Comparative connectomics: methods and applications

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These slides at:

bdpedigo.github.io/talks/aibs.html

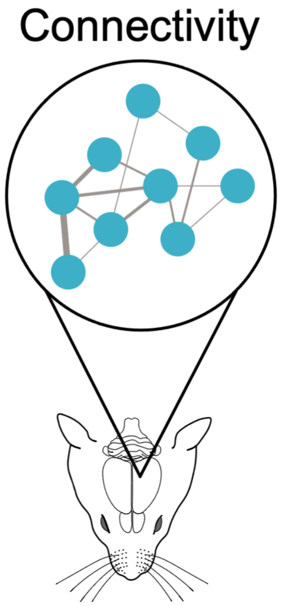
Background

- From Lake Forest Park, WA
- University of Washington for Undergrad (Bioengineering, Minor in Applied Math)
- Research on spinal cord injury (Chet Moritz's lab)
- Interned here w/ Nuno in summer of 2017
- Organized Bird Club @ UW

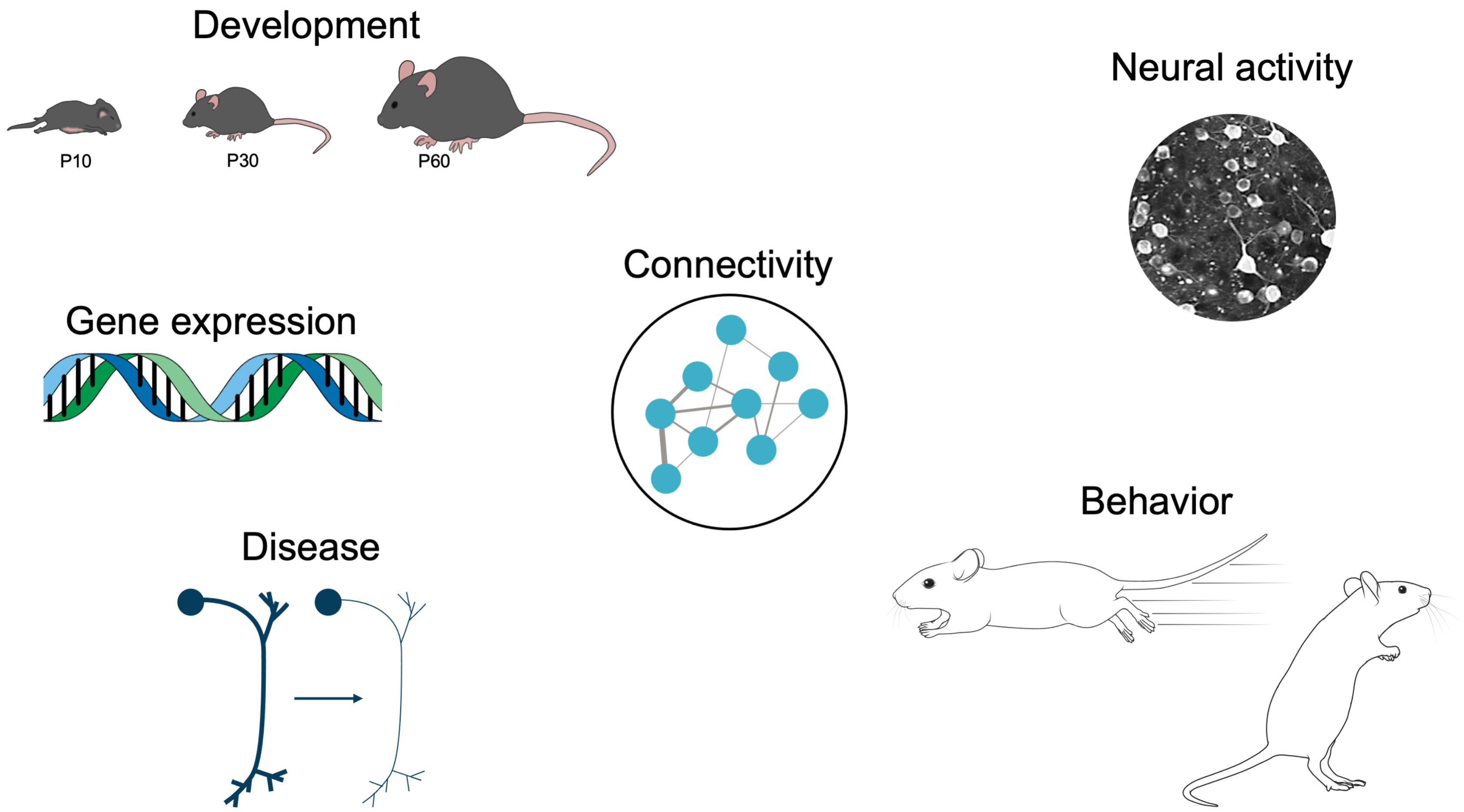
Background

- PhD in Biomedical Engineering at Johns Hopkins University
  - Joshua Vogelstein + Carey Priebe
  - Analysis of connectome networks
- Interned at Microsoft Research twice
  - Analysis of organizational communication networks, code for network methods
- Bikes, Olympic marmots

Connectomes: maps of neural wiring

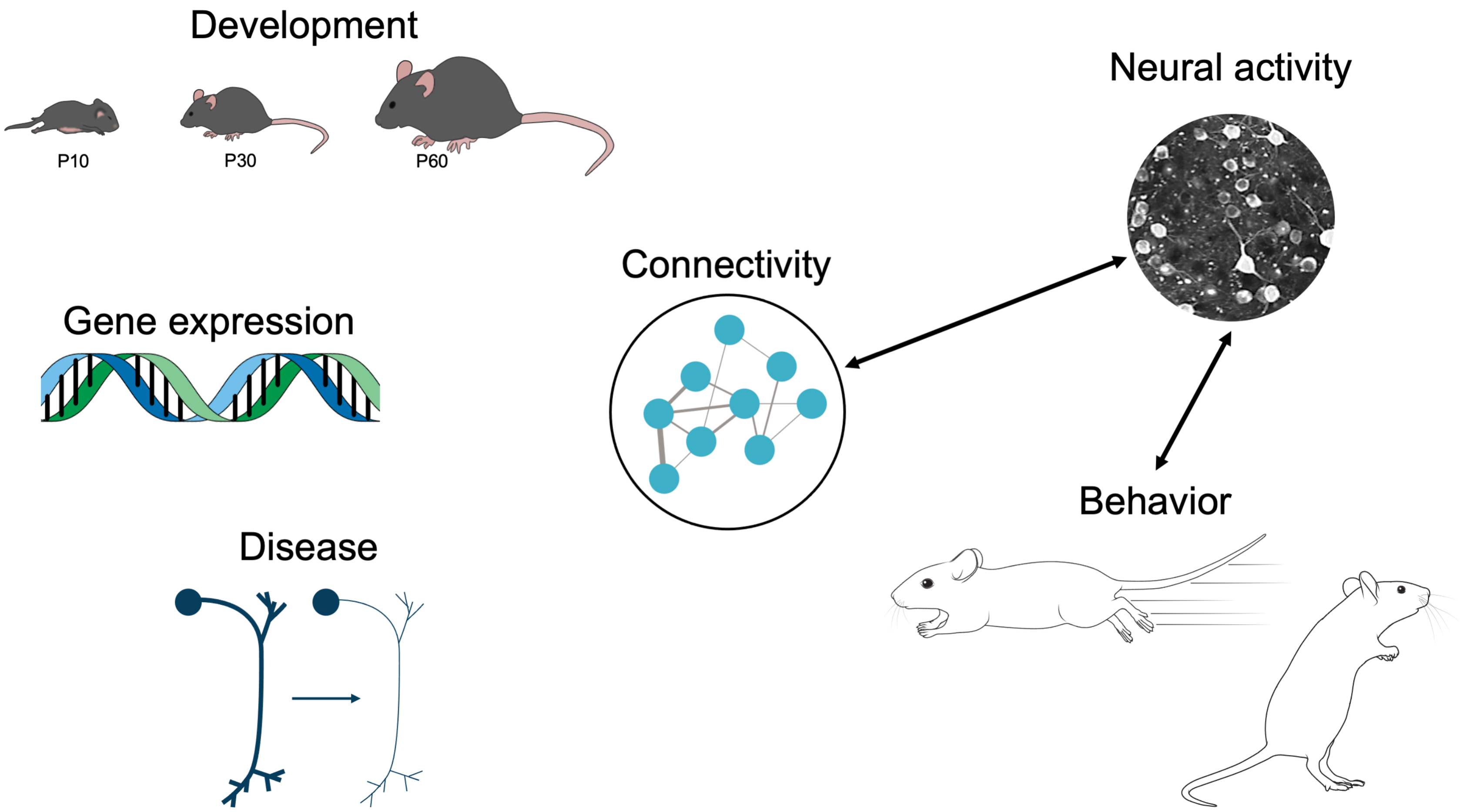


Goal: linking connectivity to other phenotypes



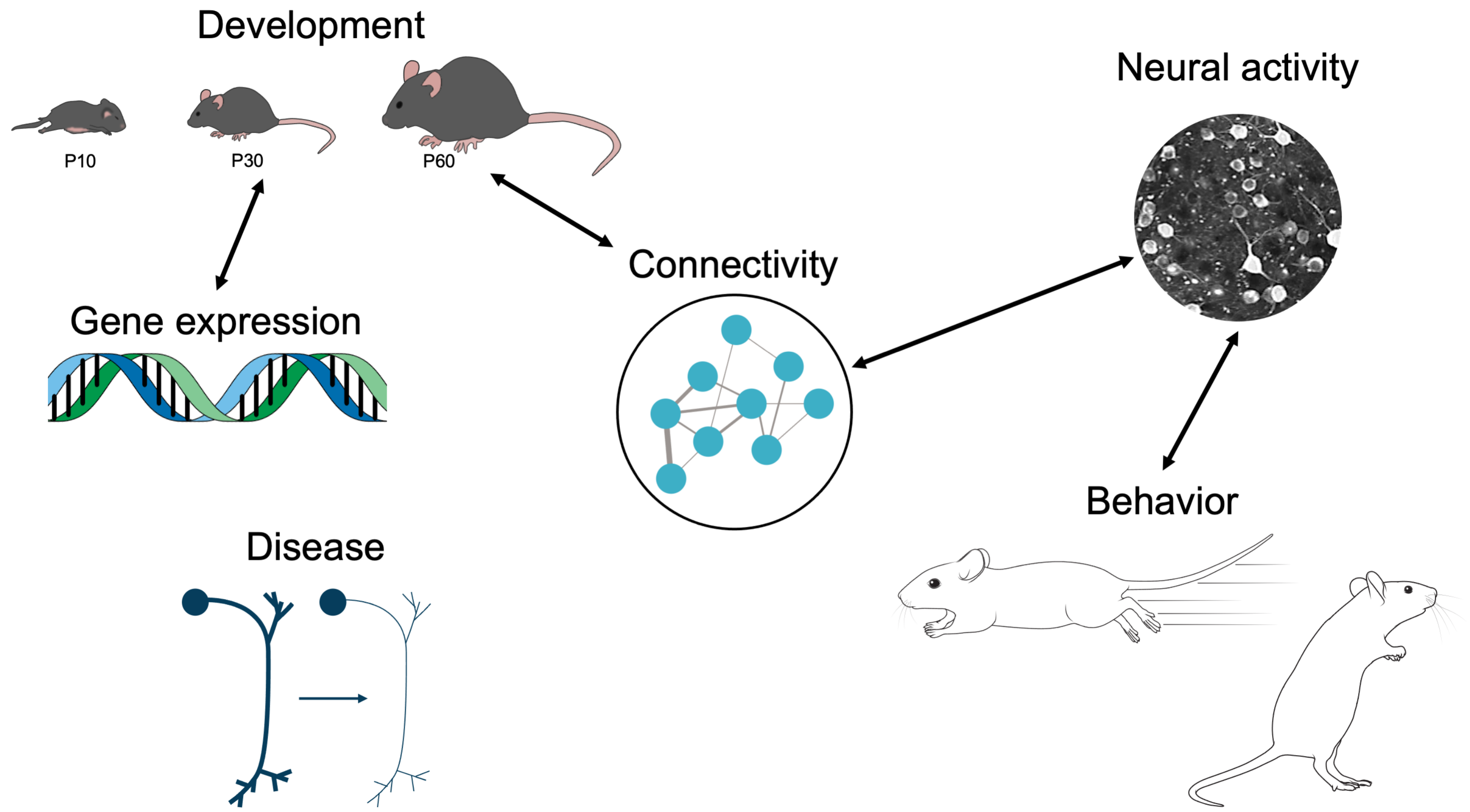
Images from brain-map.org, SciDraw

Goal: linking connectivity to other phenotypes



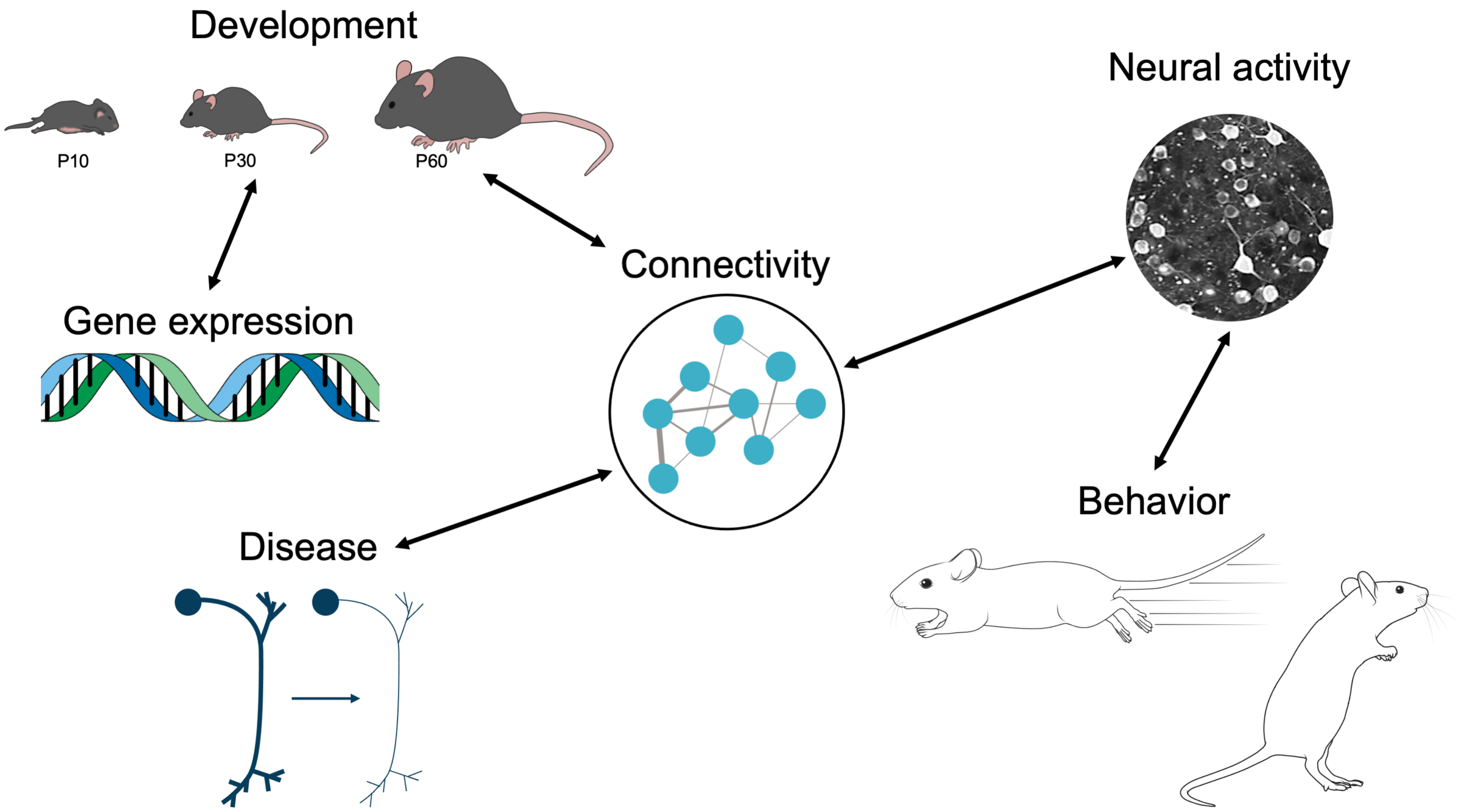
Images from brain-map.org, SciDraw

Goal: linking connectivity to other phenotypes



Images from brain-map.org, SciDraw

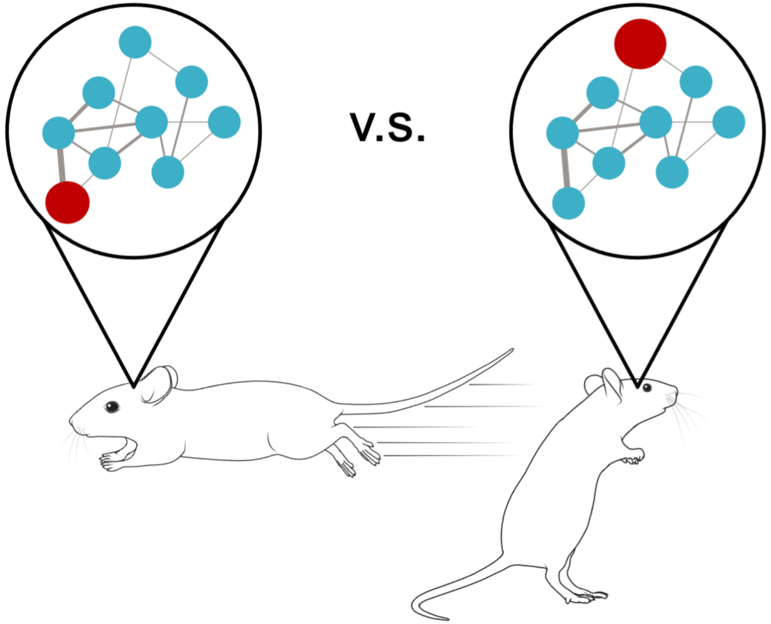
Goal: linking connectivity to other phenotypes



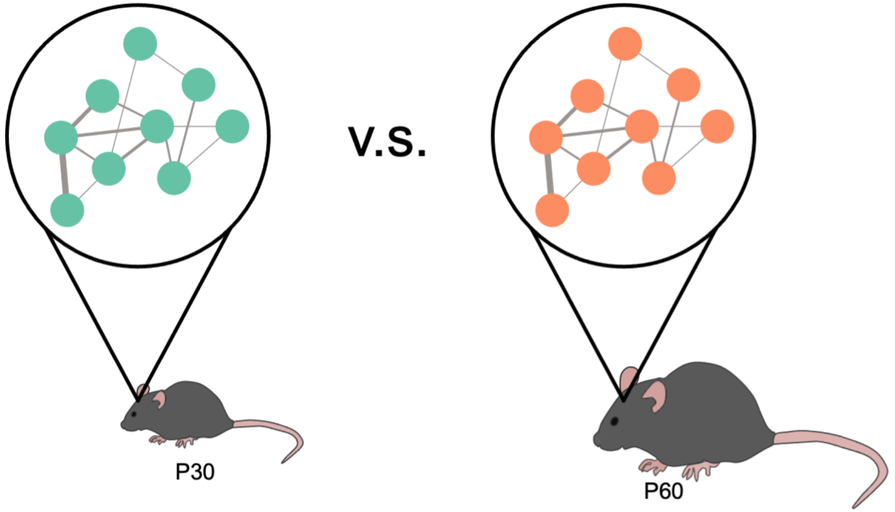
Images from brain-map.org, SciDraw

Comparative connectomics

How does a neuron's connectivity affect elicited behaviors?



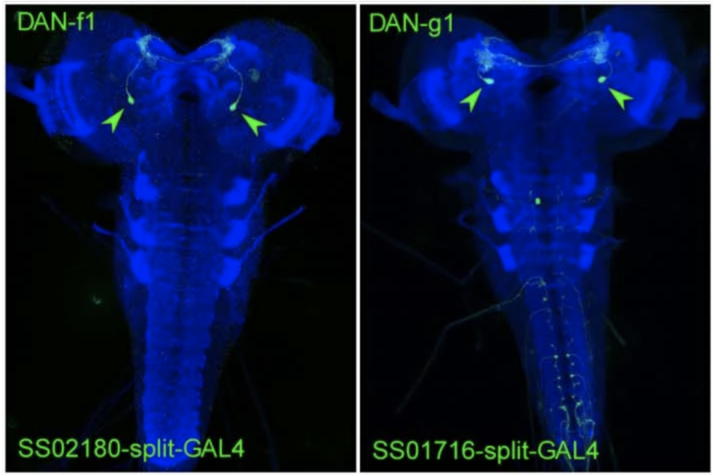
How does connectivity change during development?



Requires methods of comparing connectivity within and between connectomes

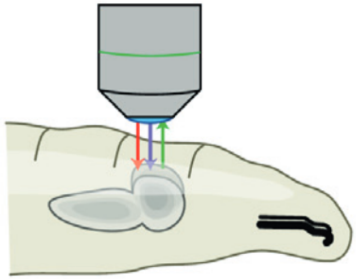
Larval *Drosophila* as a model system

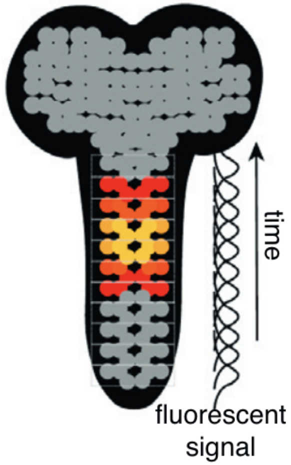
Genetics



Eschbach et al. Nat. Neuro (2020)

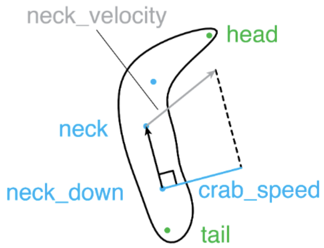
Activity

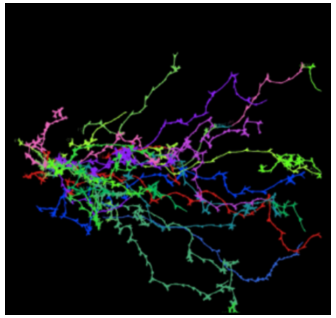




Eschbach & Zlatic Curr. Op. Neurobio. (2020)

Behavior

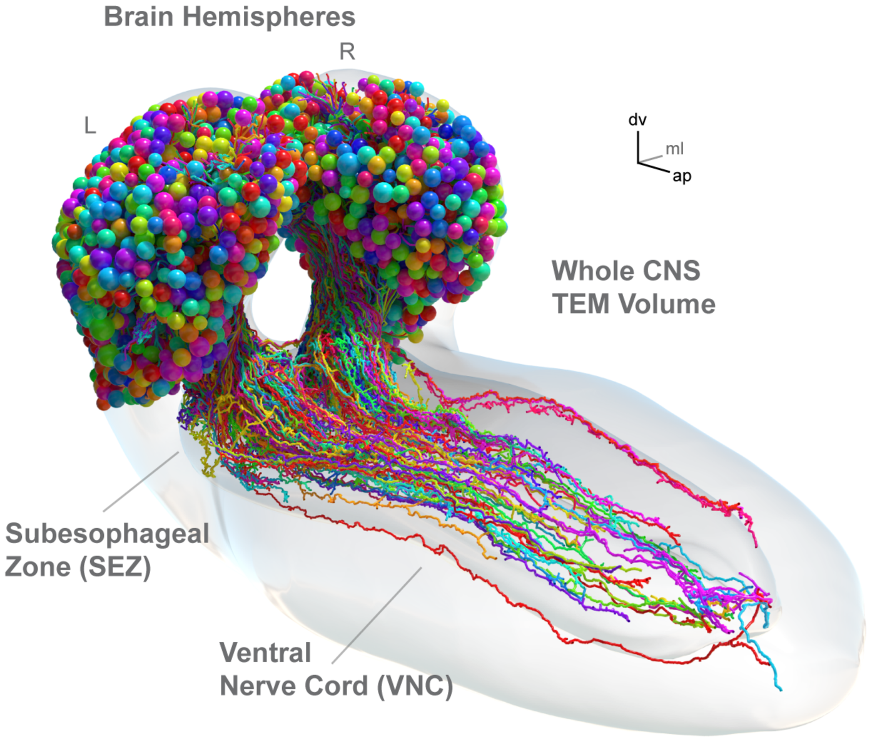




Klein et al. bioRxiv (2021)

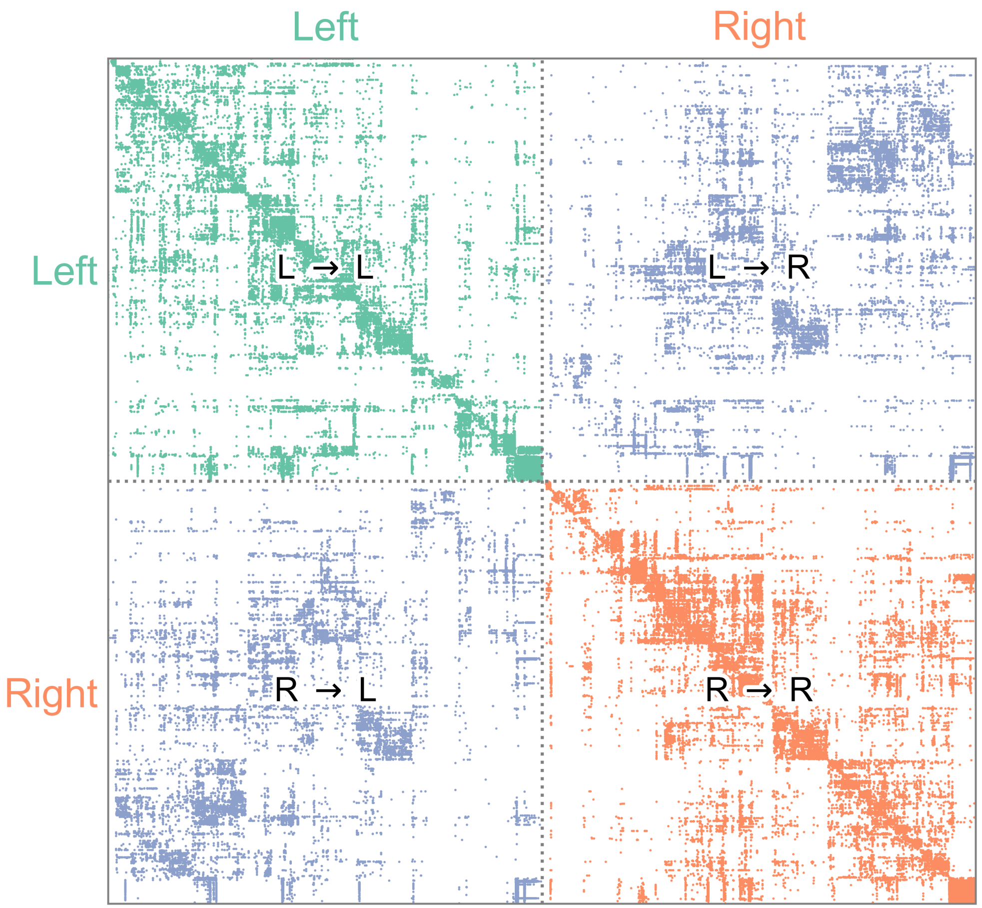
Almeida-Carvalho et al. J. Experimental Bio. (2017)

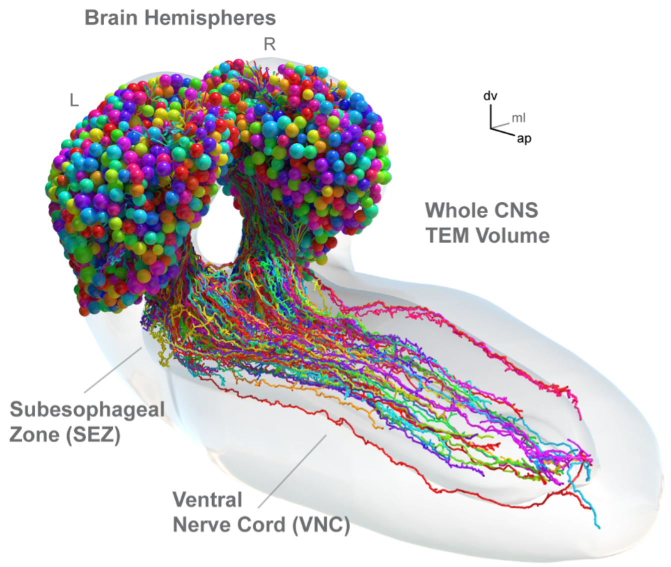
Larval *Drosophila* brain connectome



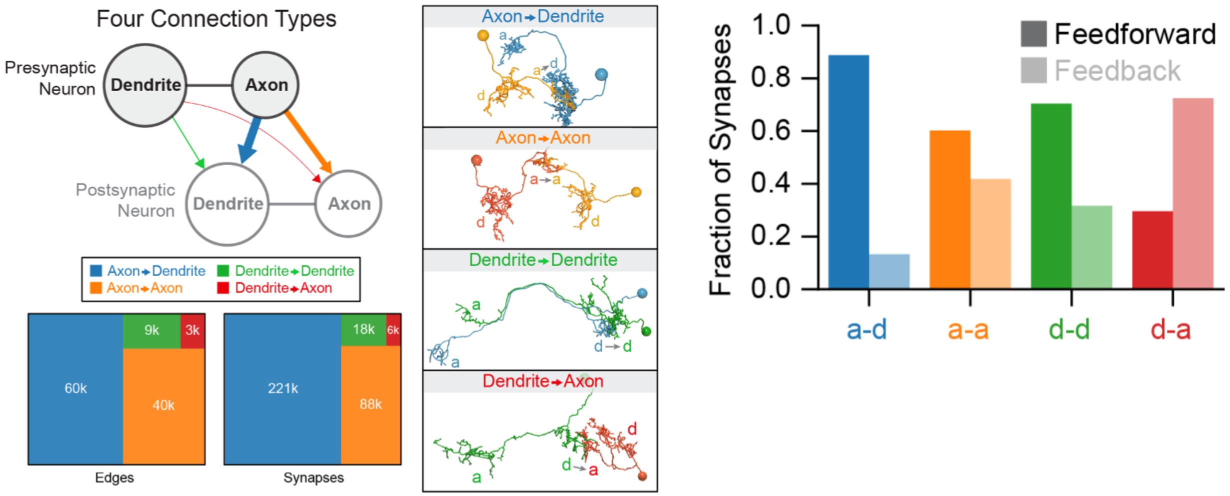
~3k neurons

Both hemispheres reconstructed

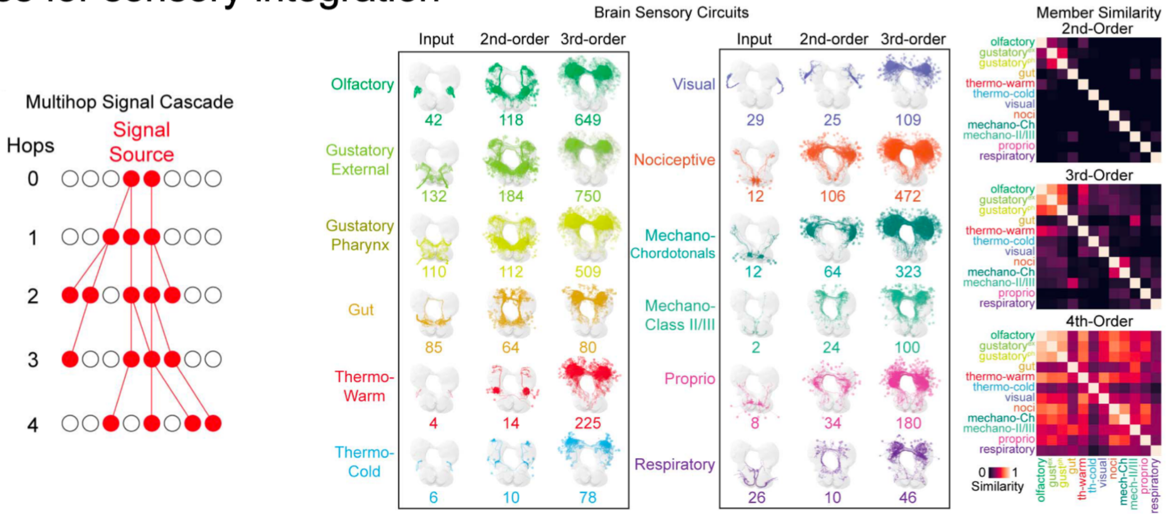




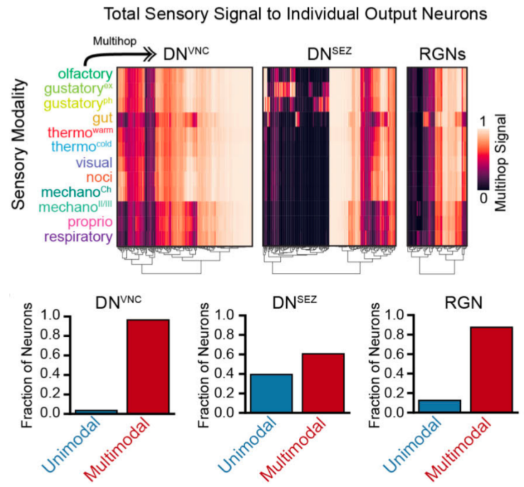
Role of connection types in feedforward/feedback flow



Routes for sensory integration



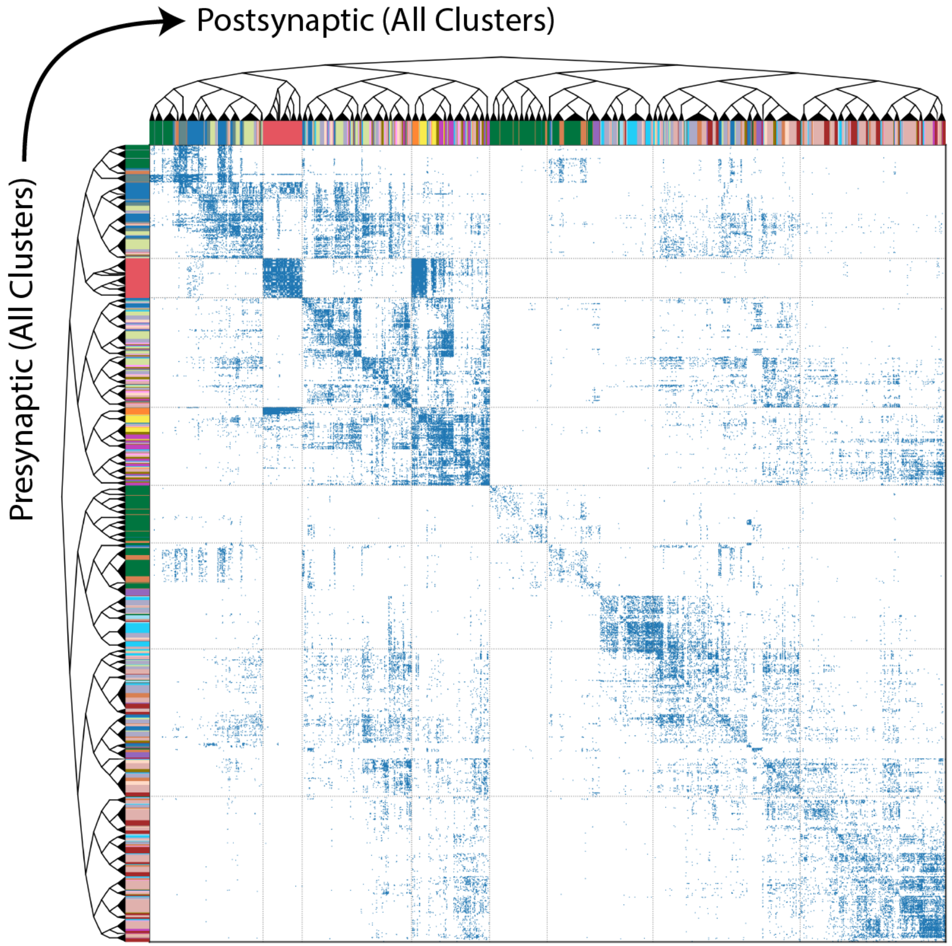
Routes to brain outputs



Outline

- Clustering the larval brain by connectivity
- Connectome comparison via network hypothesis testing
- Pairing neurons across connectomes via graph matching
- Future work

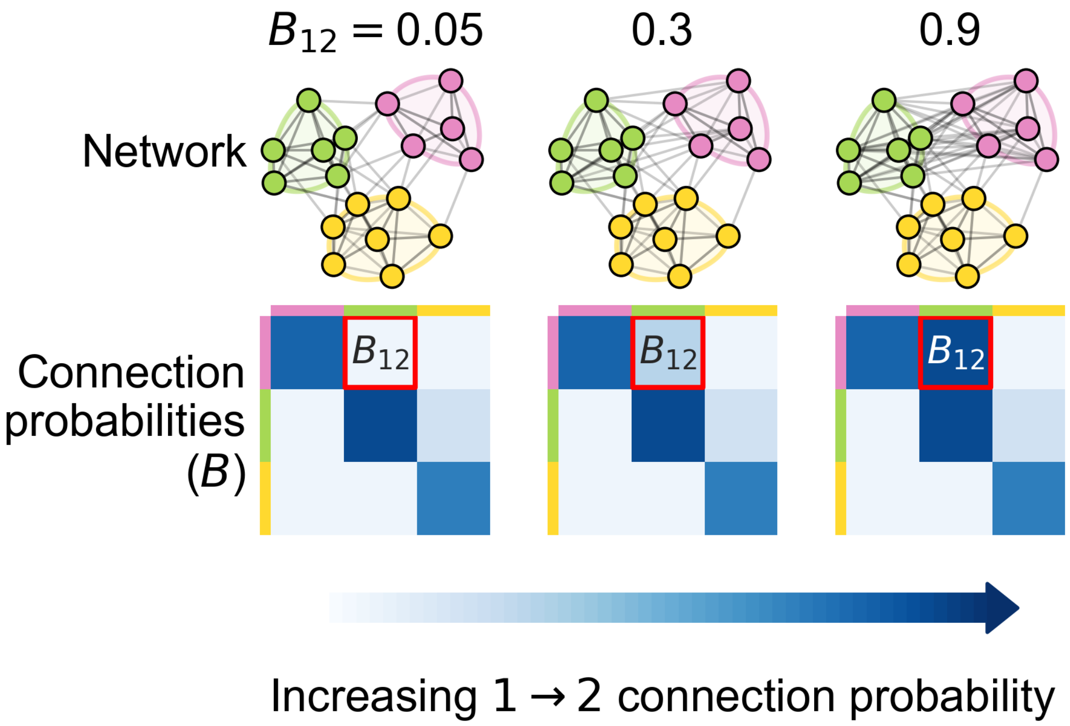
Neurons clustered by connectivity



- Used a variation on spectral clustering
- How many clusters to include?

Winding, Pedigo et al. Science (2023)

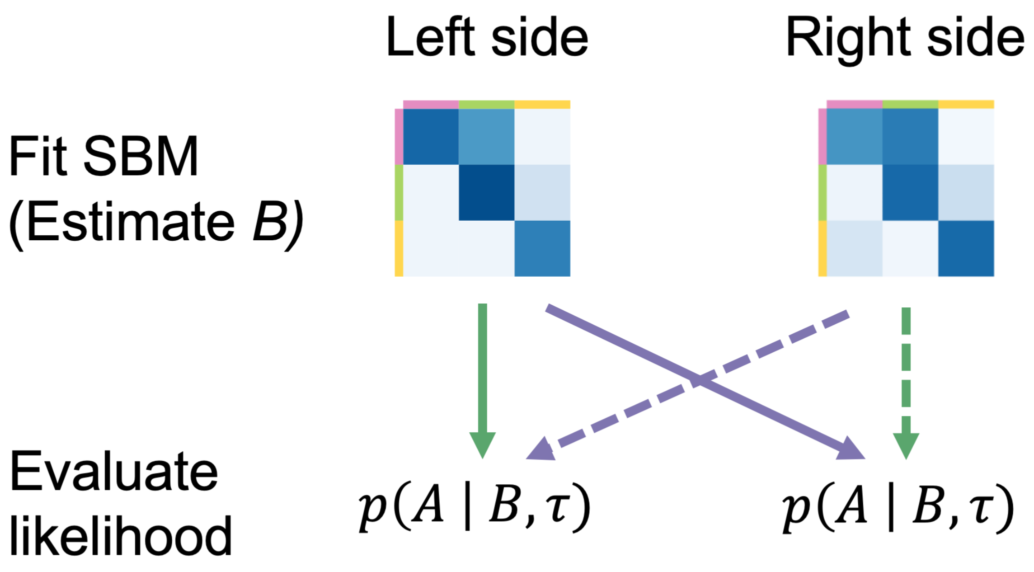
Stochastic block model

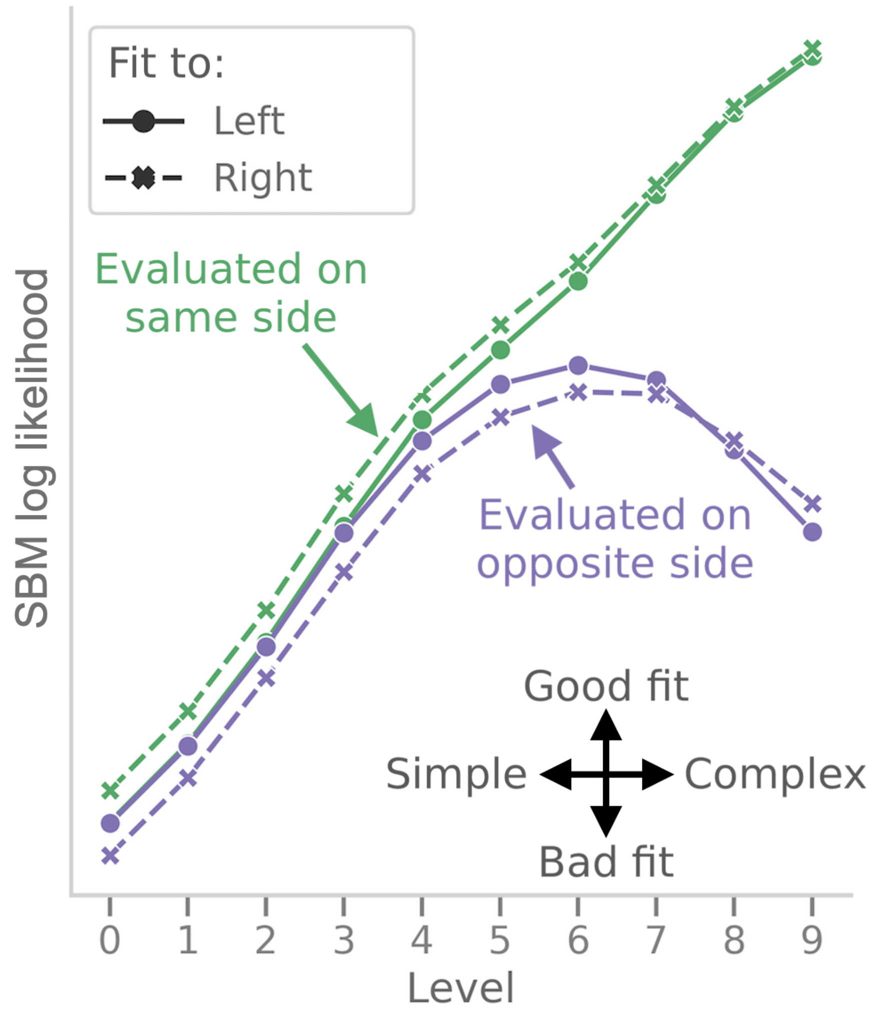


- Each node i is assigned to a group, τ_i
- B is a matrix of connection probabilities between groups
- Edges generated independently according to these probabilities:
  - $A_{ij} \sim Bernoulli(B_{\tau_i \tau_j})$

Using models to evaluate candidate groupings

- How well do these models generalize to the other side of the brain (let alone the next maggot)?





Bilateral symmetry

> "This brain is bilaterally symmetric."

> "What does that even mean? And how would we know if it wasn't?"

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

- Hints at how sterotyped wiring might be
- Testbed for connectome comparison methods

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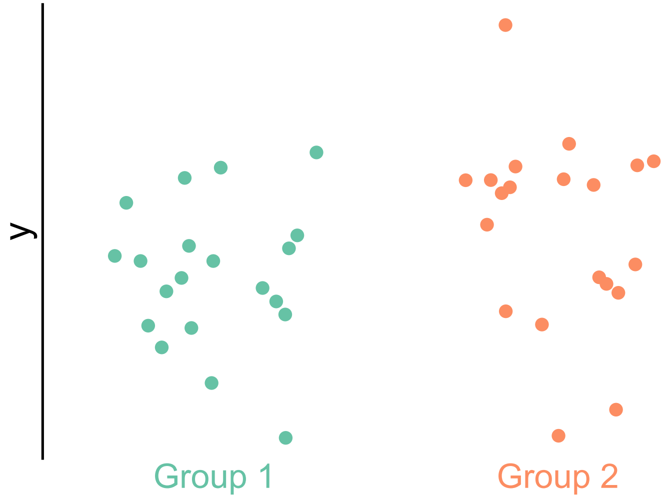
Testing for differences

Are these two populations different?



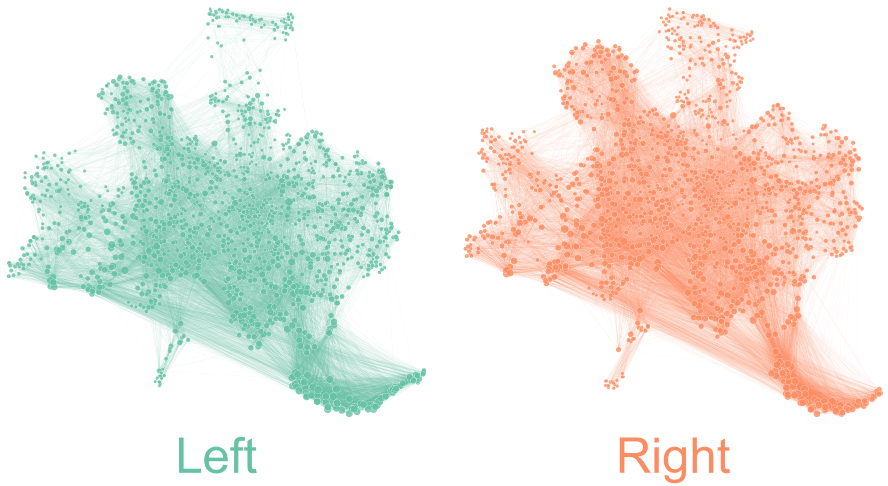
$$Y^{(1)} \sim F^{(1)} \quad Y^{(2)} \sim F^{(2)}$$

$$H_0 : F^{(1)} = F^{(2)}$$

vs.

$$H_A : F^{(1)} \neq F^{(2)}$$

Are these two *networks* different?



$$A^{(L)} \sim F^{(L)} \quad A^{(R)} \sim F^{(R)}$$

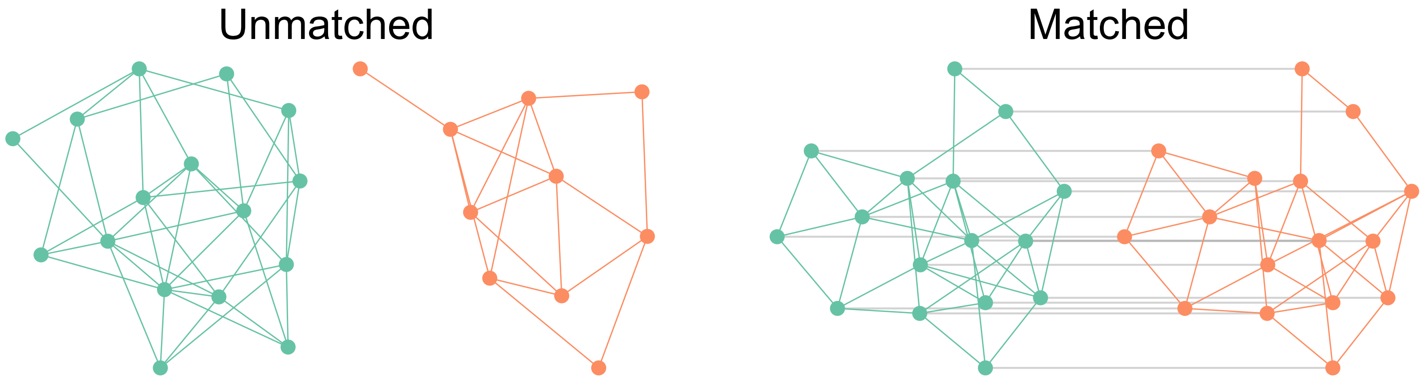
$$H_0 : F^{(L)} = F^{(R)}$$

vs.

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

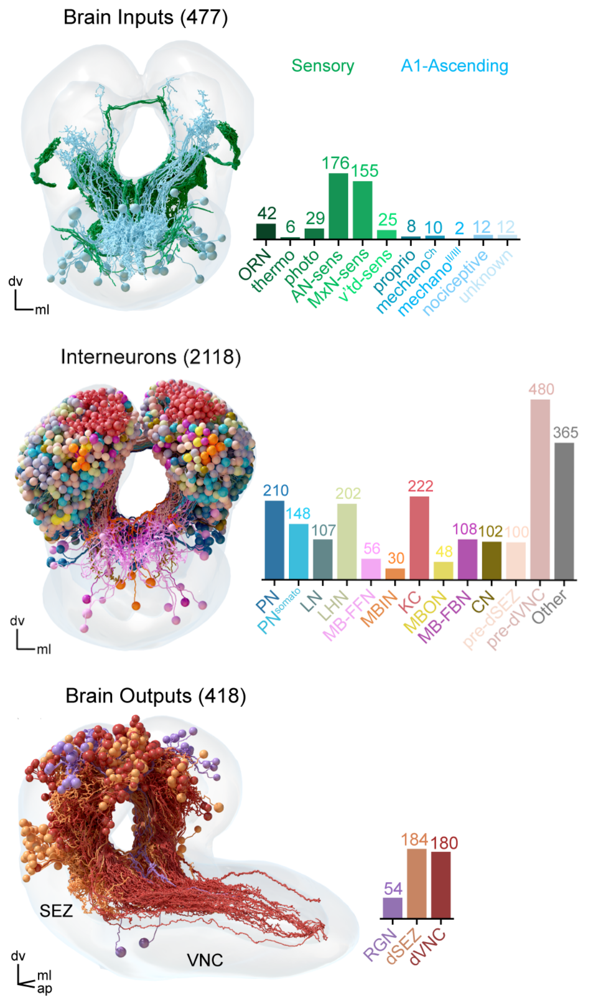
Assumptions

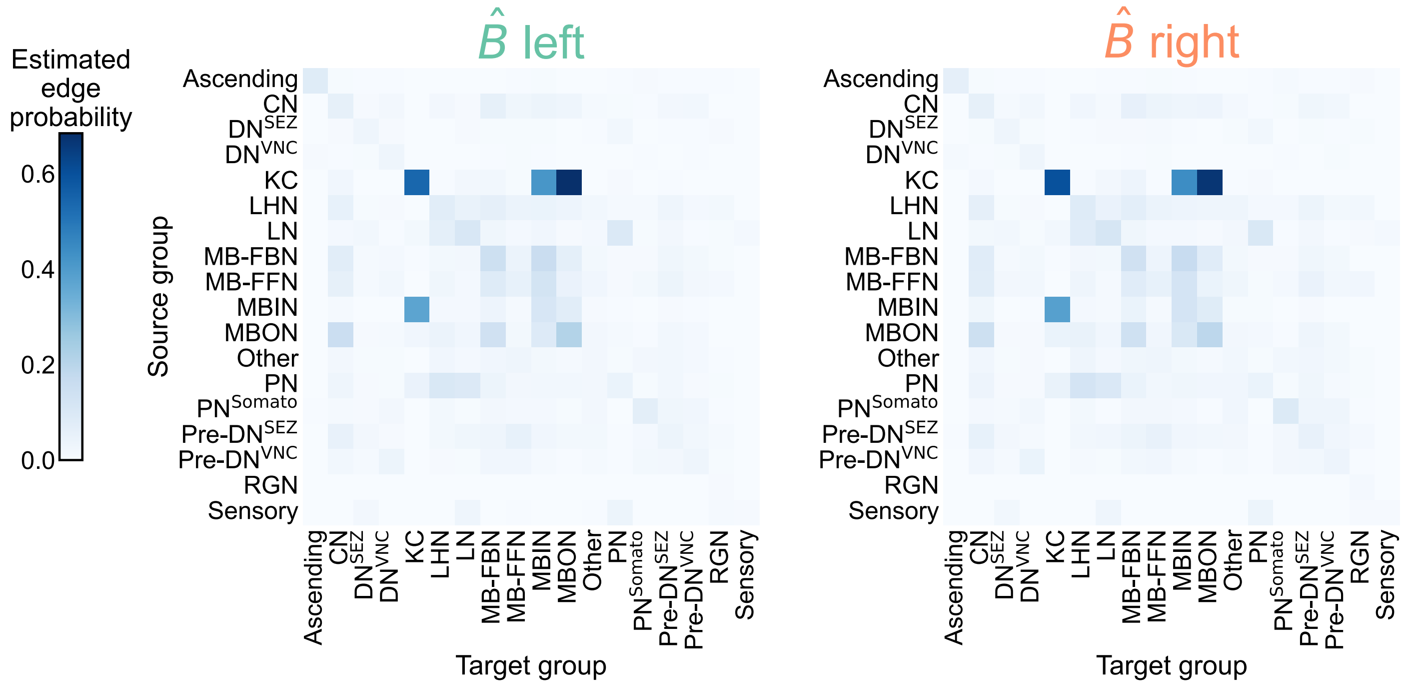
- Know the direction of synapses, so network is *directed*
- Consider networks to be *unweighted*
- Not assuming any nodes are matched:



- If F is again a stochastic block model, then...

Connection probabilities between groups

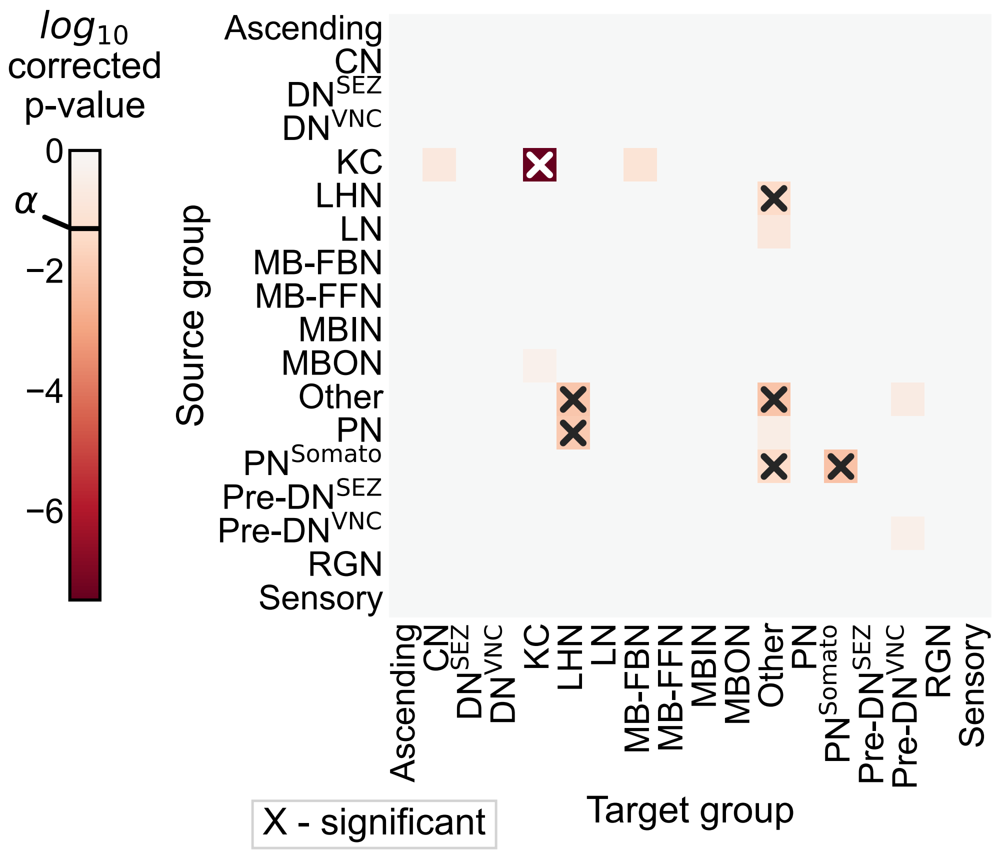




Detect differences in group connection probabilities

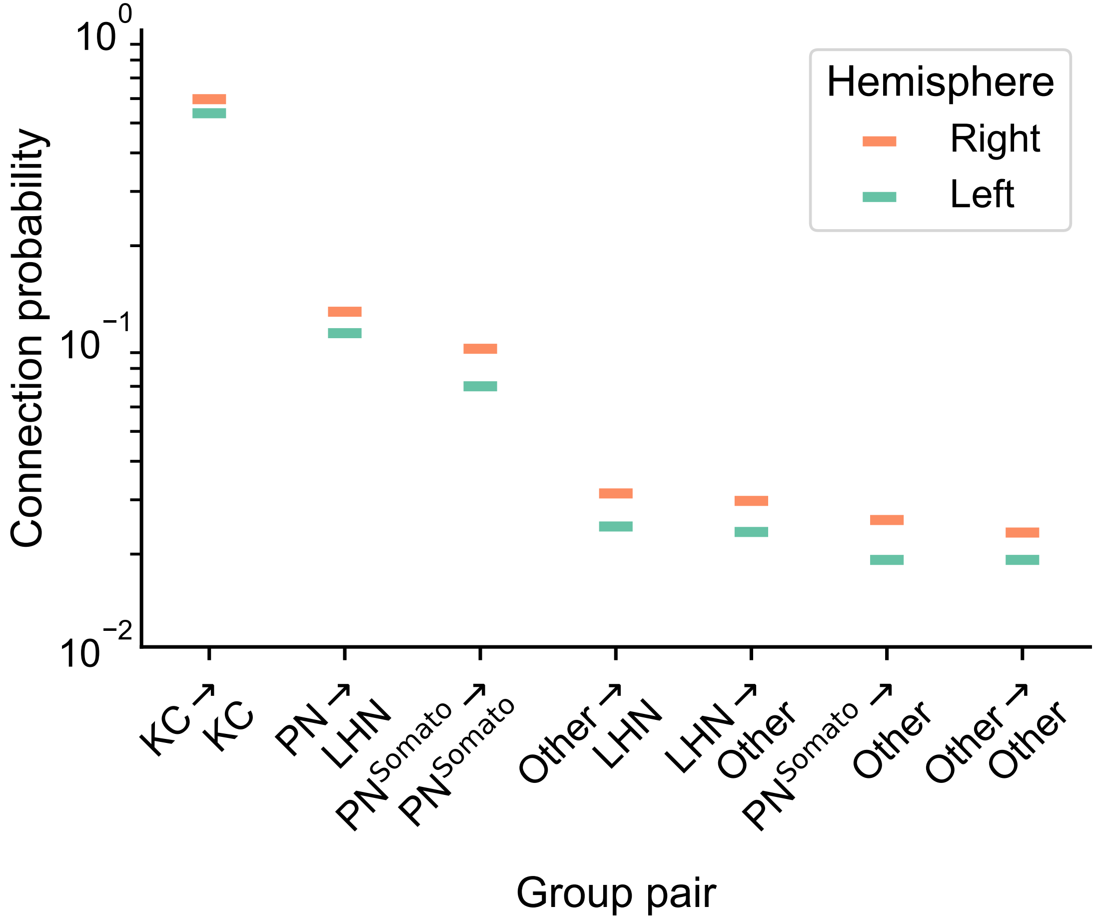
- Overall test (comparing all blocks):
  $H_0 : B^{(L)} = B^{(R)}$
  p-value $< 10^{-7}$
- 7 group-to-group connections are significantly different (after multiple comparisons correction)

$H_0 : B^{(L)}_{kl} = B^{(R)}_{kl}$

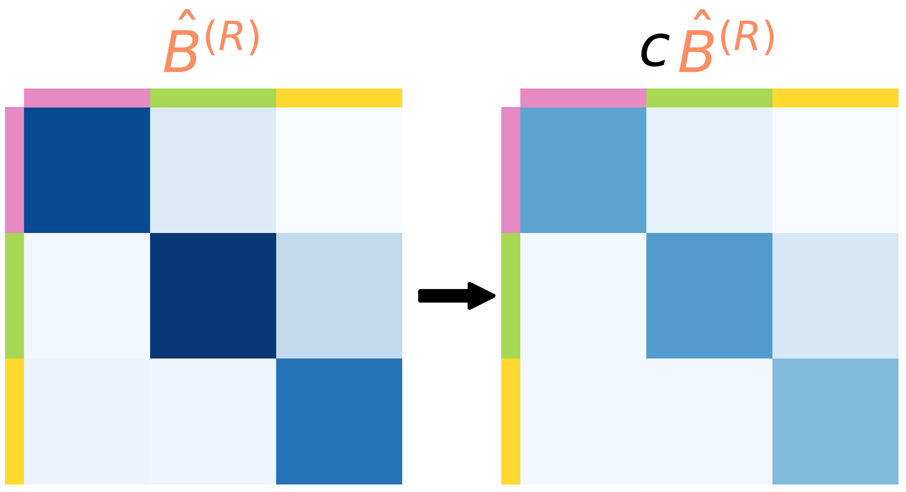


An overall difference in density

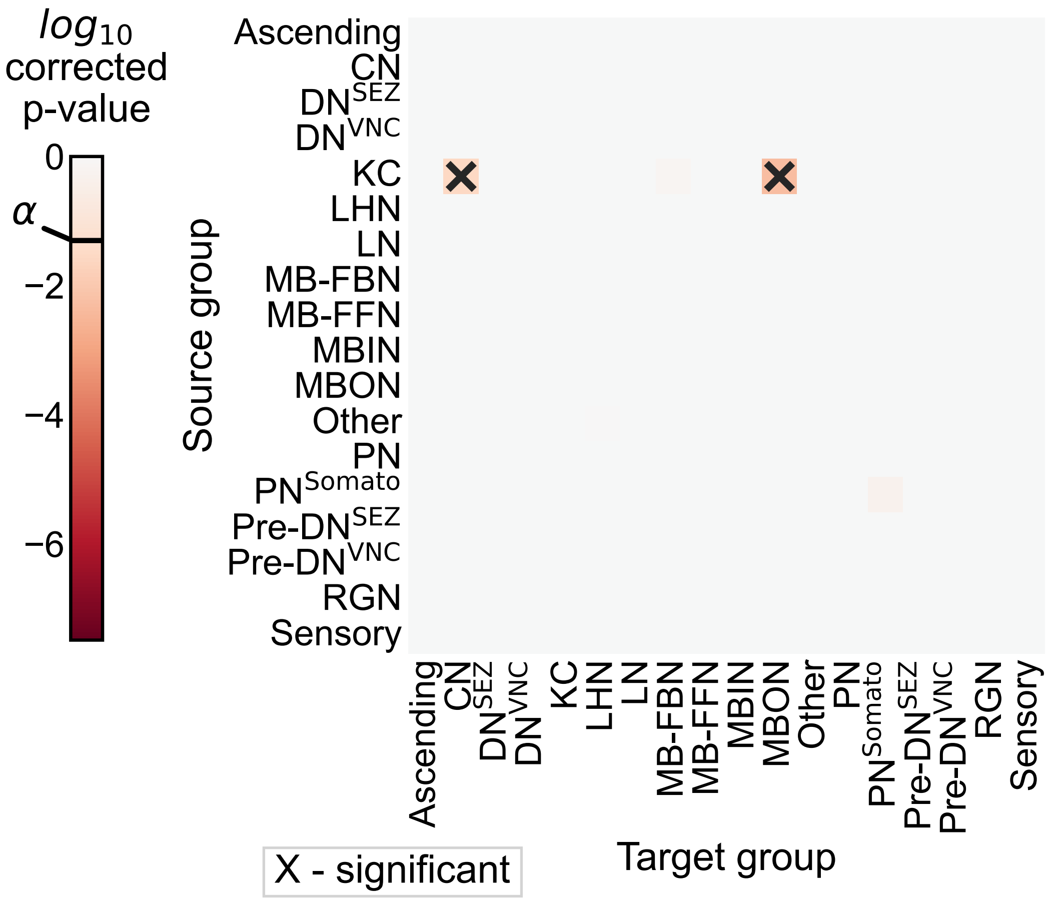
- For significant comparisons, probabilities on right side are higher
- Even network densities are different (1-block/Erdos-Renyi model)
- Maybe the right is just a "scaled up" version of the left?
  - $H_0 : B^{(L)} = cB^{(R)}$
    c is a density-adjusting constant



After adjusting for density, differences are in KCs



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



Overall p-value: $< 10^{-2}$

To sum up...

> "This brain is bilaterally symmetric."

Depends on what you mean...

With Kenyon cells

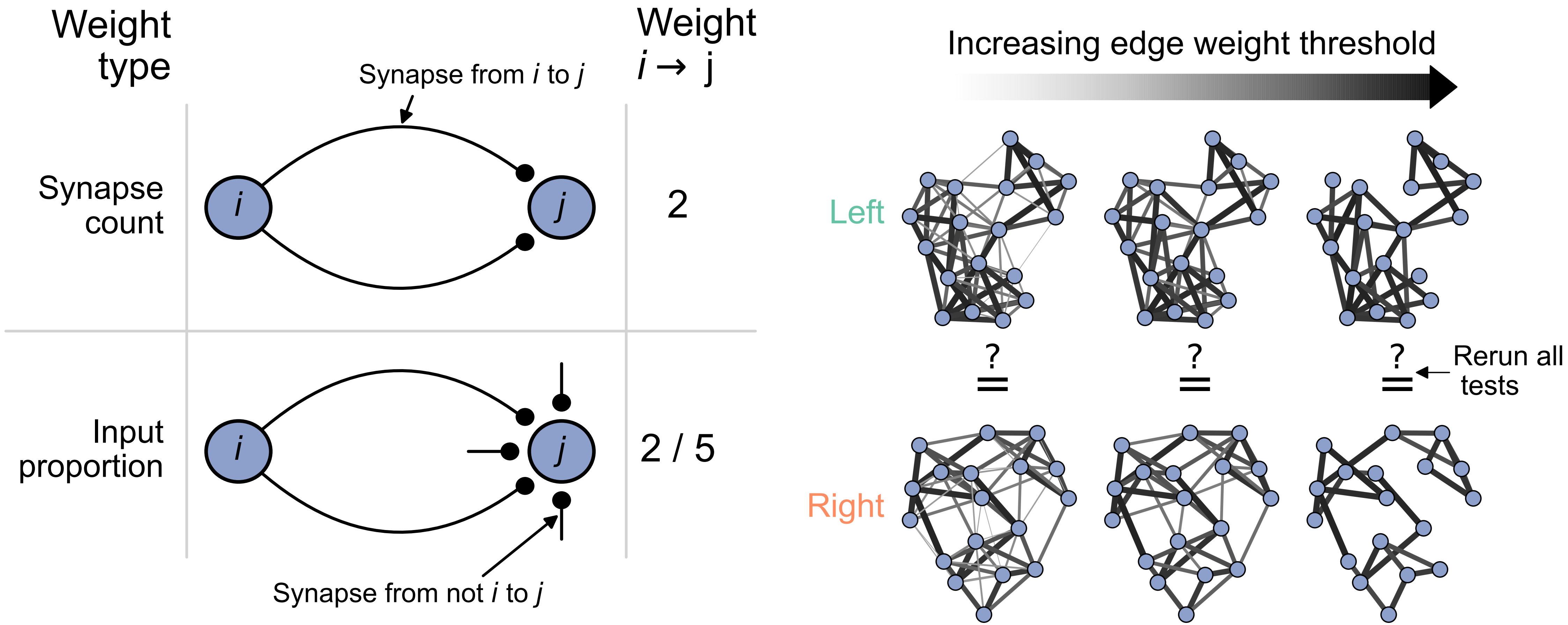
Model	H_0 (vs. $H_A \neq$)	p-value
ER	$p^{(L)} = p^{(R)}$	$<10^{-23}$
SBM	$B^{(L)} = B^{(R)}$	$<10^{-7}$
daSBM	$B^{(L)} = cB^{(R)}$	$<10^{-2}$

Without Kenyon cells

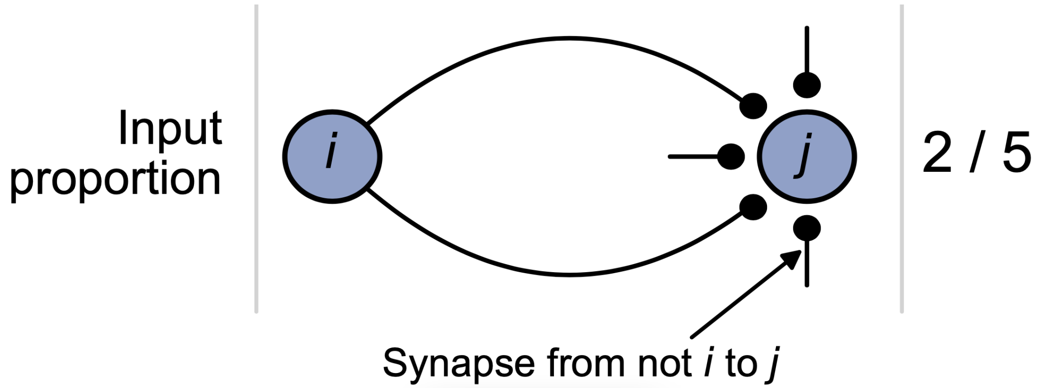
Model	H_0 (vs. $H_A \neq$)	p-value
ER	$p^{(L)} = p^{(R)}$	$<10^{-26}$
SBM	$B^{(L)} = B^{(R)}$	$<10^{-2}$
daSBM	$B^{(L)} = cB^{(R)}$	≈ 0.60

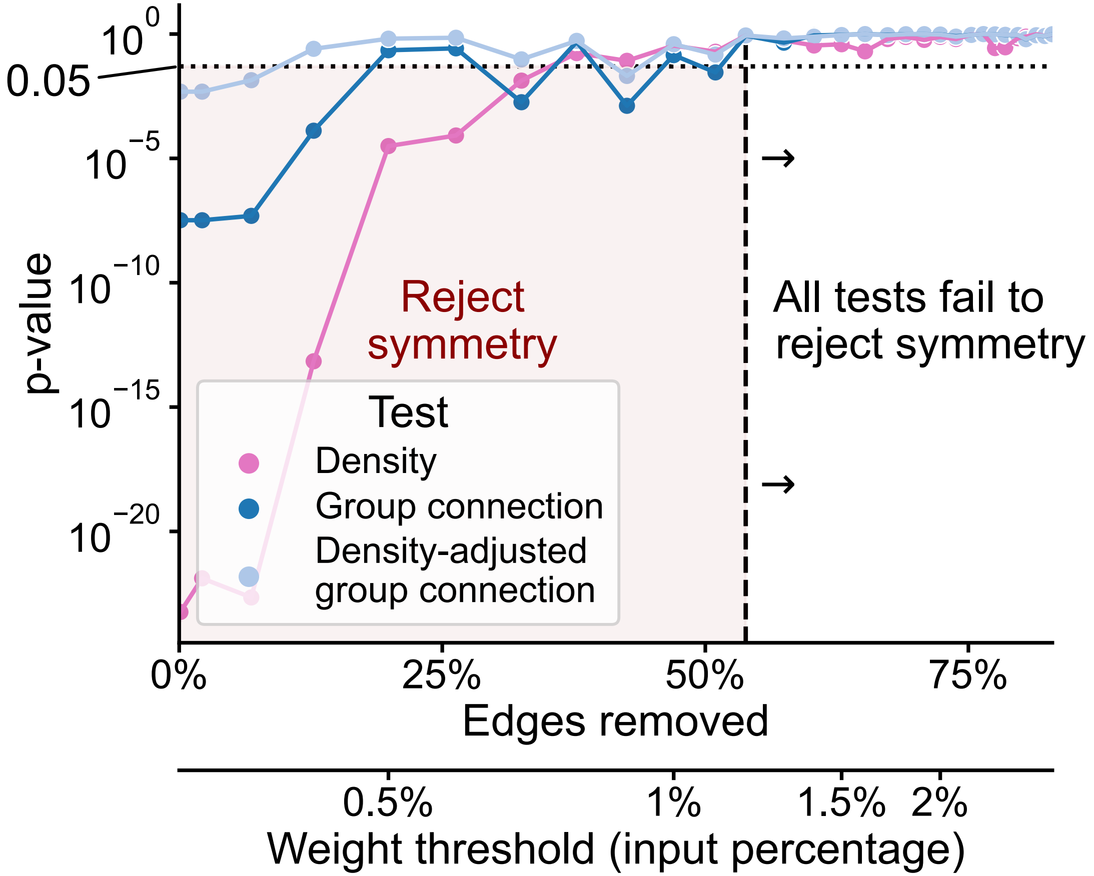
Pedigo et al. eLife (2023)

Examining the effect of edge weights



High input percentage networks show no asymmetry





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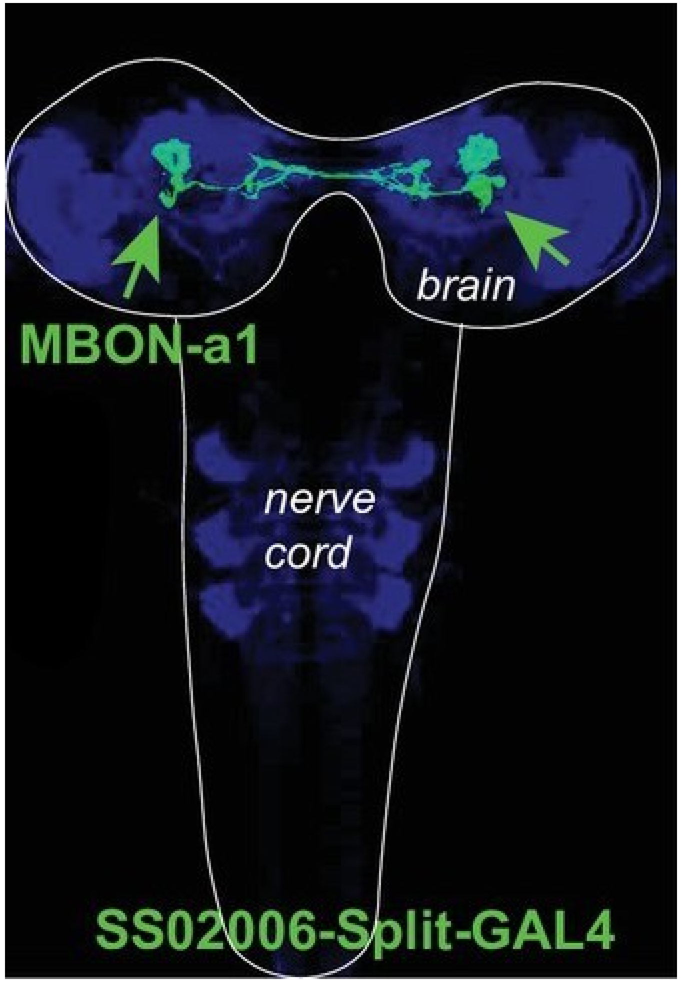
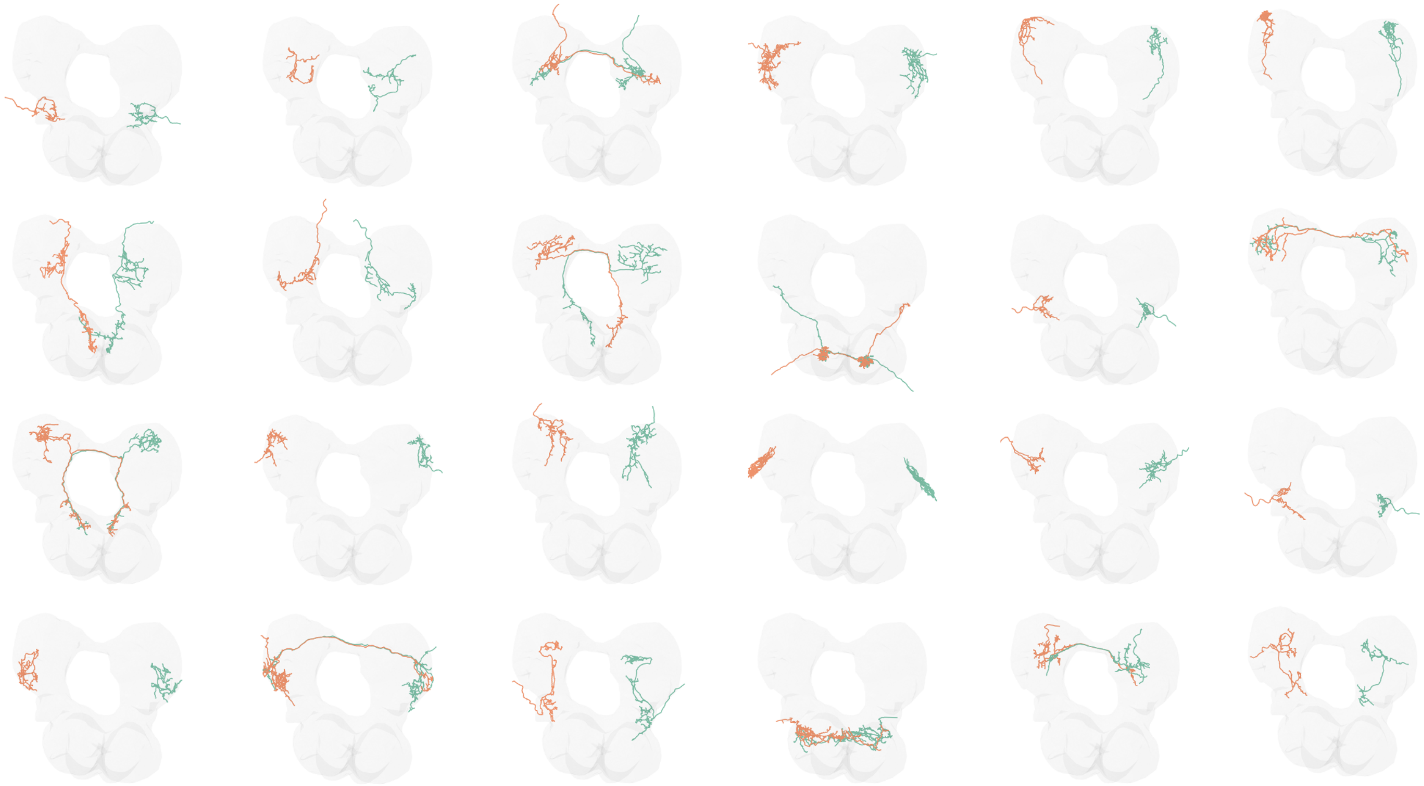
Bilaterally homologous neuron pairs

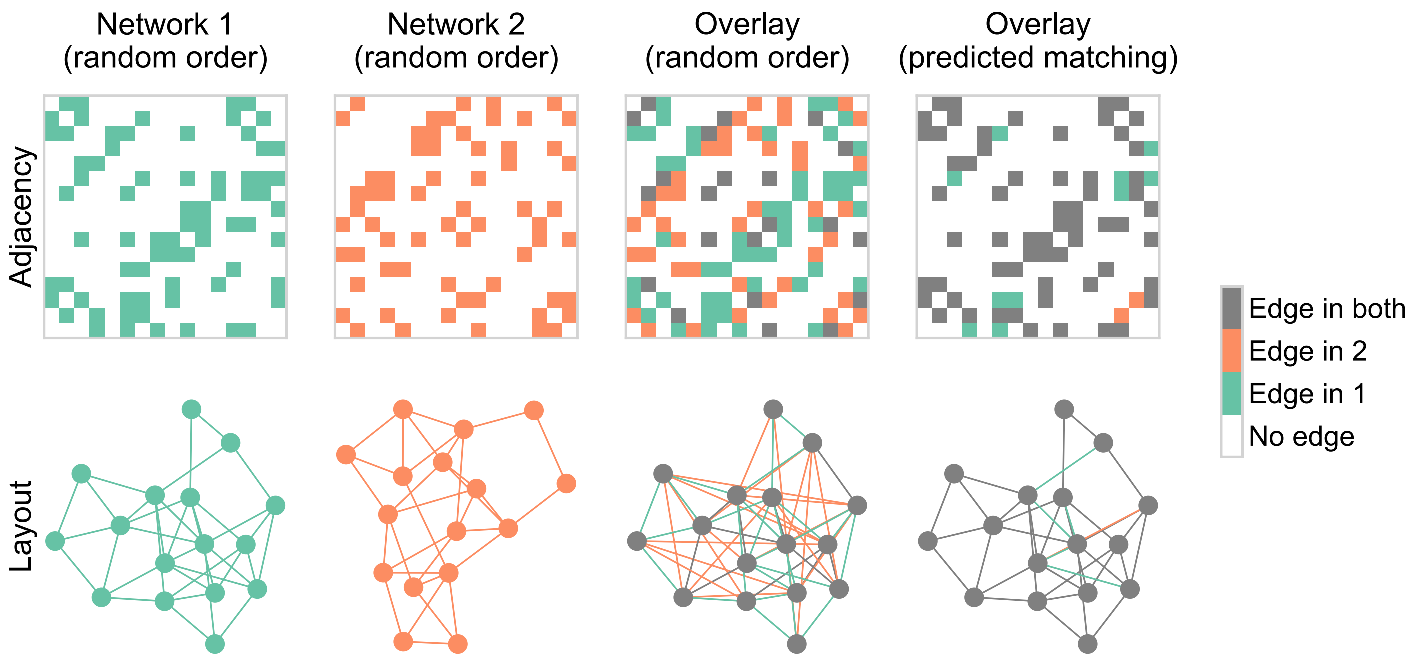




left neuron
right neuron

Eschbach et al. eLife (2021), Winding, Pedigo et al. Science (2023)

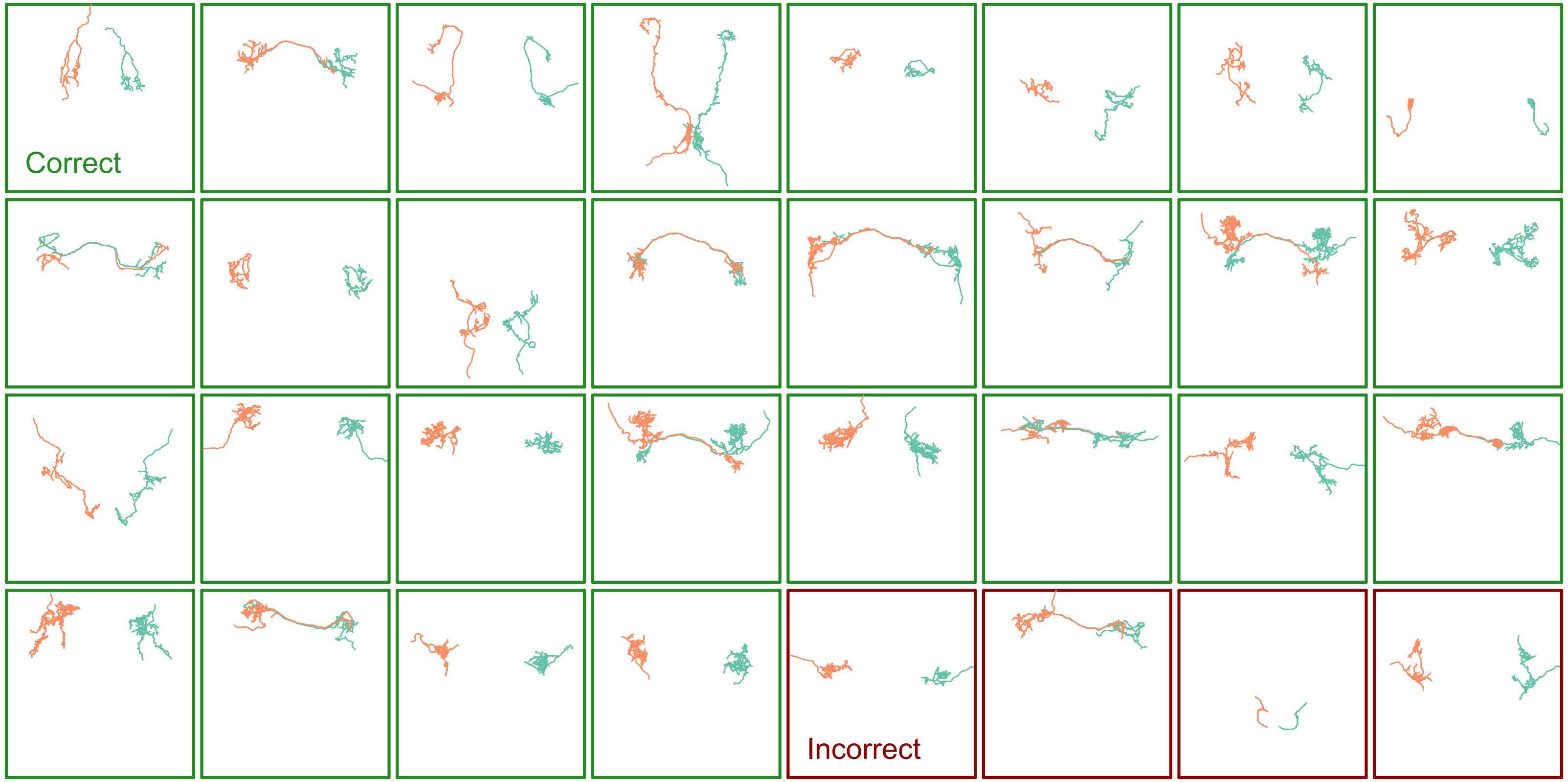
How can we pair on connectivity?



$$\min_{P \in \mathcal{P}} \underbrace{\| A_1 - \overbrace{P A_2 P^T}^{\text{reordered } A_2} \|_F^2}_{\text{distance between adj. mats.}}$$

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

Simple matching performs fairly well

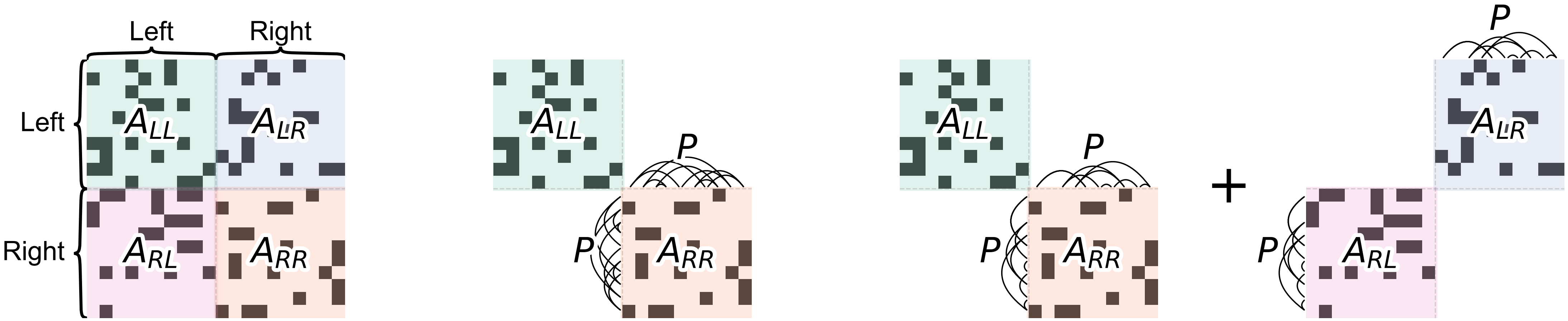


With "vanilla" graph matching: ~80% correct (according to expert annotator)...

but ignores ~1/3 of synapses!

From graph matching to bisected graph matching

Adjacency matrix | Graph matching (GM) | Bisected graph matching (BGM)



Ipsilateral → A_{LL}, A_{RR}
Contralateral → A_{LR}, A_{RL}

$$\min_P ||A_{LL} - P A_{RR} P^T||_F^2$$

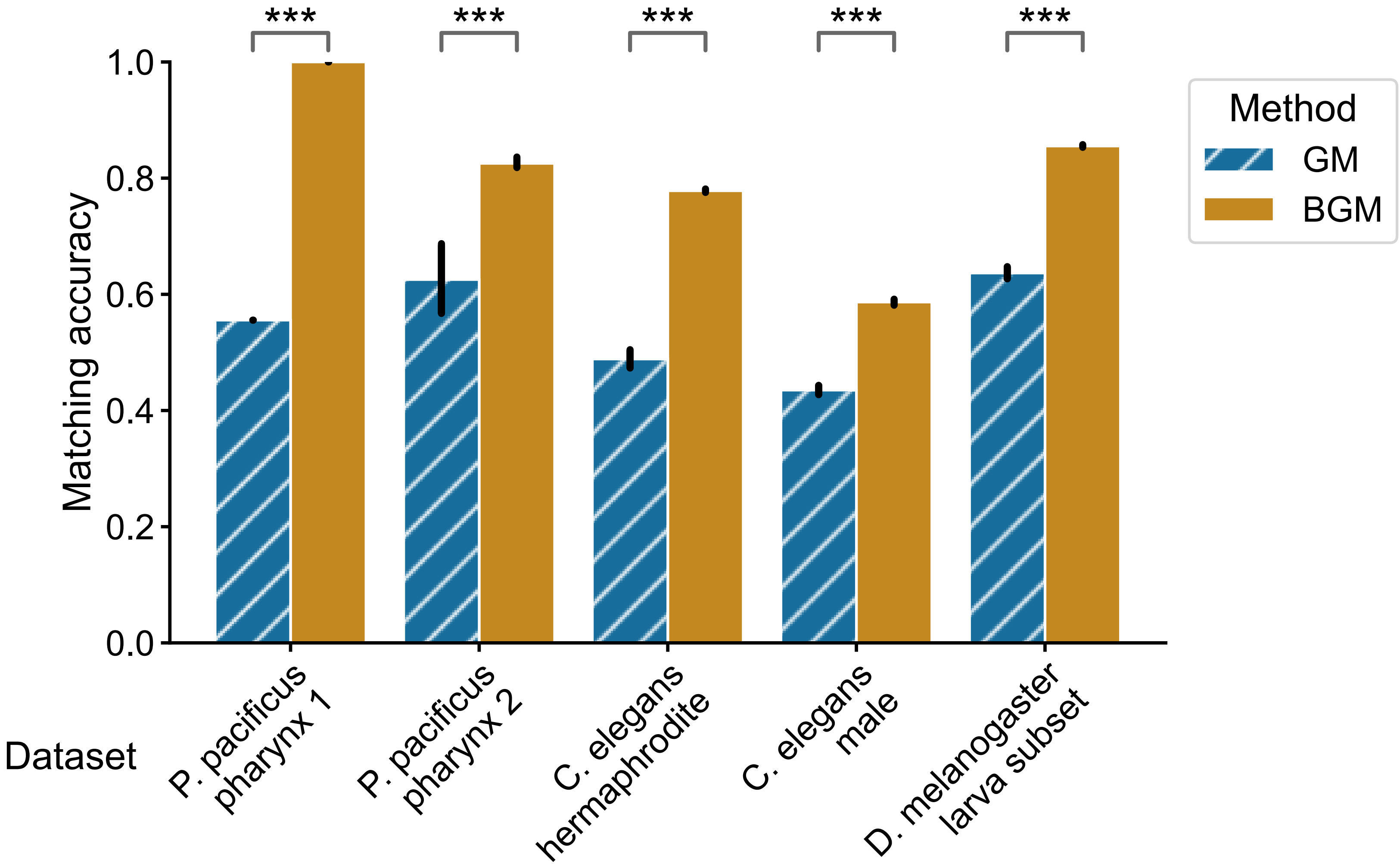
$$\min_P ||A_{LL} - P A_{RR} P^T||_F^2 + ||A_{LR} P^T - P A_{RL}||_F^2$$

We generalized a state-of-the-art GM algorithm to solve BGM!

In simulations, this helps when contralaterals have sufficient edge correlation

Pedigo et al. Network Neuroscience (2022), Vogelstein et al. PLOS One (2015)

Contralateral connections aid matching!



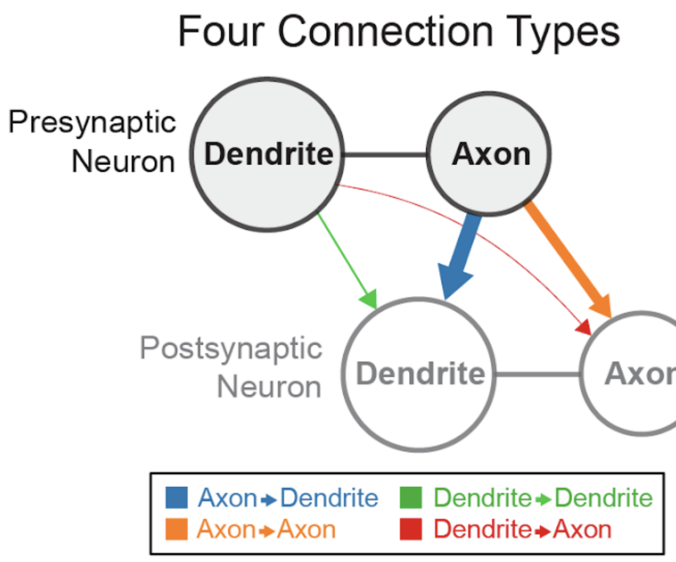
Pedigo et al. Network Neuroscience (2022)

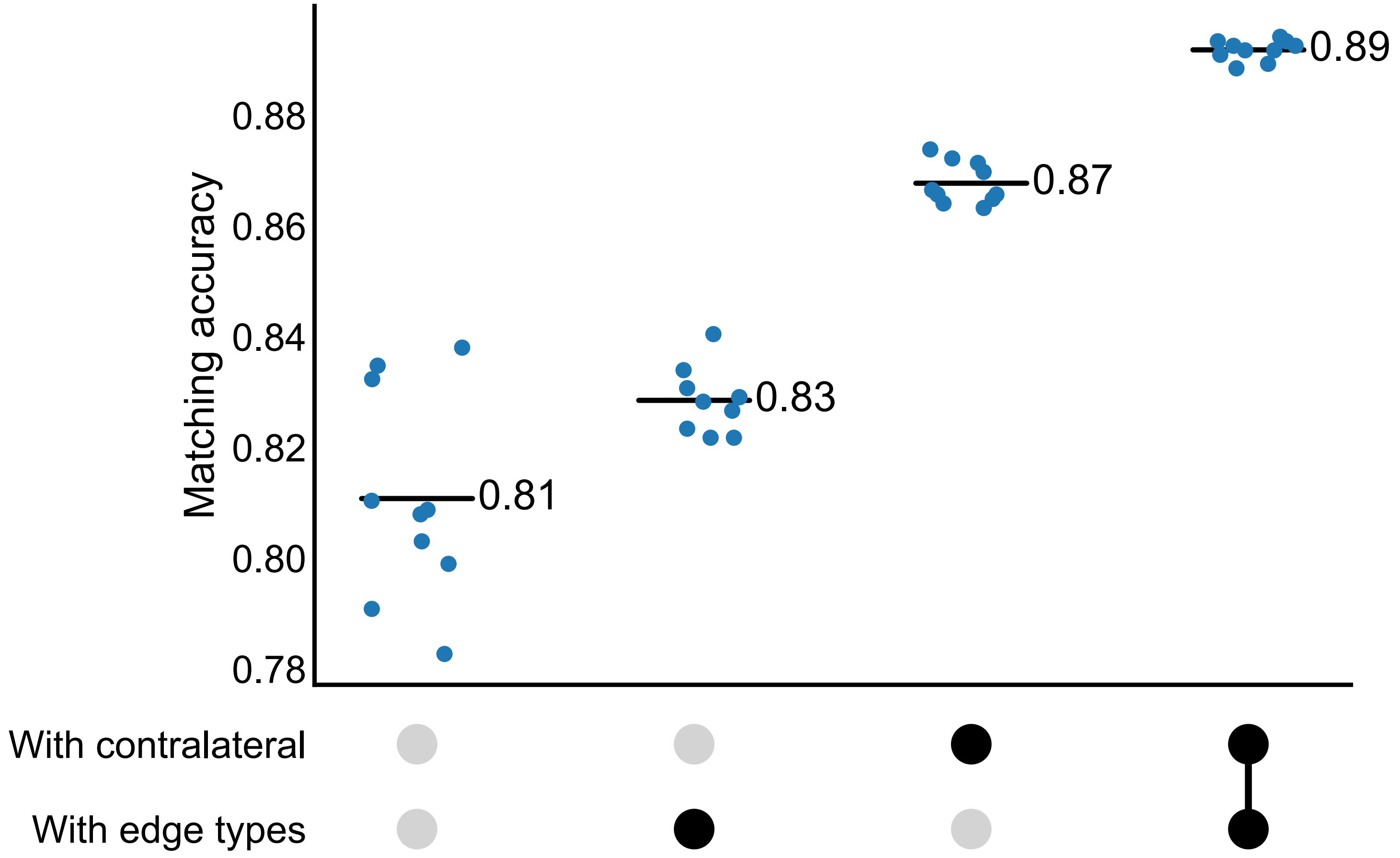
Many other ways to try to improve on matching...

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

Pantazis et al. Applied Network Science (2022), Fishkind et al. Pattern Recognition (2019)

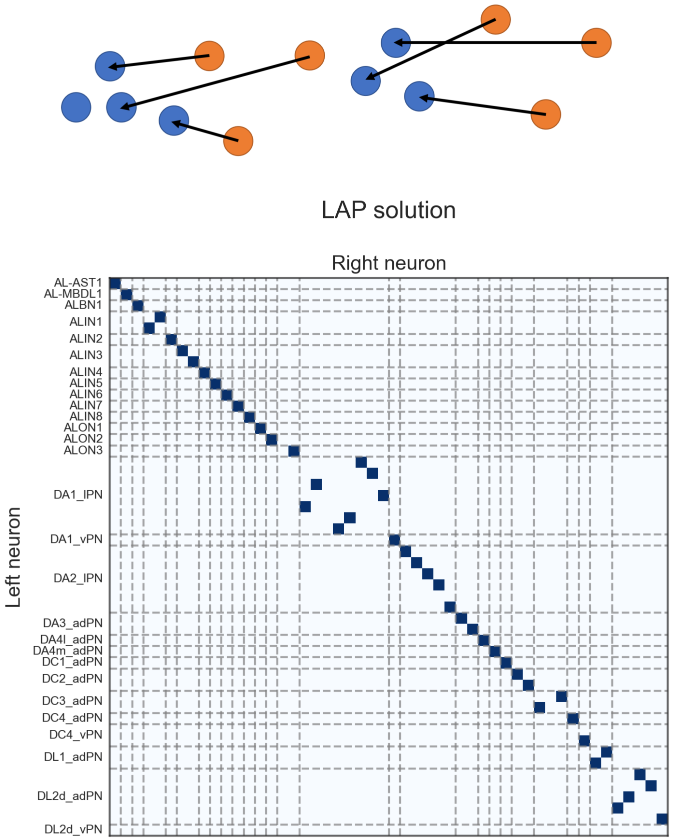
Performance improvement from edge types



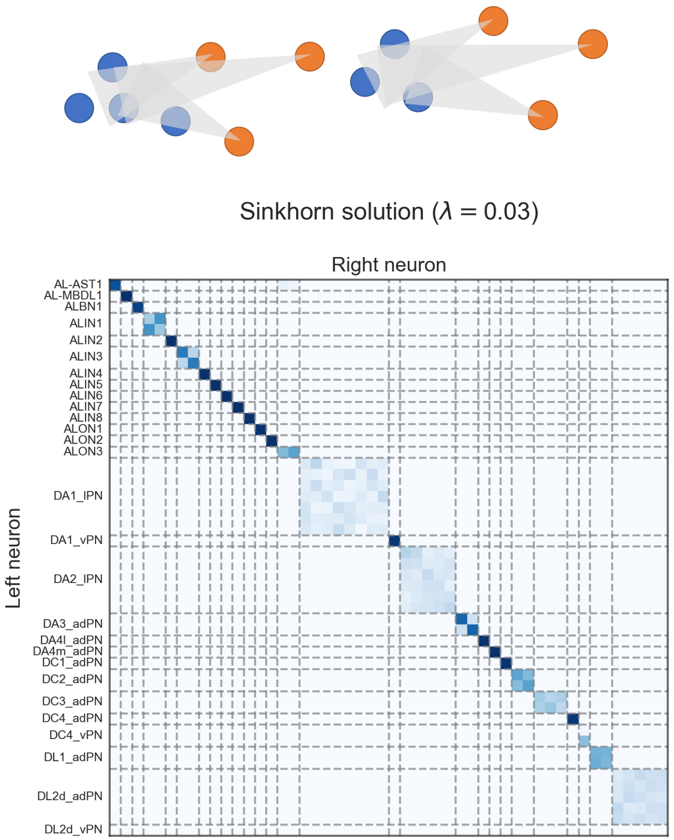


Beyond 1-to-1 neuron matching

1-to-1 matching



Soft assignment



Cuturi NeurIPS (2013), Costa et al. Neuron (2016) - Work with Philipp Schlegel, Greg Jefferis, unpublished

Open source tools

downloads 202k | Stars 305

github.com/microsoft/graspologic

Related publications

Chung, Pedigo et al. JMLR (2019)

Vogelstein et al. Curr. Opin. Neurobio. (2019)

Chung et al. Annual Review of Stats and Its Application (2021)

Application of these tools to larva brain ⇒ github.com/neurodata/graspologic-demo

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- Clustering the larval brain by connectivity
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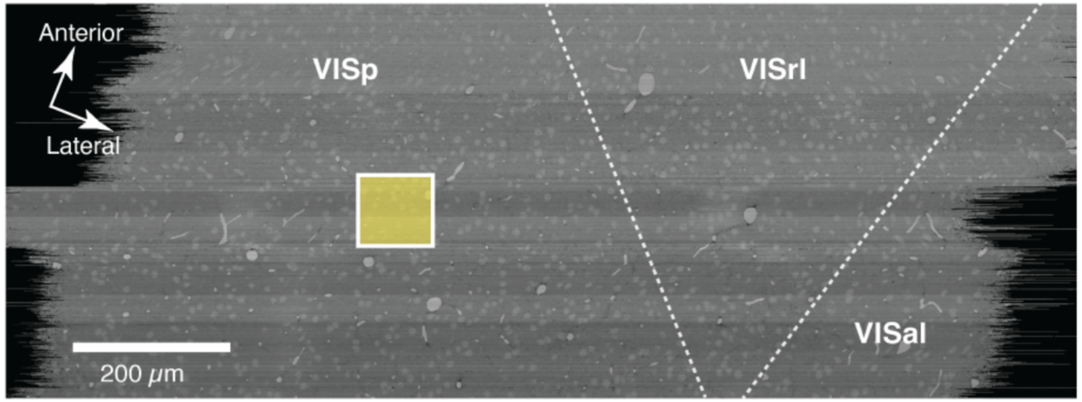
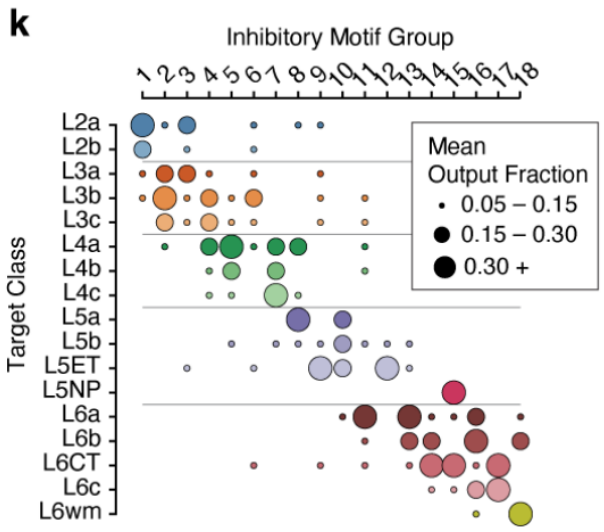
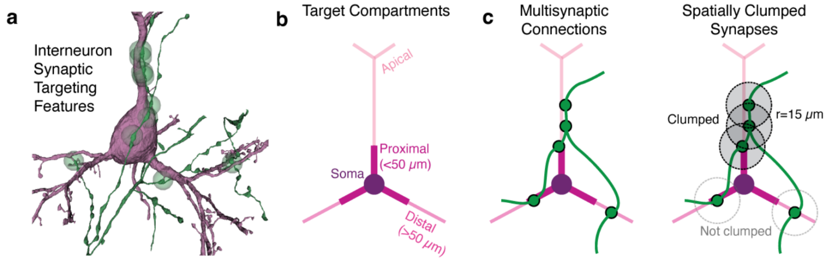
- Future work
    - Understanding stereotypy in cortical wiring diagrams

Do wiring rules generalize across region? Dataset?





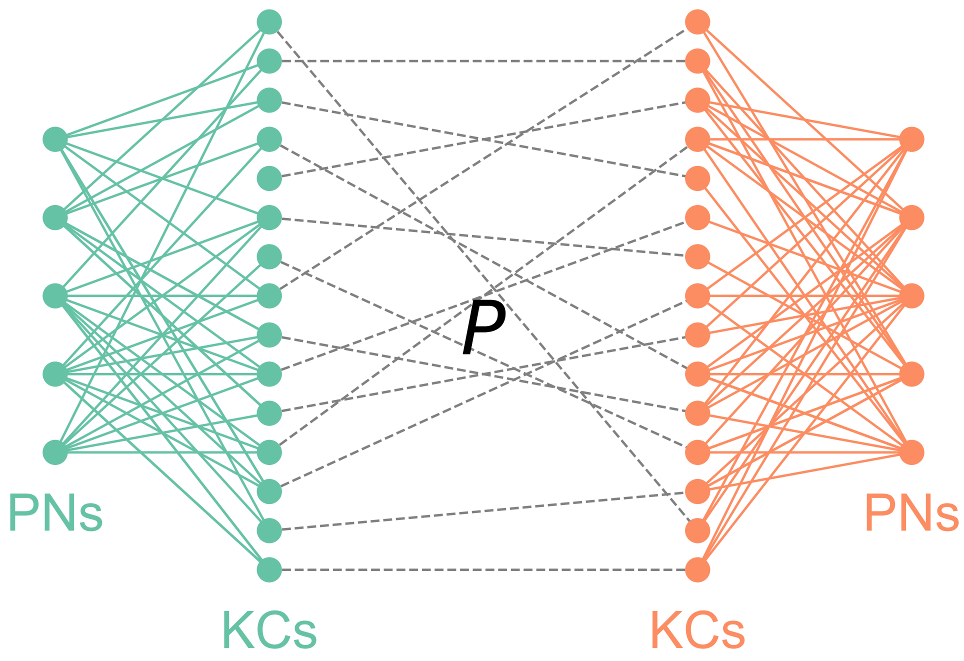
- Application of model-based network comparison tools
- Would likely require extensions:
  - Parameters to deal with subcellular wiring specificity

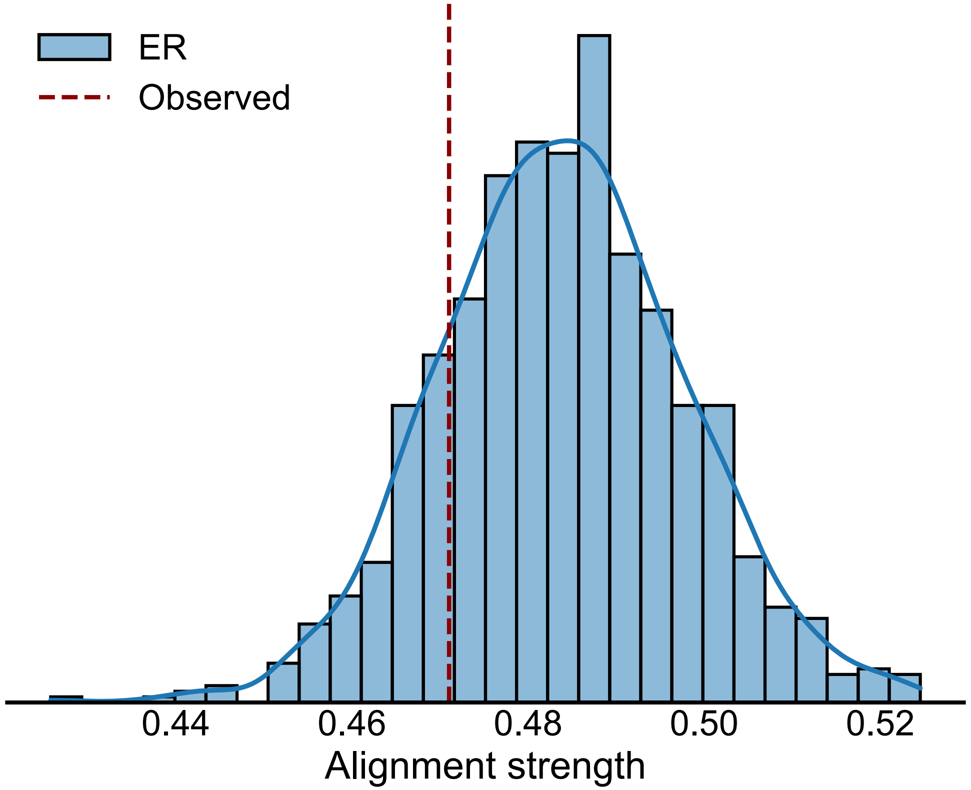


  - Modeling known errors (e.g. amount of orphan synapses)

Stereotypy beyond connection probabilities

Matching and null models can be combined to test for significant subgraph correlation in edge structure





Eichler et al. Nature (2017), Fishkind et al. Applied Network Science (2021)

My interest in Allen/EM Connectomics team

- Interested in translating neuroscience/connectomics questions into something we can test with data science techniques
- Scaling to larger problems, team science approach
- Open data and tools

References

Winding, M. & Pedigo, B.D. et al. The connectome of an insect brain. Science (2023).

Pedigo, B. D. et al. Generative network modeling reveals quantitative definitions of bilateral symmetry exhibited by a whole insect brain connectome. eLife (2023).

Pedigo, B. D. et al. Bisected graph matching improves automated pairing of bilaterally homologous neurons from connectomes. Network Neuroscience (2022).

Code

github.com/neurodata/maggot_models

github.com/neurodata/bilateral-connectome

github.com/neurodata/bgm

Acknowledgements

Team

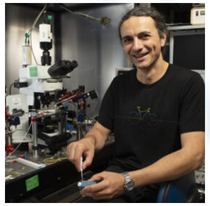
Michael Winding

Mike Powell

Eric Bridgeford

Ali Saad-Eldin

Marta Zlatic



Albert Cardona

Carey Priebe

Joshua Vogelstein

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Questions?

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- bdpedigo.github.io

These slides at:

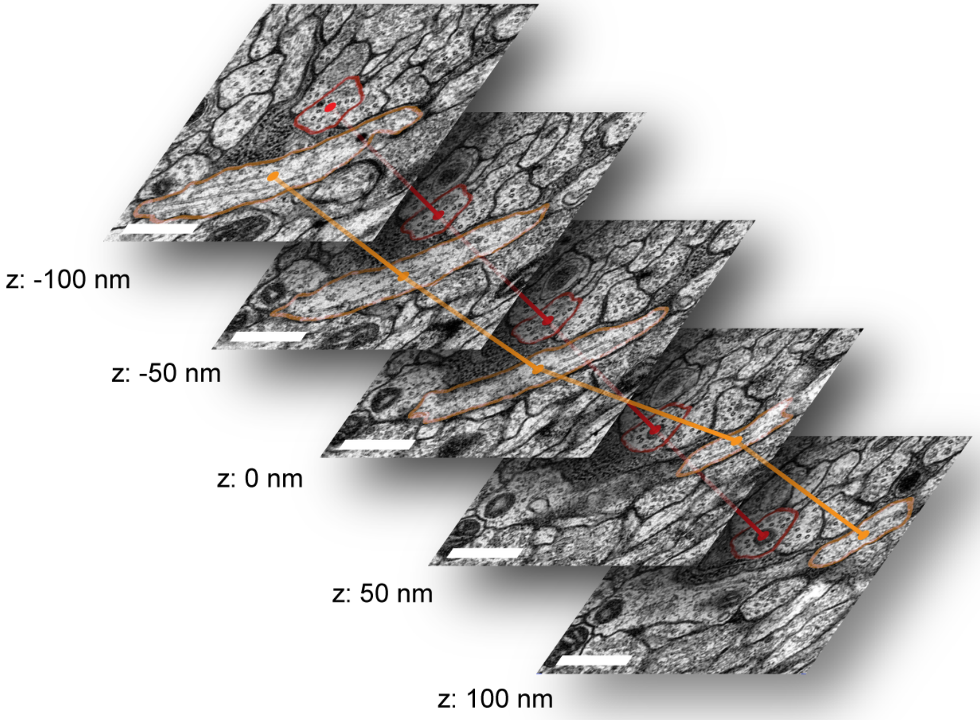
bdpedigo.github.io/talks/aibs.html

Appendix

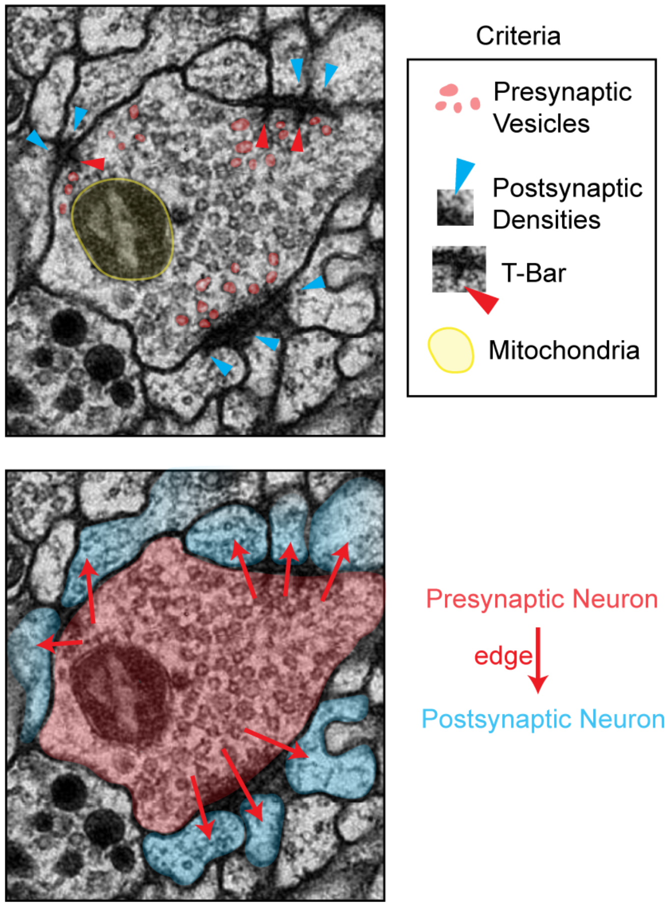
Winding, Pedigo et al. Science (2023)

Mapping a larval *Drosophila* brain connectome

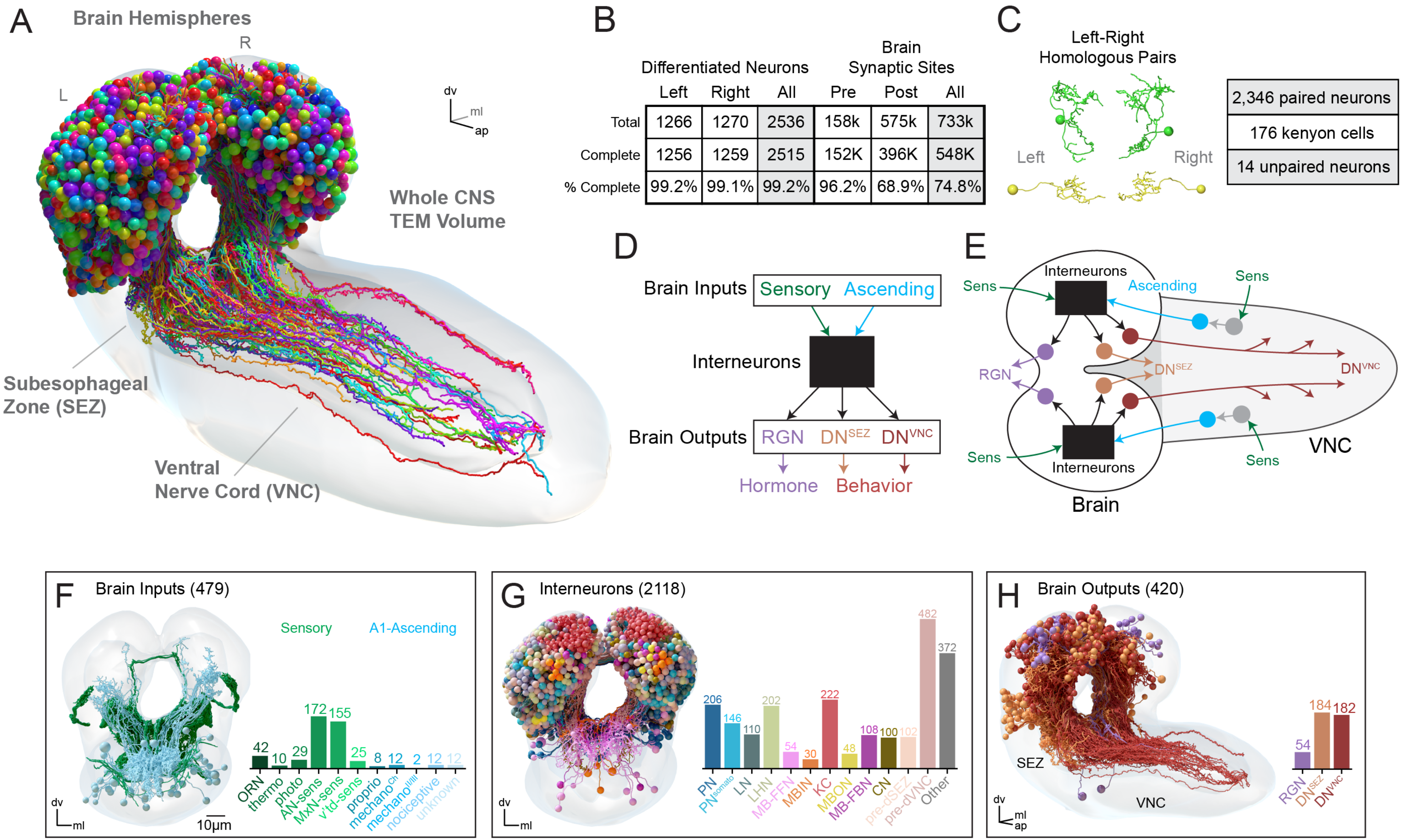
Manual Reconstruction of Arbors



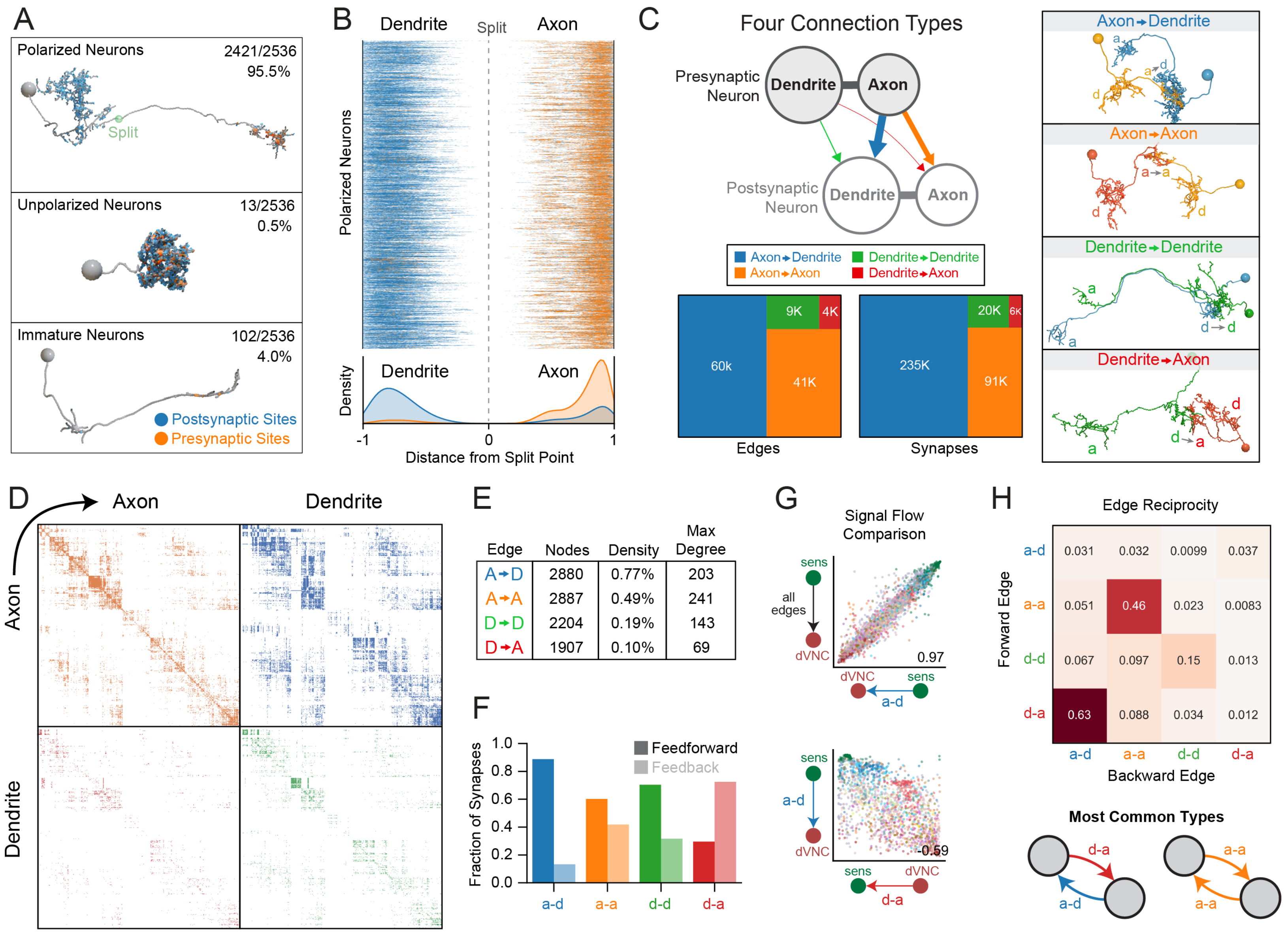
Synapse Annotation



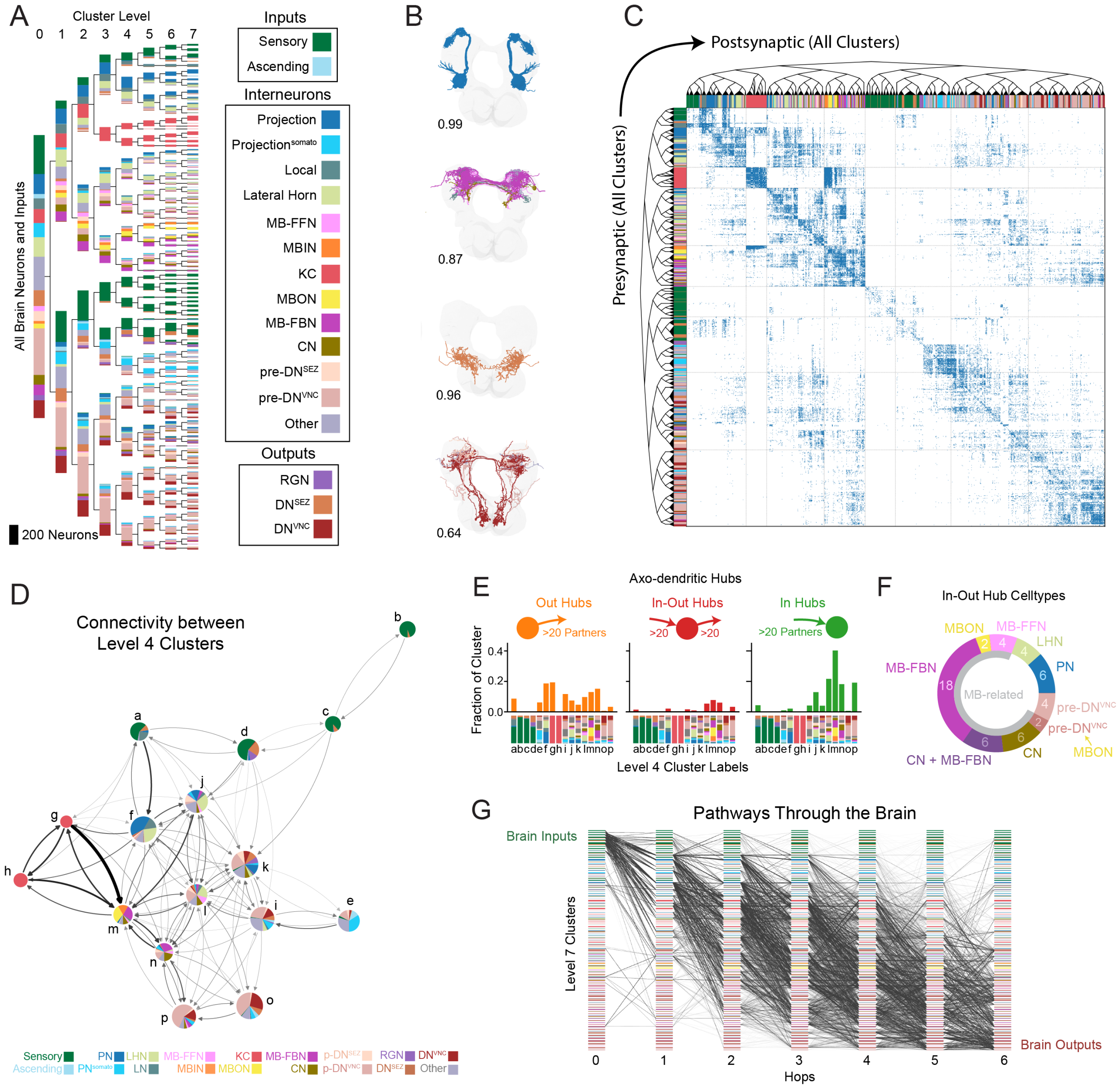
Winding, Pedigo et al. Science (2023), Ohyama et al. Nature (2015)

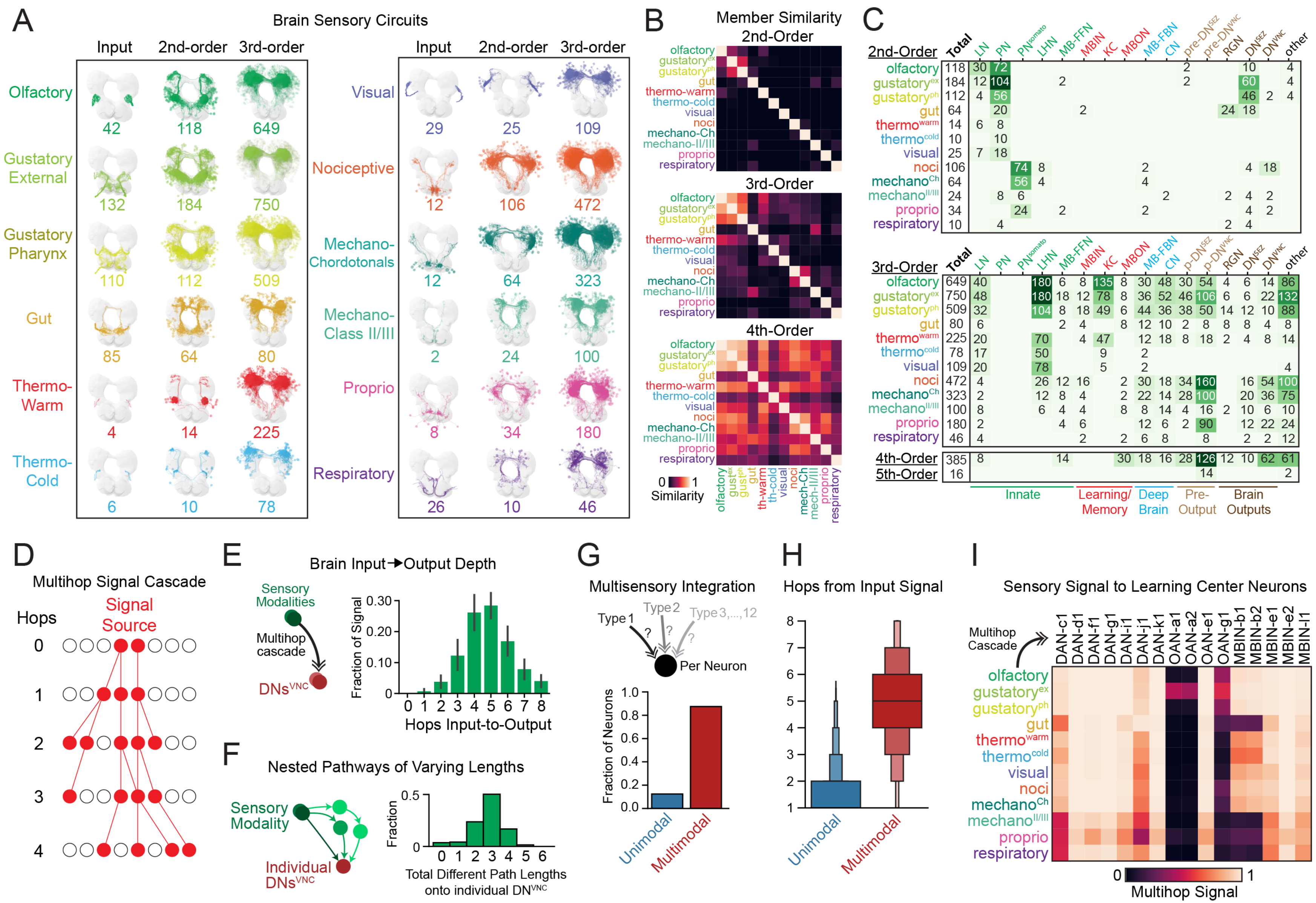


	Differentiated Neurons			Brain Synaptic Sites		
	Left	Right	All	Pre	Post	All
Total	1266	1270	2536	158k	575k	733k
Complete	1256	1259	2515	152K	396K	548K
% Complete	99.2%	99.1%	99.2%	96.2%	68.9%	74.8%

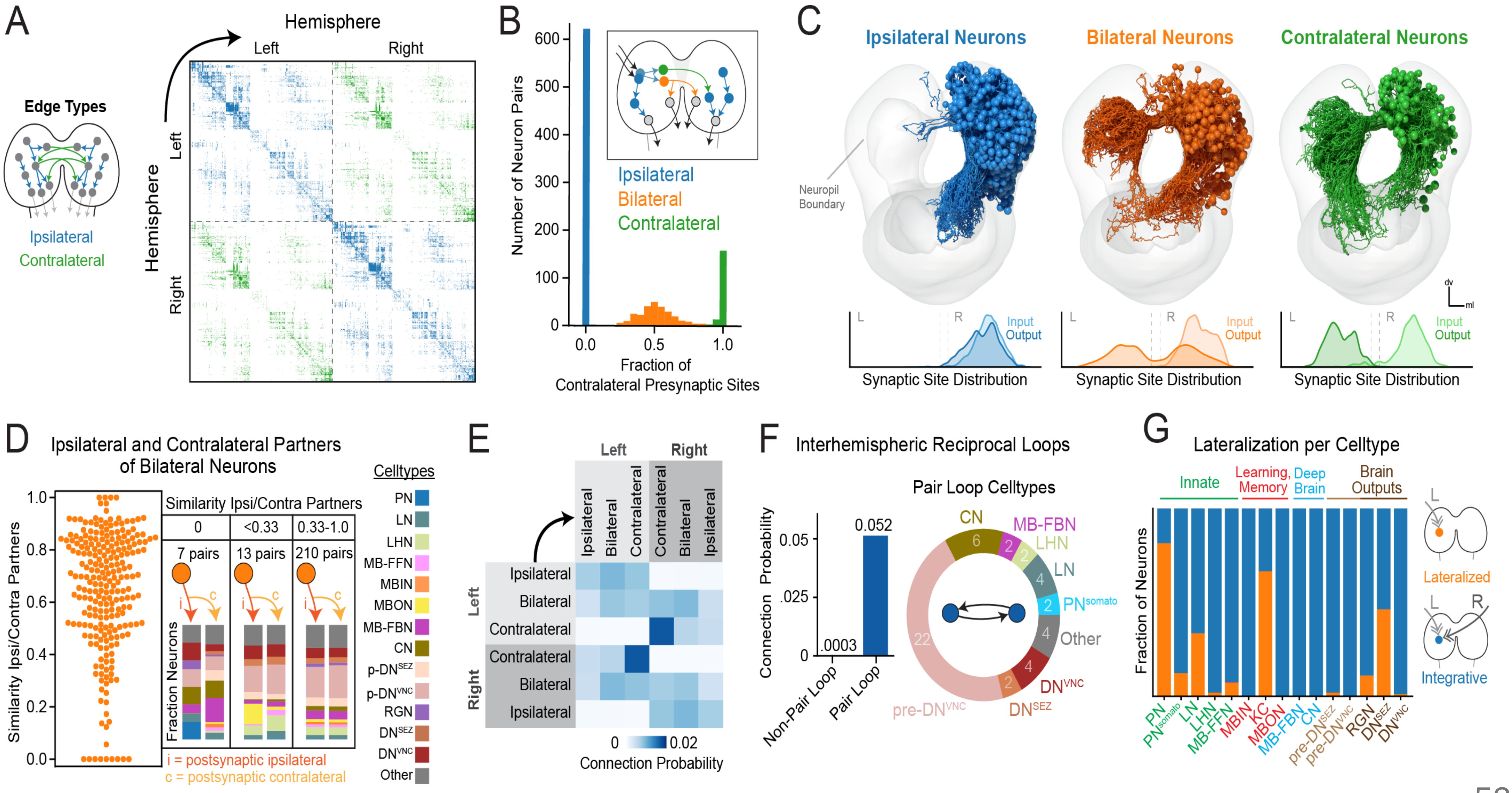


Edge	Nodes	Density	Max Degree
A→D	2880	0.77%	203
A→A	2887	0.49%	241
D→D	2204	0.19%	143
D→A	1907	0.10%	69

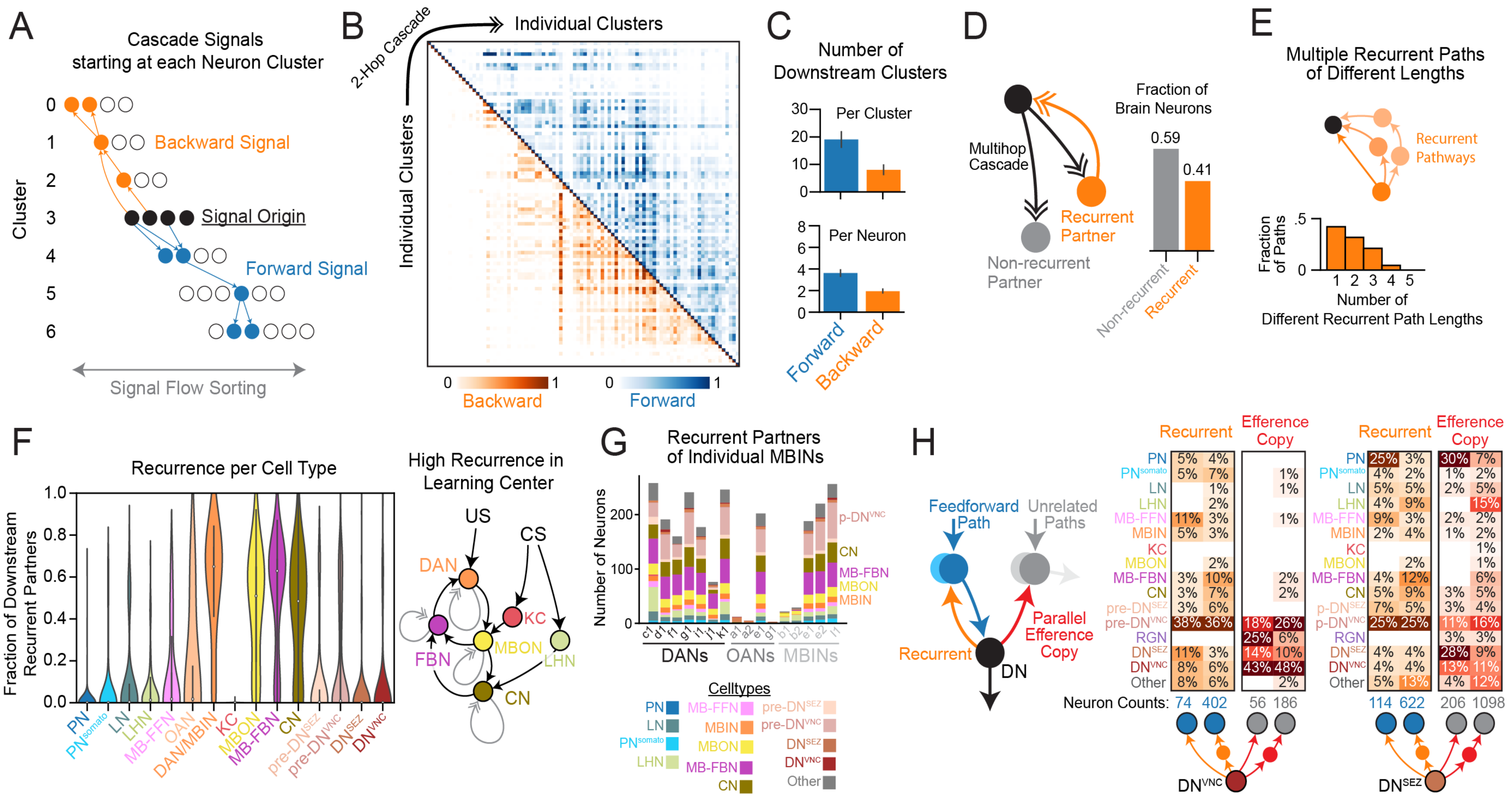

A
Cluster Level
0 1 2 3 4 5 6 7
All Brain Neurons and Inputs
200 Neurons
Inputs
Sensory
Ascending
Interneurons
Projection
Projection somato
Local
Lateral Horn
MB-FFN
MBIN
KC
MBON
MB-FBN
CN
pre-DN SEZ
pre-DN VNC
Other
Outputs
RGN
DN SEZ
DN VNC
B
0.99
0.87
0.96
0.64
C
Postsynaptic (All Clusters)
Presynaptic (All Clusters)
D
Connectivity between Level 4 Clusters
E
Axo-dendritic Hubs
Out Hubs
In-Out Hubs
In Hubs
>20 Partners
>20
Fraction of Cluster
Level 4 Cluster Labels
F
In-Out Hub Celltypes
MB-related
G
Pathways Through the Brain
Brain Inputs
Level 7 Clusters
Brain Outputs
Hops



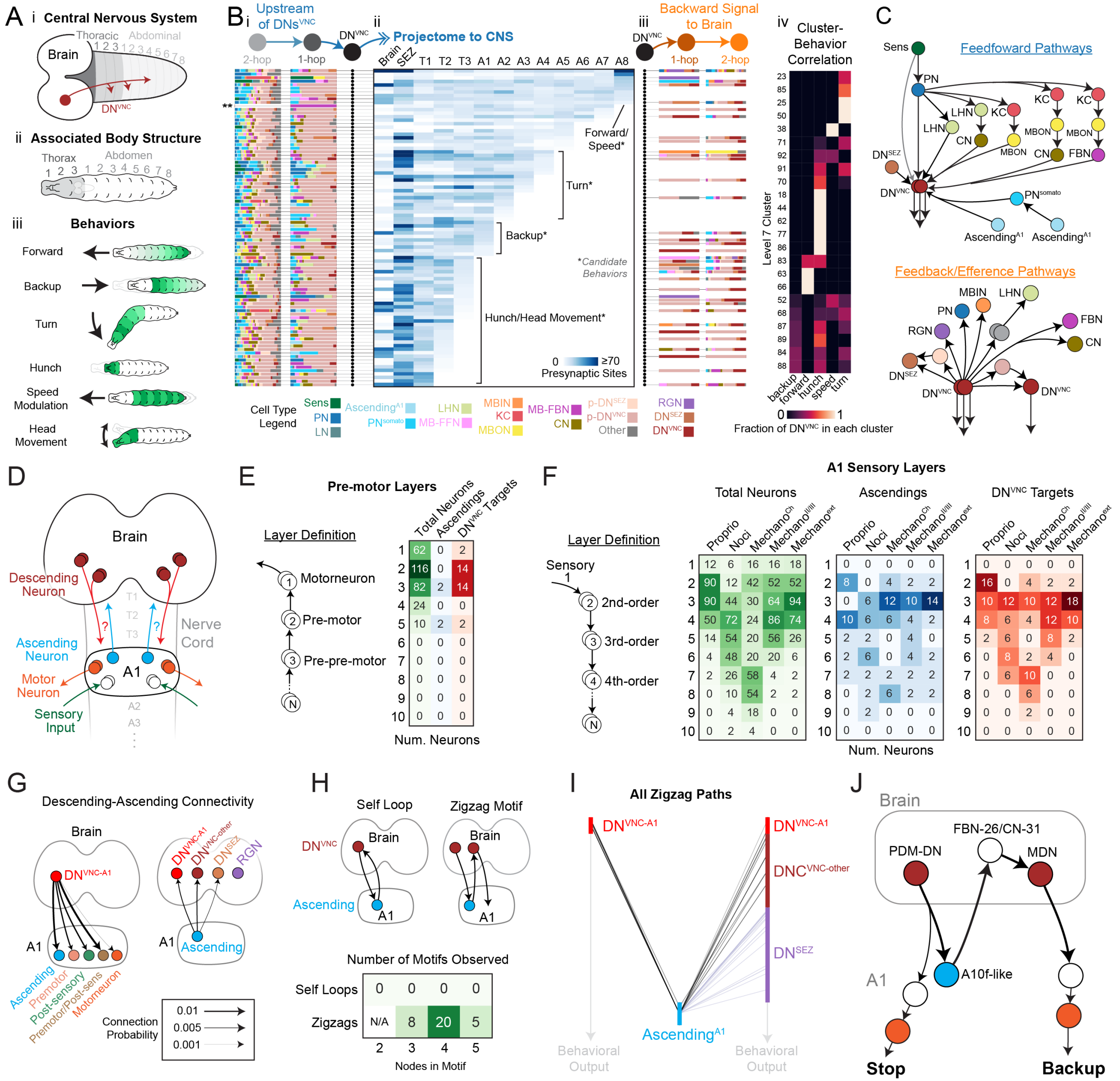
A
Brain Sensory Circuits
Input
2nd-order
3rd-order
Olfactory
Gustatory External
Gustatory Pharynx
Gut
Thermo-Warm
Thermo-Cold
Visual
Nociceptive
Mechano-Chordotonals
Mechano-Class II/III
Proprio
Respiratory
B
Member Similarity
2nd-Order
3rd-Order
4th-Order
Similarity
C
2nd-Order
3rd-Order
4th-Order
5th-Order
Total
Innate
Learning/ Memory
Deep Brain
Pre-Output
Brain Outputs
D
Multihop Signal Cascade
Hops
Signal Source
E
Brain Input→Output Depth
Sensory Modalities
Multihop cascade
Fraction of Signal
Hops Input-to-Output
F
Nested Pathways of Varying Lengths
Sensory Modality
Individual DNs
Fraction
Total Different Path Lengths onto individual DN
G
Multisensory Integration
Type 1
Type 2
Type 3,...,12
Per Neuron
Fraction of Neurons
Unimodal
Multimodal
H
Hops from Input Signal
Unimodal
Multimodal
I
Sensory Signal to Learning Center Neurons
Multihop Cascade
Multihop Signal



A
Edge Types
Ipsilateral
Contralateral
Hemisphere
Left
Right
B
Number of Neuron Pairs
Fraction of Contralateral Presynaptic Sites
Ipsilateral
Bilateral
Contralateral
C
Ipsilateral Neurons
Bilateral Neurons
Contralateral Neurons
Neuropil Boundary
Input
Output
Synaptic Site Distribution
D
Ipsilateral and Contralateral Partners of Bilateral Neurons
Similarity Ipsi/Contra Partners
7 pairs
13 pairs
210 pairs
Fraction Neurons
i = postsynaptic ipsilateral
c = postsynaptic contralateral
Celltypes
PN
LN
LHN
MB-FFN
MBIN
MBON
MB-FBN
CN
p-DNSEZ
p-DNVNC
RGN
DNSEZ
DNVNC
Other
E
Left
Right
Ipsilateral
Bilateral
Contralateral
Connection Probability
F
Interhemispheric Reciprocal Loops
Connection Probability
Non-Pair Loop
Pair Loop
Pair Loop Celltypes
Other
G
Lateralization per Celltype
Innate
Learning, Memory
Deep Brain
Brain Outputs
Fraction of Neurons
Lateralized
Integrative



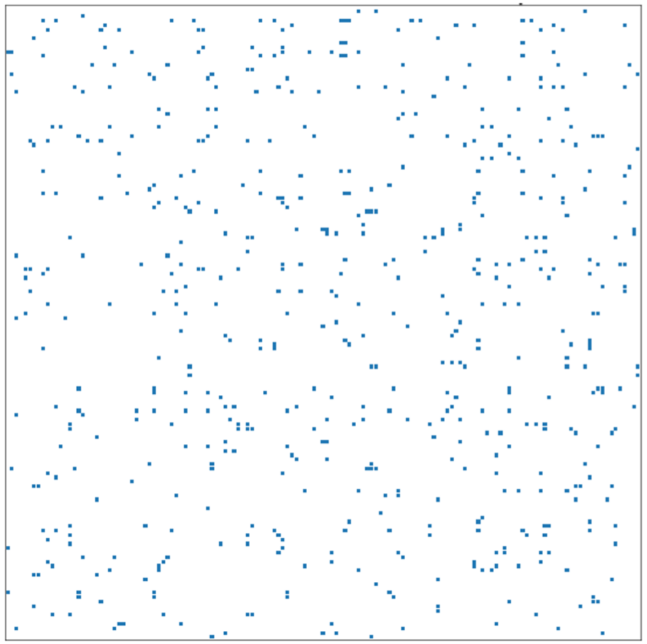
A
Cascade Signals starting at each Neuron Cluster
Cluster
0
1
2
3
4
5
6
Backward Signal
Signal Origin
Forward Signal
Signal Flow Sorting
B
2-Hop Cascade
Individual Clusters
Individual Clusters
0
1
Backward
0
1
Forward
C
Number of Downstream Clusters
Per Cluster
30
20
10
0
Per Neuron
8
6
4
2
0
Forward
Backward
D
Multihop Cascade
Recurrent Partner
Non-recurrent Partner
Fraction of Brain Neurons
0.59
0.41
Non-recurrent
Recurrent
E
Multiple Recurrent Paths of Different Lengths
Recurrent Pathways
Fraction of Paths
.5
0
1 2 3 4 5
Number of Different Recurrent Path Lengths
F
Recurrence per Cell Type
Fraction of Downstream Recurrent Partners
1.0
0.8
0.6
0.4
0.2
0.0
PN
PNsomato
LN
LHN
MB-FFN
OAN
DAN/MBIN
KC
MBON
MB-FBN
CN
pre-DNSEZ
pre-DNVNC
DNSEZ
DNVNC
High Recurrence in Learning Center
US
CS
DAN
KC
MBON
LHN
FBN
CN
G
Recurrent Partners of Individual MBINs
Number of Neurons
200
100
0
p-DNVNC
CN
MB-FBN
MBON
MBIN
c1 d1 f1 g1 i1 j1 k1 a1 a2 e1 g1 b1 b2 e1 e2 i1
DANs
OANs
MBINs
Celltypes
PN
LN
PNsomato
LHN
MB-FFN
MBIN
MBON
MB-FBN
CN
pre-DNSEZ
pre-DNVNC
DNSEZ
DNVNC
Other
H
Feedforward Path
Unrelated Paths
Recurrent
Parallel Efference Copy
DN
Recurrent
Efference Copy
PN 5% 4%
PNsomato 5% 7% 1%
LN 1% 1%
LHN 2%
MB-FFN 11% 3% 1%
MBIN 5% 3%
KC
MBON 2%
MB-FBN 3% 10% 2%
CN 3% 7% 2%
pre-DNSEZ 3% 6%
pre-DNVNC 38% 36% 18% 26%
RGN 25% 6%
DNSEZ 11% 3% 14% 10%
DNVNC 8% 6% 43% 48%
Other 8% 6% 2%
Neuron Counts: 74 402 56 186
DNVNC
Recurrent
Efference Copy
PN 25% 3% 30% 7%
PNsomato 4% 2% 1% 2%
LN 5% 5% 2% 5%
LHN 4% 9% 15%
MB-FFN 9% 3% 2% 2%
MBIN 2% 4% 1% 2%
KC 1%
MBON 2% 1%
MB-FBN 4% 12% 6%
CN 5% 9% 3% 5%
p-DNSEZ 7% 5% 3% 4%
p-DNVNC 25% 25% 11% 16%
RGN 3% 3%
DNSEZ 4% 4% 28% 9%
DNVNC 4% 4% 13% 11%
Other 5% 13% 4% 12%
114 622 206 1098
DNSEZ



A i Central Nervous System
Brain
Thoracic
Abdominal
DN^VNC
ii Associated Body Structure
Thorax
Abdomen
iii Behaviors
Forward
Backup
Turn
Hunch
Speed Modulation
Head Movement
B i Upstream of DNs^VNC
2-hop
1-hop
DN^VNC
ii Projectome to CNS
Brain SEZ T1 T2 T3 A1 A2 A3 A4 A5 A6 A7 A8
Forward/ Speed*
Turn*
Backup*
*Candidate Behaviors
Hunch/Head Movement*
0 ≥70 Presynaptic Sites
iii Backward Signal to Brain
iv Cluster-Behavior Correlation
Level 7 Cluster
backup forward hunch speed turn
Fraction of DN^VNC in each cluster
Cell Type Legend
Sens PN LN Ascending^A1 PN^somato LHN MB-FFN MBIN KC MBON MB-FBN CN p-DN^SEZ p-DN^VNC Other RGN DN^SEZ DN^VNC
C
Feedfoward Pathways
Sens PN LHN KC MBON CN FBN DN^SEZ DN^VNC PN^somato Ascending^A1
Feedback/Efference Pathways
MBIN LHN PN RGN FBN CN DN^SEZ DN^VNC
D
Brain
Descending Neuron
Ascending Neuron
Motor Neuron
Sensory Input
Nerve Cord
T1 T2 T3 A1 A2 A3
E
Pre-motor Layers
Layer Definition
1 Motorneuron
2 Pre-motor
3 Pre-pre-motor
N
Total Neurons, Ascendings, DN^VNC Targets
1: 62 0 2
2: 116 0 14
3: 82 2 14
4: 24 0 0
5: 10 2 2
6: 0 0 0
7: 0 0 0
8: 0 0 0
9: 0 0 0
10: 0 0 0
Num. Neurons
F
A1 Sensory Layers
Layer Definition
Sensory
2 2nd-order
3 3rd-order
4 4th-order
N
Total Neurons
Proprio Noci Mechano^Ch Mechano^II/III Mechano^ext
1: 12 6 16 16 18
2: 90 12 42 52 52
3: 90 44 30 64 94
4: 50 72 24 86 74
5: 14 54 20 56 26
6: 4 48 20 20 6
7: 2 26 58 4 2
8: 0 10 54 2 2
9: 0 4 18 0 0
10: 0 2 4 0 0
Ascendings
1: 0 0 0 0 0
2: 8 0 4 2 2
3: 0 6 12 10 14
4: 10 6 6 4 2
5: 2 2 0 4 0
6: 2 6 0 4 2
7: 2 2 2 2 2
8: 0 2 6 2 2
9: 0 2 0 0 0
10: 0 0 0 0 0
DN^VNC Targets
1: 0 0 0 0 0
2: 16 0 4 2 2
3: 10 12 10 12 18
4: 8 6 4 12 10
5: 2 6 0 8 2
6: 0 8 2 4 0
7: 0 6 10 0 0
8: 0 0 6 0 0
9: 0 0 2 0 0
10: 0 0 0 0 0
Num. Neurons
G
Descending-Ascending Connectivity
Brain
DN^VNC-A1
DN^VNC-A1 DN^VNC-other DN^SEZ RGN
A1
Ascending Premotor Post-sensory Premotor/Post-sens Motorneuron
Connection Probability
0.01 0.005 0.001
H
Self Loop
Zigzag Motif
DN^VNC
Brain
Ascending
A1
Number of Motifs Observed
Self Loops: 0 0 0 0
Zigzags: N/A 8 20 5
Nodes in Motif: 2 3 4 5
I
All Zigzag Paths
DN^VNC-A1
DNC^VNC-other
DN^SEZ
Ascending^A1
Behavioral Output
J
Brain
PDM-DN
FBN-26/CN-31
MDN
A1
A10f-like
Stop
Backup

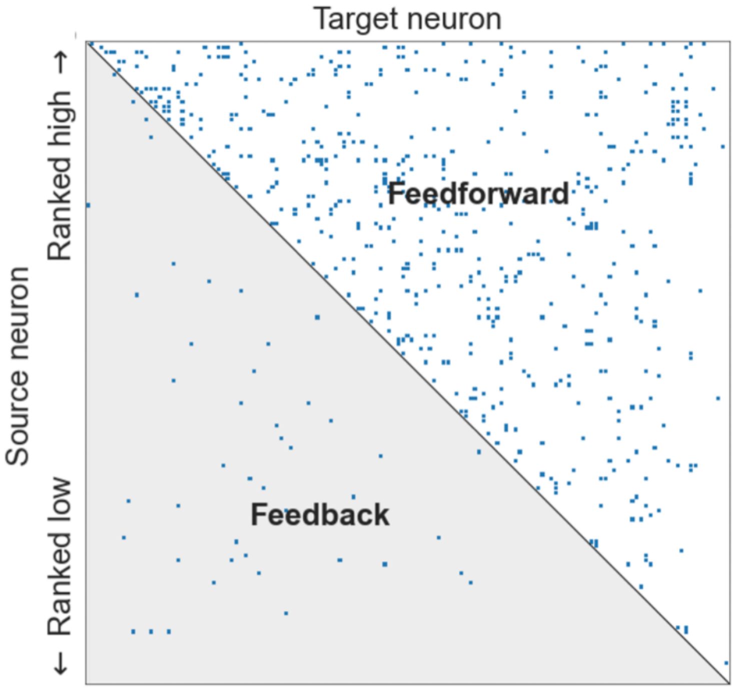
Sorting the network

Adjacency matrix



Flow ordering
- "Feedback minimization"
- Signal flow
- Random-walk based

Sorted adjacency



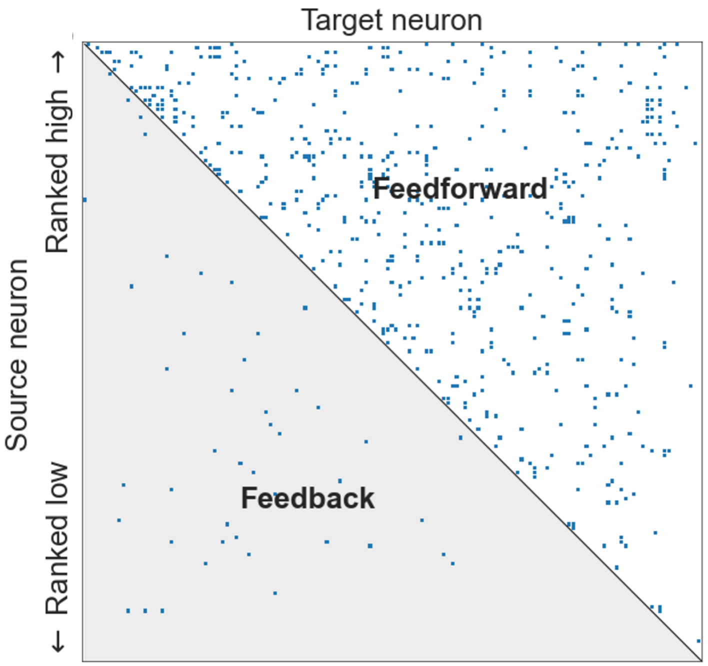
Carmel et al. IEEE Vis. and Comp. Graphics (2004), Burkard et al. Assignment Problems (2009)

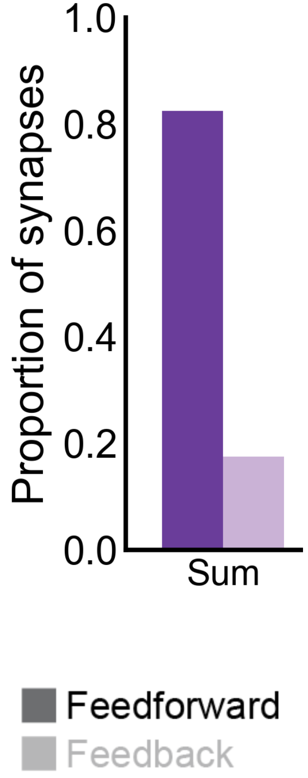
"Feedback minimization" as graph matching

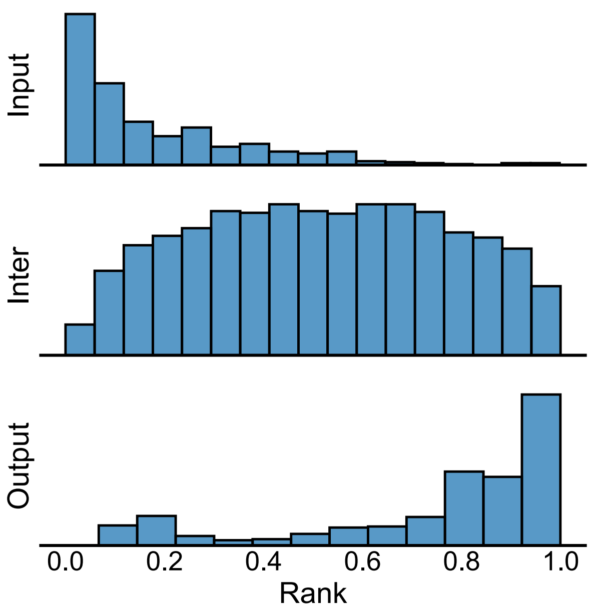
$$\min_P \sum_{i=1}^{n} \sum_{j<i}^{n} (PAP^T)_{ij}^2$$

- Minimand is the sum of squared elements in the lower triangle of reshuffled adjacency
- Solving produces an ordering of the network under which connections are likely to go "forward" in this ordering
- Equivalent to graph matching A to an upper triangular matrix of all 1s

Quantifying high-level "feedforward/feedback"

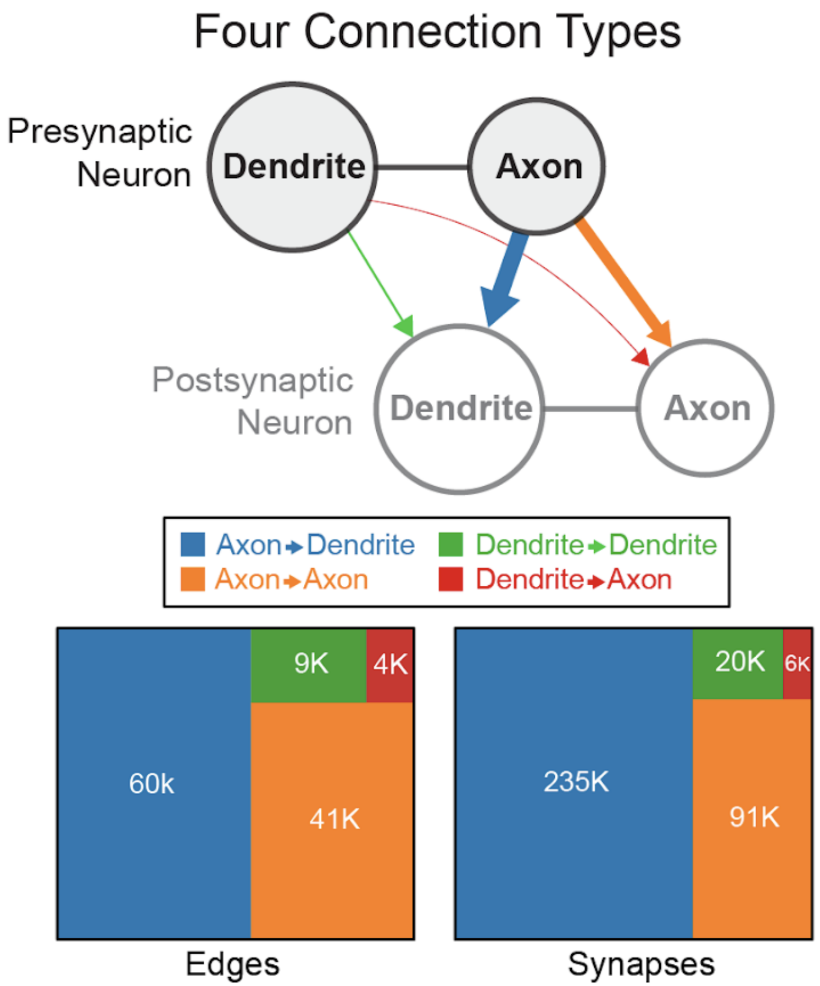


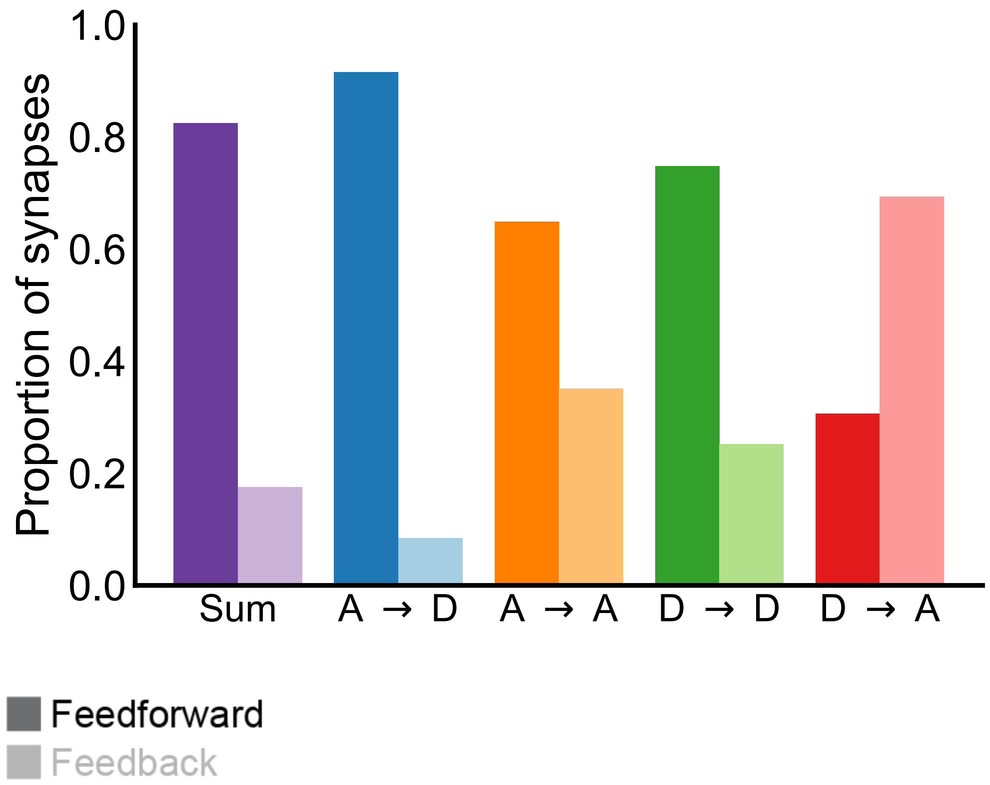




Winding, Pedigo et al. Science (2023)

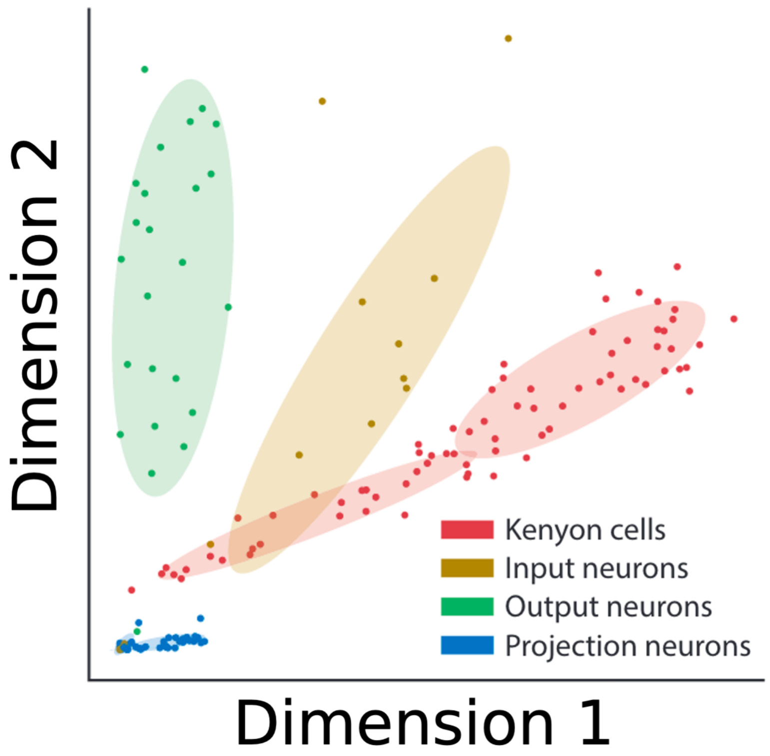
Morphology enables splitting axons/dendrites

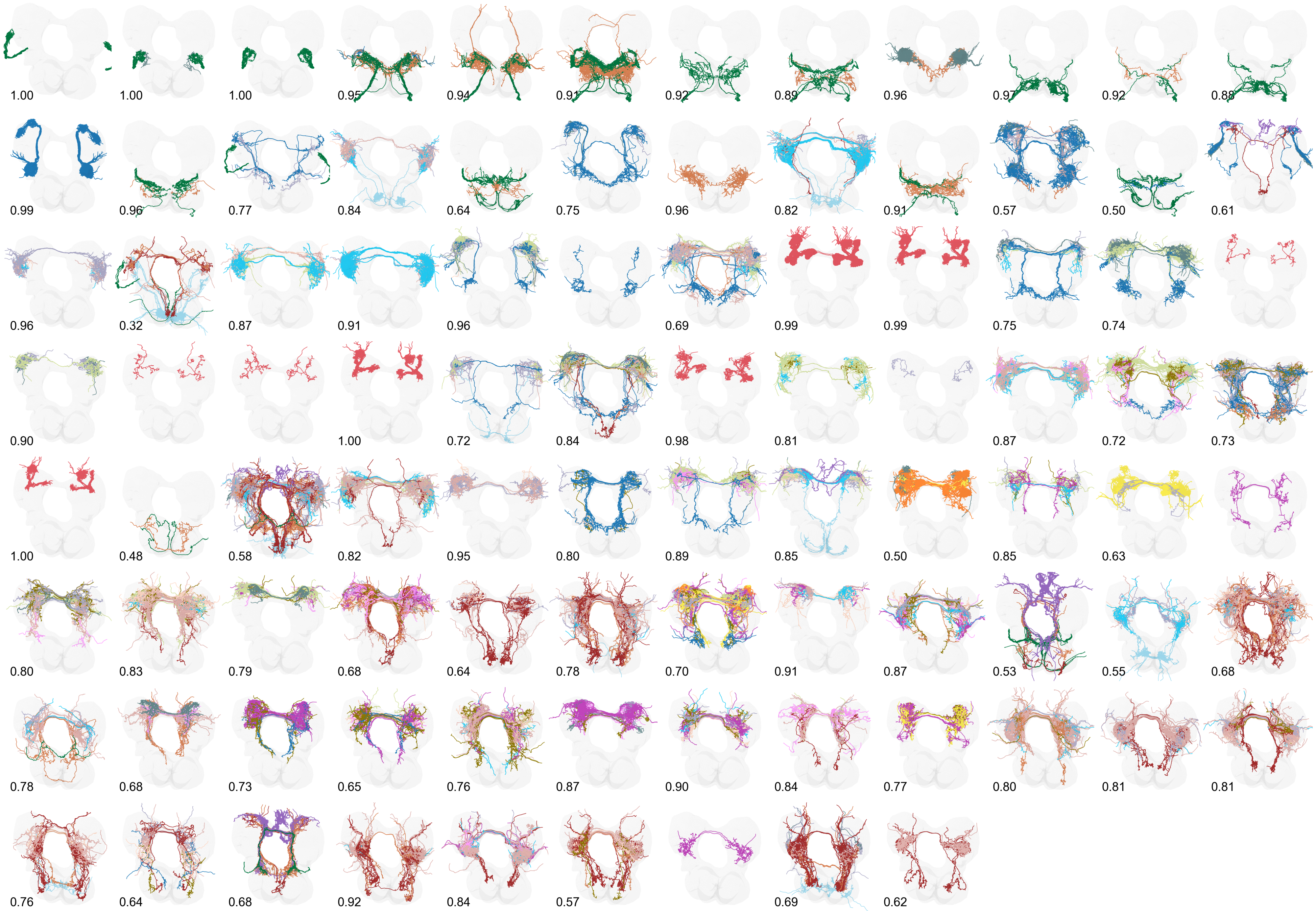




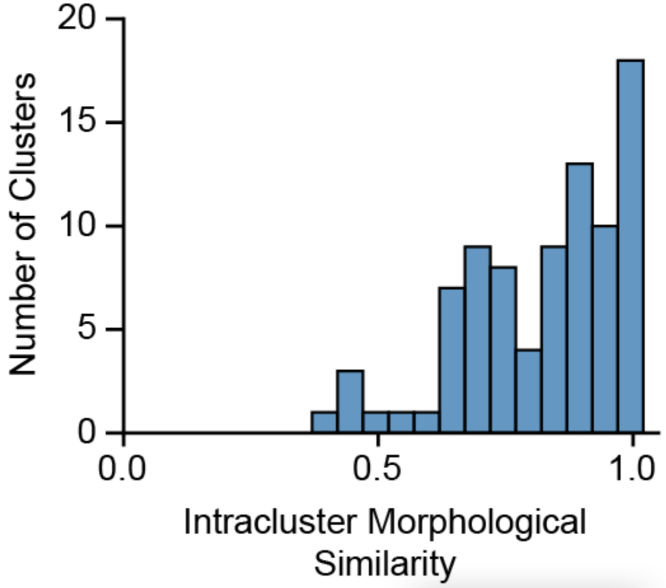
Spectral embedding

- Spectral decomposition of the adjacency matrix (or Laplacian)




1.00 1.00 1.00 0.95 0.94 0.91 0.92 0.89 0.96 0.97 0.92 0.88
0.99 0.96 0.77 0.84 0.64 0.75 0.96 0.82 0.91 0.57 0.50 0.61
0.96 0.32 0.87 0.91 0.96 0.69 0.99 0.99 0.75 0.74
0.90 1.00 0.72 0.84 0.98 0.81 0.87 0.72 0.73
1.00 0.48 0.58 0.82 0.95 0.80 0.89 0.85 0.50 0.85 0.63
0.80 0.83 0.79 0.68 0.64 0.78 0.70 0.91 0.87 0.53 0.55 0.68
0.78 0.68 0.73 0.65 0.76 0.87 0.90 0.84 0.77 0.80 0.81 0.81
0.76 0.64 0.68 0.92 0.84 0.57 0.69 0.62

Cluster morphology

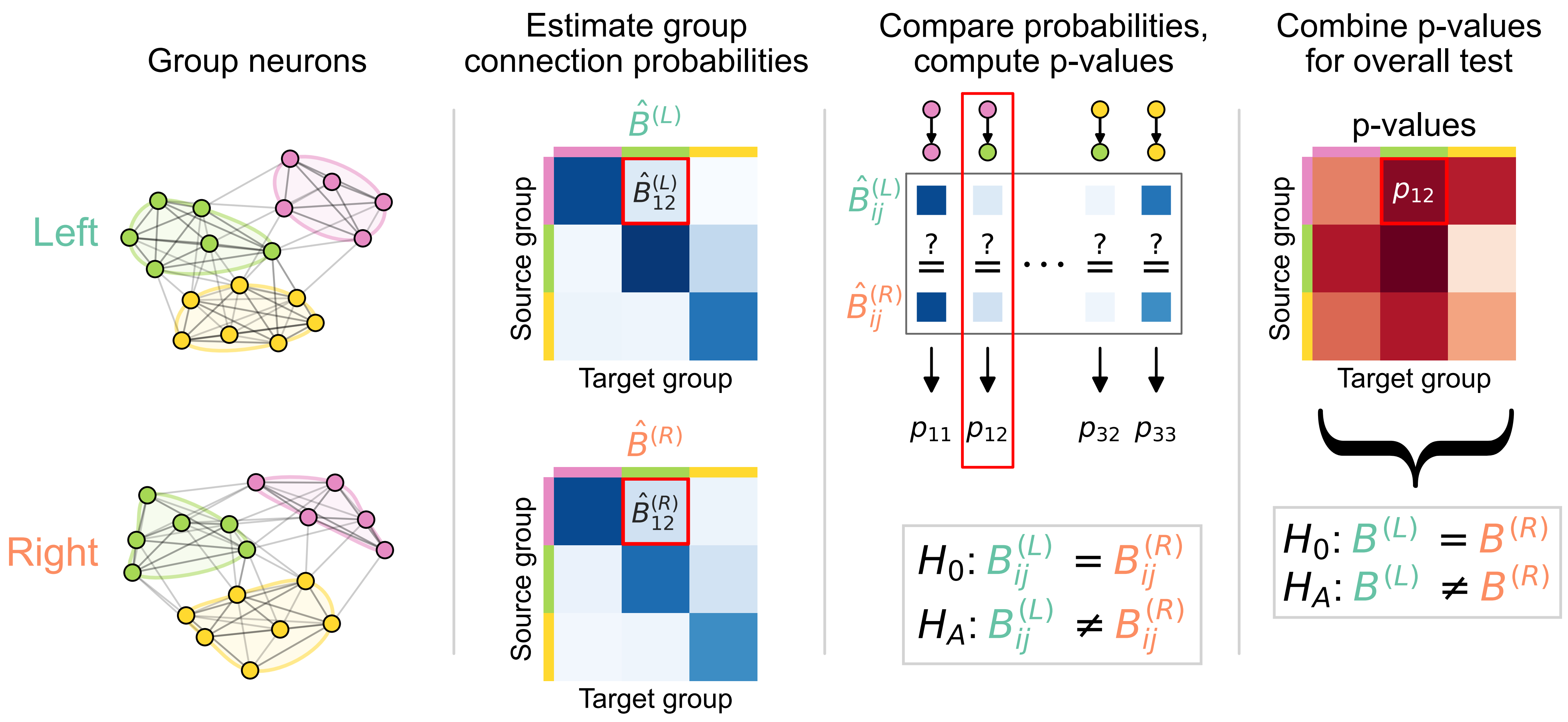


Discriminability:

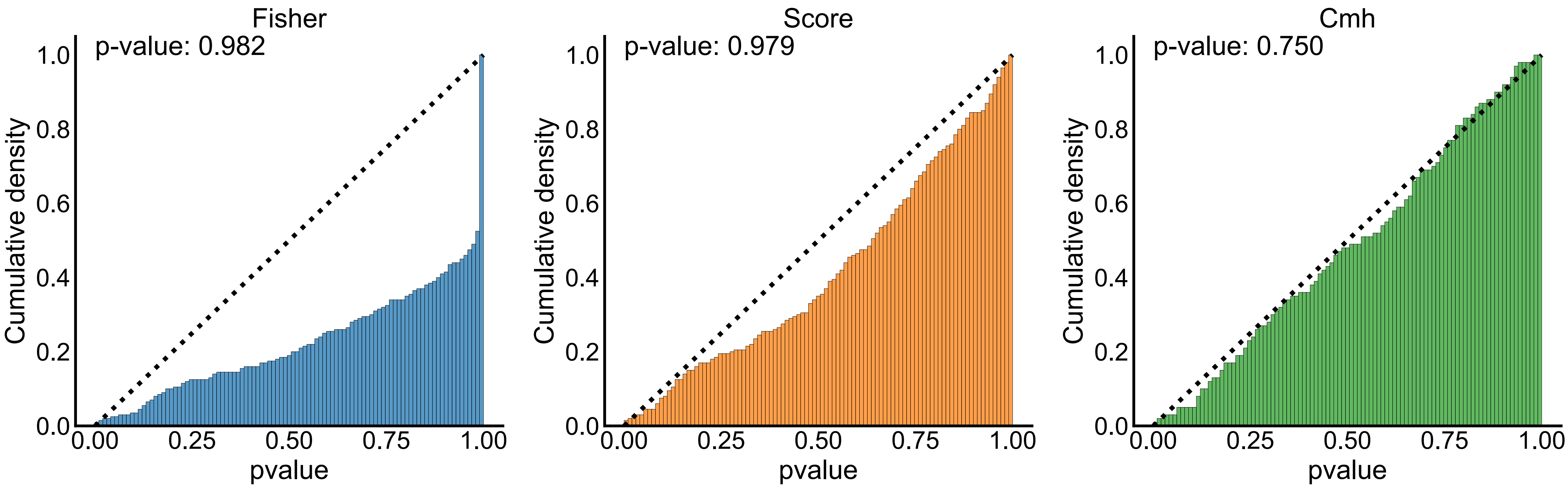
$P[\text{ within cluster NBLAST sim.} > \text{between cluster NBLAST sim.}] \approx 0.81$

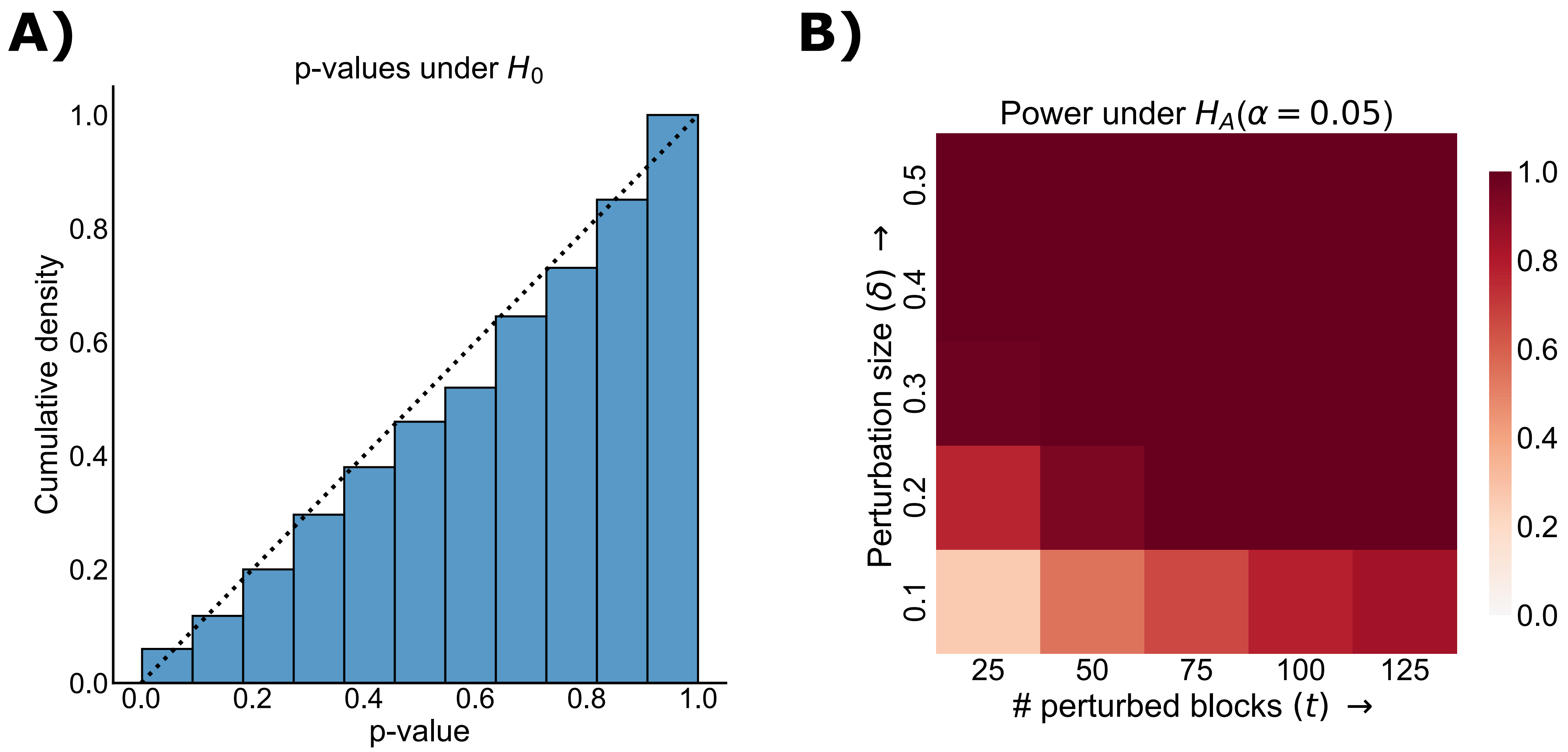
Costa et al. Neuron (2016), Bridgeford et al. PLOS Comp. Bio. (2021)

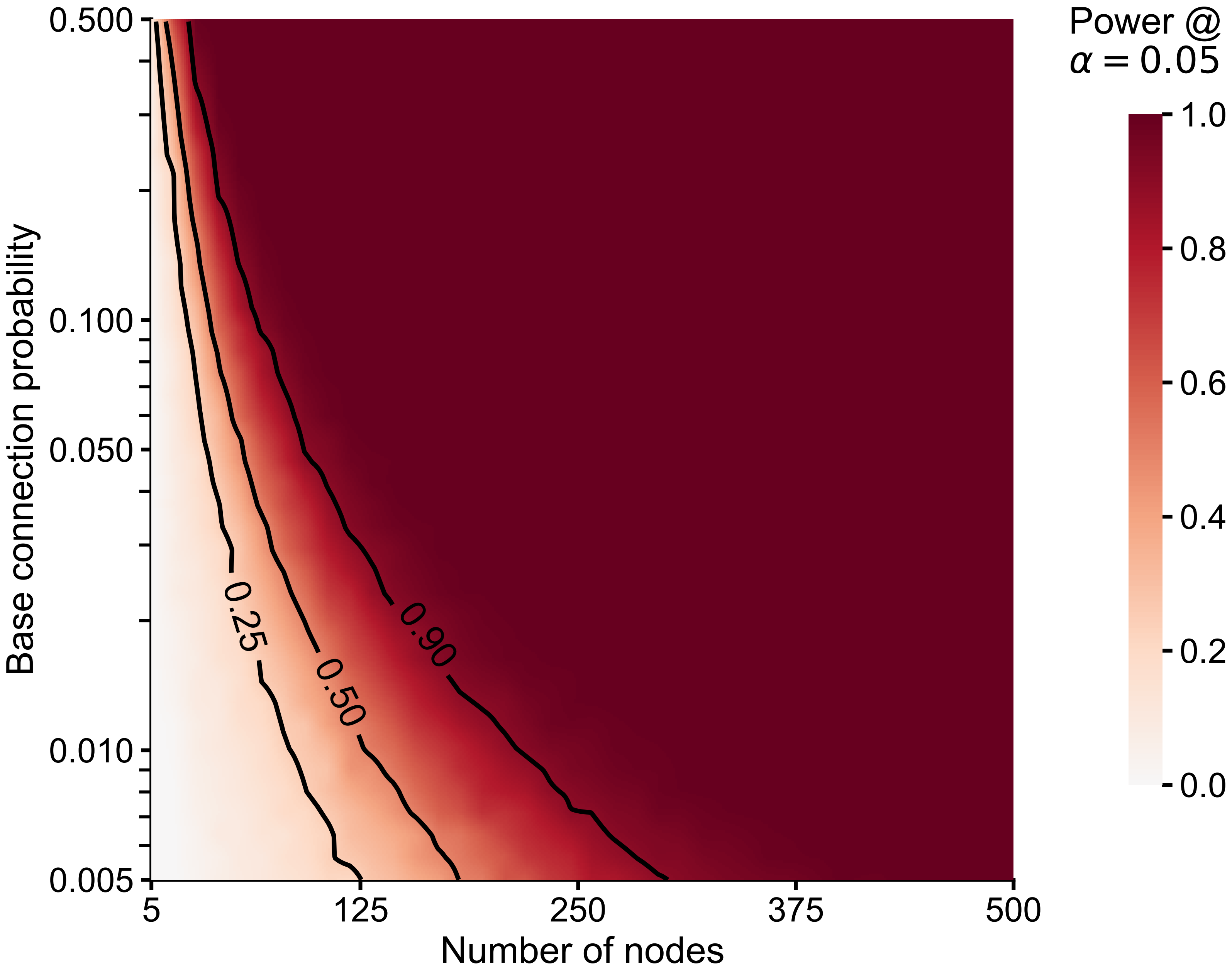
Pedigo et al. eLife (2023)



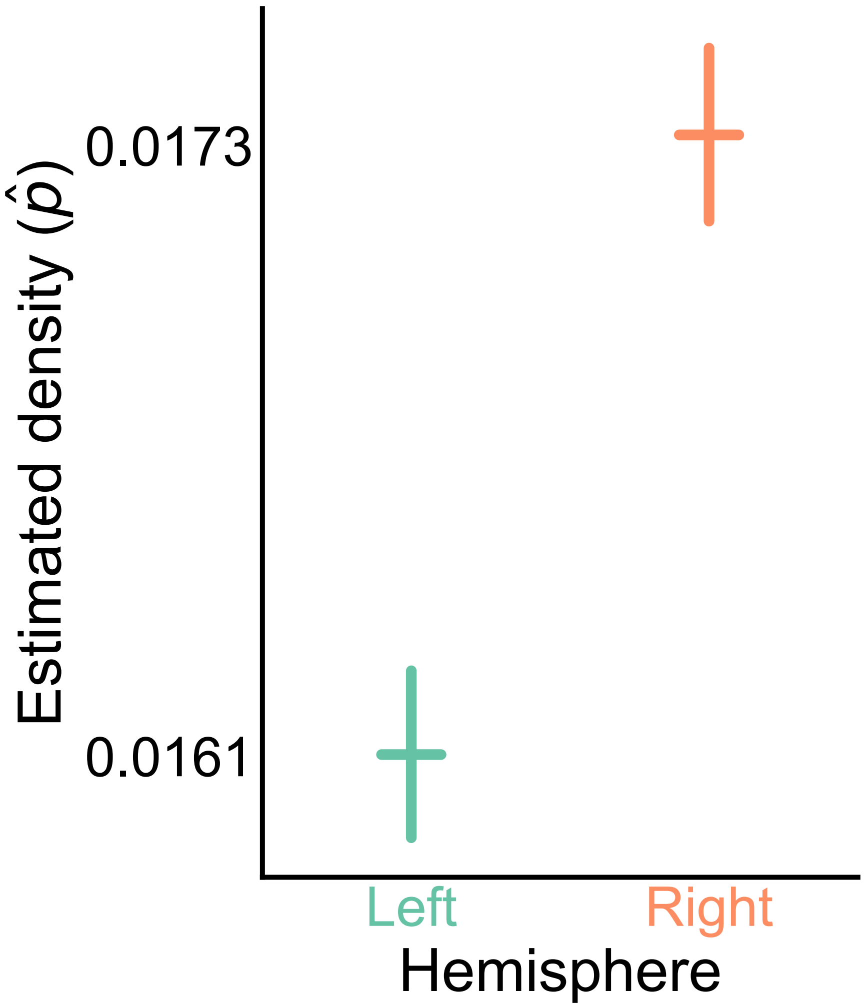
Group neurons
Estimate group connection probabilities
Compare probabilities, compute p-values
Combine p-values for overall test
Left
Right
$\hat{B}^{(L)}$
$\hat{B}^{(L)}_{12}$
Source group
Target group
$\hat{B}^{(R)}$
$\hat{B}^{(R)}_{12}$
Source group
Target group
$\hat{B}^{(L)}_{ij}$
$\hat{B}^{(R)}_{ij}$
$\stackrel{?}{=}$ $\stackrel{?}{=}$ ... $\stackrel{?}{=}$ $\stackrel{?}{=}$
p_{11} p_{12} p_{32} p_{33}
H_0: $B^{(L)}_{ij} = B^{(R)}_{ij}$
H_A: $B^{(L)}_{ij} \neq B^{(R)}_{ij}$
p-values
p_{12}
Source group
Target group
H_0: $B^{(L)} = B^{(R)}$
H_A: $B^{(L)} \neq B^{(R)}$


Fisher
p-value: 0.982
Score
p-value: 0.979
Cmh
p-value: 0.750
Cumulative density
0.0
0.2
0.4
0.6
0.8
1.0
0.00
0.25
0.50
0.75
1.00
pvalue


A)
p-values under H_0
Cumulative density
1.0
0.8
0.6
0.4
0.2
0.0
0.0
0.2
0.4
0.6
0.8
1.0
p-value
B)
Power under $H_A(\alpha = 0.05)$
Perturbation size (δ) →
0.5
0.4
0.3
0.2
0.1
25
50
75
100
125
perturbed blocks (t) →
1.0
0.8
0.6
0.4
0.2
0.0



Power @
$\alpha = 0.05$
1.0
0.8
0.6
0.4
0.2
0.0
0.500
0.100
0.050
0.010
0.005
Base connection probability
5
125
250
375
500
Number of nodes
0.25
0.50
0.90

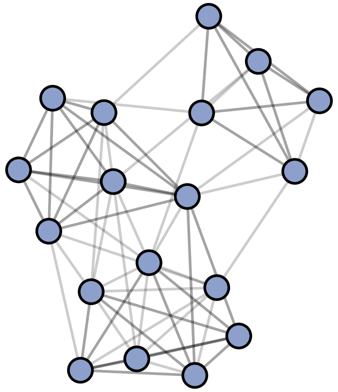


Estimated density ($\hat{p}$)
0.0173
0.0161
Left
Right
Hemisphere

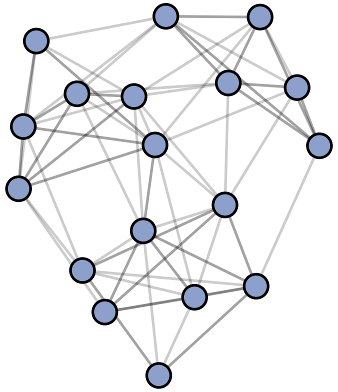
Compute global connection density

Compare ER models

Left



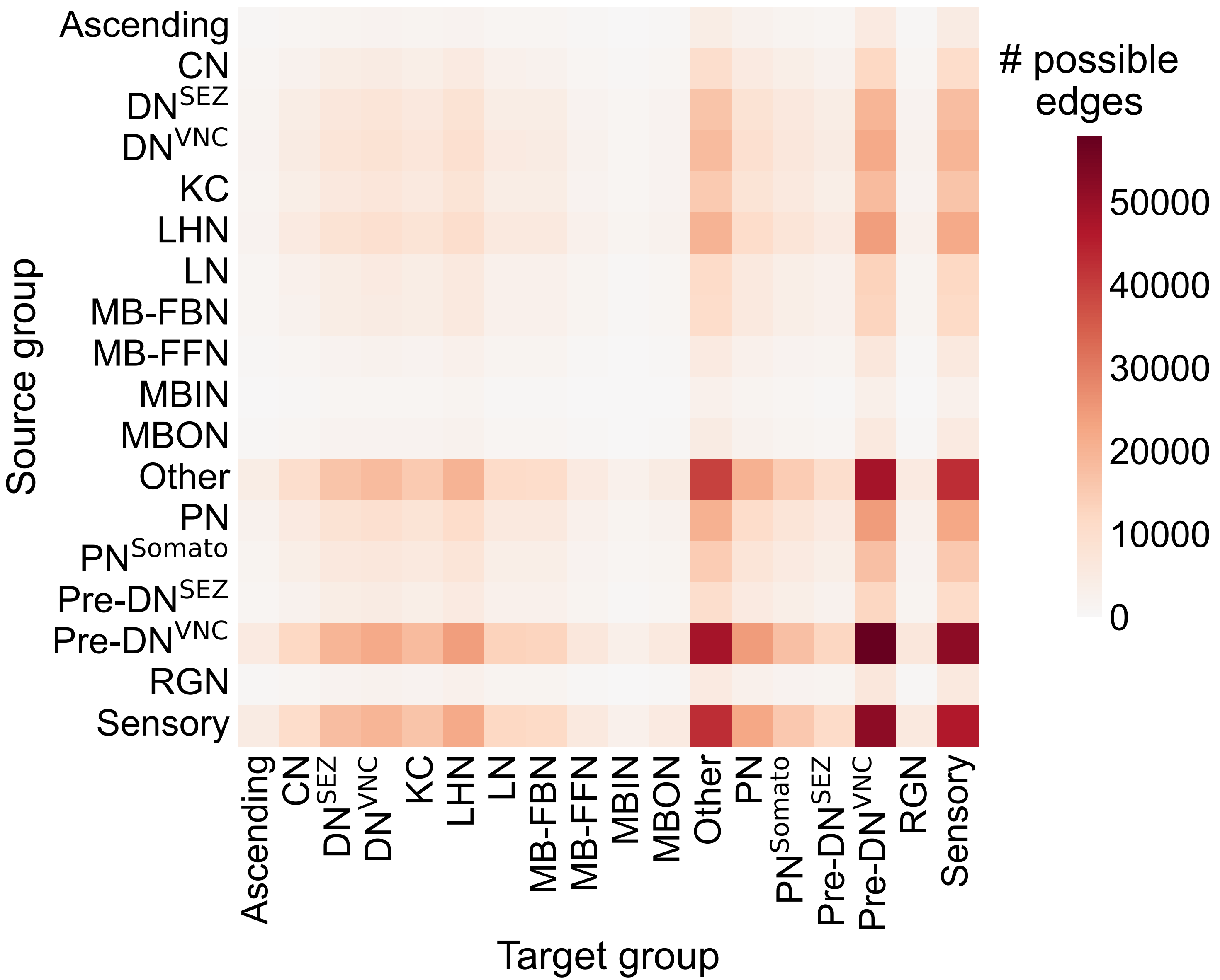
Right

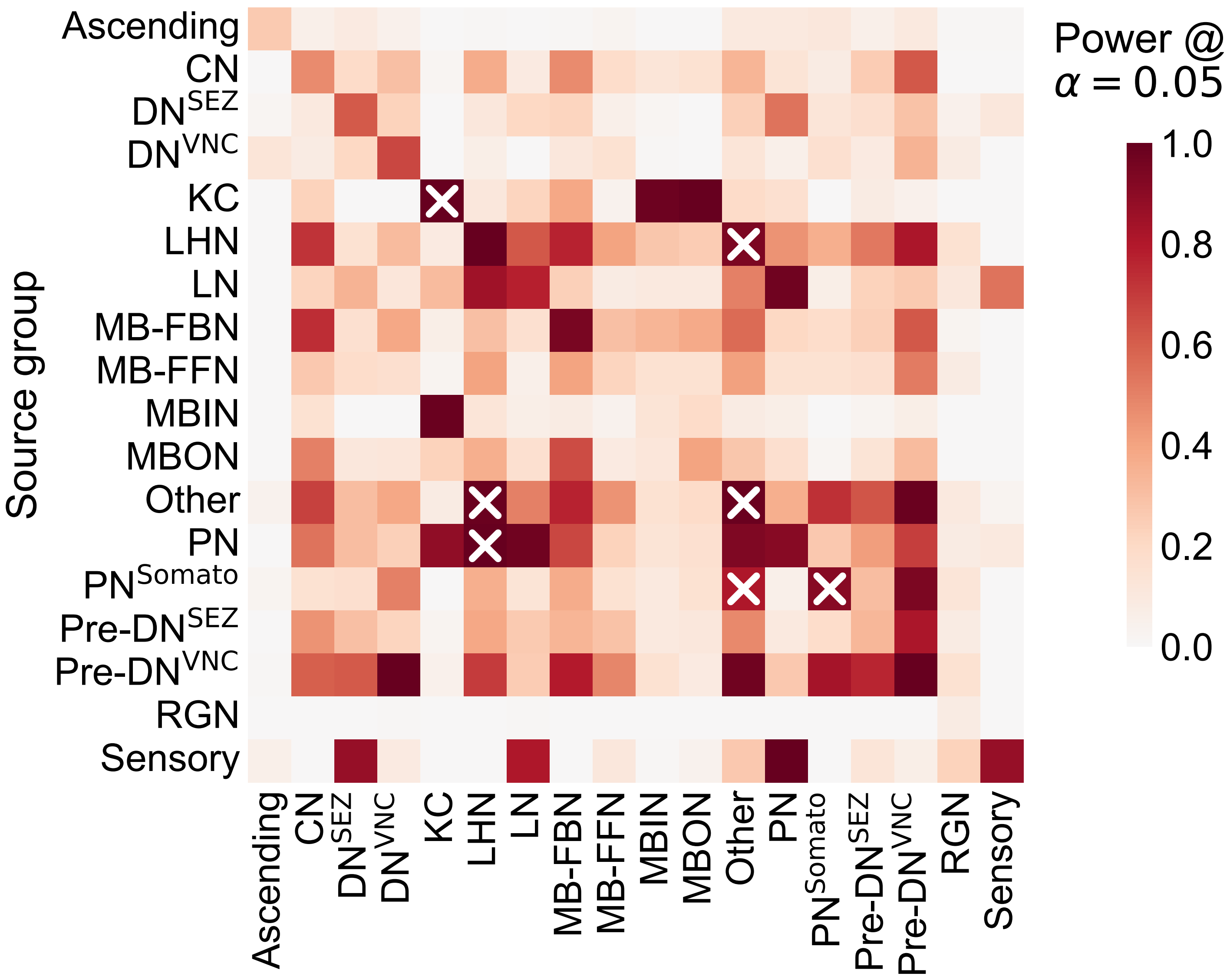


$$p = \frac{\#\ edges}{\#\ potential\ edges}$$

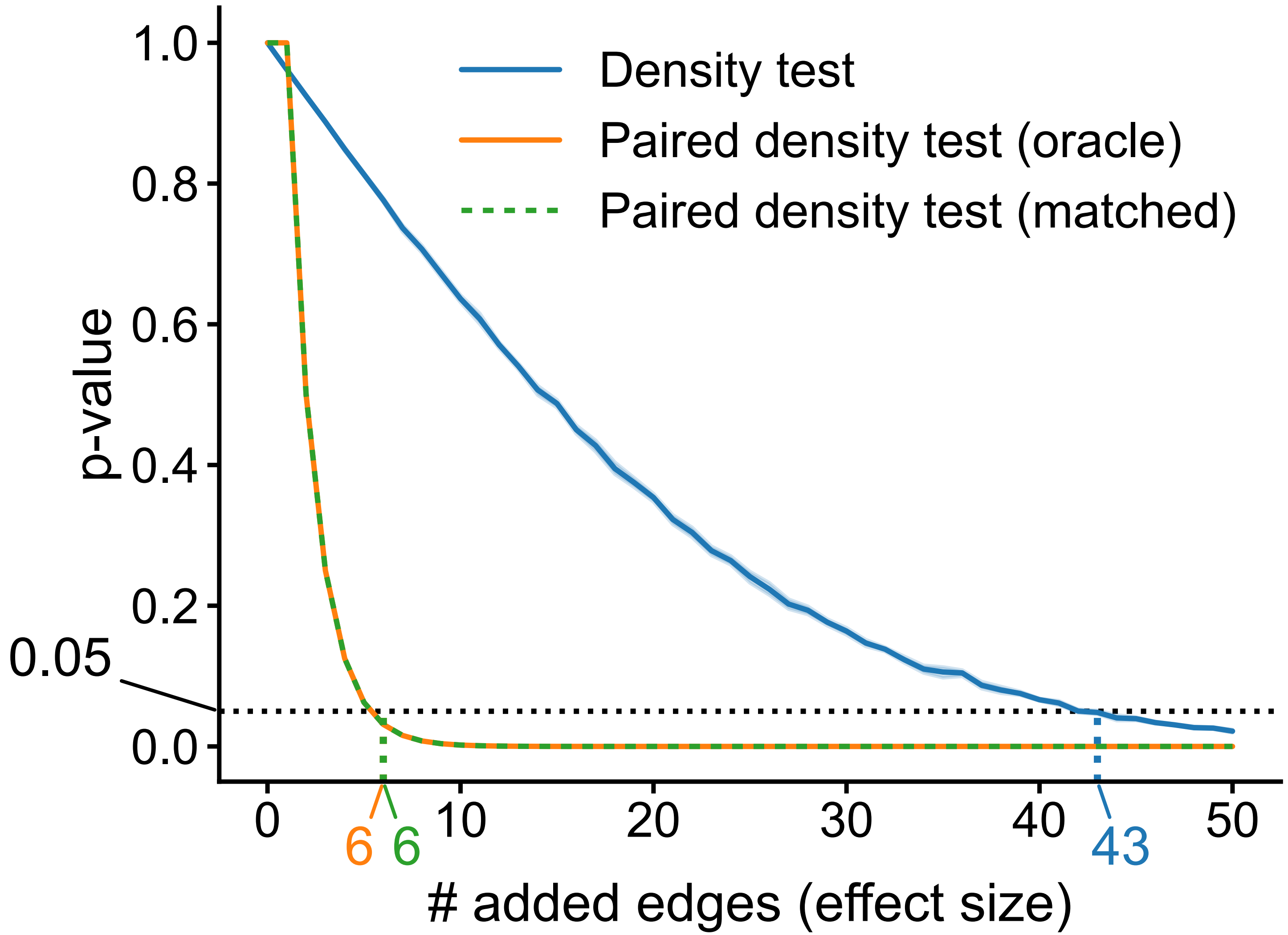
H_0: $p^{(L)} = p^{(R)}$

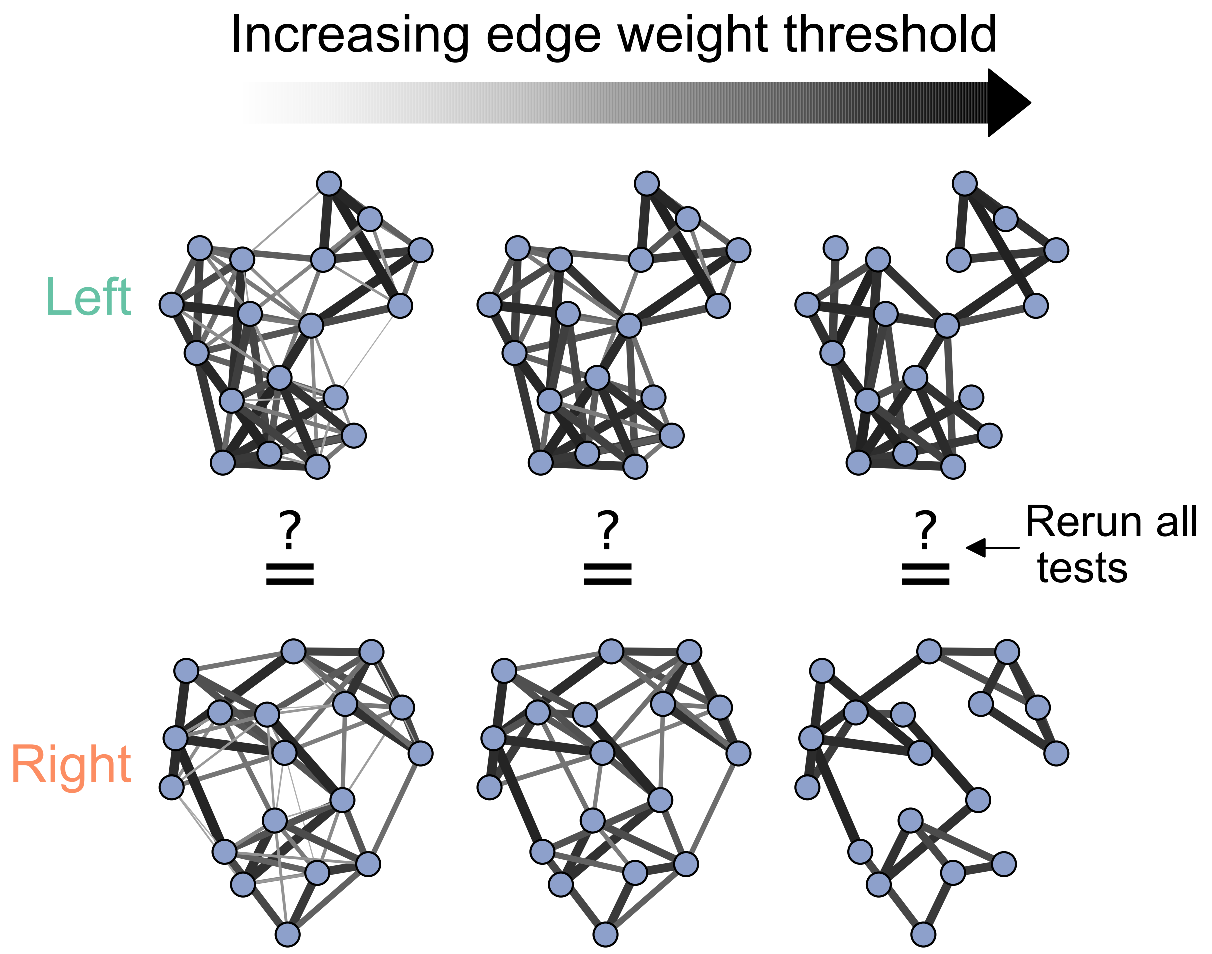
H_A: $p^{(L)} \neq p^{(R)}$

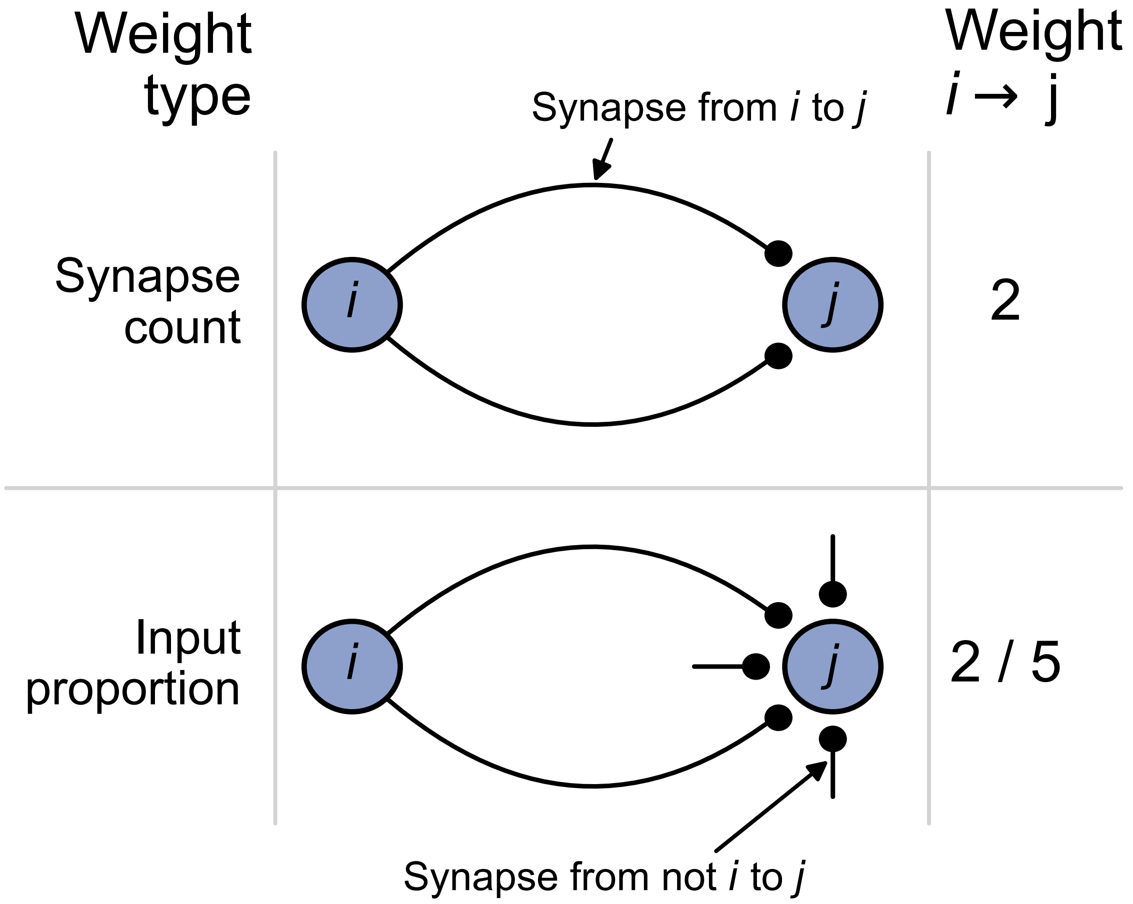

Source group
Ascending
CN
DN^{SEZ}
DN^{VNC}
KC
LHN
LN
MB-FBN
MB-FFN
MBIN
MBON
Other
PN
PN^{Somato}
Pre-DN^{SEZ}
Pre-DN^{VNC}
RGN
Sensory
Target group
possible edges
50000
40000
30000
20000
10000
0

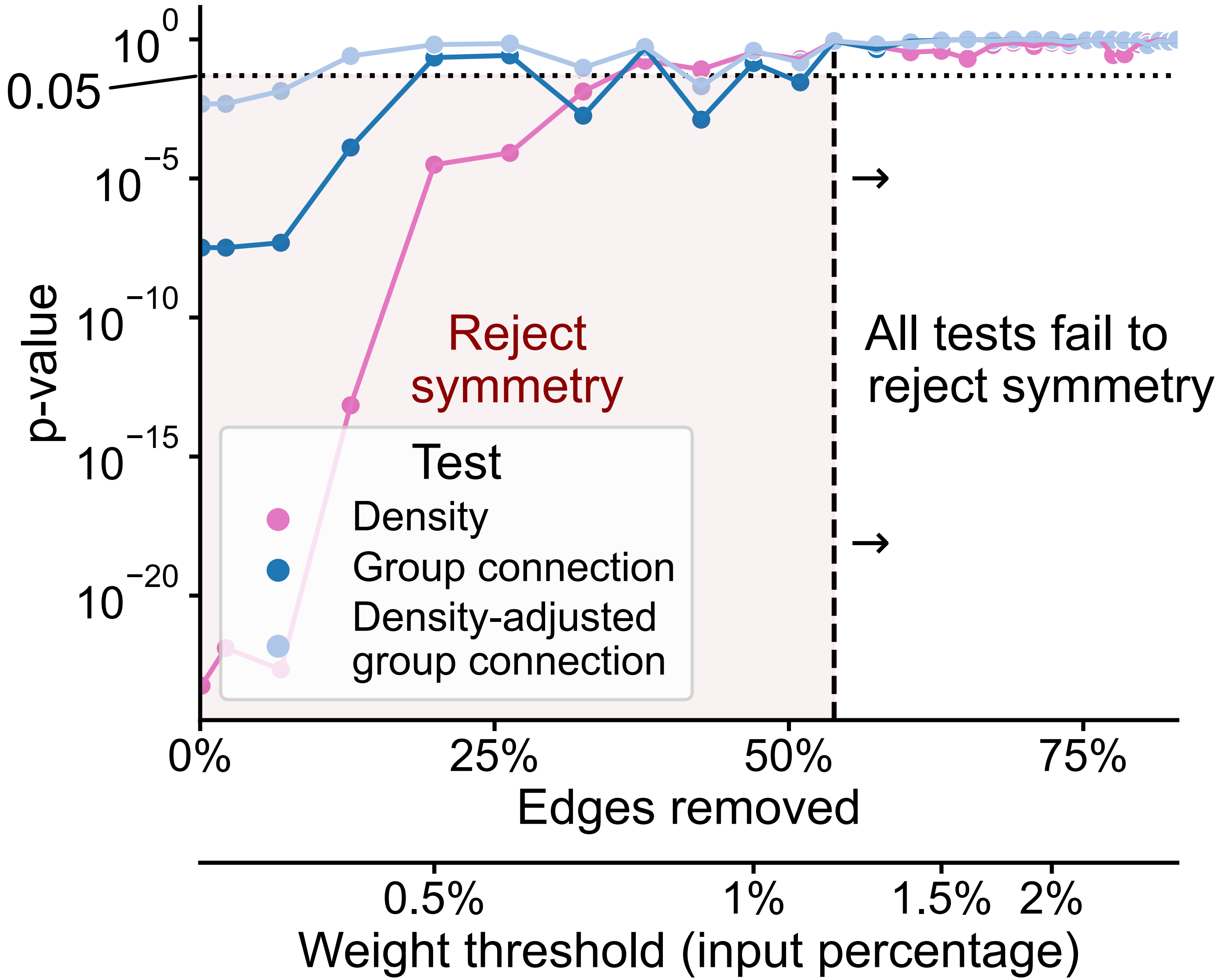


Source group
Ascending
CN
DN^SEZ
DN^VNC
KC
LHN
LN
MB-FBN
MB-FFN
MBIN
MBON
Other
PN
PN^Somato
Pre-DN^SEZ
Pre-DN^VNC
RGN
Sensory
Target group
Power @
α = 0.05
1.0
0.8
0.6
0.4
0.2
0.0

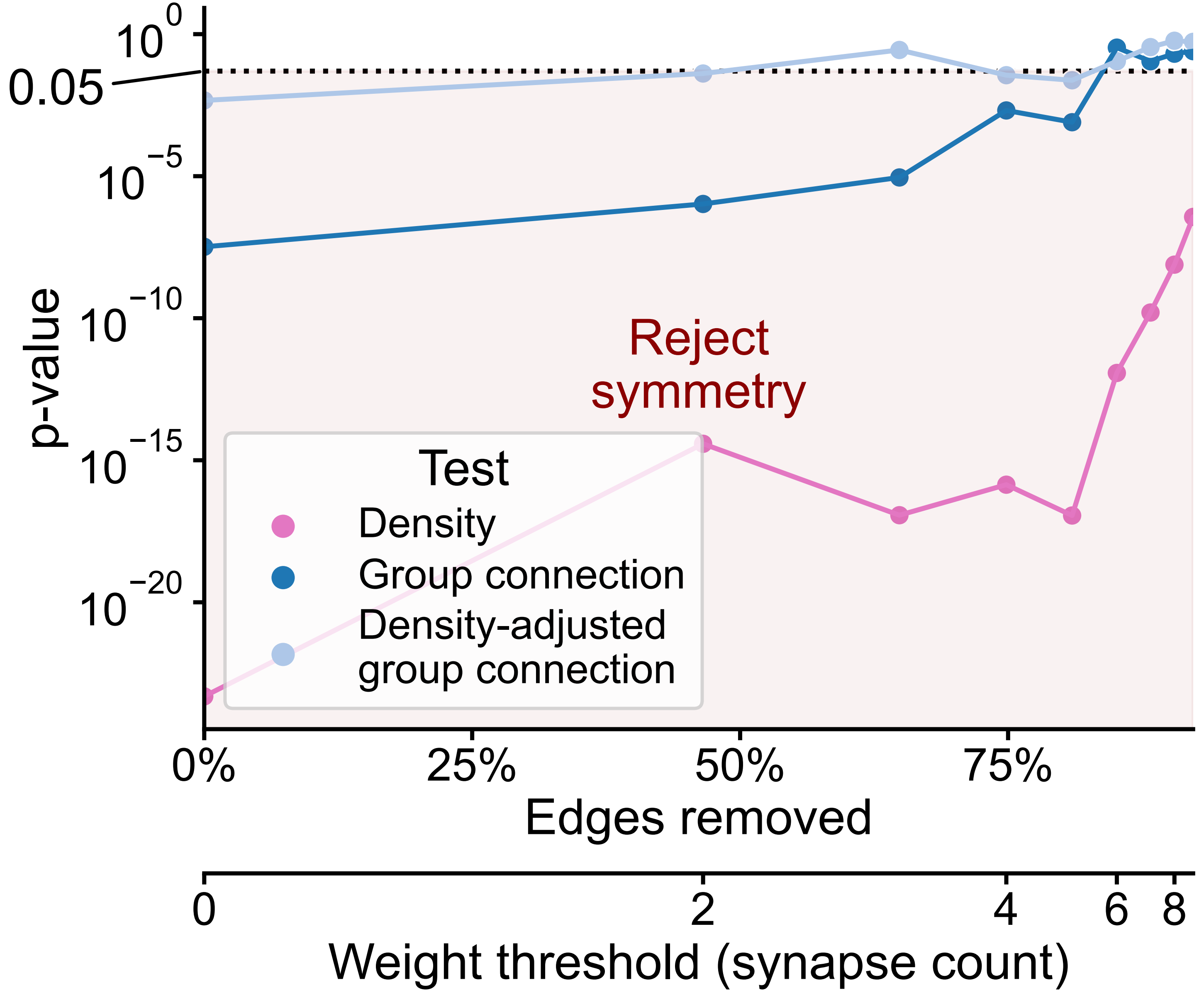

Density test
Paired density test (oracle)
Paired density test (matched)
p-value
1.0
0.8
0.6
0.4
0.2
0.05
0.0
0
10
20
30
40
50
6
6
43
added edges (effect size)

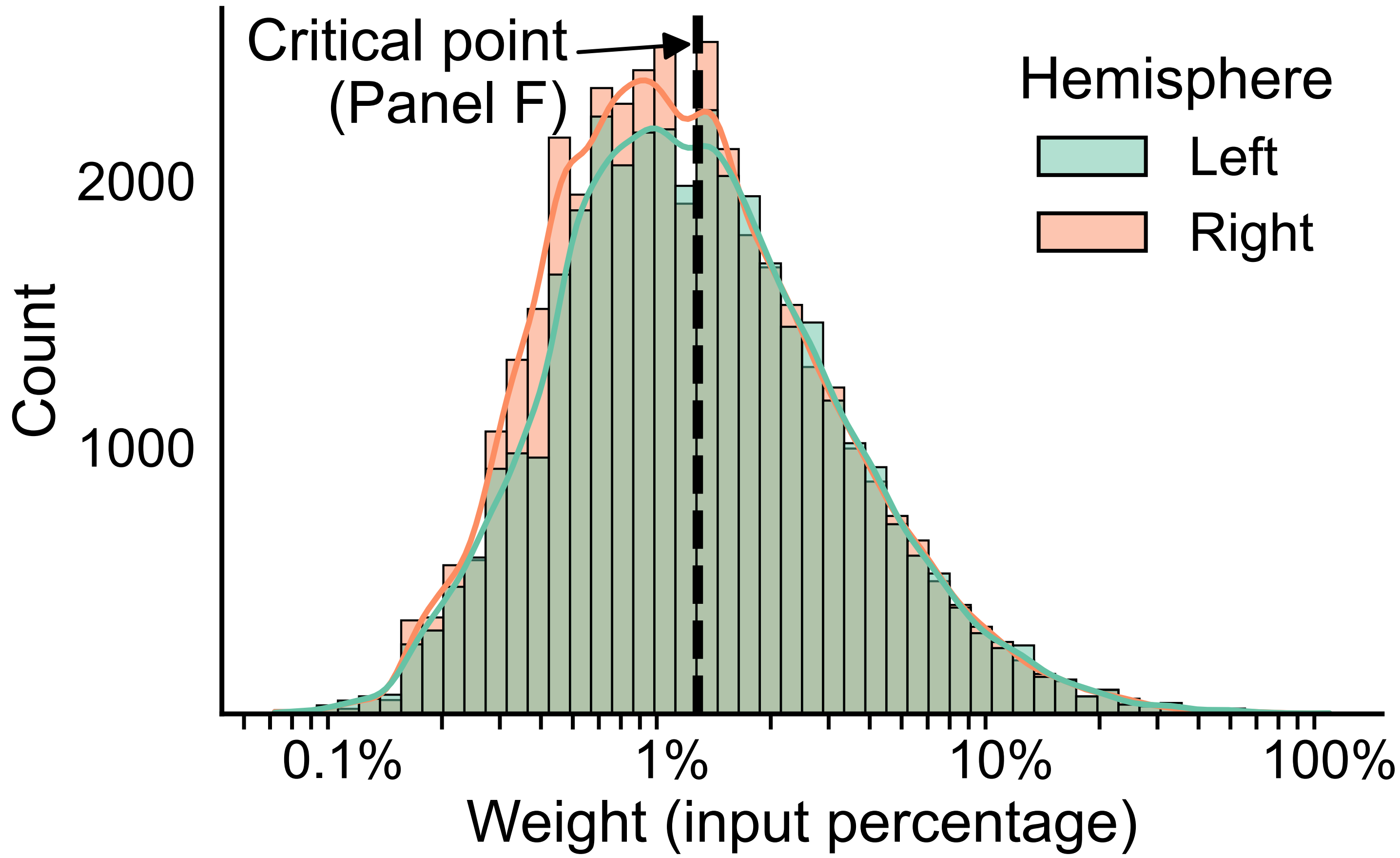

Increasing edge weight threshold
Left
?
=
?
=
?
=
Rerun all tests
Right

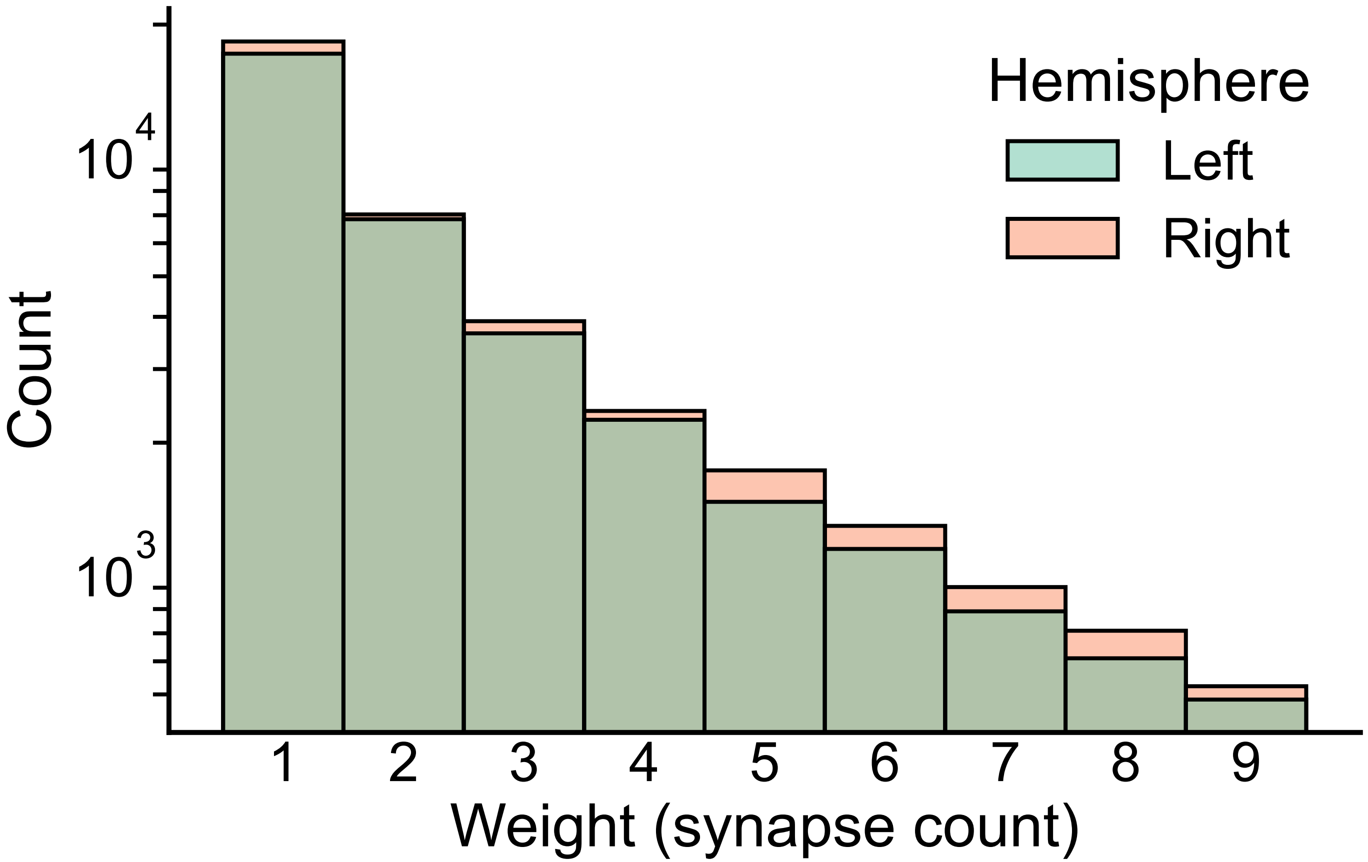

Weight type
Weight $i \rightarrow$ j
Synapse from i to j
Synapse count
i
j
2
Input proportion
i
j
2 / 5
Synapse from not i to j



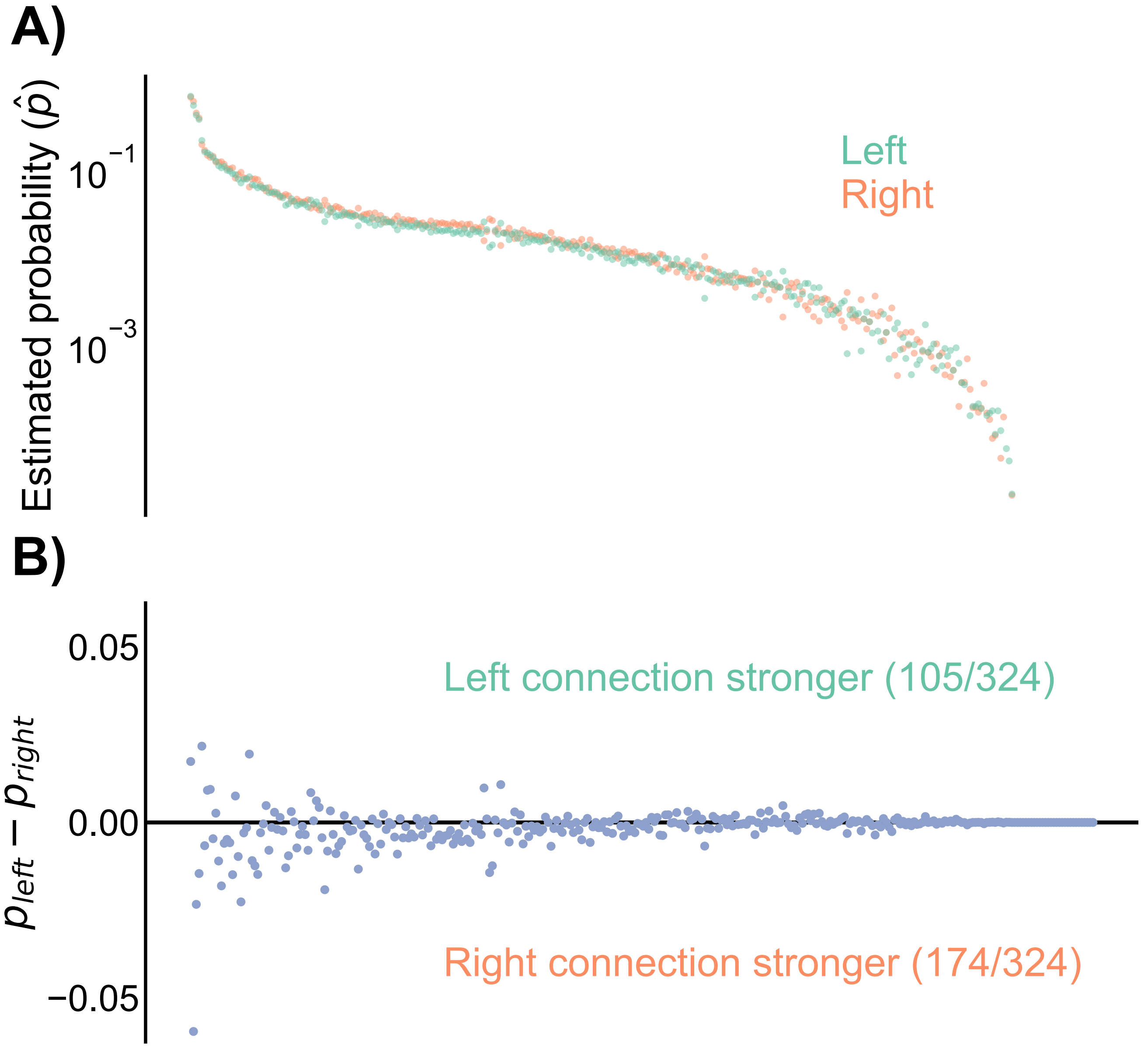
p-value
10^{0}
0.05
10^{-5}
10^{-10}
10^{-15}
10^{-20}
Reject
symmetry
All tests fail to
reject symmetry
Test
Density
Group connection
Density-adjusted
group connection
0%
25%
50%
75%
Edges removed
0.5%
1%
1.5%
2%
Weight threshold (input percentage)

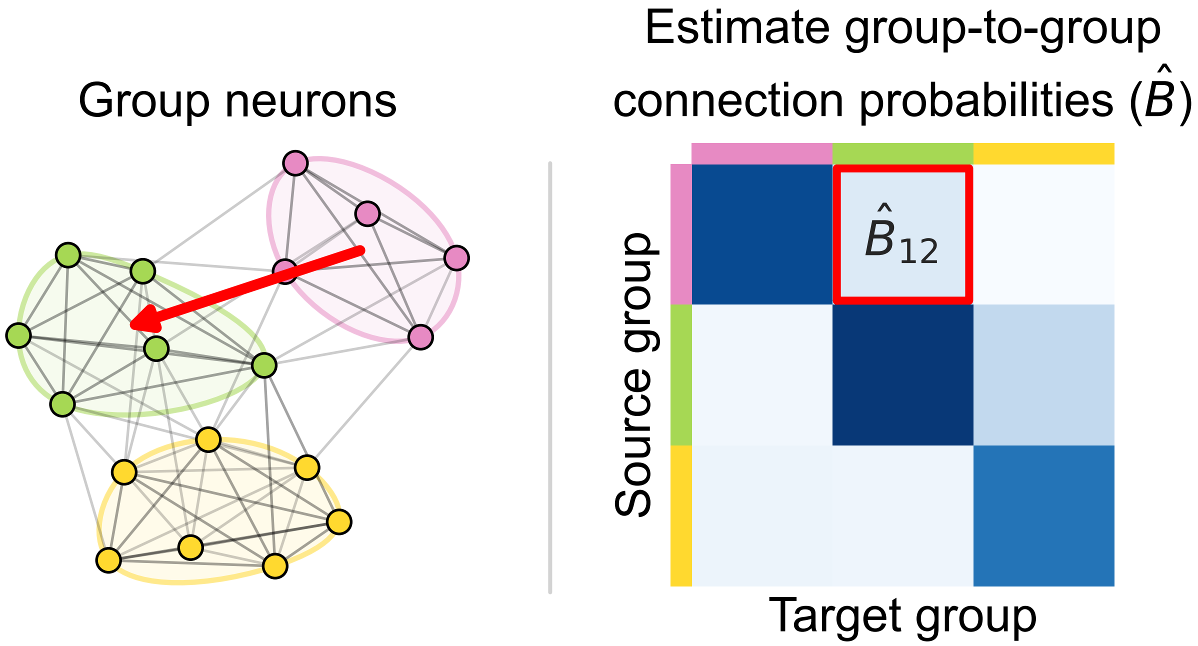

p-value
10^0
0.05
10^{-5}
10^{-10}
10^{-15}
10^{-20}
Reject symmetry
Test
Density
Group connection
Density-adjusted group connection
0%
25%
50%
75%
Edges removed
0
2
4
6
8
Weight threshold (synapse count)


Critical point
(Panel F)
Hemisphere
Left
Right
Count
2000
1000
0.1%
1%
10%
100%
Weight (input percentage)

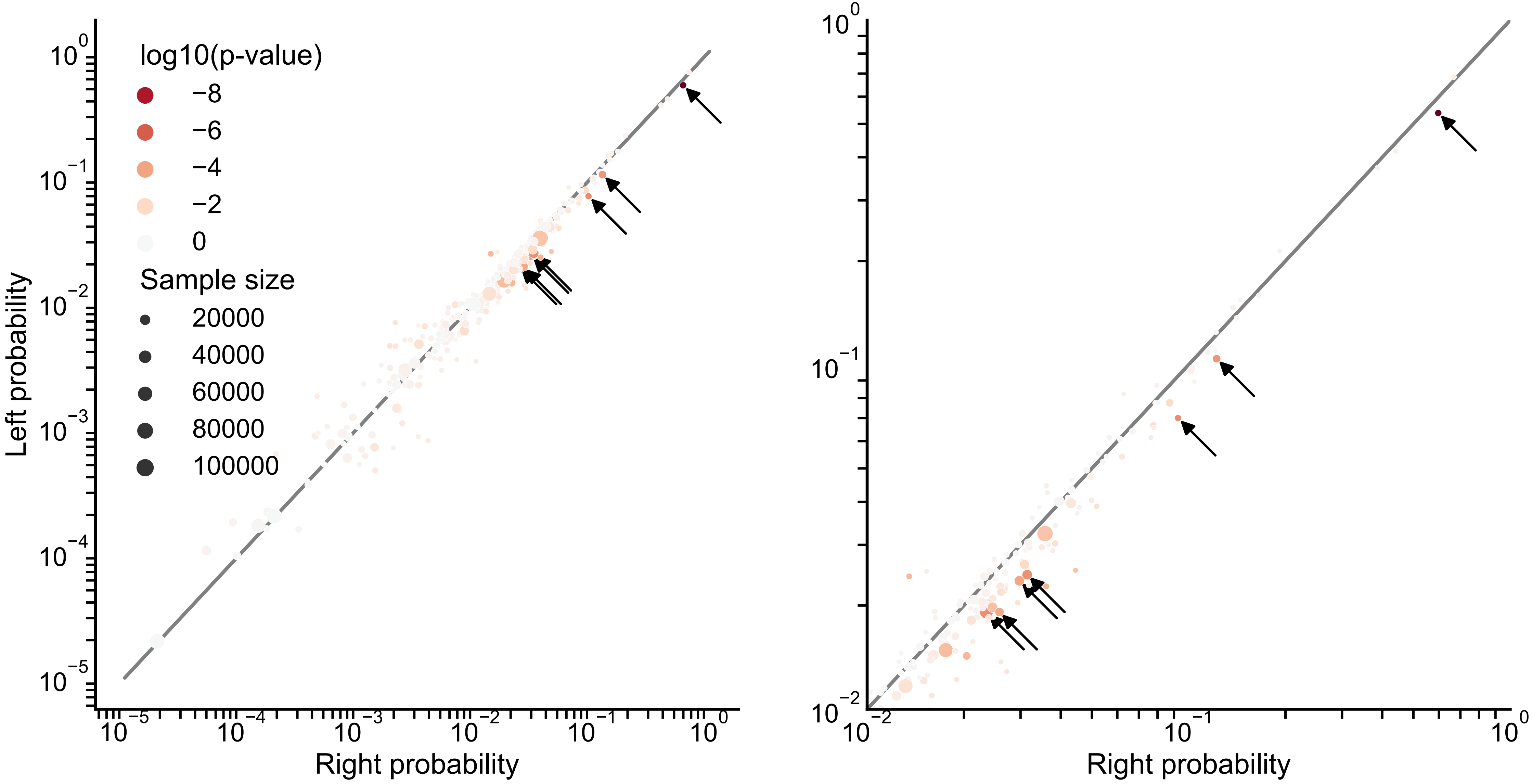


Hemisphere
Left
Right
Count
10^4
10^3
1
2
3
4
5
6
7
8
9
Weight (synapse count)

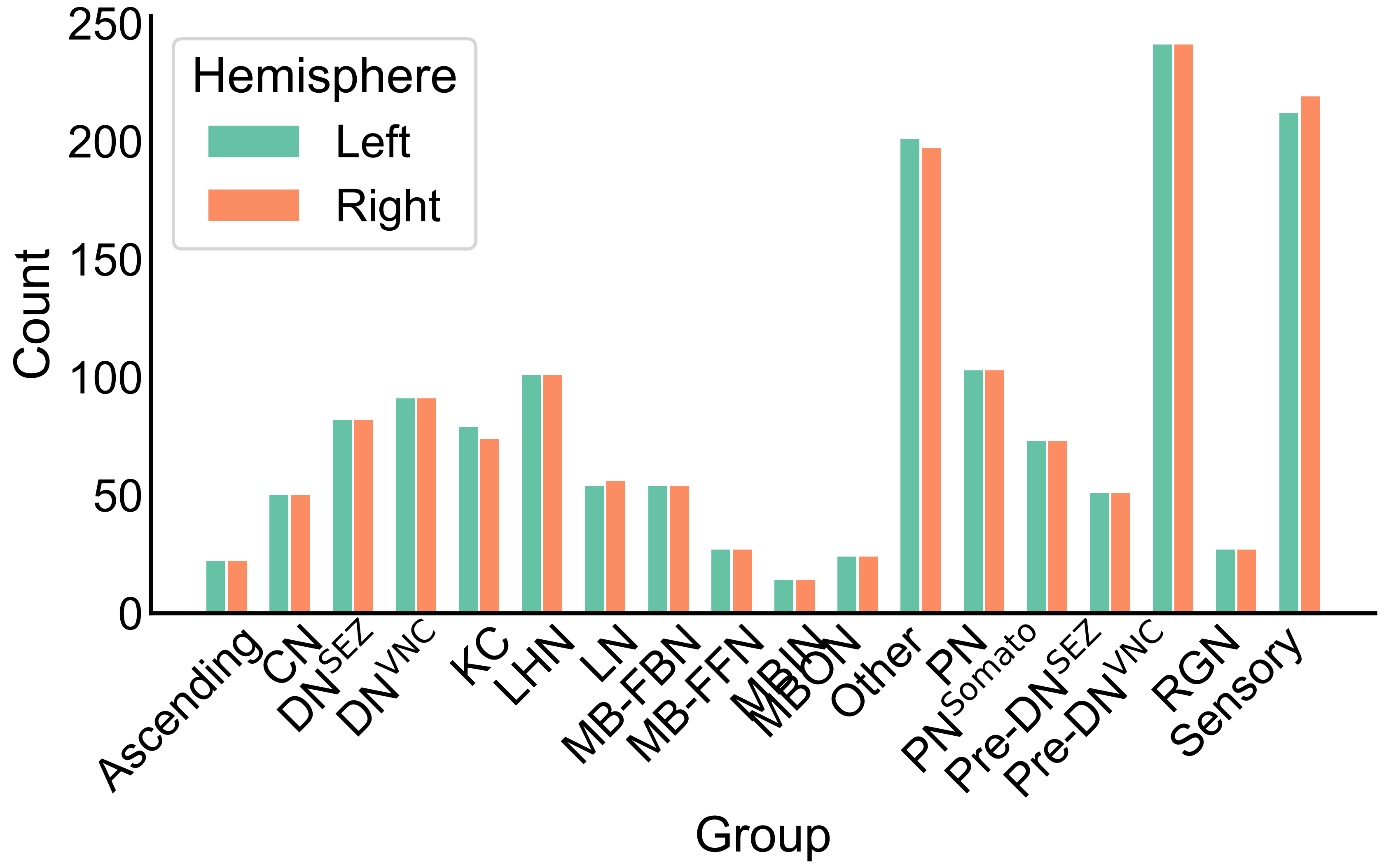

A)
Estimated probability ($\hat{p}$)
10^{-1}
10^{-3}
Left
Right
B)
$\hat{p}_{left} - \hat{p}_{right}$
0.05
0.00
−0.05
Left connection stronger (105/324)
Right connection stronger (174/324)



Group neurons
Estimate group-to-group connection probabilities ($\hat{B}$)
$\hat{B}_{12}$
Source group
Target group



log10(p-value)
−8
−6
−4
−2
0
Sample size
20000
40000
60000
80000
100000
Left probability
Right probability
Right probability



Winding, Pedigo et al. bioRxiv (2022)

Pedigo et al. Network Neuroscience (2022)

How do we do graph matching?

- Relax the problem to a continuos space
    - Convex hull of permutation matrices
- Minimize a linear approximation of objective function (repeat)
- Project back to the closest permutation matrix

Vogelstein et al. PLOS One (2015)

Algorithm

Algorithm 1 Bisected Graph Matching (BGM) via Frank-Wolfe. To recover the FAQ algorithm (Vogelstein et al., 2015) (GM), simply set A_{LR}, A_{RL} to the zero matrix.

Require: Adjacency matrices for each of the four subgraphs: $A_{LL}, A_{RR}, A_{LR}, A_{RL} \in \mathbb{R}^{n \times n}$.

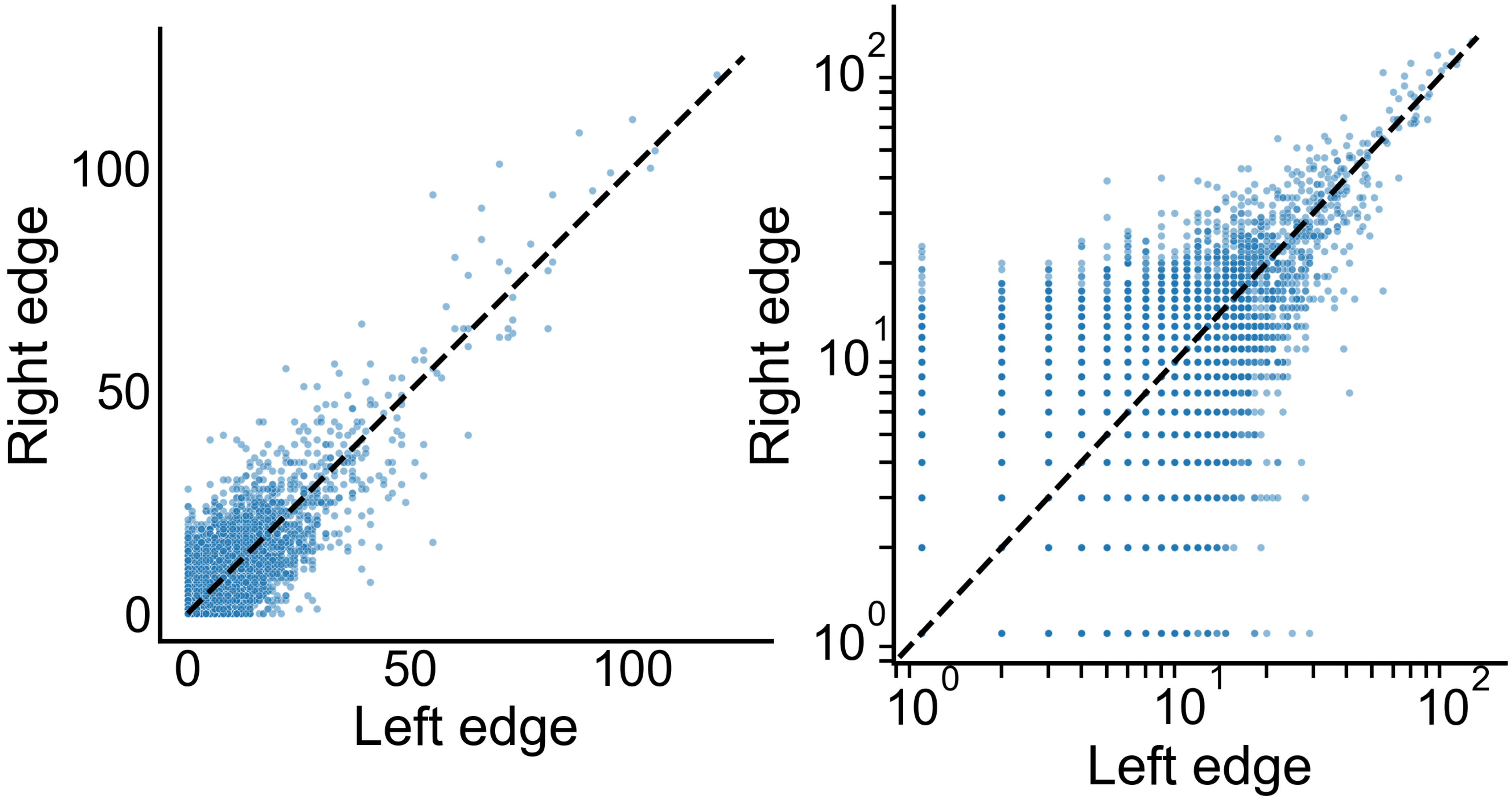
Initialize: $P_{(0)} \in \mathcal{D}$, barycenter ($P_{(0)} = \frac{1}{n}\mathbf{1}_n \times \mathbf{1}_n^\intercal$) unless otherwise specified

for $i = 1, 2, 3, \ldots$ while ($i \leq \text{MAXITER}$) and ($\|P_i - P_{i-1}\|_F \geq \text{TOLERANCE}$)) **do**

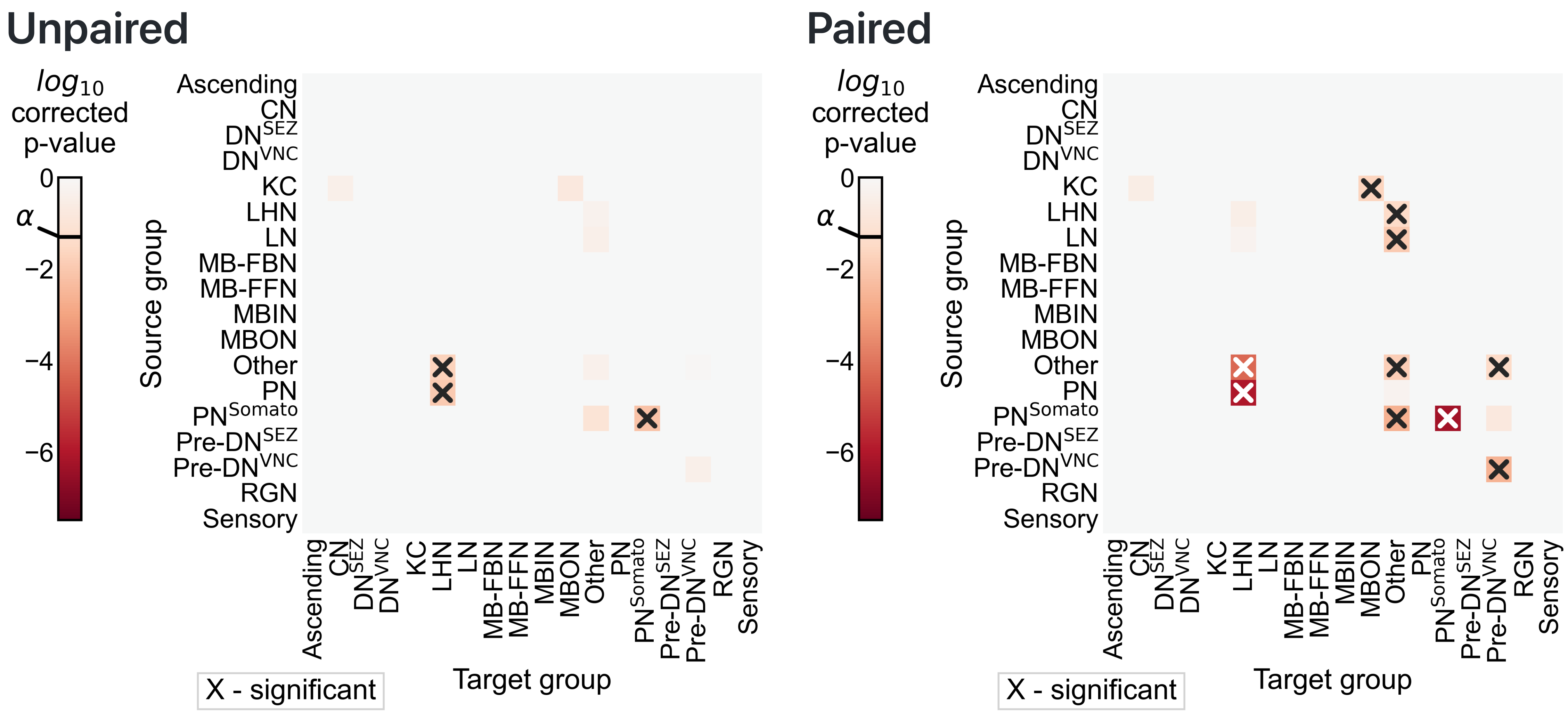
1. Compute $\nabla f(P_{(i)}) = -\left(A_{LL}P_{(i)}A_{RR}^T + A_{LL}^T P_{(i)} A_{RR} + A_{LR}P_{(i)}^T A_{RL} + A_{RL}^T P_{(i)}^T A_{LR}\right)$
2. Compute $Q_{(i)} \in \operatorname{argmin} \operatorname{tr}\left(Q^T \nabla f(P_{(i)})\right)$ over $Q \in \mathcal{D}$ via linear assignment problem solver, e.g. Hungarian algorithm (Kuhn, 1955)
3. Compute step size $\alpha^{(i)} \in \operatorname{argmin} f(\alpha P_{(i)} + (1-\alpha)Q_{(i)})$, for $\alpha \in [0, 1]$
4. Set $P_{(i+1)} = \alpha P_{(i)} + (1-\alpha)Q_{(i)}$

end for

return $\hat{Q} \in \operatorname{argmin} \operatorname{tr}\left(Q^T \nabla f(P_{(final)})\right)$ over $Q \in \mathcal{P}$ via linear assignment problem solver.

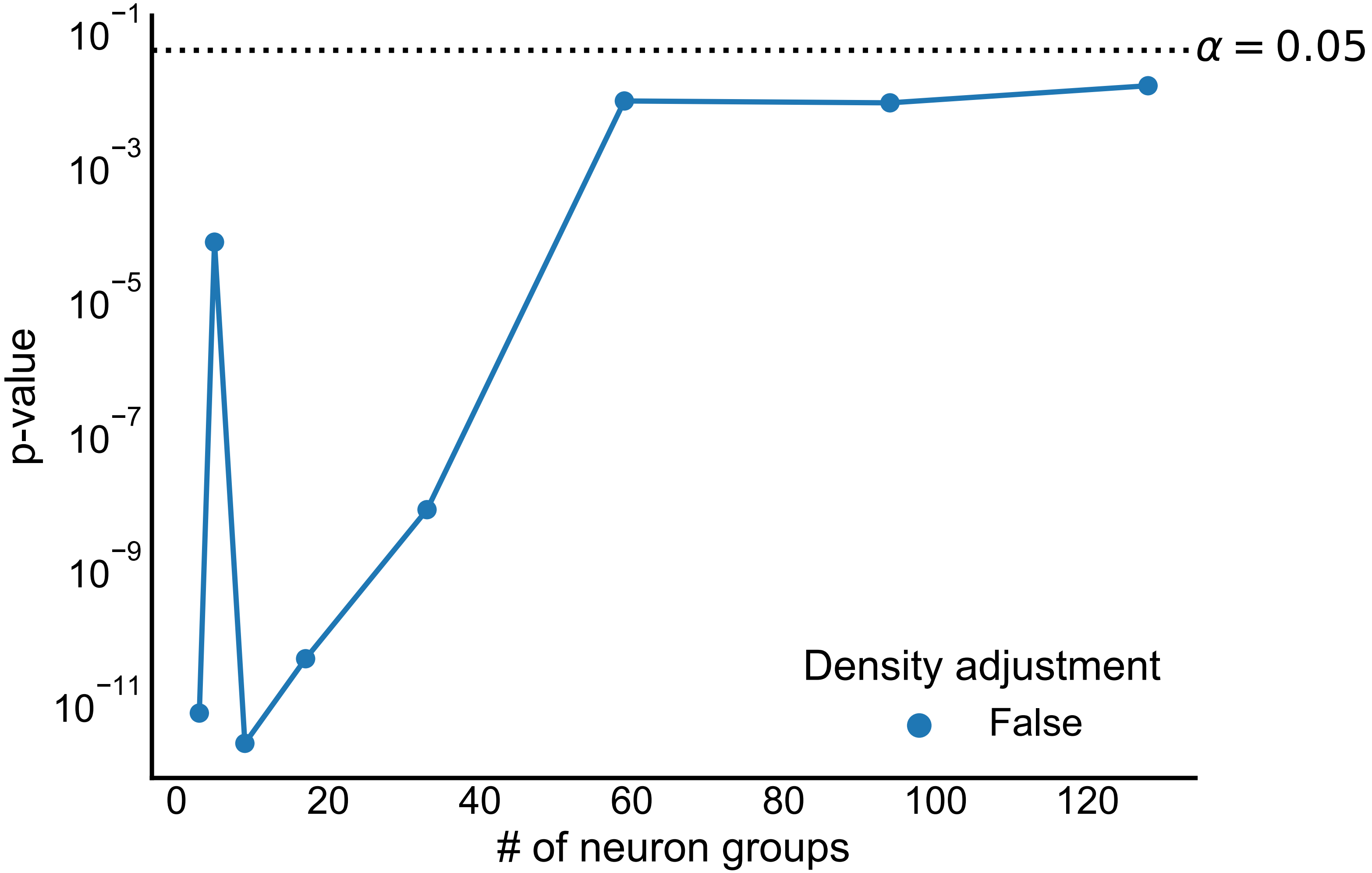


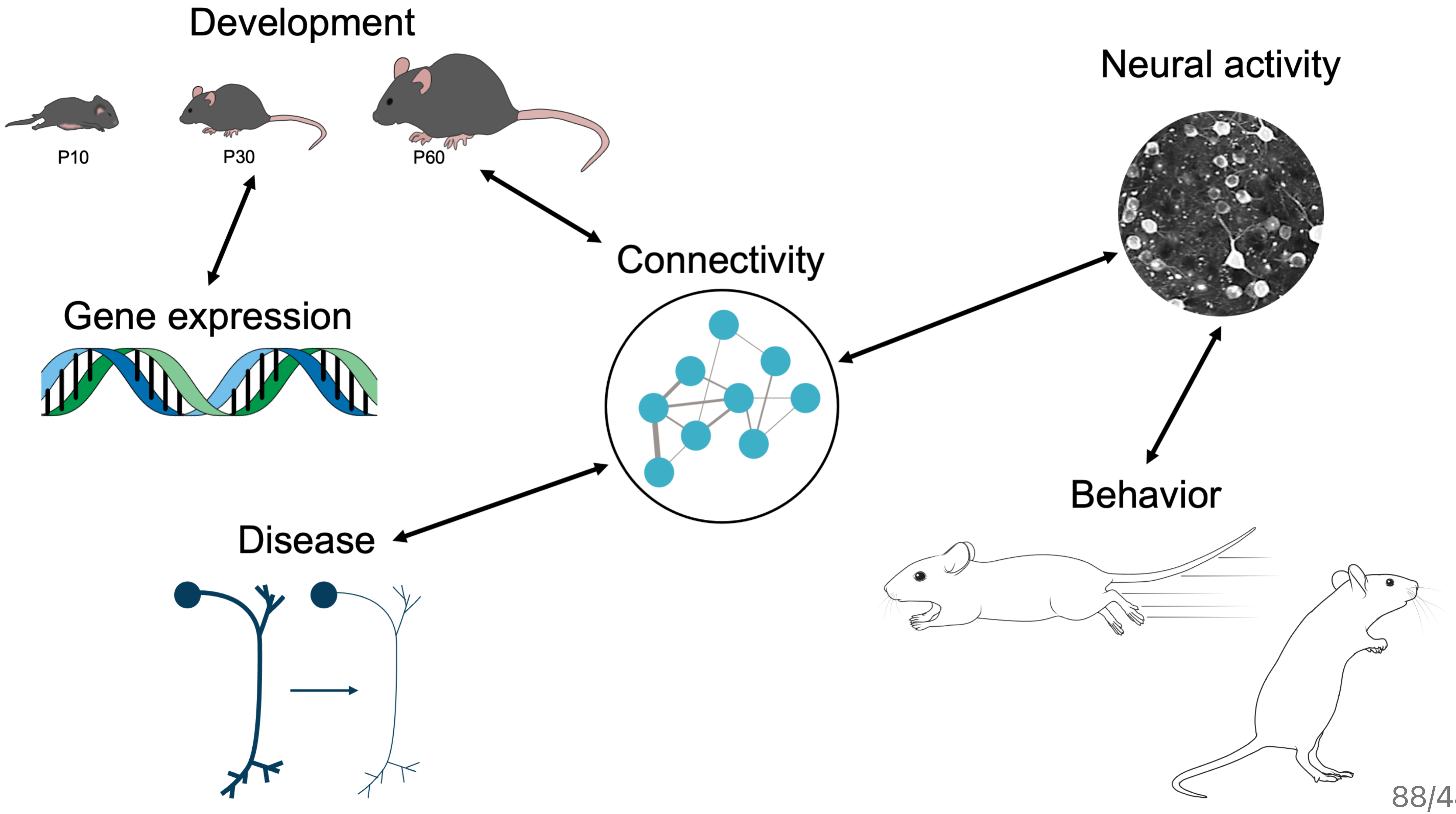
Pearson's corr = 0.82



Unpaired
Paired
log_{10} corrected p-value
0
α
−2
−4
−6
Source group
Ascending
CN
DN^{SEZ}
DN^{VNC}
KC
LHN
LN
MB-FBN
MB-FFN
MBIN
MBON
Other
PN
PN^{Somato}
Pre-DN^{SEZ}
Pre-DN^{VNC}
RGN
Sensory
Target group
X - significant

Using predicted groups

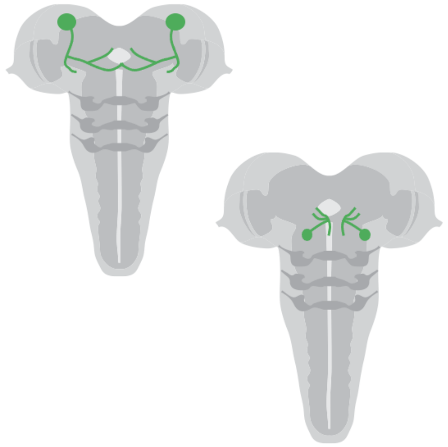




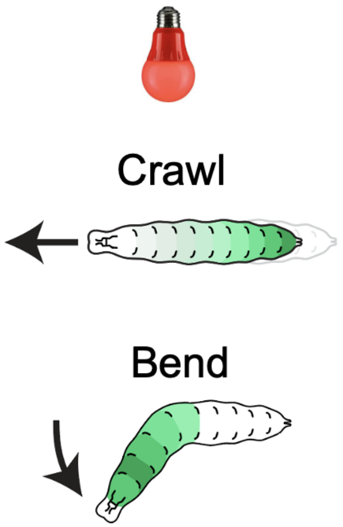
Development
P10
P30
P60
Neural activity
Connectivity
Gene expression
Behavior
Disease

A structure-function relationship in the larva

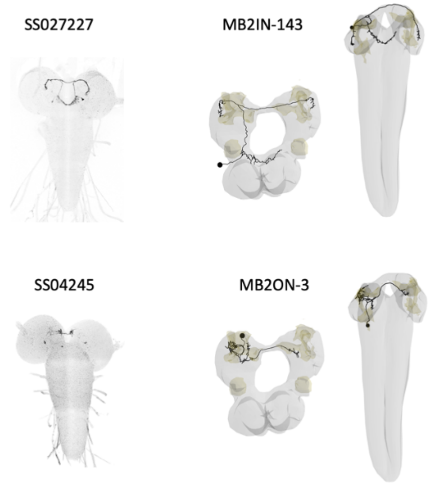
Genetic driver lines for L/R neuron pairs



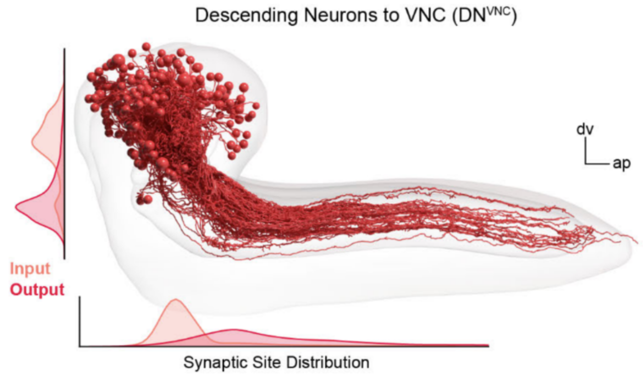
Behaviors measured under stimulation



Mapping to connectome via morphology



Comparison of projections to brain outputs



Behavior probabilities significantly related to projections to brain outputs

RV coefficient: 0.12, p-value: 0.0044

Distance correlation: 0.067, p-value: 0.0087