

Maggot brain, mirror image? A statistical analysis of bilateral symmetry in an insect brain connectome

Benjamin D. Pedigo

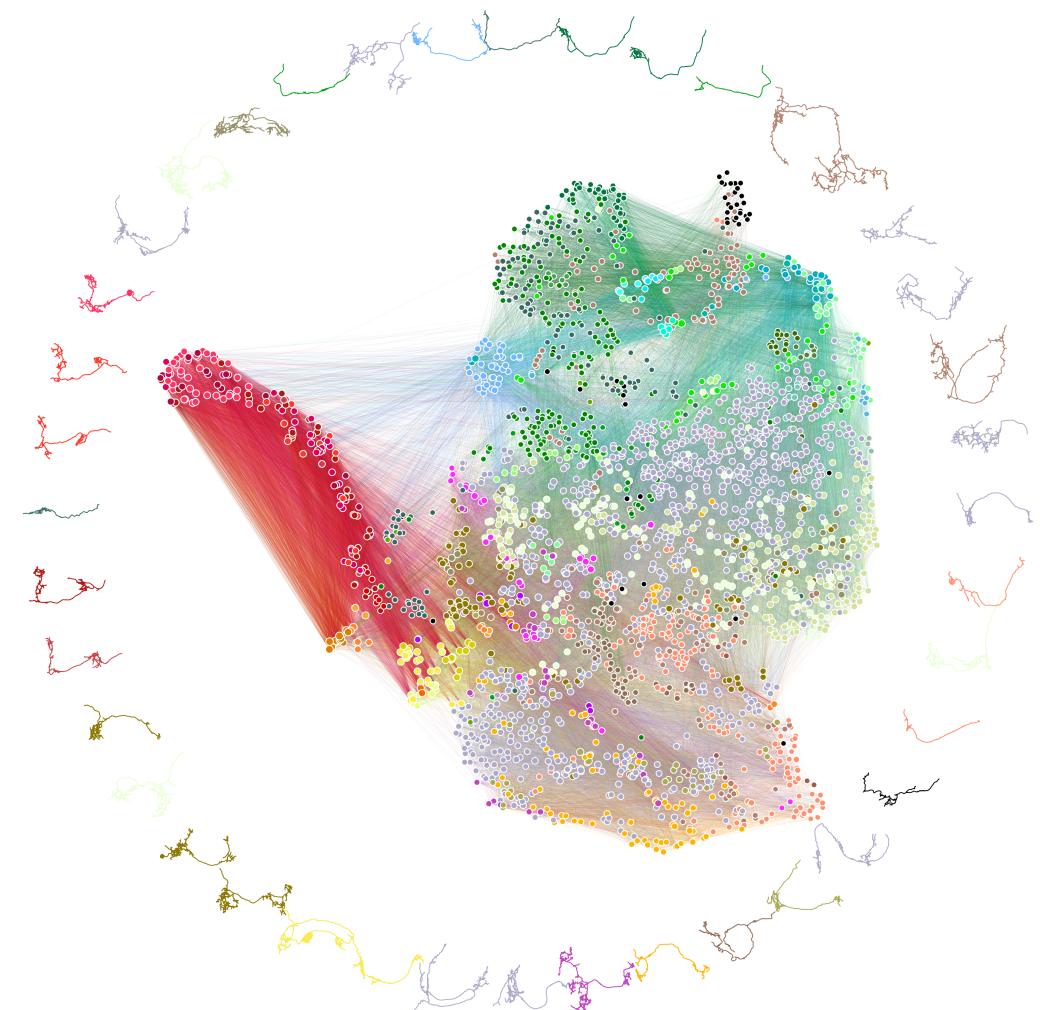
Johns Hopkins University

NeuroData lab

[@bdpedigo \(Github\)](#)

[@bpedigod \(Twitter\)](#)

bpedigo@jhu.edu



Many connectomics questions require comparison

For instance,

- Understand connectomes across evolution [1]
- Understand connectomes across development [2]
- Understand links between genetics and connectivity [3]

[1] Bartsotti + Correia et al. *Curr. Op. Neurobiology* (2021)

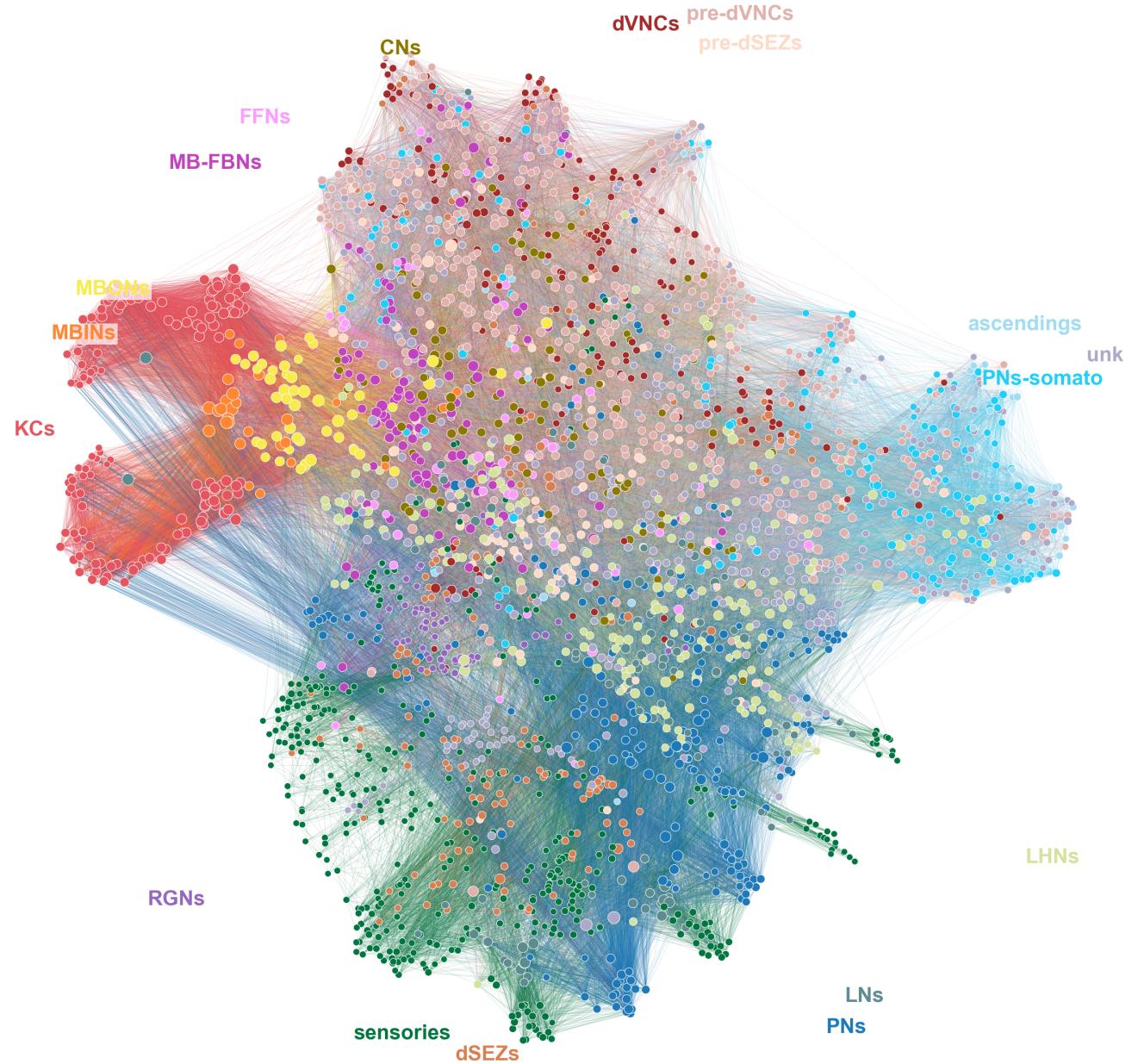
[2] Witvliet et al. *Nature* (2021)

[3] Valdes-Aleman et al. *Neuron* (2021)

Larval *Drosophila* brain connectome

See [Michael Windings's talk](#), 11 AM (EST) Dec 2nd

- ~3000 neurons,
- ~544K synapses
- Both hemispheres of the brain reconstructed

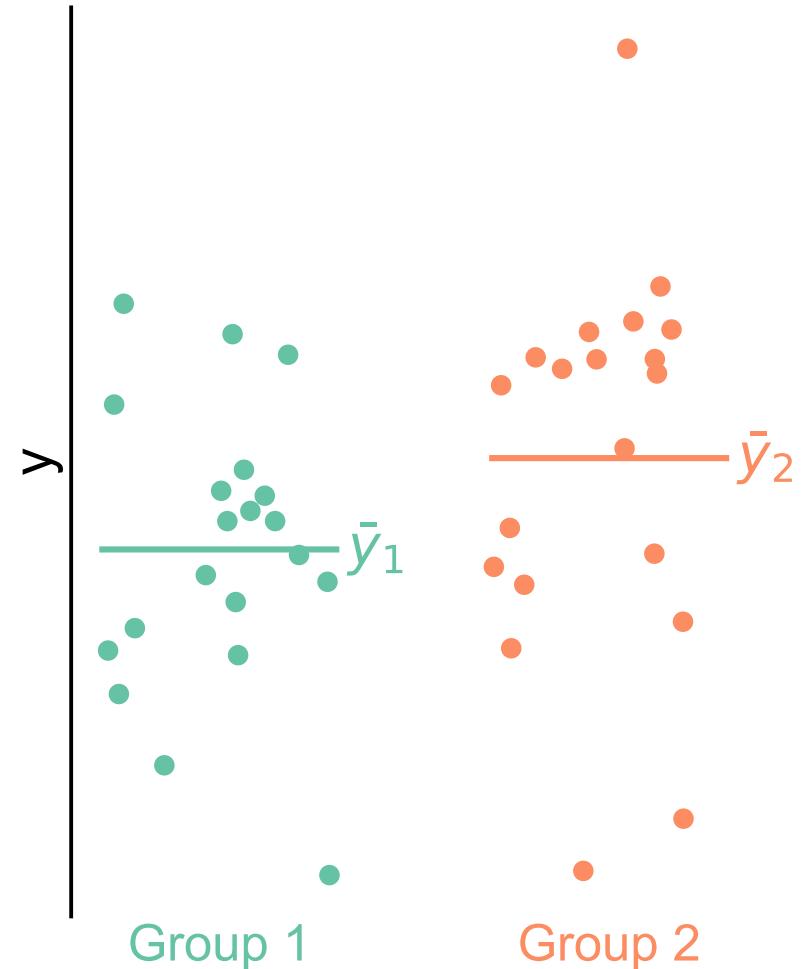


Winding et al. "The complete connectome of an insect brain." In prep (2021)

Are the **left** and **right** sides of this connectome
the same?

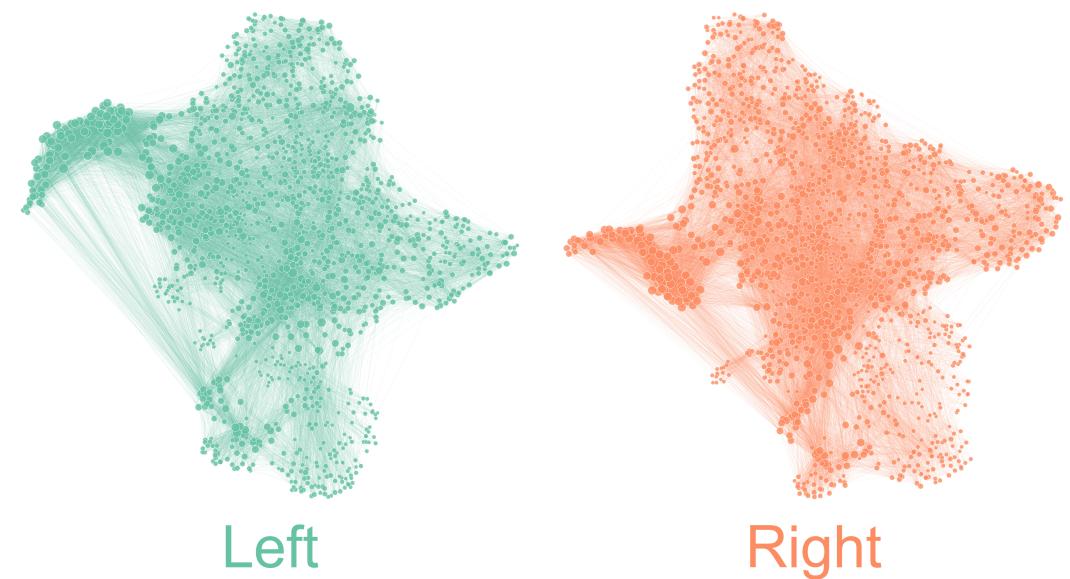
Are these populations the same?

- Known as two-sample testing
- $Y^{(1)} \sim F^{(1)}$, $Y^{(2)} \sim F^{(2)}$
- $H_0 : F^{(1)} = F^{(2)}$
- $H_A : F^{(1)} \neq F^{(2)}$



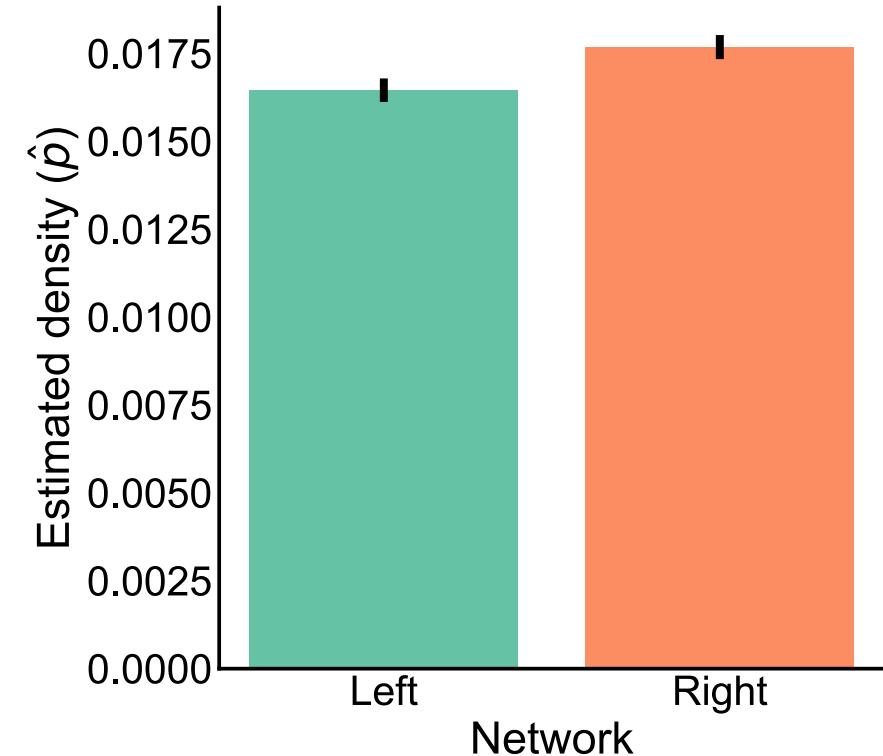
Are these two *networks* the same?

- Want a two-network-sample test!
- For simplicity (for now), consider networks to be *directed, unweighted*.
- For simplicity (for now), consider the **left \rightarrow left** and **right \rightarrow right** (ipsilateral) connections only.
- $A^{(L)} \sim F^{(L)}, A^{(R)} \sim F^{(R)}$
- $H_0 : F^{(L)} = F^{(R)}$
 $H_A : F^{(L)} \neq F^{(R)}$



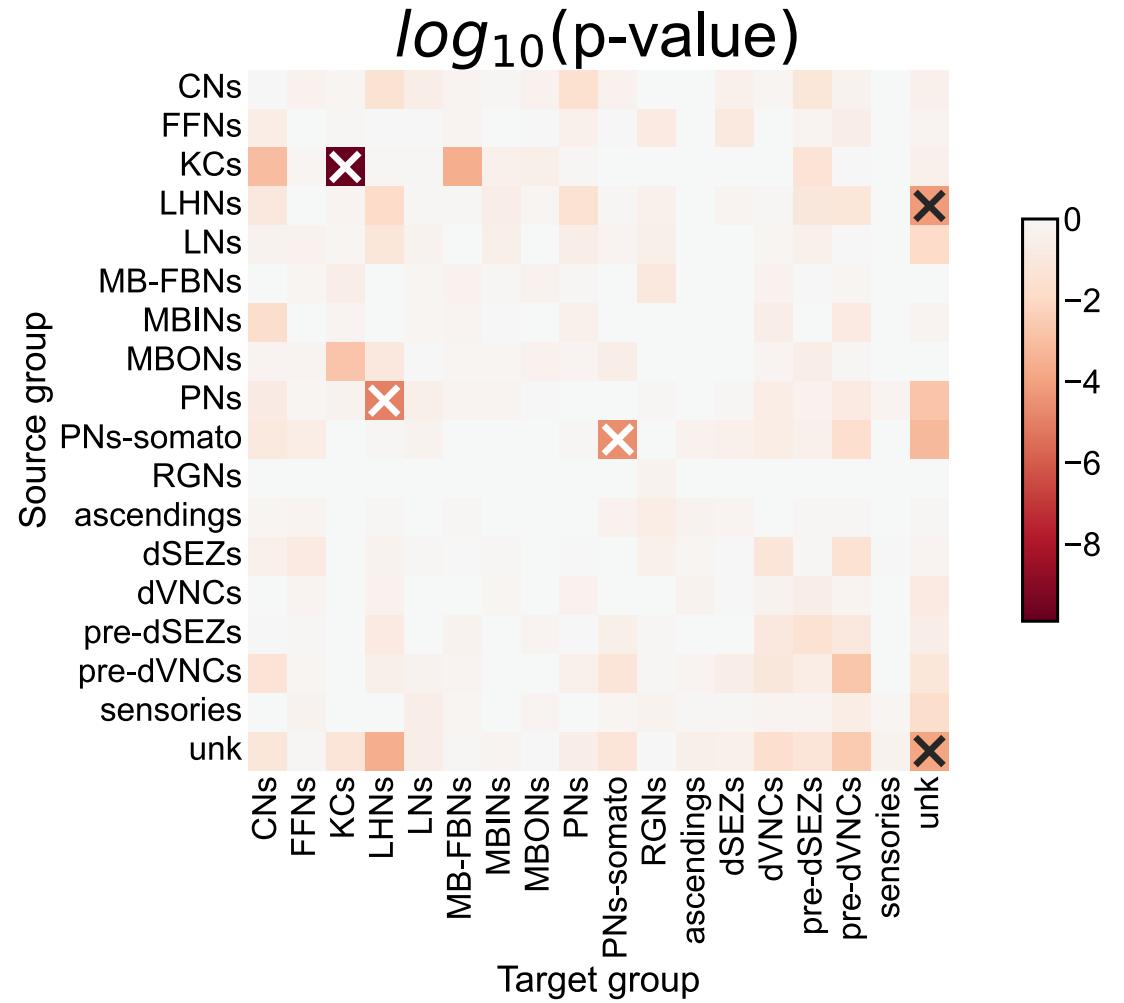
Density-based testing: Erdos-Renyi (ER) model

- Connections independent, same connection probability p for all edges
- $A_{ij} \sim Bernoulli(p)$
- Compare probabilities:
 $H_0 : p^{(L)} = p^{(R)}$
 $H_A : p^{(L)} \neq p^{(R)}$
- **p-value** $< 10^{-23}$
- Is this a difference we care about?



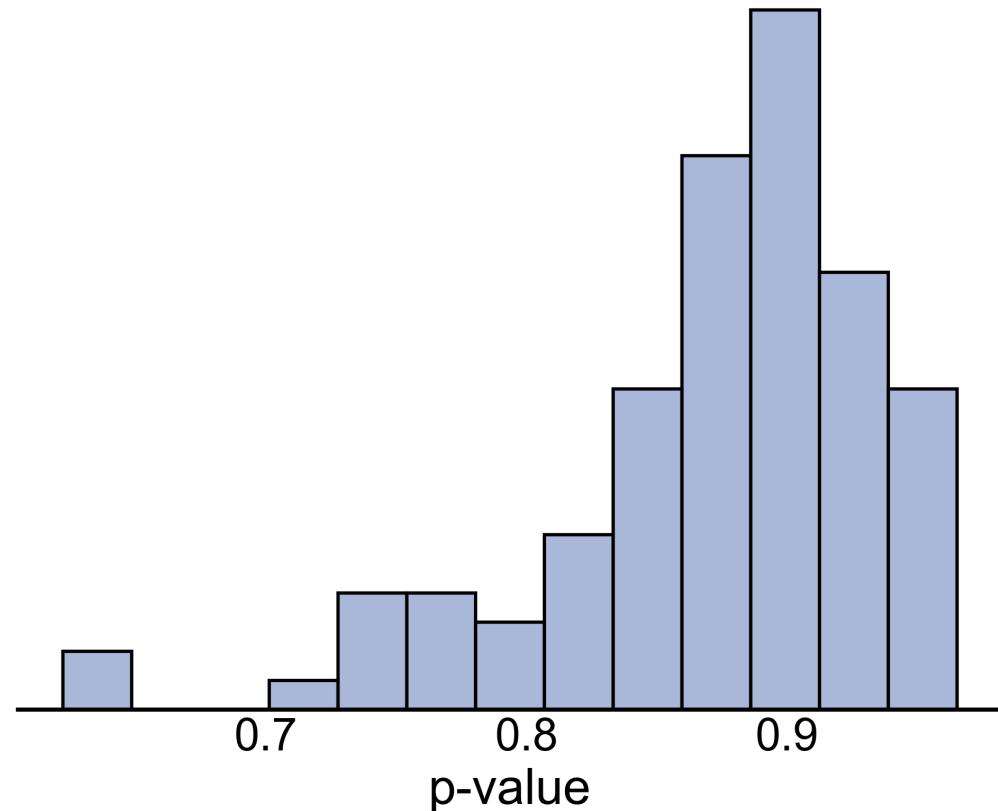
Group-based testing: stochastic block model (SBM)

- Connections independent, with probability set by the source node's group and target node's group
- $A_{ij} \sim \text{Bernoulli}(B_{\tau_i, \tau_j})$
- Compare group-to-group connection probabilities:
 $H_0 : B^{(L)} = B^{(R)}$
 $H_A : B^{(L)} \neq B^{(R)}$
- p-value $< 10^{-4}$



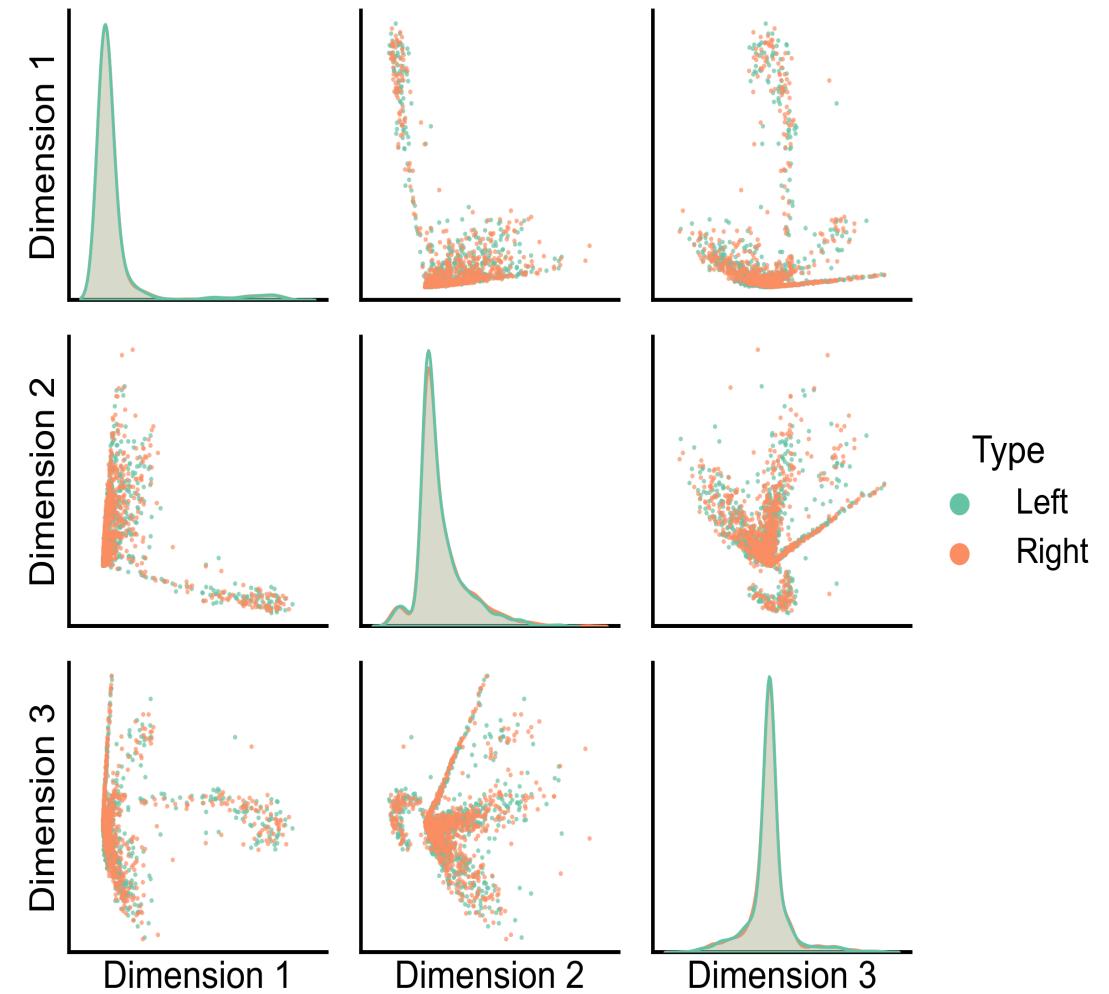
Adjusting for a difference in density

- Rejecting $B^{(L)} = B^{(R)}$ can be explained by the difference in density?
- New null hypothesis:
 $H_0 : B^{(L)} = cB^{(R)}$
where c is a density-adjusting constant, $\frac{p^{(L)}}{p^{(R)}}$
- Randomly subsample edges from denser network, rerun test
- **p-values** > 0.6



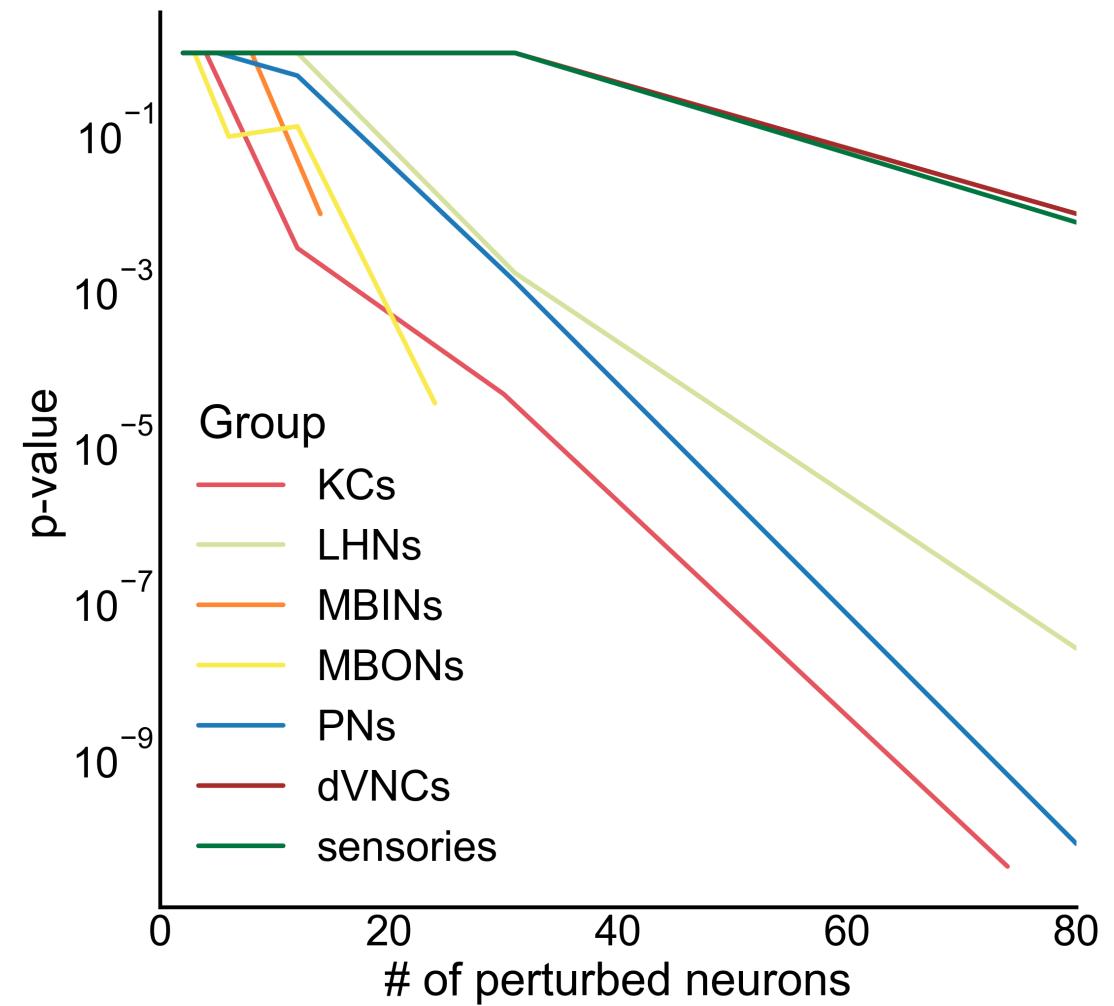
More flexibility: Random dot product graph (RDPG)

- Connections independent, probability from dot product of source node's latent vector, target node's latent vector.
- $A_{ij} \sim \text{Bernoulli}(\langle \mathbf{x}_i, \mathbf{y}_j \rangle)$
- $\mathbf{x}_i^{(L)} \sim \mathcal{F}^{(L)}$, $\mathbf{x}_i^{(R)} \sim \mathcal{F}^{(R)}$
- Compare distributions of latent vectors:
 $H_0 : \mathcal{F}^{(L)} = \mathcal{F}^{(R)}$
 $H_A : \mathcal{F}^{(L)} \neq \mathcal{F}^{(R)}$
- p-value ≈ 1



Can we detect differences when we know they exist?

- Make two copies of right hemisphere network
- Apply some perturbation to one of them:
 - Ex: Shuffle edges incident to some number of nodes in some group
- Rerun the RDPG-based test for symmetry



To sum up...

Model	H_0 (vs. $H_A \neq$)	p-value	Interpretation
ER	$p^{(L)} = p^{(R)}$	$< 10^{-23}$	Reject densities the same
SBM	$B^{(L)} = B^{(R)}$	$< 10^{-4}$	Reject cell type connection probabilities the same
SBM	$B^{(L)} = cB^{(R)}$	≈ 0.7	Don't reject the above after density adjustment
RDPG	$F^{(L)} = F^{(R)}$	≈ 1	Don't reject latent distributions the same

The answer to this very simple question totally depends on how you frame it!

- Tests are sensitive to some alternatives and not others
- Difference you might not care about (e.g. density) need to be explicitly accounted for

Future work

- Many other tests (e.g. compare subgraph counts)
- Studying the sets of alternatives each test is/is not sensitive to
- Roadmap for future principled comparisons of connectome networks!

graspologic:

github.com/microsoft/graspologic



This work:

github.com/neurodata/bilateral-connectome

The screenshot shows a documentation page for 'Bilateral Connectome' under the 'NEURODATA' brand. The page includes a search bar, navigation links for 'Abstract', 'PRELIMINARIES', and various scientific topics like 'Introduction', 'Outline', and 'Unmatched vs. matched networks'. A sidebar on the right is titled 'The Erdos-Renyi (ER) model' and contains mathematical details about the ER model, including its definition and the probability formula $P[A_{ij} = 1] = p_{ij} = p$.

Acknowledgements

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University of Cambridge / Laboratory of Molecular Biology

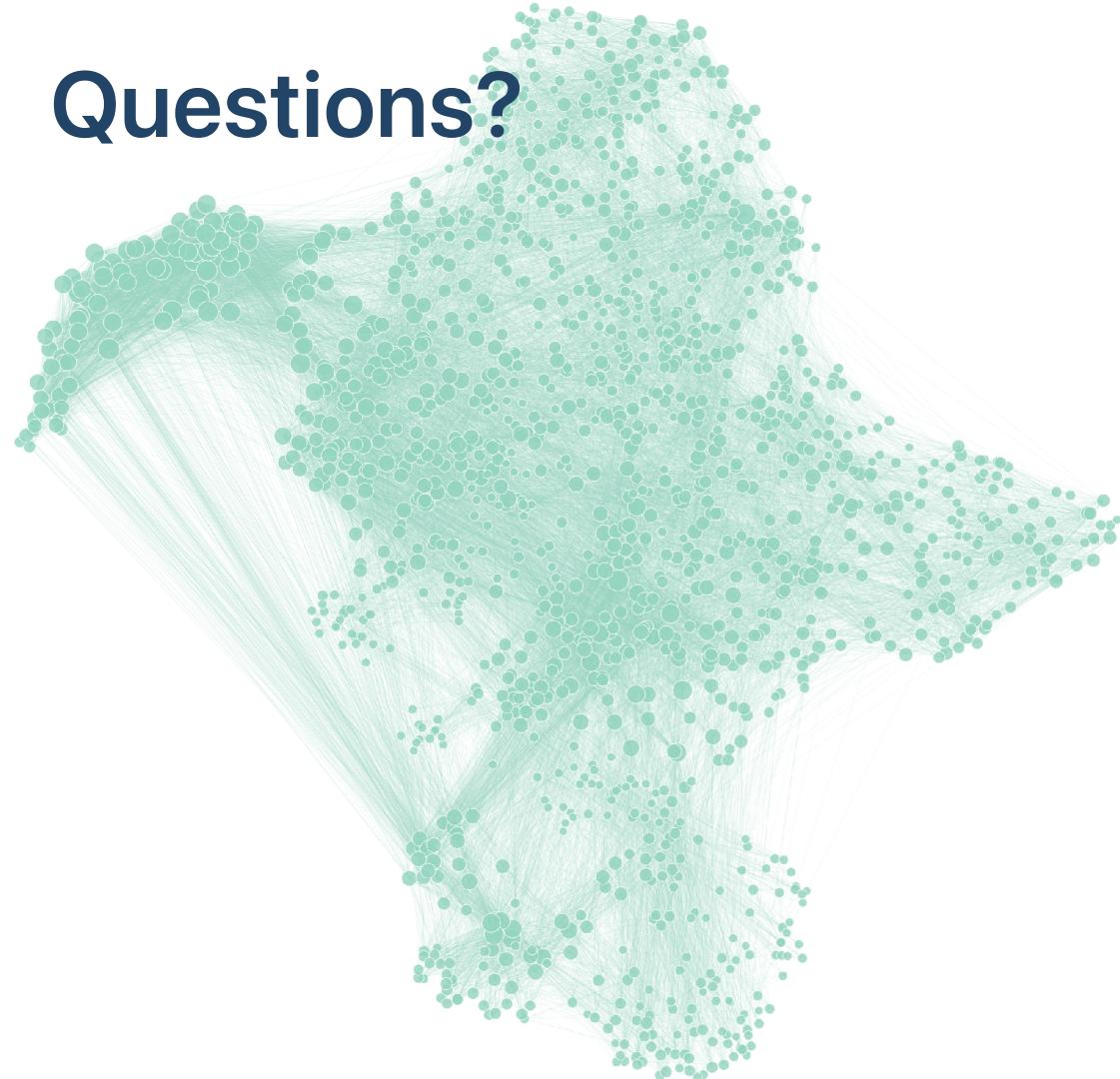
Michael Winding, Albert Cardona, Marta Zlatic, Chris Barnes

Microsoft Research

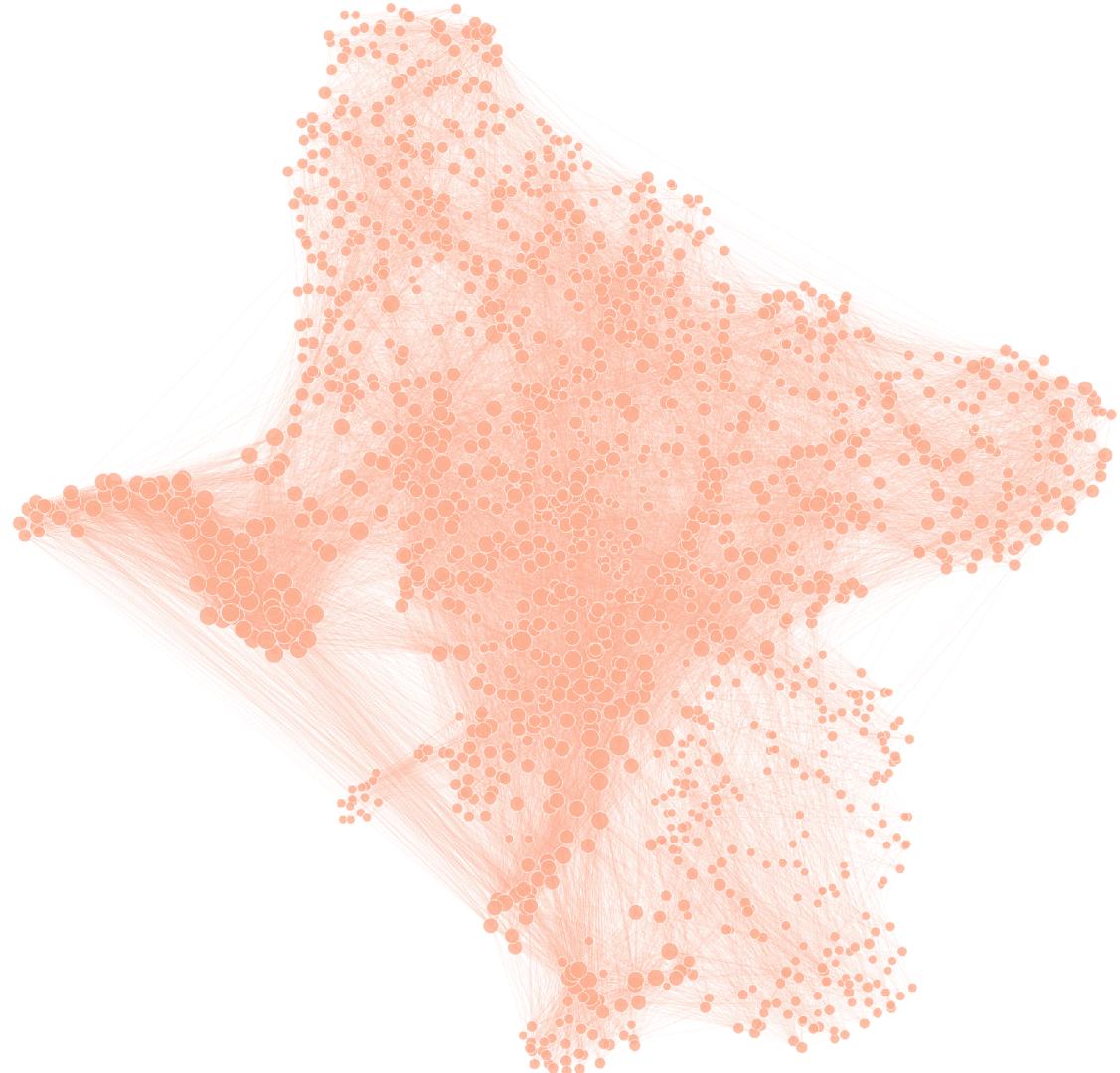
Hayden Helm, Dax Pryce, Nick Caurvina, Bryan Tower, Patrick Bourke, Jonathan McLean, Carolyn Buractaon, Amber Hoak

NMC organizers!

Questions?



Left



Right