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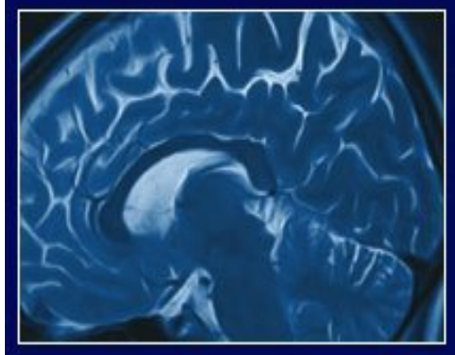

The Waisman Laboratory for Brain Imaging and Behavior

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Mapping the heritability of a large-scale functional brain network

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Functional MRI

11 monozygotic (MZ) pairs

14 dizygotic (DZ) pairs

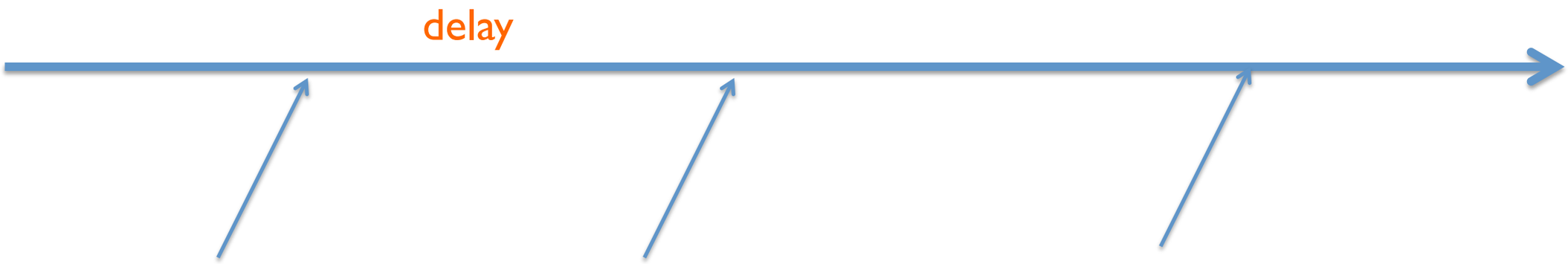
9 same-sex DZ pairs (5 male, 4 female)

5 different-sex DZ pairs

MZ-pair

DZ-pair

Reward experiment



Win if the response
button is pushed in time

3 runs of 40 randomized trials.

40 $0 rewards

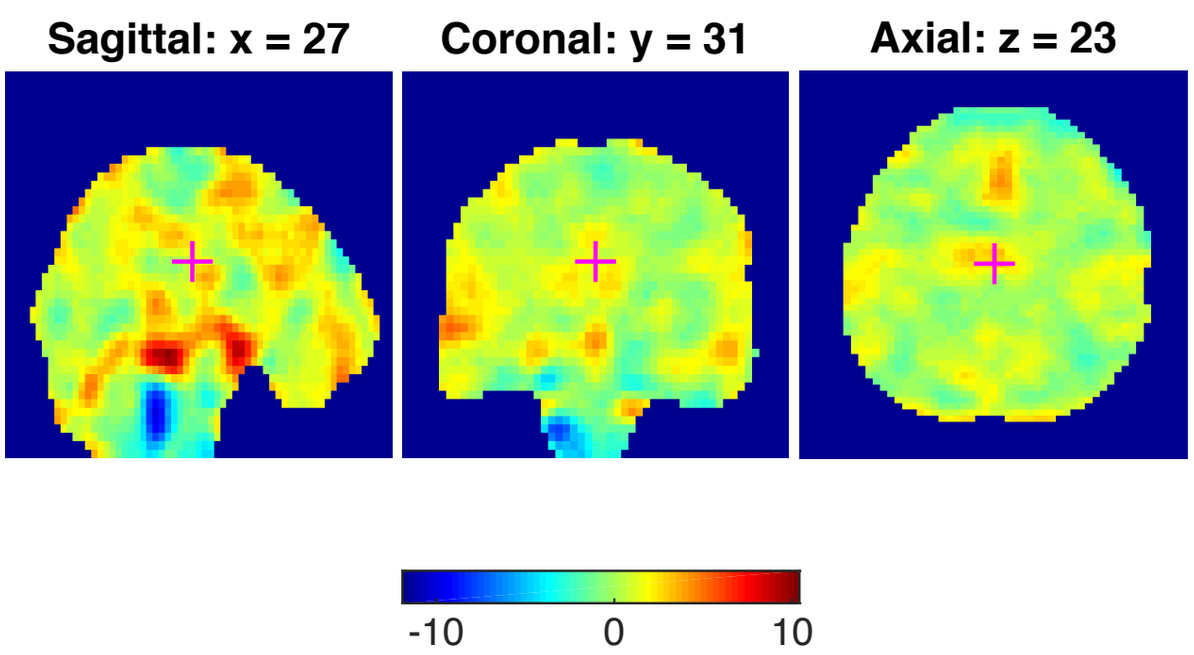
40 $1 rewards

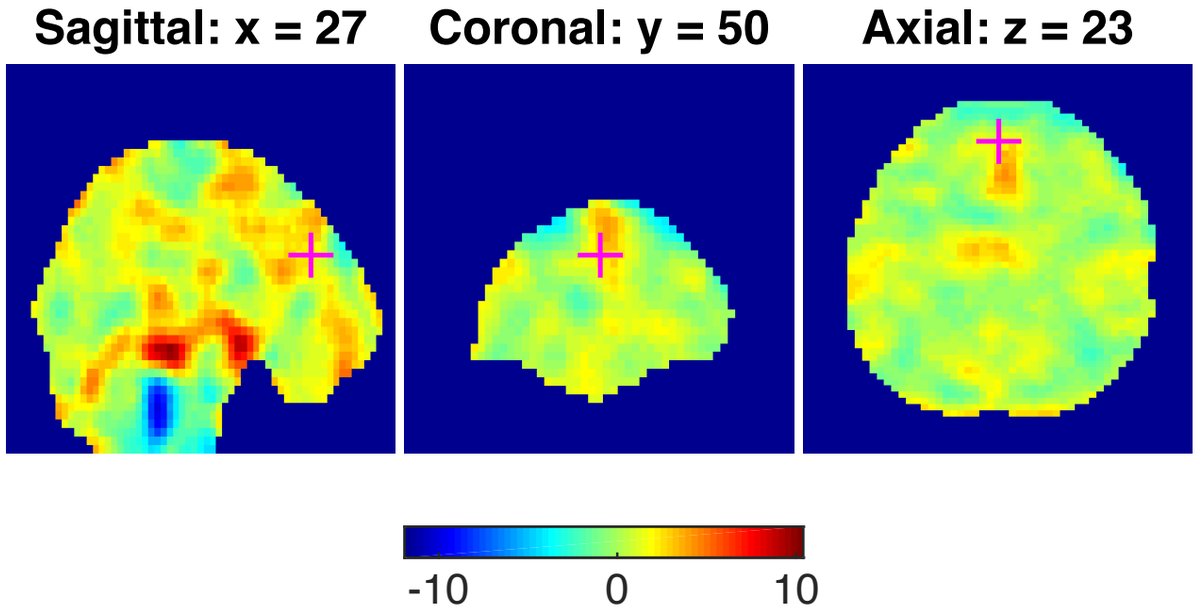
40 $5 rewards

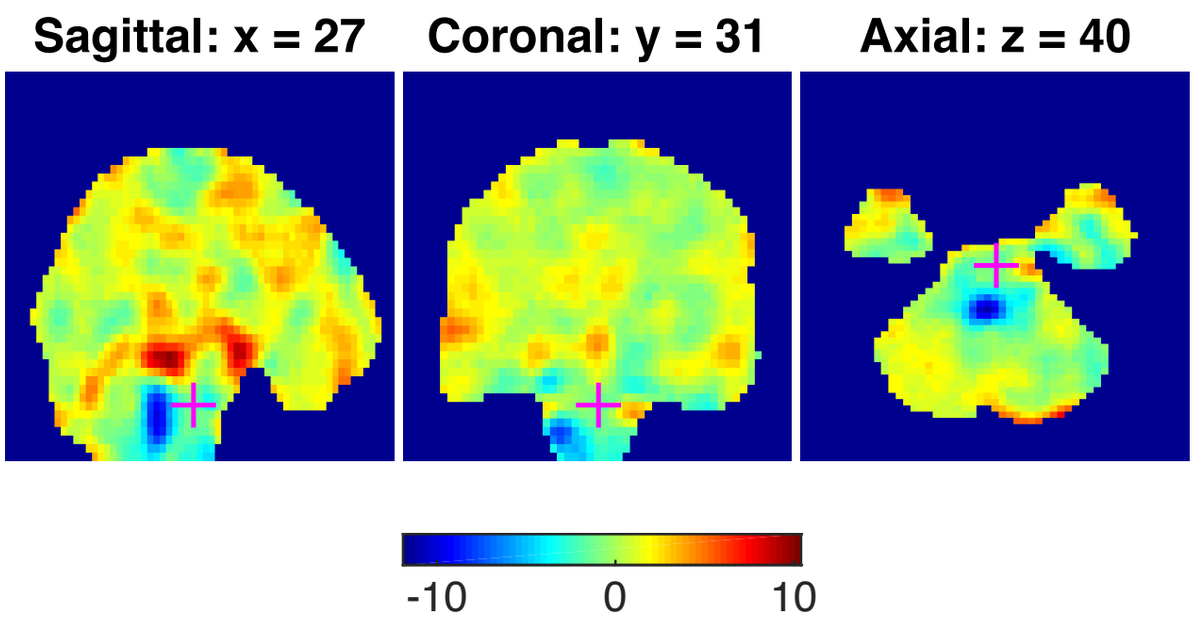
9 conditions (each condition also includes a time and a dispersion derivative):

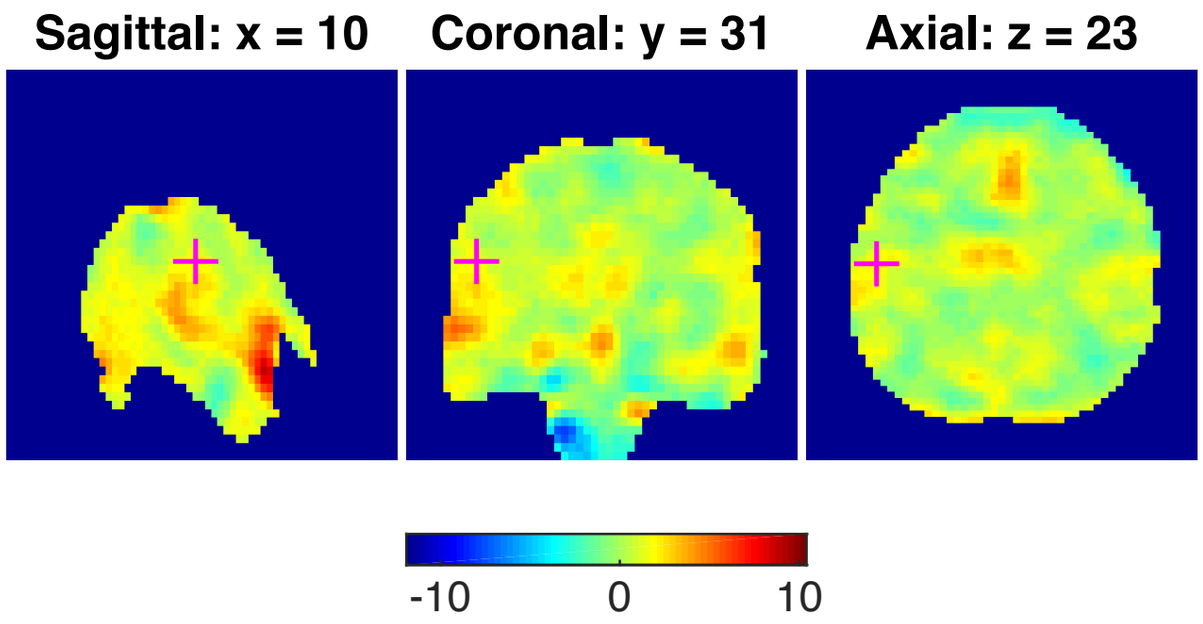
- delay for $0 trials
- delay for $1 trials
- delay for $5 trials
- reward $0
- reward $1
- reward $5
- miss $0
- miss $1
- miss $5

Contrast map after the 1st level analysis

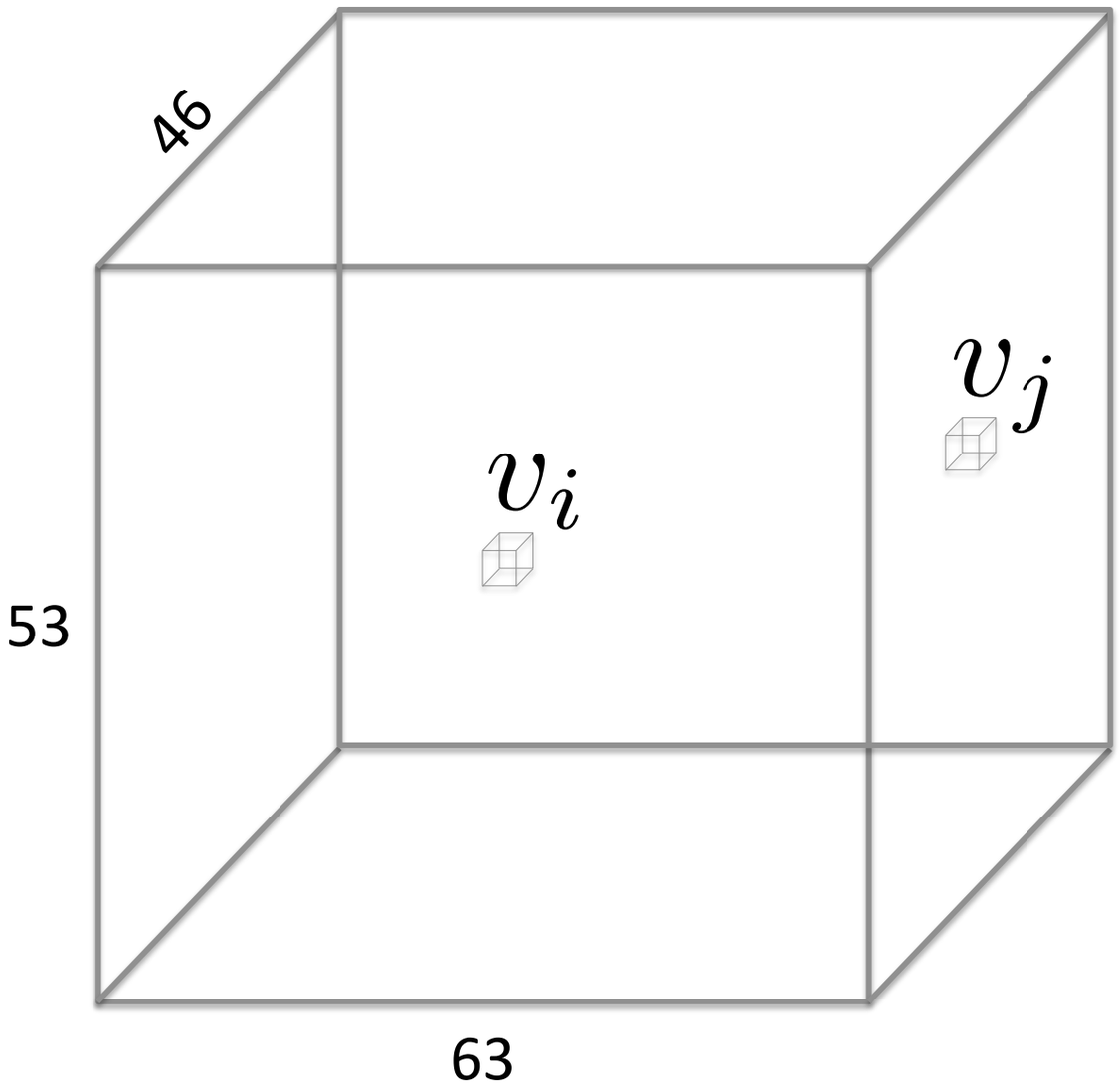


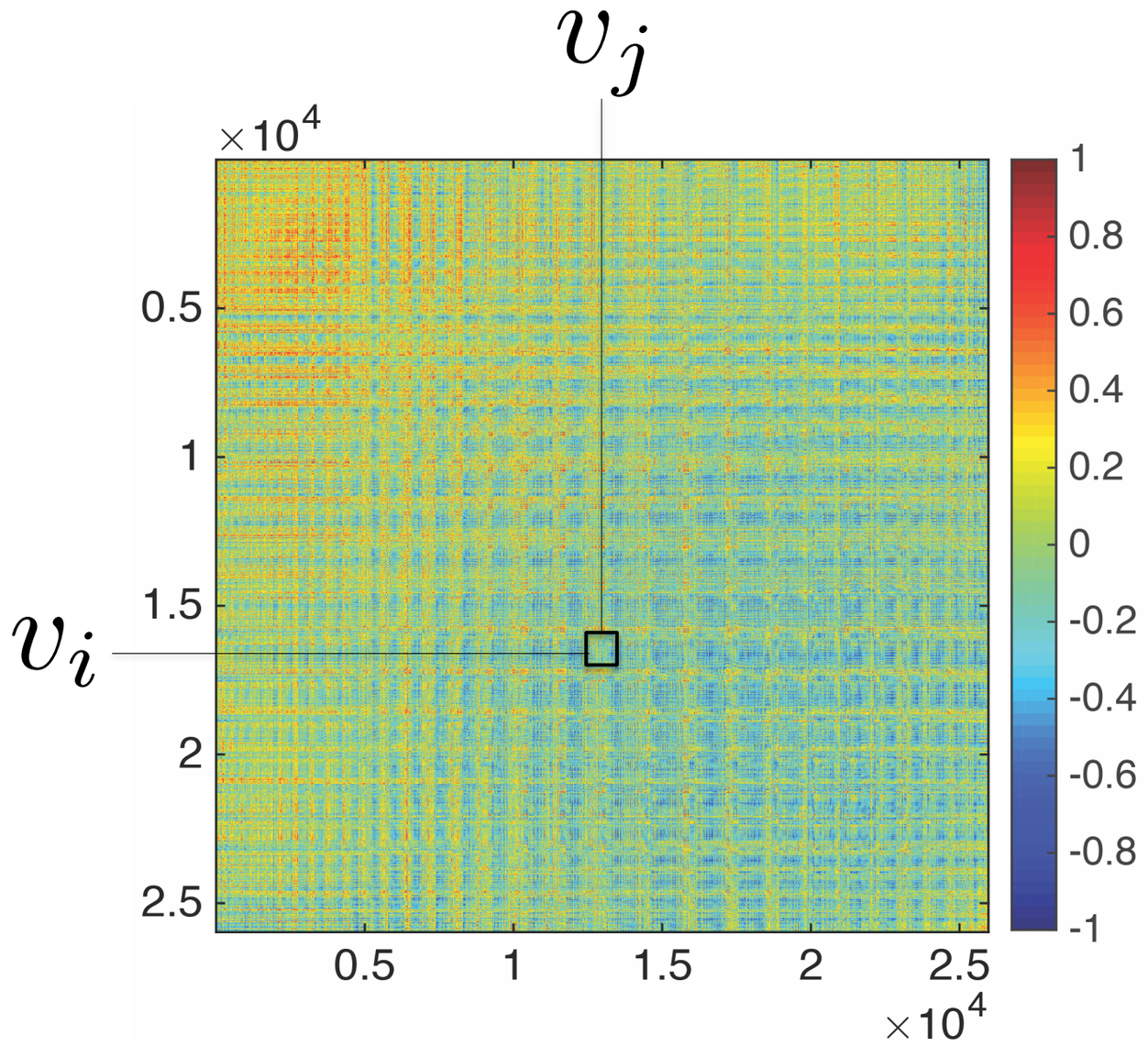






Large-scale connectivity analysis





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

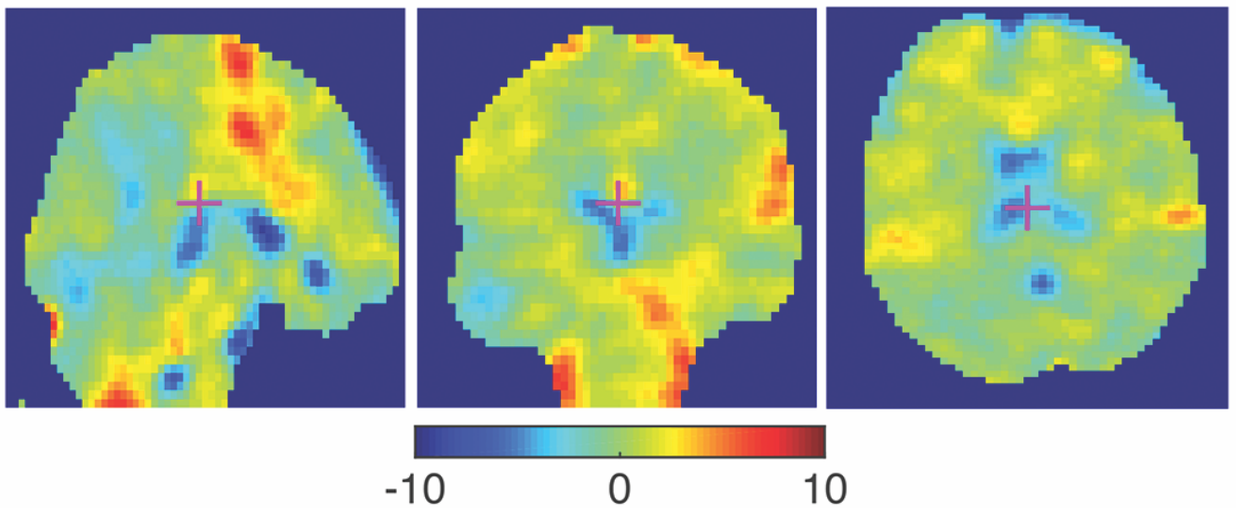
p=53 x 63 x 46 = 153594

153594 x 153594 > 2 billion connections

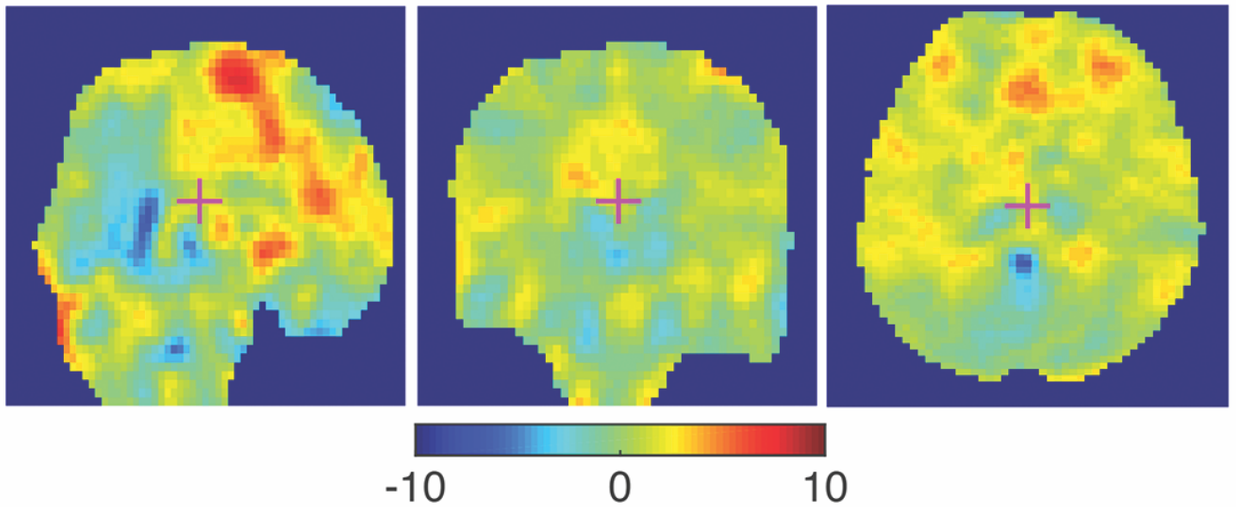
Heritability index

MZ-twins

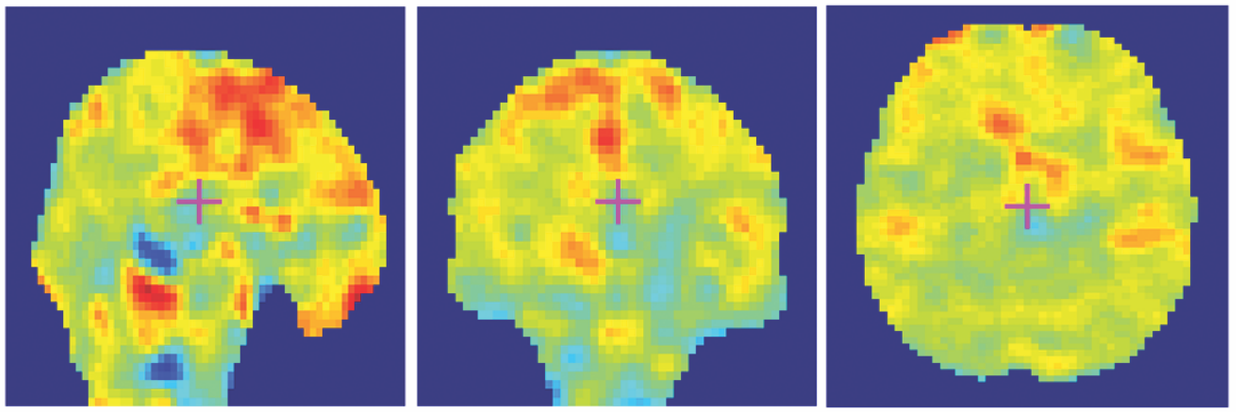
DZ-twins



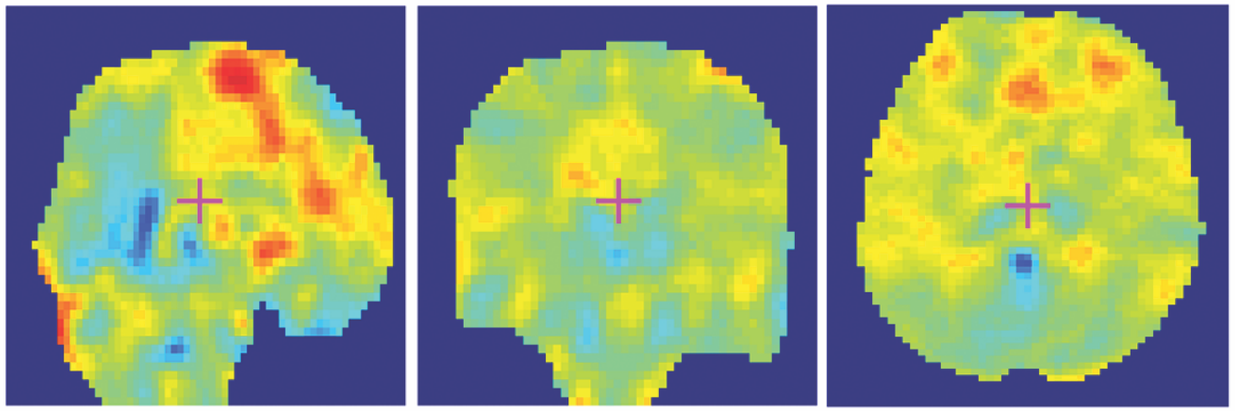
-10 0 10



-10 0 10



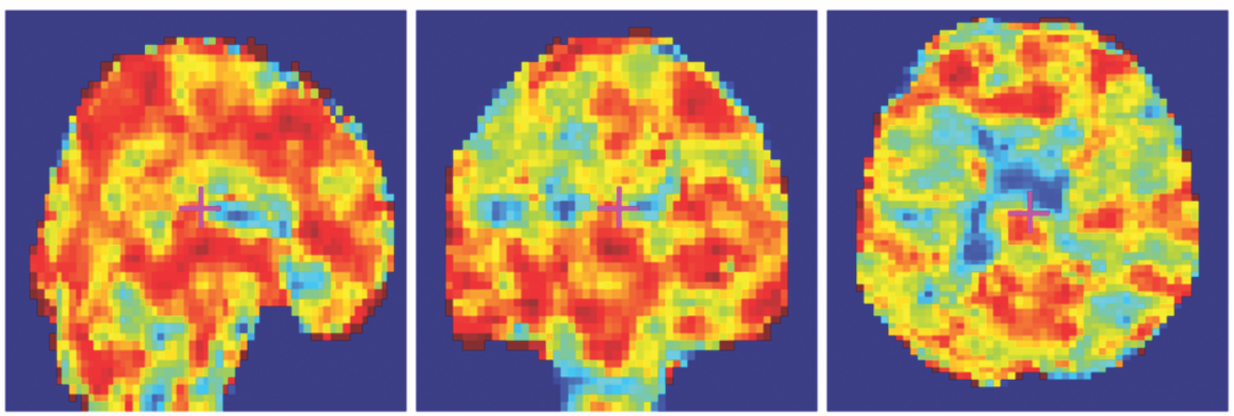
-10 0 10



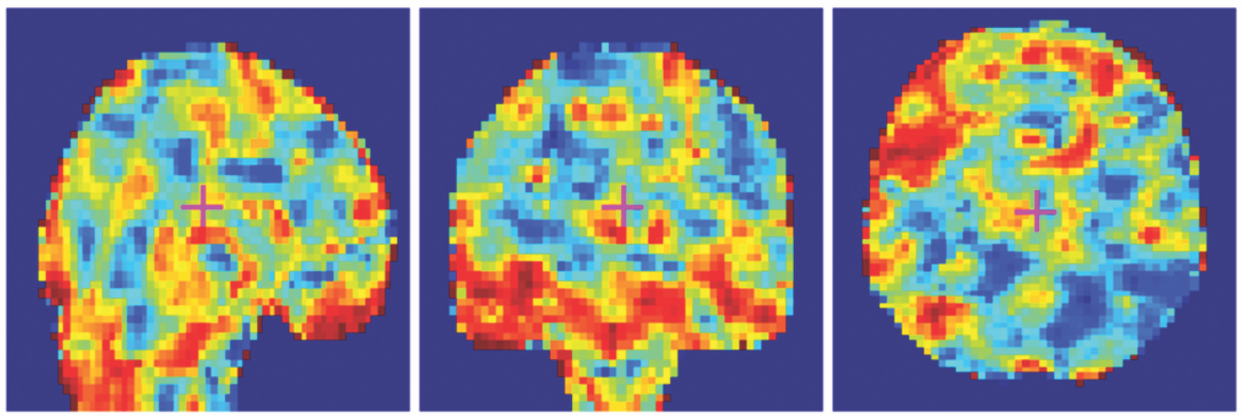
-10 0 10

ρ_{MZ}

ρ_{DZ}



-1 0 1



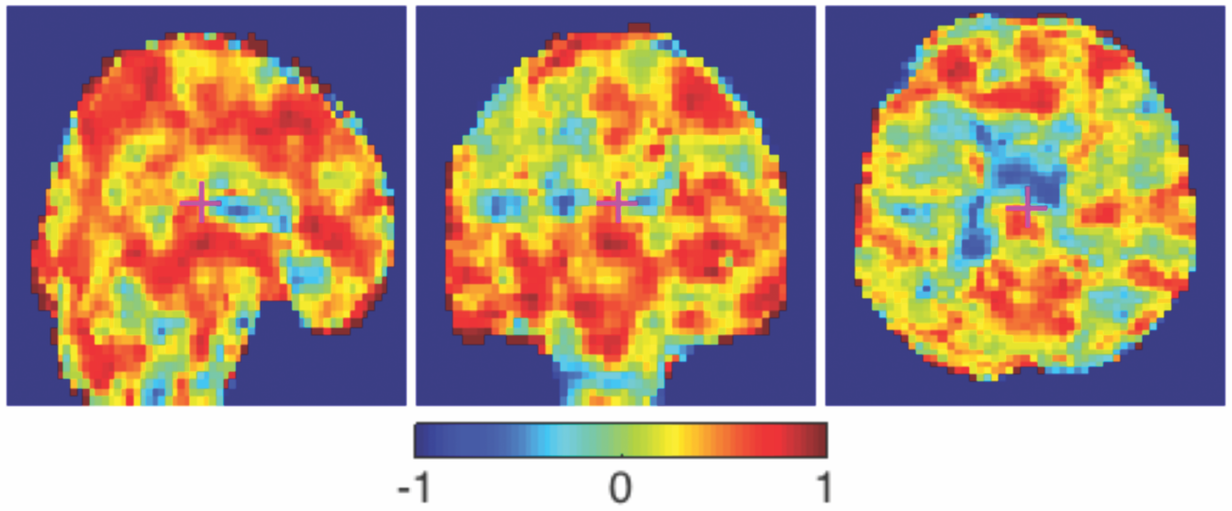
-1 0 1

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

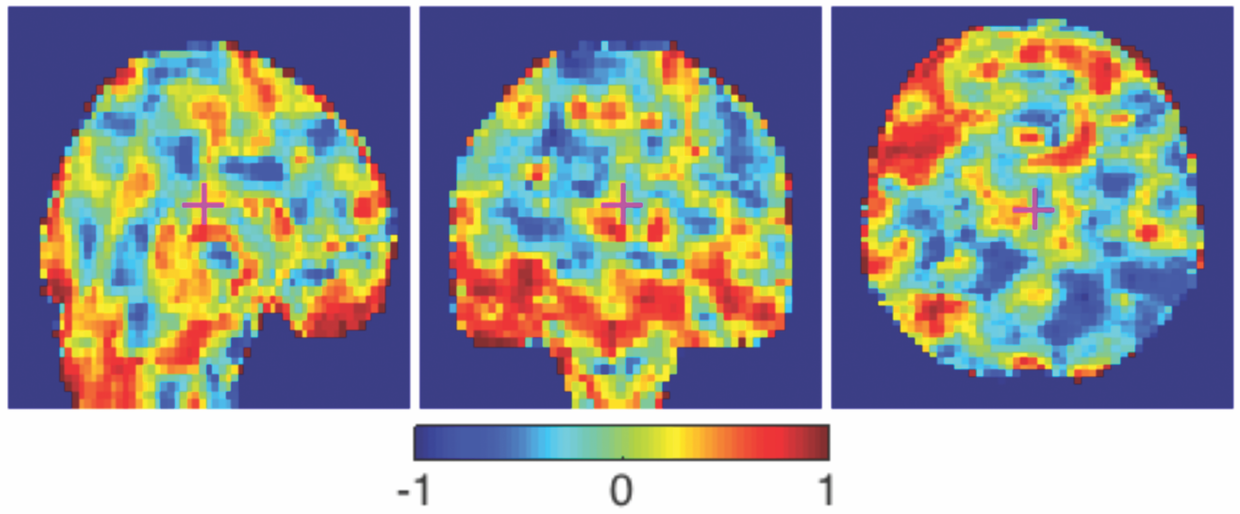
Falconer's formula:

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

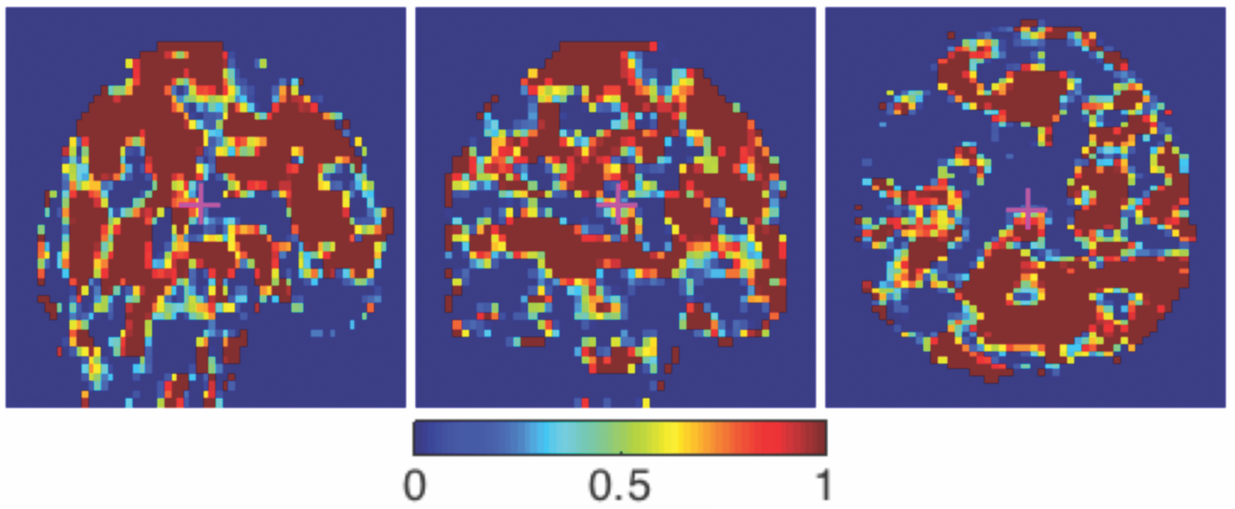
Correlation of MZ-pairs



Correlation of DZ-pairs



Heritability Index



p-value via Jackknife resampling
(multiple comparisons corrected)

Sparse Network Model

Centered and scaled data

n paired contrast maps in *p* voxels (*n* < *p*)

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

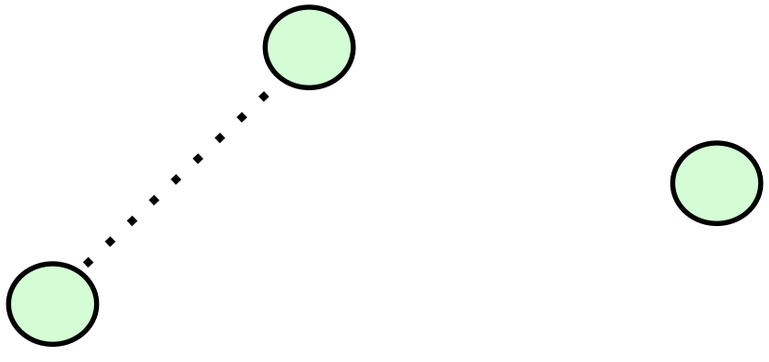
$y_k(v_i)$ *k*-th image intensity value at voxel v_i

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

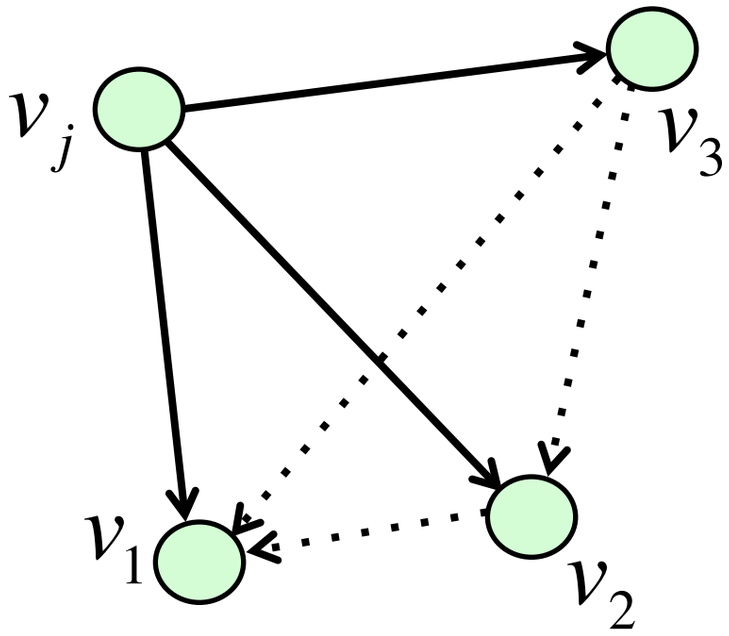
$$x = (x_1, \cdots, x_n)' \qquad y = (y_1, \cdots, y_n)'$$

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

Massive regression between nodes



$$y(v_j) = 0 + \sum_{i \neq j} \beta_{ij} x(v_i) + \varepsilon$$



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

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

Cross-correlation

Sparse cross-correlation

Cross-correlation $x'(v_i)y(v_j)$ minimizes

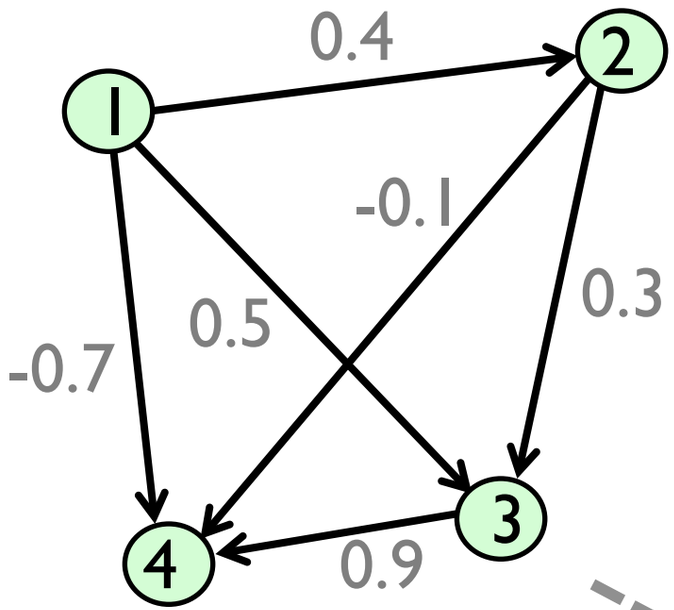
$$\sum_{i=1}^{p}\sum_{j=1}^{p}\left\|y(v_j)-\beta_{ij}x(v_i)\right\|^2$$

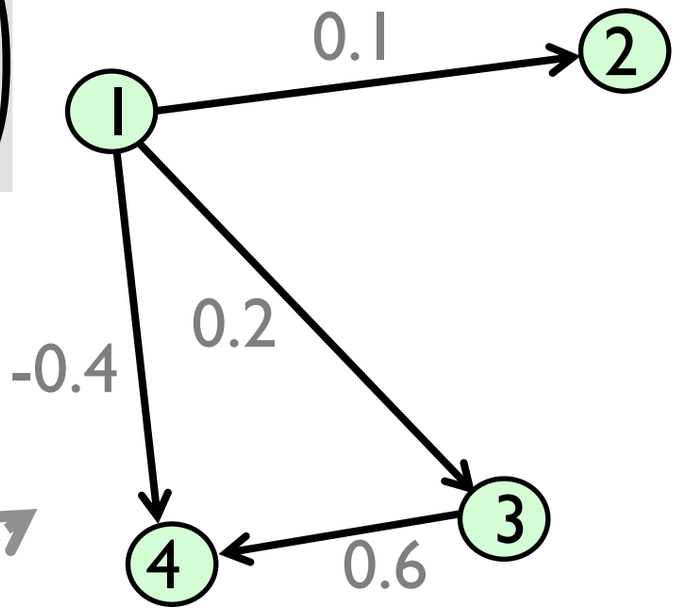
Sparse version: $\beta=(\beta_{ij})$

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

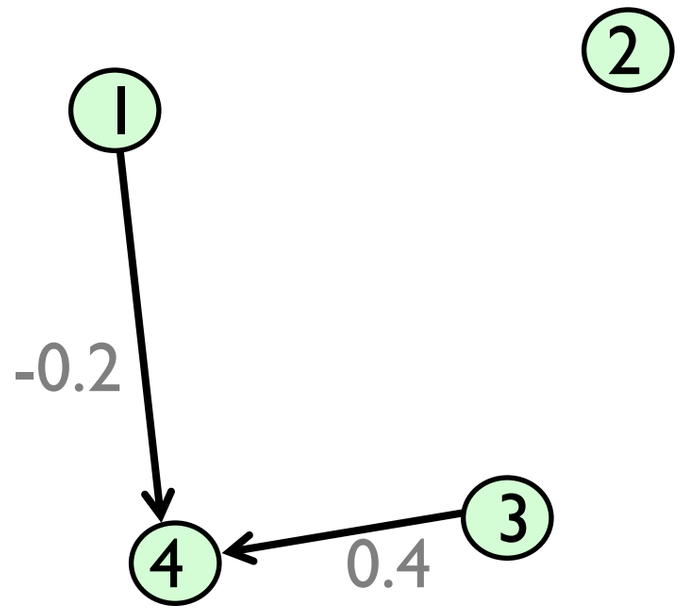
$$\mathbf{x}'\mathbf{y} = \begin{pmatrix} \times & 0.4 & 0.5 & \text{-}0.7 \\ \times & \times & 0.3 & \text{-}0.1 \\ \times & \times & \times & 0.9 \end{pmatrix}$$

optimization



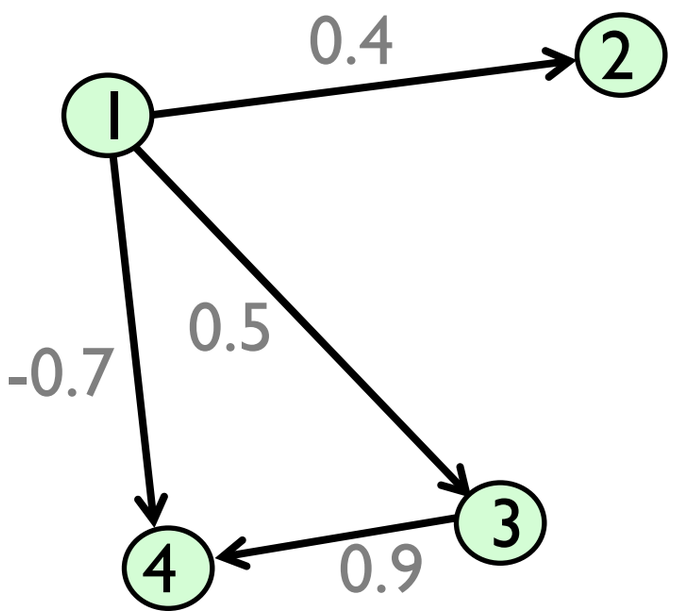


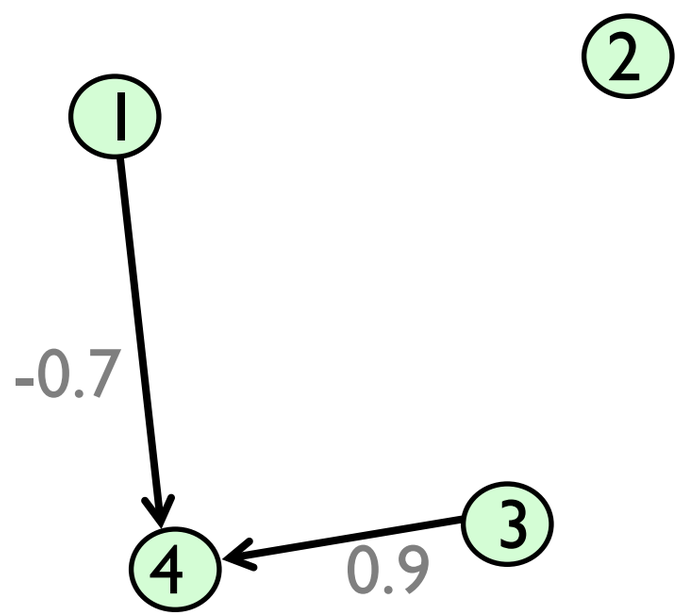
λ=0.3



λ=0.5

Soft-thresholding



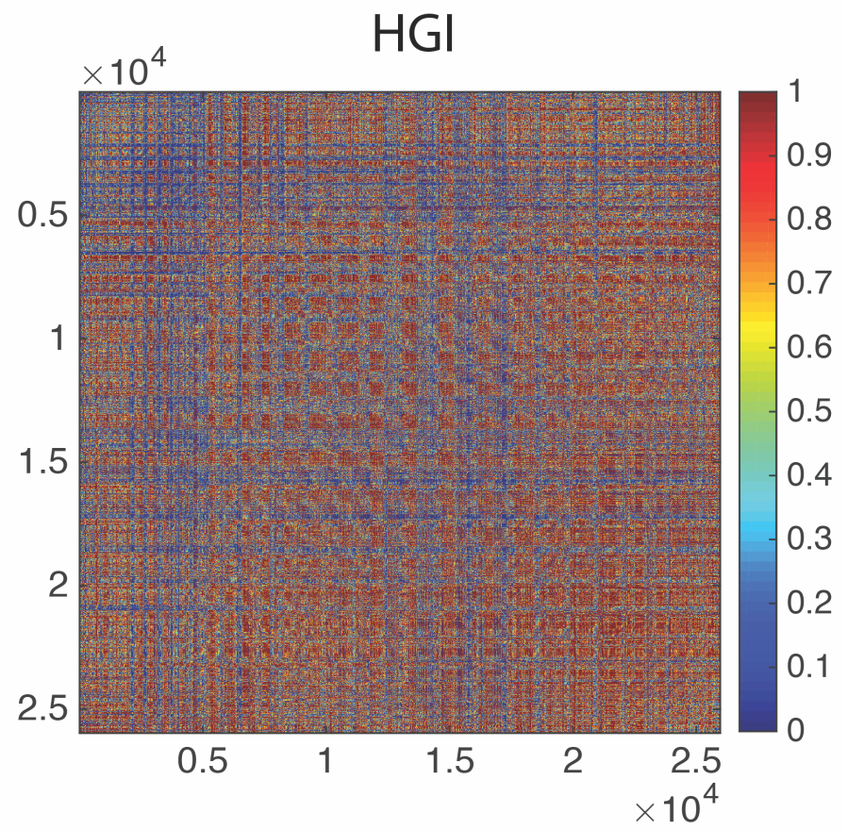


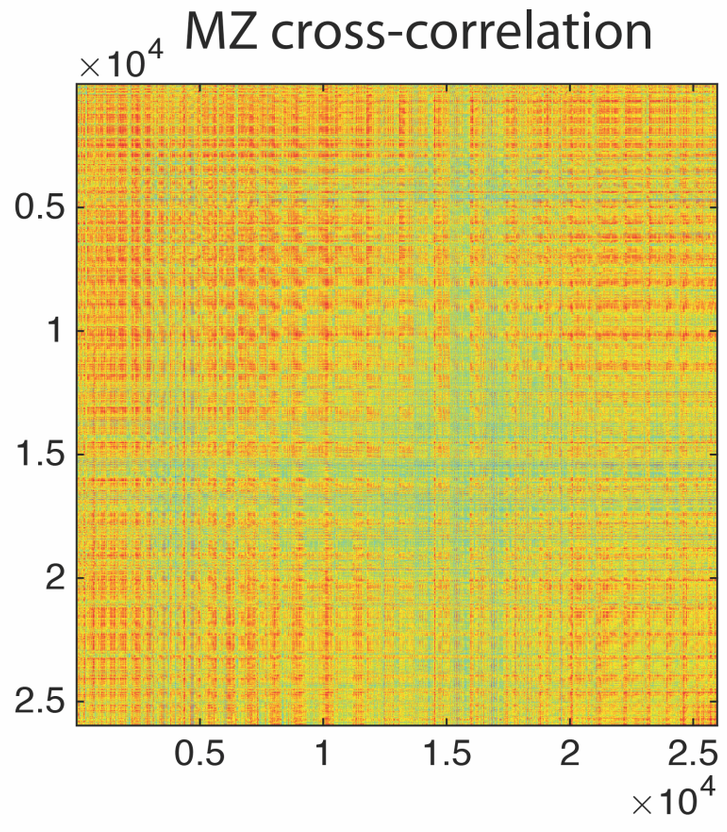
Chung et al. 2015 IEEE Trans. Medical Imaging 34:1928-1939

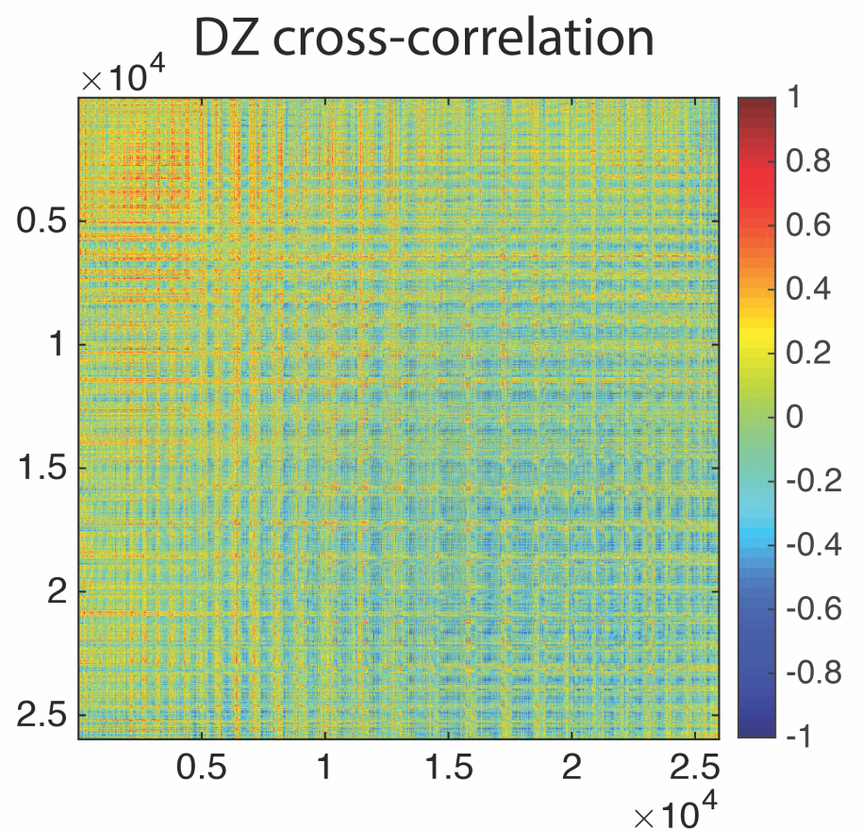
Heritability graph index

Heritability graph index (HGI):

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



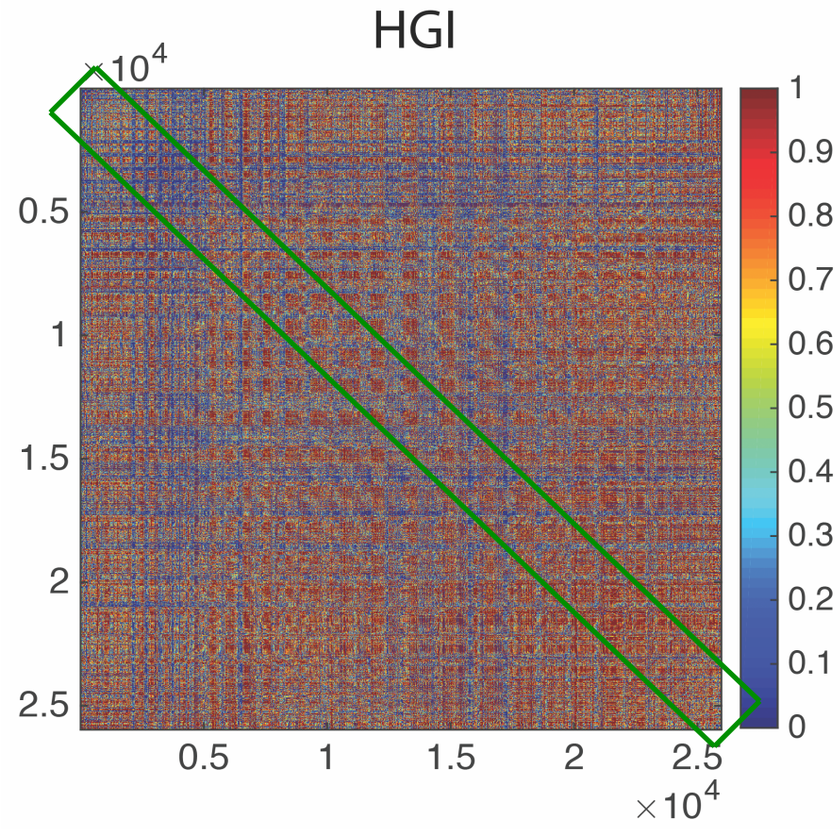


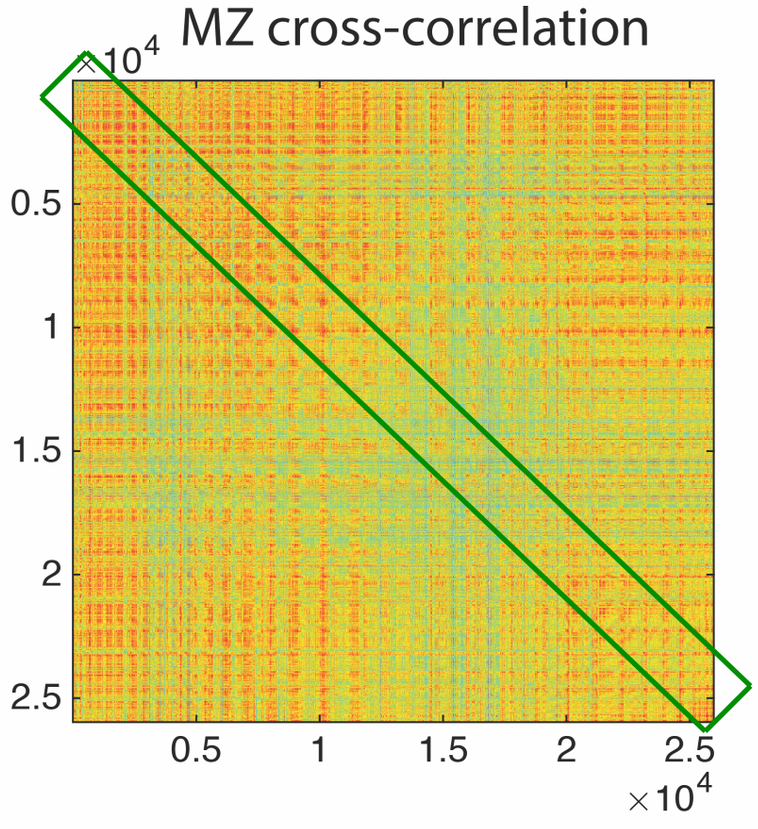


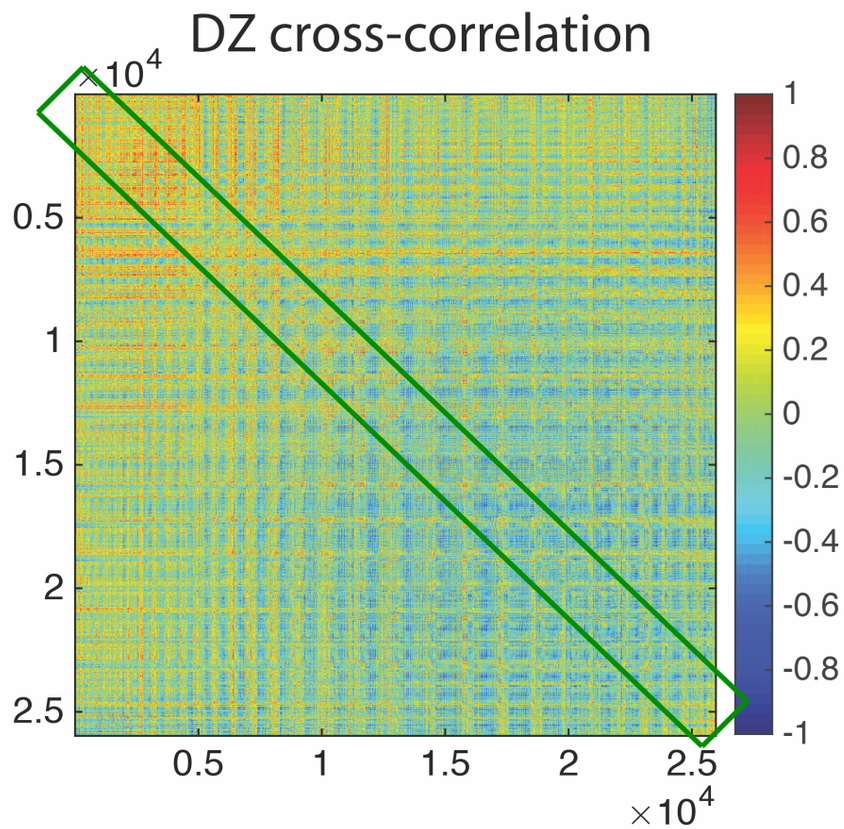
18 sec. computation per matrix

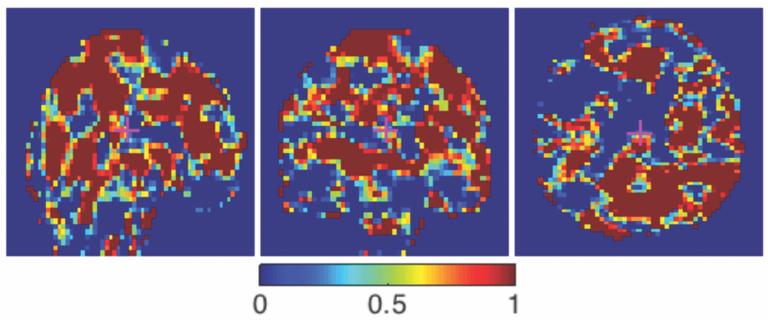
5.2GB per matrix, 3min to save to hard drive

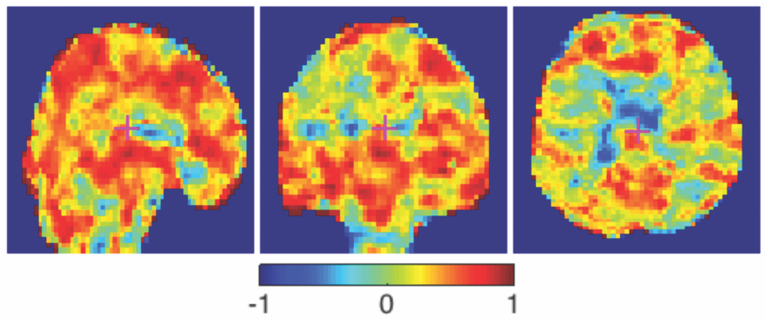
$HGI_{ii} = HI_i$

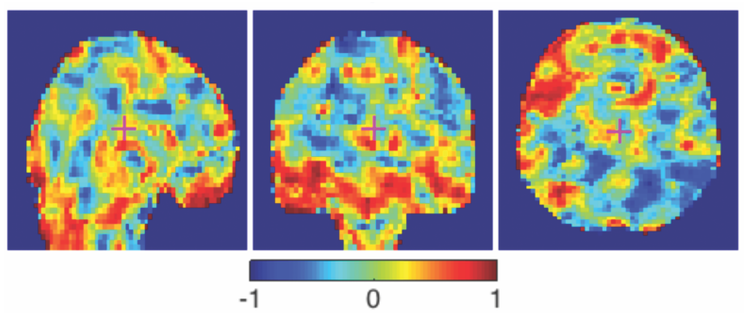

HGI
×10^4
0.5
1
1.5
2
2.5
1
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0


MZ cross-correlation
×10^4
0.5
1
1.5
2
2.5

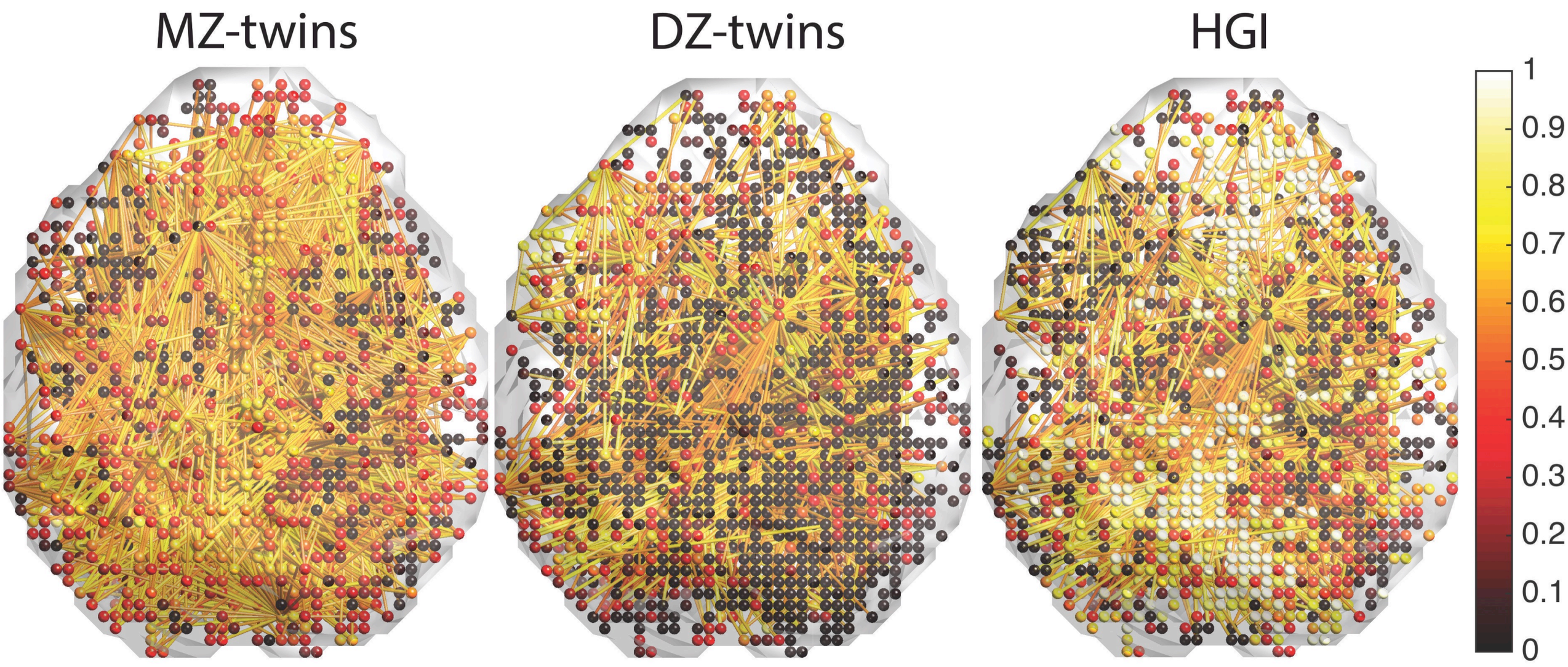

DZ cross-correlation
×10^4
0.5
1
1.5
2
2.5
1
0.8
0.6
0.4
0.2
0
-0.2
-0.4
-0.6
-0.8
-1


0
0.5
1

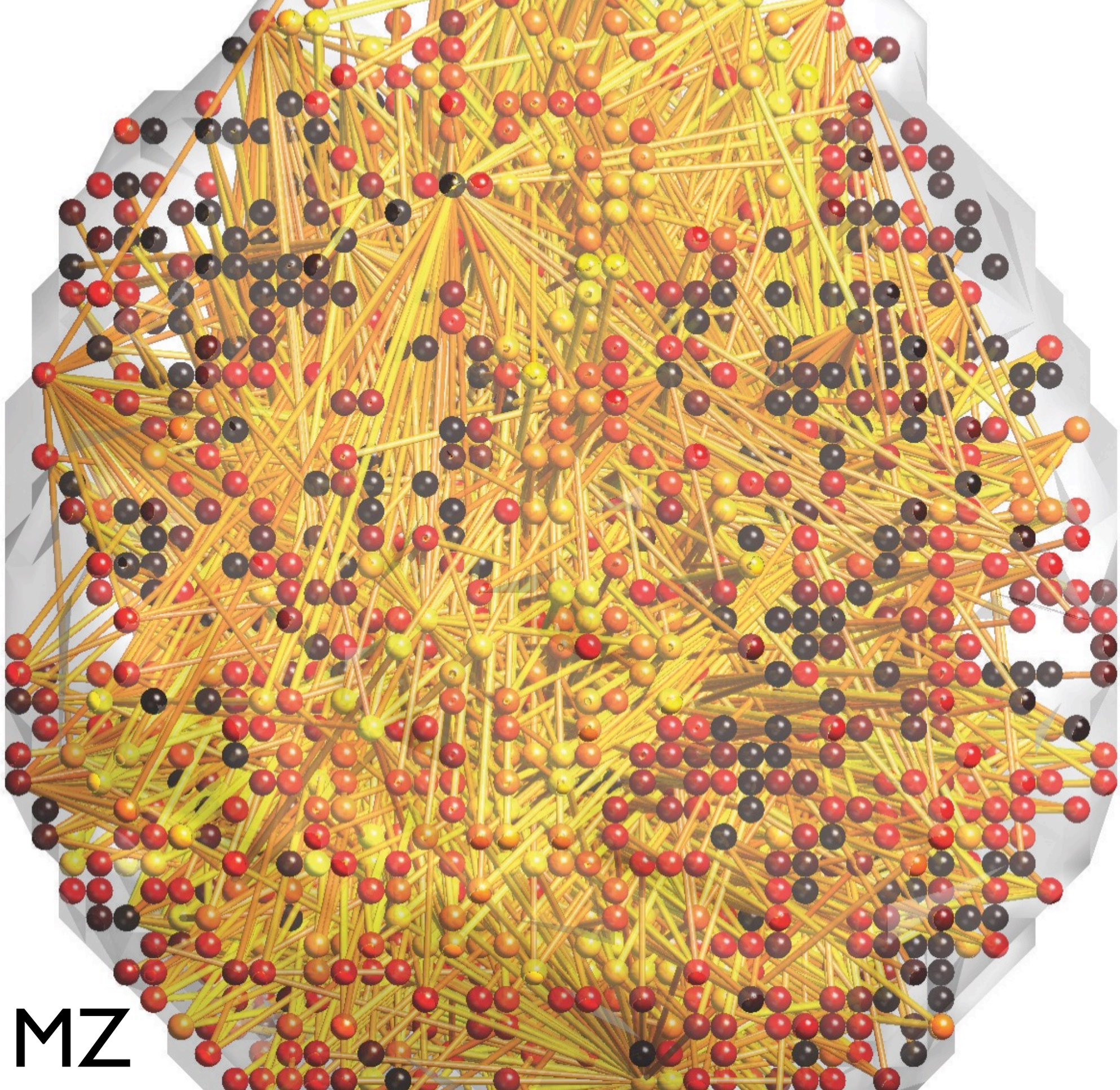

-1
0
1


-1
0
1

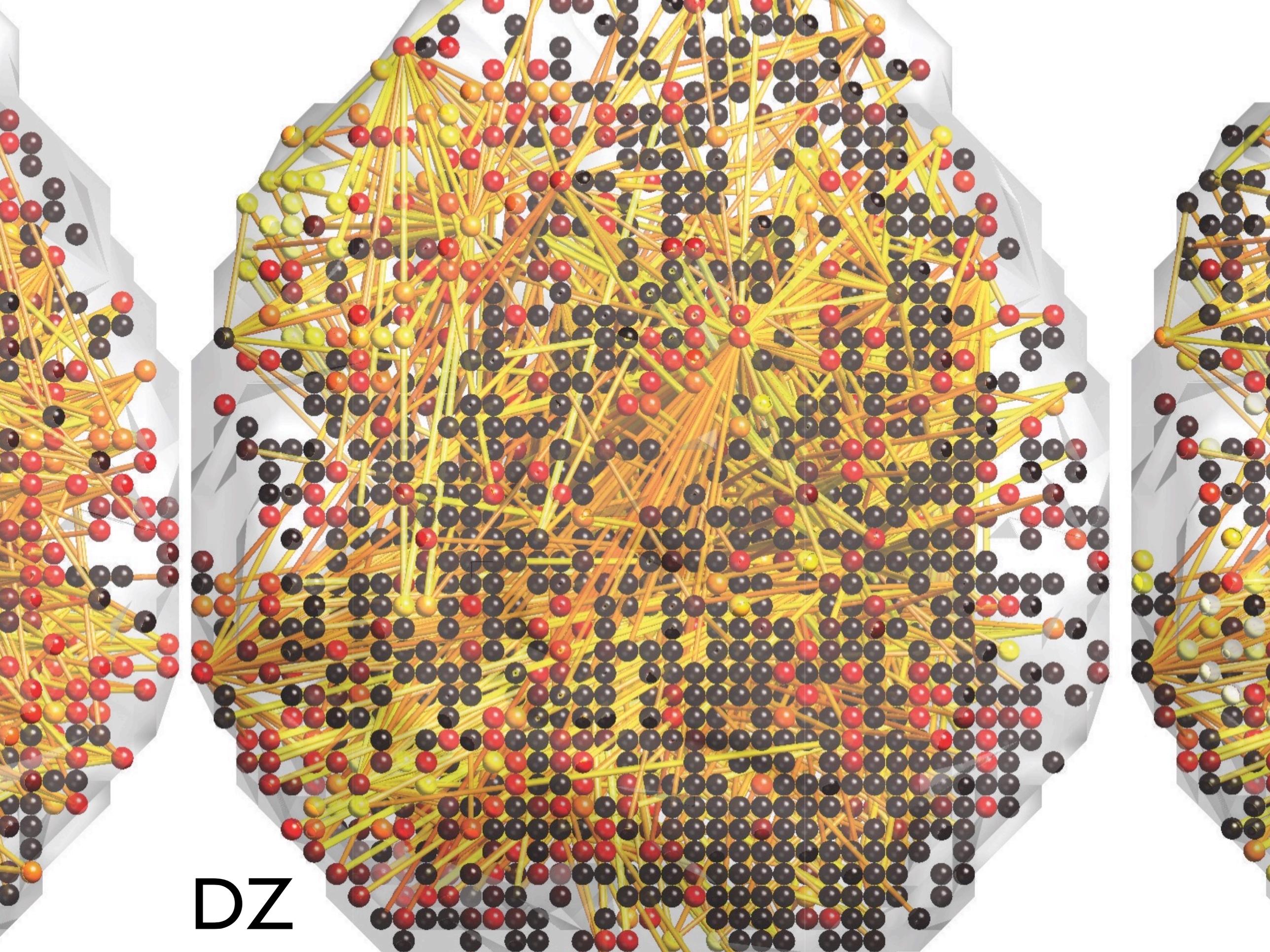
Heritability Graph Index (HGI) at sparse parameter 0.5

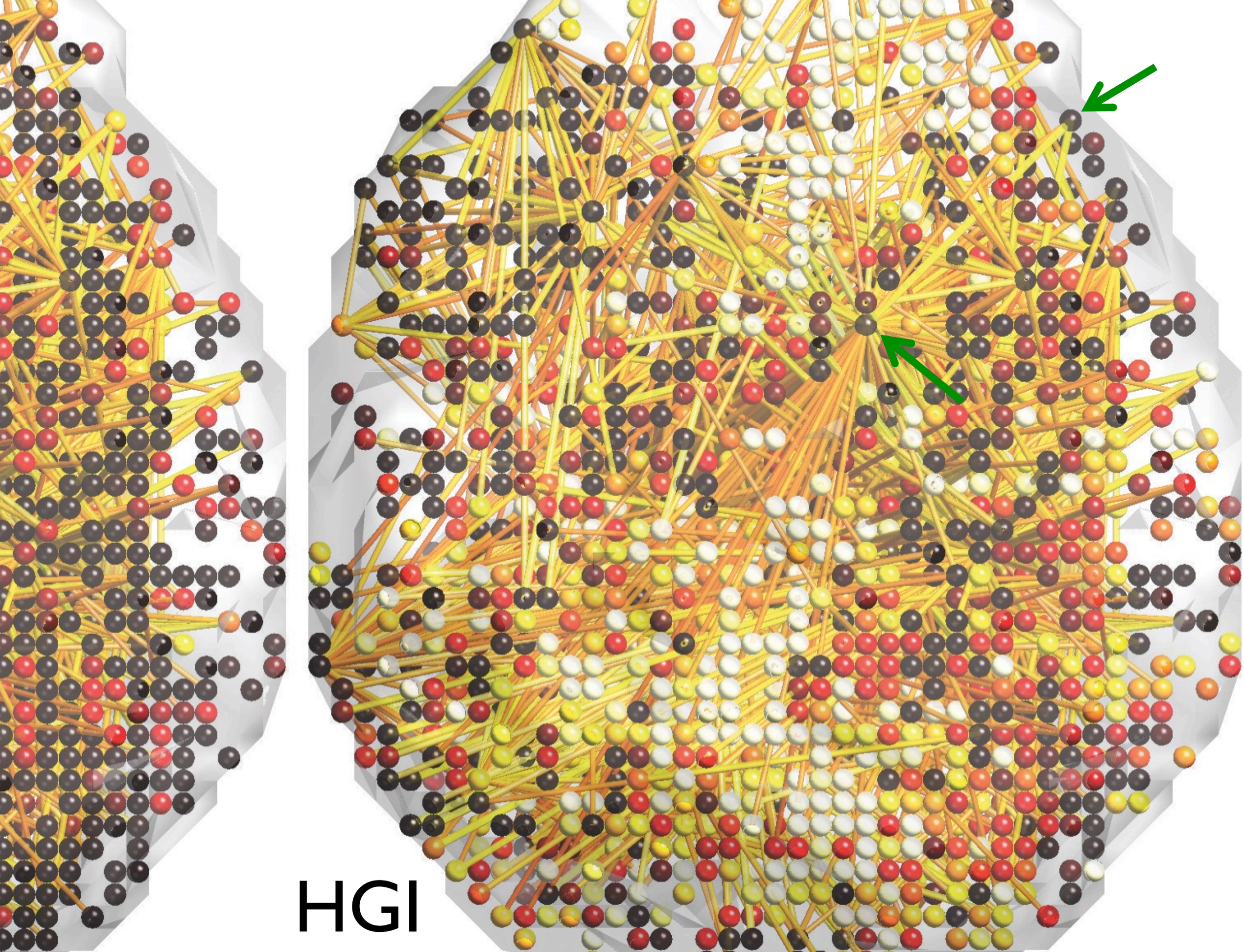


Every voxel is a network node!



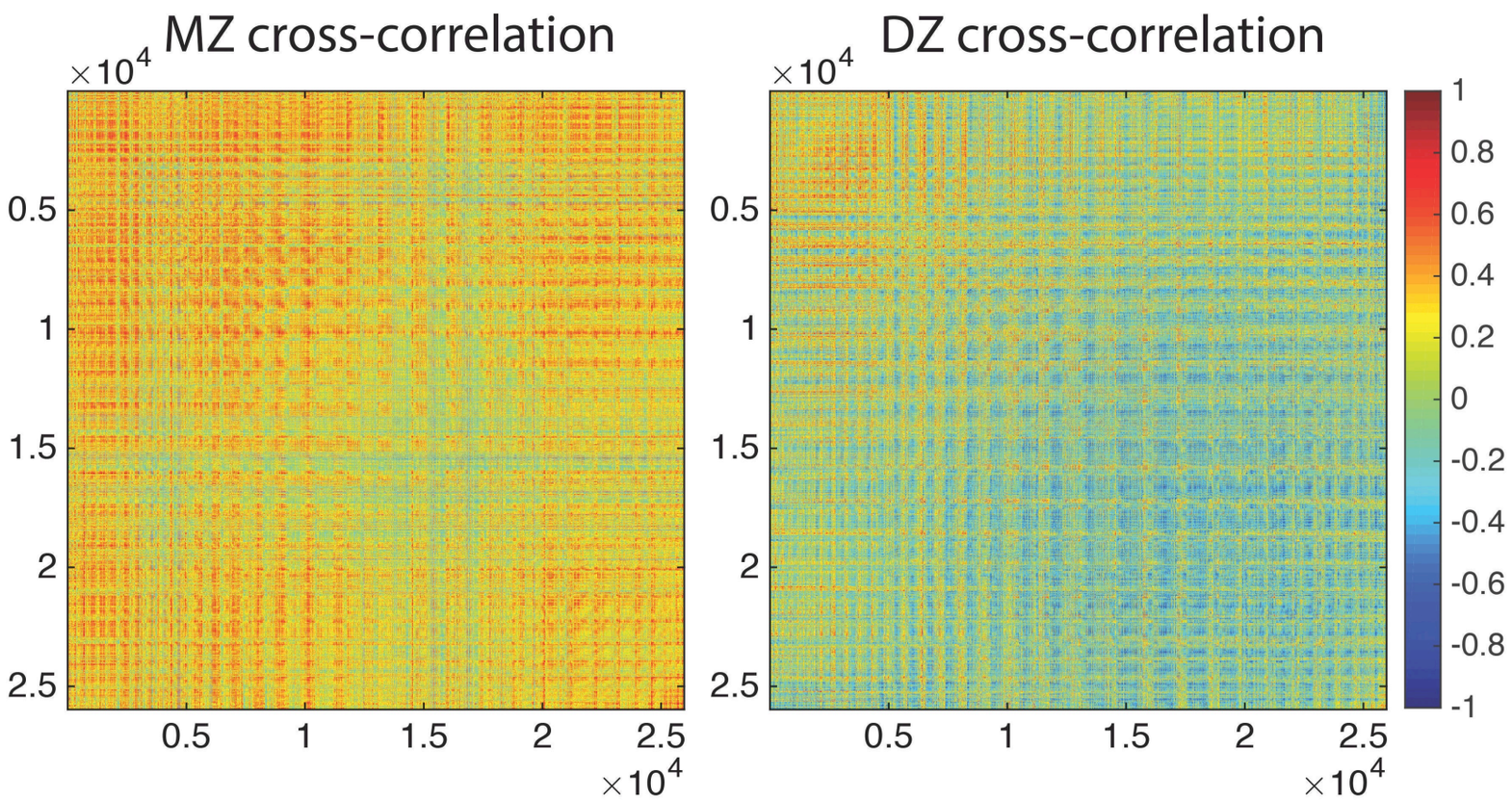
MZ


DZ


HGI

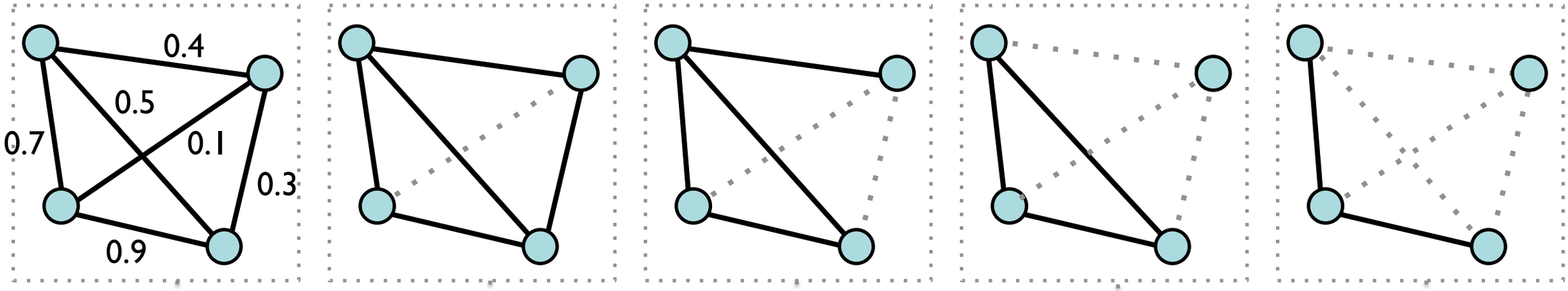
Statistical Inference

$$H_0 : \rho_{MZ} = \rho_{DZ} \quad \text{vs.} \quad H_1 : \rho_{MZ} > \rho_{DZ}$$

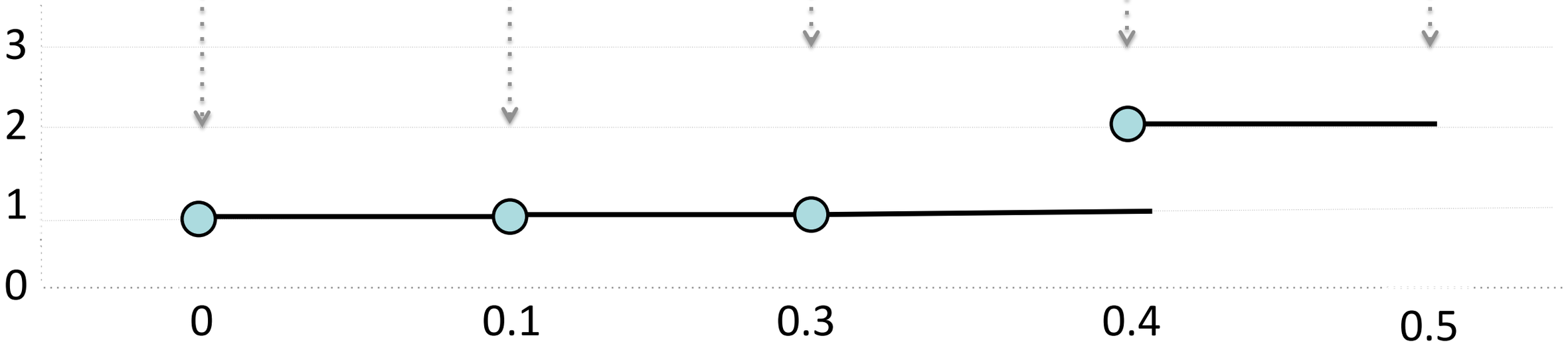


Local inference: Jackknife on the Fisher transform

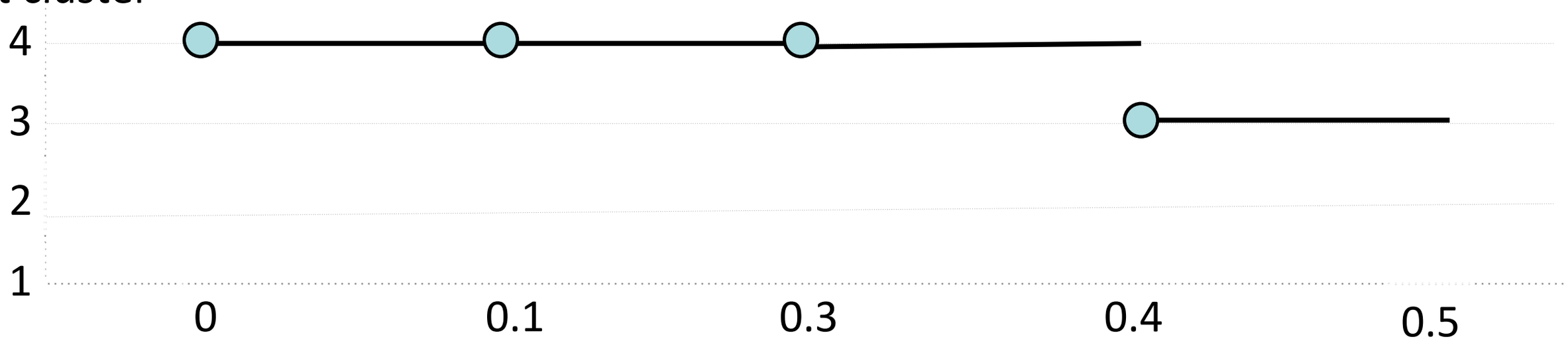
Global inference: Exact nonparametric procedure



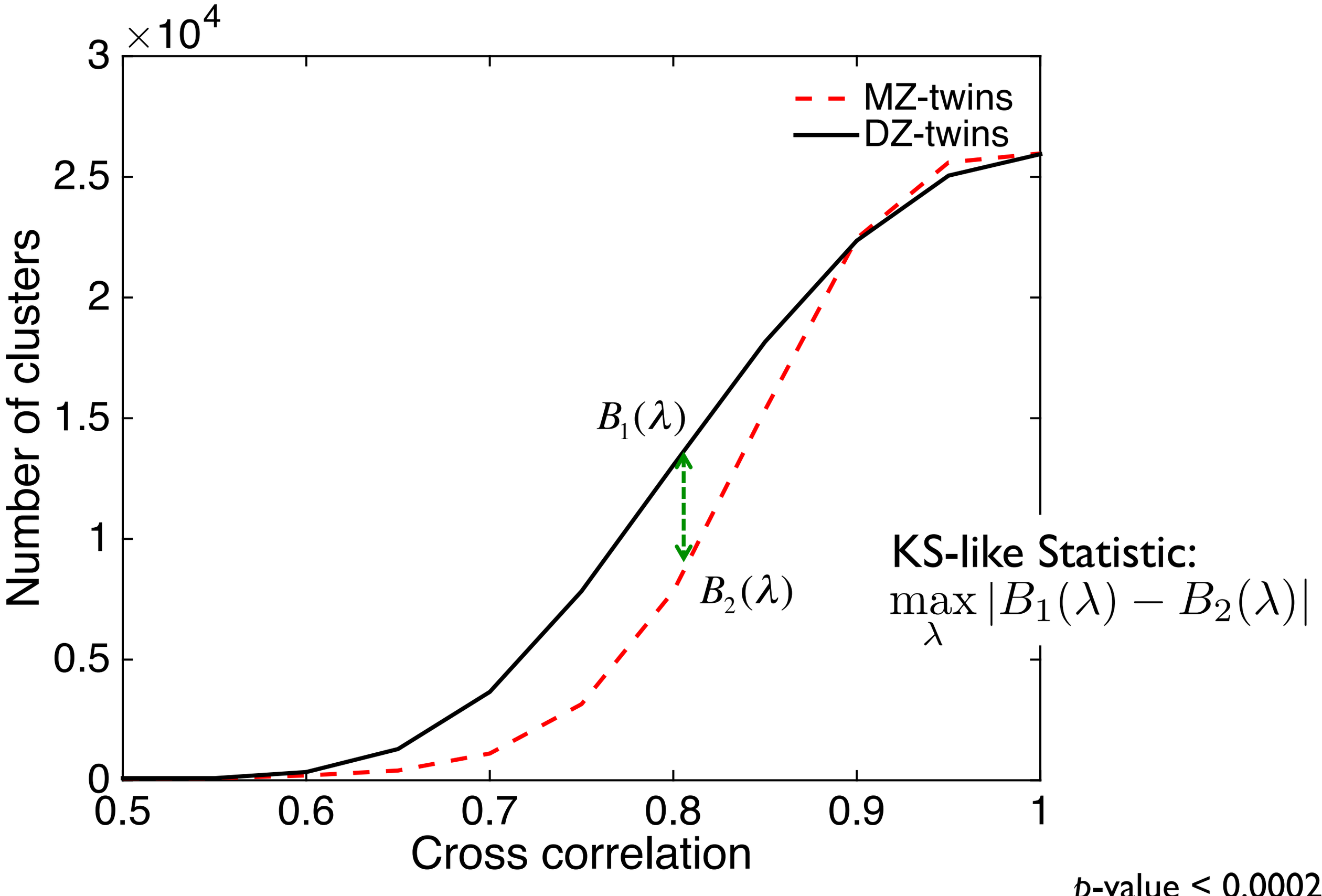
Number of clusters



Size of the largest cluster

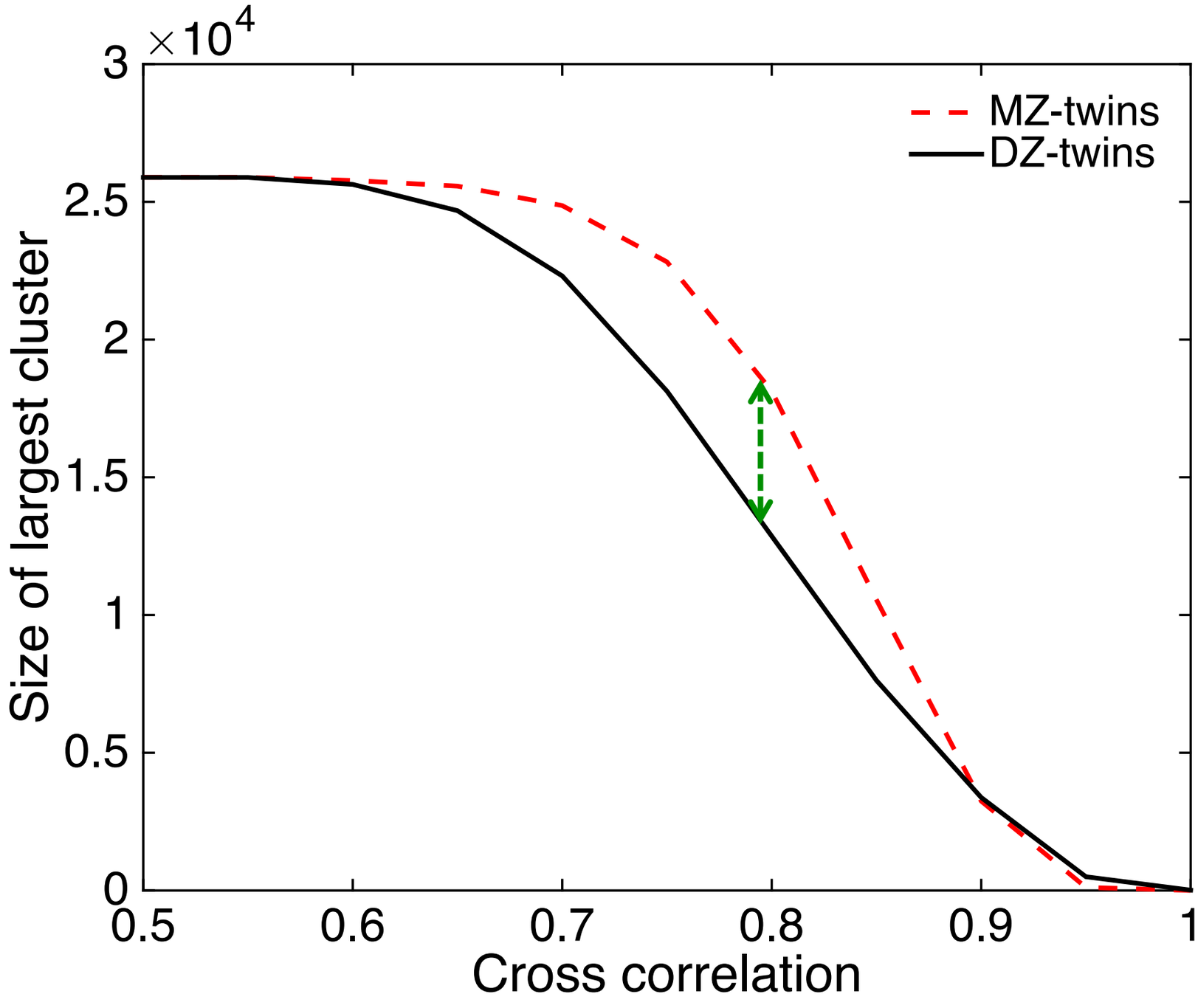


MZ-twins have more clusters of higher correlations



p-value < 0.0002

MZ-twins have more clusters of higher correlations

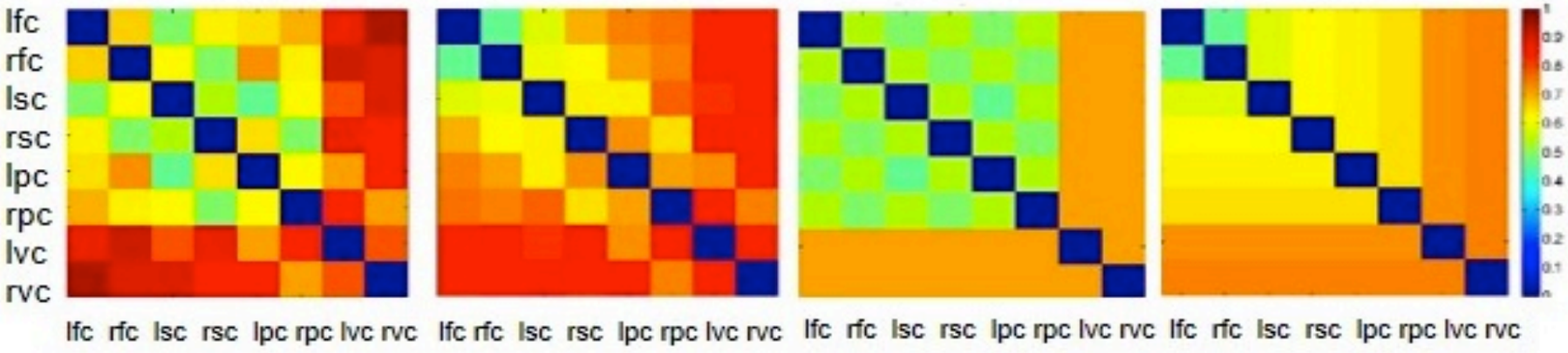


p-value < 0.0001

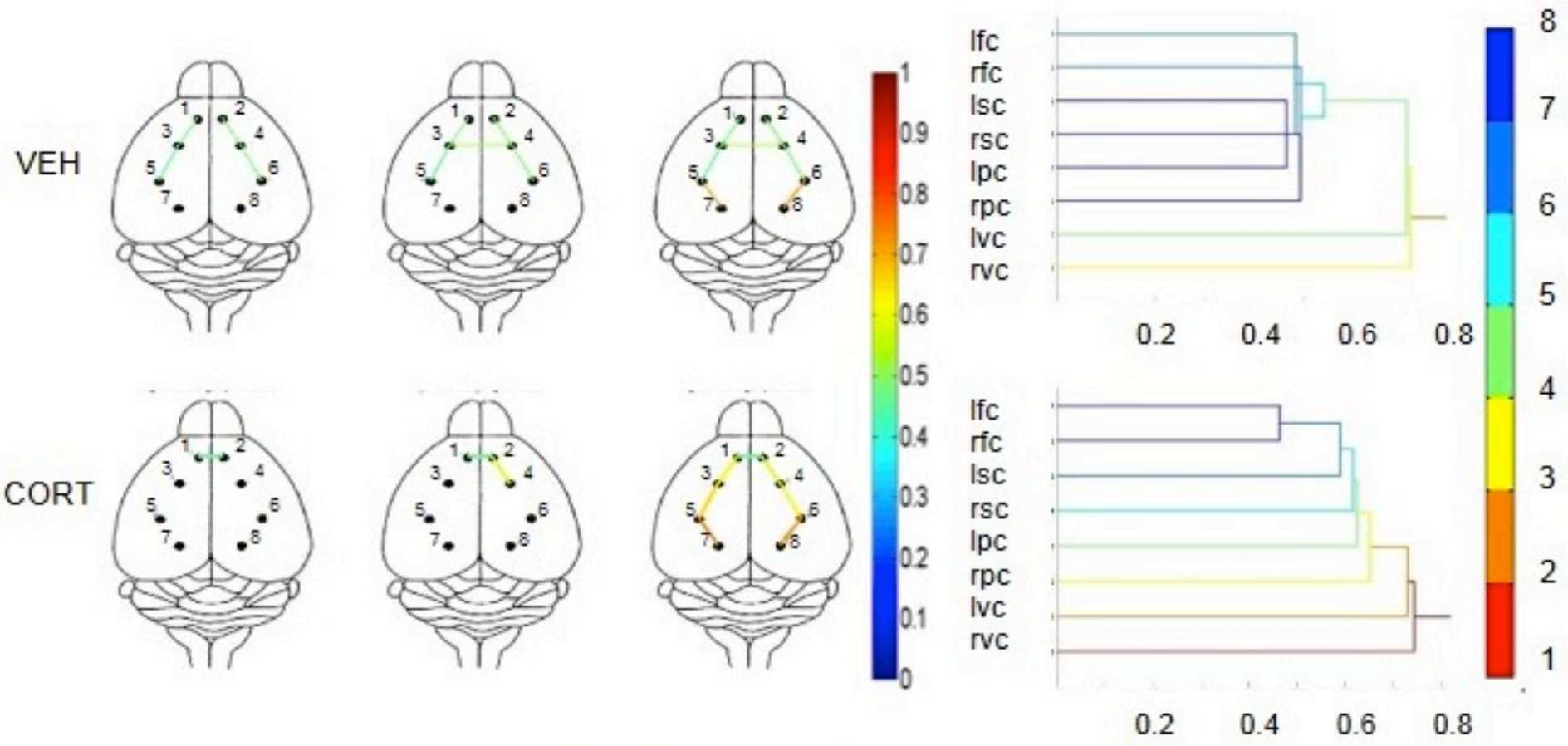
p-value can be exactly computed

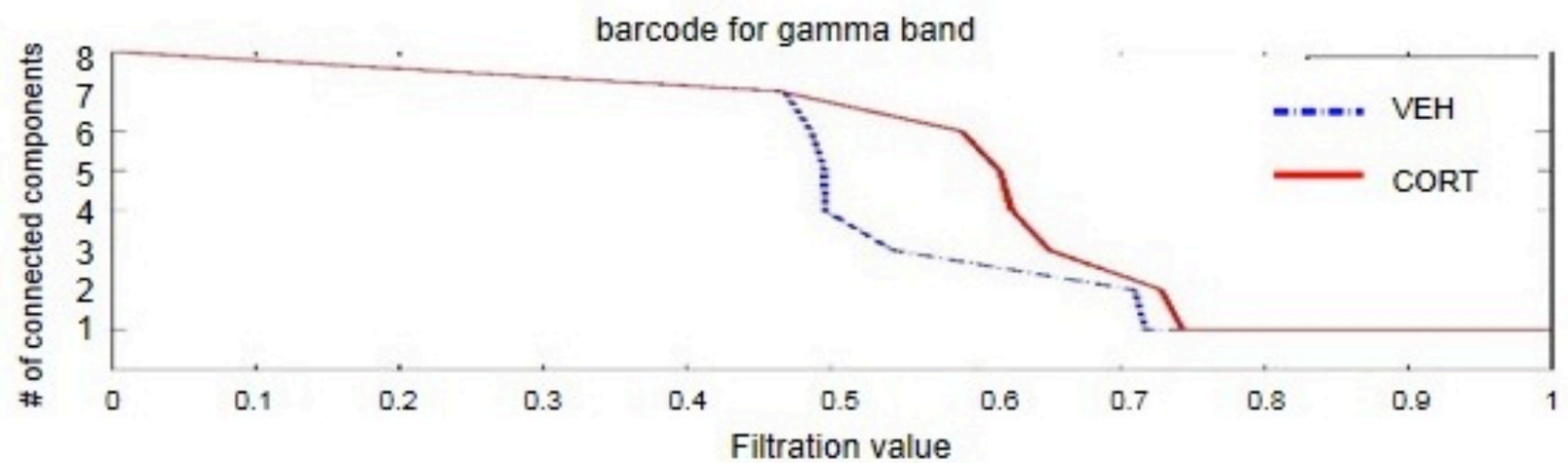
$$P(\sup_{\lambda}\left|B_1(\lambda)-B_2(\lambda)\right|\le\sqrt{2n}d)\approx 1-2e^{-2d^2}$$

Discussion



8 channel EEG mouse model of depression





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

Conclusion

Thresholding connectivity matrix is not stupid.

Brain thought pattern (reward) seems to be in large part heritable.

Thank you