Connectome-based modeling of real world clinical outcomes

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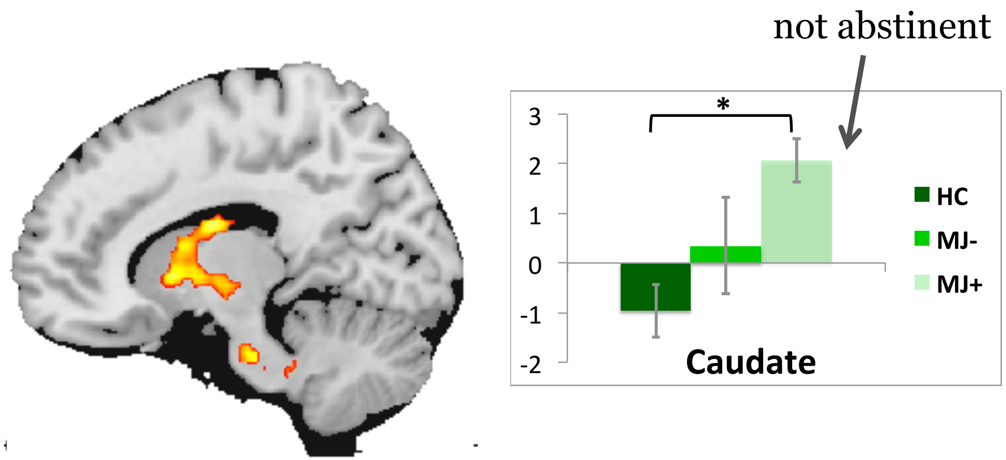
Yale SCHOOL OF MEDICINE

@yip_lab

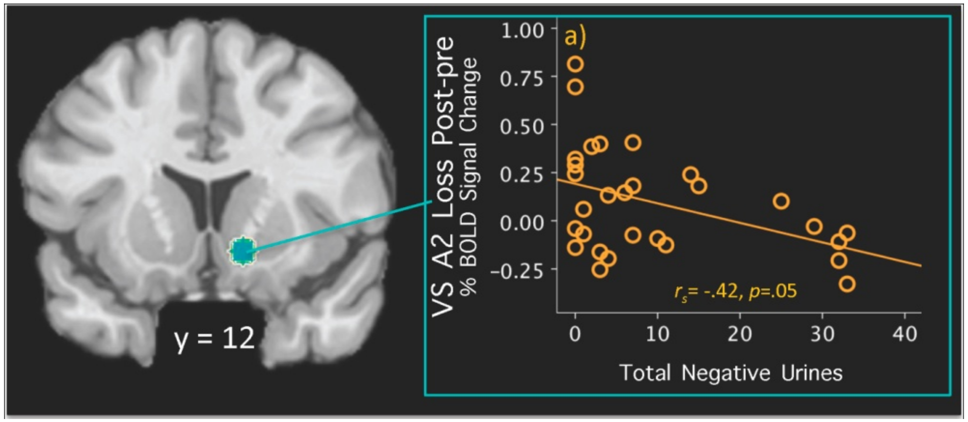
Clinical reality

- Excellent evidence-based treatments exist
- Same tx highly variable across individuals
- High relapse rates + multiple failed attempts
  - retention in opioid tx <6 months for 30-50%
  - increased overdose risk following treatment
- 'Traditional' variables do not predict outcomes
  - e.g., little variance explained by baseline cocaine use

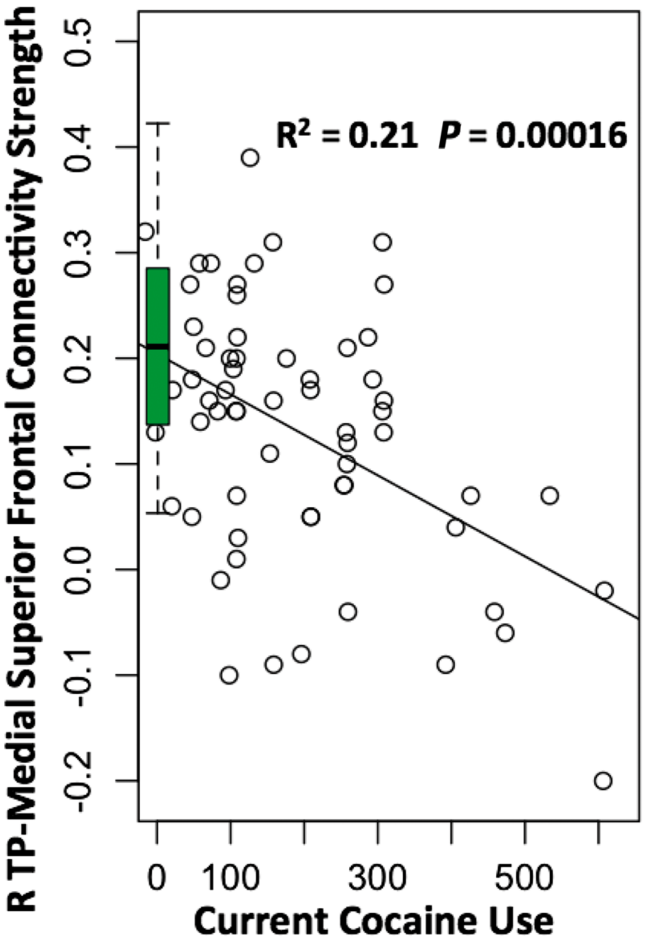
Neuroimaging of addiction outcomes



Yip et al., Drug Alcohol Depend, 2014



Balodis et al, Neuropsychopharmacol, 2016



Gu et al., Brain, 2014

Limitations

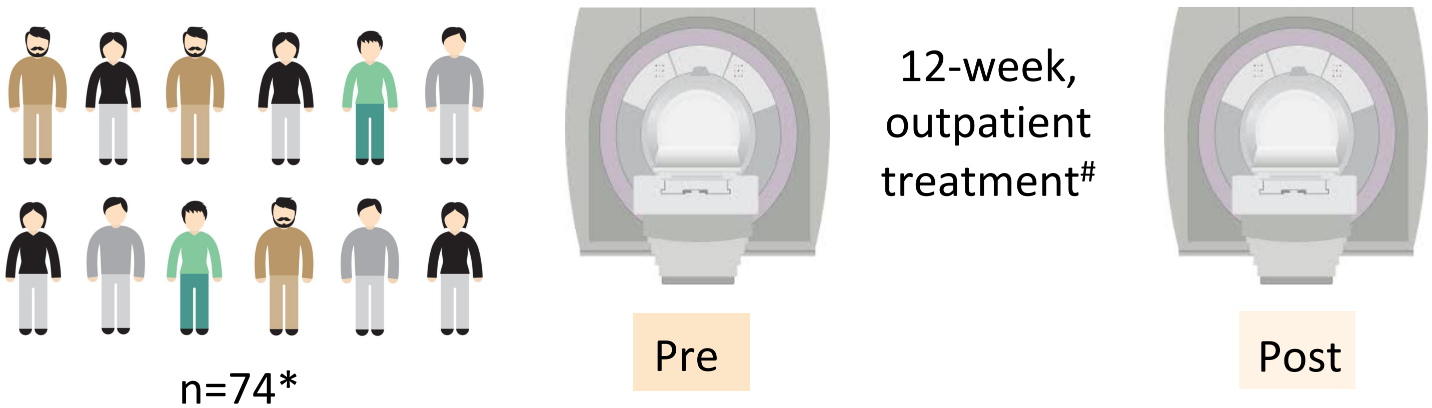
- Small sample sizes; e.g., n=25
  - reflection of complexity of translational research
- Use of methods that may overfit the data
  - inflated effect sizes
  - decreased likelihood of generalization
- Prior studies activation-based or ROI-based
  - network based approaches may be more informative
  - data-driven approaches can provide novel insight

Machine learning (aka predictive modeling)

- Training dataset > predictive model
- Test dataset > model validation
- Goal = generate predictions in novel data
- Key step for translation into clinical setting
- Can also be used for neurobiological discovery

Part I: Prediction of cocaine abstinence

Study design



*opioid-dependent, methadone-maintained

#behavioral therapy +/- galantamine to treat cocaine-use

Yip et al., *American Journal of Psychiatry*, 2019

Galantamine and Computerized Cognitive Behavioral Therapy for Cocaine Dependence:
A Randomized Clinical Trial

Kathleen M. Carroll, PhD[a,*]; Charla Nich, MS[a]; Elise E. DeVito, PhD[a]; Julia M. Shi, MD[a,b]; and Mehmet Sofuoglu, MD, PhD[a,c]

> 64% male
> 73% unemployed
> cocaine primarily smoked (70%)

> + 3 prior outpatient treatment attempts
> + 3 prior inpatient treatments attempts
> + 5 lifetime arrests

Yip et al., *American Journal of Psychiatry*, 2019

PROTOCOL

Using connectome-based predictive modeling to predict individual behavior from brain connectivity

Xilin Shen[1], Emily S Finn[2], Dustin Scheinost[1], Monica D Rosenberg[3], Marvin M Chun[2–4], Xenophon Papademetris[1,5] & R Todd Constable[1,2,6]

506 | VOL.12 NO.3 | 2017 | NATURE PROTOCOLS

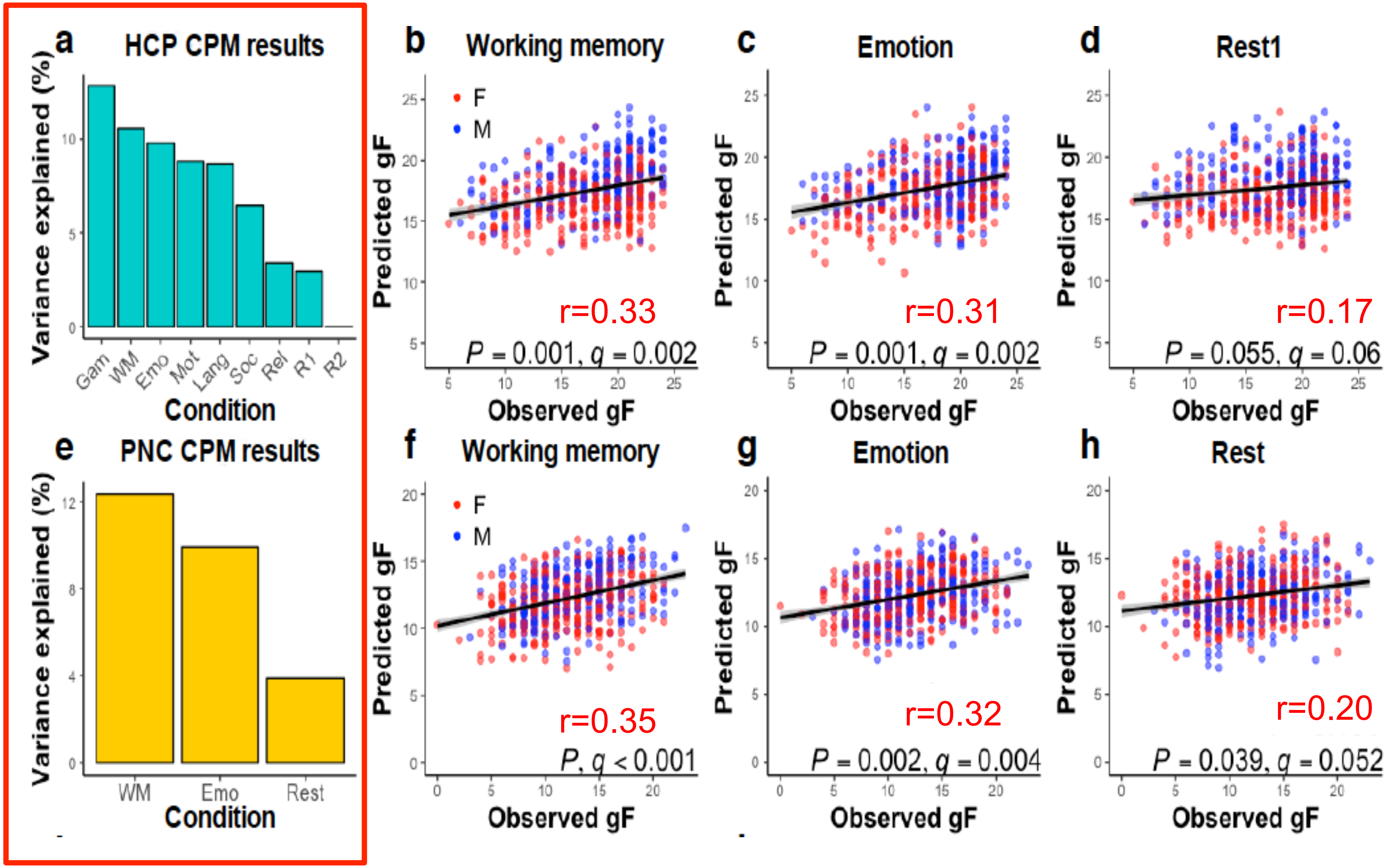
> data-driven machine learning approach

> no a priori specification of networks

> predict and identify networks

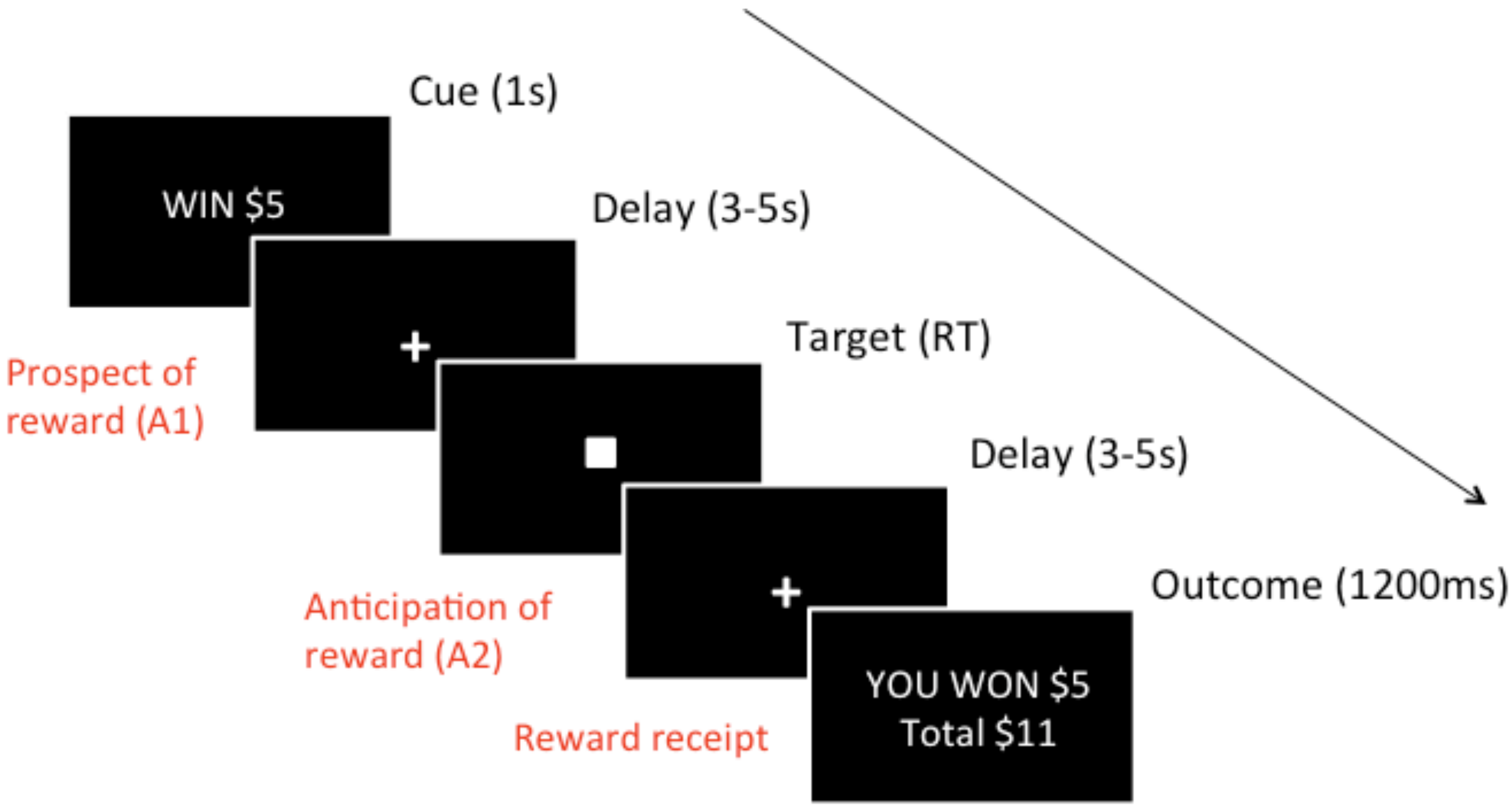
> input = task-based connectivity matrices

Brain state manipulation improves prediction

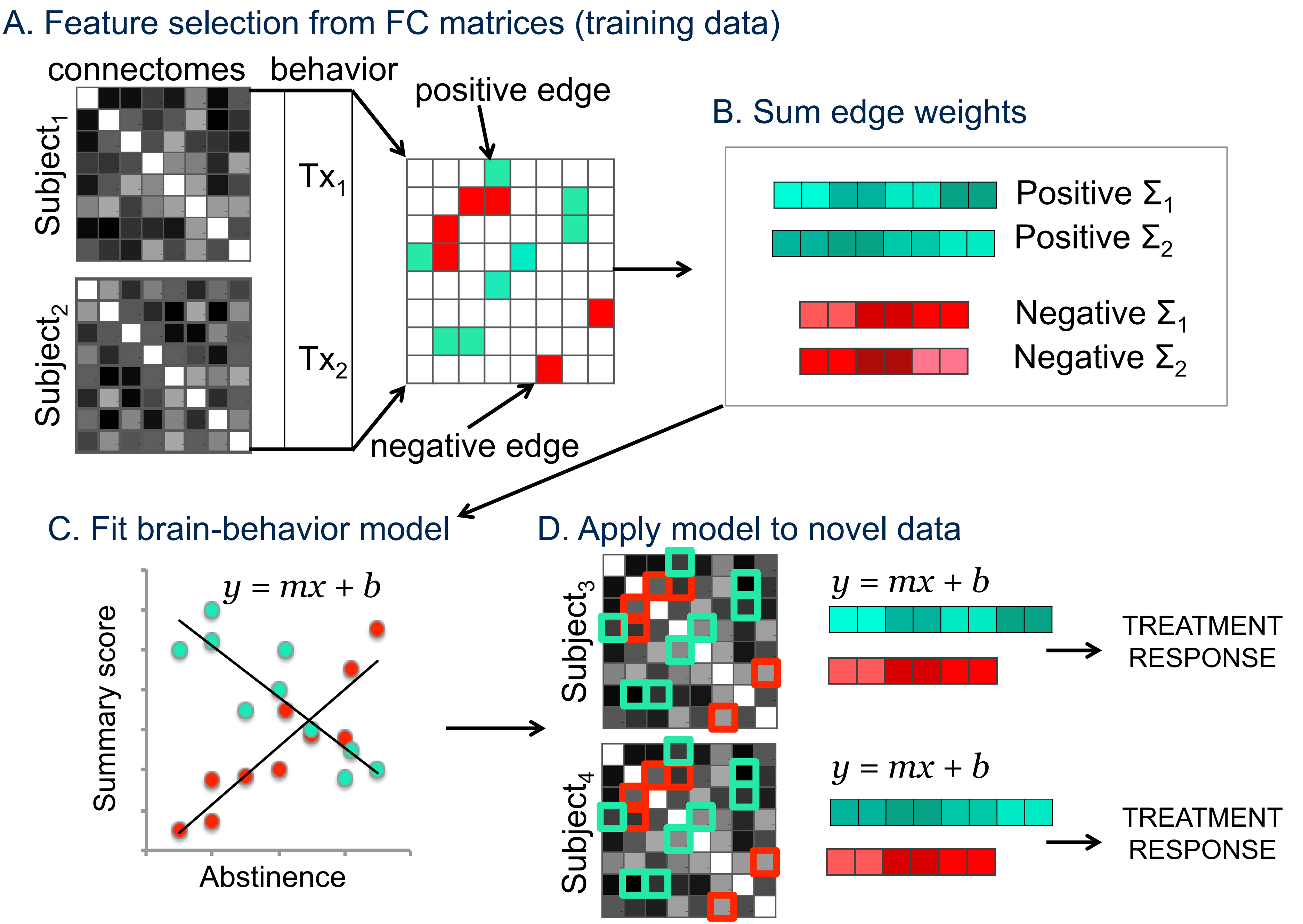


Greene et al., *Nature Communications*, 2018

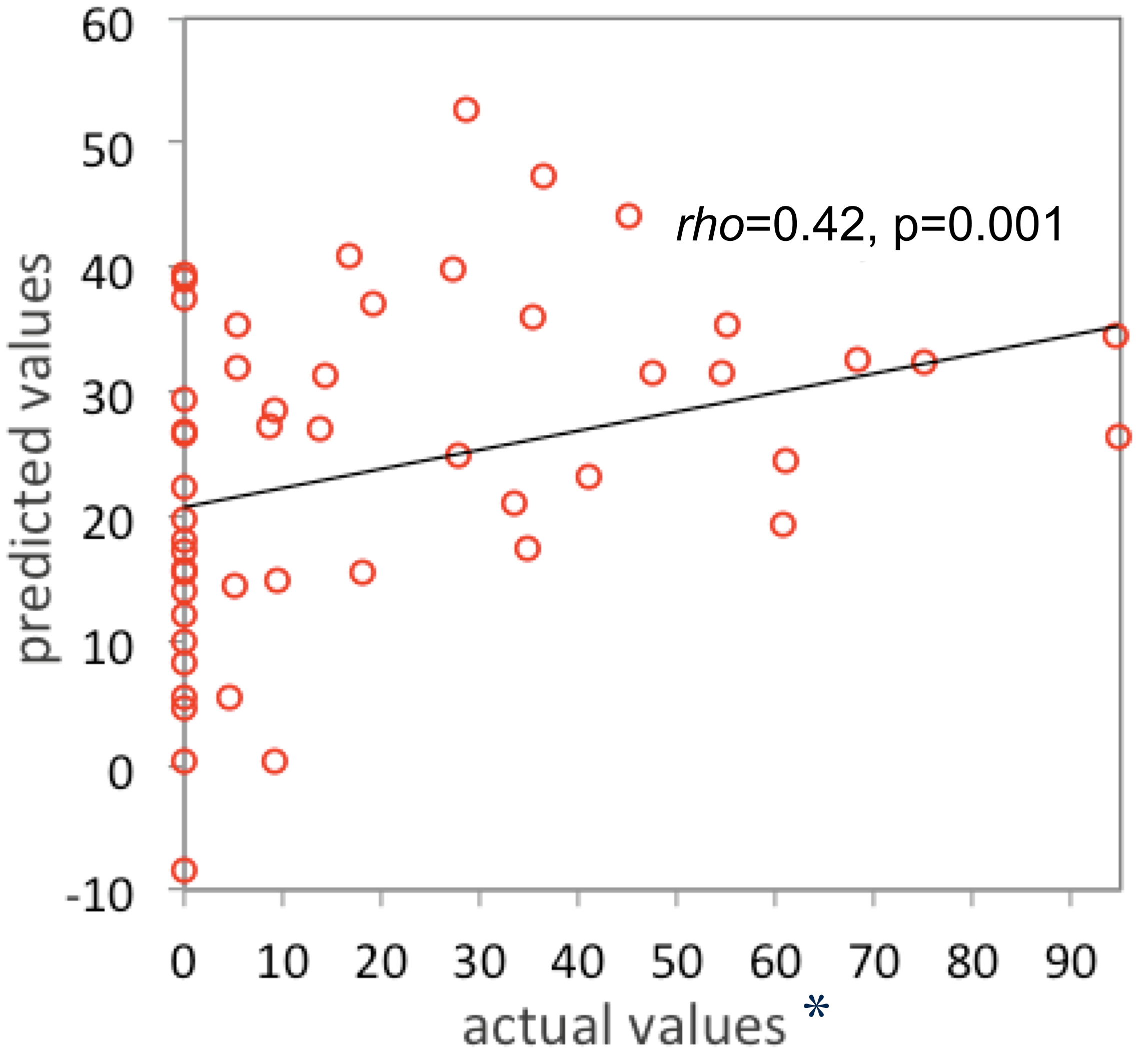
Monetary incentive delay task



Andrews et al., *Biological Psychiatry*, 2011


A. Feature selection from FC matrices (training data)
connectomes
behavior
Subject$_1$
Subject$_2$
Tx$_1$
Tx$_2$
positive edge
negative edge
B. Sum edge weights
Positive Σ$_1$
Positive Σ$_2$
Negative Σ$_1$
Negative Σ$_2$
C. Fit brain-behavior model
$y = mx + b$
Summary score
Abstinence
D. Apply model to novel data
Subject$_3$
Subject$_4$
$y = mx + b$
TREATMENT RESPONSE
$y = mx + b$
TREATMENT RESPONSE

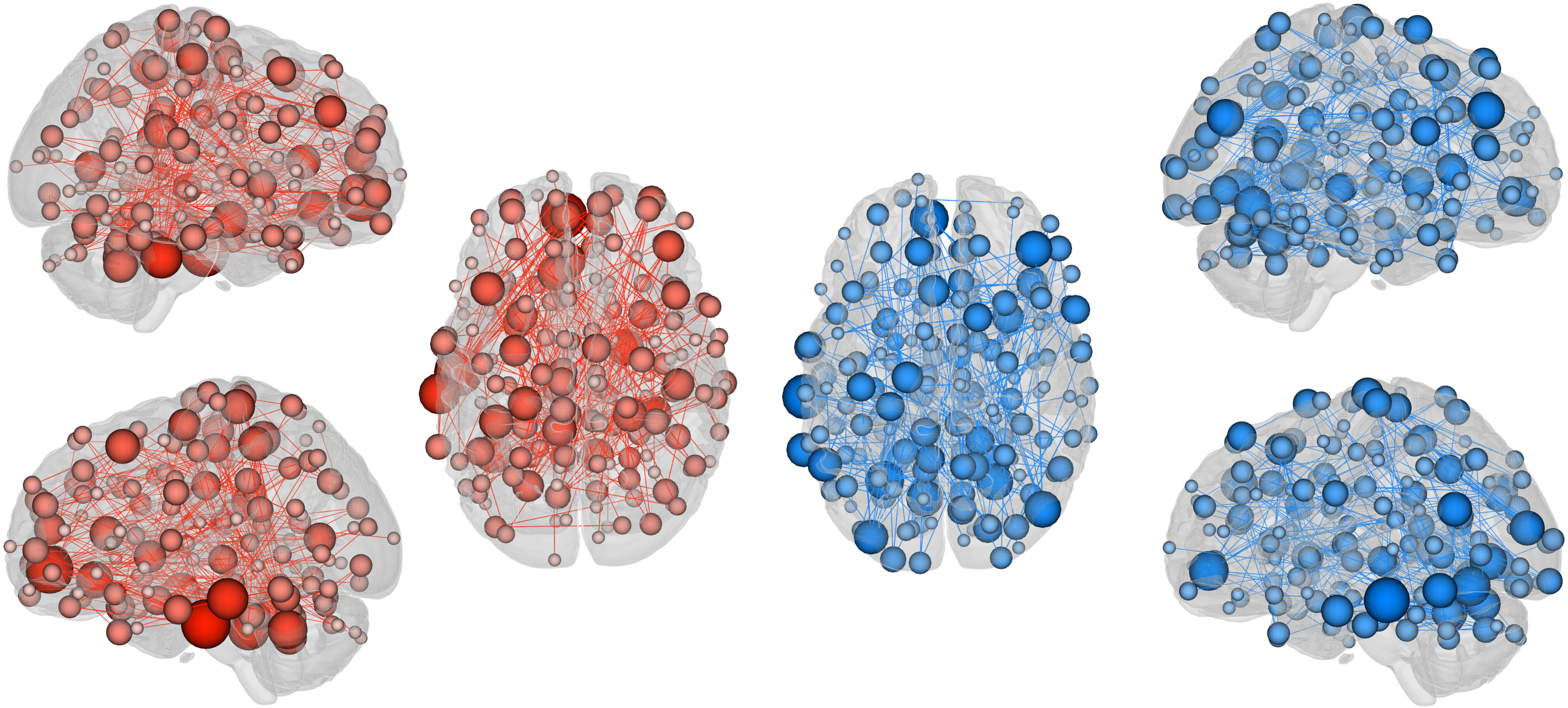
Model validation - predictive accuracy



*not associated w/ baseline cocaine-use

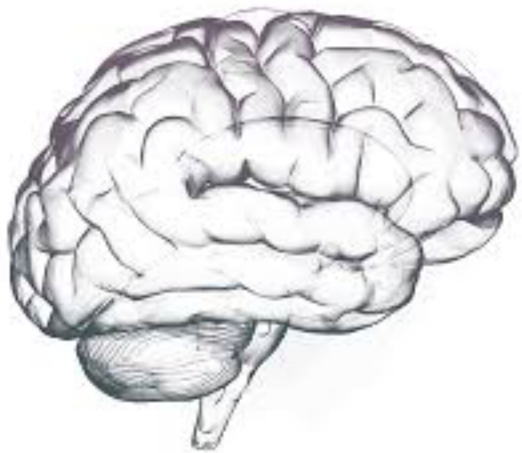
Yip et al., *American Journal of Psychiatry*, 2019

Abstinence networks*

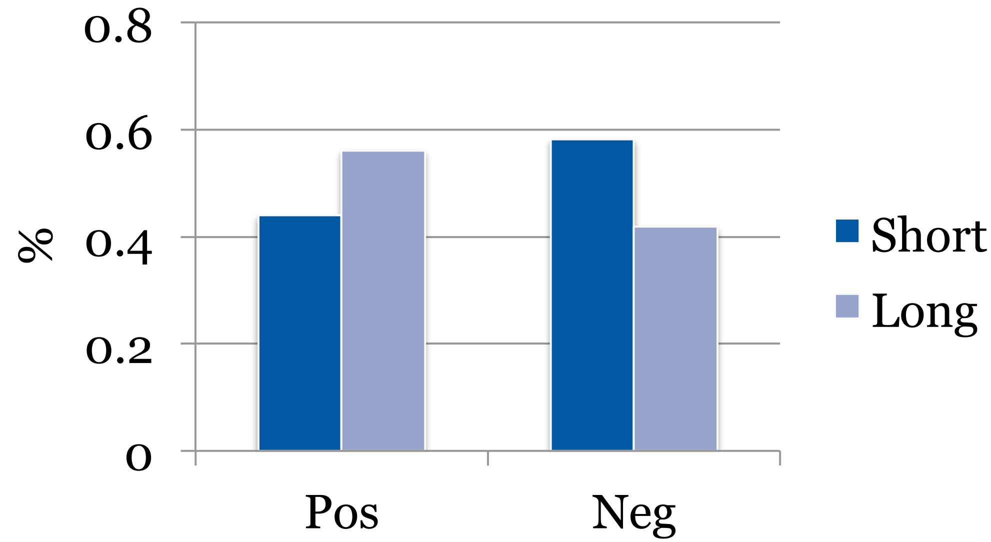


*only 539 connections <2% of possible connections

Short versus long-range connectivity

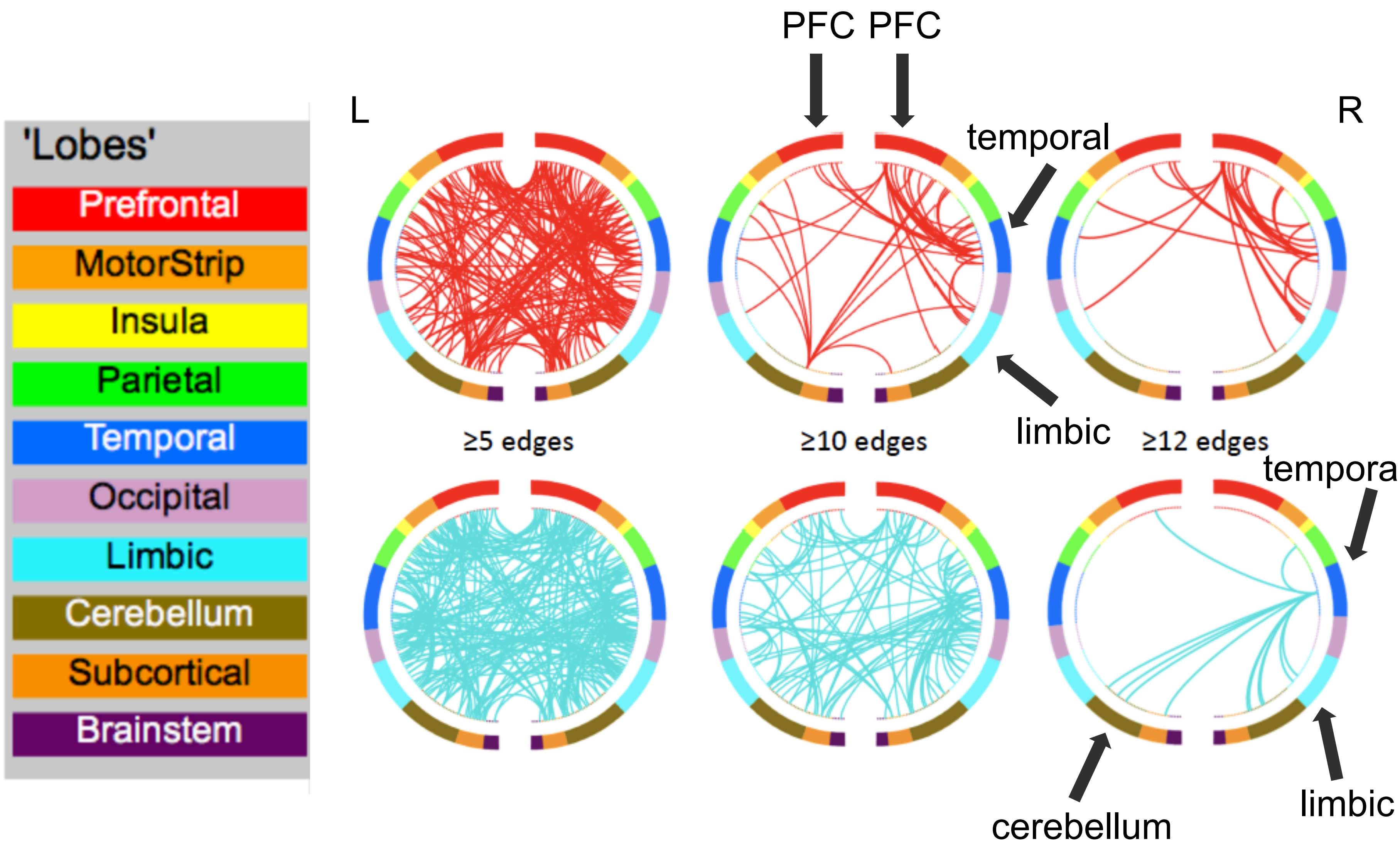


$\surd((x_0-x_1)^2+(y_0-y_1)^2+(z_0-z_1)^2)$



- Positive network (+ abstinence) > longer range
- Negative network (- abstinence) > shorter range

Regional connectivity

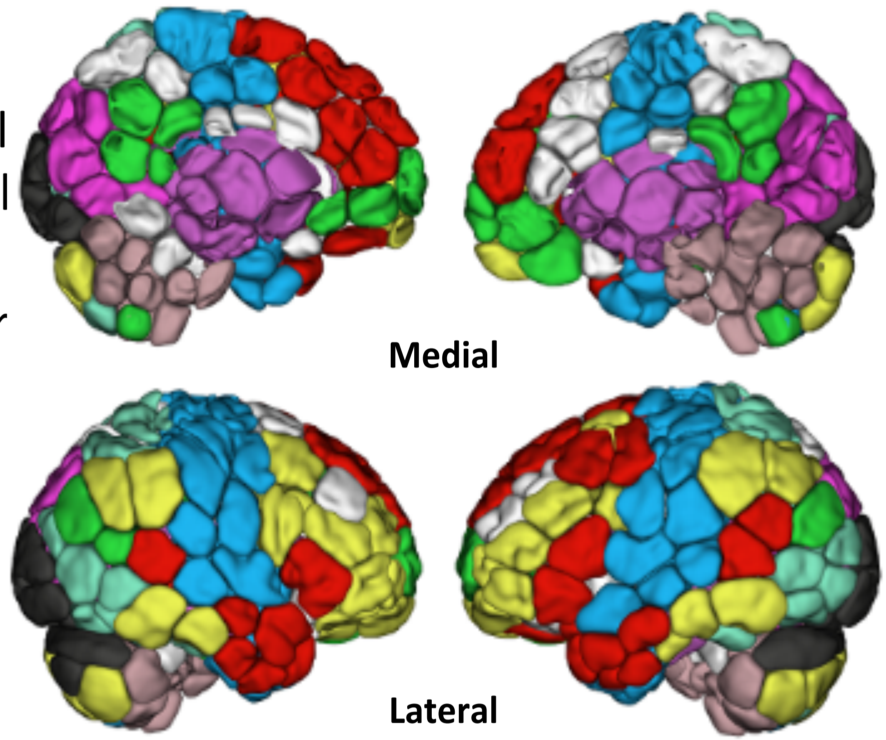


Yip et al., *American Journal of Psychiatry*, 2019

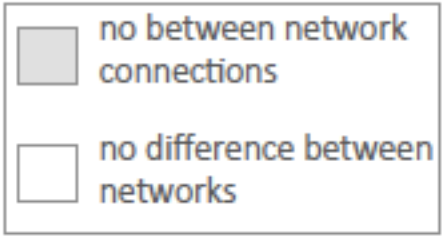
‘Canonical’ networks

Networks

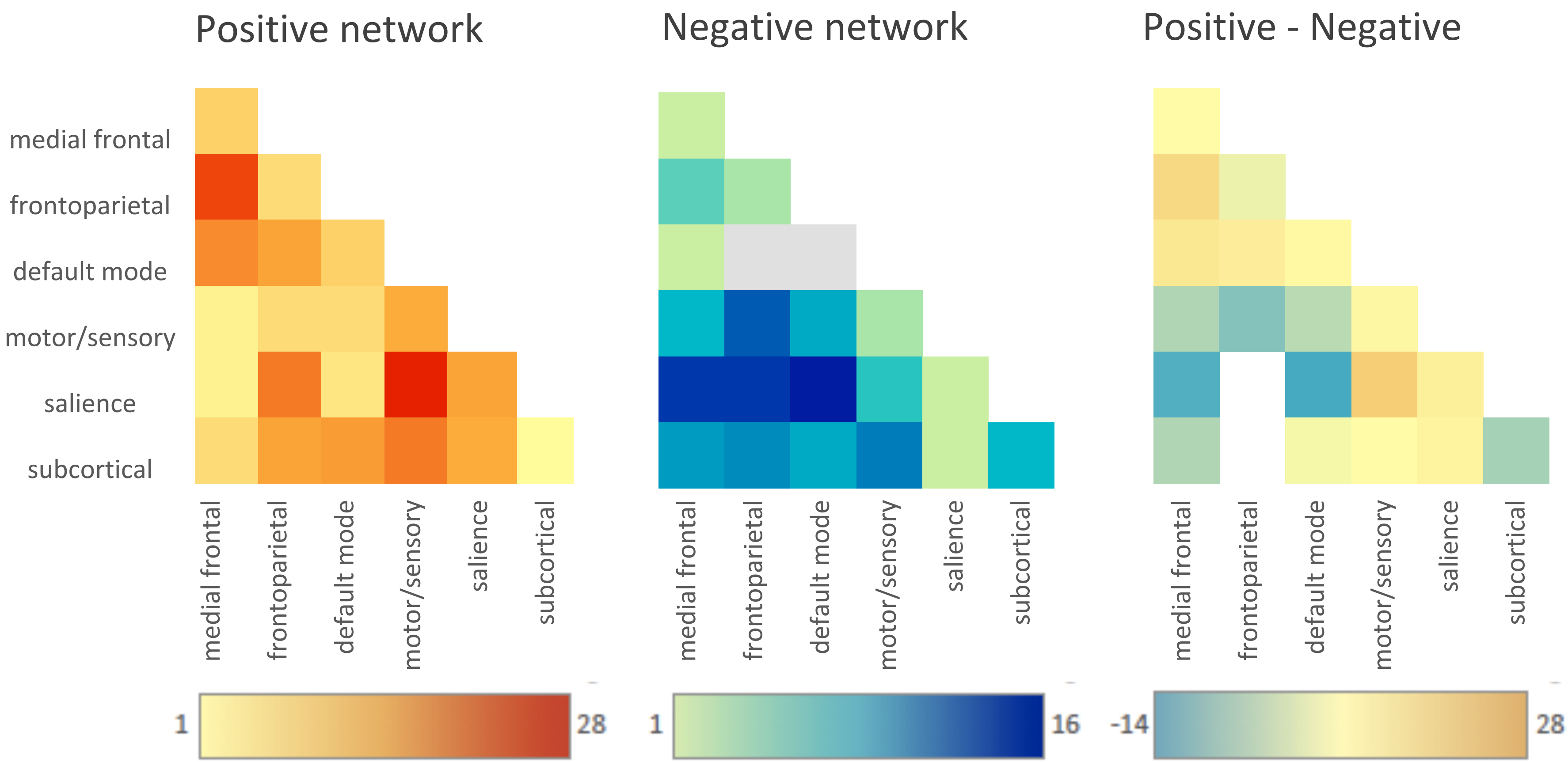
1 Medial frontal
2 Frontoparietal
3 Default mode
4 Sensori-motor
5 Visual a
6 Visual b
7 Visual asso
8 Salience
9 Subcortical
10 Cerebellum/ brain stem



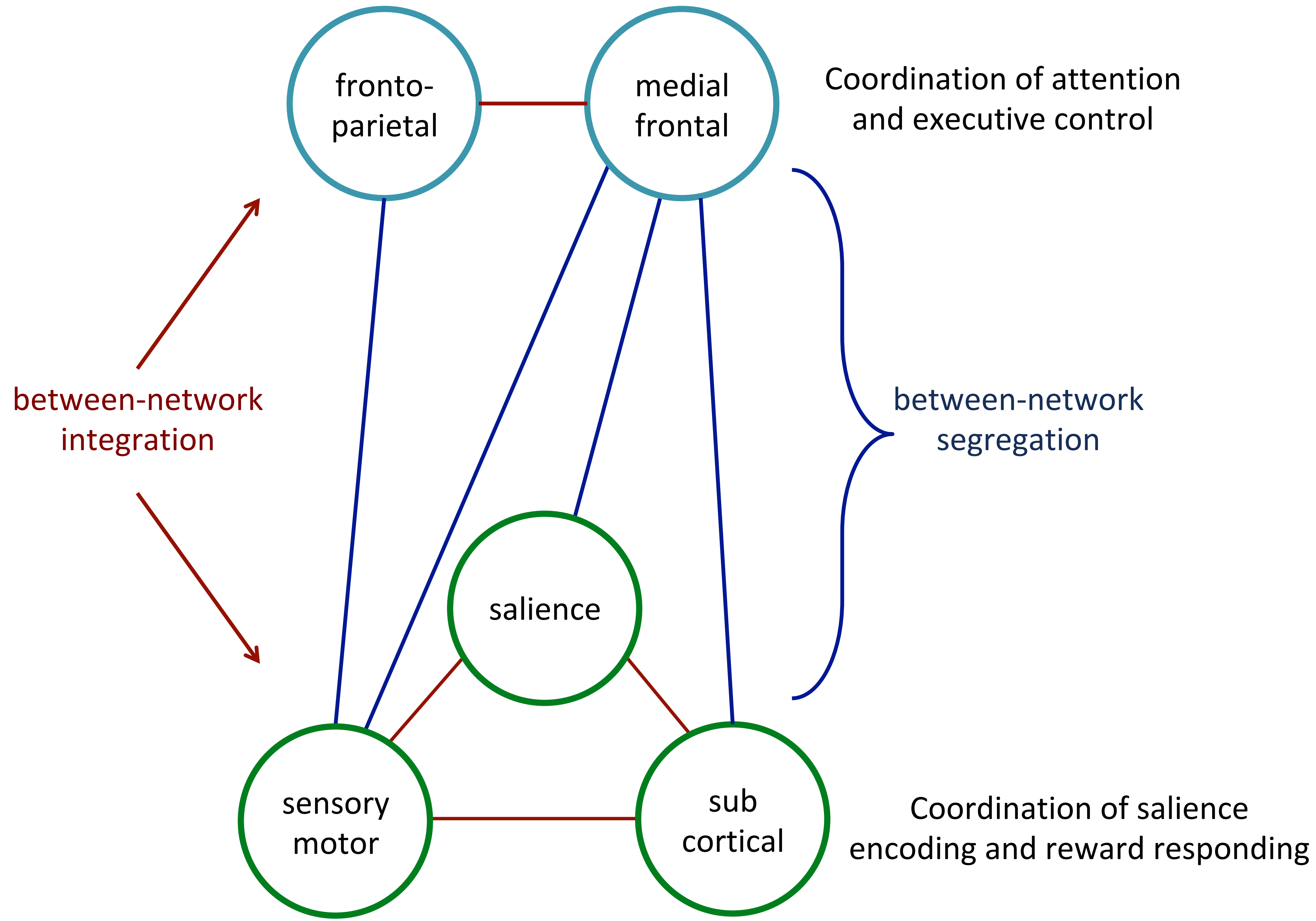
Horien et al., *NeuroImage*, 2019



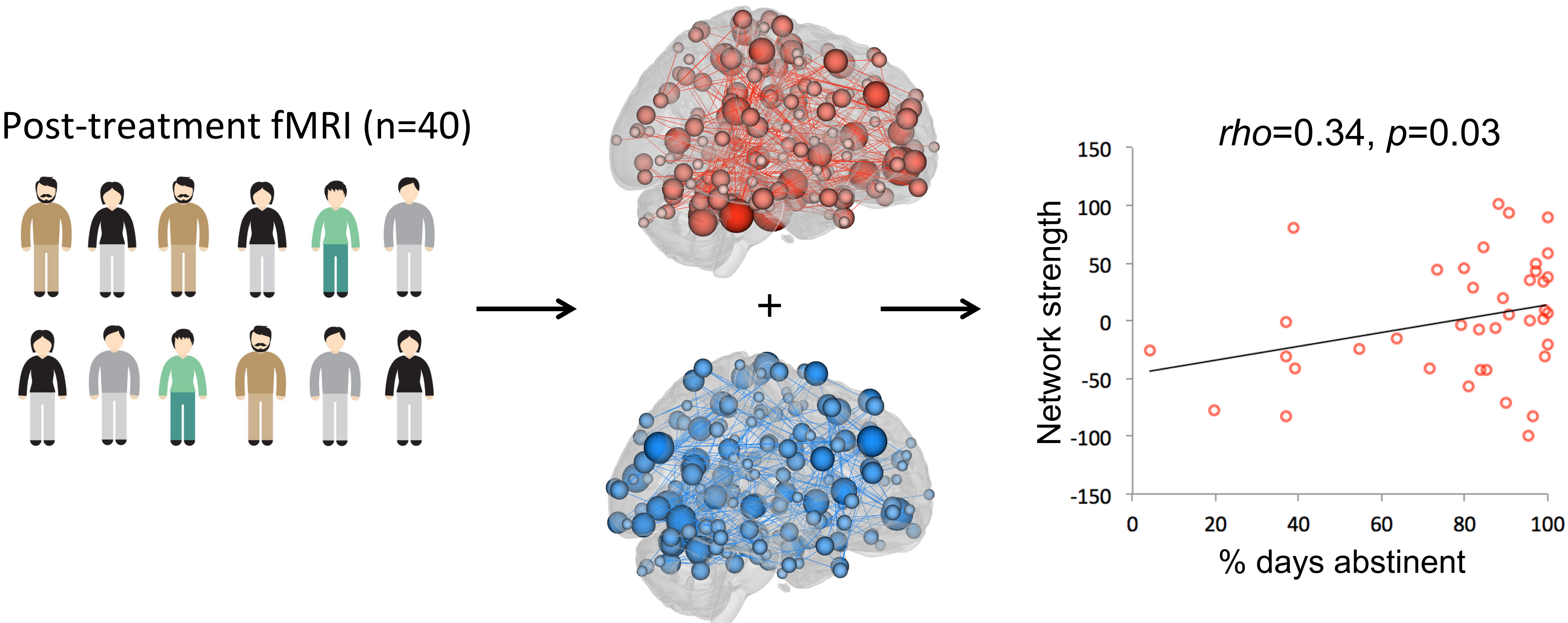
Network connectivity



Yip et al., *American Journal of Psychiatry*, 2019


fronto-
parietal
medial
frontal
Coordination of attention
and executive control
between-network
integration
between-network
segregation
salience
sensory
motor
sub
cortical
Coordination of salience
encoding and reward responding

Post-treatment networks predict abstinence*

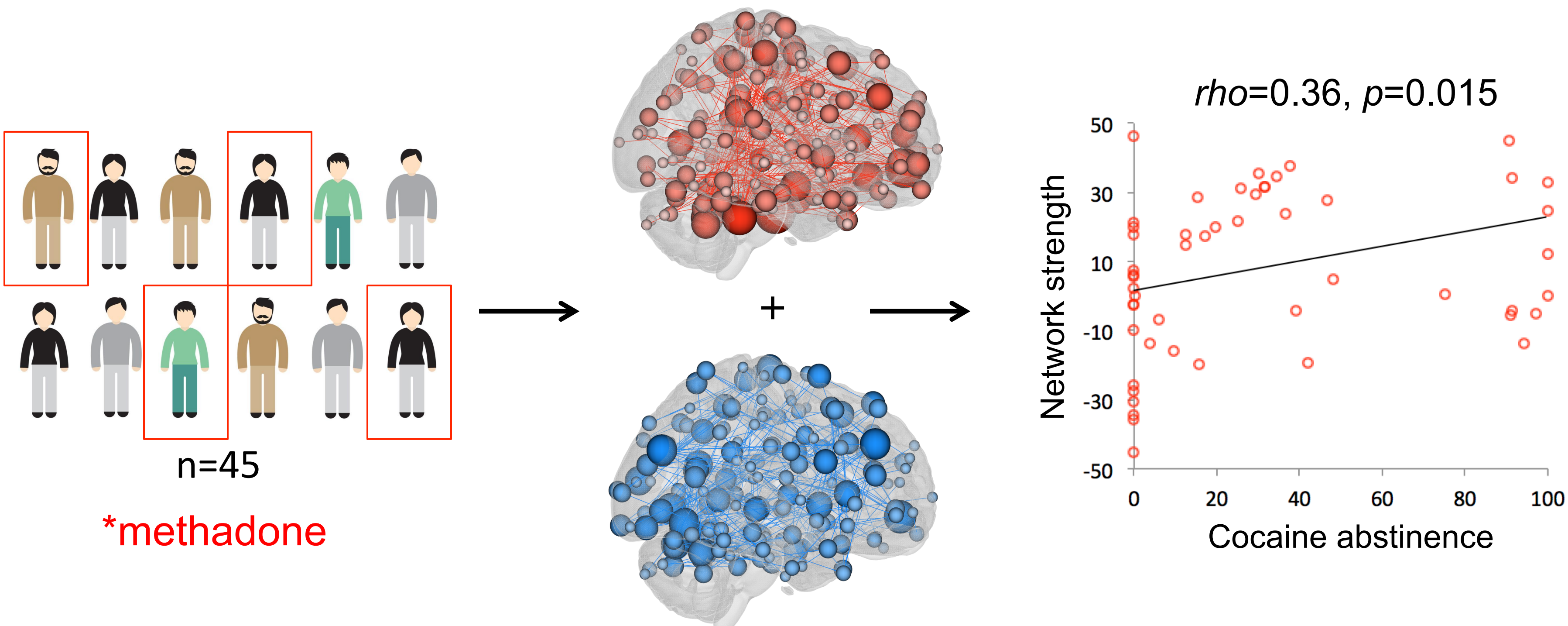


*no changes in connectivity over time

Yip et al., *American Journal of Psychiatry*, 2019

But does it replicate?

Replicates in heterogeneous, independent sample

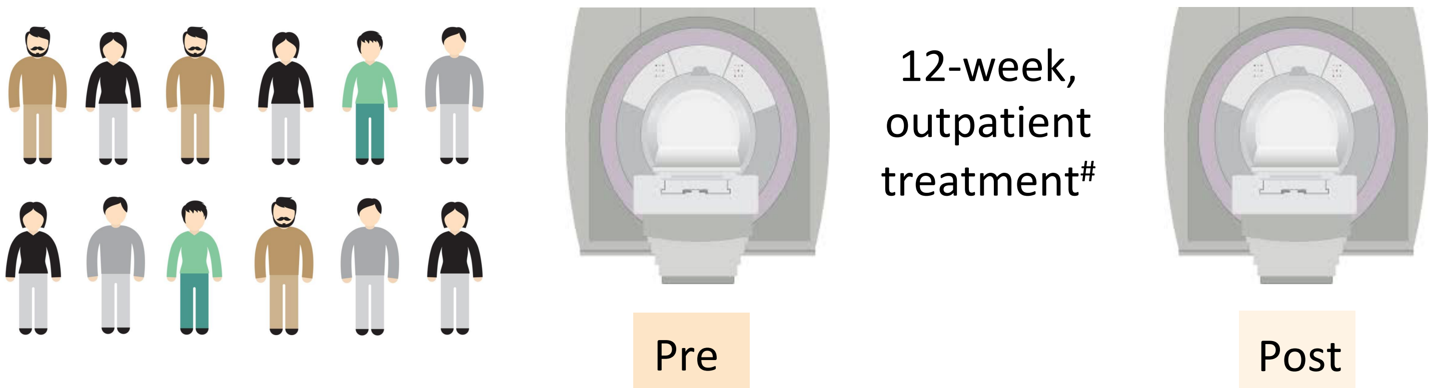


Yip et al., *American Journal of Psychiatry*, 2019

Part II: Networks across drugs and brain states

Sarah Lichenstein, PhD

Same study, different drug



*opioid-dependent, methadone-maintained

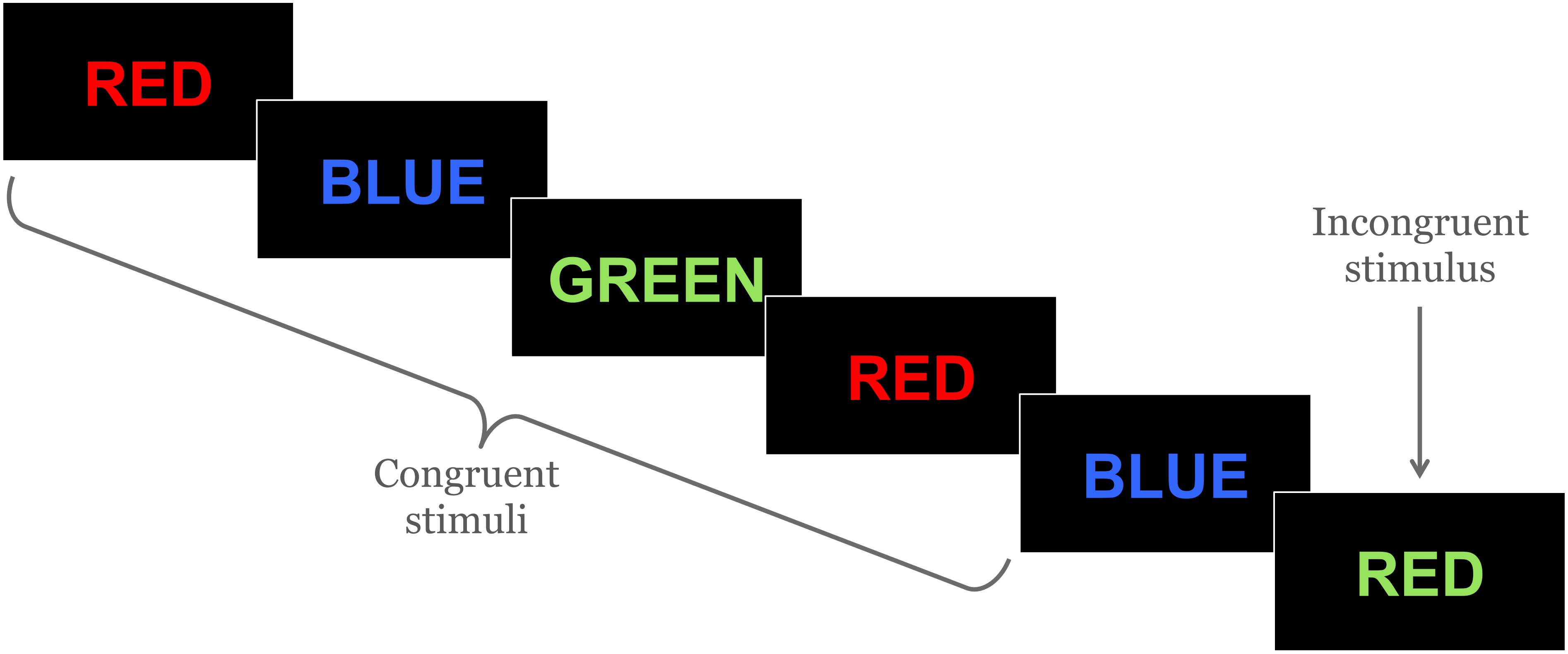
#behavioral therapy +/- galantamine to treat cocaine-use

Different mood states predict opioids vs. cocaine

Results: During the 5 hours preceding cocaine use or heroin craving, most of the 12 putative triggers showed linear increases. Cocaine use was most robustly associated with increases in participants reporting that they "saw [the] drug" (*P*<.001), were "tempted to use out of the blue" (*P*<.001), "wanted to see what would happen if I used" (*P*<.001), and were in a good mood (*P*<.001). Heroin craving was most robustly associated with increases in reports of feeling sad (*P*<.001) or angry (*P*=.01). Cocaine craving and heroin use showed few reliable associations with any of the putative triggers assessed.

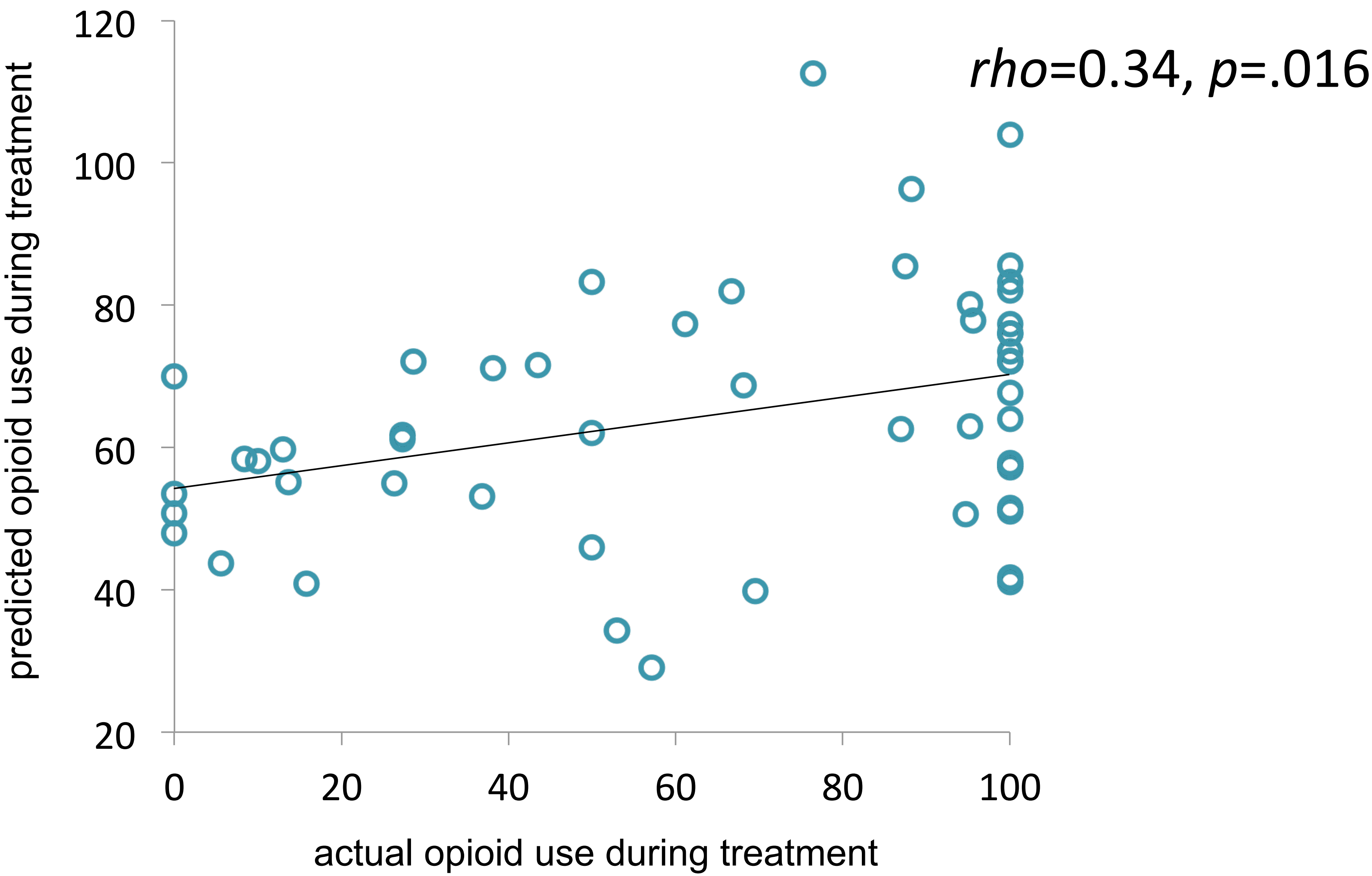
Epstein et al., *Archives of General Psychiatry*, 2009

Cognitive control (Stroop) task

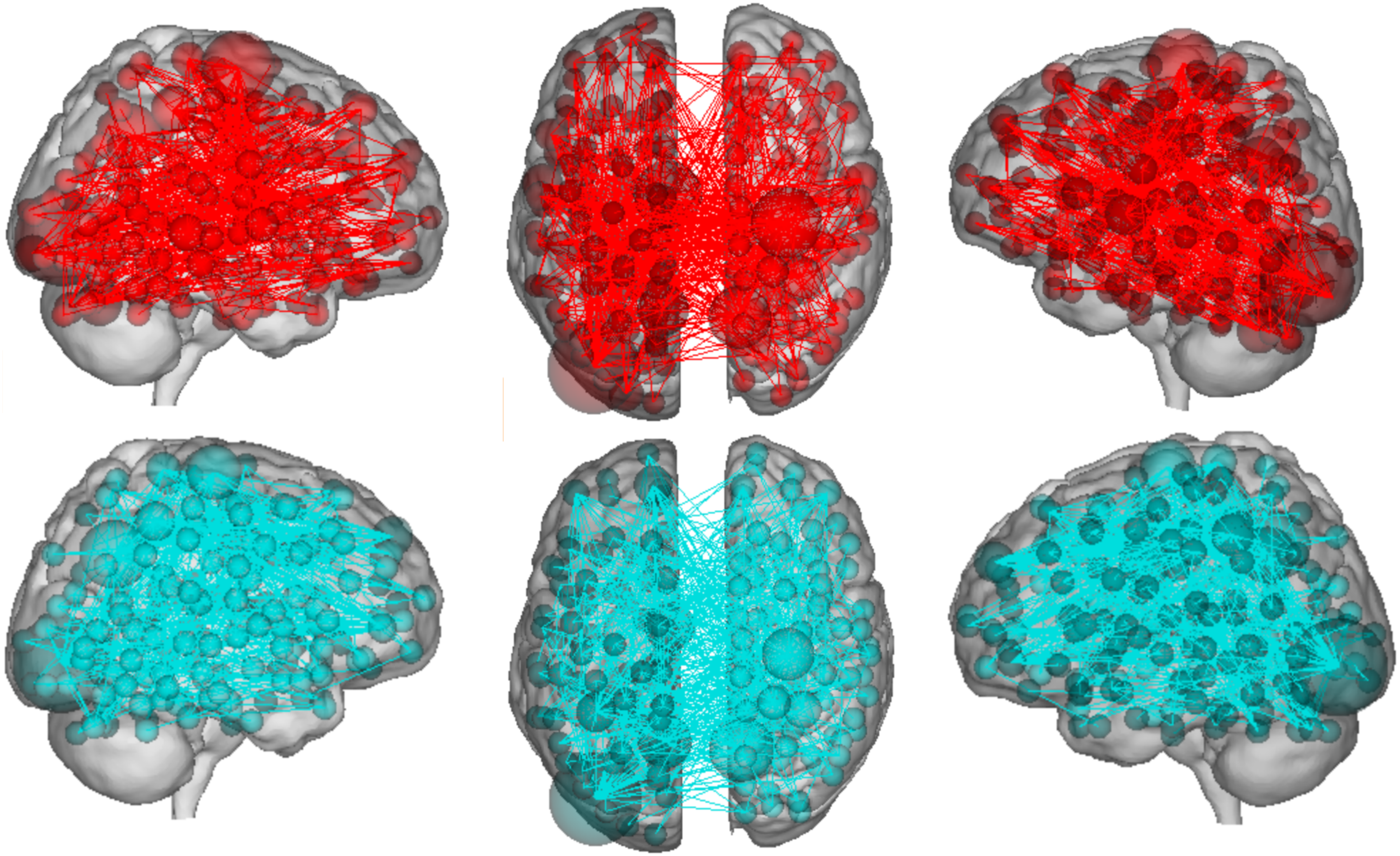


- engages fronto-parietal and cortico-striatal regions

Opioid model - predictive accuracy



Opioid network

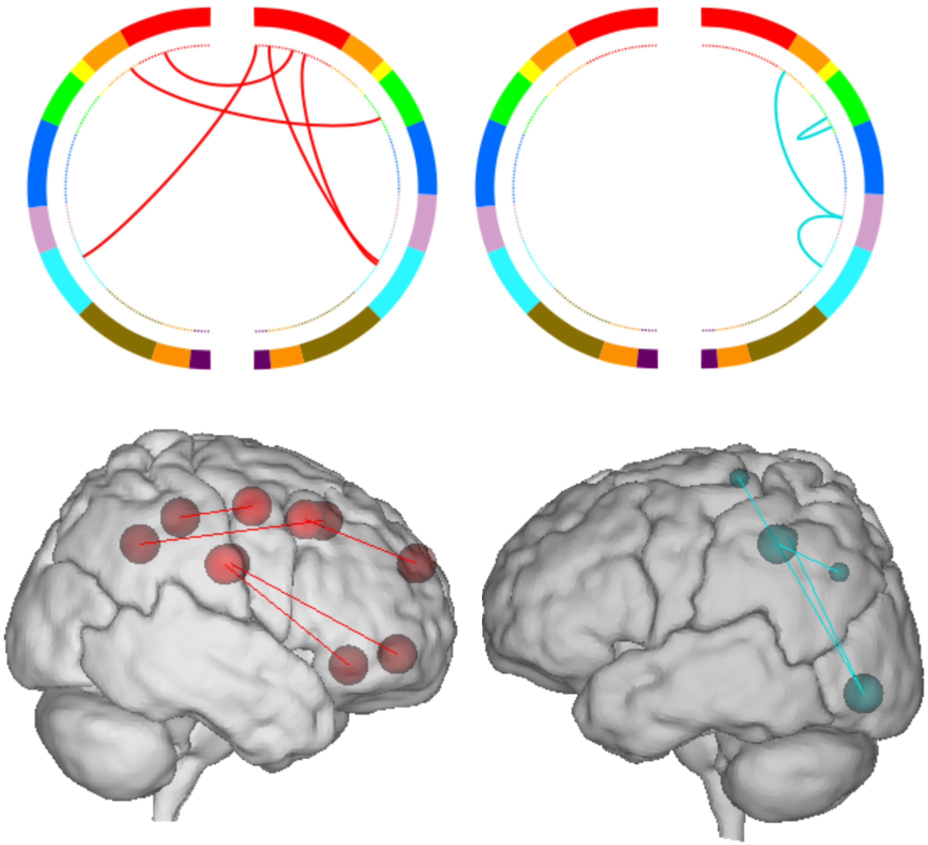


<3% of possible connections

Shared edges across opioid and cocaine networks

Consistent edges

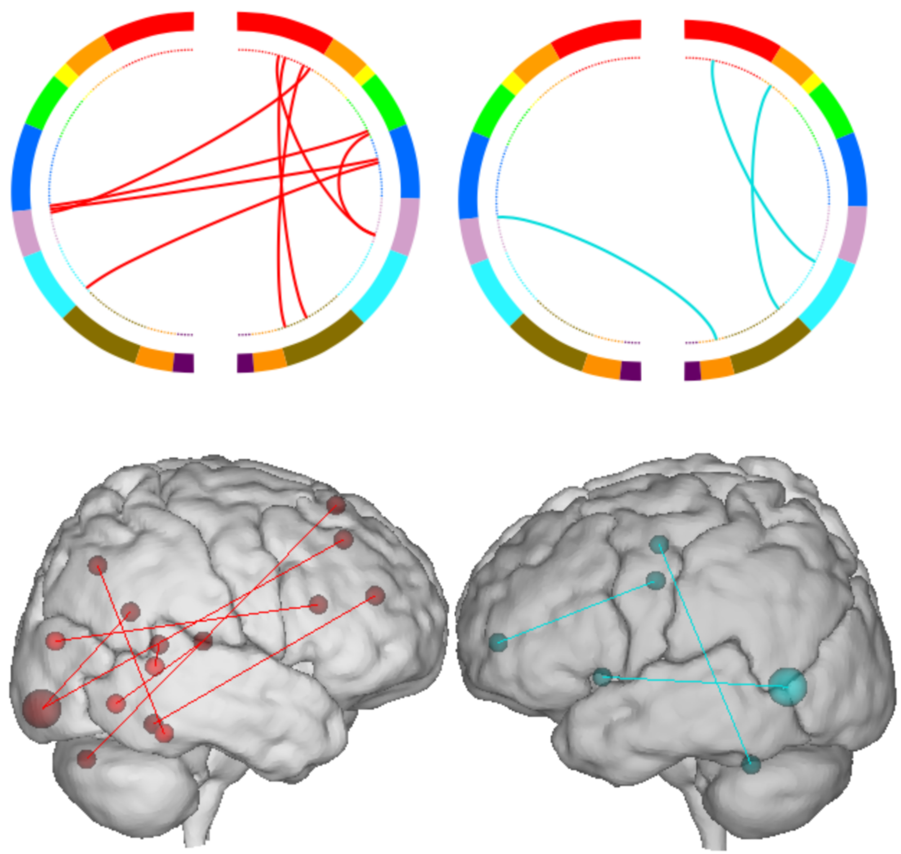
<1% overlap



cocaine+
opioid+

cocaine-
opioid-

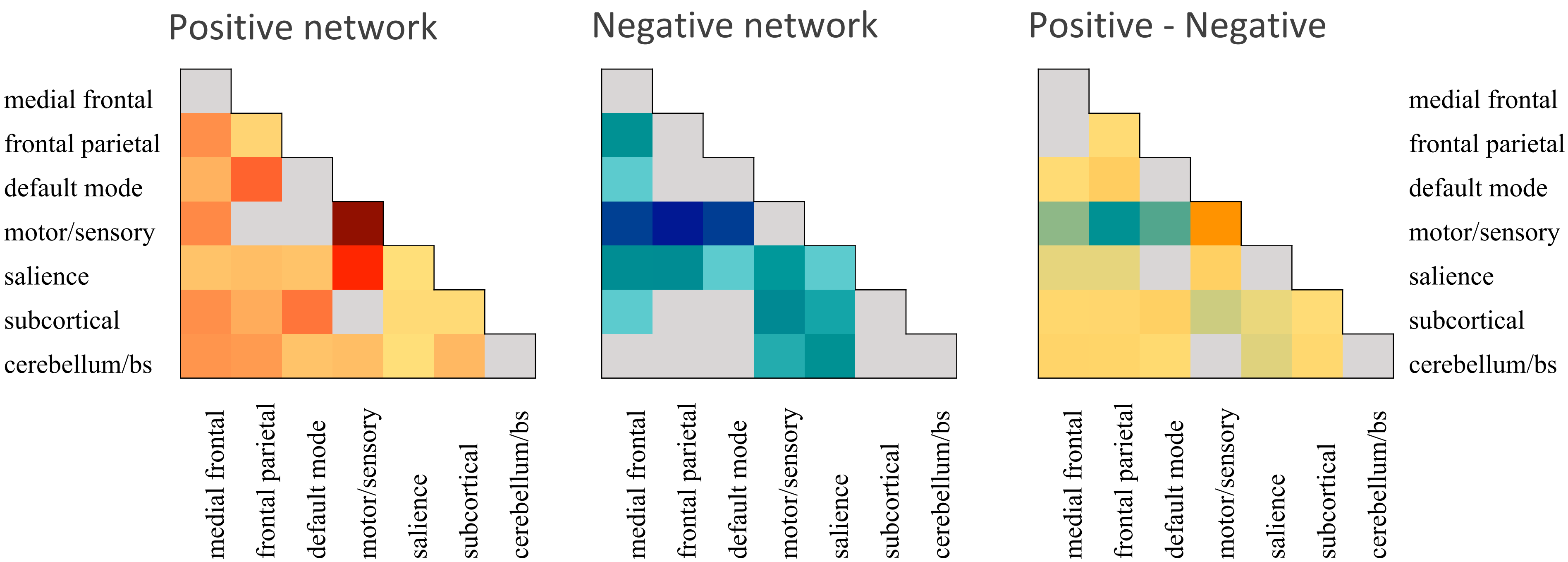
Opposing edges



cocaine+
opioid-

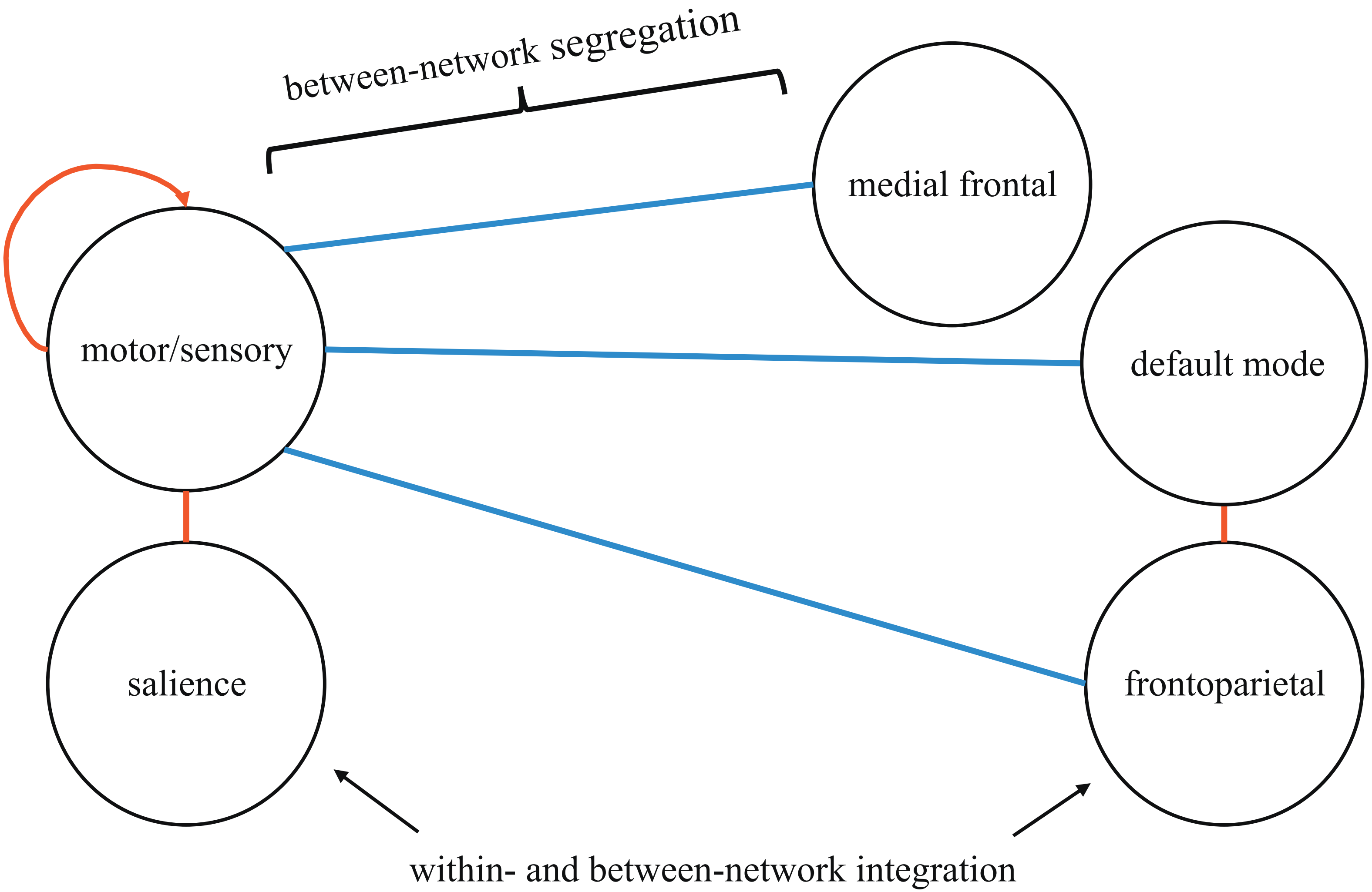
cocaine-
opioid+

Opioid network connectivity



Lichenstein et al., *Molecular Psychiatry*, In Press

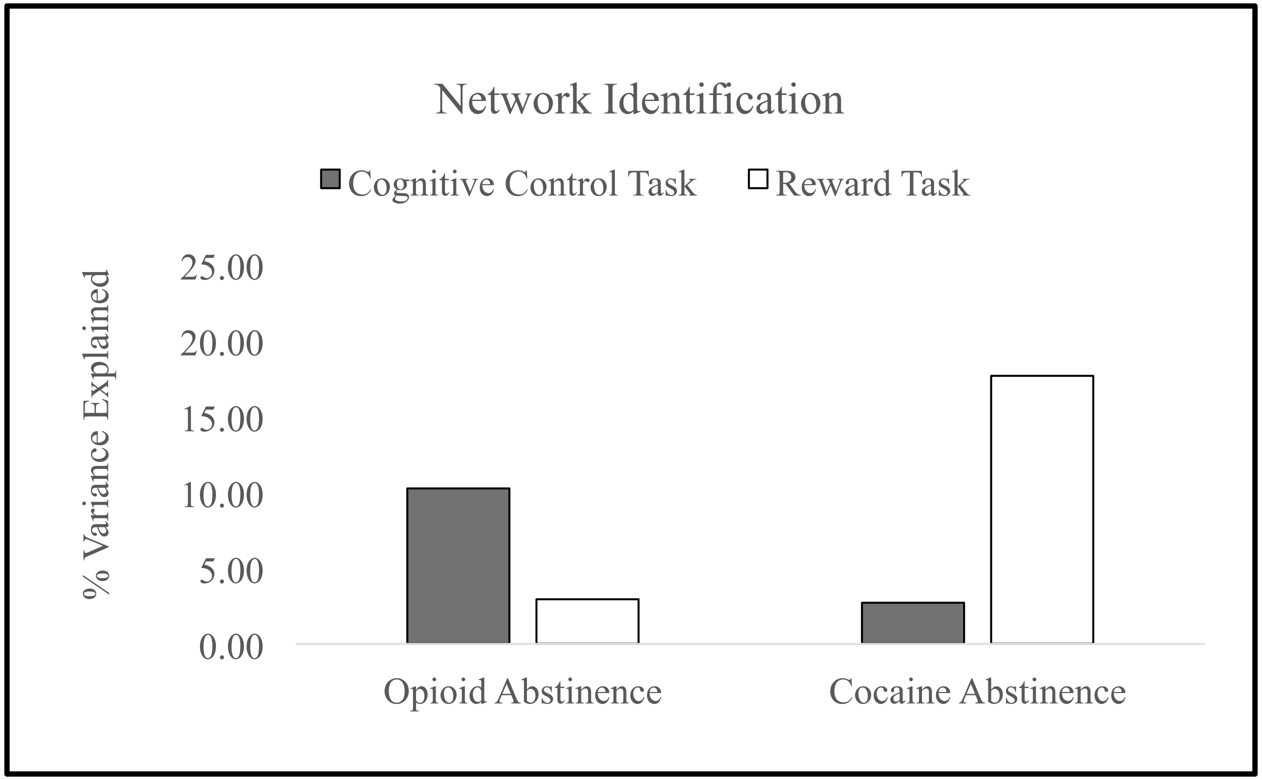
Theoretical opioid network model



Lichenstein et al., *Molecular Psychiatry*, In Press

Are networks drug or brain state specific?

Network identification is brain-state dependent

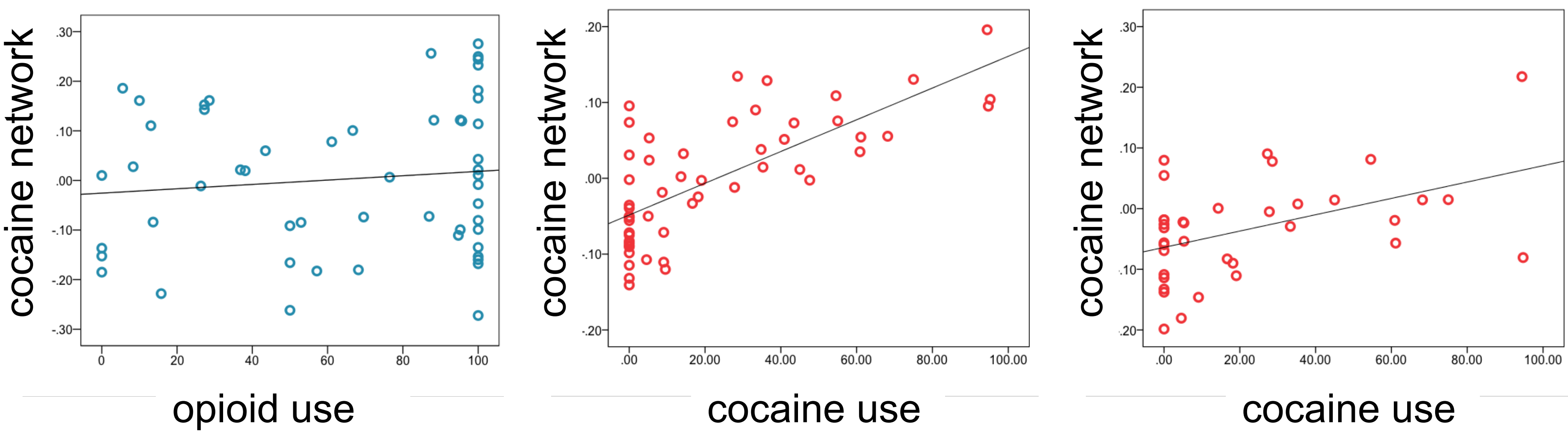


Lichenstein et al., *Molecular Psychiatry*, In Press

Cocaine network across drugs and brain states

Opioid use   Cocaine use

Reward task   Cognitive task   Resting state

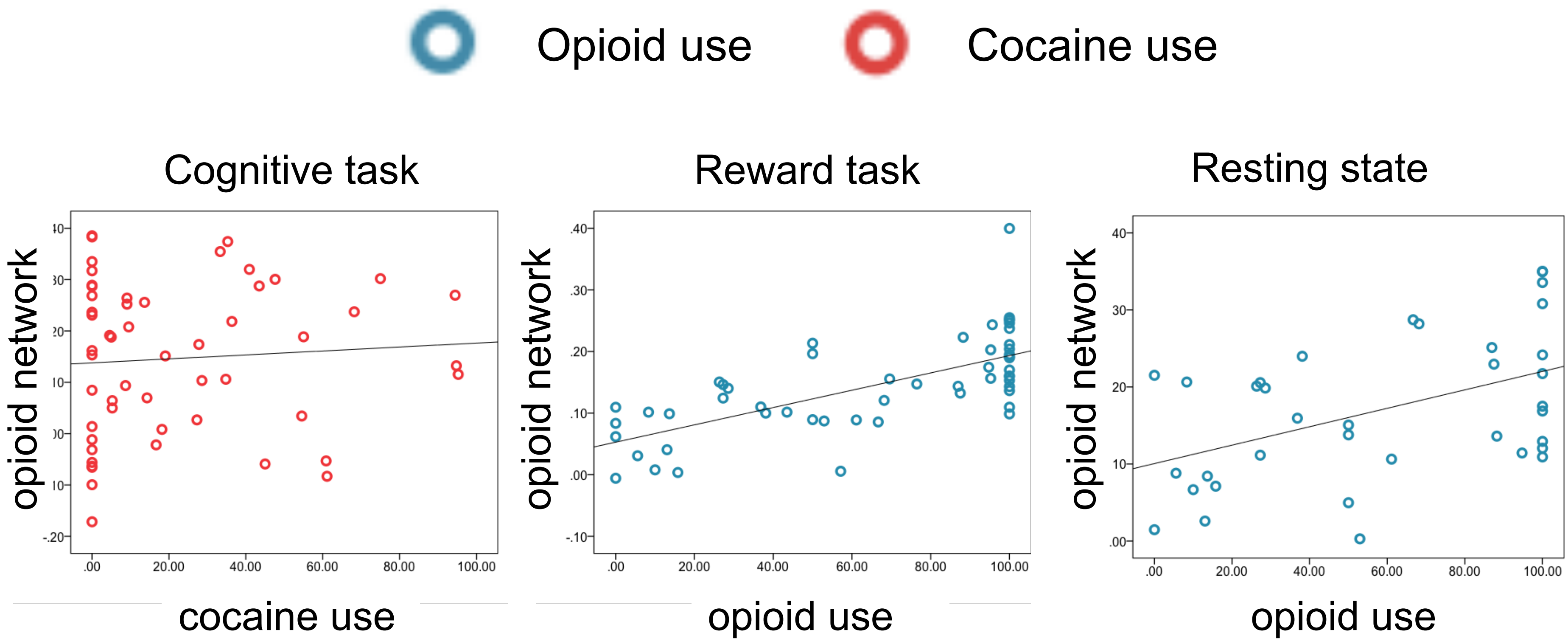


$rho_{(df=52)}=0.11$, $p=.425$ $rho_{(df=52)}=0.70$, $p<.001$ $rho_{(df=35)}=0.41$, $p=.014$

Cocaine network does <u>not</u> predict opioid use

...but does generalize across tasks.

Opioid network across drugs and brain states



rho$_{(df=52)}$=0.07, *p*=.606 *rho*$_{(df=52)}$=0.71, *p*<.001 *rho*$_{(df=35)}$=0.46, *p*=.005

Opioid network does <u>not</u> predict cocaine use

...but does generalize across tasks.

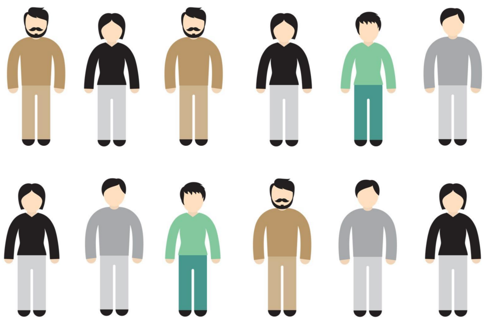
Network across drugs and brain states

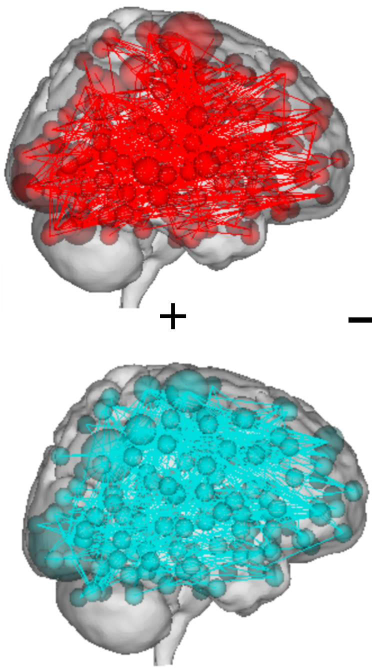
	Cocaine Network		Opioid Network	
	Cocaine	Opioid	Opioid	Cocaine
Reward	✔	x	✔	x
Cognitive	✔	x	✔	x
Resting	✔	x	✔	x

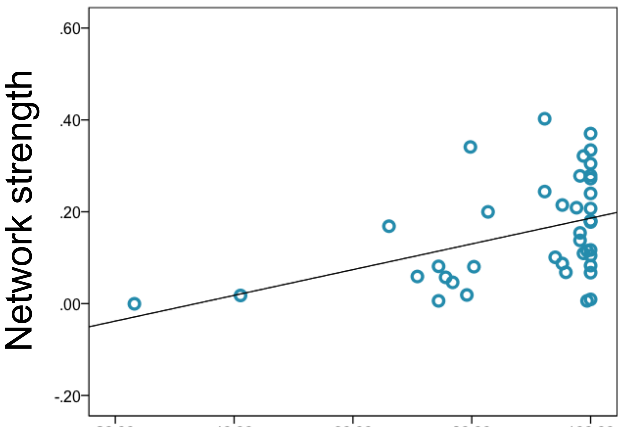
Lichenstein et al., *Molecular Psychiatry*, In Press

Post-treatment connectivity predicts opioid use*

Post-treatment fMRI (n=40)







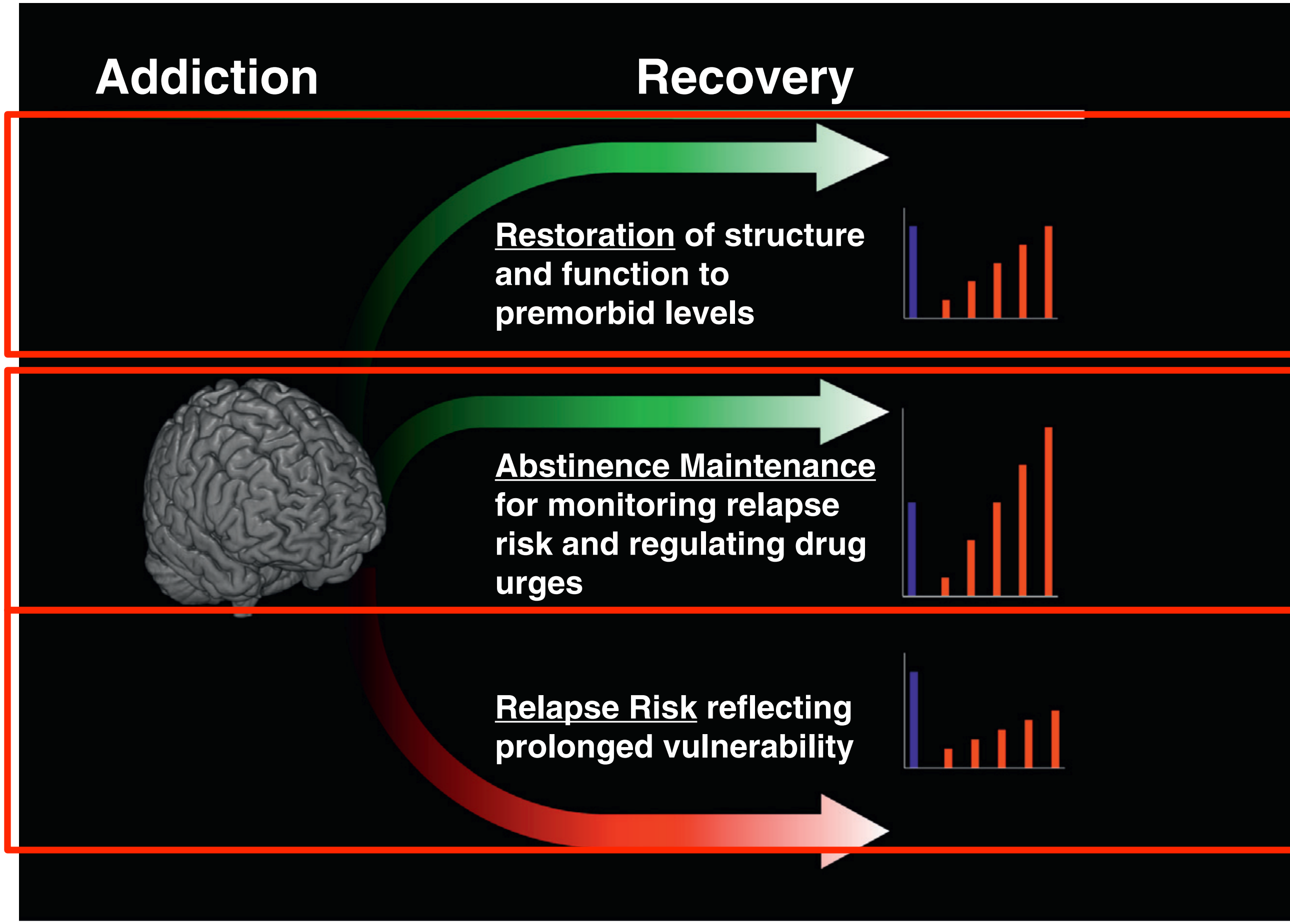
*no changes in opioid connectivity over time

Pathology versus prediction

- Pathophysiology may not predict abstinence
  - what changes w/ abstinence ≠ predict abstinence
- Initial and sustained responses may have different basis
  - motivation to change > early tx response
  - acquisition of new skills > sustained tx response
- Protracted neural change?
  - abstinence rates improve post-treatment
    - e.g., Carroll et al., Addiction, 2000

Prediction versus pathology?

Theoretical model



Current Opinion in Neurobiology

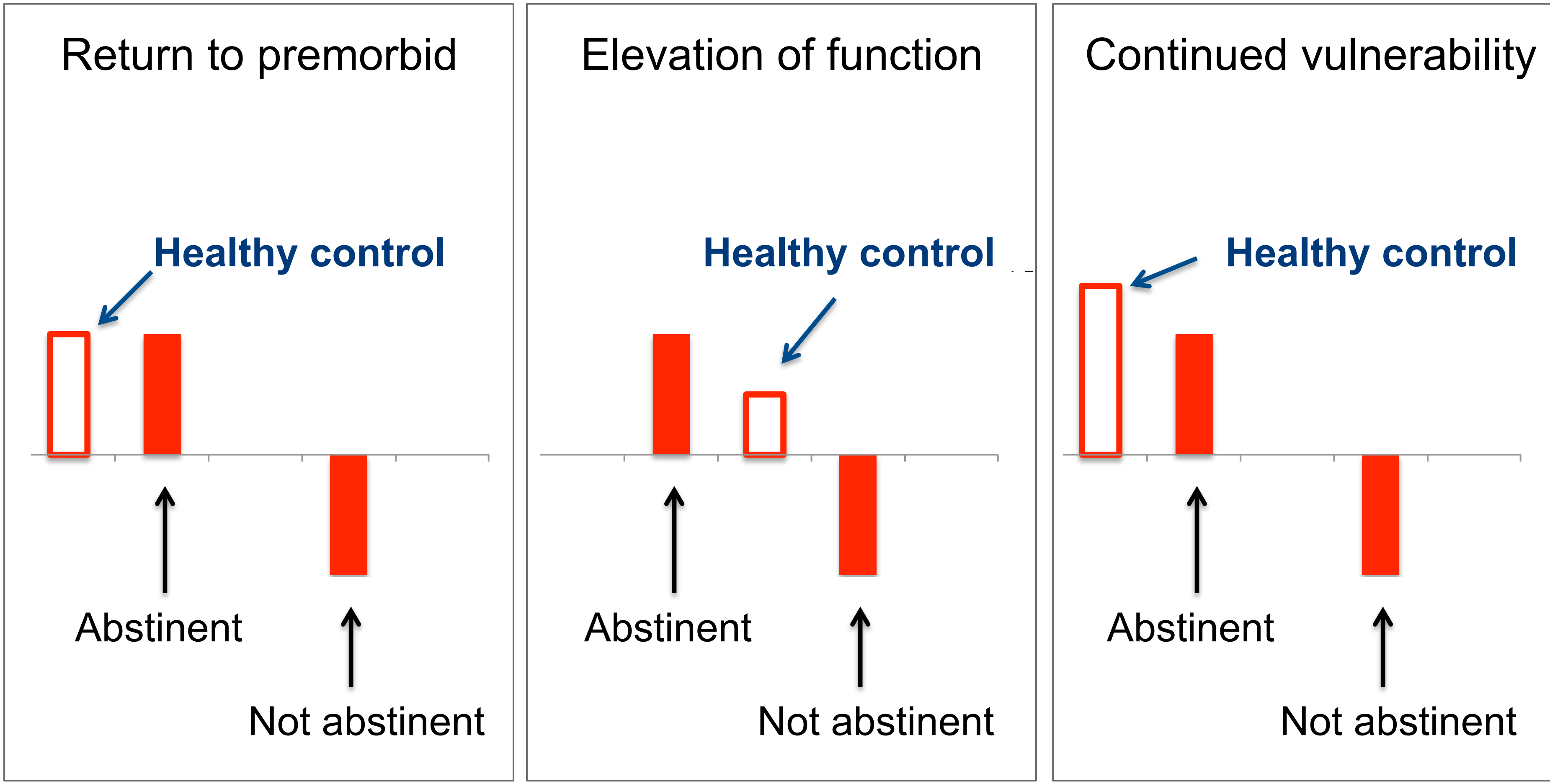
Return to premorbid levels

Elevation of function relative to controls

Continued vulnerability

Garavan et al., *Current Opinion in Neurobiology*, 2013

Theoretical model



adapted from Garavan et al., *Current Opinion in Neurobiology*, 2013

Healthy controls

n=38 controls participants

No substance-use disorders

Drawn from ongoing Yale Psychiatry research protocols

38 years old (SD=9.06)
58% male

n=53 patients

Cocaine + opioid use disorders

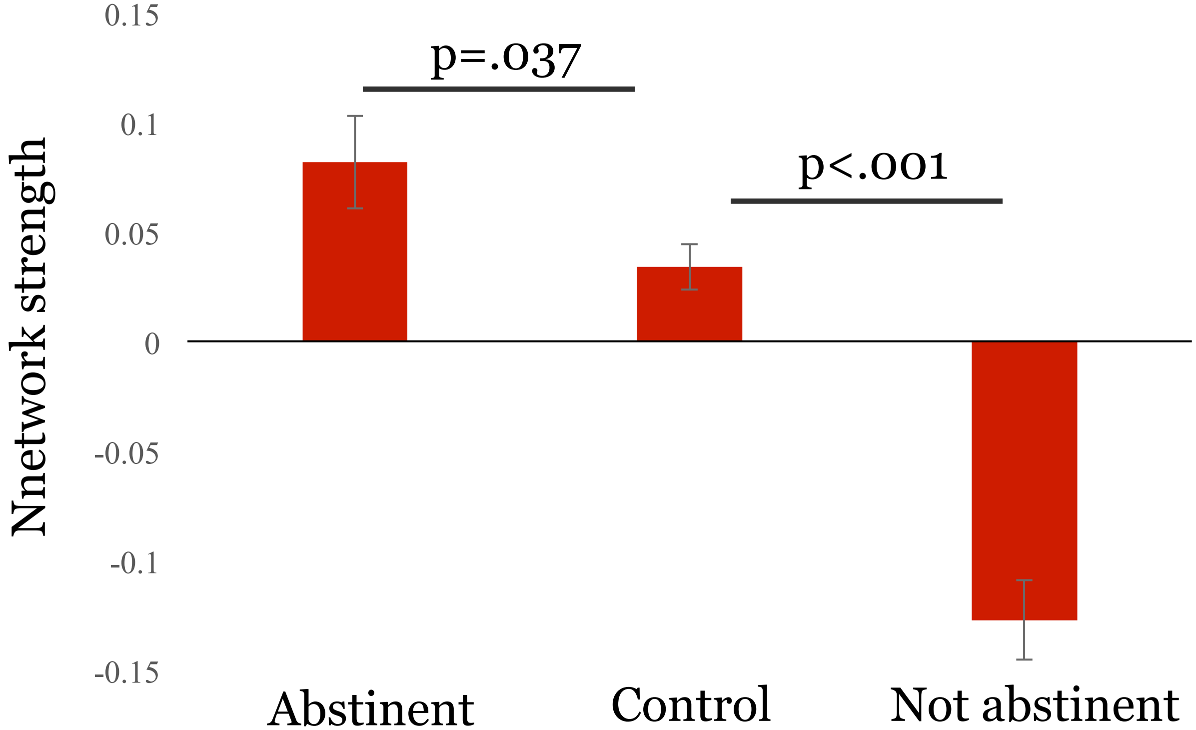
Recruited from RCT for CUD + methadone treatment for OUD

35 years old (SD=9.37)
74% male

identical acquisition, tasks & connectivity pipeline

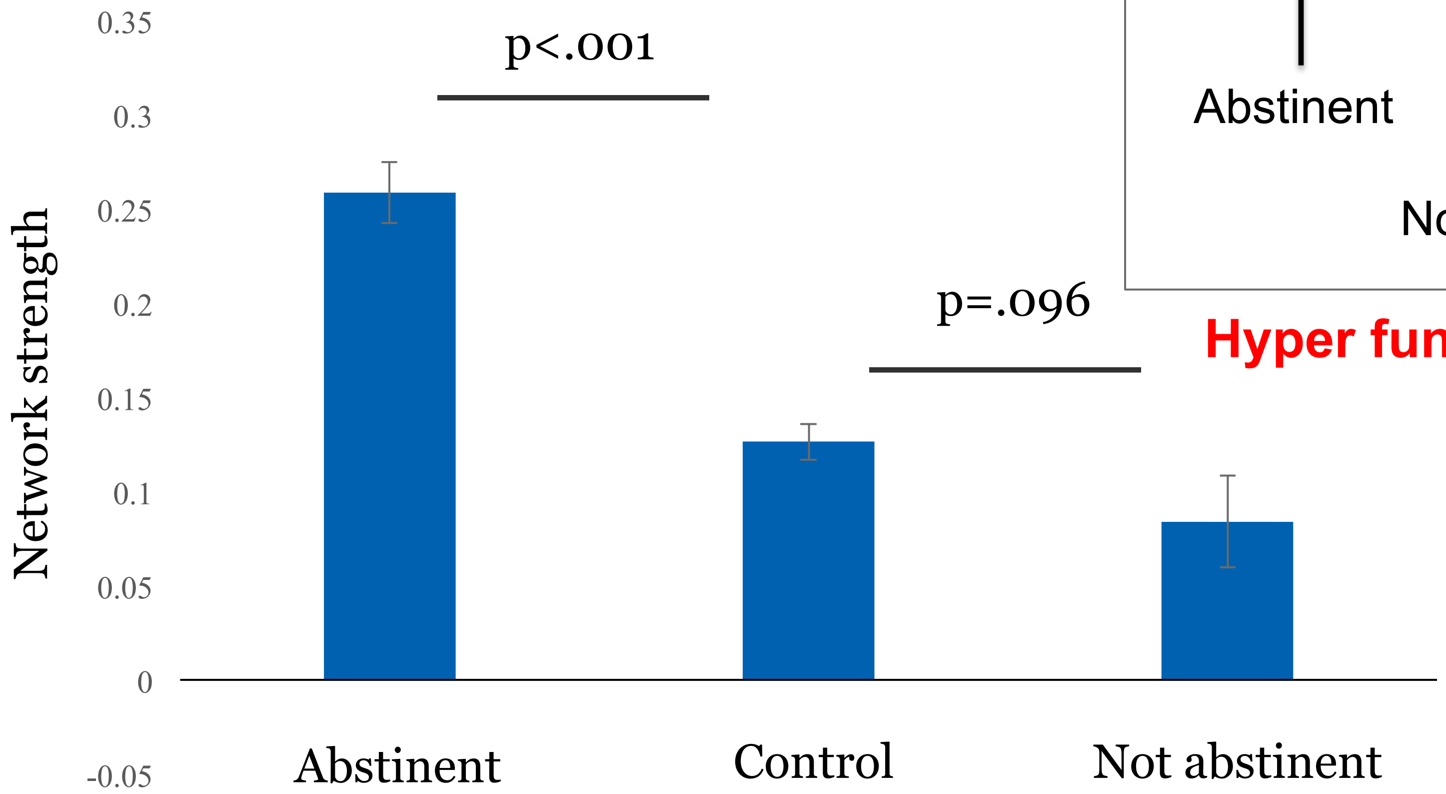
Lichenstein et al., *Molecular Psychiatry*, In Press

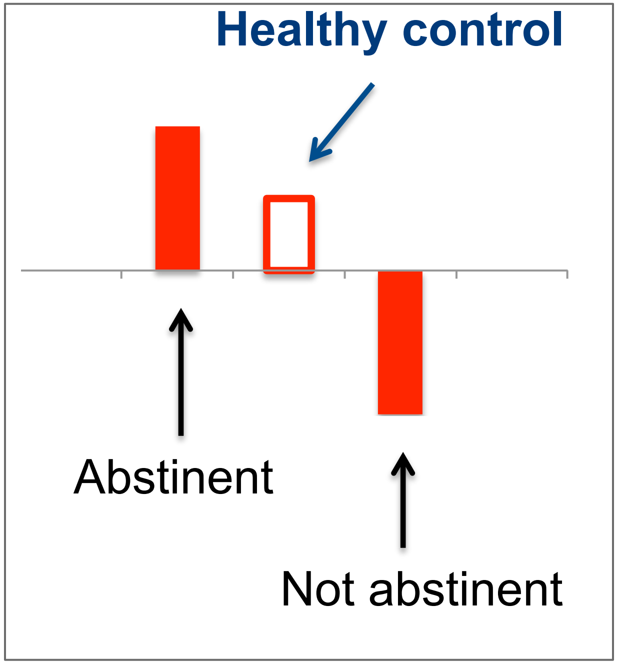
Cocaine network



Lichenstein et al., *Molecular Psychiatry*, In Press

Opioid network

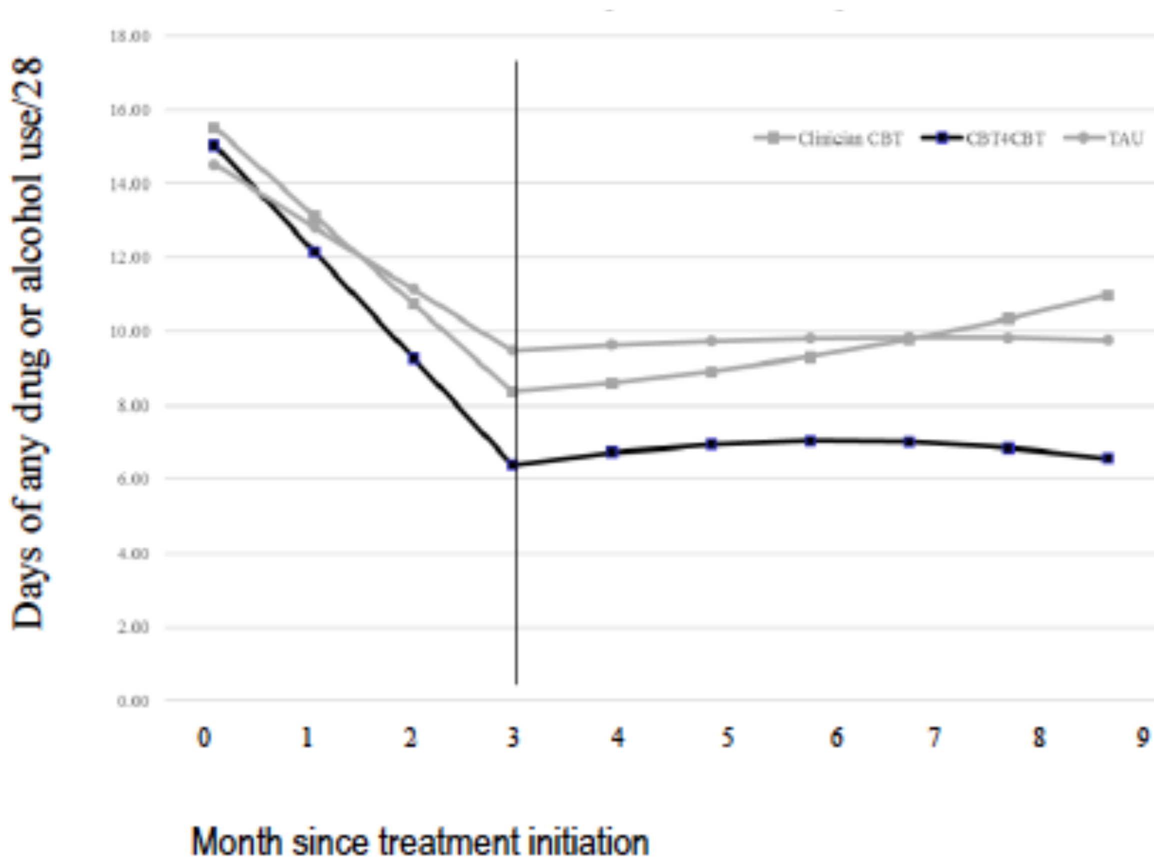




Hyper functionality

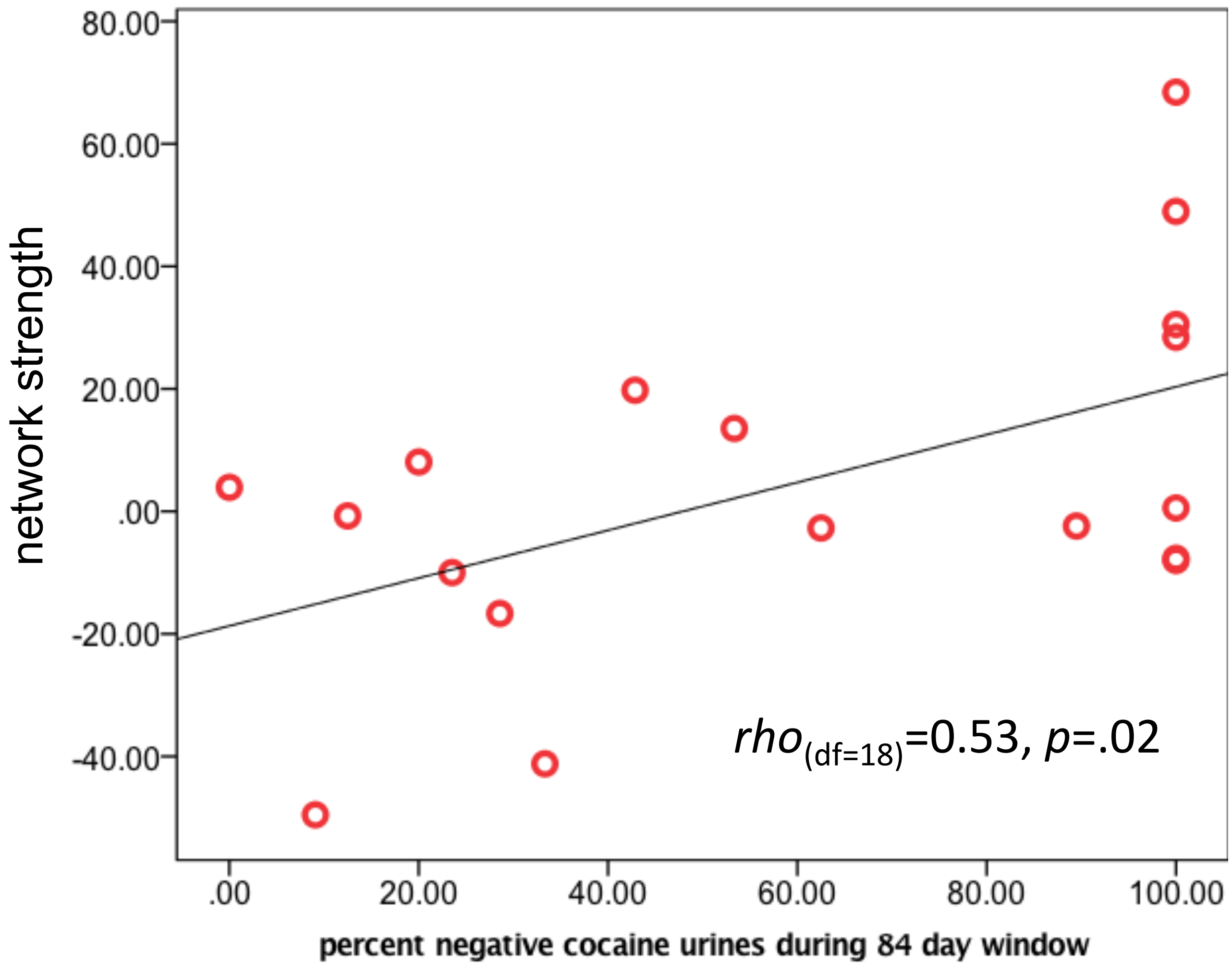
Lichenstein et al., *Molecular Psychiatry*, In Press

Protracted neural change?



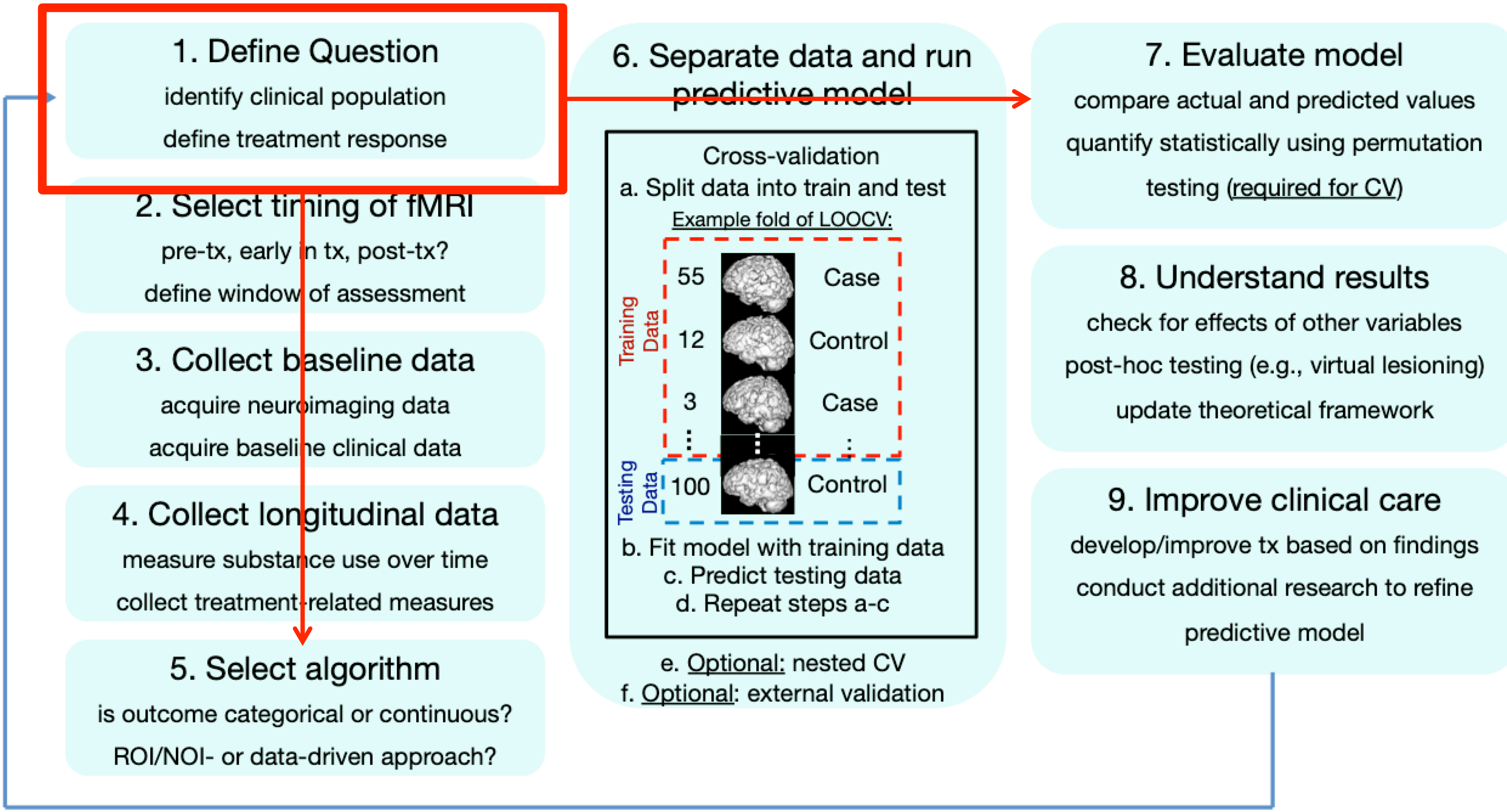
pre fMRI post fMRI follow-up fMRI

Second external replication



Part III: Considerations for clinical prediction

Clinical workflow



Yip et al., *Biological Psychiatry: CNNI*, 2020

'Best' metric depends on the question

Outcome 1. Assignment to active treatment

High sensitivity / low specificity		Low sensitivity / high specificity	
TP	FP	TP	FP
n=70	n=20	n=5	n=5
FN	TN	**FN**	TN
n=5	n=5	**n=70**	n=20

Outcome 2. Termination of active treatment

High sensitivity / low specificity		Low sensitivity / high specificity	
TP	**FP**	TP	**FP**
n=70	**n=20**	n=5	**n=5**
FN	TN	FN	TN
n=5	n=5	n=70	n=20

Yip et al., *Biological Psychiatry: CNNI*, 2020

Clinical workflow

1. Define Question
identify clinical population
define treatment response

2. Select timing of fMRI
pre-tx, early in tx, post-tx?
define window of assessment

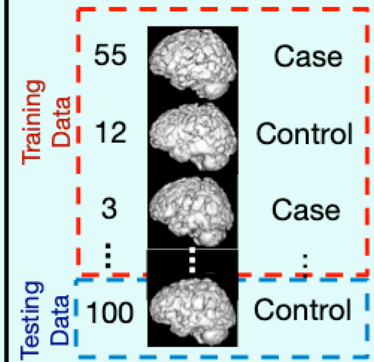
3. Collect baseline data
acquire neuroimaging data
acquire baseline clinical data

4. Collect longitudinal data
measure substance use over time
collect treatment-related measures

5. Select algorithm
is outcome categorical or continuous?
ROI/NOI- or data-driven approach?

6. Separate data and run predictive model

Cross-validation
a. Split data into train and test
Example fold of LOOCV:



b. Fit model with training data
c. Predict testing data
d. Repeat steps a-c

e. Optional: nested CV
f. Optional: external validation

7. Evaluate model
compare actual and predicted values
quantify statistically using permutation testing (required for CV)

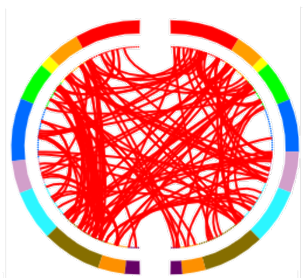
8. Understand results
check for effects of other variables
post-hoc testing (e.g., virtual lesioning)
update theoretical framework

9. Improve clinical care
develop/improve tx based on findings
conduct additional research to refine predictive model

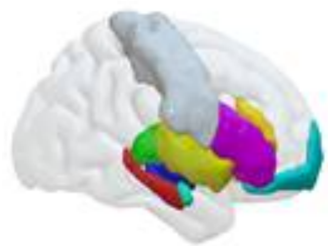
Yip et al., *Biological Psychiatry: CNNI*, 2020

Elucidation as a goal of prediction

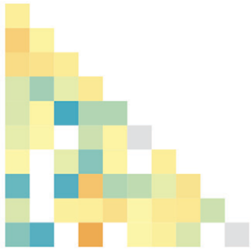
Connection (or edge) level



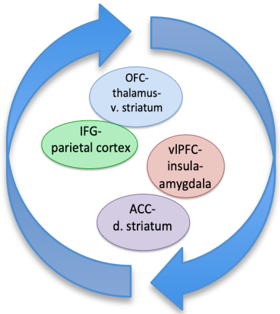
Region (or node) level



Network / systems level



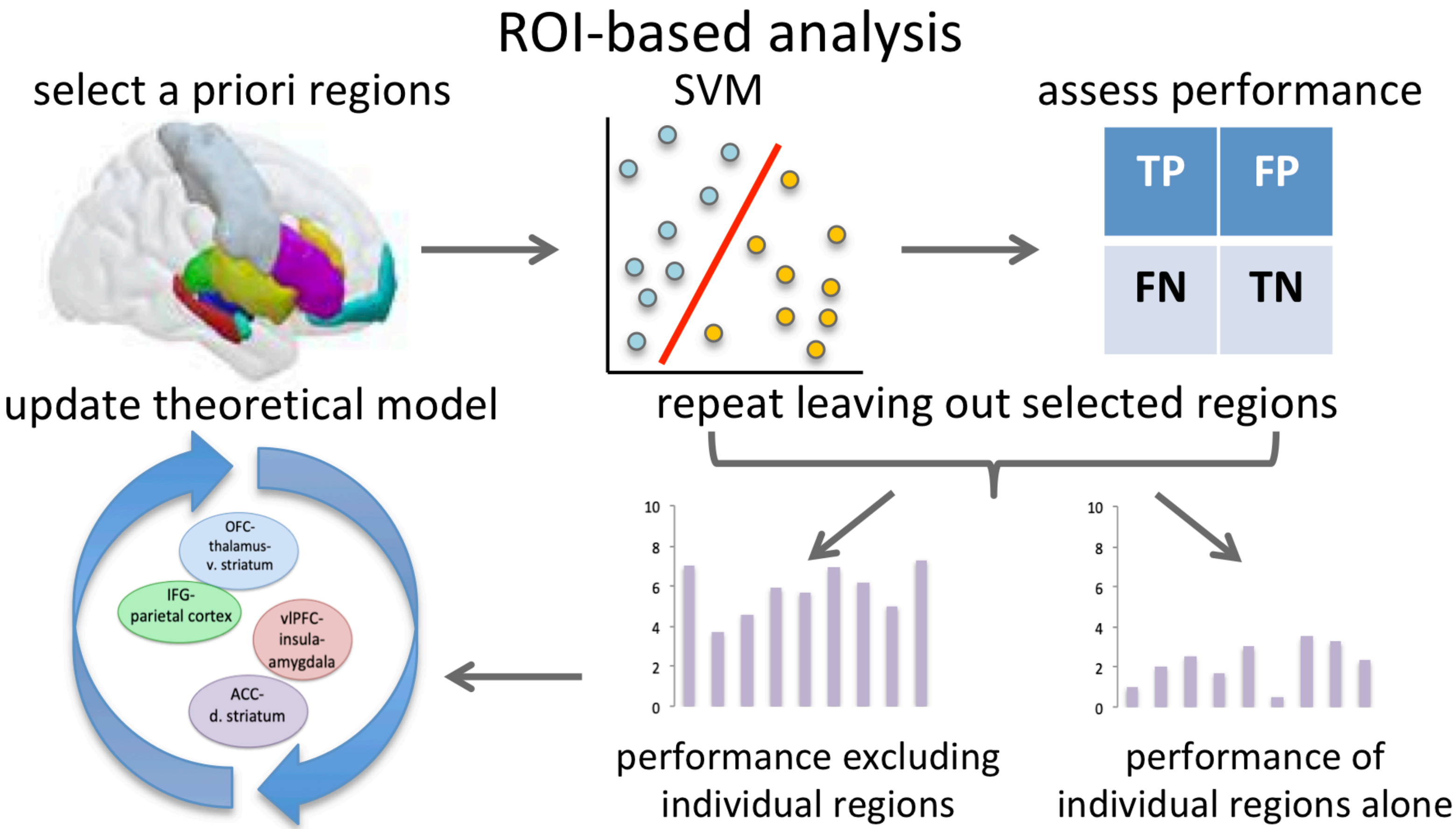
Theory / mechanism level



Levels of interpretation

Yip et al., *Biological Psychiatry: CNNI*, 2020

Elucidation as a goal of prediction



Yip et al., *Biological Psychiatry: CNNI*, 2020

Thank you!

Key collaborators: Sarah Lichenstein, PhD, Dustin Scheinost, PhD, Brian Kiluk, PhD, Marc Potenza, MD, PhD, Kathleen Carroll, PhD

Yale
Imaging &
Psychopharmacology

K01 DA039299 (Yip), P50 DA009241 (Carroll), R21 DA045969 (Yip), R21 DA049583 (Garrison/Scheinost/Yip), R01 AAA027553 (Yip/Scheinost), NARSAD Young Investigator Award (Yip)