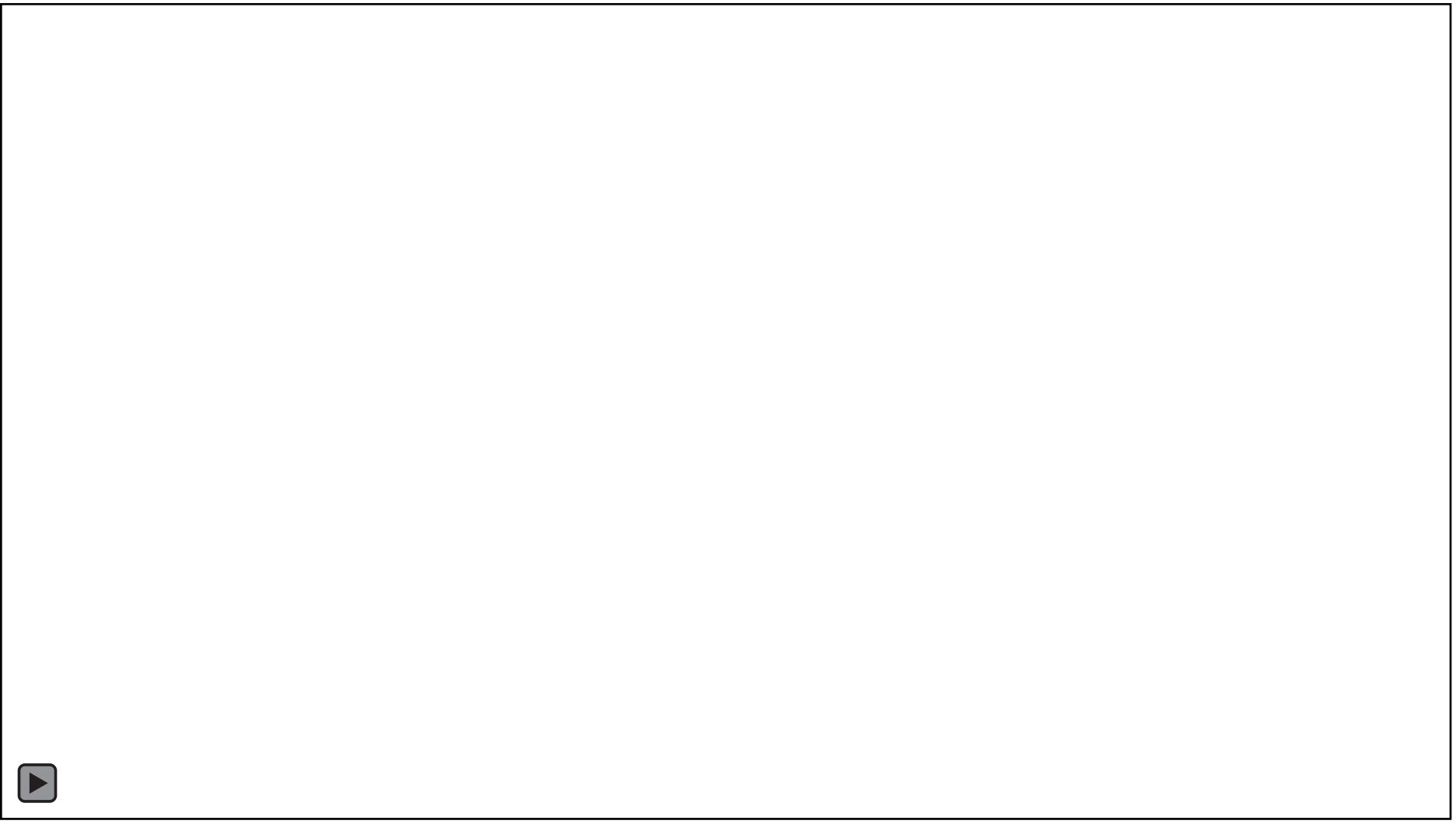
Biological networks in Alzheimer's disease

Tracy Young-Pearse	Molecular biology
Shinya Tasaki Sara Mostafavi	Systems biology
Robert Dawe	Neuroimaging
Chris Gaiteri	Glue

What will the solution to AD look like?



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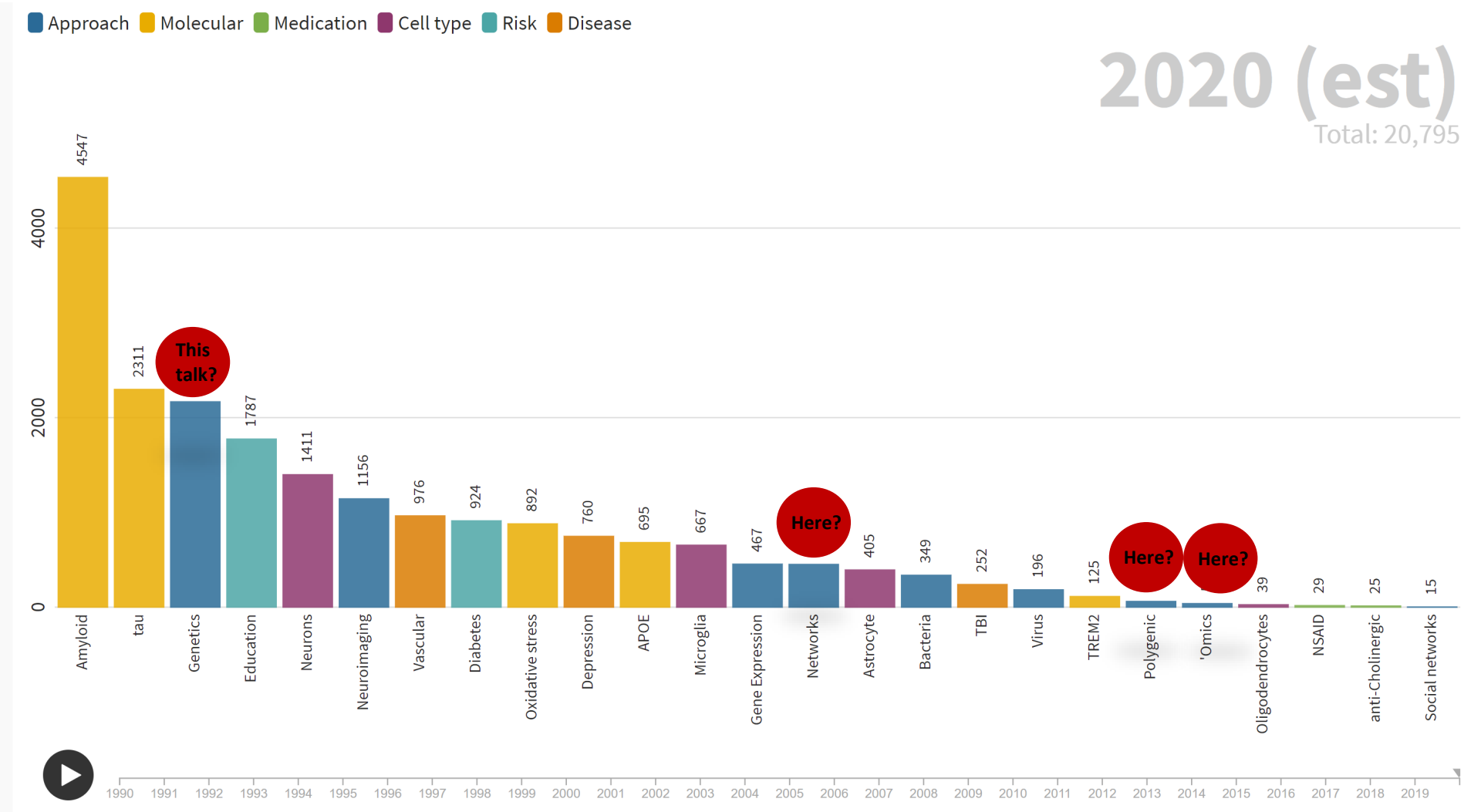

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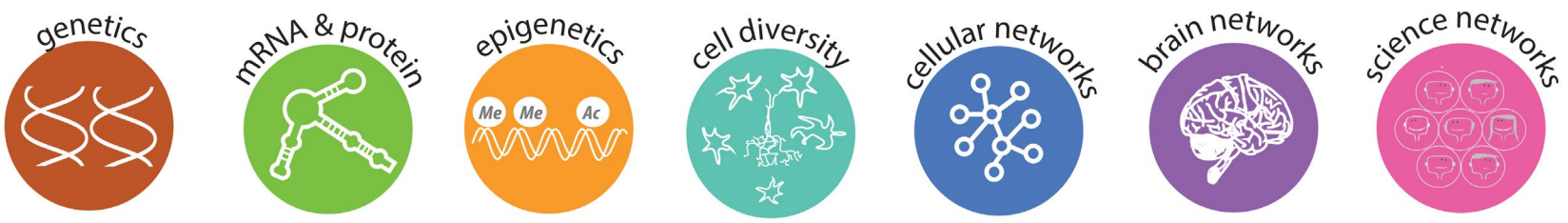

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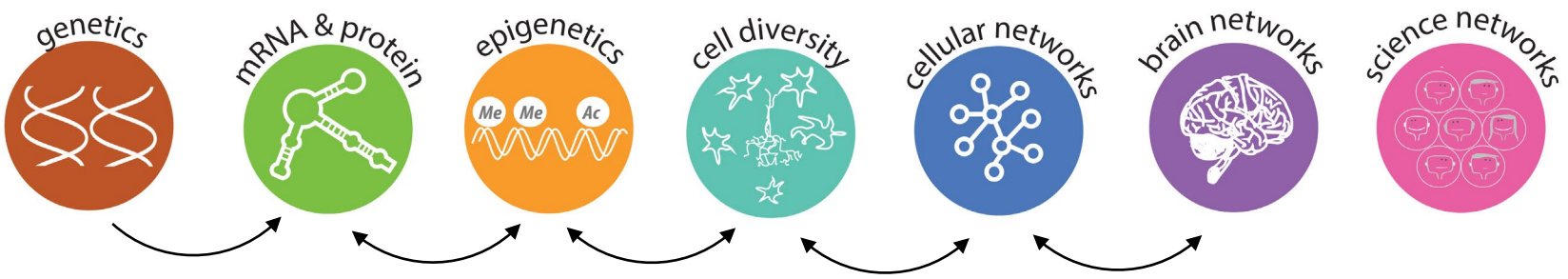

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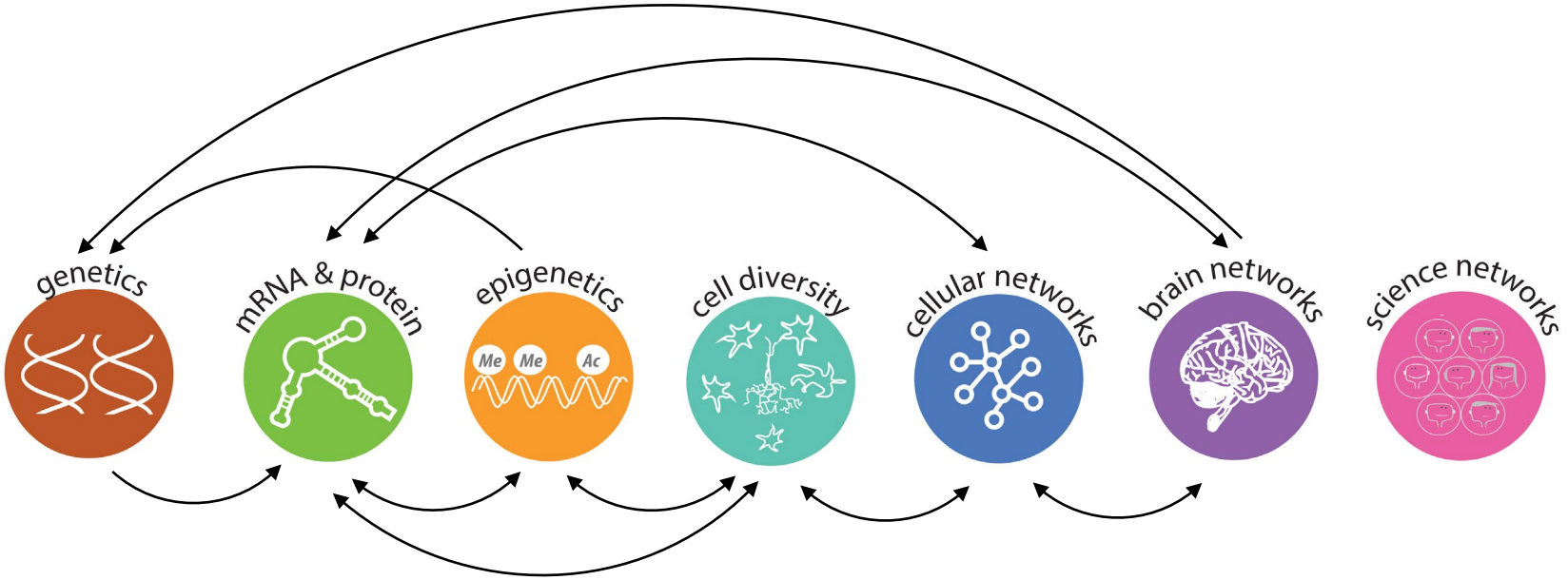

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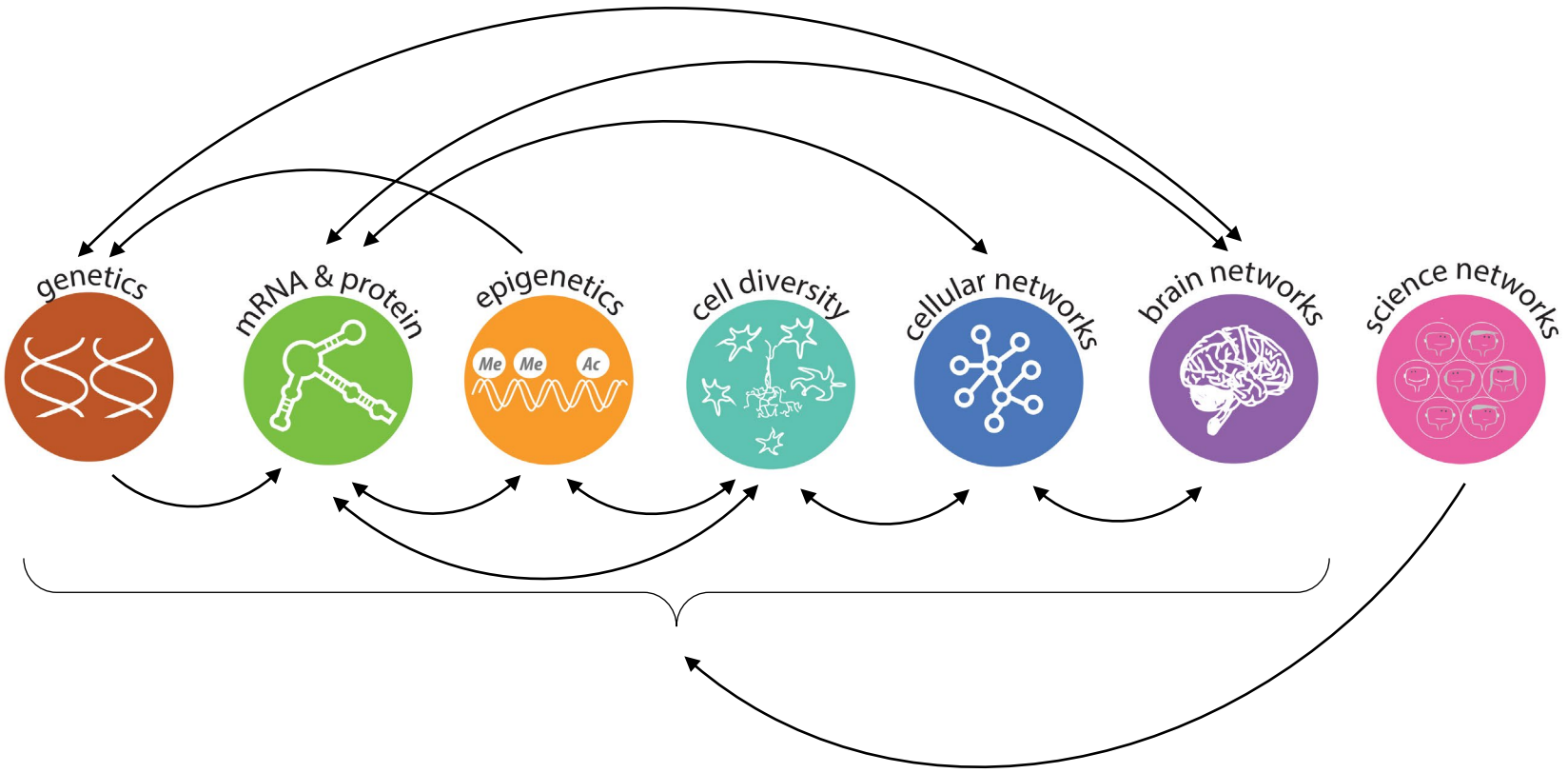

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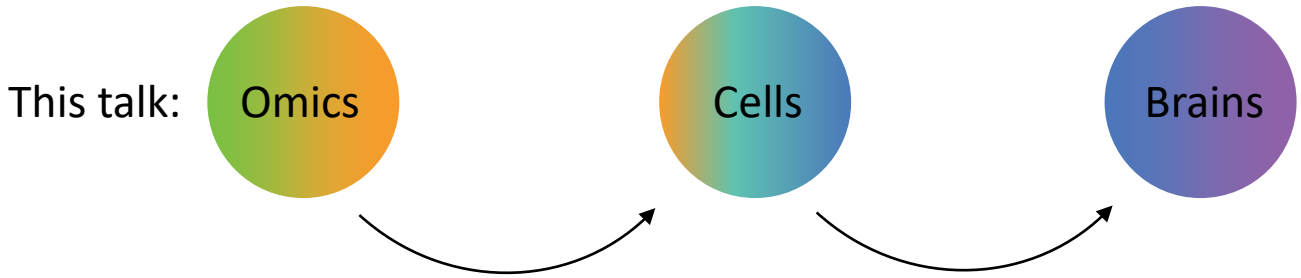

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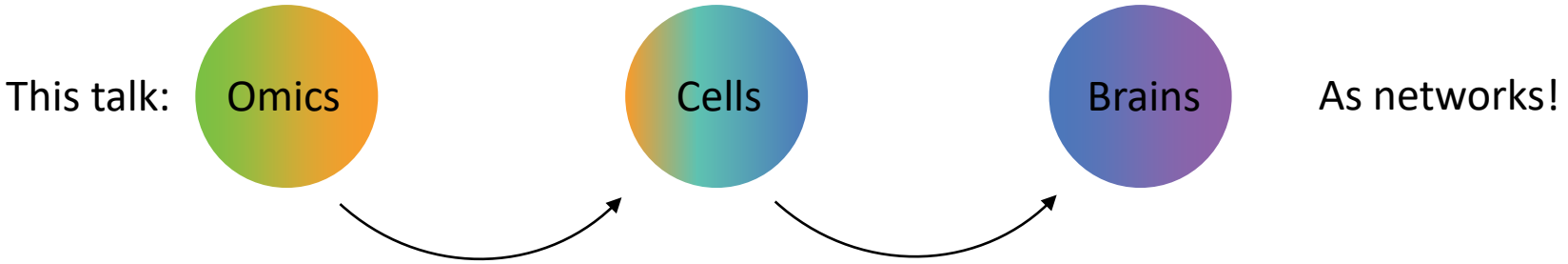
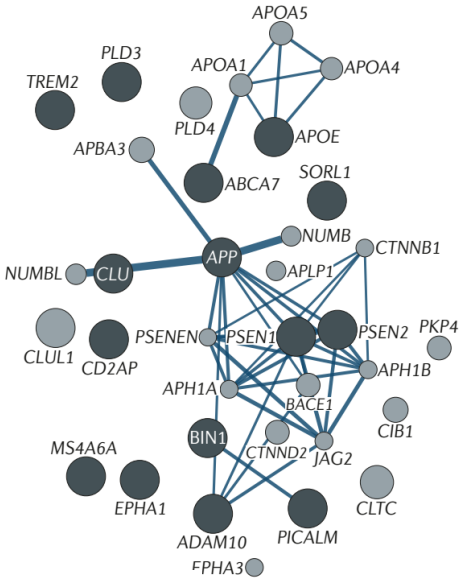


Why networks?



Literature-based connections surround classic AD targets, studied for 30 years.

There are few connections among molecules with novel AD findings.

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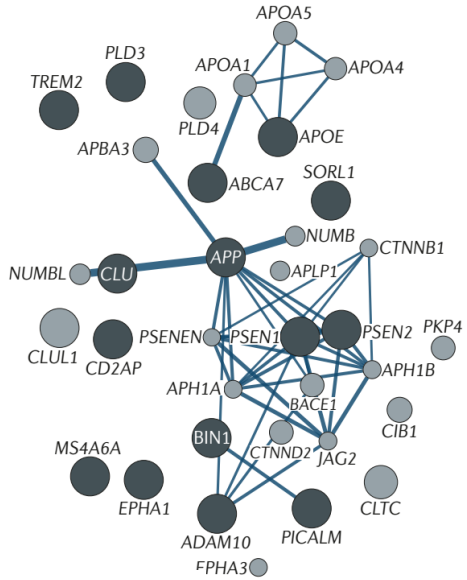

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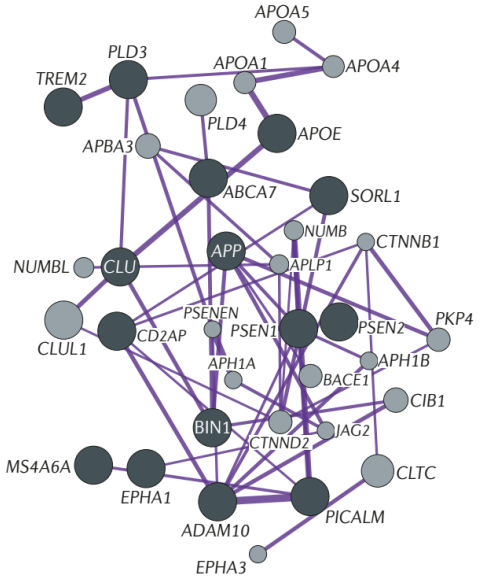

Data-driven connections can be found for AD-related molecules that are more recently of interest

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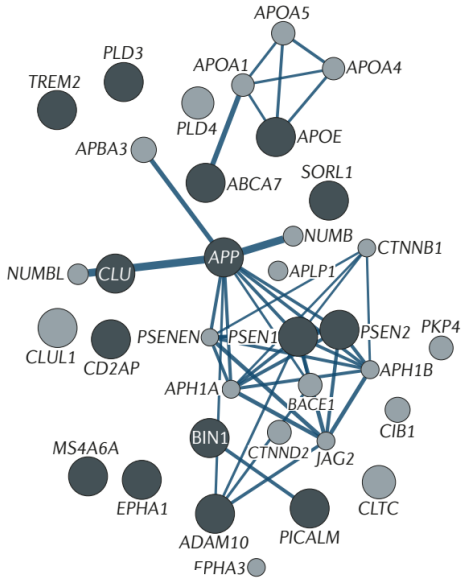

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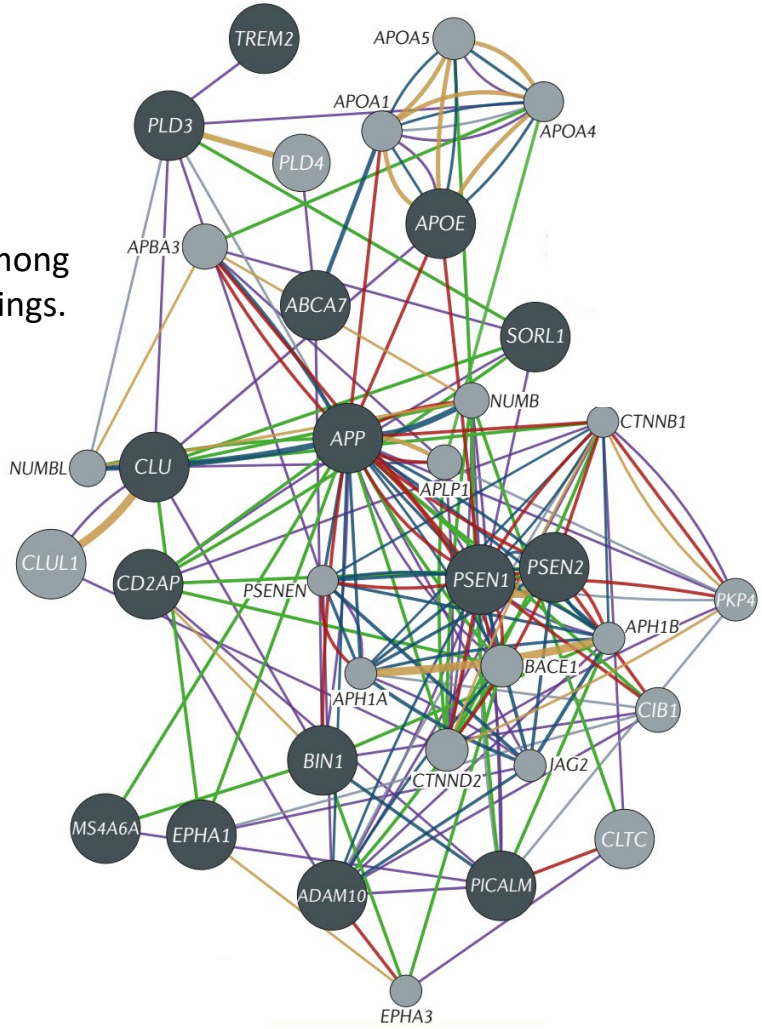

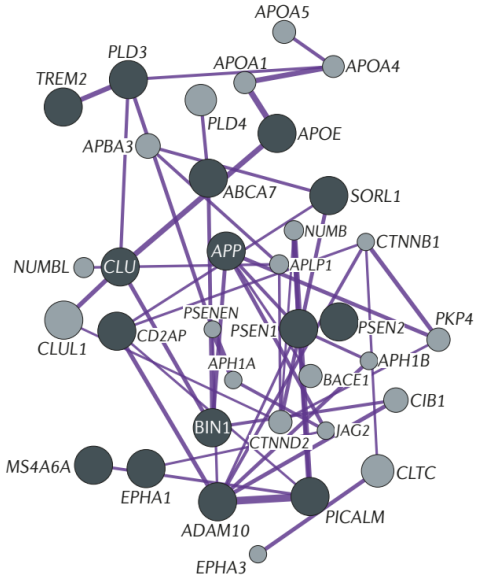

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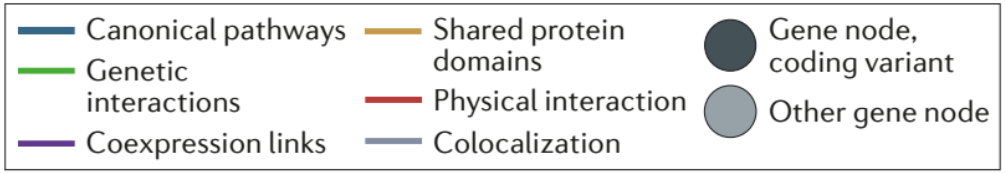
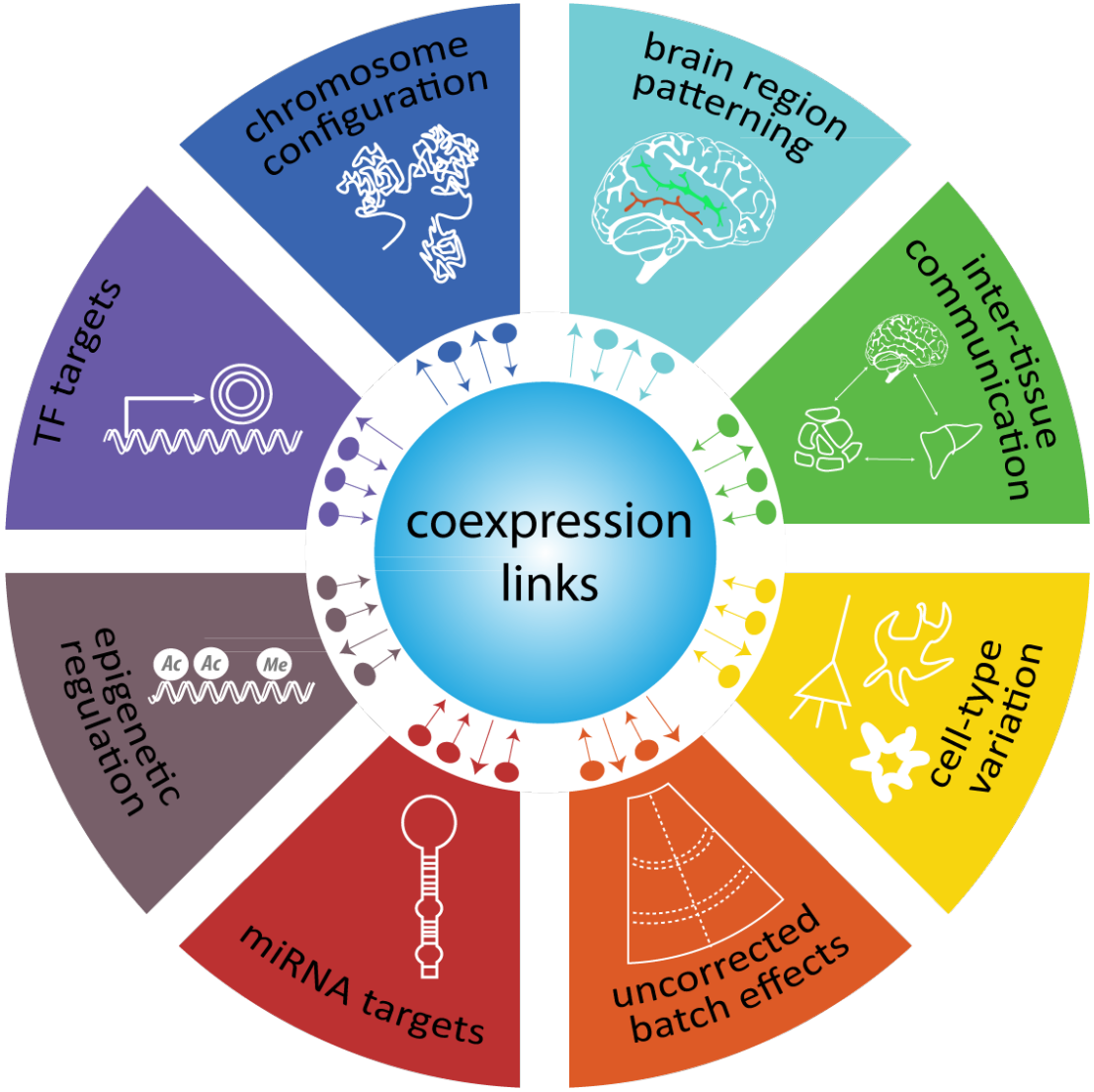


What does coexpression provide?

Several mechanisms generate coexpression networks



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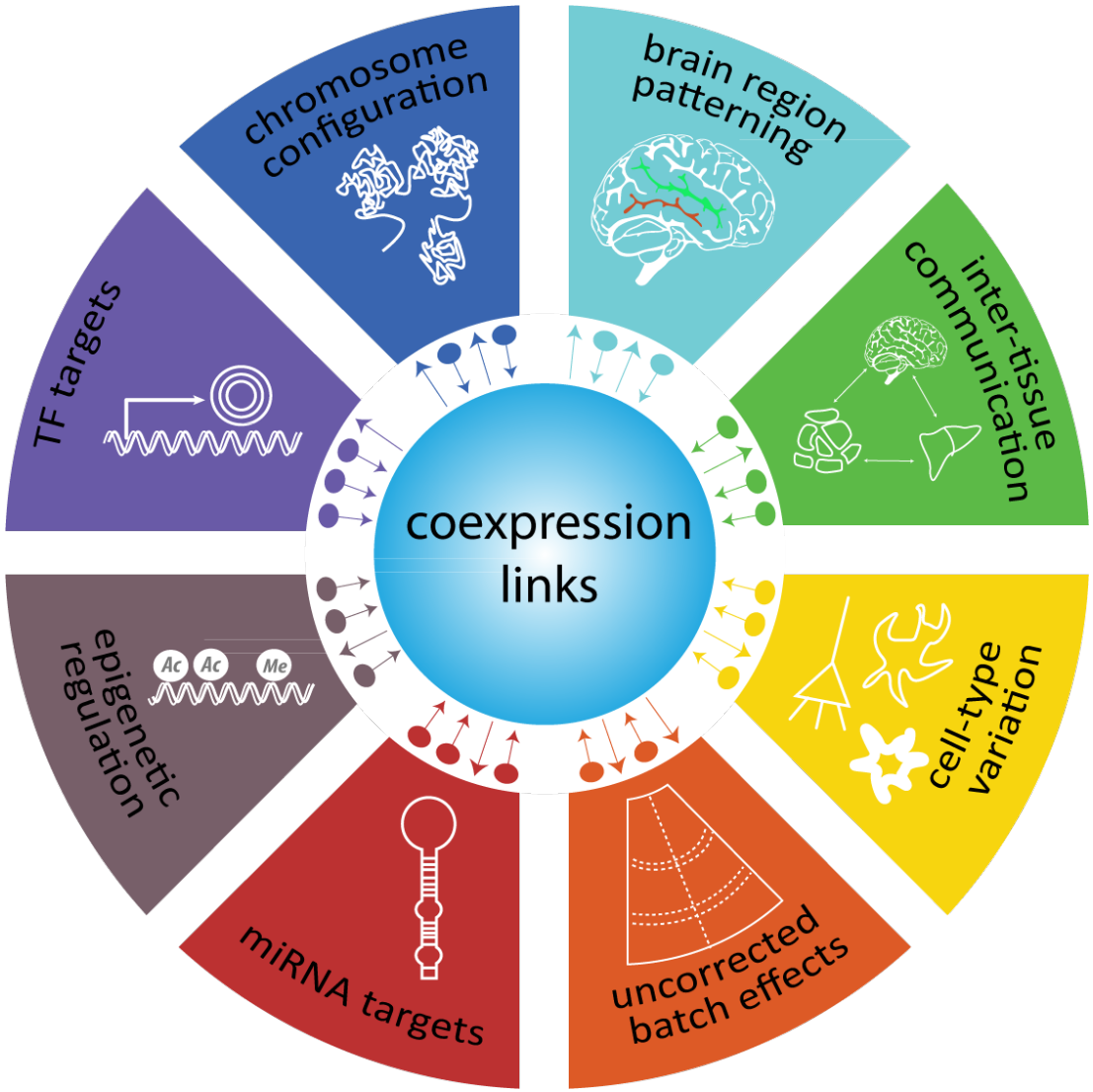

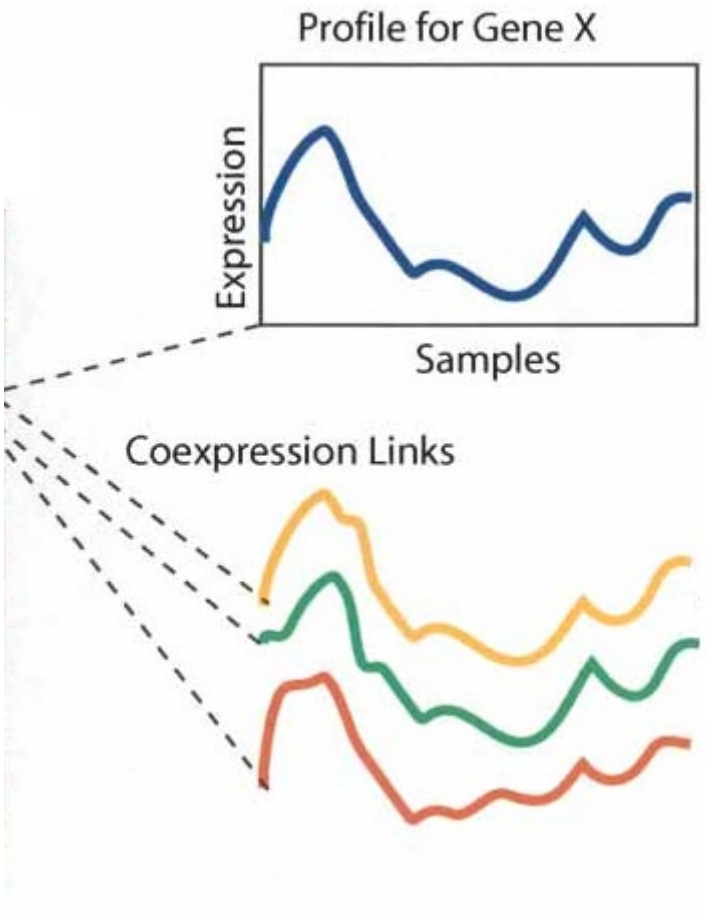

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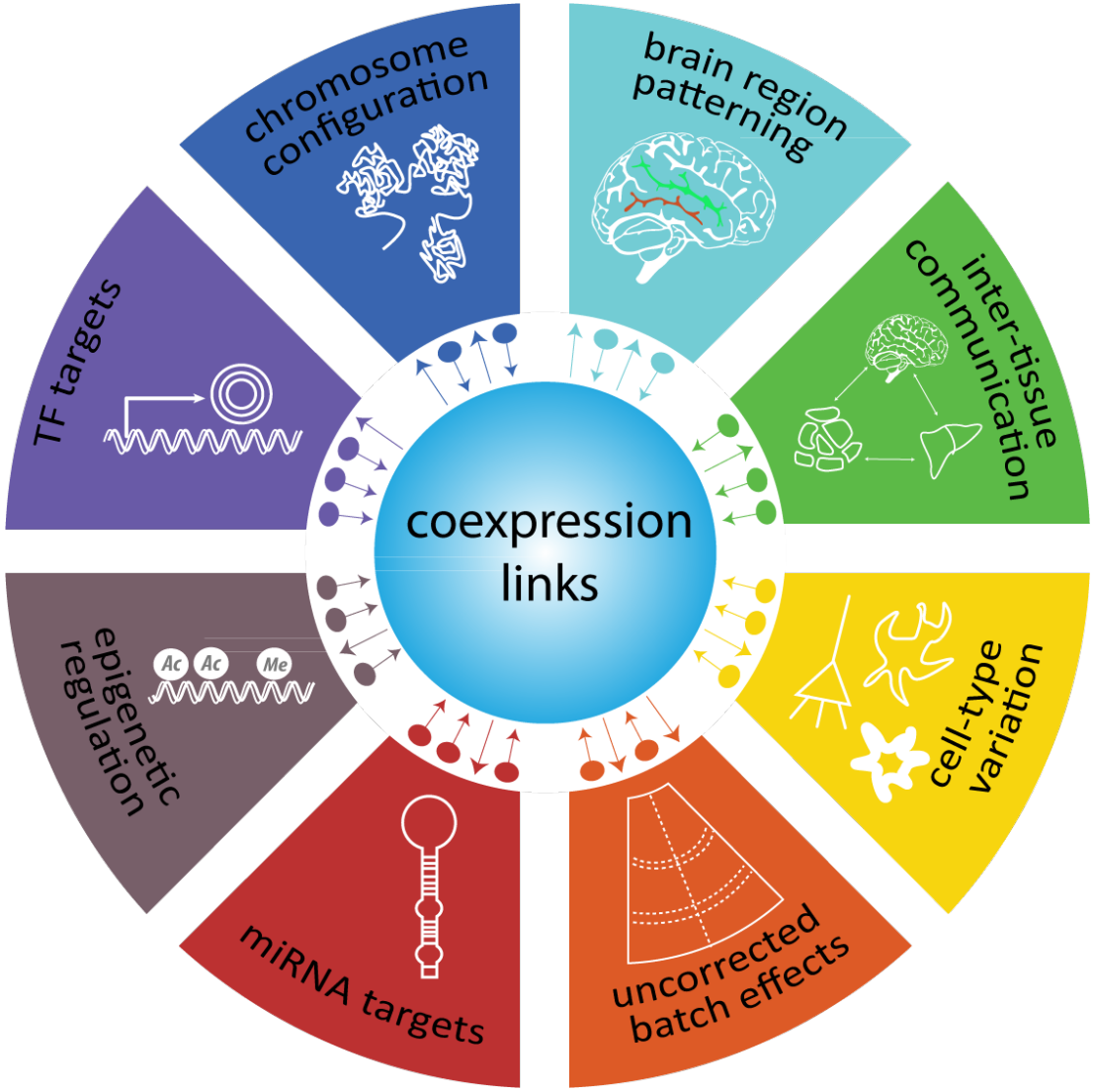
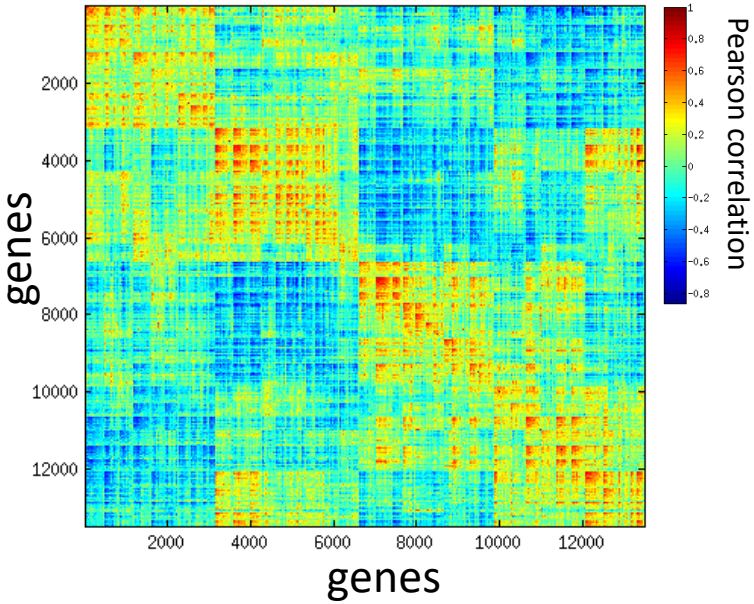


Gene-gene correlation matrix



Results from applying to DLPFC gene expression, n~1200

Data available via radc.rush.edu

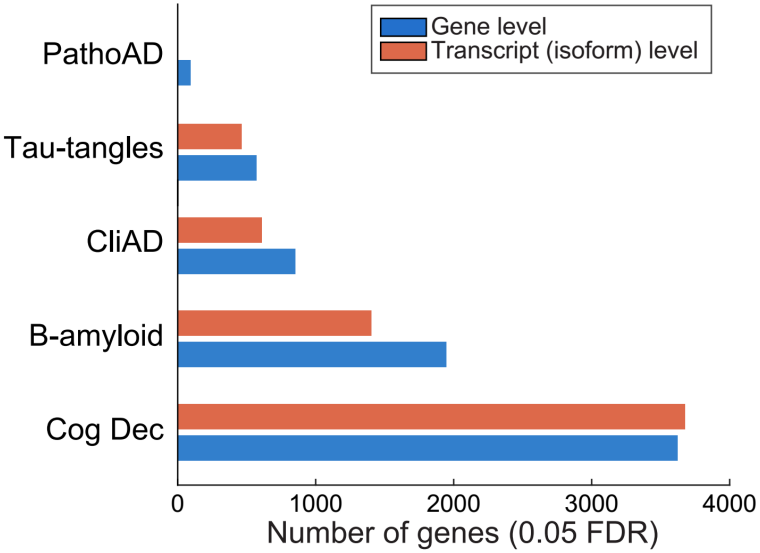
Summarizing RNAseq into molecular systems

24 of 47 (~50%) modules are enriched for biological function (0.05 FDR)

module id	# genes	# enriched functions	Representative function
9	243	112	Regulation of transcription
10	138	10	RNA processing
14	347	93	Mitochondrial part/function
16	352	137	Neuronal/Synapse part
23	251	18	Neuronal/Synapse part
106	489	19	Mitochondrial part/function
107	416	72	Membrane proteins/Neuronal System
109	390	71	Cell cycle damage response/Insulin signaling pathway/Proteasome
110	348	6	Cytoskeleton/protein motor (astrocytes)
111	244	70	Transcription
112	64	59	Cell membrane/Signaling peptide
113	313	307	Metabolism of protein
114	276	17	Immune response (NFKB pathway)
115	232	503	Immune response (IFN response)
116	224	432	Immune response (microglia)
117	409	134	Protein folding/unfolded protein response
118	405	140	Transcription/Protein metabolism/Immune
119	317	58	Transcription
121	403	42	Acetylation/Nucleic binding
123	317	153	Mitochondrial function
126	356	243	Mitochondrial function
187	30	10	Synaptic transmission

Trait associations in 2000 samples

What are the associations of gene expression and AD phenotypes?



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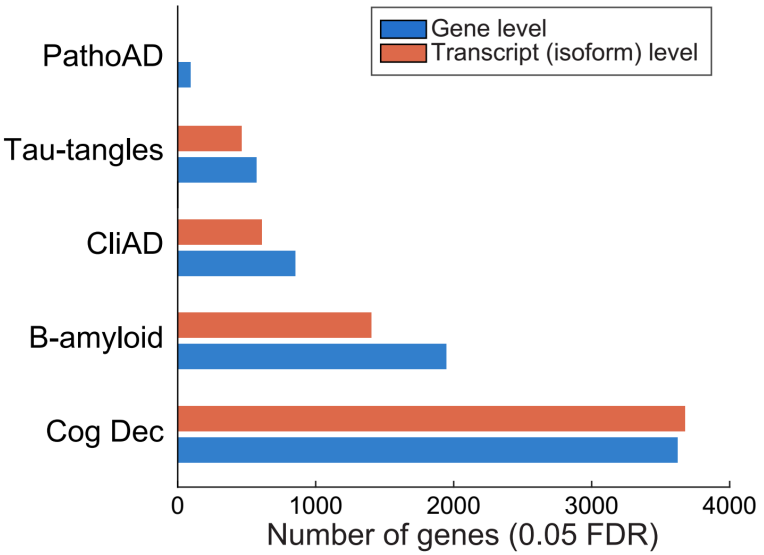

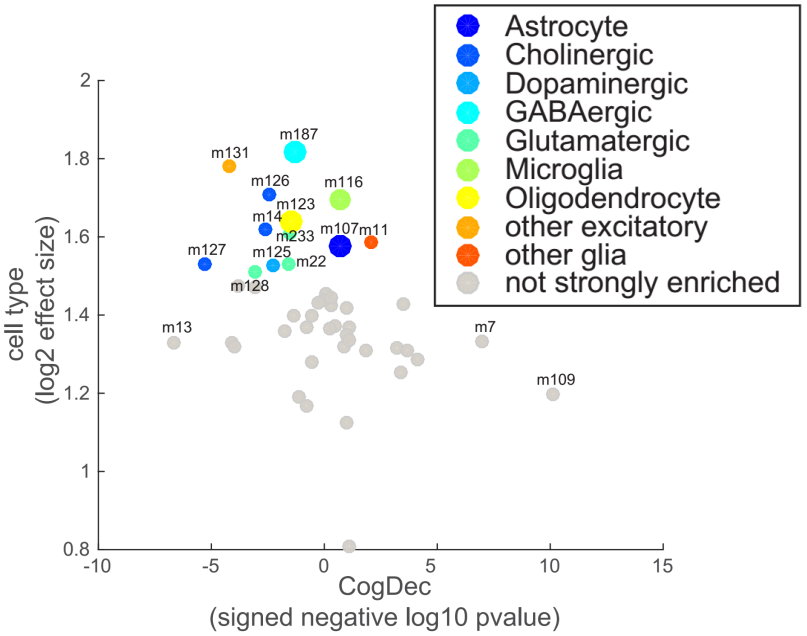

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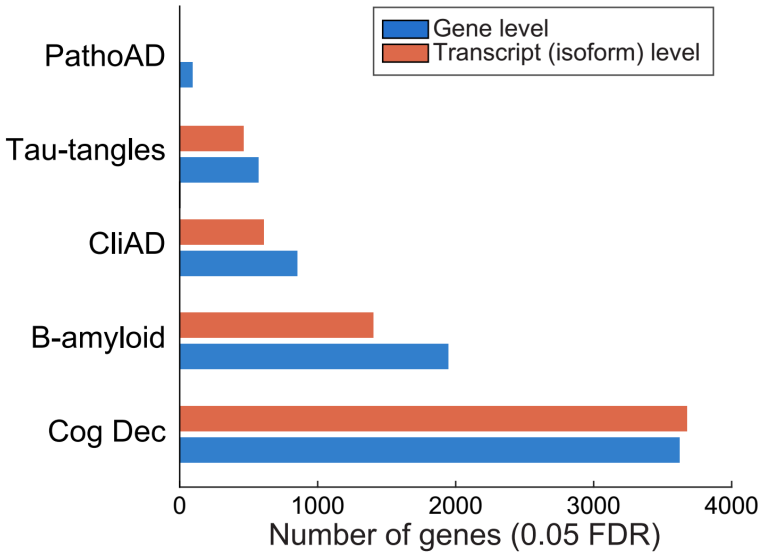

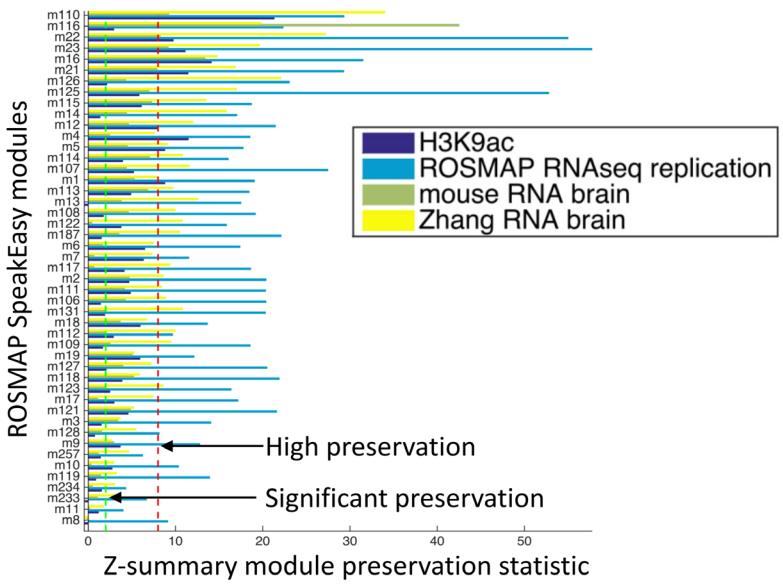

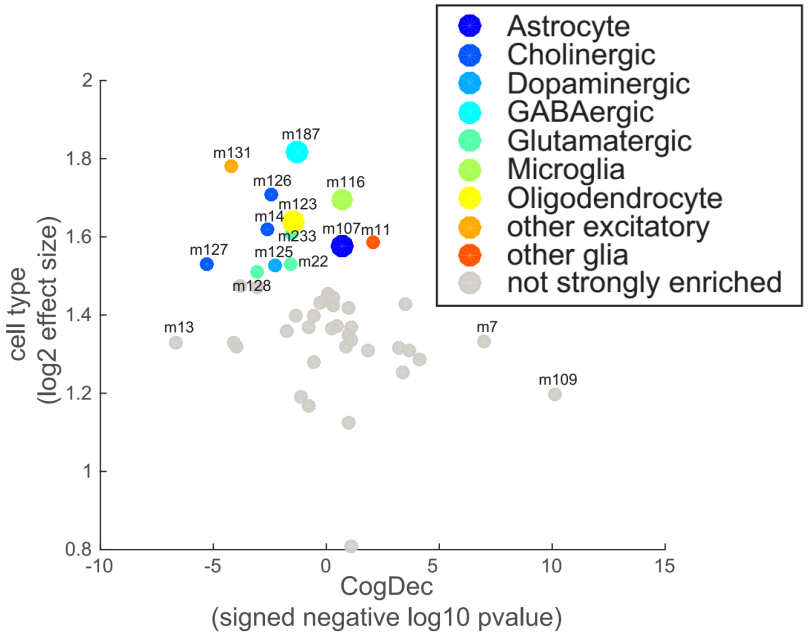

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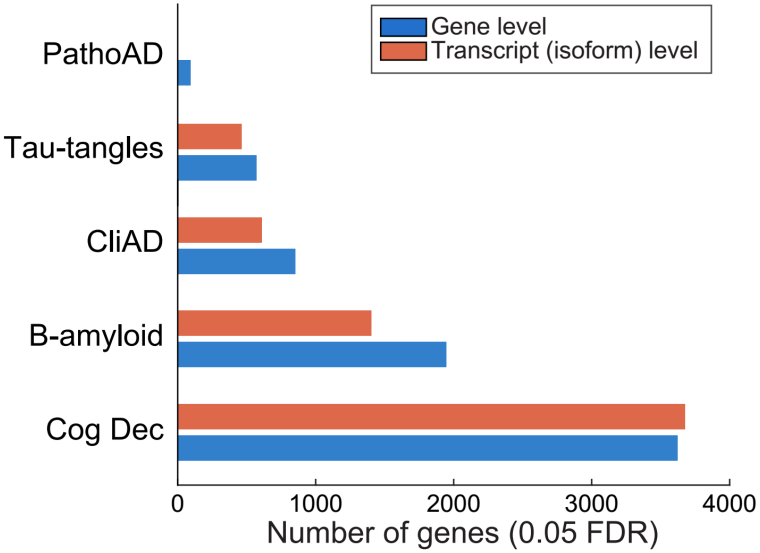

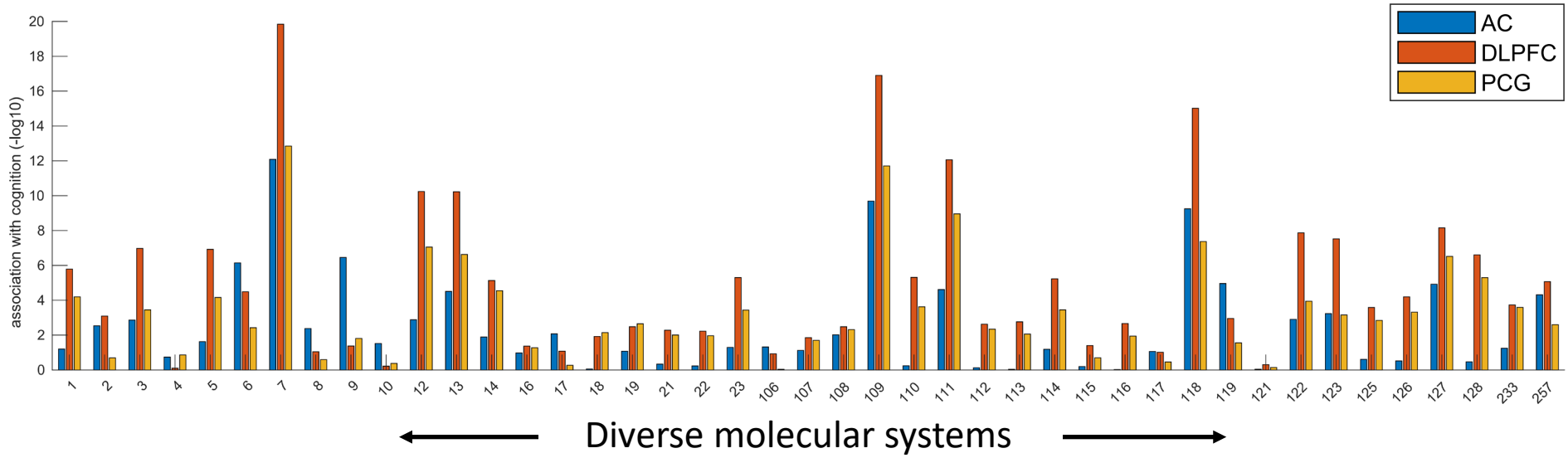

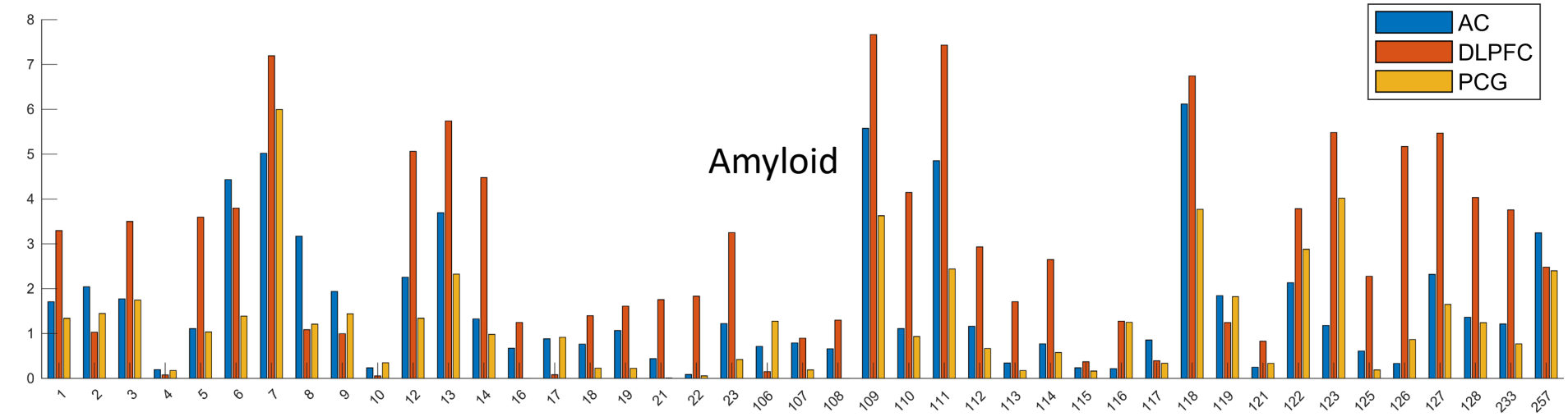
Amyloid
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DLPFC
PCG
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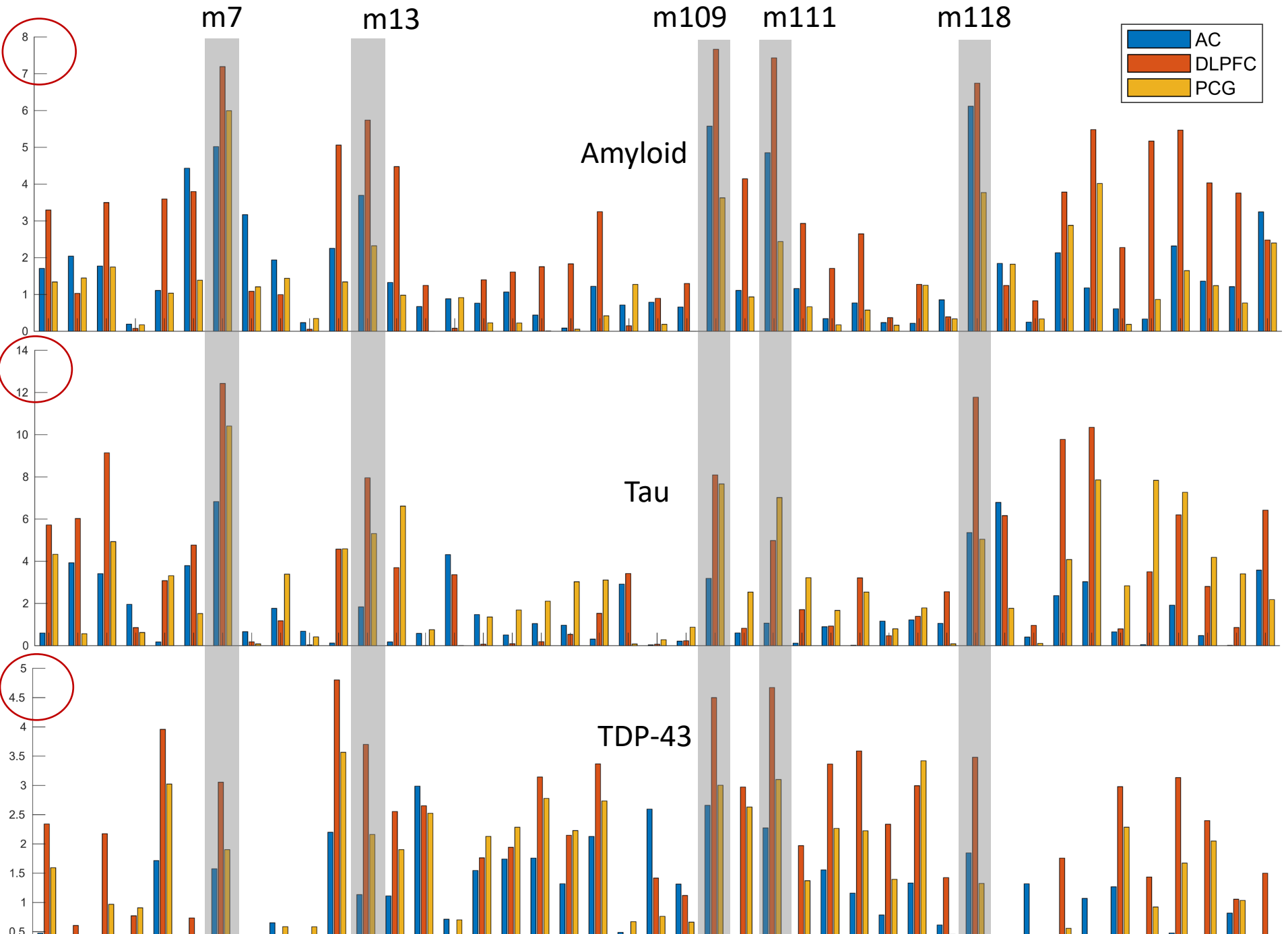
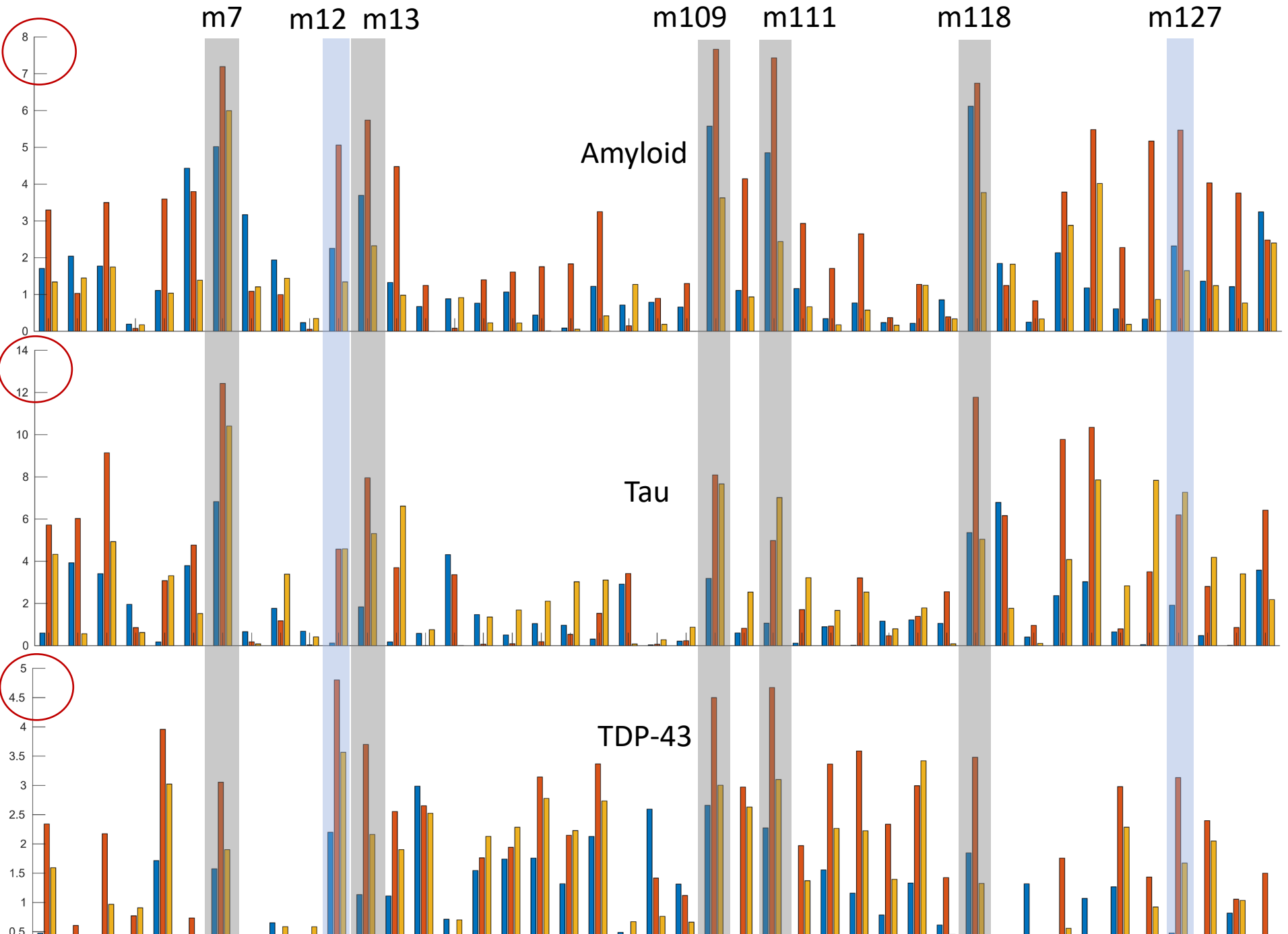

m7
m13
m109
m111
m118
AC
DLPFC
PCG
Amyloid
Tau
TDP-43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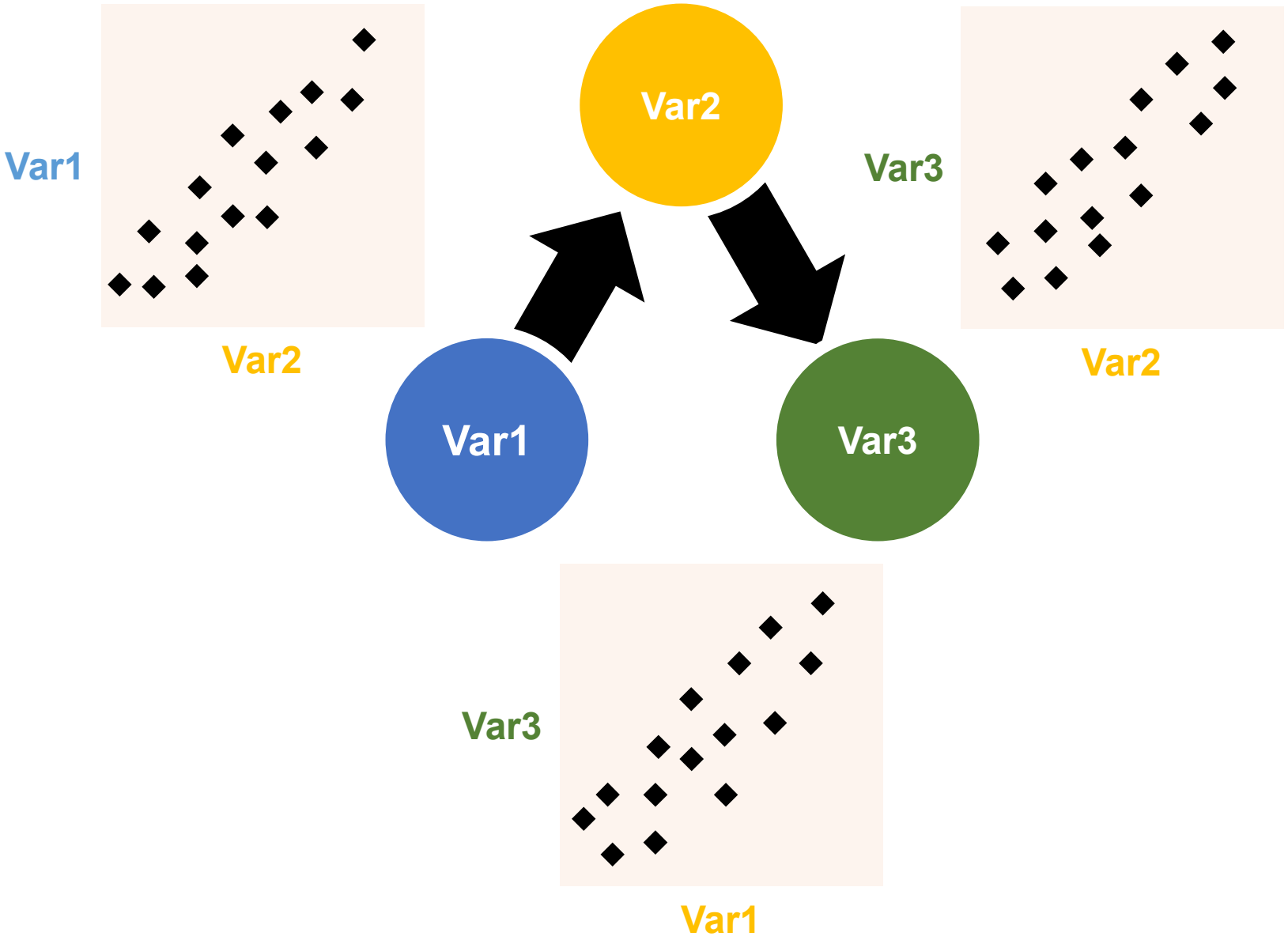
How do we prune out extra links?



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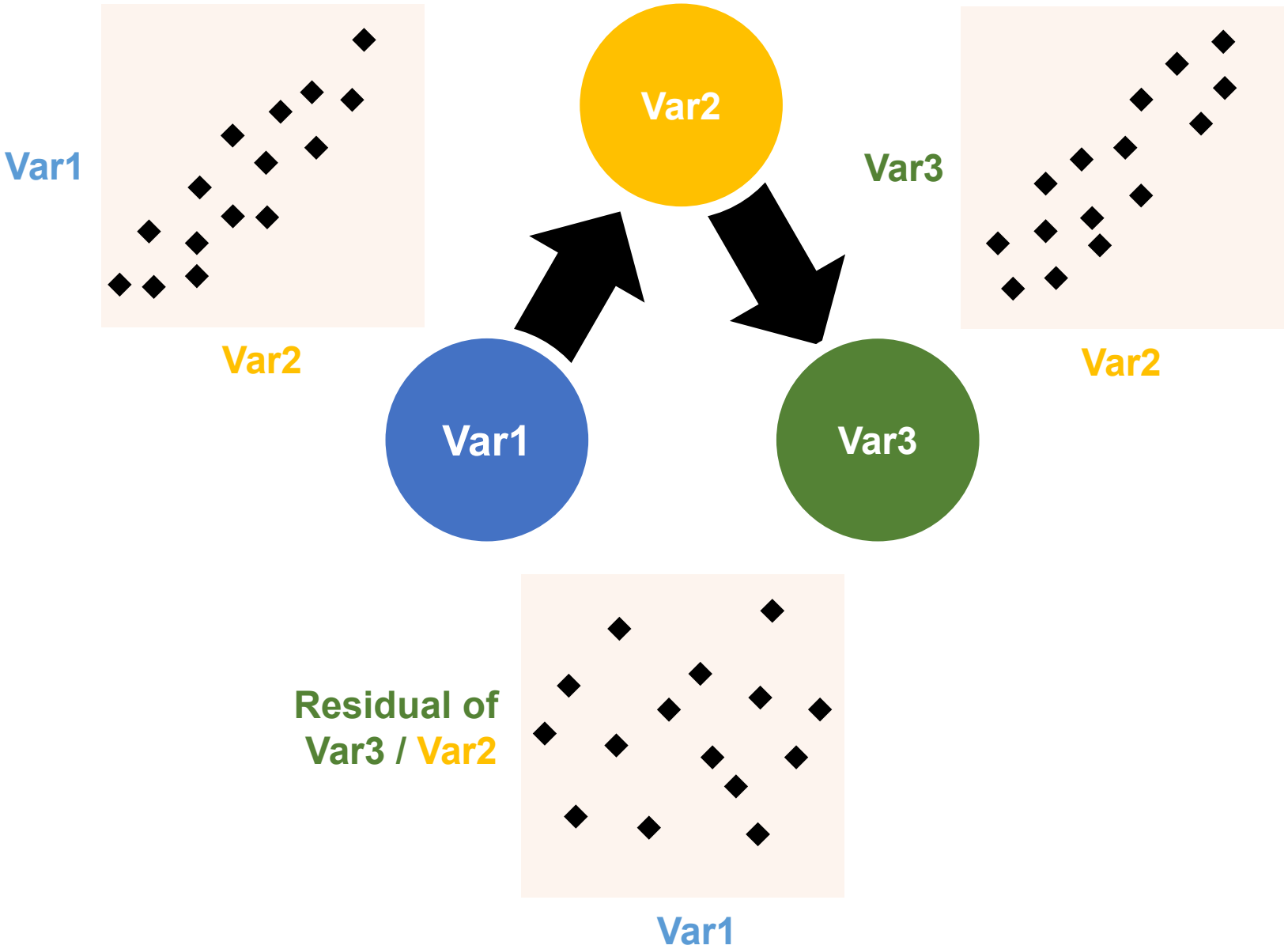
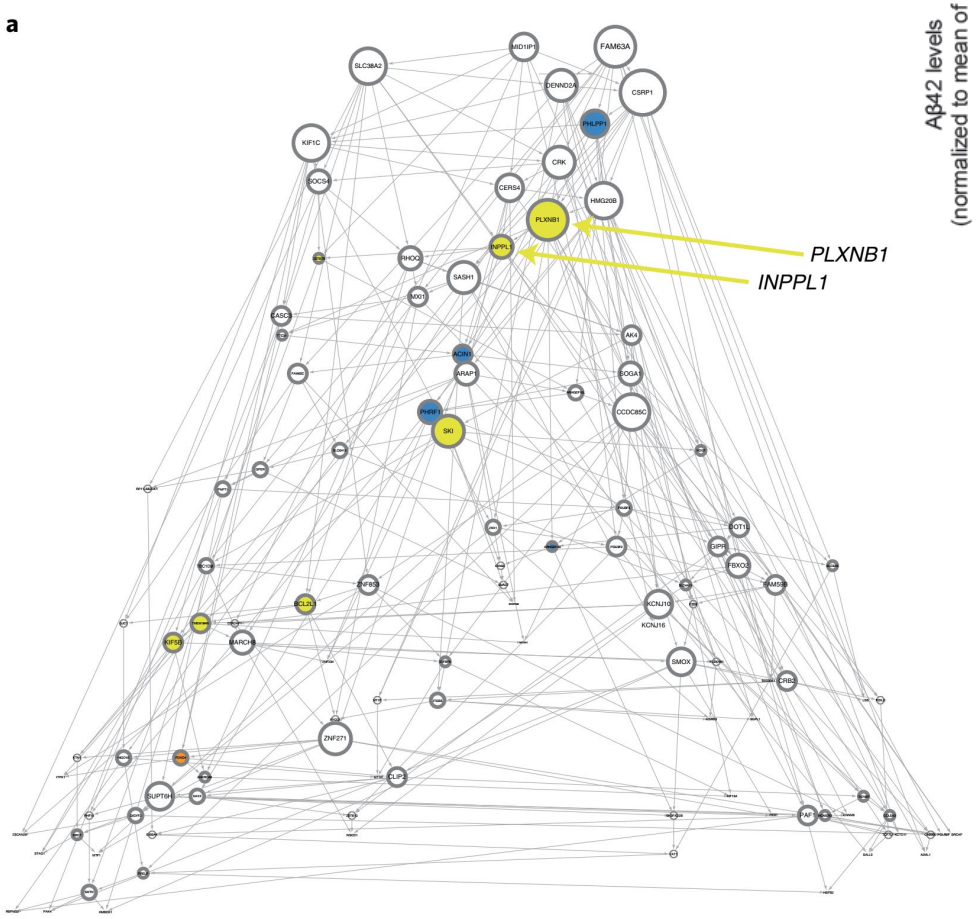
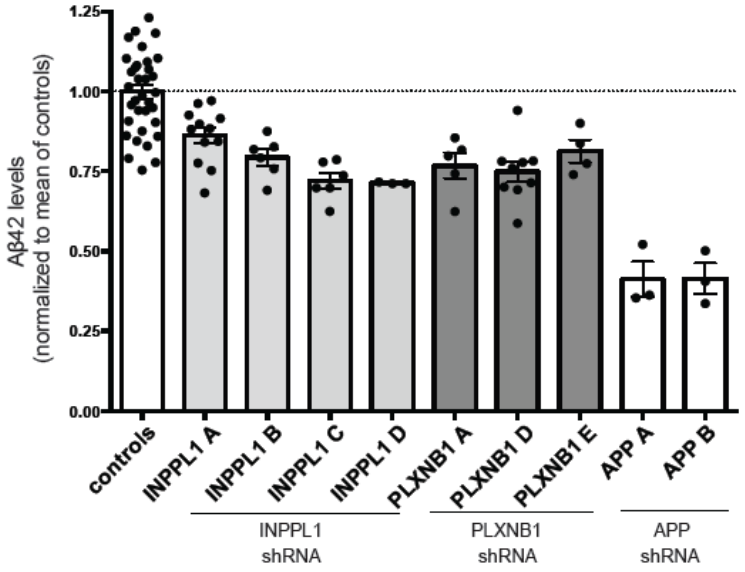
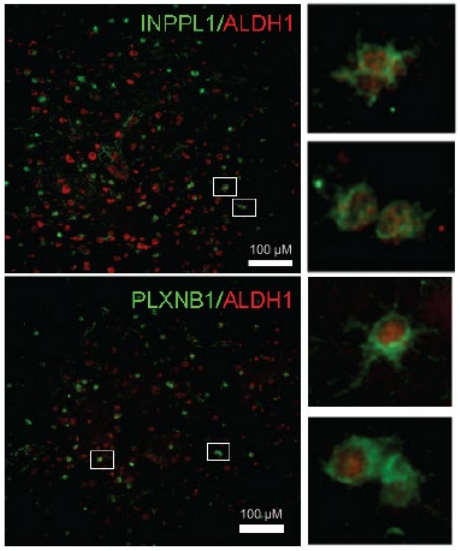


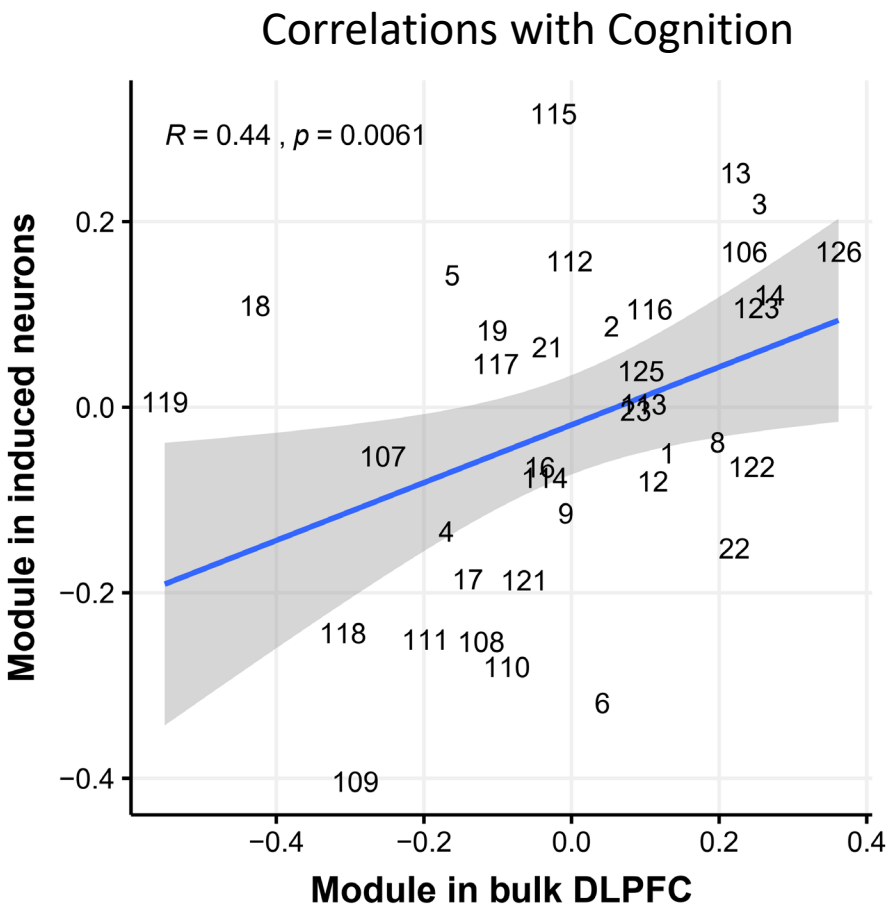
Testing network predictions







Preliminary IPSC Results



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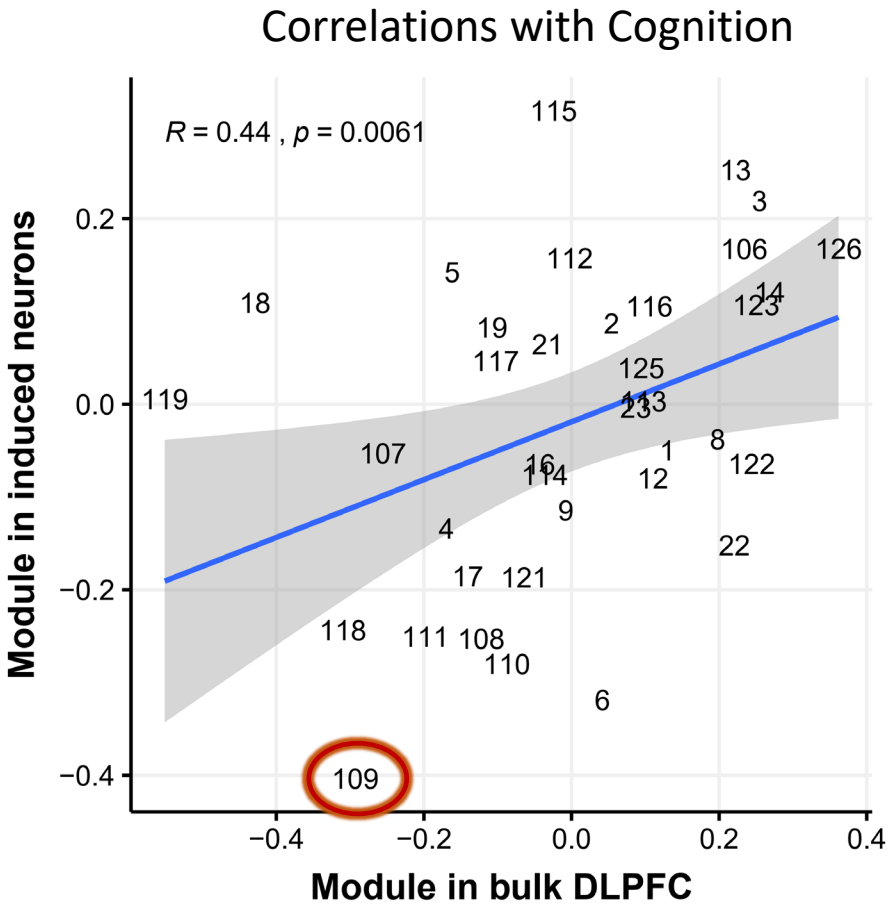
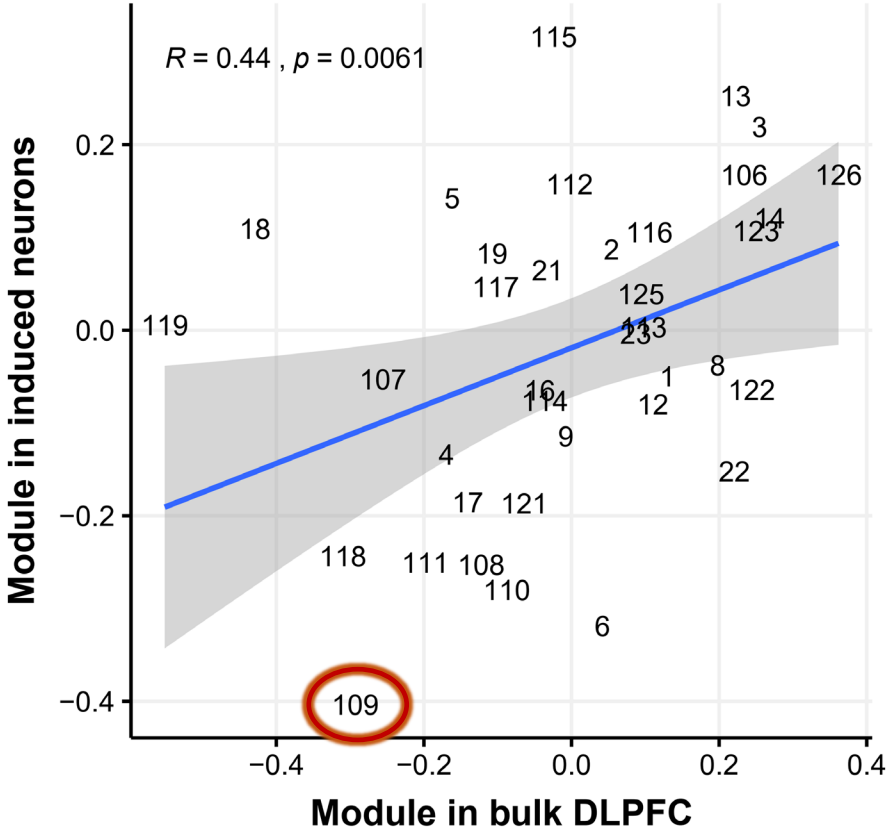


Conclusion: Overall similarity in the disease associations for wide range of molecular systems, in IPSC data

Preliminary IPSC Results

Correlations with Cognition



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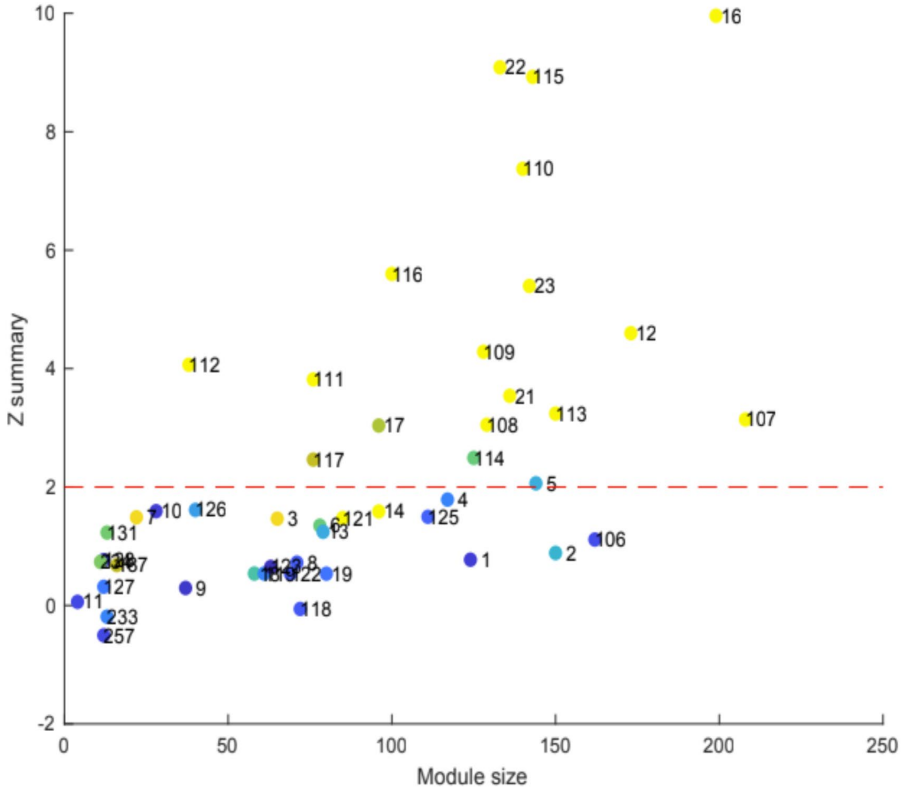
Module structure reproduction



Conclusion: Regulatory structure within many modules is similar in IPSC

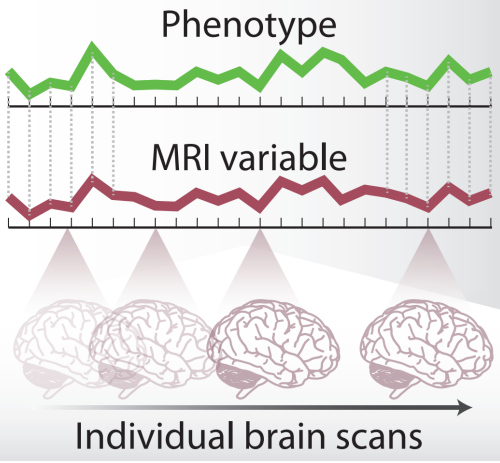
Summary of approach to “imaging-omics”

Previous Studies

Input phenotypes:	Examples:
Cognitive phenotypes	Loneliness
Disease phenotypes	Micro Infarcts
Peripheral expression	*TREM2* levels
Genetic variants	SLC6A4 variants

Brain-phenotype comparison:

Where in the brain do phenotypes and MRI covary?

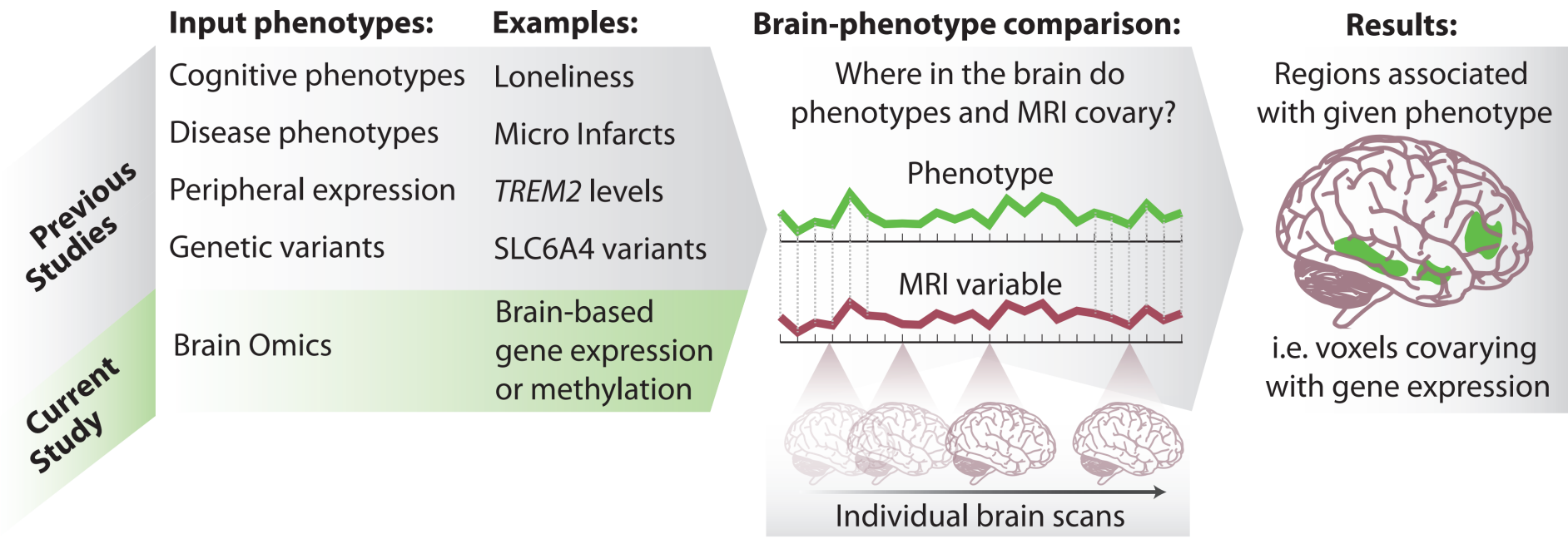


Results:

Regions associated with given phenotype

i.e. voxels covarying with gene expression

Summary of approach to “imaging-omics”

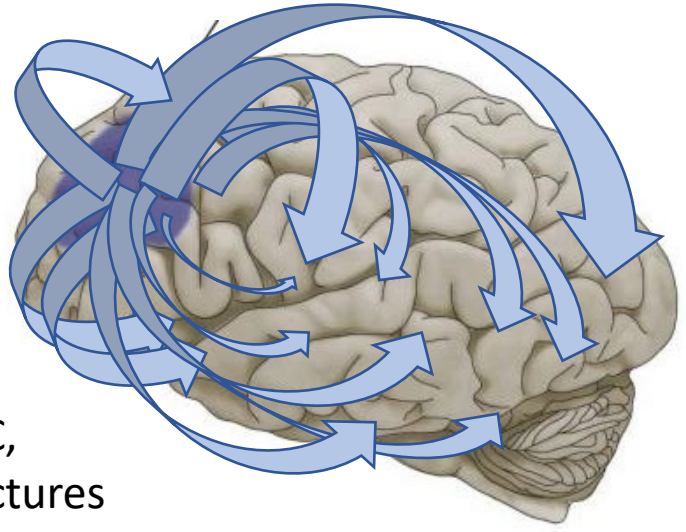


Summary of approach to “imaging-expression”

Using the ROSMAP cohort…

1. We summarize gene expression/methylation into molecular systems
2. Then we relate the activity of molecular systems to brain regions

Molecular system *A*



Molecular systems are measured in DLPFC,
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Summary of approach to “imaging-expression”

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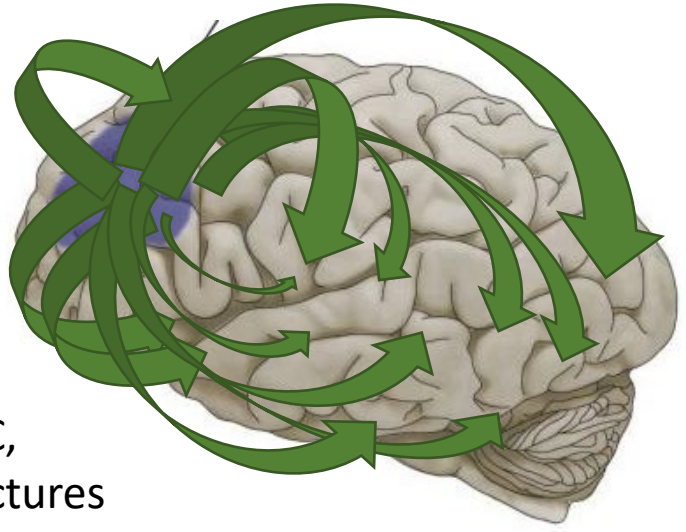
3. Repeat for each molecular system

Molecular system *A*

Molecular system *B*



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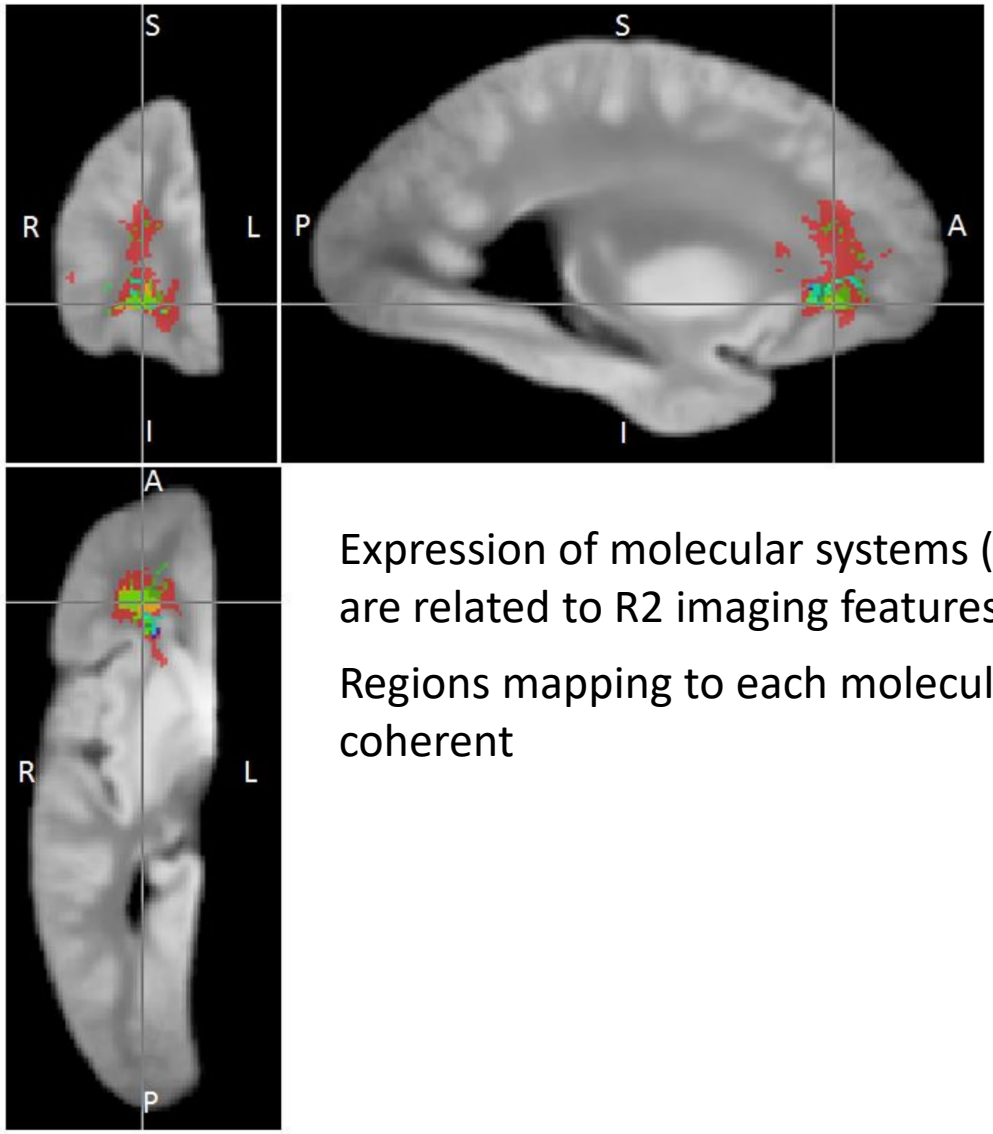
Mapping coexpressed communities to MRI voxels

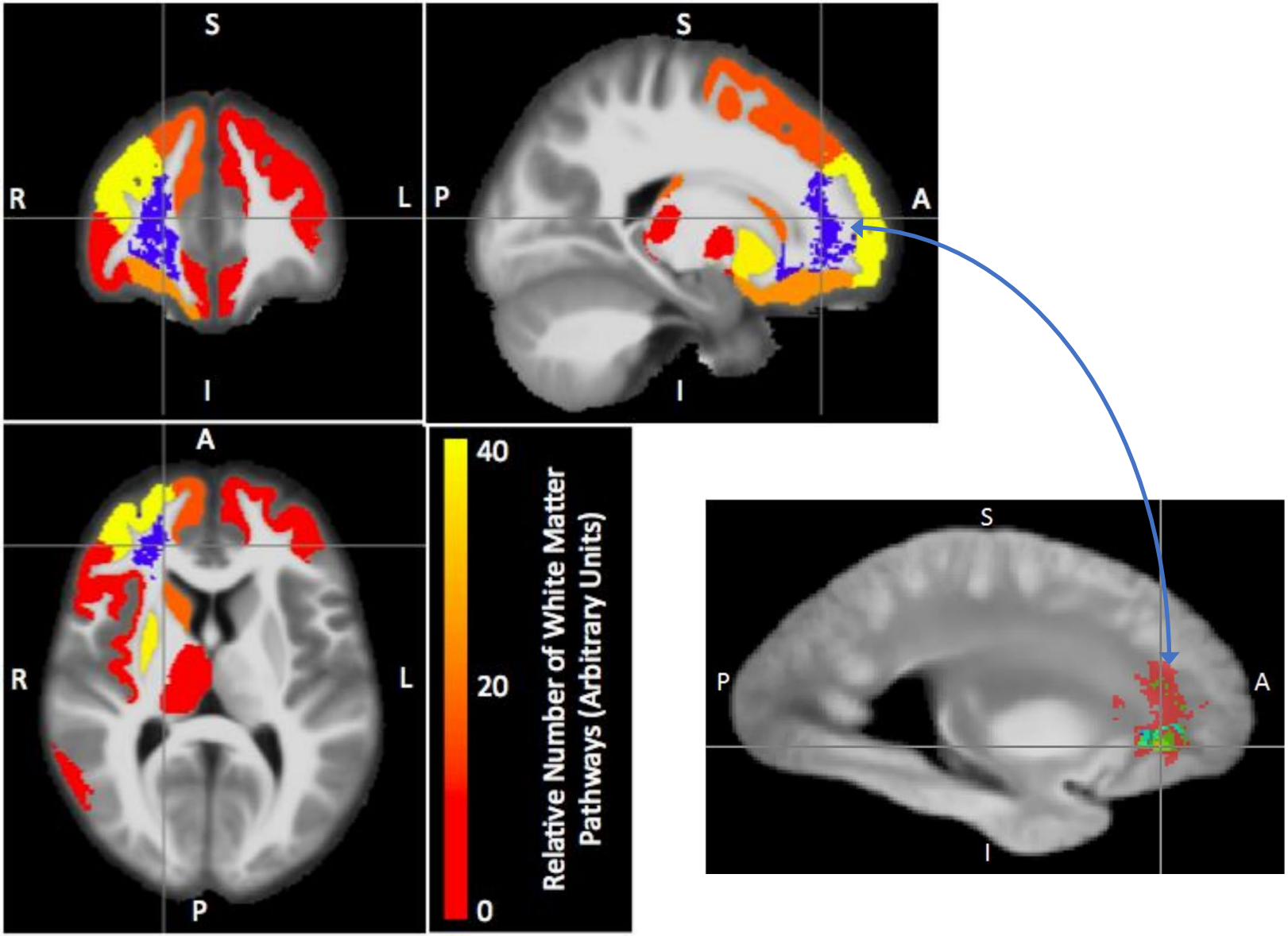


myelination
synaptic transmission
nuclear processes
transcriptional regulation

Expression of molecular systems (measured in DLPFC) are related to R2 imaging features across the brain

Regions mapping to each molecular system are spatially coherent

Tracts associated with MRI correlates of coexpression



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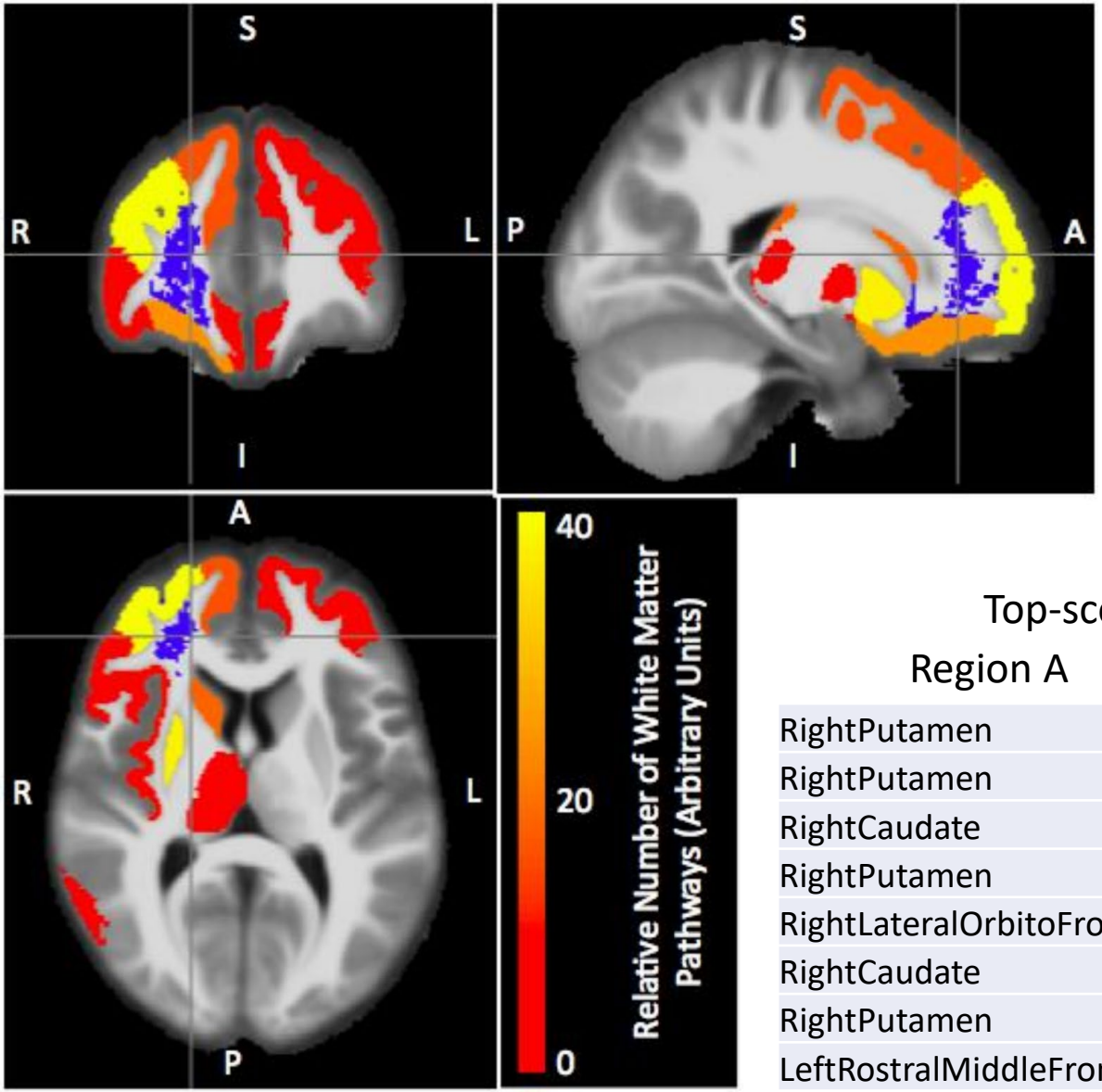
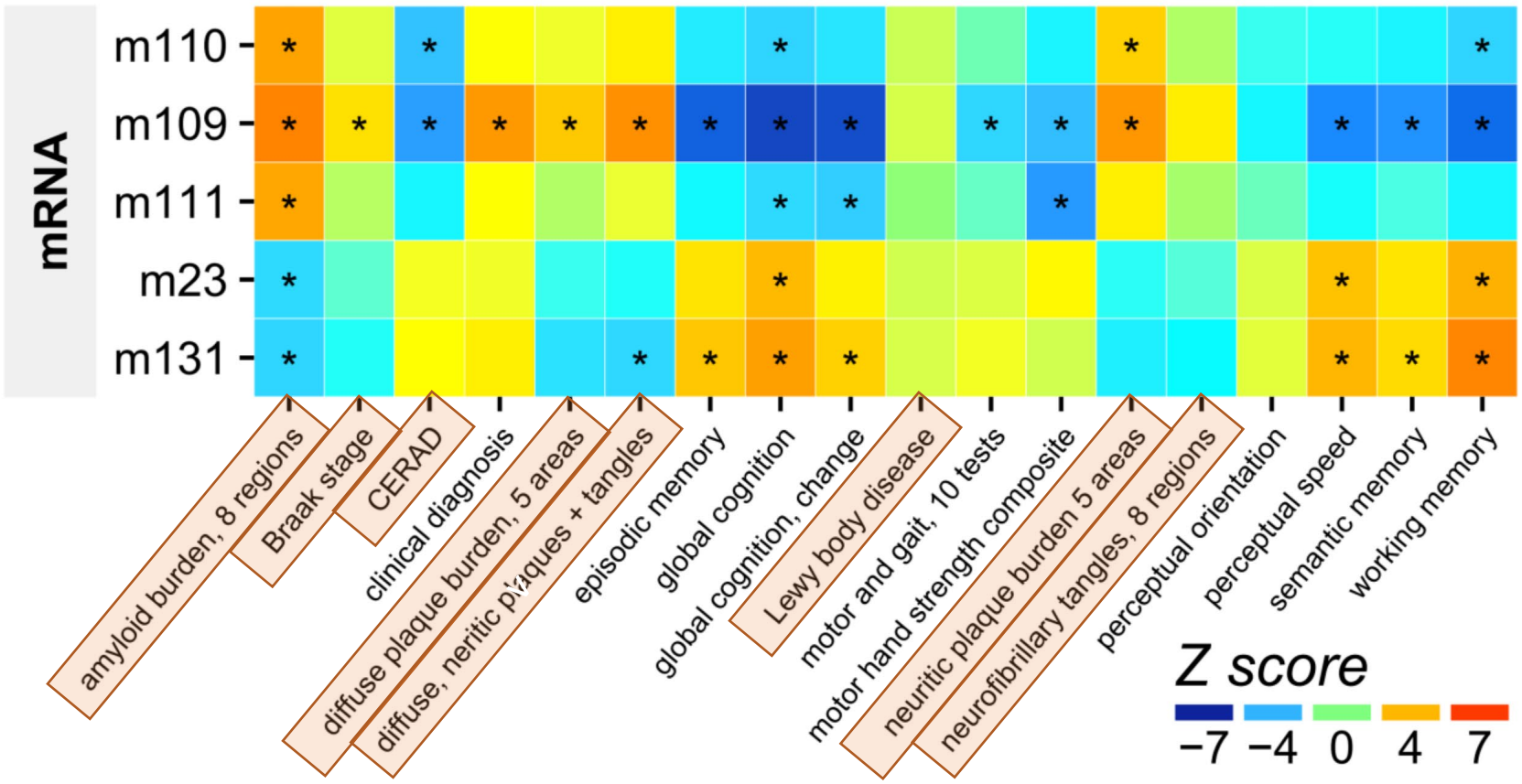


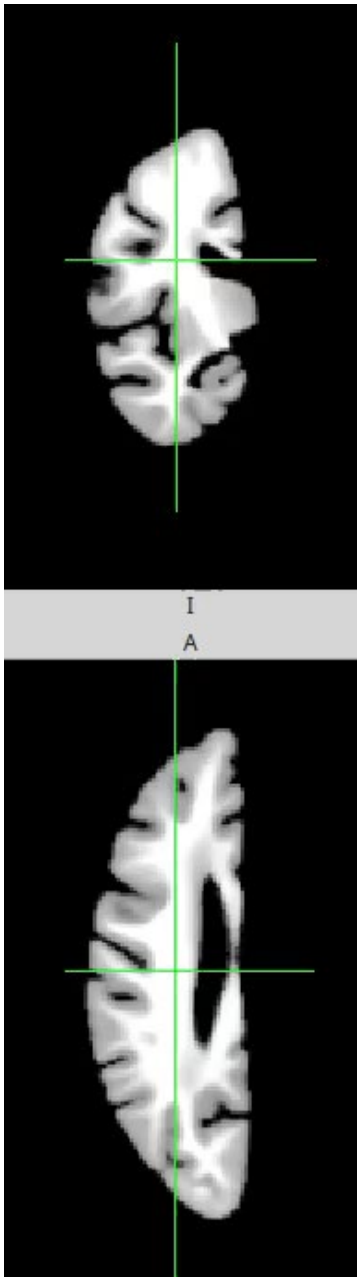
Top-scoring region pairs

Region A	Region B
RightPutamen	RightRostralMiddleFrontal
RightPutamen	RightLateralOrbitoFrontal
RightCaudate	RightRostralMiddleFrontal
RightPutamen	RightSuperiorFrontal
RightLateralOrbitoFrontal	RightInsula
RightCaudate	RightLateralOrbitoFrontal
RightPutamen	RightMedialOrbitoFrontal
LeftRostralMiddleFrontal	RightRostralMiddleFrontal

Trait associations of MRI-associated gene clusters



Mapping anterior caudate modules

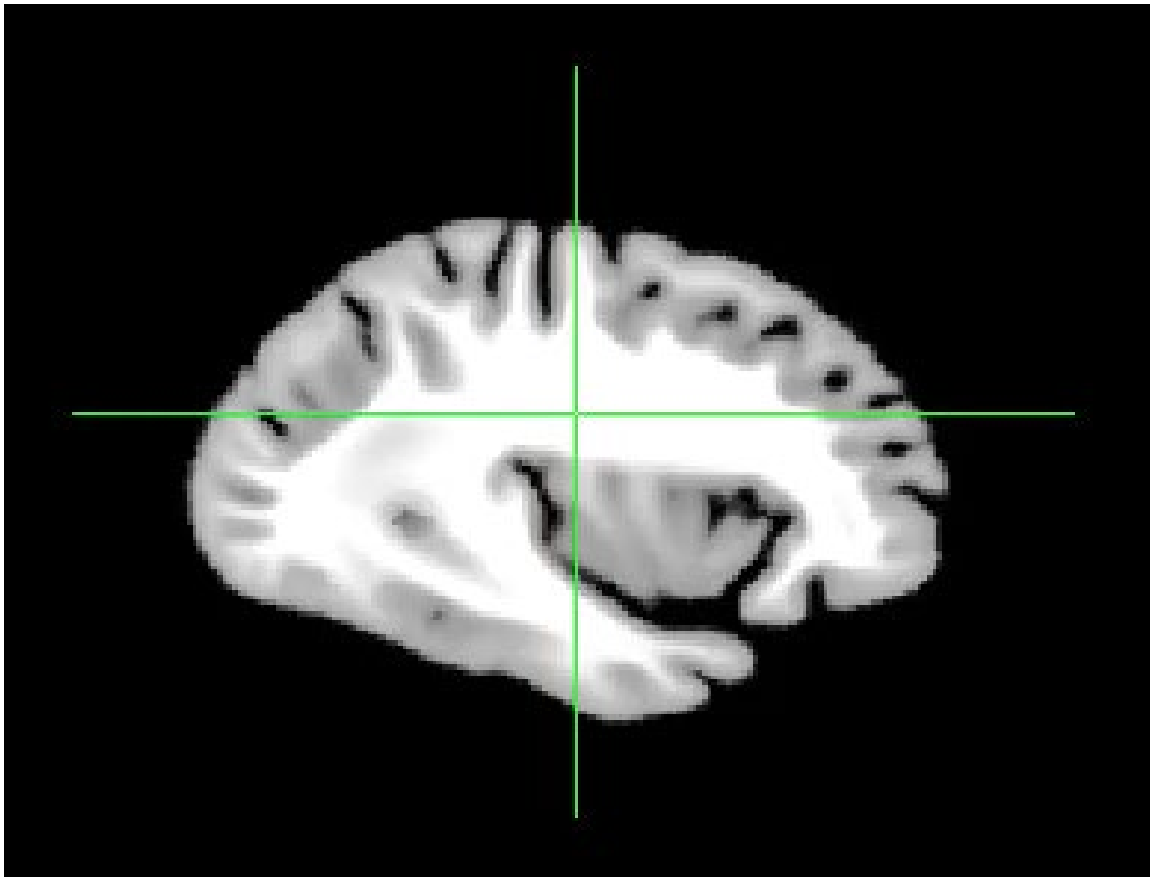


Yellow: ECM (weak)

Blue: Microglia

Red: Mitochondria

Green: Synaptic fx

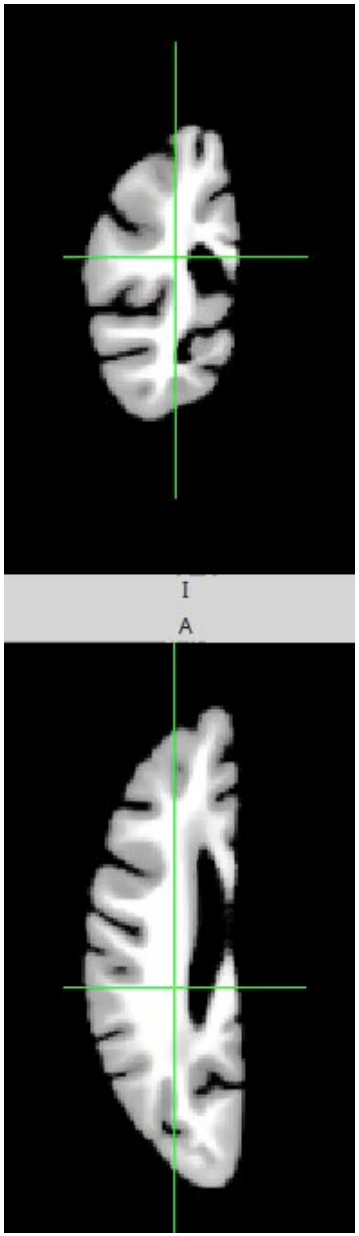


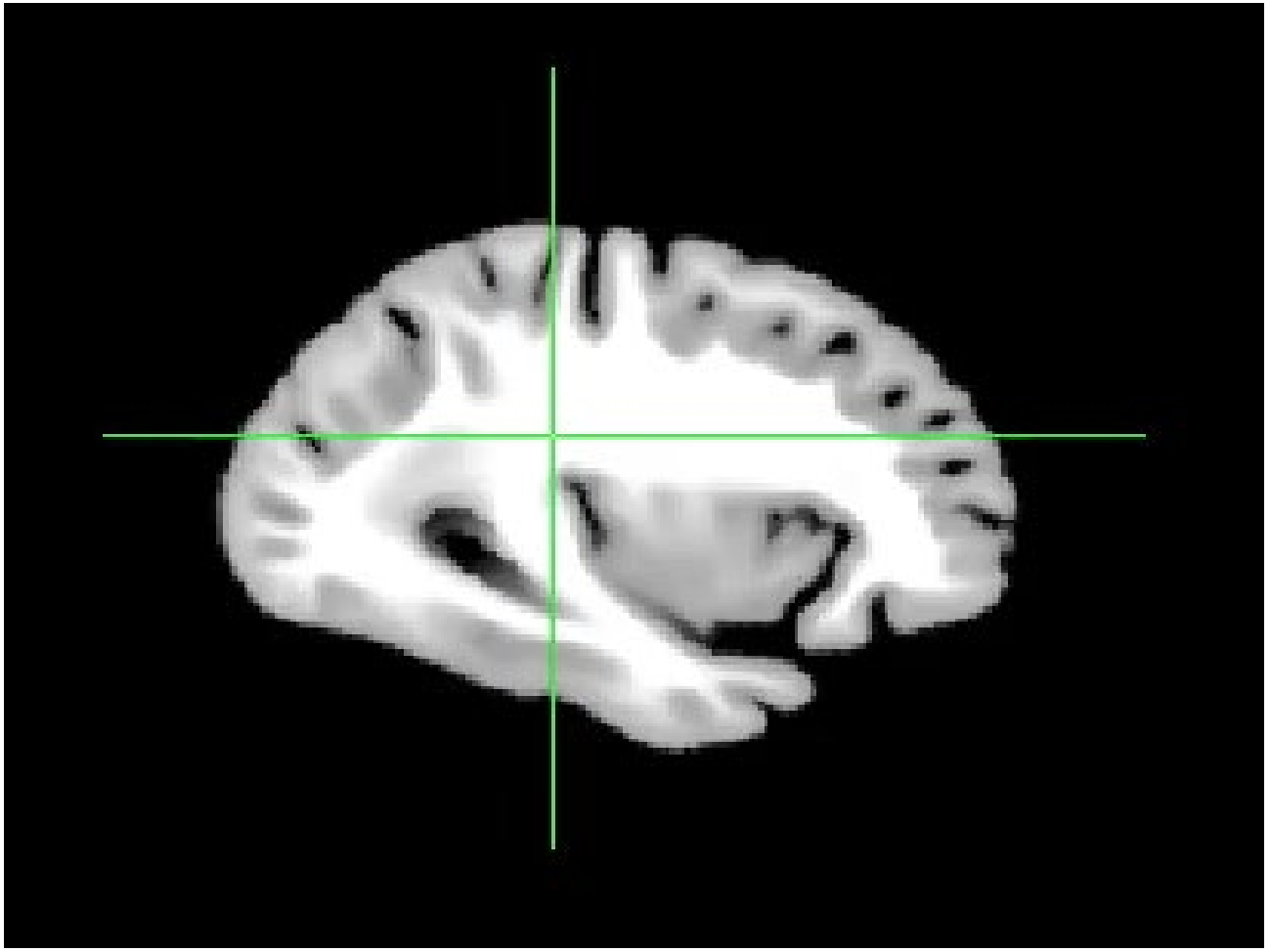
Mapping posterior cingulate modules

Indigo: RNA / m109

Green - unknown

Fusia" response to unfolder protein





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(www.differentialexpression.org - deep neural networks)

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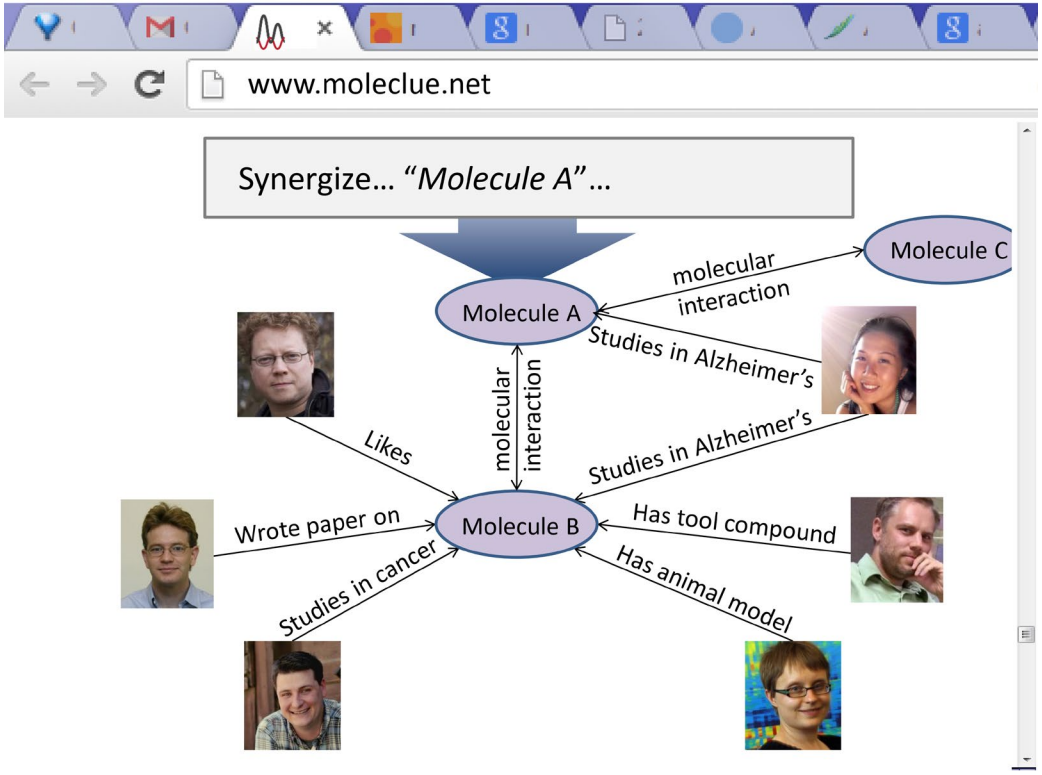

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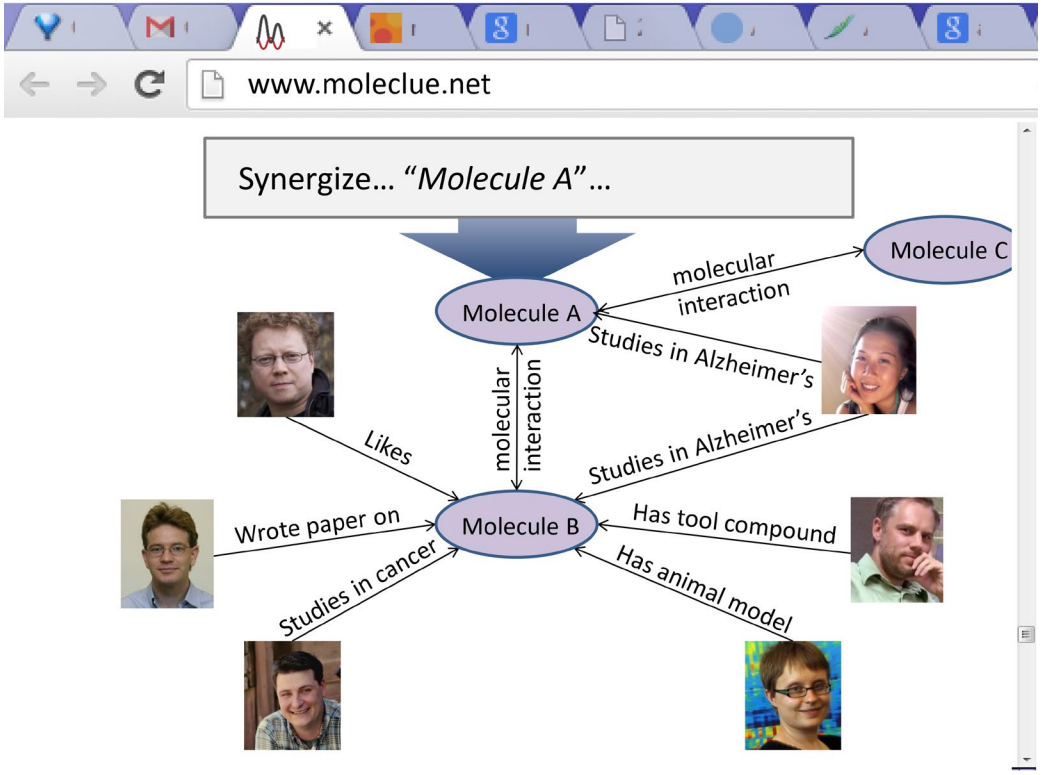


Human Cell Modeling @ Rush
Yanling Wang MD PhD
A different kind of Alzheimer's lab
Testing 100% computational predictions


Yanling Wang, MD PhD
Shinya Tasaki, PhD