

Tools for comparative connectomics: case studies from two sides of a larval Drosophila brain

```
<div class="columns"> <div>
```

Benjamin D. Pedigo

(he/him)

[NeuroData lab](#)

Johns Hopkins University - Biomedical Engineering

 bpedigo@jhu.edu

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

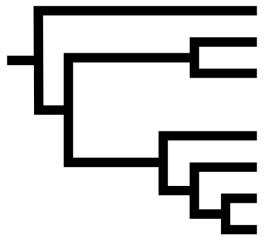
 [@bpedigod \(Twitter\)](#)

 bpedigo.github.io

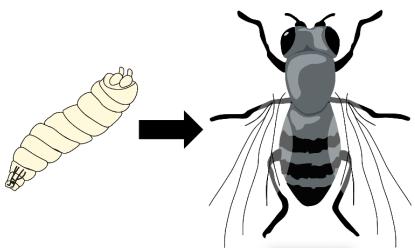
```
</div> <div>
```

These slides at:

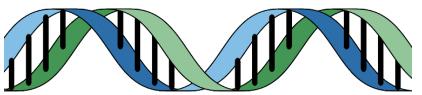
Many stated goals of connectomics are to link connectome to other properties



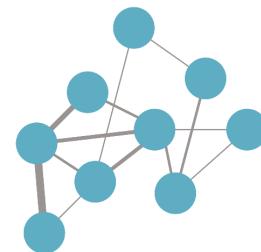
Evolution



Development



Genome



Connectome



Behavior



Activity

Connectome \leftrightarrow memory

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

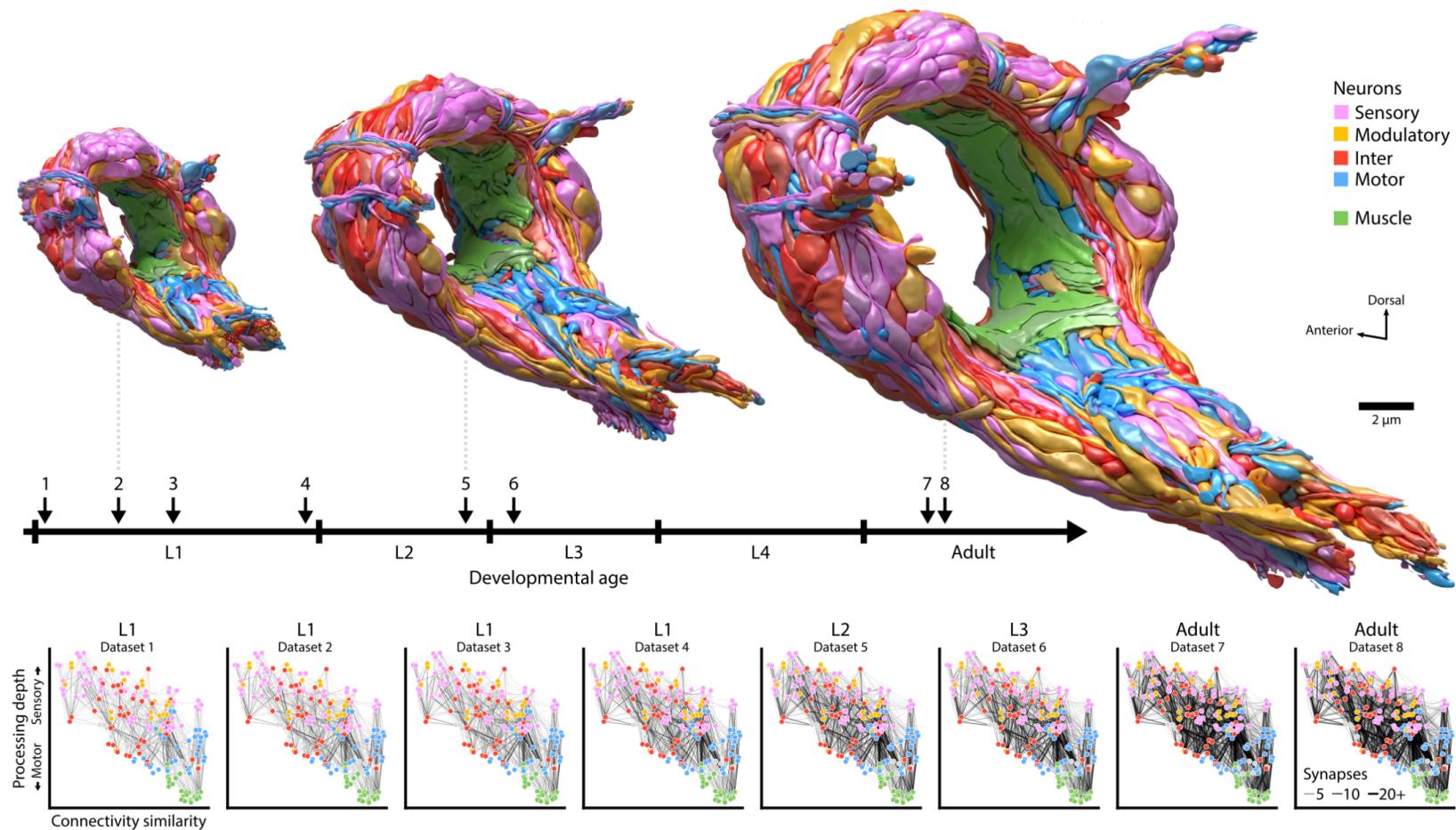
Emphasis added

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

Connectome ↔ development



Why is comparative connectomics hard?

Collecting the data is still a large effort...

But how do we even compare connectomes?

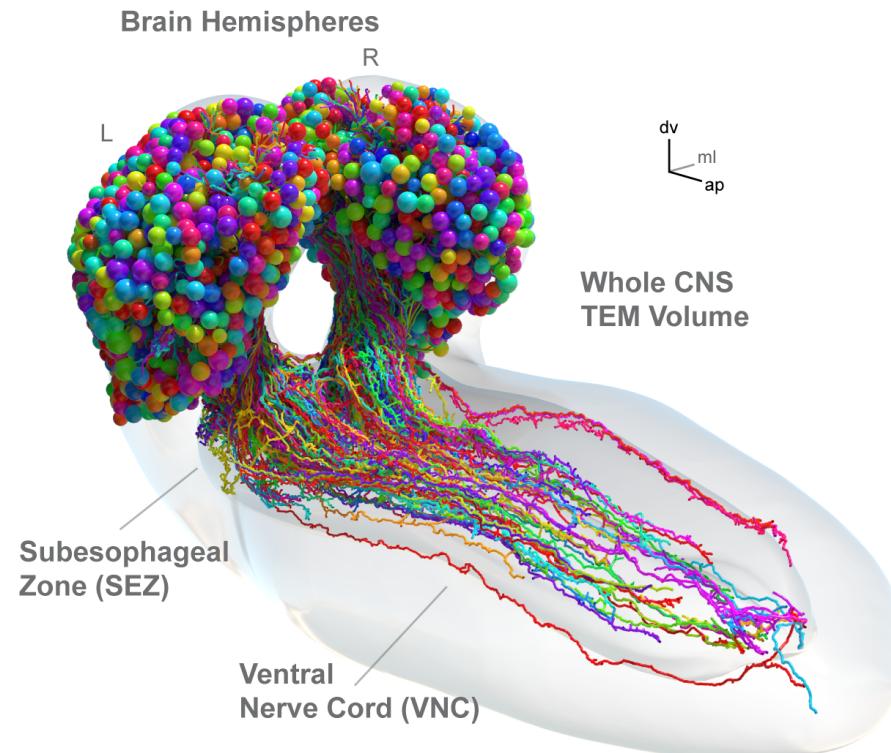
- Data are networks
 - Data are networks with rich attributes
- Data are noisy
 - "Experimental noise"
 - "Developmental noise"
- Data are big (and getting bigger)

Outline

- **Larval connectome dataset**
- **Connectome comparison via network hypothesis testing**
- **Pairing neurons across connectomes via graph matching**
- **Ongoing extensions/applications**

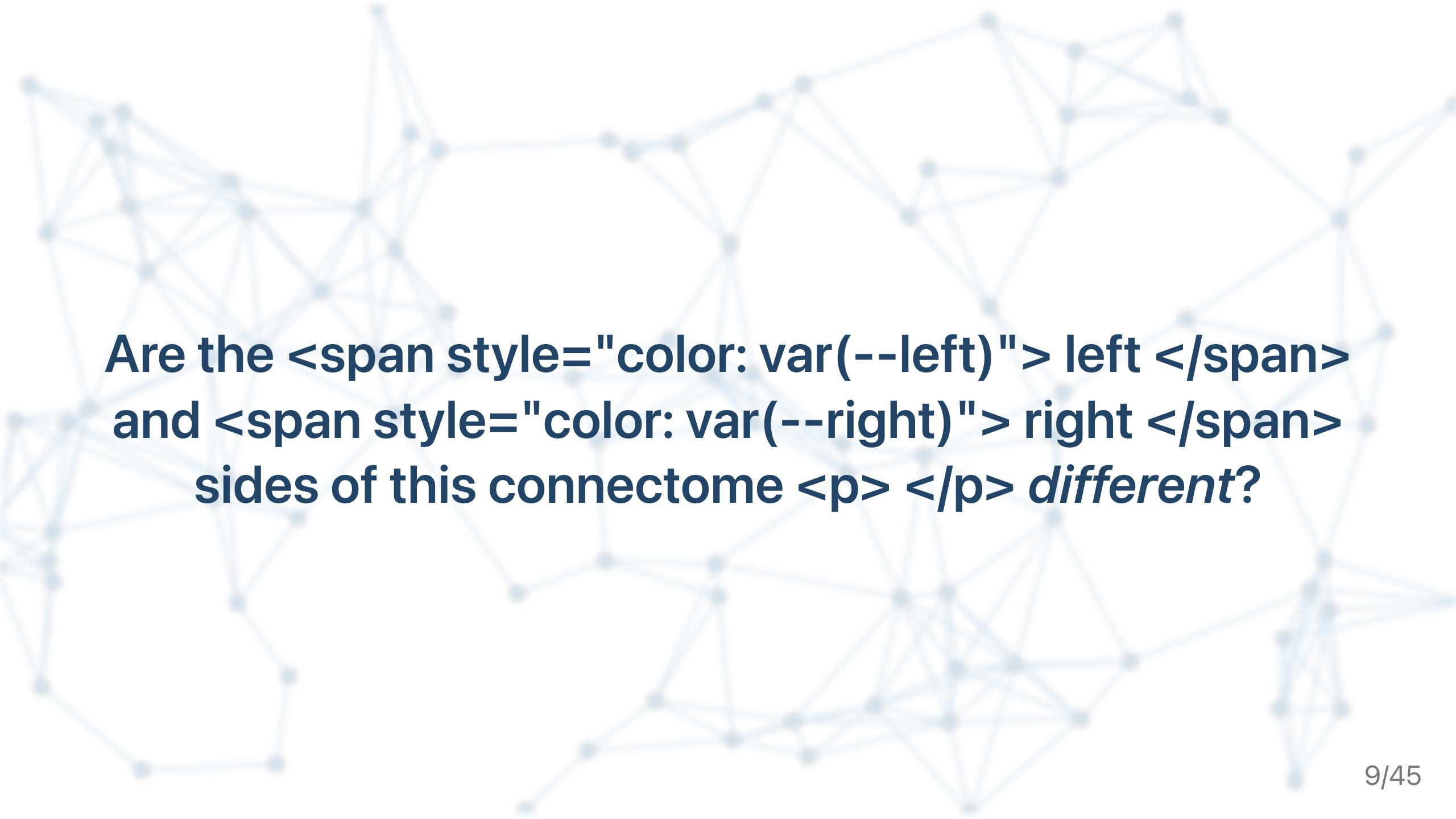
Larval *Drosophila* brain connectome

<div class="columns"> <div>



~3k neurons, ~550K synapses

Both hemispheres



**Are the left
and right
sides of this connectome

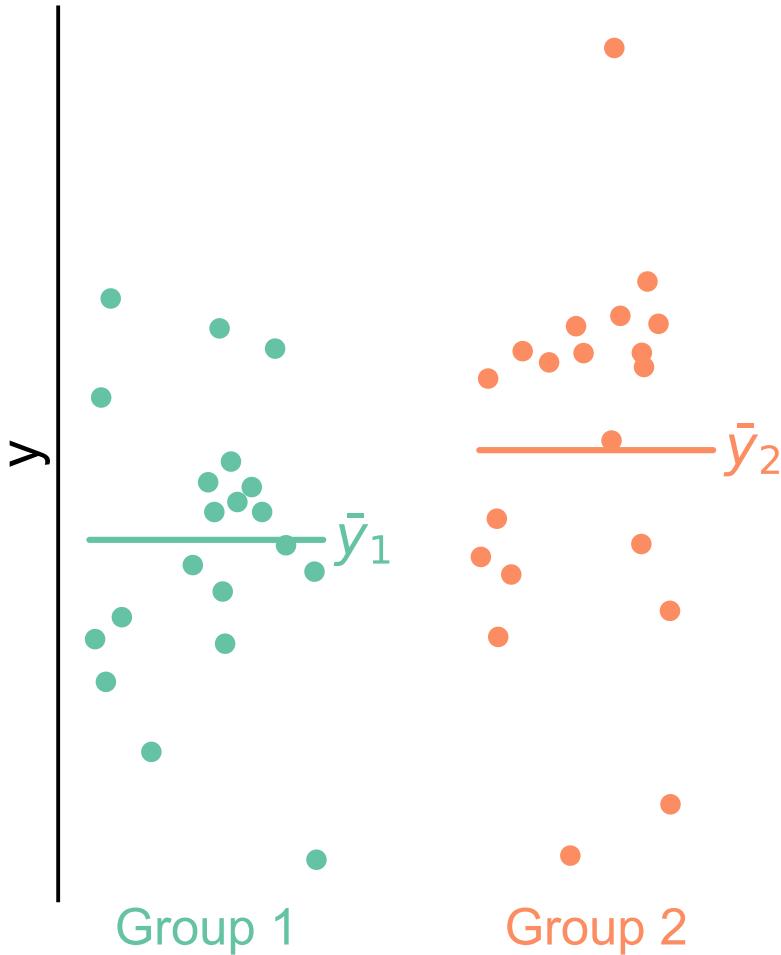
</p> different?**

Outline

- Larval connectome dataset
- Connectome comparison via network hypothesis testing
- Pairing neurons across connectomes via graph matching
- Ongoing extensions/applications

Are these populations different?

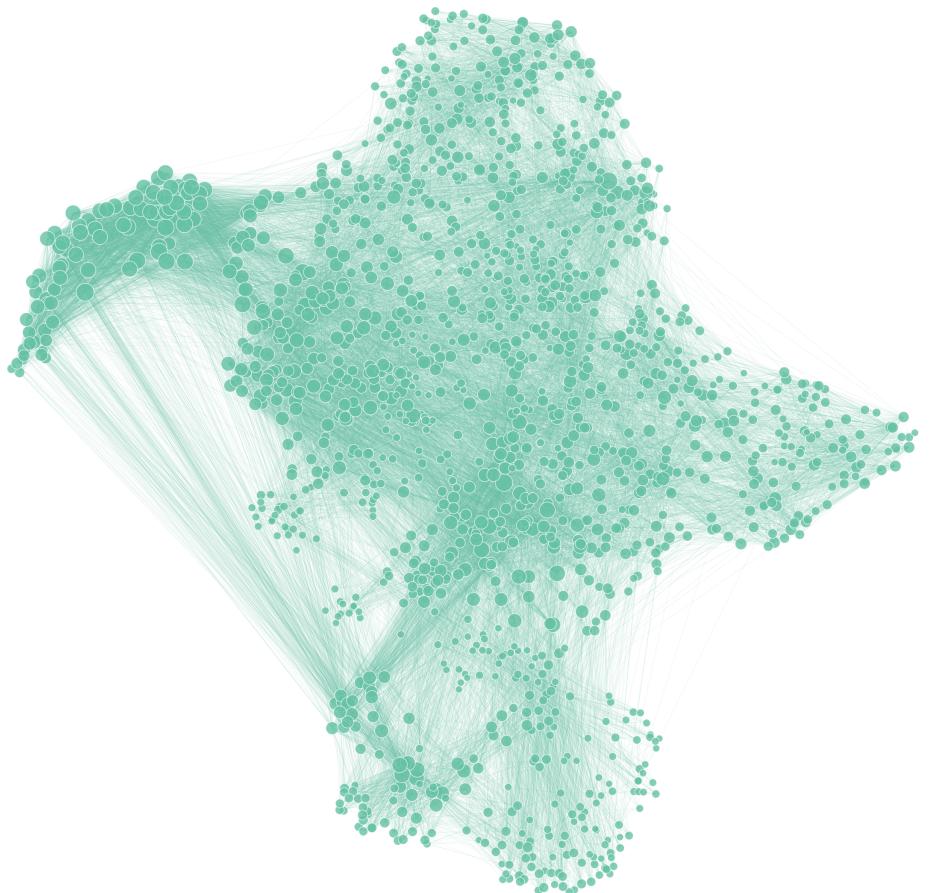
<div class="columns"> <div>



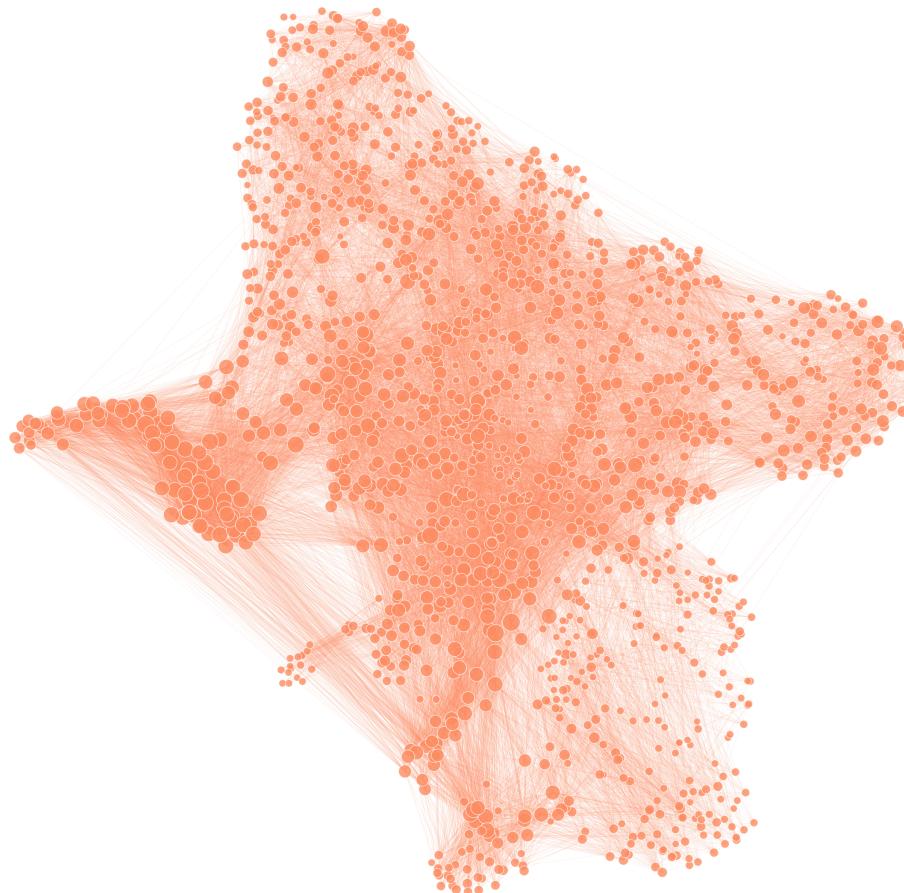
</div> <div>

Are these *networks* different?

<div class="columns"> <div>



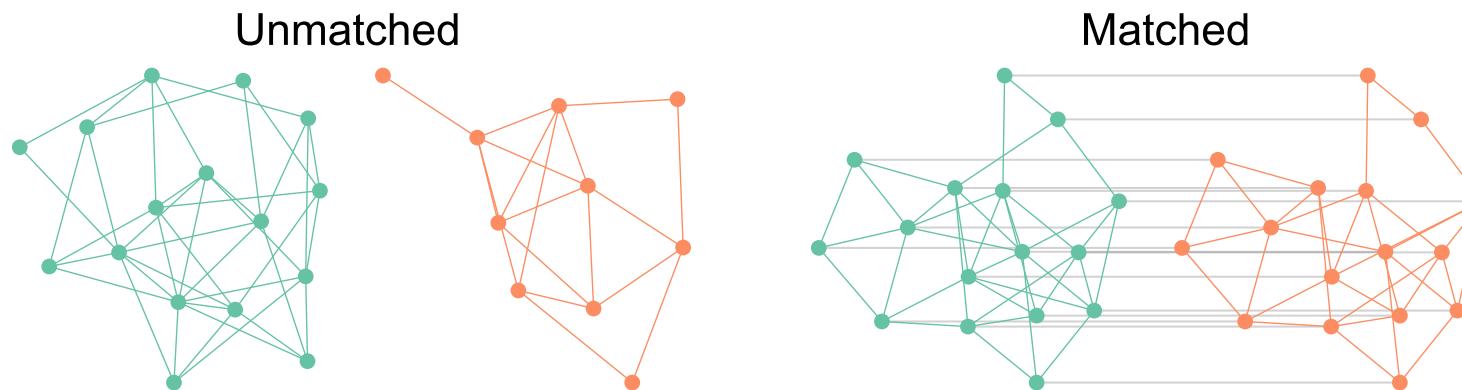
Left



Right

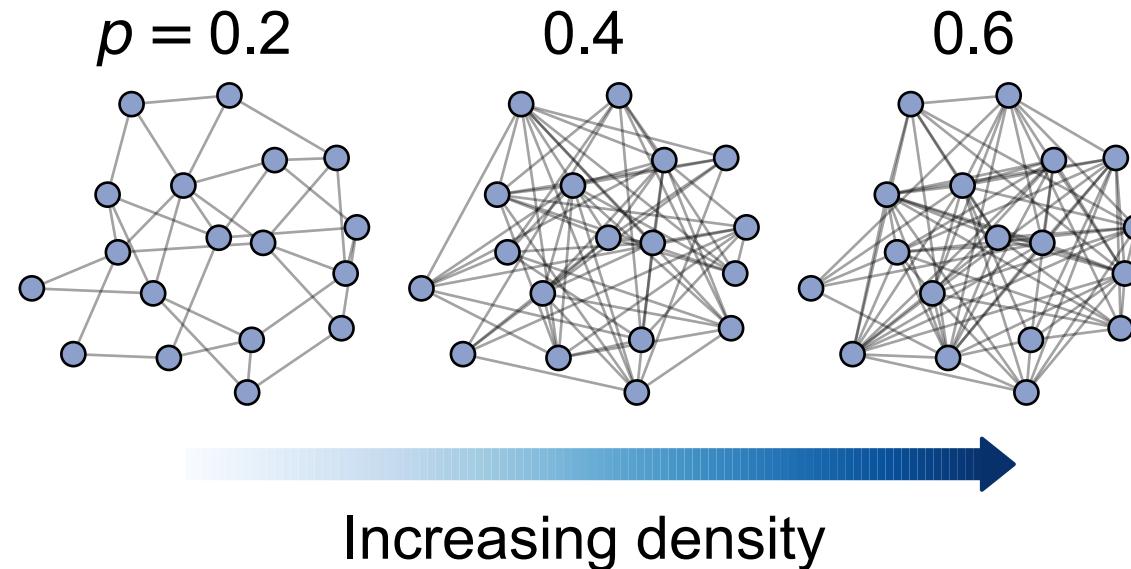
Assumptions

- 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



Erdos-Renyi model

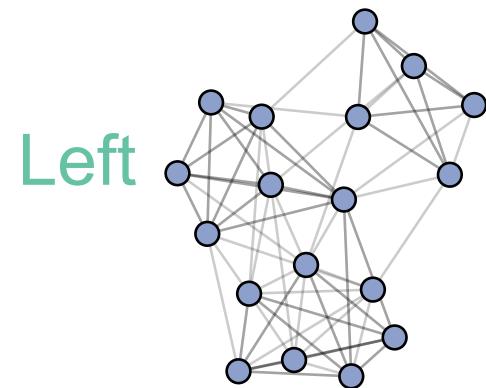
- All edges are independent
- All edges generated with the same probability, p



We detect a difference in density

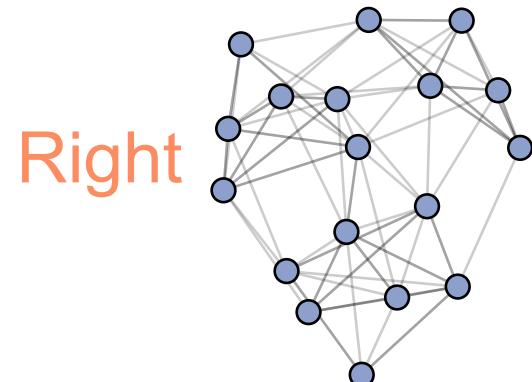
<div class="columns"> <div>

Compute global
connection density



Compare ER
models

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

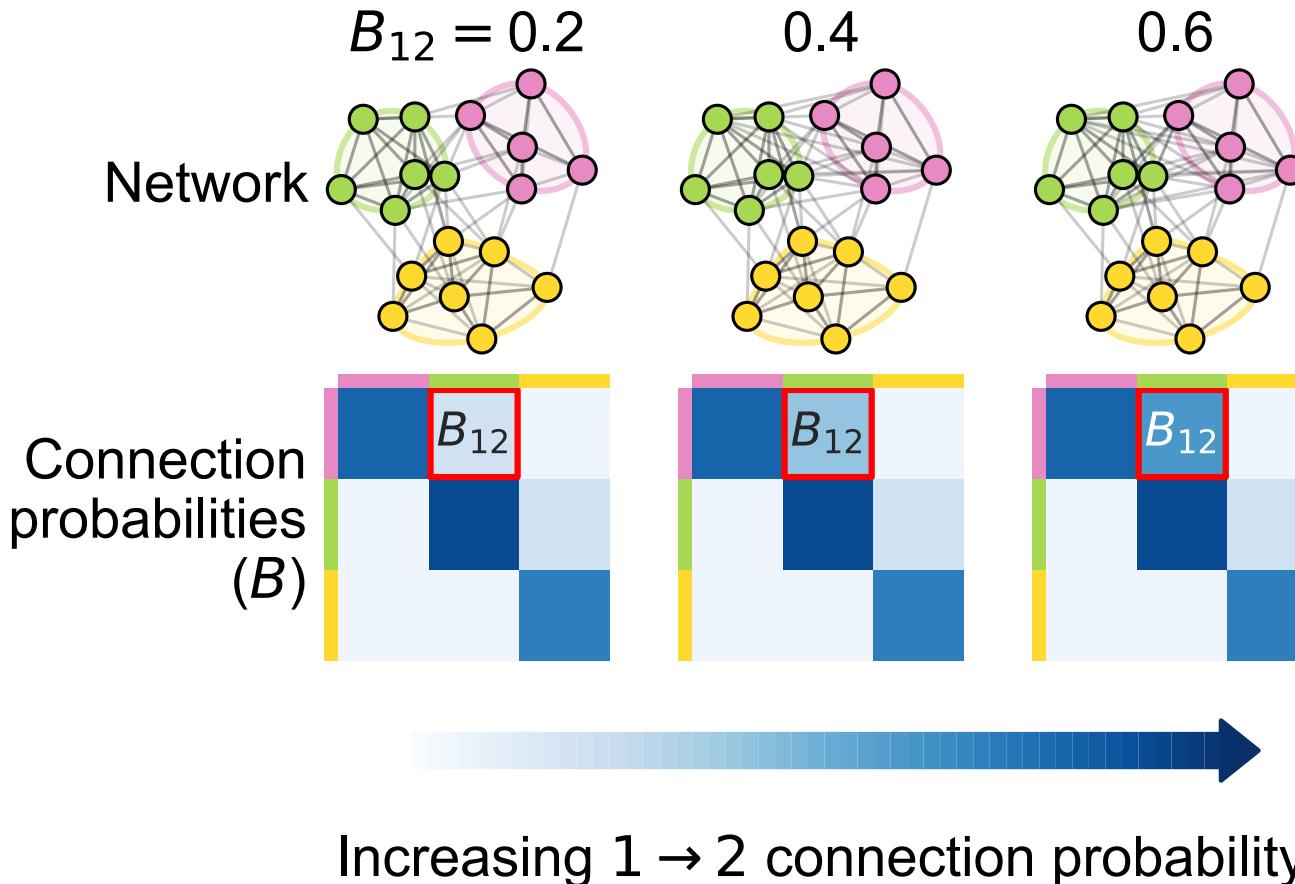


$$\begin{aligned} H_0: p^{(L)} &= p^{(R)} \\ H_A: p^{(L)} &\neq p^{(R)} \end{aligned}$$

</div> <div>

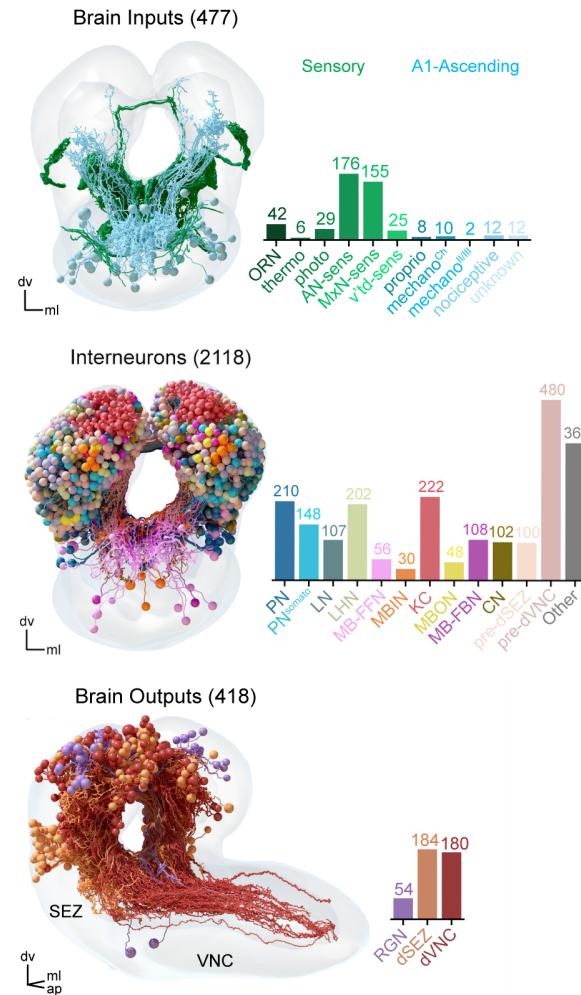
Stochastic block model

Edge probabilities are a function of a neuron's group



Connection probabilities between groups

<div class="columns"> <div>

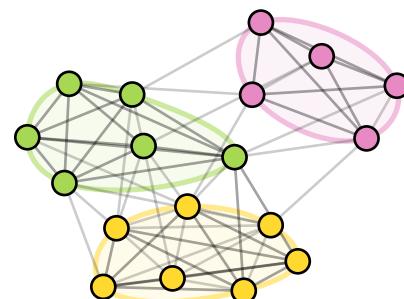


</div> <div>

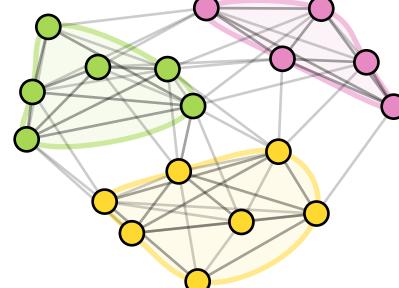
Group-based testing

Group neurons

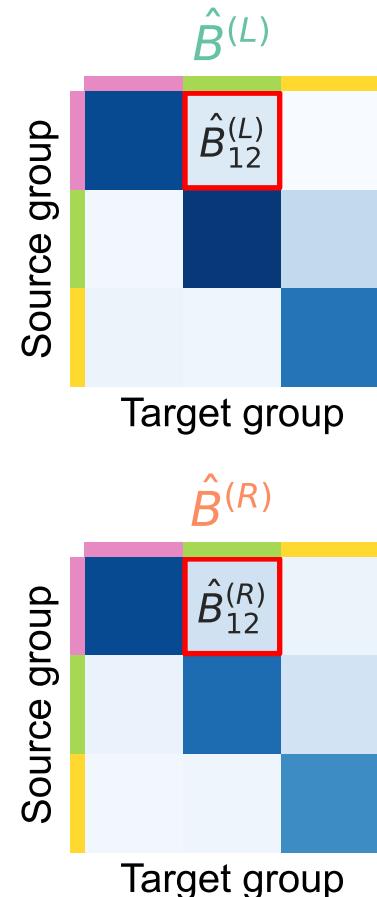
Left



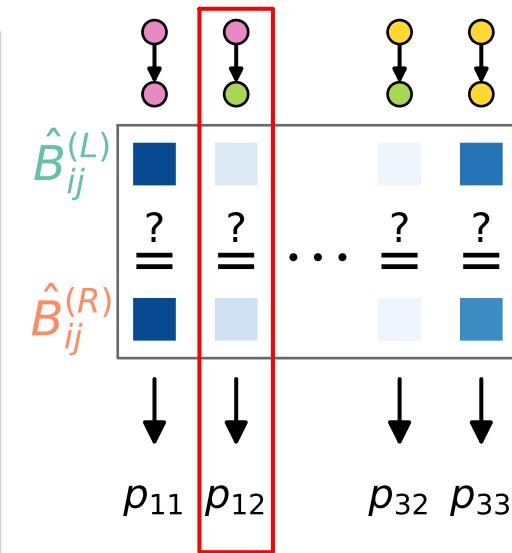
Right



Estimate group connection probabilities

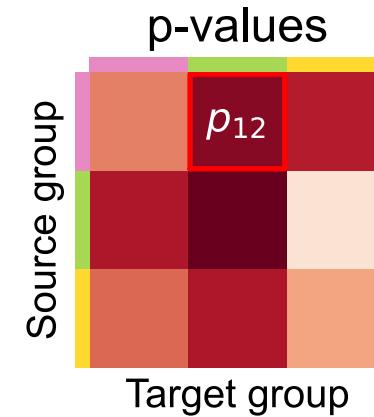


Compare probabilities, compute p-values



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

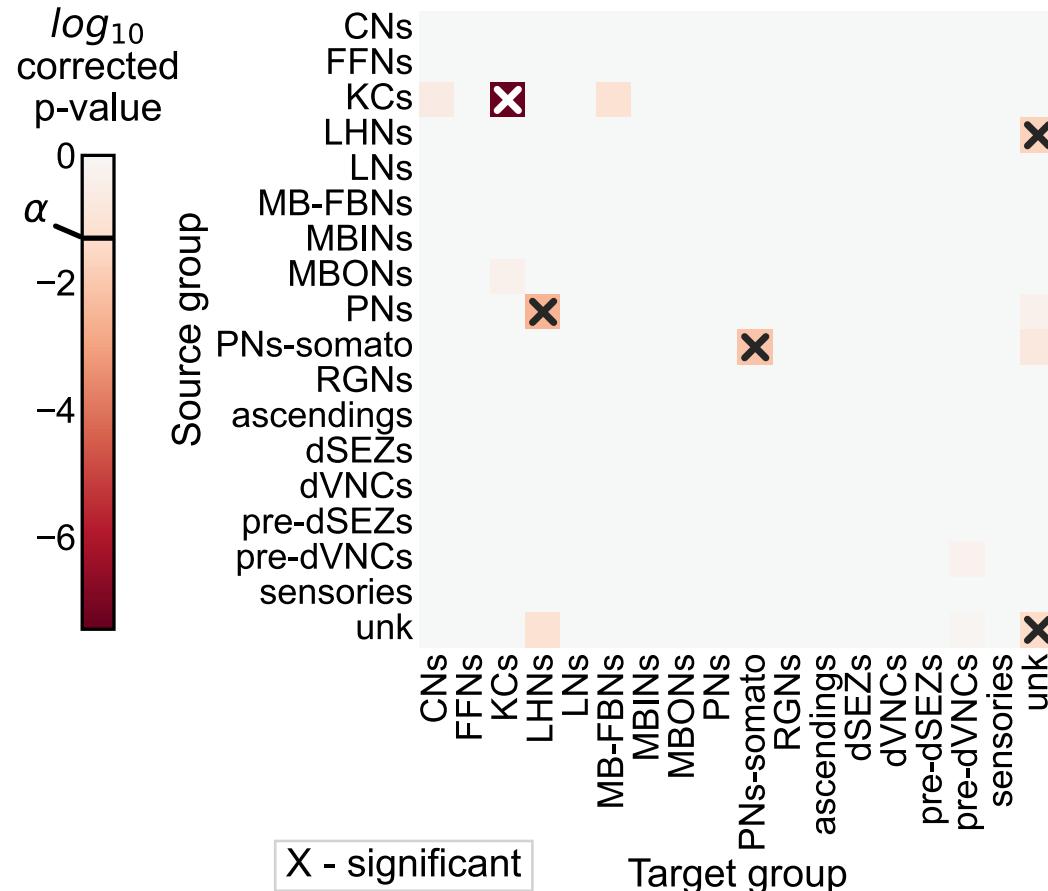
Combine p-values for overall test



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

Detect a difference in group connection probabilities

<div class="columns"> <div>



</div> <div>

- After multiple comparison, find 5 group-to-group connections which are significantly

Should we be surprised?

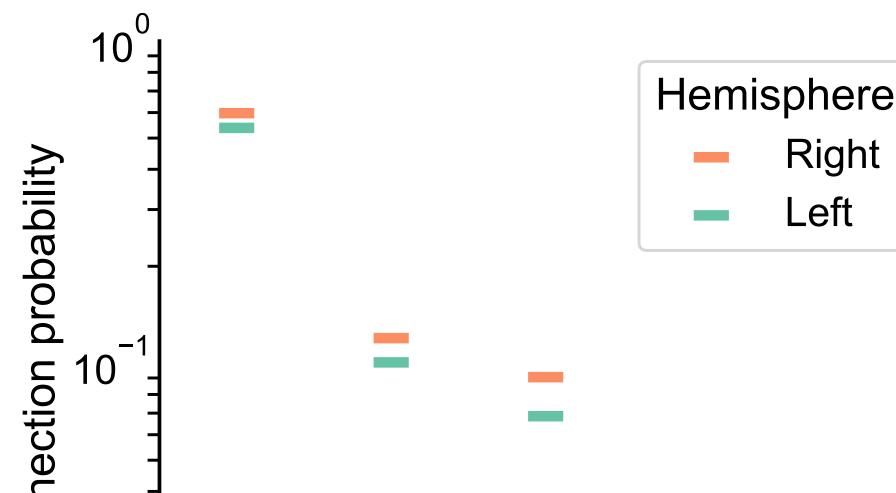
<div class="columns"> <div>

- 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, $\frac{p^{(L)}}{p^{(R)}}$

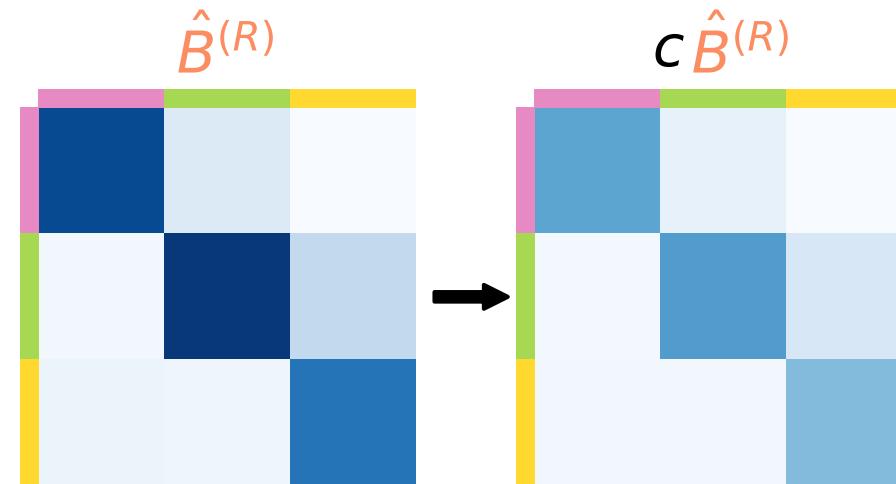
</div> <div>



After adjusting for density, differences are in KCs

<div class="columns"> <div>

Scale connection probabilities
to match densities



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

</div> <div>

\log_{10}
corrected
p-value

CNs

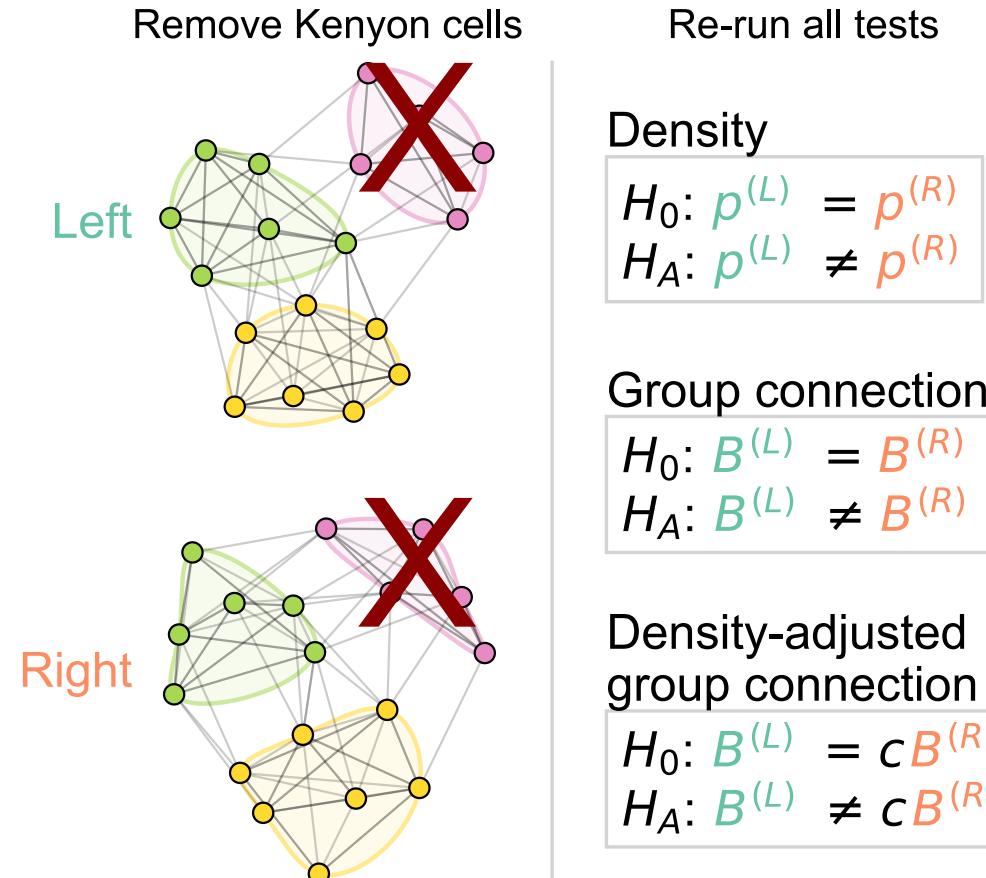
FFNs

KCs



When we remove KCs...

<div class="columns"> <div>



</div> <div>

- Density test:

To sum up...

"The brain is bilaterally symmetric"
people

Depends on what you mean...

<div class="columns"> <div>

With Kenyon cells

Model	H_0 (vs. $H_A \neq$)	p-value

</div> <div>

Without Kenyon cells

Model	H_0 (vs. $H_A \neq$)	p-value

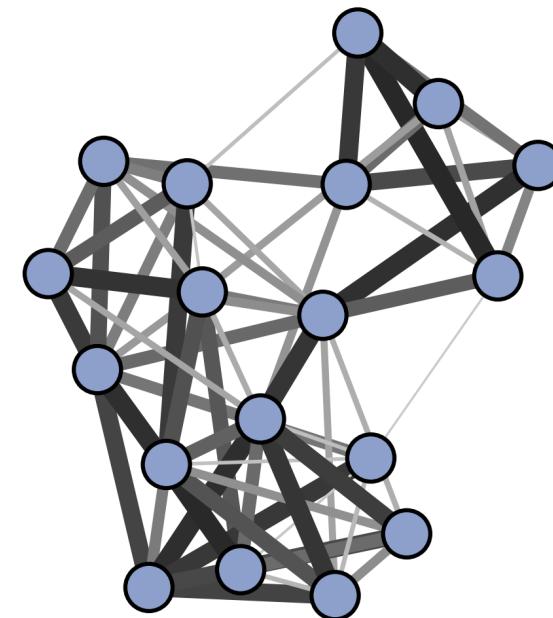
</div> </div>

Examining the effect of edge weights

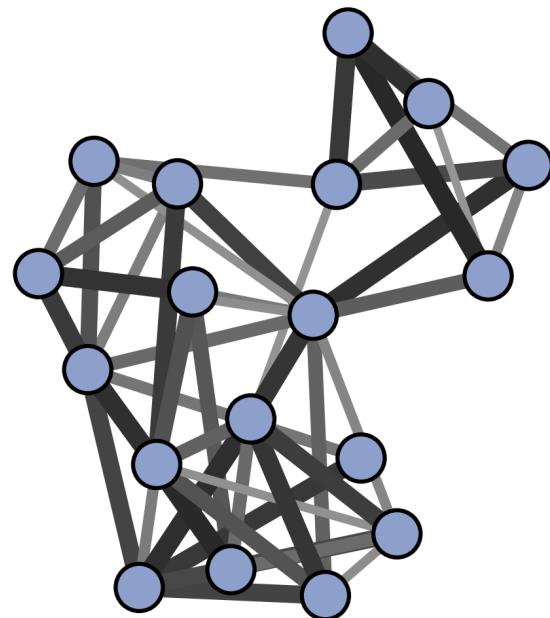
<div class='columns'> <div>

Increasing edge weight threshold

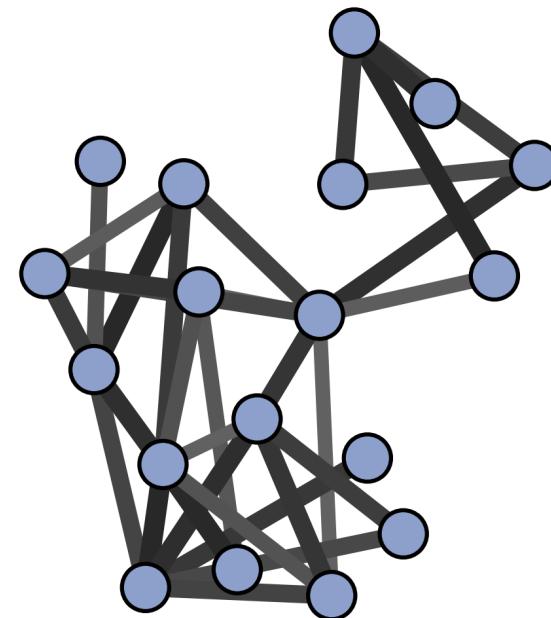
Left



3



3



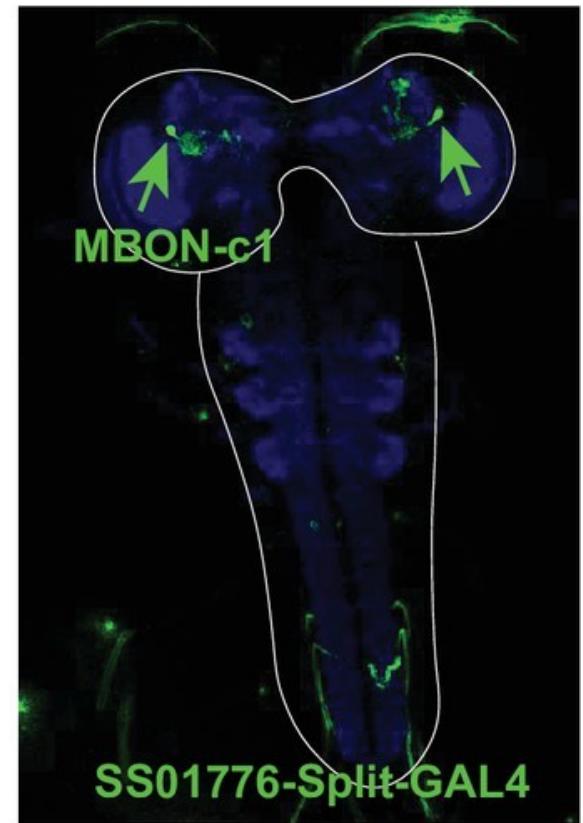
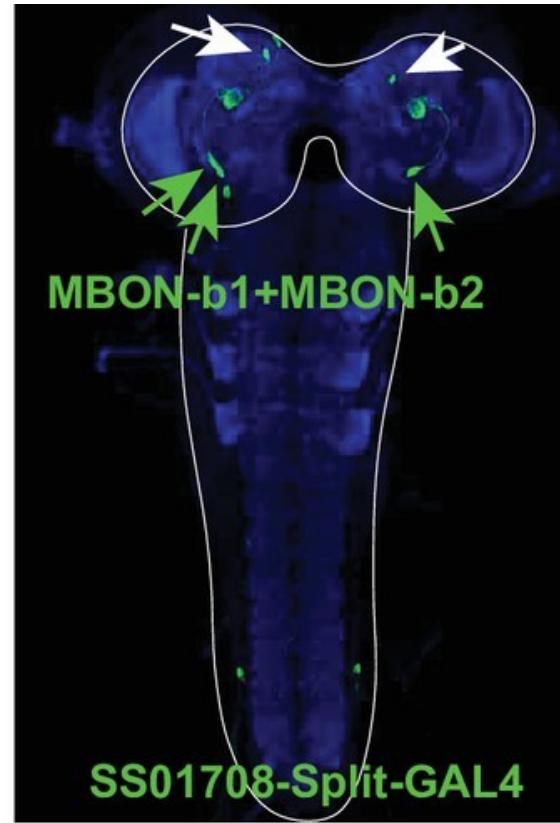
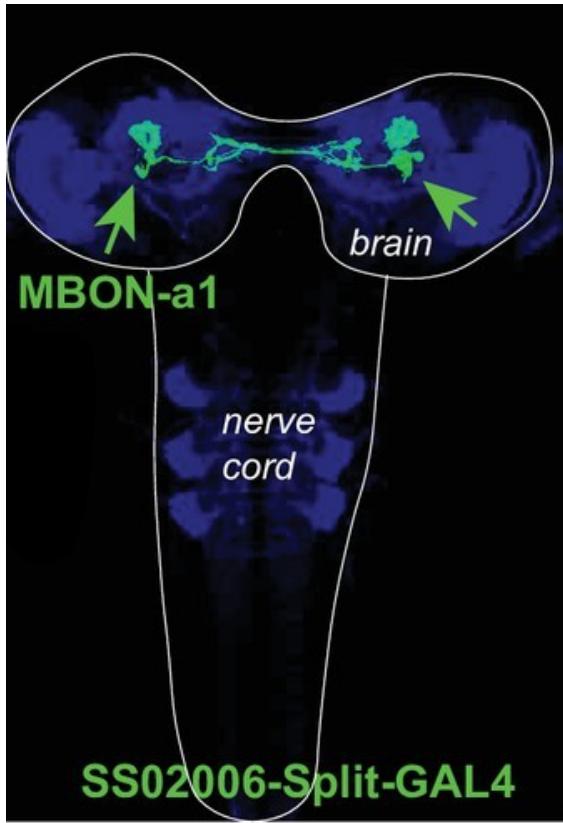
3

Borun all

Outline

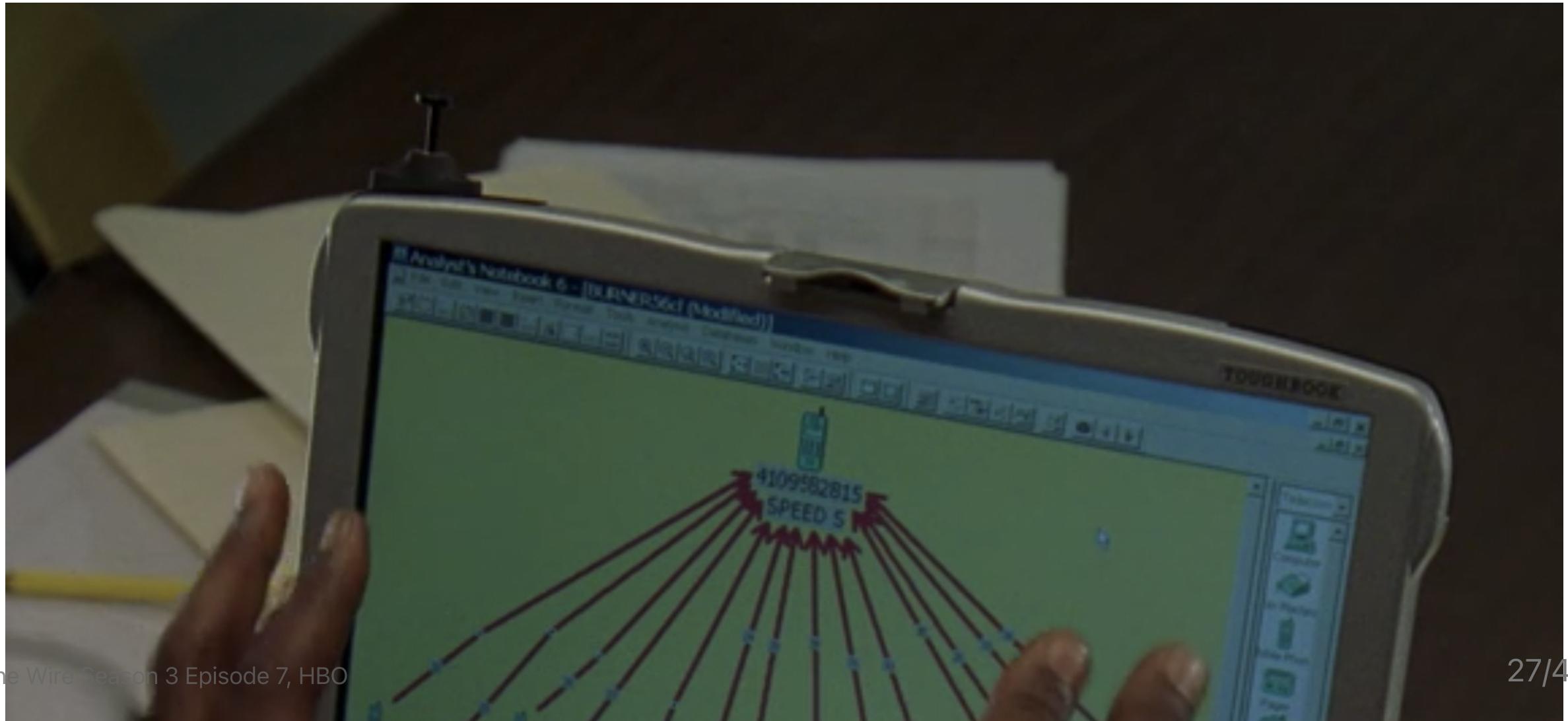
- Larval connectome dataset
- Connectome comparison via network hypothesis testing
- Pairing neurons across connectomes via graph matching
- Ongoing extensions/applications

Bilaterally homologous neuron pairs

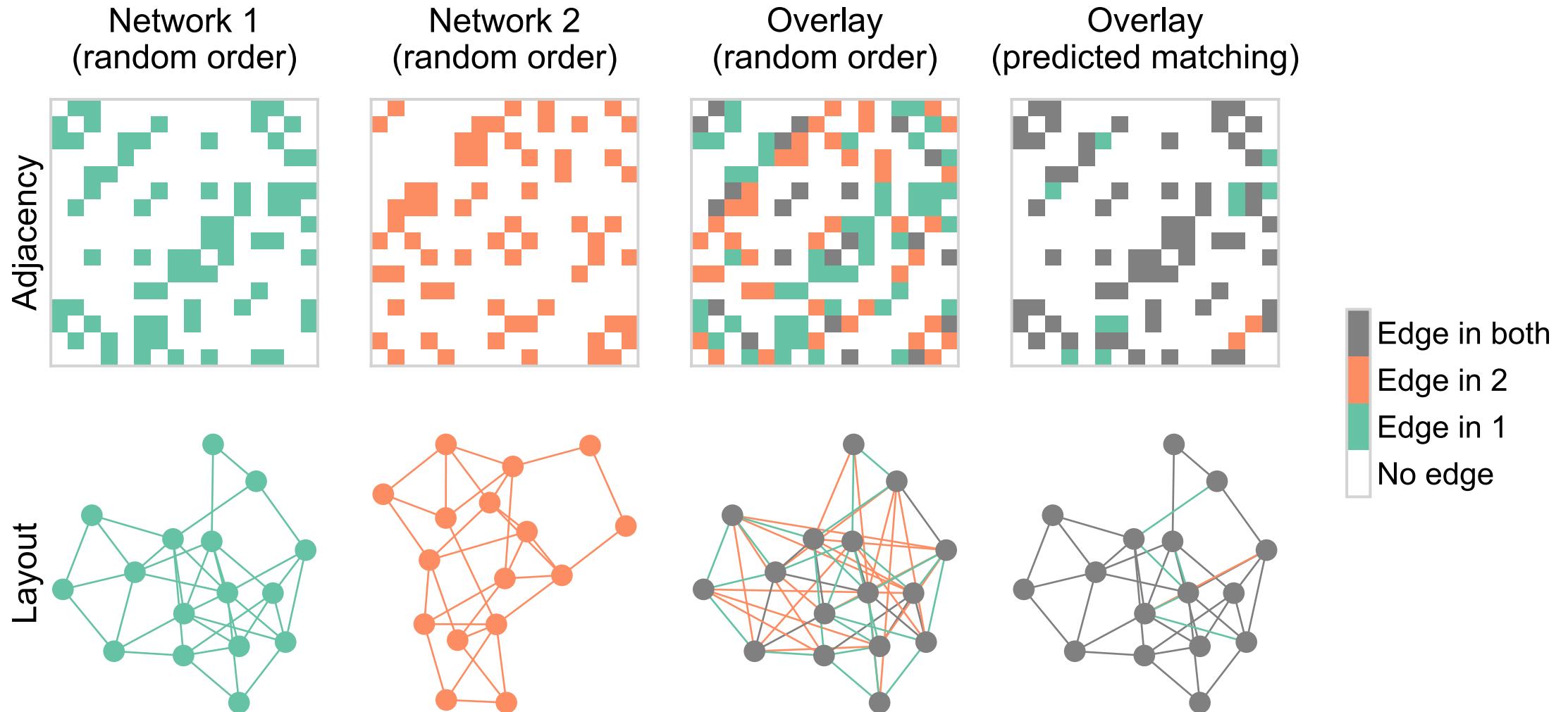


Can we use networks structure to predict this pairing?

<div class="columns"> <div>



What is graph matching?



How do we measure network overlap?

<div class="columns"> <div>

$$\min_{P \in \mathcal{P}} \|A - \underbrace{PBP^T}_{\text{distance between adj. mats.}}\|_F^2$$

reordered B

where \mathcal{P} is the set of permutation matrices

</div> <div>

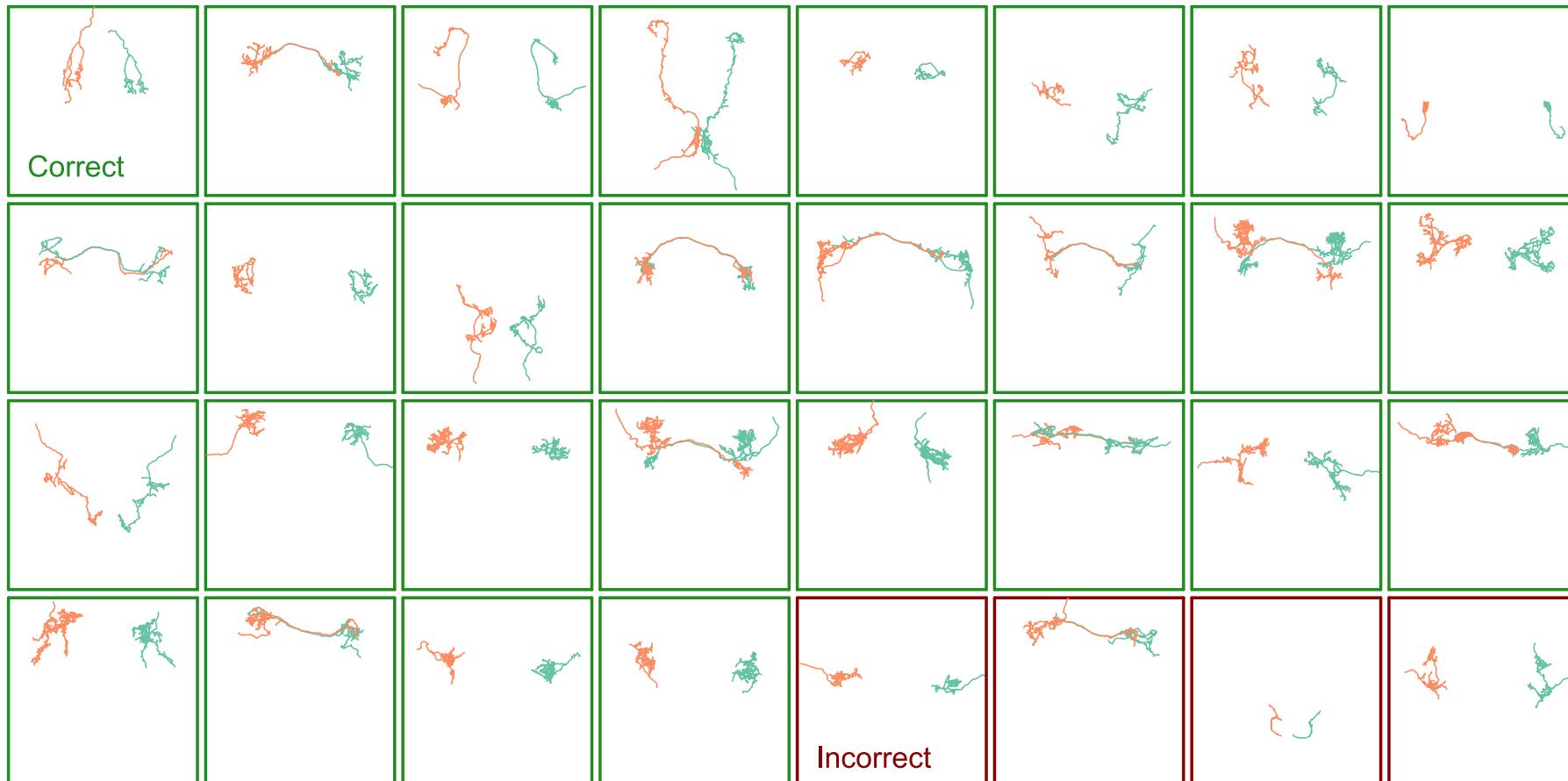
- Measures the number of edge disagreements for unweighted networks,
- Norm of edge disagreements for weighted networks

</div> </div>

How do we do graph matching?

TODO: (3) decide what to say or show here?

Matching (by connectivity only) performs fairly well



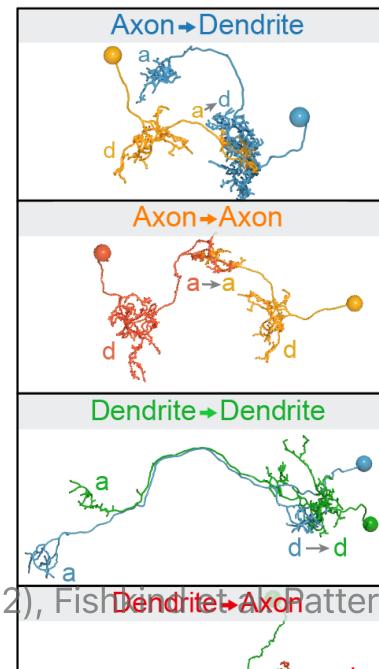
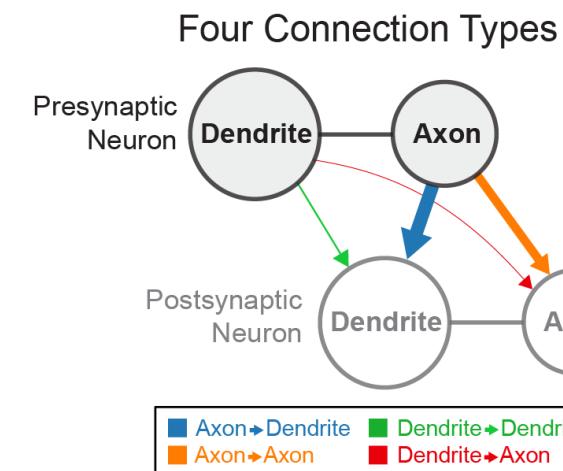
With "vanilla" graph matching: ~80% correct (according to expert annotator)

Many ways to try to improve on this...

<div class="columns"> <div>

- Edge types allow for "multilayer" graph matching
- Partial knowledge of the matching (seeds)
- Morphology (e.g. NBLAST)

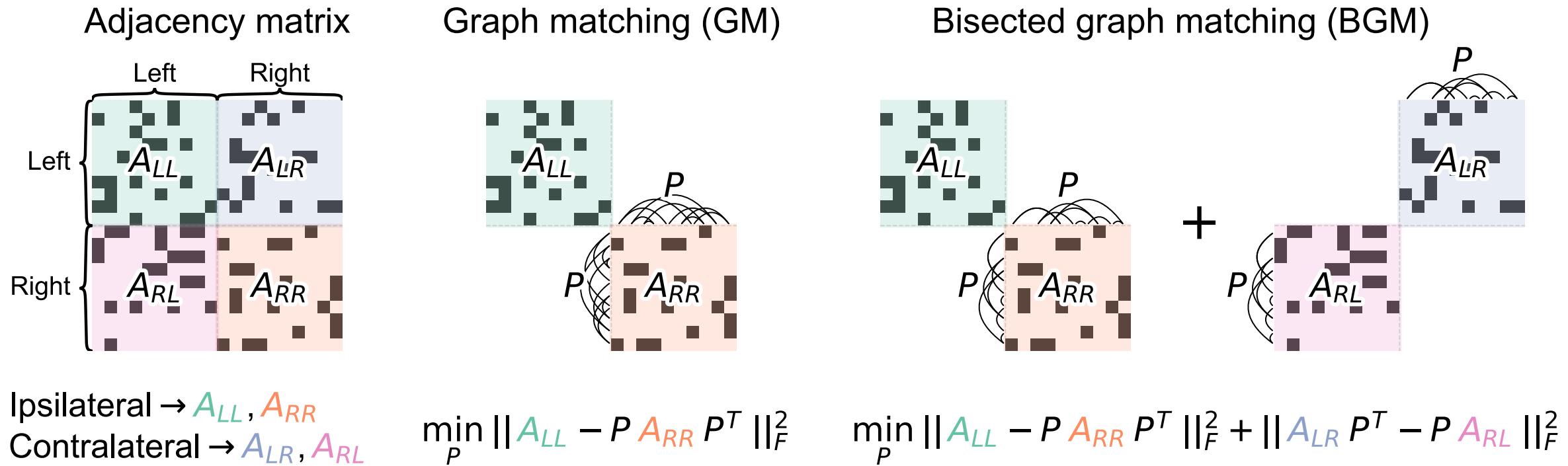
</div> <div>



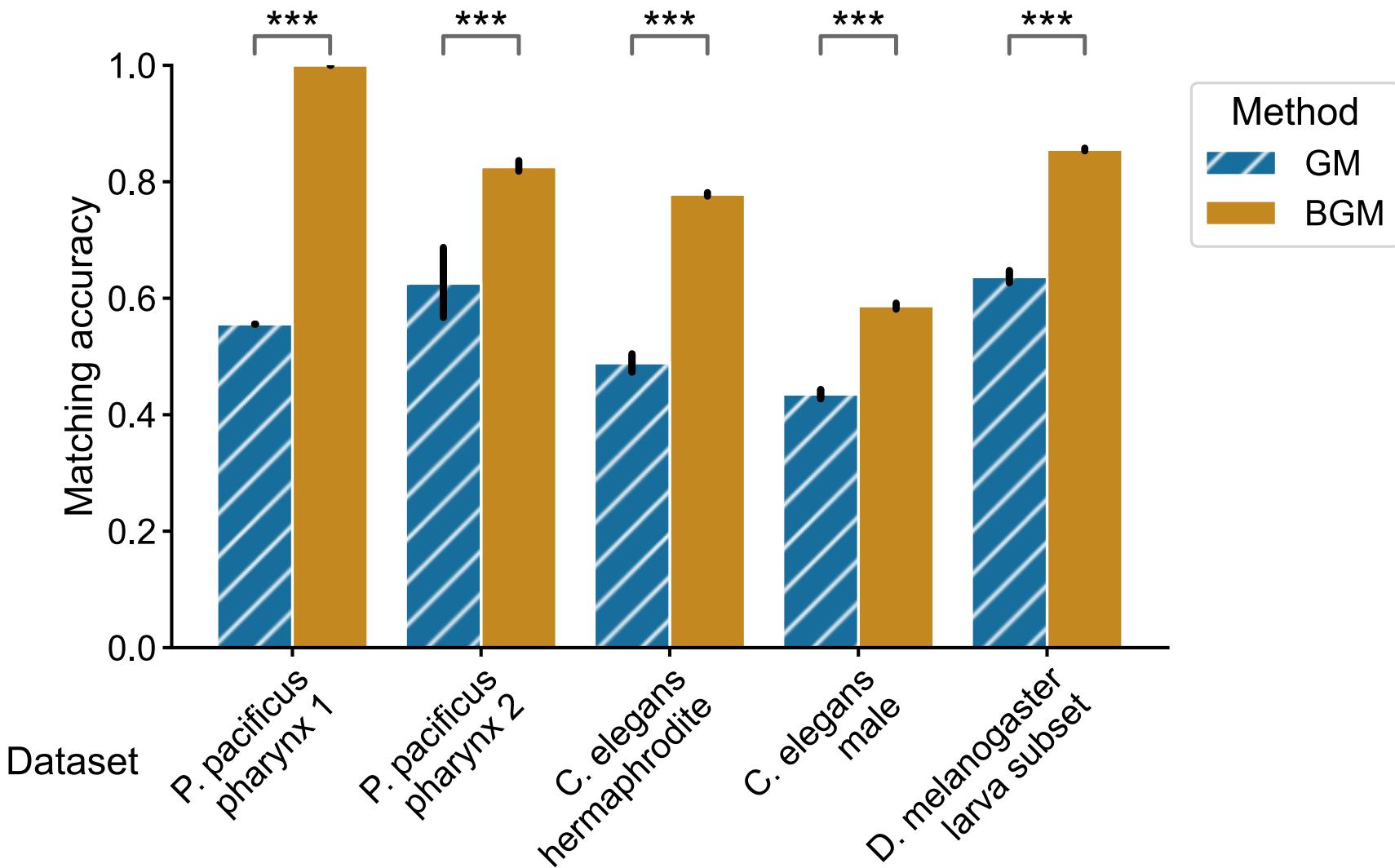
Thus far, we've not used the contralateral connections

These are about 1/3 of the edges in the brain!

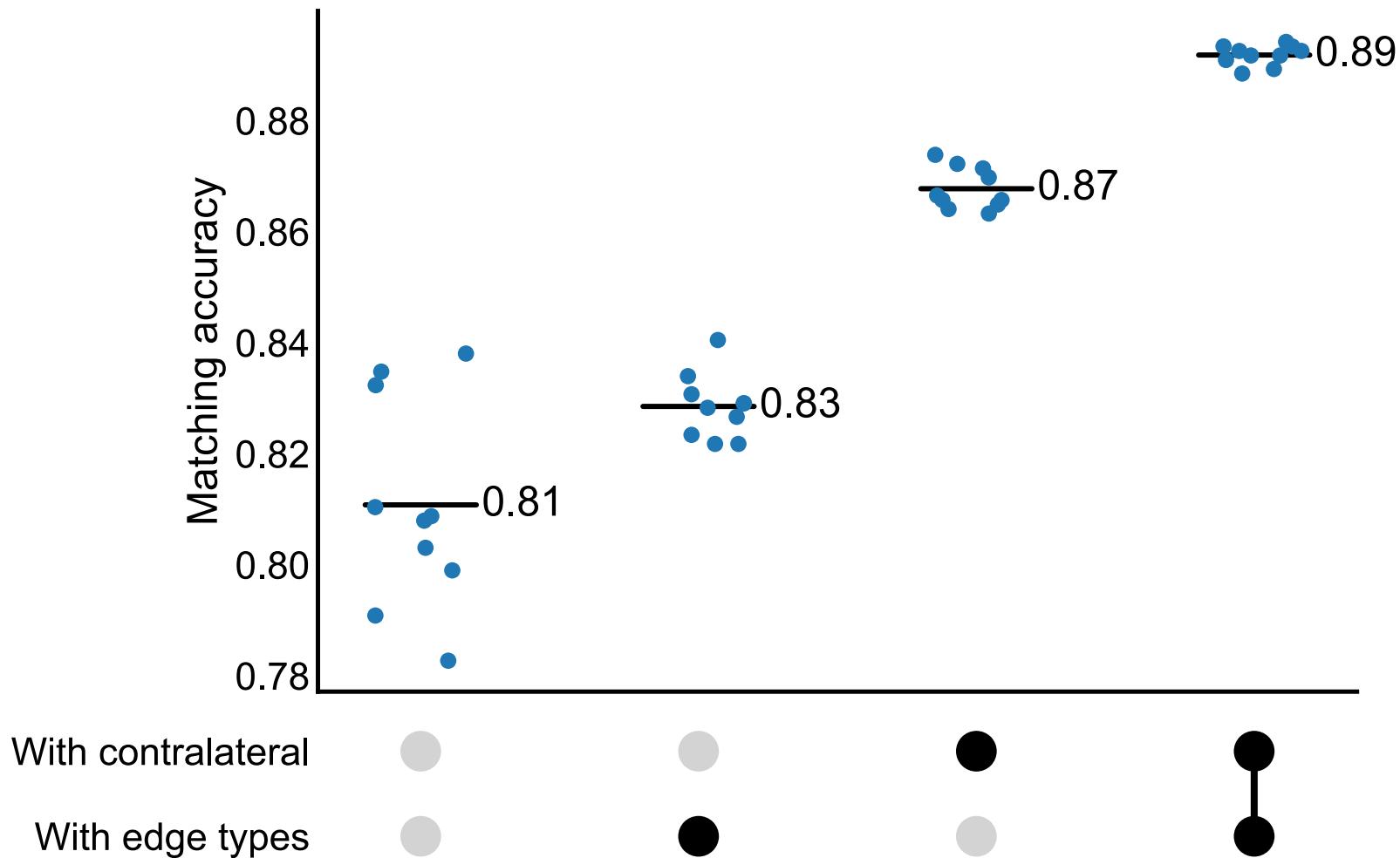
From graph matching to bisected graph matching



Contralateral connections are helpful!



Performance improvement on the full brain



Outline

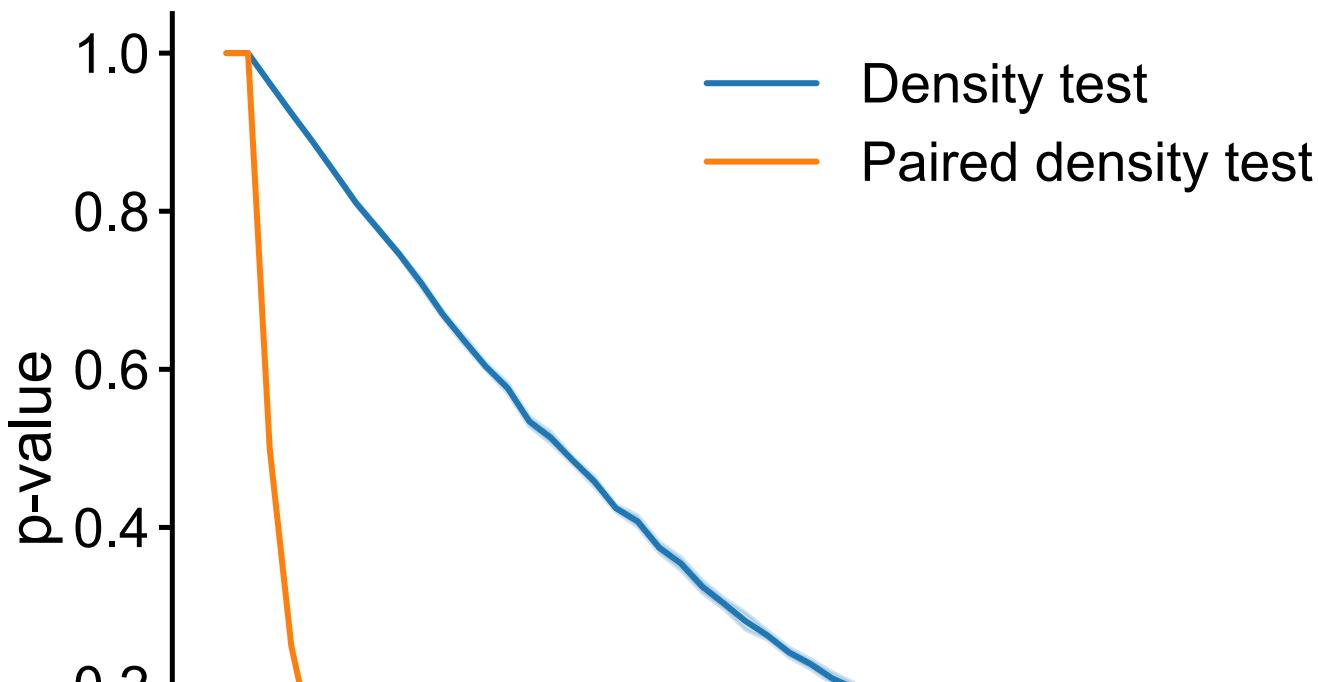
- Larval connectome dataset
- Connectome comparison via network hypothesis testing
- Pairing neurons across connectomes via graph matching
- Ongoing extensions/applications

Pairs facilitate more powerful tests

```
<div class="columns-br"> <div>
```

- Generate an Erdos-Renyi network (A)
- Perturb a copy of it (B)
- Test for differences between A and B

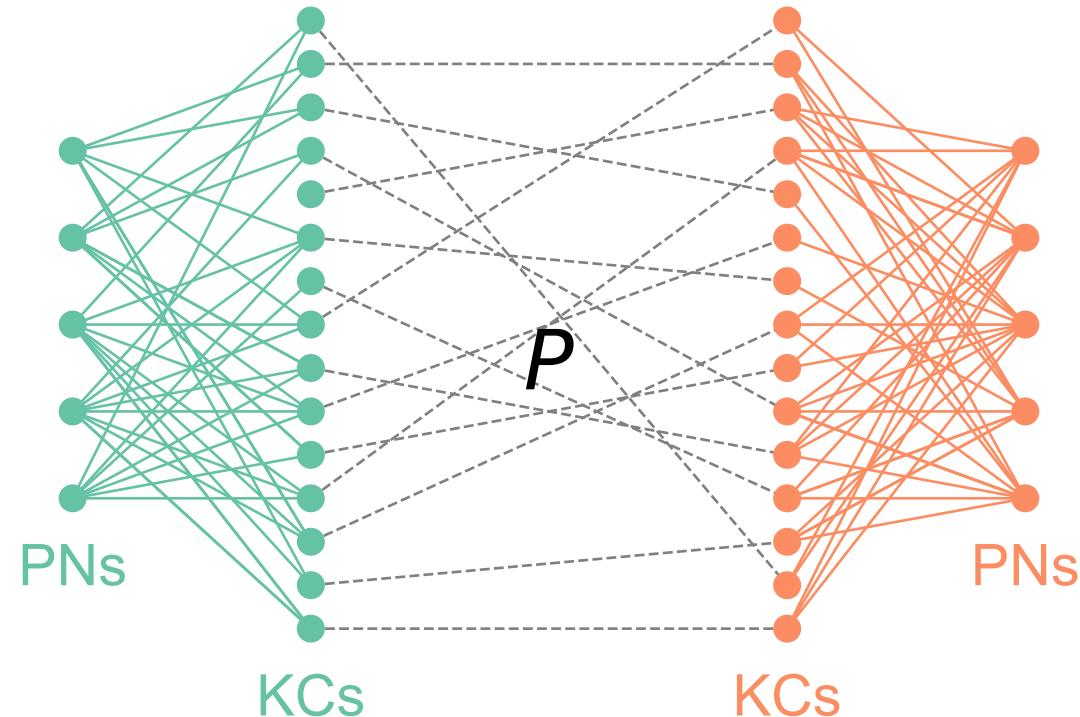
```
</div> <div>
```



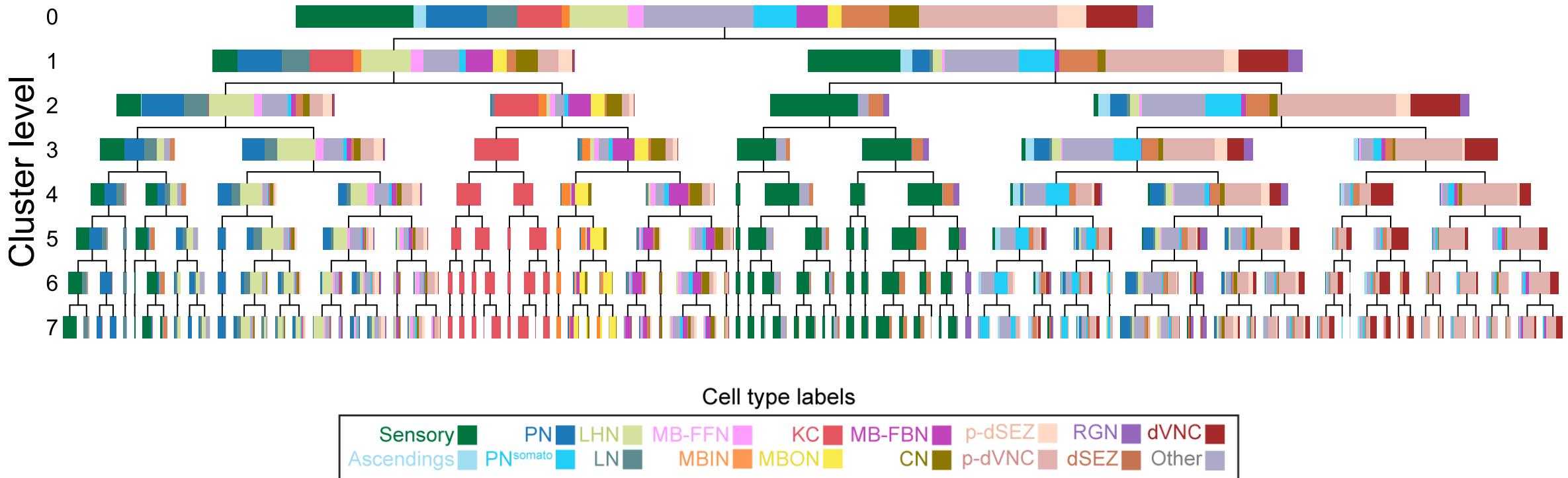
Testing for "stereotypy" at the edge level

Is matching stronger than expected under some model of independent networks?

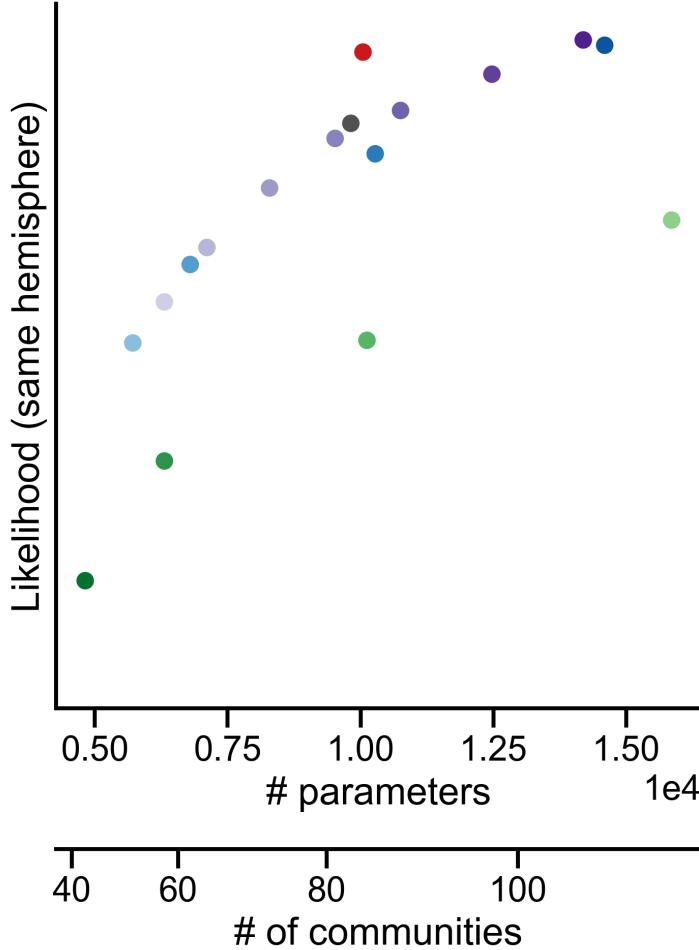
<div class="columns"> <div>



Hierarchical clustering of neurons by connectivity

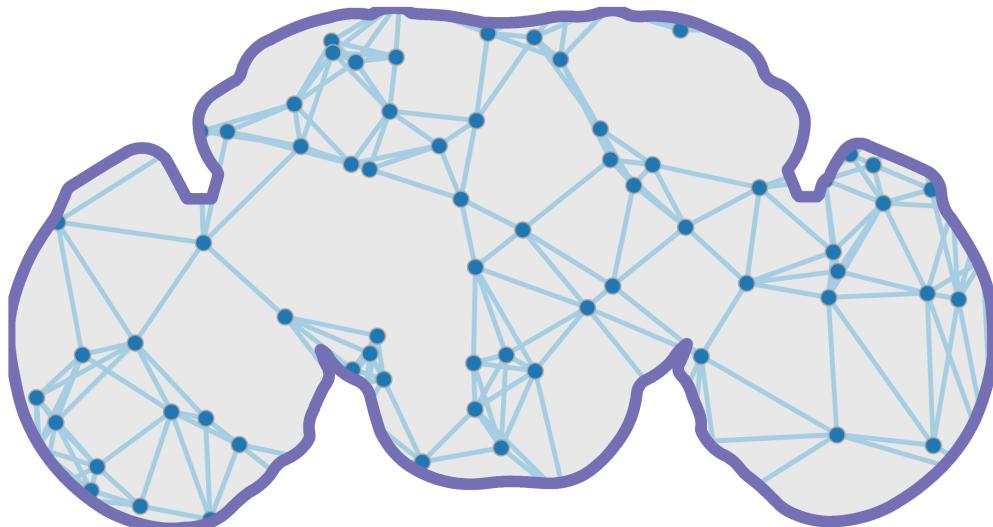
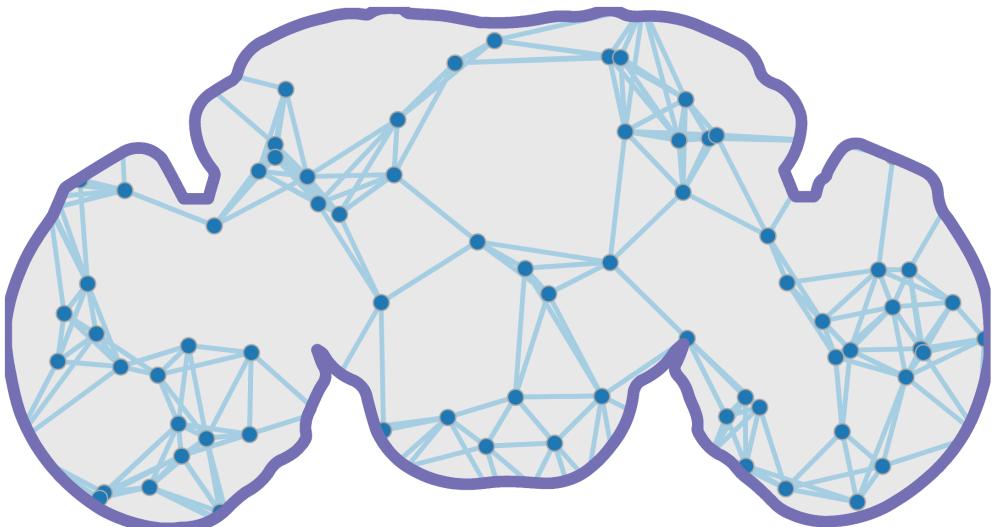


Using pairs and models to evaluate cell type groupings



Summary

<div class="columns-br"> <div>



</div> <div>

- Model-based network comparison enables testing (and refining) hypotheses about connectomes
 - We proposed a few tests, but just the beginning!

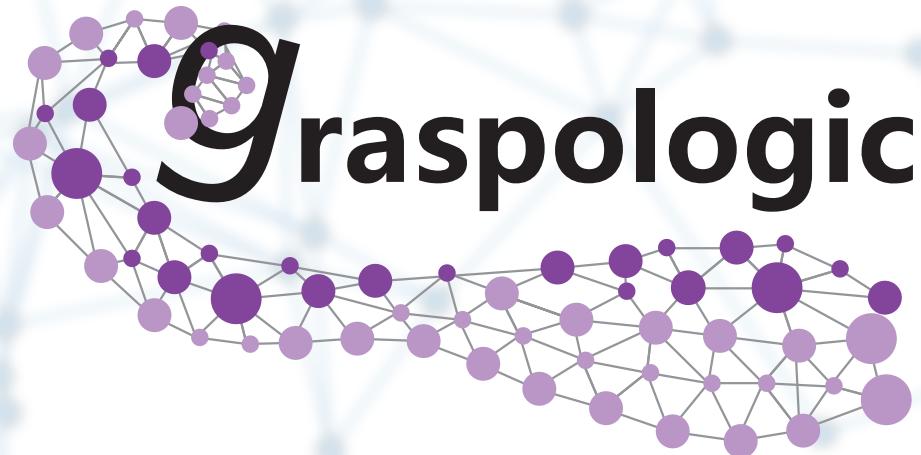
</div> </div> <div class="columns-br"> <div>

How to use these (and other) tools?

<div class="columns"> <div>

graspologic

github.com/microsoft/graspologic



downloads 139k

Stars 260

contributors 49

</div> <div>

Model-based testing

Acknowledgements

Team

```
<div class='minipanels'> <div>
```



Michael Winding

```
</div> <div>
```



Mike Powell

```
</div> <div>
```



Questions?

Slides:

tinyurl.com/princeton-bilarva

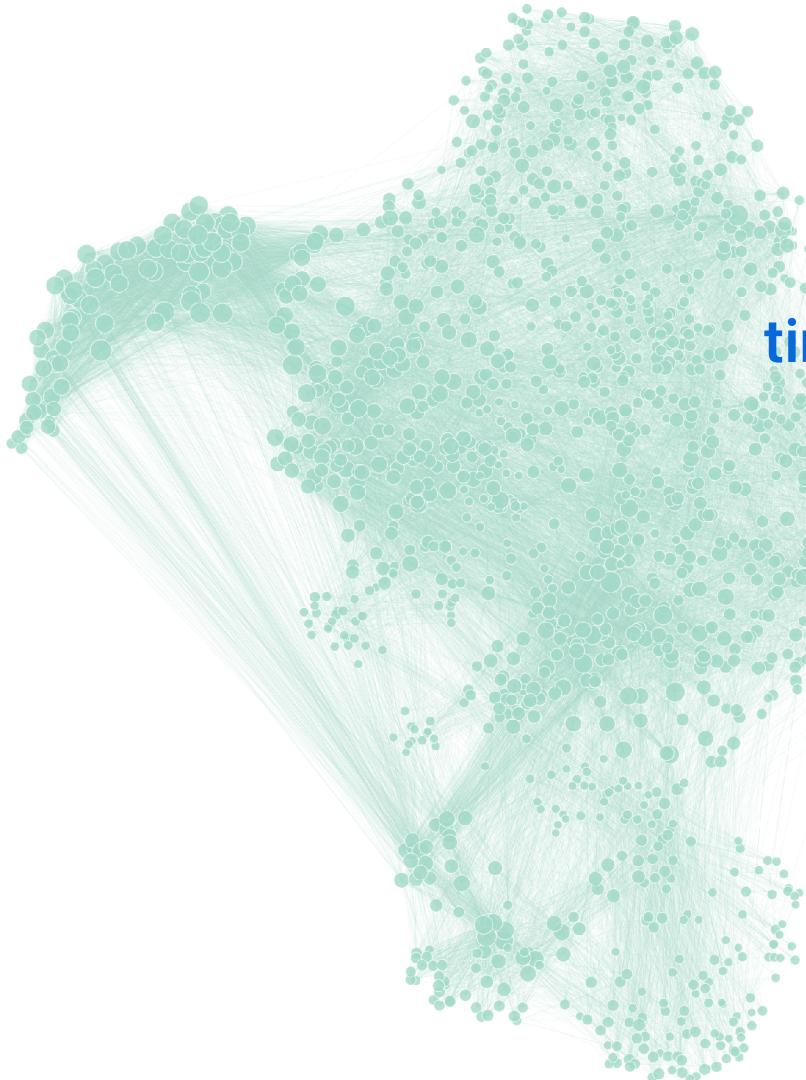
Benjamin D. Pedigo

✉ bpedigo@jhu.edu

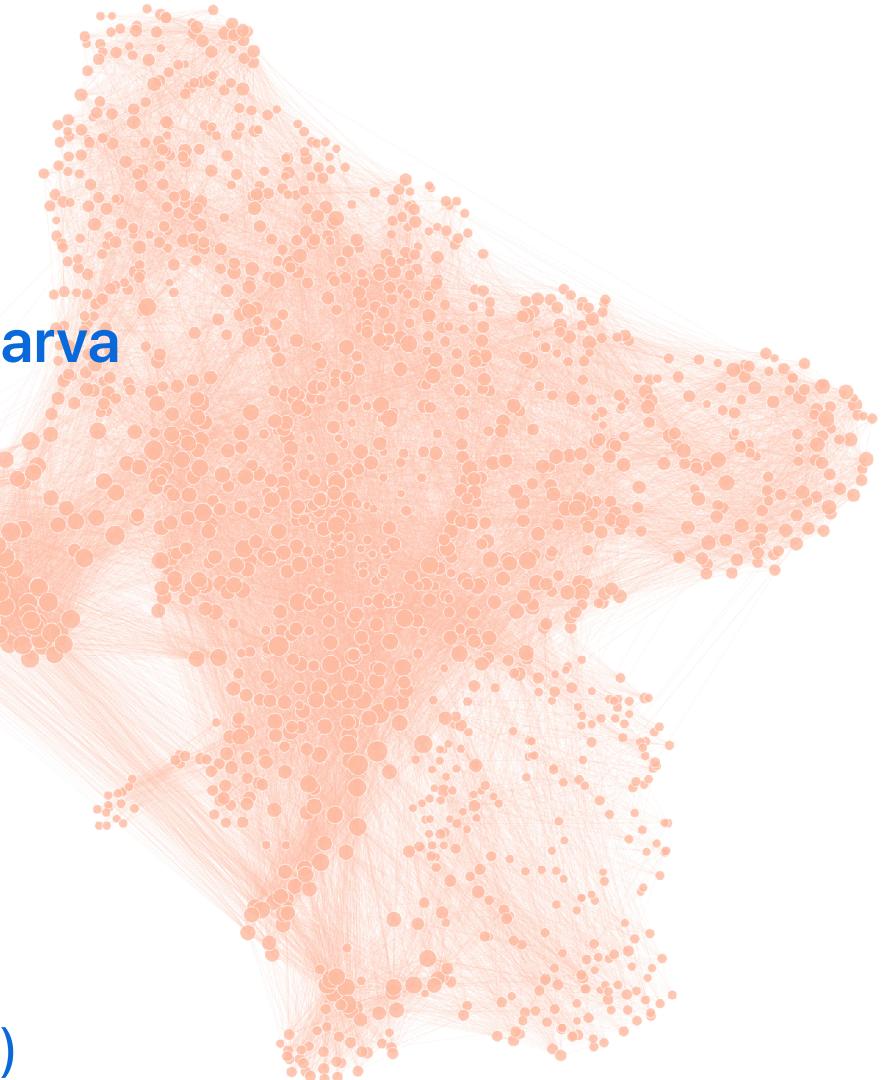
 [@bdpedigo](https://github.com/bdpedigo) (Github)

 [@bpedigod](https://twitter.com/bpedigod) (Twitter)

 bpedigo.github.io



Left



Right