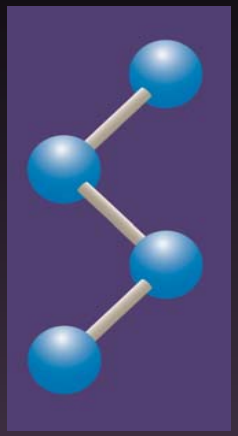

Friedbert Weiss

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Compulsive Drug-Seeking versus Hedonic Behavior Motivated by Natural Reward: Neurobehavioral Mechanisms and Novel Pharmacological Treatment Targets

Drug/Alcohol Addiction…

- ... is usually *chronic, lasting years,* with periods of exacerbation and partial or full remission (DSM-IV *American Psychiatric Association*)
- ... is a *chronic, relapsing disease that results from the prolonged effects of drugs on the brain* (Leshner, *Science* 286, 1997)
- ... is a *chronic relapsing illness*, characterized by *compulsive drug-seeking and use* (O'Brien & McLellan, *Lancet* 347, 1996**)**
- *... compulsion to use drugs does not depend on the presence of the drug*; it can occur long after drug-taking has stopped and long after any evidence of physical dependence or withdrawal has disappeared (O'Brien et al., *J of Psychopharmacology, 1988)*

Journal of Psychopharmacology 12(1) (1998) 15–22

SAGE Publications, London, Thousand Oaks, CA and New Delhi
0269-8811 [199803] 12:1; 15–22; 003051

Conditioning factors in drug abuse: can they explain compulsion?

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There is a good deal of clinical evidence suggesting that compulsion to resume drug taking is an important part of the addiction syndrome. The symptoms comprising motivation to resume drug use, namely craving and compulsion, have been studied experimentally in human subjects. While much work remains to be done, there is evidence showing that these symptoms are influenced by learning. The research has been guided by animal studies demonstrating that drug effects can be conditioned. Much attention has been directed toward demonstrating the existence of drug conditioning in human addicts and exploring the neurological structures that may underlie such learned responses. We do not yet know the relative importance of learning in the overall phenomenon of relapse, and treatments based on conditioning principles are still under investigation.

Key words: addiction; conditioning; craving; dependence

Introduction

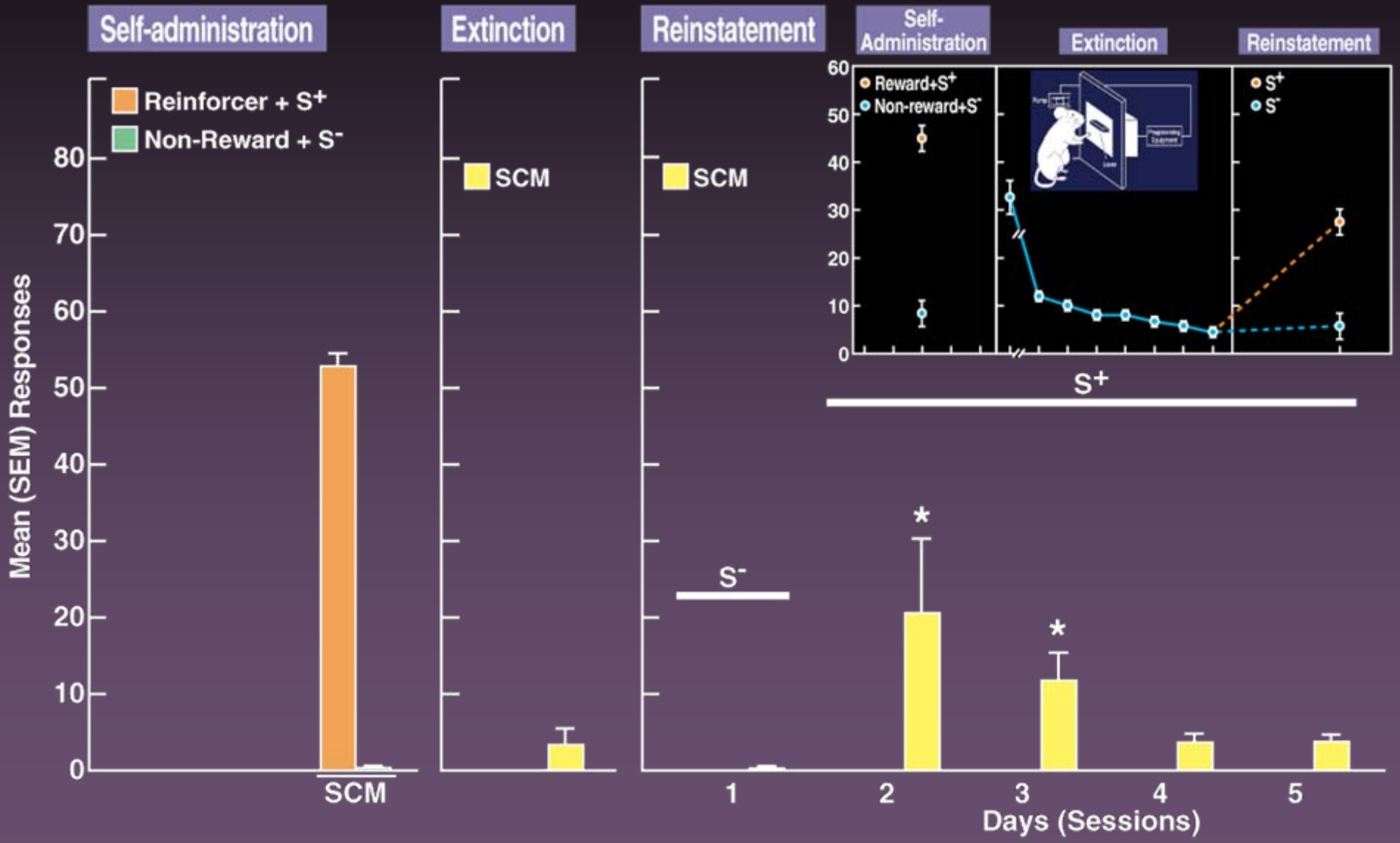
Compulsion is an integral part of the phenomenon of addiction. It is defined in the *American Heritage Dictionary* as 'an irresistible impulse to act regardless of the rationality of the motivation'. Compulsion to use drugs in a person diagnosed with a substance-use disorder does not depend on the presence of the drug; it can occur long after drug taking has stopped and long after any evidence of physical dependence or withdrawal syndrome has disappeared.

Consider this quote from a perplexed patient in treatment for the fourth time who was confirmed 5 weeks free of cocaine and was shown a videotape of simulated cocaine use: 'Doc, I don't understand what's going on. I really meant it when I told my therapy group yesterday that I never wanted to touch cocaine again. Now after seeing that video, I want cocaine more than anything and I feel the urge to go out and get it. known to clinicians. The best analog would be a study in which drug-free, formerly dependent animals were tested on the amount of shock they were willing to endure in order to self-administer a drug choice. However, most studies of drug self-administration in animals do not incorporate such a punishment contingency.

It is important to make the distinction between compulsive behavior occurring in a state of withdrawal and compulsion that occurs long after the withdrawal syndrome has disappeared. The long-lasting compulsion appears to be triggered by environmental stimuli and may be one of the most important problems faced by a clinician trying to treat drug dependence. It is not so difficult to get individuals to stop using a drug; the problem is to keep them from re-starting. Responses elicited by drug-related events may be one of the important factors producing high rates of relapse following treatment.

Drug versus Conventional Reward-Seeking

Response-Reinstating Effects of Reward-Paired Contextual Stimuli: Ethanol vs. a Palatable Natural Reinforcer



Modified from: Weiss *et al.* (2001) *Neuropsychopharmacology*; Ciccocioppo *et al.* (2001) *ACER; Weiss, CRC Press (2010)*

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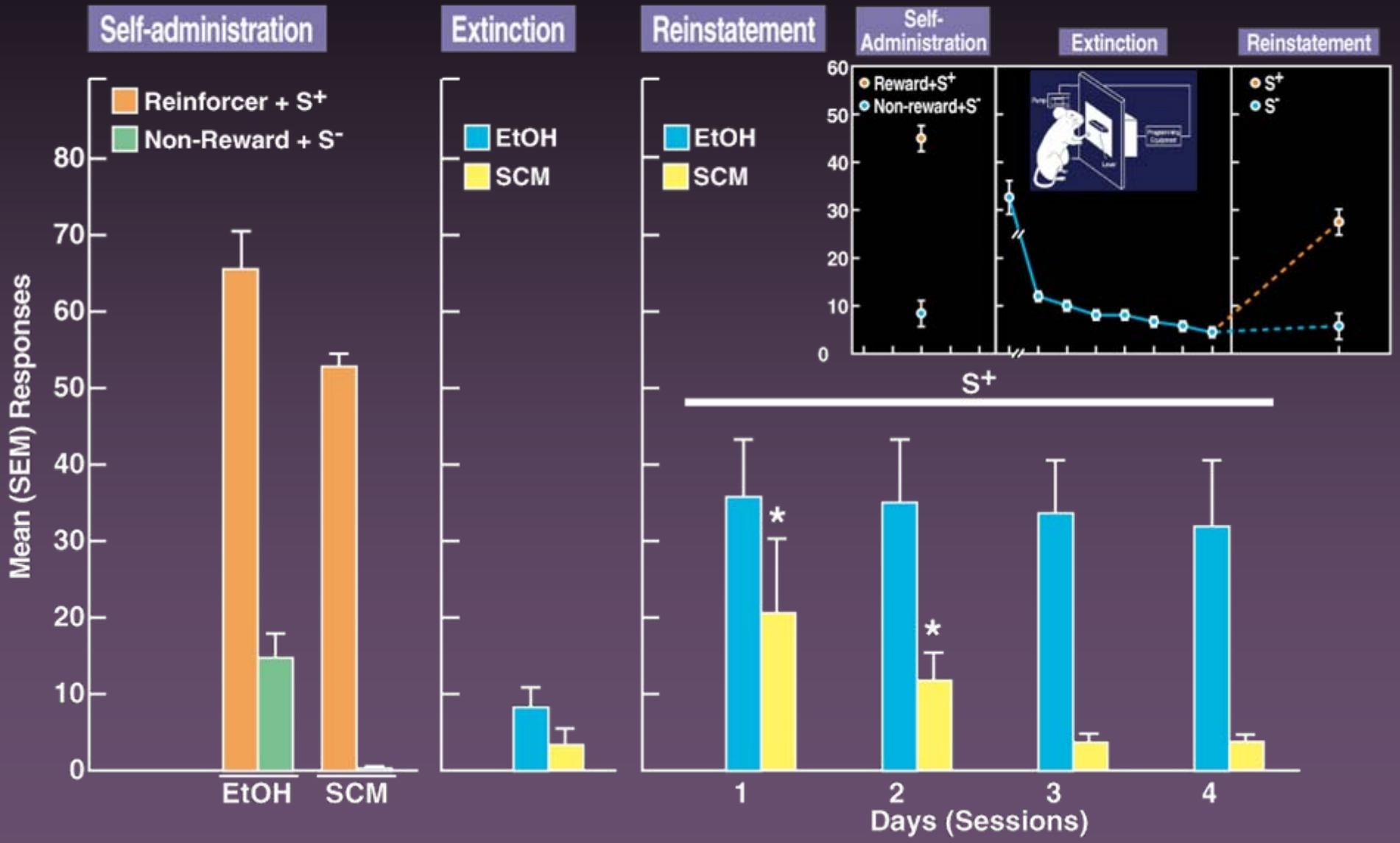

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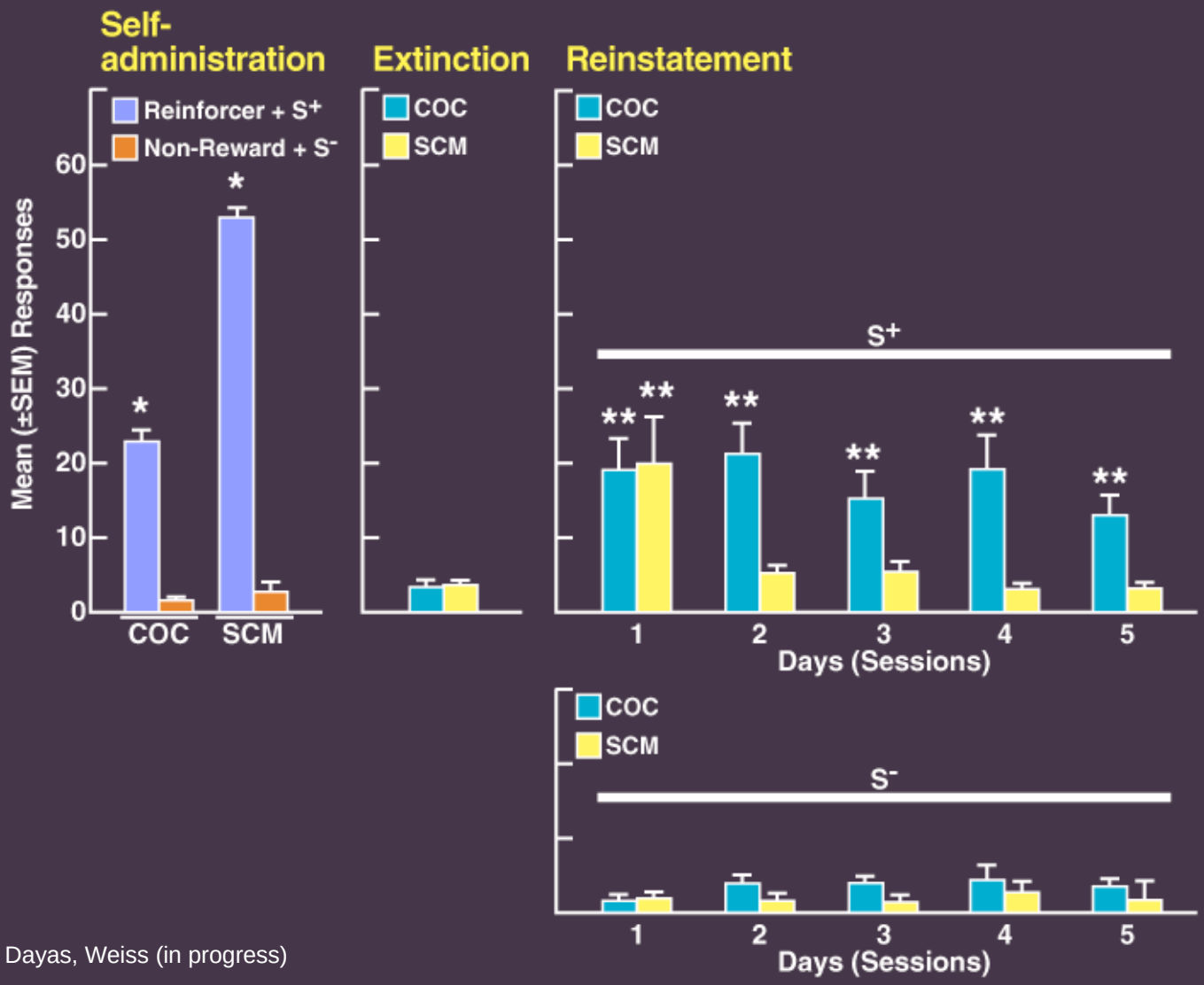
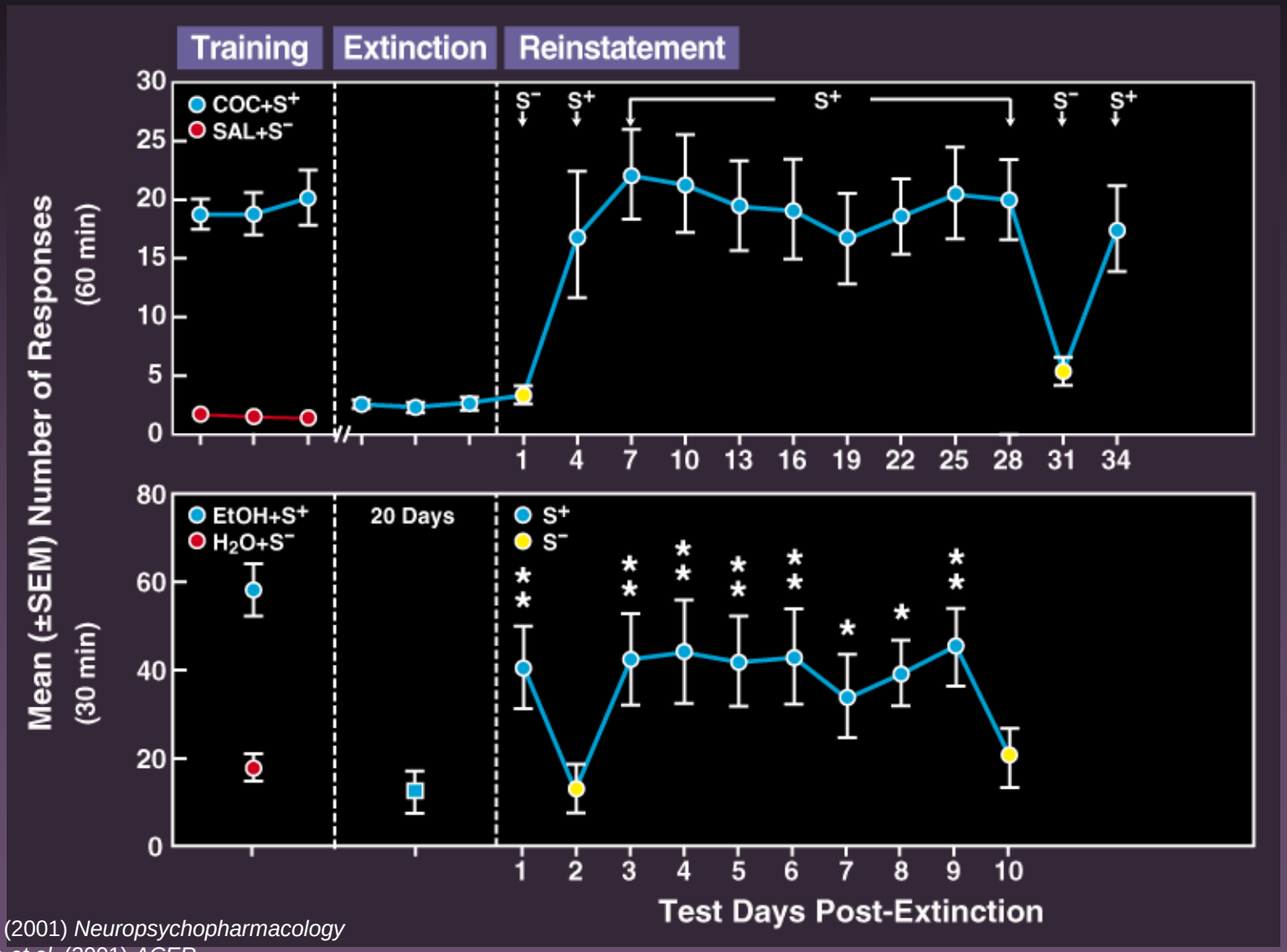
Differential Persistence of Reinstatement by Stimuli Conditioned to Cocaine vs. Palatable Natural Reward



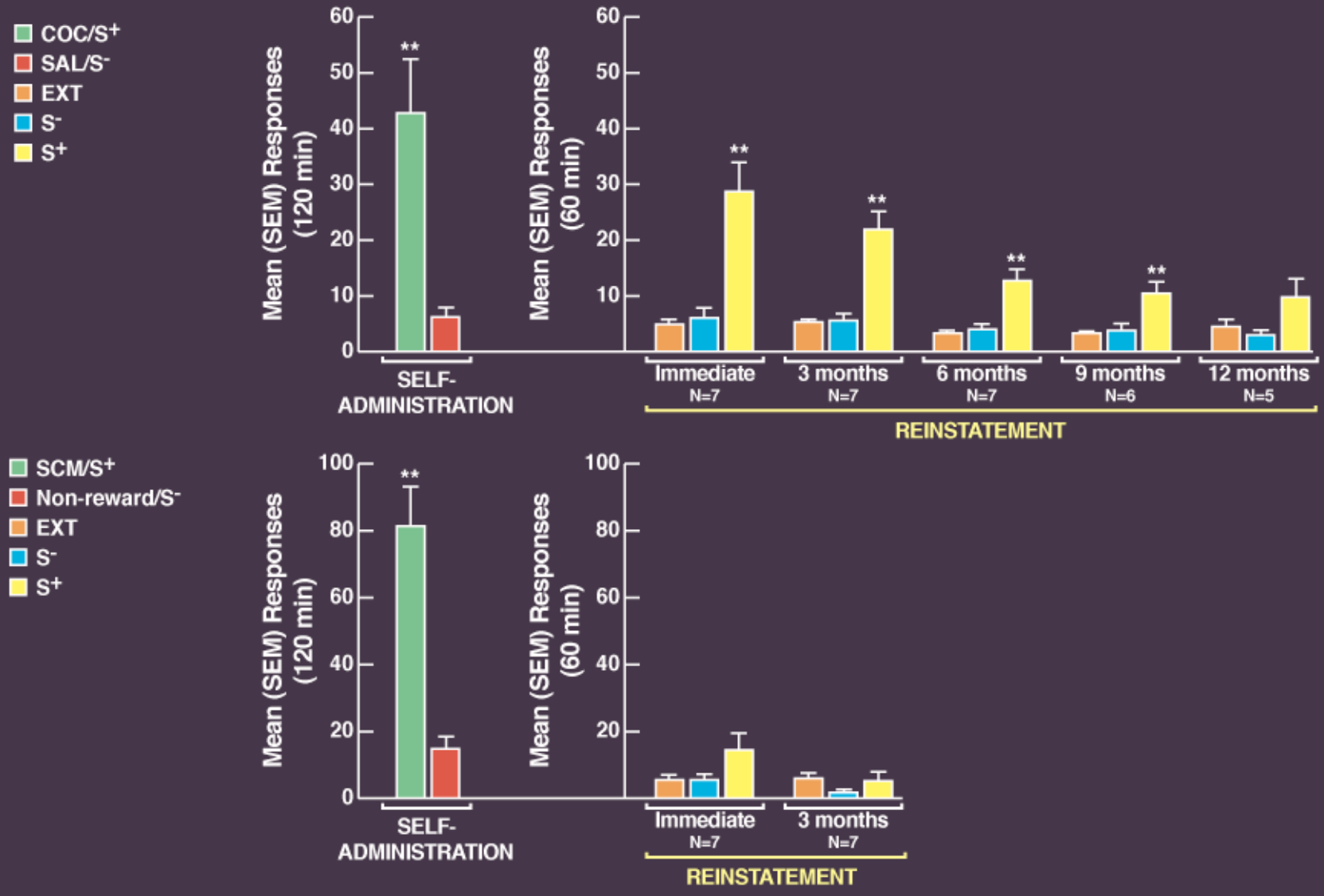
Martin-Fardon, Dayas, Weiss (in progress)

Reinstatement by Drug-Related Contextual Stimuli in Rats: Resistance to Extinction with Repeated Exposure



Weiss *et al.* (2001) *Neuropsychopharmacology*
Ciccocioppo *et al.* (2001) *ACER*

Drug-Seeking by Contextual Stimulus Paired with Cocaine in Rats with a Single Self-Administration Experience

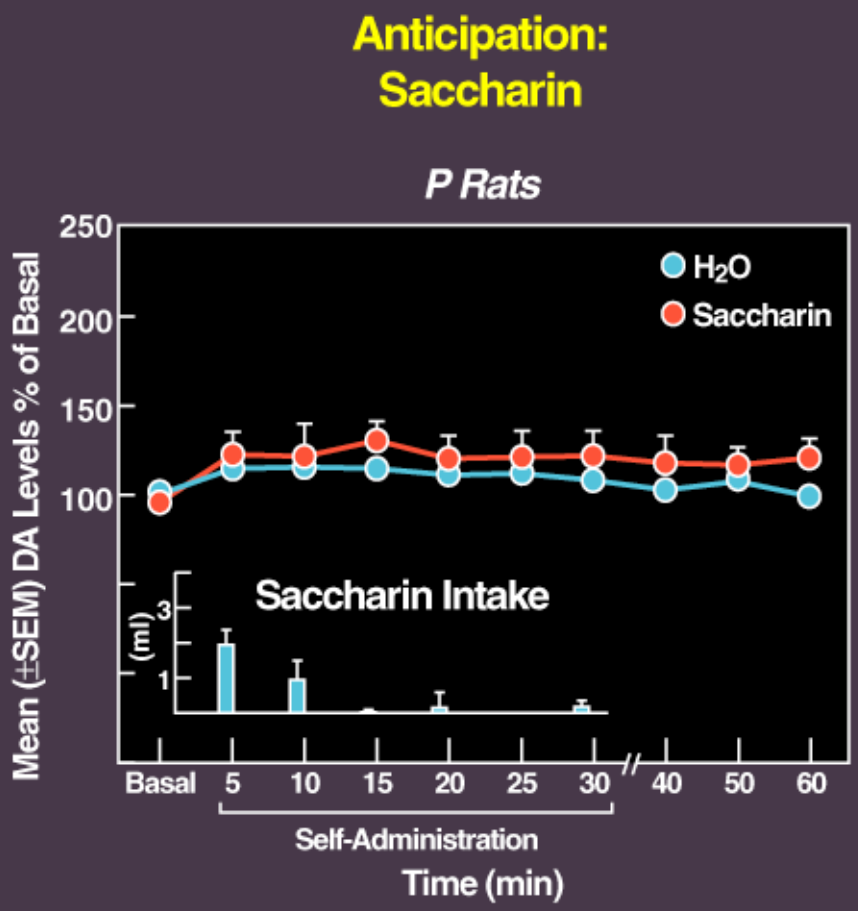


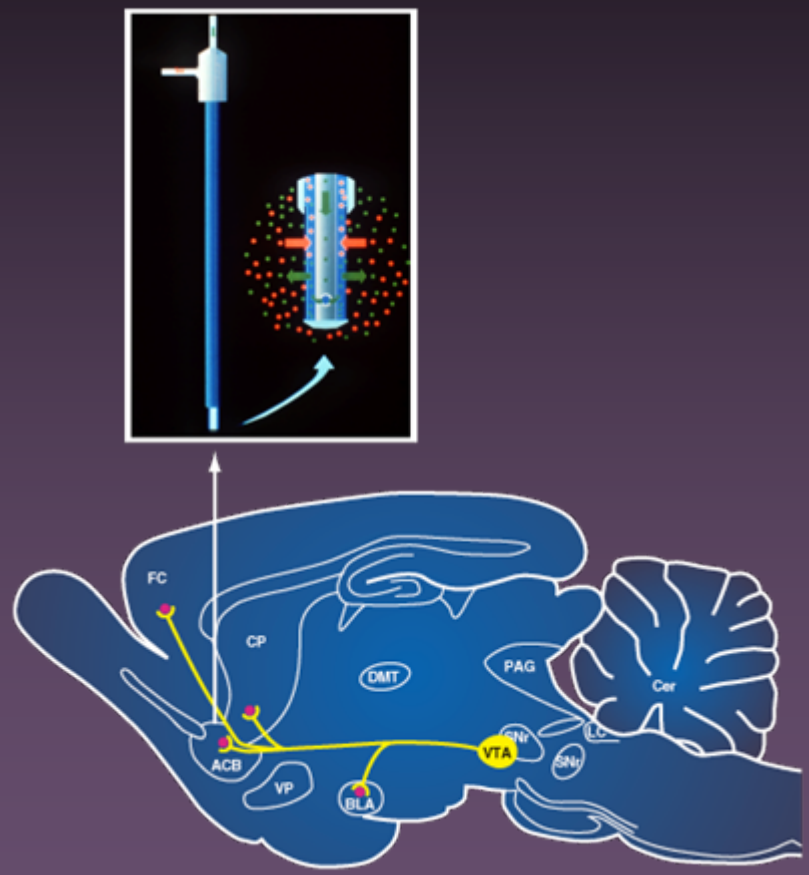
Ciccocioppo, Martin Fardon. Weiss (2004) *Nat Neurosci.*

Current Hypotheses of the Neural Control of Drug-Seeking vs. Normal Motivated Behavior

- Neural mechanisms that mediate the effects of drug cues are distinct from those controlling the conditioned effects of natural reward (or, even though within the same circuitry, may recruit different sets of neurons).
- Mechanisms controlling the effects of drug cues are not specific to addiction-related events, but "normal" circuits activated to a greater degree, thereby creating new motivational states, tilting processes that normally regulate responding for natural rewards towards drug-reward.
- Drug-induced neuroadaptation provides a switch whereby a circuit not normally involved in drug-seeking becomes responsive to drug cues.
- Self-Medication: Drug consumption during withdrawal introduces learning about a novel incentive dimension of the substance -- its capacity is to alleviate subjectively adverse states.
- "Metaplasticity" induced by chronic drug use prevents new learning or "unlearning" of maladaptive behavior.

Effects of EtOH Expectancy on Accumbal DA Release in Rats Self-Administering Saccharin





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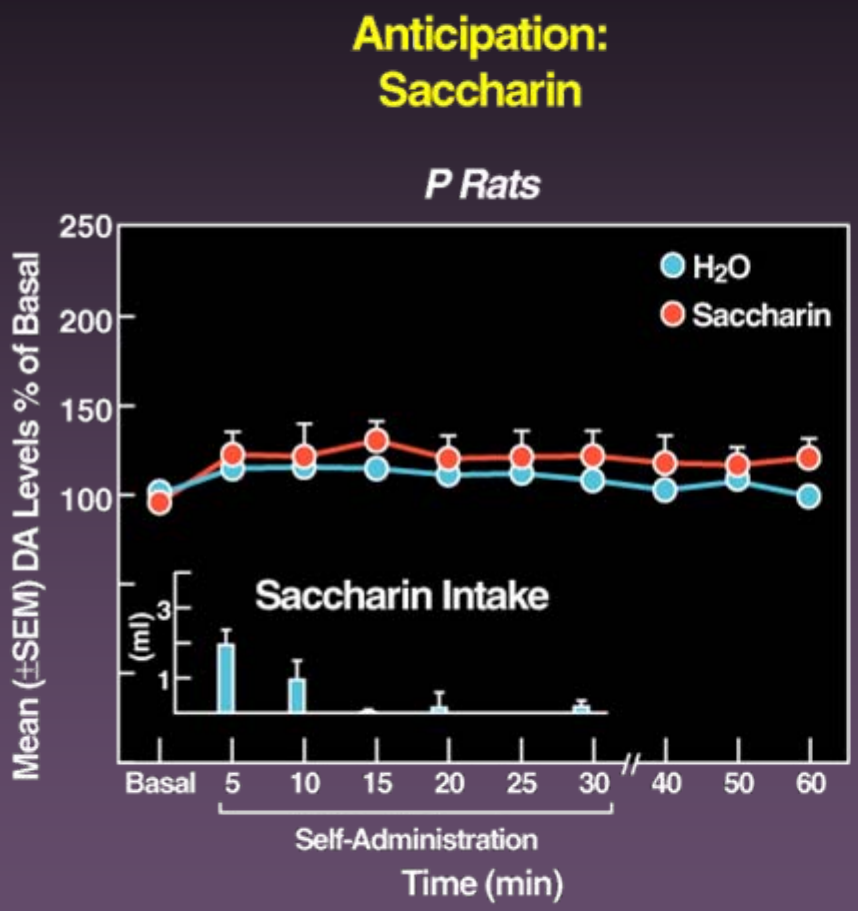

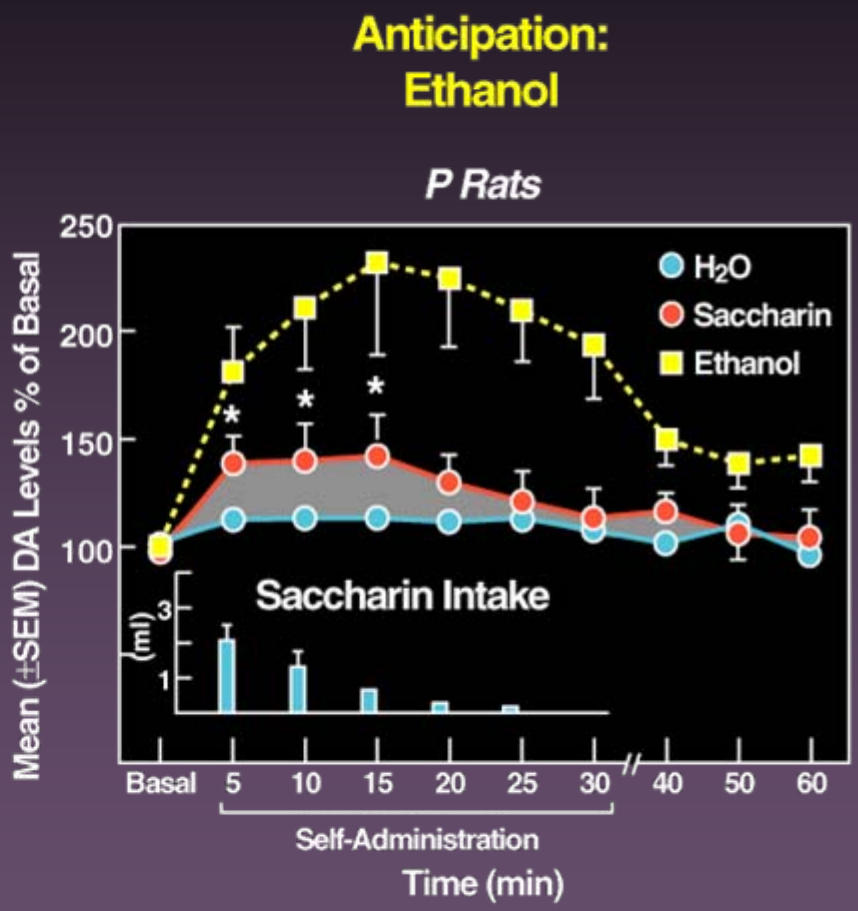

Weiss *et al.* (1993) *JPET*
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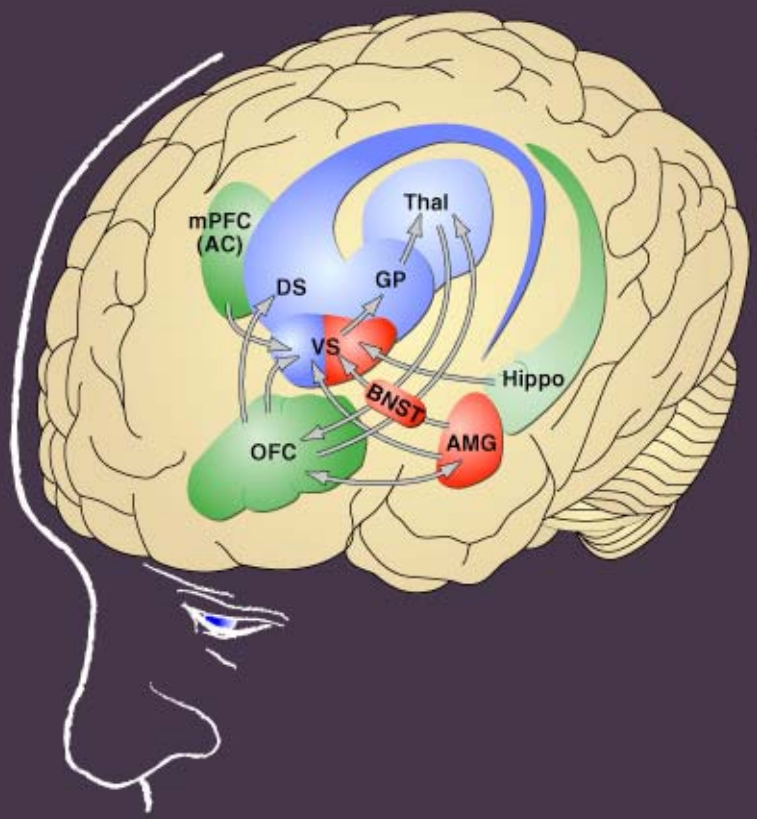
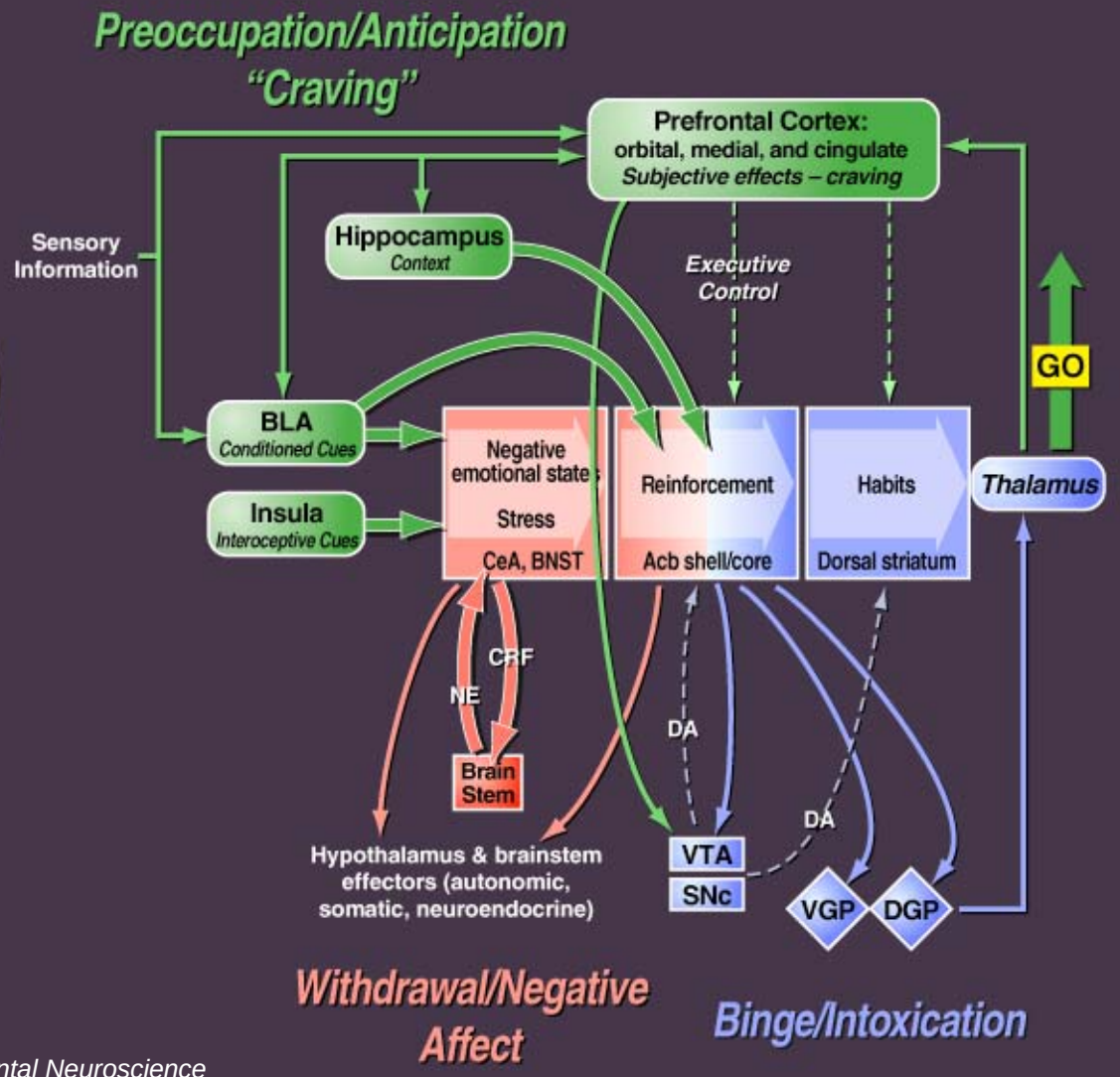
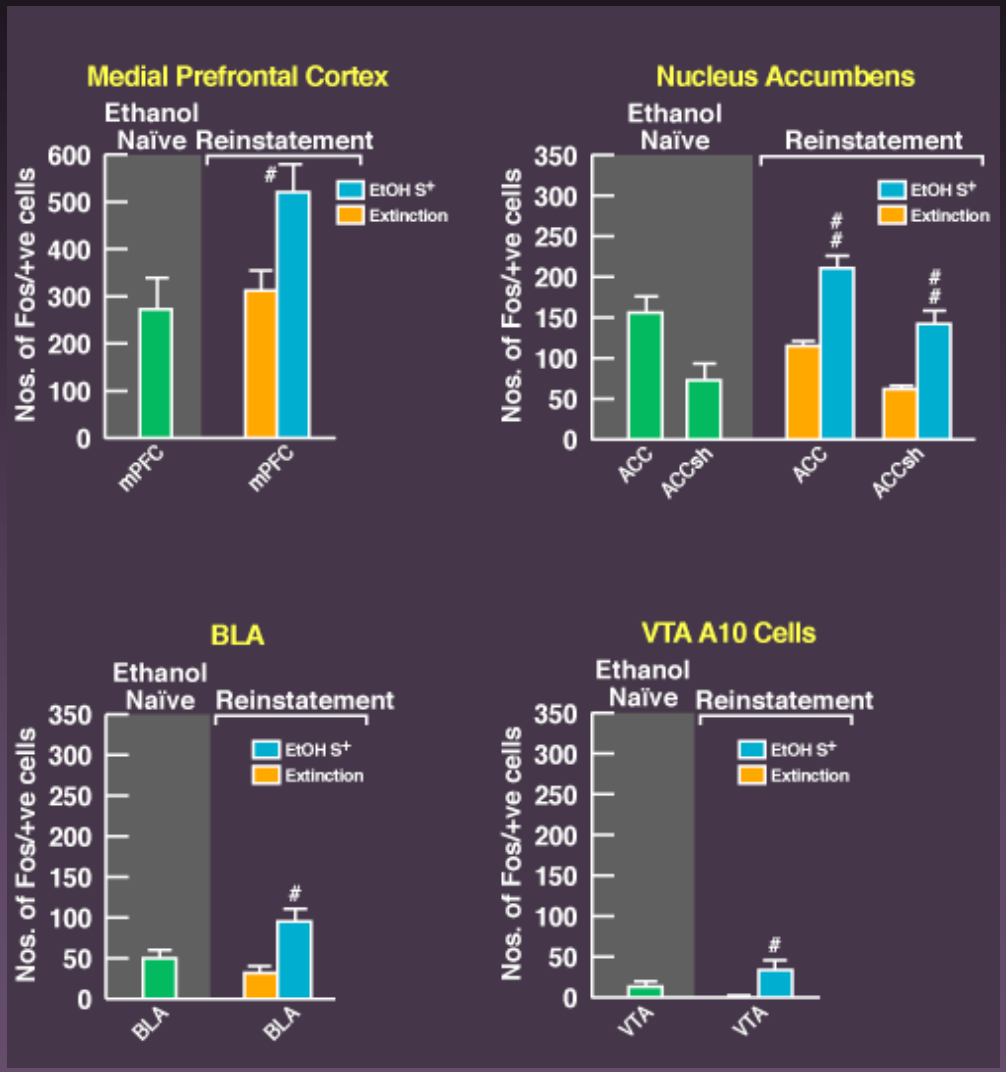
Neurocircuitry of Addiction

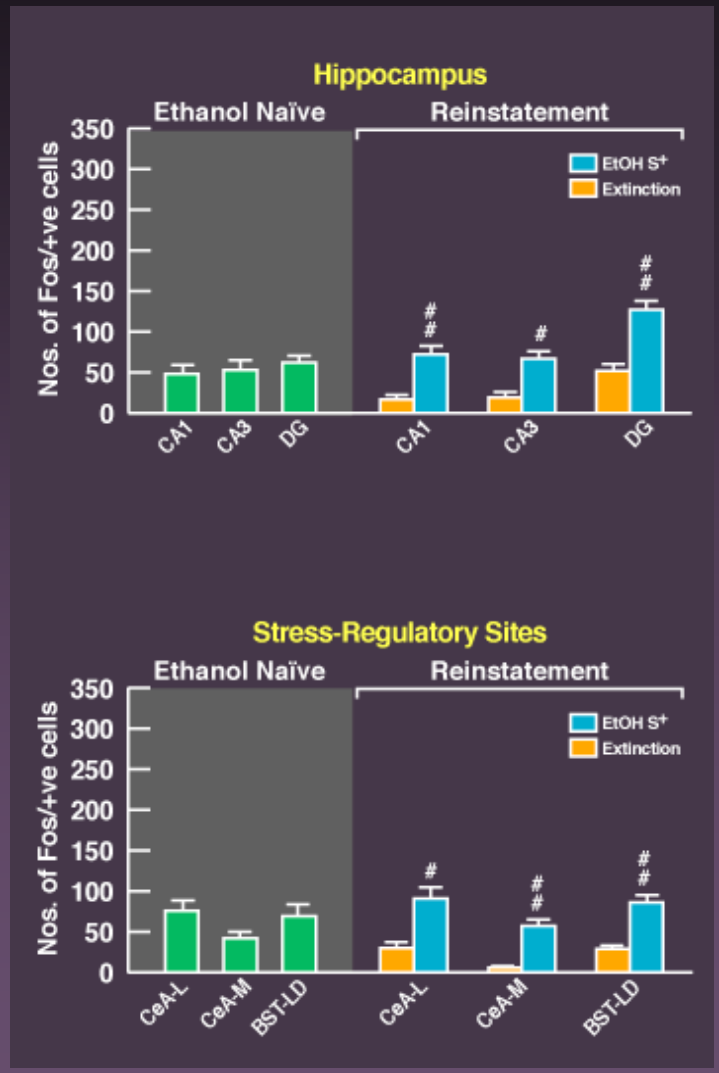




Modified from: Koob, Everitt, & Robbins (2008), in *Fundamental Neuroscience* 3rd Edn (Eds Squire, L.G. *et al.*). 987-1016 (Academic Press, Amsterdam).

Neural Activation By Ethanol-Associated Contextual Stimuli





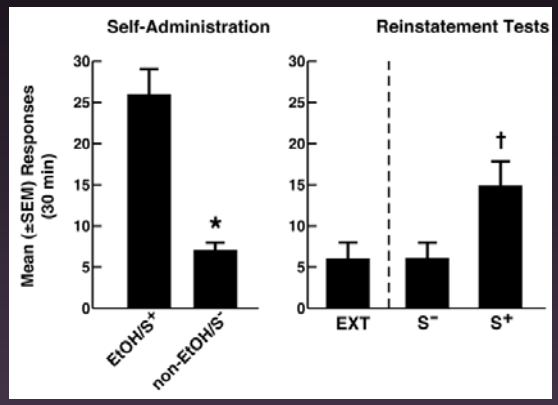
Zhao, Dayas Aujla, Baptista, Martin-Fardon, Weiss (2006) *J Neurosci*
Dayas, Zhao, Liu, Weiss (2007) *Biological Psychiatry*

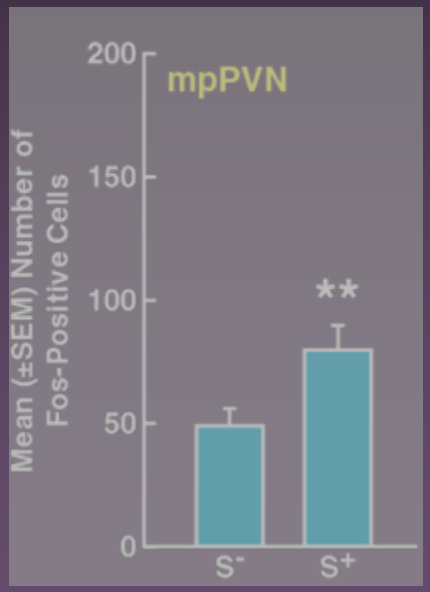
Understanding Mechanisms of the Differential Control of Normal Appetitive Behavior vs. Compulsive Drug Seeking

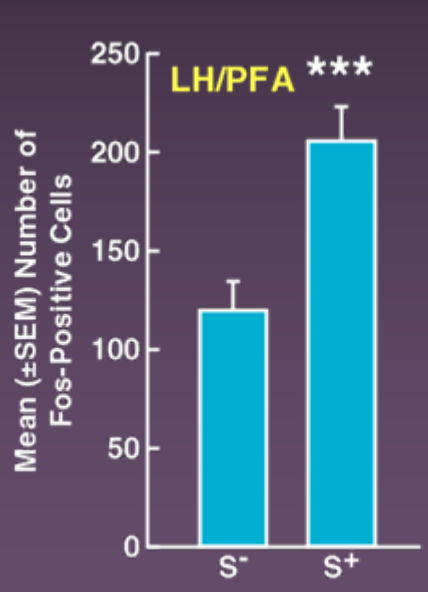
- **Neuropharmacology:** Selectivity of pharmacological manipulations for modifying drug vs. normal reward seeking

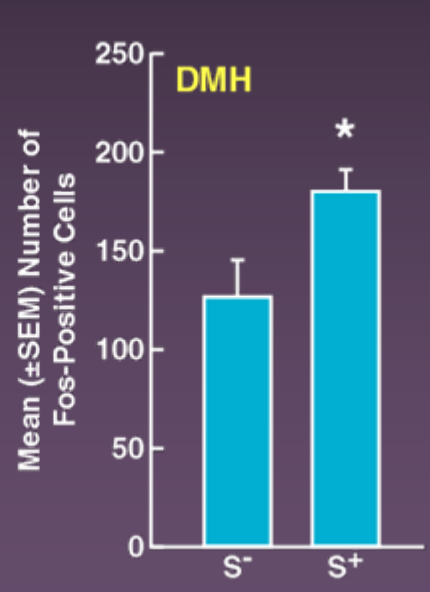
- **Effects of chronic drug/alcohol exposure (dependence):** Neuro-plasticity and behavioral consequences

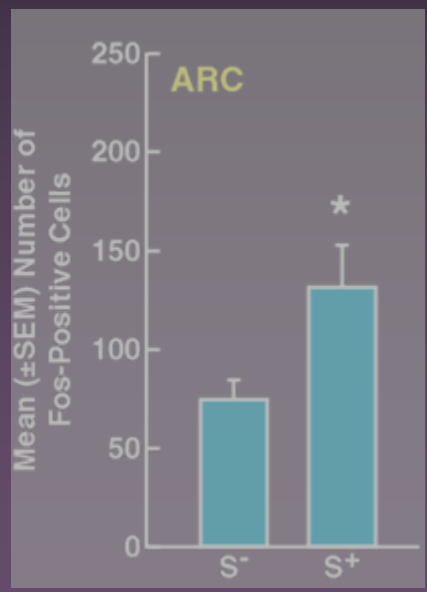
Ethanol-Related Contextual Stimuli (S^+) Activate Hypothalamic Nuclei





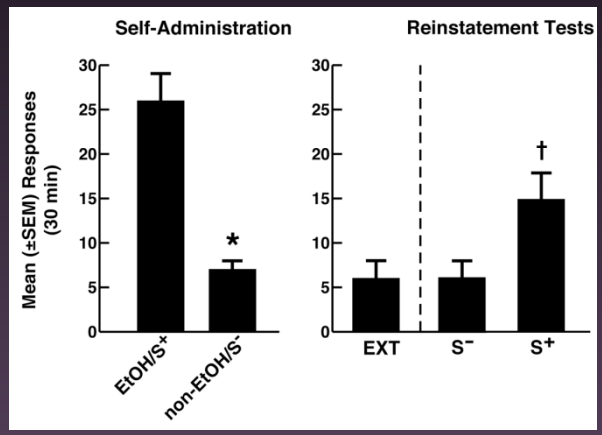


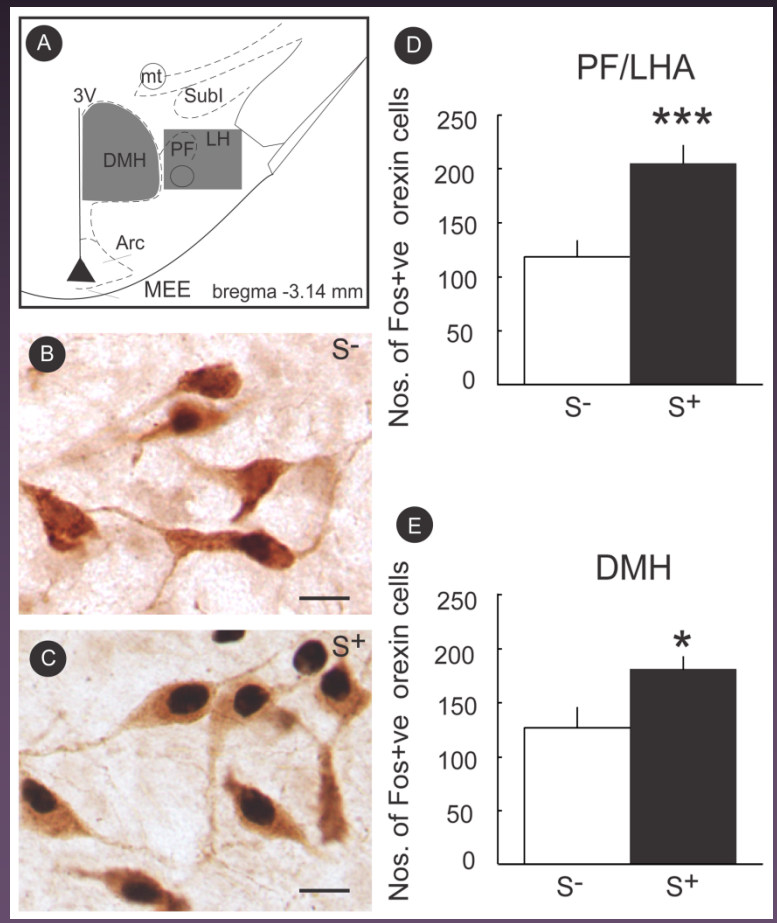




Dayas, Zhao, Martin-Fardon, Weiss *(2006) J Neurosci*;
Dayas, McGranahan, Martin-Fardon, Weiss (2008) *Biological Psychiatry*

Hypothalamic Neurons Showing Fos Activation by EtOH Cue are Orexin-Positive in the PFA/LH and DMH

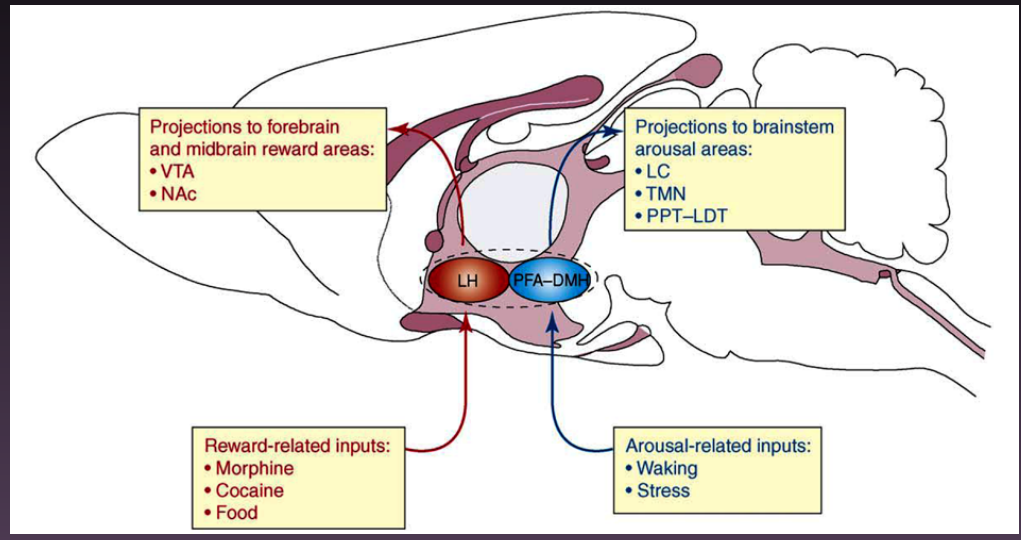




Dayas, McGranahan, Martin-Fardon, Weiss (2008) *Biological Psychiatry*

Orexin/Hypocretin

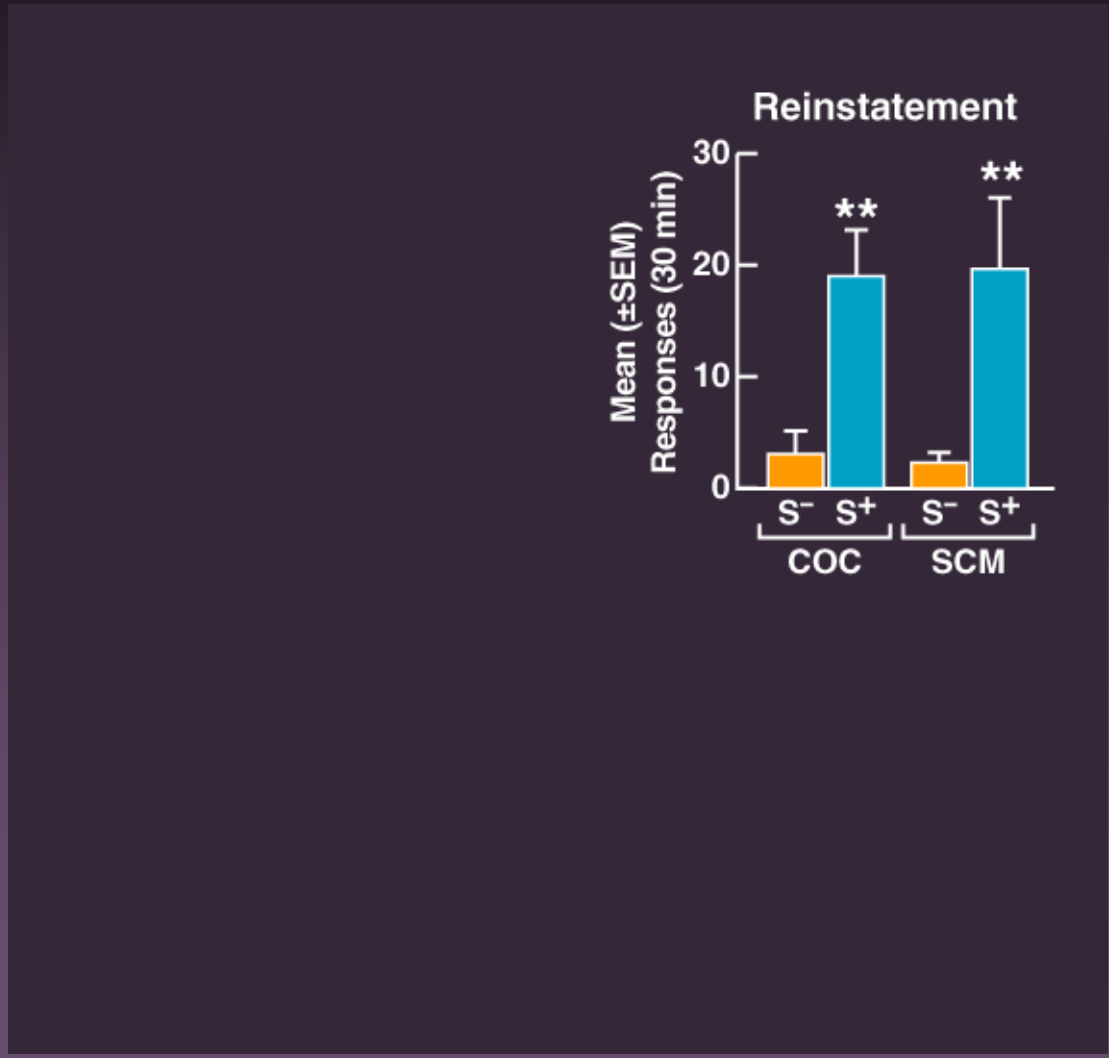
- orexigenic
- regulation of feeding
- arousal, sleep/wake states
- role in reward and addiction



From: Harris and Aston-Jones (2006) *TRENDS in Neurosciences* 29:571-577.

- **Lateral hypothalamus:**
  - *reward processing for both food and abused drugs*
  - *reward-based memory and learning*
- **Dorsomedial hypothalamus:**
  - *arousal, responses to stress*

Differential Activation of Hypothalamic Orx/Hcrt Neurons by Stimulus Conditioned to Cocaine vs. Palatable Natural Reward



Martin-Fardon, Dayas, Weiss *(in progress)*

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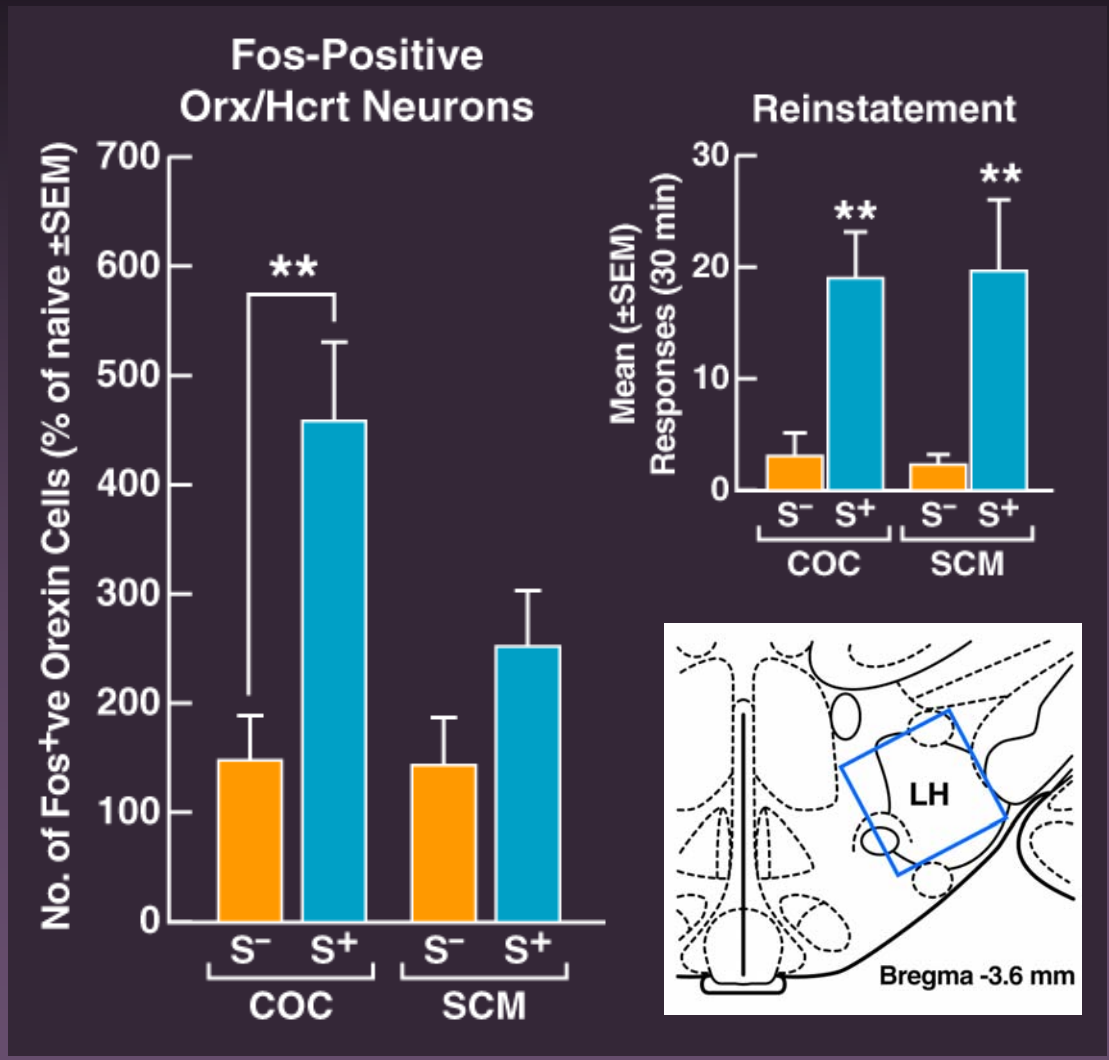
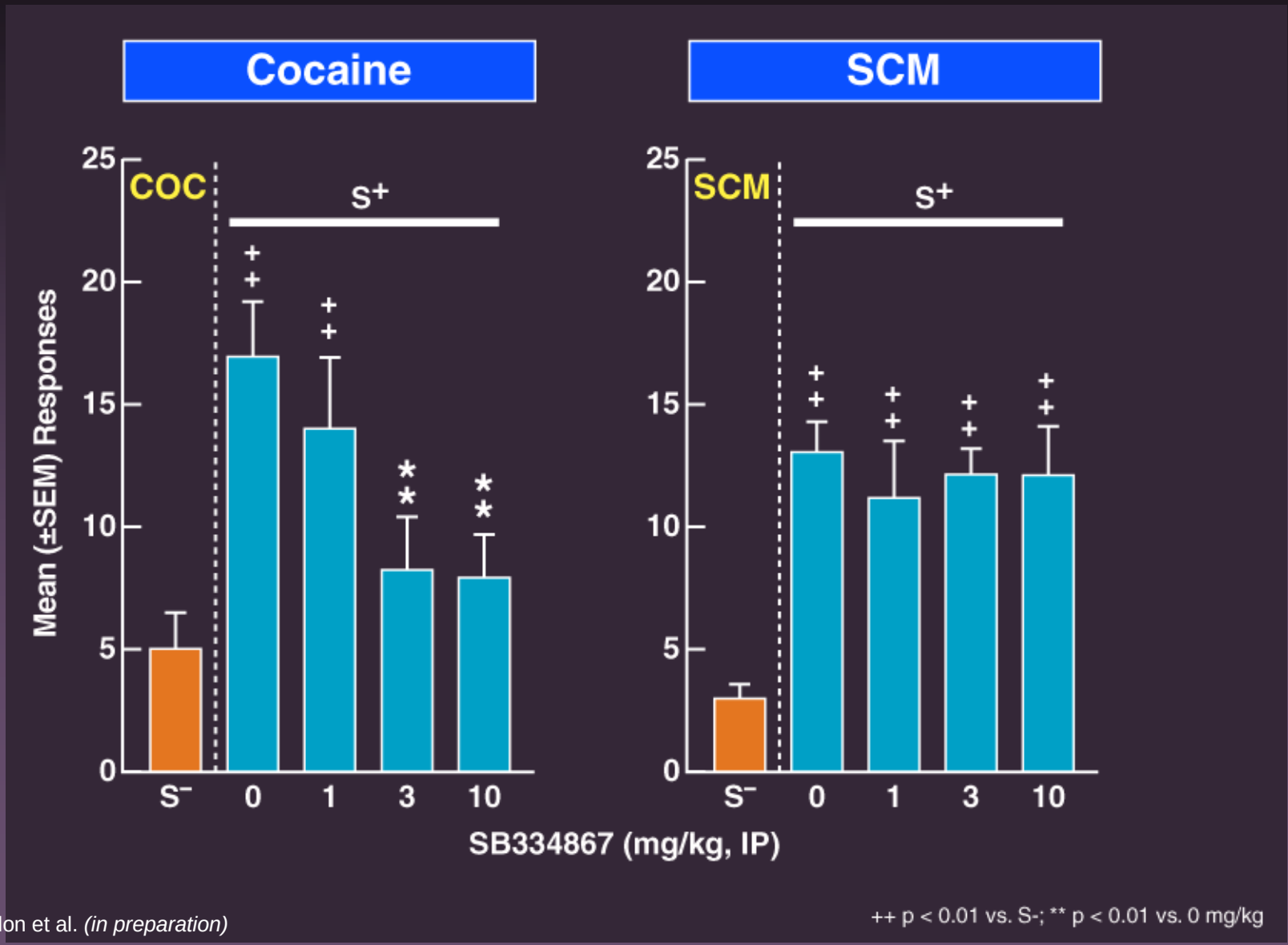


Martin-Fardon, Dayas, Weiss *(in progress)*

Hcrt-r1 Antagonist Selectively Reverses Conditioned Reinstatement of Cocaine-Seeking Behavior



Martin-Fardon et al. *(in preparation)*

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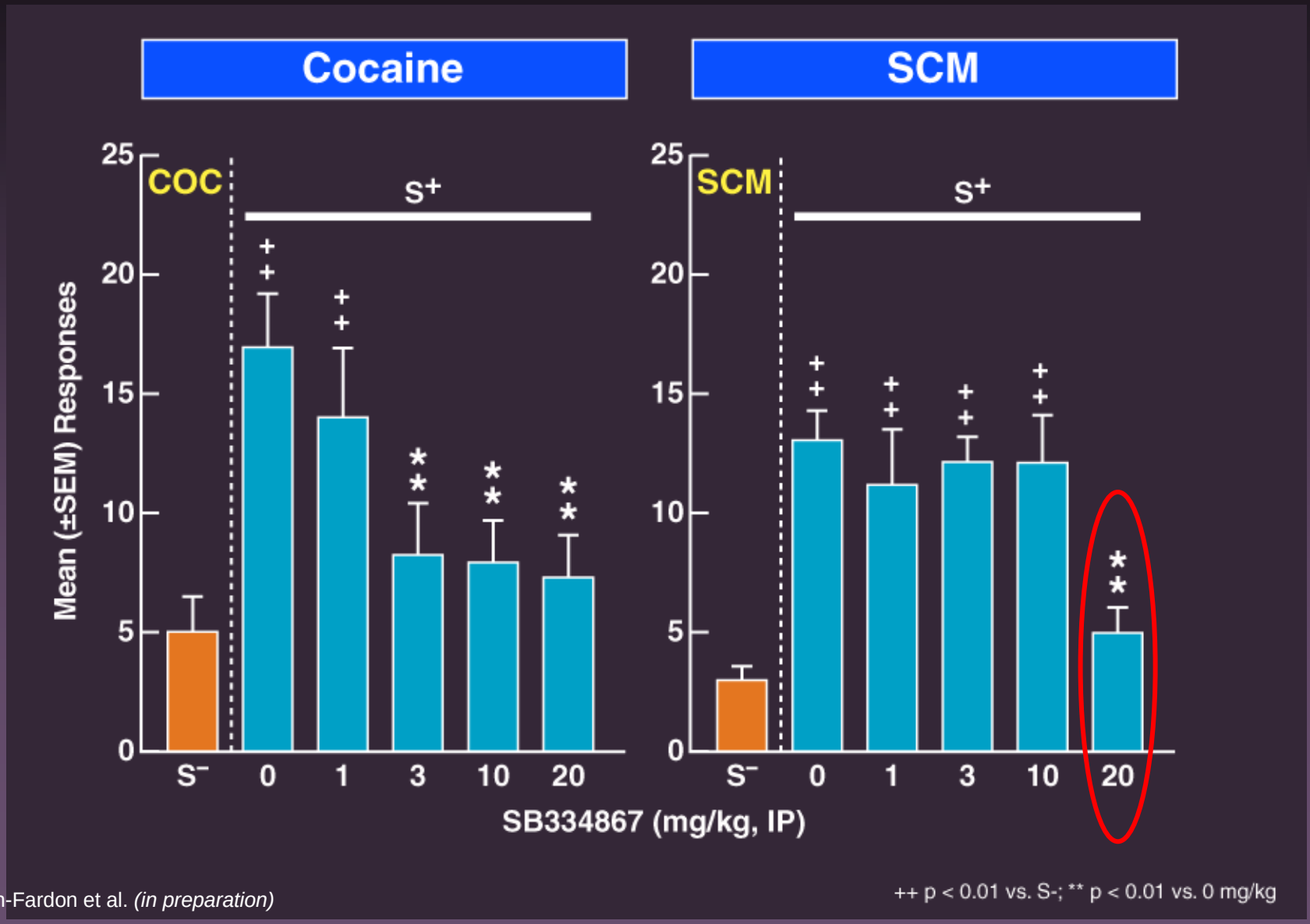
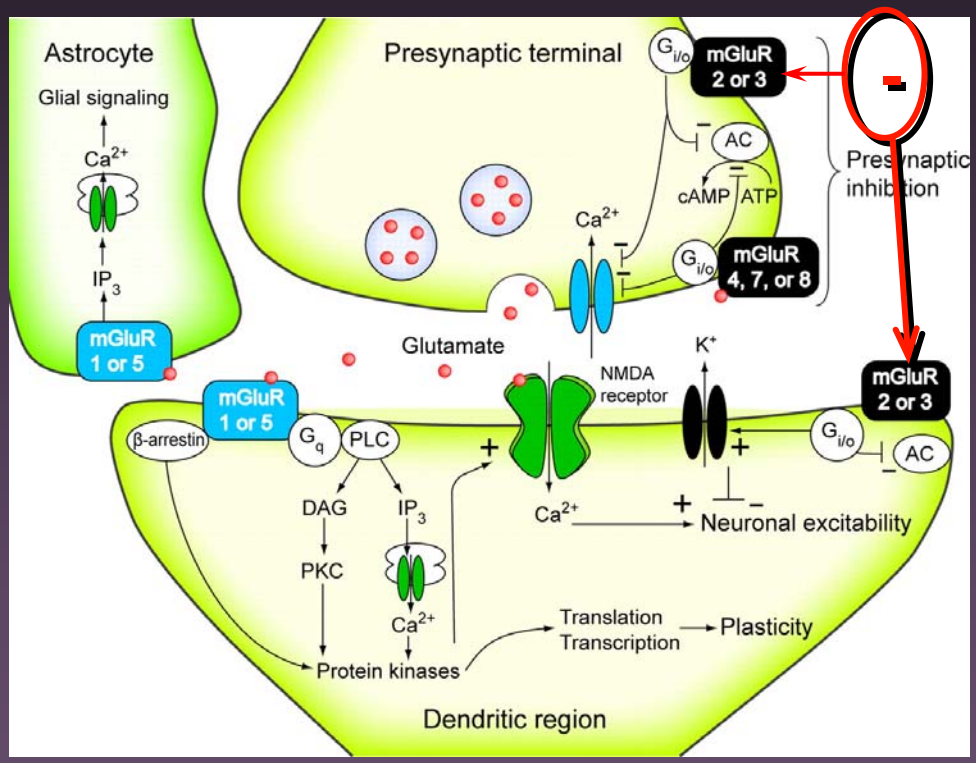


Martin-Fardon et al. *(in preparation)*

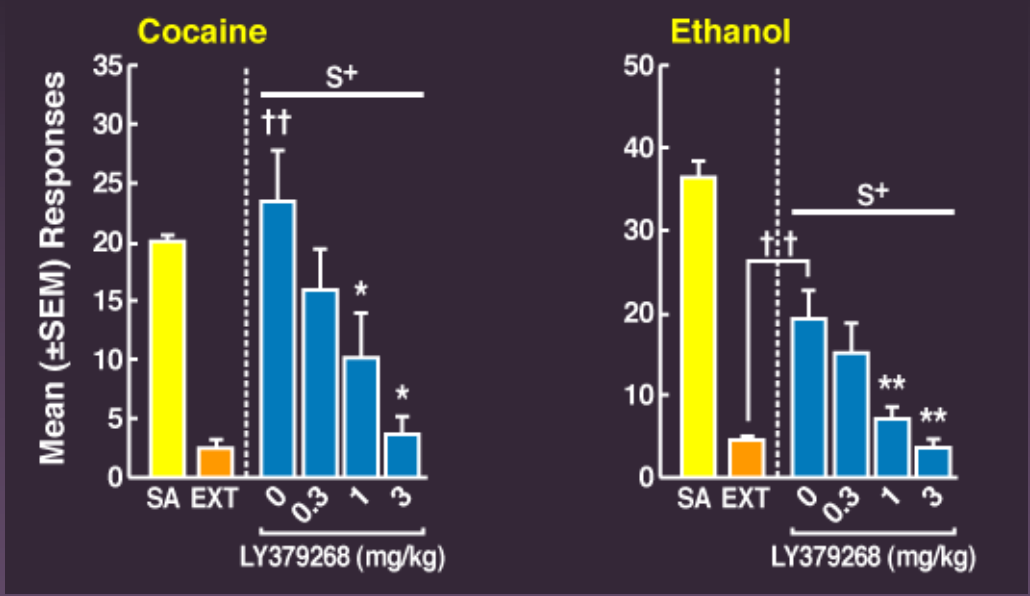
Metabotropic Glutamate Receptors (mGluRs): Cellular Location and Function



- **Group II mGluRs (*mGlu$_{2/3}$*):**
  - Negatively coupled to adenylyl cyclase via Gi/Go proteins
  - Inhibit cAMP and cAMP-dependent protein kinase A (PKA) activation
  - **Negative** modulation of excitatory synaptic transmission
  - Agonists (e.g., LY379268) inhibit GLU transmission

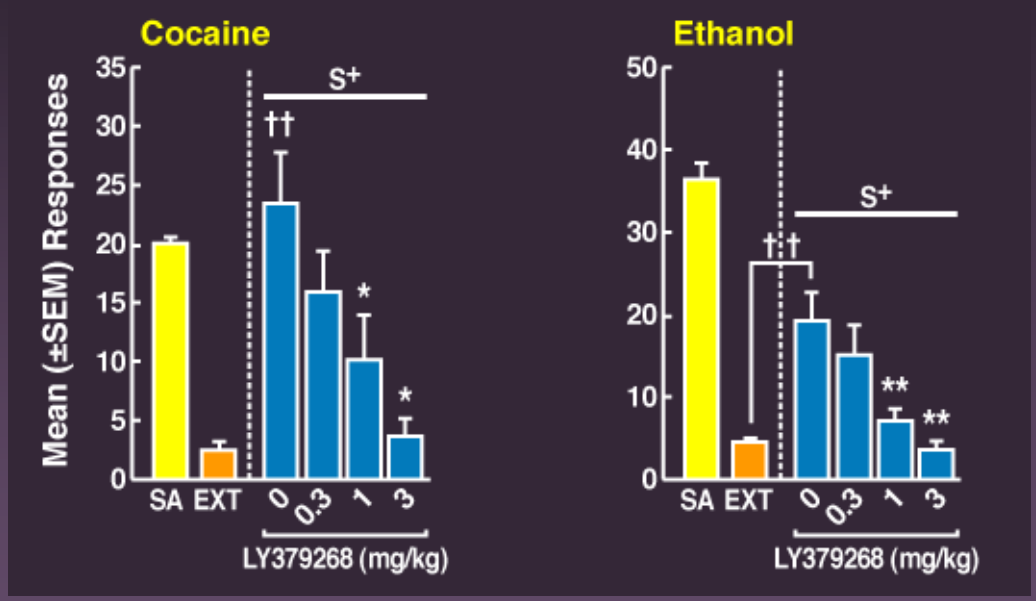
Modified from: Benarroch (2008) *Neurology*

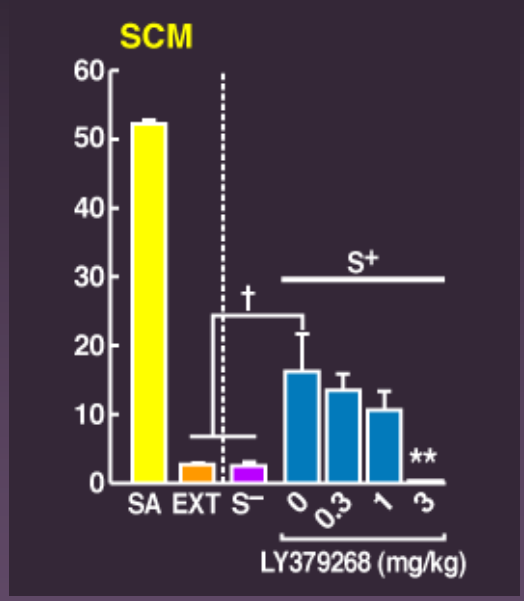
LY379268 (mGlu2/3 Agonist): Selectivity for Conditioned Drug-Seeking Behavior (Reinstatement)



Baptista et al. (2004) *J Neurosci;* Zhao *et al*. (2006) *J Neurosci;* Martin-Fardon *et al*. JPET (2009); Sidhpura *et al*. (2010) *Biol Psychiatry*

LY379268 (mGlu2/3 Agonist): Selectivity for Conditioned Drug-Seeking Behavior (Reinstatement)





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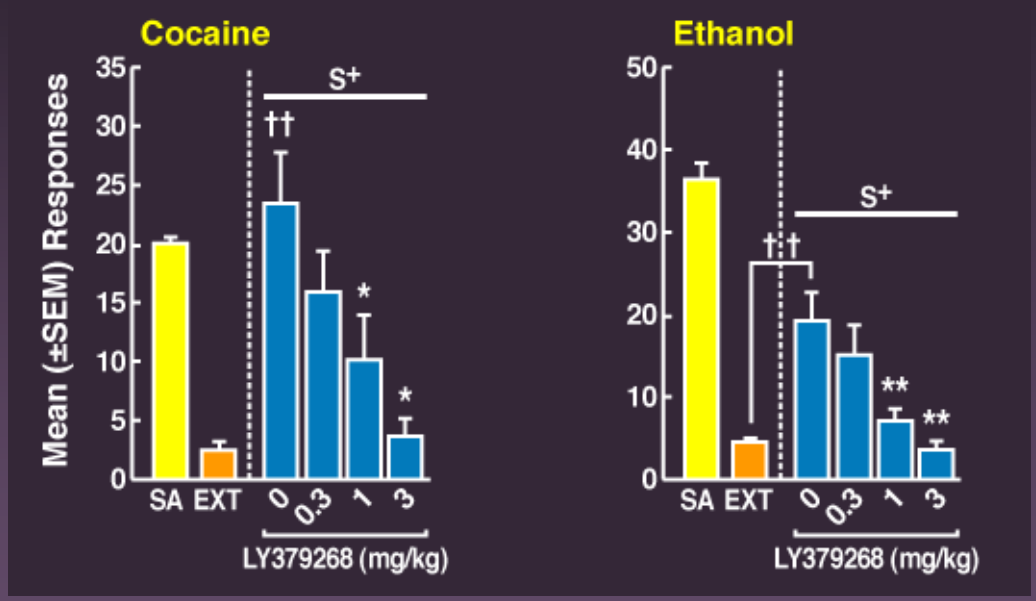
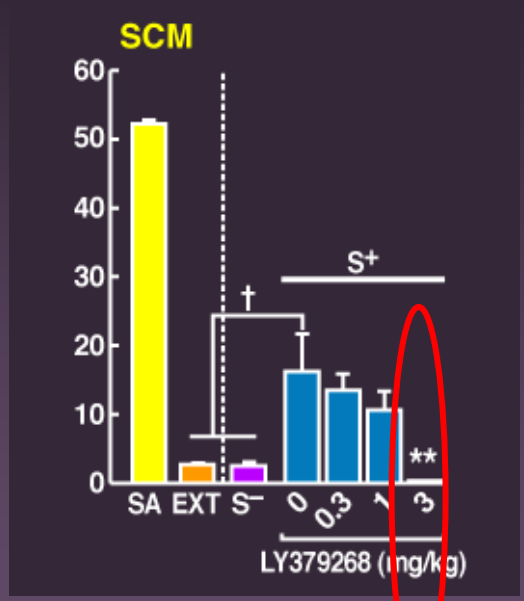


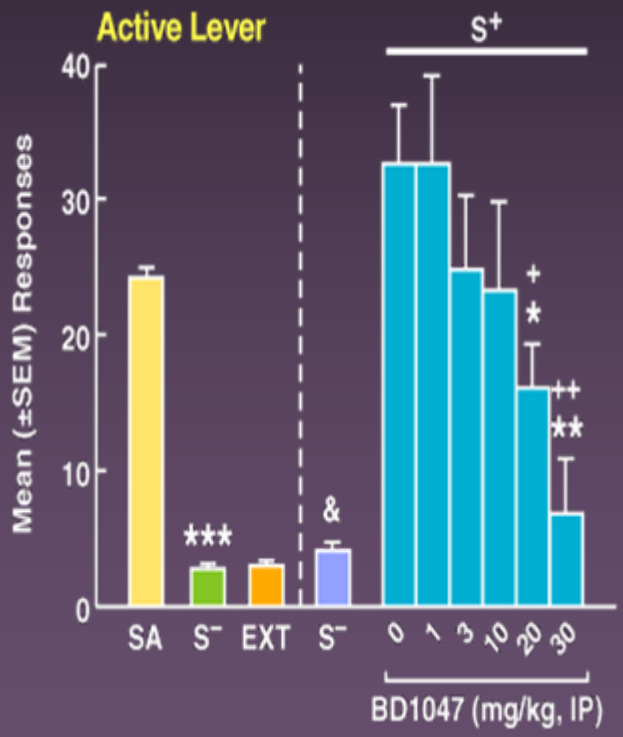


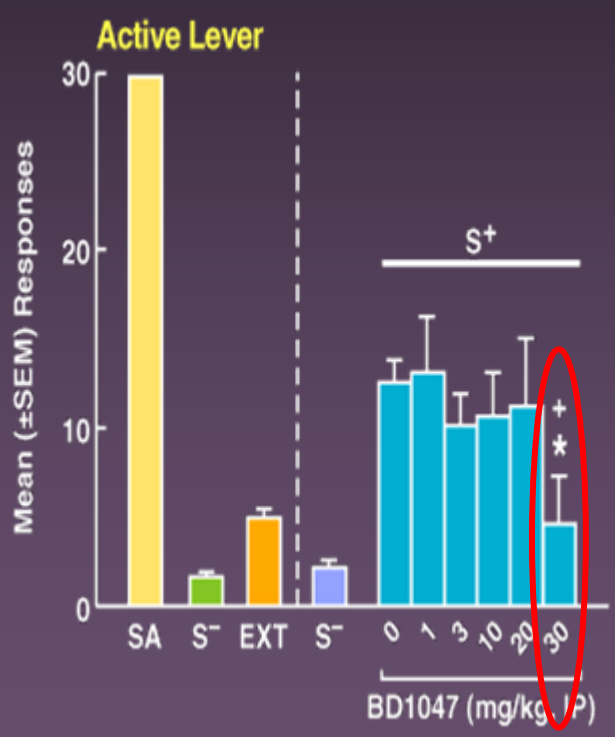
Baptista et al. (2004) *J Neurosci;* Zhao *et al*. (2006) *J Neurosci;* Martin-Fardon *et al*. JPET (2009); Sidhpura *et al*. (2010) *Biol Psychiatry*

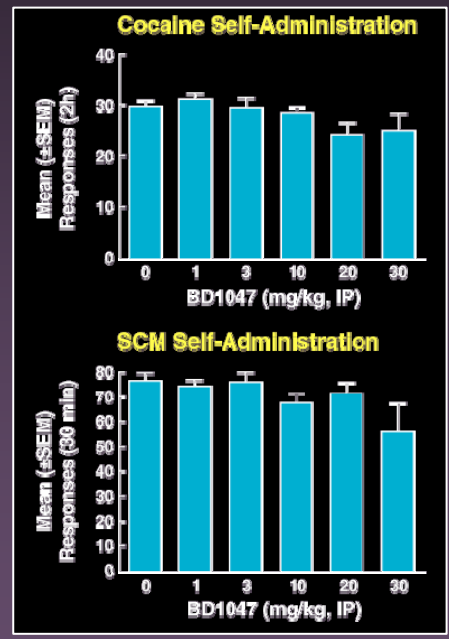
Selectivity of σ_1 Antagonist for Reinstatement Induced by Contextual Stimuli Conditioned to Cocaine vs. Natural Reward

Cocaine

SCM







Martin-Fardon R, Maurice T, Bowen WD, Weiss F (2007) *Neuropsychopharmacology*

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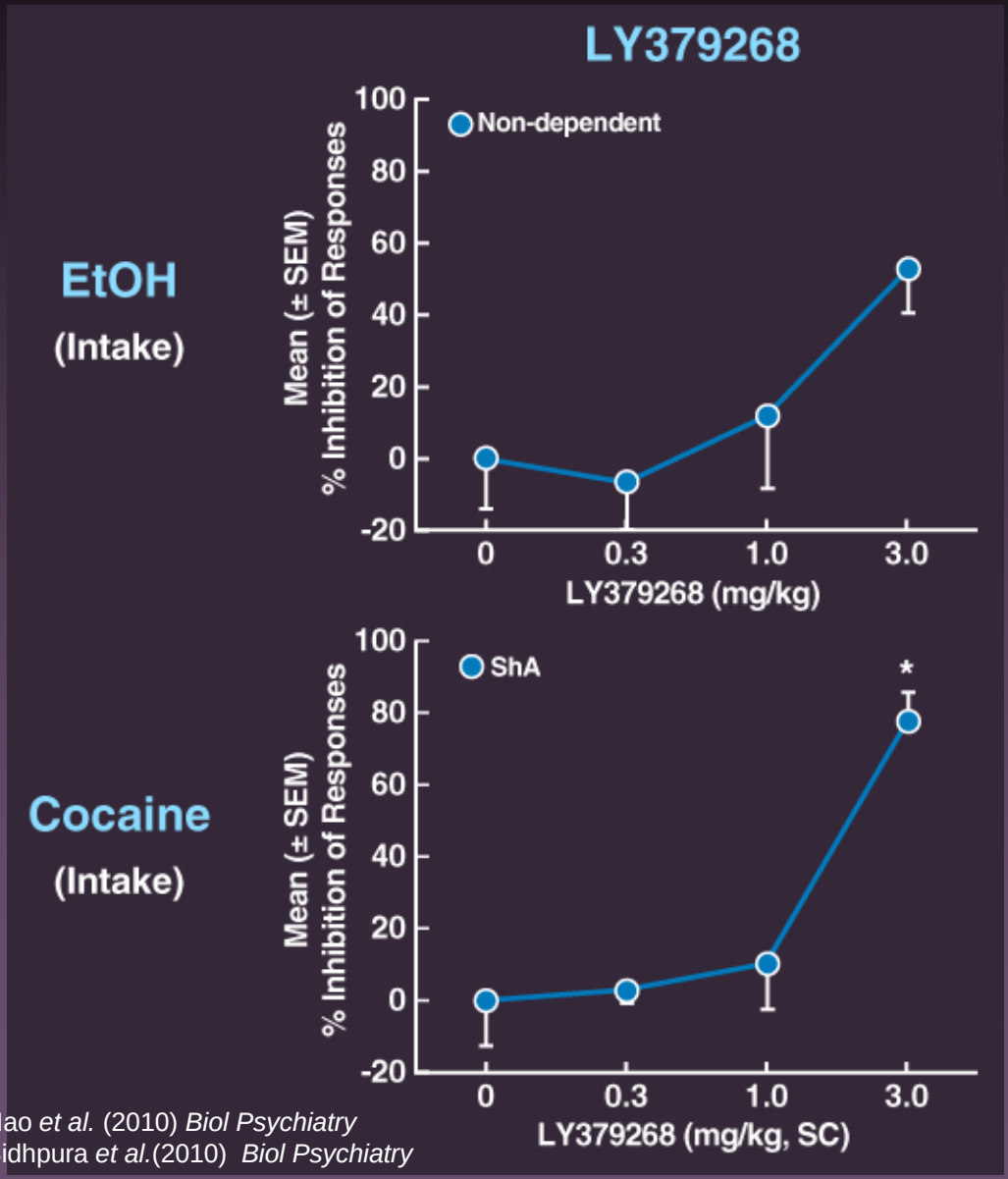
Understanding Mechanisms of the Differential Control of Normal Appetitive Behavior vs. Compulsive Drug Seeking

Chronic Drug Exposure / Dependence Induction Procedures

- COCAINE:
  - Escalation Model:
    - Short Access to IV cocaine [1 hr/day (ShA)] vs.
      Long Access to IV cocaine [6 hr/day (LgA)]

- ETHANOL:
  - Intragastric EtOH Intubation
  - (leading to significant withdrawal syndrome)

Shift in Dose-Response Profile of mGlu2/3 Agonist in Rats with a History of EtOH or Cocaine Dependence



Hao *et al.* (2010) *Biol Psychiatry*
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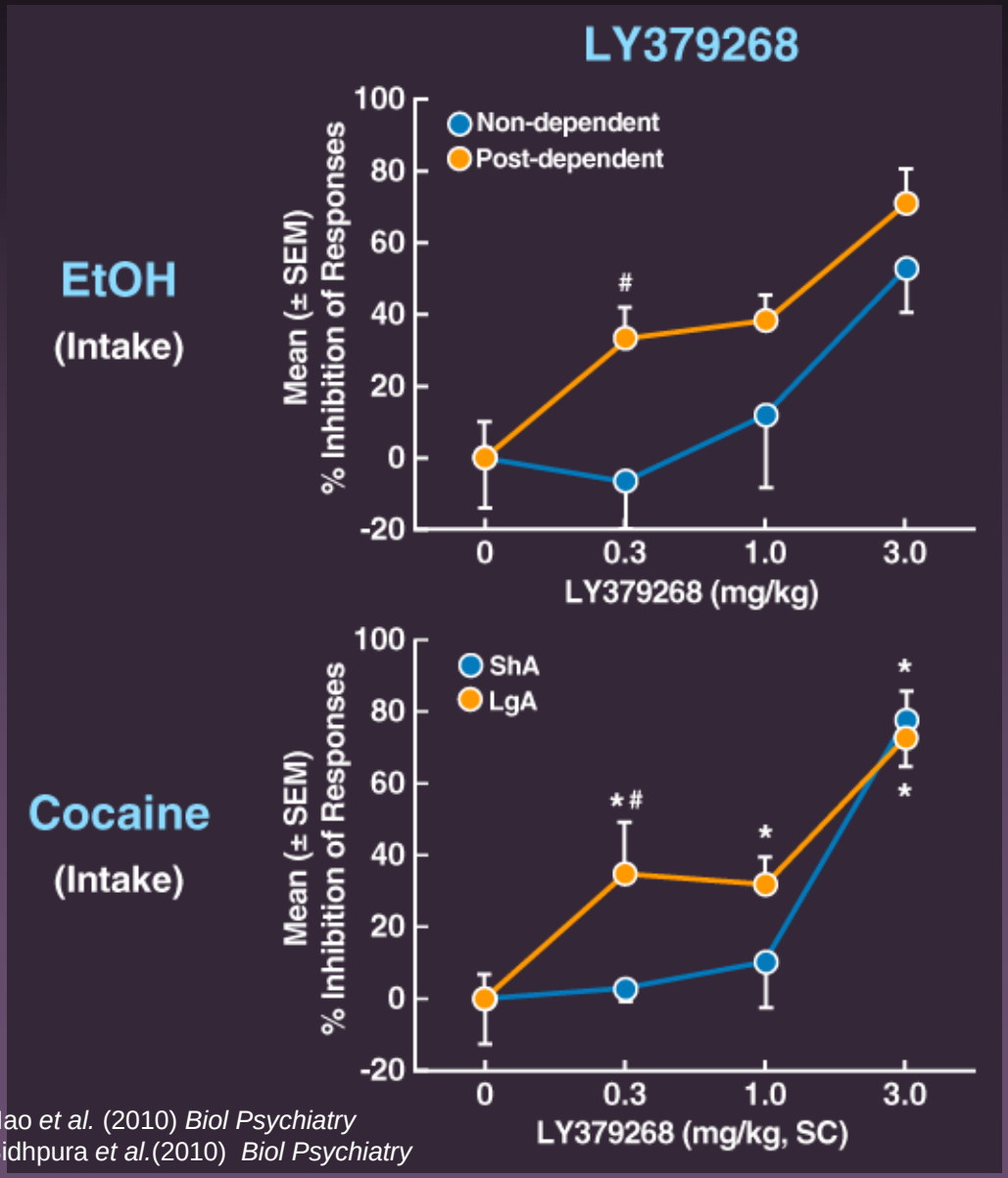

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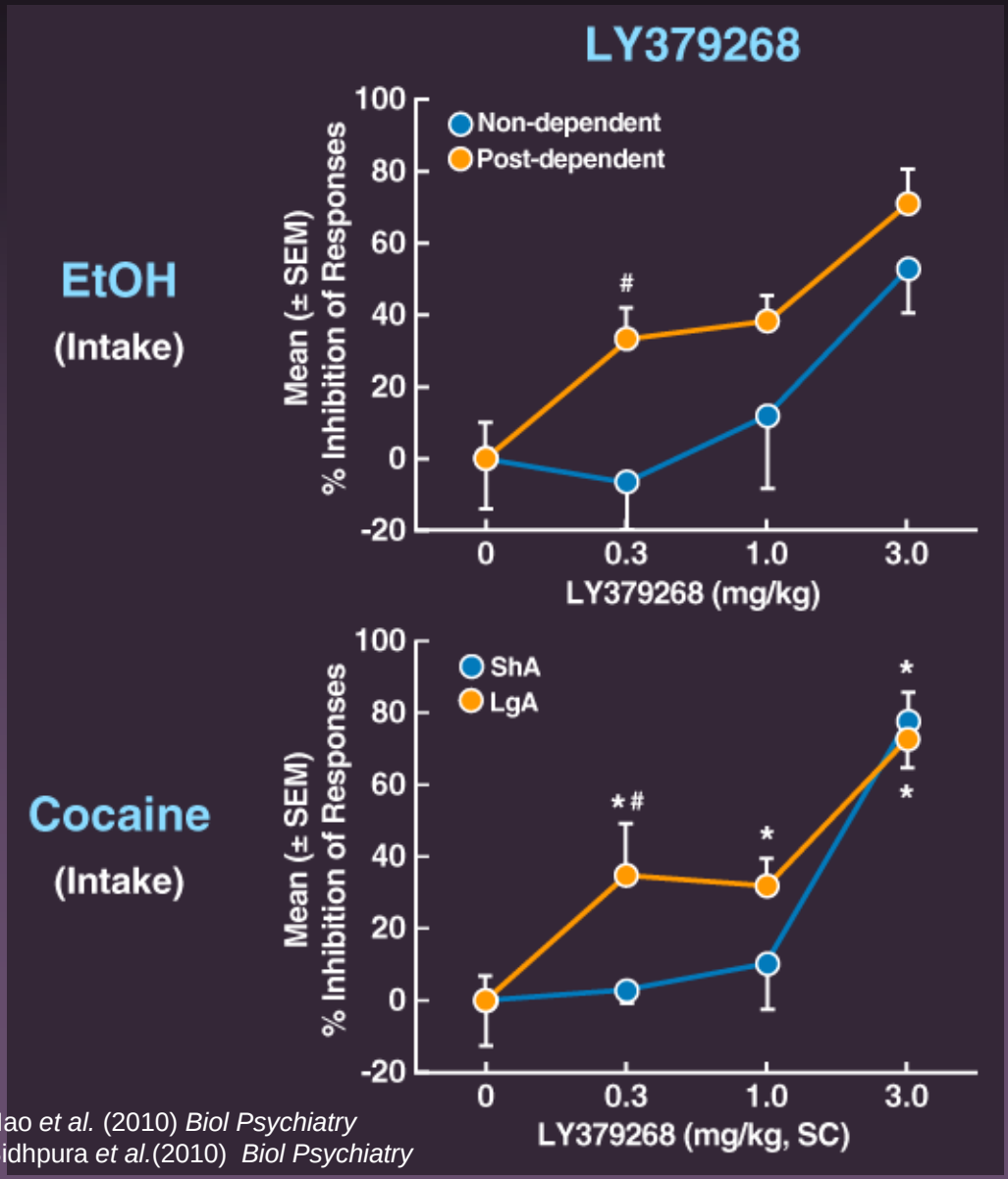
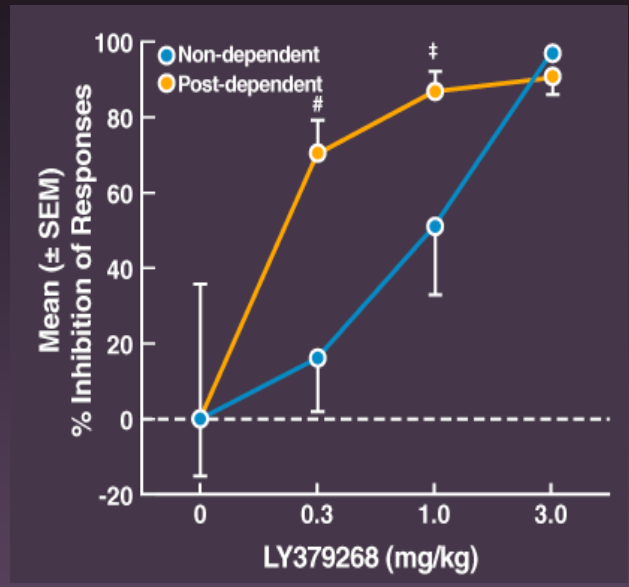


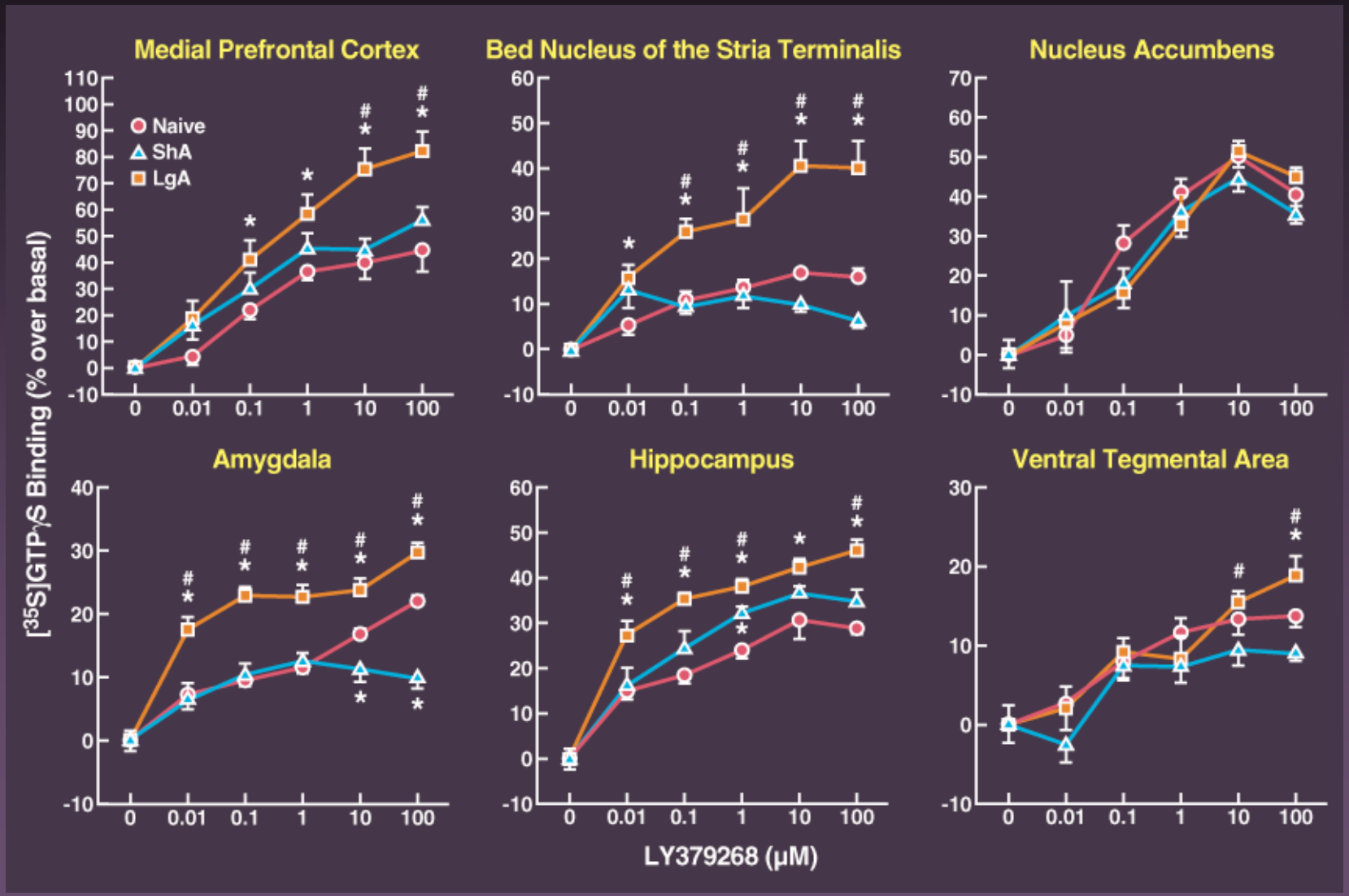


Reinstatement

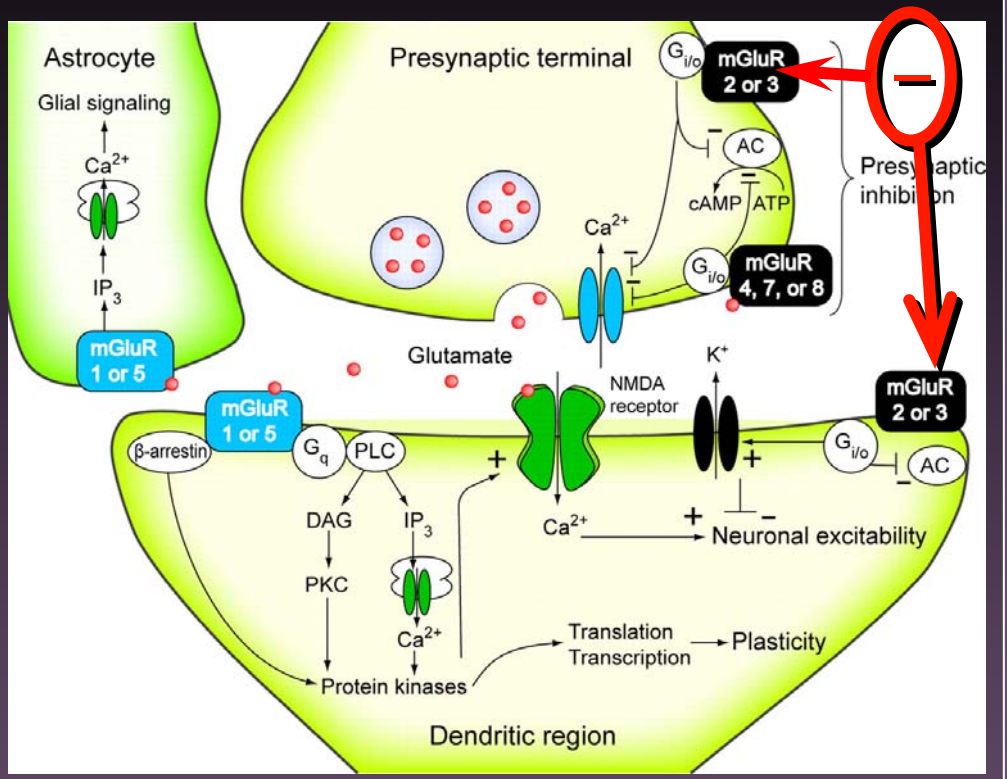
Hao *et al.* (2010) *Biol Psychiatry*
Sidhpura *et al.*(2010) *Biol Psychiatry*

Functional Coupling of mGlu2/3 to G-Protein in Rats with a History of Cocaine Escalation (LgA) vs. Non-Escalation (ShA)

[^{35}S]GTPgS Binding (% Glutamate-Stimulated Binding)



Hao, Martin-Fardon, Weiss (2010) *Biological Psychiatry*



Modified from Benarroch *Neurology* (2008)

History of Dependence
Upregulated $mGluR_{2/3}$ Function

↓

- reduced neural excitability by GLU

↓

- compensatory increase in drug intake
- GLU surges trigger relapse

Increased LY379269 efficacy (left-shift of D-R curve):

↓

- Activation by LY379268 further blunts excitability by GLU
- blocks reinforcing effects of EtOH or cocaine
- prevents surges of GLU release, normally leading to relapse.

Conditioned Cue Reactivity and Craving: Significance of History of Ethanol Dependence

- Craving induced by expectancy of EtOH is greater in severely dependent than moderately dependent drinkers[1]
- EtOH desire induced by the sight, smell and taste of EtOH is greater and longer-lasting in heavy drinkers compared to light drinkers[2]
- Urge to drink elicited by videotaped EtOH cues is positively correlated with history and degree of dependence (EtOH-dependent > moderate drinkers > light drinkers)[3]

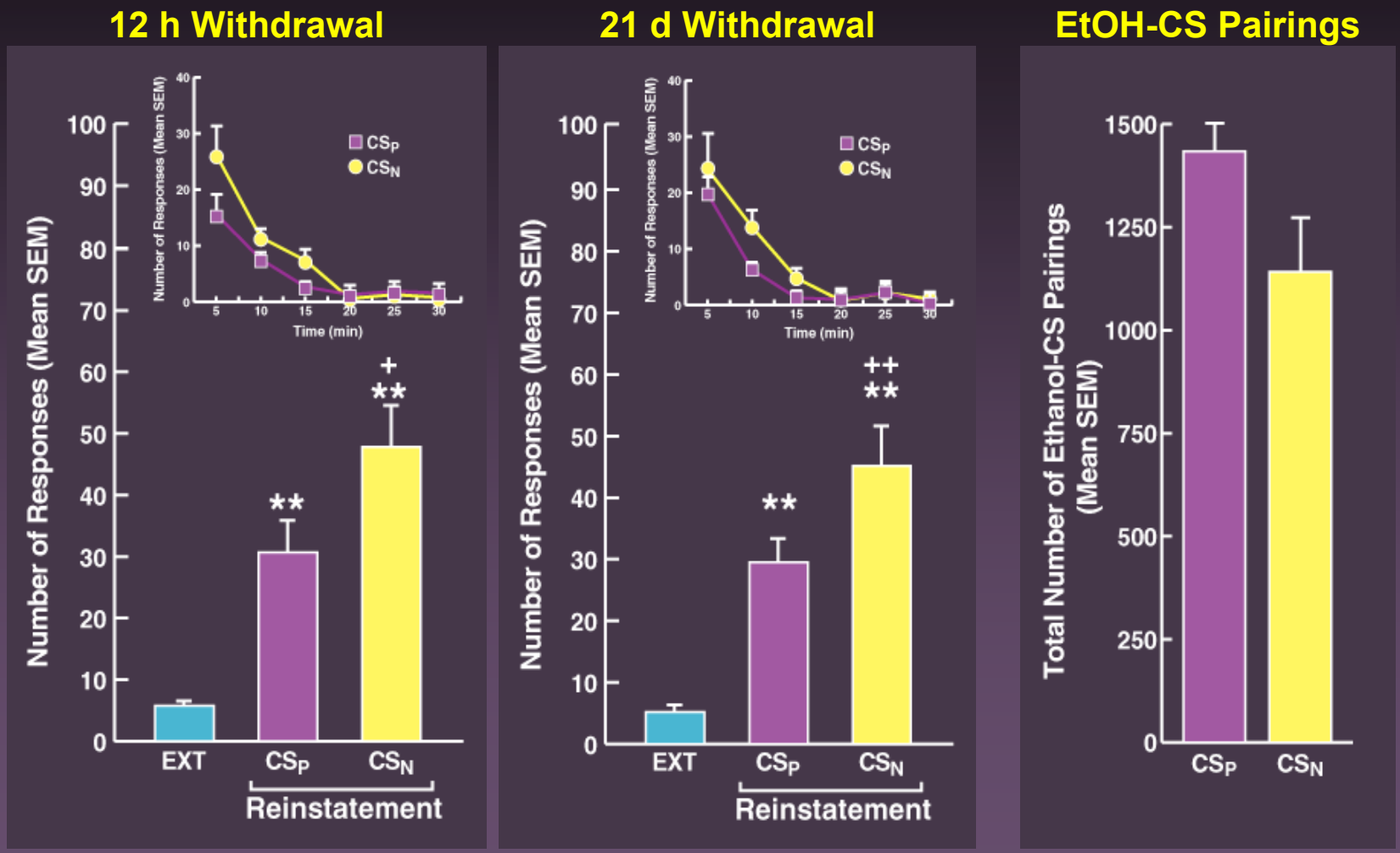
[1] Laberg (1986) *Br J Addiction*
[2] Greeley et al. (1993) *J Stud Alcohol*
[3] Streeter et al. (2002) *ACER*

History of Dependence and Withdrawal: Implications for the Incentive Valence of Drugs of Abuse

- Drug consumption during withdrawal introduces learning about a novel incentive dimension of the substance -- its capacity is to alleviate subjectively adverse states.

- This learning experience enhances a drug's reinforcing value, and thereby presumably the conditioned incentive valence of drug-related stimuli.

Reinstatement by Stimuli Conditioned Selectively to either the Positive (CS_P) or Negative (CS_N) Aspect of EtOH's Reinforcing Actions



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nature neuroscience

N-Acetylcysteine reverses cocaine-induced metaplasticity

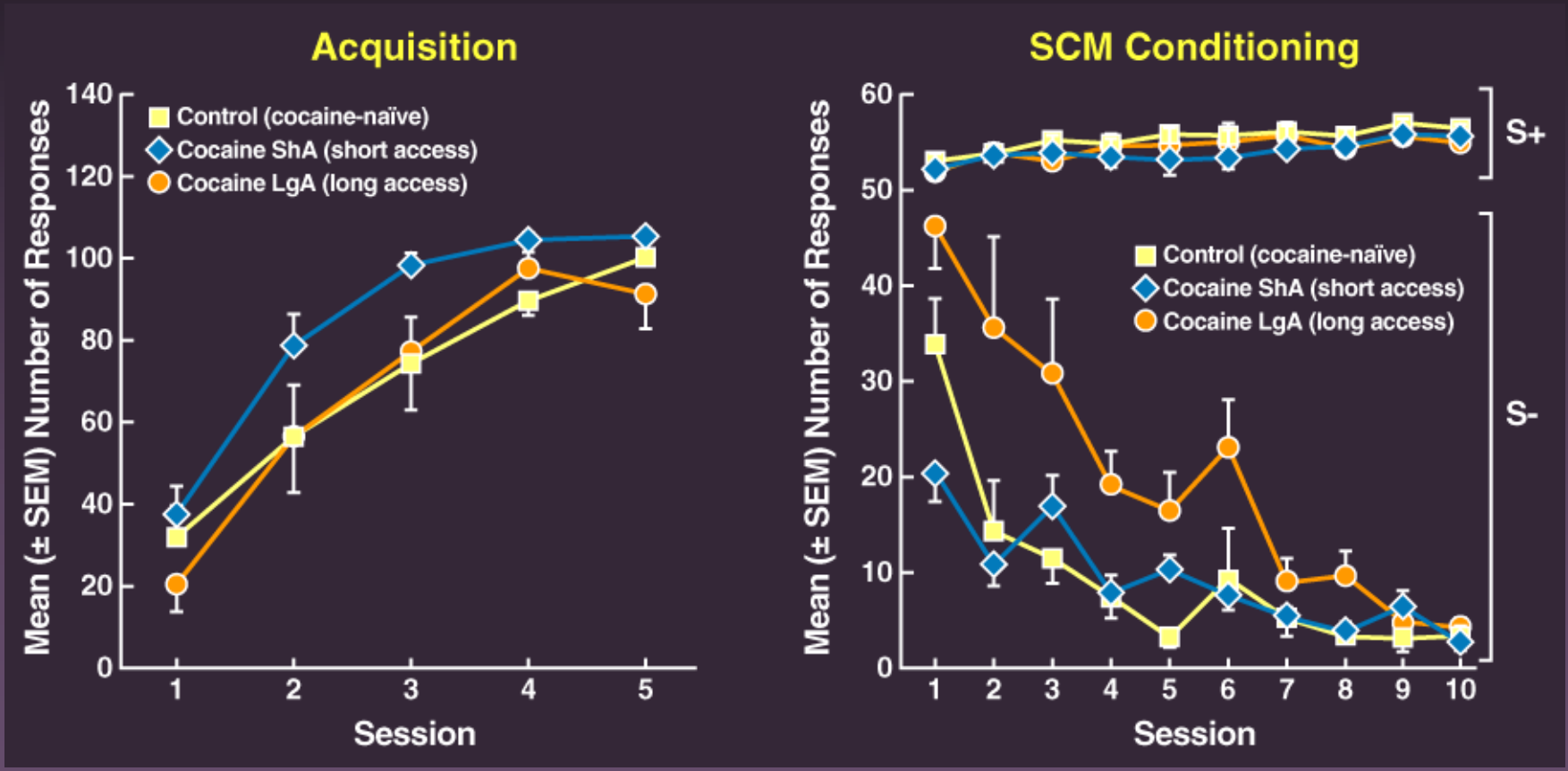
Khaled Moussawi[1], Alejandra Pacchioni[1], Megan Moran[1], M Foster Olive[2], Justin T Gass[2], Antonieta Lavin[1] & Peter W Kalivas[1]

Cocaine addiction is characterized by an impaired ability to develop adaptive behaviors that can compete with cocaine seeking, implying a deficit in the ability to induce plasticity in cortico-accumbens circuitry crucial for regulating motivated behavior. We found that rats withdrawn from cocaine self-administration had a marked *in vivo* deficit in the ability to develop long-term potentiation (LTP) and long-term depression (LTD) in the nucleus accumbens core subregion after stimulation of the prefrontal cortex. *N*-acetylcysteine (NAC) treatment prevents relapse in animal models and craving in humans by activating cystine-glutamate exchange and thereby stimulating extrasynaptic metabotropic glutamate receptors (mGluR). NAC treatment of rats restored the ability to induce LTP and LTD by indirectly stimulating mGluR2/3 and mGluR5, respectively. Our findings show that cocaine self-administration induces metaplasticity that inhibits further induction of synaptic plasticity, and this impairment can be reversed by NAC, a drug that also prevents relapse.

10 mg kg^{-1}, i.p., given with NAC and 1.5 h later; see **Fig. 5a**). MPEP blocked the capacity of NAC to restore LTD in cocaine rats but did not affect the NAC-induced restoration of LTP (**Fig. 6b**). Thus, akin to the restoration of LTP resulting from stimulating mGluR2/3, NAC-induced restoration of LTD is likely to arise from restoration of extrasynaptic glutamate and physiological tone to mGluR5, which reestablishes a crucial mechanism for inducing mGluR5-dependent LTD. **Figure 6c**

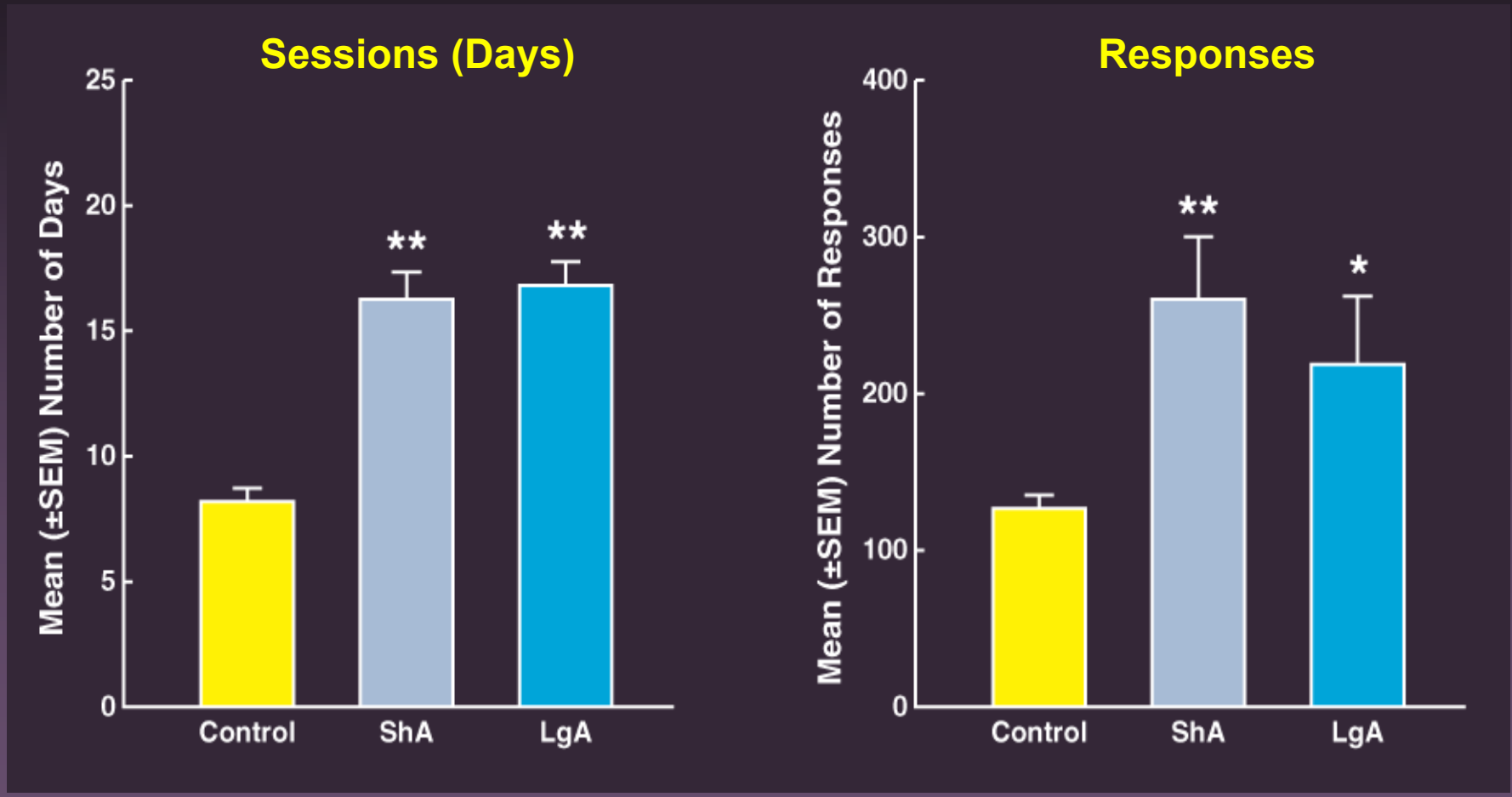
The capacity of excitatory synapses in the corticostriatal projection to undergo neuroplasticity is important for establishing well-learned habits and for allowing well-learned behaviors to be updated according to new information imposed by a changing environment[42]. Addiction has been characterized as an inability to modify or stop drug-seeking habits in spite of environmental information indicating the behavior is maladaptive[2]. Crucial to modifying striatal habit behavior is that the

SCM Self-Administration Training and Conditioning in Rats with Different Histories of Cocaine Self-Administration



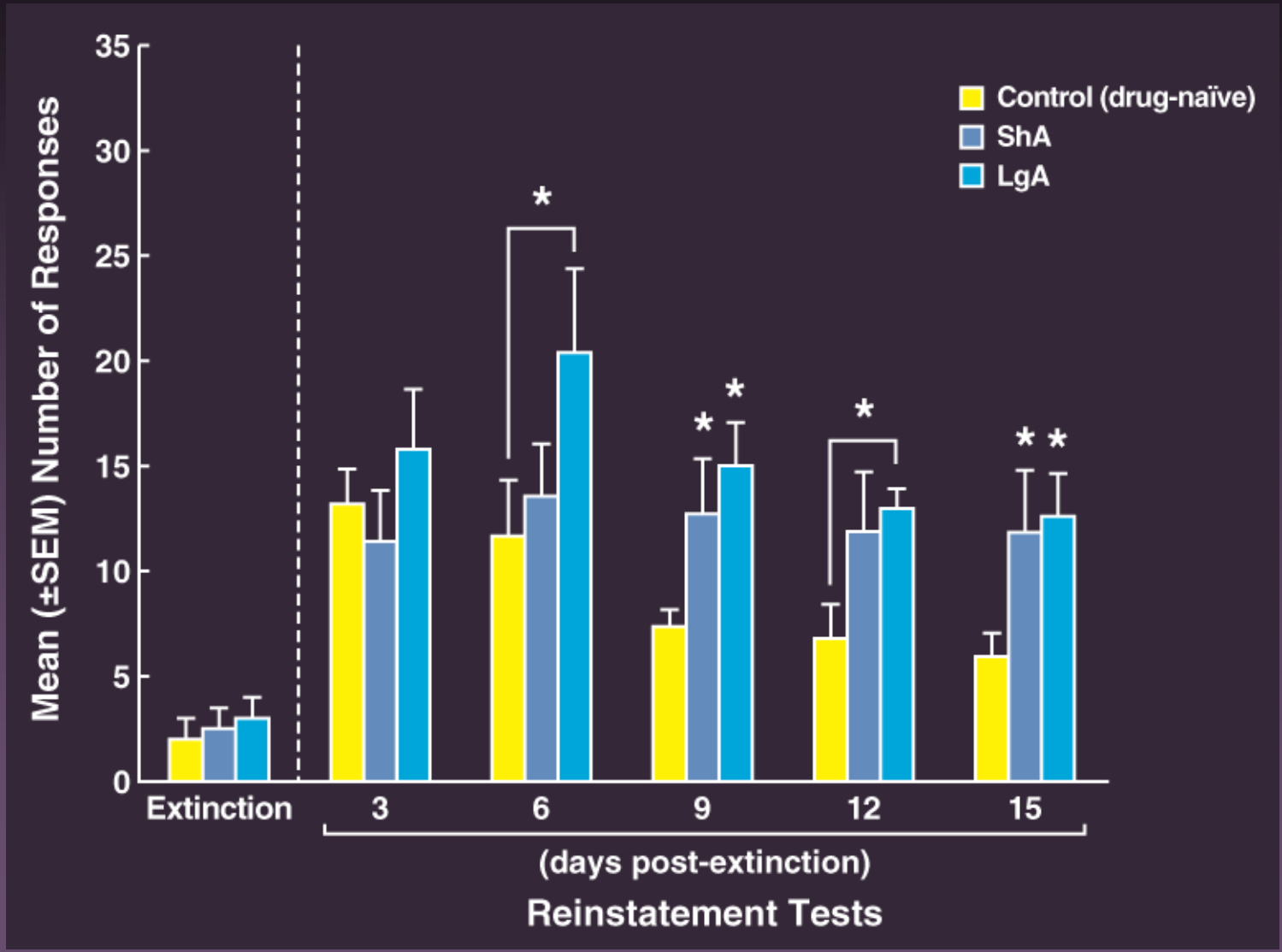
Hao et al. (*in progress*)

Total Number of Sessions (Days) and Responses to Reach the SCM Extinction Criterion (≤ 5/hr)



Hao et al. (*in progress*)

SCM-Induced Reinstatement Persists in Rats with a History of Cocaine Self-Administration



Hao et al. (*in progress*)

General Conclusions

- The inflexible, compulsive dimension that characterizes addiction can readily be demonstrated and modeled in animals.
- Unlike stimuli conditioned to natural reward, drug-related cues exert long-lasting control over drug-seeking, resembling the long-lasting nature of drug craving and relapse risk in humans.
- Neural systems controlling “normal” motivation can, over the course of chronic drug use, acquire a preferential role in mediating the effects of stimuli conditioned to drugs of abuse over natural rewards.
- Specifically, distinct neuroadaptive changes may tilt the function of the Orx/Hcrt system mGlu2/3 and σ1 receptors toward drug-directed behavior and explain the increased sensitivity of these systems to pharmacological interference with drug seeking compared to behavior directed at natural rewards.
- Chronic drug use can induce neuroadaptation that conveys compulsive character to behavior motivated by natural reward, possibly related to drug-induced “metaplasticity”.

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