ENCYCLOPEDIA OF

DRUGS, ALCOHOL & ADDICTIVE BEHAVIOR

THIRD EDITION

Volume 3

M-R

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EDITORS IN CHIEF

MACMILLAN REFERENCE USA

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XINGGUANG LUO

LEARNING

Learning factors in substance abuse have received much attention. Two basic learning mechanisms are involved when an organism repeatedly selfadministers a psychoactive substance. First, classical conditioning is engaged when environmental stimuli are associated with, and come to signal, the upcoming effects of the drug. Second, operant conditioning occurs as an organism learns that particular behaviors lead either to a drug reward or to punishment. The effects of these two processes presumably interact and influence repeated drug use and/or relapse to drug use following a period of abstinence.

Classical conditioning occurs when an organism makes an association between two events in the external environment. A typical classical conditioning situation involves learning that a biologically neutral event (the conditioned stimulus [CS], such as a familiar drug dealer) signals the upcoming occurrence of a biologically relevant event (the unconditioned stimulus [US], such as the effects of a drug). As a result of this signaling, the CS produces conditioned responses (CRs), which are related to the US and unconditioned responses (URs). A number of investigators have reported that CRs are elicited in humans by environmental events that signal upcoming drug use or withdrawal (Berger et al., 1996; Payne, McClernon, & Dobbins, 2007; Bordnick et al., 2008). Consistently, CRs to drug-related stimuli play a major role in maintaining drug-taking behavior (Sinha & Li, 2007).

Operant conditioning involves learning about contingencies between behaviors and their outcomes. A typical operant conditioning situation sets up contingencies between three different events: a response (e.g., inhalation of the drug), the outcome of that response (e.g., the reinforcing drug effects), and the stimulus situation in which that responseoutcome relationship is established (i.e., the discriminative stimulus). Drugs of abuse function as potent reinforcers for human substance abusers, as evidenced by the fact that a variety of behaviors are directed toward their attainment and use. Consequently, understanding how operant behaviors directed toward drug reinforcers are acquired is critical to understanding human substance abuse and dependence.

Classical and operant conditioning may both be active during drug seeking and self-administration. Events that have consistently signaled drug use may eventually come to evoke CRs in the form of

craving—urges to use the drug. In this way, signals of drug use may motivate the drug user to initiate drug-seeking behavior. For example, walking past someone smoking a cigarette might act as a CS for a heavy cigarette smoker, evoking the craving for nicotine. This craving might then increase the likelihood of purchasing and smoking a cigarette (the reward).

OPERANT CONDITIONING WITH DRUG REINFORCERS

A large body of data shows that many drugs abused by humans act as reinforcers for animals in operant-conditioning situations. In typical studies on the reinforcing properties of drugs, rats or monkeys are fitted with venous catheters through which a drug can be administered directly. The animal's response, such as pushing a lever, results in infusions of the drug.

These studies have found that many drugs abused by humans—including cocaine, morphine, heroin, amphetamines, pentobarbital, and alcohol—establish and maintain operant behaviors in animals. Other drugs that are typically not abused by humans—such as aspirin, antidepressants, hallucinogens, and opioid mixed agonists/antagonists—do not cause a response (Gold & Balster, 1991; Hoffmeister & Wuttke, 1975).

The degree to which a drug reinforces behavior depends more on the schedule of reinforcement than on the drug itself. A schedule of reinforcement refers to how often a drug is given. For example, ratio schedules require a certain number of responses before a reinforcer is given. Interval schedules are set up so that reinforcers occur only after a certain amount of time has passed. Reinforcers in ratio schedules depend solely on the number of responses made; therefore, these schedules typically result in higher response rates than interval schedules in which responses made too early are ineffective. Because reinforcement schedules largely determine the response rate in a given situation, the abuse potential of the various drugs cannot be reliably assessed by comparing how quickly participants respond for each substance.

One technique used to compare the reinforcing properties of various substances involves calculating a *breaking point* under a progressive ratio schedule of reinforcement. A progressive ratio schedule

requires a participant to make an increasing number of responses (the ratio) for each additional reinforcer. For a given drug dose, the breaking point is reached when the ratio becomes too high to support responding. This breaking point value then shows that drug's reinforcing properties, or reinforcing efficacy. Drugs with the highest breaking point are the most reinforcing and, hence, have the highest abuse potential. Of drugs studied using this procedure with animals, cocaine has the highest breaking point (Wang & Woolverton, 2007; Lile et al., 2005). Although there are no published laboratory data comparing the reinforcing efficacy of drugs of abuse in humans, a growing database indicates that several drugs-including cocaine and heroin—are self-administered by humans under progressive ratio schedules of reinforcement (e.g., Haney et al., 1998; Comer et al., 1999).

Choice experiments can also compare the reinforcing properties of different substances. Participants choose between two responses, each leading to different commodities (e.g., drug A vs. drug B, or a drug vs. a non-drug option). A preference for one response indicates a preference for the substance, or commodity, associated with that response. Data collected using choice procedures indicate that the choice to self-administer drugs of abuse is influenced by many factors, including dose, schedules of reinforcement, and magnitude (size or amount) of the other choice. There is a good correspondence between findings obtained for animals and for humans in choice experiments. For example, S. Stevens Negus (2003) found that monkeys self-administered less cocaine when the magnitude of the alternative reinforcer (number of food pellets) increased. Similarly, human cocaine self-administration decreased as the value of the monetary alternative increased (Higgins et al., 1994).

In sum, a body of both animal and human data now exists that documents the way drugs of abuse can act as potent reinforcers. The pattern of drug use exhibited by an individual user, however, appears to depend as much on the schedule of drug availability as on the particular properties of the chosen drug or on the presence or absence of other reinforcers. Therefore, predicting human patterns of drug taking will require a better understanding of drug availability in the real world.

CLASSICAL CONDITIONING OF DRUG-RELATED CUES

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A number of investigators have suggested that stimuli previously paired with drug use (e.g., paraphernalia) or that reliably signal drug use (e.g., meeting the drug dealer) become CSs, which elicit CRs. In turn, this relationship (CS-CR) increases the likelihood of further drug use.

Withdrawal Model. Abraham Conditioned Wikler (1973) described unpublished observations supporting this perspective, in which he administered multiple daily doses of morphine, methadone, or heroin to research participants who were previously heroin-dependant and had undergone detoxification, inducing opioid dependence. Subsequently, irregular single doses of the opioid antagonist nalorphine consistently led to withdrawal (i.e., the unpleasant symptoms experienced by drug abusers following the abrupt cessation of drug use). Wikler occasionally substituted saline for nalorphine, evoking less severe withdrawal symptoms. While this supported the role of conditioning factors in opioid withdrawal, a more systematic evaluation in humans is clearly needed.

CONDITIONED TOLERANCE MODEL

A second model using conditioning was put forth by Shepard Siegel (1975; 1979). He proposed that stimuli paired with drug use evoke conditioned compensatory responses, which oppose the direct effects of the drug. As these drug-opposite responses increase over repeated conditioning experiences in the same environment, they increasingly oppose the effects of the drug. Therefore, abusers become tolerant to drug-related effects and find that, over time, they need larger doses to achieve a given effect. Accordingly, tolerance should decrease when drugs are administered in novel environments where CSs are not present. Of course, a plethora of data demonstrates the development and maintenance of drug tolerance in stable drug-taking situations, but the mechanism(s) underlying this phenomenon are multiple and complex. Only additional research can clarify the role conditioning plays in the developing drug tolerance.

Nevertheless, according to Siegel's theory, drugrelated cues in the absence of drug-taking produce drug-opposite responses that are not canceled by the direct effects of the drug. These drug-opposite responses represent what the user experiences as

withdrawal symptoms. Viewed from this perspective, conditioning can motivate drug use in two ways. First, the withdrawal symptoms following a period of abstinence can lead to drug use aimed at relieving these unpleasant effects. Second, tolerance to the effects of a drug may motivate a user to increase his or her level of use to maintain a fixed level of desired effect.

Siegel's model has not gone unchallenged. The primary objection to it is that CSs do not always produce drug-opposite responses. Instead, CSs sometimes produce responses that resemble the direct effects of the drug (e.g., euphoria), and may motivate drug use as well. Indeed, whether CRs produced by drug-related stimuli are drug-like or drug-opposite has not been determined, and some researchers have asserted that rather than drug-opposite responses, the memory of druginduced euphoria is the major factor in continual drug use and relapse (e.g., Grant et al., 1996).

CONDITIONED INCENTIVE MODEL

Jane Stewart and colleagues (1984) have proposed that conditioned drug stimuli provide the impetus for further drug use by eliciting CRs that mimic the drug effects, which whet the appetite of the user. Such CRs are positively reinforcing and may lead to drug use by prompting the user to anticipate the pleasurable consequences of drug taking.

Some evidence for this model lies in the observation that many animals show drug-like responses to stimuli paired with drug use. This is particularly evident with stimulant drugs such as cocaine or d-amphetamine, as these drugs exhibit high abuse potential. Furthermore, researchers have found that animals that have stopped responding for a drug reinforcer may resume responding following a small unearned dose of the drug (a priming dose) and, importantly, that environmental signals for drug use may act in the same way as these priming doses (de Wit & Stewart, 1981). Some research suggests that CSs, paired with a reinforcing US, release dopamine (DA) in the brain's supposed "reward pathway" (Stewart et al., 1984; Schultz et al., 1998). Other research suggests that the contribution of multiple brain structures (e.g., amygdala, hippocampus, orbitofrontal cortex) and other neurotransmitters,

including glutamate and GABA, underlie priminginduced drug seeking.

These three conditioning models similarly propose that events paired with drug use become conditioned stimuli that, upon future presentation, encourage the drug user to initiate drug-seeking behaviors. The models differ only in the characterization of the CRs elicited by the drug-related events.

HUMAN DATA

Since the 1970s investigators have collected data from a number of sources to document that stimuli associated with drug use in humans is conditioned. Evidence for this has come from three primary sources:

- Self-reports by drug abusers about the conditions under which they experience craving and withdrawal.
- Attempts to establish drug conditioning in the laboratory.
- Assessments of responses to cues thought to be drug CSs in the natural environment (in cueexposure paradigms).

Self-reports of Conditioned Effects. Many drug abusers report drug craving and withdrawal when faced with drug-related stimuli in their home environment or in the laboratory. Several investigators have systematically documented this in response to stimuli associated with a wide range of drugs, including alcohol, cocaine, heroin, and nicotine. It has been more difficult, however, to establish a link between subjective reports of craving and/or withdrawal and drug use. Recently, Rajita Sinha and colleagues (2006) studied outpatient cocaine abusers who had recently completed drug treatment. They found that cocaine craving was predictive of relapse and that stress-induced cocaine craving was a particularly important factor. Similar findings were found for self-reported methamphetamine craving in an outpatient treatment setting (Hartz et al., 2001). Such reports support the idea that events that signal drug self-administration in the home environment can cause conditioned responses of craving, which motivate further drug use.

Laboratory Conditioning Studies. Richard Foltin and Margaret Haney (2000) found that neutral stimuli paired with cocaine administration elicited conditioned physiological (e.g., increased heart rate and blood pressure) and subjective (e.g., cocaine craving) responses. A number of other studies using neutral stimuli paired with alcohol, nicotine, and opioids also reported similar effects brought about by the experimental CSs. Interestingly, Raymond Niaura and colleagues (1989) found that such physiological responses to a laboratory-presented CS predicted relapse to cigarette smoking 90 days later.

Laboratory studies show that such conditioning occurs as a consequence of experienced users taking drugs. However, the connection between potential CSs, drug effects, and CRs in the natural environment is undoubtedly less precise than in the laboratory.

Cue-Assessment Studies. To determine whether events associated with previous drug use in the natural environment acquired conditioned properties, many studies have recreated/presented typical CSs in the laboratory and measured participant responses. In such studies drug-dependent participants are exposed to drug paraphernalia or to audiotapes, videotapes, and photographs with drug-related content (i.e., "drug cues"), while physiological and self-report responses are obtained. Responses to such drug cues are then compared with the responses participants make when they are exposed to comparable stimuli lacking a drug-specific content.

Consistent with conditioning models, exposure to drug cues seems to produce CRs. Specifically, exposure to drug cues produces subjective reports of drug craving as well as other physiological changes (e.g., decreases in skin temperature and increases in heart rate; for review, see Carter & Tiffany, 1999). Data from imaging studies indicate that DA-rich brain structures, including the ventral tegmental area, ventral striatum, and prefrontal cortex, are activated when substance-dependent individuals are presented with drug cues (Volkow et al., 2006; Sinha et al., 2007). This suggests that DA may be involved in establishing conditioned responses to drug cues. In line with this view, S. Paul Berger and colleagues (1996) demonstrated that haloperidol, a DA

antagonist, significantly reduced cocaine cue-induced anxiety and craving.

Although drug cues have repeatedly increased drug self-administration in laboratory animals (e.g., de Wit & Stewart, 1981; Epstein et al., 2006), there is a dearth of parallel data collected using humans. In one study Payne and colleagues (1991) exposed tobacco smokers to highly salient smoking cues and found that cue exposure shortened the time participants took to smoke their first cigarette and increased participants' puff duration. Because the assumption that responses to drug-related stimuli motivate actual drug use is central to learning models, more studies using drug taking as a dependent measure are clearly needed.

CLASSICAL/OPERANT CONDITIONING INTERACTION

Although much evidence suggests that psychoactive drugs of abuse have powerful reinforcing properties and that stimuli associated with those drugs elicit conditioned responses—the question remains as to whether these classically conditioned responses actually motivate drug-seeking behaviors by themselves. Indeed, much of the work on drug conditioning contains the implied notion that classical and operant learning effects combine to motivate drug use (or drug craving, even if no drug use actually occurs). The most common idea is that CSs evoke craving and/or withdrawal states, which motivate subsequent drug-seeking behaviors (via classical conditioning). In cases in which a drug is consumed, the effects of the drug further reinforce the drug-seeking behaviors (via operant conditioning).

TREATMENT IMPLICATIONS

If classical and operant conditioning motivate drug use, then substance-abuse treatments should aim at reducing the impact of these learning effects. The most commonly discussed interventions include aversion training, extinction, and behavioral and cognitive-behavioral alternatives.

Aversion therapy involves teaching drug abusers that those stimuli and responses that once led to positive drug effects will henceforth lead to unpleasant outcomes. The most common technique has been to pair self-administrations of a drug with pharmacologically induced sickness (e.g., the medication disulfiram can cause a variety of unpleasant and

uncomfortable effects when followed by the ingestion of alcohol). While disulfiram may prevent alcohol consumption in the short-term, patients are unlikely to continue to self-administer disulfiram outside the treatment setting. Further, since the treatment setting is clearly different from the home environment, drug abusers may simply learn that drug-taking behavior is reinforced at home, but punished in the clinic. In general, disulfiram is ineffective in achieving alcohol abstinence or delaying relapse (Fuller et al., 1986), although it has been useful for patients who are older, highly motivated, and more socially stable (Fuller & Gordis, 2004).

Extinction training consists of repeatedly exposing drug abusers to drug-related stimuli without letting them take drugs. This breaks the association between these stimuli and the effects of drug use. Extinction of classically conditioned stimuli typically requires drug abusers to repeatedly view drugrelated scenes, imagine scenarios, and handle paraphernalia without using the abused substance. Such training has the advantage of not subjecting the drug user to punishment. Operant extinction procedures require participants to repeatedly perform drug-use behaviors in the absence of a drug reinforcer. This can be accomplished by having participants administer their drug of abuse in the usual way-while they are maintained on a medication that blocks the effects of the abused drug (e.g., the opioid-blocking drug naltrexone). In this way druguse behaviors are not reinforced as the drug effects are absent or considerably weakened. Nevertheless, participants might give up the drug in the clinic, but still experience conditioned effects that lead to drug use at home.

Cognitive-behavioral training also reduces the impact of conditioning on behavior. Subjects are taught to identify and avoid drug-related situations and to make different responses in the presence of drug cues (Sholomskas et al., 2005). These new responses compete with drug-seeking behaviors elicited by drug cues. Rather than trying to eliminate the craving produced by drug cues, this treatment gives the patient ways to avoid cues along with alternative behaviors and strategies to replace drug use as well as general coping skills. Behavioral alternatives to drug use range from simple time-outs, to forming images inconsistent with drug use, to

acting in ways that reduce the chances of use or cue exposure (e.g., going out to eat with non-drugusing friends). Cognitive strategies include changing expectations about drug use and considering long-term consequences of behavior. Taken as a whole, these approaches are now commonly designated as cognitive therapies or relapse-prevention approaches. The advantage of these procedures over aversion therapy and extinction is that patients use their training in the clinic to deal with high-risk situations in the real world.

Contingency management is another behavioral approach used to treat substance abuse. It has generated increased interest in recent years because it has produced consistent reductions in drug-using behaviors among diverse substance-abusing populations (Higgins et al., 2004). In this approach, individuals receive immediate rewards (e.g., cash or vouchers redeemable for goods or services) for providing drug-free urine samples, and the value of the rewards increases with consecutive drug-free urine samples. However, rewards are withheld if the patient's urine sample tests positive for an illicit drug. In addition to receiving rewards, drug abusers participate in cognitive sessions similar to those described previously, where they learn a variety of skills to help them minimize substance use. One problem with contingency management is that it may be too expensive for less well-funded treatment programs. Whether these particular conditioning interventions provide lasting help to substance abusers remains to be seen, but data suggest that in alcohol-, cocaine-, nicotine-, and opioiddependent individuals, these cognitive and behavior techniques reduce the probability of relapse.

See also Addiction: Concepts and Definitions; Conditioned Tolerance; Treatment, Pharmacological Approaches to: Naltrexone; Wikler's Conditioning Theory of Drug Addiction.

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STEVEN J. ROBBINS REVISED BY HEDY KOBER (2009) ALLISON C. TURZA (2009) CARL L. HART (2009)

PERSONALITY

Clinicians and researchers alike have long posited that personality plays an important role in the etiology of substance use disorders (SUDs). Although empirical research has failed to identify a unique constellation of traits equivalent to a so-called addictive personality, a substantial body of research points to a few important traits that appear to put one at risk for developing SUDs, in particular, traits related to the tendency to experience negative emotions—e.g., neuroticism or negative emotionality—and traits related to self-control-e.g., impulsivity, sensation seeking, behavioral undercontrol (see Sher et al., 1999, for a review). Observing a statistical association between these traits and SUDs is not the end point of research on personality and SUDs but, rather, a starting point that helps to identify distinct etiological processes which contribute to the development of SUDs. Accumulating research suggests that personality is associated with multiple, distinct etiological pathways and indexes, core dimensions of individual vulnerability to SUDs that are heritable. Most, though certainly not all, research suggests that some traits represent vulnerability to a range of SUDs. However, even in the context of a general vulnerability to SUDs, it appears that some traits may differentially predispose an individual more to one type of SUD (e.g., alcohol dependence) than another (e.g., tobacco dependence).