A **gene expression enrichment axis** separates **structural connectivity** and **structural covariance**

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Introduction

- Both structural connectivity and structural covariance networks have been linked to correlated gene expression ("transcriptomic similarity")
- Transcriptomic similarity can be computed from a restricted set of genes; certain sets of genes make transcriptomic similarity networks topologically similar to other types of networks
- Including neuronal development and axon guidance genes makes transcriptomic similarity networks similar to structural connectivity (French, 2011, PMID:21253556)
- For structural covariance, human supragranular genes have been identified as being important (Romero-Garcia, 2018, PMID:29274746)
- Here, we identify an axis along which genes can be filtered
  - Constructing the transcriptomic similarity network from the **filtered** set genes makes it similar to structural connectivity,
  - Constructing the transcriptomic similarity network from the **unfiltered** set of genes makes it similar to structural covariance

30 second summary

- Many genes are required for transcriptomic similarity networks to reflect structural covariance networks

- **Removing regionally non-specific genes** and computing transcriptomic similarity (in this subset of genes with region-specific expression) results in:
  - a **decreases in similarity** to structural covariance and
  - an **increase (cortex-specific)** in similarity to structural connectivity

Methods

Imaging data

Subjects:
- 153 mice, C57Bl/6 strain
- male, young adult (P60-112)

Scanning:
- Varian 7T at the Mouse Imaging Centre (Toronto, Canada)
- T2-weighted FSE, 40-56um isotropic resolution
- acquired ex-vivo (in-cranio)
- 12-14 hours scan duration

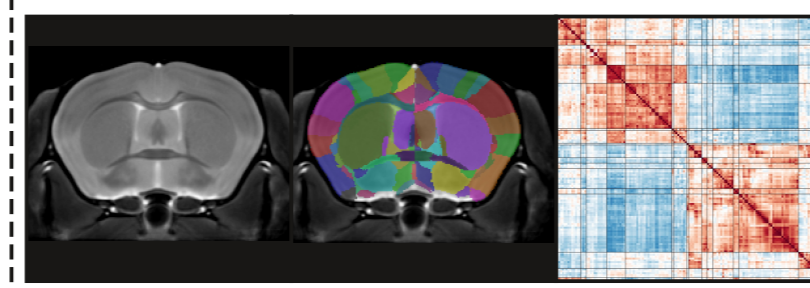See (Yee, 2018, PMID:29782994) for more details.

Structural covariance

Image registration:
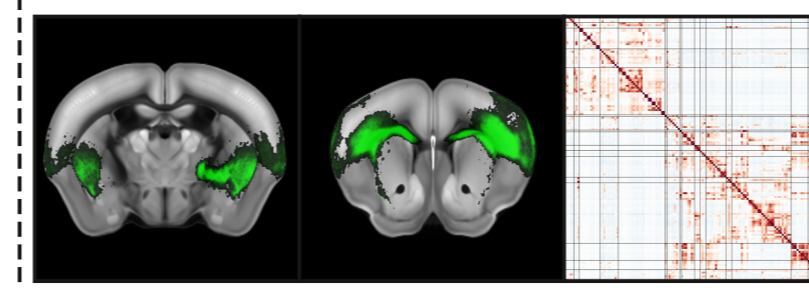- linear and nonlinear alignment to iteratively generated template via Pydpiper framework

Structure volume computation:
- "DSURQE" mouse atlas overlayed on template
- Volumes computed by summing voxels under atlas regions, weighted by Jacobian determinants of transformations (deformation-based morphometry)

Structure covariance:
- Relative volumes (proportion of total brain size) used to compute structural covariance
- Structural covariance matrix computed from Pearson correlations between volumes
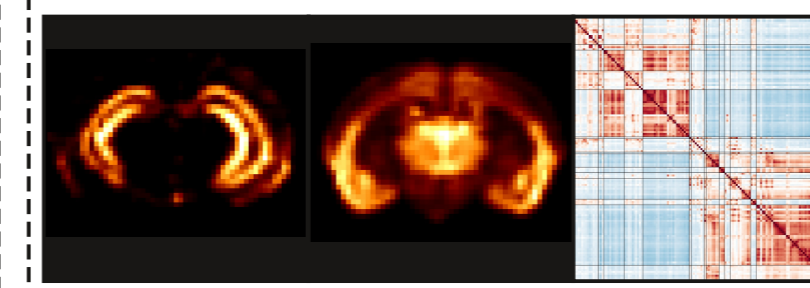
Structural connectivity

Tracer data: via Allen Institute
- 488 viral tracing experiments in adult, male, C57Bl/6 mice
- rAAV tracers expressing EGFP, anterograde, does not cross synapses
- aligned to Common Coordinate Framework and accessed at 50um resolution

Structural connectivity:
- tracer experiments also mirrored to contralateral hemisphere
- correlation between mean tracer signal ("projection density") of pairs of regions, computed over all injection experiments (provides bidirectional measure of connectivity)
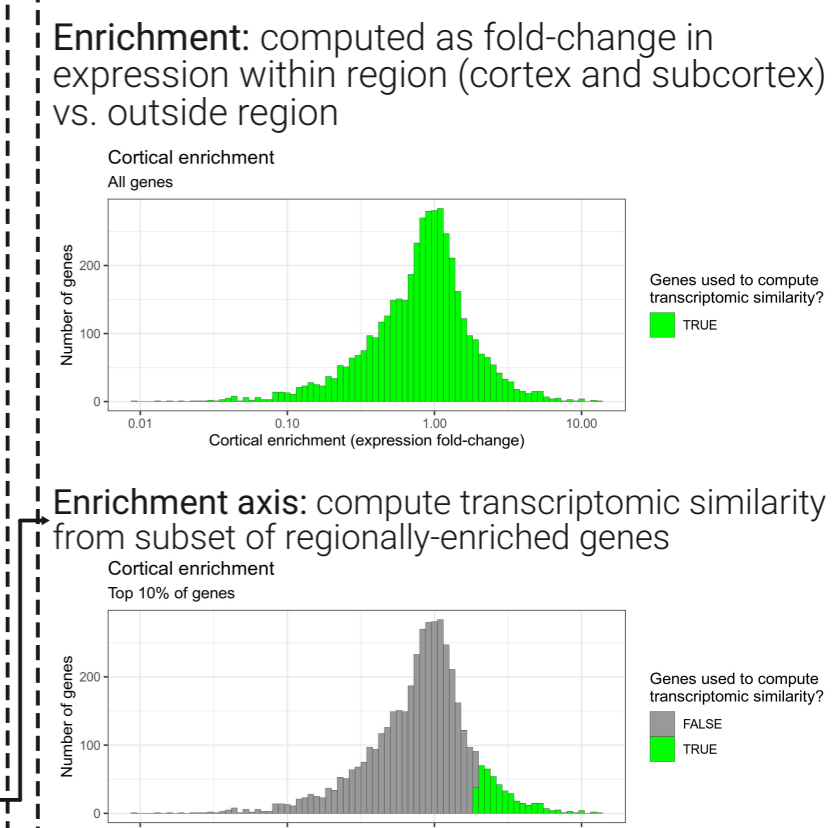
Gene expression

Gene expression data: via Allen Institute
- 4345 expression images (4082 unique genes) from coronal ISH dataset
- adult, male, C57Bl/6J mice
- aligned to Common Coordinate Framework and accessed at 200um resolution
- "expression energy" averaged within regions of DSURQE mouse atlas

Transcriptomic similarity:
- mean regional expression energy further divided by total mean region expression energy for each gene
- transcriptomic similarity computed as regional pairwise correlation over set of genes
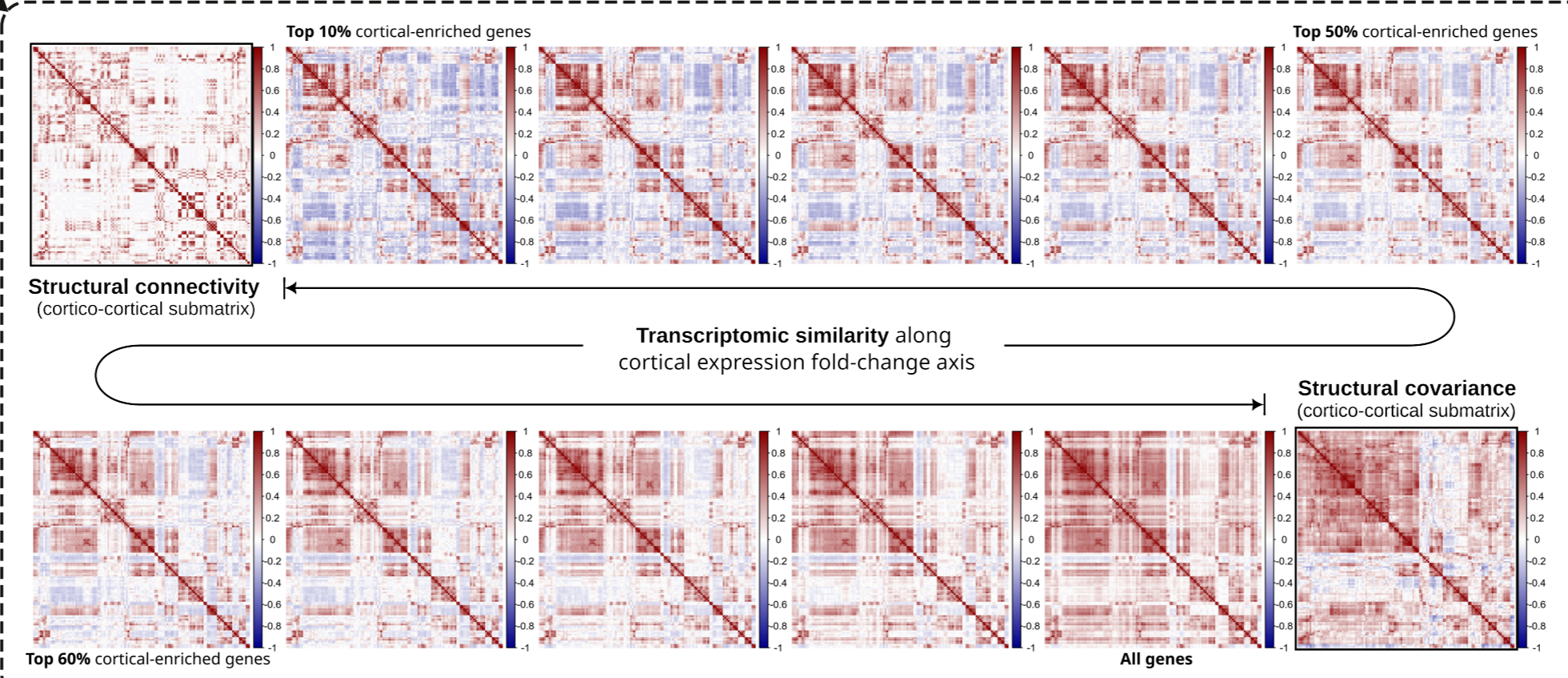- set of genes can be all genes, or filtered

Enrichment axis

Enrichment: computed as fold-change in expression within region (cortex and subcortex) vs. outside region

Enrichment axis: compute transcriptomic similarity from subset of regionally-enriched genes
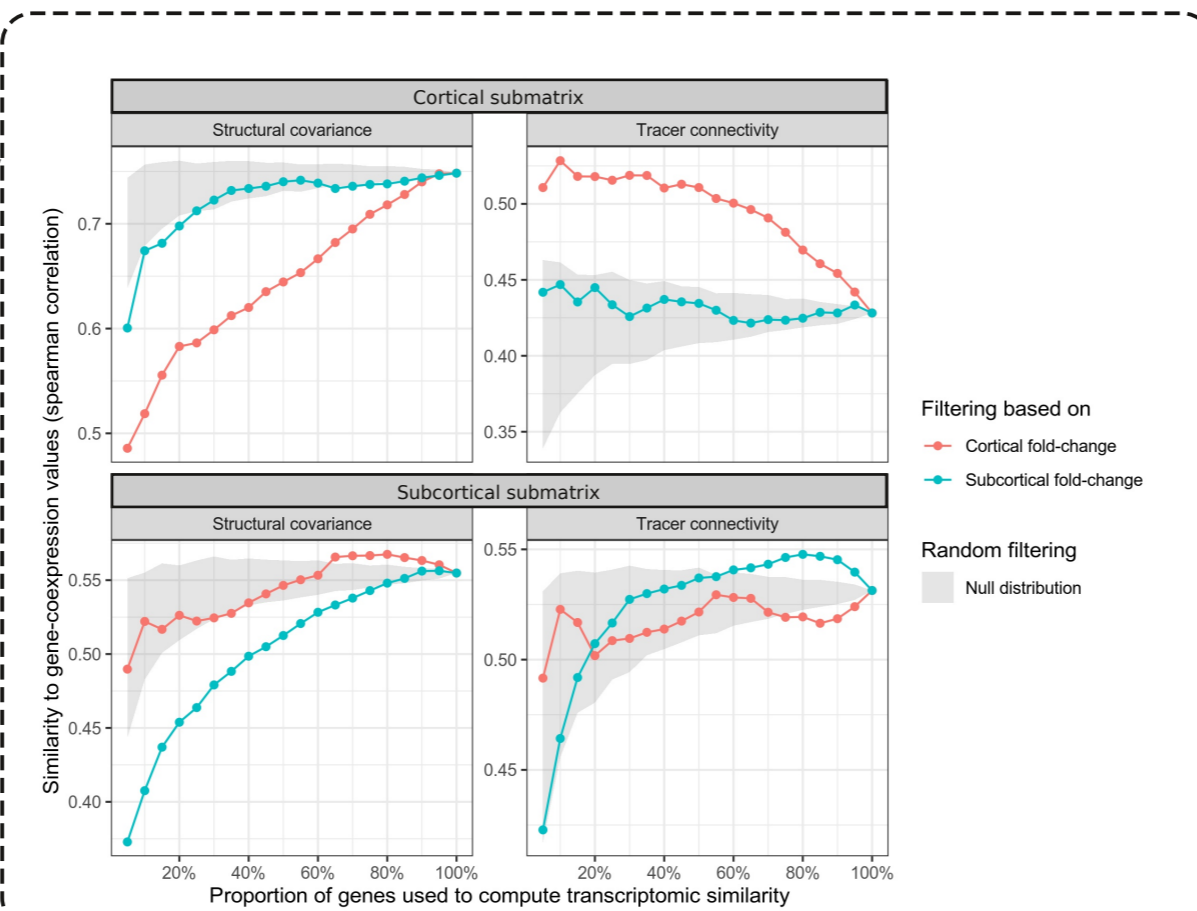
Results

1 — Enrichment axis separates connectivity from covariance

- Removing genes with expression non-specific to cortex (moving right to left in the Figure to the right) results in:
  - **increase in similarity** between cortico-cortical transcriptomic similarity and **cortico-cortical structural connectivity**
  - **decrease in similarity** between cortico-cortical transcriptomic similarity and **cortico-cortical structural covariance**

2 — Enrichment axis is specific to regional fold-change

- Quantification of similarity (Spearman correlation on variance-stabiliized matrices) between transcriptomic similarity, structural connectivity, and structural covariance as a function of proportion of genes used
- Similarity examined between cortico-cortical and subcortico-subcortical relationships when filtering genes based on cortex-specific expression (red) and subcortex-specific expression (blue)
- Filtering also examined after permuting expression enrichment 500 times (gray)

3 — GO terms and pathways

- Gene functional enrichment analysis for top 10% of cortex-specific and subcortex-specific genes, relative to base set (4082) genes
- via ToppGene
- top 10% genes specific to cortex are primarily related to excitatory neurons
- top 10% genes specific to subcortex are related to both excitatory and inhibitory neurons

Modules associated with cortex-enriched genes

Category	Name	P-value	FDR q-value
GO: Biological Process	modulation of chemical synaptic transmission	7.502e-10	2.295e-06
GO: Biological Process	regulation of trans-synaptic signaling	8.600e-10	2.295e-06
GO: Biological Process	anterograde trans-synaptic signaling	1.571e-08	1.757e-05
GO: Biological Process	chemical synaptic transmission	1.571e-08	1.757e-05
GO: Biological Process	trans-synaptic signaling	1.930e-08	1.757e-05
GO: Biological Process	regulation of synaptic plasticity	4.060e-08	3.095e-05
GO: Biological Process	synapse organization	1.114e-05	5.402e-03
GO: Biological Process	regulation of neuronal synaptic plasticity	2.106e-05	8.027e-03
GO: Biological Process	postsynapse organization	7.729e-05	2.329e-02
GO: Biological Process	cell junction organization	8.631e-05	2.424e-02
GO: Biological Process	positive regulation of synaptic transmission	9.979e-05	2.662e-02
GO: Biological Process	long-term synaptic potentiation	1.147e-04	2.914e-02
ToppCell Atlas	Striatum-Neuronal-Excitatory-eN1(Slc17a7)-eN1_1-E...	2.624e-08	1.161e-05
ToppCell Atlas	Striatum-Neuronal-Excitatory-eN1(Slc17a7)(Striatu...	2.624e-08	1.161e-05
ToppCell Atlas	Striatum-Neuronal-Excitatory-eN1(Slc17a7)-eN1_1-E...	2.624e-08	1.161e-05
ToppCell Atlas	Striatum-Neuronal-Excitatory-eN1(Slc17a7)-eN1_1(S...	2.624e-08	1.161e-05
ToppCell Atlas	Striatum-Neuronal-Excitatory-eN3(Slc17a7_Gad1Ga...	6.235e-06	1.583e-03
ToppCell Atlas	Striatum-Neuronal-Excitatory-eN3(Slc17a7_Gad1Ga...	6.235e-06	1.583e-03
ToppCell Atlas	Striatum-Neuronal-Excitatory-eN3(Slc17a7_Gad1Ga...	6.235e-06	1.583e-03
ToppCell Atlas	facs-Brain_Non-Myeloid-Hippocampus_-18m-Neuron...	8.173e-06	1.955e-03
ToppCell Atlas	facs-Brain_Non-Myeloid-Hippocampus_-18m-Neuron...	8.173e-06	1.955e-03
ToppCell Atlas	facs-Brain_Non-Myeloid-Hippocampus_-18m-Neuron...	8.173e-06	1.955e-03
ToppCell Atlas	Neuronal-Excitatory-eC(RORB)-eC_1-TWIST2(Neuro...	6.669e-05	1.180e-02
ToppCell Atlas	Neuronal-Excitatory-eC(RORB)-eC_1-TWIST2(Neuro...	6.669e-05	1.180e-02
ToppCell Atlas	Neuronal-Excitatory-eC(RORB)-eC_1-TWIST2-L3-5(N...	6.669e-05	1.180e-02

Modules associated with subcortex-enriched genes

Category	Name	P-value	FDR q-value
GO: Biological Process	neurotransmitter loading into synaptic vesicle	3.343e-07	0.0019250
GO: Biological Process	positive regulation of secretion by cell	6.397e-06	0.0184200
GO: Biological Process	neuropeptide signaling pathway	1.011e-05	0.0194100
GO: Biological Process	biogenic amine metabolic process	2.372e-05	0.0309200
GO: Biological Process	amine metabolic process	2.685e-05	0.0309200
GO: Biological Process	positive regulation of secretion	4.971e-05	0.0356100
GO: Biological Process	catechol-containing compound metabolic process	5.486e-05	0.0356100
GO: Biological Process	catecholamine metabolic process	5.486e-05	0.0356100
GO: Biological Process	ammonium ion metabolic process	5.566e-05	0.0356100
ToppCell Atlas	Thalamus-Neuronal-Excitatory-eN2(Slc17a7_Slc17a...	3.011e-07	0.0006888
ToppCell Atlas	Thalamus-Neuronal-Excitatory-eN2(Slc17a7_Slc17a...	3.011e-07	0.0006888
ToppCell Atlas	primary_visual_cortex-Neuronal-GABAergic_neuron-...	4.778e-06	0.0047220
ToppCell Atlas	primary_visual_cortex-Neuronal-GABAergic_neuron-...	4.499e-05	0.0212600
ToppCell Atlas	E16.5-Epithelial-Epithelial_Airway-Ciliated/Deutero...	9.504e-05	0.0351800
ToppCell Atlas	E16.5-Epithelial-Epithelial_Airway-Ciliated/Deutero...	9.504e-05	0.0351800
ToppCell Atlas	Endothelial-A-Donor_02(World / lung cells shred on c...	1.273e-04	0.0378400
ToppCell Atlas	ASK428-Epithelial-Transformed_epithelium(ASK428 /...	1.588e-04	0.0417800
ToppCell Atlas	Posterior_cortex-Neuronal-Excitatory-eN1(Slc17a7)-...	1.666e-04	0.0419700
ToppCell Atlas	3'-Parenchyma_lung-Mesenchymal-Fibro-meso-mes...	1.938e-04	0.0464700

Summary

- We demonstrate that within a given region, transcriptomic similarity reflects structural covariance when using many genes, and structural connectivity when using fewer, regionally-specific genes

- Cortico-cortical transcriptomic similarity constructed from top cortex-specific genes (but not subcortex-specific genes) is:
  - similar to cortico-cortical structural connectivity
  - dissimilar to cortico-cortical structural covariance

- Subcortical-subcortical transcriptomic similarity constructed from top subcortex-specific genes (but not cortex-specific genes) is:
  - dissimilar to subcortical-cortical structural covariance

- Functional enrichment for top cortex-specific genes relate to excitatory neurons, while functional enrichment for top subcortex genes relate to a more diverse set of terms, including both excitatory and inhibitory neurotransmission

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