Toward brain-based prediction of recovery: How neuroimaging can help combat the opioid epidemic

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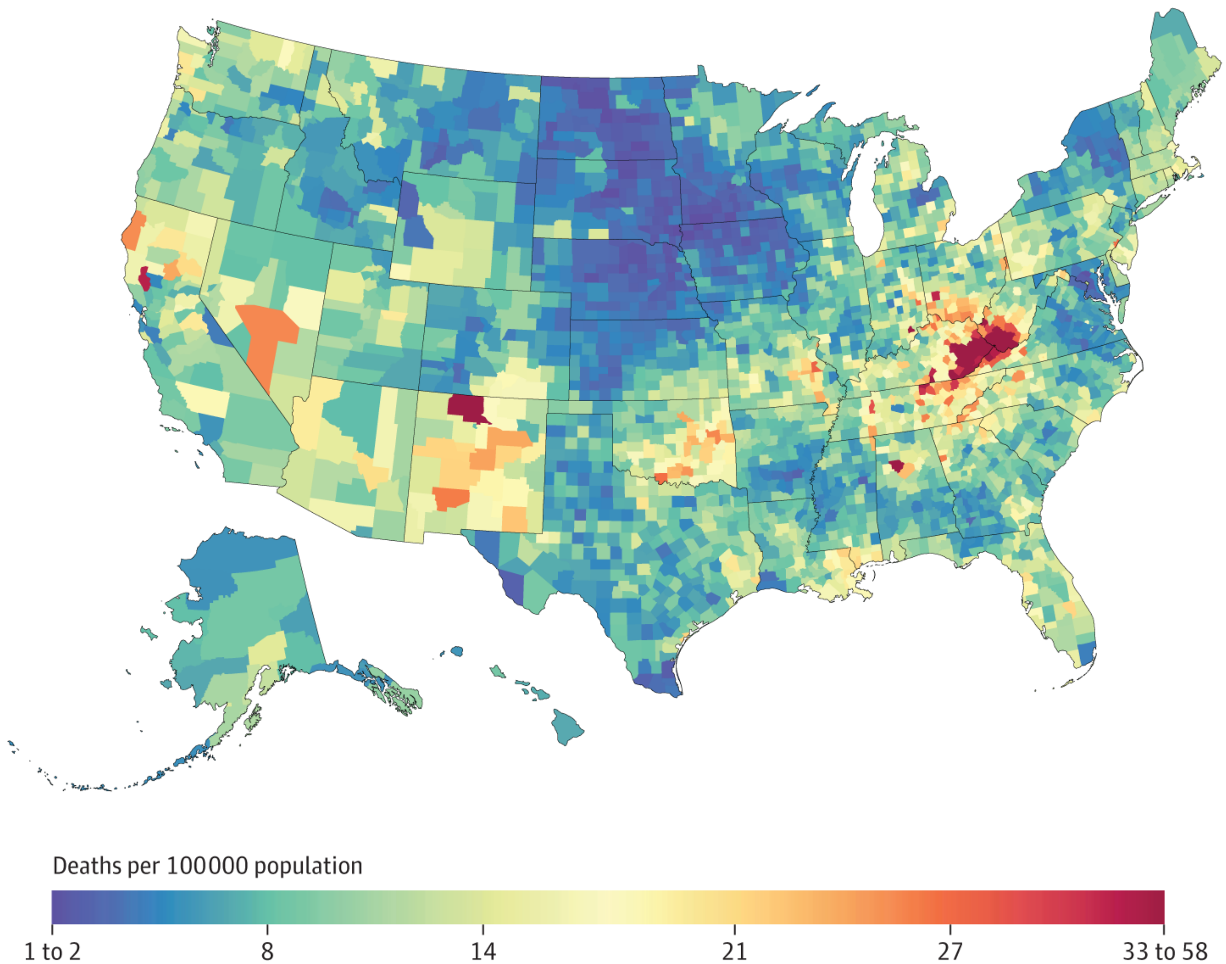
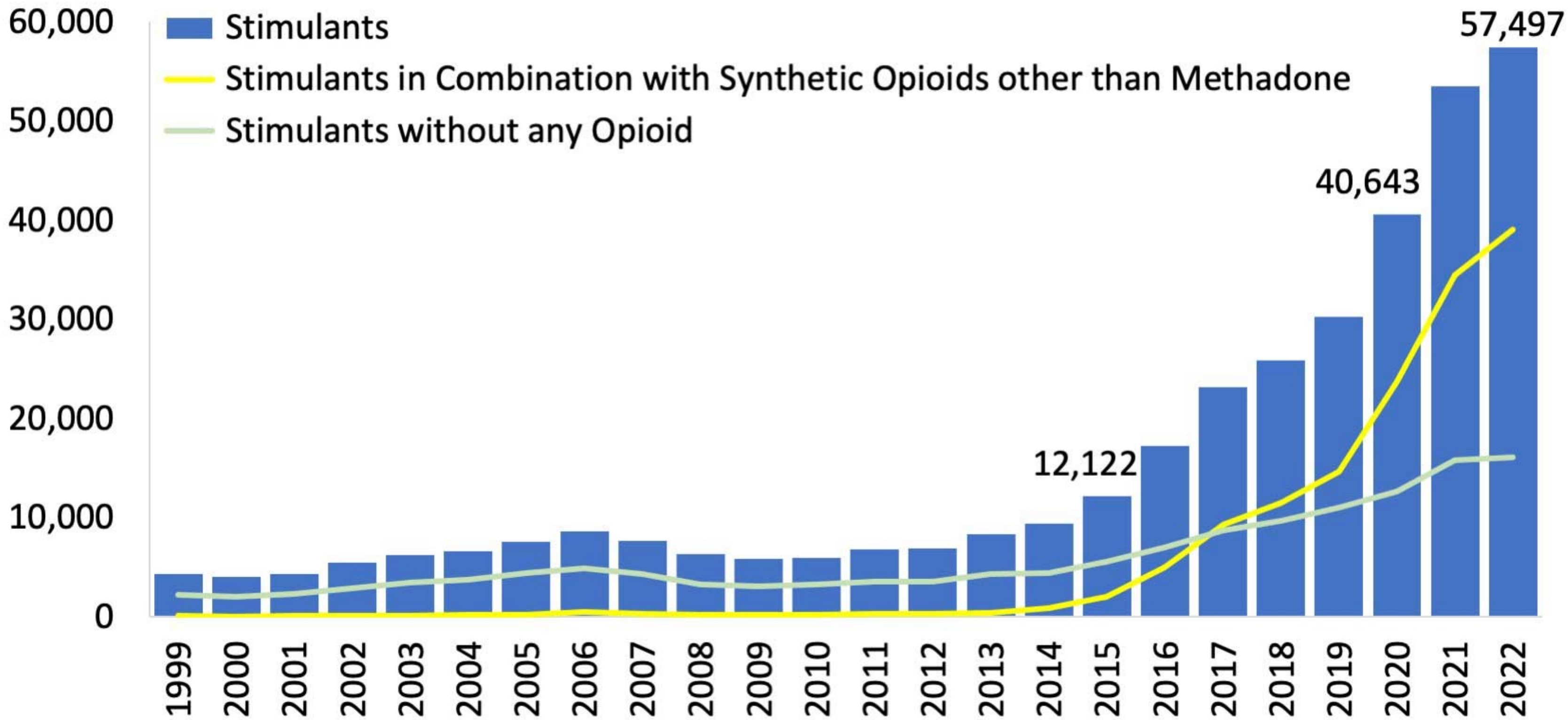
Substance use epidemic



From: **Trends and Patterns of Geographic Variation in Mortality From Substance Use Disorders and Intentional Injuries Among US Counties, 1980-2014;** JAMA. 2018;319(10):1013-1023. doi:10.1001/jama.2018.0900

Figure 6. U.S. Overdose Deaths Involving Stimulants* (cocaine and psychostimulants with abuse potential), by Opioid Involvement, 1999-2022

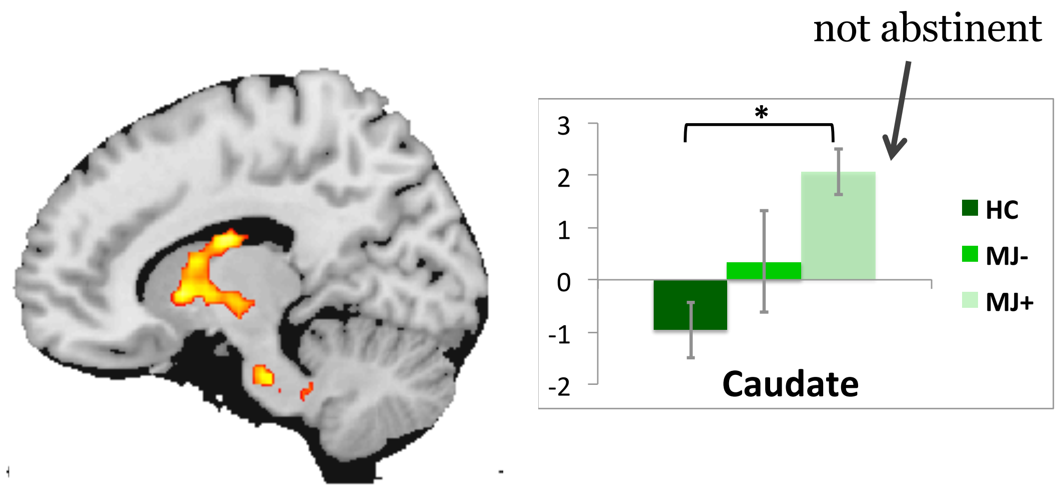


*Among deaths with drug overdose as the underlying cause, the psychostimulants with abuse potential (primarily methamphetamine) category was determined by the T43.6 ICD-10 multiple cause-of-death code. Abbreviated to *psychostimulants* in the bar chart above. Source: Centers for Disease Control and Prevention, National Center for Health Statistics. Multiple Cause of Death 1999-2022 on CDC WONDER Online Database, released 4/2024.

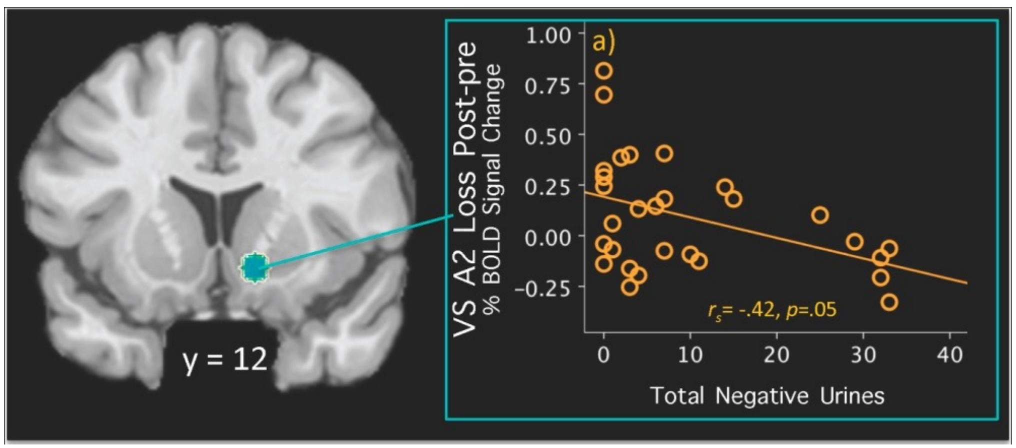
Clinical reality

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

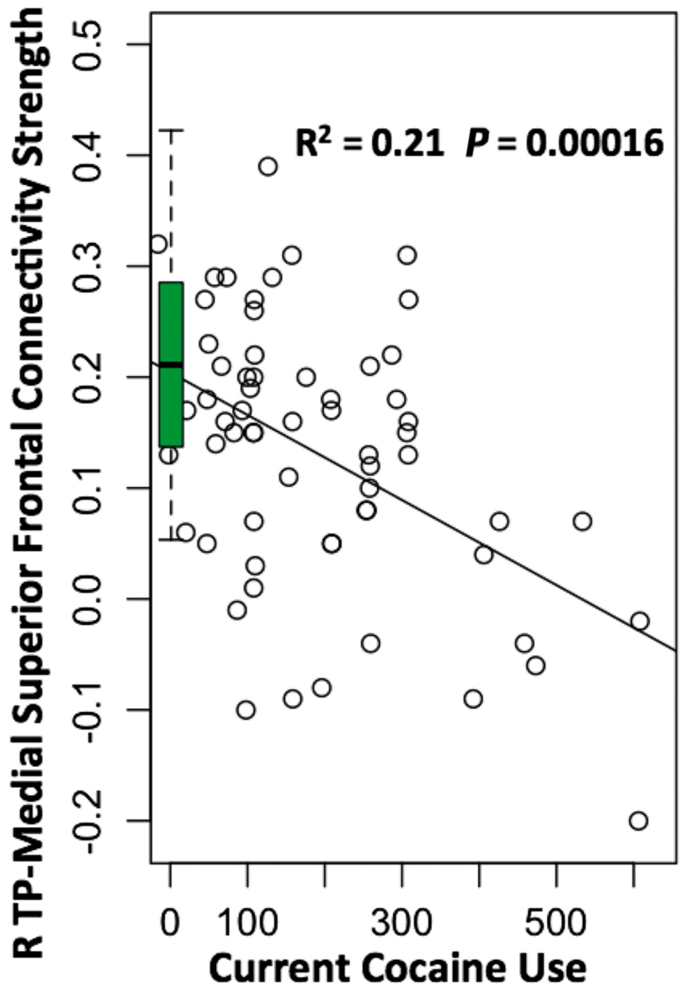
Neuroimaging of addiction outcomes



Yip et al., Drug Alcohol Depend, 2014



Balodis et al, Neuropsychopharmacol, 2016



Gu et al., Brain, 2014

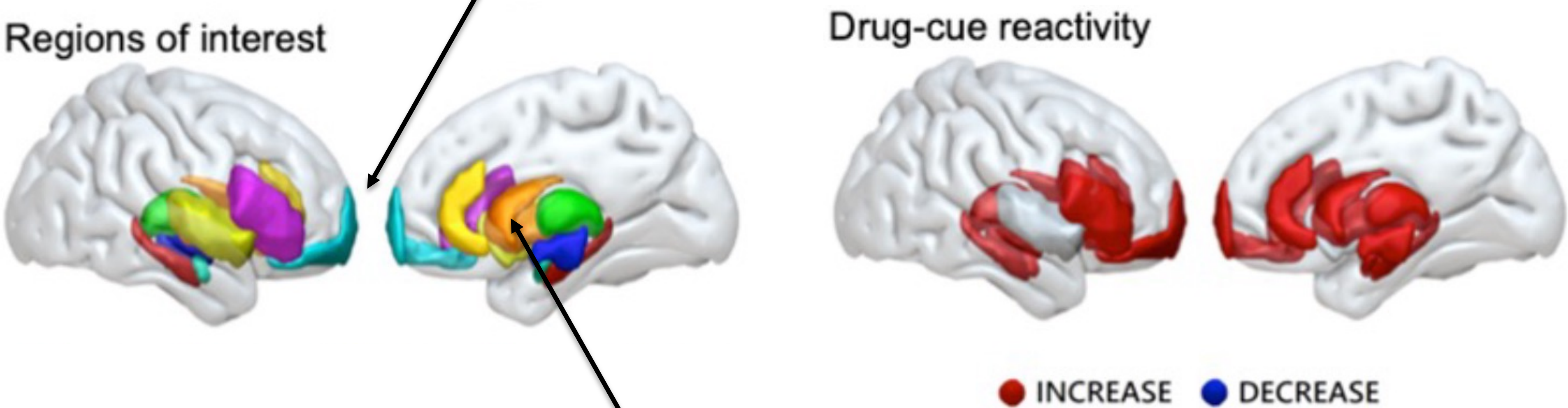
Some limitations:

> Need more studies of opioid-use disorder

> Most studies single timepoint

Drug-cue findings (aggregate)

Prefrontal cortex

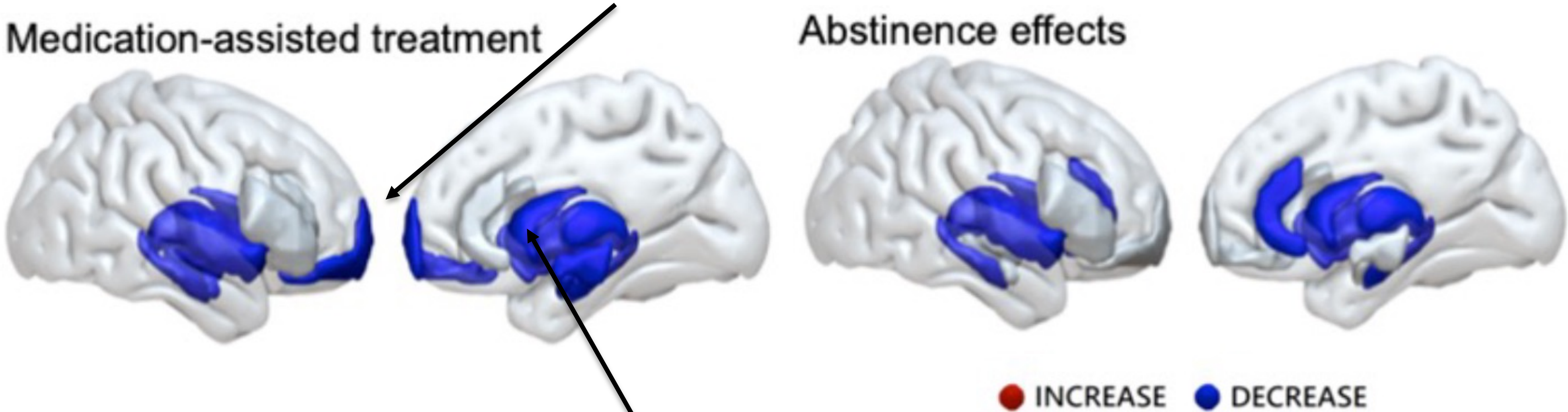


Striatum (reward)

Moningka et al., Neuropsychopharmacology 2019

Treatment and abstinence effects

Prefrontal cortex



Striatum (reward)

replication and longitudinal research needed

Moningka et al., Neuropsychopharmacology 2019

Some limitations:

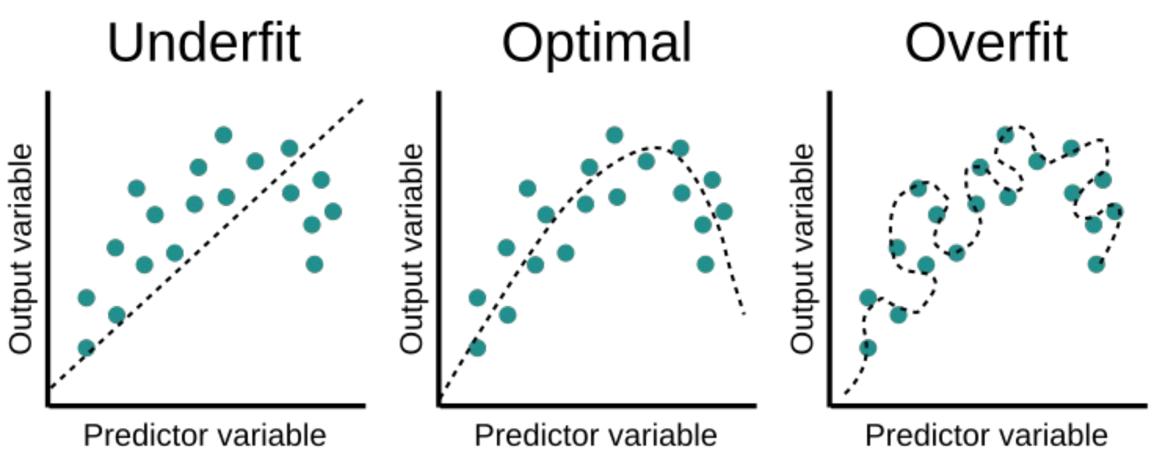
> Need more studies of opioid-use disorder
  > Systematic review
> Most studies single timepoint
  > Need to identify brain predictors

TECHNIQUES AND METHODS

When Optimism Hurts: Inflated Predictions in Psychiatric Neuroimaging

Robert Whelan and Hugh Garavan

- Term 'predicts' often misused
- Correlation ≠ prediction
- Over-fitting models limits reproducibility



https://www.educative.io/edpresso/overfitting-and-underfitting

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

PROTOCOL

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

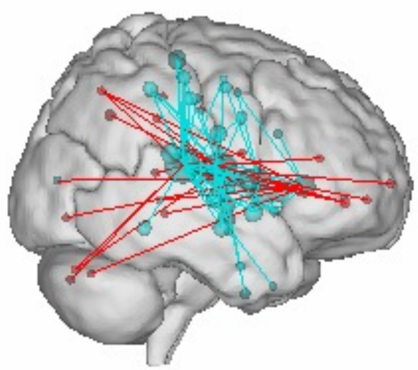
Xilin Shen[1], Emily S Finn[2], Dustin Scheinost[1], Monica D Rosenberg[3], Marvin M Chun[2–4], Xenophon Papademetris[1,5] & R Todd Constable[1,2,6]

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

> data-driven machine learning approach

> no a priori specification of networks

> predict and identify networks

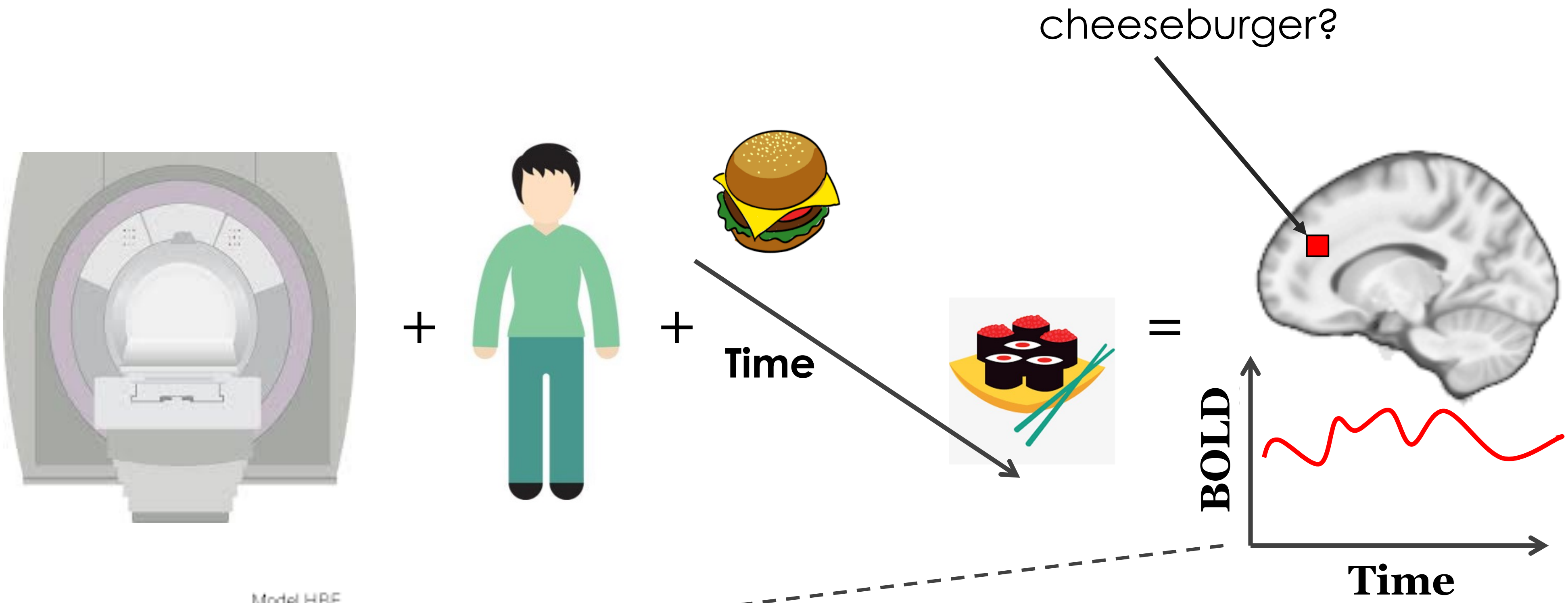


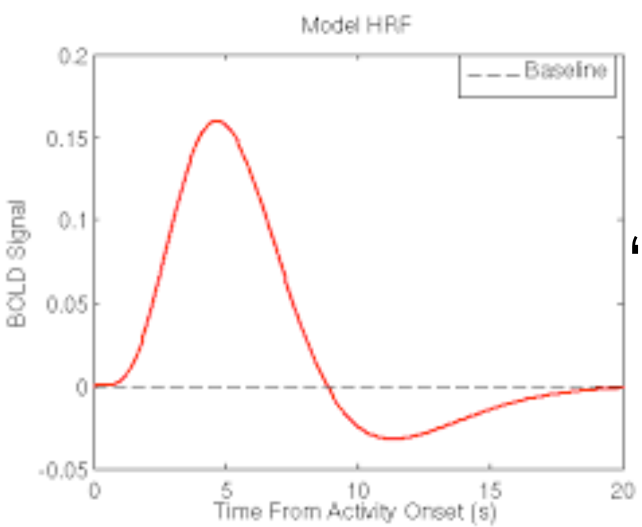
What is a connectome?

"A comprehensive…description of the network of elements and connections forming the human brain. We propose to call this dataset the human "connectome," and we argue that it is fundamentally important in cognitive neuroscience and neuropsychology."

Sporns et al., *PLOS Computational Biology* 2005

‘traditional’ fMRI overview

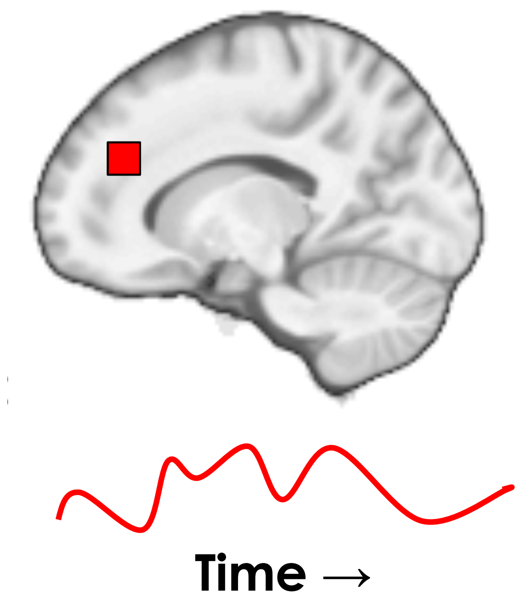




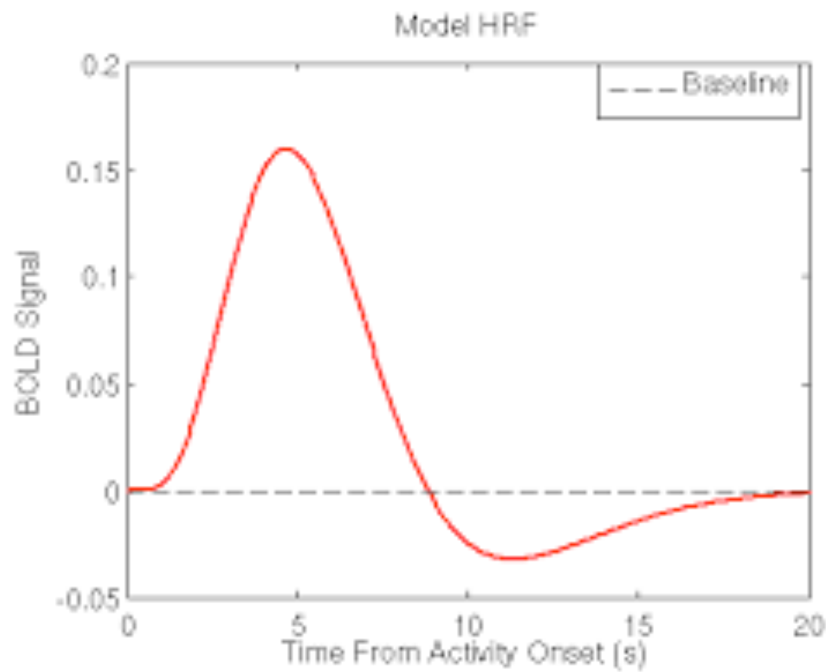
‘activity’ = BOLD response to a stimulus

Traditional fMRI

'activity' = BOLD response to a stimulus (burger)

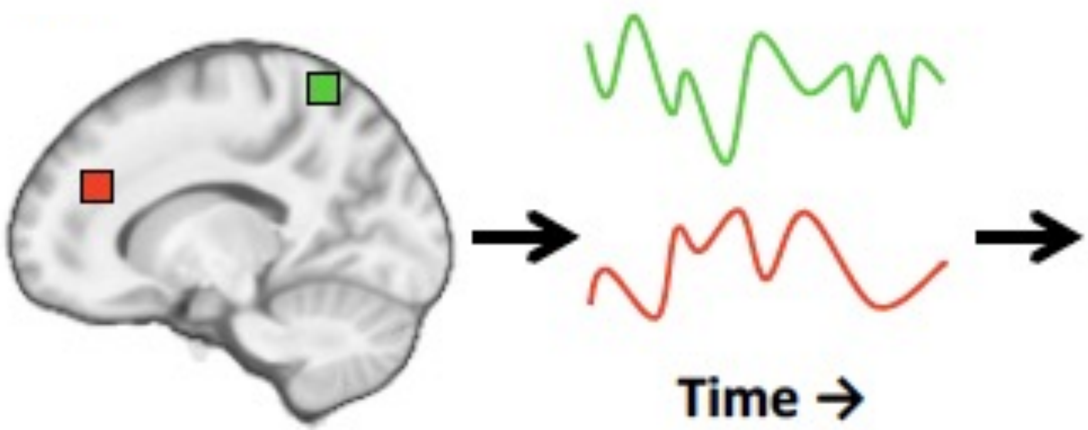


vs.



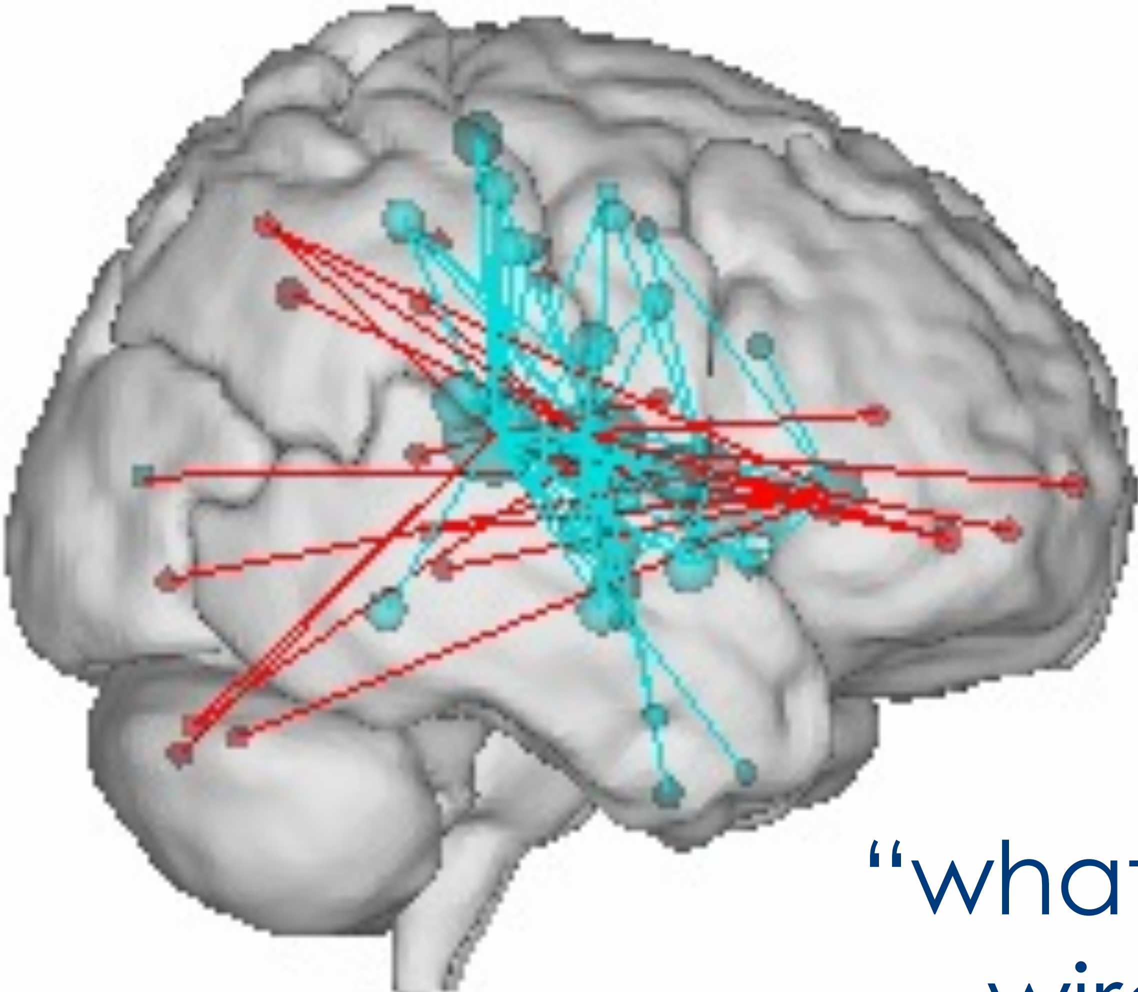
Functional connectivity (the ‘connectome’)

‘connectivity’ = temporal coherence between brain regions



connectivity strength (r)

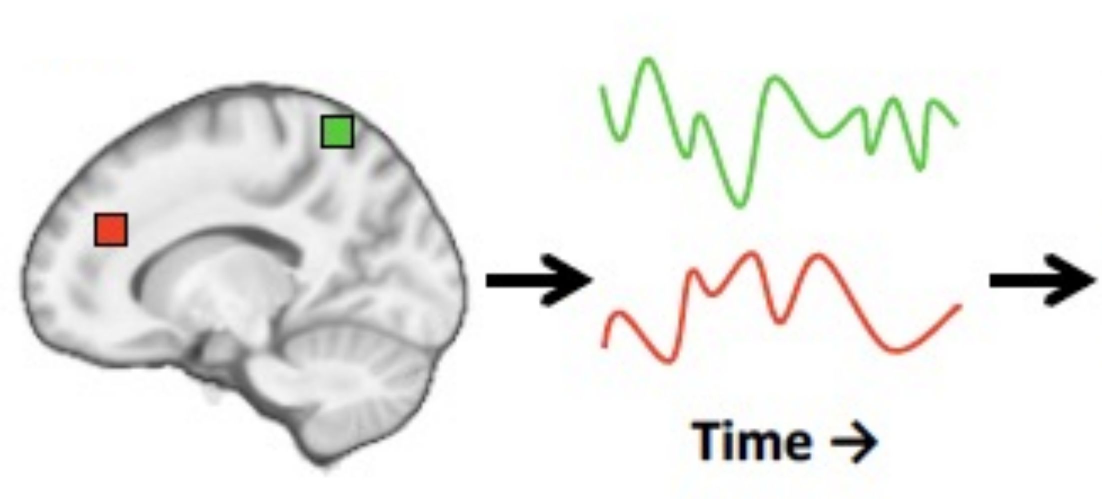
Functional connectome



“what fires together,
wires together”

Functional connectivity (the 'connectome')

'connectivity' = temporal coherence between brain regions

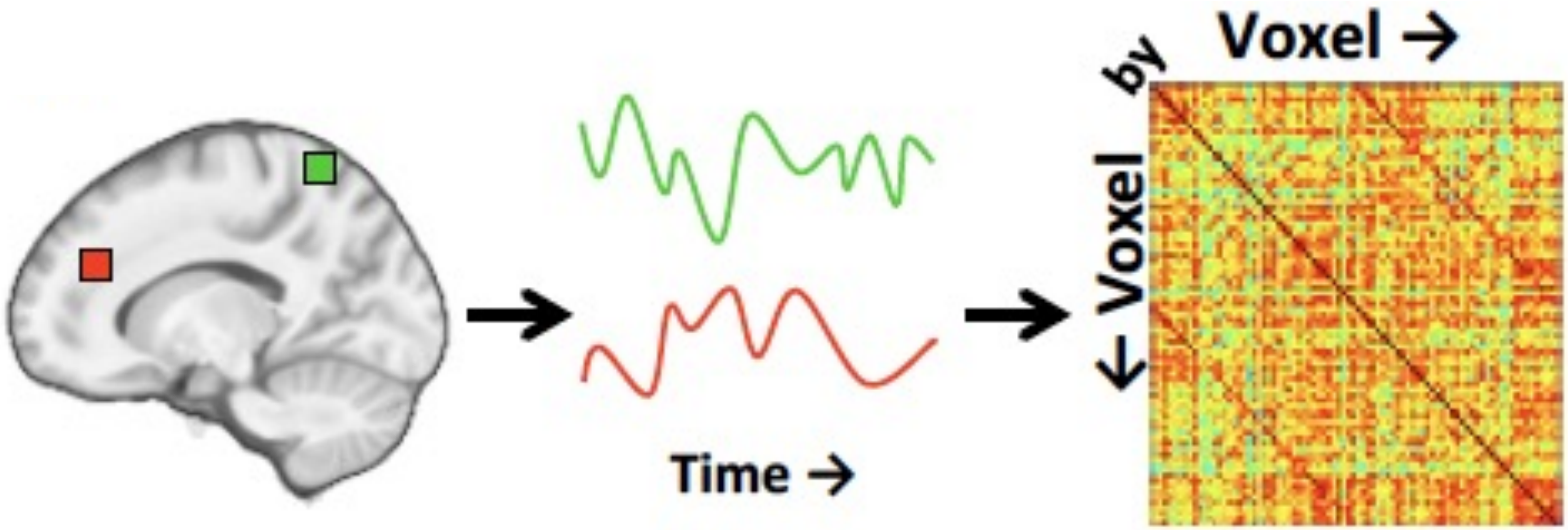


connectivity strength (r)

"You jump, I jump"

Functional connectivity (the 'connectome')

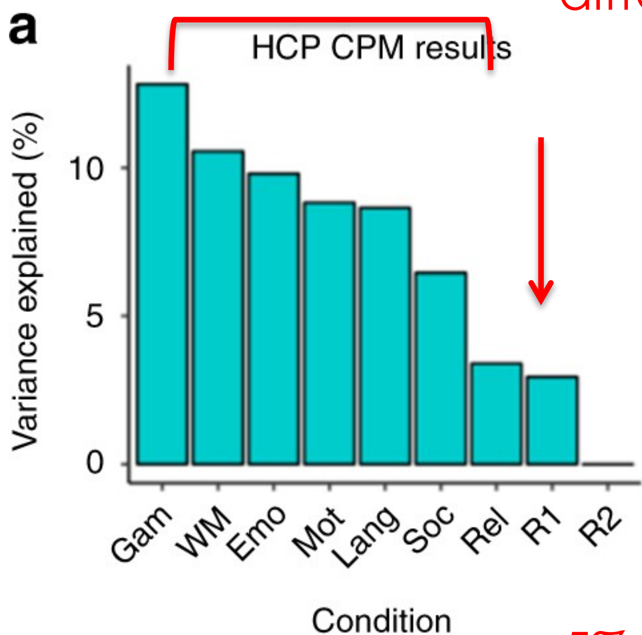
'connectivity' = temporal coherence between brain regions

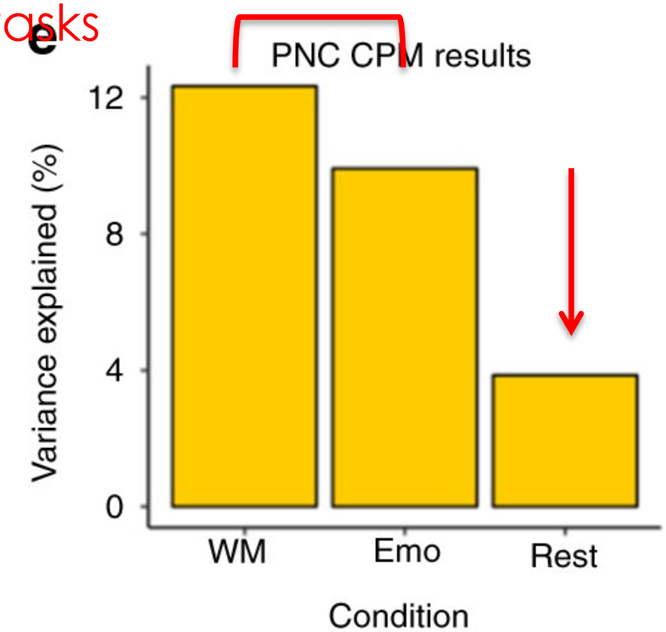


'connectome'

Brain state manipulation improves prediction

~3-12% variance in IQ explained by models using data from different tasks





<5% variance in IQ explained by model using resting state data

Greene et al., *Nature Communications*, 2018

Clinical relevance of brain state

ORIGINAL ARTICLE

Real-Time Electronic Diary Reports of Cue Exposure and Mood in the Hours Before Cocaine and Heroin Craving and Use

David H. Epstein, PhD; Jessica Willner-Reid, BSc; Massoud Vahabzadeh, PhD; Mustapha Mezghanni, MS; Jia-Ling Lin, PhD; Kenzie L. Preston, PhD

> ecological momentary assessment

> cocaine + opioid use disorders (N=114)

> track dynamic changes in mood and use

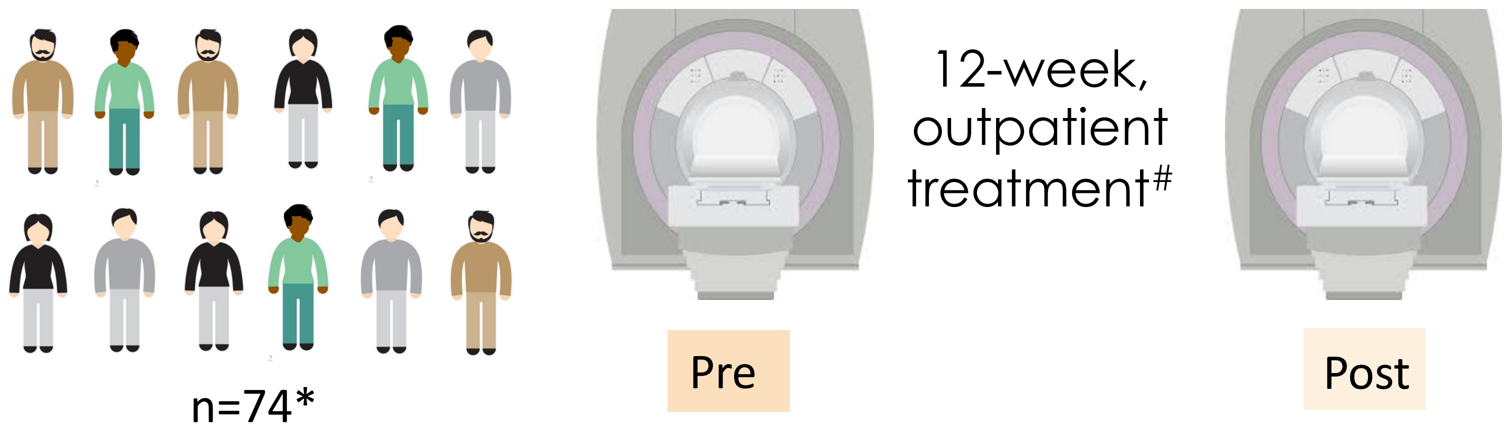
Epstein et al., *Archives of General Psychiatry*, 2009

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

Brain state study design



*opioid-dependent, methadone-maintained

#behavioral therapy +/- medication for cocaine-use

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

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]

Data-driven, whole-brain, machine leaning approach

Uses connectomes to predict behavior

Identifies individual connections underlying behavioral predictions

Distinguishes positive and negative predictive connections

ARTICLES

Connectome-Based Prediction of Cocaine Abstinence

Sarah W. Yip, Ph.D., M.Sc., Dustin Scheinost, Ph.D., Marc N. Potenza, M.D., Ph.D., Kathleen M. Carroll, Ph.D.

ARTICLE

Dissociable neural substrates of opioid and cocaine use identified via connectome-based modelling

Sarah D. Lichenstein[1] · Dustin Scheinost[1] · Marc N. Potenza[2] · Kathleen M. Carroll[2] · Sarah W. Yip[2]

Molecular Psychiatry www.nature.com/mp

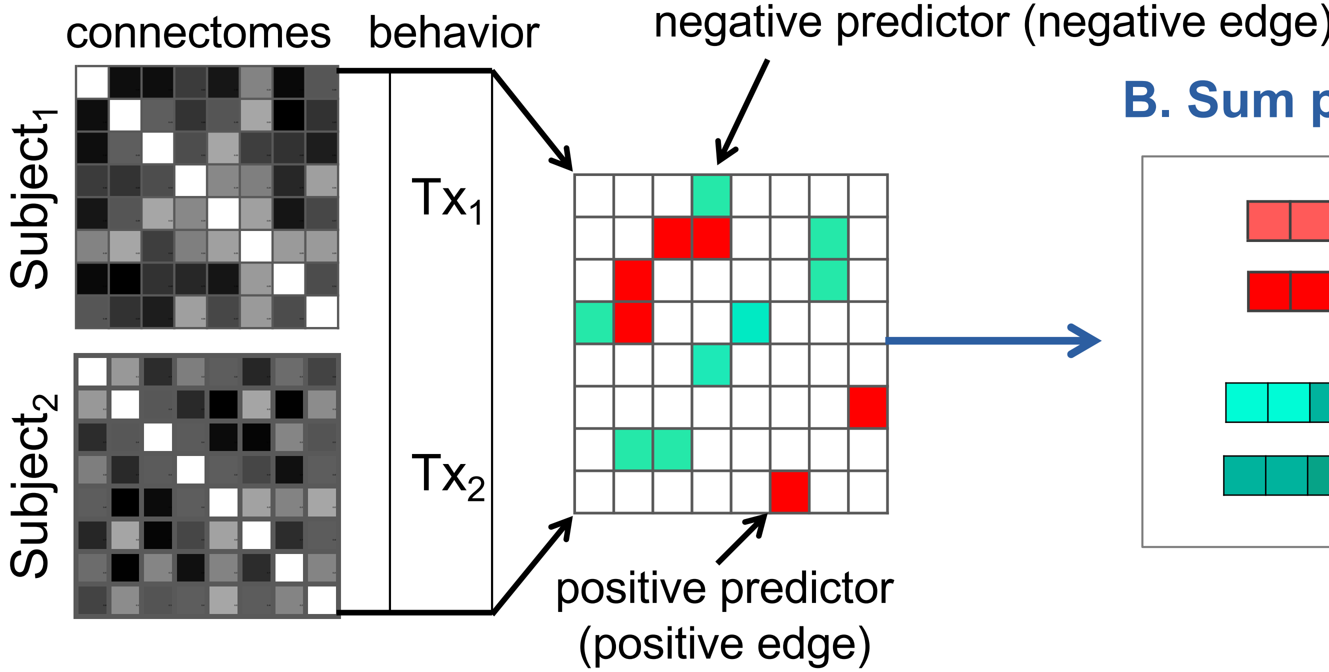
ARTICLE

Check for updates

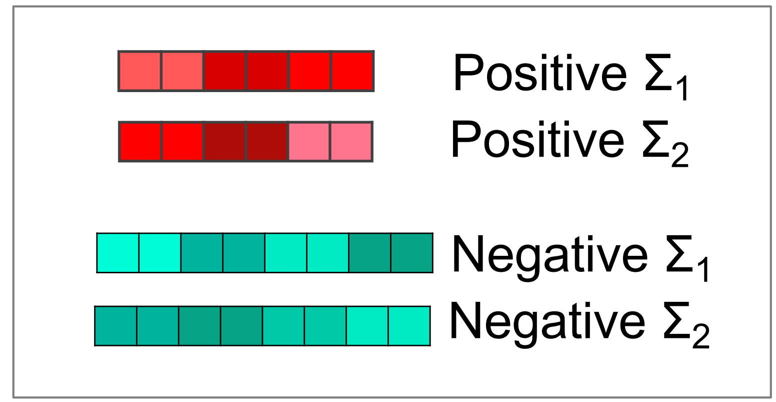
Distinct neural networks predict cocaine versus cannabis treatment outcomes

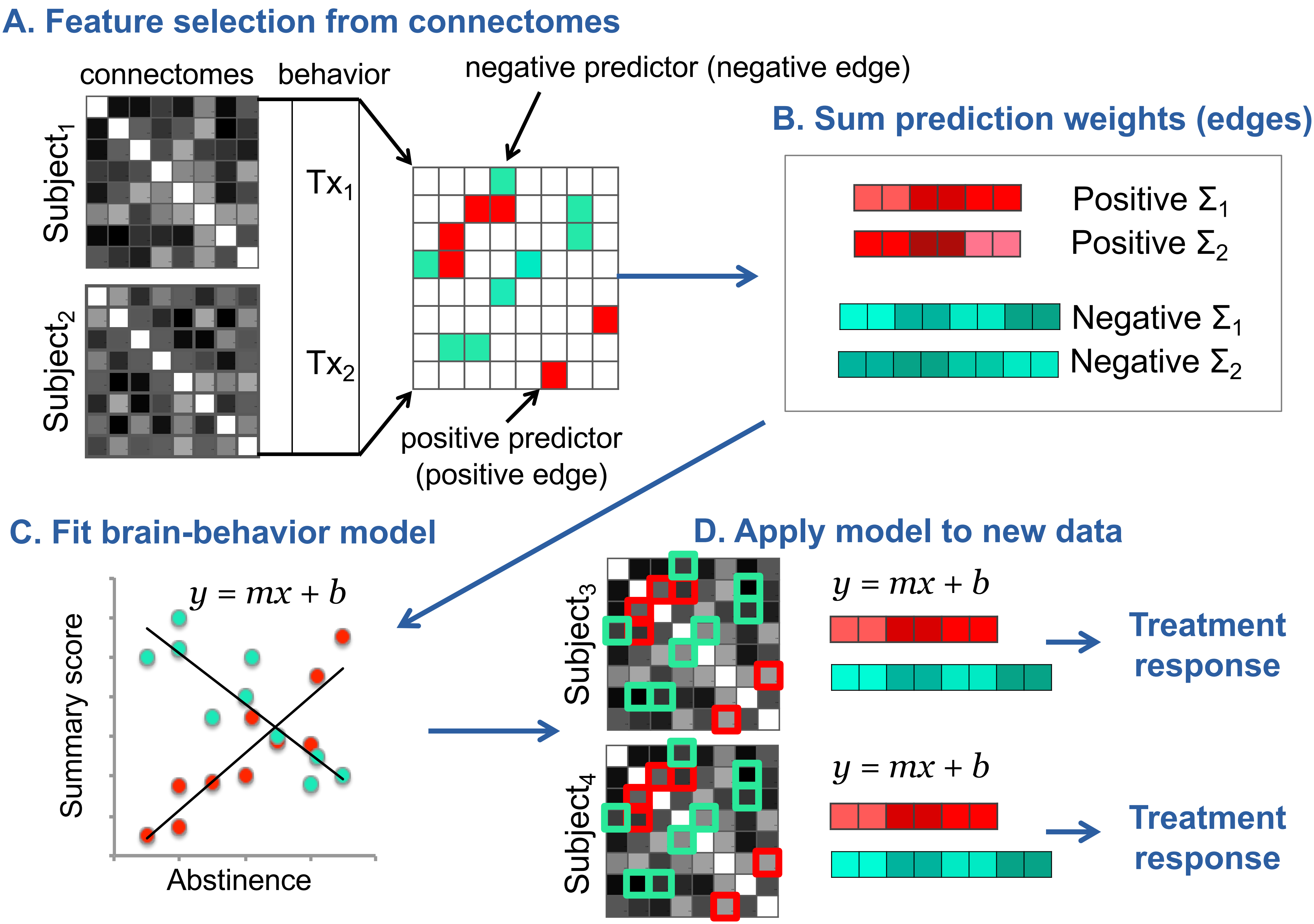
Sarah D. Lichenstein[1✉], Robert Kohler[1], Fengdan Ye[2], Marc N. Potenza[1,3,4,5,6,7], Brian Kiluk[1] and Sarah W. Yip[1,3]

A. Feature selection from connectomes



B. Sum prediction weights (edges)

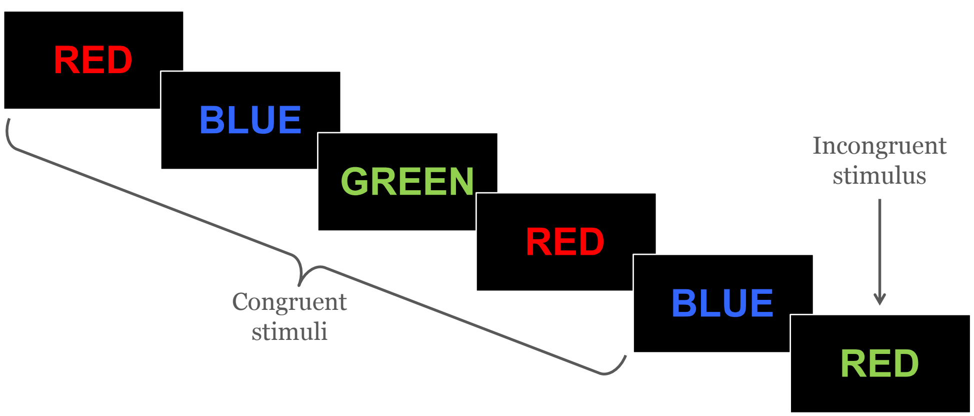



A. Feature selection from connectomes
connectomes
behavior
Subject$_1$
Subject$_2$
Tx$_1$
Tx$_2$
negative predictor (negative edge)
positive predictor
(positive edge)
B. Sum prediction weights (edges)
Positive Σ$_1$
Positive Σ$_2$
Negative Σ$_1$
Negative Σ$_2$
C. Fit brain-behavior model
$y = mx + b$
Summary score
Abstinence
D. Apply model to new data
Subject$_3$
Subject$_4$
$y = mx + b$
Treatment response
$y = mx + b$
Treatment response

Task ('brain state') selection

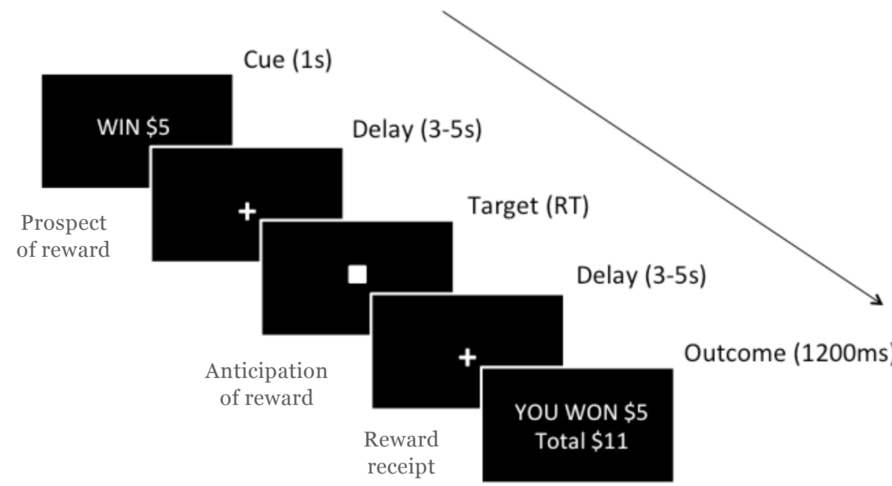
Opioid abstinence

cognitive control task (n=71)



Cocaine abstinence

reward task (n=72)

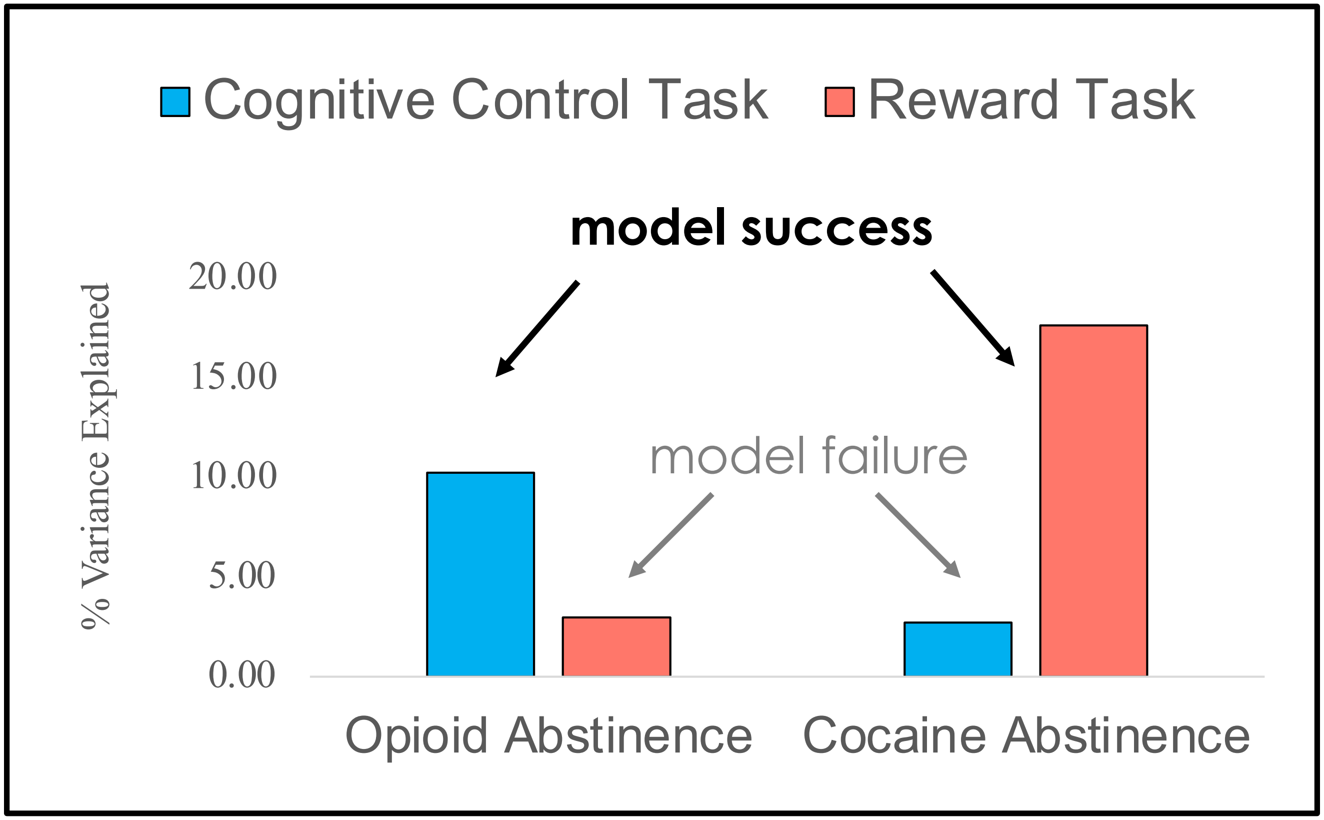


connectomes

ML model

% drug free Utox

Brain-state specific prediction of abstinence

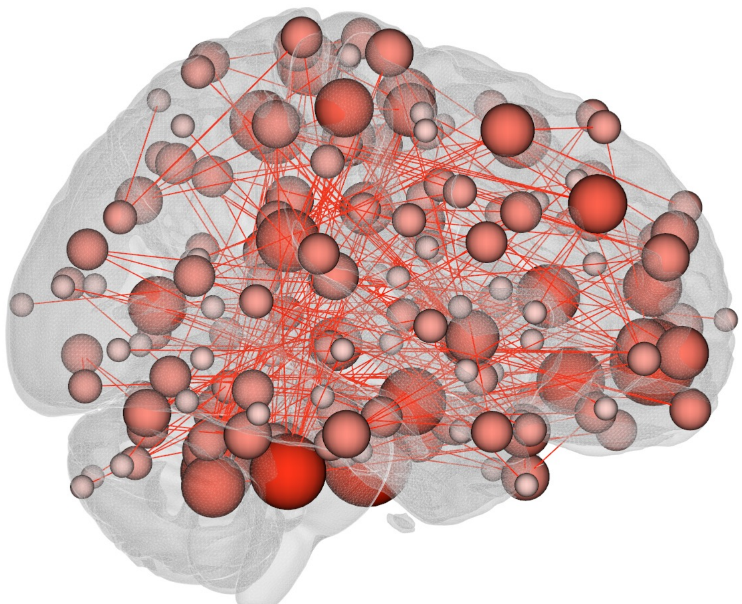


Cocaine network replicated in 2 independent samples**

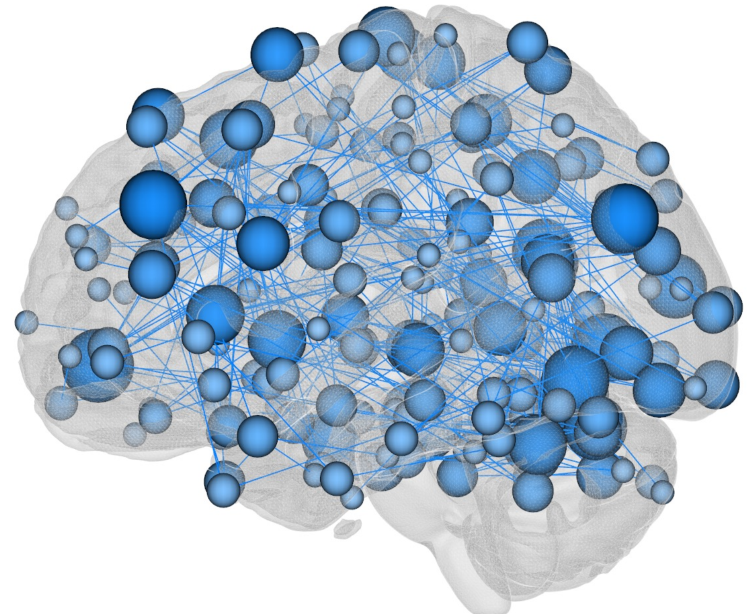
Yip et al., *American Journal of Psychiatry*, 2019*

Lichenstein, et al., *Molecular Psychiatry*, 2021, 2023*

Cocaine abstinence network*



Positive network – *increased* connectivity predicts abstinence

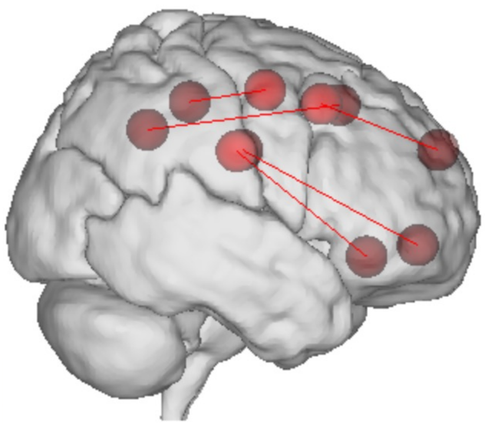


Negative network – *decreased* connectivity predicts abstinence

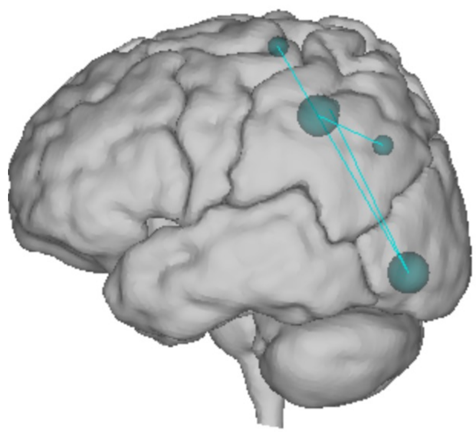
*only 539 connections, <2% of possible connections

Dissociable opioid and cocaine networks

Consistent connections*

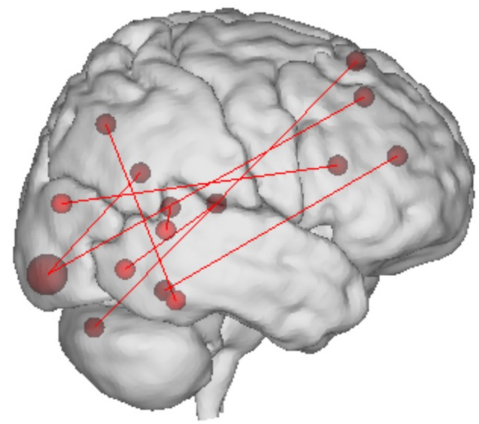


cocaine+
opioid+

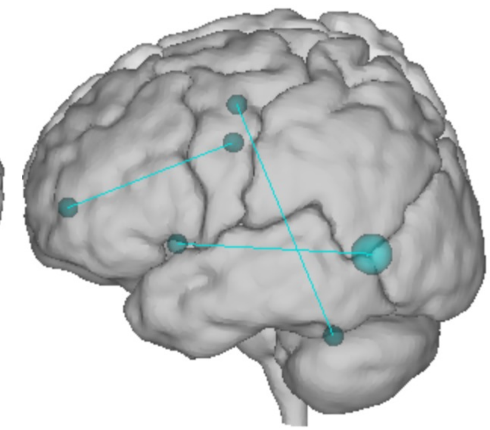


cocaine-
opioid-

Opposing connections



cocaine+
opioid-



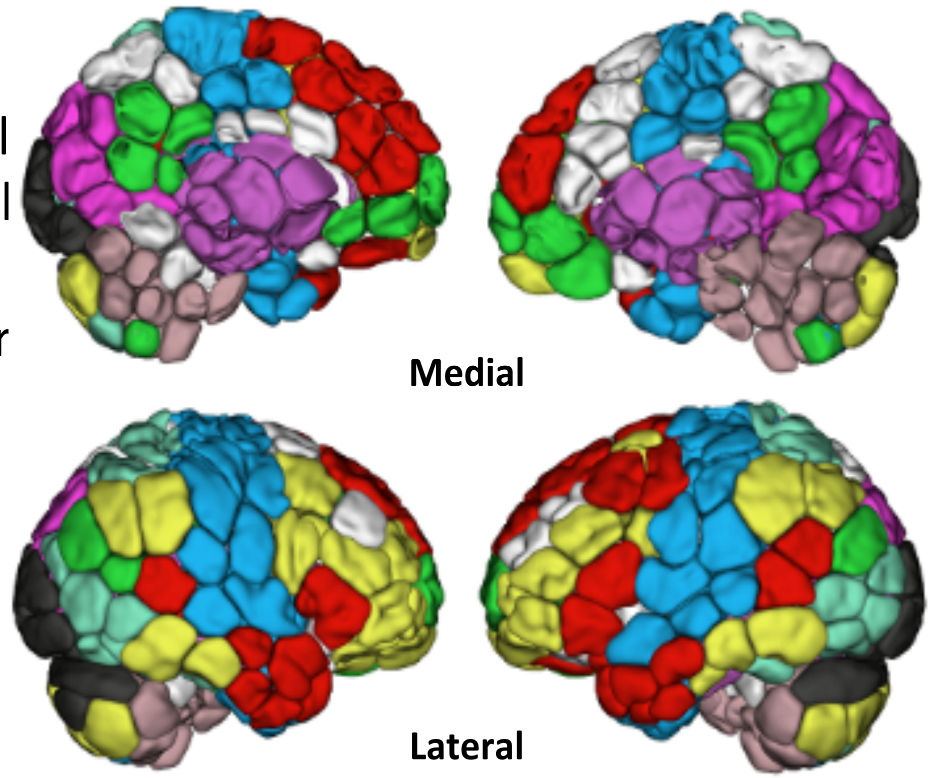
cocaine-
opioid+

*8 shared connections out of ~500

‘Canonical’ networks

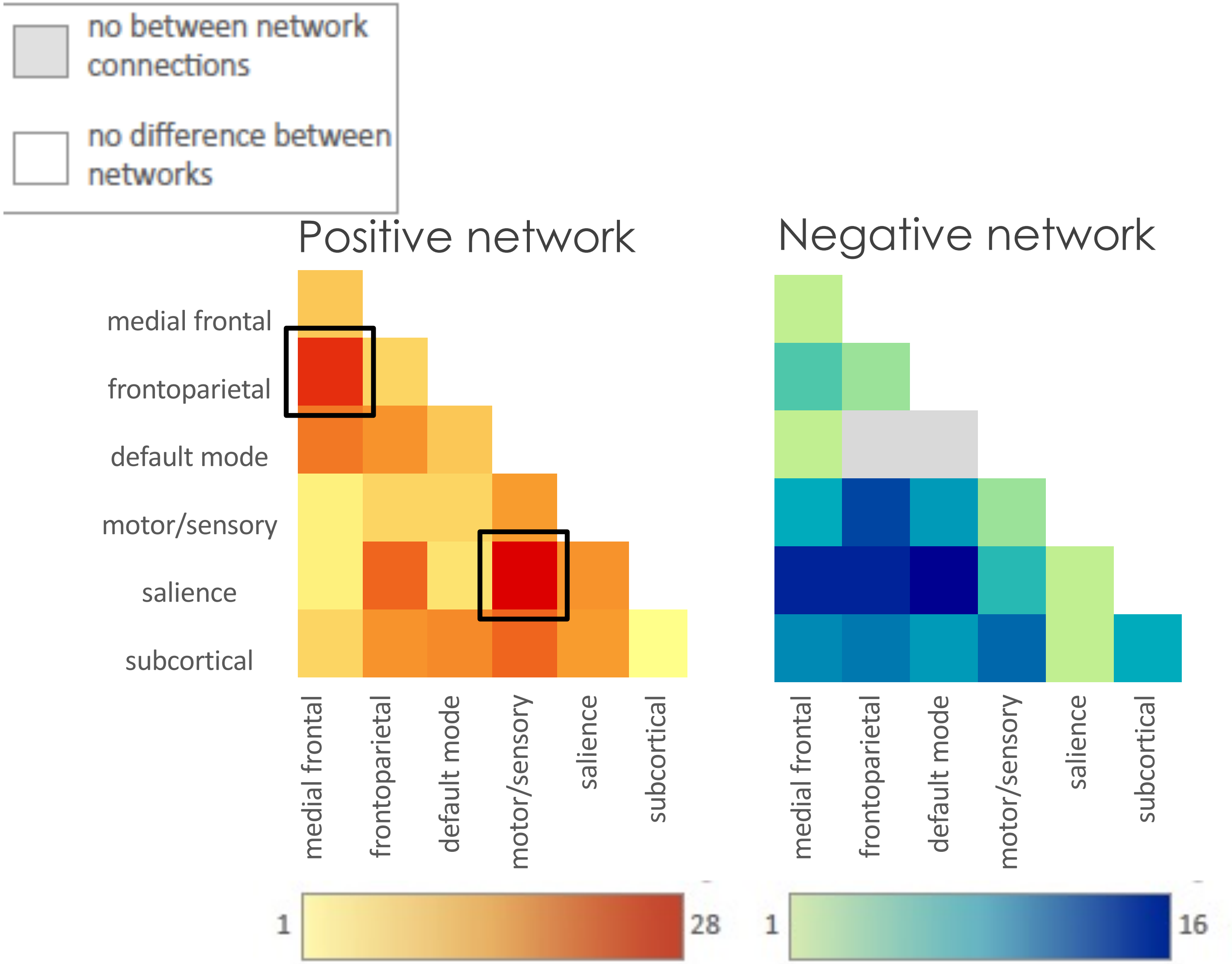
Networks

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



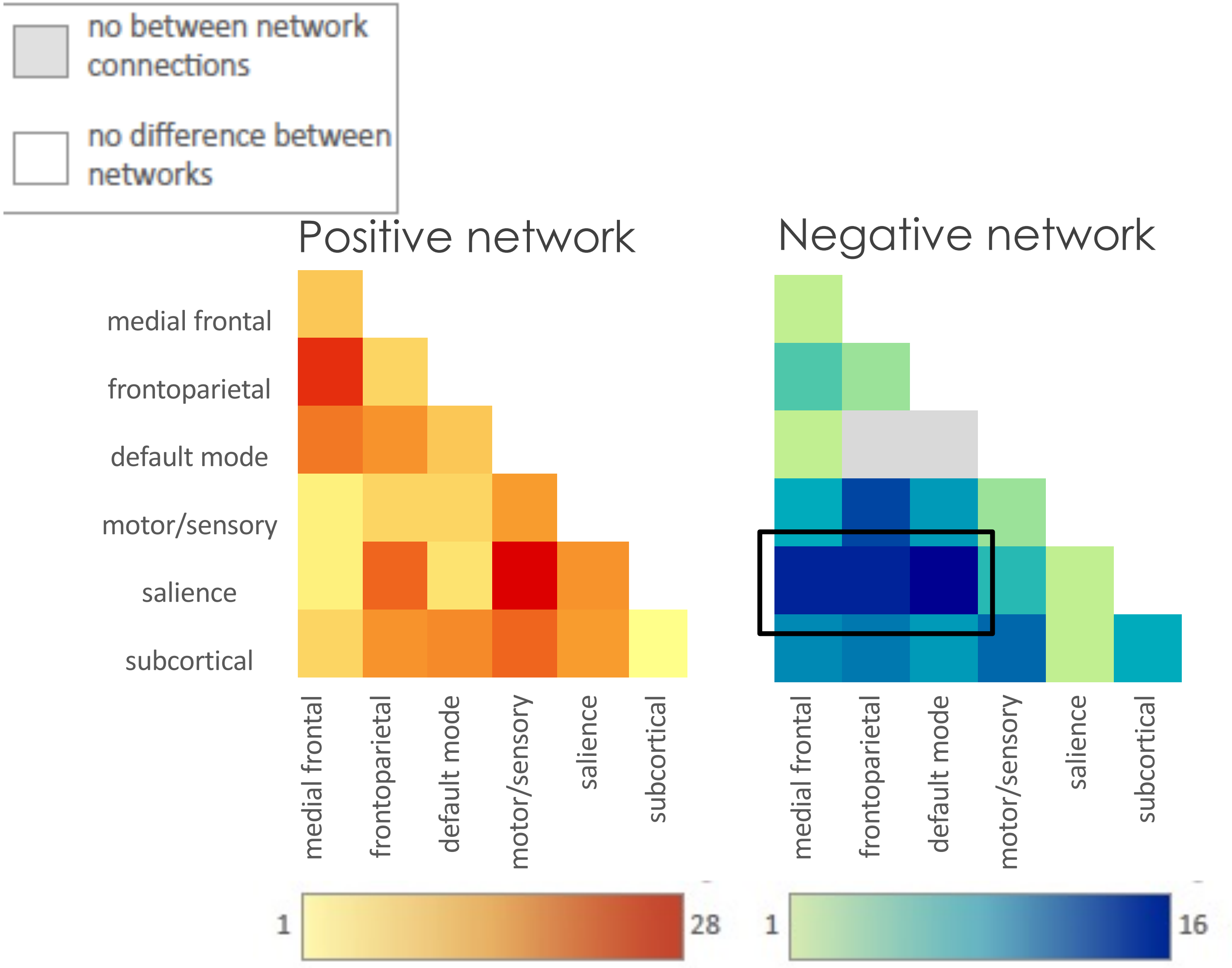
Horien et al., *Neuroimage*, 2019

Cocaine network connectivity



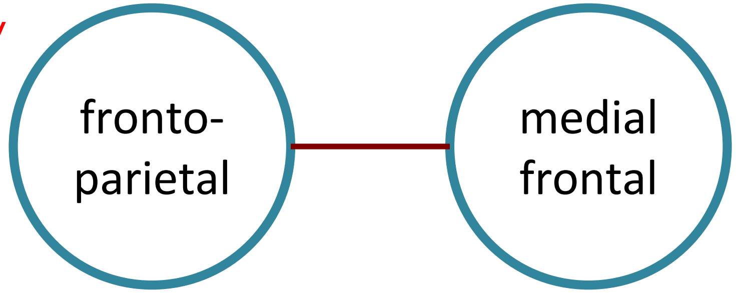
Yip et al., *American Journal of Psychiatry*, 2019

Cocaine network connectivity



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

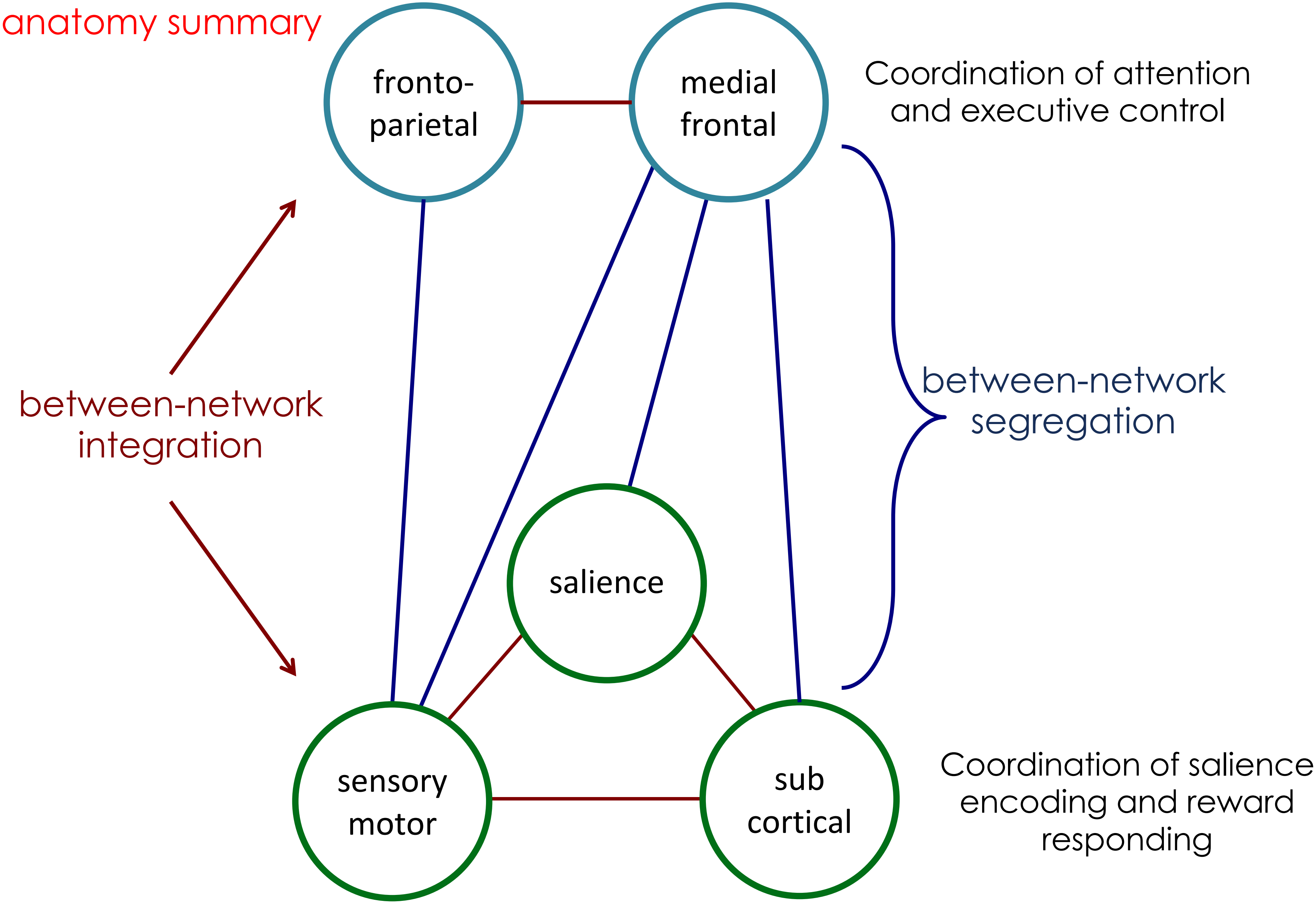
Cocaine network anatomy summary



Coordination of attention and executive control

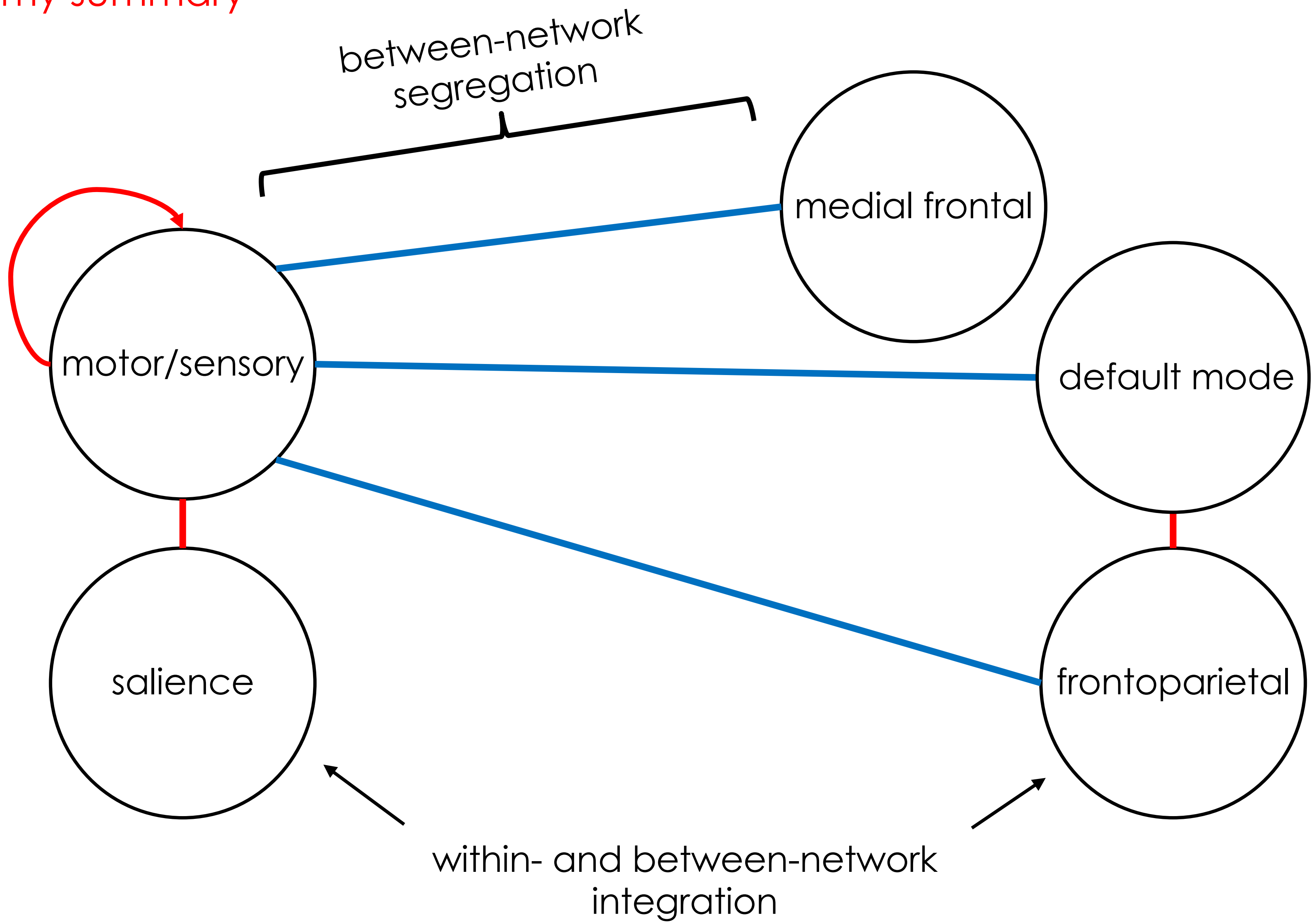
Yip et al., *American Journal of Psychiatry*, 2019

Cocaine network anatomy summary



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

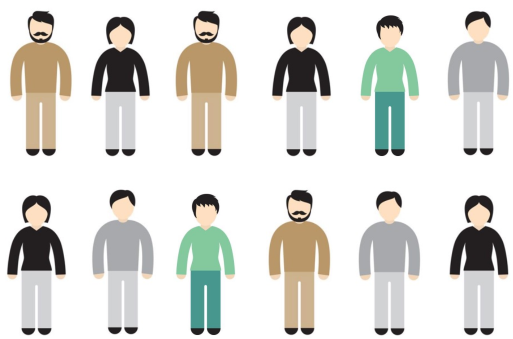
Opioid network anatomy summary



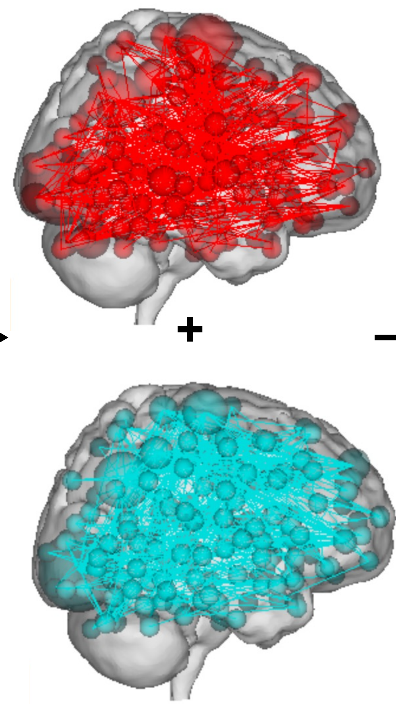
Lichenstein et al., *Molecular Psychiatry*, 2021

Post-treatment connectivity predicts post-treatment abstinence

Post-treatment fMRI (n=40)



→



→

rho=0.34, *p*=0.03*
rho=0.40, *p*<0.01#

no changes in connectivity over time

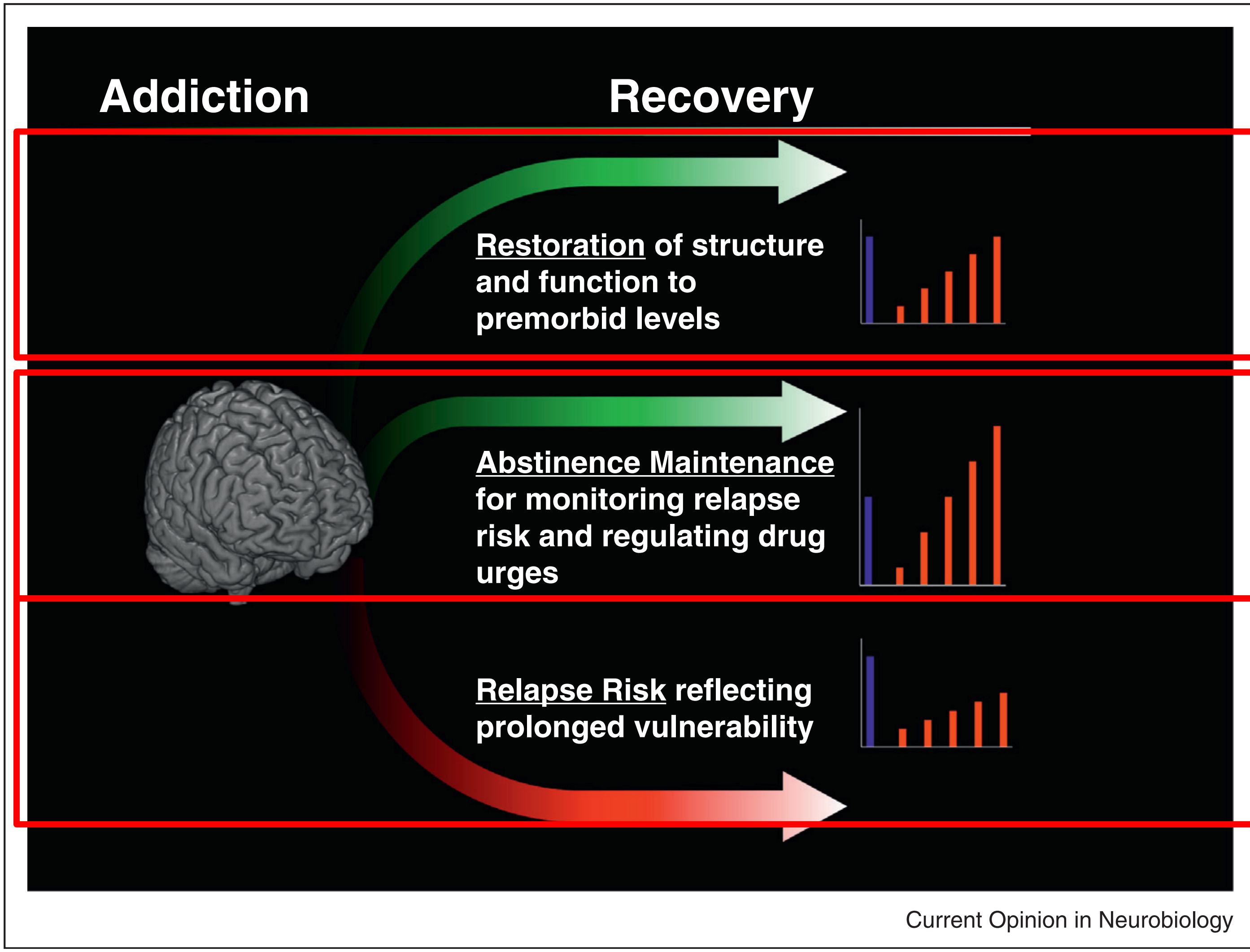
*cocaine, #opioid

Pathology versus prediction

- Pathophysiology may not predict abstinence
  - what changes w/ abstinence ≠ predict tx
- Initial vs 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



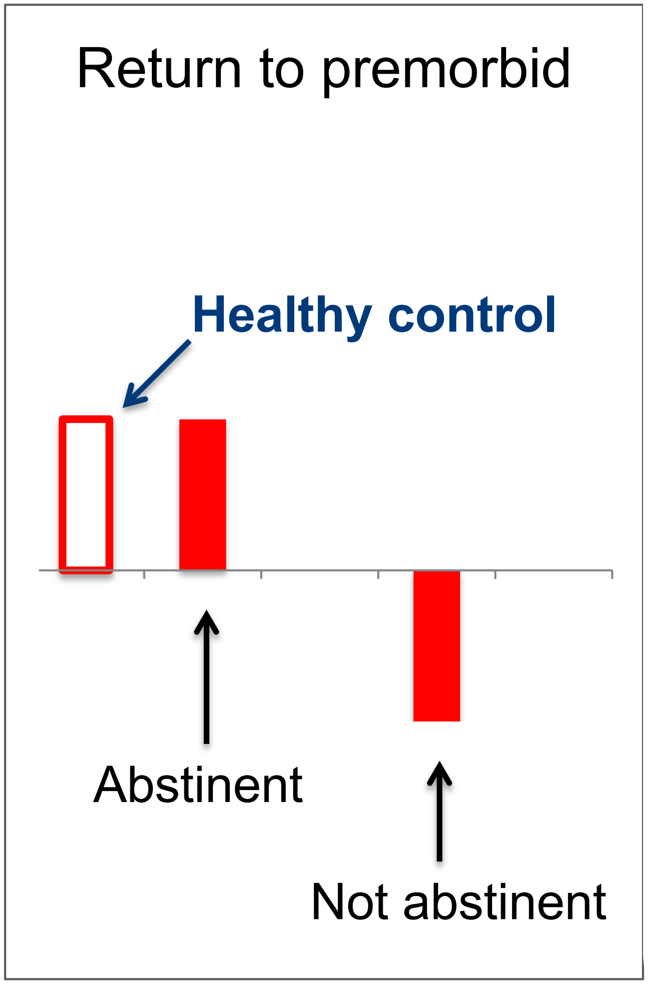
Return to premorbid levels

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

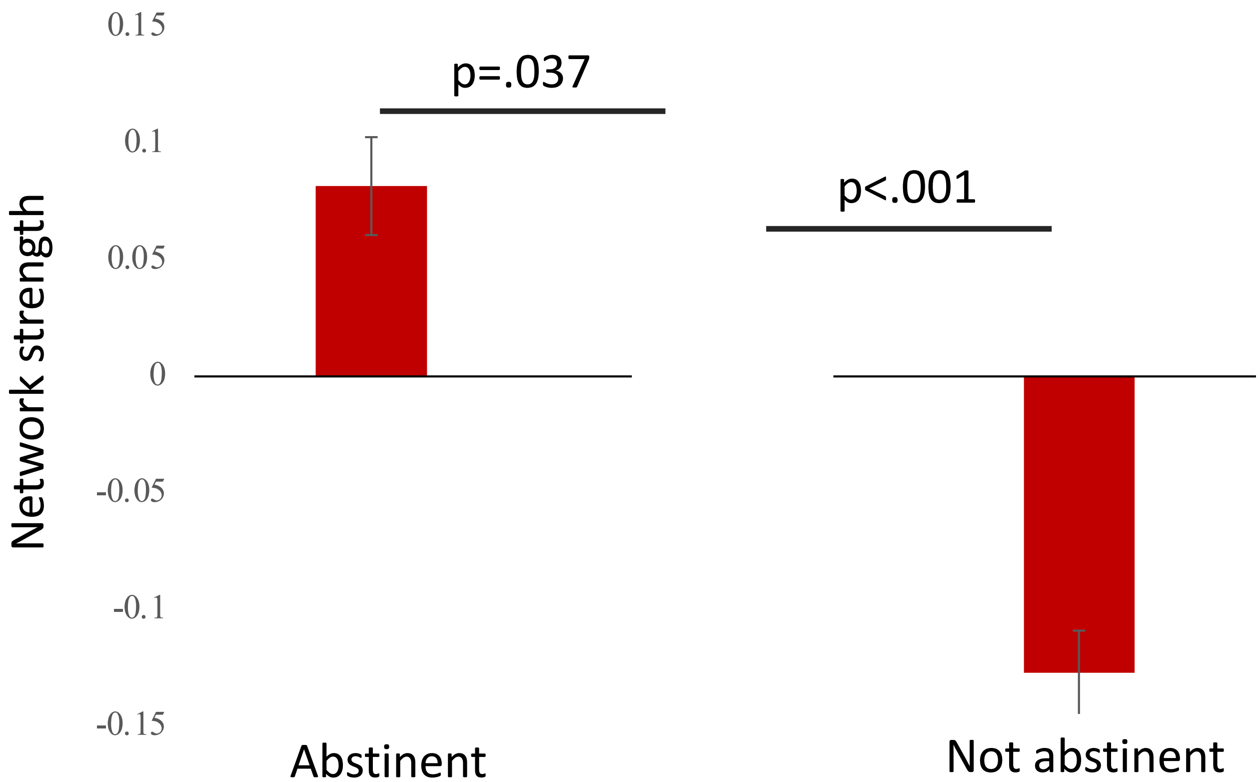
Recruited from RCT for CUD + methadone treatment for OUD

35 years old (SD=9.37)

74% male

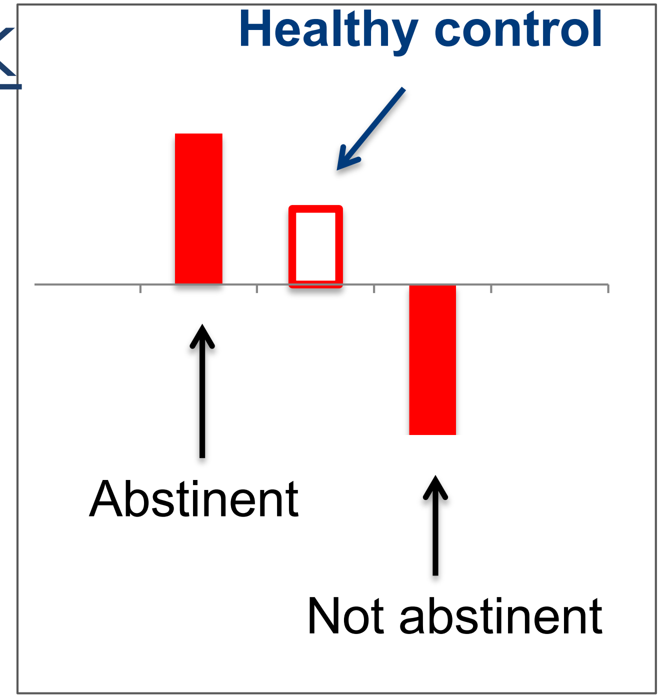
identical acquisition, tasks & connectivity pipeline

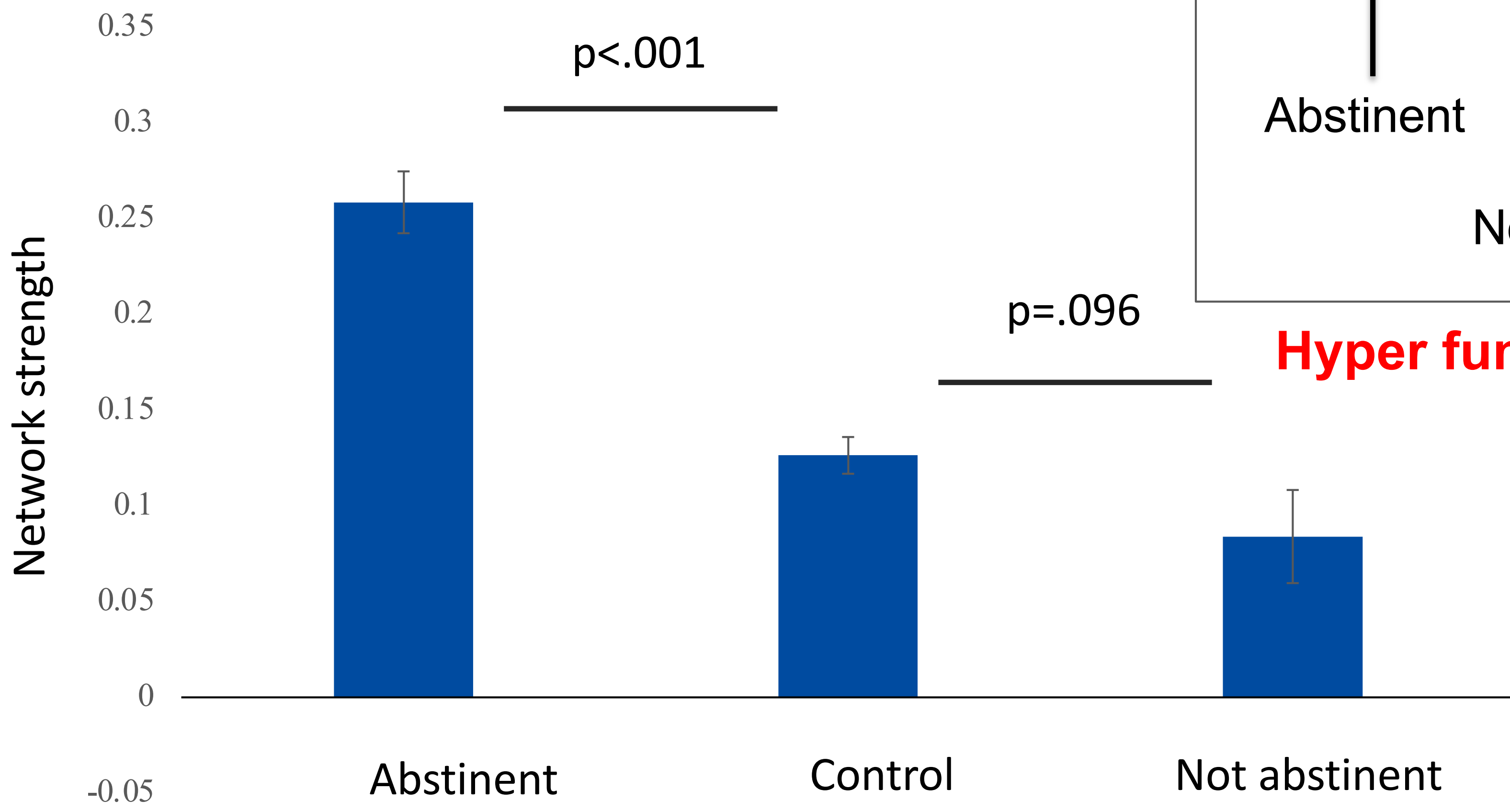
Cocaine network



Lichenstein et al., *Molecular Psychiatry*, 2021

Opioid network





Hyper functionality

Lichenstein et al., *Molecular Psychiatry*, 2021

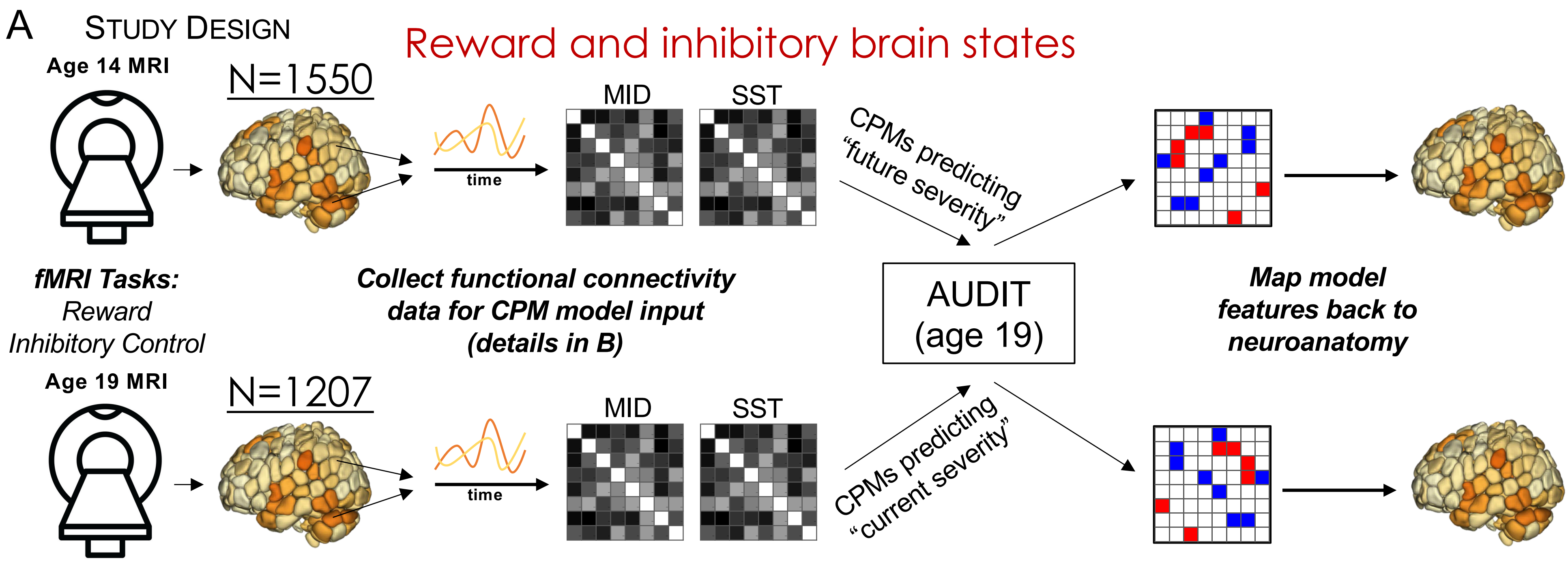
What about addiction risk?

Welcome to the IMAGEN Study

London | Nottingham | Dublin | Paris

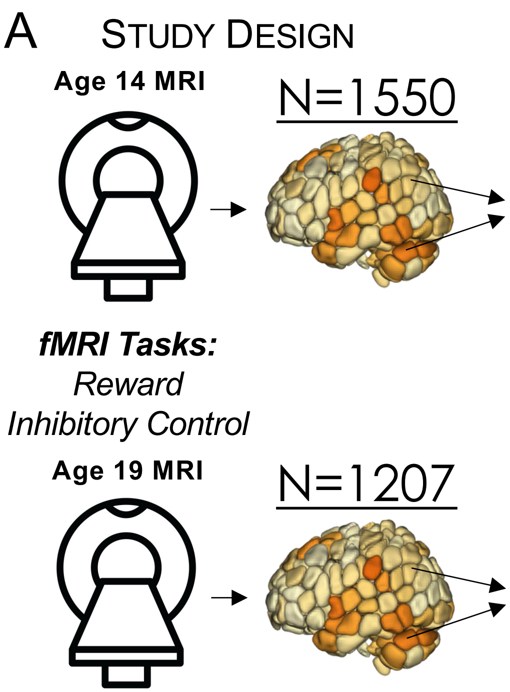
Berlin | Dresden | Hamburg | Mannheim

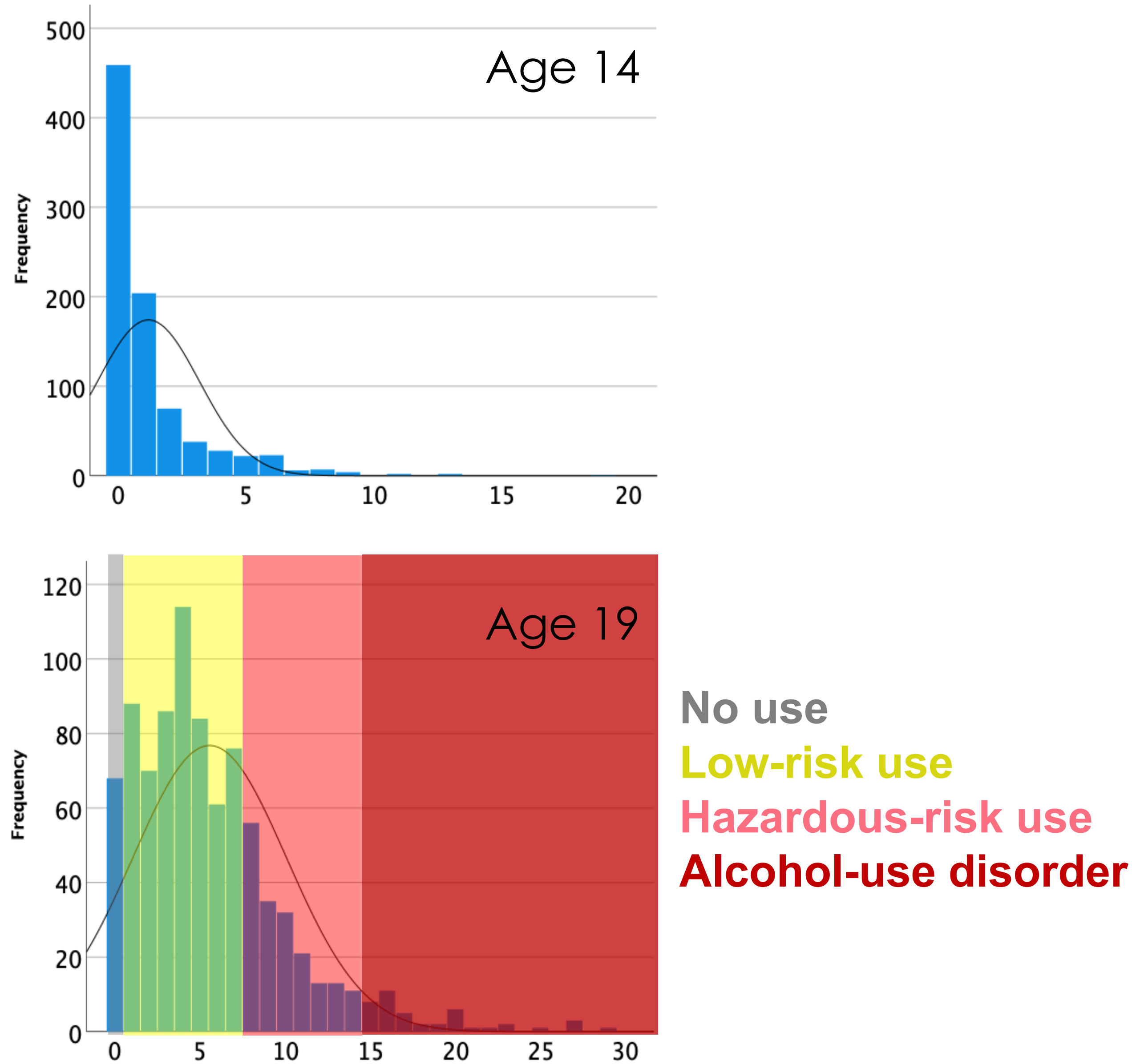
Sex-specific neuromarkers of alcohol use



Yip et al., JAMA Psychiatry, 2023

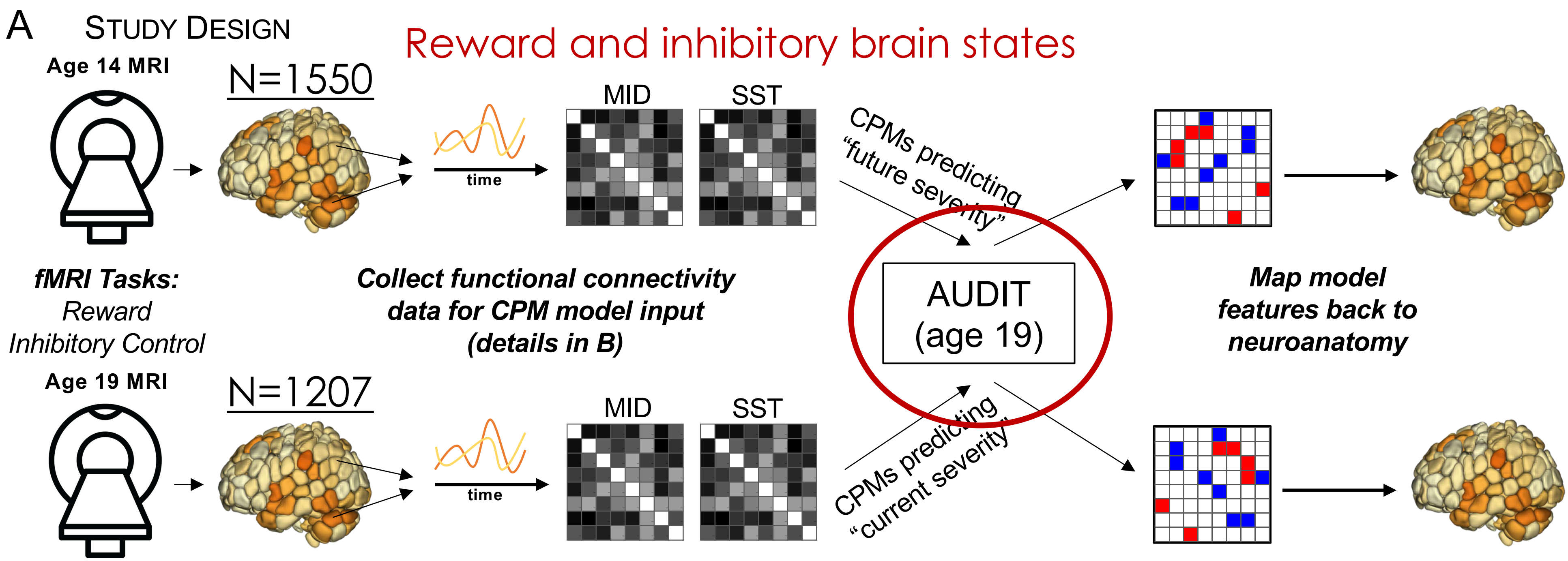
Study design + analysis workflow



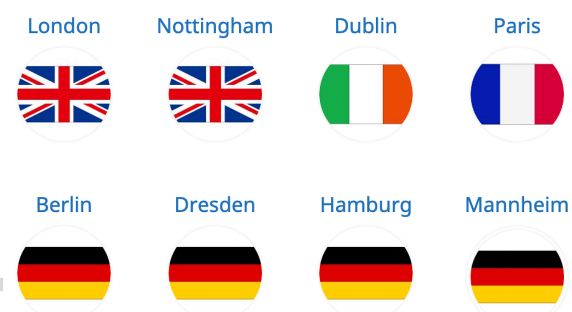


Yip et al., JAMA Psychiatry, 2023

Sex-specific neuromarkers of alcohol use

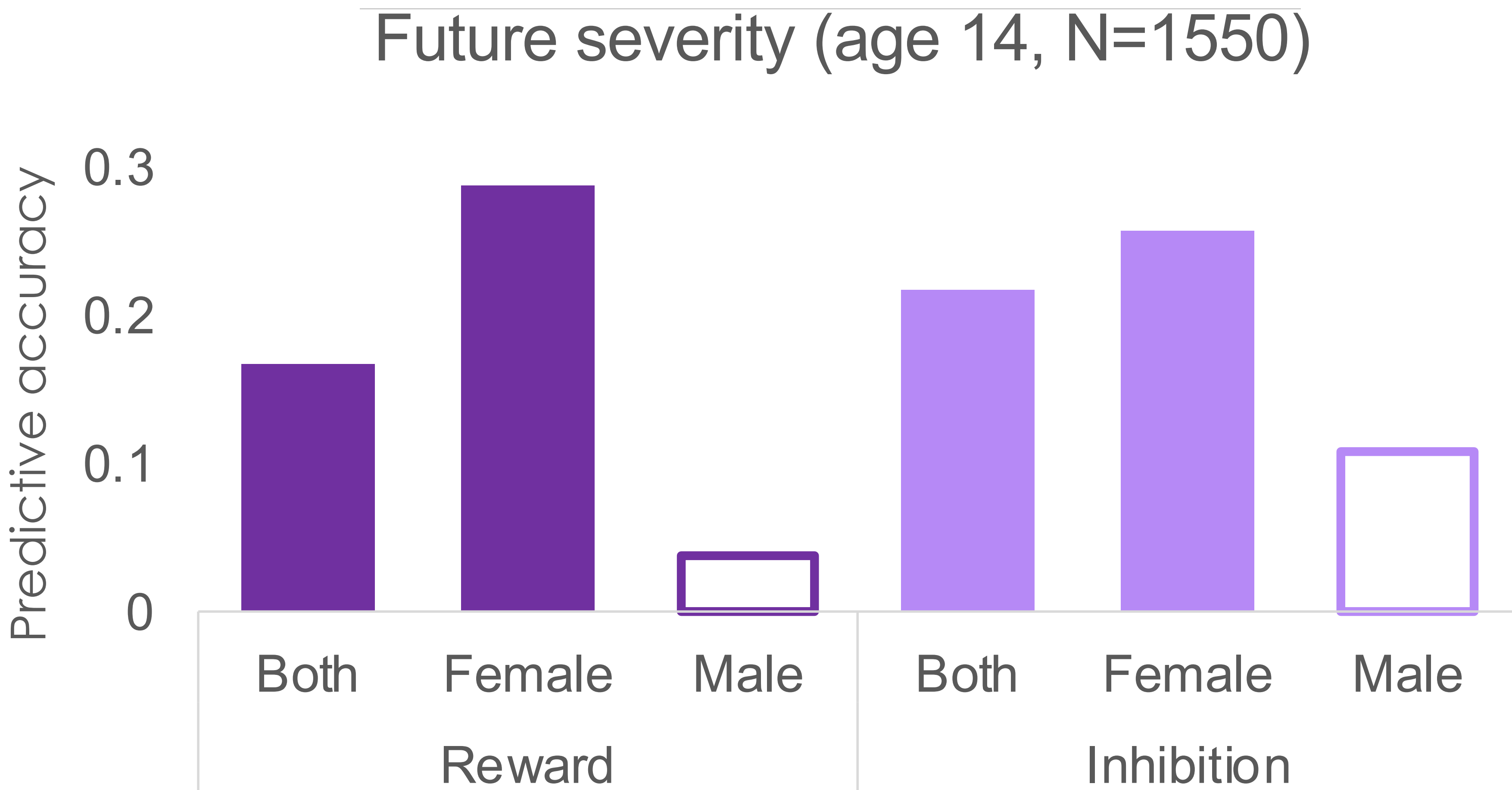


Leave-one-site-out prediction



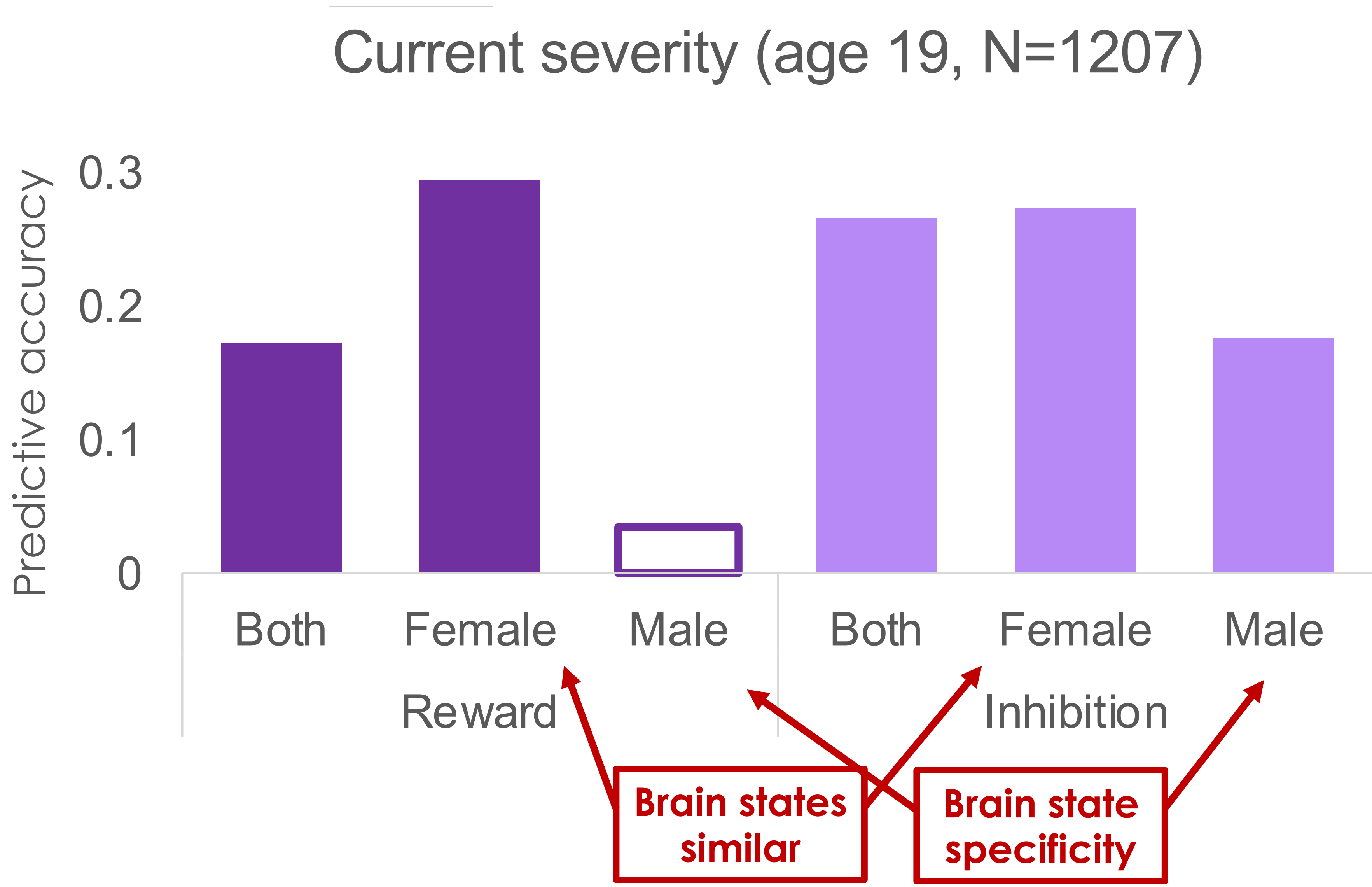
Yip et al., JAMA Psychiatry, 2023

Leave-one-site-out prediction of alcohol-use



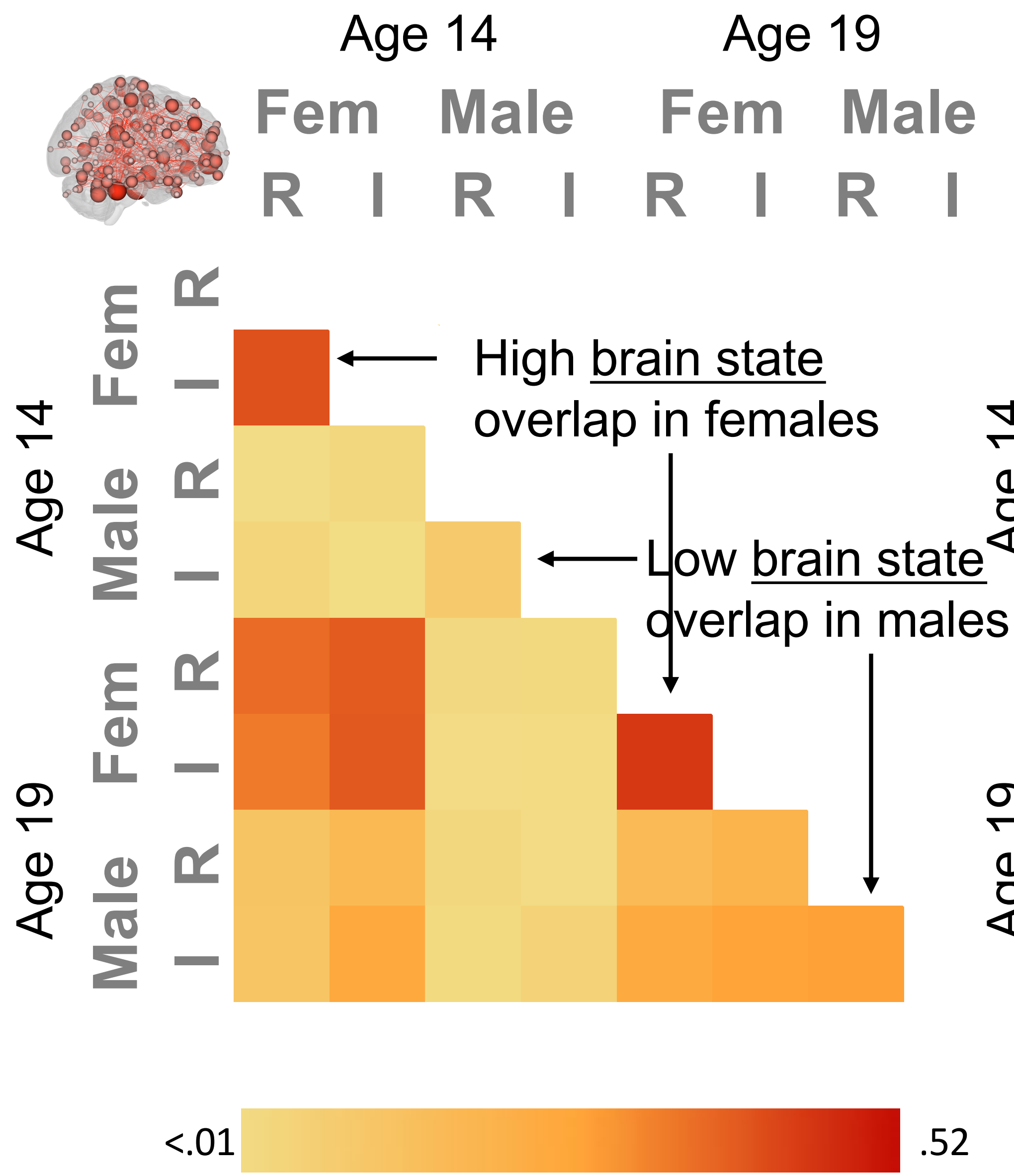
Yip et al., JAMA Psychiatry, 2023

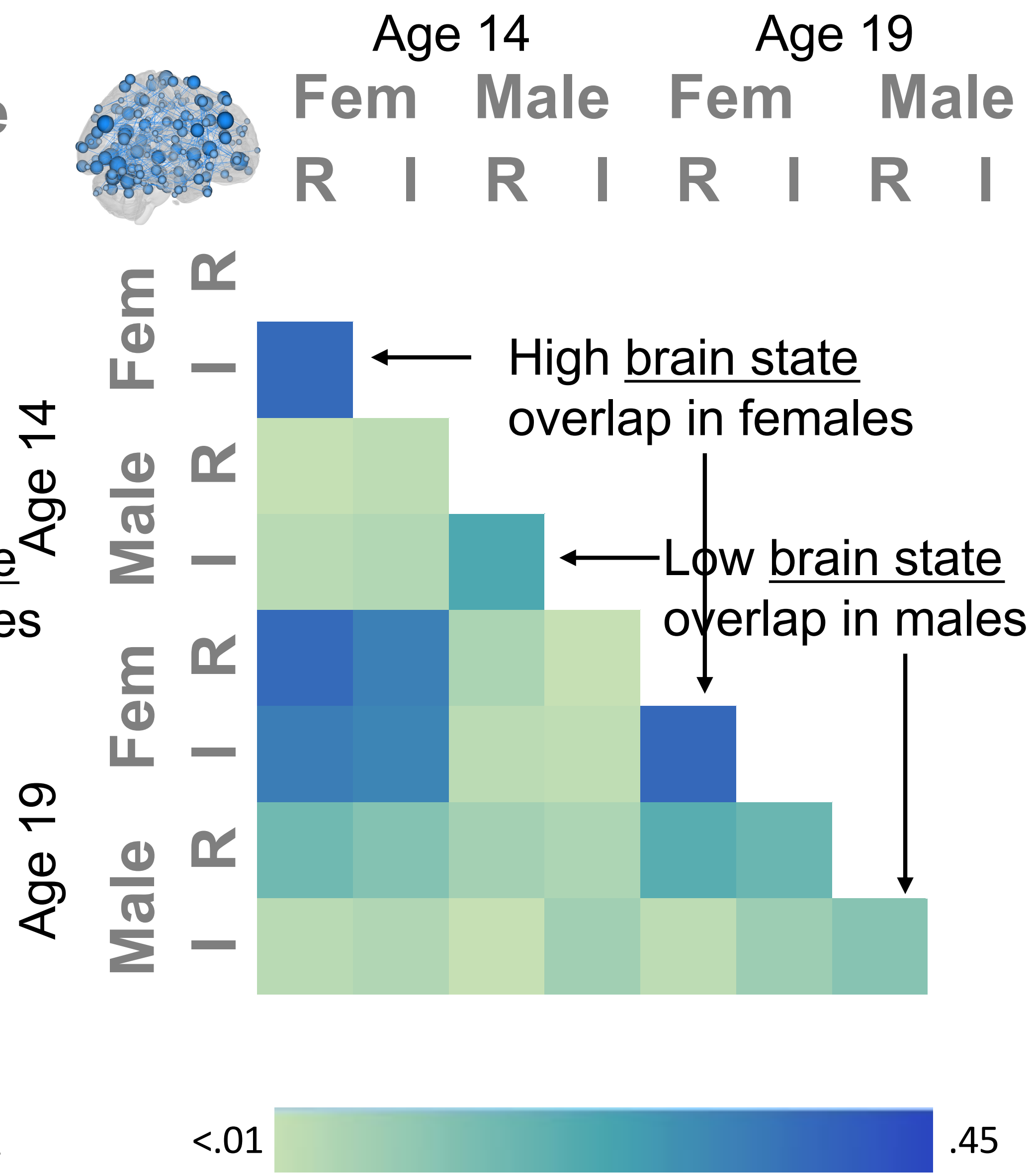
Leave-one-site-out prediction of alcohol-use



Yip et al., JAMA Psychiatry, 2023

Network overlap across models and states





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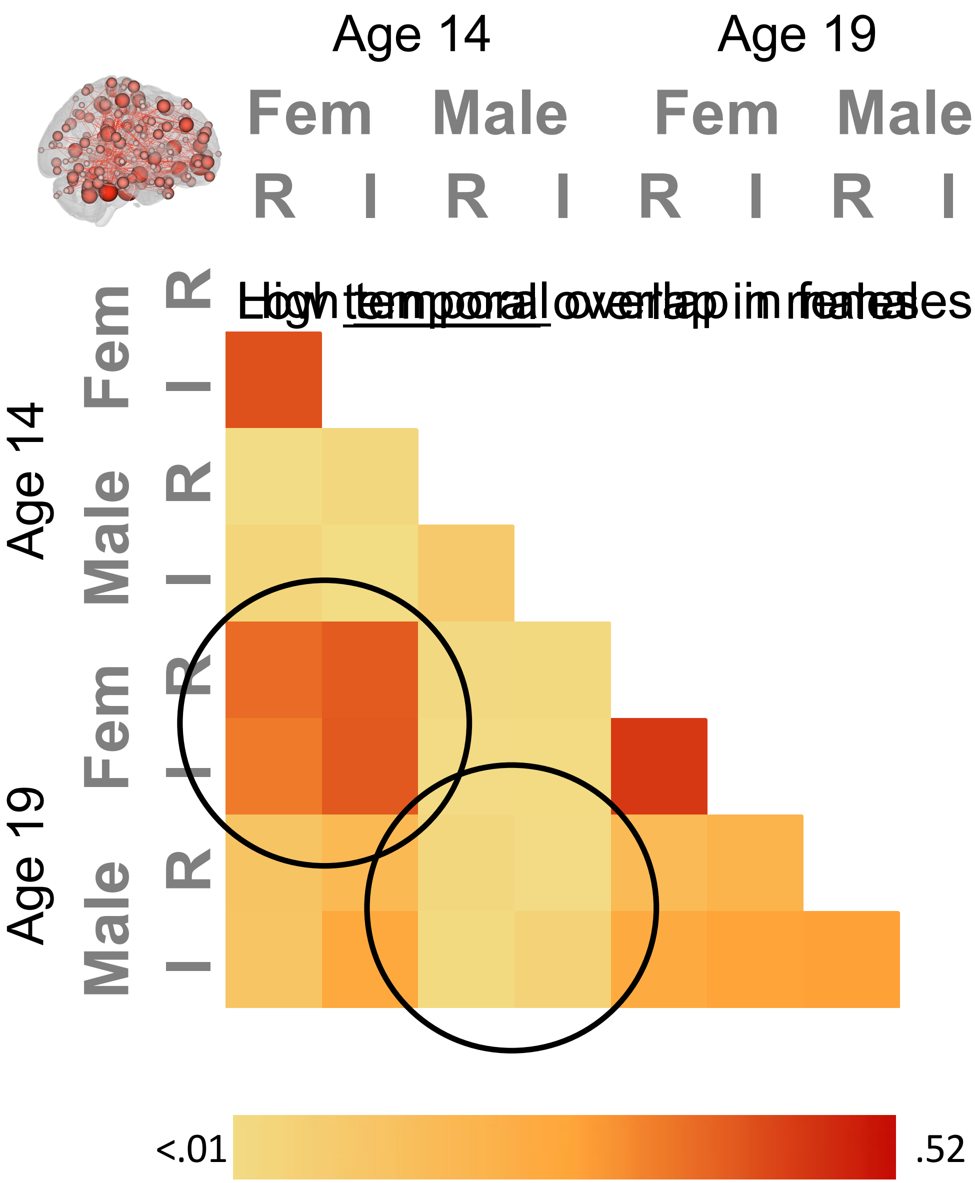
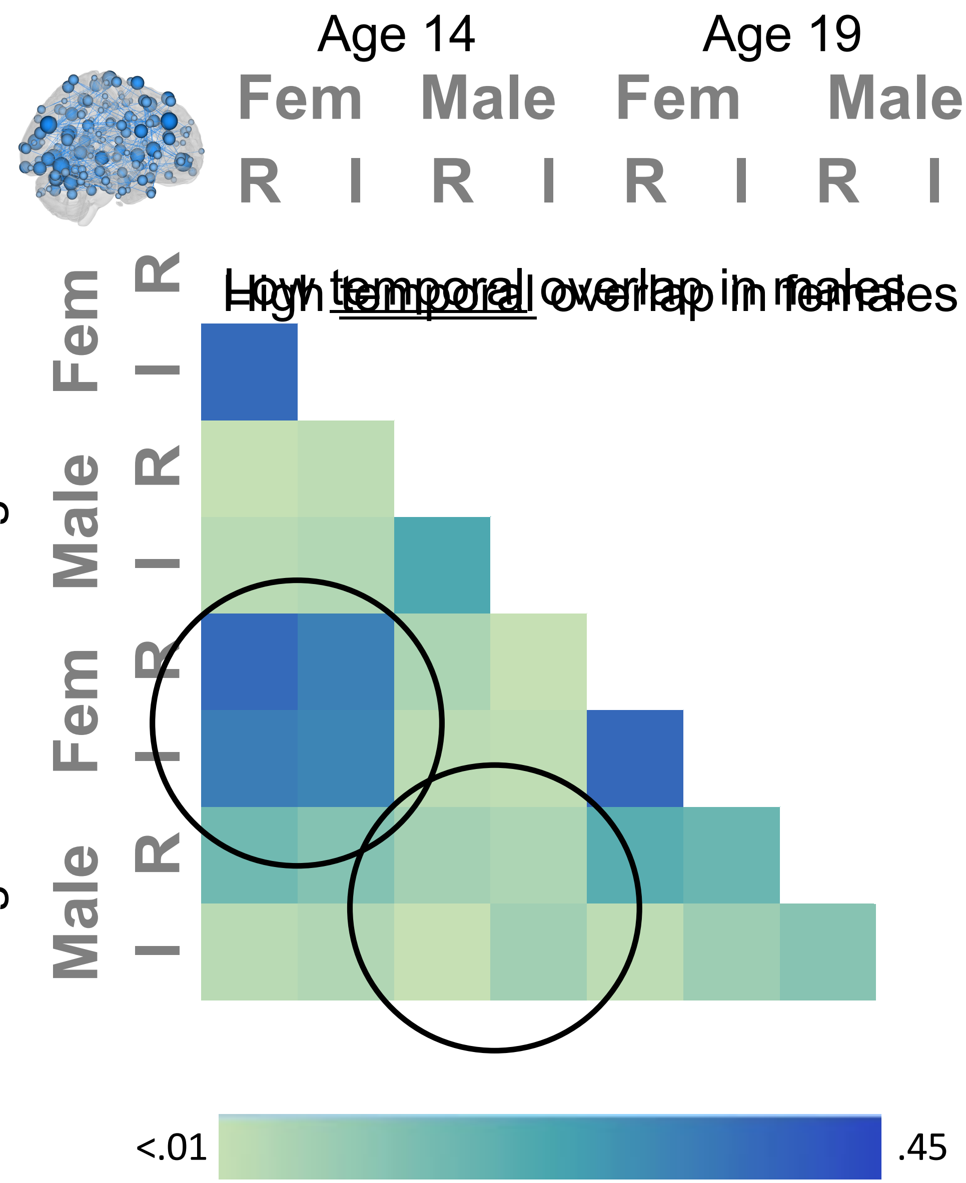
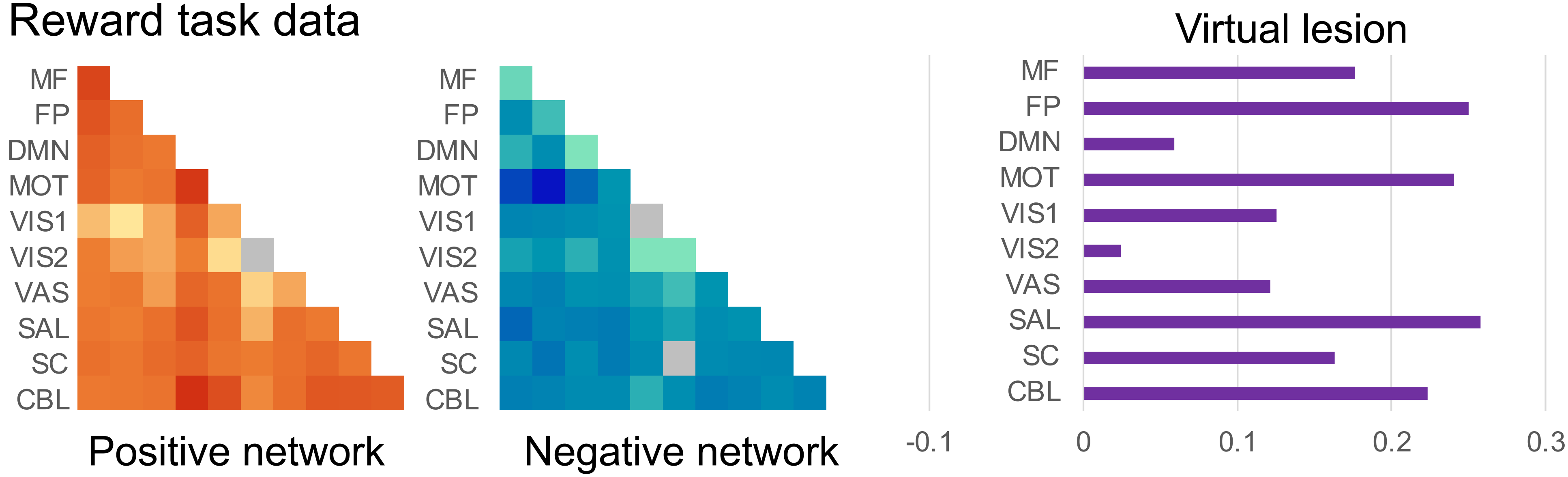


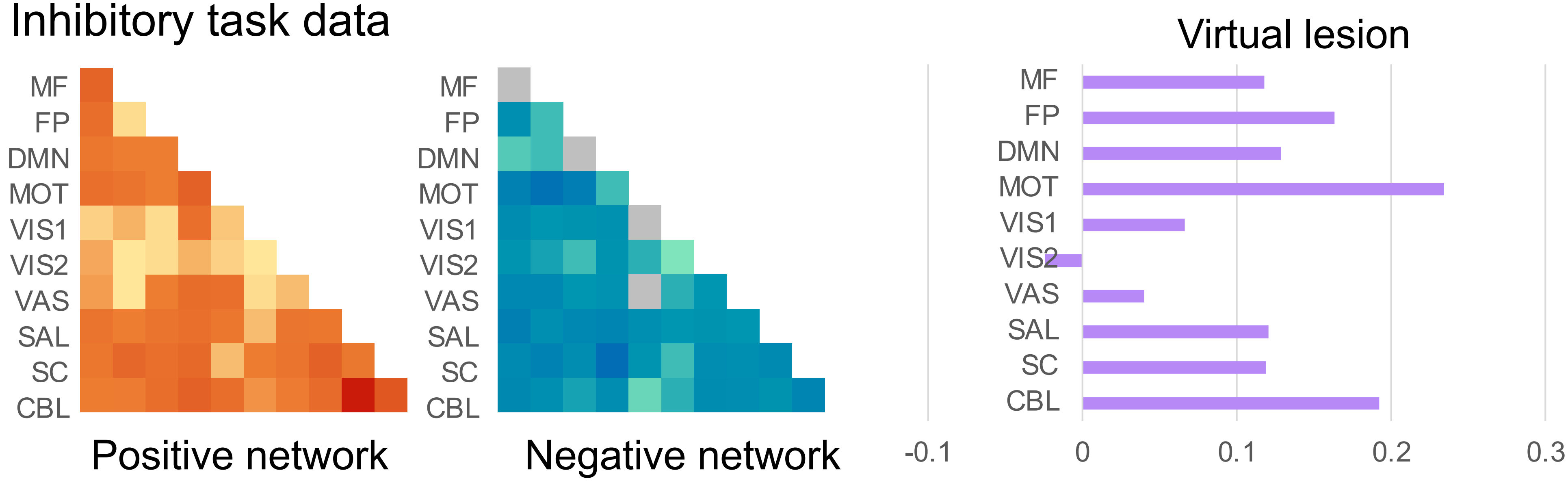


Female network anatomy, age 14

A. Reward task data



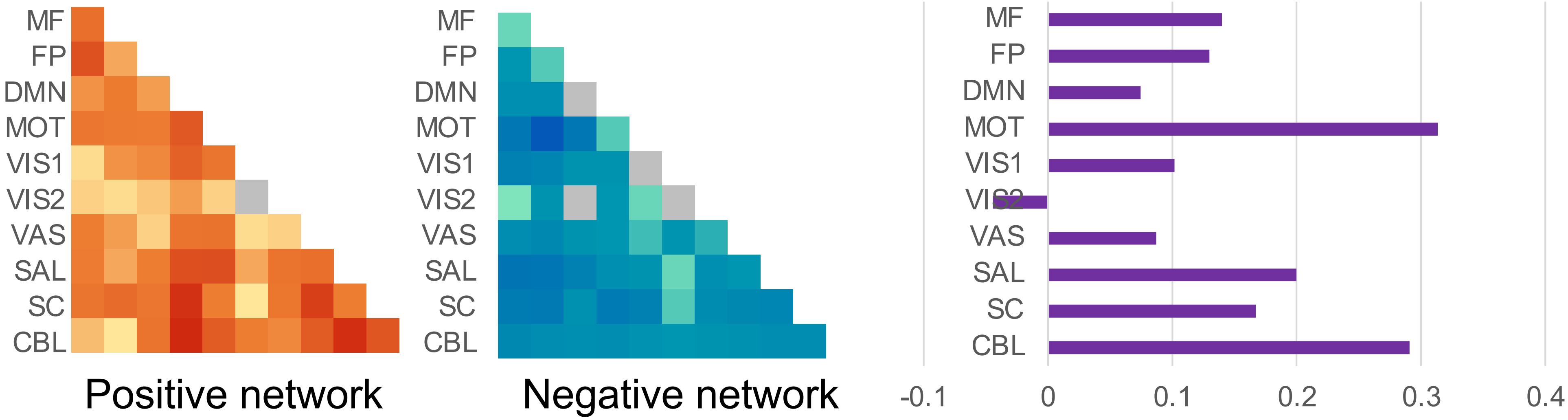
B. Inhibitory task data



Female network anatomy, age 19

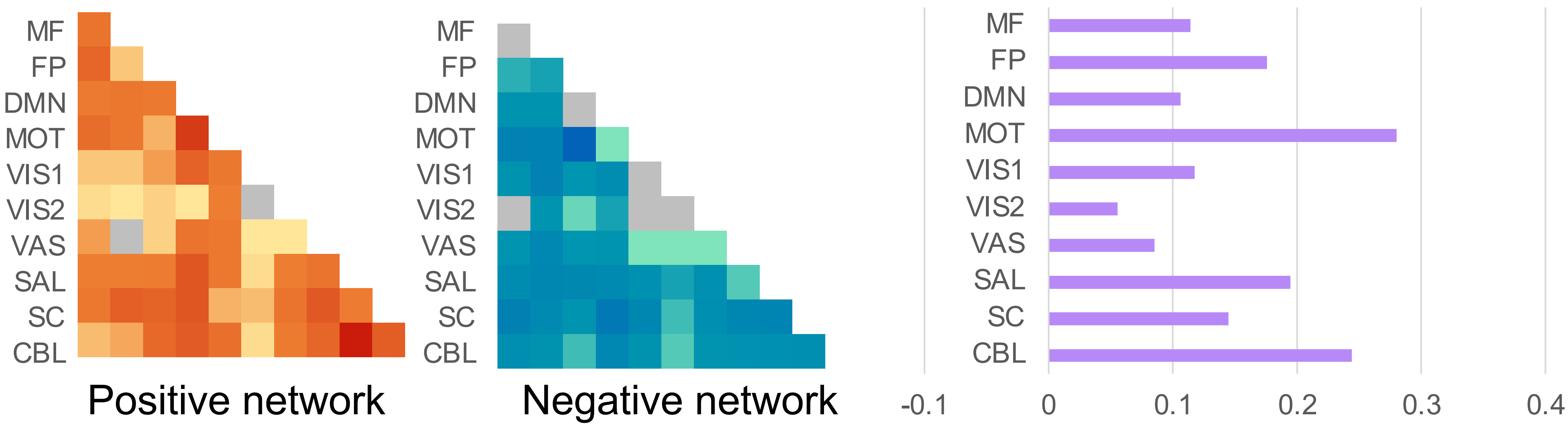
A. Reward task data

Virtual lesion



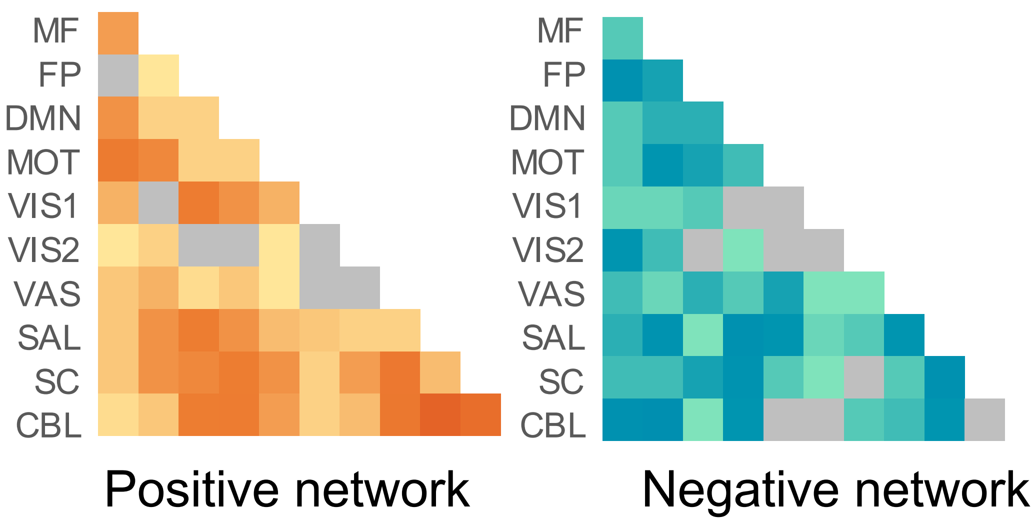
B. Inhibitory task data

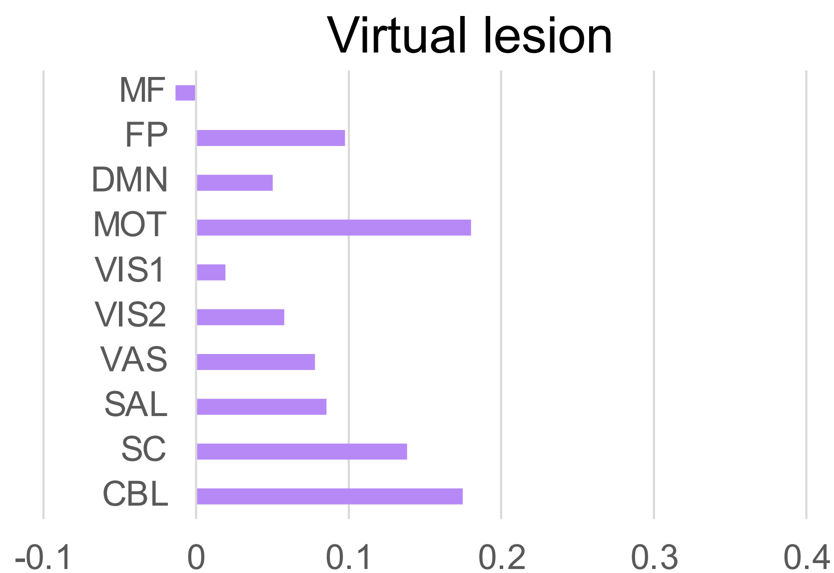
Virtual lesion



Male network anatomy, age 19

Inhibitory task data





Yip et al., JAMA Psychiatry, 2023

Sensitivity analyses

- Multi-task prediction (reward + inhibition):
  - Comparable performance in females (ages 14 & 19)
  - Decreased performance in males (age 19)
    - Not all brain states created equal

- Models robust and unchanged after controlling for:
  - Baseline alcohol-use (age 14)
  - Residual motion
  - Trait impulsivity
  - Trait neuroticism
  - Other substance use

specific to alcohol

Yip et al., JAMA Psychiatry, 2023

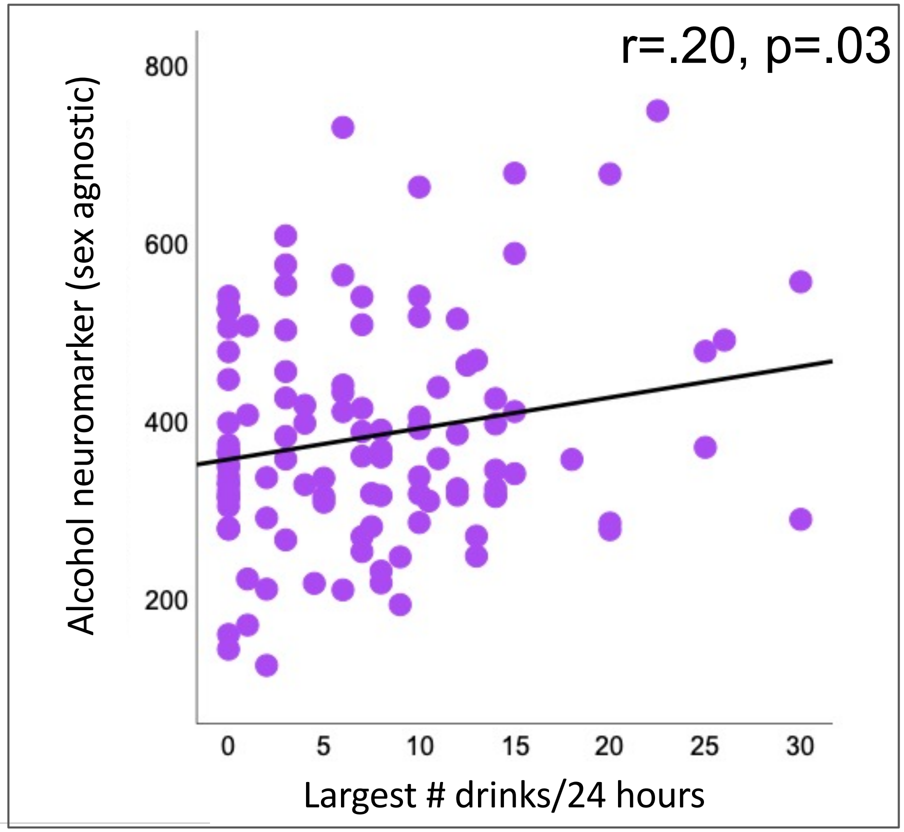
Independent sample replication (N=114)

Adolescents recruited in Connecticut, USA

Brain and Alcohol Research in College Students (BARCS)

Go/No-Go task

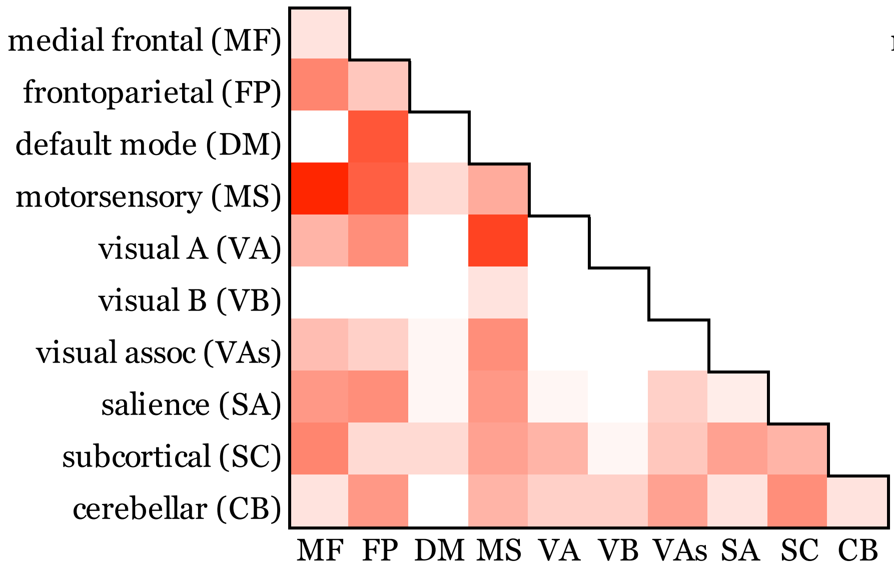
18.42 years old (SD=0.76)
54% male

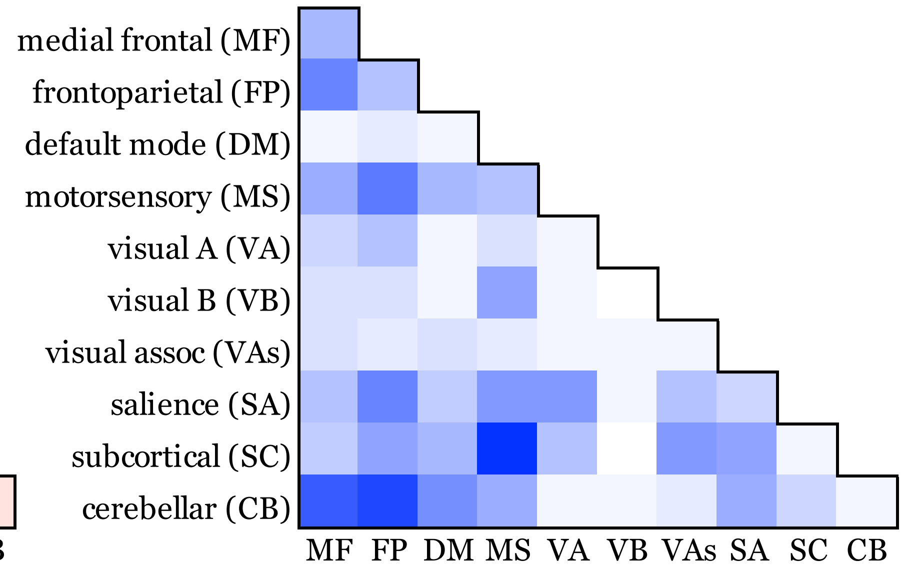


Different country, scanner, alcohol-use measure
Same underlying neurobiology!!!

Yip et al., JAMA Psychiatry, 2023

Cannabis-use in college students (n=191)





CPM identified a neural network of problem cannabis use in non-clinical sample (rho=.21, p=.009).

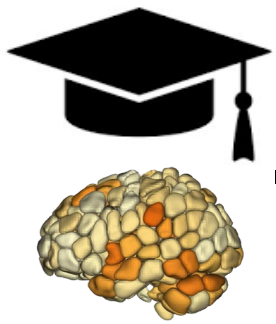
Replicated in geographically distinct adolescent sample (n=838, *t*=2.802 *p*=0.005).

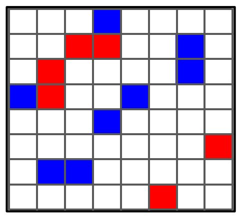
Dr. Sarah Lichenstein

Lichenstein et al., Under Revision, *Biological Psychiatry*

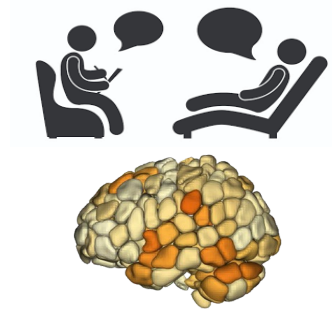
Network application in clinical sample (n=33)

Problem cannabis network identified in college sample





Applied to independent sample of patients entering cannabis treatment



Assess relationship with clinical characteristics

Patients with higher problem cannabis network strength:
- greater baseline addiction severity (rho=.38, p=.03)
- less abstinence during treatment (rho=-.38, p=.03)

Dr. Sarah Lichenstein

Lichenstein et al., Under Revision, *Biological Psychiatry*

Conclusions, recommendations & next steps

Abstinence & risk networks are...

Clinically relevant

- predict real-world outcomes

Externally valid

- generalize to novel settings and individuals

Robust

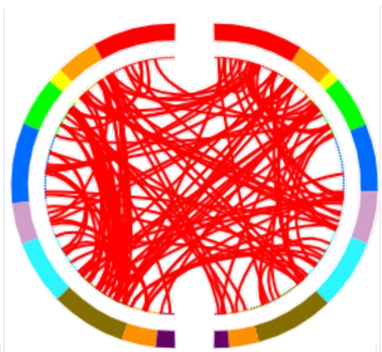
- predict after controlling for severity, related phenotypes

Biologically meaningful

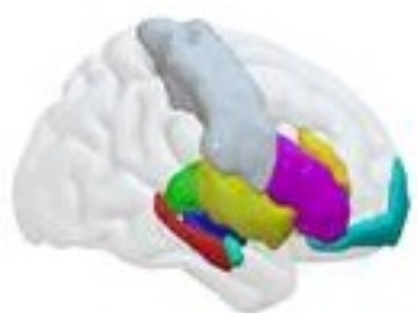
- *specific* connections subserving *specific* behaviors

Maximizing anatomical insights in connectome-wide association studies

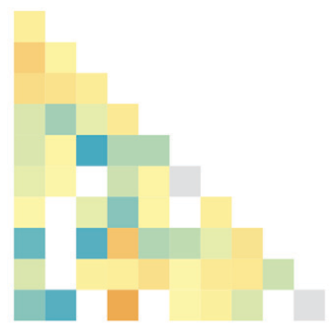
Connection / edge level



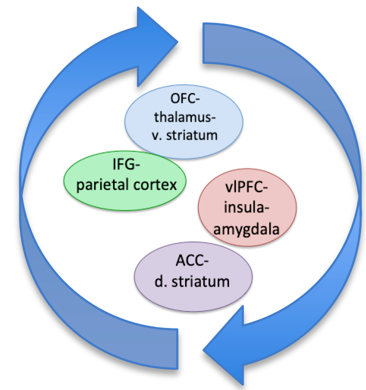
Region / node level



Network / systems level



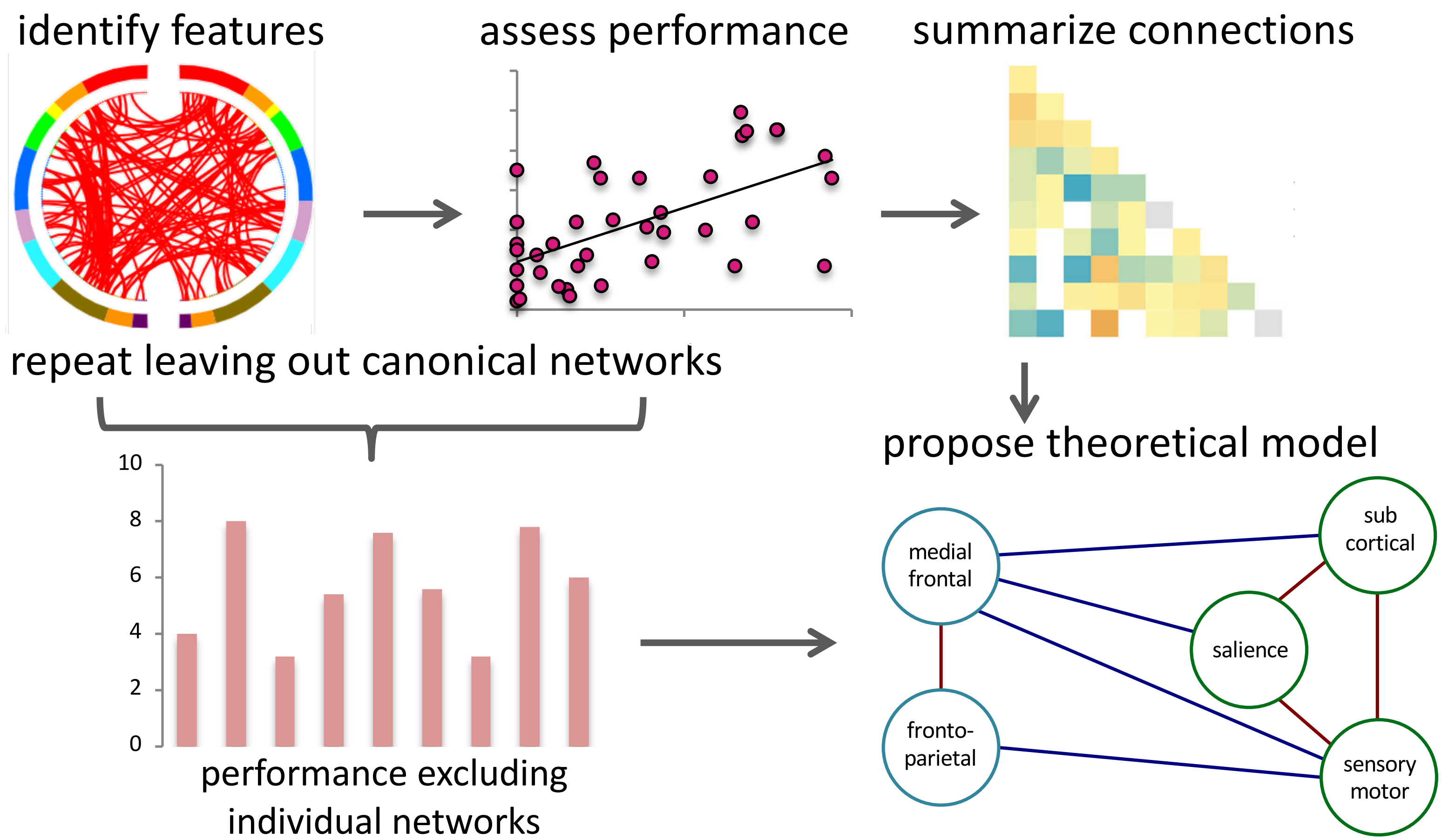
Theory / mechanism level



Levels of interpretation

Yip et al., *Biological Psychiatry: Cognitive Neuroscience and Neuroimaging*, 2020

Mechanism as a goal of prediction



Yip et al., *Biological Psychiatry: Cognitive Neuroscience and Neuroimaging*, 2020

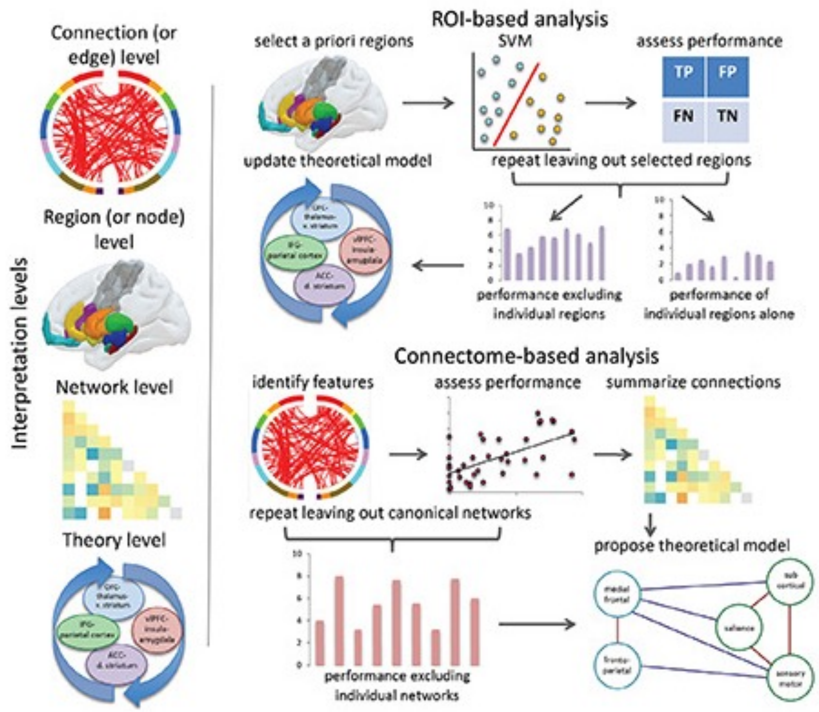
An Official Journal of the Society of Biological Psychiatry

Biological Psychiatry:

Cognitive Neuroscience and Neuroimaging

Volume 5, Number 8
August 2020

Understanding the Nature and Treatment of Psychopathology: Letting the Data Guide the Way



A journal of cognitive neuroscience, computation, and neuroimaging in psychiatry

ISSN 2451-9022
www.sobp.org/BPCNNI

Recommendations for clinical prediction

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

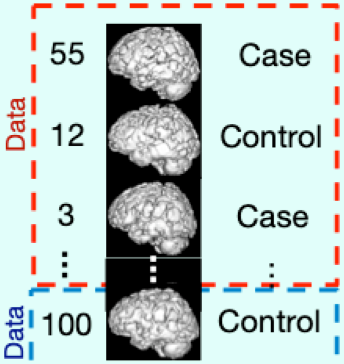
3. Collect baseline data
acquire neuroimaging data
acquire baseline clinical data

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

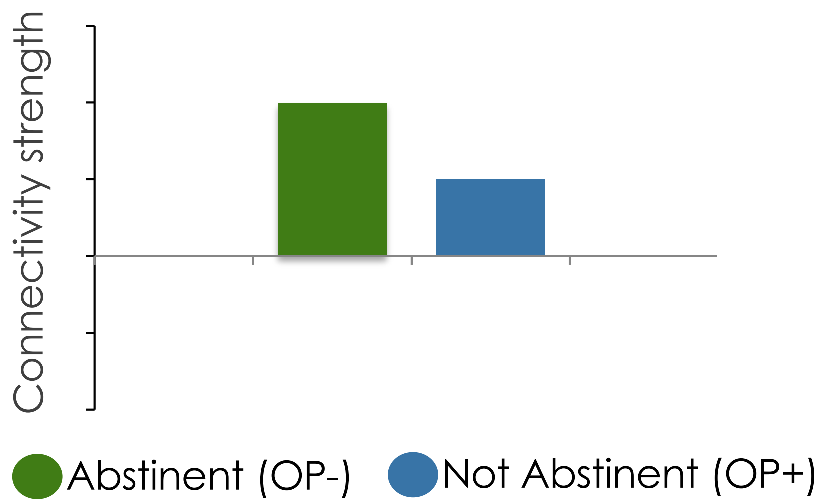
9. Improve clinical care
develop/improve tx based on findings
conduct additional research to refine predictive model

Yip et al., *Biological Psychiatry: Cognitive Neuroscience and Neuroimaging*, 2020

Longitudinal relevance of brain state

Does connectivity change in treatment?

Prior cross-sectional findings



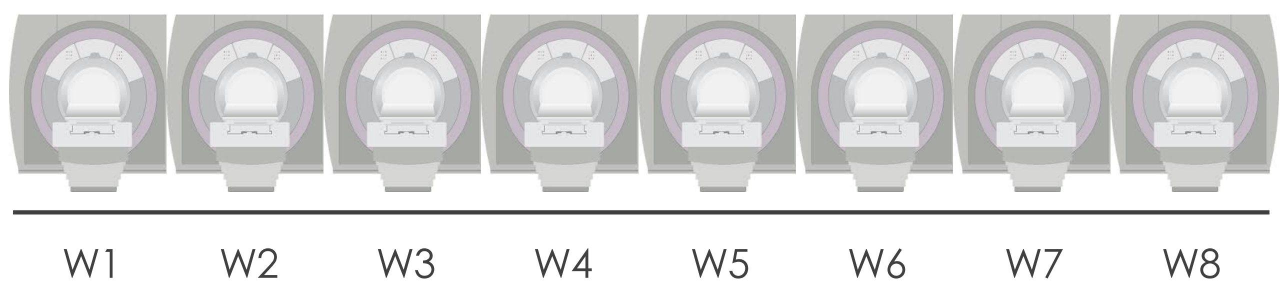
10 people scanned over 68 sessions

Acquiring 60 more scans from 10 people

>120 individual sessions from 20 people

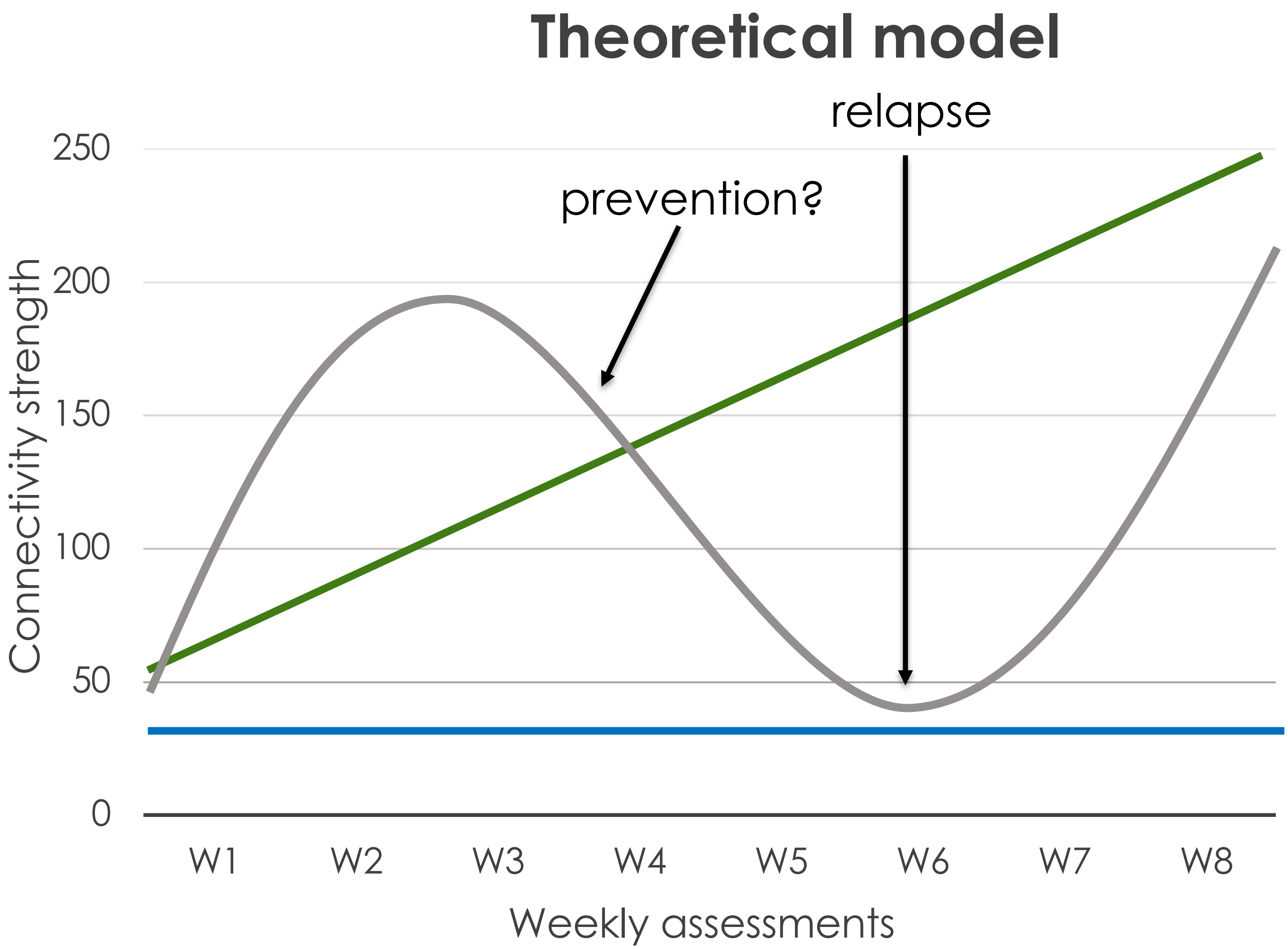
Ongoing longitudinal work

Weekly scanning for two months



Weekly Utox, Substance Use Calendar, etc

Does connectivity change in treatment?



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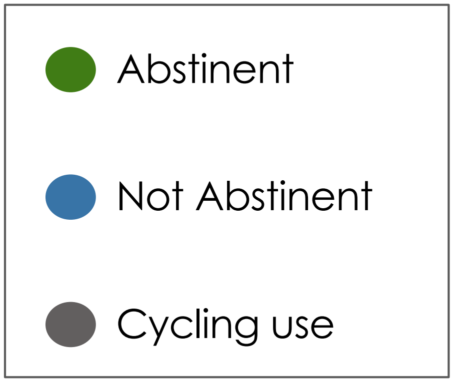


Yip & Konova, *Neuropsychopharmacology*, 2021

Densely sampled neuroimaging for maximizing clinical insight in psychiatric and addiction disorders

Sarah W. Yip[1] and Anna B. Konova[2]

Neuropsychopharmacology (2022) 47:395–396; https://doi.org/10.1038/s41386-021-01124-0

Contents lists available at ScienceDirect

NeuroImage

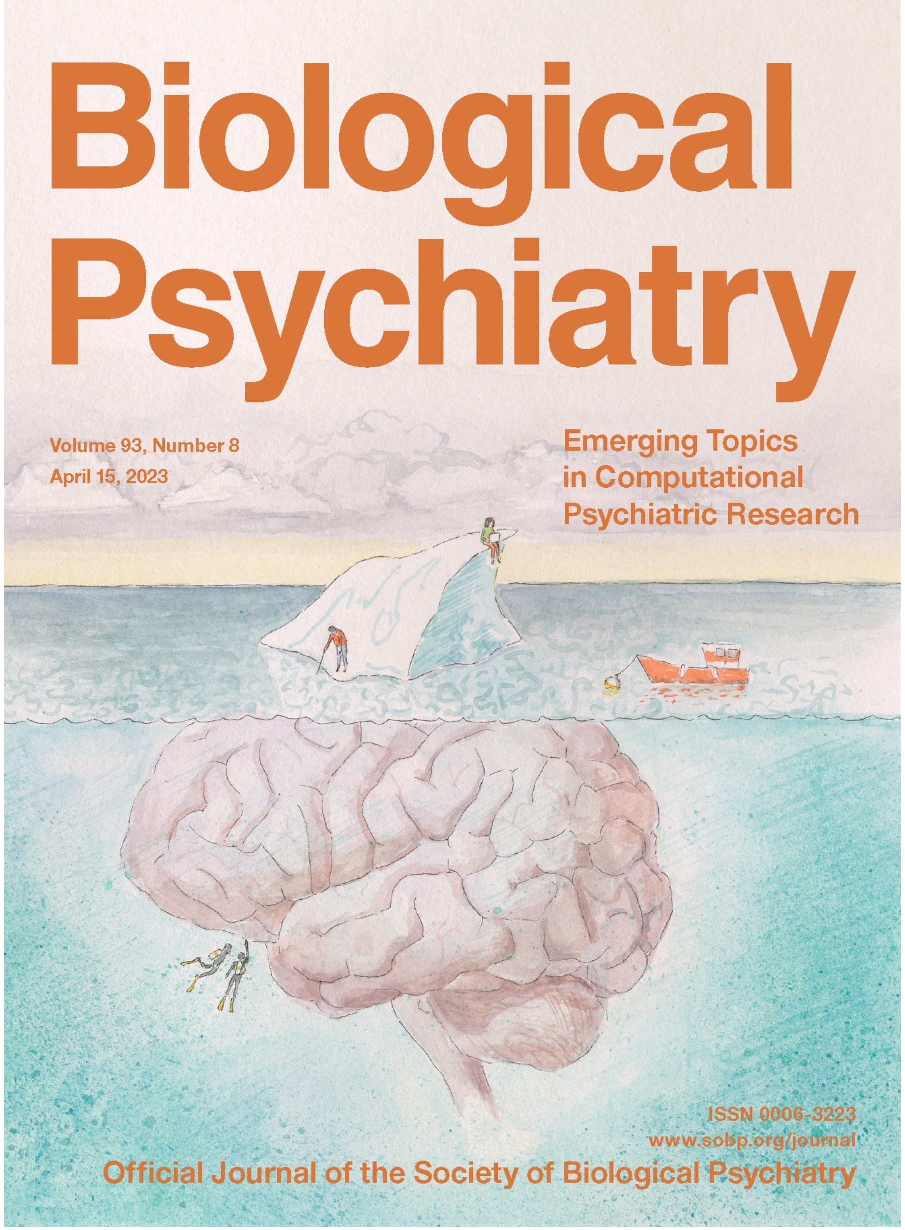
journal homepage: www.elsevier.com/locate/neuroimage

Ten simple rules for predictive modeling of individual differences in neuroimaging

Dustin Scheinost[a,b,c,d,*], Stephanie Noble[d], Corey Horien[d], Abigail S. Greene[d], Evelyn MR. Lake[a], Mehraveh Salehi[e], Siyuan Gao[f], Xilin Shen[a], David O'Connor[f], Daniel S. Barron[g], Sarah W. Yip[c,g], Monica D. Rosenberg[h], R. Todd Constable[a,d,i]

Toward Addiction Prediction: An Overview of Cross-Validated Predictive Modeling Findings and Considerations for Future Neuroimaging Research

Sarah W. Yip, Brian Kiluk, and Dustin Scheinost



Emerging Topics in Computational Psychiatry Research
Yip & Konova, Editors, 2023

BRAIN & BEHAVIOR
RESEARCH FOUNDATION

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Imaging &
Psychopharmacology

Key collaborators on presented work:

- Sarah Lichenstein, PhD
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- Dustin Scheinost, PhD
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- Brian Kiluk, PhD
- Todd Constable, PhD
- Hugh Garavan, PhD
- Bader Chaarani, PhD
- Qinghao Liang, PhD
- Alecia Dagher, PhD
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- Emma Lent, BS
- Robert Kohler, PhD
- Marzieh Babaeianjelodar, PhD
- Steve Riley, PhD
- Annie Cheng, PhD
- Diane Wong, PhD
- Damla Aksen, PhD
- Madeeha Nasir, MD, MRes

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