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

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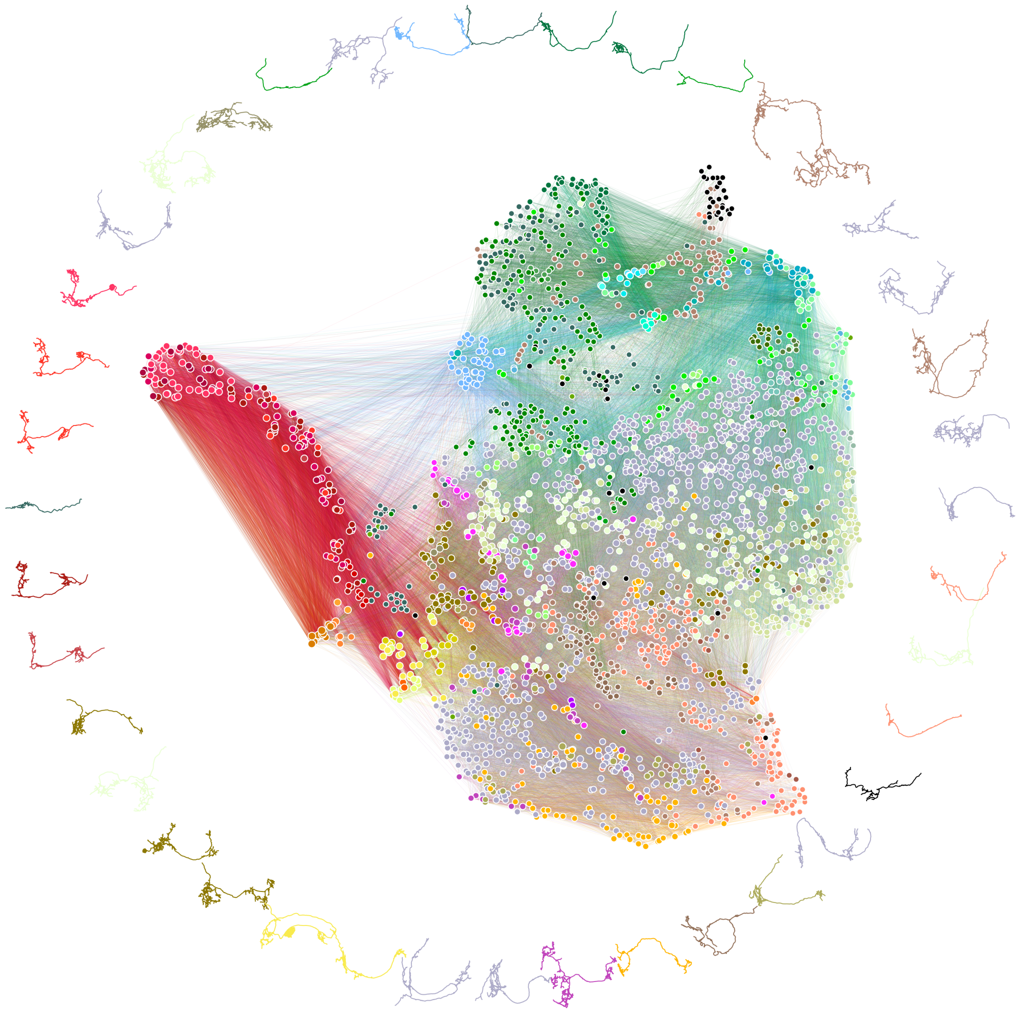
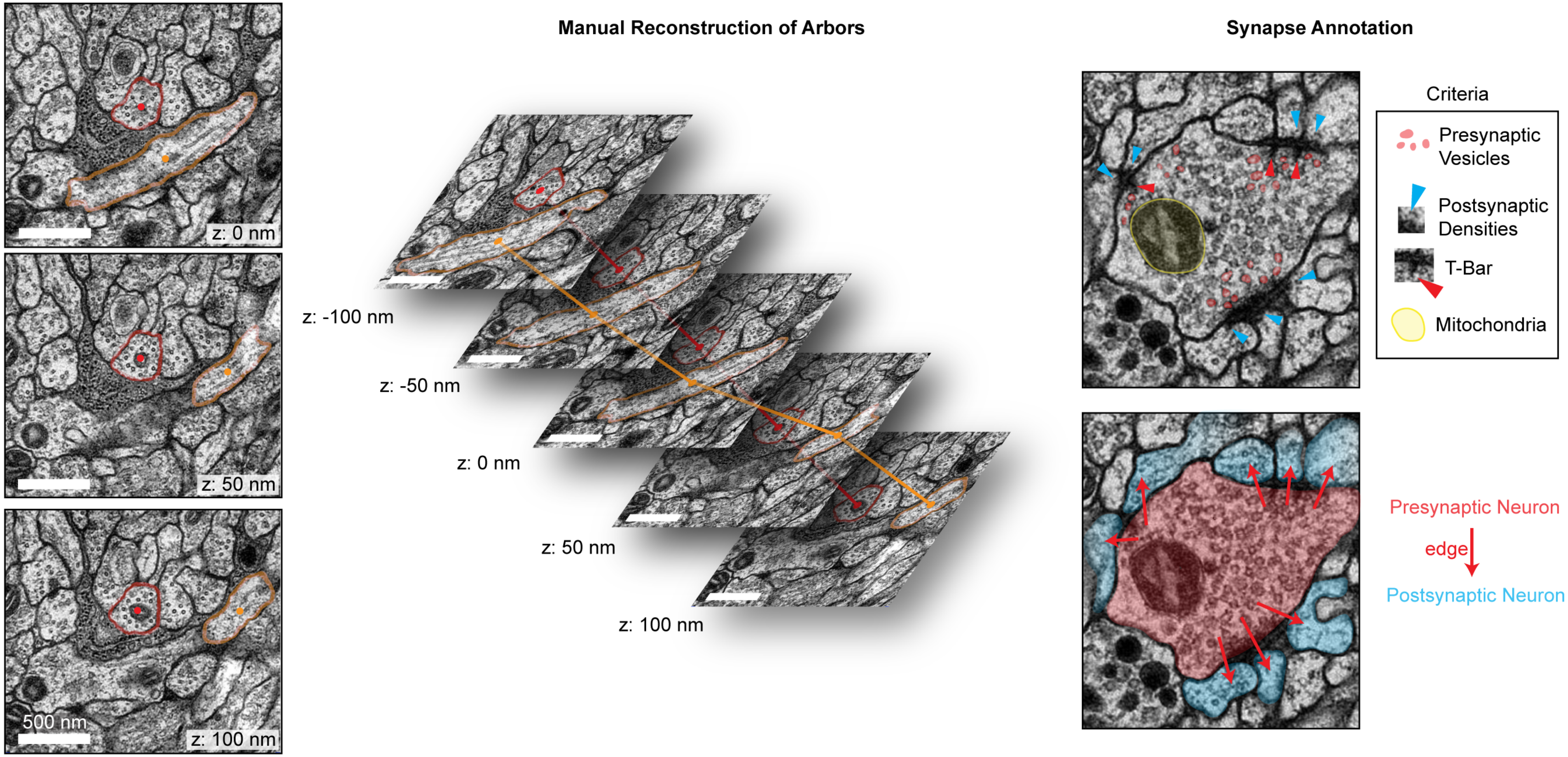


My requests

- Feedback, feedback, feedback
    - Especially with figures

Electron microscopy connectomics

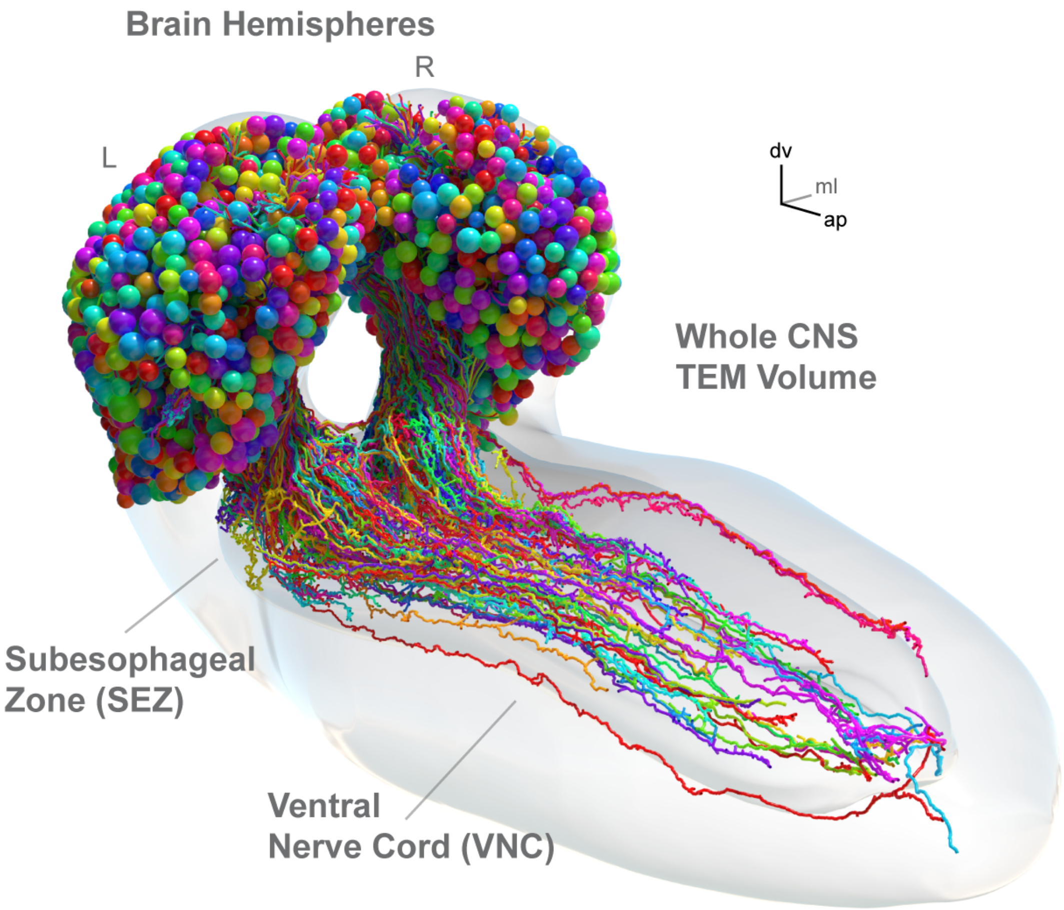


Winding, Pedigo et al. “The complete connectome of an insect brain.” In prep (2021)

Drosophila larva (AKA a maggot) brain connectome

See Michael Windings's talk

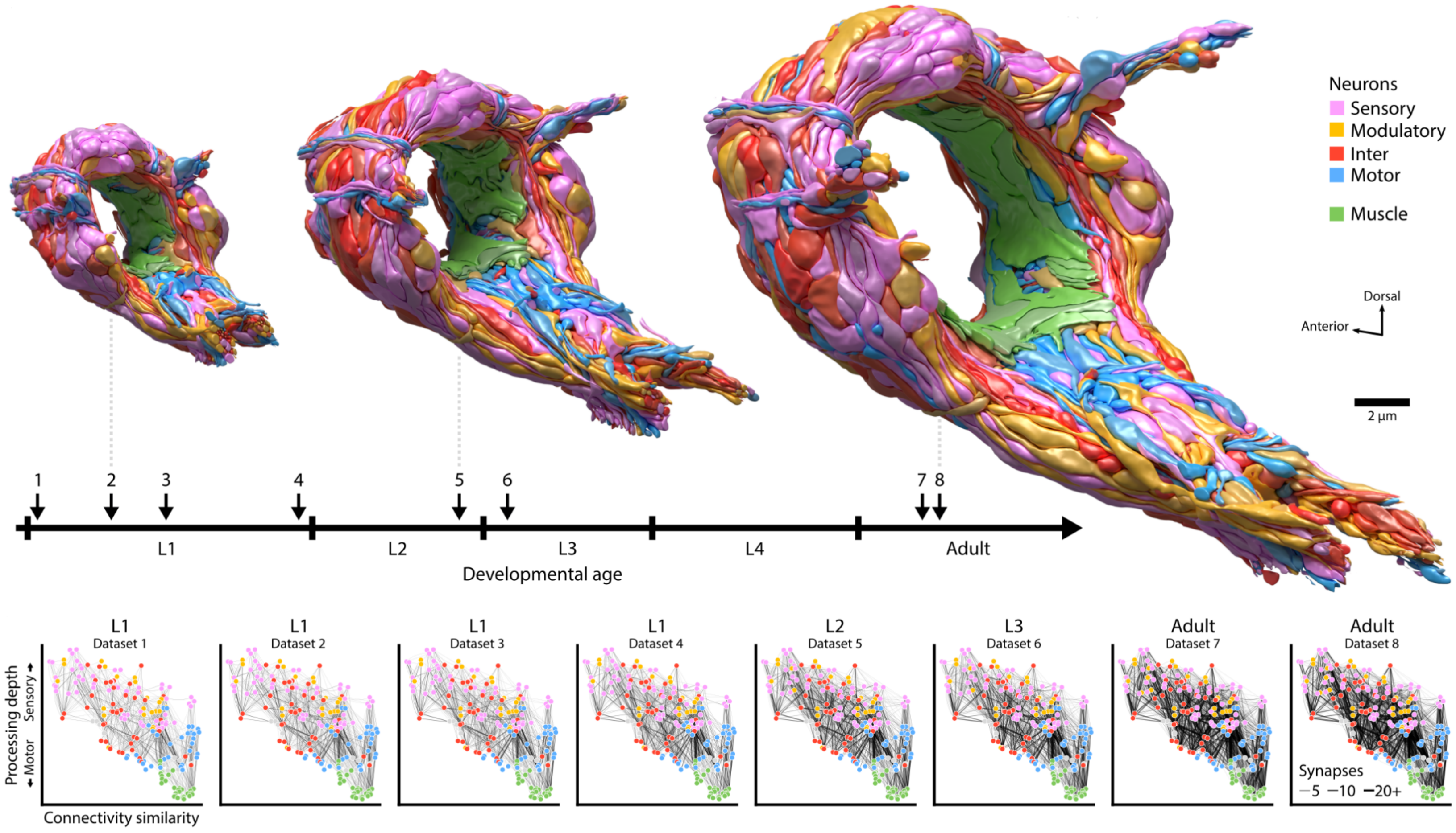
- First whole-brain, single-cell connectome of any insect
- ~3000 neurons, ~544K synapses
- Both hemispheres of the brain reconstructed



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

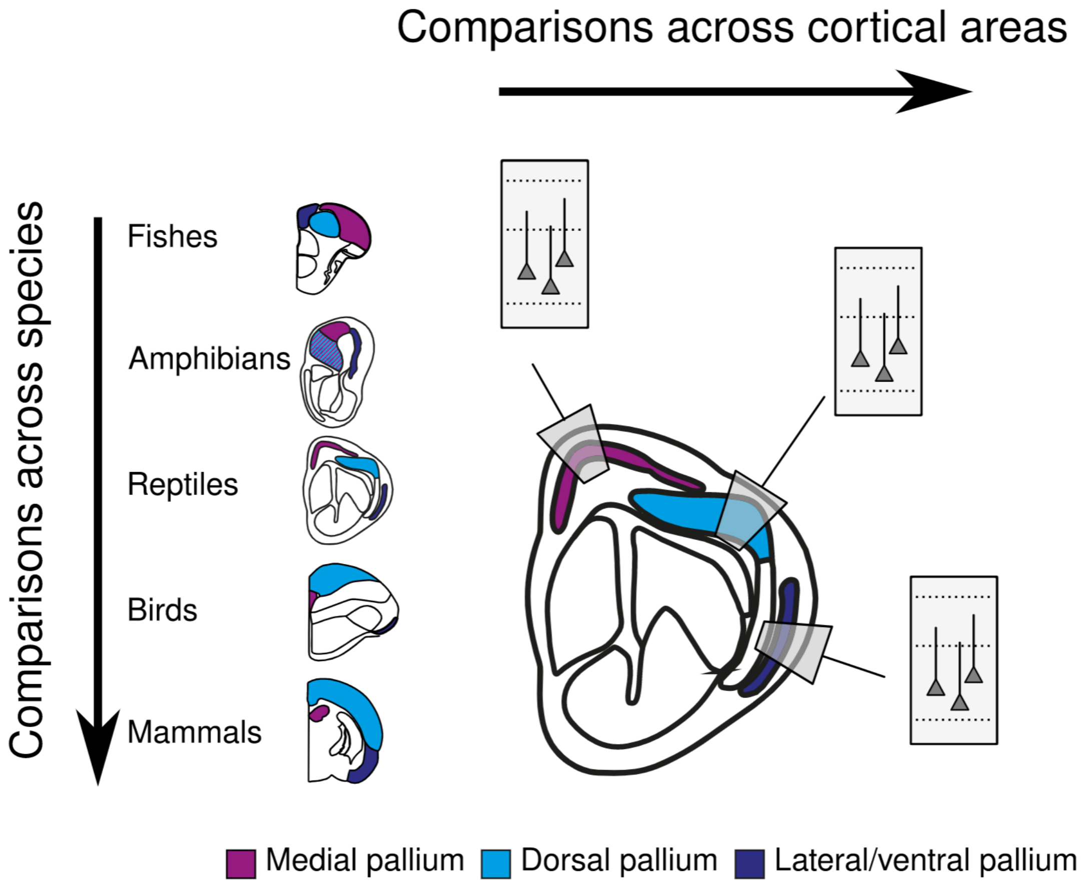
Many connectomics questions require comparison

Connectomes across development



Witvliet et al. *Nature* (2021)

Connectomes across evolution, cortex

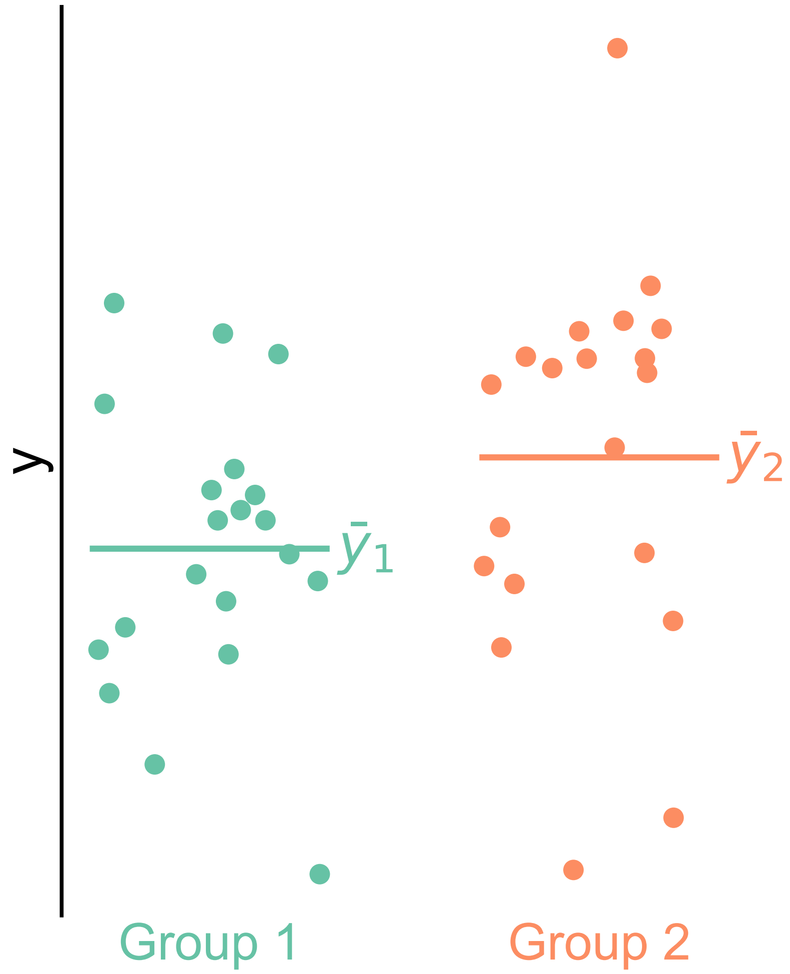


Bartsotti + Correia et al. *Curr. Op. Neurobiology* (2021)

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

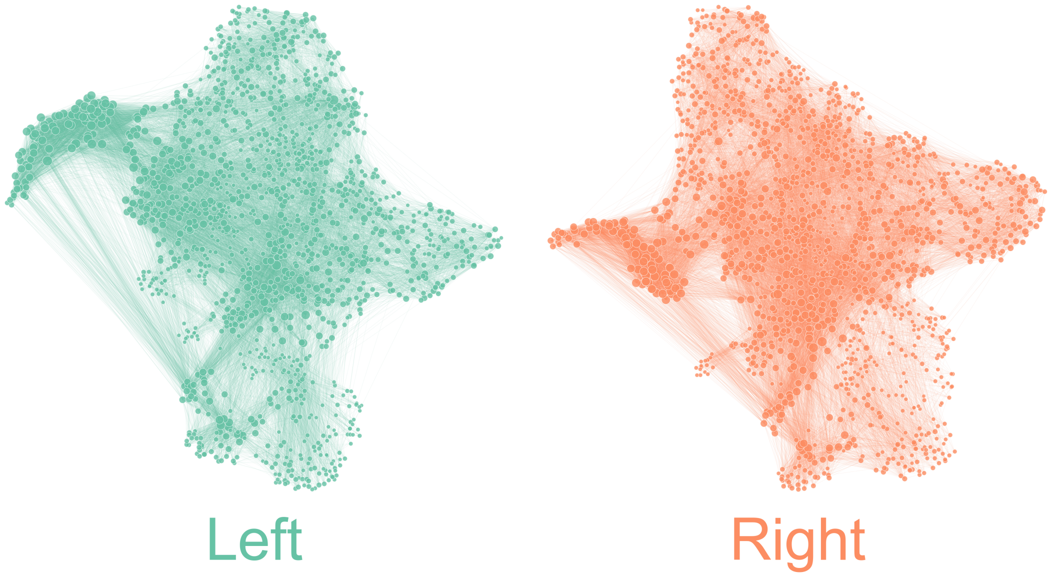
Are these populations the same?

- 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!
- $A^{(L)} \sim F^{(L)}$, $A^{(R)} \sim F^{(R)}$
- $H_0 : F^{(L)} = F^{(R)}$
  $H_A : F^{(L)} \neq F^{(R)}$



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 $\longrightarrow$ left and right $\longrightarrow$ right (*ipsilateral*) connections only.

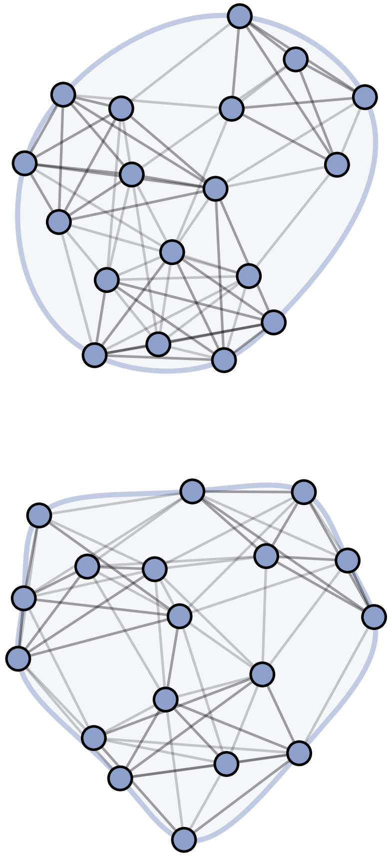
Density-based testing: Erdos-Renyi (ER) model

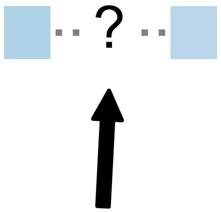
Compute global connection density

Compare ER models

Left

Right

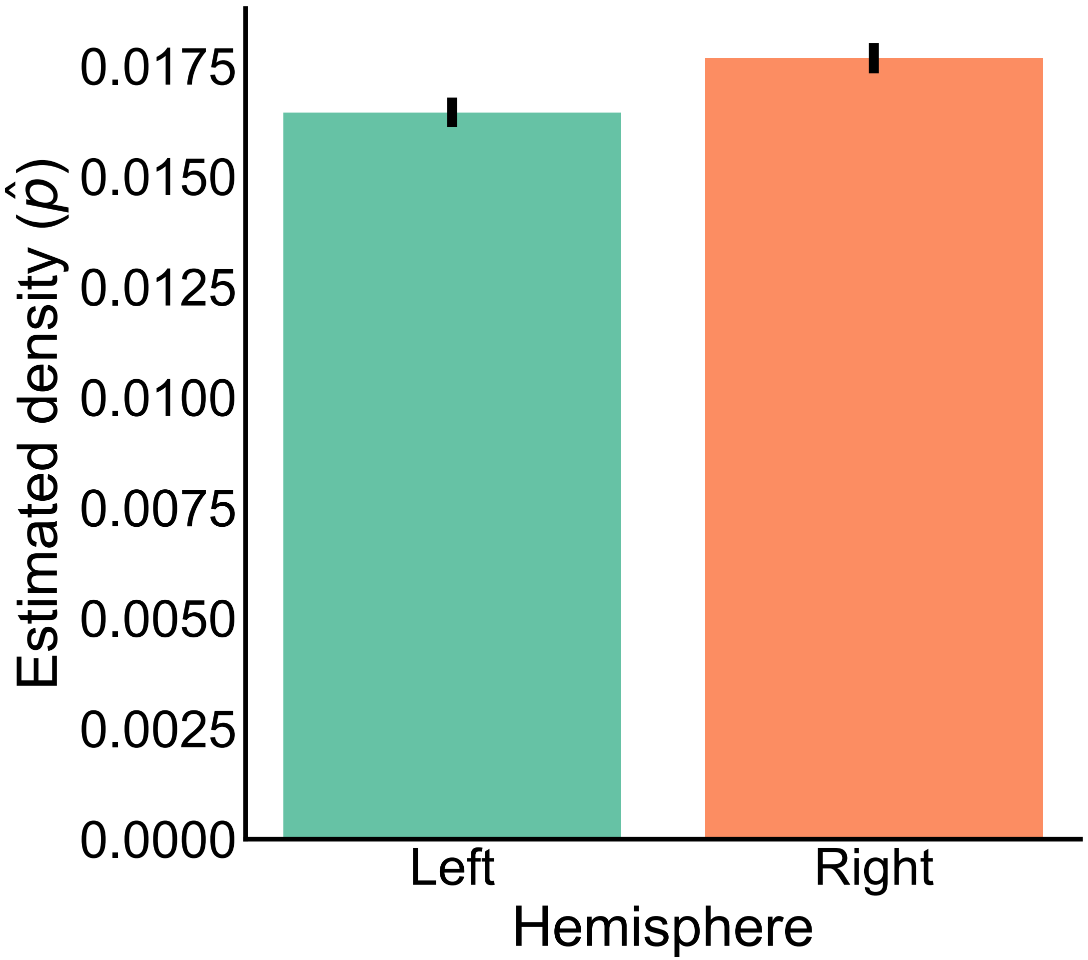




$$H_0 : p^{(L)} = p^{(R)}$$

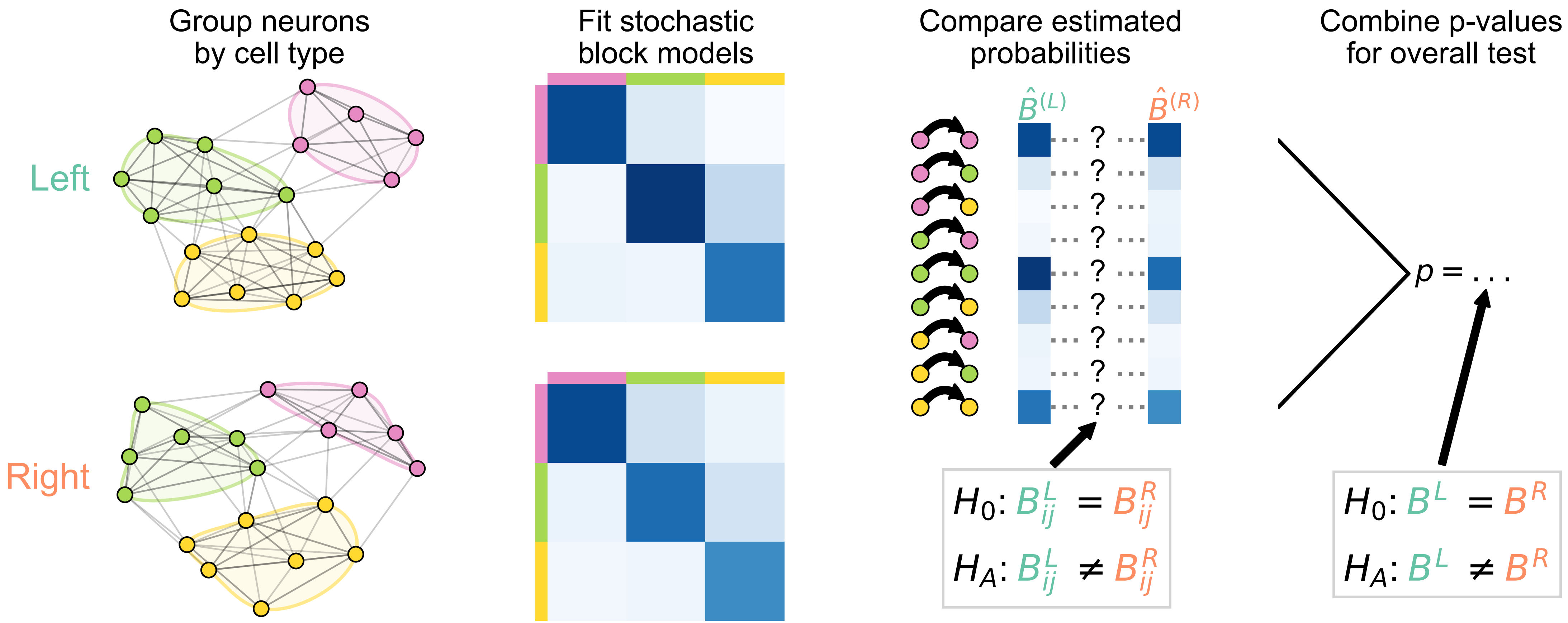
$$H_A : p^{(L)} \neq p^{(R)}$$

We detect a difference in density

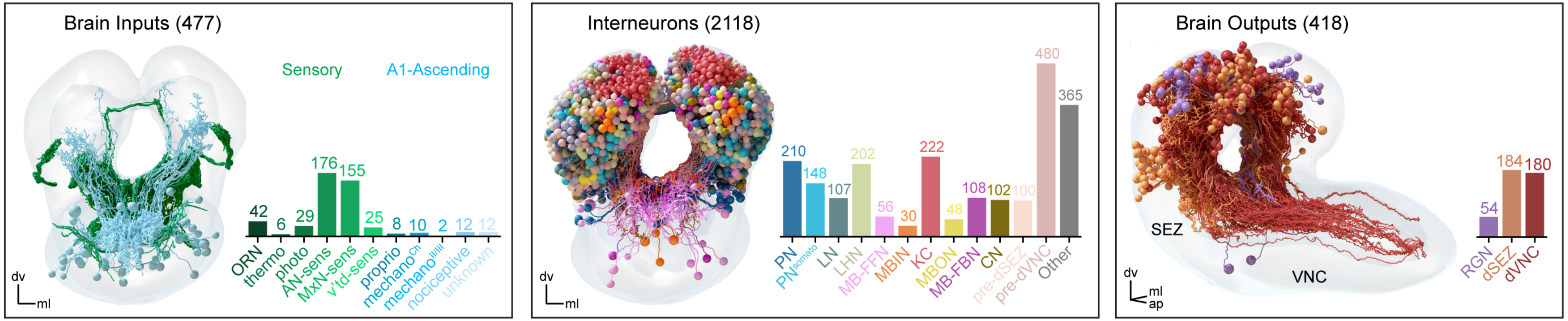


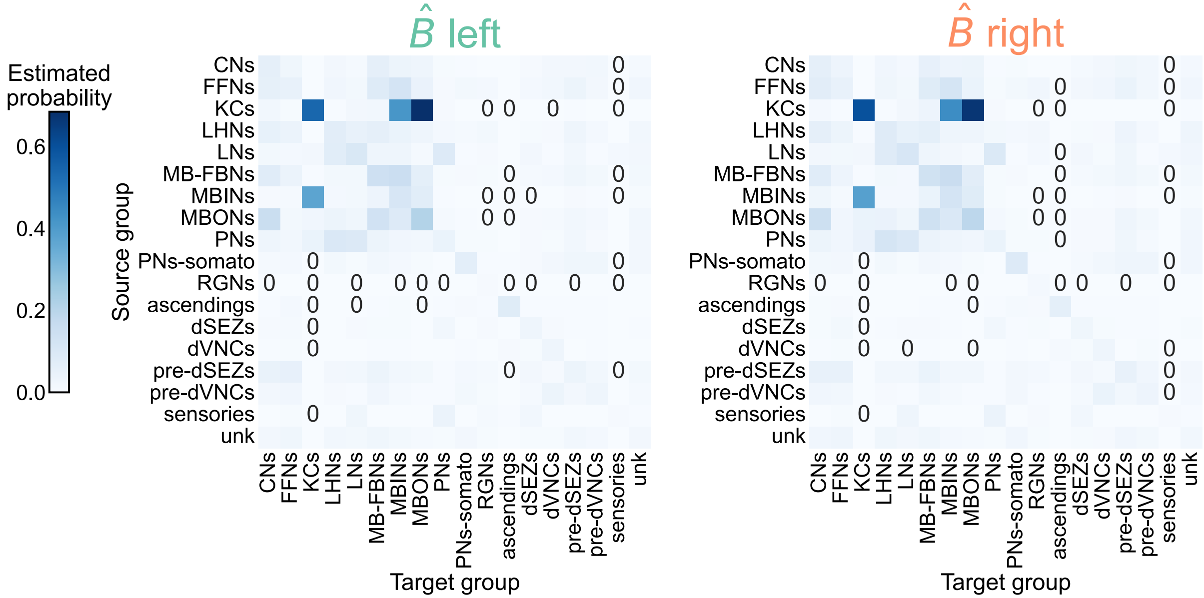
- p-value < 10^{-22}

Group-based testing: stochastic block model (SBM)

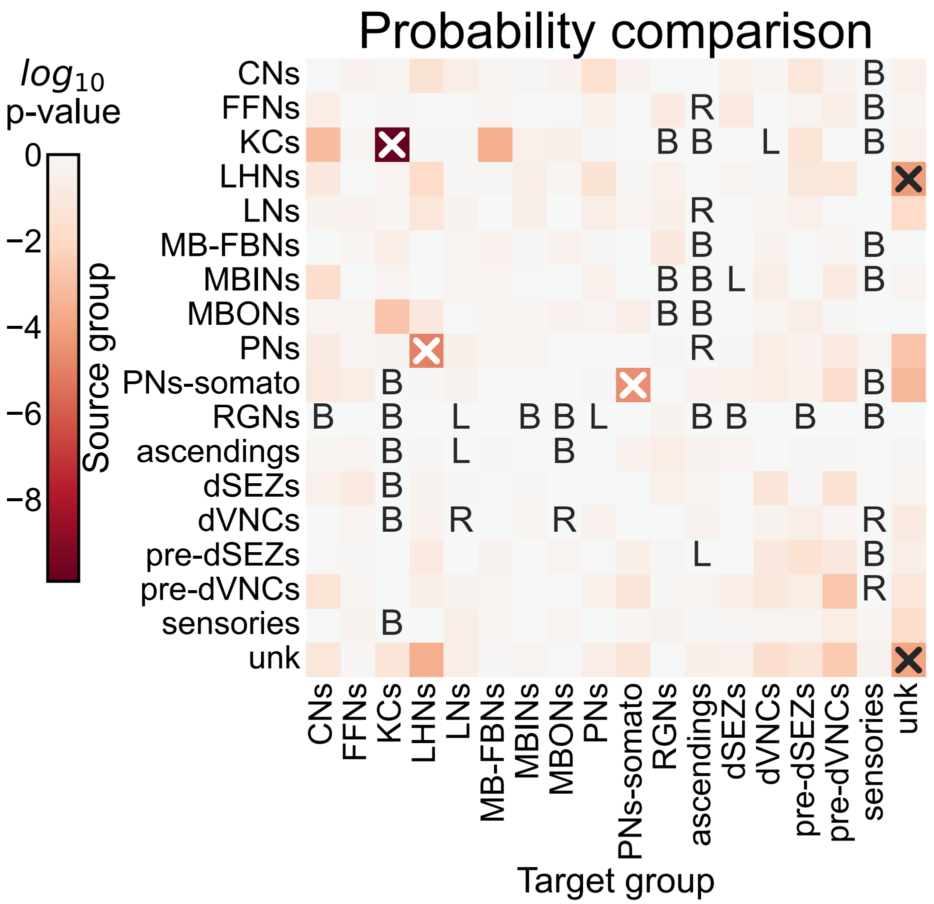


Connection probabilities between groups





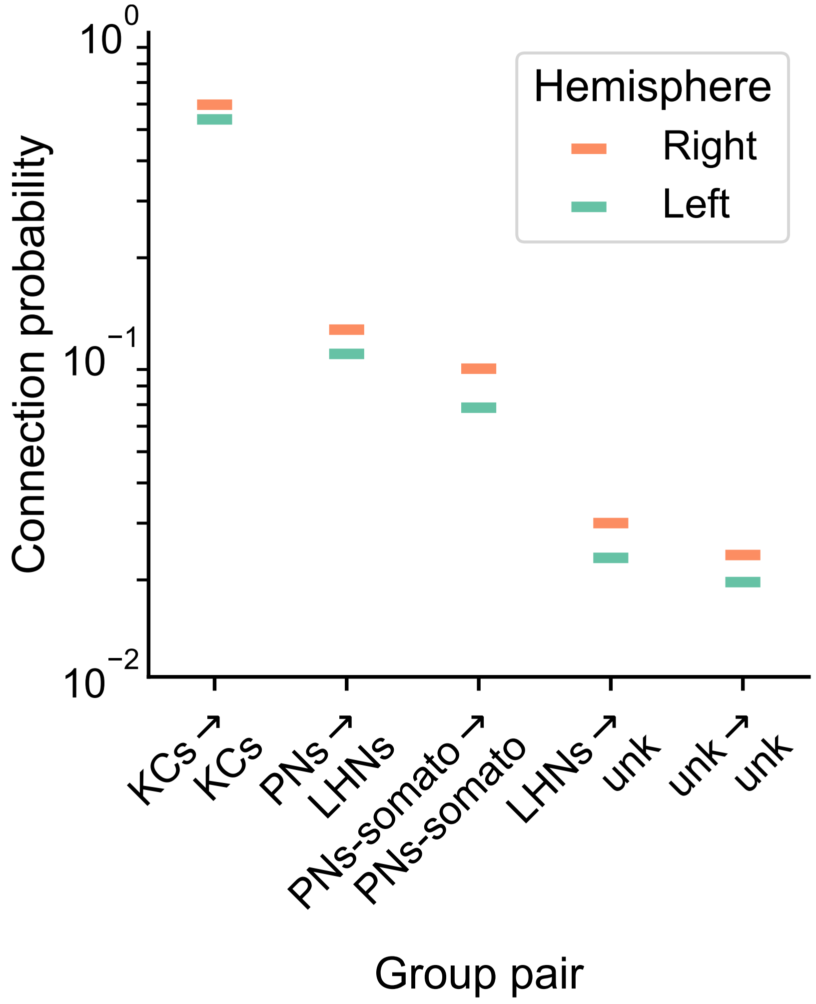
We detect a difference in group-to-group connection probabilities



- 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 $< 10^{-7}$

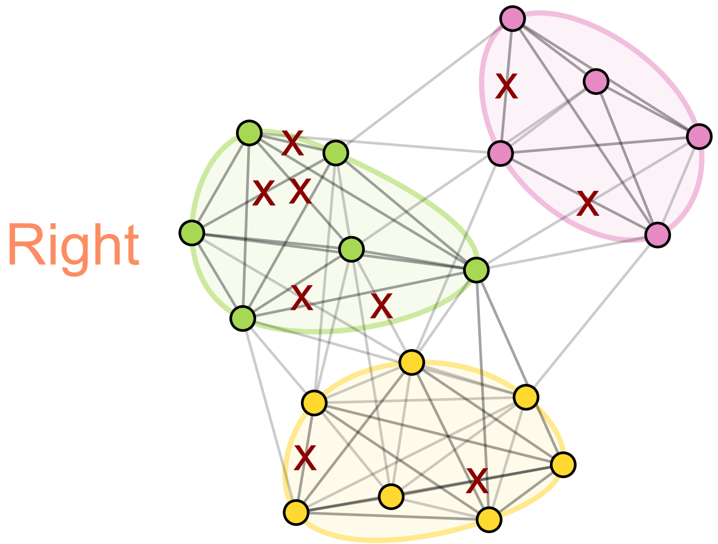
Should we be surprised?

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

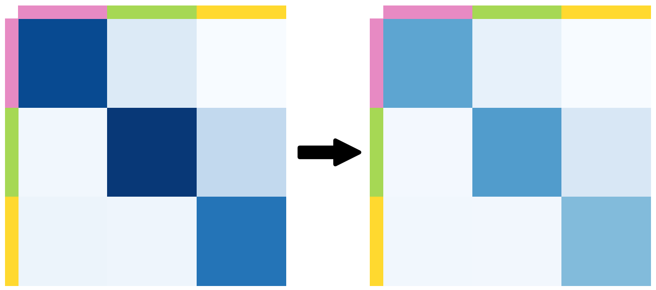


Adjusting for a difference in density

Randomly subsample edges

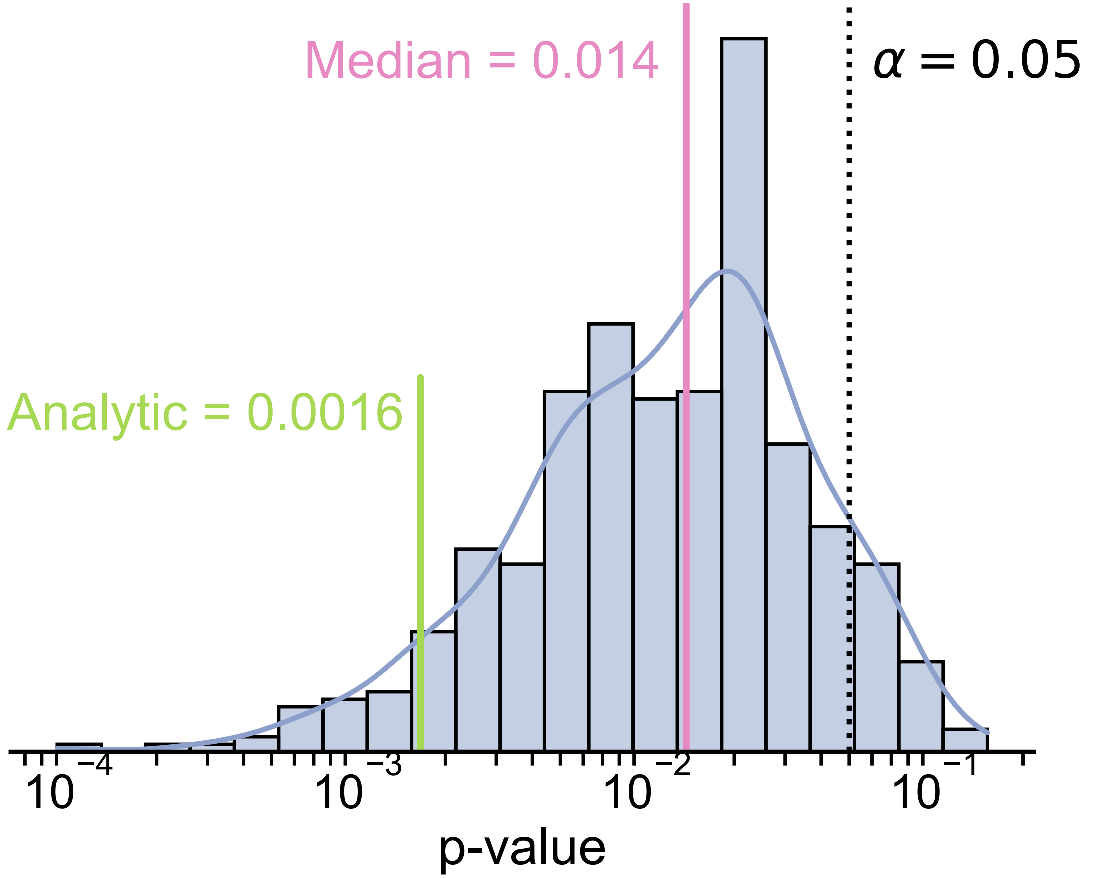


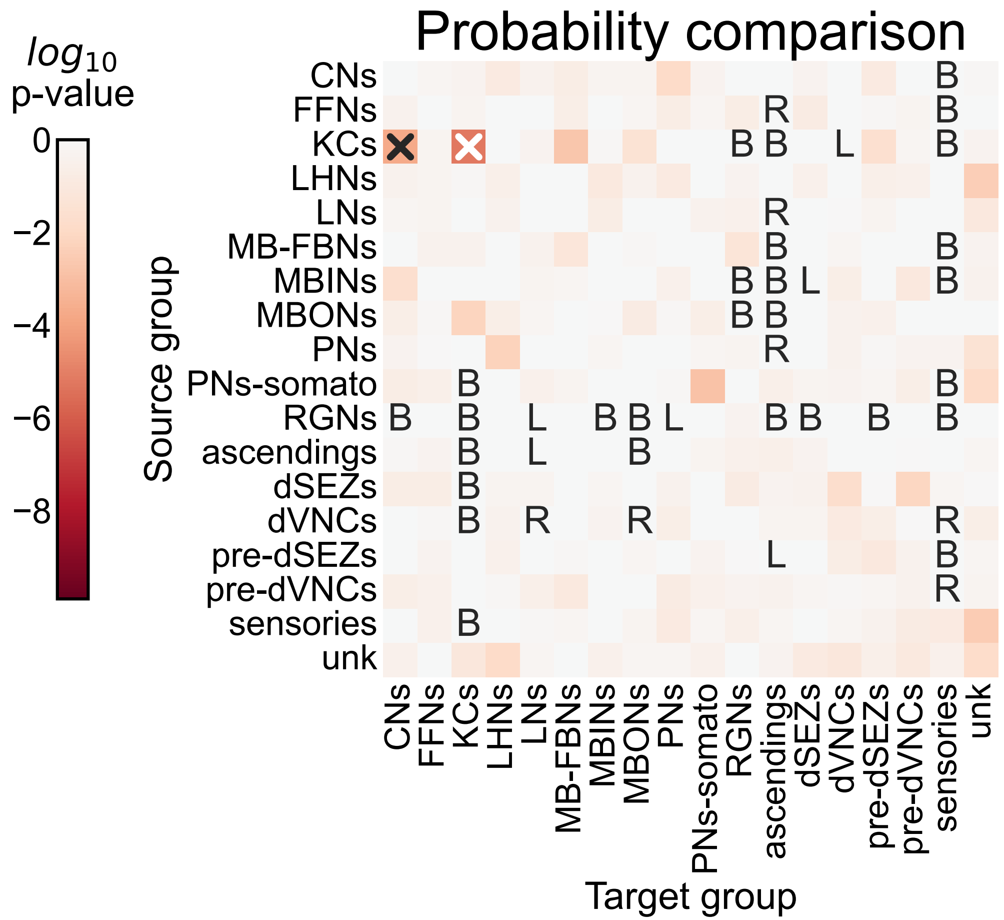
Adjust connection probabilities



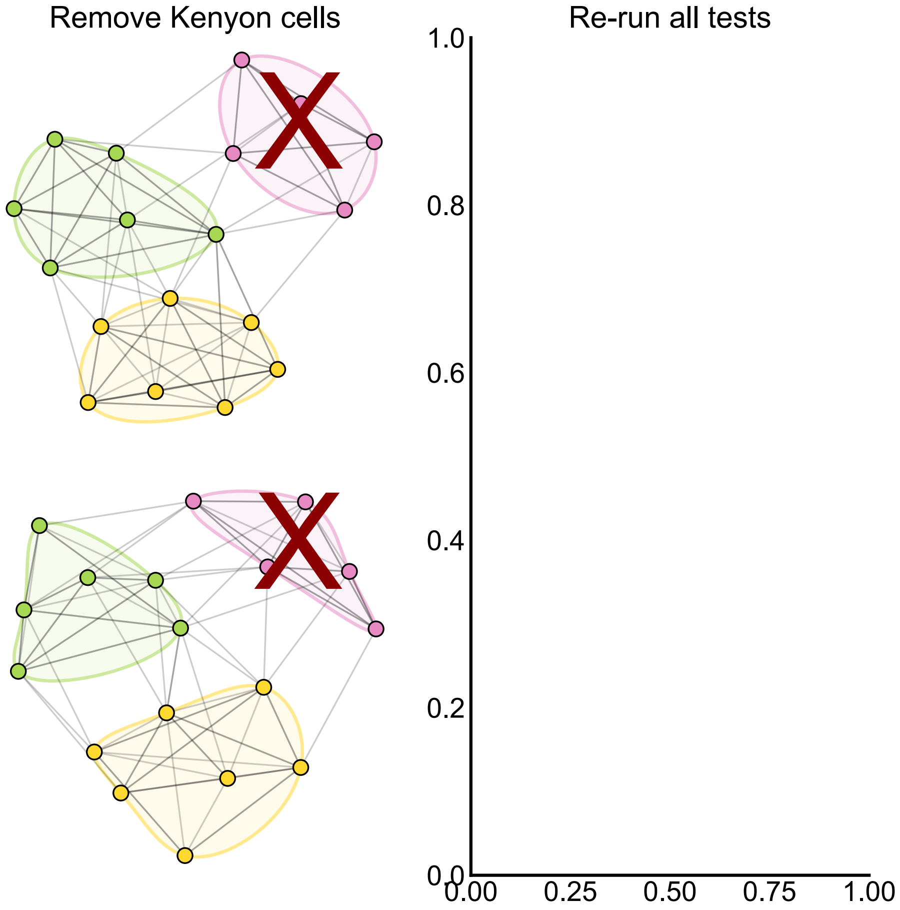
Rerun SBM testing

Even with an adjustment, still detect a difference





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



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

But wait, there's more (tests one could run)!

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)

More generally

- We studied simple ways of framing a network two sample test
- 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 provide recommendations for what to run for you future connectome comparisons

graspologic:

github.com/microsoft/graspologic

graspologic

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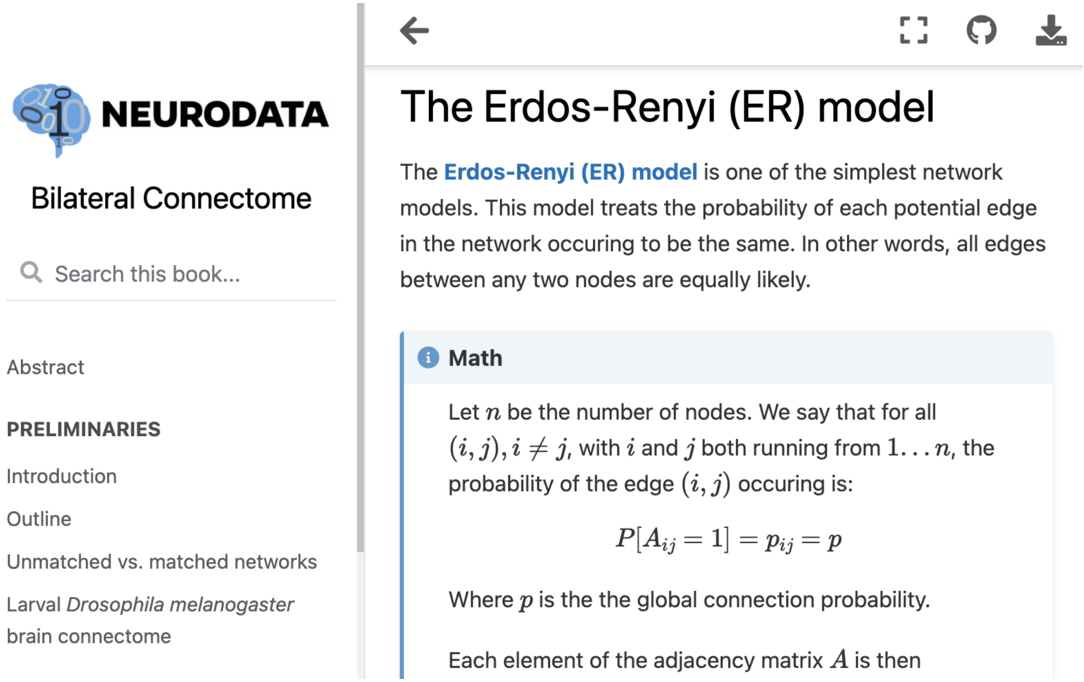
This work:

github.com/neurodata/bilateral-connectome



Chung, Pedigo et al. JMLR (2019)

Acknowledgements

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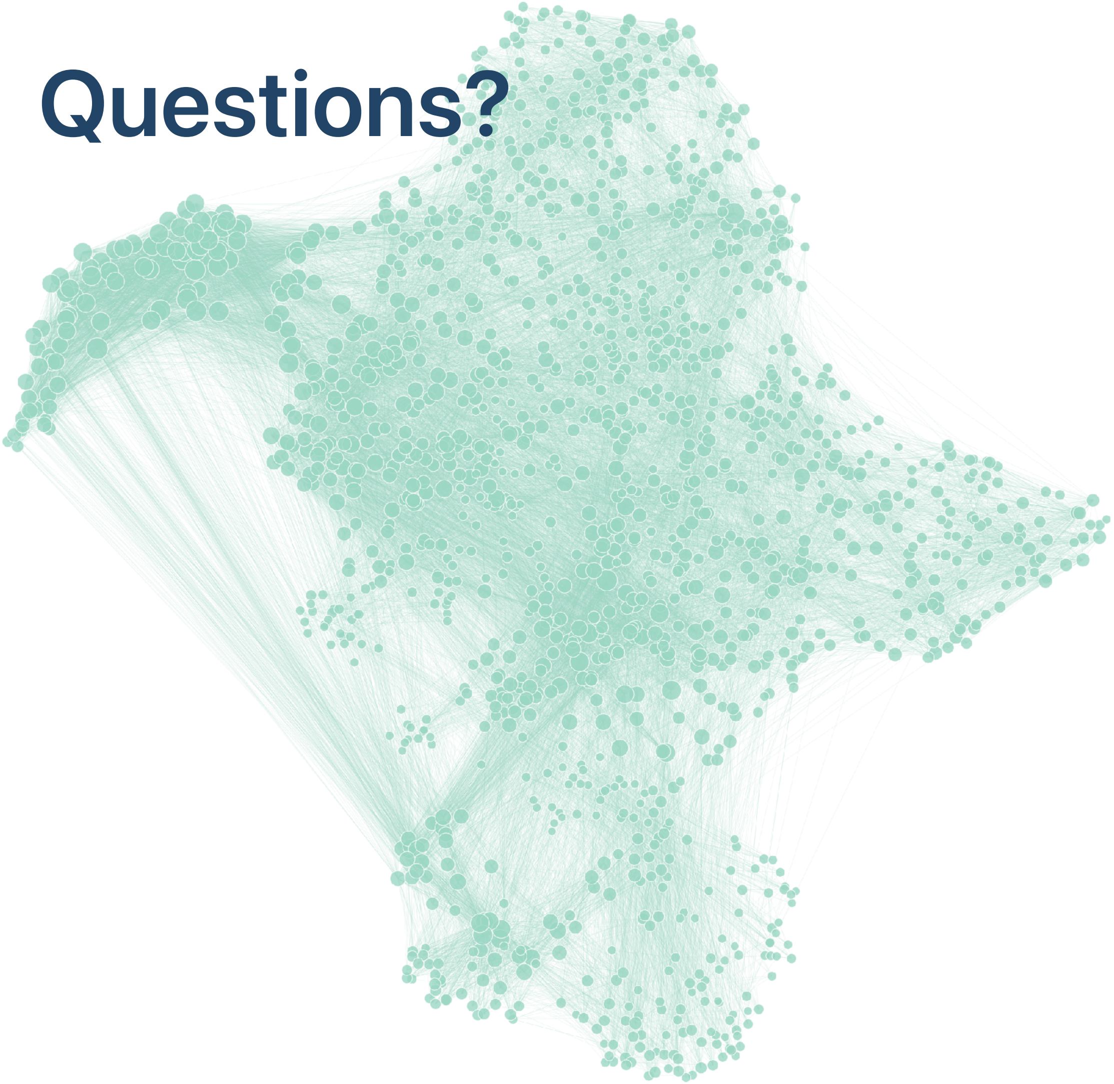
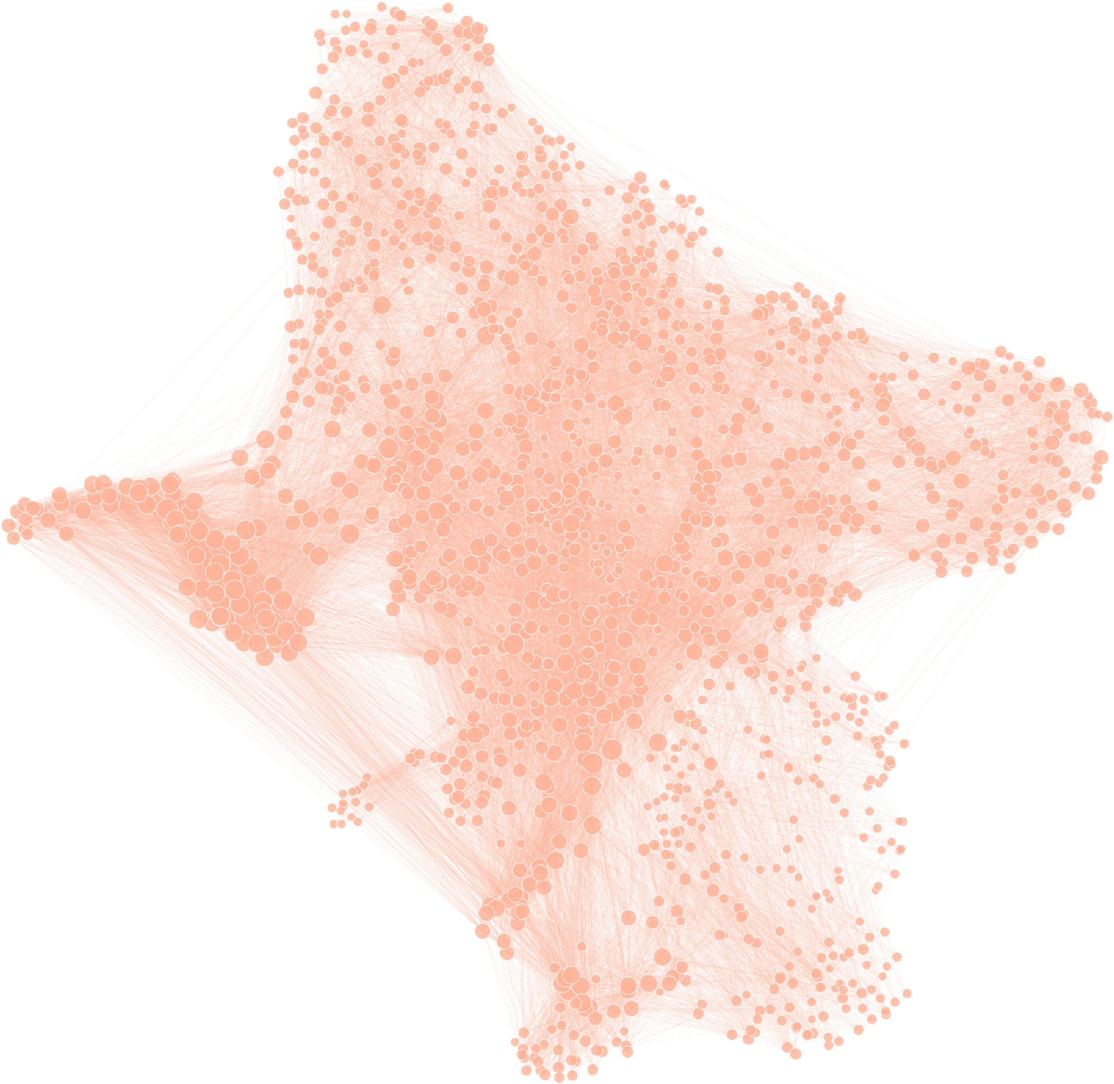
Questions?



Left



Right