

Towards a personalized cognitive neuroscience: The MyConnectome Project

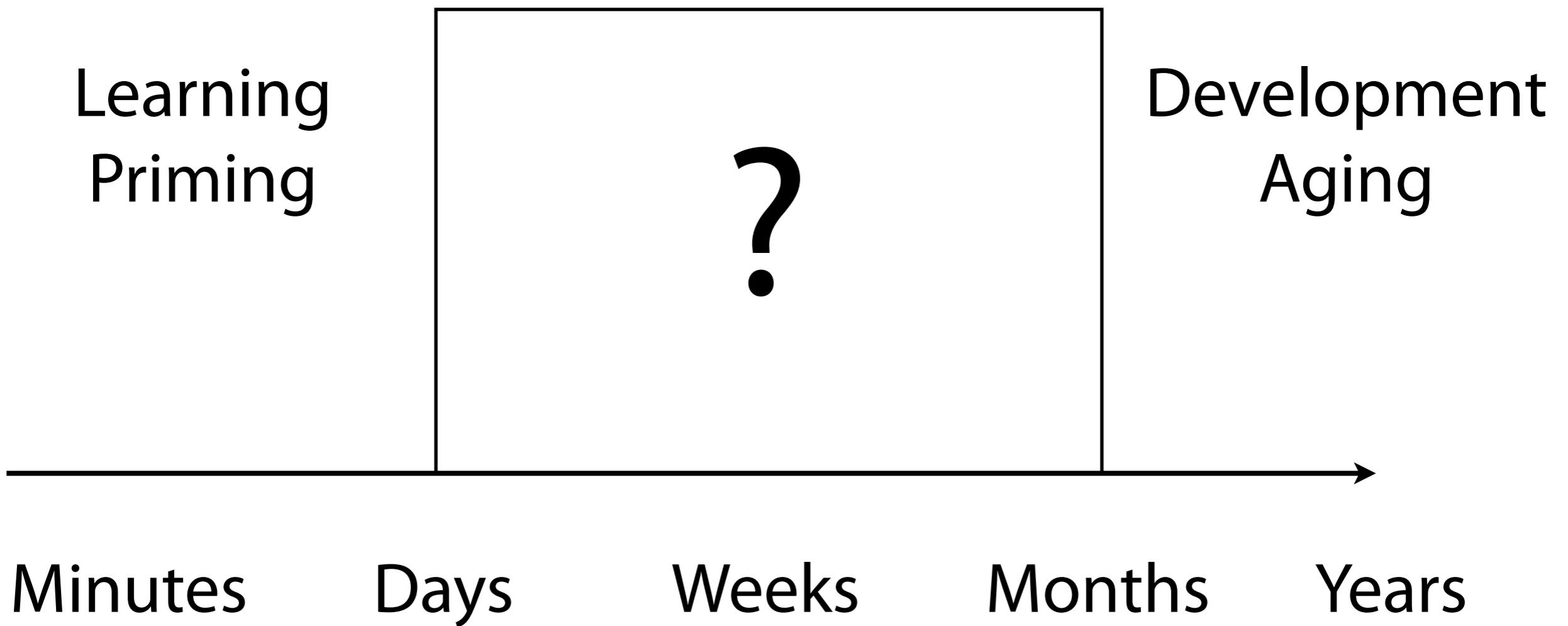
Russell Poldrack

Departments of Psychology
and Neurobiology

Imaging Research Center
University of Texas at Austin

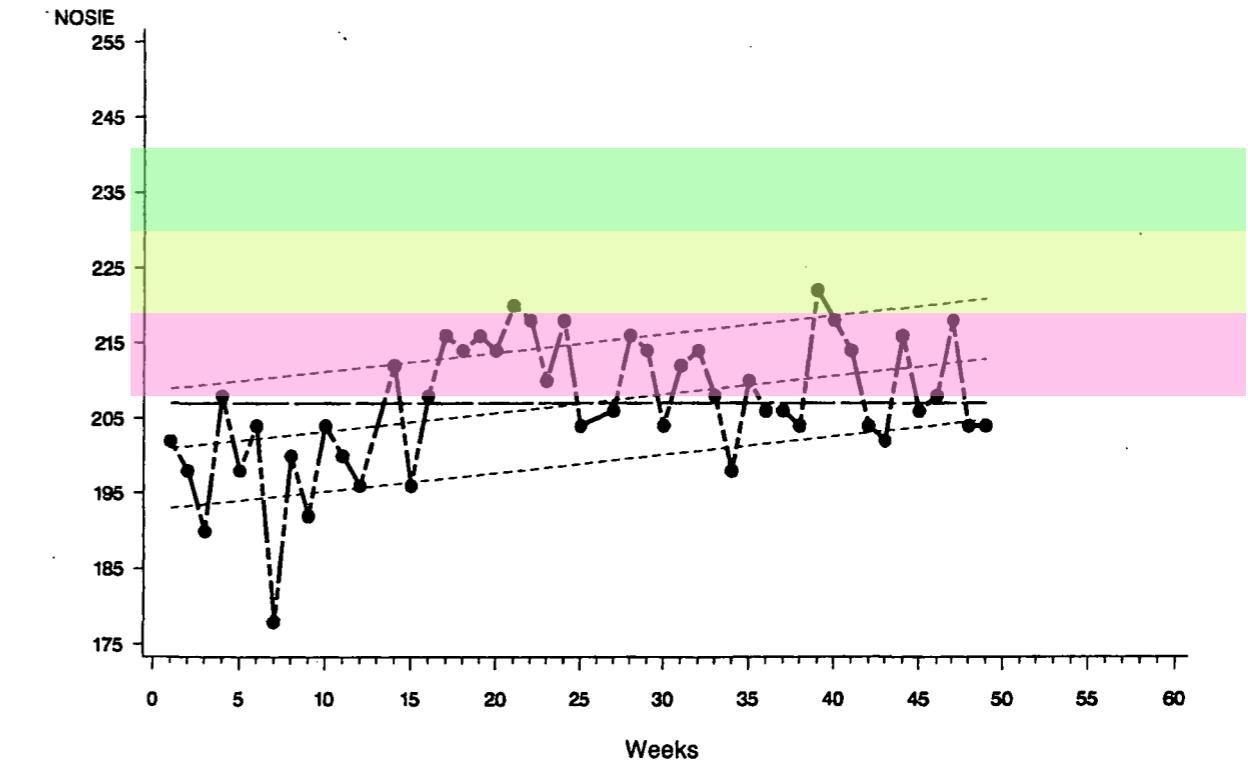
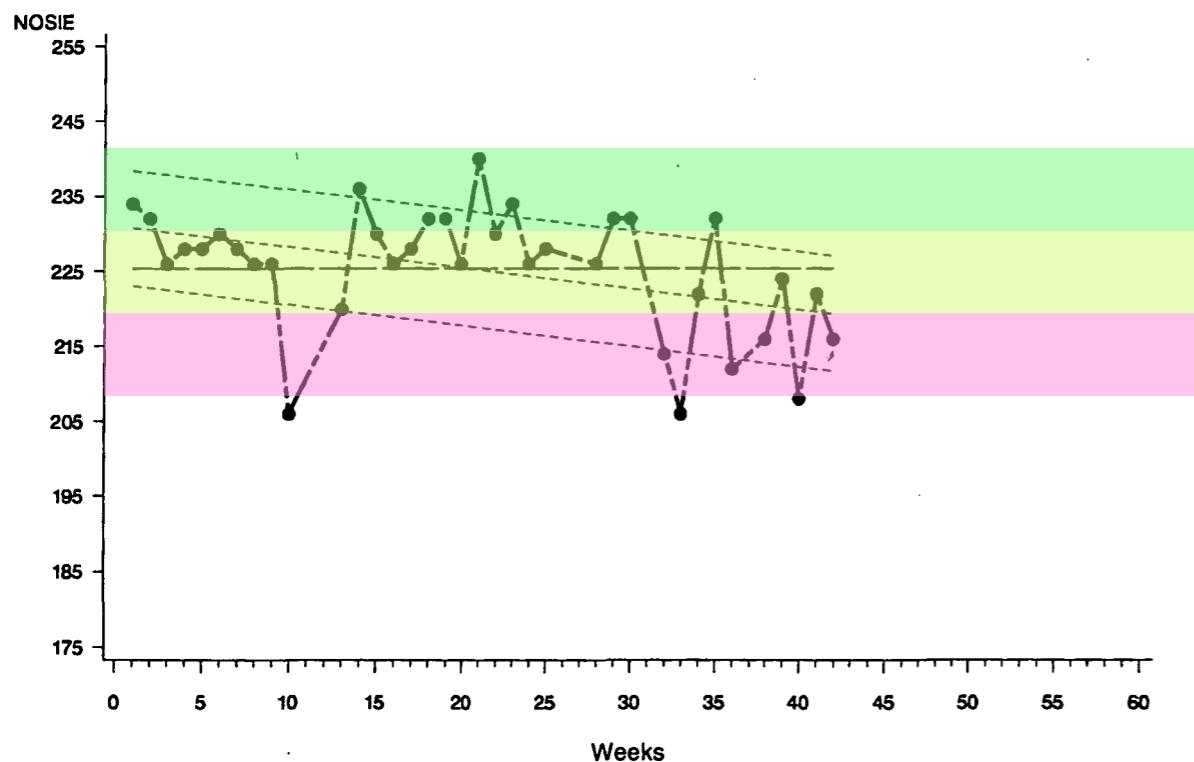
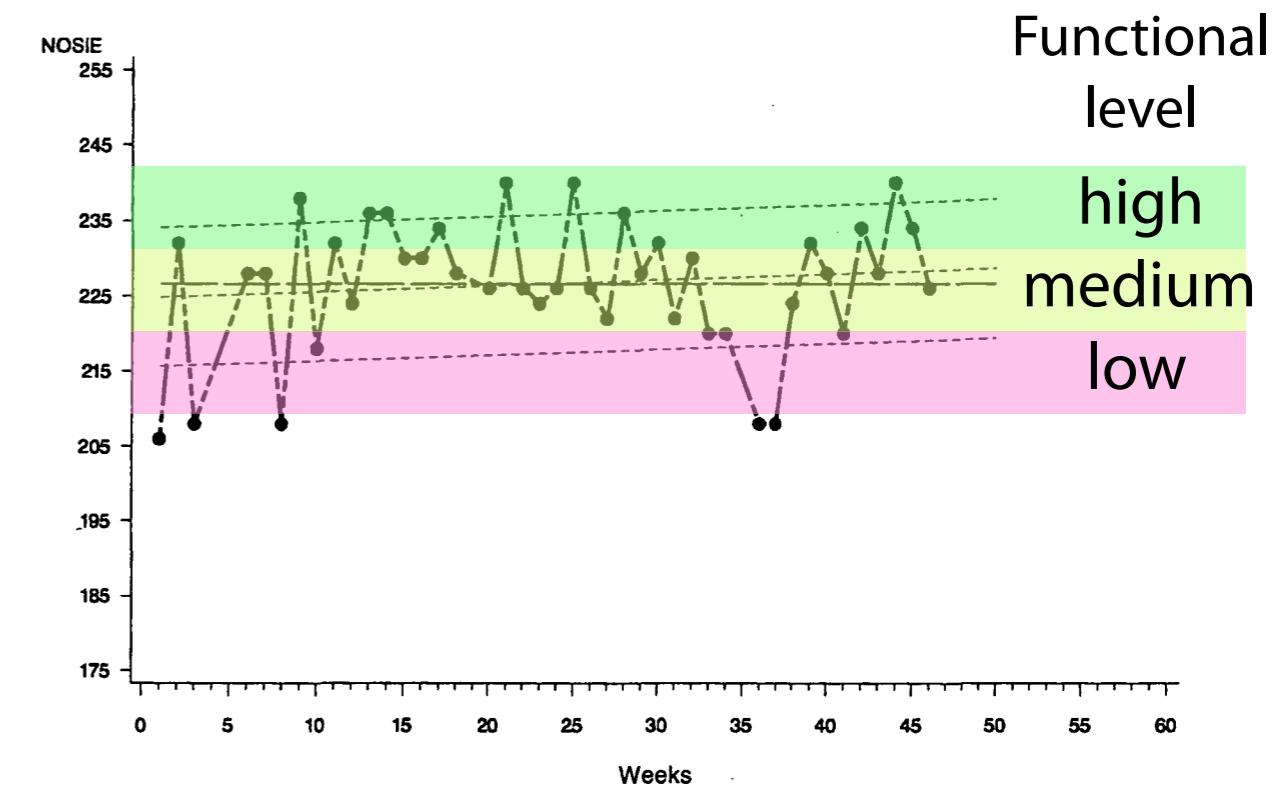
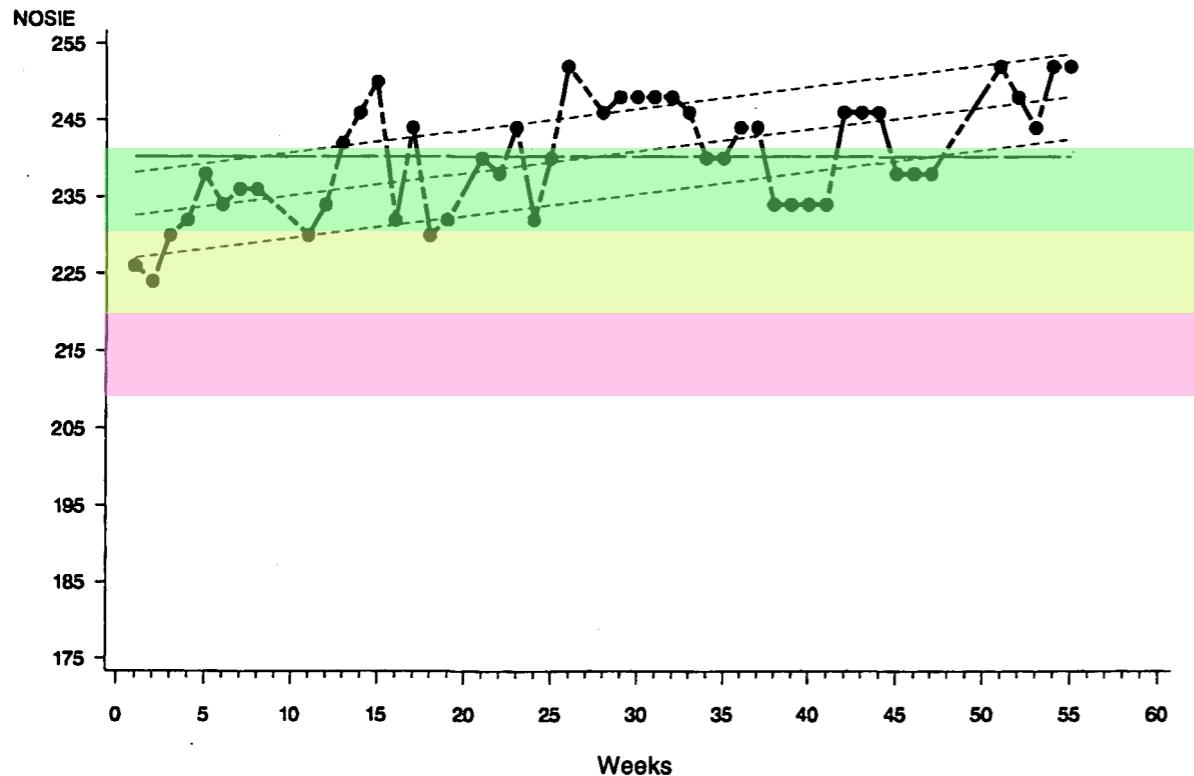


How does the human brain change over time?



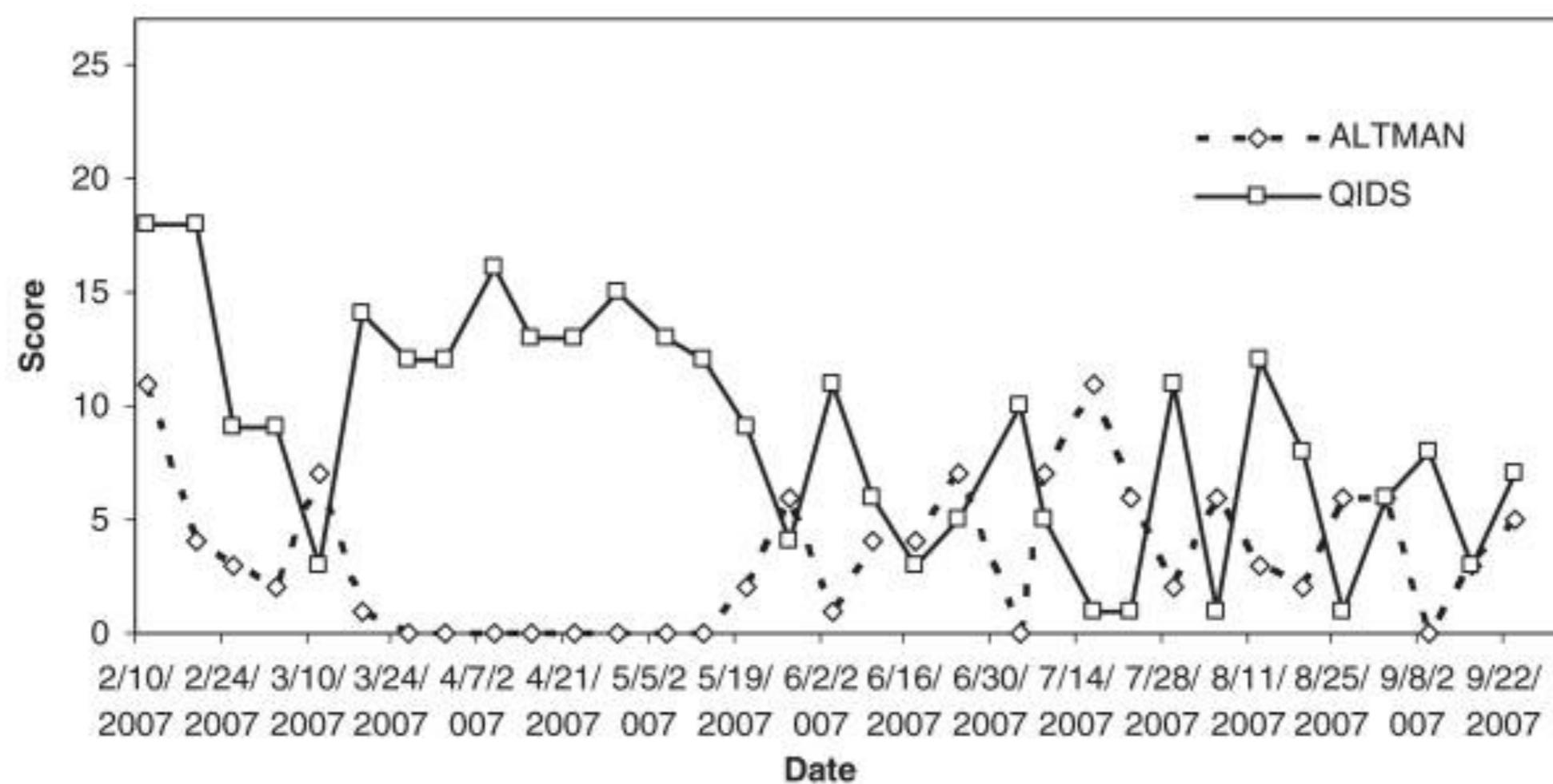
Why should we care?

Fluctuations in function of schizophrenic patients



Why should we care?

Mood fluctuations in a single bipolar patient



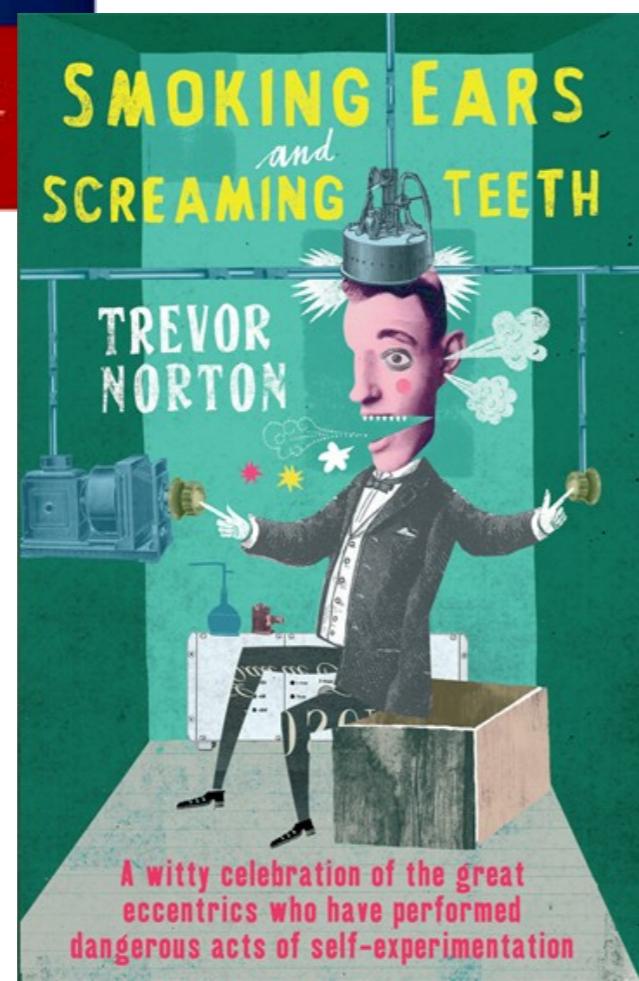
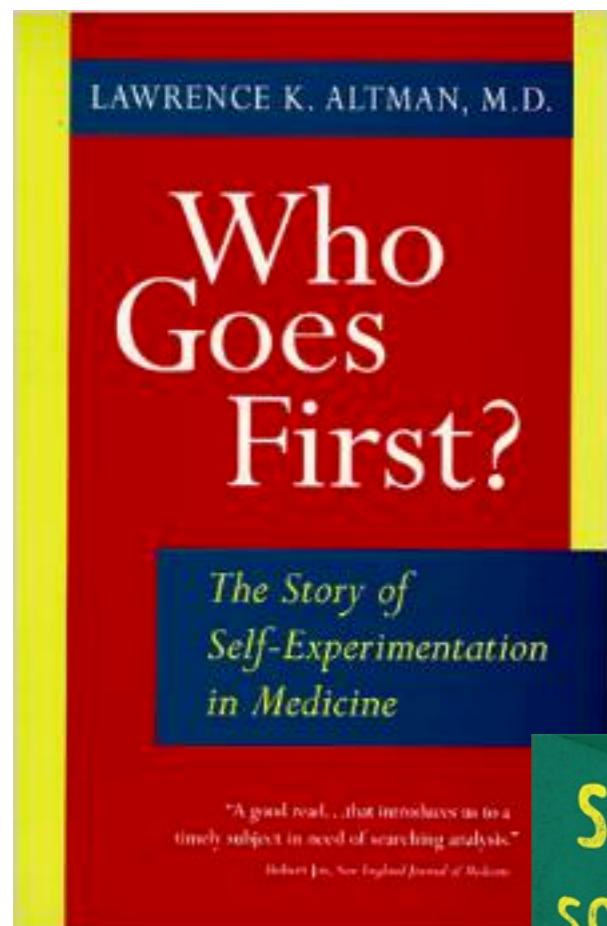
ALTMAN: Altman Self-Rating Mania Scale

QIDS: Quick Inventory for Depressive Symptoms

Bopp et al., 2010, Bipolar Disorders

- Variability in brain function is an interesting phenotype about which we know almost nothing
- Long-term volunteer studies are difficult and expensive
- How might we obtain a proof of concept?

Self-experimentation



Hermann Ebbinghaus

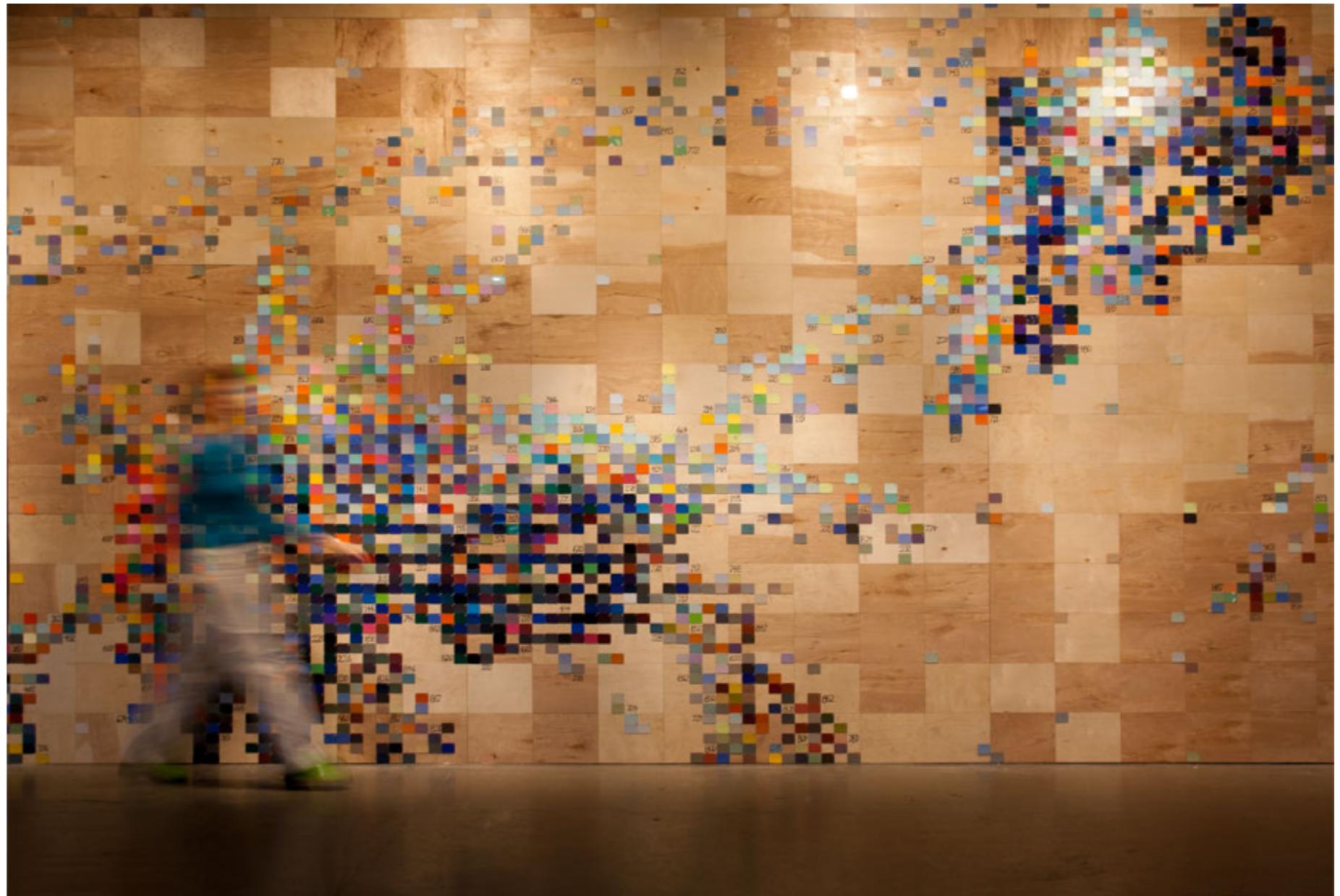


Barry Marshall

An unlikely inspiration



Laurie Frick
UT IRC
Artist-in-Residence



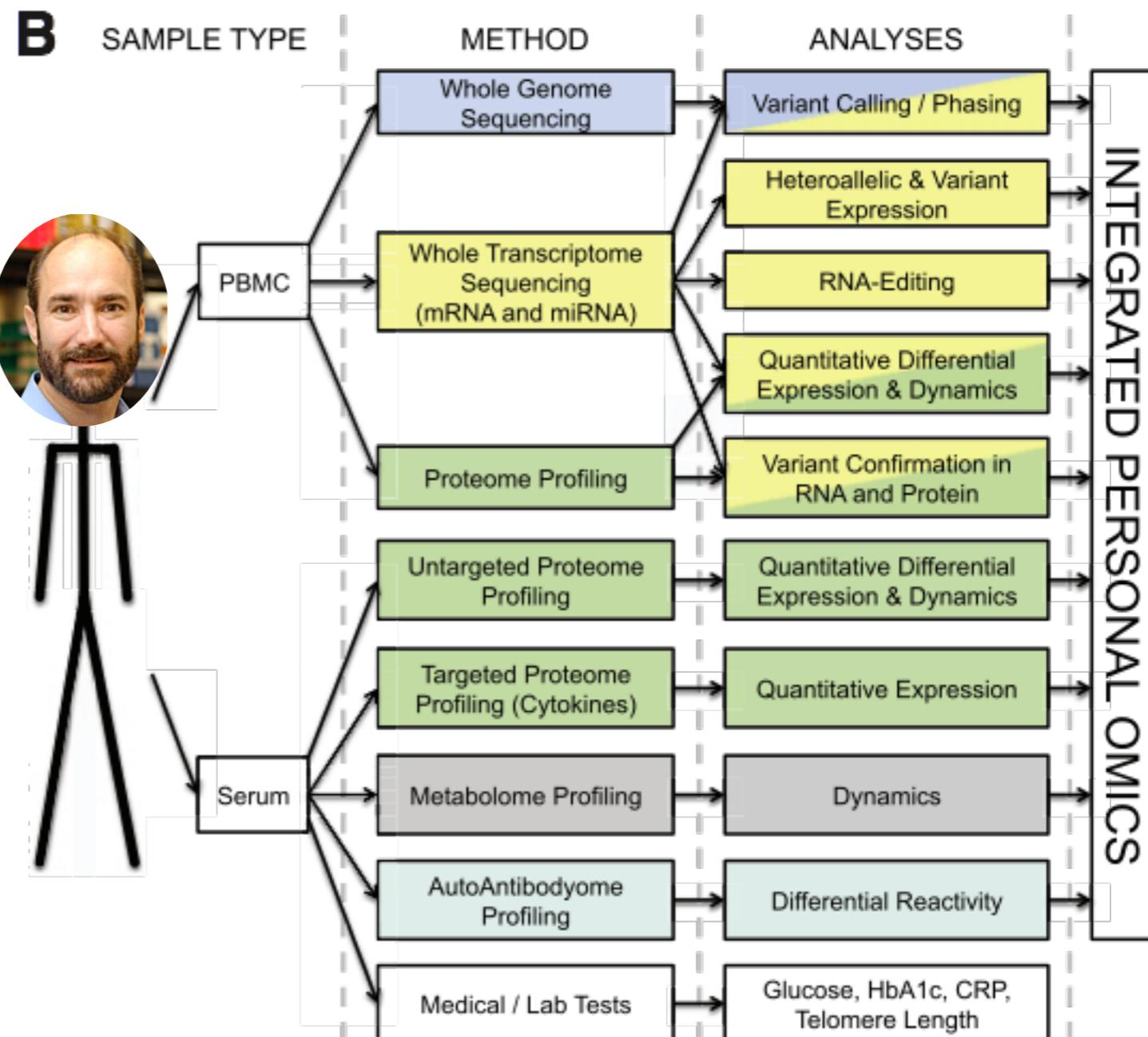
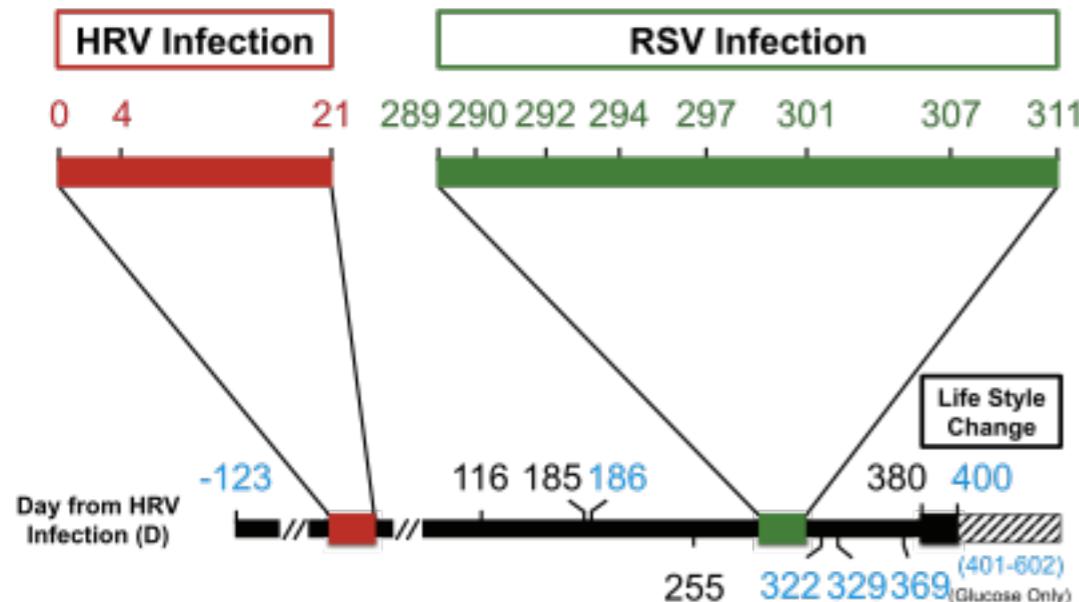
iPOP (aka “the Snyderome”)

Resource

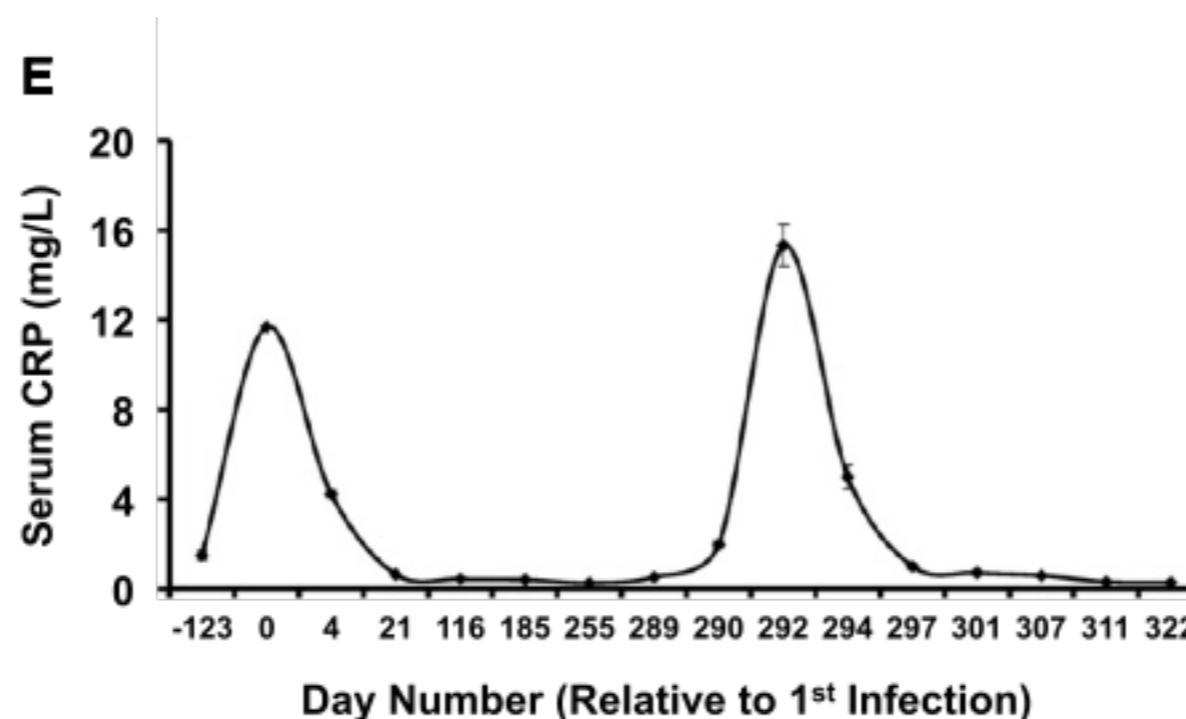
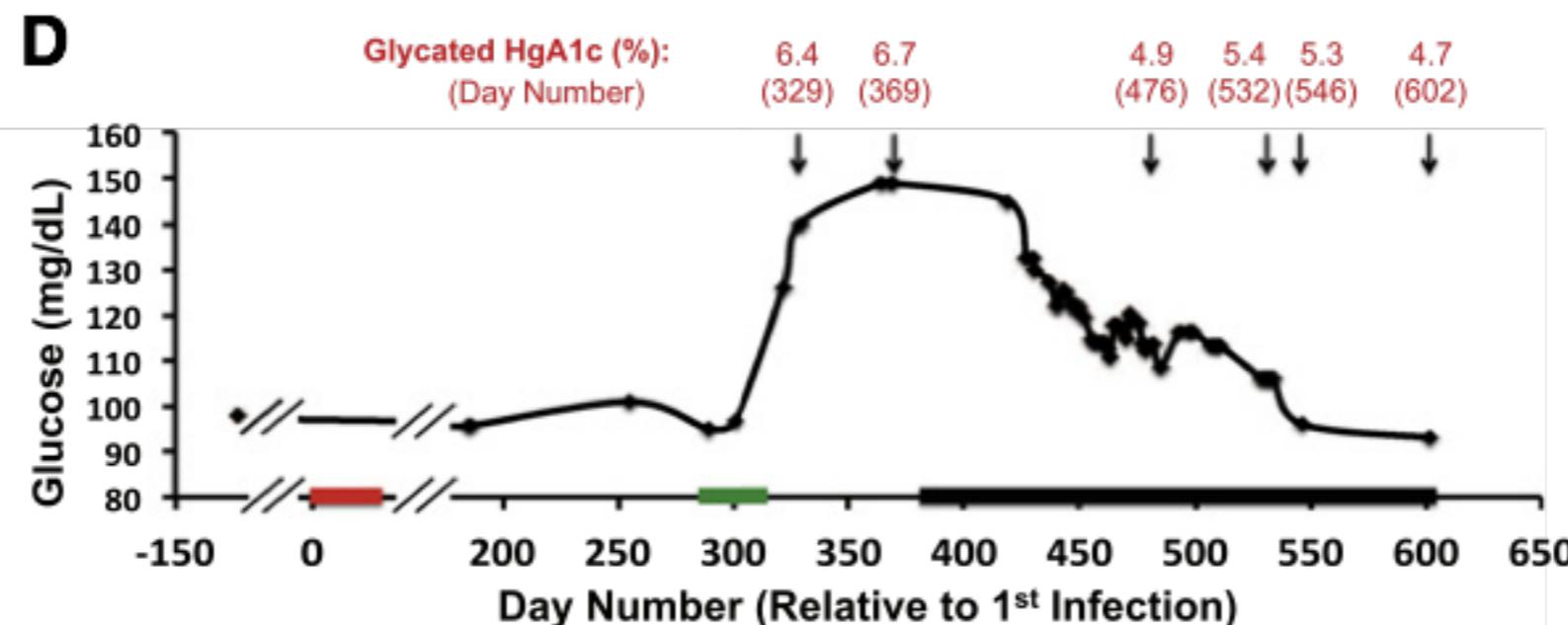


Personal Omics Profiling Reveals Dynamic Molecular and Medical Phenotypes

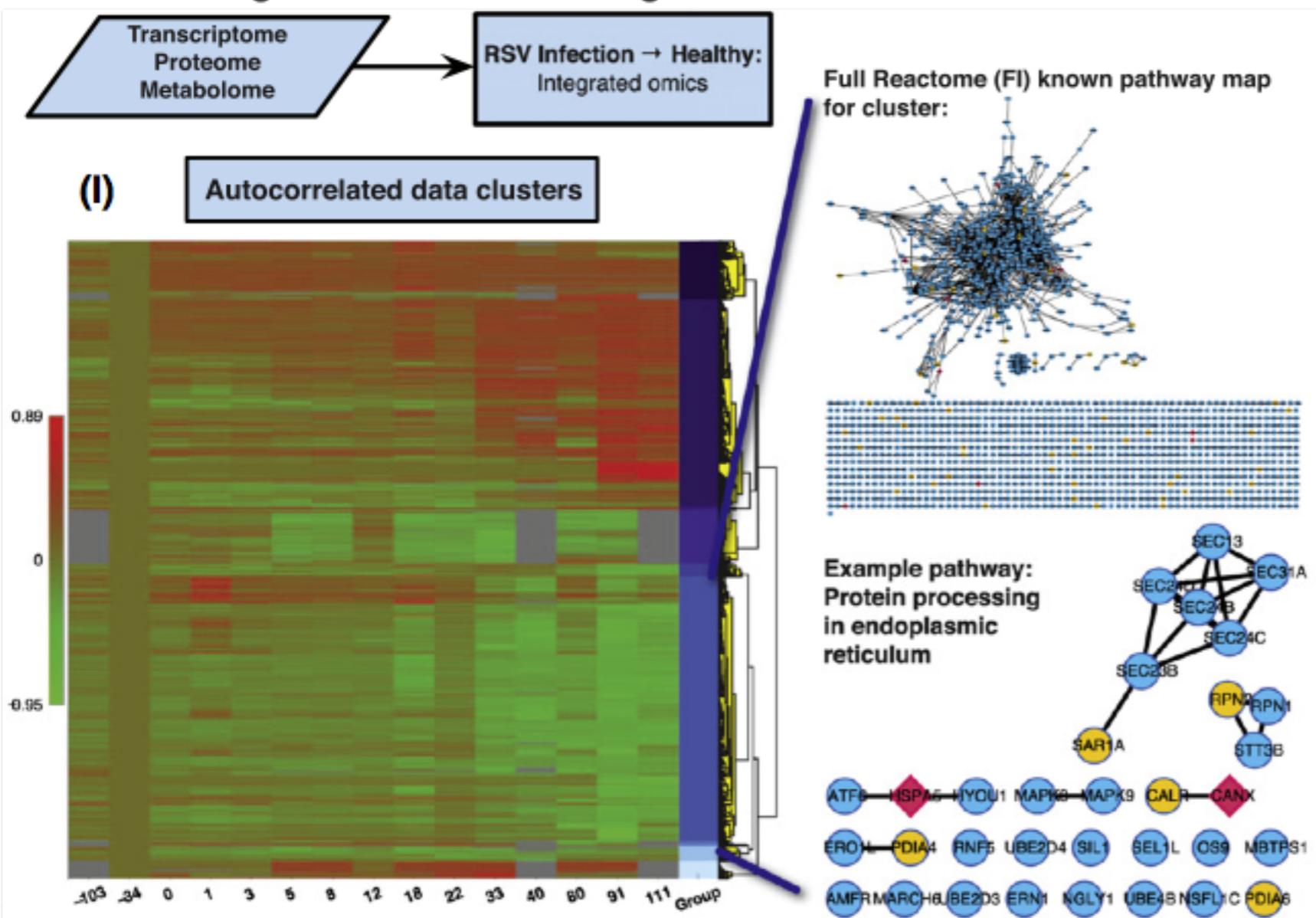
Rui Chen,^{1,11} George I. Mias,^{1,11} Jennifer Li-Pook-Than,^{1,11} Lihua Jiang,^{1,11} Hugo Y.K. Lam,^{1,12} Rong Chen,^{2,12} Elana Miriami,¹ Konrad J. Karczewski,¹ Manoj Hariharan,¹ Frederick E. Dewey,³ Yong Cheng,¹ Michael J. Clark,¹ Hogune Im,¹ Lukas Habegger,^{6,7} Suganthi Balasubramanian,^{6,7} Maeve O'Huallachain,¹ Joel T. Dudley,² Sara Hillenmeyer,¹ Rajini Haraksingh,⁷ Donald Sharon,¹ Ghia Euskirchen,¹ Phil Lacroute,¹ Keith Bettinger,¹ Alan P. Boyle,¹ Maya Kasowski,¹ Fabian Grubert,¹ Scott Seki,² Marco Garcia,² Michelle Whirl-Carrillo,¹ Mercedes Gallardo,^{9,10} Maria A. Blasco,⁹ Peter L. Greenberg,⁴ Phyllis Snyder,¹ Teri E. Klein,¹ Russ B. Altman,^{1,5} Atul J. Butte,² Euan A. Ashley,³ Mark Gerstein,^{5,7,8} Kari C. Nadeau,² Hua Tang,¹ and Michael Snyder^{1,*}



An interesting coincidence



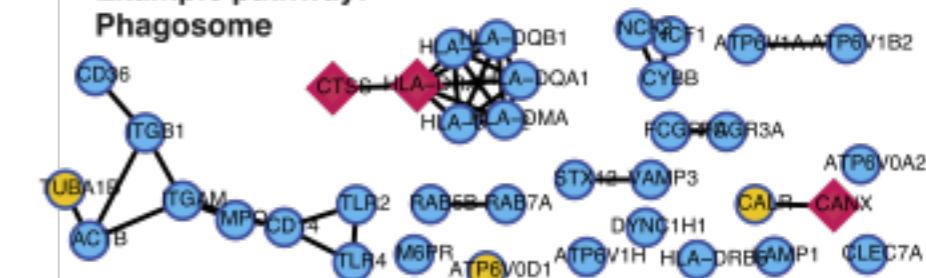
Integrated Omics clustering



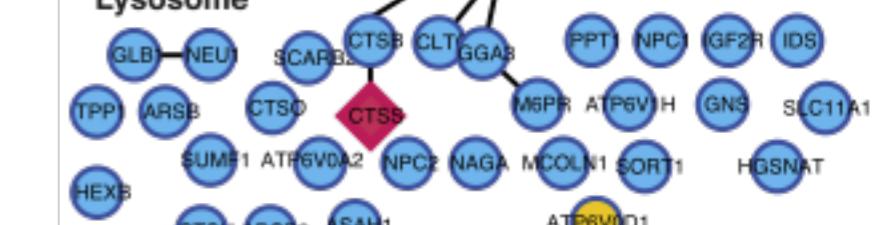
Dynamic expression pattern observed in:

- RNA
- Protein
- ◆ Both RNA + Protein

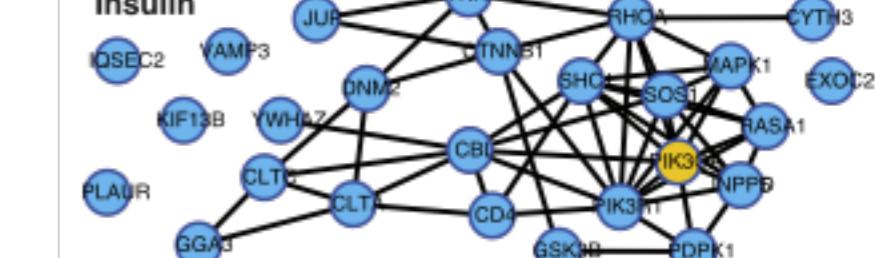
Example pathway:
Phagosome



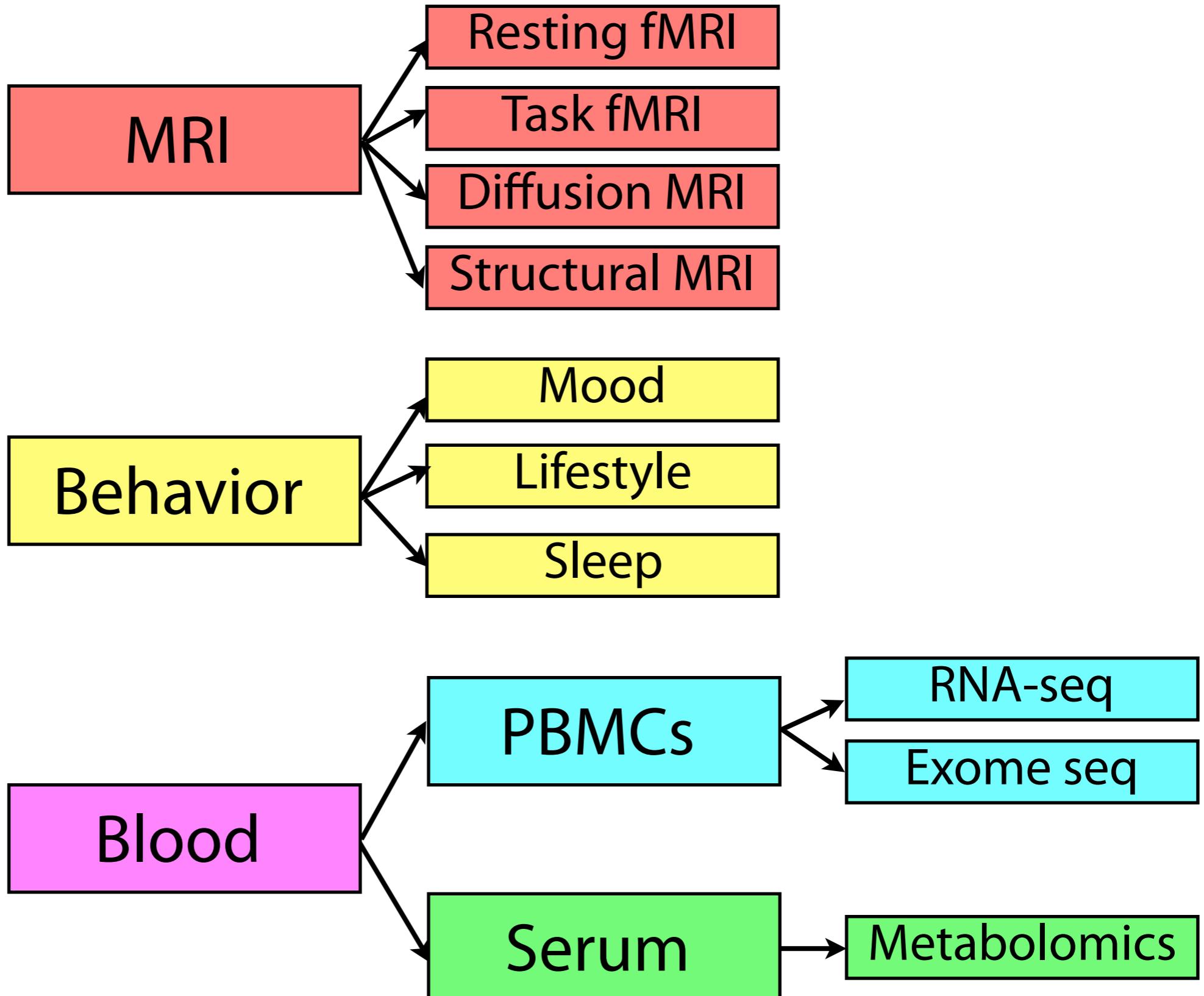
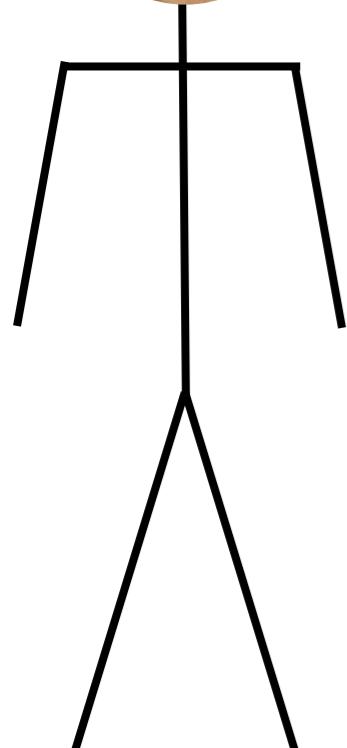
Example pathway:
Lysosome



Example pathway:
Insulin



The MyConnectome Project



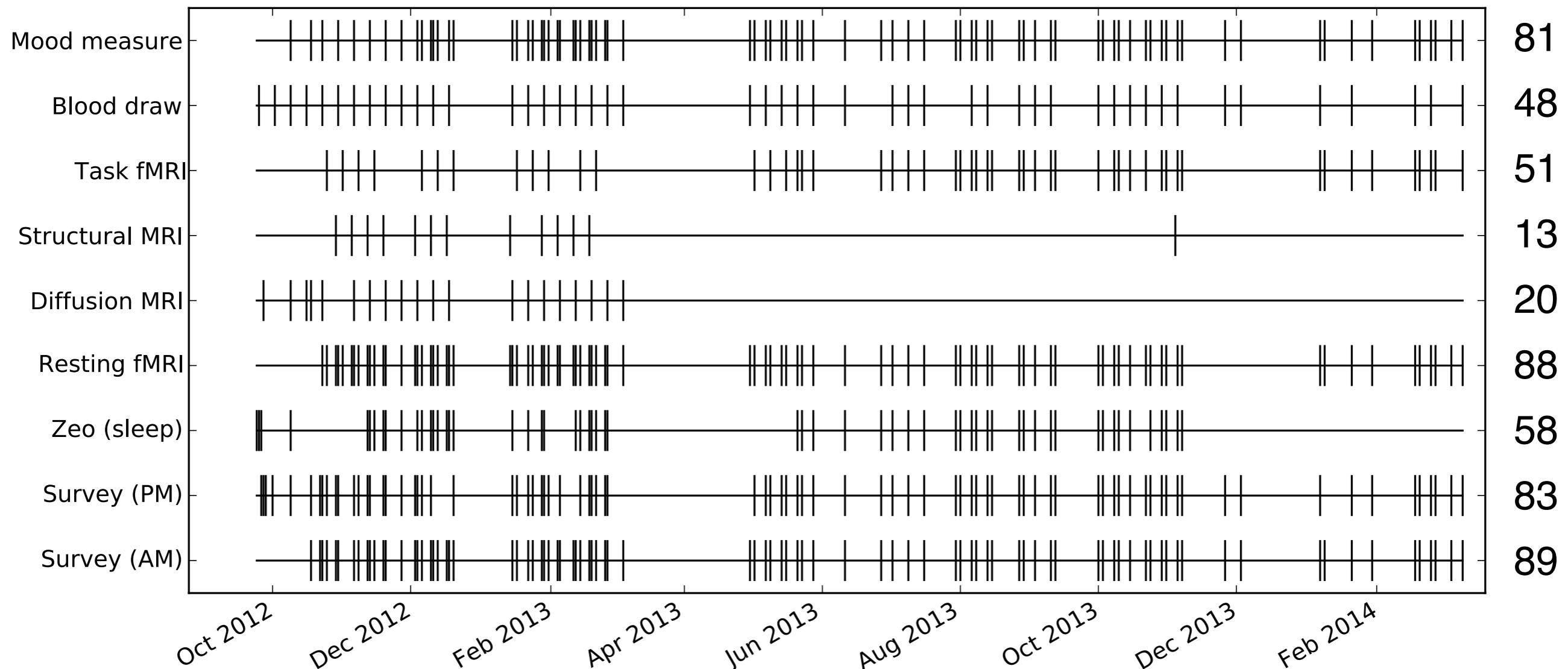
Data acquisition schedule

	Mon	Tues	Wed	Thurs	Fri
waking	BP/pulse/ratings	BP/pulse/ratings (fast until after blood draw)	BP/pulse/ratings	BP/pulse/ratings	BP/pulse/ratings
7:30 am	exercise	resting fMRI diffusion MRI	exercise	resting fMRI task fMRI	exercise
8 am		blood draw			
...					
5 pm	resting fMRI TI/T2 MRI				
bedtime	ratings	ratings	ratings	ratings	ratings

Ratings

- Morning:
 - Sleep quality
 - Soreness
 - BP/pulse
 - Weight
- Evening
 - Stress
 - Time spent outdoors
 - Psoriasis severity
 - Gut health
 - Daily events (free form)
 - Exercise
 - Food (all ingredients eaten)
 - Alcohol consumed
 - Medications/supplements
- After each scan
 - Anxiety level during scan
 - Thoughts during scan (free form)
 - BP/pulse
 - Mood (PANAS-X long form)
- Additional data
 - ZEO sleep monitor
 - Weather (avg temp)
 - Sent emails

Timeline and measurements



Is this “research”?

Date: 05/03/12
PI: Russell Poldrack, Ph.D.
Dept: Psychology
Title: High-density Phenotyping of a Single Individual

RE: Non Human Subject Research Determination

Dear Russell Poldrack:

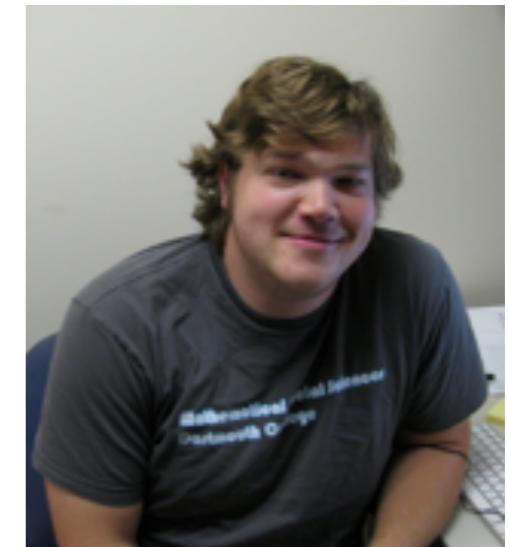
The Office of Research Support (ORS) reviewed the above study and determined it did not meet the requirements for human subject research as defined in the Common Rule (45 CFR 46) or FDA Regulations (21 CFR 50 & 56). At this time you are free to begin your research as IRB approval is not necessary. You should retain this letter with the respective research documents as evidence that IRB review and oversight is not required.

DHHS regulations define research as a systematic investigation , including research development, testing and evaluation, designed to develop or contribute to generalizable knowledge .

Other IRB's have disagreed!

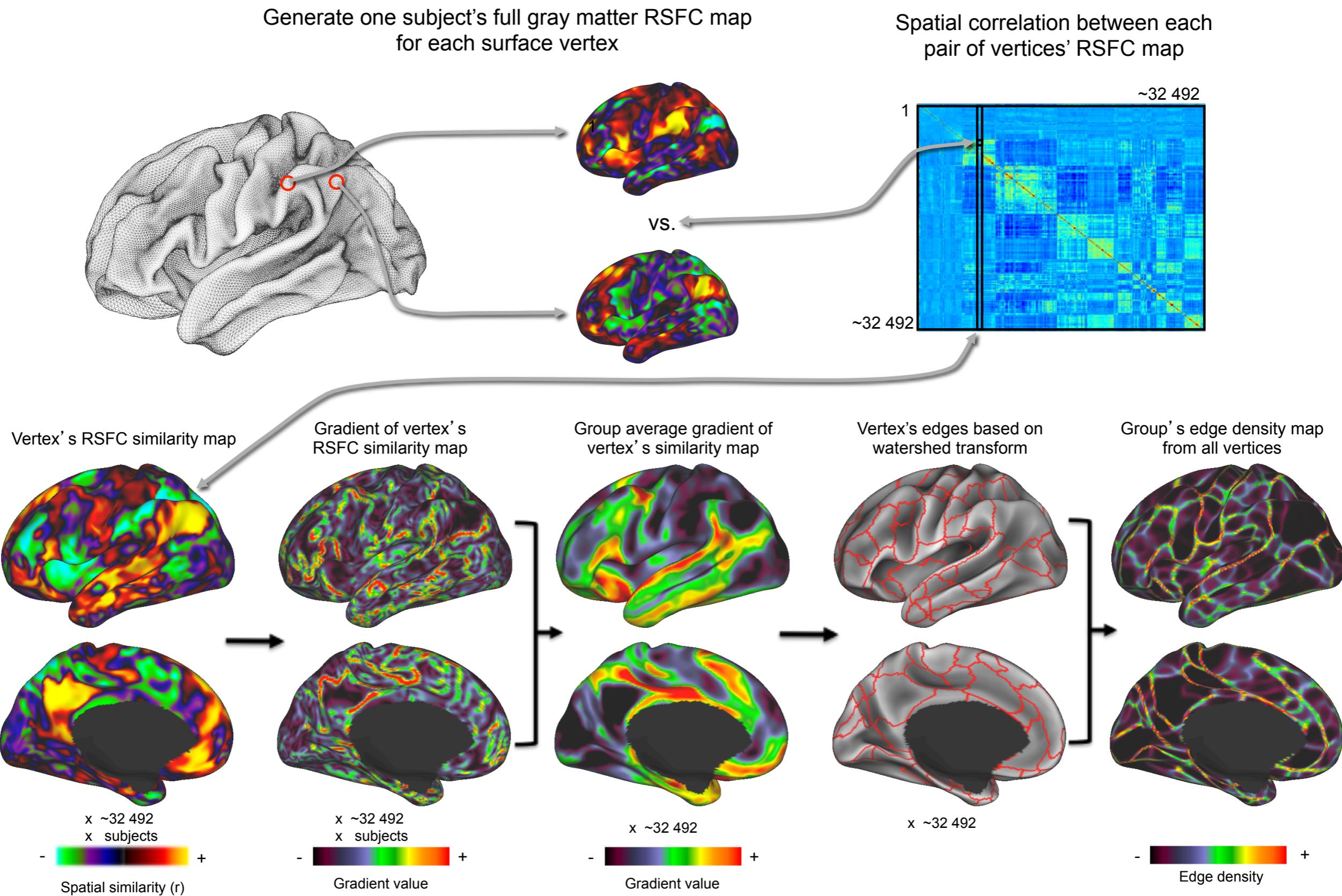
Resting fMRI

- 84 usable sessions
- 10 minutes each
 - TR = 1.16 secs (multiband EPI)
 - 2.4 mm isotropic resolution
 - eyes closed (never fell asleep!)
- Processed using Petersen lab pipeline
 - Surface-based parcellation

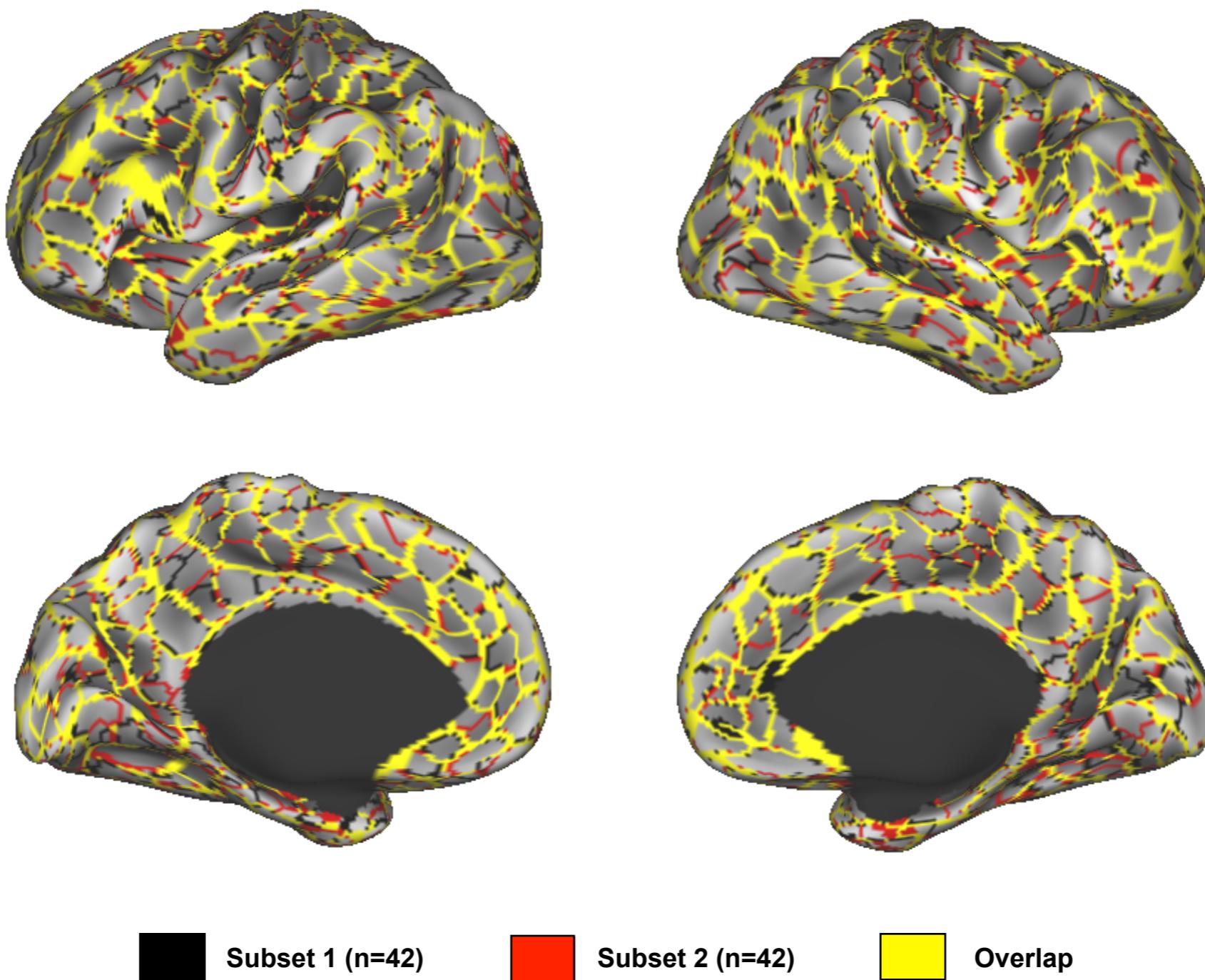


Tim Laumann
Wash-U St. Louis

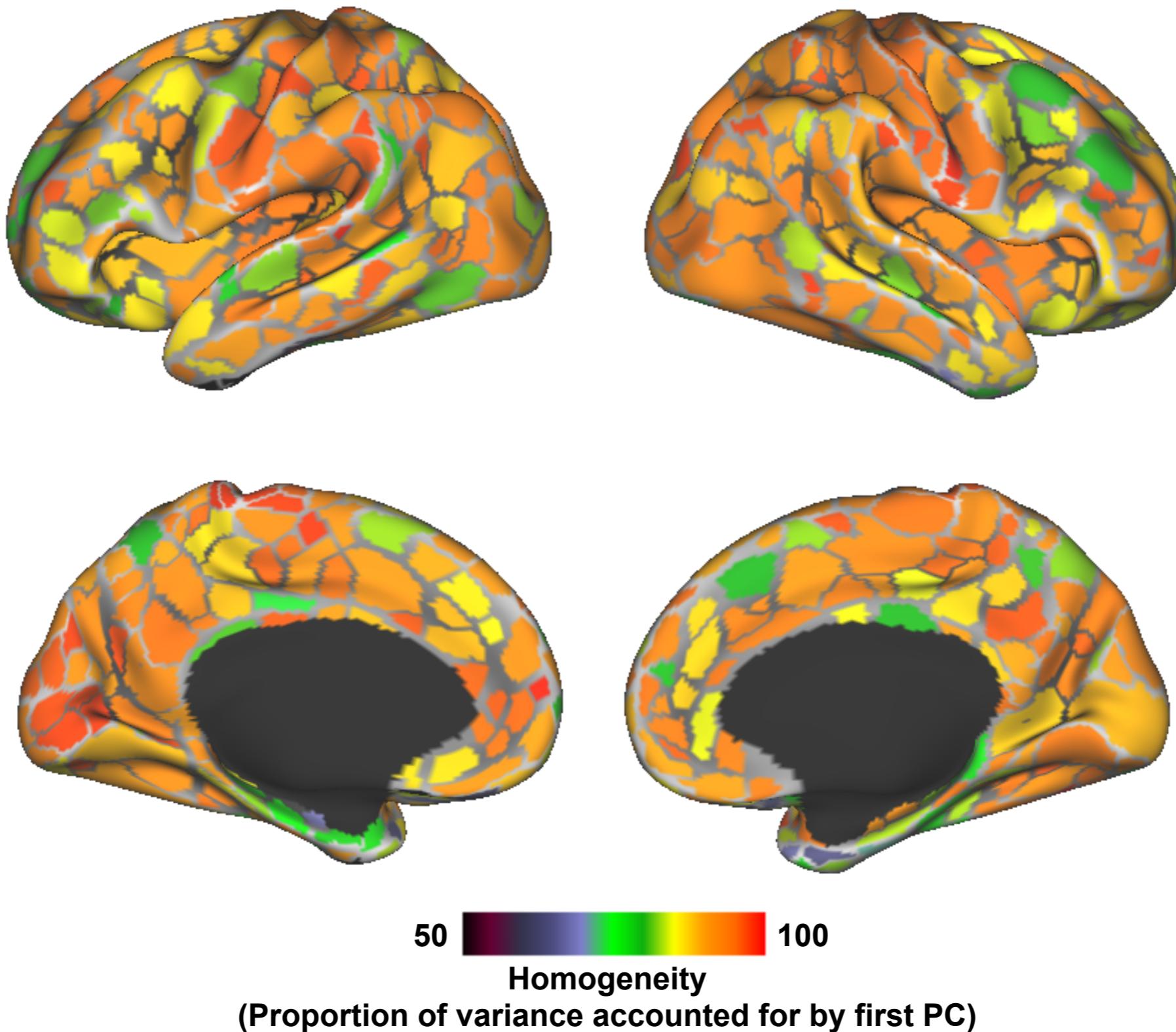
Surface-based rsfMRI parcellation



Parcellations are highly consistent

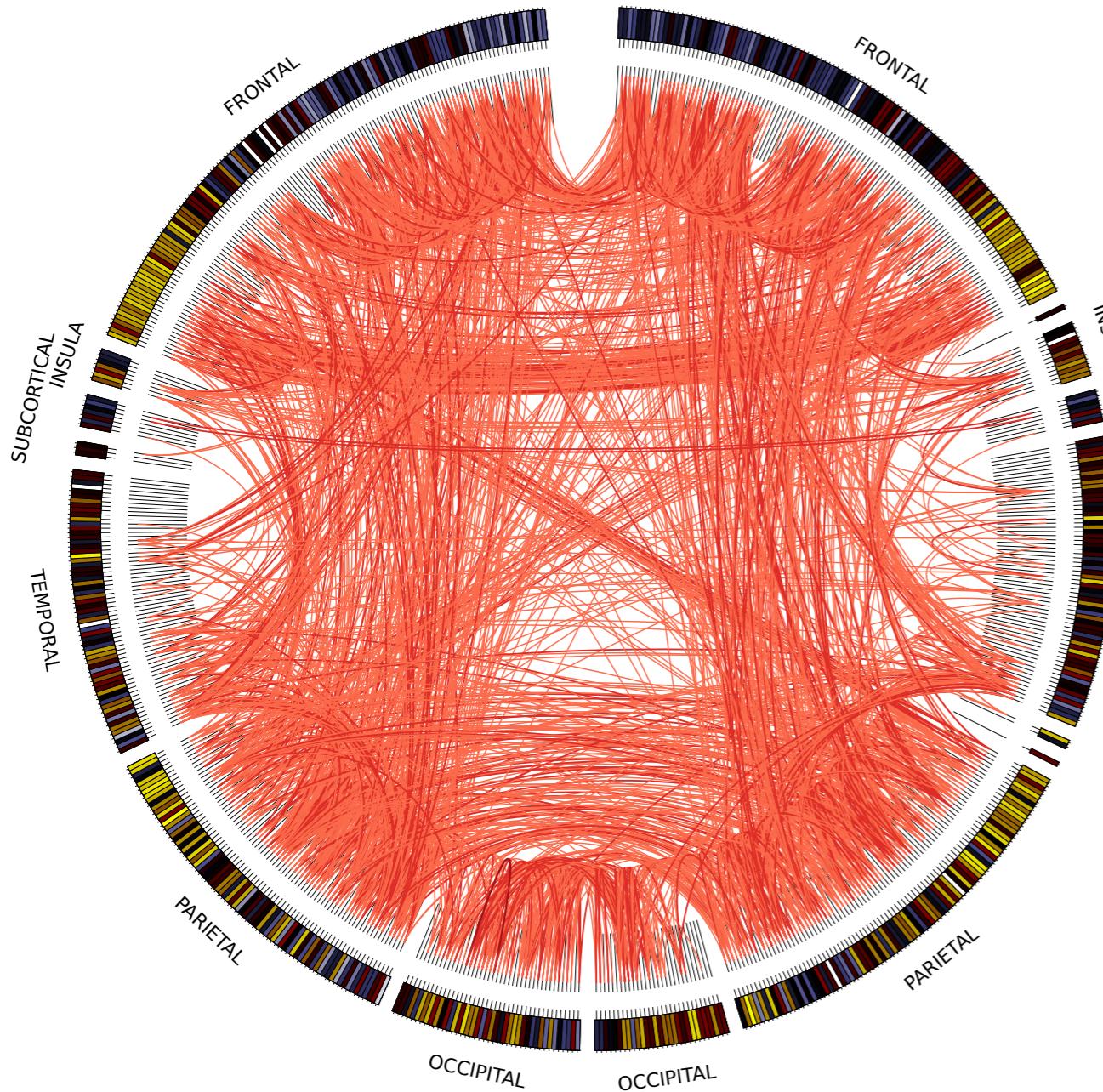


Parcels are highly homogenous

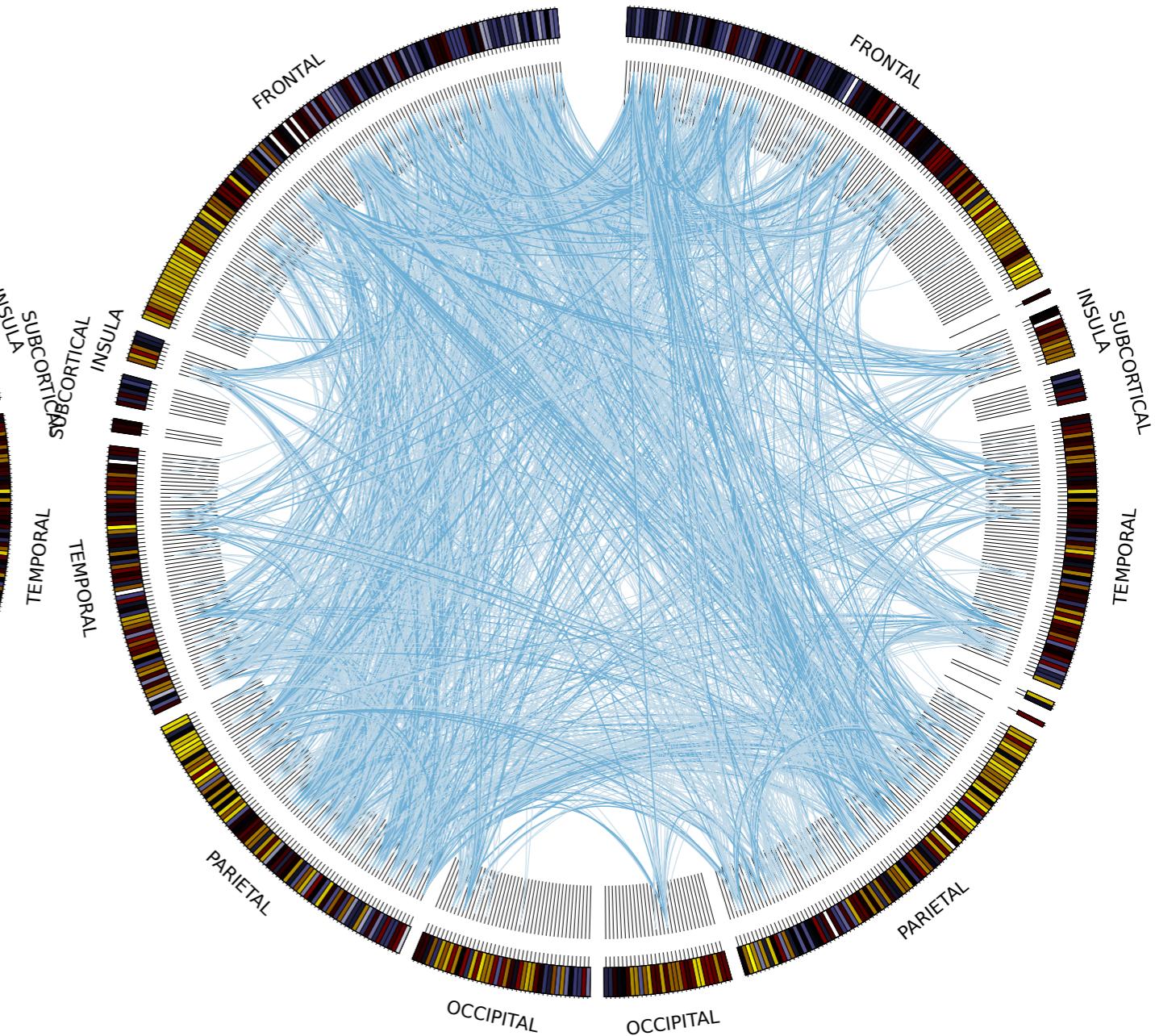


Parcellated connectome

Positive
connections



Top 1% of
connections



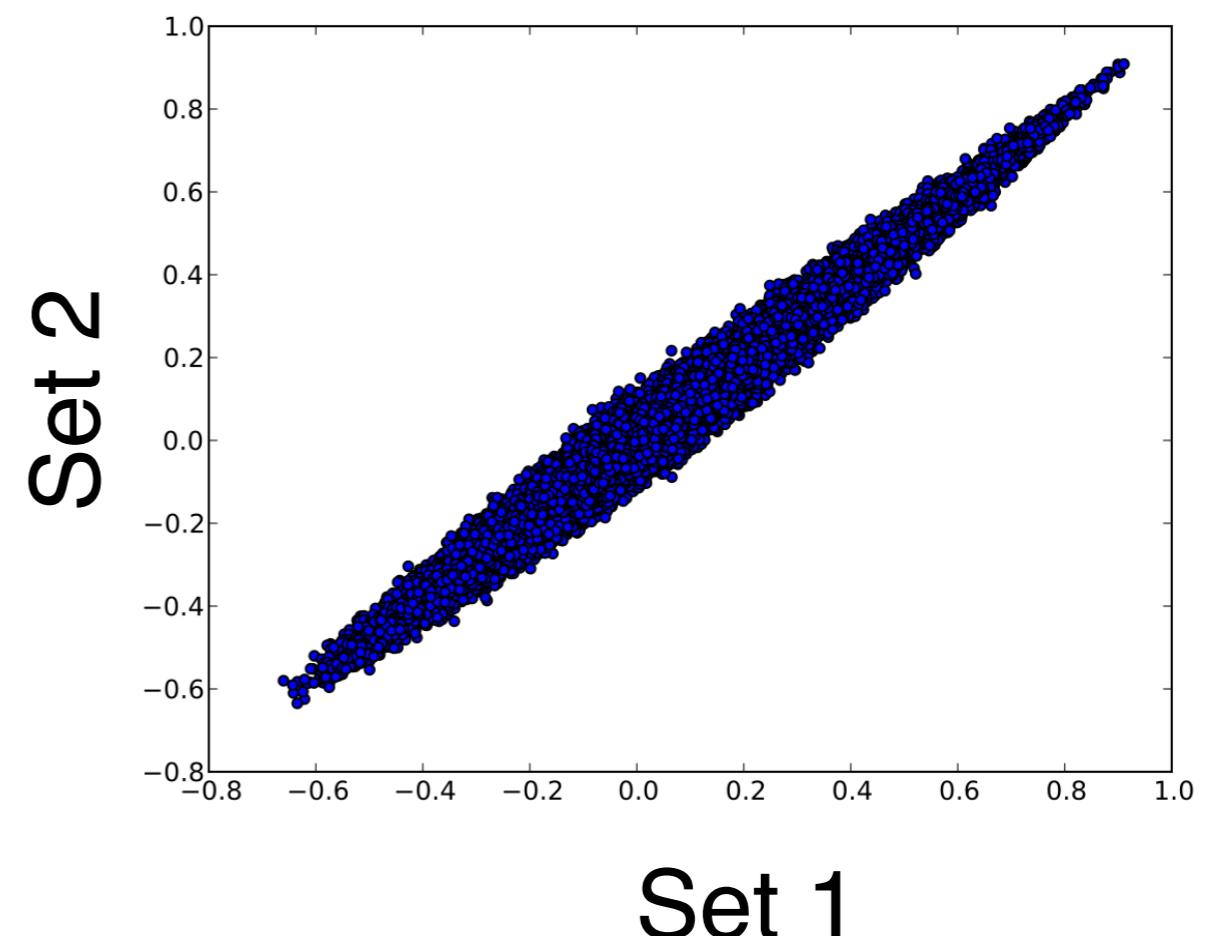
Negative
connections

620 cortical parcels + 14 subcortical ROIs

Between-session reliability of connectivity estimates

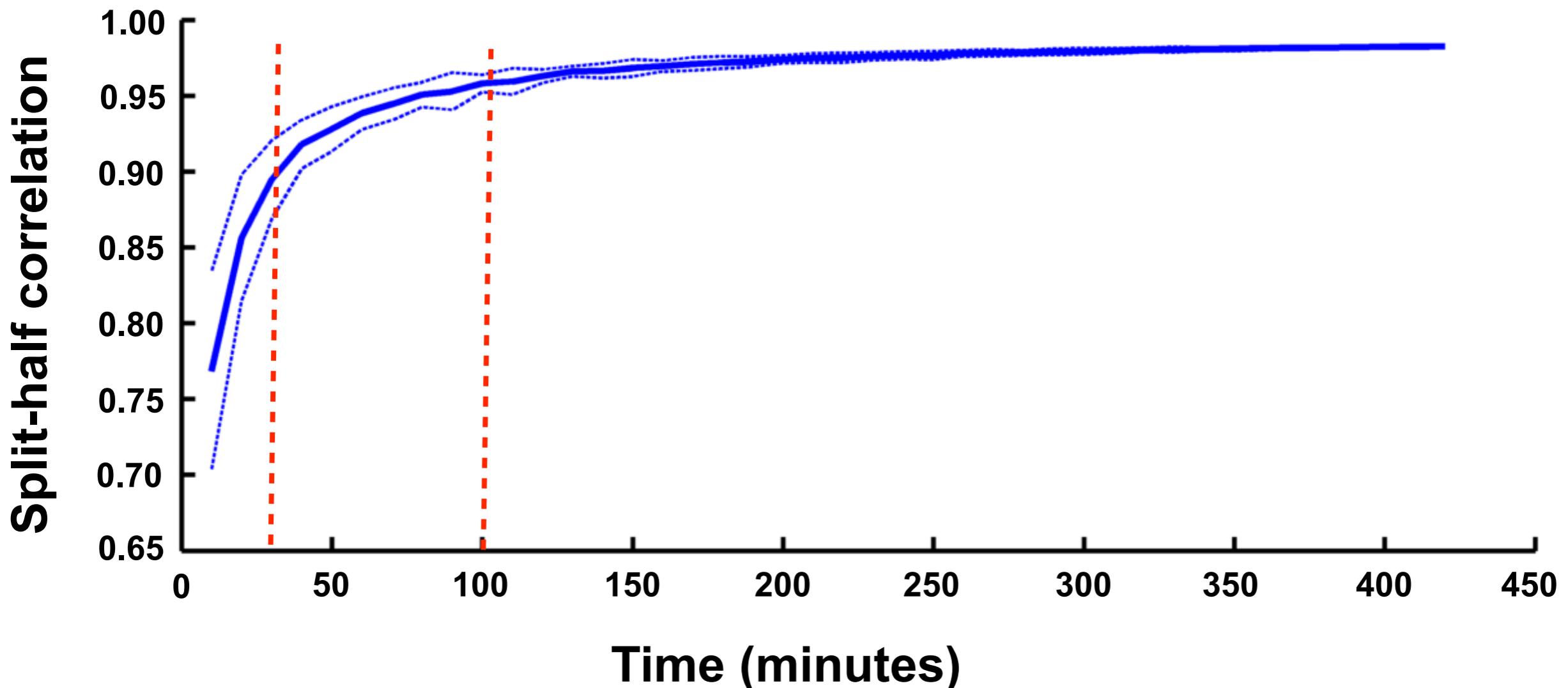
100 random splits
into two sets of 42
sessions

mean split-half $r =$
0.983



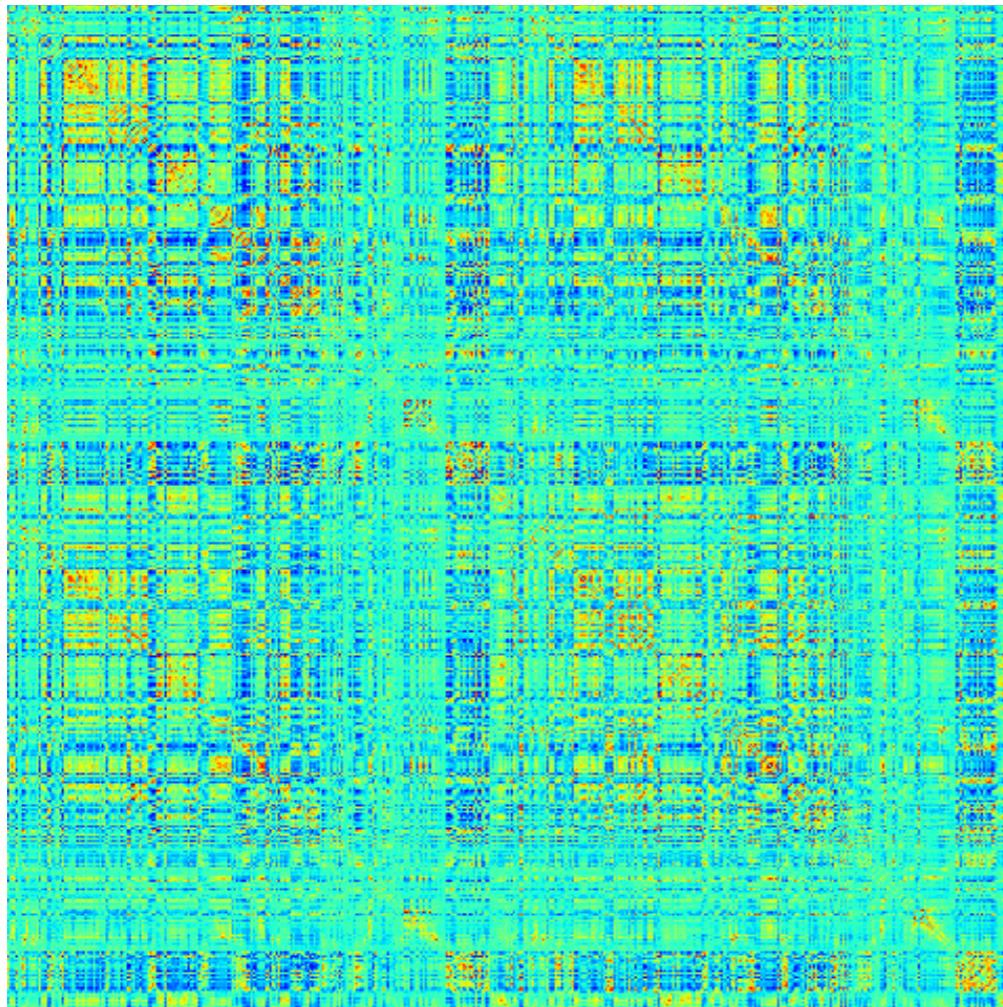
How much data is enough?

Correlation estimates quickly improve up to 30 minutes and essentially asymptote with about 100 minutes of data



Detecting network structure

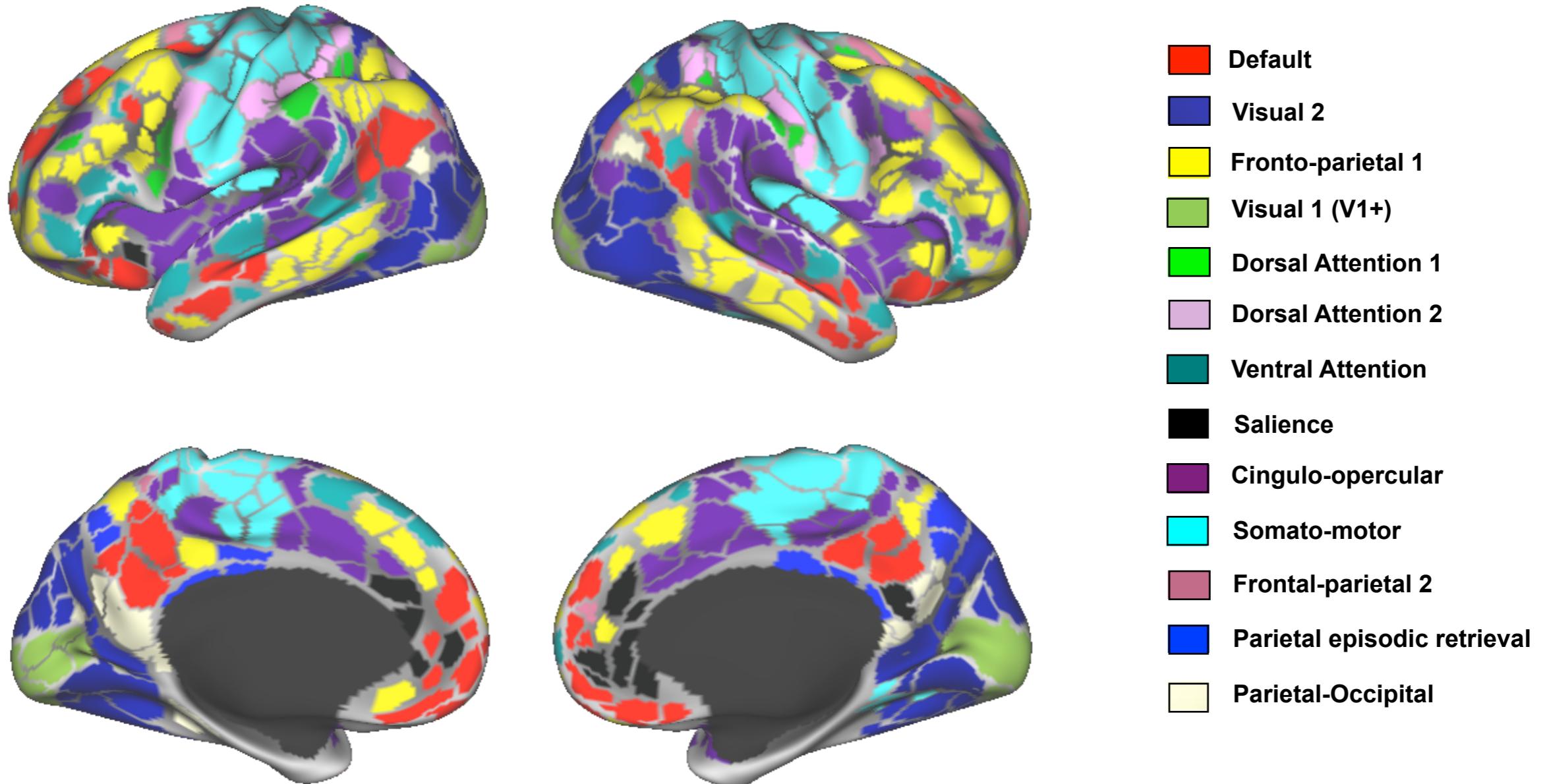
Parcels



Parcels

Parcellated
connectome
clustered to identify
network communities
using infomap
clustering algorithm

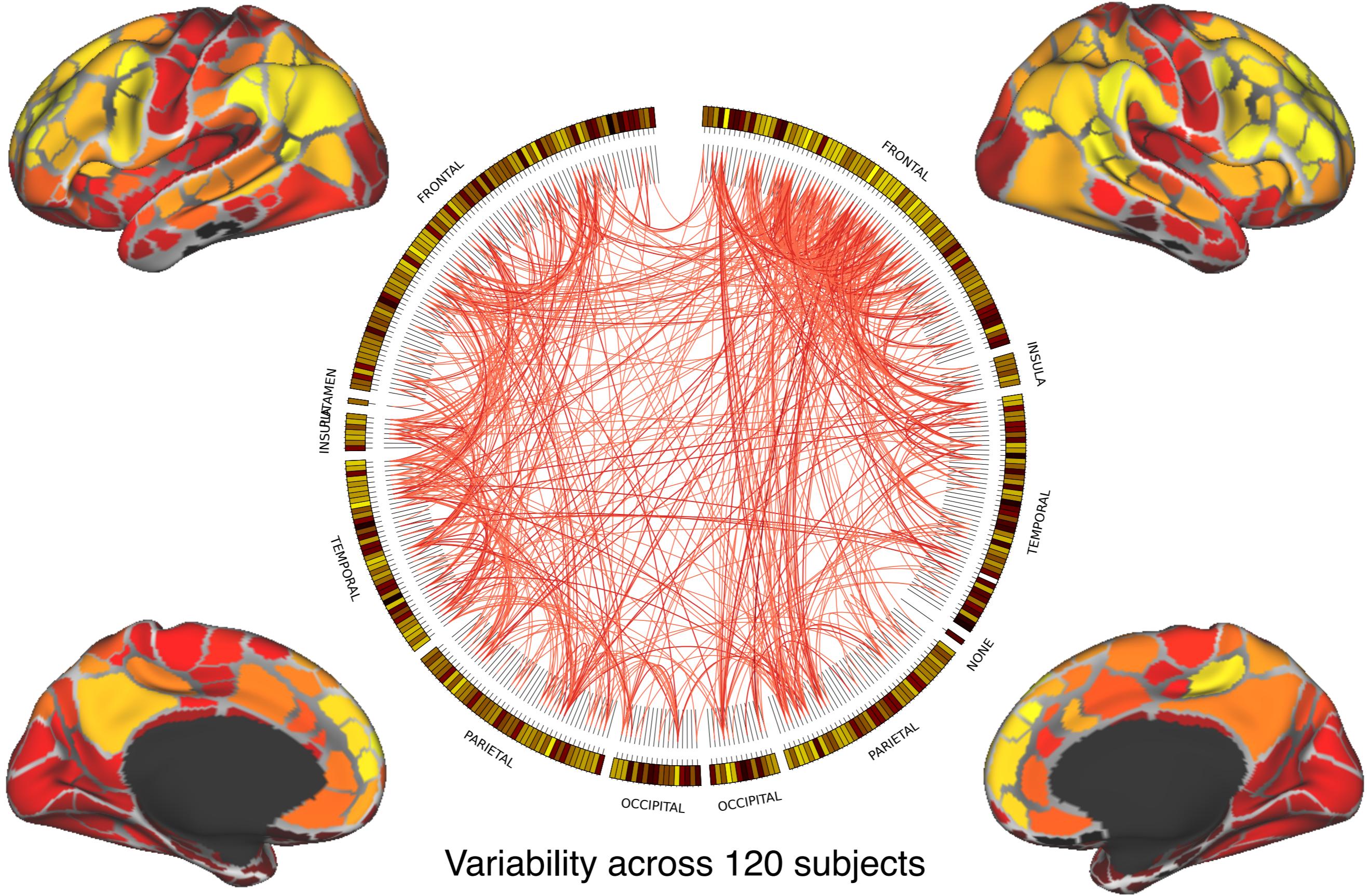
Community detection



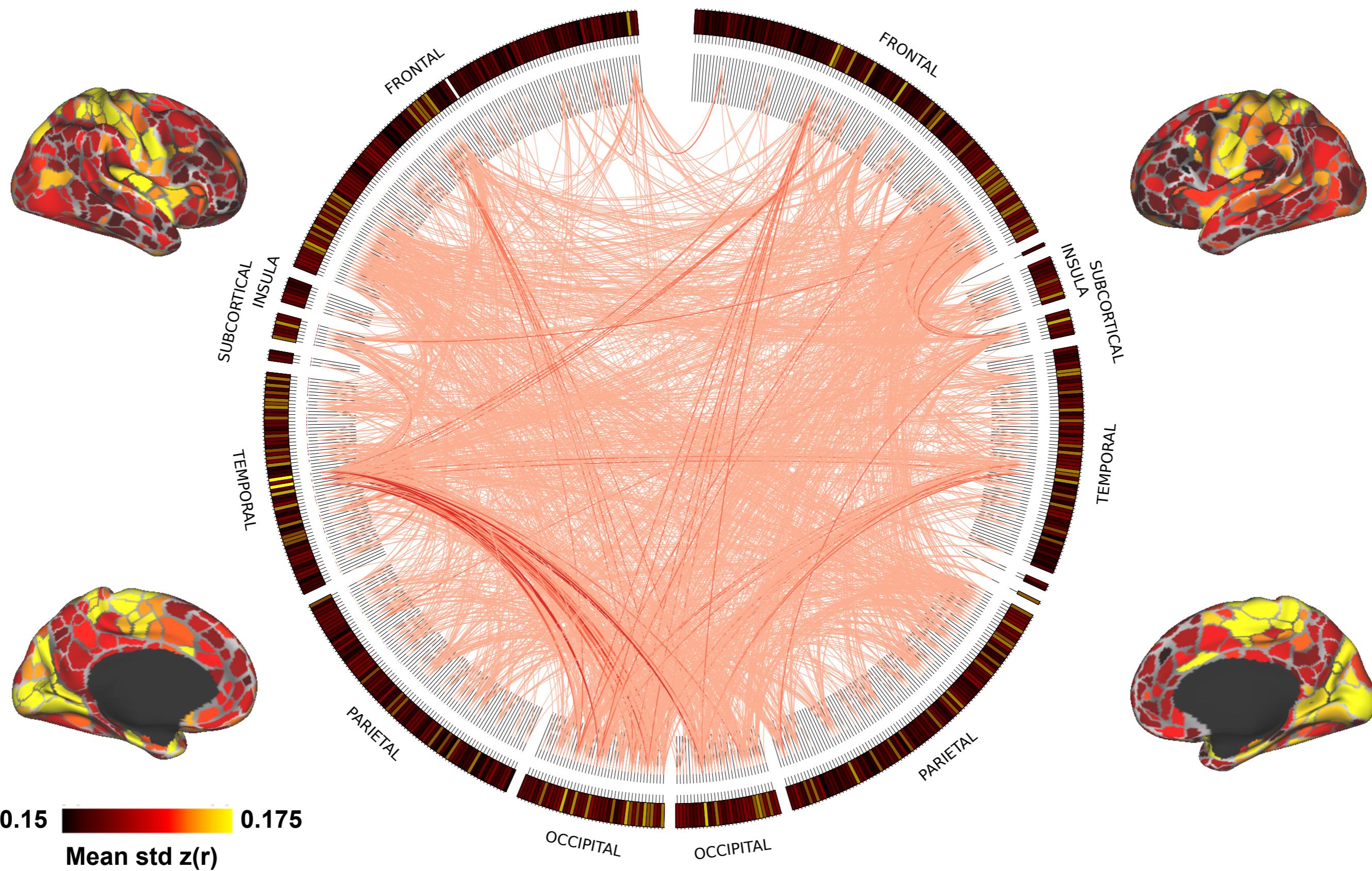
Similar community structure to previous group studies
(Power et al., 2011)

Are patterns of between-subject, between-session,
and within-session variability similar?

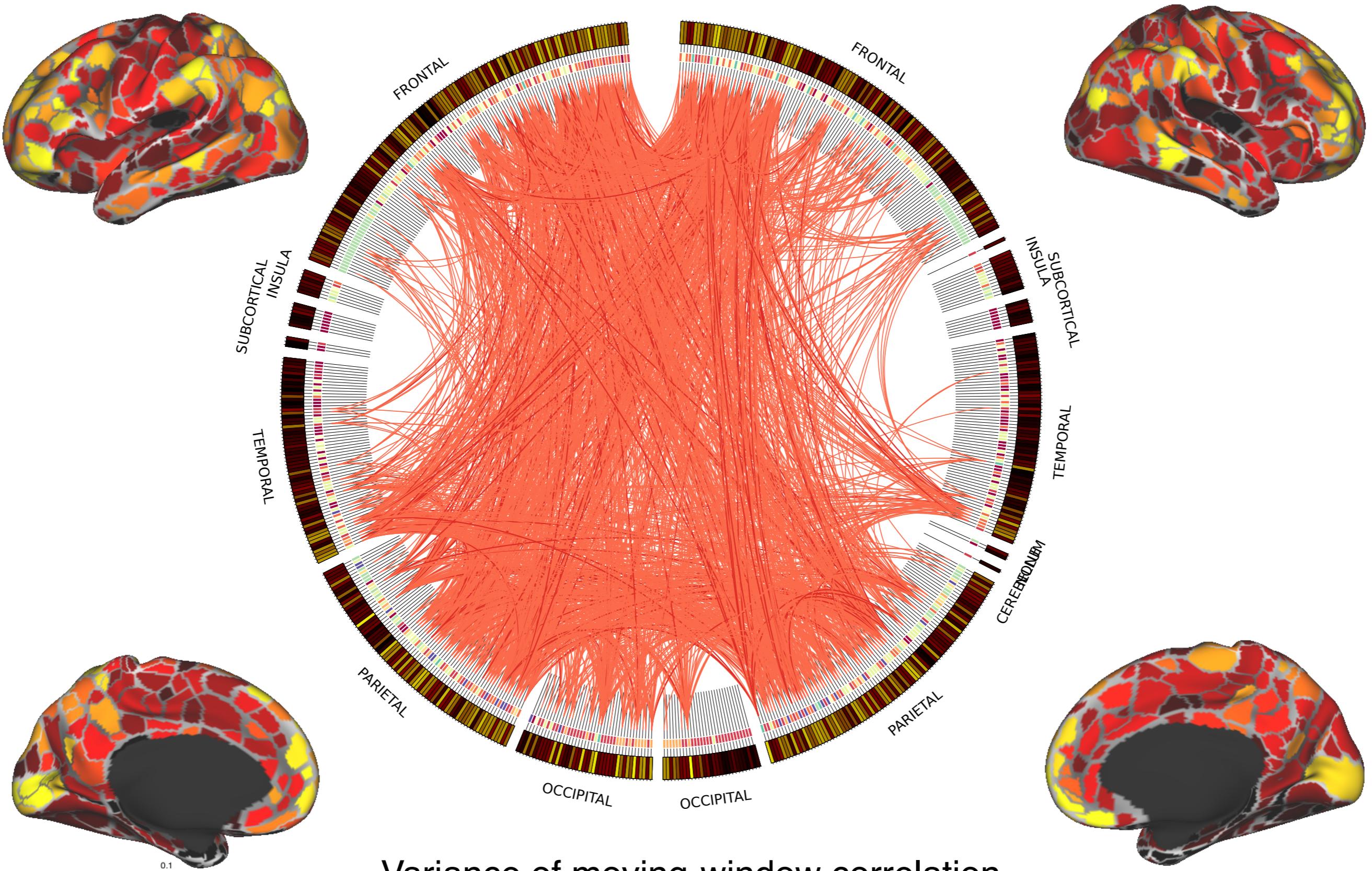
Connectome variability between subjects



MyConnectome variability across sessions



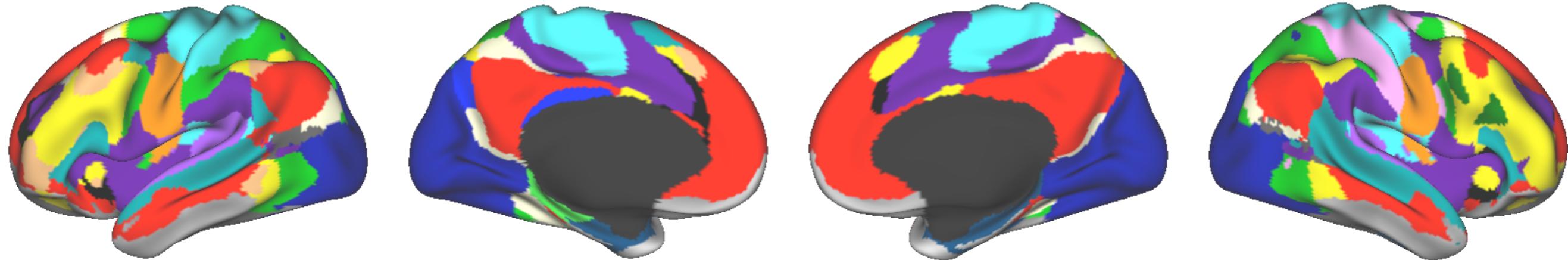
MyConnectome variability within sessions



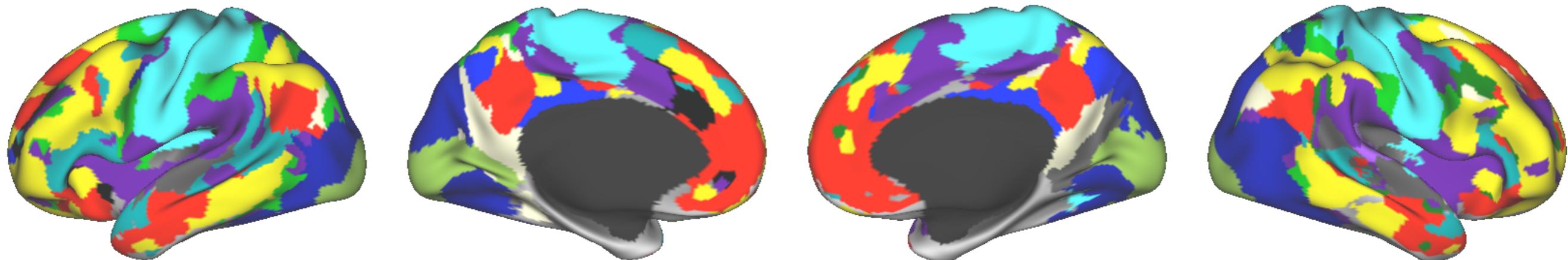
How does individual network topology
relate to group-average topology?

Group and individual show many of the same networks

Group

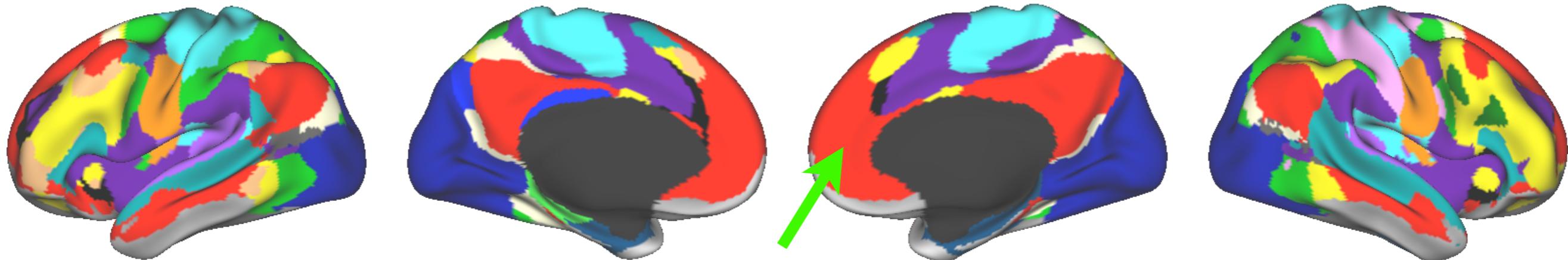


MyConnectome (n=84)

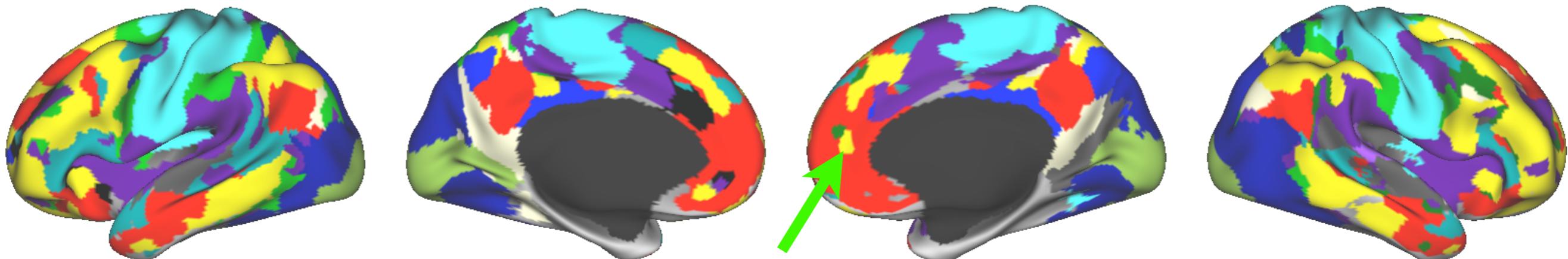


Group and individual demonstrate regions with distinct network topology

Group

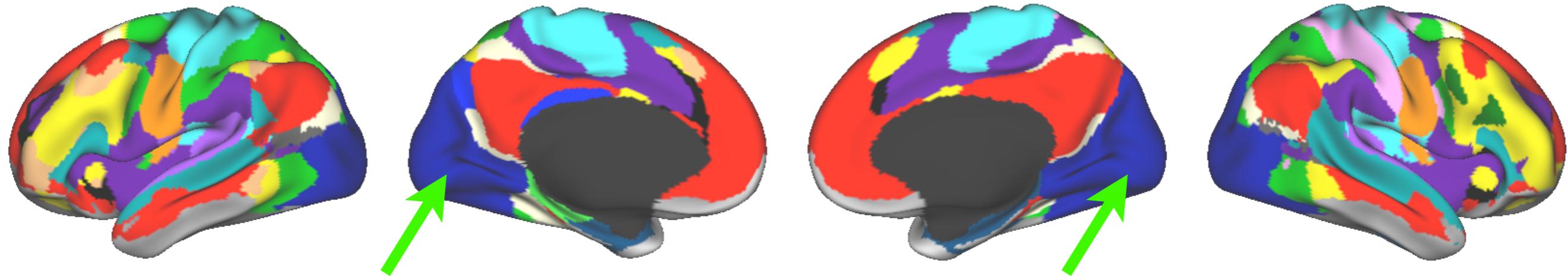


MyConnectome (n=84)

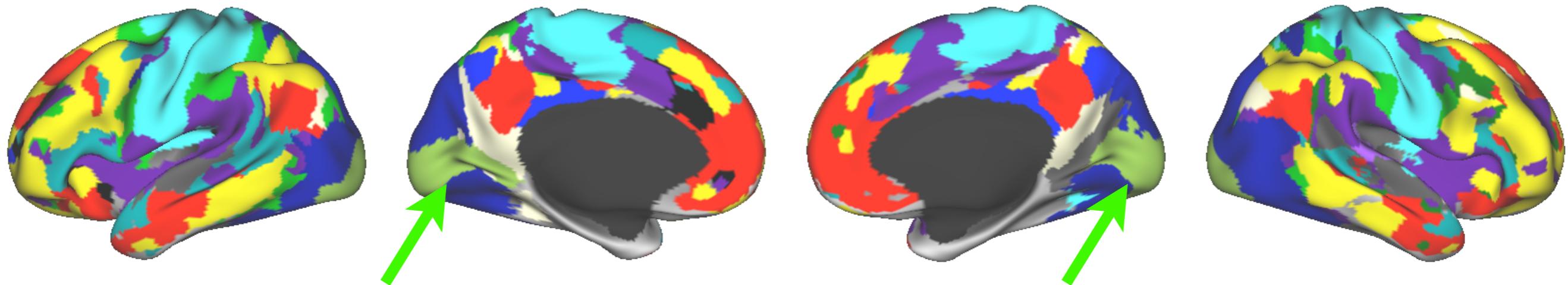


Group and individual demonstrate regions with distinct network topology

Group

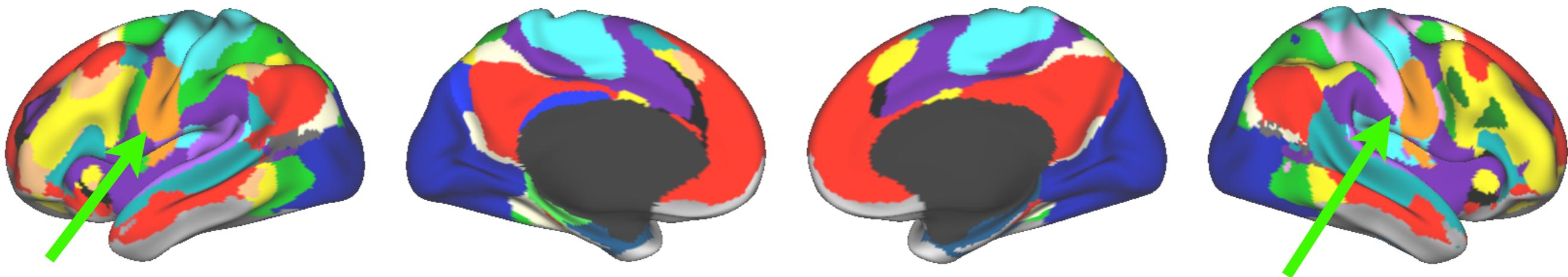


MyConnectome ($n=84$)

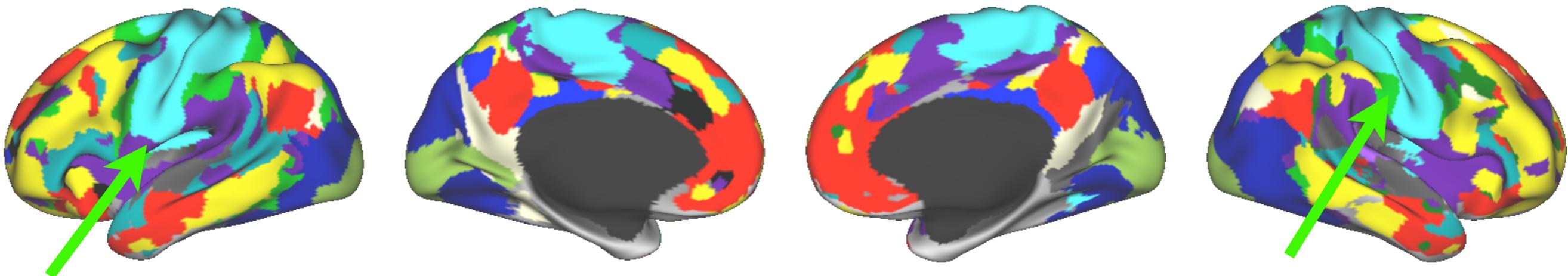


Group and individual demonstrate regions with distinct network topology

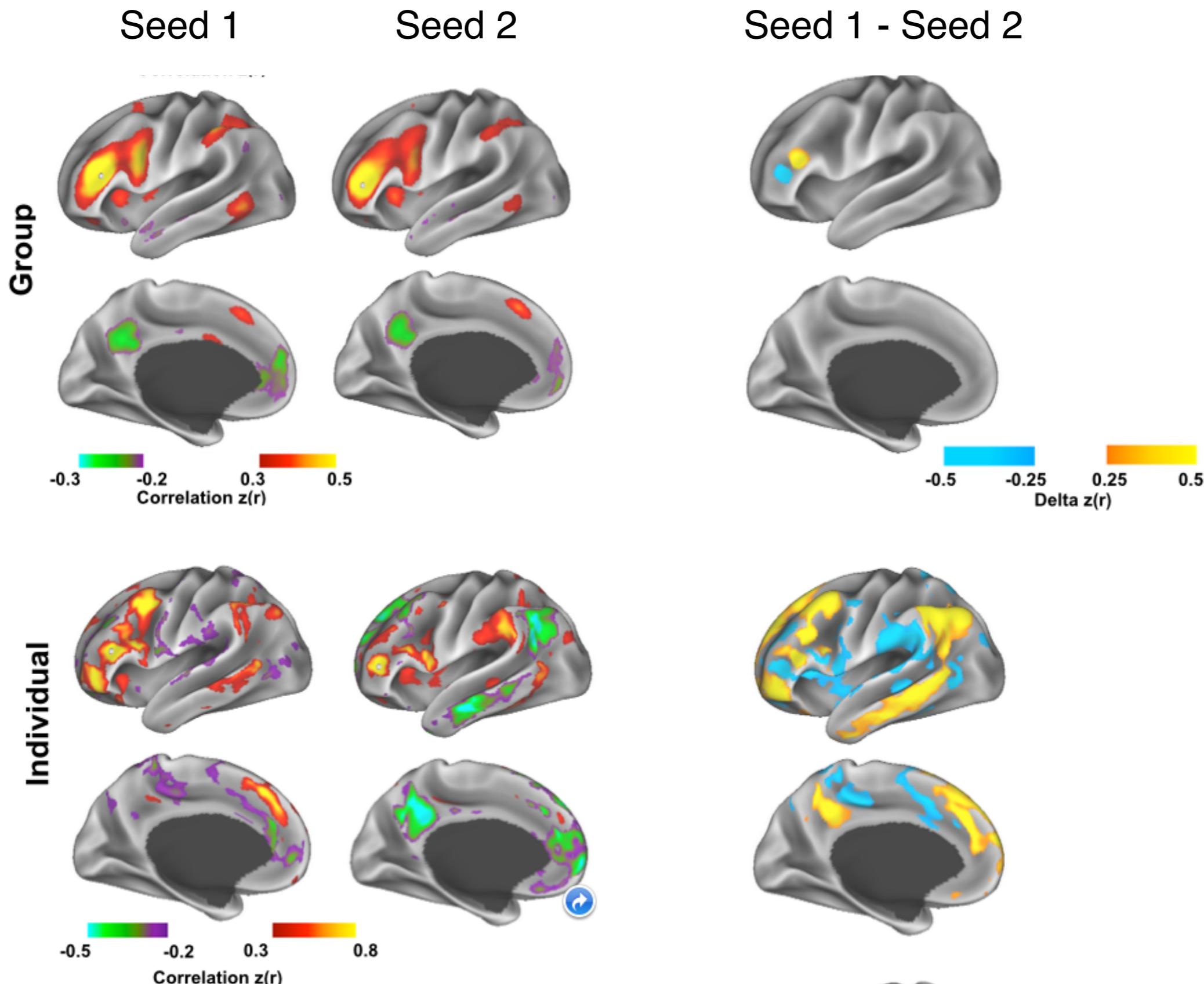
Group



MyConnectome (n=84)



Distinct connectivity patterns of nearby regions

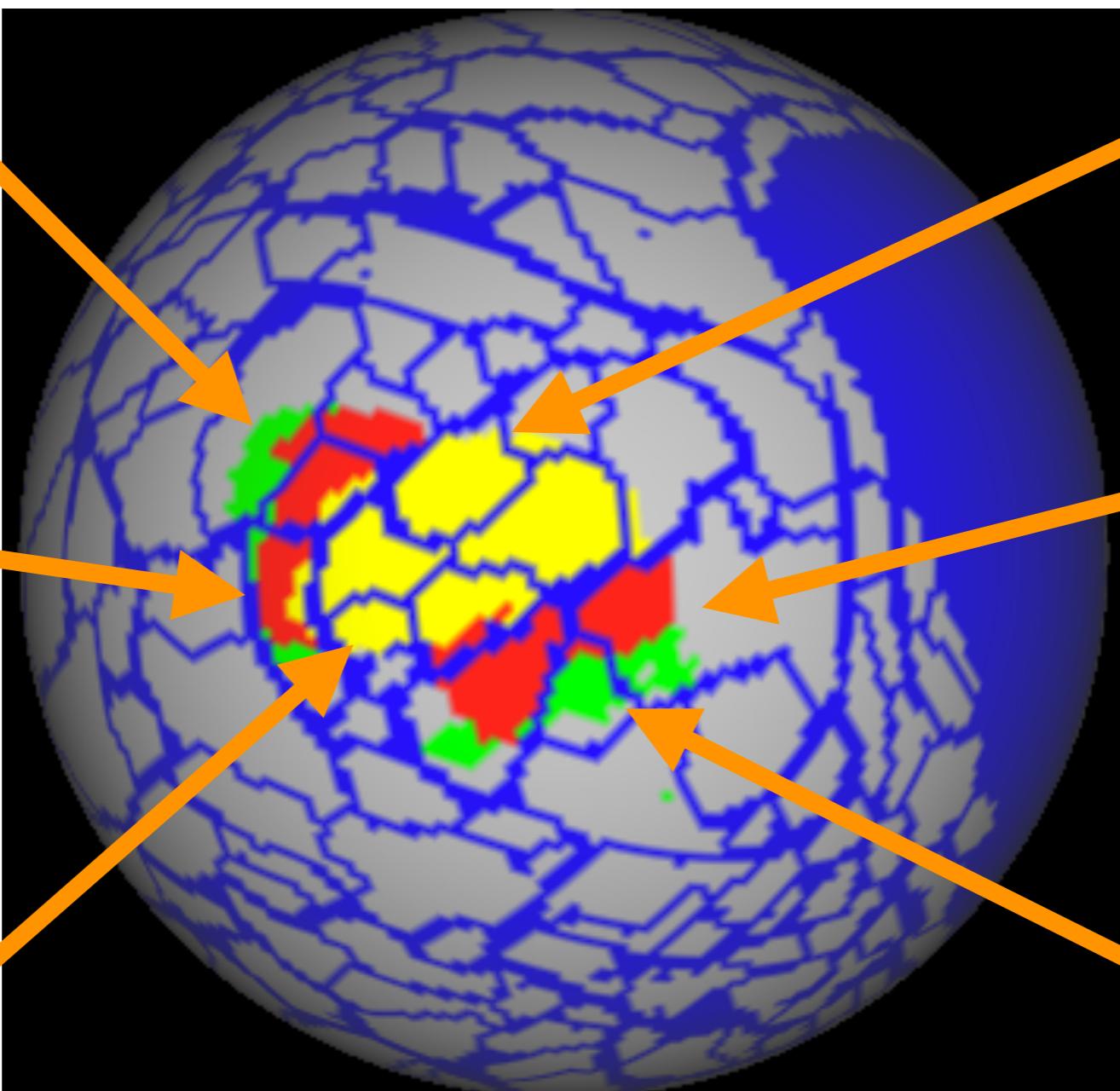
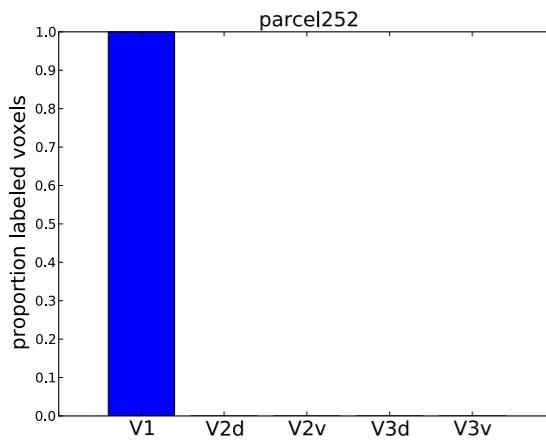
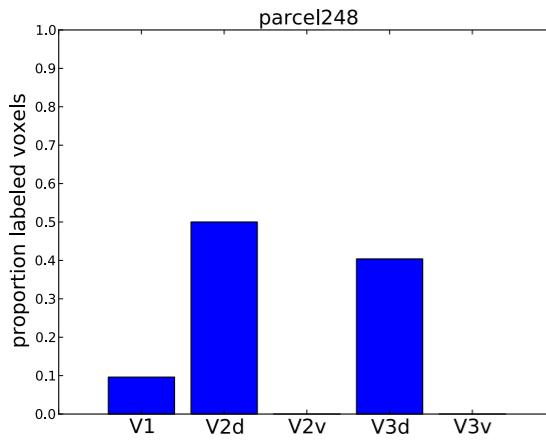
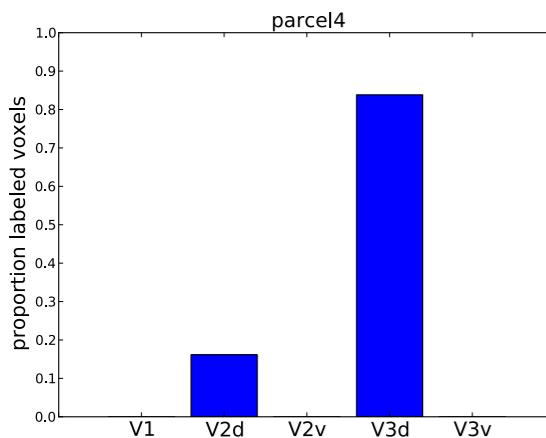


Task fMRI

Task	# sessions
N-back (1/2-back, faces/scenes/chinese chars)	15
Dot-motion discrimination w/ stop signal	8
Sentence processing	5
Spatial working memory	4
Object localizer	4 (2 runs/session)
Retinotopic mapping	1

Parcellation respects retinotopic boundaries

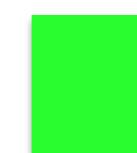
Left hemisphere



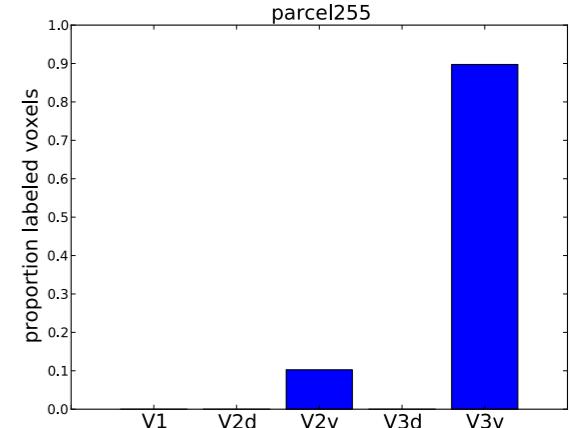
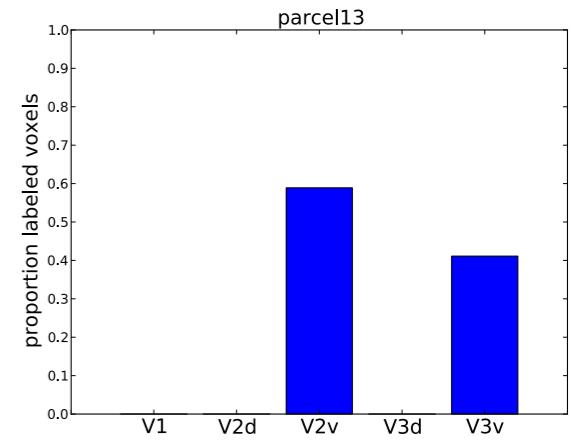
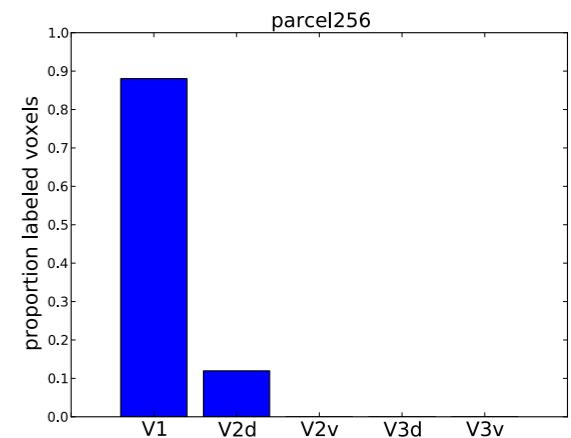
V1



V2

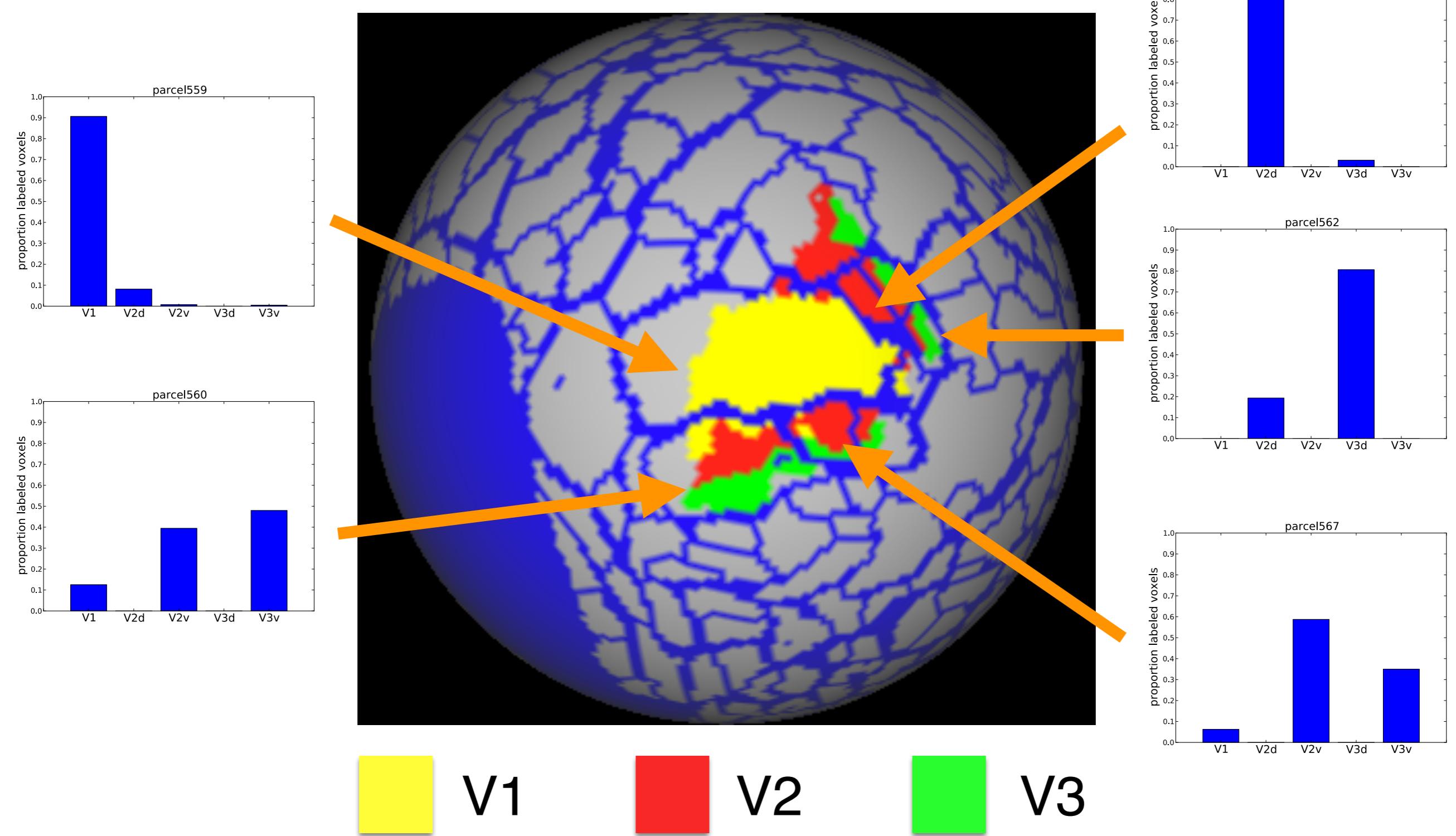


V3



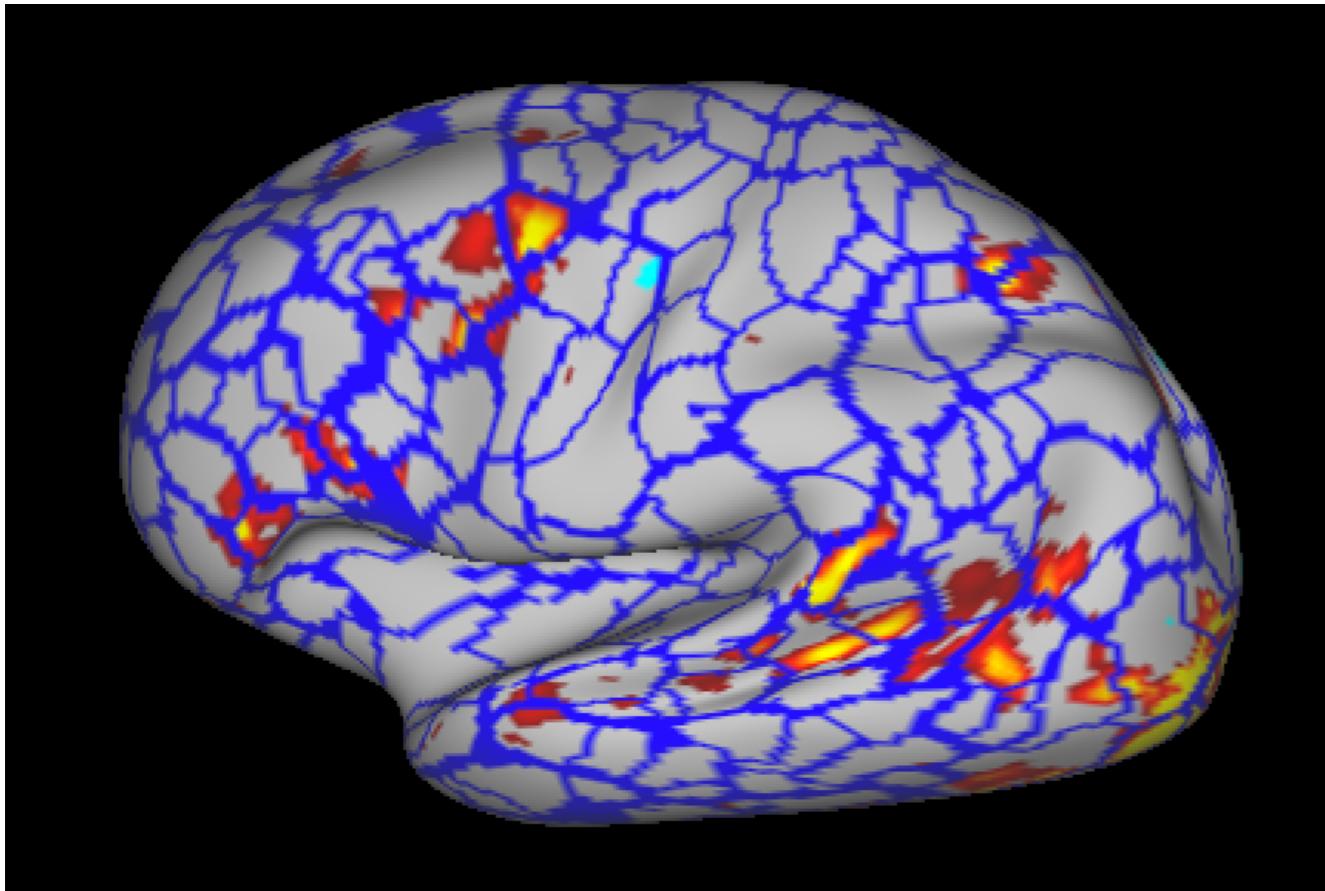
Parcellation respects retinotopic boundaries

Right hemisphere

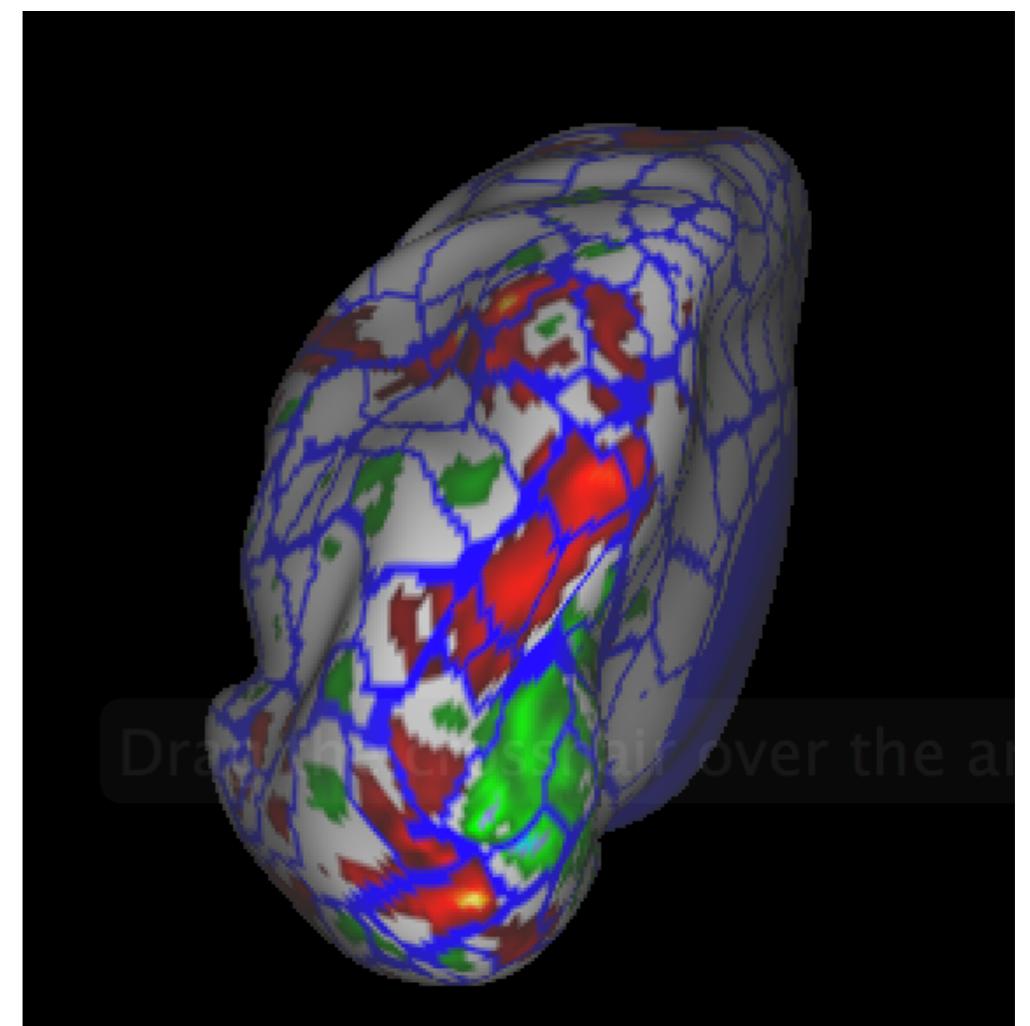


Task activation respects rsFMRI parcellation

Sentence processing

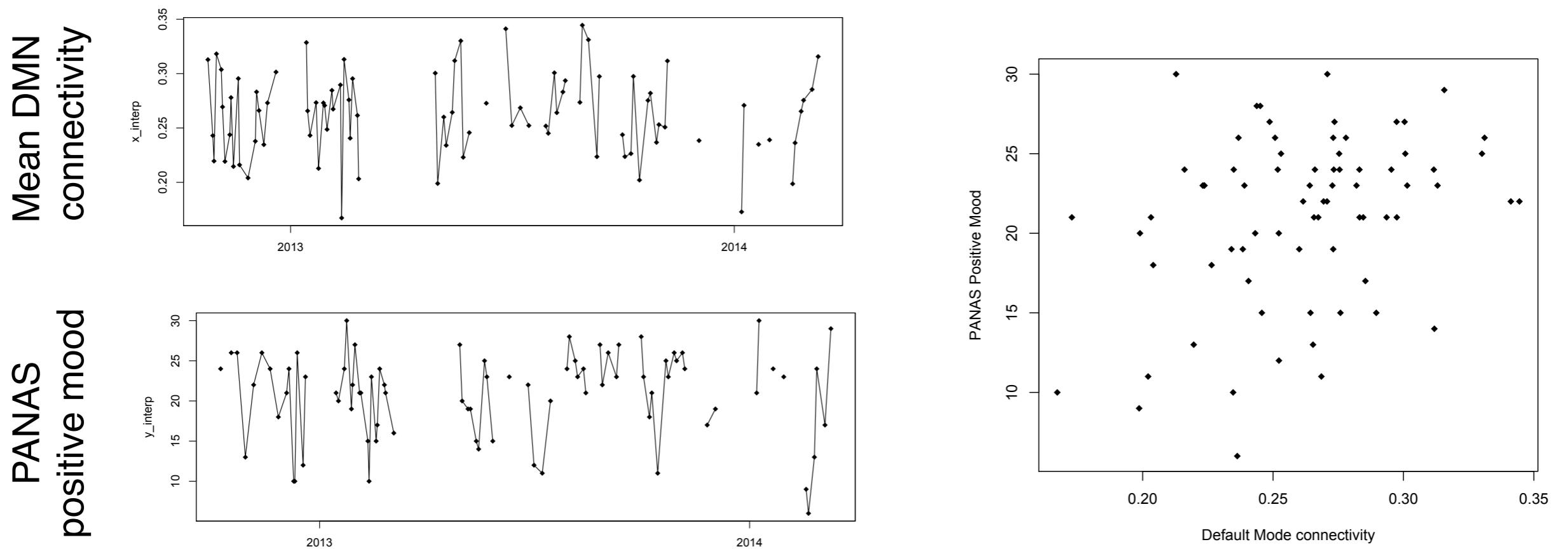


Spatial working memory



Requires quantification - not there yet!

Relating resting variability to other phenotypes



- Adopted an automated ARIMA model selection procedure (R forecast package) which handles missing values
- FDR-correction across all tests within each domain

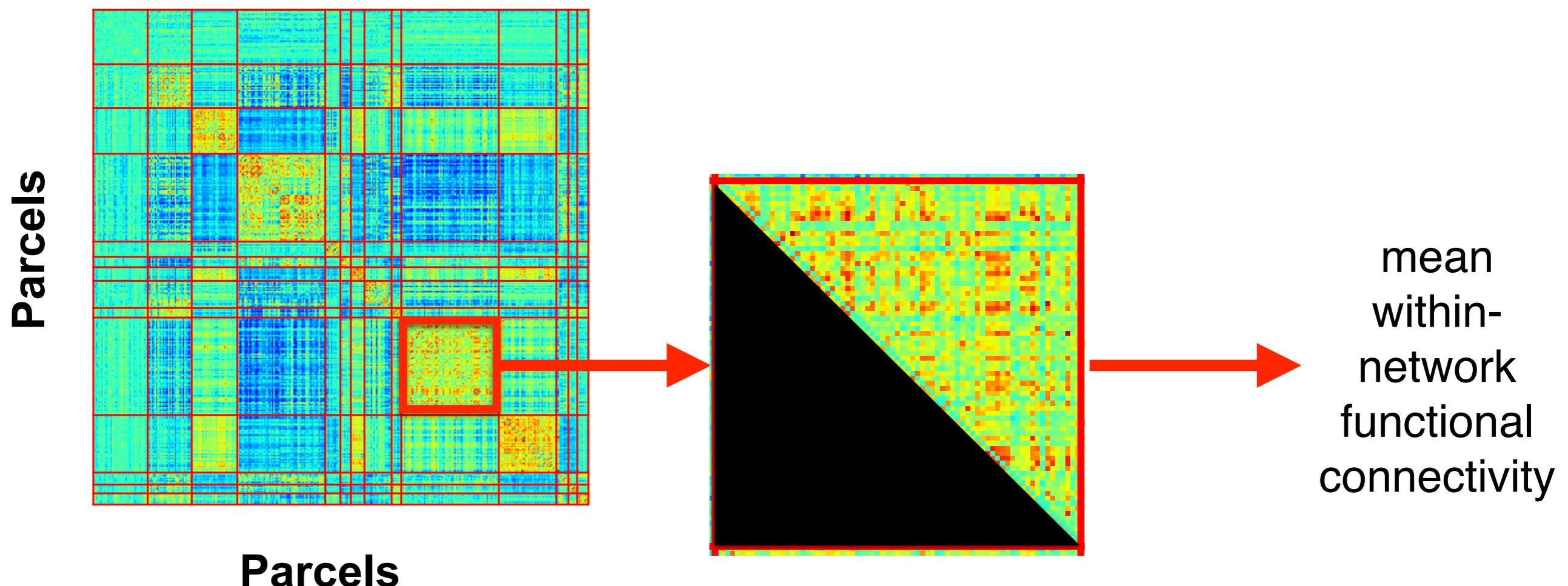


WARNING

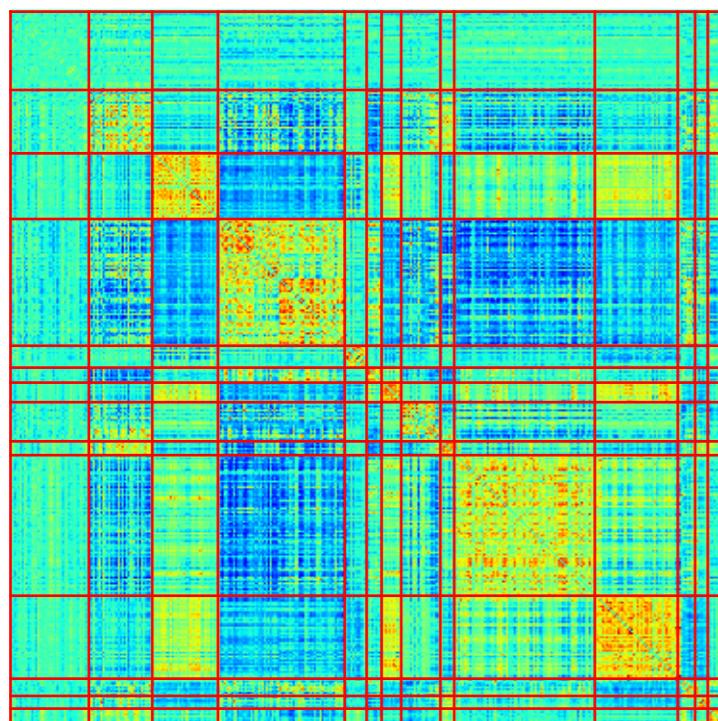
**FALSE DISCOVERY
ZONE!**

Reduced rsfMRI dimensionality: within-module connectivity

Compute mean connectivity within each of the 13 resting state networks



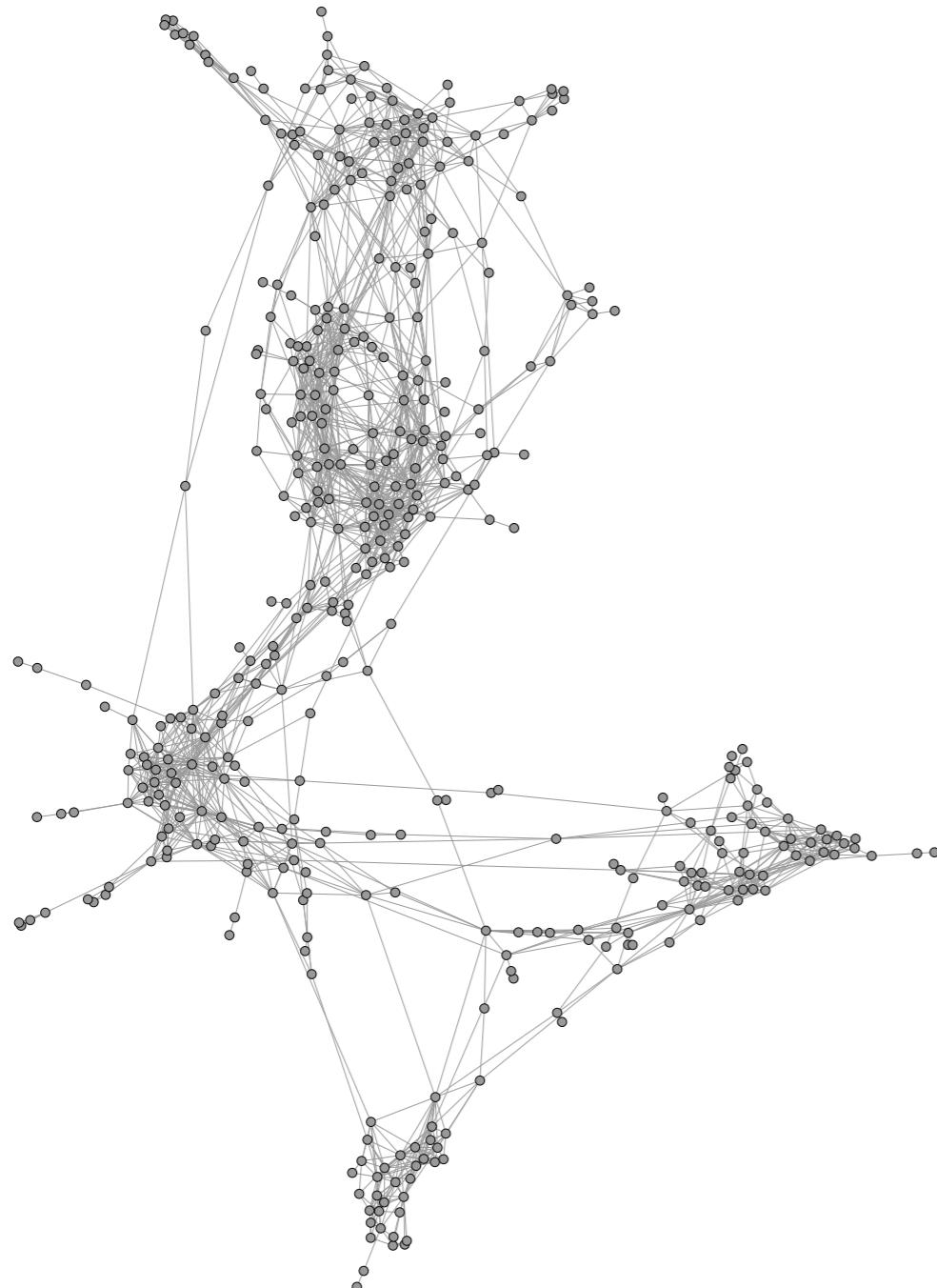
Reduced rsfMRI dimensionality: network-based measures



multiple thresholds
(0.01 - 0.1 density)



Graph-theoretic statistics



- Functional segregation
 - Clustering coefficient
 - Modularity (infomap and multilevel)
- Functional integration
 - Characteristic path length
 - Global and local efficiency
- Higher-order structure
 - Power exponent of degree distribution
 - Rich-club coefficient

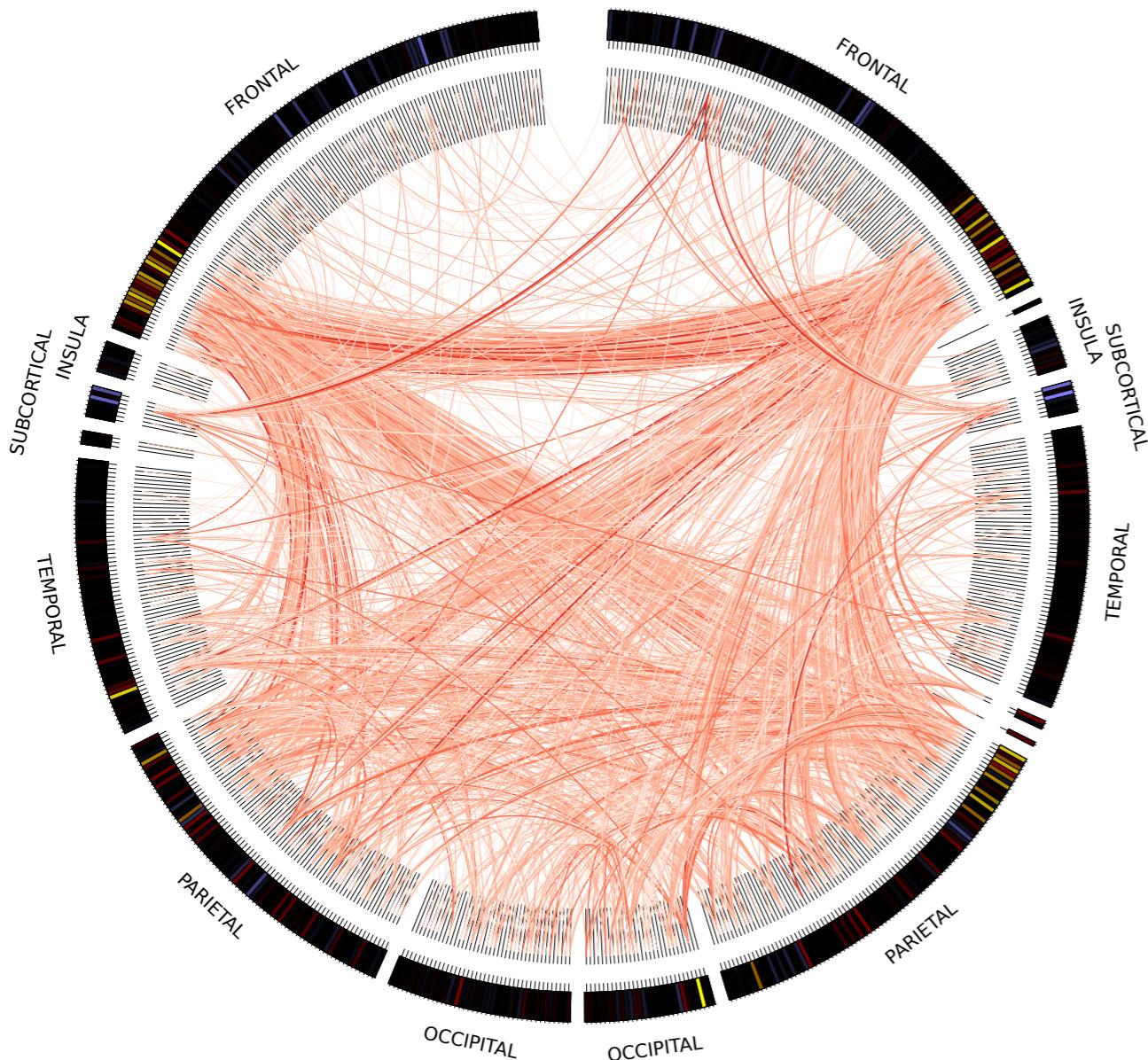
Phenotypic correlations

Connectivity within RSN	Phenotypic measure	r	p (FDR- corrected)
Default mode	Positive mood	0.32	0.018
Dorsal Attn I	Fatigue	-0.44	0.003
Dorsal Attn I	pulse after scan	0.31	0.017
Dorsal Attn II	tues vs. thurs	-0.38	0.018
Dorsal Attn II	Fatigue	0.35	0.049
Dorsal Attn II	pulse after scan	-0.39	0.003
Somatomotor	tues vs. thurs	-0.60	<0.001

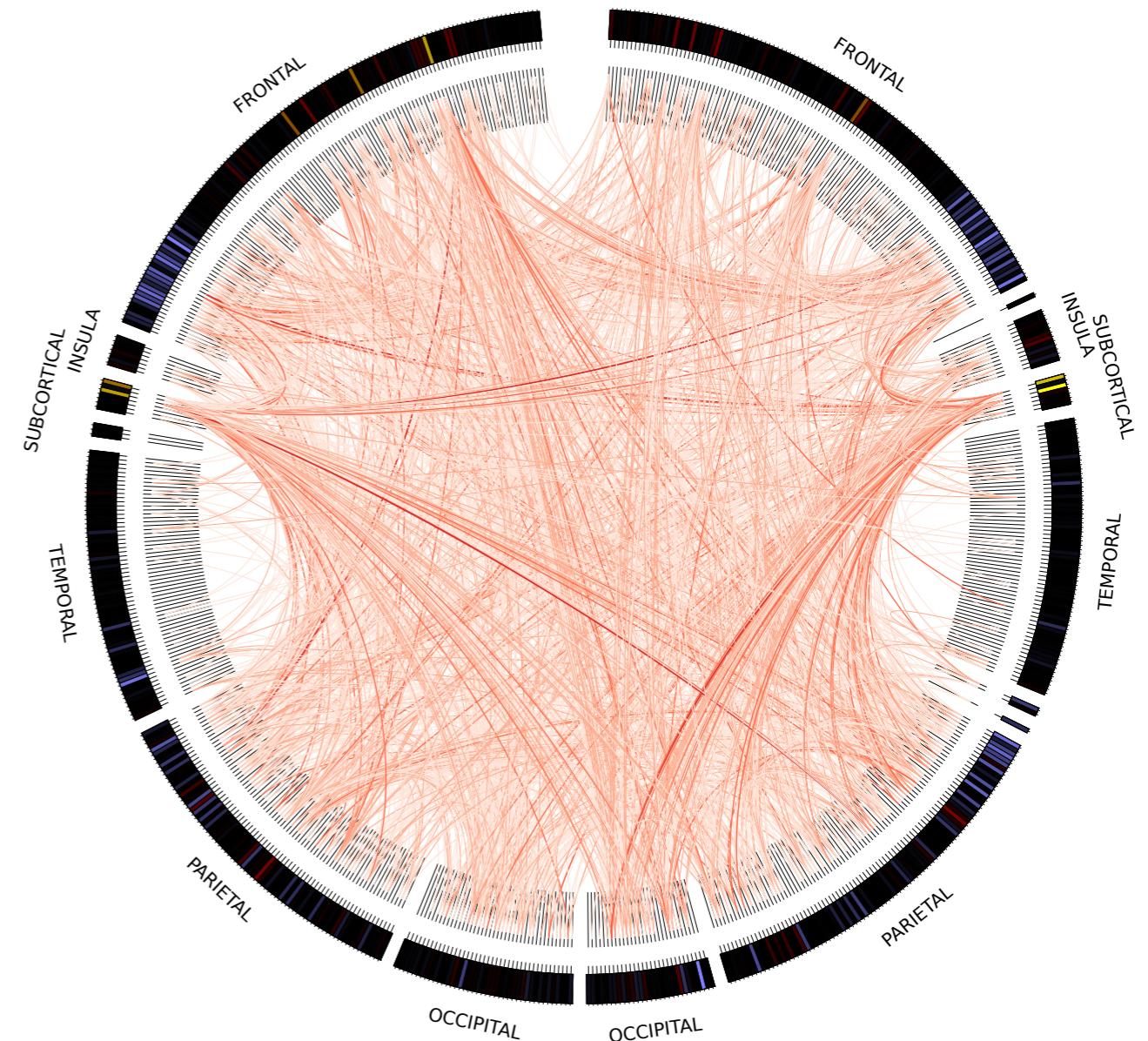
no significant associations for graph-theoretic measures or fALFF

Tuesday (fasted/no caf) vs. Thursday (fed/caf)

Tues > Thurs



Tues < Thurs



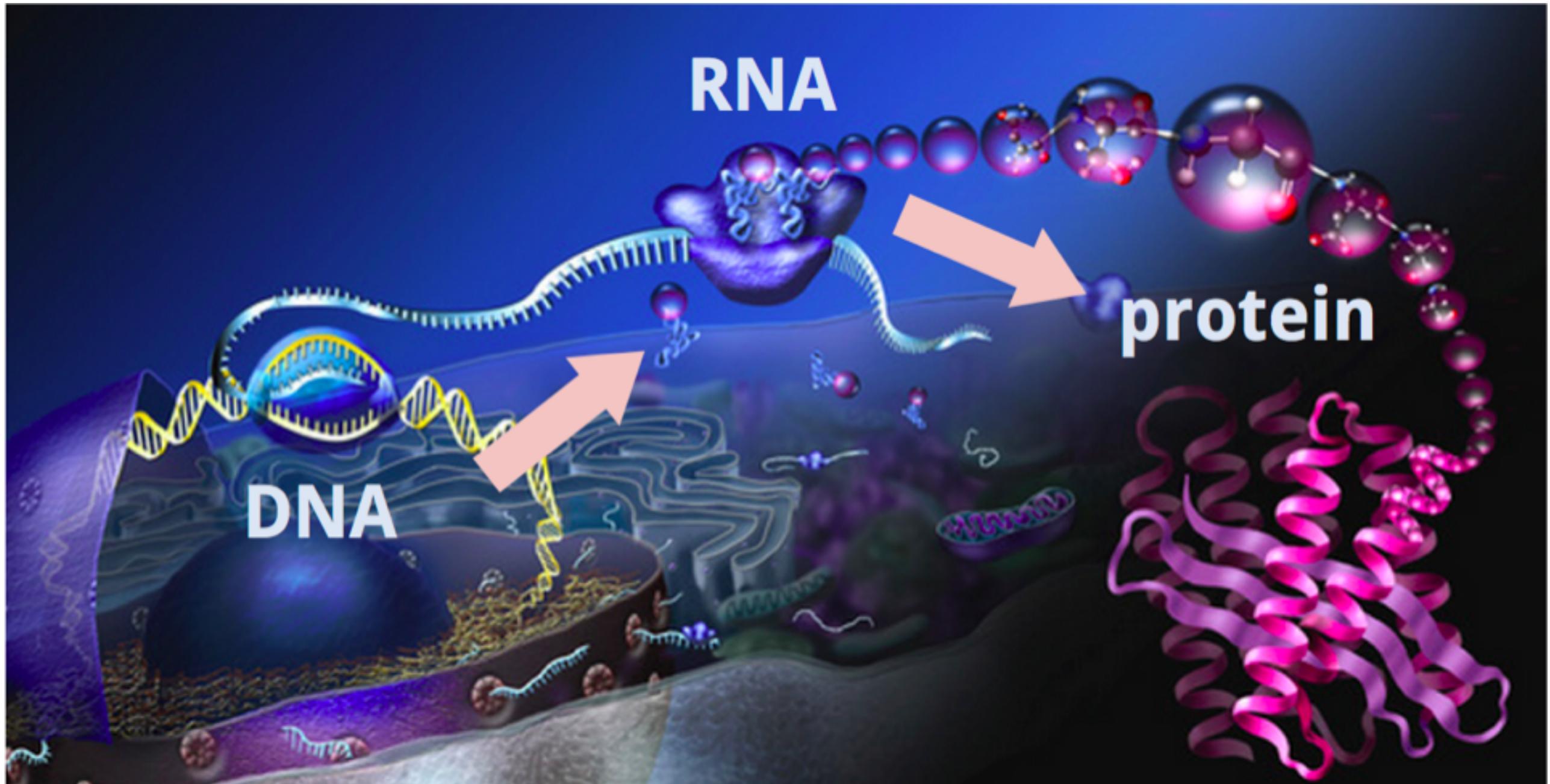
FDR-corrected $p < 0.05$

fMRI summary

- Resting state networks and parcellations are highly reliable with enough data
- Resting state parcellations overlap with task activation regions
- Within-subject variability over sessions is fundamentally different from either within-run or between-subject variability
- Functional connectivity exhibits intriguing relations to behavioral variables

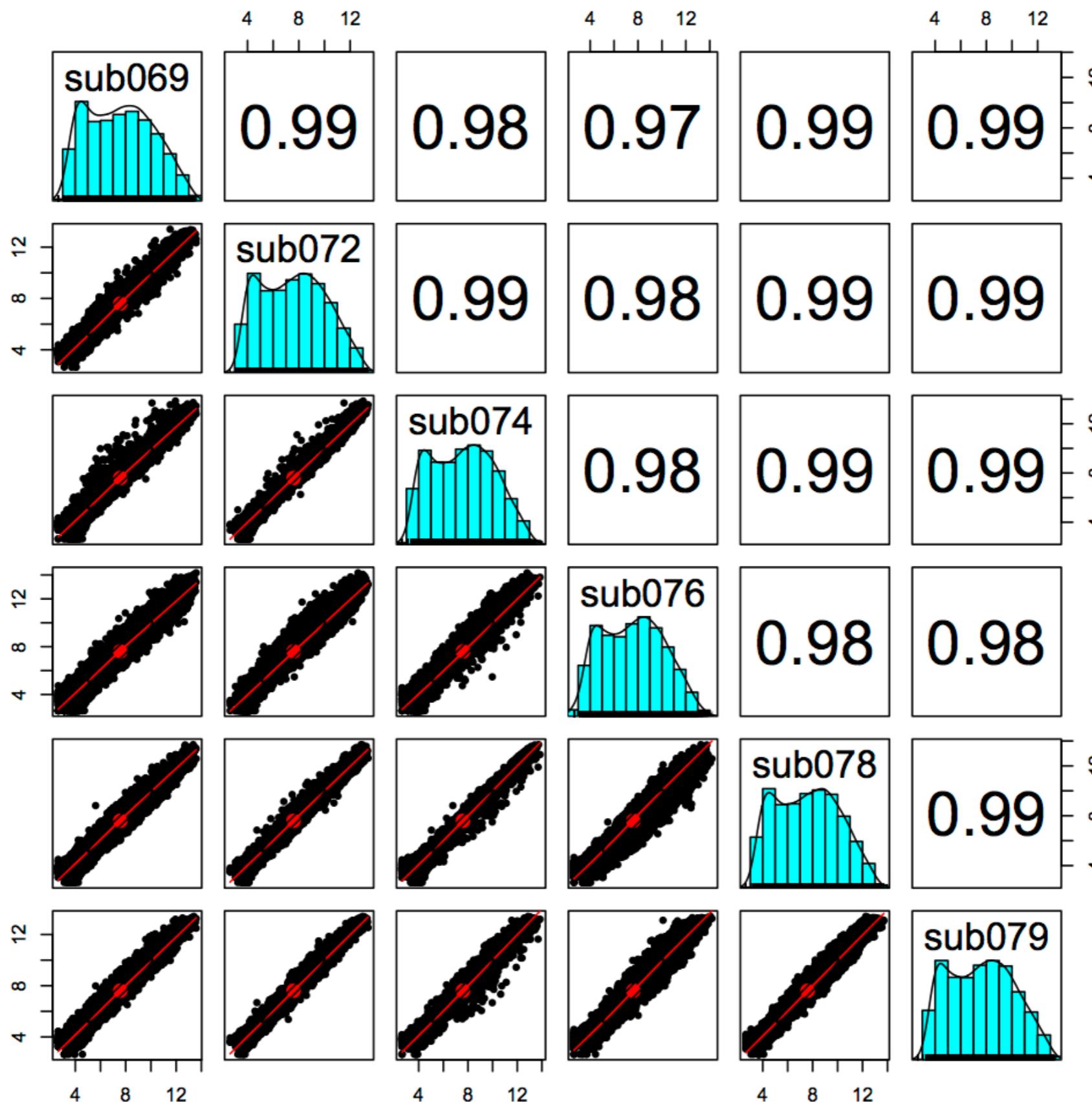
Are behavior and brain function related to fluctuations in bodily metabolism?

Gene expression using RNA sequencing



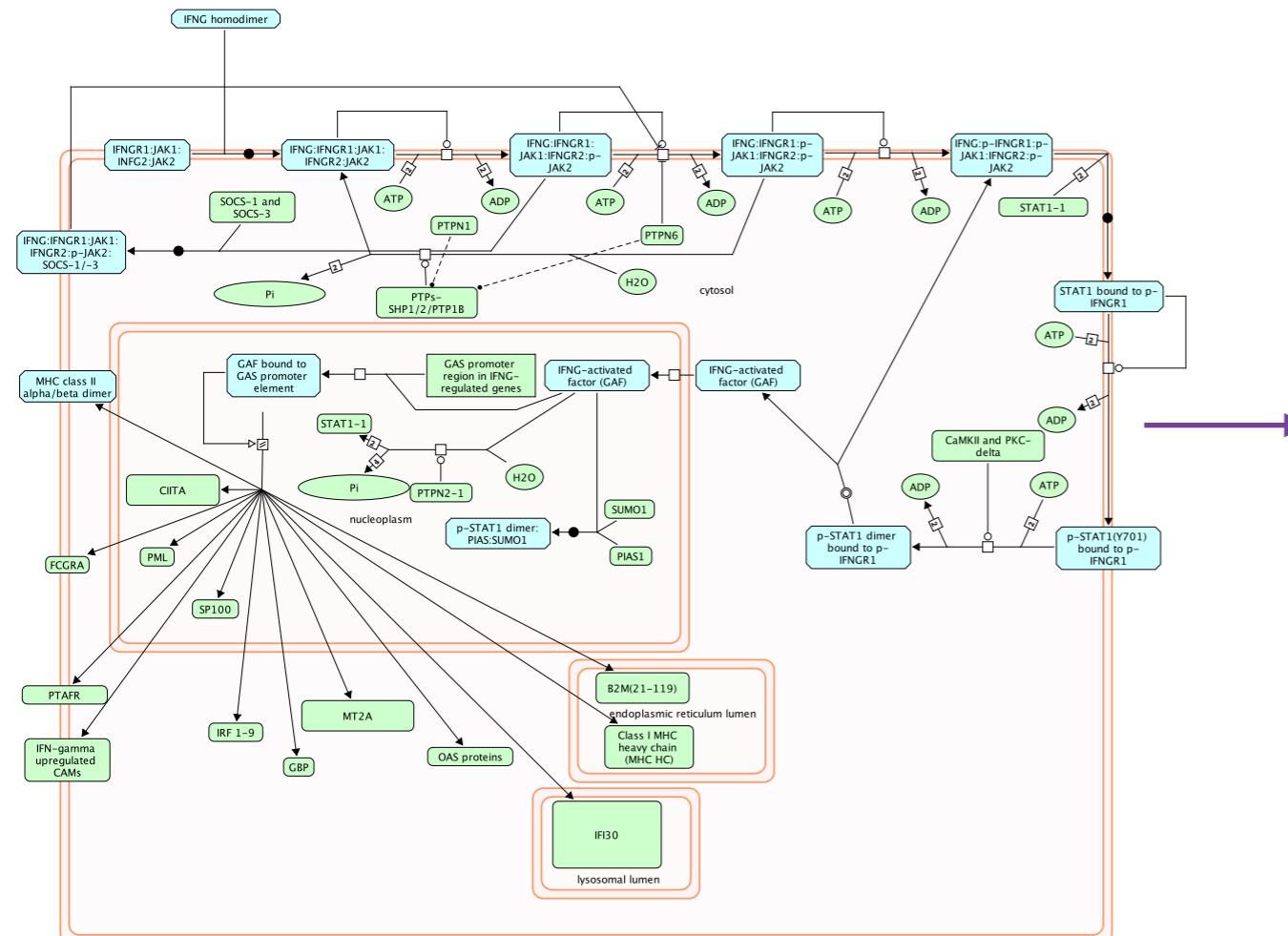
How many transcripts are present for each gene?
Can't access brain - so we use white blood cells

Gene expression is highly consistent



Pathway-based expression analysis

Interferon-gamma signalling



CAMK2D
CAMK2G
CIITA
FCGR1A
FCGR1B
GBP1
GBP2
IRF3
IRF4
IRF5
IRF6
IRF7
IRF8
IRF9
JAK2
GBP3
GBP4
GBP5
GBP6
MT2A
NCAM1
OAS1
OAS2
OAS3
OASL
PIAS1
PML
PRKCD
PTAFR
PTPN1
PTPN11
PTPN2
IFI30
IFNG
IFNCR1
IFNCR2
IRF1
IRF2
STAT1
SUMO1
SOCS1
SOCS3
SP100

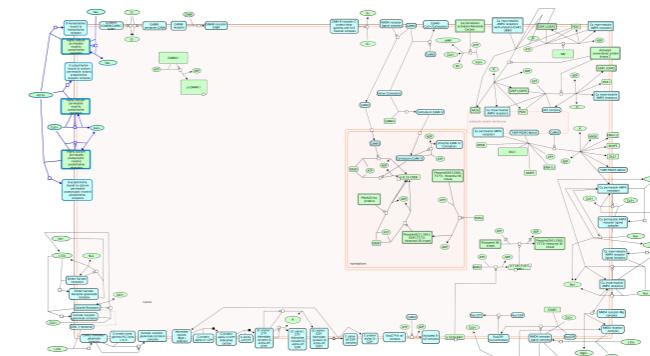
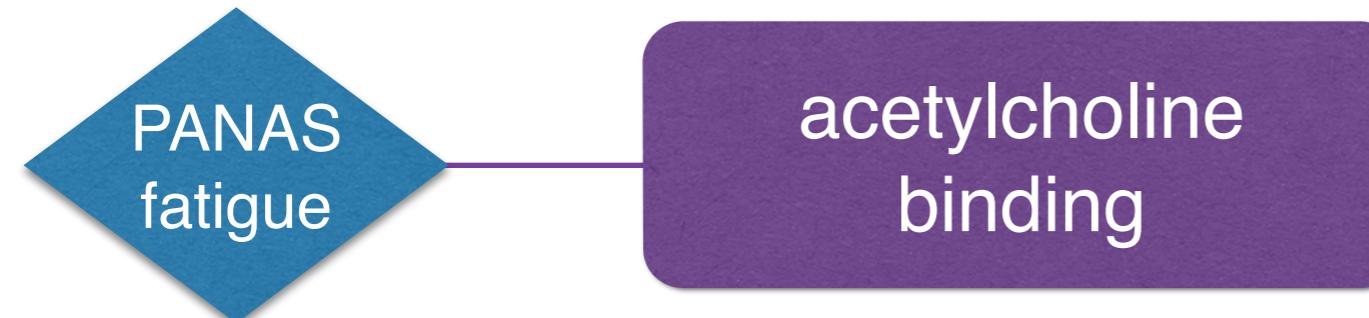
Pathway eigengene

1st principal component of expression values

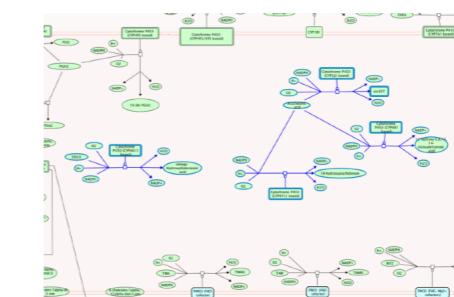
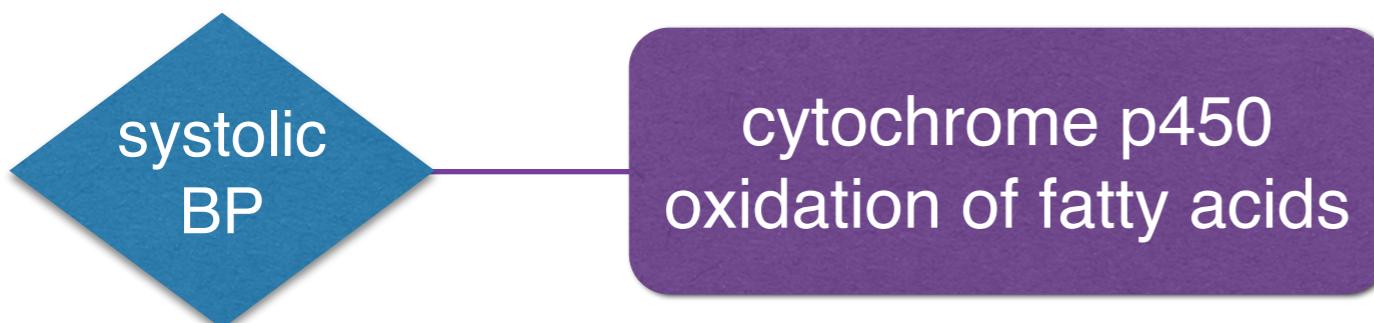
Reactome pathways (1420 with genes in set)

Reactome gene associations

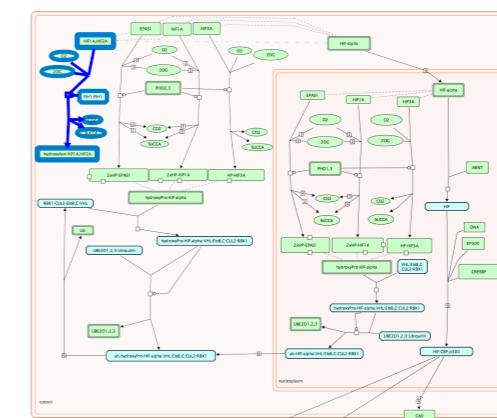
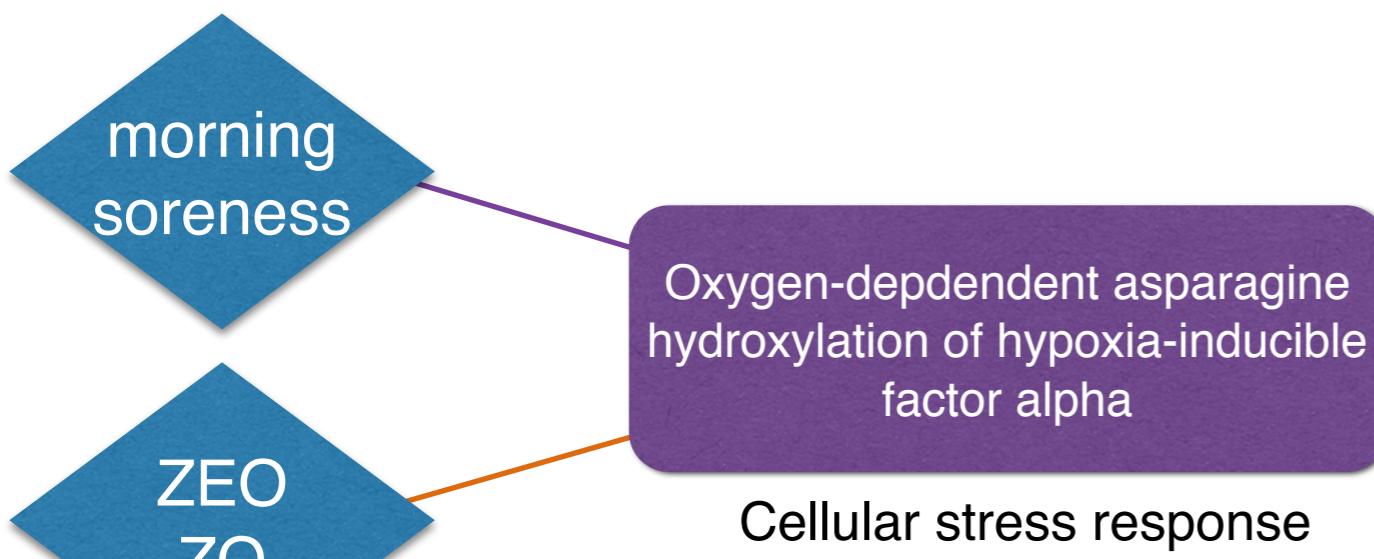
Behavior/gene expression relations



CHRNA1
CHRNA2
CHRNA3
CHRNA4
CHRNA5
CHRNA6
CHRNA7
CHRNA9
CHRNB2
CHRNB3
CHRNB4
CHRND
CHRNE
CHRNG

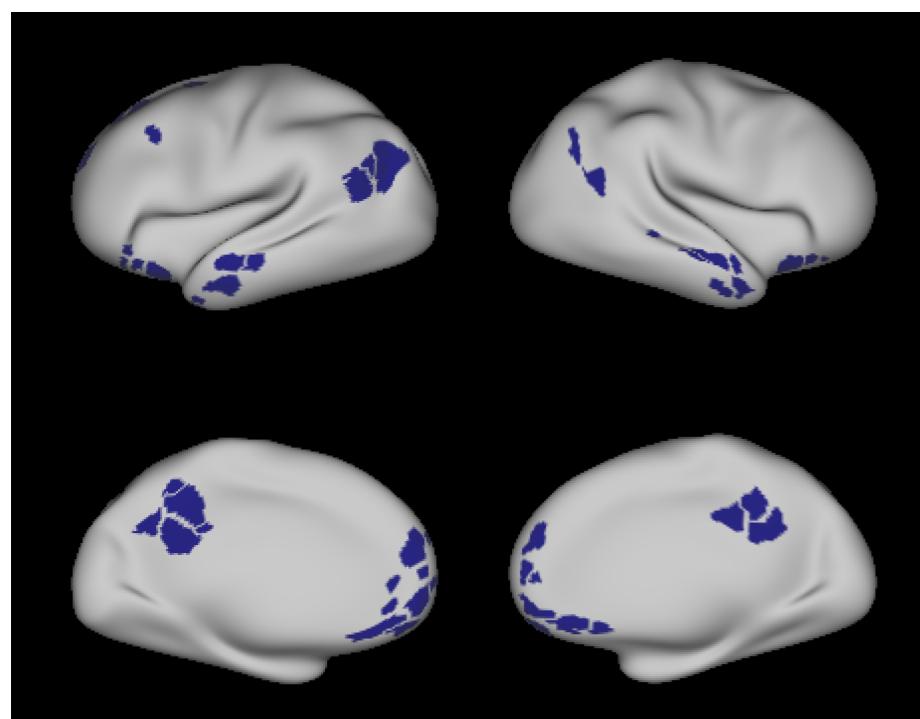


CYP2A13
CYP2A7
CYP2B6
CYP2D6
CYP2F1
CYP2J2
CYP4A11
CYP4A22
CYP4B1
CYP4F11
CYP4F12
CYP4F
CYP4F22
CYP4F3
CYP4F8



EPAS1
HIF1A
HIF1AN

Connectivity/gene expression relations



Connectivity within
default mode network

Top-level Reactome domains (DMN):

Developmental
Biology

Disease

Gene
Expression

Immune
System

Organelle
biogenesis and
maintenance

Signalling pathways:

Ca²⁺ pathway

CaM pathway

Cation-coupled chloride
cotransporters

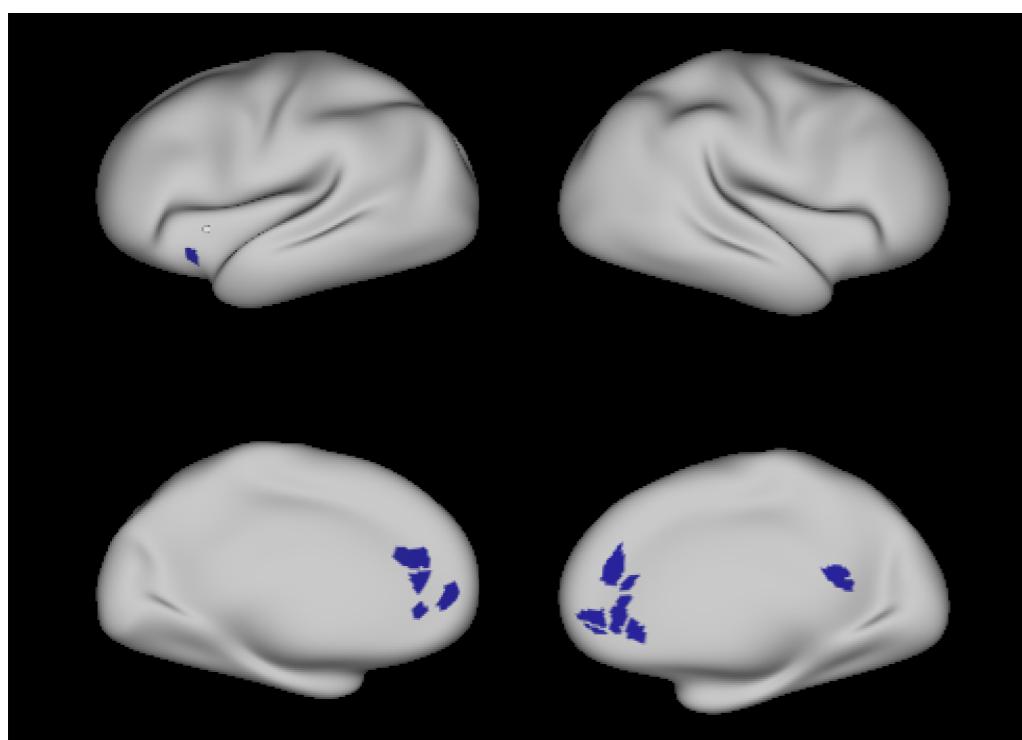
CREB phosphorylation
(Ras-mediated)

DARPP-32 events

HCN channels

Post NMDA-receptor-activation
events

Gene expression correlates of salience network

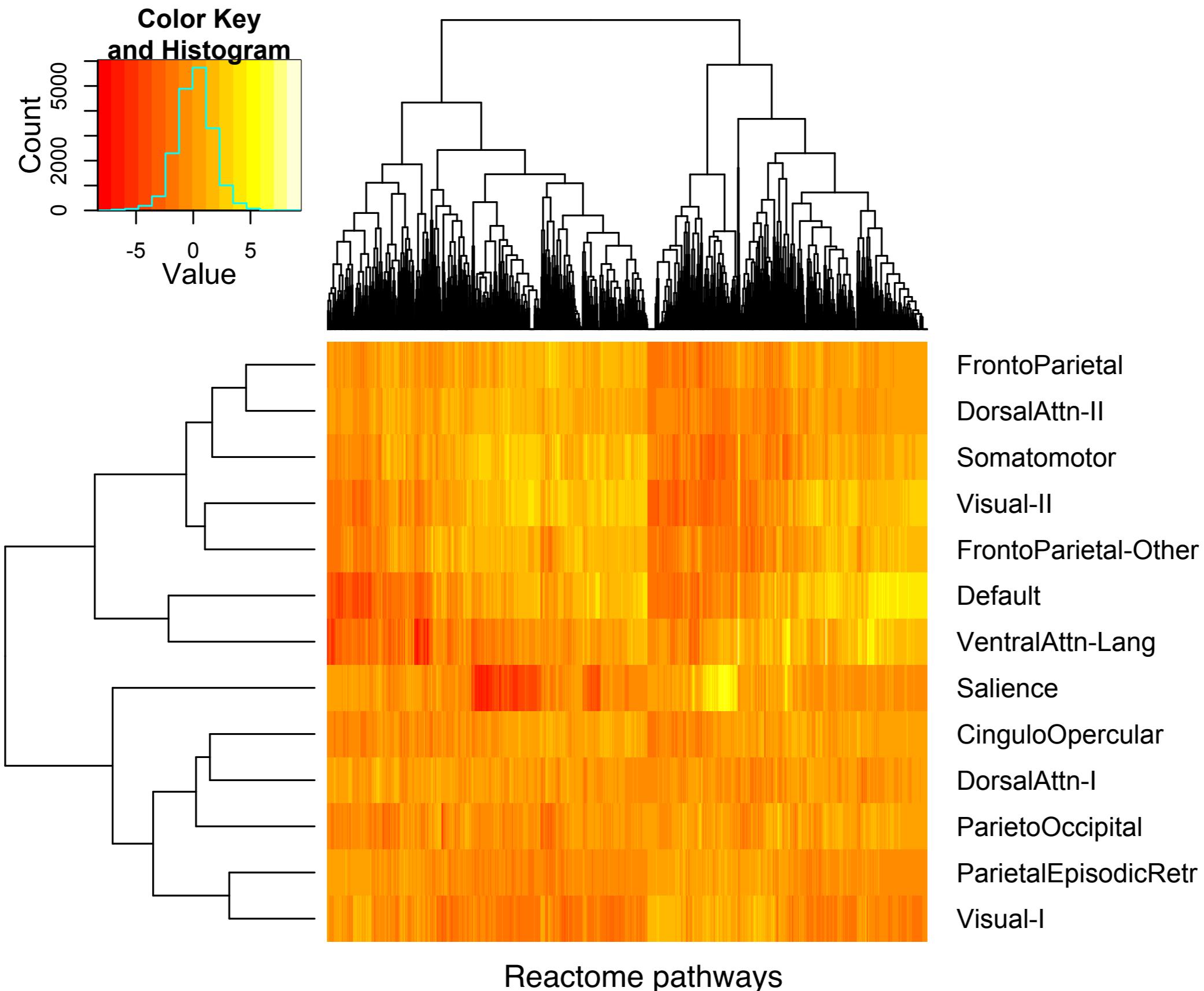


Connectivity within
salience network

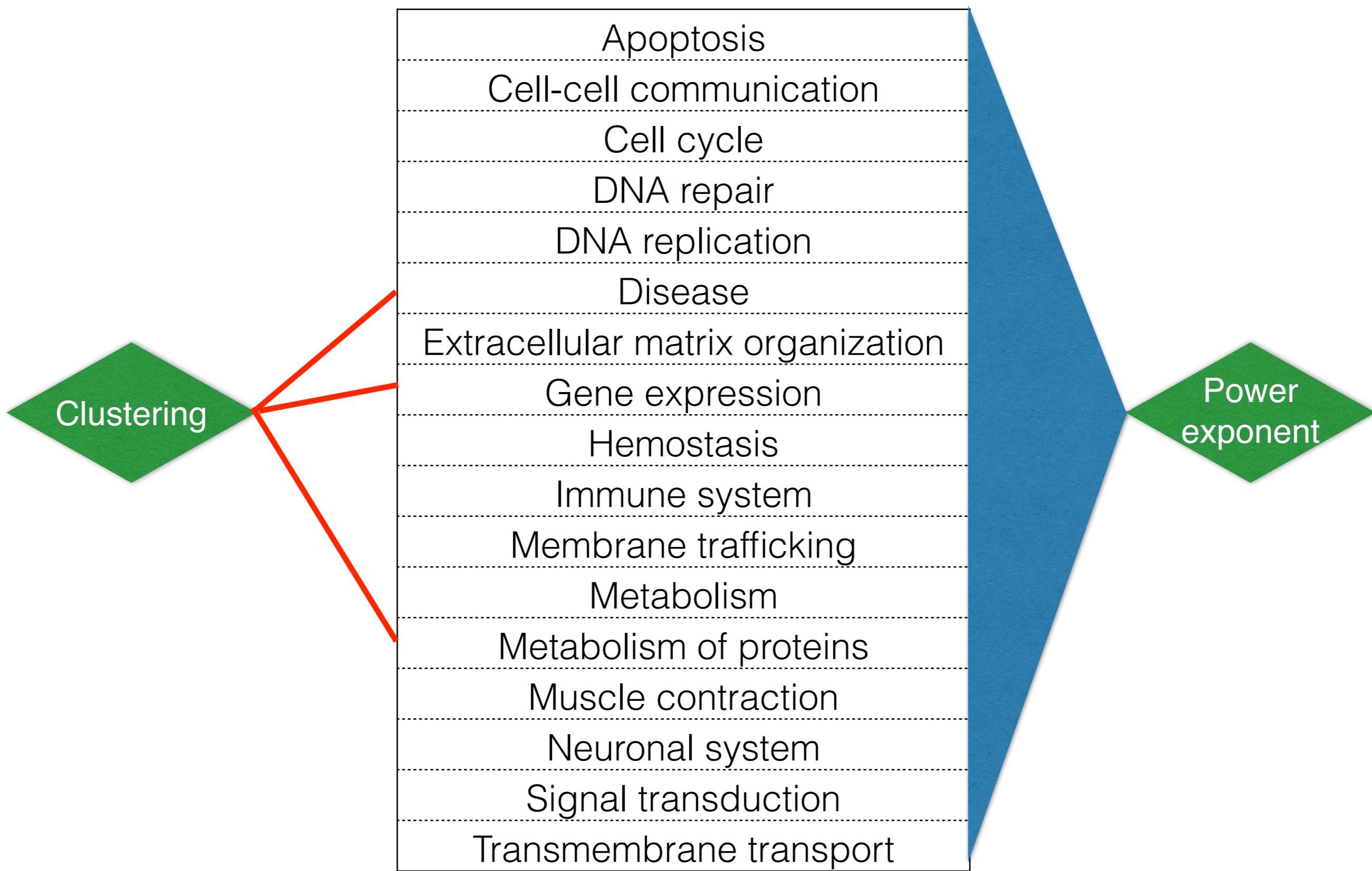
Top-level Reactome domains (salience):

Apoptosis	Membrane Trafficking
Cell Cycle	Metabolism
Cell-Cell Communication	Muscle Contraction
Cellular Responses to Stress	Neuronal System
Extracellular Matrix Organization	Reproduction
Hemostasis	Signal Transduction
Meiosis	Transmembrane Transport of Small Molecules

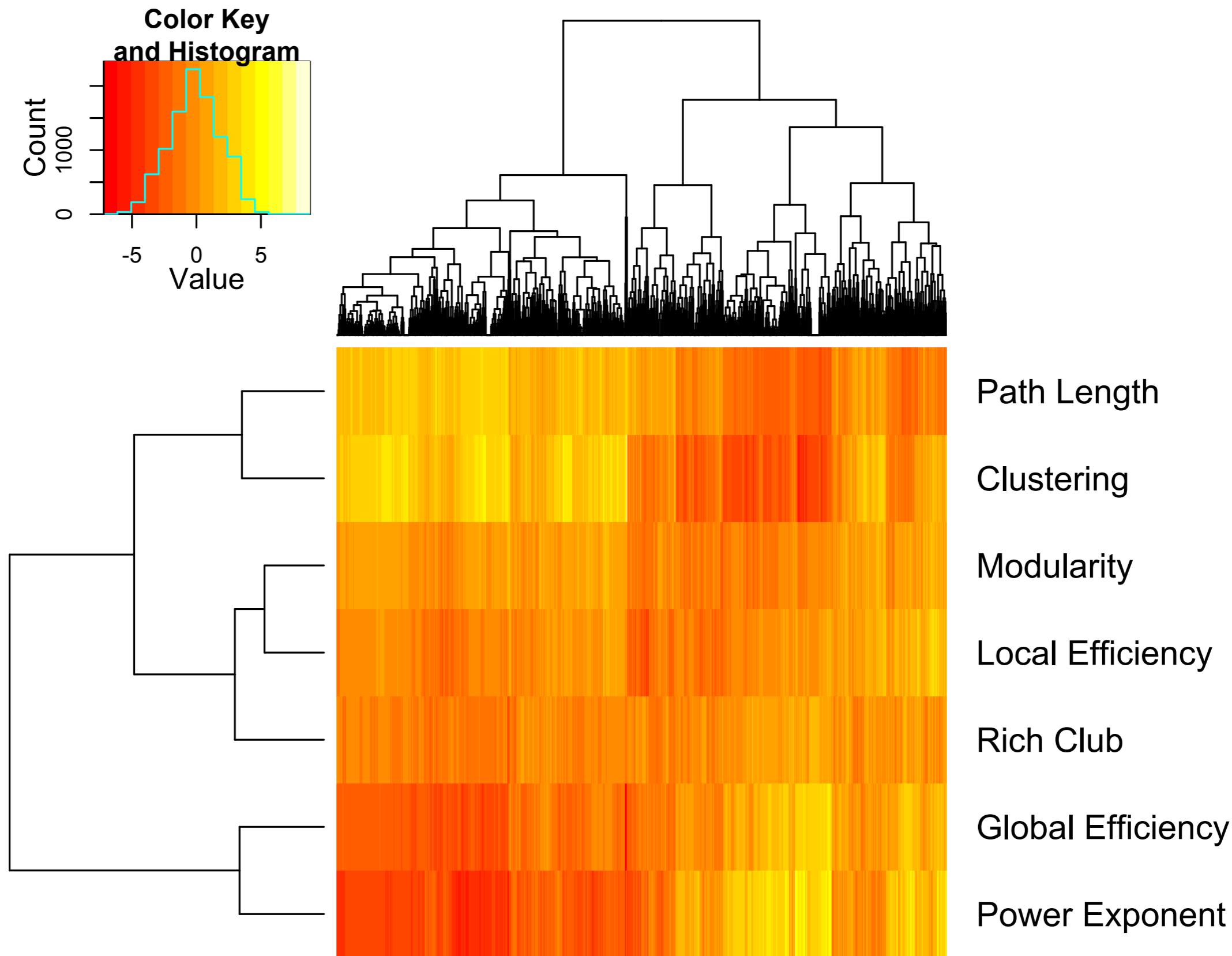
Distinct pathway signatures of RSNs



Gene expression and graph-theoretic measures

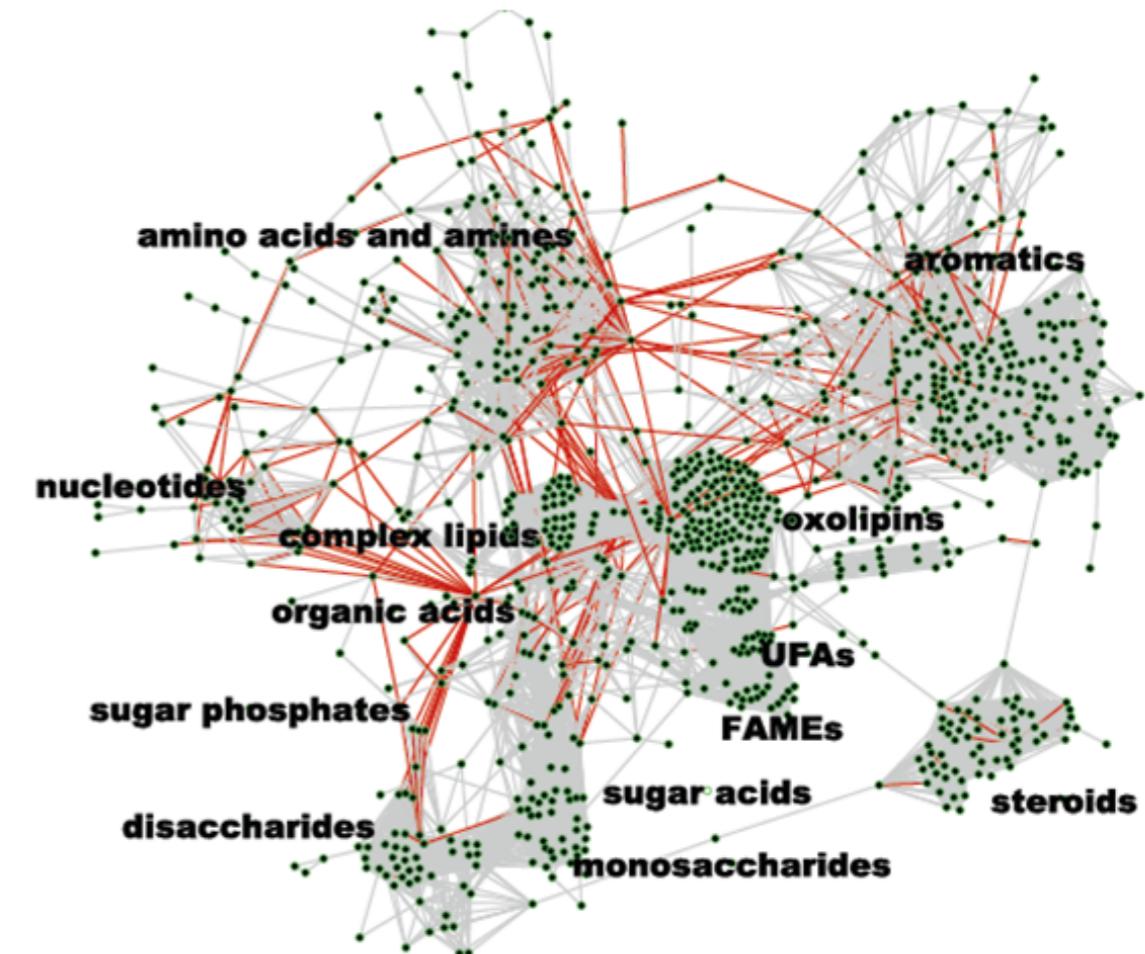


Distinct pathway signatures of graph-theoretic measures



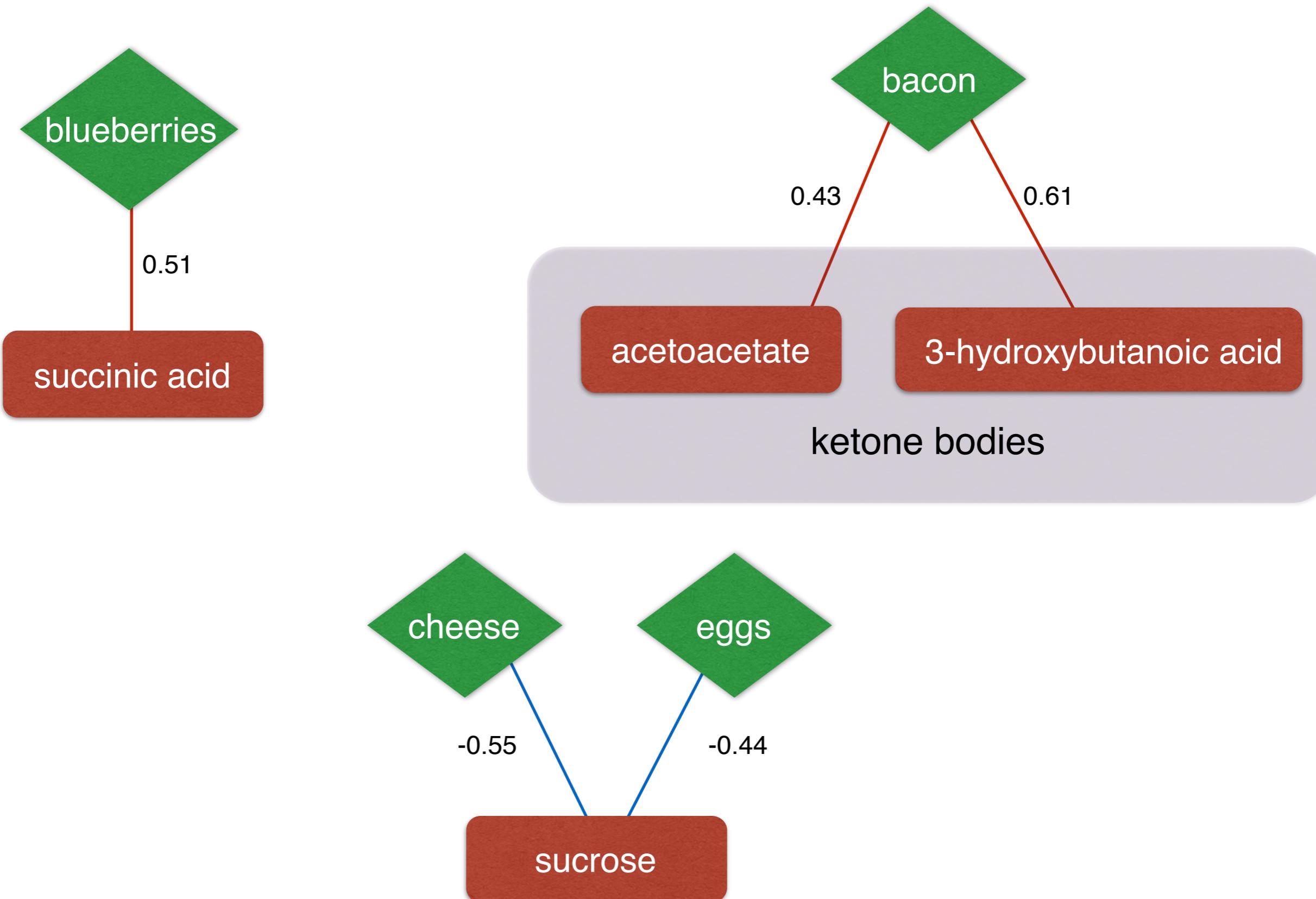
Metabolomics

- Profiling of small molecules in serum using mass spect
 - amino acids, fatty acids, sugars, etc.
 - Performed by Fiehn lab at UC Davis
- 106 named metabolites measured for each session

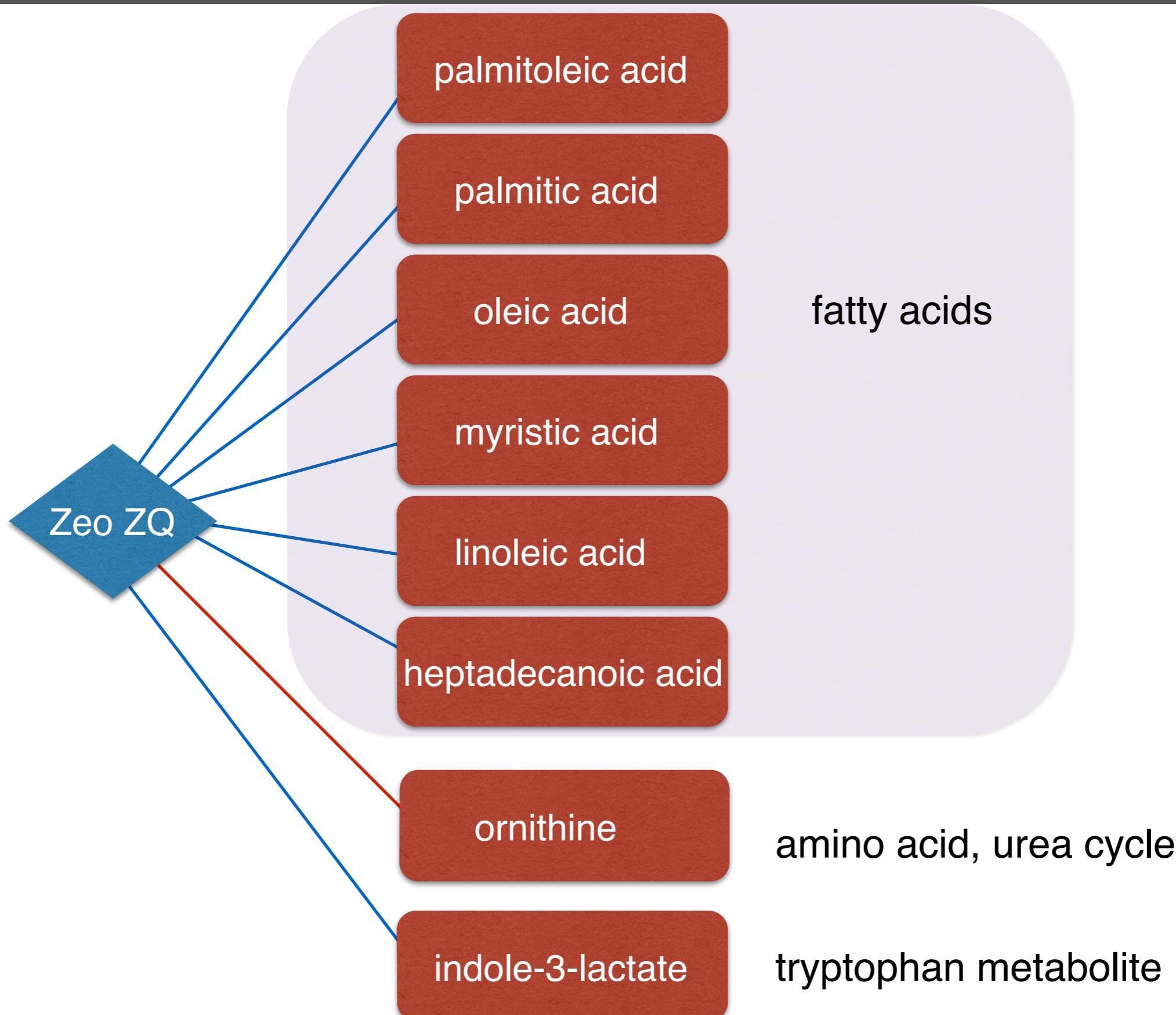


<http://metabolomics.ucdavis.edu/>

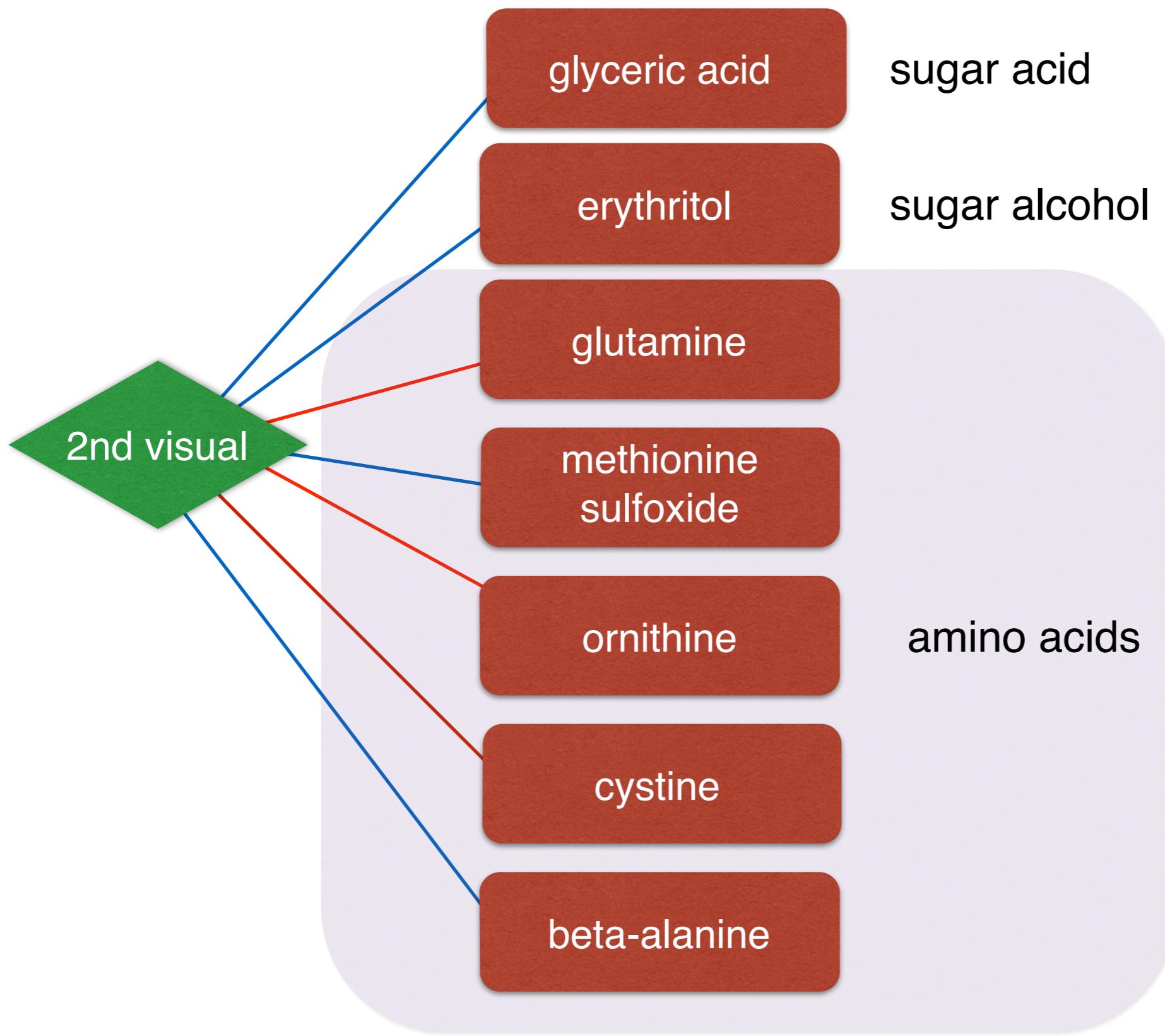
You are what you eat: metabolome vs. food



Behavioral phenotypes vs. metabolome



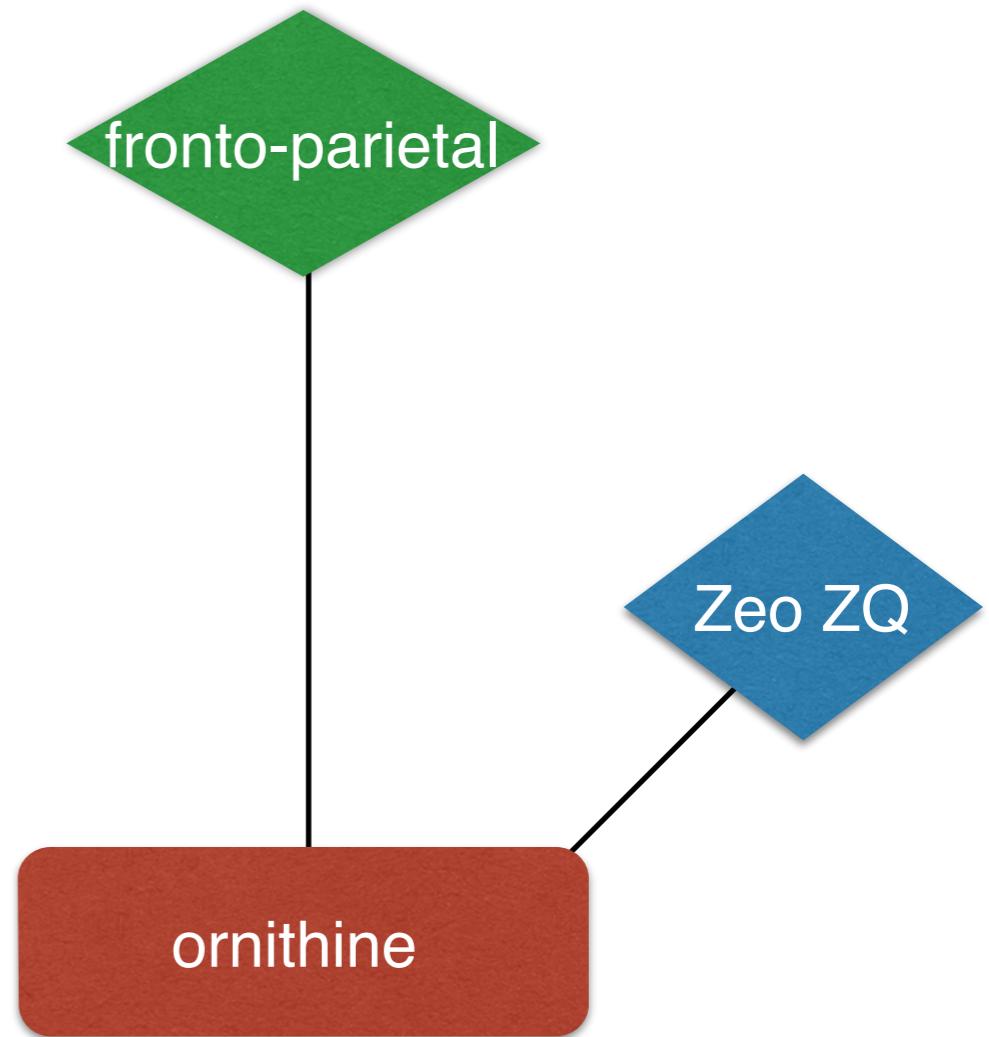
Metabolome vs. brain connectivity



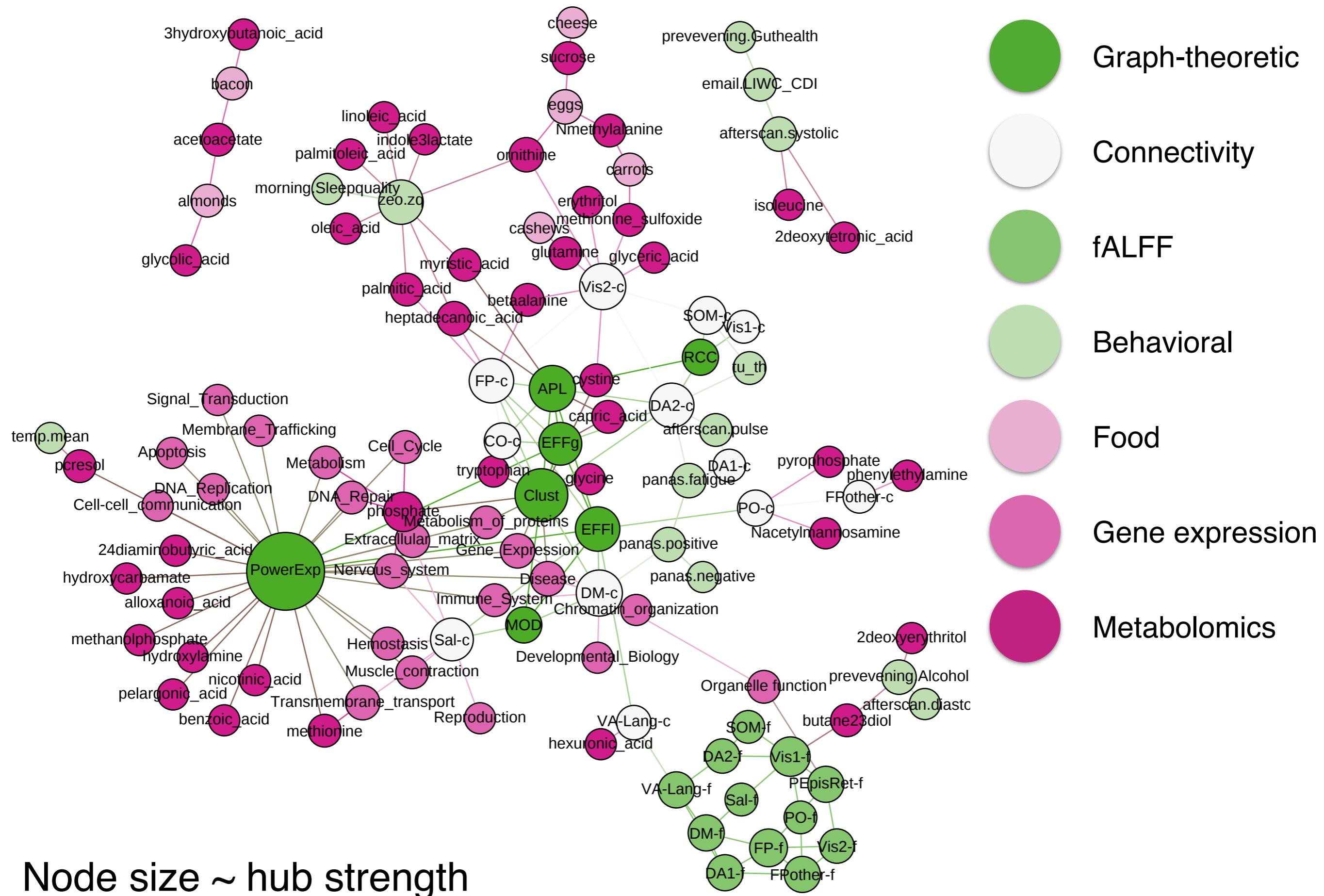
Phenome-wide network analysis

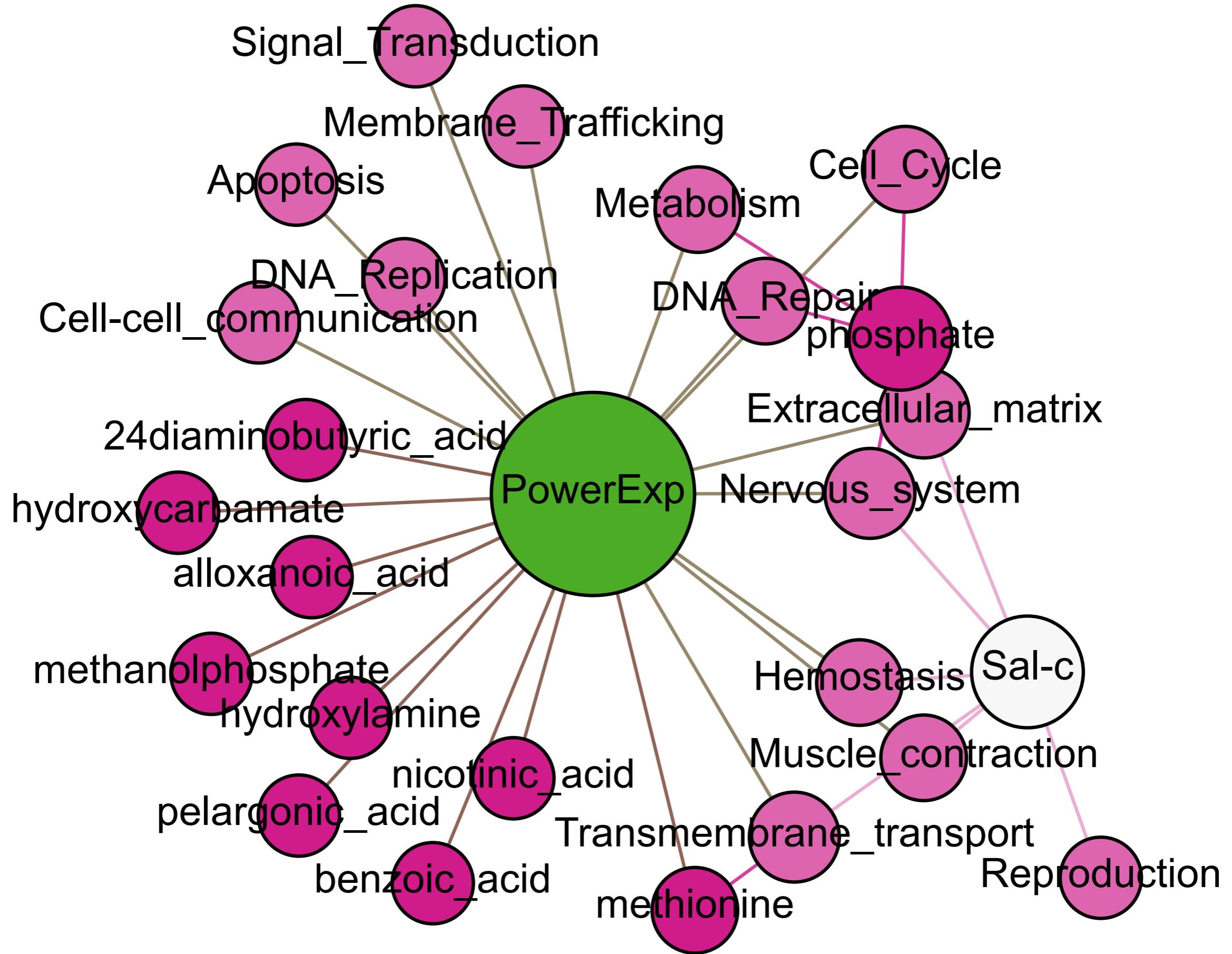
Treat each variable as a node
in a graph

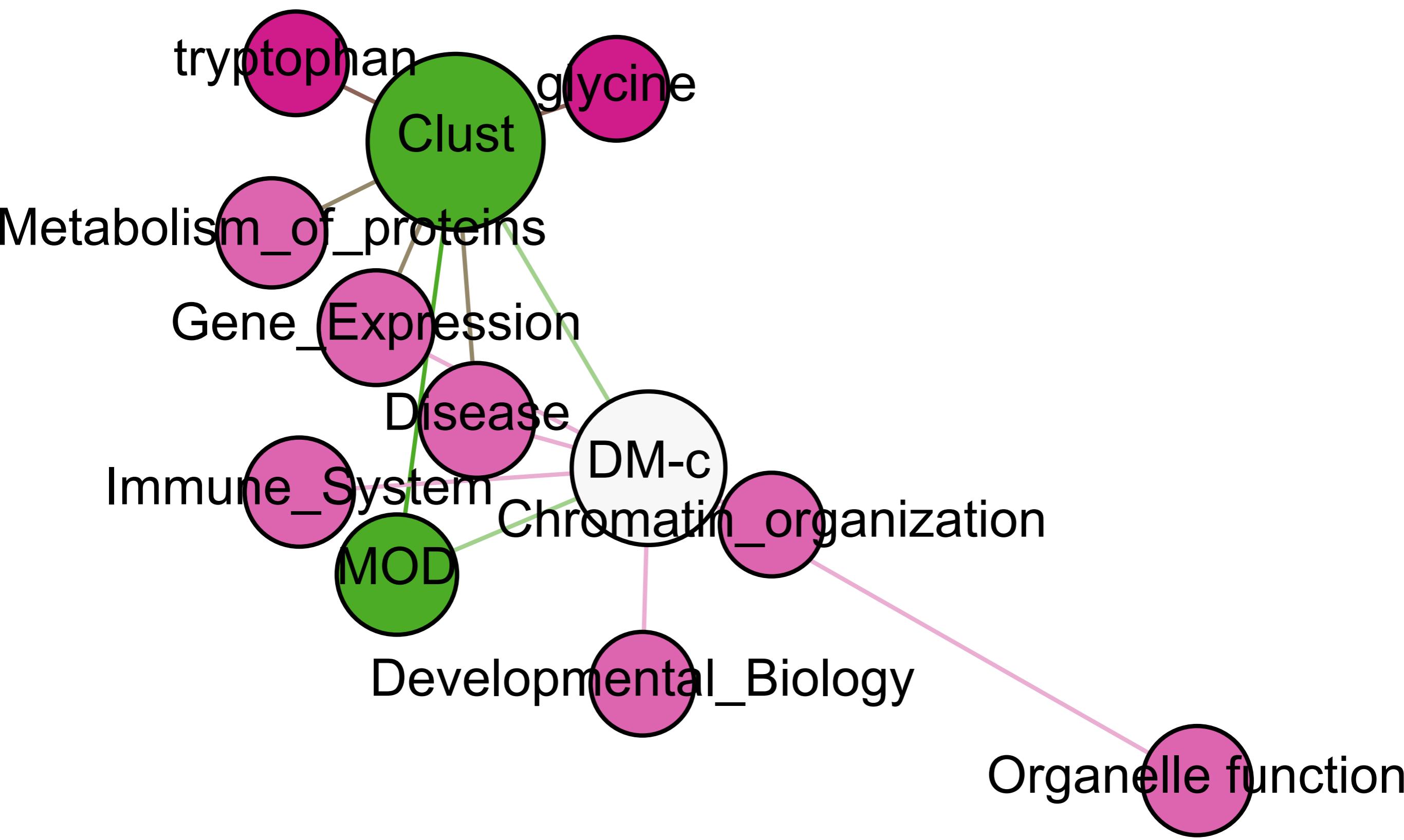
Treat significant associations
as edges in a graph



Phenome-wide Network Analysis







Conclusions

- There are interesting and novel brain dynamics over weeks and months
- There are intriguing relations between brain function, behavior, and metabolism
- We know almost nothing about these!
- Discoveries in this domain will be difficult but fundamental
- We can learn a lot by studying ourselves

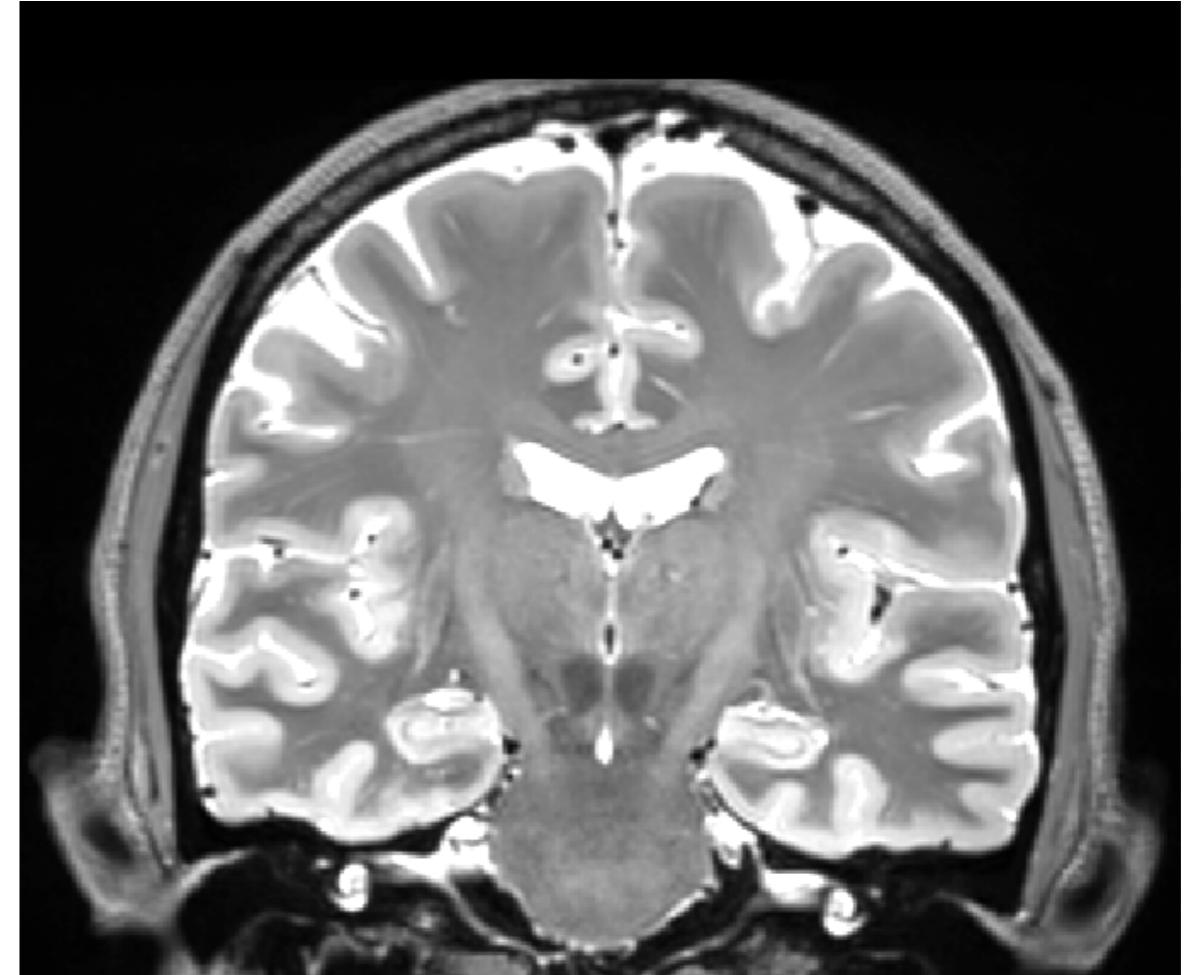
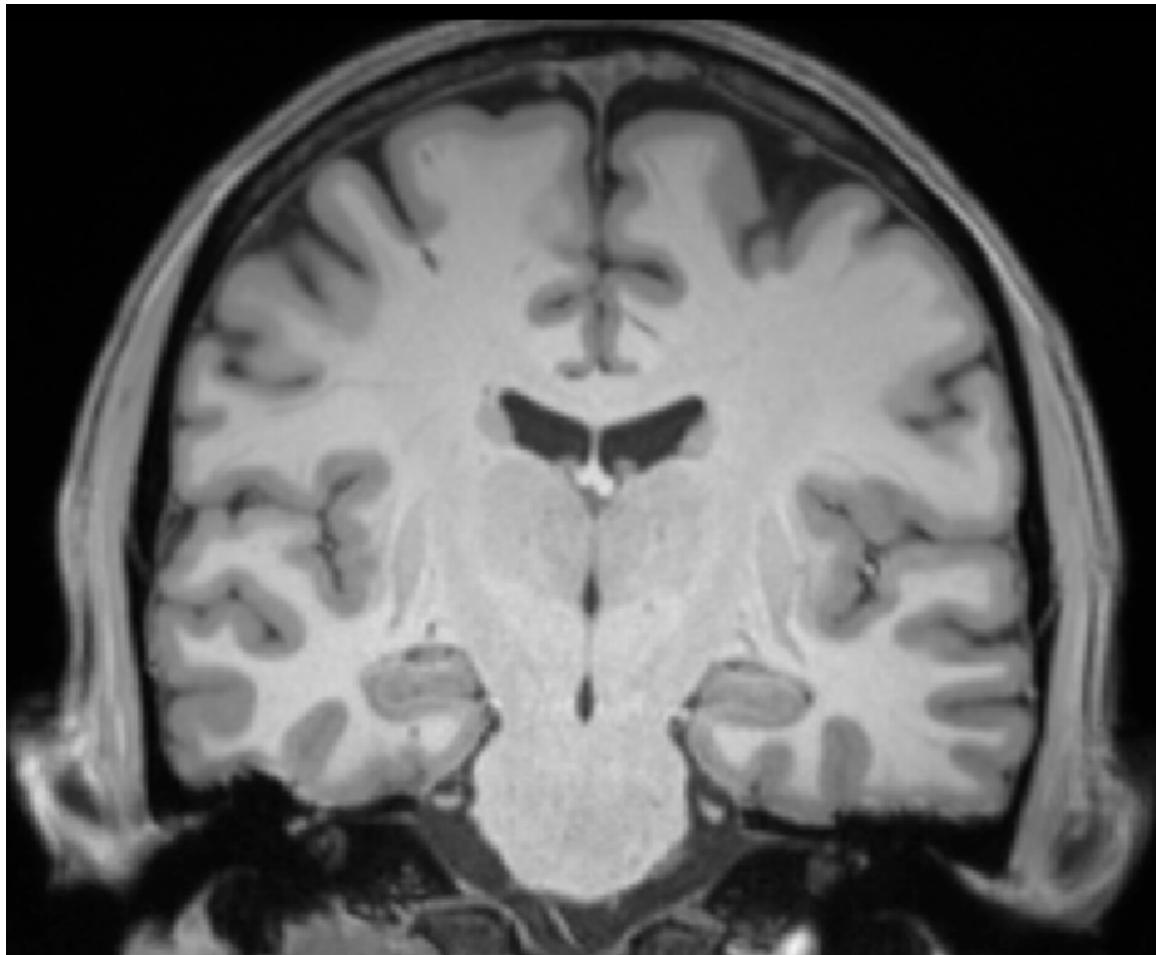
Thanks!

- Inspiration
 - Laurie Frick
 - Michael Snyder
- Statistics
 - Jeanette Mumford
 - Sanmi Koyejo
- MRI
 - Jeff Luci
 - Steve Petersen
 - Timothy Laumann
 - Evan Gordon
 - Babatunde Adeyemo
 - Avi Snyder
- Data collection/analysis
 - Ashleigh Hover
 - Brenda Gregory
 - Natalie Pichetti
- Email mining
 - Ryan Boyd
- Medicine
 - Thomas Caven
- Genomics
 - Scott Hunicke-Smith
- Dhivya Arasappan
- Edward Marcotte
- George Georgiou
- John Blangero
- David Glahn
- Blood collection
- Neeta Bhakta

follow the project at myconnectome.org

Structural MRI

- T1- and T2-weighted structural scans (800 μm)



oversampled to 400 μm

Diffusion MRI

- 30 directions X 2 b-values (1000 and 2000)
 - 2 runs, L->R and R-L phase encoding
 - distortion correction using topup

