

# Learning mechanisms of drug dependence.

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*University of Cambridge*

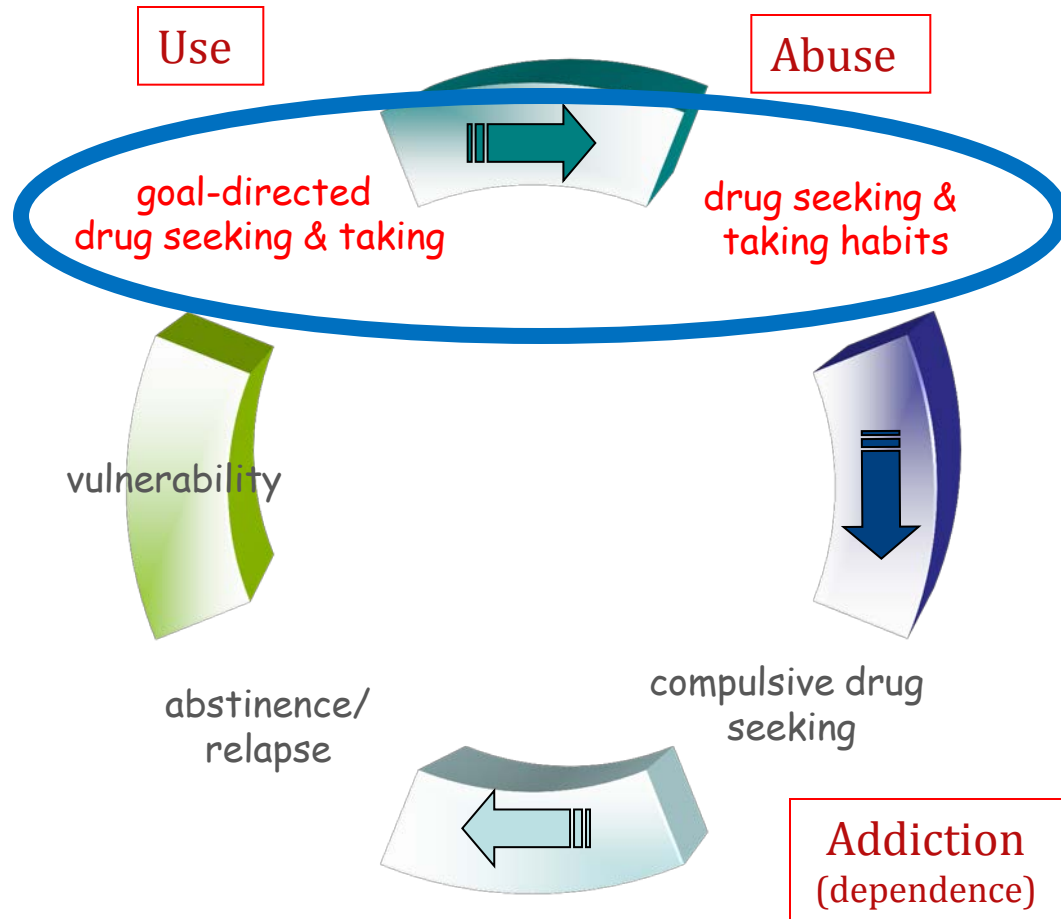


# In this talk...

- Development of drug habits.
- Impact of environmental cues.
- Cue exposure therapy.
- Extending the drug cue.

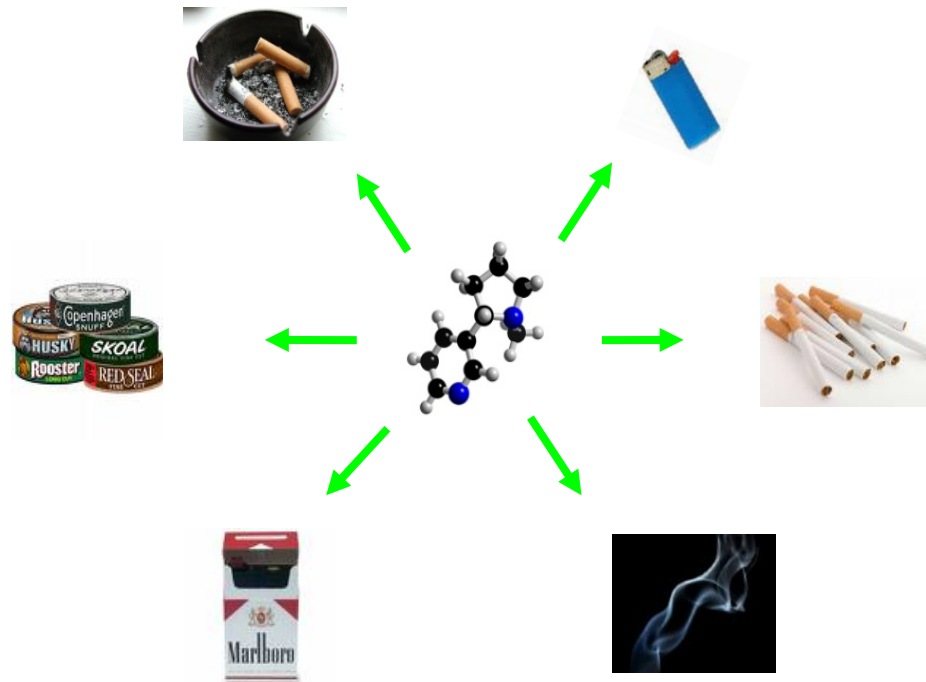


# Stages in drug addiction

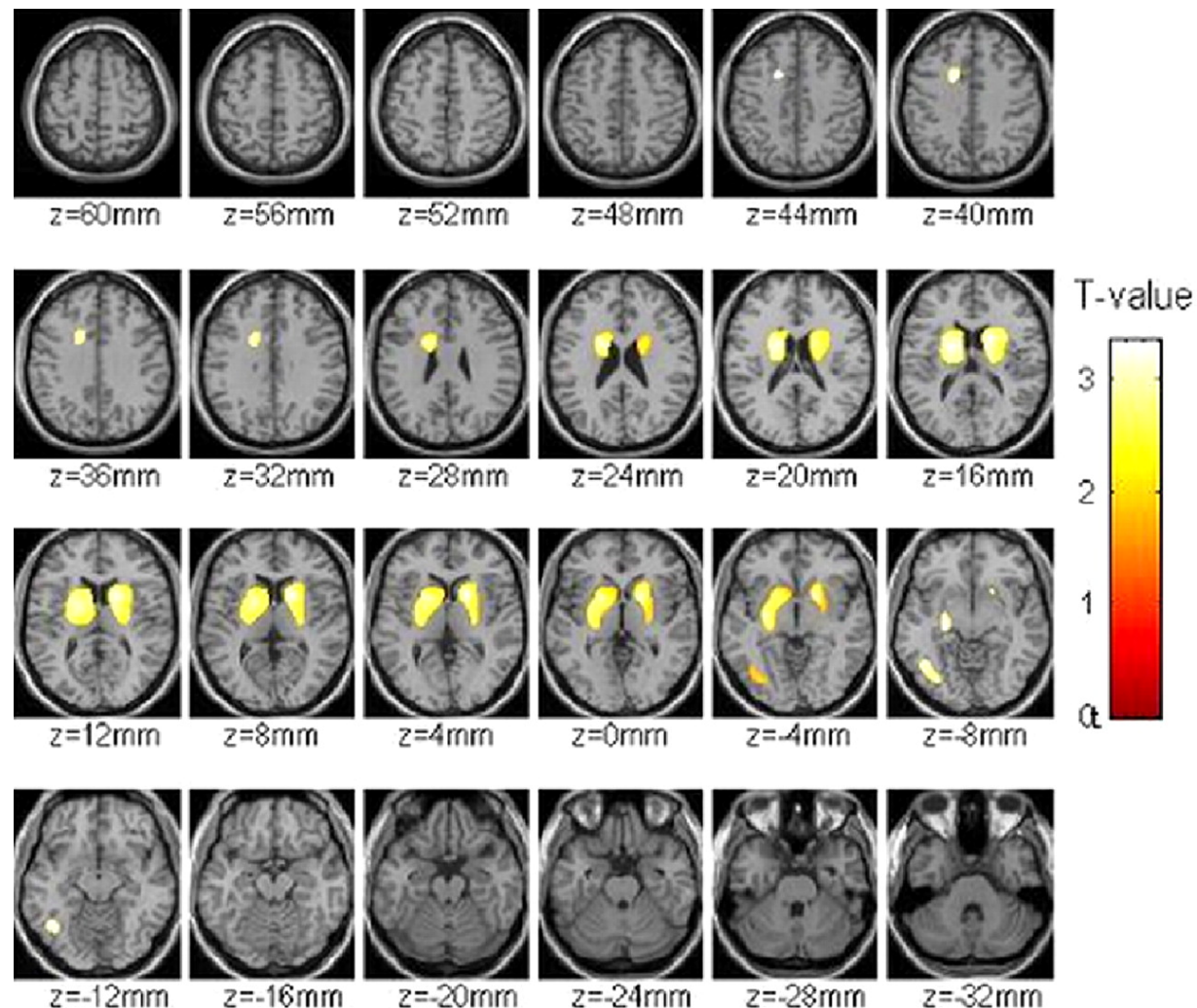


# Development of a drug-seeking habit?

Drug-associated stimuli come to drive drug seeking and ultimately drug use.



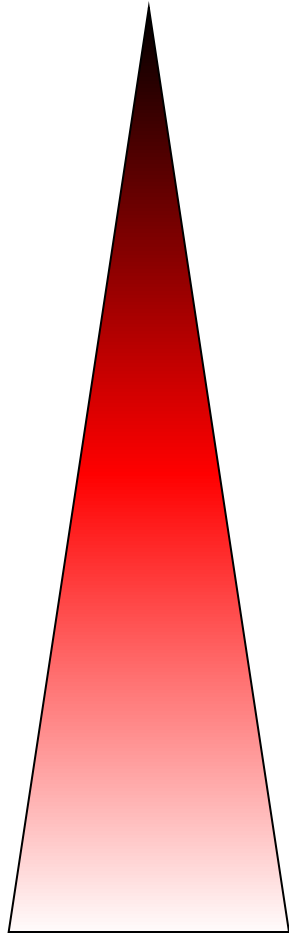
# Caudate putamen dopamine evoked by cocaine cues





# Stages in drug addiction

Drug-associated Stimuli



1<sup>st</sup> exposures



Use

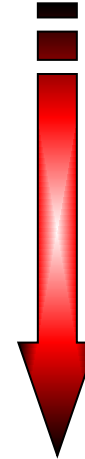


Abuse



Addiction

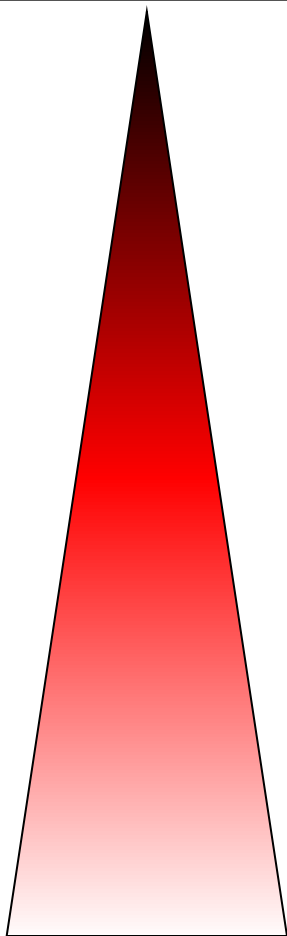
Goal directed: A-O learning



Habits: S-R learning

# Cocaine Self Administration in Rats

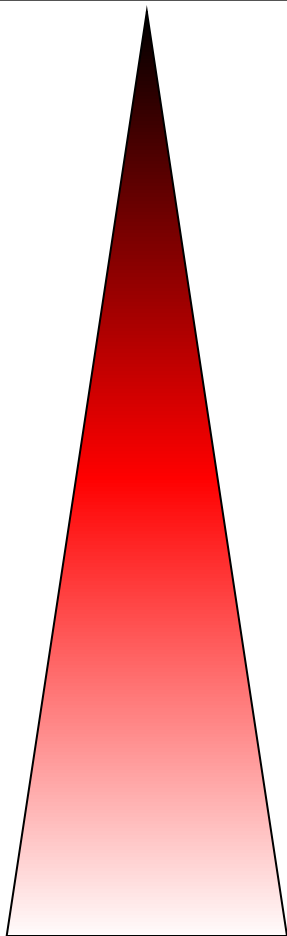
Drug-associated  
Stimuli



FR1

# Cocaine Self Administration in Rats

Drug-associated  
Stimuli



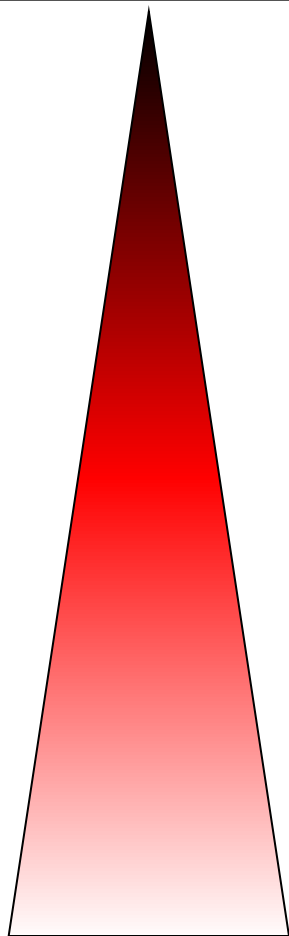
FR1





# Cocaine Self Administration in Rats

Drug-associated  
Stimuli

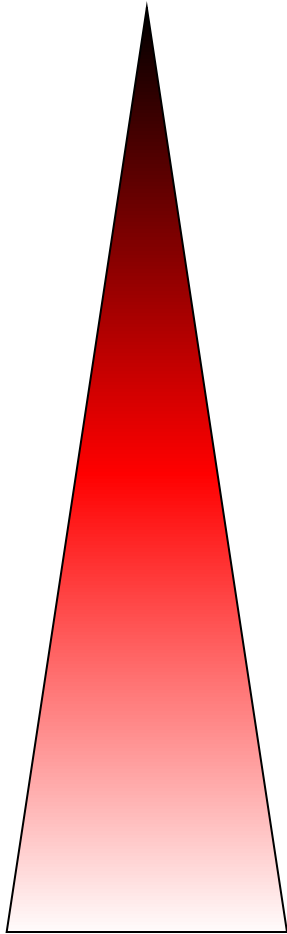


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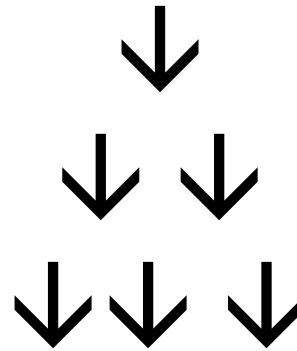


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Drug-associated  
Stimuli

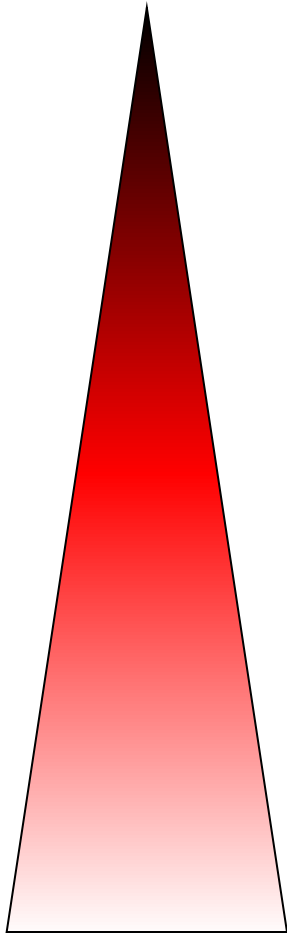


FR1

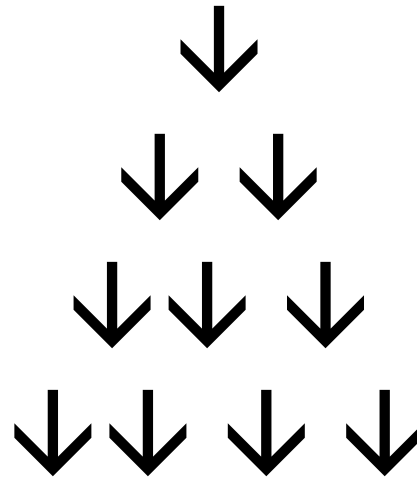


# Cocaine Self Administration in Rats

Drug-associated  
Stimuli

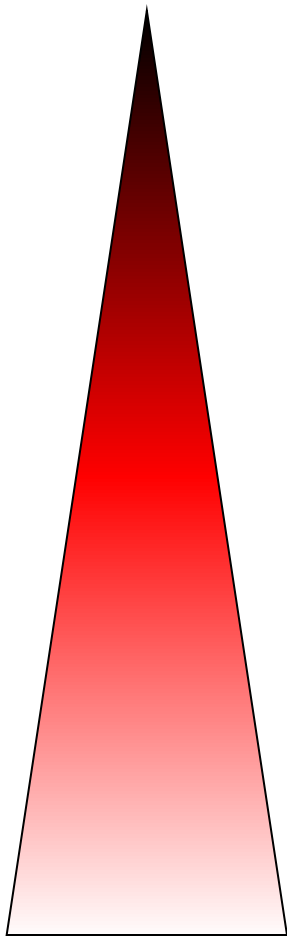


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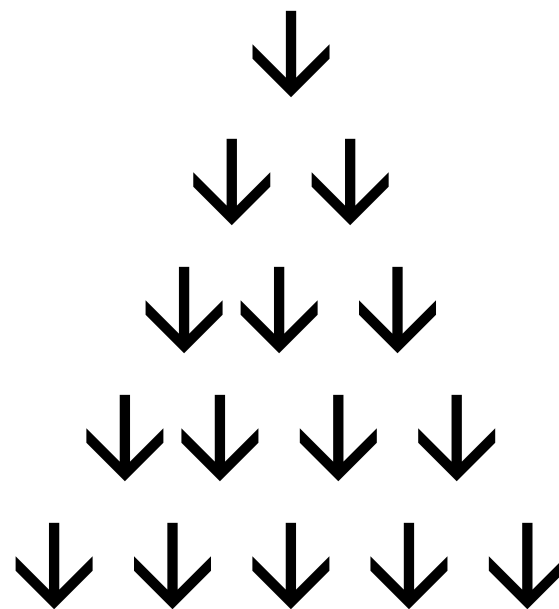


# Cocaine Self Administration in Rats

Drug-associated  
Stimuli

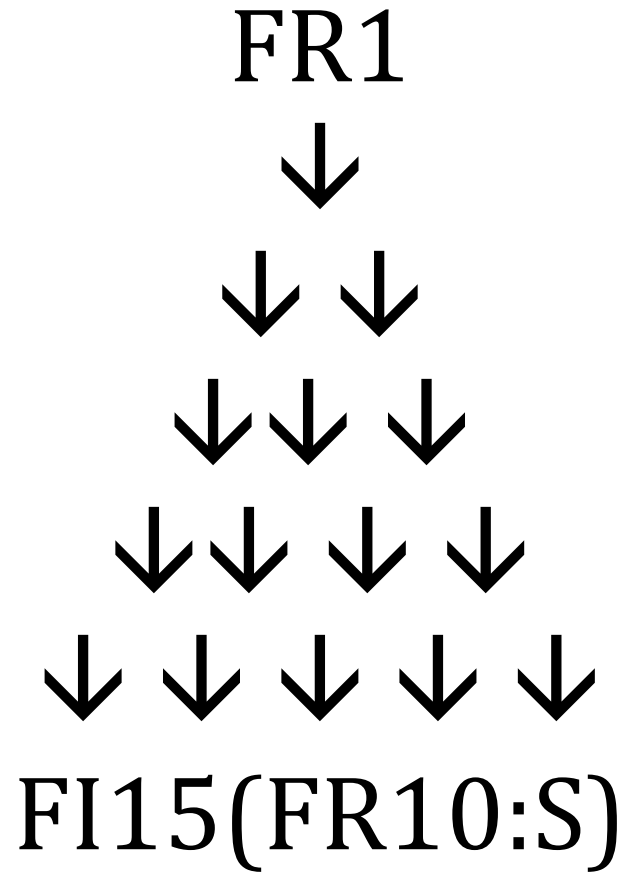
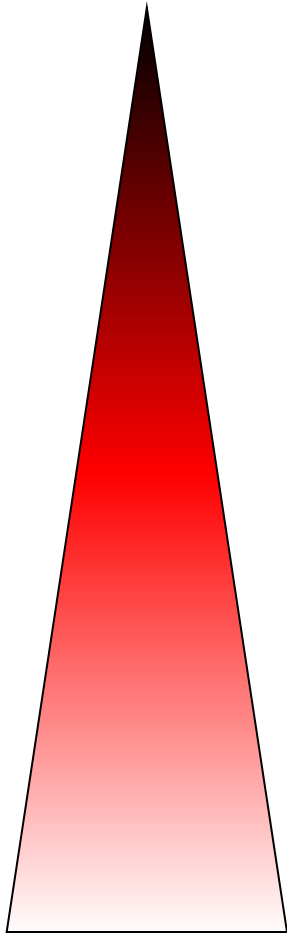


FR1

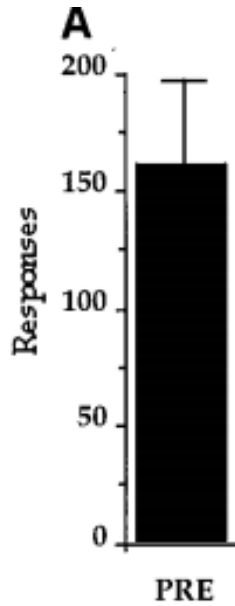
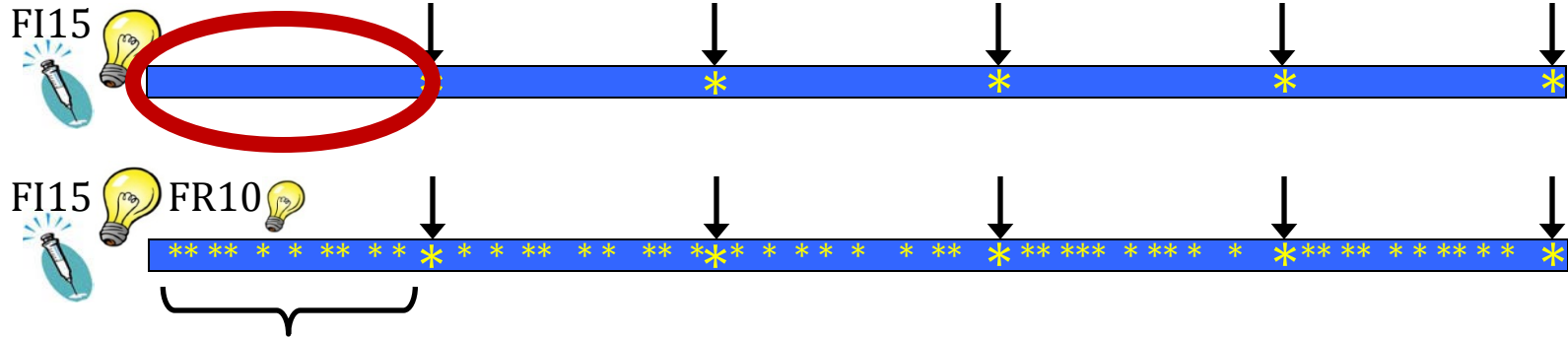


# Cocaine Self Administration in Rats

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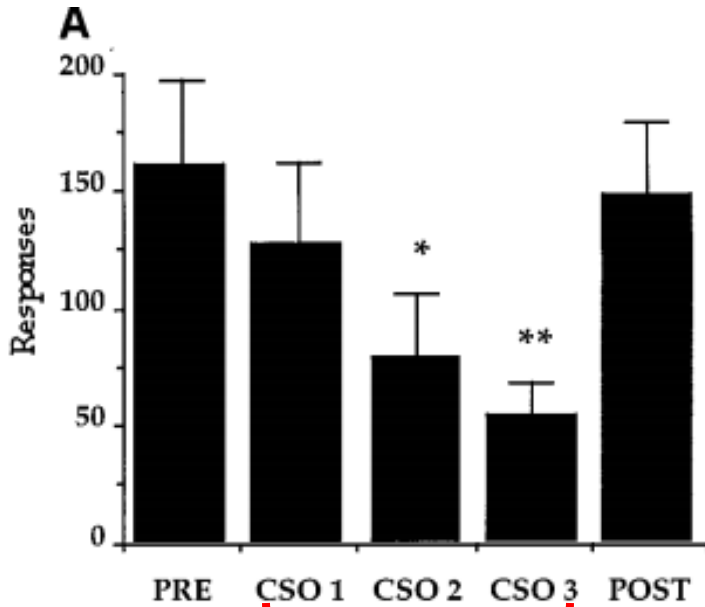
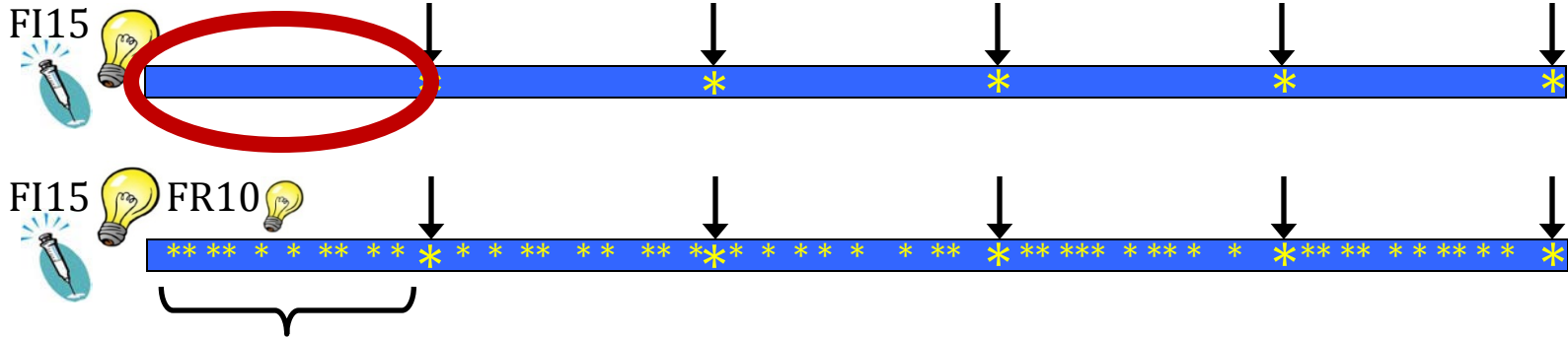


# Assignment of Incentive Salience



Arroyo et al, 1998,  
*Psychopharmacology*

# Assignment of Incentive Salience

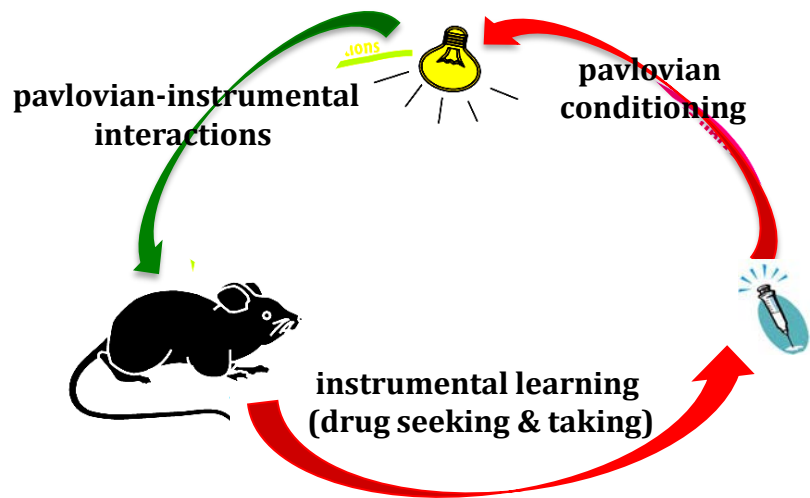


omission

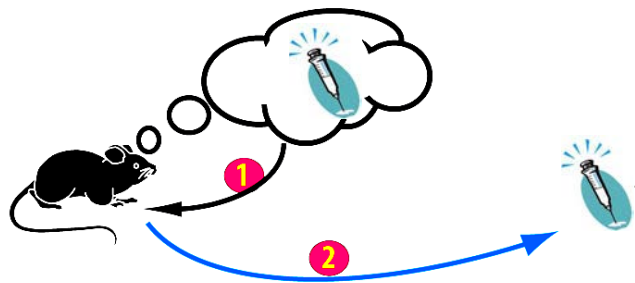
Arroyo et al, 1998,  
*Psychopharmacology*



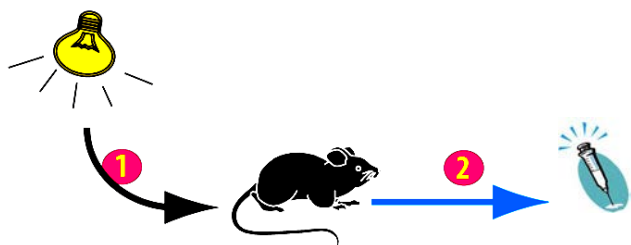
**A** Learning mechanisms involved in drug seeking and drug taking behaviour



**B** Drug seeking under Action-Outcome control



**C** Drug seeking under habitual or Stimulus-Response control

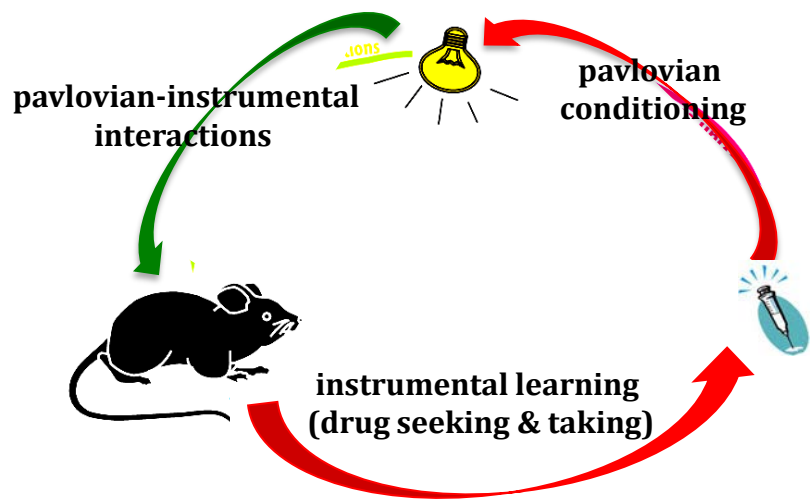


Belin et al. 2009

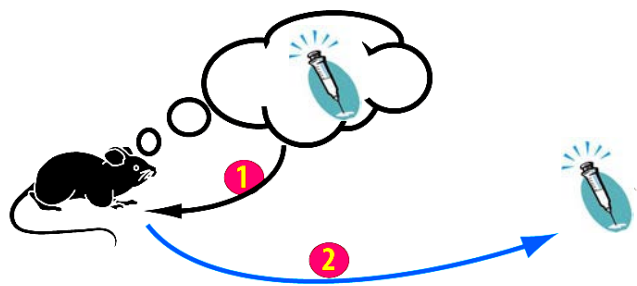




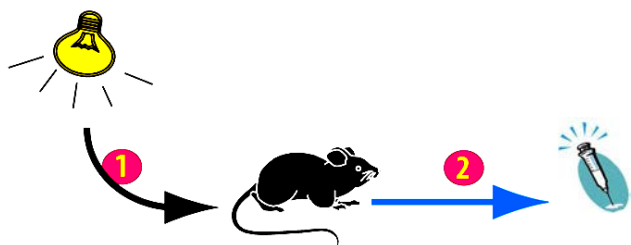
# A Learning mechanisms involved in drug seeking and drug taking behaviour



## B Drug seeking under Action-Outcome control



## C Drug seeking under habitual or Stimulus-Response control

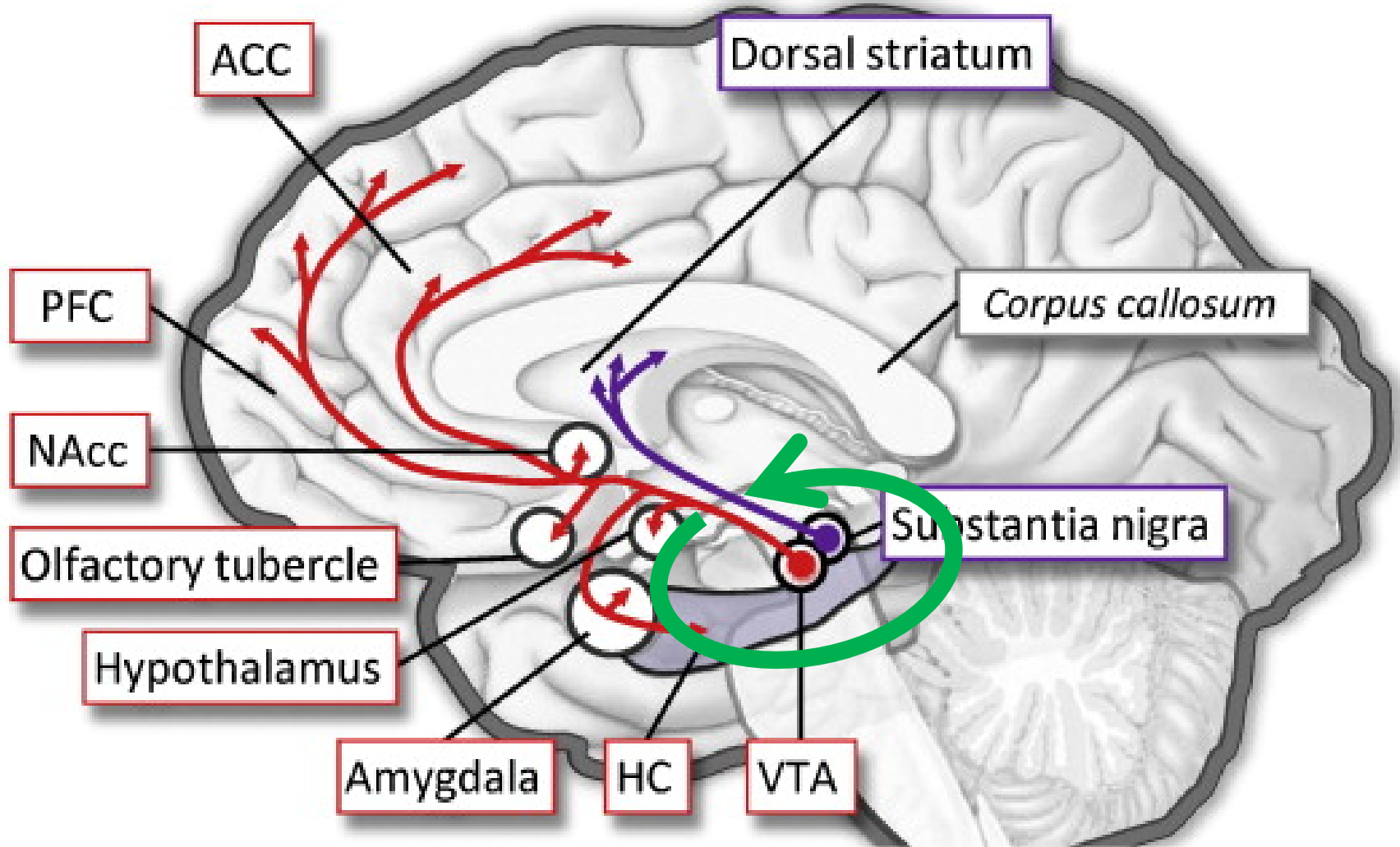


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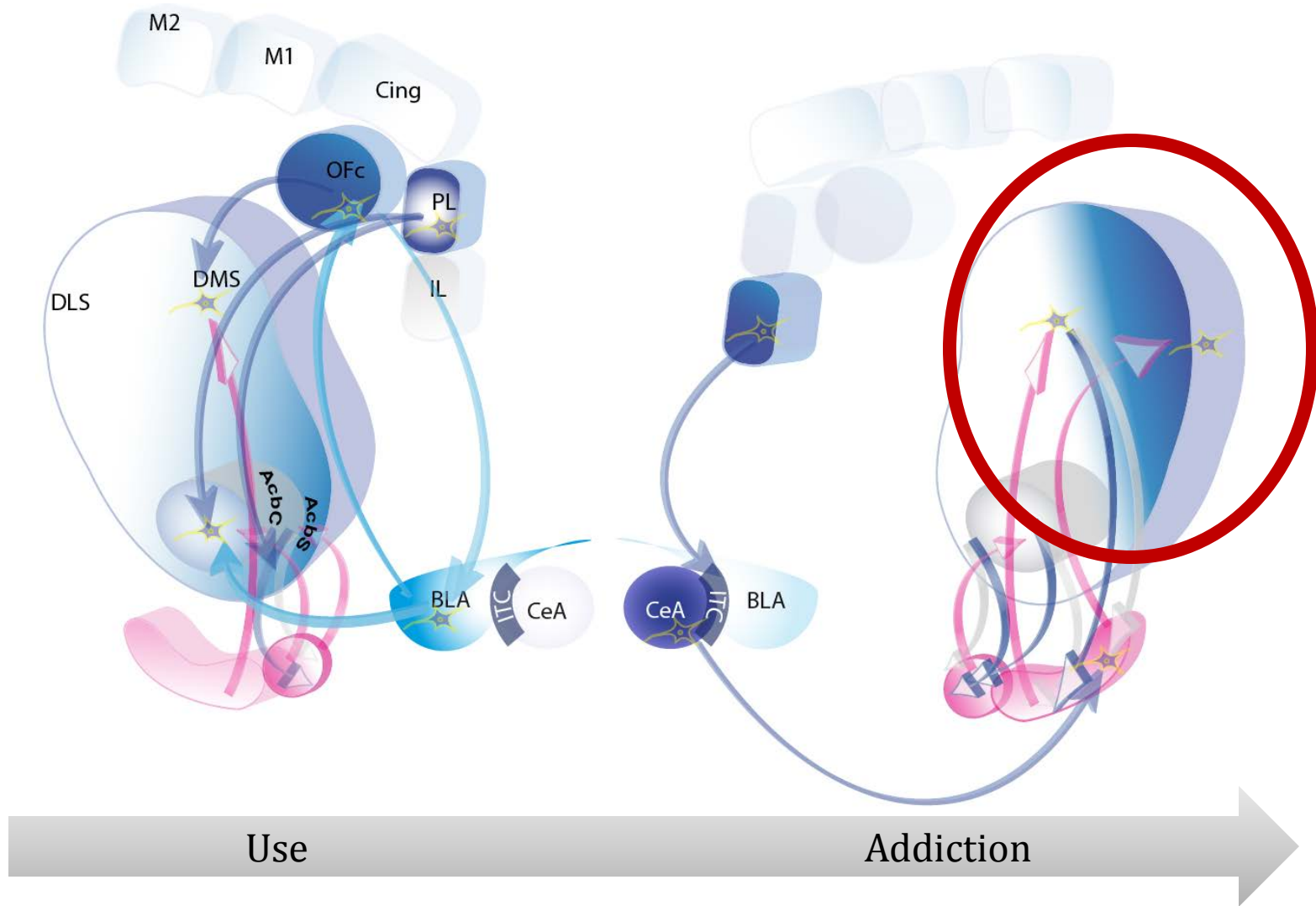
# The other dopamine pathway

Mesolimbic pathway

Nigrostriatal pathway

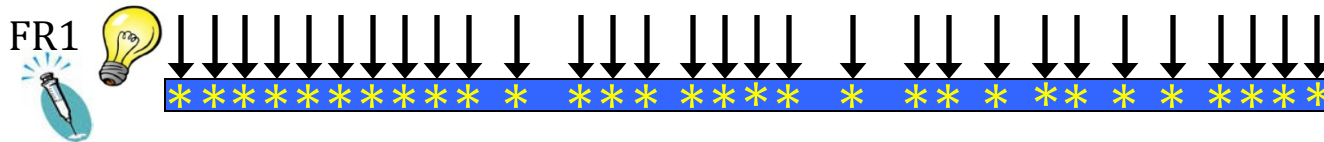


# Working neurological model

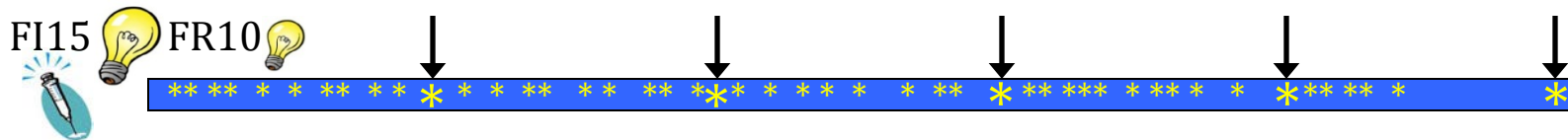


# Circuitry recruitment...

- Begin on FR1

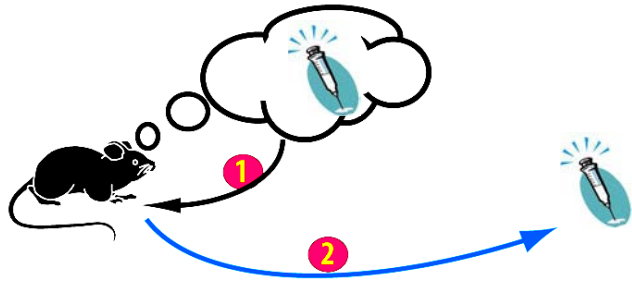


- Gradually move up to FI15(FR10:S)



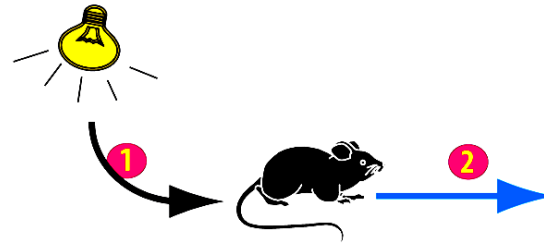
# Blocking DA receptors in the dorsal striatum during goal-directed and habitual cocaine seeking

## B Drug seeking under Action-Outcome control

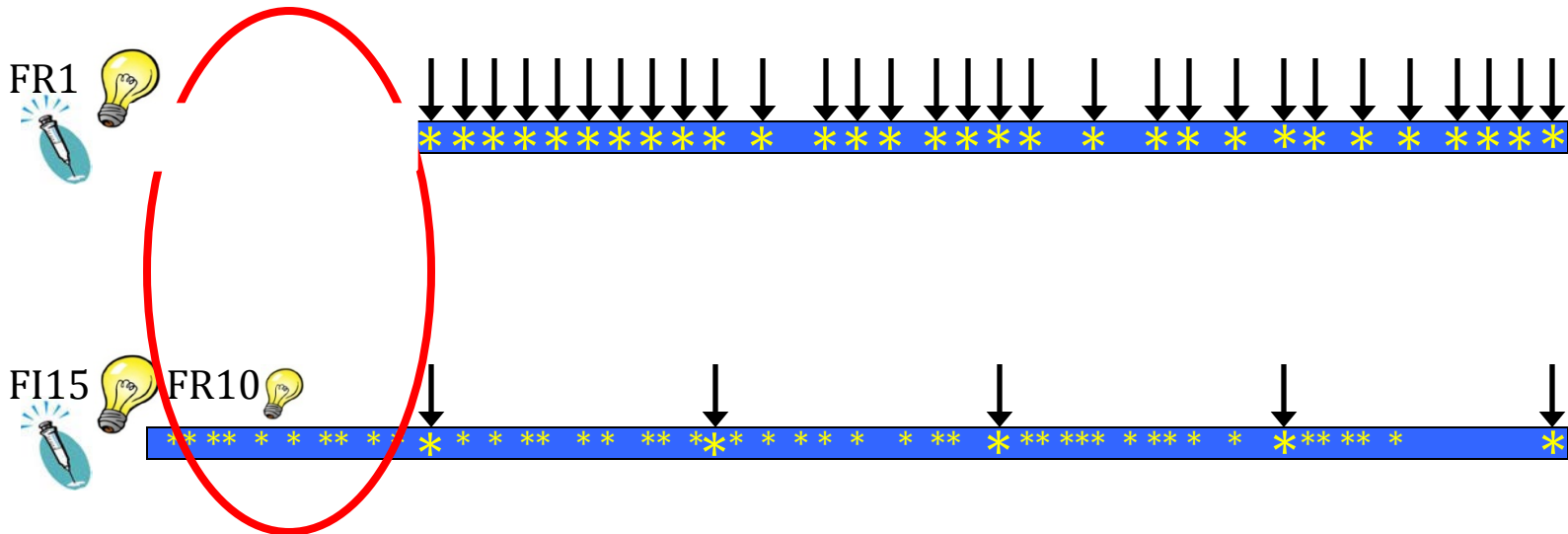


FR1

## C Drug seeking under habitual or Stimulus-Response control

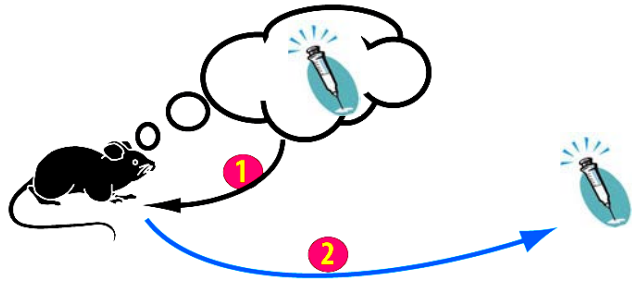


FI15(FR10:S)

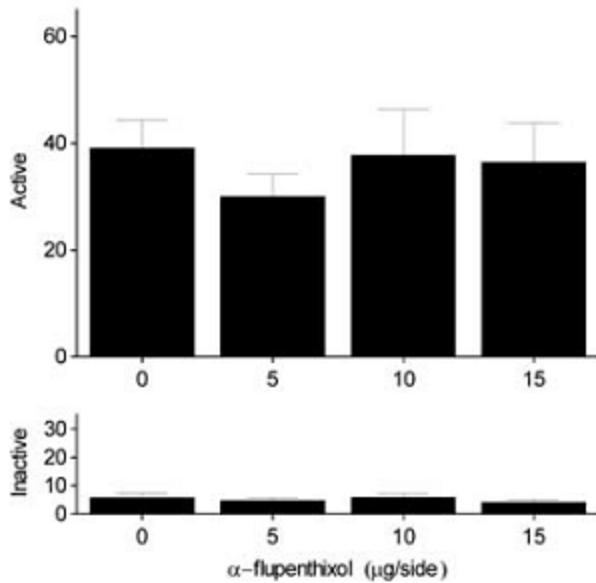


# Blocking DA receptors in the dorsal striatum during goal-directed and habitual cocaine seeking

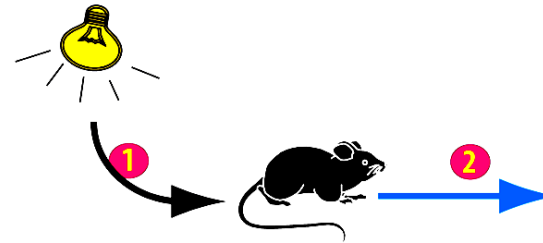
## B Drug seeking under Action-Outcome control



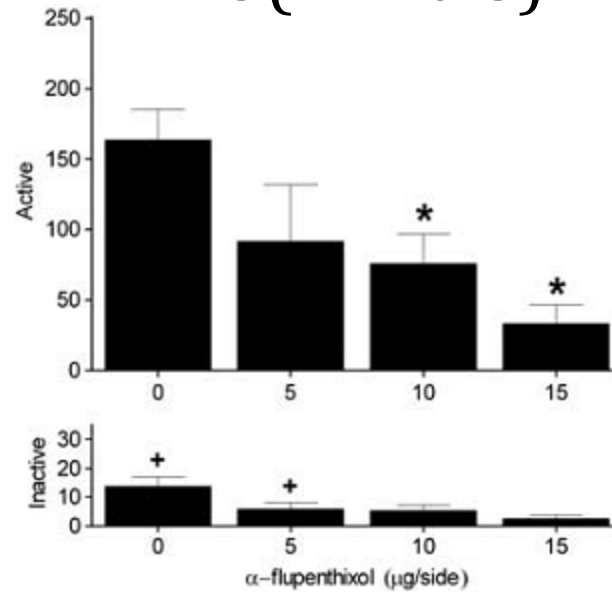
FR1



## C Drug seeking under habitual or Stimulus-Response control



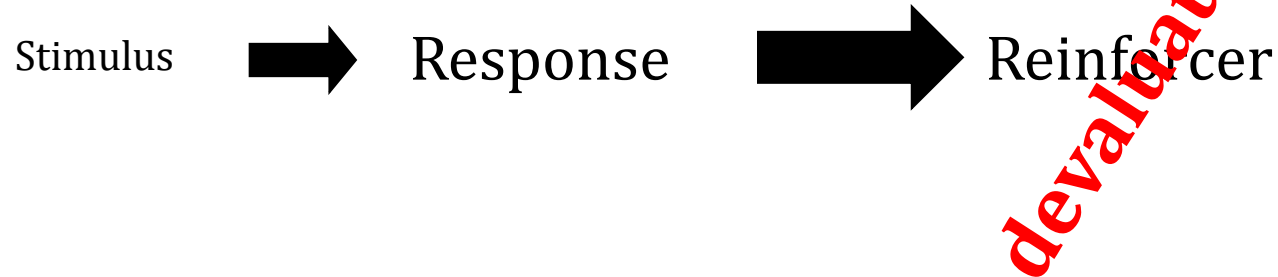
FI15(FR10:S)



# Instrumental learning in addiction

differential effects of reinforcer devaluation

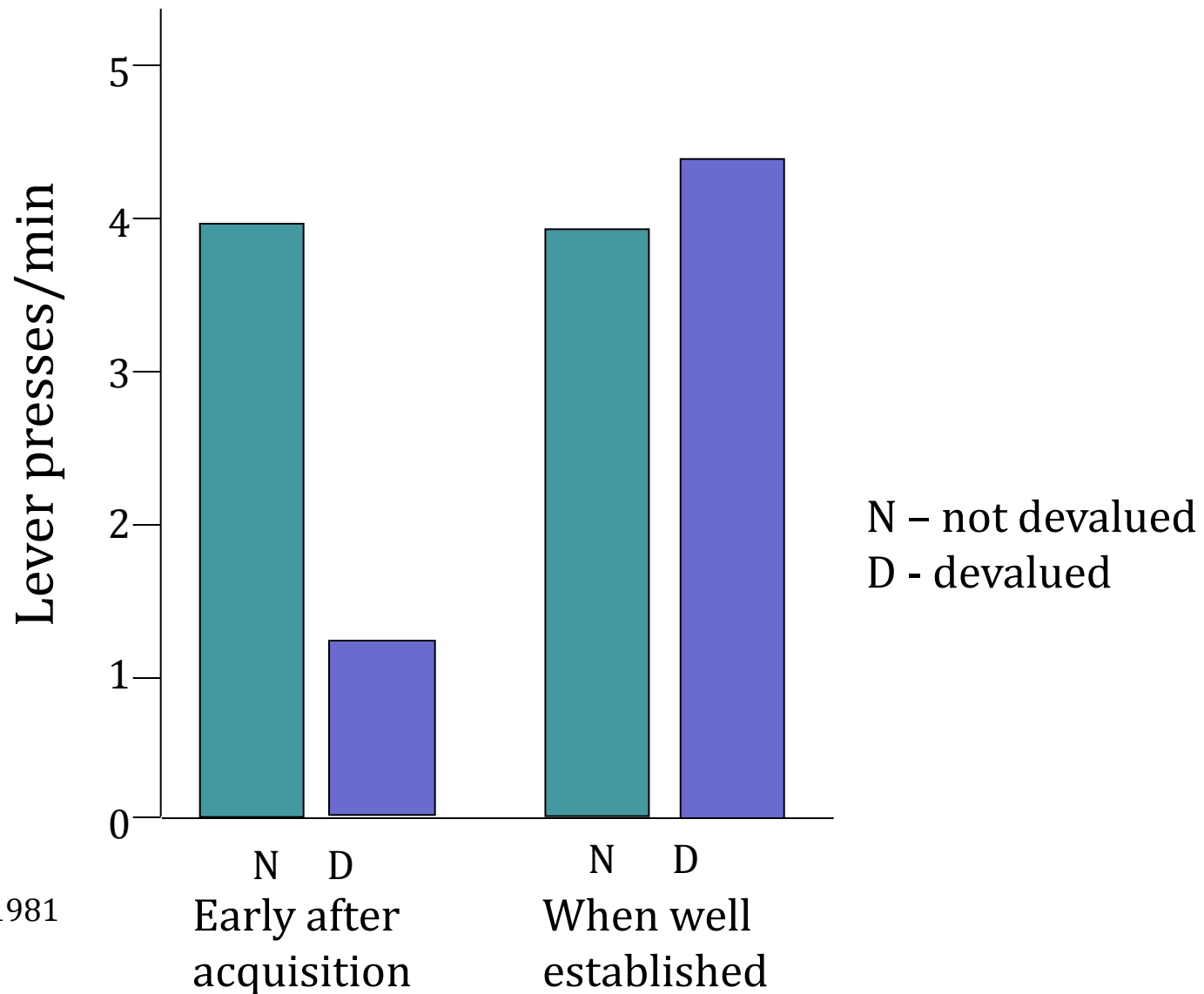
## 1. Action-Outcome: Goal-directed drug seeking and taking



## 2. Stimulus-Response: Habitual drug seeking and taking



# Prolonged training and the development of a S-R habit: resistance to reinforcer devaluation

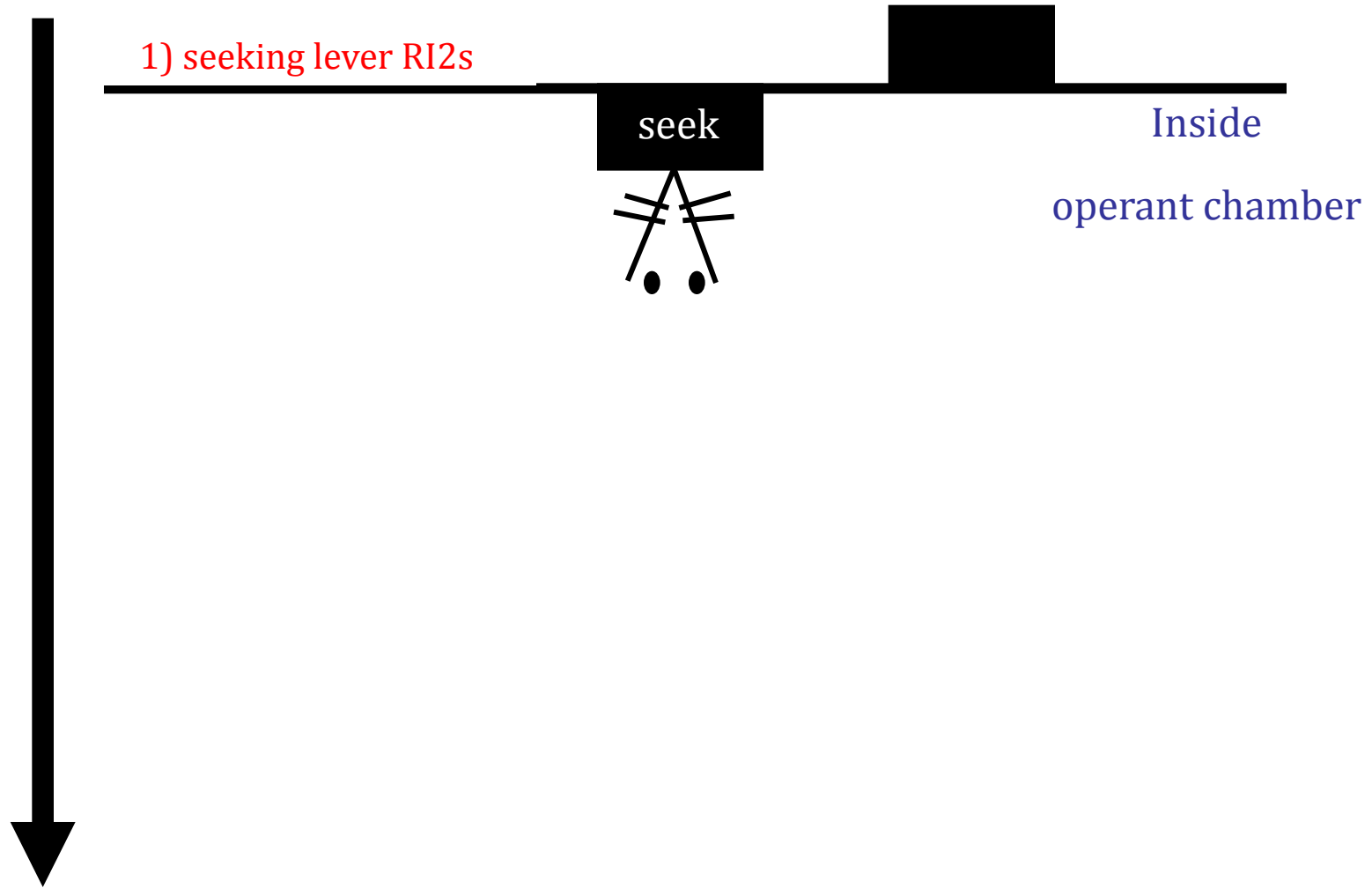


Adams & Dickinson 1981



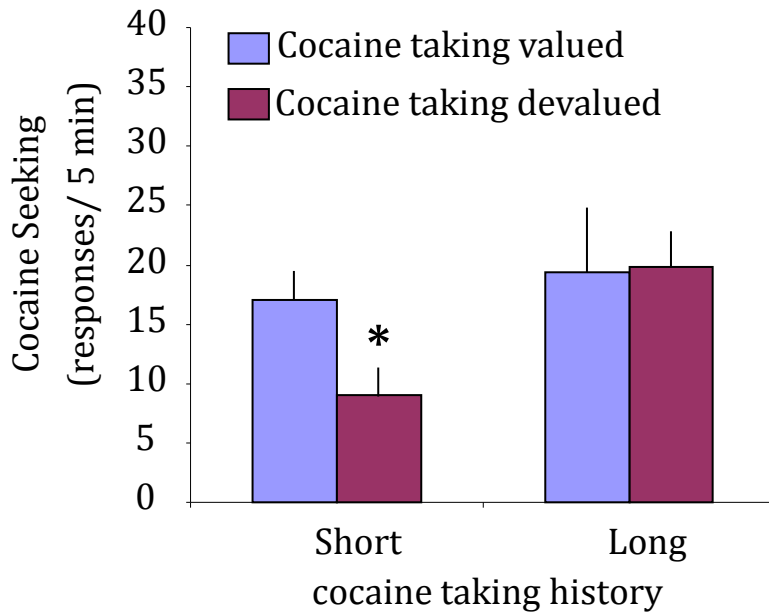


# Cocaine seeking-taking chained schedule

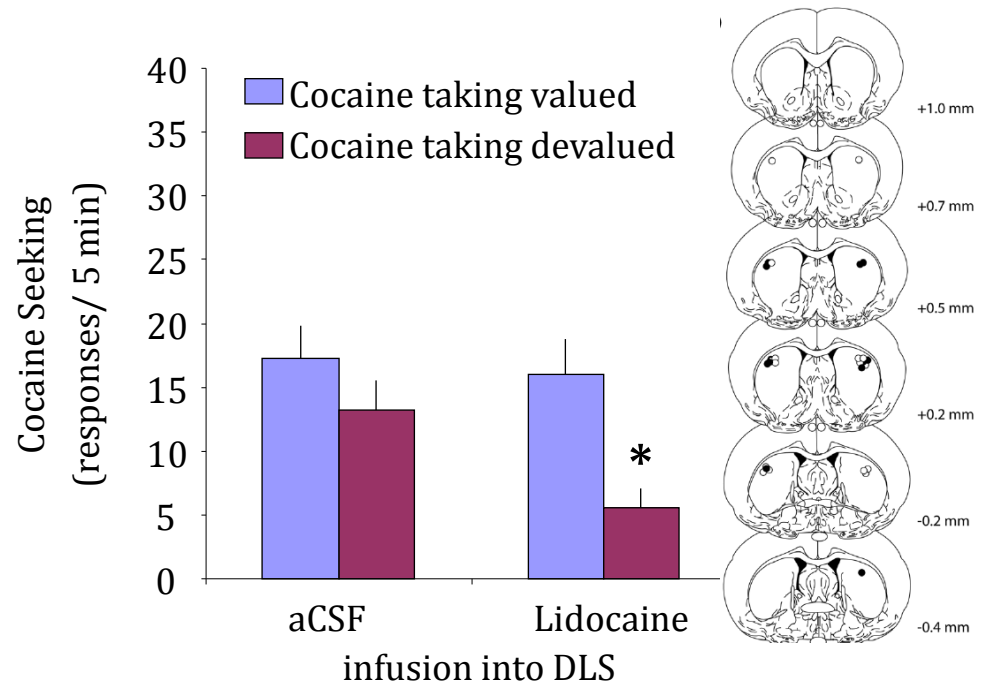


Zapata, Minney & Shippenberg, J. Neurosci 2010  
from: Olmstead, Lafond, Everitt & Dickinson 2001

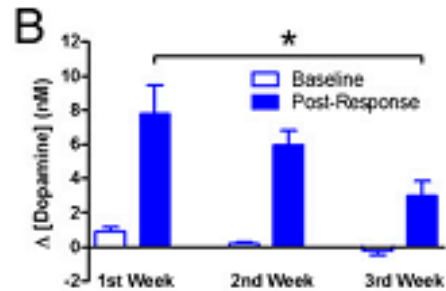
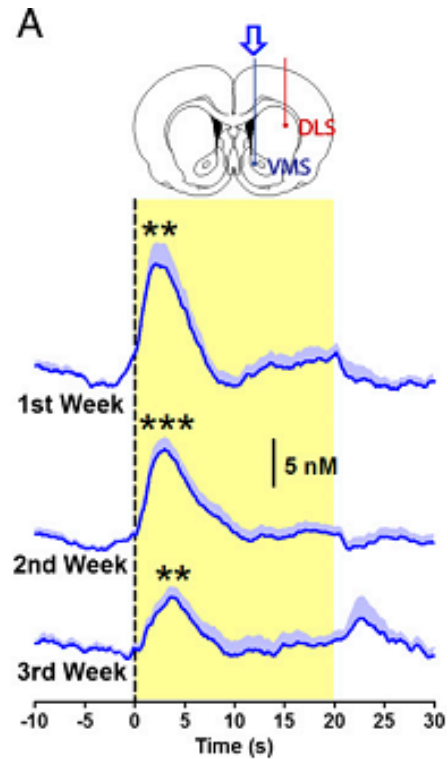
Cocaine seeking is resistant to reinforcer devaluation – habitual – after a long, but not brief, cocaine taking history



Inactivation of the dorsolateral striatum reinstates sensitivity to reinforcer devaluation – i.e. goal-directed

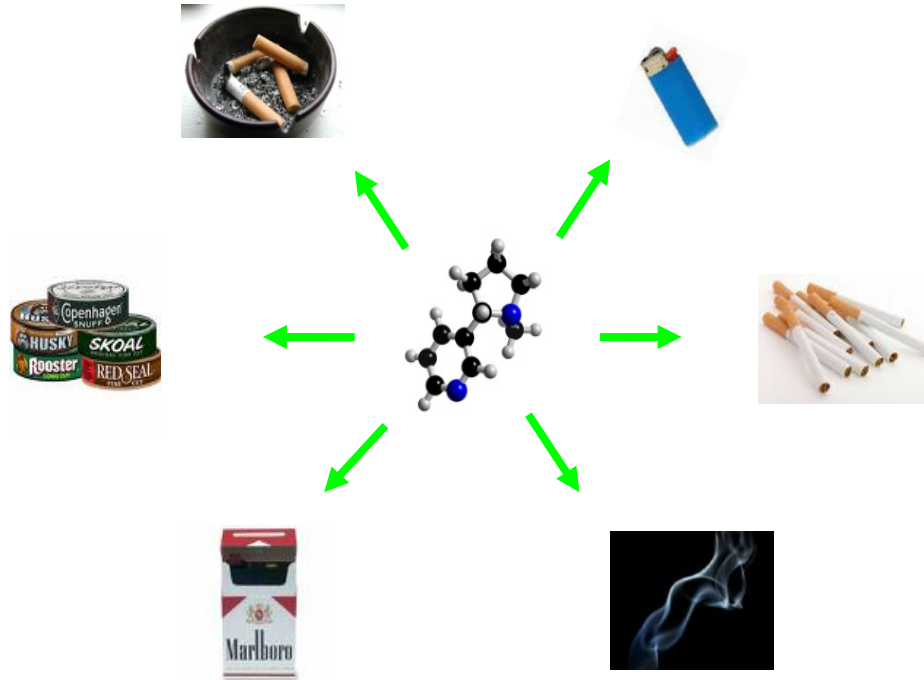


# Conditioned Stimuli – Conditioned Reinforcers



# Conditioned Stimuli – Conditioned Reinforcers

Drug-associated stimuli come to drive drug seeking and ultimately drug use.



# 'Needle Freaks'

“When you are new to injecting you start to sort of feel the hit as soon as the needle hits your skin even though it can not have possibly entered your blood stream or hit your brain, you do feel it and they call that needle buzzing. It is so strong; it is like the buzz itself before it actually hits you.”

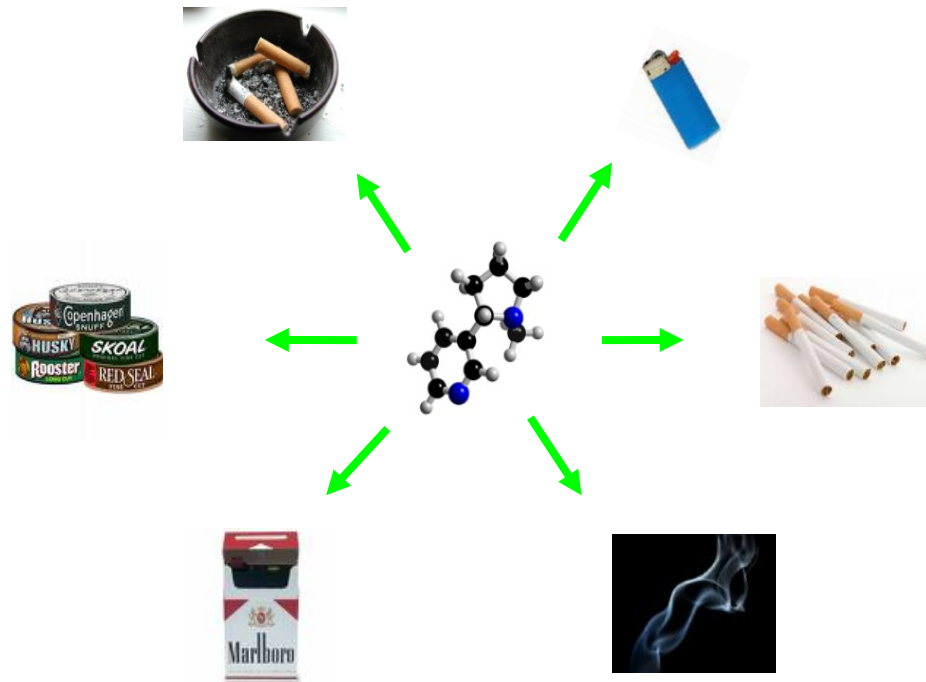
-Male, 41 years old, amphetamine injector, 7 years injecting



McBride et al, 2001, *Addiction*

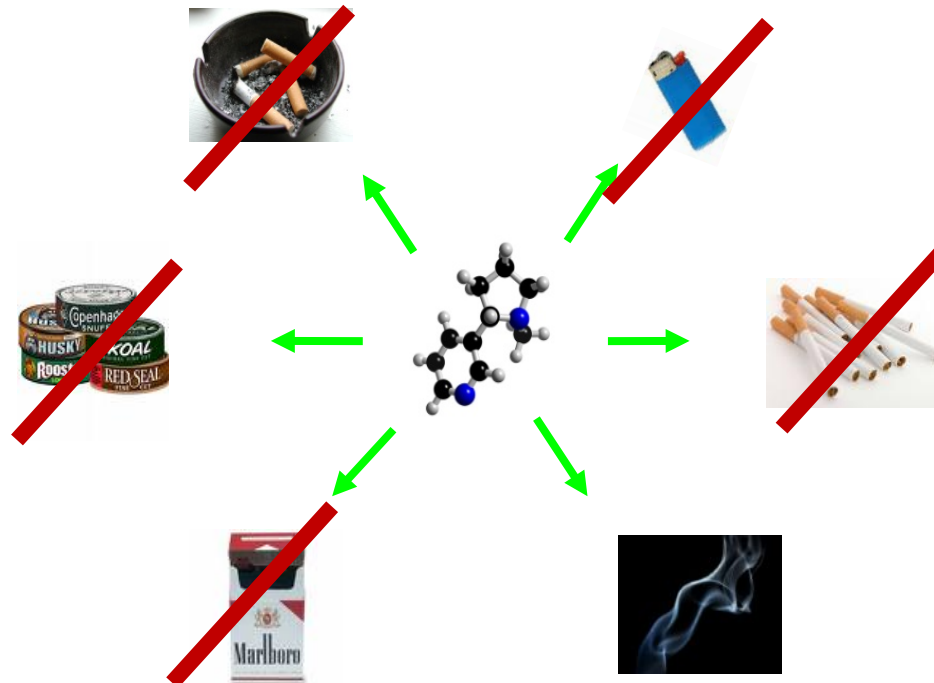
# Cue-exposure therapy

- Exploits association between interoceptive unconditioned/rewarding drug effects and exteroceptive stimuli that have been associated with those effects.



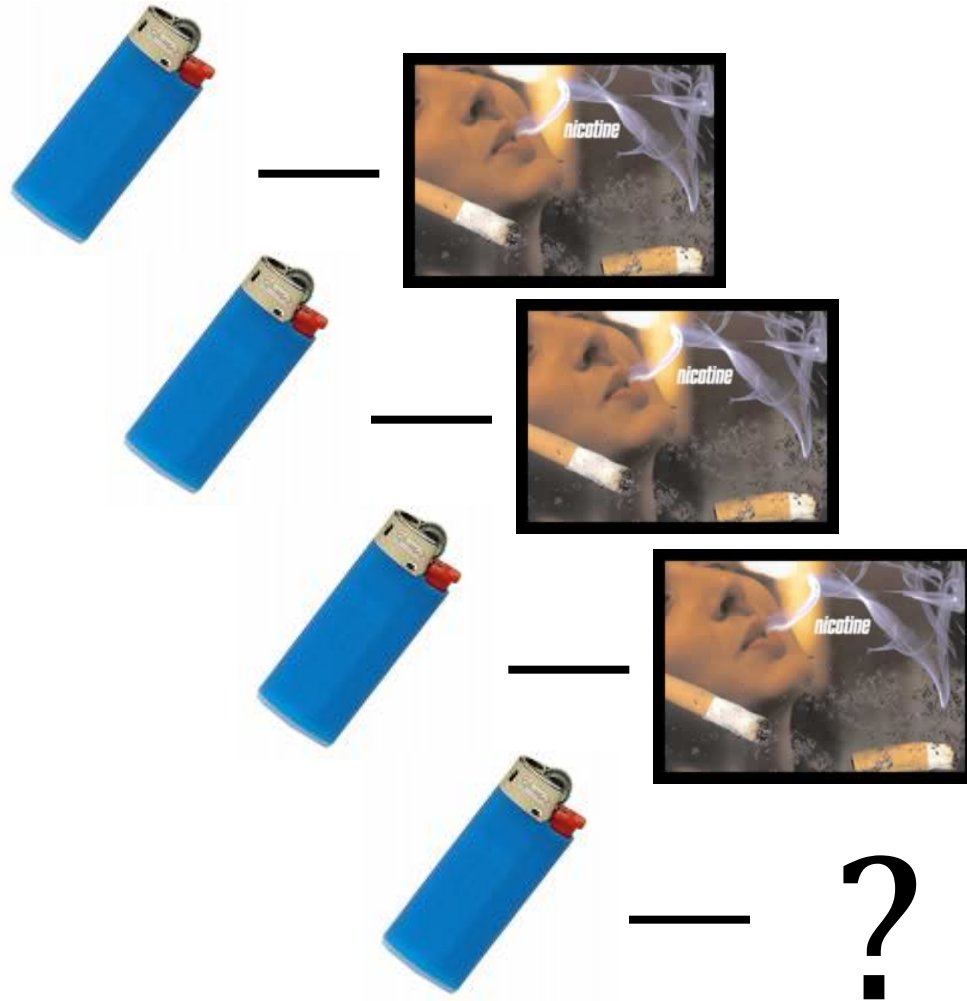
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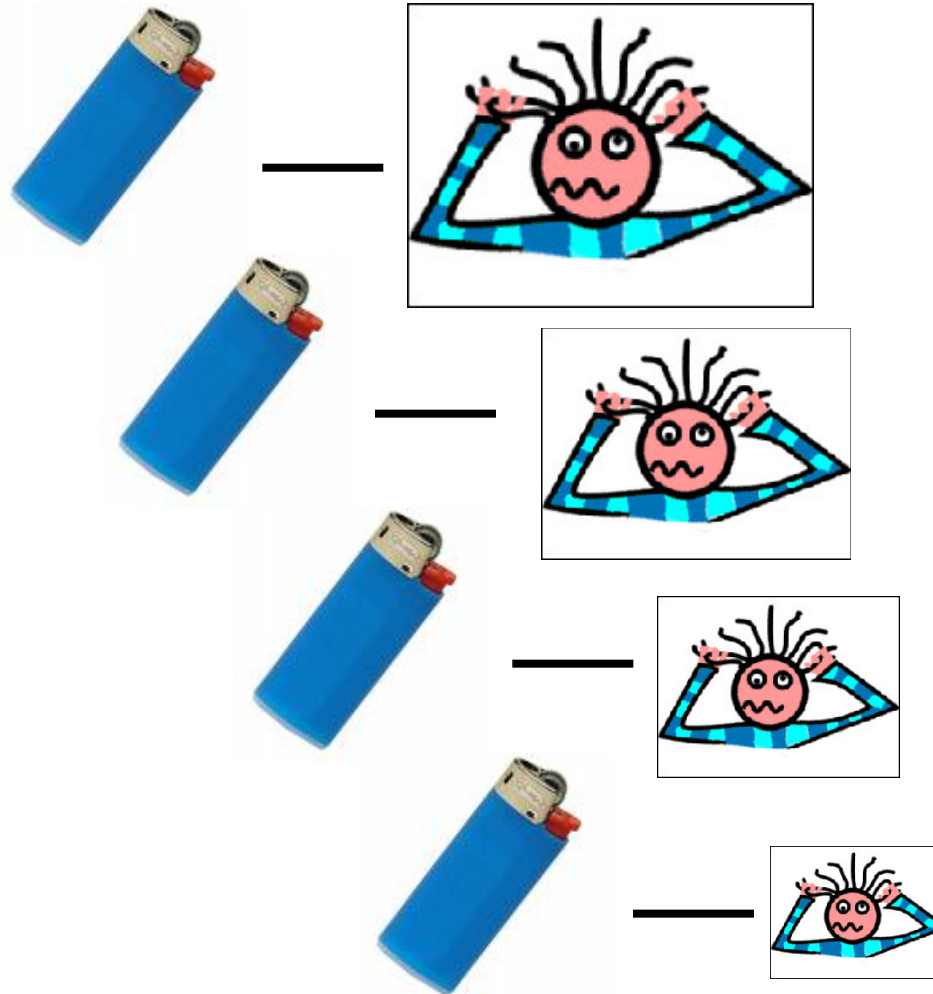
Extinguish stimuli associated with the unconditioned/rewarding/reinforcing effects of drug

# Urge to use

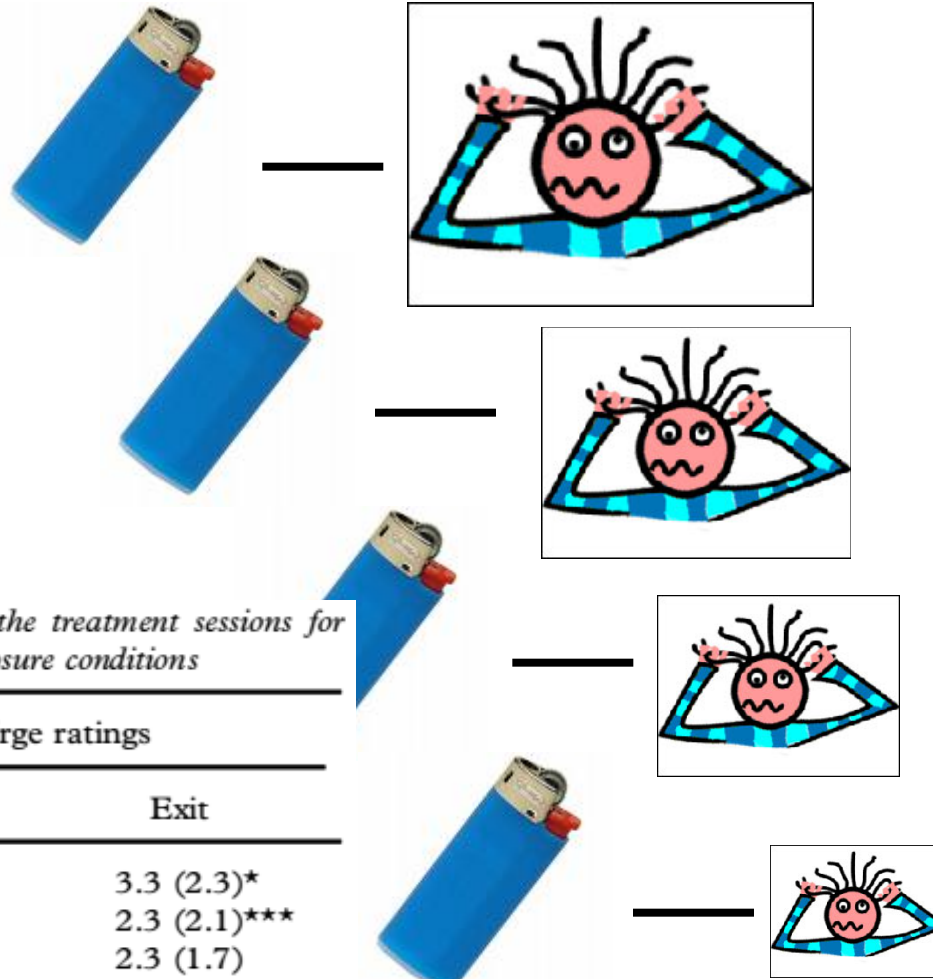




# Extinction



# Extinction

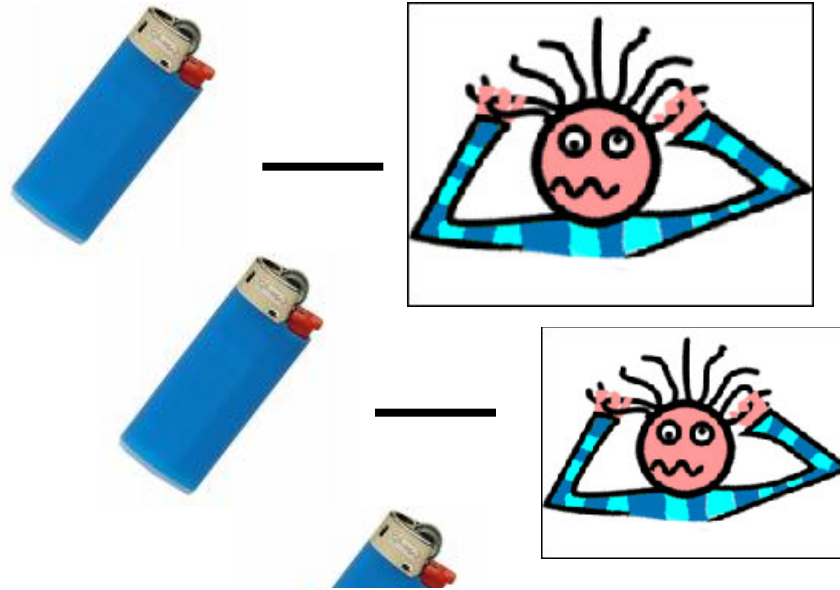


**Table 1.** Urge changes during the treatment sessions for subjects in the cue exposure conditions


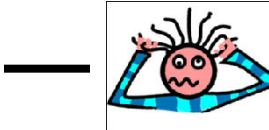
	Urge ratings	
	Enter	Exit
Session 1	4.0 (3.0)	3.3 (2.3)*
Session 2	4.1 (3.3)	2.3 (2.1)***
Session 3	2.7 (2.5)	2.3 (1.7)
Session 4	2.3 (2.3)	1.7 (1.4)
Session 5	3.4 (3.1)	2.6 (1.9)

\* $p < 0.10$ ; \*\*\* $p < 0.001$ .

# Extinction



## Treatment condition

	Brief cognitive-behavioral	Cognitive-behavioral and nicotine gum	Cognitive-behavioral and cue exposure	
1 month	34.4% (11/32)	48.6% (17/35)	32.3% (10/31)	
3 months	34.4% (11/32)	34.3% (12/35)	19.4% (6/31)	
6 months	25.0% (8/32)	20.0% (7/35)	16.1% (5/31)	
12 months	12.5% (4/32)	14.3% (5/35)	12.9% (4/31)	

# Cue-exposure therapy

**Table 1**  
**Treatment Effects of Controlled Trials of Cue Exposure Treatment for Alcohol, Tobacco, and Opiate Dependence as Reported by Conklin and Tiffany (2002)**

Study	Drug	Effect size	Magnitude	Treatment effect	Modality
Drummond and Glautier (1994)	Alcohol	+0.17 to 0.30	Small	Favorable	Inpatient
Monti et al. (2001)	Alcohol	+0.5420	Medium	Favorable	Inpatient
Sitharthan et al. (1997)	Alcohol	+0.6070	Medium	Favorable	Outpatient
Monti et al. (1993)	Alcohol	+0.7345	Large	Favorable	Inpatient
Raw and Russell (1980)	Tobacco	-0.0251	-	-	Outpatient
Niaura et al. (1999)	Tobacco	-0.2029	Medium	Unfavorable	Outpatient
Corty and McFall (1984)	Tobacco	-0.4500	Medium	Unfavorable	Outpatient
Lowe et al. (1980)	Tobacco	-0.5180	Large	Unfavorable	Outpatient
Dawe et al. (1993)	Heroin	+0.0805	-	-	Inpatient

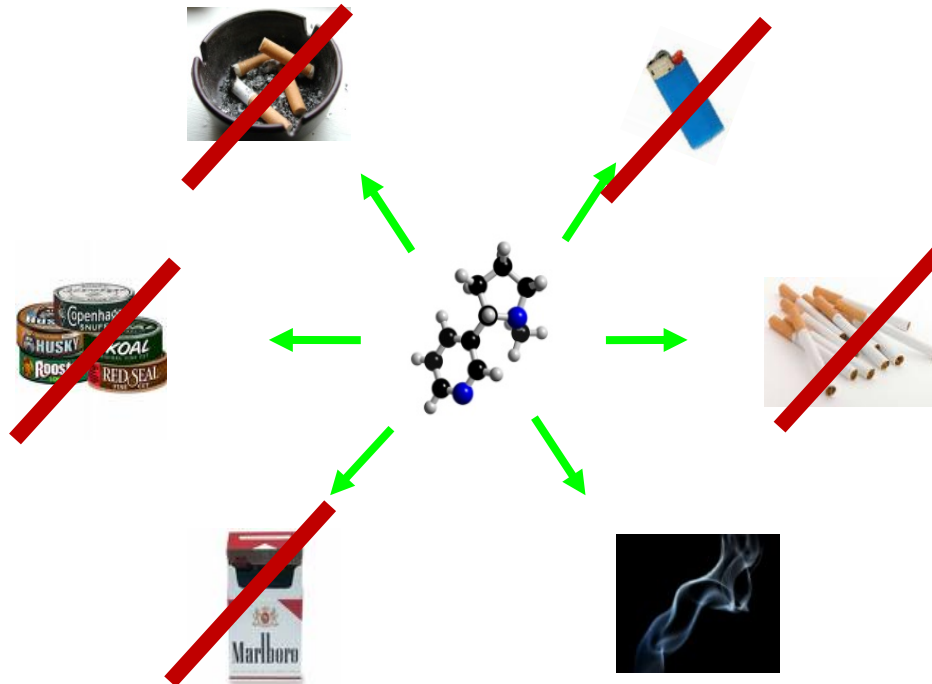
*Notes:* Magnitude designations are based on Cohen (1988): small =  $\sim 0.20$ , medium =  $\sim 0.5$ , large =  $\sim 0.8$ . Favorable or unfavorable designations are based on the effect size valence: positive effect sizes reflect favorable CET outcomes and negative effect sizes reflect unfavorable CET outcomes. Effect sizes smaller than 0.10 were considered ambiguously close to zero and were not designated with a magnitude or as being favorable or unfavorable.

# 'Threats to extinction'

- Renewal – context specific
- Reinstatement – cue/drug/stress
- Spontaneous recovery – time as context

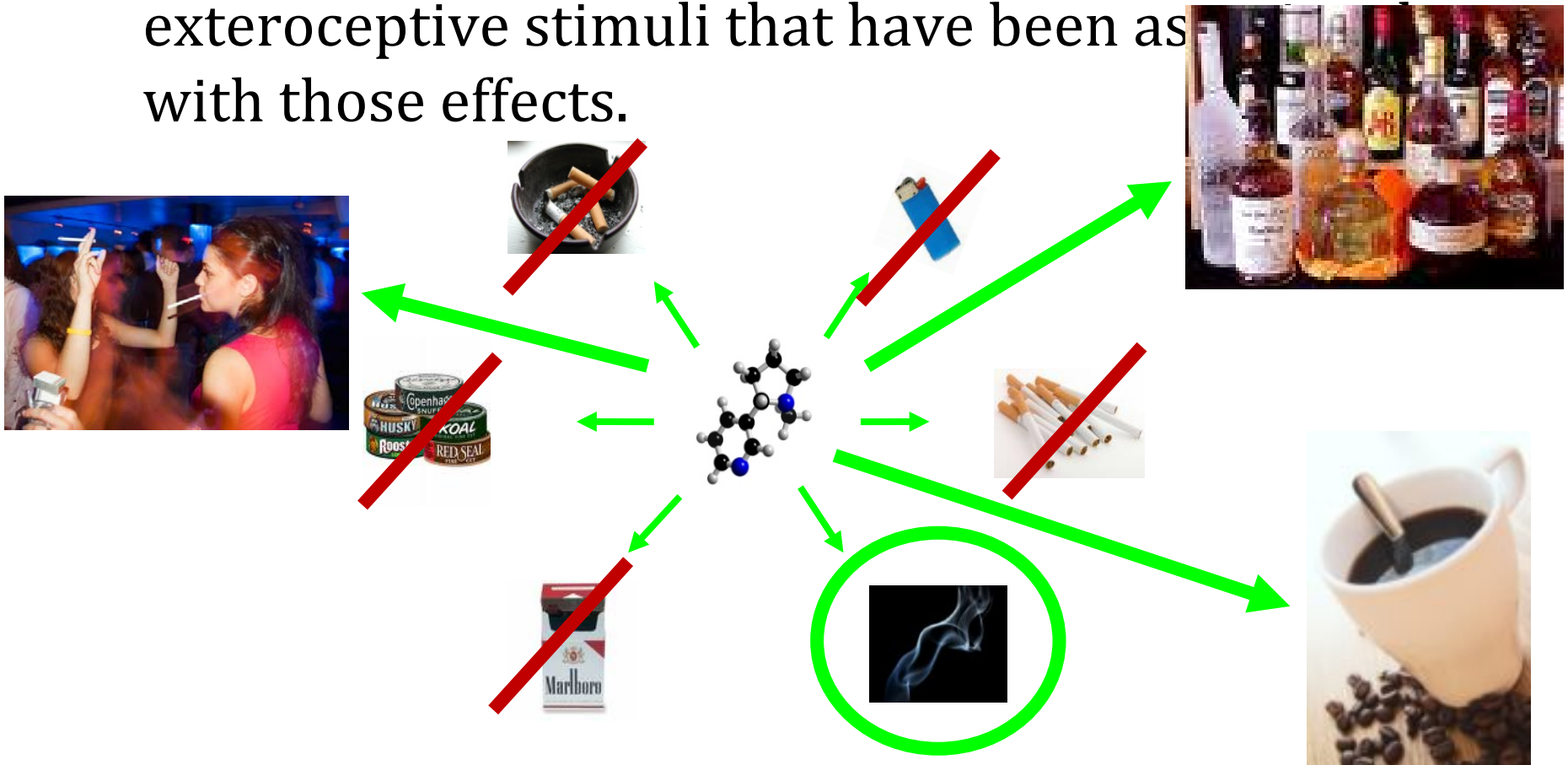
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# Cue-exposure therapy

- Exploits association between interoceptive unconditioned/rewarding drug effects and exteroceptive stimuli that have been associated with those effects.



Drug is more than reward or reinforcer





# Drug states as stimuli



# Drug states as stimuli



# Drug states as stimuli



# Drug states as stimuli



Drug can serve as an interoceptive CS

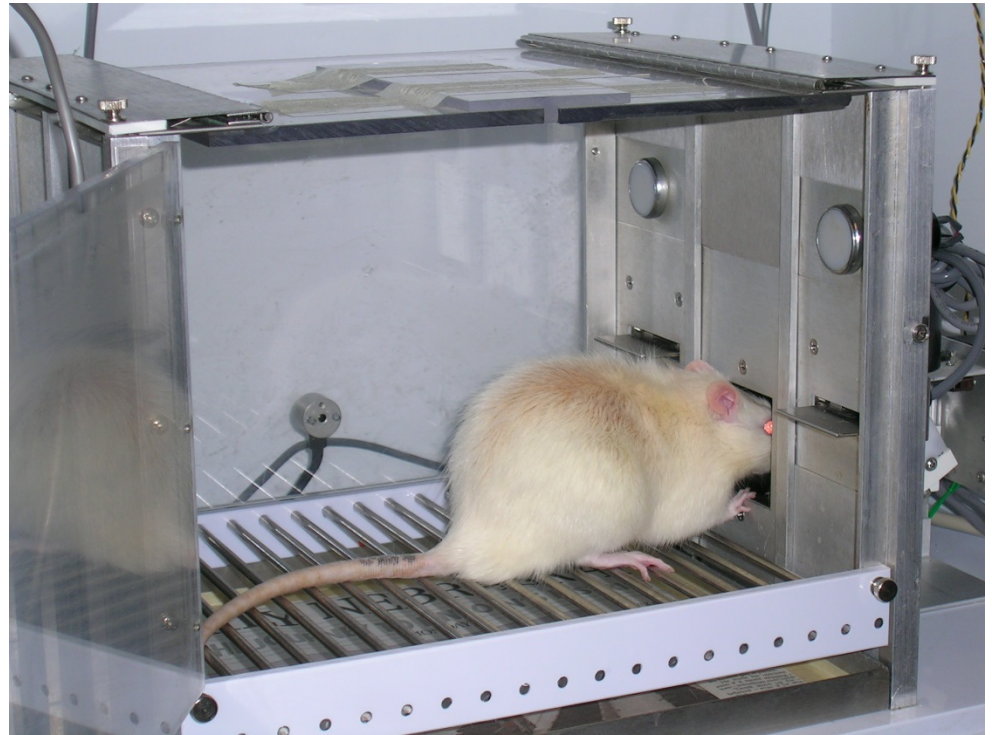
# Pavlovian Drug Discrimination



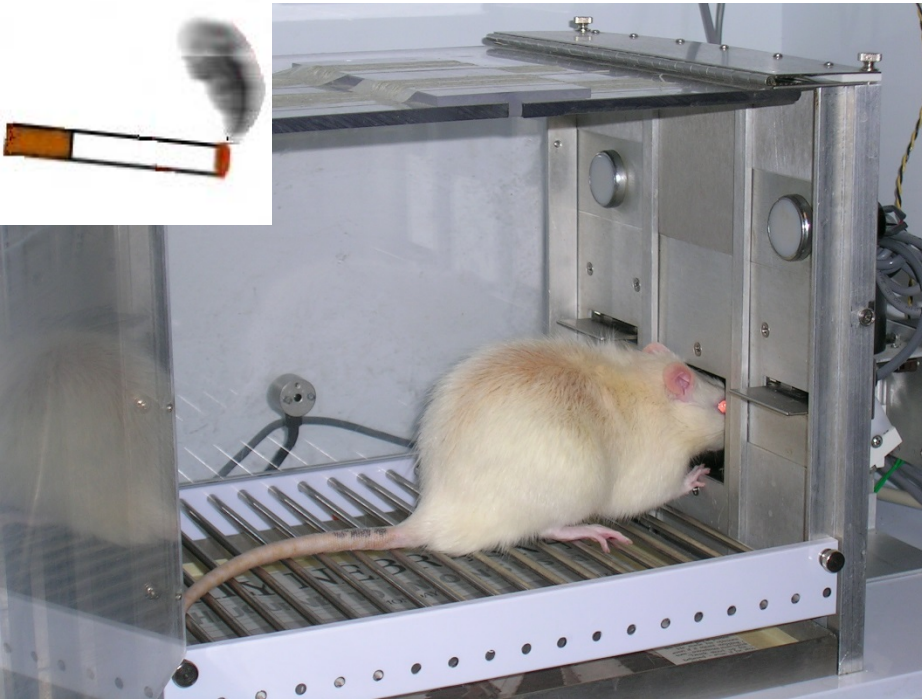
Nicotine  
or



Saline



# Measure



36x

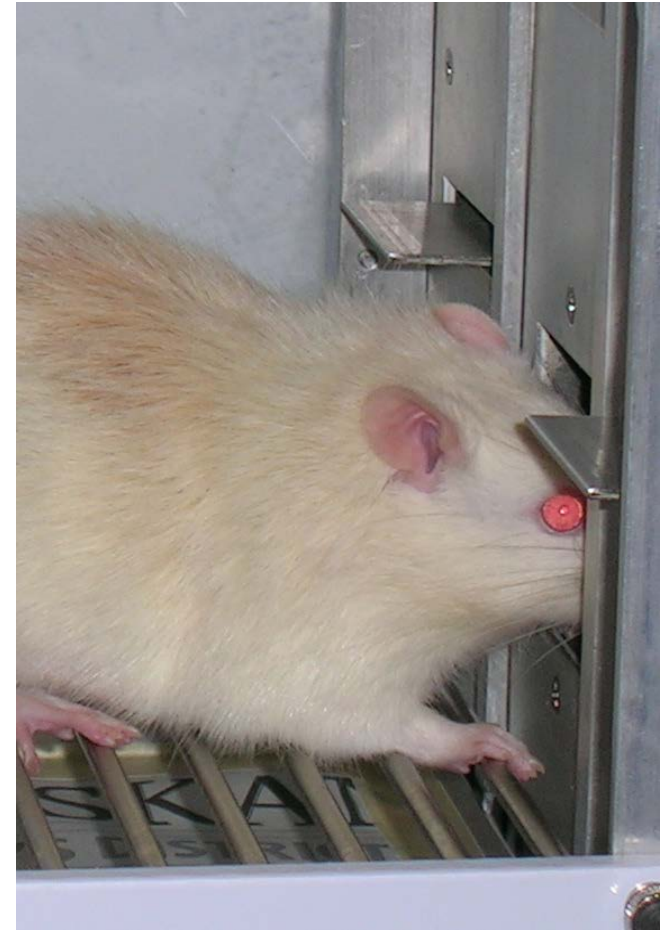
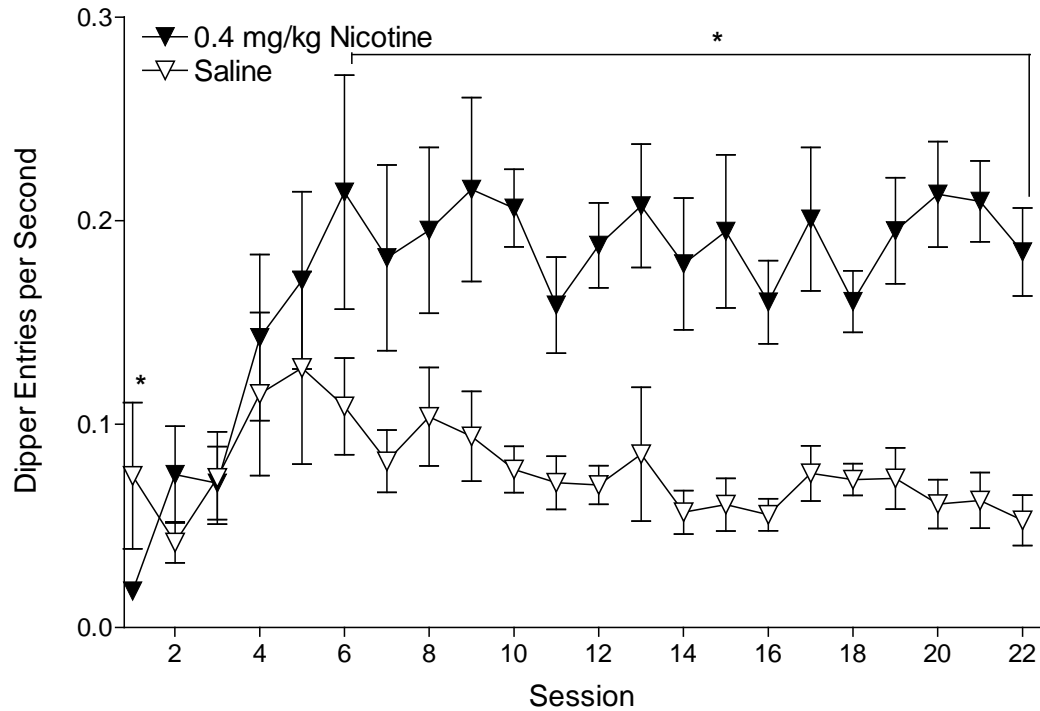


0x



20 min

# Pavlovian Drug Discrimination





# Nicotine Conditioned Stimulus



# Drug can act like an exteroceptive CS

- Cue competition - Overshadowing

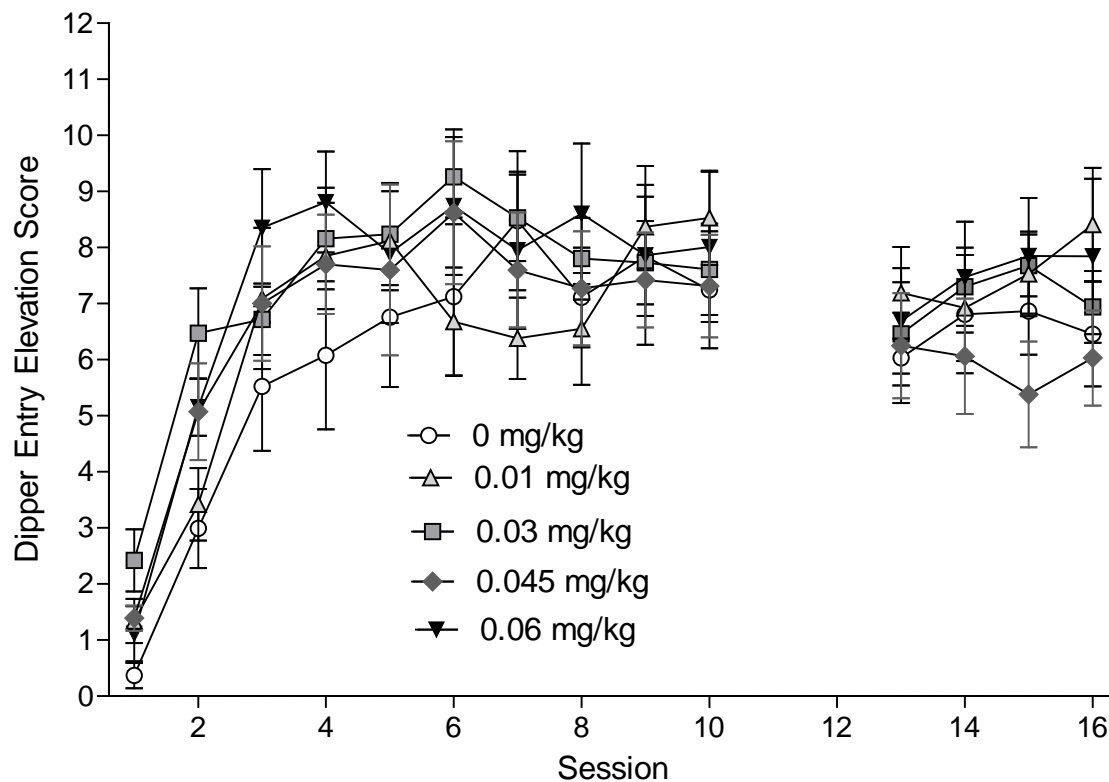
Train Together



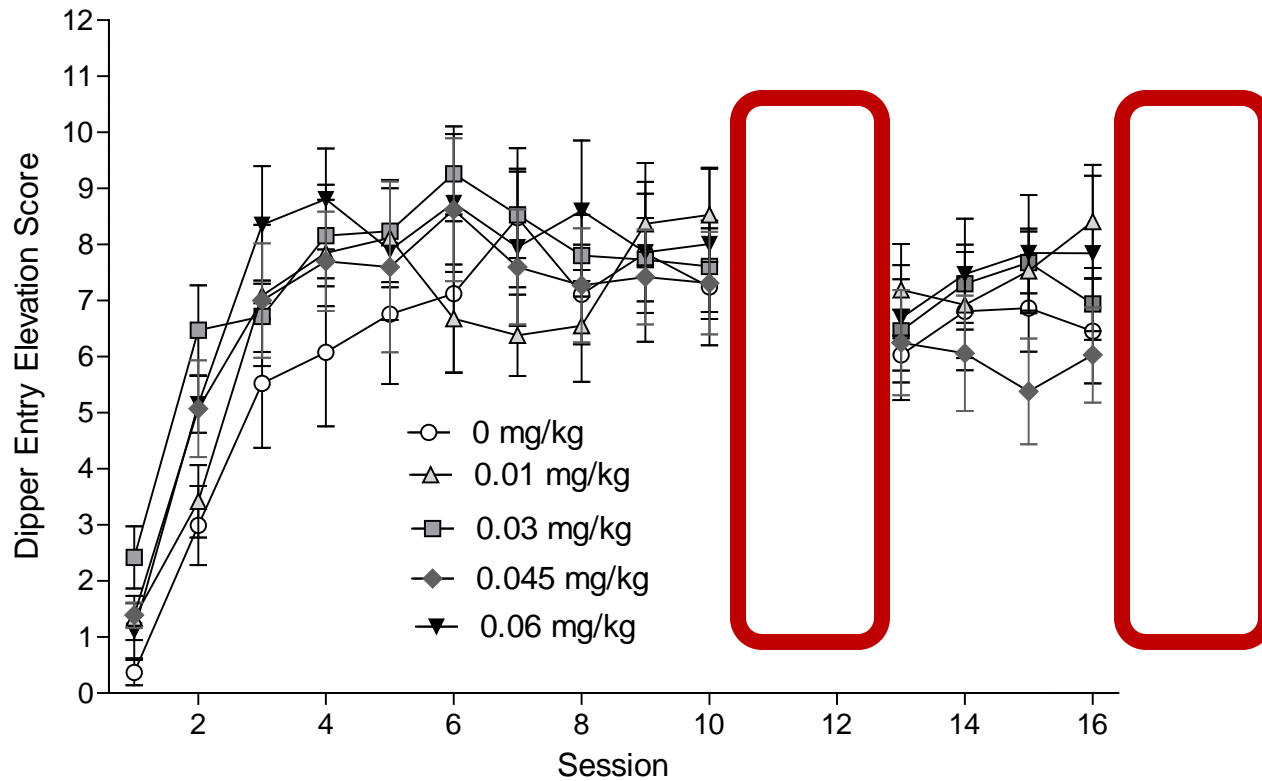
Test Separately



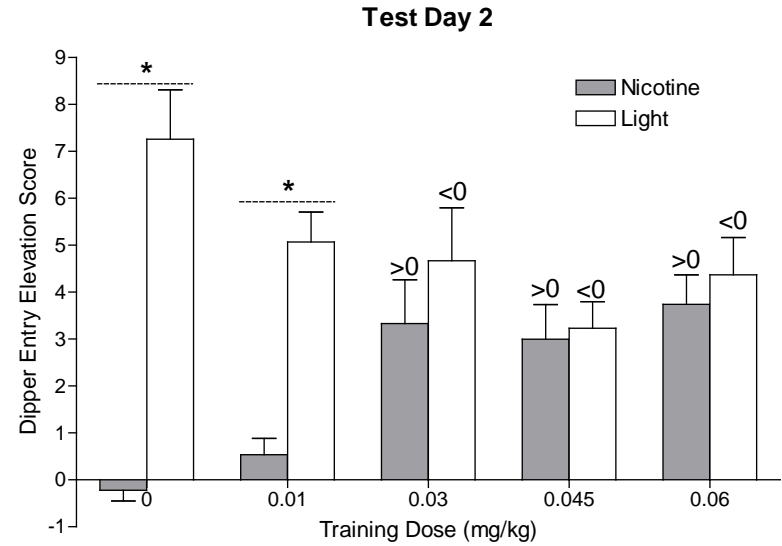
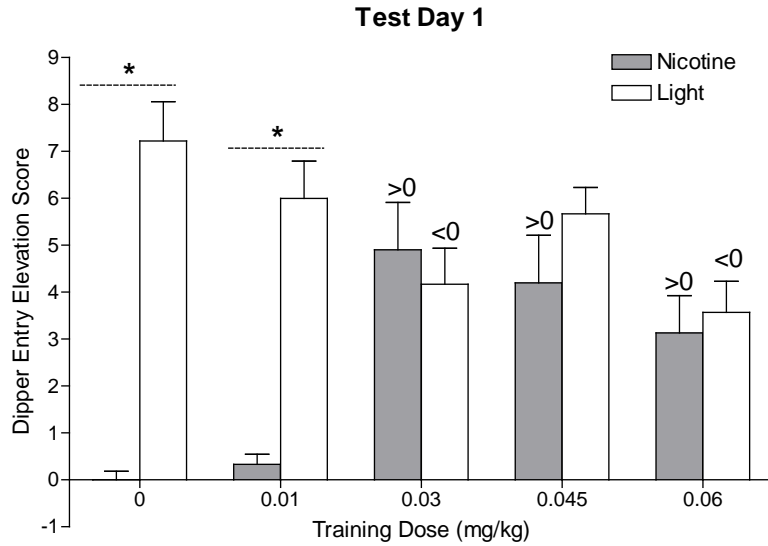
# Compound Acquisition



# Compound Acquisition

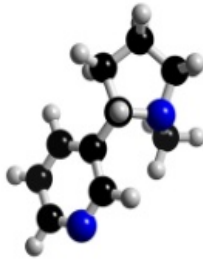


# Element Testing



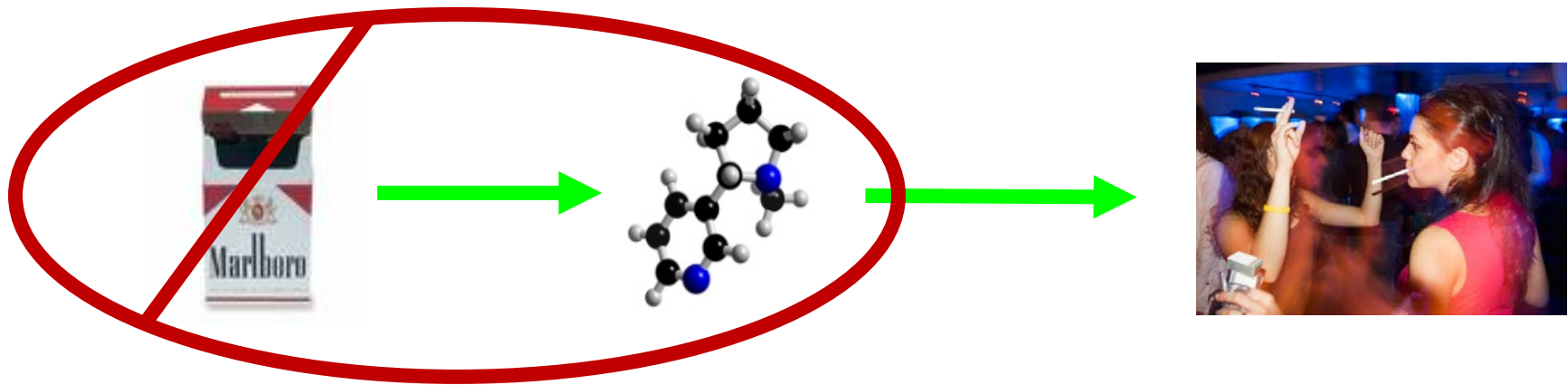
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# Alcohol exposure therapy

Rankin, Hodgson, & Stockwell (1983) Cue exposure and response prevention with alcoholics: A controlled trial. *Behaviour Research and Therapy*, 21:435-446.



Sitharthan, Sitharthan, Hough, & Kavanagh (1997) Cue exposure in moderation drinking: A comparison with cognitive-behavior therapy. *Journal of Consulting and Clinical Psychology*, 65:878-882.



# Alcohol exposure therapy



**Table 2**  
*Mean Changes (and Standard Deviations) in Outcome Measures at 6 Months Compared With Pretreatment*

Outcome measure	CE (n = 22)		CBT (n = 20)	
	Pretreatment	6 Months	Pretreatment	6 Months
Drinking frequency (days per month) <sup>a</sup>	21.64 (7.99)	6.23 (8.24)	18.40 (7.99)	11.93 (10.18)
Consumption per occasion (standard drinks) <sup>a</sup>	8.80 (1.67)	3.75 (2.97)	8.83 (1.94)	5.85 (3.25)
SADQ-C <sup>b</sup>	19.00 (1.38)	4.55 (4.33)	18.60 (1.79)	7.45 (6.82)
ICQ <sup>b</sup>	13.00 (0.44)	4.14 (3.78)	13.10 (0.72)	6.65 (4.70)
CDSSES	36.36 (10.49)	78.18 (15.63)	35.50 (9.45)	66.50 (25.60)

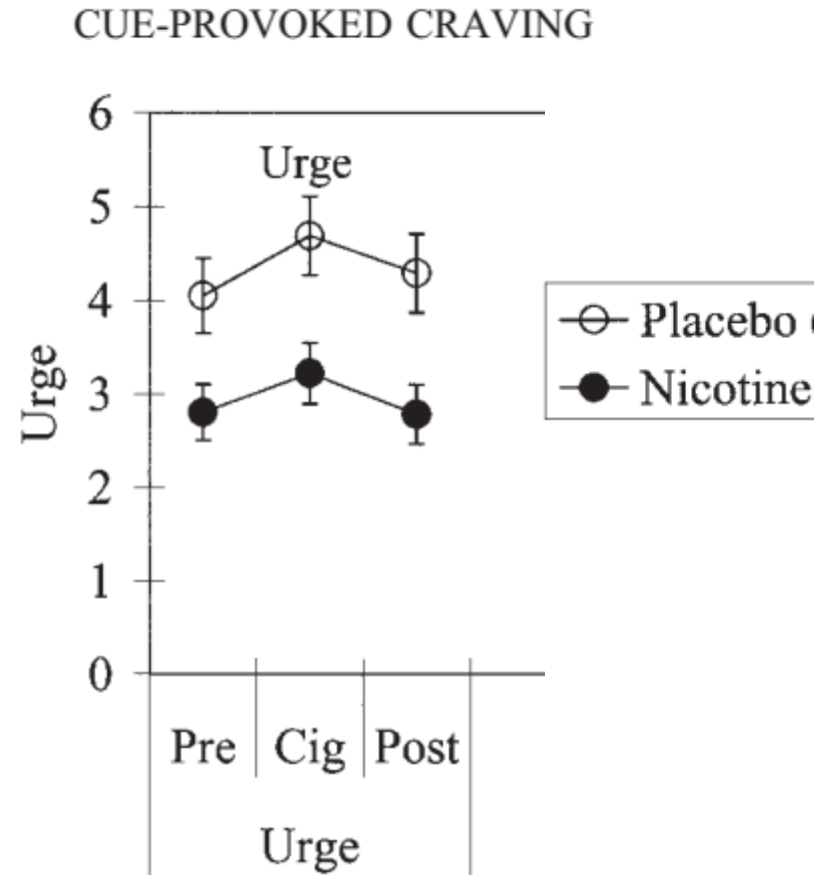
*Note.* Time effects were significant at  $p < .001$  on all measures. CE = cue exposure; CBT = cognitive-behavioral therapy; SADQ-C = Severity of Alcohol Dependence Questionnaire—Form C; ICQ = Impaired Control Questionnaire; CDSSES = Controlled Drinking Self-Efficacy Scale.

<sup>a</sup> For Group  $\times$  Time interactions,  $p < .05$ . <sup>b</sup> For Group  $\times$  Time interactions,  $p < .10$ .

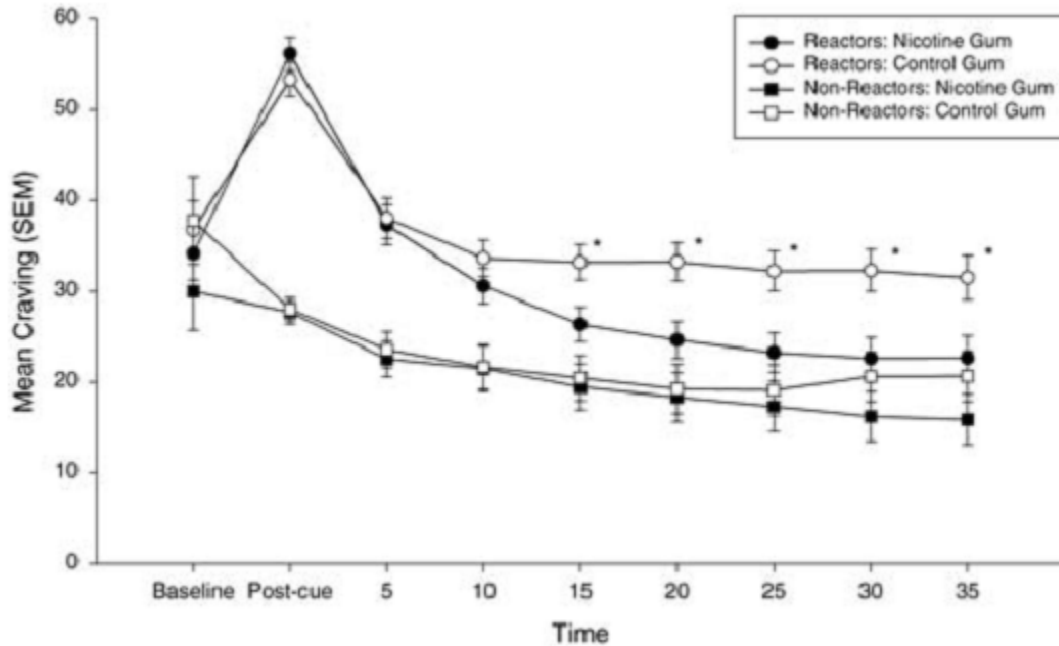
# Pharmacokinetic contributions



Tonic

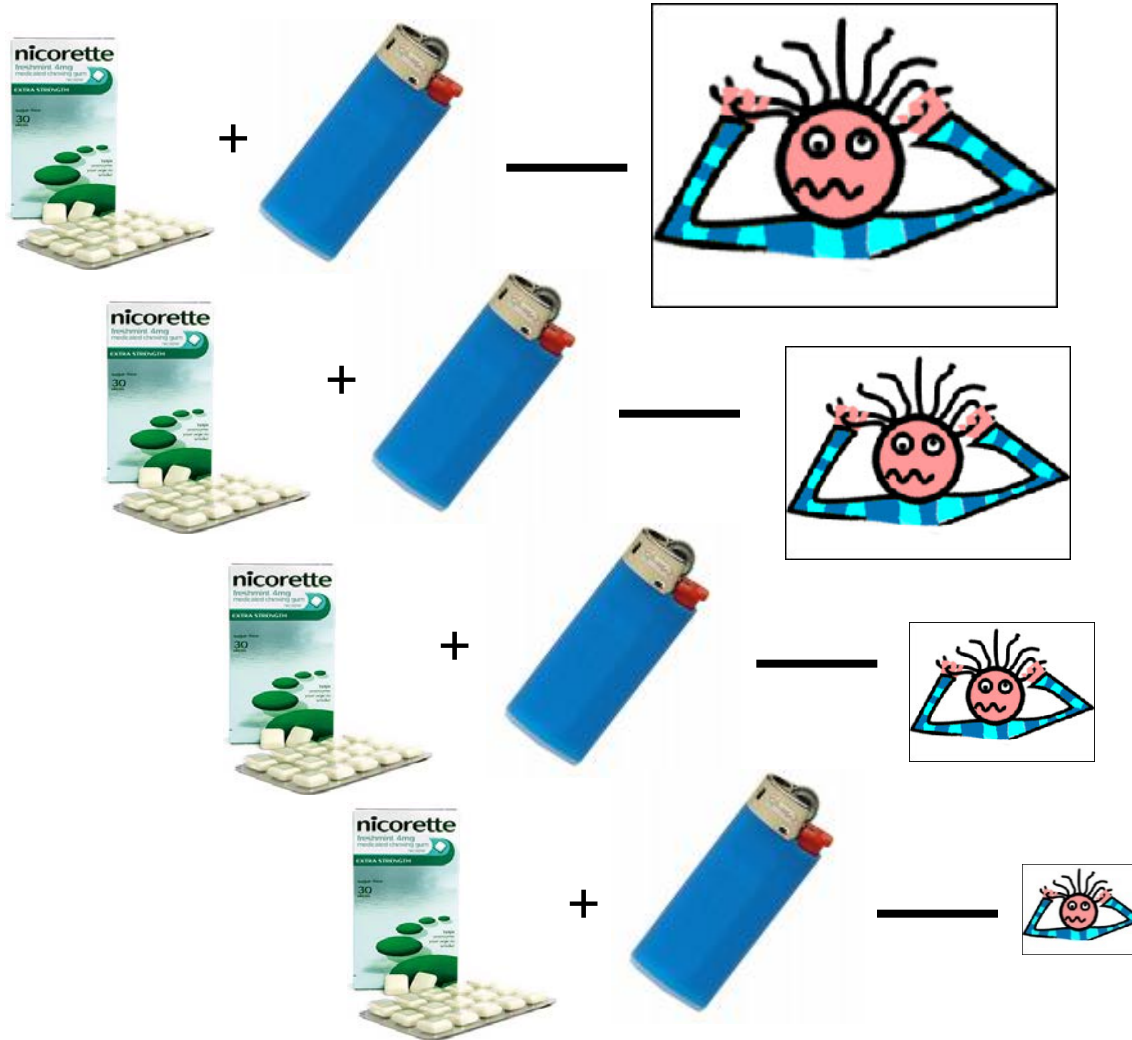


# Pharmacokinetic contributions



Phasic

# Extinction



# In summary...

- Development of drug habits.
- Impact of environmental cues.
- Cue exposure therapy.
- Extending the drug cue.



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