Identifying novel behavioral and protein biomarkers in addiction-related behaviors

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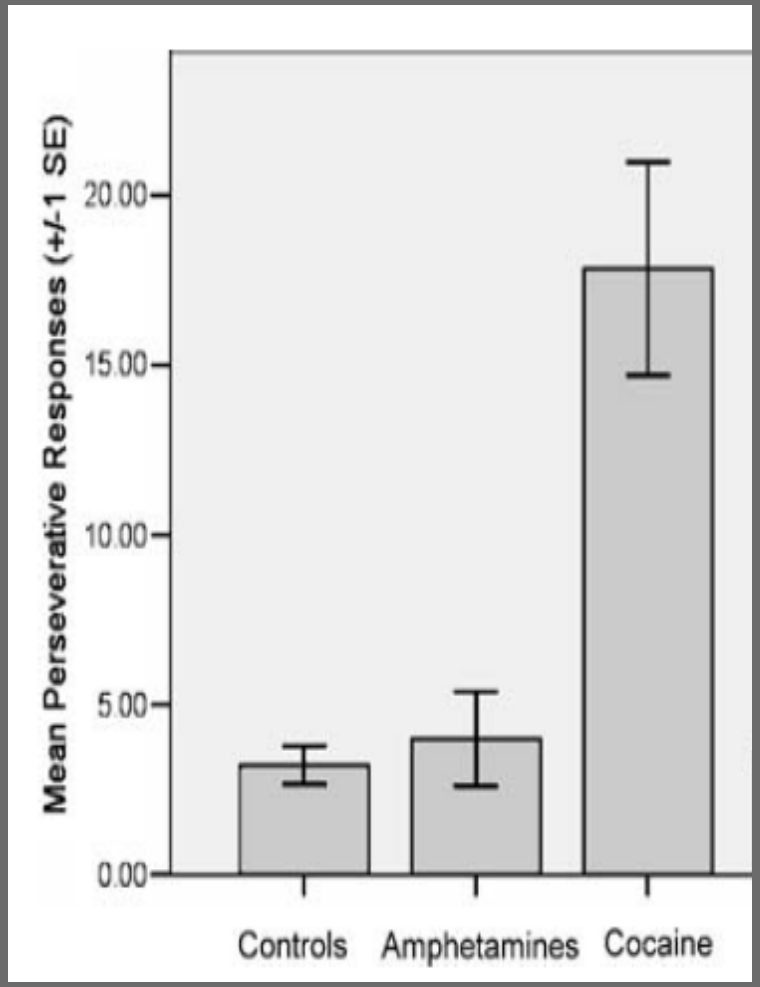
Addiction: a disorder of poor decision-making

- *Taking drug in larger and longer amounts than intended*
- *Wanting to cut down or quit but not being able to*
- *Difficulty stopping or reducing drug use despite negative consequences*



Ersche et al., 2008; Fillmore and Rush, 2003

Addiction: a disorder of poor decision-making

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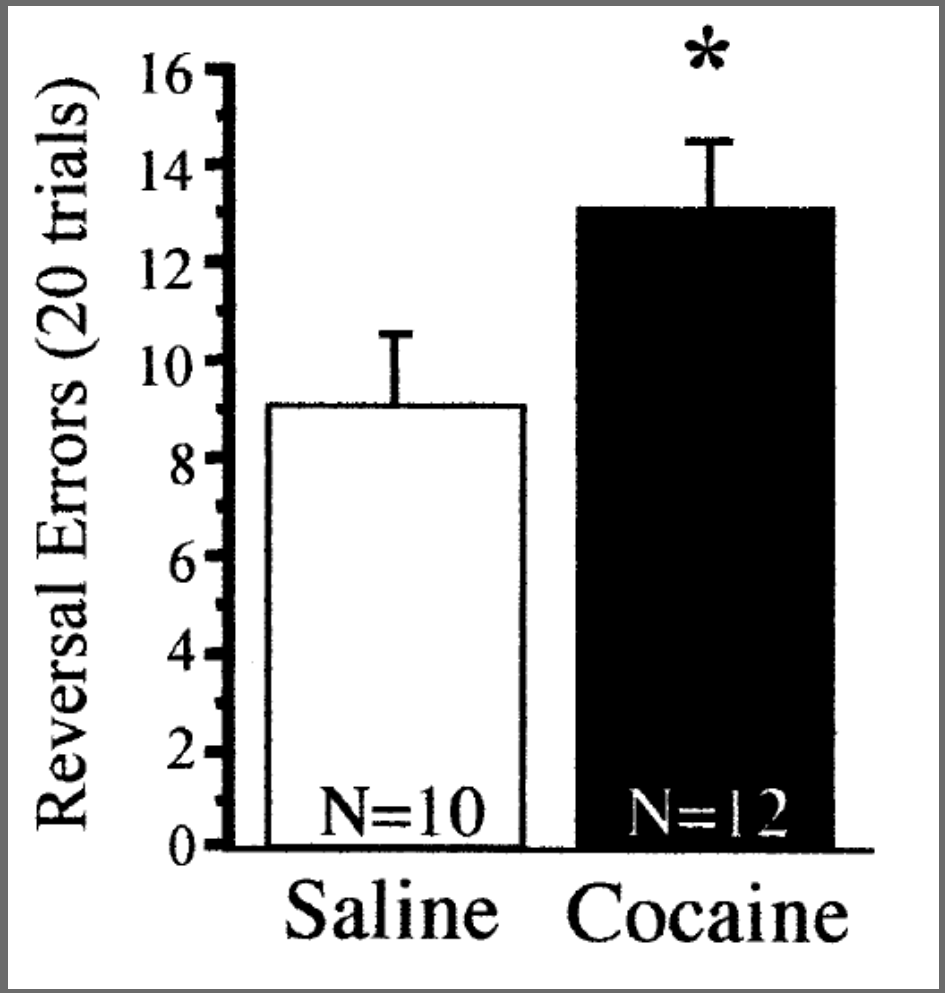
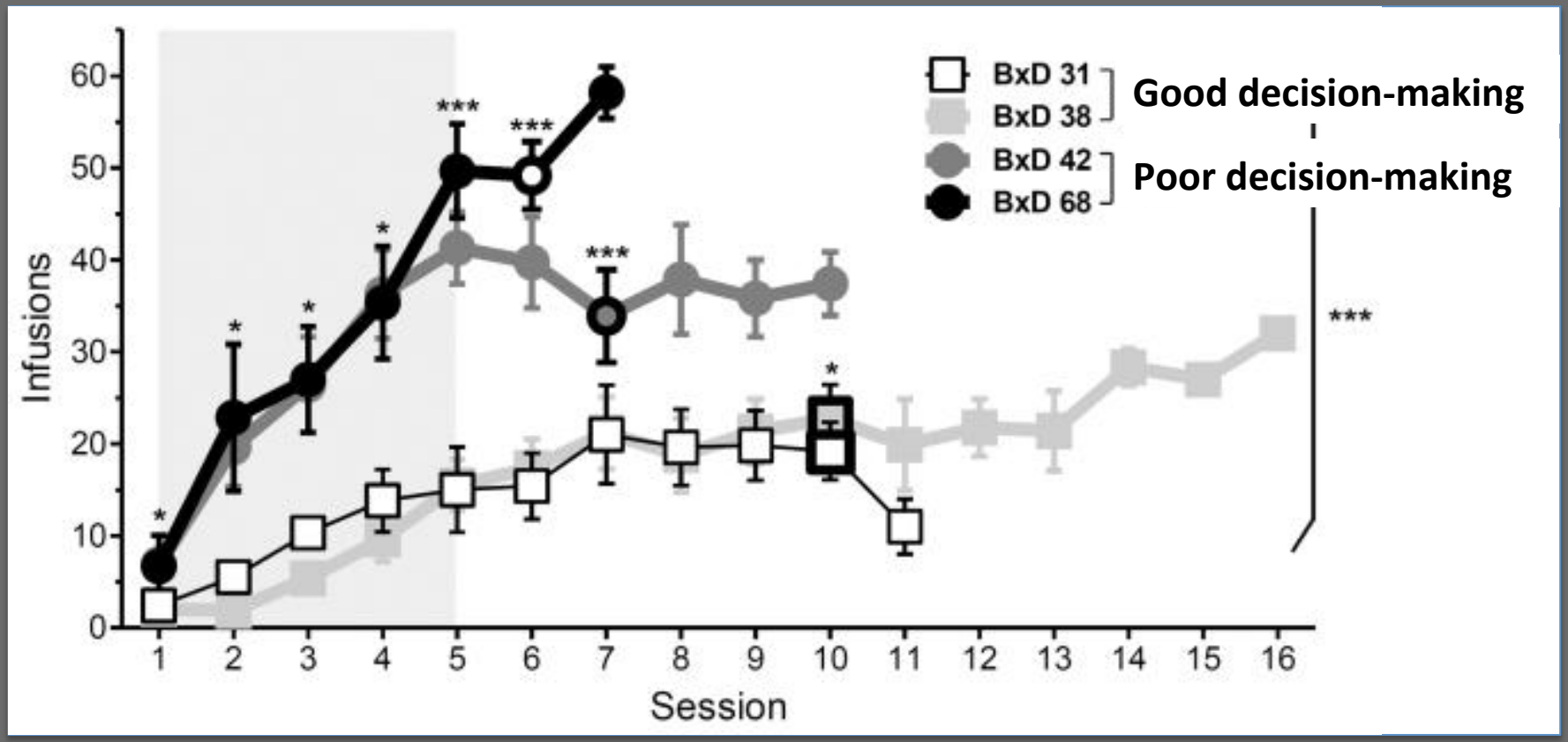


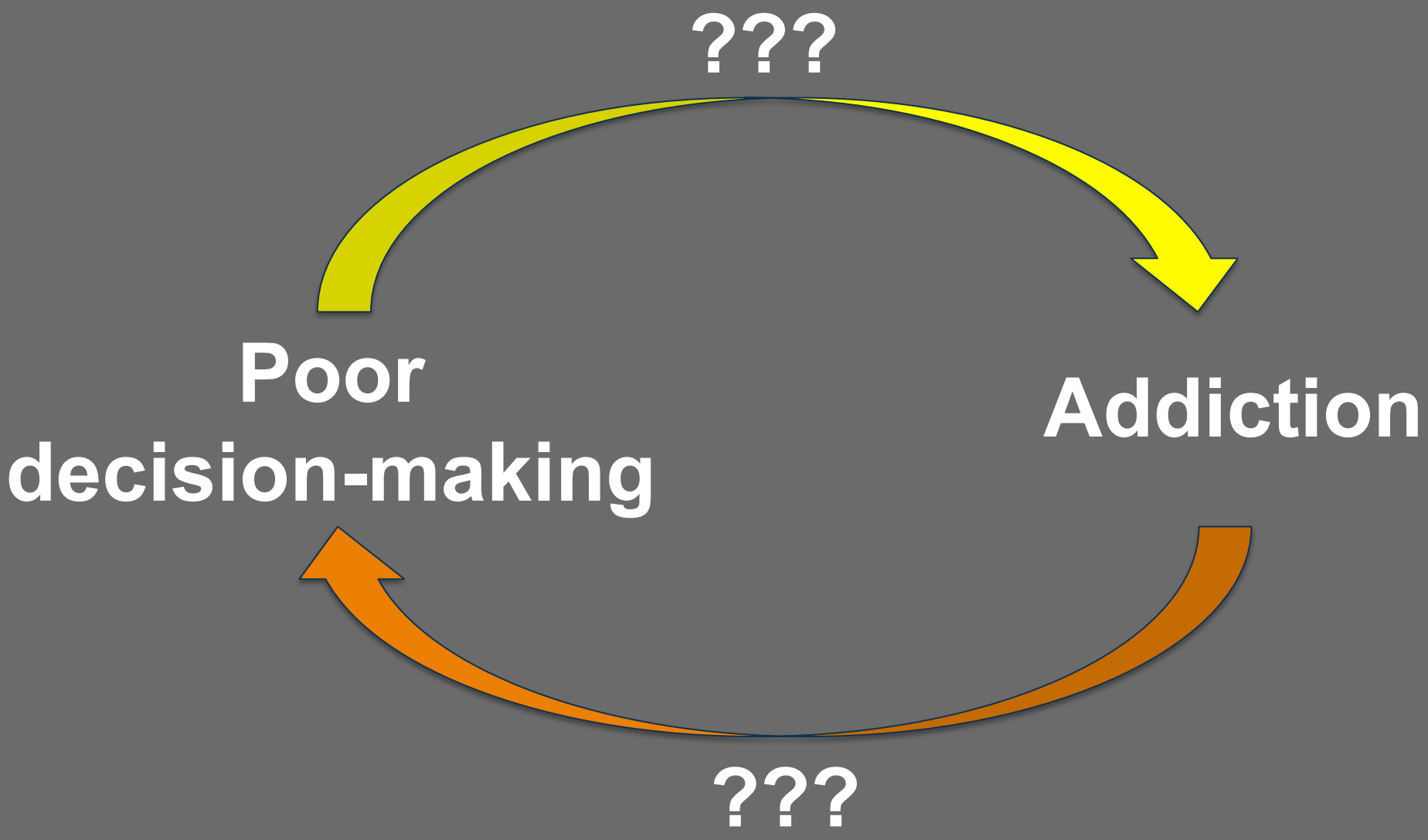
Jentsch et al., 2002; Schoenbaum et al., 2003

Decision-making: a risk-factor for addiction?

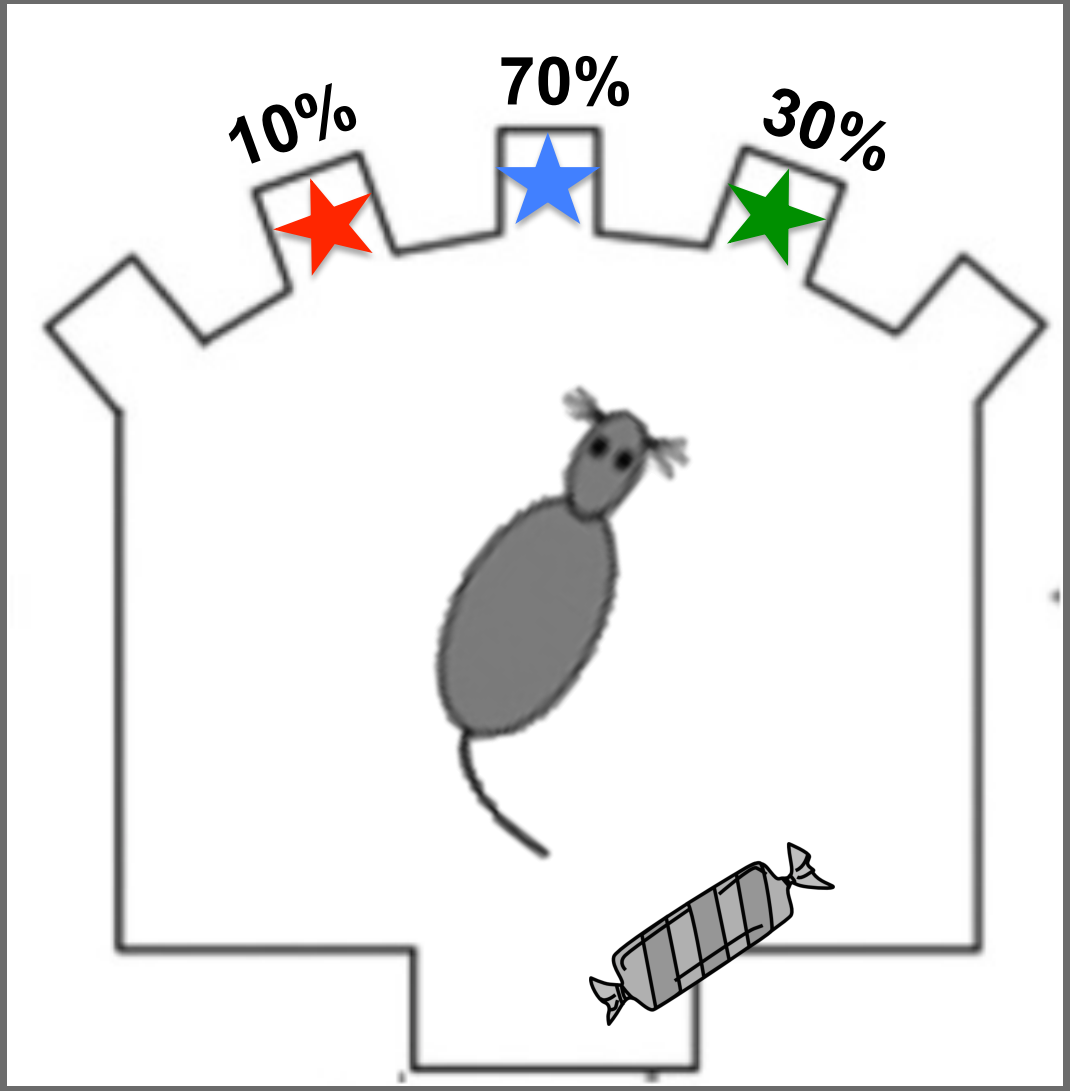


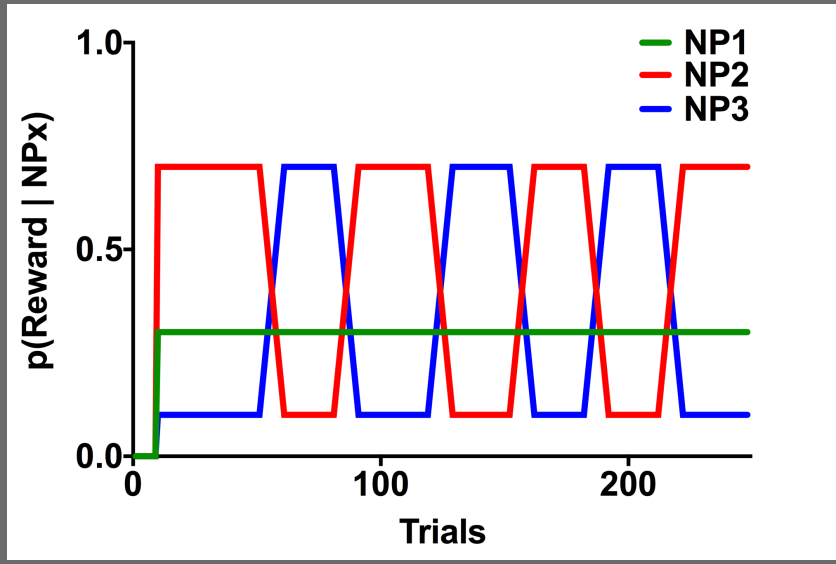
Cervantes et al. 2013

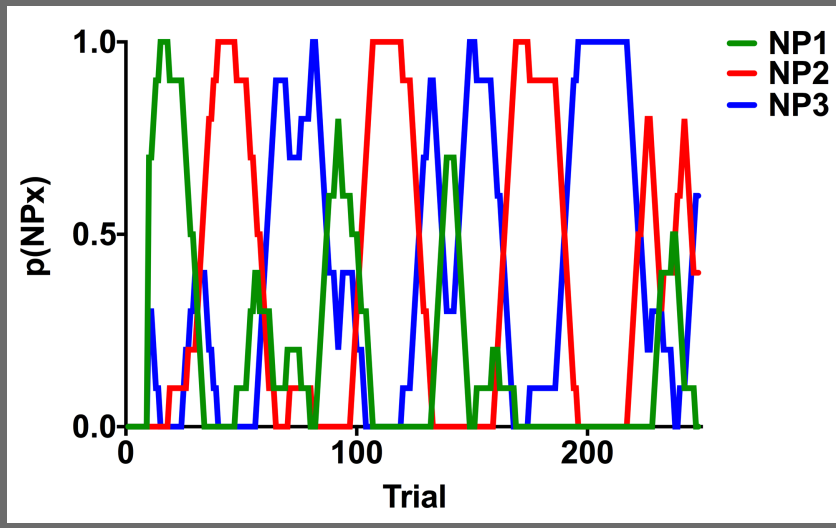
Decision-making as a biomarker of addiction?



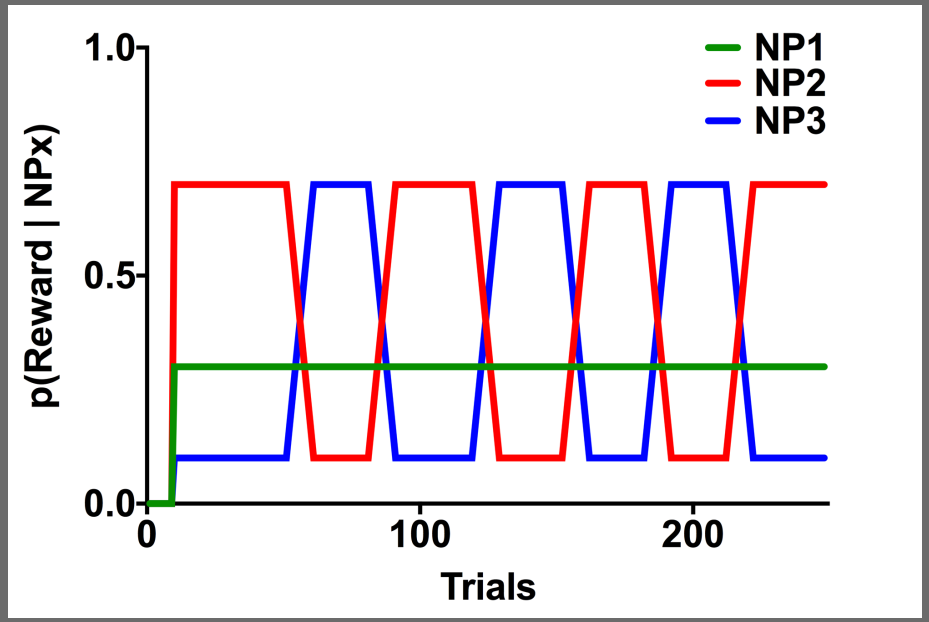
Decision-making in the rat: Probabilistic reversal learning





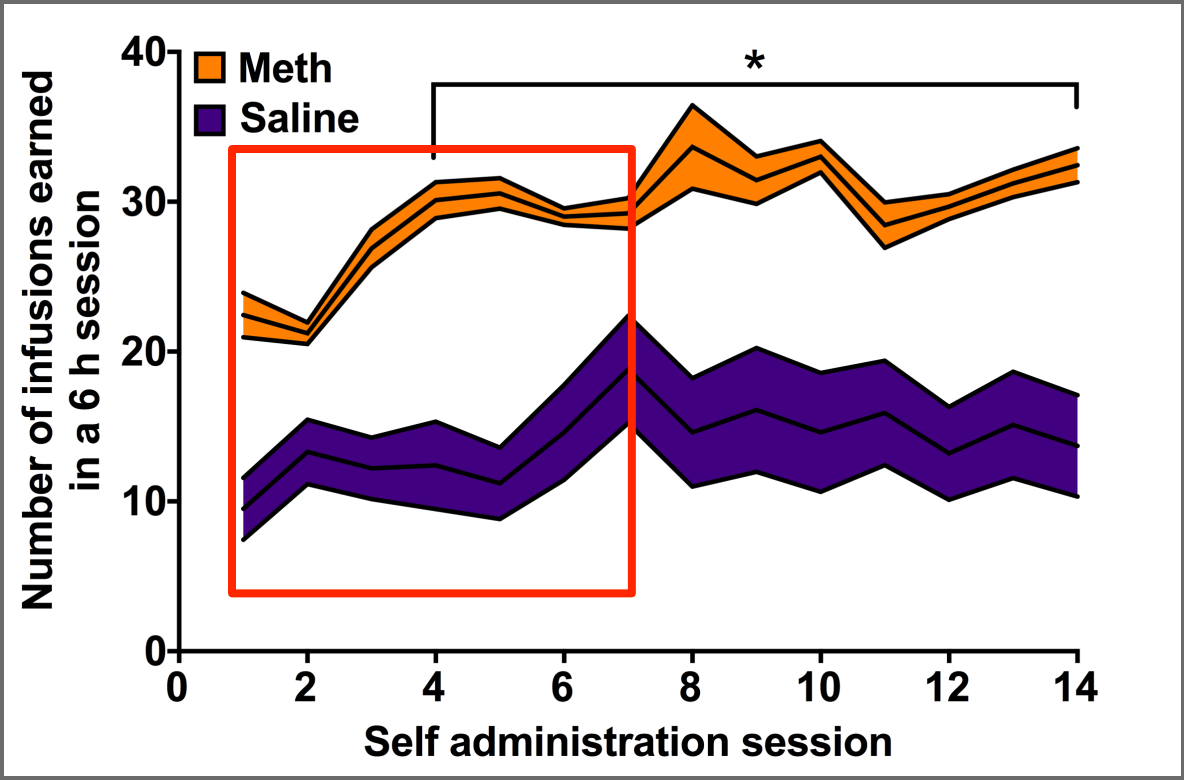


Investigating decision-making in addiction pathophysiology



PRL assessments

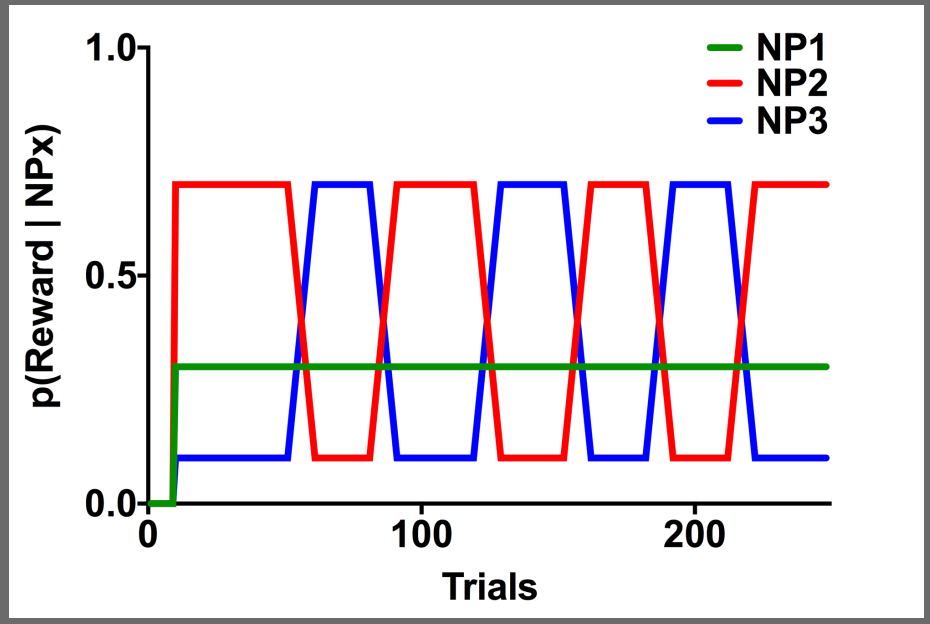
Investigating decision-making in addiction pathophysiology



PRL assessments

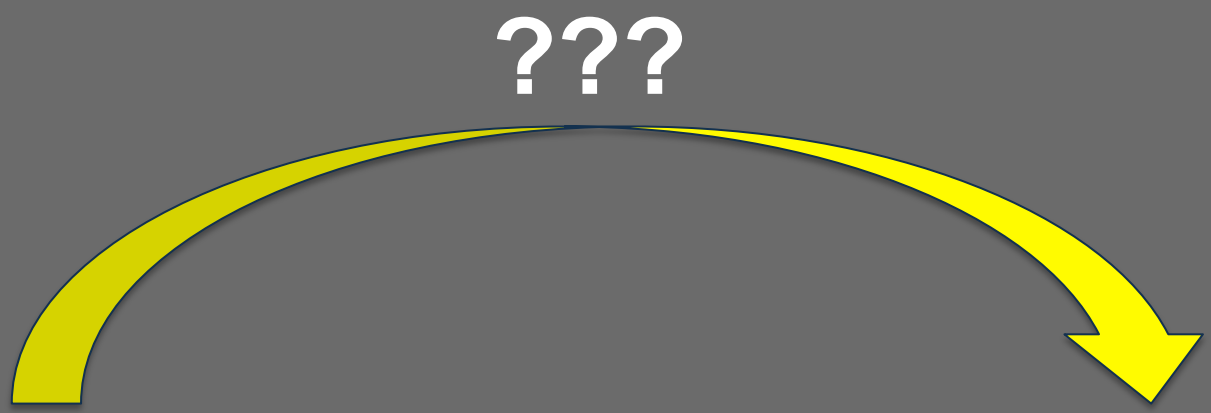
Self administration (saline or meth)

Investigating decision-making in addiction pathophysiology



PRL assessments → Self administration (saline or meth) → PRL assessments

Decision-making as a biomarker of addiction?

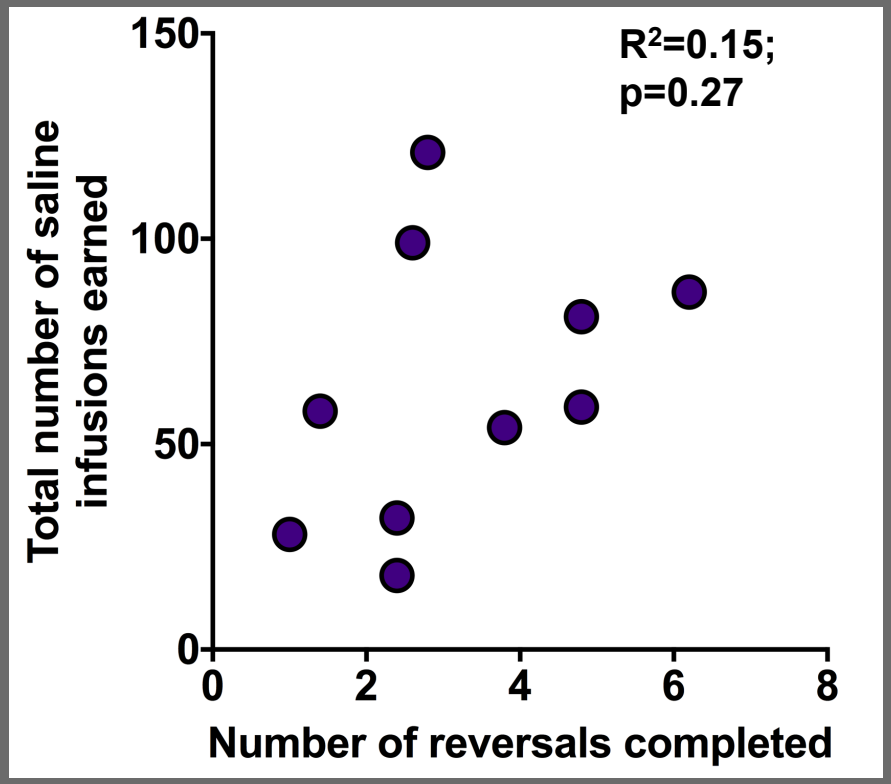


Poor decision-making

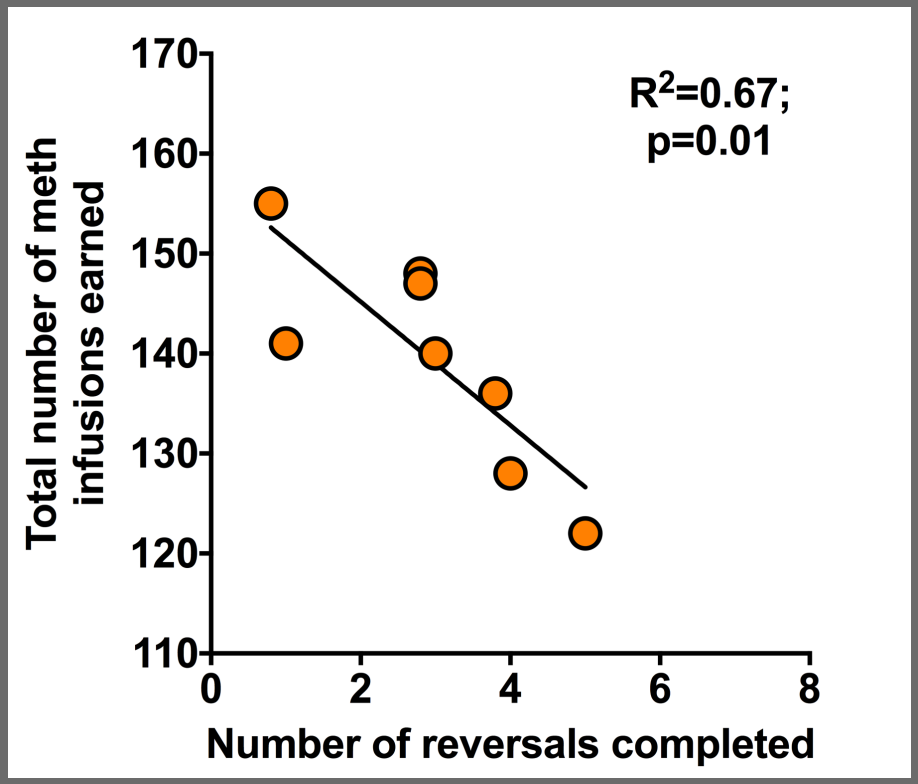
Addiction

PRL performance predicts early-stages of meth use

SALINE



METH



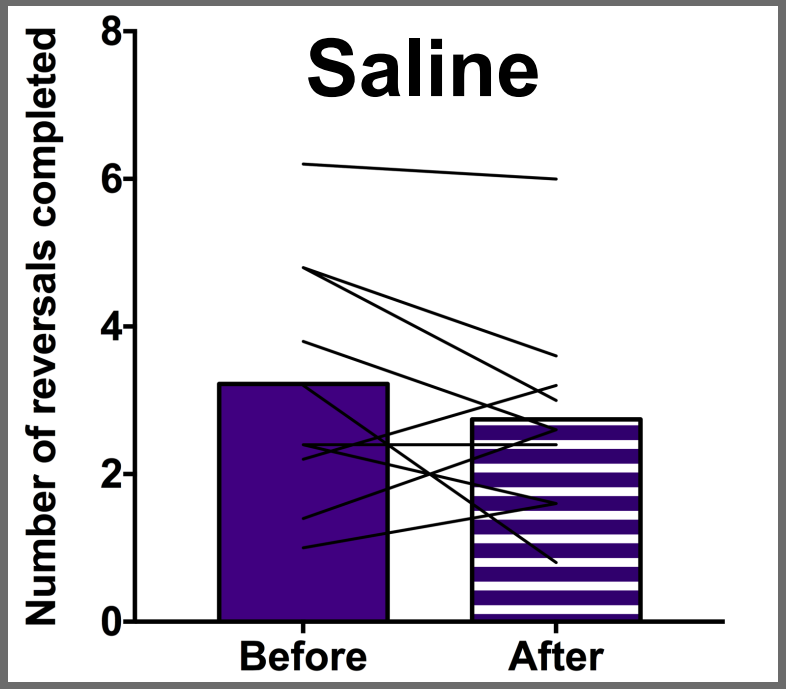
Decision-making as a biomarker of addiction?

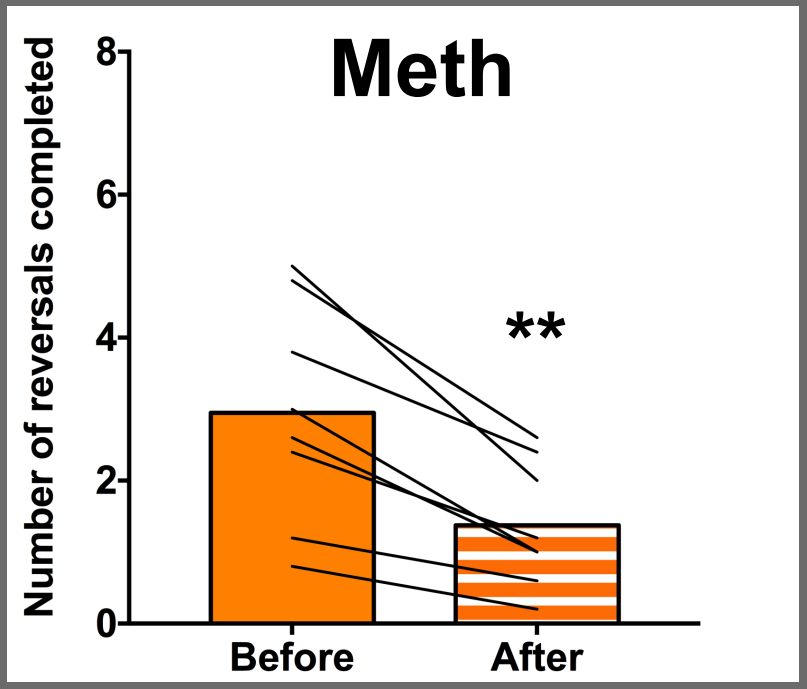
Poor decision-making

Addiction

???

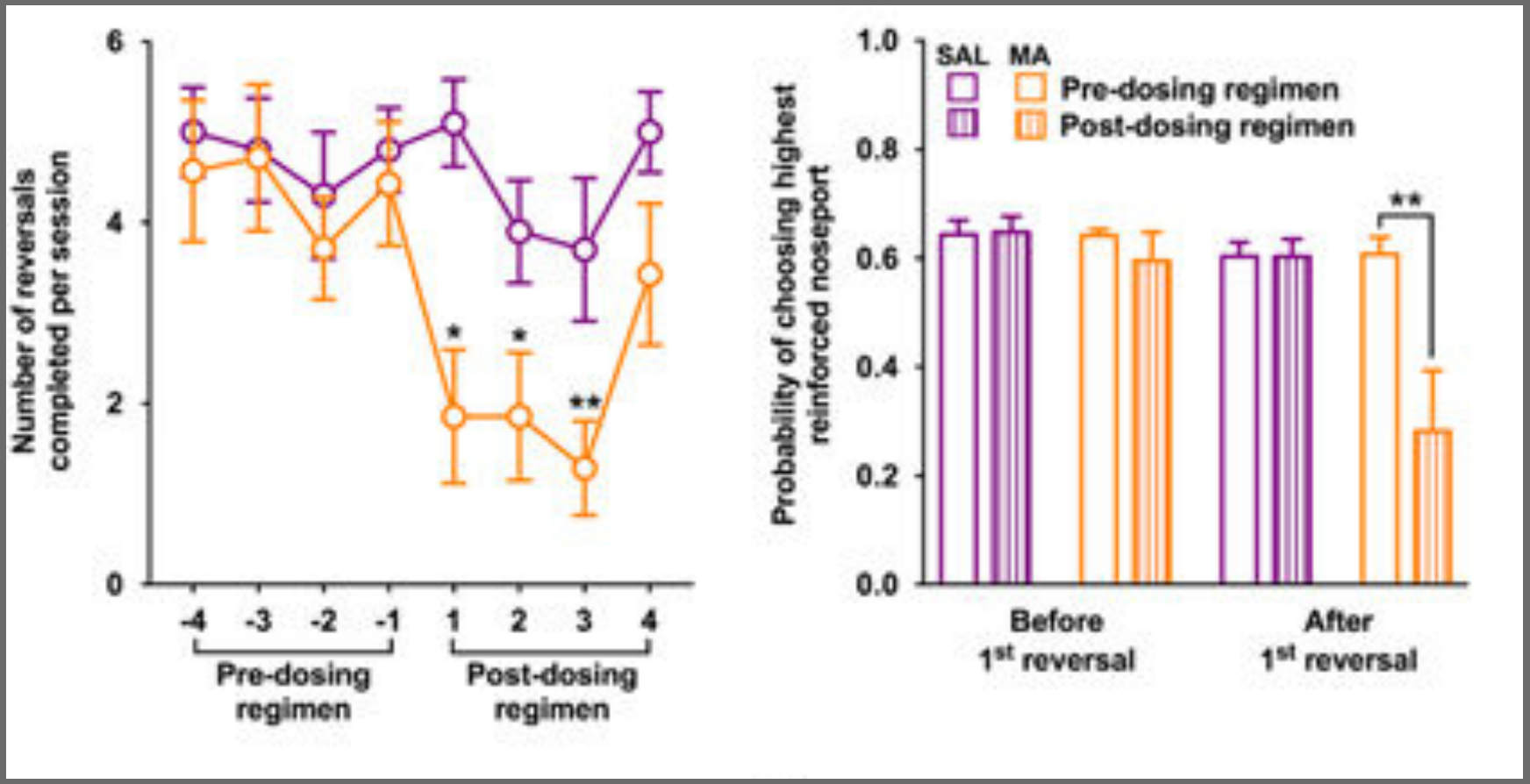
Self-administration of meth disrupts decision-making in PRL





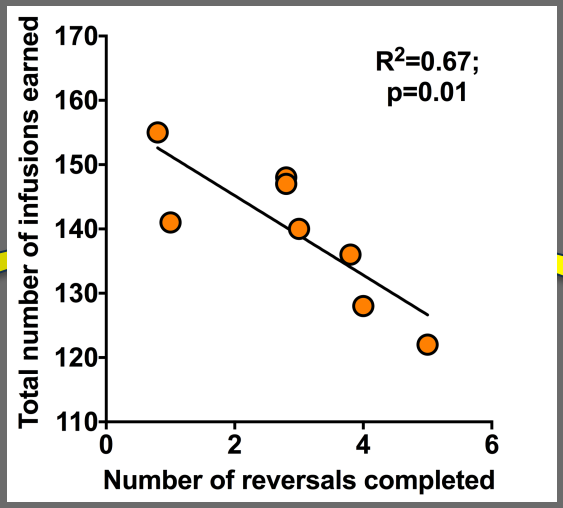
Time x group: $F_{(1,16)}$=4.81; p=0.04
Group: $F_{(1,16)}$=16.94; p=0.0008
Time: $F_{(1,16)}$=1.70; p=0.21

Disruptions in PRL caused by experimenter administered meth



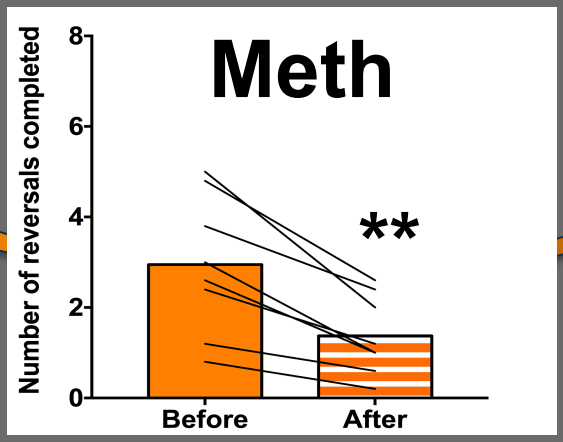
Groman et al., 2017

Decision-making: a biomarker of addiction



Addiction

Poor decision-making



Delineating decision-making processes

Reinforcement learning model (Barraclough et al., 2004):

If trial is rewarded:

$V(t) = \alpha * V(t) + \Delta_1$

If trial is unrewarded:

$V(t) = \alpha * V(t) + \Delta_2$

Unchosen actions:

$V(t) = \alpha * V(t)$

Three free parameters:

α = forgetting rate

- ↑ retain action values longer

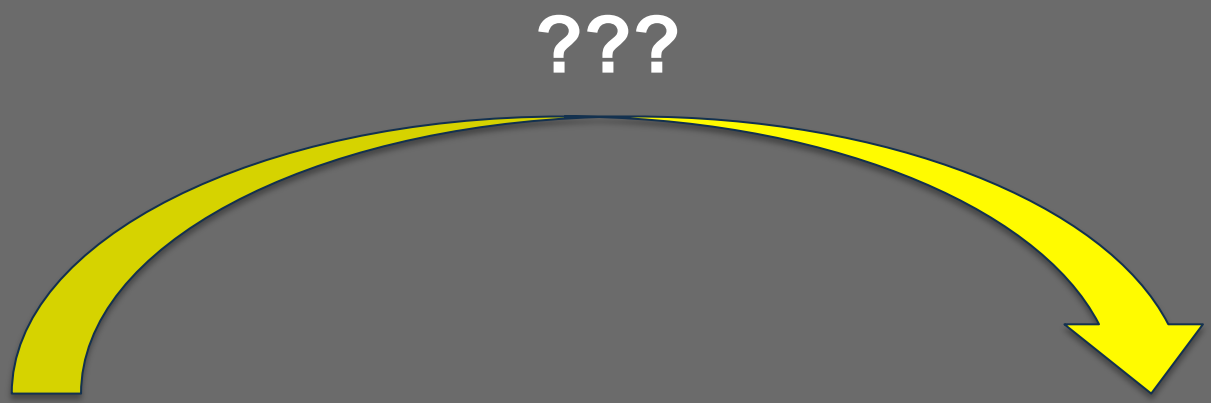
Δ_1 = appetitive strength of rewards

- ↑ greater influence of rewards on choices

Δ_2 = aversive strength of no reward

- ↓ greater influence of no rewards on choices

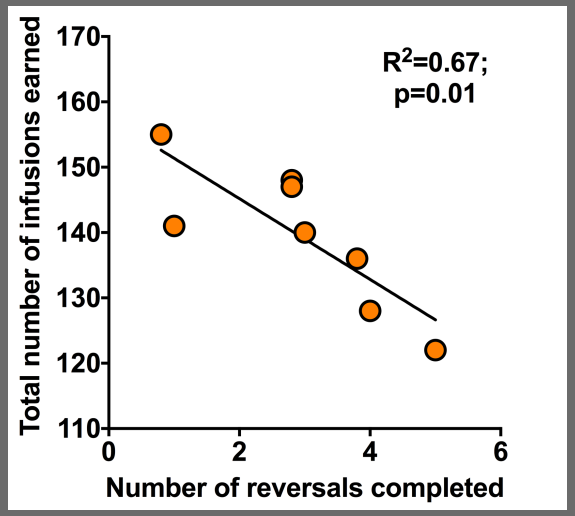
Decision-making processes that influence addiction vulnerability



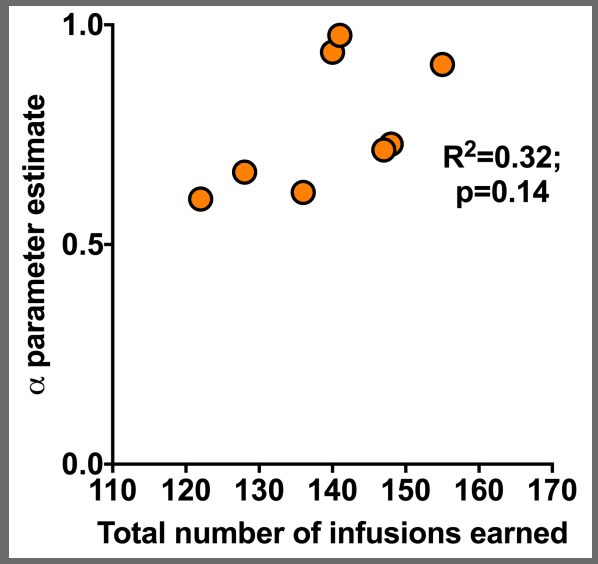
Poor decision-making

Addiction

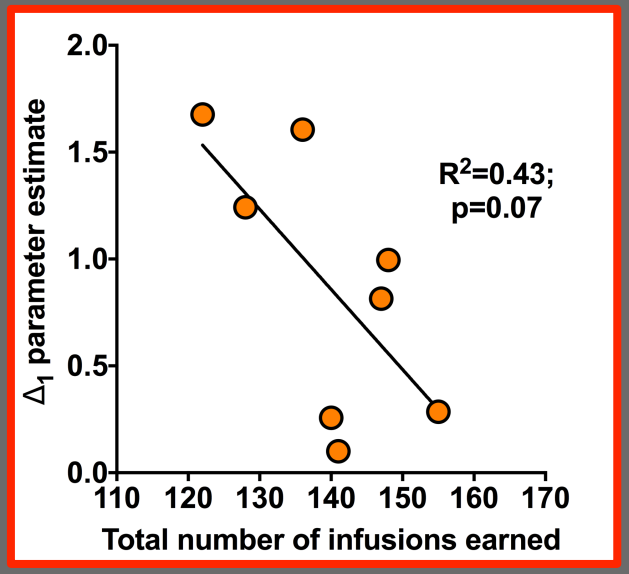
Appetitive strength of rewards predicts future drug use



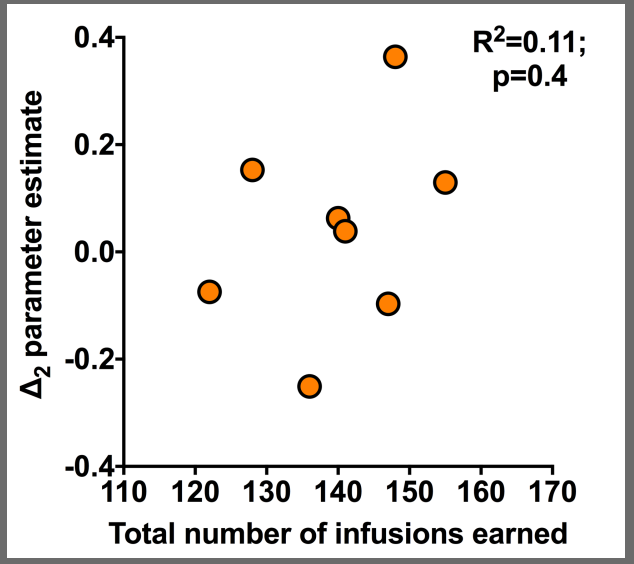
α parameter



Δ_1 parameter



Δ_2 parameter



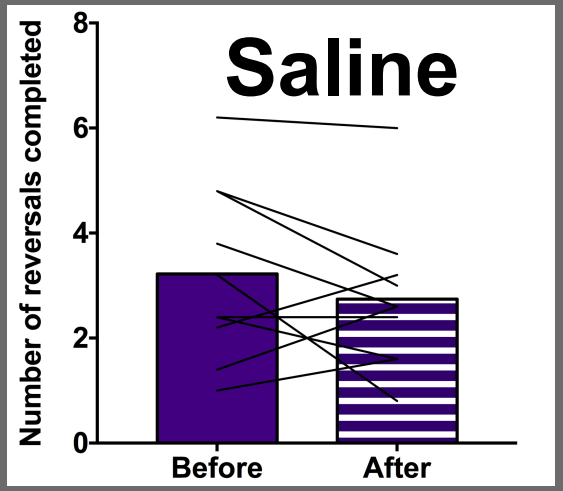
Decision-making process disrupted by drugs

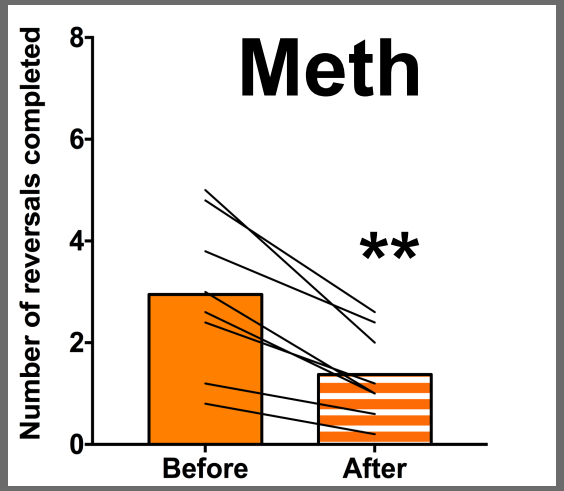
Poor decision-making

Addiction

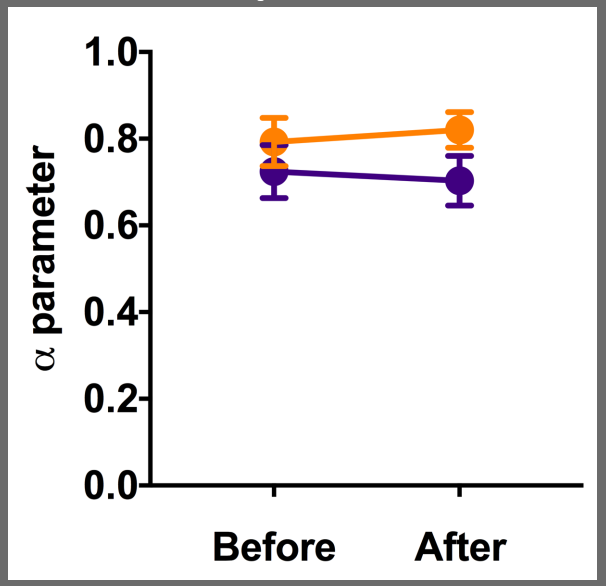
???

Effects of meth on decision-making

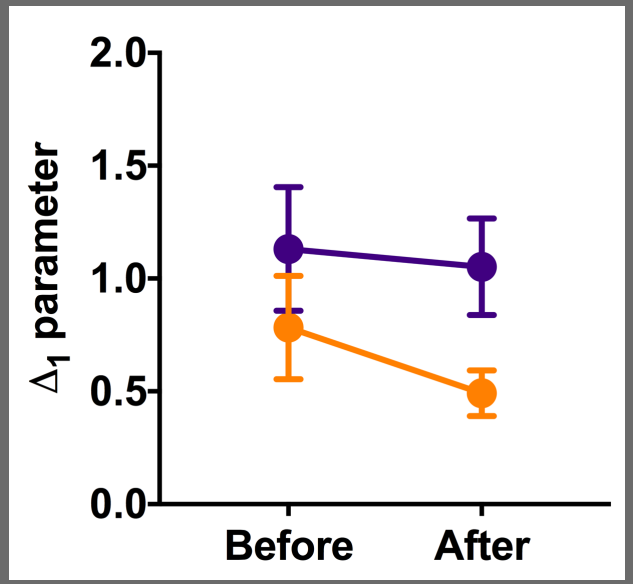




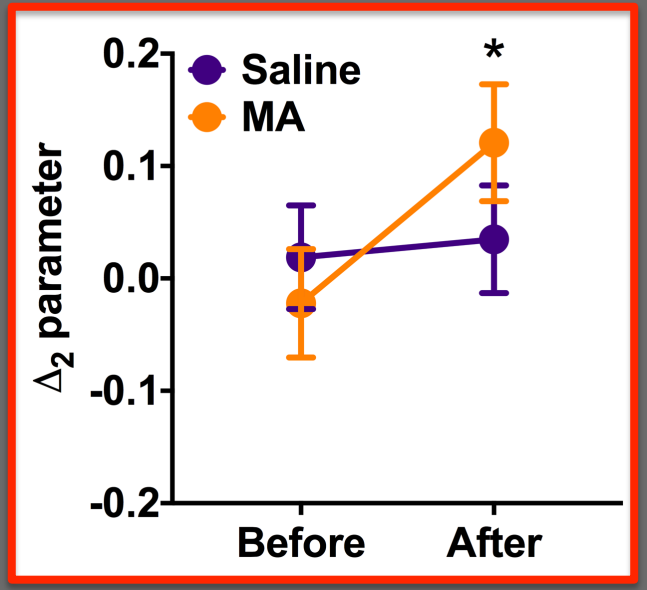
α parameter



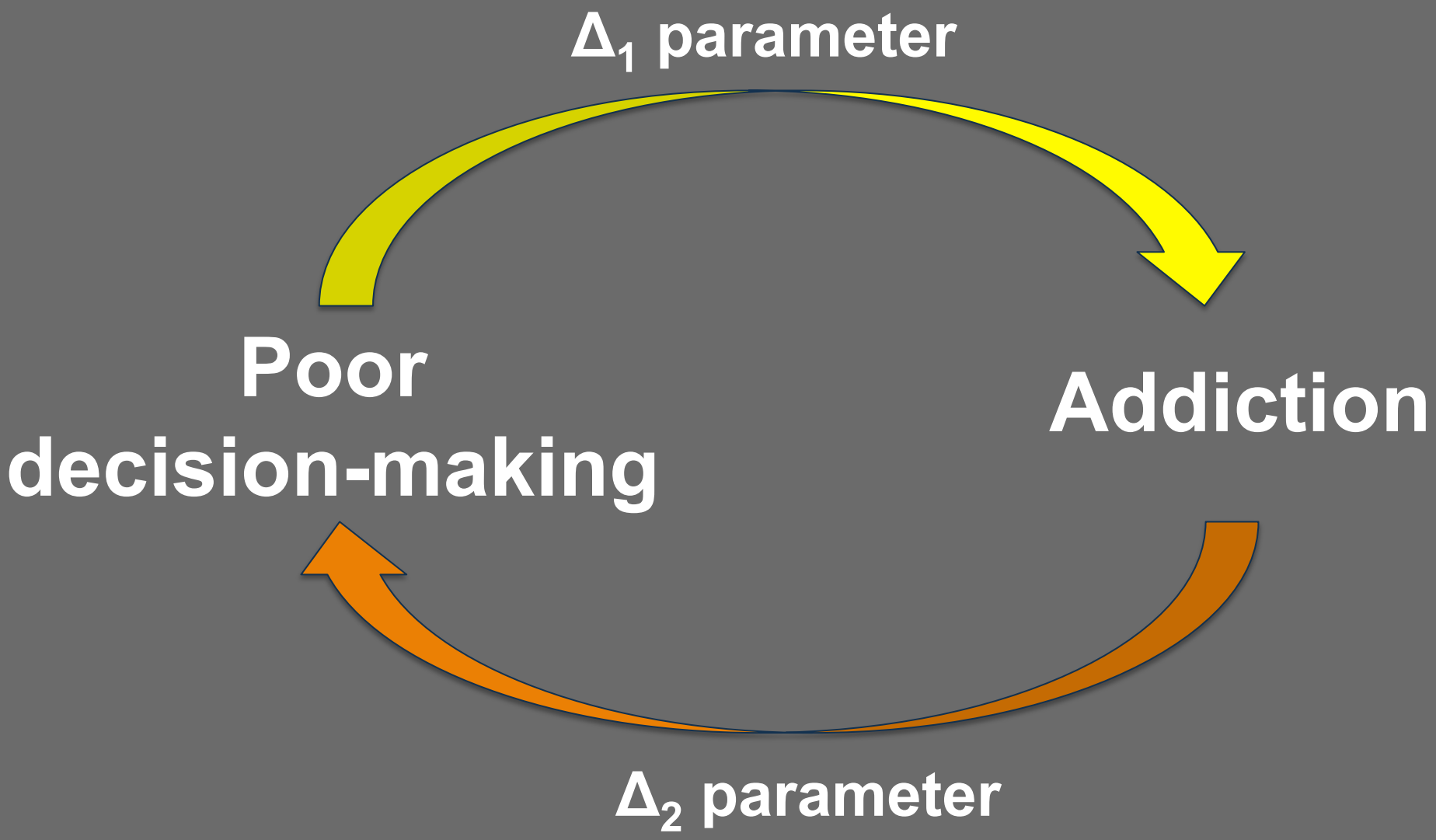
Δ_1 parameter



Δ_2 parameter



Decision-making: a biomarker of addiction



Decision-making and addiction interventions

Prevention	Treatment
Gene X	Chronic drug use
Disruptions in Protein Y	Disruptions in Protein Z
Decision-making problems due to low Δ_1 values	Decision-making problems due to reductions in Δ_2 values
Heightened vulnerability to addiction	Compulsive drug taking

Protein discovery with proteomics

Sample collection

Sample preparation

Protein digest (Trypsin) to create unique peptides for mass spec analysis

Processing protein digests

Liquid chromatography for peptide separation
Tandem mass spec to identify and quantify each peptide

Data processing

Matching peptides to protein sequences

Data analysis

Compare protein measurements to decision-making phenotypes

Identifying behavior-protein correlates

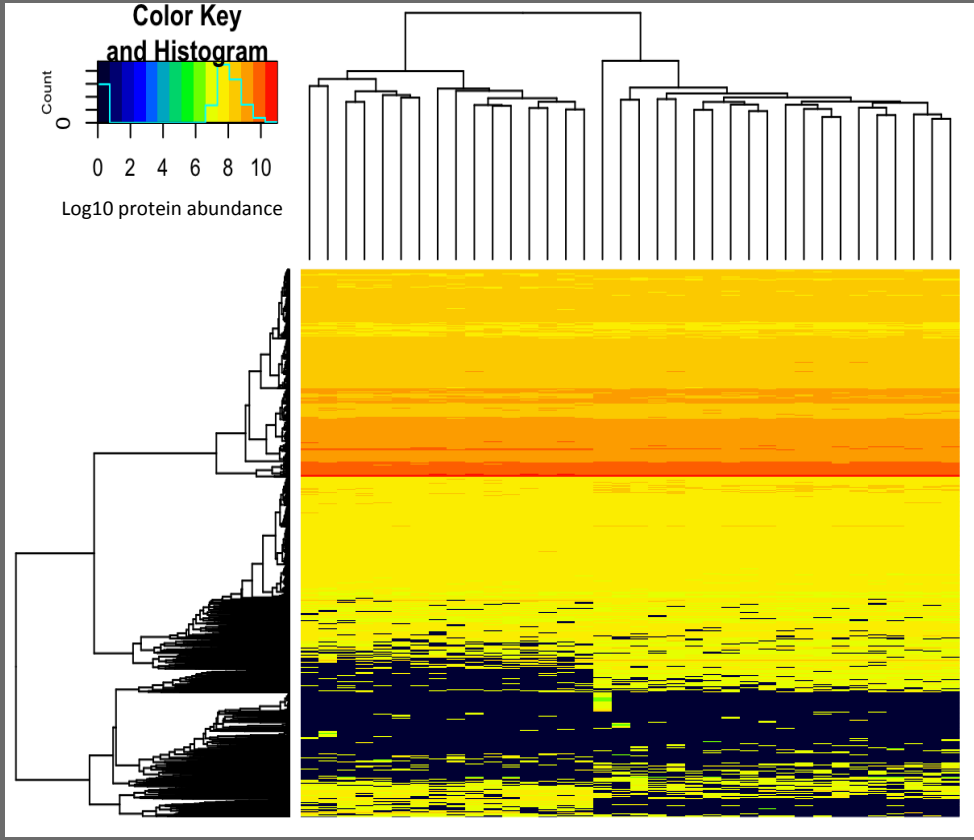
Behavior-protein correlates (N=16)

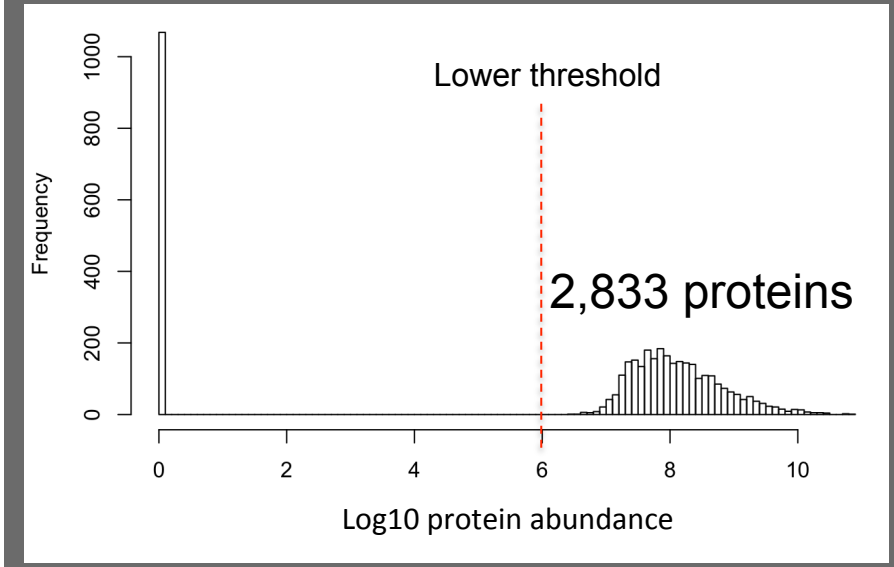
- PRL assessments
- Tissue collection (ventral striatum)
- Protein expression (LC-MS/MS)

Post-drug behavioral-protein correlates (N=18)

- PRL assessments
- Meth self-administration (6 h/day for 14 days)
- PRL assessments
- Tissue collection (ventral striatum)
- Protein expression (LC-MS/MS)

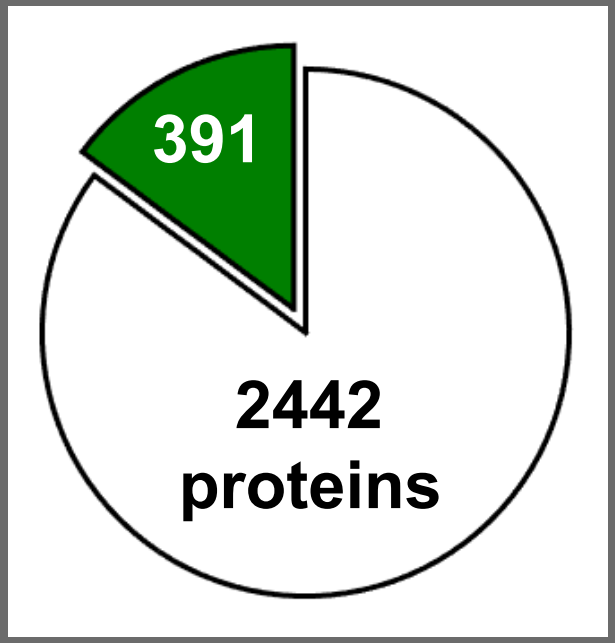
Data processing

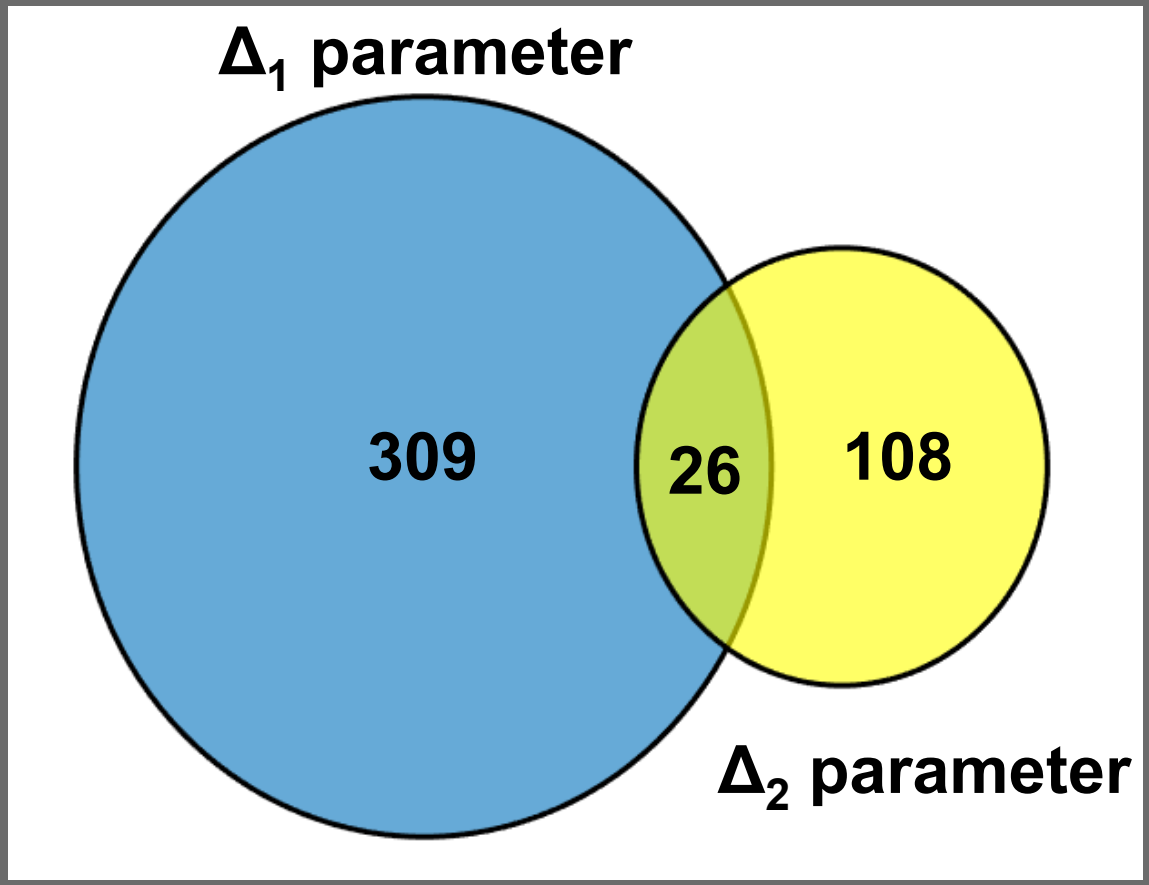




Proteins must be detected in at least 25% of samples. Abundance lower threshold was set at 10^6

Protein-behavior correlates



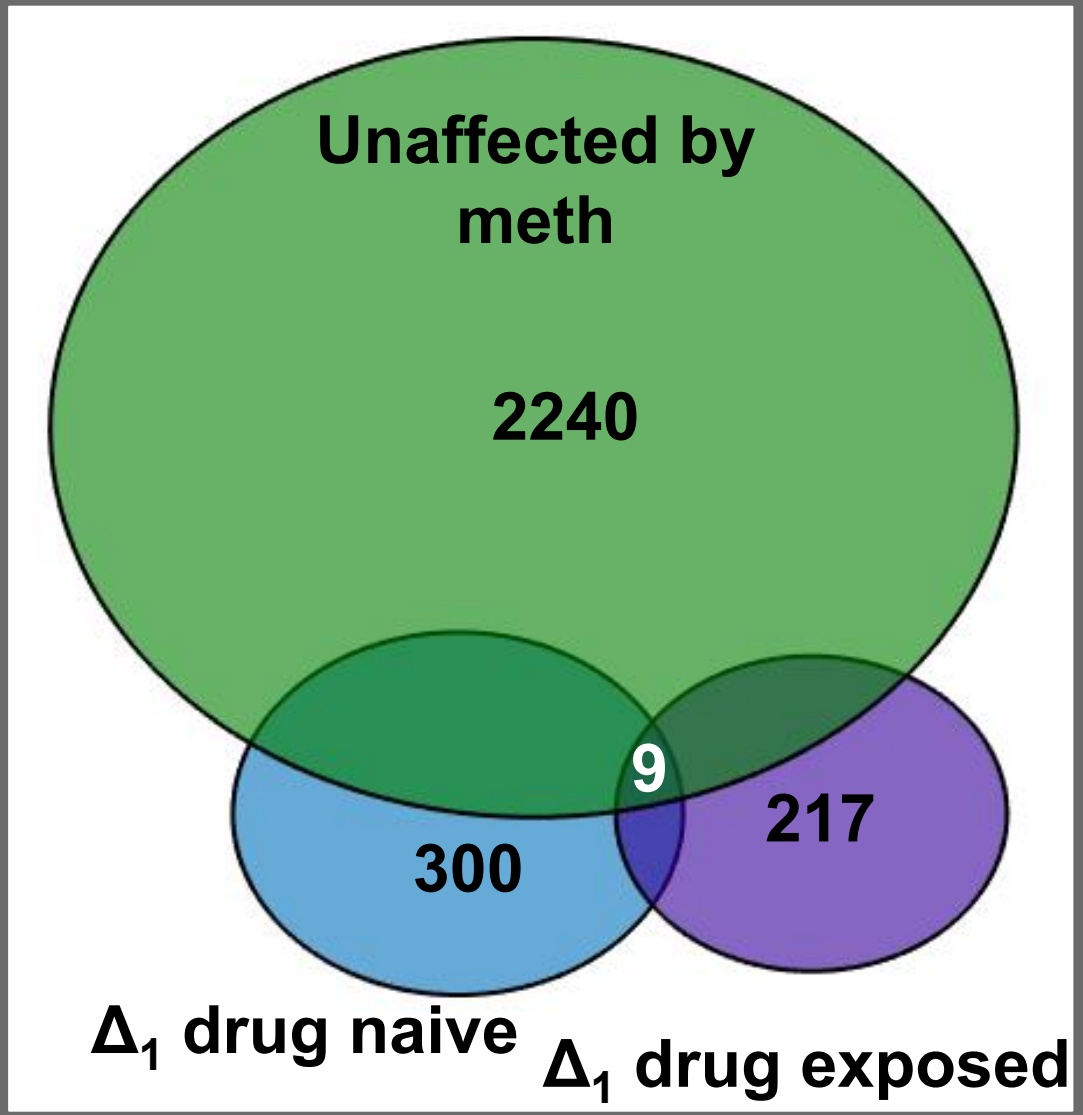


p<0.05; not corrected for multiple comparisons

Isolating protein targets involved in addiction vulnerability

Criterion:

- Correlates with Δ_1 parameter in drug-naïve rats
- Correlates with Δ_1 parameter in drug-exposed rats
- Is NOT disrupted in rats exposed to meth



Protein targets involved in addiction vulnerability

Gene	Protein	Function	Link 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)

Addiction vulnerability proteins

- Ryr2 (ryanonide receptor 2): forms channels that transport Ca2+
  - Target for heart disease (might be difficult to target systemically)

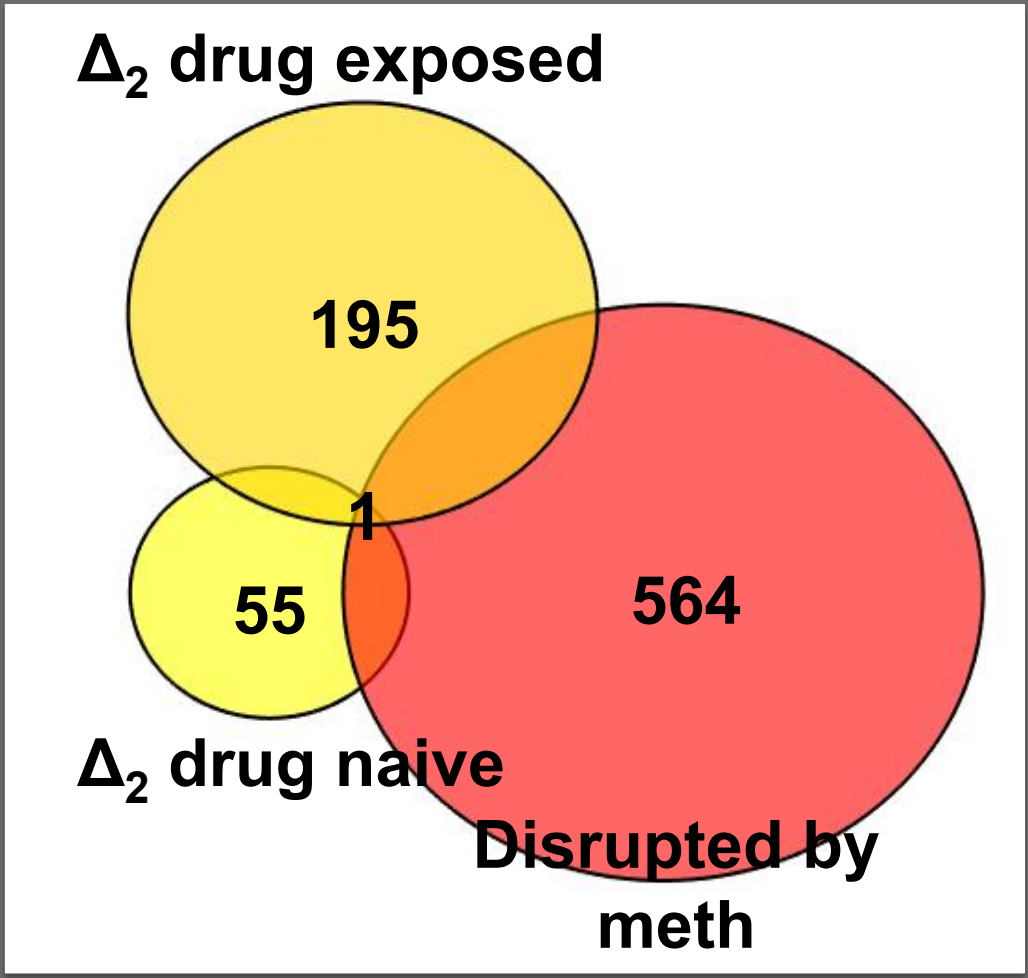
- Snx1 (sorting nexin 1): involved in intracellular trafficking
  - Possible role in regulating GIRK channels

- Atxn2l (Ataxin-2 like): unknown function but part of the spinocerebellar ataxia family
  - Seems to be important in dopamine signaling (Atxn2 KO mice have lower D2 receptors)

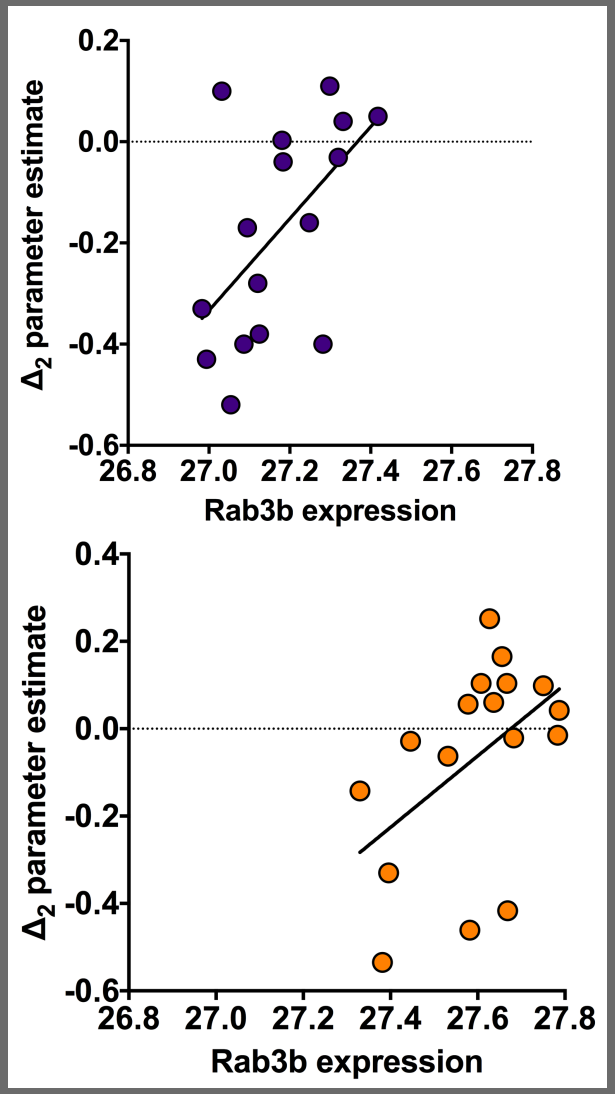
Isolating behaviorally relevant protein targets altered by meth

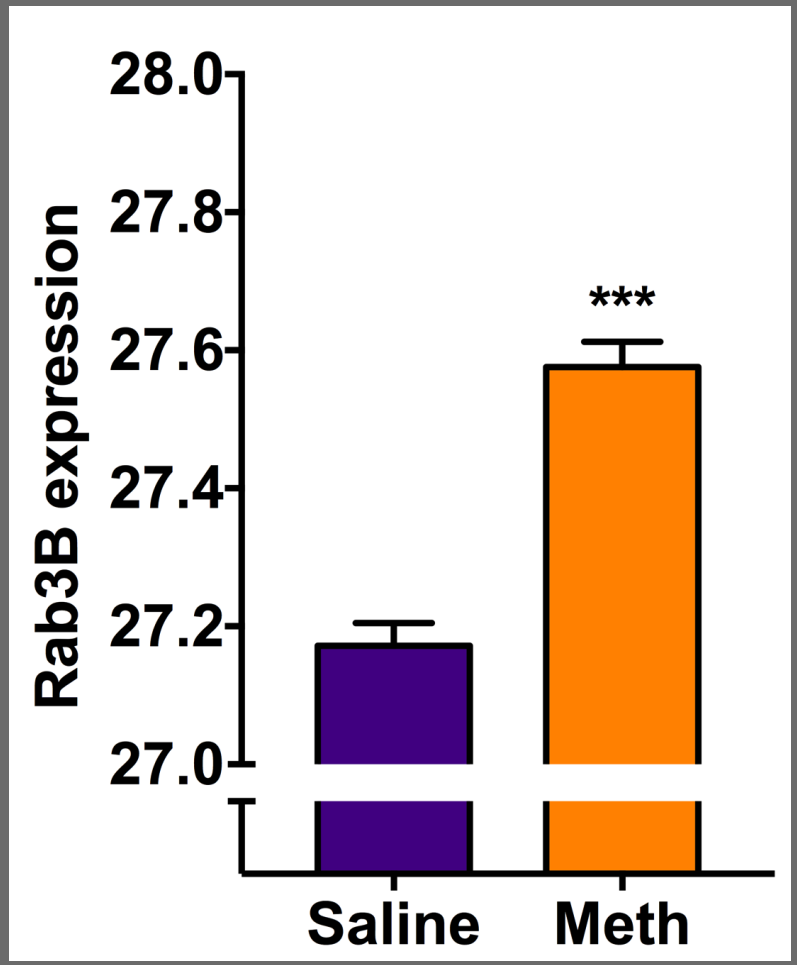
Criterion:

- Correlates with the Δ_2 parameter in drug-naïve rats
- Correlates with the Δ_2 parameter in meth-exposed rats
- Disrupted in rats exposed to meth



Rab3B: a mechanism for drug-induced impairments?





Ras-related protein (Rab-3b)

- Monoameric GTPase protein enriched in synaptic vesicles
  - Involved in synaptic transmission and vesicle trafficking

- Knock down of Rab3B in the hippocampus impairs inhibitory LTD and improves reversal learning (Tsetsenis et al., 2011)

- Overexpression of Rab3B protects DA neurons from 6-OHDA insults (Chung et al., 2009)

Future studies

Reduce addiction vulnerability

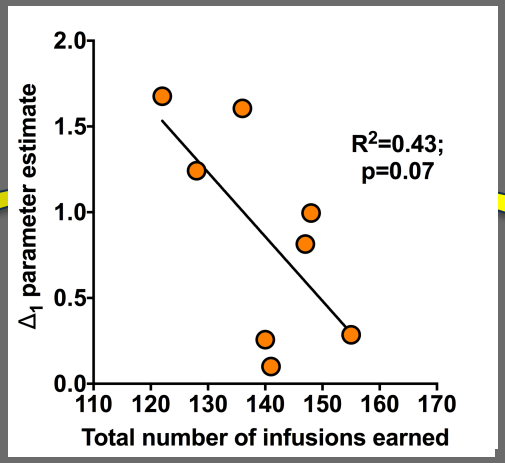
- Increase expression of Ryr2, Snx1, or Atxn2l (via viral techniques)
  - Improve decision-making → reduce drug taking

Restore decision-making

- Reduce Rab3B expression
  - Improve decision-making → reduced relapse-related behaviors

Summary

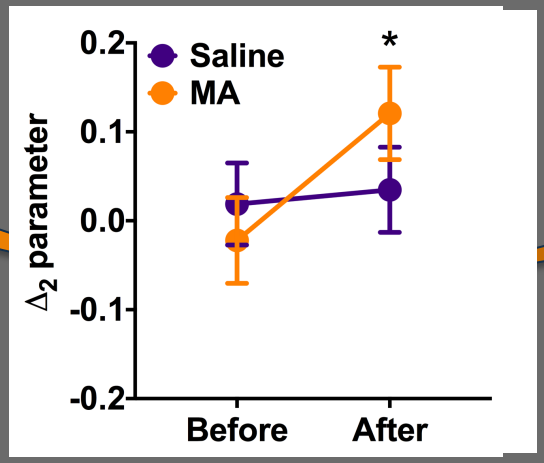
Ndufb10 Setd7 Dpp10 Ryr2 Sort1 Naa15 Gamt Snx1 Atxn2l



Poor decision-making

Addiction

Rab3B



Acknowledgements

Taylor Lab

Jane R. Taylor, Ph.D.

Nathaniel Smith, Ph.D.

Colby Keistler, Ph.D.

Stacey Quick, Ph.D.

Carol Gianessi

Dayshalis Ofray

Nairn Lab

Angus Nairn, Ph.D.

Becky Carlyle, Ph.D. **(MGH)**

Rashaun Wilson, Ph.D.

Yale/NIDA Proteomics Center

Jean Kanyo

NIDA NATIONAL INSTITUTE ON DRUG ABUSE

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