Connectome-based modeling of real world clinical outcomes

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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

n=74*

12-week, outpatient treatment#

*opiod-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\textsuperscript{a,*}; Charla Nich, MS\textsuperscript{a}; Elise E. DeVito, PhD\textsuperscript{a}; Julia M. Shi, MD\textsuperscript{a,b}; and Mehmet Sofuoglu, MD, PhD\textsuperscript{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
Using connectome-based predictive modeling to predict individual behavior from brain connectivity

Xilin Shen¹, Emily S Finn², Dustin Scheinost¹, Monica D Rosenberg³, Marvin M Chun²–⁴, Xenophon Papademetris¹,⁵ & R Todd Constable¹,²,⁶

> 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)

B. Sum edge weights

C. Fit brain-behavior model

D. Apply model to novel data

\[ y = mx + b \]
Model validation - predictive accuracy

rho = 0.42, p = 0.001

*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

\[ \sqrt{(x_0 - x_1)^2 + (y_0 - y_1)^2 + (z_0 - z_1)^2} \]

- 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

Positive network

Negative network

Positive - Negative

Yip et al., *American Journal of Psychiatry*, 2019
Coordination of attention and executive control
between-network segregation

Coordination of salience encoding and reward responding
between-network integration
Post-treatment fMRI (n=40)

*no changes in connectivity over time

Yip et al., *American Journal of Psychiatry*, 2019
But does it replicate?
Replicates in heterogeneous, independent sample

$n=45$

*methadone

$\rho=0.36, p=0.015$

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
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

\[ \rho = 0.34, \ p = 0.016 \]
Opioid network

<3% of possible connections
Shared edges across opioid and cocaine networks

Consistent edges
<1% overlap

Opposing edges
Opioid network connectivity

Positive network

Negative network

Positive - Negative

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

Cocaine network does **not** predict opioid use

...but does generalize across tasks.
Opioid network across drugs and brain states

- Opioid use
- Cocaine use

Cognitive task
- Opioid network
  - $\rho_{(df=52)} = 0.07, p = 0.606$

Reward task
- Opioid network
  - $\rho_{(df=52)} = 0.71, p < 0.001$

Resting state
- Opioid network
  - $\rho_{(df=35)} = 0.46, p = 0.005$

Opioid network does **not** predict cocaine use

...but does generalize across tasks.
Network across drugs and brain states

<table>
<thead>
<tr>
<th></th>
<th>Cocaine Network</th>
<th>Opioid Network</th>
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<tbody>
<tr>
<td></td>
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Lichenstein et al., *Molecular Psychiatry*, In Press
Post-treatment connectivity predicts opioid use*

*no changes in opioid connectivity over time

Post-treatment fMRI (n=40)

\[ r = 0.34, \ p = 0.03 \]

\[ \rho = 0.404, \ p = 0.009 \]
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

Addiction

Restoration of structure and function to premorbid levels

Recovery

Abstinence Maintenance for monitoring relapse risk and regulating drug urges

Return to premorbid levels

Elevation of function relative to controls

Relapse Risk reflecting prolonged vulnerability

Continued vulnerability

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

Return to premorbid

Elevation of function

Continued vulnerability

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

Lichenstein et al., *Molecular Psychiatry*, In Press
Protracted neural change?

Days of any drug or alcohol use/28

Month since treatment initiation

pre fMRI  post fMRI  follow-up fMRI
Second external replication

\[
\rho_{(df=18)} = 0.53, \ p = 0.02
\]
Part III: Considerations for clinical prediction
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:
     - Training Data:
       - 55 Case
       - 12 Control
     - Testing Data:
       - 3 Case
       - 100 Control
     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
‘Best’ metric depends on the question

### Outcome 1. Assignment to active treatment

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<tr>
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<th>Low sensitivity / high specificity</th>
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<tbody>
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### Outcome 2. Termination of active treatment

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Yip et al., *Biological Psychiatry: CNNI*, 2020
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   12
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   3
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   ... 
   
   100
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   update theoretical framework

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   develop/improve tx based on findings
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Yip et al., Biological Psychiatry: CNNI, 2020
Elucidation as a goal of prediction

Levels of interpretation

Yip et al., *Biological Psychiatry*: CNNI, 2020
Elucidation as a goal of prediction

ROI-based analysis

select a priori regions

SVM

assess performance

TP
FP
FN
TN

repeat leaving out selected regions

update theoretical model

performance excluding individual regions

performance of individual regions alone

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

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