion	✗	✓
5	Regress on Both	✓	✓

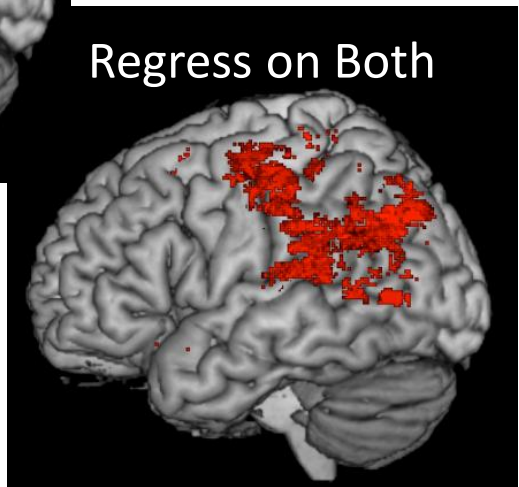
(DeMarco et al 2017)


dTLVC




Regress on Lesion

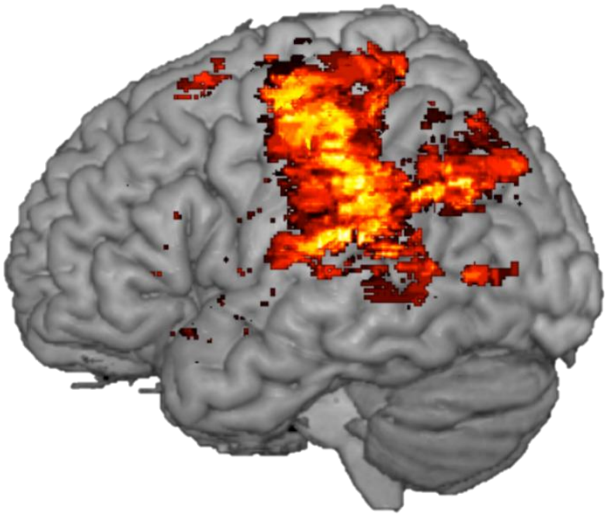

Regress on Behavior


Regress on Both

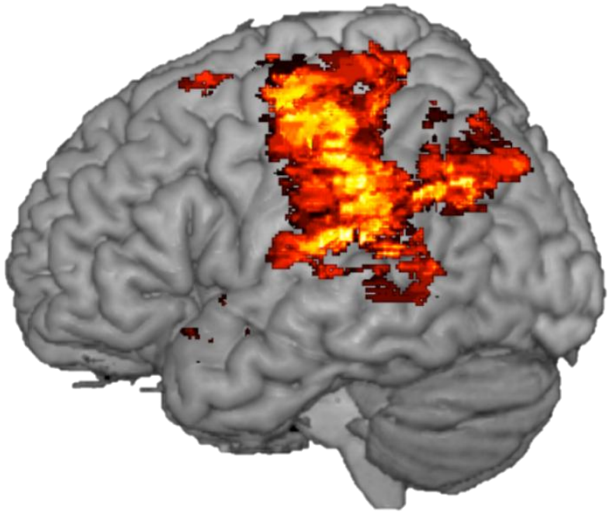
SVR-LSM:
Correcting for multiple comparisons

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

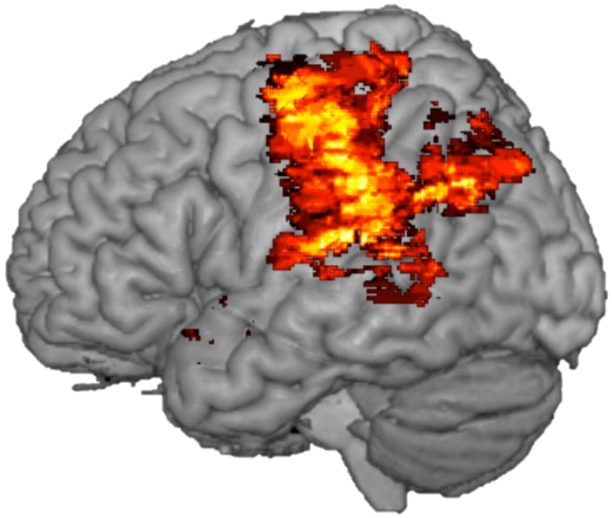
No Correction



Cluster-size threshold



Cluster-size Correction

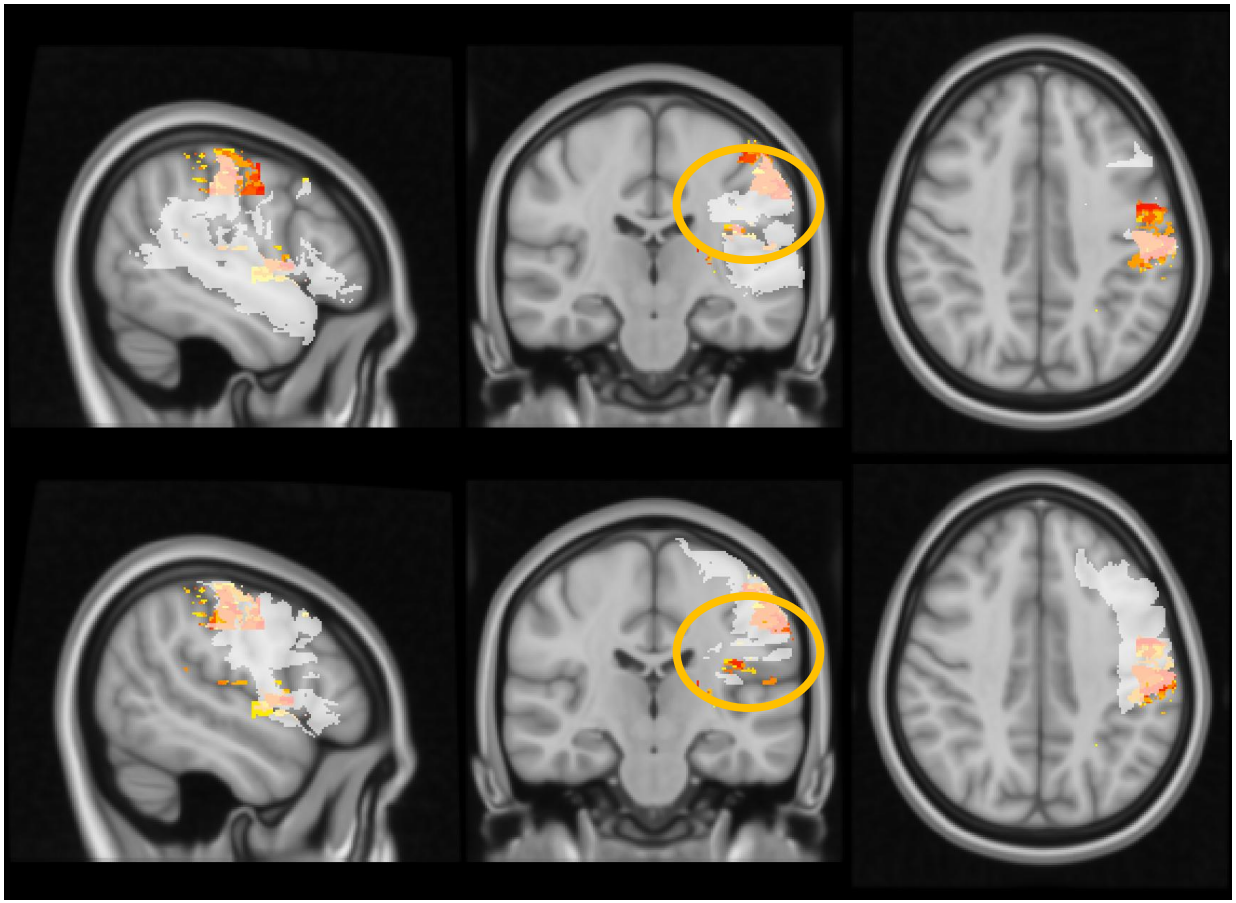


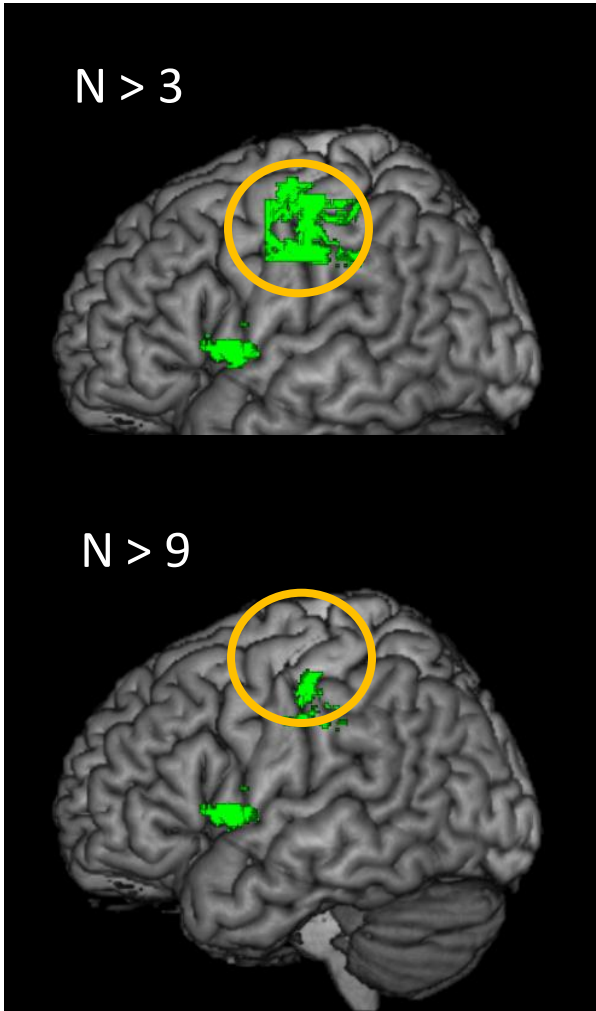
SVR-LSM: Correcting for multiple comparisons

- 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

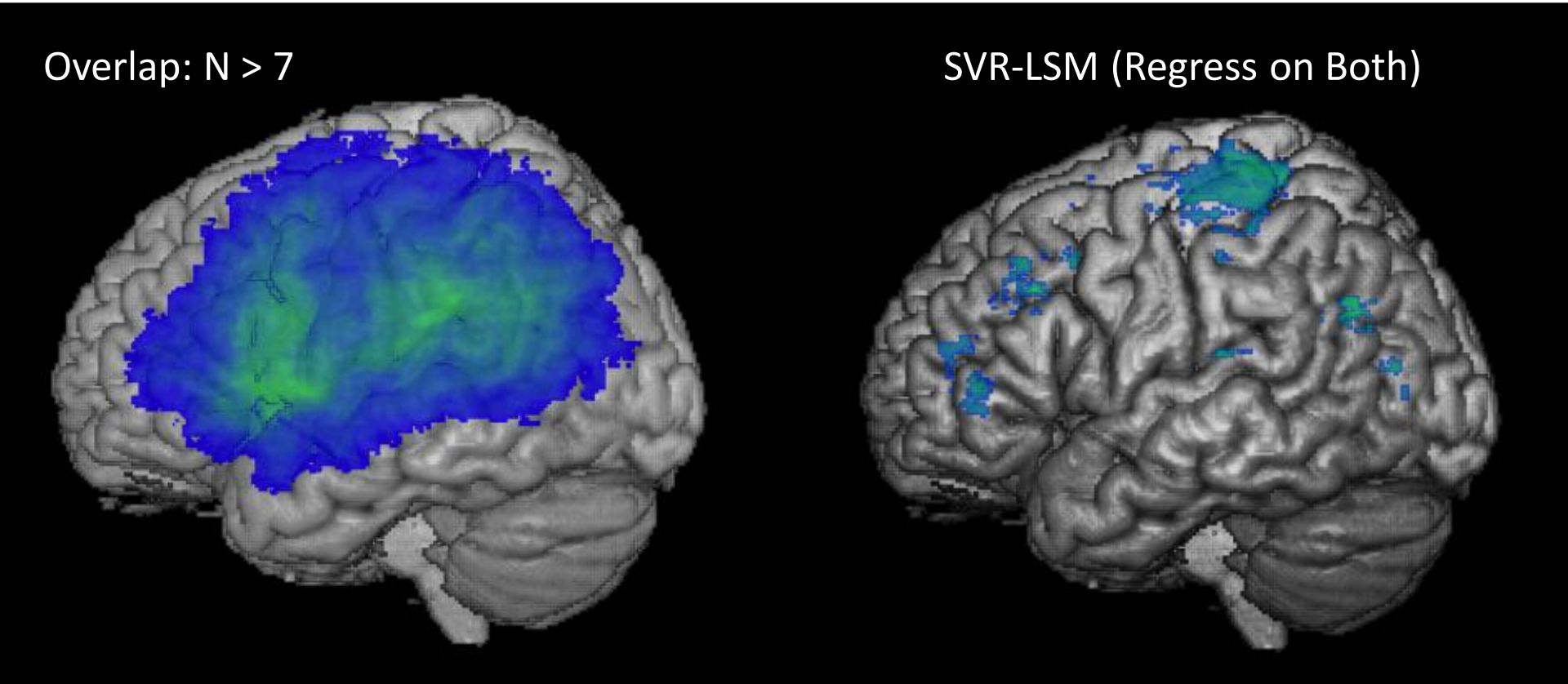
- A few subjects can strongly influence the outcome (e.g., at low N)





SVR-LSM: Boundary Effects

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



SVR-LSM

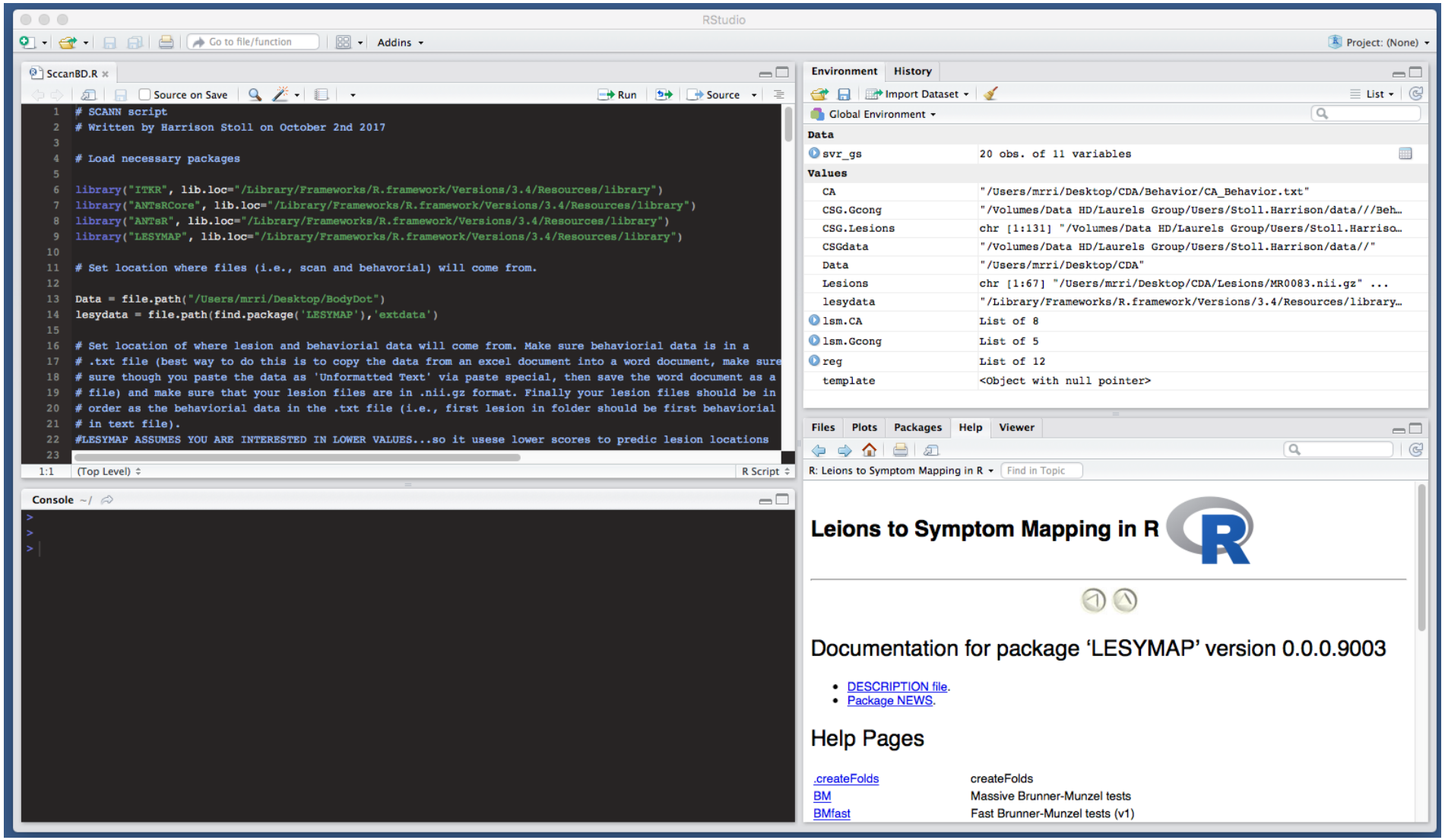
- Theoretically an improvement over VLSM
- In practice, SVR-LSM is not without its own set of problems
- Is SVR-LSM the right tool for low N?
- We try to look for consistency across analyses/correction techniques (but does this invalidate your stats?)

➢ ***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)



Canonical Correlation Analysis (CCA)

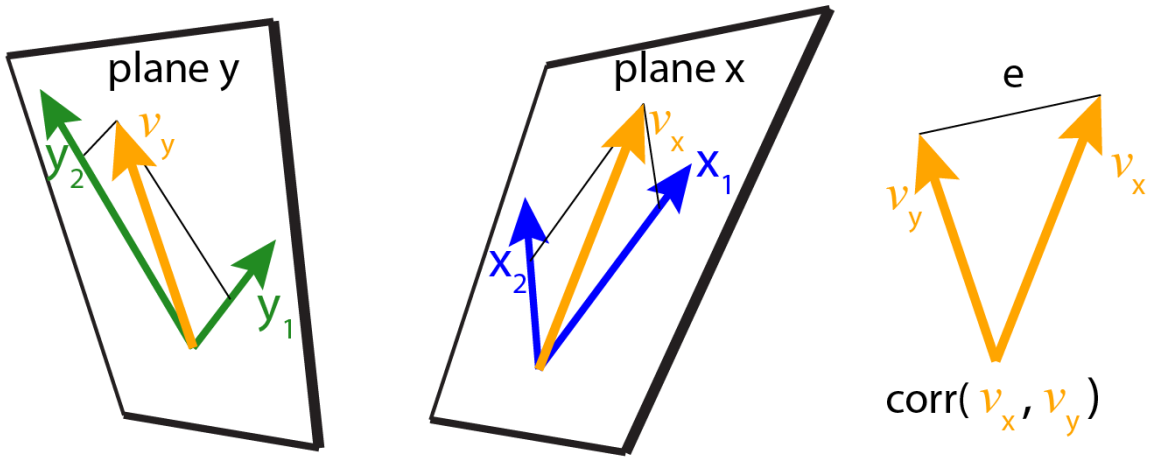
- Say we have two sets of variables:

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

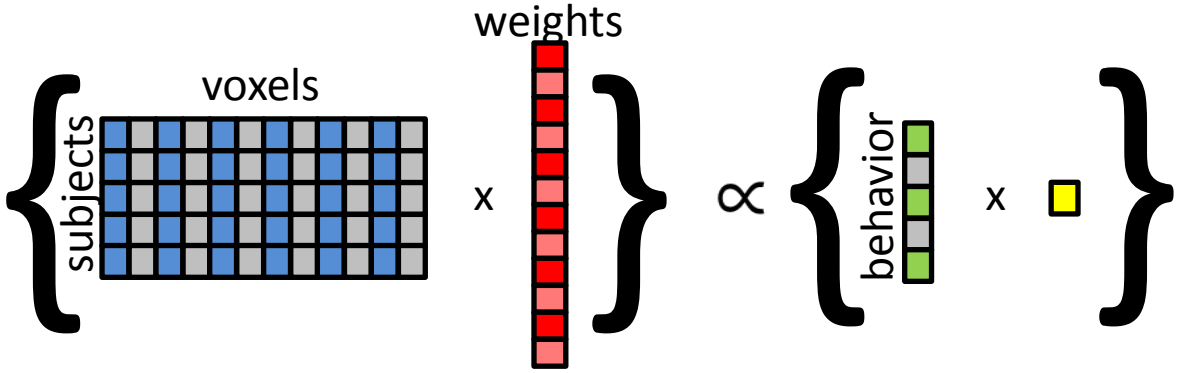
  $\mathbf{y} = \{y_1, y_2\}$
- We define some **a** and **b** such that

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

  $v_y = \mathbf{b}^T\mathbf{y}$
- We will choose **a** and **b** that maximize the *correlation* between v_x and v_y



SCCAN: An extension of CCA

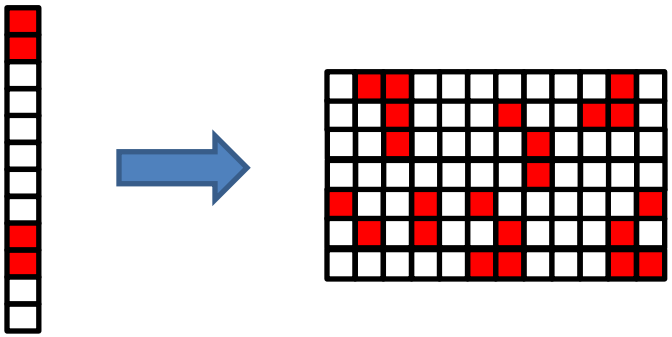


- We have a matrix of voxels on one hand, and a vector of behavior on the other
- We look for a [pair of] basis (feature weight) vectors such that the correlation of the projected voxel and behavioral data into that basis set is maximized
  - We require that basis vectors be sparse, i.e. that most of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

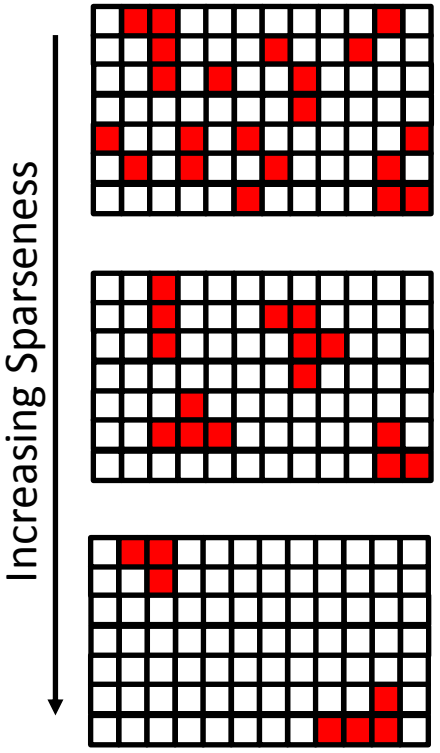
- The extent of the map depends on the sparseness value



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 threshholding a beta map)

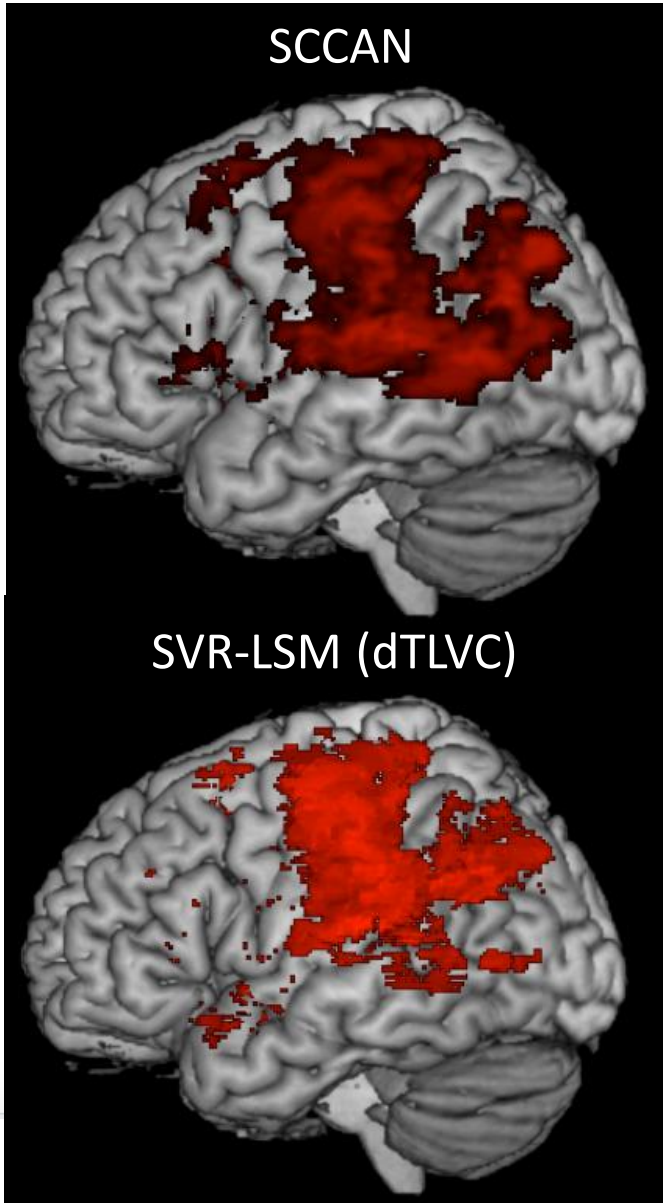


- Cross-validation gives us one *p* value for the entire map
  - This tells us if the map is interpretable or random

- 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
```



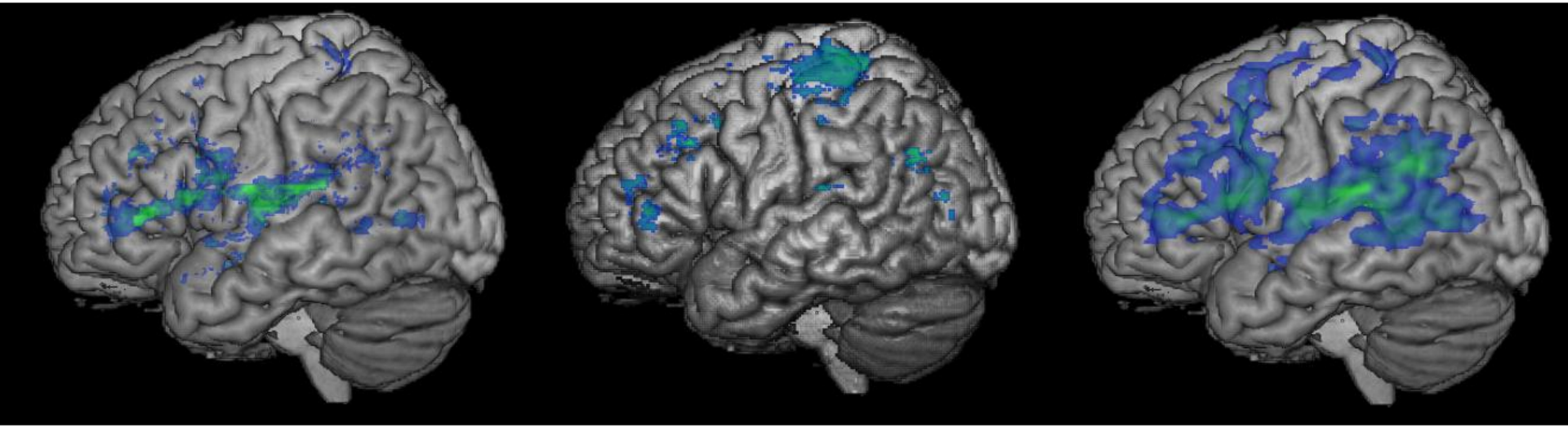
SCCAN versus other methods

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

T-test
Lesion Correction: None

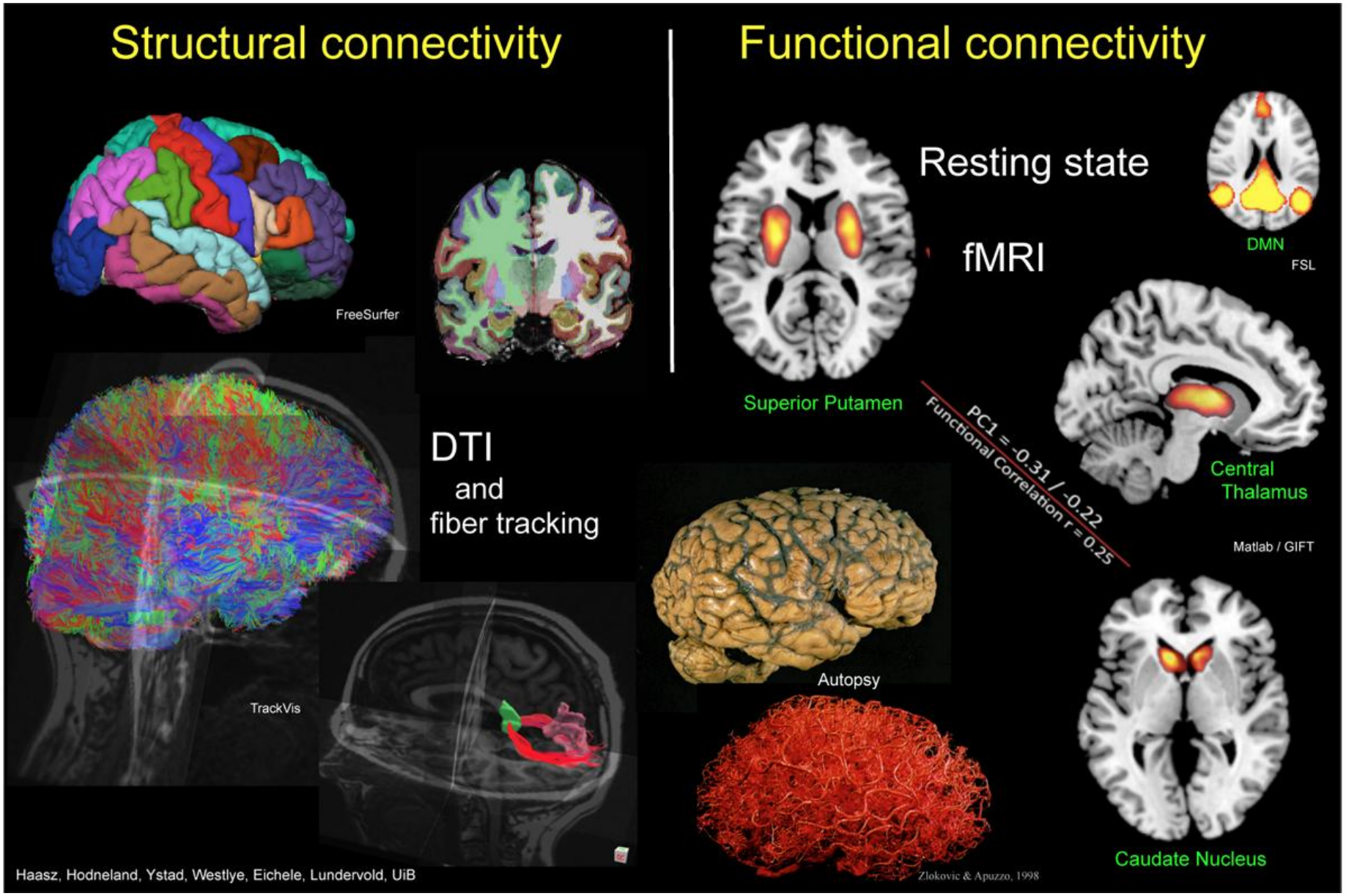
SVR Voxel-Corrected Map
Lesion Correction: Regress on Both

SCCAN

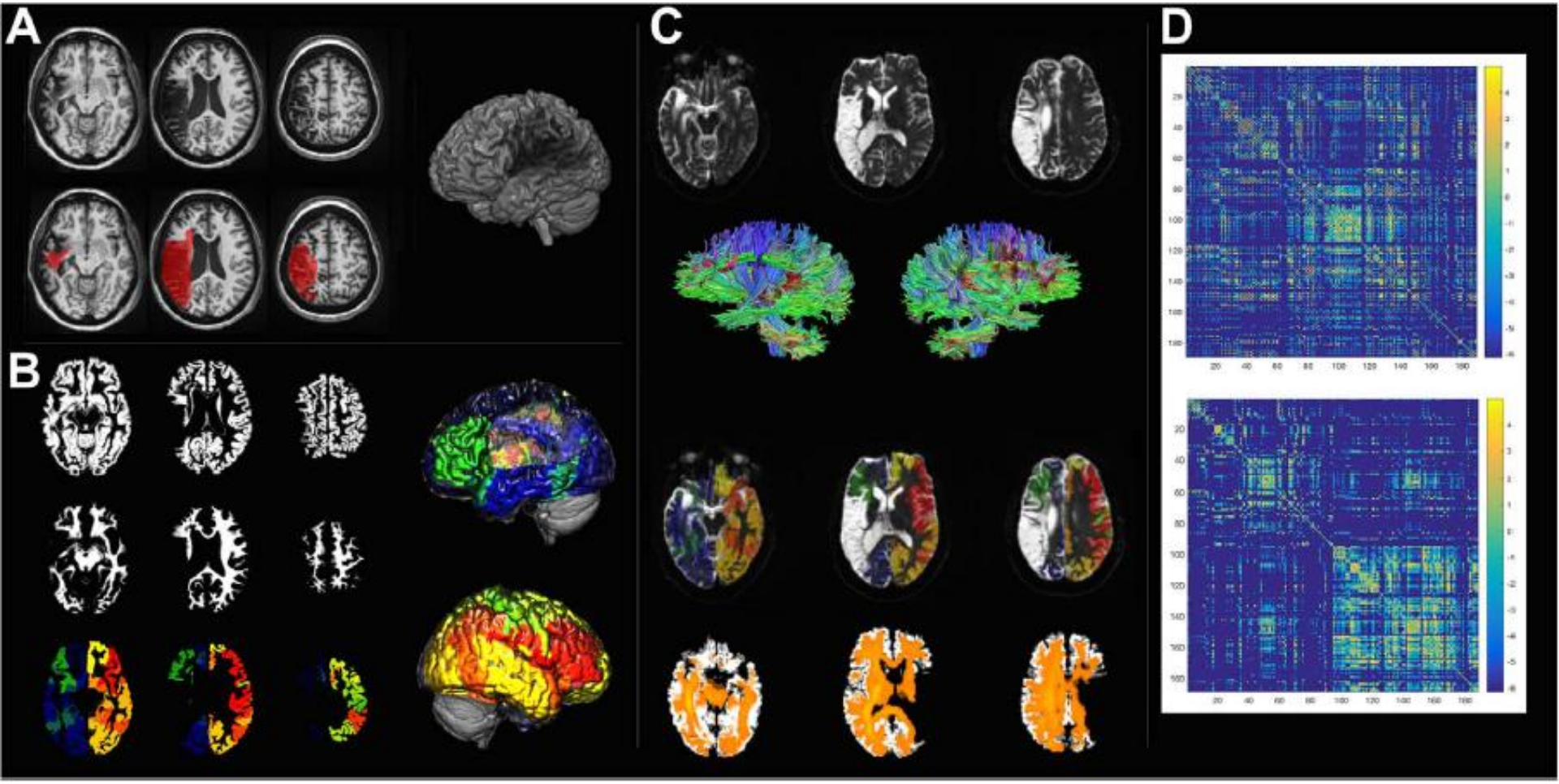


- How do we decide these findings are real and not spurious?
  - No total lesion volume correction by default
  - No voxel-level multiple-comparisons correction necessary
  - Built-in minimum cluster size; should we still threshold post-hoc?

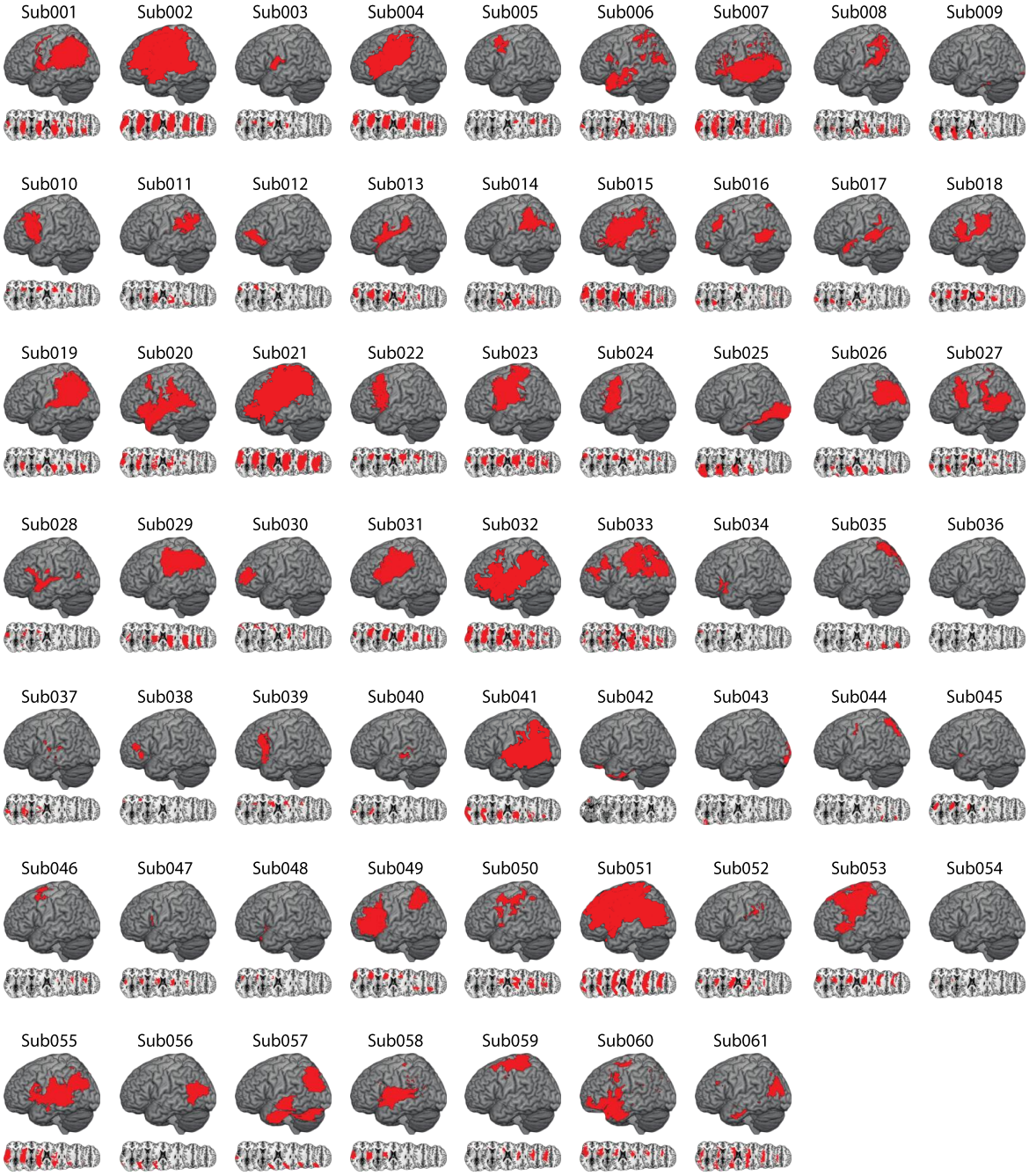
Connectome-based Lesion Symptom Mapping



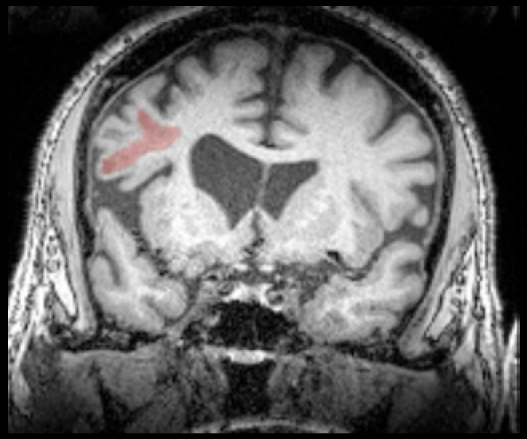
Connectome-based Lesion Symptom Mapping

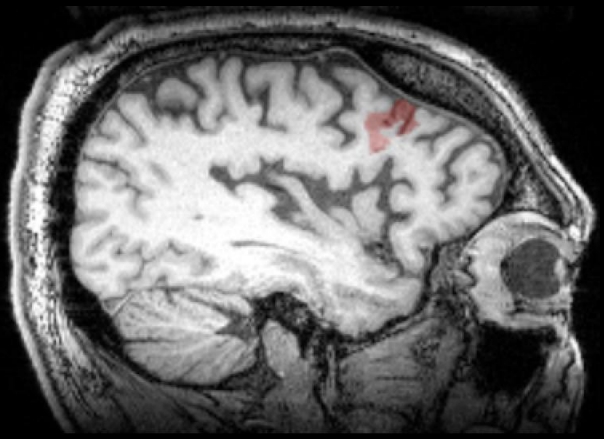


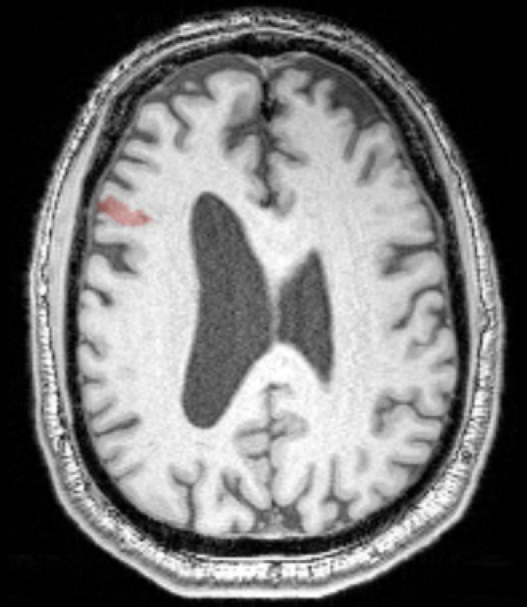
Gleichtgerrcht et al., 2018, Neuroimage: Clinical

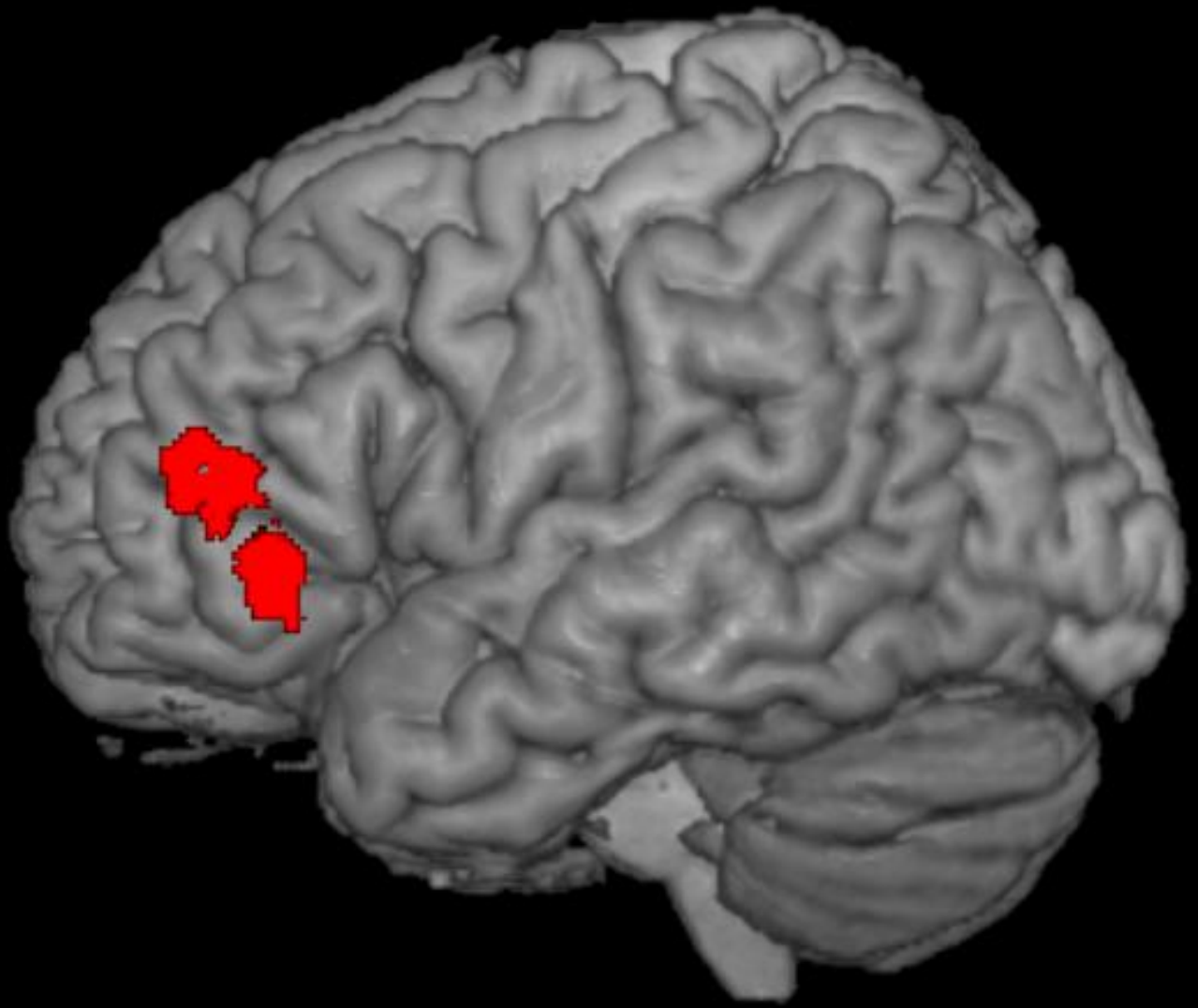


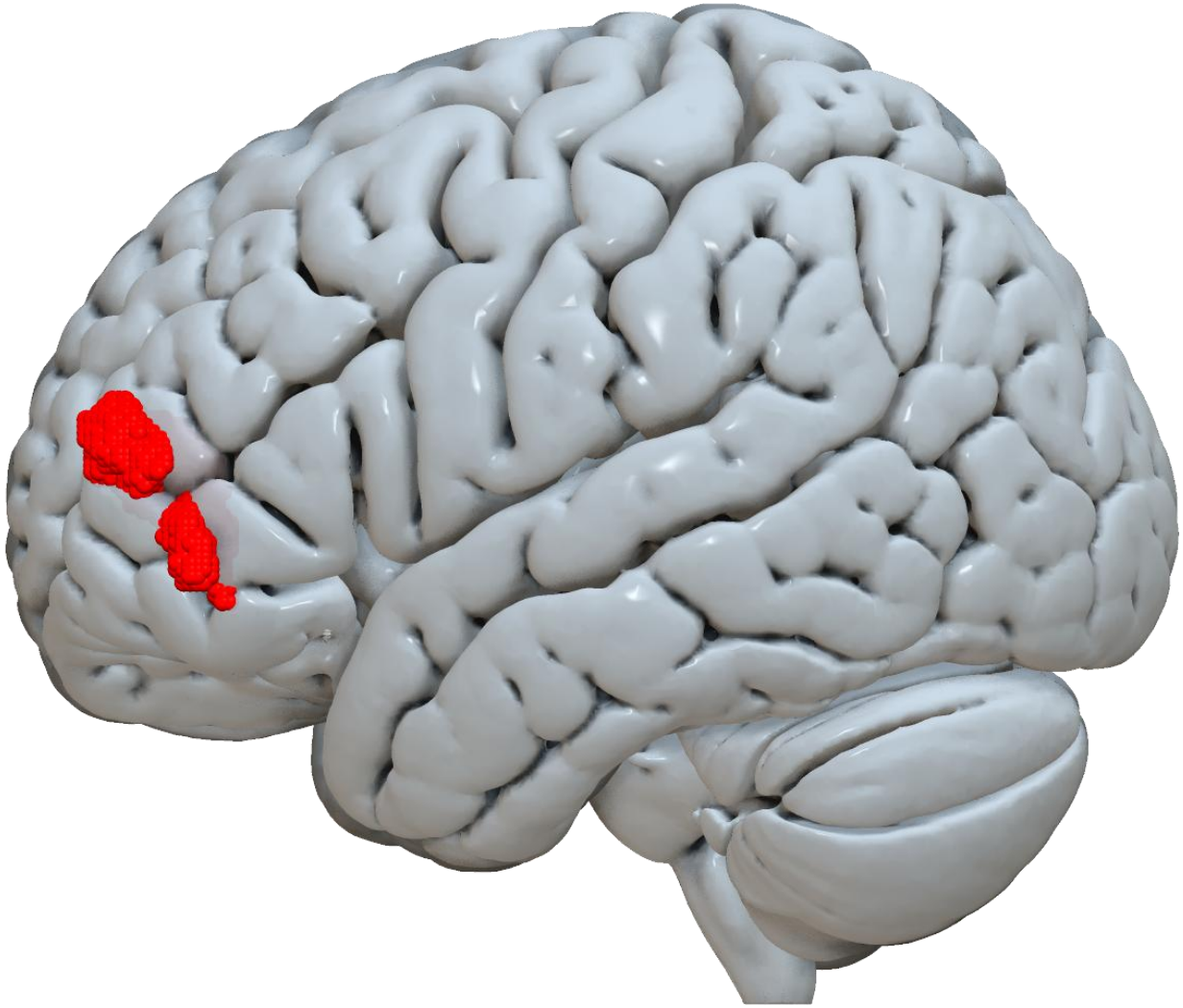
Garcea et al., in prep.

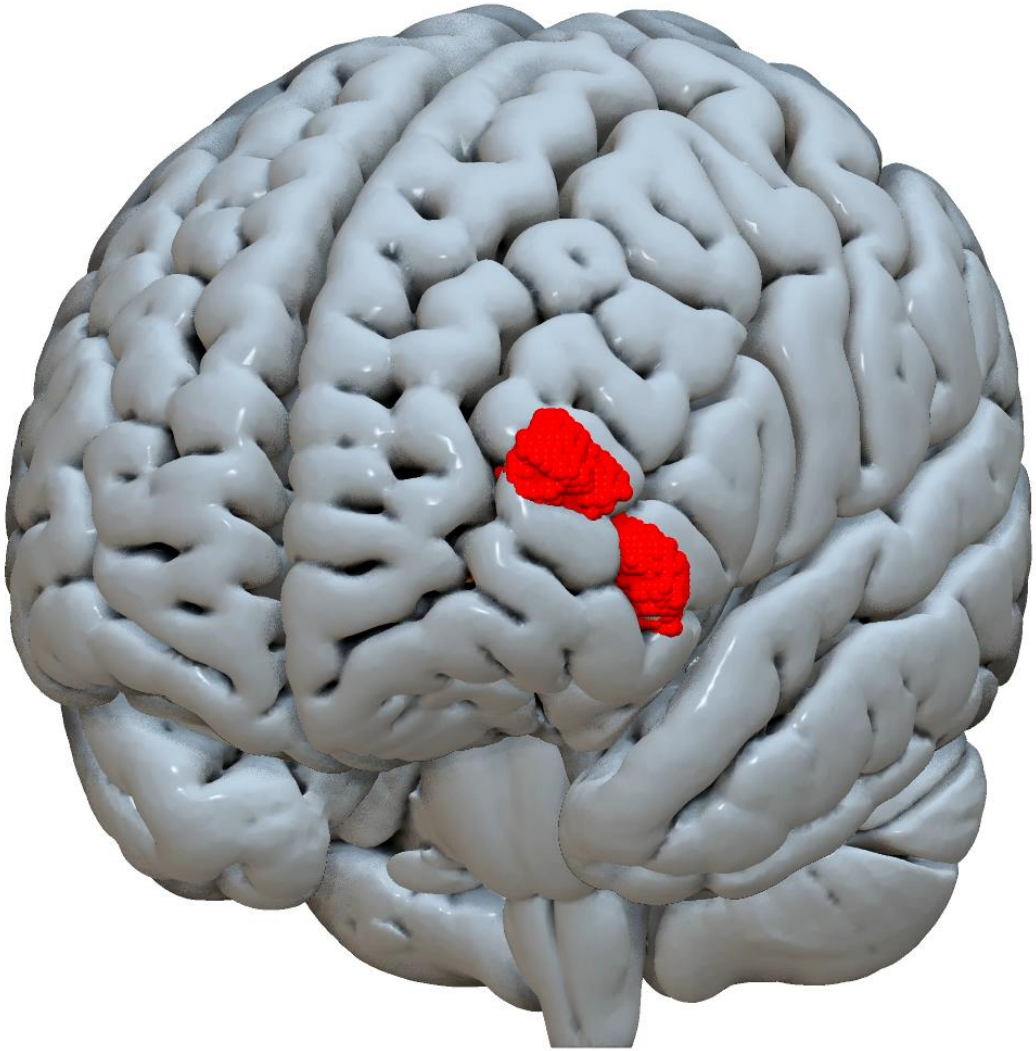


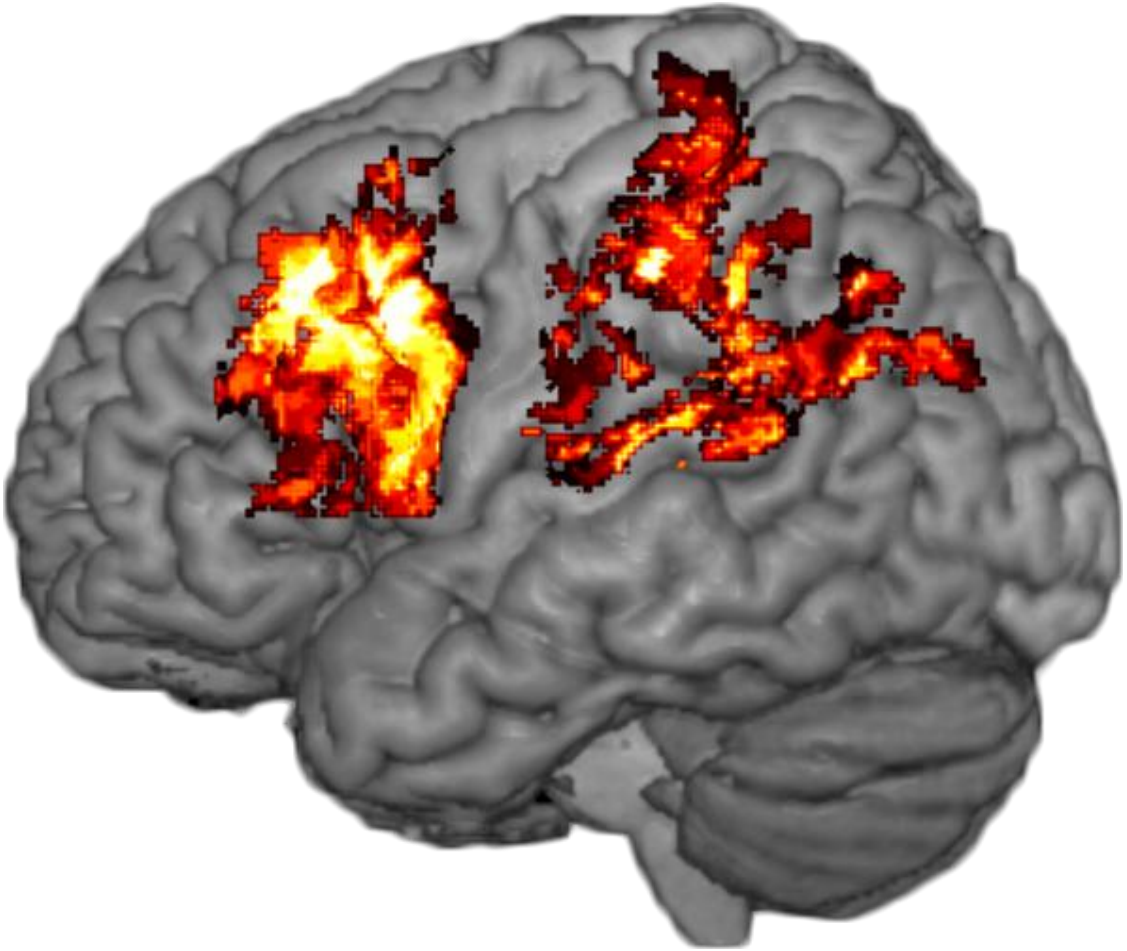




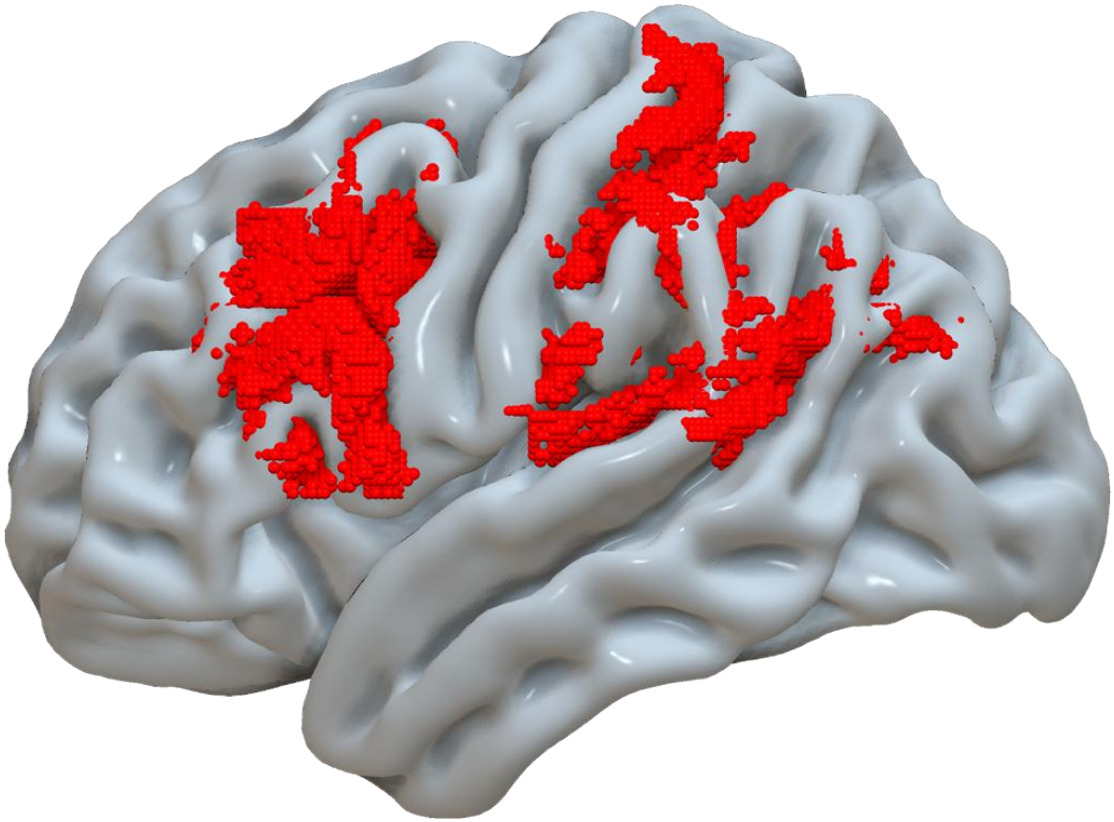








Garcea et al., in prep.



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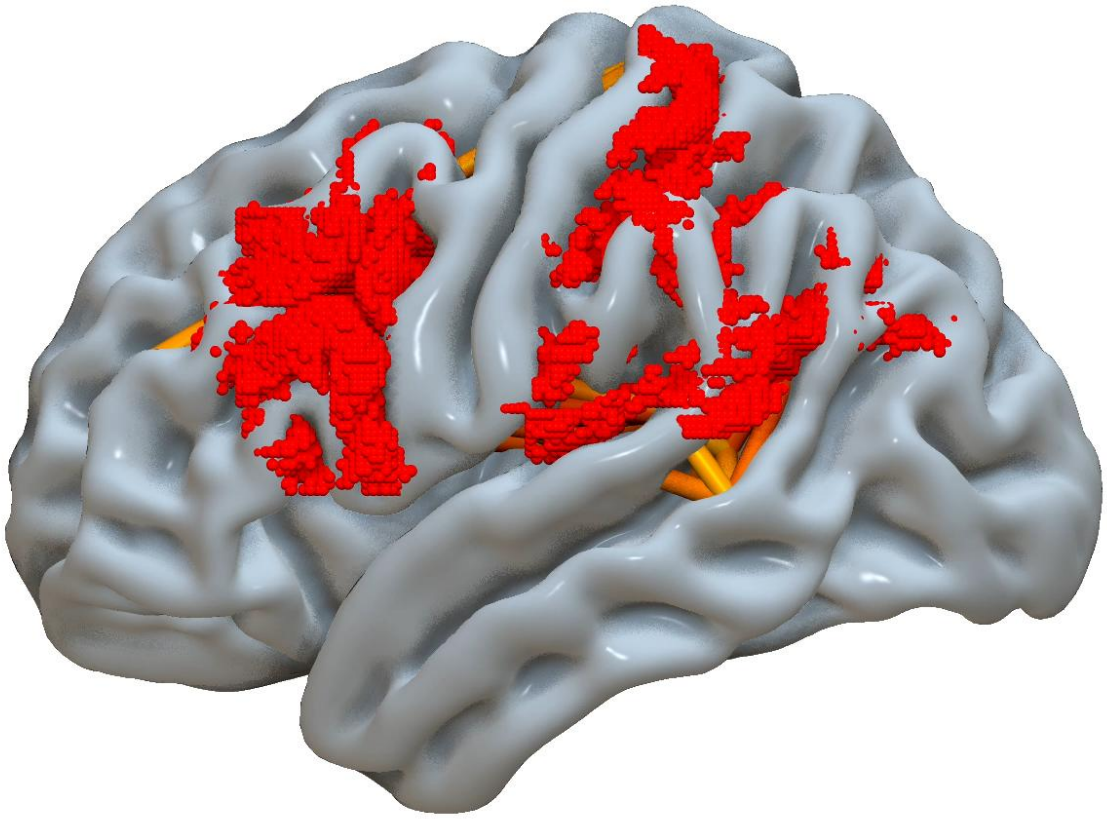
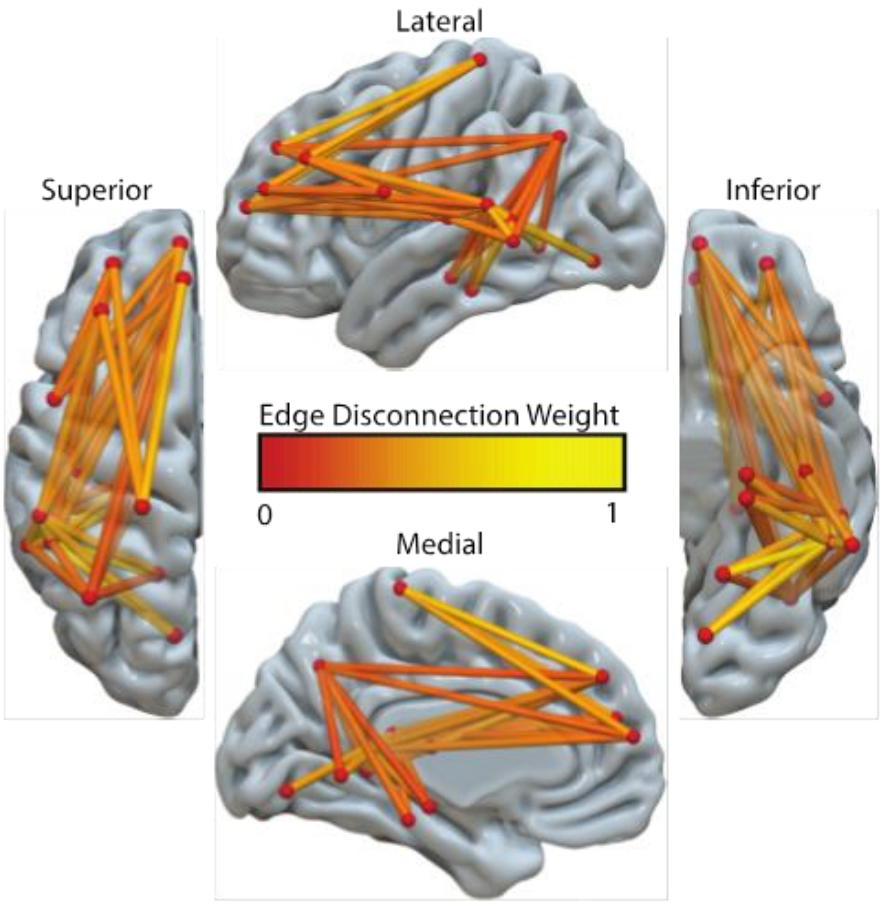
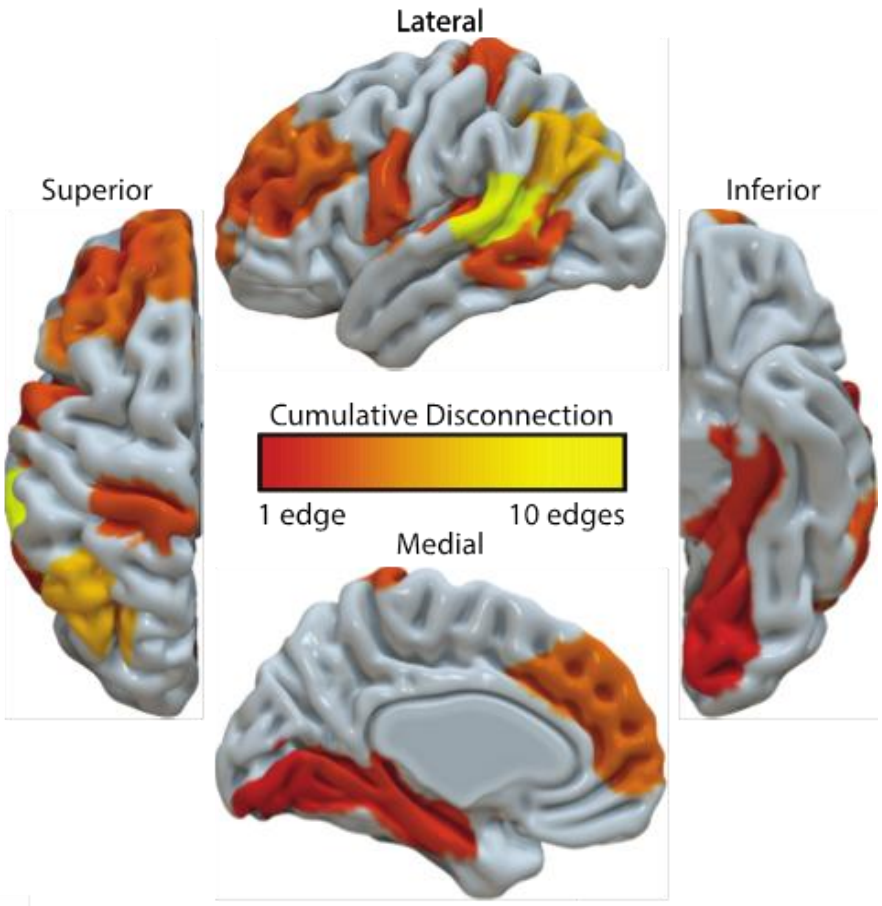


Tool Use Disconnection Network





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