Lessons from the Neuroscience of Addiction

Attendees will be able to:
1. describe the proposed DSM-5 substance use disorder category
2. describe the roles of major brain structures in addiction
3. explain the common effects of abused drugs on brain reward circuits
4. explain how the brain changes as drug abuse becomes addiction

5. explain how stress, learning, and memory influence addiction and relapse
Gratitude

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Gratitude

Truman graduate Andrew Westermann provided invaluable assistance with the literature review and proofing. I’m indebted to Andrew for years of collaboration and friendship.
Gratitude


Part 1: Substance Use Disorder

Substance Use Disorder

National Survey on Drug Use and Health (NSDUH) Dependence or Abuse of Specific Substances

Figure 7.1 Substance Dependence or Abuse in the Past Year among Persons Aged 12 or Older: 2002-2010

<table>
<thead>
<tr>
<th>Substance</th>
<th>Numbers in Thousands</th>
</tr>
</thead>
<tbody>
<tr>
<td>Marijuana</td>
<td>3.470</td>
</tr>
<tr>
<td>Pain Reliever</td>
<td>1.387</td>
</tr>
<tr>
<td>Cocaine</td>
<td>842</td>
</tr>
<tr>
<td>Tranquilizer</td>
<td>311</td>
</tr>
<tr>
<td>Hallucinogen</td>
<td>267</td>
</tr>
<tr>
<td>Heroin</td>
<td>159</td>
</tr>
<tr>
<td>Inhalant</td>
<td>59</td>
</tr>
<tr>
<td>Sedative</td>
<td>36</td>
</tr>
<tr>
<td>Naloxone</td>
<td>16</td>
</tr>
</tbody>
</table>
Substance Use Disorder

 DSM-5 will probably require checking off 4 of these 5 criteria for **severe substance use disorder**.

The presence of either tolerance or withdrawal will add the specifier “**with physiological dependence**” (Kring et al., 2012).

**Tolerance** means that either an individual needs to ingest progressively larger doses to achieve a desired effect or that a drug’s effects strikingly diminish when taking the usual dose.
Substance Use Disorder

**Withdrawal** involves the unpleasant medical and psychological effects that are triggered by abstinence from a drug or reducing its dose. Withdrawal symptoms are the opposite of a drug's principal effects and can range from discomfort to life-threatening seizures (Schuckit, Daeppen, Tipp, et al., 1998).

Substance Use Disorder

Koob (2006) defined drug addiction as a: “Chronically relapsing disorder that is characterized by a compulsion to seek and take a drug, loss of control in limiting intake, and emergence of a negative emotional state (e.g., dysphoria, anxiety, irritability) when access to the drug is prevented (here, defined as the ‘dark side’ of addiction).”

Substance Use Disorder

**Dual Diagnosis**

About 1/3 of individuals who are physically dependent on an illicit drug or alcohol have been diagnosed with a comorbid psychiatric disorder (Julien et al., 2011).
Substance Use Disorder

Significant percentages of individuals with a lifetime diagnosis of an Axis 1 psychiatric disorder either abuse or are physically dependent on substances.

<table>
<thead>
<tr>
<th>Disorder</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bipolar Disorder</td>
<td>50%</td>
</tr>
<tr>
<td>Schizophrenia</td>
<td>47%</td>
</tr>
<tr>
<td>Obsessive Compulsive Disorder</td>
<td>32.8%</td>
</tr>
<tr>
<td>Depression</td>
<td>31%</td>
</tr>
<tr>
<td>Anxiety</td>
<td>23.7%</td>
</tr>
</tbody>
</table>

Substance Use Disorder

Take away: Comorbid psychiatric disorders complicate the treatment of substance use disorders.
Part 2: A Paradigm Shift

A Paradigm Shift

The view before 1969 was that addiction is fueled by a state of drug dependence. According to this negative reinforcement model, addicts ingest their next dose to avoid or escape unpleasant withdrawal effects.

A Paradigm Shift

The negative reinforcement model was incomplete because addicts still crave drugs after they completely withdraw from them.
A Paradigm Shift

For example, Vietnam war veterans who had become addicted to high-purity heroin during their service suddenly relapsed after years of abstinence while back in the US.

A Paradigm Shift

A more complete model of addiction emerged when researchers demonstrated that nonhuman animals will self-administer virtually all of the addictive drugs abused by humans.

A Paradigm Shift

These studies showed that animals will:
1. inject abused drugs without physical dependence
2. prefer the place where they received the drug
3. expend considerable effort to obtain more of the drug
4. still work for the drug if it produces aversive consequences like shock
5. relapse after withdrawal when exposed to stressors, drug cues, and the original drug
A Paradigm Shift

Which other species does this resemble?

A Paradigm Shift

These findings shifted the focus from an addict's personality to the reinforcing properties of the drug (Bergman & Paronis, 2006).

A Paradigm Shift

The revolutionary new view was that a drug's reinforcing properties are due to its actions at specialized receptors.

If you breed animals without the necessary receptor, they won't self-administer the drug.
The Circuits of Addiction

Most abused drugs target the **mesolimbic dopamine pathway** that mediates reward.

This circuit extends from the midbrain ventral tegmental area (VTA) to the forebrain nucleus accumbens (NAc), amygdala, hippocampus, and prefrontal cortex.
The Circuits of Addiction

Using different mechanisms, they directly and indirectly increase dopamine (DA) release to receptors on the nucleus accumbens, amygdala, hippocampus, and frontal lobe.

The Circuits of Addiction

Cocaine increases DA levels on neurons in the nucleus accumbens by blocking DA reuptake into ventral tegmental area neurons (Stahl, 2008; Thomsen et al., 2009).

The Circuits of Addiction

Amphetamine increases DA levels on neurons in the nucleus accumbens by causing DA release from presynaptic storage sites and blocking its reuptake into VTA neurons (Barr et al., 2006; Stahl, 2008).
The Circuits of Addiction

Opiates bind to receptors on GABA neurons and inhibit GABA release, which increases DA release (Stahl, 2008).

The Circuits of Addiction

Alcohol increases DA levels through multiple mechanisms involving GABA, glutamate, and opioid receptors (Stahl, 2008).

The Circuits of Addiction

Cannabinoids indirectly increase DA levels by binding to receptors on GABAergic neurons in the ventral tegmental area (VTA). At the VTA they inhibit GABA release, which disinhibits DA neurons that project to the nucleus accumbens and increases DA delivery (Stahl, 2008).
How do we know that a drug’s increase of DA neurotransmission is related to its pleasurable subjective effects?

While three decades of nonhuman animal research were consistent with this hypothesis, a study of human cocaine addicts provided confirming evidence.

The addicts received methylphenidate (Ritalin) during a brain scan. Like cocaine, methylphenidate increases synaptic DA by blocking the reuptake transporter.

Addicts’ ratings of their “high” were strongly correlated with the percentage of blocked DA transporters (Volkow et al., 1997).
The Circuits of Addiction

Dopamine release by the mesolimbic pathway produces both the pleasurable effects of drugs and those of primary reinforcers like food, drink, sex, and exercise.

The Circuits of Addiction

These regions are not surprisingly involved in compulsive behaviors like pathological overeating and gambling, and sexual addiction (Nestler, 2005).

The Circuits of Addiction

The nucleus accumbens and ventral tegmental area are also activated during self-disclosure (Tamir & Mitchell, in press).
The Circuits of Addiction

How does excessive drug use affect the mesolimbic pathway?
Can there really be too much of a good thing?

The Circuits of Addiction

Chronic excessive drug use produces *tolerance* within the mesolimbic pathway.
For example, the number of dopamine D2 receptors is reduced in chronic cocaine users (Volkow et al., 2004).

The Circuits of Addiction

Both addictive drugs and natural reinforcers progressively produce less dopamine binding and enjoyment. Both naturally-rewarding behaviors and drug ingestion can become less enjoyable (Nestler, 2005).
Addicts may experience greater *dysphoria* (unpleasant feelings) in between doses and during abstinence (Julien et al., 2011).

Take away:
Addicts experience diminished pleasure from natural reinforcers and may progressively experience dysphoria during drug withdrawal.
The Circuits of Addiction

Why do only a fraction of people who use drugs like alcohol become addicted?

The *reward deficiency hypothesis* proposes that dysfunctional dopamine receptor systems (involving the A1 allele) may predispose people to addiction.

The Circuits of Addiction

Addicts may experience less pleasure from natural reinforcers than their healthy counterparts and they may engage in more intense activities like compulsive drug use and gambling to achieve normal pleasure (Blum et al., 1996).

The Circuits of Addiction

This hypothesis is also consistent with findings that subjects who reported that methylphenidate injections were pleasant had lower D2 receptor levels than those who found them unpleasant.
The Circuits of Addiction

Subjects who enjoyed the injections had similar D2 receptor levels to cocaine addicts, although they did not abuse drugs (Volkow et al., 2004).

The Circuits of Addiction

Both qEEG and LORETA studies of alcoholics reveal a hyperarousal pattern characterized by increased beta power and decreased alpha and delta/theta power compared to healthy controls (Saletu et al., 2002).

The Circuits of Addiction

Increased low-voltage beta activity suggests central nervous system hyperarousal, while decreased alpha and delta/theta power may indicate brain damage (Coutin-Churchman et al., 2006).

The greater the frontal lobe hyperarousal, the worse the prognosis (Bauer, 2001; Winterer et al., 1998).
The Circuits of Addiction

Sokhadze et al. (2008) concluded that the inheritance of genes that code for GABA receptors may be a common link between the development of alcohol dependence and EEG abnormalities.

The Circuits of Addiction

Take away:
Low D2 receptor density and a hyper-arousal pattern may be among the biological vulnerabilities that predispose individuals to addiction.

The Circuits of Addiction

Since alcohol ingestion reduces prefrontal cortical excitability (Kähkönen et al., 2003), alcoholics may use this drug and other CNS depressants to self-medicate.
The Circuits of Addiction

Take away:
Addicts may use their drugs to self-medicate. Biofeedback and neurofeedback training can provide addicts healthy ways to achieve the same physiological changes.

The Circuits of Addiction

The Transition from Abuse to Addiction
While chronic drug use makes primary and secondary reinforcers less reinforcing, it paradoxically sensitizes the prefrontal cortex to drugs and the discriminative stimuli that predict their availability (Pierce & Kumaresan, 2006; Volkow et al., 2004, 2006).

The Circuits of Addiction

Both drugs and drug-associated cues increase dopamine transmission to a prefrontal cortex that is less able to inhibit motivation to acquire and ingest addictive drugs (Julien et al., 2011).
The Circuits of Addiction

Drug-related stimuli progressively exert greater control over behavior than those associated with natural reinforcers like exercise.

Stimuli associated with drugs or the drug-taking environment produce craving, the motivation to acquire and ingest drugs, in a complex circuit that involves the prefrontal cortex (orbitofrontal cortex, cingulate cortex, and insula), amygdala, hippocampus, and ventral tegmental area (Pierce & Kumaresan, 2006).
The Circuits of Addiction

The orbitofrontal cortex is the region of the prefrontal cortex that lies immediately above the orbits that house the eyes.

The Circuits of Addiction

The orbitofrontal cortex may aid planning by evaluating the consequences (rewards and punishments) of our actions and helping to generate the motivation to ingest drugs.

The Circuits of Addiction

Phineas Gage's profound personality changes were produced by damage to this subdivision, the ventromedial prefrontal cortex, and 11% of Gage's white matter (Van Horn et al., 2012).
The Circuits of Addiction

The cingulate cortex, located in the dorsal prefrontal cortex above the corpus callosum, is another important component of the craving circuit.

The Circuits of Addiction

The anterior cingulate cortex plays an important role in attention and is activated during working memory.
The Circuits of Addiction

The anterior cingulate cortex mediates emotional and physical pain, and has cognitive (dorsal anterior cingulate) and affective (ventral anterior cingulate) conflict-monitoring components.

The Circuits of Addiction

The anterior cingulate cortex provides feedback regarding whether our outcomes matched our expectations.

The Circuits of Addiction

Damage to the anterior cingulate cortex may deprive addicts of warning signals and result in repeated poor decisions that cost them their jobs, marriages, and friendships (Kennerley et al., 2011).
The Circuits of Addiction

The posterior cingulate cortex may mediate our reactivity to drug cues (sight of drug paraphernalia) and drug cravings (Garavan, 2009).

The Circuits of Addiction

The insular cortex lies deep within the lateral sulcus that divides the temporal and parietal lobes.

Source: Wikimedia Commons

The Circuits of Addiction

The insular cortex has been implicated in the experience of pain and basic emotions, including anger, disgust, fear, happiness, and sadness.
The Circuits of Addiction

The insular cortex receives reports of internal states, like hunger and drug craving, and motivates individuals to engage in consummatory behavior.

The Circuits of Addiction

The insular cortex is stimulated by drug-related cues. It may produce conscious awareness of the aversive feelings produced by drug withdrawal and may activate memories of pleasurable drug-related experiences.

The Circuits of Addiction

The insular cortex is activated by urges for alcohol, cocaine, heroin, marijuana, and nicotine (Garavan, 2009).

Stroke damage to the insular cortex can eliminate nicotine addiction (Naqvi et al., 2007).
Craving requires that the brain remember the behaviors performed and the emotions associated with drug use.

Craving recruits the **hippocampus** for memory of previous drug-related behaviors and the **amygdala** for emotions associated with drug use (Fowler et al., 2007).
The Circuits of Addiction

Stressors also activate the craving circuit. Stress plays an important role in the predisposition to develop addiction, increased drug consumption, and relapse following drug abstinence (Julien et al., 2011).

After drug abuse has been extinguished, drug ingestion and exposure to conditioned drug cues and stressors (including an abstinence syndrome) can quickly reestablish an addiction.
The Circuits of Addiction

Take away: Interventions like cognitive behavior therapy and biofeedback, that can enhance a patient’s ability to manage stress, can help prevent the development of addiction and relapse following sobriety.

The Circuits of Addiction

Long-term compulsive drug use can produce a phenomenon called hypofrontality in which the metabolic activity of the prefrontal cortex and the performance of executive functions are compromised.

The Circuits of Addiction

Full recovery of these functions may not occur after 4 months of drug abstinence (Julien et al., 2011).
The Circuits of Addiction

The frequent relapses seen in addicts when they return to the physical environment and social network in which they previously used drugs can be explained by the concepts of craving and hypofrontality.

Take away:
Sensitization to drug-cues explains why addicts often need to avoid the physical environment (place cues) and social networks associated with their drug use.
Social and physical cues produce powerful motivation (craving) to acquire and self-administer drugs in the prefrontal cortex, which has a crippled ability to inhibit disastrous decisions (hypofrontality).

Take away:
Hypofrontality helps explain why addicts may be unable to resist drug cravings and why they often make impulsive decisions.

Take away:
Consider neurofeedback to normalize the hyperarousal pattern commonly observed in addicts.
Addiction produces diverse biochemical changes in the nucleus accumbens and extended amygdala. Increased $\Delta FosB$ levels are observed as physical dependence develops (Koob, 2006).

Chronic ingestion of alcohol, amphetamine, cannabinoids, cocaine, nicotine, opiates, and phencyclidine increases the buildup of the protein $\Delta FosB$ in the nucleus accumbens.

The activation of the gene that codes for $\Delta FosB$ throws the *first switch* that transforms a healthy brain into an addicted one.
ΔFosB induction plays a pivotal role in both drug and natural addictions by regulating the expression of common target genes.

ΔFosB turns on the gene for the production of a glutamate receptor in the nucleus accumbens.

This sensitizes the nucleus accumbens to cocaine, opiates, exercise, and sucrose.
**Biochemical Changes in the Reward Circuit**

*Sensitization* means that drug-related cues produce a greater reinforcing effect.

While drug enjoyment progressively declines, drug-associated cues increasingly produce craving by activating the prefrontal cortex and amygdala.

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**Biochemical Changes in the Reward Circuit**

When this happens, drug stimuli become more salient to the addict and motivation to relapse increases (Julien et al., 2011).

For example, metabolic scans show increased activation of a cocaine addict's amygdala and anterior cingulate during a cocaine video versus a nature video. (The color red means high activation while violet means low activation.)

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**Biochemical Changes in the Reward Circuit**

![Image of brain scans showing activation differences between cocaine and nature videos.](image)

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Biochemical Changes in the Reward Circuit

The production of new glutamate receptors in the nucleus accumbens, located on freshly created dendritic spines, throws the second switch required to produce an addicted brain (Briand & Blendy, 2010; Robinson & Kolb, 1997; Vargas-Perez et al., 2009).

Biochemical Changes in the Reward Circuit

Cocaine addicts only produce ΔFosB after repeated cocaine use, which may span several years.

While an individual’s genome may increase vulnerability to addiction, it doesn’t ensure that the addiction will develop (Nestler, 2002).

Biochemical Changes in the Reward Circuit

Take away:
Intervene early to stop ΔFosB production in the nucleus accumbens (first switch), which starts the transformation of a healthy brain into an addicted one.
Addiction involves functional and structural changes in anterior cingulate and orbitofrontal cortical glutamatergic control over the nucleus accumbens.

As the prefrontal cortex suffers a decreased capacity to respond to biological rewards and control drug-seeking, its hyperresponsiveness to drug cues increases glutamate release at the nucleus accumbens, which promotes relapse.

Summary
Summary

1. Comorbid psychiatric disorders complicate the treatment of substance use disorders.

2. Addicts experience diminished pleasure from natural reinforcers and may progressively experience dysphoria during drug withdrawal.

3. Low D2 receptor density and a hyperarousal pattern may be among the biological vulnerabilities that predispose individuals to addiction.

Summary

4. Addicts may use their drugs to self-medicate. Biofeedback and neurofeedback training can provide addicts with healthy ways to achieve the same physiological changes.

5. Interventions like cognitive behavior therapy and biofeedback, that can enhance a patient's ability to manage stress, can help prevent the development of addiction and relapse following sobriety.

Summary

6. Sensitization to drug-cues explains why addicts often need to avoid the physical environment (place cues) and social networks associated with their drug use.

7. Hypofrontality helps explain why addicts may be unable to resist drug cravings and why they often make impulsive decisions.
Summary

8. Consider neurofeedback to normalize the hyperarousal pattern commonly observed in addicts.

9. Intervene early to stop ΔFosB production in the nucleus accumbens (first switch), which starts the transformation of a healthy brain into an addicted one.

Glossary

As allele: an abnormal form of the A1 gene, which results in defective D2 receptors, is found in most severe alcoholics. Reduced D2 receptor activity may produce a reward deficiency syndrome.

Abstinence syndrome: medical and psychological effects, which are the opposite of a drug's principal effects, produced by the cessation of drug intake.

Addiction: chronic disease of brain reward, motivation, and memory that involves physical dependence and pathological drug use.

Agonist: a molecule that facilitates the action of a neurotransmitter.

Allele: a version of a gene.

Alpha rhythm: 8-12 Hz activity that is primarily generated by an intracortical network with only a moderate contribution from thalamo-cortical neurons. Researchers have correlated the alpha rhythm with "relaxed wakefulness."
Glossary

**amygdala**: Limbic structure that helps a person evaluate whether stimuli are reinforcing or threatening, establish unconscious emotional memories, learn conditioned emotional responses, and produce anxiety and fear responses.

**antagonist**: A molecule that interferes with neurotransmitter action.

**anterior cingulate**: Division of the prefrontal cortex that plays an important role in attention and working memory. It mediates emotional and physical pain, and has cognitive (dorsal anterior cingulate) and affective (ventral anterior cingulate) conflict-monitoring components.

**autoreceptors**: Metabotropic receptors that can be located on the membrane of any part of a neuron. They detect neurotransmitters released by a neuron itself, generate IPSPs that inhibit a neuron from reaching threshold, and regulate internal processes like transmitter synthesis and release through the second messenger system.

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**basal ganglia**: Forebrain nuclei, including the caudate nucleus, globus pallidus, and putamen, that participate in movement and cognitive processes.

**beta rhythm**: 12-36 Hz rhythm associated with arousal and attention that is generated by brainstem reticular activation that depolarizes neurons in both the thalamus and cortex. Researchers divide the beta rhythm into multiple ranges.

**cerebral cortex**: The outer six layers covering the cerebral hemispheres that are responsible for higher brain functions.

**cingulate cortex**: A region of medial cerebral cortex, superior to the corpus callosum, that participates in attention and working memory, craving, and pain perception.

**cortisol**: A glucocorticoid stress hormone released by the adrenal cortex.

**ΔFosB**: Component of an AP-1 transcription factor that accumulates in critical brain regions after chronic exposure to drugs of abuse, including alcohol, amphetamine, cocaine, and morphine.

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**D2 receptors**: Postsynaptic dopamine receptors. Reduced activity in these receptors may produce a reward deficiency syndrome.

**delta rhythm**: 1-3 Hz oscillations generated by thalamocortical neurons that identify stage 3/4 sleep.

**dendrite**: Branched structure designed to receive messages from networked neurons via axodendritic synapses (junctions between axons and dendrites) which help determine whether the axon hillock will initiate an action potential.

**dendritic spines**: Protrusions on the shaft of dendrites, which increase the surface area available for receptors.

**dopamine (DA)**: Monoamine neurotransmitter that binds to at least six postsynaptic receptors, which are all linked to G proteins, where it functions as a neuromodulator. The two major families include D2 (D2L and D2S) and D2 (D2A, D2B, D3, and D4).

**executive functions**: High-level activities like attention, planning, and problem-solving.
Glossary

**frontal lobes**: the most anterior cortical lobes of the brain that include the motor cortex, premotor cortex, and prefrontal cortex.

**gamma-aminobutyric acid (GABA)**: a widely-distributed inhibitory amino acid transmitter.

**glutamate**: a widely-distributed excitatory amino acid transmitter.

**hippocampus**: limbic structure located in the medial temporal lobe that is involved in 4-7 Hz theta activity, control of the endocrine system's response to stressors, formation of explicit memories, and navigation. Sustained elevated cortisol levels disrupt these functions.

**hypofrontality**: underactivation of the frontal lobes.

**limbic system**: a network of brain nuclei implicated in emotion.

**mesolimbocortical pathway**: dopaminergic axons that arise from the ventral tegmental area in the midbrain and innervate the limbic system and cortex.

**monoamine neurotransmitters**: amine neurotransmitters that include dopamine, norepinephrine, and epinephrine (catecholamines) and serotonin (indoleamines). These neurotransmitters are released using volume transmission and generally have modulating effects, altering the performance of diffuse networks of target neurons.

**negative reinforcement**: a type of reinforcement in which the occurrence of a behavior is followed by the removal or avoidance of an aversive stimulus, which increases in the future probability of the behavior.

**neuroplasticity**: the ability of the nervous system to structurally and functionally change in response to experience or the environment.

**nigrostriatal pathway**: dopaminergic pathway from the substantia nigra to the basal ganglia (caudate nucleus and putamen) that controls movement. This pathway progressively degenerates in Huntington's disease and Parkinson's disease.

**norepinephrine (NE)**: a monoaminergic excitatory neurotransmitter, which has a catecholamine chemical structure, that is involved in alertness, concentration, aggression, and motivation.

**nucleus accumbens**: a limbic structure that is a target of dopamine released by the mesolimbic pathway. The nucleus accumbens is activated by primary reinforcers and adding drugs, and plays a crucial role in drug craving.

**opiates**: compounds derived from opium that reduce pain sensitivity.

**opioid peptide**: endogenous peptide that binds to opioid receptors and produces analgesia and reinforcement.

**opioids**: peptides synthesized by the brain that bind to opioid receptors and act like opiates.

**orbitofrontal cortex**: frontal lobe subdivision that evaluates the affective value of stimuli and helps inhibit inappropriate behavior. Phineas Gage's profound personality changes were produced by damage to this region and a network of white matter.
Glossary

**phencyclidine (PCP):** dissociative analgesic hallucinogen that blockades NMDA glutamate receptor ion channels.

**physical dependence:** state in which drug ingestion is required for normal functioning and withdrawal symptoms occur during drug abstinence.

**positive reinforcement:** learning process in which a consequence that follows a behavior increases its future probability.

**prefrontal cortex:** the most anterior frontal lobe division, which is subdivided into dorsolateral, medial, orbitofrontal, and anterior cingulate regions. This region is responsible for executive functions like attention, problem-solving, and planning.

**reuptake:** the primary method that neurons use to terminate neurotransmitter action. Reuptake transporters located in terminal buttons and astrocytes remove neurotransmitters from the synaptic cleft.

**reward deficiency syndrome:** Blum’s hypothesis that an abnormal form of the A1 allele is present in most severe alcoholics and results in defective D2 receptors. Reduced D2 receptor activity may reduce the activation of the nucleus accumbens and hypothalamus, and result in dysphoria, drug craving, and compulsive drug seeking and abuse.

**second messenger:** a slow-acting molecule within the postsynaptic cell that amplifies the effects of synaptic activity and signals synaptic activity within the postsynaptic cell.

**sensitization:** 1. nonassociative learning in which an organism responds more strongly to most stimuli after exposure to unusually intense or painful stimuli. 2. a process in which the body responds more powerfully to a drug after successive doses.

**serotonin (5-hydroxytryptamine, 5HT):** indoleamine neurotransmitter distributed in both the central and the peripheral nervous system that is involved in functions like affect, appetite, sleep, and sexual activity.

**substance use disorders:** substance abuse and substance dependence.

**theta rhythm:** 4–7 Hz rhythm generated by a cholinergic septohippocampal system that receives input from the ascending reticular formation and a noncholinergic system that originates in the entorhinal cortex.

**tolerance:** reduced responsiveness to a drug, which requires increased drug doses to produce an effect once achieved by lower doses.

**ventral tegmental area (VTA):** midbrain structure whose dopaminergic (DA) axons project to the nucleus accumbens. Serotonin receptors on endorphin-releasing neurons in the hypothalamus may increase the activity of DA reward pathways by inhibiting GABA release at receptors on the cell bodies of VTA neurons.
References


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