



Biological Psychology

M5X00908 Brain, Behaviour, and Cognition (BBC)

Lecture 9: Drug Addiction and the Brain's Reward

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Basic Principles of Drug Action

- **Psychoactive drugs** – drugs that influence subjective experience and behavior by acting on the nervous system.
- **Drug administration** – route of administration influences the rate at which and the degree to which the drug reaches its site of action



Drug Administration & Absorption

Oral Ingestion:

- Easy and relatively safe
- Absorption via digestive tract is unpredictable

Inhalation (tobacco & marijuana):

- Absorbed through capillaries in lungs

Injection (bypasses digestive tract):

- Subcutaneously (SC): under the skin
- Intramuscularly (IM): into large muscles
- Intravenously (IV): into veins, drug delivered directly to brain

Absorption through mucous membranes:

- Nose, mouth, rectum

Mechanisms of Drug Action



- In order for a psychoactive drug to have an effect, it must get to the brain – it must pass through the blood-brain barrier.
- Action of most drugs terminated by enzymes in the liver – drug **metabolism**.
- Small amounts may also be excreted in urine, sweat, feces, breath, and mother's milk.

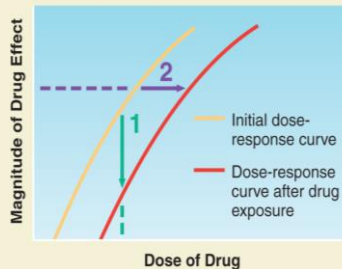
Drug Tolerance



- Decreased sensitivity to a drug as a consequence of exposure to it
 - Shift in the dose-response curve to the right

Drug tolerance is a shift in the dose-response curve to the right. Therefore,

- 1 In tolerant subjects, the same dose has less effect.
- 2 In tolerant subjects, a greater dose is required to produce the same effect.



Drug Tolerance



- **Cross tolerance** – one drug can produce tolerance to similar drugs
Example: alcohol and benzodiazepines.
- Tolerance often develops to some effects & not others of a drug. Can also have an “**inverse tolerance**,” or sensitization.
- No single mechanism that underlies all examples of tolerance.

Drug Tolerance



Metabolic

- Less drug is getting to the site of action

Functional

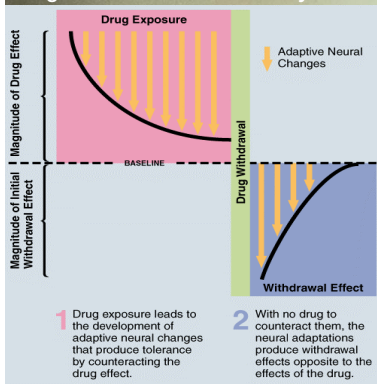
- Decreased responsiveness at the site of action; fewer receptors; decreased efficiency of binding at receptors; receptors less responsive

Drug Withdrawal Effects & Physical Dependence



- Seen when drug use is terminated
- Symptoms are the opposite of the drug's effects
- Body has made changes to compensate for drug's presence – functions normally with the drug present
- Severity varies with drug and pattern of use

Drug Withdrawal Effects & Physical Dependence



Relation between Drug Tolerance and Withdrawal Effects

Addiction: What Is It?



- “Addicts” are those who continue to use a drug despite its adverse effects on health and social life
- Addiction and physical dependence may occur together or separately
 - After withdrawal symptoms due to physical dependence have subsided, addicts may still crave the drug

Role of Learning in Drug Tolerance



- Contingent drug tolerance
 - Tolerance only develops to drug effects that are experienced.
- Conditioned drug tolerance
 - Maximal tolerance effects are seen in the environment in which a drug is usually taken.
- Conditioned withdrawal effects
 - Withdrawal elicited by drug-related cues.

Conditioned Tolerance and Withdrawal



- Situational specificity of drug tolerance is well documented
- Addicts are more likely to overdose in unfamiliar surroundings
- **Exteroceptive** or **interoceptive** cues associated with drug-taking become conditioned stimuli that elicit conditioned compensatory responses, producing tolerance prior to drug use or withdrawal in the absence of the drug

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Commonly Abused Drugs:

- Tobacco
- Alcohol
- Marijuana
- Cocaine
- Opiates

Tobacco



- Nicotine – major psychoactive ingredient
- About 70% of those who experiment with smoking become addicted
- Nicotine acts on nicotinic cholinergic receptors in the brain.

Effects of Long-Term Tobacco Use

- Smoker's syndrome – chest pain, labored breathing, wheezing, coughing, increased susceptibility to respiratory infections
- Susceptible to various lethal lung disorders – pneumonia, bronchitis, emphysema, lung cancer
- Increased risk of cardiovascular disorders: can culminate in a heart attack or stroke.

Alcohol



- A depressant
- Heritability estimate for alcohol addiction is about 55%
- Metabolic and functional tolerance develops
- Affects almost every tissue in the body

Effects of Chronic Alcohol Consumption

- Severe withdrawal in 3 phases:
 - 5-6 hrs post drinking: tremors, nausea, sweating, vomiting, etc.
 - 15-30 hrs: convulsive activity
 - 24-48 hrs: **delirium tremens** (DTs) – may last 3-4 days
- **Korsakoff's syndrome**
- **Cirrhosis**
- **Fetal alcohol syndrome** (affects children of mothers who were heavy alcohol users during pregnancy)



Marijuana

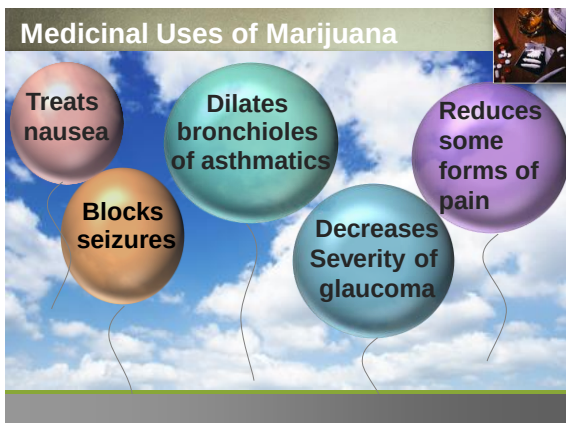
- **Cannabis sativa** – common hemp plant
- **THC** – primary psychoactive constituent – although 80 others are present
- Endogenous transmitter is anandamide
- High doses impair short-term memory and interfere with task involving multiple steps
- Negative effects of long-term use are far less severe than those associated with alcohol and tobacco



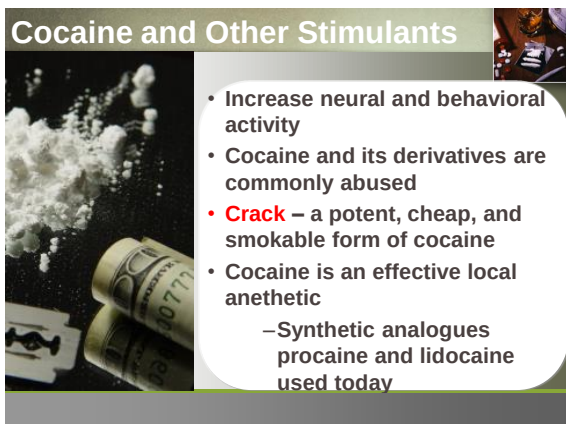
Adverse Effects of Heavy Marijuana Use

- Respiratory problems – cough, bronchitis, asthma
- Single large doses can trigger heart attacks in susceptible individuals
- No evidence that marijuana causes permanent brain damage
- Possible correlation between marijuana use and schizophrenia, but no causal link has been shown

Medicinal Uses of Marijuana



Cocaine and Other Stimulants



Cocaine



- Cocaine binges or sprees may lead to cocaine psychosis
 - Mistakenly diagnosed as paranoid schizophrenia
- While tolerance may develop to most effects of cocaine (i.e., to the euphoria), sensitization is seen to its motor and convulsive effects
- Although highly addictive, withdrawal is relatively mild

Other Stimulants



- Amphetamine ("speed")
 - Effects like cocaine – can produce psychosis
- MDMA ("ecstasy")
 - Impairs dopaminergic and serotonergic function in animal studies; human relevance unclear
 - Impairs executive function, inhibitory control, and decision making (as shown by cortex and limbic functional brain scan abnormalities)

Opiates: Heroin and Morphine



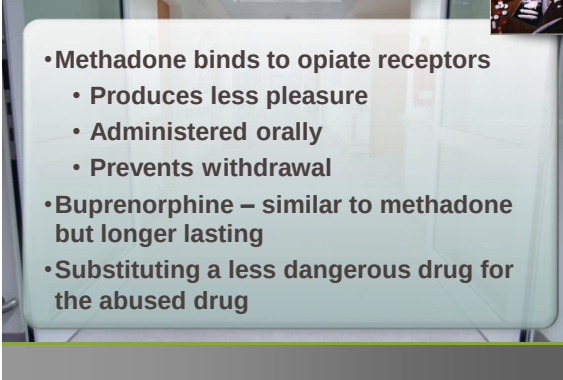
- Morphine & codeine obtained from the opium poppy
- Opiates – these drugs and others with similar structures or effects
- Medicinal uses
 - Analgesics (painkillers)
 - Treatment of cough and diarrhea
- High risk of addiction

Opiate Addiction



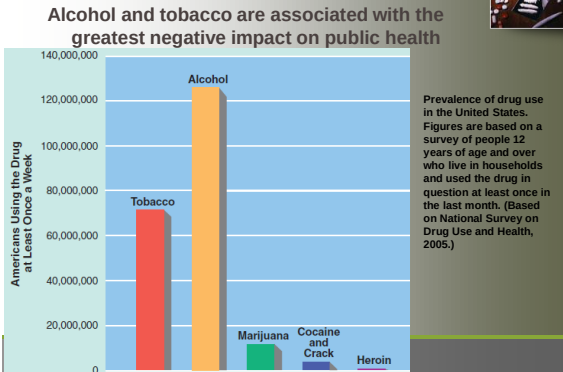
- Drawn to use by the rush following IV injection
- Tolerance and physical dependence develop
- Desire to avoid withdrawal adds to motivation to use
- Although highly addictive, direct health hazards are relatively minor
- Many health hazards related to use of needles
- Severity of withdrawal has been exaggerated

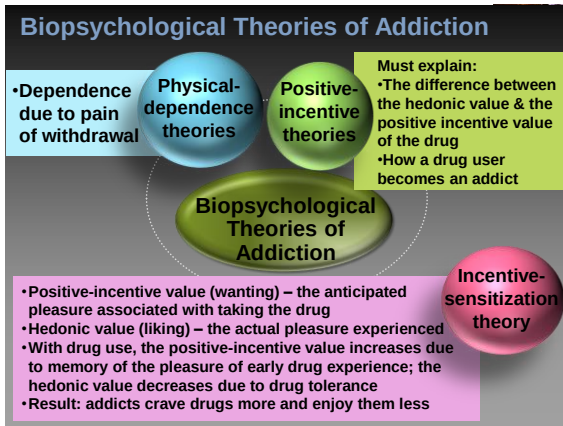
Treatment for Heroin Addiction



- **Methadone binds to opiate receptors**
 - Produces less pleasure
 - Administered orally
 - Prevents withdrawal
- **Buprenorphine** – similar to methadone but longer lasting
- **Substituting a less dangerous drug for the abused drug**

Comparison of the Hazards of Tobacco, Alcohol, Marijuana, Cocaine, and Heroin





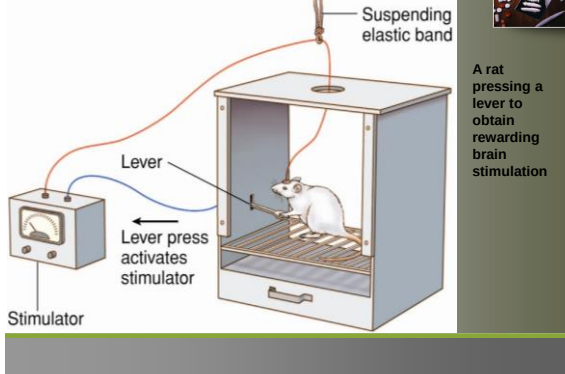
Relapse and Its Causes

- **Stress** – drug use as a coping mechanism
- **Priming** – a single exposure leads to a relapse
- **Environmental cues**
 - Conditioned drug tolerance
 - Returning to place where drugs once taken (or even thinking about drug) causes conditioned compensatory responses (tolerance/withdrawal), craving, and relapse

Intracranial Self-Stimulation and Brain “Pleasure Centers”

- Brain circuitry exists that reinforces behaviors
- Many species will work for stimulation of brain “pleasure centers”
- Discovered by Olds and Milner (1954)
- Drug use may be reinforced by acting on this circuitry

Intracranial Self-Stimulation and Brain "Pleasure Centers"



Mesotelencephalic Dopamine System and Intracranial Self-Stimulation

•Neurons projecting from two midbrain areas to telencephalon

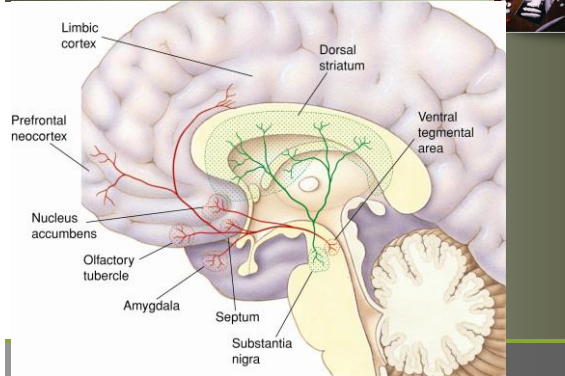
- Nigrostriatal pathway

- Substantia nigra neurons projecting to dorsal striatum (degenerates in Parkinson's disease)

- Mesocorticolimbic pathway

- Ventral tegmental area neurons projecting to cortical and limbic sites, including the nucleus accumbens (the major "reward" pathway for ICSS, natural rewards, and addictive drugs)

Mesotelencephalic Dopamine System and Intracranial Self-Stimulation





Mesocorticolimbic Pathway and Reward

- Self-stimulation sites that do not contain dopaminergic neurons project here
- Increase in dopamine release seen here in self-stimulation studies
- Dopamine agonists tend to increase self-stimulation and antagonists to decrease
- Lesions here disrupt self-stimulation

Two Key Methods for Measuring Drug-Produced Reinforcement in Laboratory Animals



- **Drug self-administration** through cannulas to the bloodstream
- **Conditioned place-preference**: lab animals choose to spend more time in cage compartment where drugs were administered than elsewhere



Two Key Methods for Measuring Drug-Produced Reinforcement in Laboratory Animals

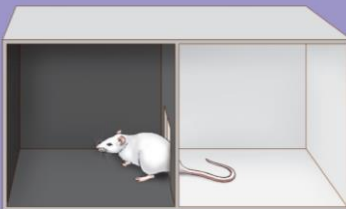


Drug Self-Administration



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

Conditioned Place Preference



A rat repeatedly receives a drug in one of two distinctive compartments. Then, on the test, the tendency of the rat, now drug-free, to prefer the drug compartment is assessed.

Two behavioral paradigms that are used extensively in the study of the neural mechanisms of addiction: the drug self-administration paradigm and the conditioned place-preference paradigm.

Dopamine and Drug Addiction



- Dopamine's role suggested by self-stimulation studies
- Dopamine antagonists interfere with self-stimulation and reduce the reinforcing effects of addictive drugs and food
- Nucleus accumbens appears to play a primary role

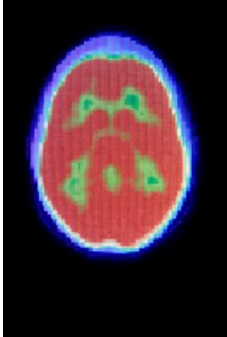
Nucleus Accumbens (NA) & Drug Addiction



- Animals self-administer microinjections of addictive drugs into NA
- Microinjection of drugs into NA produce conditioned place preferences
- Lesion NA or ventral tegmental area – no drug self-administration or drug-related place preference
- Both self-administration of addictive drugs and natural reinforcers result in increased dopamine in the NA



Support for the Involvement of Dopamine in Addiction: Evidence from Imaging Human Brains



- PET displacement studies indicate dopamine increases in the NA during drug intake are correlated with self-reported "high" and euphoria
- Overall dopamine function is diminished in human addicts, except during drug or drug cue exposure

Dopamine Release in the NA: What Is Its Function?

- Role is well-established as necessary for reinforcing effects of most drugs of abuse
- Emerging theory is that normally NA dopamine signals discrepancies between expected and actual rewards



Current Approaches to Brain Mechanisms of Addiction

Current approach takes into account historical theories regarding reward and drug conditioning



Current Issues in Modern Addiction Research

- Addiction is psychologically complex
- Addicts show poor decision making and lack of self control, suggestive of prefrontal cortex role
- Drug addiction may be related to other non-adaptive behaviors, such as compulsive eating, gambling, sexual behavior, klepto-mania, shopping, etc.
- Other neurotransmitters: glutamate, endogenous opioids, norepinephrine, GABA, and endocannabinoids



Brain Structures That Mediate Addiction: The Current View

- Initial drug taking – involvement of mesocorticolimbic pathway (nucleus accumbens), prefrontal lobes, hippocampus, amygdala
- Craving and compulsive drug use – dorsal striatum and hypothalamic stress circuits take over
- Relapse – priming doses (prefrontal cortex), drug associated cues (amygdala), and stress (hypothalamic stress circuits)



Case Study

A Noteworthy Case of Addiction

Subject:
Sigmund Freud

- Famous essay “Song of Praise” (July, 1884), created a wave of interest in using cocaine
- After 3 years, Freud stopped using the drug
- 7 years later, his physician ordered him to stop smoking due to a heart condition
- Despite having no difficulty ceasing all use of cocaine, Freud could not stop smoking and died from cancer in 1939

Next Week....



Biopsychology of psychiatric disorders

Essential Reading....

Pinel, J. P. J. *Biopsychology* – Chapter 18
