

Negative Reinforcement Theories of Addiction

- Sub-Types of Negative Reinforcement Models
 - Self-Medication Hypothesis
 - Drugs are used to self-medicate, i.e., relieve symptoms that occur independent of drug use (e.g., pain, anxiety)
 - Physical Dependence Hypothesis
 - Distress Syndrome Reduction Theories, withdrawal avoidance
 - With the development of tolerance and physical dependence drug use is sustained in order to avoid the unpleasant consequences associated with withdrawal
 - people continue to take drugs to ease “distress syndrome” (physical and/or psychological) associated with the cessation of drug use
 - perhaps due to adaptations in brain reward systems (compensatory rebound idea), or opponent process

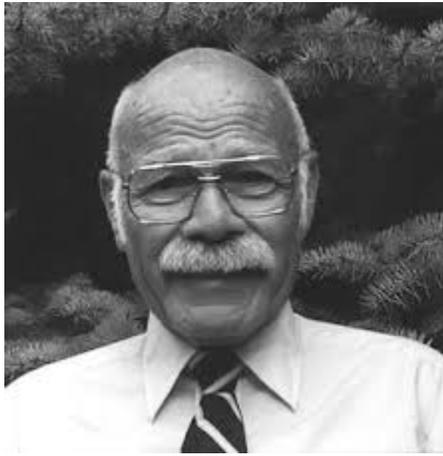
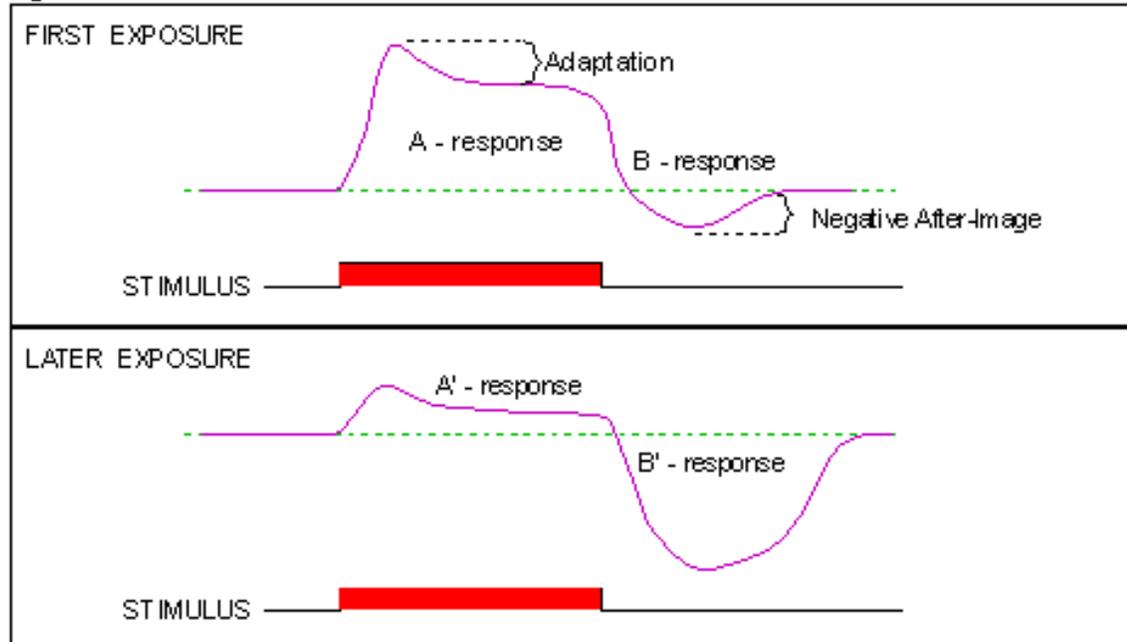
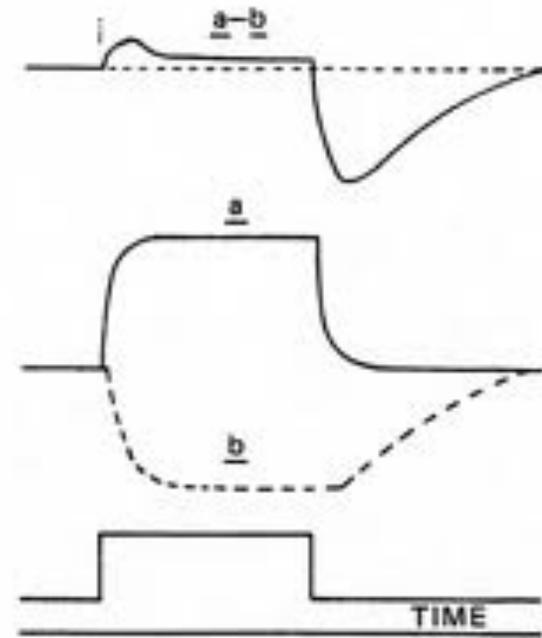


Figure 9 - 9

Hamilton - Timmons

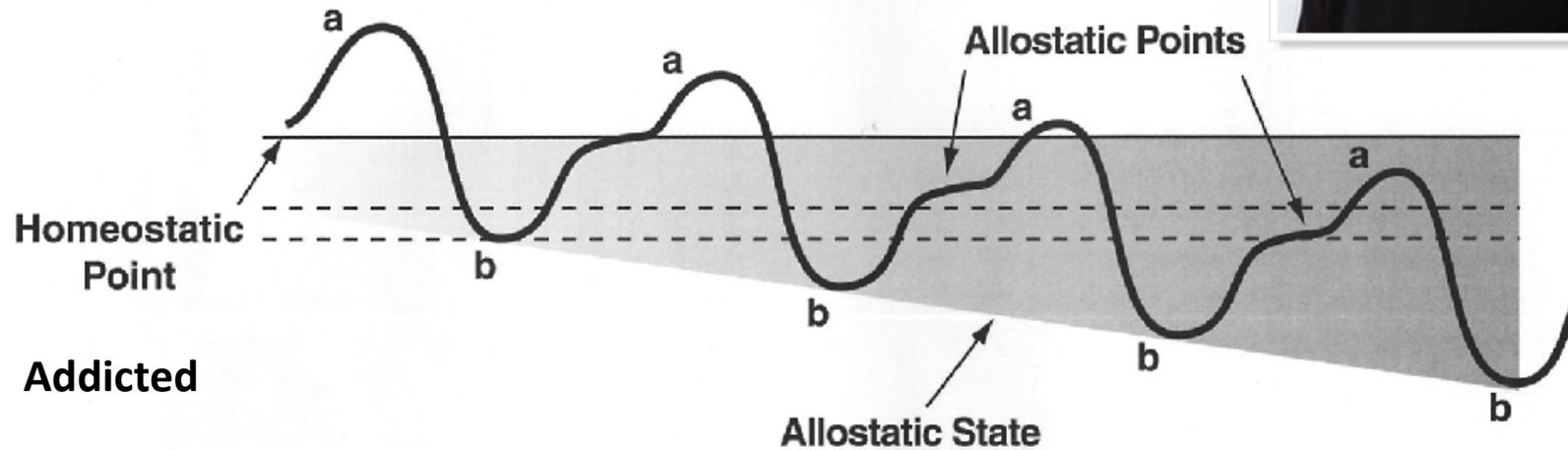
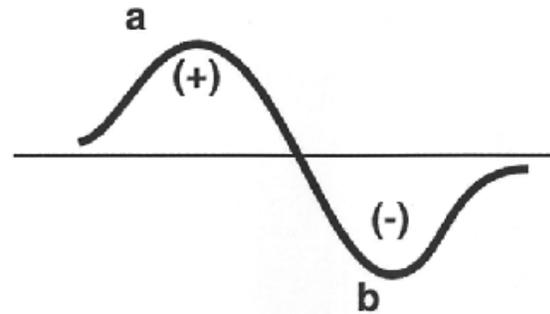


Panel B.
AFTER MANY STIMULATIONS



Brain Dysregulation in Addiction (CNS activity, mood, behavior)

Normal

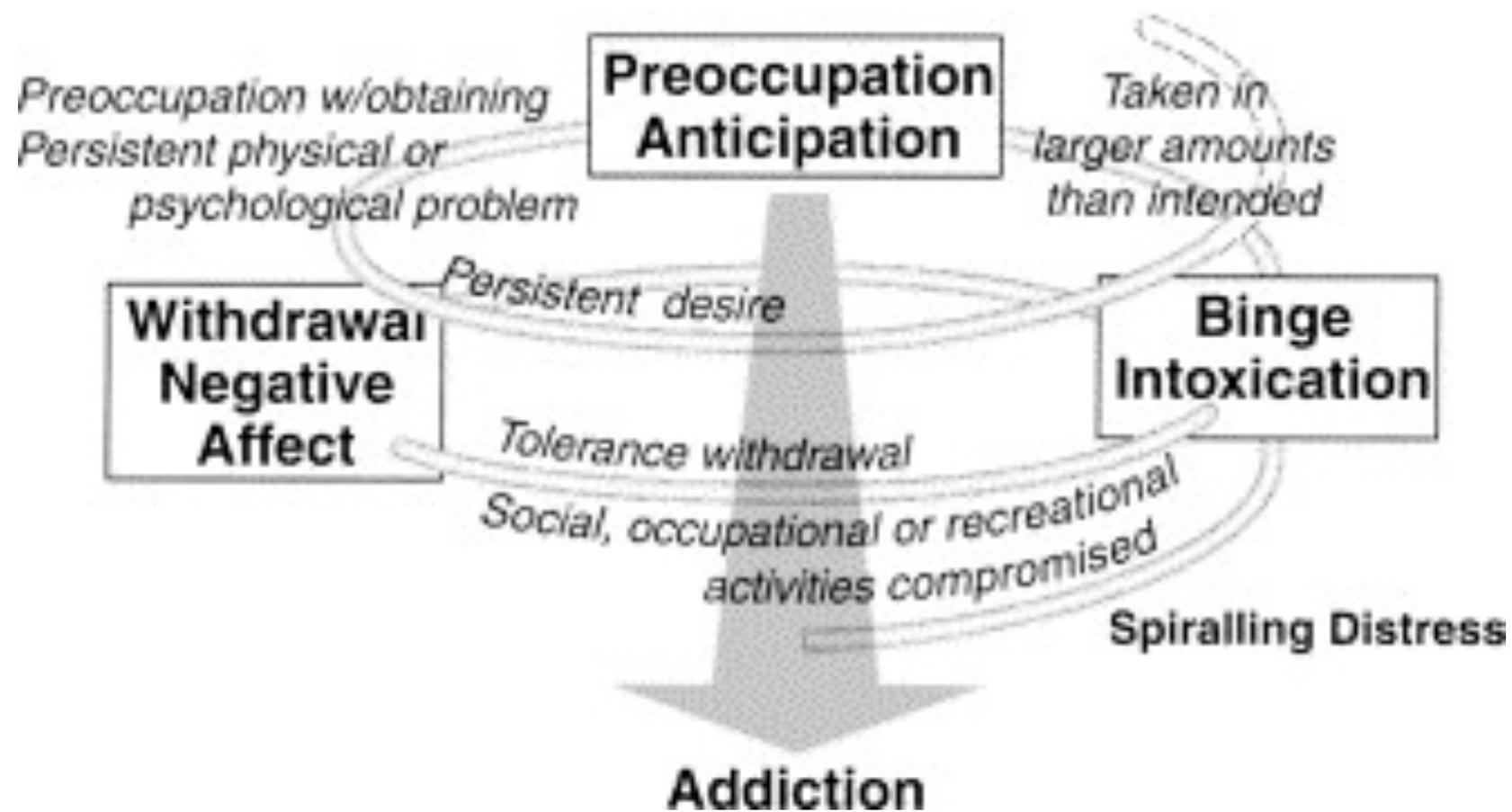


Homeostatic
Point

Addicted

Allostatic State

Criteria for Substance Dependence (DSM-IV)



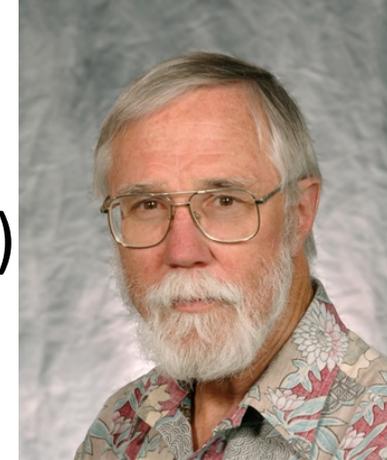
Problems

- People and animals self-administer drugs at doses that are too low to produce physical dependence
- There is a high tendency to relapse even after an extended period of abstinence, long after withdrawal

Conclusion: physical dependence and withdrawal are neither necessary nor sufficient conditions for addiction

- • *“Physical dependence is currently viewed not so much as a direct cause of drug dependence but as one of several factors that contribute to its development”*
 - *(J.H. Jaffe, in A. Gilman et al. (eds.), The Pharmacological Basis of Therapeutics, 1990)*
- *“For rats and monkeys physical dependence is neither a necessary nor sufficient condition for opiates to act as reinforcers”*
 - *(C. Schuster, in G. Edwards et al. (eds.), The Nature of Drug Dependence, 1990)*
- *“The role of physical dependence in addiction is suggested to vary from drug to drug and to be of secondary importance in the understanding of compulsive drug self-administration*
 - *(R.A. Wise & M.A. Bozarth, Psychological Review, 1987)*

- *Tolerance and withdrawal are still widely studied*
 - Ethanol inhalation
 - Withdrawal-induced seizures
 - Antinociceptive tolerance (hot-plate test)



Positive reinforcement theory of addiction

- *Drug taking is maintained because drugs act as positive reinforcers:*
 - thus increase the probability of preceding behavior (drug-taking)
 - positive reinforcement models generally equate positive reinforcement with pleasure
 - (“pleasure-seeking” model)

Positive reinforcement

- *“The only existing positive reinforcement view of addiction that might qualify as an explanatory theory identifies positive reinforcement with drug euphoria”.*
- Primary motivational force driving drug seeking and drug-taking behavior in the addict is the desire to obtain pleasure

(R.A.Wise & M.A. Bozarth, Psychological Review, 1987, 94:469)

Problems: “euphoria” models

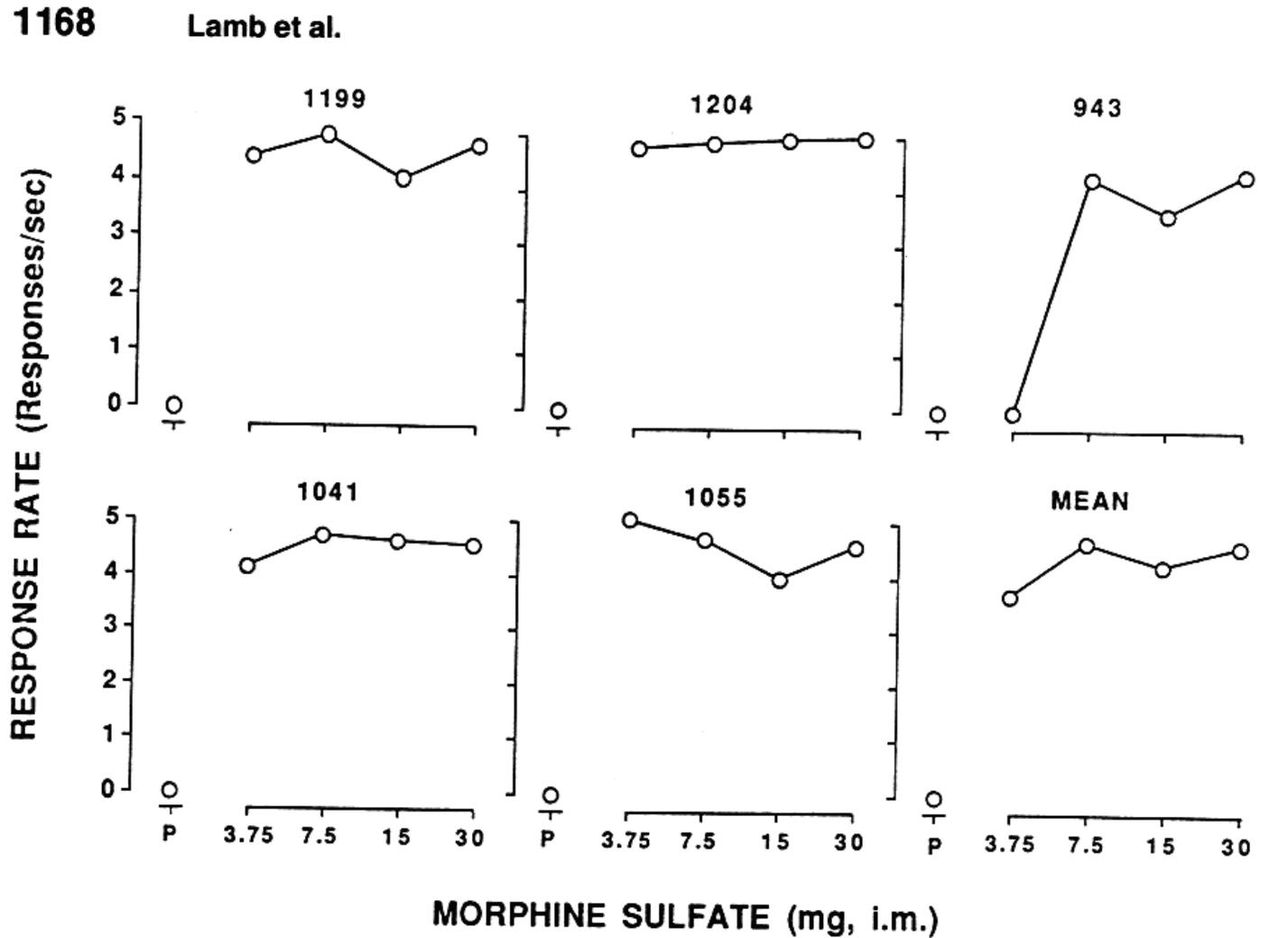
- *“... it was supposed that the prediction of addiction liability was essentially equivalent to prediction of euphorigenic power. As with most self-evident ideas, the mere matter of there being essentially no evidence in favor of it, and much against it, had little effect on its acceptance.” (Dews, 1977)*

Problems: “euphoria” models

- The incentive value of drugs is dissociable from their subjective pleasurable effects
- “Wanting” drugs (motivation to take drugs) is dissociable from their subjective pleasurable effects (“liking” drugs)

- How can we assess the *abuse potential* of different drugs, and study the mechanisms by which drugs produce rewarding effects and dependence
- Can examine the stimulus properties of drug
 - (*“what does it feel like?”*)
- Can examine the reinforcing/incentive properties of drugs
 - (*“will you work for it?”; “do you ‘want’ it?”*).
- With a measure of these drug effects, we can assess e.g. if a particular neurotransmitter is involved in drug reward

People “want” drugs that they don’t “like”



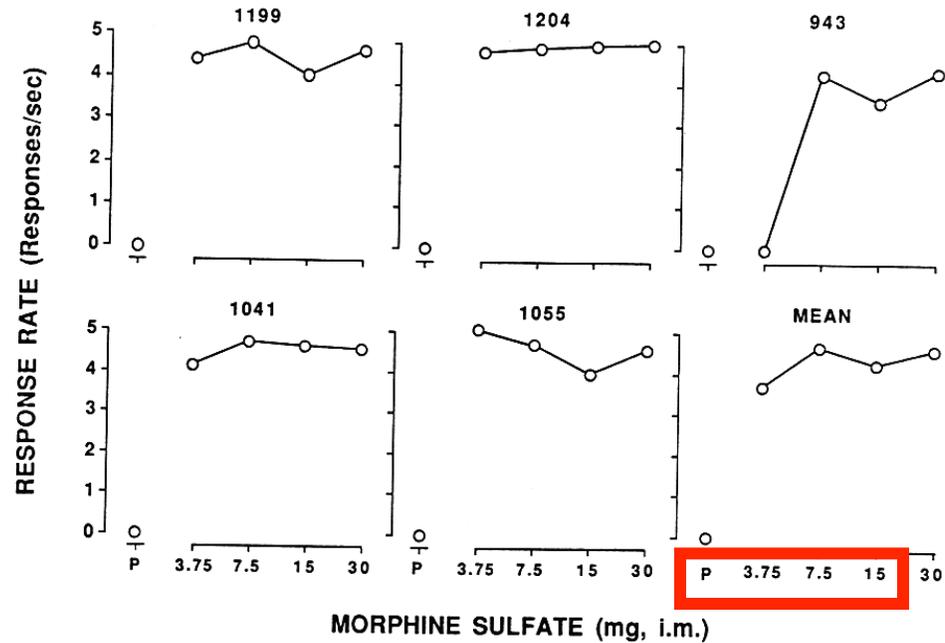


TABLE 3

Scores on several self-report measures after the first injection of each morphine dose

	Morphine Dose (mg)				
	0	3.75	7.5	15	30
Drug liking					
Likert	0.0 (0) ^a	0.0 (0)	1.0 (0.3)	0.4 (0.2)	2.6 (0.2)
Yesterday	0.0 (0)	0.0 (0)	3.0 (1.8)	2.0 (0.8)	20 (4.4)
Good effects	0.0 (0)	0.0 (0)	4.6 (2.9)	0.2 (0.2)	19 (6.4)
Bad effects	0.4 (0.4)	0.4 (0.4)	0.0 (0)	0.0 (0)	2.2 (2.0)
Strength of drug effect	0.0 (0)	0.0 (0)	2.6 (1.2)	0.4 (0.2)	14 (5.4)
Amount of drug (bags)	0.0 (0)	0.0 (0)	0.2 (0.2)	0.0 (0)	2.4 (1.7)
Dollar value of drug	0.0 (0)	0.0 (0)	4.6 (3.9)	0.4 (0.2)	15 (5.0)
Change scores ARCI measures					
MBG scale	-2.2 (1.7)	-3.0 (1.9)	0.6 (1.7)	0.0 (0.8)	3.0 (1.9)
PCAG scale	1.2 (0.7)	0.6 (0.4)	-0.4 (0.7)	0.2 (0.2)	2.8 (1.0)
LSD scale	0.2 (0.5)	1.0 (0.3)	-0.8 (0.9)	0.2 (0.4)	2.0 (0.7)
Opioid withdrawal scale	1.0 (0.5)	0.4 (0.5)	-0.4 (0.5)	-0.2 (0.4)	0.4 (1.1)

^a Mean (S.E.M.).

PHASES OF MOTIVATED BEHAVIOR:

(e.g. "seeking" vs. "taking")

Instrumental phase

Accumbens DA DEPENDENT

INVIGORATION

Homeostatic state and salient predictive stimuli invigorate the organism to approach the reinforcer, overcoming work and tolerating delays in flexible ways

**APPROACH / AVOIDANCE
BEHAVIORS**

Consummatory phase

Accumbens DA INDEPENDENT

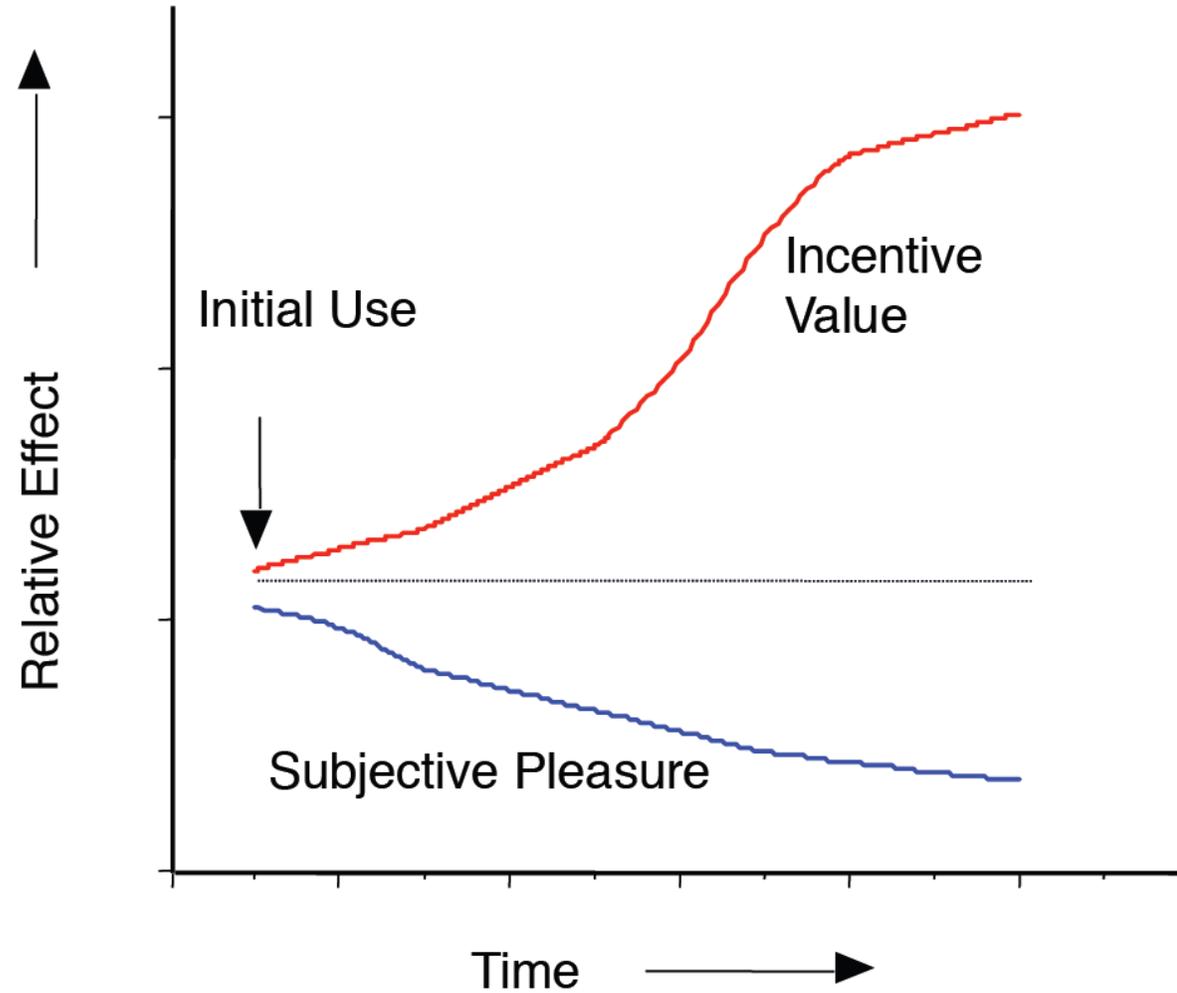
**Appetite or Preference
Hedonic reaction**

Direct interaction with the goal stimulus

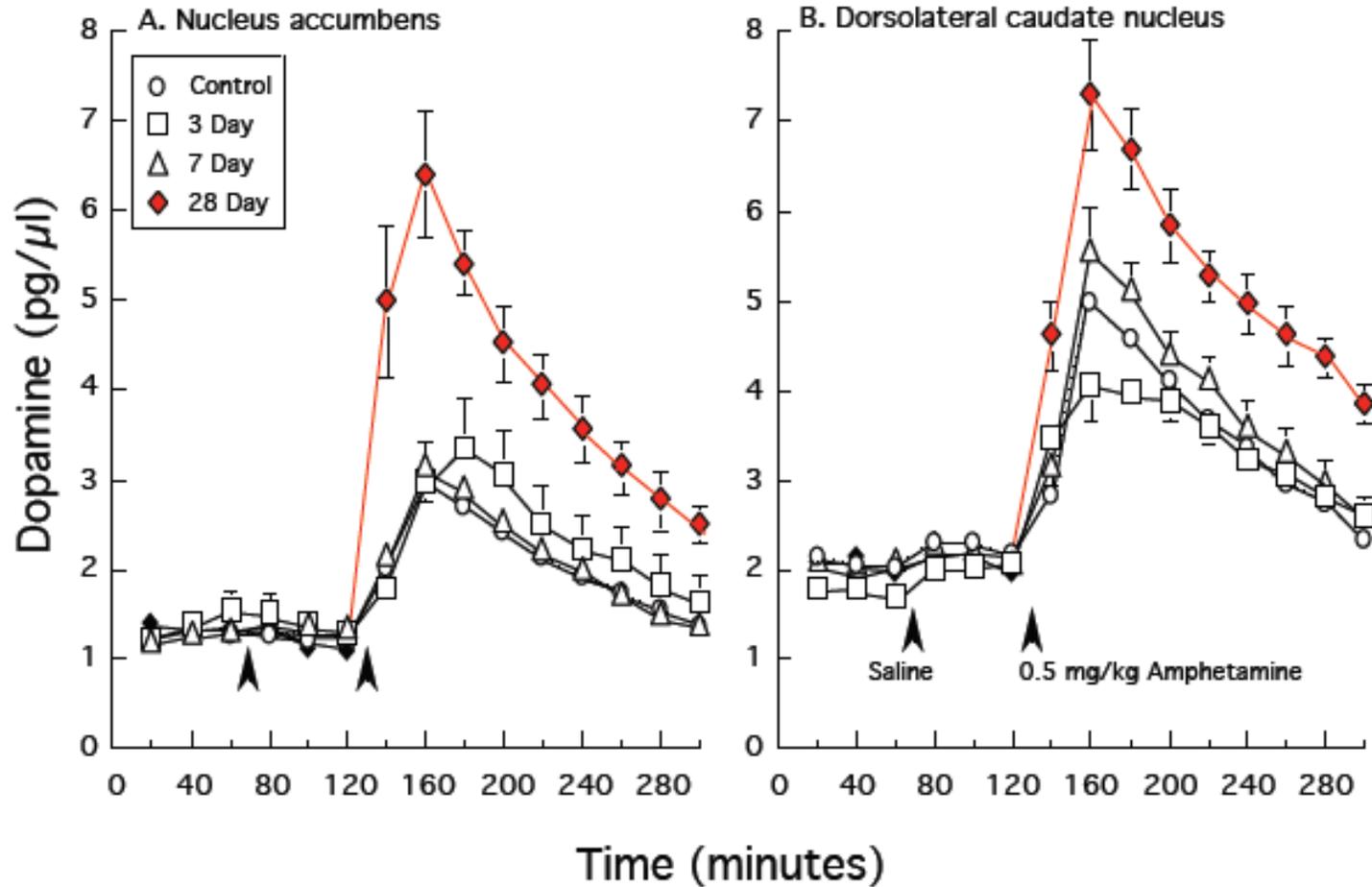
**GOAL STIMULI:
FOOD, WATER, SEX, DRUGS,
PREDATORS, PAIN, DISCOMFORT**

Key Point: Dopamine mediates "wanting" or "drug-seeking" or "incentive motivation"

Incentive to take drug increases during addiction



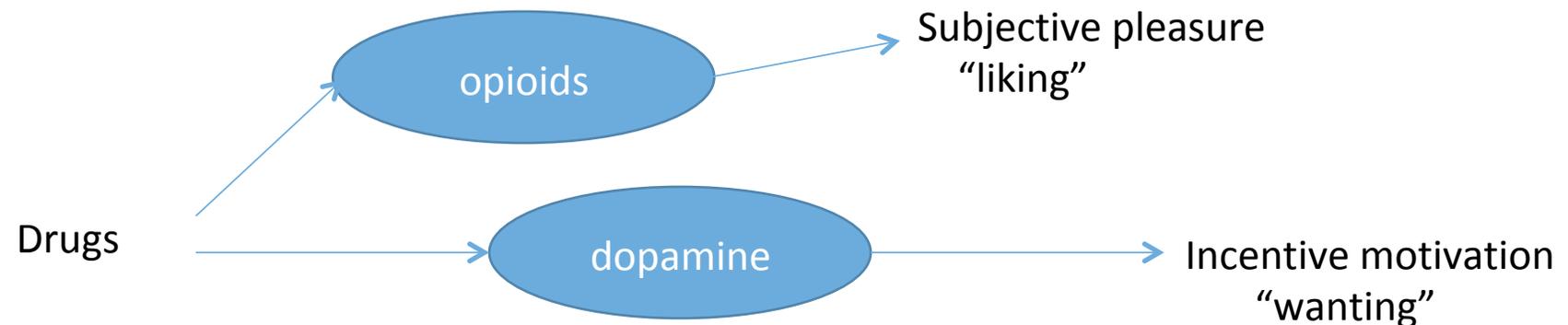
Drug-induced dopamine increases as a function of withdrawal



Opioids for hedonic experience and dopamine to get ready for it

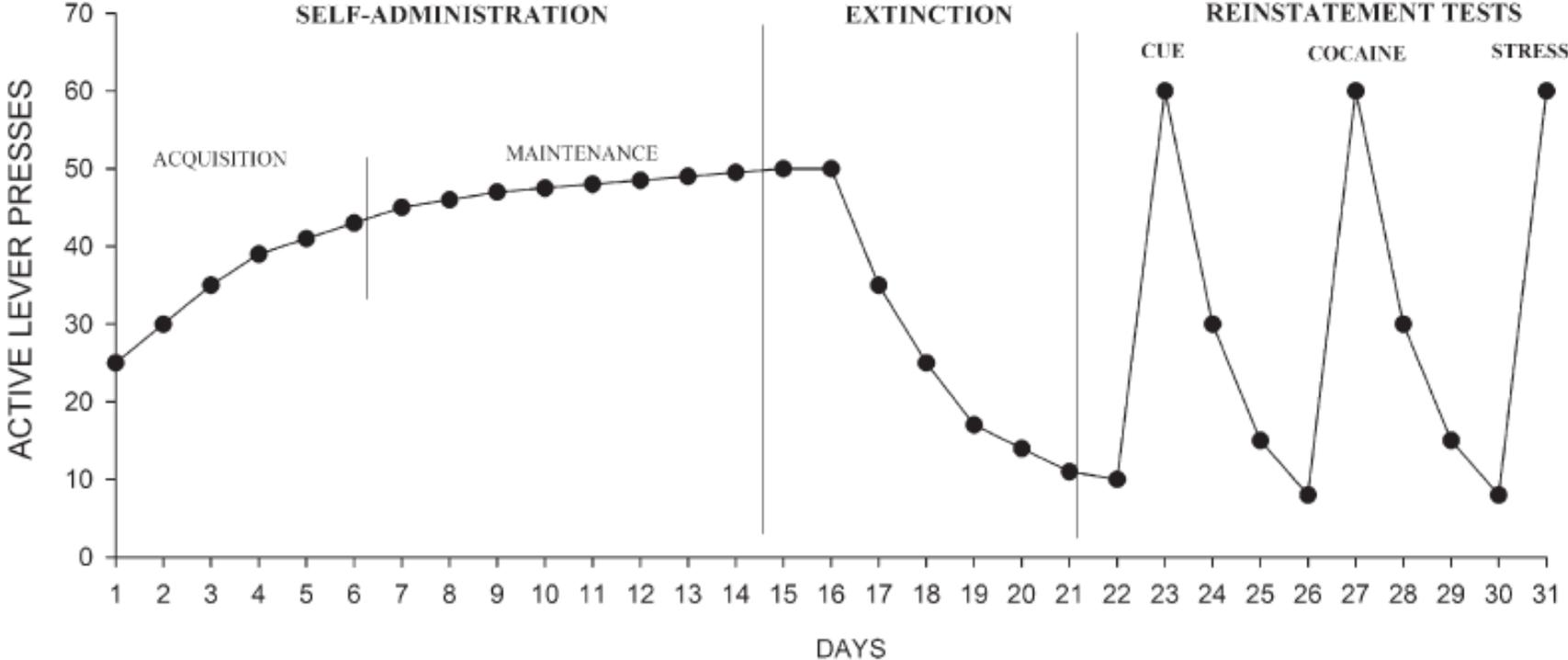
M. Flavia Barbano • Martine Cador

i.e., opioid receptors mediate pleasure, but dopamine mediates the incentive/addictive properties

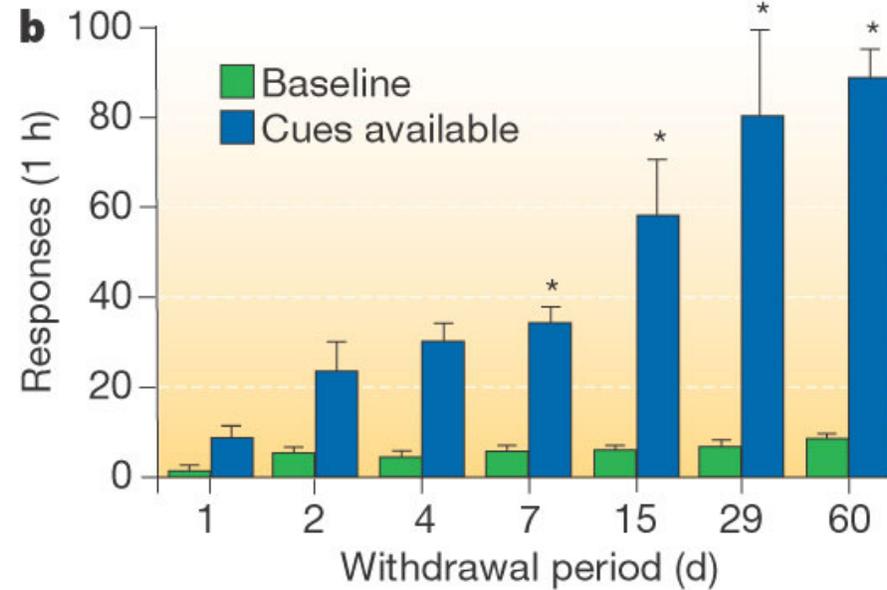
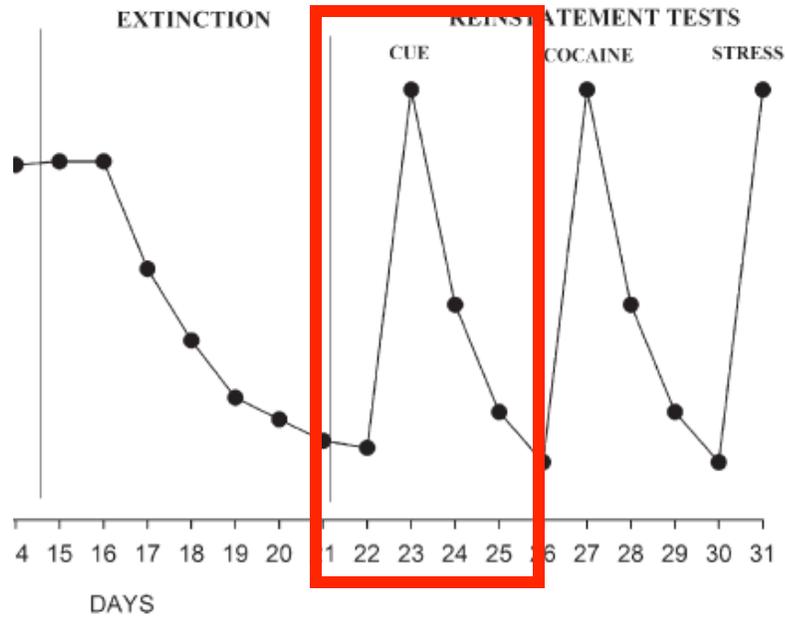




Phases of SA



Incubation of craving during drug self-administration



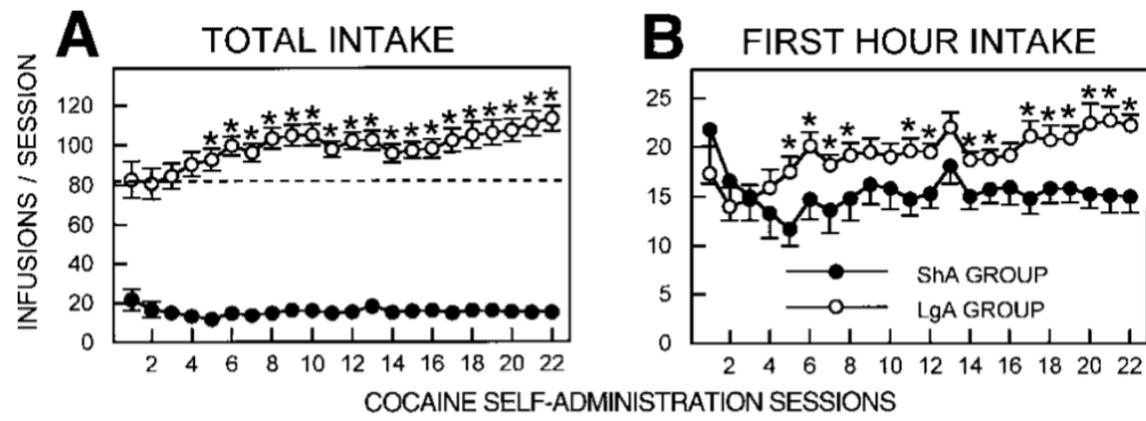
Transition from Moderate to Excessive Drug Intake: Change in Hedonic Set Point

S. H. Ahmed* and G. F. Koob

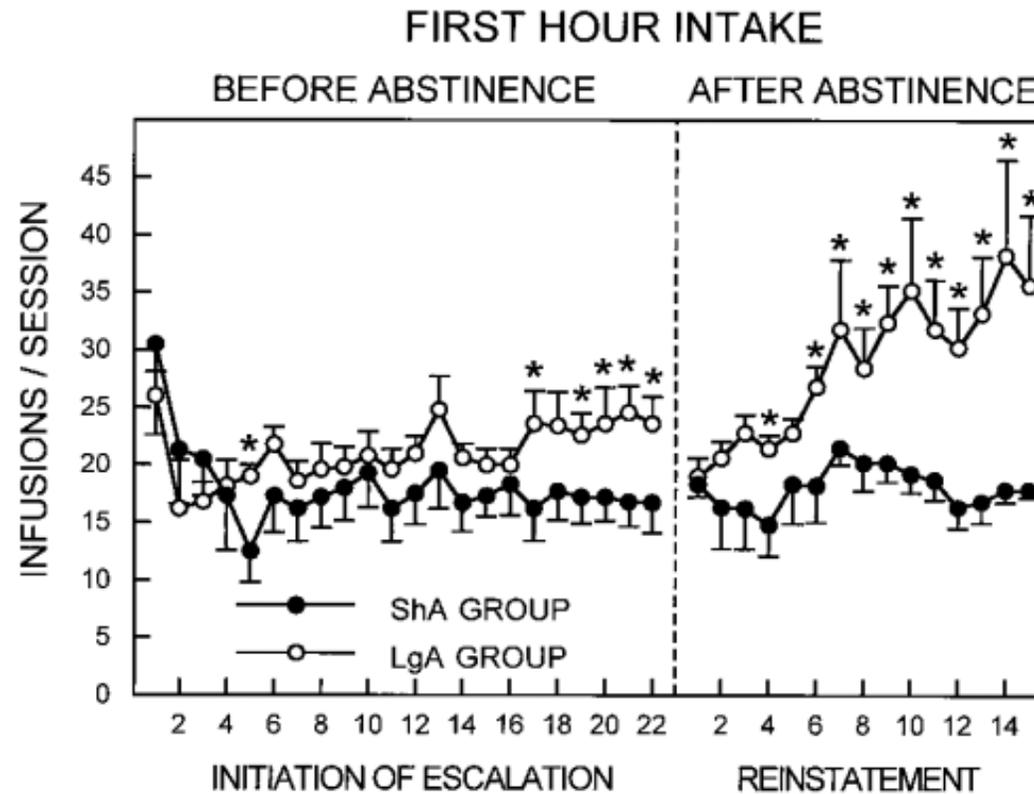
Differential access to cocaine self-administration produced two patterns of drug intake in rats. With 1 hour of access per session, drug intake remained low and stable. In contrast, with 6 hours of access, drug intake gradually escalated over days. After escalation, drug consumption was characterized by an increased early drug loading and an upward shift in the cocaine dose-response function, suggesting an increase in hedonic set point. After 1 month of abstinence, escalation of cocaine intake was reinstated to a higher level than before. These findings may provide an animal model for studying the development of excessive drug intake and the basis of addiction.



- Two groups:
 - Short access (1 hour/day)
 - Long access (6 hours/day)



Withdrawal-induced escalation apparent in LgA rats.



Face validity to the extreme: addicted rats

Evidence for Addiction-like Behavior in the Rat

Véronique Deroche-Gamonet, David Belin, Pier Vincenzo Piazza*

Although the voluntary intake of drugs of abuse is a behavior largely preserved throughout phylogeny, it is currently unclear whether pathological drug use ("addiction") can be observed in species other than humans. Here, we report that behaviors that resemble three of the essential diagnostic criteria for addiction appear over time in rats trained to self-administer cocaine. As in humans, this addiction-like behavior is present only in a small proportion of subjects using cocaine and is highly predictive of relapse after withdrawal. These findings provide a new basis for developing a true understanding and treatment of addiction.

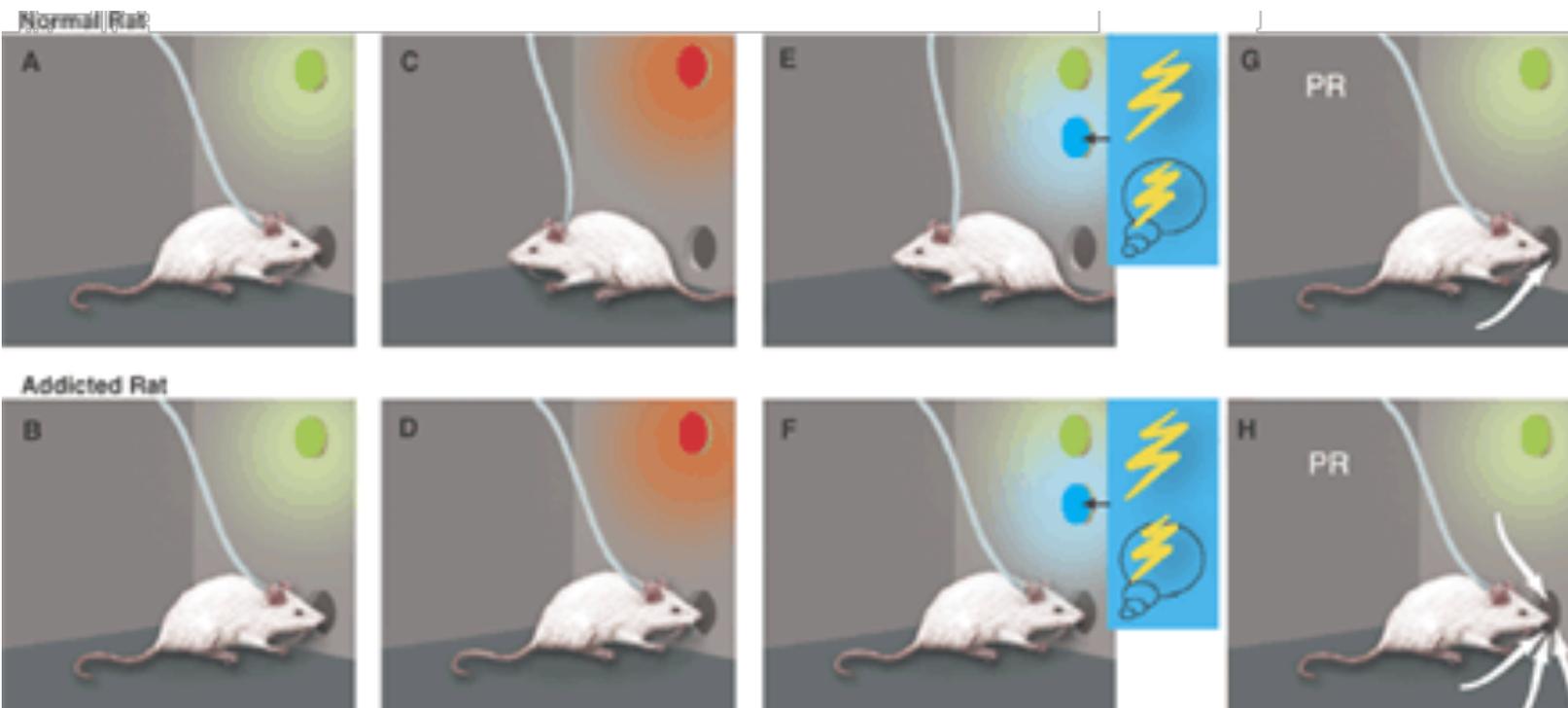


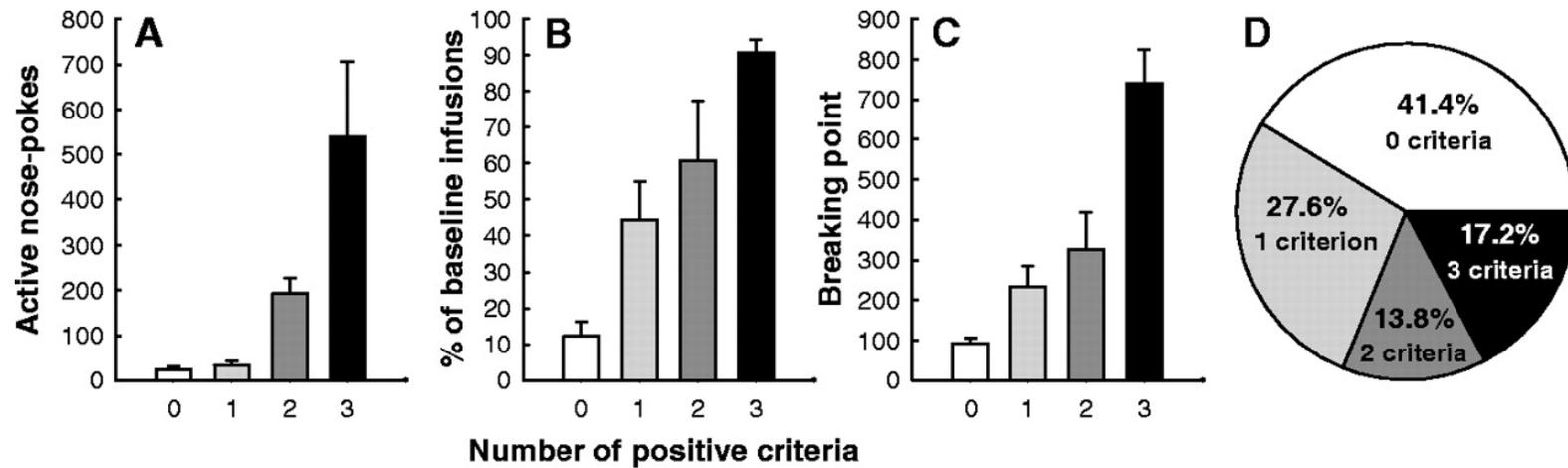
Table 1 Comparison of the diagnostic items of drug use related disorders in DSM IV and DSM 5, sufficient and necessary conditions for a diagnosis of addiction and corresponding major behavioral dimensions usable within an RDoC-like approach to behavioral pathologies

DSM IV criteria for drug abuse (1994)	DSM V criteria for Substance Use Disorders (SUDs) (2013)	Sufficient conditions	Necessary condition	RDoC-Like Dimensional Approach
At least one of these four criteria	0-1 unaffected; 2-3 Mild; 4-5 Moderate; 6 or more Severe			
1. Recurrent failure to fulfill major role obligations	1. Recurrent failure to fulfill major role obligations	DSM IV Abuse		Sustained Escalated drug intake with high motivation for the drug
2. Recurrent substance use in physically hazardous situations	2. Recurrent substance use in physically hazardous situations			
3. Recurrent substance-related legal problems				
4. Continued substance use despite persistent or recurrent social or interpersonal problems	3. Continued substance use despite persistent or recurrent social or interpersonal problems			
DSM IV criteria for drug addiction (1994)		DSM V Mild and Moderate	DSM IV Dependence/ DSM V Severe SUD	
Three out of these seven criteria				
1. Tolerance	4. Tolerance			Physiological adaptations to drug intake
2. Withdrawal	5. Withdrawal			
3. The substance is often taken in larger amounts or over a longer period than intended	6. The substance is often taken in larger amounts or over a longer period than intended			
4. Persistent desire or unsuccessful efforts to cut down	7. Persistent desire or unsuccessful efforts to cut down			
	8. Craving			
5. Considerable time spent in obtaining the substance or using, or recovering from its effects	9. Considerable time spent in obtaining the substance or using, or recovering from its effects			
6. Important social, work, or recreational activities given up because of use	10. Important social, work, or recreational activities given up because of use			
7. Continued use despite knowledge of problems caused by or aggravated by use	11. Continued use despite knowledge of problems caused by or aggravated by use			

- Rats self-administered intravenous cocaine for three months
 - The DSM criteria evaluated:
 - The subject has difficulty stopping drug use or limiting drug intake
 - The subject has an extremely high motivation to take the drug, with activities focused on its procurement and consumption
 - Substance use is continued despite its harmful consequences.

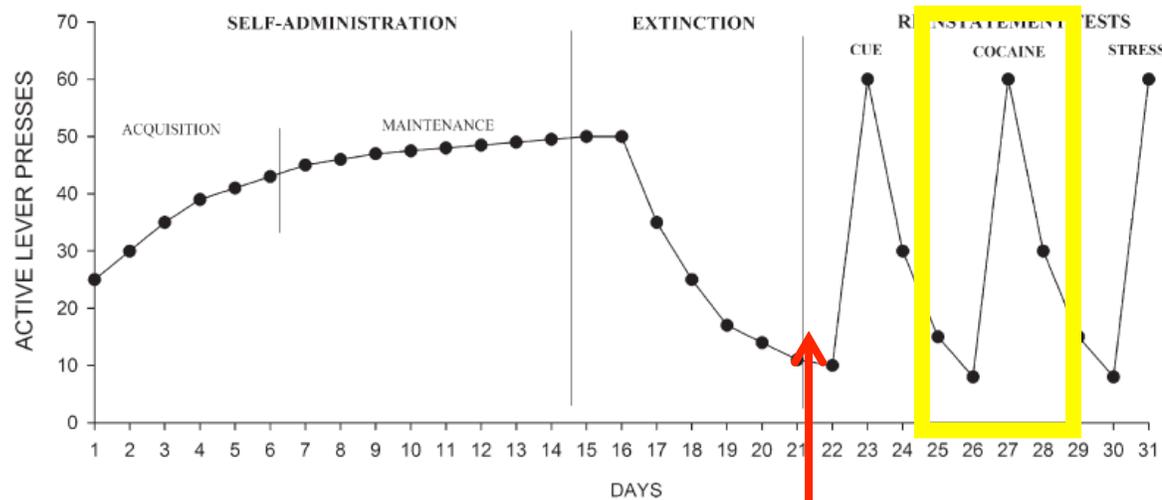




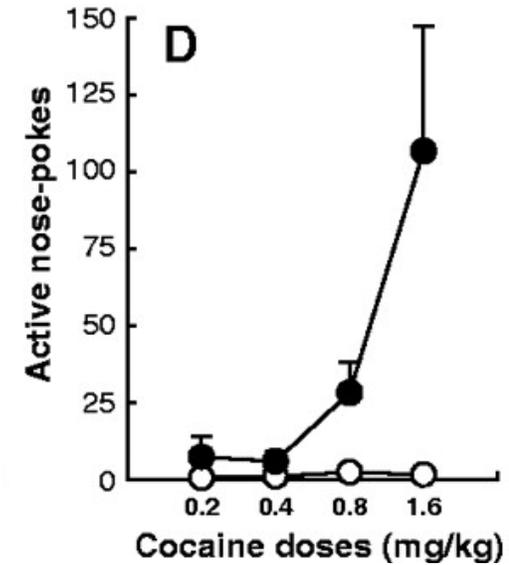


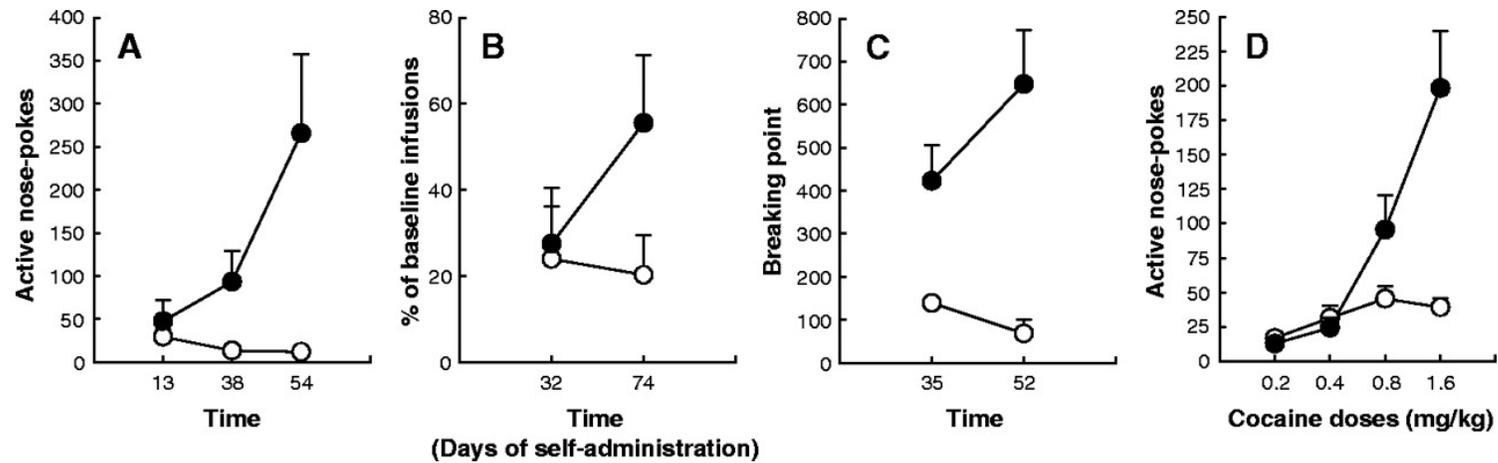
- (A to D) Addiction-like behaviors in rats positive for the presence of zero, one, two, or three addiction-like criteria.
- An individual was considered positive for an addiction-like criterion when its score for one of the three addiction-like behaviors was in the 66th to 99th percentile of the distribution.
 - (A) Persistence in drug seeking, as measured by number of nose-pokes in the cocaine-associated device during the no-drug period of the 54th SA session.
 - (B) Resistance to punishment, as measured by change in the number of cocaine self-infusions (expressed as percentage of baseline SA) when cocaine delivery was associated with an electric shock between the 72nd and 74th SA sessions.
 - (C) Motivation for the drug, as measured by the breaking point during a progressive-ratio schedule performed between the 52nd and 60th SA sessions.
 - (D) Percentage of the total population ($n = 58$) of rats positive for zero, one, two, or three addiction-like criteria.

- rats showing high (black circles, HRein) or low (open circles, LRein) cocaine-induced reinstatement after **30 days** of withdrawal



30 days





- Development of addiction-like behaviors over subsequent cocaine SA sessions in rats showing high (black circles, HRein) or low (open circles, LRein) cocaine-induced reinstatement after 5 days of withdrawal.
- **(A)** Persistence in drug seeking, as measured by number of nose-pokes in the cocaine-associated device during the no-drug period.
- **(B)** Resistance to punishment, as measured by change in the number of cocaine self-infusions (expressed as percentage of baseline SA) when cocaine delivery was associated with an electric shock.
- **(C)** Motivation for the drug, as measured by the breaking point during a progressive-ratio schedule.
- **(D)** Drug-induced reinstatement, as measured by number of nose-pokes in the drug-associated device as a function of the priming dose of cocaine. LRein and HRein contained the rats ($n = 7$ per group) with the lowest and highest reinstatement, respectively, induced by cocaine infusion at 1.6 mg/kg.