PsychENCODE:

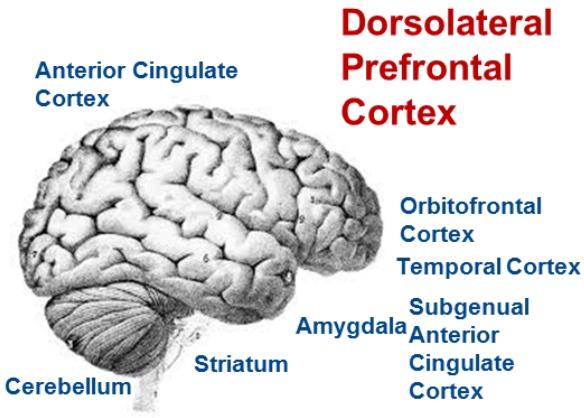
Using population-scale functional genomics to understand neuro-psychiatric disease

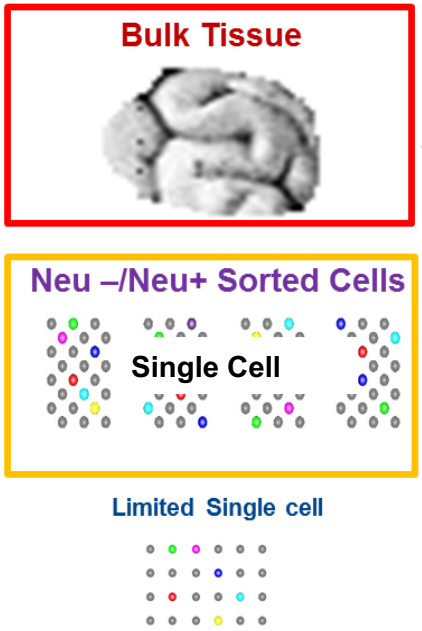
Mark Gerstein, Yale

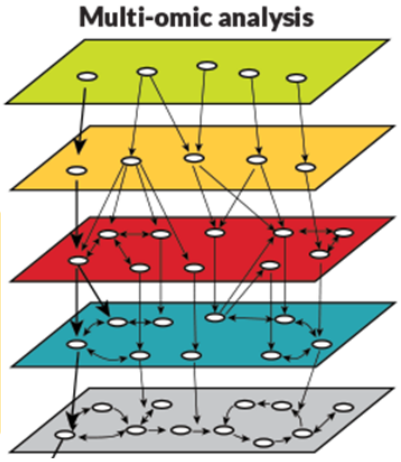
Slides freely downloadable from **Lectures.GersteinLab.org** & "tweetable" (via **@markgerstein**). See last slide for more info.

Sample Sources: >2,500 brains

Cross-disorder: ASD, SCZ, BP, Neurodevelopmental, Neurotypical







Genome:
WGS, genotype

Epigenome:
ChIP-seq, ATAC-seq, HiC, ERRBS, Array Methylation, NOMeSeq

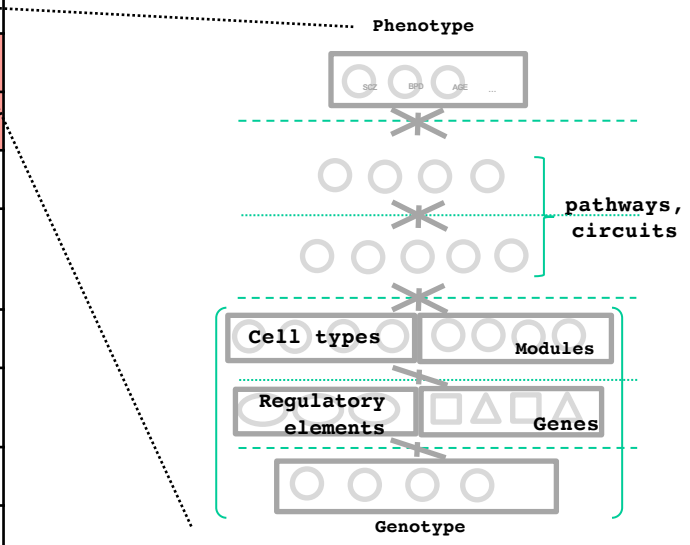
Transcriptome:
RNA-seq, lncRNAseq,

Proteome:
MWP, LC-MS/MS

The PsychENCODE Consortium

A core issue addressed by PsychENCODE: Using functional genomics to reveal molecular mechanisms between genotype and phenotype in brain disorders

Disease	Heritability*	Molecular **Mechanisms**
Schizophrenia	**81%**	**(C4A)**
Bipolar disorder	70%	-
Alzheimer's disease	58 - 79%	Apolipoprotein E (APOE), Tau
Hypertension	30%	Renin–angiotensin–aldosterone
Heart disease	34-53%	Atherosclerosis, VCAM-1
Stroke	32%	Reactive oxygen species (ROS), Ischemia
Type-2 diabetes	26%	Insulin resistance
Breast Cancer	25-56%	BRCA, PTEN



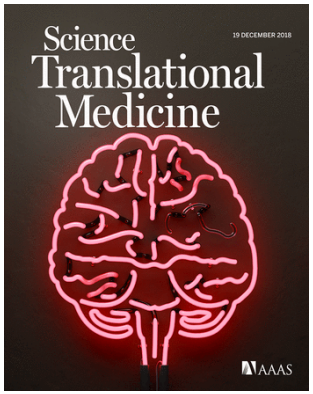
*https://www.snpedia.com/index.php/Heritability

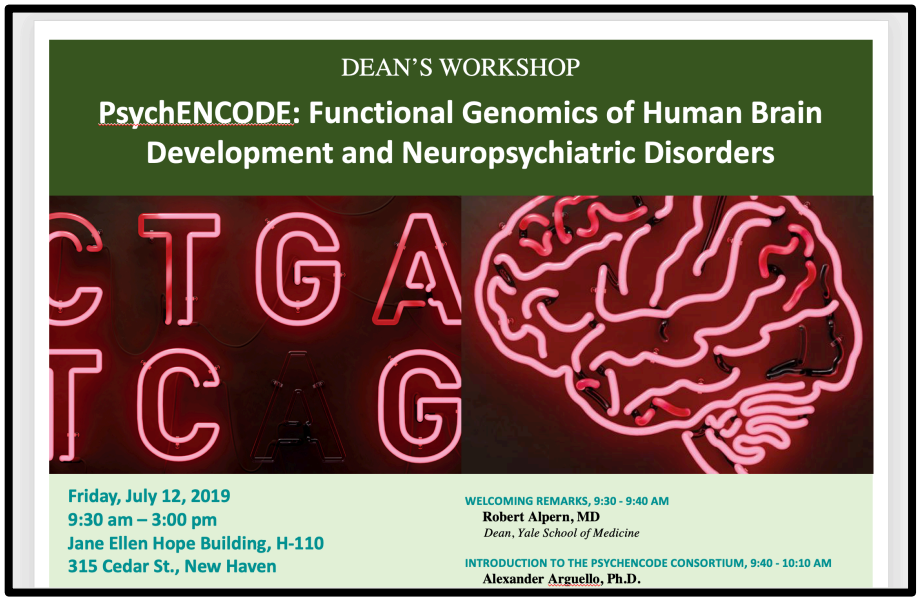
Many psychiatric conditions are highly heritable
- Schizophrenia: up to 80%

But we don't understand basic molecular mechanisms underpinning this association (in contrast to many other diseases such as cancer & heart disease)

Thus, interested in developing predictive models of psychiatric traits which:
- Use observations at intermediate (molecular levels) levels to inform latent structure
- Use the predictive features of these "molecular endo phenotypes" to begin to suggest actors involved in mechanism

2018 PsychENCODE "Rollout"





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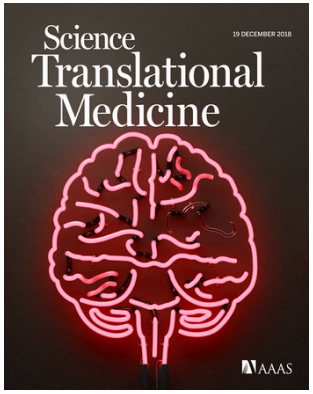

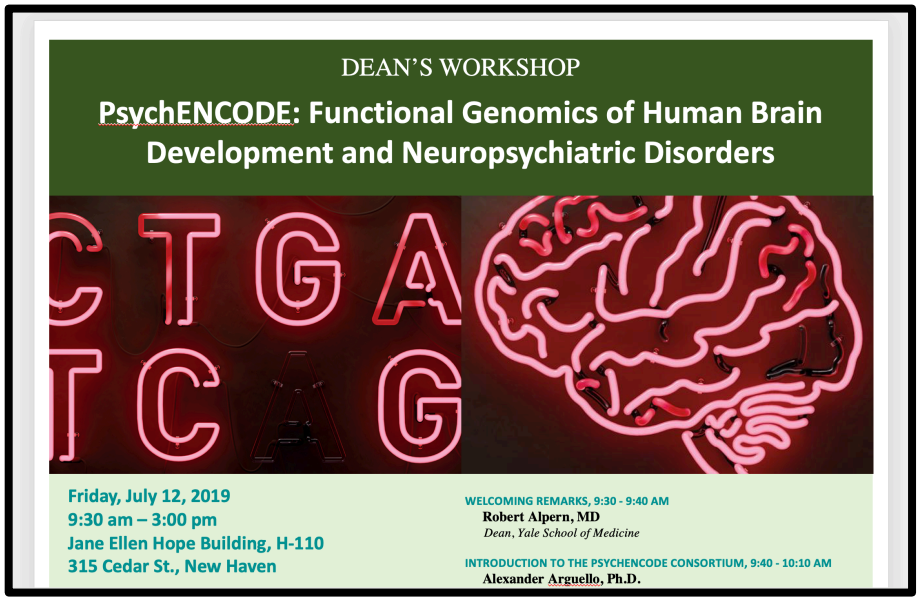

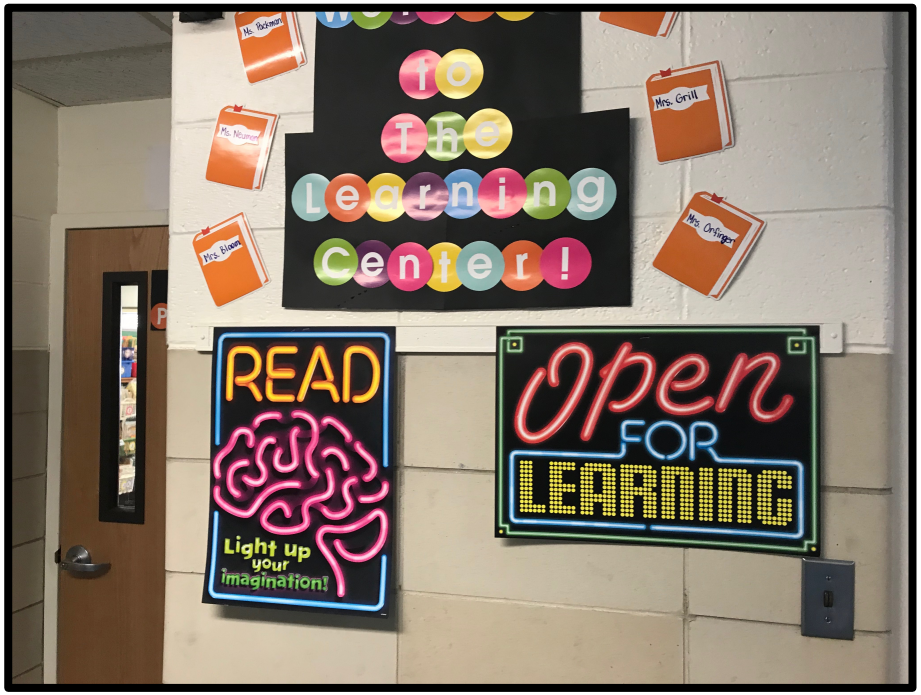

[School pic from D Wang]

PsychENCODE: Using population-scale functional genomics to understand neuropsychiatric disease

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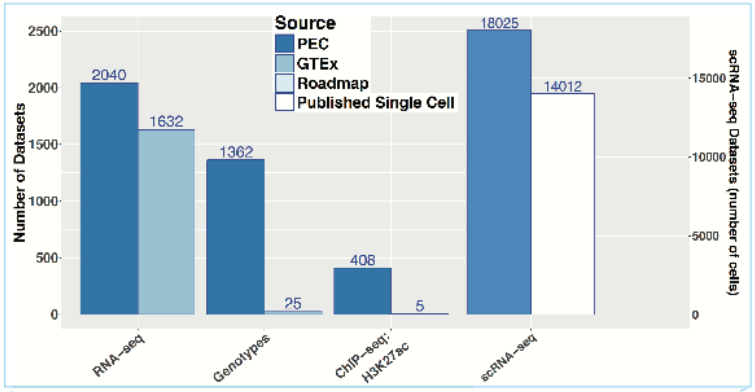
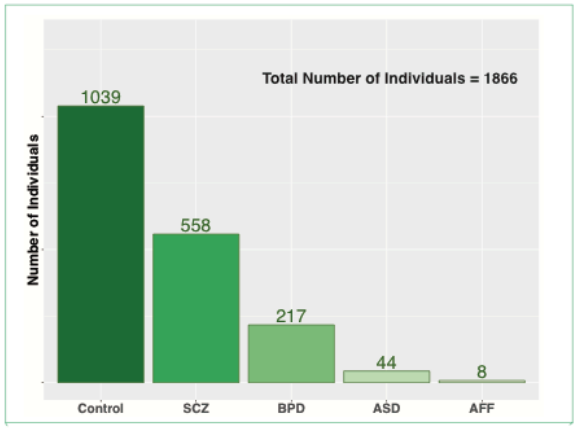


Assay

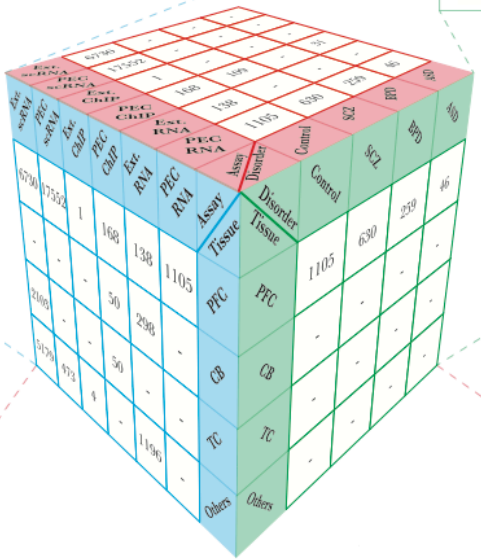


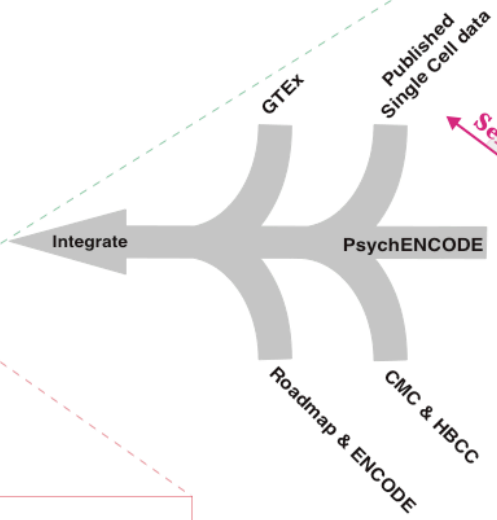
Disorder

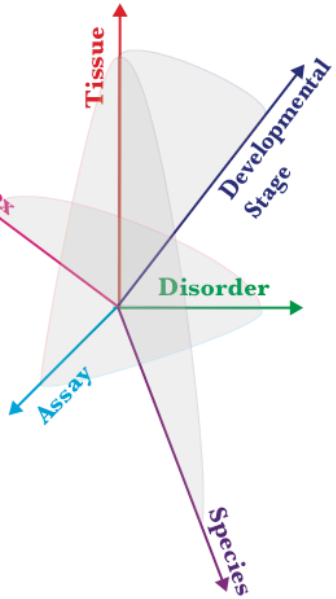
1866 Individuals
~3.7K bulk RNA-seq
~32K single-cells

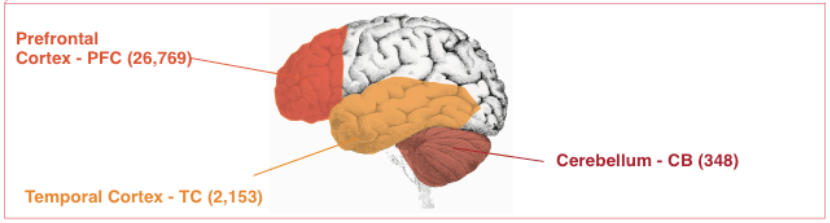
Collecting functional genomic datasets for the adult brain

from PsychENCODE, other large consortia & single cell studies





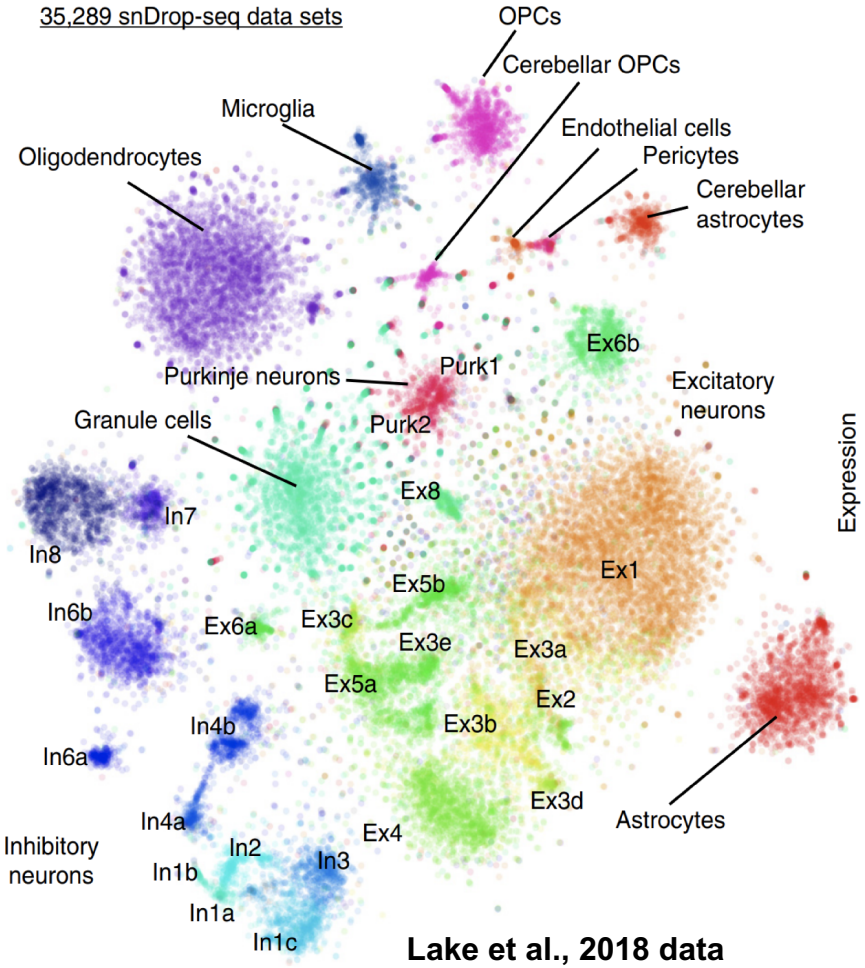




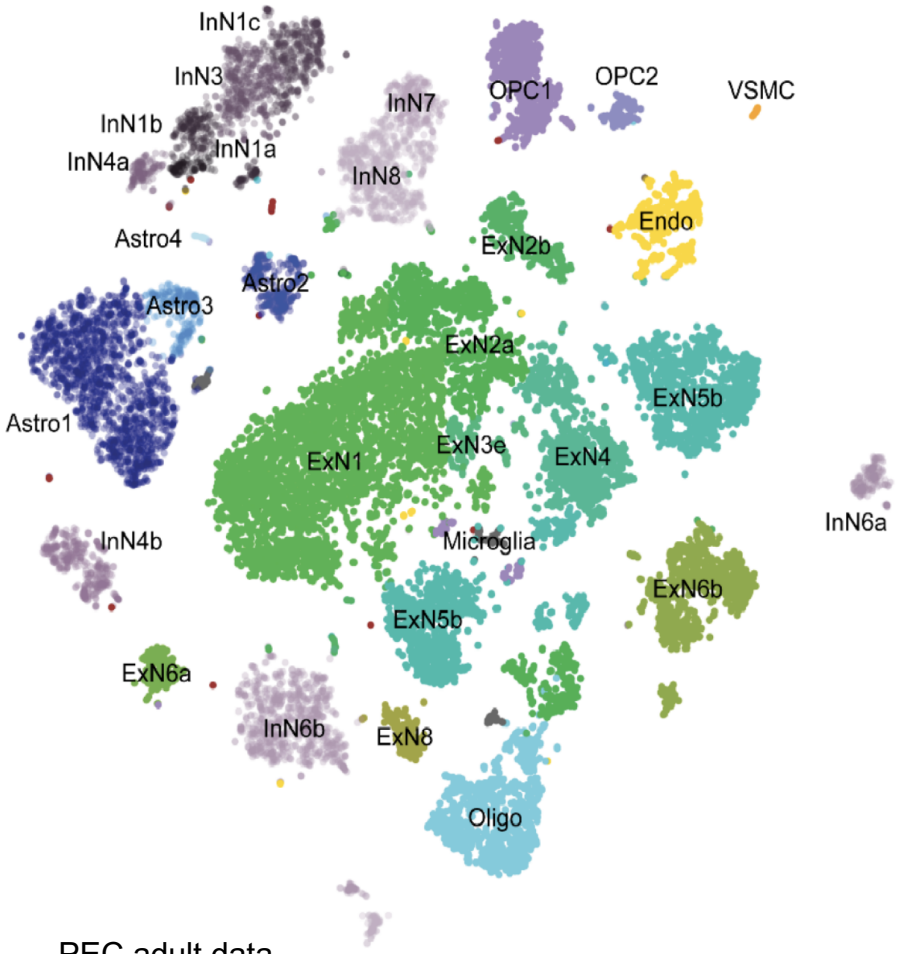
Merging & Clustering Single Cell Data Sets

Single cell signatures, from:

- ~14K cells
  (Lake et al.,'16 & '18)
- ~400 cells
  (Darmanis et al., PNAS, '15)
- ~18K cells (PsychENCODE)



Lake et al., 2018 data

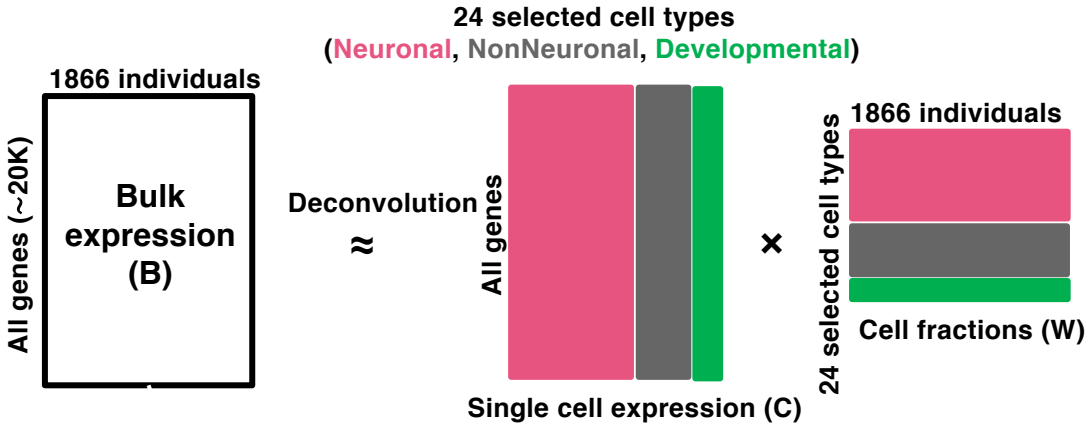


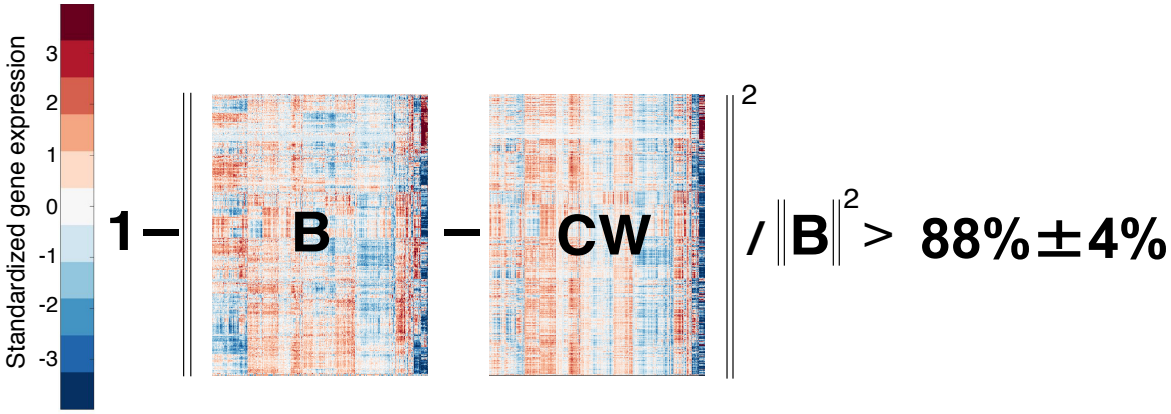
PEC adult data
[Li et al. ('18), Science. Wang et al. ('18). Science]

Single-cell deconvolution

Step 1:

Supervised learning to estimate cell fractions

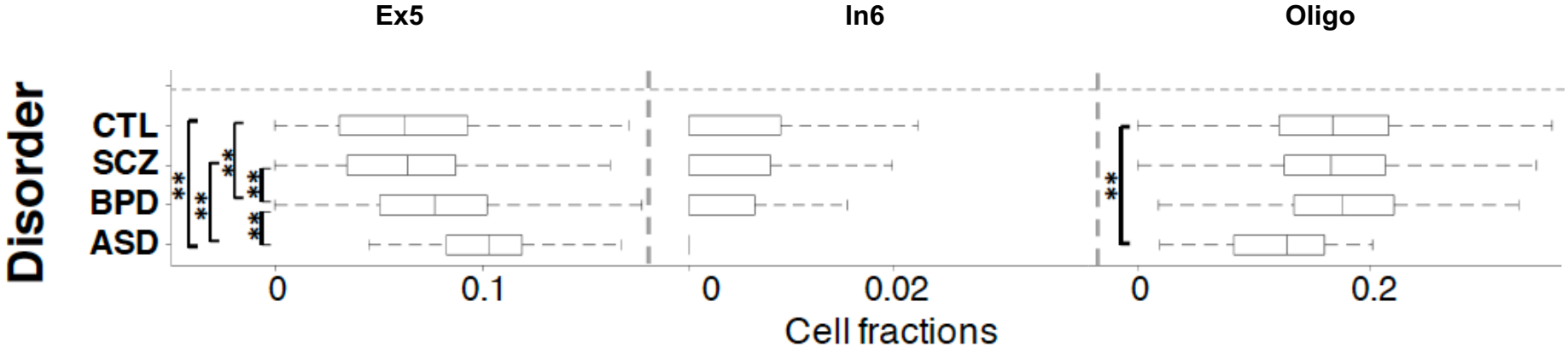




Individual and cross-population reconstruction accuracy via deconvolution

[Wang et al. ('18) Science]

Different neuronal & glial cell fractions across disorders



Excitatory to Inhibitory imbalance at neuronal subtype level for ASD*

*** Rubenstein et al., Model of autism: increased ratio of excitation/inhibition in key neural systems, Genes Brain Behav. 2003**

[Wang et al. ('18) Science]

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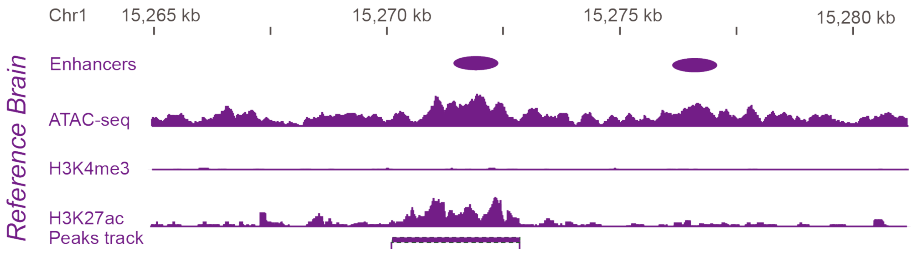
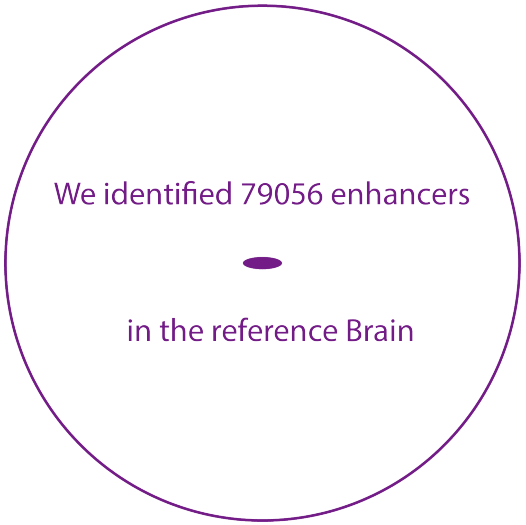
Developing a Reference Set of ~79K PFC Enhancers & Studying Their Population Variation





Consistent with ENCODE, active enhancers are identified as open chromatin regions enriched in H3K27ac and depleted in H3K4me3

[Wang et al. (‘18) Science]

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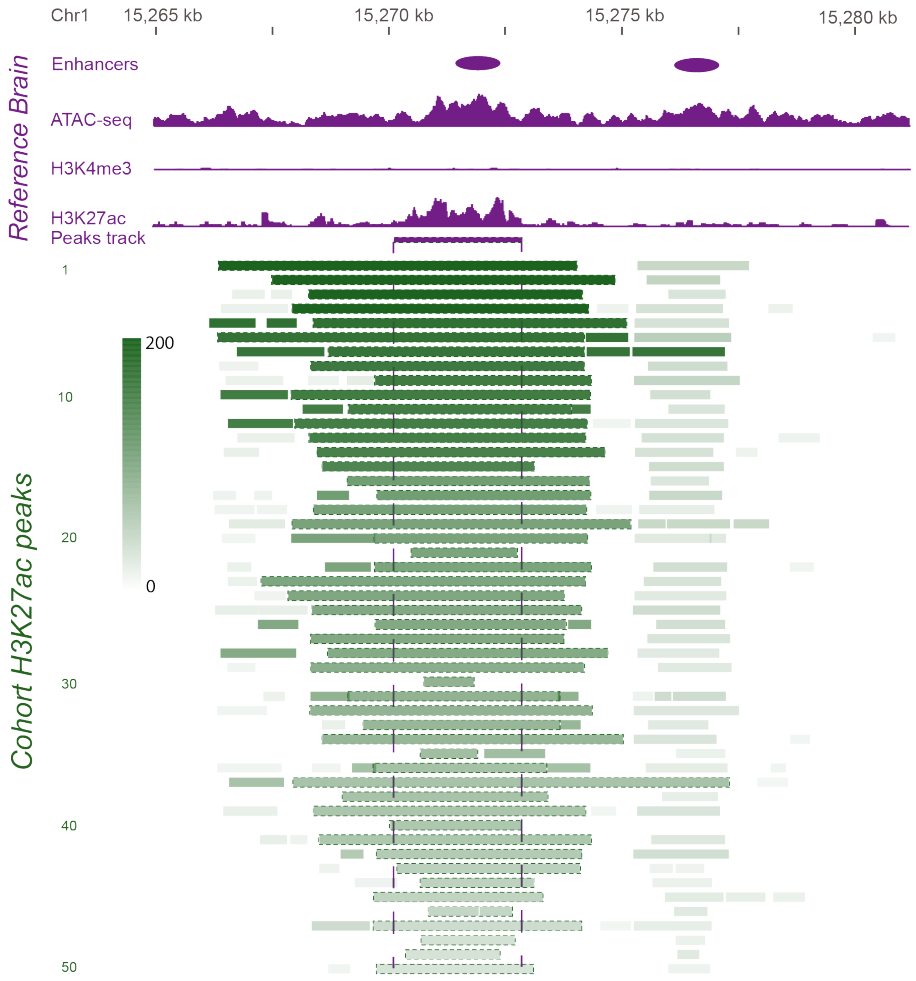
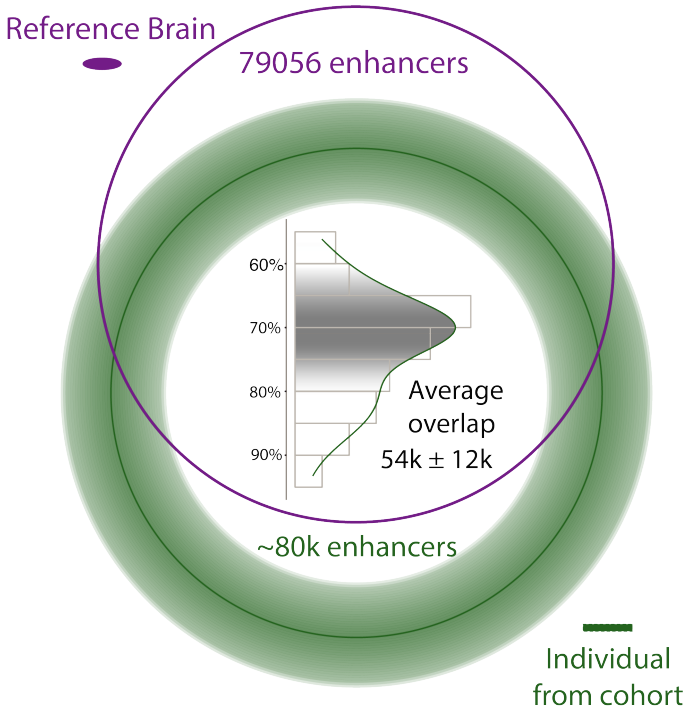
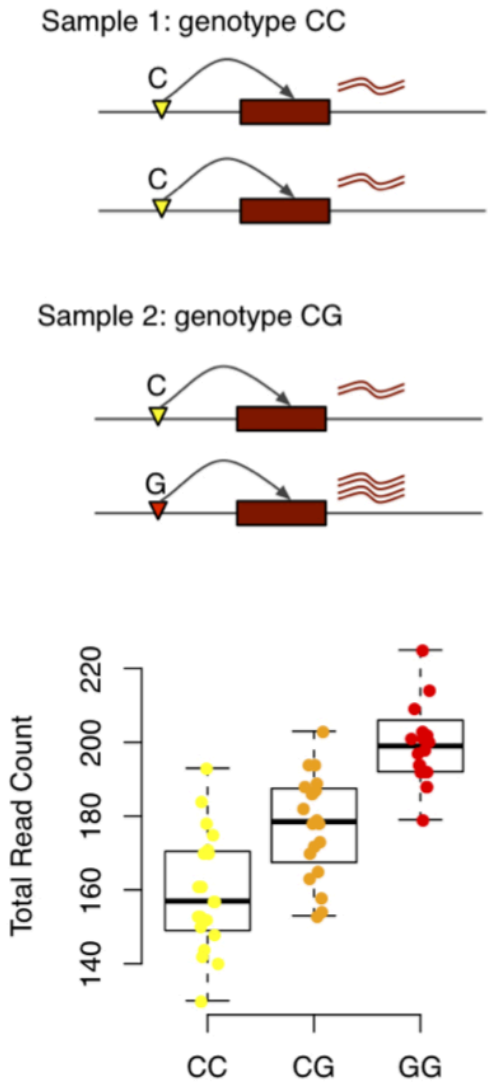




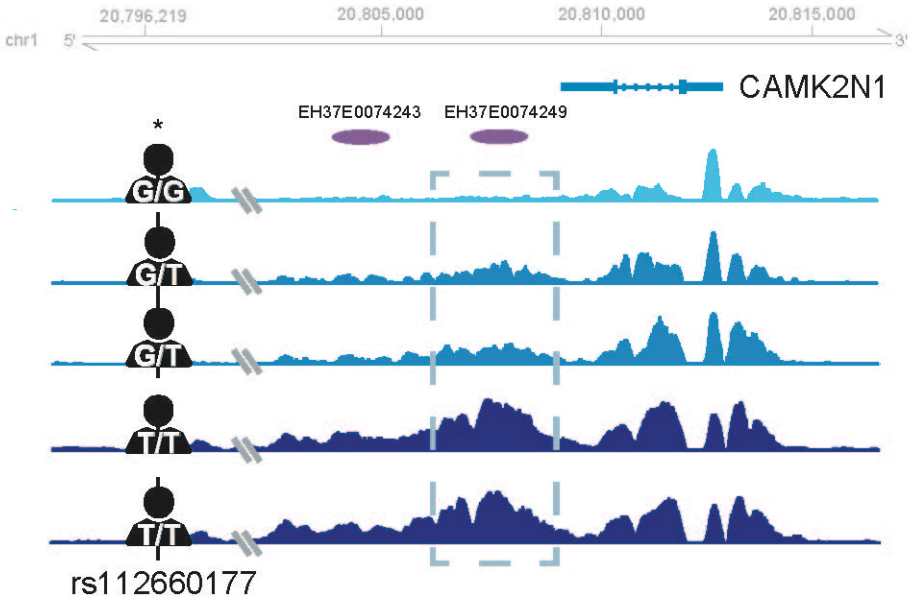
[Wang et al. ('18) Science]

Quantitaive Trait Loci (QTLs) associated with variation

Gene expression (eQTL)



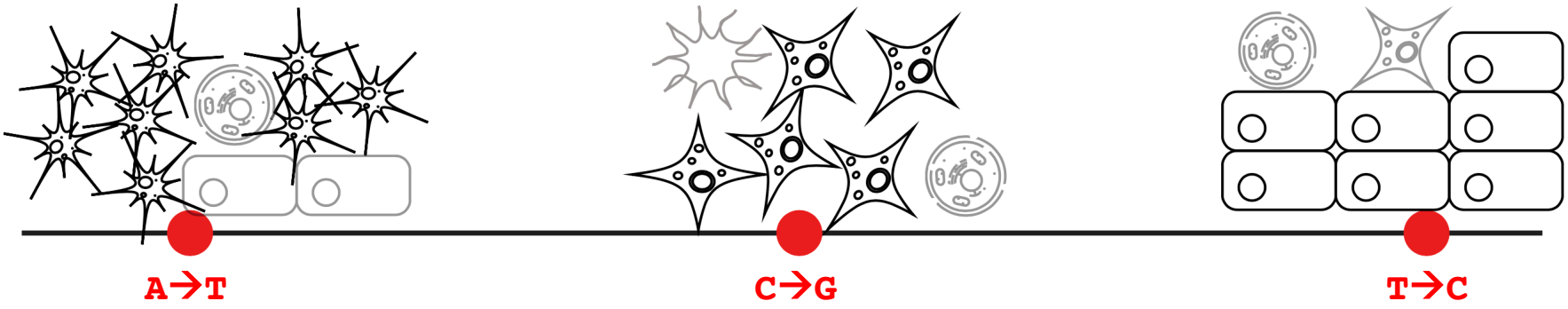
Chromatin (cQTL)

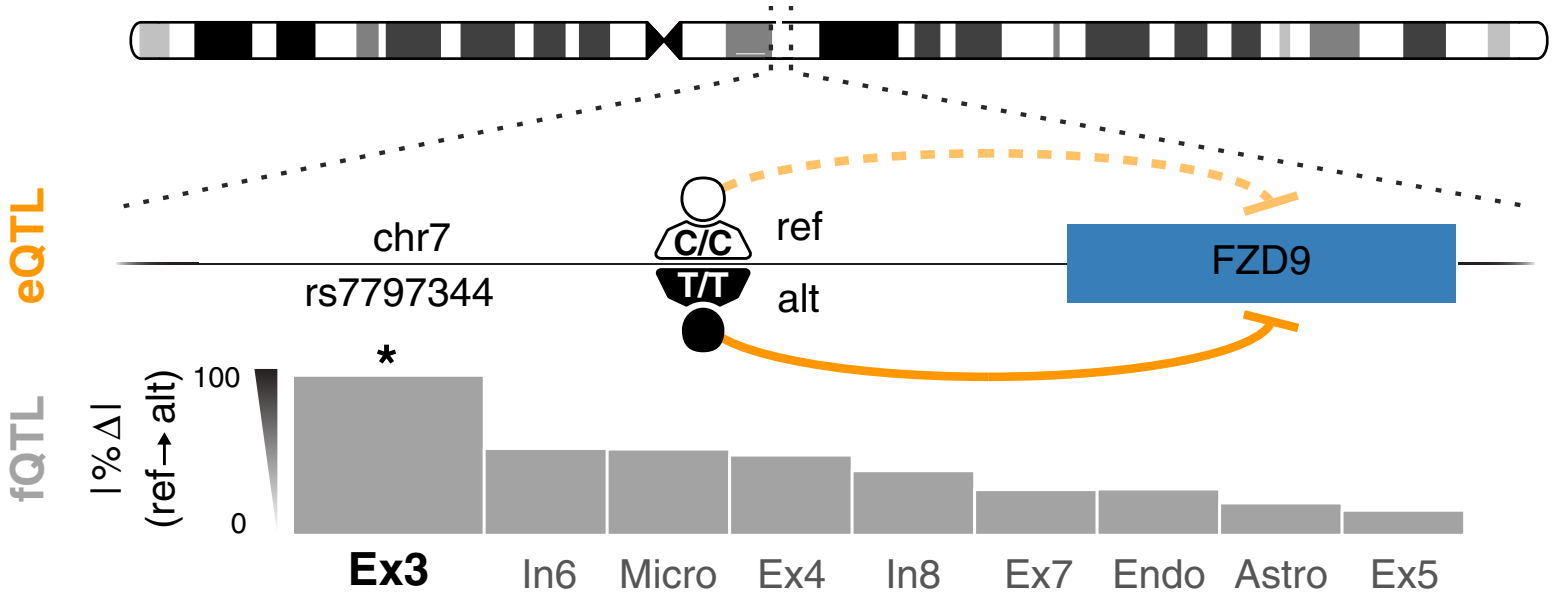


[Wang et al. ('18) Science]

Sun, Wei, and Yijuan Hu. "eQTL mapping using RNA-seq data." *Statistics in biosciences* 5.1 (2013): 198-219.

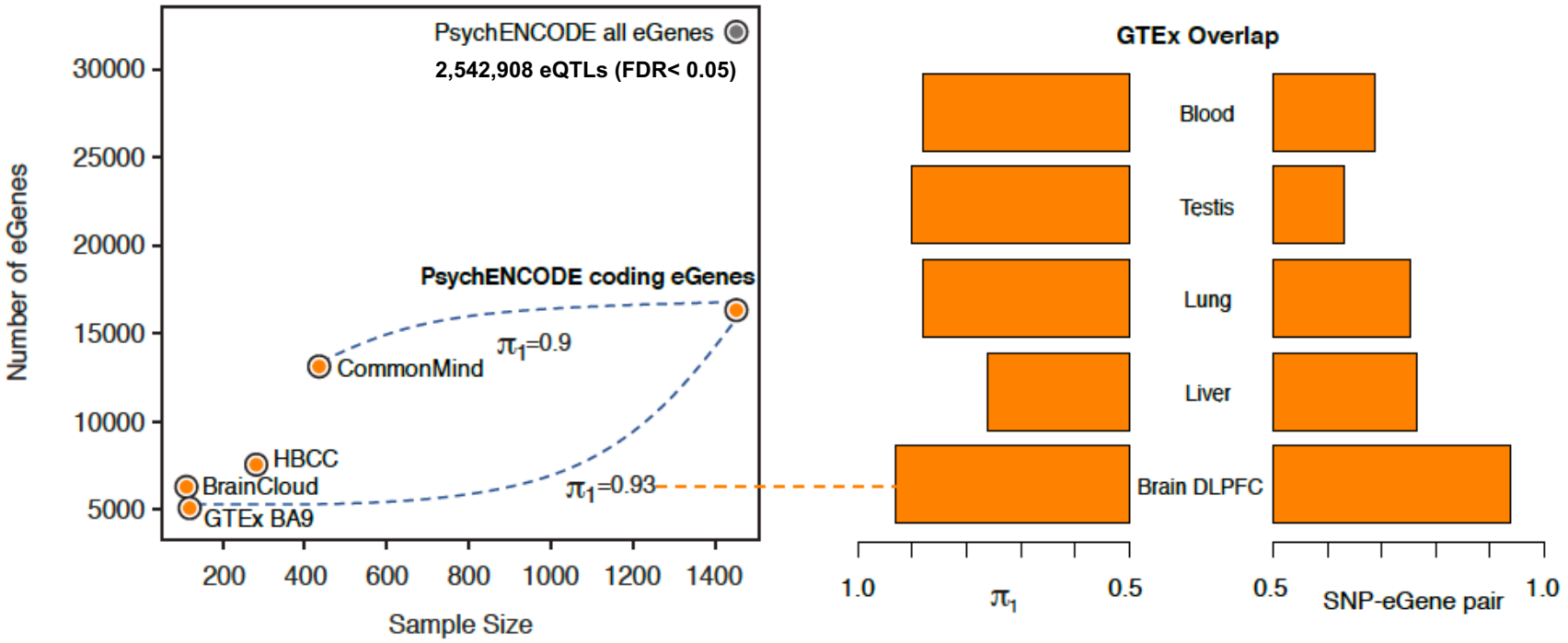
Cell fraction QTLs (fQTLs)





[Wang et al. ('18) Science]

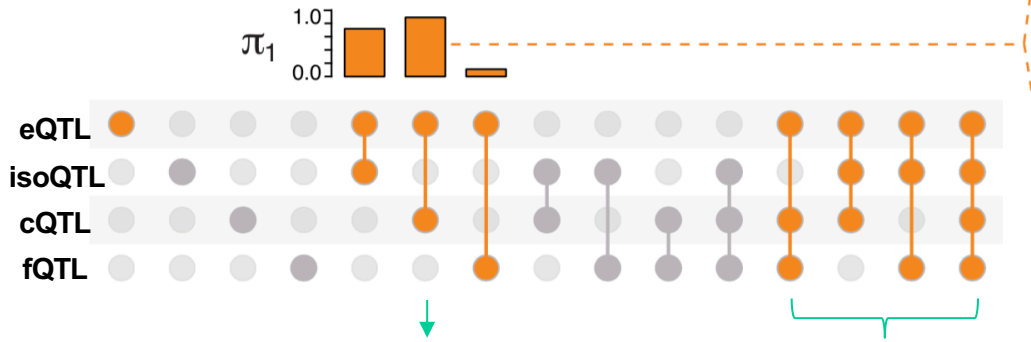
Larger brain eQTL sets than previous studies, but strong overlap with them



[Wang et al. ('18) Science]

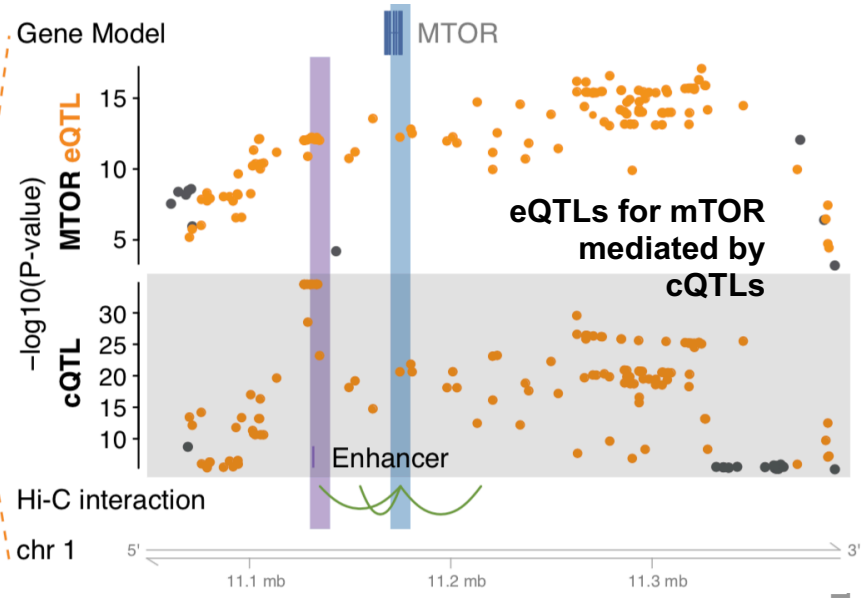
multi-QTLs from overlapping different types of QTLs: cQTL, fQTL, eQTL & isoQTL

	Numbers of QTLs	eGenes Enhancers Cell types	SNPs
eQTL	2,542,908	32,944	1,341,182
isoQTL	2,628,259	19,790	1,052,939
cQTL*	8,464	8,484	7,983
fQTL	4,199	9	1,672



eQTLs and cQTLs significantly overlap

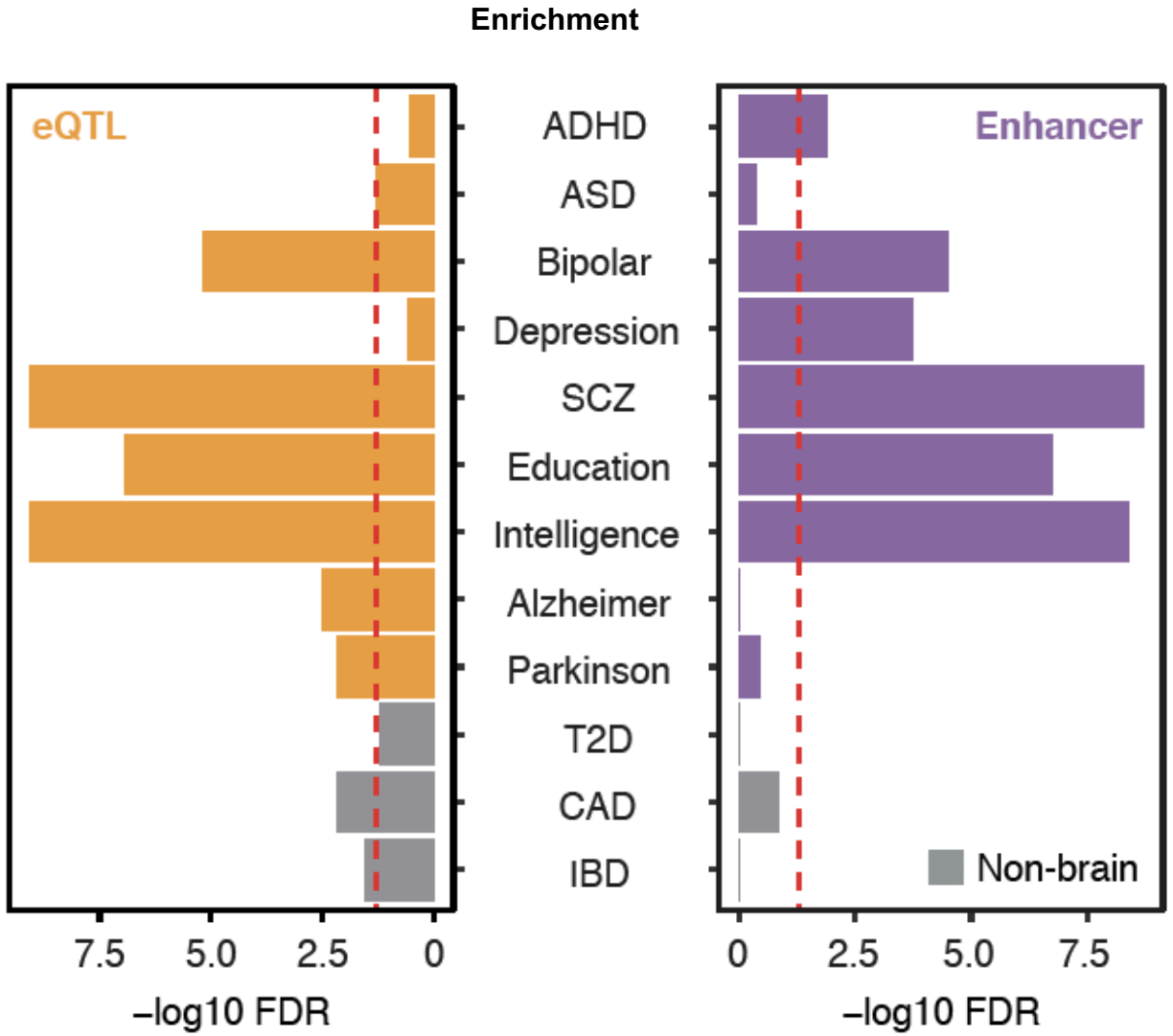
1391 SNPs (multi-QTLs) in at least three types among eQTLs, isoQTLs, cQTLs, fQTLs



eQTLs for mTOR mediated by cQTLs

[Wang et al. ('18) Science]

Brain eQTLs and enhancers enriched with GWAS SNPs for brain disorders



Wang, et al., *Science*, 2018

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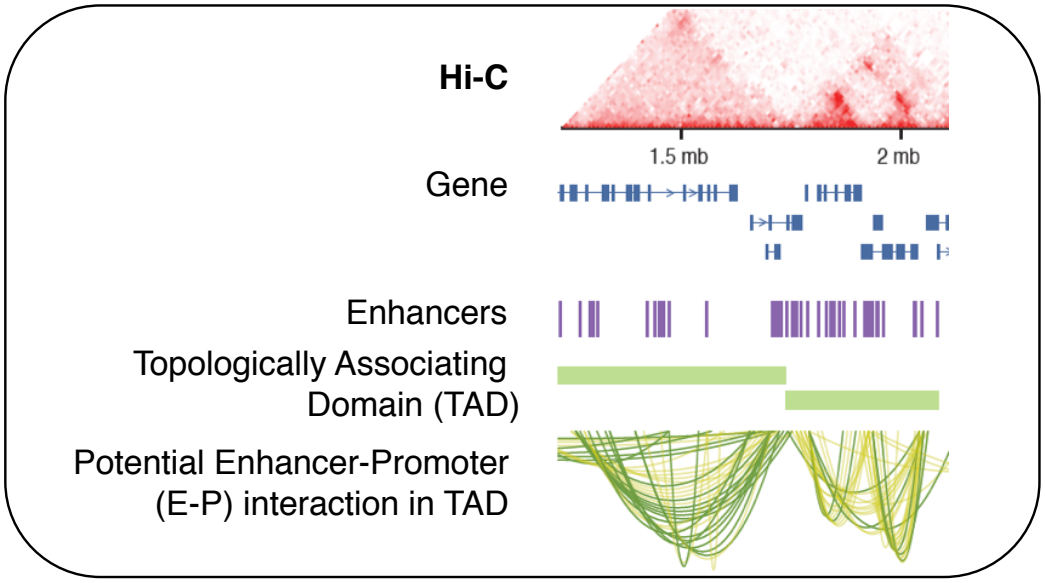
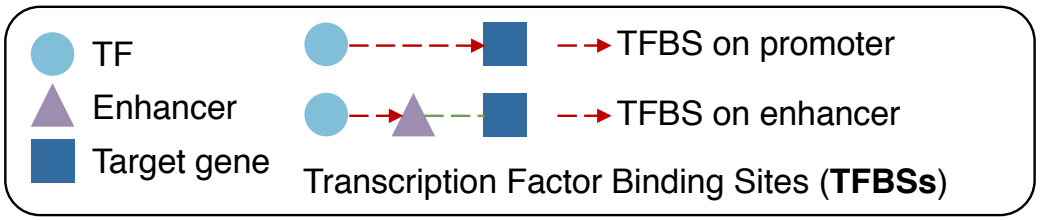
Gene regulatory network inference from Hi-C, QTLs & Activity Correlations

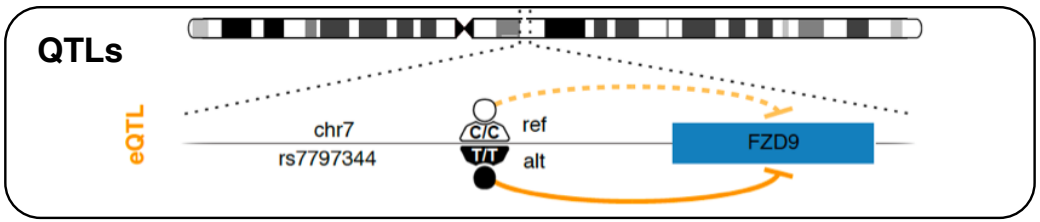




Expression activity relationship

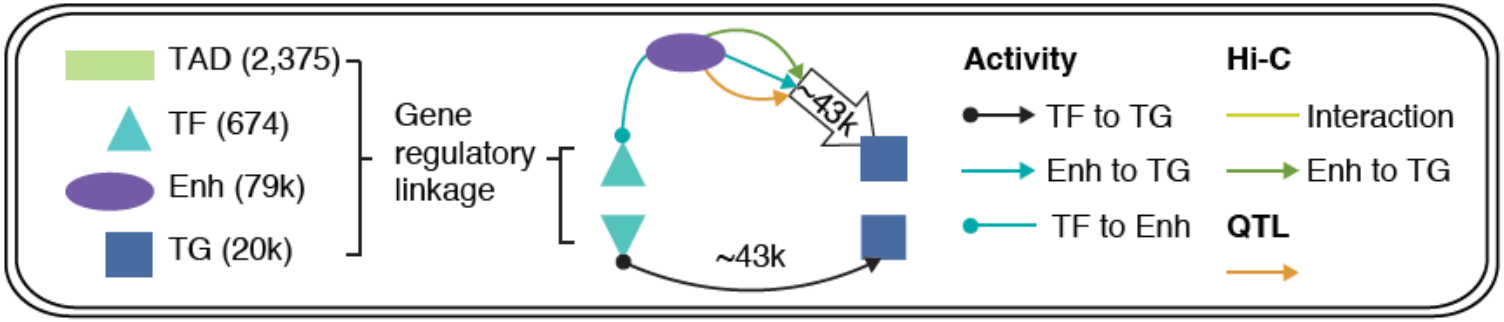
$C^* = argmin_C(\|Y - XC\|^2 + a\|C\|^2 + b\|C\|_{L1})$

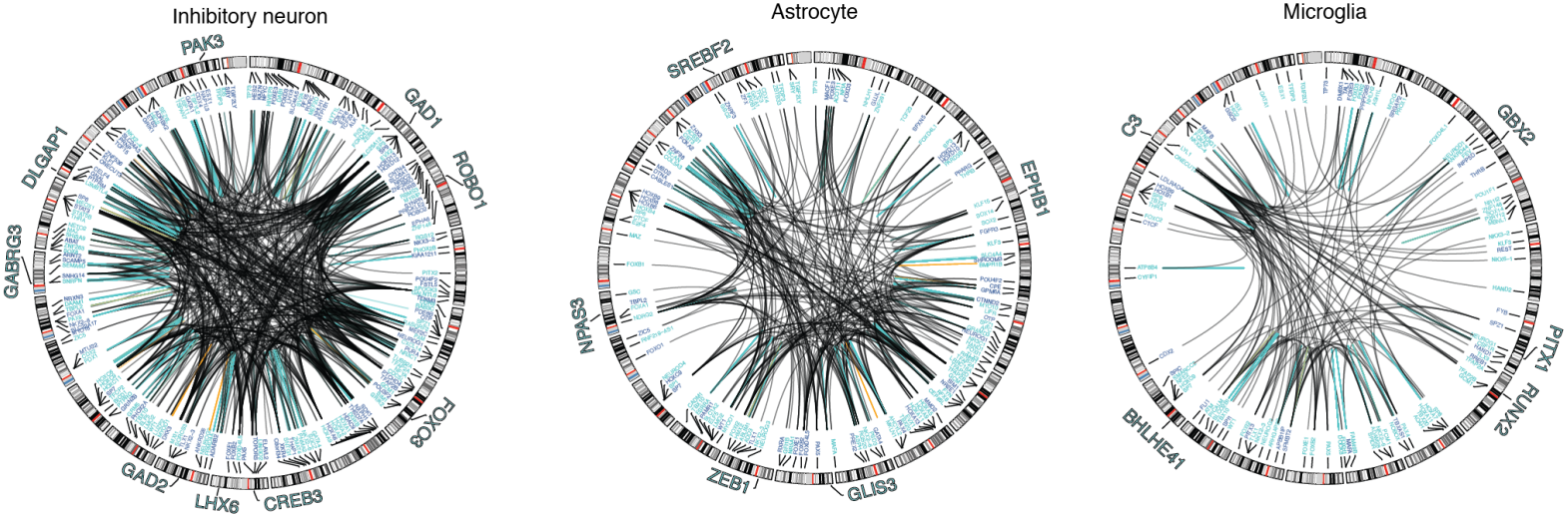
TF expression (X) to predict target gene expression (Y) using Elastic net regression



[Wang et al. ('18) Science]

Imputed gene regulatory network for the human brain





subnetworks targeting single cell marker genes

[Wang et al. ('18) Science]

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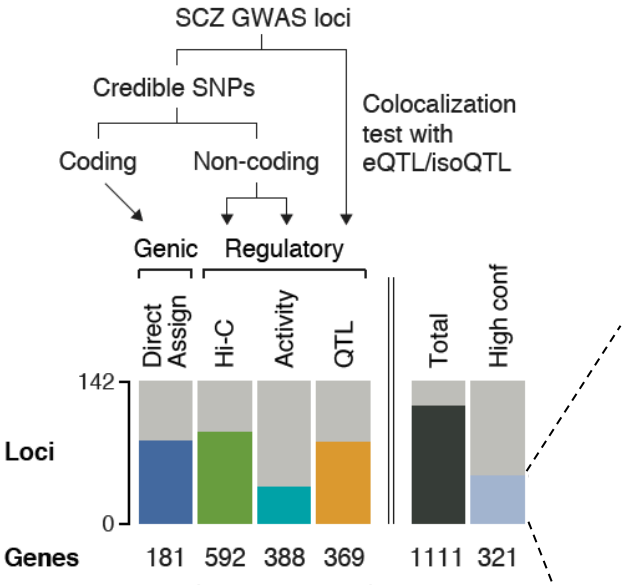
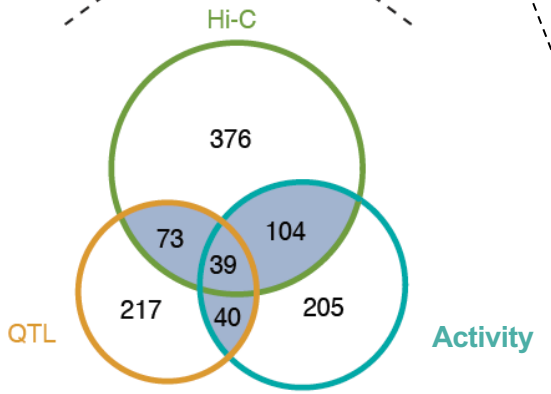
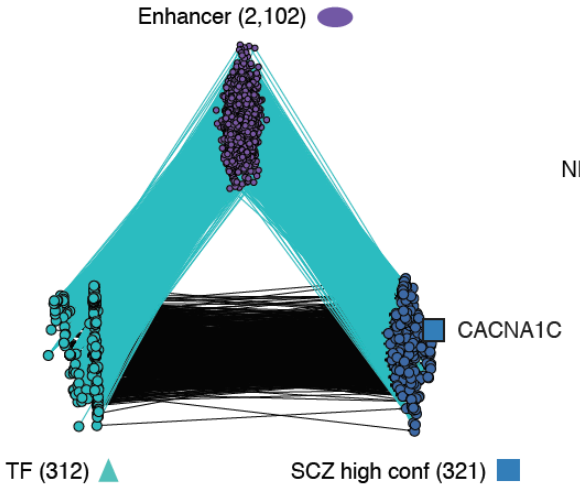
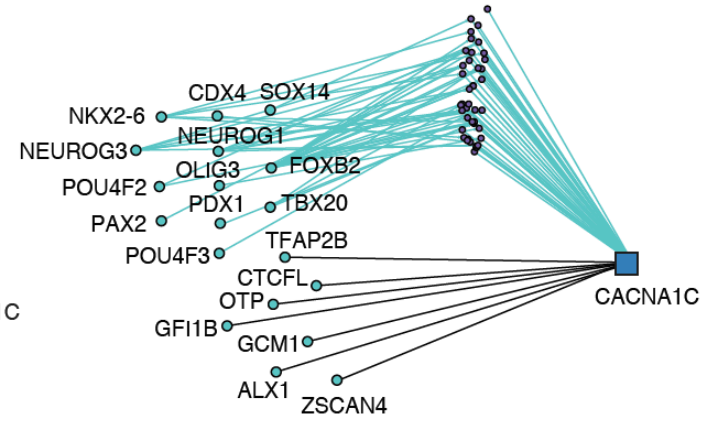
Linking GWAS SNPs to disease genes using the regulatory network









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high-confident SCZ genes

[Wang et al. ('18) Science]

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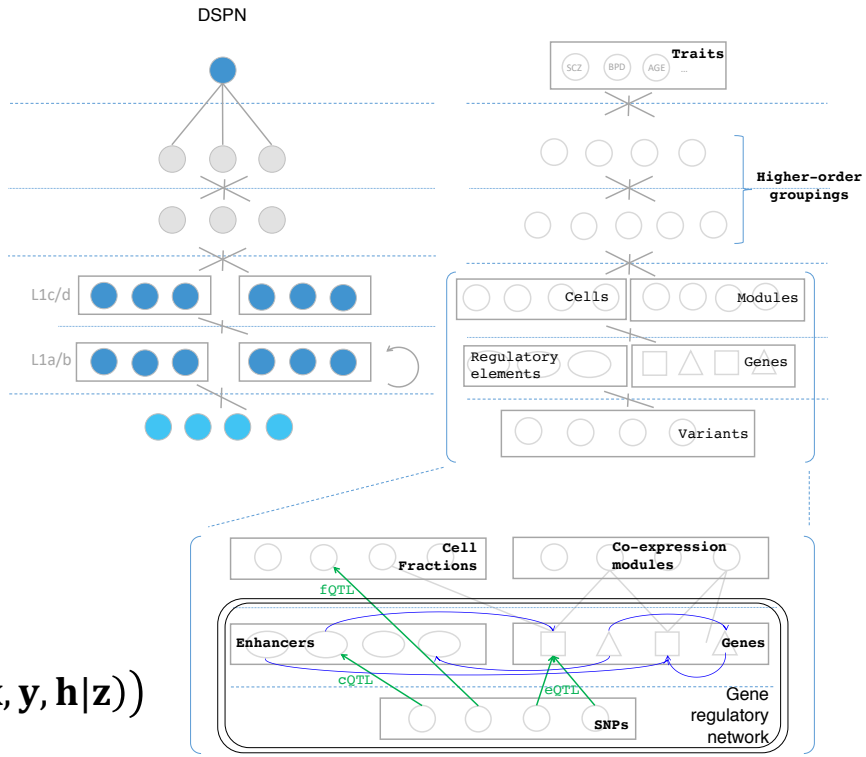
Deep Structured Phenotype Network (DSPN)

Gene regulatory network builds skeleton



Boltzmann machine

y: phenotypes

h: hidden units (e.g., circuits)

x: intermediate phenotypes (e.g., genes, enhancers)

z: genotypes (e.g., SNPs)

W: weights (e.g., regulatory network)

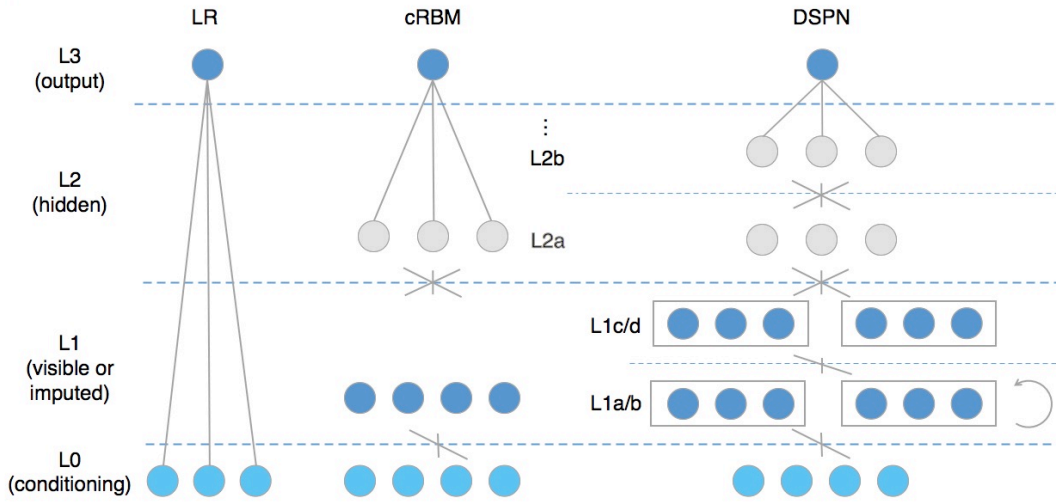
Energy model:

$$p(\mathbf{x}, \mathbf{y}, \mathbf{h}|\mathbf{z}) \propto \exp\left(-E(\mathbf{x}, \mathbf{y}, \mathbf{h}|\mathbf{z})\right)$$

$$E(\mathbf{x}, \mathbf{y}, \mathbf{h}|\mathbf{z}) = -\mathbf{z}^{\mathrm{T}}\mathbf{W}_1\mathbf{x} - \mathbf{x}^{\mathrm{T}}\mathbf{W}_2\mathbf{x} - \mathbf{x}^{\mathrm{T}}\mathbf{W}_3\mathbf{h} - \mathbf{h}^{\mathrm{T}}\mathbf{W}_4\mathbf{h} - \mathbf{h}^{\mathrm{T}}\mathbf{W}_5\mathbf{y} - \boldsymbol{Bias}$$

[Wang et al. ('18) Science]

DSPN improves brain disease prediction by adding deep layers



Method	LR-genotype	LR-transcriptome	cRBM	DSPN-imputation	DSPN-full
Schizophrenia	**54.6%**	63.0%	70.0%	59.0%	**73.6%**
Bipolar Disorder	**56.7%**	63.3%	71.1%	67.2%	**76.7%**
Autism Spectrum Disorder	**50.0%**	51.7%	67.2%	62.5%	**68.3%**

X 6.0

Accuracy = chance to correctly predict disease/health

[Wang et al. ('18) Science]

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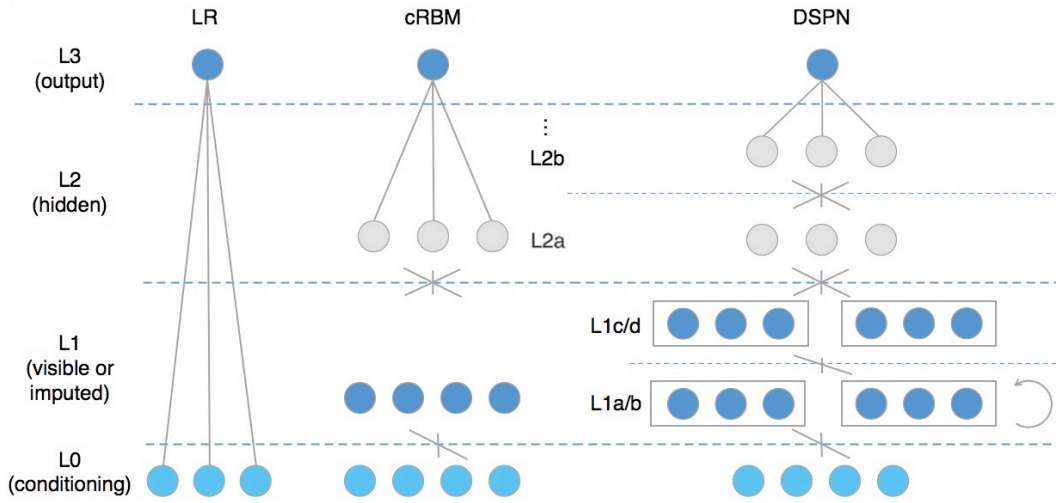

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X 2.5

Accuracy = chance to correctly predict disease/health

[Wang et al. ('18) Science]

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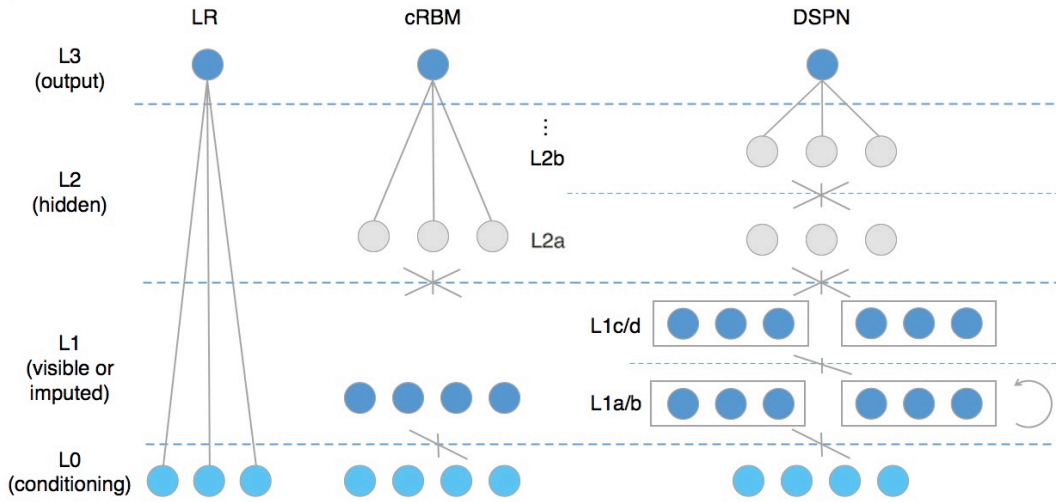

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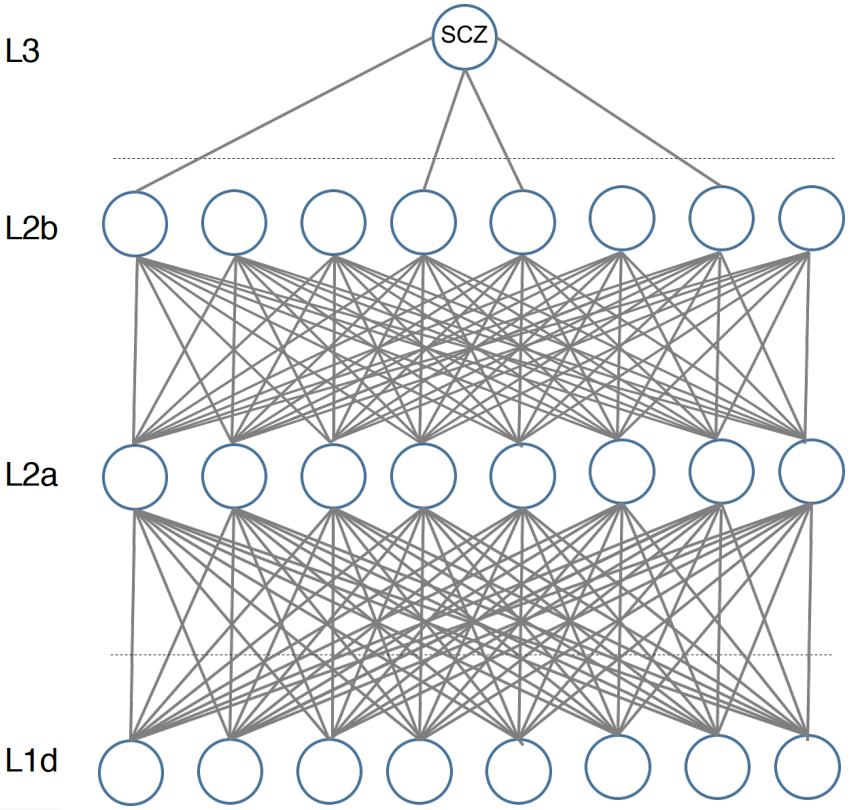
X 3.1

Accuracy = chance to correctly predict disease/health

[Wang et al. ('18) Science]

Multilevel Network Interpretation

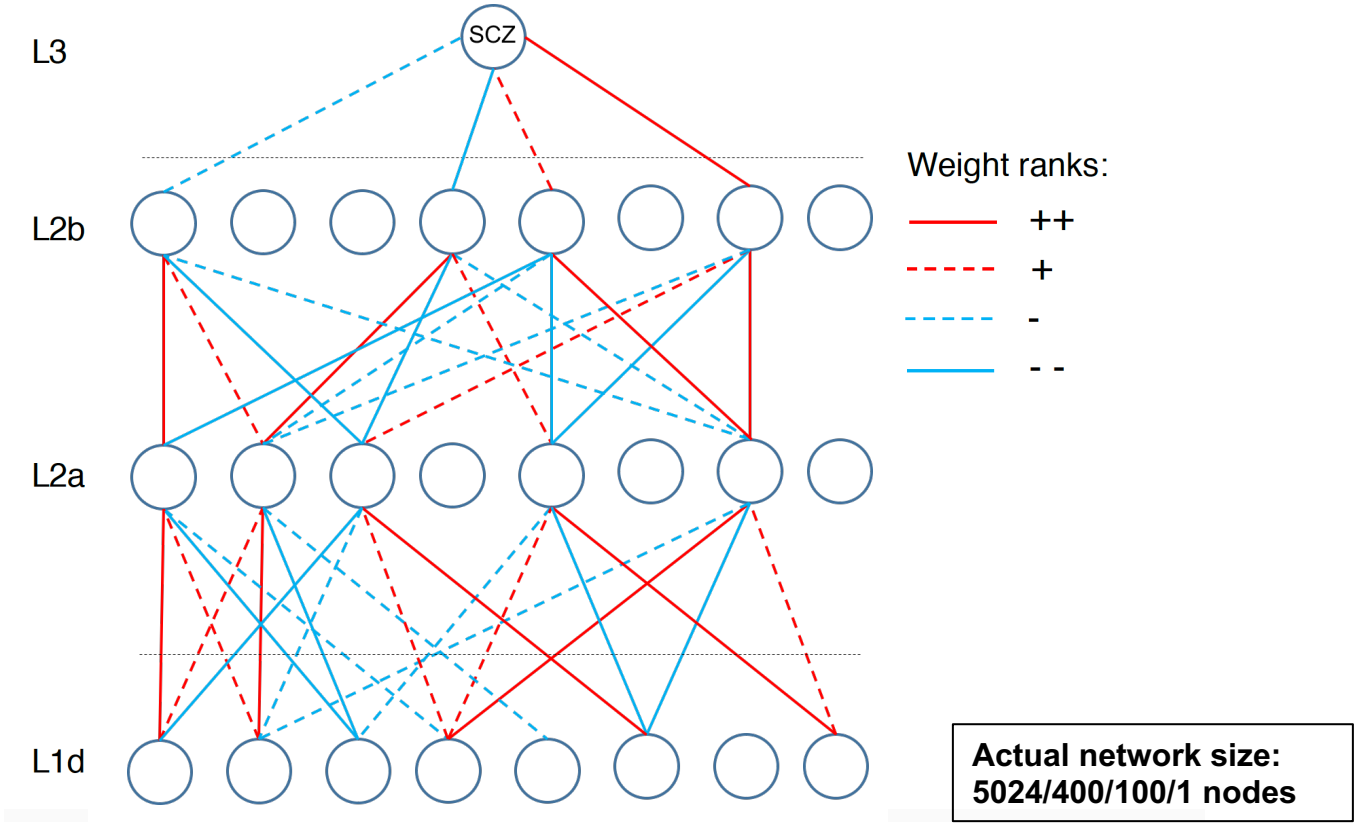


Actual network size:
5024/400/100/1 nodes

- Start with a fully connected trained network

[Wang et al. (‘18) Science]

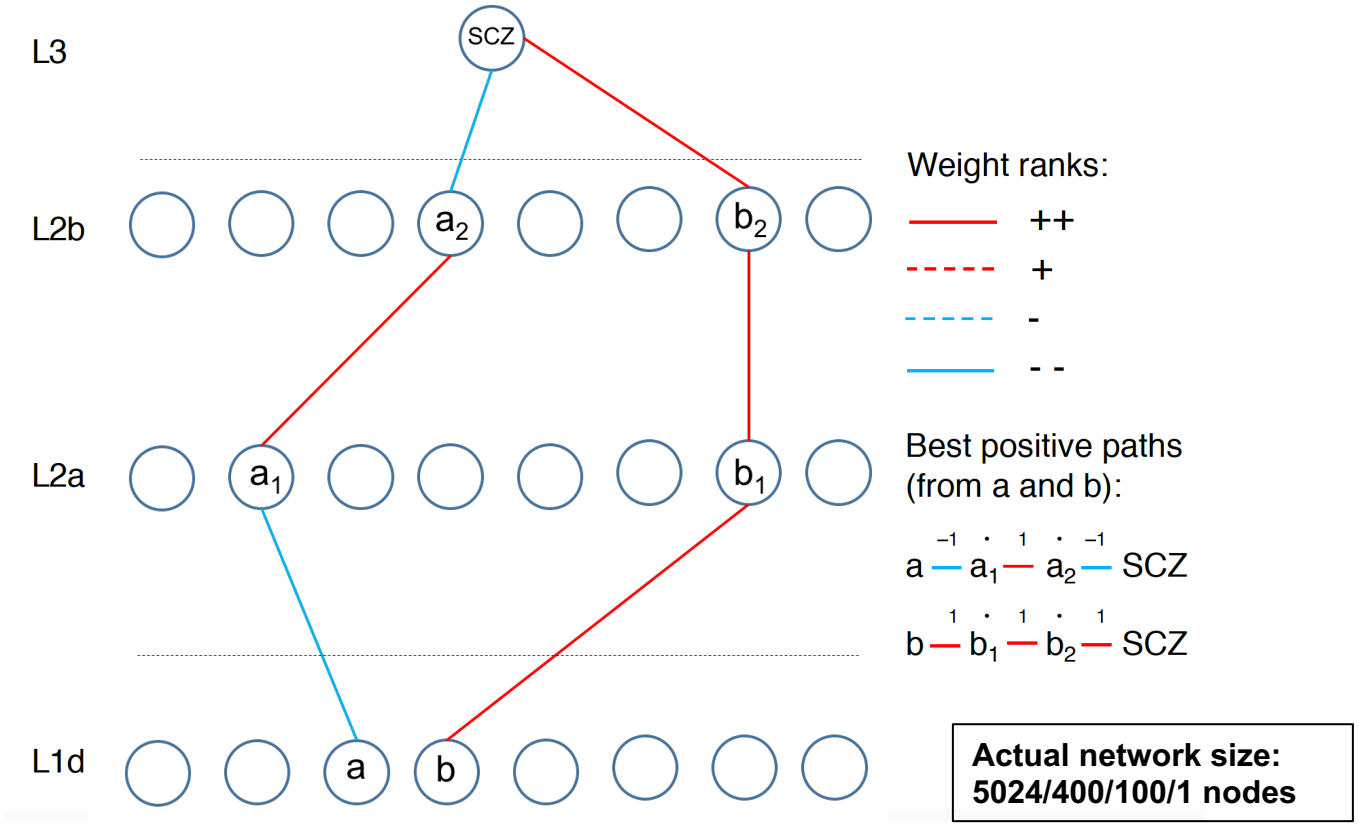
Multilevel Network Interpretation



- Start with a fully connected trained network
- Sparsify network using edges with largest absolute weights (+/-)

[Wang et al. (‘18) Science]

Multilevel Network Interpretation

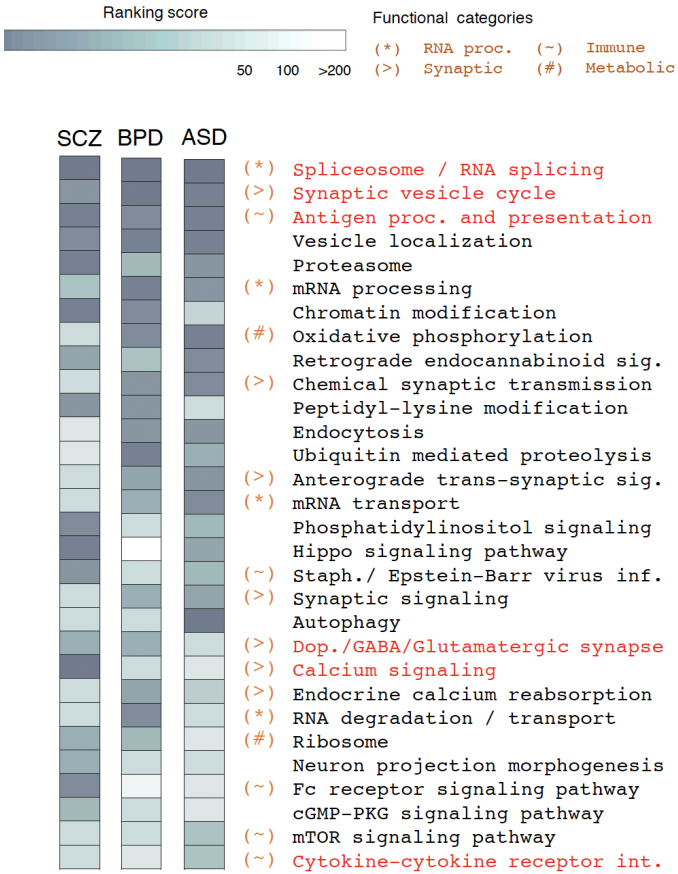


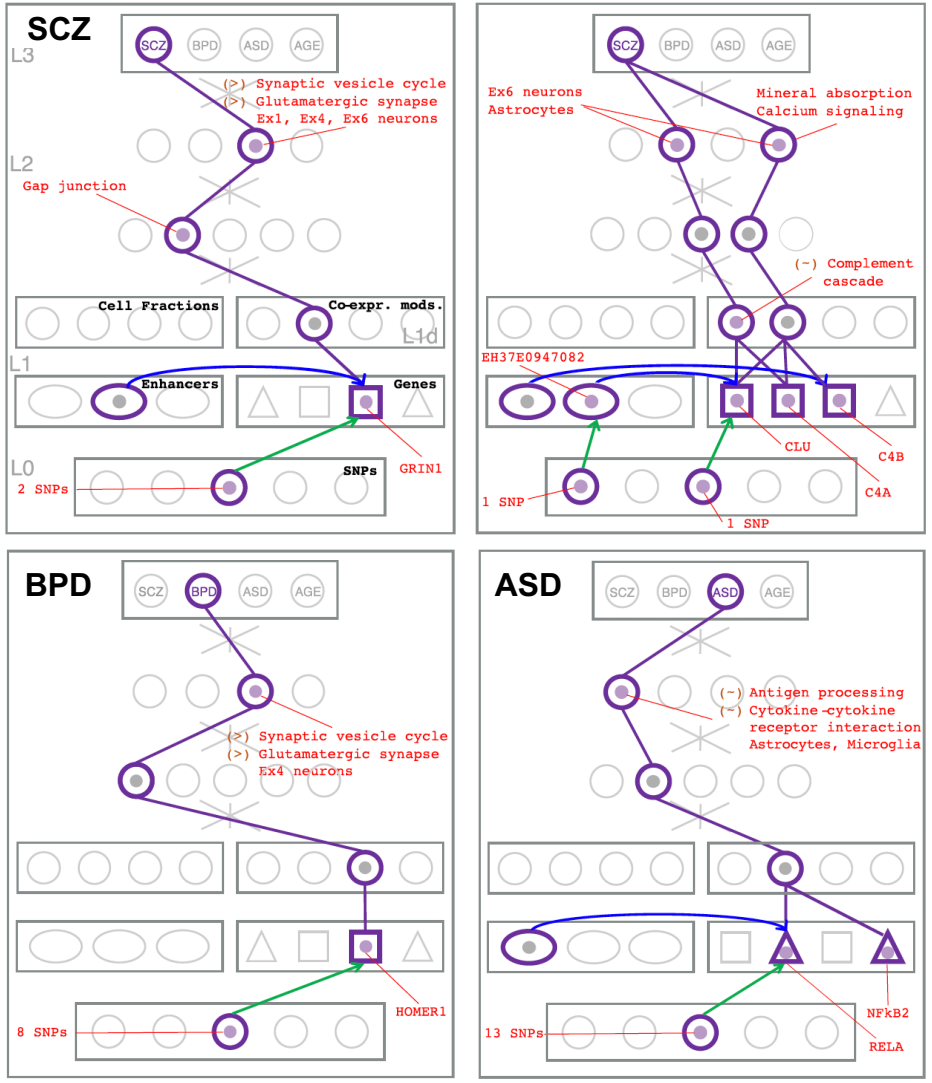
- Start with a fully connected trained network
- Sparsify network using edges with largest absolute weights (+/-)
- Extract 'best positive paths' to each prioritized module (e.g. a-a_1-a_2-SCZ) by summing weights and multiplying signs

[Wang et al. ('18) Science]

DSPN discovers enriched pathways and linkages to genetic variation

Cross-disorder MOD/HOG enrichment ranking





[Wang et al. ('18) Science]

PsychENCODE: Using population-scale functional genomics to understand neuropsychiatric disease

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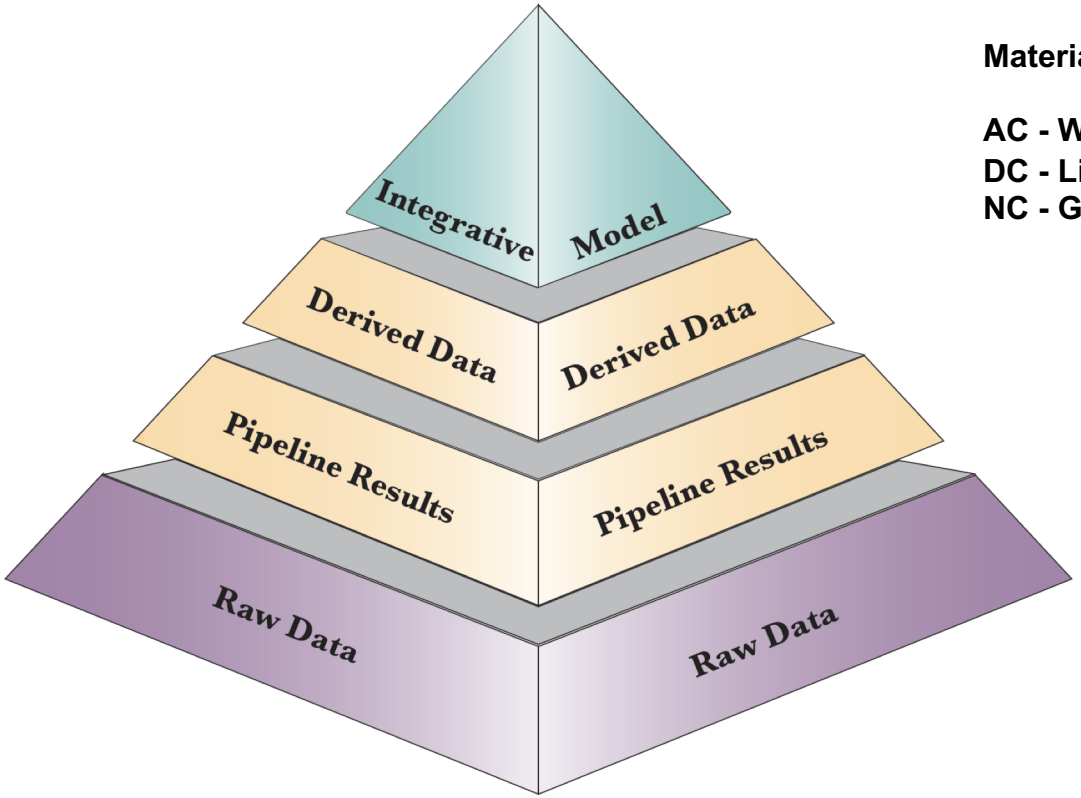
Phase 1 PsychENCODE capstone resource: Layers of distributed information



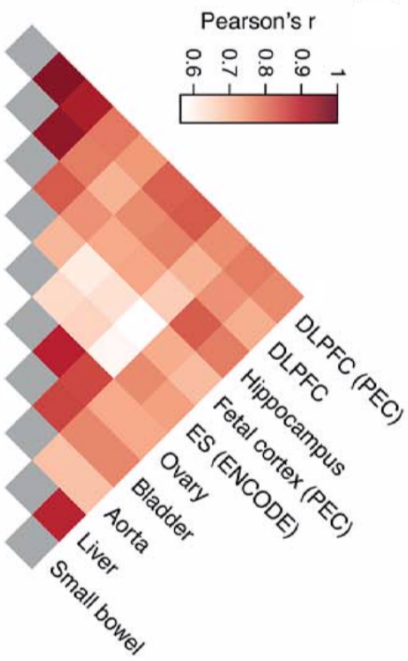
Material in the 3 capstones:

AC - Wang et al. ('18)
DC - Li et al. ('18)
NC - Gandal et al. ('18)

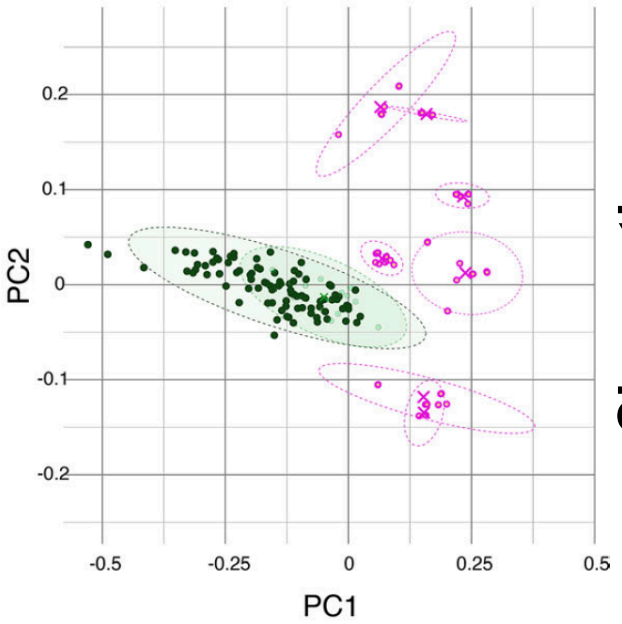
Resource.psychencode.org
Development.psychencode.org

Cross tissue variation in Chromatin & Expression

Placing the Brain in context of all other Body Tissues

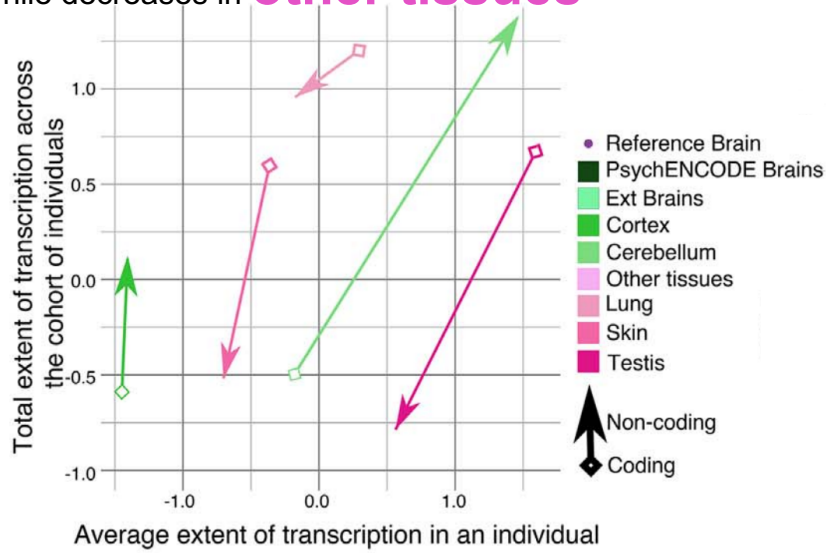


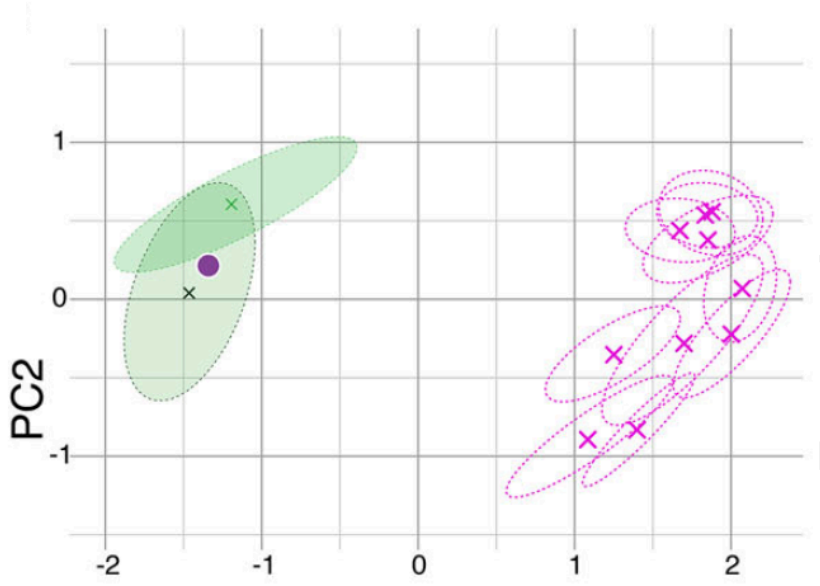
Hi-C



Chromatin

Transcriptome diversity increases in the non-coding portion of the **brain genome** while decreases in **other tissues**



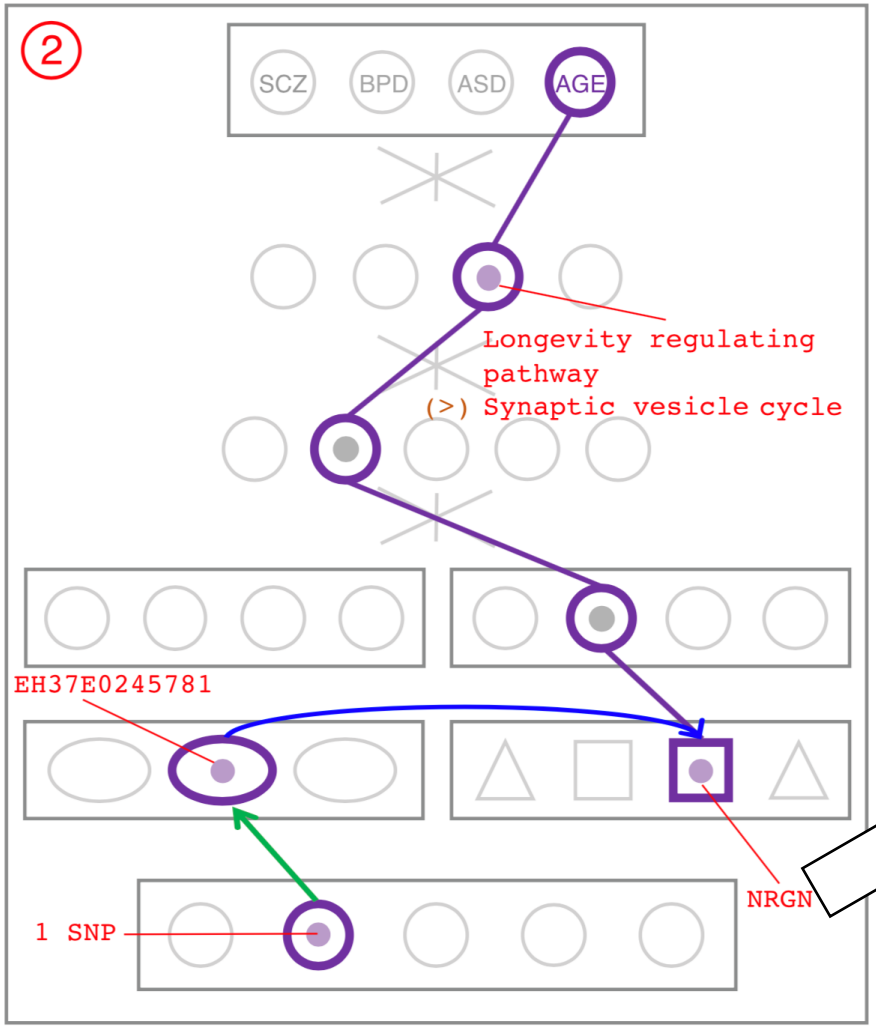


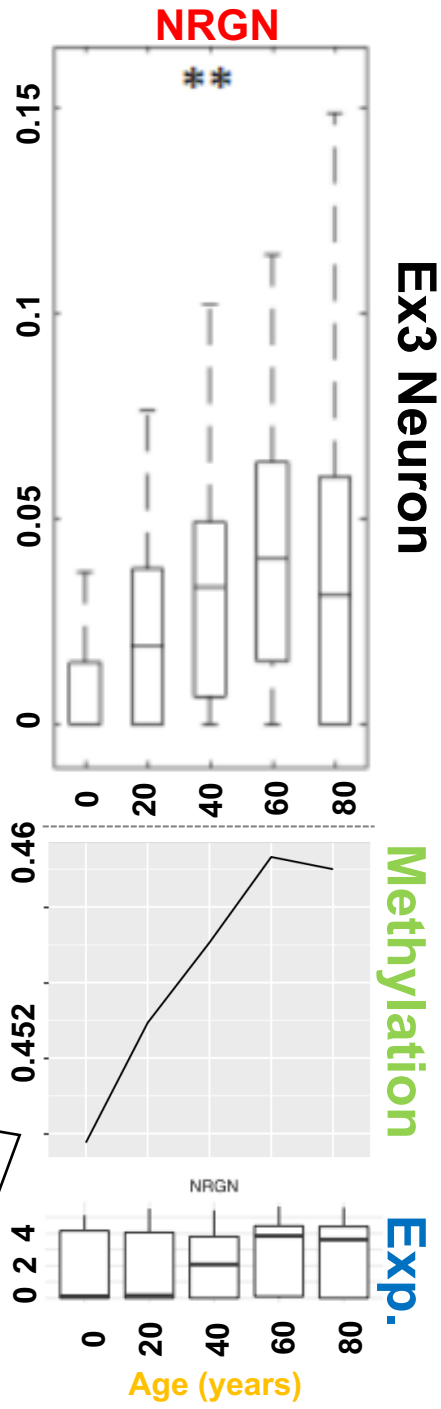
Expression

[Wang et al. (‘18) Science]

NRGN has variable expression over age and is in Synaptic vesicle cycle pathway is enriched in SCZ, BPD, ASD

NGRN is a gene associated with the **Synaptic vesicle pathway** and NGRN **expression** and **methylation** is correlated with **Age**





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Dedicated to **Pamela Sklar**

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