A ‘targeted’ approach to identify the proteins underlying the biobehavioral mechanisms of addiction

Stephanie Groman, Ph.D.
Associate Research Scientist
Department of Psychiatry
Addiction: vulnerability vs. consequence

Vulnerability

Consequence

Escalation in drug use

Heritability estimates of addiction are ~50%

Prevention

Treatment
Decision-making in addiction

- Jentsch et al., 2002; Schoenbaum et al., 2003
- Ersche et al., 2008; Fillmore and Rush, 2003
- Cervantes et al., 2013
Decision-making: a biomarker of addiction

Consequence

Chronic drug use → Decision-making deficits

Vulnerability
Probabilistic reversal learning (PRL) task
Decision making in addiction-relevant behaviors

Vulnerability

\[ R^2 = 0.25 \]
\[ p = 0.03 \]

Number of reversals (z-score)

Consequence

Number of reversals completed

**
Computational mechanisms of addiction pathology

Chronic drug use

Decision-making deficits

Reinforcement learning process A?

Reinforcement learning process B?
Reinforcement-learning model

\[ V(t + 1) = \gamma V(t) + \Delta_j \]

- \( i f \ r(t) = 1, \Delta_j = \Delta_1 \)
- \( i f \ r(t) = 0, \Delta_j = \Delta_2 \)

3 free parameters:

\( \gamma \) Forgetting rate
\( \Delta_1 \) Appetitive strength of rewards
\( \Delta_2 \) Aversive strength of no rewards

Barraclough et al., 2004
Different reinforcement learning mechanisms underlie addiction vulnerability vs. consequence.

**Vulnerability**

Number of drug infusions (z-score) vs. $\Delta_1$ parameter (z-score)

**Consequence**

$\Delta_2$ parameter vs. Time (Before vs. After)

- Saline
- MA

* Significant difference
Decision-making as a tool for identifying novel protein targets for addiction

Protein A?

Chronic drug use

Value updating to negative outcomes

Decision-making deficits

Value updating to positive outcomes

Protein B?
Identification of protein-computational correlates

- PRL assessments
- Sample collection (ventral striatum)
- Protein extraction/purification
- Peptide fractionation
- Label-free mass spectrometry

Δ₁ parameter

Δ₂ parameter

309
26
108
Narrowing in on protein targets

**Drug-naïve study**
- Assess decision-making in rats
- Collect tissue from the ventral striatum
- Protein expression (LC-MS/MS)

**Drug self admin study**
- Assess decision-making in rats
- Meth self-administration
- Reassess decision-making in rats
- Collect tissue from the ventral striatum
- Protein expression (LC-MS/MS)
Narrowing in on addiction vulnerability targets

<table>
<thead>
<tr>
<th>Gene (Protein)</th>
<th>Link to addiction?</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ryr2 (Ryanodine receptor 2)</td>
<td>Genetic association with impulsivity and gambling (Khadka et al., 2014; Lind et al., 2012)</td>
</tr>
<tr>
<td>Snx1 (sorting nexin 1)</td>
<td>Reduced following meth CPP (Yang et al., 2008)</td>
</tr>
<tr>
<td>Gdap1 (Ganglioside-induced differentiation-associated protein 1)</td>
<td>Methylation of GDAP1 is correlated with alcohol use (Bruckmann et al., 2016)</td>
</tr>
<tr>
<td>Plppr4 (Phospholipid phosphatase-related protein type 4)</td>
<td>Not directly – but involved in postnatal neural development</td>
</tr>
<tr>
<td>Hsbp1 (Heat shock factor binding protein 1)</td>
<td>Not directly, but HSP are heavily implicated</td>
</tr>
</tbody>
</table>
Narrowing in on addiction consequence targets

\[ \Delta_2 \text{ drug exposed} \]
\[ \Delta_2 \text{ drug naive} \]

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<th>Gene (Protein)</th>
<th>Function</th>
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</tr>
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<tbody>
<tr>
<td>Rab3B (Ras-related protein 3B)</td>
<td>Involved in synaptic transmission and vesicle trafficking</td>
<td>Identified as putative QTL acute cocaine response (Philip et al., 2012)</td>
</tr>
</tbody>
</table>
Decision-making to identifying novel protein targets for addiction

- Decision-making deficits
- Value updating to negative outcomes
- Value updating to positive outcomes
- Chronic drug use
- Rab3B
- Snx1
- Ryr2
- Hspbp1
A ‘targeted’ approach to identify the proteins underlying the biobehavioral mechanisms of addiction

Hypothesis 1: Decision making and proteins linked to addiction vulnerability phenotype (e.g., Ryr2, Snx1) will be altered in animal models known to have addiction-related vulnerabilities.

Hypothesis 2: Decision making and protein linked to the addiction consequence phenotype (e.g., Rab3B) will be altered in animals following heroin self-administration.
Pilot Grant: Experimental design

Prenatal morphine (or vehicle) self-admin

Cross foster to drug naïve dams

Assess PRL performance

Tissue collection for targeted proteomics

Assess heroin-taking behaviors

Hypothesis 1

Hypothesis 2

Tissue collection for targeted proteomics
Pilot Grant: Experimental design

- *Prenatal morphine (or vehicle) self-admin* → Cross foster to drug naïve dams → Tissue collection for targeted proteomics → Assess PRL performance → Assess heroin-taking behaviors → Tissue collection for targeted proteomics

**Hypothesis 1**
(N=40)

**Hypothesis 2**
(N=40)

N=80
Summary and future directions

• Computational analyses of decision making can be used to disentangle the pathology of addiction

• Proteomics combined with computational tools provides a mechanistic bridge between signaling mechanisms and complex behaviors
  • High translatability to humans

• Ongoing studies will provide experimental support for these protein-computational correlates to potentially identify novel targets for the prevention and treatment of addiction
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Reinforcement learning mechanisms predicting MA-taking behaviors

\[ \gamma \text{ Forgetting rate} \quad \Delta_1 \text{ Appetitive strength of rewards} \quad \Delta_2 \text{ Aversive strength of no rewards} \]
MA-induced disruptions in reinforcement learning mechanisms

- **Forgetting rate** ($\gamma$)
- **Appetitive strength of rewards** ($\Delta_1$)
- **Aversive strength of no rewards** ($\Delta_2$)

![Graphs showing changes in parameters before and after treatment with MA and saline.](image-url)
Rab3B

\[ \Delta_2 \text{ parameter estimate} \]

![Scatter plot of Rab3b expression vs. \[ \Delta_2 \text{ parameter estimate} \]]

![Bar graph comparing Rab3B expression in Saline and Meth conditions]

- Saline
- Meth

The graph shows a positive correlation between Rab3b expression and \[ \Delta_2 \text{ parameter estimate} \]. The bar graph indicates a significant increase in Rab3B expression in the Meth condition compared to Saline, with a statistical significance indicated by the "***" symbol.