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

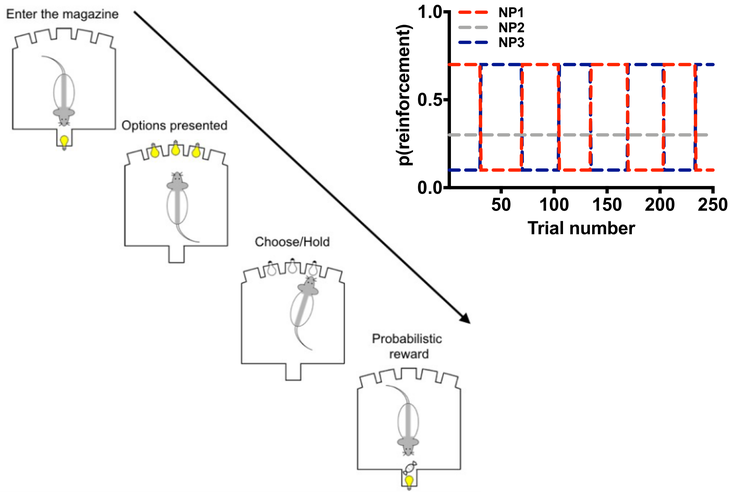
INTRODUCTION

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

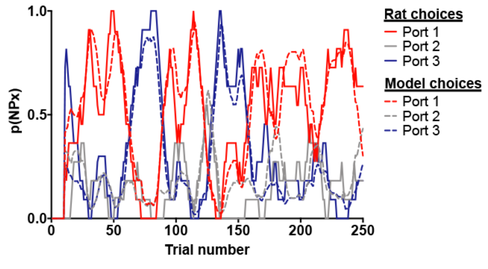
Choice data was analyzed with a reinforcement-learning algorithm. Action values for each option were updated according to the following equation:

$$Q(t+1) = \gamma\, Q(t) + \Delta_i$$

where the decay rate γ determines how quickly the action values decay and Δ_i 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 Δ_+, the appetitive strength of reward. If the outcome was no reward, then the value function of the chosen noseport was updated by Δ_0, the aversive strength of no reward. Decay of action values for unchosen options was determined by the γ parameter.

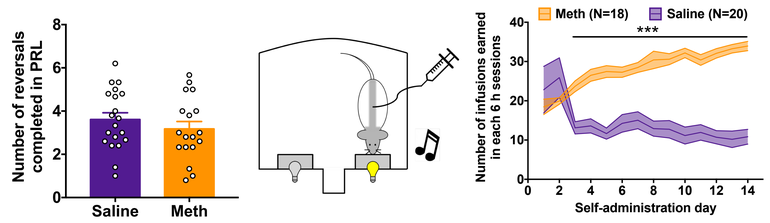
Three free parameters:

- γ – decay rate
- Δ_+ – appetitive strength of rewards
- Δ_0 – aversive strength of no rewards

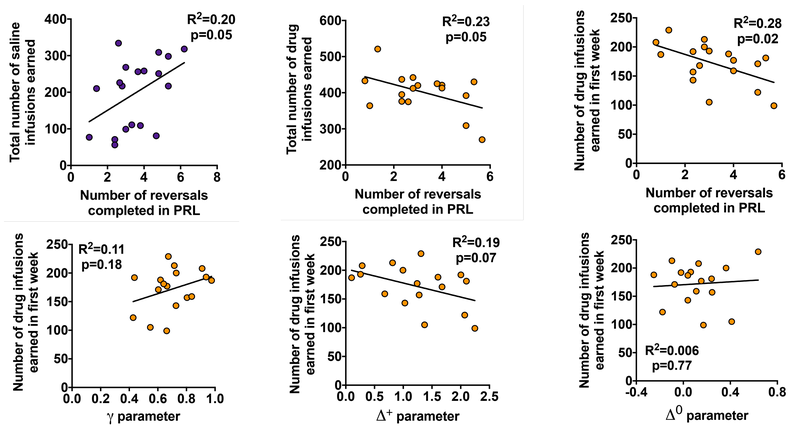


Methamphetamine self-administration

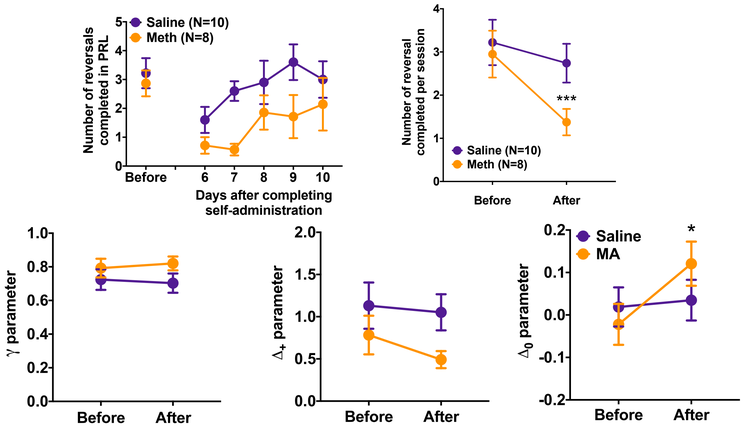
After PRL testing, rats (N=40) were implanted with intra-jugular catheters and trained to self-administer methamphetamine (0.05 mg/kg/infusion) or saline in 6 h long-access sessions for 14 days.



Decision making predicts future drug use

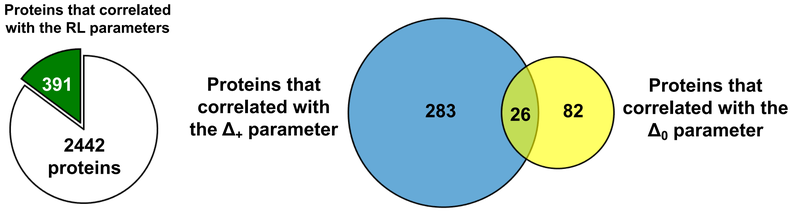


Decision making is disrupted by drug use

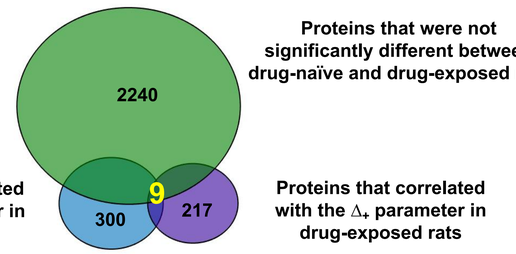


Proteomics

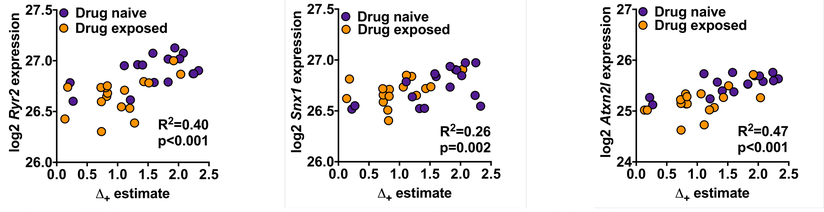
Tissue from the ventral striatum was collected from rats tested on the PRL task who were either drug-naïve (N=18) or had self-administered meth for 14 days (N=16). Proteins were extracted and purified, and peptides fractionated for liquid chromatography mass spectrometry (LC-MS/MS). Expression of each protein was correlated to the individual reinforcement-learning parameters for each rat to identify proteins that co-varied with separable aspects of reinforcement learning.



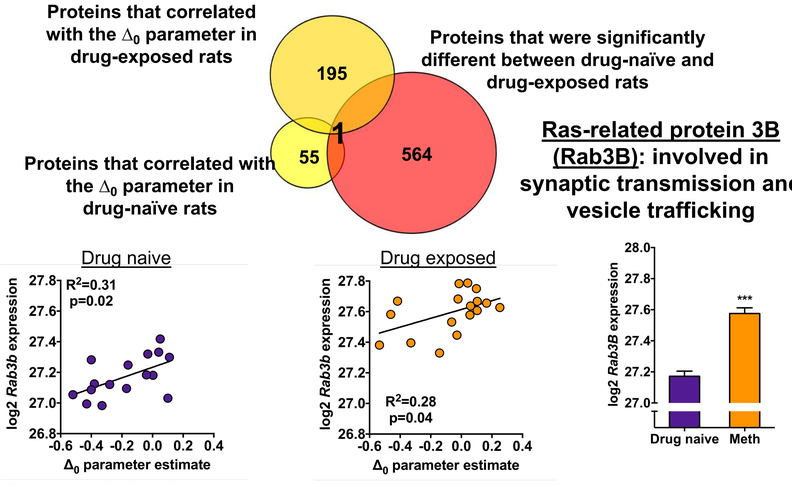
Identifying protein targets mediating addiction susceptibility



Gene	Protein	Function	Previously linked to addiction?
Ndufb10	NADH: ubiquinone oxidoreductase subunit B10	Subunit of mitochondrial membrane respiratory	Altered in alcohol preferring rats (McClintick et al., 2017)
Dpp10	Inactive dipeptidyl peptidase 10	Promotes surface expression of KCND2	
Setd7	Histone-lysine N-methyltransferase SETD7	Monomethylates Lys-4 of histone 3 (methylates nkkb and histones – wb hlk4); histone extraction; histone here repssive at lysine9	Genetic association with smoking behaviors (Thorgeirsson et al., 2010)
Sort1	Sortilin	Sorting receptor in the Golgi compartment	Low expression in high novelty seeking rats (Kabbaj et al., 2004)
Ryr2	Ryanodine receptor 2	Channel that mediates Ca2+ release from sarcoplasmic reticulum	Genetic association with impulsivity and gambling (Khadka et al., 2014; Lind et al., 2012)
Snx1	Sorting nexin-1	Intracellular trafficking	Reduced following meth CPP (Yang et al., 2008)
Gamt	Guanidinoacetate N-methyltransferase	Converts guanidoacetate to creatine	Reduced in alcohol dependent individuals (Sokolov et al., 2003)
Naa15	N(alpha)-acetyltransferase 15	Subunit of NatA complex; important for neuron growth	Gene expression disrupted in rats prenatally exposed to alcohol (Downing et al., 2012)
Atxn2l	Ataxin 2-like	Involved in stress granule and P-body formation	Genetic association with lifetime THC use (Pasman et al., 2018)



Identifying protein targets mediating addiction consequence



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 DA041480, DA043443, Yale/NIDA Proteomics Center (DA018343) and a Young Investigator Award from the Brain & Behavior Research Foundation.