

Neurobiology and Psychopharmacology of Addiction

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What is Addiction?

- A state in which a behavior is compulsively repeated despite negative long-term consequences.

Why do we have addictive behaviors?

- Our brains are wired such that they are very good at identifying things that “make us feel better” (rewards). Experiencing these rewards motivates us to learn and repeat behaviors that obtained these rewards in the first place. We learn to identify when these rewards are available, how to make them available, and how to behave to get more of them.

This learning is very context dependent.

- For example:
 - People learn to take aspirin when they have a headache.
 - People learn to eat a cookie when they are hungry.
 - People learn to whine when they are in pain and someone that comforted them before is present.
- These behaviors are thus limited to learned contexts and emotional states.

How Does this Work?

- Our Limbic Filter:

The Neuroscience Version

Dopaminergic Pathways

- The dopaminergic pathways that terminate in the nucleus accumbens are especially important for detecting rewards and motivating reward-seeking behaviors. One of the ways that reward is encoded in this system is via the rate of rise of dopamine in the nucleus accumbens

Why are some substance addictive?

- All known addictive substances (but not all drugs of abuse) cause rapid increases in dopamine levels in the nucleus accumbens via direct action on neurocircuitry in the system. Different drugs do this in different ways, but the end result is the same.

Generally, the more rapid the rise in dopamine levels that is produced, the more addictive the substance.

- Substances taken IV or smoked are more addictive than the same substance taken orally.
- Substances with more direct actions on dopaminergic systems (cocaine, amphetamines) are more addictive than those that act through more indirect pathways (alcohol, MJ).

The gain on the system is modulated by past experience

- Social stressors, pain, novelty, and substance of abuse all activate the nucleus accumbens and turn the gain up. Repeated strong stimulation of the NAc may cause neurobiological changes that produce greater responses to a given stimulus.
 - Rewards will be more rewarding
 - Aversive stimuli will be more aversive

Stress can make drugs more rewarding

- This may partially explain the prevalence of addiction in persons with low SES

The NAc is required to choose larger delayed rewards over smaller immediate ones.

- Rats with NAc lesions will not work for a delayed gain.
- Similar deficits are seen in patients with Addiction

Temporal Discounting

Active, but not recovered (at least for nicotine) substance users will choose smaller immediate awards over larger delayed rewards to a greater extent than normal. They make decisions over a shortened time scale.

This is similar to the effect that stressors have on one's body.

How can you stop an addictive behavior?

- Prevent it from being learned in the first place
- Learn to avoid contexts with which the behavior is associated
- Try to inhibit the behavior via the conscious efforts of your frontal cortex (generally only works short-term)
- Learn another behavior which is just as rewarding in similar contexts
- Extinguish it – make it no longer rewarding

What properties of substances complicate addiction?

DEPENDENCE

When exposed to environments over time, brains/bodies adjust to maintain homeostasis in that condition. With repeated drug use, our brains/bodies adjust to maintain homeostasis in the presence of the drug. We become normal when the drug is there, and removal of the drug will throw us out of balance.

Withdrawal

- Because the adjustments are specific for the drug, the effects seen when the drug is removed will be specifically opposite to the effects of the drug when taken in a naïve state. These effects are referred to as an abstinence syndrome or withdrawal.

- Generally, as addictive drugs “make you feel better”, withdrawal will make you feel worse. And because the adjustments were specific to the drug, the only thing that will make you really feel normal while withdrawing is the drug itself (or another in the same class) Once a person becomes substance dependent, withdrawal can drive further substance use, and make addictive behaviors that much more difficult to break.

Dependence vs. Addiction

- Dependence is NOT addiction
 - Dependence is simply a need for a substance to maintain normal physiological function. A dependent person will not necessarily drug seek. The drug seeking behavior must be learned on its own and is a separate disorder.
 - For example, one can be dependent on opioids without being addicted. A patient kept on long-term opioid therapy for pain may undergo withdrawal when his opioid treatment is stopped, but that doesn't mean that he will run down the street and buy some heroin, or steal opioids from his pharmacy, or even seek out another MD to renew his opioid treatment.

Dependence can drive ongoing addiction

Relief from withdrawal symptoms is a reward of its own. Patients who learn that a drug will eliminate withdrawal symptoms will often learn to seek out that drug when they are withdrawing. This can obviously become circular.

Tolerance

- Tolerance is a loss of effect of a drug with repeated use (or need for more drug to produce the same effect)
- Tolerance isn't really a big deal in terms of addictive behaviors.
 - Relevant for overdose deaths and in planning medication doses for patients.

- Note:
 - Tolerance can be context dependent.
 - Tolerance can be extreme.
 - Tolerance occurs to different drug effects at different rates.