Identification of Novel Regulators of Cocaine Associated Memories

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Why Memory?

Why Memory?


Corona
Extra
LA CERVEZA MAS FINA
BEER
12 FL. OZ.
Brewed and bottled by
CERVECERIA MODELO, S.A. DE C.V.
MEXICO, D.F.

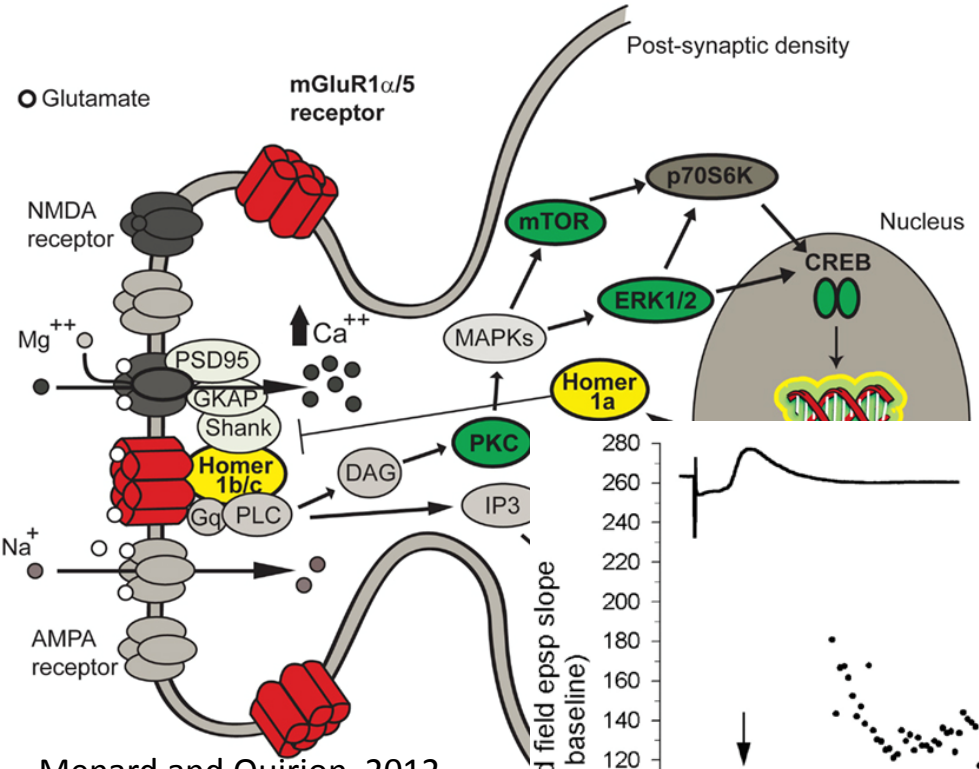
Stages of Memory

“HIGH”

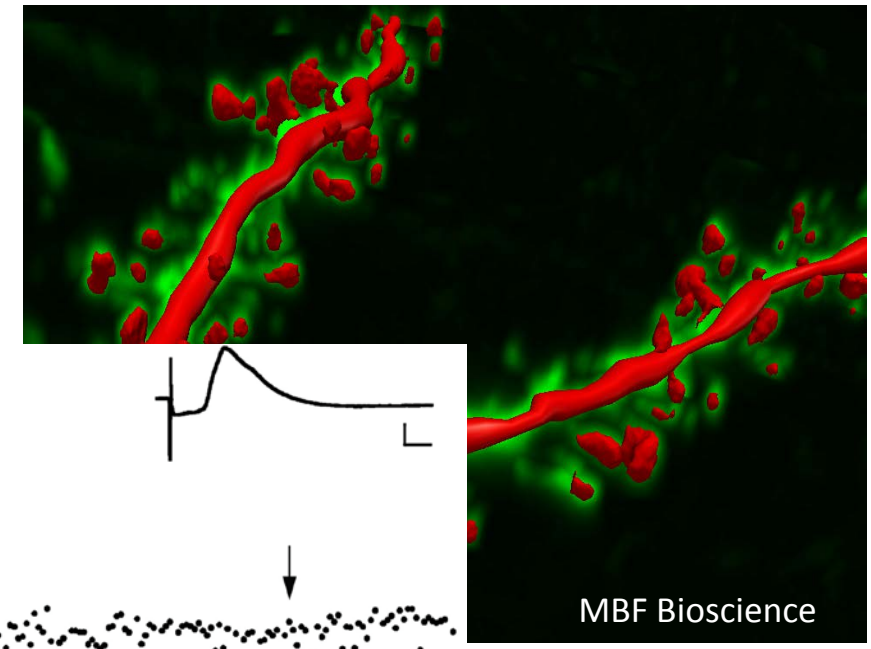
Consolidation:

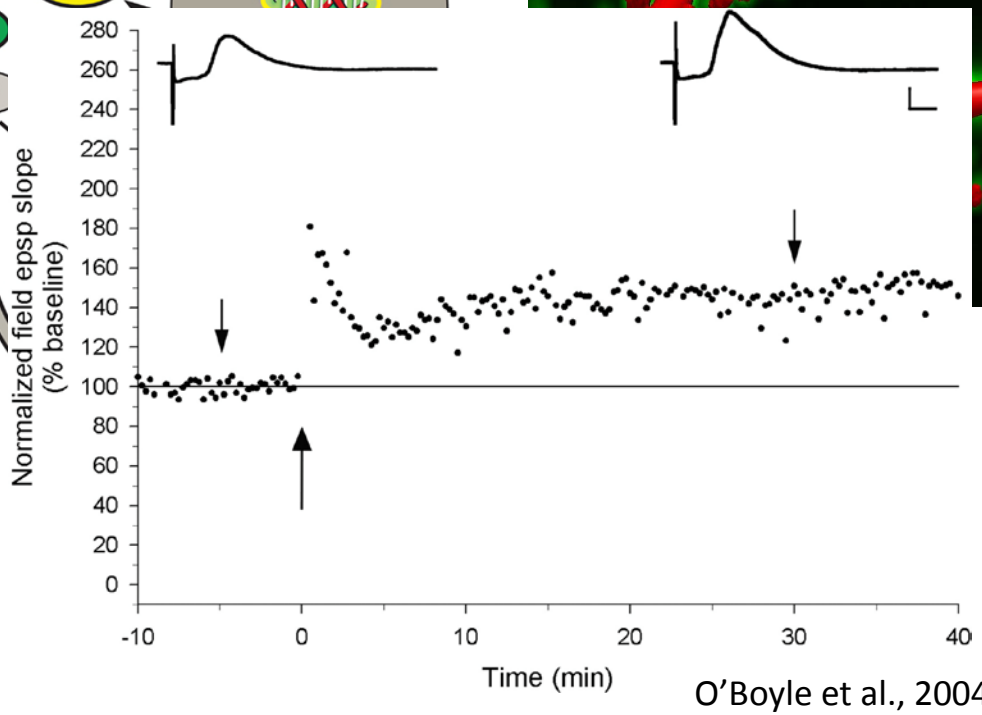
Establishment of stable long term memory

What Happens in the Brain?



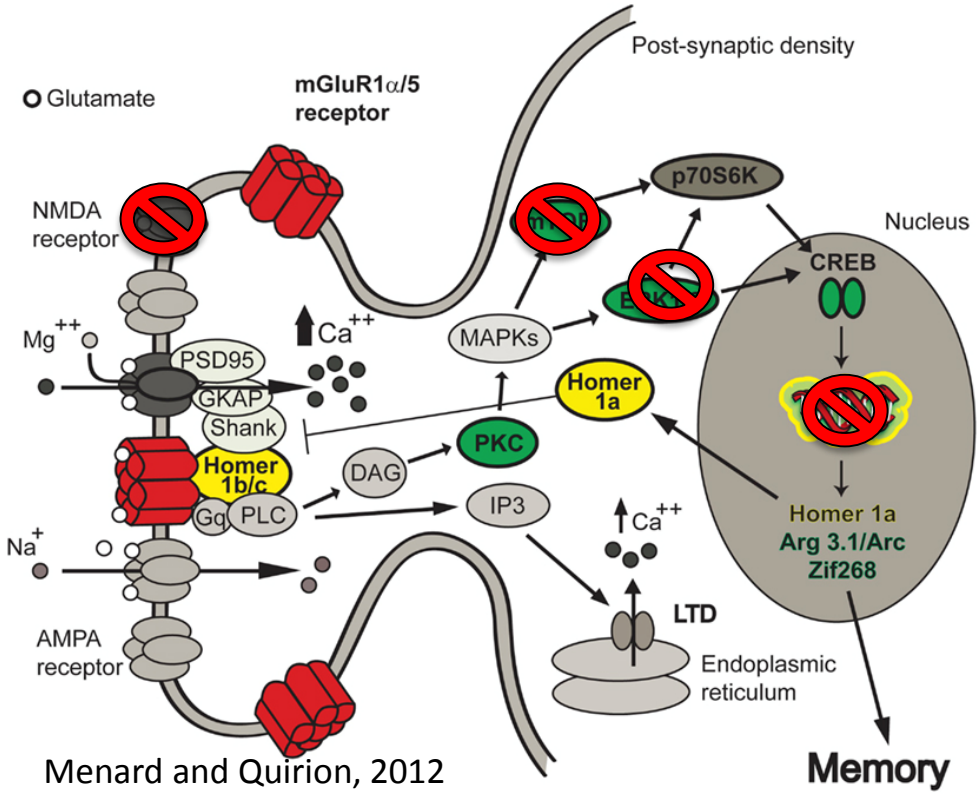
Menard and Quirion, 2012





O'Boyle et al., 2004

Memory Interference



Menard and Quirion, 2012

Memory Retrieval "Reactivation"

= Memory Weakening Reconsolidation

Craving

Relapse

Memory Extinction

COCAIN

≠

COCAINE

COCAINE

COCAINE

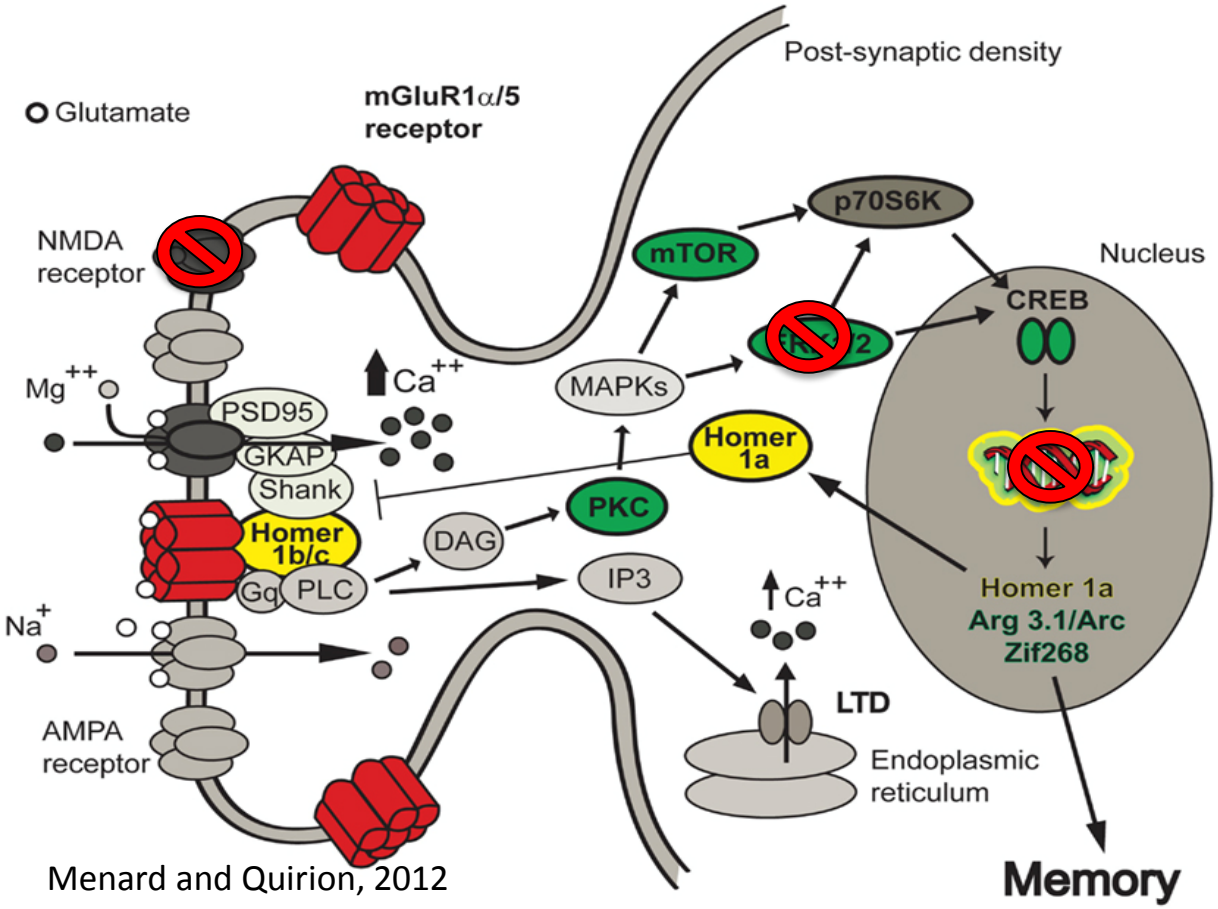
COCAINE

COCAINE

Craving

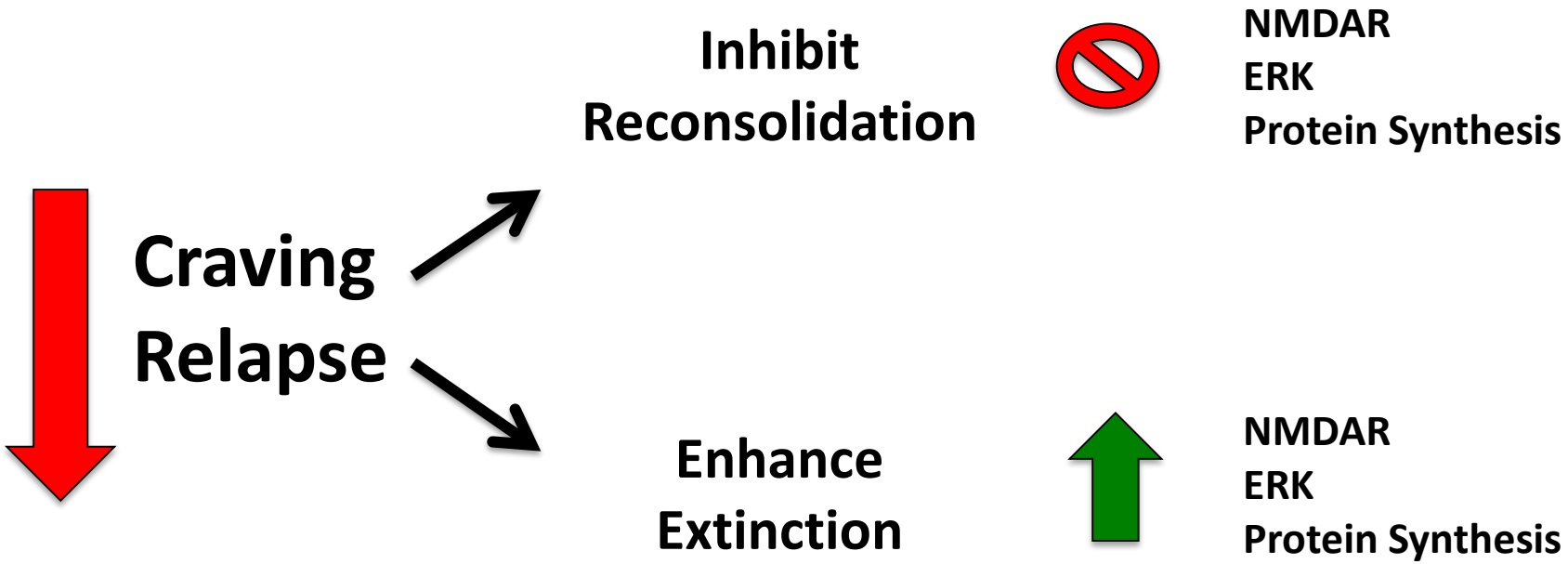
Relapse

Extinction in the Brain



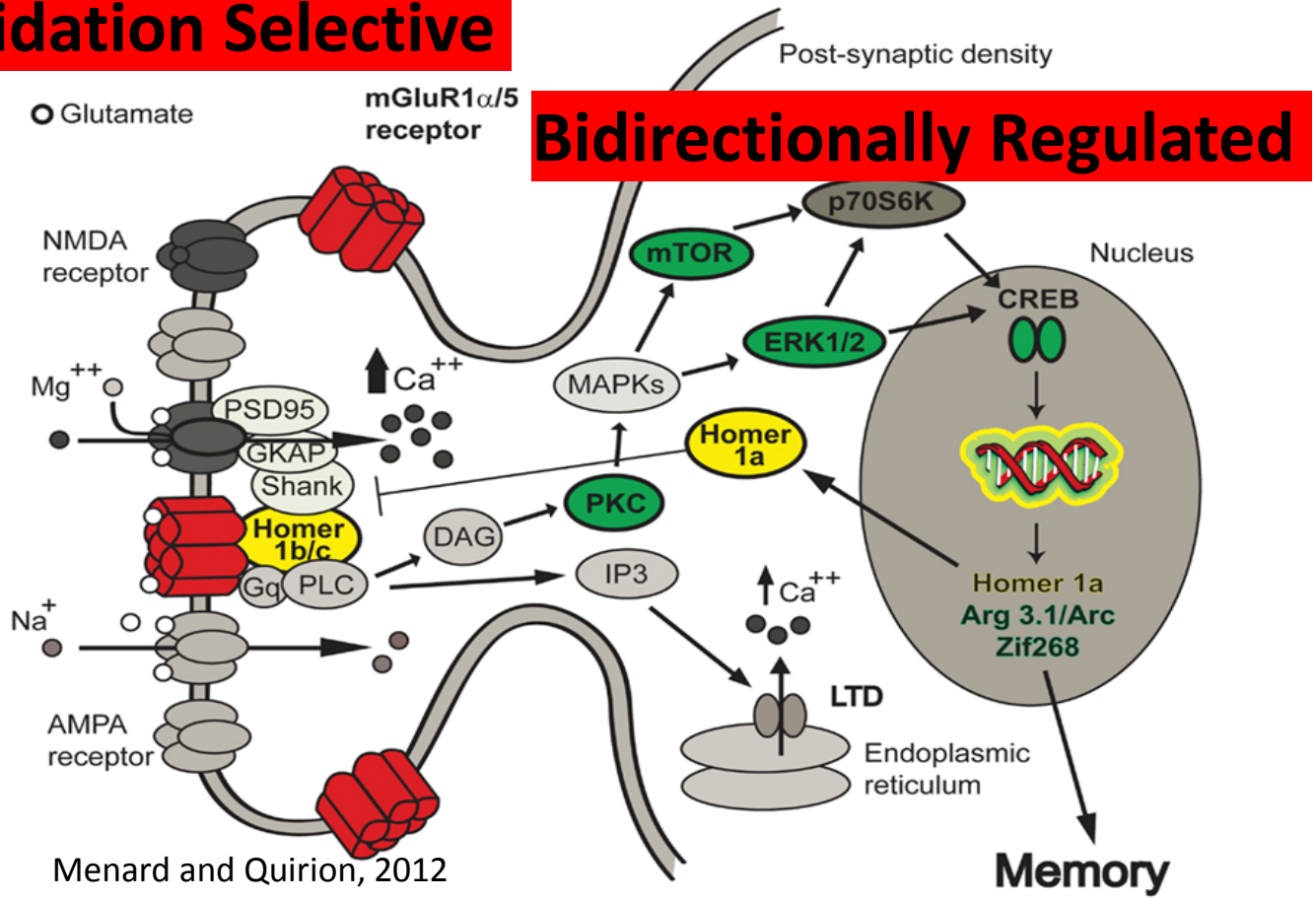
Menard and Quirion, 2012

Consolidation of New Extinction Memory


Craving
Relapse
Inhibit
Reconsolidation
NMDAR
ERK
Protein Synthesis
Enhance
Extinction
NMDAR
ERK
Protein Synthesis

What's the Solution?

Reconsolidation Selective



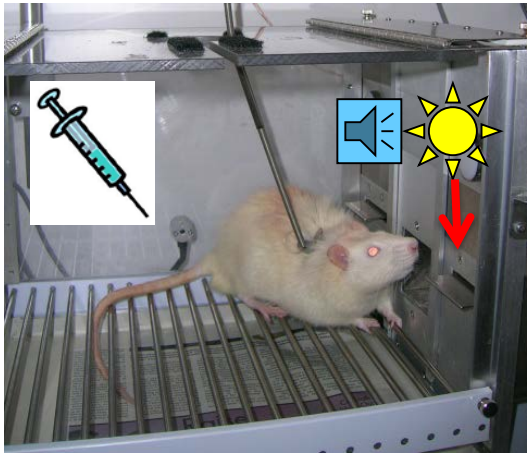
Bidirectionally Regulated

Menard and Quirion, 2012

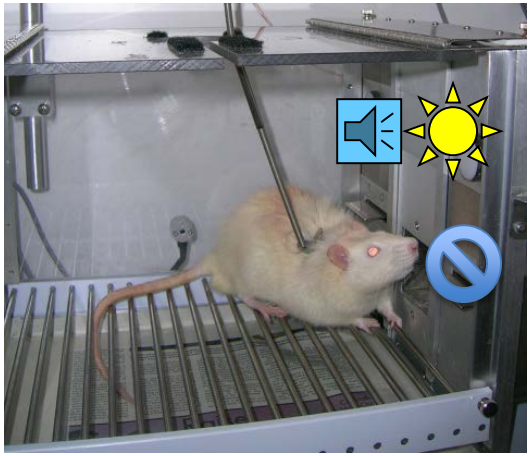
Extinction Selective

Animal Model

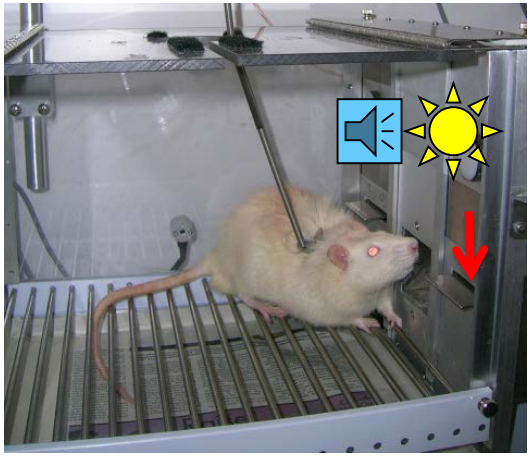
TRAINING



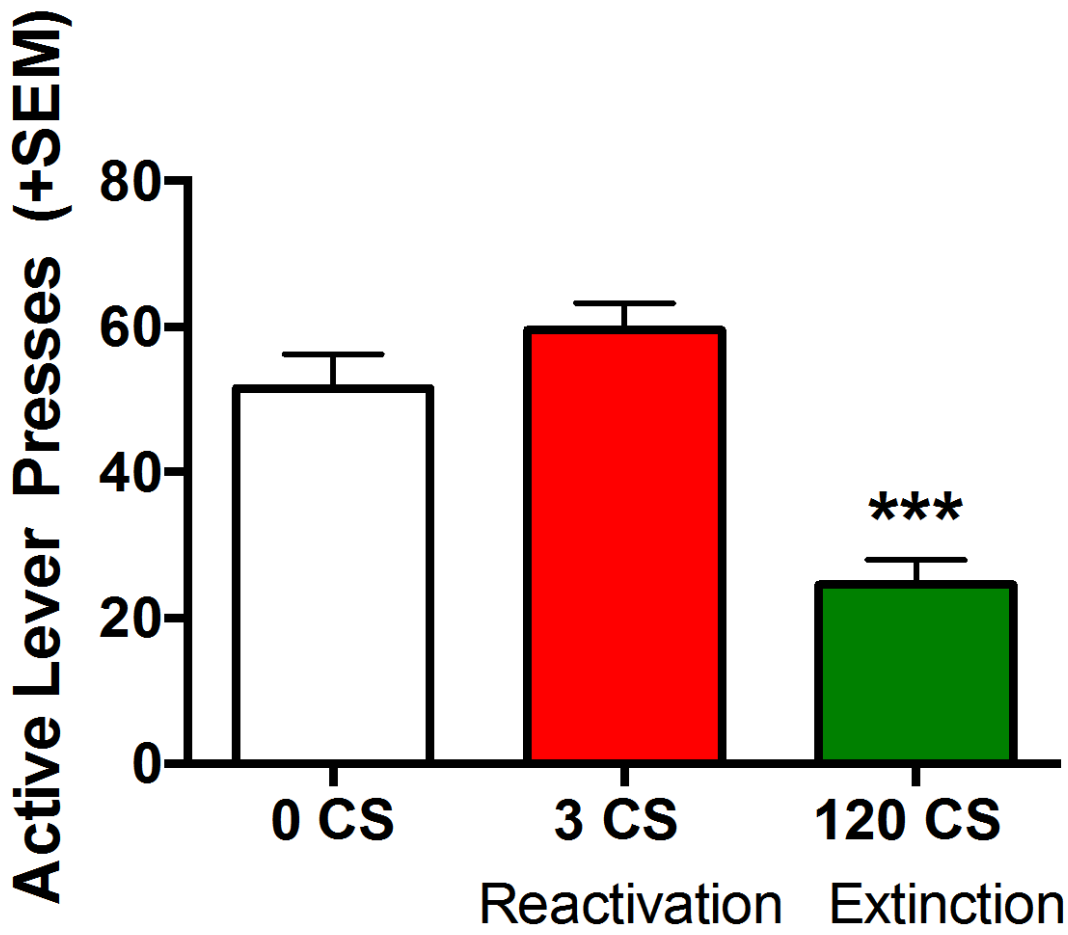
0 CUES
3 CUES
120 CUES



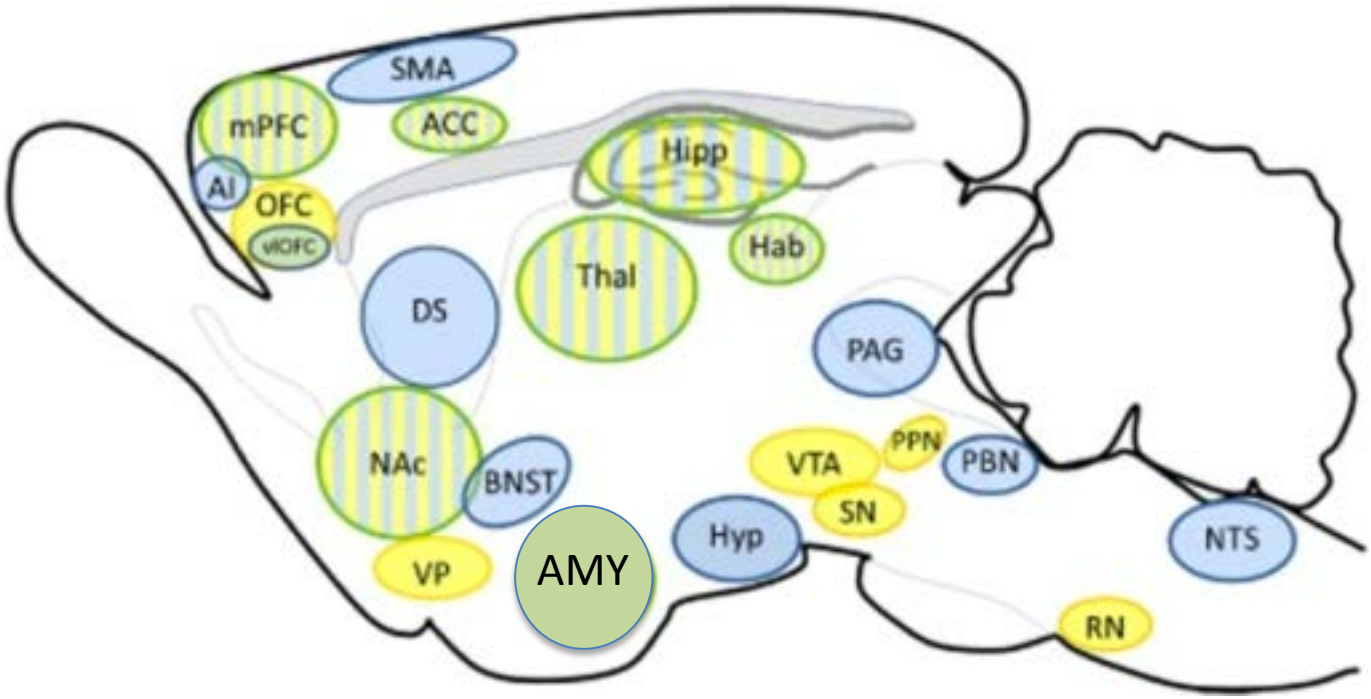
“RELAPSE” TEST



Relapse-Like Behavior

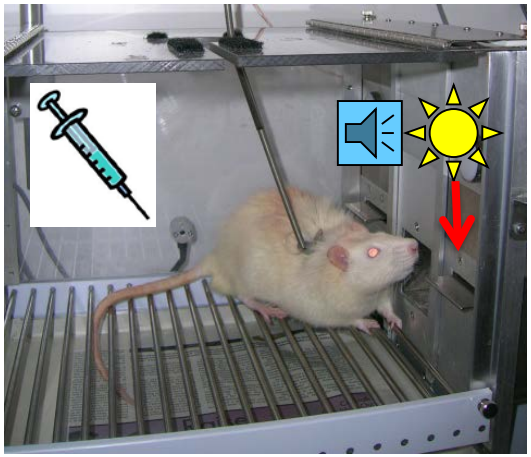


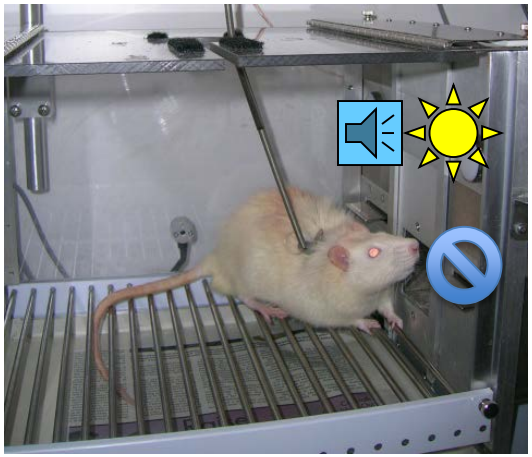
Where in the Brain?



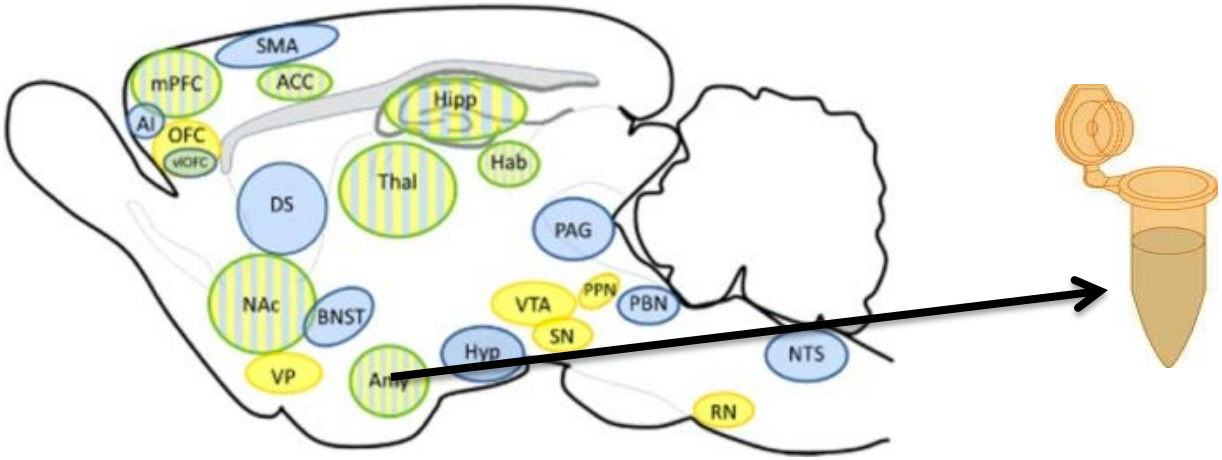
Phosphoproteomics: Experimental Design

TRAINING



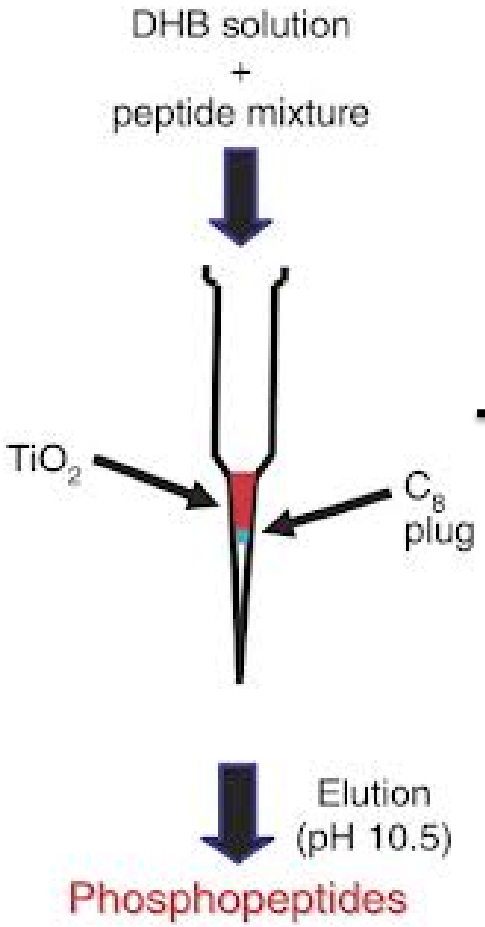


0 CUES
3 CUES
120 CUES



Homogenize
Trypsin Digestion

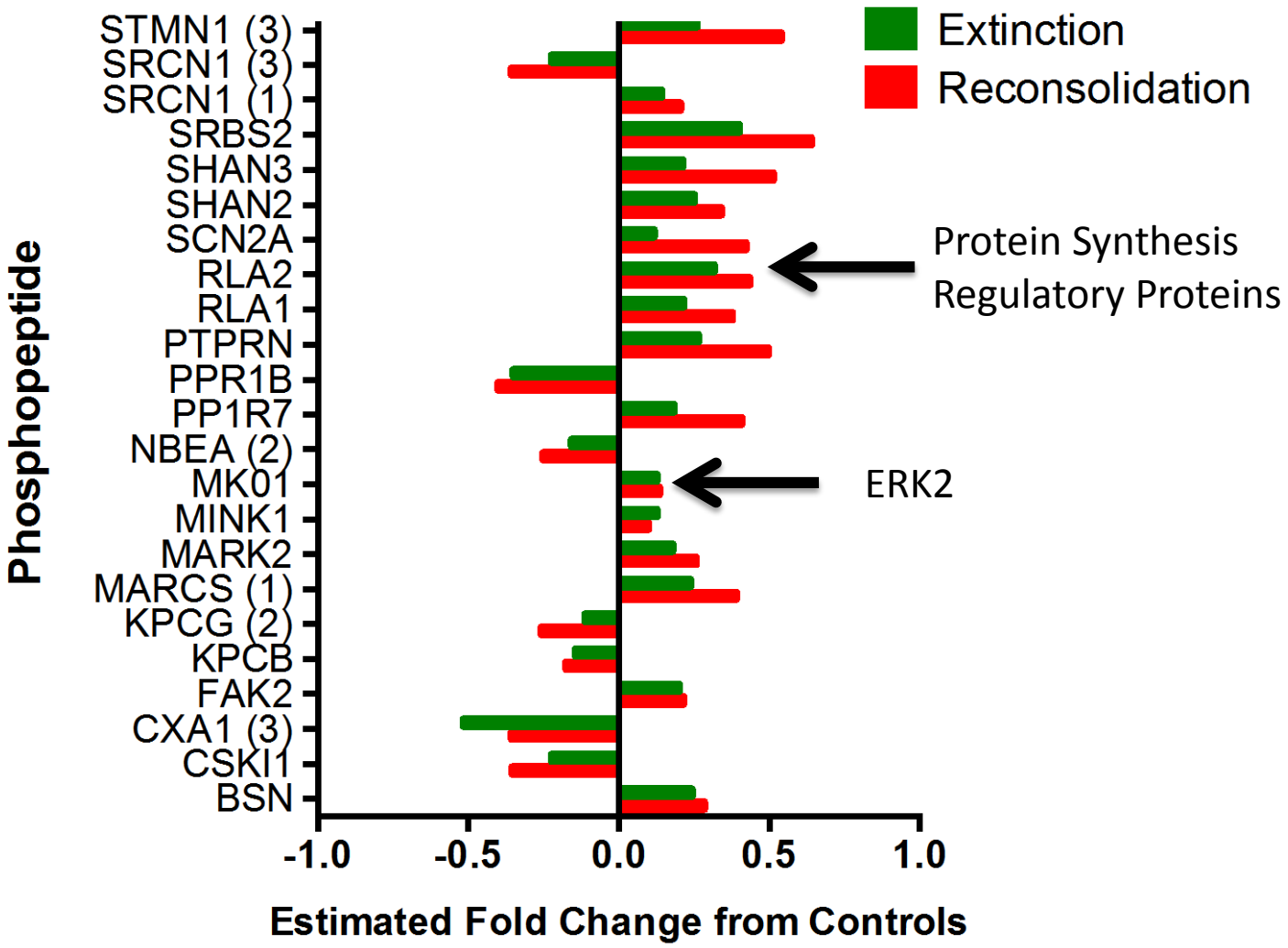
Experimental Design



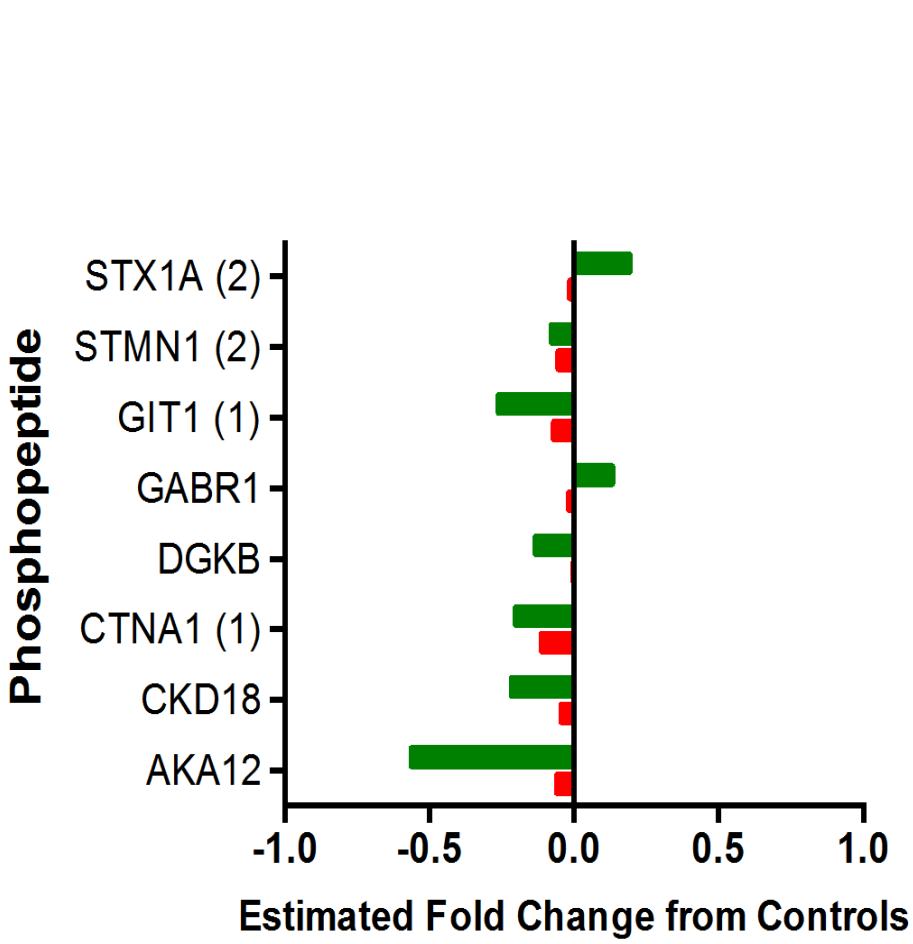
Discovery Phase:
Label Free Analysis

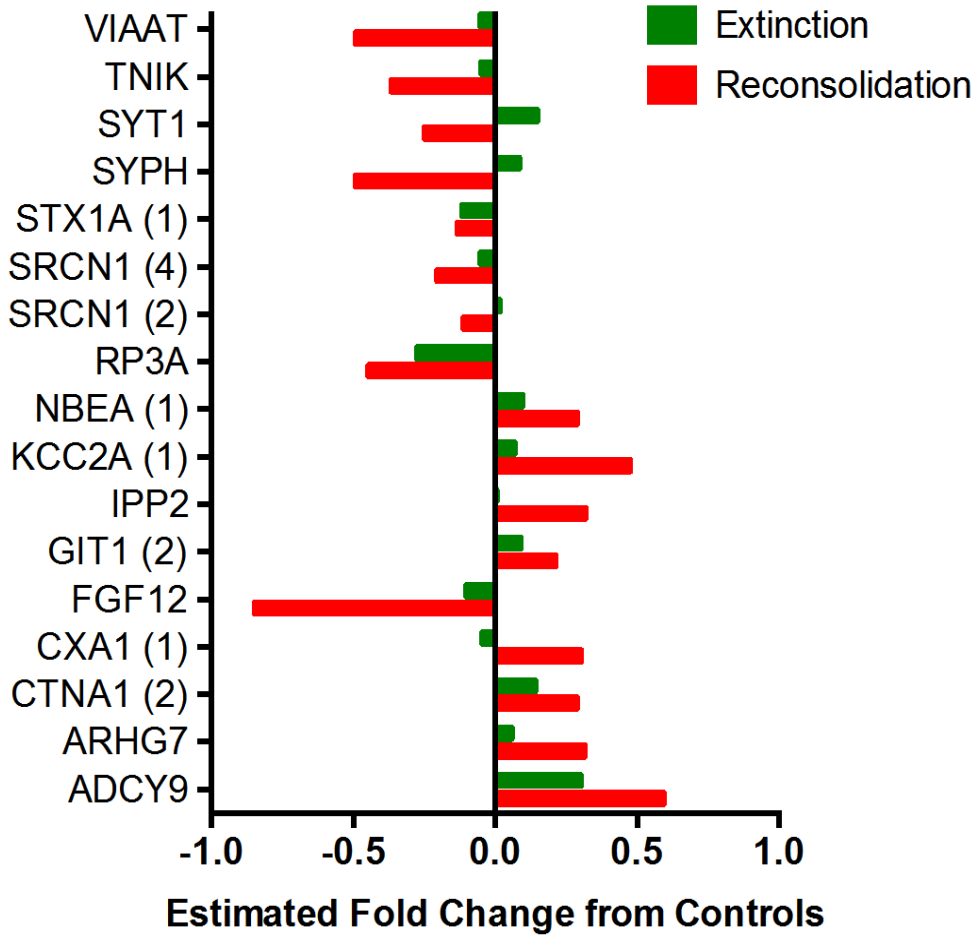
Validation Phase:
MRM Analysis

Common Signaling Events

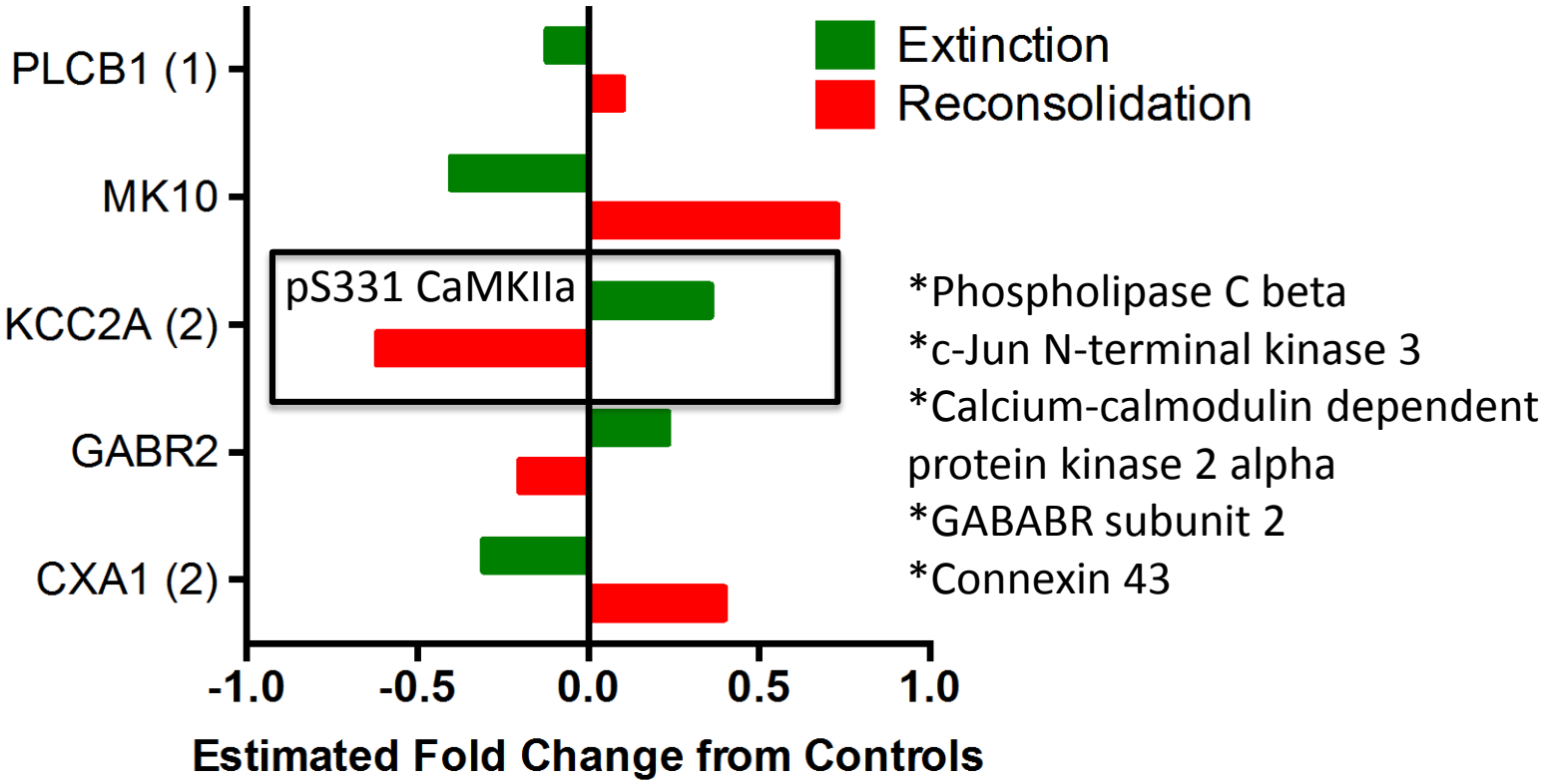


Selective Signaling Events



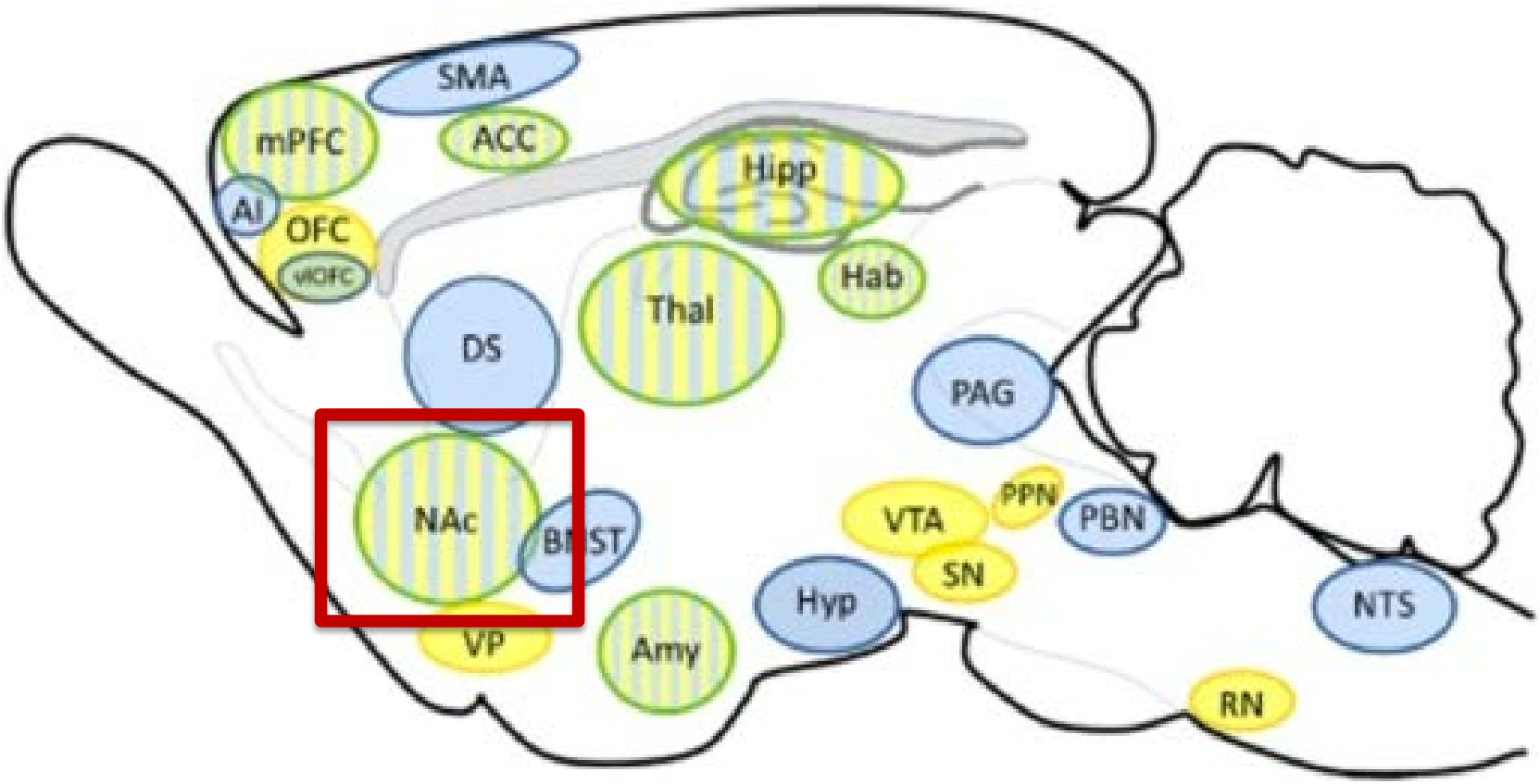


Bidirectional Signaling Events



Rich et al., J Neurosci, 2016

What about other brain regions?

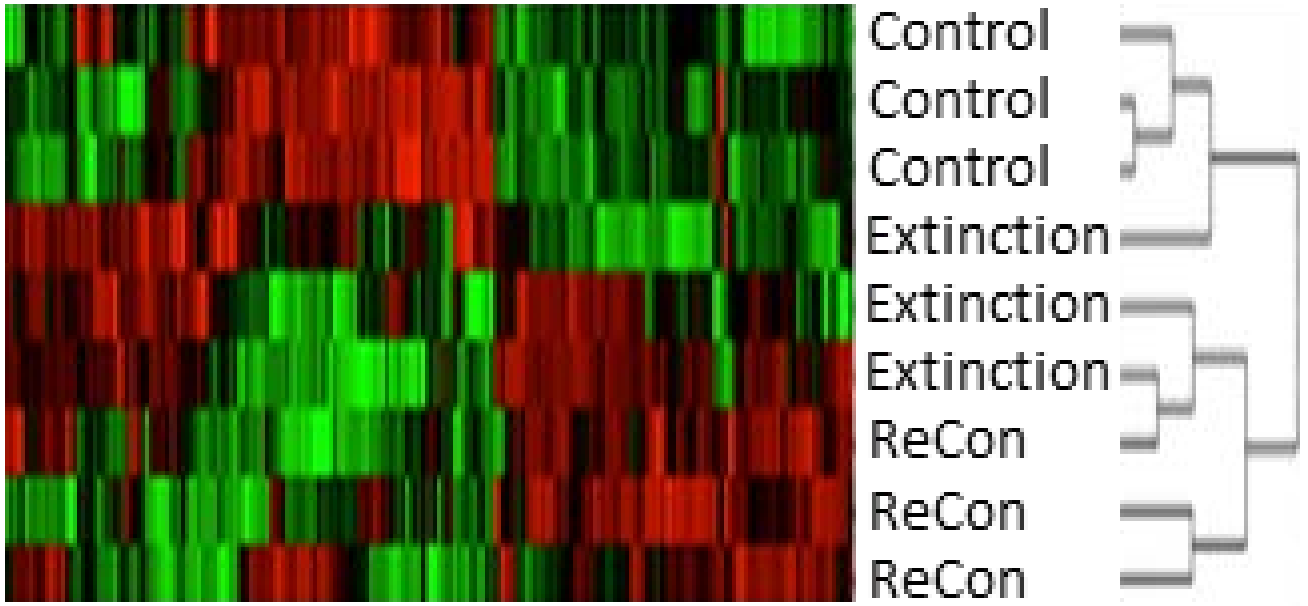


The Nucleus Accumbens and Drug Memory

- ERK signaling in the nucleus accumbens is required for reconsolidation of a cocaine CPP memory. *Miller and Marshall, 2005*
- NMDA receptor signaling in the nucleus accumbens mediates extinction of a cocaine cue memory. *Torregrossa et al., 2013*

What happens to the accumbens phosphoproteome?

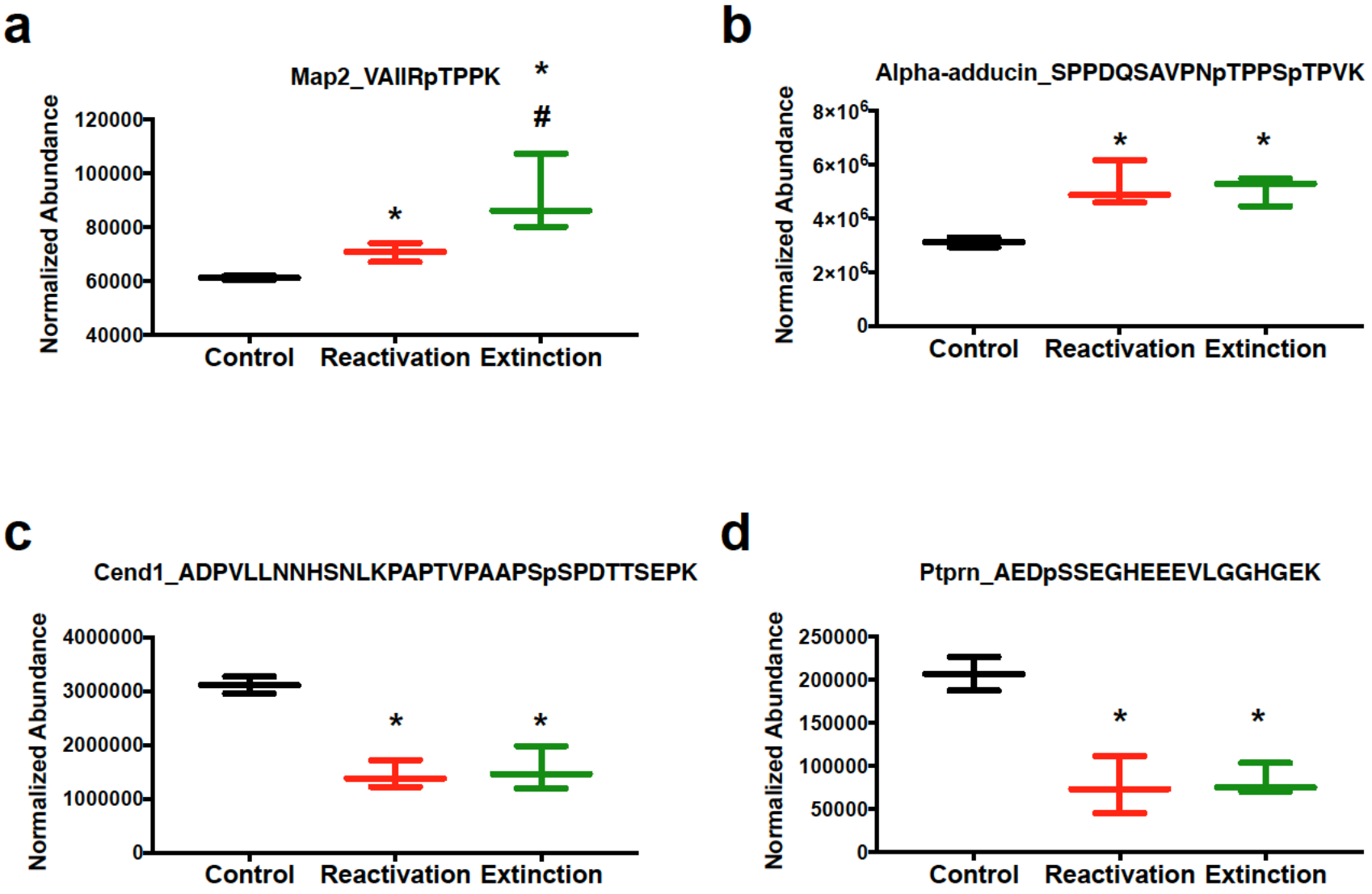
Discovery Phase:
Label Free Analysis



3 Take Home Messages

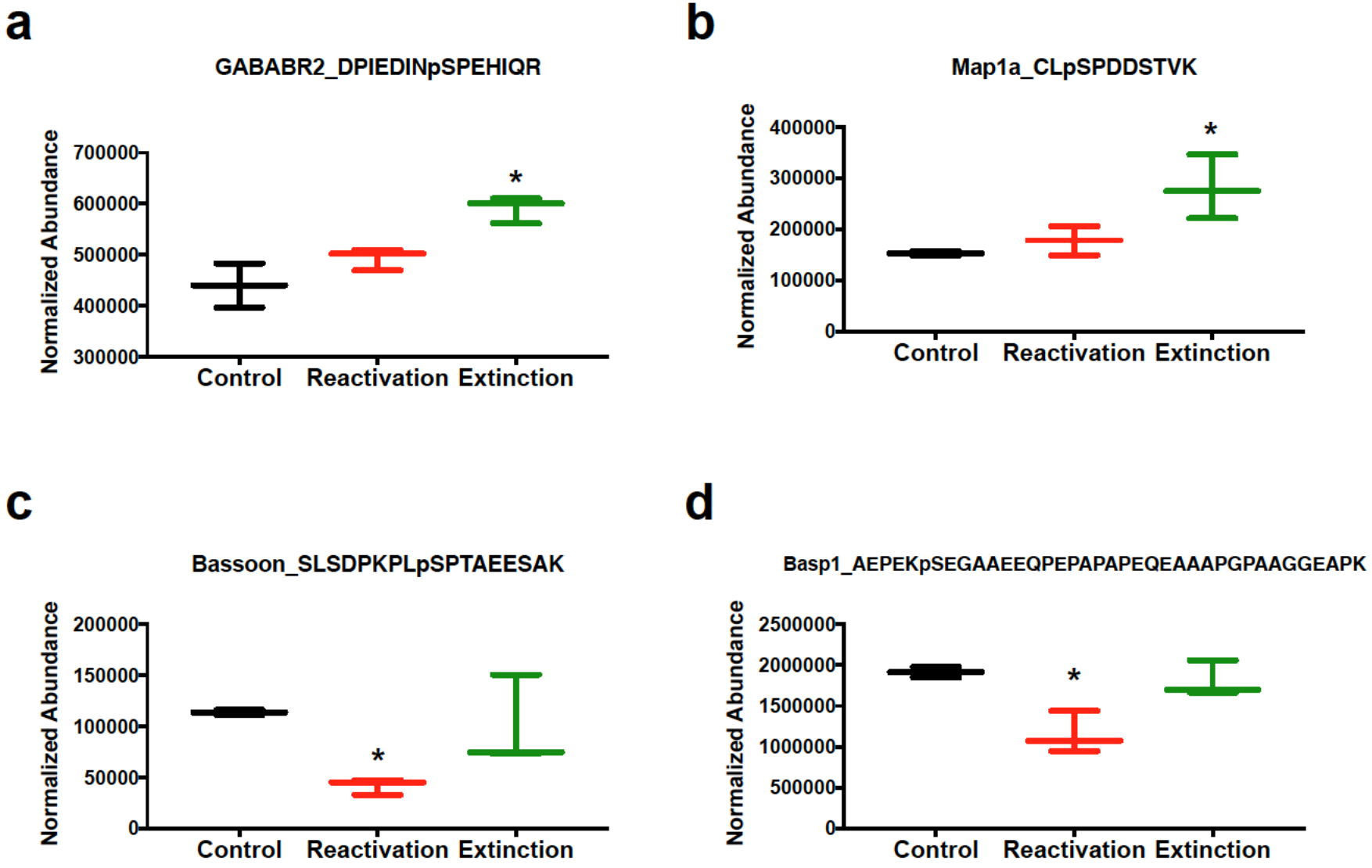
Torregrossa et al, Psychopharmacol, 2016

1. No Bidirectional Signaling in the NAc



Torregrossa et al, Psychopharmacol, 2016

2. Some Selective Signaling in NAc

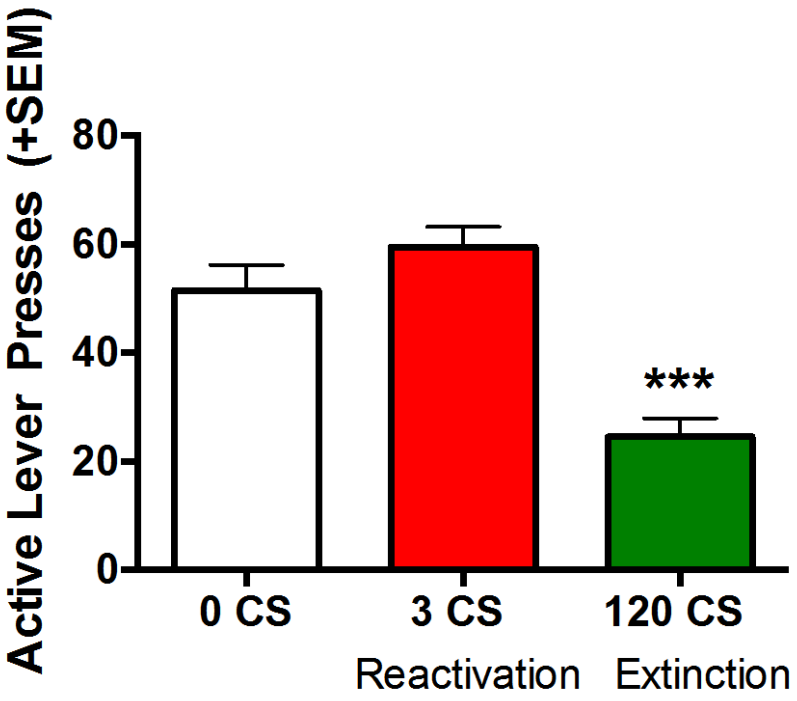


Torregrossa et al, Psychopharmacol, 2016

3. Extinction Resulted in more Selective Phosphorylation Changes than Reconsolidation (12 vs. 4)

BLA Plasticity Regulates Cocaine Memory Strength

NAc Translates Memory into Behavior



Common Signaling Across Brain Regions

Protein (gene name)	*Phosphopeptide NAc*	*Phosphopeptide BLA*	*NAc Fold Change from Con*	*BLA Fold Change from Con*
Gamma-aminobutyric acid type B receptor subunit 2 (Gabbr2)	**DPIEDINpSPEHIQR**	**DPIEDINpSPEHIQR**	**1.35**	**1.23**
Syntaxin-1A (Stx1a)	**TAKDpSDDDDDVTVTVDRDR**	**TAKDpSDDDDDVTVTVDRDR**	**1.61**	**1.19**
Caskin-1 (Caskin1)	KVPLPGPGpSPEVK	KVPLPGPGpSPEVK	1.24	0.77
Receptor-type tyrosine-protein phosphatase-like N (Ptprn)	AEDpSSEGHEEEVLGGHGEK	LPEEGGSpSRAEDSpSEGHEEEVLGGHGEK	0.4	1.27
Sodium channel protein type 2 subunit alpha (Scn2a)	GKEDEGpTPIKEDIITDK	RFSpSPHQpSLLSIR	1.16	1.12
SRC kinase signaling inhibitor 1 (Srcin1)	RGpSDELTVPR	DSGSSSVFAEpSPGGK	1.52	1.14
	RGpSDELTVPR	RFpSNVGLVHTSER	1.52	0.77
Stathmin (Stmn1)	DLpSLEEIQK	ESVPEFPLpSPPK	1.34	0.92
	DLpSLEEIQK	RASpGQAFELILpSPR	1.34	1.26
Protein bassoon (Bsn)	pSLSDPKPLpSPTAEESAK	SPQVLYpSPVpSPLSPHR	1.64	1.25
Misshapen-like kinase 1 (Mink1)	LDSpSPVLSPGNK	SDSVLPASHGHLPQAGpSLER	1.76	1.13
SH3 and multiple ankyrin repeat domains protein 3 (Shank3)	SApSDINLK	SRpSPpSPpSPLPSPSPGSGPSAGPR	2.49	1.21

Torregrossa et al, Psychopharmacol, 2016

What can we achieve using phosphoproteomics?

- Identify novel protein regulators of a disease, state, or process.
- Gain insight into the differential function of brain regions to a disease, state, or process.
- Compare regulators of different diseases, states, or processes.
- Identify targets for developing novel treatments, potentially by looking for common regulatory events across brain regions.

Thank You!

Torregrossa Lab

Matthew Rich
Jillian Weeks
Vidhya Nagarajan
Megan Bertholomey
Erin Kirschmann
Jenna Parrish
Jennifer Zeak
Sierra Stringfield
Tara Cahanap
Dana Smith
Brooke Bender

Yale Collaborators

Jane Taylor
Angus Nairn

Yale/NIDA Neuroproteomics Center

Ken Williams
TuKiet Lam
Kathy Stone
Erol Gulcicek
Chris Colangelo
Mary Lopresti
Tom Abbott
Lisa Chung

Pitt Collaborators

Yanhua Huang
Ivet Bahar
Filippo Pullara

Funding

K01DA031745
R01DA042029
R21AA025547
R21DA041563