

¹ RESEARCH

² **Modelling the cell-type specific murine connectome**

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⁶ **Keywords:** [a series of capitalized words, separated with commas]

ABSTRACT

⁷ The Allen Brain Connectivity Atlas consists of thousands of labelling experiments targeting
⁸ interrogating diverse structures and classes of projecting neurons. This paper describes the
⁹ conversion of these experiments into class-specific connectivity matrices representing the connection
¹⁰ between source and target structures. We introduce and validate a novel statistical model for creation
¹¹ of connectivity matrices that combines spatial and categorical smoothing to share information
¹² between similar neuron classes. We then illustrate overall and cell-type specific connectivity patterns
¹³ in the resultant connectivities.

AUTHOR SUMMARY

INTRODUCTION

¹⁴ The animal nervous system enables an extraordinary range of natural behaviors, and has inspired
¹⁵ much of modern artificial intelligence. Neural connectivities - axon-dendrite connections from one
¹⁶ region to another - form the architecture underlying this capability. These connectivities vary by
¹⁷ neuron type, as well as axonic source and dendritic target structure. Thus, characterization of the

18 relationship between neuron type and source and target structure is an important step to
19 understanding the nervous system.

20 Viral tracing experiments - in which a viral vector expressing GFP is transduced into neural cells
21 through stereotaxic injection - are a useful tool for understanding these connections on the mesoscale
22 (???). The GFP protein moves from axon to dendrite through the process of anterograde projection, so
23 neurons 'downstream' of the injection site will also fluoresce. Two-photon tomography imaging can
24 then determine the location and strength of the fluorescent signals in two-dimensional slices. These
25 locations can then be mapped back into three-dimensional space, and the signal is partitioned into
26 the transduced source and merely transfected target regions.

27 The conversion of such experiment-specific signals into an overall estimate of the connectivity
28 strength of two regions is accomplished by a statistical model. ? and ? describe two such methods.
29 Intuitively, both of these models provide some improvement over simply averaging the projection
30 signals of injections in a given region. is another. These models are evaluated based off of their ability
31 to predict held-out experiments in leave-one-out cross validation. A model that performs well in such
32 validation experiments is then assumed to generate the most accurate connectivity.

33 Both ? and ? develop models for mostly wild-type mice using a standardized vector over all
34 experiments. However, recent work (?) has extended these datasets to include viral tracing
35 experiments inducing cell-type specific fluorescence. This is accomplished by injecting vectors with
36 Cre-recombinase triggered GFP promoters into transgenic mice with cell-type specific
37 Cre-recombinase expression Thus, the this paper extends the methodology of ? and ? to deal with the
38 diverse set of cre-lines described in ?.

39 This extension relies on a to our knowledge novel estimator that takes into account both the spatial
40 position of the labelled source, as well as the categorical cre-label. This model outperforms the model
41 of ?, even for wild-type experiments.

42 The resulting cell-type specific connectivity matrices form a multi-way *neural connection tensor* of
43 information about neural structure. We do not attempt an exhaustive analysis of this data, but do
44 demonstrate several basic phenomena. First, we verify several cell-type specific patterns found
45 elsewhere in the literature. Second, we discover cell-type specific signals in the neural connection

⁴⁶ tensor. Finally, we decompose the overall (wild-type) connectivity matrix into factors representing
⁴⁷ archetypal connective patterns.

METHODS

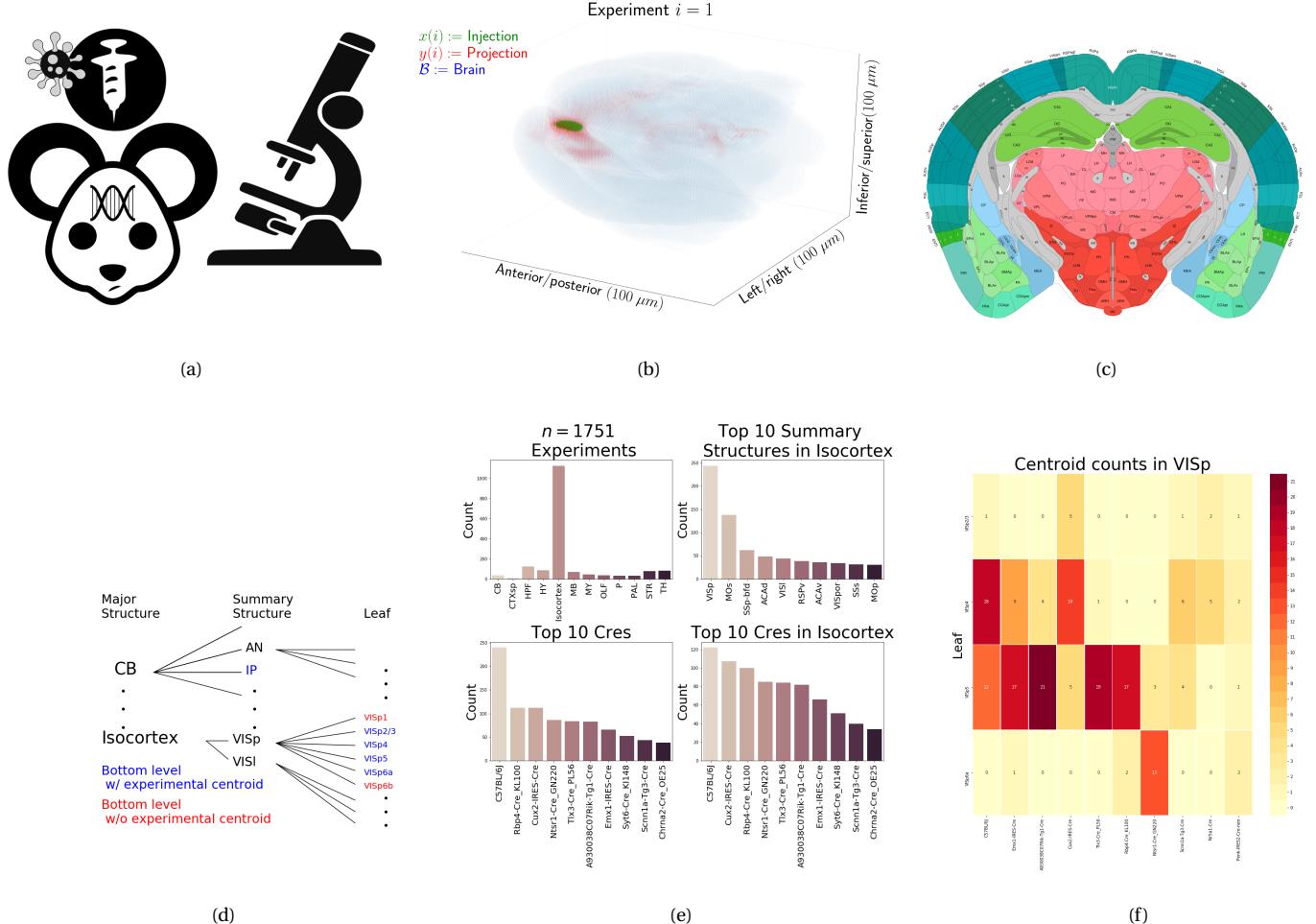


Figure 1: a) Background on histology. a) Within the brain (blue), injection (green) and projection (red) areas are determined via histological analysis and alignment to the Allen Common Coordinate Framework (CCF). b) An example of the segmentation of projection and injection for a single experiment. c) Example of structural segmentation within a horizontal plane. d) Explanation of nested structural ontology highlighting lowest-level and data-relevant structures. e) Abundances of celines and structural injections. f) Co-occurrence of layer-specific centroids and celine within VISp

48 Our main result is the creation of cell-type specific connectivity matrices using a model trained on
49 murine viral-tracing experiments. This section first describes the data used to generate the model, the
50 model itself, evaluation of the model, and the use of the model in creation of the connectivity
51 matrices. The model we ultimately propose is selected based off it's preferable performance in
52 creation of connectivity matrices with greater accuracy than alternative approaches. We accompany
53 these matrices with exploratory analyses of the resulting connectivities that illustrate their key
54 features.

55 ***Mice***

56 (SK's comment:**Experiments involving mice were approved by the Institutional Animal Care and**
57 **Use Committees of the Allen Institute for Brain Science in accordance with NIH guidelines.**)

58 ***Data***

59 Our dataset \mathcal{D} consists of $n = 1751$ experiments from the Allen Mouse Brain Connectivity Atlas. Figure
60 2 describes the key features of the dataset. Each experiment is performed by injecting a GFP-labelled
61 transgene cassette with a potentially cre-specific promoter into a particular location in a cre-driver
62 mouse. The resultant fluorescent signal is imaged, and aligned into the Allen Common Coordinate
63 Framework (CCF), a three-dimensional idealized model of the brain that is consistent between
64 animals.

65 Within the dataset generating the connectivity model reported in this paper, certain structure and
66 cre-line combinations (S, V) appear frequently, while others appear not at all. Since users of the
67 connectivity matrices may be interested in particular combinations, or interested in the amount of
68 data used to generate a particular connectivity estimate, we exhaustively present this information
69 about all experiments in Appendix ??.

70 ***Data processing***

71 We discretize the fluorescent intensity photographically determined through histological image
72 analysis at the $100 \mu\text{m}$ voxel level. Thus, the fluorescence is represented as a tensor $\mathcal{F} \in \mathbb{R}^B$ where
73 $B \subset [1 : 132] \times [1 : 80] \times [1 : 104]$ corresponds to the subset of the voxelized $(1.32 \times 0.8 \times 1.04)$ cm
74 rectangular space occupied by the standard mouse brain. This fluorescence is segmented into

75 injection and projection areas corresponding to areas of transduction and transduction/transfection,
76 respectively. For a given experiment, we denote these as $x(i)$ and $y(i)$, respectively. An example of
77 such segmentation areas is given in Figure ??. In order to relate the regularly discretized 3D space B
78 with biologically informative structures such as the cortex, we also apply several levels of
79 regionalization, as shown in Figure 2. Mathematically, we refer to the regionalization map as
80 $r : \mathcal{B} \times \mathbb{R} \rightarrow \mathcal{R} \times \mathbb{R}$. Given a vector a , we also define a normalization map $n : a \mapsto \frac{a}{\sum_{t \in T} a_t}$. A detailed
81 mathematical description of these data preprocessing steps is given in Appendix ??.

*82 **Connectivity***

83 Our goal is the estimation of structural connectivity from one structure to another. At an essential
84 level, cell-class specific neural connectivity is representable as a function $f : \mathcal{V} \times \mathbb{R}^3 \times \mathbb{R}^3 \rightarrow \mathbb{R}^+$ giving
85 the connection of a particular cell-class from a source position to a target position. As mentioned in
86 the previous section, our injection and projection intensities are discretized into $100\mu\text{m}$ cubic voxels.
87 These voxels are contained within structures, so mathematically we can write a region $R = \{r\}$. We
88 generically denote source regions $S = \{s\}$ and target regions $T = \{t\}$.

There are several notions of structural connectivity worth considering based on normalization with respect to the sizes of the source and/or target regions. Given a set of source regions $\mathcal{S} = \{S\}$, target regions $\mathcal{T} = \{T\}$, and cre-lines \mathcal{V} we shall estimate the following tensors:

connectivity strength $\mathcal{C} \in \mathcal{V} \times \mathcal{S} \times \mathcal{T} \times \mathbb{R}_{\geq 0}$ with $\mathcal{C}(V, S, T) = \sum_{s \in S} \sum_{t \in T} f(v, s, t)$

normalized connectivity strength $\mathcal{C}^S \in \mathcal{V} \times \mathcal{S} \times \mathcal{T} \times \mathbb{R}_{\geq 0}$ with $\mathcal{C}^S(V, S, T) = \frac{1}{|S|} \sum_{s \in S} \sum_{t \in T} f(v, s, t)$

normalized projection density $\mathcal{C}^D \in \mathcal{V} \times \mathcal{S} \times \mathcal{T} \times \mathbb{R}_{\geq 0}$ with $\mathcal{C}^D(V, S, T) = \frac{1}{|S||T|} \sum_{s \in S} \sum_{t \in T} f(v, s, t)$.

89 Our goal is to estimate $\mathcal{C}(V, S, T)$ with data \mathcal{D} . We call this estimator $\hat{\mathcal{C}}$.

*90 **Modelling connectivity***

Construction of such an estimator raises the important questions of 1) what data to use for estimating which connectivity, 2) how to featurize the dataset, 3) what statistical estimator to use, and 4) how to reconstruct the connectivity using the chosen estimator. Mathematically, we represent these

considerations as

$$\widehat{\mathcal{C}}(V, S, T) = e^*(\widehat{e}(e_*(\mathcal{J}(\mathcal{D}))). \quad (1)$$

This makes explicit the data featurization e_* , statistical estimator \widehat{e} , and any potential subsequent transformation e^* such as averaging over the source region, as well as the fact that different data \mathcal{D} may be used to estimate different connectivities. For example, a simple model would be to take the mean regionalized projection of all the experiments with injection centroid in a given structure. Table 1 reviews estimators used for this data-type, and explain the intuition behind our new cell-class specific estimator. Additional information is given in Appendix ??

Model	e^*	\widehat{e}	e_*	Training Data
(?)	$\widehat{e}(S)$	NNLS(X,Y)	$X = r(x(I)), Y = r(y(I))$	$I = I_M$
(?)	$\sum_{s \in S} \widehat{e}(s)$	NW(X,Y)	$X = c(x(I)), Y = r(y(I))$	$I = I_M$
Cre-NW	$\sum_{s \in S} \widehat{e}(s)$	NW(X,Y)	$X = c(x(I)), Y = n(r(y(I)))$	$I = I_S \cap I_V$
Expected-loss	$\sum_{s \in S} \widehat{e}(s)$	EL _S (X, Y, V)	$X = c(x(I)), Y = n(r(y(I))), V = v(I)$	$I = I_S$

Table 1: Estimation of \mathcal{C} using connectivity data. The regionalization, estimation, and featurization steps are denoted by e^* , \widehat{e} , and e_* , respectively. The training data used to fit the model is given by I . We generically denote the set of experiments used to train a particular model as I , and experiments from particular major brain divisions, summary structures, and leafs as I_M , I_U , and I_L , respectively.

Our new methodological contributions in this area - the Cre-NW and Expected-loss models - have several differences from the previous methods. Both the ? non-negative least squares and ? Nadaraya-Watson take into account s and t , but not v . Since our goal is creation of cre-specific connectivities, our new estimators specifically account for this information. The cre-specific Nadaraya-Watson estimator only uses experiments from a particular cre-line to predict cell-class connectivity, while the Lxpected Loss estimator shares information between cre-lines. We also normalize projections by total intensity to account for differences in the cre-driven expression of eGFP via the various transgene promoters.

105 **Evaluating connectivity models**

106 The final modeling question is how to select optimum functions from within and between our
 107 estimator classes. Examining Equation 1, we can see the equation in 3D coordinates,
 108 $\hat{f}(v, s, t) = \hat{e}(e_*(\mathcal{J}(\mathcal{D})))$ includes a deterministic step e^* . Since this step is included without input by
 109 the data, we can evaluate our model by its ability to predict held-out experiments in cross-validation.
 110 We use in particular *leave-one-out* cross validation, a simple and effective method for evaluating
 111 estimator performance. In order to compare between methods, we necessarily restrict to the smallest
 112 set of evaluation experiments suggested by any of our models. The surface smooth level requires
 113 computation of a mean for each cre-line. For cross-validation to be possible, two-experiments must
 114 be present - one with which to compute the mean, and one on which to evaluate the model. This is
 115 true even if experiments from other cre-lines are present within the structure.

116 CONSTRUCTION OF THE EVALUATION SET

116 CONSTRUCTION OF THE EVALUATION SET If we construct cre-means at the summary-structure level,
 117 then even if we smooth at the leaf level, we can evaluate estimator performance on the
 118 summary-structure set as long as there at least 1 experiments of any cre-line in that leaf. Predicting an
 119 experiment with summary-structure surface and summary-smoothing requires another of the same
 120 cre-line in the summary structure, and one of any cre-line in the same summary structure. Predicting
 121 an experiment with summary-structure surface and leaf-smoothing requires another of the cre-line in
 122 the summary structure, and one of any cre-line in the same leaf. This gives the same evaluation set as
 123 summary-surface summary-smooth but with experiments that are the only exemplar of their cre-line
 124 in the leaf removed. Predicting an experiment with leaf-structure surface and leaf-smoothing requires
 125 another of the same cre-line in the same leaf.

126 That is, $E_{sum}^{cre} \cap E_{leaf}^{NW}$. We note that since the number of parameters fit is quite low relative to the size
 127 of the evaluation set, we do not make use of a formal validation-test split. However, evaluating
 128 likelihood solely on the training set is trivially a bad idea in Nadaraya-Watson methods.

	Total	Cre-Summary	Cre-Summary, Leaf	Cre-Leaf
0	36	10	9	4
1	7	2	2	2
2	122	79	79	62
3	85	41	41	41
4	1128	838	829	732
¹²⁹	5	68	23	18
6	46	7	7	7
7	35	17	17	17
8	33	8	8	8
9	30	11	11	11
10	78	45	45	45
11	83	29	29	29

¹³⁰ Certain aspects of out-of-sample performance are not assessable via LOOCV. In particular, we
¹³¹ cannot evaluate model performance in regions where there are not enough experiments targeting a
¹³² particular cell-class. This raises the question of whether we should model these regions at all. We
¹³³ therefore make a scientifically-motivated distinction between wild-type non-cre injections and
¹³⁴ cell-class specific injections. Since wild-type connectivities are the sum of the component cell-types,
¹³⁵ even if, for example, a summary-structure specific estimator for a particular cre-line with
¹³⁶ leaf-smoothing will use exclusively non-wild type experiments, this will elucidate component
¹³⁷ cell-class connectivities. However, such For the wild-type mice without cre-specific injection, the
¹³⁸ neural connectivity is the sum of the included cell-types, so this is reasonable. However, for cell-class
¹³⁹ specific connectivity, this can lead to predictions of connectivity

LOSS METRICS The loss-function used to evaluate estimator performance on the evaluation set.

We use l_2 -loss and weighted l_2 -loss to evaluate these predictions:

$$\text{l2-loss } l(\hat{f}) = \frac{1}{|I_M|} \sum_{i \in I_M} \|r(y(i)) - \hat{f}(c(i))\|_2^2$$

$$\text{weighted l2-loss } l(\hat{f}) = \frac{1}{|\{S, V\}|} \sum_{s, v \in \{S, V\}} \frac{1}{|I_{s, v}|} \sum_{i \in I_{s, v}} l(r(y(i)), \hat{f}(\mathbb{D} \setminus i))$$

140 As a final modelling step, we establish a lower limit of detection. This is covered in Appendix.

141 ***Connectivity analyses***

142 We quantify and illustrate some of the interesting neuronal processes underlying our estimated
 143 connectome. First, we cluster projection pattern by cell-class and source structure. This shows that
 144 cell-class has a dominating effect on projection in certain regions. Second, we extend the
 145 characterization of ? on structural differences in short-range projections. These are primarily
 146 assumed to be due to diffusion, and the diffusion-rate helps to characterize the basic structural
 147 anatomy. Third, since the overall wild-type connectome results from the combination of underlying
 148 cell-classes, we apply non-negative matrix factorization (NMF) to decompose the observed
 149 long-range connectivity into *connectivity archetypes* that linearly combine to reproduce the observed
 150 connectivity. These methods identify structures with both known and plausible biological meaning,
 151 and simplistically exemplify useful posthoc analyses for data of this type. Technical details of these
 152 approaches are given in Appendix.

RESULTS

153 Our results include evaluation of model fit, the cre-specific connectivity matrices themselves, and
 154 retrospective analyses of these matrices for patterns related to cre-type and source and target regions.

155 ***Model evaluation***

156 Table contains the sizes of these evaluation sets in each major structure. This information may be
 157 cross-referenced visually with the figures in Our two-stage model generally performs better than the
 158 cre-line specific NW estimator.

	Estimator	EL	NW	Average	NW	NW-wt
Smoothing		SS	Cre-SS	Cre-SS	SS	M
Target		SS	SS	SS	SS	SS
Structure	# Eval exps					
CB	10	0.044	0.081	0.081	0.058	0.439
CTXsp	2	0.497	0.497	0.497	0.497	0.000
HPF	79	0.122	0.140	0.143	0.155	0.471
HY	41	0.241	0.266	0.269	0.244	1.019
Isocortex	838	0.173	0.195	0.202	0.234	0.404
MB	23	0.151	0.151	0.166	0.139	0.759
MY	7	0.186	0.233	0.233	0.184	0.452
OLF	17	0.069	0.095	0.100	0.073	0.110
P	8	0.236	0.239	0.239	0.264	0.984
PAL	11	0.190	0.198	0.198	0.260	1.401
STR	45	0.084	0.088	0.089	0.097	0.265
TH	29	0.351	0.678	0.678	0.365	1.088

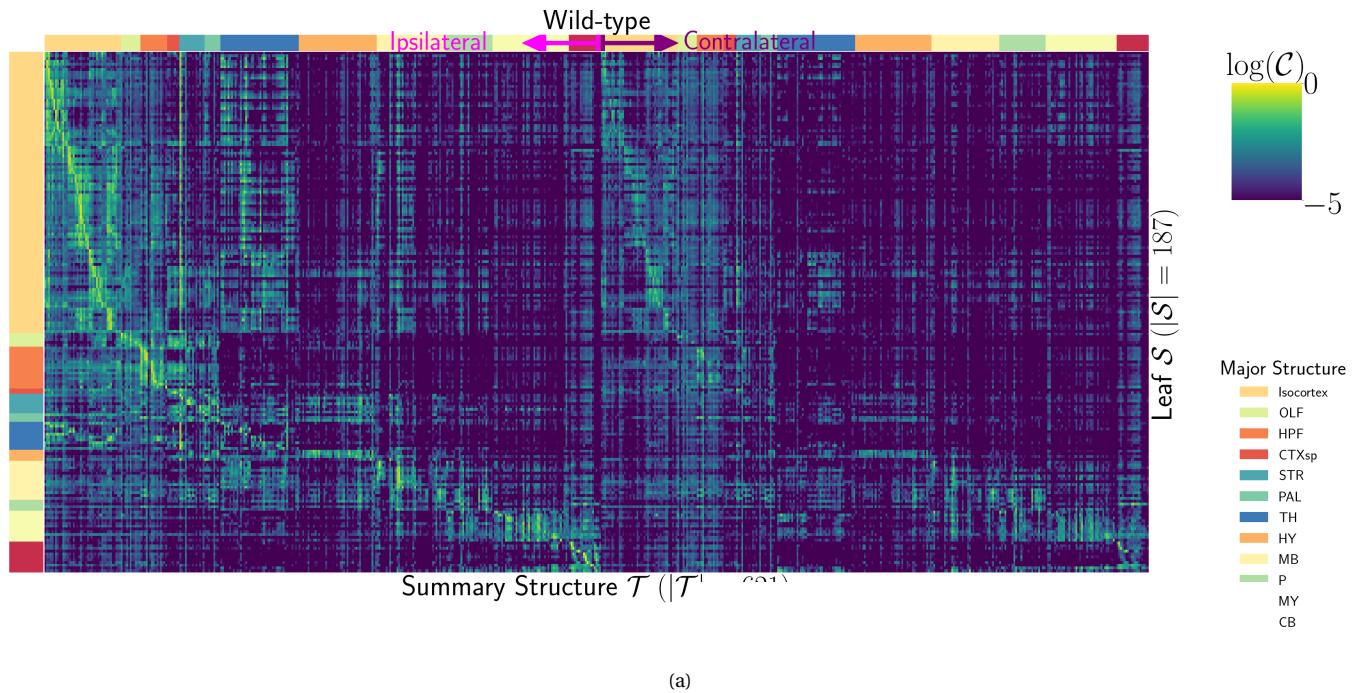
Table 2: Weighted losses with summary structure targets.

159 **Connectivities**

160 Our main result is the estimation of matrices $\hat{\mathcal{C}}_v$, representing connections of source structures to
161 target structures for particular cre-lines v . We exhibit several characteristics of interest, and confirm
162 the detection of several well-established connectivities within our tensor. Many additional interesting
163 biological processes are visible within this matrix - more than we can report in this paper - and it is
164 our expectation that these will be identified by users of our results. The connectivity tensor and code
165 to reproduce it are available at ([SK's comment:footnote](#)).

166 The connectivity matrix for wild-type connectivities from leaf sources to summary structure targets
167 is illustrated in Figure ???. The clear intraareal connectivities mirror previous estimates in ? and ? and
168 descriptive depictions of individual experiments in ?. Compared with ?, our more discretized source
169 smoothing and greater number of experiments leads to a significantly more discretized connectivity
170 matrix. This is generally expected - for example, different cortical layers have more substantially
171 different connectivities.

172 The cell-type specific connectivities that we provide also conform to well-known behaviors.
173 Examples from the visual processing and motor control regions of the cortex are given in Figure ?? for
174 both wild type and several cre-lines. Rbp4-Cre and Ntsr1-Cre target layers 5 and 6, respectively. As in
175 ?, layer 5 projects to anterior basolateral amygdala (BLA) and capsular central amygdala (CEA), while
176 layer 6 does not.



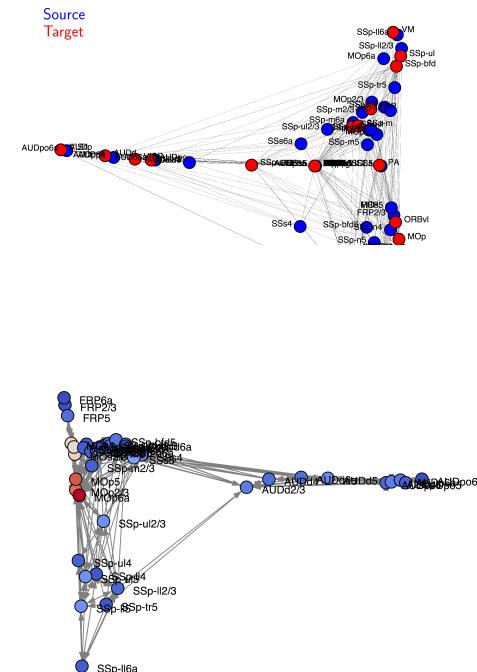
(a)

	# Ipsilateral Leaf Targets	Top Entropy	Bottom Sparsity	Bottom Entropy	Top Sparsity
Isocortex	51	CP	BAC	BAC	ENT1
OLF	11	TMv	III	III	NaN
HPF	15	IG	EPv	PA	NaN
CTXsp	7	TT	FC	APr	TT
STR	14	RPA	ISN	PVR	TU
PAL	9	PG	ACVII	GR	MG
TH	44	NOD	DN	SSp-ll	SCm
HY	44	CLA	SH	LSc	DG
MB	39	NDB	SubG	SGN	SUB
P	26	MT	Acs5	SOC	NDB
MY	43	RT	NaN	OV	EPd
CB	18	ECT	AOB	MOB	GU

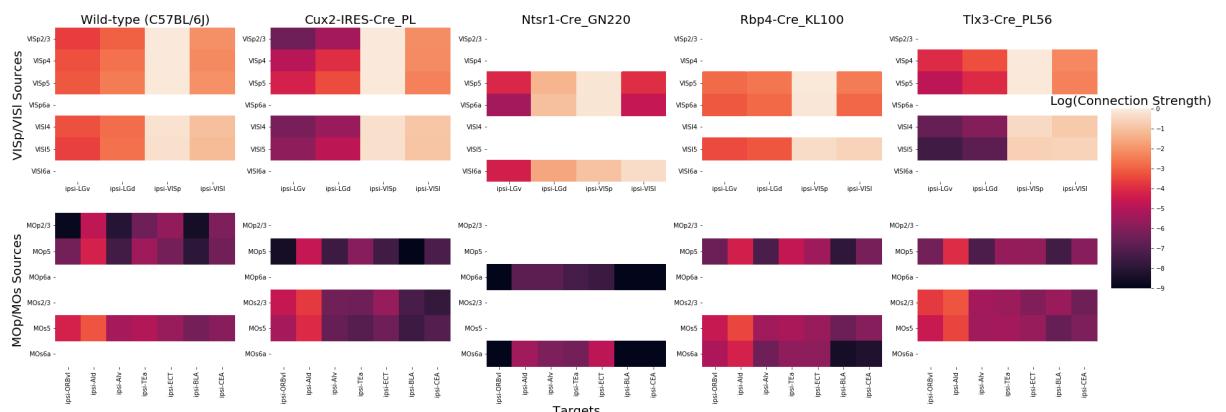
(b)

	# Ipsilateral Leaf Targets	Top Entropy	Bottom Sparsity	Bottom Entropy	Top Sparsity
Isocortex	51	CP	BAC	BAC	ENT1
OLF	11	TMv	III	III	NaN
HPF	15	IG	EPv	PA	NaN
CTXsp	7	TT	FC	APr	TT
STR	14	RPA	ISN	PYR	TU
PAL	9	PG	ACVII	GR	MG
TH	44	NOD	DN	SSp-ll	SCm
HY	44	CLA	SH	LSc	DG
MB	39	NDB	SubG	SGN	SUB
P	26	MT	Acs5	SOC	NDB
MY	43	RT	NaN	OV	EPd
CB	18	ECT	AOB	MOB	GU

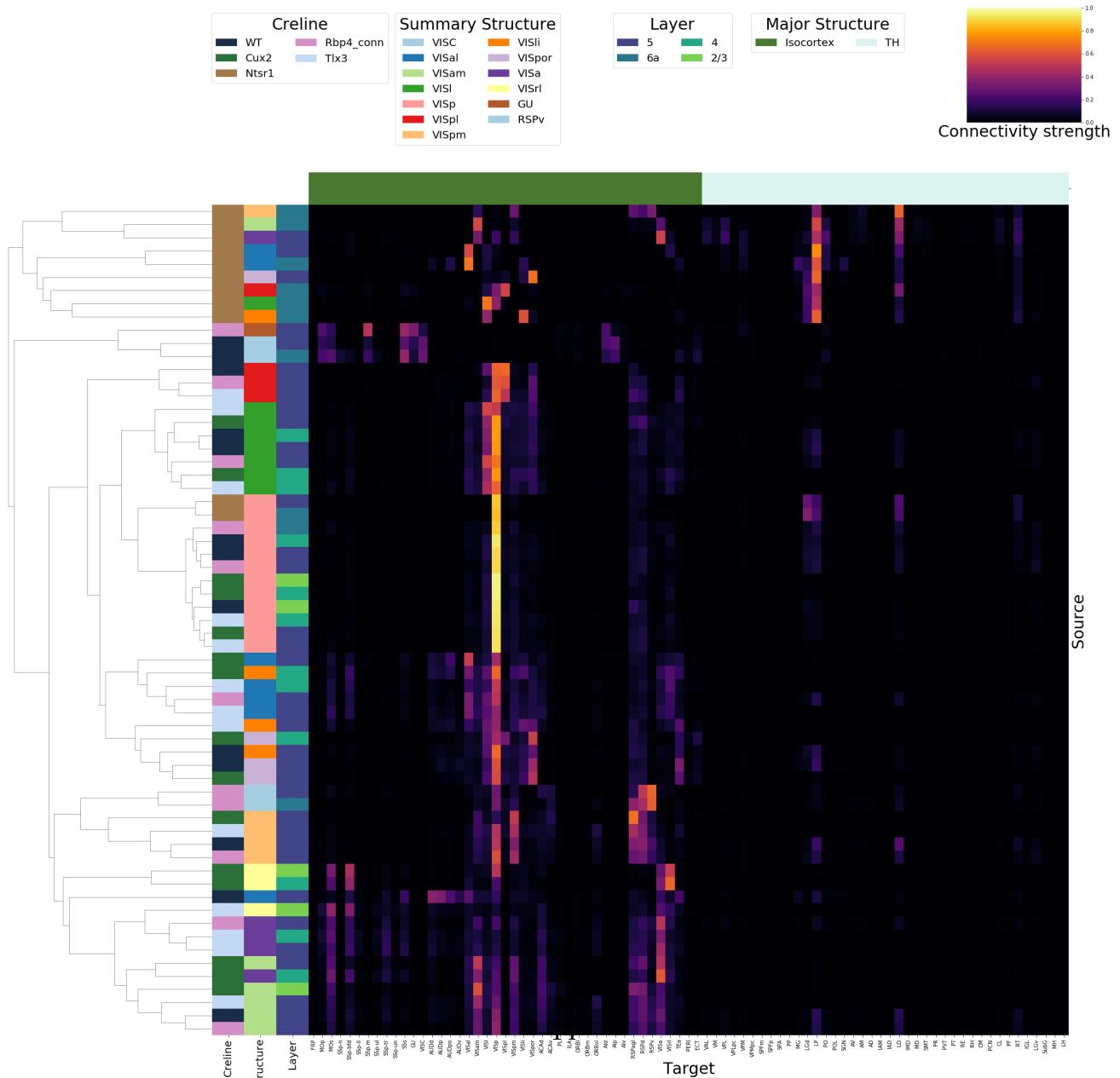
(d)



(e)



(a)



177 **Connectivity Analyses**

178 The connectivity matrix represents a collection of relatively few biological processes. For example,
179 certain cell-types and layers have a characteristic connectivity pattern, and structures tend to connect
180 most strongly to the most proximal areas. We elucidate these patterns through two types of analyses.
181 First, we demonstrate cell-type specific connectivity patterns by hierarchical clustering of
182 connectivities from multiple cre-lines, and showing that cre-line is a key factor driving the observed
183 behavior. Then, we perform a different unsupervised analysis - non-negative matrix factorization - of
184 distal wild-type connectivities, to estimate underlying overall connectivity patterns.

185 Figure 3 shows a collection of connectivity strengths generated using cre-specific models for
186 wild-type, Cux2, Ntsr1, Rbp4, and Tlx3 cre-lines from visual signal processing leafs in the cortex to
187 cortical and thalamic nucleii. Heirarchical clustering is applied to sort the different source/cre
188 combinations by the similarity of their connectivities to summary-structure targets. This analysis
189 shows that Ntsr1 cre-lines tend to target thalamic nucleii, in particular LP and LD ?. However, with
190 this exception, for the other plotted cre-lines, connectivity tends to cluster by source structure. That
191 the tendency for structures to connect to themselves is quite strong emphasizes the special nature of
192 the Ntsr1-Thalamic connection in this analysis.

193 The overall wild-type connectivity strength matrix also displays an underlying modellable
194 structure. As discussed in ?, one of the most basic processes underlying the observed connectivity is
195 the tendency of each source region to predominantly project to proximal regions. The heatmap in ??a)
196 shows intraregion distances clearly contains an overall pattern reminiscent of the connectivity matrix
197 in ?. This relationship is plotted in ?? b), showing that there exists substantial variability that would
198 be impossible to model with low-error in a univariate model, even using the diffusion model
199 suggested in ?. These connections are biologically meaningful, but also unsurprising, and their
200 relative strength biases learned latent coordinate representations away from long-range structures.
201 For this reason, we establish a $1500\mu m$ 'distal' threshold within which to exclude connections for our
202 analysis. We then apply non-negative matrix factorization (NMF) to decompose the remaining
203 censored matrix into a relatively small number of distinct projection signals, and apply an

204 unsupervised cross-validation method to select the optimum number of signals ([SK's](#)

205 [comment:Percent error... show reconstruction? log scale?](#)).

DISCUSSION

206 Flattening \mathcal{C} prior to unsupervised analysis is not necessarily recommended, but provides an easy
207 solution for this problem.

208 With respect to the model, a Wasserstein-based measure of injection similarity per structure would
209 combine both the physical simplicity of the centroid model while also incorporating structural
210 knowledge.

211 The Nadaraya-Watson weighting procedure introduced here is, to our knowledge, novel. In
212 particular, our method of utilizing the expected loss to weight points differs from the minimization
213 task of fitting data to weighted sums of neighbors (?). We make a key assumption: that the additional
214 statistical accuracy of including more samples makes up for the fact that their expected accuracy is
215 lower. Note that this assumption can be easily violated, if, for example, the data is distributed on a
216 circle without error, and only nearest neighbors are most predictive.

217 Model averaging based off of cross-validation has been implemented in ?, but we note that our
218 approach makes use of a non-parametric estimator, rather than an optimization method for selecting
219 the weights. ([SK's comment:CITE METHOD THAT SELECTS WEIGHTS IN KERNEL \(has catchy
220 name\)](#))

ACKNOWLEDGMENTS

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²³¹ less) definitions for each term, avoiding in these definitions the use of jargon, or highly technical or
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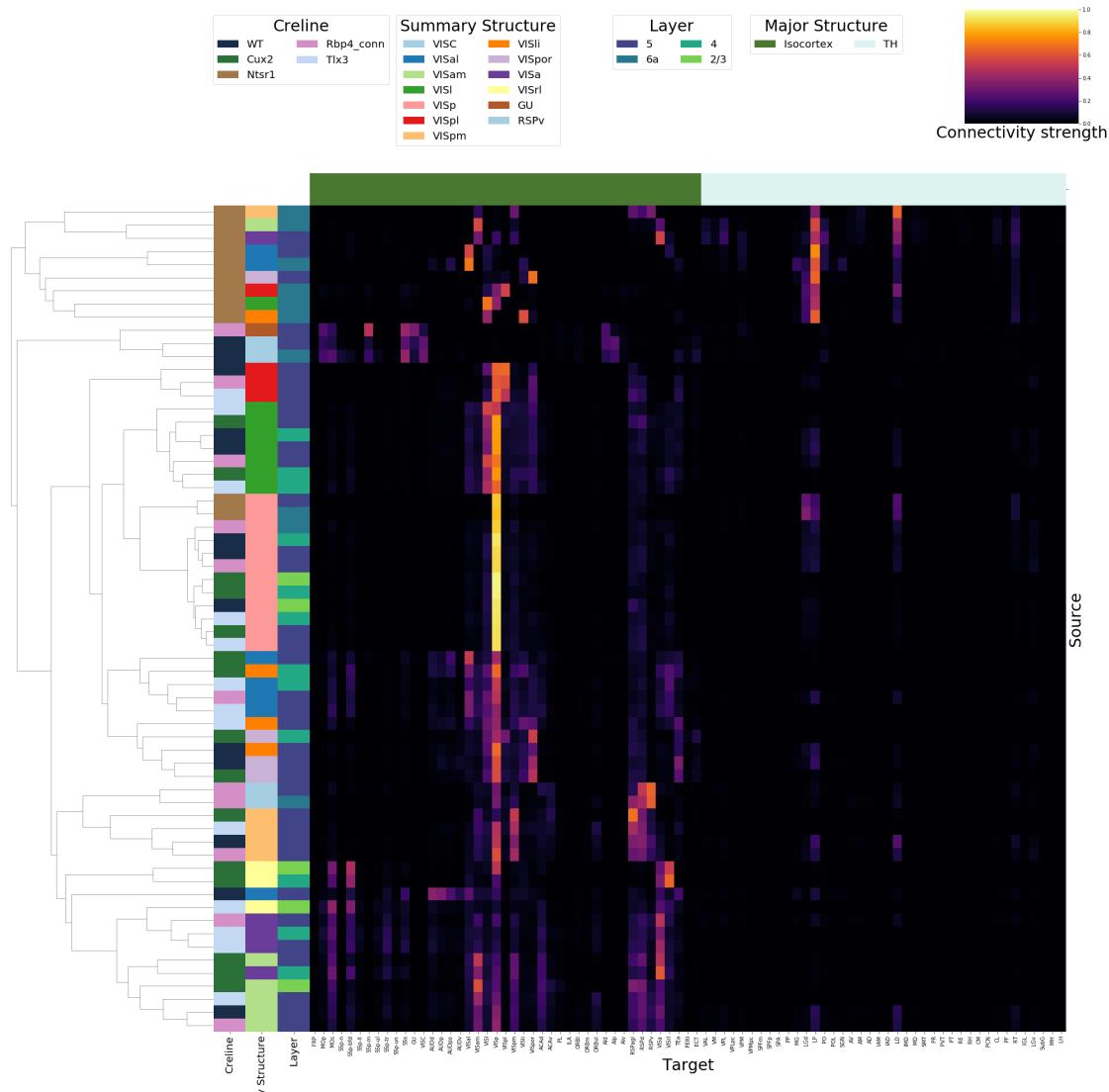
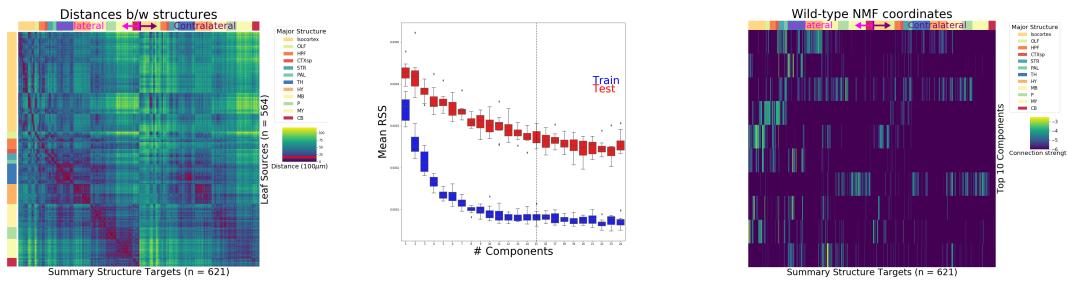


Figure 3: Heirarchical clustering of connectivity strengths from visual signal processing cell-types to cortical and thalamic targets. Cre-line, summary structure, and layer are labelled on the sources. Note that sources/cre combinations are only included if there is at least one experiment of that cre-line in that particular leaf.



(a)

(b)

(c)

