Comparative connectomics: methods and applications

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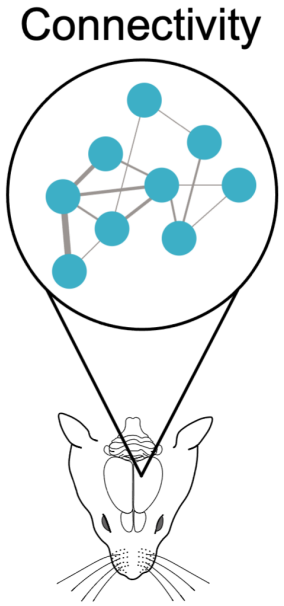
These slides at:

bdpedigo.github.io/talks/si.html

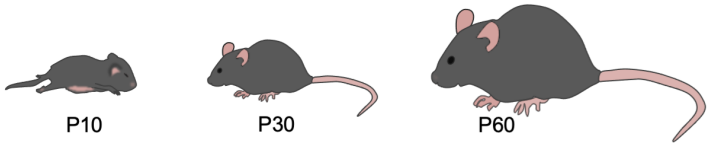
Connectomes: maps of neural wiring



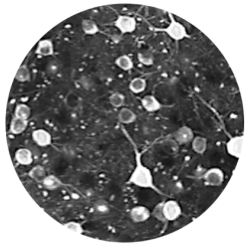
Images from brain-map.org, SciDraw

Goal: linking connectivity to other phenotypes

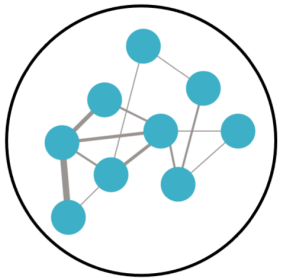
Development



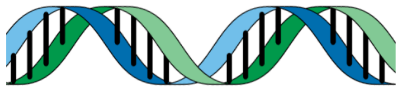
Neural activity



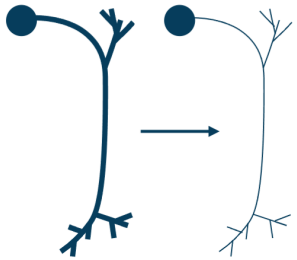
Connectivity



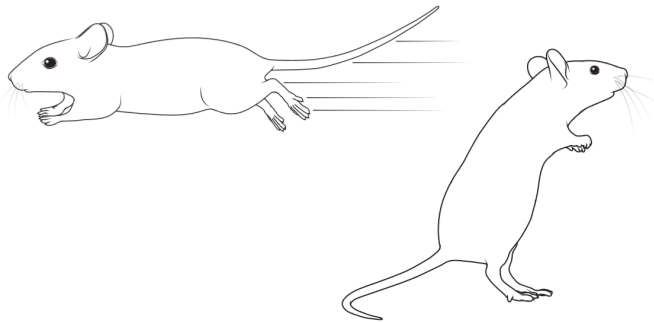
Gene expression



Disease

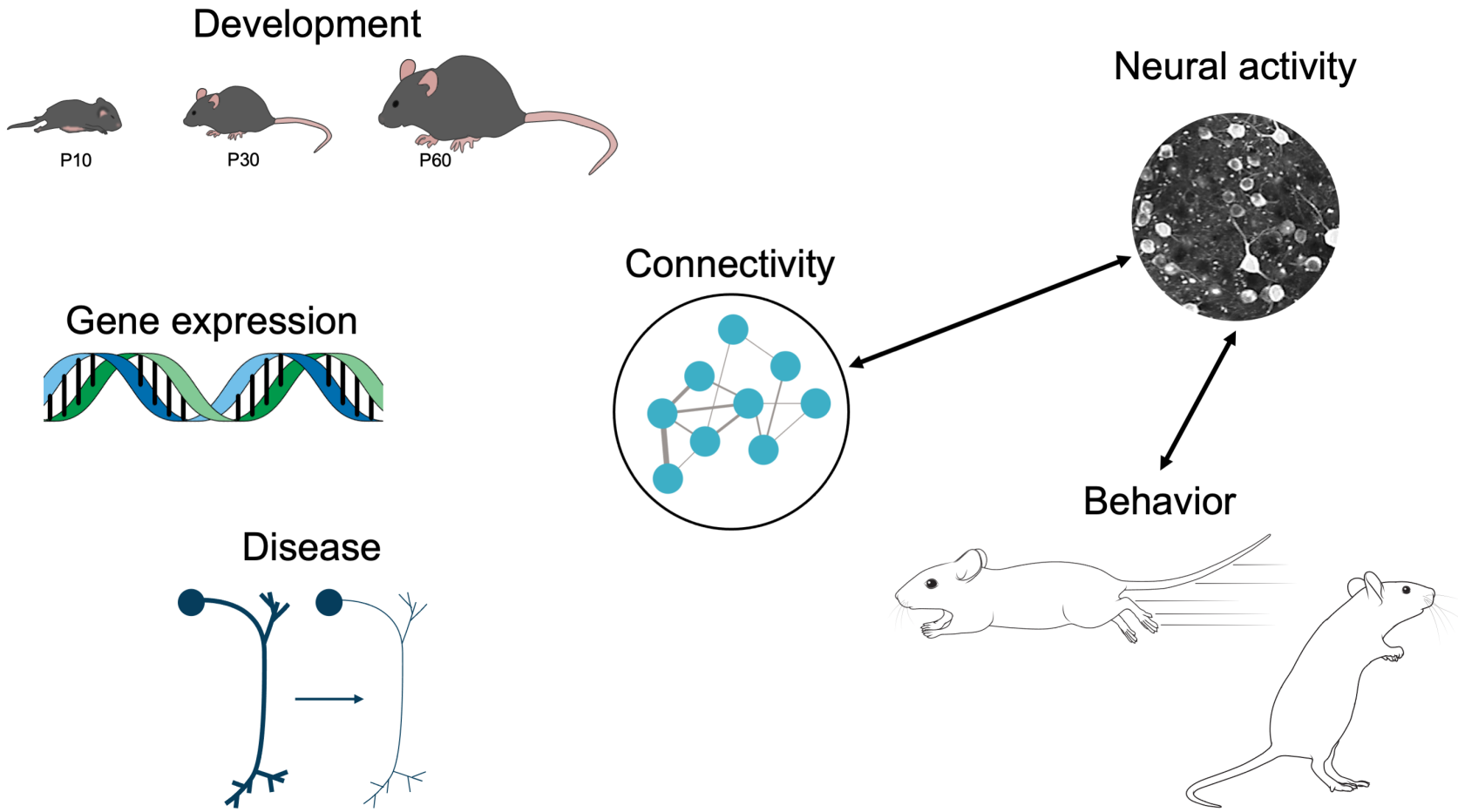


Behavior



Images from brain-map.org, SciDraw

Goal: linking connectivity to other phenotypes



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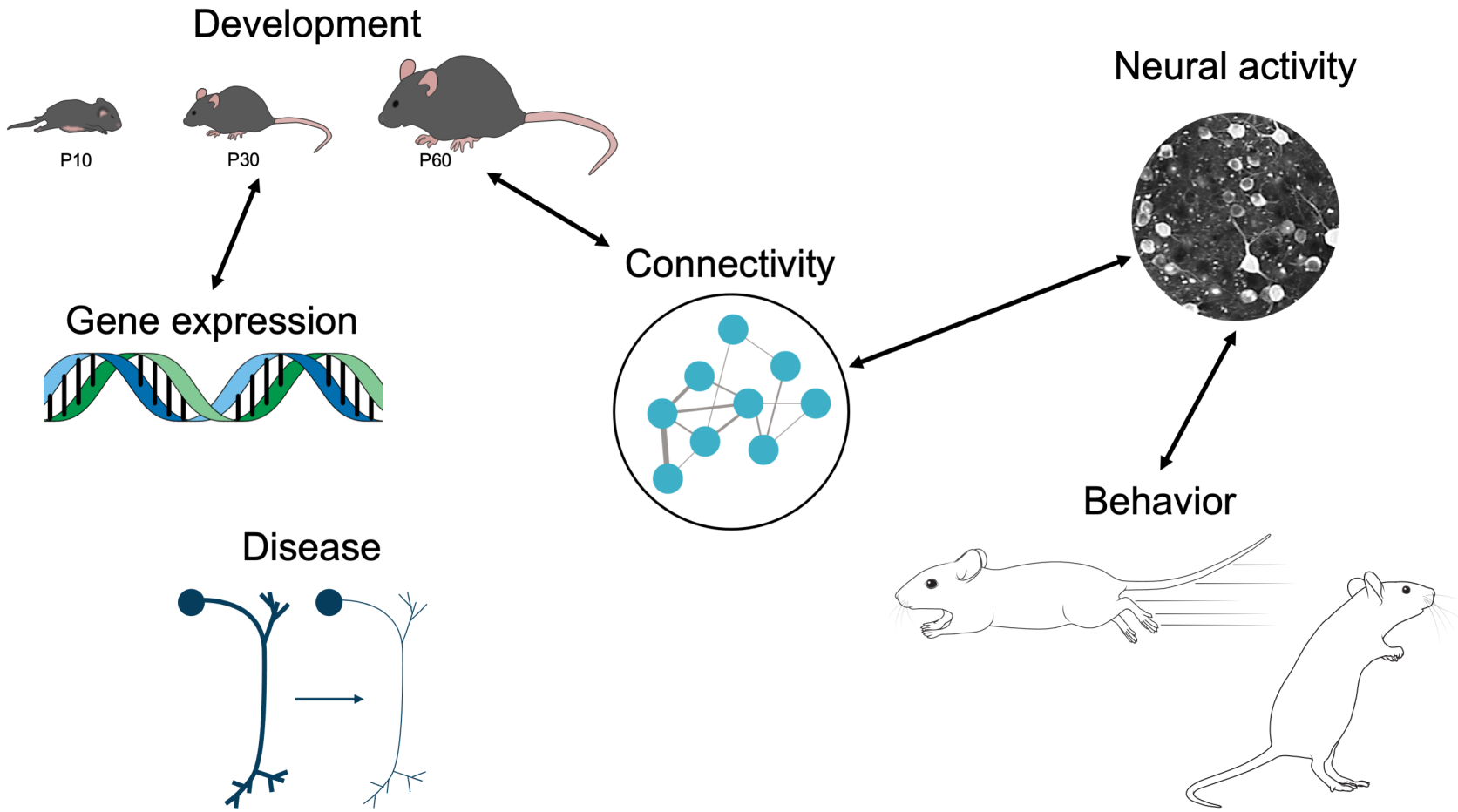
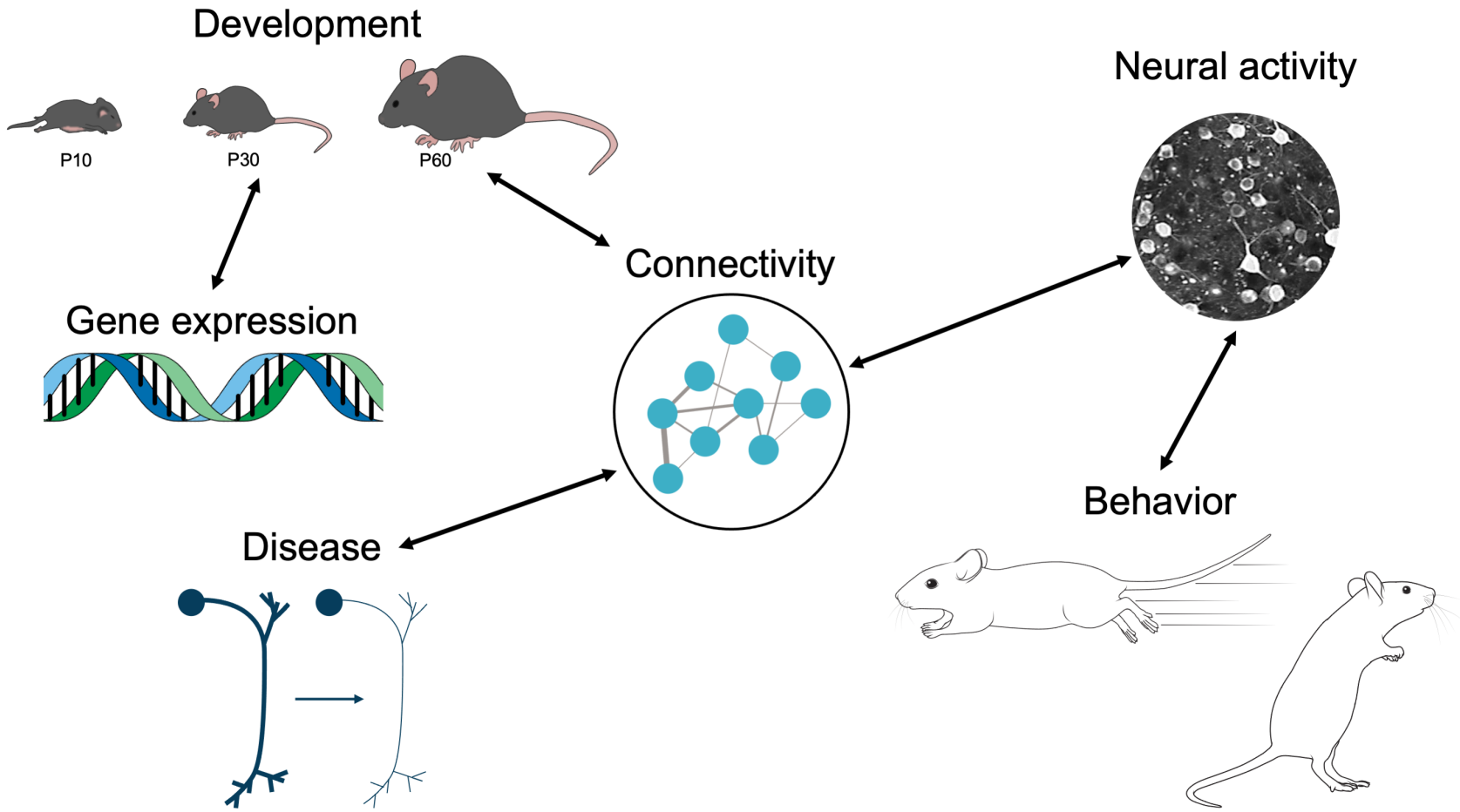
Goal: linking connectivity to other phenotypes



Images from brain-map.org, SciDraw

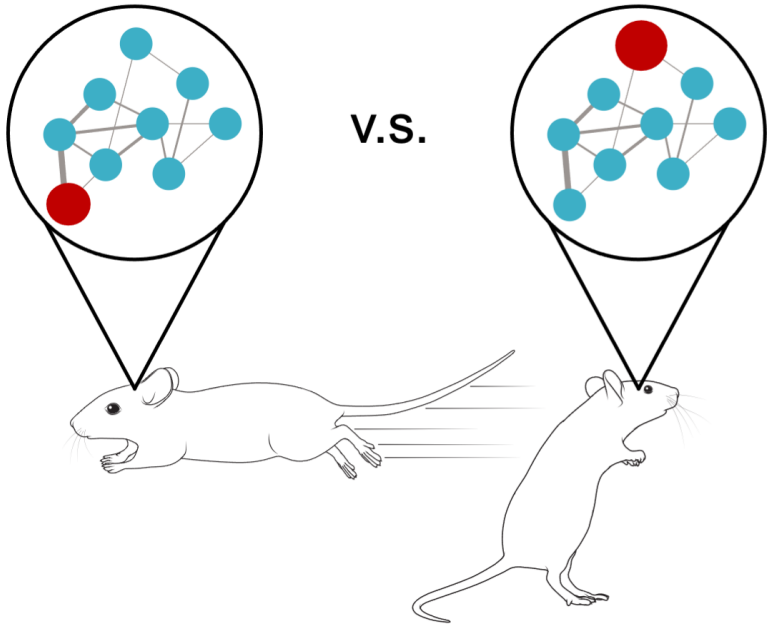
Goal: linking connectivity to other phenotypes



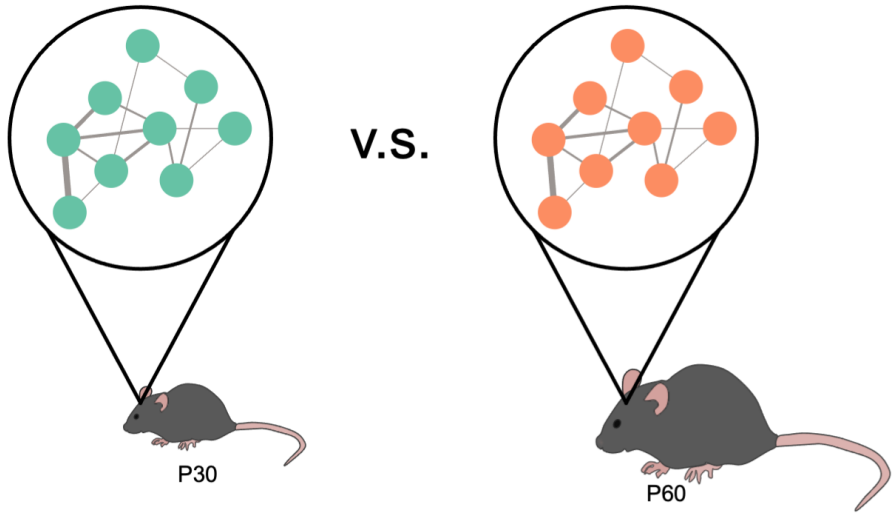
Images from brain-map.org, SciDraw

Comparative connectomics

How does a neuron's connectivity affect elicited behaviors?



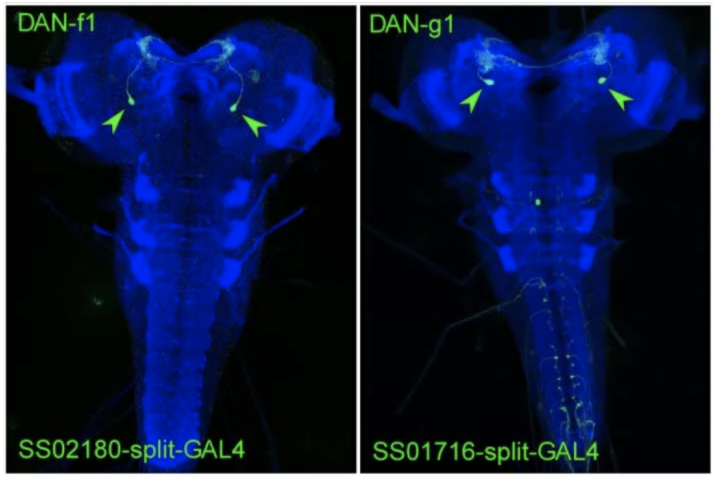
How does connectivity change during development?



Requires methods of comparing connectivity within and between connectomes

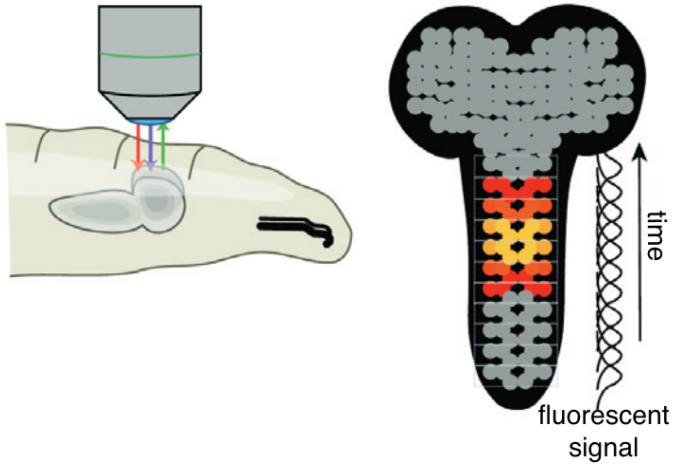
Larval *Drosophila* as a model system

Genetics



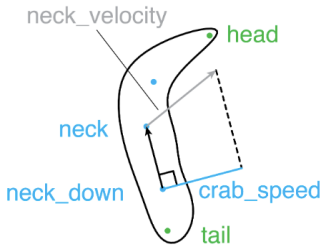
Eschbach et al. Nat. Neuro (2020)

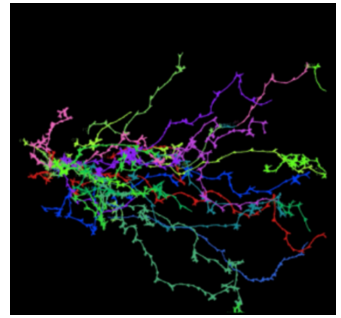
Activity



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

Behavior

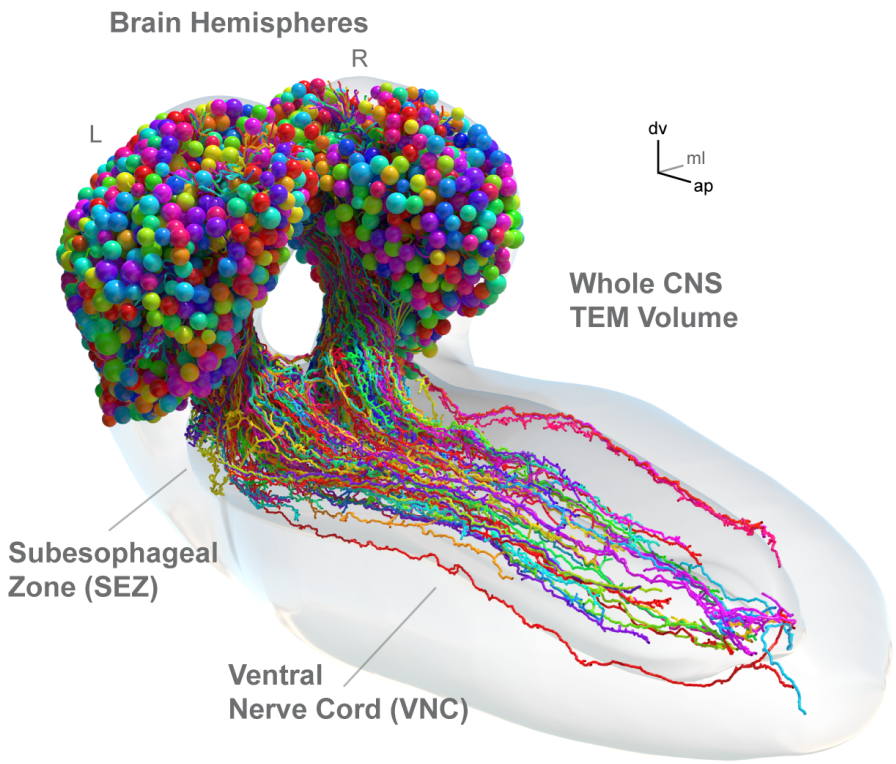


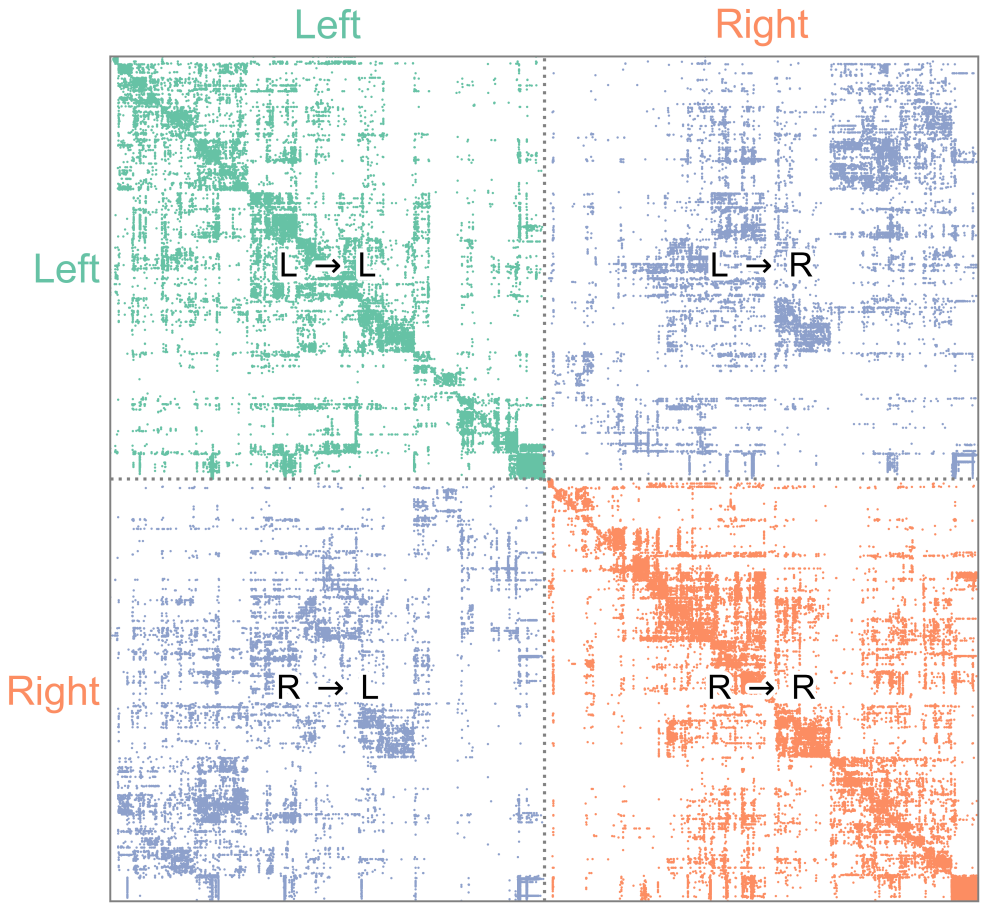


Klein et al. bioRxiv (2021)

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

Larval *Drosophila* brain connectome

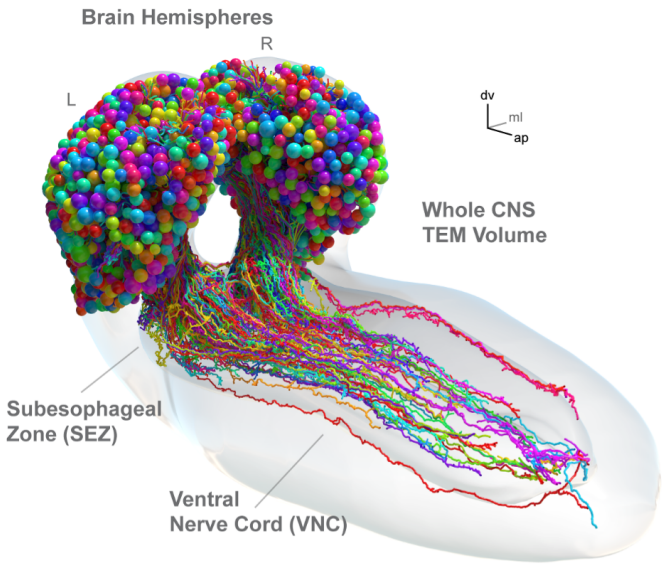




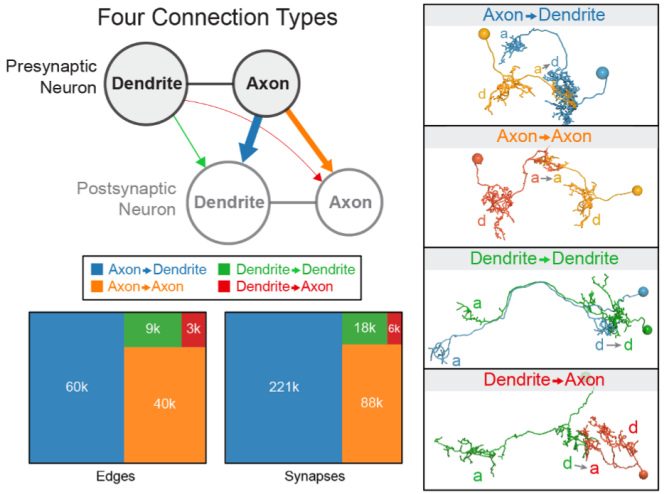
~3k neurons, ~550K synaptic sites

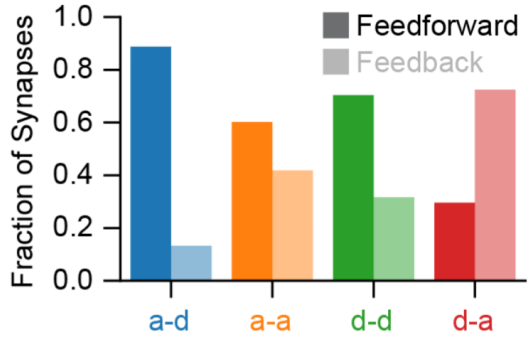
Both hemispheres

Winding, Pedigo et al. Science (2023)

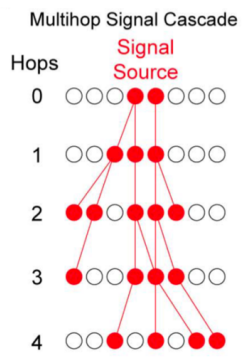


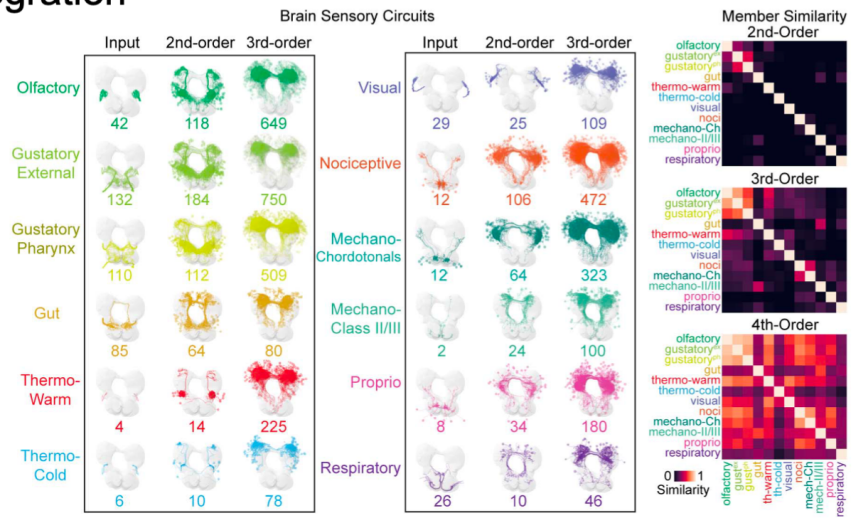
Role of connection types in feedforward/feedback flow



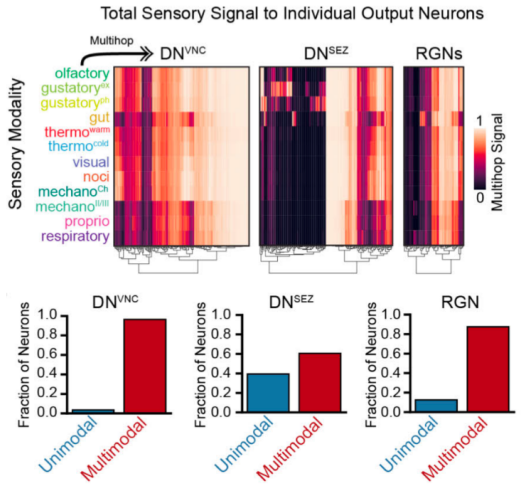


Routes for sensory integration





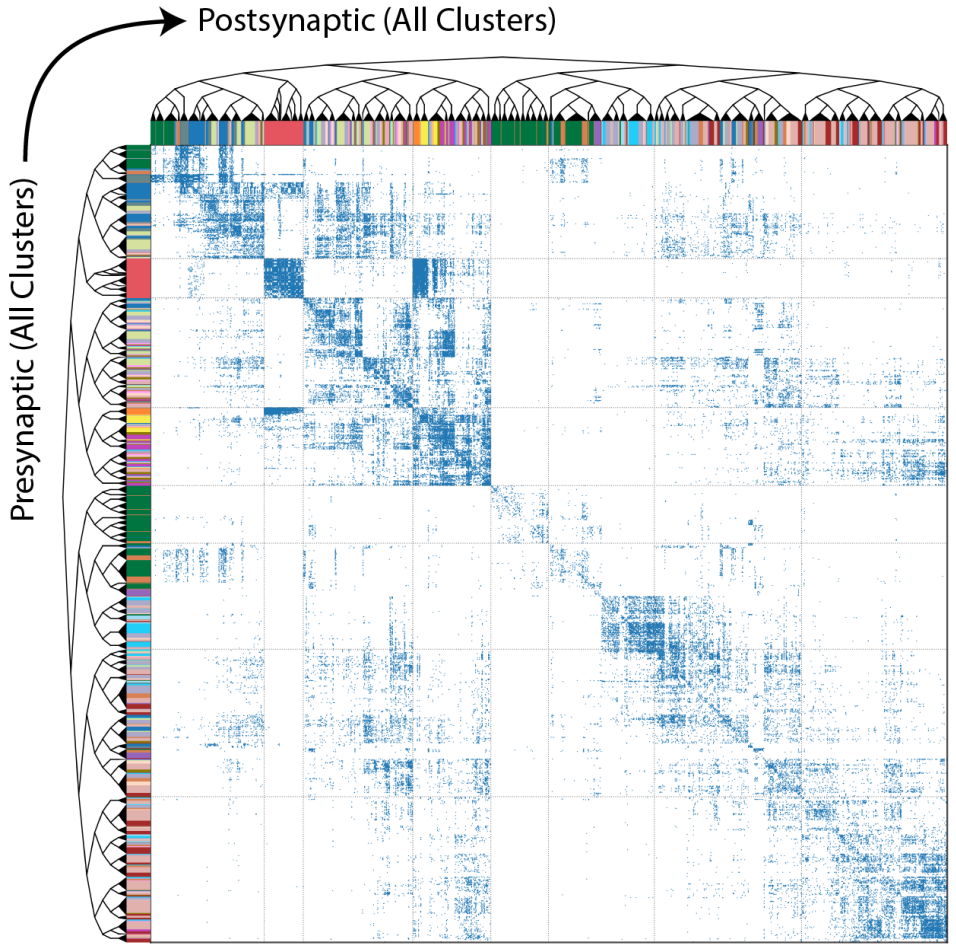
Routes to brain outputs



Outline

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

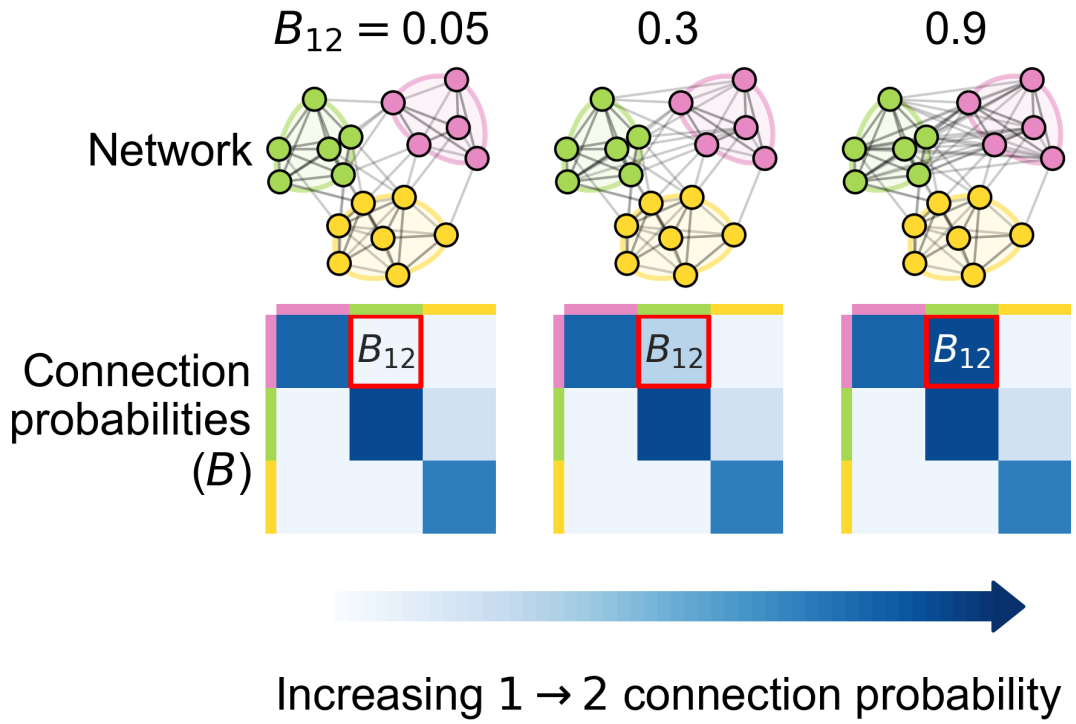
Neurons clustered by connectivity



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

Winding, Pedigo et al. Science (2023)

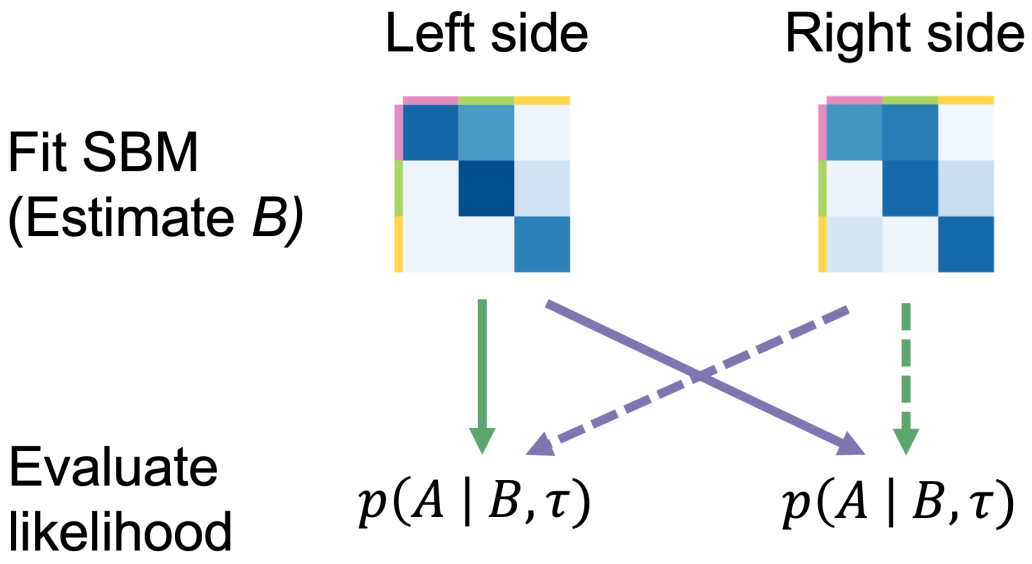
Stochastic block model



- 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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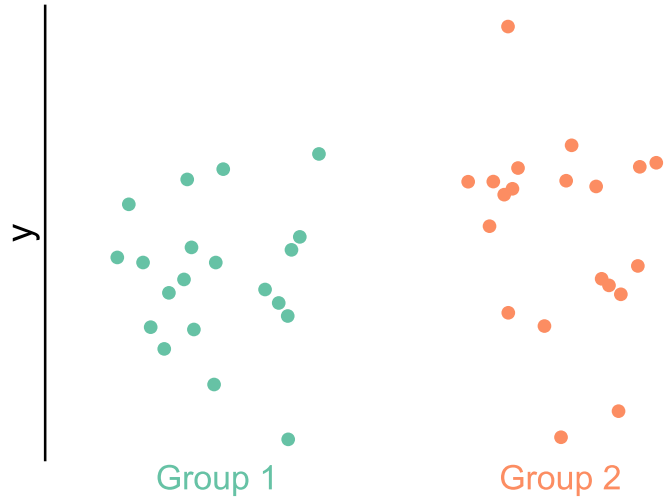
Testing for differences

Are these two populations different?



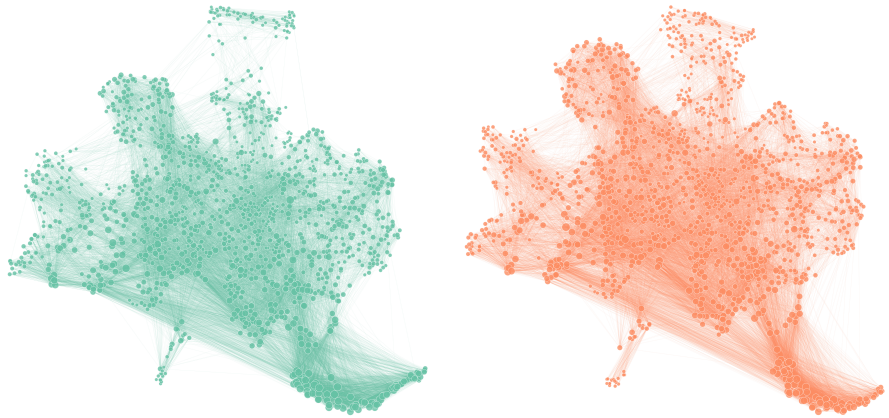
$$Y^{(1)} \sim F^{(1)} \quad Y^{(2)} \sim F^{(2)}$$

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

vs.

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

Are these two *networks* different?



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

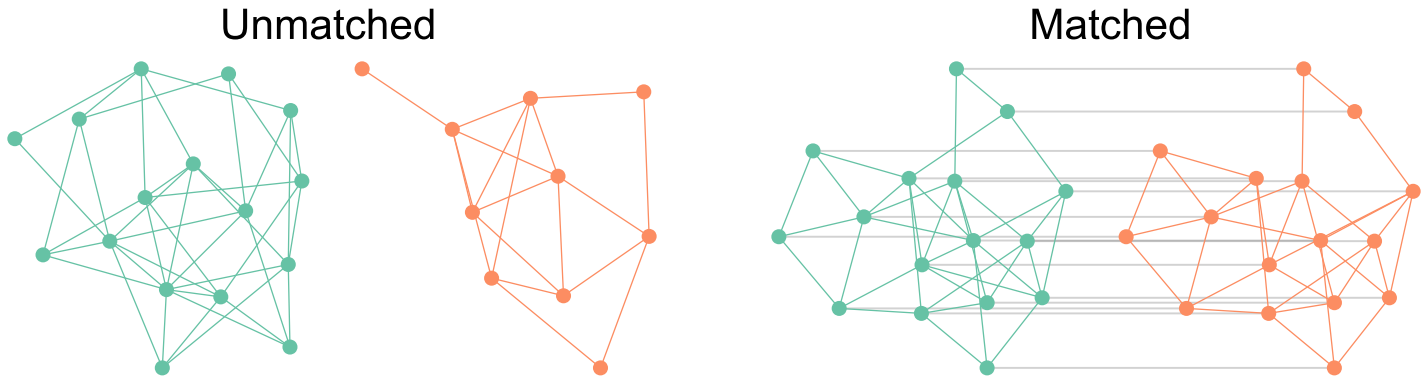
$$H_0 : F^{(L)} = F^{(R)}$$

vs.

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

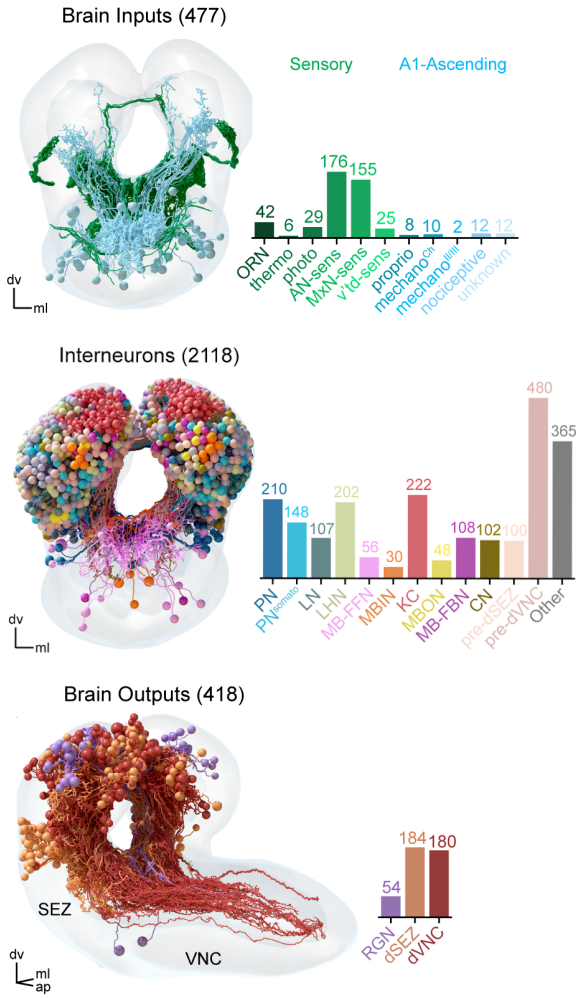
Assumptions

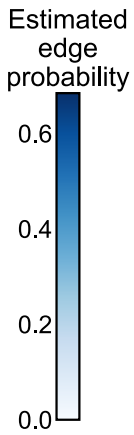
- Know the direction of synapses, so network is *directed*
- Consider networks to be *unweighted*
- Not assuming any nodes are matched:

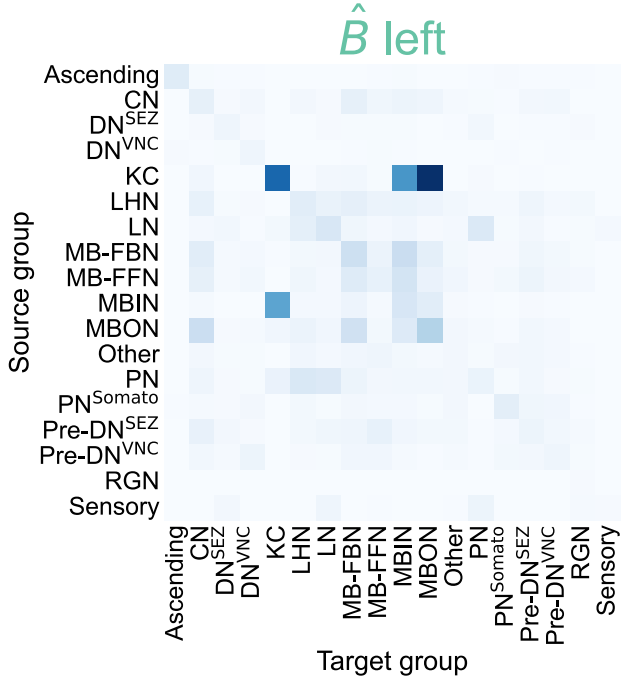


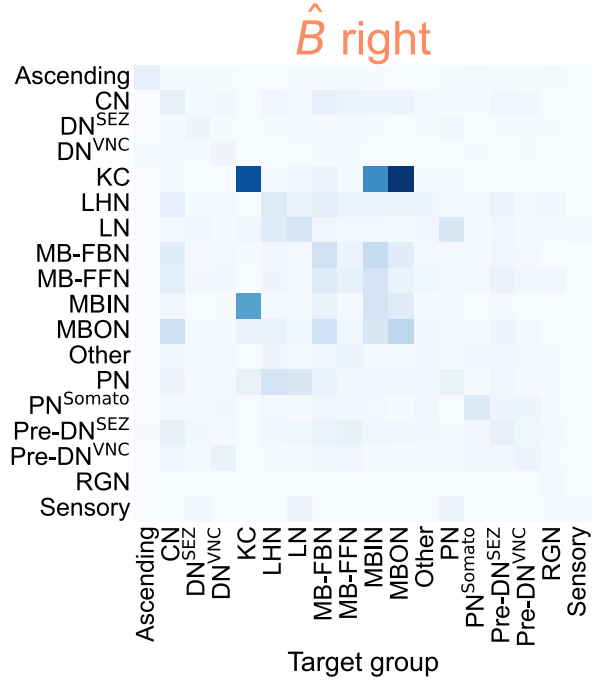
- If F is again a stochastic block model, then...

Connection probabilities between groups





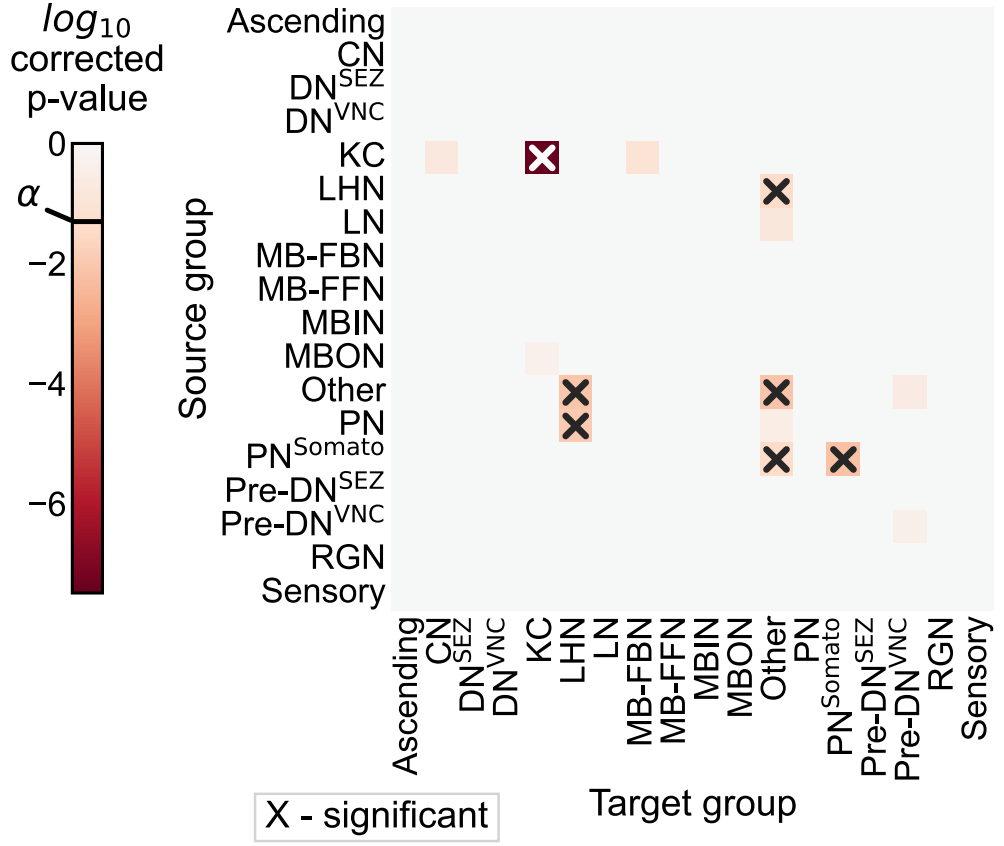




Detect differences in group connection probabilities

- 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)

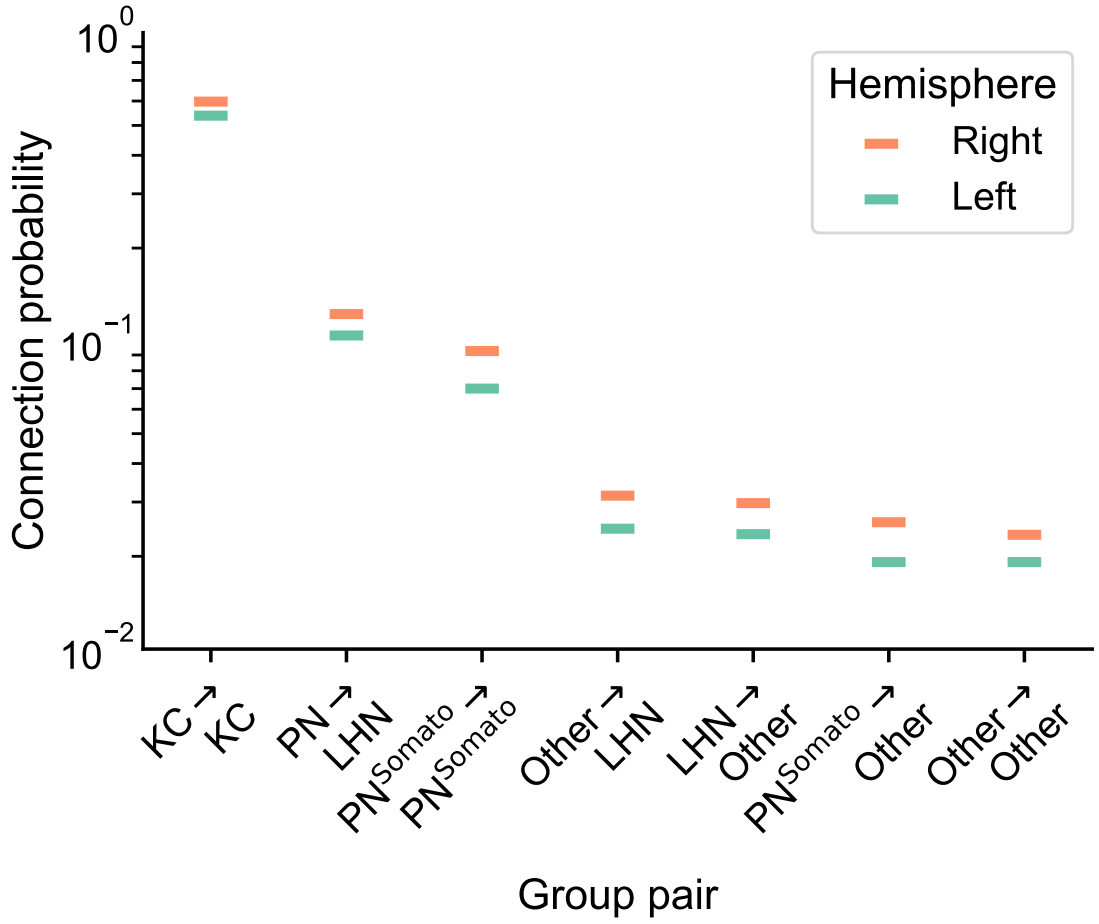
$$H_0 : B^{(L)}_{kl} = B^{(R)}_{kl}$$



An overall difference in density

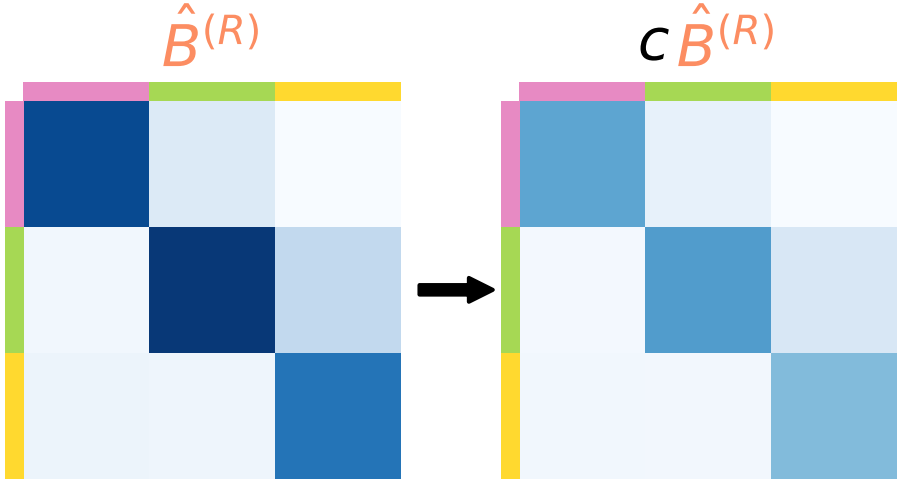
- For significant comparisons, probabilities on right side are higher
- Even network densities are different (1-block/Erdos-Renyi model)
- Maybe the right is just a "scaled up" version of the left?
  - $H_0 : B^{(L)} = cB^{(R)}$

    c is a density-adjusting constant

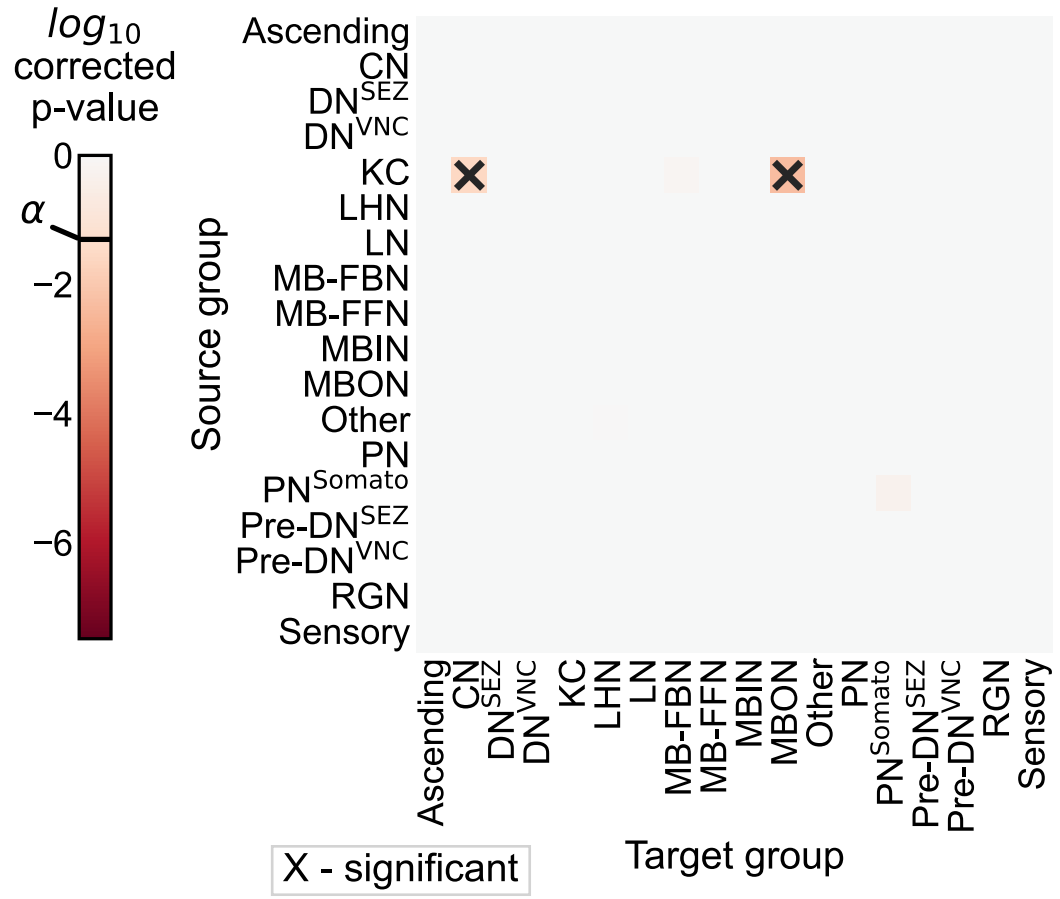


After adjusting for density, differences are in KCs

Scale connection probabilities to match densities



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



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)

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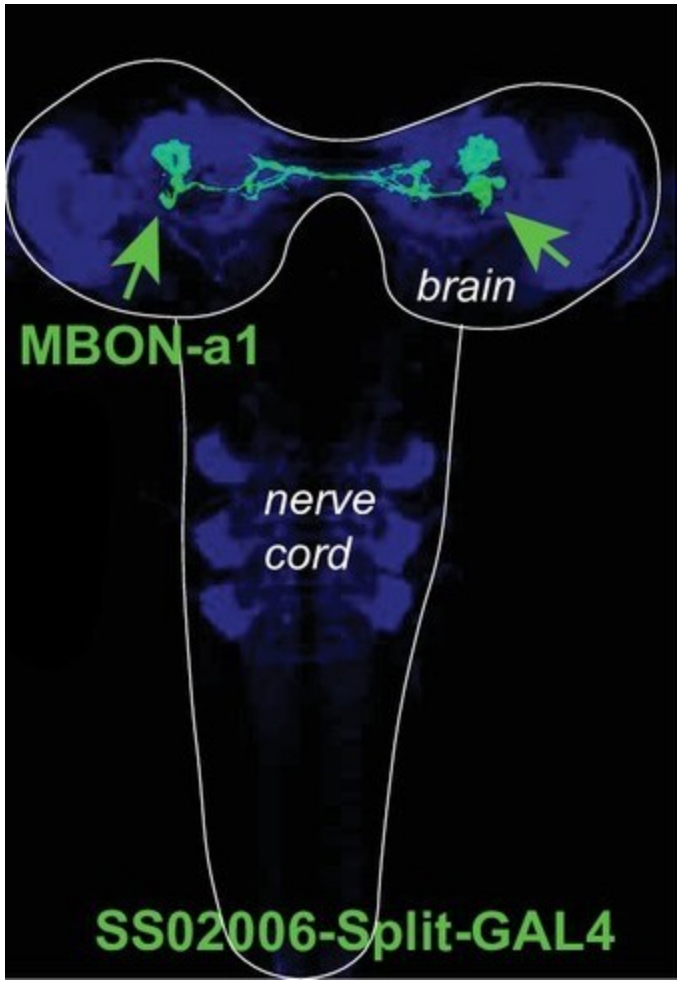
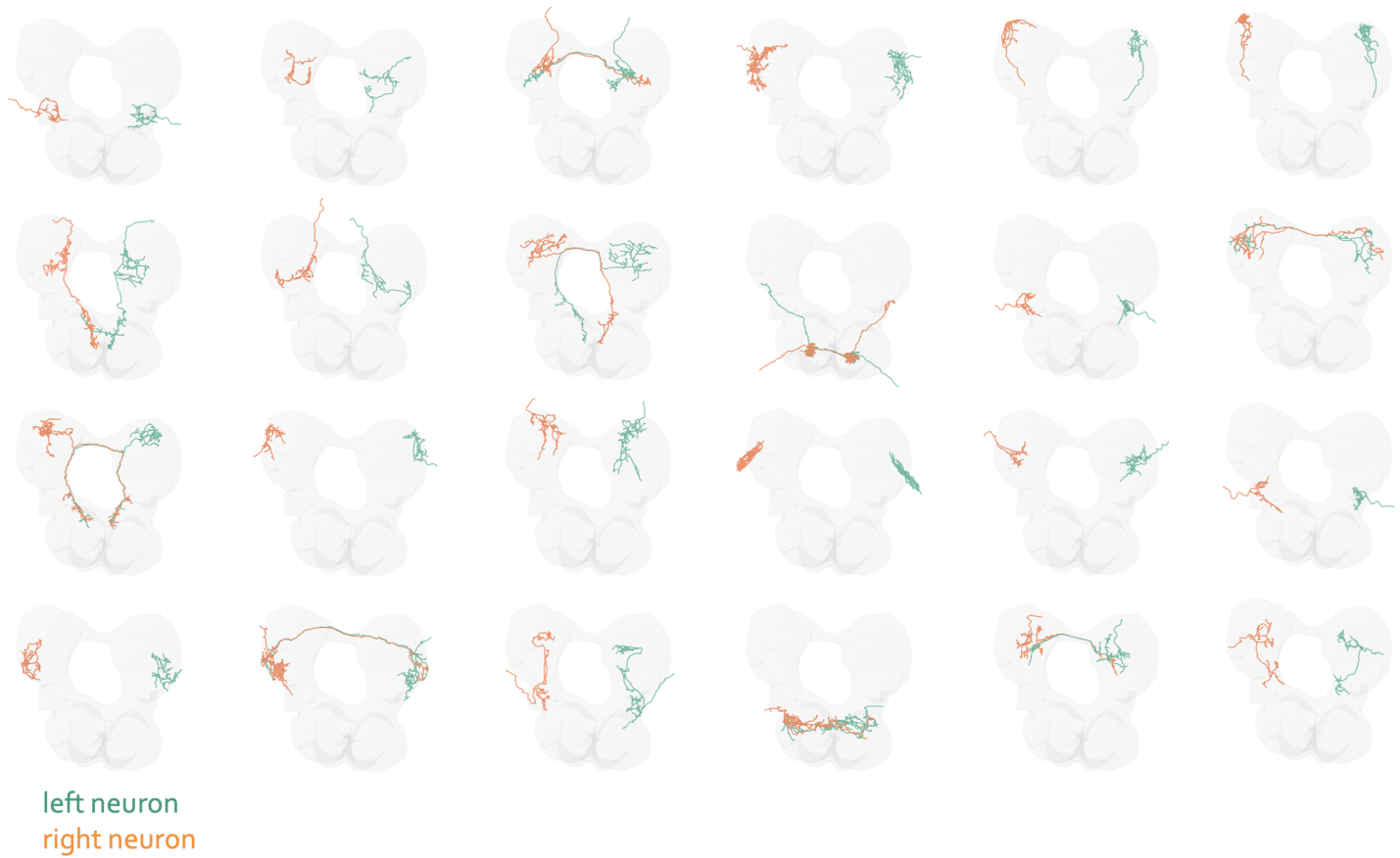
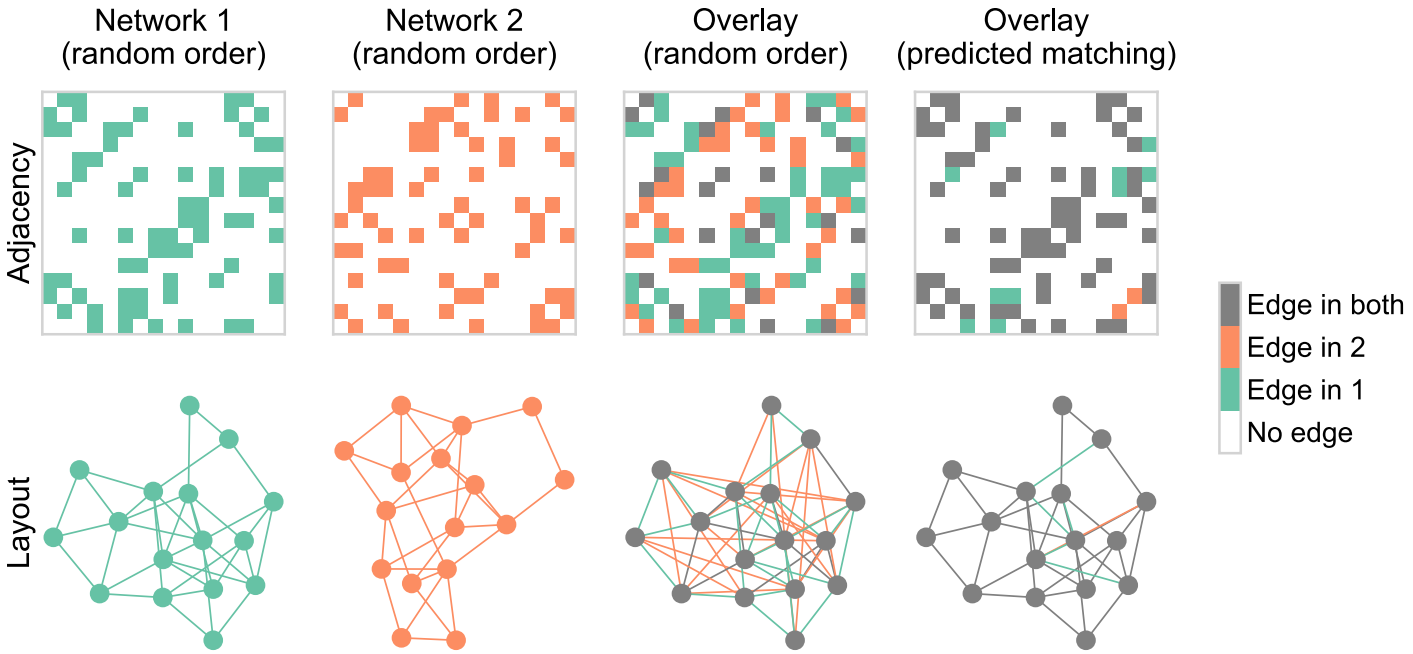
Bilaterally homologous neuron pairs





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

How can we pair on connectivity?

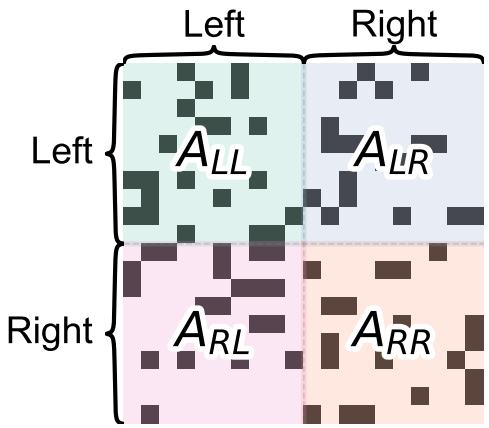


$$\min_{P \in \mathcal{P}} \underbrace{\| A_1 - \overbrace{P A_2 P^T}^{\text{reordered } A_2} \|_F^2}_{\text{distance between adj. mats.}}$$

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

From graph matching to bisected graph matching

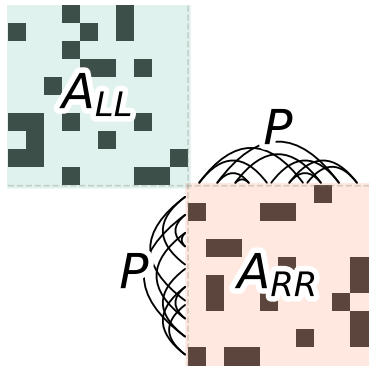
Adjacency matrix



Ipsilateral → A_{LL}, A_{RR}

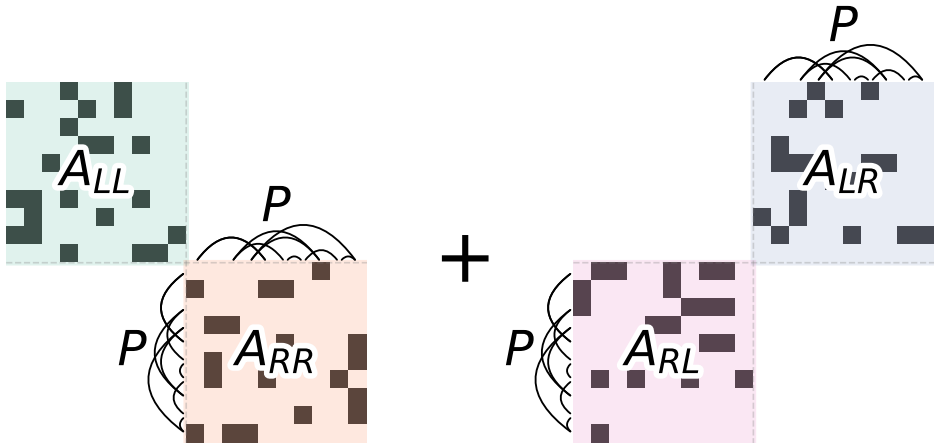
Contralateral → A_{LR}, A_{RL}

Graph matching (GM)



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

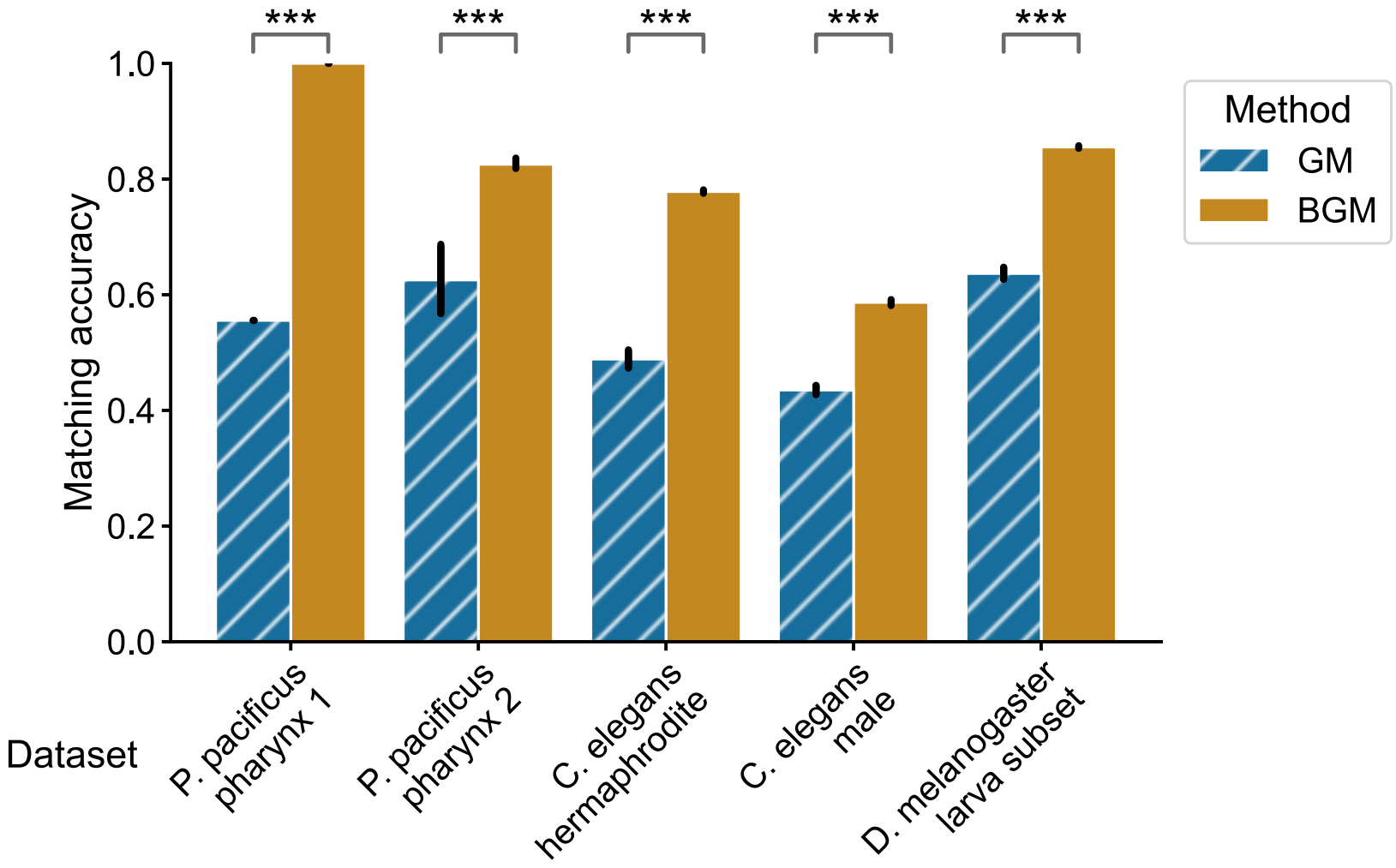
Bisected graph matching (BGM)



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

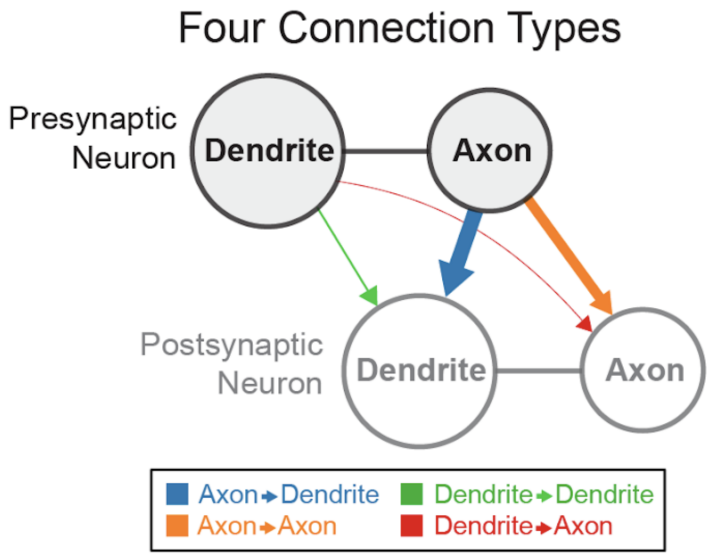
We generalized a state-of-the-art GM algorithm to solve BGM!

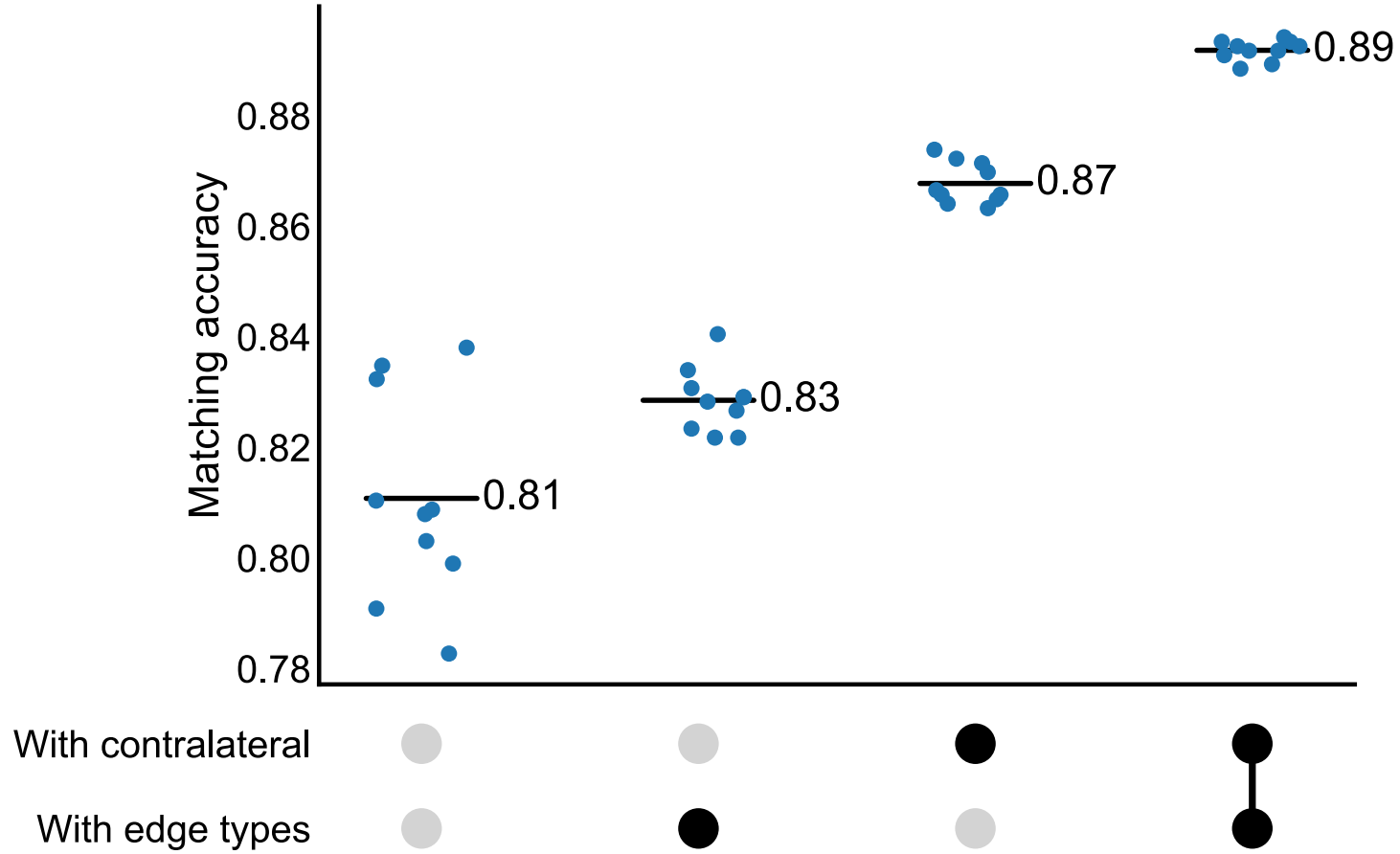
Contralateral connections aid matching!



Pedigo et al. Network Neuroscience (2022)

Performance improvement on the full brain





Open source tools

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)

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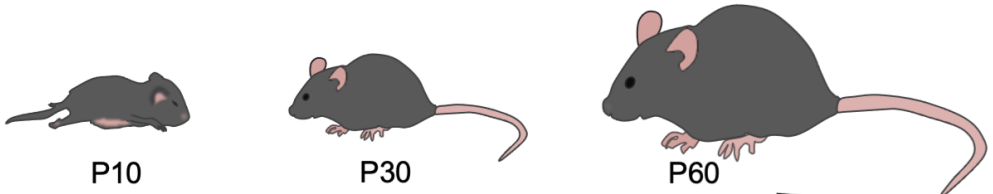
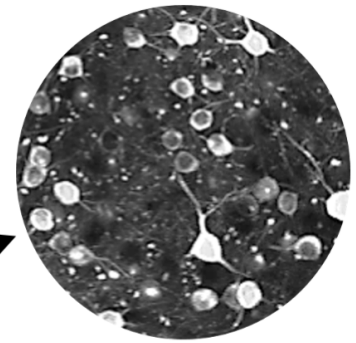
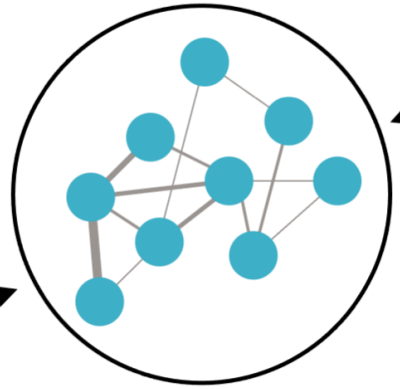


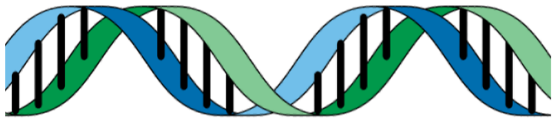
Neural activity



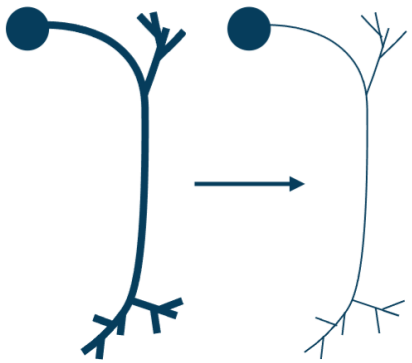
Connectivity



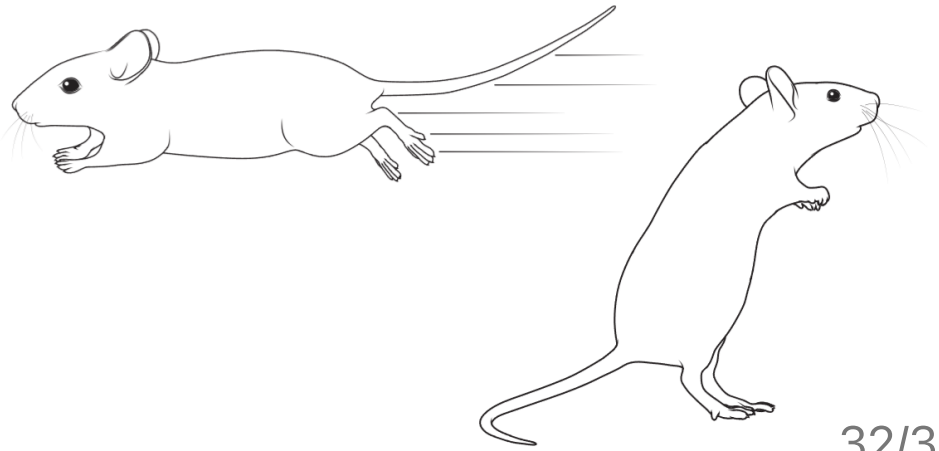
Gene expression



Disease

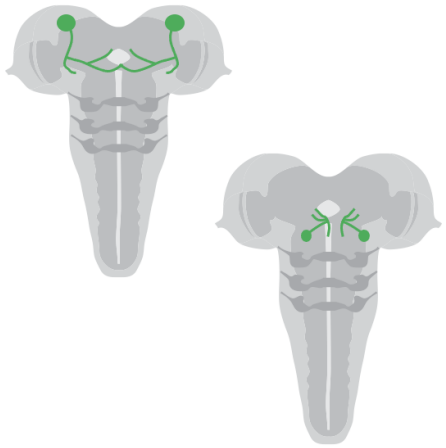


Behavior

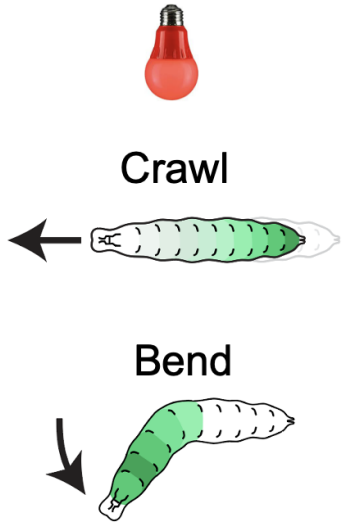


A structure-function relationship in the larva

Genetic driver lines for L/R neuron pairs

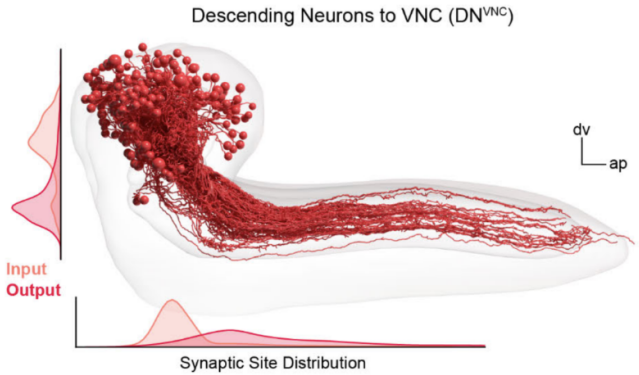


Behaviors measured under stimulation



Mapping to connectome via morphology

Comparison of projections to brain outputs



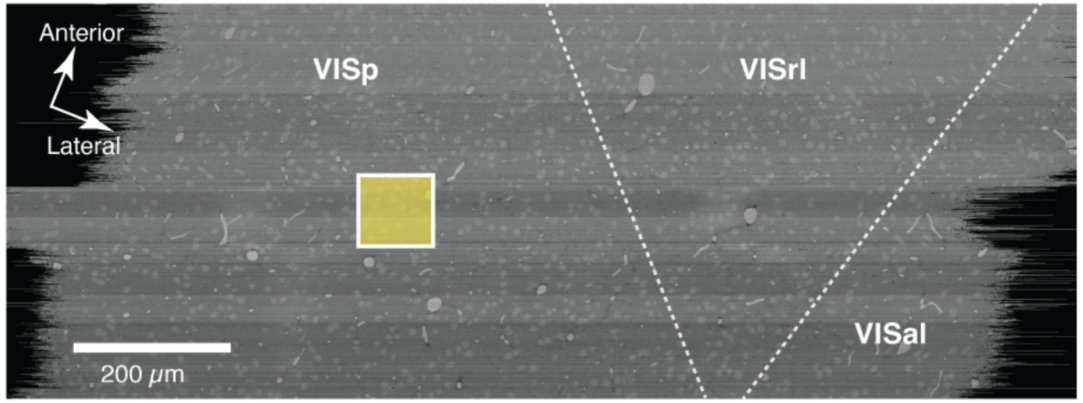
Behavior probabilities significantly related to projections to brain outputs

RV coefficient: 0.12, p-value: 0.0044

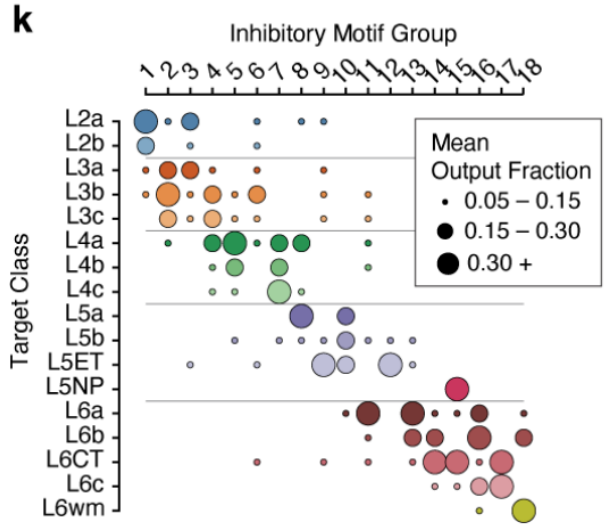
Distance correlation: 0.067, p-value: 0.0087

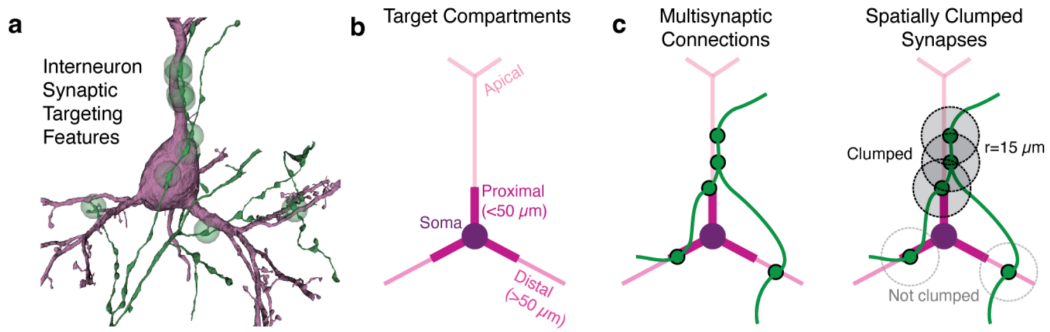
Work w/ L. Venkatasubramanian, C. Barré, JB Masson, C. Priebe, M. Zlatic

Example: do wiring rules generalize across region?



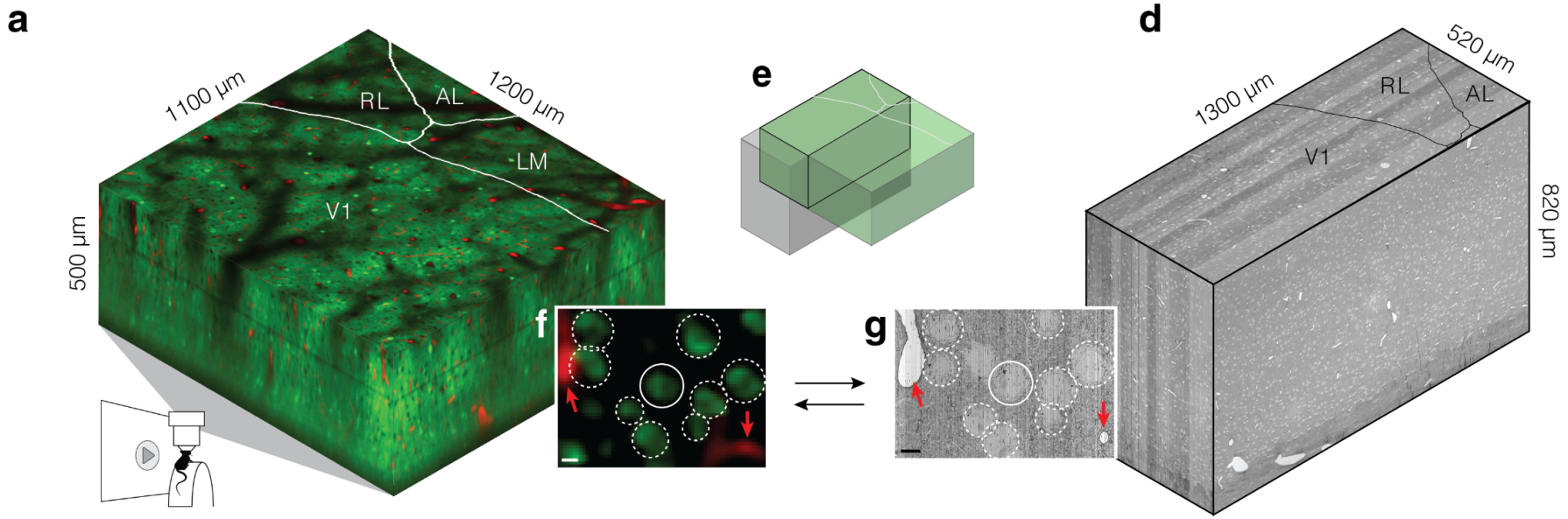
- Application of model-based network comparison
- Would likely require extensions of our simple models to account for details of wiring in cortex!





MICrONS Consortium et al. bioRxiv (2021), Schneider-Mizell et al. bioRxiv (2023)

...and does any variation relate to function?



MICrONS Consortium et al. bioRxiv (2021), Ding, Fahey, Papadoueoulos et al. bioRxiv (2023)

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

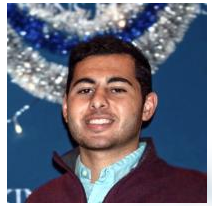
Acknowledgements

Team

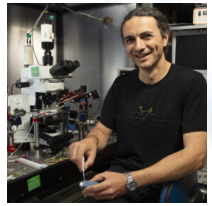

Michael Winding


Mike Powell


Eric Bridgeford


Ali Saad-Eldin


Marta Zlatic


Albert Cardona


Carey Priebe


Joshua Vogelstein

Tracers who contributed to larva connectome, Lalanti Venkatasubramanian, Chloé Barré, Jean-Baptiste Masson, Heather Patsolic, Youngser Park, NeuroData lab, Microsoft Research

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Questions?

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 @bpedigod

 bdpedigo.github.io

These slides at:

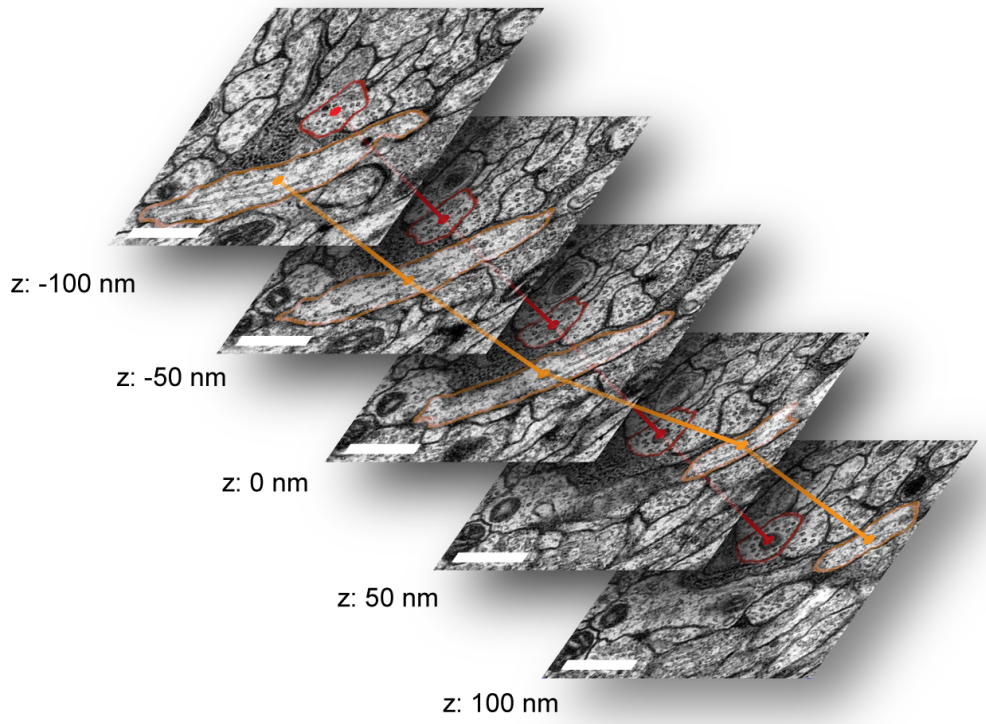
bdpedigo.github.io/talks/si.html

Extras

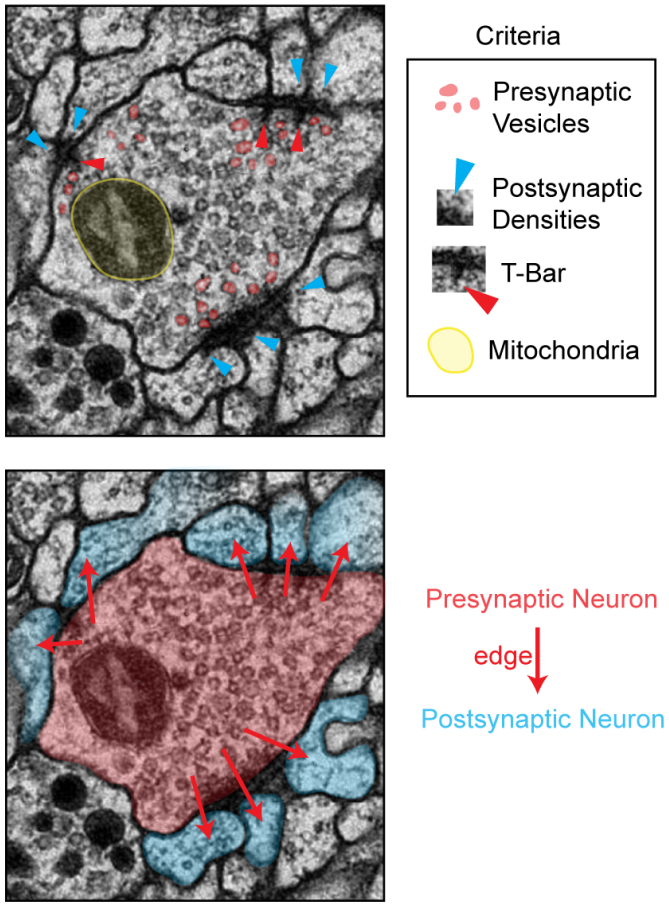
Winding, Pedigo et al. Science (2023)

Mapping a larval *Drosophila* brain connectome

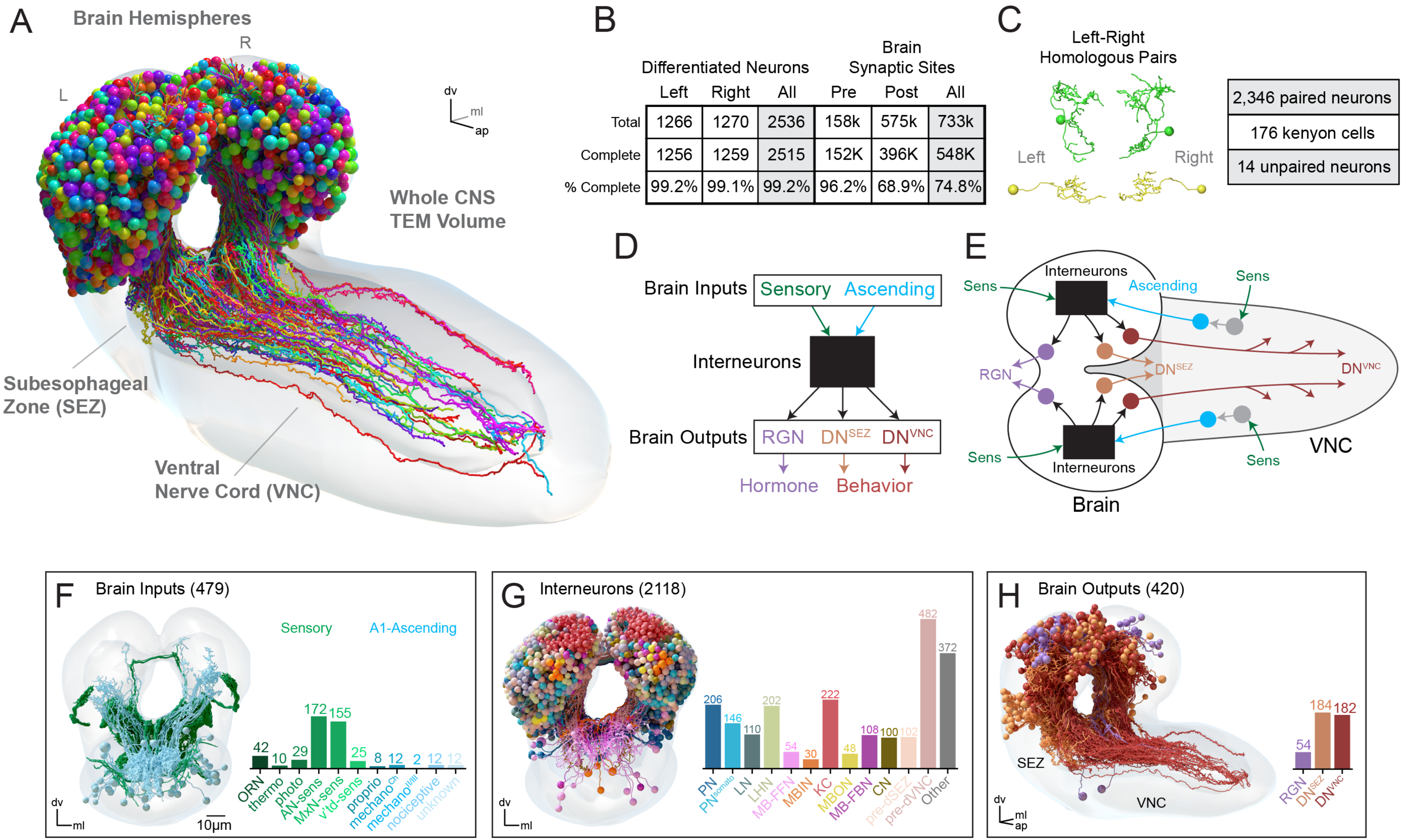
Manual Reconstruction of Arbors

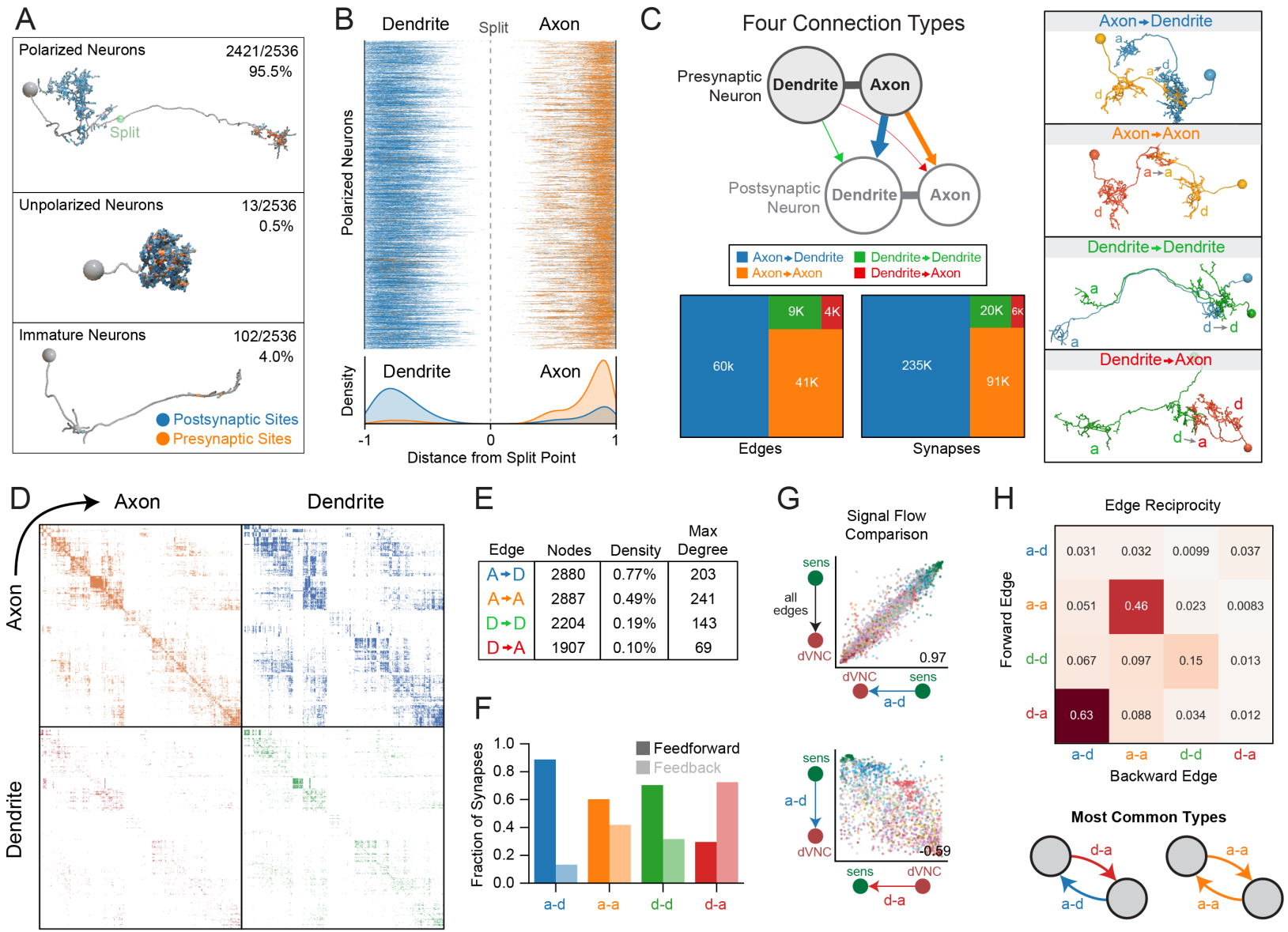


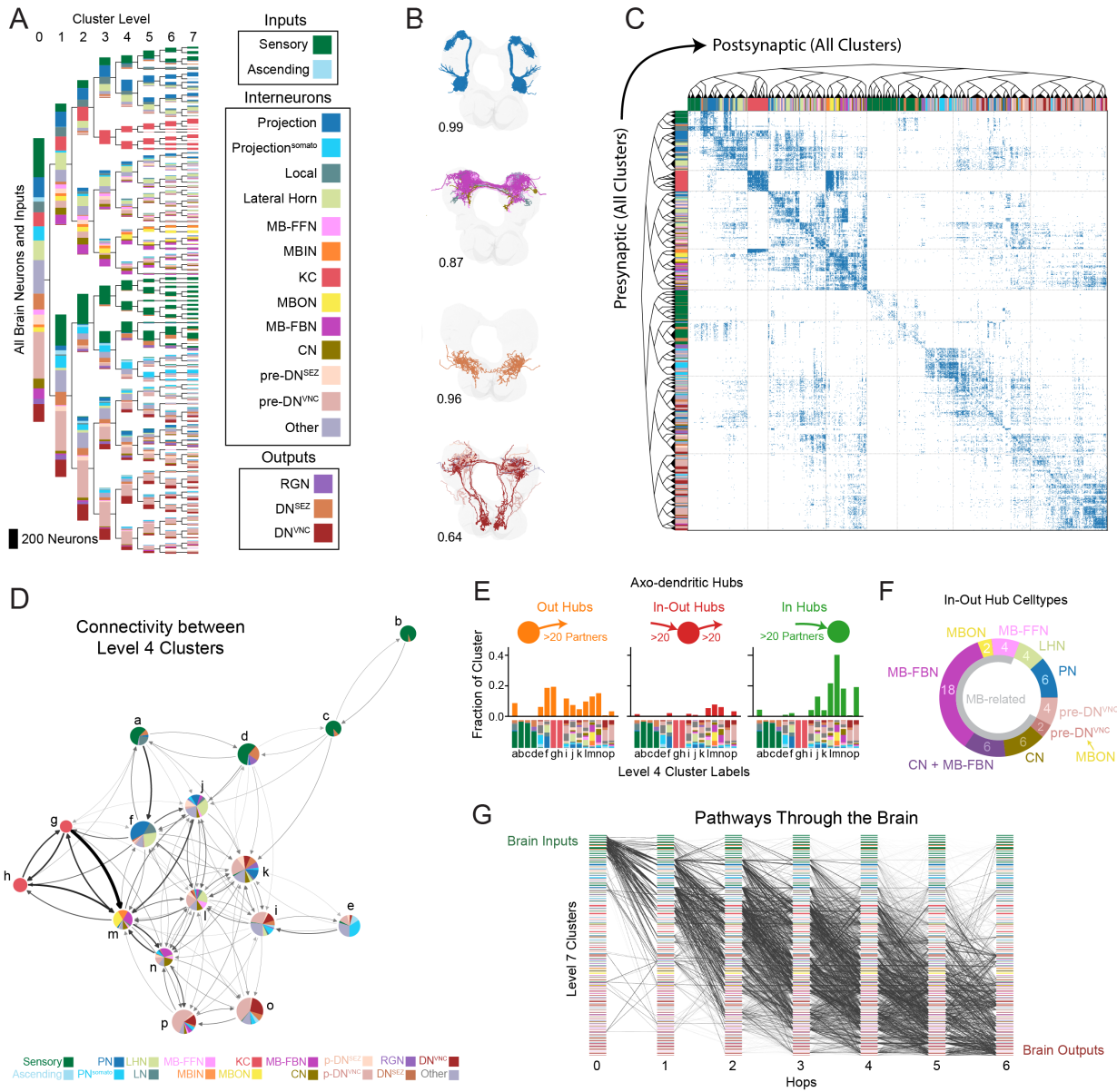
Synapse Annotation

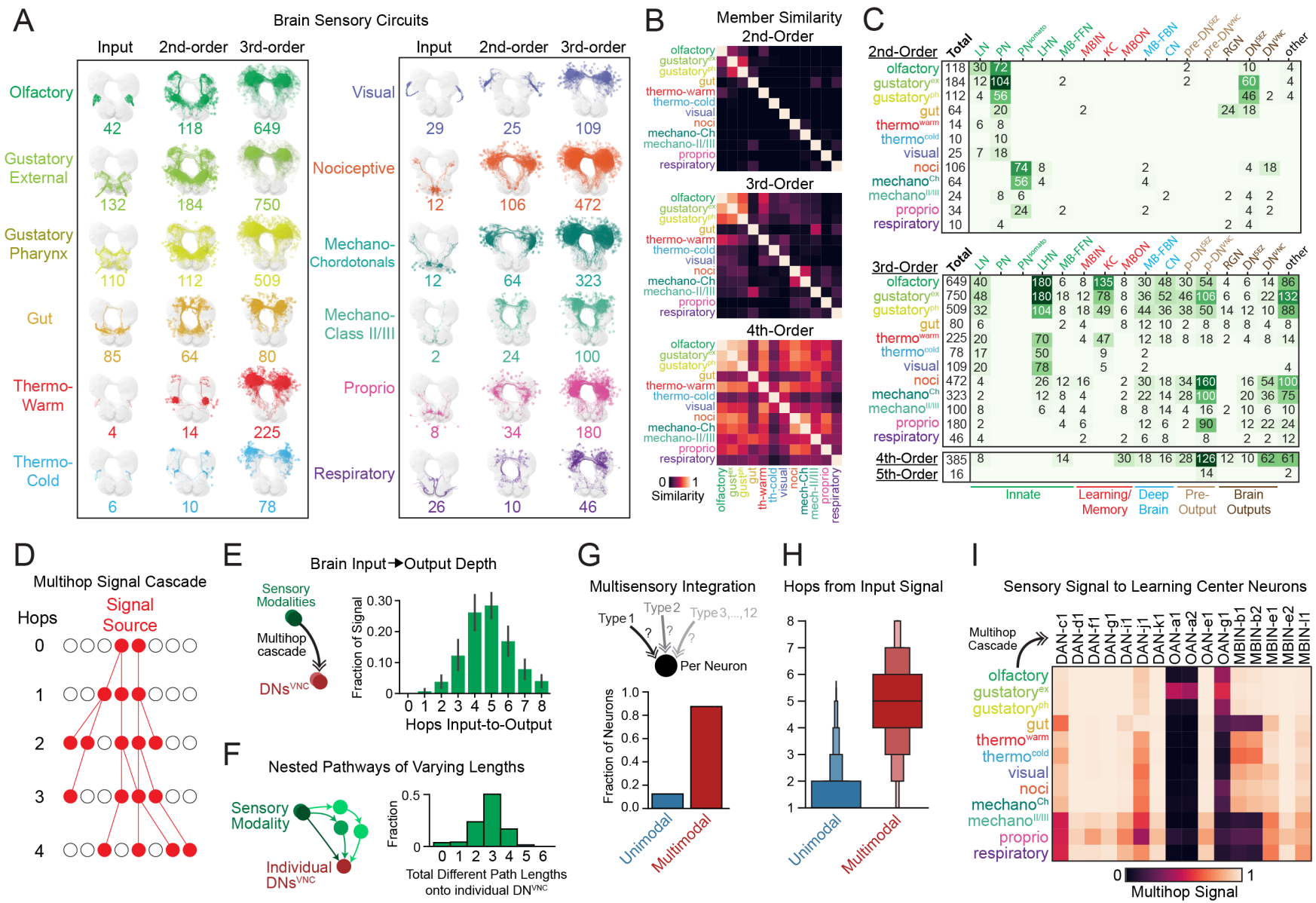


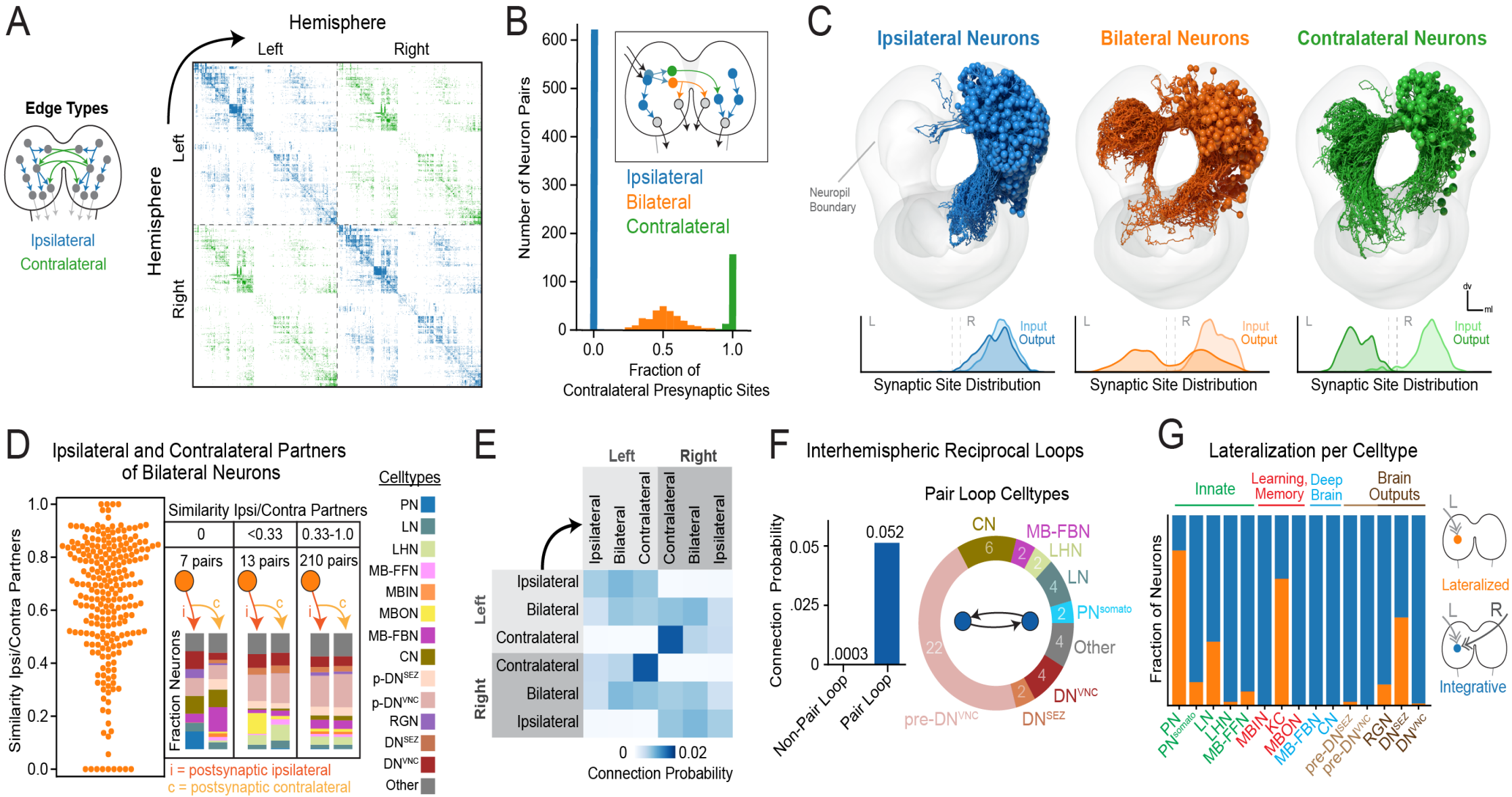
Winding, Pedigo et al. Science (2023), Ohyama et al. Nature (2015)

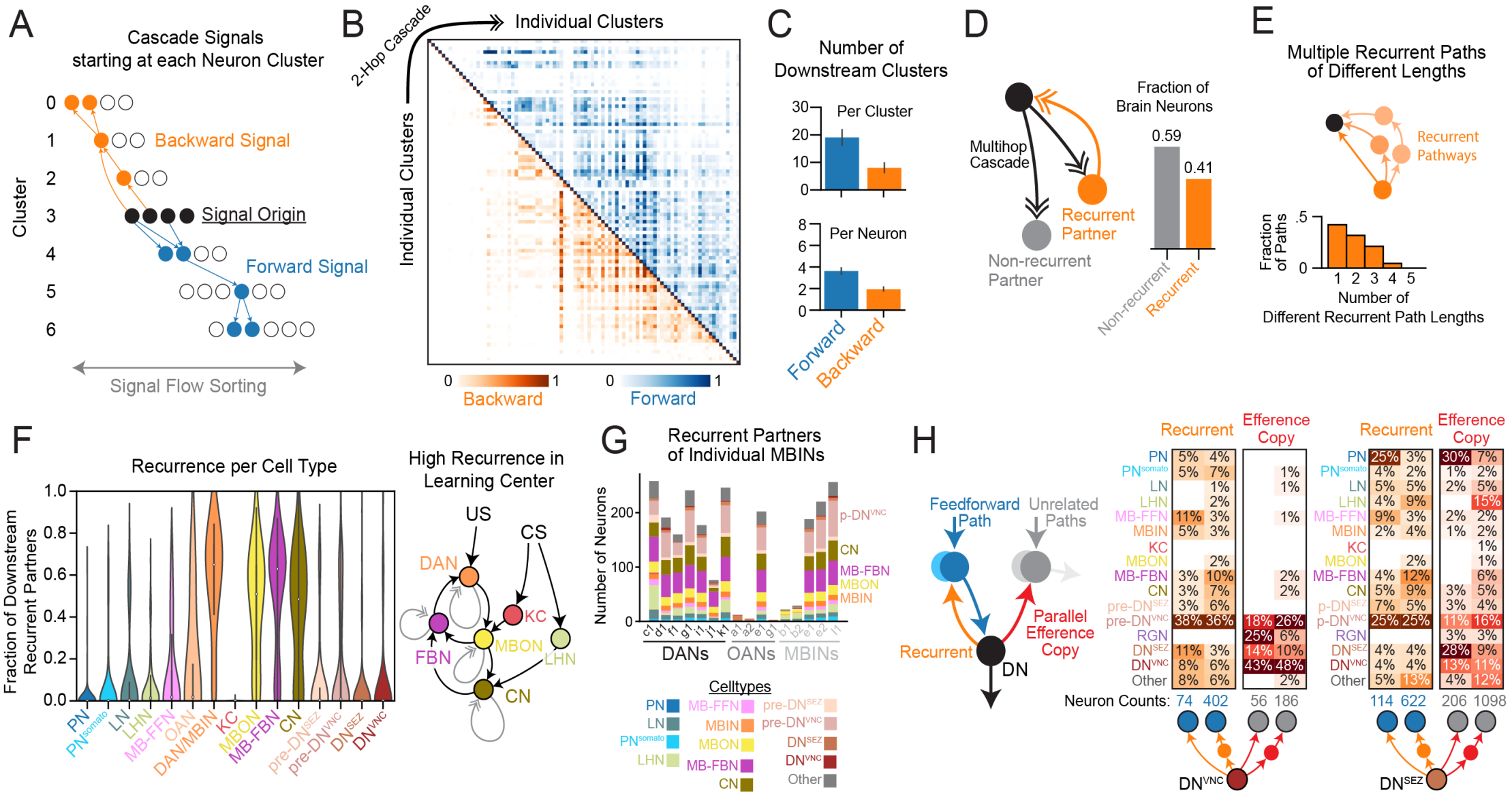

A
Brain Hemispheres
R
L
dv
ml
ap
Whole CNS
TEM Volume
Subesophageal
Zone (SEZ)
Ventral
Nerve Cord (VNC)
B
Differentiated Neurons
Brain
Synaptic Sites
Left Right All Pre Post All
Total 1266 1270 2536 158k 575k 733k
Complete 1256 1259 2515 152K 396K 548K
% Complete 99.2% 99.1% 99.2% 96.2% 68.9% 74.8%
C
Left-Right
Homologous Pairs
Left
Right
2,346 paired neurons
176 kenyon cells
14 unpaired neurons
D
Brain Inputs
Sensory
Ascending
Interneurons
Brain Outputs
RGN
DNSEZ
DNVNC
Hormone
Behavior
E
Interneurons
Sens
Ascending
Sens
RGN
DNSEZ
DNVNC
Sens
Interneurons
Sens
VNC
Brain
F
Brain Inputs (479)
Sensory
A1-Ascending
42 10 29 172 155 25 8 12 2 12 12
ORN
thermo
photo
AN-sens
MxN-sens
v'td-sens
proprio
mechano
mechano
nociceptive
unknown
dv
ml
10μm
G
Interneurons (2118)
206 146 110 202 54 30 222 48 108 100 102 482 372
PN
PN
LN
LHN
MB-FFN
MBIN
KC
MBON
MB-FBN
CN
pre-dSEZ
pre-dVNC
Other
dv
ml
H
Brain Outputs (420)
SEZ
VNC
54 184 182
RGN
DNSEZ
DNVNC
dv
ml
ap

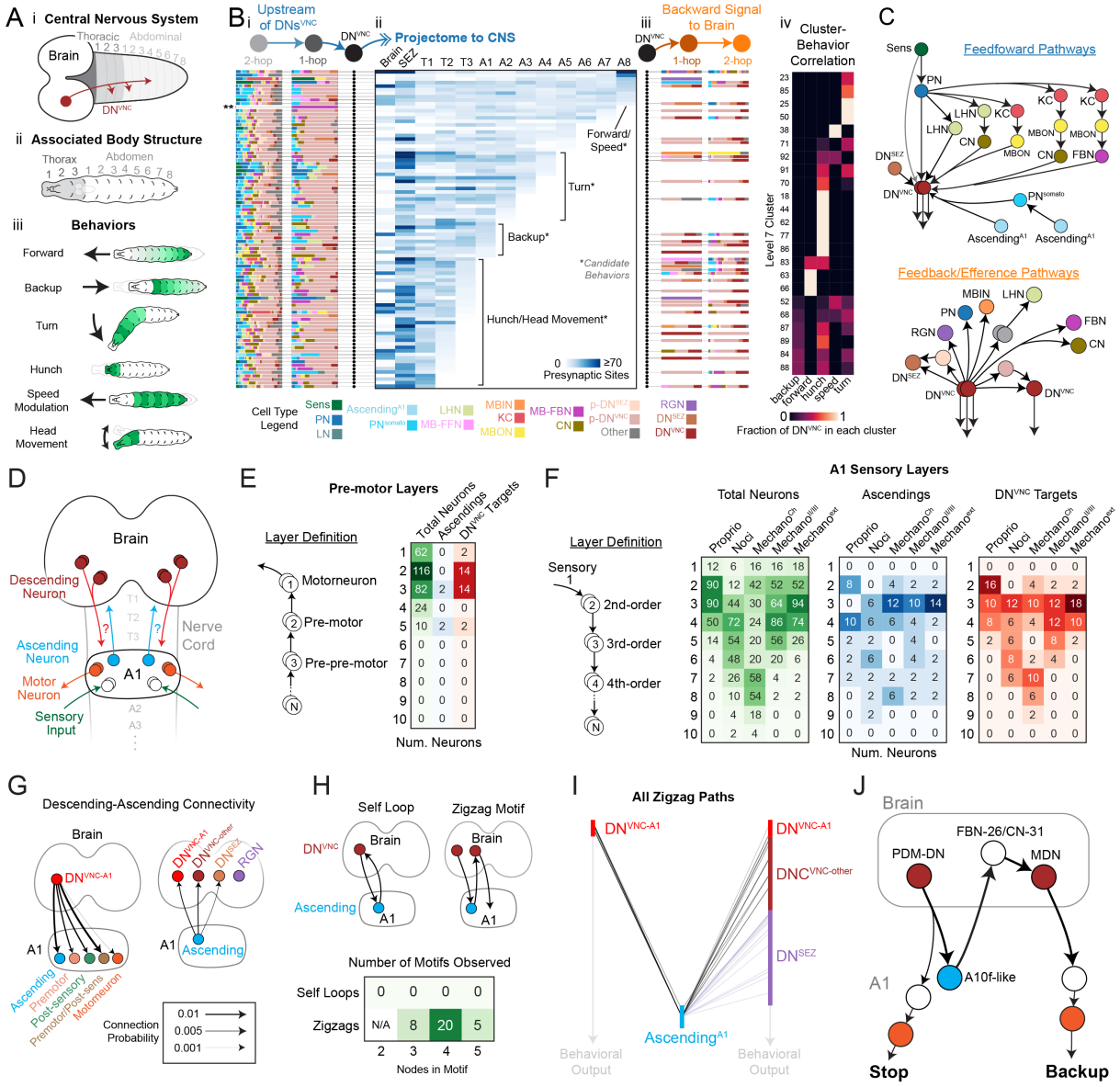

A
Polarized Neurons
2421/2536
95.5%
Split
Unpolarized Neurons
13/2536
0.5%
Immature Neurons
102/2536
4.0%
Postsynaptic Sites
Presynaptic Sites
B
Dendrite
Split
Axon
Polarized Neurons
Density
Dendrite
Axon
-1
0
1
Distance from Split Point
C
Four Connection Types
Presynaptic Neuron
Dendrite
Axon
Postsynaptic Neuron
Dendrite
Axon
Axon→Dendrite
Dendrite→Dendrite
Axon→Axon
Dendrite→Axon
60k
9K
4K
41K
235K
20K
6K
91K
Edges
Synapses
Axon→Dendrite
Axon→Axon
Dendrite→Dendrite
Dendrite→Axon
D
Axon
Dendrite
Axon
Dendrite
E
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
F
Fraction of Synapses
1.0
0.8
0.6
0.4
0.2
0.0
Feedforward
Feedback
a-d
a-a
d-d
d-a
G
Signal Flow Comparison
sens
all edges
dVNC
0.97
dVNC
sens
a-d
sens
a-d
dVNC
-0.59
sens
dVNC
d-a
H
Edge Reciprocity
Forward Edge
a-d
0.031
0.032
0.0099
0.037
a-a
0.051
0.46
0.023
0.0083
d-d
0.067
0.097
0.15
0.013
d-a
0.63
0.088
0.034
0.012
a-d
a-a
d-d
d-a
Backward Edge
Most Common Types
d-a
a-d
a-a
a-a


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
a b c d e f g h i j k l m n o p
Sensory PN LHN MB-FFN KC MB-FBN p-DN SEZ RGN DN VNC
Ascending PN somato LN MBIN MBON CN p-DN VNC DN SEZ Other
E
Axo-dendritic Hubs
Out Hubs
In-Out Hubs
In Hubs
>20 Partners
>20
>20
>20 Partners
Fraction of Cluster
0.4
0.2
0.0
abcdefghijklmnop
Level 4 Cluster Labels
F
In-Out Hub Celltypes
MBON
MB-FFN
LHN
PN
MB-FBN
MB-related
pre-DN VNC
pre-DN VNC
CN + MB-FBN
CN
MBON
2 4 4 6 4 2 6 6 18
G
Pathways Through the Brain
Brain Inputs
Level 7 Clusters
Brain Outputs
0 1 2 3 4 5 6
Hops


A
Brain Sensory Circuits
Input
2nd-order
3rd-order
Olfactory
42
118
649
Gustatory External
132
184
750
Gustatory Pharynx
110
112
509
Gut
85
64
80
Thermo-Warm
4
14
225
Thermo-Cold
6
10
78
Visual
29
25
109
Nociceptive
12
106
472
Mechano-Chordotonals
12
64
323
Mechano-Class II/III
2
24
100
Proprio
8
34
180
Respiratory
26
10
46
B
Member Similarity
2nd-Order
3rd-Order
4th-Order
olfactory
gustatory^ex
gustatory^ph
gut
thermo-warm
thermo-cold
visual
noci
mechano-Ch
mechano-II/III
proprio
respiratory
0 1
Similarity
C
2nd-Order
3rd-Order
4th-Order
5th-Order
Total
LN
PN
PN^somato
LHN
MB-FFN
MBIN
KC
MBON
MB-FBN
CN
pre-DN^SEZ
pre-DN^VNC
RGN
DN^SEZ
DN^VNC
other
Innate
Learning/ Memory
Deep Brain
Pre-Output
Brain Outputs
D
Multihop Signal Cascade
Hops
Signal Source
0
1
2
3
4
E
Brain Input→Output Depth
Sensory Modalities
Multihop cascade
DNs^VNC
Fraction of Signal
Hops Input-to-Output
F
Nested Pathways of Varying Lengths
Sensory Modality
Individual DNs^VNC
Fraction
Total Different Path Lengths onto individual DN^VNC
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
DAN-c1
DAN-d1
DAN-f1
DAN-g1
DAN-i1
DAN-j1
DAN-k1
OAN-a1
OAN-a2
OAN-e1
OAN-g1
MBIN-b1
MBIN-b2
MBIN-e1
MBIN-e2
MBIN-i1
0 1
Multihop Signal

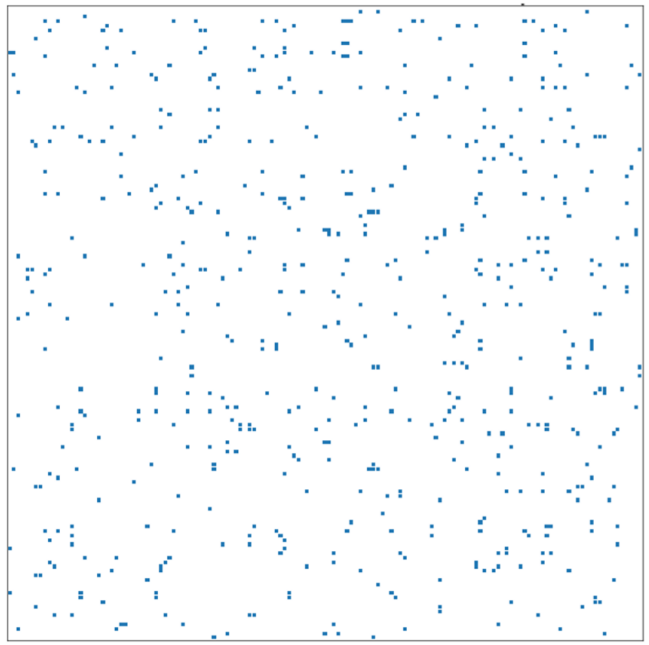

A
Edge Types
Ipsilateral
Contralateral
Hemisphere
Left
Right
Hemisphere
Left
Right
B
Number of Neuron Pairs
600
500
400
300
200
100
0
0.0
0.5
1.0
Fraction of
Contralateral Presynaptic Sites
Ipsilateral
Bilateral
Contralateral
C
Ipsilateral Neurons
Bilateral Neurons
Contralateral Neurons
Neuropil
Boundary
dv
ml
L
R
Input
Output
Synaptic Site Distribution
D
Ipsilateral and Contralateral Partners
of Bilateral Neurons
Similarity Ipsi/Contra Partners
1.0
0.8
0.6
0.4
0.2
0.0
Similarity Ipsi/Contra Partners
0
<0.33
0.33-1.0
7 pairs
13 pairs
210 pairs
i
c
Fraction Neurons
i = postsynaptic ipsilateral
c = postsynaptic contralateral
Celltypes
PN
LN
LHN
MB-FFN
MBIN
MBON
MB-FBN
CN
p-DN^SEZ
p-DN^VNC
RGN
DN^SEZ
DN^VNC
Other
E
Left
Right
Ipsilateral
Bilateral
Contralateral
Contralateral
Bilateral
Ipsilateral
Left
Right
0
0.02
Connection Probability
F
Interhemispheric Reciprocal Loops
Pair Loop Celltypes
Connection Probability
0.05
.025
0
0.052
.0003
Non-Pair Loop
Pair Loop
CN
MB-FBN
LHN
LN
PN^somato
Other
DN^VNC
DN^SEZ
pre-DN^VNC
6
2
2
4
2
4
2
22
G
Lateralization per Celltype
Innate
Learning, Memory
Deep Brain
Brain Outputs
Fraction of Neurons
PN
PN^somato
LN
LHN
MB-FFN
MBIN
KC
MBON
MB-FBN
CN
pre-DN^SEZ
pre-DN^VNC
RGN
DN^SEZ
DN^VNC
L
Lateralized
L
R
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%
LN 1%
LHN 2%
MB-FFN 11% 3%
MBIN 5% 3%
KC
MBON 2%
MB-FBN 3% 10%
CN 3% 7%
pre-DNSEZ 3% 6%
pre-DNVNC 38% 36%
RGN
DNSEZ 11% 3%
DNVNC 8% 6%
Other 8% 6%
1%
1%
1%
2%
2%
18% 26%
25% 6%
14% 10%
43% 48%
2%
Neuron Counts: 74 402 56 186
DNVNC
PN 25% 3%
PNsomato 4% 2%
LN 5% 5%
LHN 4% 9%
MB-FFN 9% 3%
MBIN 2% 4%
KC
MBON 2%
MB-FBN 4% 12%
CN 5% 9%
p-DNSEZ 7% 5%
p-DNVNC 25% 25%
RGN
DNSEZ 4% 4%
DNVNC 4% 4%
Other 5% 13%
30% 7%
1% 2%
2% 5%
15%
2% 2%
1% 2%
1%
1%
6%
3% 5%
3% 4%
11% 16%
3% 3%
28% 9%
13% 11%
4% 12%
114 622 206 1098
DNSEZ


A
i Central Nervous System
Thoracic
Abdominal
Brain
DNVNC
ii Associated Body Structure
Thorax
Abdomen
iii Behaviors
Forward
Backup
Turn
Hunch
Speed Modulation
Head Movement
B
i Upstream of DNsVNC
ii Projectome to CNS
iii Backward Signal to Brain
iv Cluster-Behavior Correlation
2-hop
1-hop
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
Level 7 Cluster
backup
forward
hunch
speed
turn
Fraction of DNVNC in each cluster
Cell Type Legend
Sens
PN
LN
Ascending A1
PNsomato
LHN
MB-FFN
MBIN
KC
MBON
MB-FBN
CN
Other
p-DNSEZ
p-DNVNC
RGN
DNSEZ
DNVNC
C
Feedfoward Pathways
Sens
PN
LHN
KC
CN
MBON
FBN
DNSEZ
DNVNC
PNsomato
Ascending A1
Feedback/Efference Pathways
MBIN
LHN
PN
RGN
FBN
CN
DNSEZ
DNVNC
D
Brain
Descending Neuron
Ascending Neuron
Motor Neuron
Sensory Input
Nerve Cord
A1
E
Pre-motor Layers
Layer Definition
Motorneuron
Pre-motor
Pre-pre-motor
Total Neurons
Ascendings
DNVNC Targets
Num. Neurons
F
A1 Sensory Layers
Layer Definition
Sensory
2nd-order
3rd-order
4th-order
Total Neurons
Ascendings
DNVNC Targets
Proprio
Noci
MechanoCh
MechanoWdl
MechanoNxt
Num. Neurons
G
Descending-Ascending Connectivity
Brain
DNVNC-A1
DNVNC-other
DNSEZ
RGN
A1
Ascending
Premotor
Post-sensory
Premotor
Post-sens
Motorneuron
Connection Probability
0.01
0.005
0.001
H
Self Loop
Zigzag Motif
Brain
DNVNC
Ascending
A1
Number of Motifs Observed
Self Loops
Zigzags
N/A
Nodes in Motif
I
All Zigzag Paths
DNVNC-A1
DNCVNC-other
DNSEZ
Ascending A1
Behavioral Output
J
Brain
FBN-26/CN-31
PDM-DN
MDN
A1
A10f-like
Stop
Backup

Sorting the network

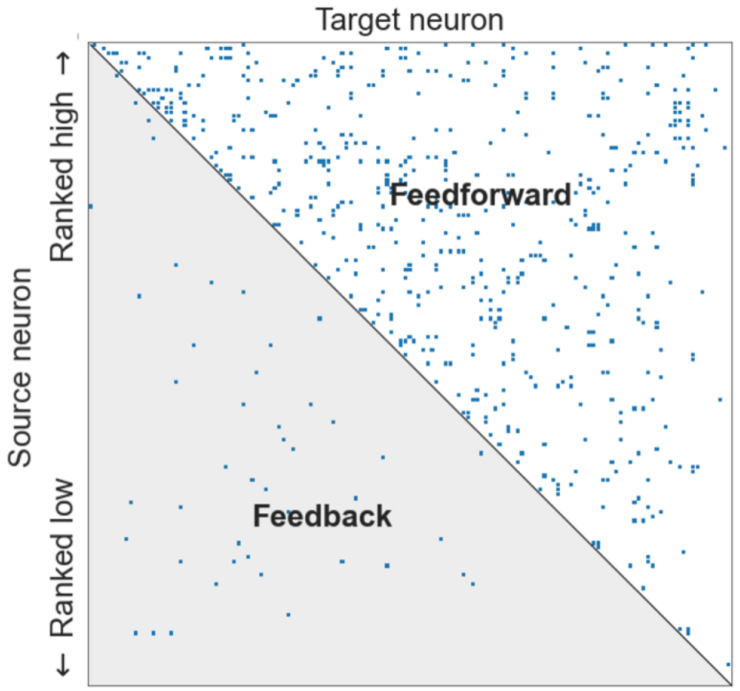
Adjacency matrix



Flow ordering

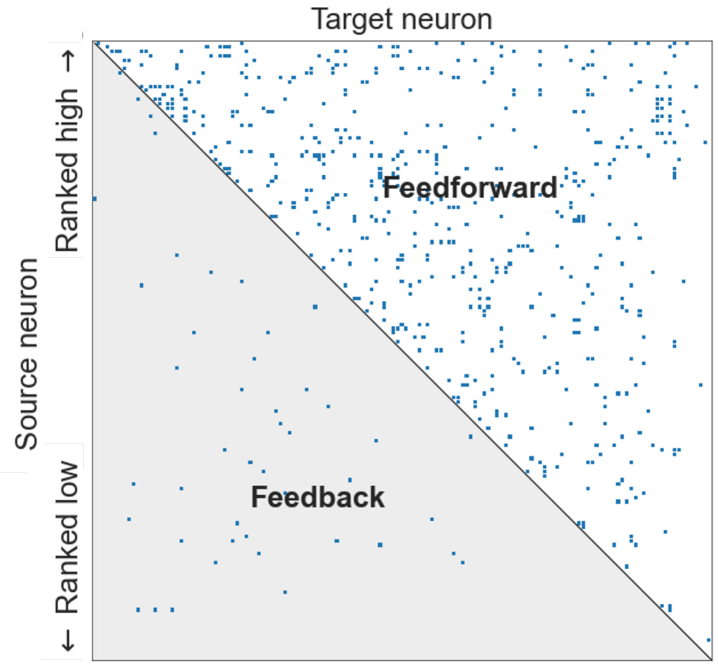
- “Feedback minimization”
- Signal flow
- Random-walk based

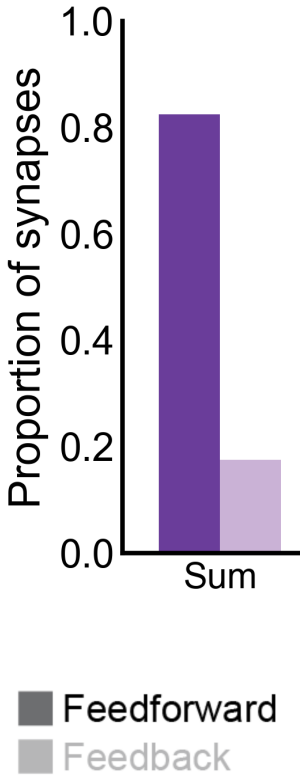
Sorted adjacency

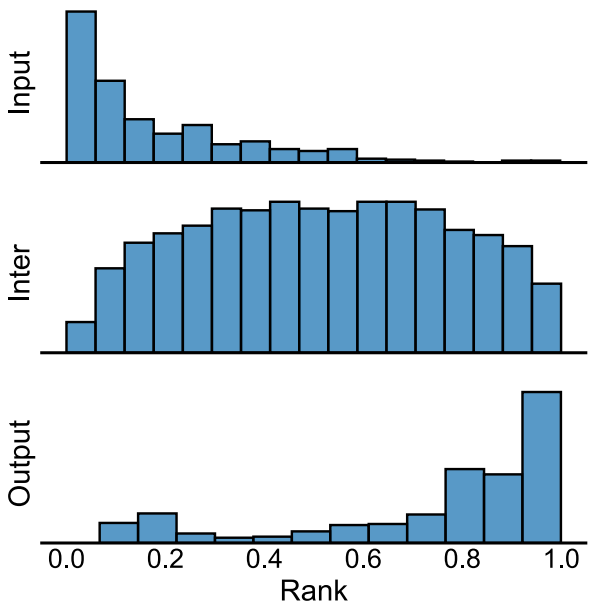


Carmel et al. IEEE Vis. and Comp. Graphics (2004), Burkard et al. Assignment Problems (2009)

Quantifying high-level "feedforward/feedback"

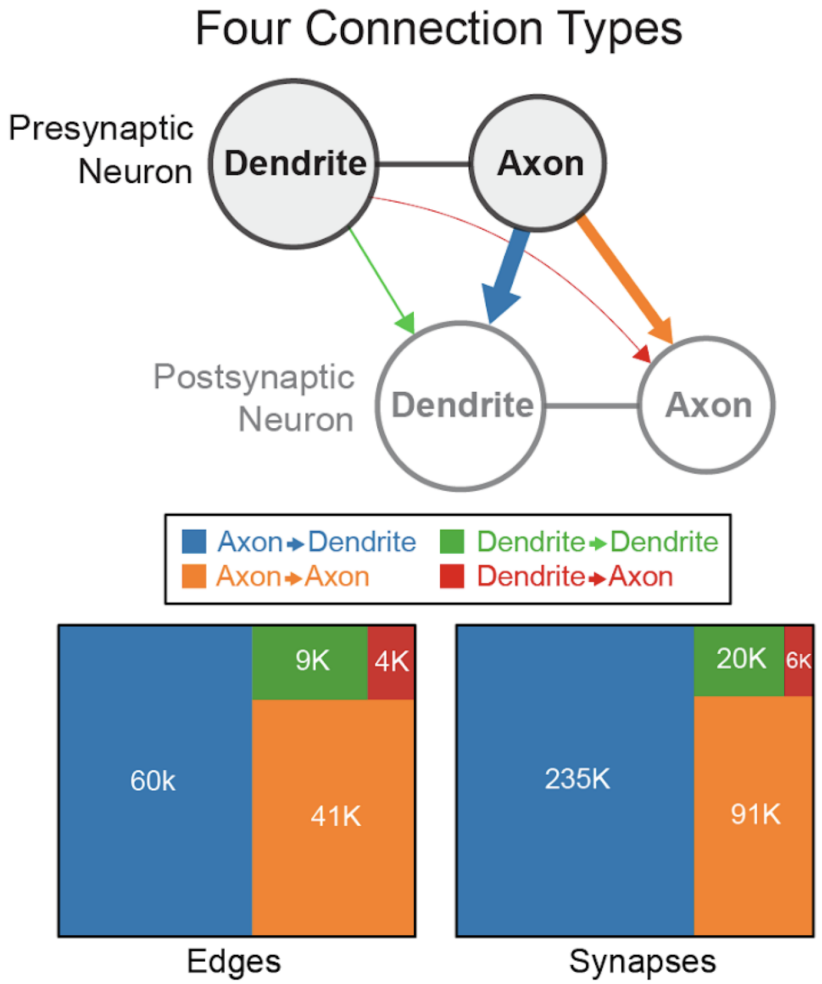


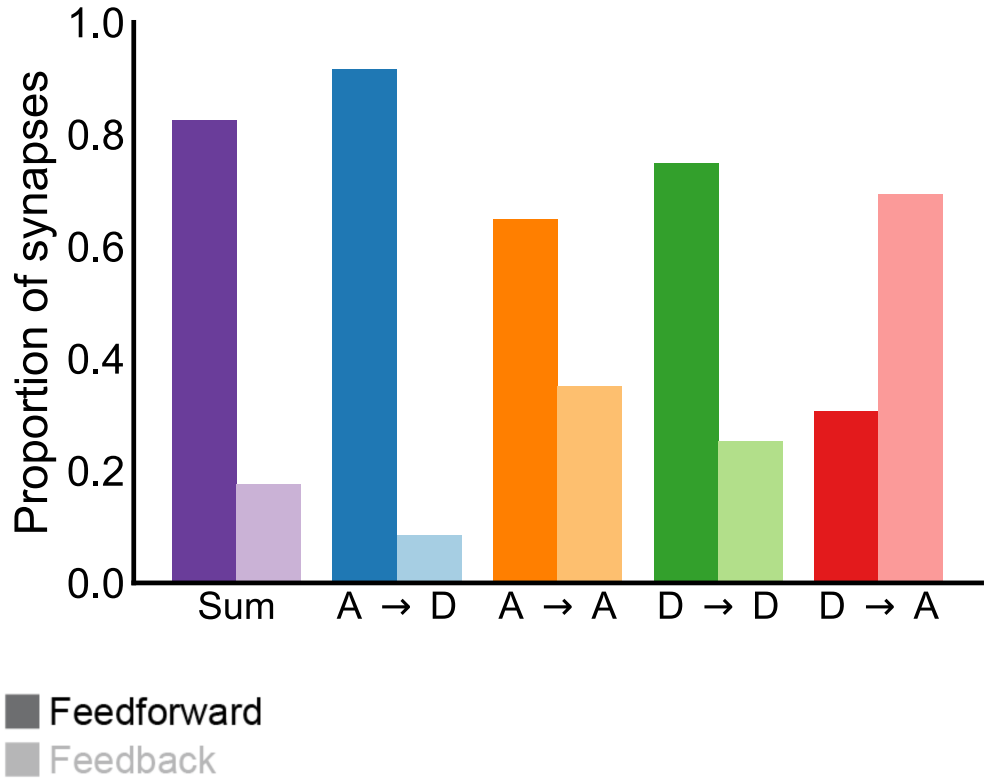




Winding, Pedigo et al. Science (2023)

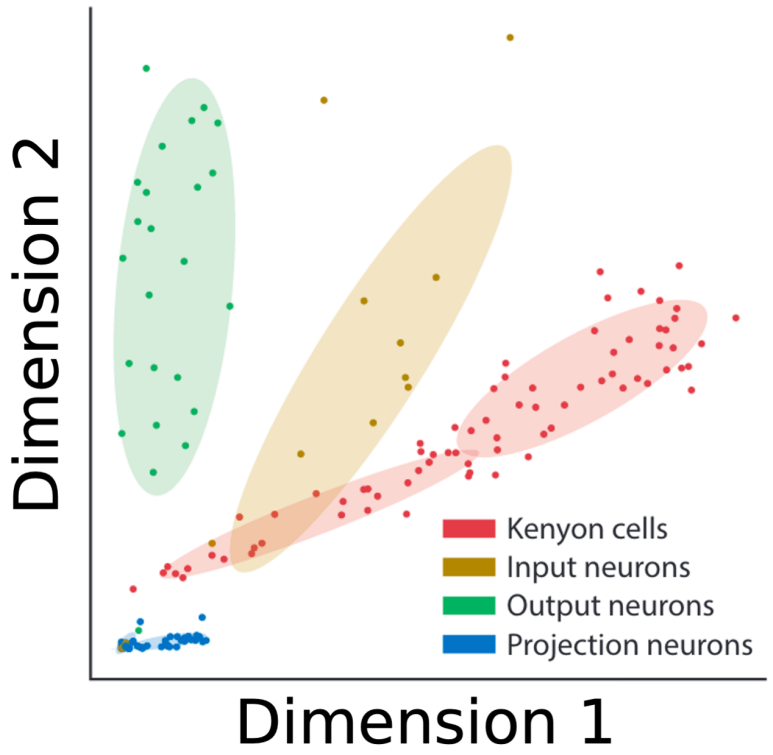
Morphology enables splitting axons/dendrites

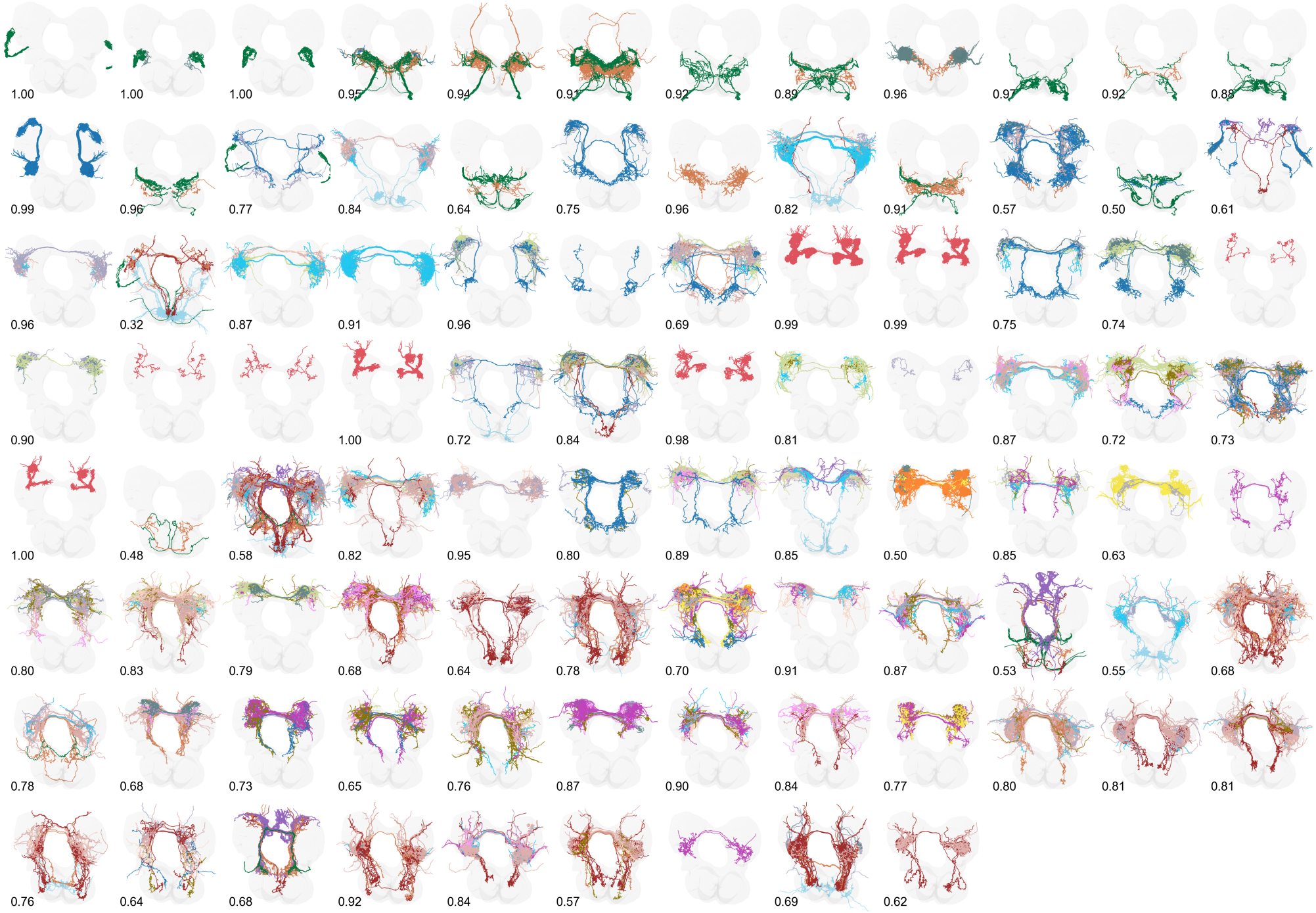




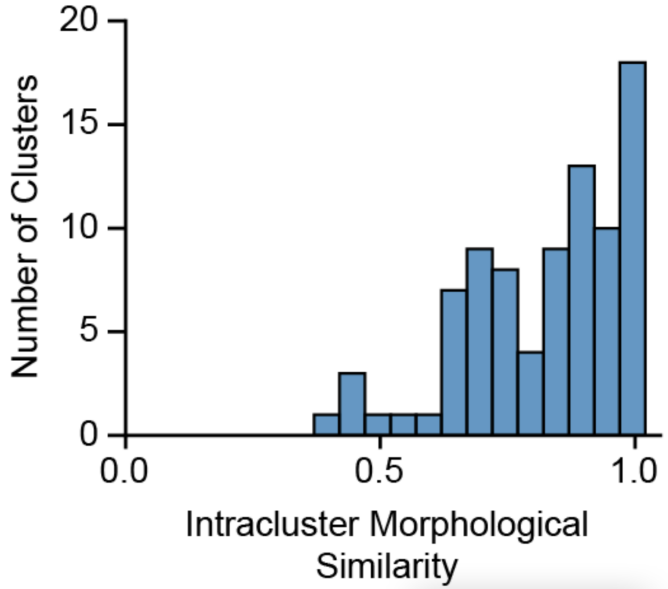
Spectral embedding

- 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:

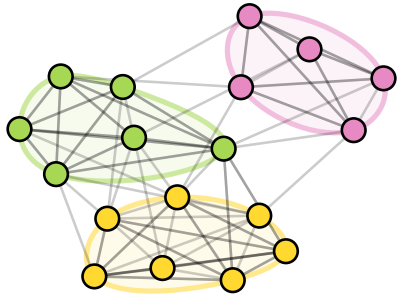
$$P[\text{ within cluster NBLAST sim.} > \text{between cluster NBLAST sim.}] \approx 0.81$$

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

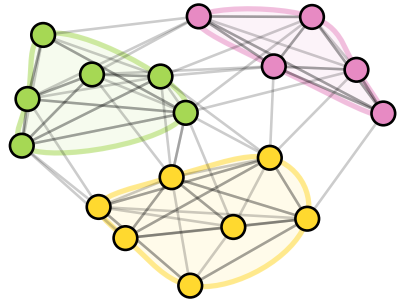
Pedigo et al. eLife (2023)

Group neurons

Left

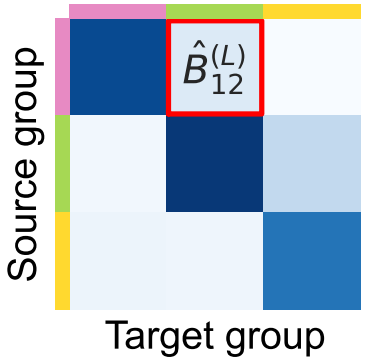


Right

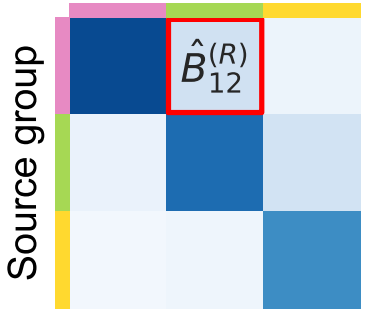


Estimate group connection probabilities

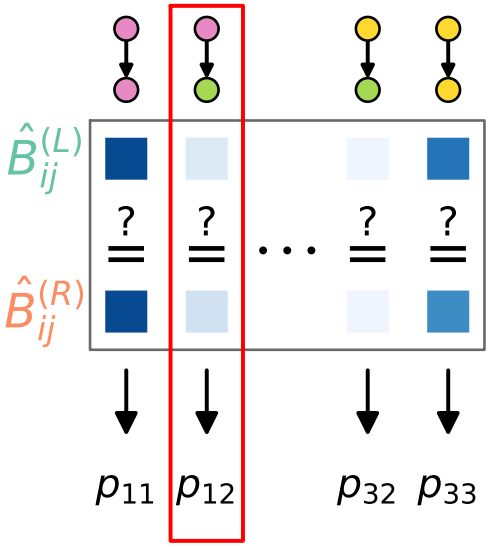
$\hat{B}^{(L)}$



$\hat{B}^{(R)}$



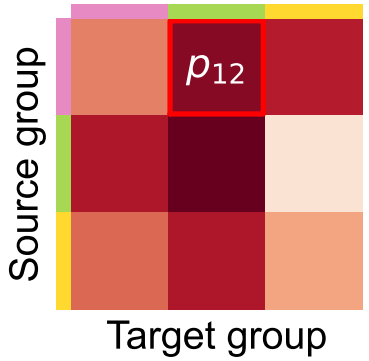
Compare probabilities, compute p-values



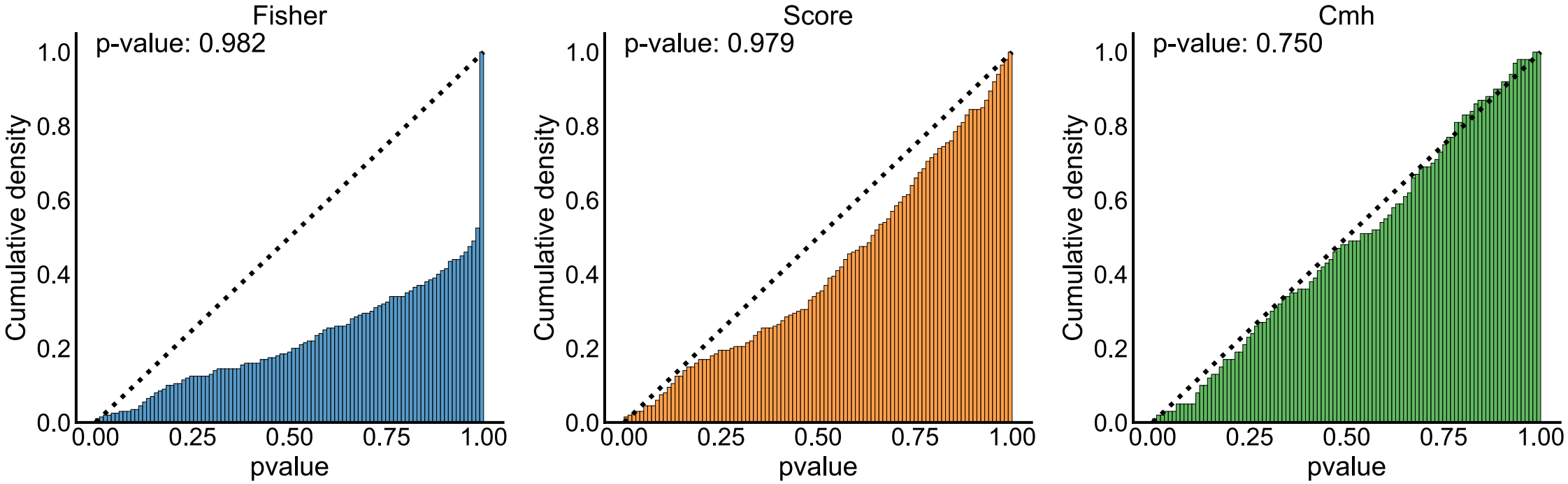
$$H_0: B^{(L)}_{ij} = B^{(R)}_{ij}$$
$$H_A: B^{(L)}_{ij} \neq B^{(R)}_{ij}$$

Combine p-values for overall test

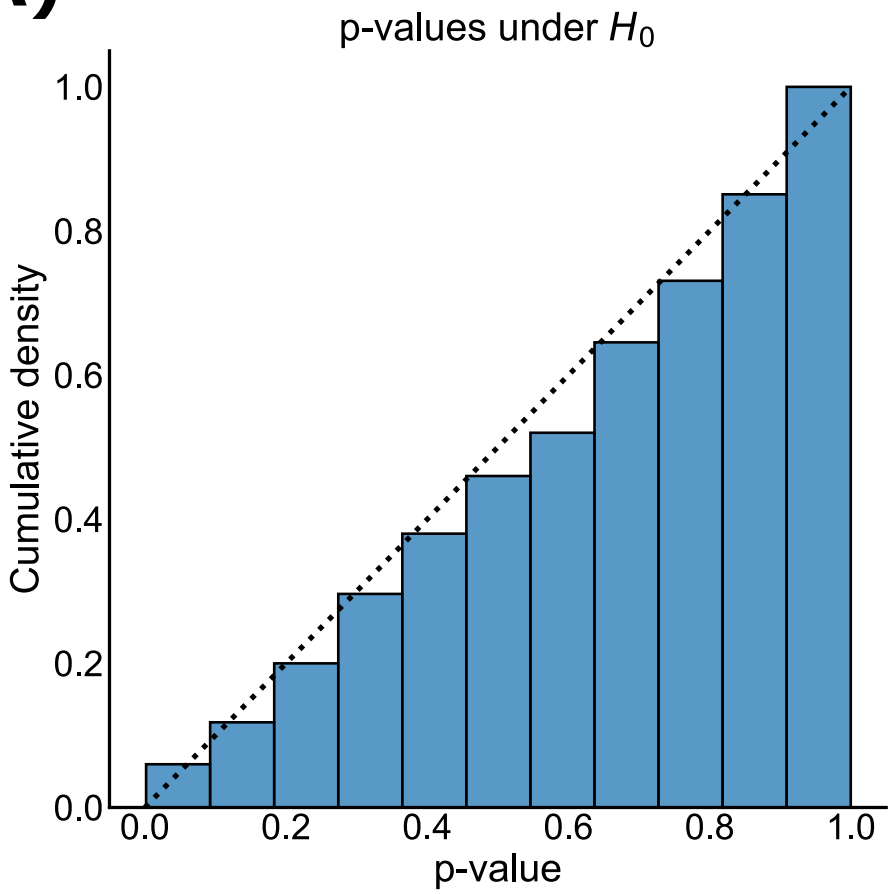
p-values



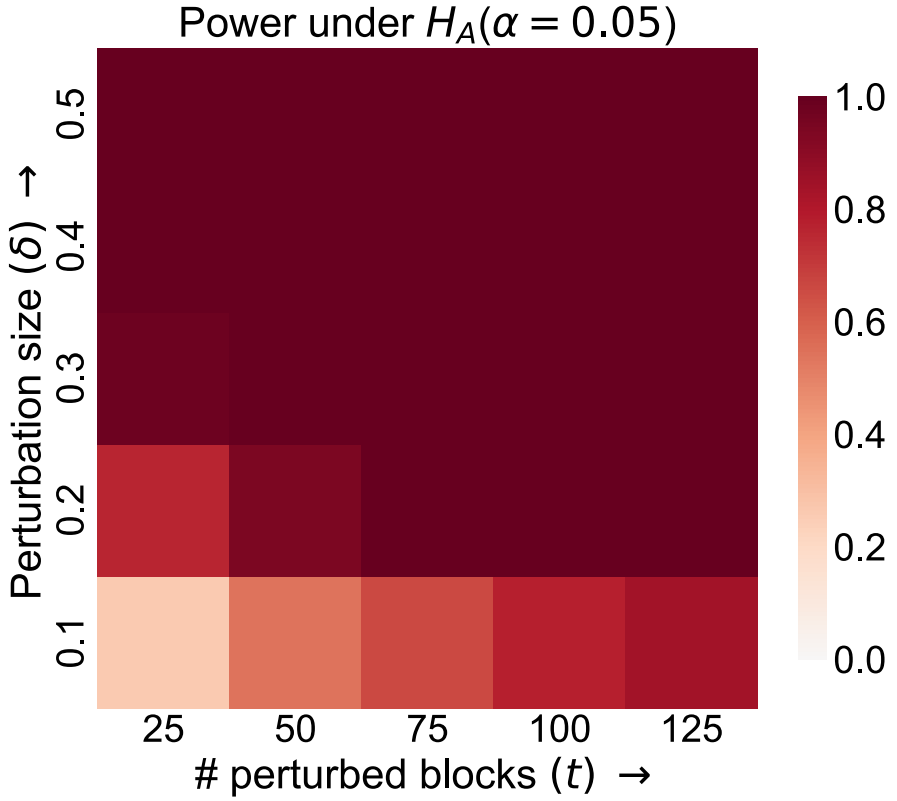
$$H_0: B^{(L)} = B^{(R)}$$
$$H_A: B^{(L)} \neq B^{(R)}$$

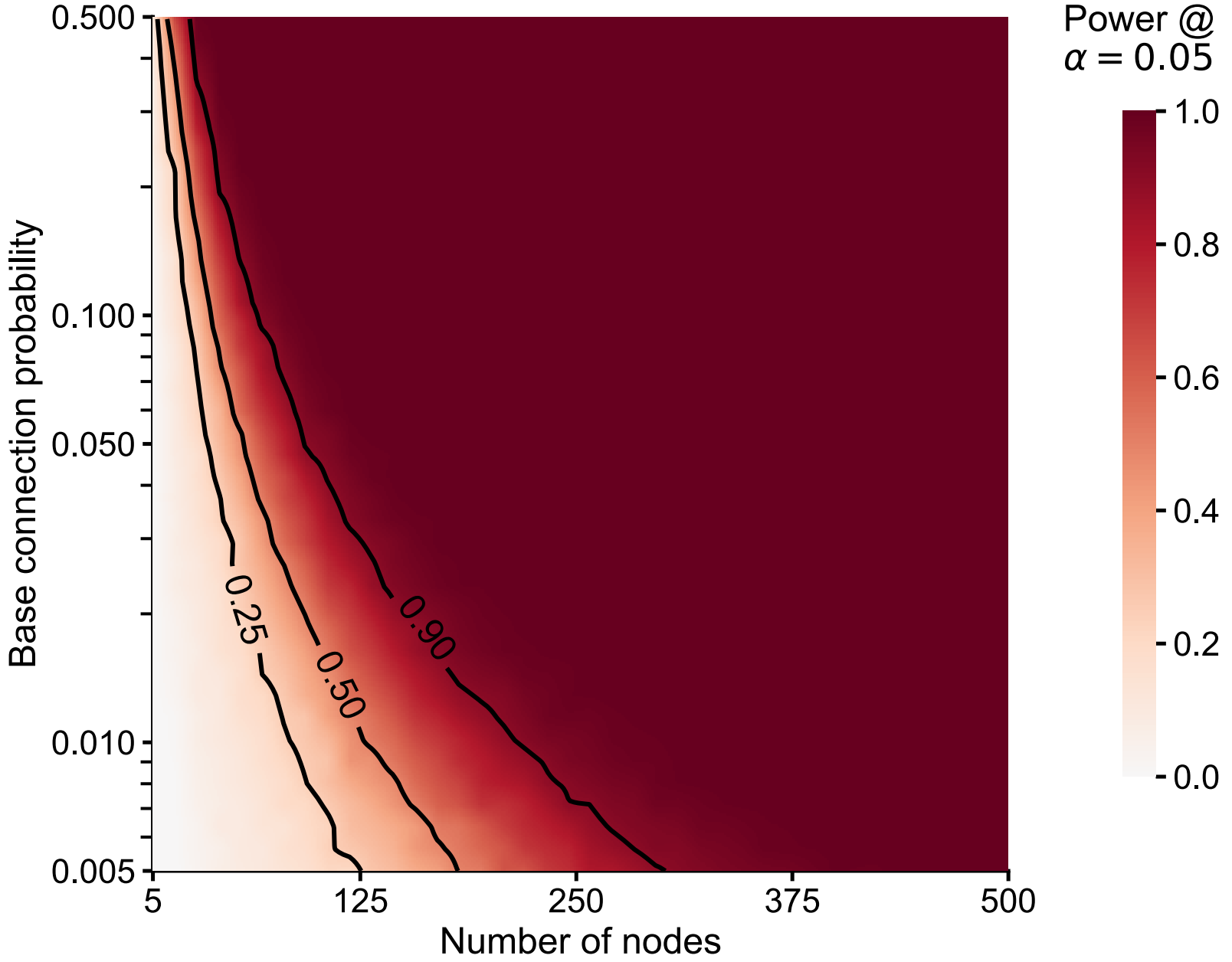

Fisher
p-value: 0.982
Score
p-value: 0.979
Cmh
p-value: 0.750
Cumulative density
pvalue
0.0
0.2
0.4
0.6
0.8
1.0
0.00
0.25
0.50
0.75
1.00

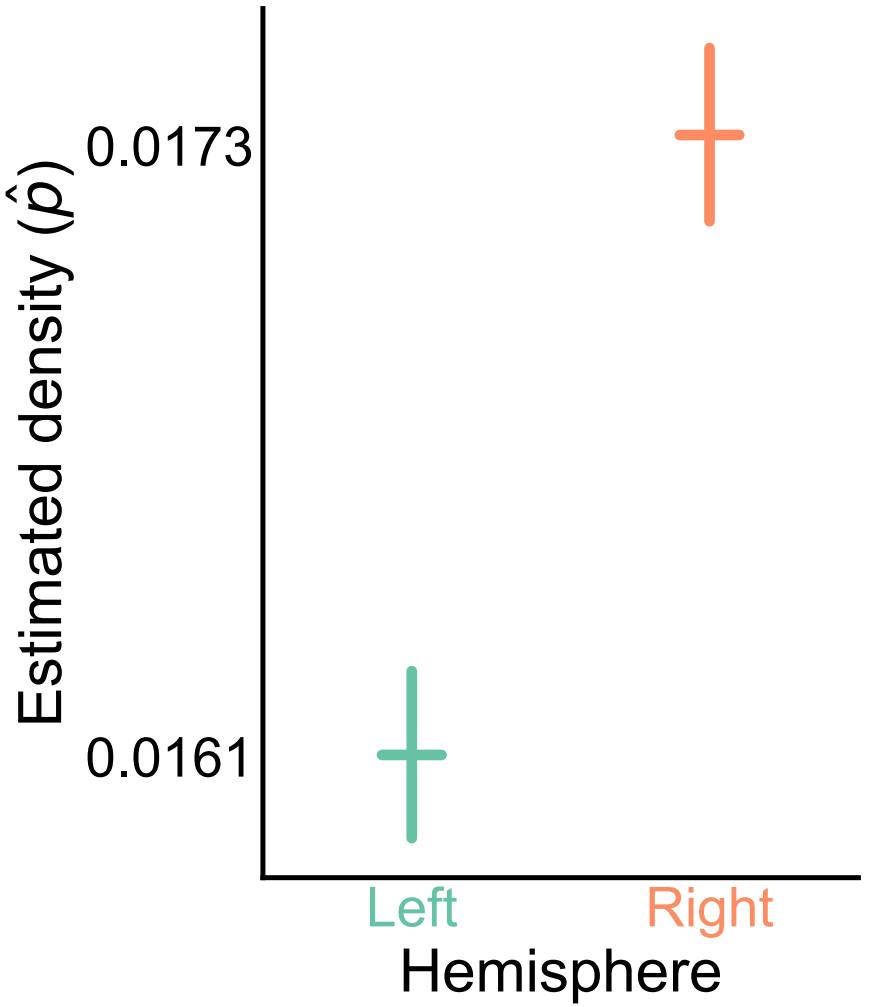
A)


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

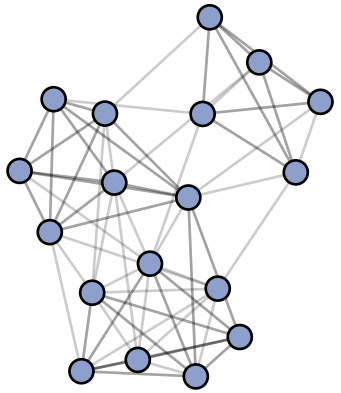

0.500
0.100
0.050
0.010
0.005
Base connection probability
5
125
250
375
500
Number of nodes
0.25
0.50
0.90
Power @
$\alpha = 0.05$
1.0
0.8
0.6
0.4
0.2
0.0


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

Compute global connection density

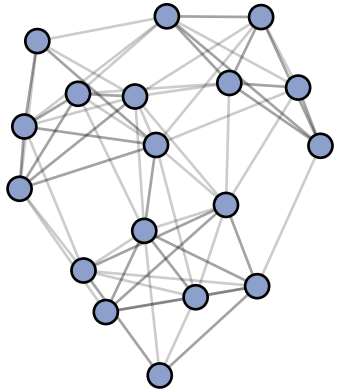
Compare ER models

Left

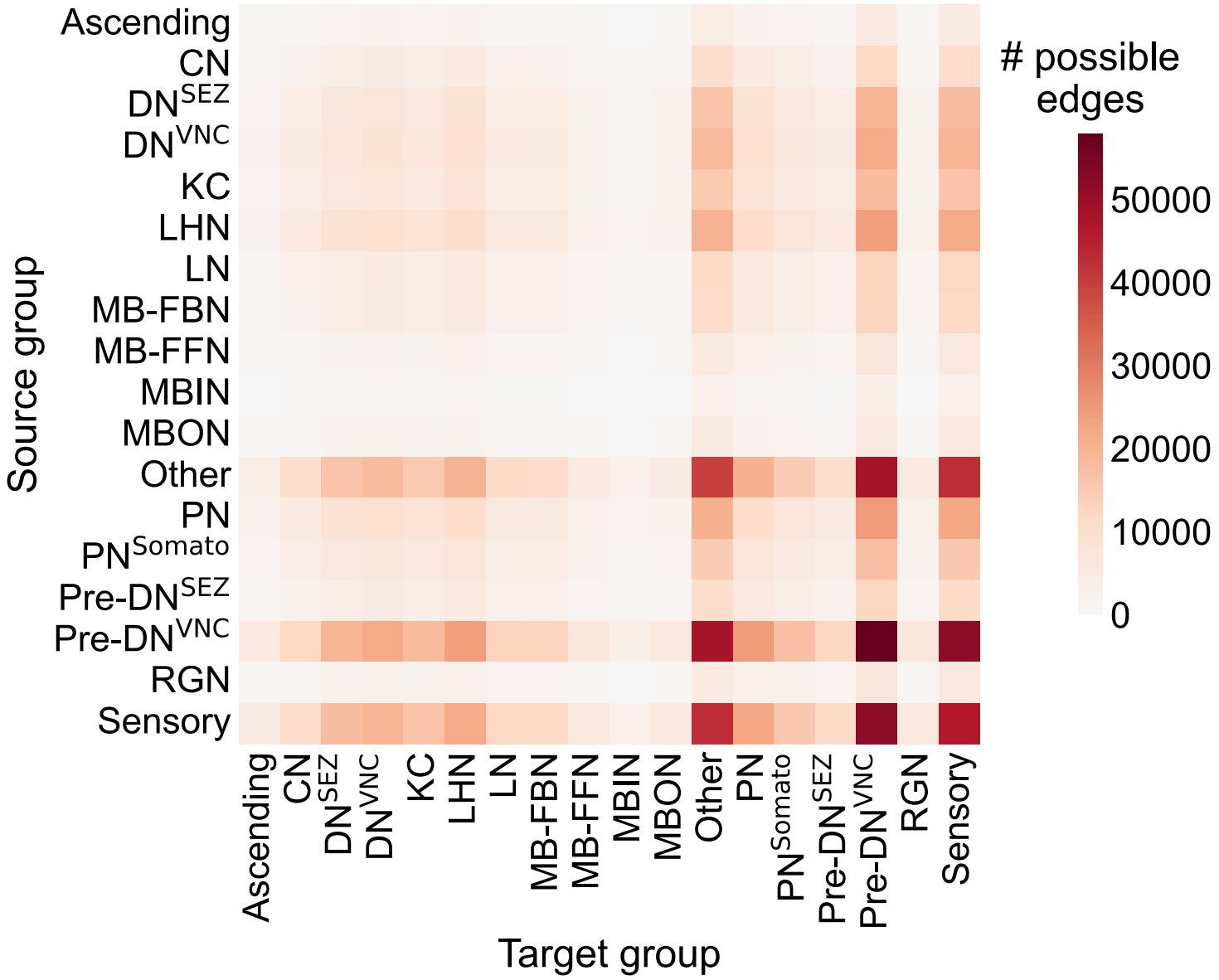


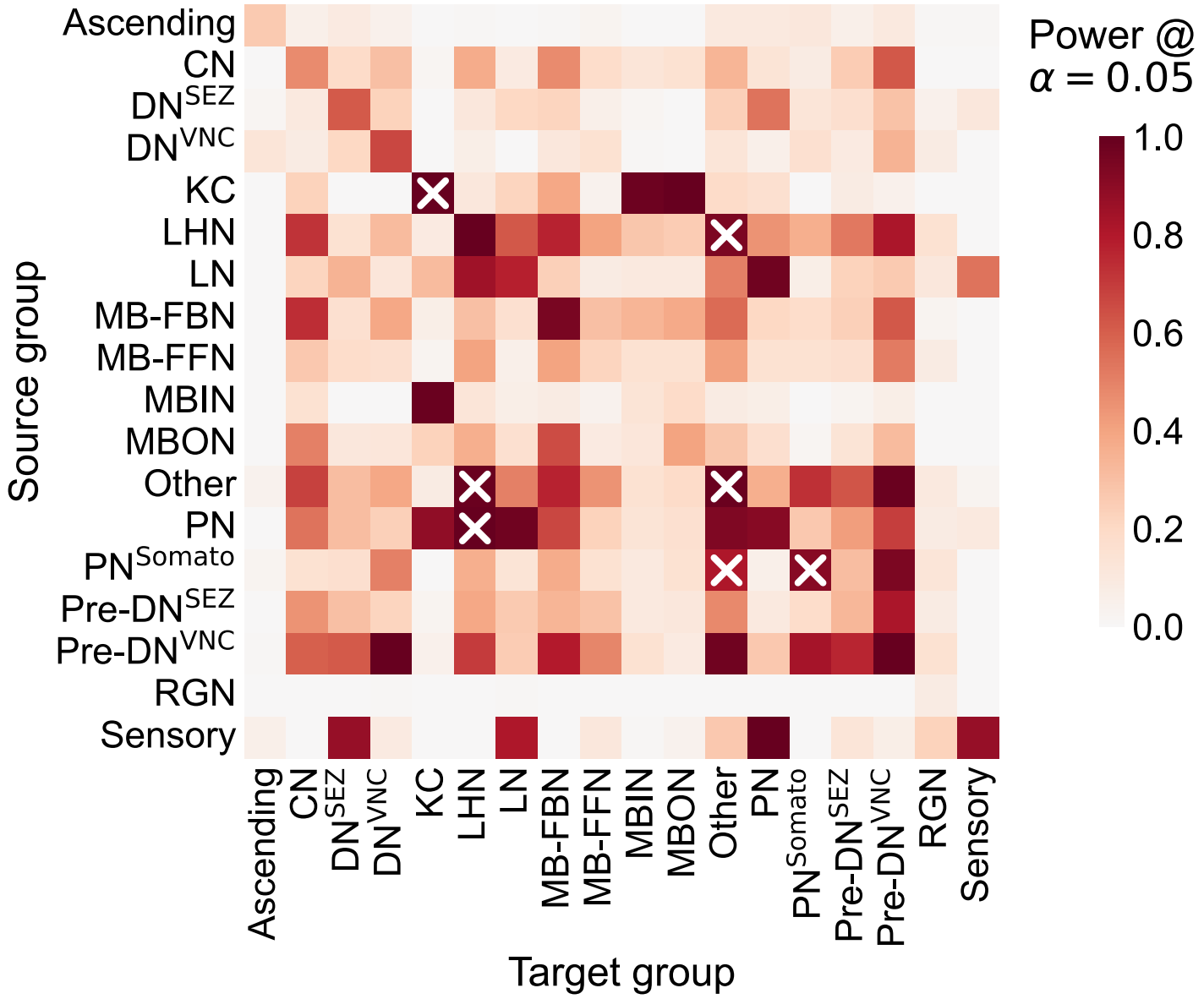
$$p = \frac{\#\ edges}{\#\ potential\ edges}$$

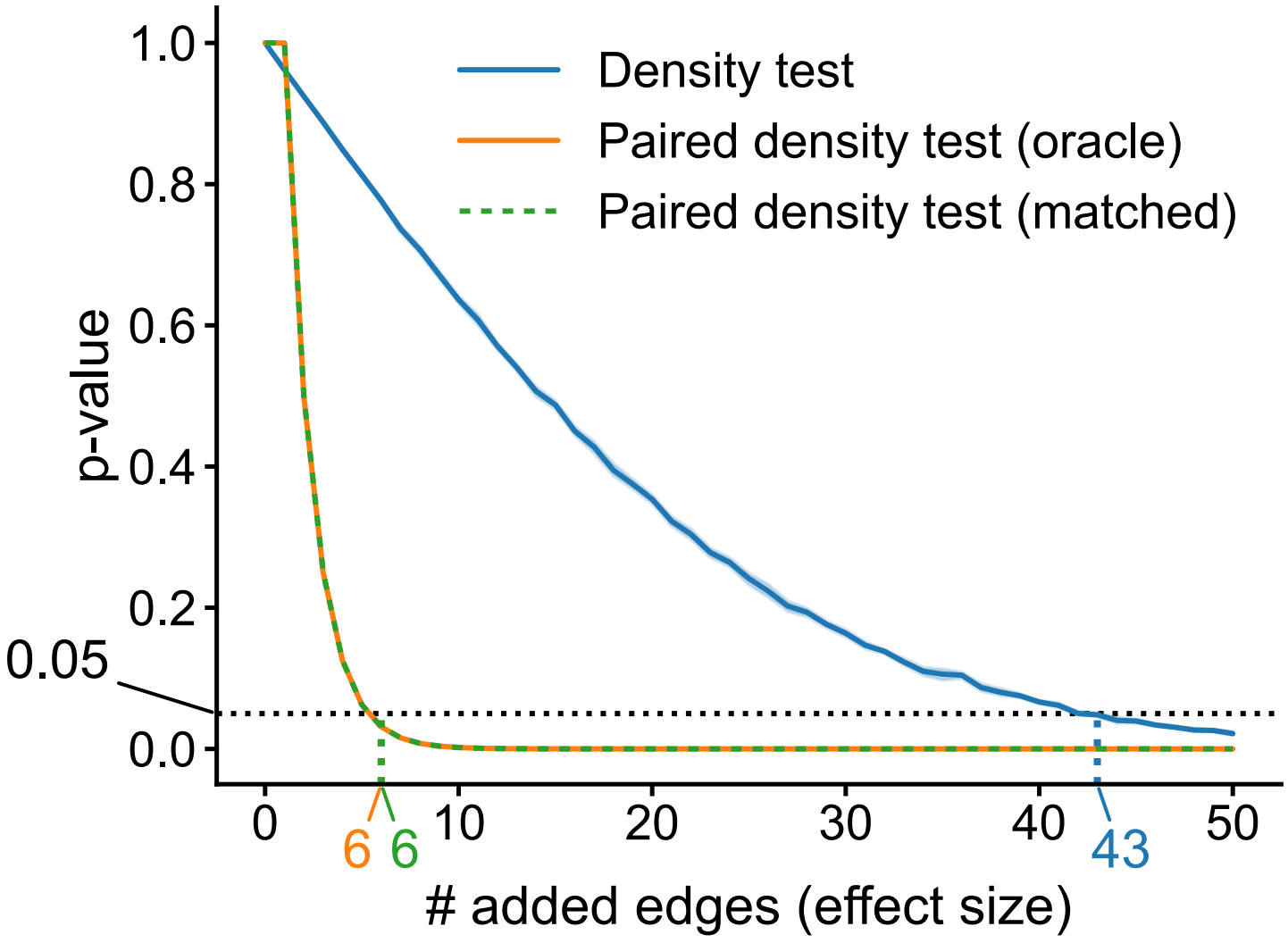
Right

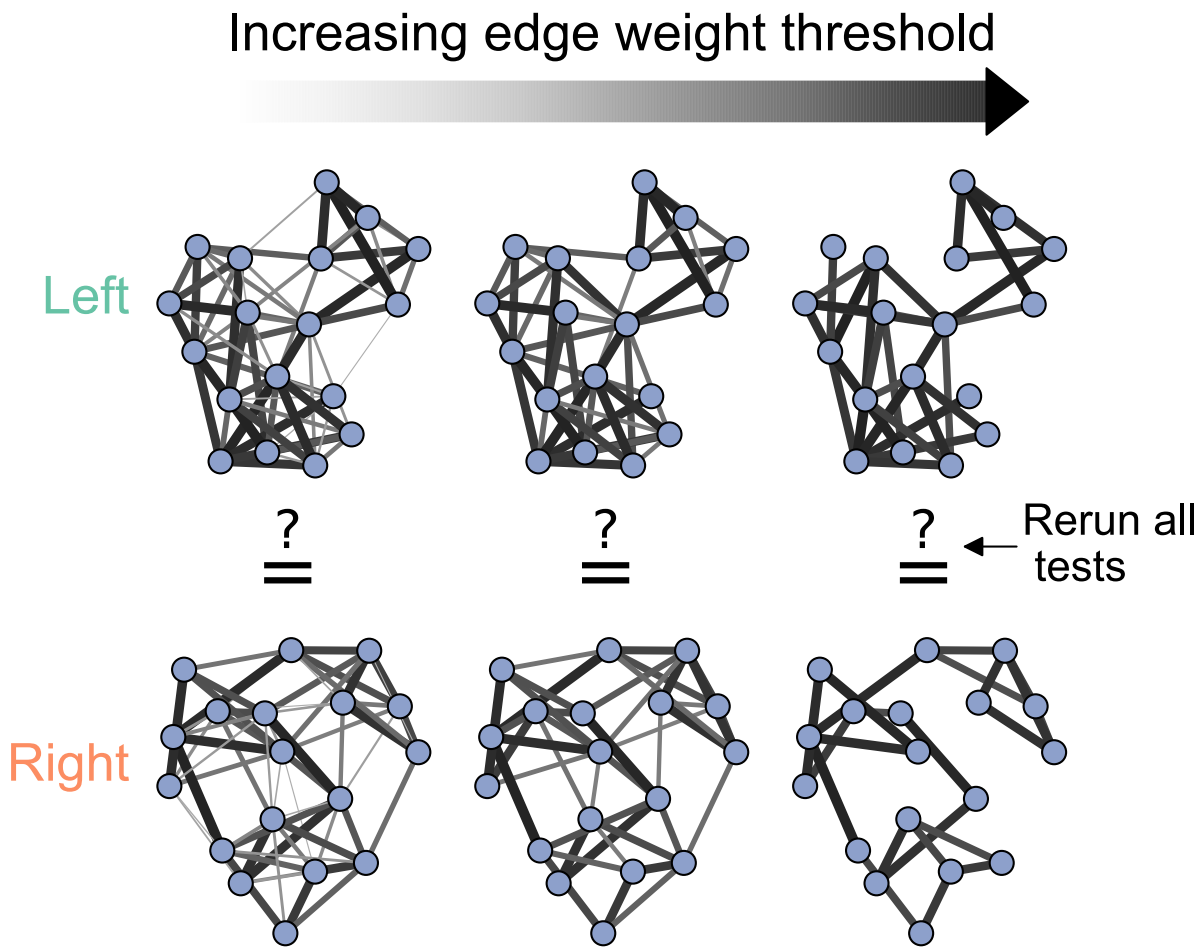


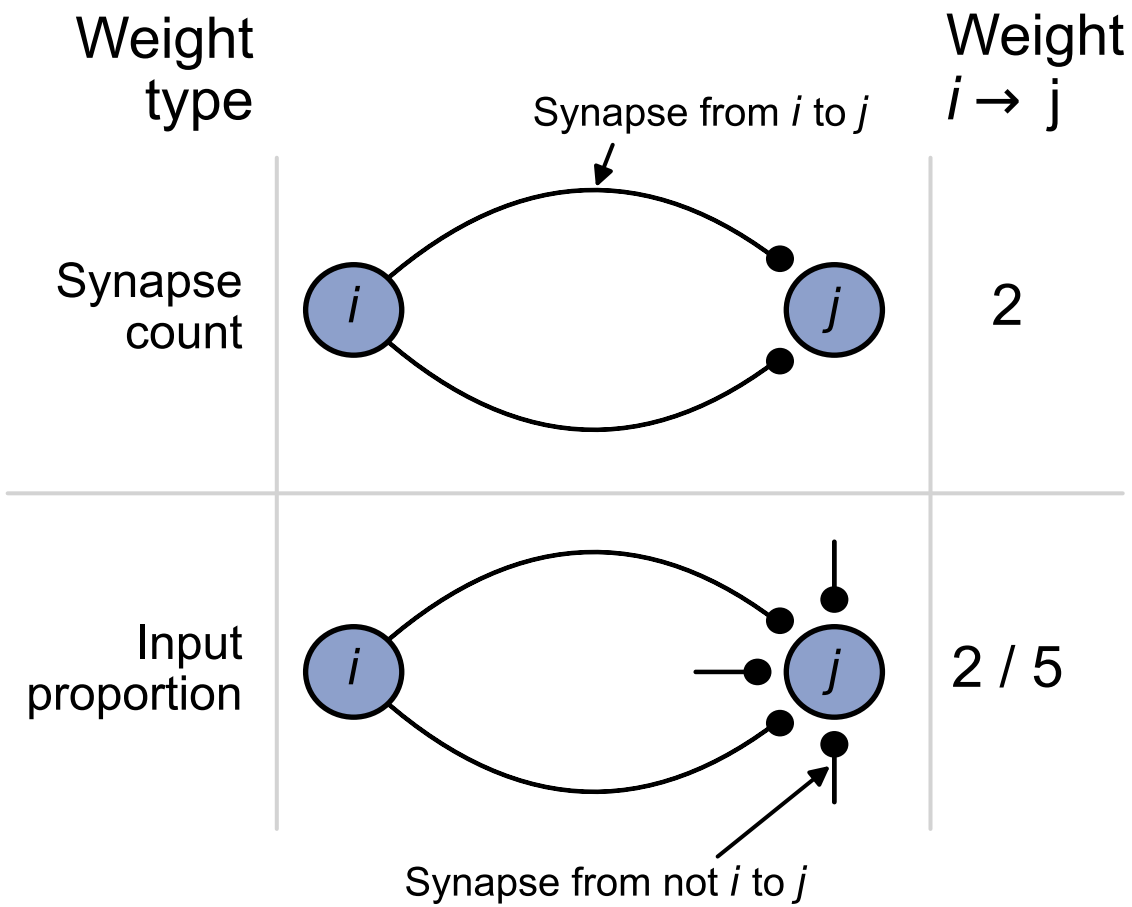
$$H_0: p^{(L)} = p^{(R)}$$
$$H_A: p^{(L)} \neq p^{(R)}$$

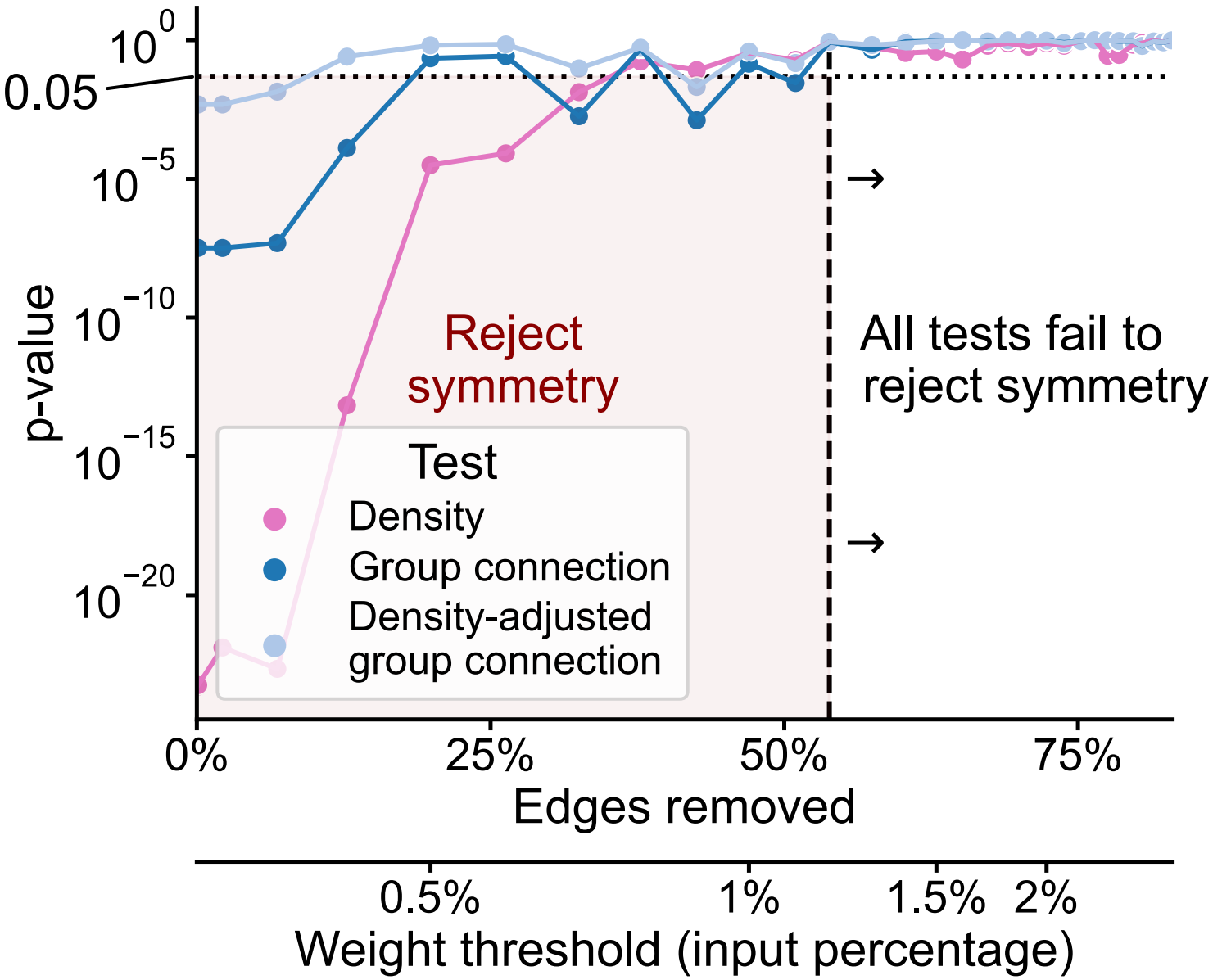

Source group
Ascending
CN
DN^SEZ
DN^VNC
KC
LHN
LN
MB-FBN
MB-FFN
MBIN
MBON
Other
PN
PN^Somato
Pre-DN^SEZ
Pre-DN^VNC
RGN
Sensory
Target group
possible edges
50000
40000
30000
20000
10000
0

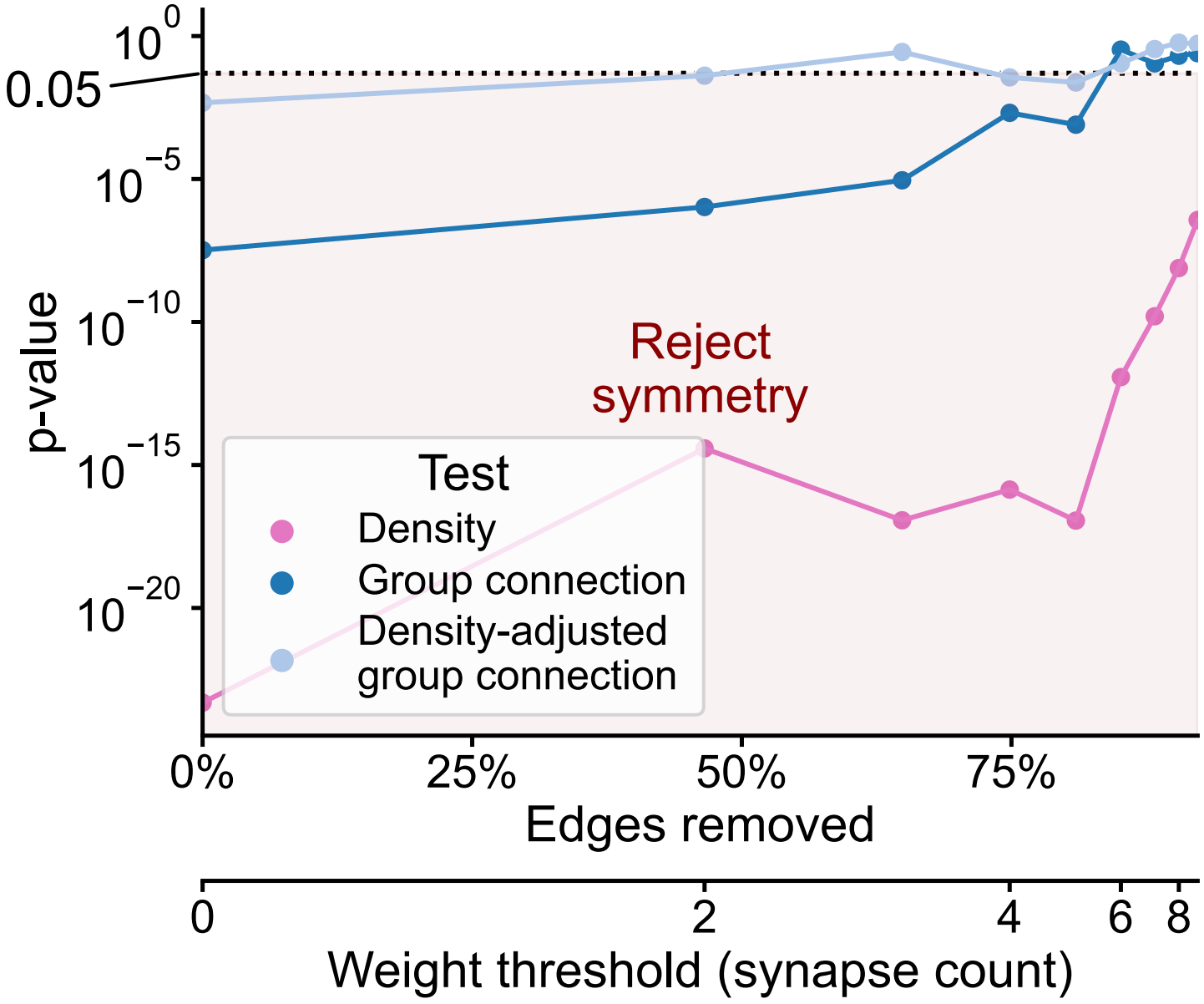

Ascending
CN
DN^SEZ
DN^VNC
KC
LHN
LN
MB-FBN
MB-FFN
MBIN
MBON
Other
PN
PN^Somato
Pre-DN^SEZ
Pre-DN^VNC
RGN
Sensory
Source group
Target group
Power @ α = 0.05
1.0
0.8
0.6
0.4
0.2
0.0

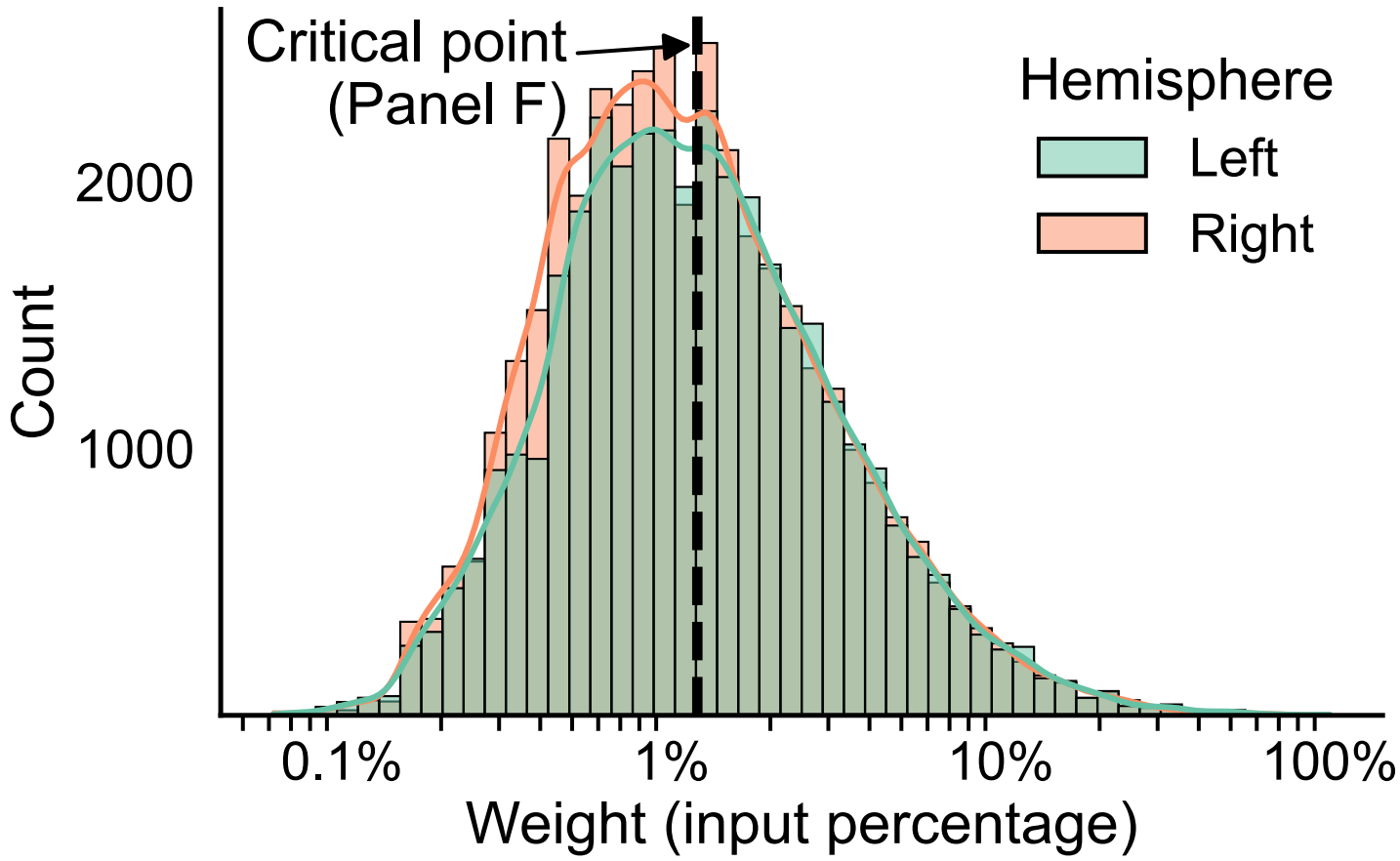

Density test
Paired density test (oracle)
Paired density test (matched)
p-value
1.0
0.8
0.6
0.4
0.2
0.05
0.0
0
6
6
10
20
30
40
43
50
added edges (effect size)

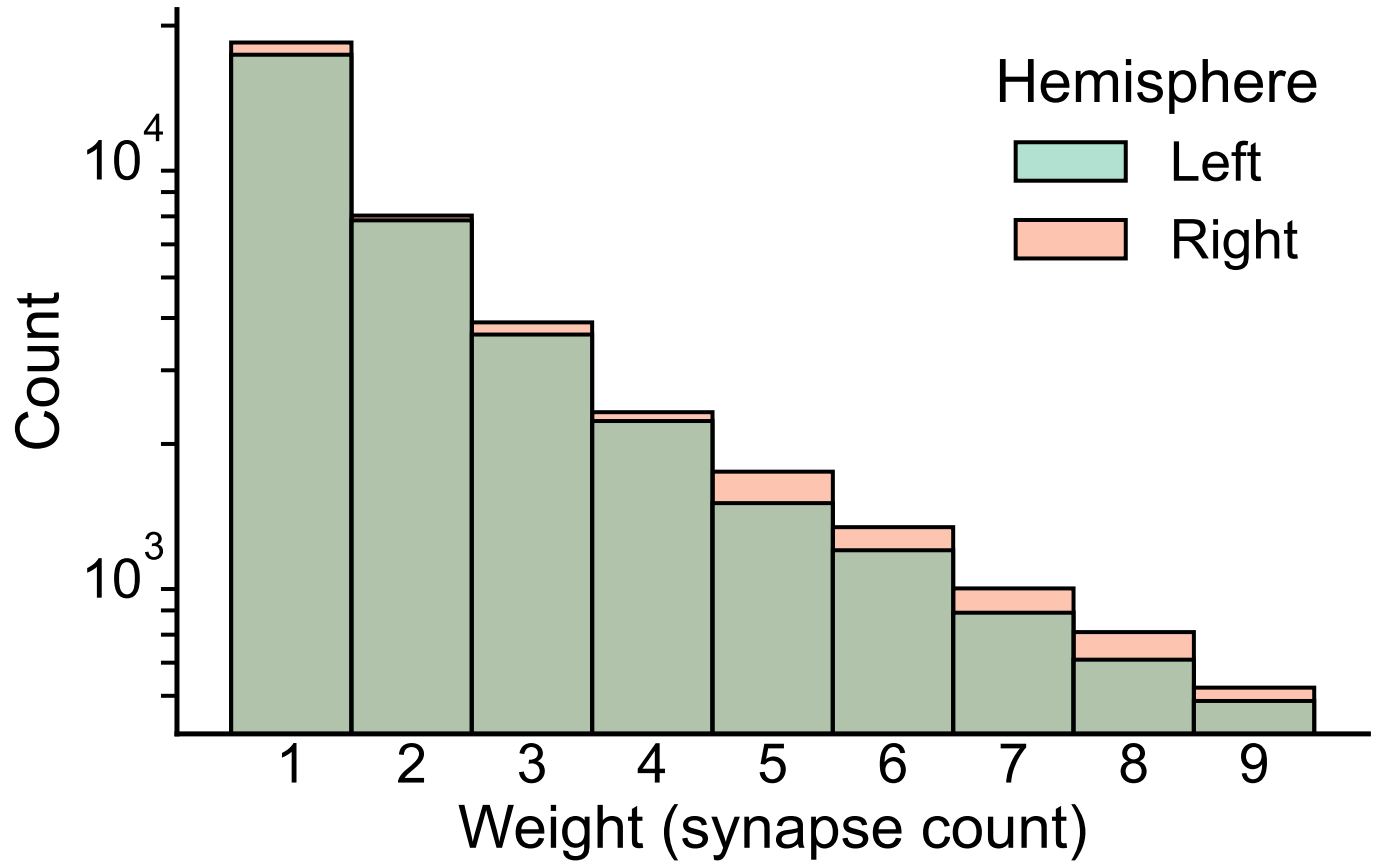

Increasing edge weight threshold
Left
Right
?
?
?
Rerun all tests

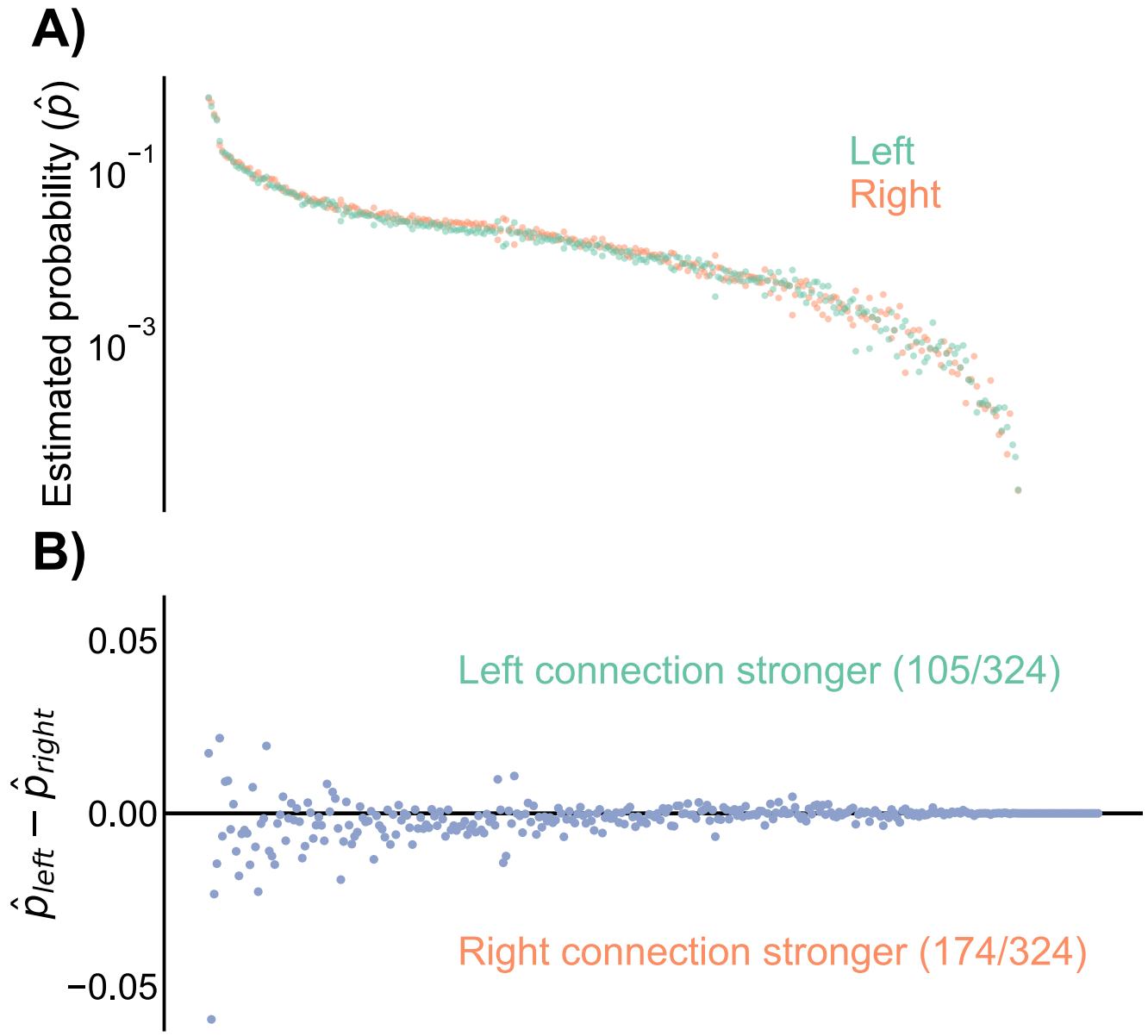

Weight type
Weight $i \rightarrow$ j
Synapse from *i* to *j*
Synapse count
2
Input proportion
2 / 5
Synapse from not *i* to *j*


10^{0}
0.05
10^{-5}
10^{-10}
10^{-15}
10^{-20}
p-value
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)


10^{0}
0.05
10^{-5}
10^{-10}
10^{-15}
10^{-20}
p-value
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)

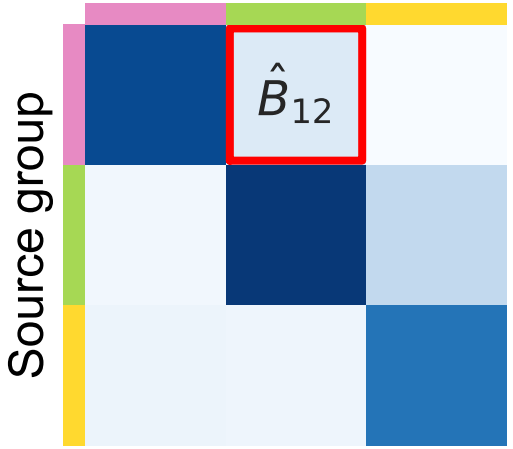

Critical point
(Panel F)
Hemisphere
Left
Right
2000
1000
Count
0.1%
1%
10%
100%
Weight (input percentage)

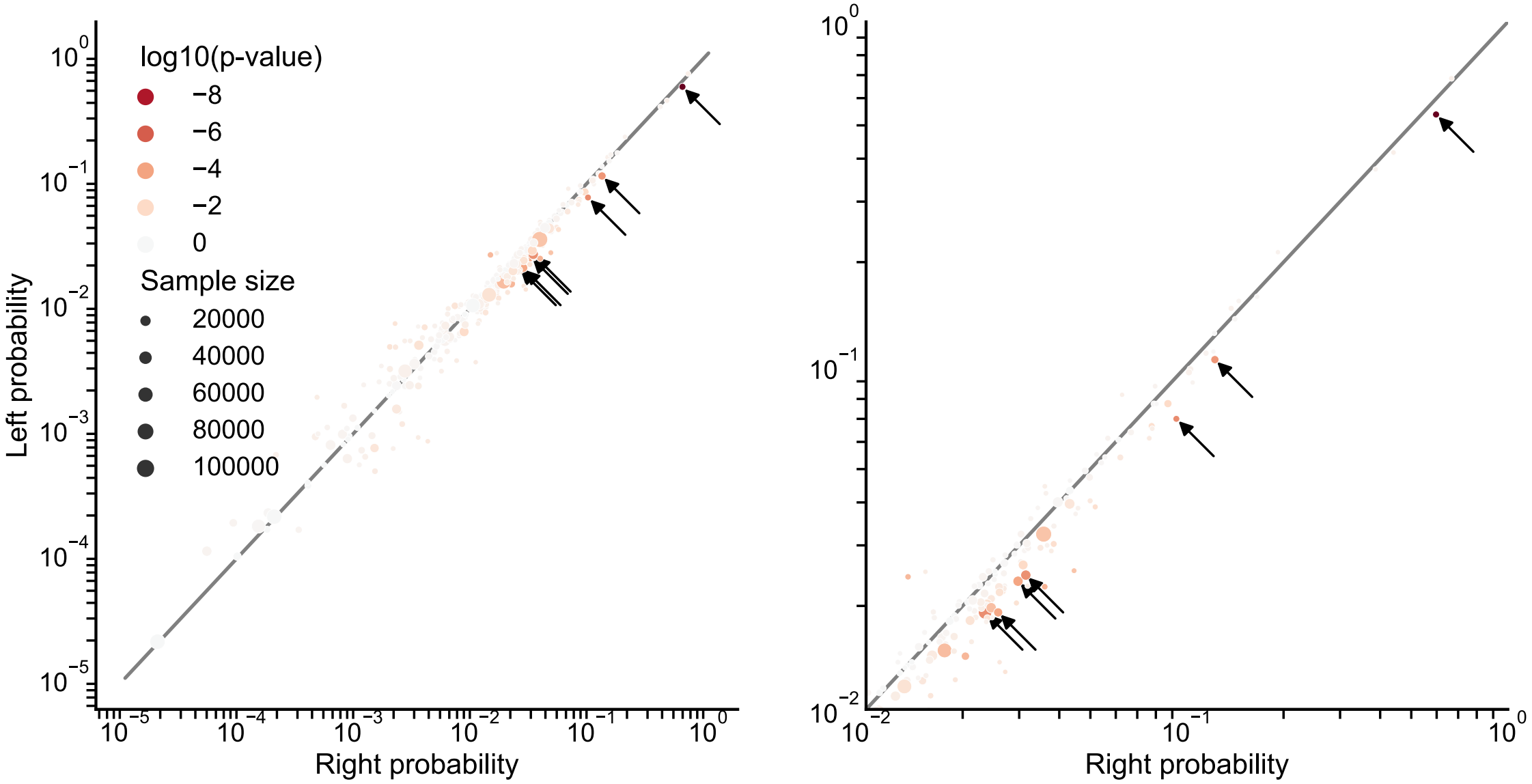

Hemisphere
Left
Right
Count
10^4
10^3
1
2
3
4
5
6
7
8
9
Weight (synapse count)

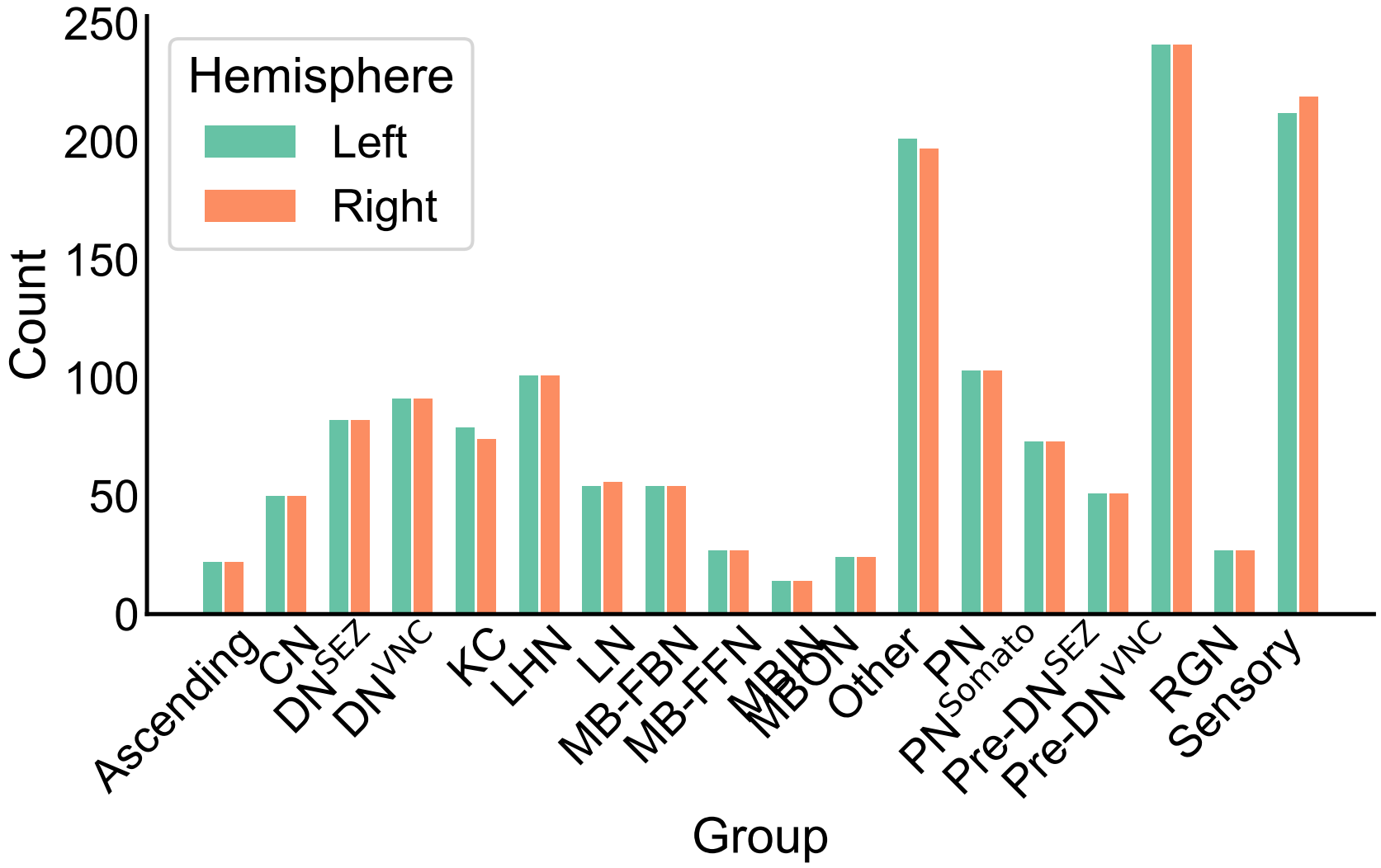

A)
Estimated probability ($\hat{p}$)
10^{-1}
10^{-3}
Left
Right
B)
$\hat{p}_{left} - \hat{p}_{right}$
0.05
0.00
−0.05
Left connection stronger (105/324)
Right connection stronger (174/324)

Group neurons

Estimate group-to-group connection probabilities ($\hat{B}$)




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.

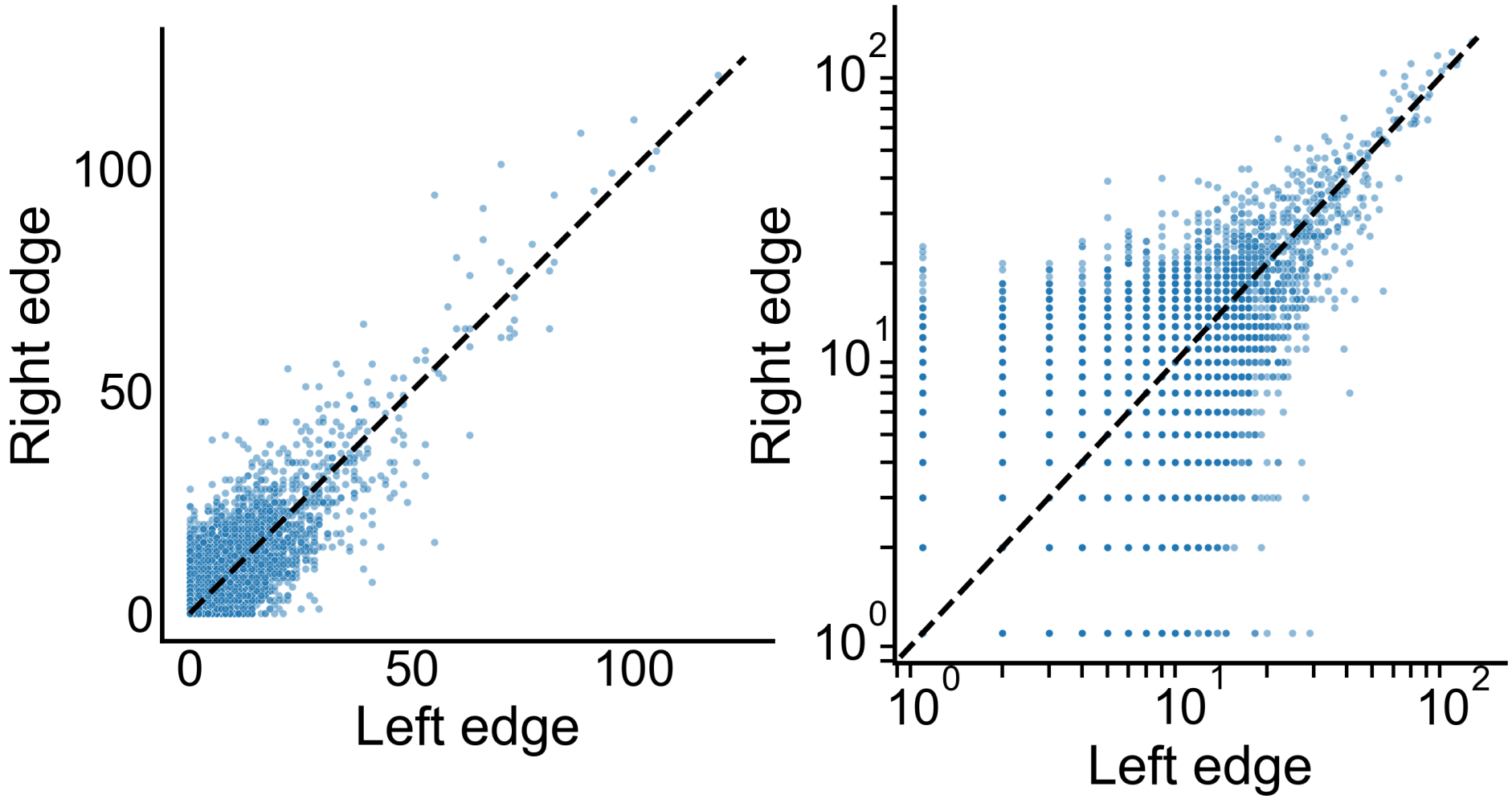
Require: Adjacency matrices for each of the four subgraphs: $A_{LL}, A_{RR}, A_{LR}, A_{RL} \in \mathbb{R}^{n \times n}$.

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 ($i \leq$ MAXITER) and ($\|P_i - P_{i-1}\|_F \geq$ TOLERANCE)) **do**

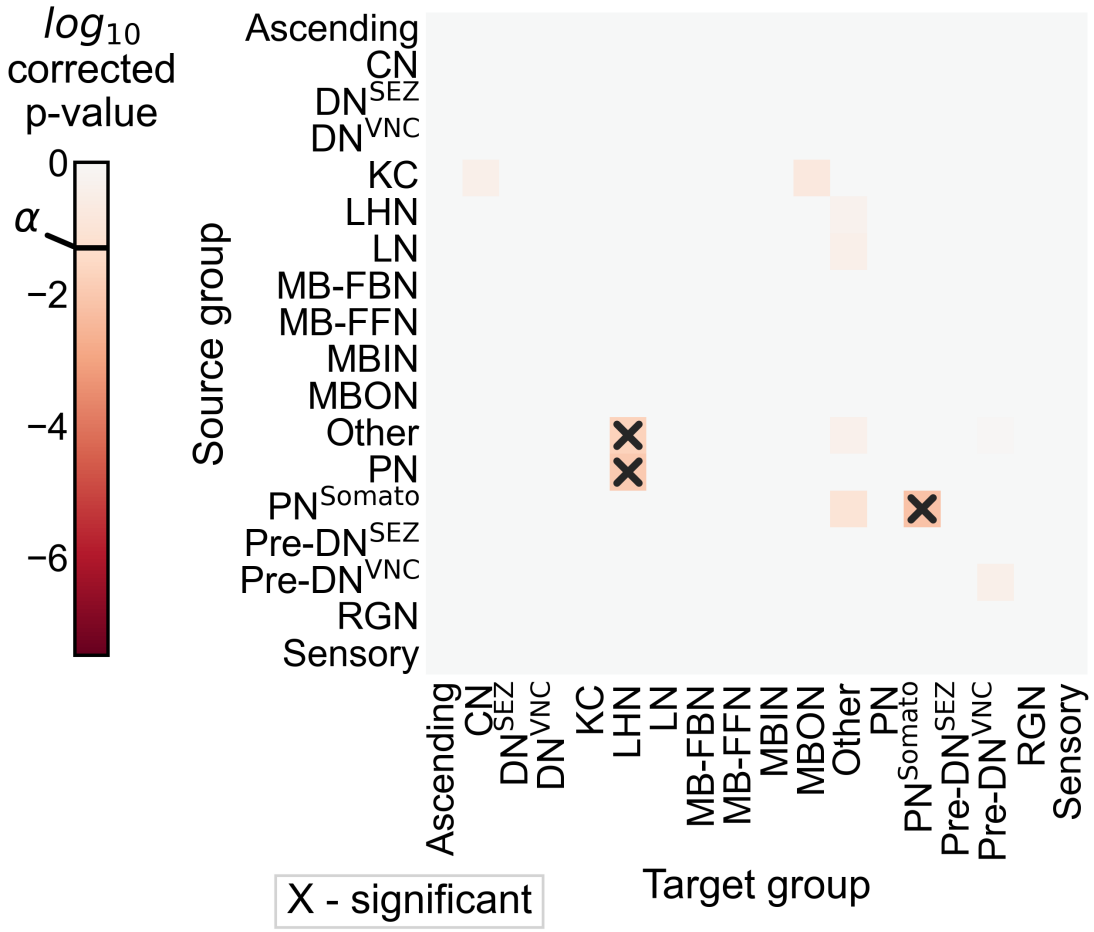
1. Compute $\nabla f(P_{(i)}) = -\left(A_{LL}P_{(i)}A_{RR}^T + A_{LL}^T P_{(i)} A_{RR} + A_{LR}P_{(i)}^T A_{RL} + A_{RL}^T P_{(i)}^T A_{LR}\right)$
2. Compute $Q_{(i)} \in \operatorname{argmin} \operatorname{tr}\left(Q^T \nabla f(P_{(i)})\right)$ over $Q \in \mathcal{D}$ via linear assignment problem 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

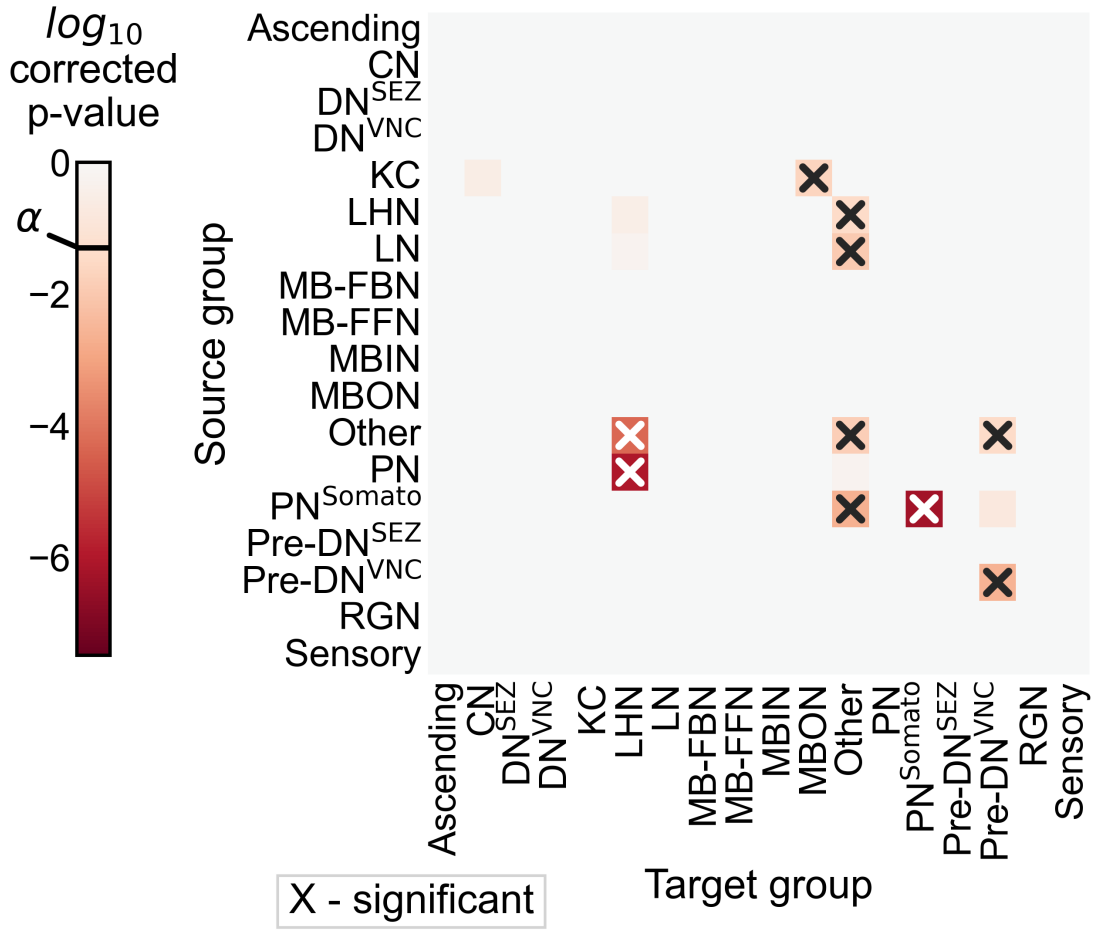


Pearson's corr = 0.82

Unpaired

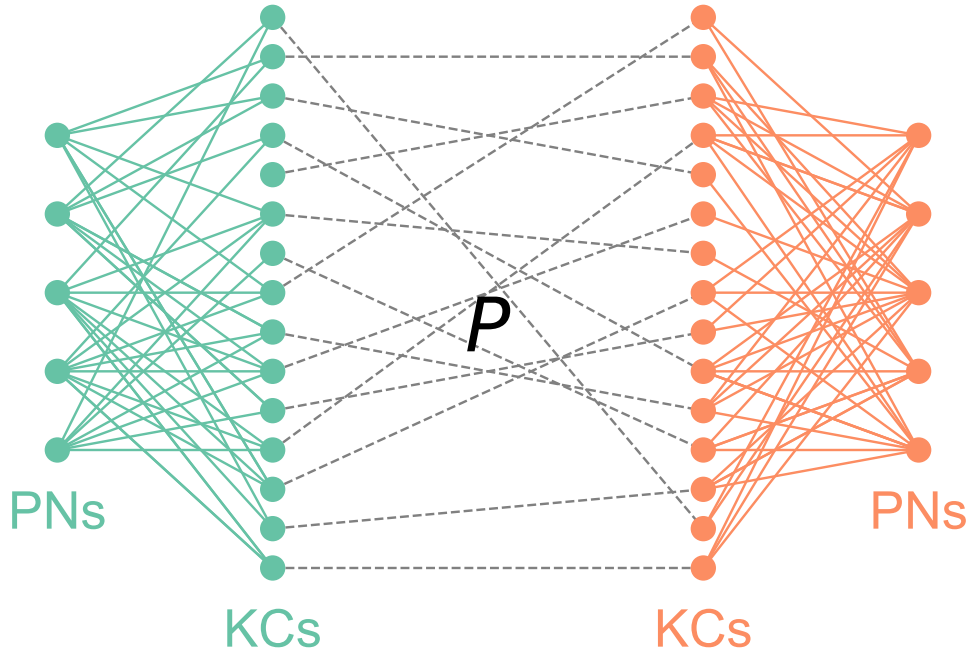


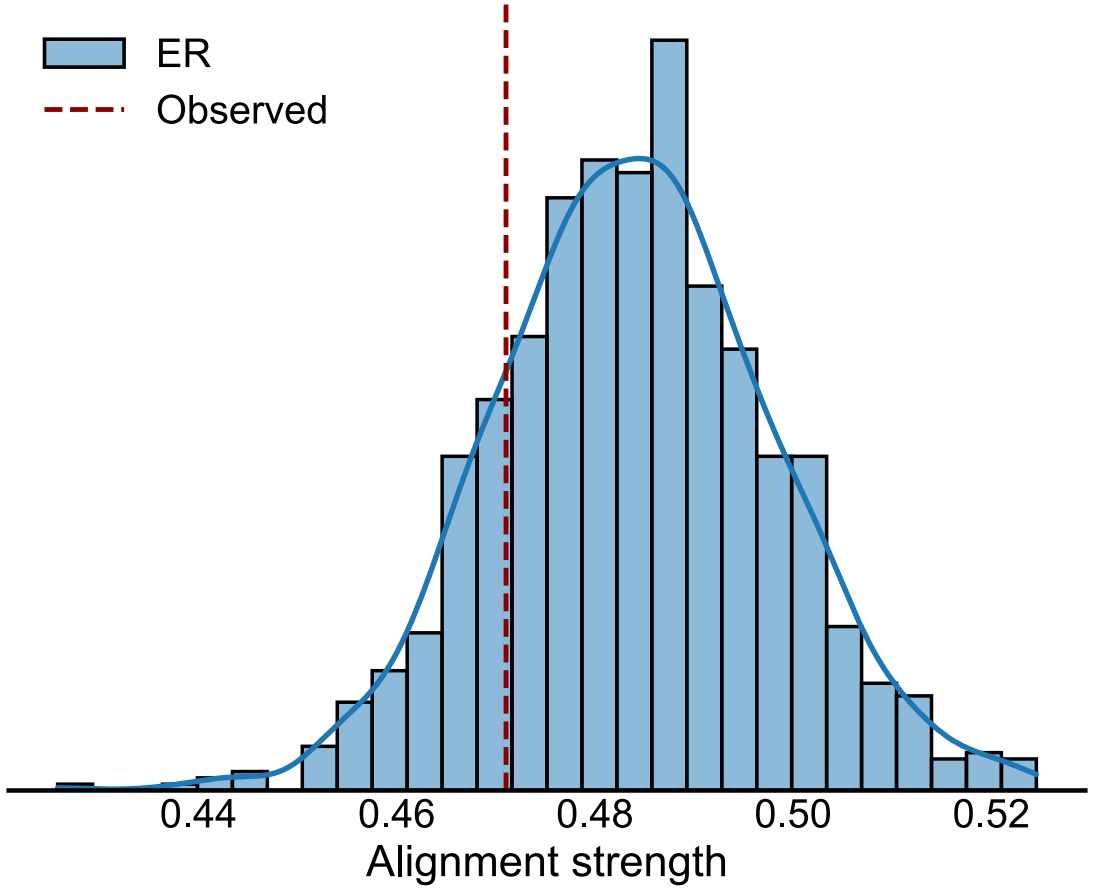
Paired



Testing for "stereotypy" in edge structure

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





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