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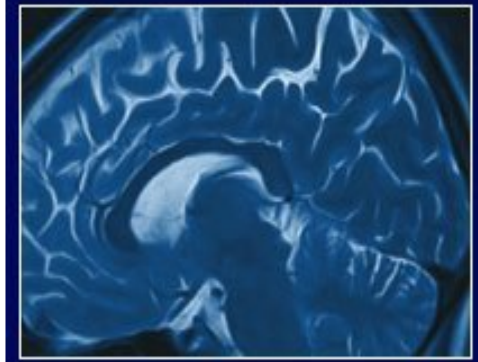

The Waisman Laboratory for Brain Imaging and Behavior

February 1, 2016 Banff Station

Learning Large-scale Brain Networks for Twin fMRI

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Functional MRI

11 monozygotic (MZ) pairs

14 dizygotic (DZ) pairs

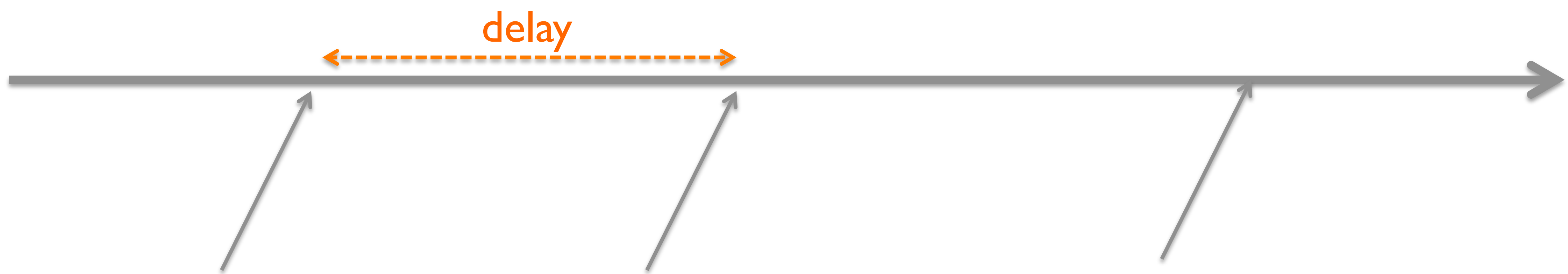
9 same-sex DZ pairs (5 male, 4 female)

5 different-sex DZ pairs

MZ-pair

DZ-pair

Reward experiment: 120 randomized trial



Cue for reward
$0, $1, $5

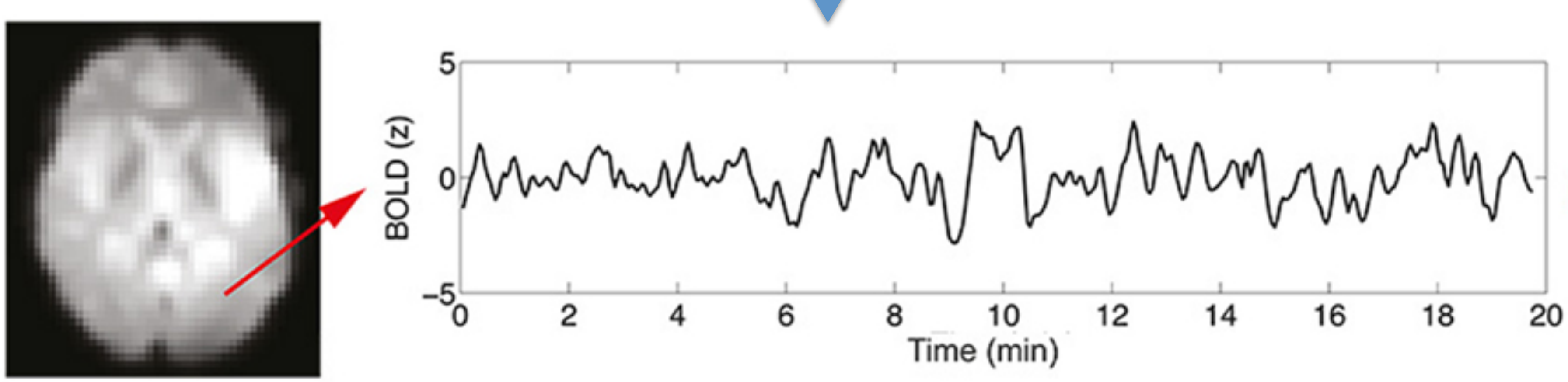
White star flashes
on screen.

Win if the response
button is pushed in time

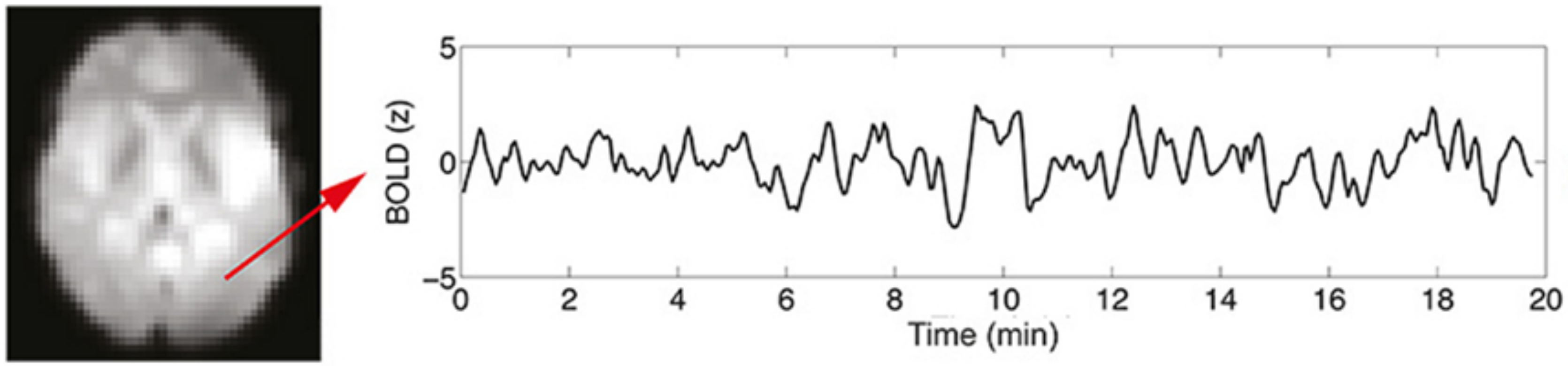
Feedback

9 conditions (each condition also includes a time and a dispersion derivative):

- delay for $0 trials
- delay for $1 trials
- delay for $5 trials
- reward $0
- reward $1
- reward $5
- miss $0
- miss $1
- miss $5



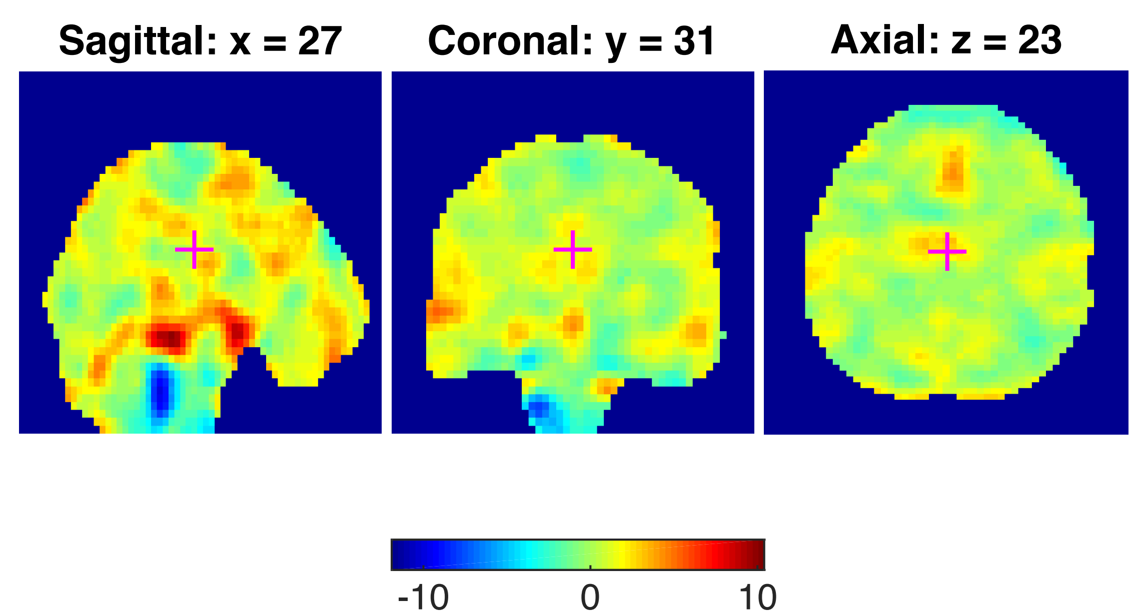
1^{st} level analysis: general linear model



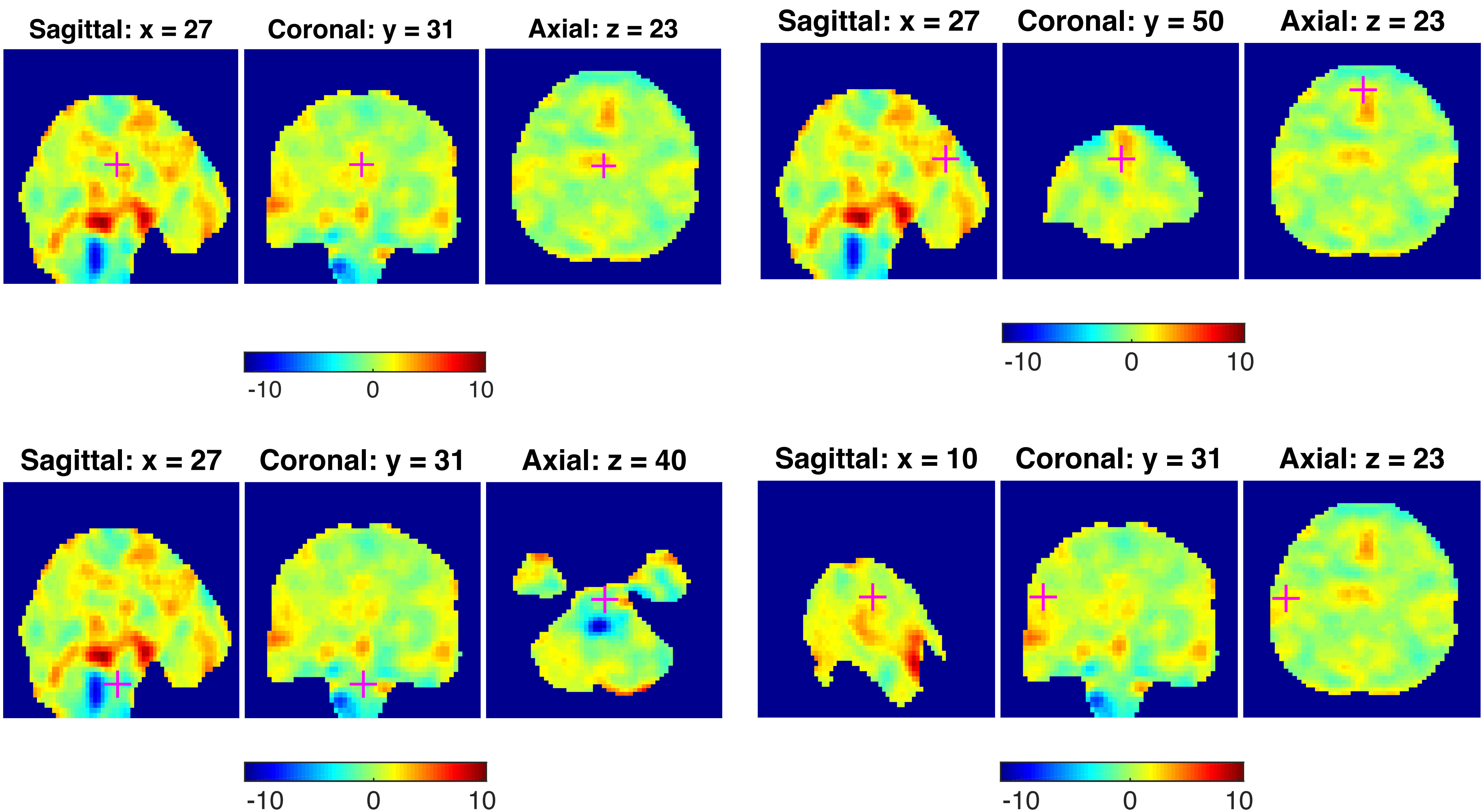
$$Y(v_i) = X\beta(v_i) + \varepsilon(v_i)$$

BOLD

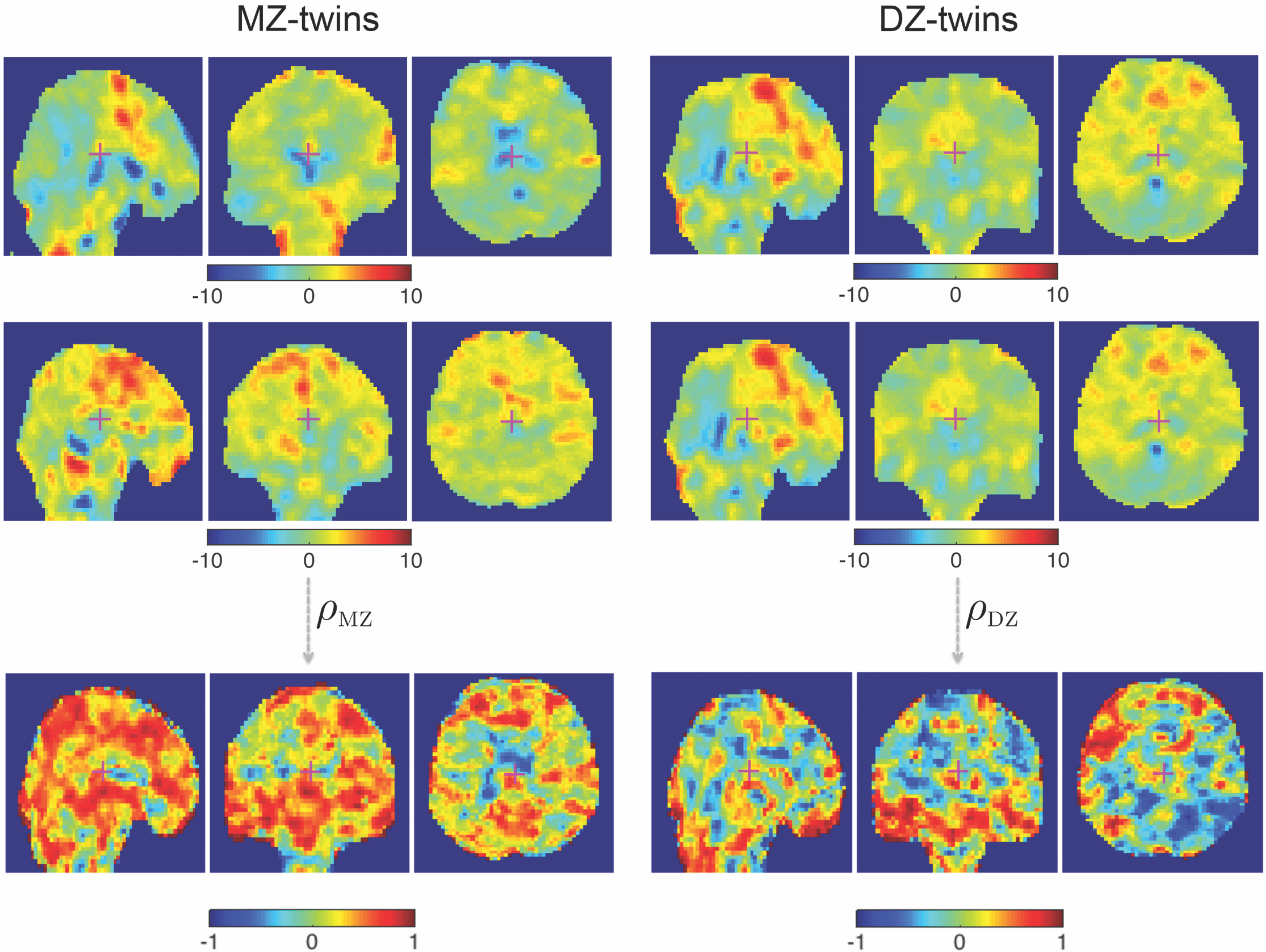
Contrast map: $c^T\beta(v_i)$



Contrast map: one subject



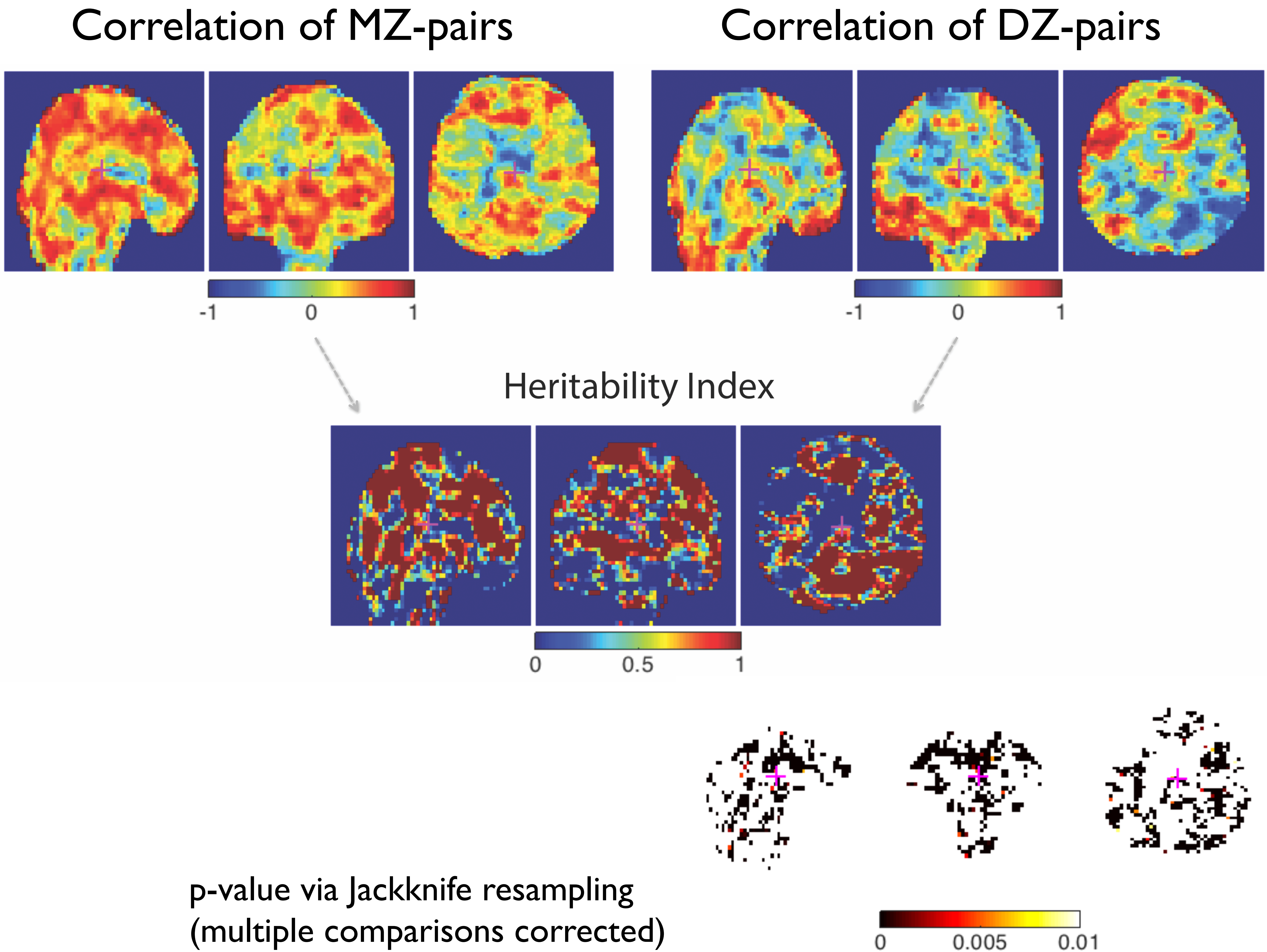
Heritability index


MZ-twins
DZ-twins
-10
0
10
ρ_{MZ}
ρ_{DZ}
-1
0
1

Heritability index (HI) determines the amount of variation due to genetic influence as percentage (%).

Falconer's formula at voxel v_i :

$$\mathrm{HI}(v_i) = 2\left[\rho_{\mathrm{MZ}}(v_i) - \rho_{\mathrm{DZ}}(v_i)\right]$$


Correlation of MZ-pairs
Correlation of DZ-pairs
-1
0
1
-1
0
1
Heritability Index
0
0.5
1
p-value via Jackknife resampling
(multiple comparisons corrected)
0
0.005
0.01

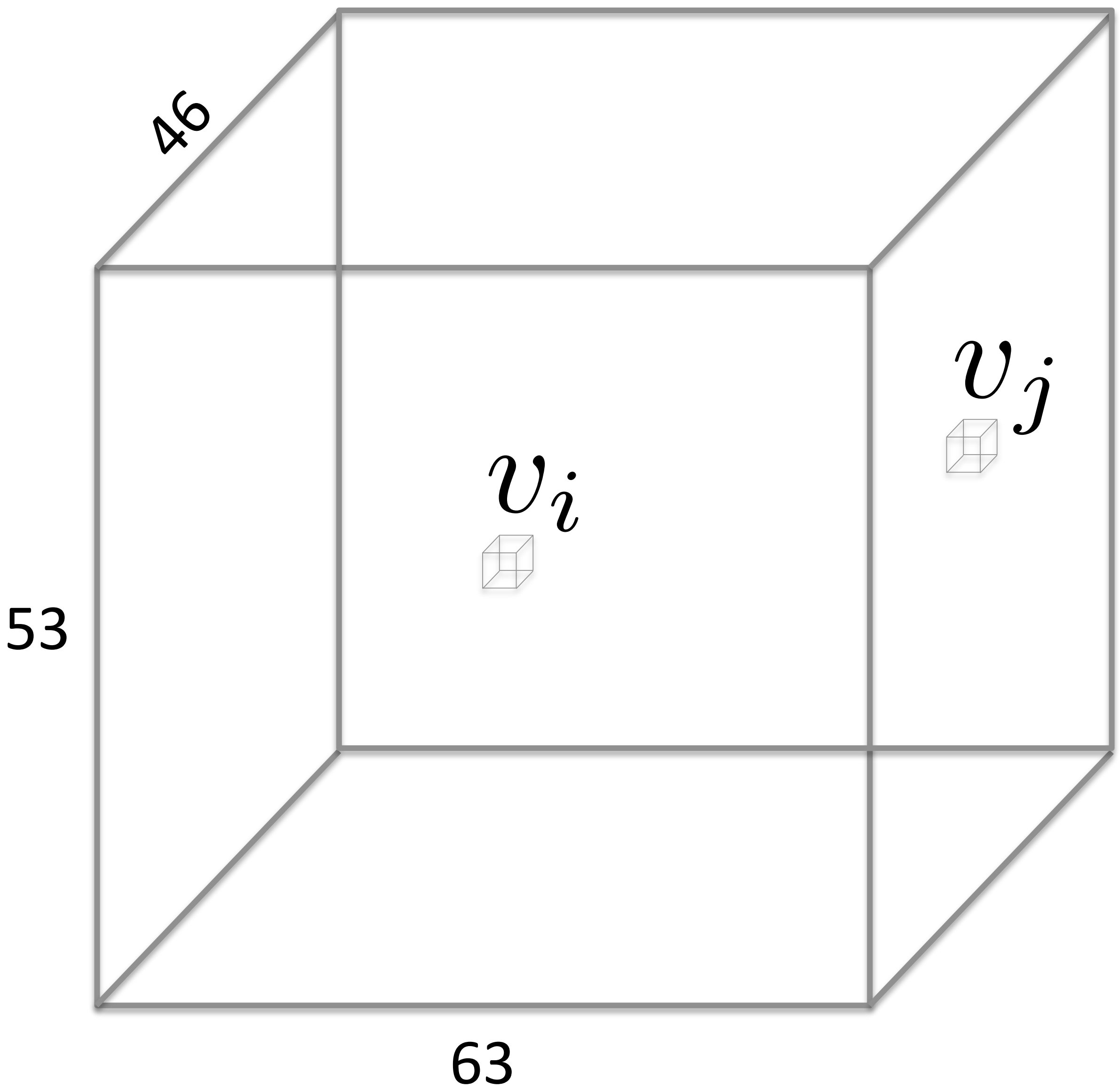
Three aims:

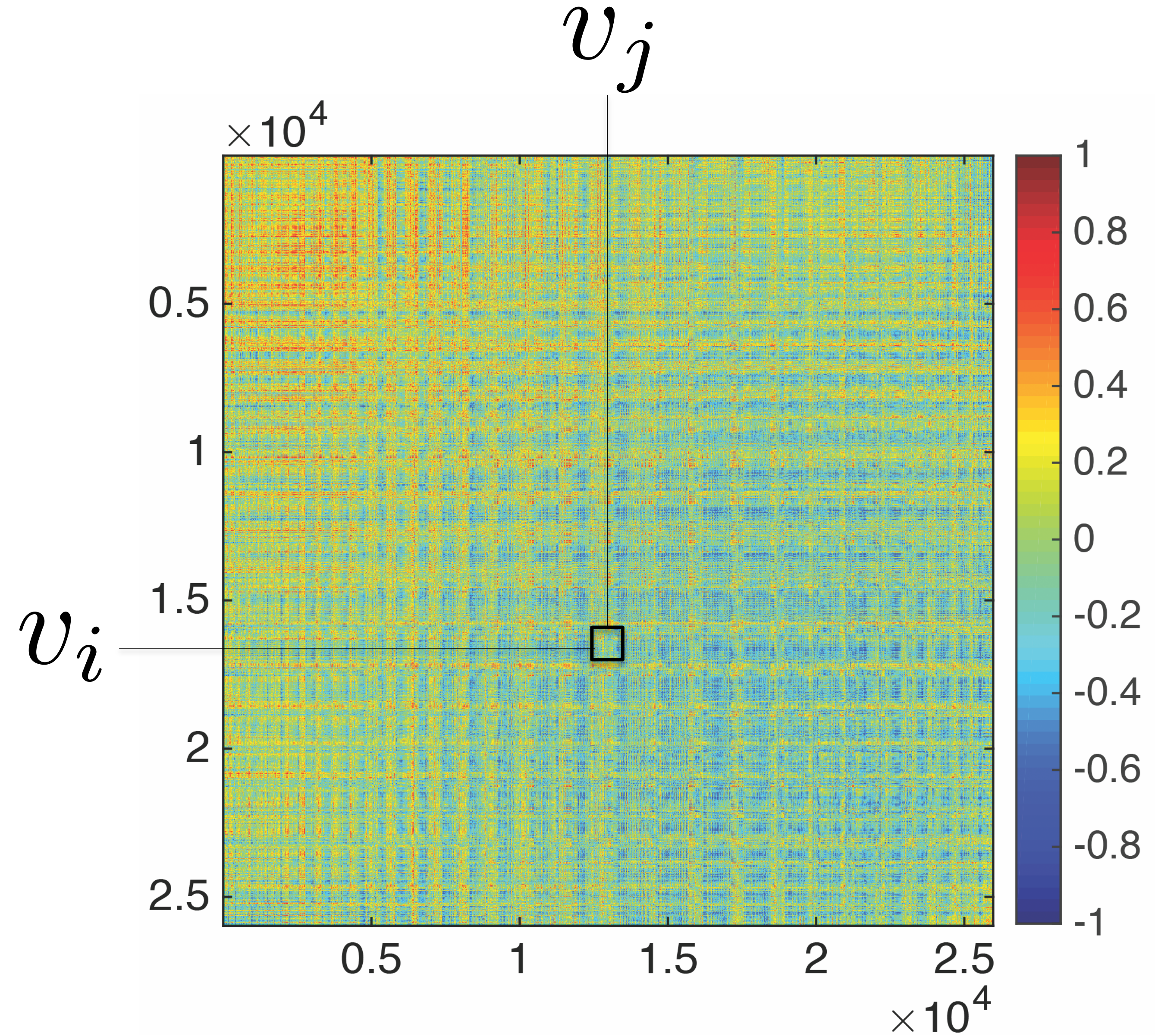
1) Construct a large-scale brain network

2) Compute HI of the large-scale network

3) Determine the statistical significance of HI

Large-scale connectivity analysis





p=(53 x 63 x 46) x (53 x 63 x 46)

Node set $V = \{v_1, v_2, \cdots, v_p\}$

(53 x 63 x 46) x (53 x 63 x 46) = 1.3 billion directed edges

Sparse Cross Correlations

Center and scaled data

n paired images in *p* voxels (*n* < *p*)

$x_k(v_i)$ *k*-th image intensity value at voxel v_i

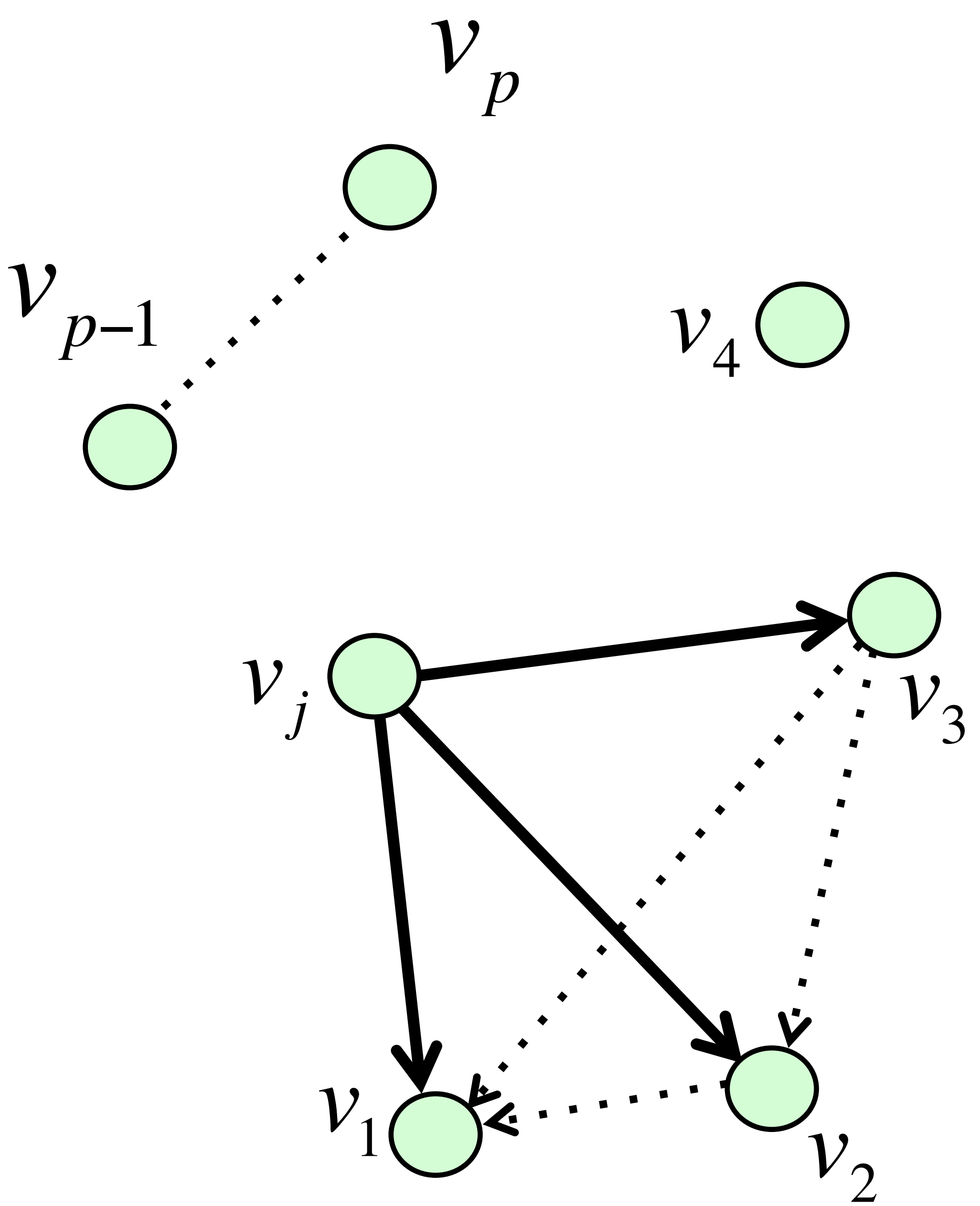
$y_k(v_i)$ *k*-th image intensity value at voxel v_i

$$\sum_{k=1}^{n} x_k(v_i) = \sum_{k=1}^{n} y_k(v_i) = 0$$

$$x = (x_1, \cdots, x_n)' \qquad y = (y_1, \cdots, y_n)'$$

$$\|x\|^2 = x'x = \|y\|^2 = y'y = 1$$

Massive regressions between nodes



$$y(v_j) = \sum_{i \neq j} \beta_{ij} x(v_i) + \varepsilon$$

$$y(v_j) = \beta_{ij} x(v_i) + \varepsilon$$

Least-squares estimation:

$$\hat{\beta}_{ij} = x'(v_i) y(v_j)$$

1.3 billion cross-correlations

Sparse cross-correlation network

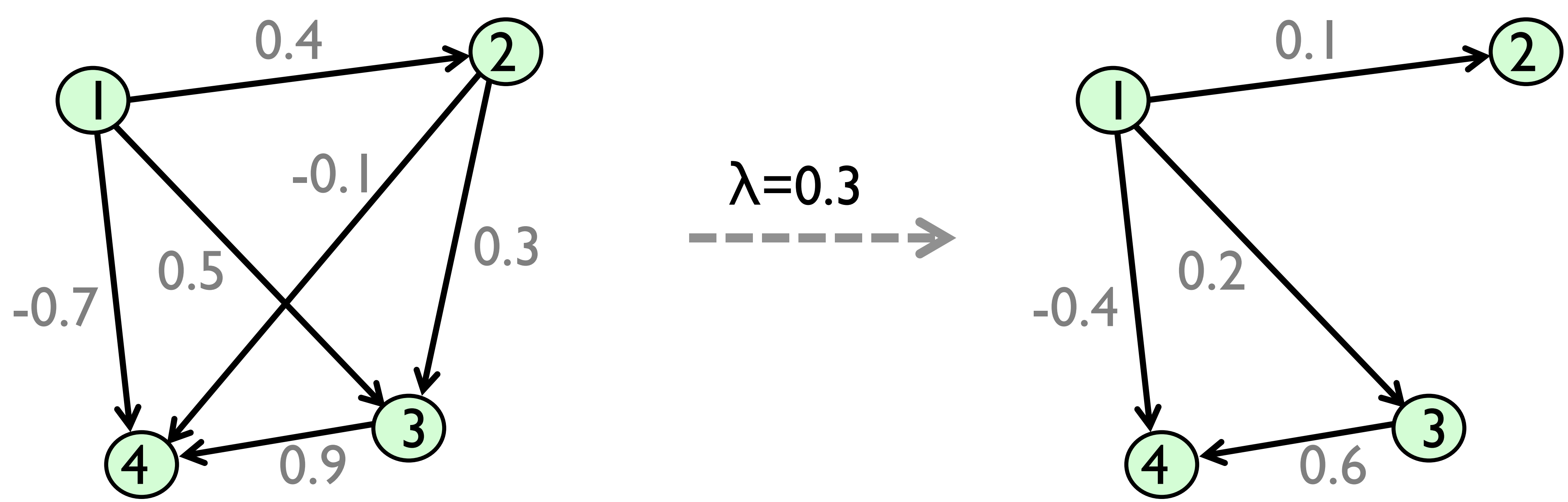
$$\hat{\beta} = \operatorname{argmin}_{\beta} \ \frac{1}{2}\sum_{i=1}^{p}\sum_{j=1}^{p}\left\| x(v_i) - \beta_{ij} y(v_j) \right\|^2 + \lambda \sum_{i,j} |\beta_{ij}|$$

Adjacency matrix

$$b_{ij}(\lambda) = \begin{cases} 1 \text{ if } \hat{\beta}_{ij} \neq 0 \\ 0 \text{ otherwise} \end{cases}$$

Sparse network

$$G(\lambda) = \{V, b(\lambda)\}$$



Soft-thresholding

LASSO
L1-optimization

$$b_{ij}(\lambda) = \begin{cases} 1 \text{ if } \hat{\beta}_{ij}(\lambda) \neq 0 \\ 0 \text{ otherwise} \end{cases}$$

$\longleftrightarrow$

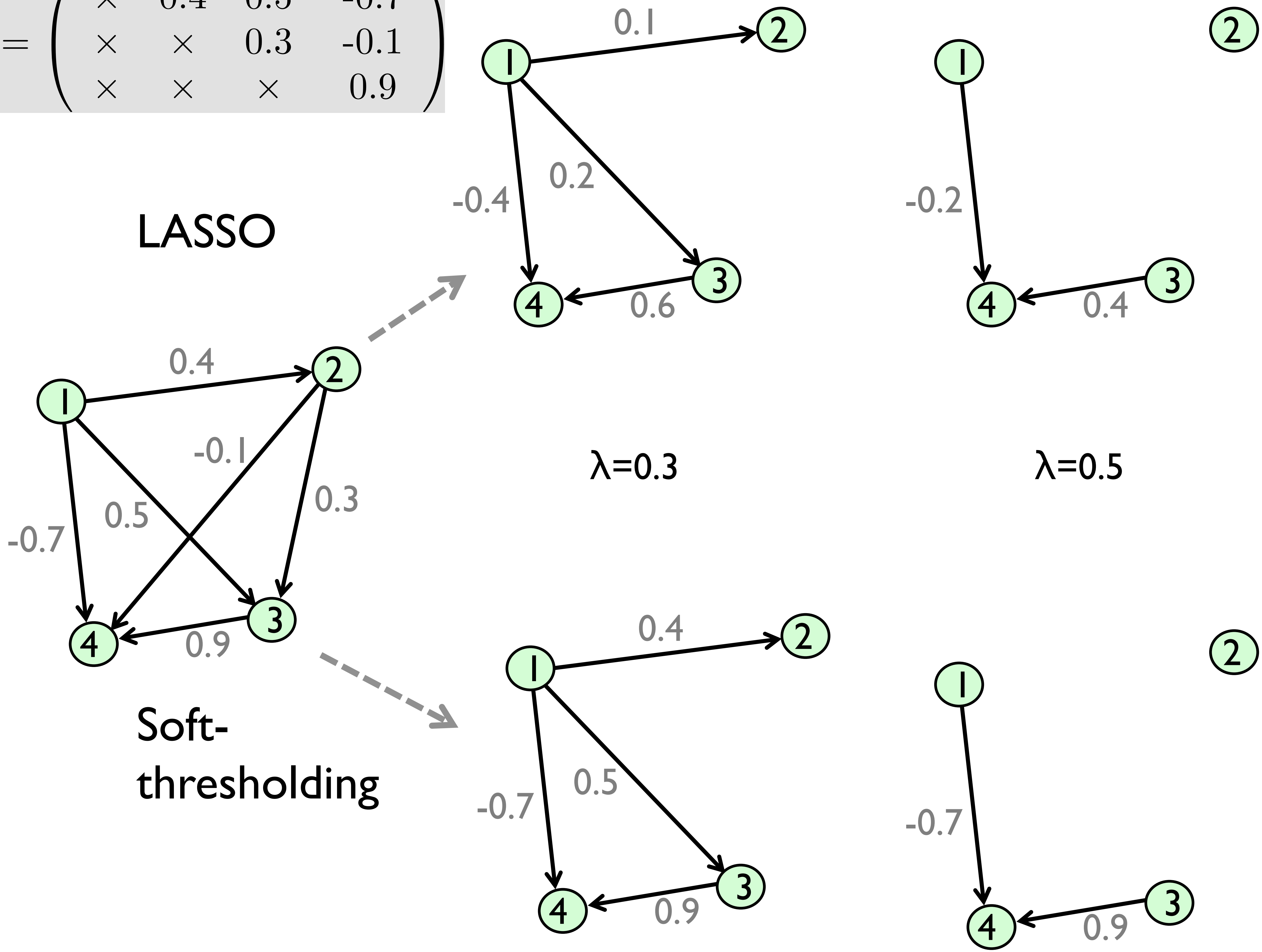
Soft-thresholding

$$b_{ij}(\lambda) = \begin{cases} 1 \text{ if } |x'(v_i)y(v_j)| > \lambda \\ 0 \text{ otherwise} \end{cases}$$

Threshold correlations at $\pm\lambda$ and get the identical sparse network.

Chung et al. 2015 IEEE Trans. Medical Imaging 34:1928-1939

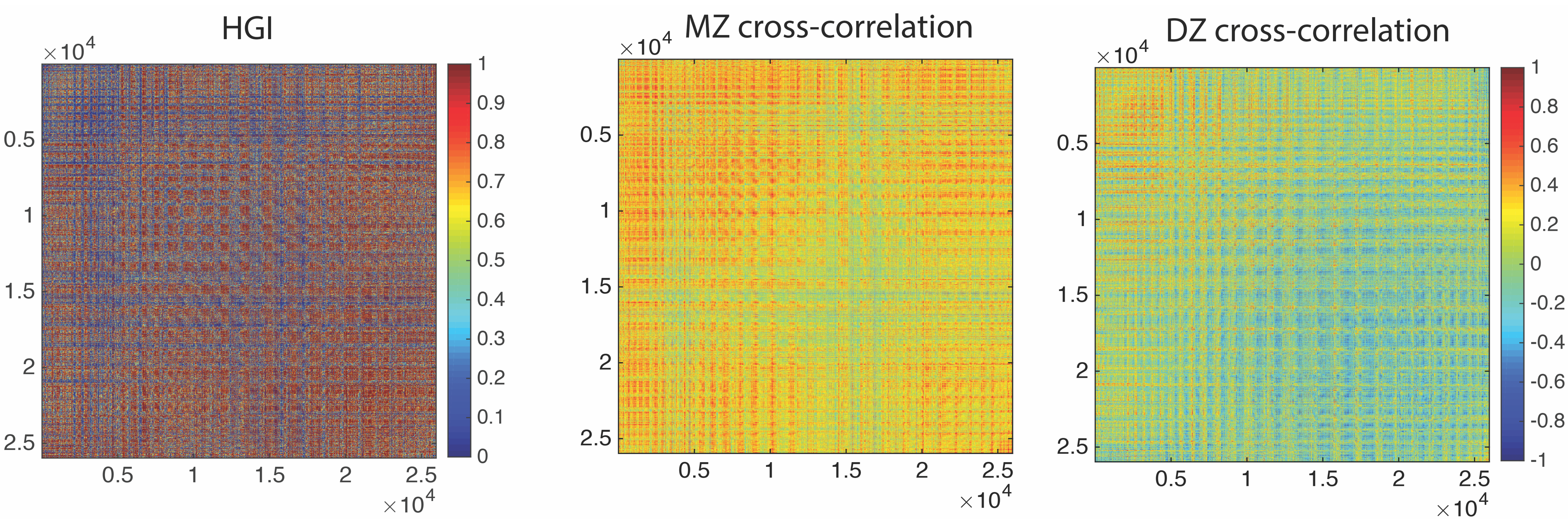
$$\mathbf{x}'\mathbf{y} = \begin{pmatrix} \times & 0.4 & 0.5 & -0.7 \\ \times & \times & 0.3 & -0.1 \\ \times & \times & \times & 0.9 \end{pmatrix}$$



Heritability graph index

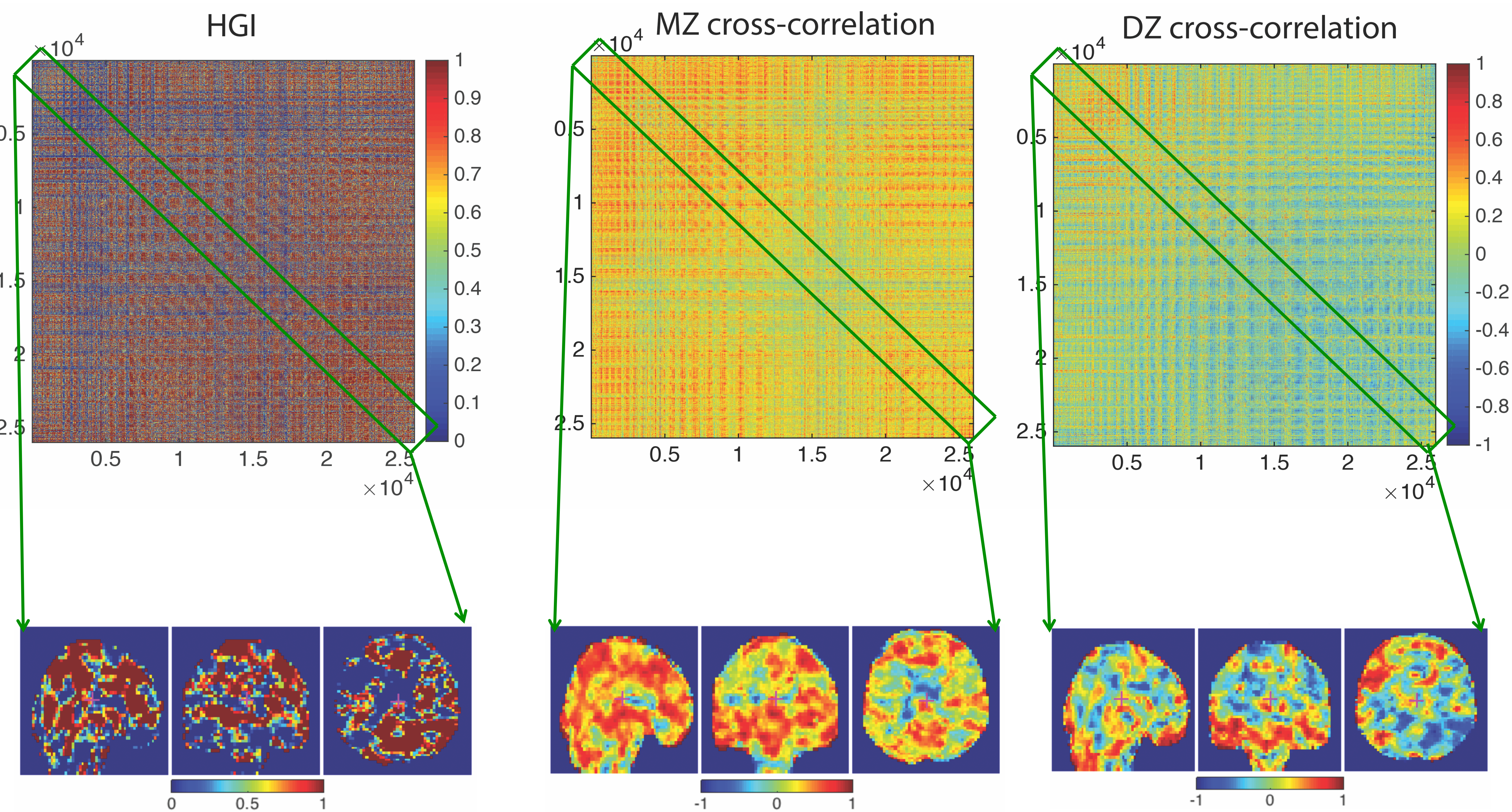
Heritability graph index (HGI):

$$\mathrm{HGI}(v_i, v_j) = 2\left[\rho_{\mathrm{MZ}}(v_i, v_j) - \rho_{\mathrm{DZ}}(v_i, v_j)\right]$$

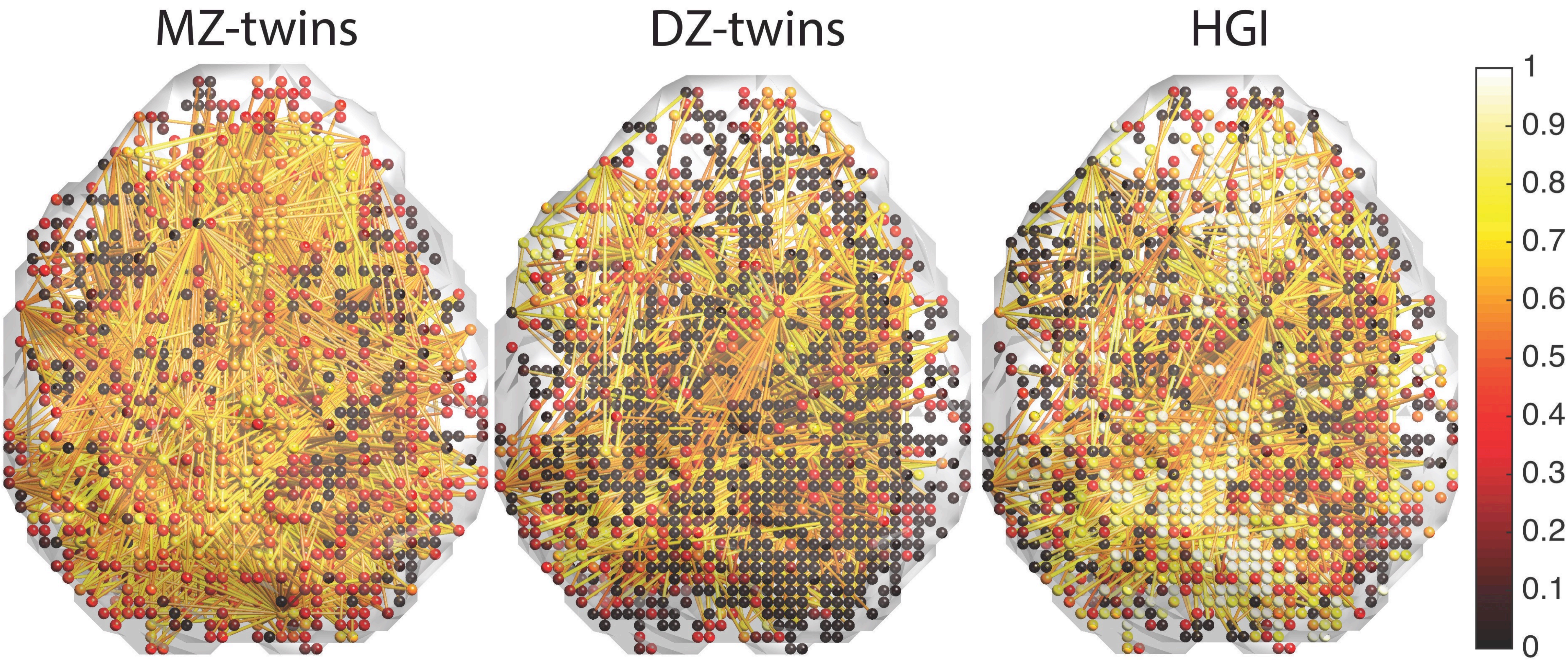


18 sec. computation per matrix
5.2GB per matrix, 3min to save to hard drive

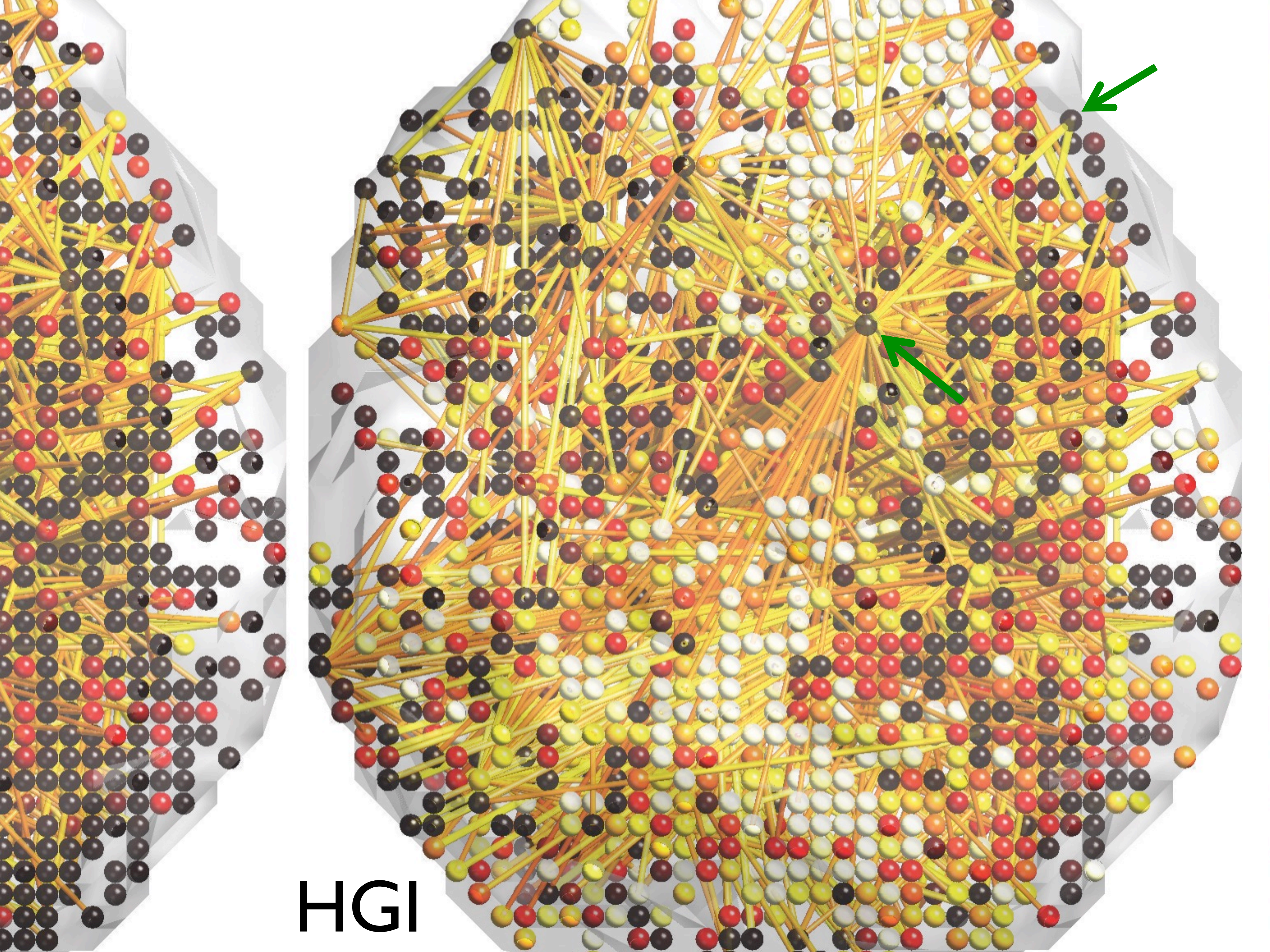
$$\mathrm{HGI}(v_i, v_i) = \mathrm{HI}(v_i)$$



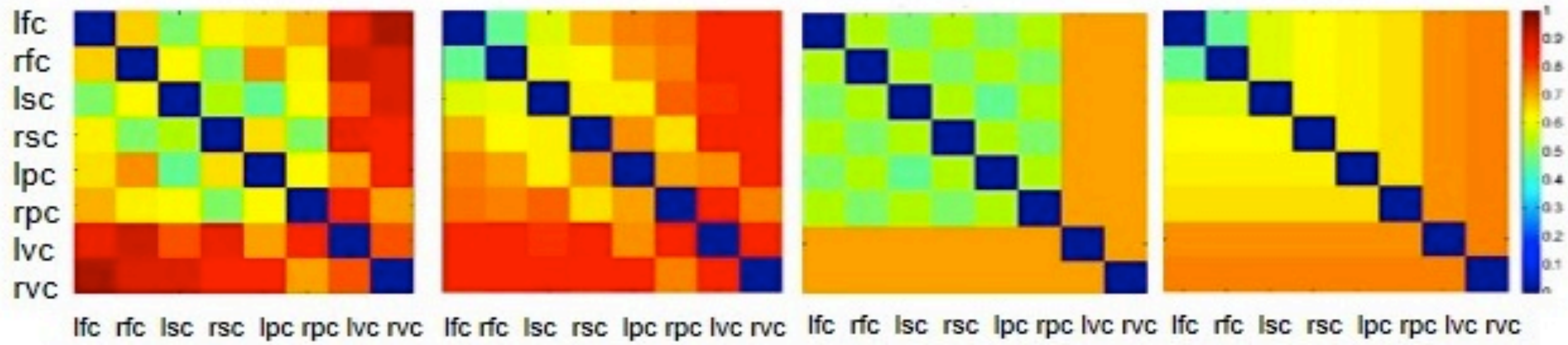
Heritability Graph Index (HGI) at sparse parameter 0.5



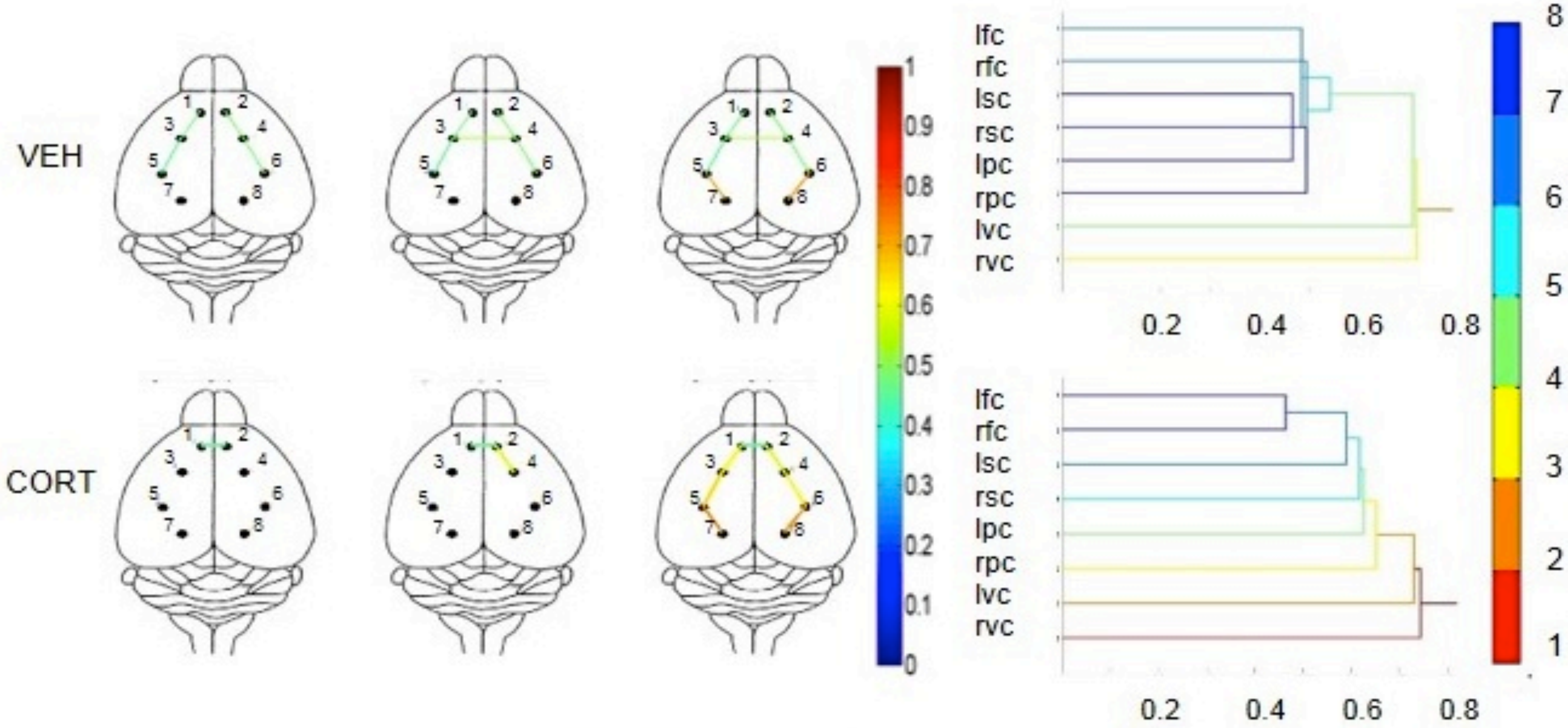
Each voxel is a network node!


HGI

Optimal sparse parameter?

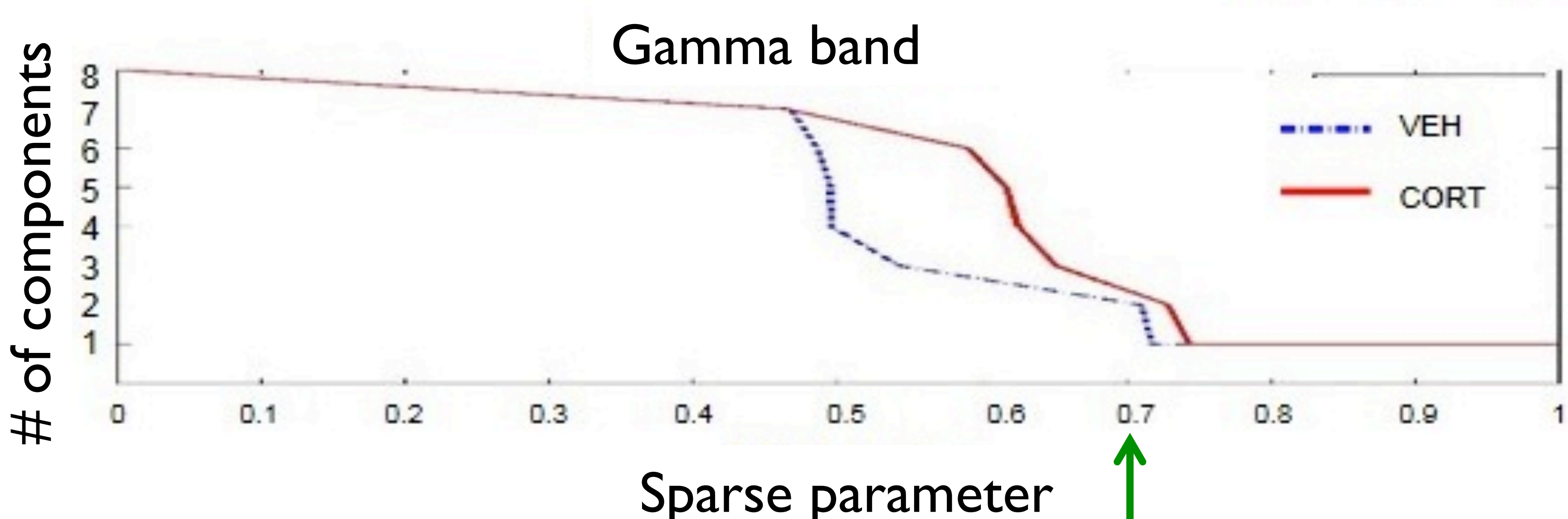


8 channel EEG mouse model of depression



~~Single optimal parameter is not useful!~~

~~Existing Multi-tresholding, Multi-scale methods~~

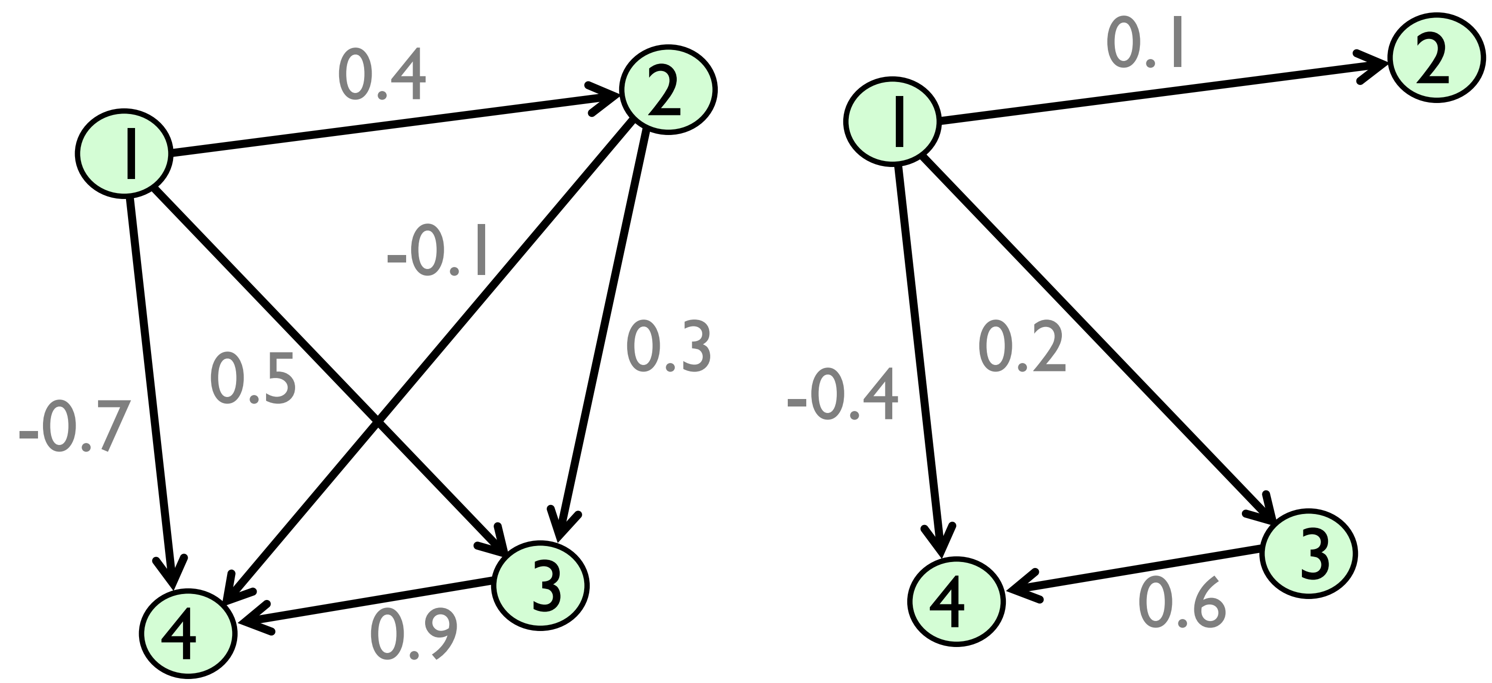


Khalid et al. 2014, NeuroImage 101:351-363

Graph filtration / persistent homology

Analyze the infinite collection of networks

$$\{G(\lambda), \lambda \in \mathrm{R}^{+}\}$$



$$G(0) \supset G(0.3)$$

Graph filtration

$$G(\lambda_1) \supset G(\lambda_2) \supset G(\lambda_3) \supset \cdots$$

for $\lambda_1 \leq \lambda_2 \leq \lambda_3 \leq \cdots$

Lee et al. 2011
MICCAI 6892:302-309

Topological Inference

$H_0 : \mathrm{HGI}(\lambda) = 0$ for all $\lambda \geq 0$

vs.

$H_1 : \mathrm{HGI}(\lambda) \neq 0$ for some $\lambda \geq 0$

$H_0 : \rho_{MZ}(\lambda) = \rho_{DZ}(\lambda)$ for all $\lambda \geq 0$

vs.

$H_1 : \rho_{MZ}(\lambda) \geq \rho_{DZ}(\lambda)$ for some $\lambda \geq 0$

$H_0 : G_{MZ}(\lambda) = G_{DZ}(\lambda)$ for all $\lambda \geq 0$

vs.

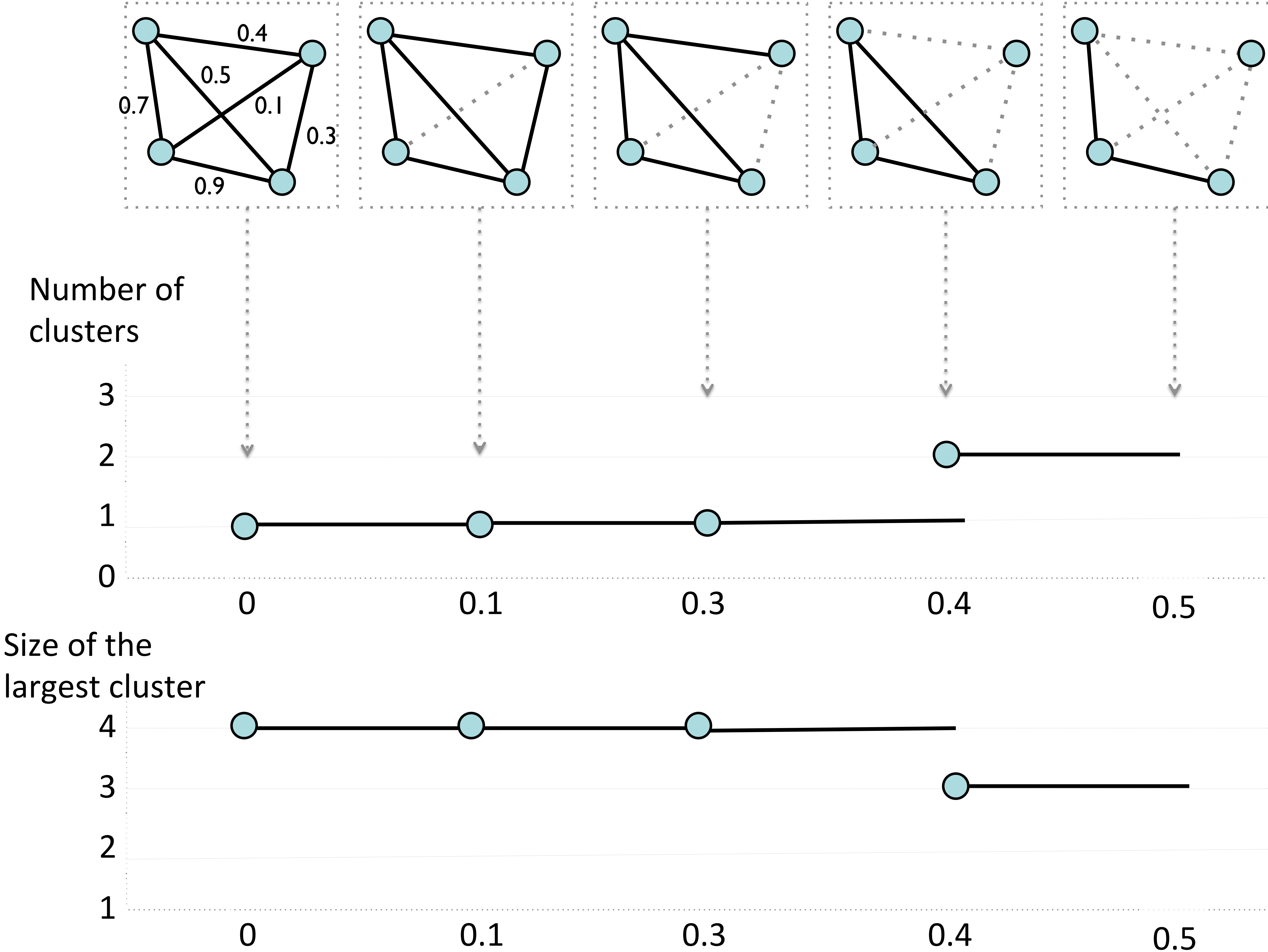
$H_1 : G_{MZ}(\lambda) \neq G_{DZ}(\lambda)$ for some $\lambda \geq 0$

$H_0 : f(G_{MZ})(\lambda) = f(G_{DZ})(\lambda)$ for all $\lambda \geq 0$

vs.

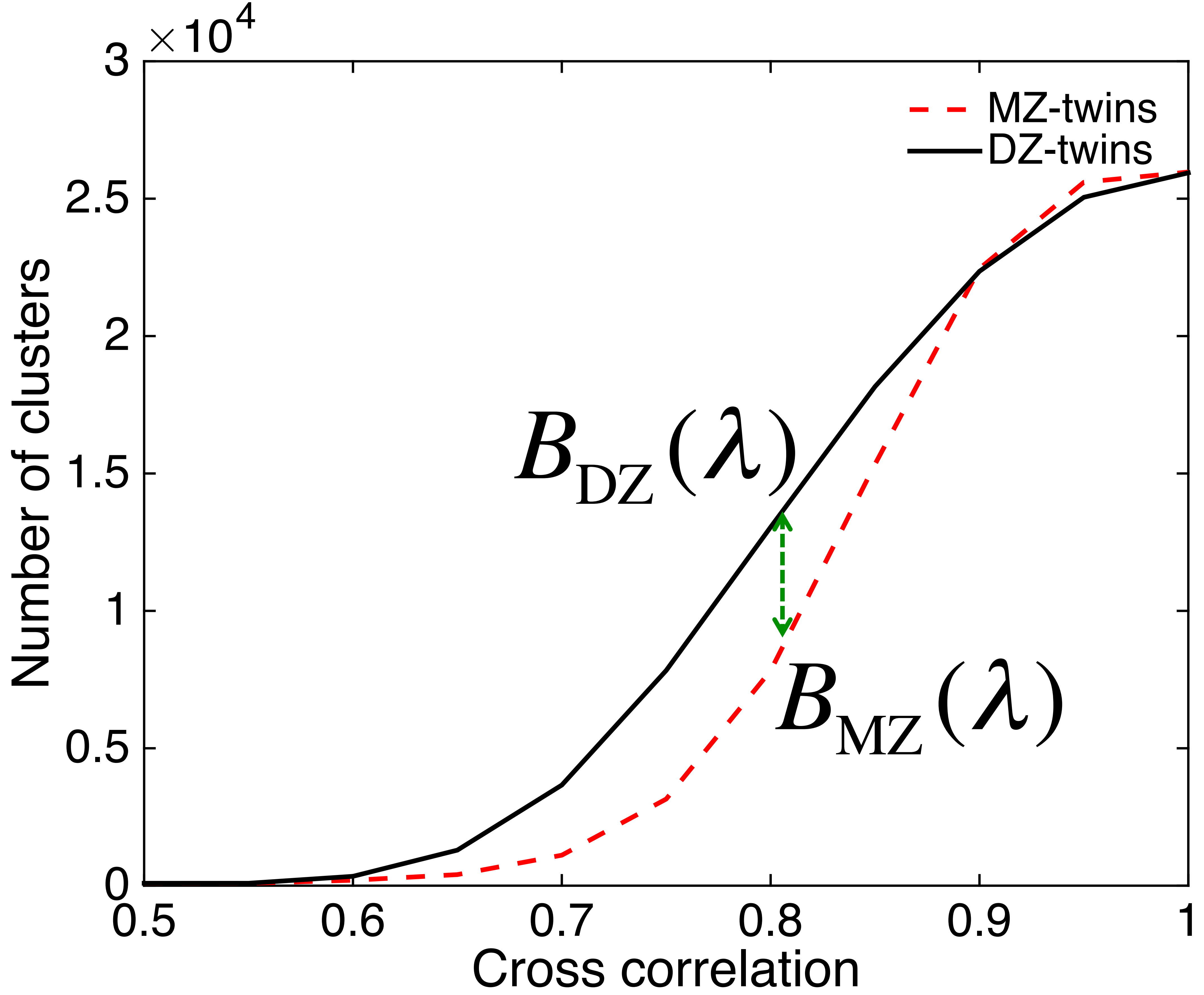
$H_1 : f(G_{MZ})(\lambda) \neq (G_{DZ})(\lambda)$ for some $\lambda \geq 0$

with monotonic graph function $f(G)(\lambda_1) \leq f(G)(\lambda_2) \leq f(G)(\lambda_3) \leq \ldots$

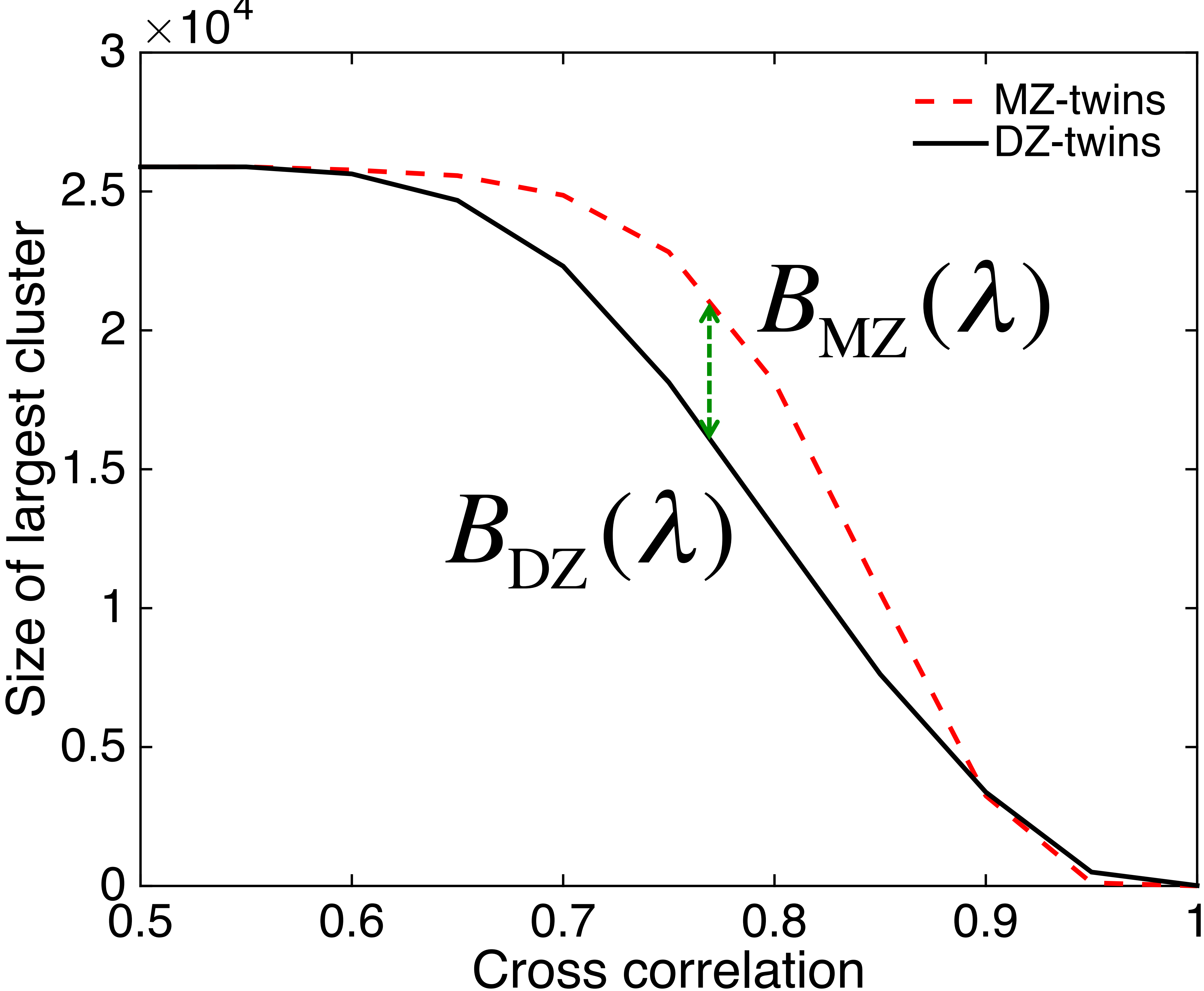

0.4
0.5
0.7
0.1
0.3
0.9
Number of clusters
3
2
1
0
0
0.1
0.3
0.4
0.5
Size of the largest cluster
4
3
2
1
0
0.1
0.3
0.4
0.5

Betti plots

$$D = \min_{\lambda} \left| B_{MZ}(\lambda) - B_{DZ}(\lambda) \right|$$



p-value < 0.0002



p-value < 0.0001

$$p\text{-value} = P\left(\max_{\lambda} \left| B_{\mathrm{MZ}}(\lambda) - B_{\mathrm{DZ}}(\lambda) \right| \geq \sqrt{2(p-1)}d\right) \approx 2e^{-2d^2} + \ldots$$

Chung et al. 2015 arxiv:509.04771

Discussion

Multiscale methods are usually better than monoscale methods. Infinite scale methods will be even better.

Thresholding feature/connectivity is not a bad idea.

The method can be easily generalized to other sparse models: full LASSO with LARS.

Thank you