Addiction and dependence

Addiction refers to the *pattern* of self-administration

"A behavioral pattern of drug use, characterized by overwhelming involvement with the use of a drug (compulsive use), the securing of its supply, and a high tendency to relapse after withdrawal"

Definitions

Addiction is not:

- Experimental drug use
- Recreational (casual) use
- Circumstantial use
  (Drug-taking is not *compulsive* drug-seeking and drug-taking)
**Biopsychosocial models**

**Assumptions**

- The ‘habit-forming’ or rewarding effects of drugs are due to their action on endogenous neurotransmitter systems that normally play a role in the control of behavior by natural reinforcers
  
  (Need to understand neural systems normally involved in reward and motivated behavior)

**Reinforcement models**

- Drugs as negative reinforcers
  - largely based on experience with alcohol, opiates, barbiturates

- Drugs as positive reinforcers
  - cocaine, amphetamine, heroin
### Negative reinforcement models

**Drugs as negative reinforcers:**
- Drugs serve to increase the probability of further drug-seeking and drug-taking behavior because of their ability to alleviate unpleasant states.

### Sub-Types of Negative Reinforcement Models

#### Self-Medication Hypothesis
Drugs are used to self-mediate, i.e., relieve symptoms that occur independent of drug use (e.g., pain, anxiety).

#### Physical Dependence Hypothesis
With the development of tolerance and physical dependence drug use is sustained in order to avoid the unpleasant consequences associated with withdrawal.
Psychological dependence

Distress Syndrome Reduction Theories
- 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

Withdrawal avoidance models

Relapse

Relapse after detoxification

The negative reinforcement view
- classically conditioned withdrawal

Withdrawal to an environmental context

CS produces "drug-opposite" effect
Positive Reinforcement Models

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)

Relapse - The positive reinforcement view

**CS produces “drug-like” effect**
(a “conditioned high”; “needle freak”)

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<th>Drug administered</th>
<th>Human - effects</th>
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Relapse - The positive reinforcement view

**CS produces “drug-like” effect**

Drug CR Timecourse

- Control (R+H+)
- Paired (R+H+)
- Unpaired (3+H+)

Minutes: Sal.5, Sal.10, Sal.15
Neural basis of reward

Where do drugs act to produce positive reinforcement and reward?

- β-endorphin
- GABA
- Ventral tegmental area (VTA)
- VTA > accumbens DA system
- Mesolimbic dopamine
- DA antagonists
- Local injection studies
- Neurochemical lesions
- Common psychostimulant properties
- Common actions on synaptic DA

Dopamine and natural rewards

DA is implicated in mediating the effects of many rewards

- Intracranial self-stimulation
- Food
- Water
- Sex
- Conditioned reinforcers
DA and reward

DA mediates drug reward

- Increase self-administration because that behavior is reinforced by action of drug on DA systems ("positive reinforcement model")
- Increase because DA increase pleasure ("pleasure-seeking" model)

Traditional approaches

“Drug craving is characterized by both the desire to experience the positive hedonic effects of the drug ... and the desire to avoid aversive withdrawal symptoms ...”

Traditional approaches

There are problems with both traditional positive (hedonia) and negative reinforcement models of addiction

Negative reinforcement

Motivated by desire to relieve unpleasant state
Problems:
- People and animals self-administer opioids 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 symptoms have subsided
  - conditioned withdrawal as explanation

Problems with conditioned withdrawal

- Many opiate addicts deny the existence of conditioned withdrawal signs
- Although many are aware of conditioned withdrawal they do not cite this as the reason for resuming drug use
“No, Doc, craving is when you want it - want it so bad you can almost taste it ... but you ain’t sick ... sick is, well sick.”


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Problems with conditioned withdrawal

- There is a poor correlation between craving (wanting drugs) and the occurrence of conditioned withdrawal

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Conclusion: physical dependence and withdrawal are not 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*, 1985)

- “For rats and monkeys physical dependence is neither a necessary nor sufficient condition for opiates to act as reinforcers”
  

- “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”
  
Positive reinforcement models

Drugs promote drug-taking because of the action of drugs as positive reinforcers

Positive reinforcers have the property that they increase the probability of the preceding behavior (drug-taking in this case)

The reason people take drugs is because drugs increase the probability of drug-taking

Drug self-administration is maintained because of the state drugs induce, not because they alleviate an unpleasant state

“The only existing positive reinforcement view of addiction that might qualify as an explanatory theory identifies positive reinforcement with drug euphoria”.

(R.A. Wise & M.A. Bozarth, Psychological Review, 1987, 94:469)
Primary motivational force driving drug-seeking and drug-taking behavior in the addict is the desire to obtain pleasure (euphoria).

Hedonic effects of drugs are mediated by their actions on dopamine systems.

Problems with a euphoria model

We must assume that the subjective pleasurable effects of drugs are enormous.

Problems with a euphoria model

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).
Dopamine does NOT mediate pleasure

- DA is not necessary for rats to make normal hedonic judgements about taste stimuli
- DA neurons often discharge in anticipation of rewards, not during commerce with the reward, when presumably subjective pleasure is experienced
- DA is released in the accumbens in response to aversive events and to stimuli previously associated with aversive events
- In humans DA antagonists do not reduce amphetamine-induced euphoria, but may reduce ratings of wanting amphetamine

Hedonia ("pleasure-seeking") view of addiction

- Primary motivational force driving drug-seeking and drug-taking behavior in the addict is the desire to obtain pleasure (euphoria)
- Hedonic effects of drugs are mediated by their actions on dopamine systems

If NO: How does the action of addictive drugs on dopamine systems promote drug-taking behavior?
An Incentive-Sensitization View
Evidence for sensitization of neural systems mediating drug reward

- Psychomotor sensitization
- Sensitization of drug reward
- Sensitization of DA/accumbens system

Psychomotor sensitization

Drug
- Amphetamine
- Cocaine
- Phenylethylamine
- Morphine
- Phencyclidine
- MDMA
- Ethanol
- Nicotine
- etc.

Sample reference
- Segal & Mandell 1974
- Post & Contel 1983
- Borison et al. 1977
- Babbini et al. 1975
- Greenberg & Segal 1986
- Spanos & Yamamoto 1989
- Masur & Boerngen 1980
- Kita et al. 1992
Sensitization of drug reward

- Facilitate acquisition of drug self-administration

- Facilitate conditioned place preference
  (e.g., Lah 1995; Gaiardi et al. 1991; Shippenberg et al. 1995, 1996)

- Increase in "breakpoint" (progressive ratio)
  (e.g., Mendrek et al., 1998; Vezina, 1998)

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Neurobiology of Sensitization

Microdialysis

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Increased dendritic length and spine density in amphetamine sensitized rats

Saline  Amphetamine

(From Robinson & Kolb, 1997)
The repeated administration of many drugs of abuse can produce persistent neuroadaptations in the neural systems responsible for incentive salience attribution, adaptations that render these systems hypersensitive ("sensitized").

**An Incentive-Sensitization View**

Sensitization leads to pathological "wanting", that can be dissociated from the hedonic effects of drugs ("liking").
### Incentive-sensitization

- Addictive drugs can produce persistent neuroadaptations in brain regions involved in the process of reward, adaptations that render these regions hypersensitive ("sensitized")

  *These neuroadaptations alter the process of reward to render susceptible individuals hypersensitive to the incentive motivational effects of drugs (and drug-related stimuli), leading to more and more compulsive patterns of drug-seeking and drug-taking behavior.*

- The persistence of neural sensitization leaves addicts susceptible to relapse even long after the discontinuation of drug use