Resilience to Alzheimer's in gene networks & neuroimaging

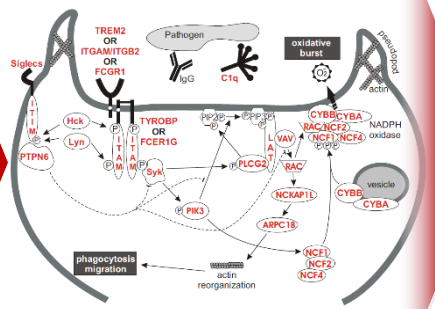
Chris Gaiteri PhD, Rush Alzheimer's Disease Center

How does Alzheimer’s unfold?

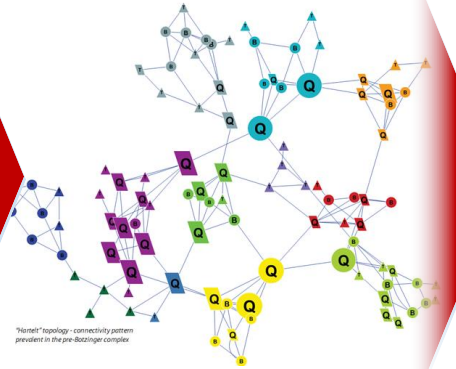
Genetics

Environment

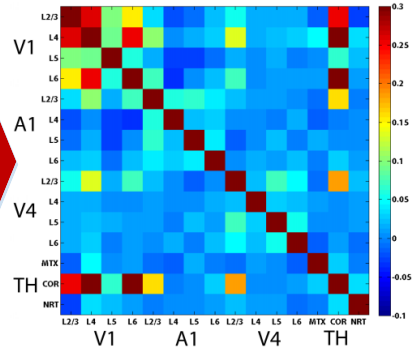
Molecular level



Cellular level



Brain level



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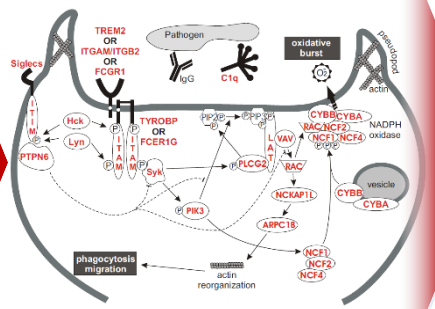

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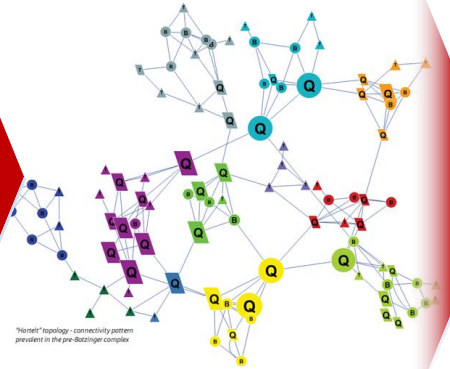

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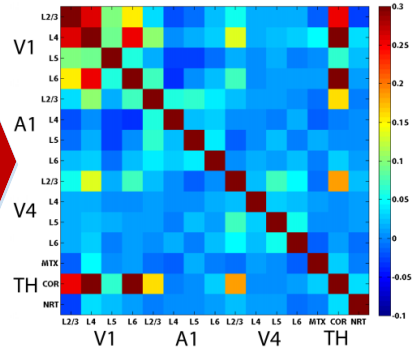


Publications

13k publications
0.3% networks

23k publications
1.7% networks

42k publications
0.6% networks

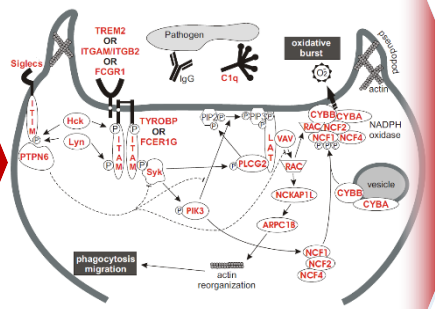
6k publications
4% networks

How does Alzheimer's unfold?

Genetics

Environment

Molecular level



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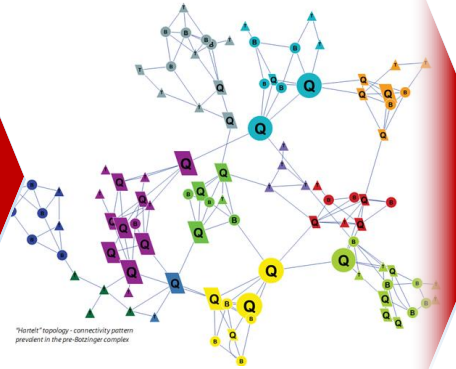

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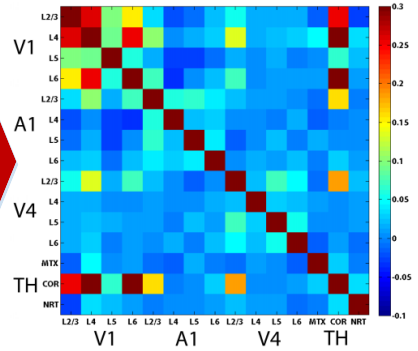

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Cross-scale Alzheimer's publications (n=100)

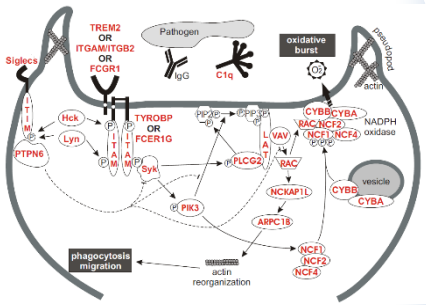
How does Alzheimer's unfold?

Project – molecules & neuroimaging

Genetics

Environment

Molecular level



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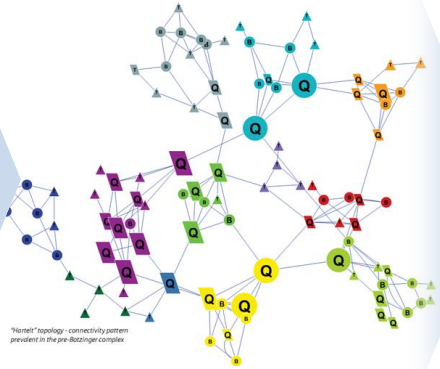

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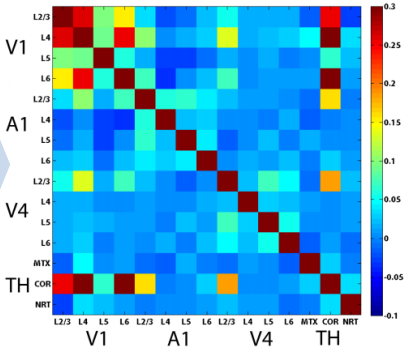
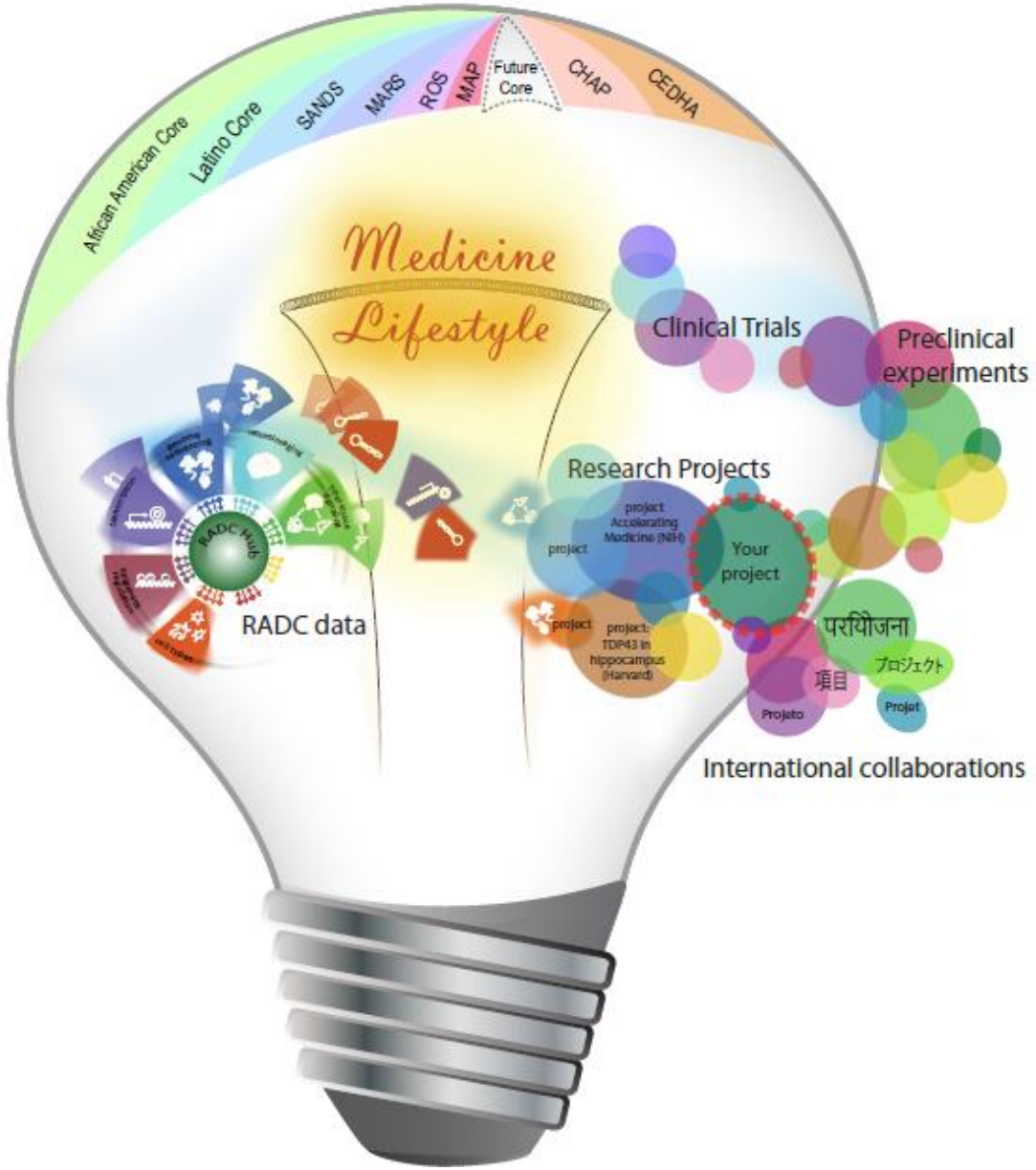


Current and ongoing data sources – ROS and MAP aging studies



Current and ongoing data sources – ROS and MAP aging studies

Omics

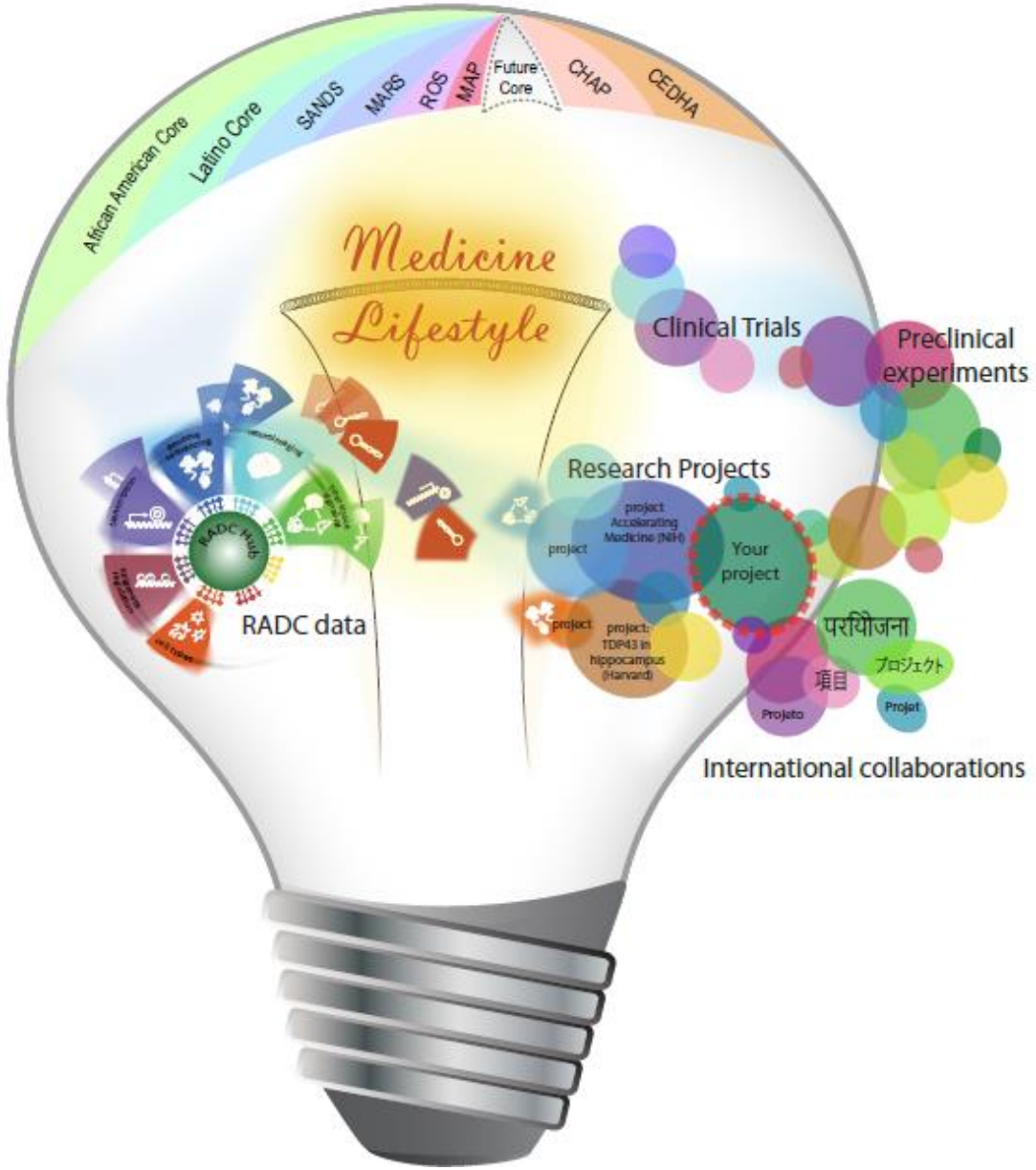
Bulk RNAseq from four brain regions
DNA methylation Illumina 450K (n=700)
50 iPSC lines
- **with Broad**

ATACseq on purified cell types
TMT proteomics (n=300 people, 3 regions)
- **with Emory**

WGS (n=800 individuals)
Metabolomics (n=300+)
- **with Duke**

Histone marks (n=500)
Starting single nucleus / cell RNAseq
- **with Columbia**

Structural and functional neuroimaging (700+)



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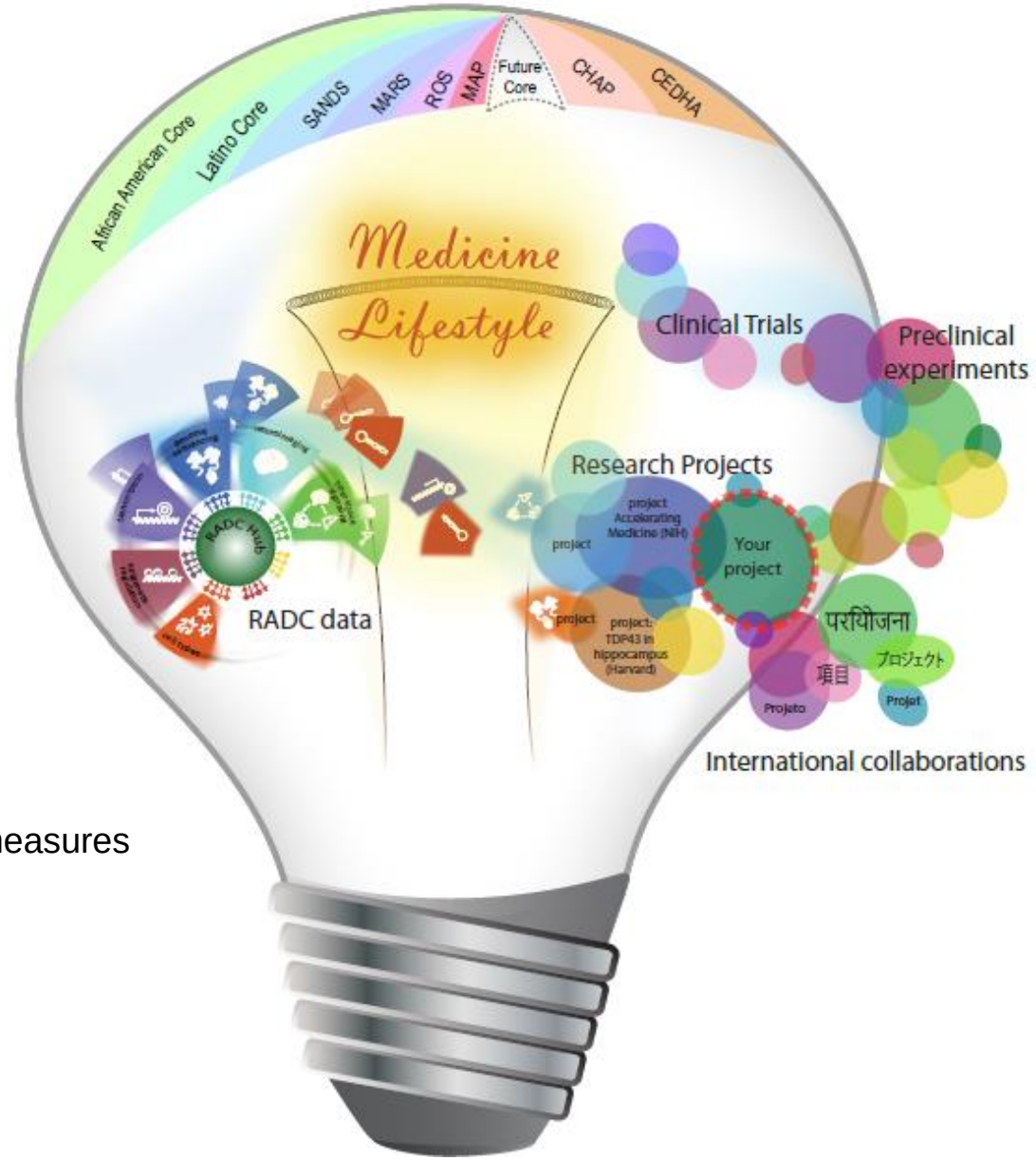
Clinical

19 cognitive domain tests
Personality, psychiatric, motor, sleep & lifestyle measures



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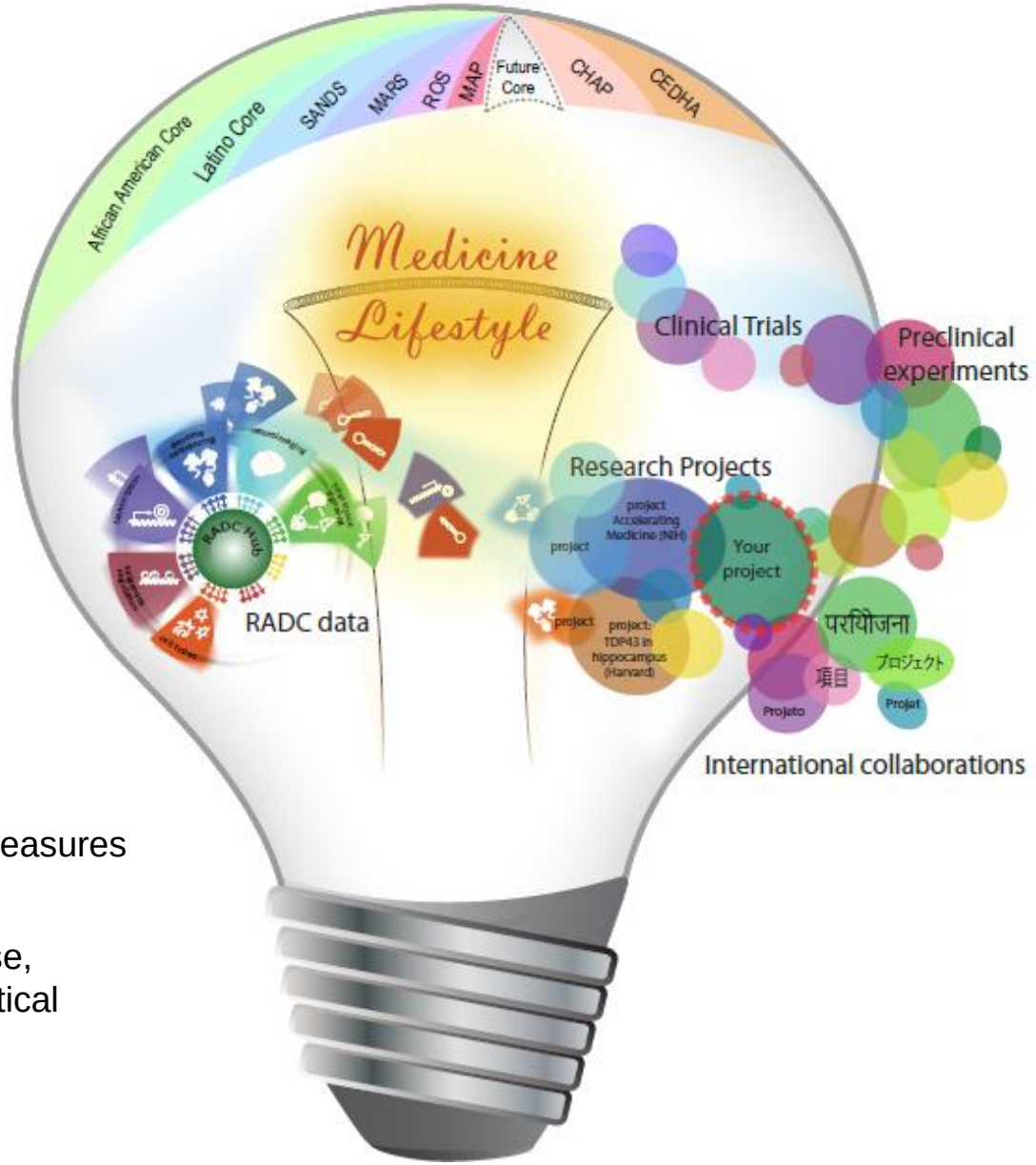
Personality, psychiatric, motor, sleep & lifestyle measures

Pathological

AD pathology (8 regions), cerebrovascular disease, hippocampal sclerosis, Nigral, limbic, and neocortical Lewy bodies, TDP-43 pathology



Data access – radc.rush.edu

RADC Research Resource Sharing Hub

Log In

The Rush Alzheimer's Disease Center (RADC), one of 29 Alzheimer's disease (AD) Research Centers across the country designated and funded by the National Institute on Aging (NIA), is dedicated to supporting research about the cause, treatment, and prevention of AD, other dementias, and a range of other common chronic conditions of aging. The many RADC studies generate an enormous variety of unique data and biospecimens to support this effort. RADC faculty and staff are committed to sharing these resources with the wider aging and AD research community to accelerate the pace at which new knowledge is created for the treatment and prevention of dementia and other age-related chronic neurologic conditions, and have distributed data across the United States and the world.

The **RADC Research Resource Sharing Hub** was specifically designed to help you, the non-RADC investigator, navigate the complex data and biospecimens available for sharing, and to assist you in identifying data and biospecimens that you can use to support your own projects. We invite you to explore the site, see what is available, and submit your data and/or biospecimen request.

—David A. Bennett, MD, Director of RADC

Browse Documentation

Learn about RADC cohort studies through enrollment and autopsy timelines, and study design papers. Explore organized categories of available data such as omics, cognitive assessments, and neuropathology. Search documentation of variables and data collection procedures.

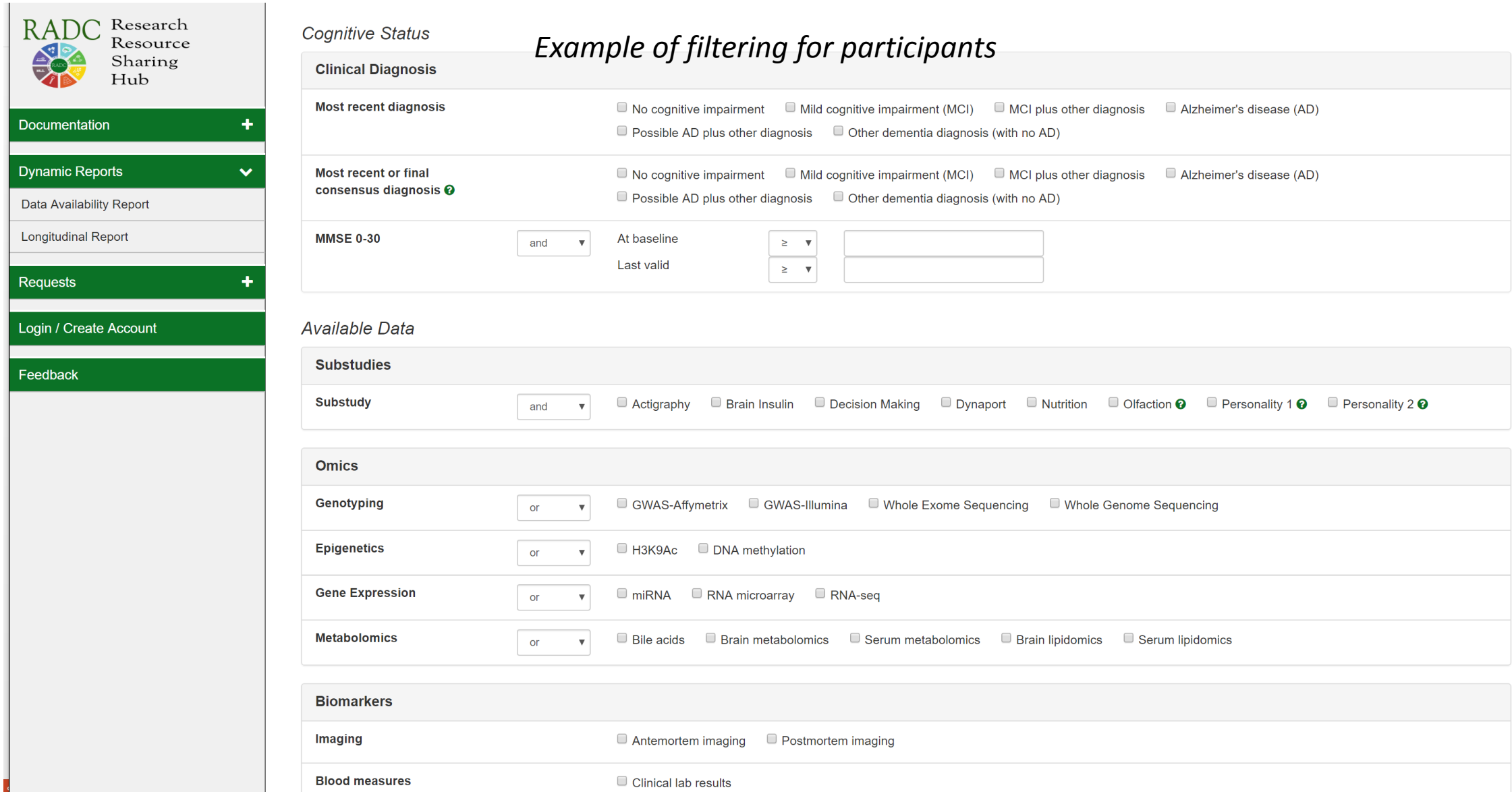
Query Frequency Reports

Generate reports on participant frequency for selected criteria, broken down by demographics. Use the Data Availability Report to examine RADC data and biospecimen availability and determine how available resources match a project's requirements. Use the Longitudinal Report to examine participant frequency across multiple waves of assessments.

Request Data/Specimens

Submit a request for data, biospecimens, or personal identifiers. Learn about the request submission, review, and distribution processes including requirements for material transfer and data use agreements.

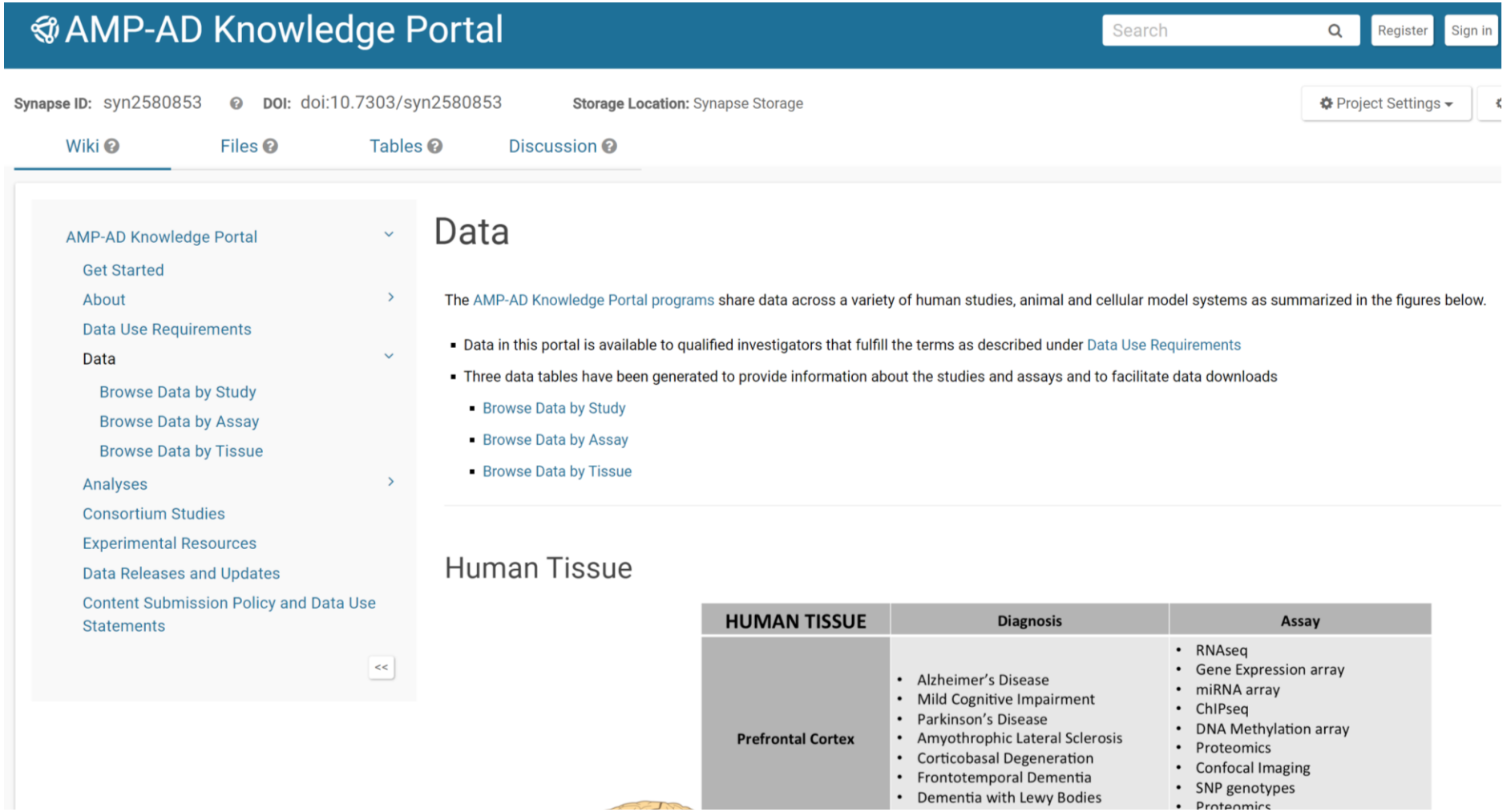
Data access – radc.rush.edu



Find data subsets of interest, and wide range of clinical and pathological measures

Data access – synapse.org

Synapse.org/ampad

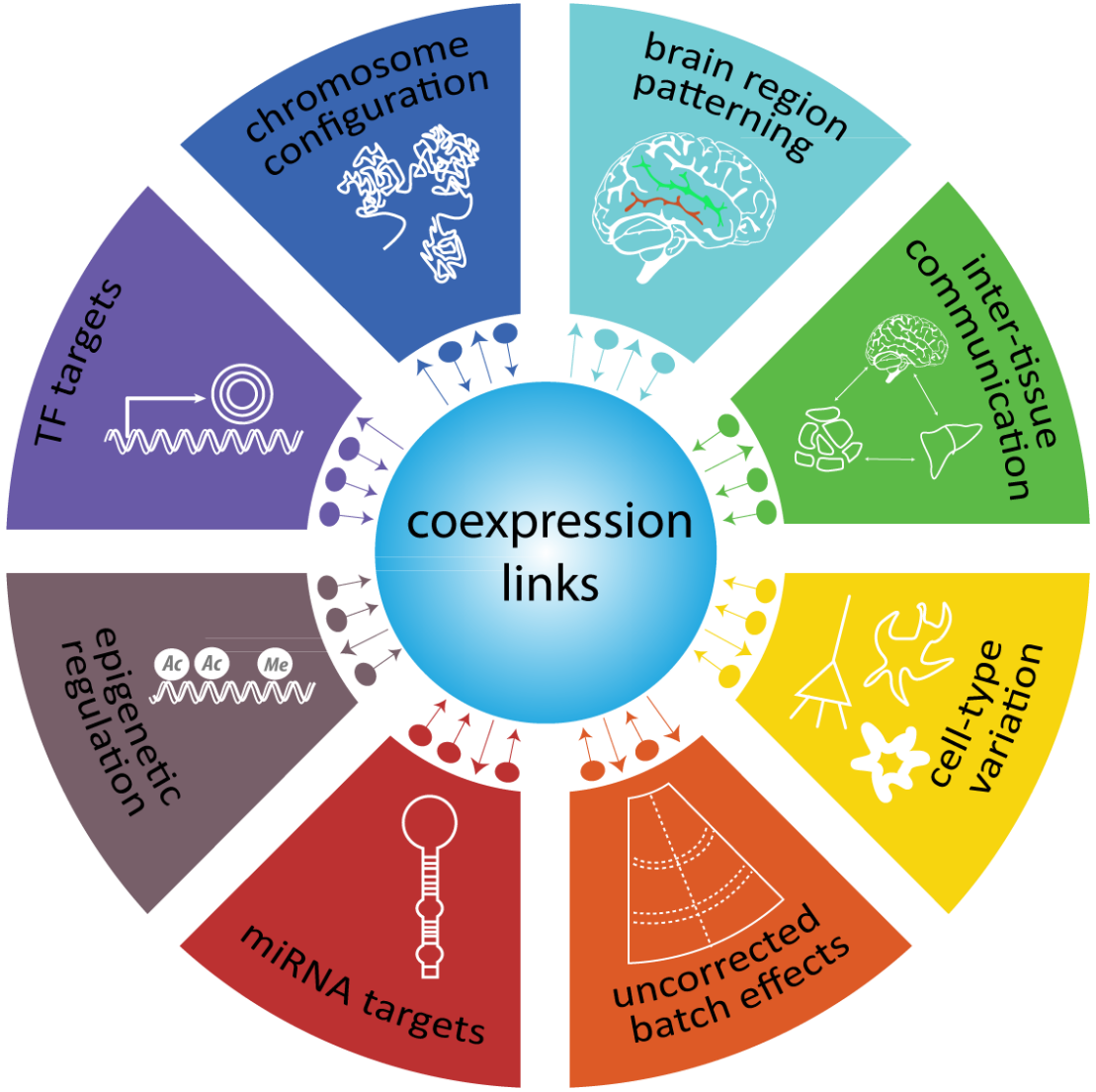


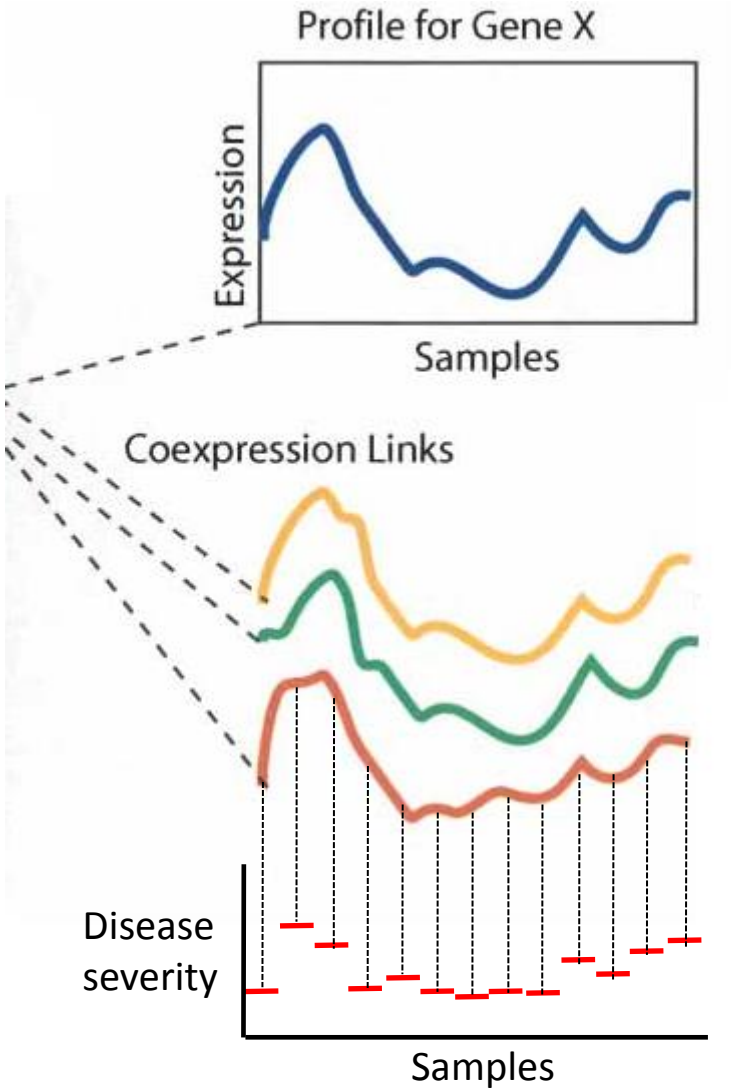
ROSMAP omics, and other cohort omics all available here

Current study uses gene expression, DNA methylation, post-mortem imaging

Foundation of expression-imaging: sources of coexpression

Several mechanisms generate coexpression networks





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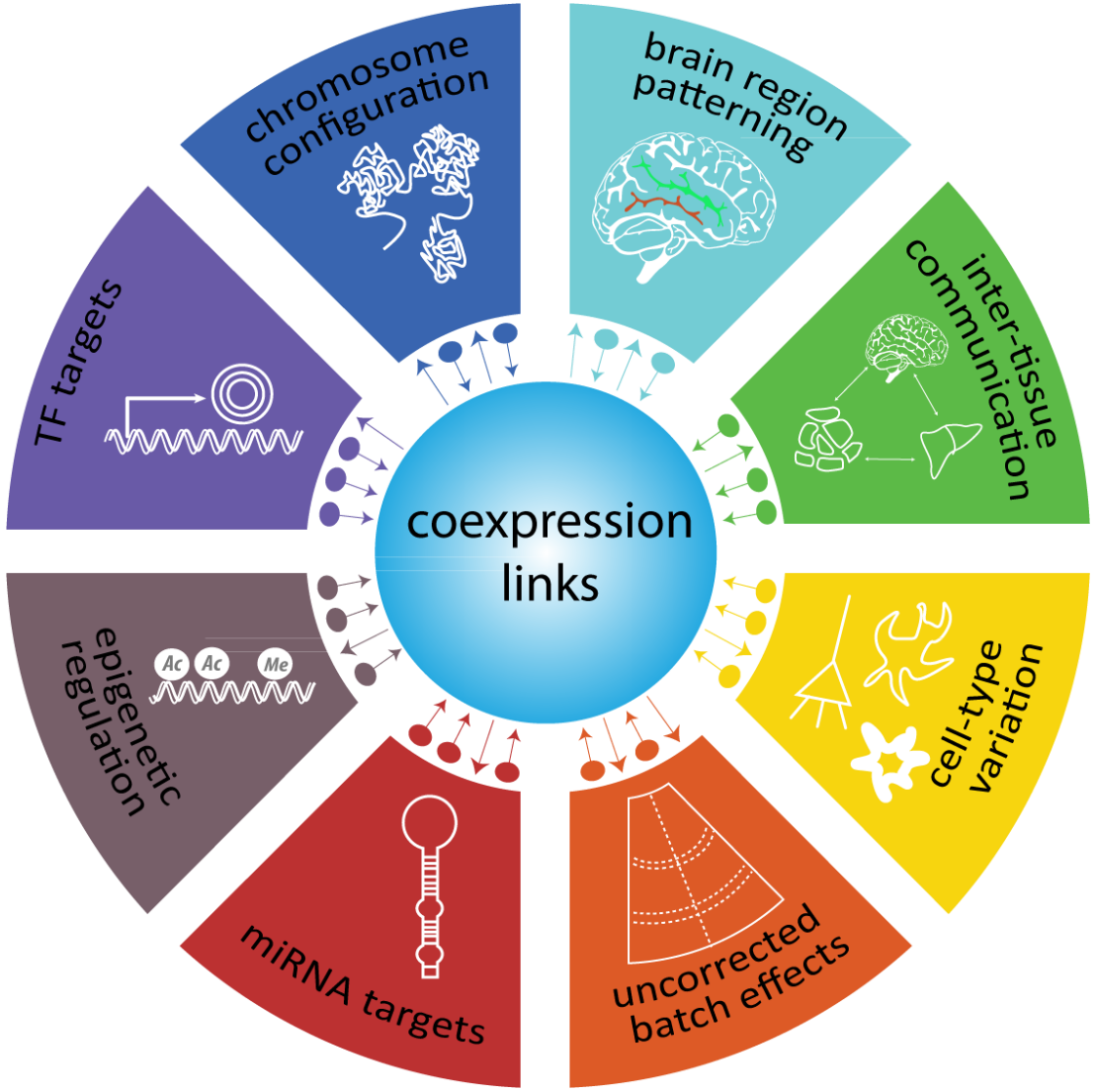
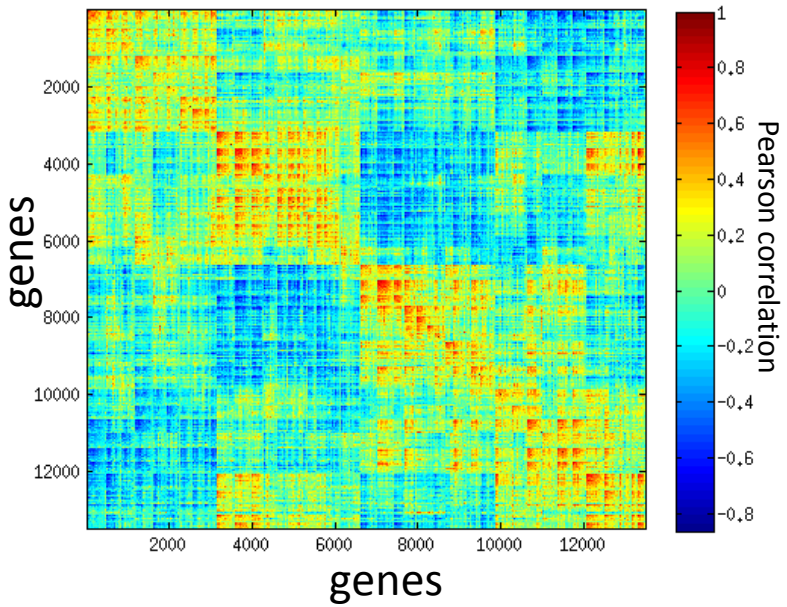
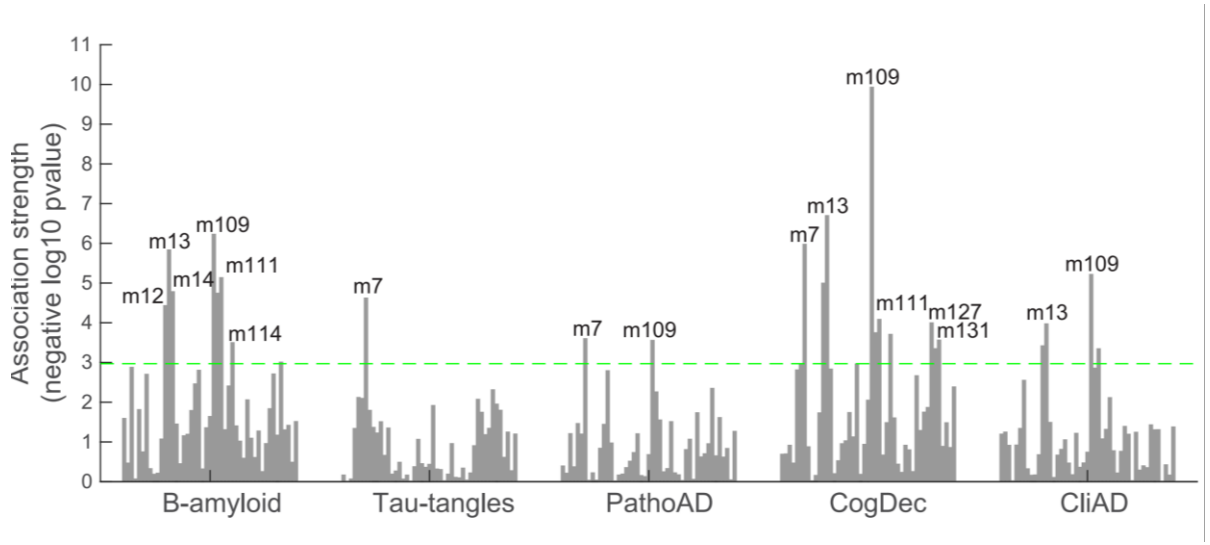


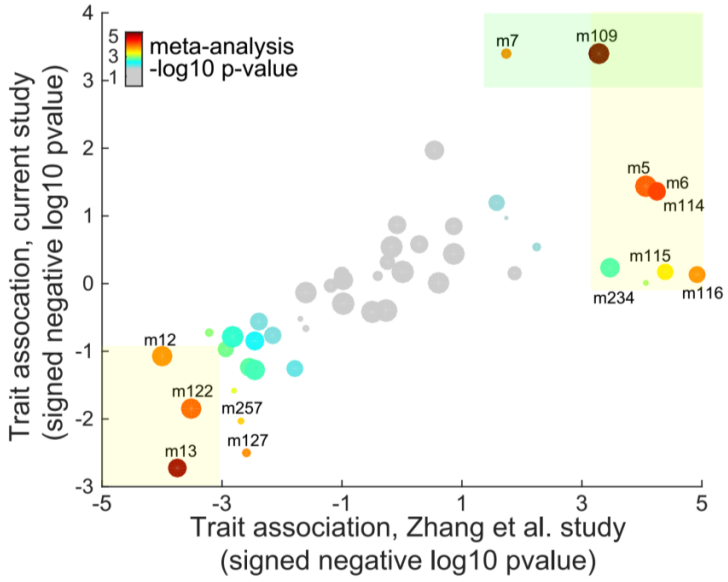
Gene-gene correlation matrix

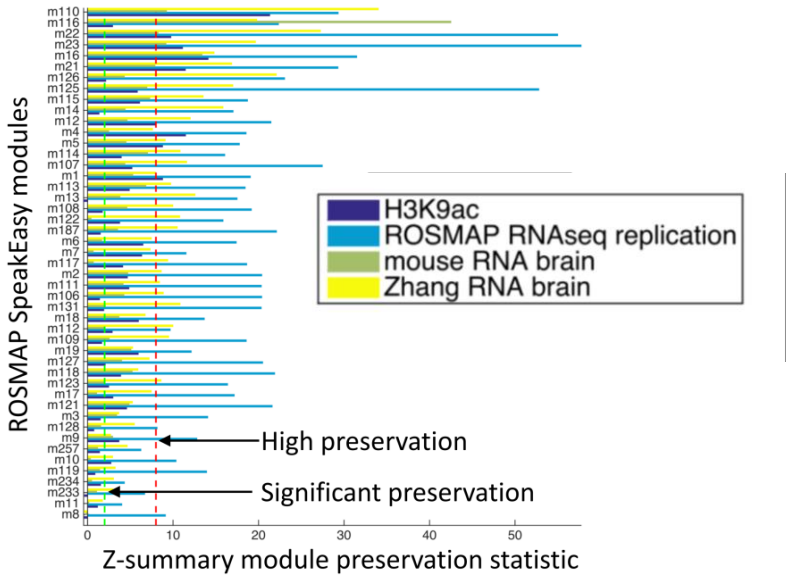


Typically we check for relationships between clusters and clinical or pathological phenotypes

Molecular systems related to AD







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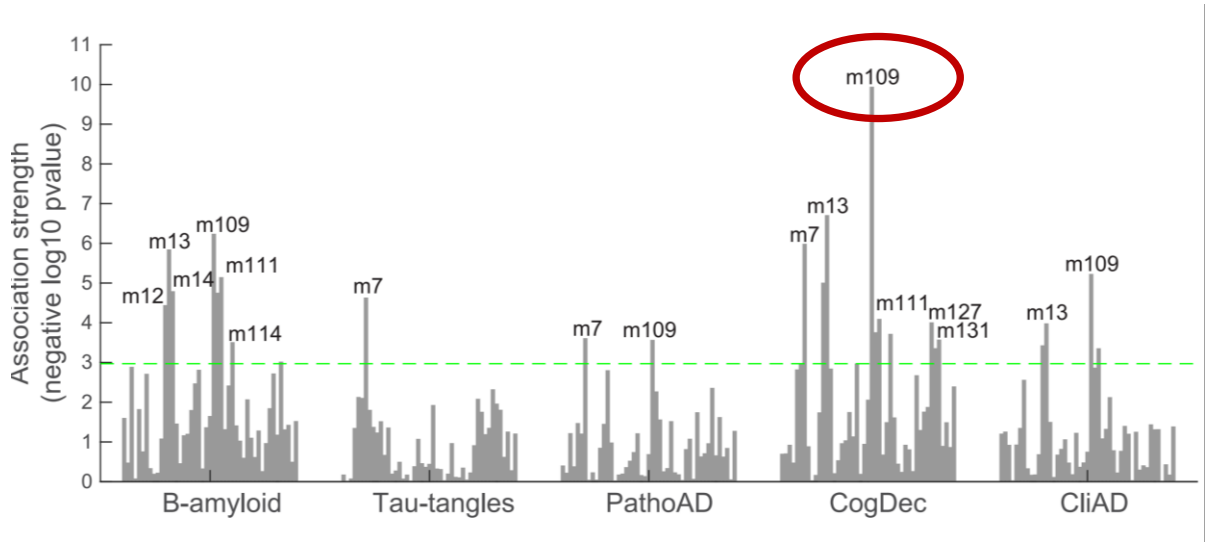
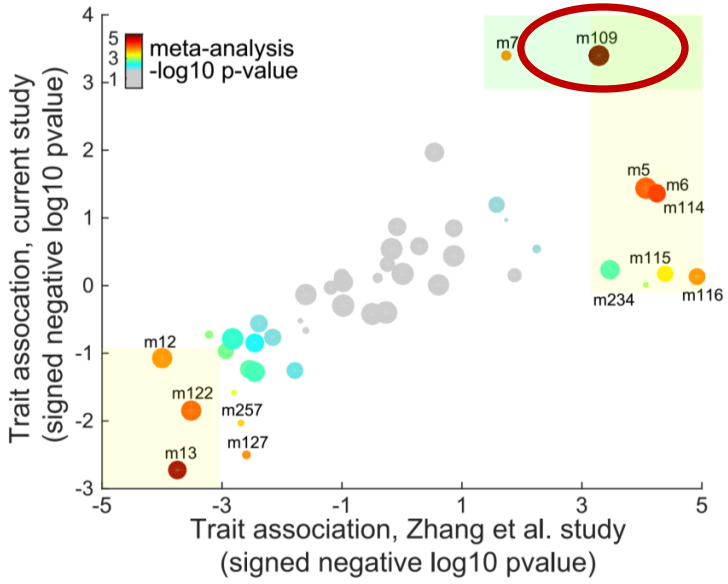
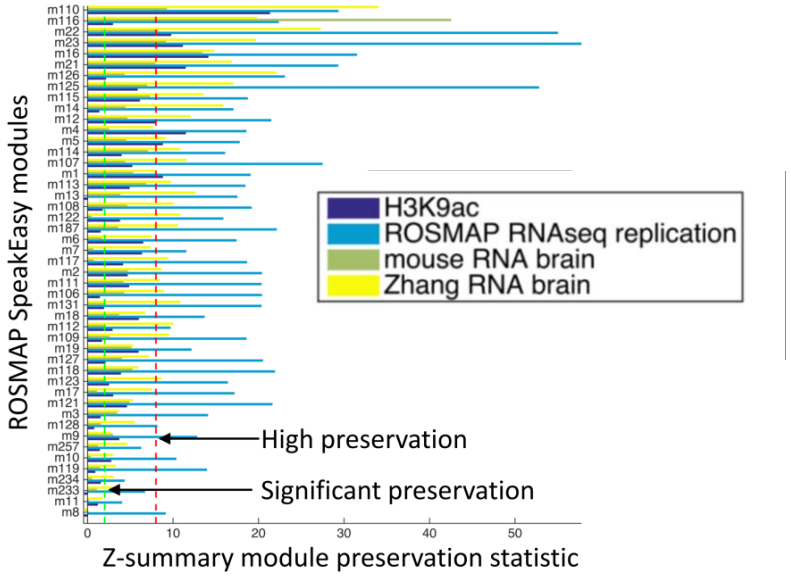
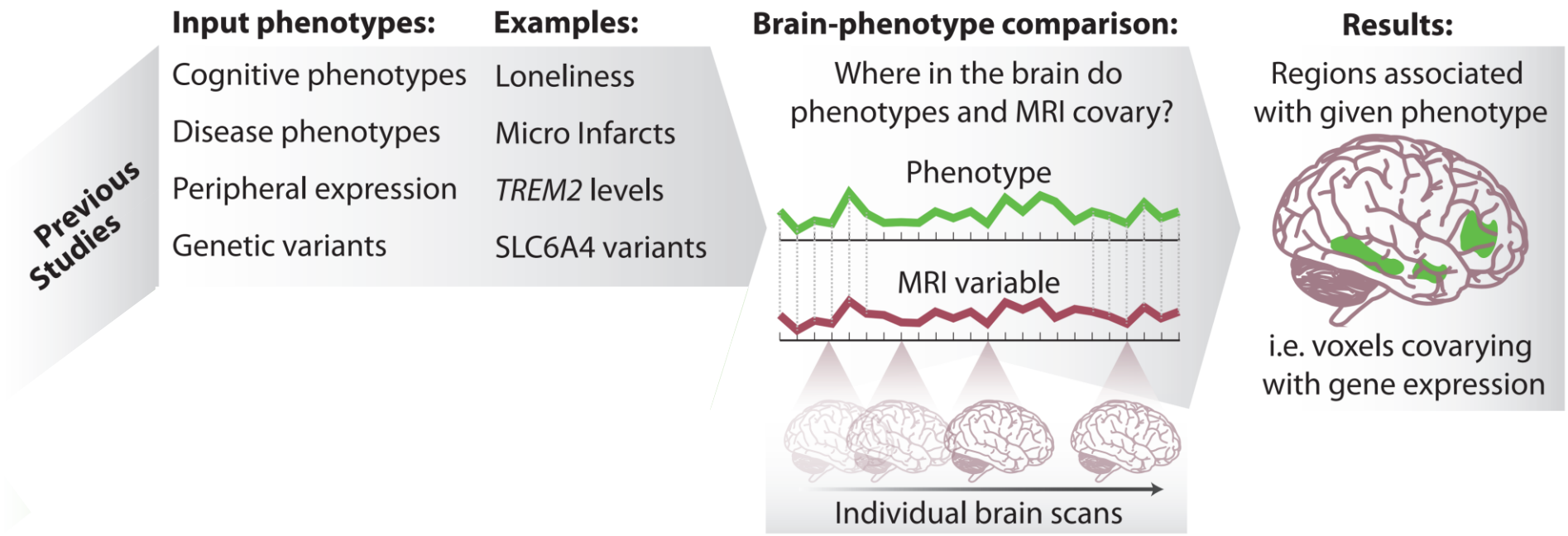






Methodology - summary of approach to “imaging-omics”



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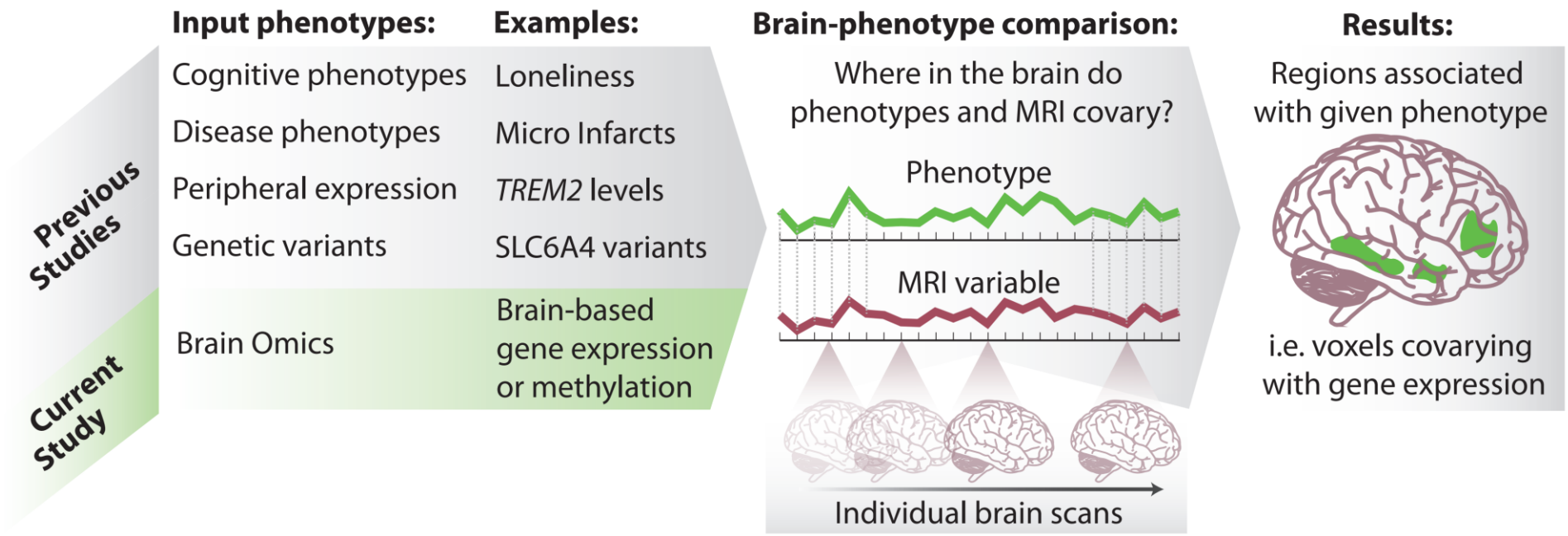
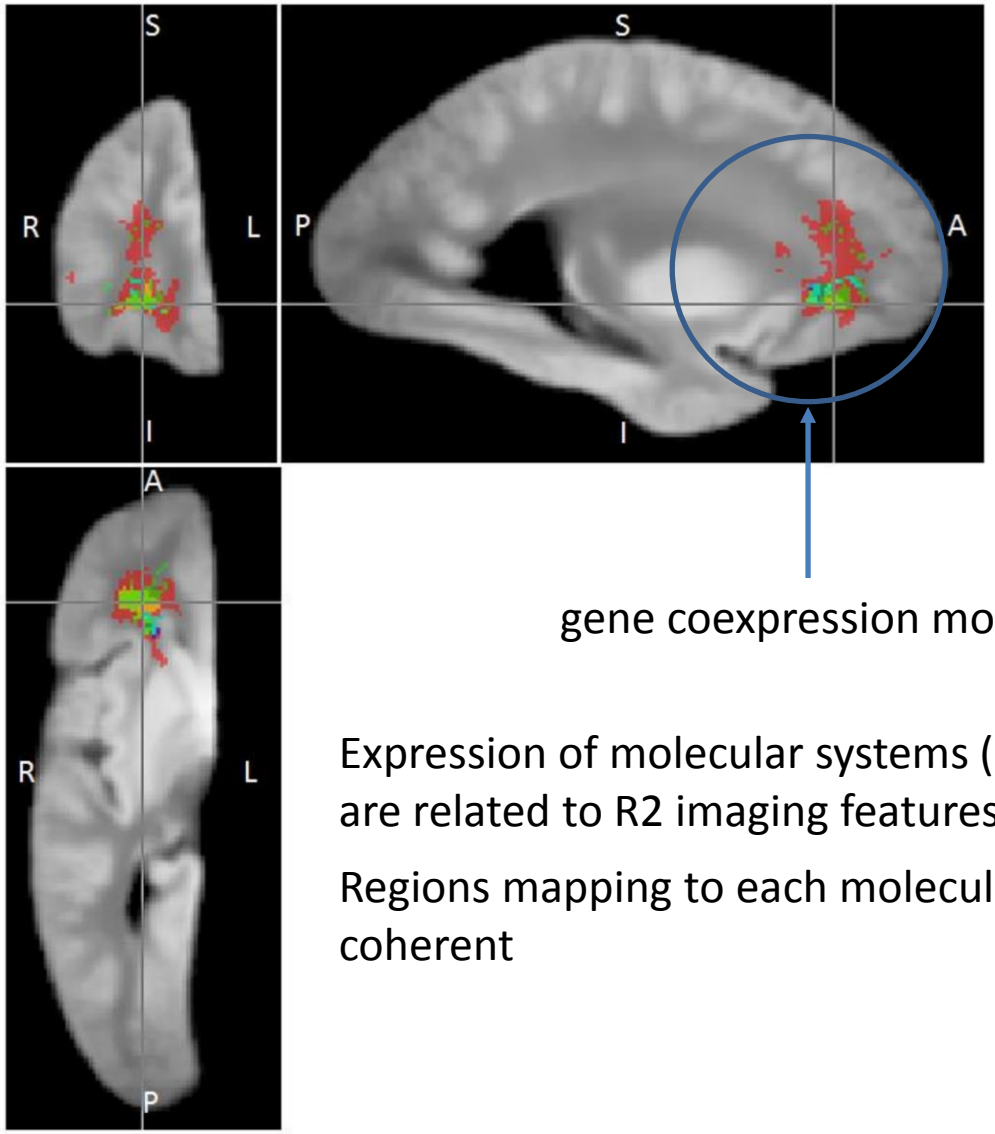


Mapping molecular systems to MRI voxels



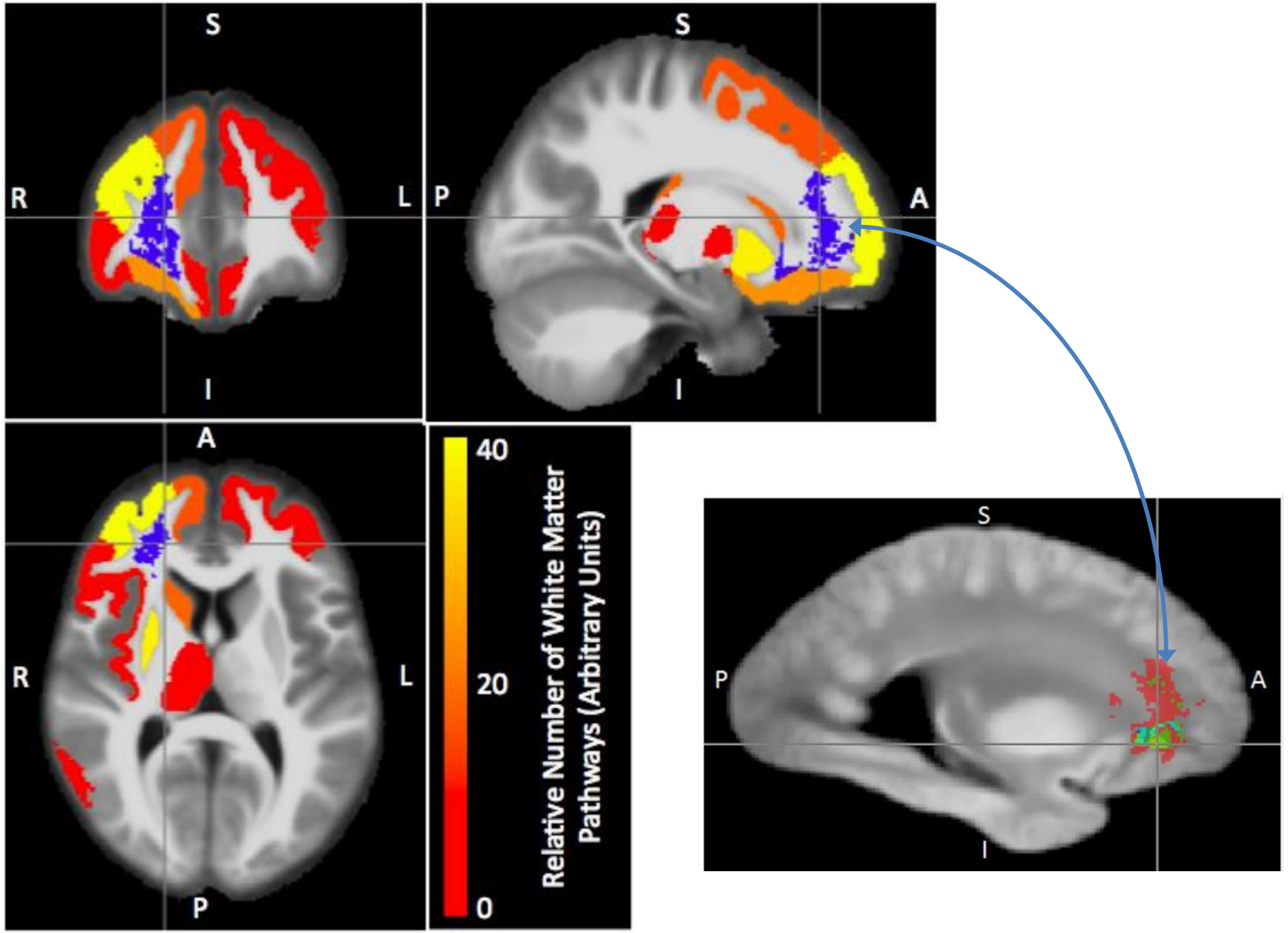
myelination
synaptic transmission
nuclear processes
transcriptional regulation

gene coexpression modules

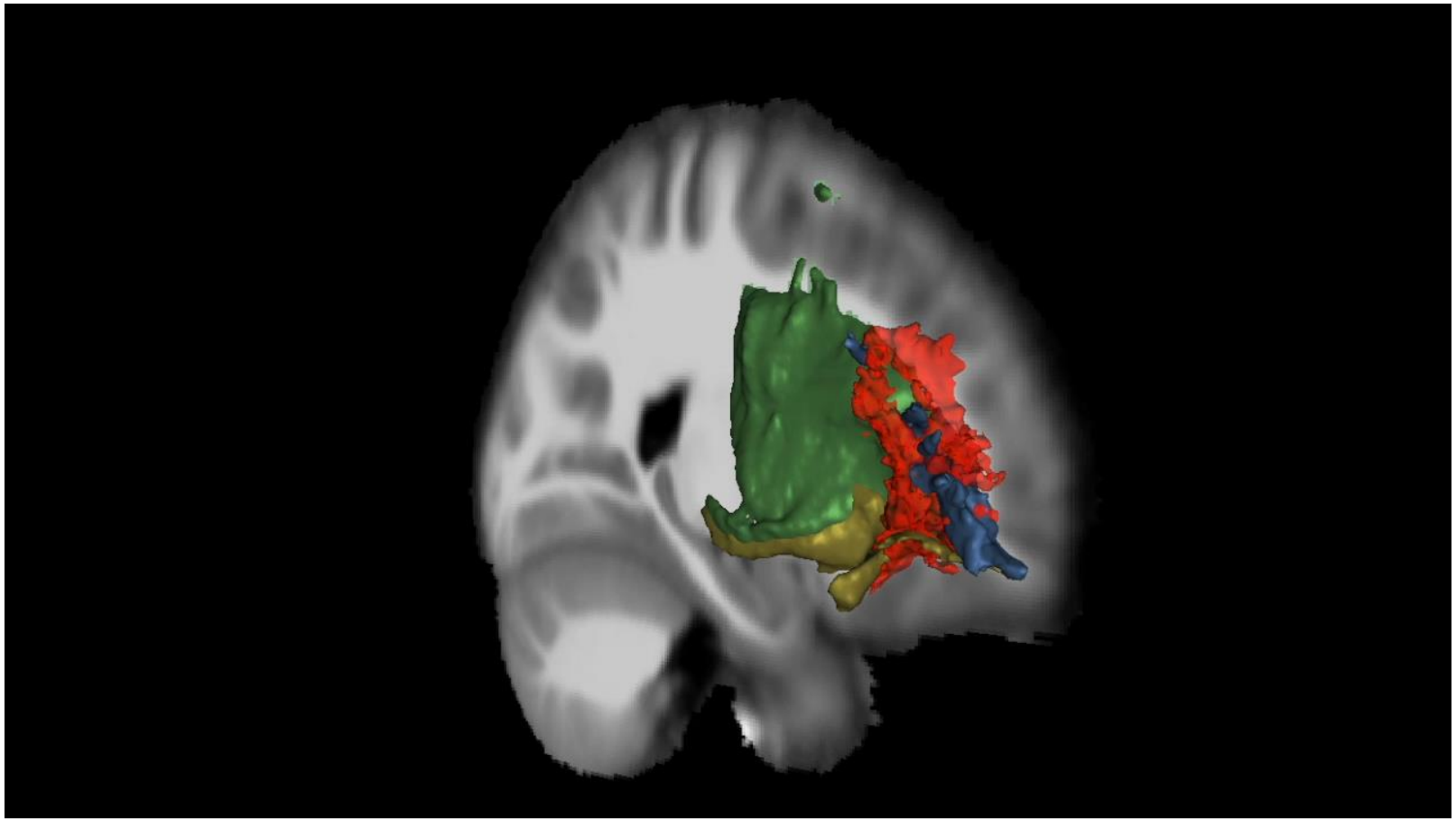
Expression of molecular systems (measured in DLPFC) are related to R2 imaging features across the brain

Regions mapping to each molecular system are spatially coherent

Tracts associated with MRI correlates of coexpression

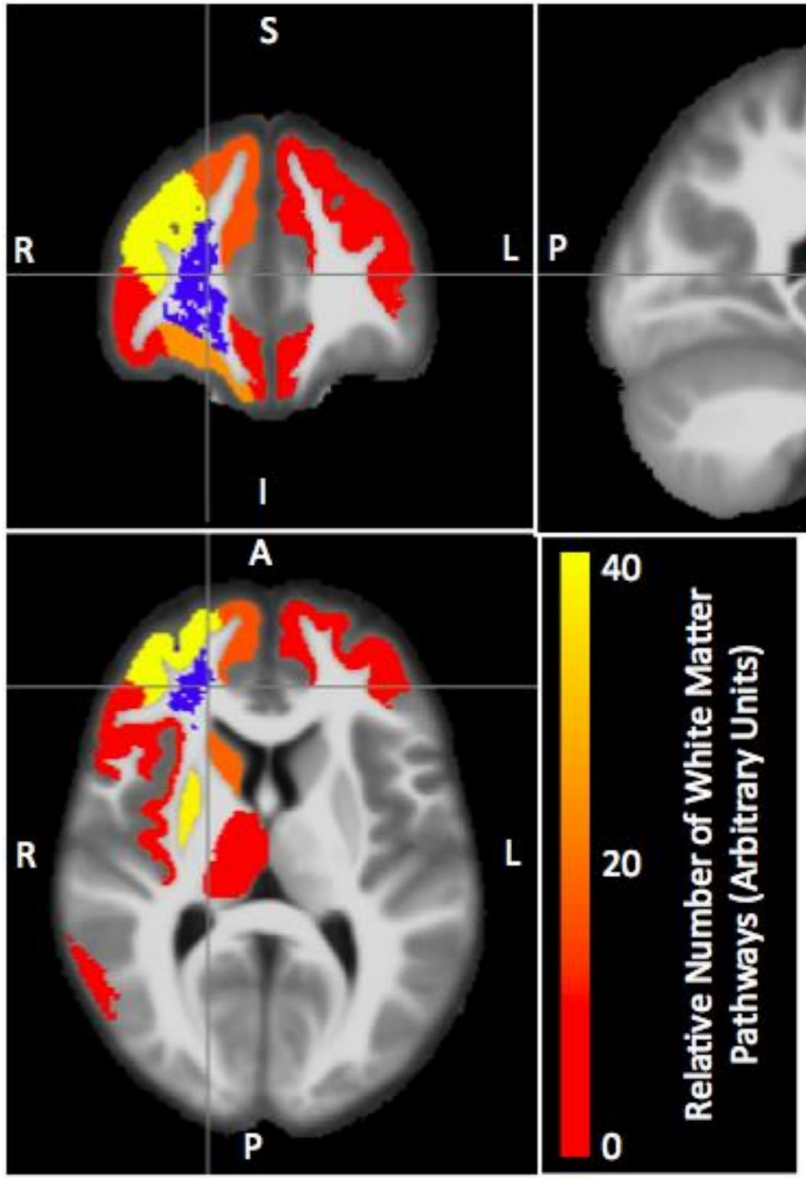


Tracts associated with MRI correlates of coexpression (top 3/4)



Yellow is the connection between putamen and lateral orbitofrontal.
Green is the connection between putamen and superior frontal.
Blue is the connection between caudate and rostral middle frontal.
The other connection in the top four, between putamen and rostral middle frontal, is omitted here for clarity.

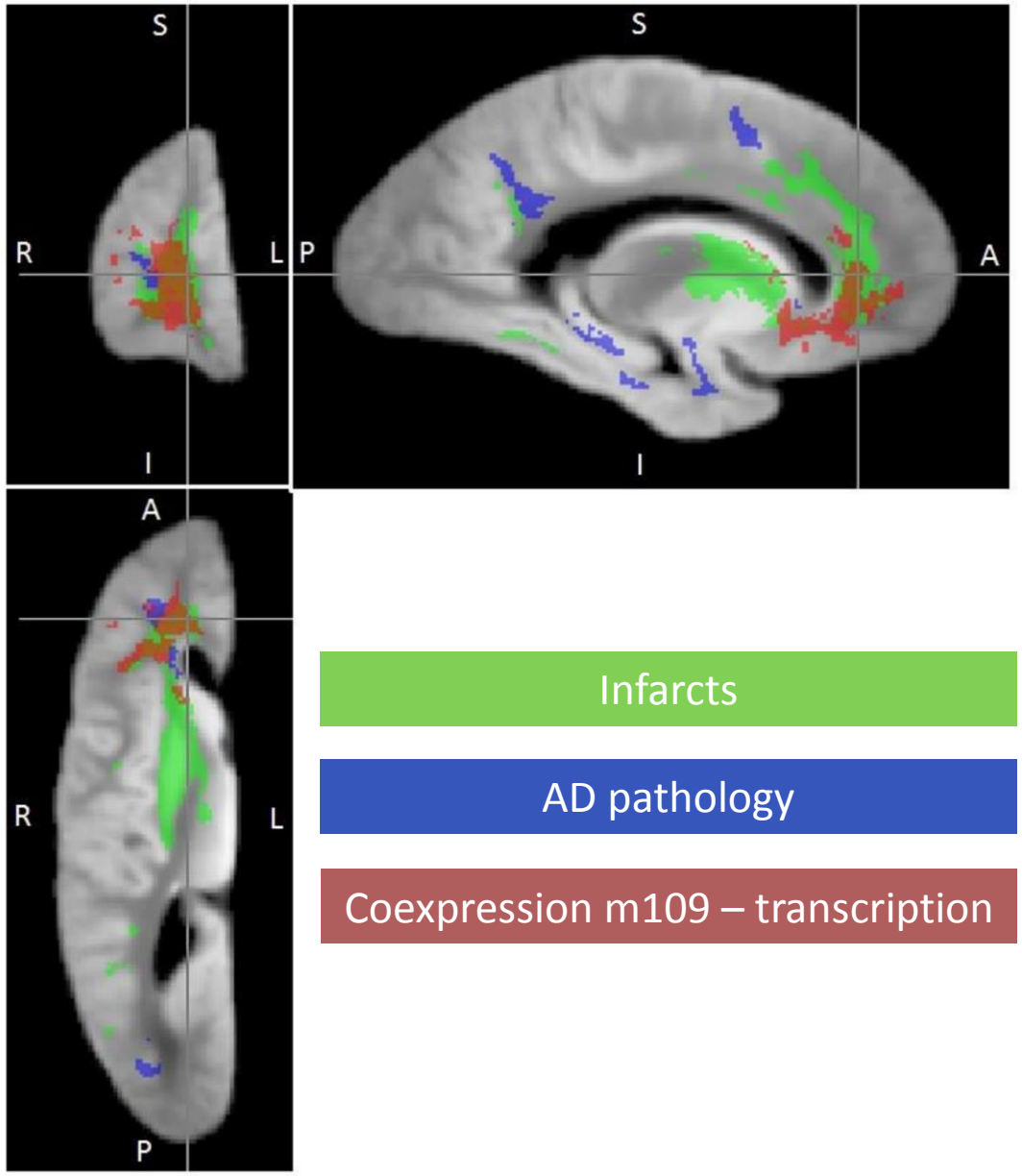
Tracts associated with MRI correlates of coexpression



Top-scoring region pairs

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

Coexpression in MRI vs pathology

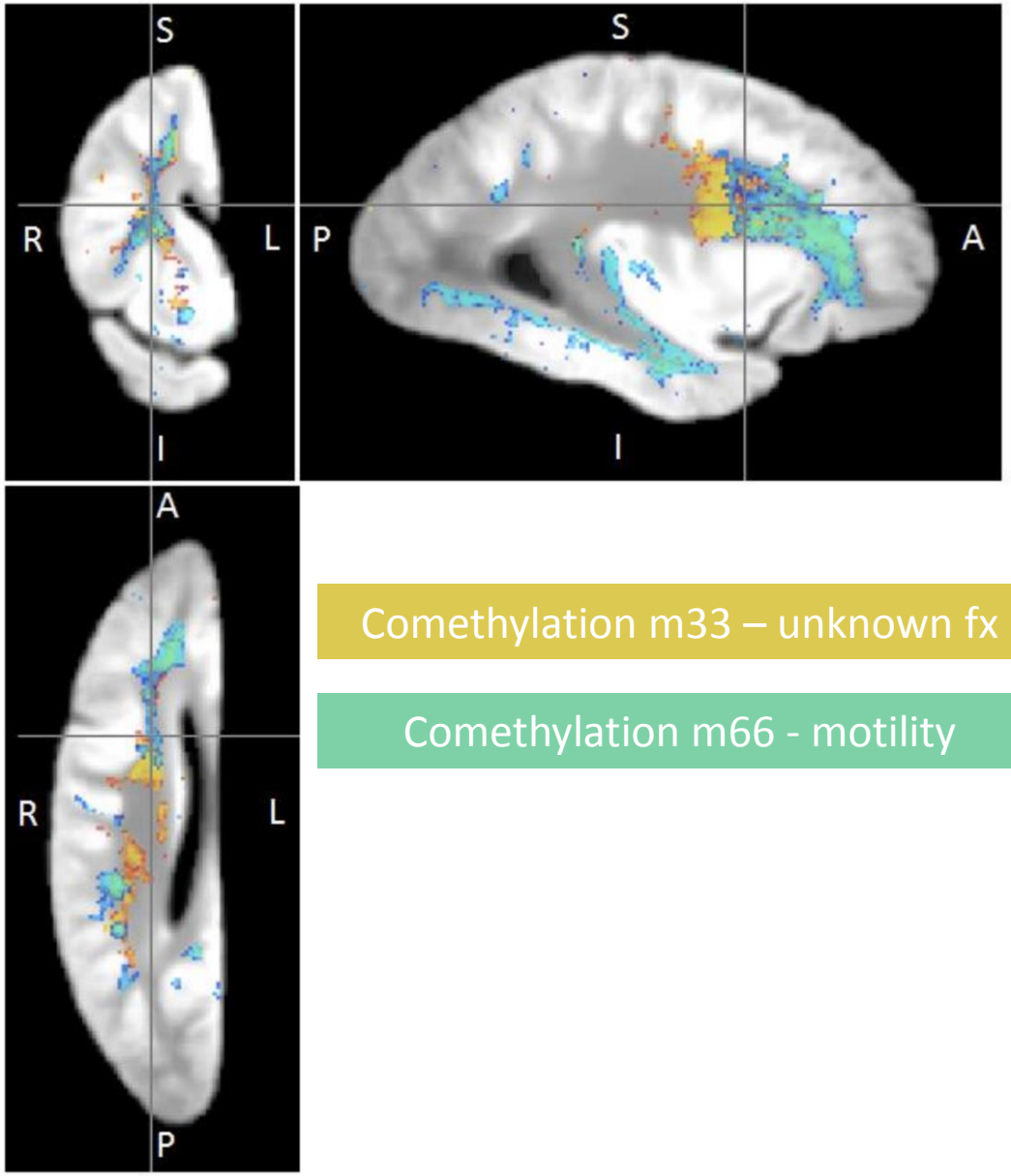


Infarcts

AD pathology

Coexpression m109 – transcription

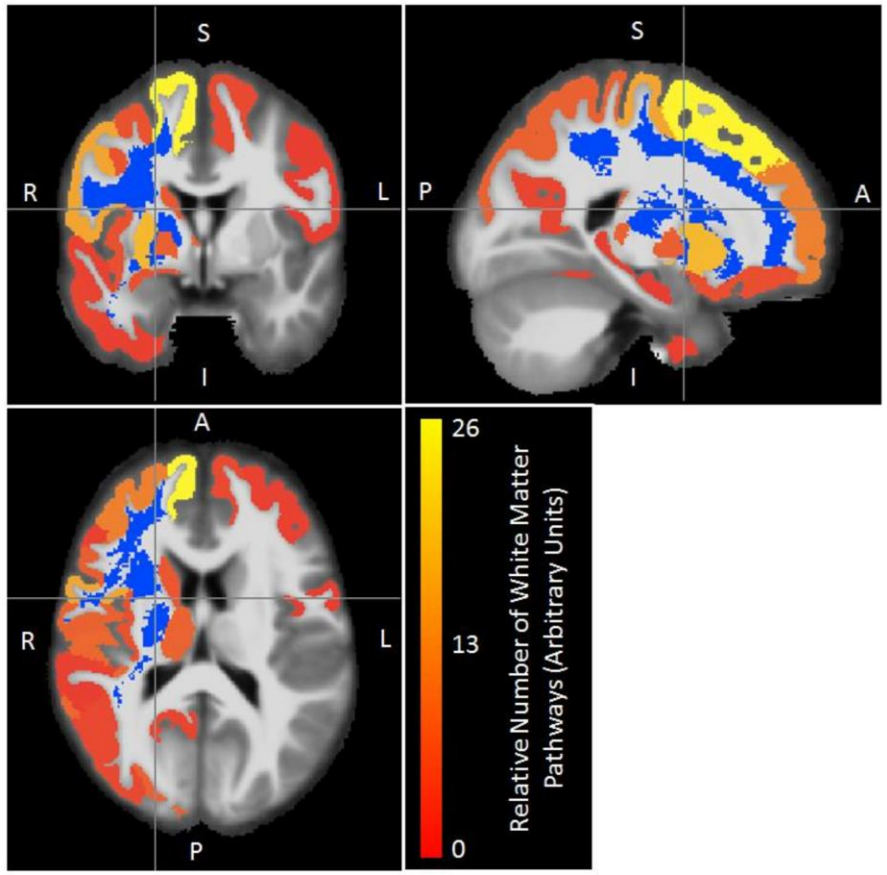
Comethylation modules with MRI correlates



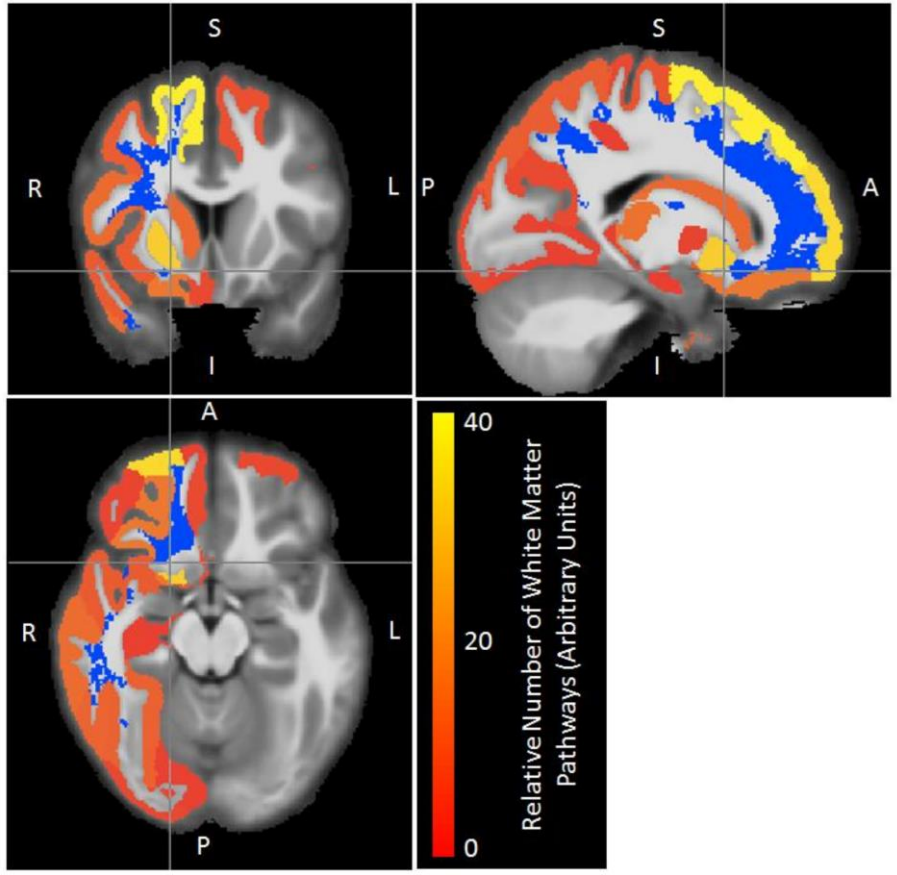
Comethylation m33 – unknown fx

Comethylation m66 - motility

Gray matter connected to comethylation modules with MRI correlates



Comethylation m33 – unknown fx



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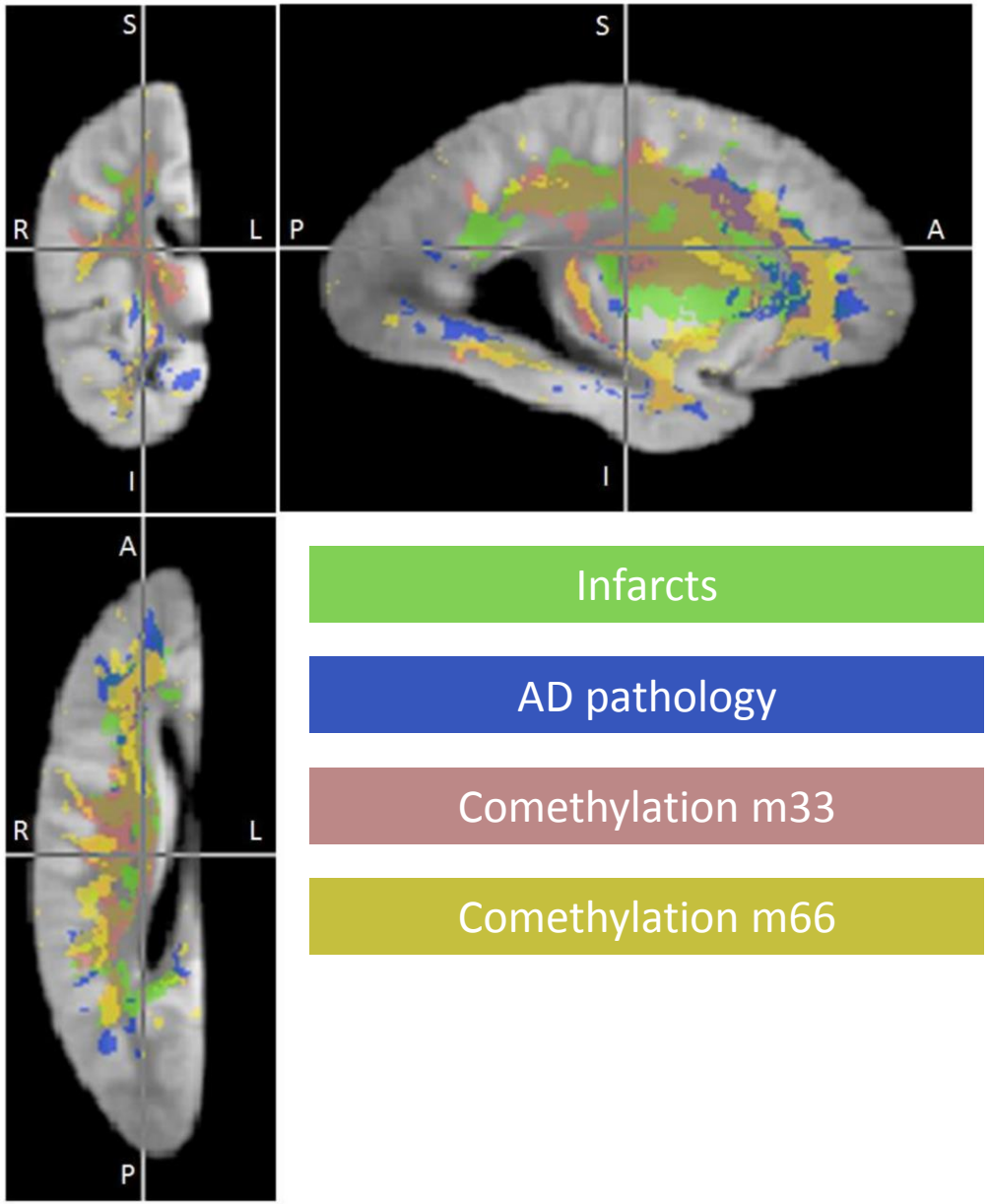
Comethylation in MRI vs pathology



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AD pathology

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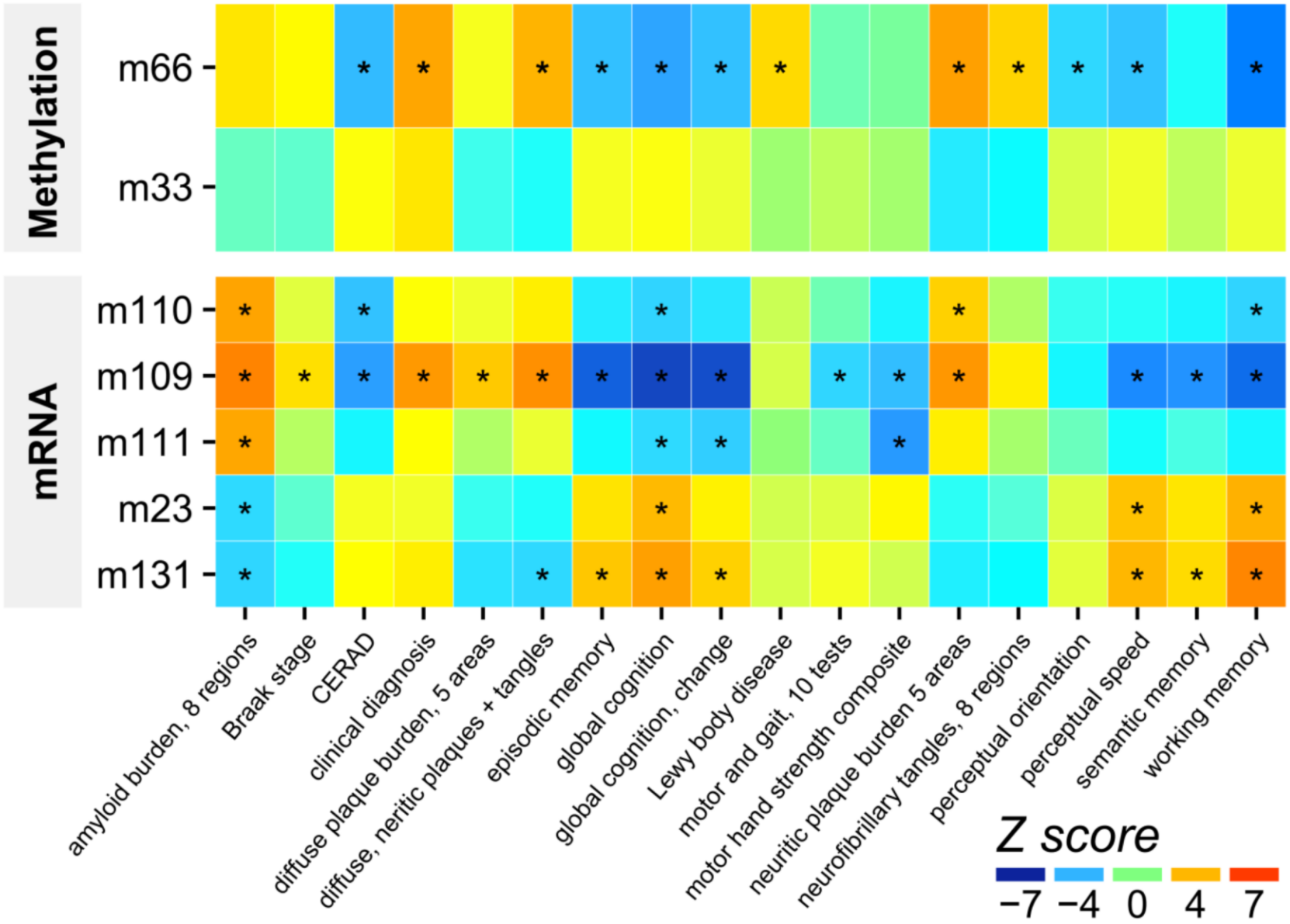
Comethylation m66

Trait associations of MRI-associated gene/methylation clusters



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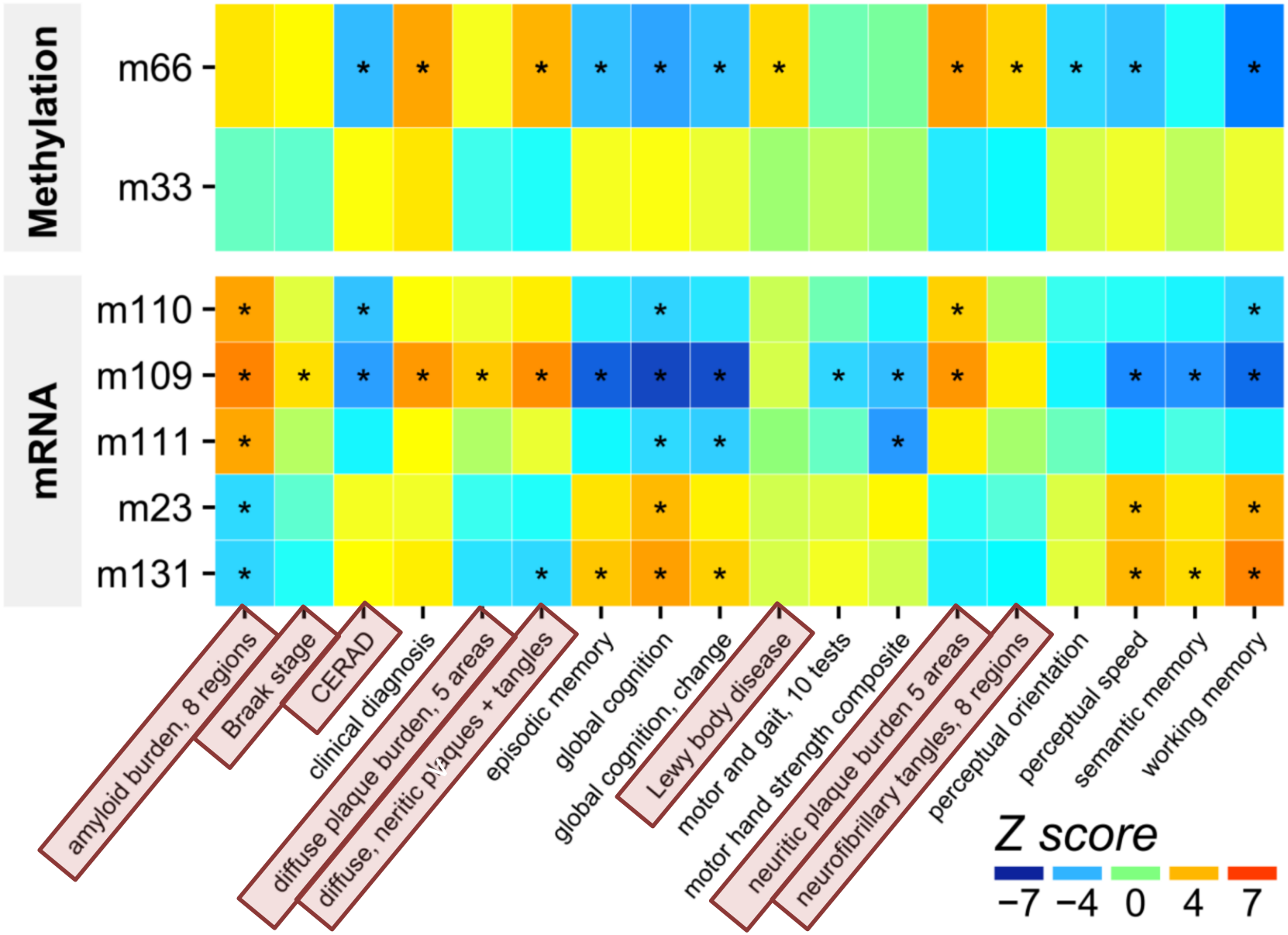
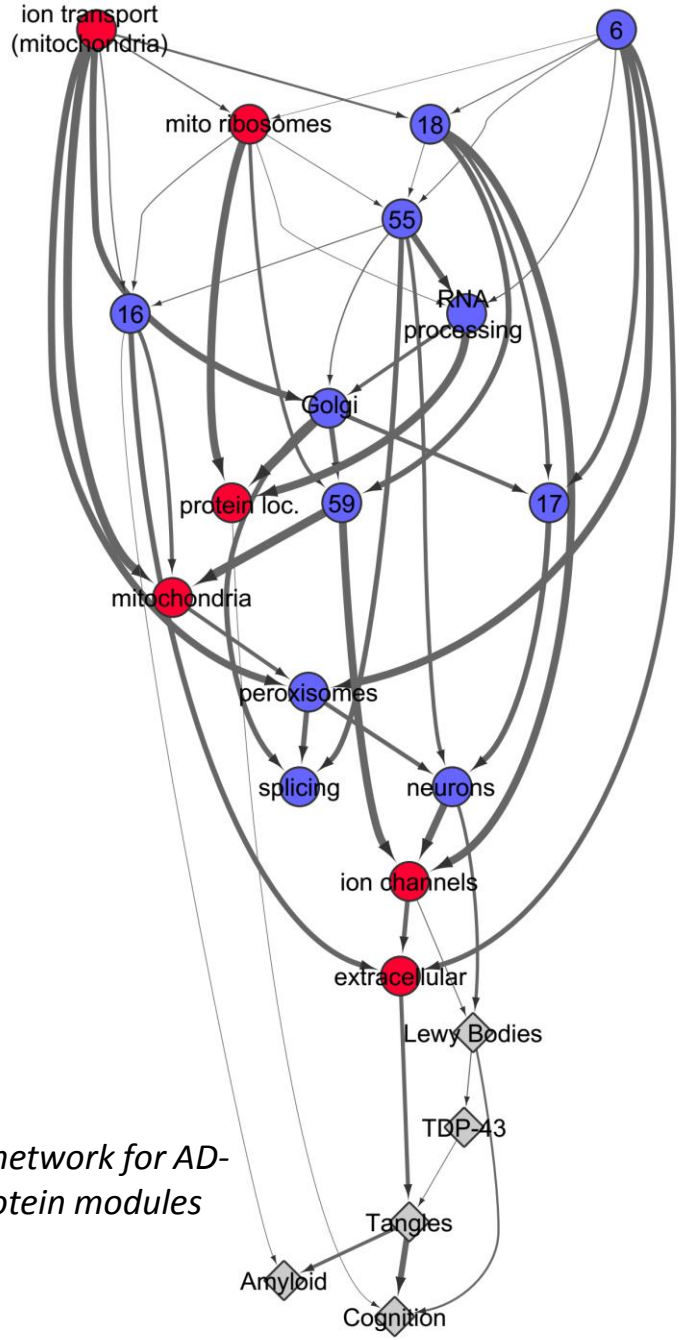


Protein modules associated with AD-related traits (via Emory U.)

Many molecular systems associated with cognition, or tdp43, Lewy Bodies, amyloid or tau:

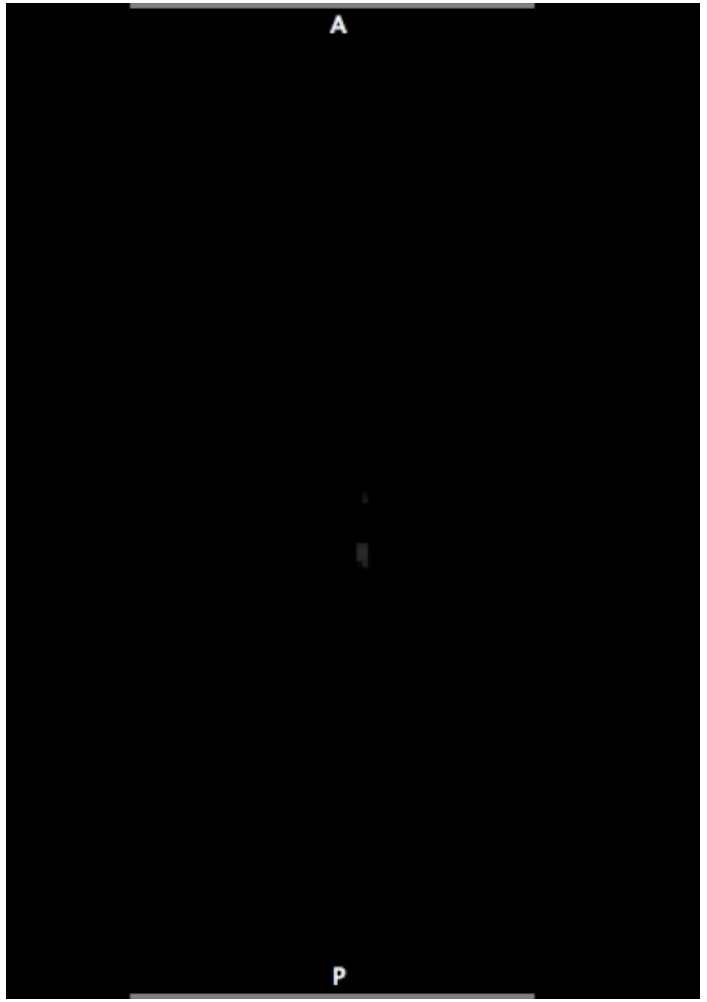
- Mitochondria (specifically transcription of mitochondrial genes and ribosomes)
- Protein localization
- Endoplasmic reticulum
- RNA processing
- Splicing
- Peroxisomes
- Certain classes of synaptic ion channels
- Exosomes and extracellular processes



Module-trait network for AD-associated protein modules

Structural imaging of protein modules

with data partially measured…
largest signals are for protein modules related to RNA processing and two others with unclear functions



Protein MRI correlates

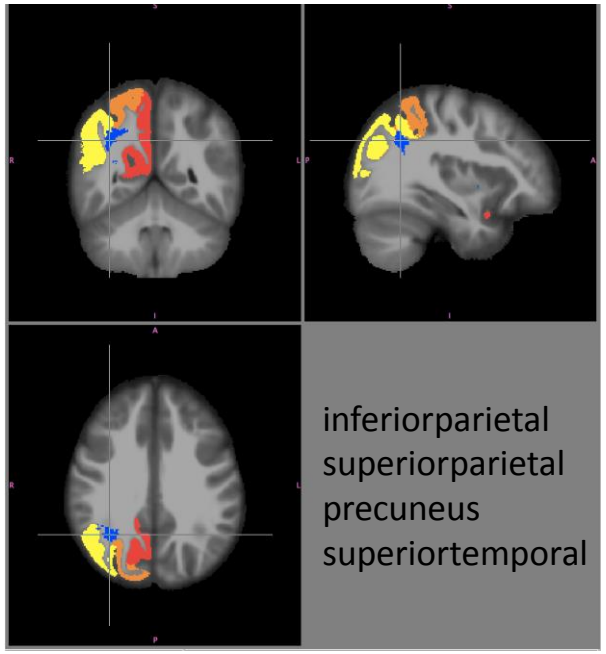
With ~100 paired MRI-proteomes we see several molecular systems with correlated voxels.

These are spatially extensive and far-removed from the site of protein measurements in DLPFC.

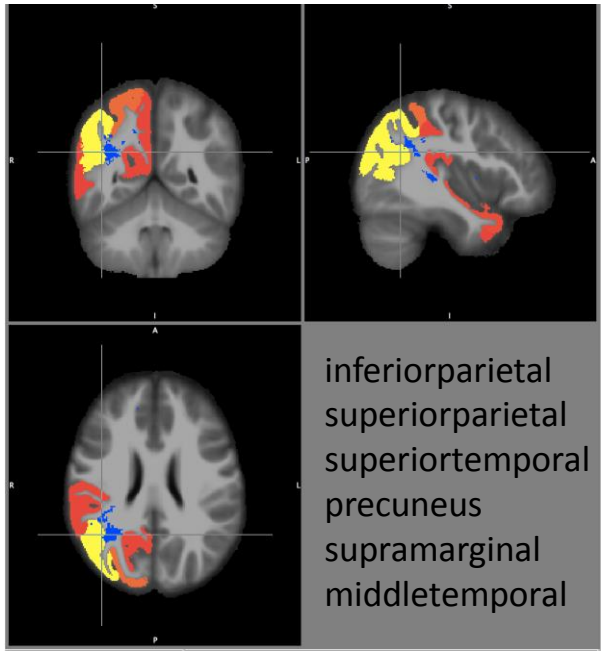
Next step is relating fMRI and antemortem structural imaging to protein abundance.

Major remaining question is the diversity of protein-imaging maps as function of site of biopsy.

RNA processing protein modules

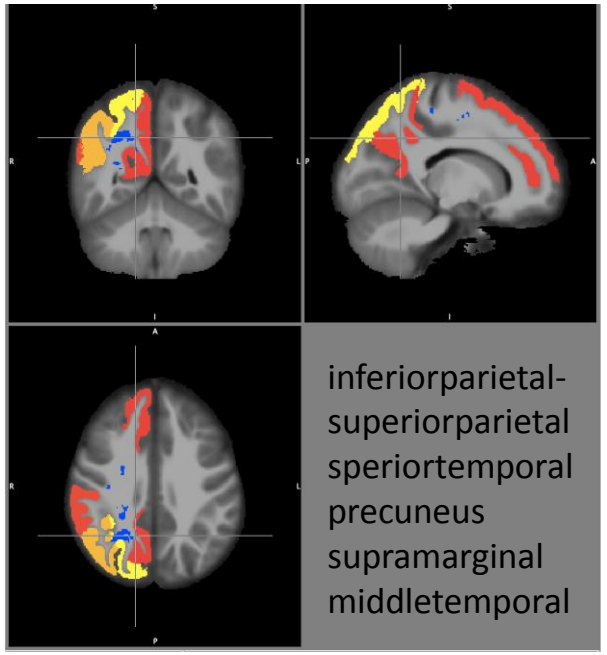


inferiorparietal
superiorparietal
precuneus
superiortemporal

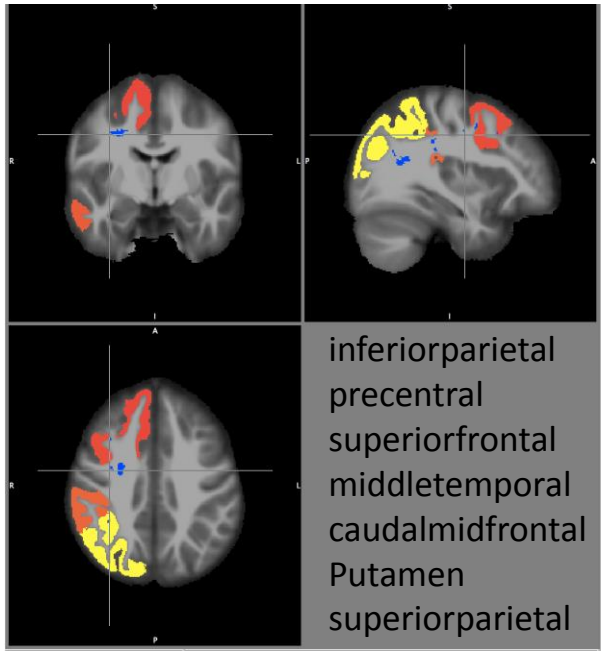


inferiorparietal
superiorparietal
superiortemporal
precuneus
supramarginal
middletemporal

Protein modules of unclear fx



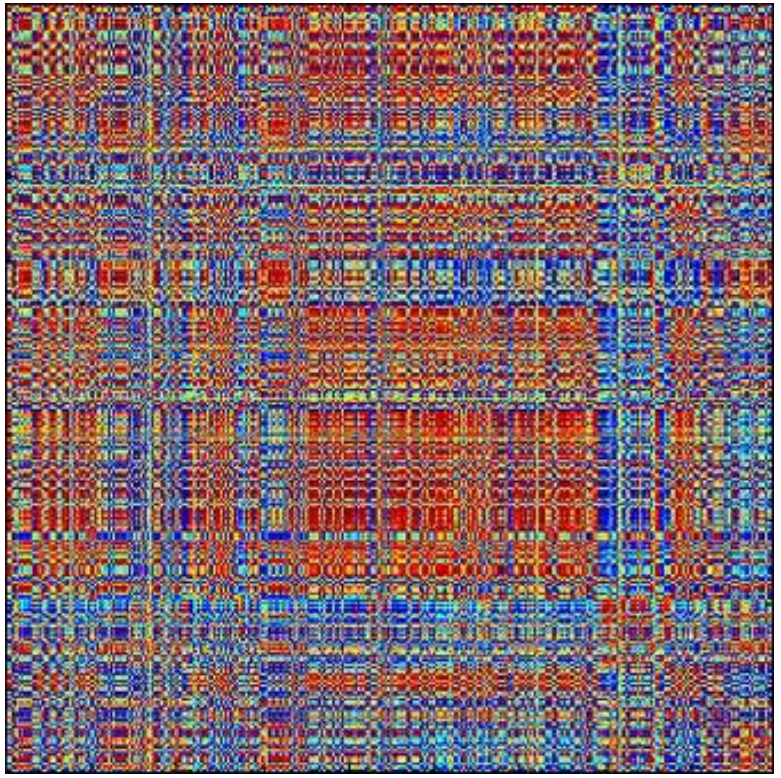
inferiorparietal-
superiorparietal
speriortemporal
precuneus
supramarginal
middletemporal

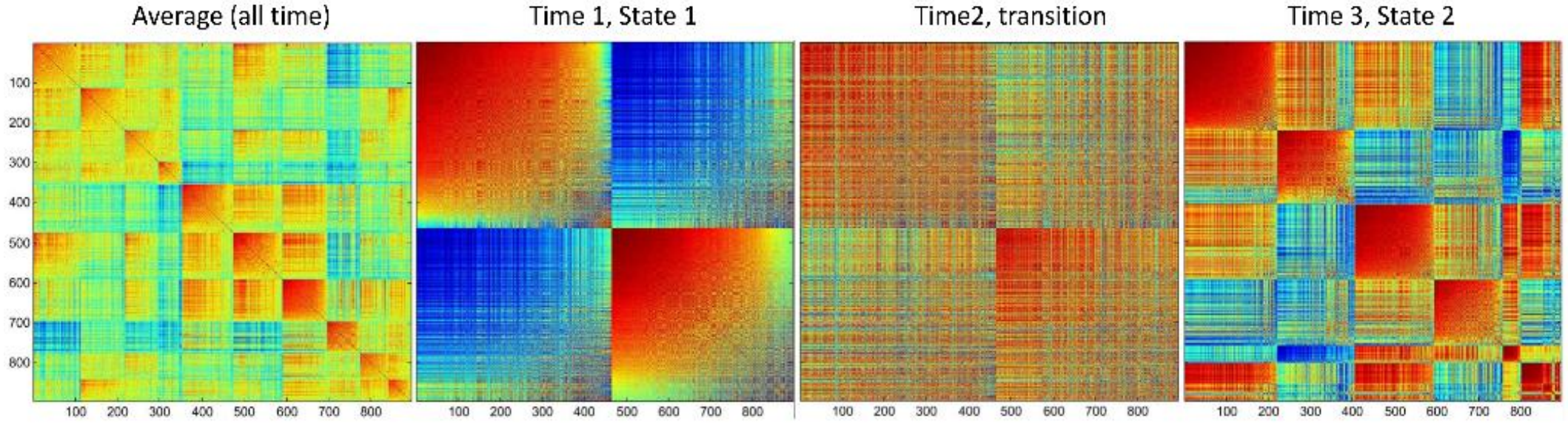


inferiorparietal
precentral
superiorfrontal
middletemporal
caudalmidfrontal
Putamen
superiorparietal

Protein fMRI correlates…pending

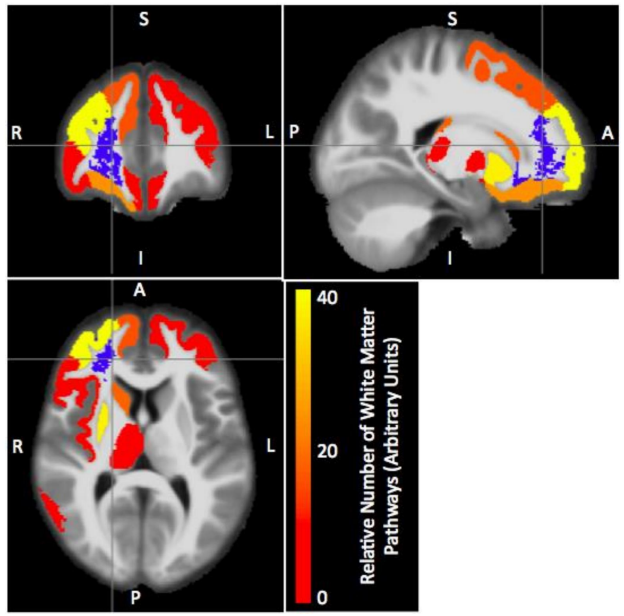
Next step is relating fMRI and antemortem structural imaging to protein abundance.





Rush targets guided by confluence of:

Neuroimaging



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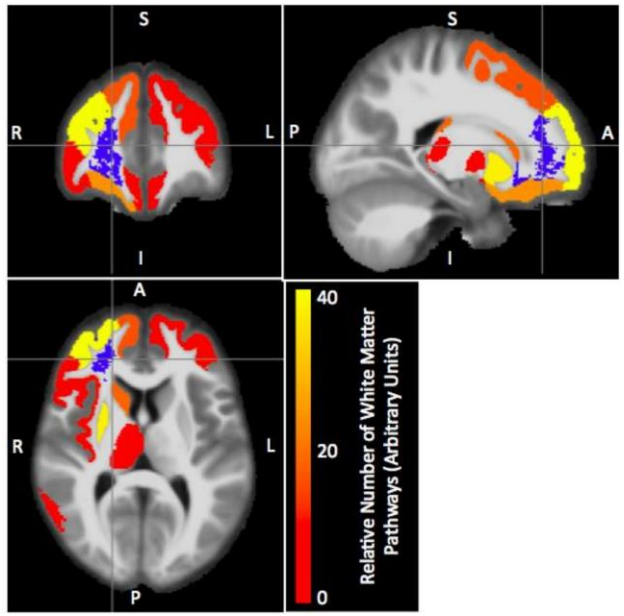
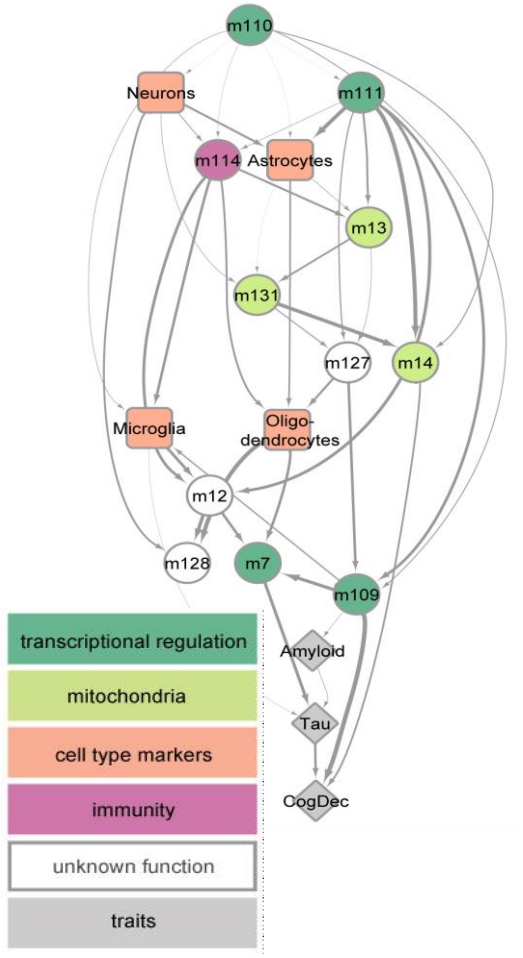


Computational & systems biology



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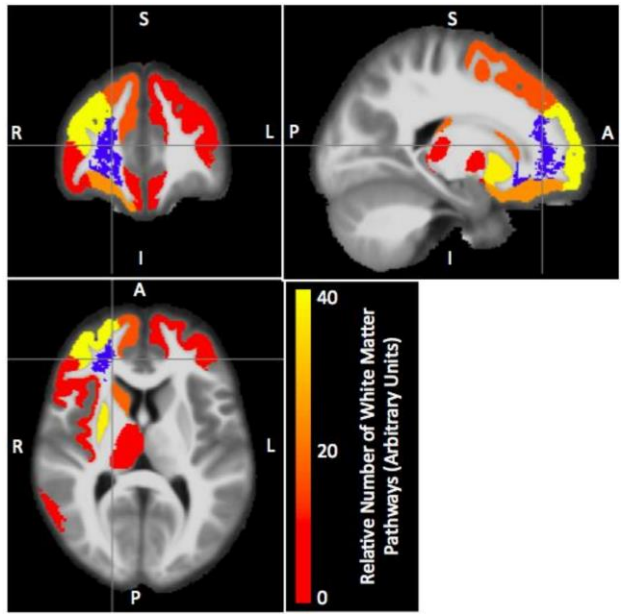

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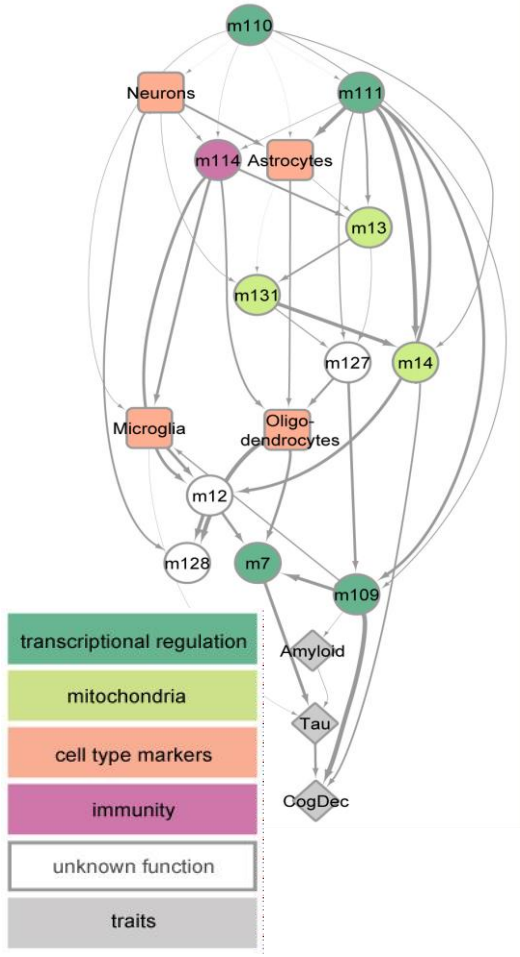
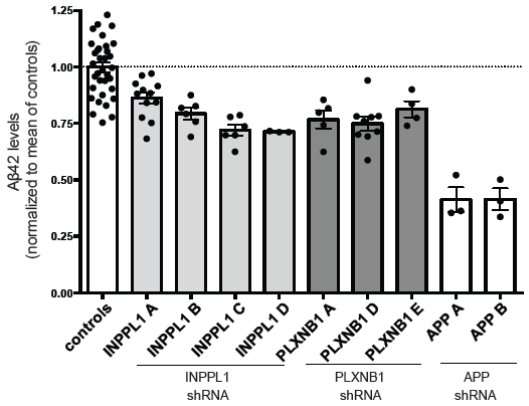
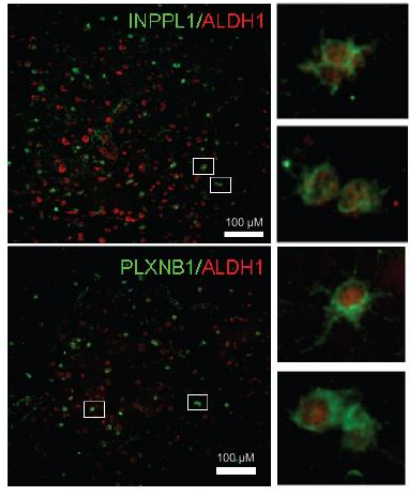


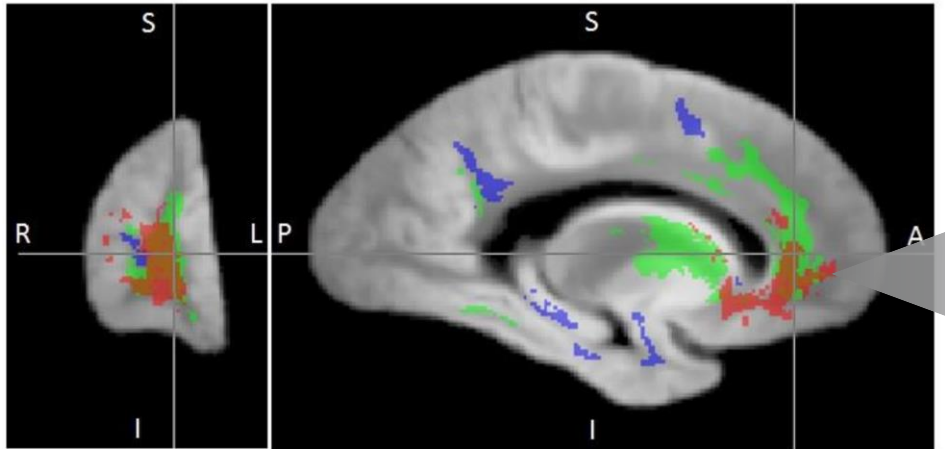
Molecular biology experiments

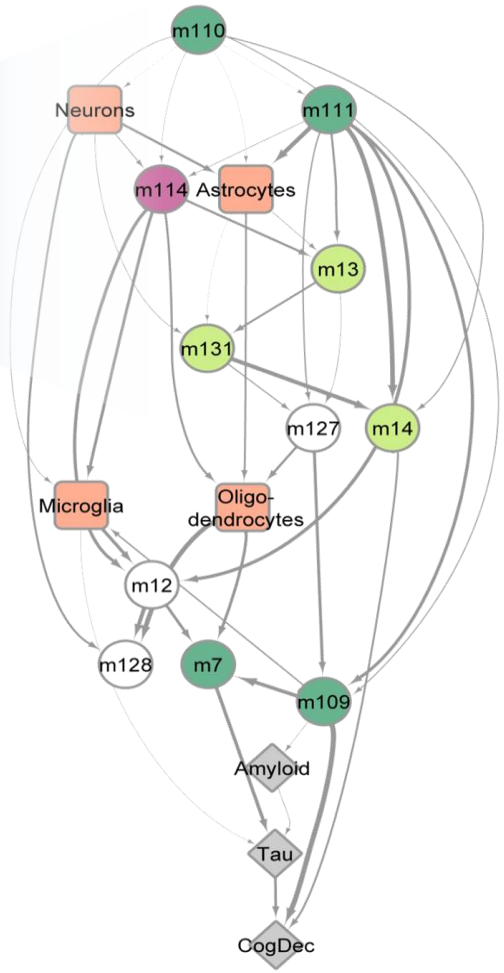




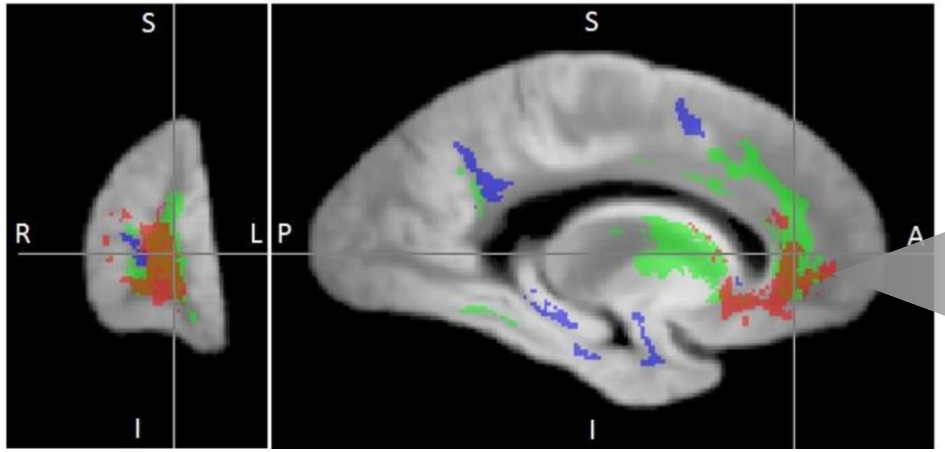
Three different perspectives with concordant findings – impact of proposed targets

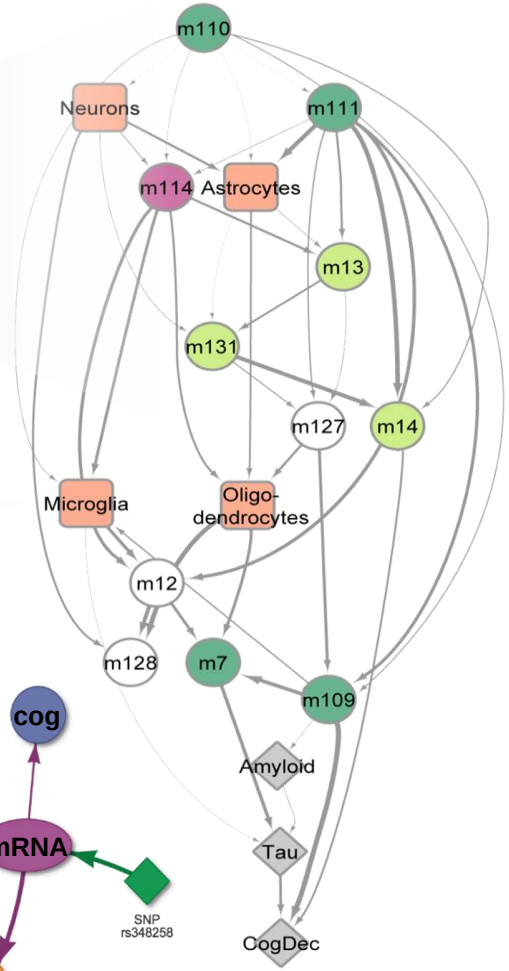
The future-present – coherent understanding via AMP-AD data

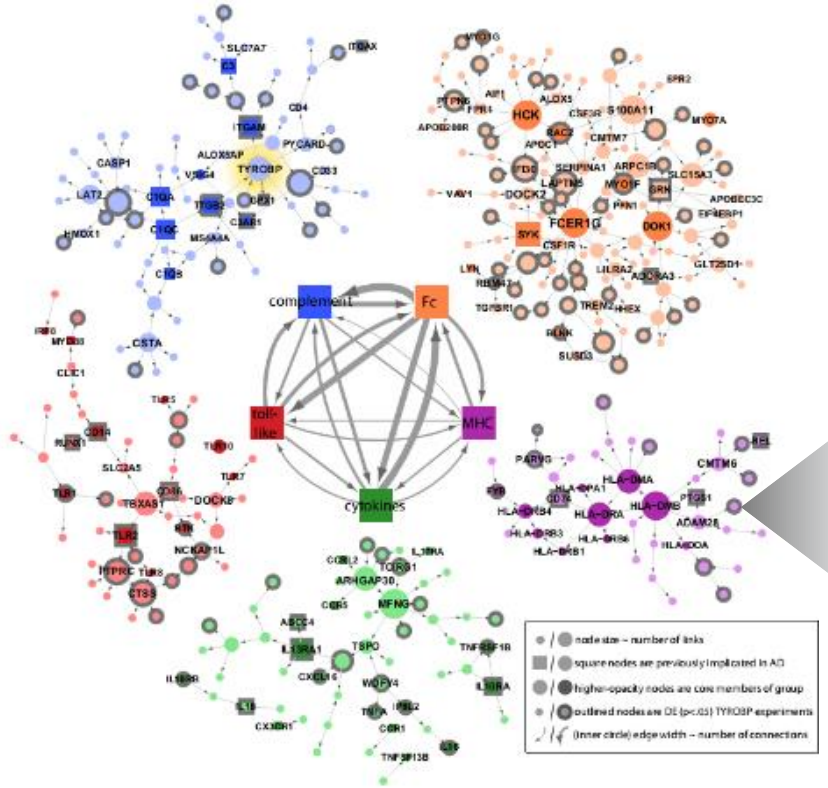


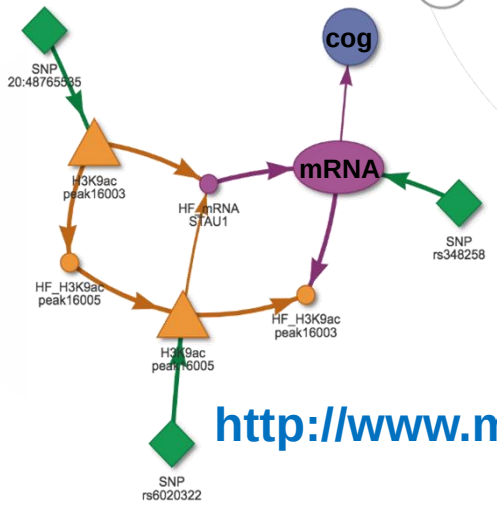


The future-present – coherent understanding via AMP-AD data









http://www.molecular.network/

Thank you:

NIA and Suzana Petanceska for invitation
Namhee Kim, **Bob Dawe**, Shinya Tasaki, Konstantinos Arfanakis, David Bennett (Rush University)
Sara Mostafavi (UBC), Tracy Pearse (Harvard), Phil De Jager (Columbia)
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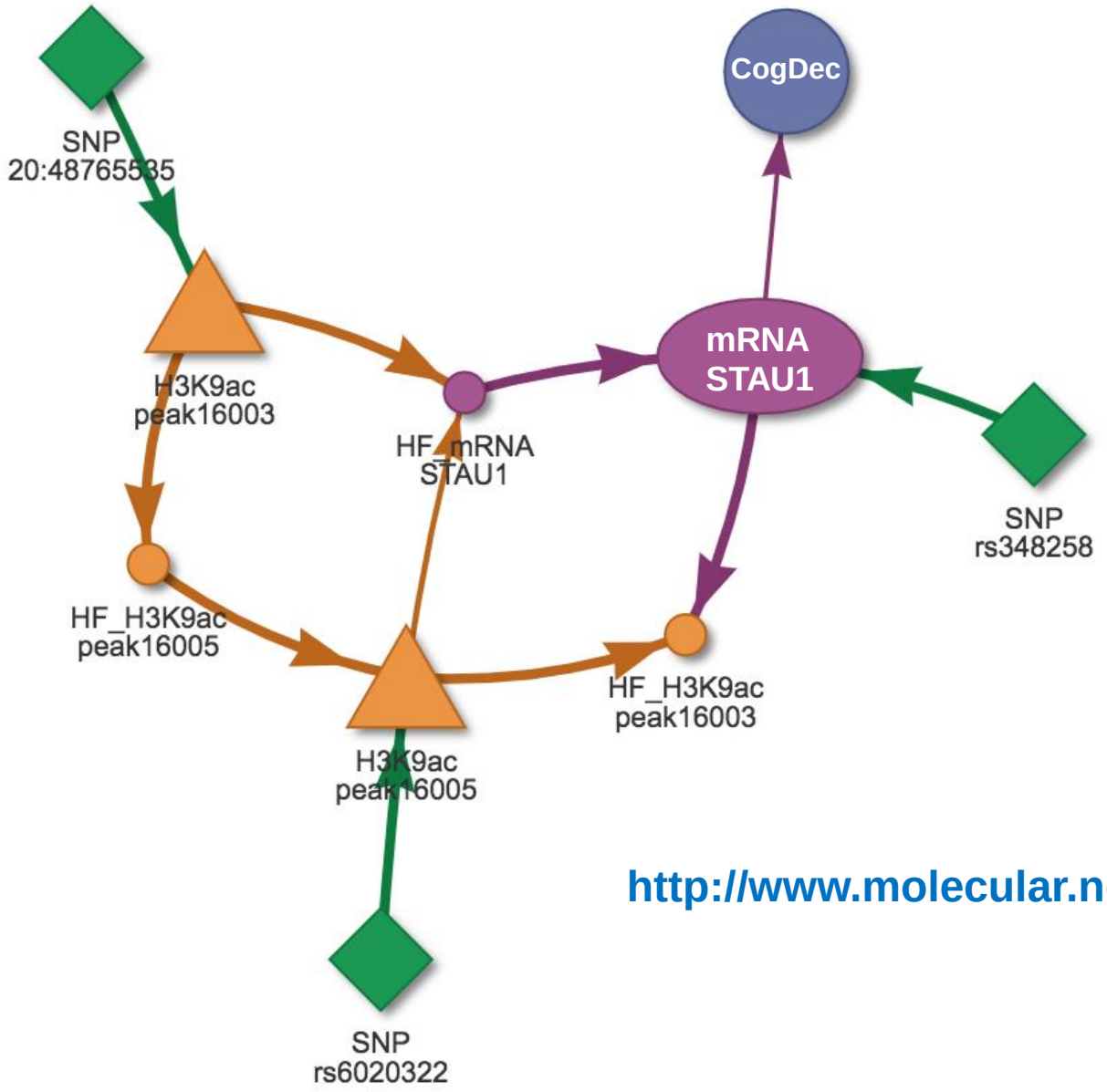
Join us!

New “Cogdishion” lab with Yanling Wang MD PhD
- Molecular biology postdocs in CRISPR and stem cells in Alzheimer’s available
- Computational postdoc and assistant professor positions

Contact christopher_gaiteri@rush.edu

Genomic & Epigenomic networks
(Shinya Tasaki)



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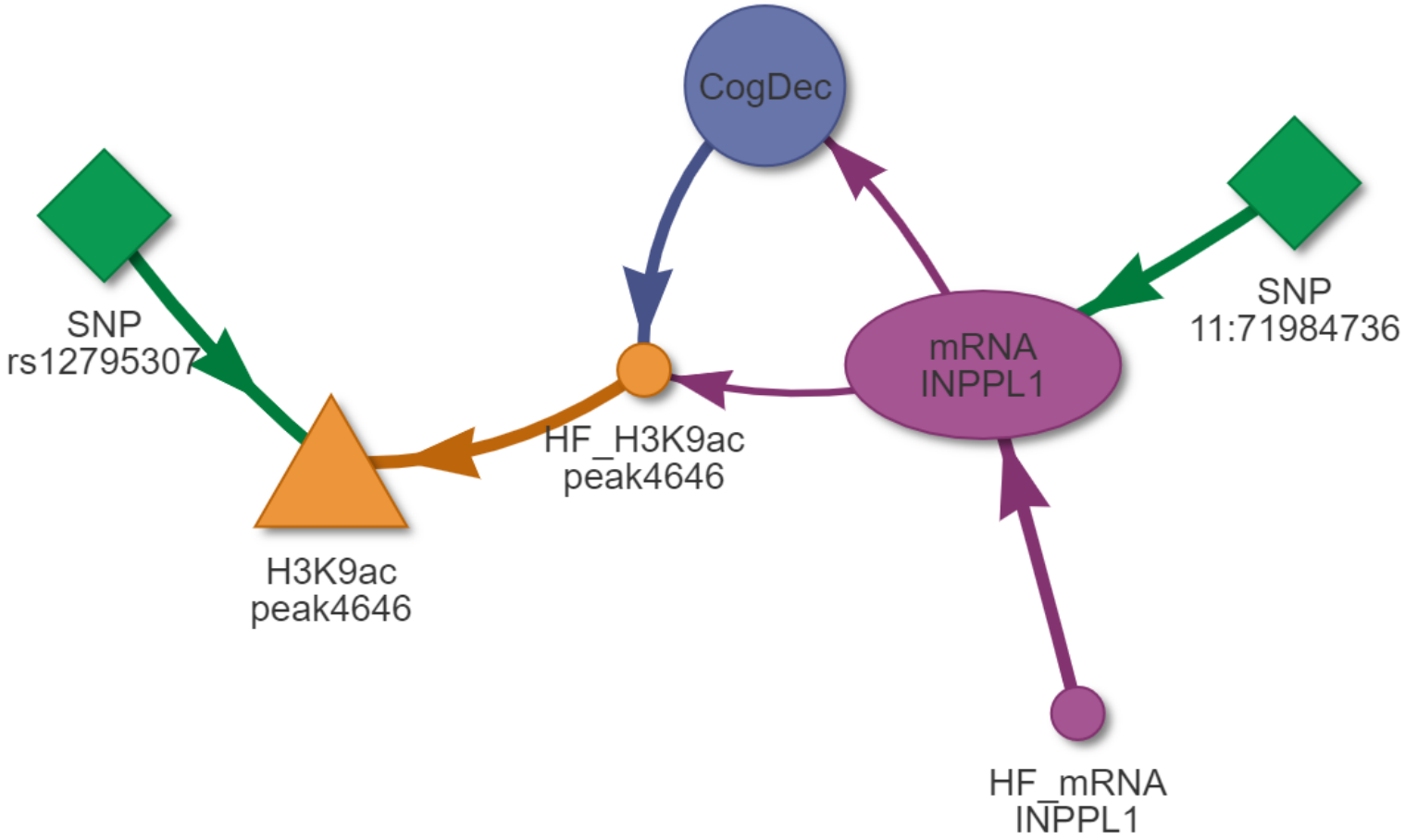

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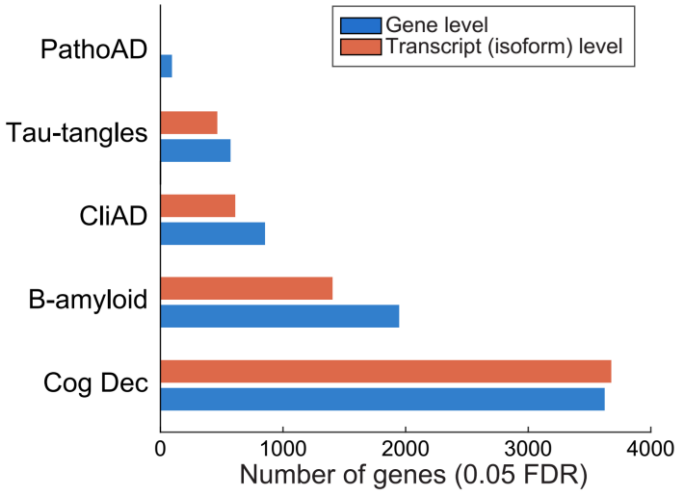
Molecular systems related to AD



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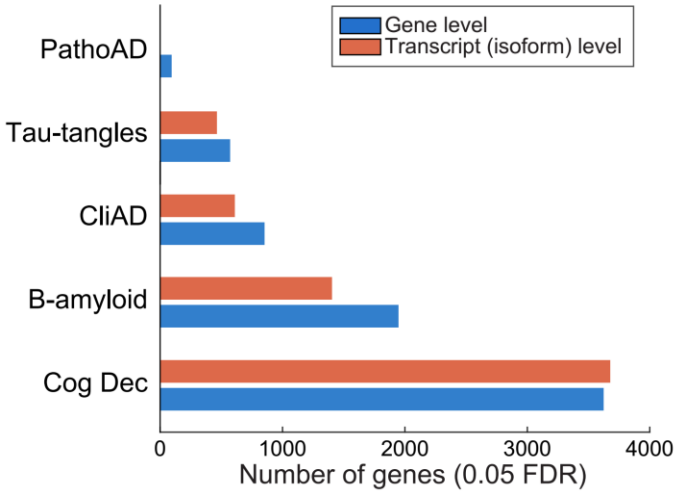
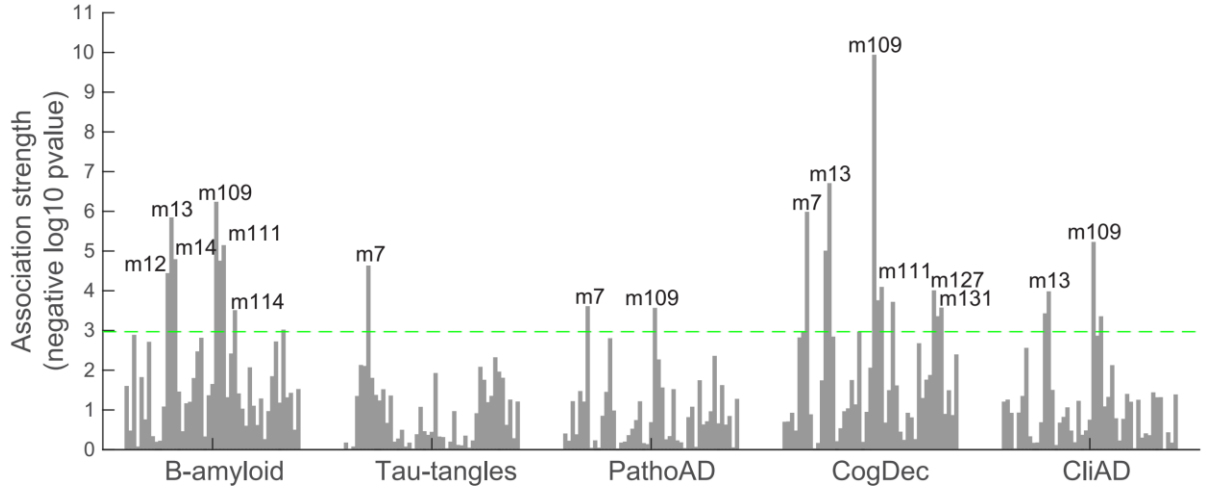
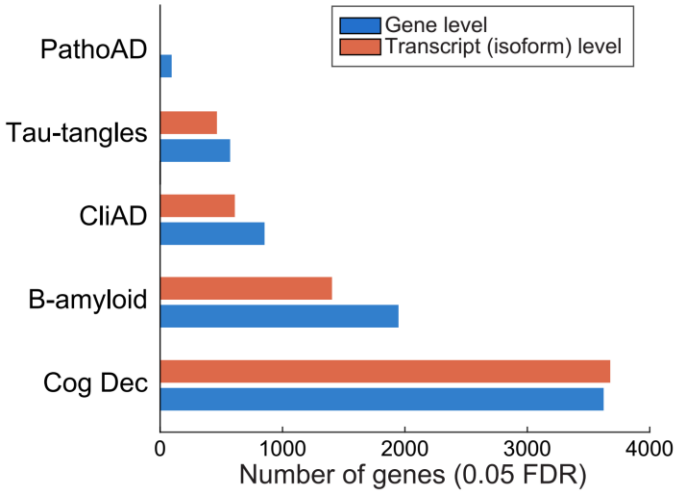
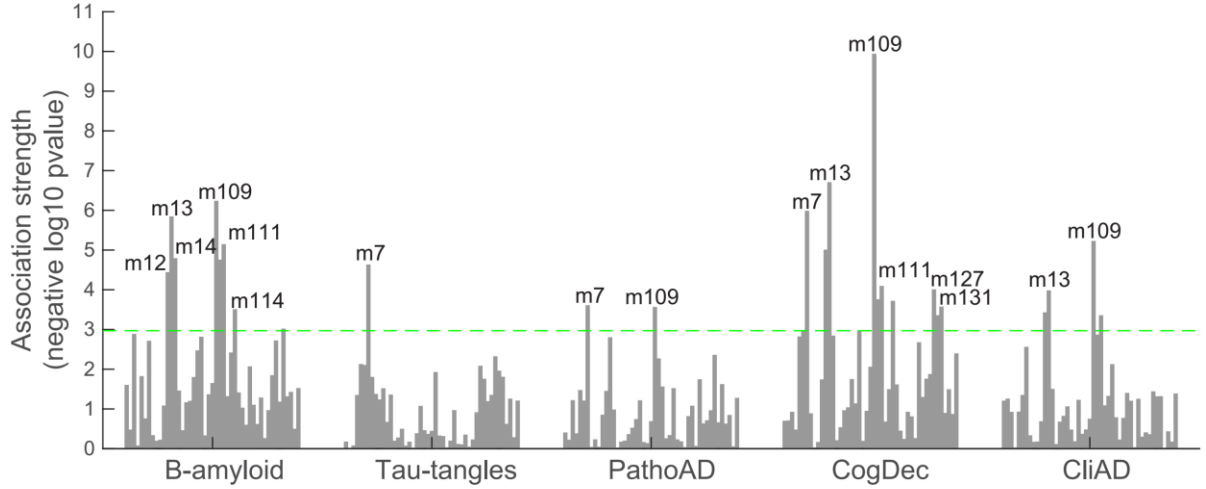
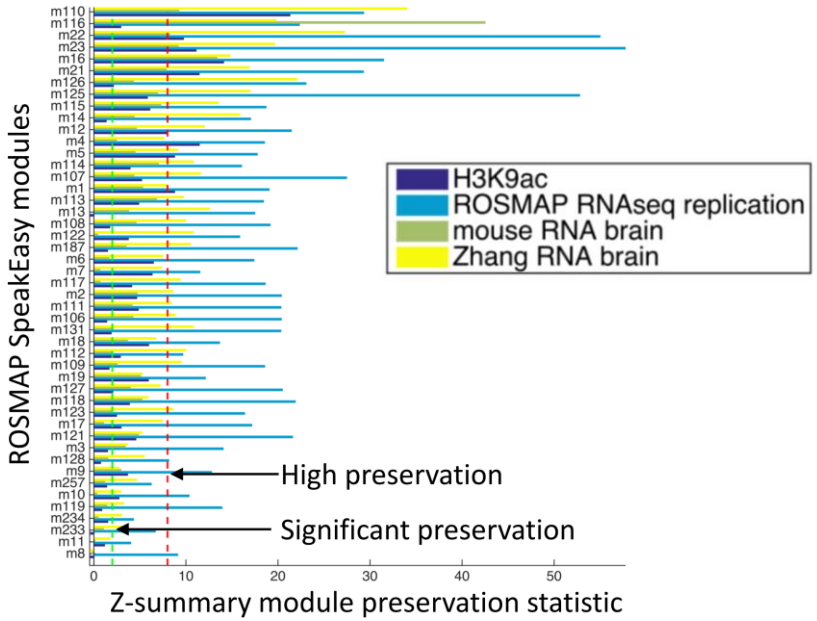




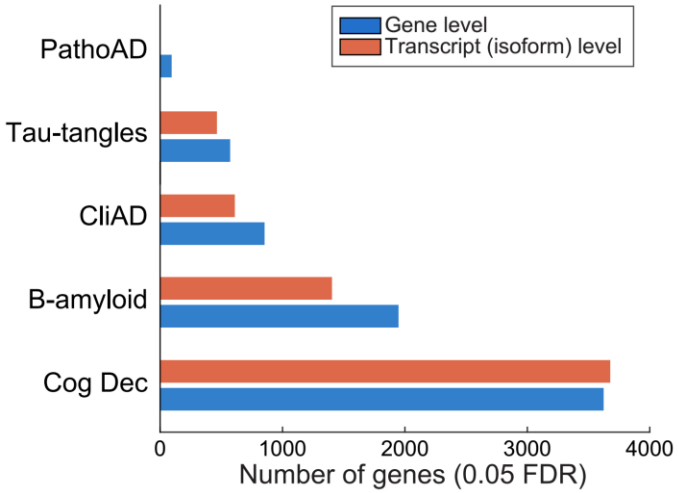
Molecular systems related to AD

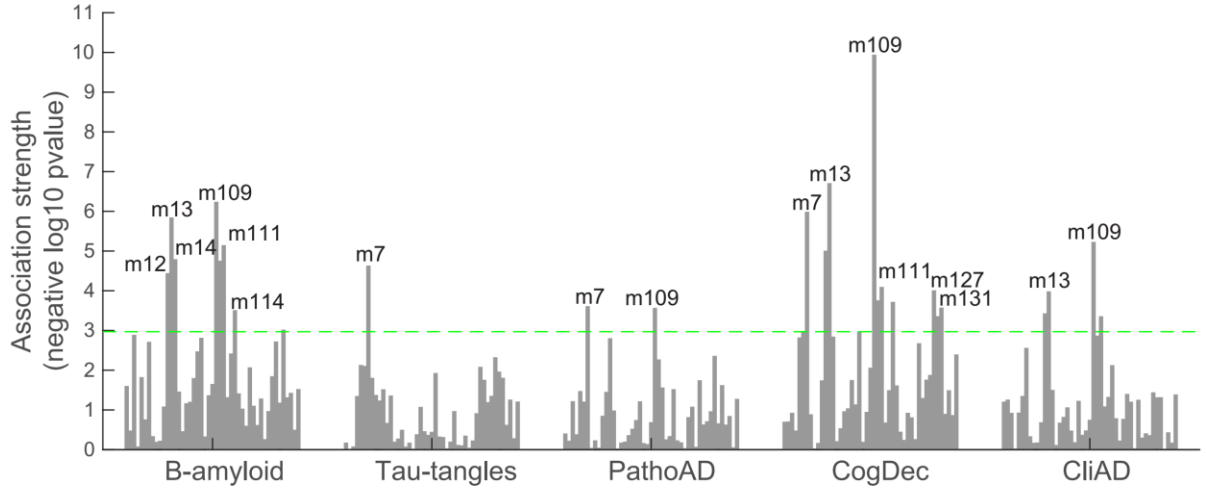


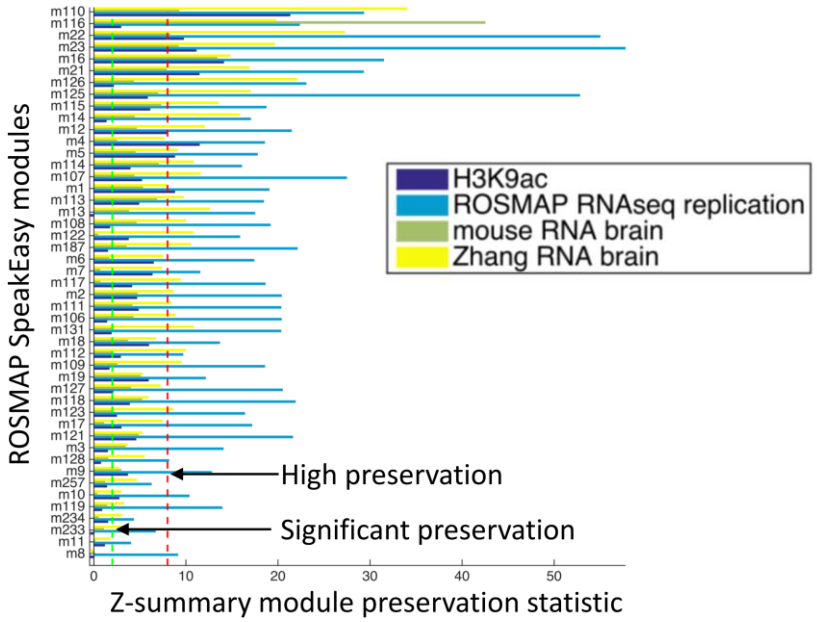


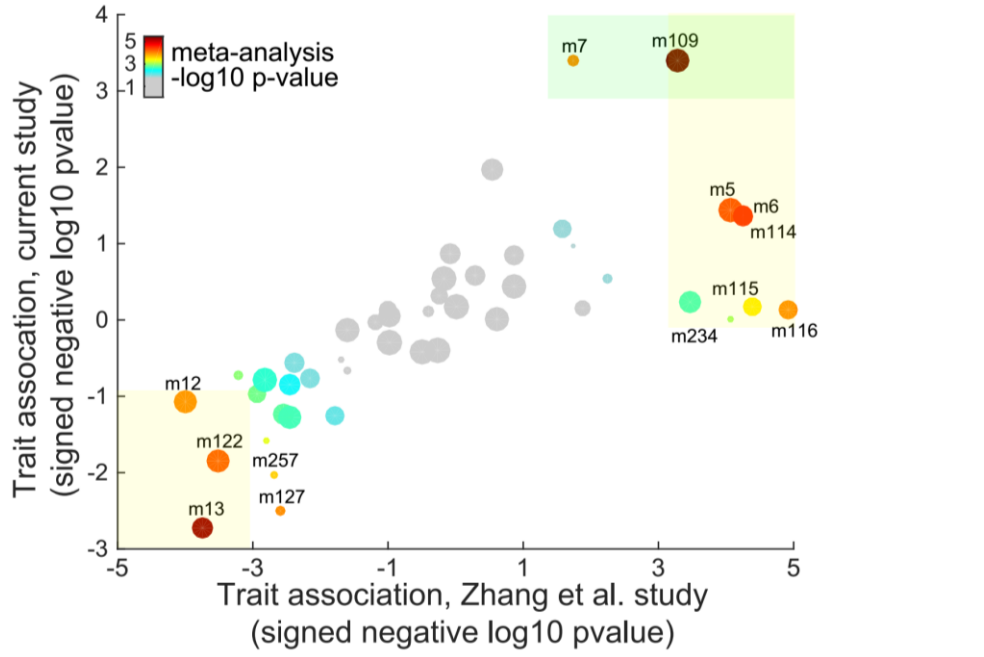


Molecular systems related to AD









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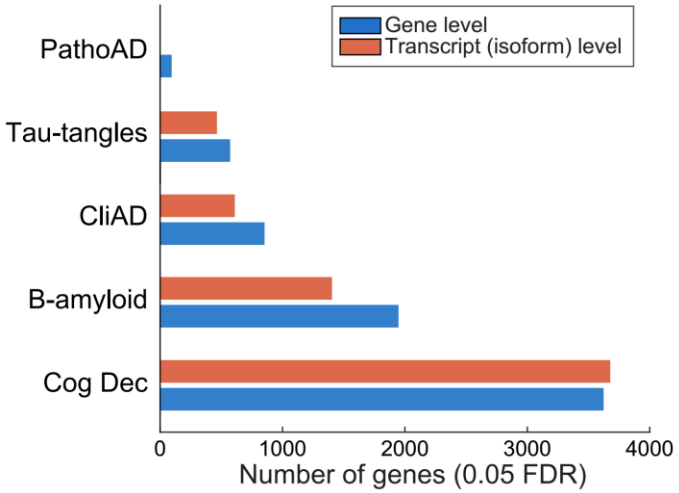
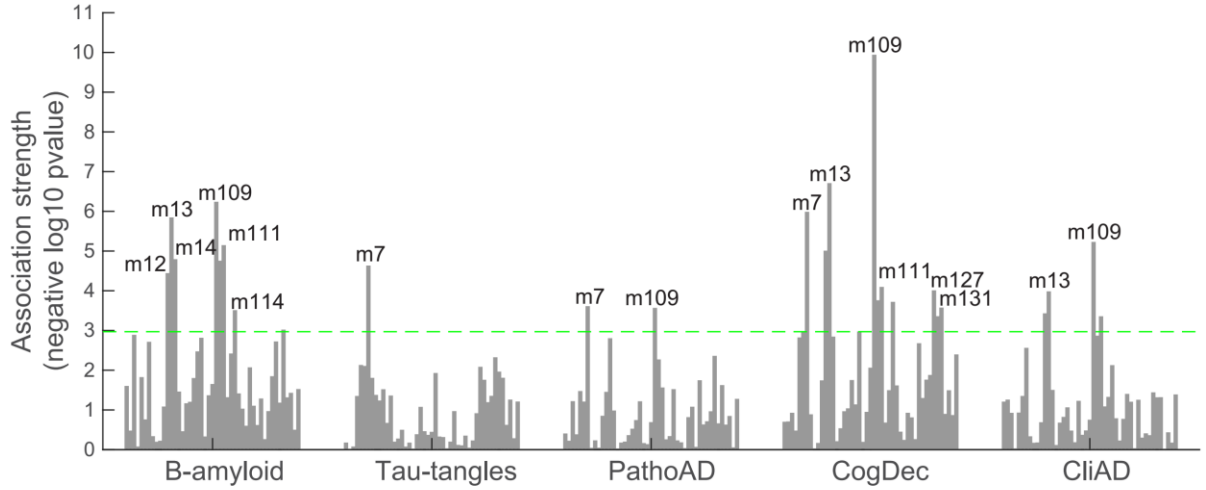
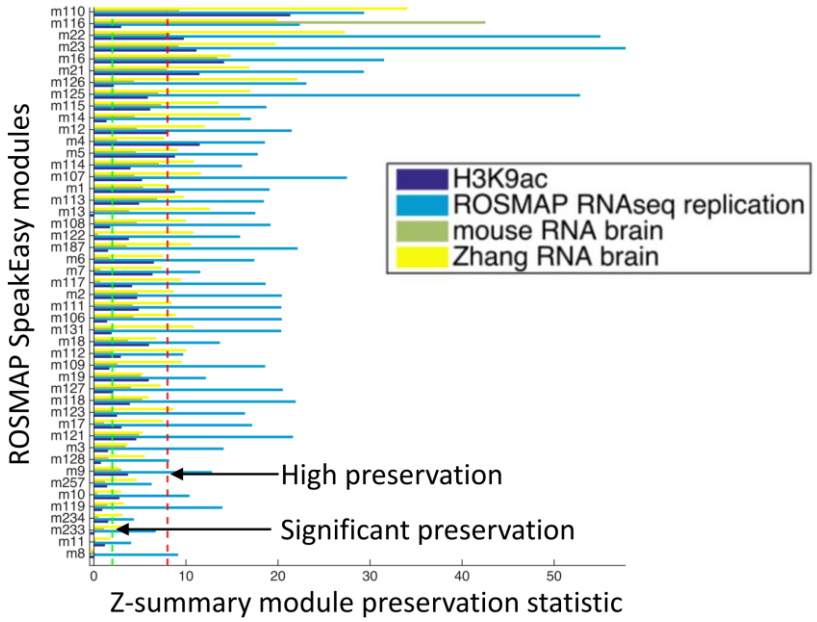
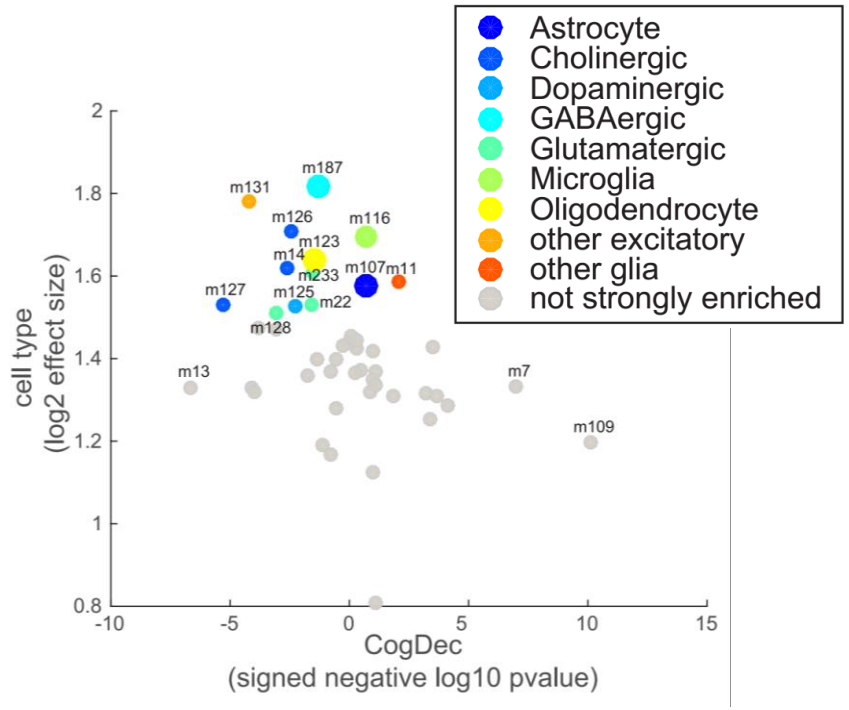
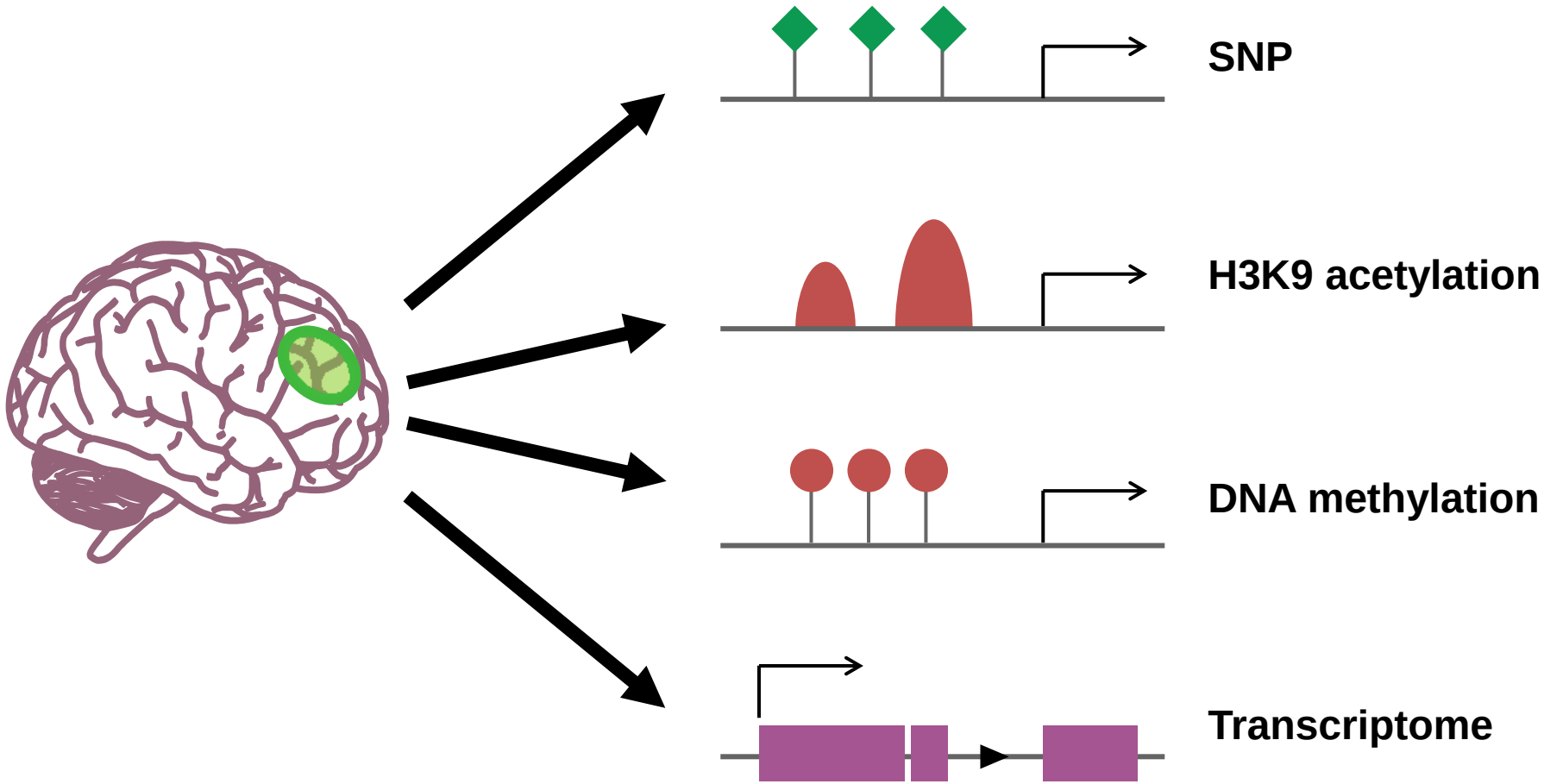








Multi-omic profiling of aged brains

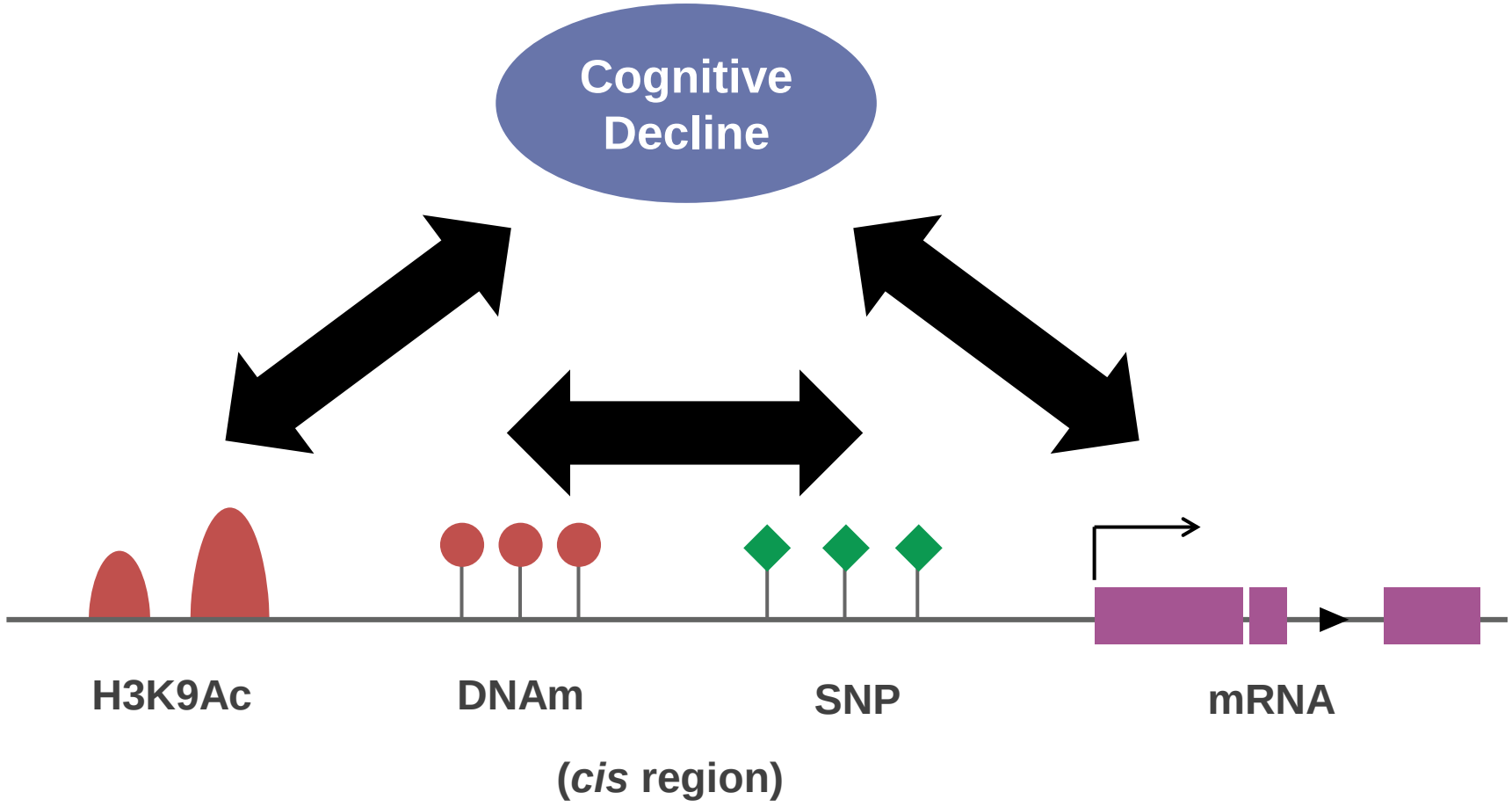


Multi-omic convergence analysis

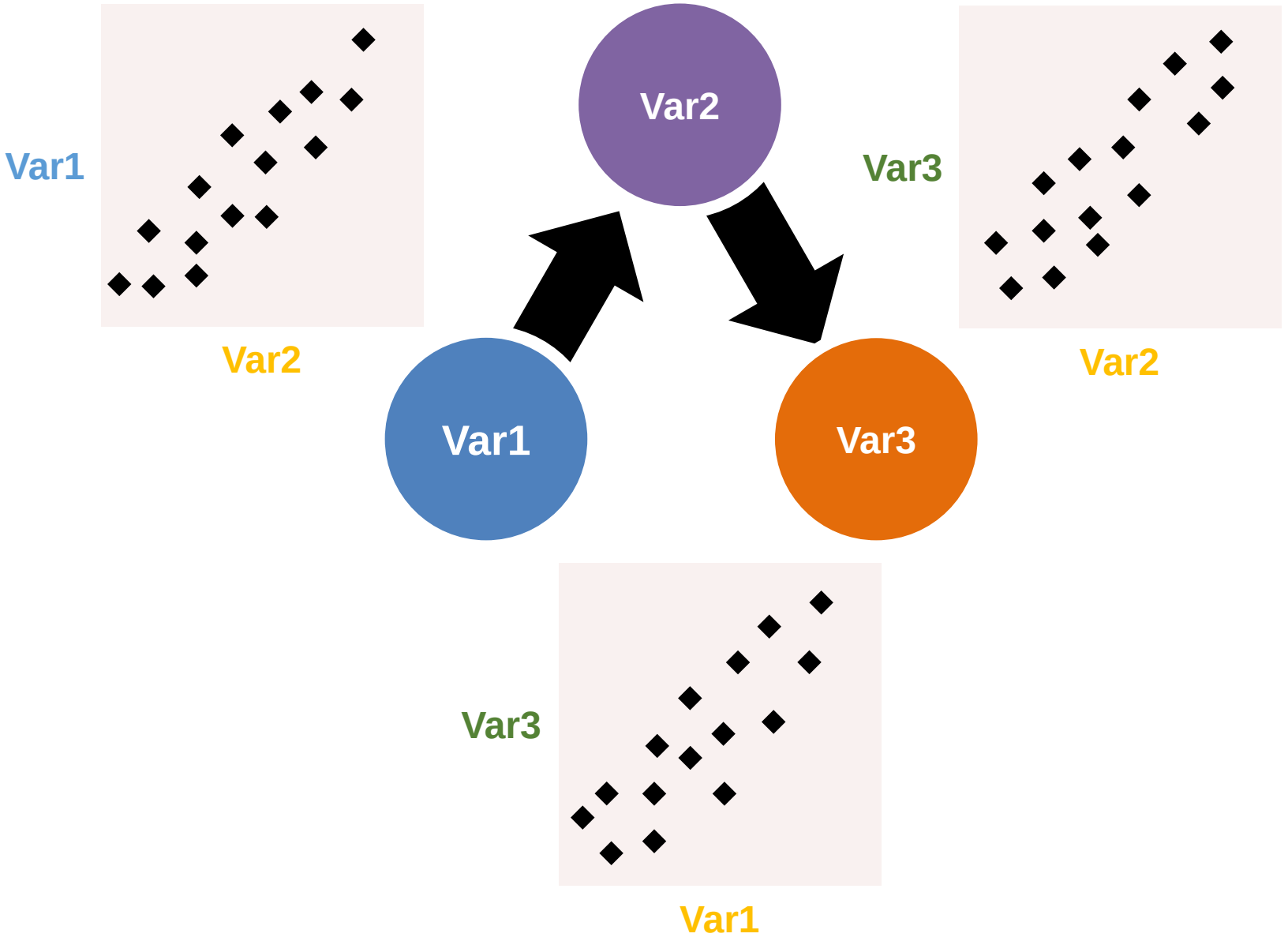
Local regulatory networks

Hans-Ulrich Klein

Combining regulatory elements to describe causal basis of disease



How does the integration actually happen?



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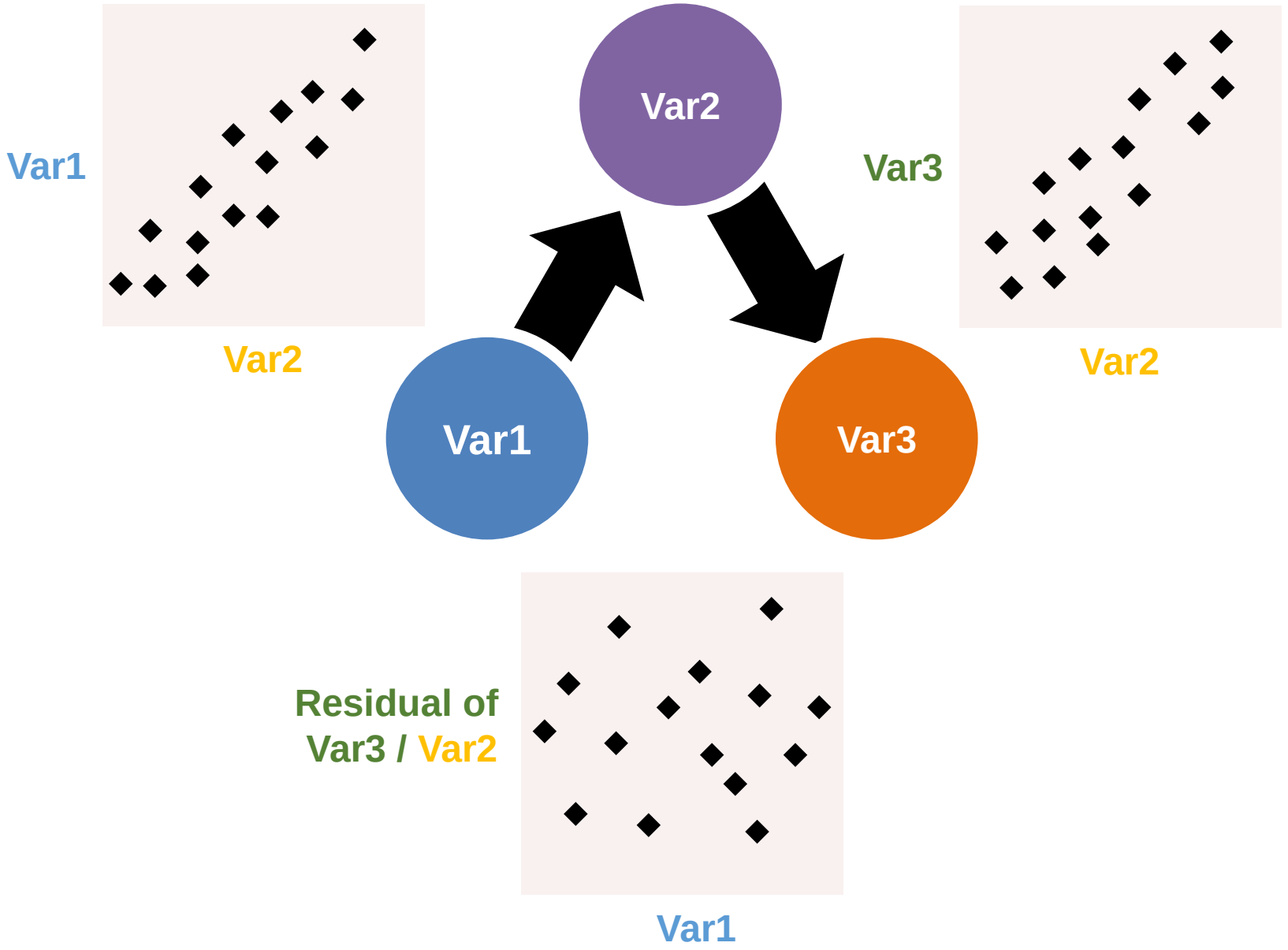
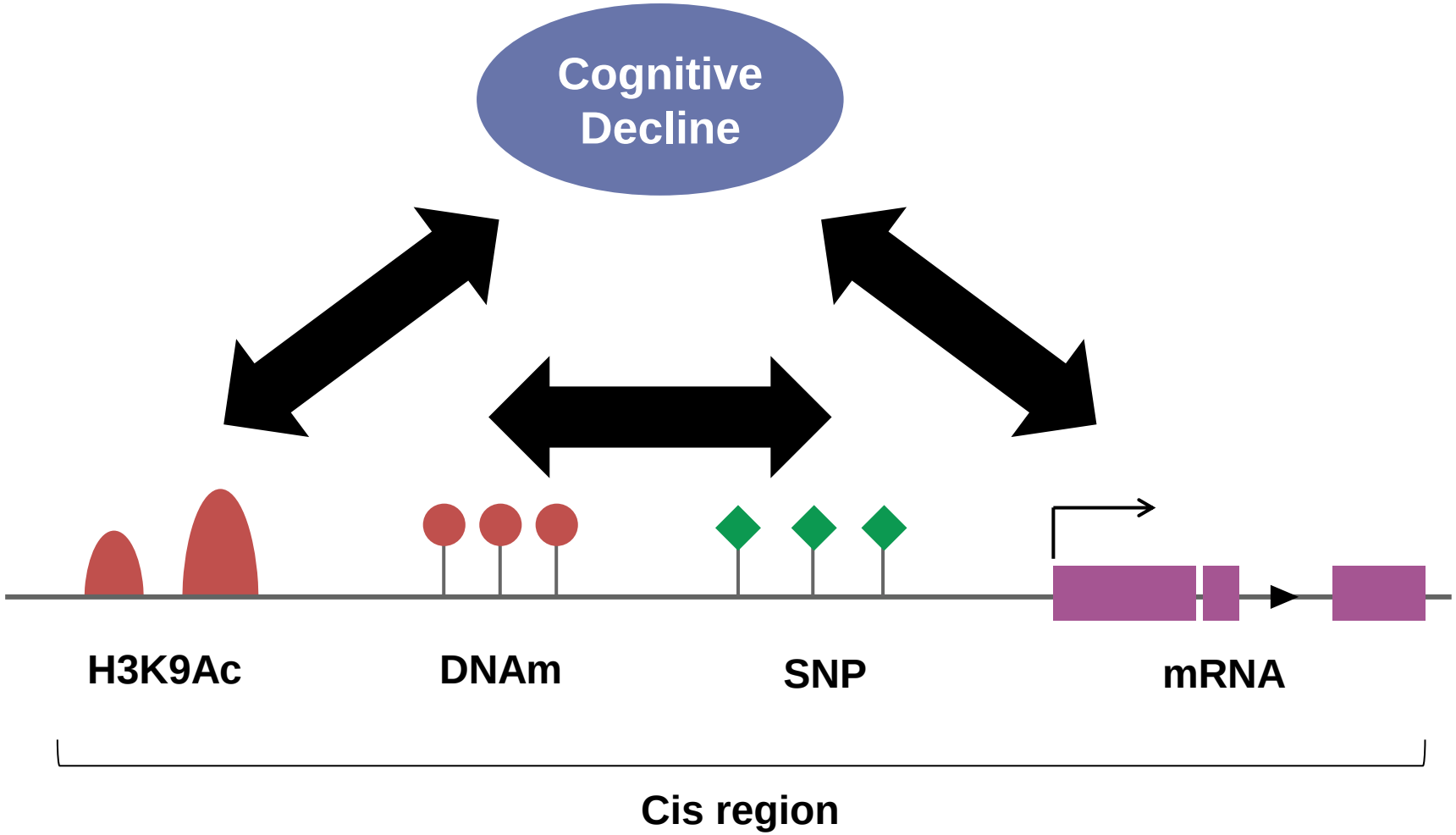


Modeling local regulatory networks



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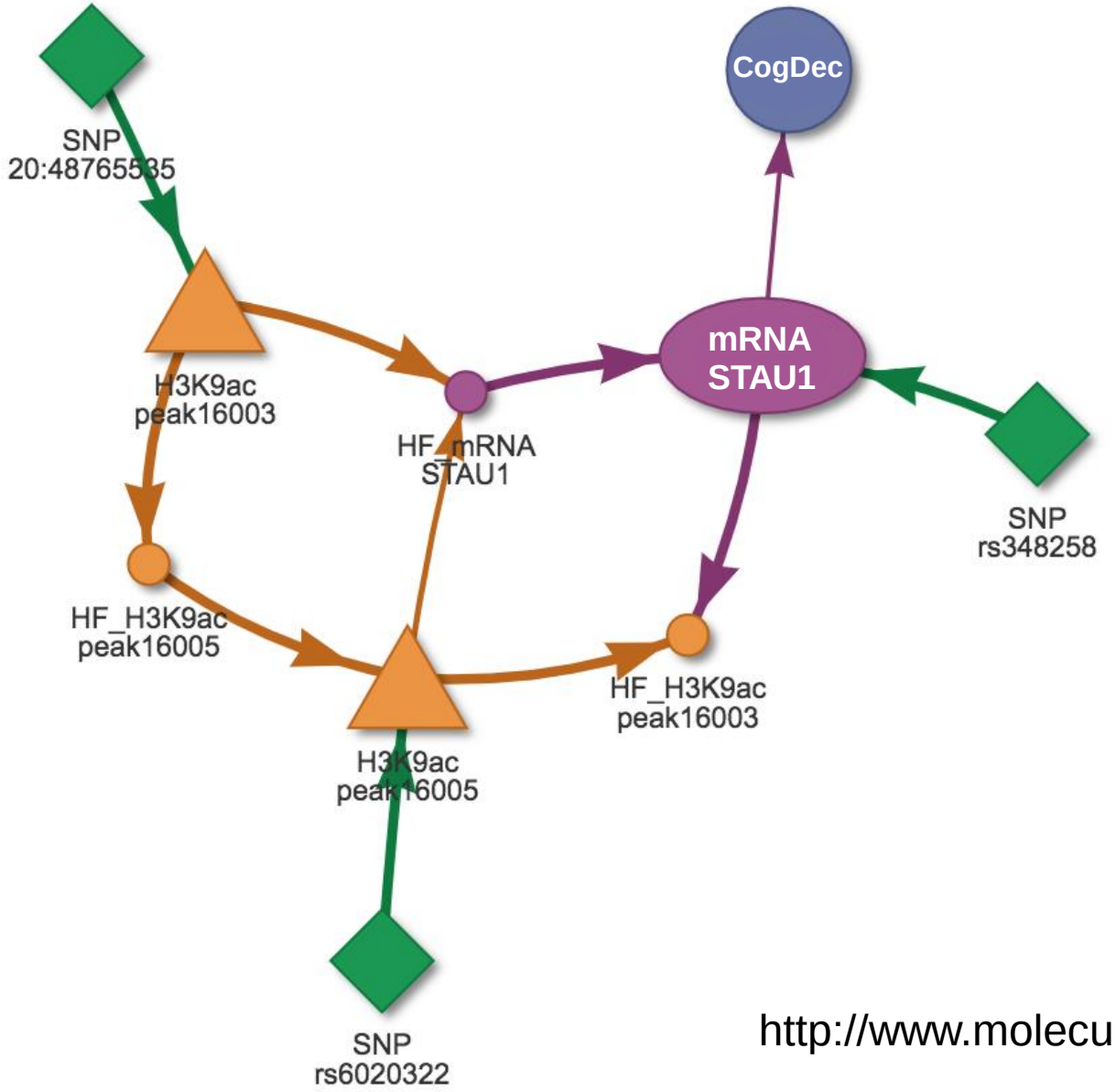

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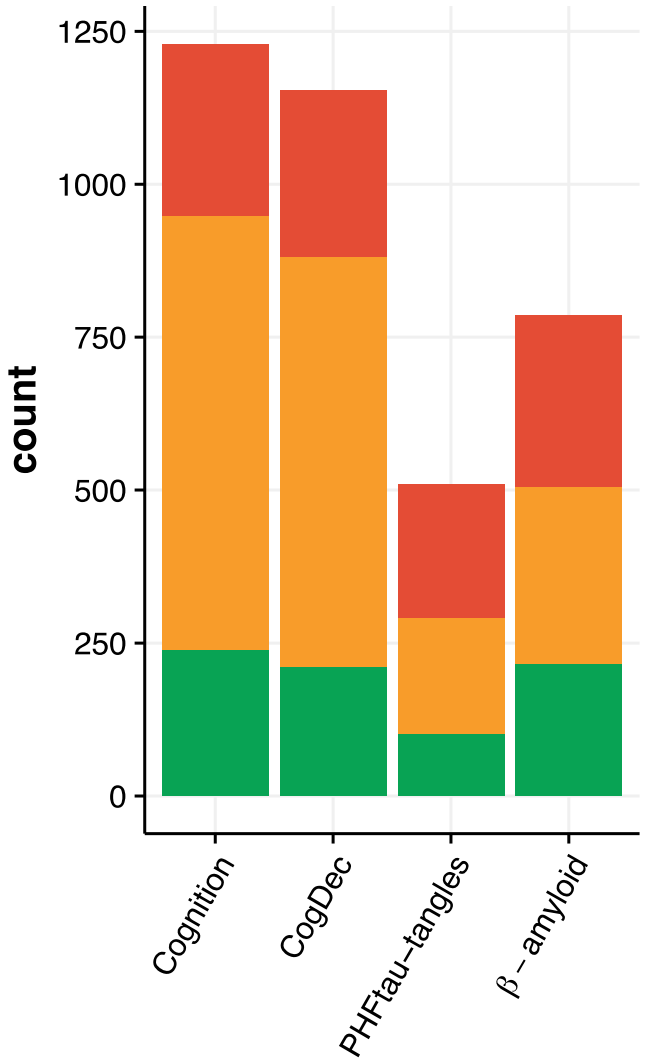
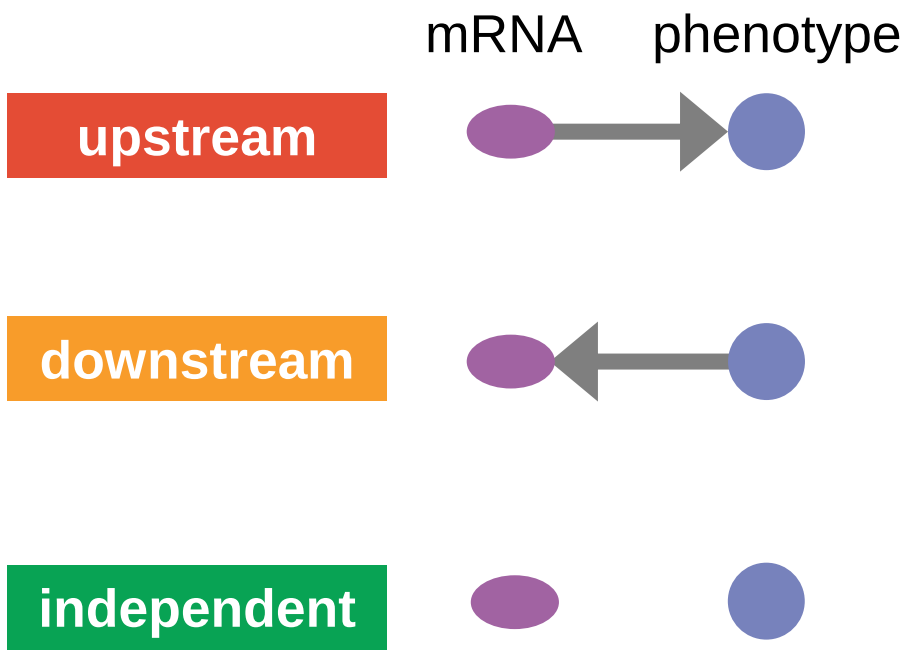
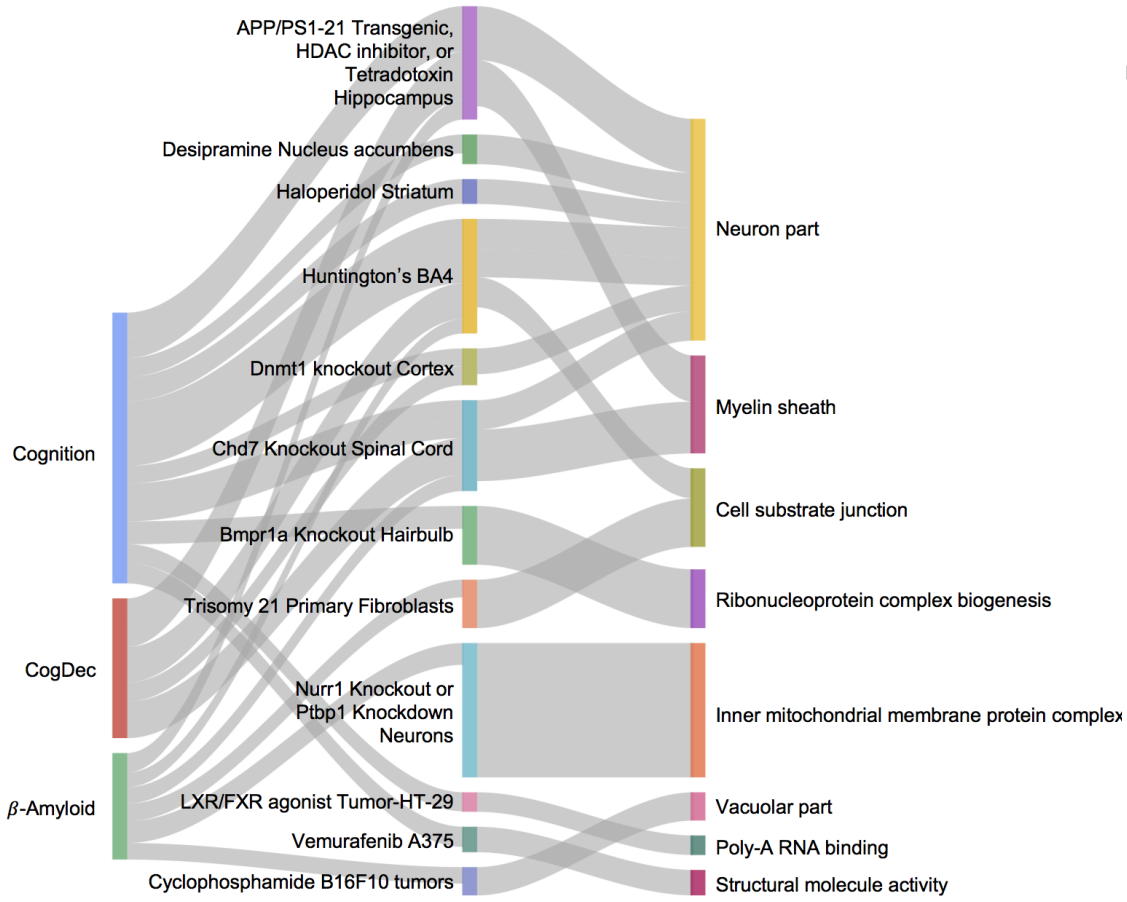
Going beyond differential expression



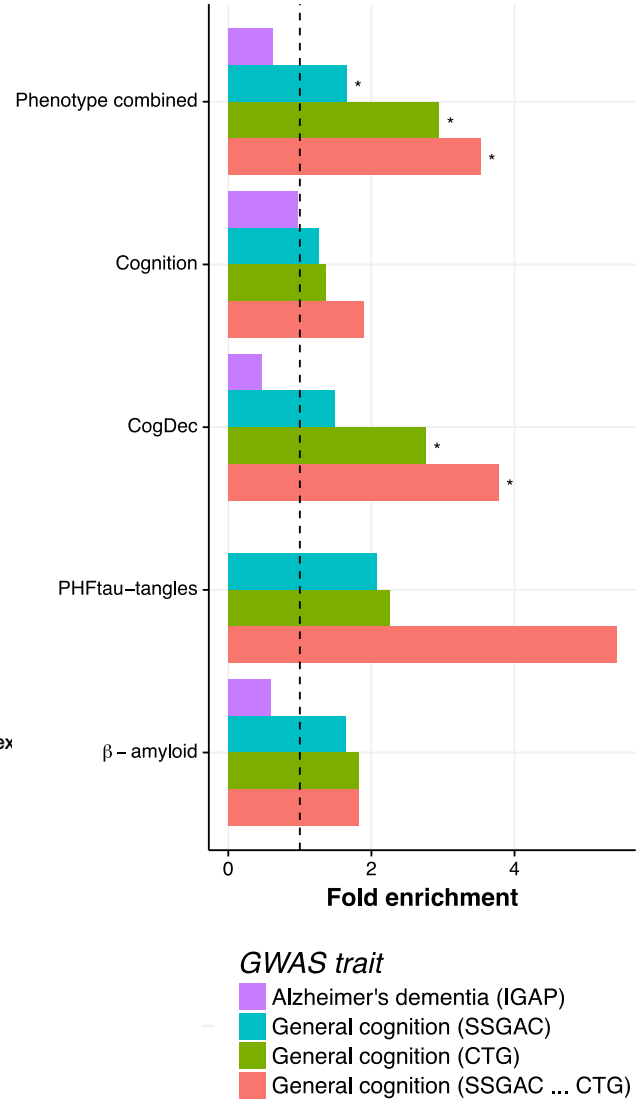


Neuron, mitochondria, RNA-binding, cognition

Molecular systems related with upstream genes

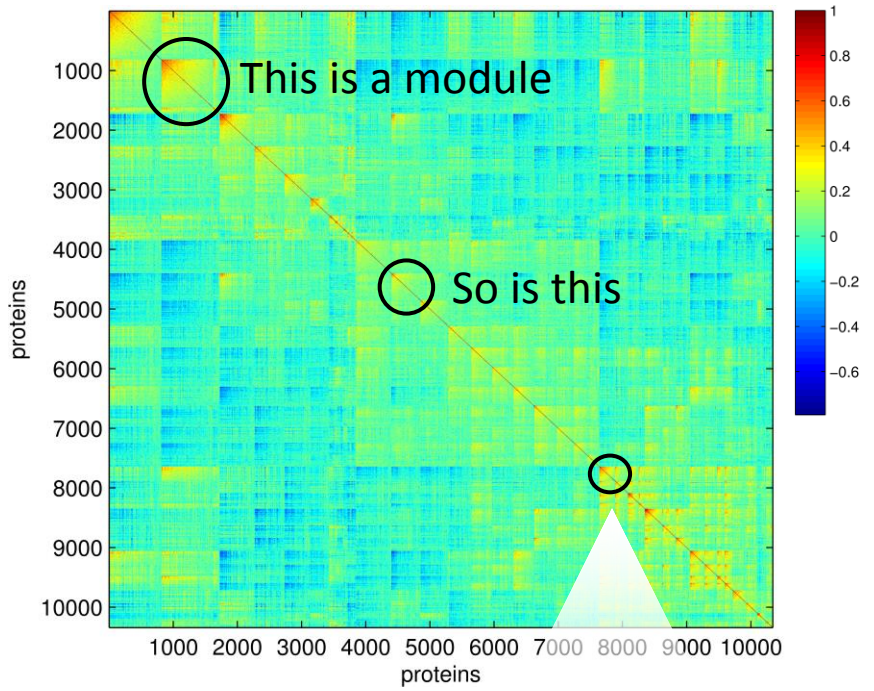


GWAS overlap

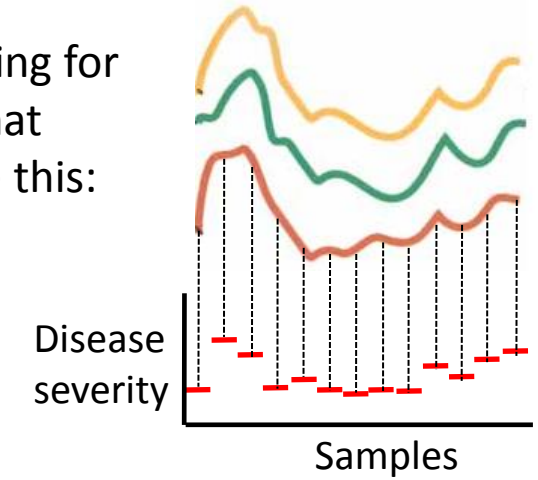


New (last thursday) TMT protein data contributes to targets

- TMT protein measurements from Emory, providing ~10K proteins on 160 ROSMAP participants (400 in process)
- No major artifacts found in data
- Diverse coabundant molecular systems observed in data – some systems not found in RNA, including splicing, extracellular, ER and protein localization
- Also some trait-associated systems found in protein, which were in RNA but not trait-correlated



We're looking for modules that behave like this:



Approach to generating protein targets

- Identify coabundant protein sets
- Compute all trait associations
- Build module-trait networks
- Get genetic priors
- Check cell type enrichment
- Build LRN’s integrating all prior data
- Compare to gene expression and other protein datasets
- Integrate with neuroimaging

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We made it to here (ish)

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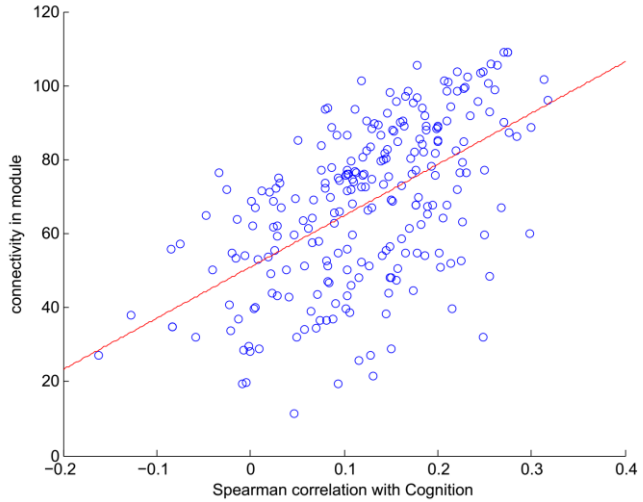
Abbreviated approach: Coabundance hubs in systems associated with AD traits



Protein modules associated with AD-related traits

Many molecular systems associated with cognition, or tdp43, Lewy Bodies, amyloid or tau:

Mitochondria (specifically transcription of mitochondrial genes and ribosomes)

Protein localization

ER

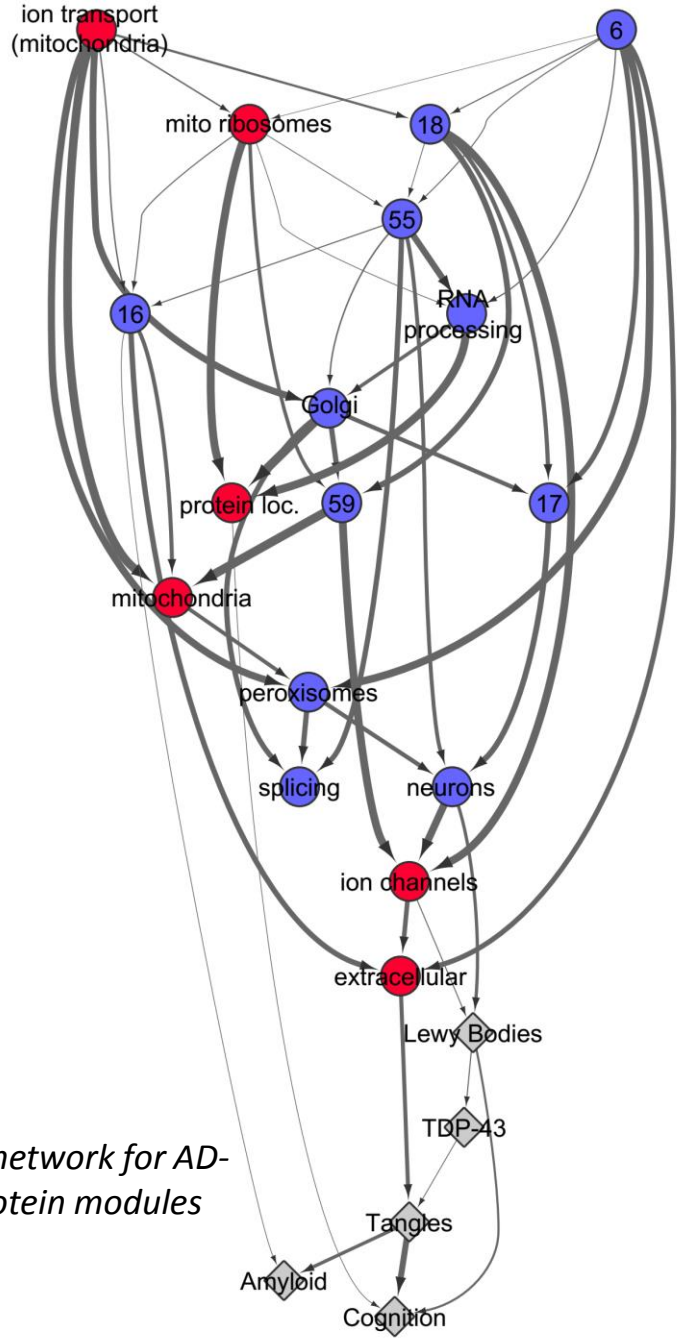
RNA processing

Splicing

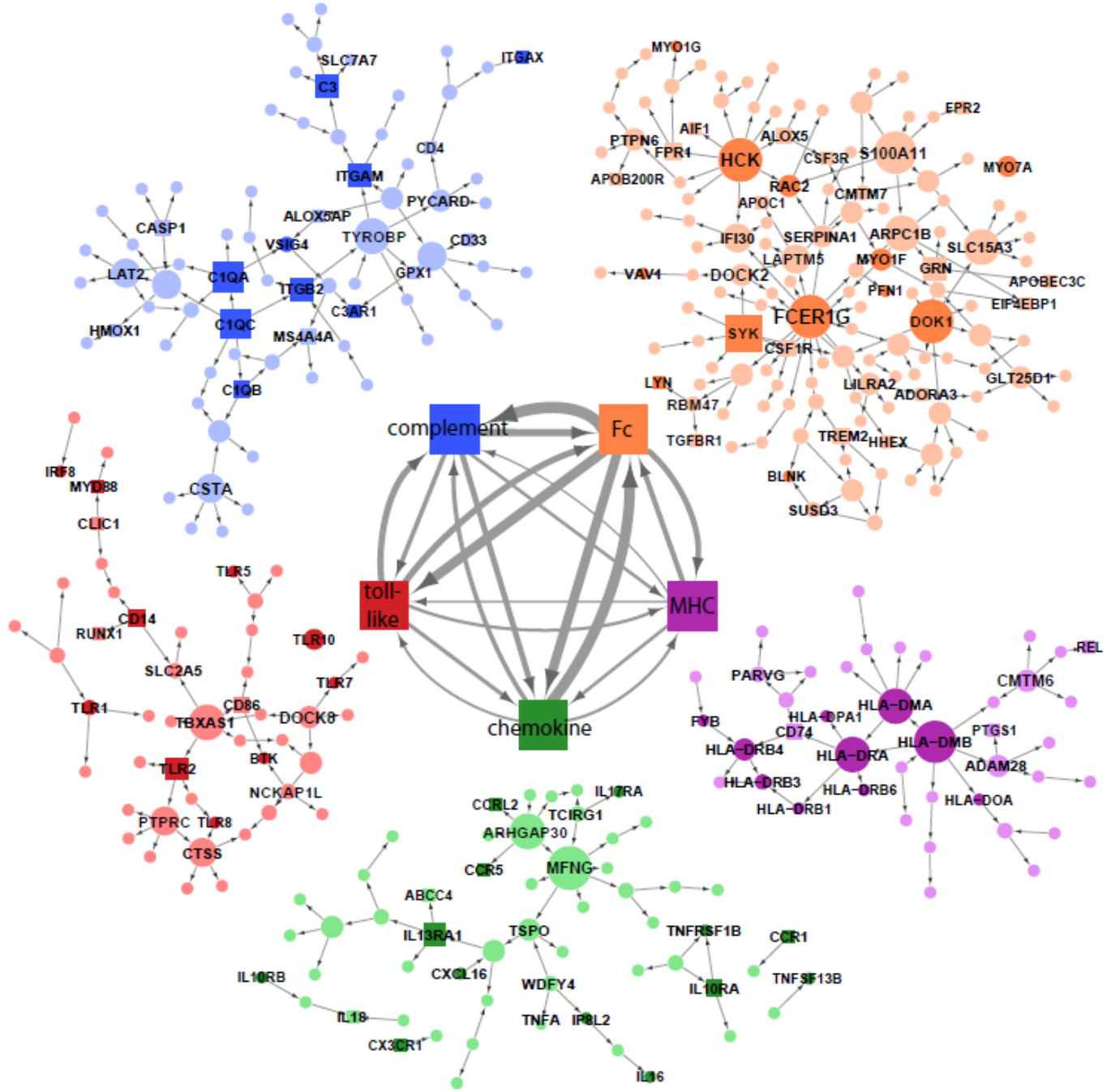
Peroxisomes

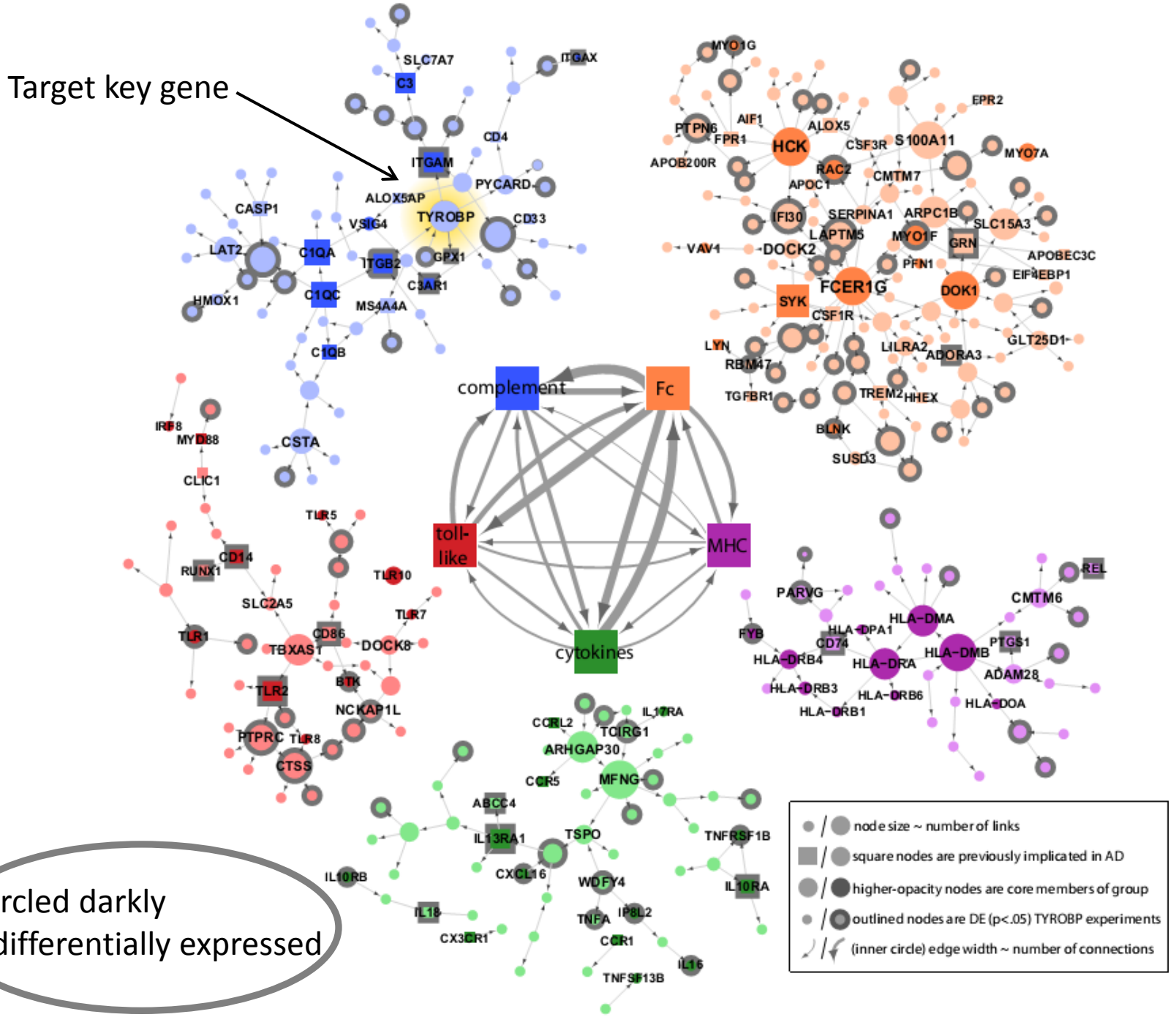
Certain classes of synaptic ion channels

Exosomes and extracellular processes



Module-trait network for AD-associated protein modules


complement
Fc
toll-like
MHC
chemokine
SLC7A7
C3
ITGAX
CD4
ITGAM
PYCARD
ALOX5AP
TYROBP
CD33
CASP1
VSIG4
LAT2
C1QA
TYROBP
GPX1
C3AR1
HMOX1
C1QC
MS4A4A
C1QB
CSTA
MYO1G
EPR2
AIF1
PTPN6
ALOX5
FPR1
HCK
CSF3R
S100A11
MYO7A
APOB200R
RAC2
CMTM7
APOC1
IFI30
SERPINA1
ARPC1B
SLC15A3
LAPTM5
MYO1F
GRN
VAV1
DOCK2
PFN1
APOBEC3C
EIF4EBP1
FCER1G
SYK
DOK1
CSF1R
LYN
LILRA2
ADORA3
GLT25D1
RBM47
TGFBR1
TREM2
HHEX
BLNK
SUSD3
IRF8
MYD88
CLIC1
TLR5
CD14
RUNX1
TLR10
SLC2A5
TLR7
TLR1
CD86
TBXAS1
DOCK8
BTK
TLR2
NCKAP1L
PTPRC
TLR8
CTSS
REL
PARVG
CMTM6
HLA-DMA
FYB
HLA-DPA1
CD74
PTGS1
HLA-DRB4
HLA-DRA
HLA-DMB
ADAM28
HLA-DRB3
HLA-DRB6
HLA-DOA
HLA-DRB1
CCRL2
IL12RA
TCIRG1
ARHGAP30
CCR5
MFNG
ABCC4
TSPO
IL13RA1
TNFRSF1B
CCR1
CXCL16
IL10RA
TNFSF13B
IL10RB
WDFY4
IL18
TNFA
IFNL2
CX3CR1
IL16

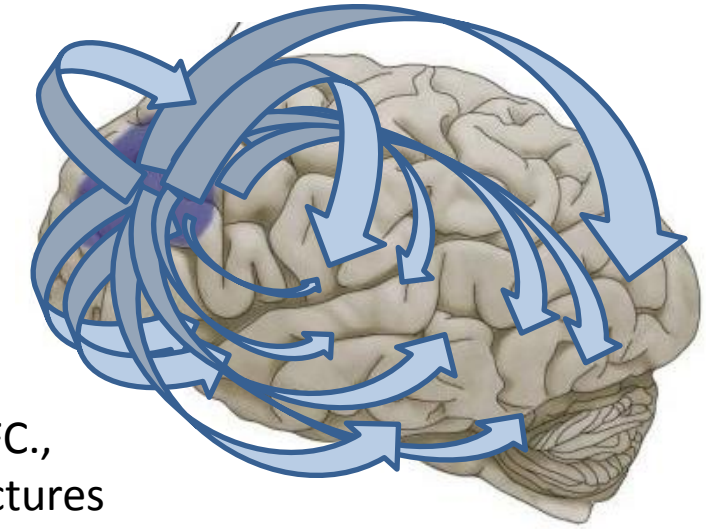

Target key gene
complement
Fc
toll-like
MHC
cytokines
SLC7A7
C3
ITGAX
CD4
ITGAM
PYCARD
ALOX5AP
TYROBP
CD33
CASP1
VSIG4
LAT2
C1QA
ITGB2
GPX1
C3AR1
HMOX1
C1QC
MS4A4A
C1QB
CSTA
IRF8
MYD88
CLIC1
TLR5
CD14
RUNX1
TLR10
SLC2A5
TLR7
TLR1
CD86
TBXAS1
DOCK8
BTK
TLR2
NCKAP1L
PTPRC
TLR8
CTSS
MYO1G
EPR2
AIF1
PTPN6
ALOX5
FPR1
HCK
CSF3R
S100A11
MYO7A
APOB200R
RAC2
CMTM7
APOC1
IFI30
SERPINA1
ARPC1B
SLC15A3
LAPTM5
MYO1F
GRN
VAV1
DOCK2
APOBEC3C
PFN1
EIF4EBP1
SYK
FCER1G
DOK1
CSF1R
LYN
LILRA2
ADORA3
GLT25D1
RBM47
TGFBR1
TREM2
HHEX
BLNK
SUSD3
CCRL2
IL17RA
TCIRG1
ARHGAP30
CCR5
MFNG
ABCC4
TNFRSF1B
IL13RA1
TSPO
IL10RB
CXCL16
WDFY4
IL10RA
IL18
TNFA
IP8L2
CX3CR1
CCR1
IL16
TNFSF13B
PARVG
REL
CMTM6
FYB
HLA-DPA1
HLA-DMA
CD74
HLA-DRB4
HLA-DRA
HLA-DMB
PTGS1
ADAM28
HLA-DRB3
HLA-DRB6
HLA-DOA
HLA-DRB1
node size ~ number of links
square nodes are previously implicated in AD
higher-opacity nodes are core members of group
outlined nodes are DE (p<.05) TYROBP experiments
(inner circle) edge width ~ number of connections
Circled darkly
=differentially expressed

Summary of approach to “imaging-omics”

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.,
But we map them onto global brain structures

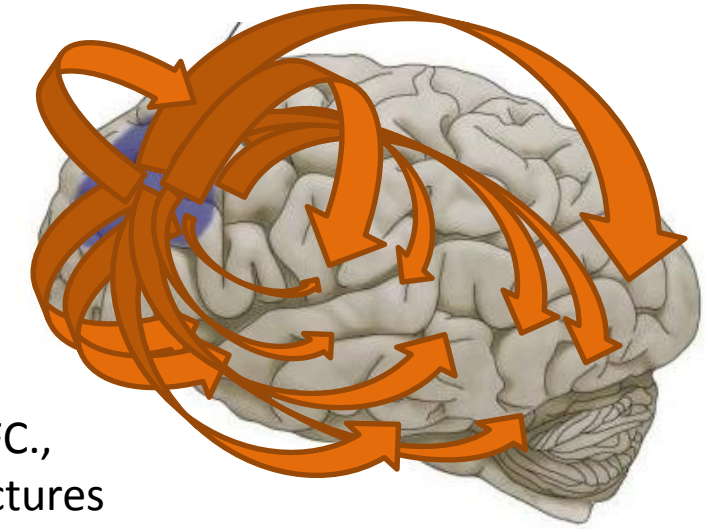
Summary of approach to “imaging-omics”

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
3. Repeat for each molecular system

Molecular system *A*

Molecular system *B*



Molecular systems are measured in DLPFC.,
But we map them onto global brain structures