Stopping cocaine before it gets to the brain: new frontiers in treatment

CELAC Symposium "Progress and Challenges in Scientific Research on Treatments, Pharmacological Strategies and Vaccines against Drug Addiction"

Marilyn E. Carroll [1]

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NIDA Tested Medications for Treatment of Cocaine Dependence

- Amantadine
- Lys-dex amphetamine
- Aripriprazole*
- Atomoxetine
- Baclofen
- Buprenorphine
- Bup/naloxone
- Bupropion
- Buspirone
- Clonidine
- DHEA
- Desipramine
- d-Amphetamine
- Dextrometorphan
- Disulfiram
- Divalproex
- Dronabinol
- Fluoxetine*
- Gabapentin
- GBR12909
- GCP44352
- Gammavinyl GABA
- Hydromorphone
- LAAM
- L-Dopa/Carbidopa
- L-tryptophan
- Lofexidine
- Lobeline
- LY544344
- Mecamylamine
- Memantine
- Methamphetamine
- Methylphenidate
- Methadone
- Modafinil
- N-acetyl-aspartate
- Naltrexone x 2
- Olanzapine
- Pergolide
- Progesterone
- Propanolol
- Reboxetine
- Risperidone
- RTI compounds
- Selegiline
- Sertraline
- Tiagabine
- Topiramate
- Vigagatrin
- Venlafaxine
- Yohimbine
- … and More

3 studies of cocaine hydrolase (CocH) treatment to acutely block:

1. **Cocaine self-administration (progressive ratio)**
2. **Cocaine escalation**
3. **Cocaine reinstatement**

3 studies of CocH viral vector (VEC) treatment to chronically block:

1. **Cocaine reinstatement**
2. **Cocaine-induced locomotor sensitization with cocaine vaccine (VAC)**
3. **Cocaine self-administration (VEC + VAC)**

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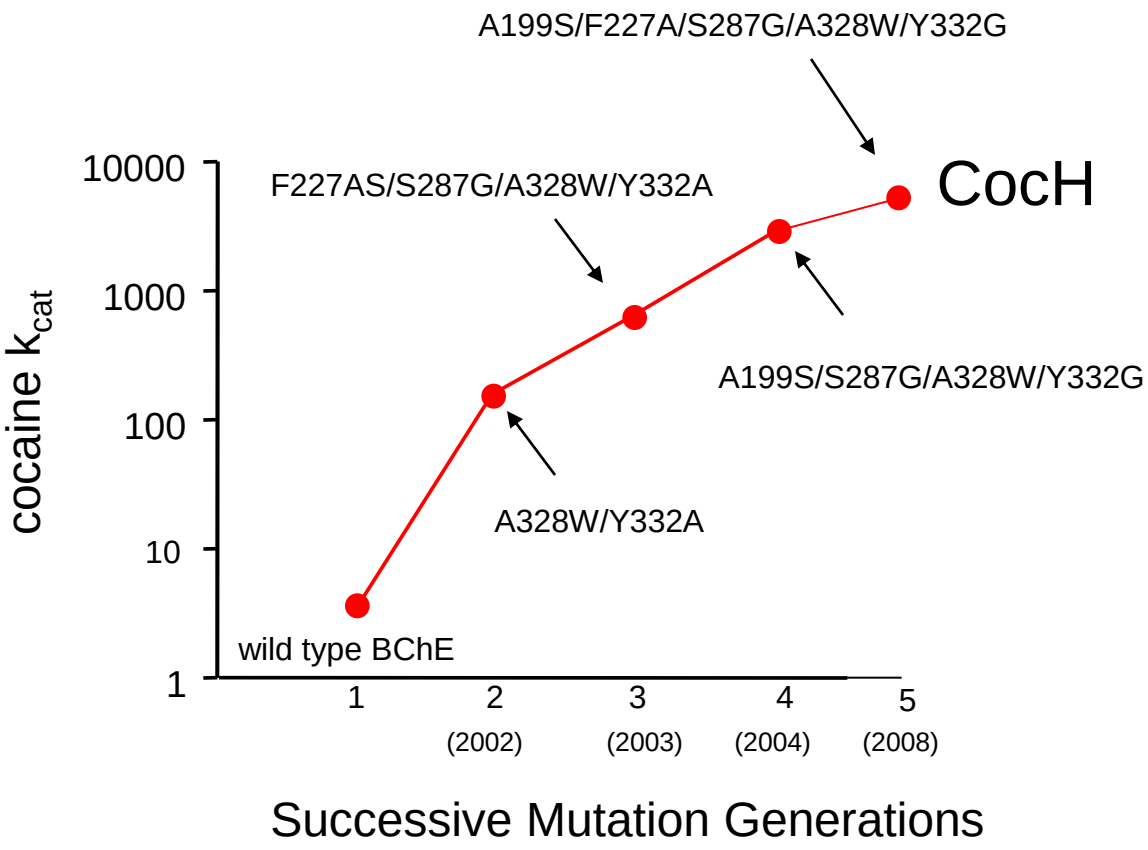
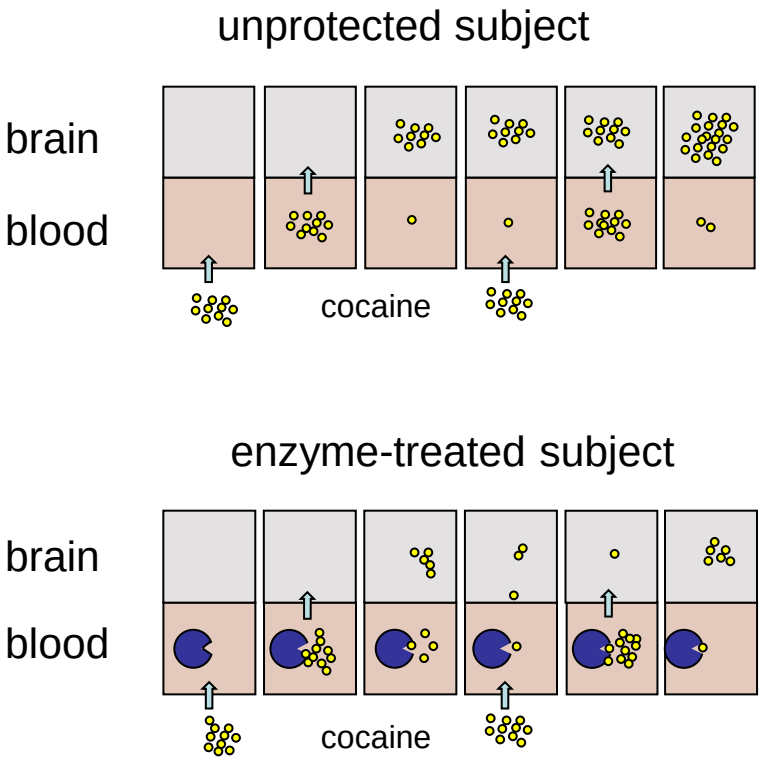
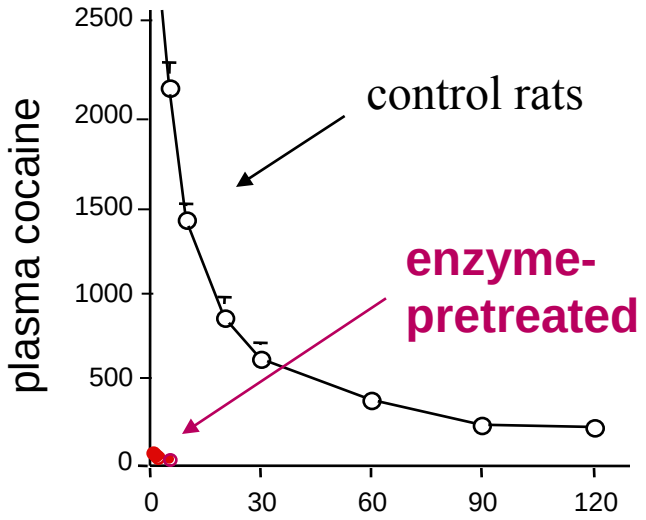
BChE - cocaine hydrolase (CocH) - genetically engineered from human BChE



Molecular interception by enzyme ("Pac-man model")



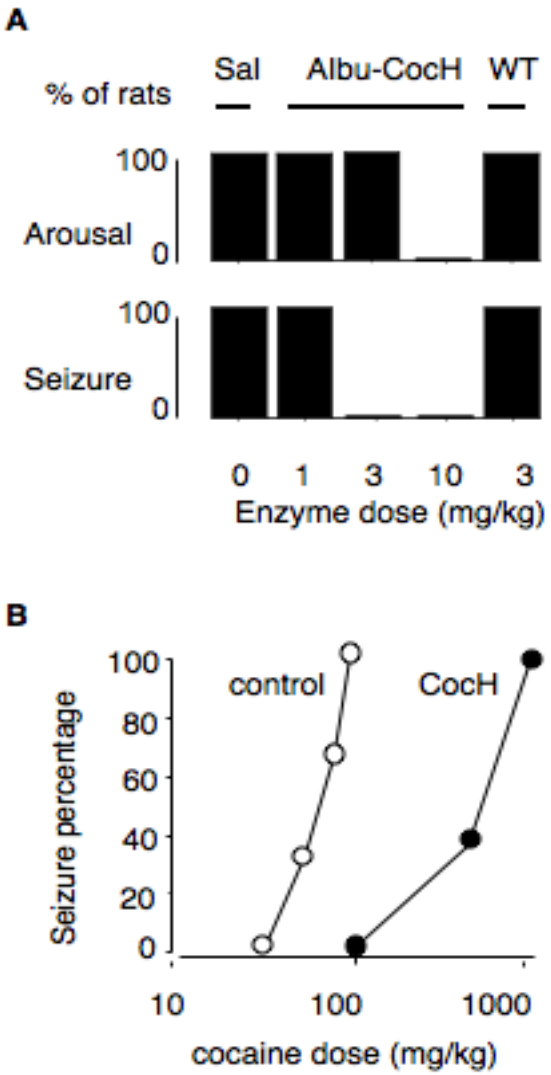
CocH drastically accelerates cocaine metabolism in rats



Gao et al, Chemico-Biol. Interact. 2010

Brimijoin et al. Neuropsychopharmacol 33: 2715-2725, 2008

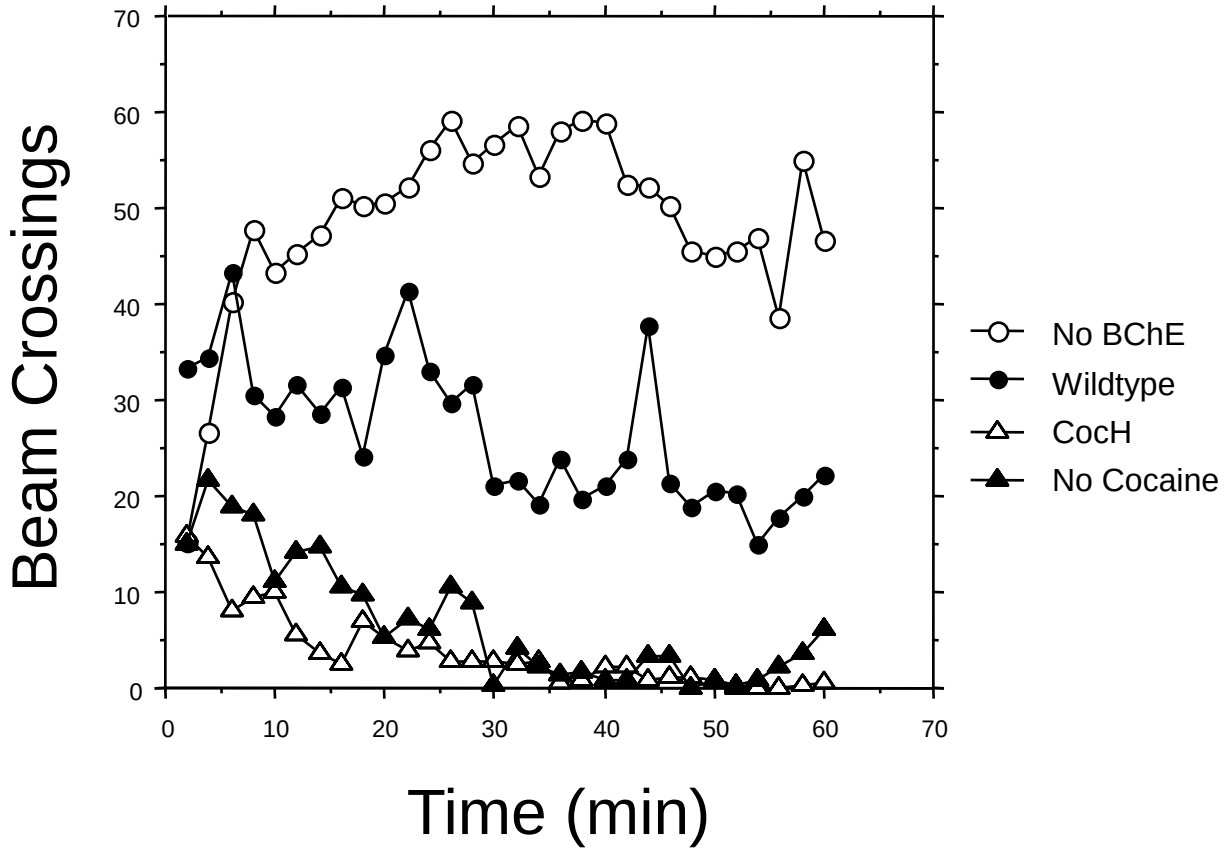
CocH rescues rats from cocaine-induced seizures



Brimijoin et al. Neuropsychopharmacol 33: 2715-2725, 2008

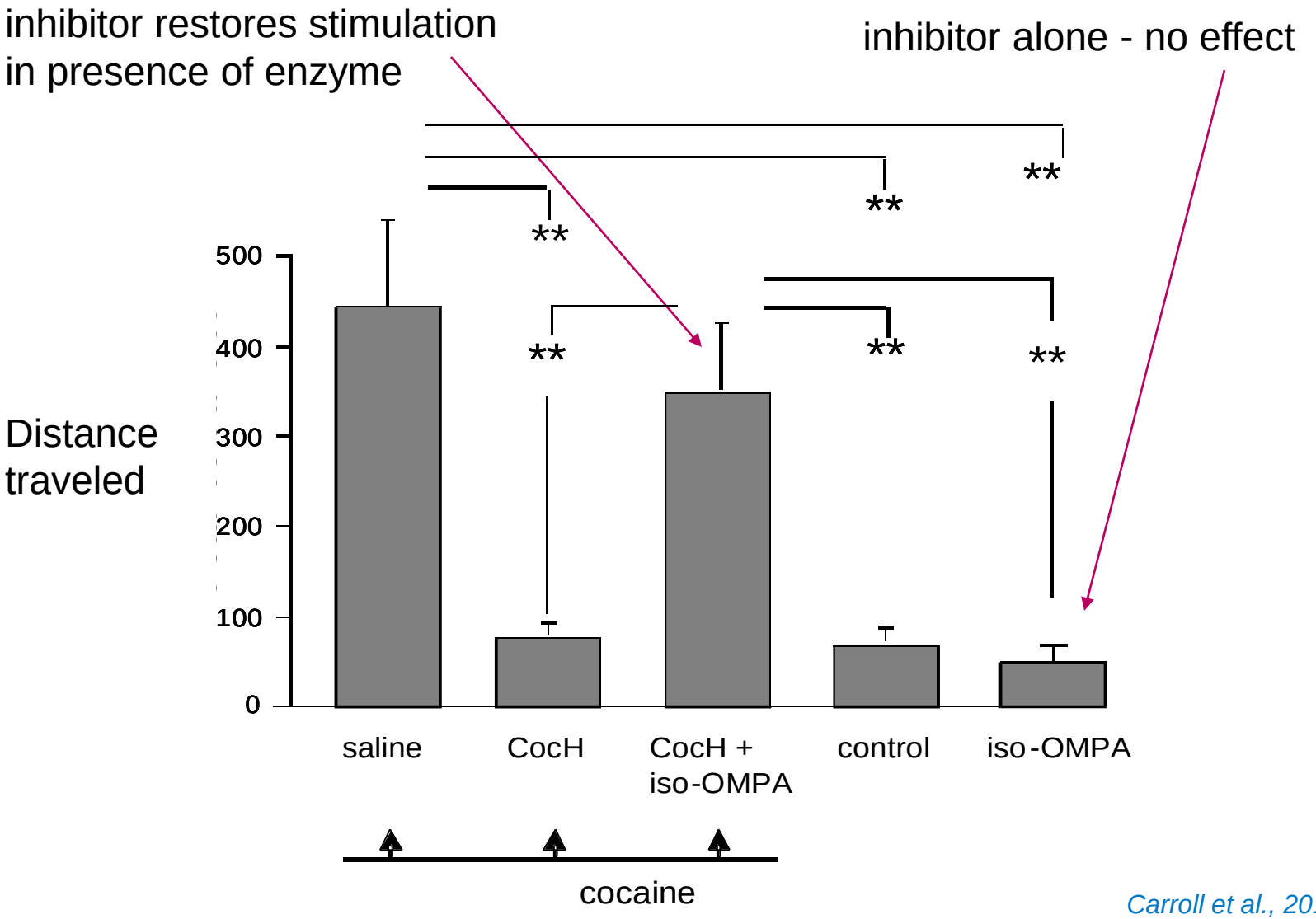
Locomotor activity apparatus

CocH prevents cocaine-induced locomotor activity in mice



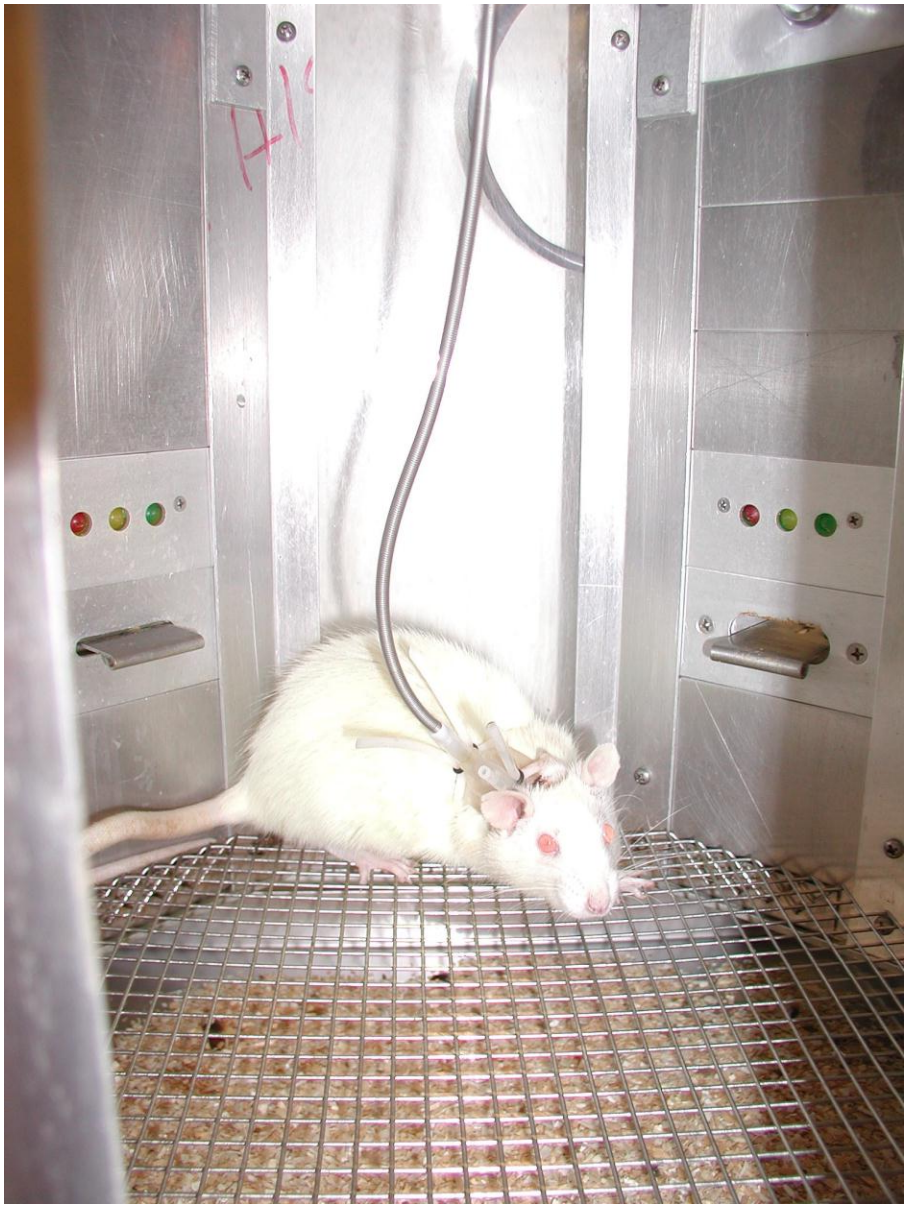
Brimijoin et al. Neuropsychopharmacol 33: 2715-2725, 2008

Cocaine hydrolase treatment requires enzyme activity to suppress cocaine-stimulation in mice
Cholinesterase inhibitor, iso-OMPA, blocked enzyme activity

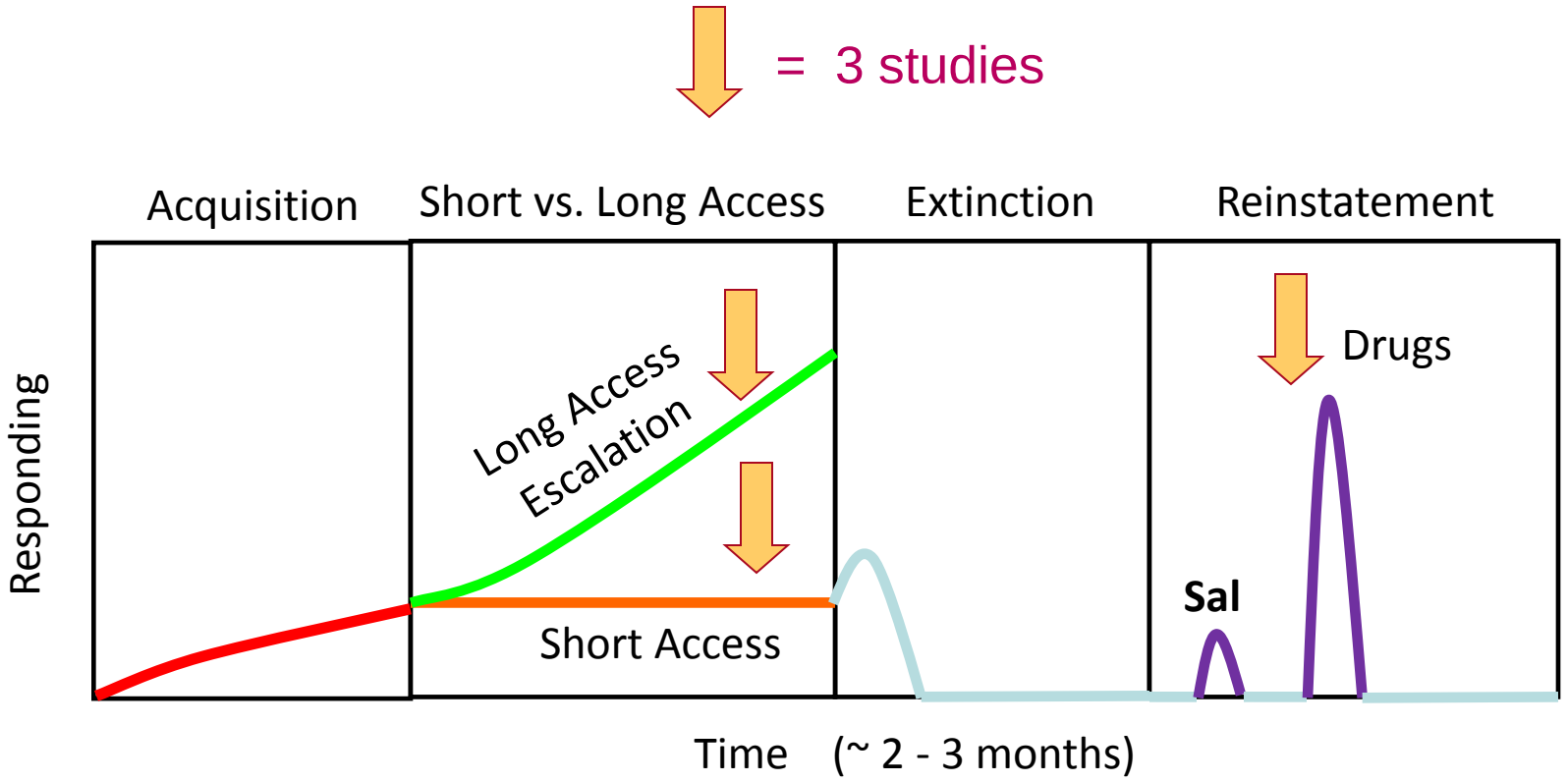


Carroll et al., 2012

IV drug self-administration apparatus

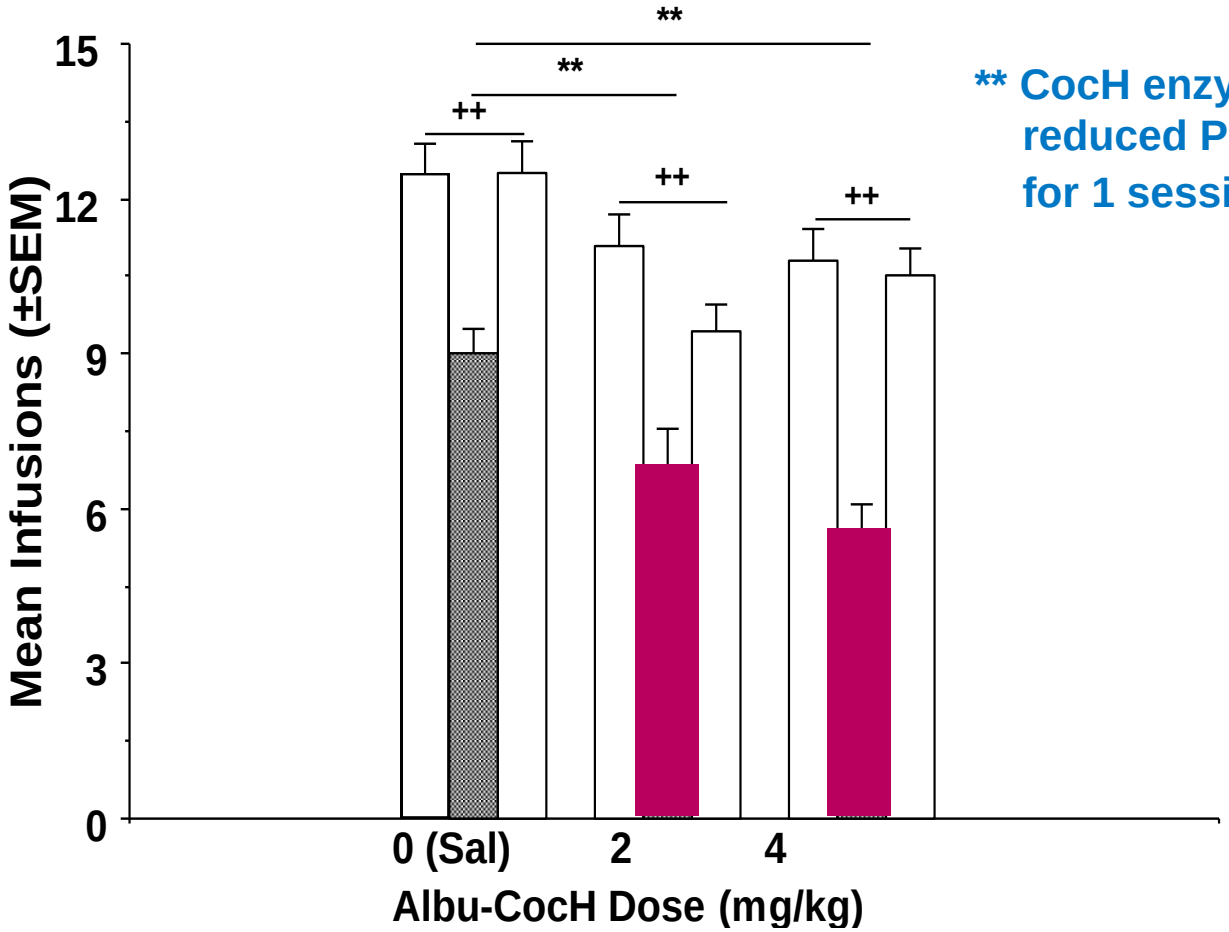


Phases of Drug Abuse Process



Modified from de Vries (1998) and Ahmed and Koob (1998)

Cocaine self-administration during short access (2 h) under a progressive-ratio (PR) schedule to assess motivation

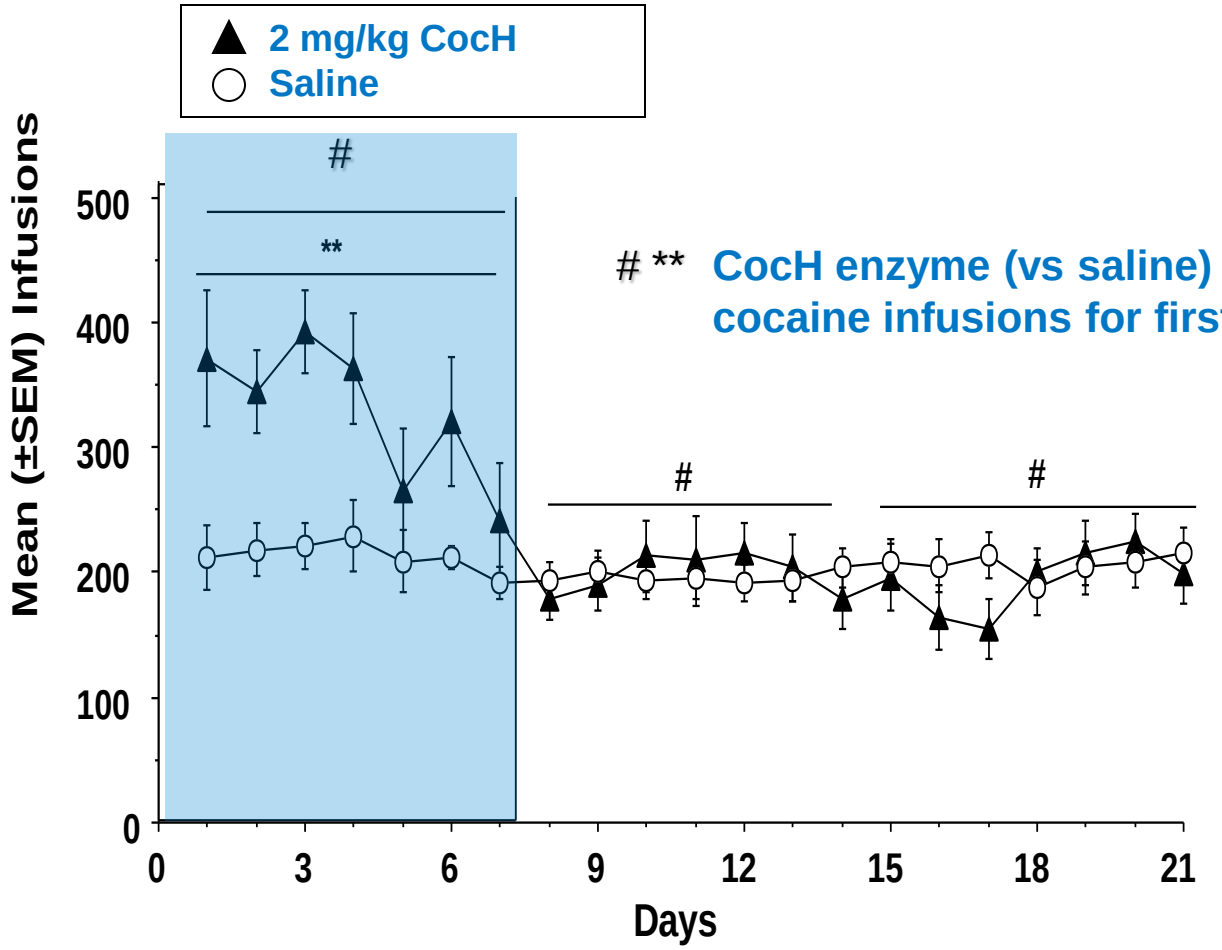


** CocH enzyme (vs saline) reduced PR performance for 1 session

Carroll et al. Psychopharmacology, 2011

Escalation of cocaine self-administration during long access (6 h)

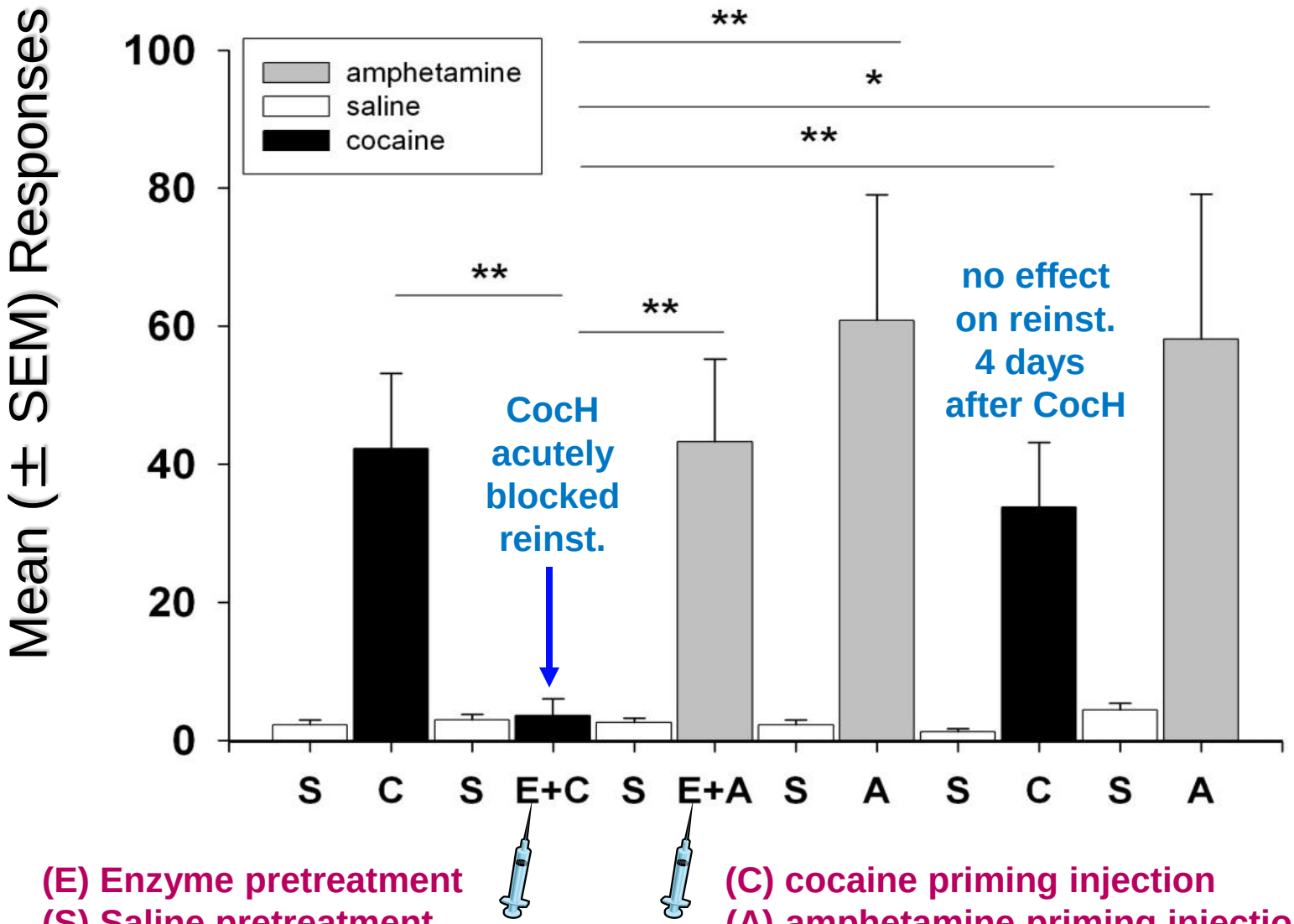
Saline or enzyme treatment
For first 7 days



 # ** CocH enzyme (vs saline) increased cocaine infusions for first 4 (of 7) days

Carroll et al. Psychopharmacology, 2011

Reinstatement (relapse) responses with CocH enzyme



(E) Enzyme pretreatment
(S) Saline pretreatment

(C) cocaine priming injection
(A) amphetamine priming injection

Brimijoin et al. Neuropsychopharmacology 2008

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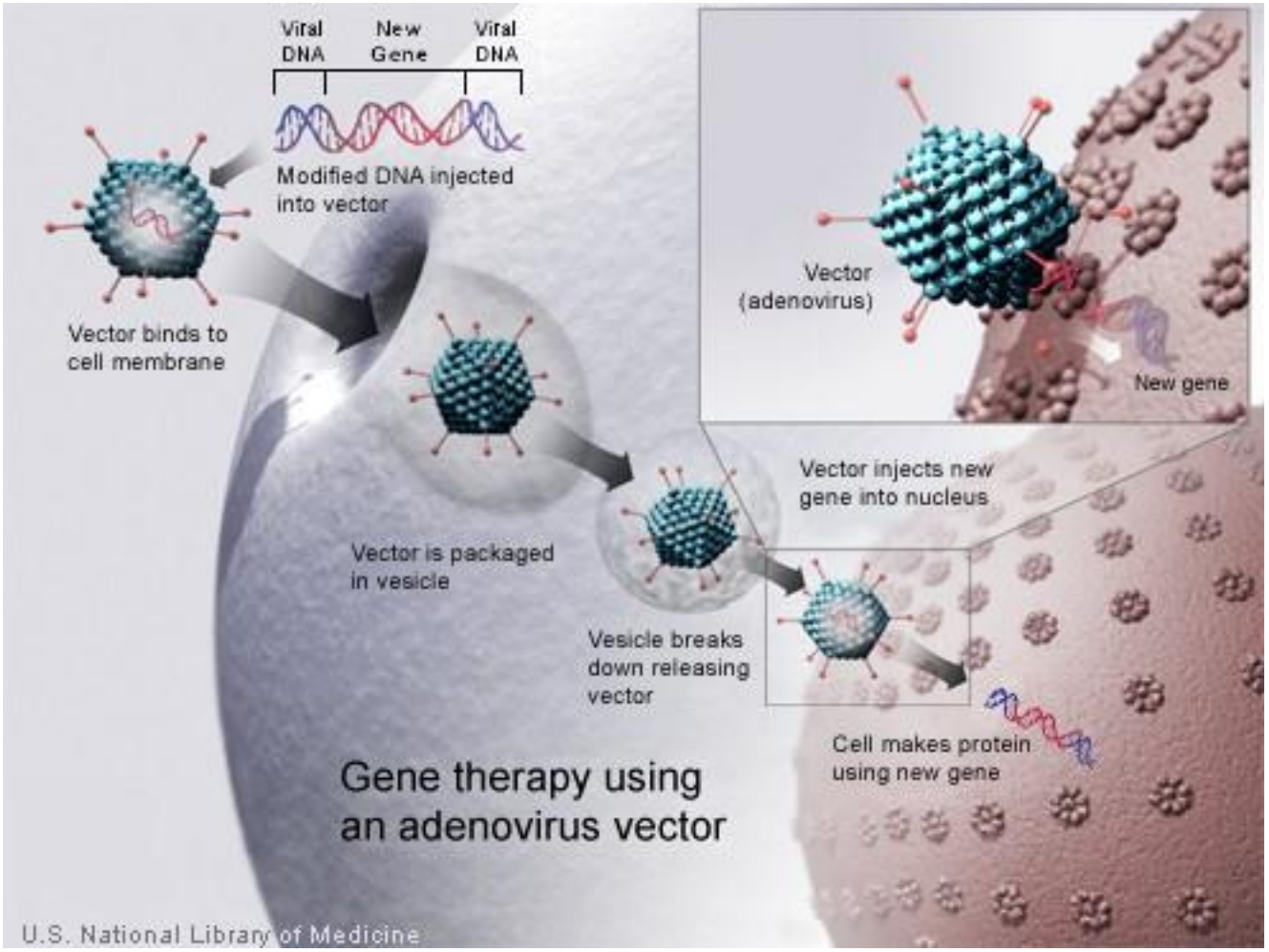
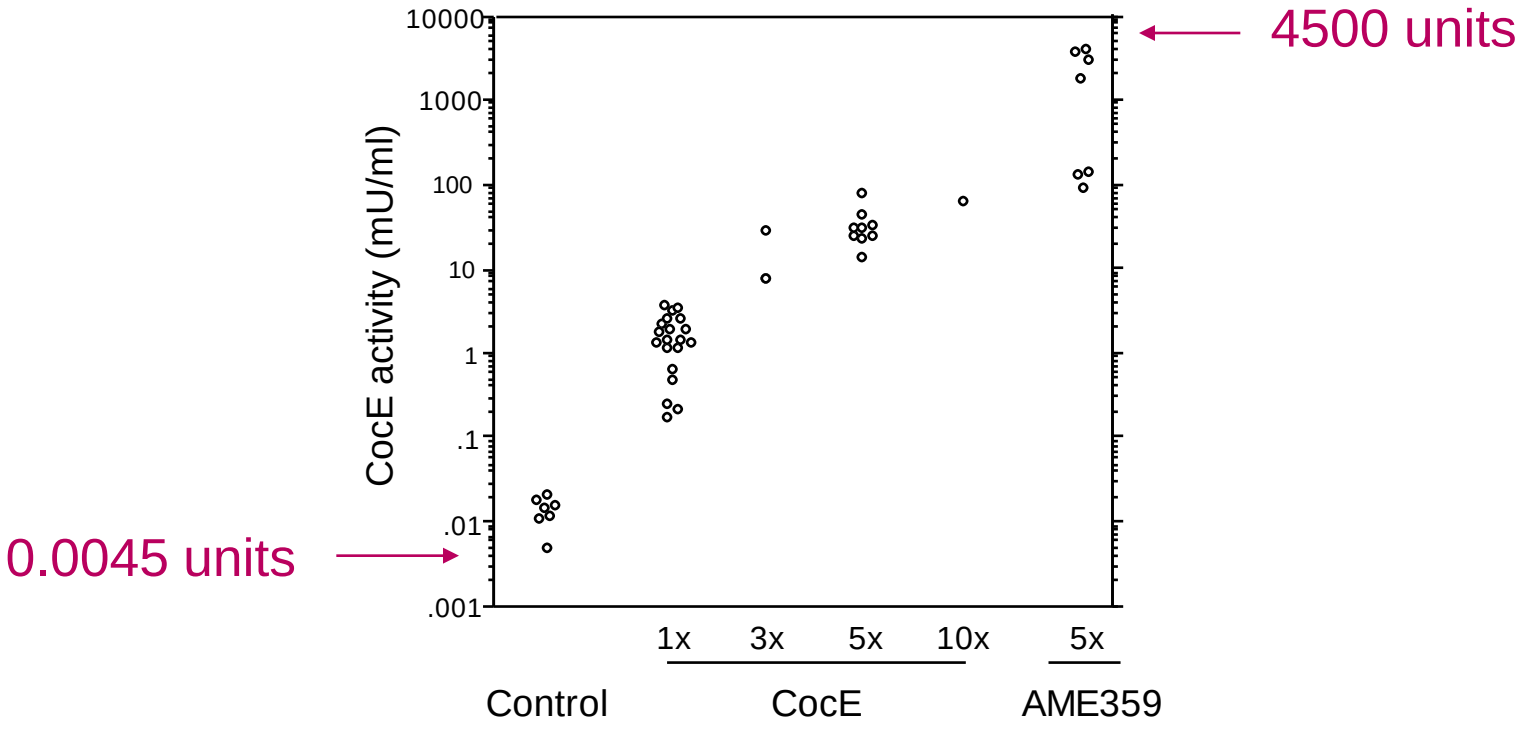
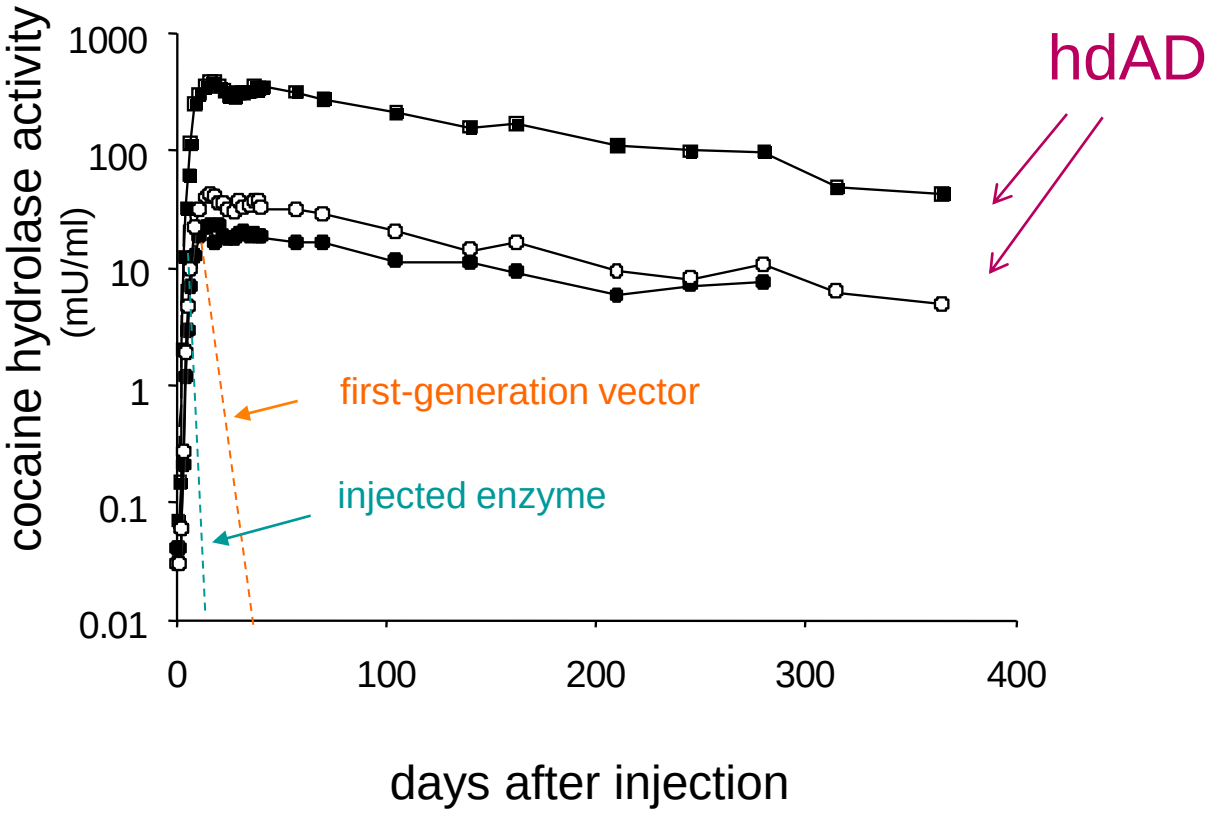
Adenoviral gene delivery for long-term actions



Hydrolase transduction raises cocaine-hydrolase activity in plasma up to 1,000,000-fold



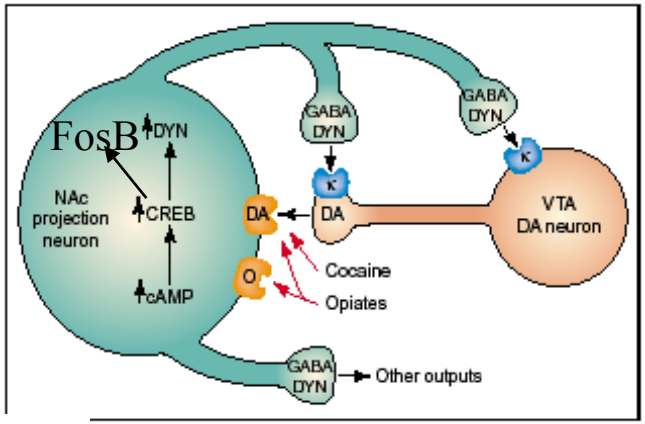
Year-long generation of CocH with helper-dependent adenoviral vector (hdAD) by gene transfer



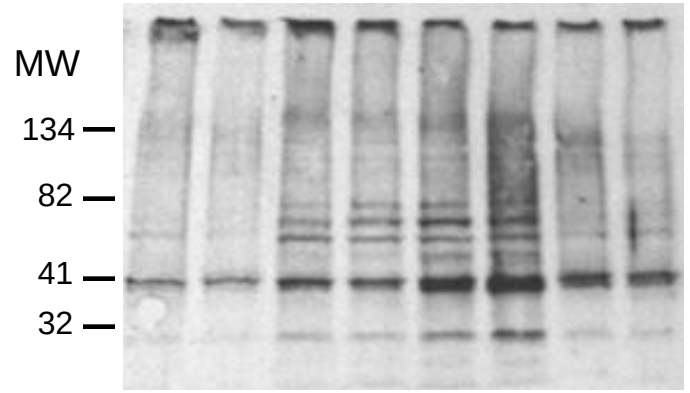
Ottawa, Mayo

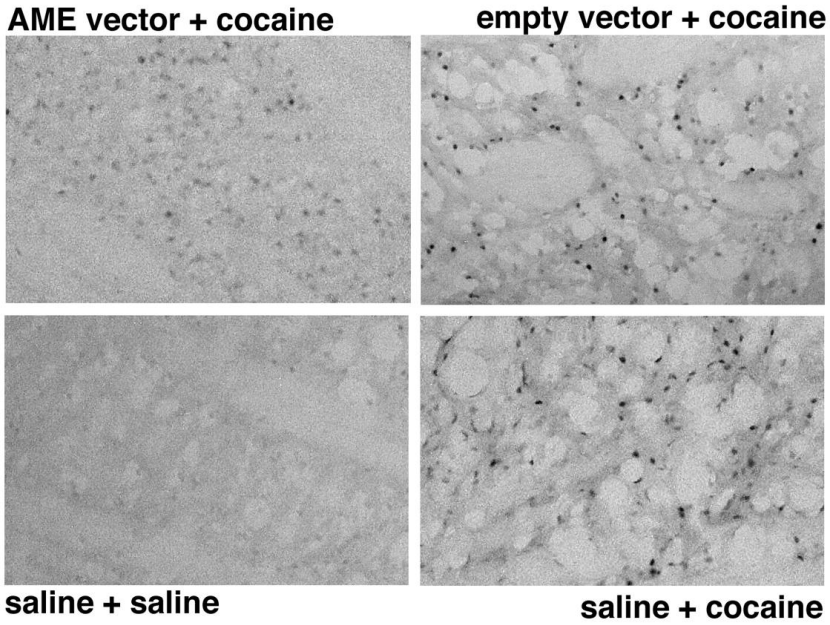
Gao and Brimijoin J Pharmacol Exp Ther 330:449-457, 2009

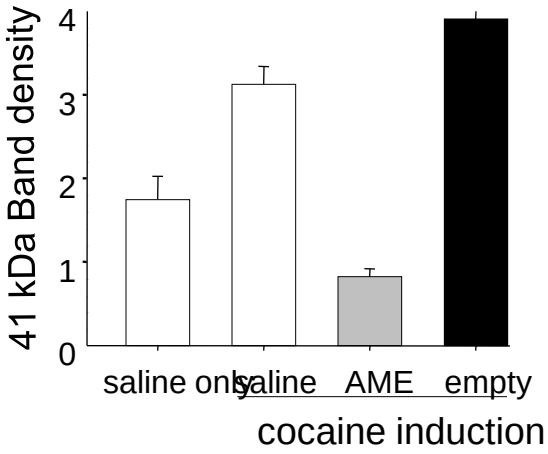
Gene transfer of hydrolase blocks fosB induction in neostriatum in rats given repeated cocaine treatment



CocH

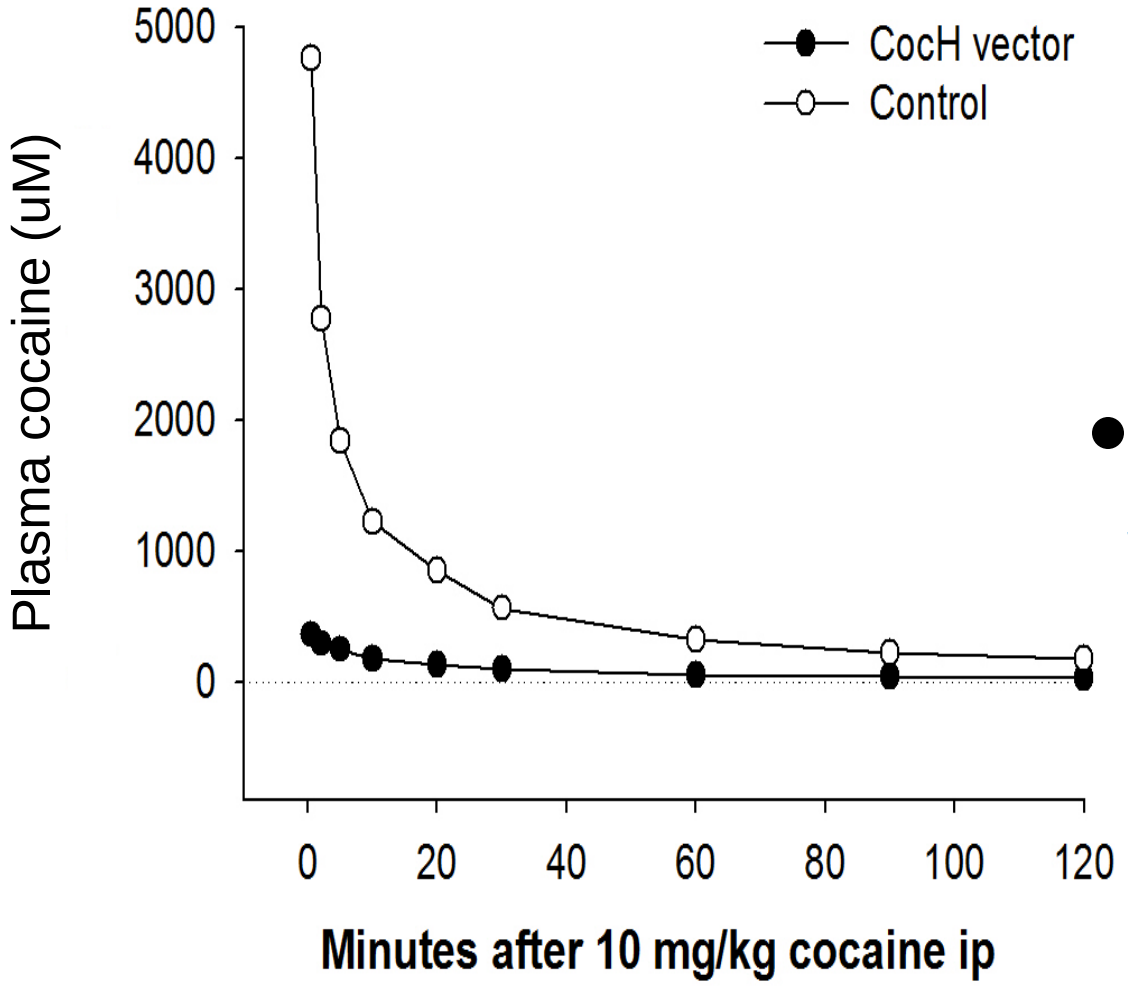






Gao and Brimijoin J Pharmacol Exp Ther 330:449-457, 2009

Cocaine clearance in blood plasma in rats treated 2 weeks earlier with CocH vector or saline controls



● **Plasma cocaine minimal in CocH vector-treated group**

Anker et al., Biol. Psychiatry, 2011

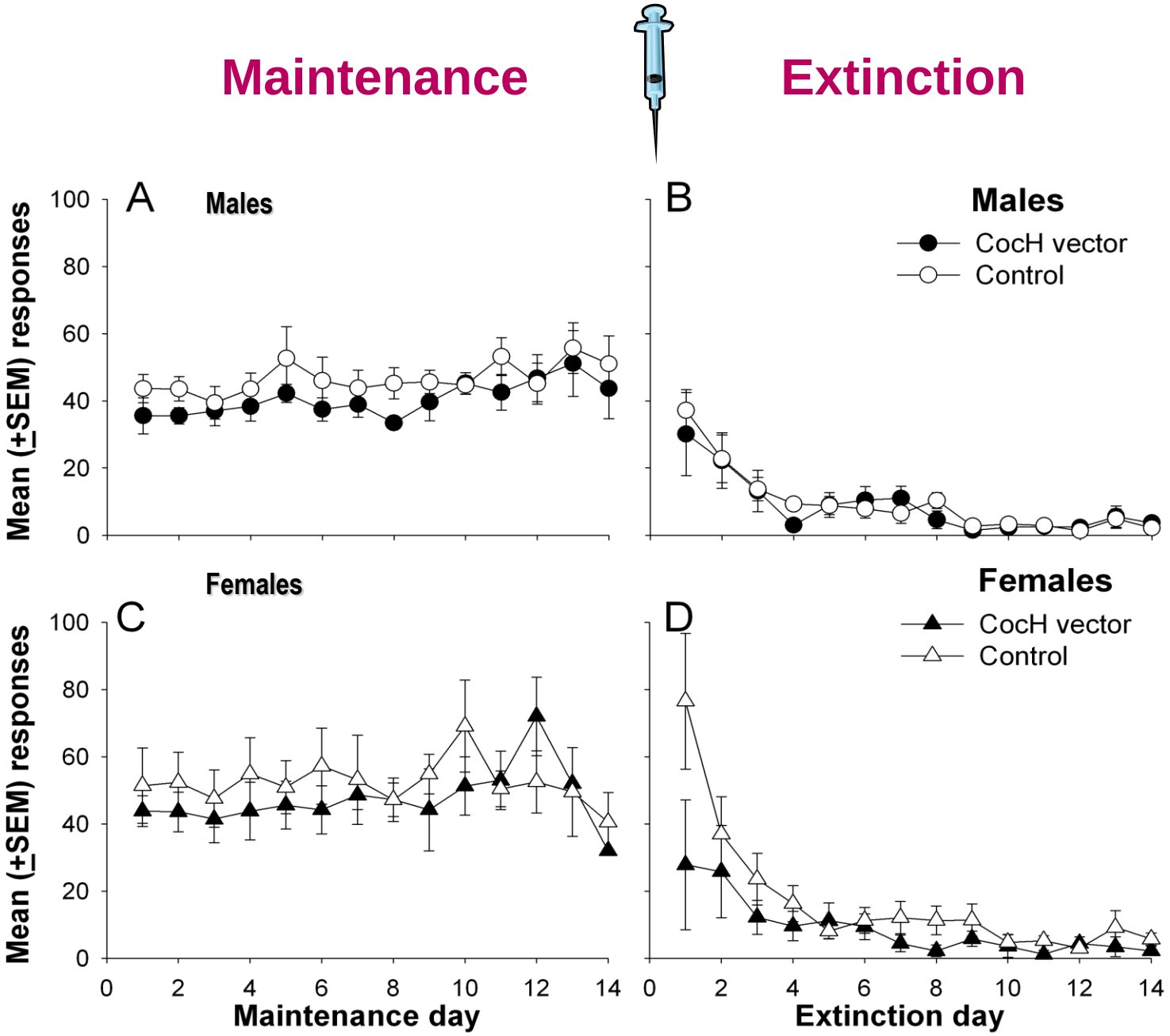
CocH vector reinstatement procedure

1 injection of CocH vector or saline
1 day before extinction

Phase (days)	ACQ (~10)	MAINT (~10)	EXT (14)	Reinstatement (8)	Protracted Reinstatement							
				SC SC SC SC SA	SC	SC	SC	SC	SC	SC	SC	SC SA
Dose (mg/kg, i.p.)	C 0.4 mg/kg, i.v.			C (5, 10, 15); A (2)	C (10)				C (10); A (2)			
Weeks post vector	N/A	N/A		3	5	6	7	8	12	16	20	24

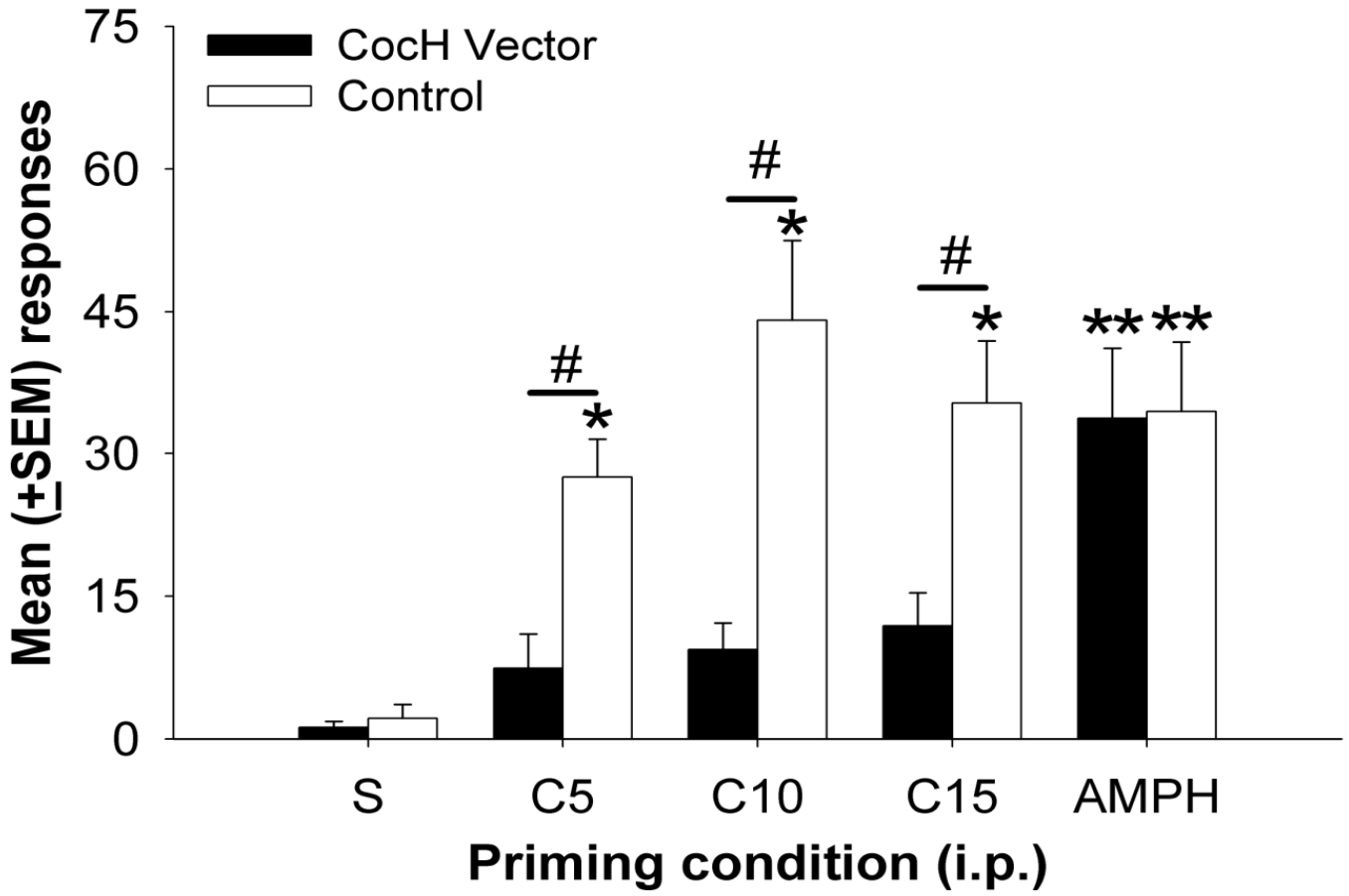
Blood draws for CocH levels weekly then monthly

Anker et al., Biol. Psychiatry, 2011



Anker et al. Biol. Psychiatry, 2011

Reinstatement after CocH vector (week 3) by cocaine priming dose

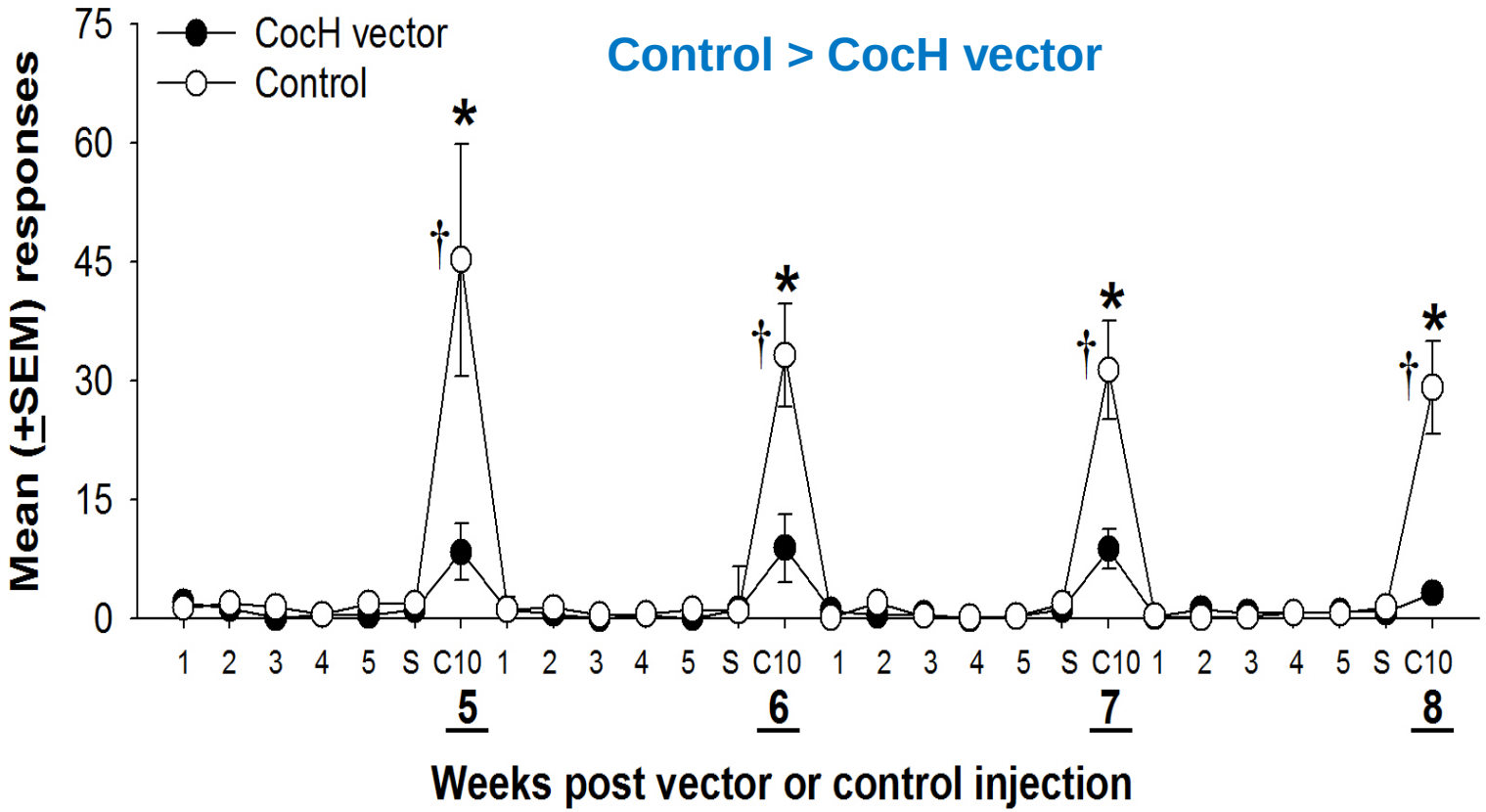


15 16 17 18 19 20 21 22 23 24

Days post CocH vector injection

Anker et al., Biol. Psychiatry, 2011

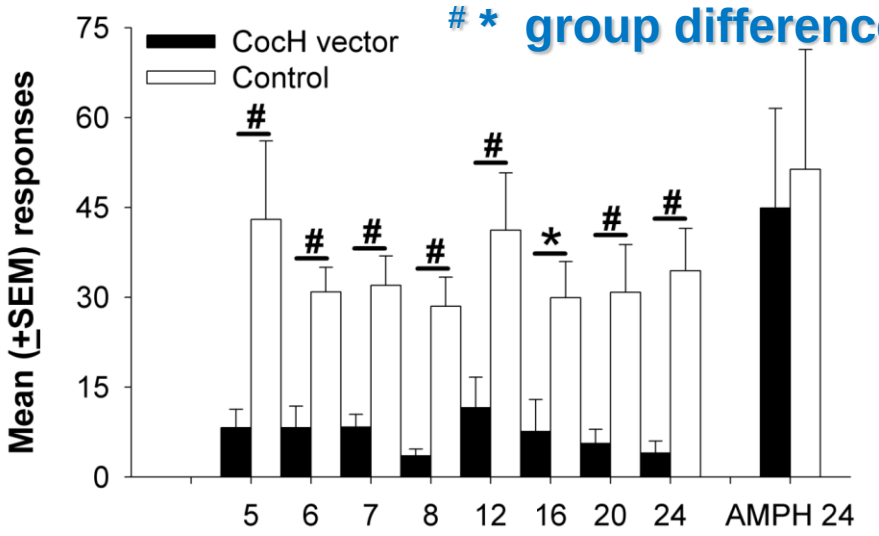
Reinstatement responding after CocH vector (weeks 5 - 8)



Minimal responding on days of saline (S)
or no priming injections (1-5)

Anker et al., Biol. Psychiatry, 2011

Active lever reinstatement responding



Anker et al., Biol. Psychiatry, 2011

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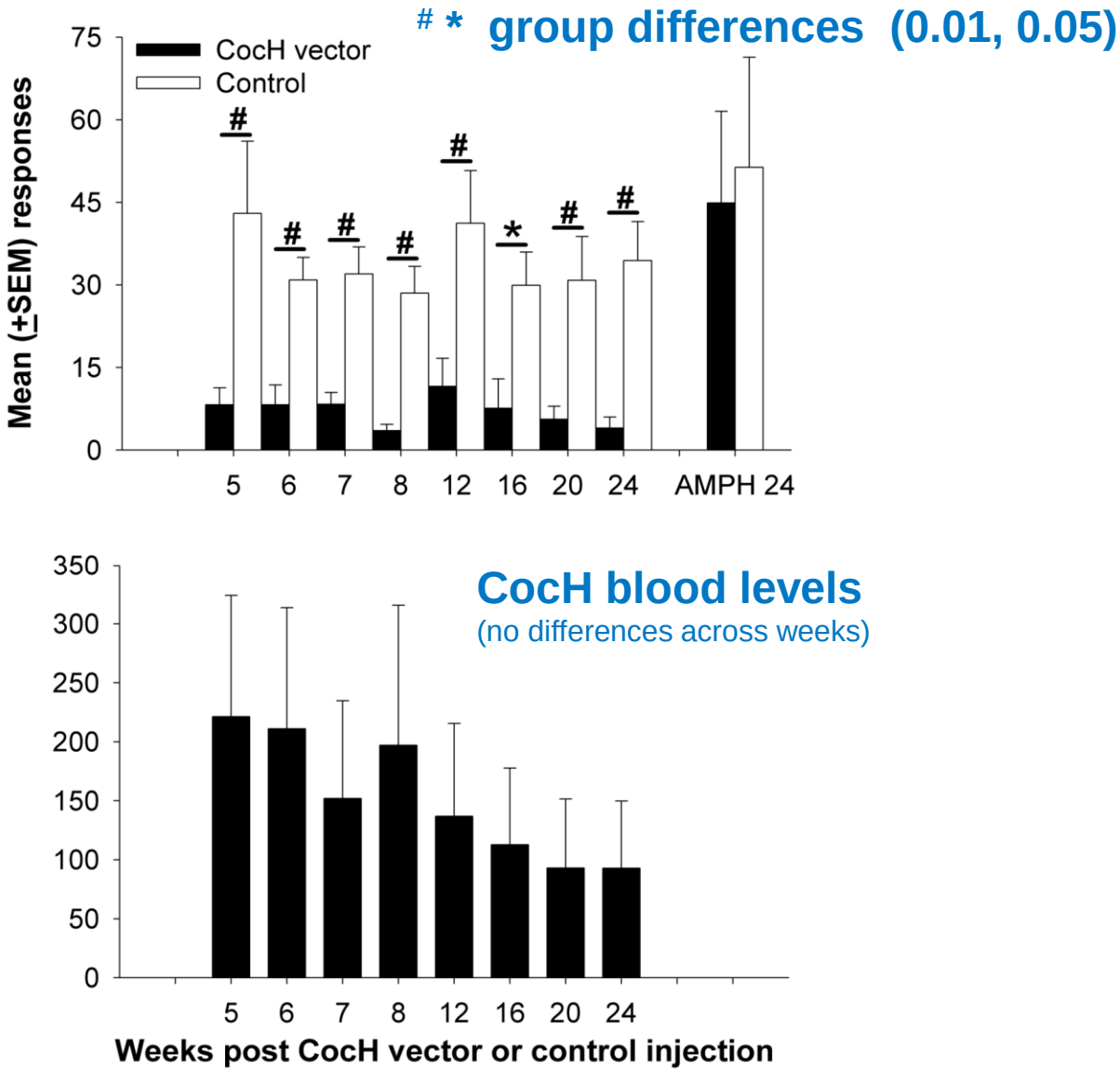
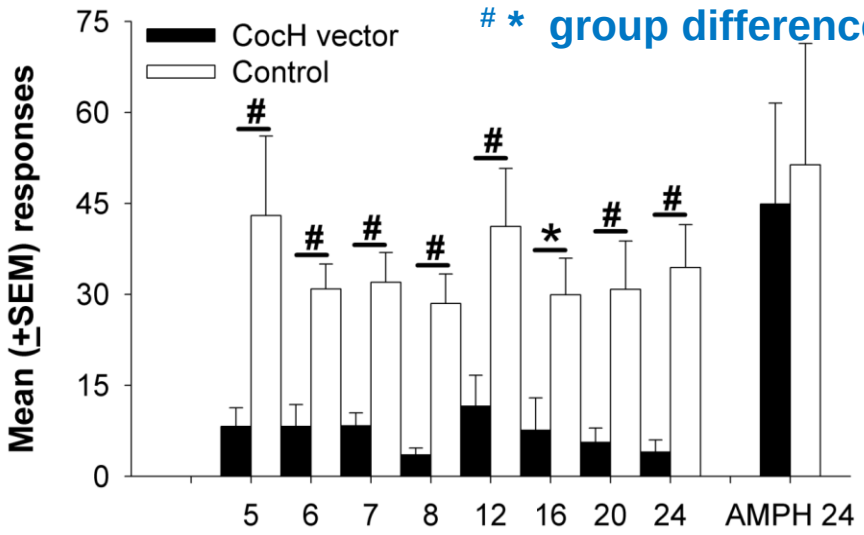


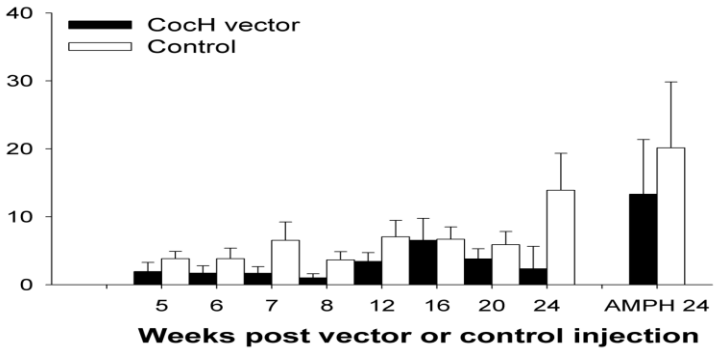
Anker et al., Biol. Psychiatry, 2011

Active lever reinstatement responding



* group differences

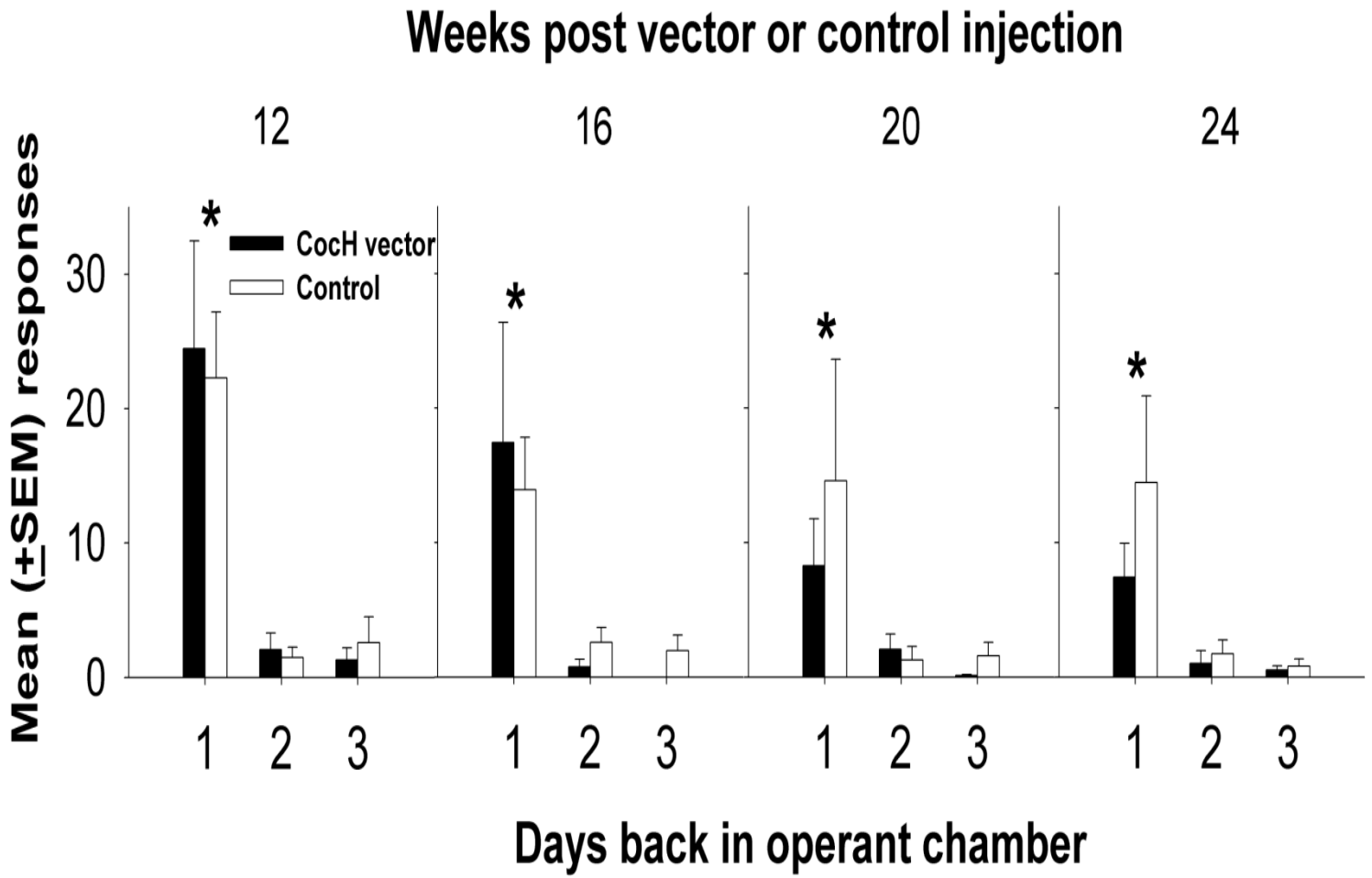
Inactive lever responding - control for general behavioral suppression



no group differences

Anker et al., Biol. Psychiatry, 2011

Active lever responding first 3 days after return to operant chamber for monthly reinstatement testing

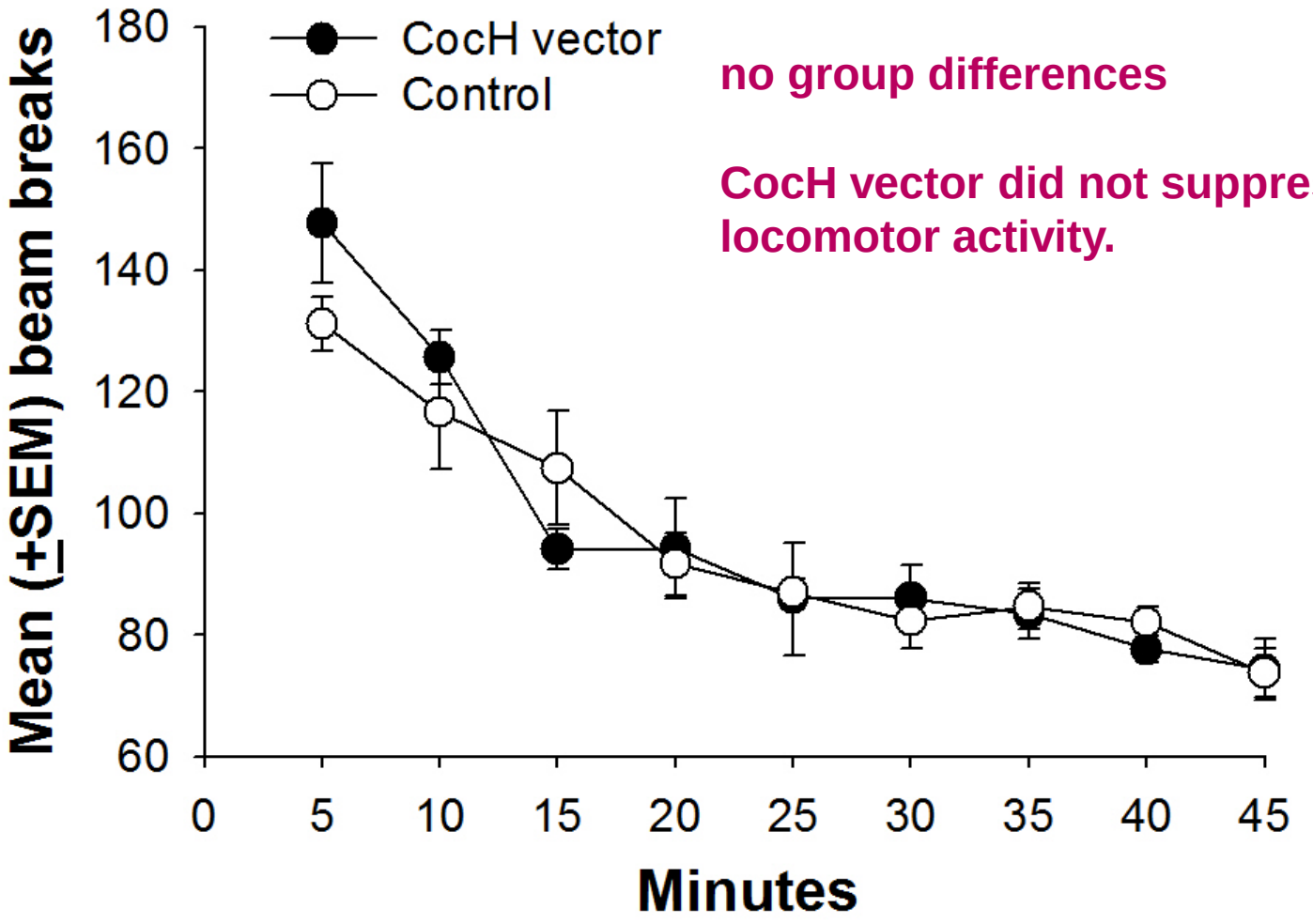


* Day 1 > Days 2 and 3

no group differences

Anker et al., Biol. Psychiatry, 2011

Spontaneous locomotor behavior during 3 45 min sessions - - CocH vector vs control (no cocaine administered)



no group differences

CocH vector did not suppress locomotor activity.

Anker et al., Biol. Psychiatry, 2011

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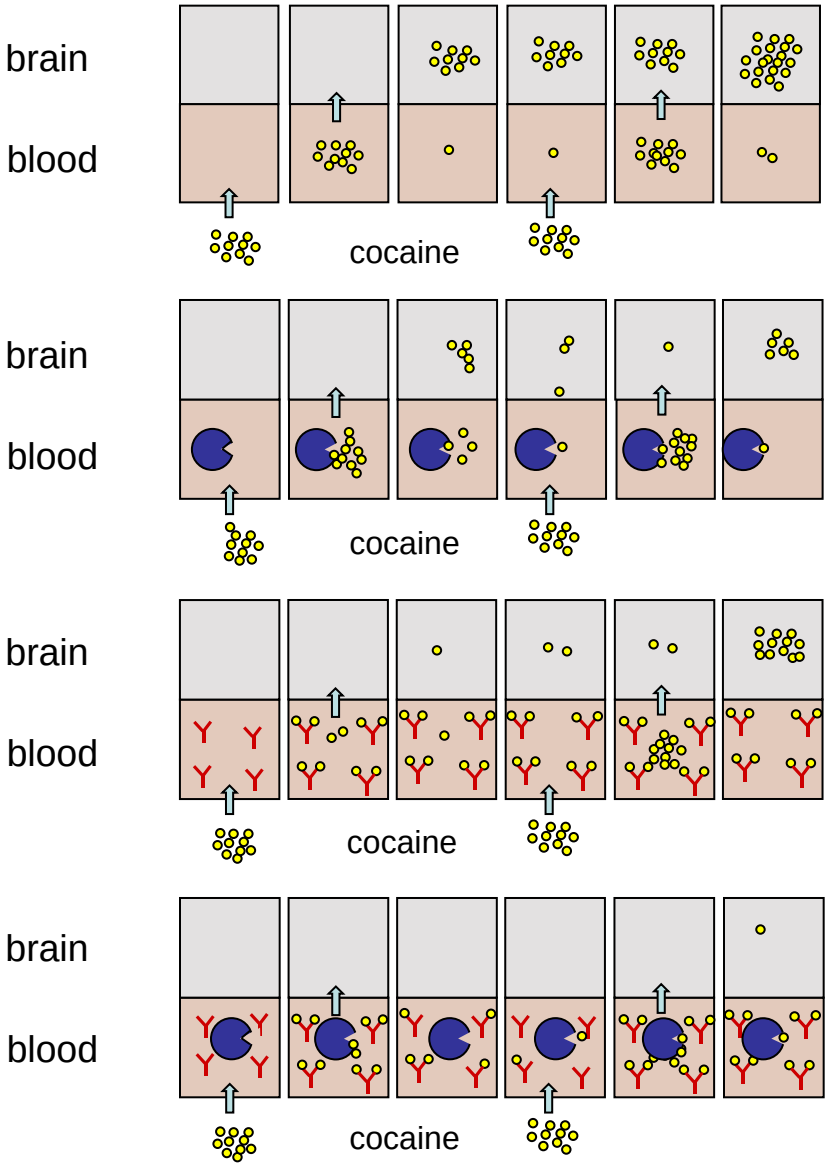
Enhanced interception with Enzyme & Vaccine



unprotected subject

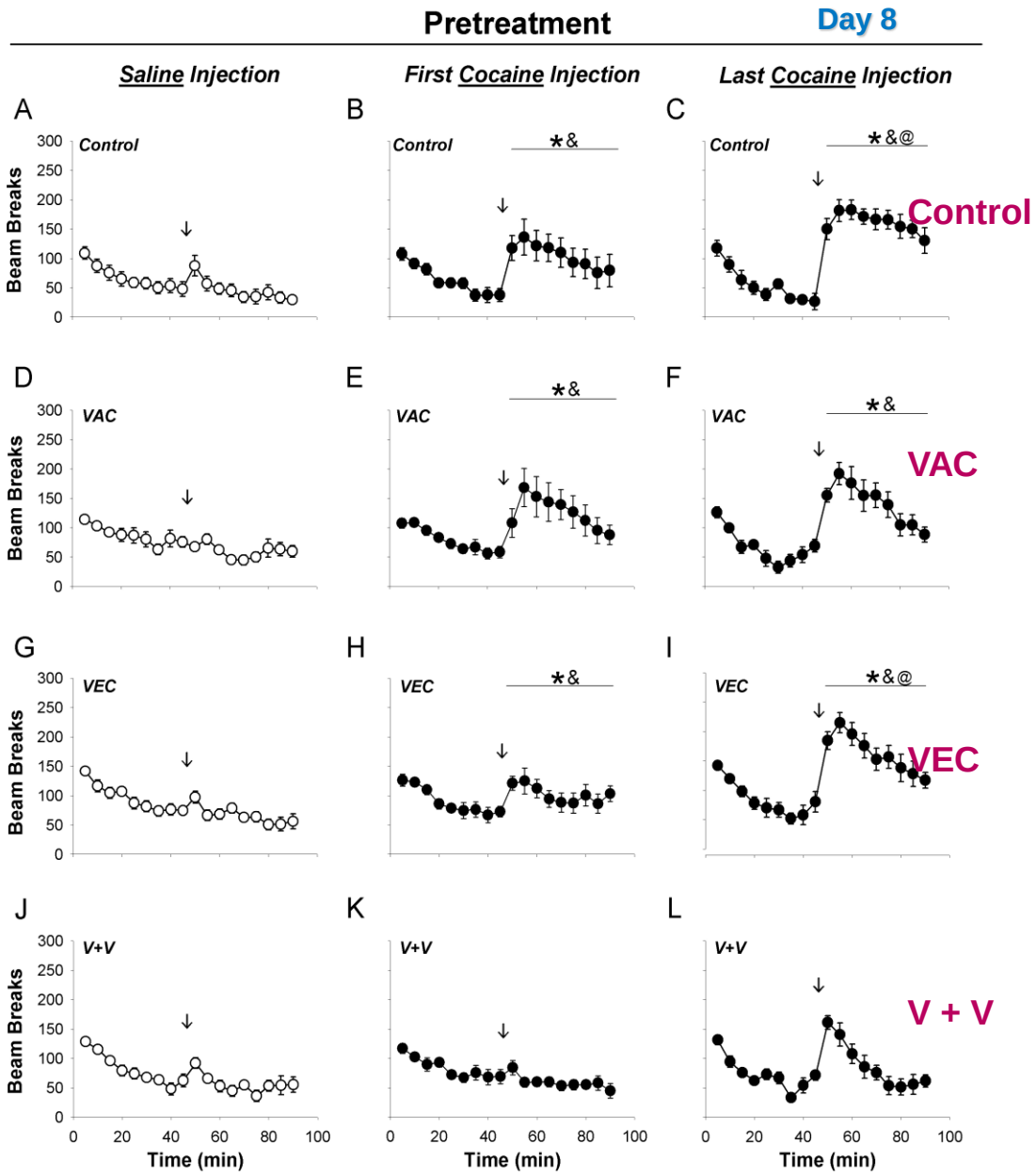
enzyme-treated

antibody-treated

enzyme plus antibody

Locomotor activity apparatus

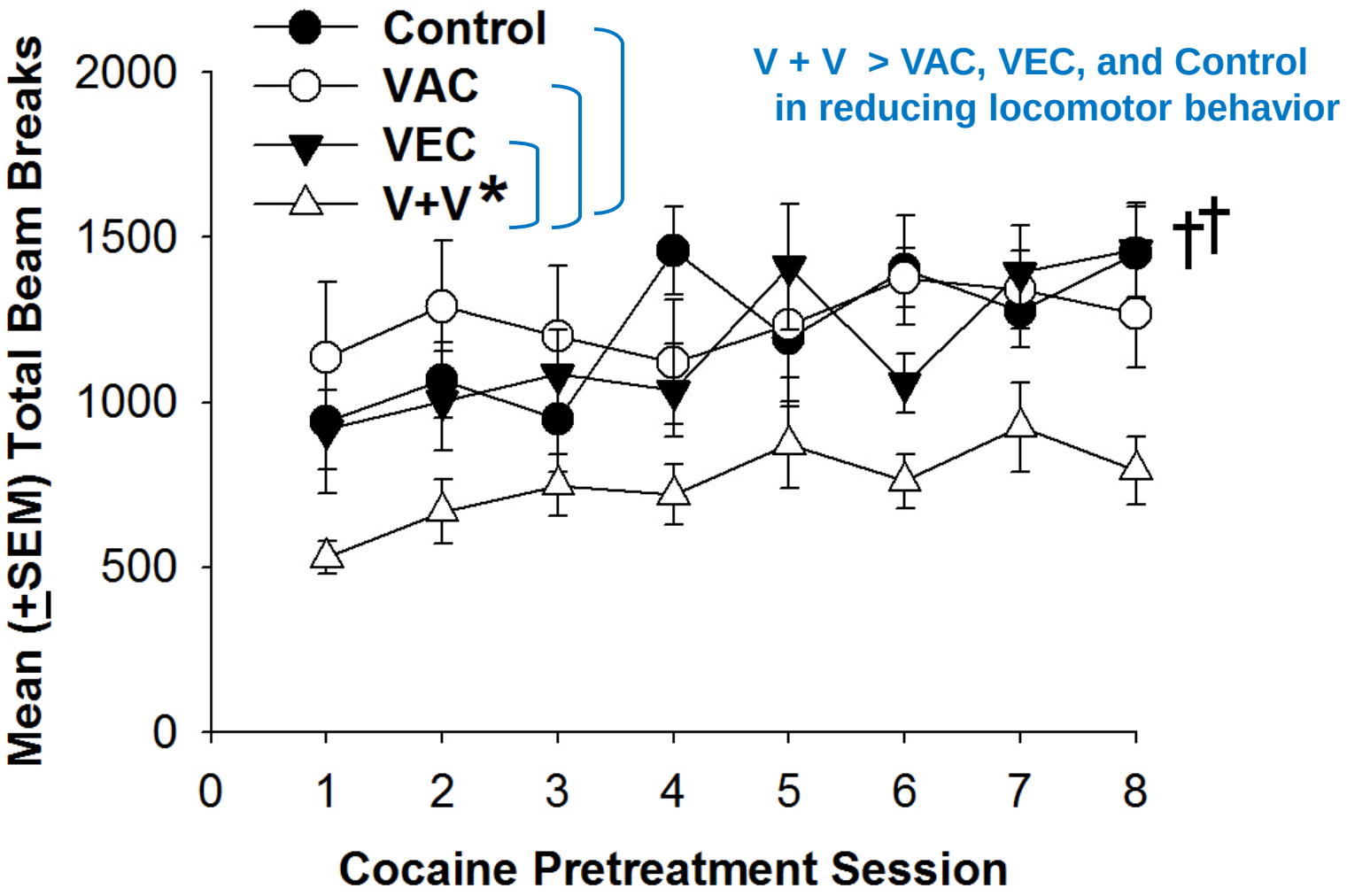
Each session = Saline - locomotor chamber (45 min) then cocaine (10 mg/kg) - locomotor chamber (45 min)



Locomotor activity		Sensitization
Coc > Sal	> V+V	Day 1 vs 8
Yes	Yes	Yes
Yes	Yes	blocked
Yes	Yes	Yes
blocked		blocked

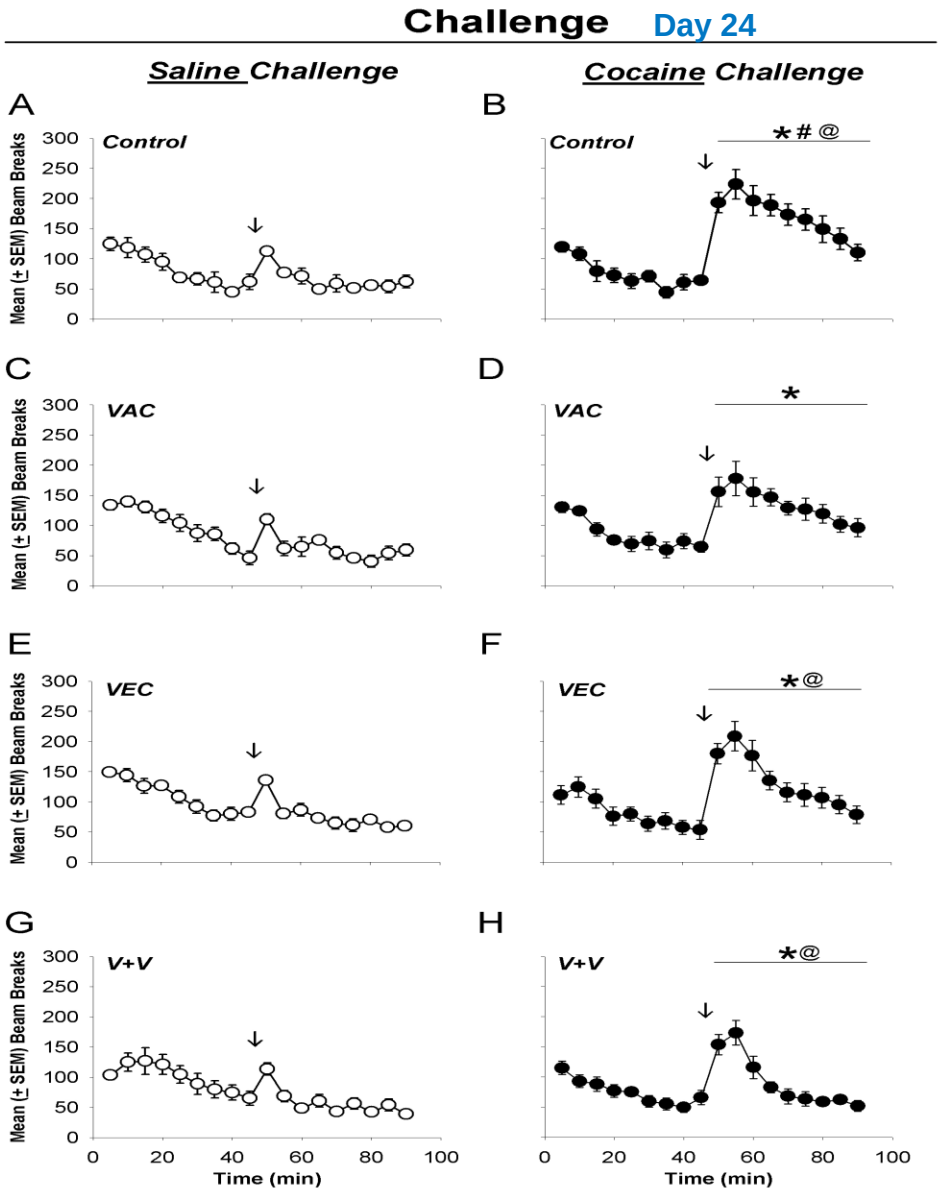
Carroll et al., 2012

Mean beam breaks over 45 min following cocaine injections across the 8 days of cocaine treatment



Carroll et al., 2012

Challenge = saline or cocaine injected 15 days after the 8 treatment days

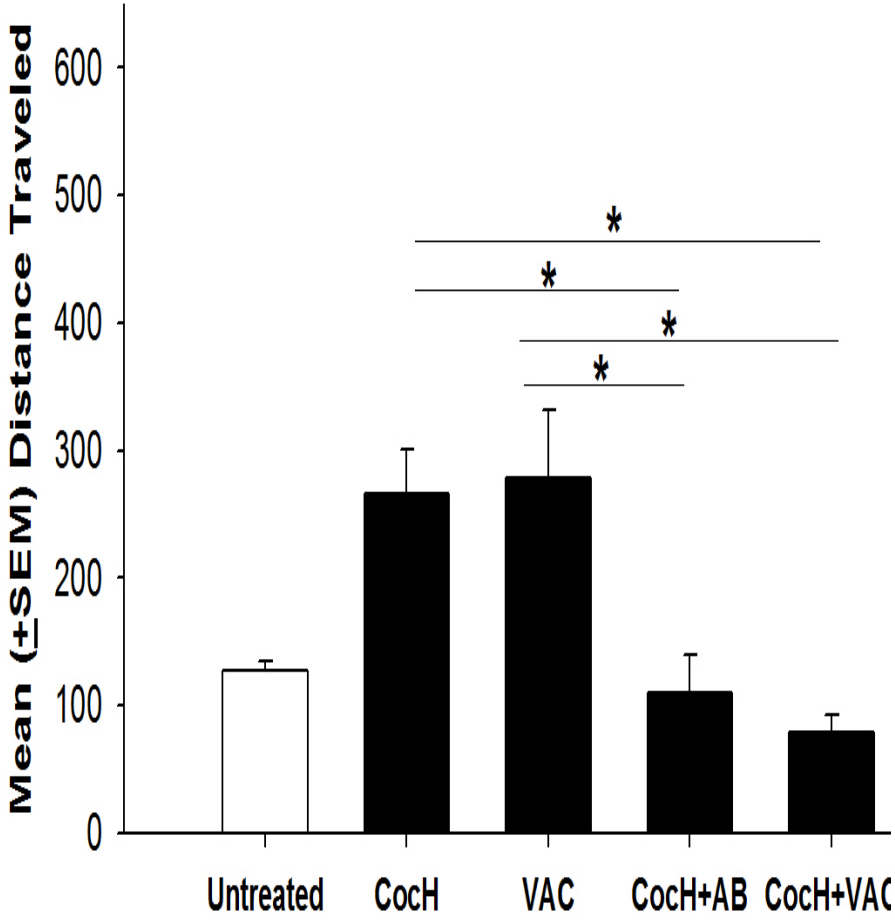


	Locomotor activity Coc > Sal	Locomotor activity < Control	Sensitization Day 1 vs 23
Control	Yes		Yes
VAC	Yes	Yes	blocked
VEC	Yes	Yes	Yes
V + V	Yes	blocked	Yes

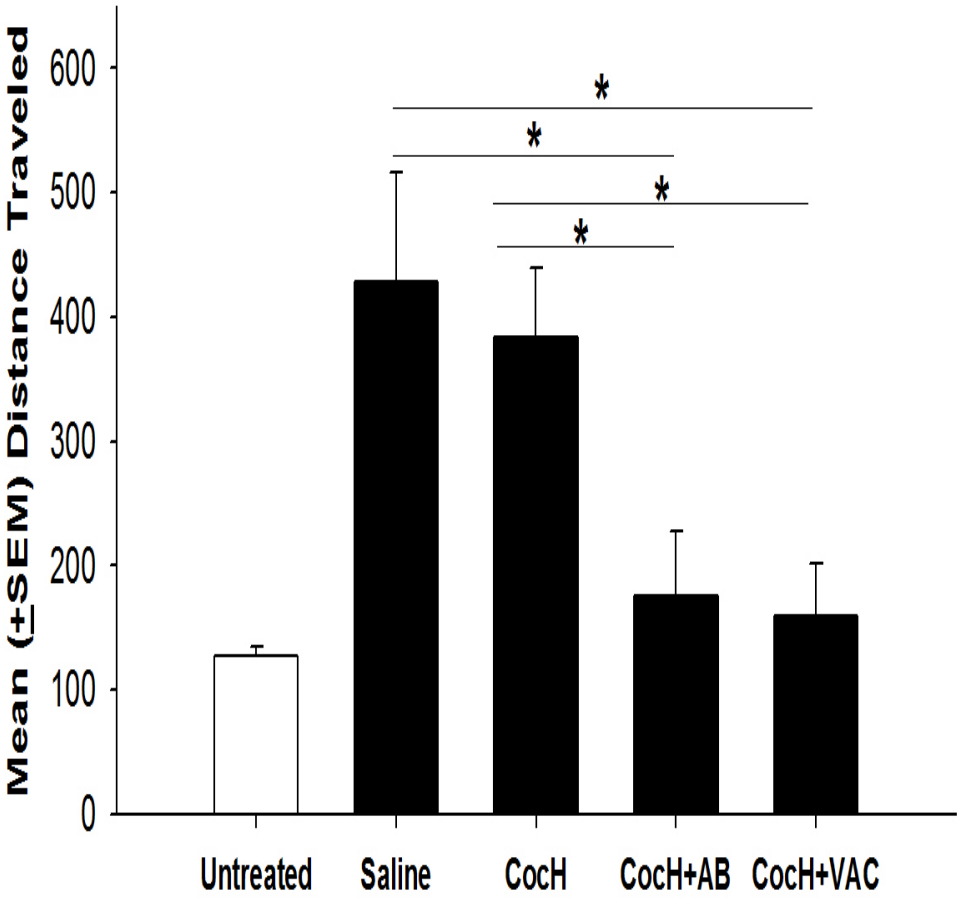
Carroll et al., 2012

High dose cocaine in mice and VEC + VAC combinations
Effect on locomotor behavior

100 mg/kg cocaine



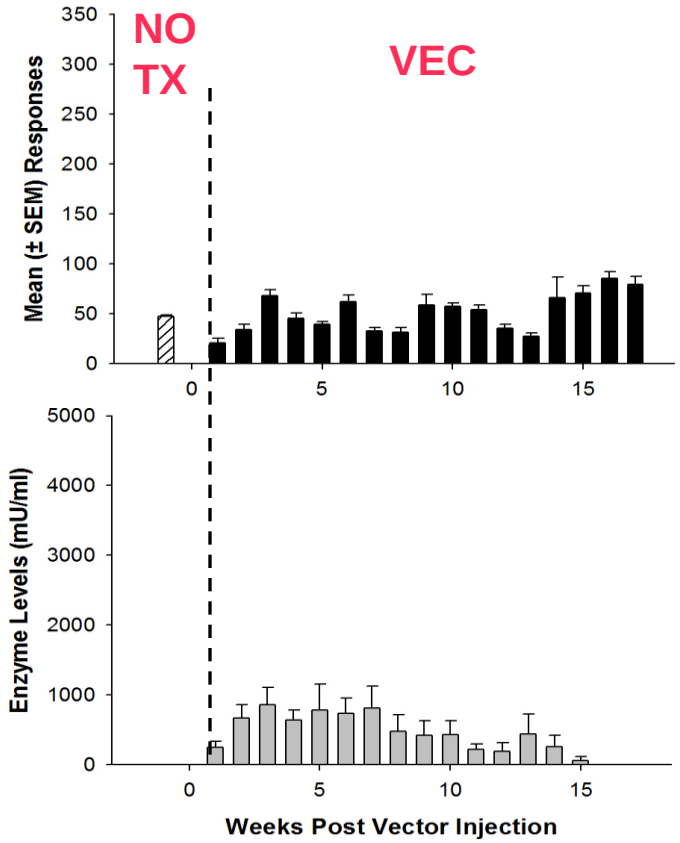
120 mg/kg, divided (60) 10 min apart



CocH + VAC (AB) > VAC, CocH, SAL and Control in reducing locomotor behavior

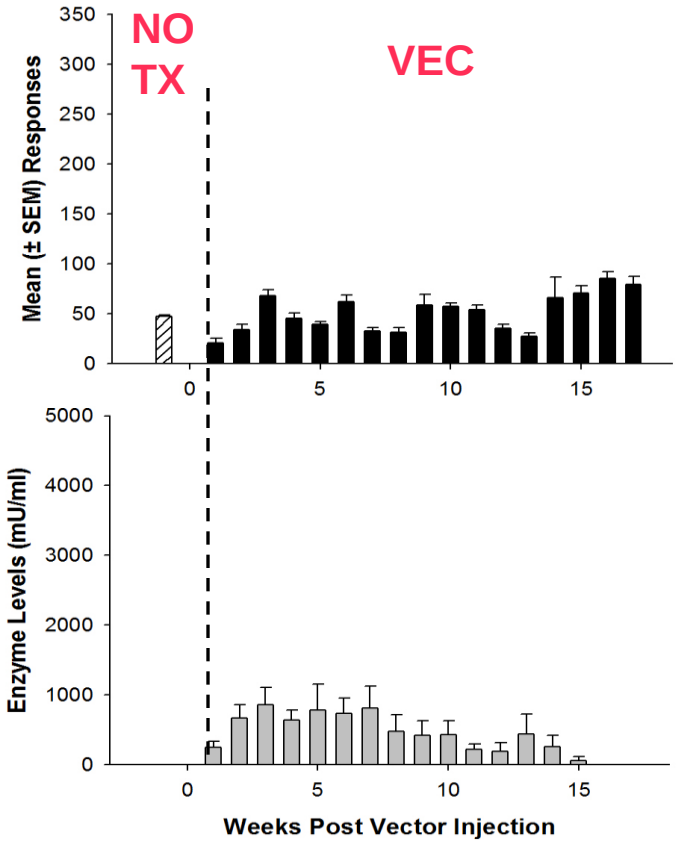
Carroll et al., 2012

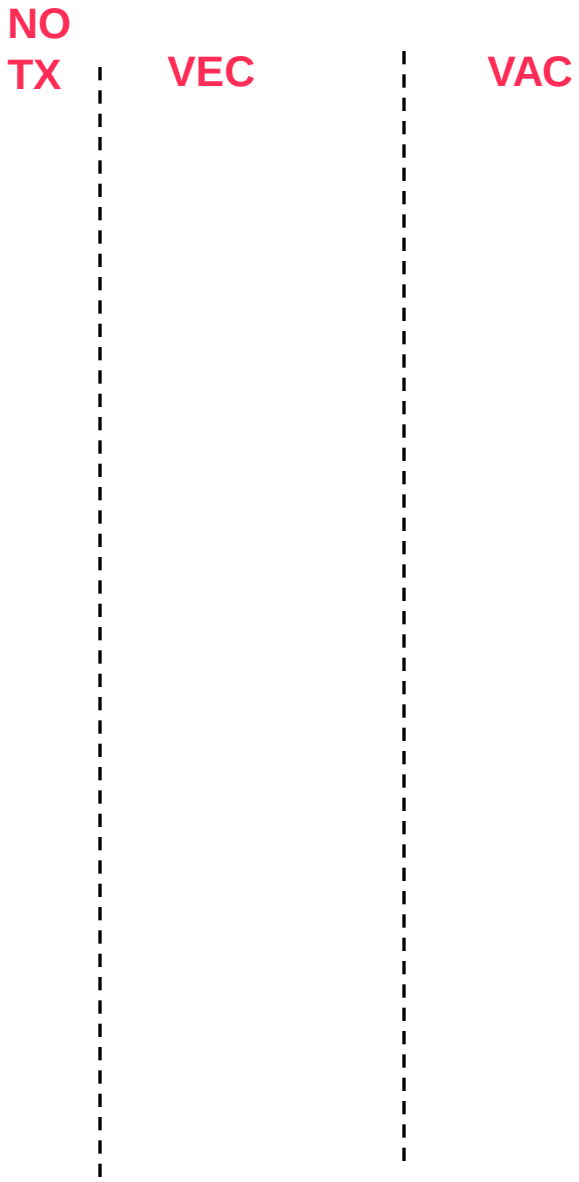
VEC + VAC effects on cocaine (0.4 mg/kg) self-administration during 2-hr sessions



Zlebnik et al., 2012

VEC + VAC effects on cocaine (0.4 mg/kg) self-administration during 2-hr sessions





Zlebnik et al., 2012

Summary

Cocaine abuse treatment model	Treatment effect
Acute (repeated pre-session CocH)	
2-hr self-administration PR schedule	reduction
6-hr escalation FR 1	increase
reinstatement	reduction
Chronic (CocH vector - 1 injection)	
reinstatement	6-month reduction
2-hr self-administration FR 1	increase
VAC + CocH vector (V + V)	Reduction up to 1 month
locomotor activity	V + V > VAC = VEC > Control
locomotor sensitization	V + V > VAC = VEC > Control
2-hr self-administration FR 1	VAC improved VEC treatment

Advantages - Disadvantages of CocH-based Treatments

CocH enzyme

Advantages:

- Rescue for OD in ER
- Reduces motivation to take cocaine
- Blocks relapse

Disadvantages:

- Increases long-access self-administration 2-fold
- Blocks relapse to cocaine but not other drugs

Vector-delivered CocH enzyme

Advantages:

- Blocks relapse 6 months or more
- Reduces cocaine sensitization which may be related to cocaine self-administration
- Adds to effects of VAC on sensitization and self-administration during short access FR 1

Disadvantage:

- Increases short-access self-administration

Acknowledgements

Faculty collaborators:

Thomas R. Kosten	Baylor College of Medicine

Postdoctoral associates:

Liyi Geng	Mayo Clinic
Justin Anker	University of Minnesota

Undergraduate students:

Alex Claxton	University of Minnesota
Seth Johnson	"
Amy Saykao	"

Enzyme development and biochemistry

Liyi Geng, Molecular Pharmacology, Mayo Clinic, Rochester MN

hdAD-Vector development

Robin Parks, Ottawa Hospital Research Inst., Ottawa CN

Cocaine vaccine and antibody

Frank Orson, VA Med Center, Houston TX

Tom Kosten, Baylor College of Medicine, Houston TX

Berma Kinsey, Baylor College of Medicine, Houston TX

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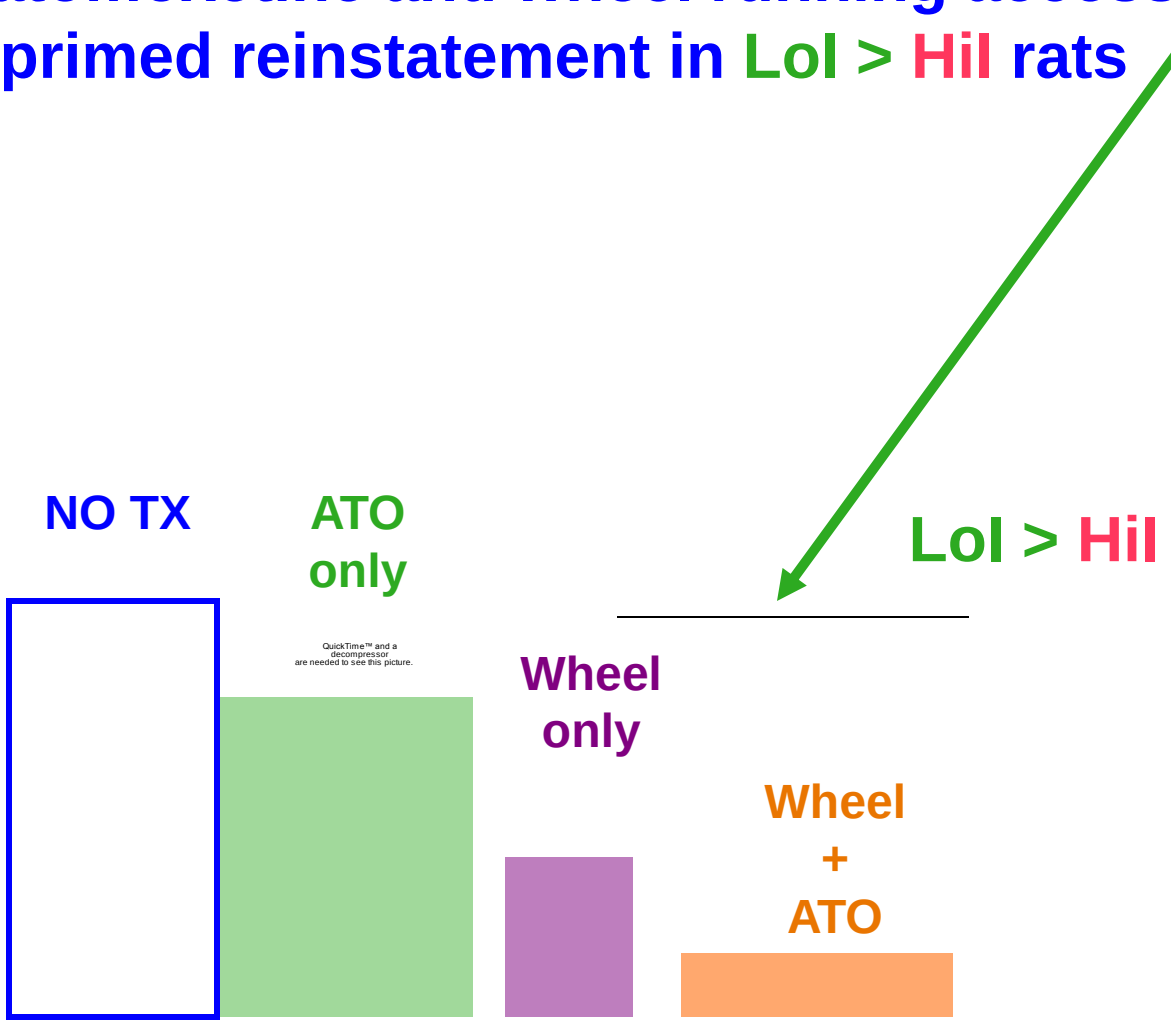
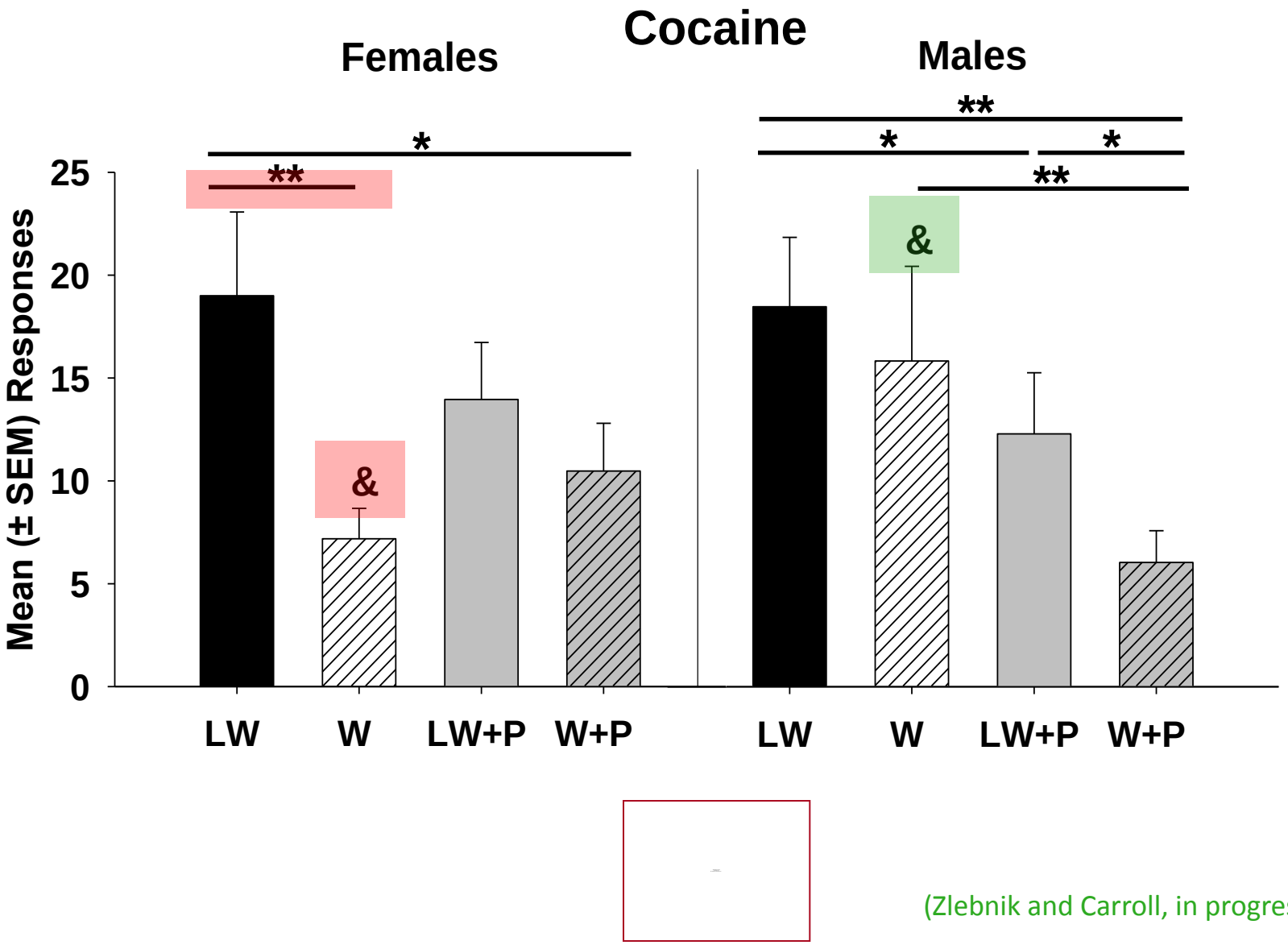
Additive effect of atomoxetine and wheel running access on cocaine-primed reinstatement in Lol > Hil rats



(Zlebnik and Carroll, in progress)

Additive effect of wheel access + progesterone

Males > females



(Zlebnik and Carroll, in progress)

Next Frontier…..

Deep Brain Stimulation (DBS) for Cocaine Addiction

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Wallin Foundation Grant, 2011 - 2012

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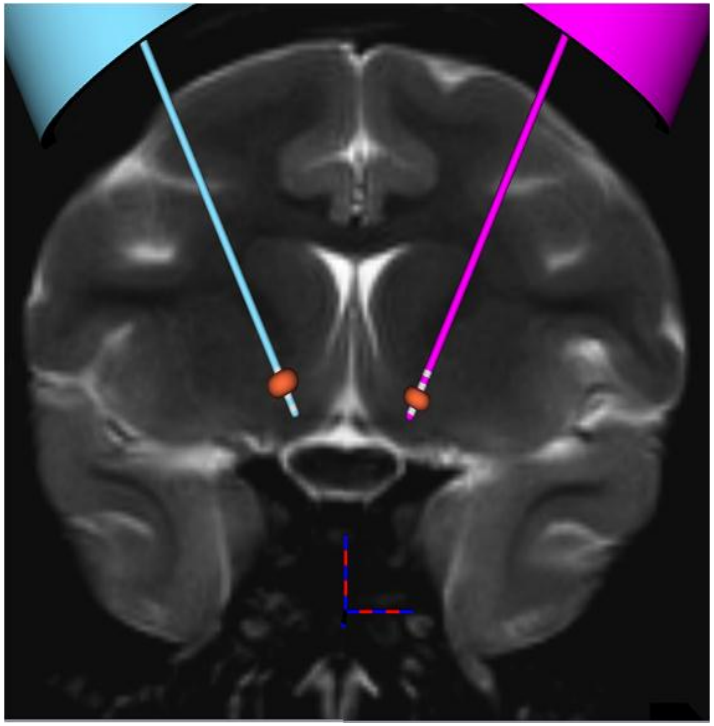
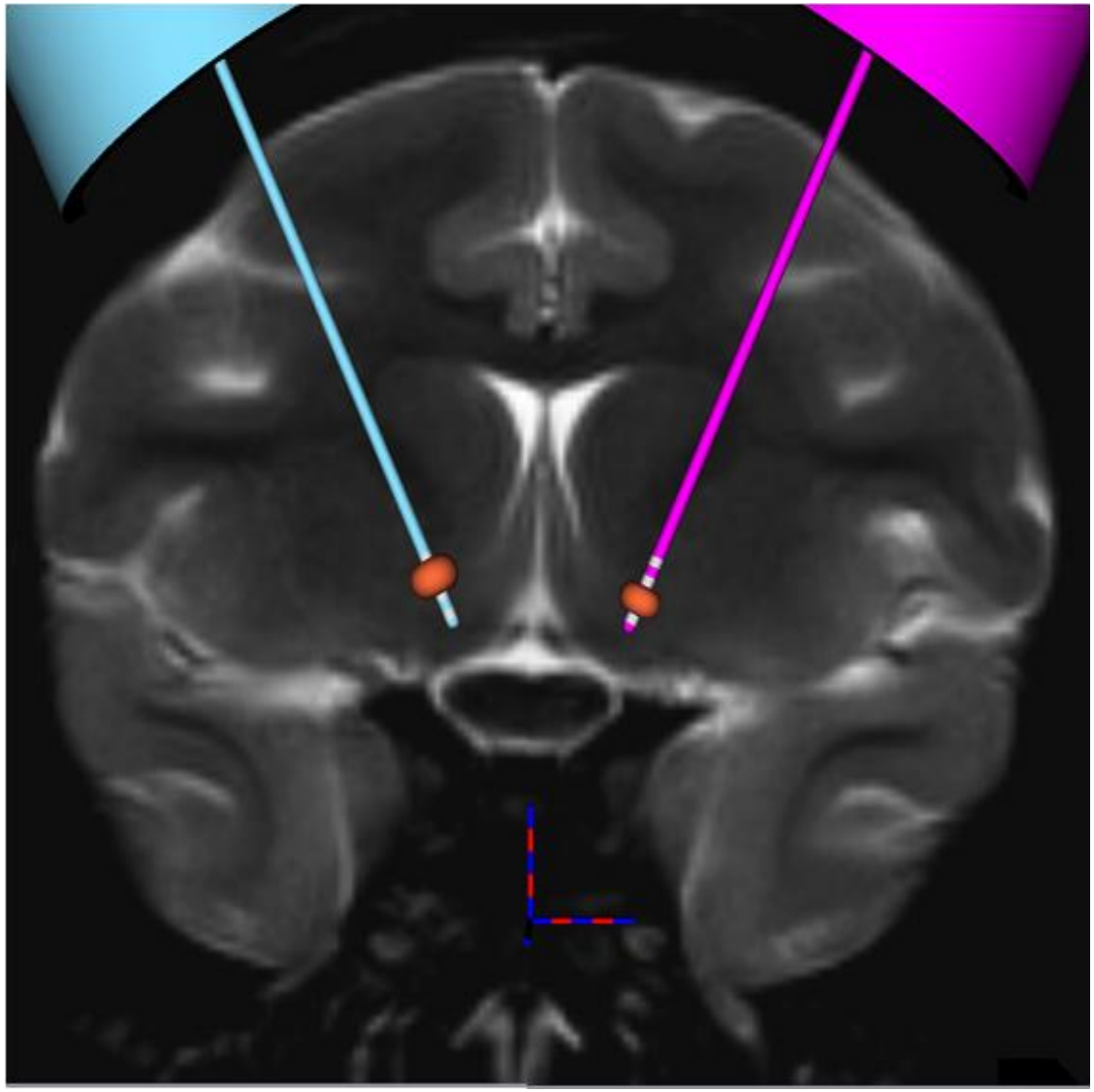
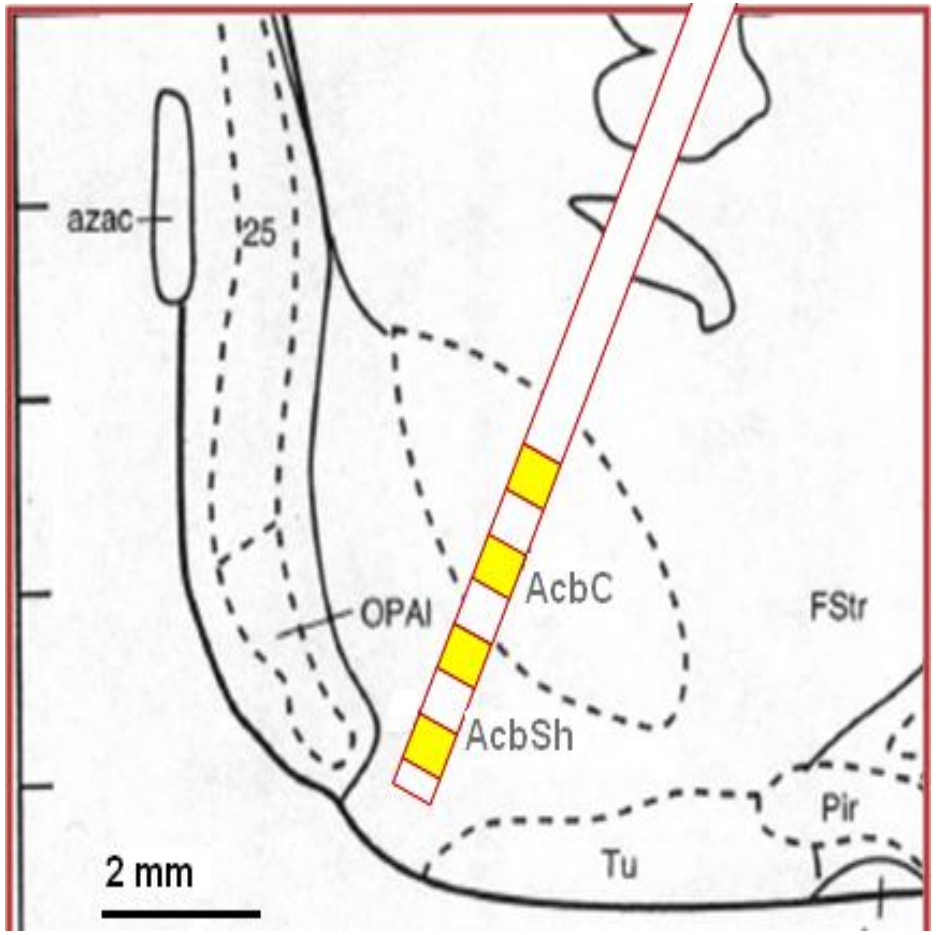




Left and right DBS leads implanted in the region of the NA superimposed on MRI. VTAs are shown in orange



A schematic of the scaled DBS lead with 4 contacts

Results of DBS with drug-rewarded behavior in rats

Target	Drug reinforcer - Task	Effect	Authors
NAcc shell vs dorsal striatum	Cocaine Reinstatement	↓ Shell: reinstatement	Vassoler et al. 2008
NAcc shell vs core	Cocaine Reinstatement	↓ Shell: reinstatement Core: no effect	Vassoler et al. 2008
NAcc shell vs core	Alcohol consumption	↓ Shell and core: Consumption	Knapp et al. 2009
NAcc core- unilateral	Morphine (CPP)	↓ 75% reduction in morphine preference	Liu et al. 2008
Lateral habenula	Cocaine reinstatement	↓ Reinstatement	Friedman et al. 2010
Med forebrain bundle Prefrontal cortex	Cocaine, sucrose Progressive ratio	↓ Reinstatement	Levy et al. 2007
Subthalamic nucleii	Cocaine progressive ratio	↓ Break point for cocaine (motivation for reward) ↑ Break point food	Rouaud et al. 2010 (Baunez)

Results of DBS with drug-rewarded behavior in humans (case studies)

Target	Addictive Behavior	Effect	Authors
Subthalamic Nucleii	Abuse of dopamine replacement therapy	↓	Witjas et al. 2005
Subthalamic Nucleii	Abuse of DA drug Gambling Hypersexuality	↓	Ardouin et al. 2006
STN for movement disorder	Smoking	↑ Cessation	Kuhn et al. 2009
STN for movement disorder	Smoking	↑ Cessation Weight loss	Mantione et al. 2010
NAcc	Heroin	↓ drug use, craving	Valencia Alfonso et al. 2012
NAcc	Heroin	↓ drug use	Zhou et al. 2011
NAcc	Alcohol	↑ Abstinence Quality of life ↓ Craving	Muller et al. 2009 *
		↓ Cue related Craving	Heinze et al. 2009