Drug Addiction
Substance Abuse and Addictions

• **Substance abuse:** a pattern of substance use that produces clinically significant impairment or distress.

• Most recognize it as harmful but continue the addictive behavior, anyway.

• Addictive substances increase dopamine activity in certain areas of the brain.

• James Olds and Peter Milner (1954) reported that rats in a Skinner box pressed a lever that resulted in self-stimulation of the brain.
Olds & Milner

- Their initial discovery was an accident. They planned to test whether electrical stimulation of a specific brain area would enhance learning of a discrimination task.
- They wanted to be sure that the stimulation was not painful. So, they would stimulate it only when the rat was in one corner of a box. They thought that if the stimulation was painful, the rat would avoid that corner.
- The rat looked around and sniffed. Instead of avoiding the corner, he came back again and again.
Olds & Milner

• Olds & Milner then let it press a lever to get stimulation of the area.
• It and other rats sometimes pressed the lever 2000/hour.
• It was later learned that stimulation of the area in the lateral part of the hypothalamus increased the release of the transmitter dopamine in the mesolimbic dopamine tract.
A section through a rat’s brain
Substance Abuse and Addictions

• Other behaviors that release dopamine in humans include sexual excitement, gambling, and video games.

• fMRI (functional magnetic resonance imaging): the mesolimbic tract is excited in MEN during viewing of “attractive” women.
  – DECREASED activity when viewing attractive men.
Substance Abuse and Addictions

• Dopamine neurons in flies and worms regulate responses to food and drugs.
• Therefore, it is an ancient system to get us to do the things that keep us and our species alive.
• Abnormalities may lead to compulsive gambling, eating, sex, depression.
• Berridge and Robinson (1998) emphasized an important distinction between “liking” and “wanting” behaviors.
• Dopamine activity in the mesolimbic tract seems to be related to “wanting”.
• Some facial expressions in various species denote “liking” versus negative affect. “Liking” may be elicited by opioid transmitters (those that are similar to opiate drugs), rather than by dopamine.
Motivation circuits in the brain

• Food, water and sex are “biological” or “primary” reinforcers.
• Ancient (subcortical) brain circuits evolved to ensure that these behaviors are performed.
• These circuits lie at the border between the limbic system (which controls emotions), and the areas that initiate and control movement.
• They learn and judge what things in the environment are worth wanting. They then turn this wanting into action to get that goal.
Dopamine and reward learning

- Wolfram Schultz proposed the “error signal hypothesis” of dopamine function. Dopamine is a “teaching signal.”
- He found:
  - 75% of mesolimbic dopamine neurons show a burst of firing when animals find a hidden bit of food or are given a food reward
  - This firing pattern can be transferred to secondary reinforcers (light or tone) that predict them.
Schultz’ error prediction hypothesis

• Monkeys are given a visual discrimination task (press a lever under one of two images they’ve seen before).

• If they choose of the correct image they get a few drops of sweet fruit juice.
Schultz’ error prediction hypothesis

- In the first few trials dopamine neurons show a burst of activity right after the reward is given.
- After the monkey has learned which lever to press, this ‘burst firing’ decreases and disappears. So even though the juice reward is being given, there is no increase in dopamine activity.
• After Schultz’s monkeys learned the task and expected a juice reward for picking the correct image, Schultz conducts ‘error trials’ where he doesn’t give them the juice they have earned.

• When the monkey presses the right lever – surprise – no juice!

• In these cases there is a decrease in firing of dopamine neurons.
Schultz’ error prediction hypothesis

• Dopamine neurons fire more when outcomes are better than predicted, stay the same when outcomes occur as predicted, and decrease their activity when outcomes are worse.

• So, while dopamine may not be ‘rewarding’ by itself, increased dopamine activity may consolidate Stimulus-Response associations during learning. It may also promote more “wanting.”
Addiction: Withdrawal Effects

• When a drug is chronically present, the brain and body compensate by *downregulating* the natural systems that the drug mimics. For example, opiate receptors disappear after prolonged heroin use.

• After this downregulation has occurred, the brain and body rely mostly on the drug to fill the role of the natural transmitter.

• Stop taking the drug suddenly (withdraw), and now there’s neither drug nor transmitter.
Addiction: Withdrawal Effects

• Therefore, any process that the transmitter normally would have done, won’t occur because transmitter levels have been lowered.

• The only way reduce withdrawal effects is by taking more drug or by waiting (days, weeks) for the brain and body to regain homeostasis.
# Addiction and Withdrawal

<table>
<thead>
<tr>
<th><strong>Acute action of opiates</strong></th>
<th><strong>Opiate withdrawal symptoms</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>Analgesia</td>
<td>Pain and irritability</td>
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<tr>
<td>Respiratory depression</td>
<td>Rapid breathing</td>
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<tr>
<td>Euphoria</td>
<td>Depression</td>
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<tr>
<td>Relaxation and sleep</td>
<td>Restlessness and insomnia</td>
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<tr>
<td>Decreased blood pressure</td>
<td>Increased blood pressure</td>
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<tr>
<td>Constipation</td>
<td>Diarrhea</td>
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<tr>
<td>Vasodilation, flushed skin</td>
<td>Chills and “gooseflesh”</td>
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Addiction and Withdrawal

- Withdrawal from marijuana does not cause sickness, because it is fat-soluble and stays in the body a long time.
- However there is receptor down-regulation of its receptors in the mesolimbic dopamine tract.
• Tolerance:
• Dopamine in the mesolimbic tract after saline, heroin, or cocaine on day 1 (white circles) and day 5 (black circles) of self administration.
• No change with saline, but heroin & cocaine have less effect on day 5
Incentive-sensitization

- Sensitization and tolerance can coexist: A person can become tolerant to some effects of a drug and become more sensitive to others.
Models of Addiction: Sensitization

- Sensitization has several behavioral, neurochemical and anatomical correlates:

- Animals given repeated doses of some drug of abuse will self-administer other drugs at higher rates and work harder to get drugs

- Sensitized animals also show enhanced dopamine response to amphetamine

Substance Abuse and Addictions

• Receiving a drug during a withdrawal period is a powerful experience that produces sensitization.

• The user learns that the drug relieves the distress caused by withdrawal and this heightens its effects.

• Subjects that have abstained from a drug show increased seeking of the drug when they experience any reminder of the drug.
Substance Abuse and Addictions

<table>
<thead>
<tr>
<th>Experimental group</th>
<th>Day 1</th>
<th>Day 3</th>
<th>Day 5</th>
<th>Day 7</th>
<th>…2 weeks…</th>
<th>Test Day</th>
</tr>
</thead>
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- **Control**
  - Saline

- **Experimental group**
  - Saline

Sensitization of craving!!!

Amphetamine effect.
How do drugs affect dopamine?

• Amphetamine makes dopamine vesicles in axon terminals “leaky” & reverses the transporters (molecular “pumps” that bring dopamine back into the neuron after release). This produces a flood of dopamine in synapses.

• Cocaine blocks the transporters. Then dopamine cannot be removed from synapses after release. Therefore, more dopamine is left in the synapses.
MAOIs block the enzyme MAO, preventing it from breaking transmitters into inactive metabolites.

Tricyclic drugs and SSRIs block reuptake.

Fig. 15-9, p. 463
Is Ritalin addictive?

• Ritalin also blocks the dopamine transporters. However, taken orally as prescribed for attention-deficit disorder, it is not addictive because drug delivery is slow, rather than sudden.
• Similarly, cocaine, if delivered steadily by an implanted device, does not promote addiction.
• Smoking crack cocaine is more addictive than “regular” cocaine because of its rapid availability via blood vessels in the nose.
Why is nicotine addictive?

• Nicotinic receptors on dopamine terminals and cell bodies increase dopamine release.

• Therefore, nicotine increases dopamine activity in the mesolimbic tract in 2 ways: increasing firing at the cell body and increasing release at the axon terminals.
What do opiates do?

- They inhibit GABA neurons that synapse on dopamine neurons. Because GABA normally inhibits dopamine neurons, this leads to disinhibition. Dopamine cell firing increases.
Drugs of Abuse: Marijuana

• *Marijuana* contains $\Delta^9$-tetrahydrocannabinol…

• Which binds to receptors in cortex, hippocampus, basal ganglia, cerebellum, & cells in the mesolimbic dopamine tract.

• It increases attention to sensory stimuli, but causes memory impairment. It also seems to slow time.
Drugs of Abuse: Marijuana

• Endocannabinoids provide a major way of signaling in the brain.
• They are retrograde messengers that decrease presynaptic transmitter release, especially glutamate.
More permanent effects

• Drug dependence lasts more than weeks or months.
• Cocaine increases dendrite branching on postsynaptic neurons at the end of the mesolimbic dopamine tract. This may lead to sensitization of “wanting” or “craving” the drug.
• Therefore, temporary biochemical changes MAY lead to changes in morphology.
Normal number of dendritic spines on neurons postsynaptic to the mesolimbic tract: left and center; spines after sensitization to cocaine: right
More permanent effects

• If rats are given only one high-dose injection of amphetamine, they will still show locomotor sensitization a year later. That is a long time in a rat’s life!
• Humans who have quit taking drugs or smoking still feel severe urges years later, when they see or smell reminders of the drug.
Role of Environment

- Experiment: administer drugs in home cage or novel cage
  - Sensitization: increased motor activity in response to a previously ineffective dose
- Low doses $\Rightarrow$ sensitization only in the novel cage.
- High doses $\Rightarrow$ sensitization in both cages.

Therefore, stress response to a novel environment may contribute to addiction.
Effects of stress

15.17 Autonomic Activation during a Stress Situation (Part 1)

(a) Response systems affected in jump situation

- Hypothalamus
- Pituitary gland
- Thyroid
- Spleen
- Pancreas
- Adrenal gland
- Heart
- Liver
- Intestines
- Bladder
- Testes

- Cranial
- Cervical
- Thoracic
- Lumbar
- Sacral

Hormonal responses
Parasympathetic responses
Sympathetic responses
Effects of Stress

• Uncontrollable electric footshock to rats increased their self-administration of low doses of cocaine.
• All self-administered doses increased the main adrenal stress hormone. (Goeders, 2002)
Effects of Stress

• Injections of the adrenal stress hormone, without any shock, produced the same effects as uncontrollable stress.
  – It also increased the dopamine increase in response to cocaine.
• Removal of the rats’ adrenal glands blocked the acquisition of self-administration of cocaine, but not of food.
• Neither stress nor the stress hormone affected MAINTENANCE of previously-learned self-administration—only its acquisition.
  (Goeders, 2002)
Damage to the Insula Disrupts Addiction to Cigarette Smoking
NH Naqvi, et al., 2007

- Functional imaging studies showed that:
  - Drug-associated cues activate anterior cingulate cortex, orbitofrontal cortex, and the insula.
  - Activity in the insula on both sides correlates with perceived cue-induced drug urges.
Naqvi, et al., 2007

• 19 cigarette smokers with brain damage that included the insula were studied.
  – 6 had right insula damage, and 13 had left insula damage.
• 50 cigarette smokers with damage that did not include the insula were the control subjects.
• All patients had smoked > 5 cigarettes per day for > 2 years at time of lesion onset.
• 12 of 19 patients with insula lesions quit smoking and had a complete loss of addiction.
• 6 others with insula lesions did not quit smoking.
• 1 quit smoking, but did not lose the urge to smoke.
• Only 4 of 50 patients with non-insula damage lost the urge to smoke and quit.
• The insula is the only region on either side of the brain where a lesion was significantly associated with a disruption of smoking addiction.
Discussion

• One patient said his "body forgot the urge to smoke."
• There was no reduction in eating or pleasure from food.
• Sensory replacements for smoking (de-nicotinized cigarettes, irritant inhalers) reduce urges and promote abstinence.
  – They may work by mimicking the smoking-induced stimuli in the airway, as represented in the insula, thereby satisfying the "bodily need" to smoke.
Addictions in women

• Jill Becker has studied male and female rats that were allowed to self-administer amphetamine. Females showed much greater addiction than did males. This was a function of both early organizational hormones and adult activational hormone effects.

• Similarly, women are less likely to start taking drugs or smoking, but when they do, it is much harder for them to quit.
Addictions in women

• Estrogen administration leads to a rapid increase in dopamine release in the mesolimbic tract, which may add to the effects of a drug.

• Very recent evidence suggests that progesterone, in both women and rats, can partially reverse the effects of estrogen.
  – A metabolite of progesterone increases GABA’s inhibitory effects.
Alcohol Abuse and Addictions

• Alcohol has a long history of use; it is used widely throughout the world.
• In moderate amounts, alcohol \(\rightarrow\) relaxation.
• In greater amounts it impairs judgment and damages the liver and other organs.
• Alcoholism, or alcohol dependence, is defined as continued use of alcohol despite medical or social harm, even after one has decided to quit or decrease drinking.
Drugs of Abuse: Alcohol

- Alcohol is a ‘dirty’ drug, acting at GABA, glutamate, and serotonin receptors, depending on dose.
- Alcohol’s GABA receptor activity is similar to that of anti-anxiety drugs and barbiturates.
Alcoholism

- There are two types of alcoholism:
  - Type I:
    - Later onset.
    - Gradual onset.
    - Fewer genetic relatives with alcoholism.
    - Equal numbers of men and women.
    - Less severe.
Alcoholism

- **Type II:**
  - Earlier onset (usually before 25).
  - More rapid onset.
  - More genetic relatives with alcoholism.
  - Men outnumber women.
  - Often severe.
  - Often associated with criminality.
Alcoholism

- Risk factors for alcoholism: children who are impulsive, risk-taking, easily bored, sensation-seeking, and out-going.
- Twin studies and family studies show a genetic basis for Type II alcoholism.
- However, drinking during pregnancy increases the risk of alcoholism in the offspring.
- Genes increase the likelihood of alcoholism in several ways:
  - Increasing impulsive risk-taking behaviors.
  - Increasing the stress response when trying to quit.
Fig. 15-3, p. 455

Sons of alcoholic fathers

Several who will become alcoholics later

Test each man’s reactions to alcohol

Follow up years later to find which men actually became alcoholics

Young men with no alcoholic relatives

Few or none who will become alcoholics
Alcoholism

• Sons with alcoholic fathers show:
  – Less intoxication after moderate drinking.
  – Greater than 60% probability of developing alcoholism.
  – Alcohol decreases stress response more.
  – Smaller amygdala in the right hemisphere.

• These characteristics were apparent BEFORE the sons became alcoholic. Therefore, they were not the effect of their own alcohol consumption.
Summary

• Reinforcing brain stimulation, reinforcing experiences, and self-administered drugs increase dopamine release in the mesolimbic dopamine tract.

• Activity in this tract may relate more to “wanting” than to “liking.” Addiction also relates more to wanting (craving).

• Sensitization of the mesolimbic tract → greater response to the addictive activity and less to other kinds of reinforcement. The decreased response to other reinforcements is called tolerance.
Summary

• Tolerance also includes the decreased pleasure elicited by the abused drug. In order to get the same pleasure, more drug is needed. So, there is greater "wanting" of the drug, but less "liking" of it. "Liking" may be mediated by opioid synapses.

• Stress and being female make quitting drugs and smoking much more difficult.
Summary

- Compared with Type I alcoholism, Type II alcoholism starts sooner, progresses faster, is usually more severe, and affects more men than women.
- Genes influence alcoholism in several ways, including effects on impulsiveness, responses to stress, and overall calmness.
- Risk factors for alcoholism, in addition to a family history, include feeling little intoxication after moderate drinking and experiencing much relief from stress after drinking.