ADDICTION
Lecture 12

What is Drug Addiction?
Not the same thing as drug abuse...
Hard to define, & definition has changed over the years. Modern definition of Addiction (Jaffe):
"a behavioral pattern of drug use, characterized by
1) overwhelming involvement with the use of a
drug (compulsive use)
• does not necessarily imply that addiction = physical
dependence (many addictive drugs do not produce
much physical dependence)
2) the securing of its supply (compulsive drug-
seeking), &
3) a high tendency to relapse after withdrawal"

Addiction Outline
1. Theories of addiction
   a) Negative Reinforcement Models
      Physical dependence (withdrawal) theory
      – driven largely by opiates, barbiturates, alcohol
      – based largely on tolerance and physical dependence
      Self-Medication Hypothesis
   b) Positive Reinforcement Models
      Positive incentive (reward) theory
      – driven largely by cocaine, amphetamine, nicotine
      – based largely on reward and reinforcement
2. Common mechanism of addiction/reward
   – pathways in the brain
**Opiates & addiction: Because it hurts to quit?**

**Why are some opiates addictive?**

**Original explanation:** Physical Dependence Theory of Addiction:
- Stop taking opiates -> physical withdrawal -> start drug again

**Withdrawal**: marked physiological disturbance that occurs upon cessation of the drug, OPPOSITE of drug effects
- **Withdrawal syndrome is due to physical dependence**
  - Physical dependence: withdrawal occurs upon cessation of the drug

**Physical dependence** occurs because of homeostasis
- Body tries to compensate for changes caused by taking the drug

**Physical dependence & withdrawal syndrome**

**Example:**
1. Temperature goes up when take drug
2. Body has a set point (homeostasis) for temperature & compensatory changes, bring it back to set point

**ON drug, physically-dependent**
- Drug effect
- Compensatory adaptations
- Set point

**OFF drug, withdrawal syndrome**
- Withdrawal effects are the opposite of the drug effects
- Compensatory adaptations
- Set point

**Opiates and past theories of addiction**

- Bodily compensatory changes develop over time with drug use
  - These compensations form the basis for tolerance: drug effect gets weaker with repeated administration, OR the need to take more drug to get the same effect.

- So at a certain time in history (1970s), dependence and tolerance were the basis for addiction...
Physical dependence theory

Take drugs to avoid unpleasant consequences of withdrawal:

**Physical dependence theory of addiction**

Take drug -> nasty withdrawal goes away

So by this theory, if you treat withdrawal (or wait for it to go away), you treat addiction.

• Note that this theory assumes addiction = dependence
• Escalating drug use is attributed to tolerance

Alcohol also fits the physical dependence model of addiction...

• Alcohol activates GABA-A receptor (among other actions); causes IPSP (inhibitory)
• Produces severe dependence & very severe withdrawal
  (Life Threatening: seizures & delirium tremens or DTs)
  • much > severe than opiates

Works well for Opiates, Barbiturates, & Alcohol, not stimulants

Problems with the Physical dependence theory

1. No good relationship between strength of withdrawal & strength of addiction:
   - Withdrawal: alcohol and barb worse than heroin
   - Addiction: heroin more addictive than alcohol or barb
   - Changing the rise time of the drug (e.g., route of admin) has no effect on physical dependence but big effect on addiction

2. Can treat withdrawal (wait for it to go away - detox), but addiction remains. Relapse very high even years later.

3. Drugs that do not produce much dependence (withdrawal) still very addictive: Amphetamine, Cocaine, Nicotine
   - probably more so than the other drugs
   - do not confuse craving with withdrawal

4. Only very high doses of drugs produce dependence
An alternative model of addiction

Positive incentive theory of addiction:
Positive reinforcement - response that is followed by pleasant consequences likely to be repeated

- Take drug to get euphoria or drug "high"
- Can account for addictiveness (most to least):
  Amphetamine > Heroin = Cocaine > Nicotine > Alcohol
- Also can account for difference in heroin & morphine...

Positive incentive theory & the delay of reinforcement gradient

Heroin is converted to morphine in the brain.
Main difference = speed with which drug gets into brain (heroin faster than morphine). This is critical to abuse potential

- E.g., injection > inhale > pill
e.g., crack cocaine vs snorting
- Many non-addictive versions of drugs are simply ones where drug onset is slow
  (e.g., crystal meth vs. desoxyn(time release))
- Key concept in ALL reinforcement =
  Delay of Reinforcement Gradient: inverse relationship between delay & reinforcing properties
  (GREATER delay of onset = LESS reinforcing)

I.V. cocaine is most addictive, oral is least

1. Concentration of Cocaine in Blood Plasma

   ![Graph showing concentration of cocaine in blood plasma over time]

   Source: Adapted from Pollinier, Bowers, and Guzman, 1987; after Jones, 1985.
   Copyright © 2007 by Allyn & Bacon
Measuring the reinforcing properties of drugs

Problem was no good way to measure reinforcement in animals (easy to measure withdrawal)...

In the late 60's two models developed:
1. Self-administration paradigm
2. Conditioned place preference

Self-Administration Model ("drug taking")

- Two Behavioral Paradigms

The rat presses the lever to self-inject a drug, either into an area of its brain or into general circulation

Conditioned Place Preference Model ("drug seeking")

- Two Behavioral Paradigms (continued)

A rat repeatedly receives a drug in 1 of 2 distinctive compartments. Then, on the test, the tendency of the rat, now drug-free, to prefer the drug compartment is assessed.
Positive incentive theory & animal studies

- Animal work in these 2 positive reinforcement models lined up well with addict reports.
  - Liked:
    - amphetamine > cocaine = heroin > nicotine > alcohol
  - could also discriminate b/w morphine & heroin (heroin > addictive)
- Interest shifted to amphetamine and cocaine...

Mechanisms of action of cocaine and amp

- Amphetamine & cocaine’s actions on dopamine (DA) are the key to their reinforcing qualities.
  - Cocaine jams the DA reuptake pump ("DA transporter"), released DA stays active longer
  - Amphetamine reverses the DA transporter, dumping large pools of cytoplasmic DA into the synapse

Nicotine and dopamine’s role in addiction

- Nicotine acts on acetylcholine (Ach) receptors... but this also leads to enhanced DA release.
  - "ALL reinforcers (food, sex, etc.) seem to activate DA release
- Dopamine’s role in addiction: addictive drugs "hijack" the natural reinforcement pathway
  - What is this pathway?
**The Dopamine VTA-Accumbens and Accumbens-Prefrontal Cortex Pathways are KEY**

- Prefrontal cortex
- Ventral tegmental area
- Nucleus accumbens
- Amygdala
- Substantia nigra

**Planning**
**Inhibition**
**Self-control**

**Reward**
**Emotional memory**

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**Cocaine & Amphetamine directly activate DA in the accumbens**

Dopamine concentration in the nucleus accumbens of rats

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**Drugs abused by humans preferentially increase synaptic dopamine concentrations in the mesolimbic system of freely moving rats**

**Drugs that increase extracellular dopamine**

- amphetamine
- cocaine
- opiates (morphine, heroin)
- MDMA
- ethanol (alcohol)
- PCP
- nicotine
Sensitization

But what supports pattern of escalating use?
Some drug EFFECTS show sensitization, the opposite of tolerance ("reverse tolerance")
• True of DA release & DA effects of drugs.

Behavioral Sensitization
Amphetamine injections in rat sensitize psychomotor (rotation/activity) response

Sensitization Hypothesis

Neurochemical sensitization: cellular DA release

So, cellular DA release sensitizes

From the previous graph:
• The longer a rat is treated with amphetamine (i.e., 3 days vs. 28 days), the more DA that is released when a "test" amphetamine injection is given at a later time…
  
• This could be the cellular basis for what addicts define as "craving"
Sensitization & increased drug use

- The memory of how good the high was sensitizes in addicts.
- **Incentive-Sensitization Theory:** escalating drug use is due to sensitization of positive-incentive value of the drug (i.e., increased “craving” or “wanting”)
- No known way to reverse sensitization
- Lasts long after withdrawal (seems to last forever)
- Major focus is to develop treatments to block and reverse neural (cellular) sensitization in brain

Problems with Positive Incentive Theory

1. Doesn’t address relapse, at least in this form:
   - Why do addicts start taking the drug again long after they quit?
   - maybe reminder cues/drug context??
     - we know that drug-related cues (alone) can cause DA release in the brain....

Classical conditioning in Pavlov’s dogs

1. Before conditioning
   - Food → response
   - Unconditioned stimulus → Unconditioned response
2. Before conditioning
   - Tuning fork → response
   - Neutral stimulus → No unconditioned response
3. During conditioning
   - Food, Tuning fork → response
   - Unconditioned stimulus, Neutral stimulus → response
4. After conditioning
   - Food, Tuning fork → response
   - Unconditioned stimulus, Neutral stimulus → response


Conditioning of drug-like effects: contributing to relapse?

Initial exposure
Sight of syringe, needle, room, etc.

Drug (e.g., Amphetamine) DA release, activity, etc.

Neutral stimuli US UR

Later effects
Sight of stimuli associated with drug taking CR

DA release, activity

CS

Anagnostaras & Robinson, 1996

Relapse-Positive Reinforcement View

CS produces “drug-like” effect

Drug CR Timecourse

Thanks for being a great class!

See you on Thursday...