CHAPTER

6

Learning mechanisms of addiction: Pavlovian conditioning

Introduction

> I used heroin for around 5 years … Life, in general, was completely miserable … the dependency was unbearable. Feeling like I need a substance to live … was such a gross feeling.[1]

Andrew Warwick was first introduced to heroin at 20 years of age and initially used it to help self-medicate his bipolar disorder. At first, he enjoyed the effects of heroin, describing it as "slightly euphoric".[1] With continued drug use, Andrew noticed that he no longer enjoyed using the drug as he felt miserable. However, in Andrew's words, he felt like he needed heroin to survive. In the last chapter, you learned about the role of operant conditioning in maintaining drug-taking behaviors. In this chapter, you will learn about another learning phenomenon that drives continued drug use despite its negative consequences: **Pavlovian conditioning**. Specifically related to this form of learning, you will learn how certain stimuli in our environment become paired with drug use. These cues can elicit strong drug cravings even when the individual is not particularly interested in using the drug. You will learn more about the dissociation between "liking" and "wanting" (or "needing") a drug. Andrew is not alone when stating that he felt like he needed heroin to live. When many individuals with substance use disorders (SUDs) are interviewed, a common theme is that they no longer enjoy using the drug, but they feel they need the drug to function during the day.

Learning objectives

By the end of this chapter, you should be able to …

(1) Differentiate unconditioned stimuli/responses from conditioned stimuli/responses.
(2) Discuss the influence of Pavlovian conditioning on operant conditioning.
(3) Explain how Pavlovian conditioning contributes to addiction.
(4) Describe the compensatory response and the incentive sensitization theories of addiction.

Determinants of Addiction
https://doi.org/10.1016/B978-0-323-90578-7.00005-0

(5) Explain how paradigms such as Pavlovian conditioned approach and conditioned place preference are used to study addiction.
(6) Compare and contrast treatment options that utilize Pavlovian conditioning in clinical populations.

Overview of Pavlov's study

Dr. Ivan Pavlov (1849–1936) is one of the most heavily discussed figures in Psychology, but funnily enough, he was not a psychologist. He was a physiologist interested in studying digestion. In fact, he received the Nobel Prize in the Physiology or Medicine category in 1904 for his work on the digestive system. In his work, Pavlov often used dogs as subjects. Pavlov would make an incision in the dog's cheek, which would allow him to externalize the salivary gland. This then allowed Pavlov to collect salivary secretions when dogs were presented with different types of food, as well as other substances like marbles or sand. During his studies, Pavlov noticed something strange—dogs started to salivate when they heard Pavlov's assistant walking toward them to deliver food. Pavlov, being the good scientist that he was, decided to conduct a study to investigate what he originally called "psychic secretions".[2]

In what is now one of the most famous Psychology experiments ever conducted, Pavlov first presented dogs food by itself. Not surprisingly, the dogs salivated at the sight of the food. Next, Pavlov presented a metronome, a device that produces an audible clicking sound at regular intervals, by itself. The metronome failed to elicit salivation in the dogs. Pavlov then presented the metronome before presenting the food. Because dogs had access to the food, they started salivating again. Pavlov repeated the metronome-food pairings across multiple sessions. Eventually, Pavlov presented the metronome by itself. The dogs began to salivate at the sight/sound of the metronome! The dogs had learned to associate the metronome with the food.[2] Learning to associate two stimuli with each other is now known as Pavlovian (or classical) conditioning. Pavlovian conditioning is also known as stimulus-stimulus (S–S) learning.

The key distinction between Pavlovian conditioning and operant conditioning is the type of association that is formed. In Pavlovian conditioning, organisms learn to associate two stimuli together, regardless of the behavior that is occurring. In operant conditioning, an organism learns to associate a specific behavior with an outcome. Even though these two phenomena measure distinct aspects of learning, they often work in tandem to influence behaviors. We will come back to this topic later in this chapter. But first, I need to cover some basic principles of Pavlovian conditioning.

Principles of Pavlovian conditioning

In Pavlov's study, food naturally produced saliva in the dog. Stimuli that elicit a natural, unlearned response from an organism are known as **unconditioned stimuli (US)**. In other words, animals do not have to learn to produce saliva when presented with food. Salivating in response to food is an example of an **unconditioned response (UR)**. Unconditioned responses are those that are unlearned or occur naturally in response to a specific stimulus.

Before conditioning, the metronome was a *neutral* stimulus that did not trigger a response from the animal. Because the animal associated the metronome with food over repeated pairings, the metronome eventually elicited salivation. The metronome became a **conditioned stimulus (CS)**. Salivating in response to the metronome is a **conditioned response (CR)**. Unlike URs, learning must occur for a CR to manifest. The dogs in Pavlov's experiment learned that the presence of the metronome meant that they were about to eat; therefore, they started salivating in anticipation of the food. Fig. 6.1 shows a depiction of Pavlov's seminal study.

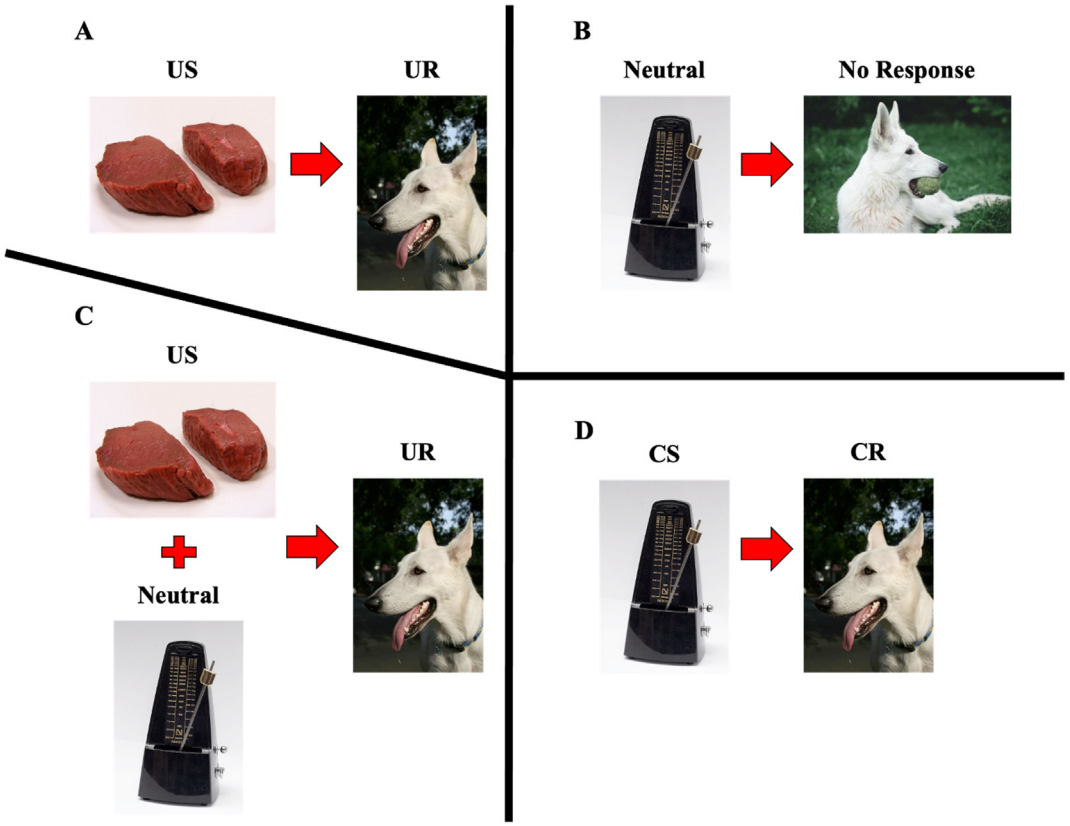


FIGURE 6.1 Process of Pavlovian conditioning. (A) Presentation of an unconditioned stimulus (US) such as food elicits a natural response, or unconditioned response (UR), from an animal such as a dog. (B) The presentation of a neutral stimulus like a metronome does not elicit a response from the organism other than an orienting response. (C) When the US is paired with the neutral stimulus, the dog will show a UR. The UR occurs because of the presence of the US. (D) After repeated pairings of the US and the neutral stimulus, the neutral stimulus becomes a conditioned stimulus (CS) that elicits a conditioned response (CR). *The figure was created by the author using Microsoft PowerPoint. The image of the steaks was obtained through Wikimedia Commons and was posted by Venison Steaks (https://commons.wikimedia.org/wiki/File:Venison_Steaks.jpg). The image of the drooling dog was obtained through Wikimedia Commons and was posted by Ildar Sagdejev (https://commons.wikimedia.org/wiki/File:2008-08-12_White_German_Shepherd_drooling_in_the_sun.jpg). The image of the metronome was obtained through Wikimedia Commons and was posted by Vincent Quach (https://commons.wikimedia.org/wiki/File:Metronome_Nikko.jpg). The image of the dog playing with the ball was obtained through Pexels and was posted by Daniel Bendig (https://www.pexels.com/photo/photography-of-a-dog-biting-green-tennis-ball-931876).*

Based on his findings, Pavlov developed a theory of conditioning that posited that CSs take on the same properties as the US and that CRs are functionally the same as URs.[2] Through conditioning, the metronome took on the same properties as the food, which is why dogs salivated in response to the food and to the metronome following conditioning. This is known as the **stimulus substitution theory of conditioning**.

Pavlovian conditioning gets more complicated than what was presented above. In my Animal Learning course, students often assume the section on Pavlovian conditioning will be easy because they have heard the story of Pavlov several times before enrolling in my class. To their surprise, they soon realize that Pavlovian conditioning is so much more than dogs drooling when presented with a metronome. Luckily for you, this is not an Animal Learning course, so you will not need to learn the mathematical theories of conditioning, nor will you need to learn about some of the more advanced concepts of conditioning such as blocking or overshadowing. I do want to cover two forms of conditioning that will become highly relevant when discussing addiction. The first type of Pavlovian conditioning that can occur is known as **sensory preconditioning**[3] (Fig. 6.2A). Suppose Pavlov had two neutral stimuli: a metronome and a blue light. He could expose dogs to both the metronome and the blue light repeatedly. Notice that no food is presented at this point. After dogs have learned to associate the metronome with the blue light, Pavlov could begin conditioning the dog to associate the metronome with the food. During this stage of conditioning, the blue light is never presented. By now, you know that the metronome, when presented by itself, will elicit a CR. What happens if Pavlov presents the blue light by itself? The blue light has never been directly paired with the food, so intuition says that the blue light should do nothing. However, the blue light can elicit a CR. Because the blue light has been previously paired with the metronome, it takes on the same features as the metronome, thus becoming a CS. The example I like to give my students is this: imagine you are at a party, and you see two individuals talking. You assume that these two individuals are friends by the way they are talking with one another. Eventually, one of these individuals comes up to you and is a complete jerk. Through sensory preconditioning, you may assume that the other individual is also a jerk, despite never interacting with this individual.

Another advanced type of Pavlovian conditioning that can occur is **higher-order** (**second-order**) **conditioning**[4] (Fig. 6.2B). Imagine after Pavlov completed his initial experiment, he wanted to begin pairing the metronome with another neutral stimulus, such as the blue light I used in the sensory preconditioning example above. The metronome at this stage is an established CS. As Pavlov begins pairing the CS with the blue light, food is never presented. Eventually, the blue light is presented on its own. Amazingly, the light can elicit a CR even though it was never paired with food. Like sensory preconditioning, the blue light, through its pairings with the metronome, begins to take on the same psychophysical properties as the metronome, thus eliciting a CR. To give you another example: imagine that you go through a bad breakup with someone. Each time you now see this person, you may have feelings of anger or sadness. Eventually, you notice that your ex begins hanging out with a new friend (not a new romantic partner, just a friend). Through higher-order conditioning, you may begin to develop feelings of resentment toward this person even though you have never met them. They could be the nicest person in the world, but because they are now associated with your ex, you begin to equate this person with your ex.

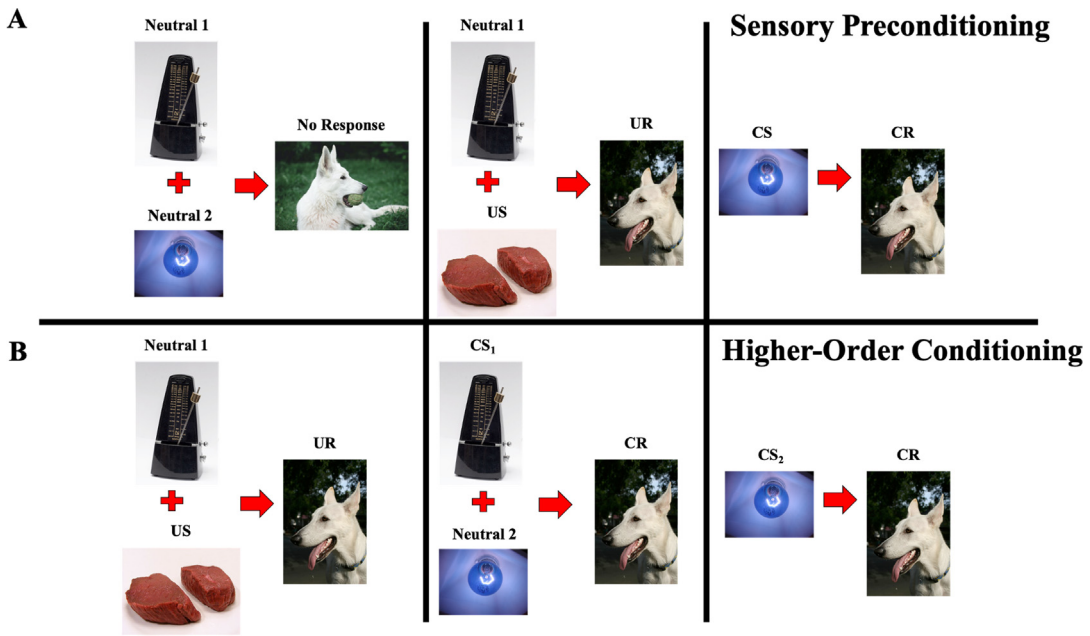


FIGURE 6.2 (A) An example of sensory preconditioning. In the left panel, two neutral stimuli are repeatedly paired in the absence of an unconditioned stimulus (US). The presentation of these two stimuli will not elicit a response from the animal. In the middle panel, only one neutral stimulus (in this case, a metronome) is paired with the US. Because the meat (US) is presented, the animal will salivate, which is an unconditioned response (UR). After repeated pairings of the metronome and the food, the researcher can present the second neutral stimulus, the blue light, by itself (depicted in the right panel). Even though the light was never explicitly paired with the meat, the light becomes an effective conditioned stimulus (CS), which elicits a conditioned response (CR). (B) An example of higher-order conditioning. In the left panel, a neutral stimulus is paired with a US as in a typical Pavlovian conditioning experiment. Over time, the metronome becomes an effective CS due to its repeated pairing with the US. In the middle panel, the CS is now paired with a second neutral stimulus. In the right panel, the second neutral stimulus acts as a second CS due to its repeated pairings with the first CS. Notice that sensory preconditioning and higher-order conditioning have almost identical steps. The key difference is the timing of when the two neutral stimuli are paired together. In sensory preconditioning, the neutral stimuli are paired together before one of them is paired with the US. In higher-order conditioning, one neutral stimulus (now a CS) is paired with a second neutral stimulus after the first one has been paired with the US. *The figure was created by the author using Microsoft PowerPoint. The image of the steaks was obtained through Wikimedia Commons and was posted by Venison Steaks (https://commons.wikimedia.org/wiki/File:Venison_Steaks.jpg). The image of the drooling dog was obtained through Wikimedia Commons and was posted by Ildar Sagdejev (https://commons.wikimedia.org/wiki/File:2008-08-12_White_German_Shepherd_drooling_in_the_sun.jpg). The image of the metronome was obtained through Wikimedia Commons and was posted by Vincent Quach (https://commons.wikimedia.org/wiki/File:Metronome_Nikko.jpg). The image of the dog playing with the ball was obtained through Pexels and was posted by Daniel Bendig (https://www.pexels.com/photo/photography-of-a-dog-biting-green-tennis-ball-931876/). The image of the blue light was obtained through Wikimedia Commons and was posted by Andrew Bossi (https://commons.wikimedia.org/wiki/File:IMG_6077_-_Bathroom_Light.JPG).*

In each of these examples, the CS appears to take on the same properties as the US, and the CR is strikingly similar to the UR, thus providing support for Pavlov's stimulus substitution theory. As you are about to learn, this theory has a major limitation that cannot account for all CRs.

Pavlovian processes involved in addiction

In the last chapter, you learned that drugs are reinforcers. They are also USs. Individuals do not need to learn that cocaine makes one hyperactive or that opioids cause sedation. The effects of the drug (e.g., increased activity following stimulants; increased analgesia following opioids) are URs. For an individual using drugs, there are many stimuli that can act as a CS. In the case of someone who injects a drug, a syringe become a CS that signals availability of the drug. CSs are not limited to paraphernalia. The environment in which the drug-taking behavior occurs can become a CS. Even peers can become a CS. In contrast to Pavlov's theory of conditioning, drug-paired stimuli do not elicit CRs that are identical to the drug's effects.[5] Individuals that encounter drug paraphernalia will not feel analgesia like they do when they inject heroin. Instead, they will experience increased pain sensitivity. This example highlights that CRs are not always identical to the UR. This finding suggests that Pavlov's stimulus substitution theory does not provide a full account of conditioning. Indeed, many studies have reported CRs that are not the same as the URs. Because of this major shortfall, the stimulus substitution theory is no longer a widely accepted theory of conditioning.

Contingency and contiguity are important mechanisms for developing associations between drugs and drug-paired stimuli. Take a person that smokes cigarettes or cannabis. Each time this individual smokes, they use a lighter to ignite one end of the cigarette/joint. The time needed to light the cigarette/joint is brief. Over time, the lighter becomes an effective CS. In addition to contingency and contiguity, sensory preconditioning and higher-order conditioning are relevant for SUDs. Before an individual begins smoking, lighters can become associated with other neutral stimuli, such as candles. If the individual uses the lighter frequently enough before smoking, something as innocuous as a candle may trigger a CR in the individual, which can lead to increased cravings. This process can occur after the individual begins smoking. If the individual begins using the lighter for other functions, new CSs can be created. The fact that numerous stimuli can become paired with drug use is one major reason why treating SUDs is difficult. An individual can abstain from drug use for years, but they may encounter a random stimulus that increases the urge to use the drug.

Pavlovian conditioned approach (PCA)

Although CSs elicit CRs, they can sometimes elicit more complex behaviors. One interesting finding in conditioning experiments is that some animals become almost fixated on the CS. In the case of Pavlov's dogs, a visiting researcher noted that one dog would approach the CS and then wag its tail before barking at and attempting to jump on the stimulus. An animal's interaction with and/or approach to a CS is known as **sign-tracking** and results from Pavlovian conditioning.[6] Not all animals engage in sign-tracking behavior. When the CS is presented, some animals will not approach it. Instead, they will wait for delivery of the US. These animals display **goal-tracking** behavior instead of sign-tracking behavior. Sign-tracking and goal-tracking are often measured in an operant chamber using **Pavlovian conditioned approach (PCA)**. When pigeons are used, a stimulus light is illuminated before food is delivered. Pigeons do not need to peck the light to receive food. The food is always delivered, regardless of the pigeons' actions. Sign-tracking pigeons will peck at the light

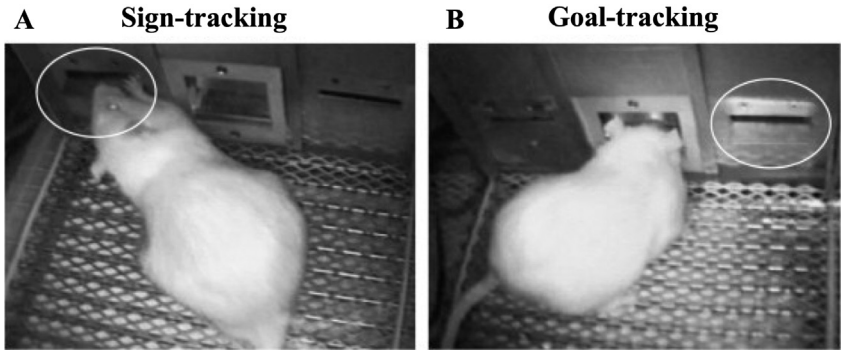


FIGURE 6.3 To measure sign-tracking/goal-tracking in rodents, a lever is inserted into the operant chamber for a short period of time (e.g., 8 s). Once the lever retracts, food is delivered to the center tray. In (A), the rat approaches the lever while it is extended and chews/presses on it. This is an example of sign-tracking behavior. In (B), the rat immediately goes to the food tray when the lever is extended into the operant chamber. Because obtaining food is the "goal" of the animal, going straight to the source of the food is goal tracking. In each panel, the extended lever is circled. *Image modified from Fig. 1 of Flagel SB, Akil H, Robinson TE. Individual differences in the attribution of incentive salience to reward-related cues: implications for addiction.* Neuropharmacology. *2009;56(Supplement 1):139–148. https://doi.org/10.1016/j.neuropharm.2008.06.027. Copyright 2009, with permission from Elsevier.*

before receiving food. To measure sign-tracking in rats, a lever is extended for a certain amount of time before food is delivered. Sign-tracking rats will press/chew on the lever while it is extended into the chamber. If a pigeon or a rat is a goal-tracker, they will simply wait until the food is delivered. Animals that engage in sign-tracking are said to attribute *incentive salience* to the CS. Fig. 6.3 shows an image of a rat engaging in sign-tracking behavior and in goal-tracking behavior.

Animals often develop sign-tracking behavior when a CS is consistently paired with drug delivery. If a lever is extended into an operant chamber immediately before intravenous infusion of cocaine, rats will begin to approach the lever.[8] Remember, this is not an operant procedure; as such, the rat does not need to interact with the lever to receive drug infusions. Sign-tracking of a drug-paired CS has been observed for ethanol,[9,10] nicotine,[11] and the opioid remifentanil.[12] This research suggests that animals become "attracted" to drug-paired stimuli. In the last chapter, you learned about secondary reinforcers (e.g., money), which become reinforcing due to their repeated pairings with primary reinforcers. Secondary reinforcers are also known as conditioned reinforcers because this association represents Pavlovian conditioning. Drug-paired CSs become reinforcing as you learned when reading about the second-order schedule of reinforcement in the previous chapter. We will come back to this concept.

Understanding sign-tracking is important because research has shown that animals that attribute incentive salience to CSs are more likely to display certain addiction-like behaviors.[13] Sign-tracking rats self-administer more cocaine,[14] are more likely to treat cocaine as an inelastic good,[15] and choose cocaine over food more frequently[16] compared to goal-tracking rats. Increased sign-tracking is predictive of reinstatement of methamphetamine seeking[17] and nicotine seeking.[18] Pohořalá et al.[19] recently used the DSM-IV-based 3-criteria (3-CRIT) model to assess the role of sign-tracking on three addiction-like behaviors: (1) motivation to self-administer cocaine; (2) persistence of cocaine seeking; and (3) resistance

to punishment. The persistence of cocaine seeking was determined by measuring rats' responses during alternating drug-ON and drug-OFF periods. During the drug-ON period, responses on a manipulandum led to drug reinforcement. During the drug-OFF period, cocaine was never delivered. Drug-seeking was characterized by increased response during the drug-OFF periods. Motivation to self-administer cocaine was assessed in a progressive ratio schedule, and resistance to punishment was measured in a compulsive drug-seeking paradigm. Recall that in the compulsive drug-seeking paradigm, foot shocks are paired with each drug infusion. If rats met certain criteria across each measure, they were given a score of one for each task, with three being the maximum score. Sign-tracking is positively correlated with resistance to punishment, but not motivation to self-administer cocaine or persistence of cocaine seeking. Overall, these results indicate that increased sign-tracking may be a predisposing factor for compulsive drug seeking.

Not only does sign-tracking predict addiction-like behaviors, but drugs can alter sign-tracking behavior. For example, cocaine and nicotine self-administration increase sign-tracking.[20–22] Interestingly, ethanol can either increase[23,24] or decrease[25] sign-tracking. The discrepancy across studies may be dependent on when animals are exposed to ethanol. McClory and Spear found that adolescent rats exposed to ethanol show increased sign-tracking behavior during adulthood; however, adult rats treated with ethanol do not show altered sign-tracking or goal-tracking behavior.[24] This finding suggests that adolescents are at heightened risk for attributing incentive salience to drug-paired stimuli. Collectively, these studies are important because they show that continued drug use can further increase the attraction to drug-paired stimuli, thus increasing the likelihood that these stimuli precipitate drug cravings when an individual tries to quit using the drug.

Attentional bias

Sign-tracking is not limited to pigeons or rats. Humans can become overly sensitive to drug-related stimuli, a phenomenon known as **attentional bias** or *cue reactivity*. In a typical cue reactivity experiment, participants are shown different images or videos, some of which include a drug or related paraphernalia and some of which include "neutral" objects (i.e., items not related to drug use). Participants then evaluate their subjective feelings of craving. Additionally, researchers can collect physiological measures like heart rate and skin conductance. Evidence has shown enhanced cue reactivity for ethanol,[26,27] cigarettes,[28] cocaine,[29] heroin,[30,31] and cannabis.[32] Higher-order conditioning has also been used to examine cue reactivity to ethanol-paired cues in individuals with low sensitivity to ethanol and in individuals with high sensitivity to ethanol.[33] The first CS was an olfactory cue isolated from either ethanol, sweet foods, or nonedible substances. This CS was paired with a neutral visual stimulus. Individuals with low sensitivity to ethanol, but not high sensitivity to ethanol, attributed greater incentive salience to the visual cues that had been paired with the ethanol-associated olfactory stimuli. These results suggest that individuals with low sensitivity to ethanol may be at higher risk for developing an alcohol use disorder because they attribute too much incentive salience to ethanol-paired cues.

Attentional bias can be measured with several tasks. Some of these tasks will be detailed below, as well as research examining the relationship between attentional bias and SUDs.

Eye-tracking experiments

Researchers can have individuals view words, single-object images, or complex scenes on a computer, and eye-tracking equipment can detect where an individual directs their gaze and for how long they look at a particular spot on the screen. To measure attentional bias, individuals look at drug-paired stimuli and neutral stimuli during the experiment. Given the ubiquity of tobacco and ethanol use, most eye-tracking experiments have focused on these two drugs. Increased cigarette cravings are positively correlated with an attentional bias toward smoking-related cues.[34] Similarly, individuals that score higher on ethanol craving and ethanol use problems spend more time looking at alcoholic beverages compared to nonalcoholic drinks.[35] Directly related to this finding, individuals that engage in heavy drinking spend more time looking at alcoholic beverages compared to light drinkers.[36] Even adolescent (14–16 years of age) social drinkers spend more time viewing ethanol-related stimuli compared to nondrinkers, although social drinkers spend a near equivalent amount of time viewing ethanol and neutral stimuli.[37] However, adolescent heavy drinkers spend significantly more time viewing ethanol stimuli compared to neutral stimuli.[36,37]

While the studies listed above had participants view drug-associated or neutral images on a computer screen, one study attempted to measure eye tracking in a more natural setting. Monem and Fillmore[38] had participants wear eye-tracking glasses and allowed them to explore a room containing ethanol-paired stimuli and neutral stimuli. During the first test session, participants spent a similar amount of time viewing both types of stimuli. However, during the second test session, participants spent less time viewing neutral stimuli. Monem and Fillmore also found that heavy drinkers spent more time viewing ethanol-paired stimuli.[38] Overall, these studies show increased attentional bias to drug-paired stimuli in individuals that use certain drugs. This increased attentional bias can promote individuals to continue using the drug as the drug-paired stimuli are more likely to capture the attention of these individuals.

Dot-probe task

In the *dot-probe task* (also known as the visual probe task), participants are asked to view a computer screen. A fixation cross (+) appears on the center of the screen for a short duration. Next, two images or words are quickly flashed on the screen for approximately 500 ms. After the images vanish, a dot appears in the location of one of the former stimuli. Individuals are asked to identify the location of the dot as quickly as possible. Faster reaction times indicate greater attentional bias. When the drug dot-probe task is used to measure attentional bias to drug-paired stimuli, individuals are presented with a neutral stimulus and a drug-paired stimulus (Fig. 6.4A). Increased attentional bias toward drug-paired stimuli has been observed in individuals that drink ethanol,[41,42] smoke cigarettes,[43,44] use opioids,[45–47] and use ketamine.[48] Increased attentional bias is also observed in those with cocaine dependence or concurrent cocaine/ethanol dependence.[49] Additionally, current smokers, but not former smokers or nonsmokers, spend more time viewing e-cigarette cues compared to neutral cues, suggesting that e-cigarette cues may contribute to tobacco cigarette cravings.[50] Attentional bias to one drug can be correlated to attentional bias to another drug. For example, individuals that show increased attentional bias to smoking-related cues are more likely to show attentional bias to ethanol-paired stimuli.[51] This finding makes sense considering the high concordance of ethanol and tobacco use.

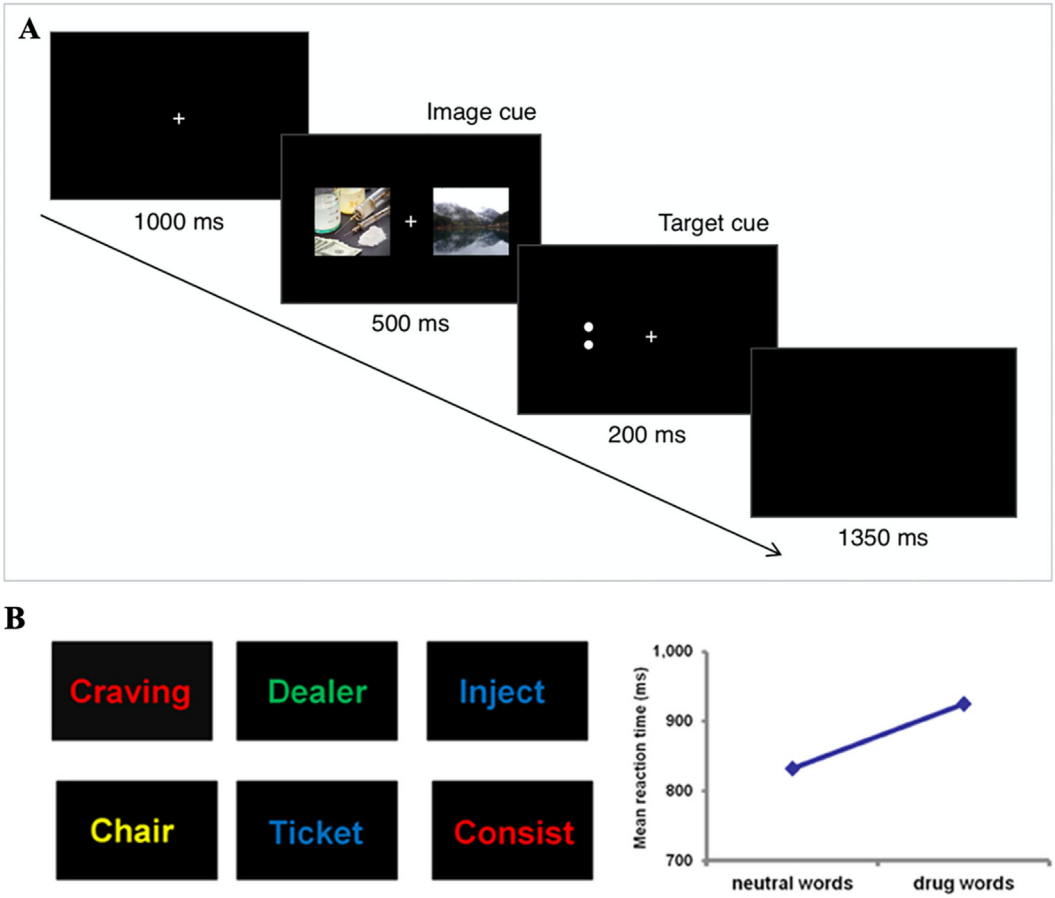


FIGURE 6.4 Two paradigms used to detect increased attentional bias to drug-paired stimuli: the dot-probe task (A) and the drug (emotional) Stroop task (B). In the dot-probe task, two stimuli are flashed on the screen. One image contains drug stimuli while the other image contains neutral stimuli (like nature scenes). After the images disappear, a dot (or dots in the illustration above) appears on one side of the screen, and participants must identify the location of the dot(s). If the dot(s) appear(s) on the same side as the drug-associated image, participants are much faster to respond. In the drug Stroop task, participants are presented drug-related words and neutral words in various colors. The object of the task is to name the color of the font as quickly as possible. Individuals with a SUD often take longer to respond when presented with drug-associated words, indicating that they become more fixated on the word as opposed to the color font. *Panel (A) comes from Fig. 1 of Zhao Q, Li H, Hu B, et al. Neural correlates of drug-related attentional bias in heroin dependence.* Front Hum Neurosci. *2018;1:646. https://doi.org/10.3389/fnhum.2017.00646. This is an open-access article distributed under the terms of the Creative Commons Attribution 4.0 International License (https://creativecommons.org/licenses/by/4.0/). Panel (B) comes from Fig. 2 of Murphy A, Taylor E, Elliott R. The detrimental effects of emotional process dysregulation on decision-making in substance dependence.* Front Integr Neurosci. *2012;6:101. https://doi.org/10.3389/fnint.2012.00101. This is an open-access article distributed under the terms of the Creative Commons Attribution 4.0 International License (https://creativecommons.org/licenses/by/4.0/).*

Drug cravings are often associated with increased attentional bias. Individuals with chronic pain that have become physically dependent on opioids are more likely to report opioid cravings if they show increased attentional bias to opioid-paired cues.[46] Not only is attentional bias associated with opioid cravings, but it is associated with an increased risk of opioid misuse in individuals with chronic pain.[47] Positive correlations between attentional bias and drug craving have also been observed for individuals with an alcohol use disorder[52] and in cannabis users.[53] Even social drinkers that show increased attentional bias are more likely to experience cue-induced craving.[54] However, the association between attentional bias and drug craving is not observed in individuals attempting to quit tobacco use.[55]

One interesting and somewhat paradoxical finding is that cocaine-dependent individuals who *avoid* ethanol-paired stimuli are *more* likely to drop out of treatment.[56] Why is this the case? One potential explanation is that those trying to abstain from drug use may develop an avoidance strategy; that is, they may try to avoid viewing drug-paired stimuli. In theory, this sounds like something one should do when going through therapy. However, actively avoiding these stimuli may make completing therapy more difficult. Think of it this way: there may be times in your life when you must encounter a stressful situation. Interviewing for a job is stressful. You may also have to have a difficult conversation with a loved one. Although these situations are stressful and unpleasant, they are important to face. The same thing applies to those with a SUD. Part of the therapy entails encountering drug-paired stimuli as you will learn at the end of this chapter. When individuals adopt an avoidance strategy, they may have increased difficulty during therapy because they are forced to confront difficult situations, which leads to dropout.[57] There is some evidence that supports this hypothesis. In one study, three groups of participants were asked to use one of three strategies to regulate emotions associated with smoking. Some individuals were tasked with reappraising their emotions, some were instructed to accept their emotions, and some were told to suppress (i.e., avoid) their emotions. Those that reappraised their emotions showed decreased cravings and attentional bias for cigarette-paired stimuli compared to those instructed to avoid their emotions.[58]

Drug Stroop Task

Another way to measure cue reactivity in individuals is by modifying the *Stroop task*. You will learn about the traditional Stroop task in the next chapter. In the drug-variant of the Stroop task (also known as the emotional Stroop task), words related to drugs (e.g., "cocktail", "syringe") and neutral words (e.g., "shirt", "coffee") are presented in various colors.[59] Participants are asked to name the color of the font, not the word itself (Fig. 6.4B). Research has shown that college students that engage in binge drinking (more than four alcoholic beverages during a single drinking episode for women/five drinks for men) show greater interference when presented with ethanol-associated words compared to neutral words, an effect that is absent in nonbinge drinkers.[60] Similar interference is observed in individuals that use cigarettes[61–63] or cannabis,[64–66] as well as in those with opioid use disorder/opioid dependence[67,68] and cocaine dependence.[67,69,70] Interestingly, while Carpenter et al.[69] did not observe differences in reaction time for cannabis-paired or heroin-paired words relative to neutral words in those with cannabis or heroin use disorder, they did find that these individuals were slower to respond to cocaine-associated words compared to neutral words.

Increased attentional bias in the drug Stroop task is predictive of poor treatment outcomes for those with a SUD. Relapse to ethanol is higher in individuals that show increased

attentional bias.[71] Individuals that show increased cocaine Stroop interference provide more drug-positive urine samples and complete fewer weeks of therapy.[69] Individuals with increased attentional bias are more likely to use crack cocaine.[72] Attentional bias is also predictive of relapse to heroin[73] and to methamphetamine.[74] Similarly, in those with heroin use disorder, attentional bias increases immediately before relapse, and those that relapse show significantly higher attentional bias compared to those that do not relapse.[75] At least one exception has been noted in the literature; attentional bias to cannabis cues does not predict long-term (6 months) treatment progression for adolescents with a cannabis use disorder.[76]

Pavlovian-to-instrumental transfer (PIT)

Pavlovian conditioning and operant conditioning may measure distinct forms of learning, but they are closely intertwined with one another. In the previous chapter, you encountered an example of how Pavlovian conditioning influences operant conditioning: the second-order schedule of reinforcement. Even though animals earn few drug infusions in this schedule of reinforcement, they exhibit high rates of responding. This occurs because they can earn access to stimuli that have been previously associated with each drug infusion. These stimuli become conditioned reinforcers that can motivate the animal to continue responding. The fact that animals often approach drug-paired stimuli can be used to a researcher's advantage when first training an animal to self-administer a drug. An *autoshaping* procedure can be used to ensure animals acquire an operant response to earn drug infusions.[77] During an autoshaping session, animals earn drug reinforcement by responding on a manipulandum. This manipulandum will be made available to the animal for a certain amount of time. If the animal fails to respond on the manipulandum, the drug will be infused into the animal's catheter. Eventually, animals will develop a sign-tracking response in which they approach the manipulandum more frequently and emit a response to earn drug reinforcement. Ultimately, the researcher can stop using the autoshaping procedure after animals consistently respond on the manipulandum when it is available.

Given the influence of conditioned stimuli on behavior, one experimental design has been used to further examine how these stimuli affect operant conditioning: the **Pavlovian-to-instrumental transfer (PIT)** task. In a PIT task, animals are first conditioned to associate a neutral stimulus such as a light or a tone to the US, typically food. Following the Pavlovian conditioning phase, animals are trained to respond on a manipulandum to receive the US; the US is now a reinforcer as it maintains operant responding. Finally, the CS is presented to the animal, and responses on the manipulandum are recorded.[78] Importantly, reinforcement is not provided during this final part of testing. If the presentation of the CS increases operant responding, this means that the CS has become an effective secondary reinforcer that can increase motivation. Why have the PIT task? What does this tell us that we do not already know? Imagine someone that uses heroin by injecting it. They experience both Pavlovian conditioning and operant conditioning during the drug-taking experience. The individual will prepare for the heroin injection by heating the heroin, placing it in a syringe, and then inserting the needle into the skin. The operant response is to inject the heroin, which is reinforcing. Because these two learning phenomena occur at nearly the same time, there is some difficulty determining if continued drug taking purely results from operant conditioning or if it is influenced by Pavlovian conditioning. In the PIT task, if behavior is maintained purely by operant conditioning, presenting the CS should not increase responding on a manipulandum. If Pavlovian conditioning is important, one would expect to see an increase in responding when the CS is presented.

Most PIT studies involving drug self-administration have focused on the effects of a CS on ethanol consumption,[10,79–87] but other studies have used cocaine as the US.[88,89] Overall, these studies show that responding to drug-paired manipulanda, even when reinforcement is no longer made available, can be facilitated by exposure to a drug-paired CS. Additionally, animals that show enhanced PIT self-administer more cocaine.[90] Interestingly, Takahashi et al. argue that the positive correlation between PIT and cocaine self-administration does not necessarily mean that enhanced PIT is a risk factor for addiction.[90] Why? Takahashi et al. conducted an additional experiment in which they used the 3-CRIT model as described earlier in this chapter. Takahashi et al. did not observe any differences in PIT between addicted-like and nonaddicted-like rats. As such, they argue that the significant correlation observed between PIT and cocaine self-administration may reflect general differences in learning of the association between CSs and drug stimuli.[90] One issue with this interpretation is that relapse-like behavior is not explicitly measured in the 3-CRIT. As you will later learn, drug-paired stimuli are able to elicit intense drug cravings and can precipitate withdrawal symptoms, which can promote relapse. Overall, the PIT task shows that many behaviors are maintained by Pavlovian conditioning, including drug self-administration, providing further evidence of the influence of Pavlovian conditioning on addiction.

Pavlovian-based theories of addiction

As you learned earlier in this chapter, Pavlov developed the stimulus substitution theory to explain why Pavlovian conditioning occurs. One major weakness of Pavlov's theory is that it cannot explain why CRs to drug-paired CSs are opposite of the URs that result from exposure to the US. To understand why an individual with a SUD can experience intense physiological symptoms that mimic withdrawal when encountering a drug-paired CS, we need to cover Dr. Shepard Siegel's *compensatory response* theory.[91]

Compensatory response theory

Before we can dive into Siegel's theory, we need to back up a little and talk about Dr. Greg Kimble's preparatory response theory of conditioning.[92] Kimble argued that the function of the CR is to prepare an organism for the upcoming US. In the case of Pavlov's dogs, the dogs hear the metronome and begin to salivate (CR). According to Kimble, the dogs begin salivating to *prepare* themselves for the food that has been associated with the metronome previously. In humans, researchers can elicit a conditioned eyeblink response by pairing a tone with a puff of air to the eye. The US is the puff of air, and the CS is the tone. Both the puff of air and the tone elicit the same behavioral response: blinking of the eye. According to Pavlov's theory, this occurs because the tone takes on the same properties as the puff of air, thus causing the person to respond to it as they would to the tone. However, Kimble's theory states that this response occurs because the tone prepares the person for the arrival of the puff of air. By blinking early, the individual's eye is partially closed by the time the puff of air is delivered. Unlike Pavlov's theory, the preparatory response theory can account for CRs that are different from URs. For example, if a rat is given a foot shock, its response is to jump because getting shocked on the foot does not feel great. However, if a tone is repeatedly

paired with the shock, the rat freezes when it hears the tone. Freezing most likely occurs because this is what rats do to avoid detection from a predator.

How does this relate to Siegel's theory? The compensatory response theory is a variant of the preparatory response theory. Siegel argued that the CR results from the organism preparing for delivery of the US by *compensating* for its effects. In one of his earlier studies, Siegel[91] gave rats injections of insulin. The US is the insulin, which decreases blood glucose levels (the UR). After repeated injections, the syringe becomes the CS. Eventually, Siegel injected rats with saline. The saline should not have affected blood glucose levels. However, Siegel found that blood glucose levels had increased! Now, imagine an individual using a syringe to inject heroin. Over time, the syringe becomes a CS that becomes paired with heroin (US). As I have already mentioned, the CR is not feeling analgesia; instead, individuals experience hyperalgesia (increased pain sensitivity). This occurs because the body is preparing itself to receive a substance that reduces pain. Recall from Chapter 5 that homeostasis refers to the body's attempts to maintain equilibrium. When an individual injects him/herself with a drug, homeostasis is lost. When the individual sees a CS like heroin, the body prepares itself for the incoming drug by producing symptoms that are opposite of the drug's effects like hyperalgesia. When the drug enters the body, its effects cancel out what the body has done before the drug enters the body; thus, homeostasis is maintained.

Conditioned tolerance

In one study, Siegel et al.[93] wanted to determine how Pavlovian conditioning controls tolerance to a drug's effects. Specifically, they wanted to determine if Pavlovian conditioning affects morphine's perceived analgesic effects. To test this possibility, Siegel et al. gave one group of rats morphine injections that occurred in the presence of distinct CSs (increasing brightness in the testing chamber and noise reduction). Following conditioning, rats were exposed to the CS before receiving an injection of morphine and being placed on a hot plate. Siegel et al. measured how much time was needed for rats to start licking their paws, a sign of pain/discomfort. If more time passed before a paw-lick response occurred, this indicated that the morphine's analgesic effects worked. To interpret the data, Siegel et al. had to test two additional groups of rats. One group of rats received injections of morphine but did not experience the CS. Another group of rats experienced the CS, but they received injections of saline instead of morphine. Siegel et al. found that rats given morphine injections in the presence of the CS took less time to lick their paws during the test session compared to the other two groups. This means that rats exposed to a CS during morphine injections developed tolerance to morphine's analgesic effects (i.e., the morphine became less effective at reducing pain). Importantly, the effect observed in this experiment does not merely reflect general tolerance, as rats injected with morphine in the absence of the CS took longer to lick their paws compared to the experimental group, and the time needed to lick their paws was similar to the group of rats that had previously received saline injections. This phenomenon is known as **conditioned tolerance** and highlights the role Pavlovian conditioning has on the development of drug tolerance. Siegel's work with rats has been replicated in humans using opioids.[94]

Conditioned tolerance is a potential explanation as to why some individuals overdose even when using the same dose over an extended period of time. If an individual uses a particular drug in the same location in the presence of the same stimuli (e.g., injecting heroin in one's living room), they may develop a conditioned tolerance to the drug's effects. It is important to emphasize that conditioned tolerance is specific to that one location. If the

individual uses the drug in a novel environment (e.g., the bathroom of a club), their body will not be able to prepare itself for the drug. Even if the individual uses the same amount of drug they have used previously, this dose can now be potentially lethal as the body has not adequately compensated for the drug's effects. See Fig. 6.5 for a depiction of conditioned tolerance.

Conditioned withdrawal symptoms

Not only can conditioned stimuli increase tolerance to a drug's effects, but they can precipitate withdrawal symptoms, a phenomenon known as **conditioned withdrawal**. In one experiment, Krank and Perkins[95] tested three groups of rats. The first group of rats received injections of morphine in a distinct environment and saline injections in their home cage. The second group of rats received injections of saline in the distinct environment and morphine injections in their home cage. The final group of rats received saline injections in both the distinct environment and in the home cage. Eventually, each group of rats was placed in a distinct environment, and the researchers observed each rat for withdrawal symptoms such as wet dog shakes, jumping, twitches, ear wipes, head shakes, and paw tremors, to name a few. Krank and Perkins found that rats treated with morphine in a distinct environment showed more withdrawal symptoms compared to the other groups.[95] Because these rats showed more withdrawal symptoms compared to rats treated with morphine in the home cage, one can conclude that the environment, not just morphine exposure alone, can lead to the development of withdrawal symptoms. Fig. 6.6 provides an example of conditioned withdrawal.

The implications of conditioned withdrawal should be obvious. The ability of drug-paired stimuli to produce withdrawal symptoms in the absence of drugs may significantly contribute to increased drug use. As you learned in the previous chapter, individuals often continue using the drug to avoid withdrawal symptoms. If an individual goes into withdrawal by merely encountering a CS associated with the drug, they are going to be more likely to use the drug. Given that many stimuli become associated with drugs, whether directly or indirectly through sensory preconditioning/higher-order conditioning, this increases the difficulty of treating SUDs.

Incentive sensitization theory of addiction

Given that drugs increase sign-tracking and PIT and that drug-paired stimuli can become powerful conditioned reinforcers, Dr. Terry Robinson and Dr. Kent Berridge, both professors at the University of Michigan, developed the **incentive sensitization theory of addiction** to provide a framework for the neurobiological basis of addiction.[96] According to Robinson and Berridge, repeated drug use in susceptible individuals causes the neural circuits responsible for incentive salience attribution to become hypersensitive. To better understand this theory, we need to review a distinction that has already been discussed: "liking" something is not the same thing as "wanting" something. In the last chapter, we equated liking to the positive reinforcing effects of some experience (like eating cheesecake) and wanting as a form of negative reinforcement. However, wanting reflects more than negative reinforcement. In the incentive sensitization theory of addiction, wanting is equated more to a "desire" to use a drug that is independent of one's "liking" of the drug. When an individual uses a drug for the first time, dopamine levels increase in the mesocorticolimbic pathway. The individual may experience the positive reinforcing effects

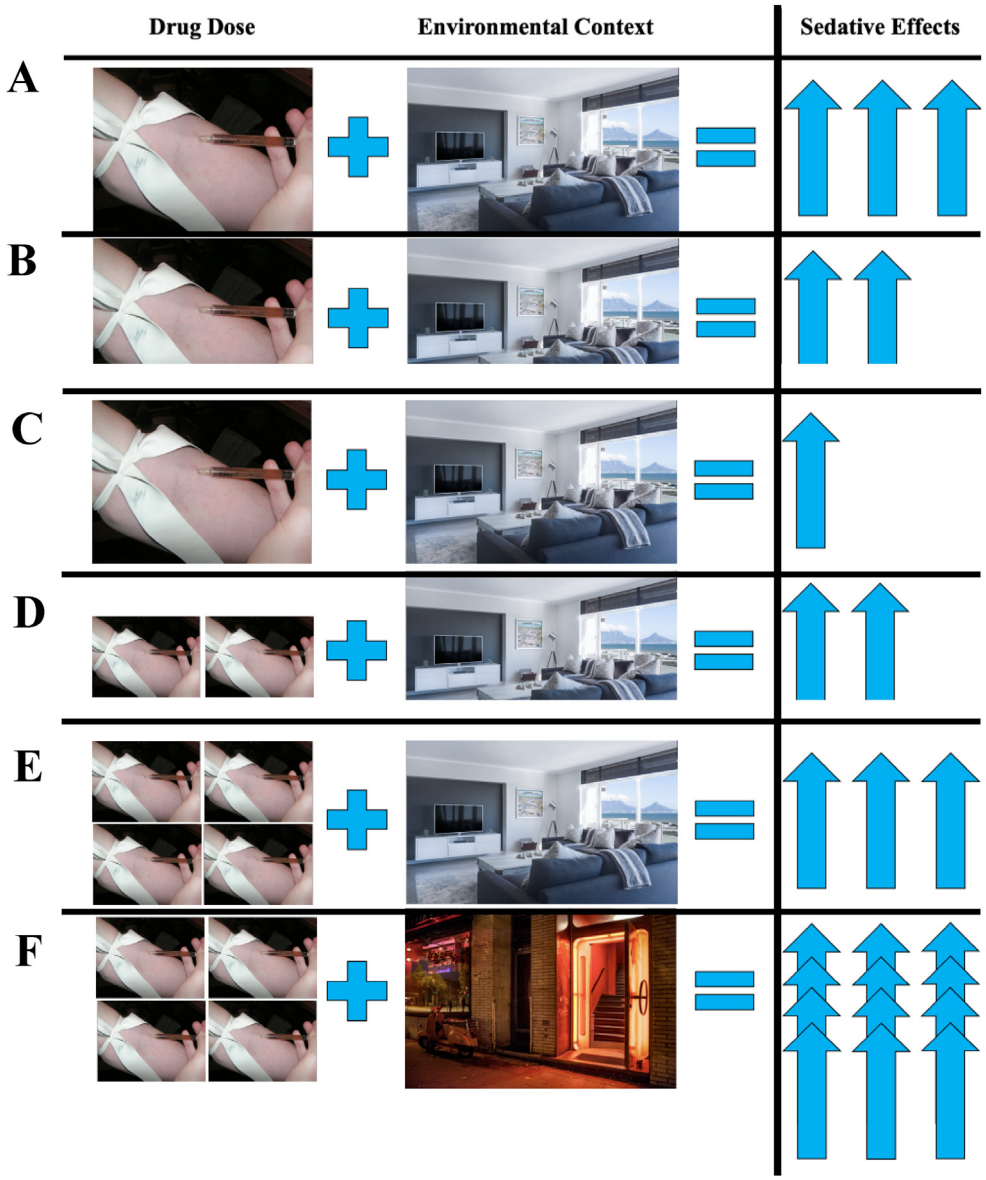


FIGURE 6.5 An example of conditioned tolerance to the sedative effects of heroin. With initial heroin use, the individual experiences a robust sedative effect (A). With repeated drug use, the individual develops tolerance to heroin's sedative effects (B and C). To compensate for tolerance, the individual increases the drug dose to experience the same "high" as they did initially (D and E). Notice that the environmental context in which the individual uses heroin is the same for panels A–E. In (F), the individual uses the same dose as they did in (E), but the drug use now occurs in a novel location. Because the body is not expecting an influx of heroin at this moment in time, there is no compensatory mechanism to protect the user from an overdose. Now, the same dose that the individual has been using produces a massive sedative effect, which can tragically lead to overdose and death. *The image was created by the author using Microsoft PowerPoint. The image of heroin injection comes from Wikimedia Commons and was posted by user Psychonaught (https://commons.wikimedia.org/wiki/File:Injecting_Heroin.JPG). The image of the living room and the bar come from Pexels and were posted by Jean van der Meulen (https://www.pexels.com/photo/photo-of-living-room-1457842/) and Mali Maeder (https://www.pexels.com/photo/white-motor-scooter-near-open-door-219095/), respectively.*

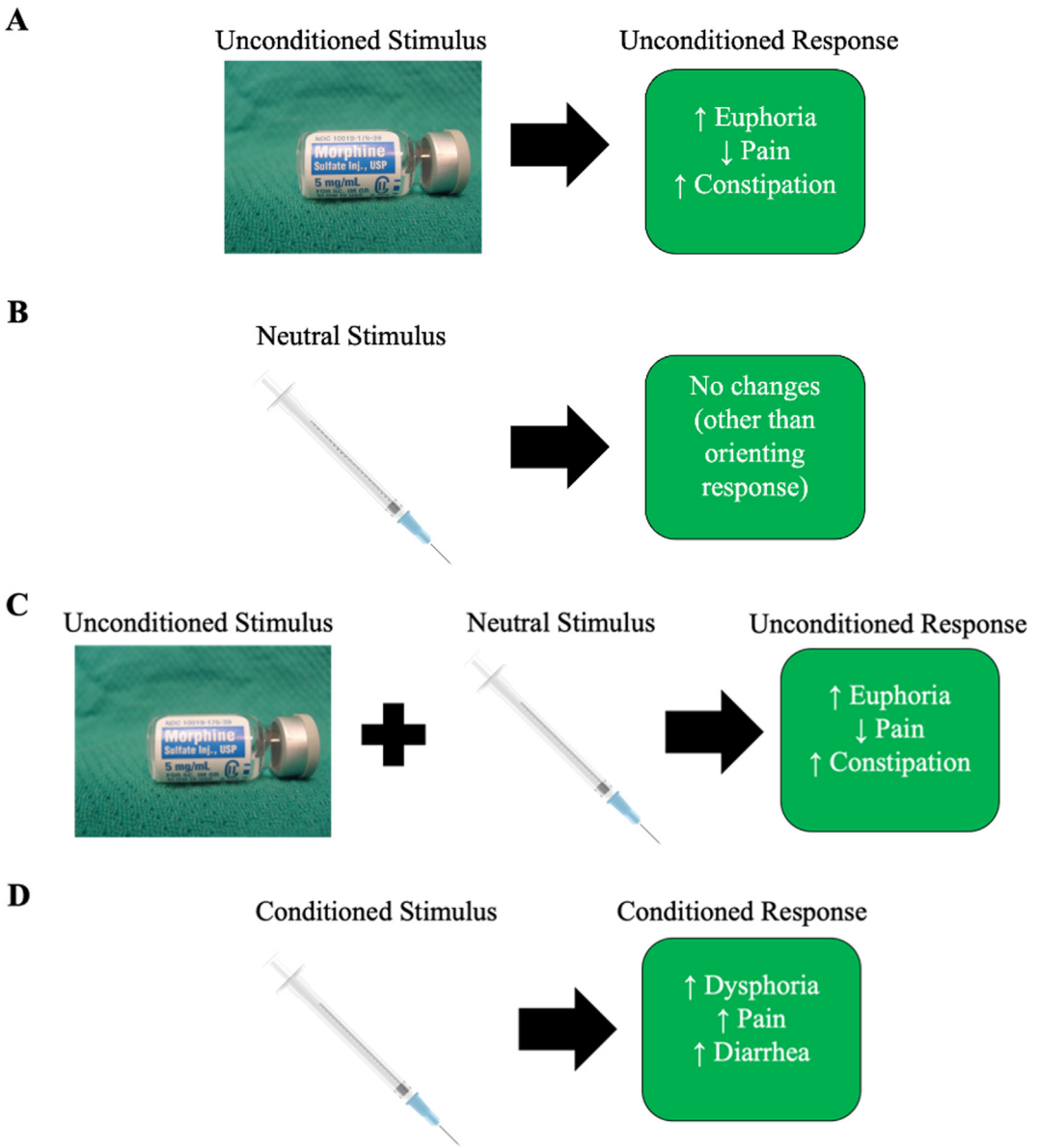


FIGURE 6.6 Illustration showing conditioned withdrawal. In (A), morphine (unconditioned stimulus [US]) produces euphoria while decreasing pain sensitivity and increasing constipation (unconditioned responses [URs]). In (B), the presentation of a neutral stimulus such as a syringe does not elicit much of a response from individuals. Panel (C) depicts conditioning. When an individual uses a syringe to inject morphine, they will experience the same effects as described in (A). As such, the individual will begin pairing the syringe with morphine. Over time, the presentation of the syringe, now a conditioned stimulus (CS), will elicit a conditioned response (CR) (D). However, the CRs are not the same as the URs. Individuals feel more dysphoric, experience increased pain sensitivity and experience diarrhea. The conditioned withdrawal symptoms can precipitate continued use of the drug. *The figure was created by the author of this textbook using Microsoft Powerpoint. The image of morphine comes from Wikimedia Commons and was posted by user Vaprotan (https://commons.wikimedia.org/wiki/File:Morphine_vial.JPG). The image of the syringe comes from https://openclipart.org/detail/1887/syringe.*

of the drug and may "like" those effects. At the same time, they may experience a "desire" to use the drug again in the future. With continued drug use, individuals begin to "like" the drug less due to neuroadaptations that lead to decreased dopamine release, as you learned about in Chapters 3 and 4. However, as other stimuli become paired with the drug (e.g., syringes, ashtrays, pint glasses, etc.), the neurocircuits responsible for incentive salience become sensitized. Fig. 6.7 shows a schematic of the incentive sensitization theory of addiction.

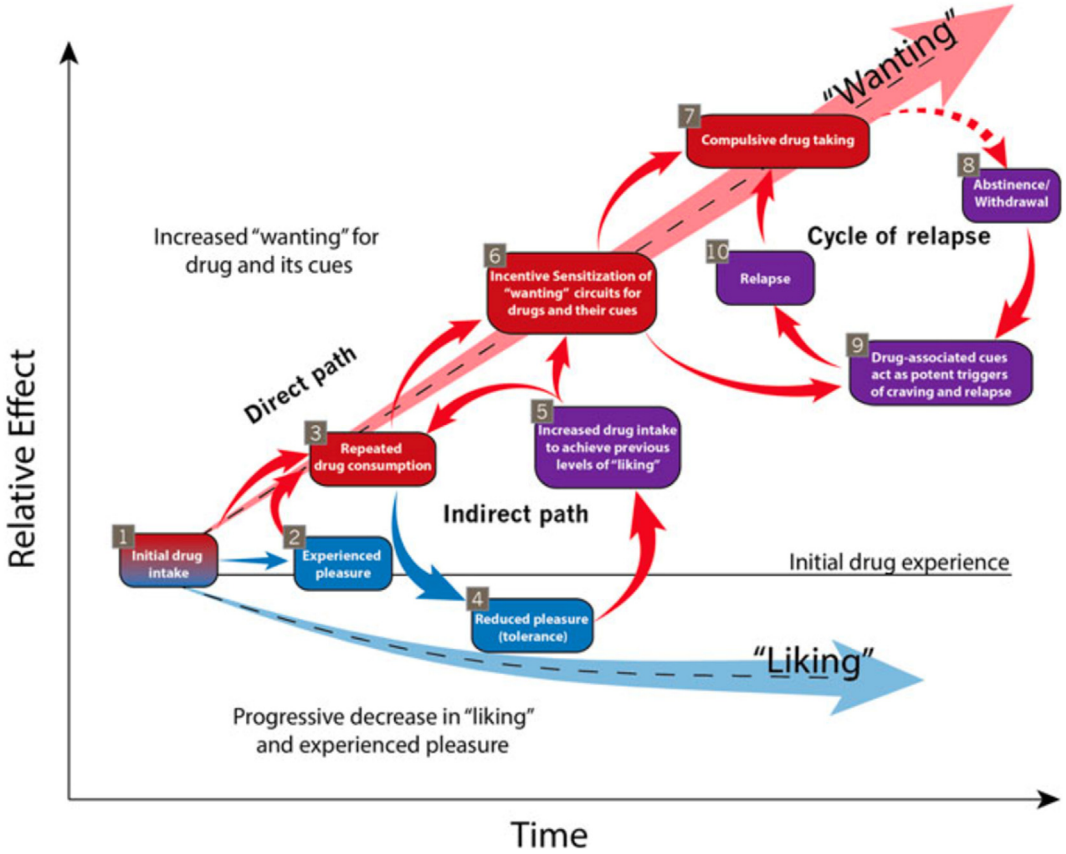


FIGURE 6.7 Schematic depicting the incentive sensitization theory of addiction. Initial drug use (1) leads to pleasure (2). This experience promotes the individual to continue using the drug (3), which then leads to tolerance to the reinforcing effects of the drug (4). To achieve the same "high" as initially experienced, the individual will increase their drug intake (5). Notice that this causes a loop to form between repeated drug consumption, increased tolerance, and increased drug intake. Eventually, the neural circuits responsible for attributing incentive salience to drugs and their cues become sensitized (6). Now, individuals have a strong desire to continue using drugs, which can promote compulsive drug seeking (7). If an individual stops using the drug (8), they may experience intense cravings after encountering drug-paired cues (9). These cravings can precipitate relapse (10), which then leads back to compulsive drug seeking. Over time, "liking" decreases, whereas "wanting" increases. *Image is from Fig. 2 of Robinson MJ, Fischer AM, Ahuja A, Lesser EN, Maniates H. Roles of "wanting" and "liking" in motivating behavior: gambling, food, and drug addictions.* Curr Top Behav Neurosci. *2016;27:105–136. https://doi.org/10.1007/7854_2015_387.*

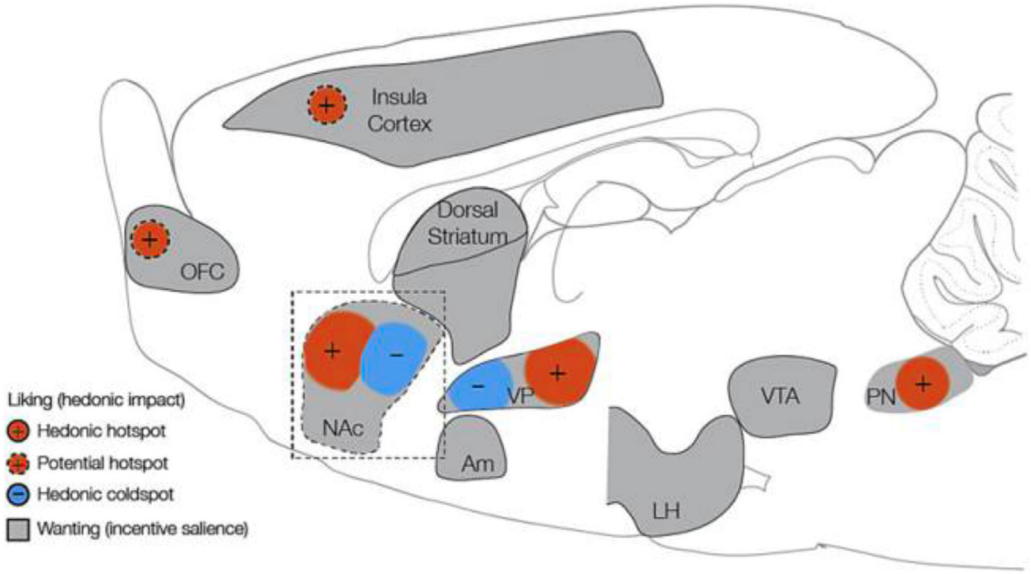


FIGURE 6.8 The neurobiology of incentive sensitization. Areas highlighted in gray indicate those that are associated with "wanting". Areas colored in red represent hedonic hotspots. A region surrounded by a dashed line is a potential hotspot, but more work is needed to verify if the region controls hedonic responses to drugs. Areas colored in blue are considered hedonic coldspots. Stimulating these areas decreases hedonic responses to sucrose. *Am*, amygdala; *LH*, lateral hypothalamus; *NAc*, nucleus accumbens; *OFC*, orbitofrontal cortex; *PN*, parabrachial nucleus (located in pons); *VP*, ventral pallidum; *VTA*, ventral tegmental area. *Image comes from Fig. 2 of Kringelbach ML, Berridge KC. Neuroscience of reward, motivation, and drive. In: Kim SI, Reeve J, Bong M. eds.* Recent Developments in Neuroscience Research on Human Motivation (Advances in Motivation and Achievement*): Emerald Publishing Limited; 2016:23–35. https://doi.org/10.1108/S0749-742320160000019020. © Emerald Publishing Limited all rights reserved.*

The nucleus accumbens (NAc) shell is important for mediating the pleasure we experience when we receive a reward. As such, this region contains a *hedonic hot spot* that helps control liking for drug-paired stimuli. Importantly, this hot spot does not encompass the entire NAc shell; instead, it occupies a 1 cubic mm site in the rostrodorsal region of the shell.[98] The question becomes: "how does one determine the location of a hedonic hot spot?". Rodents will display certain hedonic facial expressions when given a sweet solution, such as sticking their tongue out or engaging in a licking response. Stimulating the rostrodorsal region of the NAc shell, but not other subregions of the shell increases these hedonic expressions. A hedonic hot spot has also been identified in the posterior region of the ventral pallidum.[99] Other brain regions have been proposed to contain hedonic hot spots, including the parabrachial nucleus of the pons, the insula, and the orbitofrontal cortex (OFC)[100] (Fig. 6.8). Interestingly, "liking" does not appear to be controlled by dopamine; instead, opioids and endocannabinoids are more important for this response.[98,99,101]

You previously learned that the NAc core and the ventral pallidum coordinate actions toward reward-paired cues. As such, these regions are involved in attributing incentive salience to drug-paired stimuli. In contrast to the "liking" system, the "wanting" system is composed of numerous brain regions, including those that contain hedonic hot spots (like the ventral

pallidum). Other areas implicated in wanting are the NAc shell, the dorsal striatum, the ventral tegmental area (VTA), the lateral habenula, the amygdala, the insula, the OFC, and the parabrachial nucleus (Fig. 6.8). Wanting appears to be largely mediated by the dopaminergic system.[102] Indeed, depleting dopamine levels in the NAc impairs PCA.[103] This finding is consistent with what we know about addiction. When an individual uses a drug, there is a large increase of dopamine in the NAc. Not only is dopamine important for the direct reinforcing effects of the drug, but it is important for learning associations between the drug and environmental stimuli. However, "wanting" can be influenced by the opioid system as direct injection of mu-opioid receptor agonists into the NAc shell and into parts of the ventral pallidum increases consummatory behavior.[98,99]

Interestingly, cocaine self-administration impairs higher-order conditioning.[104] Recall that in higher-order conditioning, animals first learn to associate a CS with a US before learning to associate a second CS with the original CS. Although cocaine increases dopamine levels, long-term cocaine self-administration causes NAc neurons to become less active during higher-order conditioning. This finding is important because it may help explain why addiction is a relapsing disorder. Individuals that have used a drug for an extended period may have difficulty learning new associations (e.g., lighters are used for more than lighting a cigarette) upon drug cessation. Instead, the old associations persist, which can precipitate relapse.

Quiz 6.1

Read the following scenario before answering the questions:

An individual begins smoking cannabis daily in their basement. The individual places the cannabis in a pipe before lighting it. Initially, the individual feels relaxed when using cannabis. Over time, the individual notices that they no longer feel as relaxed when using cannabis, so they increase how much cannabis they use during the day.

1. What stimulus/stimuli can become paired with cannabis use?
2. What is the unconditioned stimulus?
   - **a.** Basement
   - **b.** Cannabis
   - **c.** Lighter
   - **d.** Pipe
3. What is most likely to happen if the individual encounters a drug-paired CS when not actively using cannabis?
   - **a.** The individual will experience diarrhea
   - **b.** The individual will feel irritable
   - **c.** The individual will not feel anything
   - **d.** The individual will feel relaxed
4. What could happen if the individual uses cannabis in a location other than his/her basement?
   - **a.** Nothing will happen
   - **b.** They can die
   - **c.** They can experience anxiety/paranoia
   - **d.** They will feel more relaxed than normal

5. According to the incentive sensitization theory of addiction, which brain region will become hypersensitive to stimuli paired with cannabis?
   a. Dorsal striatum
   b. NAc core
   c. NAc shell
   d. All of the above

Answers to quiz 6.1

1. The lighter, the pipe, the basement, and any items in the basement can become paired with cannabis use.
2. b — Cannabis.
3. b — The individual will feel irritable (remember, irritability is a sign of cannabis withdrawal).
4. c — They can experience anxiety/paranoia (these are symptoms of cannabis overdose).
5. d — All of the above.

Conditioned place preference

You are already familiar with the term conditioned place preference (CPP) as I briefly discussed this research paradigm in Chapter 3. CPP is used to measure the conditioned rewarding effects of a stimulus. CPP chambers are composed of separate compartments that have different colors and/or patterns on the walls of the compartments. The floors of each compartment can differ, as some compartments have smooth PVC floors, whereas others have steel rod floors or wire mesh floors. In some studies, researchers add scented items under the floor to provide different olfactory cues. A normal CPP experiment begins with a pretest. The animal, in a drug-free state, is allowed to explore each compartment. Then, in alternating sessions, the animal is given a drug of interest and is then isolated to one of the compartments. In sessions in which the animal does not receive the drug, they receive a vehicle injection and are isolated to a different compartment. In the case of a three-compartment CPP chamber, animals are never isolated to the center compartment. Animals are then given a posttest, in which they are allowed to explore all compartments in a drug-free state. Spending more time in the environment previously paired with the drug is considered CPP. Conversely, *conditioned place aversion* (*CPA*) occurs when the animal spends significantly less time in the compartment paired with the drug.

Not surprisingly, animals develop CPP to most drugs commonly used by humans,[105] but there are some inconsistencies in the literature. Historically, the barbiturate pentobarbital has failed to produce CPP in animals[106]; in fact, Lew and Parker found that pentobarbital produced CPA in animals.[106] However, Bossert and Franklin showed that rats could develop CPP to pentobarbital.[107] PCP is another drug that often produces CPA in animals.[108,109] Although PCP does not consistently produce CPP, there are newer synthetic dissociative drugs that reliably produce CPP in animals.[110,111]

Interestingly, if animals are pretreated with PCP (that is, they receive PCP injections before they are tested in the CPP experiment), they develop CPP.[112,113] This phenomenon has been

observed with cocaine, *d*-amphetamine, nicotine, and morphine.[114,115] This finding somewhat defies what we know about Pavlovian conditioning. In a typical Pavlovian conditioning experiment, preexposing an animal to the US before pairing it with the CS weakens conditioning. This is known as the *US preexposure effect*.[116] In the case of drug CPP, why does preexposing an animal to the drug prior to conditioning enhance CPP instead of weakening it? According to Bardo et al.[117] there are a couple of reasons why preexposure to the drug can increase CPP. First, exposure to the drug can enhance its rewarding aspects, thus making it easier to associate them with a novel environment. Think of it this way: someone may not initially "enjoy" smoking a cigarette or drinking ethanol the first time they try it. Over time, the individual may start to enjoy the effects of the drug more. Second, preexposure to the drug may lead to tolerance to any aversive effects of the drug that may arise from acute withdrawal. By the time conditioning begins, the animal does not experience as many acute withdrawal symptoms but still experiences the rewarding effects of the drug.

One reason why drugs like PCP do not always produce CPP may be related to the methodology of the CPP experiment. When conducting a CPP experiment, the researcher must consider the dose(s) of the drug that will be paired with a specific environment. The researcher must also consider how much time passes between drug administration and being placed in the testing chamber. As mentioned, PCP often produces CPA instead of CPP. Marglin et al.[118] were able to establish CPP for acute injections of PCP. They were able to accomplish this by treating animals with a lower dose of PCP compared to other studies and by waiting less time to test the animals following drug administration. Another important methodological consideration will be discussed below.

Biased versus unbiased design

There are two major designs one can use in a CPP experiment: a biased design and an unbiased design. In a biased design, the researcher first measures preference for each compartment during the pretest. The researcher will then assign the initially nonpreferred chamber to be the drug-paired chamber. In an unbiased design, the researcher will counterbalance which compartment is paired with the drug. That is, half of the subjects will receive the drug in their initially preferred compartment, and half will receive the drug in the initially nonpreferred compartment. Is one design better than the other? The answer depends on what type of CPP apparatus one has. Just as there is a biased and unbiased design, there are biased and unbiased CPP chambers. A biased CPP chamber exists when animals spend most of their time in one compartment over the other during the pretest. For example, rats often spend more time in a compartment that has a wire mesh floor instead of a steel rod floor. If animals spend similar amounts of time in each compartment, the researcher has an unbiased CPP chamber. If one has an unbiased CPP chamber, using either a biased design or an unbiased design is acceptable. However, when using a biased apparatus, caution needs to be taken when using either design. Why? One concern with using a biased design with a biased apparatus is that any increased time spent in the initially nonpreferred compartment following conditioning may reflect decreased anxiety as opposed to increased reward.[119] Conversely, imagine some animals spend more time in the compartment that becomes paired with the drug. A researcher may not be able to observe an increase in the time spent in the drug-paired compartment because these animals already show a high preference for this compartment. This is known as a *ceiling effect*.

Cunningham et al.[120] showed how a biased/unbiased apparatus can alter CPP for ethanol. In experiment 1, an unbiased apparatus was used; in experiment 2, Cunningham et al. created a biased apparatus by changing the type of flooring in each compartment. In both experiments, an unbiased design was used. Results showed that when an unbiased apparatus was used, mice developed ethanol CPP, regardless of which floor type was used. However, when a biased apparatus was used, significant CPP was observed in animals that received ethanol in the compartment with the bar floor only (Fig. 6.9). When examining the data, what you will notice is that CPP was not observed in animals that had a high baseline preference for the compartment that was paired with ethanol. This made observing any further increases in preference following conditioning difficult. This is an example of a ceiling effect that I mentioned in the previous paragraph. Other studies have shown discrepant results when using a biased design compared to an unbiased design. For example, CB_1 knockout mice fail to develop MDMA CPP when an unbiased design is used, but they develop CPP when a biased design is used.[121]

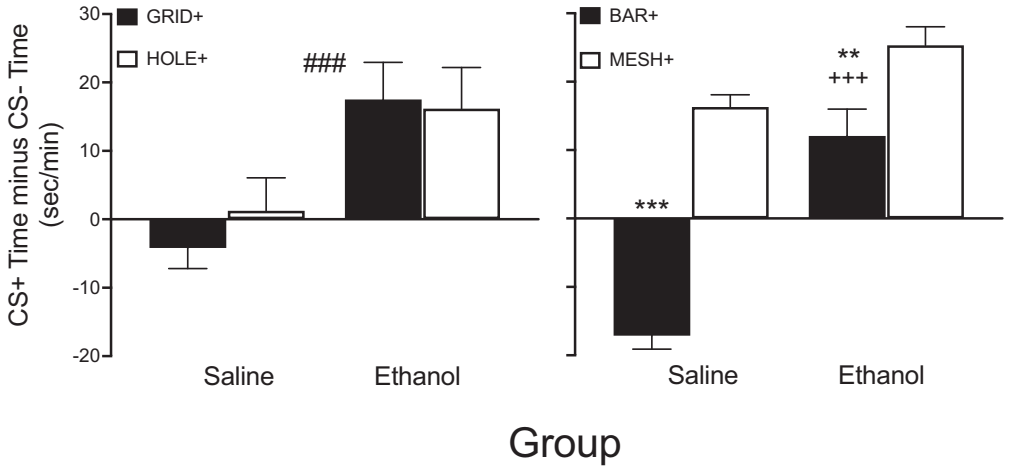


FIGURE 6.9 Cunningham et al. tested mice for ethanol CPP. There were two major experiments. In one experiment, mice were exposed to a CPP apparatus that had either a grid floor (2.3-mm steel rods mounted 6.4 mm apart) or a hole floor (perforated steel floor with 6.4-mm round holes on 9.5-mm staggered centers). Mice do not show a strong preference for one-floor type over the other. In the second experiment, mice were exposed to a CPP apparatus that had either a bar floor (6.4-mm steel rods mounted 13 mm apart) or a mesh floor (6.4-mm galvanized hardware cloth squares). In this experiment, mice show a strong bias toward the mesh floor. In both experiments, half of the mice were randomly assigned to receive ethanol in one compartment and saline in another compartment. The other half received saline in both compartments. The graphs show the time spent in the CS+ (ethanol) compartment subtracted by the time spent in the CS− (saline) compartment during the posttest. The left panel shows data for animals conditioned in an unbiased apparatus. The right panel shows data for animals conditioned in a biased apparatus. For the unbiased experiment, mice do not spend significantly more time in the compartment with the grid floor compared to the hole floor; this is why difference scores hover around 0 for each subgroup. Conversely, animals that received ethanol in either the grid-paired compartment or the hole-paired compartment developed significant CPP. For the biased experiment, mice treated with saline spent significantly more time in the mesh-paired compartment compared to the rod-paired compartment. Consequently, mice that received ethanol in the bar-paired compartment developed CPP, whereas mice that received ethanol in the mesh compartment did not. The null effect observed for this group most likely is the result of a ceiling effect. *Image recreated from Fig. 4 of Cunningham CL, Ferree NK, Howard MA. Apparatus bias and place conditioning with ethanol in mice.* Psychopharmacology. *2003;170(4):409–422. https://doi.org/10.1007/s00213-003-1559-y. Copyright 2003.*

Acquisition versus expression of CPP

One major use of CPP is to screen potential pharmacotherapies for SUDs.[117] If a drug is effective in treating SUDs, it should be able to block the conditioned rewarding effects of a drug. One can test a potential pharmacotherapy for its ability to block the *acquisition* and/or the *expression* of drug-induced CPP. Acquisition is somewhat analogous to the initial learning of a drug-taking response. Think of an adolescent/young adult trying ethanol for the first time. If individuals enjoy ethanol, they will continue consuming it. They are not dependent on the drug, yet, but they have acquired the behavioral response of drinking. Expression is akin to someone that has been using a substance for an extended period. These descriptions of acquisition and expression are overly simplified. We will come back to the acquisition and the expression of CPP in the next chapter. For now, I will discuss how researchers test the effects of a potential pharmacotherapy on the acquisition and expression of CPP. To test acquisition, the potential pharmacotherapy is administered before the drug during conditioning sessions. To test expression, the potential pharmacotherapy is administered before the posttest only. Because individuals with a SUD have already acquired the drug-taking behavior, testing a potential pharmacotherapy on the expression of drug CPP may be more applicable to real life. Just because a drug blocks the acquisition of CPP, this does not mean that it will block the expression of CPP and vice-versa. For example, the drug SCH 23990 (dopamine D_1-like receptor antagonist) blocks acquisition, but not expression, of MDMA CPP.[122] Similarly, my students and I have shown that the GluN2B subunit antagonist Ro 63−1908 blocks acquisition, but not expression, of methamphetamine CPP.[123]

CPP in humans

Almost all drug CPP studies use animal subjects, although there have been a few studies that have used human participants. The first documented case of the human drug CPP was published by Dr. Harriet de Wit, a research professor at the University of Chicago. Childs and de Wit[124] gave one group of participants amphetamine in one room and placebo in a separate room; this is the paired group. Another group of participants received amphetamine and placebo in both rooms; this is the unpaired group. At the end of the experiment, participants rated their preference for each room. Participants in the paired group rated the amphetamine-paired room higher than the placebo-paired room, whereas participant ratings of each room did not differ in the unpaired group. In a follow-up study, Childs and de Wit found that participants in the paired group reported greater stimulation and drug craving the second time receiving amphetamine, an effect that was not observed in the unpaired group.[125] This finding suggests that environmental context enhances the stimulant effects and the rewarding effects of amphetamine. de Wit has also shown that humans develop CPP for ethanol. When social drinkers are allowed to explore one of two rooms, they spend more time in the room that had previously been associated with ethanol.[126] Overall, these studies show that humans can be conditioned to associate one environment with a specific drug. We can see examples of CPP in the real world. Individuals with alcohol use disorder prefer to stay in an environment that allows them to consume ethanol, such as at home or at a bar.

Advantages and disadvantages of CPP

A major advantage to CPP is that it can be used to study more than just drugs. Animals will develop CPP to natural rewards like food, water, social interaction, and novelty. This is important because if we want to determine if a potential pharmacotherapy blocks the conditioned rewarding effects of a drug, we want to ensure that the pharmacotherapy does not interfere with general reward learning. For example, Ma et al. found that the drug ifenprodil, an antagonist at GluN2B-containing NMDA receptors, blocks the acquisition and the expression of morphine CPP without affecting food CPP or social interaction CPP.[127] This finding provides greater credence to the idea of targeting the GluN2B subunit for the treatment of SUDs.

Another advantage of CPP is that it does not require catheter implantation surgery like drug self-administration. Catheter implantation surgeries can be laborious and can be difficult to train in some individuals. This poses a challenge for researchers that work primarily with undergraduate research assistants, although it is possible to conduct drug self-administration experiments at primarily undergraduate institutions. Researchers such as myself and Dr. Mark Smith of Davidson College conduct drug self-administration experiments while working with undergraduate students.[128,129] Regardless, because catheter implantation surgery is invasive, complications can arise during or following surgery. There is always the risk that an animal reacts poorly to anesthesia or has health complications following surgery. These issues can lead to *attrition*, thus decreasing one's sample size. Because CPP does not involve surgery, the risk of attrition is negligible.

One major disadvantage to CPP is that it requires more animal subjects compared to drug self-administration. In drug self-administration, multiple doses of a drug can be tested in the same animal to generate a *dose-response curve*. As discussed in the previous chapter, responding to a drug typically follows an inverted U-shape function; that is, animals respond maximally to intermediate doses of a drug. In CPP, because the same dose is used during conditioning, separate groups are needed to test the conditioned rewarding effects of various doses of the drug. To provide an illustration: in the previous chapter, you saw a graph of an inverted U-shaped dose-response curve for cocaine (see Fig. 5.6 of the previous chapter). Using six doses of cocaine (0.03, 0.06, 0.12, 0.25, 0.5, and 1.0 mg/kg/inf), Piazza et al. found that rats respond most for 0.12 mg/kg/inf of cocaine, followed by 0.25, 0.06, 0.5, 0.03, and 1.0 mg/kg/inf, respectively.[130] In a CPP experiment, generating a dose response curve would require six separate groups of animals, greatly increasing the number of animal subjects needed. This is cost prohibitive for some researchers.

Using Pavlovian concepts to treat addiction

Because Pavlovian conditioning appears to play a pivotal role in precipitating relapse, several therapeutic approaches have been used to mitigate the role of CSs on conditioned drug cravings. A few of the major techniques will be reviewed below.

Cue exposure therapy (extinction training)

In Pavlovian conditioning, repeatedly presenting the CS without presenting the US results in extinction; that is, over time, the animal will stop showing a CR when presented with the

CS. Given that individuals with a SUD experience cravings and physiological changes when exposed to a drug-paired stimulus, one therapeutic approach is to repeatedly expose an individual to drug-related stimuli without giving him/her the opportunity to use the drug. This is known as **cue exposure therapy**. Cue exposure therapy reduces cravings and drug use in a laboratory setting.[131–133] The major limitation to cue exposure therapy is that its effectiveness is limited to the environment in which one experiences the therapy. What I mean by this is that extinguishing craving in a lab setting does not mean that extinction has occurred in other types of settings. As you have learned, the environment can serve as a powerful stimulus that signals the availability of the drug. Because cue exposure therapy has occurred in a single environment, there is no guarantee that the individual will be able to avoid conditioned withdrawal and/or conditioned craving. How can one ensure that cue exposure therapy can be implemented outside of a laboratory setting?

As of February 2021, approximately 97% of Americans own a cell phone. Some research has attempted to take advantage of this fact by providing individuals *extinction reminders* during cue exposure therapy. During cue exposure therapy, a therapist can present a novel stimulus like a tone when an individual reports little to no drug craving. This tone becomes a CS that predicts the absence of drug craving. When the individual encounters an environment associated with drug use, the individual can call a number to hear the tone. Presentation of the tone can help reduce drug cravings.[134]

Virtual reality exposure therapy (VRET)

Virtual reality is a technology in which a user experiences computer-generated images while wearing a headset. In recent years, video games have incorporated virtual reality. You may be familiar with Oculus or PlayStation VR. However, virtual reality can be used to treat multiple psychiatric conditions, including SUDs, in the form of **virtual reality exposure therapy (VRET)**.[135] As the name suggests, VRET combines cue exposure therapy with virtual reality. The researcher generates images of environments in which drug-taking behaviors normally occur and can present the participant with images of drug-specific stimuli. For example, in one study, Hernández-Serrano et al. presented participants with images of four environments associated with ethanol use: bar, restaurant, pub, and home. Each environment included images of ethanol, and participants could interact with the alcohol bottles via the virtual reality setup.[136] So far, VRET has been effective at reducing craving for ethanol[136,137] and cigarettes.[138] One interesting finding is that the effectiveness of VRET has been shown to depend on the status of one's drug use. For example, using highly realistic scenarios decreases cravings for current smokers, but increases cravings in those that have recently quit smoking.[138]

Although VRET improves the generalizability of cue exposure therapy, there are several weaknesses to using this approach for the treatment of SUDs. As noted by Vinci et al., creating virtual environments is cost and time-prohibitive.[139] I can attest to the time commitment needed to develop a virtual environment. Although I am an animal researcher, I supervised an honors student who wanted to create a virtual environment to help those with social anxiety disorder. My student spent most of the semester creating a single environment. Now, imagine having to create multiple environments like the study described above. The second criticism of VRET is that the images projected to the user are not always realistic.

This can limit how much the individual immerses him or herself into the environment. Related to the first point, because creating multiple environments can take a considerable amount of time, studies often use a single environment. This is problematic because this limits the generalizability of the treatment to multiple contexts. One can use ethanol in multiple environments, such as at home, at a friend's house, at a bar/pub, at a sporting event, and so on.

Augmented reality

If you ever played *Pokémon Go*, you have experienced **augmented reality**, a technology that superimposes digital objects into the real world through a device like a smartphone or a headset. According to Vinci et al., addiction scientists should start using augmented reality to help treat individuals with a SUD.[139] Researchers can project drug-related stimuli such as glasses of ethanol, ashtrays, or syringes into the individual's environment. This approach is advantageous as it allows individuals to experience cue exposure therapy in their living space or in areas in which they would realistically use the drug. Another advantage is that VR equipment is not needed. Despite these advantages, augmented reality has not been extensively tested as a potential therapeutic for SUDs. However, one study used augmented reality to teach children about the health impacts of smoking.[140] Children from 5 to 13 years of age could point a tablet at a mannequin wearing a T-shirt. Images of the lungs or the heart appeared on the shirt. These images depicted the heart/lungs of a healthy individual or the heart/lungs of a chronic smoker (Fig. 6.10). Following the demonstration, children reported a decreased interest in tobacco products. Given that approximately 85% of individuals in the United States own a smartphone,[141] augmented reality is an easy way to engage individuals in cue exposure therapy.

Aversion therapy and counterconditioning

In **aversion therapy**, the goal is to pair something aversive with unwanted behavior. In the novel *A Clockwork Orange*, the main character Alex is the leader of a gang and engages in

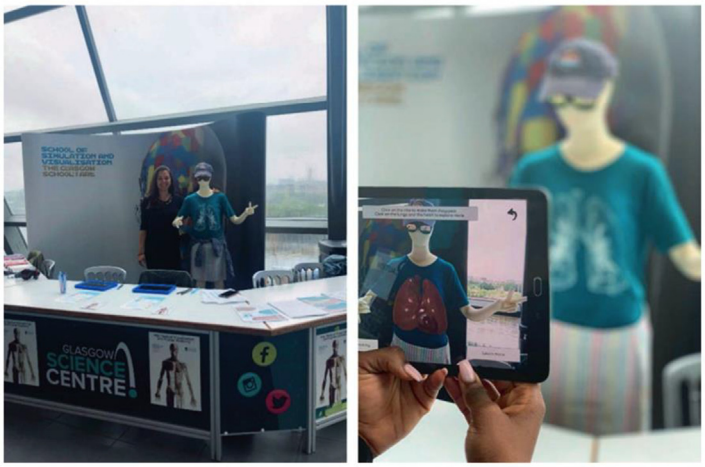


FIGURE 6.10 An example of how augmented reality can be used to teach individuals about the risks of drug use. In the current application, individuals can use a tablet to project an image of internal organs on a T-shirt worn by a mannequin. Individuals can examine healthy lungs or lungs affected by chronic smoking. *Image comes from Fig. 4.31 Borovanska Z, Poyade M, Rea PM, Buksh ID. Engaging with children using augmented reality on clothing to prevent them from smoking. In: Rea PM, ed.* Advances in Experimental Medicine and Biology. *Springer; 2020;1262:59–94. https://doi.org/10.1007/978-3-030-43961-3_4. Copyright 2020.*

violent acts. Eventually, he is arrested and subjected to a form of aversion therapy known as the Ludovico Technique. Alex is injected with a drug that makes him sick and is forced to view violent videos. Following aversion therapy, Alex becomes physically ill when he thinks of violence. As related to SUDs, you have already learned about one form of aversion therapy: the use of disulfiram (Antabuse) for the treatment of alcohol use disorder. If an individual drinks ethanol after taking disulfiram, they will experience nausea. The goal is for the individual to associate nausea with ethanol use, thus decreasing their desire to use ethanol in the future.

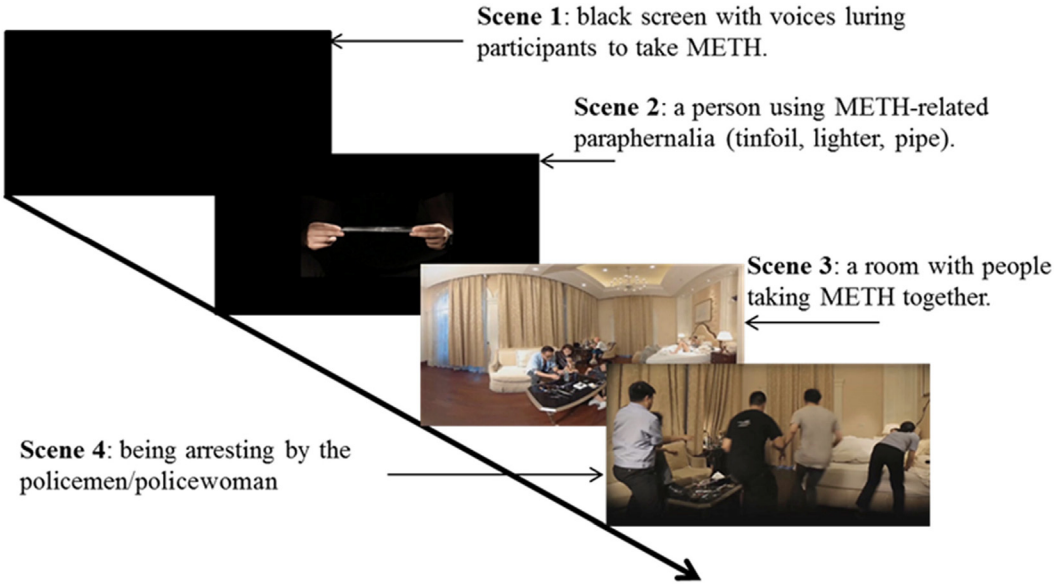
Aversion therapy is a form of **counterconditioning**. The goal of counterconditioning, as the name suggests, is to reverse (counter) conditioning that has previously occurred. Because drug-paired stimuli can elicit strong cravings, the goal of aversion therapy is to make these stimuli less enticing. While disulfiram can decrease ethanol consumption, additional research has examined alternative forms of aversion therapy for other drugs. In an early study, individuals with a SUD received mild electric shocks to the wrist as they verbalized and imagined past drug-using experiences.[142] Participants reported decreased drug-related thoughts and showed low relapse rates 2 years following the experiment. One caveat to this experiment is that participants were also in group therapy; therefore, the low relapse rates may have been influenced more by this form of therapy instead of aversion therapy. In addition to cocaine, the use of electric shocks has been used to decrease ethanol,[143] nicotine,[144] and cannabis[145] use. While disulfiram is the only FDA-approved form of aversion therapy for alcohol use disorder, other chemicals have been used in counterconditioning experiments. In one experiment, Frawley and Smith[146] allowed patients to either snort a cocaine substitute (combination of 2% tetracaine and 1% quinine), smoke a cocaine substitute (either white candy or white soap that emits smoke when burned), or "inject" a white powder (D-xylose) dissolved in a liquid (note, patients did not actually inject anything into their arm; the liquid is pushed out of the syringe just above the forearm). Before patients engaged in these "drug-taking behaviors", they were given emetine. If you are not familiar with emetine, it is an alkaloid found in ipecac syrup, which causes extreme nausea and vomiting. The emetine was delivered such that its effects would occur around the same time as the patient "used" cocaine. After 18 months following the experiment, 38% of cocaine users reported complete abstinence.

One major drawback to aversion therapy is that compliance is often low. Individuals do not want to engage in activities that are uncomfortable. Counterconditioning does not have to incorporate aversive stimuli. Recently, virtual reality has been combined with counterconditioning to better decrease drug cravings. The Experiment Spotlight details such an experiment.

Experiment Spotlight: A virtual reality counterconditioning procedure to reduce methamphetamine cue-induced craving (Wang et al.[147])

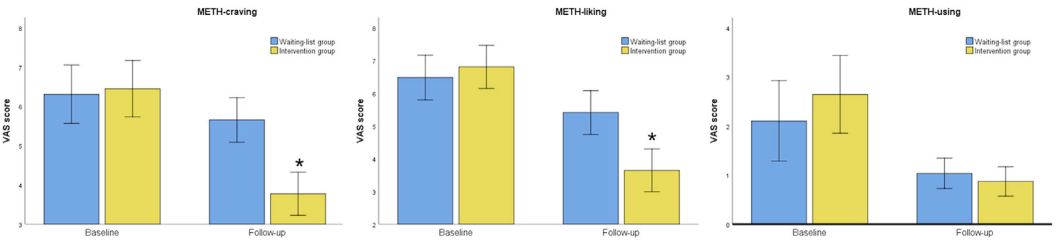
Considering there are currently no approved pharmacotherapies for methamphetamine use disorder, Wang et al.[147] determined if a virtual reality counterconditioning procedure (VRCP) can be an effective treatment option for those with methamphetamine use disorder. Initially, 87 individuals were interviewed about their fears related to methamphetamine use. The six most common fears were: (1) being arrested by the police; (2) experiencing severe hallucinations; (3)

developing skin ulcers or an infection; (4) contracting a sexually transmitted illness; (5) tooth decay; and (6) death. The researchers used these concerns to design six VR videos. Each video consisted of two parts. The first part of each video was composed of three scenes: (1) a black screen with voices telling the participant to use methamphetamine; (2) a person using methamphetamine-related paraphernalia; and (3) individuals using methamphetamine in a room. The second part of the video depicted one of the six common fears described above (e.g., being arrested). The figure below shows example screenshots of one VR video.



The image comes from Fig. 2 of Wang YG, Liu MH, Shen ZH. A virtual reality counterconditioning procedure to reduce methamphetamine cue-induced craving. J Psychiatr Res. *2019;116:88–94. https://doi.org/10.1016/j.jpsychires.2019.06.007.*

There were two groups in this experiment. The first group experienced six VR videos and continued to receive their normal therapy. The second group was in a *waiting-list control group* in which they continued receiving their usual therapy only. Immediately before and during testing, individuals were given an electrocardiogram (ECG or EKG) to measure electrical signals in the heart. Participants were asked to rate their drug craving, drug liking, and drug use before and following the VRCP using a *visual analog scale*. The figure below shows the data for this experiment.



The image comes from Fig. 3 of Wang YG, Liu MH, Shen ZH. A virtual reality counterconditioning procedure to reduce methamphetamine cue-induced craving. J Psychiatr Res. *2019;116:88–94. https://doi.org/10.1016/j.jpsychires.2019.06.007. Copyright 2019, with permission from Elsevier.*

Participants exposed to VRCP had decreased drug craving and drug liking scores compared to participants that received treatment as usual. Both groups showed decreased methamphetamine use at the follow-up compared to baseline.

Questions to consider:

(1) Why does the waiting-list control group receive treatment as well? Should the researchers have included a control group that does not receive any treatment?
(2) Why was an ECG used in the current experiment?
(3) Why do you think methamphetamine use decreased for both groups of participants?

Answers to questions:

(1) From an ethical standpoint, individuals that are currently seeking treatment for a SUD cannot be denied treatment. Waiting-list control groups are often used as a control group in these experiments because the treatment of interest can be compared to another group that does not receive that treatment. A control group of individuals that does not receive any treatment can be used. If an individual specifies that they are not currently seeking treatment for their SUD, they do not have to receive treatment.
(2) Because CRs can elicit physiological reactions, the ECG is used to measure something known as *heart rate variability (HRV)*. When our heart beats, it does not do so in a consistent fashion. For simplicity, if your heart beats 60 times per minute, this does not mean that your heart beats exactly every second. Instead, your heart may beat at 0.8 s and then at 1.1 s. This is HRV. Drug-paired cues can increase HRV. Thus, Wang et al. wanted to determine if VRCP can reduce this drug-induced increase in HRV. This is exactly what they found.
(3) If you look closely at the *y*-axis of each graph above, you will see that drug craving and drug liking scores go up to eight on the graph; however, the methamphetamine use scale ranges from 0 to 4. Considering that both groups were at 2−2.5, there is not much room to observe differential decreases in methamphetamine use across groups (i.e., this is a floor effect). Another thing to consider is that the control group received treatment as usual during the experiment. Thus, their normal treatment may have been effective at reducing methamphetamine use without altering cravings or liking for the drug.

One advantage to using virtual reality in conjunction with counterconditioning is that the therapist does not need to make the patient sick to create a negative association between the drug and drug-paired stimuli.

Reducing attentional bias

Attentional bias can be reduced with some interventions. Individuals given cognitive-behavioral therapy (CBT) that had 3 weeks of abstinence show reductions in the cocaine Stroop effect, indicating decreased attentional bias to cocaine-paired stimuli.[70] Individuals given behavioral therapy with transcranial alternating current stimulation applied to the PFC show reduced attentional bias toward cigarette-paired stimuli.[148] Certain pharmacological

interventions can ameliorate attentional bias to drug-paired stimuli. For example, the ADHD medication atomoxetine (Strattera) reduces attentional bias to cocaine cues.[149]

Another way to improve attentional bias is by using the Alcohol/Drug Attention Control Training Program (AACTP/DACTP). Originally developed to reduce attentional bias to ethanol-paired cues,[150] the AACTP/DACTP exposes individuals to three "levels" of the drug Stroop task that increase in difficulty. During the first level, individuals are presented with a single image, either an alcoholic beverage/drug-paired stimulus or a neutral stimulus. These images are presented in random order and are surrounded by a colored background. The second level is similar to the first level, with the exception that each stimulus is surrounded by a colored outline as opposed to a background. During the third level, both stimuli are presented simultaneously, and each stimulus is surrounded by a colored outline (as in the second level). During the first two levels, individuals are asked to name the color of the background/border, and reaction times are recorded for each type of stimulus. During the third level, individuals name the color of the border for the neutral stimulus. This forces the individual to ignore the ethanol/drug-paired stimulus. To progress from one level to the next, individuals need to display a certain level of accuracy (e.g., 90%) while responding within a particular timeframe.[151] Within an individual level, the time needed to respond decreases. This manipulation is important because it forces individuals to decrease the amount of time needed to divert their attention away from drug-paired stimuli to neutral stimuli. During training, individuals receive feedback from the experimenter, which allows them to track their progress during the training program. So far, the AACTP/DACTP has been shown to reduce attentional bias to ethanol-, opioid-, and methamphetamine-paired cues.[150,151] Individuals given the DACTP also report less temptation to use drugs and are less likely to relapse following training.[151] Likewise, hazardous drinkers (i.e., drinking 22–50 units [men] or 15–35 units [women] of ethanol within a 1-week period) and harmful drinkers (drinking more than 50 units [men] or 35 units [women] of ethanol within a 1-week period) report less attentional bias following the AACTP, and harmful drinkers consume less ethanol following training.[150]

Quiz 6.2

1. Which of the following drugs is the most difficult to establish consistent CPP?
   - **a.** Cocaine
   - **b.** Ethanol
   - **c.** Morphine
   - **d.** PCP
2. What are two advantages of CPP over drug self-administration?
3. How does a CPP acquisition experiment differ from a CPP expression study?
4. Which of the following therapeutic approaches is most likely to cause compliance issues in patients?
   - **a.** Aversion therapy
   - **b.** Augmented reality
   - **c.** Counterconditioning
   - **d.** Cue exposure therapy

5. Which therapy enables the patient to use a smartphone to insert drug-paired stimuli into their environment?
   a. Aversion therapy
   b. Augmented reality
   c. Counterconditioning
   d. Virtual reality exposure therapy

Answers to quiz 6.2

1. d — PCP.
2. CPP can be tested with other types of USs like food, which allows one to determine if a potential pharmacotherapy specifically decreases CPP for drugs. CPP also does not require surgical interventions, which decreases the likelihood of attrition.
3. To determine if a potential pharmacotherapy alters the acquisition of CPP, the pharmacotherapy is administered before the drug during conditioning sessions. To determine if a potential pharmacotherapy alters the expression of CPP, the pharmacotherapy is administered before the posttest.
4. a — Aversion therapy.
5. b — Augmented reality.

Chapter summary

The finding that drug-paired stimuli can precipitate relapse poses a significant challenge for individuals trying to abstain from drug use. Numerous stimuli can become paired with the drug either directly (such as an ashtray or a syringe) or indirectly (objects in the environment in which drug use occurs). Individuals at risk of developing a SUD are drawn to these drug-paired stimuli (attentional bias), which can trigger intense physiological and emotional responses such as drug craving. This can then lead to relapse even if someone has been abstinent for years. Even if techniques like cue exposure therapy or counterconditioning can reduce the incentive salience to some drug-paired stimuli, there are many other stimuli that can still serve as a CS that can trigger withdrawal symptoms and/or drug cravings. Pavlovian conditioning may also be a major cause of overdose deaths. Take the story of Tom that you read about in the Introduction of the previous chapter. Tom's heroin overdose occurred in a motel room, which may not have been where Tom normally used heroin. Even if Tom used the same amount of heroin as normal, the change in environment, in conjunction with combining heroin with cocaine, could have significantly contributed to overdose. Overall, Pavlovian conditioning is a major contributing factor to SUDs and often works in conjunction with operant processes to influence an individual's continued drug use, even when they no longer enjoy the experience.

Glossary

Attentional bias – focusing on certain elements in the environment while ignoring other salient elements.
Augmented reality – a technology that allows one to project virtual images into the environment.

Aversion therapy – a form of conditioning in which an unpleasant stimulus is paired with another stimulus in an effort to decrease an organism's preference for that stimulus; e.g., disulfiram treatment is a form of aversion therapy aimed at reducing ethanol use.

Conditioned response (CR) – a type of behavior that only results after an organism has learned the association between two stimuli (e.g., salivating to the sound of a metronome that has been paired with food).

Conditioned stimulus (CS) – a type of stimulus that has been repeatedly paired with a stimulus that naturally elicits a response from an organism; over time, this stimulus can elicit a response from the organism (e.g., a metronome that has been repeatedly paired with food).

Conditioned tolerance – a phenomenon in which individuals develop tolerance to the effects of a drug in some environments, but not in others.

Conditioned withdrawal – a phenomenon in which the presentation of a drug-paired stimulus can elicit withdrawal symptoms.

Counterconditioning – a conditioning technique in which the pleasurable or aversive effects of a conditioned stimulus are reversed by pairing that stimulus with a new unconditioned stimulus.

Cue exposure therapy – a form of therapy in which individuals are repeatedly exposed to a conditioned stimulus without presenting the unconditioned stimulus. Eventually, individuals will learn that the conditioned stimulus no longer predicts the onset of the unconditioned stimulus (also known as extinction training).

Goal-tracking – a behavioral phenotype characterized by enhanced attention to a reinforcer instead of reinforcer-paired stimuli.

Higher-order (second-order) conditioning – a form of Pavlovian conditioning in which an already established conditioned stimulus can be paired with a new neutral stimulus, making the new neutral stimulus a second conditioned stimulus; note that the second conditioned stimulus is never paired with the unconditioned stimulus.

Incentive sensitization theory of addiction – emphasizes that continuous exposure to drug-paired cues causes the neural circuitry underlying incentive salience to become hypersensitive, causing these cues to elicit intense drug cravings.

Pavlovian (classical) conditioning – a form of learning in which an organism learns to associate two stimuli with one another.

Pavlovian conditioned approach (PCA) – an experimental procedure used to measure a type of behavioral response that occurs following the presentation of a conditioned stimulus that predicts the onset of an unconditioned stimulus.

Pavlovian-to-instrumental transfer (PIT) – the phenomenon in which conditioned stimuli alter operant conditioning.

Sensory preconditioning – a form of Pavlovian conditioning in which a neutral stimulus that has never been paired with an unconditioned stimulus can elicit a conditioned response; this occurs because the neutral stimulus was previously paired with a second neutral stimulus that was eventually paired with the unconditioned stimulus.

Sign-tracking – a behavioral phenotype characterized by excessive interaction with stimuli that become paired with a reinforcer.

Stimulus substitution theory of conditioning – Ivan Pavlov's theory of conditioning states that conditioned stimuli take on the same properties as unconditioned stimuli, thus eliciting conditioned responses that are identical to unconditioned responses.

Unconditioned response (UR) – behavior that results from the presentation of a stimulus that naturally elicits that behavior (e.g., salivation in response to food presentation).

Unconditioned stimulus (US) – a type of stimulus that naturally elicits a response from an organism (e.g., food).

Virtual reality exposure therapy (VRET) – a form of therapy in which individuals are exposed to problematic stimuli using a virtual reality headset; this allows the user to experience these stimuli without having to directly interact with them.

Supplementary data related to this chapter can be found online at https://educate.elsevier.com/9780323905787.

References

1. Chapel Hill Medical Detox. *Interview with a Heroin Addict*; May 27, 2020. https://www.chapelhilldetox.com/interview-with-a-heroin-addict/.

2. Pavlov IP. *Conditioned Reflexes: an Investigation of the Physiological Activity of the Cerebral Cortex*. Oxford University Press; 1927.
3. Brogden WJ. Sensory pre-conditioning. *J Exp Psychol*. 1939;25(4):323–332. https://doi.org/10.1037/h0058944.
4. Finch G, Culler E. Higher order conditioning with constant motivation. *Am J Psychol*. 1934;46(4):596–602.
5. Newlin DB. Conditioned compensatory response to alcohol placebo in humans. *Psychopharmacology*. 1986;88(2):247–251. https://doi.org/10.1007/BF00652249.
6. Hearst E, Jenkins H. *Sign-tracking: the Stimulus-Reinforcer Relation and Directed Action*. Austin: Monograph of the Psychonomic Society; 1974.
7. Flagel SB, Akil H, Robinson TE. Individual differences in the attribution of incentive salience to reward-related cues: implications for addiction. *Neuropharmacology*. 2009;56(Supplement 1):139–148. https://doi.org/10.1016/j.neuropharm.2008.06.027.
8. Uslaner JM, Acerbo MJ, Jones SA, Robinson TE. The attribution of incentive salience to a stimulus that signals an intravenous injection of cocaine. *Behav Brain Res*. 2006;169(2):320–324. https://doi.org/10.1016/j.bbr.2006.02.001.
9. Cunningham CL, Patel P. Rapid induction of Pavlovian approach to an ethanol-paired visual cue in mice. *Psychopharmacology*. 2007;192(2):231–241. https://doi.org/10.1007/s00213-007-0704-4.
10. Krank MD. Pavlovian conditioning with ethanol: sign-tracking (autoshaping), conditioned incentive, and ethanol self-administration. *Alcohol Clin Exp Res*. 2003;27(10):1592–1598. https://doi.org/10.1097/01.ALC.0000092060.09228.DE.
11. Yager LM, Robinson TE. Individual variation in the motivational properties of a nicotine cue: sign-trackers vs. goal-trackers. *Psychopharmacology*. 2015;232(17):3149–3160. https://doi.org/10.1007/s00213-015-3962-6.
12. Yager LM, Pitchers KK, Flagel SB, Robinson TE. Individual variation in the motivational and neurobiological effects of an opioid cue. *Neuropsychopharmacology*. 2015;40(5):1269–1277. https://doi.org/10.1038/npp.2014.314.
13. Tomie A, Grimes KL, Pohorecky LA. Behavioral characteristics and neurobiological substrates shared by Pavlovian sign-tracking and drug abuse. *Brain Res Rev*. 2008;58(1):121–135. https://doi.org/10.1016/j.brainresrev.2007.12.003.
14. Beckmann JS, Marusich JA, Gipson CD, Bardo MT. Novelty seeking, incentive salience and acquisition of cocaine self-administration in the rat. *Behav Brain Res*. 2011;216(1):159–165. https://doi.org/10.1016/j.bbr.2010.07.022.
15. Kawa AB, Bentzley BS, Robinson TE. Less is more: prolonged intermittent access cocaine self-administration produces incentive-sensitization and addiction-like behavior. *Psychopharmacology*. 2016;233(19–20):3587–3602. https://doi.org/10.1007/s00213-016-4393-8.
16. Tunstall BJ, Kearns DN. Sign-tracking predicts increased choice of cocaine over food in rats. *Behav Brain Res*. 2015;281:222–228. https://doi.org/10.1016/j.bbr.2014.12.034.
17. Everett NA, Carey HA, Cornish JL, Baracz SJ. Sign tracking predicts cue-induced but not drug-primed reinstatement to methamphetamine seeking in rats: effects of oxytocin treatment. *J Psychopharmacol*. 2020;34(11):1271–1279. https://doi.org/10.1177/0269881120954052.
18. Versaggi CL, King CP, Meyer PJ. The tendency to sign-track predicts cue-induced reinstatement during nicotine self-administration, and is enhanced by nicotine but not ethanol. *Psychopharmacology*. 2016;233(15–16):2985–x2997. https://doi.org/10.1007/s00213-016-4341-7.
19. Pohořalá V, Enkel T, Bartsch D, Spanagel R, Bernardi RE. Sign- and goal-tracking score does not correlate with addiction-like behavior following prolonged cocaine self-administration. *Psychopharmacology*. 2021;238(8):2335–2346. https://doi.org/10.1007/s00213-021-05858-z.
20. Overby PF, Daniels CW, Del Franco A, et al. Effects of nicotine self-administration on incentive salience in male Sprague Dawley rats. *Psychopharmacology*. 2018;235(4):1121–1130. https://doi.org/10.1007/s00213-018-4829-4.
21. Saddoris MP, Wang X, Sugam JA, Carelli RM. Cocaine self-administration experience induces pathological phasic accumbens dopamine signals and abnormal incentive behaviors in drug-abstinent rats. *J Neurosci*. 2016;36(1):235–250. https://doi.org/10.1523/JNEUROSCI.3468-15.2016.
22. Stringfield SJ, Madayag AC, Boettiger CA, Robinson DL. Sex differences in nicotine-enhanced Pavlovian conditioned approach in rats. *Biol Sex Differ*. 2019;10(1):37. https://doi.org/10.1186/s13293-019-0244-8.

23. Madayag AC, Stringfield SJ, Reissner KJ, Boettiger CA, Robinson DL. Sex and adolescent ethanol exposure influence Pavlovian conditioned approach. *Alcohol Clin Exp Res*. 2017;41(4):846–856. https://doi.org/10.1111/acer.13354.
24. McClory AJ, Spear LP. Effects of ethanol exposure during adolescence or in adulthood on Pavlovian conditioned approach in Sprague-Dawley rats. *Alcohol*. 2014;48(8):755–763. https://doi.org/10.1016/j.alcohol.2014.05.006.
25. Fiorenza AM, Shnitko TA, Sullivan KM, et al. Ethanol exposure history and alcoholic reward differentially alter dopamine release in the nucleus accumbens to a reward-predictive cue. *Alcohol Clin Exp Res*. 2018;42(6):1051–1061. https://doi.org/10.1111/acer.13636.
26. Walitzer KS, Sher KJ. Alcohol cue reactivity and ad lib drinking in young men at risk for alcoholism. *Addict Behav*. 1990;15(1):29–46. https://doi.org/10.1016/0306-4603(90)90005-i.
27. Witteman J, Post H, Tarvainen M, et al. Cue reactivity and its relation to craving and relapse in alcohol dependence: a combined laboratory and field study. *Psychopharmacology*. 2015;232(20):3685–3696. https://doi.org/10.1007/s00213-015-4027-6.
28. Payne TJ, Smith PO, Sturges LV, Holleran SA. Reactivity to smoking cues: mediating roles of nicotine dependence and duration of deprivation. *Addict Behav*. 1996;21(2):139–154. https://doi.org/10.1016/0306-4603(95)00043-7.
29. Robbins SJ, Ehrman RN, Childress AR, O'Brien CP. Using cue reactivity to screen medications for cocaine abuse: a test of amantadine hydrochloride. *Addict Behav*. 1992;17(5):491–499. https://doi.org/10.1016/0306-4603(92)90009-k.
30. Franken IH, de Haan HA, van der Meer CW, Haffmans PM, Hendriks VM. Cue reactivity and effects of cue exposure in abstinent posttreatment drug users. *J Subst Abuse Treat*. 1999;16(1):81–85. https://doi.org/10.1016/s0740-5472(98)00004-x.
31. Li Q, Li W, Wang H, et al. Predicting subsequent relapse by drug-related cue-induced brain activation in heroin addiction: an event-related functional magnetic resonance imaging study. *Addiction Biol*. 2015;20(5):968–978. https://doi.org/10.1111/adb.12182.
32. Gray KM, LaRowe SD, Upadhyaya P. Cue reactivity in young marijuana smokers: a preliminary investigation. *Psychol Addict Behav*. 2008;22(4):582–586. https://doi.org/10.1037/a0012985.
33. Fleming KA, Cofresí RU, Bartholow BD. Transfer of incentive salience from a first-order alcohol cue to a novel second-order alcohol cue among individuals at risk for alcohol use disorder: electrophysiological evidence. *Addiction*. 2021;116(7):1734–1746. https://doi.org/10.1111/add.15380.
34. Kang OS, Chang DS, Jahng GH, et al. Individual differences in smoking-related cue reactivity in smokers: an eye-tracking and fMRI study. *Prog Neuro Psychopharmacol Biol Psychiatr*. 2012;38(2):285–293. https://doi.org/10.1016/j.pnpbp.2012.04.013.
35. Soleymani A, Ivanov Y, Mathot S, de Jong PJ. Free-viewing multi-stimulus eye tracking task to index attention bias for alcohol versus soda cues: satisfactory reliability and criterion validity. *Addict Behav*. 2020;100:106117. https://doi.org/10.1016/j.addbeh.2019.106117.
36. McAteer AM, Hanna D, Curran D. Age-related differences in alcohol attention bias: a cross-sectional study. *Psychopharmacology*. 2018;235(8):2387–2393. https://doi.org/10.1007/s00213-018-4935-3.
37. McGivern C, Curran D, Hanna D. Alcohol attention bias in 14-16 year old adolescents: an eye tracking study. *Psychopharmacology*. 2021;238(3):655–664. https://doi.org/10.1007/s00213-020-05714-6.
38. Monem RG, Fillmore MT. Measuring heightened attention to alcohol in a naturalistic setting: a validation study. *Exp Clin Psychopharmacol*. 2017;25(6):496–502. https://doi.org/10.1037/pha0000157.
39. Zhao Q, Li H, Hu B, et al. Neural correlates of drug-related attentional bias in heroin dependence. *Front Hum Neurosci*. 2018;11:646. https://doi.org/10.3389/fnhum.2017.00646.
40. Murphy A, Taylor E, Elliott R. The detrimental effects of emotional process dysregulation on decision-making in substance dependence. *Front Integr Neurosci*. 2012;6:101. https://doi.org/10.3389/fnint.2012.00101.
41. Miller MA, Fillmore MT. The effect of image complexity on attentional bias towards alcohol-related images in adult drinkers. *Addiction*. 2010;105(5):883–890. https://doi.org/10.1111/j.1360-0443.2009.02860.x.
42. Townshend JM, Duka T. Attentional bias associated with alcohol cues: differences between heavy and occasional social drinkers. *Psychopharmacology*. 2001;157(1):67–74. https://doi.org/10.1007/s002130100764.

43. Ehrman RN, Robbins SJ, Bromwell MA, Lankford ME, Monterosso JR, O'Brien CP. Comparing attentional bias to smoking cues in current smokers, former smokers, and non-smokers using a dot-probe task. *Drug Alcohol Depend*. 2002;67(2):185–191. https://doi.org/10.1016/s0376-8716(02)00065-0.
44. Hogarth LC, Mogg K, Bradley BP, Duka T, Dickinson A. Attentional orienting towards smoking-related stimuli. *Behav Pharmacol*. 2003;14(2):153–160. https://doi.org/10.1097/00008877-200303000-00007.
45. Constantinou N, Morgan CJ, Battistella S, O'Ryan D, Davis P, Curran HV. Attentional bias, inhibitory control and acute stress in current and former opiate addicts. *Drug Alcohol Depend*. 2010;109(1–3):220–225. https://doi.org/10.1016/j.drugalcdep.2010.01.012.
46. Garland EL, Froeliger BE, Passik SD, Howard MO. Attentional bias for prescription opioid cues among opioid dependent chronic pain patients. *J Behav Med*. 2013;36(6):611–620. https://doi.org/10.1007/s10865-012-9455-8.
47. Garland EL, Howard MO. Opioid attentional bias and cue-elicited craving predict future risk of prescription opioid misuse among chronic pain patients. *Drug Alcohol Depend*. 2014;144:283–287. https://doi.org/10.1016/j.drugalcdep.2014.09.014.
48. Morgan CJ, Rees H, Curran HV. Attentional bias to incentive stimuli in frequent ketamine users. *Psychol Med*. 2008;38(9):1331–1340. https://doi.org/10.1017/S0033291707002450.
49. Marks KR, Pike E, Stoops WW, Rush CR. The magnitude of drug attentional bias is specific to substance use disorder. *Psychol Addict Behav*. 2015;29(3):690–695. https://doi.org/10.1037/adb0000084.
50. Lochbuehler K, Wileyto EP, Tang KZ, Mercincavage M, Cappella JN, Strasser AA. Do current and former cigarette smokers have an attentional bias for e-cigarette cues? *J Psychopharmacol*. 2018;32(3):316–323. https://doi.org/10.1177/0269881117728418.
51. MacLean RR, Sofuoglu M, Waters AJ. Naturalistic measurement of dual cue attentional bias in moderate to heavy-drinking smokers: a preliminary investigation. *Drug Alcohol Depend*. 2020;209:107892. https://doi.org/10.1016/j.drugalcdep.2020.107892.
52. Field M, Mogg K, Mann B, Bennett GA, Bradley BP. Attentional biases in abstinent alcoholics and their association with craving. *Psychol Addict Behav*. 2013;27(1):71–80. https://doi.org/10.1037/a0029626.
53. Field M, Mogg K, Bradley BP. Cognitive bias and drug craving in recreational cannabis users. *Drug Alcohol Depend*. 2004;74(1):105–111. https://doi.org/10.1016/j.drugalcdep.2003.12.005.
54. Manchery L, Yarmush DE, Luehring-Jones P, Erblich J. Attentional bias to alcohol stimuli predicts elevated cue-induced craving in young adult social drinkers. *Addict Behav*. 2017;70:14–17. https://doi.org/10.1016/j.addbeh.2017.01.035.
55. Begh R, Smith M, Ferguson SG, Shiffman S, Munafò MR, Aveyard P. Association between smoking-related attentional bias and craving measured in the clinic and in the natural environment. *Psychol Addict Behav*. 2016;30(8):868–875. https://doi.org/10.1037/adb0000231.
56. Díaz-Batanero C, Domínguez-Salas S, Moraleda E, Fernández-Calderón F, Lozano OM. Attentional bias toward alcohol stimuli as a predictor of treatment retention in cocaine dependence and alcohol user patients. *Drug Alcohol Depend*. 2018;182:40–47. https://doi.org/10.1016/j.drugalcdep.2017.10.005.
57. Spruyt A, De Houwer J, Tibboel H, et al. On the predictive validity of automatically activated approach/avoidance tendencies in abstaining alcohol-dependent patients. *Drug Alcohol Depend*. 2013;127(1–3):81–86. https://doi.org/10.1016/j.drugalcdep.2012.06.019.
58. Szasz PL, Szentagotai A, Hofmann SG. Effects of emotion regulation strategies on smoking craving, attentional bias, and task persistence. *Behav Res Ther*. 2012;50(5):333–340. https://doi.org/10.1016/j.brat.2012.02.010.
59. Cox WM, Fadardi JS, Pothos EM. The addiction-stroop test: theoretical considerations and procedural recommendations. *Psychol Bull*. 2006;132(3):443–476. https://doi.org/10.1037/0033-2909.132.3.443.
60. Hallgren KA, McCrady BS. Interference in the alcohol Stroop task with college student binge drinkers. *J Behav Health*. 2013;2(2):112–119. https://doi.org/10.5455/jbh.20130224082728.
61. Canamar CP, London E. Acute cigarette smoking reduces latencies on a Smoking Stroop test. *Addict Behav*. 2012;37(5):627–631. https://doi.org/10.1016/j.addbeh.2012.01.017.
62. Greenaway R, Mogg K, Bradley BP. Attentional bias for smoking-related information in pregnant women: relationships with smoking experience, smoking attitudes and perceived harm to foetus. *Addict Behav*. 2012;37(9):1025–1028. https://doi.org/10.1016/j.addbeh.2012.04.005.
63. Rusted JM, Caulfield D, King L, Goode A. Moving out of the laboratory: does nicotine improve everyday attention? *Behav Pharmacol*. 2000;11(7–8):621–629. https://doi.org/10.1097/00008877-200011000-00009.

64. Cousijn J, Watson P, Koenders L, Vingerhoets WA, Goudriaan AE, Wiers RW. Cannabis dependence, cognitive control and attentional bias for cannabis words. *Addict Behav*. 2013;38(12):2825–2832. https://doi.org/10.1016/j.addbeh.2013.08.011.
65. Field M. Cannabis 'dependence' and attentional bias for cannabis-related words. *Behav Pharmacol*. 2005;16(5–6):473–476. https://doi.org/10.1097/00008877-200509000-00021.
66. Metrik J, Aston ER, Kahler CW, et al. Cue-elicited increases in incentive salience for marijuana: craving, demand, and attentional bias. *Drug Alcohol Depend*. 2016;167:82–88. https://doi.org/10.1016/j.drugalcdep.2016.07.027.
67. Gardini S, Caffarra P, Venneri A. Decreased drug-cue-induced attentional bias in individuals with treated and untreated drug dependence. *Acta Neuropsychiatr*. 2009;21(4):179–185. https://doi.org/10.1111/j.1601-5215.2009.00389.x.
68. MacLean RR, Sofuoglu M, Brede E, Robinson C, Waters AJ. Attentional bias in opioid users: a systematic review and meta-analysis. *Drug Alcohol Depend*. 2018;191:270–278. https://doi.org/10.1016/j.drugalcdep.2018.07.012.
69. Carpenter KM, Schreiber E, Church S, McDowell D. Drug Stroop performance: relationships with primary substance of use and treatment outcome in a drug-dependent outpatient sample. *Addict Behav*. 2006;31(1):174–181. https://doi.org/10.1016/j.addbeh.2005.04.012.
70. DeVito EE, Kiluk BD, Nich C, Mouratidis M, Carroll KM. Drug Stroop: mechanisms of response to computerized cognitive behavioral therapy for cocaine dependence in a randomized clinical trial. *Drug Alcohol Depend*. 2018;183:162–168. https://doi.org/10.1016/j.drugalcdep.2017.10.022.
71. Cox WM, Hogan LM, Kristian MR, Race JH. Alcohol attentional bias as a predictor of alcohol abusers' treatment outcome. *Drug Alcohol Depend*. 2002;68(3):237–243. https://doi.org/10.1016/s0376-8716(02)00219-3.
72. Nuijten M, Blanken P, Van den Brink W, Goudriaan AE, Hendriks VM. Impulsivity and attentional bias as predictors of modafinil treatment outcome for retention and drug use in crack-cocaine dependent patients: results of a randomised controlled trial. *J Psychopharmacol*. 2016;30(7):616–626. https://doi.org/10.1177/0269881116645268.
73. Marissen MAE, Franken IHA, Waters AJ, Blanken P, van den Brink W, Hendriks VM. Attentional bias predicts heroin relapse following treatment. *Addiction*. 2006;101(9):1306–1312. https://doi.org/10.1111/j.1360-0443.2006.01498.x.
74. Hester R, Lee N, Pennay A, Nielsen S, Ferris J. The effects of modafinil treatment on neuropsychological and attentional bias performance during 7-day inpatient withdrawal from methamphetamine dependence. *Exp Clin Psychopharmacol*. 2010;18(6):489–497. https://doi.org/10.1037/a0021791.
75. Marhe R, Waters AJ, van de Wetering BJM, Franken IHA. Implicit and explicit drug-related cognitions during detoxification treatment are associated with drug relapse: an ecological momentary assessment study. *J Consult Clin Psychol*. 2013;81(1):1–12. https://doi.org/10.1037/a0030754.
76. Cousijn J, van Benthem P, van der Schee E, Spijkerman R. Motivational and control mechanisms underlying adolescent cannabis use disorders: a prospective study. *Develop Cogn Neurosci*. 2015;16:36–45. https://doi.org/10.1016/j.dcn.2015.04.001.
77. Carroll ME, Lac ST. Autoshaping i.v. cocaine self-administration in rats: effects of nondrug alternative reinforcers on acquisition. *Psychopharmacology*. 1993;110(1–2):5–12. https://doi.org/10.1007/BF02246944.
78. Cartoni E, Balleine B, Baldassarre G. Appetitive pavlovian-instrumental transfer: a review. *Neurosci Biobehav Rev*. 2016;71:829–848. https://doi.org/10.1016/j.neubiorev.2016.09.020.
79. Alarcón DE, Delamater AR. Outcome-specific Pavlovian-to-instrumental transfer (PIT) with alcohol cues and its extinction. *Alcohol*. 2019;76:131–146. https://doi.org/10.1016/j.alcohol.2018.09.003.
80. Corbit LH, Janak PH. Ethanol-associated cues produce general pavlovian-instrumental transfer. *Alcohol Clin Exp Res*. 2007;31(5):766–774. https://doi.org/10.1111/j.1530-0277.2007.00359.x.
81. Corbit LH, Janak PH. Changes in the influence of alcohol-paired stimuli on alcohol seeking across extended training. *Front Psychiatr*. 2016;7:169. https://doi.org/10.3389/fpsyt.2016.00169.
82. Glasner SV, Overmier JB, Balleine BW. The role of Pavlovian cues in alcohol seeking in dependent and nondependent rats. *J Stud Alcohol*. 2005;66(1):53–61. https://doi.org/10.15288/jsa.2005.66.53.
83. Krank MD, O'Neill S, Squarey K, Jacob J. Goal- and signal-directed incentive: conditioned approach, seeking, and consumption established with unsweetened alcohol in rats. *Psychopharmacology*. 2008;196(3):397–405. https://doi.org/10.1007/s00213-007-0971-0.

84. Lamb RJ, Ginsburg BC, Schindler CW. Effects of an ethanol-paired CS on responding for ethanol and food: comparisons with a stimulus in a Truly-Random-Control group and to a food-paired CS on responding for food. *Alcohol*. 2016;57:15–27. https://doi.org/10.1016/j.alcohol.2016.10.009.
85. Lamb RJ, Ginsburg BC, Greig A, Schindler CW. Effects of rat strain and method of inducing ethanol drinking on Pavlovian-Instrumental-Transfer with ethanol-paired conditioned stimuli. *Alcohol*. 2019;79:47–57. https://doi.org/10.1016/j.alcohol.2019.01.003.
86. Lamb RJ, Schindler CW, Ginsburg BC. Ethanol-paired stimuli can increase reinforced ethanol responding. *Alcohol*. 2020;85:27–34. https://doi.org/10.1016/j.alcohol.2019.10.007.
87. Milton AL, Schramm MJ, Wawrzynski JR, et al. Antagonism at NMDA receptors, but not β-adrenergic receptors, disrupts the reconsolidation of pavlovian conditioned approach and instrumental transfer for ethanol-associated conditioned stimuli. *Psychopharmacology*. 2012;219(3):751–761. https://doi.org/10.1007/s00213-011-2399-9.
88. Kruzich PJ, Congleton KM, See RE. Conditioned reinstatement of drug-seeking behavior with a discrete compound stimulus classically conditioned with intravenous cocaine. *Behav Neurosci*. 2001;115(5):1086–1092. https://doi.org/10.1037//0735-7044.115.5.1086.
89. LeBlanc KH, Ostlund SB, Maidment NT. Pavlovian-to-instrumental transfer in cocaine seeking rats. *Behav Neurosci*. 2012;126(5):681–689. https://doi.org/10.1037/a0029534.
90. Takahashi TT, Vengeliene V, Enkel T, Reithofer S, Spanagel R. Pavlovian to instrumental transfer responses do not correlate with addiction-like behavior in rats. *Front Behav Neurosci*. 2019;13:129. https://doi.org/10.3389/fnbeh.2019.00129.
91. Siegel S. Conditioning of insulin-induced glycemia. *J Comp Physiol Psychol*. 1972;78(2):233–241. https://doi.org/10.1037/h0032180.
92. Kimble GA. *Hilgard and Marquis' Conditioning and Learning*. 2nd ed. Appleton-Century-Crofts; 1961.
93. Siegel S, Hinson RE, Krank MD. The role of predrug signals in morphine analgesic tolerance: support for a Pavlovian conditioning model of tolerance. *J Exp Psychol Anim Behav Process*. 1978;4(2):188–196. https://doi.org/10.1037/0097-7403.4.2.188.
94. Ehrman R, Ternes J, O'Brien CP, McLellan AT. Conditioned tolerance in human opiate addicts. *Psychopharmacology*. 1992;108(1–2):218–224. https://doi.org/10.1007/BF02245311.
95. Krank MD, Perkins WL. Conditioned withdrawal signs elicited by contextual cues for morphine administration. *Psychobiology*. 1993;21(2):113–119.
96. Robinson TE, Berridge KC. The neural basis of drug craving: an incentive-sensitization theory of addiction. *Brain Res Rev*. 1993;18(3):247–291. https://doi.org/10.1016/0165-0173(93)90013-p.
97. Robinson MJ, Fischer AM, Ahuja A, Lesser EN, Maniates H. Roles of "wanting" and "liking" in motivating behavior: Gambling, food, and drug addictions. *Curr Top Behav Neurosci*. 2016;27:105–136. https://doi.org/10.1007/7854_2015_387.
98. Peciña S, Berridge KC. Hedonic hot spot in nucleus accumbens shell: where do mu-opioids cause increased hedonic impact of sweetness? *J Neurosci*. 2005;25(50):11777–11786. https://doi.org/10.1523/JNEUROSCI.2329-05.2005.
99. Smith KS, Berridge KC. The ventral pallidum and hedonic reward: neurochemical maps of sucrose "liking" and food intake. *J Neurosci*. 2005;25(38):8637–8649. https://doi.org/10.1523/JNEUROSCI.1902-05.2005.
100. Kringelbach ML, Berridge KC. Neuroscience of reward, motivation, and drive. In: Kim S-I, Reeve J, Bong M, eds. *Recent Developments in Neuroscience Research on Human Motivation (Advances in Motivation and Achievement)*. Emerald Publishing Limited; 2016:23–35. https://doi.org/10.1108/S0749-742320160000019020.
101. Mahler SV, Smith KS, Berridge KC. Endocannabinoid hedonic hotspot for sensory pleasure: nandamide in nucleus accumbens shell enhances 'liking' of a sweet reward. *Neuropsychopharmacology*. 2007;32(11):2267–2278. https://doi.org/10.1038/sj.npp.1301376.
102. Berridge KC, Robinson TE. Liking, wanting, and the incentive-sensitization theory of addiction. *Am Psychol*. 2016;71(8):670–679. https://doi.org/10.1037/amp0000059.
103. Parkinson JA, Dalley JW, Cardinal RN, et al. Nucleus accumbens dopamine depletion impairs both acquisition and performance of appetitive Pavlovian approach behaviour: implications for mesoaccumbens dopamine function. *Behav Brain Res*. 2002;137(1–2):149–163. https://doi.org/10.1016/s0166-4328(02)00291-7.

104. Saddoris MP, Carelli RM. Cocaine self-administration abolishes associative neural encoding in the nucleus accumbens necessary for higher-order learning. *Biol Psychiatr*. 2014;75(2):156–164. https://doi.org/10.1016/j.biopsych.2013.07.037.
105. Bardo MT, Bevins RA. Conditioned place preference: what does it add to our preclinical understanding of drug reward? *Psychopharmacology*. 2000;153:31–43. https://doi.org/10.1007/s002130000569.
106. Lew G, Parker LA. Pentobarbital-induced place aversion learning. *Anim Learn Behav*. 1998;26:219–224. https://doi.org/10.3758/BF03199214.
107. Bossert JM, Franklin KB. Pentobarbital-induced place preference in rats is blocked by GABA, dopamine, and opioid antagonists. *Psychopharmacology*. 2001;157(2):115–122. https://doi.org/10.1007/s002130100772.
108. Acquas E, Carboni E, Leone P, Di Chiara G. SCH 23390 blocks drug-conditioned place-preference and place-aversion: anhedonia (lack of reward) or apathy (lack of motivation) after dopamine-receptor blockade? *Psychopharmacology*. 1989;99(2):151–155. https://doi.org/10.1007/BF00442800.
109. Noda Y, Nabeshima T. Neuronal mechanisms of phencyclidine-induced place aversion and preference in the conditioned place preference task. *Methods Find Exp Clin Pharmacol*. 1998;20(7):607–611. https://doi.org/10.1358/mf.1998.20.7.485726.
110. Abiero A, Botanas CJ, Custodio RJ, et al. 4-Meo-PCP and 3-MeO-PCMo, new dissociative drugs, produce rewarding and reinforcing effects through activation of mesolimbic dopamine pathway and alteration of accumbal CREB, deltaFosB, and BDNF levels. *Psychopharmacology*. 2020;237(3):757–772. https://doi.org/10.1007/s00213-019-05412-y.
111. Ryu IS, Kim OH, Lee YE, et al. The abuse potential of novel synthetic phencyclidine derivative 1-(1-(4-fluorophenyl)cyclohexyl)piperidine (4′-F-PCP) in rodents. *Int J Mol Sci*. 2020;21(13):4631. https://doi.org/10.3390/ijms21134631.
112. Kitaichi K, Noda Y, Hasegawa T, Furukawa H, Nabeshima T. Acute phencyclidine induces aversion, but repeated phencyclidine induces preference in the place conditioning test in rats. *Eur J Pharmacol*. 1996;318(1):7–9. https://doi.org/10.1016/s0014-2999(96)00875-8.
113. Miyamoto Y, Noda Y, Komori Y, Sugihara H, Furukawa H, Nabeshima T. Involvement of nitric oxide in phencyclidine-induced place aversion and preference in mice. *Behav Brain Res*. 2000;116(2):187–196. https://doi.org/10.1016/s0166-4328(00)00274-6.
114. Lett BT. Repeated exposures intensify rather than diminish the rewarding effects of amphetamine, morphine, and cocaine. *Psychopharmacology*. 1989;98(3):357–362. https://doi.org/10.1007/BF00451687.
115. Shoaib M, Stolerman IP, Kumar RC. Nicotine-induced place preferences following prior nicotine exposure in rats. *Psychopharmacology*. 1994;113(3–4):445–452. https://doi.org/10.1007/BF02245221.
116. Randich A, LoLordo VM. Associative and nonassociative theories of the UCS preexposure phenomenon: implications for Pavlovian conditioning. *Psychol Bull*. 1979;86(3):523–548. https://doi.org/10.1037/0033-2909.86.3.523.
117. Bardo MT, Horton DB, Yates JR. Conditioned place preference as a preclinical model for screening pharmacotherapies for drug abuse. In: Markgraf CG, Hudzik TJ, Comptom DR, eds. *Nonclinical Assessment of Abuse Potential for New Pharmacotherapies*. London: Academic Press; 2015:151–196.
118. Marglin SH, Milano WC, Mattie ME, Reid LD. PCP and conditioned place preferences. *Pharmacol, Biochem Behav*. 1989;33(2):281–383. https://doi.org/10.1016/0091-3057(89)90500-5.
119. Carr GD, Fibiger HC, Phillips AG. Conditioned place preference as a measure of drug reward. In: Liebman JM, Cooper SJ, eds. *Neuropharmacological Basis of Reward*. Oxford; 1989:264–319.
120. Cunningham CL, Ferree NK, Howard MA. Apparatus bias and place conditioning with ethanol in mice. *Psychopharmacology*. 2003;170(4):409–422. https://doi.org/10.1007/s00213-003-1559-y.
121. Rodríguez-Arias M, Valverde O, Daza-Losada M, Blanco-Gandía MC, Aguilar MA, Miñarro J. Assessment of the abuse potential of MDMA in the conditioned place preference paradigm: role of CB1 receptors. *Prog Neuro Psychopharmacol Biol Psychiatr*. 2013;47:77–84. https://doi.org/10.1016/j.pnpbp.2013.07.013.
122. Vidal-Infer A, Roger-Sanchez C, Daza-Losada M, Aguilar MA, Minarro J, Rodriguez-Arias M. Role of the dopaminergic system in the acquisition, expression and reinstatement of MDMA-induced conditioned place preference in adolescent mice. *PLoS One*. 2012;7(8):e43107. https://doi.org/10.1371/journal.pone.0043107.
123. Yates JR, Campbell HL, Hawley LL, Horchar MJ, Kappesser JL, Wright MR. Effects of the GluN2B-selective antagonist Ro 63-1908 on acquisition and expression, of methamphetamine conditioned place preference in

male and female rats. *Drug Alcohol Depend*. 2021;225:108785. https://doi.org/10.1016/j.drugalcdep.2021.108785.
124. Childs E, de Wit H. Amphetamine-induced place preference in humans. *Biol Psychiatr*. 2009;65(10):900–904. https://doi.org/10.1016/j.biopsych.2008.11.016.
125. Childs E, de Wit H. Contextual conditioning enhances the psychostimulant and incentive properties of d-amphetamine in humans. *Addiction Biol*. 2013;18(6):985–992. https://doi.org/10.1111/j.1369-1600.2011.00416.x.
126. Childs E, de Wit H. Alcohol-induced place conditioning in moderate social drinkers. *Addiction*. 2016;111(12):2157–2165. https://doi.org/10.1111/add.13540.
127. Ma Y-Y, Guo C-Y, Yu P, Lee DY-W, Han J-S, Cui C-L. The role of NR2B containing NMDA receptor in place preference conditioned with morphine and natural reinforcers in rats. *Exp Neurol*. 2006;200:343–355. https://doi.org/10.1016/j.expneurol.2006.02.117.
128. Horchar MJ, Kappesser JL, Broderick MR, Wright MR, Yates JR. Effects of NMDA receptor antagonists on behavioral economic indices of cocaine self-administration. *Drug Alcohol Depend*. 2022;233:109348. https://doi.org/10.1016/j.drugalcdep.2022.109348.
129. Smith MA, Schmidt KT, Sharp JL, et al. Lack of evidence for positive reinforcing and prosocial effects of MDMA in pair-housed male and female rats. *Eur J Pharmacol*. 2021;913:174646. https://doi.org/10.1016/j.ejphar.2021.174646.
130. Piazza PV, Deroche-Gamonent V, Rouge-Pont F, Le Moal M. Vertical shifts in self-administration dose-response functions predict a drug-vulnerable phenotype predisposed to addiction. *J Neurosci*. 2000;20(11):4226–4232. https://doi.org/10.1523/JNEUROSCI.20-11-04226.2000.
131. Childress AR, McLellan AT, O'Brien CP. Abstinent opiate abusers exhibit conditioned craving, conditioned withdrawal and reductions in both through extinction. *Br J Addiction*. 1986;81(5):655–660. https://doi.org/10.1111/j.1360-0443.1986.tb00385.x.
132. Drummond DC, Glautier S. A controlled trial of cue exposure treatment in alcohol dependence. *J Consult Clin Psychol*. 1994;62(4):809–817. https://doi.org/10.1037//0022-006x.62.4.809.
133. Unrod M, Drobes DJ, Stasiewicz PR, et al. Decline in cue-provoked craving during cue exposure therapy for smoking cessation. *Nicotine Tob Res*. 2014;16(3):306–315. https://doi.org/10.1093/ntr/ntt145.
134. Rosenthal MZ, Kutlu MG. Translation of associative learning models into extinction reminders delivered via mobile phones during cue exposure interventions for substance use. *Psychol Addict Behav*. 2014;28(3):863–871. https://doi.org/10.1037/a0037082.
135. Maples-Keller JL, Bunnell BE, Kim SJ, Rothbaum BO. The use of virtual reality technology in the treatment of anxiety and other psychiatric disorders. *Harv Rev Psychiatr*. 2017;25(3):103–113. https://doi.org/10.1097/HRP.0000000000000138.
136. Hernández-Serrano O, Ghită A, Figueras-Puigderrajols N, et al. Predictors of changes in alcohol craving levels during virtual reality cue exposure treatment among patients with alcohol use disorder. *J Clin Med*. 2020;9(9):3018. https://doi.org/10.3390/jcm9093018.
137. Ghită A, Gutiérrez-Maldonado J. Applications of virtual reality in individuals with alcohol misuse: a systematic review. *Addict Behav*. 2018;81:1–11. https://doi.org/10.1016/j.addbeh.2018.01.036.
138. de Bruijn G-J, de Vries J, Bolman C, Wiers R. (No) escape from reality? Cigarette craving in virtual smoking environments. *J Behav Med*. 2021;44(1):138–143. https://doi.org/10.1007/s10865-020-00170-1.
139. Vinci C, Brandon KO, Kleinjan M, Brandon TH. The clinical potential of augmented reality. *Clin Psychol Sci Pract*. 2020;27(3):e12357. https://doi.org/10.1111/cpsp.12357.
140. Borovanska Z, Poyade M, Rea PM, Buksh ID. Engaging with children using augmented reality on clothing to prevent them from smoking. In: Rea PM, ed. *Advances in Experimental Medicine and Biology*Vol. 1262.
141. Pew Research Center. *Mobile Fact Sheet*; 2021. Accessed on May 29, 2021 https://www.pewresearch.org/internet/fact-sheet/mobile/.
142. Copemann CD. Drug addiction: II. An aversive counterconditioning technique for treatment. *Psychol Rep*. 1976;38(3 Pt 2):1271–1281. https://doi.org/10.2466/pr0.1976.38.3c.1271.
143. Jackson TR, Smith JW. A comparison of two aversion treatment methods for alcoholism. *J Stud Alcohol*. 1978;39(1):187–191. https://doi.org/10.15288/jsa.1978.39.187.
144. Smith JW. Long term outcome of clients treated in a commercial stop smoking program. *J Subst Abuse Treat*. 1988;5(1):33–36. https://doi.org/10.1016/0740-5472(88)90036-0.

145. Smith JW, Schmeling G, Knowles PL. A marijuana smoking cessation clinical trial utilizing THC-free marijuana, aversion therapy, and self-management counseling. *J Subst Abuse Treat*. 1988;5(2):89–98. https://doi.org/10.1016/0740-5472(88)90018-9.
146. Frawley PJ, Smith JW. Chemical aversion therapy in the treatment of cocaine dependence as part of a multimodal treatment program: treatment outcome. *J Subst Abuse Treat*. 1990;7(1):21–29. https://doi.org/10.1016/0740-5472(90)90033-m.
147. Wang YG, Liu MH, Shen ZH. A virtual reality counterconditioning procedure to reduce methamphetamine cue-induced craving. *J Psychiatr Res*. 2019;116:88–94. https://doi.org/10.1016/j.jpsychires.2019.06.007.
148. Mondino M, Lenglos C, Cinti A, Renauld E, Fecteau S. Eye tracking of smoking-related stimuli in tobacco use disorder: a proof-of-concept study combining attention bias modification with alpha-transcranial alternating current stimulation. *Drug Alcohol Depend*. 2020;214:108152. https://doi.org/10.1016/j.drugalcdep.2020.108152.
149. Passamonti L, Luijten M, Ziauddeen H, et al. Atomoxetine effects on attentional bias to drug-related cues in cocaine dependent individuals. *Psychopharmacology*. 2017;234(15):2289–2297. https://doi.org/10.1007/s00213-017-4643-4.
150. Fadardi JS, Cox WM. Reversing the sequence: reducing alcohol consumption by overcoming alcohol attentional bias. *Drug Alcohol Depend*. 2009;101(3):137–145. https://doi.org/10.1016/j.drugalcdep.2008.11.015.
151. Ziaee SS, Fadardi JS, Cox WM, Yazdi SA. Effects of attention control training on drug abusers' attentional bias and treatment outcome. *J Consult Clin Psychol*. 2016;84(10):861–873. https://doi.org/10.1037/a0040290.