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ADDS 5031
Applied Psychopharmacology
Spring 2015

Substance Use Disorders
(Mainly Alcohol)

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Lecture Outline

- DSM-5 criteria set for addiction
- Some preliminaries
- Neurobiology of addiction
- Integrated Dual Disorders Treatment (IDDT)
- Medication-Assisted Treatment (MAT)

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Alcohol Use Disorder

Diagnostic Criteria

A. A problematic pattern of alcohol use leading to clinically significant impairment or distress, as manifested by at least two of the following, occurring within a 12-month period:

1. Alcohol is often taken in larger amounts or over a longer period than was intended.
2. There is a persistent desire or unsuccessful efforts to cut down or control alcohol use.
3. A great deal of time is spent in activities necessary to obtain alcohol, use alcohol, or recover from its effects.
4. Craving, or a strong desire or urge to use alcohol.
5. Recurrent alcohol use resulting in a failure to fulfill major role obligations at work, school, or home.
6. Continued alcohol use despite having persistent or recurrent social or interpersonal problems caused or exacerbated by the effects of alcohol.
7. Important social, occupational, or recreational activities are given up or reduced because of alcohol use.

DSM-5, p. 490–491.

8. Recurrent alcohol use in situations in which it is physically hazardous.

9. Alcohol use is continued despite knowledge of having a persistent or recurrent physical or psychological problem that is likely to have been caused or exacerbated by alcohol.

10. Tolerance, as defined by either of the following:

    a. A need for markedly increased amounts of alcohol to achieve intoxication or desired effect.

    b. A markedly diminished effect with continued use of the same amount of alcohol.

11. Withdrawal, as manifested by either of the following:

    a. The characteristic withdrawal syndrome for alcohol (refer to Criteria A and B of the criteria set for alcohol withdrawal, pp. 499–500).

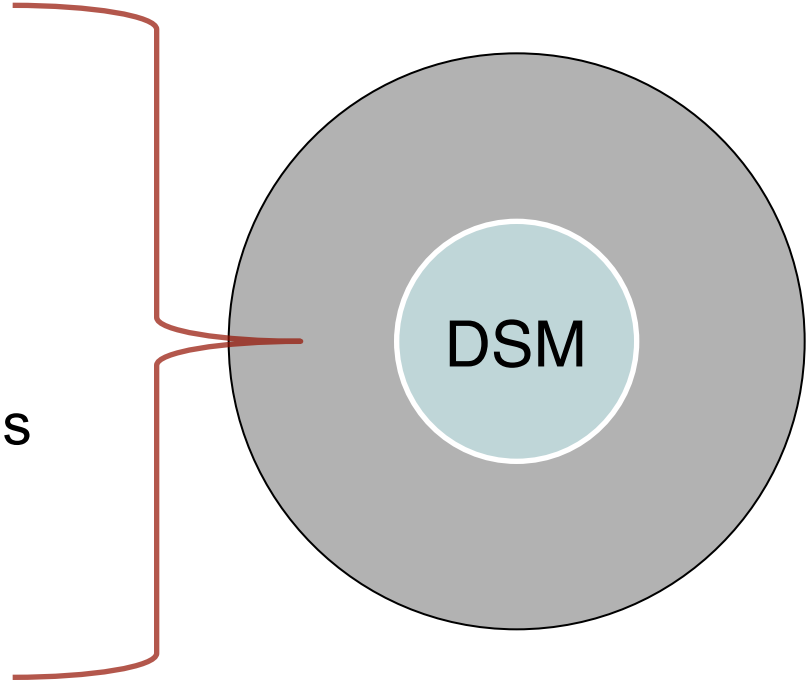
    b. Alcohol (or a closely related substance, such as a benzodiazepine) is taken to relieve or avoid withdrawal symptoms.

DSM-5, p. 490–491.

DSM-5	DSM-IV-TR
A1—Larger/longer	Dependence—3
A2—Cut down/control	Dependence—4
A3—Time	Dependence—5
A4—Craving	—
A5—Role obligations	Abuse—A1
A6—Social/interpersonal problems	Abuse—A4
A7—Activities given up/reduced	Dependence—6
A8—Use in hazardous situations	Abuse—A2
A9—Physical/psychological problem	Dependence—7
A10—Tolerance	Dependence—1
A11—Withdrawal	Dependence—2

Bigger Picture

- Poor self-awareness
- Low frustration tolerance
- Dysregulated emotions
- Impaired interpersonal skills
- Impulsivity



DSM = Diagnostic and Statistical Manual of Mental Disorders.

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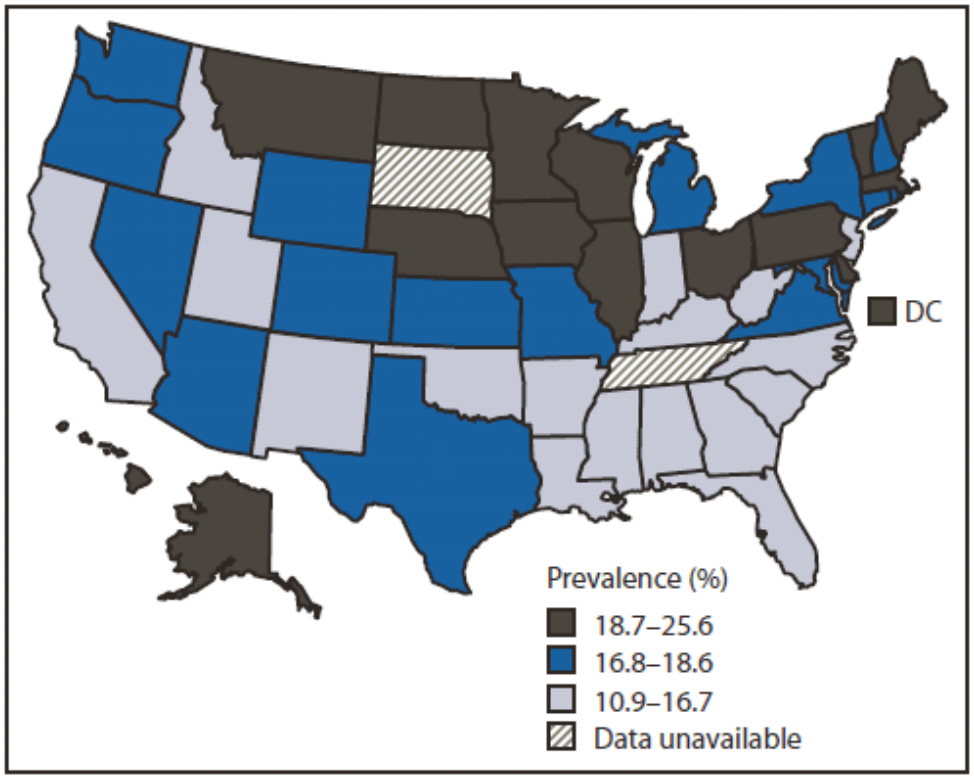
Binge Drinking



MMWR Morb Mortal Wkly Rep 2012;61(1):14.

Alcohol Addiction | 12-Month Prevalence

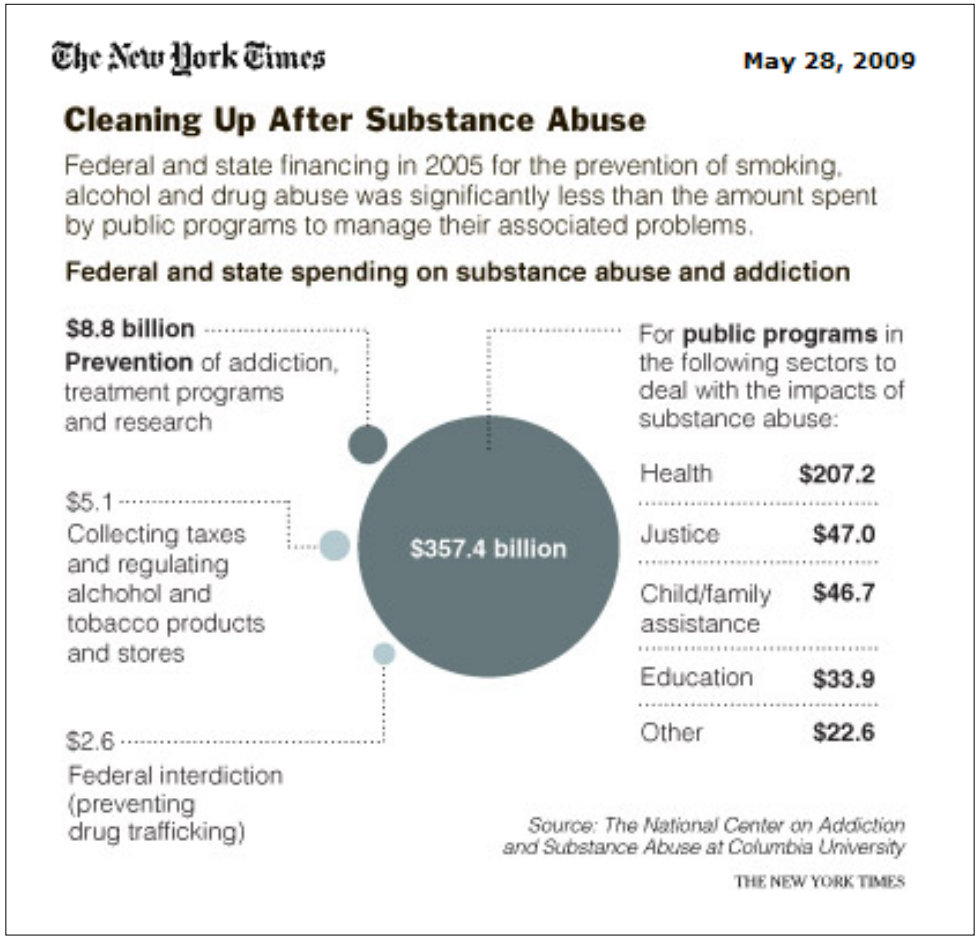
- Alcohol Abuse
  - Male: 6.9%
  - Female: 2.6%
  - Total: 4.7%
- Alcohol Dependence
  - Male: 5.4%
  - Female: 2.3%
  - Total: 3.8%

Drug Alcohol Depend 2004;74:223.

Public Enemy #3

- Excessive alcohol consumption is the third leading preventable cause of death in the United States
- There are approximately 76,000 alcohol-attributable deaths per year and 2.3 million years of potential life lost
- About 30 years of life are lost per each alcohol-attributable death

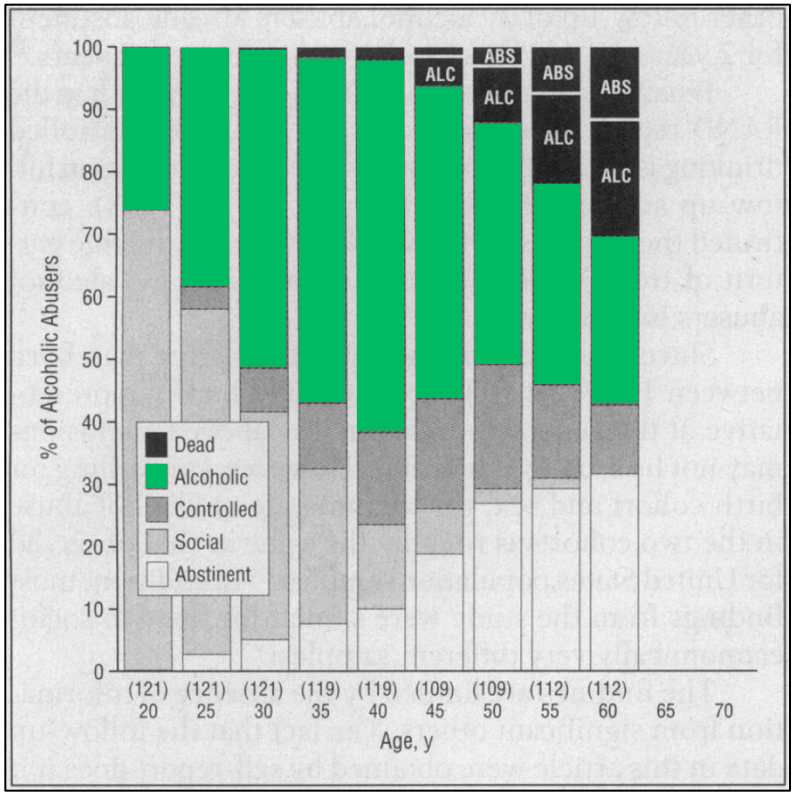
MMWR Morb Mortal Wkly Rep 2004;53(37):866.



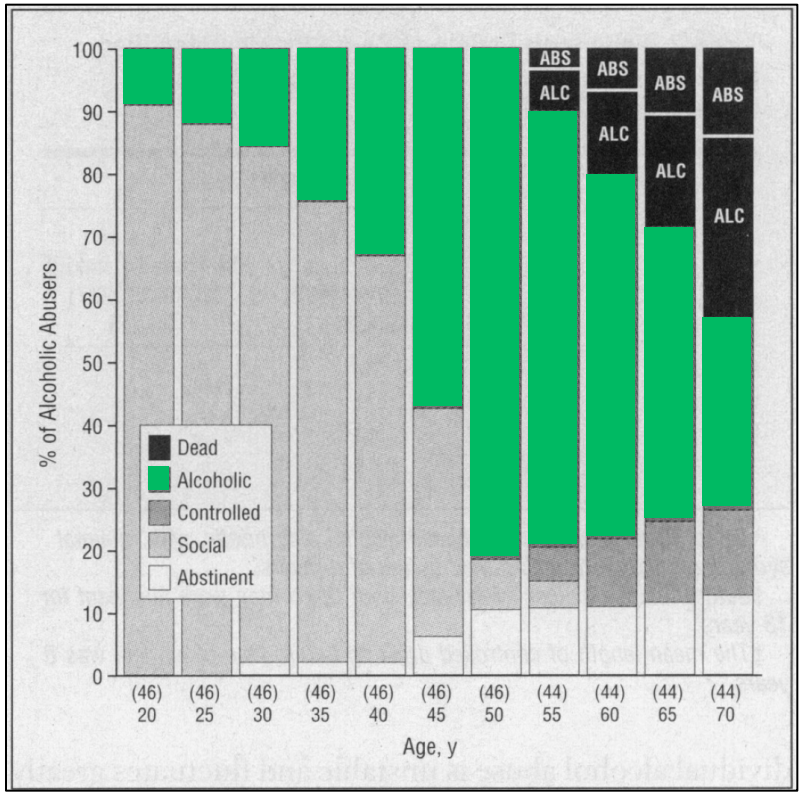
NY Times (Print) 2008 May 28:A15.

Chronic Brain Disease

- Addiction tends to be relapsing-remitting
- Chronic disease paradigms are more appropriate for management
  - Chronic care management



Core city cohort (overall prevalence 33%)



College cohort (overall prevalence 21%)

Arch Gen Psychiatry 1996;53:243.

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Addiction

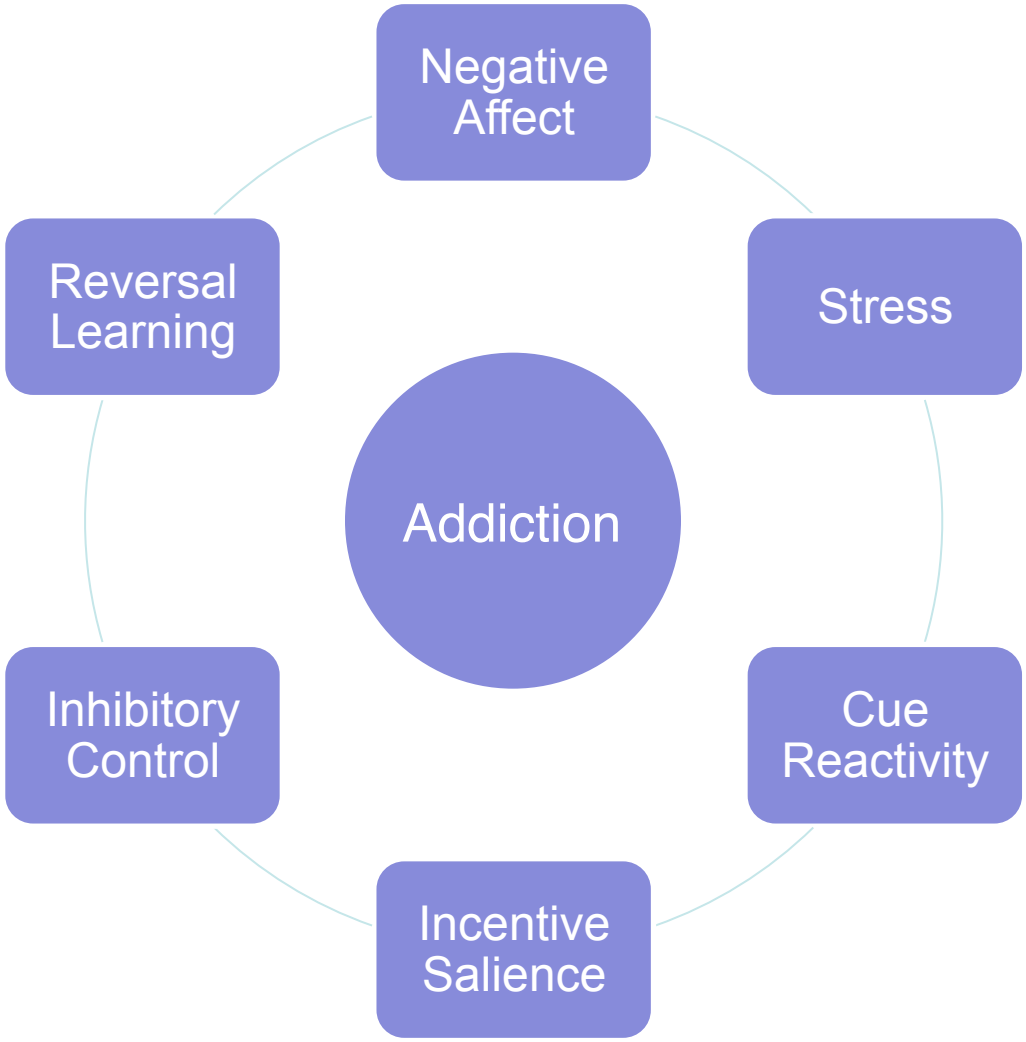
Chronic brain disease

Consisting of

Continuing

Compulsive substance use despite

Consequences



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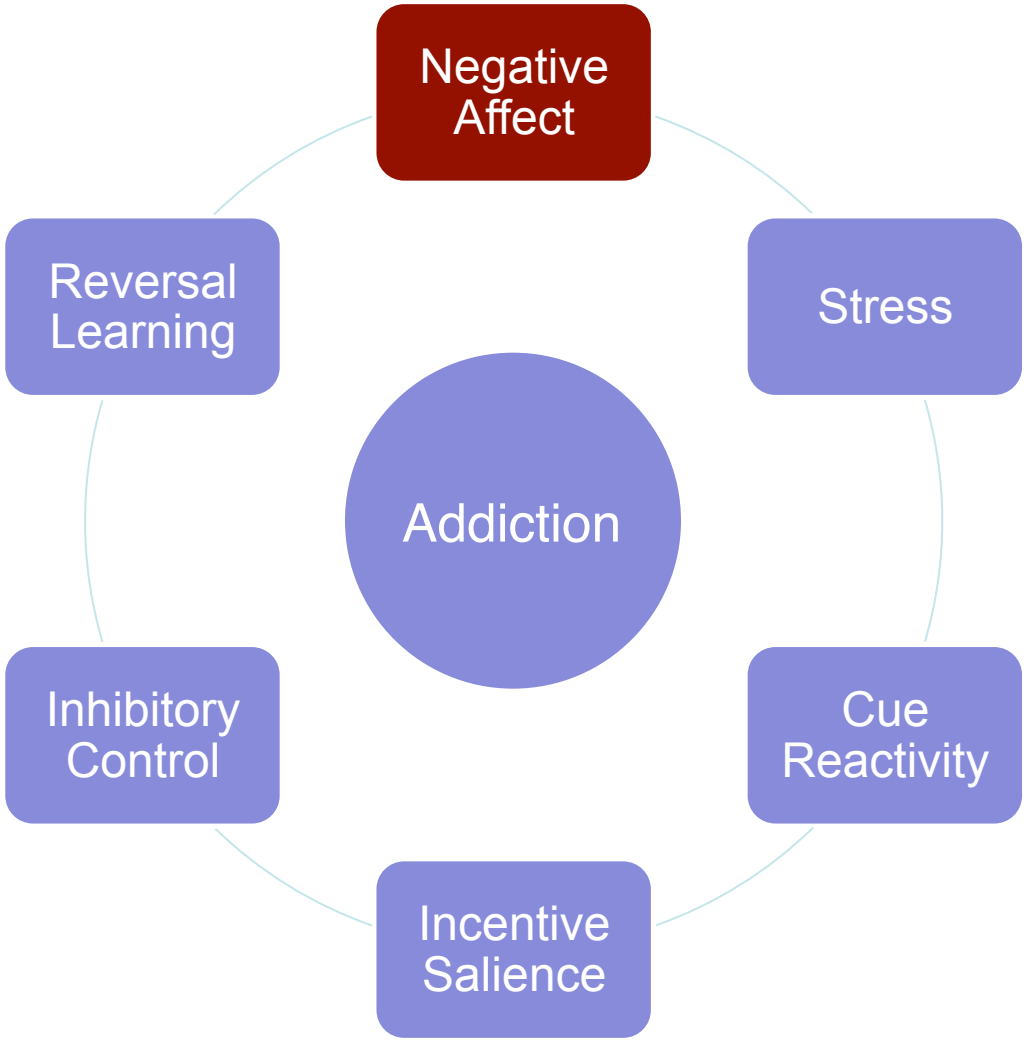

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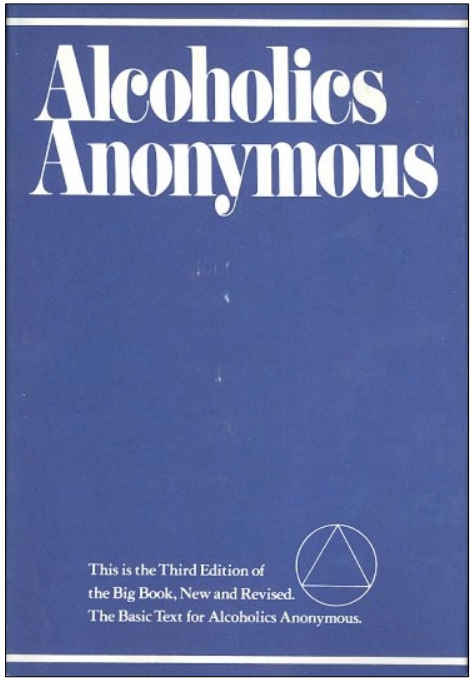
Big Book



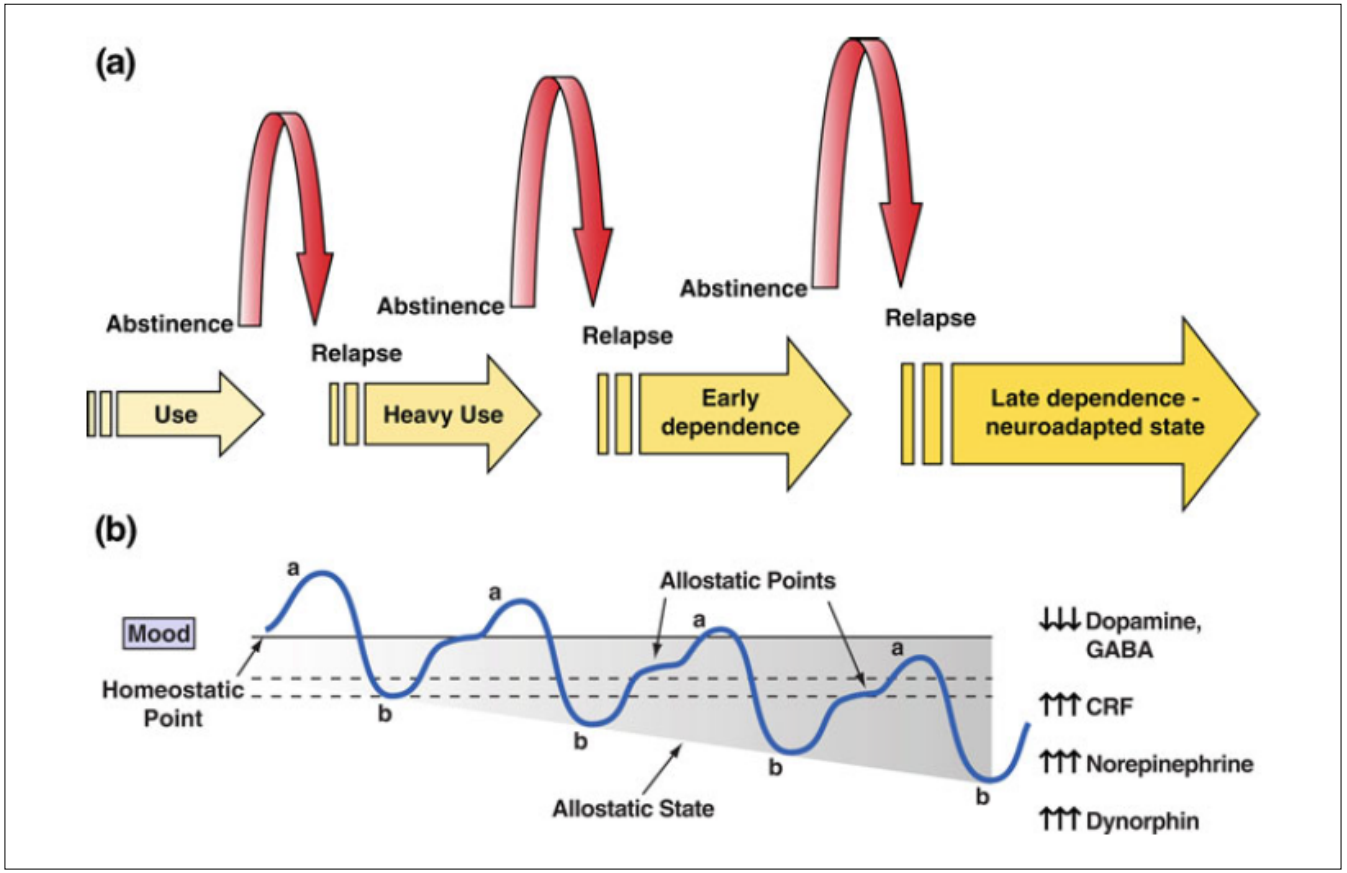
“ They are restless, irritable and discontented… ”

Alcoholics Anonymous, 3d ed (7th printing), 1980, p. xxvi.

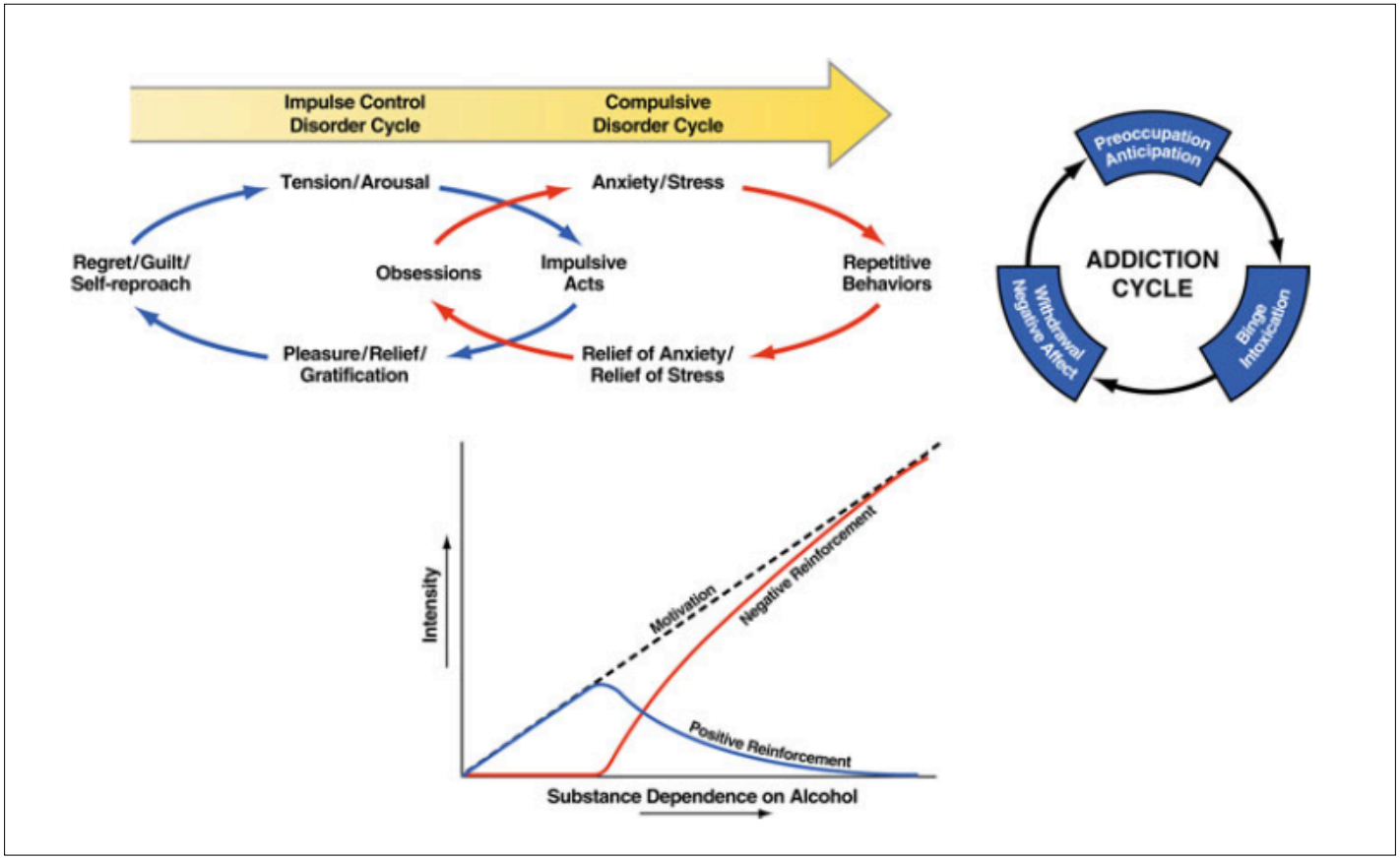
Affect

Positive		Negative	
Enthusiastic	Alert	Scared	Nervous
Interested	Active	Afraid	Ashamed
Determined	Strong	Upset	Guilty
Excited	Proud	Distressed	Irritable
Inspired	Attentive	Jittery	Hostile

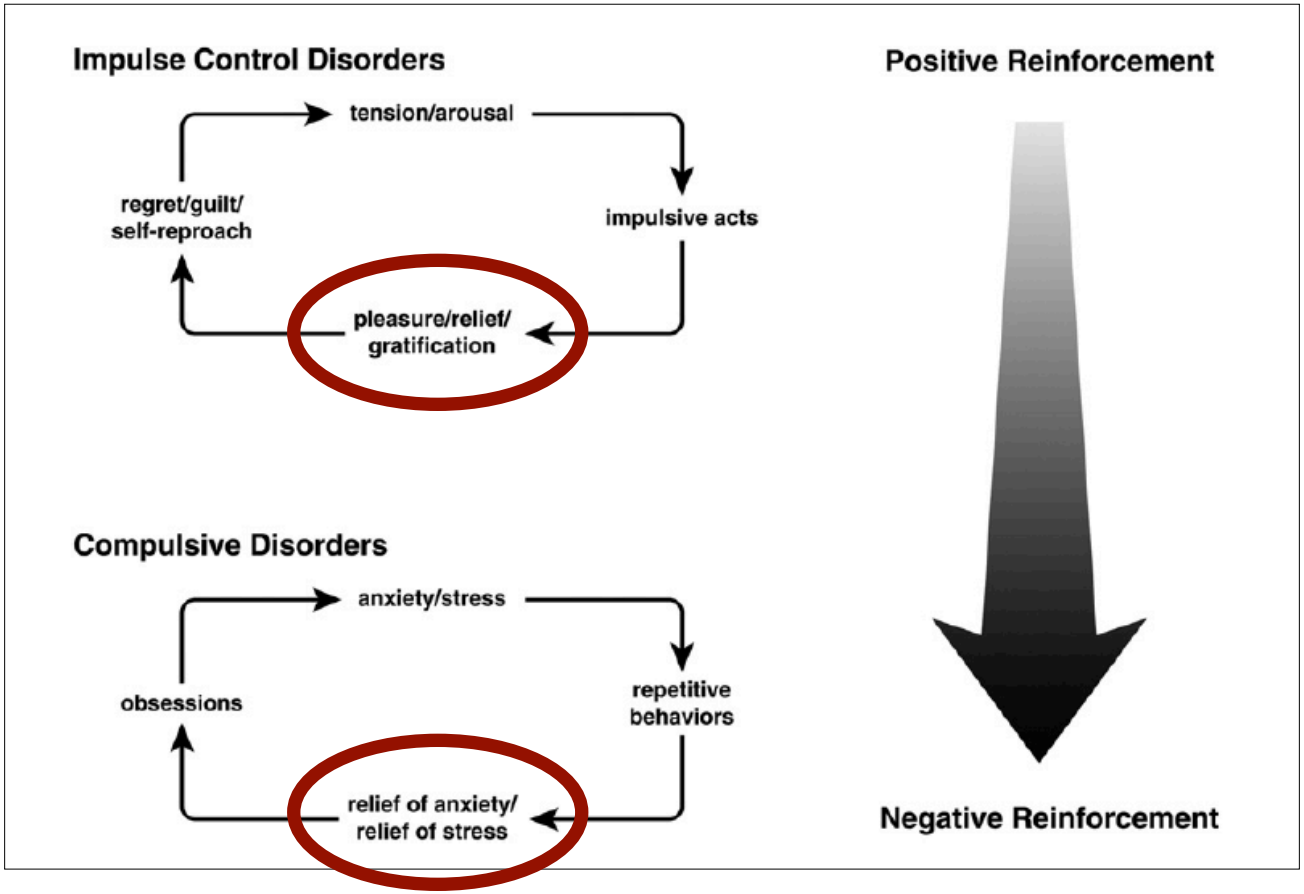
J Pers Soc Psychol 1988;54:1063.



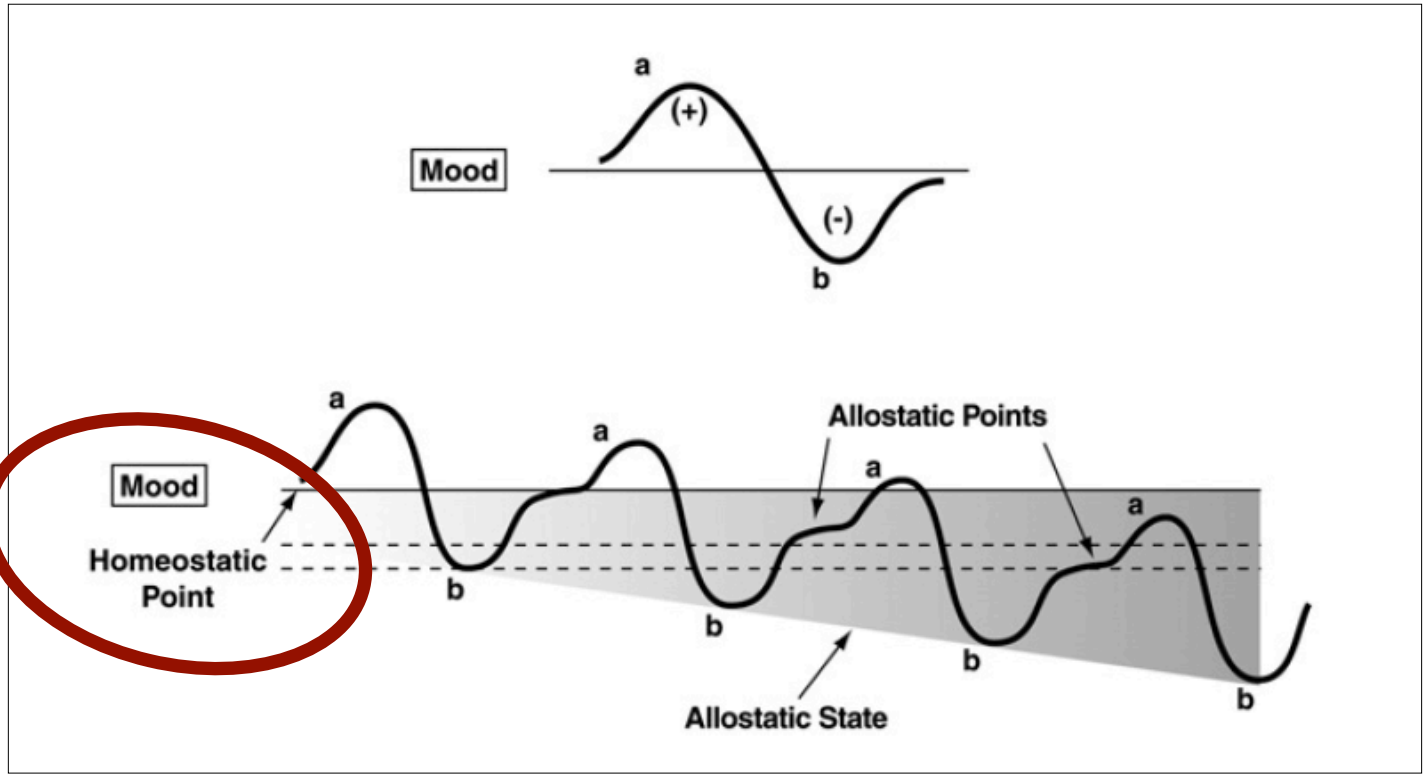
Curr Top Behav Neurosci 2013;13:3.



Curr Top Behav Neurosci 2013;13:3.

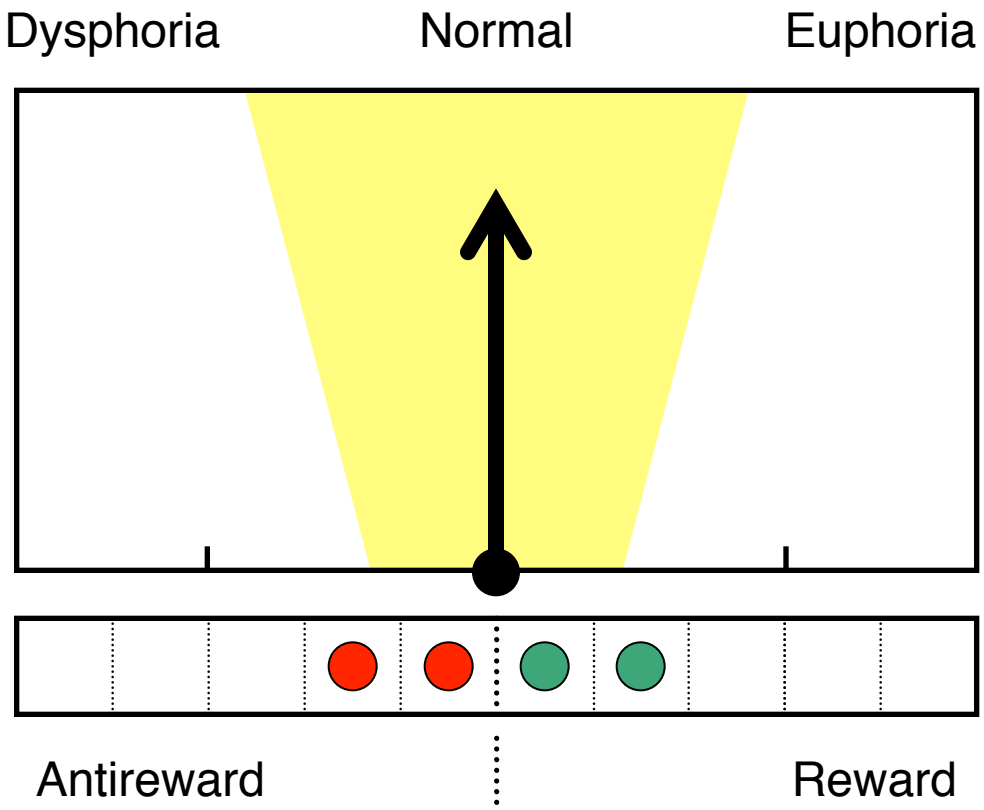


Eur Neuropsychopharmacol 2007;17:377.



Eur Neuropsychopharmacol 2007;17:377.

Hedonic Tone



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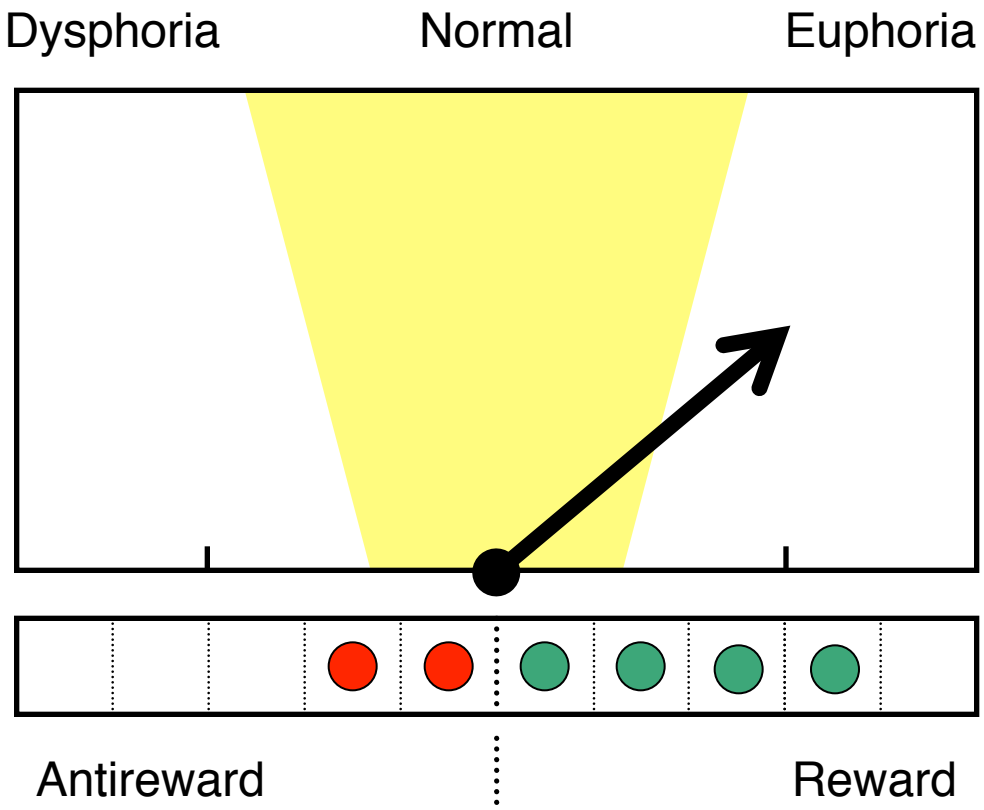
Acute Drug Use | Intoxication



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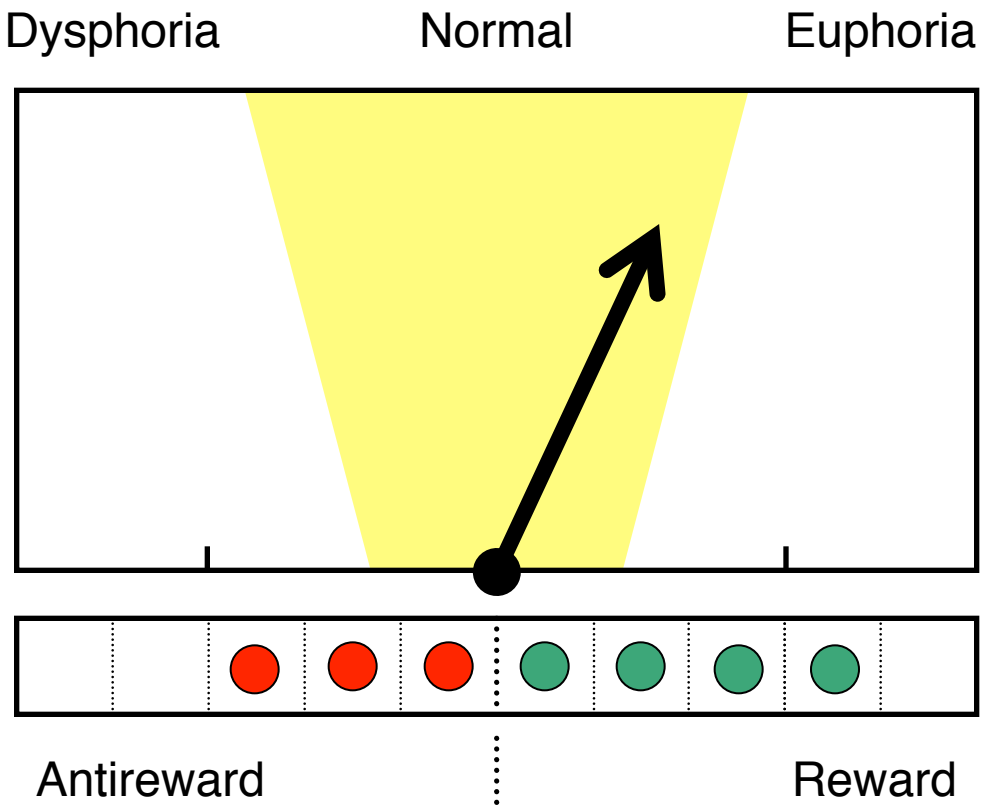
Acute Drug Use | Antireward



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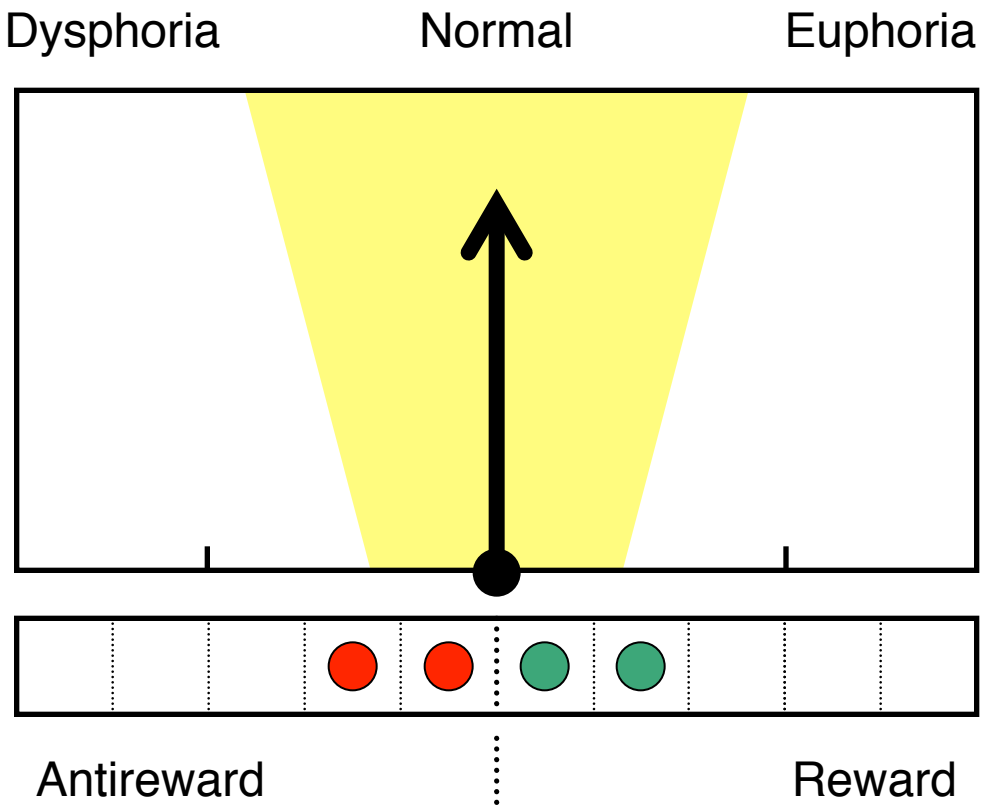
Acute Drug Use | Return to Baseline



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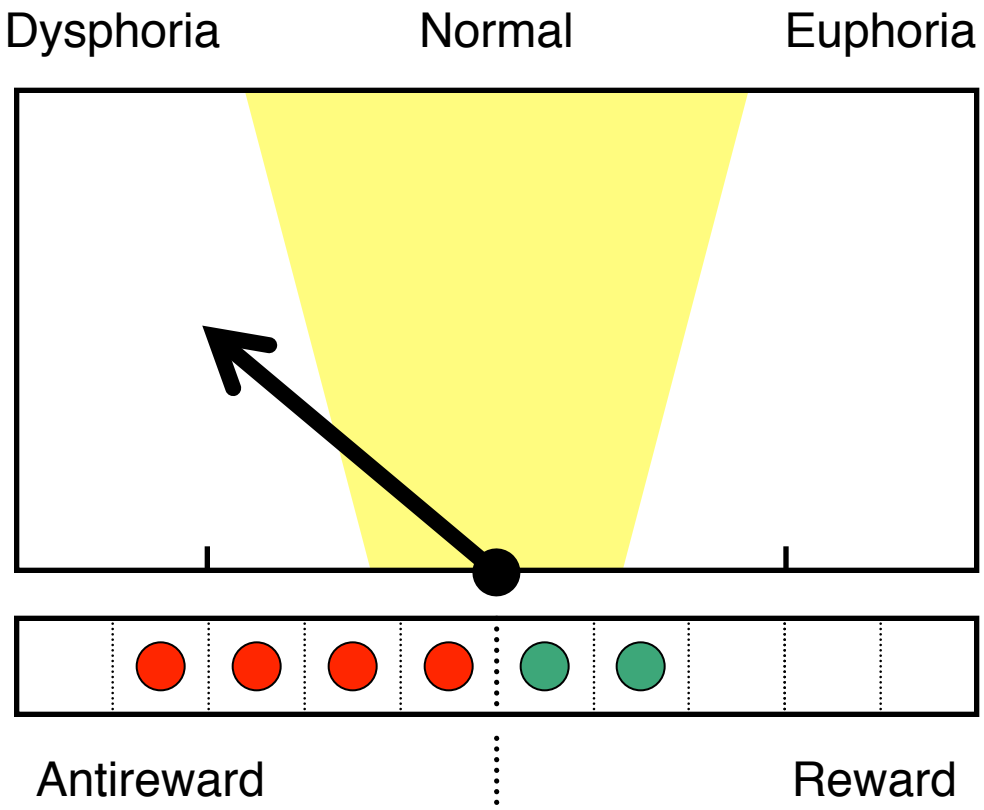
Addiction | New Baseline



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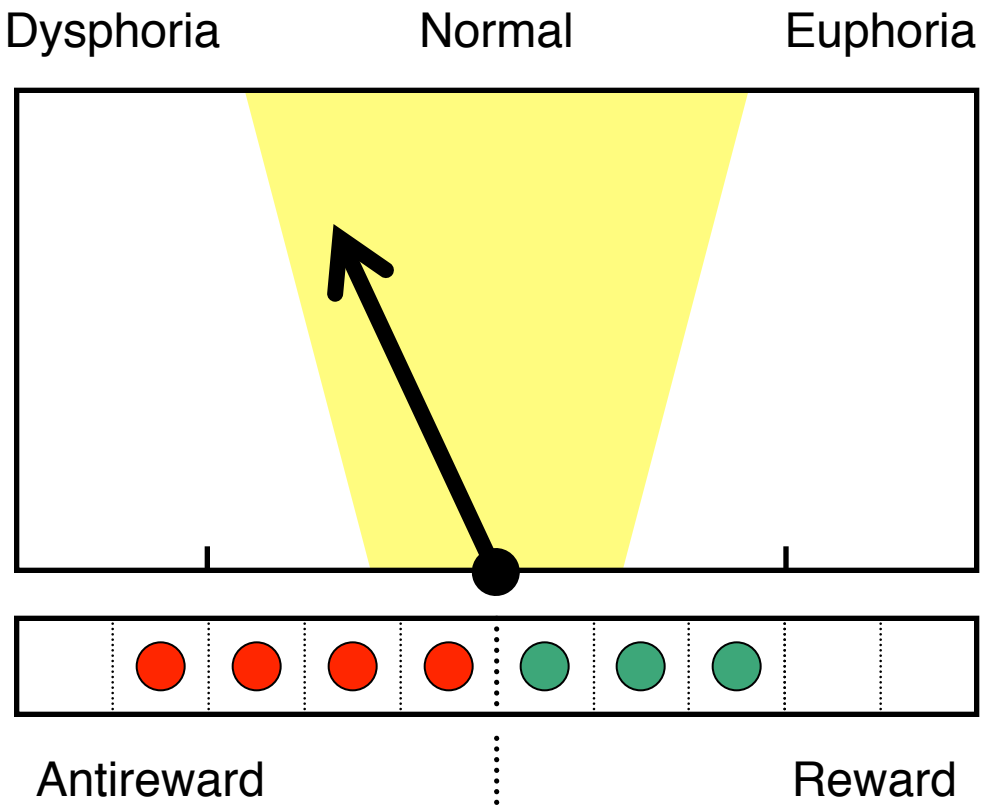
Addiction | Superimposed Drug Use



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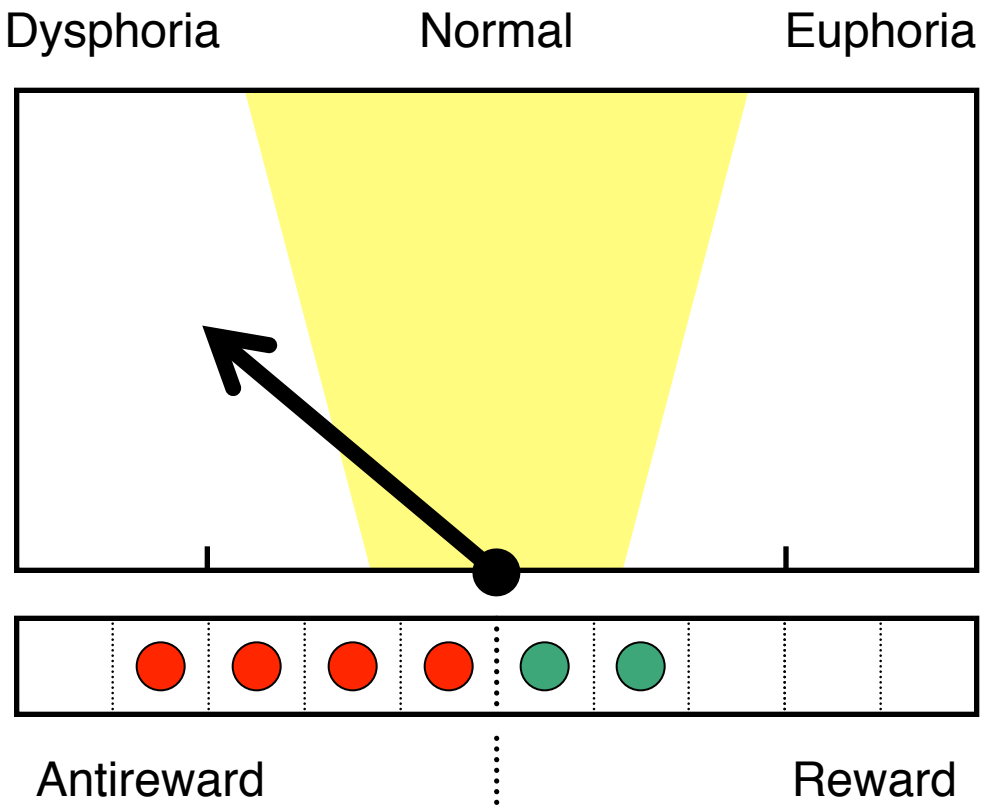
Addiction | Return to Baseline



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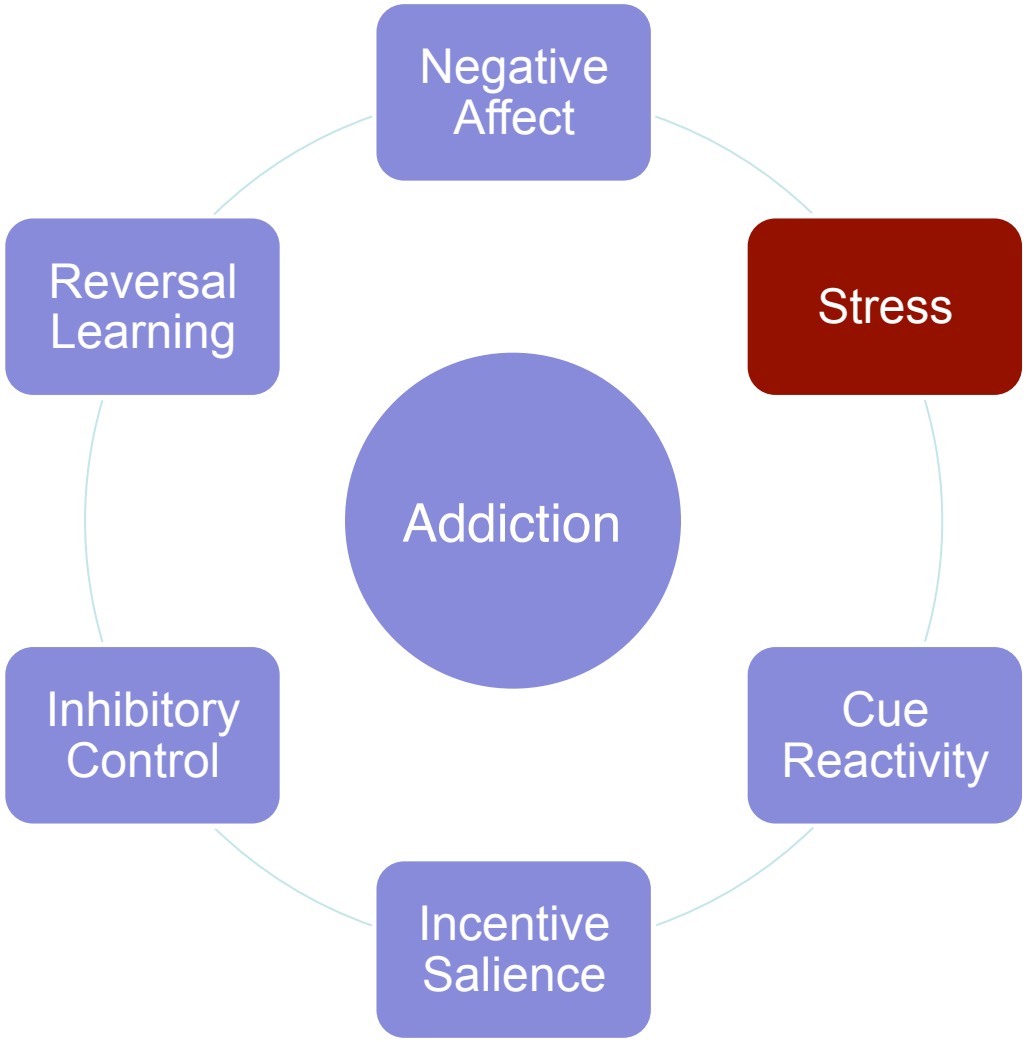

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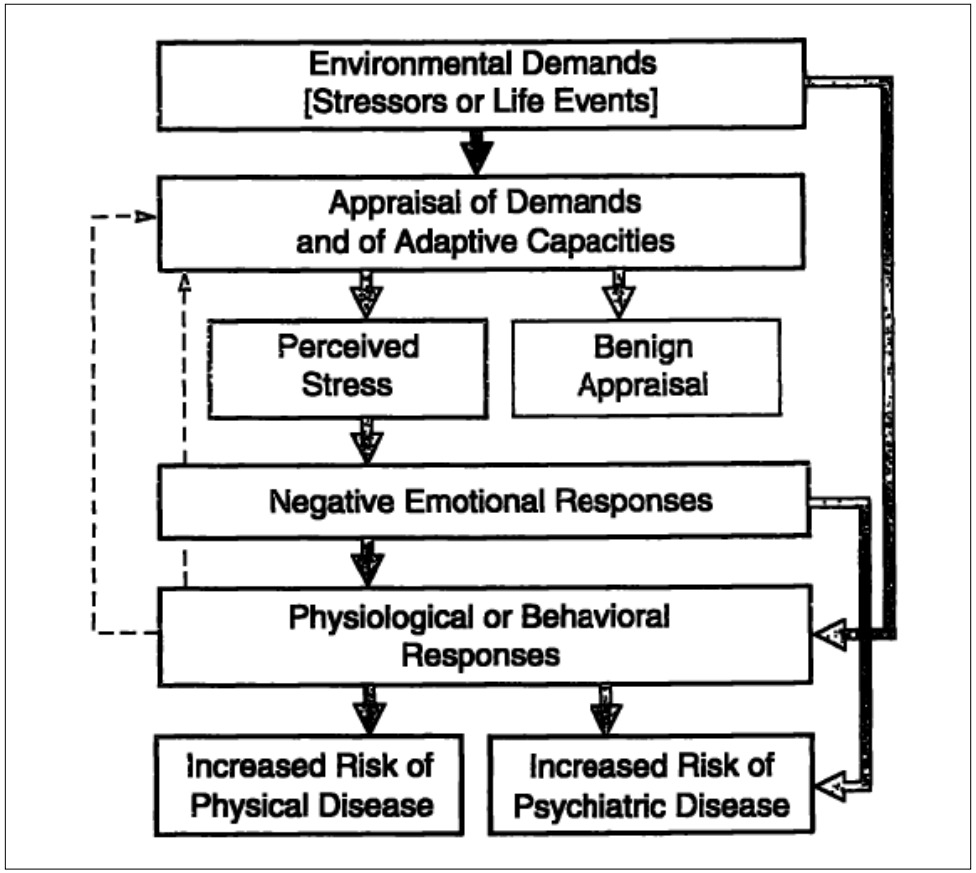
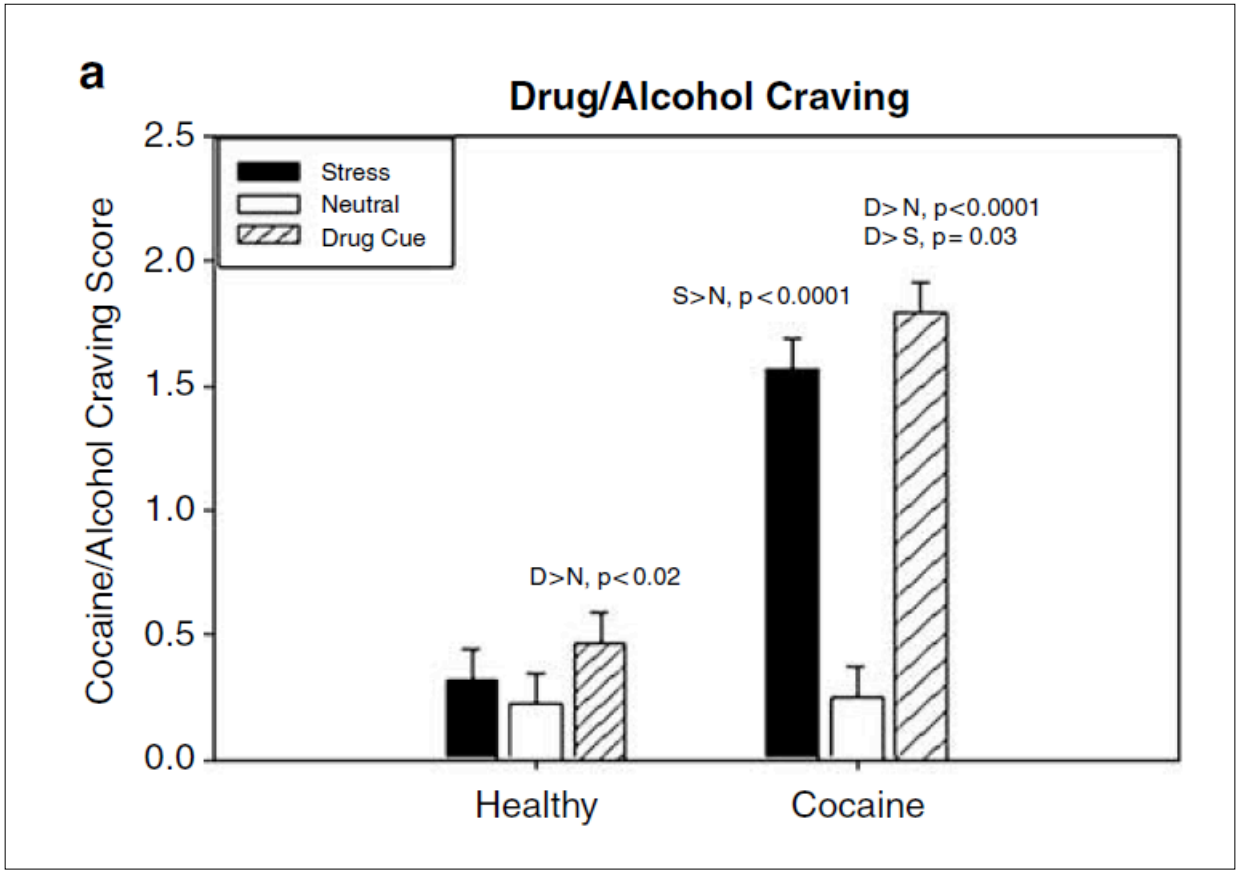
Stress

“ Environmental demands tax or exceed the adaptive capacity of an organism, resulting in psychological and biological changes that may place persons at risk for disease. ”

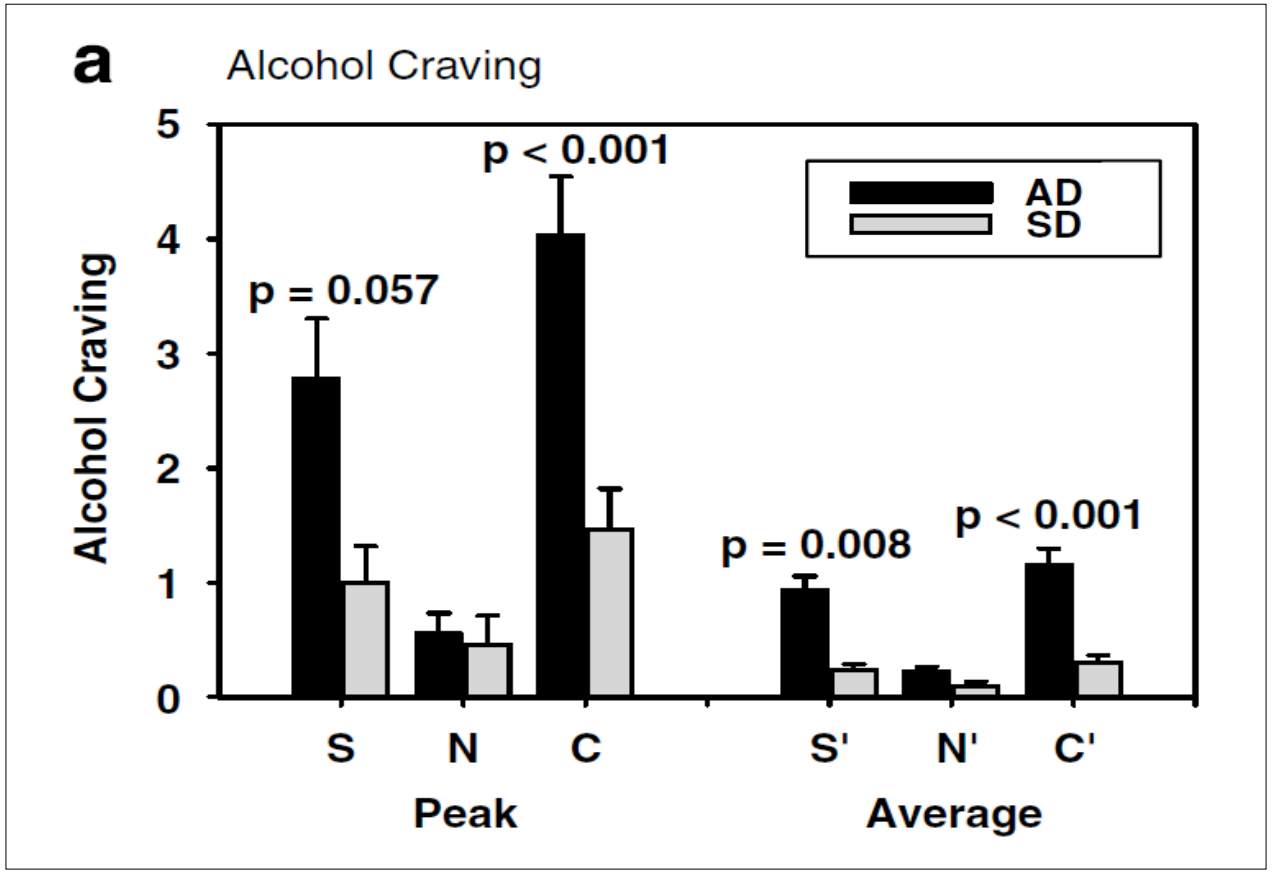
Measuring Stress. New York: Oxford University Press, 1995, p. 3ff.



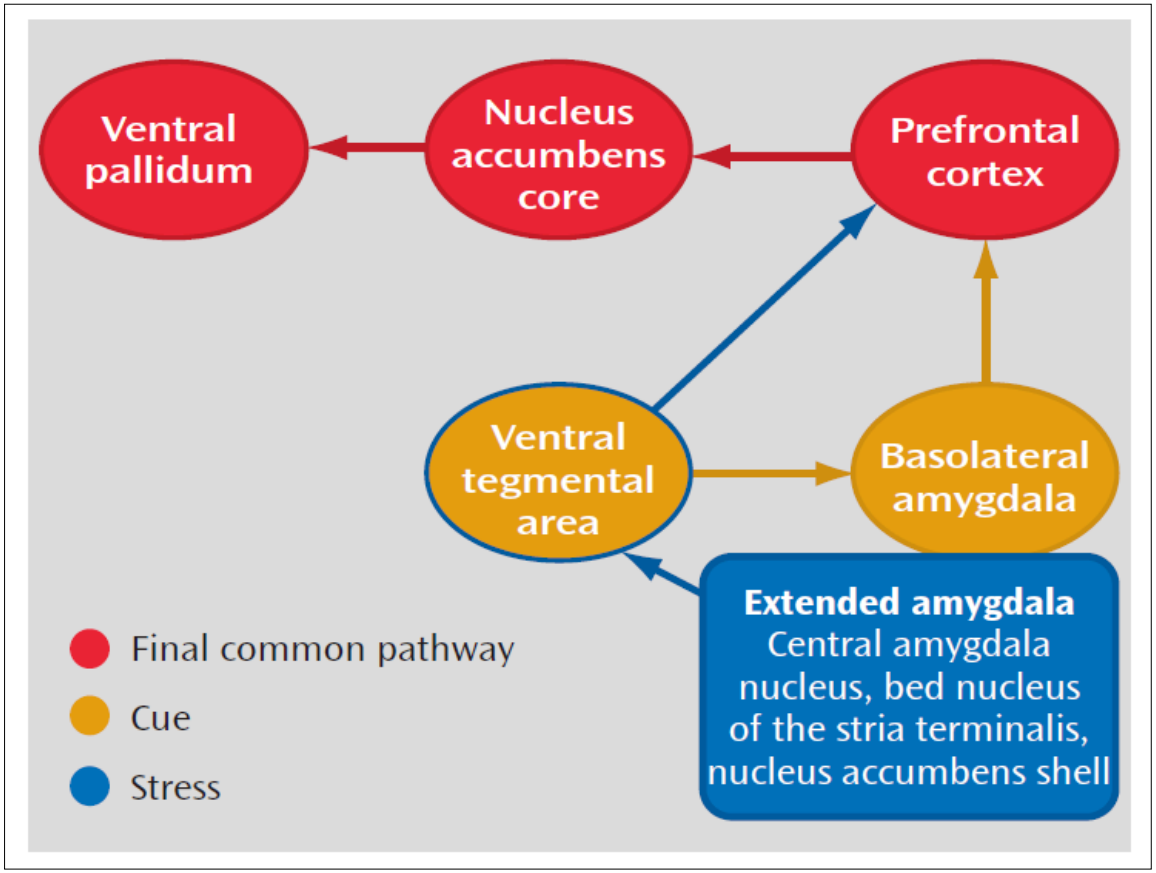
Measuring Stress. New York: Oxford University Press, 1995, p. 3ff.



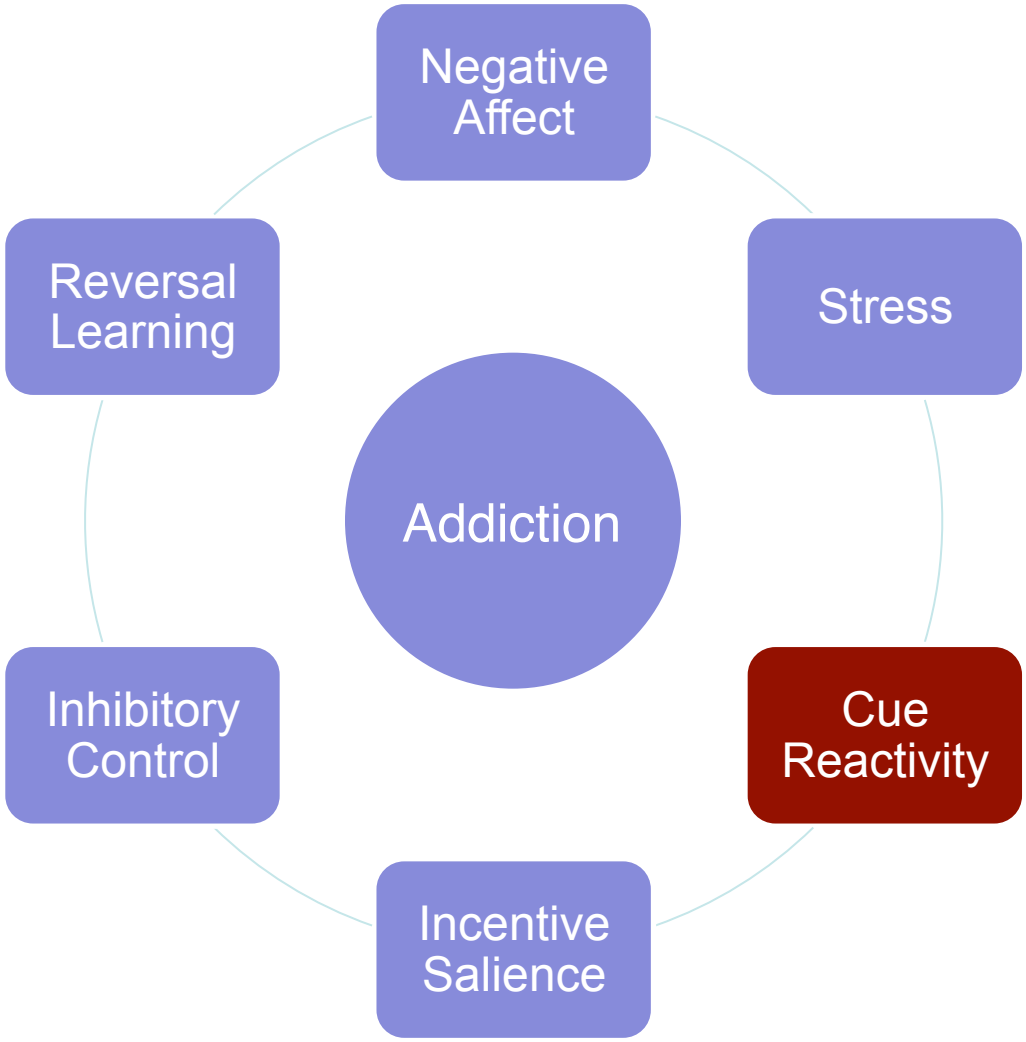
Neuropsychopharmacology 2008;33:796.



Neuropsychopharmacology 2009;34:1198.



Am J Psychiatry 2012;169:351.



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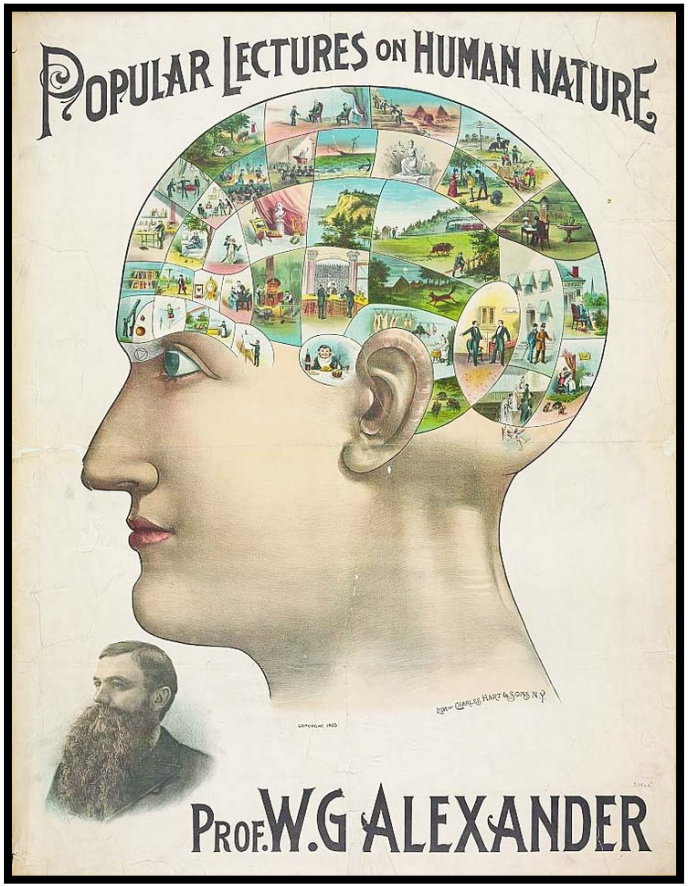


[Lapham's Quarterly](#).

- Cocaine abusers
- PET scans
- Radiolabelled D_2 antagonist
- Neutral versus cocaine cues
- Cocaine cues = dopamine release

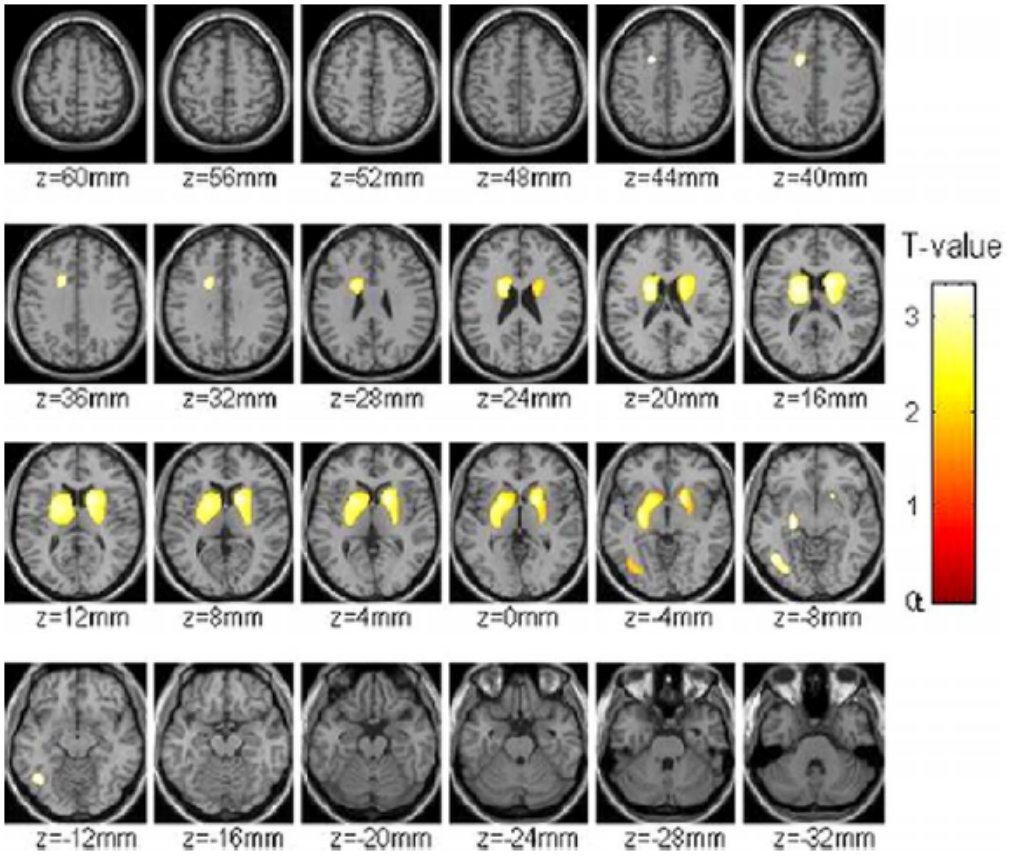
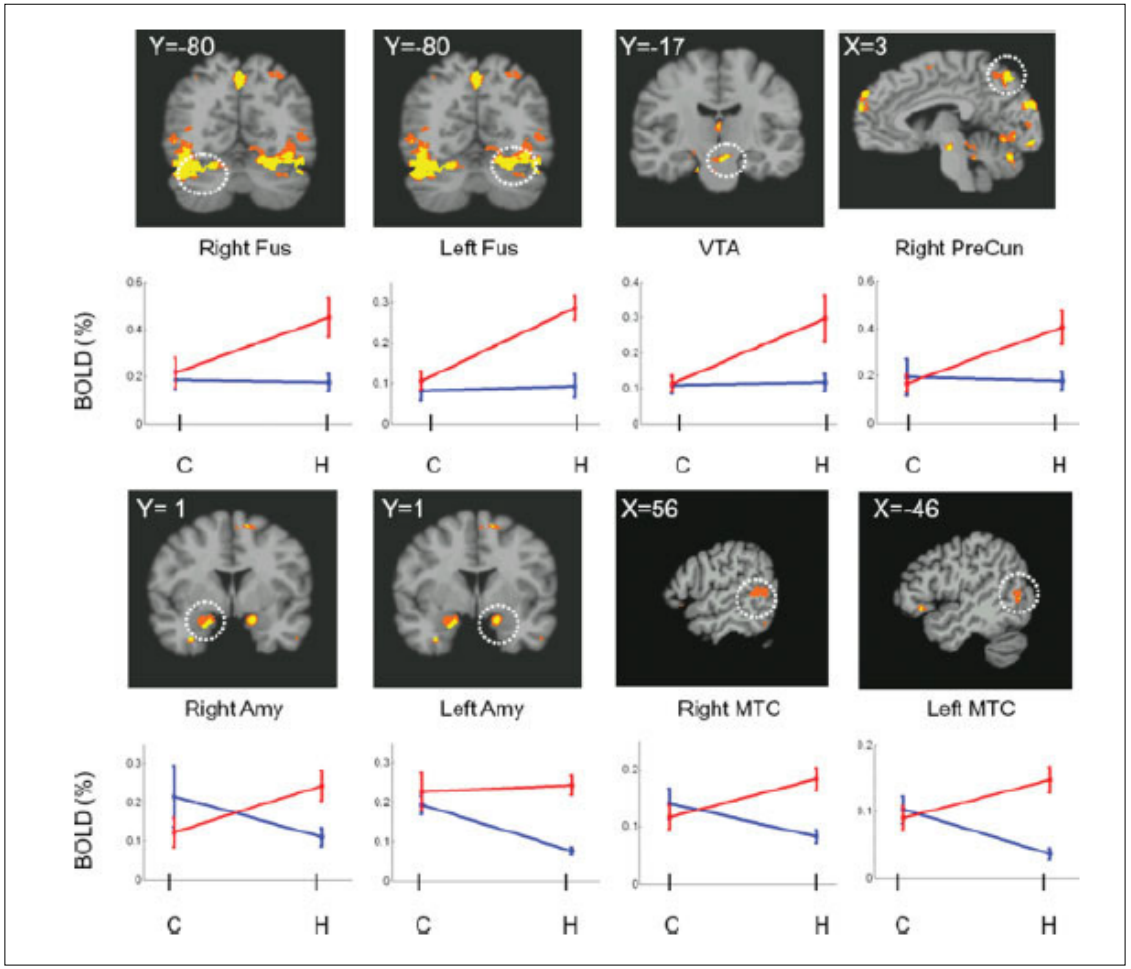


Figure 1. Brain maps obtained with SPM showing the difference in the distribution volume of [^{11}C]raclopride between the neutral and the cocaine-cue conditions ($p < 0.05$, uncorrected, threshold >100 voxels). Note that there were no differences in the ventral striatum (−8 canthomeatal plane).

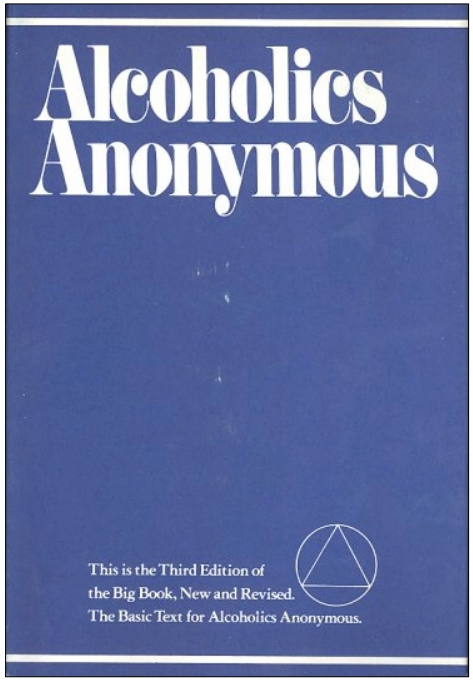
J Neurosci 2006;26:6583.

- Heroin abusers + controls
- fMRI scans
- Neutral versus heroin cues
- Heroin cues = more activation



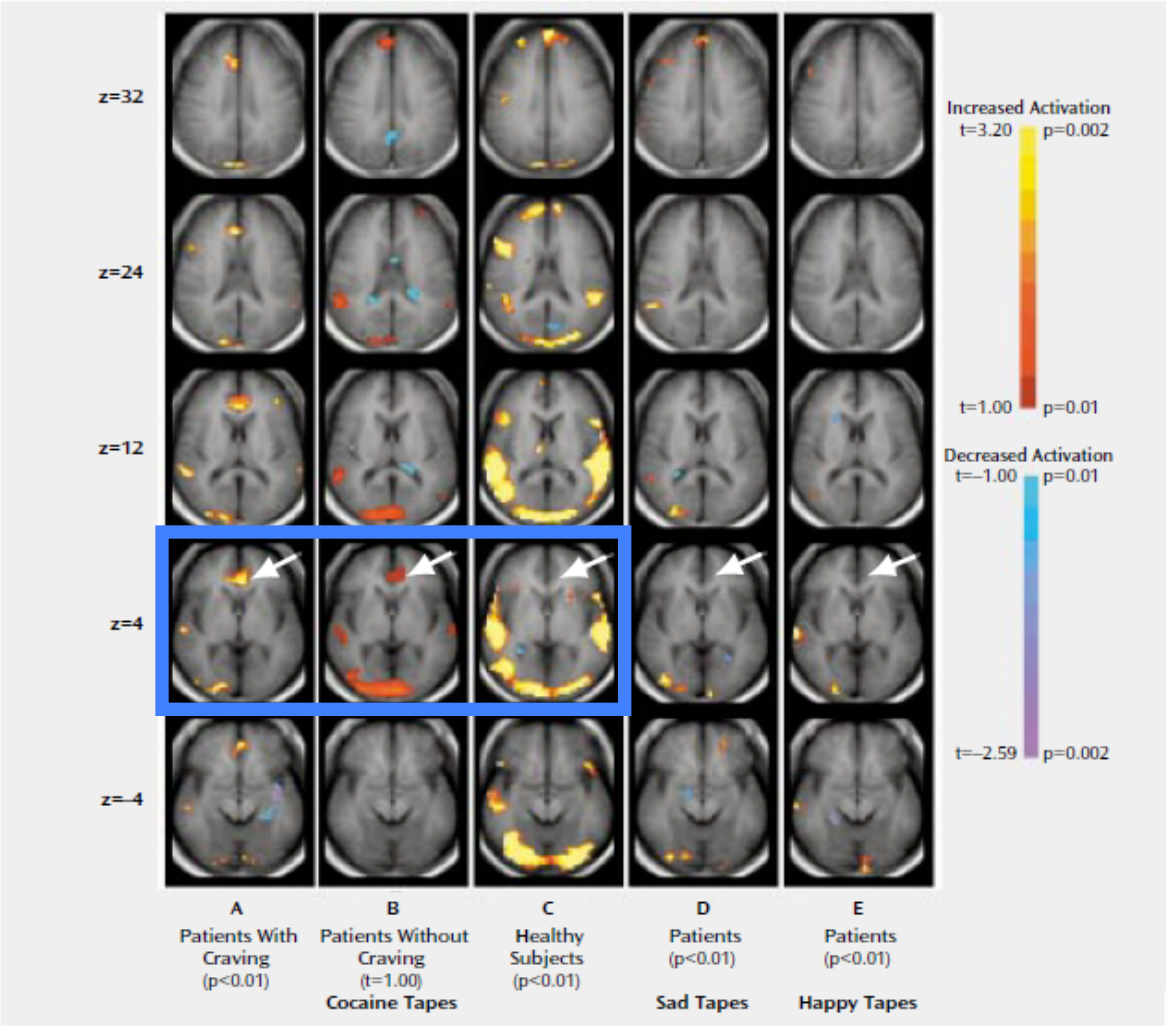
Hum Brain Mapp 2009;30:766.

Big Book



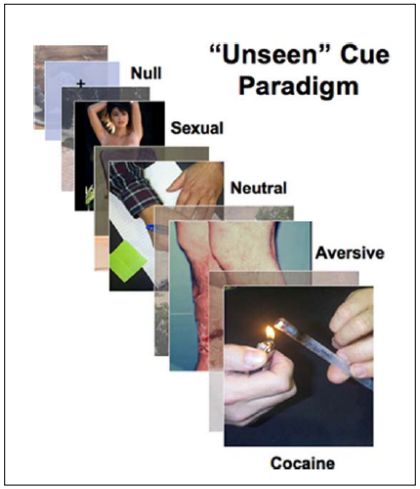
“ Remember that we deal with alcohol—cunning, baffling, powerful! ”

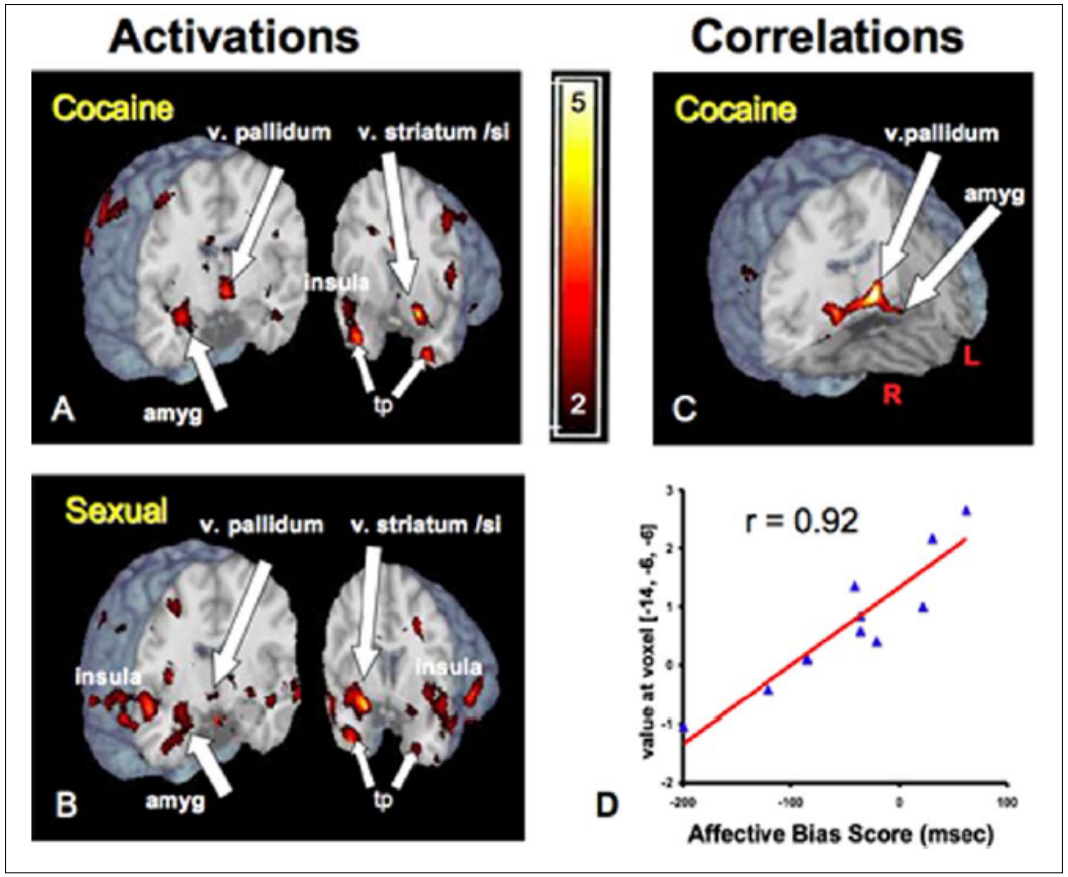
Alcoholics Anonymous, 3d ed (7th printing), 1980, p. xxvi.



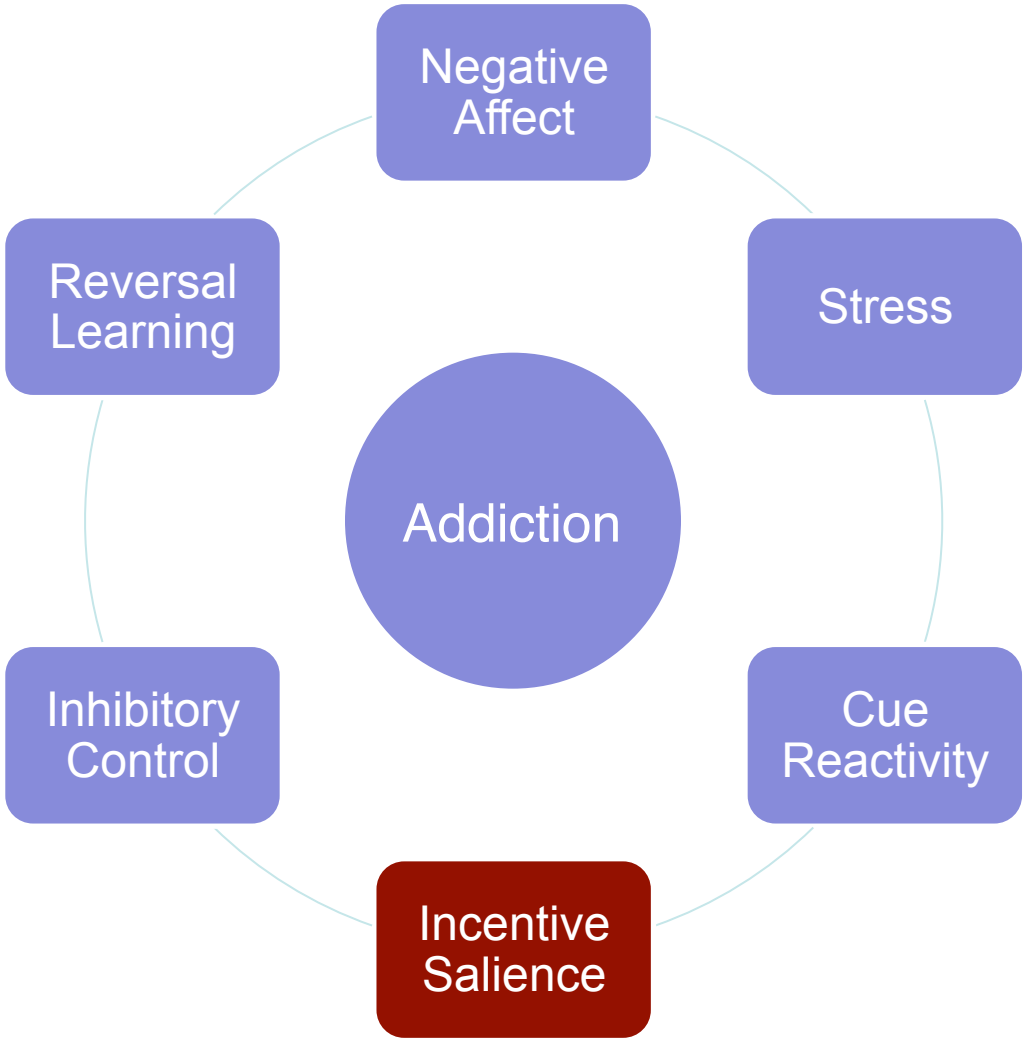
Am J Psychiatry 2001;158:86.

- Recently abstinent cocaine abusers
- fMRI scans
- Random presentation of images (33 msec) and neutral “masking” stimuli (467 msec)





PLoS One 2008;3:e1506.



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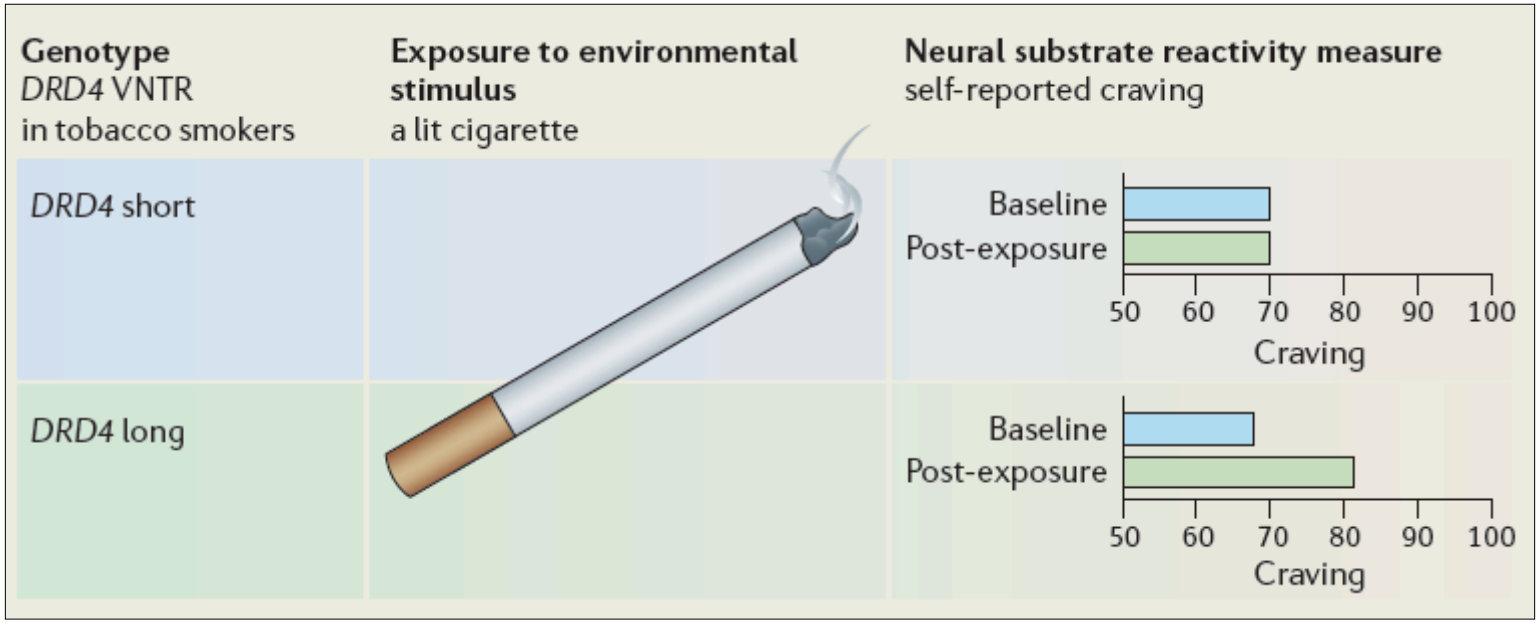
J Vis 2009;9:15.1.

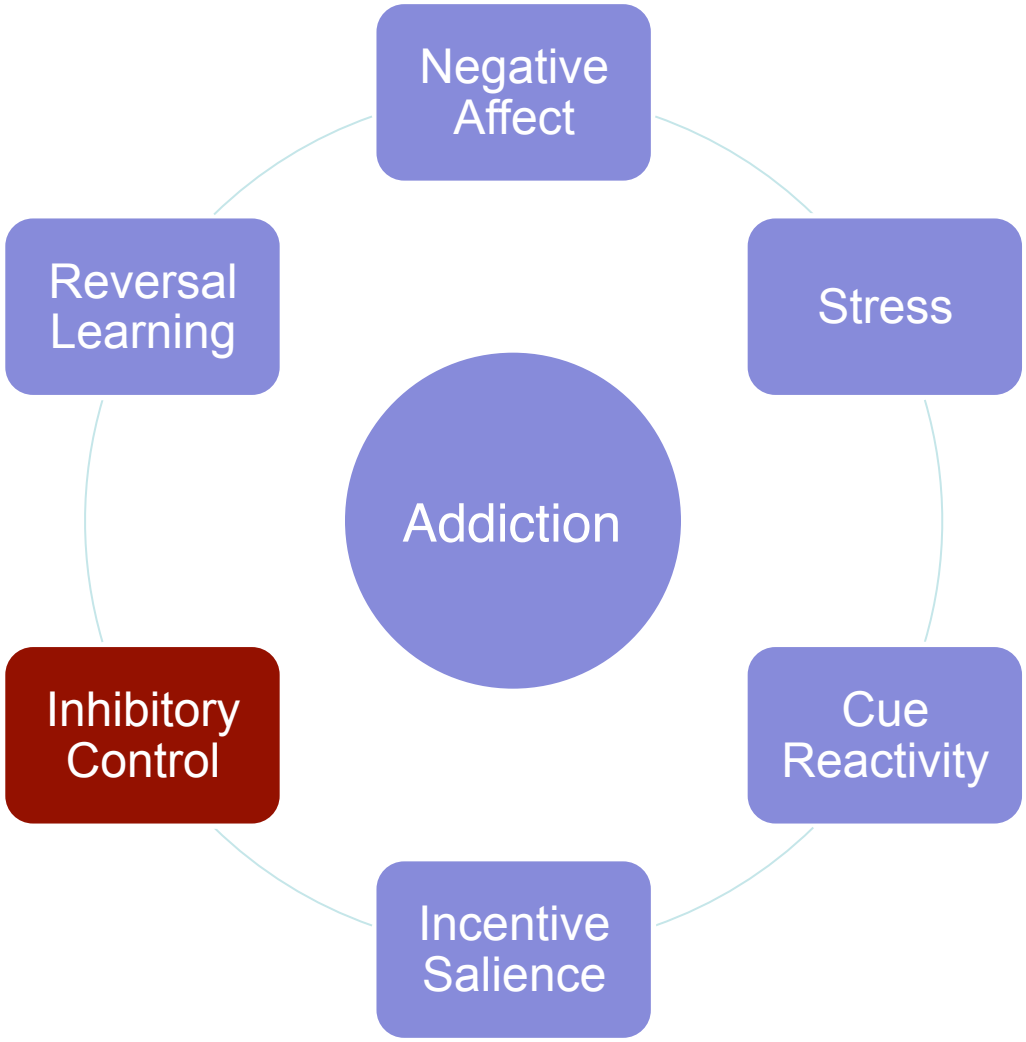
Incentive Salience

- Motivational “wanting” associated with reward-predicting stimuli
- Narrows the brain’s focus to drug-seeking at the expense of natural rewards
  - Preoccupation
  - Cravings
  - Drug-seeking/taking

Annu Rev Psychol 2003;54:25 § Neuropsychopharmacology 2010;35:217 § Kent Berridge.



Nat Rev Neurosci 2006;7:583.



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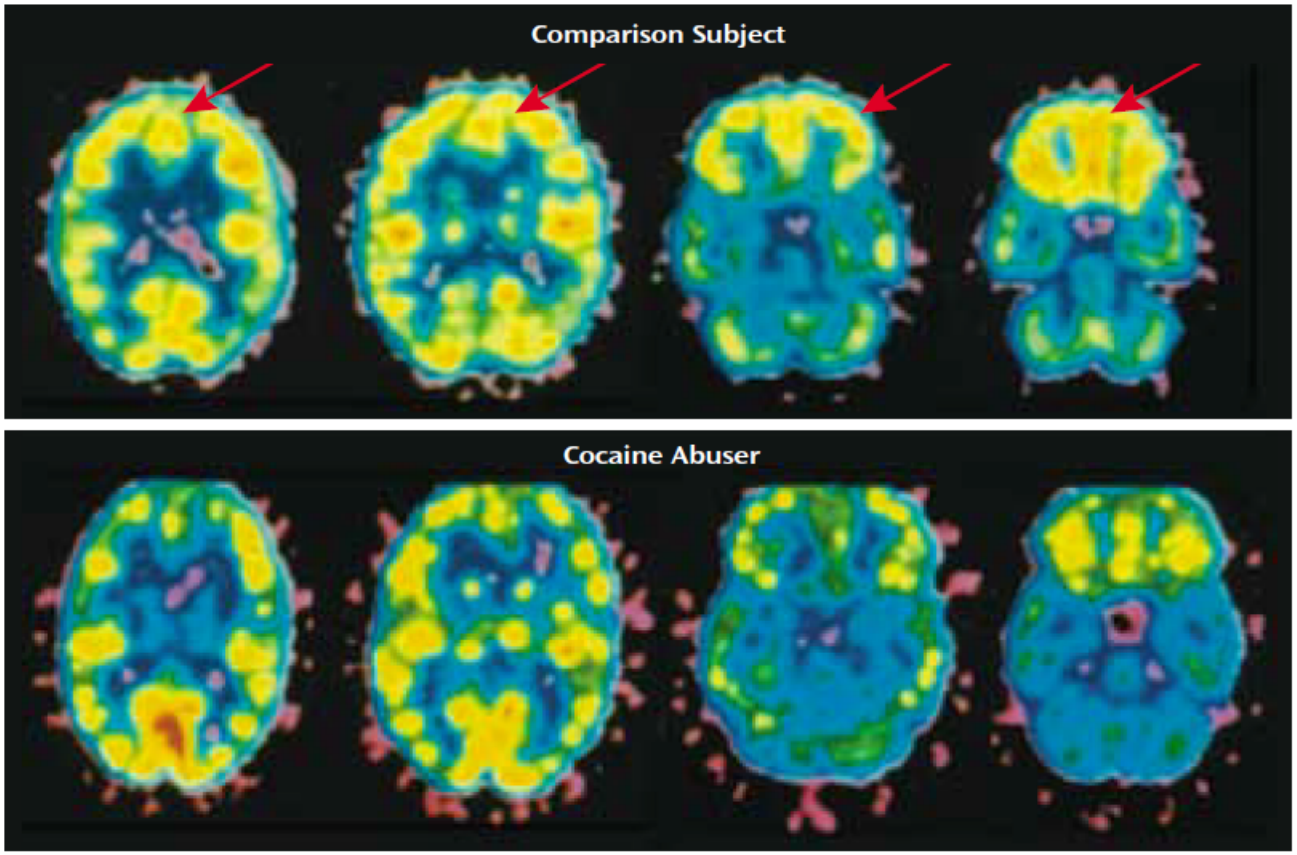
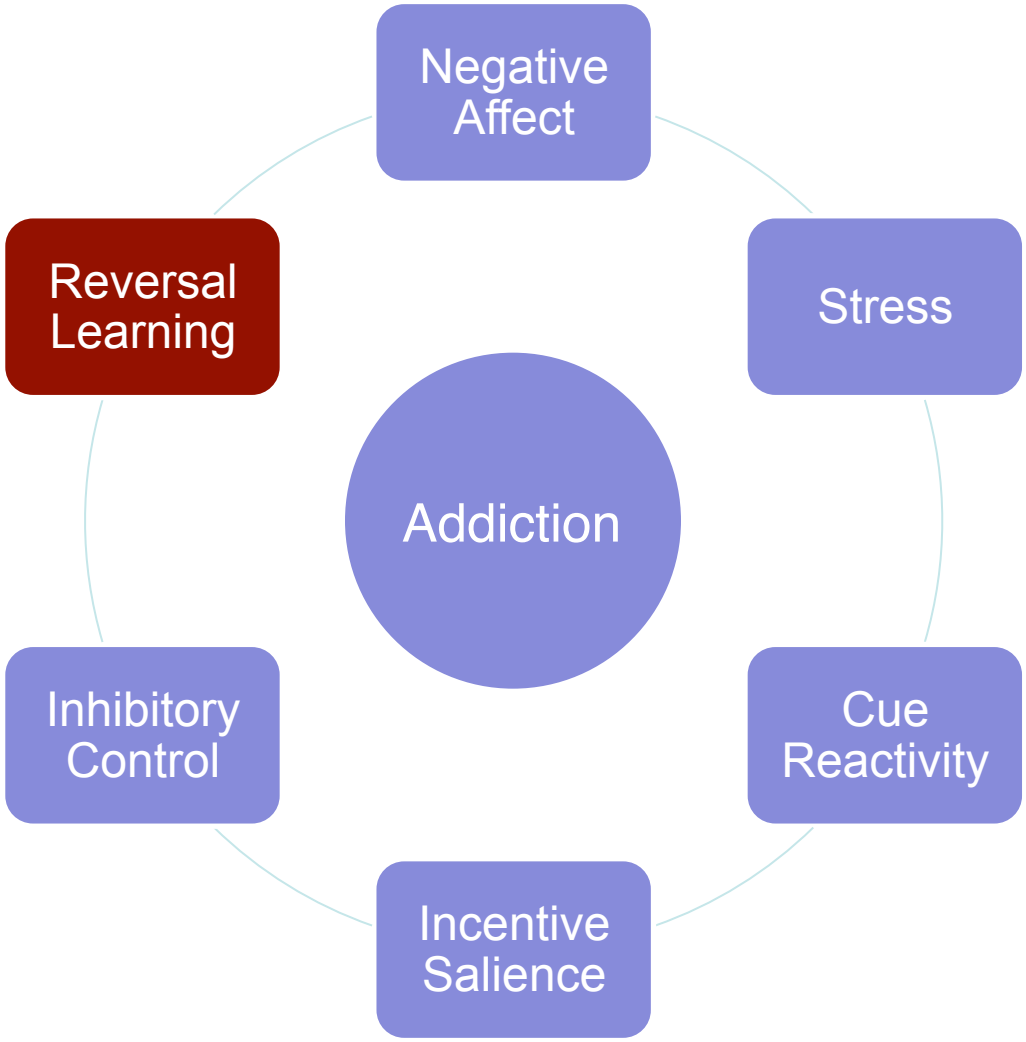


Am J Psychiatry 2002;159:1642.



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Reversal Learning

- Addiction is a learned behavior that addicts have a hard time unlearning
- Initial Rule
  - "This substance gives me a great high"
- New Rule
  - "This substance is screwing up my life"

Sci Am Mind 2013;24(1):40.

Example

- Cocaine and alcohol users versus health controls
- Initial Rule
  - Please a key when a green rectangle appears on the screen
- New Rule
  - Don’t press a key when a green rectangle appears on the screen
- Results
  - Healthy controls adapted
  - Addicts kept pressing even when given feedback

Sci Am Mind 2013;24(1):40.

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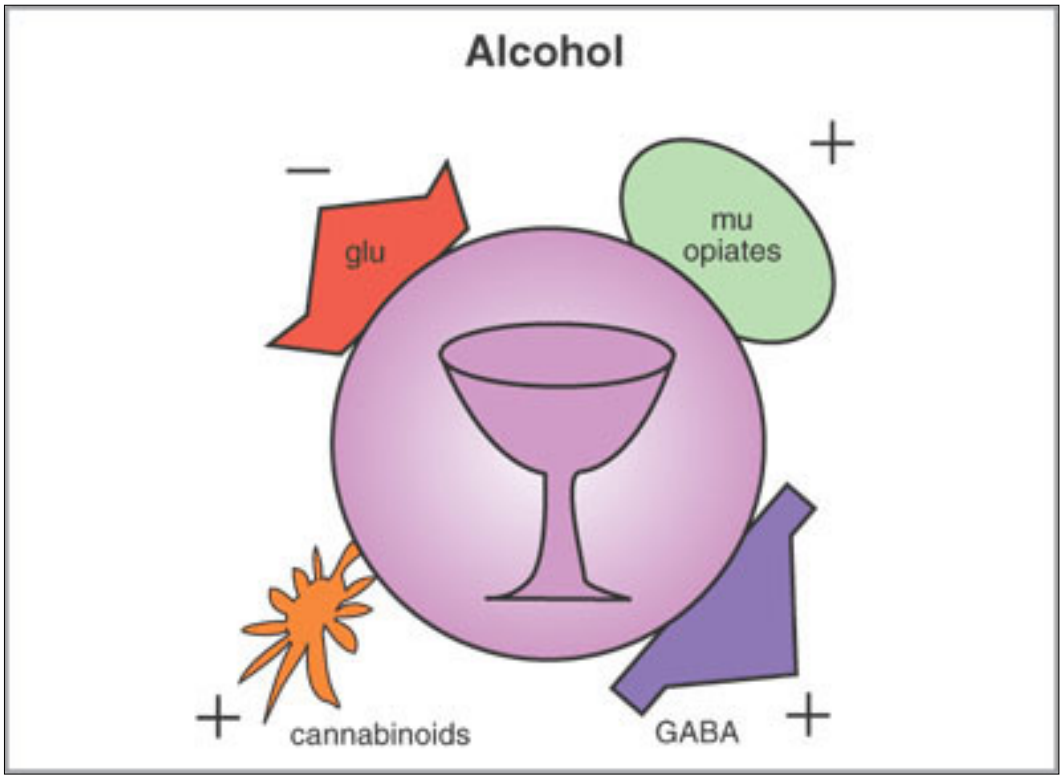
Alcohol

- Is sometimes described as a “dirty drug”
- In reality, has a complex mechanism of action

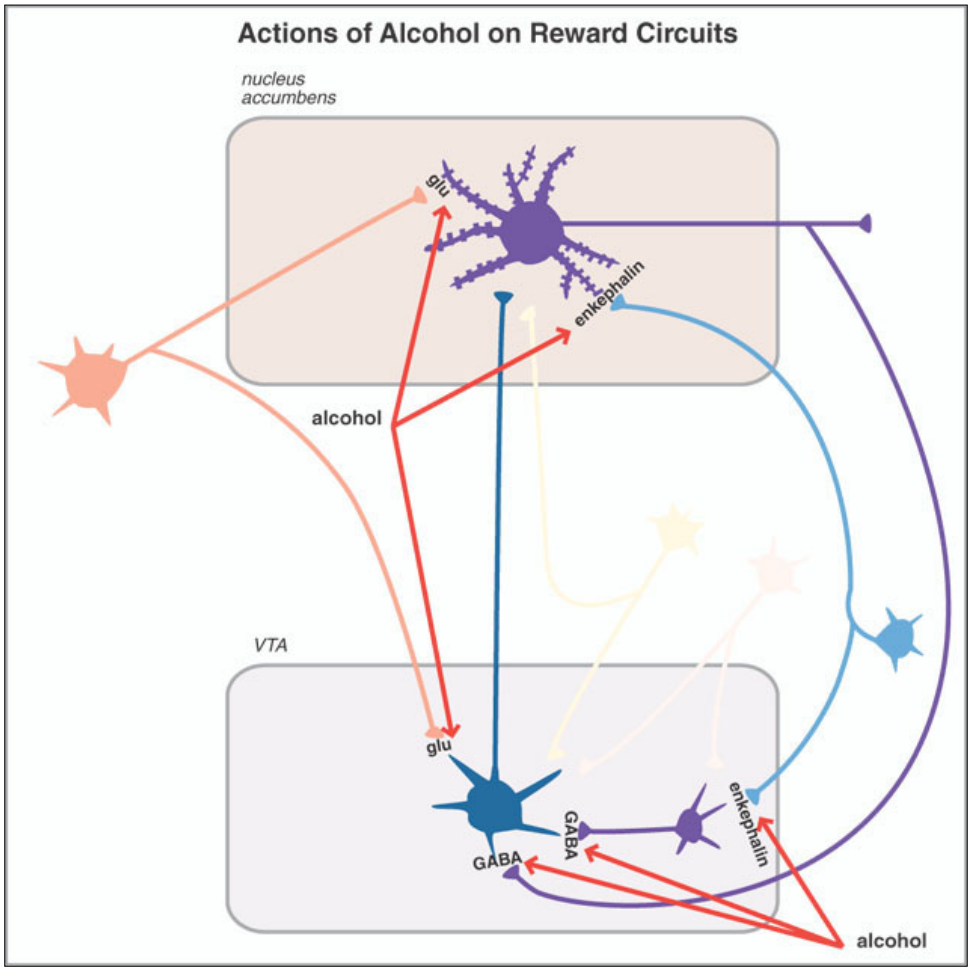
Complex Mechanism of Action

Neurotransmitter System	Acute Effects
GABA	Enhances
Glycine	Enhances
Acetylcholine	Enhances and Inhibits
Serotonin	Enhances
ATP	Enhances and Inhibits
Glutamate	Inhibits
Voltage-gated	Enhances and Inhibits

Principles of Addiction Medicine, 4th ed, 2009, p. 89.



Stahl's Essential Psychopharmacology (online edition).



Stahl's Essential Psychopharmacology (online edition).

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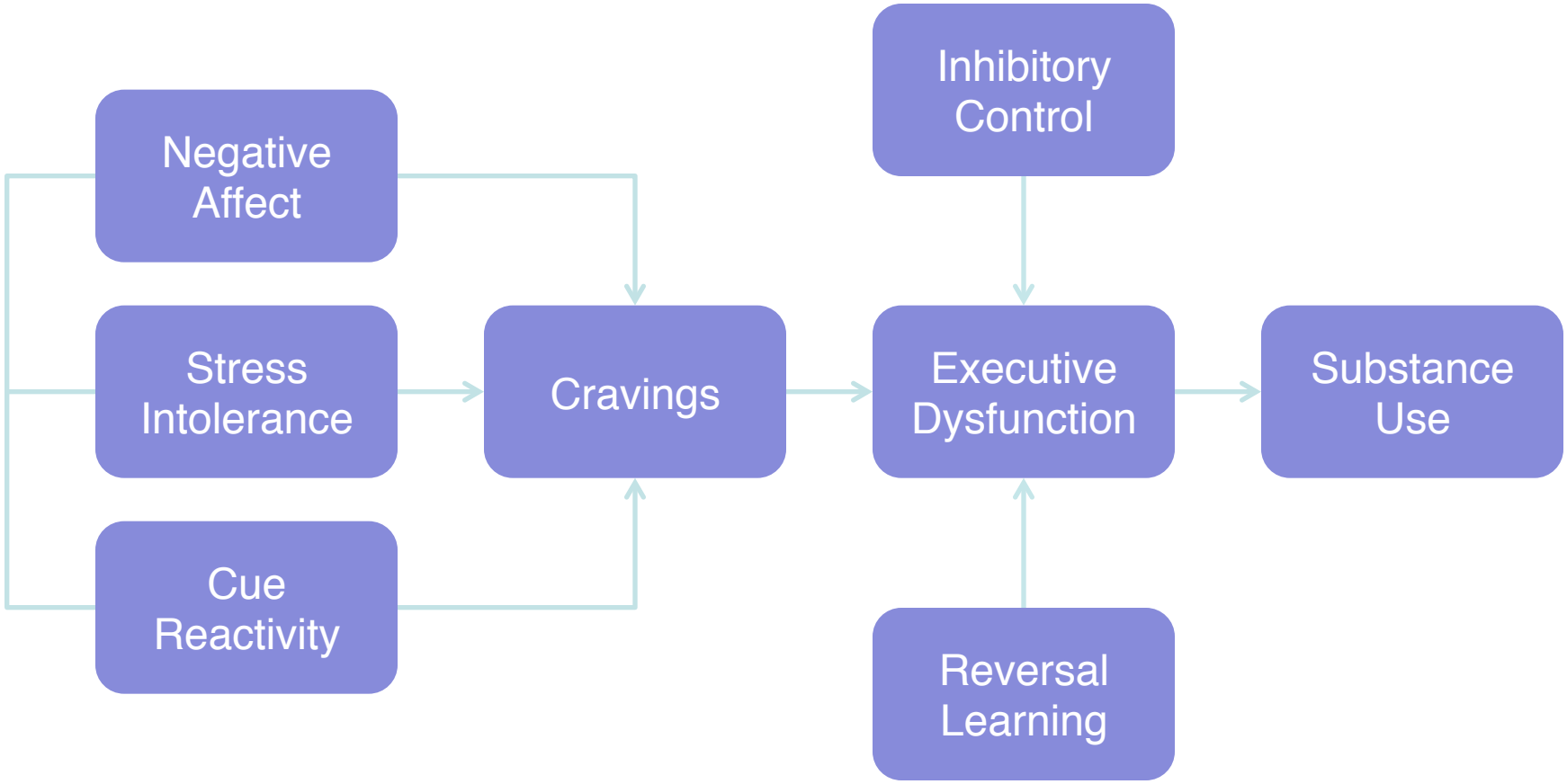
Symptoms → Treatment

- Symptoms
- Brain Regions
- Neural Circuits
- Neurotransmitters
- Treatment



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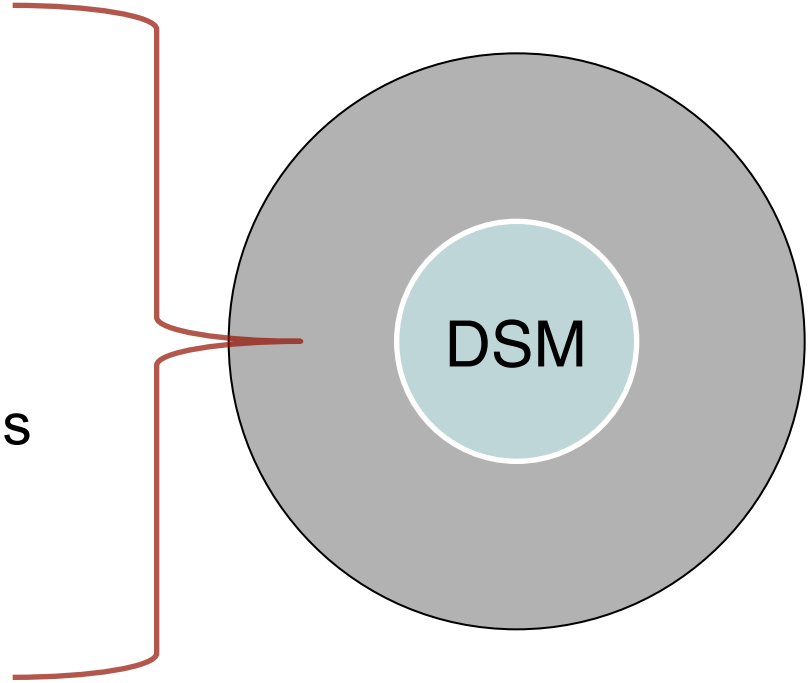
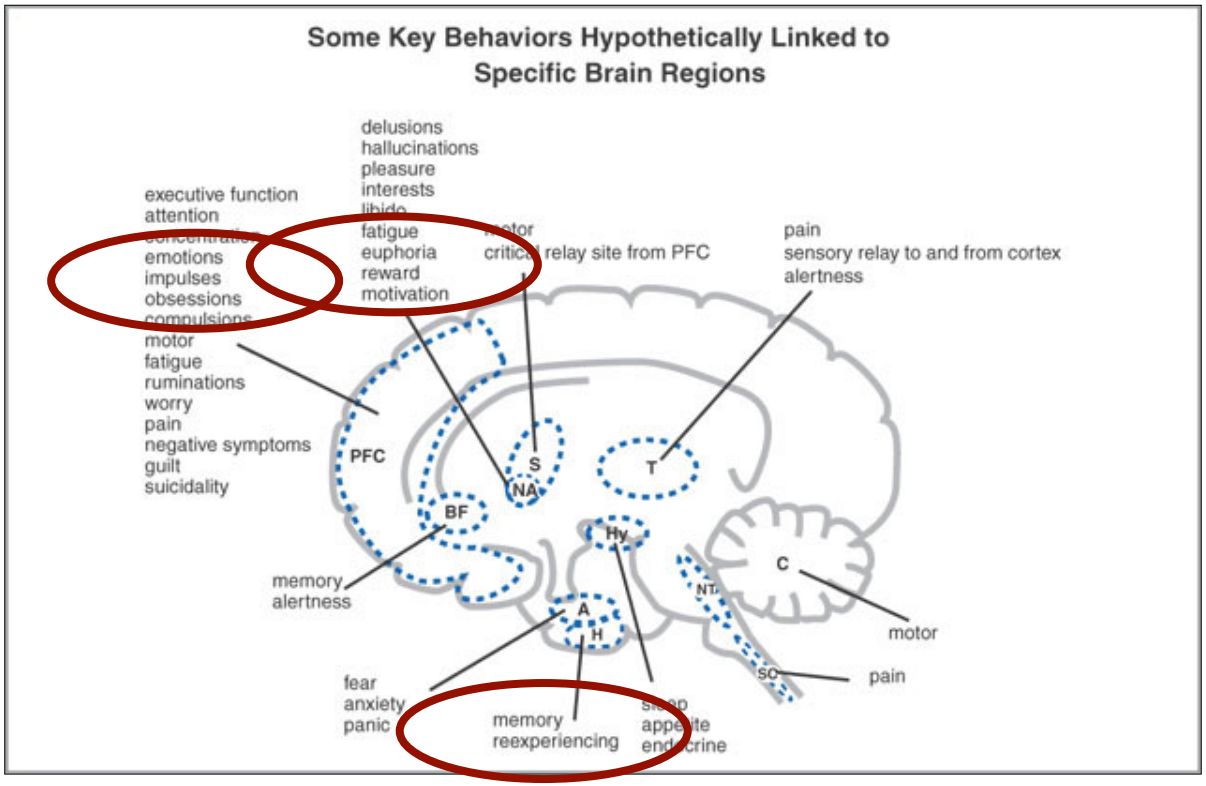
Bigger Picture

- Poor self-awareness
- Low frustration tolerance
- Dysregulated emotions
- Impaired interpersonal skills
- Impulsivity



DSM = Diagnostic and Statistical Manual of Mental Disorders.

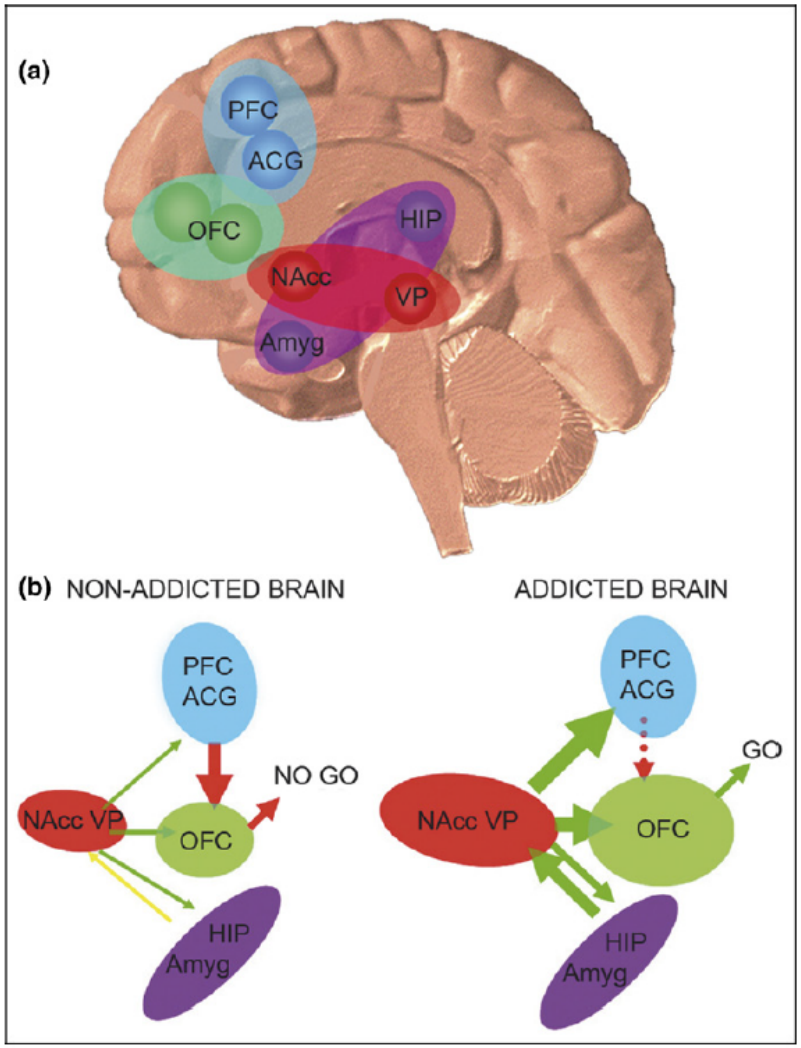
Symptoms → Brain Regions



Stahl's Essential Psychopharmacology (online edition).

NAcc + VP
Reward Prediction
Pleasure

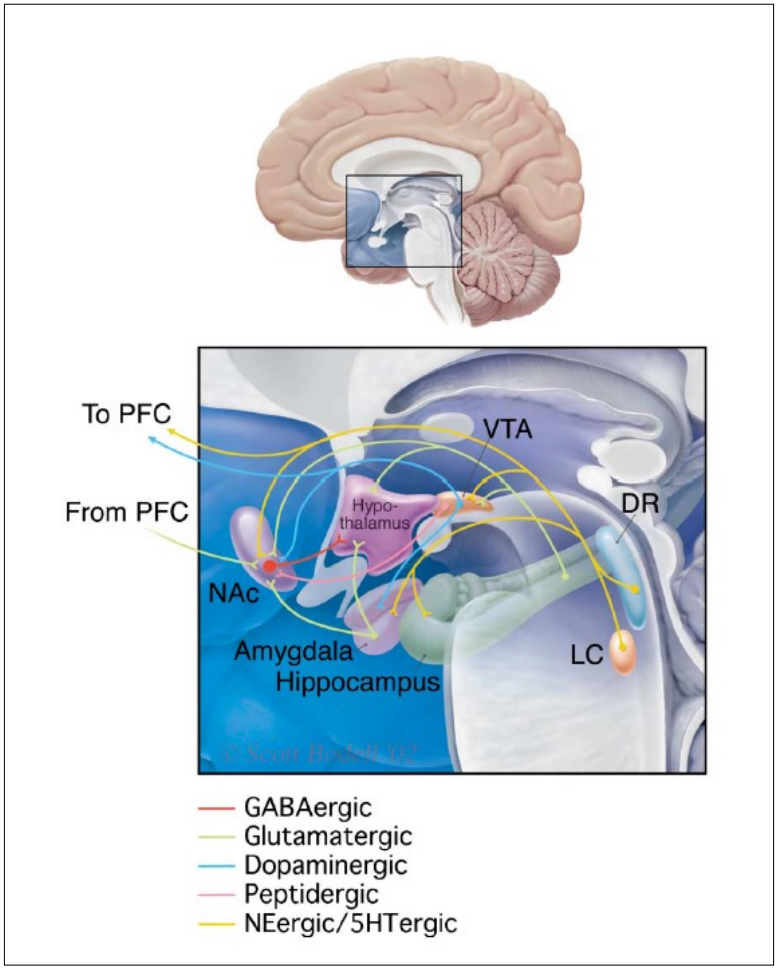
Amyg + HIP
Memory
Learning



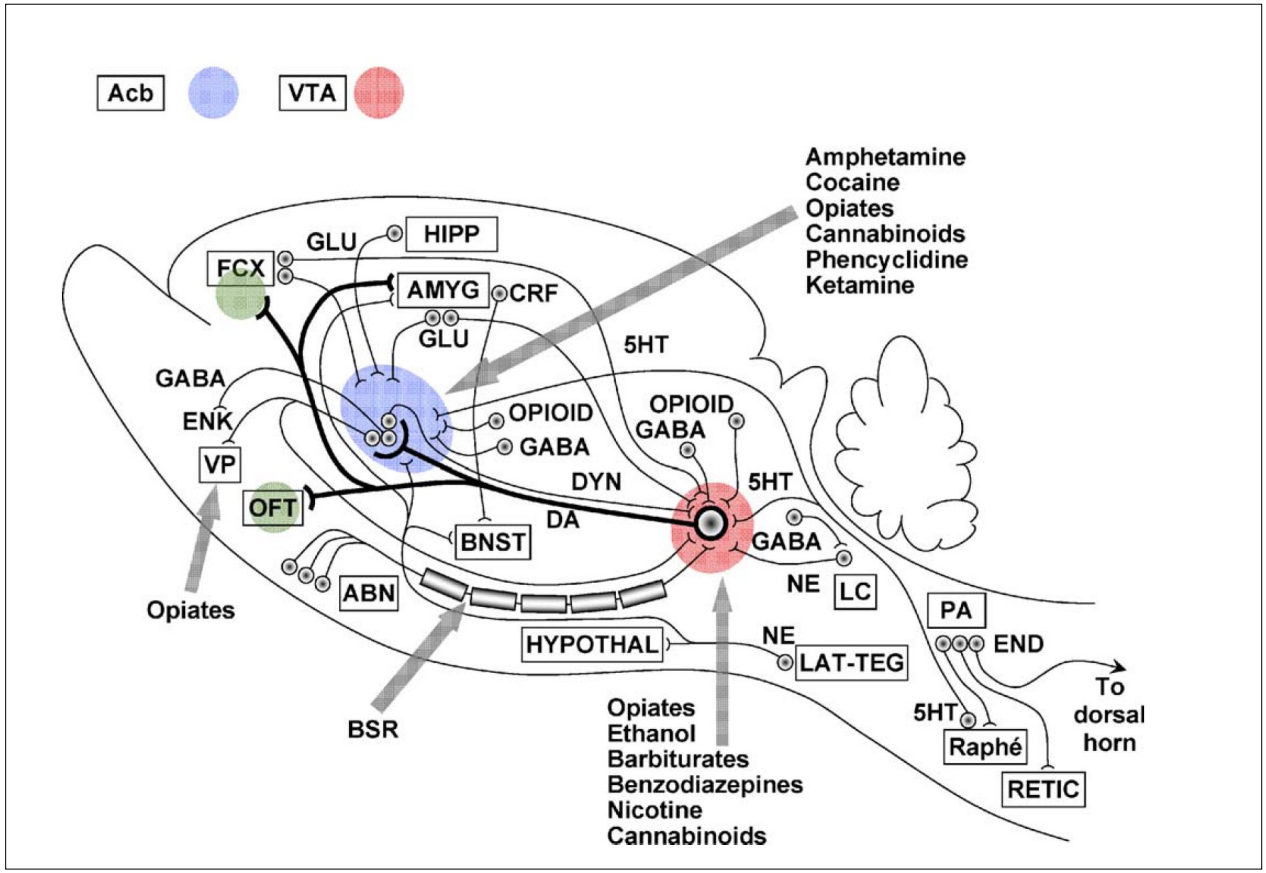
OFC
Motivation
Drive

PFC + ACG
Cognitive Control
Restrain Cravings

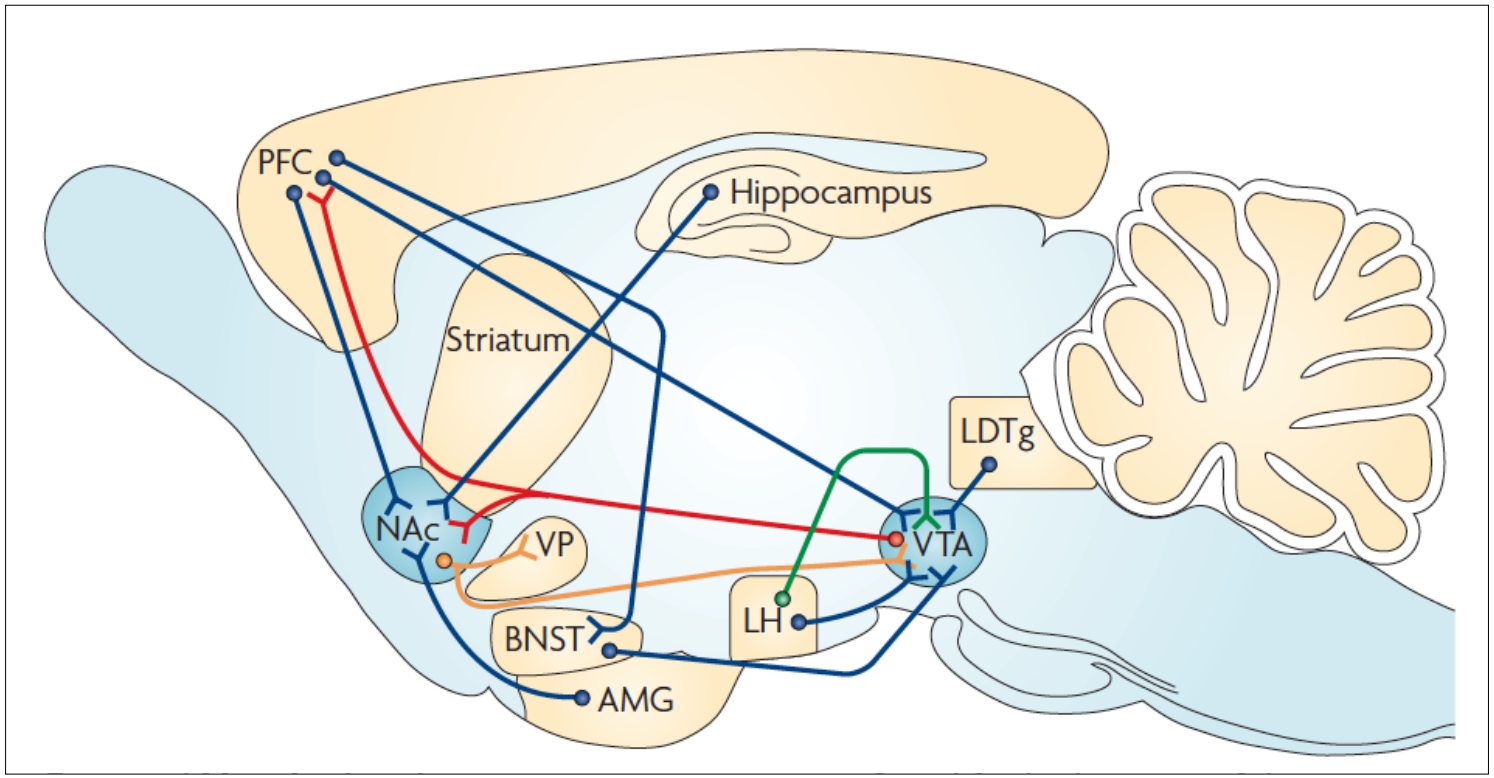
Trends Mol Med 2006;12:559.



Neuron 2002;34:13.

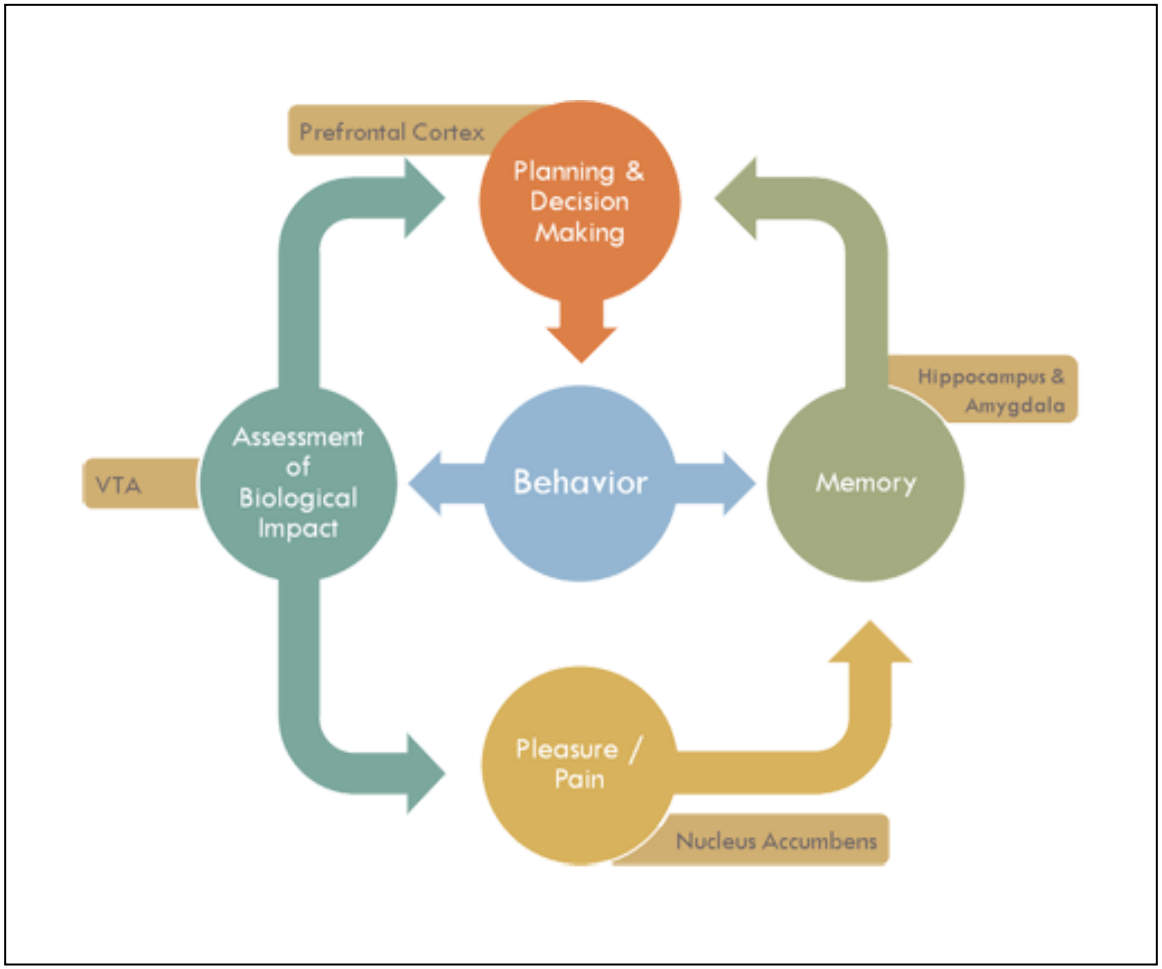


Pharmacol Ther 2005;108:18.

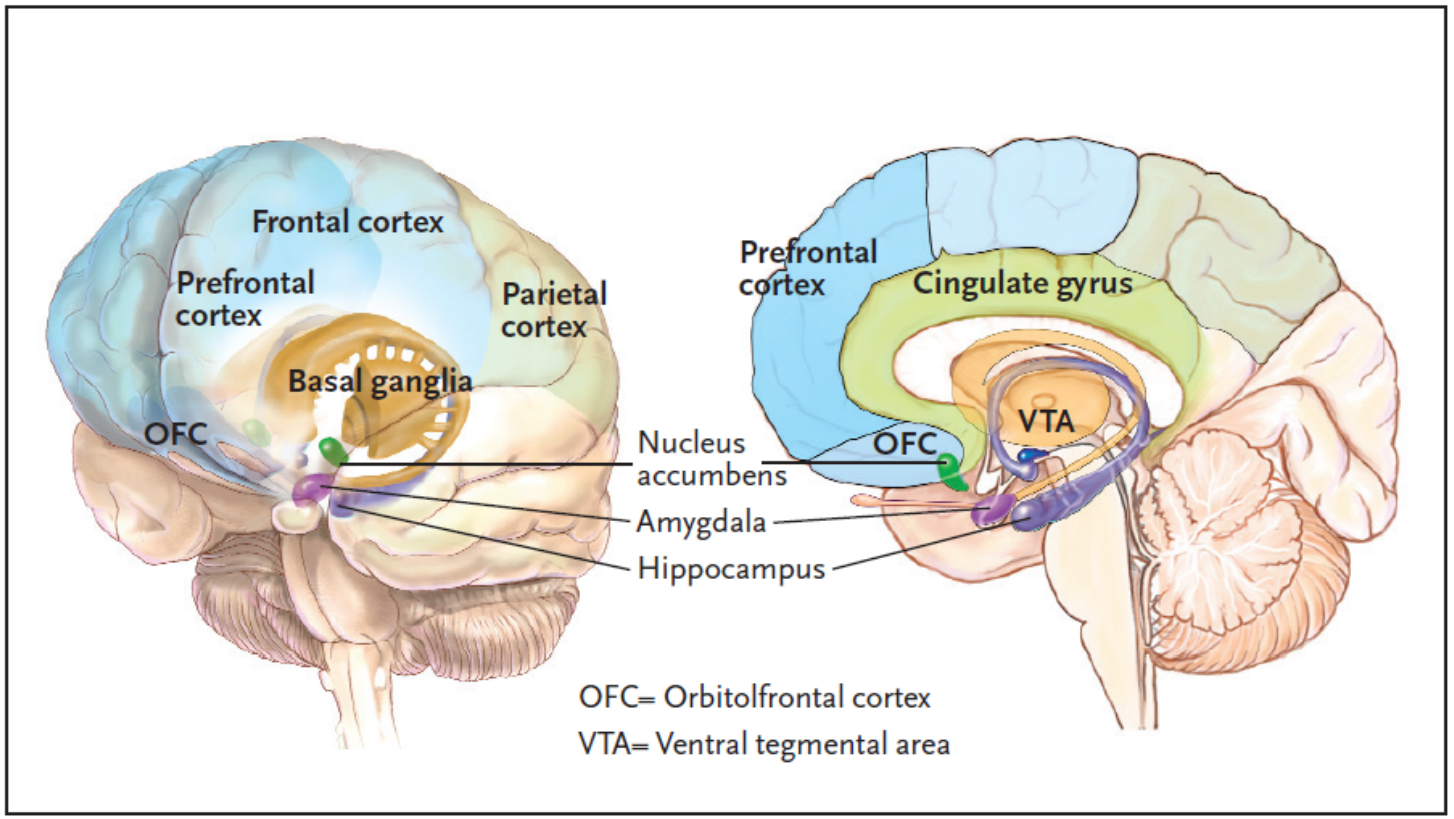


Blue arrows: glutamate; Red arrows: dopamine; Orange arrows: GABA; Green arrow: orexin.

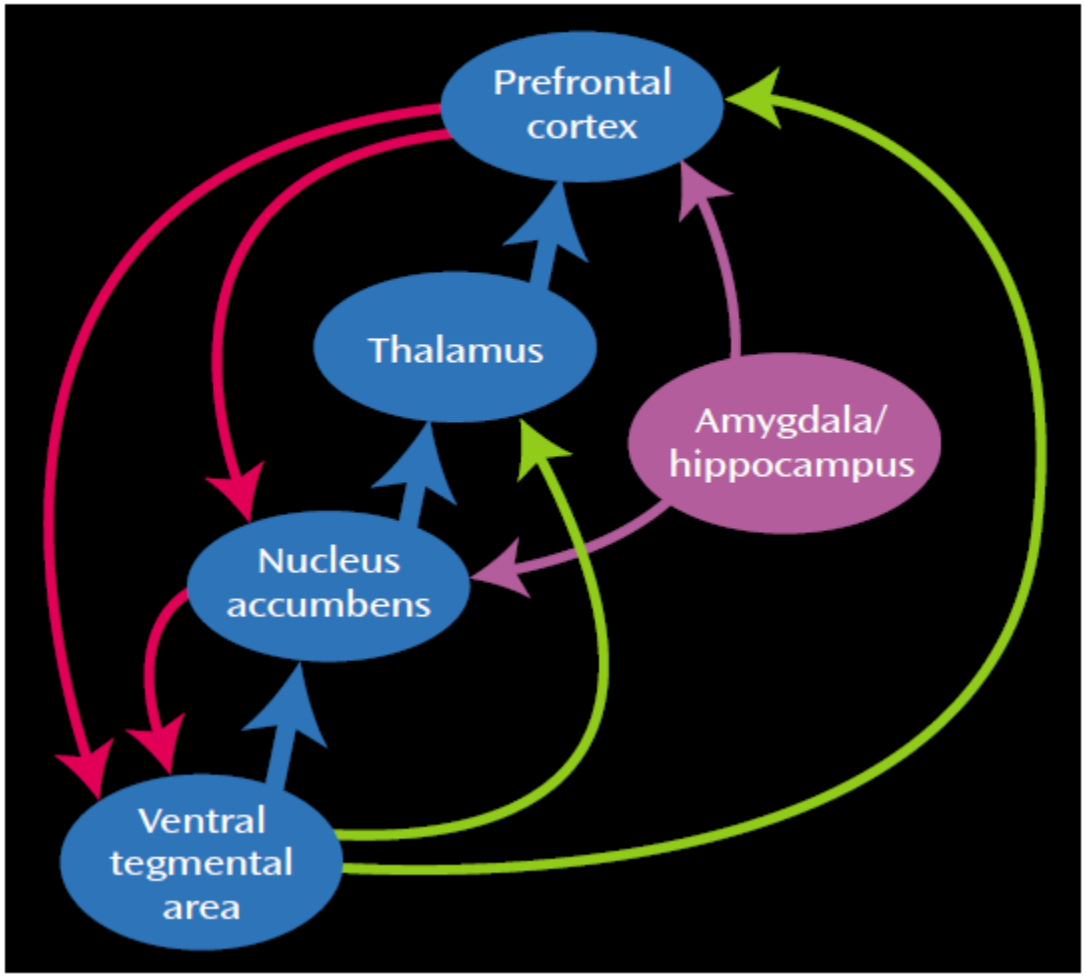
Nat Rev Neurosci 2007;8:844.



CrystalMethSolutions.org.



Sci Pract Perspect 2007;3:4.



Am J Psychiatry 2002;159:1642.

Seeking & Experiencing Reward

"Go"	"Stop"
Reward circuitry	Executive function
Mesolimbic pathway	Prefrontal cortex
Dopamine	Serotonin
Glutamate	Gamma-aminobutyric acid
Risk taking	Risk avoidance
Experimentation	Harm reduction

Am J Addict 2008;17:6.

Craving | 1

“ Memory of the rewarding aspects of drug use superimposed on a negative emotional state ”

Annu Rev Psychol 2008;59:29.

Cravings | 2

Positive Cravings

Desire to get intoxicated or "high"

Type 1 Cravings

Induced by drugs or stimuli that have been paired with prior drug use

Negative Cravings

Desire to relieve uncomfortable emotional symptoms

Type 2 Cravings

Negative emotional state, combined with Type 1, that causes drug seeking

Cleve Clin J Med 2006;73:641 § Annu Rev Psychol 2008;59:29.

Cravings | 3

Positive Cravings

Desire to get intoxicated or "high"

Type 1 Cravings

People, places and things

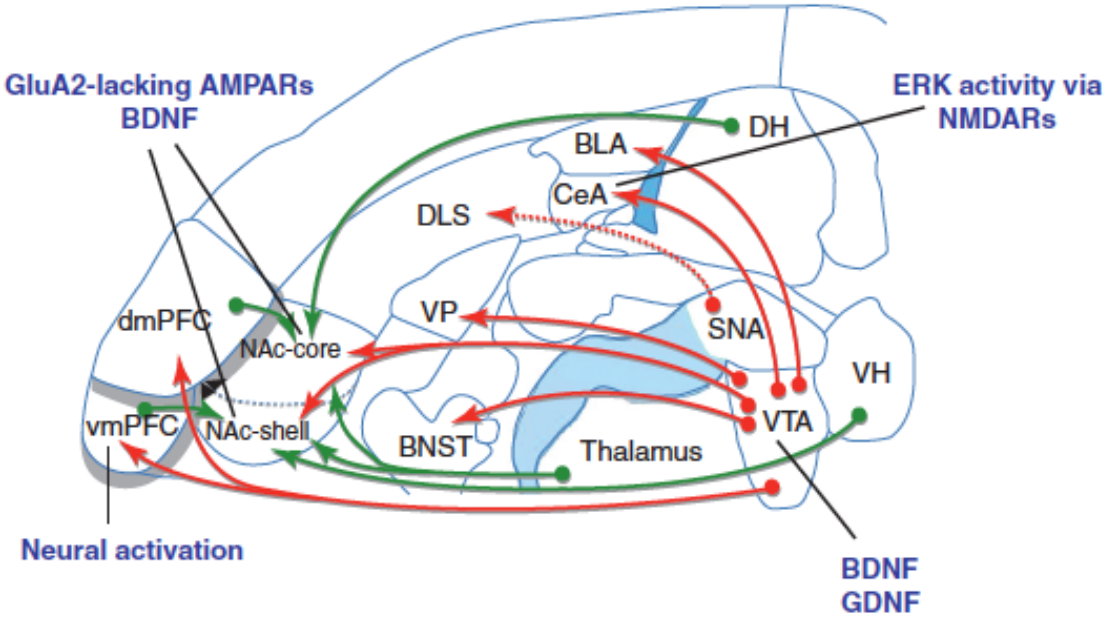
Negative Cravings

Restless, irritable and discontented

Type 2 Cravings

Negative cravings + Type 1 cravings

Cravings | 4



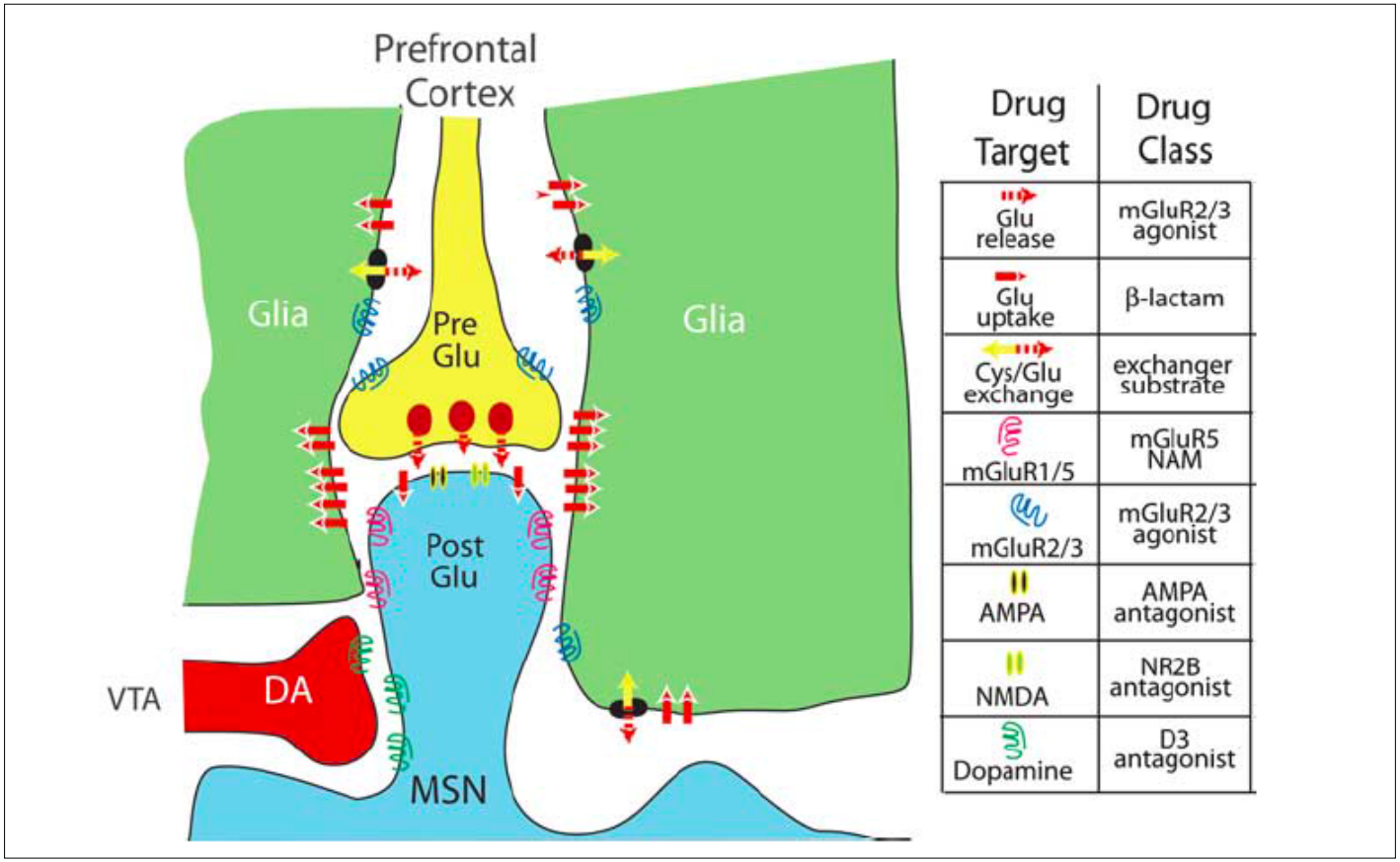
Red arrows: dopamine; Green arrows: glutamate.

Trends Neurosci 2011;34:411.

Reversal Learning | Strung-Out Circuit

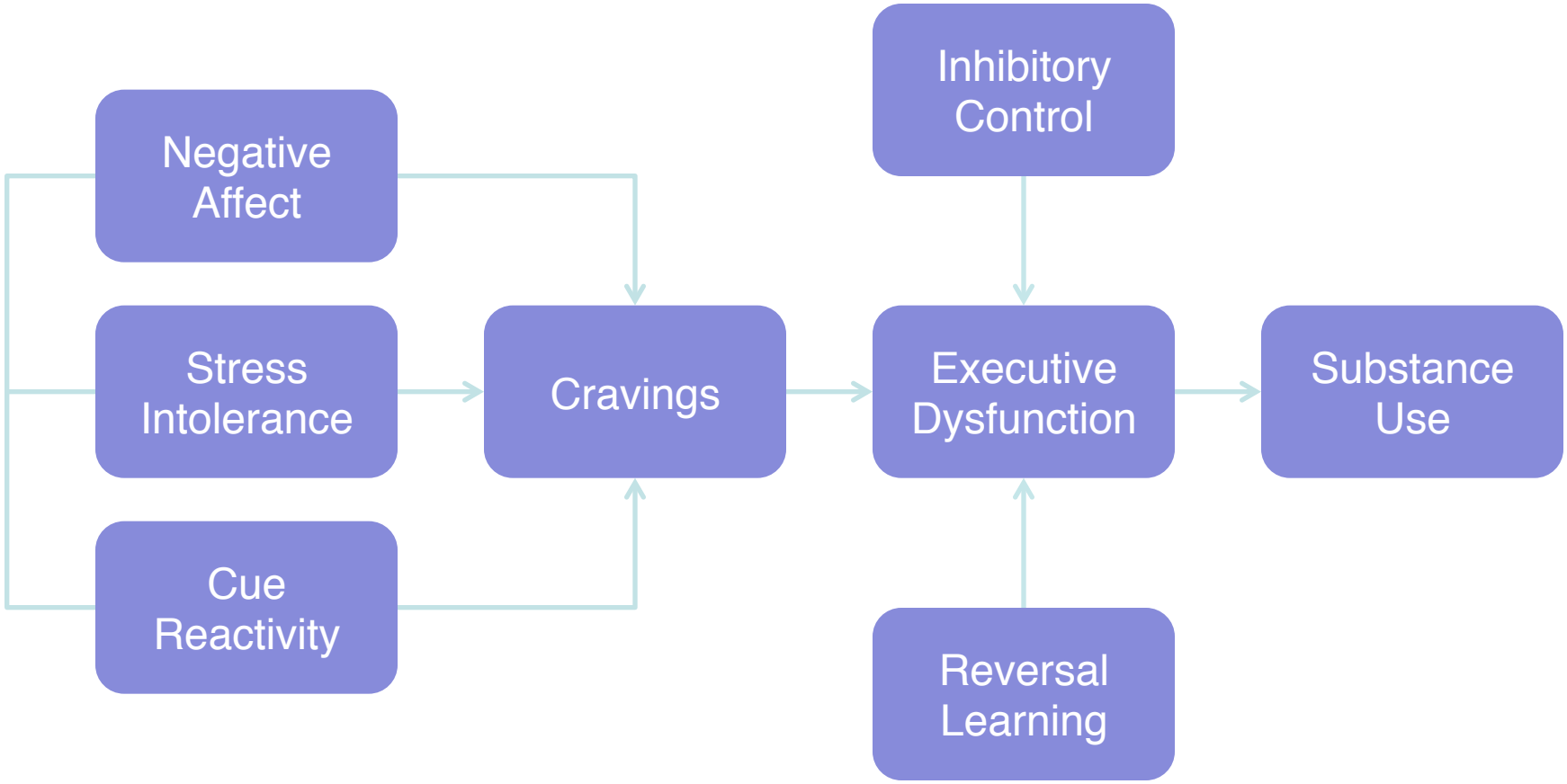
- Defective signaling between the prefrontal cortex and reward circuitry
- Glutamate appropriately released by the prefrontal cortex
- Post-synaptic problems in the reward circuitry

Sci Am Mind 2013;24(1):40.



Mol Psychiatry 2011;16:974.

Minneapolis Institute of Arts.



David Frenz, M.D.

Integrated Dual Disorders Treatment | 1

Problem, Vulnerability or Driver	Rx	PsyTx	Env
Negative Affect	+	+	
Stress	±	+	+
Cue Reactivity	±	+	+
Incentive Salience			
Inhibitory Control	±	+	
Reversal Learning	+	±	

Rx = Pharmacotherapy; PsyTx = Psychological Therapies; Env = Environmental Restructuring

Integrated Dual Disorders Treatment | 2

Treatment Goal	Rx	PsyTx	Env
Mindfulness	±	+	
Distress Tolerance	+	+	±
Emotion Regulation	+	+	±
Interpersonal Effectiveness	±	+	
Decreased Preoccupation, Cravings	+	+	+
Impulse Control	±	+	±

Rx = Pharmacotherapy; PsyTx = Psychological Therapies; Env = Environmental Restructuring

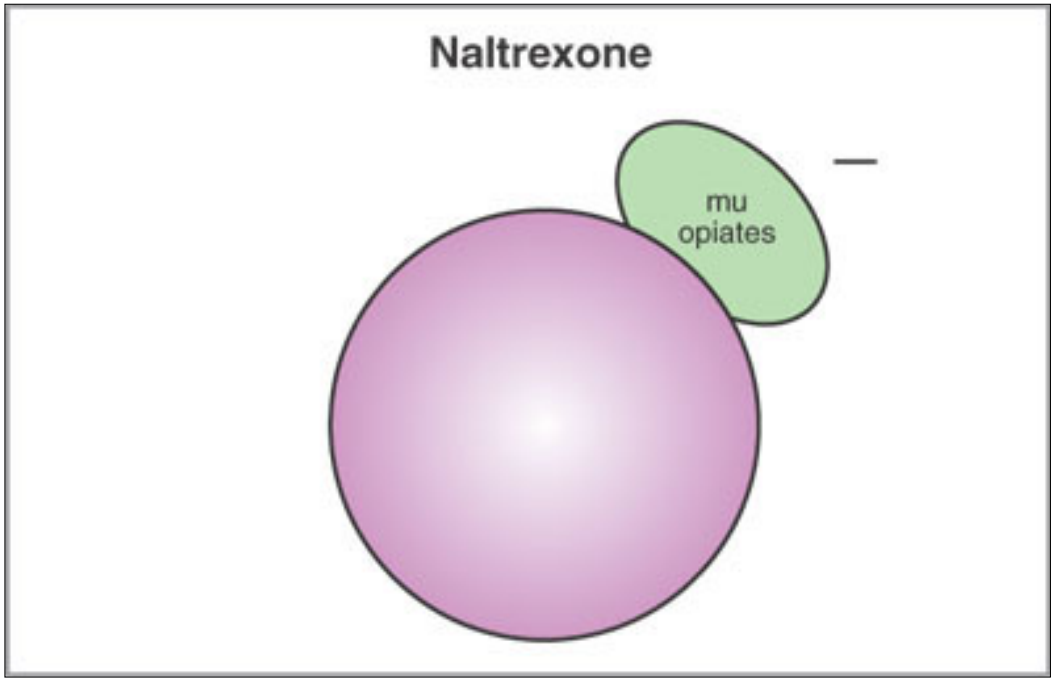
Medication-Assisted Treatment

- Addition of medications to psychological therapies to augment their effects

Naltrexone (ReVia, Vivitrol)

- FDA approved for alcohol use disorders
- Alcohol increases the activity of opioid pathways that affect the dopaminergic reward system
- Naltrexone blocks (antagonizes) the opioid receptor, thereby blunting (attenuating) the function of this pathway
- Most effective for patients with a positive family history

Clev Clin J Med 2006;73:641.



Stahl's Essential Psychopharmacology (online edition).

Acamprosate (Campral) | 1

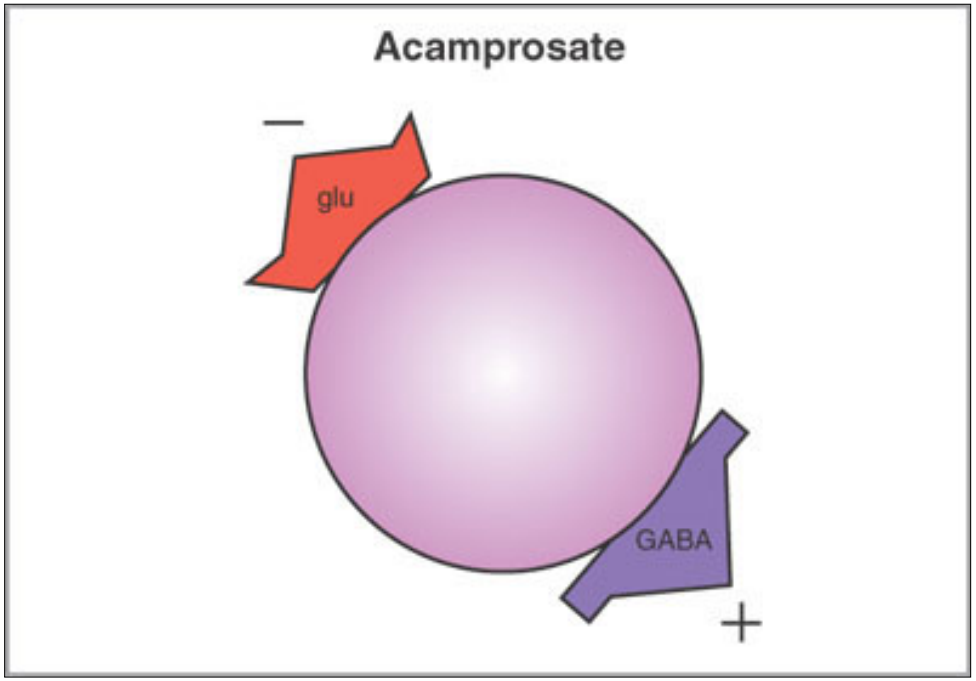
- FDA approved for alcohol use disorders
- Alcohol alters the balance between gamma-aminobutyric acid (GABA) and glutamate
- Acamprosate's exact mechanism of action is somewhat uncertain but likely affects the glutamate system
  - Reduces negative cravings

Clev Clin J Med 2006;73:641.

Acamprosate (Campral) | 2

- Is possibly more effective
  - When started after abstinence is achieved ("lead in abstinence")
  - When abstinence is the patient's stated goal

Clev Clin J Med 2006;73:641.



Stahl's Essential Psychopharmacology (online edition).

Topiramate (Topamax) | 1

- Not FDA approved for alcohol use disorders
- Alcohol alters the balance between gamma-aminobutyric acid (GABA) and glutamate
- Topiramate increases GABA and decreases glutamate function
  - Attenuates dopamine release associated with alcohol consumption (positive cravings)
  - Attenuates symptoms of alcohol withdrawal (negative cravings)

Clev Clin J Med 2006;73:641.

Topiramate (Topamax) | 2

- Appears to reduce heavy drinking and alcohol-related harm
- Cognitive slowing (side effect) can limit its use
  - "Dopamax"

Clev Clin J Med 2006;73:641.

Disulfiram (Antabuse) | 1

- FDA approved for alcohol use disorders
- Irreversibly inhibits a key enzyme needed to metabolize alcohol
- Acetaldehyde accumulates when alcohol is consumed
  - Causes a noxious reaction involving nausea, vomiting, fast heart rate (tachycardia), low blood pressure (hypotension) and skin flushing

Clev Clin J Med 2006;73:641.

Disulfiram (Antabuse) | 2

- In theory, should provide mental and physical disincentives to drink
- In reality, only modestly decreases alcohol use but does not lead to a higher rate of abstinence
- Potentially dangerous for patients with poor underlying health

Clev Clin J Med 2006;73:641.

Minneapolis Institute of Arts.