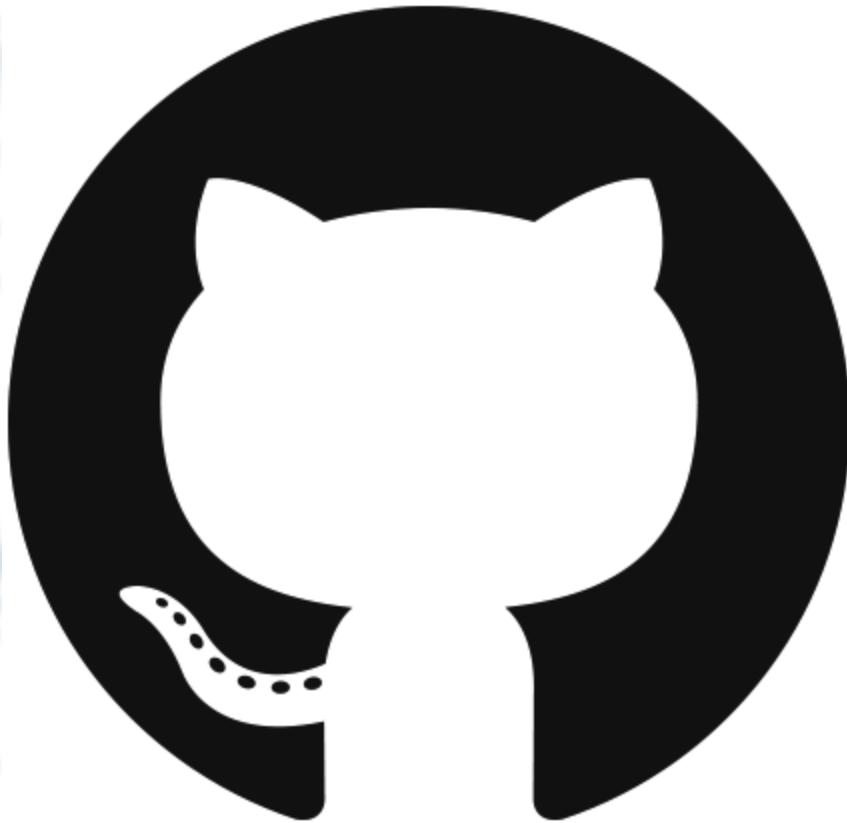


[bpedigo@jhu.edu](mailto:bpedigo@jhu.edu)

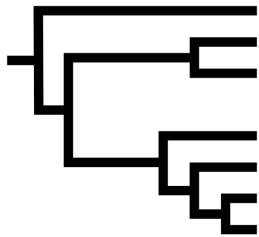


[@bdpedigo \(Github\)](#)

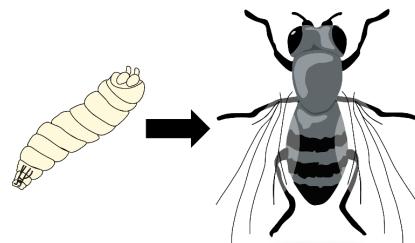


**Connectomics is useful...**

# Many of the stated goals of connectomics rely on linking connectome to other domains...



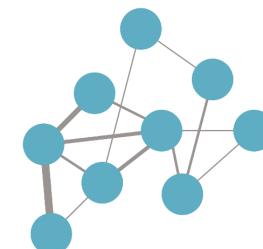
Evolution



Development



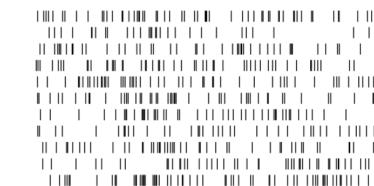
Genome



Connectome



Behavior



Activity

## Connectome ↔ memory

...the acquisition of wiring diagrams across multiple individuals will yield insights into  
**how experiences shape neural connections.**

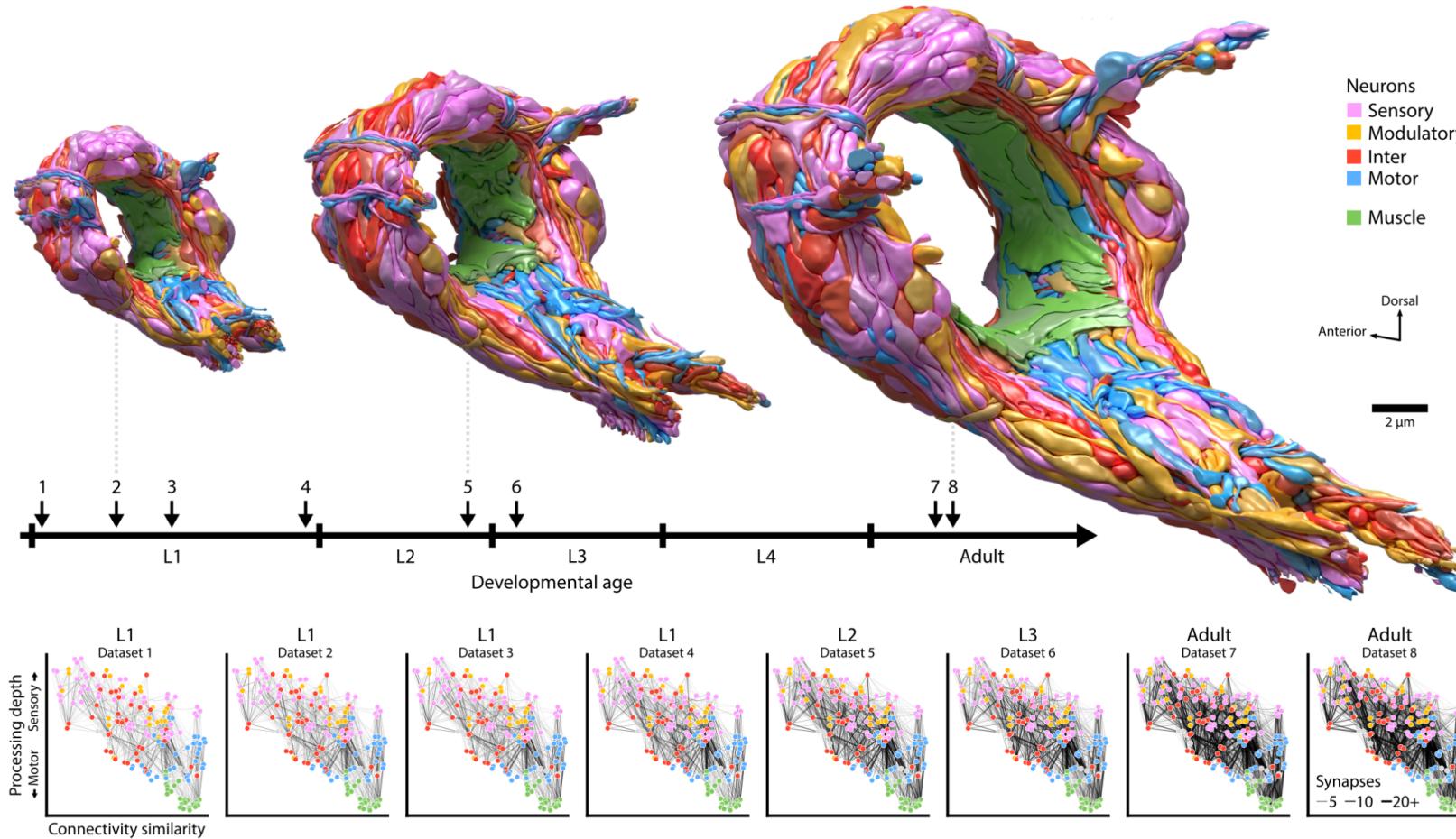
*Emphasis added*

## Connectome ↔ evolution

Comparative connectomics of [...] species across the phylogenetic tree can infer the archetypal neural architecture of each bauplan and identify any circuits that possibly converged onto a shared and potentially optimal, structure.

*Emphasis added*

# Connectomes across development



**But it is methodologically hard to compare  
connectomes! this is a test**

# Outline for today

- Describe a dataset that I'll use for these examples throughout
- Show how connectome comparison can be framed as network hypothesis testing
- Show how we can use automated tools for predicting the correspondence of neurons across datasets
- Mention some extensions to use/combine/extend these tools that we're working on

# *Drosophila* larva (AKA a maggot) brain connectome

```
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```

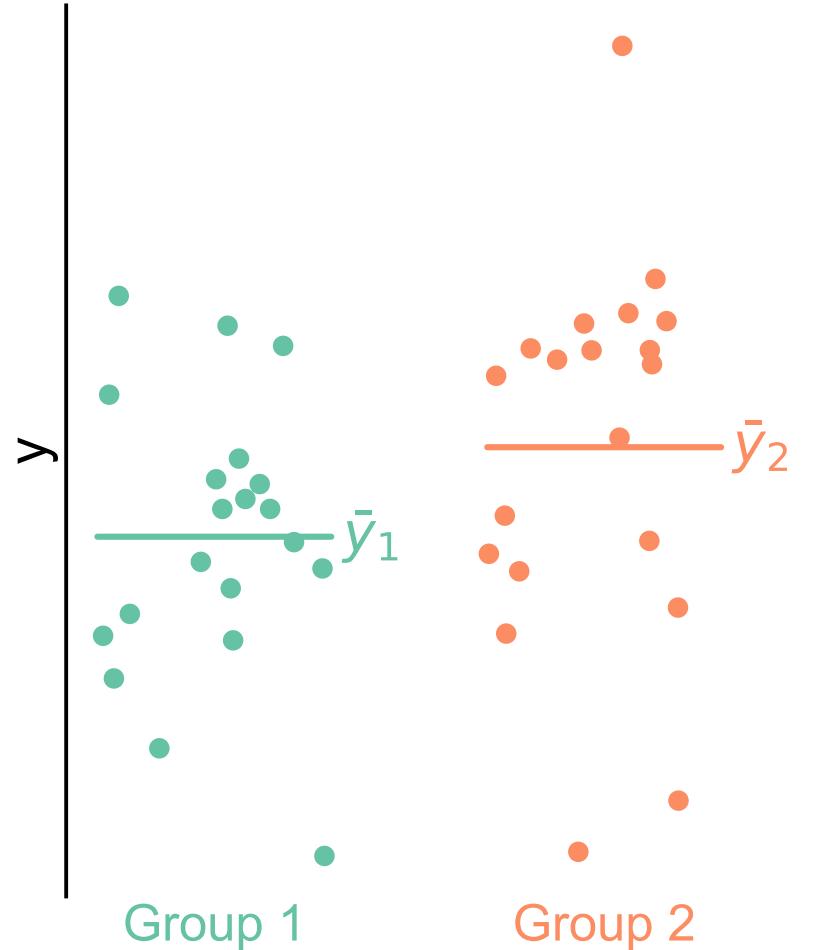
- Collaboration with Marta Zlatic/Albert Cardona's groups - led by Michael Winding
- First whole-brain, single-cell connectome of any insect
- ~3000 neurons, ~550K synapses
- Both hemispheres of the brain reconstructed

```
</div> <div> </div> </div> <footer> Winding, Pedigo et al. "The complete connectome of  
an insect brain." In prep. (2022) </footer>
```



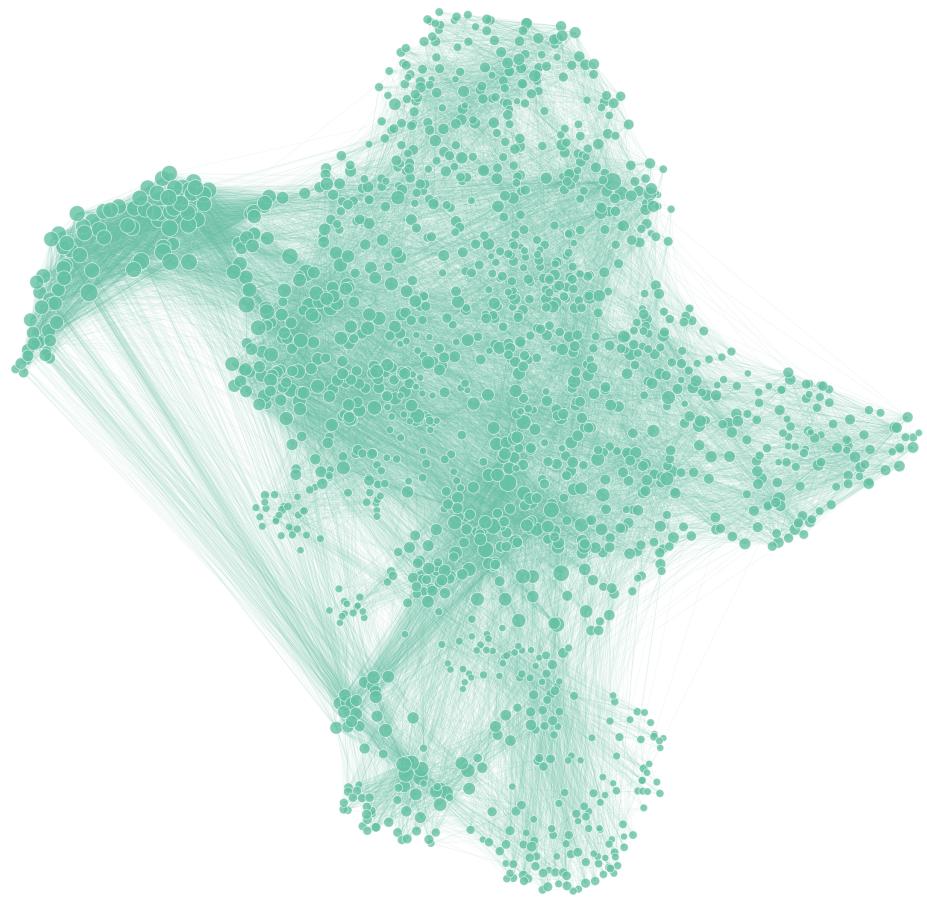
**Are the `<span style="color: var(--left)"> left </span>`  
and `<span style="color: var(--right)"> right </span>`  
sides of this connectome `<p> </p>` different?**

<div class="columns"> <div>

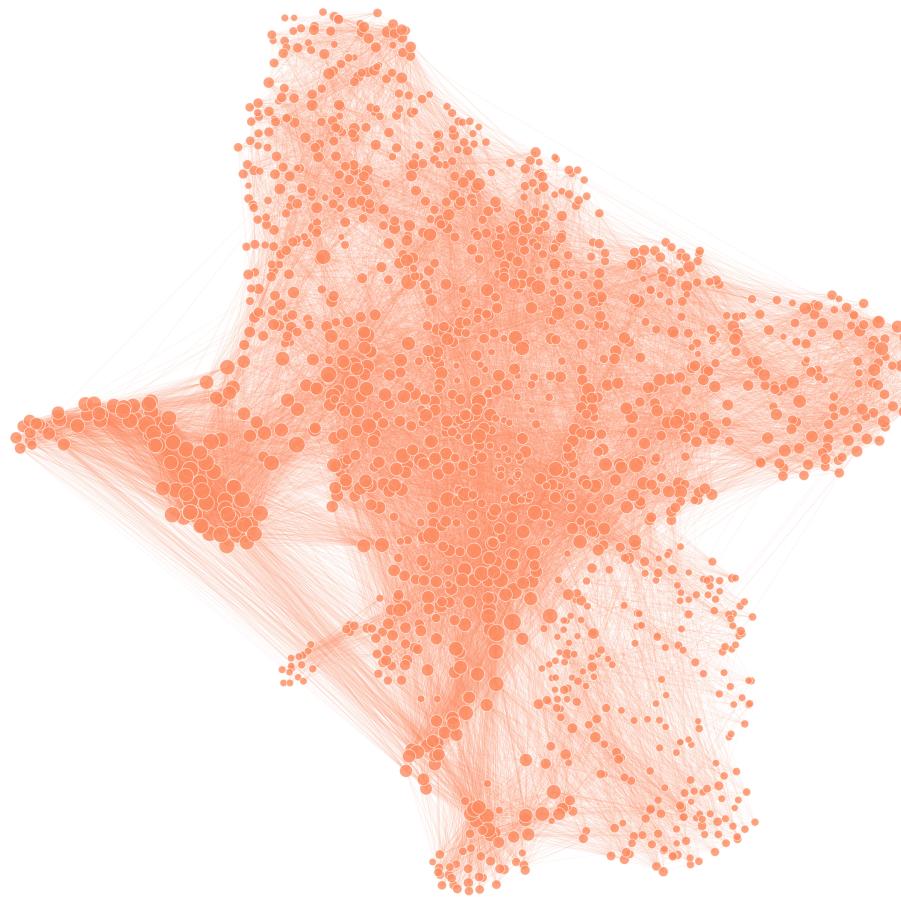


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- Known as two-sample testing
- $Y^{(1)} \sim F^{(1)}$ ,  $Y^{(2)} \sim F^{(2)}$
- $H_0 : F^{(1)} = F^{(2)}$



Left



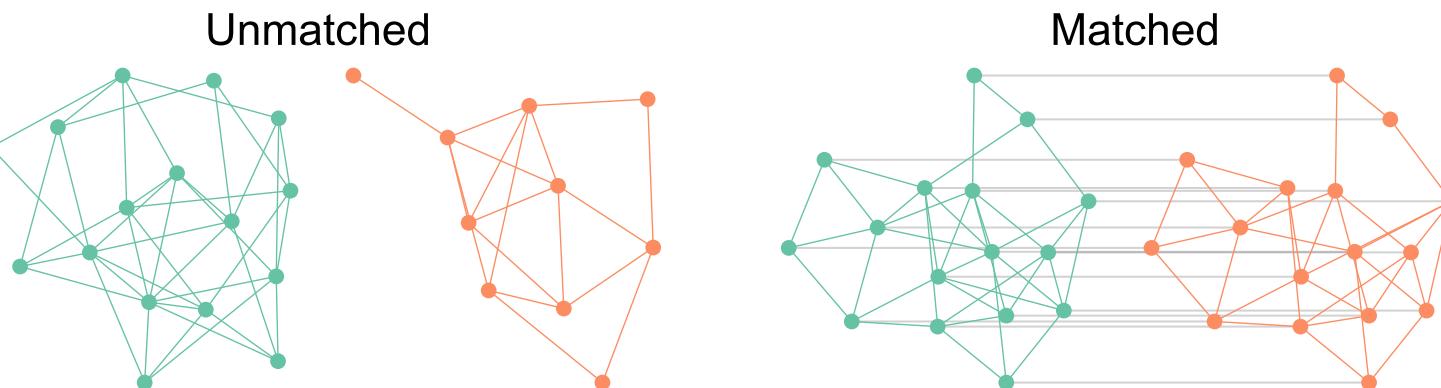
Right

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

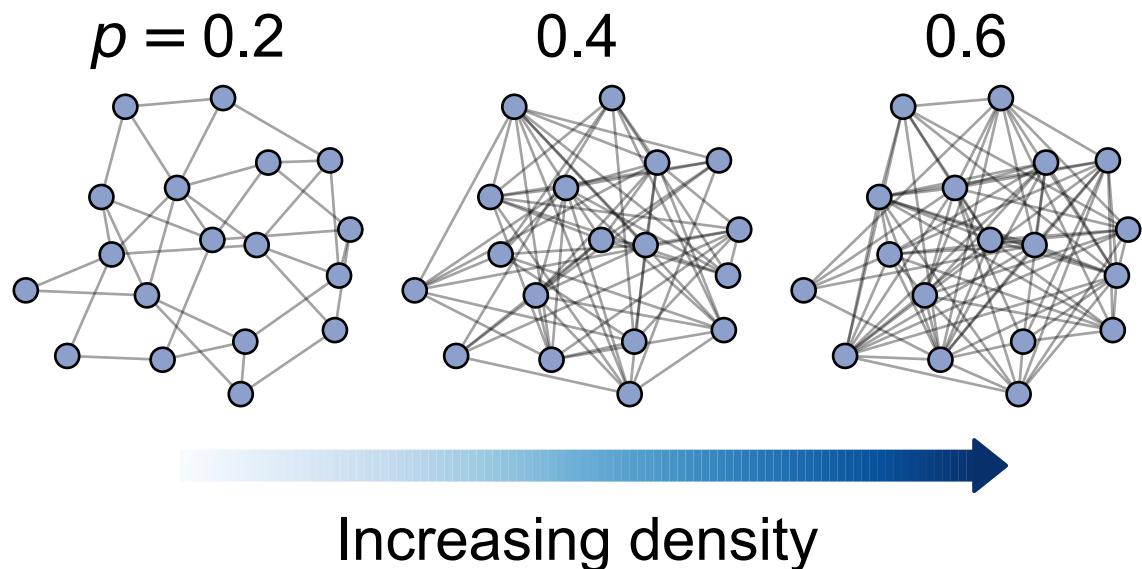
# Assumptions

- 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 `<span style='color: var(--left)'> left → left </span>` and `<span style='color: var(--right)'> right → right </span>` (*ipsilateral*) connections only.
- Not going to assume any nodes are matched



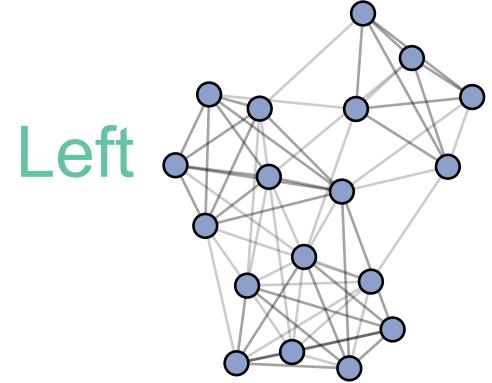
# Erdos-Renyi model

- All edges are independent
- All edges generated with the same probability,  $p$



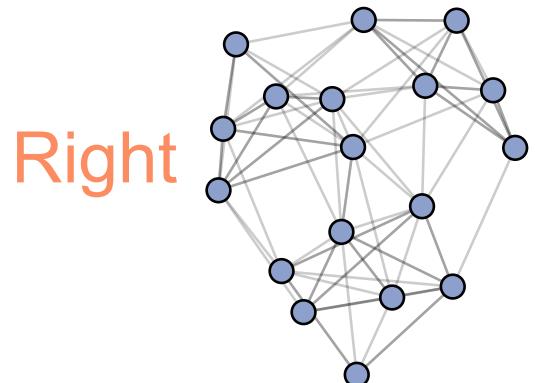
# Density-based testing

Compute global  
connection density



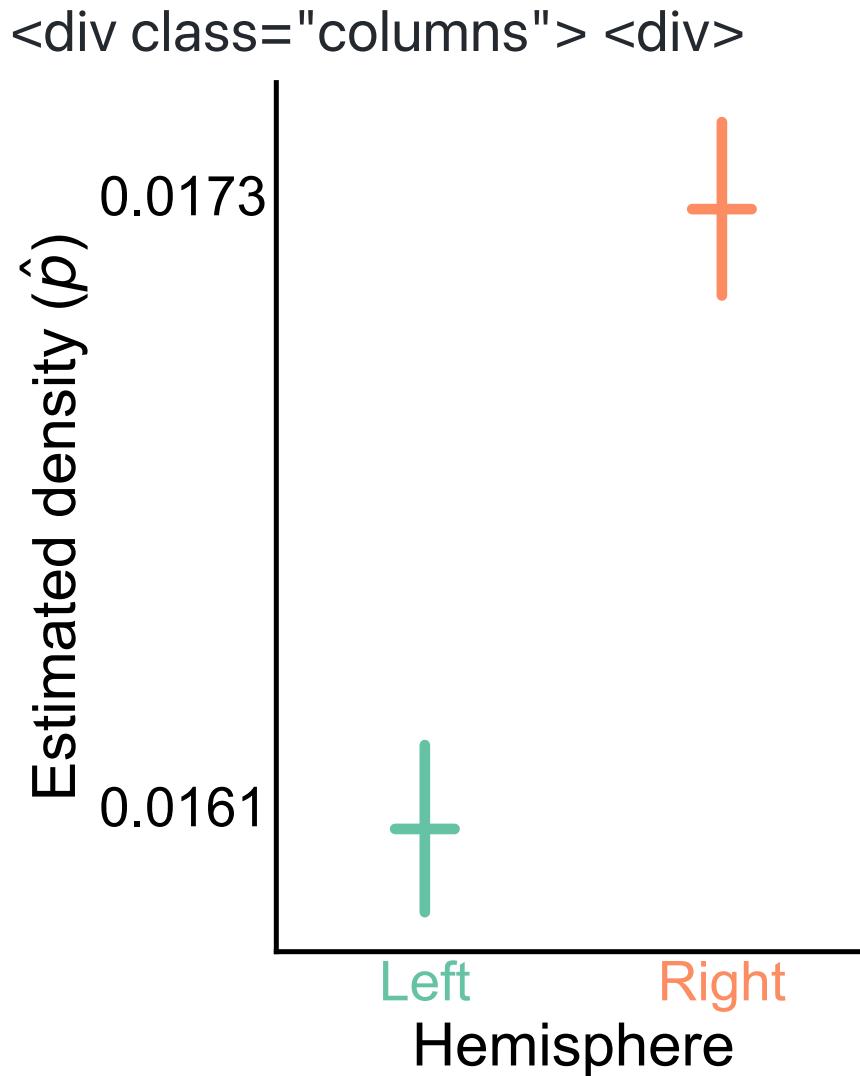
Compare ER  
models

$$p = \frac{\# \text{ edges}}{\# \text{ potential edges}}$$



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

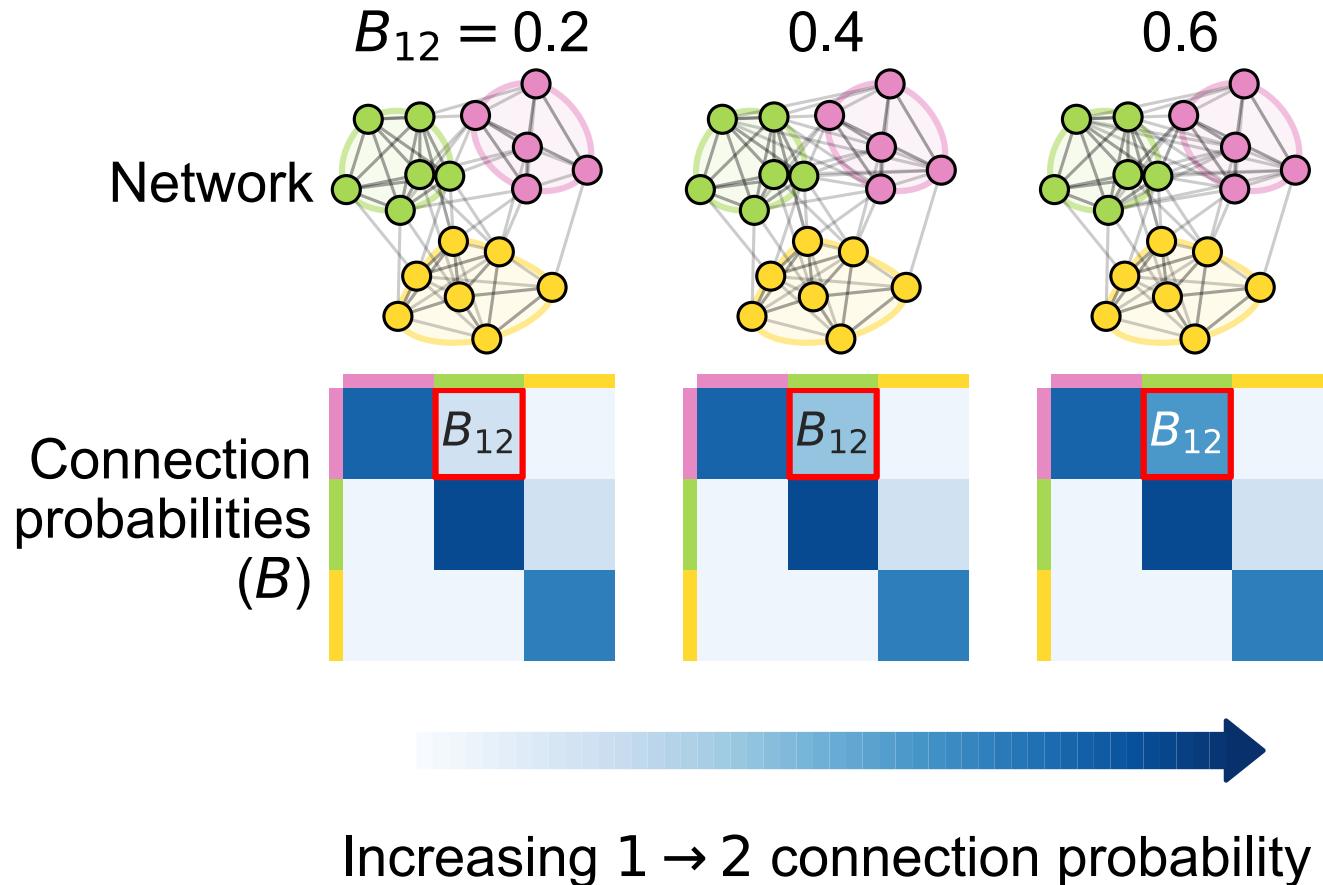
# We detect a difference in density

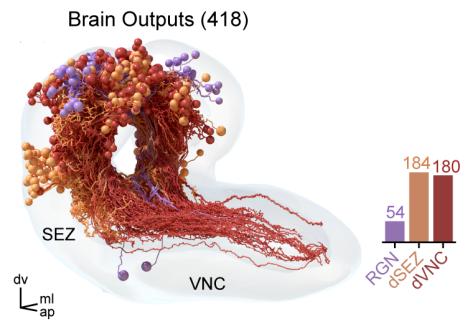
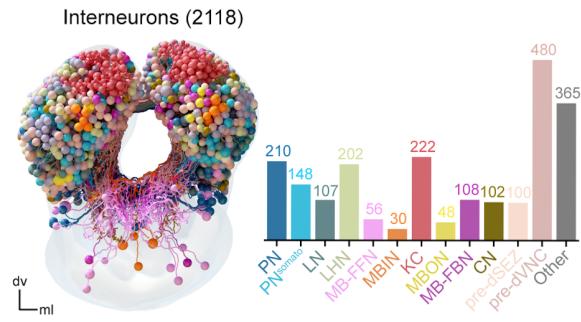
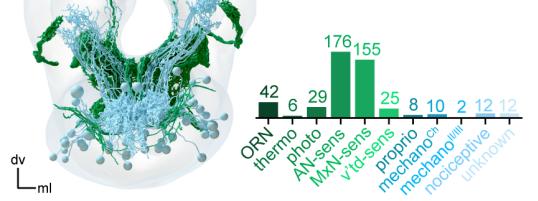


- p-value  $< 10^{-22}$

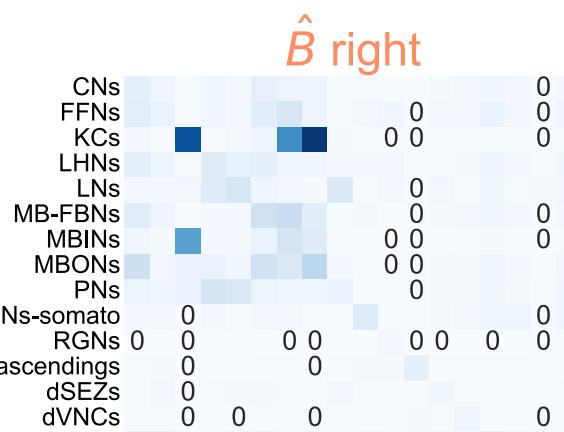
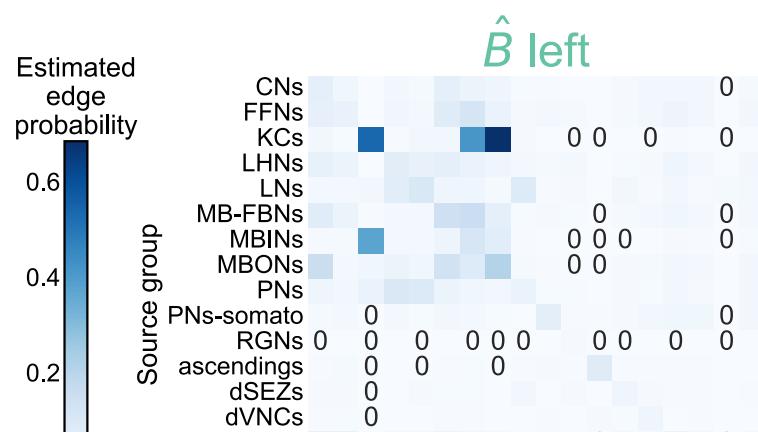
# Stochastic block model

- Edge probabilities are a function of a neuron's group



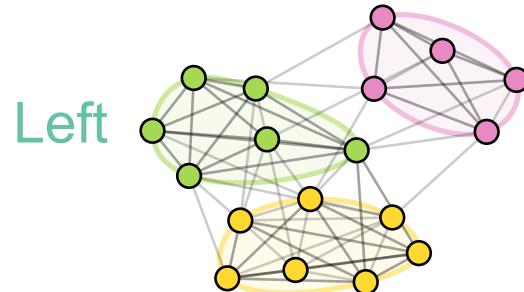


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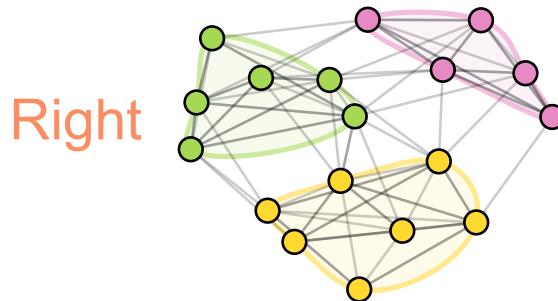


# Group-based testing

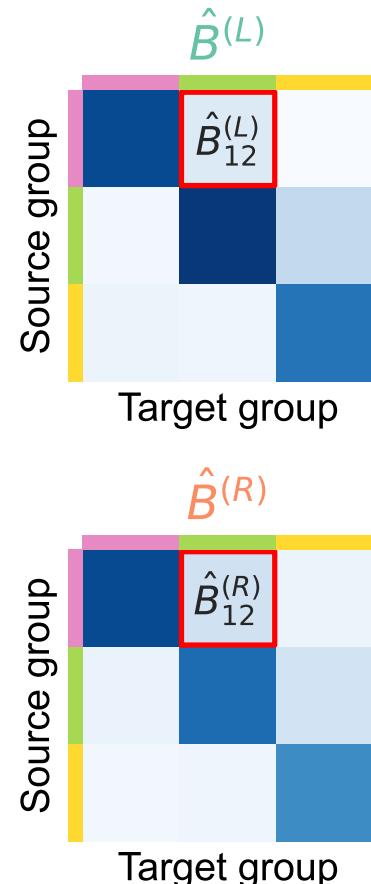
Group neurons



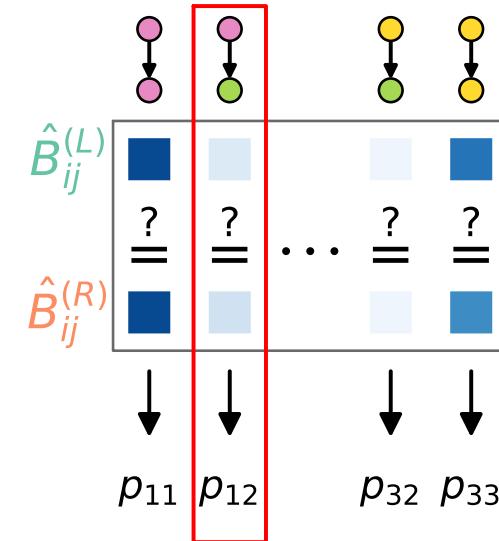
Right



Estimate group connection probabilities

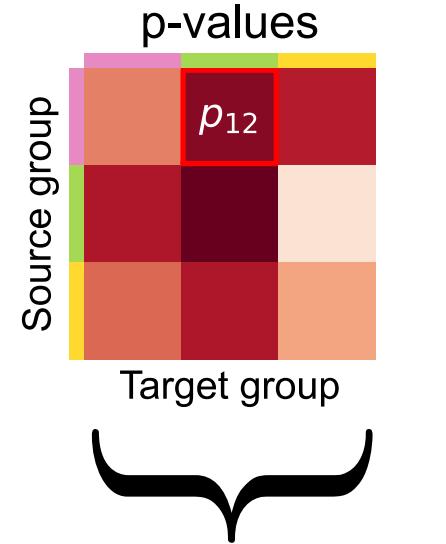


Compare probabilities, compute p-values

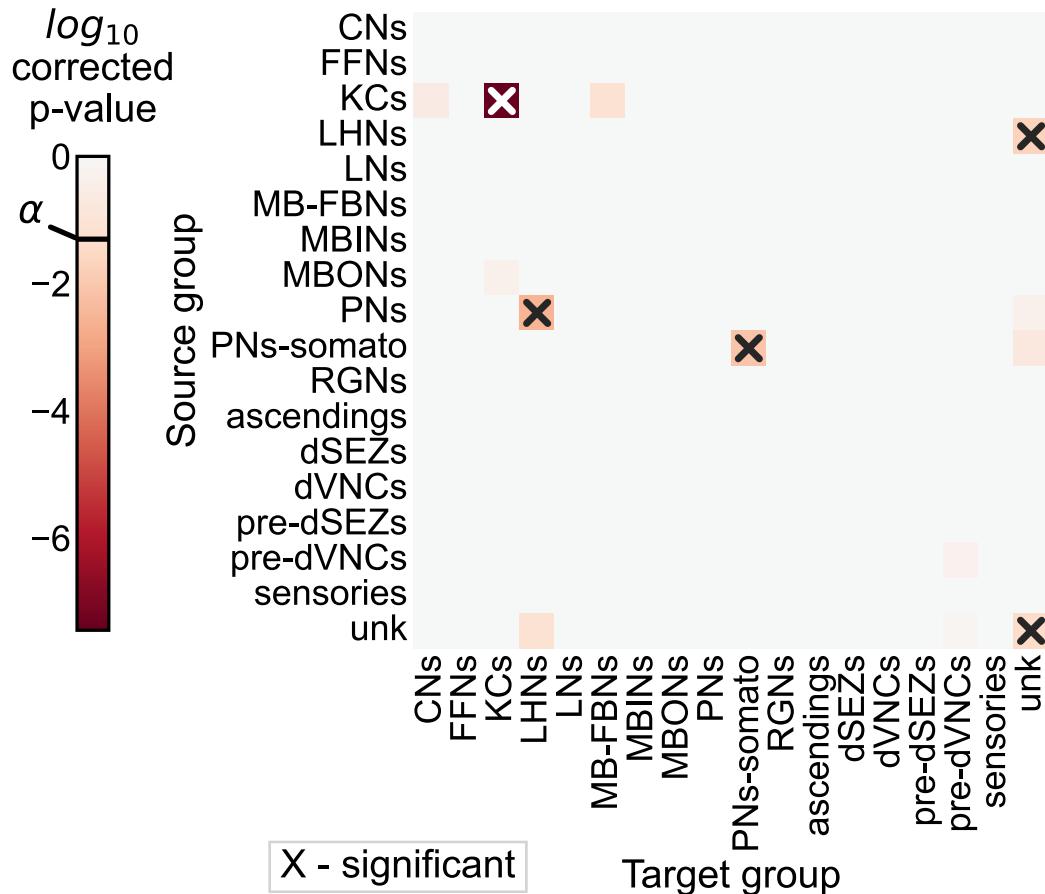


$$H_0: \hat{B}_{ij}^{(L)} = \hat{B}_{ij}^{(R)}$$
$$H_A: \hat{B}_{ij}^{(L)} \neq \hat{B}_{ij}^{(R)}$$

Combine p-values for overall test



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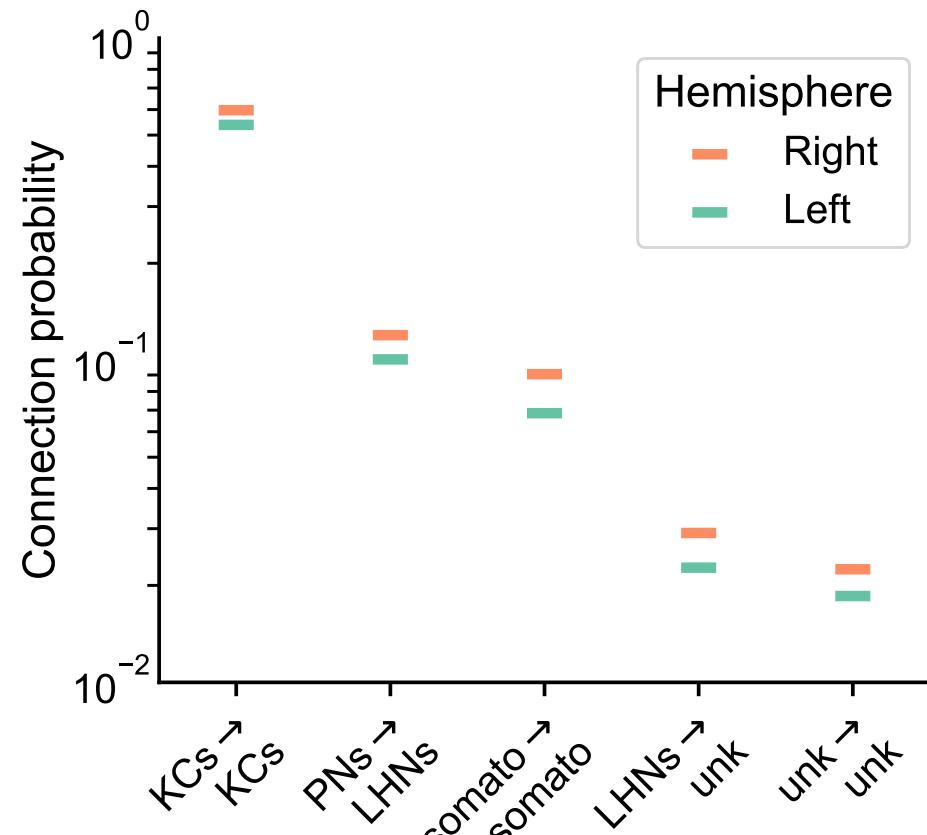
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- After multiple comparison, find 5 group-to-group connections which are significantly different
- Combine (uncorrected) p-values (like a meta-analysis), leads to p-value for overall

- 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?
  - $H_0 : B^{(L)} = cB^{(R)}$

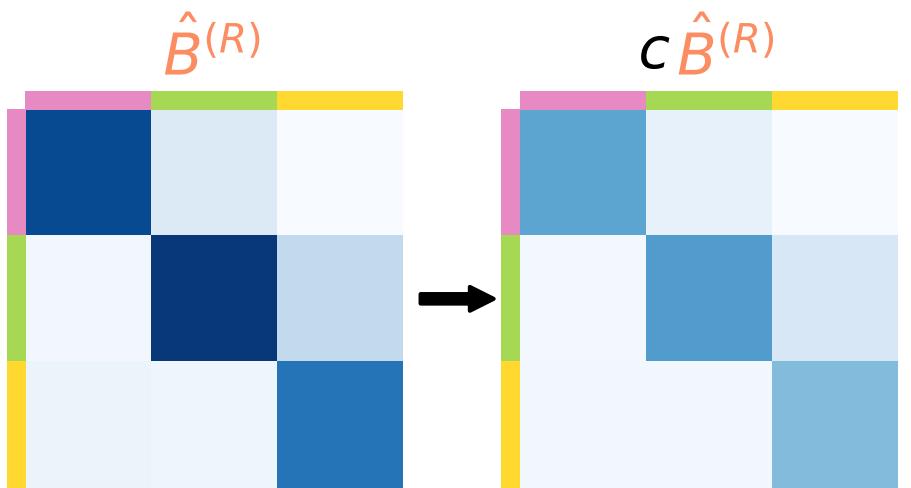
where  $c$  is a density-adjusting constant,  $\frac{p^{(L)}}{p^{(R)}}$

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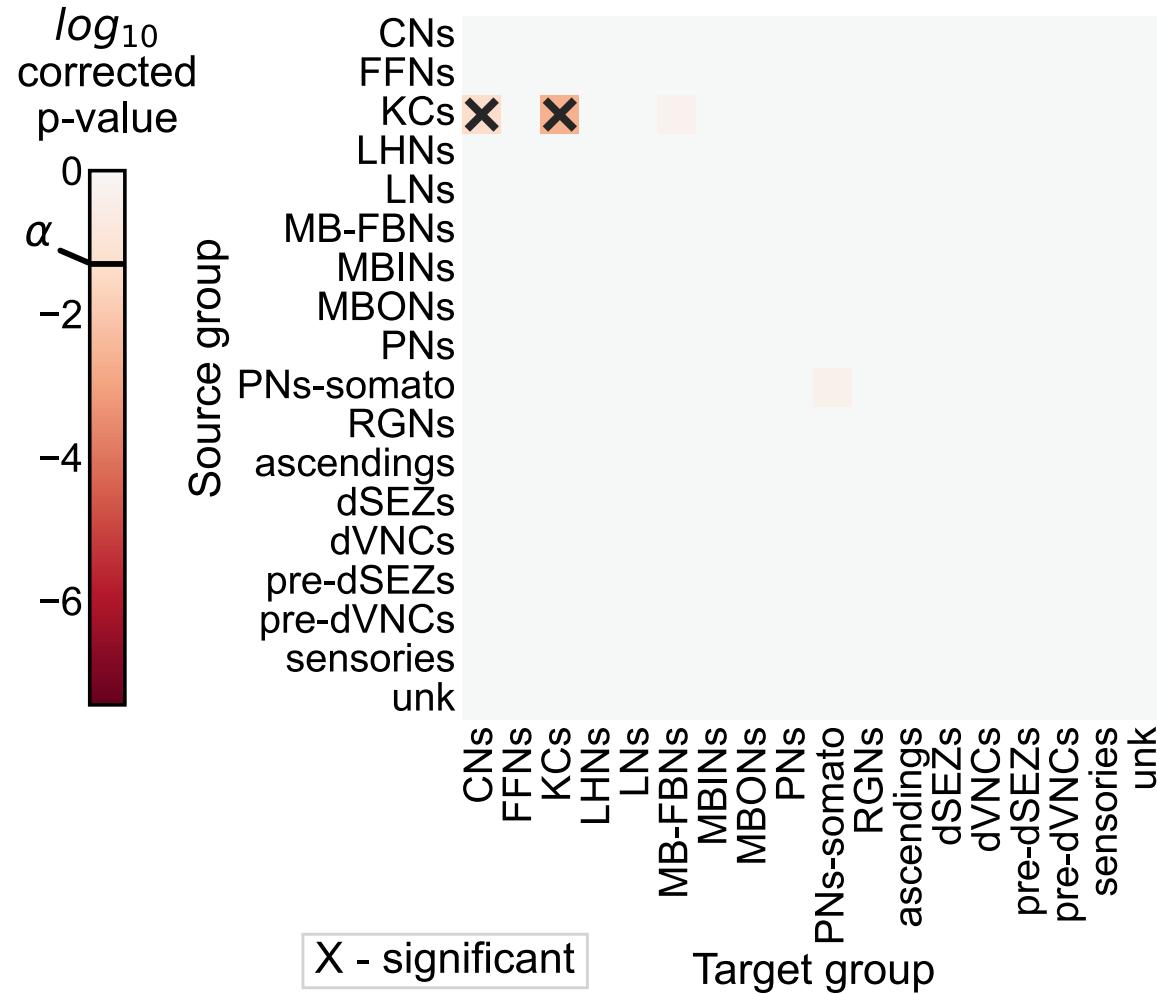
# Adjusting for a difference in density

Scale connection probabilities  
to match densities



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

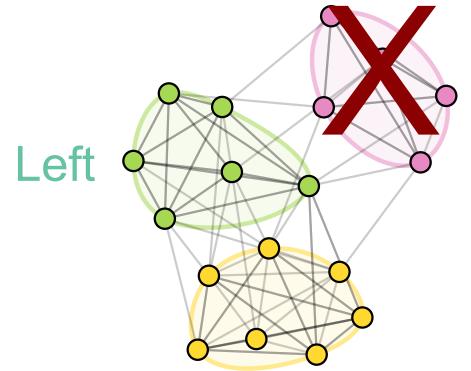
# Remaining differences are isolated to KCs



# we detect remaining differences...

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Remove Kenyon cells



Re-run all tests

Density

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

Group connection

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



Density-adjusted  
group connection

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

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- ER test:  $p < 10^{-26}$
- SBM test:  $p \approx 0.003$

## To sum up...

Model	$H_0$ (vs. $H_A \neq$ )	KCs	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	$B^{(L)} = cB^{(R)}$	+	$\approx 0.002$	Reject above even after accounting for density
ER	$p^{(L)} = p^{(R)}$	-	$< 10^{-26}$	Reject densities the same (w/o KCs)
SBM	$B^{(L)} = B^{(R)}$	-	$\approx 0.003$	Reject group connection probabilities the same (w/o KCs)
aSBM	$B^{(L)} = cB^{(R)}$	-	$\approx 0.43$	Don't reject above after density adjustment (w/o KCs)

## Matching neurons

## Extensions and ongoing work

## **matched versions of our tests**

- we think greater power, basically

## testing for a significant matching

- evaluate stereotypy at a single neuron level, basically

## the value of pairs - looking at models

- show the hierarchical clustering
- SBM cross validation curve

# Summary

# **How to use these tools?**

**graspologic**

**bilateral repo**

**bgm**

**get in touch!**



Eric Bridgeford

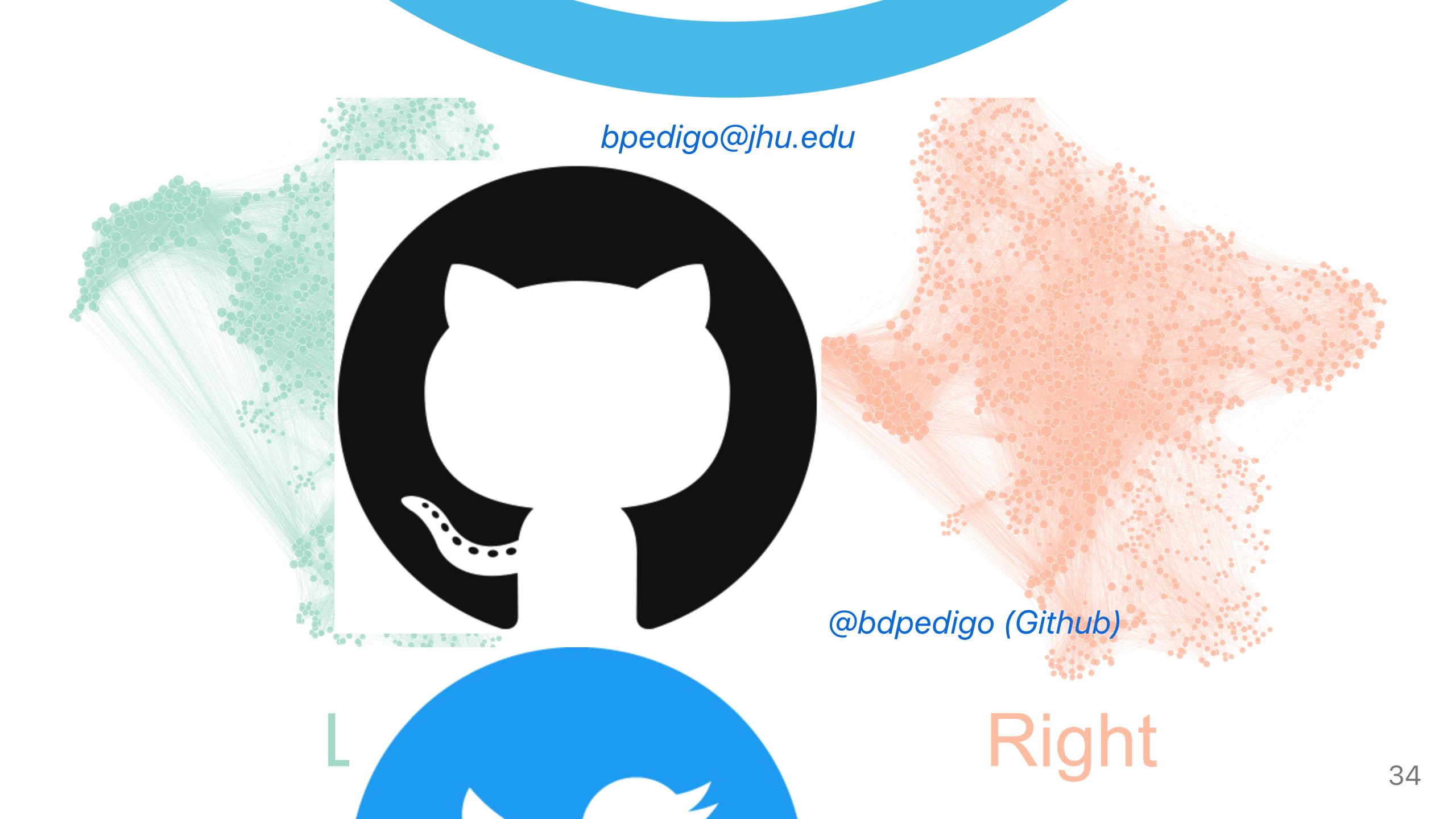
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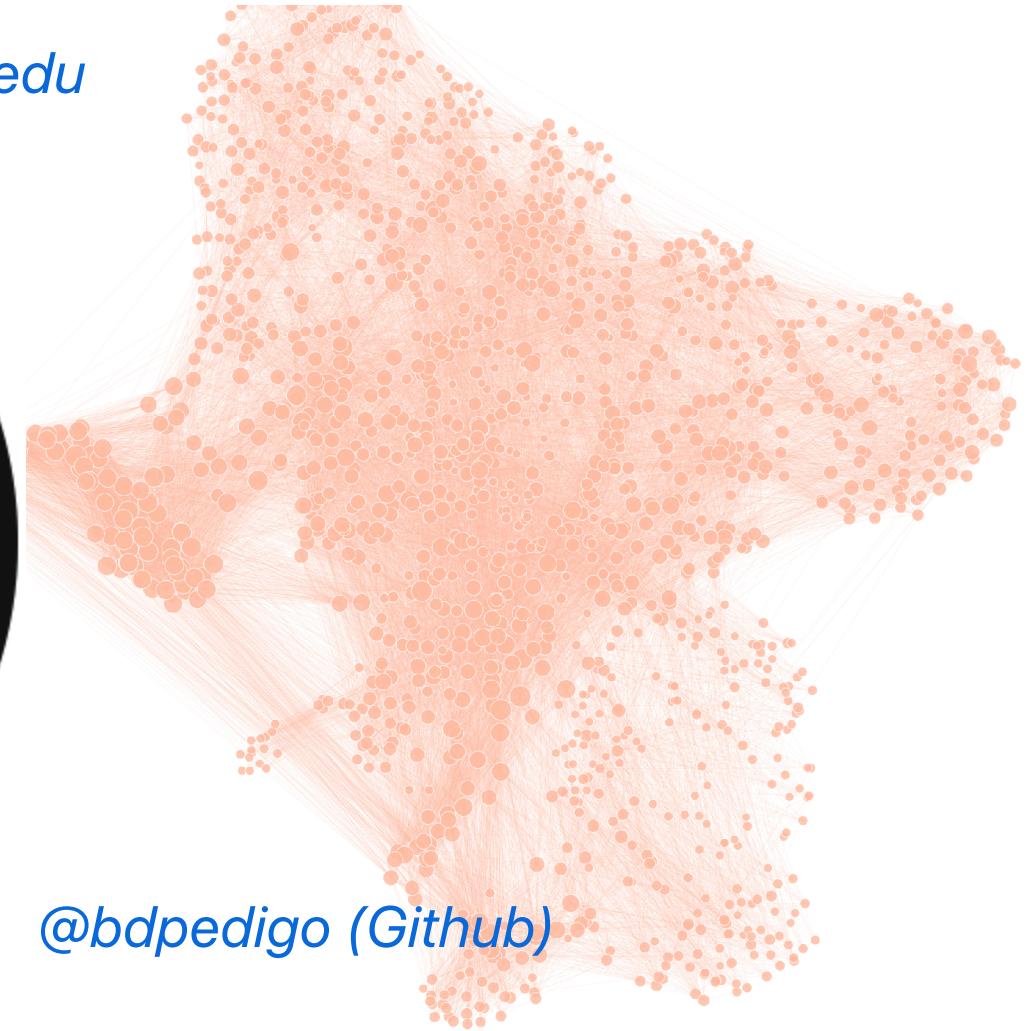
Ali  
Saad-Eldin

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[bpedigo@jhu.edu](mailto:bpedigo@jhu.edu)



Right