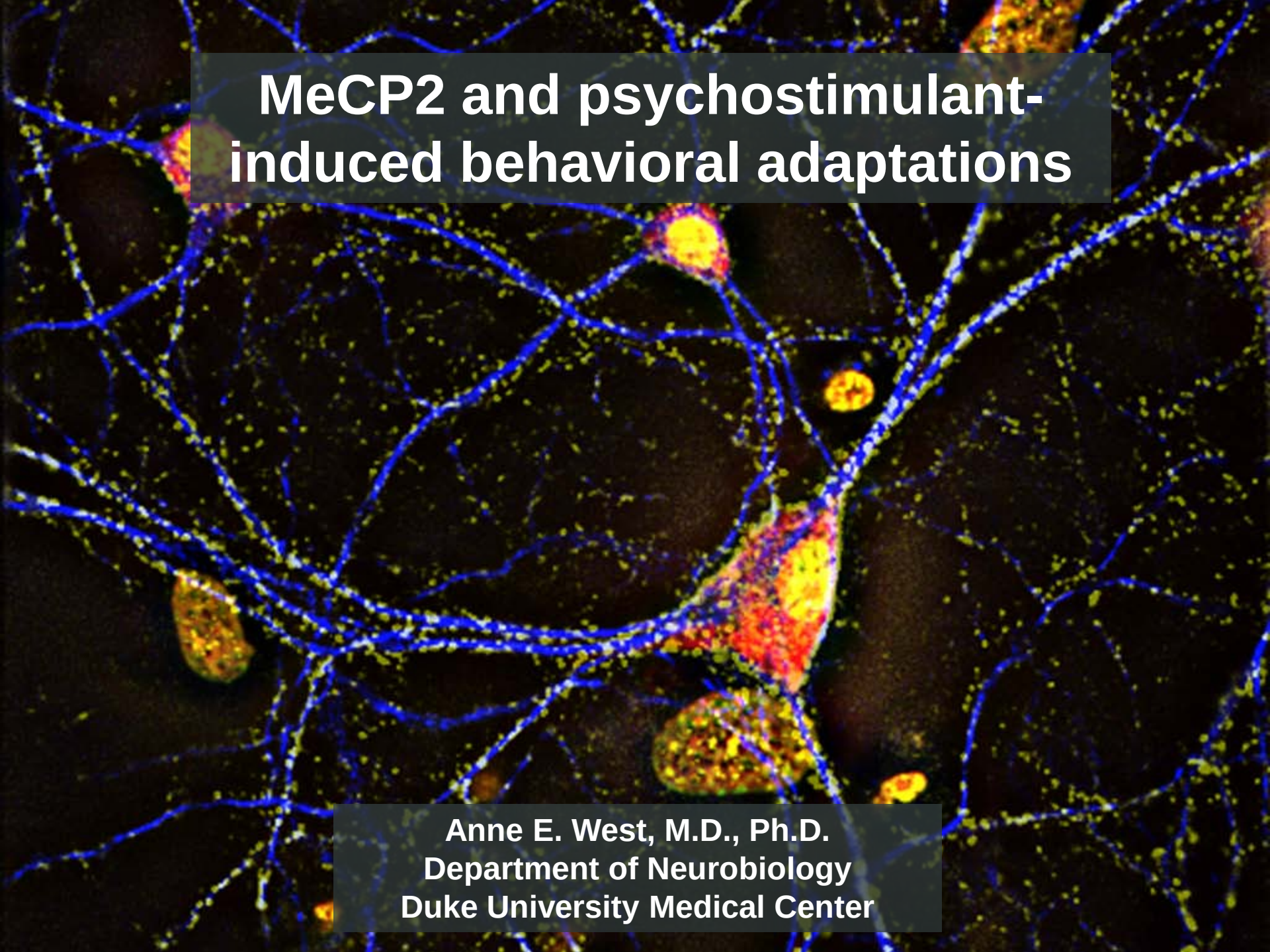
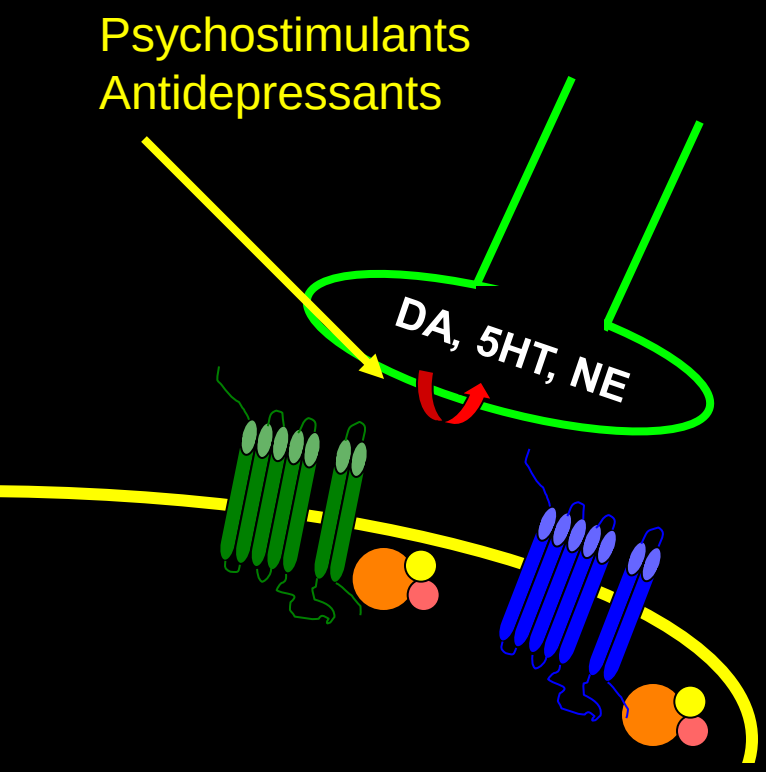
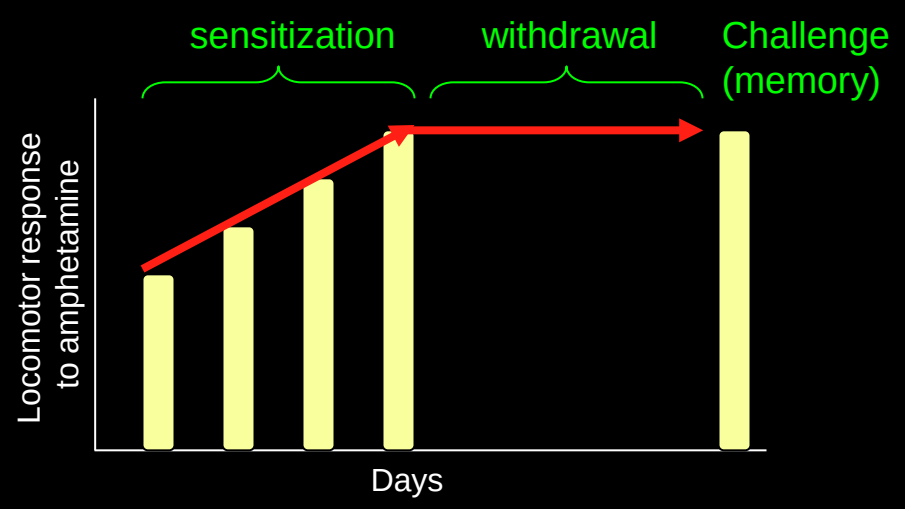


MeCP2 and psychostimulant-induced behavioral adaptations

Anne E. West, M.D., Ph.D.
Department of Neurobiology
Duke University Medical Center

Psychostimulants and antidepressants slowly change behavior

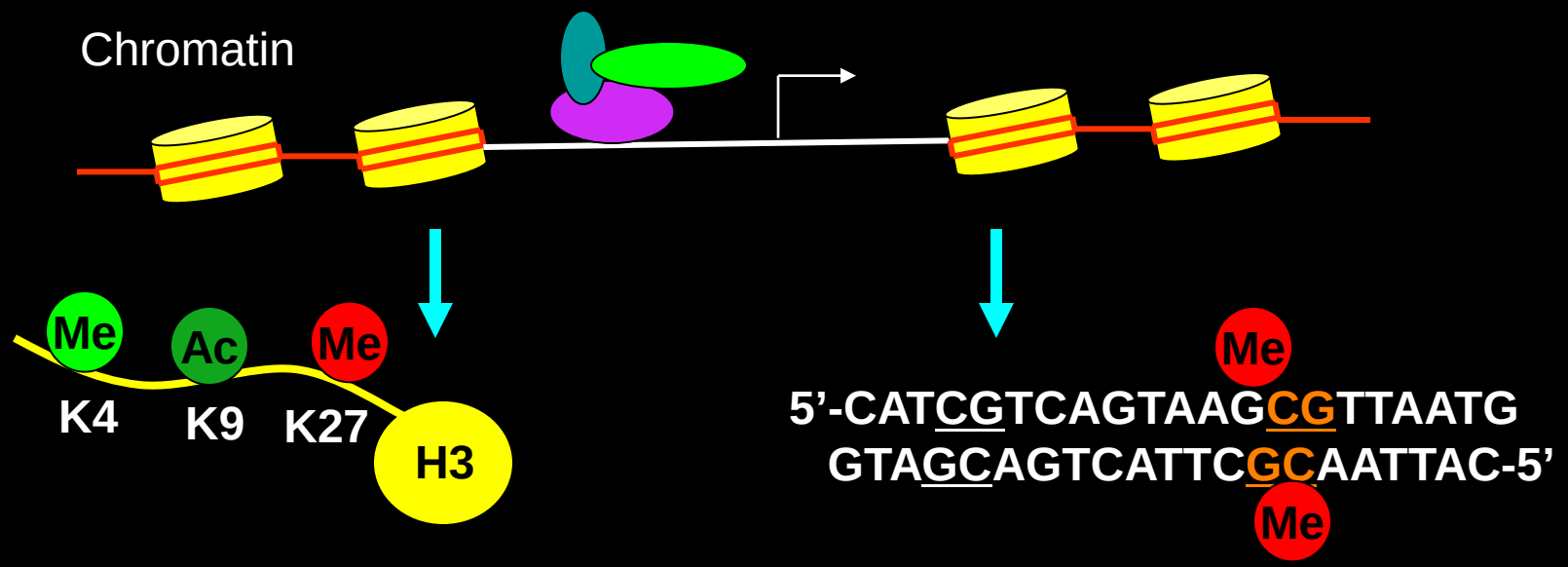




Rapid pharmacological action

Slow, persistent behavioral response

Chromatin regulation:
A mechanism of cellular memory?



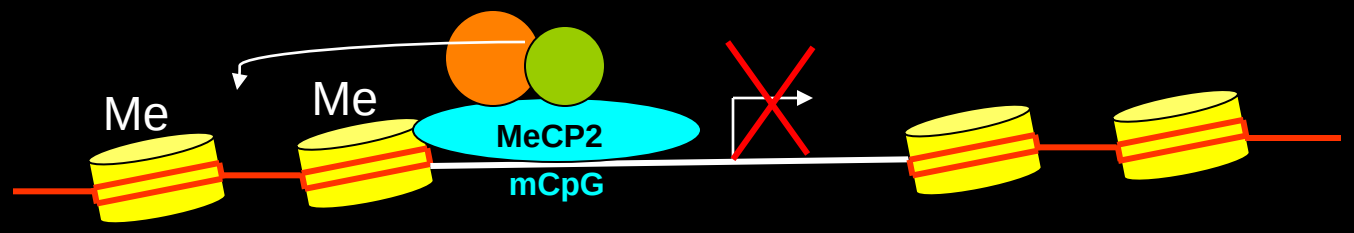
Histone modifications
(acetylation, methylation)

DNA methylation

Persistent

Stimulus-regulated

Methyl CpG Binding Protein 2 (MeCP2)



- Required in CNS development and function
- Target of regulation by calcium signaling pathways

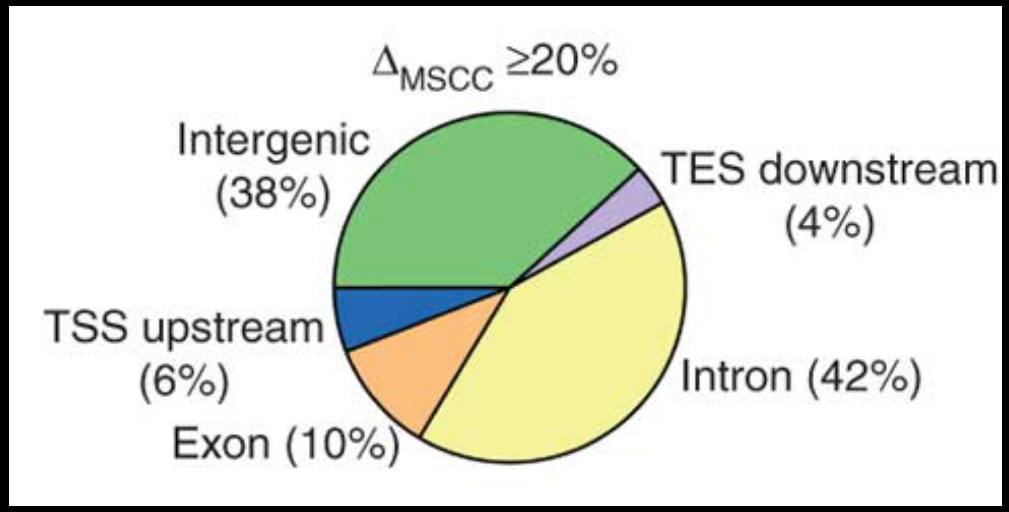
DNA methylation is global

~70% of all CpG dinucleotides are methylated

Lister 2009 Nature 462:315

50,000,000

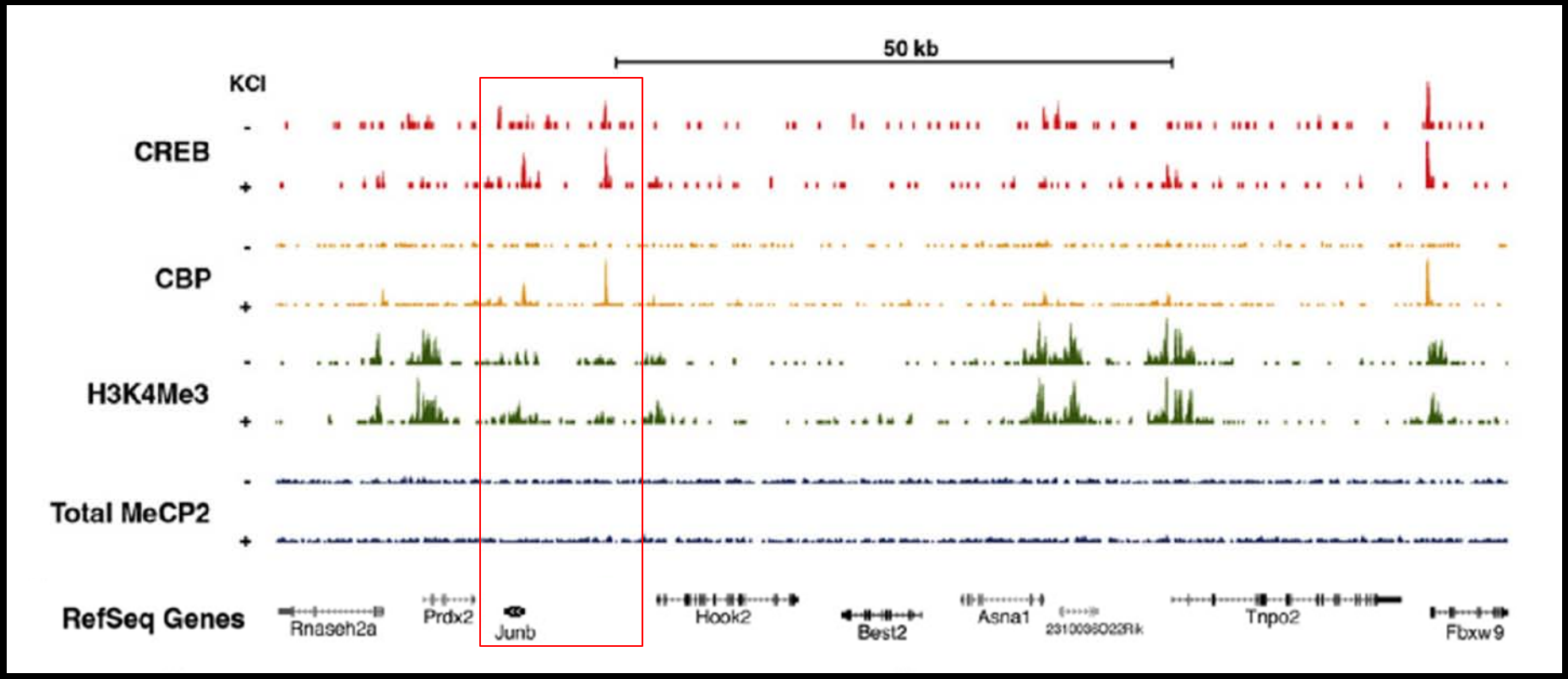
Widespread activity-induced changes in DNA methylation



500,000

Guo 2011 Nat Neurosci 14:1345

MeCP2 is bound widely across the genome



Cohen *et al* (2011) Neuron 72:35

Loss-of-function mutations in *Mecp2* are associated with global hyperacetylation

Shahbazian *et al* (2002) Neuron 35:243
Skene *et al* (2010) Mol Cell 37:457

Challenge:

Demonstrate that DNA methylation-dependent chromatin plasticity contributes to the persistent behavioral changes induced by chronic psychostimulant and/or antidepressant exposure.

Approach:

Use molecular genetic techniques to <u>selectively</u> disrupt the stimulus-regulated functions of MeCP2 and study the effects on behavior.

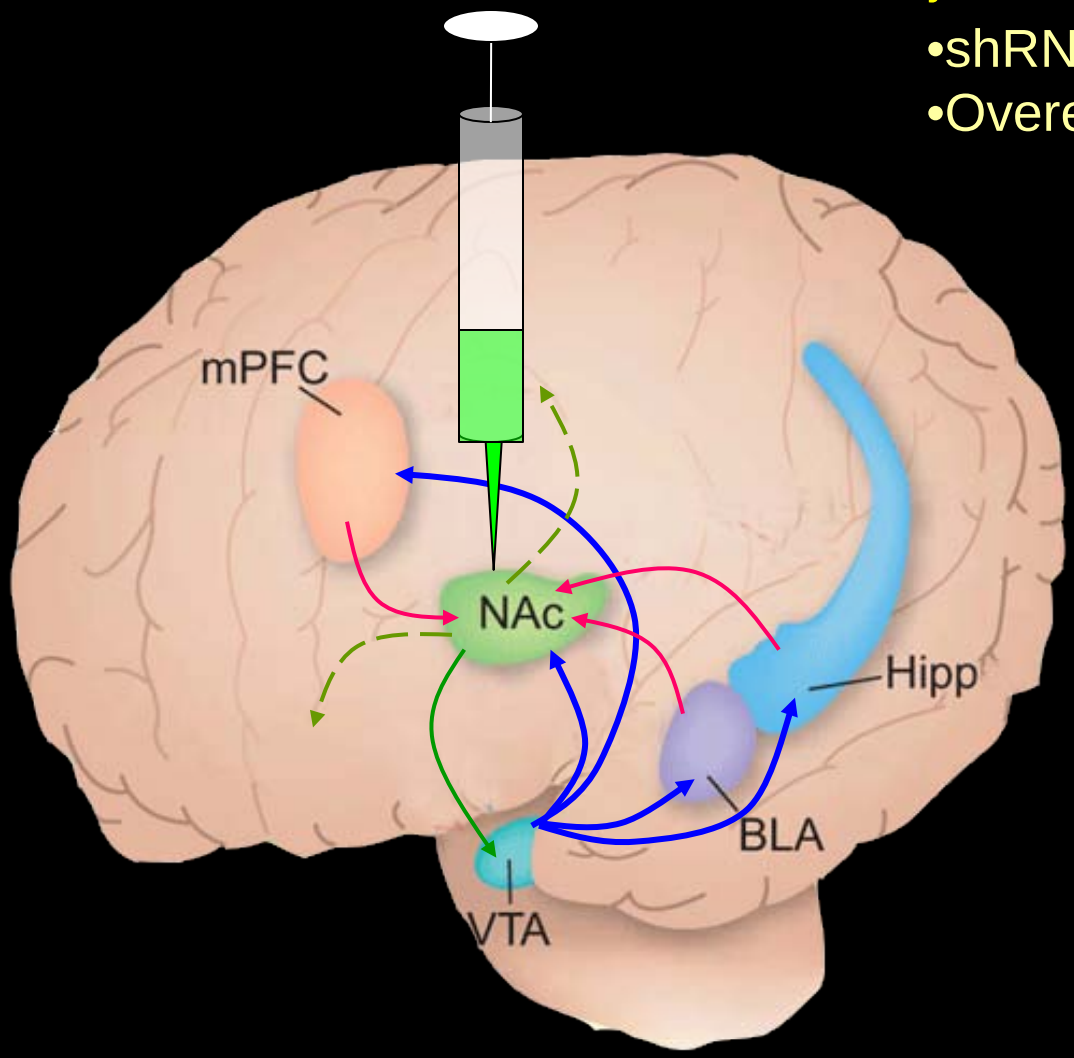
Overview

- MeCP2 is involved in modulating behavioral adaptations to psychostimulants.

- Ser421 phosphorylation couples MeCP2 to psychostimulant and antidepressant exposure.

- Mutation of MeCP2 Ser421 selectively alters behavioral adaptations to chronic psychostimulant and antidepressant treatment.

Mesolimbocortical dopaminergic circuit



Inject lentivirus in NAc

- shRNA knockdown
- Overexpression

mPFC – medial Prefrontal Cortex

NAc – Nucleus Accumbens

BLA – Basal Lateral Amygdala

Hipp – Hippocampus

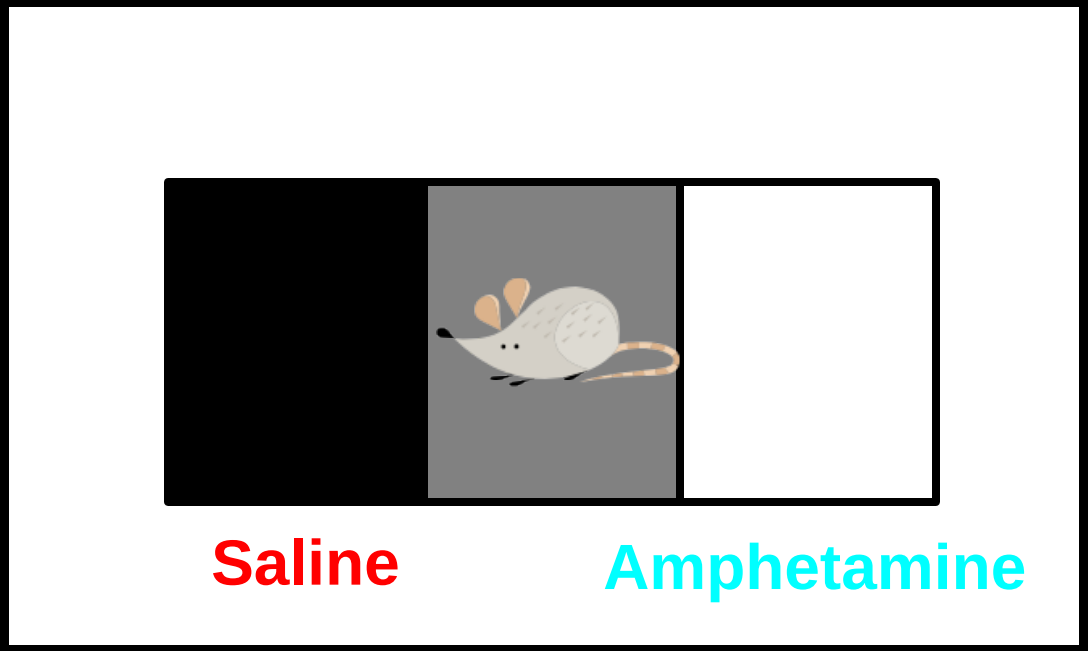
VTA – Ventral Tegmental Area

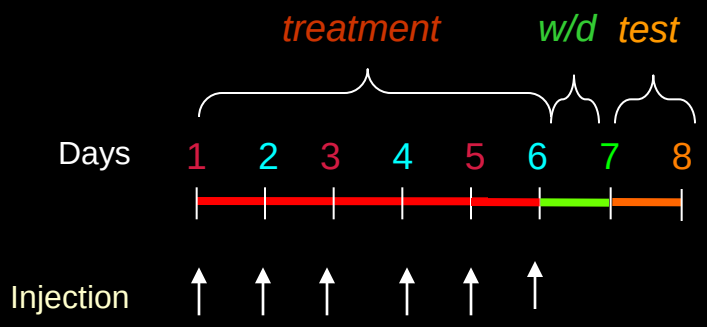
→ Dopaminergic Projection

→ Glutamatergic Projection

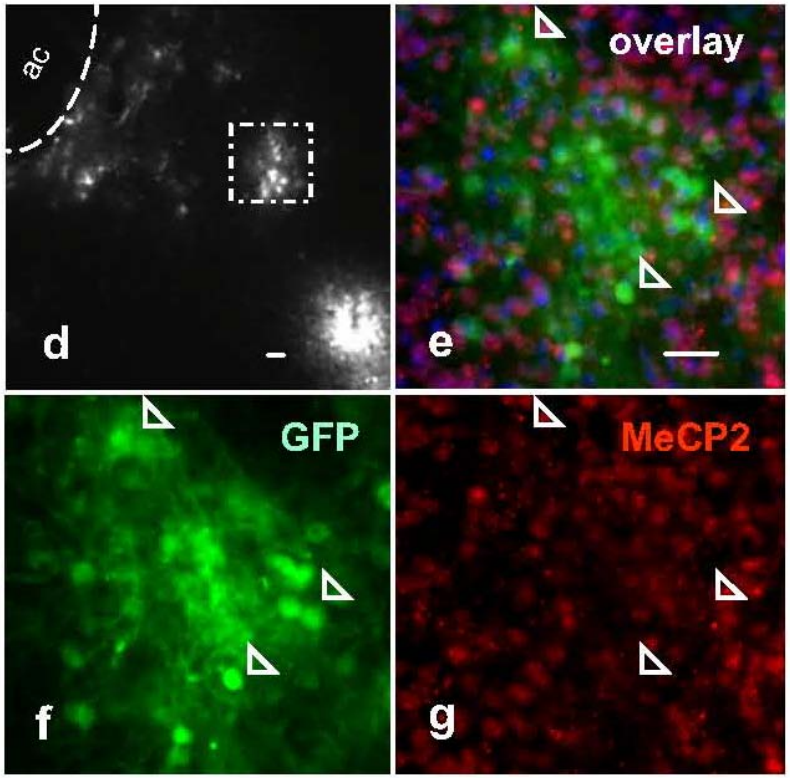
→ GABAergic Projection

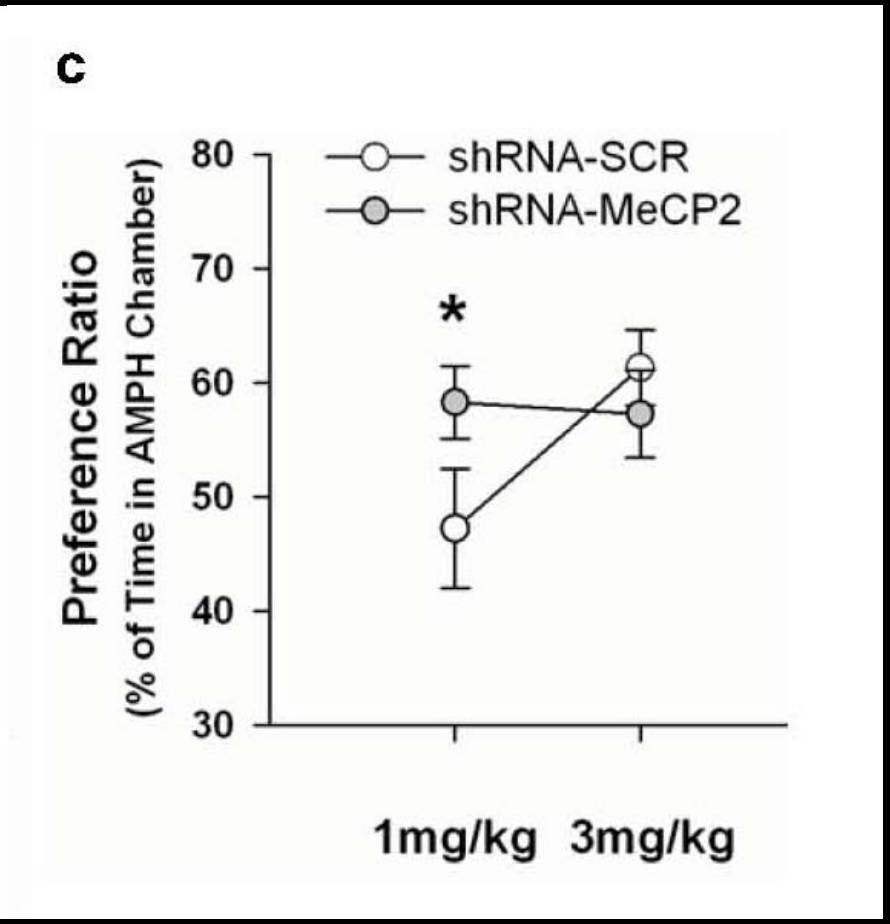
Conditioned Place Preference (CPP) as a measure of psychostimulant reward





Viral RNAi-mediated knockdown of MeCP2 in NAc increases CPP to AMPH

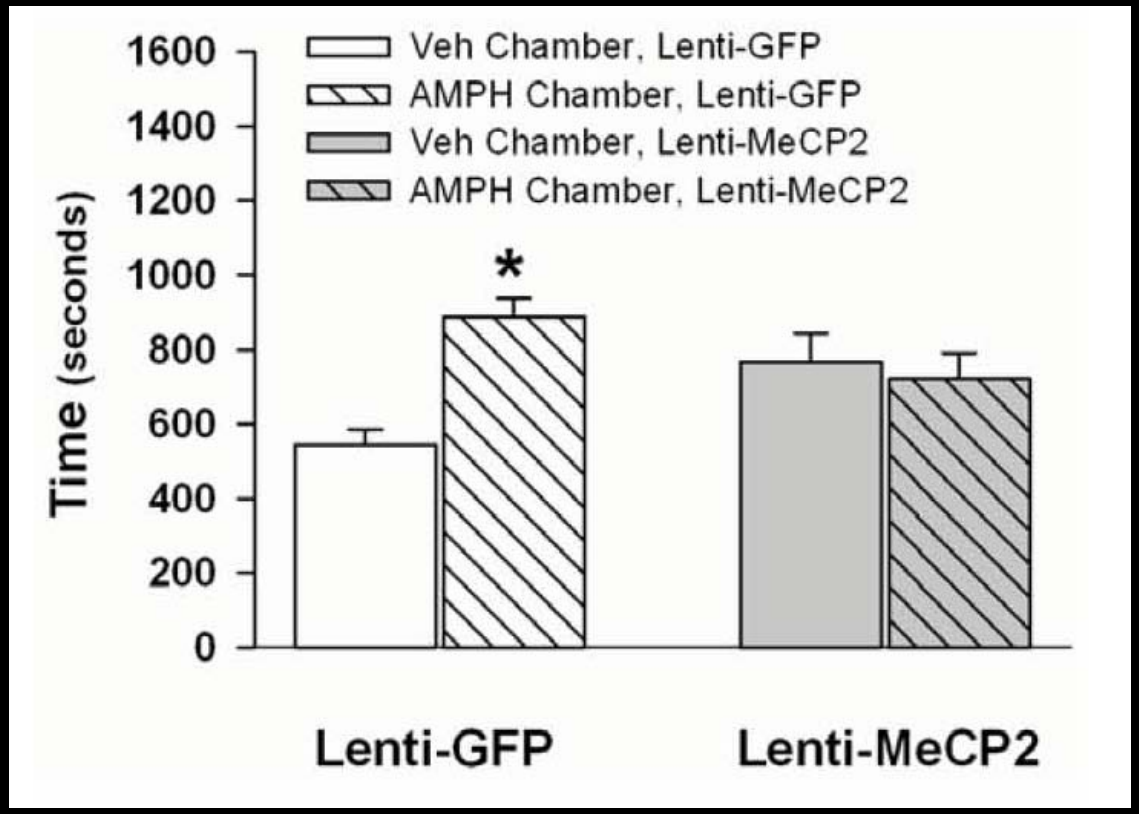




AMPH = amphetamine

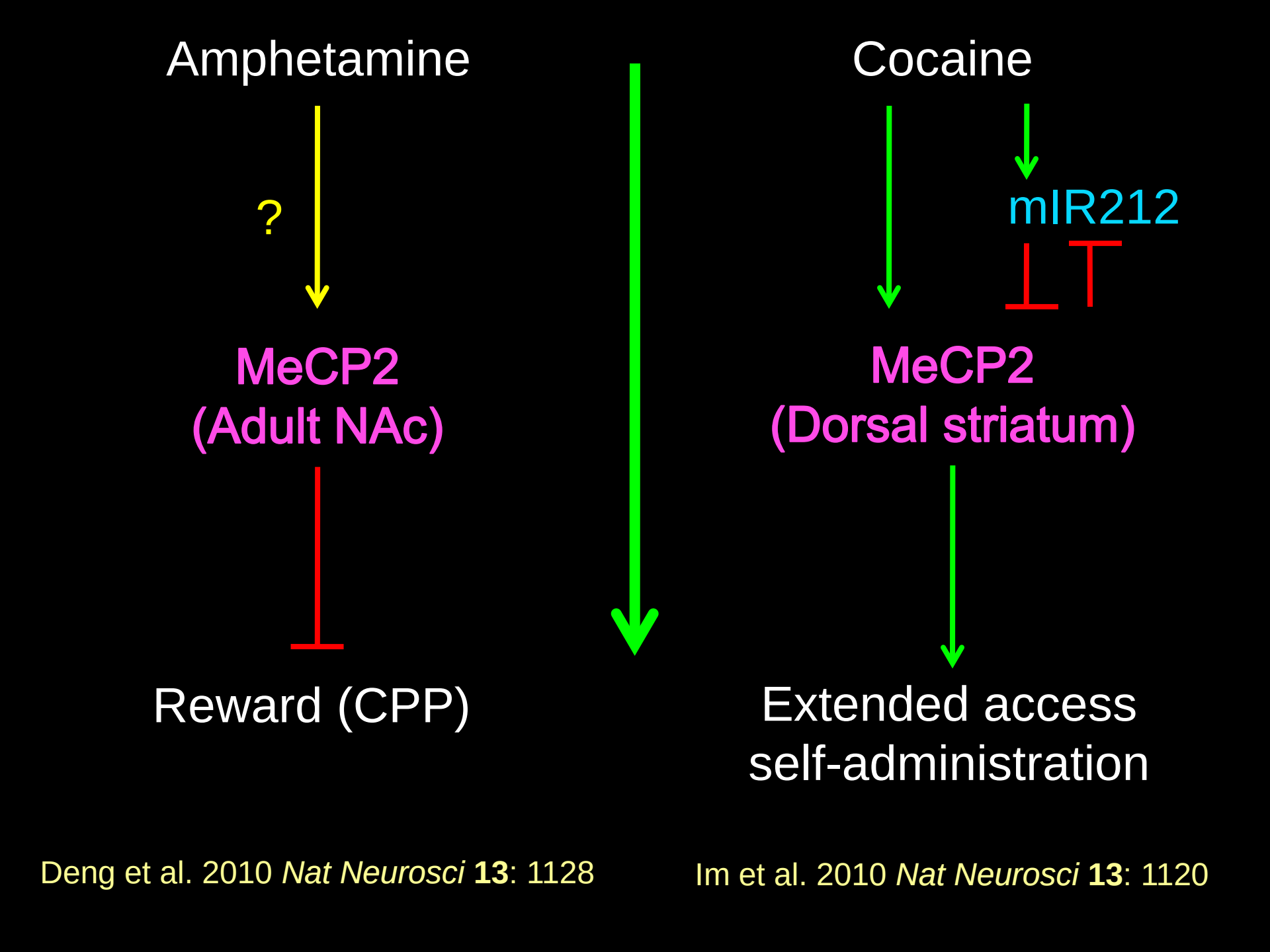
Deng et al. 2010 *Nat Neurosci* **13**: 1128

Viral overexpression of MeCP2 in NAc decreases CPP to AMPH

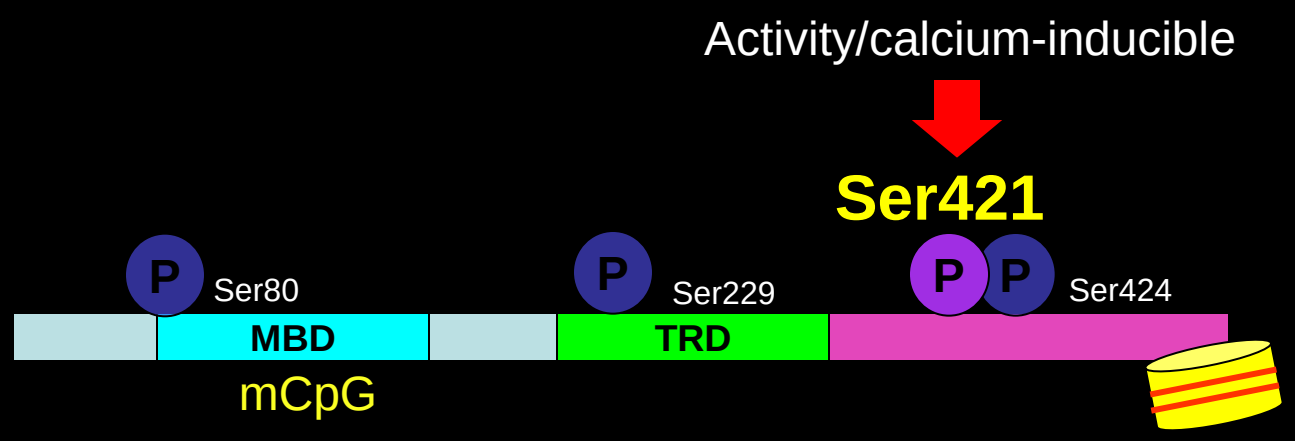


3mg/kg AMPH

Deng et al. 2010 *Nat Neurosci* **13**: 1128

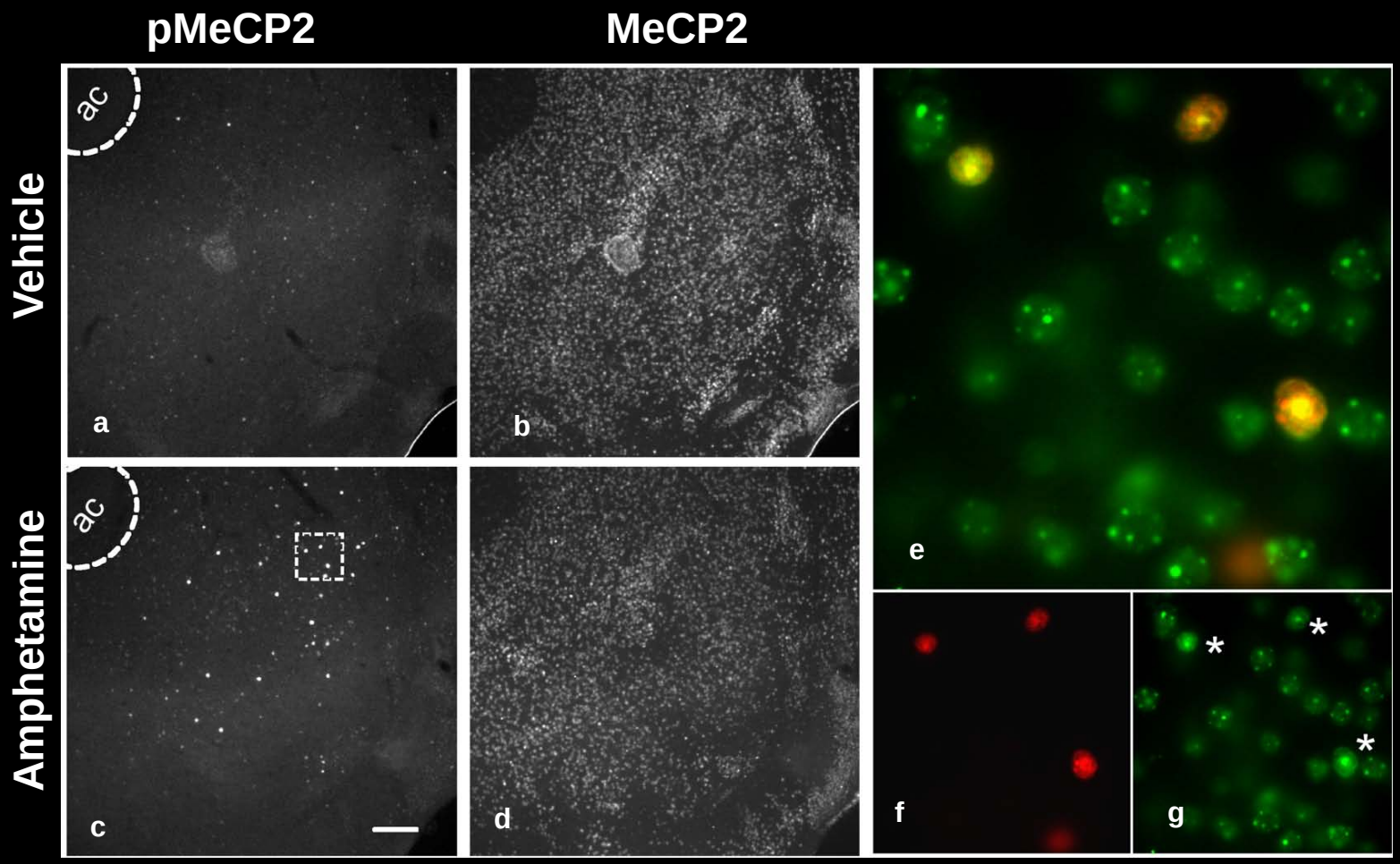

Amphetamine
?
MeCP2
(Adult NAc)
Reward (CPP)
Cocaine
mIR212
MeCP2
(Dorsal striatum)
Extended access
self-administration
Deng et al. 2010 *Nat Neurosci* **13**: 1128
Im et al. 2010 *Nat Neurosci* **13**: 1120

Post-translational modifications of MeCP2



Chen (2003) *Science* ***302****: 885*
Zhou (2006) *Neuron* ***52:*** *255*
Tao (2009) *PNAS* ***106****: 4882*

MeCP2 Ser421 phosphorylation (pMeCP2) is induced in the NAc by amphetamine

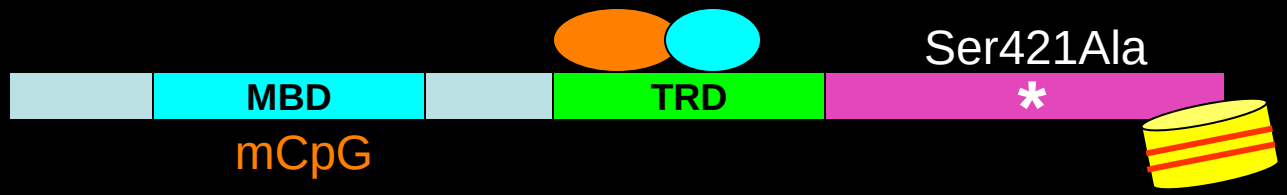


Deng et al. 2010 *Nat Neurosci* **13**: 1128

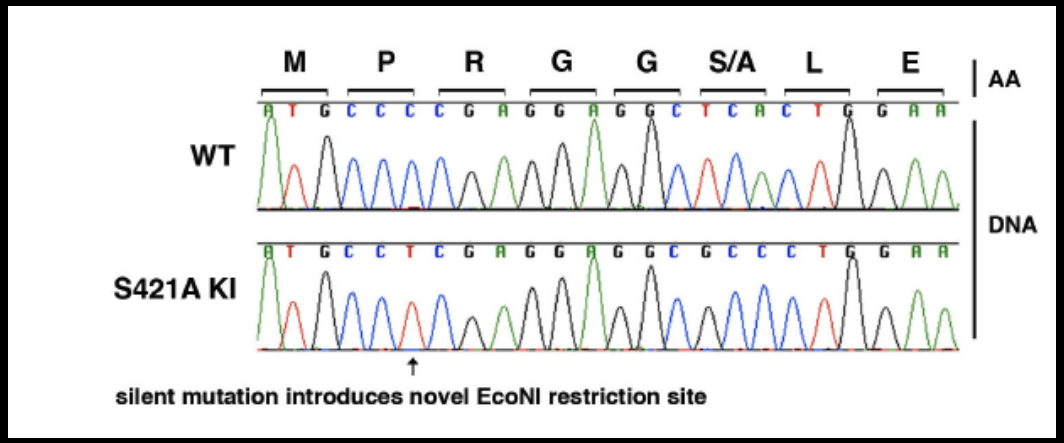
Also see induction in prelimbic cortex

No induction in VTA, dorsal striatum, amygdala or hippocampus

Generation of MeCP2 Ser421Ala knockin (KI) mice



Mecp2 **S421A**



No significant change in MeCP2 expression or localization

Cohen *et al.* (2011) Neuron 72:35

Normal baseline behaviors in MeCP2 KI mice

Motor function (rotarod, wire hang, open field locomotor activities)

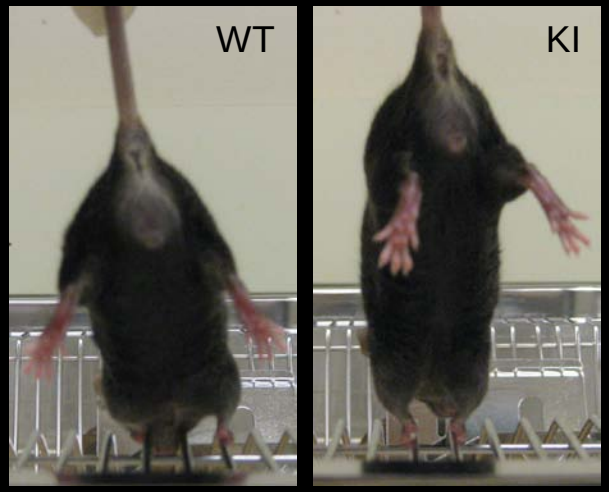
Anxiety (light dark box, elevated zero maze, thigmotaxis)

Spatial learning and memory (Morris water maze/reversal)

Contextual fear conditioning

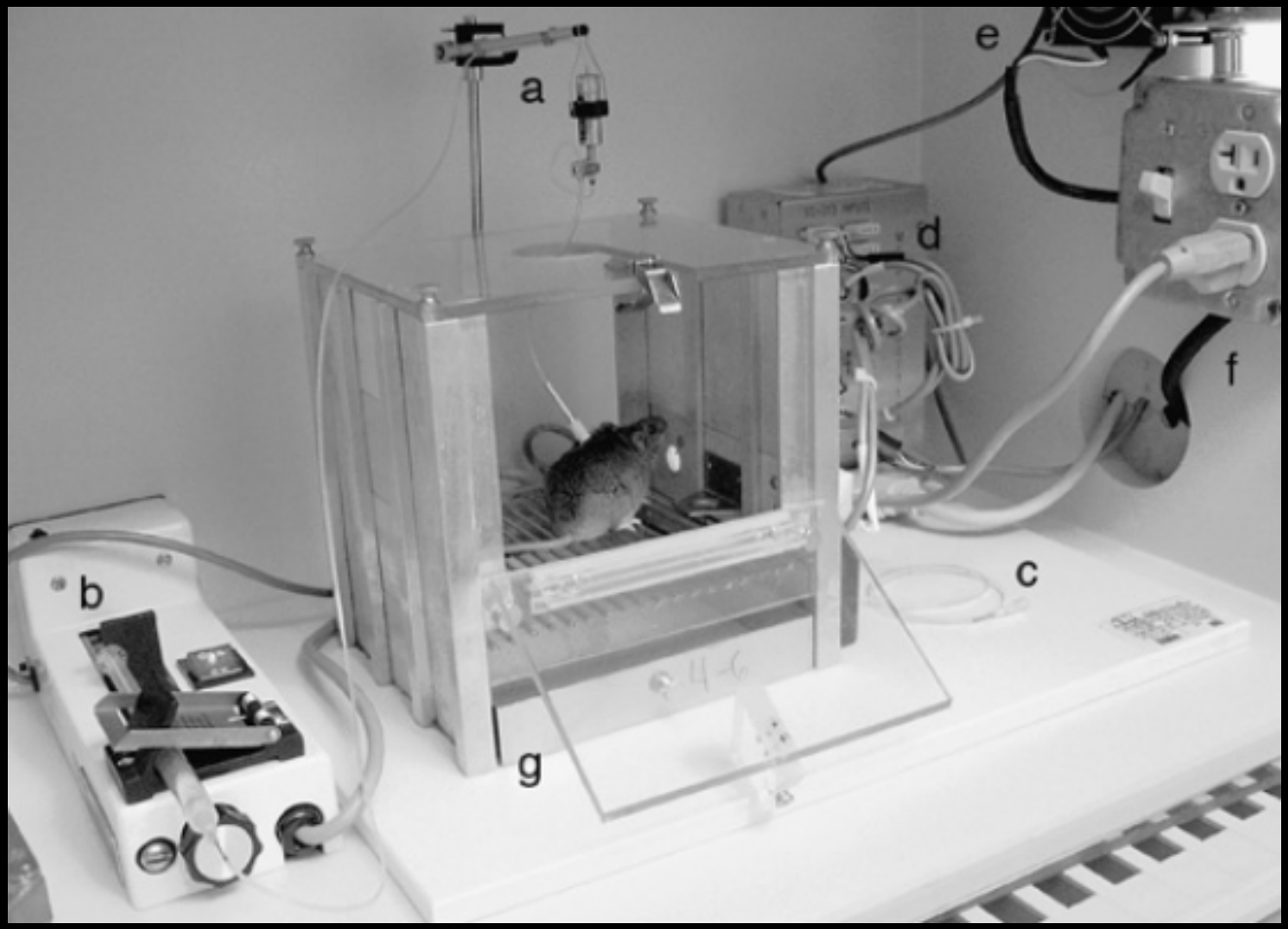
Sociability

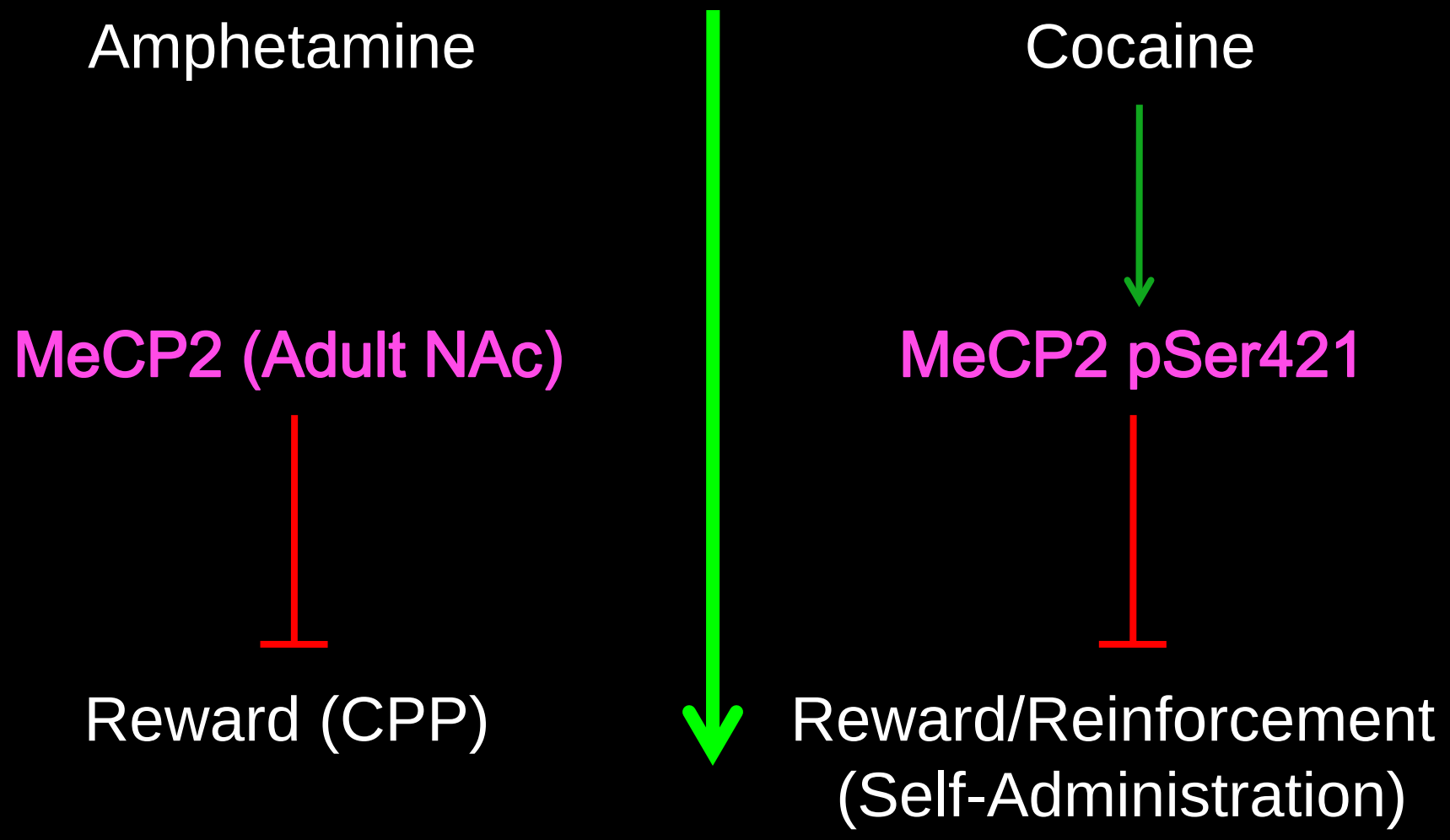
Cohen *et al.* (2011) Neuron 72:35



Behavioral responses to acute and chronic treatment with psychostimulants and antidepressants

Operant chamber for testing cocaine self-administration (SA) in mice

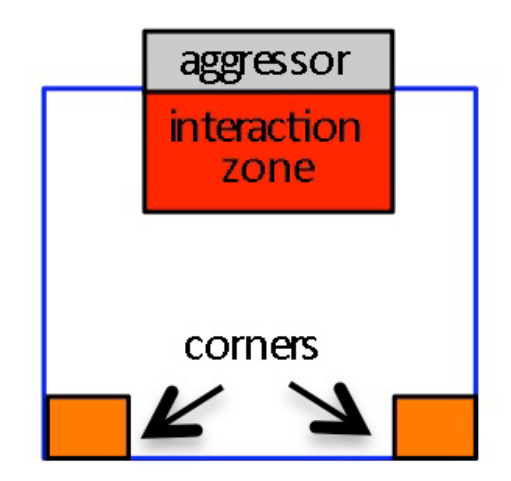



Amphetamine
Cocaine
MeCP2 (Adult NAc)
MeCP2 pSer421
Reward (CPP)
Reward/Reinforcement
(Self-Administration)

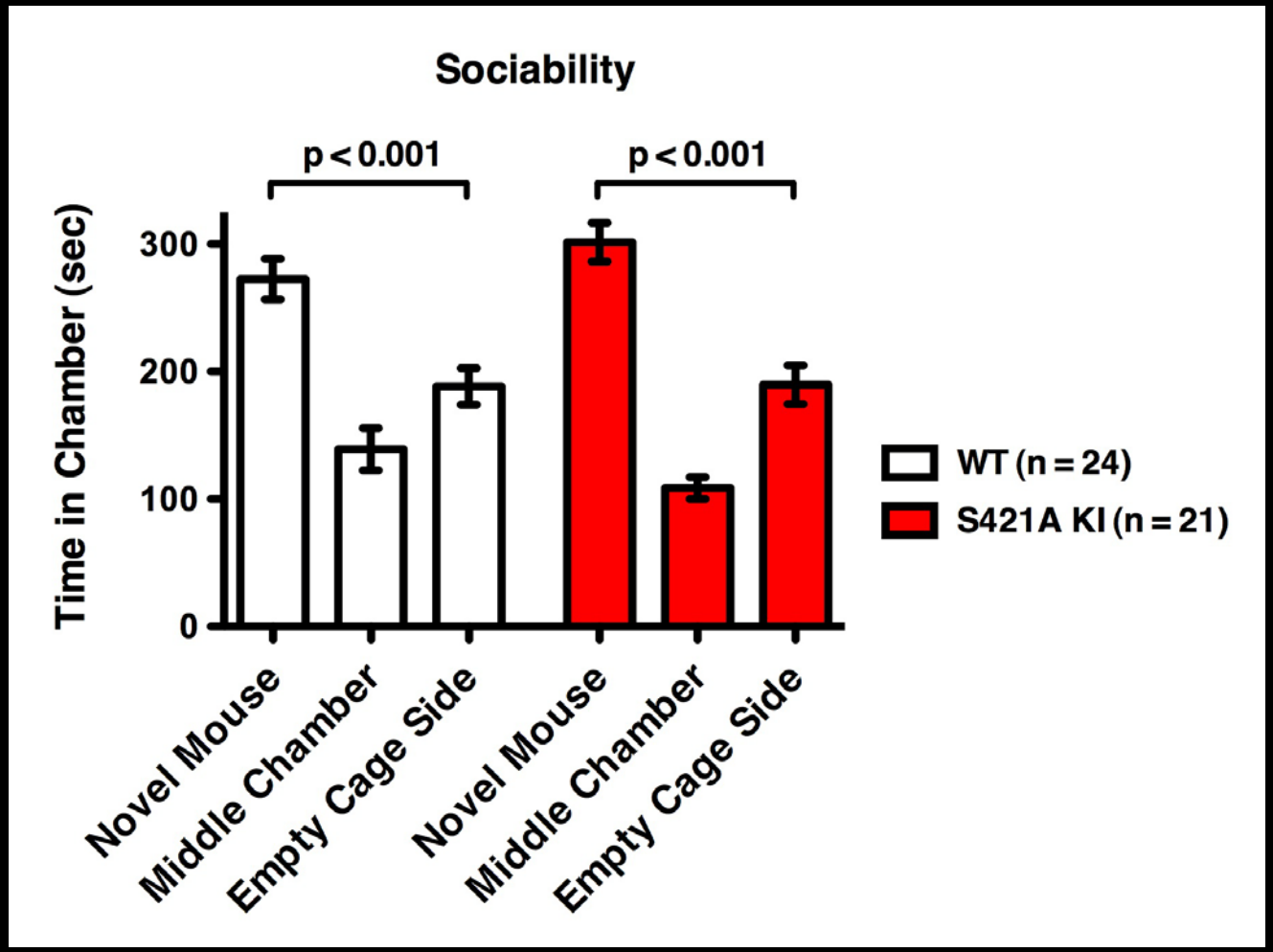
Social defeat stress: A behavioral model for the study of chronic antidepressant action

A

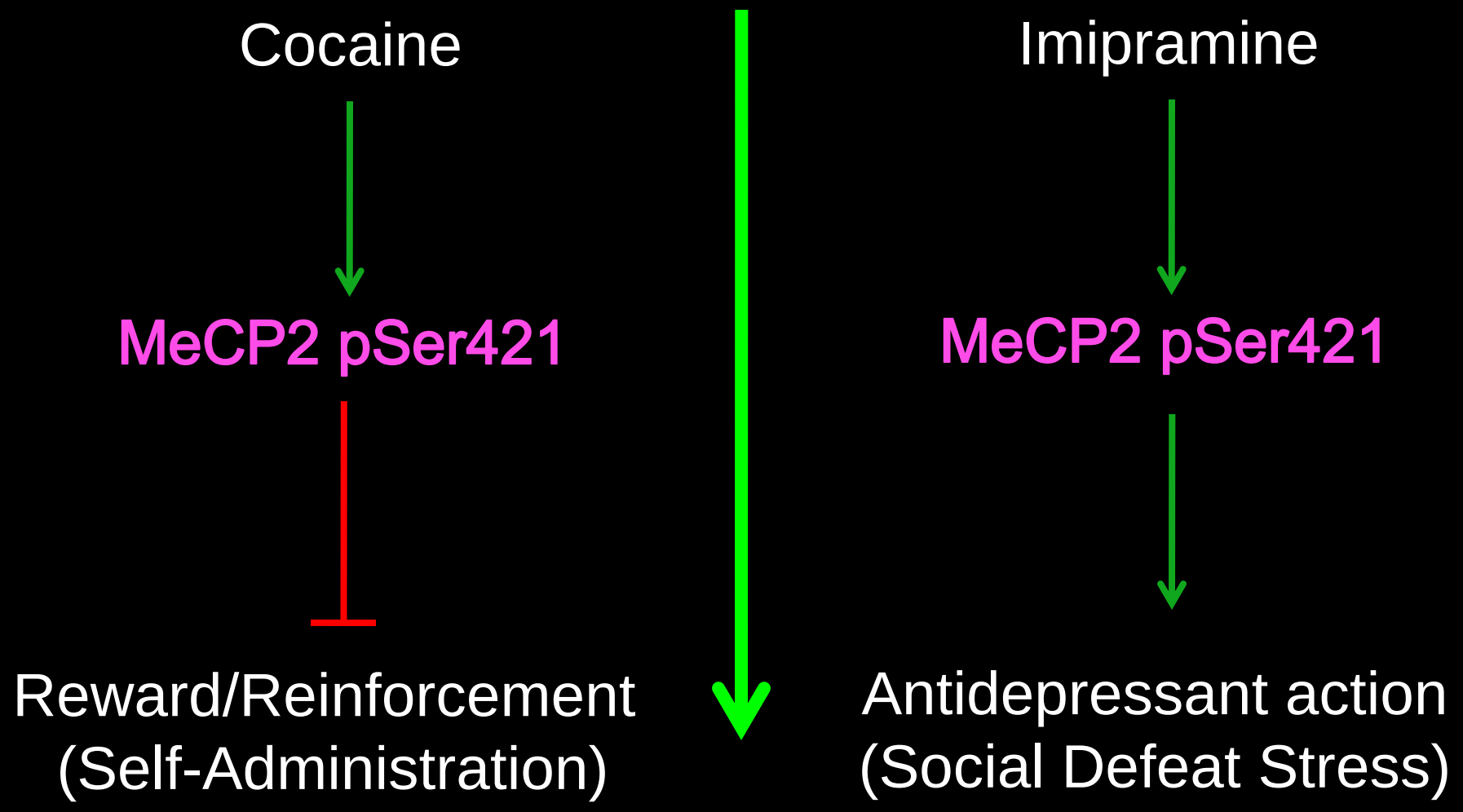
	Day 1-10	Day 11	Day 12-38	Day 39	Day 40
	Defeat	Test	Treat (chronic)	Treat (acute)	Test
Control:	no defeat	test	vehicle	vehicle	test
Acute:	defeat	test	vehicle	antidepressant	test
Chronic:	defeat	test	antidepressant	antidepressant	test



The MeCP2 KI mice are sociable



Cohen *et al.* (2011) Neuron 72:35



Stress can interact with addictive-like behaviors

Conclusions

MeCP2 in the NAc modulates psychostimulant reward

Drugs that elevate dopamine and serotonin drive pMeCP2 in neurons within mesolimbocortical brain regions

Ser421Ala phosphorylation of MeCP2 is required for at least a subset of behavioral responses to chronic psychostimulant and antidepressant exposure

Two sites of pMeCP2 induction that are relevant to both reward and stress are the NAc and the lateral habenula

Jay Deng
Ashley Hutchinson
Michelle Tougas
Ranjula Wijayatunge
Young May Cha
Charlotte Schwarz
Liang-Fu Chen

Duke
Bill Wetsel
Herb Covington

Harvard
Michael Greenberg
Sonia Cohen

Scripps, Florida
Paul Kenny

NIDA
NARSAD
March of Dimes
Whitehall Foundation
Ruth K. Broad Biomedical Research Foundation