

A statistical analysis of bilateral symmetry in an insect connectome

Benjamin D. Pedigo

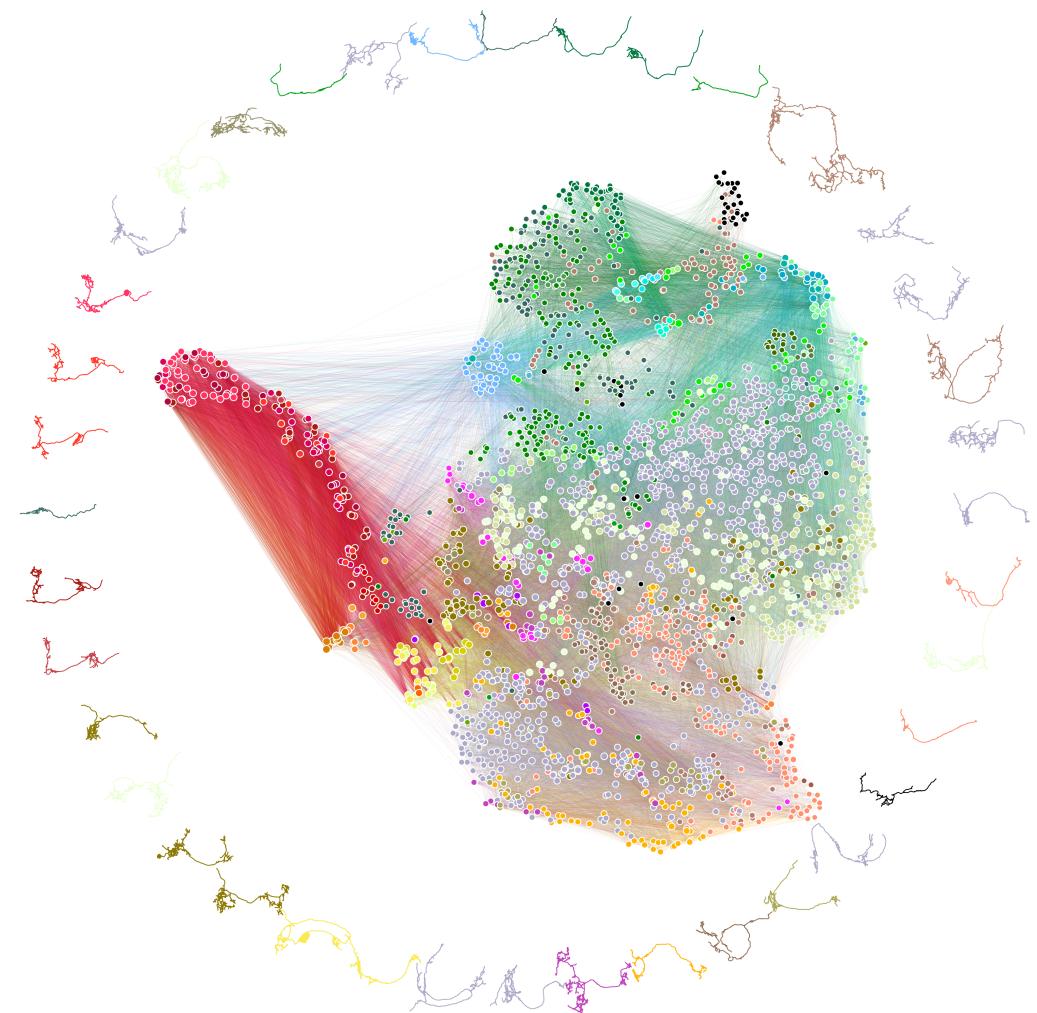
Johns Hopkins University

NeuroData lab

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

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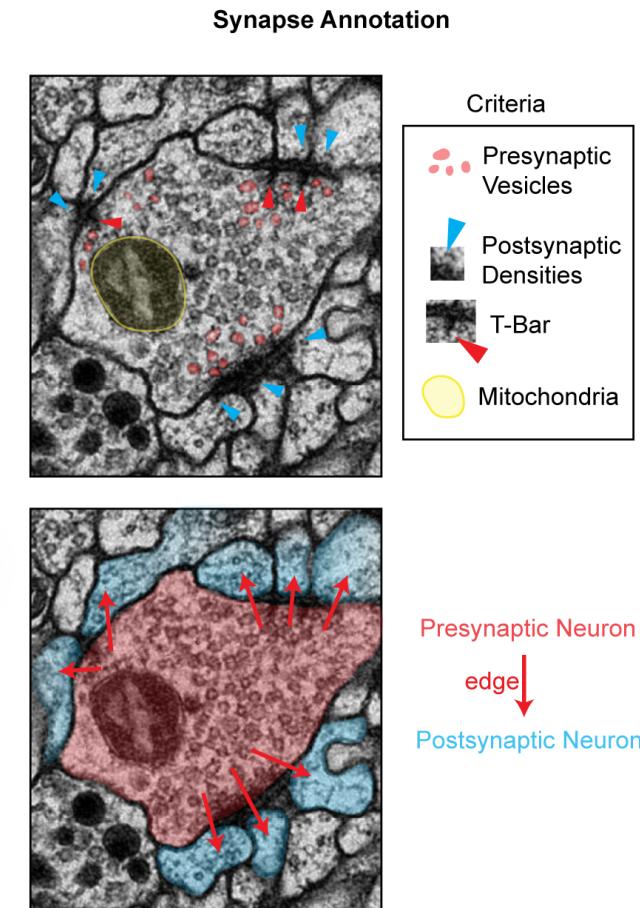
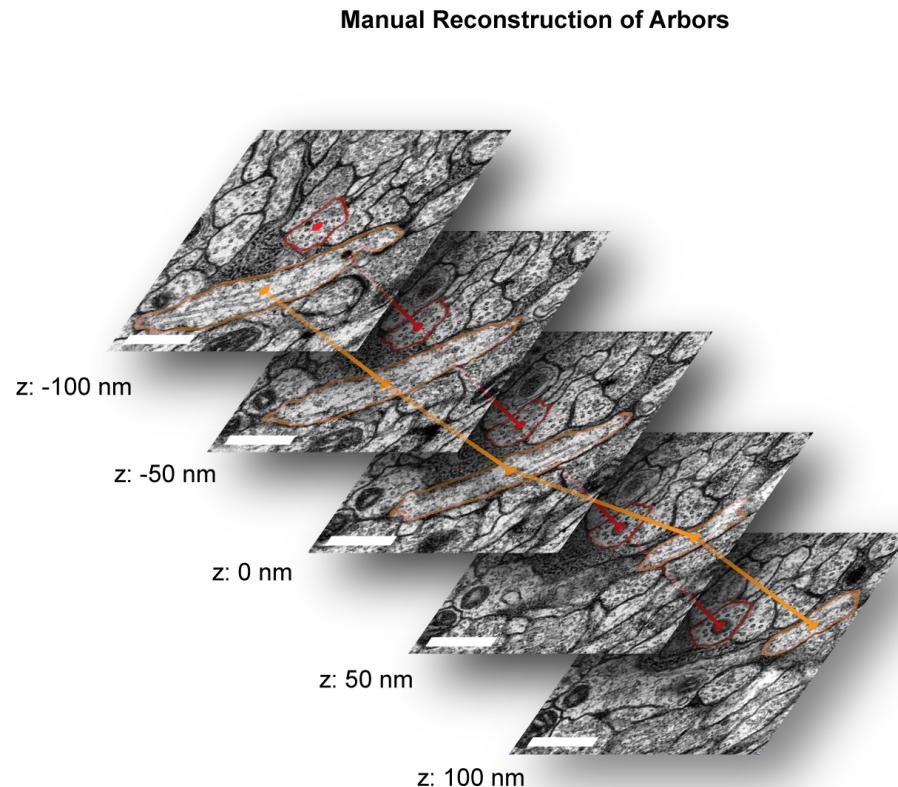
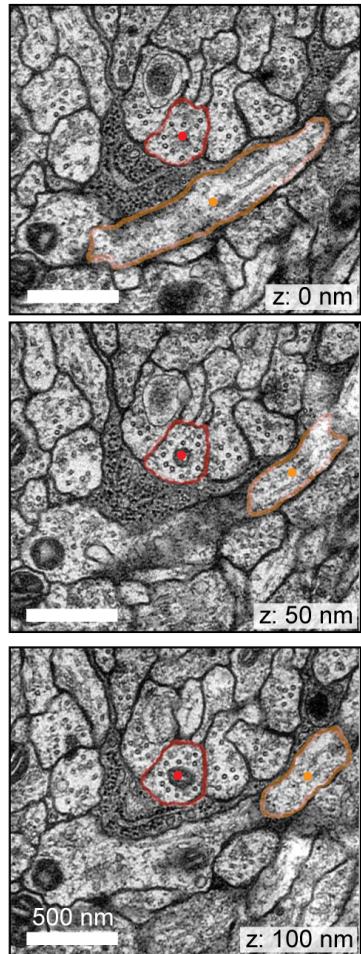
bpedigo@jhu.edu



My requests

- Feedback, feedback, feedback
 - Especially with figures

Electron microscopy connectomics



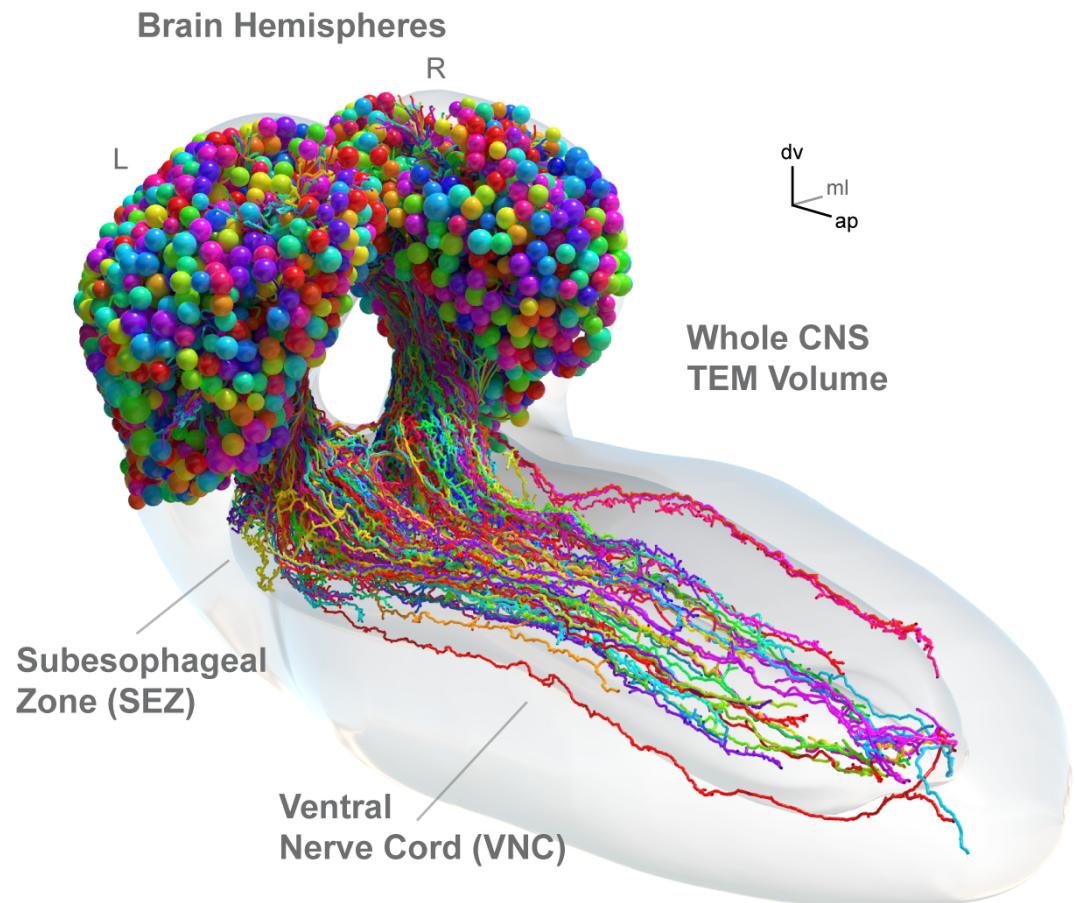
Why are we talking about maggot brain?



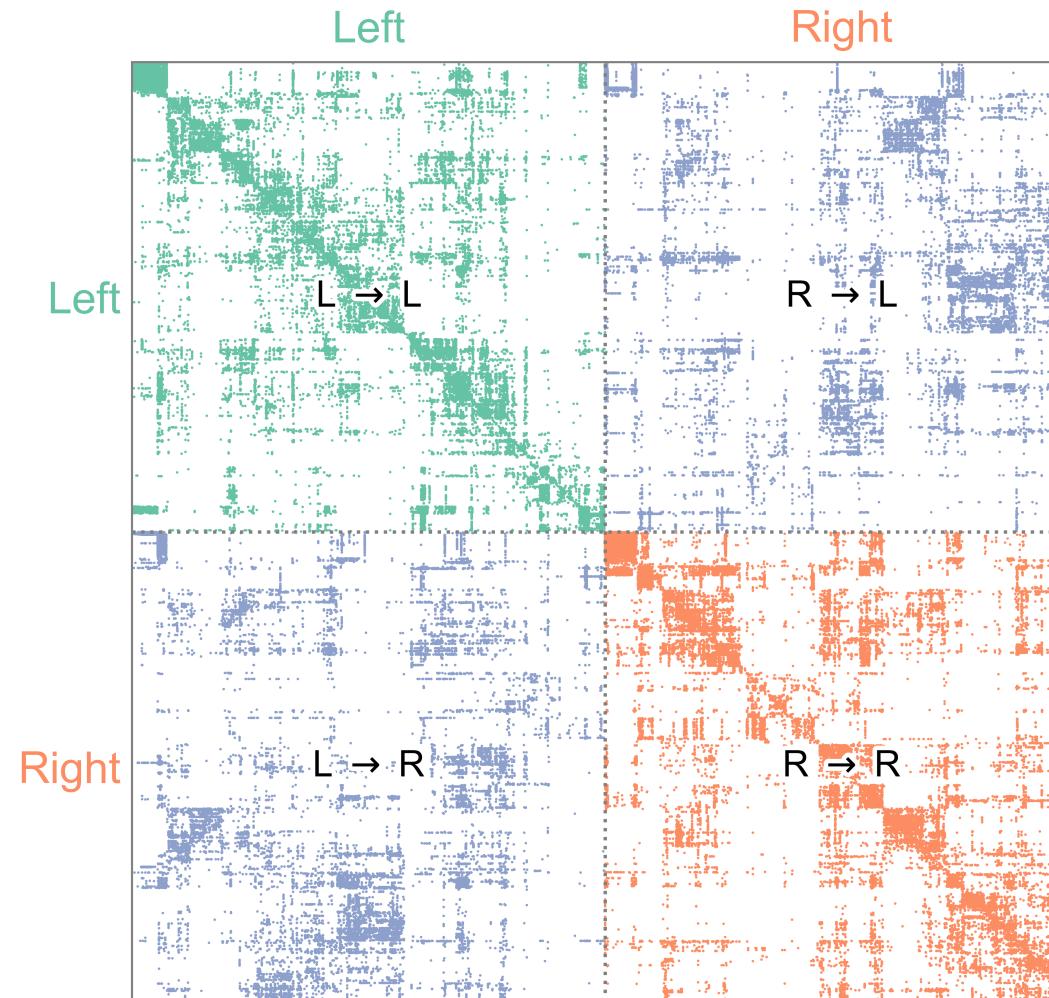
Drosophila larva (AKA a maggot) brain connectome

See [Michael Windings's talk](#)

- First whole-brain, single-cell connectome of any insect
- ~3000 neurons, ~544K synapses
- Both hemispheres of the brain reconstructed



We're just going to consider this to be a network



Why bilateral symmetry?

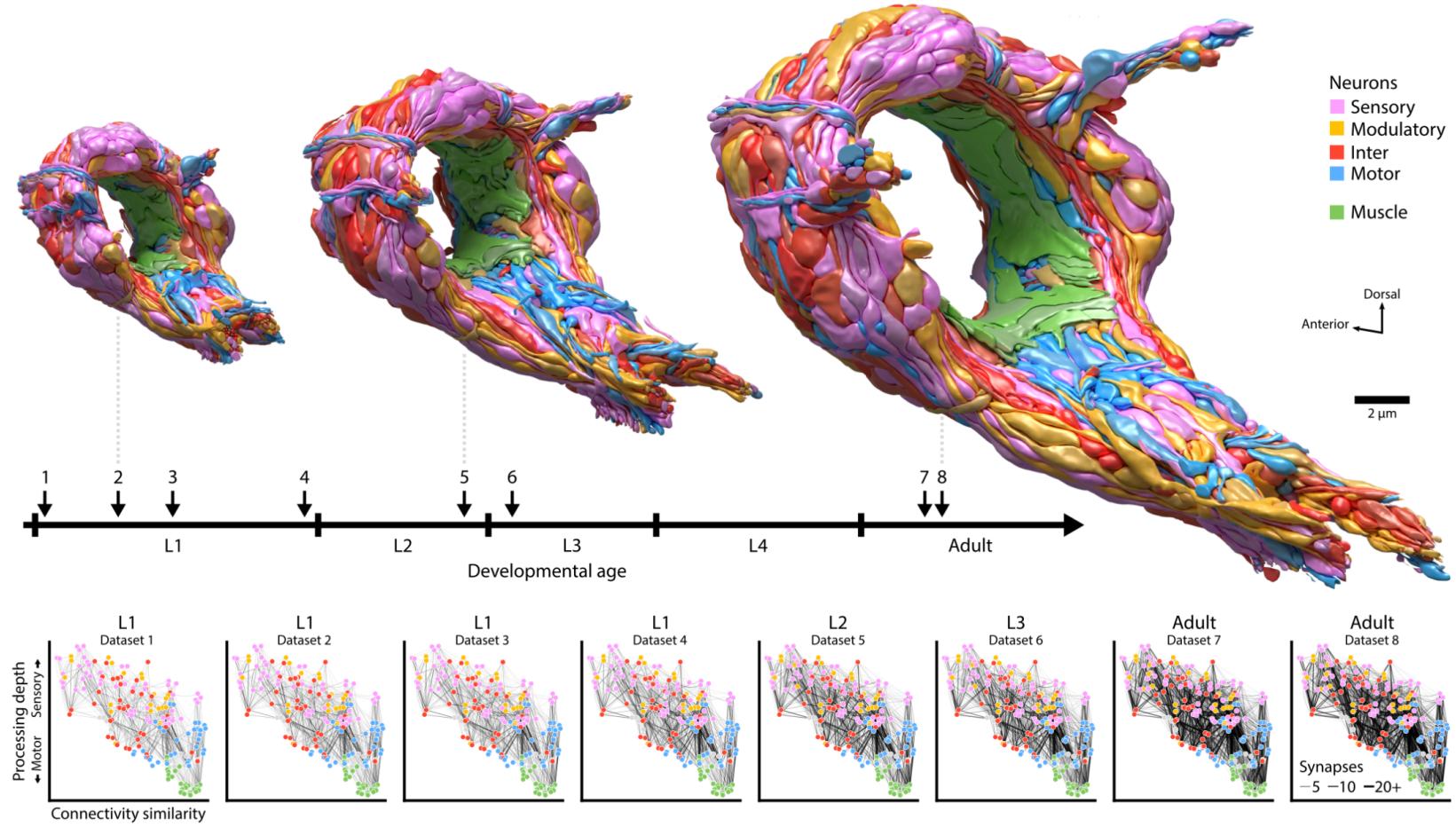
We examined the connectivity of members of left–right homologous neuron pairs onto left–right homologous targets in the nerve ring of the hermaphrodite reconstruction to assess the amount of natural variability in connectivity. ...

Differences between individual worms will be expected to be at least this large. This information is used in the following section to identify sex differences.

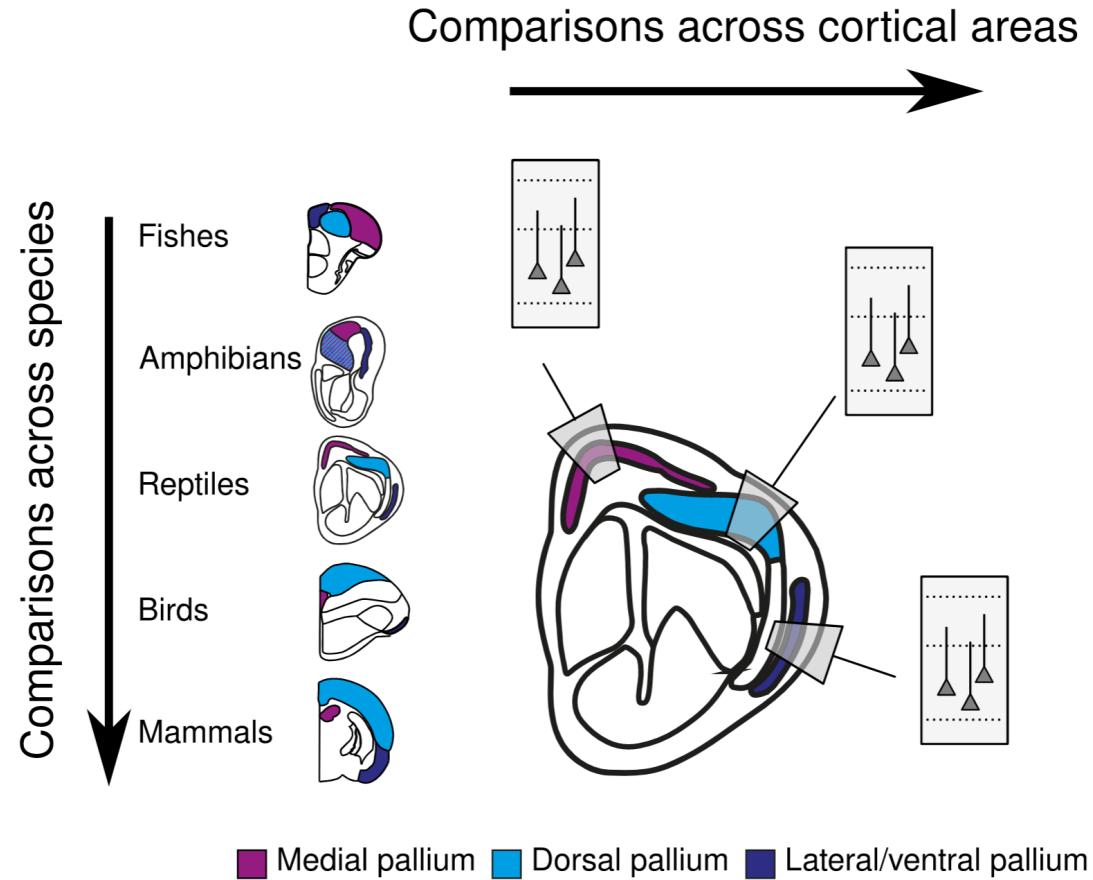
In both sexes, the gustatory neuron ASEL (that is, the left neuron of the pair) has greater chemical connectivity than ASER (that is, the right neuron of the pair) to the olfactory neuron class AWC. The ASEL–ASER pair is known to be lateralized in its ability to sense chemosensory cues

Many connectomics questions require comparison

Connectomes across development



Connectomes across evolution, cortex



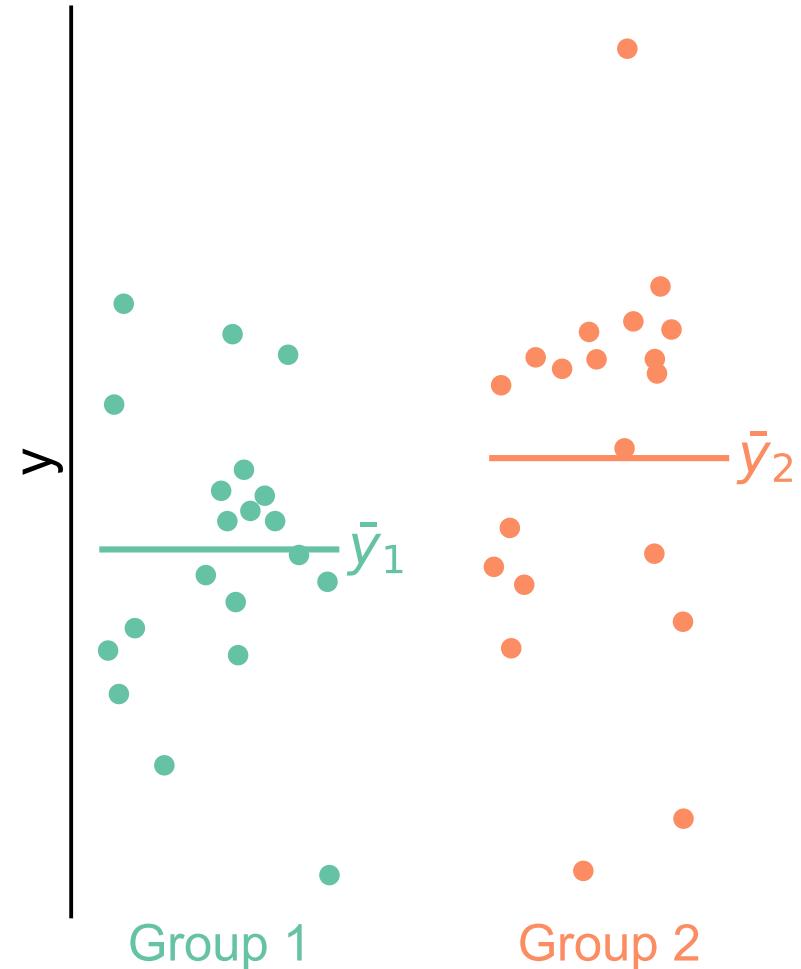
So, studying bilateral symmetry here lets us

- Try to formalize what we even mean by this property, and make claims about what we find in this connectome, and
- Test out methods for comparing networks for these future pursuits

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

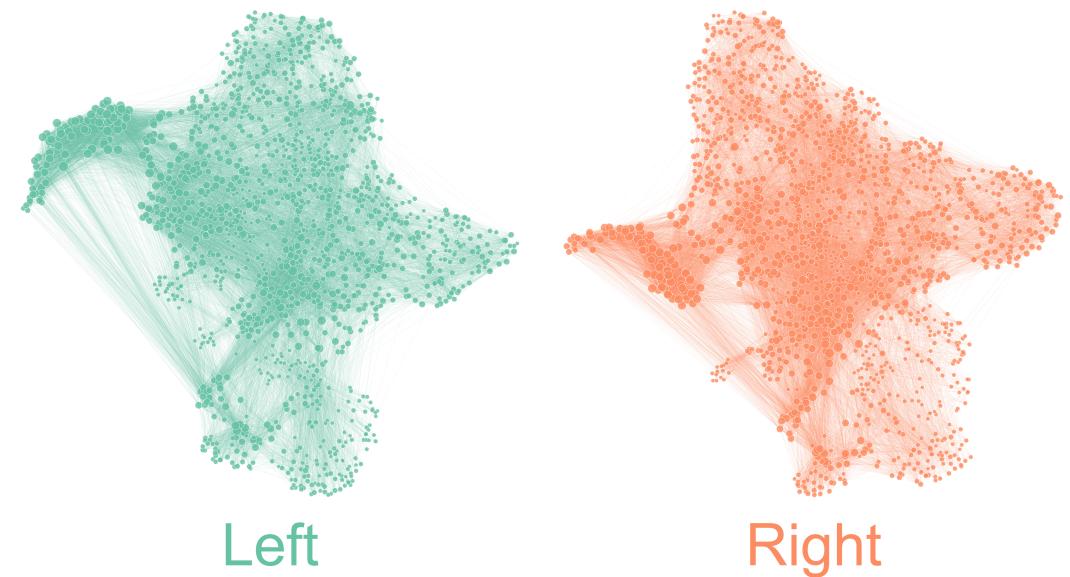
Are these populations the same?

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



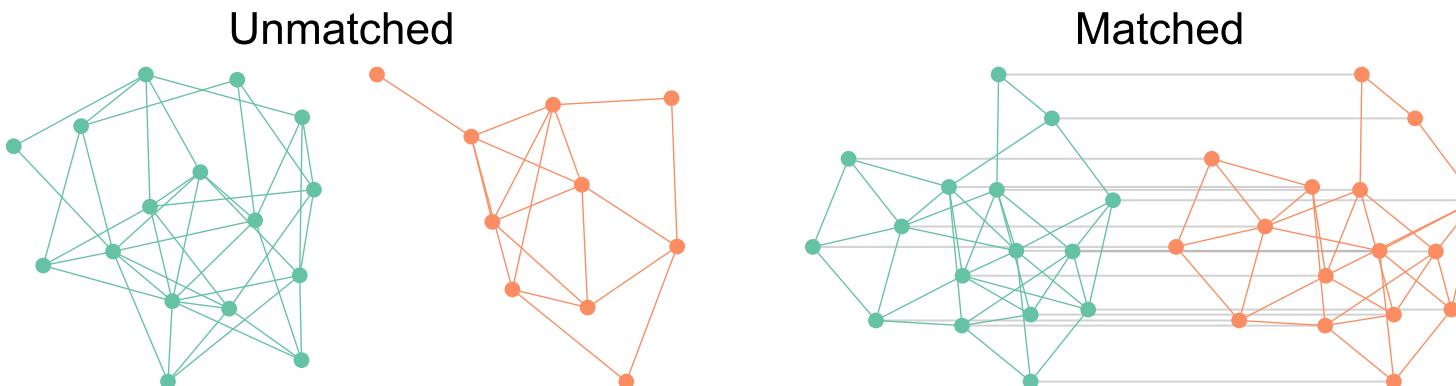
Are these two *networks* the same?

- Want a two-network-sample test!
- $A^{(L)} \sim F^{(L)}$, $A^{(R)} \sim F^{(R)}$
- $H_0 : F^{(L)} = F^{(R)}$
 $H_A : F^{(L)} \neq F^{(R)}$

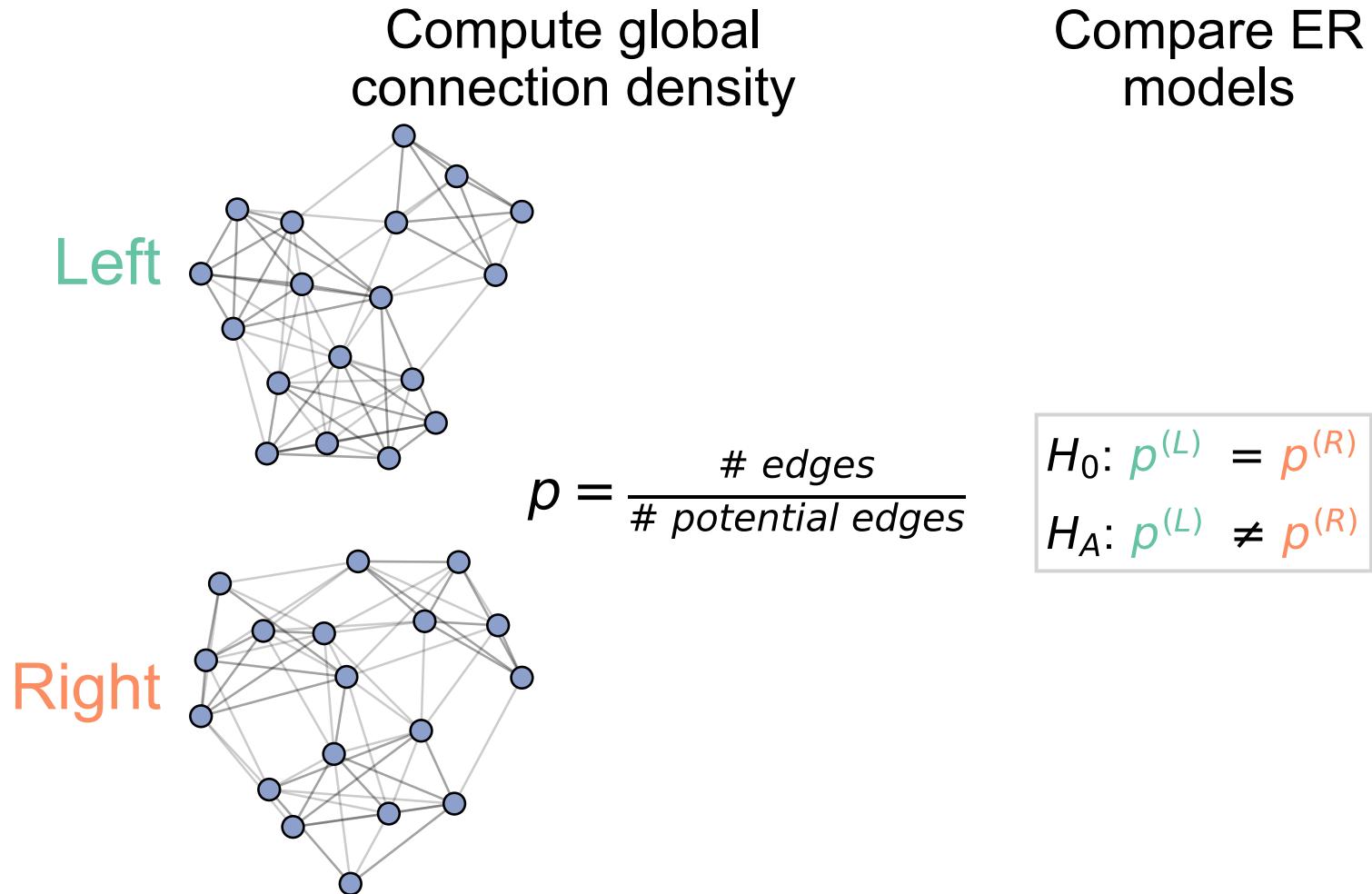


Assumptions

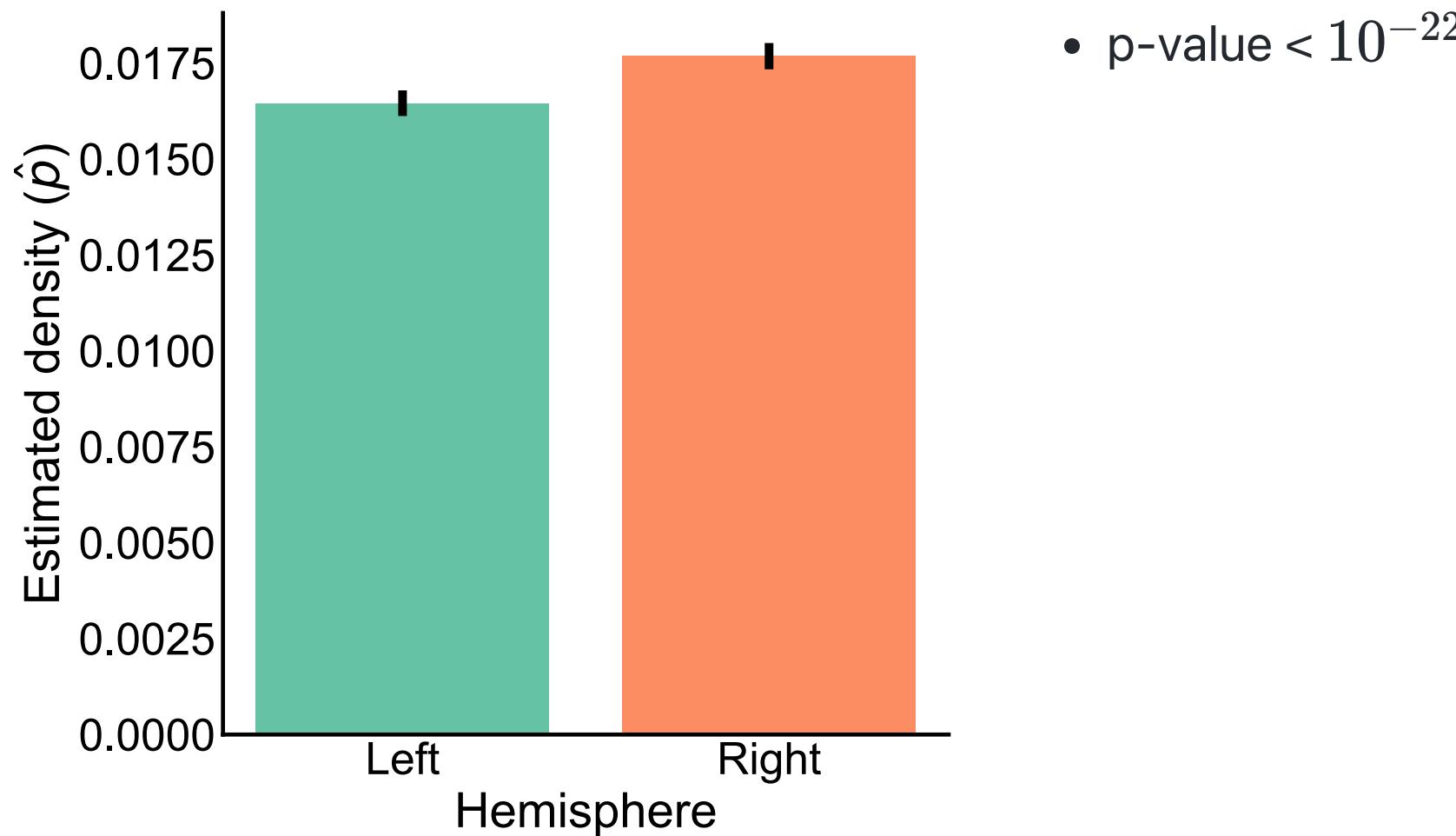
- We know the direction of synapses, so network is *directed*.
- For simplicity (for now), consider networks to be *unweighted*.
- For simplicity (for now), consider the **left** → **left** and **right** → **right** (*ipsilateral*) connections only.
- Not going to assume any nodes are matched



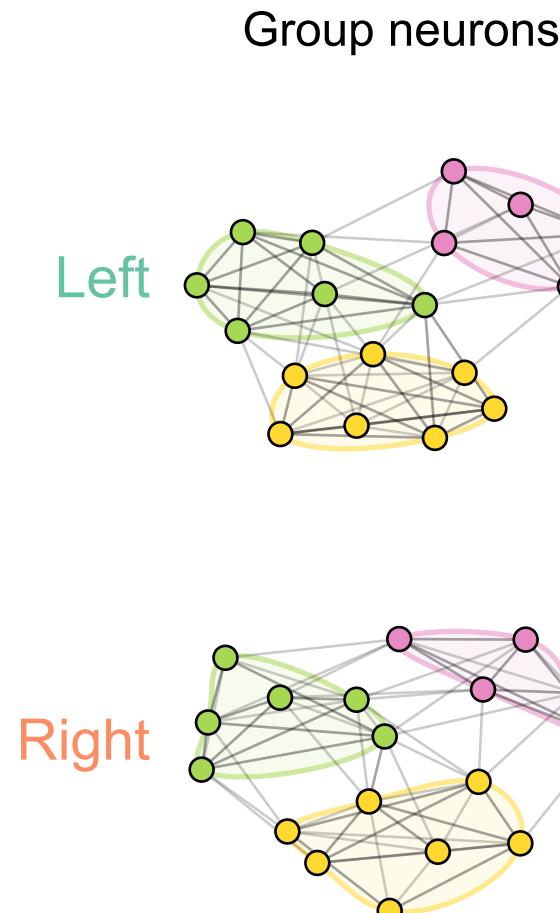
Density-based testing: Erdos-Renyi (ER) model



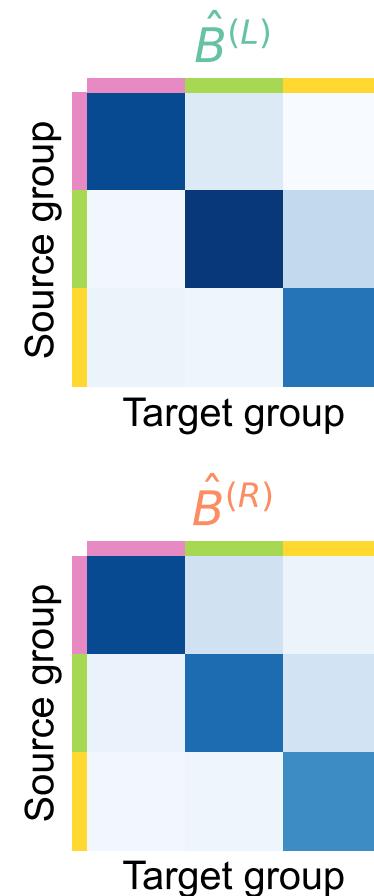
We detect a difference in density



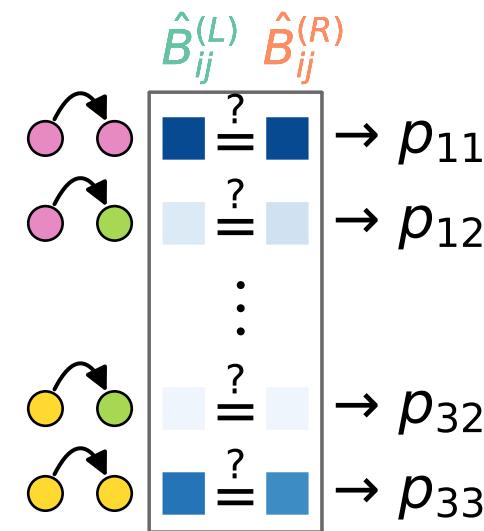
Group-based testing: stochastic block model (SBM)



Estimate group-to-group connection probabilities

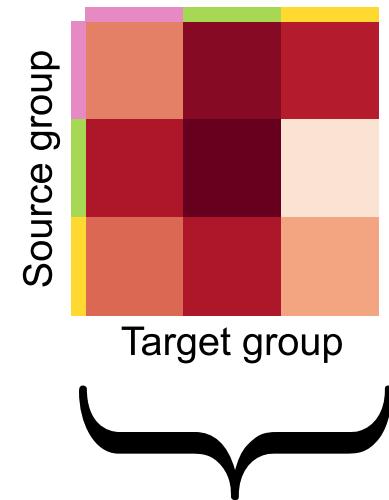


Compare estimated probabilities



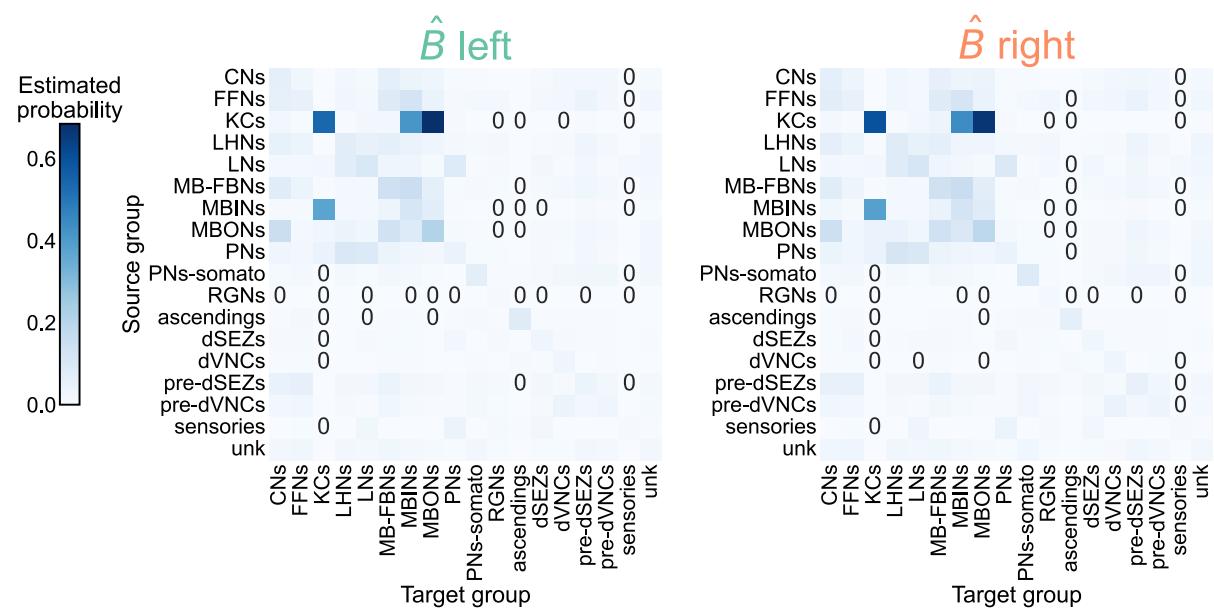
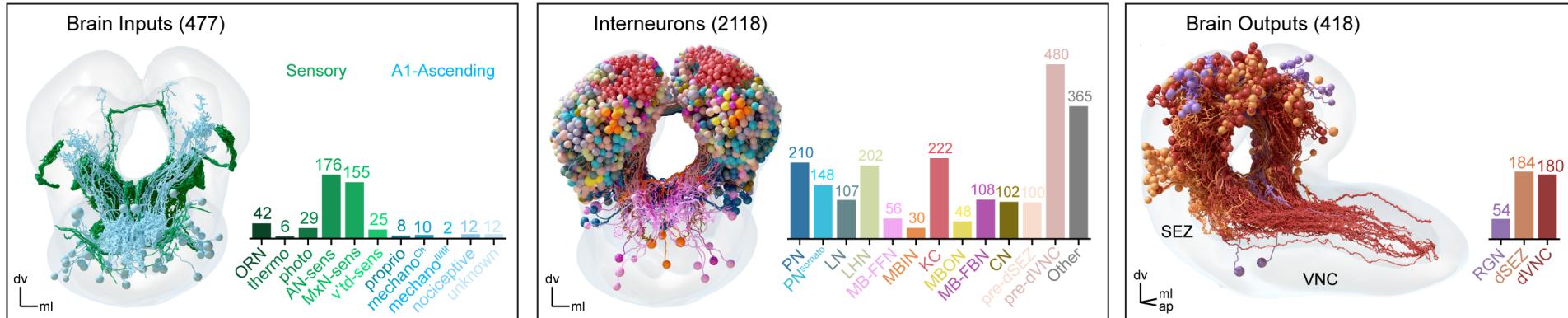
$$H_0: \hat{B}_{ij}^{(L)} = \hat{B}_{ij}^{(R)}$$
$$H_A: \hat{B}_{ij}^{(L)} \neq \hat{B}_{ij}^{(R)}$$

Combine p-values for overall test

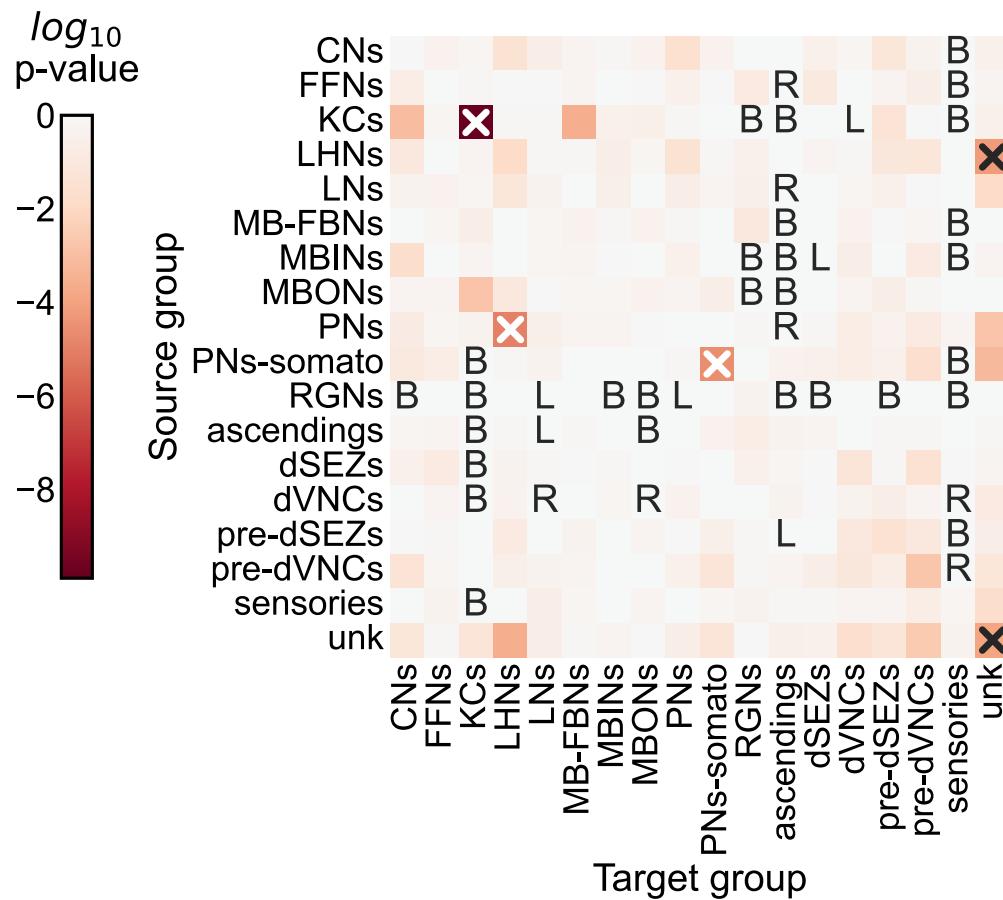


$$H_0: \hat{B}^{(L)} = \hat{B}^{(R)}$$
$$H_A: \hat{B}^{(L)} \neq \hat{B}^{(R)}$$

Connection probabilities between groups



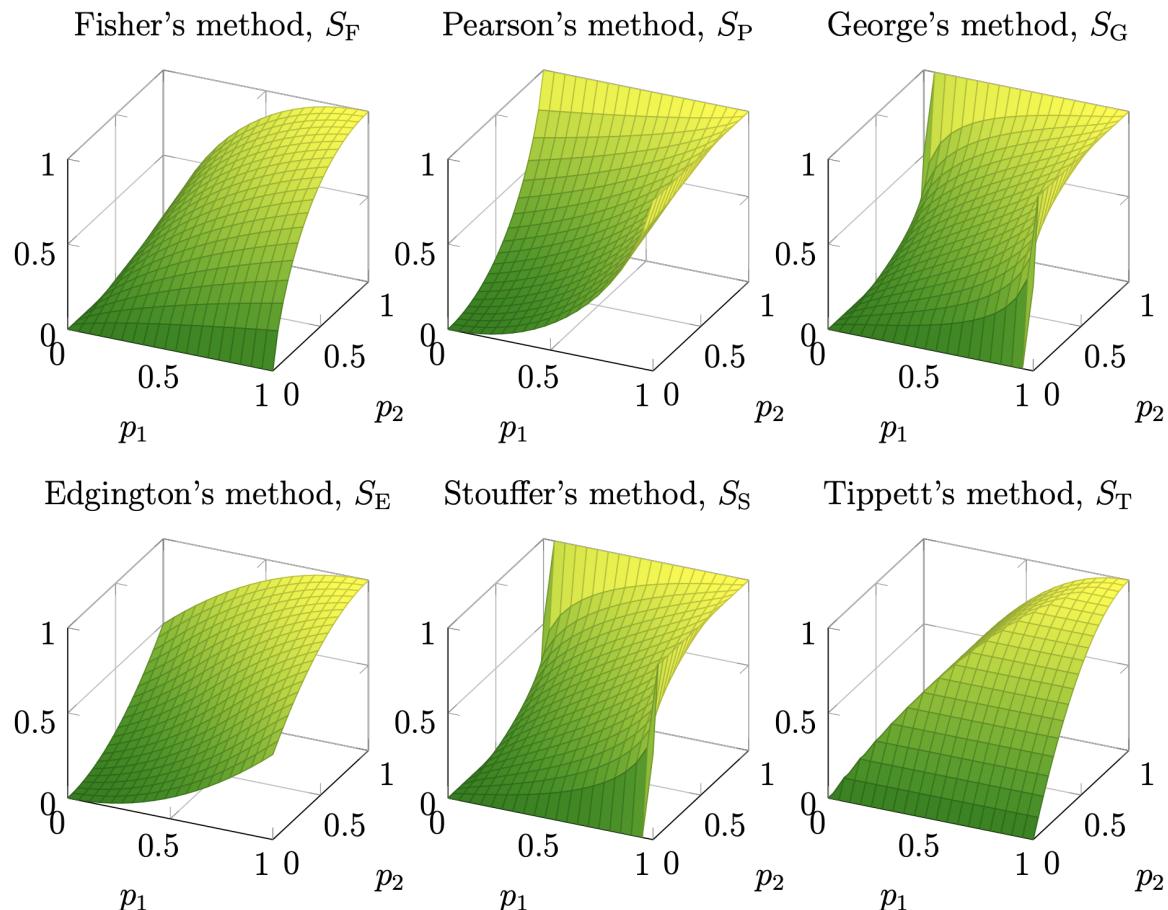
We detect a difference in group-to-group connection probabilities



- After multiple comparison, find 5 group-to-group connections which are significantly different
- Combine (uncorrected) p-values (like a meta-analysis), leads to p-value for overall test of $< 10^{-7}$

A massive aside

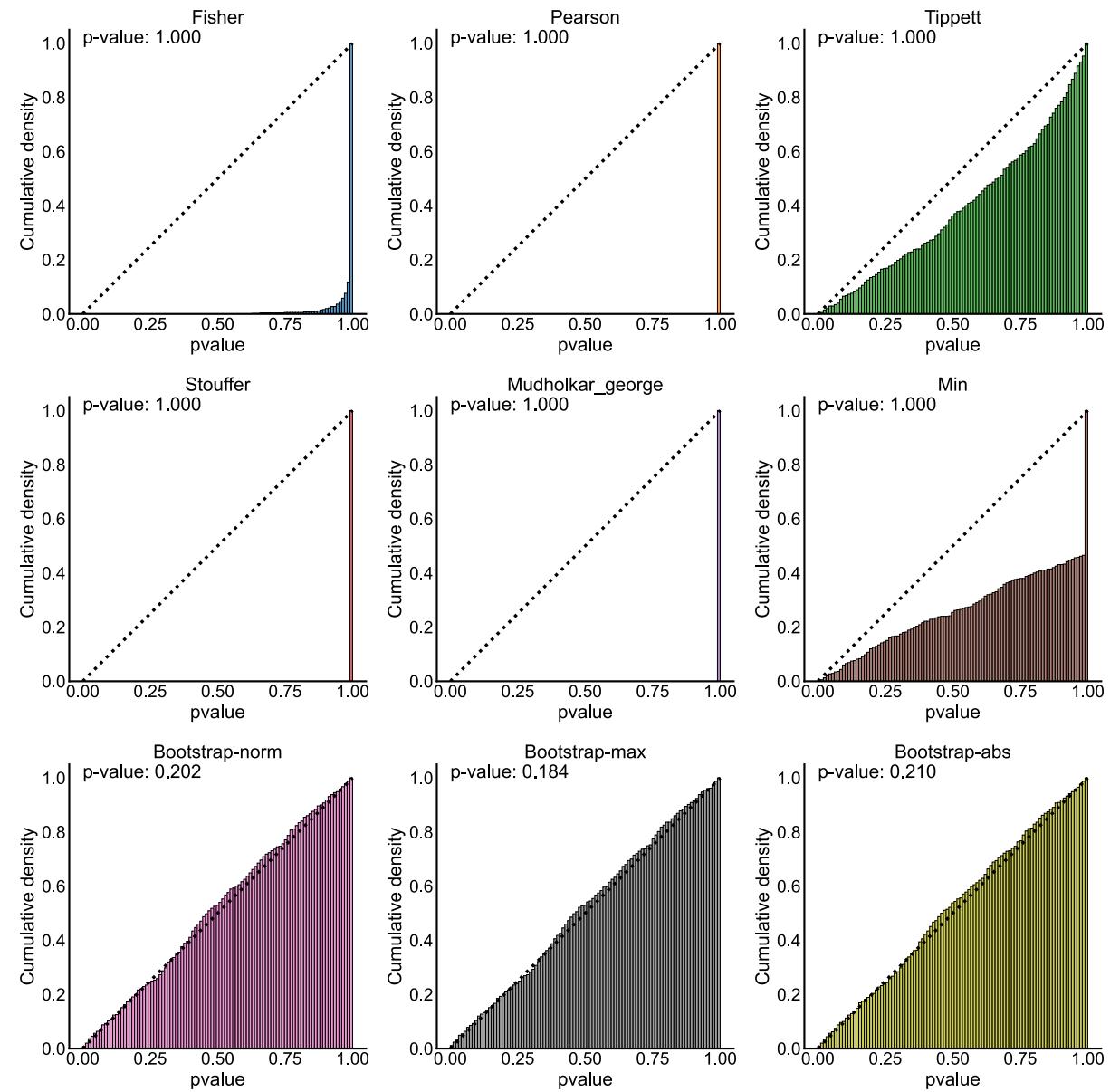
Combining p-values: nobody's perfect



Combining p-values: don't trust scipy

```
    elif method == 'tippett':  
        statistic = np.min(pvalues)  
        pval = distributions.beta.sf(statistic, 1, len(pvalues))  
        pval = distributions.beta.cdf(statistic, 1, len(pvalues))
```

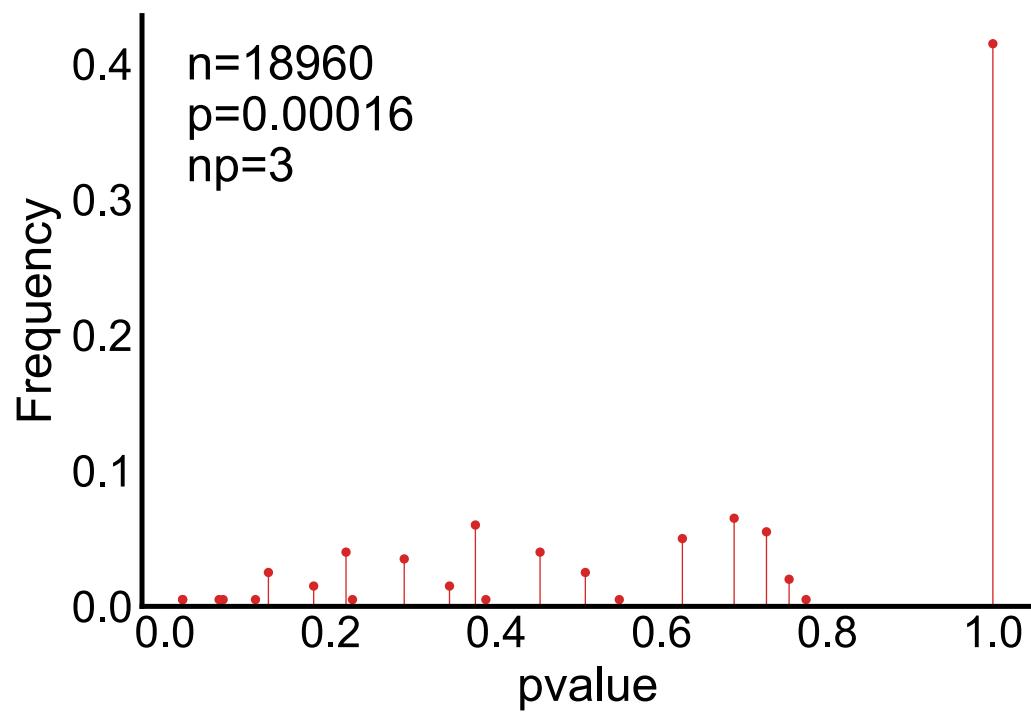
Distribution under the null for combining p-values



Combining p-values: be careful with discreteness

THE COMBINATION OF PROBABILITIES ARISING FROM DATA
IN DISCRETE DISTRIBUTIONS

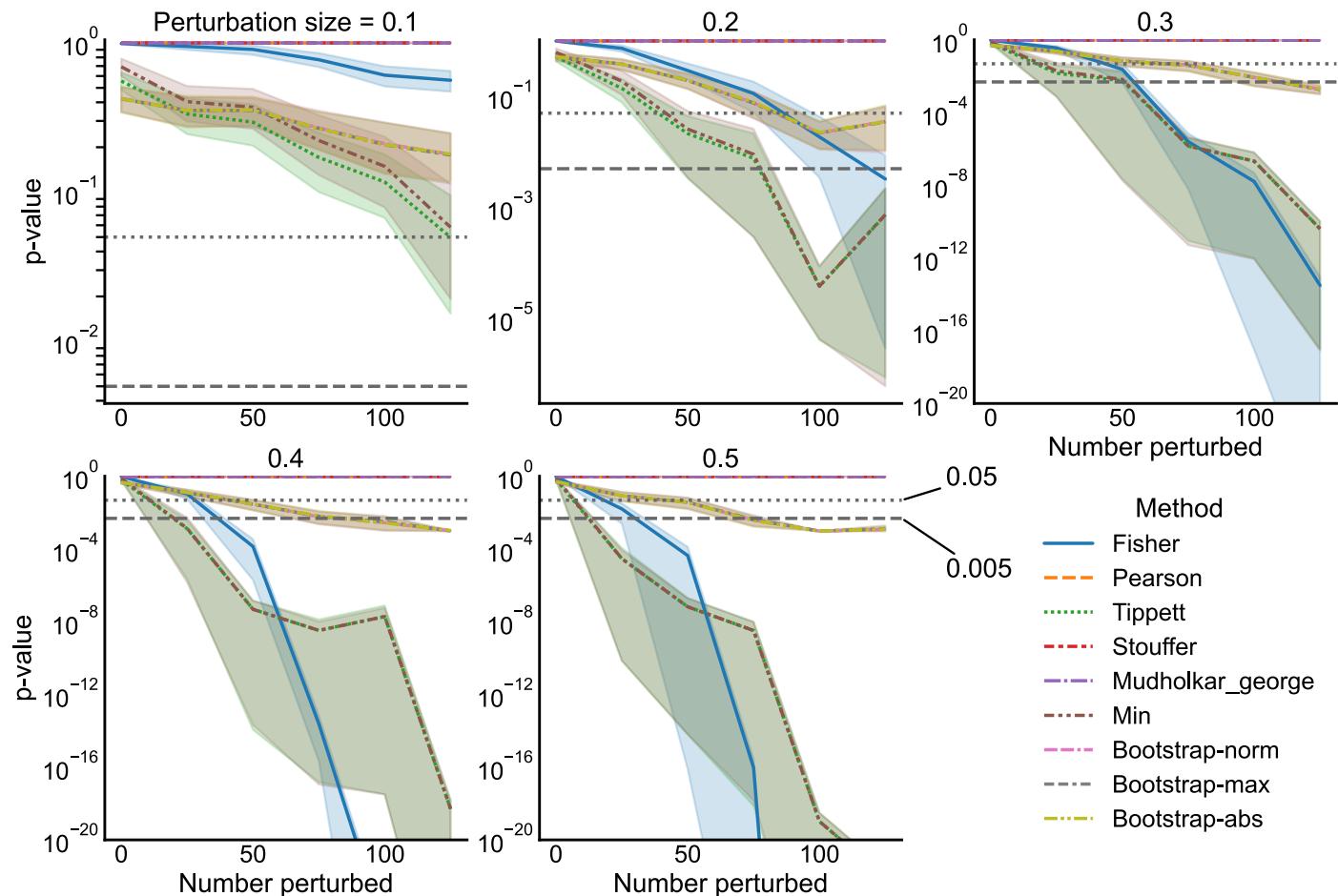
BY H. O. LANCASTER, *Rockefeller Fellow in Medicine*



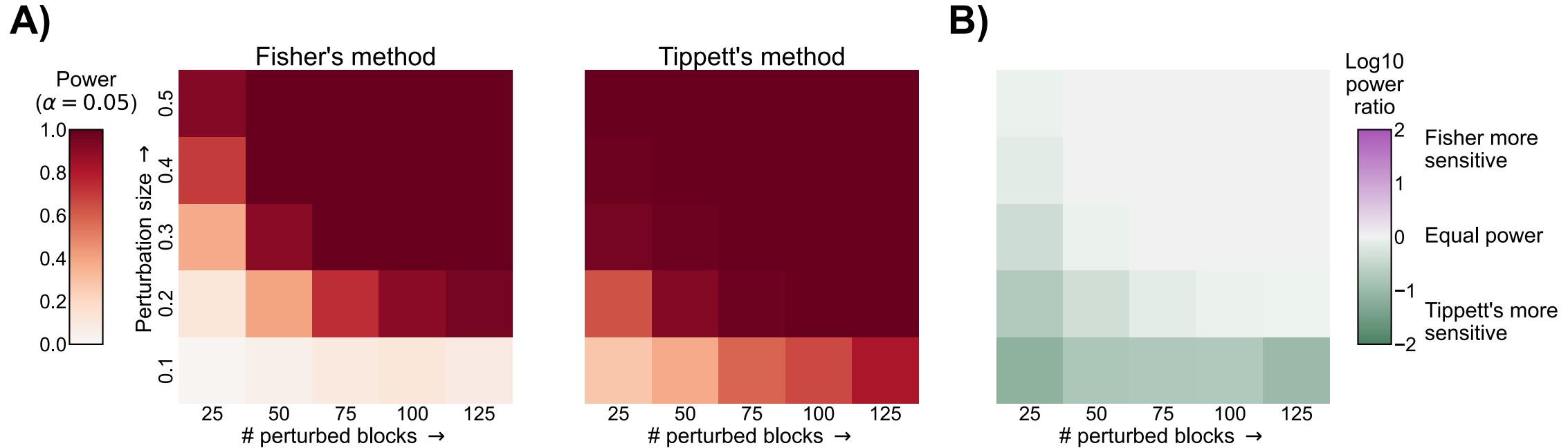
← We are trying to approximate this null distribution with something continuous $Uniform(0, 1)$

Power for combining p-values

- We perturb:
 - Some # of them (x-axis)
 - By some amount (panels)



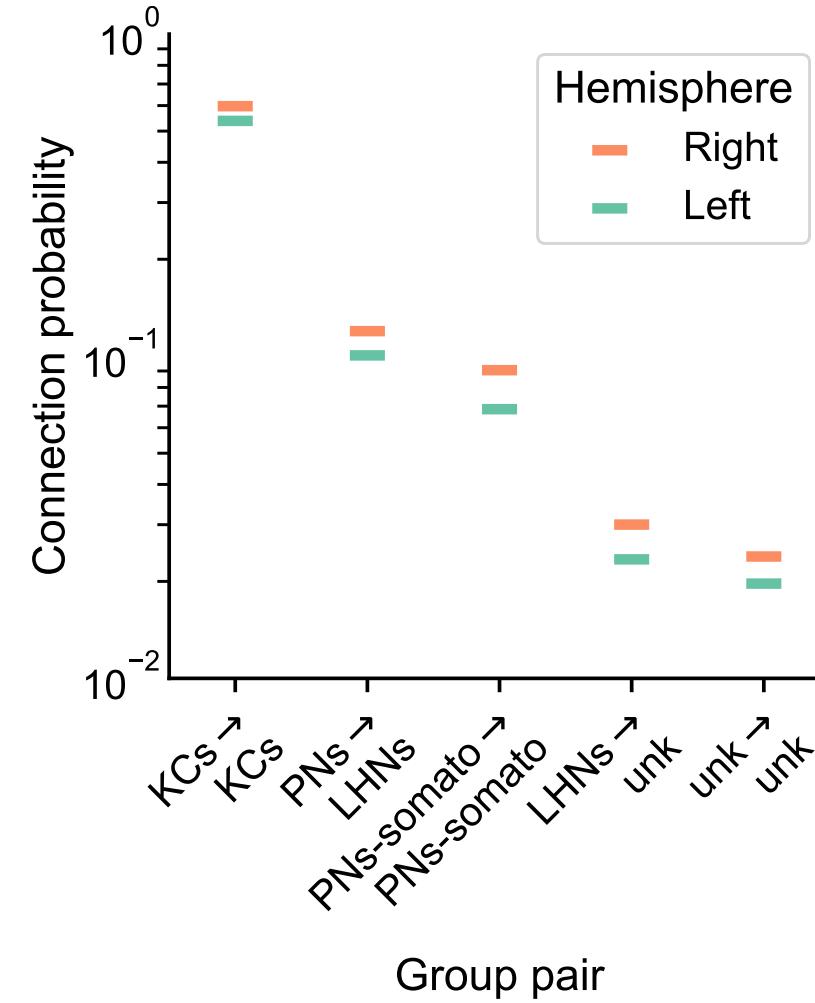
Relative power (Fisher's vs Tippett's)



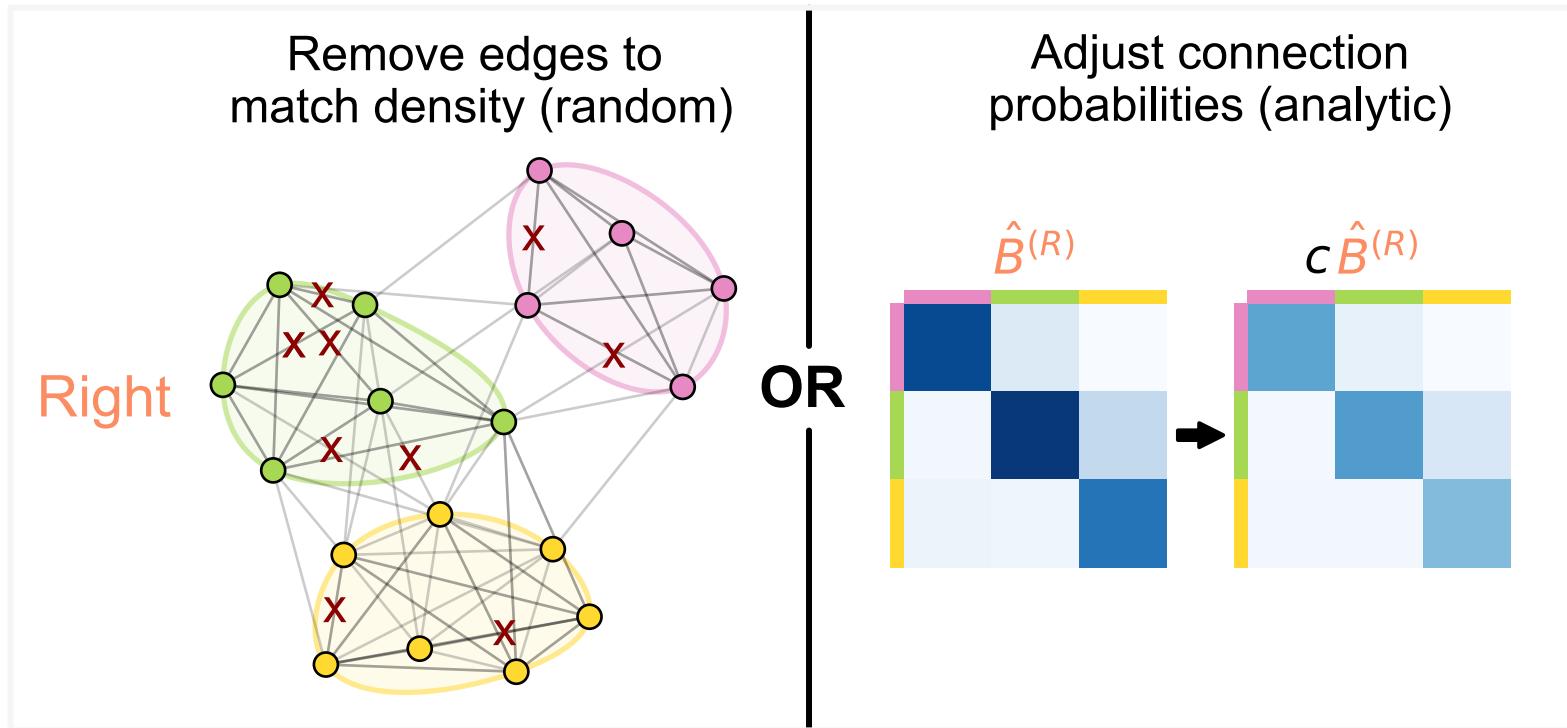
Back to the main thread...

Should we be surprised?

- Already saw that even the overall densities were different
- For all significant comparisons, probabilities on the right hemisphere were higher
- Maybe the right is just a "scaled up" version of the left?
 - $H_0 : B^{(L)} = cB^{(R)}$ where c is a density-adjusting constant, $\frac{p^{(L)}}{p^{(R)}}$



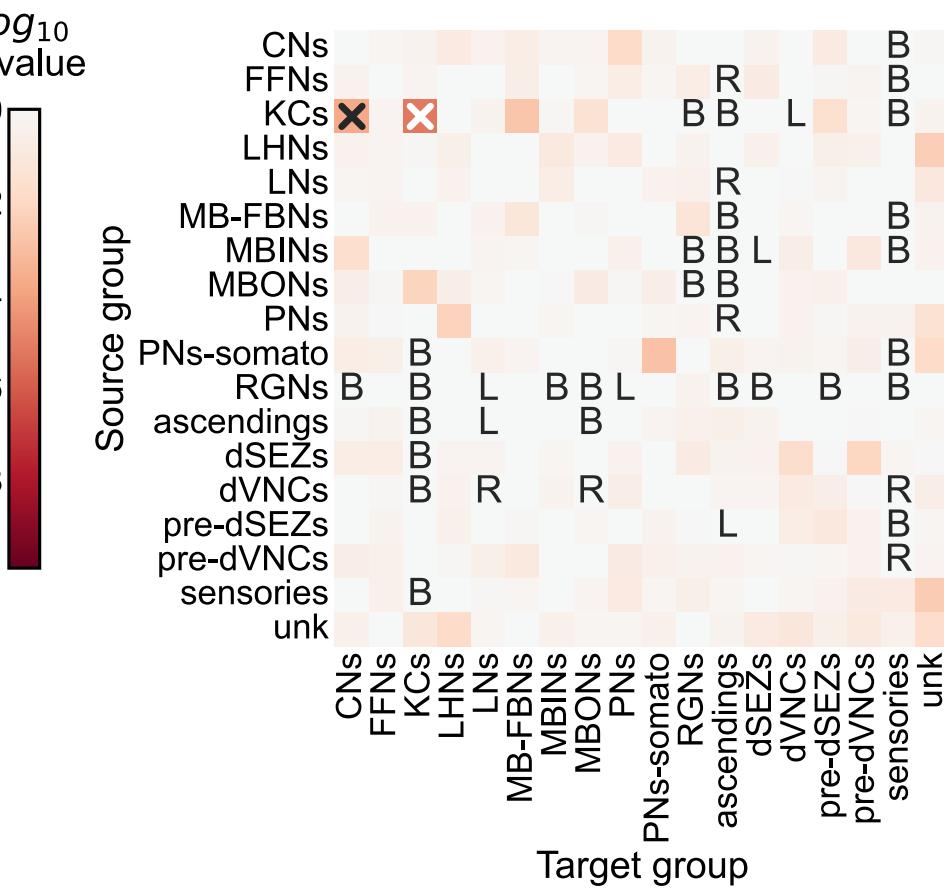
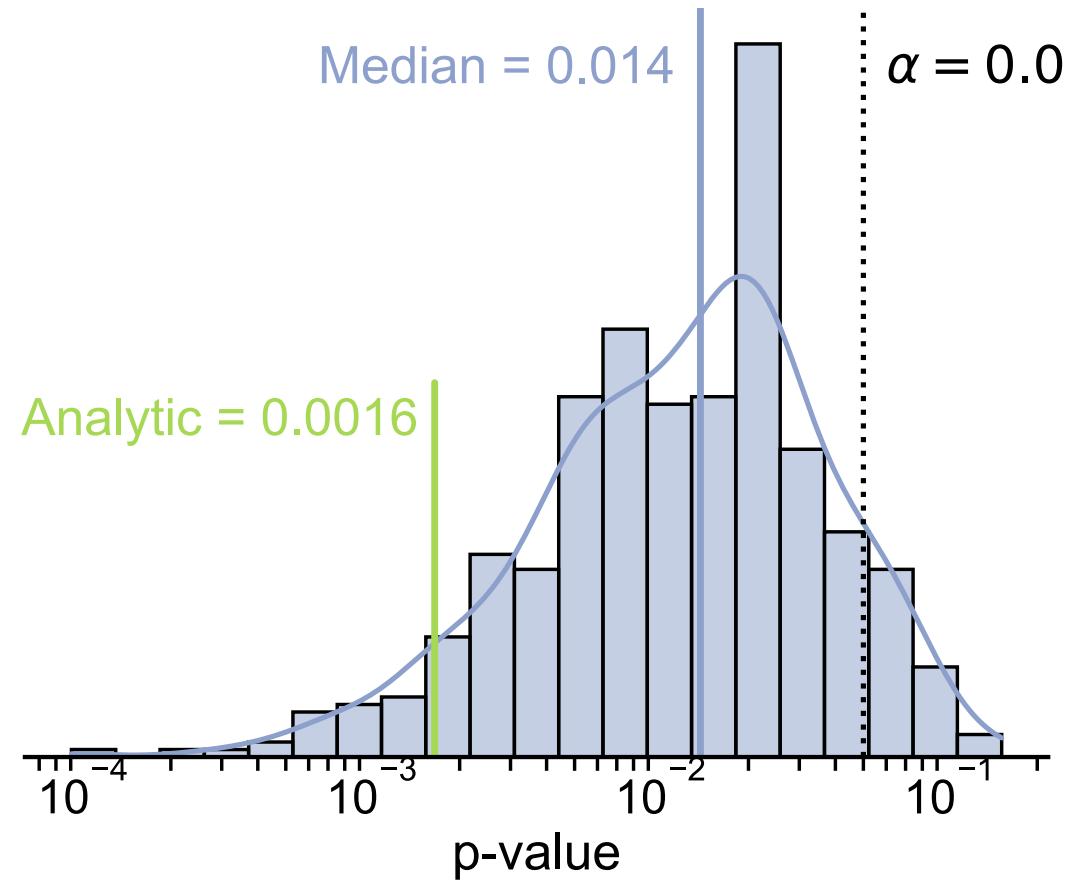
Adjusting for a difference in density



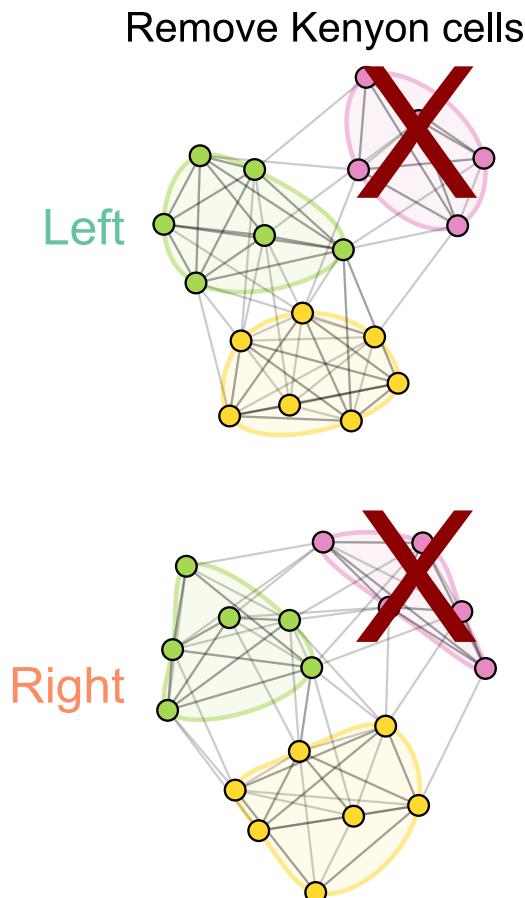
Rerun SBM testing

$$H_0: B^{(L)} = c B^{(R)}$$
$$H_A: B^{(L)} \neq c B^{(R)}$$

Even with density adjustment, we detect a difference



So the Kenyon cells are the only group with remaining differences...



Re-run all tests

ER

$$\begin{aligned} H_0: p^{(L)} &= p^{(R)} \\ H_A: p^{(L)} &\neq p^{(R)} \end{aligned}$$

SBM

$$\begin{aligned} H_0: B^{(L)} &= B^{(R)} \\ H_A: B^{(L)} &\neq B^{(R)} \end{aligned}$$

aSBM

$$\begin{aligned} H_0: B^{(L)} &= c B^{(R)} \\ H_A: B^{(L)} &\neq c B^{(R)} \end{aligned}$$

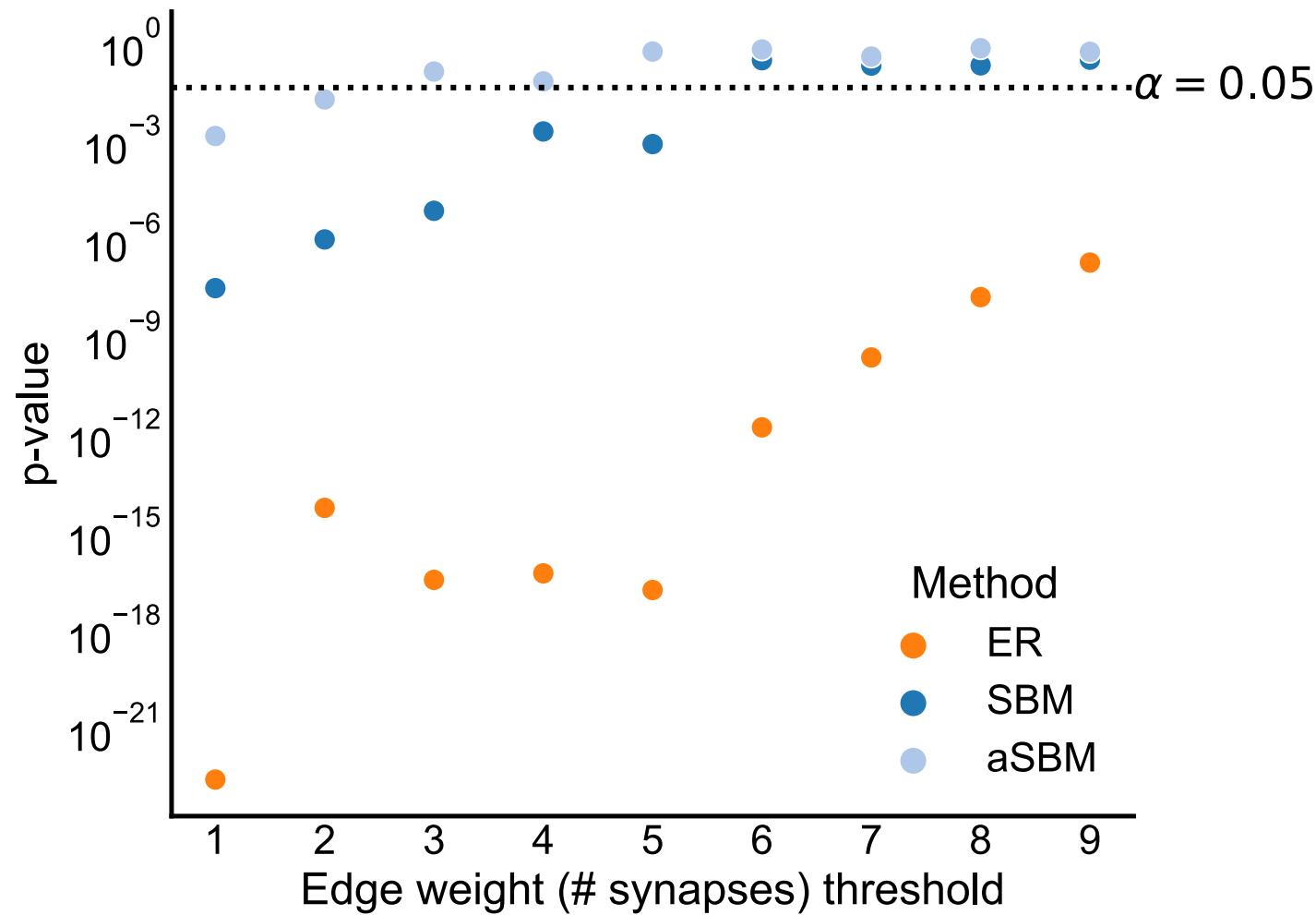
- ER test: $p < 10^{-26}$
- SBM test: $p \approx 0.0027$
- Adjusted SBM test: $p \approx 0.43$

To sum up...

Model	H_0 (vs. $H_A \neq$)	KC	p-value	Interpretation
ER	$p^{(L)} = p^{(R)}$	+	$< 10^{-23}$	Reject densities the same
SBM	$B^{(L)} = B^{(R)}$	+	$< 10^{-7}$	Reject group connection probabilities the same
aSBM	$B^{(L)} = cB^{(R)}$	+	≈ 0.0016	Reject above even after accounting for density
ER	$p^{(L)} = p^{(R)}$	-	$< 10^{-26}$	Reject densities the same (w/o KCs)
SBM	$B^{(L)} = B^{(R)}$	-	≈ 0.0027	Reject group connection probabilities the same (w/o KCs)
aSBM	$B^{(L)} = cB^{(R)}$	-	≈ 0.43	Don't reject above after density adjustment (w/o KCs)

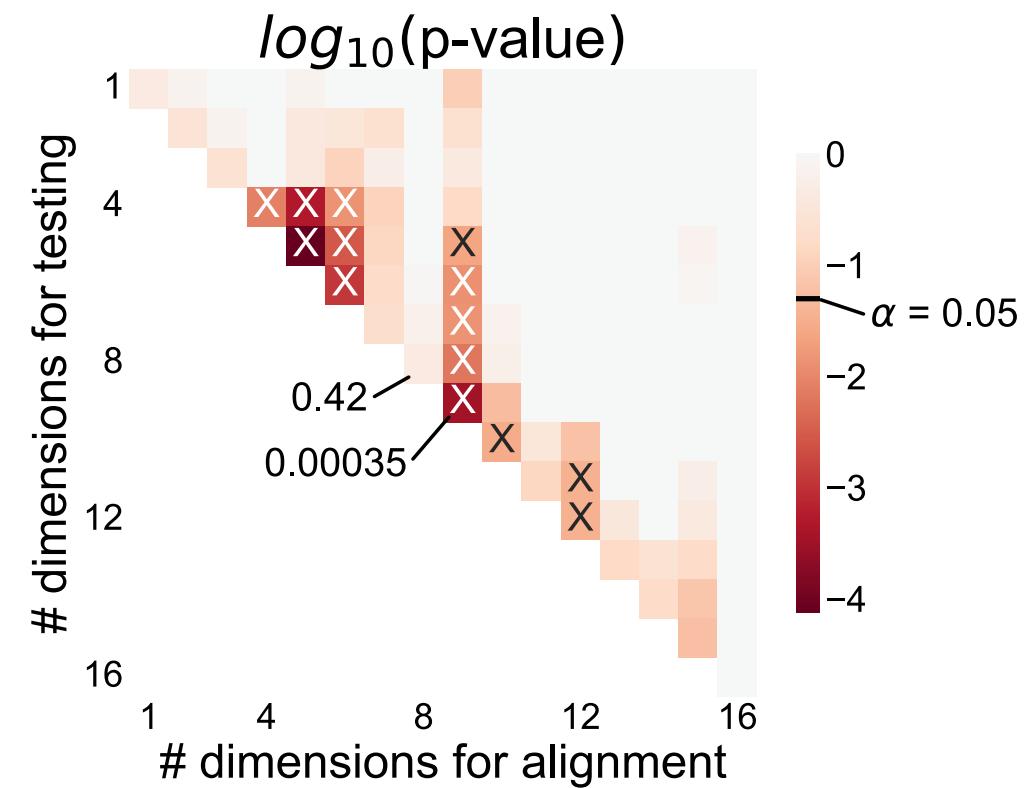
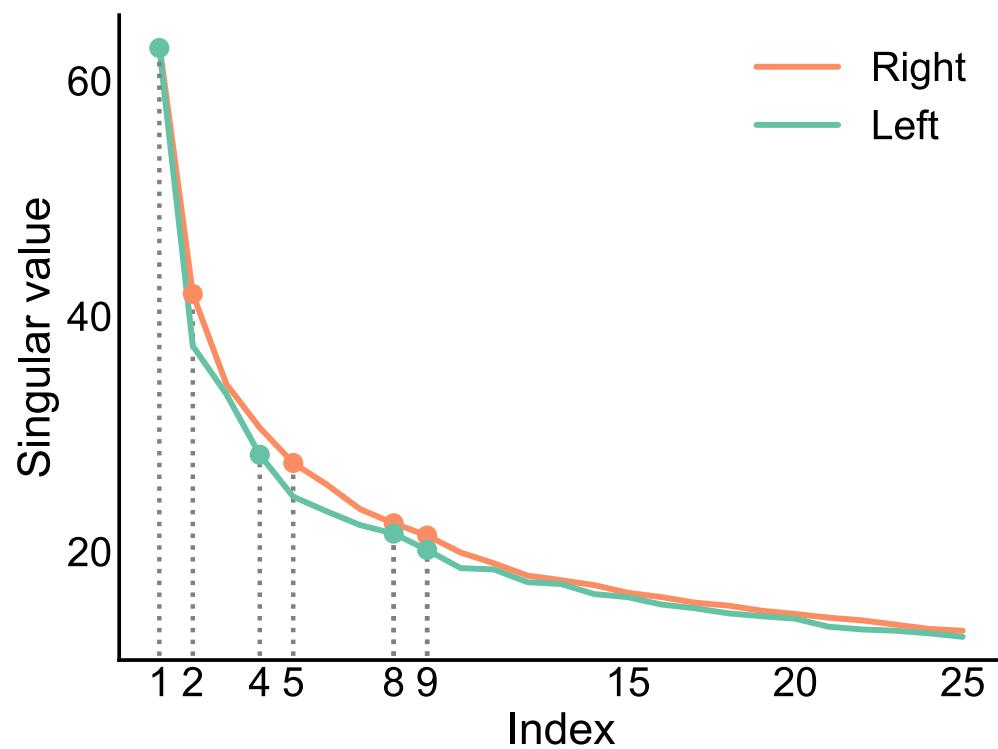
Extensions

But you threw out all of the edge weights!



There are so many other models!

Latent distribution test (random dot product graph)

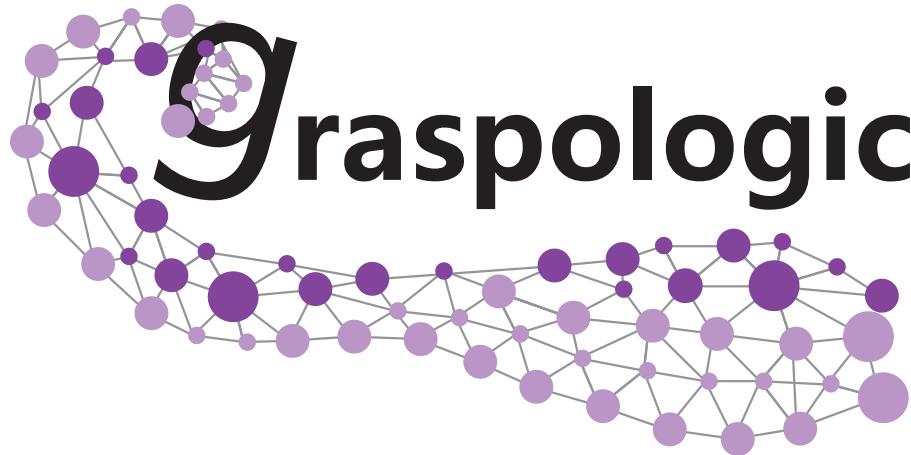


In summary...

- We studied simple ways of framing a network two sample test, and proposed test procedures for each
 - We found that it can be important to "mod out" by other simple network statistics if you don't care about them (like density)
- We found that all of these tests find the left and the right hemispheres to be significantly different, unless you ignore Kenyon cells and adjust for the difference in density
- The tests proposed here provide a foundation for future principled comparisons of connectomes

graspologic:

github.com/microsoft/graspologic



downloads 104k



243

contributors 46

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This work:

github.com/neurodata/bilateral-connectome

A screenshot of a web page titled "Bilateral Connectome" under the "NEURODATA" section. The page includes a search bar, a sidebar with links like "Abstract", "PRELIMINARIES", and "Math", and a main content area describing the Erdos-Renyi (ER) model. The "Math" section contains mathematical notation and text about global connection probability p .

Acknowledgements

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Mike Powell, Eric Bridgeford, Carey Priebe, Joshua Vogelstein, Kareef Ullah, Diane Lee, Sambit Panda, Jaewon Chung, Ali Saad-Eldin, NeuroData lab

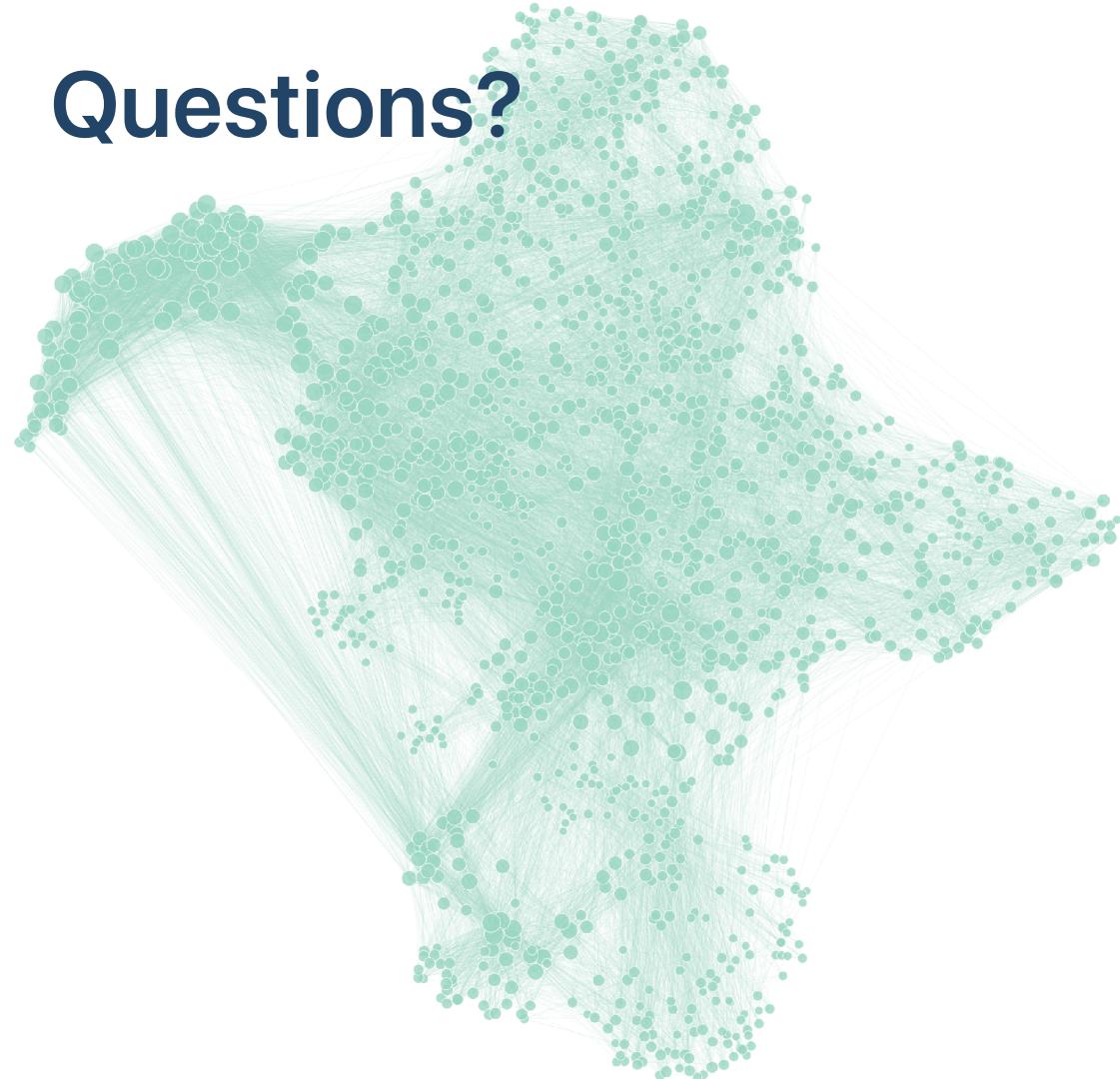
University of Cambridge / MRC Laboratory of Molecular Biology

Michael Winding, Albert Cardona, Marta Zlatic, Chris Barnes

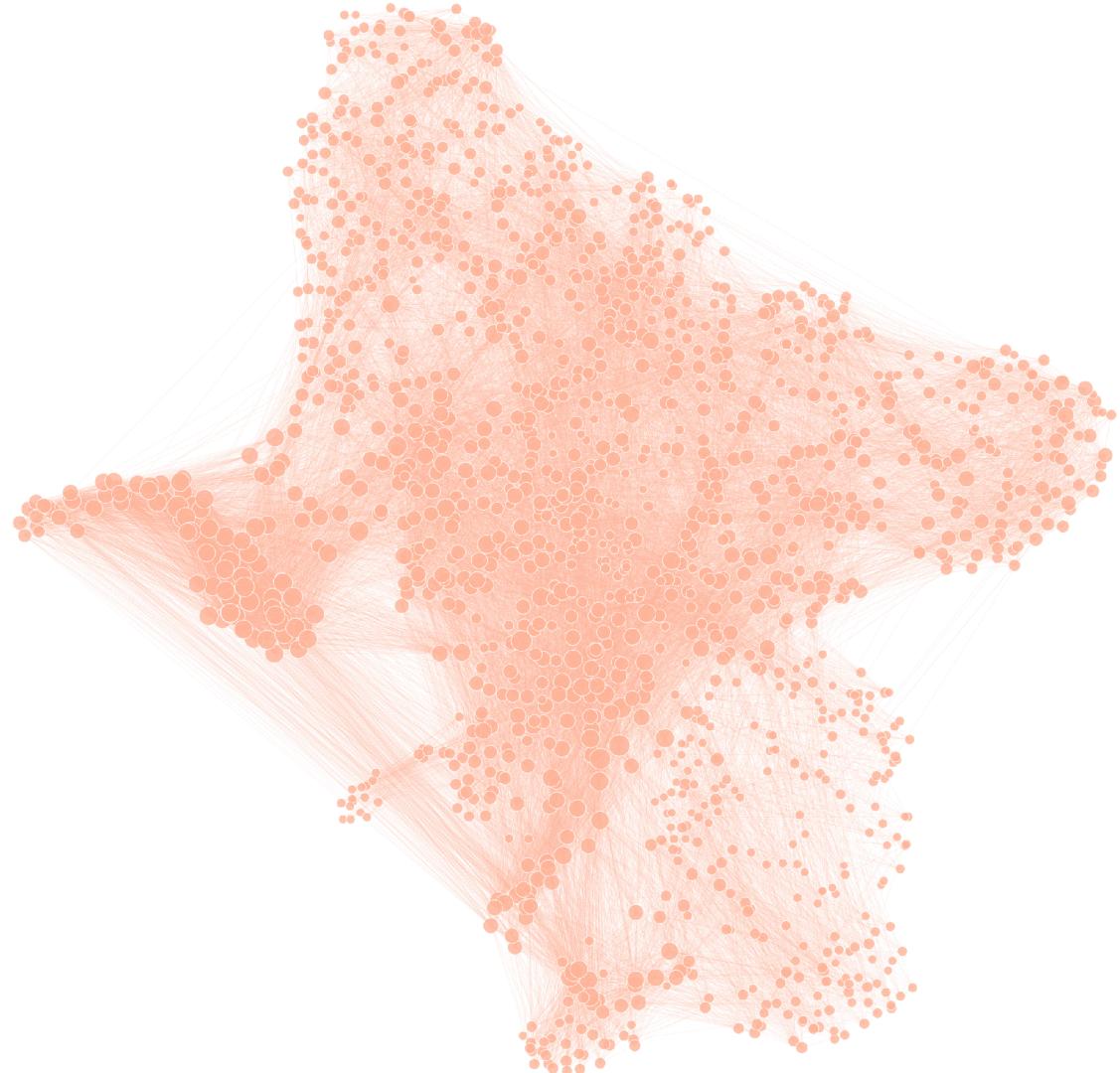
Microsoft Research

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

Questions?



Left



Right