

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

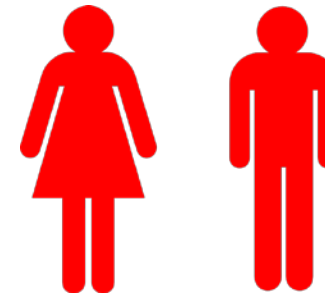
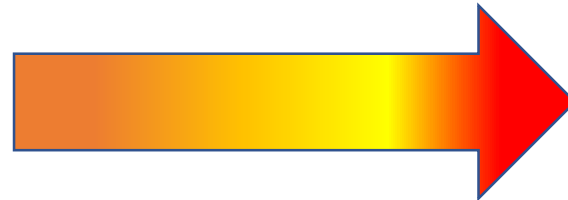


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Addiction: vulnerability vs. consequence

Vulnerability

Consequence



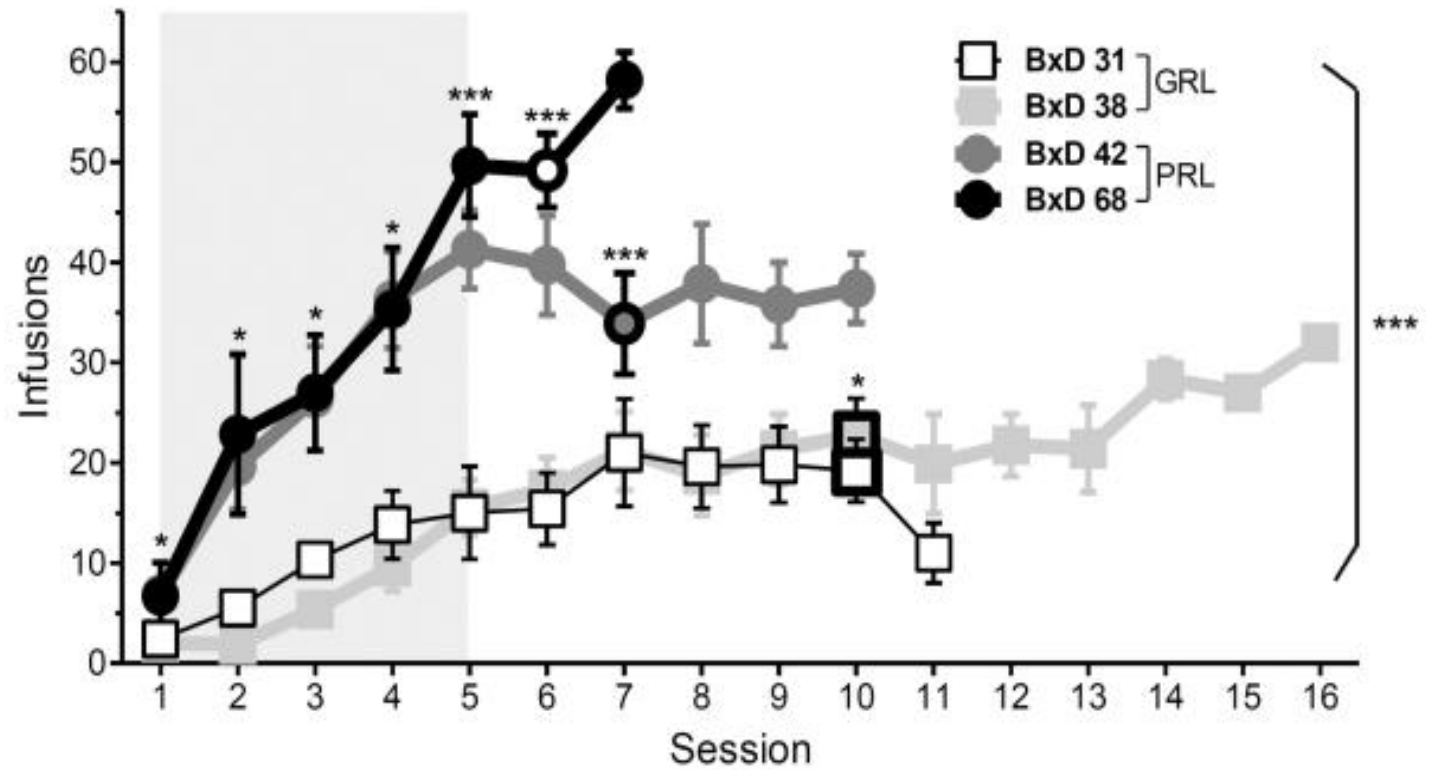
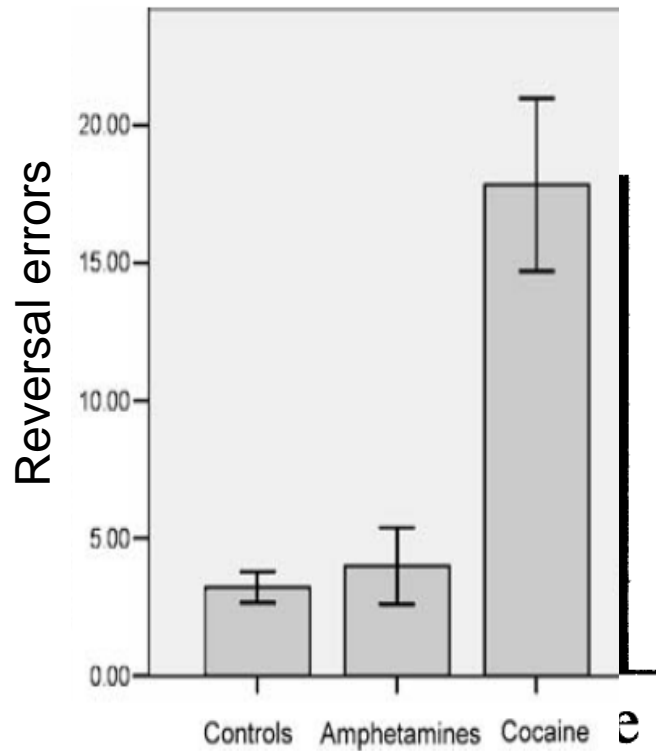
Escalation in drug use

Heritability estimates of addiction are ~50%

Prevention

Treatment

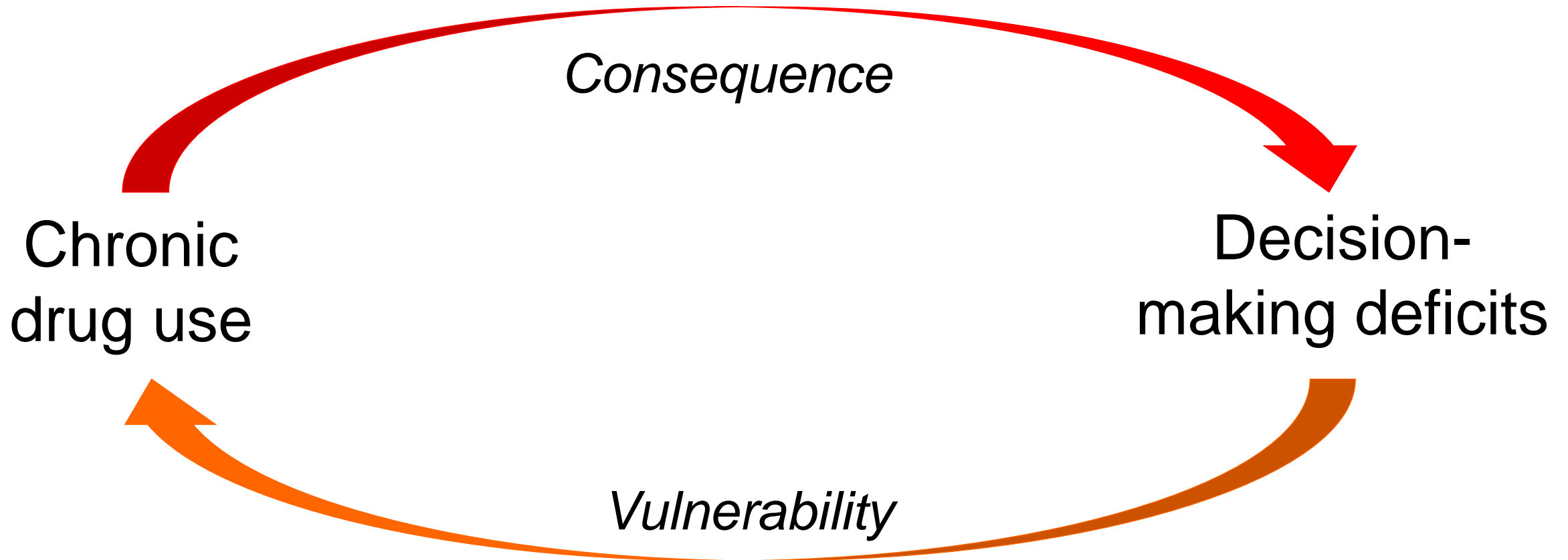
Decision-making in addiction



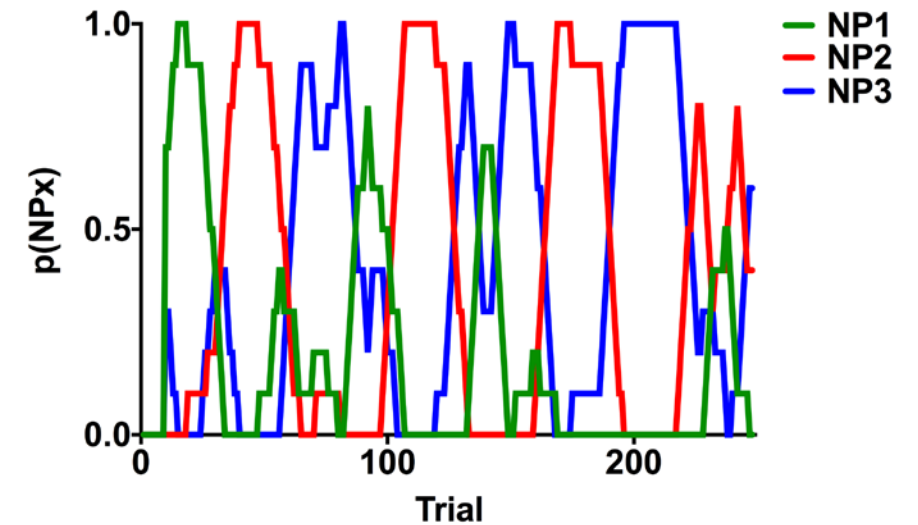
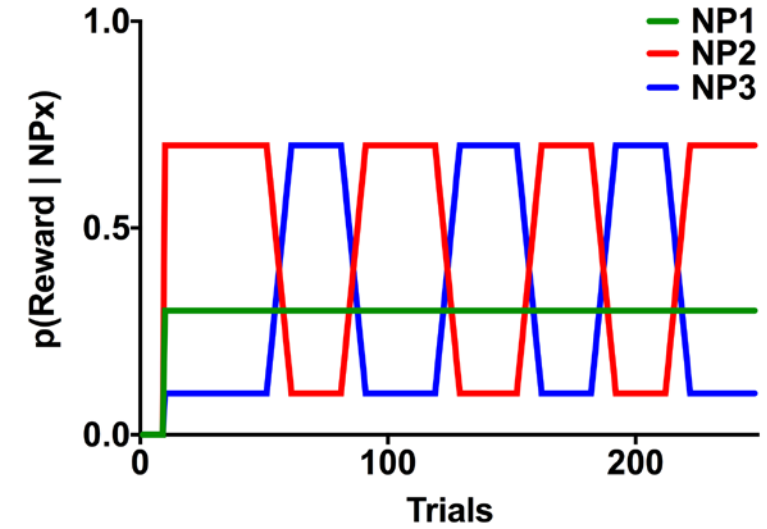
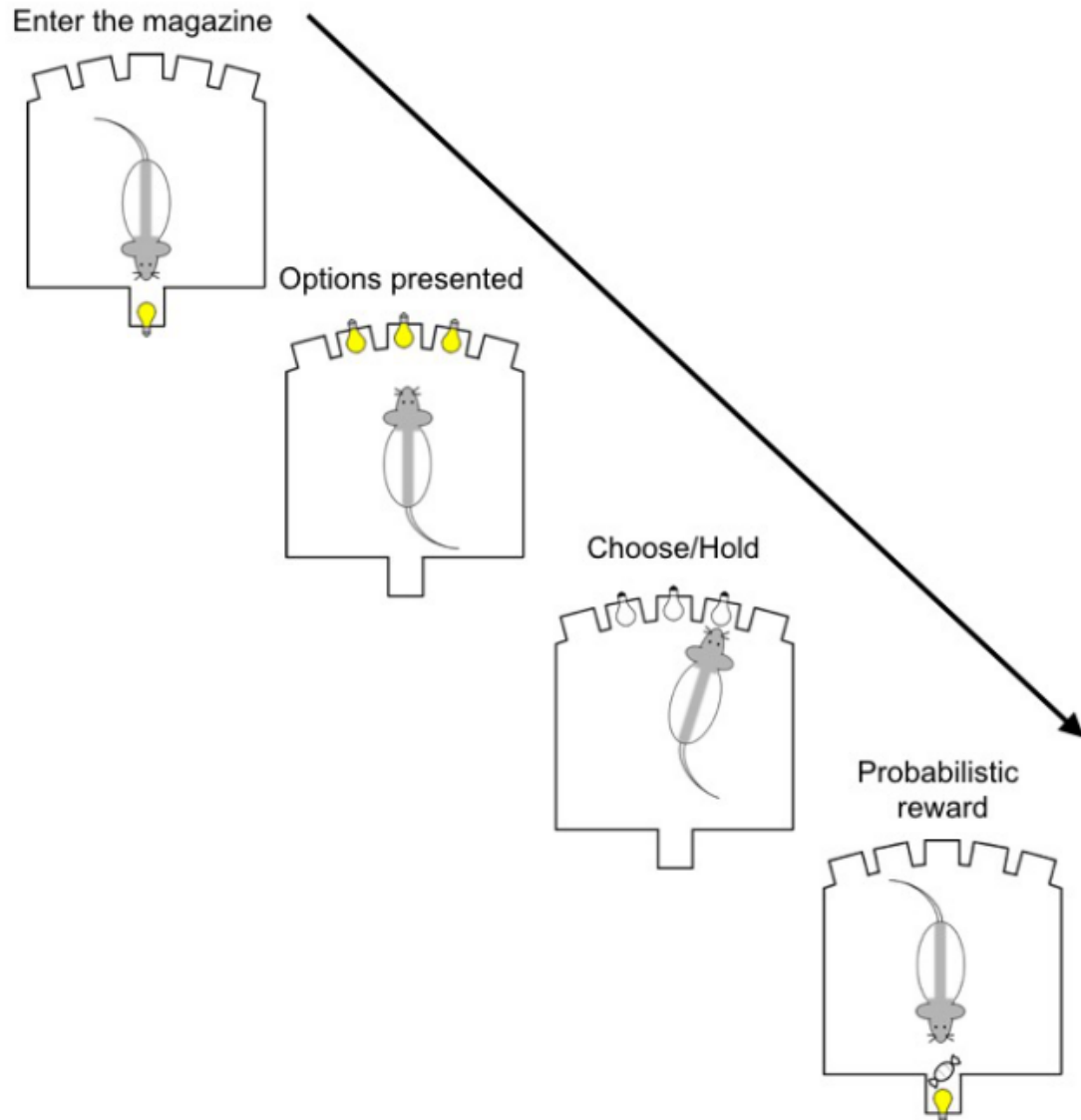
Jentsch et al., 2002; Schoenbaum et al., 2003
 Ersche et al., 2008; Filmore and Rush, 2003

Cervantes et al., 2013

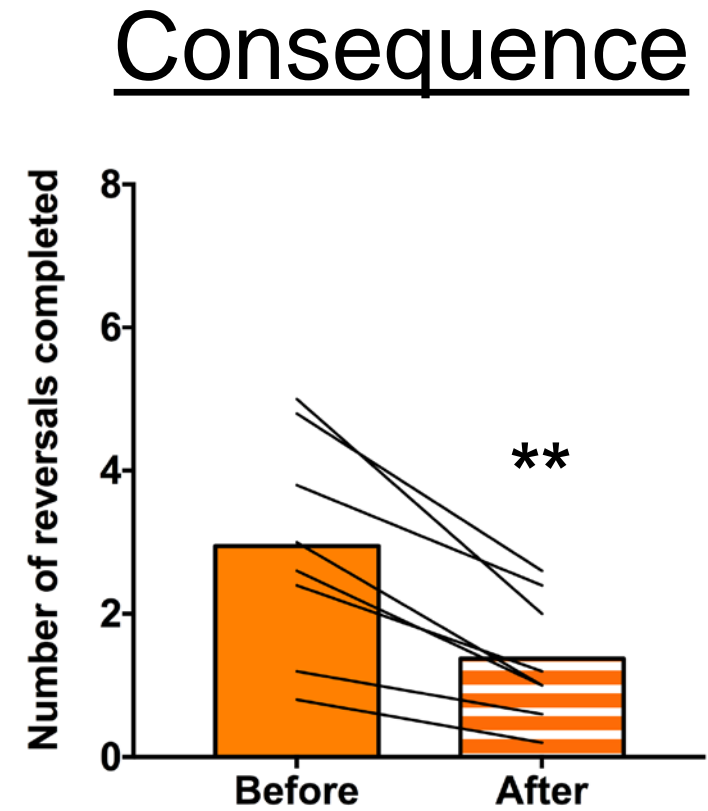
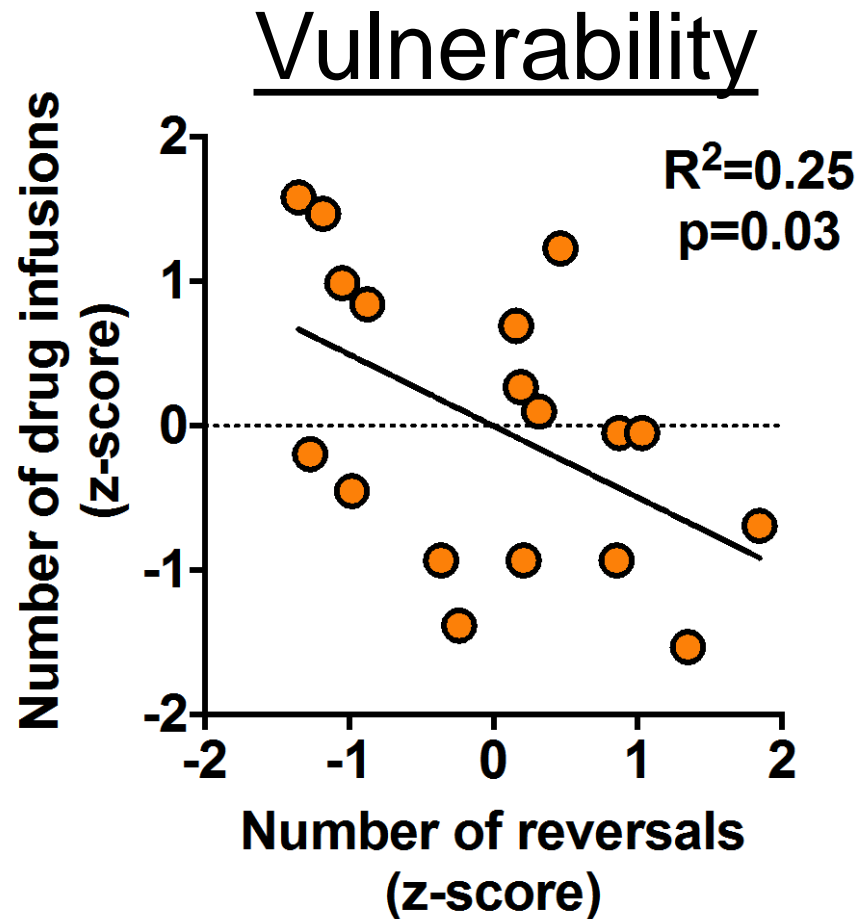
Decision-making: a biomarker of addiction



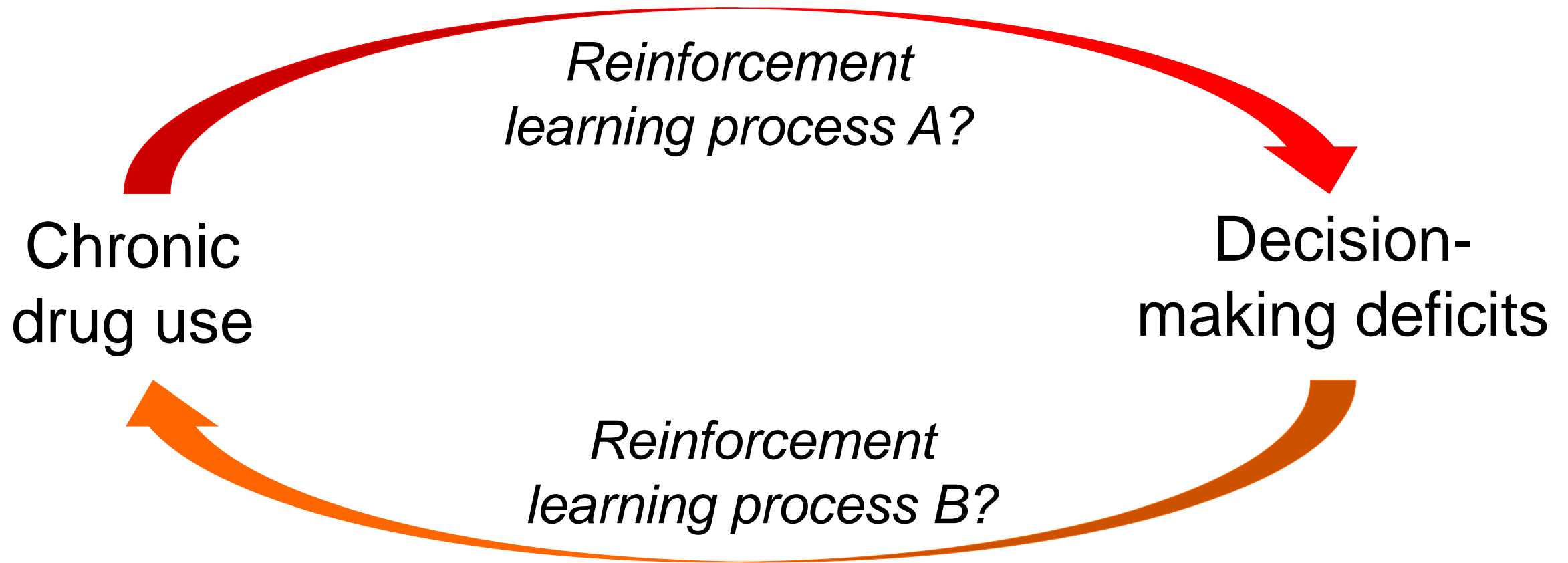
Probabilistic reversal learning (PRL) task



Decision making in addiction-relevant behaviors



Computational mechanisms of addiction pathology



Reinforcement-learning model

$$V(t + 1) = \gamma V(t) + \Delta_j$$

$$\text{if } r(t) = 1, \Delta_j = \Delta_1$$

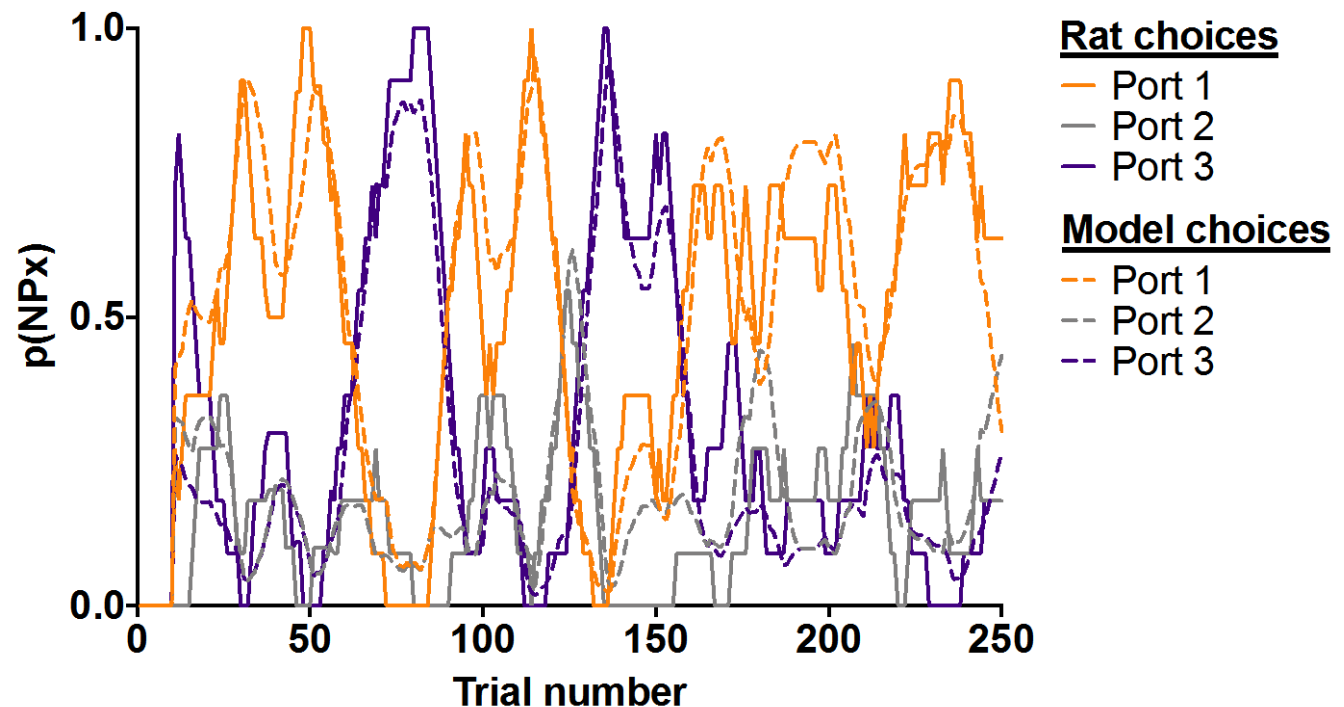
$$\text{if } r(t) = 0, \Delta_j = \Delta_2$$

3 free parameters:

γ Forgetting rate

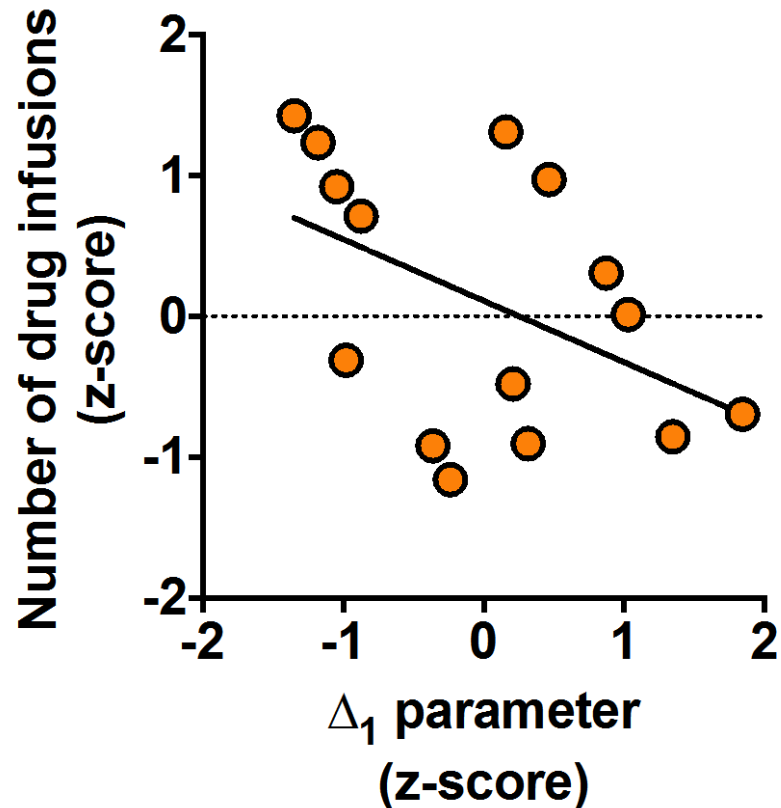
Δ_1 Appetitive strength of rewards

Δ_2 Aversive strength of no rewards

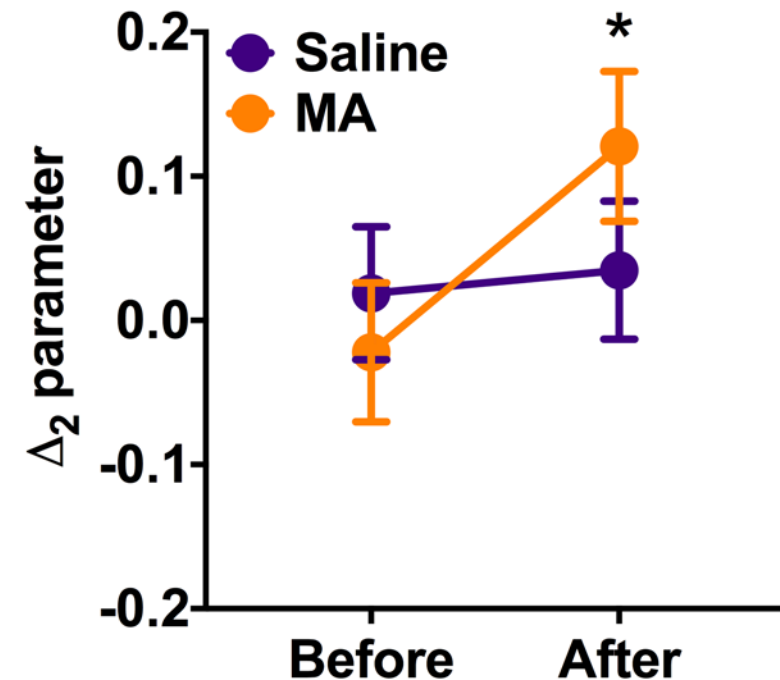


Different reinforcement learning mechanisms underlie addiction vulnerability vs. consequence

Vulnerability



Consequence



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

Protein A?

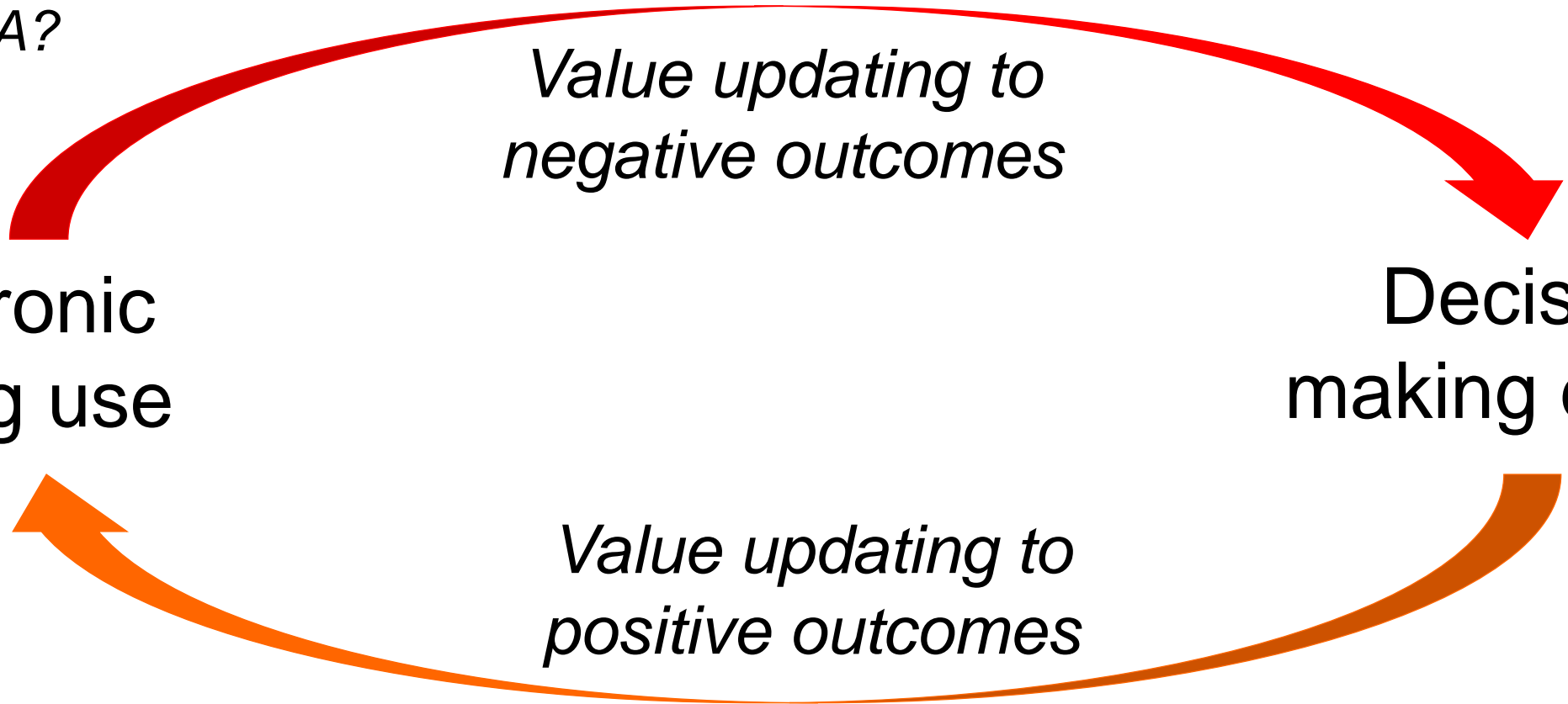
*Value updating to
negative outcomes*

Chronic
drug use

Decision-
making deficits

*Value updating to
positive outcomes*

Protein B?



Identification of protein-computational correlates

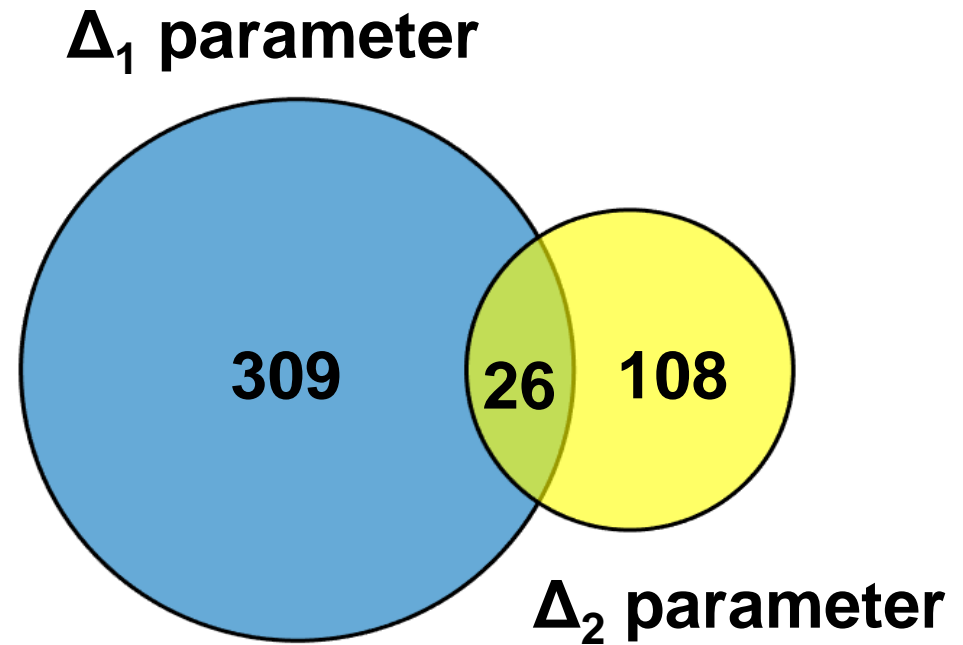
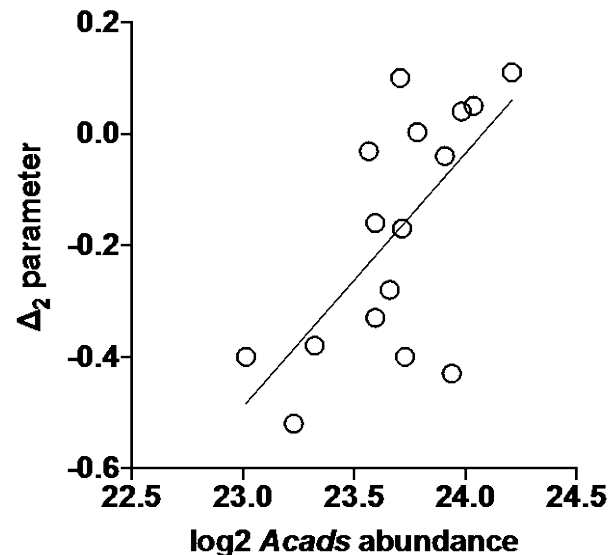
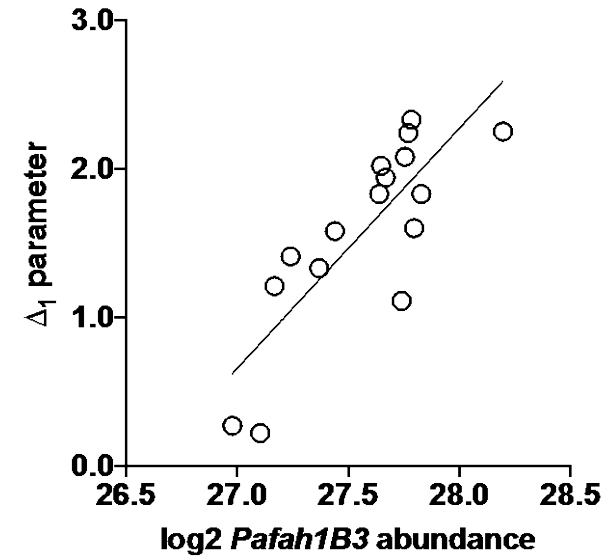
PRL assessments

Sample collection
(ventral striatum)

Protein
extraction/purification

Peptide fractionation

Label-free mass
spectrometry



Narrowing in on protein targets

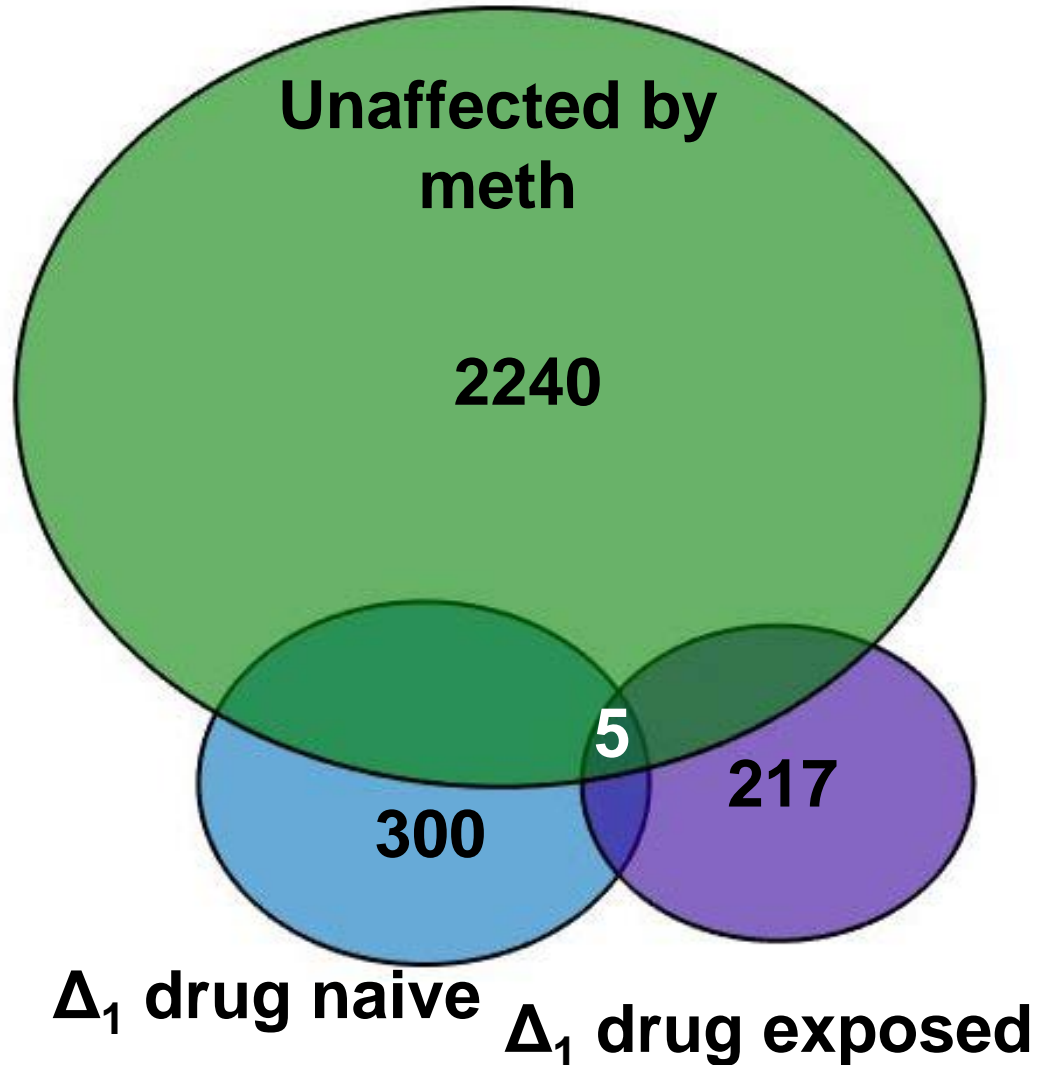
Drug-naïve study

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

Drug self admin study

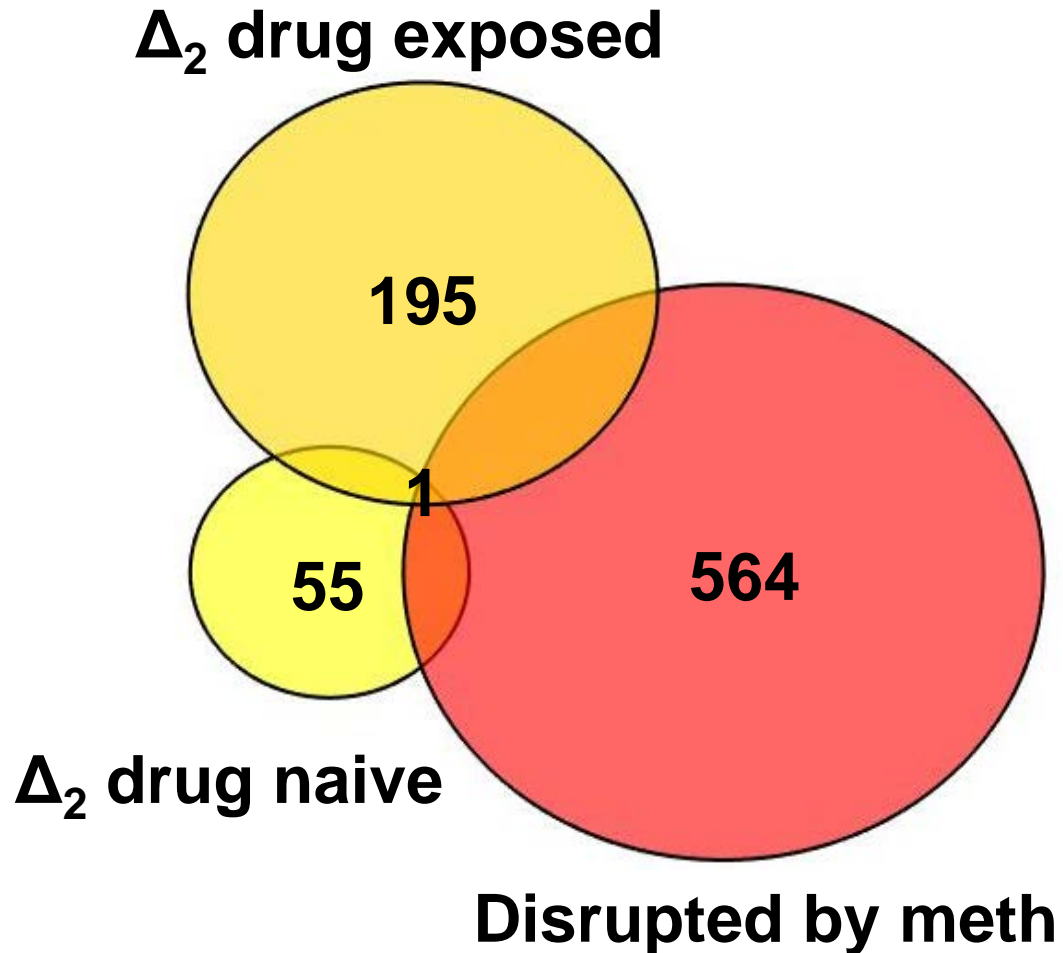
- Assess decision-making in rats
- Meth self-administration
- Reassess decision-making in rats
- Collect tissue from the ventral striatum
- Protein expression (LC-MS/MS)

Narrowing in on addiction vulnerability targets



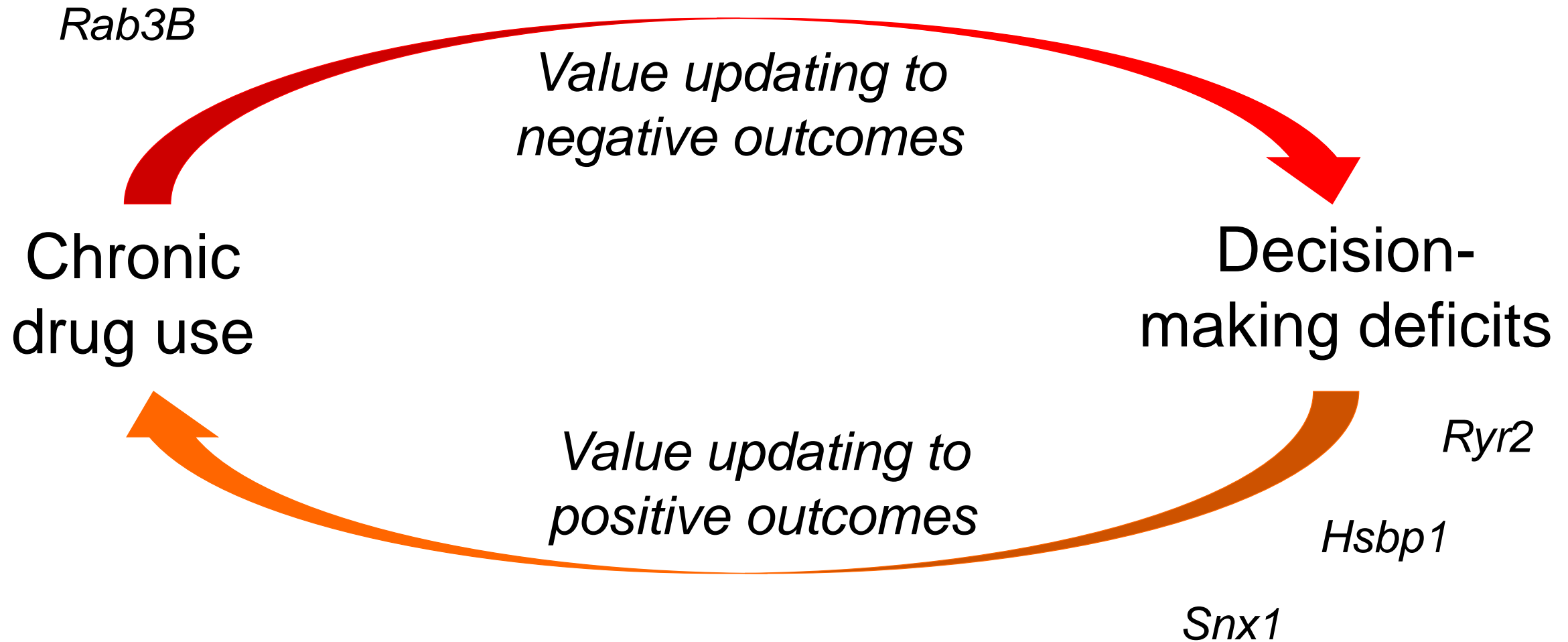
Gene (Protein)	Link to addiction?
Ryr2 (Ryanodine receptor 2)	Genetic association with impulsivity and gambling (Khadka et al., 2014; Lind et al., 2012)
Snx1 (sorting nexin 1)	Reduced following meth CPP (Yang et al., 2008)
Gdap1 (Ganglioside-induced differentiation-associated protein 1)	Methylation of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

Narrowing in on addiction consequence targets



Gene (Protein)	Function	Link to addiction?
Rab3B (Ras-related protein 3B)	Involved in synaptic transmission and vesicle trafficking	Identified as putative QTL acute cocaine response (Philip et al., 2012)

Decision-making to identifying novel protein targets for addiction



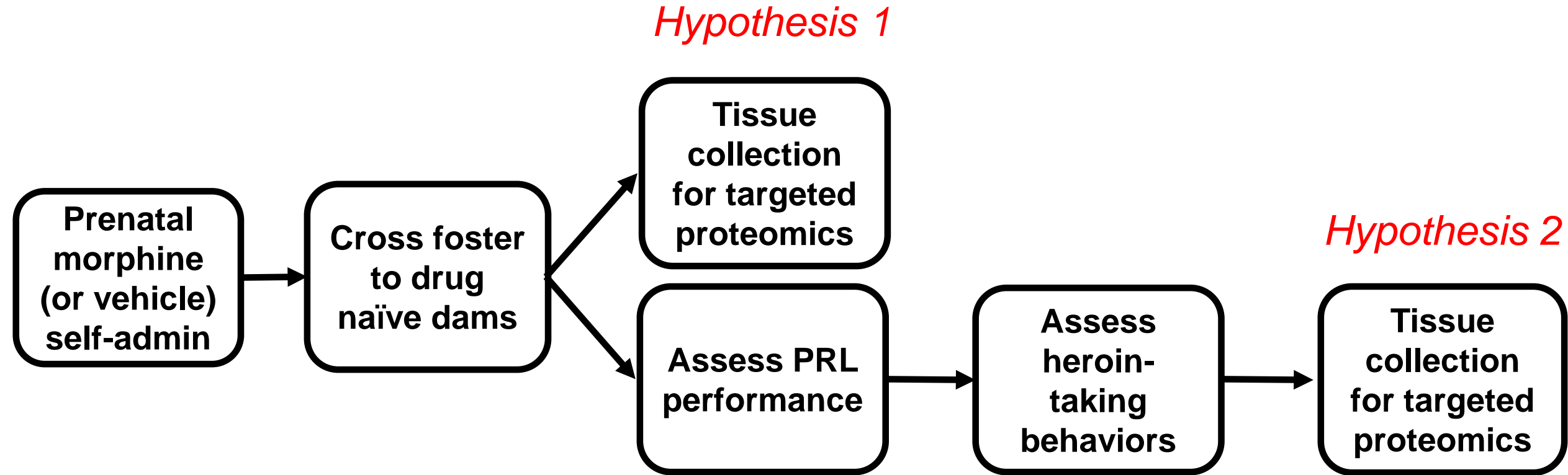
NIDA/Yale Neuroproteomics Center Pilot Grant

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

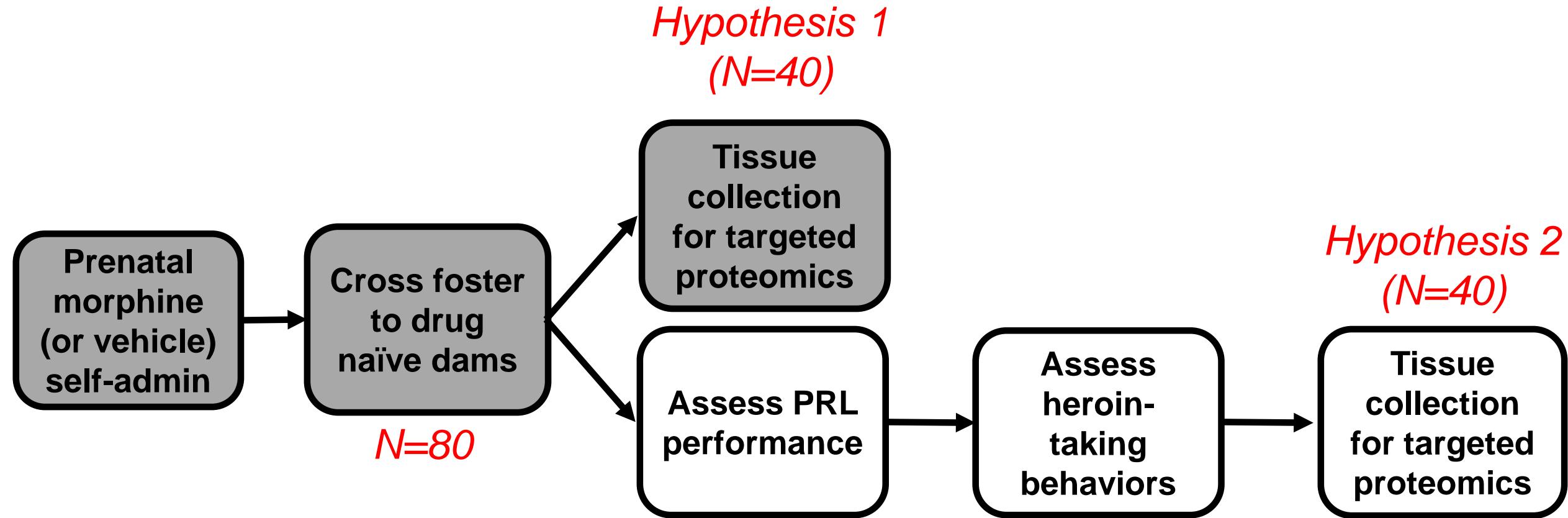
Hypothesis 1: Decision making and proteins linked to addiction vulnerability phenotype (e.g., Ryr2, Snx1) will be altered in animal models known to have addiction-related vulnerabilities.

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



Pilot Grant: Experimental design



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

Acknowledgements

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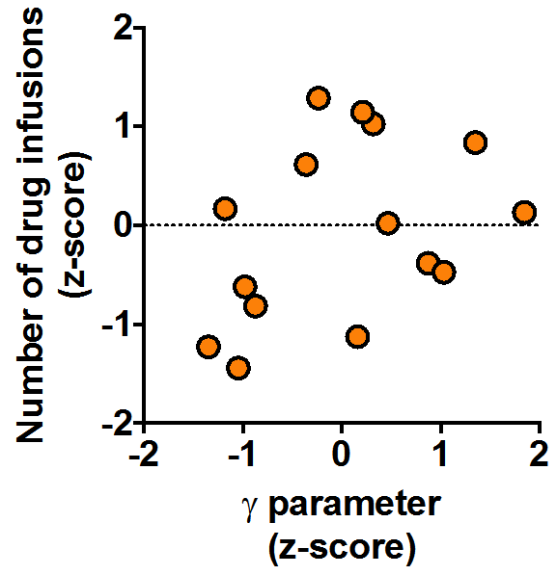
Bronson Krull

Yale/NIDA Neuroproteomics
Core

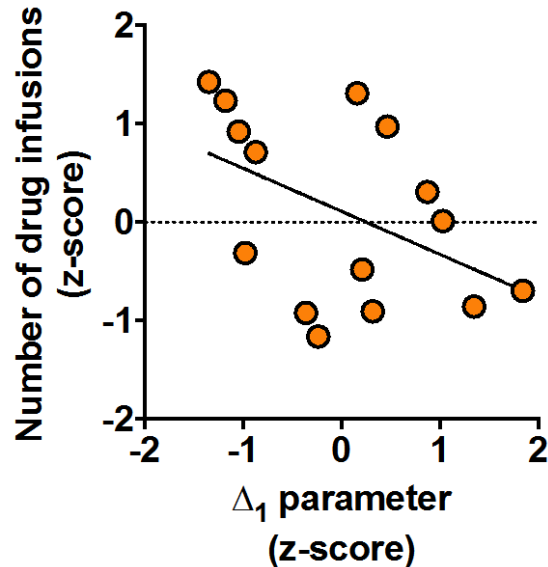


Reinforcement learning mechanisms predicting MA-taking behaviors

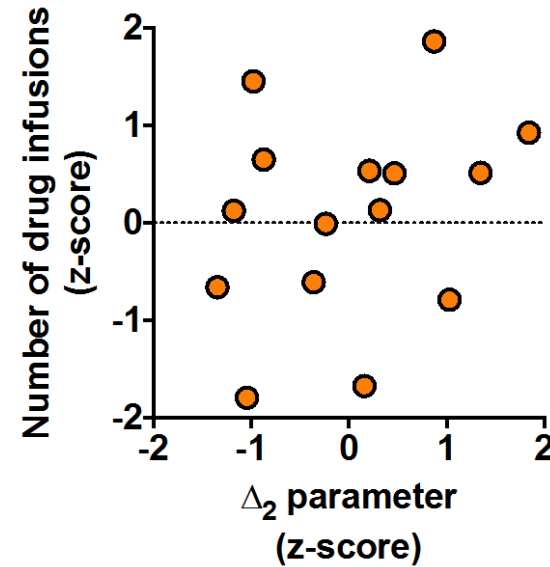
γ Forgetting rate



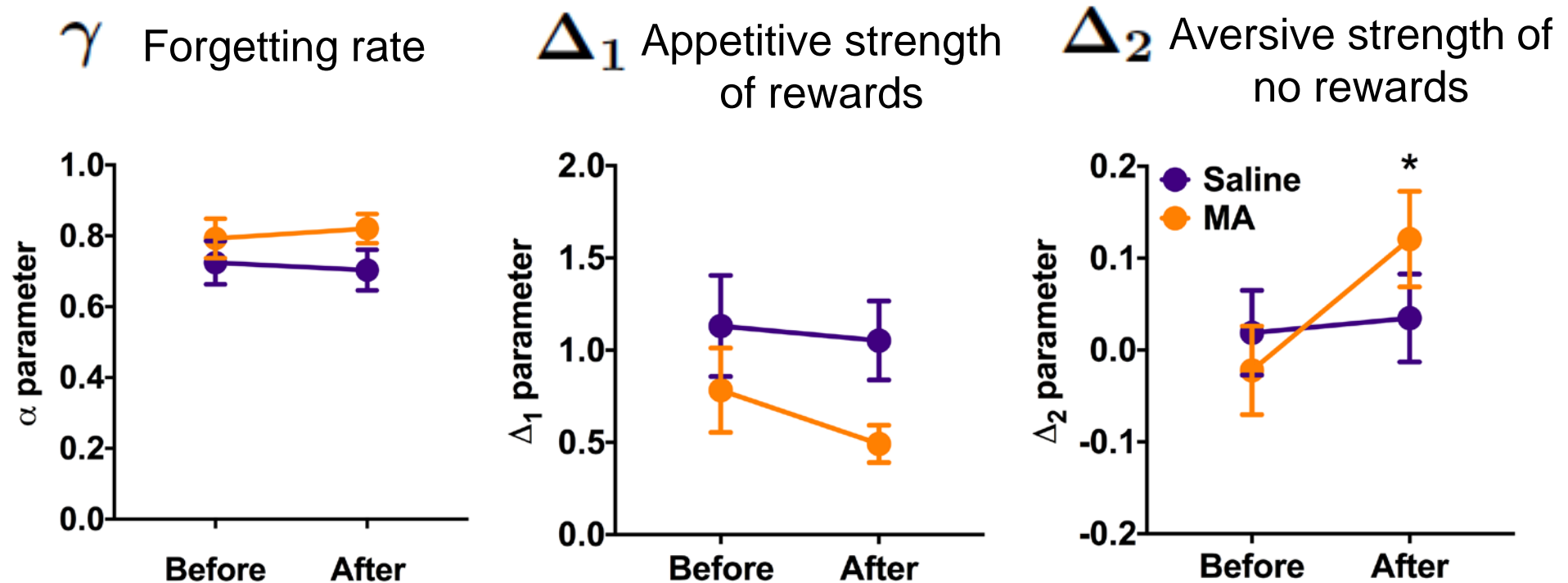
Δ_1 Appetitive strength of rewards



Δ_2 Aversive strength of no rewards



MA-induced disruptions in reinforcement learning mechanisms



Rab3B

