

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

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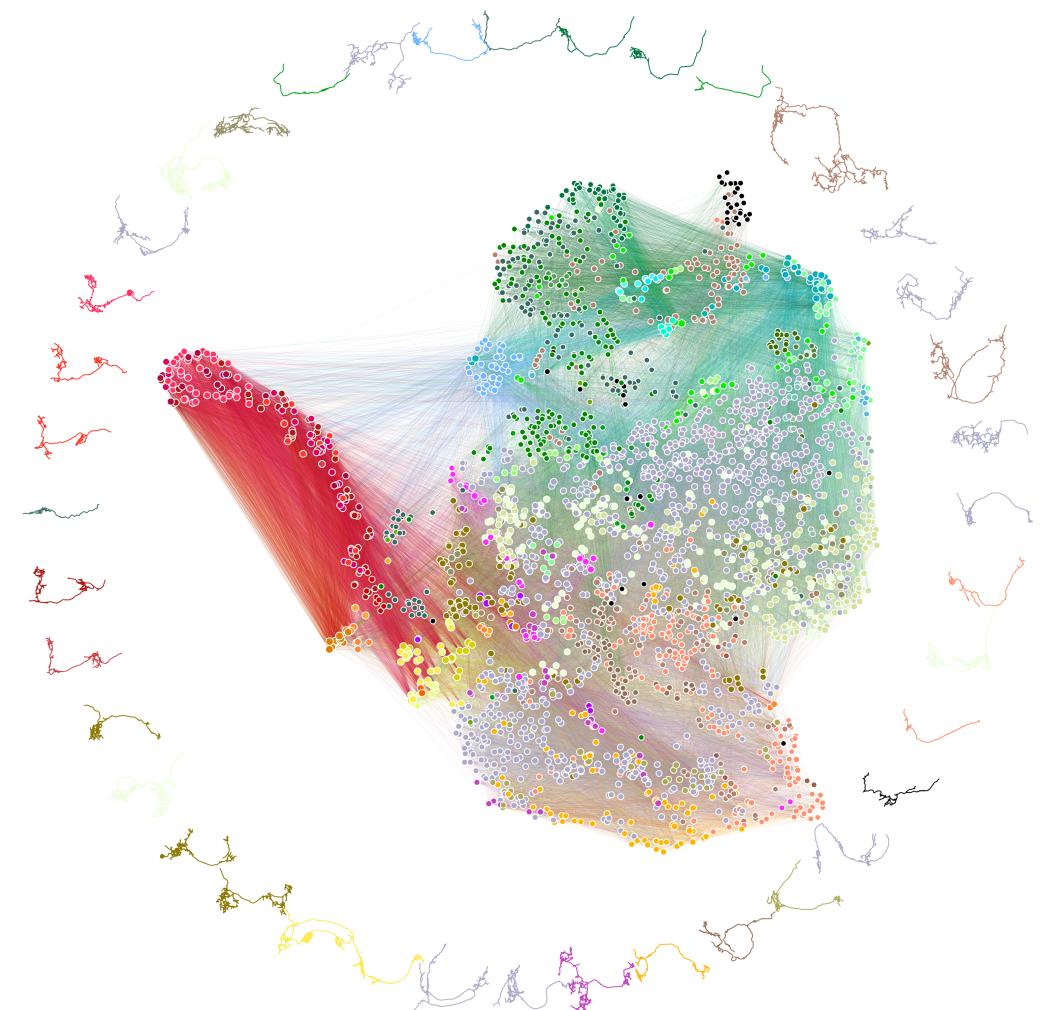
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What is a connectome? (for *this* talk)

A **connectome** is a network model of brain structure consisting of nodes which represent individual neurons and edges which represent the presence of a synaptic connection between those neurons.

Many connectomics questions require comparison

- Understand wiring substrate of learning/memory
- Understand links between genetics or disease and connectivity
- Understand how different neural architectures lead to different computational abilities

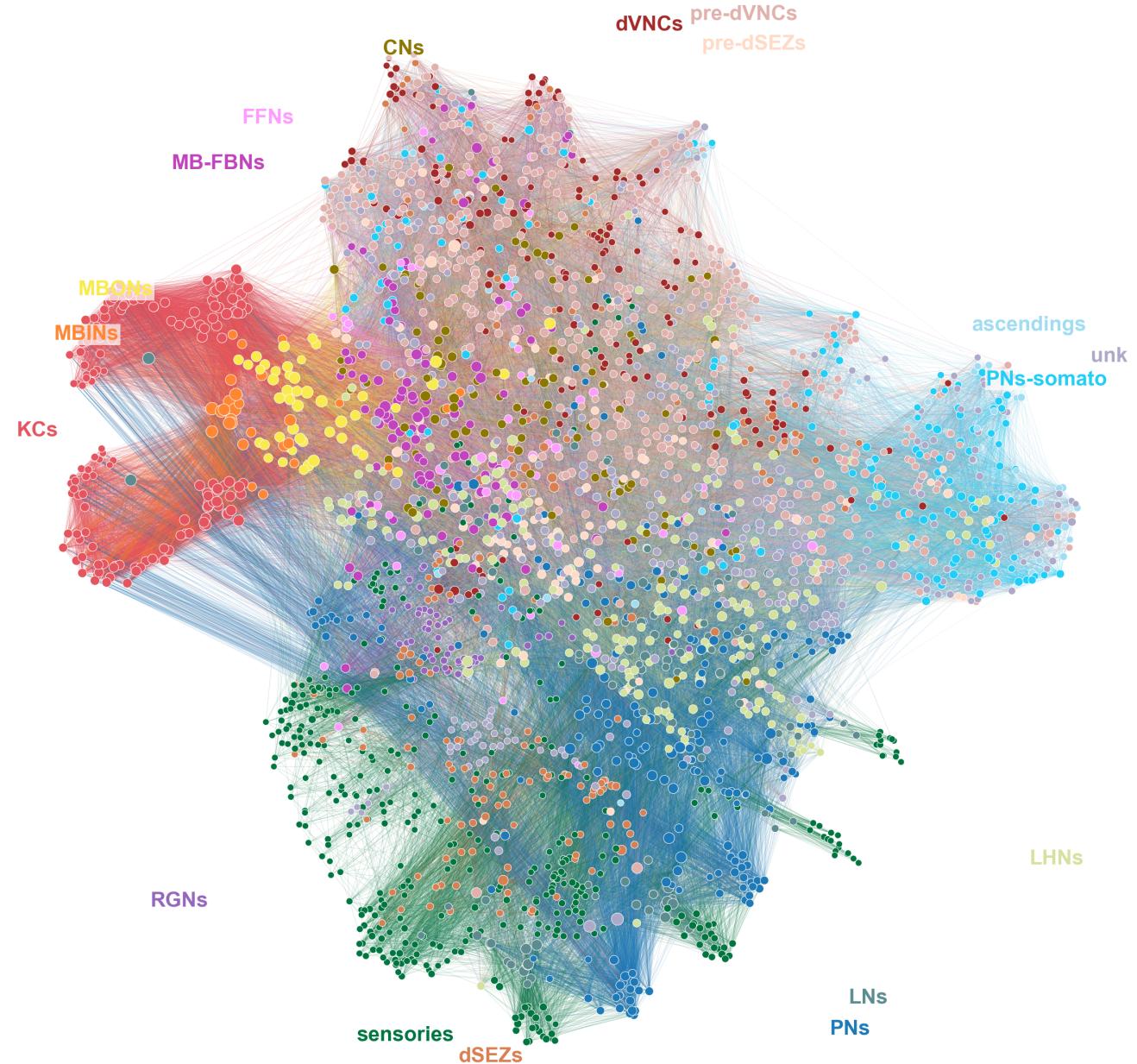
"Understanding statistical regularities and learning which variations are stochastic and which are secondary to an animal's life history will help define the substrate upon which individuality rests and *require comparisons between circuit maps within and between animals.*" [1] (emphasis added)

Larval *Drosophila* brain connectome

- ~2500 brain neurons +
~500 sensory neurons
- ~544K synapses
- Both hemispheres of
the brain reconstructed

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

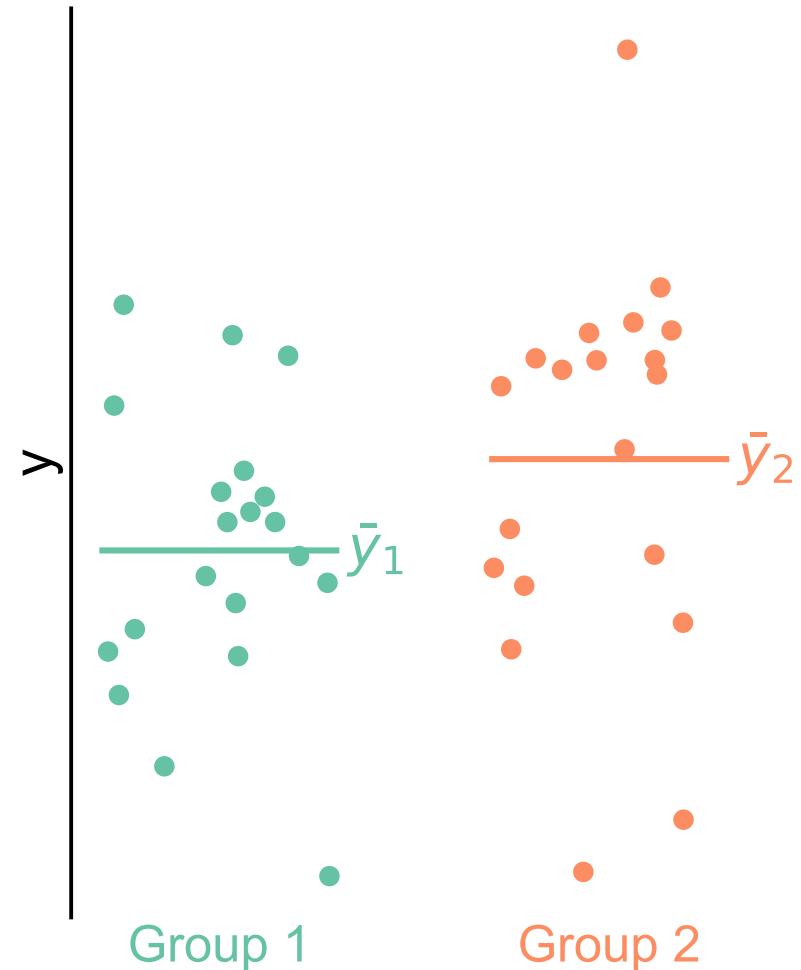
Winding et al. "The complete connectome of an insect brain." In prep (2021)



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

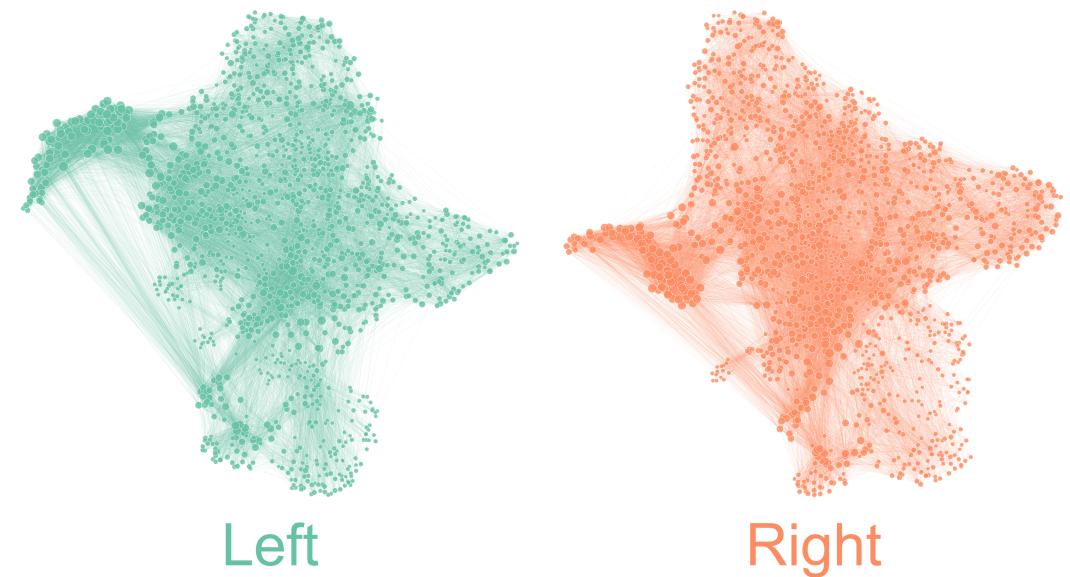
Are these populations the same?

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



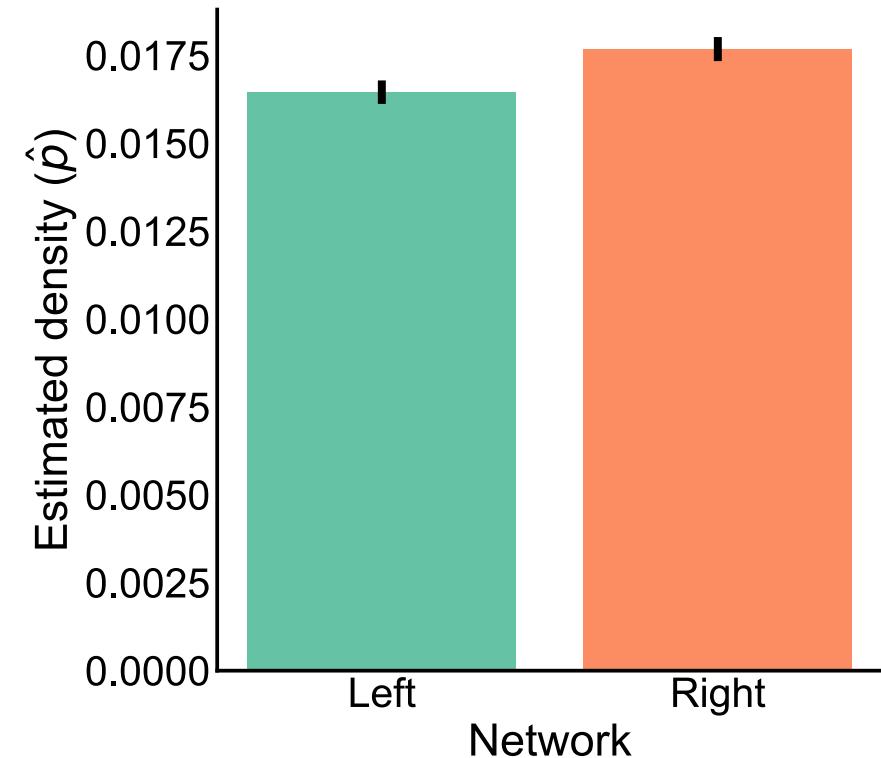
Are these two *networks* the same?

- We want a two-network sample test!
- Left side network: $A^{(L)} \sim F^{(L)}$
- Right side network: $A^{(R)} \sim F^{(R)}$
- $H_0 : F^{(L)} = F^{(R)}$
- $H_A : F^{(L)} \neq F^{(R)}$



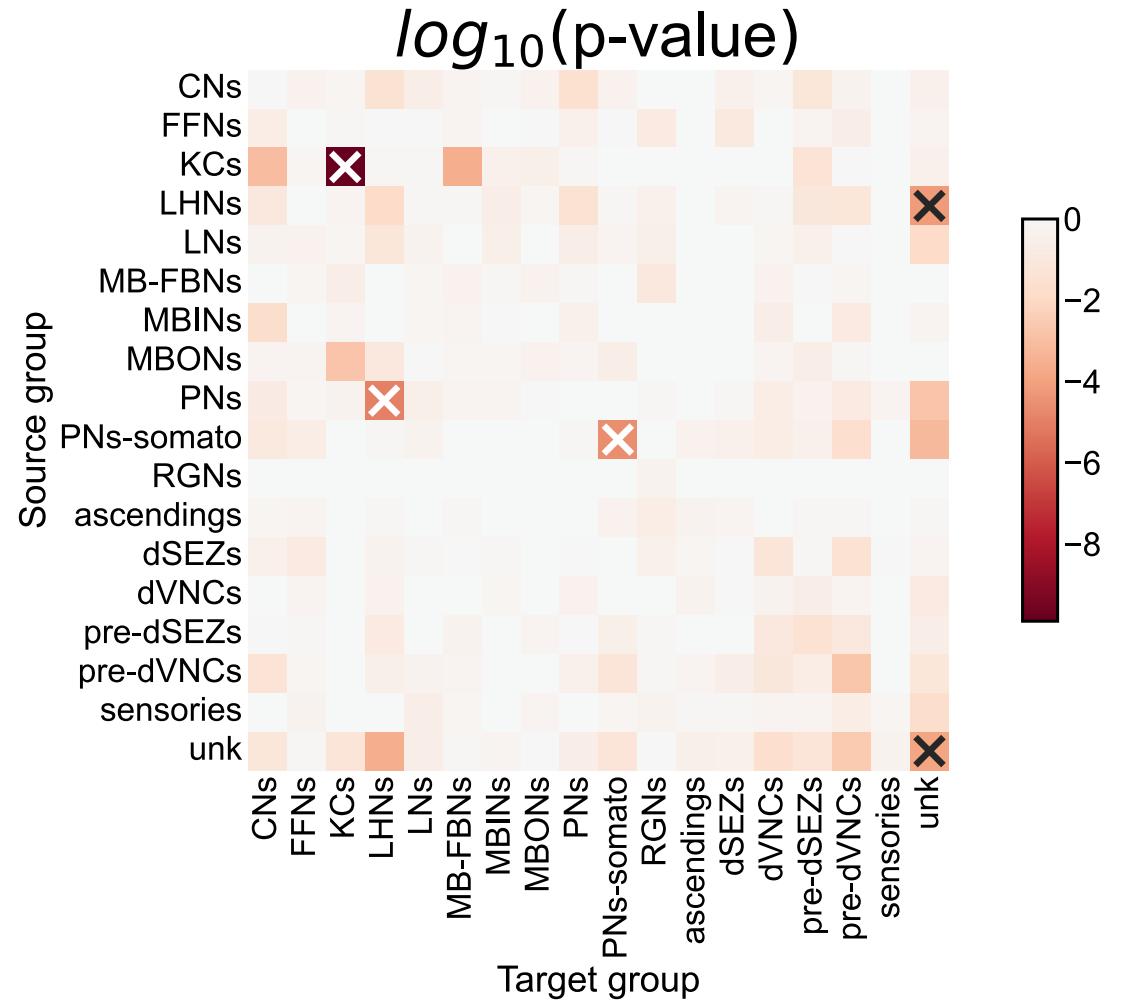
Density-based testing: Erdos-Renyi (ER) model

- 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** $< 10^{-23}$



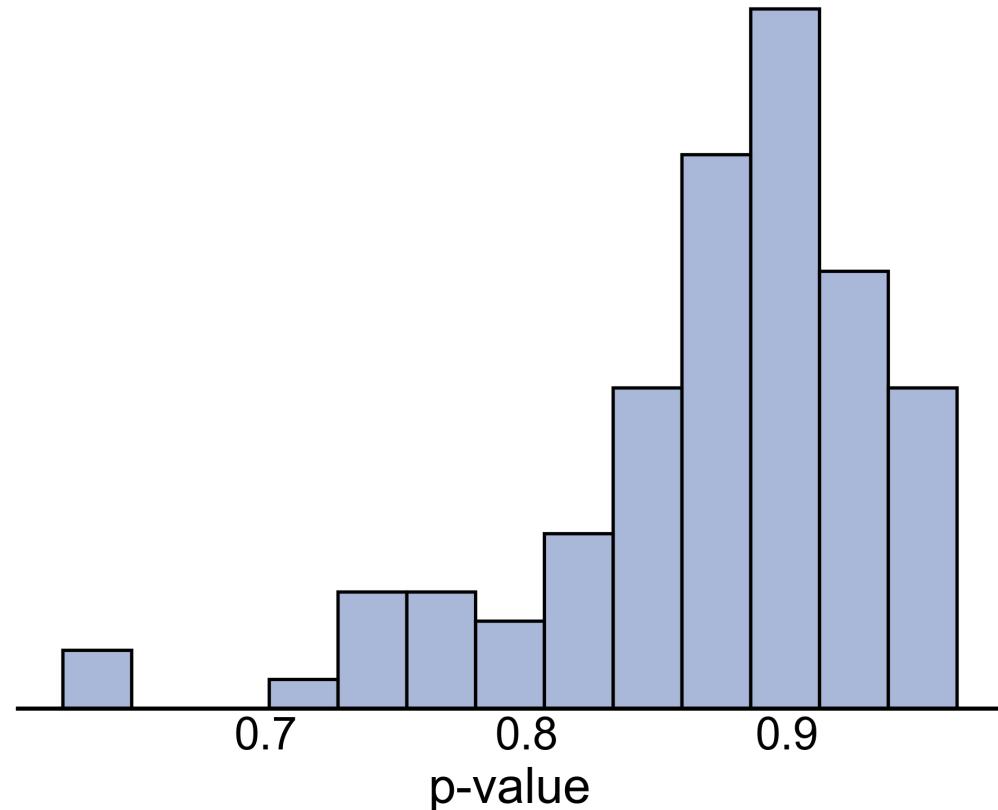
Group-based testing: stochastic block model (SBM)

- 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:
 $H_0 : B^{(L)} = B^{(R)}$
 $H_A : B^{(L)} \neq B^{(R)}$
(Many binomial tests)
- p-value $< 10^{-4}$



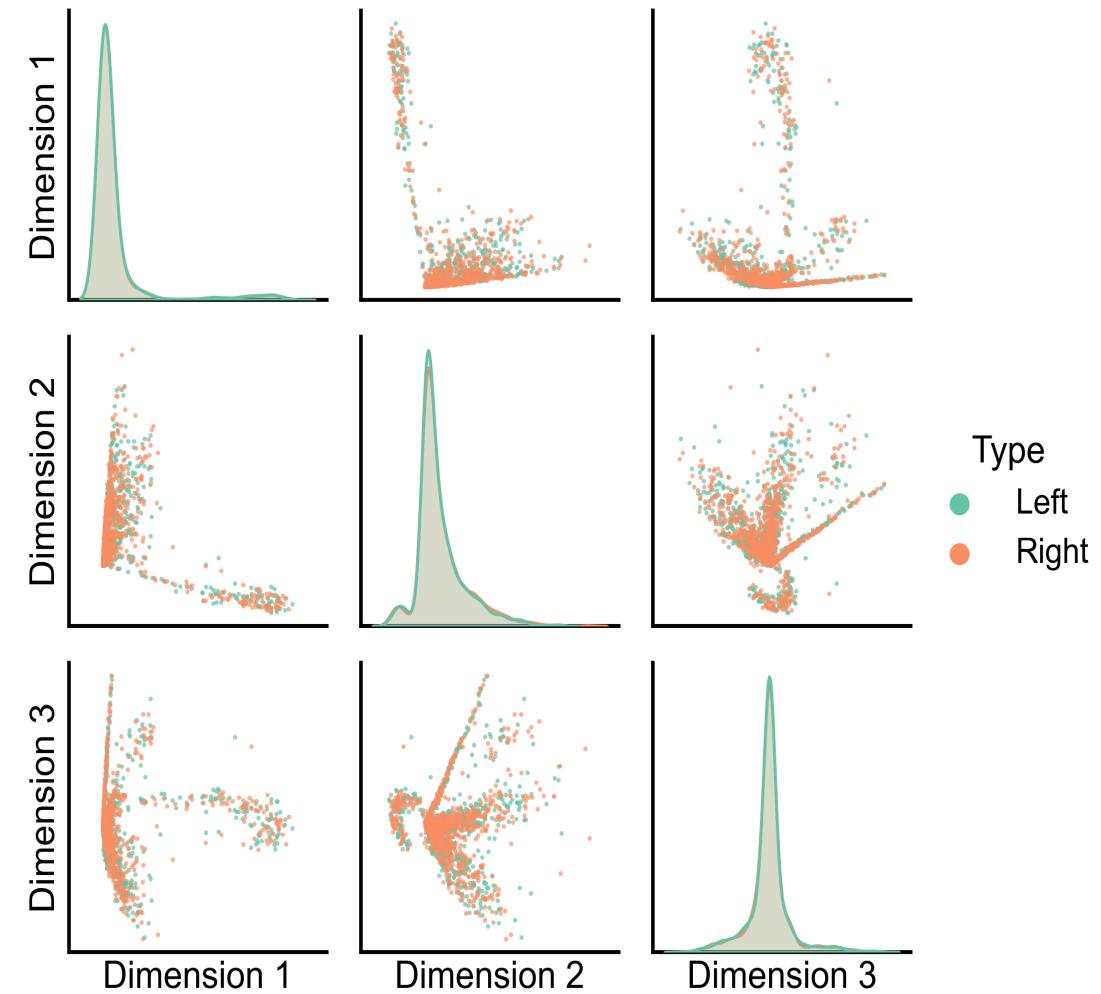
Adjusting for a difference in density

- 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 .
- $A_{ij} \sim \text{Bernoulli}(\langle x_i, y_j \rangle)$
- $x_i^{(L)} \sim F^{(L)}$, $x_i^{(R)} \sim F^{(R)}$
- Compare distributions of latent vectors:
 $H_0 : F^{(L)} = F^{(R)}$
 $H_A : F^{(L)} \neq F^{(R)}$
- p-value ≈ 1



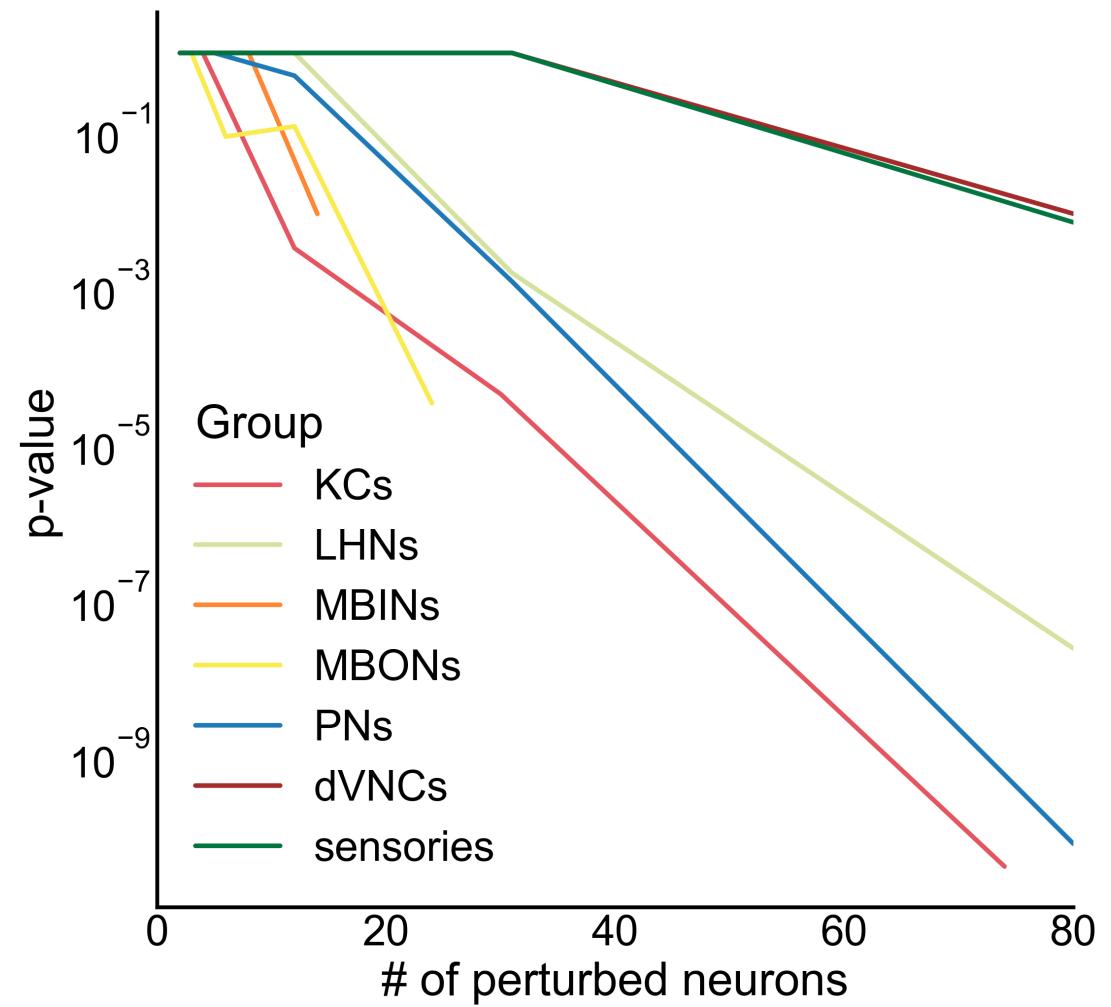
To sum up so far...

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!

Can we detect differences when we know they exist?

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



Summary

- Many ways to write "*Are the left and right the same?*" as a statistical hypothesis
 - Each yields a different test procedure
 - Each test is sensitive to some alternatives and not others
- May not care about some differences (e.g. density) and any test will need to adjust
- Techniques apply anytime one wants to compare connectomes/networks

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 page from a book titled "Bilateral Connectome" by NEURODATA. The title of the page is "The Erdos-Renyi (ER) model". The text explains that the Erdos-Renyi (ER) model is one of the simplest network models, where all edges between any two nodes are equally likely. A "Math" section provides the formula $P[A_{ij} = 1] = p_{ij} = p$ for the probability of an edge occurring, where n is the number of nodes and i, j are node indices. The page also includes links to "Abstract", "PRELIMINARIES", and other chapters like "Introduction" and "Outline".

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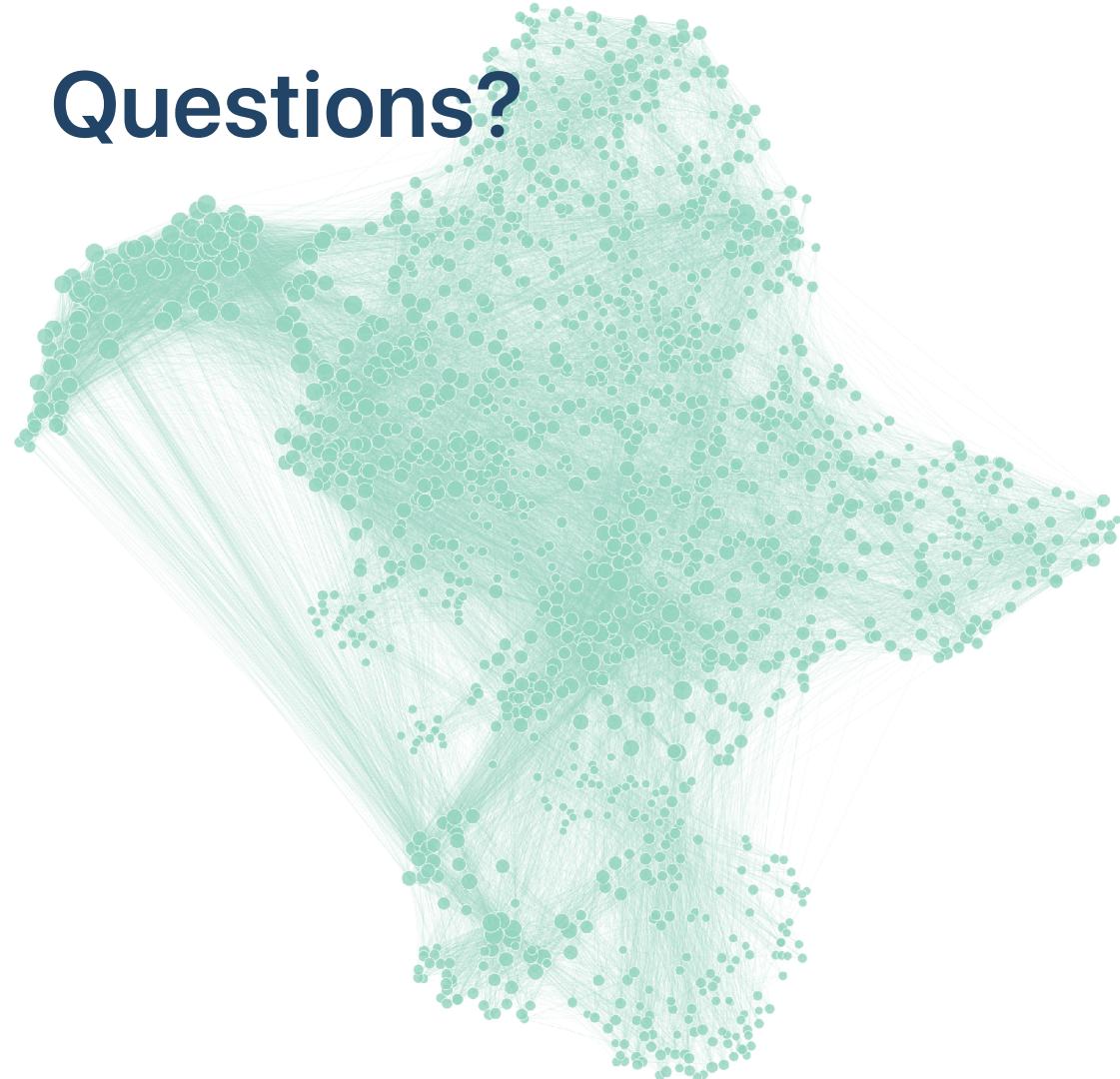
University of Cambridge / Laboratory of Molecular Biology

Michael Winding, Albert Cardona, Marta Zlatic, Chris Barnes

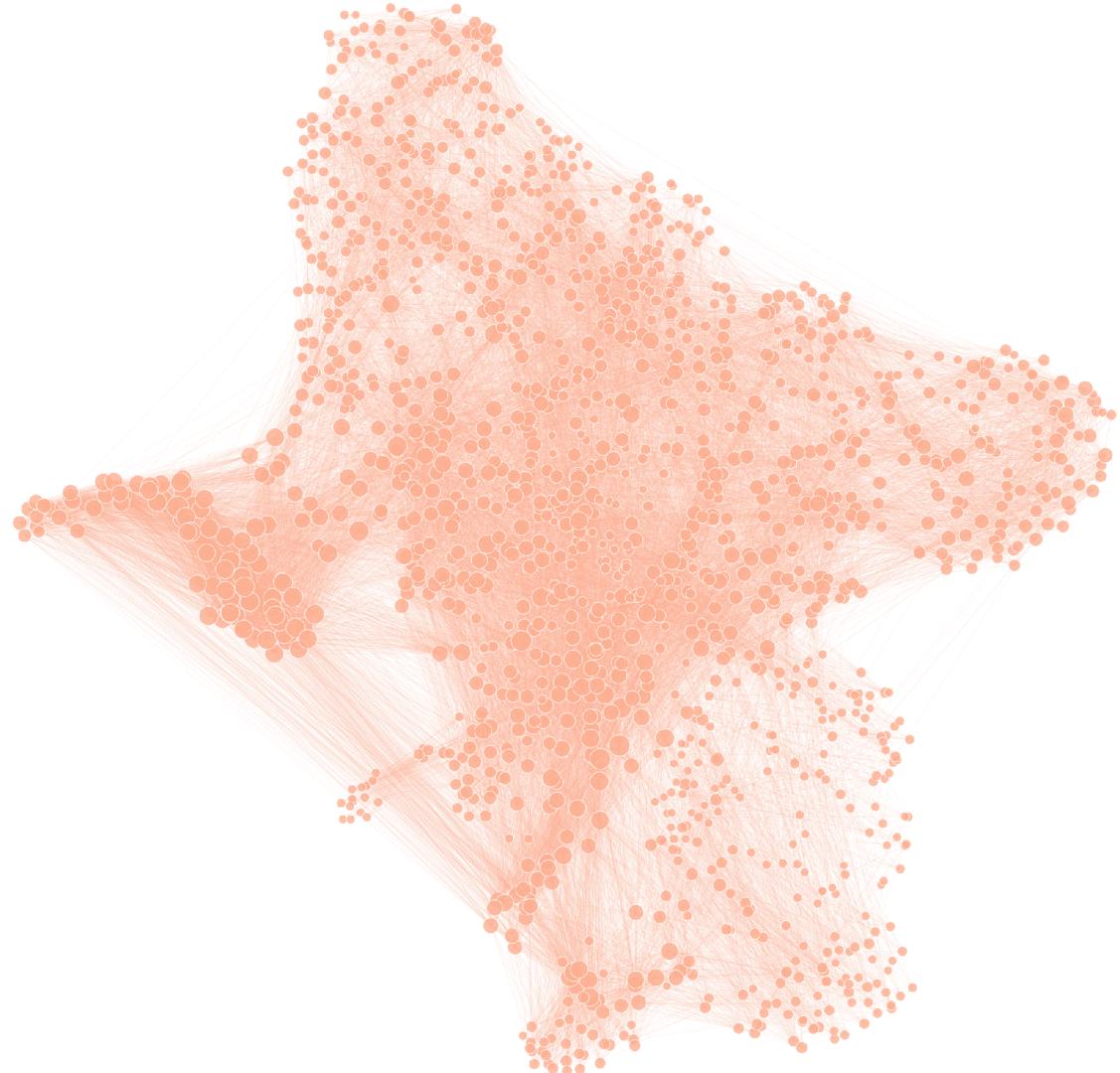
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Questions?



Left



Right