Dissociating the signaling mechanisms underlying addiction vulnerability from the consequences of drug use

Stephanie M. Groman, Becky Carlyle, Rashaun Wilson, Angus Nairn, and Jane R. Taylor
Department of Psychiatry, Yale University

INTRODUCTION
Adaptive, flexible decision-making is disrupted in addicted individuals and believed, in part, to be a consequence of chronic drug use. Recent studies, however, have suggested that pre-existing alterations in decision-making might influence future drug-taking behaviors. Decision-making may, therefore, be a critical biomarker for understanding the neural mechanisms of addiction. Here, we investigated in rats the role of decision-making in methamphetamine self-administration to isolate the proteins involved in addiction susceptibility from those involved in addiction consequence.

METHODS
Probabilistic reversal learning task
Adult, male Long-Evans rats (N=80) were trained on a three-choice, probabilistic reversal-learning (PRL) task. Reinforcement probabilities for each noseport were assigned at the beginning of each session. These probabilities remained stable until rats met a performance criterion (24 correct in last 30 trials completed) at which point the probabilities between two choices reversed and remained stable until the performance criterion was met again. Rats could complete up to 8 reversals each session.

Computational analysis
Choice data was analyzed with a reinforcement-learning algorithm. Action values for each option were updated according to the following equation:

\[ Q(t+1) = Q(t) + \gamma (r + \Delta_n - Q(t)) \]

where the decay rate \( \gamma \) determines how quickly the action values decay and \( \Delta_n \) indicates the change in the action value that depends on the outcome from the chosen noseport. If the outcome was reward, then the value function of the chosen noseport was updated by \( \Delta_n \), the appetitive strength of reward. If the outcome was no reward, then the value function of the chosen noseport was updated by \( \Delta_n \), the aversive strength of no reward. Decay of action values for unchosen options was determined by the \( \gamma \) parameter.

Three free parameters:
- \( \gamma \) – decay rate
- \( \Delta_n \) – appetitive strength of rewards
- \( \Delta_n \) – aversive strength of no rewards

Methamphetamine self-administration
After PRL testing, rats (N=40) were implanted with intra-jugular catheters and trained to self-administer methamphetamine (0.05 mg/kg/infusion) or saline in 6 h long-access sessions for 14 days.

Decision making predicts future drug use

Decision making is disrupted by drug use

Proteomics
Tissue from the ventral striatum was collected from rats tested on the PRL task who were either drug-naïve (N=18) or had self-administered meth for 14 days (N=16). Proteins were extracted and purified, and peptides fractionated by nanoLC/MS/MS. After protein digestion and fractionation, peptides were analyzed by nanoLC/MS/MS and identified with search tools. The proteins that correlated with the \( \Delta_n \) parameter in drug-naive rats were expressed in the brain.

Conclusions
These data indicate that the protein-behavior correlates mediating addiction susceptibility differ from those that are disrupted by drug use. Future studies will manipulate expression of these proteins to demonstrate causal evidence for these correlations. Our innovative platform highlights the potential of decision-making biomarkers to isolate protein targets that could be manipulated to promote addiction resilience or treat addiction.

Funded by PHS grants DAO41480, DAO43443, Yale/NIDA Proteomics Center (DAO18343) and a Young Investigator Award from the Brain & Behavior Research Foundation.