Preclinical Animal Models of Addiction: Novel Targets from the Brain Stress Systems

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Koob GF, A Role for Brain Stress Systems in Addiction, Neuron 59 (2008) 11-34

Koob GF, Lloyd GK, Mason BJ. Development of pharmacotherapies for drug addiction: a Rosetta Stone approach Nature Review Drug Discovery, 2009, 8:500-515.

Koob, G. F. and Volkow. N. D. Neurocircuitry of Addiction, Neuropsychopharmacology Reviews 35 (2010) 217-238

Bottom lines

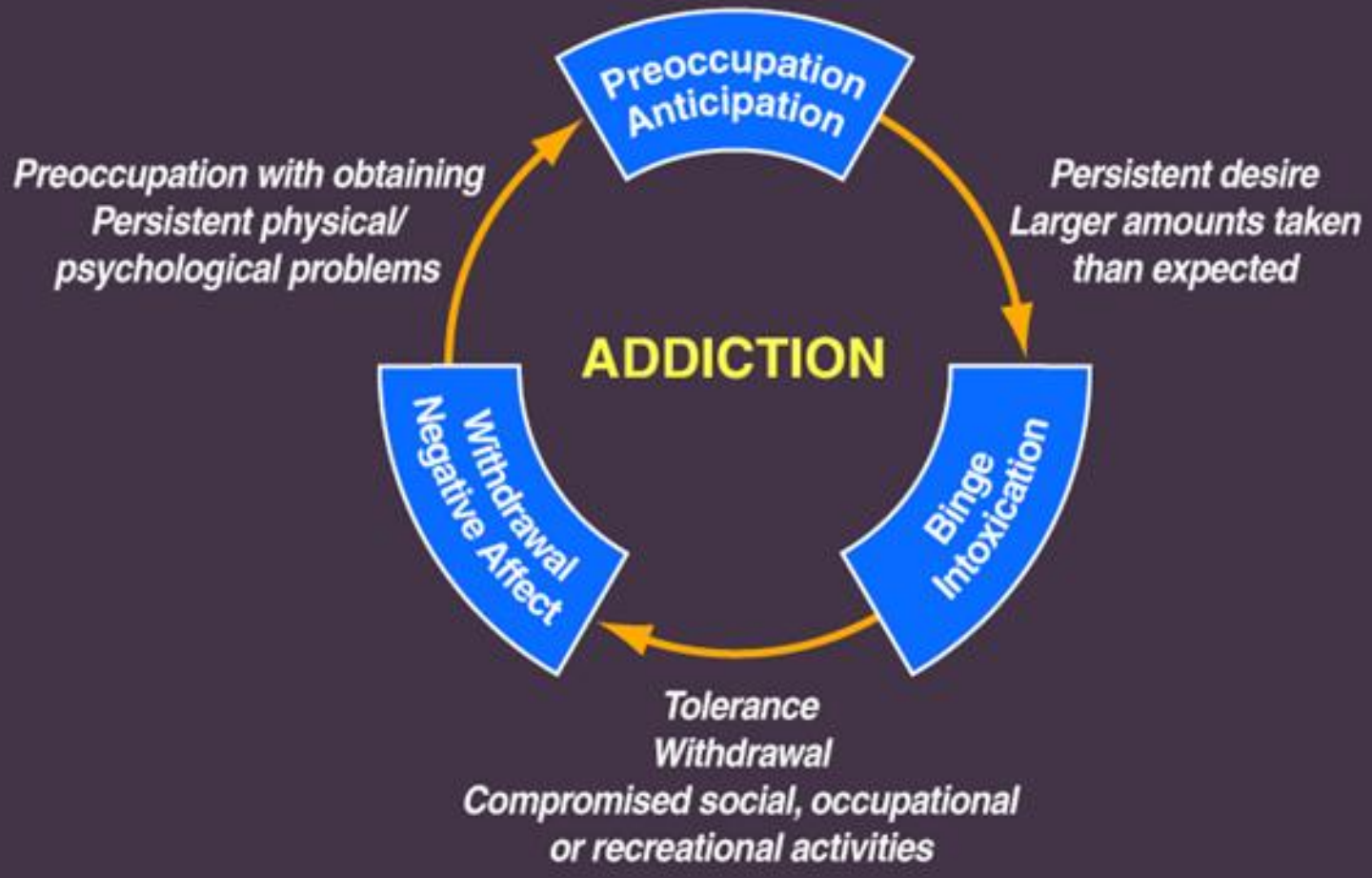
1. Addiction is a reward deficit disorder

2. Addiction is an stimulus-response perseveration disorder

3. Addiction is a self-regulation disorder

4. Addiction is a stress surfeit disorder

Stages of the Addiction Cycle

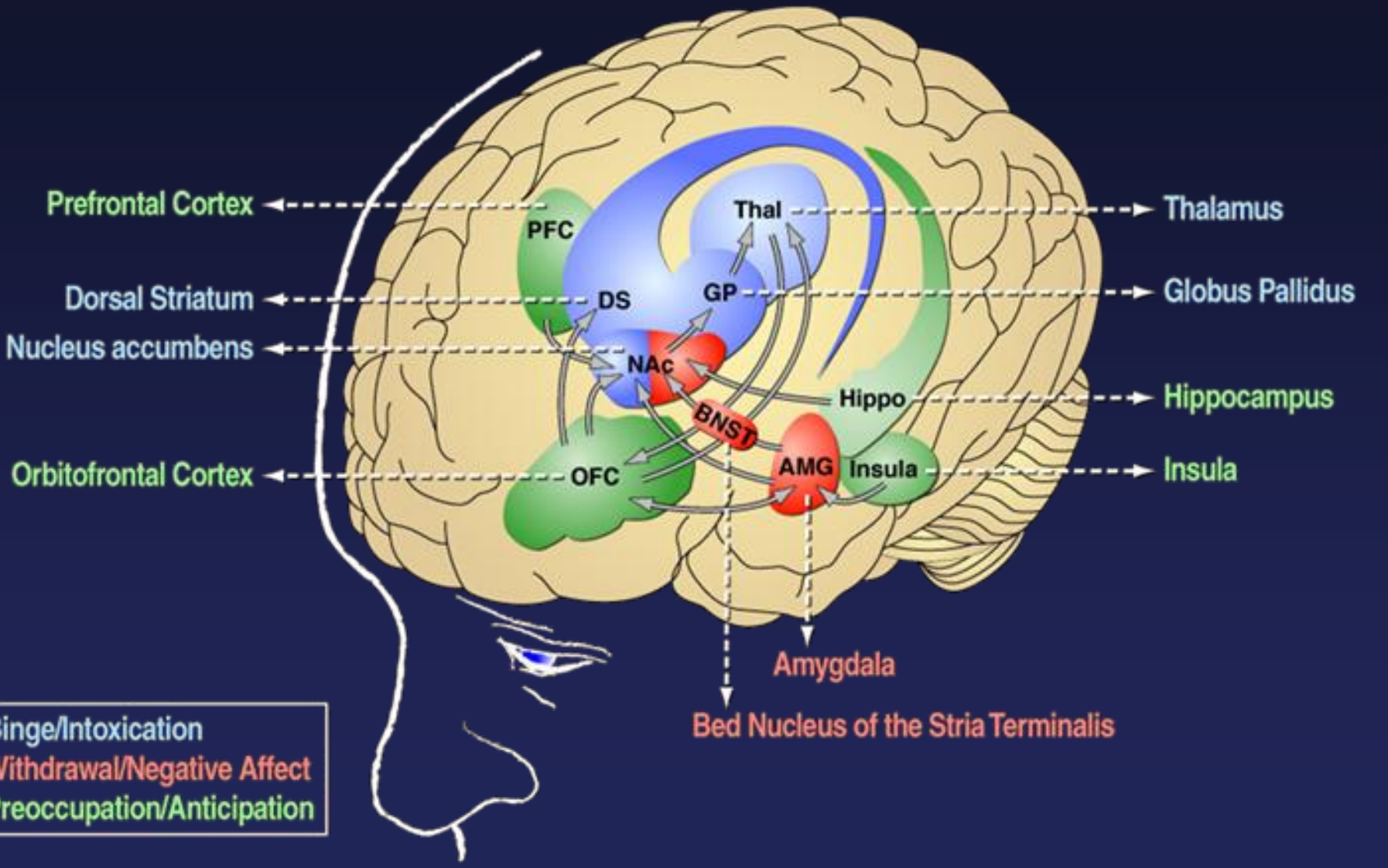


Animal and Human Laboratory Models of the Different Stages of the Addiction Cycle

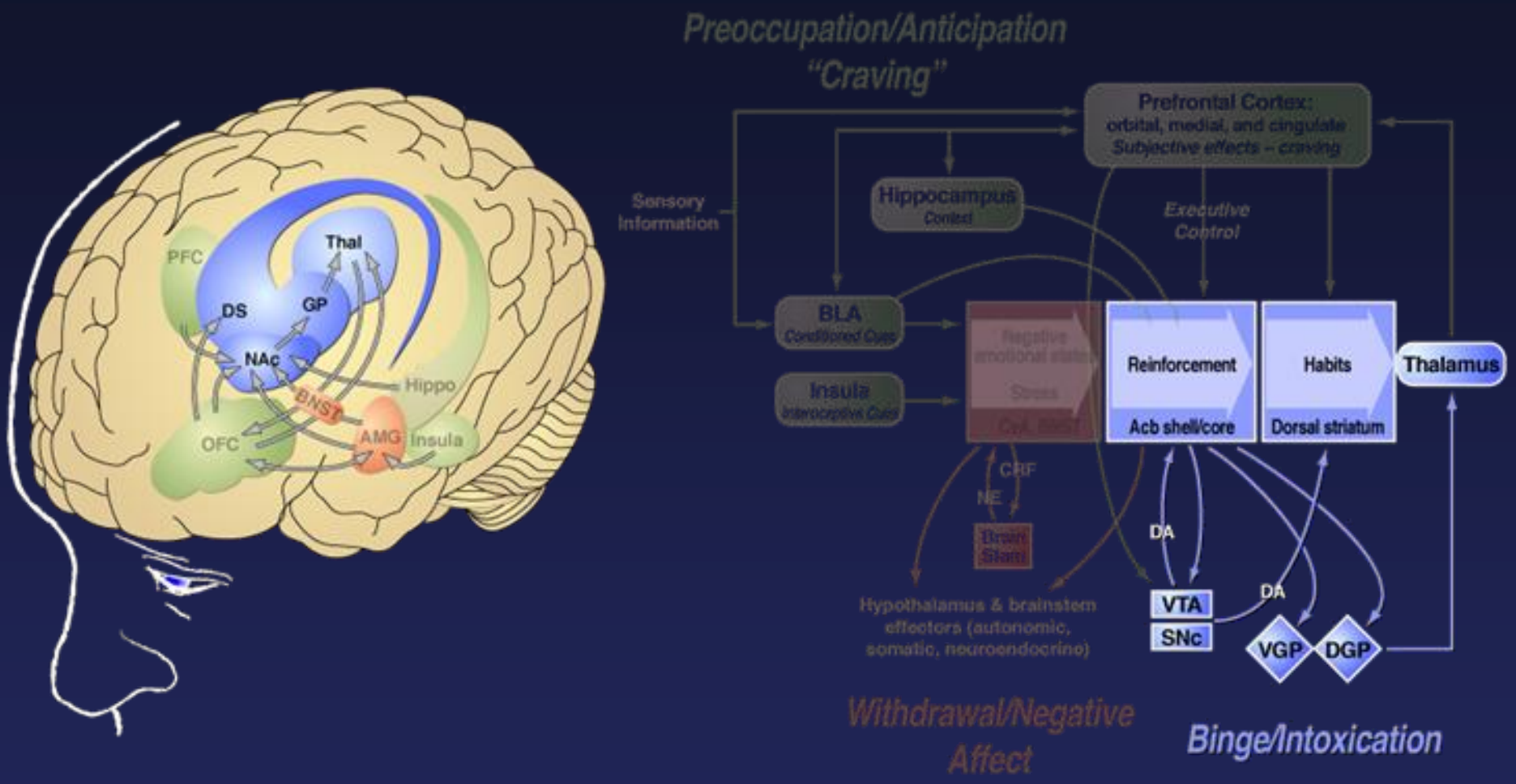
Stage of Addiction Cycle	Animal Models	Human Laboratory Models
Binge/Intoxication	Drug/alcohol self-administration Conditioned place preference Brain stimulation reward thresholds Increased motivation for self-administration in dependent animals	Self-administration in dependent subjects Impulsivity
Withdrawal/Negative Affect	Anxiety-like responses Conditioned place aversion Elevated reward thresholds Withdrawal-induced increases in drug self-administration	Acute withdrawal Self-medication
Preoccupation/Anticipation	Drug-induced reinstatement Cue-induced reinstatement Stress-induced reinstatement	Drug reinstatement Cue reactivity Emotional reactivity Stress-induced craving Resistance to relapse Cue-induced brain imaging responses

From: Koob GF, Lloyd GK, Mason BJ. Nat Rev Drug Discov, 2009, 8:500-515.

Neurobiology of Addiction

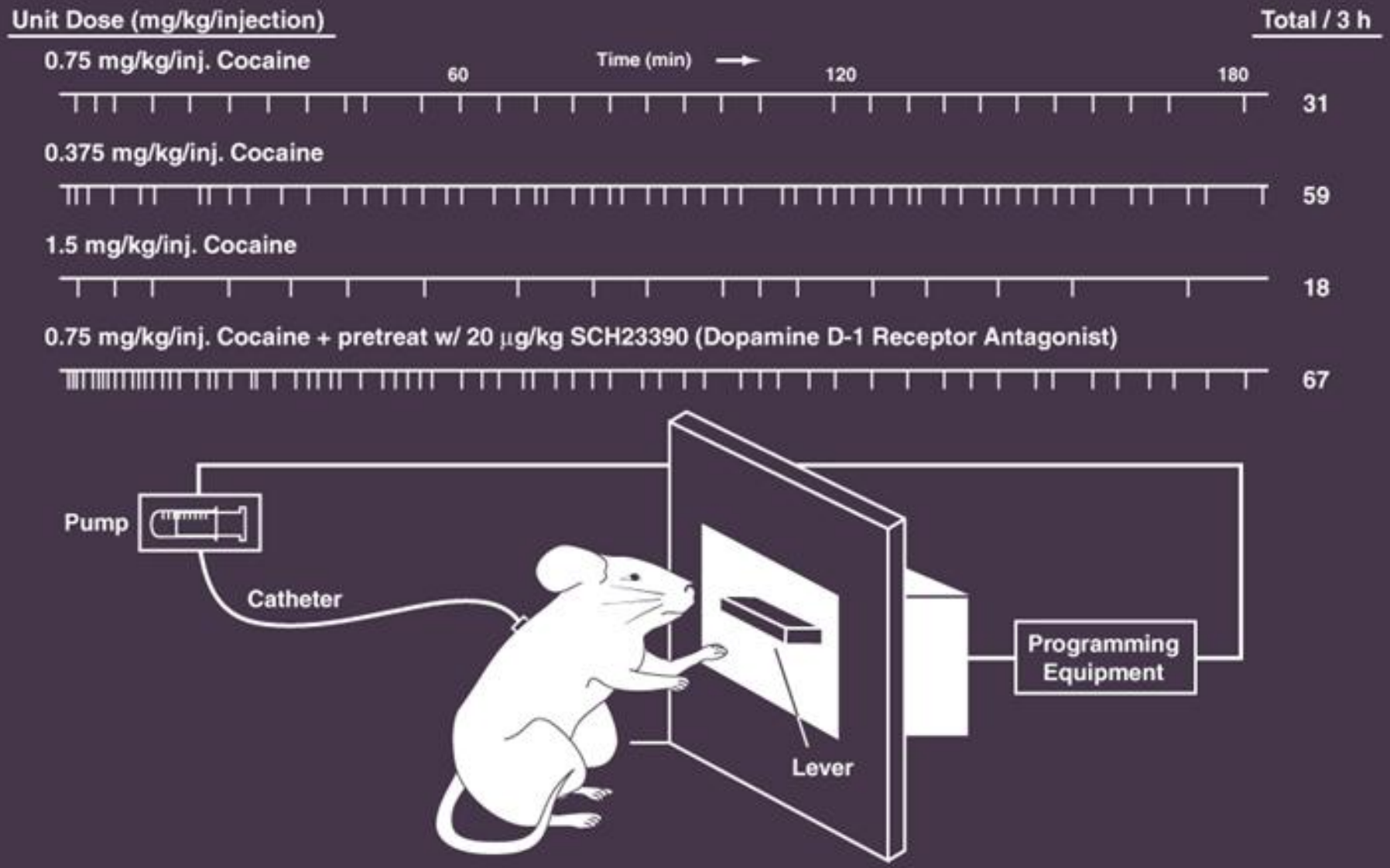


Binge/Intoxication Stage



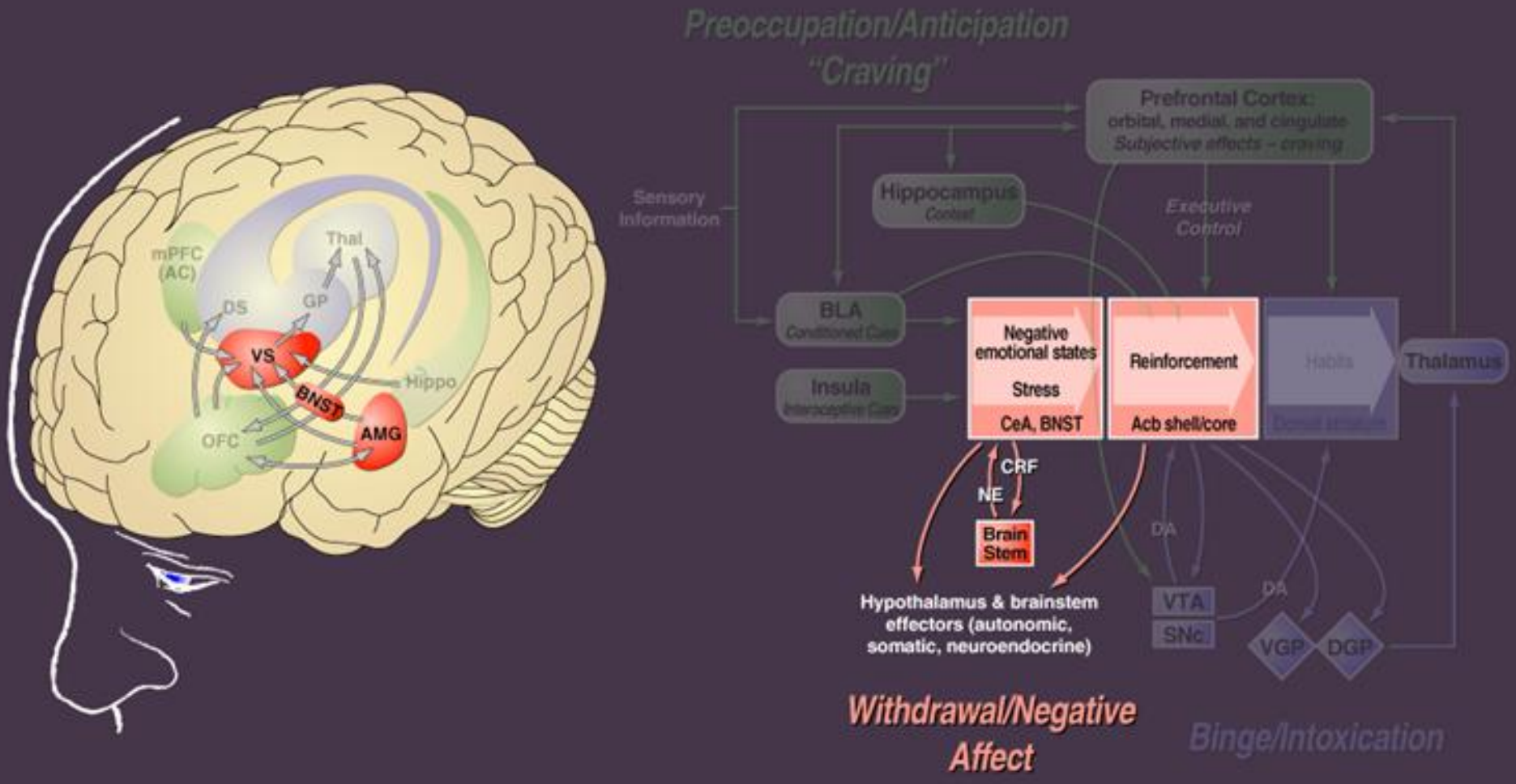
From: Koob, G. F. and Volkow. N. D. Neurocircuitry of Addiction, Neuropsychopharmacology reviews 35 (2010) 217-238

Cocaine Self-Administration

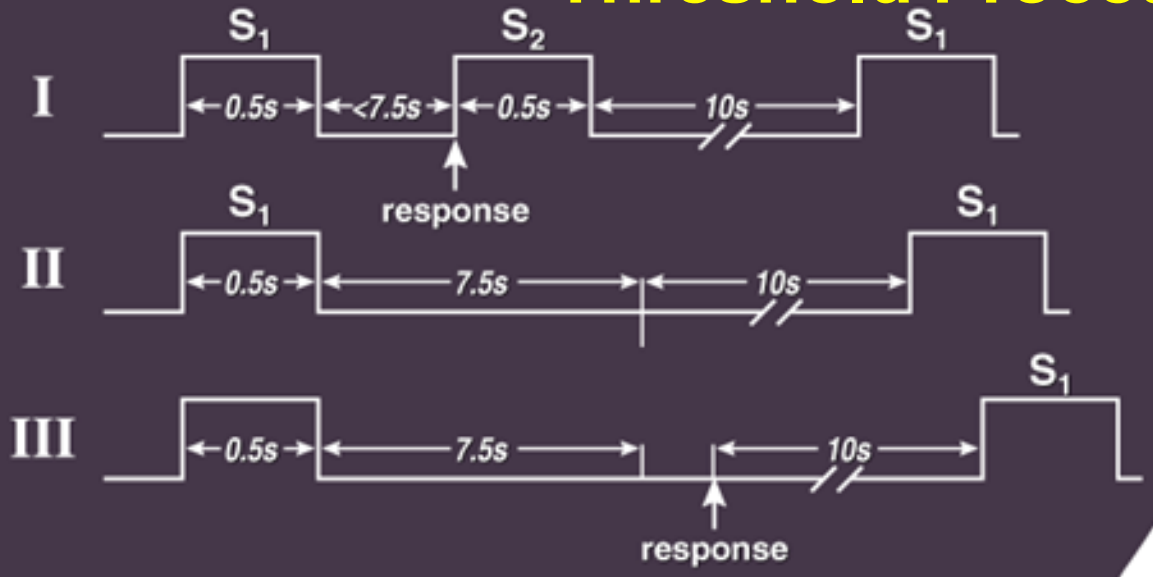


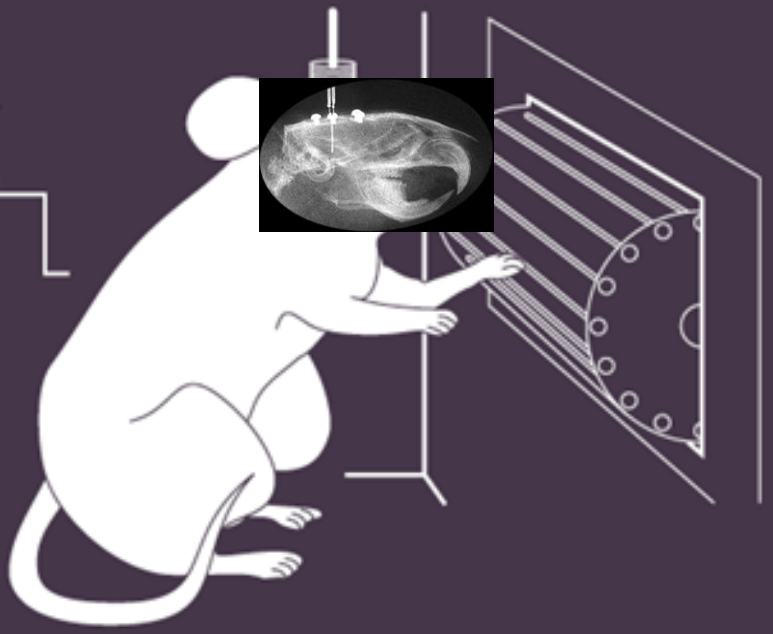
From: Caine SB, Lintz R and Koob GF. in Sahgal A (ed) Behavioural Neuroscience: A Practical Approach, vol. 2, IRL Press, Oxford, 1993, pp. 117-143.

Withdrawal/Negative Affect Stage



Intracranial Self-Stimulation (ICSS) Threshold Procedure



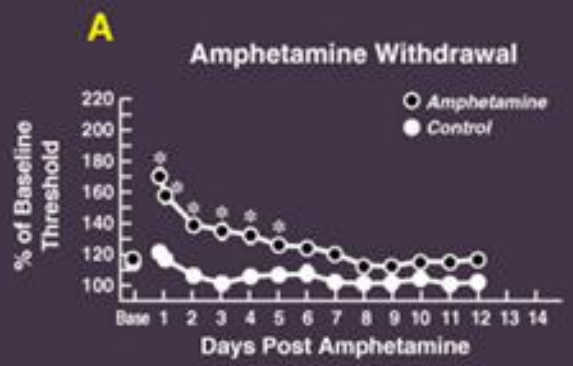


Current (μA)	Descending	Ascending	Descending	Ascending
180	+ + +		+ + +	+ + +
175	+ + +	+ + +	+ + +	+ + +
170	+ + +	+ + +	+ + +	+ + +
165	+ - +	- - -	+ - -	- - -
160	- - -	- + -	- + +	- - -
155	- - -	- - -	- - -	- - +
150		- - -	- - -	- - -
145				- - -
	162.5	167.5	157.5	167.5

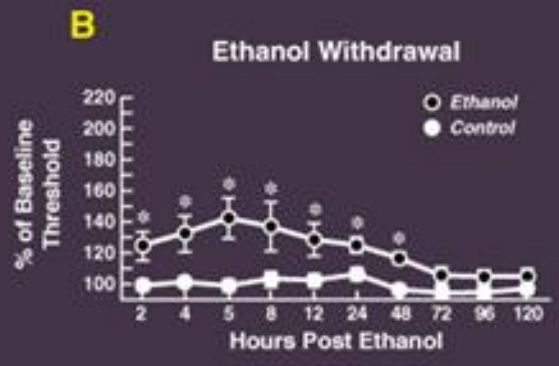
Threshold = 163.75 μA

Adapted from: Markou A and Koob GF, Physiol Behav, 1992, 51:111-119.

Elevations in ICSS Reward Thresholds During Withdrawal

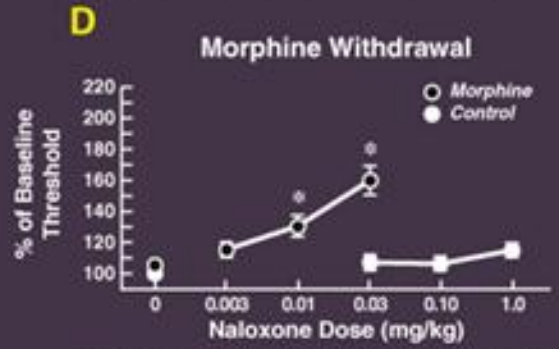


[Paterson *et al.*, Psychopharmacology 2000, 152:440]

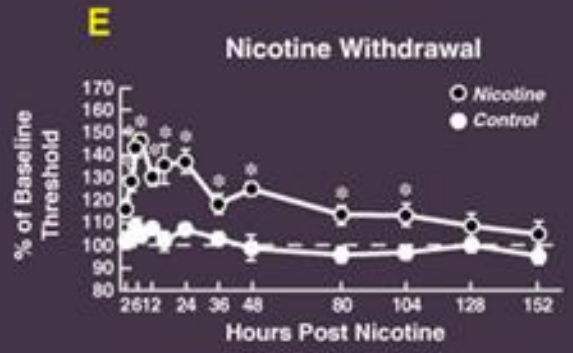


[Schulteis *et al.*, Proc Natl Acad Sci USA 1995, 92:5880]

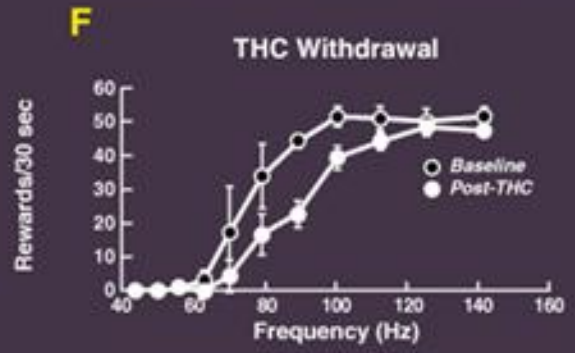
[Markou & Koob, Neuropsychopharmacology 1991, 4:17]



[Schulteis *et al.*, J Pharmacol Exp Ther 1994, 271:1391]

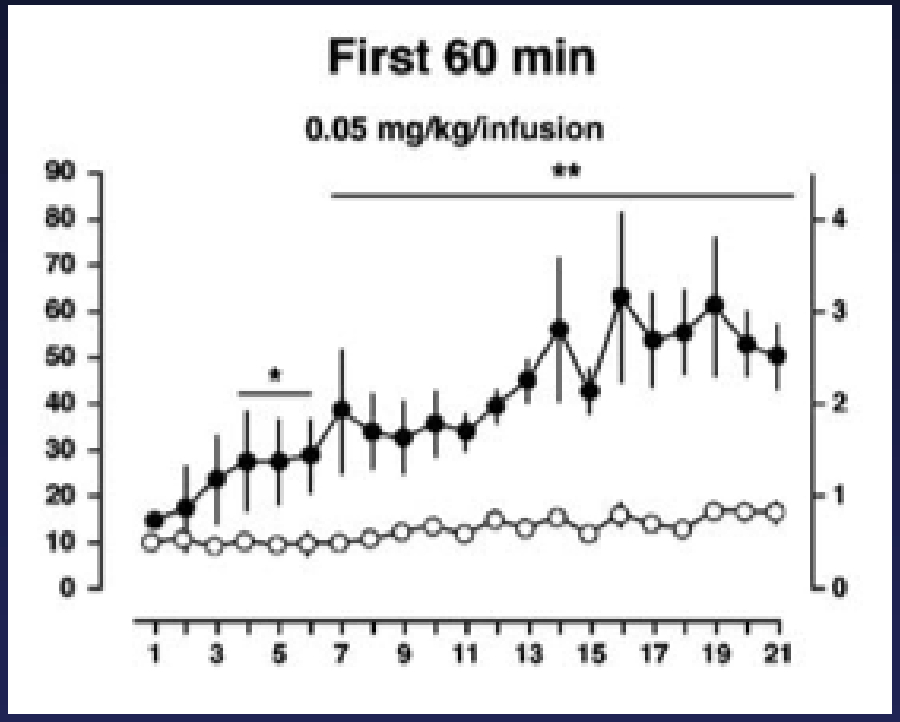


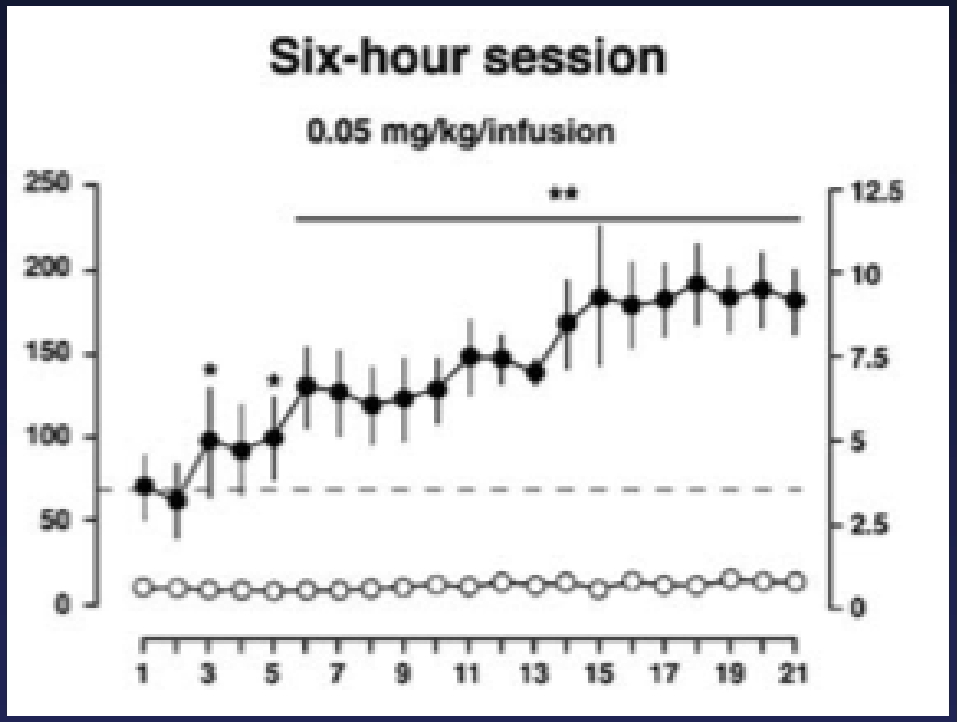
[Epping-Jordan *et al.*, Nature 1998, 393:76]



[Gardner & Vorel, Neurobiol Dis 1998, 5:502]

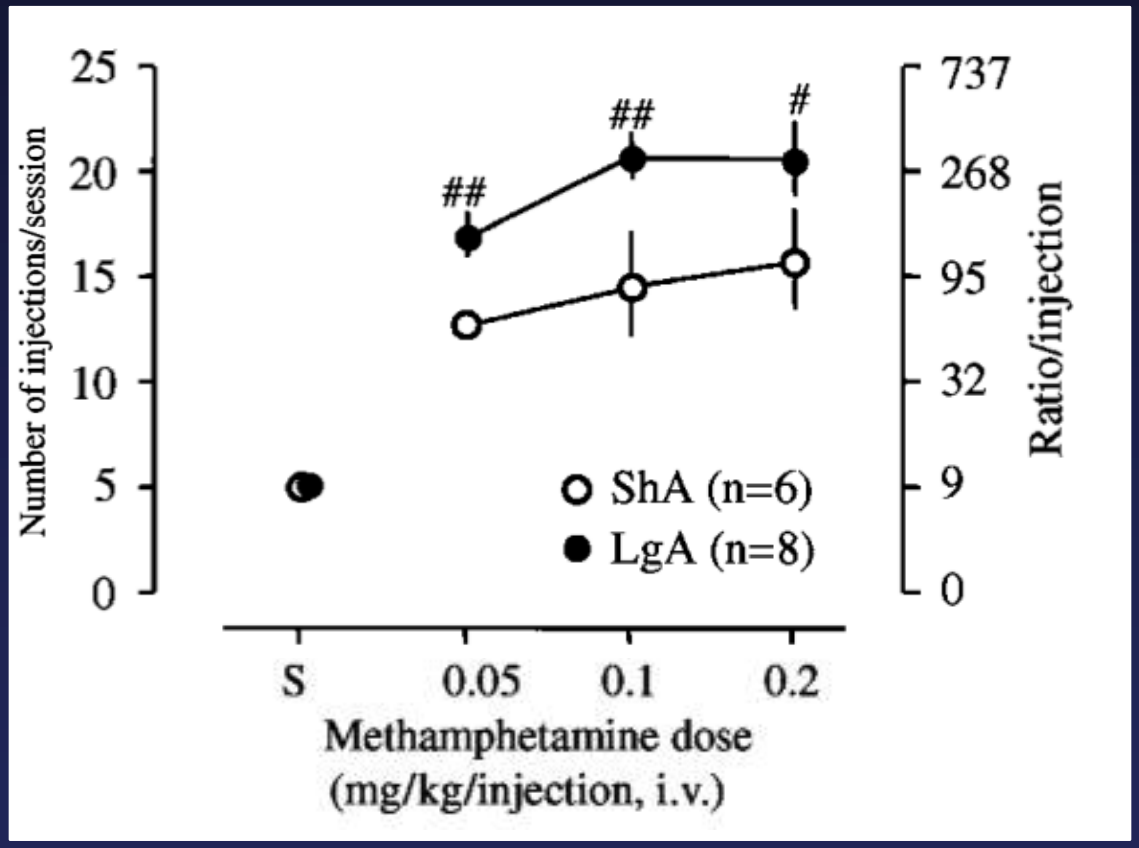
Animal Models: Extended Access Psychostimulant Self-Administration





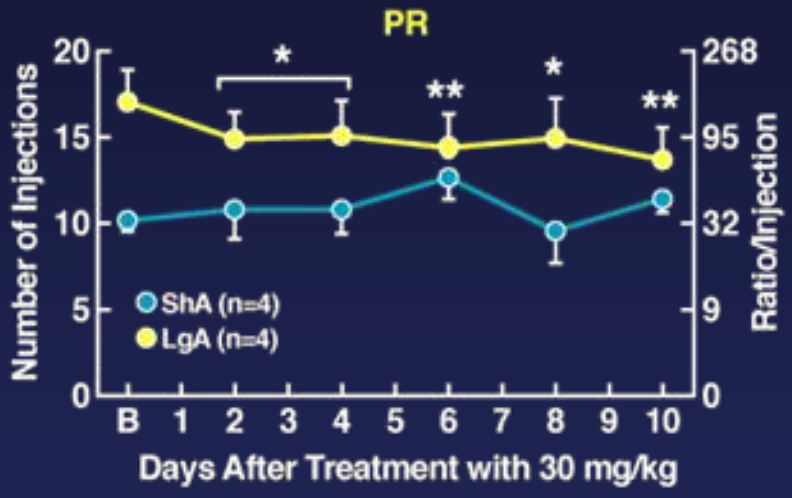
Extended access (6hr) leads to escalation of methamphetamine intake

Animal Models: Progressive Ratio (PR) Schedule



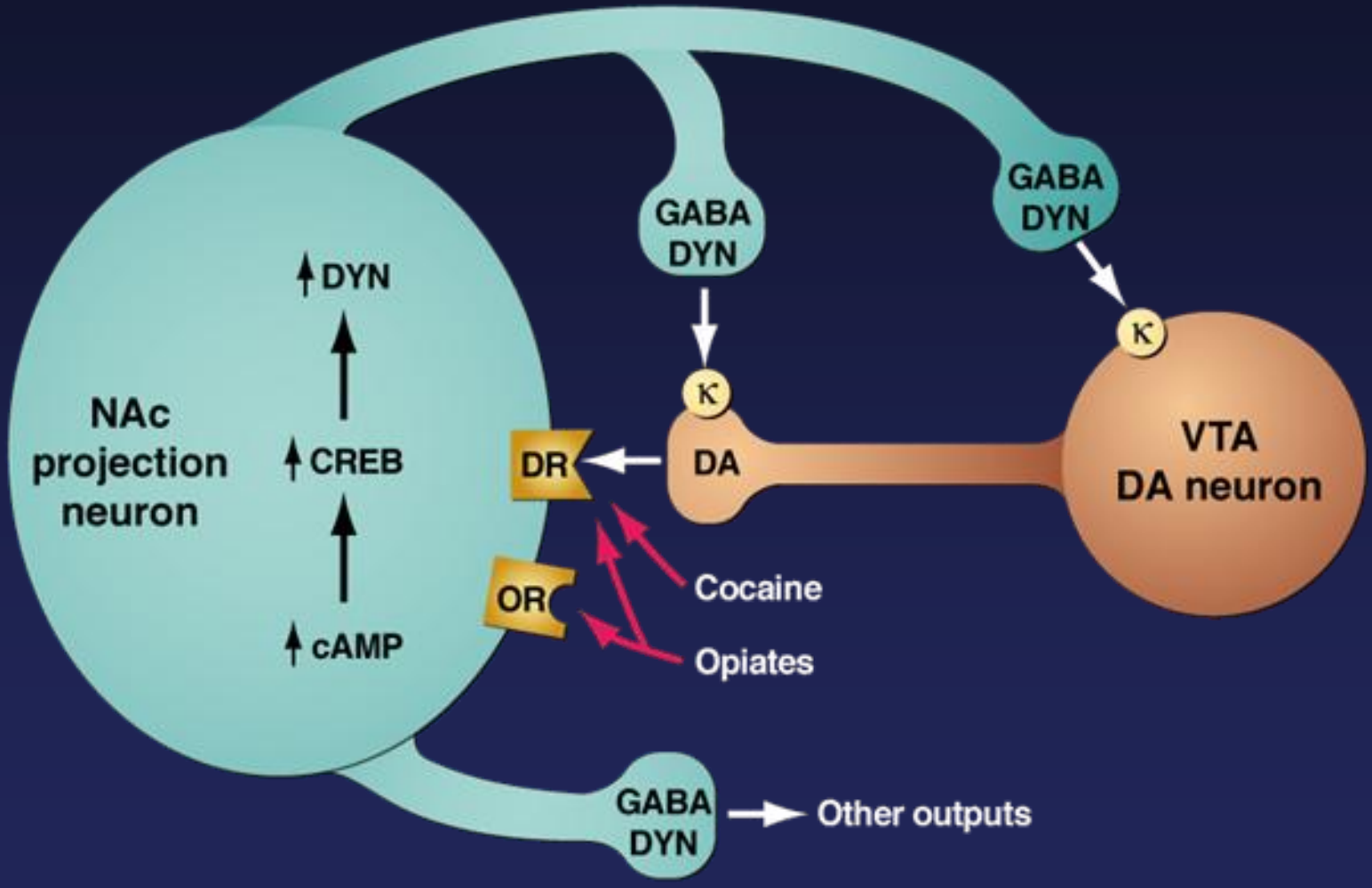
Extended access (6hr) self-administration leads to higher PR breakpoints

Effects of κ Opioid Antagonist NorBNI on Extended Access Cocaine Self-administration (Compulsive Drug Taking)



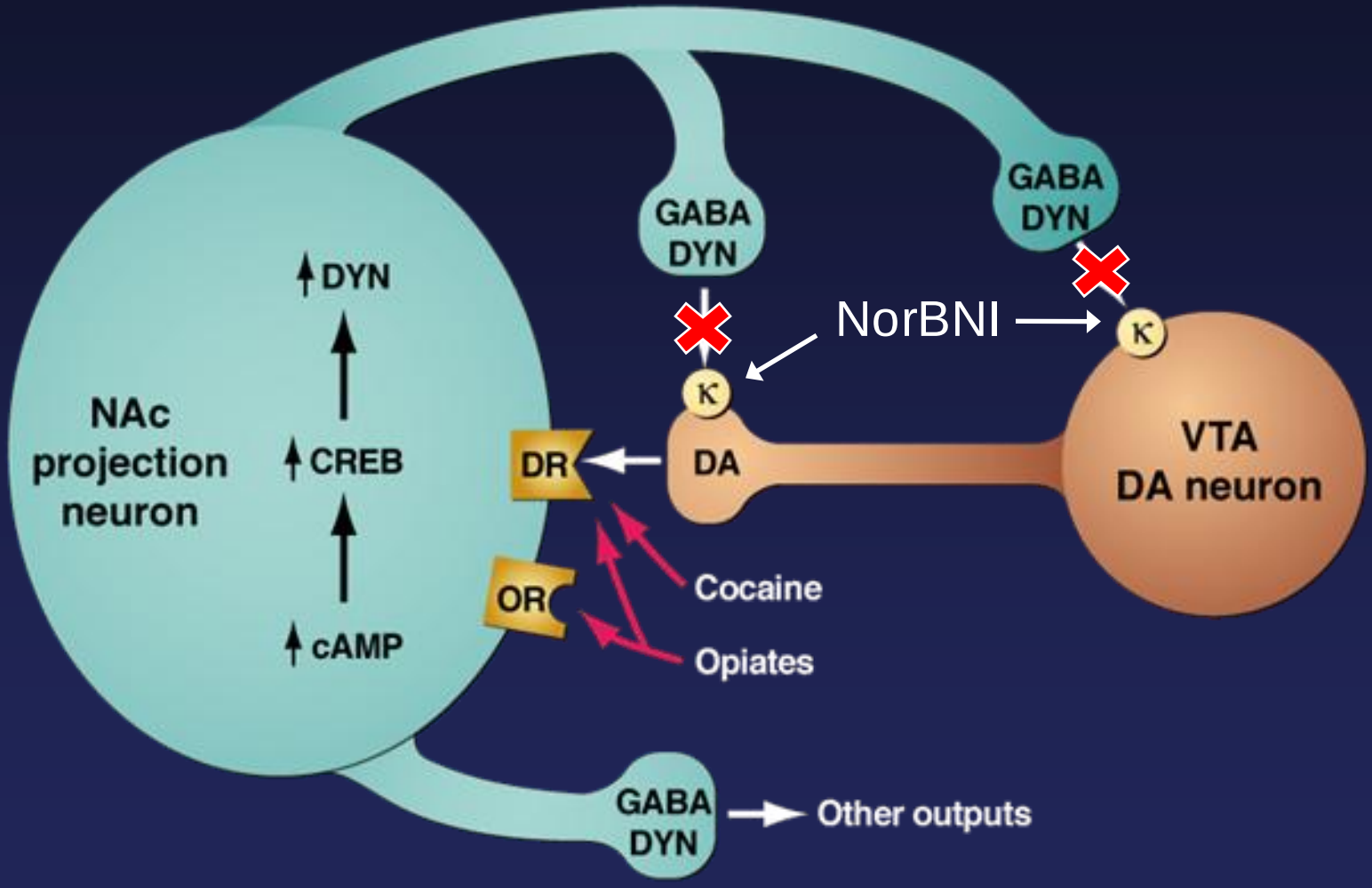
From: Wee S, Orio L, Ghirmai S, Cashman J, Koob GF. Psychopharmacology, 2009, 205:565-575.

Dynorphin Control of Mesocorticolimbic Dopamine- Within System?



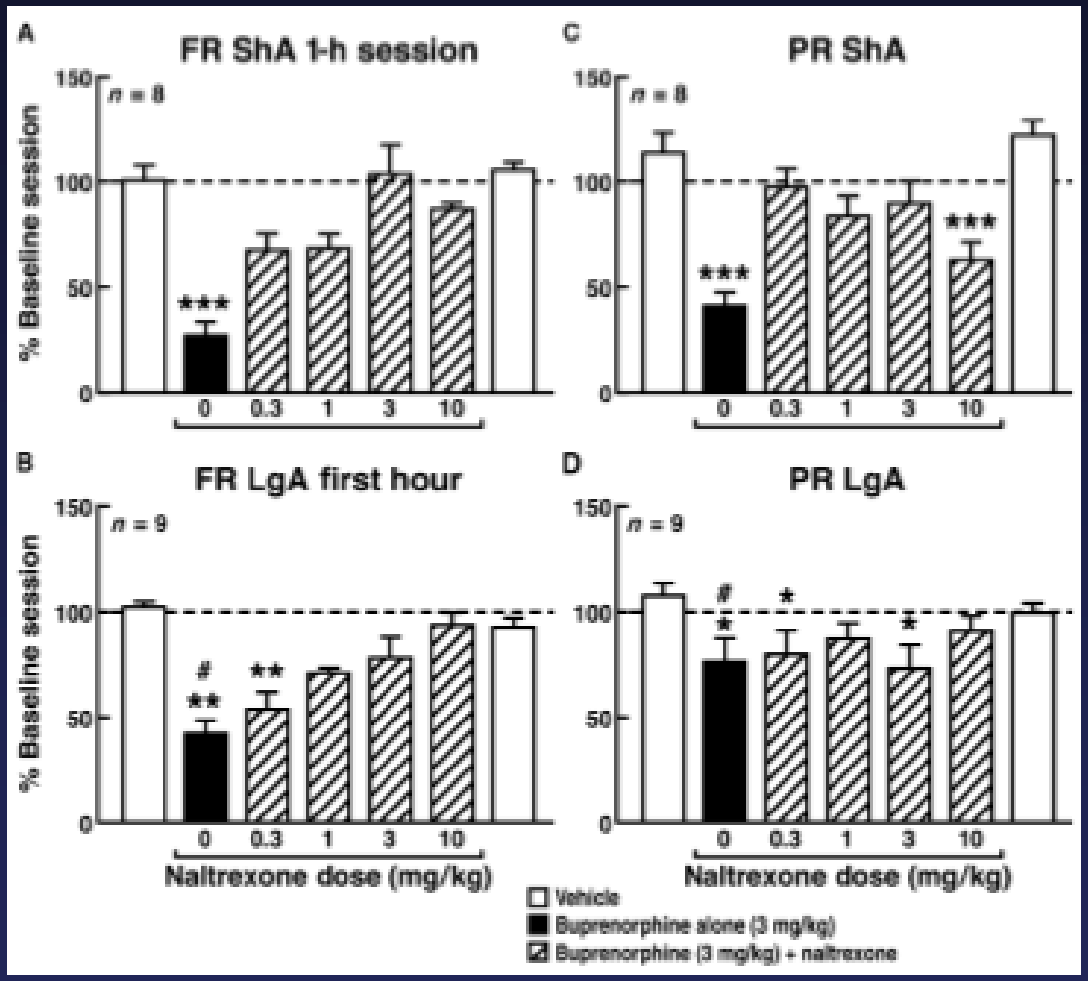
From: Nestler EJ. Nat Rev Neurosci, 2001, 2:119-128.

Dynorphin Control of Mesocorticolimbic Dopamine- Within System?



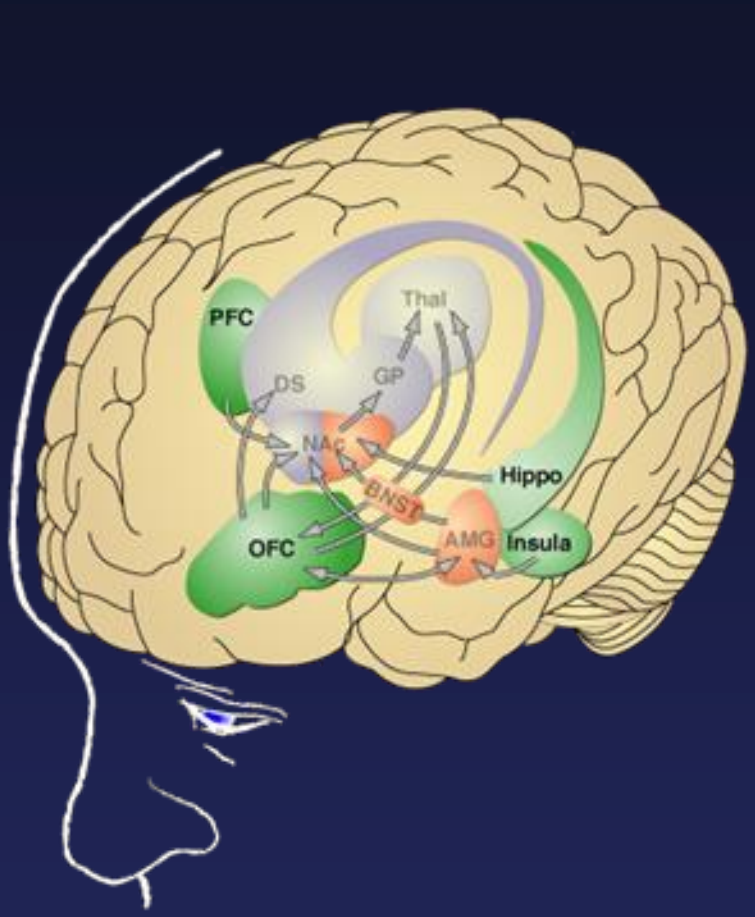
From: Nestler EJ. Nat Rev Neurosci, 2001, 2:119-128.

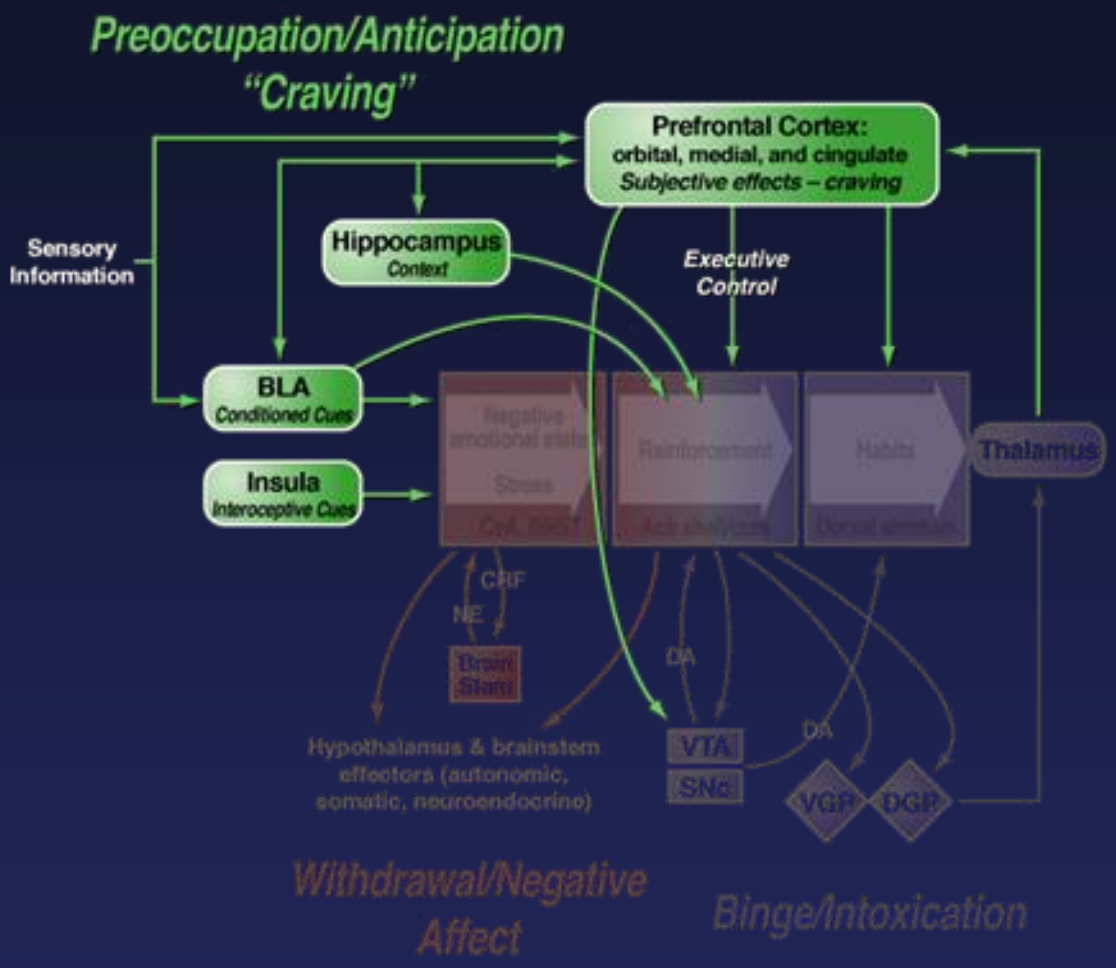
Buprenorphine Combined with Naltrexone Decreases Cocaine Self-administration in Rats with a History of Extended Access



From: Wee, S.,Vendruscolo, LF, Misra, KK, Schlosburg, JE and Koob GF,. Science Translational Medicine, 2012, in press.

Preoccupation/Anticipation (Craving) Stage





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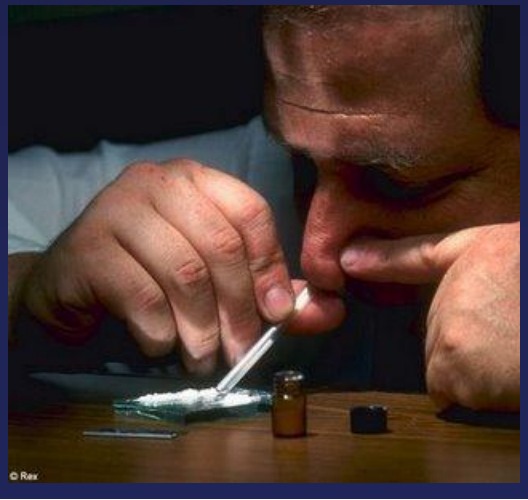
Relapse can be triggered by…

Stress

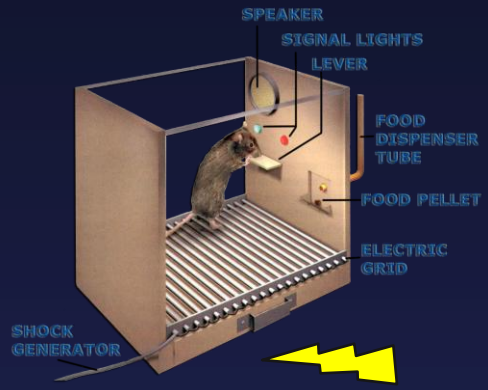
Drug-Associated Cues

Environmental Cues



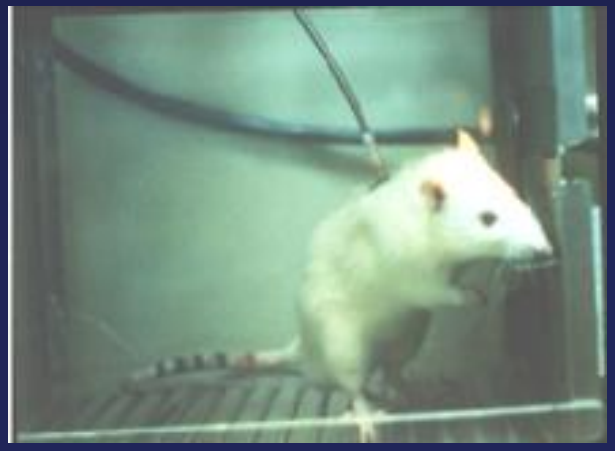
Relapse can be triggered by…

Stress

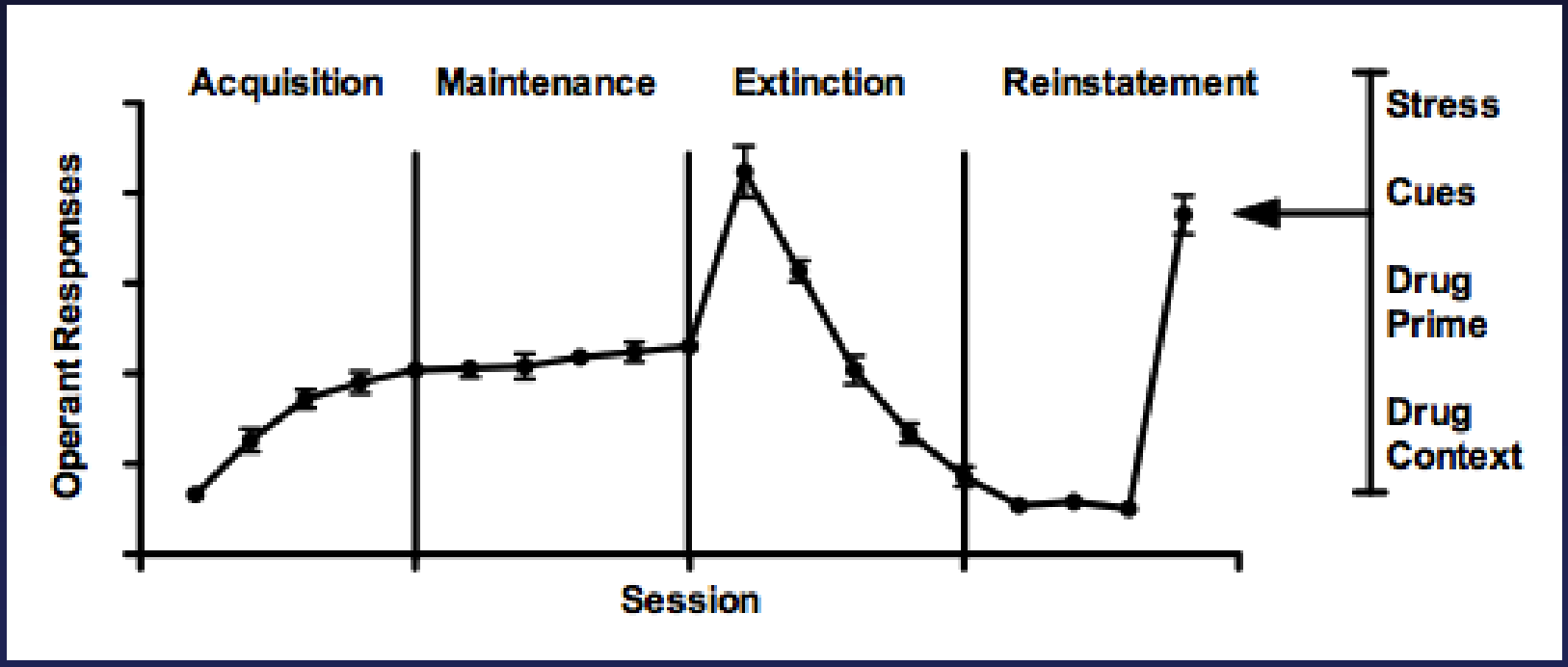


Drug-Associated Cues

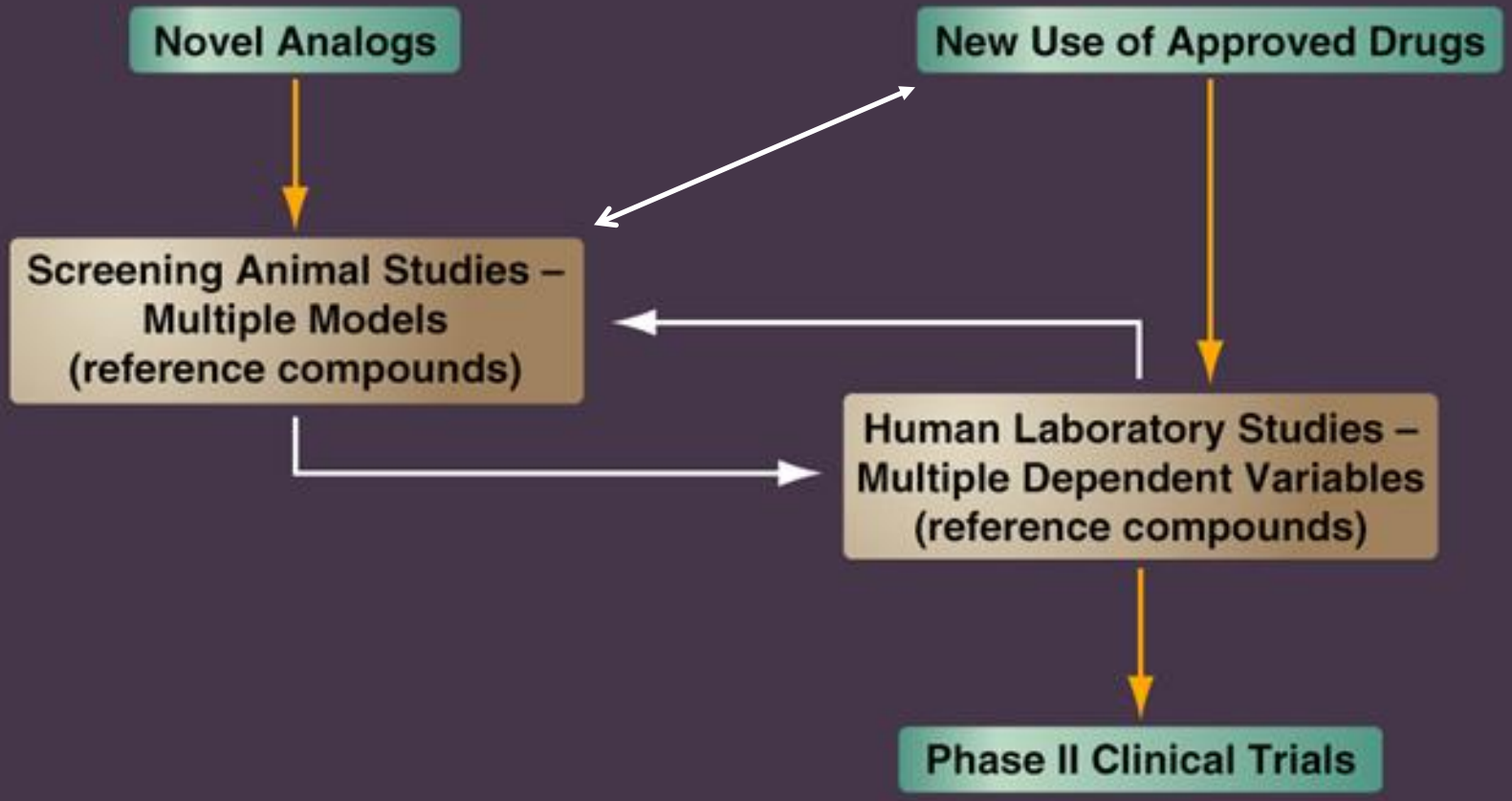
Contextual Cues



Reinstatement of Drug Seeking



Medications Development- A Rosetta Stone Approach



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Stress and Anti-stress Neurotransmitters Implicated in the Motivational Effects of Drugs of Abuse

↑ Corticotropin-releasing factor

↑ Norepinephrine

↑ Vasopressin

↑ Orexin (hypocretin)

↑ Dynorphin

↑ Substance P

↓ Neuropeptide Y

↓ Nociceptin (orphanin FQ)

↓ Endocannabinoids

Targets for Medications Development Derived from Preclinical Basic Research

Class	Target
Dopamine receptor partial agonists	D_2 receptor partial agonist (aripiprazole) D_3 receptor partial agonist
Modulators of γ-aminobutyric acid	Gabapentin
Modulators of brain stress systems	CRF_1 receptor antagonist Kappa opioid antagonist Neurokinin-1 receptor antagonist
Modulators of glutamate	AMPA receptor antagonist NMDA receptor antagonist Metabotropic glutamate receptor agonist Glutamate-5 receptor antagonist Topiramate

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Key Findings and Conclusions

Extended access to drugs of abuse is associated with compulsive use— as reflected in escalation in drug intake, increased progressive ratio responding, and motivational withdrawal upon abstinence.

Withdrawal from all major drugs of abuse — produces decreases in dopamine function, increases in stress-like responses, increases in CRF activity in the amygdala, and increases in basal ganglia dynorphin activity that are of motivational significance

Development of compulsive drug use associated with dependence— may be mediated by a progressive recruitment of brain stress systems such as the HPA axis, CRF in the VTA, frontal cortex and amygdala, and dynorphin in the basal ganglia

The dark side of the neurocircuitry of addiction--- may involve multiple stages of the addiction cycle to initiate and perpetuate the negative emotional states that drive dependence on drugs of abuse

Brain-arousal stress systems in the extended amygdala--- may be key target for medications development for the negative emotional states that drive dependence and relapse in addiction