



The Brain, Biology and Cognition (BBC)

Biological and Cognitive effects of drugs

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Commonly Abused Drugs:

- Tobacco
- Alcohol
- Marijuana
- Cocaine
- Opiates

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Mechanisms of Drug Action



- To have effect, drugs must pass blood-brain barrier.
- Drugs affect nervous system, either diffusely
- Or bind to specific synaptic receptors.
- Action of most drugs terminated by liver enzymes – metabolism.
- Eliminates drug's ability to pass lipid membranes of cells, so cannot penetrate blood-brain barrier

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Drug Tolerance

Experience decrease sensitivity to drug from repeated exposure

Demonstrated in 2 ways: dose has less effect than before or more of drug required to produce same effect.

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.

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Drug Tolerance

- 3 aspects about specificity of drug tolerance

1. **Cross tolerance** – one drug can produce tolerance to similar drugs – e.g., alcohol & benzodiazepines.
2. Tolerance develops to some effects, not others. Can also have an “**inverse tolerance**,” or sensitization.
3. Not a unitary phenomenon – no single mechanism underlies all examples of tolerance

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Drug Tolerance

2 categories of changes that underlie drug tolerance:

Metabolic	Functional
• Reduced amount of drug is getting to site of action	• Decreased responsiveness at site of action; fewer receptors; decreased efficiency of binding at receptors; receptors less responsive

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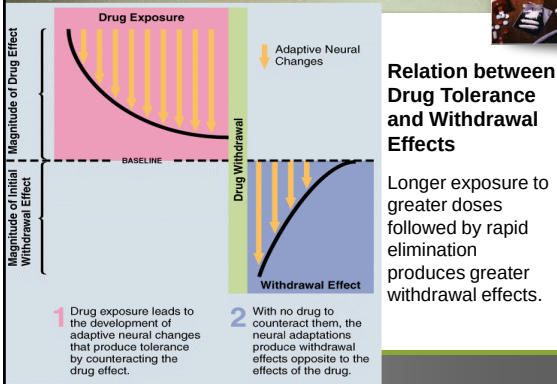
Drug Withdrawal Effects & Physical Dependence



- Sudden elimination triggers adverse physiological reaction: withdrawal syndrome.
- Body makes changes to compensate for drug's presence – functions normally with drug present
- Withdrawal effect usually opposite to initial effect of drug
- Withdrawal effect may be produced by same neuronal changes producing drug tolerance.

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Drug Withdrawal Effects & Physical Dependence



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Pharmacology of Synaptic Transmission



Drugs influence on synaptic activity

- Agonists
- Antagonists
- Drug may alter neurotransmitter activity at any point in "life cycle"

Pharmacology examines behavioural effects of neurotransmitters.

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Complete the Agonistic and Antagonistic effects of drugs worksheet

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Addiction: What Is It?



- “Addicts” continue to use drug despite adverse effects on health, cognition, and social life and despite repeated efforts to stop.
- Many equate addiction and physical dependence:
 - See addicts as trapped in cycle of drug taking, withdrawal, & further drug taking to combat withdrawal
- But this is inconsistent with evidence and taking drugs to alleviate withdrawal symptoms is not major factor.
- Some addicts start taking drug again after months, years, or decades without it.

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Role of Learning in Drug Tolerance



- Research suggests learning and cognition plays role in drug tolerance
- Two phenomena:
 1. **Contingent** drug tolerance: tolerance develops only to drug effects that are actually experienced.
 2. **Conditioned** drug tolerance: tolerance effects maximally expressed only when drug is administered in same situation previously administered.

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Conditioned Tolerance and Withdrawal

- **Situational specificity**
- Siegel et al. addicts susceptible to lethal effects of drug overdose when drug administered in new context.
- Hypothesis: addicts become tolerant when repeatedly self-administer drug in same environment, thus take larger doses to counteract diminution of drug effect.
 - If they administer huge dose in new situation, tolerance effects are not present to counteract effects of the drug.
- Research evidence: Siegel et al. many more heroin-tolerant rats died following high dose of heroin administered in a novel situation than died in the usual injection environment.

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Treatment for Heroin Addiction

- **Main treatment: Methadone (an opiate itself)**
- **Binds to opiate receptors, but....**
 - Produces less pleasure than heroin
 - Administered orally
 - Prevents withdrawal
- **Buprenorphine: similar but longer lasting**
- **Substitute less dangerous drug for abused drug**

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Biopsychological Theories of Addiction

- Dependence due to pain of withdrawal
- But doesn't explain relapse

Physical-dependence theories

Positive-incentive theories

Must explain:

- Difference between hedonic value & positive incentive value of drug
- How a drug user becomes an addict

Biopsychological Theories of Addiction

- Positive-incentive value (wanting) – anticipated pleasure associated with taking the drug
- Hedonic value (liking) – actual pleasure experienced
- With drug use, positive-incentive value increases due to memory of the pleasure of early drug experience; the hedonic value decreases due to drug tolerance
- Result: addicts crave drugs more and enjoy them less

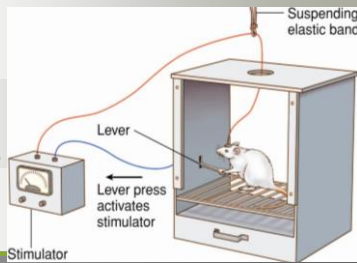
Incentive-sensitization theory

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Intracranial Self-Stimulation and Brain "Pleasure Centers"

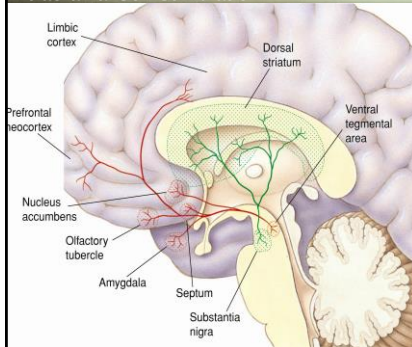
- Circuitry in brain that reinforces behaviour and species (inc. humans) will administer brief bursts of weak electrical stimulation to them.

- Olds and Milner (1954): specific brain sites mediating self-stimulation are those that usually mediate pleasurable effects of natural rewards (e.g., food and water).



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Mesotelencephalic Dopamine System and Intracranial Self-Stimulation



Two pathways:

Ventral tegmental area in red projecting to its various areas

Substantia nigra in green projecting to its various areas.

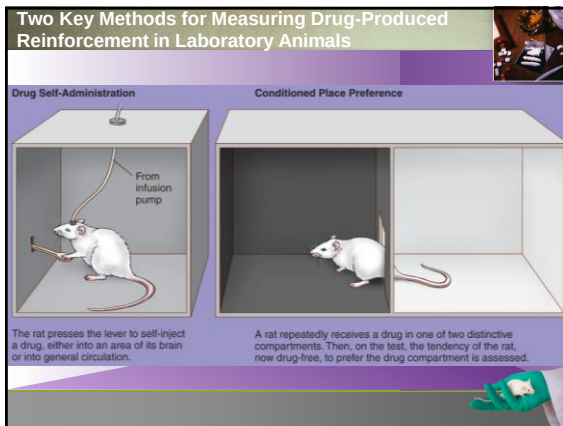
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Mesocorticolimbic Pathway & Reward

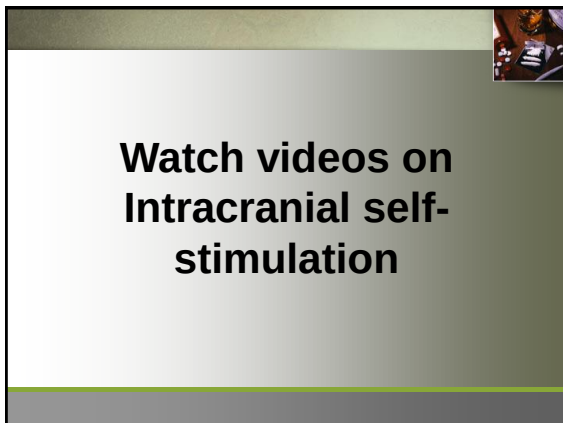
- Mesocorticolimbic pathway of mesotelencephalic dopamine system plays role in mediating intracranial self-stimulation...

1. Brain sites where self-stimulation occurs are part of the mesotelencephalic dopamine system.
2. Intracranial self-stimulation often associated with increase in dopamine release in mesocorticolimbic pathway.
3. Dopamine agonists tend to increase intracranial self-stimulation, while dopamine antagonists decrease it.
4. Lesions of mesocorticolimbic pathway disrupts intracranial self-stimulation.

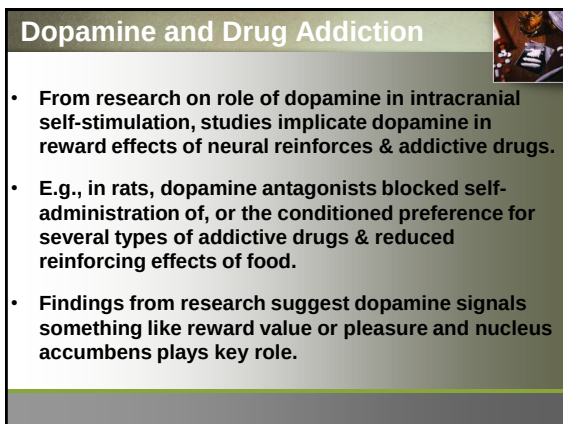
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Nucleus Accumbens (NA) & Drug Addiction



Once evidence suggested link between dopamine with natural reinforcers and drug-induced reward, research on lab animals looked at specific sites in mesocorticolimbic dopamine pathway.

Events in nucleus accumbens and dopaminergic input to it from ventral tegmental area appeared to be clearly related to experience of reward and pleasure.

Four main findings emerged:



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Nucleus Accumbens (NA) & Drug Addiction



- Lab animals would self-administer microinjections of addictive drugs directly into nucleus accumbens.
- Microinjection of drugs into NA produced conditioned place preference for compartment administered.
- Lesions to NA blocked self-administration of drugs into general circulation or development of drug-associated conditioned place preferences.
- Self-administration of addictive drugs & experience of natural reinforcers associated with elevated levels of extracellular dopamine in NA.



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



- Volkow et al. administered various doses of radioactively labelled cocaine to addicts and asked to rate the high.
 - PET to measure degree labelled cocaine bound to dopamine transporters.
 - Intensity of high correlated with degree of binding
 - No high was experienced unless 50% receptors bound.
- Healthy non-addicted humans given amphetamine injection.
 - As dopamine levels in NA increased, reports of euphoria increased.

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Dopamine Release in the NA: What Is Its Function?

- But reward is complex process with many psychological components – so what is role in reward of dopamine release in the NA?
- Extracellular dopamine levels increase following presentation of natural reward (e.g., food or addictive drug)
- Ventral tegmental neurons, which release dopamine into NA fire in response to stimulus at rate proportional to its reward.
- Dopamine released in NA is related to expectation of reward rather than experience itself.



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Current Issues in Modern Addiction Research

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

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Brain Structures That Mediate Addiction: The Current View

- **Current research not in complete agreement but consensus other areas involved in....**

1. Initial drug taking: mediated in same way as pleasure activity, with mesocorticolimbic pathway (particularly NA).
 - But does not act alone
 - Interacts with 3 other areas:
 - Prefrontal lobes (decision making);
 - Hippocampus: info about previous experiences;
 - Amygdala: coordinates positive and negative reactions.

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Brain Structures That Mediate Addiction: The Current View

2. Craving & compulsive drug use: repeated consumption brings major changes in motivation as addict develops habit & compulsion despite adverse effects.

– Direct neural response to repeated exposure of drug-induced pleasure and product of conditioned response to drug-associated cues.

– Several changes in brain's response contribute to development of addiction:

• Change in how striatum reacts to drugs, which spreads from NA to dorsal striatum (role in habit formation).

• At same time, prefrontal cortex in controlling behavior declines & stress circuits in hypothalamus interact with dorsal striatum.

• Development of addiction is pathological neuro-plastic response.

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Brain Structures That Mediate Addiction: The Current View

3. Relapse – triggered by 3 factors:

• Stress – drug use as coping mechanism

• Priming – single exposure leads to relapse

• Environmental cue – certain people, times, places, objects previously associated with the drug

• Evidence from animal studies shows:

– Prefrontal cortex mediates priming-induced relapse,

– Amygdala mediates condition cue induced relapse,

– Hypothalamus mediates stress-induced relapse.

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