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ADDICTION

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■ **Abstract** The development of addiction involves a transition from casual to compulsive patterns of drug use. This transition to addiction is accompanied by many drug-induced changes in the brain and associated changes in psychological functions. In this article we present a critical analysis of the major theoretical explanations of how drug-induced alterations in psychological function might cause a transition to addiction. These include: (*a*) the traditional hedonic view that drug pleasure and subsequent unpleasant withdrawal symptoms are the chief causes of addiction; (*b*) the view that addiction is due to aberrant learning, especially the development of strong stimulus-response habits; (*c*) our incentive-sensitization view, which suggests that sensitization of a neural system that attributes incentive salience causes compulsive motivation or "wanting" to take addictive drugs; and (*d*) the idea that dysfunction of frontal cortical systems, which normally regulate decision making and inhibitory control over behavior, leads to impaired judgment and impulsivity in addicts.

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INTRODUCTION

Many people experiment with potentially addictive drugs. About 60% of Americans sample an illicit drug at least once in their lifetime, and even after excluding marijuana, the lifetime prevalence for illicit drug use is about 32% (Johnston et al. 2001). If alcohol is included, the percentage of Americans exposed to a potentially addictive drug rises to over 90%, but few of these people become addicts. Even for a very addictive drug like cocaine, only 15–16% of people become addicted within 10 years of first use (Wagner & Anthony 2002). Substantial numbers of people do become addicts, of course, but the fact remains that drug use does not inevitably lead to addiction. Addiction is more than mere drug use. It is defined specifically as a compulsive pattern of drug-seeking and drug-taking behavior that takes place at the expense of most other activities. The key questions in addiction, therefore, are why do some susceptible individuals undergo a transition from casual drug use to compulsive patterns of drug use, and why do addicts find it so difficult to stop using drugs (Edwards 1981)?

To address these questions requires some consideration of how drugs affect the brain. Thus, much research on the transition to addiction has aimed at identifying and characterizing brain systems that mediate the rewarding effects of potentially addictive drugs and how these brain systems are changed by drug use. It is now well accepted that addictive drugs usurp neural circuitry normally involved in pleasure, incentive motivation, and learning (Wise 1989, Robbins & Everitt 1996, Berridge & Robinson 1998, Di Chiara 1999, Kelley 1999, Hyman & Malenka 2001, Kelley & Berridge 2002). These brain reward circuits include dopamine projections from the ventral tegmental area and substantia nigra to the nucleus accumbens (NAcc) and striatum, as well as glutamate inputs from the prefrontal cortex, amygdala and hippocampus, and other key parts of this network that we refer to as *NAcc-related circuitry*. This circuitry did not evolve to mediate the effects of drugs, of course, but to endow stimuli beneficial for survival, such as nutrients, water, sexual partners, and safety, with psychological reward properties. Thus, NAcc-related circuitry is critical for natural rewards to acquire and exert motivational control over behavior (Kelley & Berridge 2002). However, addictive drugs not only engage these brain reward systems, often more potently than natural rewards, but they can also change them. Persistent drug-induced neuroadaptations in NAcc-related circuitry have been found at molecular, cellular, and neural system levels (Nestler et al. 1993; Robinson & Berridge 1993, 2000; Vanderschuren & Kalivas 2000; Hyman & Malenka 2001; Everitt & Wolf 2002; De Vries & Shippenberg 2002). These drug-induced neuroadaptations are thought by many to be critical in the transition to addiction. It is not well understood, however, what psychological functions are changed as a consequence of these drug-induced neuroadaptations, or how those changes cause addiction. That is the topic of this chapter.

The major theoretical explanations for the transition to addiction all incorporate the idea that drugs change the brain and thereby change some psychological function. They differ in terms of which psychological changes are thought to carry

the weight of explanatory burden. We first discuss a traditional view that emphasizes tolerance and associated decreases in pleasurable drug effects and the corresponding growth of unpleasant withdrawal symptoms (Wikler 1948, Koob et al. 1997, Koob & Le Moal 1997). Second, we discuss the idea that drug-taking habits are caused by aberrant learning, because drugs subvert neuronal mechanisms involved in normal learning and memory (Tiffany 1990, O'Brien et al. 1992, Berke & Hyman 2000, Everitt et al. 2001). Third, we present our incentive-sensitization theory, first proposed in 1993, which suggests that drug-induced sensitization of brain systems that mediate a specific incentive-motivational function (incentive salience) causes drugs to become compulsively and enduringly "wanted," independent of drug pleasure, withdrawal, habits, or memories (Robinson & Berridge 1993, 2000; Berridge & Robinson 1995). Finally, we discuss the notion that drug-induced dysfunction of frontocortical systems may impair normal cognition and inhibitory control over behavior, further leading to impaired judgment and promoting impulsivity (Jentsch & Taylor 1999, Robbins & Everitt 1999b).

PLEASURE, WITHDRAWAL, AND OPPONENT PROCESSES

The most intuitive explanation for addiction is the traditional view that drugs are taken first because they are pleasant, but with repeated drug use homeostatic neuroadaptations lead to tolerance and dependence, such that unpleasant withdrawal symptoms ensue upon the cessation of use. Compulsive drug taking is maintained, by this view, to avoid unpleasant withdrawal symptoms. This two-sided hedonic hypothesis has gone by many different names: pleasure-pain, positive-negative reinforcement, opponent processes, hedonic homeostasis, hedonic dysregulation, reward allostasis, etc. (Wikler 1948; Solomon 1977; Koob et al. 1997; Koob & Le Moal 1997, 2001). No matter what the name, these hypotheses posit the same basic explanatory logic: Addictive drugs are taken initially simply to achieve pleasant drug "highs," and after addiction, to escape withdrawal "lows."

Opponent Process Theory of Addiction

The most elegant psychological version of the pleasure/withdrawal view of addiction is the opponent process theory of Solomon and colleagues (Solomon & Corbit 1973, Solomon 1977). The opponent process theory makes testable predictions and describes the underlying positive and negative affective processes of addiction in graphic ways that allow the transition to addiction to be visualized (Figure 1).

The opponent process theory posits that pleasant doses of a drug activate a dose-dependent a-process in brain reward circuits, which in turn triggers activation of a negative or opponent b-process. Usually the b-process serves to help restore homeostasis and bring brain states back to normal. The summation of the a- and b-processes creates the final subjectively experienced state felt by the person. The resulting experience is called the A-state when the summed effect is

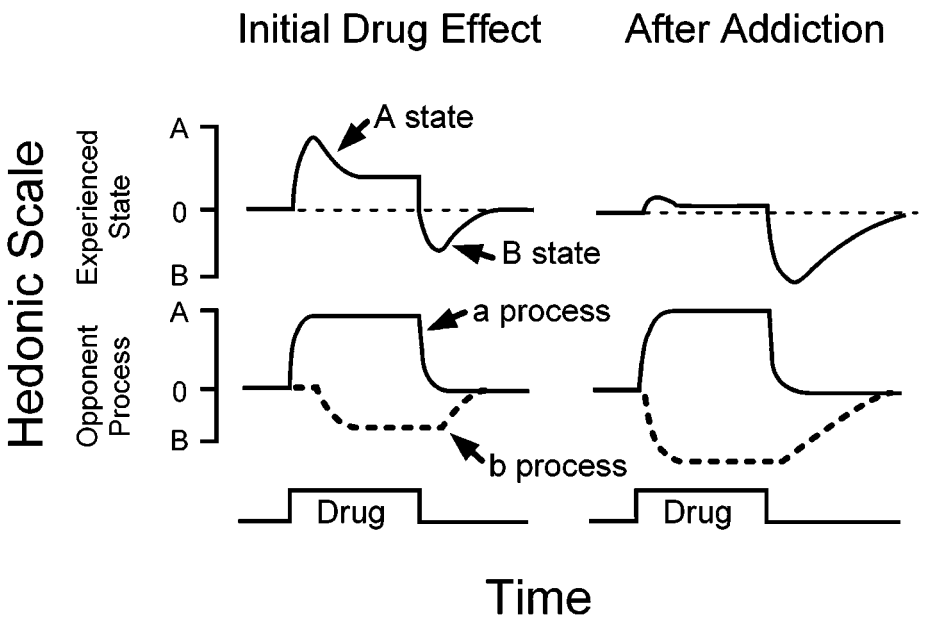

Figure 1 Opponent process model of addiction. According to the opponent process theory the affective (hedonic or emotional) response to a stimulus (a drug in this case) is the underlying a-process, which in turn elicits the opponent b-process (*bottom*). The underlying processes add together to cause the initial pleasant A-state, which is actually experienced, followed by an opponent unpleasant B-state. Initially the pleasant A-state is large, followed by a small B-state. With repeated drug use and in addiction, however, the opponent b-process increases in magnitude and duration, leading to an experience dominated by the unpleasant symptoms associated with withdrawal. (Adapted from Solomon 1977 and Solomon & Corbit 1973.)

pleasantly drug-like (a-process > b-process) and the B-state when it is unpleasantly drug-opposite (b-process > a-process). The euphoric high of the drug A-state is directly caused by the a-process. The b-process is manifest first as mild decay of the drug's high after the initial peak (A-state decay). Later if the drug is taken again the b-process is strengthened and manifest as tolerance to drug euphoria (reduced A-state). Finally, unpleasant withdrawal is caused when drug effects wear off because the sluggish b-process is posited to last longer than the a-process (B-state) [similar to a neural opponent process involved in visual color processing (Hurvich 1981)]. Further, only the b-process is posited to change with repeated drug taking: It grows both in magnitude and in duration (Figure 1). Once the b-process is strengthened, even a small drug dose can instate it and thereby trigger withdrawal again. Conversely, prolonged abstinence from the drug would decay the b-process, and the ability to reactivate it would return to normal. Once the b-process returns back to normal, the person would no longer be addicted.

Neural versions of the opponent process theory have been offered, most notably by Koob and colleagues (Koob et al. 1997; Koob & Le Moal 1997, 2001). For example, Koob & Le Moal (1997) suggest the positive a-process is caused by activation of mesolimbic dopamine projections to the nucleus accumbens and amygdala that mediate "the acute reinforcing effects" of drugs. Repeated drug use, they suggest, induces tolerance or downregulation in the mesolimbic dopamine system, decreasing the drug A-state. Sudden cessation of drug use causes dopamine (and serotonin) neurotransmission to further drop below normal levels, at least for several days, resulting in a dysphoric B-state of withdrawal. Finally, they suggest that repeated drug use also activates an additional b-process via the hypothalamic-pituitary axis stress system, causing release of corticotropin releasing factor (CRF) in the amygdala, as well as other stress responses (Koob et al. 1997, Koob & Le Moal 1997). As a result, addicts who originally take drugs to gain a positive hedonic state are spiraled into a predominantly negative hedonic state, which according to Koob and colleagues causes the transition to addiction.

An implication of hedonic/withdrawal views of addiction, whether couched in psychological or neural terms, is that they tend to interpret all aspects of addiction in terms of affective processes. Even drug-induced changes that render NAcc-related circuitry hypersensitive, such as sensitization of dopamine neurotransmission (see below), may be considered as hedonic or pleasurable in nature by such theorists. For example, Koob & Le Moal (1997) depict neural sensitization as magnifying the positive hedonic a-process caused by drugs (Figure 2). The conclusion that with repeated use addicts derive more pleasure from drugs may seem counterintuitive, and we know of little evidence for this. However, true or false, the claim becomes more understandable when viewed as a conclusion forced by a pure hedonic or opponent process framework.

Limitations of Pleasure-Withdrawal Opponent Process Explanations

Everyone agrees that addicts sometimes take drugs chiefly for pleasure and sometimes chiefly to escape withdrawal or other dysphoric states (e.g., life stresses). However, there are several major problems with hedonic/withdrawal theories as full explanations of drug addiction. One of the most striking is that drug withdrawal actually may be much less powerful at motivating drug-taking behavior than people generally think. Relative to positive incentive processes caused directly by drugs themselves, or stress, withdrawal states are not especially potent in motivating drug-seeking behavior (Stewart & Wise 1992). For example, in animal studies Stewart and colleagues have examined what causes rats to "relapse" into drug-seeking behavior if they previously were dependent on cocaine or heroin but have been drug-free for some time (for reviews see Shaham et al. 2000, Stewart 2000, Shalev et al. 2002). Stewart, Shaham, and colleagues measured lever pressing to obtain drug infusions under extinction conditions after activating either an a-process or b-process. To activate the a-process the rats were simply given a

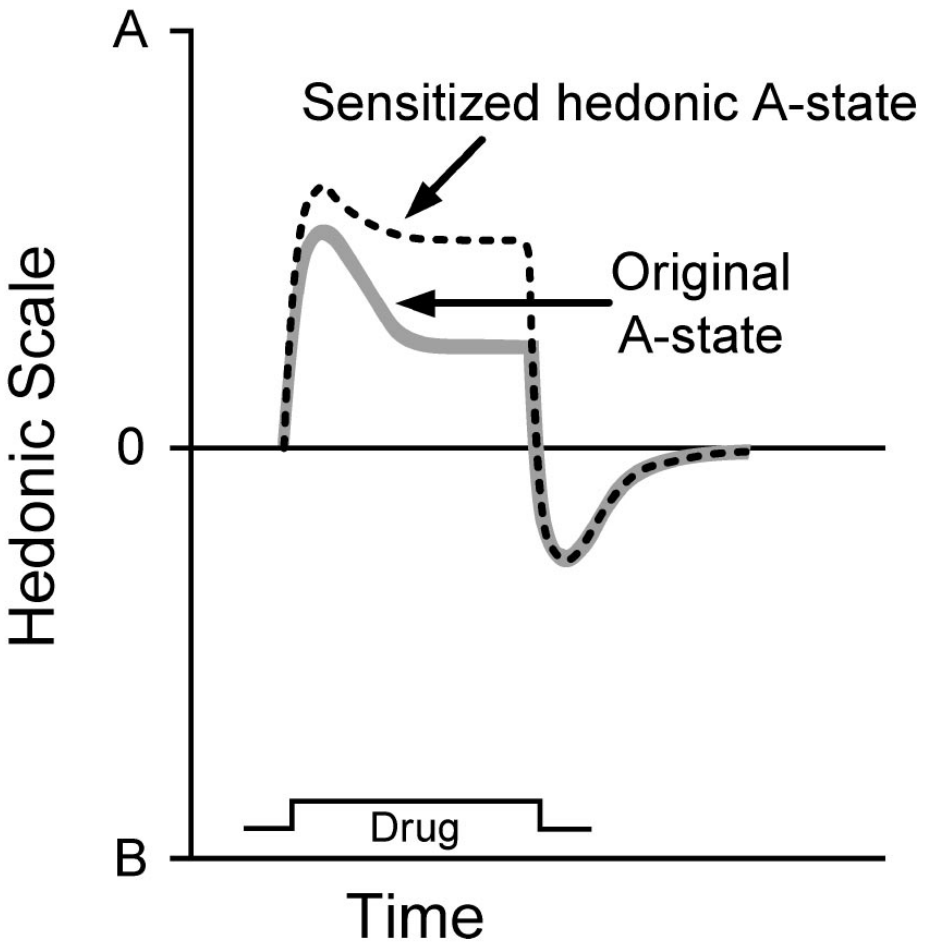

Figure 2 Adaptation of Figure 4 (panel B) in Koob & Le Moal (1997, p. 56), in which they depict sensitization as amplifying the hedonic a-process. They state that this panel shows an "affective stimulus in an individual with an intermittent history of drug use that may result in sensitized response. The shaded line illustrates . . . the initial experience. The dotted line represents the sensitized response" (p. 56). Note that sensitization is hypothesized to increase the hedonic A-state by this view, which would be experienced as enhanced drug pleasure.

small injection of their old drug prior to the test (called a priming injection). To activate the b-process rats received naltrexone, an opioid antagonist drug that blocks opioid receptors in the brain and can induce "precipitated withdrawal" symptoms in individuals who are heroin dependent. Precipitated withdrawal is clearly a B-state and thus would be expected by any withdrawal-based hypothesis of addiction to be the most powerful cause for reactivating drug-seeking behavior. However, a priming drug injection (or a stressor; see below) turns out to be far more effective at reinstating drug-seeking than naltrexone administration (Stewart & Wise 1992,

Shalev et al. 2002). Thus, activation of an a-process appears to be far more effective than the b-process at motivating drug pursuit. Furthermore, withdrawal symptoms are maximal within 1–2 days after the cessation of drug use, but the susceptibility to reinstatement continues to grow for weeks to months (Grimm et al. 2001, Shalev et al. 2001).

The finding that drug withdrawal can be relatively weak at motivating drug-seeking is counterintuitive to many and is a direct contradiction of the opponent process prediction. However, it fits with the reports of some human addicts who say that their sick feelings of withdrawal are quite different from their most intense feelings of drug craving. As one heroin addict explained to a researcher studying craving, "No doc, craving is when you want it—want it so bad you can almost taste it . . . but you ain't sick . . . sick is, well sick" (Childress et al. 1988).

Another major problem for withdrawal theories is explaining why addicts so often relapse into drug-taking again even after they are free from withdrawal. After long periods of drug abstinence, the b-process should decay away. Yet elimination of withdrawal symptoms does not protect against future relapse, as the many recidivist graduates of detoxification programs can attest. One explanation for this is suggested by conditioned opponent theories, namely, that associative conditioning causes predictive drug cues to elicit conditioned tolerance and conditioned withdrawal essentially as conditioned b-processes (Wikler 1948, Schull 1979, Ramsay & Woods 1997, Siegel & Allan 1998). Conditioned withdrawal effects have been found in studies of human drug addicts as well as in animal studies and in principle could prompt relapse long after unconditioned withdrawal symptoms have subsided. However, many human addicts report that cues often fail to elicit conditioned withdrawal. Plus, drug cues often elicit quite different effects, such as conditioned feelings of a drug high (a-process), or feelings of drug craving by themselves (O'Brien et al. 1988). Indeed, McAuliffe (1982) found that only 27.5% of heroin addicts experienced conditioned withdrawal, and of these, only 5% indicated this was a reason for relapse.

In conclusion, conditioned feelings of withdrawal do not seem to be sufficiently strong or reliable to serve as the principal explanation for relapse. These and other considerations have prompted many researchers to explore other explanations for the transition to addiction and for relapse (for more on limitations of hedonic reinforcement/withdrawal theories, see Wise & Bozarth 1987; Robinson & Berridge 1993, 2000).

ABERRANT LEARNING

Recently considerable attention has been paid to the role of learning in the transition to addiction, prompted in part by the realization that NAcc-related circuitry is involved in reward learning (for reviews see White 1996, Kelley 1999, Schultz 2000). For example, cues that predict the availability of rewards can powerfully activate NAcc-related circuitry in both animals and humans (Schultz 1998, Childress et al. 1999, Knutson et al. 2001), sometimes even better than the reward itself

(Schultz 1998). Further, repeated exposure to drugs of abuse facilitates some forms of learning (Harmer & Phillips 1998, 1999) and triggers some of the same types of neuroadaptations in reward-related neurons as seen in learning (Hyman & Malenka 2001). Several researchers have hypothesized, therefore, that the transition to addiction results from the ability of drugs to promote *aberrant learning* (Tiffany 1990, O'Brien et al. 1992, White 1996, Robbins & Everitt 1999a, Di Chiara 1999, Berke & Hyman 2000, Everitt et al. 2001, Hyman & Malenka 2001).

Most aberrant learning hypotheses of addiction have focused at the level of neuronal systems. Few have provided a psychological step-by-step account of how abnormal learning could actually produce addiction. Nevertheless, most suggest that drugs produce abnormally strong or aberrant associations involved in reward learning, more powerful than natural reward associations. In principle, these associations could be any of several types [e.g., act-outcome (A-O: cognitive, explicit recognition of the causal relationship between an act and its outcome), stimulus-response (S-R: a habitual link between a specific stimulus and a specific response), stimulus-stimulus (S-S: associations among two or more stimuli)] (see below) and could be either explicit (declarative, conscious) or implicit (procedural, unconscious).

Explicit Learning?

The first possibility is that abnormally strong declarative (explicit) learning could contribute to addiction. This is the most straightforward version of the hypothesis that drugs promote aberrant learning. When people take drugs they learn at a declarative conscious level about causal relationships between their actions and an outcome, such as a drug effect (A-O cognition). They also learn declarative predictive relationships between certain cues in the environment and ensuing rewards (explicit S-S learning). That is, people (and presumably many animals) have declarative, conscious expectations about rewards (Balleine & Dickinson 1998, Cardinal et al. 2002). Abnormally strong explicit learning might distort declarative memories or expectations in two ways. (*a*) Conscious memories of the hedonic drug experience might be especially vivid and/or abnormally intrusive. (*b*) Drugs could exaggerate or distort declarative memories such that memory-based cognitive expectations about drugs become excessively optimistic. Such memories or expectations would be both false and dangerous because they make inaccurate predictions about the consequences of taking drugs.

Can vivid declarative memories, even excessively optimistic or inaccurate memories, explain the transition to addiction? Probably not. When distilled to its essence this explanation suggests that the fundamental problem in addiction is that cognitively accessible memories of drug pleasure are exaggerated or otherwise altered. That idea seems strained when compared with what addicts typically say about their lives. Most addicts do not seem to have rose-colored delusions of reward implied by a hypothesis of exaggerated declarative memories or expectations

of drug pleasure. Instead, they accurately predict drug pleasure and often agree their drug use is not justified by the pleasure they get.

Implicit Learning?

S-R HABIT LEARNING What about the idea that drugs cause pathologically strong implicit learning (unconscious S-R or S-S learning processes), which is not necessarily conscious or accessible to cognitive declaration (Tiffany 1990, Robbins & Everitt 1999a, Berke & Hyman 2000, Everitt et al. 2001)? The most prominent implicit learning view of addiction is the automatic S-R habit hypothesis. This proposes that the transition to addiction involves a transition from behavior originally controlled by explicit and cognitively guided expectations about A-O relationships (i.e., the memory of drug pleasure) to more automatic behavior consisting primarily of S-R habits. Implicit S-R habits occur without explicit cognitive expectations of a given outcome (i.e., "automatically"). Like the procedural memory of how to tie your shoe, once started they simply play out automatically. In an excellent and illuminating formulation Everitt, Dickinson, & Robbins (2001, p. 134) propose neural bases for this "progression from action to habit." They suggest, "drug-seeking actions, mediated by the A-O (act-outcome) process, eventually consolidate habitual S-R drug-seeking through the engagement of corticostriatal loops operating through the dorsal striatum" (also see Robbins & Everitt 1999a, White 1996, Everitt & Wolf 2002). Similarly, Berke & Hyman (2000) suggest that "the engagement of these striatal 'habit'-learning mechanisms by addictive drugs could promote a tendency for drug-related cues and contexts to provoke specific behaviors, such as drug self-administration" (p. 523). These ideas are similar (although not identical) to the earlier suggestion by Tiffany (1990) that "with sufficient practice, performance on any task . . . can become automatic . . . " and "drug-use behavior in the addict represent one such activity, controlled largely by automatic processes" (p. 152). So how do these hypotheses explain addiction? Basically they suggest that over-learned habits become so automatic that they essentially become compulsive.

Habit (S-R) learning formulations are attractive because they are conceptually simple and straightforward. They also fit well with operant studies of drug-taking behavior in rats, in which the same lever is pressed again and again, a situation that strongly promotes the formation of S-R habits. Furthermore, the phrase "drug habits" captures the ritualized automatic habits addicts sometimes display when taking drugs. But can extra-strong S-R learning explain a pathological desire to take drugs, or explain the varied and complex behavior often necessary to obtain drugs?

We suggest that habit learning theories do not explain the compulsive nature of addiction for several reasons. First, habit learning theories mistake automatic performance for motivational compulsion. However, habits are not intrinsically compulsive in any motivational sense, no matter how automatic they are. For example, tying your shoe, brushing your teeth, and many other habits in daily life are highly automatic and may be executed without need of cognitive attention.

However, none of these behaviors are performed compulsively (except perhaps in obsessive-compulsive disorder, which requires a separate explanation). You probably have no overwhelming motivational urgency to tie your shoe, and you can stop brushing your teeth midway without distress at leaving the habit unfinished. You would not sacrifice your home, your job, your friends, and all that is dear in your life to engage in a shoe-tying habit, even though it is strongly learned and quite automatic. Its practiced automaticity does not compel you to perform it. No matter how strong implicit S-R associations, no matter how over-learned or pharmacologically boosted, there is no reason to believe that automatic S-R associations per se can confer compulsive qualities.

Further, as mentioned above, many aspects of addictive drug pursuit are flexible and not habitual. Human addicts face a situation different from rats that merely lever-press for drugs. We suspect that if animals were required to forage freely in a complex environment for drugs the picture seen in animal neuroscience might look more like the situation in human addiction, and automatic habit hypotheses would be less tempting. An addict who steals, another who scams, another who has the money and simply must negotiate a drug purchase—all face new and unique challenges with each new victim or negotiation. Instrumental ingenuity and variation are central to addictive drug pursuit in real life. When an addict's drug-taking ritual is interrupted, for example, by lack of available drugs, flexible and compulsive pursuit is brought to the fore (Tiffany 1990). The strongest S-R habit in the world does not explain the frantic behavior that ensues. Thus, the formation of S-R habits may explain the rituals addicts display in consuming drugs, but they do not account for the flexible and deliberate behaviors involved in obtaining drugs. We believe the flexible and compulsive nature of drug-seeking behavior in the addict requires an additional motivational explanation, separate from habit learning (see Figure 3 for a graphic representation of the critical change in addiction posited by the S-R habit learning hypothesis versus the incentive-motivational explanation described below).

S-S LEARNING Finally, it is possible that addictive drugs cause over-learning of implicit S-S associations among reward-related stimuli. For example, drugs might distort "the process by which the drug abuser connects a specific cue such as a particular place with drug-induced states" (Robbins & Everitt 1999a, p. 569). Similarly, Schultz (2000) suggests that "drugs of abuse that mimic or boost the phasic dopamine reward prediction error might generate a powerful teaching signal and might even produce lasting behavioral changes through synaptic modifications" (p. 205). Although we regard implicit S-S associations as very important in addiction (see below), no aberrant learning hypothesis of this sort has clearly described the psychological mechanism by which implicit over-prediction could cause addiction. Conceivably strong S-S learning might exaggerate implicit Pavlovian conditioned highs (in which the associative learning can be implicit even though the final product is conscious euphoria) or strengthen conditioned reinforcement (e.g., when a Pavlovian cue increases any response it follows by strengthening

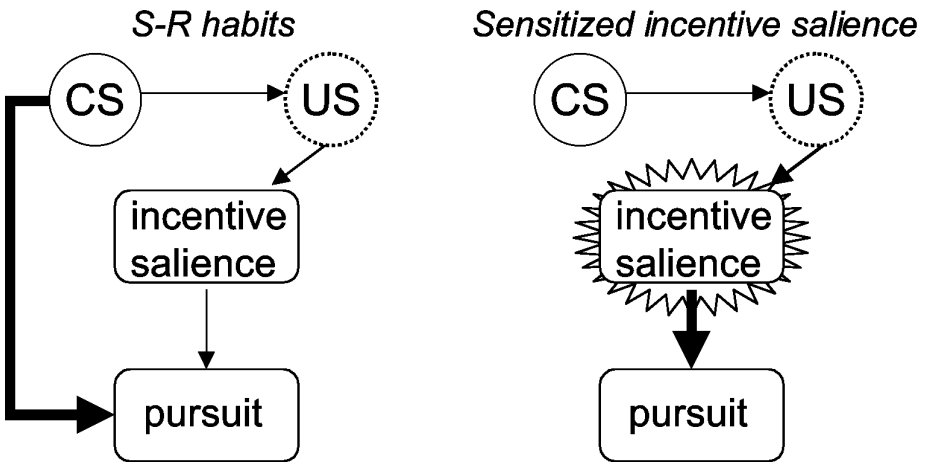

Figure 3 Comparison of the critical change in addiction leading to compulsive drug pursuit according the stimulus-response (S-R) habit learning hypothesis (*left*) and the incentive-sensitization hypothesis (*right*). According to the S-R habit learning model addiction (compulsive drug pursuit) is primarily due to the development of very strong S-R habits [indicated by the thick arrow from a drug cue (CS) to a response (drug pursuit)]. According to the incentive-sensitization view the critical change is in the ability of representations of drug cues (the dashed US evoked by a drug cue) to engage a sensitized motivational response of incentive salience (as indicated by the starburst). This enhanced motivational response is primarily responsible for compulsive drug pursuit (*thick arrow*) in addiction according to our view.

S-R associations). However, conditioned highs are usually weak, and conditioned reinforcement explanations, if taken literally, would require presentation of the reinforcer immediately after emission of the action to be reinforced, but cues are often encountered first, and the cue causes the action to follow (relapse). This is not explicable by conditioned reinforcement in its technical sense.

Despite our criticisms of learning hypotheses of addiction, we hasten to emphasize that we agree that implicit S-S associations are very important in addiction, as described below. However, we believe the problem is not because the S-S associations themselves are aberrant or pathologically strong. The problem is not in learning per se but in the motivational impact of drug-associated cues, that is, in their ability to engage brain motivational systems. The relationship between cues and drug effects are learned, and this learning is important, but by itself it will not generate compulsive behavior. We suggest that most implicit S-S associations may actually remain normal in addicts. What is aberrant in addiction is the response of brain motivational systems to Pavlovian-conditioned drug cues (see Figure 3).

In summary, we suggest the transition to addiction may not be reducible to aberrant learning per se, just as it is not reducible to withdrawal. Knowledge, in any implicit or explicit form of association, no matter how strong, does not

necessarily compel the pursuit of drugs. The critical question is, what goads addicts to action? We believe the answer lies in understanding how learning and incentive-motivational processes are joined in the transition to addiction. We take up this topic next.

INCENTIVE SENSITIZATION

The incentive-sensitization theory of addiction focuses on how drug cues trigger excessive incentive motivation for drugs, leading to compulsive drug seeking, drug taking, and relapse (Robinson & Berridge 1993, 2000). The central idea is that addictive drugs enduringly alter NAcc-related brain systems that mediate a basic incentive-motivational function, the attribution of incentive salience. As a consequence, these neural circuits may become enduringly hypersensitive (or "sensitized") to specific drug effects and to drug-associated stimuli (via activation by S-S associations). The drug-induced brain change is called neural sensitization. We proposed that this leads psychologically to excessive attribution of incentive salience to drug-related representations, causing pathological "wanting" to take drugs. (The term "wanting" in quotation marks is used as a shorthand to refer to activation of incentive-salience processes; for a detailed discussion see Berridge & Robinson 1998).

The activation of a sensitized system that attributes incentive salience to drug-associated stimuli and their representations can sometimes be manifest implicitly in drug-seeking behavior. If the "wanting" system is activated implicitly it can instigate and guide behavior without a person necessarily having conscious emotion, desire, or a declarative goal. For example, in normal people the brief subliminal presentation of faces expressing positive emotions (backward masked and so brief they do not cause any conscious feeling of emotion at the time they are presented) can activate implicit "wanting," increasing subsequent consumption of a beverage (Berridge & Winkielman 2002). In addicts, doses of drugs that are too low to produce any conscious experience of pleasure can activate implicit "wanting," as indicated by an increase in drug-seeking behavior (Lamb et al. 1991, Fischman & Foltin 1992). Implicit "wanting" is similar to implicit memory and to unconscious perception (e.g., blindsight), which can occur and influence behavior without conscious awareness (Schacter 1996, Weiskrantz 1997). At other times incentive-sensitization can be manifest explicitly, when cognitive elaboration translates incentive salience attributions into the level of conscious awareness of the corresponding representations. In those cases, the initial activation of an implicit "wanting" system contributes to the explicit subjective experience of a conscious desire for drugs, in the ordinary sense of wanting. Finally, the sensitized neural systems responsible for excessive incentive salience can be dissociated from neural systems that mediate the hedonic effects of drugs, how much they are "liked." In other words, "wanting" is not "liking." Hedonic "liking" is a different psychological process that has its own neural substrates (e.g., NAcc opioid neurotransmission; Berridge 2002). Neural sensitization by drugs increases

only "wanting." We suggest that this incentive-sensitization process is the fundamental problem in the transition to addiction and in relapse (Robinson & Berridge 1993, 2000; Berridge & Robinson 1995).

What is Sensitization?

Pharmacologists use the term sensitization to refer to an increase in a drug effect with repeated drug administration. In other words, the change in drug effect is in the opposite direction as seen with the development of tolerance (a decrease in a drug effect with repeated administration). When drugs are given repeatedly some effects undergo tolerance, some effects undergo sensitization, and yet other effects do not change. This is because the biological systems that mediate different drug effects adapt in different ways to repeated drug exposure. There are two major classes of drug effects that are sensitized by addictive drugs: psychomotor activating effects and incentive motivational effects. Both of these classes of drug effects are mediated at least in part by NAcc-related circuitry, and therefore sensitization of these behaviors is thought to reflect reorganization and sensitization of this neural system (Robinson & Becker 1986, Robinson & Berridge 1993).

Psychomotor Sensitization

In humans and animals many potentially addictive drugs can increase arousal, attention, and motor behavior, producing heightened locomotion, exploration, and approach. At higher doses psychomotor effects can also include intense repetitive stereotyped movements (Wise & Bozarth 1987). These psychomotor-activating effects are easy to measure and are mediated by brain systems that overlap with those involved in reward (involving NAcc dopamine, etc.) (Wise & Bozarth 1987), and therefore they provide an excellent means for studying neurobehavioral sensitization. The study of psychomotor sensitization has provided a great deal of information about factors that influence both the induction and expression of neurobehavioral sensitization, including genetic, hormonal, and experiential determinants of individual differences in susceptibility to sensitization, the roles of pharmacological factors such as drug dose, and of psychological factors such as learning, stress, etc. (Robinson & Becker 1986, Robinson 1988, Stewart & Badiani 1993, Robinson et al. 1998). For example, they have shown that sensitization is produced by many different drugs of abuse, including amphetamines, cocaine, opiates, methylphenidate, ethanol (alcohol), and nicotine. Sensitization is strongest when high or escalating doses are given, especially when the drug is administered rapidly (Samaha et al. 2002) and intermittently (continuous infusions are relatively ineffective). Psychomotor sensitization has also revealed one of the most important features of sensitization for addiction, namely, its remarkable persistence. In animals psychomotor sensitization can persist for months to years after drug treatment is discontinued (Paulson et al. 1991, Castner & Goldman-Rakic 1999). Psychomotor sensitization has also been described in humans (Strakowski et al. 1996, Strakowski & Sax 1998), and if in humans the neural adaptations responsible

for sensitization last a proportional length of time as in rats, it could amount to most of a lifetime.

Another important feature of sensitization for addiction concerns individual differences in susceptibility to sensitization. Some individuals sensitize readily, whereas others are more resistant. That may help explain why only some drug users become addicts. Susceptibility to sensitization is determined by a host of factors, including genes, sex hormones, stress hormones, past trauma, etc., in addition to individualized patterns of drug exposure (Robinson 1988). Further, once sensitized, most individuals show cross-sensitization, which means that sensitization to one drug can cause sensitized effects for other drugs as well. Even more intriguing, cross-sensitization can occur between drugs and nondrug stress. Animals previously exposed to stress may become sensitized to some potentially addictive drugs. Conversely, animals sensitized by drugs may become hypersensitive to stress (Antelman et al. 1980, Antelman & Chiodo 1983, Robinson 1988). Stress-drug cross-sensitization might be especially important in influencing stress-precipitated relapse, as well as initial susceptibility to addiction (Piazza et al. 1991, Shaham et al. 2000). (Also see Miczek & Pilotte, eds., *Psychopharmacology*, Vol. 158(4), 2001 for a special issue on "Stress and Drug Abuse.")

Neurobiology of Sensitization

What changes in the brain are involved in drug sensitization? We now know that neural sensitization involves many long-lasting changes in NAcc-related reward circuitry. For example, behavioral sensitization is accompanied by an increase in the ability of a number of drugs to promote dopamine efflux in the NAcc (Robinson & Berridge 2000). In addition, dopamine D1 receptors on neurons in the NAcc become hypersensitive after sensitization, presumably further potentiating the mesolimbic dopamine signal (White & Kalivas 1998). However, more than dopamine is involved in reward and sensitization. Glutamate is also released in the NAcc by neurons from the neocortex, amygdala, and hippocampus, and recent studies of neural sensitization have found distinct changes in glutamate neurotransmission in sensitized animals (Wolf 1998, Vanderschuren & Kalivas 2000, Hyman & Malenka 2001, Everitt & Wolf 2002). In fact, sensitization-related changes have been described in many neurotransmitter systems that are integral to the function of NAcc-related reward circuits including serotonin, norepinephrine, acetylcholine, opioid, and GABA systems (as well as changes in a number of intracellular signaling pathways that are activated by these neurotransmitters). Thus, sensitization globally alters the neurochemistry of NAcc-related reward circuitry (Robinson & Berridge 2000).

Consistent with circuit-level alterations (Pierce & Kalivas 1997, Everitt & Wolf 2002), sensitization is also associated with persistent changes in the physical structure of neurons themselves (Robinson & Kolb 1997, 1999a,b). For example, cells in the NAcc and prefrontal cortex show changes in the length of dendrites and the extent to which dendrites are branched. At an even finer level changes also occur in the density and types of dendritic spines, which are the primary site of

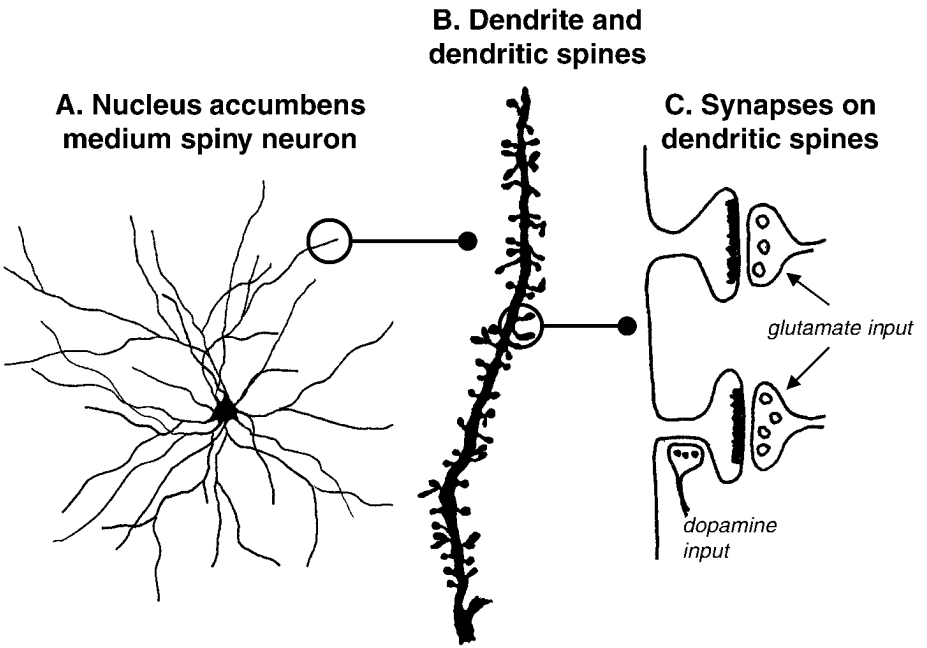

Figure 4 Graphic representation of the sites on neurons at which drugs have been shown to produce morphological changes. (*A*) The most common type of neuron in the nucleus accumbens, a medium spiny neuron. Past experience with amphetamine, cocaine, or morphine has been shown to alter the number of dendritic branches seen radiating away from the cell body. (*B*) Magnified view of a dendrite that is studded with many dendritic spines. As indicated by the schematic drawing in (*C*), dendritic spines are the site of synapses, and spines on the distal dendrites on medium spiny neurons receive both glutamate and dopamine inputs. Treatment with amphetamine, cocaine, or morphine also produces persistent changes in the number of dendritic spines on these neurons and therefore presumably in the number of synapses (Robinson & Kolb 1997, 1999a,b; Robinson et al. 2001). Camera lucida drawings (*A* and *B*) courtesy of Grazyna Gorny.

excitatory glutamate synapses (see Figure 4). These sensitization-related changes in dendritic structure may reflect changes in patterns of synaptic connectivity within these brain regions and therefore may alter information processing within NAcc-related circuitry. Although many questions concerning causal relationships remain to be addressed, it is now well accepted that sensitization is accompanied by a major reorganization of brain reward systems (Pierce & Kalivas 1997, Wolf 1998, Robinson & Berridge 2000, Hyman & Malenka 2001, Everitt & Wolf 2002, Vanderschuren & Kalivas 2000).

ROLE OF LEARNING AND CONTEXT Neural sensitization itself appears to be a non-associative process, but learning powerfully modulates both the expression and the induction of behavioral sensitization, and contextual learning about where drugs

are taken seems to be especially important (Robinson et al. 1998). For example, if rats are given repeated drug treatments in one distinct environment and they develop robust psychomotor sensitization in that environment, they often fail to express behavioral sensitization if they are later tested with a drug challenge in a different environment, where they have never experienced drug. In this case the expression of behavioral sensitization is said to be "context specific" (Pert et al. 1990, Anagnostaras & Robinson 1996).

The failure to express behavioral sensitization when context is shifted does not occur because drug treatments failed to induce neural sensitization but because learning about context modulates whether neural sensitization is expressed in behavior at any given place or time. There are two ways learning appears to modulate the behavioral expression of sensitization. (*a*) An inhibitory associative process (Stewart & Vezina 1991, Anagnostaras et al. 2002) can prevent the expression of behavioral sensitization in contexts in which the drug is not expected. (*b*) Excitatory Pavlovian associations can increase the drug-induced psychomotor response when animals are placed in environments where the drug is expected [the opposite of conditioned opponent-processes and conditioned tolerance (Pert et al. 1990)]. These two associative processes may combine to modulate the expression of sensitization, which may be why contextual factors are so important in drug craving and relapse (Anagnostaras & Robinson 1996, Anagnostaras et al. 2002).

In addition to expression, the *induction* of sensitization—that is, whether drugs change the brain in the first place—also is modulated by the context in which drugs are administered (Robinson et al. 1998). For example, when amphetamine, cocaine, or morphine are given to rats in a distinct and relatively novel environment they induce much more robust sensitization than when they are given in the home cage (Badiani et al. 1995a,b, 2000). This does not appear to be due simply to the ability of a distinct environment to act as a drug predictive cue, thereby facilitating an associative learning process (Crombag et al. 2001, 2000). Instead, environmental factors also directly modulate the neurobiological impact of drugs. For example, drugs such as amphetamine or cocaine cause some neurons to express immediate early genes, including c-*fos* and *arc*, which can be visualized and used as an indicator of what circuitry is engaged by drugs. In many brain regions the intensity of c-*fos* and *arc* expression is greater if drugs are given in a novel environment than if they are given at home (Badiani et al. 1998, Klebaur et al. 2002). This novelty-dependent increase in immediate early gene expression is not just due to increased expression within the same neurons but also involves recruitment of additional populations of neurons when drugs are given in a novel environment. For example, when given at home, amphetamine or cocaine induce c-*fos* mRNA in only one subpopulation of neurons in the striatum, neurons that project to the substantia nigra and contain mRNA for the opioid neurotransmitter, dynorphin. However, when given in a novel environment, amphetamine and cocaine also induce c-*fos* mRNA in a different subpopulation of neurons, one that projects to the globus pallidus and contains mRNA for enkephalin (Badiani et al. 1999, Uslaner

et al. 2001). Therefore, something about a novel environment determines which neuronal populations in the striatum are engaged by sensitizing drugs and enhances susceptibility to sensitization. Although again many causal relationships remain to be determined, these studies highlight the extent to which the neurobiological impact of drugs, and their ability to sensitize the brain, is modulated by environmental and psychological factors.

Sensitization of Drug Reward Pursuit

More direct evidence for our hypothesis that neural sensitization increases the "wanting" for drug rewards comes from studies that quantify the pursuit of drugs and other rewards. For example, many studies using operant techniques have shown that sensitization decreases the threshold dose necessary for rats to learn to self-administer drugs and facilitates how quickly they learn (Piazza et al. 1989, 1990; Horger et al. 1990, 1992; Valadez & Schenk 1994; Pierre & Vezina 1998). Sensitized rats also show an increase in "breakpoint" when tested using progressive ratio schedules, indicating that they will work harder than normal to gain drug reward (Mendrek et al. 1998, Lorrain et al. 2000). Sensitization also increases rats' learning of a conditioned place preference for a location paired with a drug reward (Lett 1989, Shippenberg & Heidbreder 1995, Shippenberg et al. 1996) and increases their motivation to obtain a cocaine reward in a runway, reflected by running speed for that reward (Deroche et al. 1999). Furthermore, in an animal model of relapse, sensitization is associated with the ability of a priming drug injection to reinstate drug-seeking responses after extinction of the behavior (De Vries et al. 1998, 2002). Finally, sensitization can also increase the incentive value of other rewards, such as sugar, food, a sexually receptive female (for male rats), and conditioned stimuli for such rewards (Fiorino & Phillips 1999a,b; Taylor & Horger 1999; Wyvell & Berridge 2001; Nocjar & Panksepp 2002).

In addicts, of course, the primary excessive motivation is for drugs in particular, although evidence suggests some cocaine addicts are hypersexual (Washton & Stone-Washton 1993) and some substance-dependent individuals may even be hyper-responsive to money rewards (Bechara et al. 2002), raising the possibility of a degree of motivation spillover to nondrug rewards. A major question that is only beginning to be addressed is how the focus of sensitized reward value becomes directed to one particular target, such as taking drugs. Associative learning about the temporal relationships between reward-related cues and sensitizing stimuli, as well as nonassociative individual factors, may be involved (Robinson & Berridge 1993, Nocjar & Panksepp 2002). In any case it is clear that motivation for rewards can be enhanced as a consequence of sensitization caused by addictive drugs.

Incentive-Sensitization

The evidence for sensitization of drug reward pursuit described above is compatible with the incentive-sensitization view of addiction, but it is not conclusive, because it could be alternatively explained by changes in a number of other

components of reward or learning (Wyvell & Berridge 2000, Cardinal et al. 2002). Our hypothesis is quite specific regarding the nature of the psychological process that is sensitized in addiction. We hypothesize that it is specifically sensitization of incentive salience attribution to representations of drug cues and drug-taking that causes the compulsive pursuit of drugs and persisting vulnerability to relapse in addiction. Incentive salience attribution is hypothesized to transform the neural representations of otherwise neutral stimuli into salient incentives, able to "grab" attention, and makes them attractive and "wanted." Individuals are guided to incentive stimuli by the influence of Pavlovian stimulus-stimulus (S-S) associations on motivational systems, which is psychologically separable from the symbolic cognitive systems that mediate conscious desire, declarative expectancies of reward, and act-outcome representations (Berridge 1999, Dickinson et al. 2000, Robinson & Berridge 2000). Indeed, different brain systems appear to mediate cognitive versus incentive salience forms of motivation. Prefrontal and other cortical areas primarily mediate cognitive forms of desire and act-outcome representations, whereas NAcc-related circuitry (especially dopamine-related systems) play a more important role in Pavlovian-guided attributions of incentive salience (Balleine & Dickinson 1998, 2000; Berridge & Robinson 1998; Dickinson et al. 2000; De Borchgrave et al. 2002).

In order to test whether sensitization can specifically enhance incentive salience or "wanting" triggered by reward cues (S-S associations), it is necessary to design experiments to exclude alternative explanations. A true test for a sensitized "wanting" process requires a rigorous experimental design that prevents results from being influenced by changes in other components of reward or learning, such as "liking" or hedonic impact of the pleasant reward, cognitive predictive expectancies about it, the formation of S-S associations during learning trials, automatic stimulus-response (S-R) habits triggered by cues toward rewards, and conditioned reinforcement of reward-seeking responses by subsequent contingent cues among other alternative explanations.

Wyvell provided such evidence as part of her dissertation studies at the University of Michigan (Wyvell & Berridge 2000, 2001). She showed that both sensitization (by prior drug administration) and direct stimulation of dopamine neurotransmission in the NAcc (by amphetamine microinjection) specifically increased incentive salience attributed to a cue for sugar reward, causing that cue to elicit exaggerated "wanting" for the reward. To separate incentive salience from the other potential explanations above, Wyvell used a pure conditioned incentive paradigm based on a more general learning procedure known as a Pavlovian-instrumental transfer task (in which Pavlovian predictive cues for food, shock, etc. alter ongoing instrumental performance) (Rescorla & Solomon 1967, Dickinson & Balleine 1994). The conditioned incentive effect refers to the observation that brief presentation of a Pavlovian-conditioned cue (such as a light or a distinct sound) that has been paired with a reward can enhance instrumental responding (such as lever pressing) for that reward—even under conditions that exclude contributions from changes in hedonic "liking," S-R habits, conditioned reinforcement of

instrumental responses, etc. In a conditioned incentive experiment the cue is presented under extinction conditions, which excludes contributions from any change in "liking," hedonic impact, or primary reinforcement. Predictive S-S associations about the Pavlovian-conditioned cue are learned in separate sessions from the instrumental training sessions to exclude contributions from automatic S-R habits and from operant discriminative stimulus signals that a response will be rewarded. Finally, the cue is never presented contingent upon lever pressing during the extinction test, so it cannot act by strengthening a preceding response, excluding conditioned-reinforcement explanations for an increase in instrumental responding. Under these restricted conditions, the only plausible explanation for why a Pavlovian-conditioned cue would suddenly intensify pursuit of a reward is that incentive salience is attributed to the Pavlovian cue and its associated reward, causing cue-triggered "wanting."

Dopamine neurotransmission in the NAcc is increased by amphetamine, and if the drug is placed directly into NAcc by microinjection, it increases dopamine release there. In order to test whether amphetamine-induced dopamine release in the NAcc increases incentive salience, as hypothesized, amphetamine was microinjected into the NAcc immediately before testing using the conditioned-incentive paradigm (Wyvell & Berridge 2000). "Intra-accumbens amphetamine increased the ability of a sucrose cue to spur performance for a sucrose reward, even under extinction conditions" (p. 8129). The excessive "wanting" for reward after amphetamine microinjections was strongly under the control of the sugar cue, returning each time the cue was presented and decaying within minutes after it was removed. In parallel studies the effect of intra-NAcc amphetamine on "liking" was measured, based on affective facial reactions to the taste of sugar that are homologous to the affective facial expressions that sweet tastes elicit from human infants (Berridge 2000). It was found that microinjections of amphetamine into the NAcc did not increase the hedonic impact or "liking" for sugar, even though they had increased "wanting" for the sugar. These studies show, therefore, that intra-accumbens amphetamine, and presumably an increase in dopamine neurotransmission in the NAcc, can magnify "wanting" without changing "liking." They show, as we have suggested, that the primary role of learning in this situation is to guide incentive salience attributions so that cues trigger "wanting" as a *conditioned motivational response*. This conclusion is consistent with that of a converse experiment by Dickinson et al. (2000), who found that dopamine antagonists selectively suppress the Pavlovian-instrumental transfer effect (and further excluded an alternative explanation that dopamine changes the cognitive declarative expectation regarding act-outcome relations).

Most important to our incentive-sensitization hypothesis of addiction, Wyvell & Berridge (2001) also examined the effect of sensitization on cue-triggered "wanting" for a sugar reward. In this experiment rats were first sensitized by several injections of amphetamine. Then, after being drug free for about 2 weeks, they were tested using the conditioned-incentive paradigm described above. In

sensitized rats the Pavlovian-conditioned sugar cue produced a greater wanting for sugar than in nonsensitized rats. Thus, sensitized rats attributed excessive cue-elicited incentive salience to their reward at a time when they had received no drug at all for many days—and under conditions that exclude the alternative hypotheses above. This situation seems to model that of the drug-abstinent and "recovered" addict who suddenly relapses again after encountering drug cues. Wyvell's results suggest that relapse in human addicts after attempts to quit might also be caused by persisting sensitization in brain systems that mediate incentive salience. Upon encountering drug cues, the addict might suddenly "want" to take drugs again—to an excessive and compulsive degree—regardless of cognitive expectancies about "liking," declarative goals, absence of withdrawal, etc.

Of course, human addiction is far more complex than rats "wanting" a sugar reward. Nevertheless, these results have important implications for understanding what sensitization does to brain systems that generate motivated behavior. Sensitization enhances the ability of drug-associated cues to trigger irrational bursts of "wanting" for their reward, and in human addicts, who may have many years of drug experience with all the attendant opportunity for sensitization and learning, this may lead to the compulsive pursuit of drugs. In this view an optimal future medication for addiction would be one that reduces or prevents the expression of sensitized attributions of excessive incentive salience to drug cues and representations, thereby reducing compulsive "wanting" to take drugs (unfortunately such a medication has not yet been identified).

In summary, we suggest that at its heart, addiction is a disorder of aberrant incentive motivation due to drug-induced sensitization of neural systems that attribute salience to particular stimuli. It can be triggered by drug cues as a *learned motivational response* of the brain, but it is not a disorder of aberrant learning per se (see Figure 3). Once it exists, sensitized "wanting" may compel drug pursuit whether or not an addict has any withdrawal symptoms at all. And because incentive salience is distinct from pleasure or "liking" processes, sensitization gives impulsive drug "wanting" an enduring life of its own.

DECISION-MAKING AND LOSS OF INHIBITORY CONTROL

In addicts the excessive incentive salience posited by the incentive-sensitization theory can not only lead to the pathological pursuit of drugs (drug "wanting") but to apparently irrational choices to take drugs. The irrationality of the sensitized pursuit of drugs arises from several features of incentive sensitization. For example, even if a person knows cognitively that the drug will not give much pleasure (e.g., if the dose is low or quality is poor), sensitized implicit "wanting" can overcome low expectations of "liking." The distinction between "wanting" and "liking" can sometimes result in strange dissociations in addicts, in which goal-directed drug-seeking behavior occurs in the absence of conscious awareness

that pursuit is underway, and is dissociated from the ability of drugs to produce pleasure; that is, addicts will pursue drugs they do not like, as well as those they like (Lamb et al. 1991, Fischman & Foltin 1992). Second, irrationality could arise from the temporary reversibility of cue-triggered "wanting," which momentarily overrides more rational and stable life priorities (Elster 1999). Even if a person's explicit declarative goal is abstinence, implicit incentive salience attributions can undermine these explicit goals. And even if a person has a stable rational resolution to abstain from taking drugs, an encounter with drug cues may trigger "wanting" that competes with, and may momentarily surpass, rational intentions, precipitating a binge of relapse.

For some addicts and some drugs, additional alterations in the function of neocortical systems may further weaken the "rational brake" of cognitive regulatory processes that normally inhibit strong motivational impulses. Although prefrontal cortical systems may engage NAcc-related incentive processes (Kelley 1999, Park et al. 2002), frontocortical systems are also involved in executive processes such as decision-making and the ability to make judgments about the future consequences of one's actions (Balleine & Dickinson 1998, Smith & Jonides 1999, Bechara et al. 2000). Frontostriatal projections may be especially important in regulating emotions and providing inhibitory control over behavior (Davidson et al. 2000). In an excellent paper Jentsch & Taylor (1999) review evidence that chronic exposure to some drugs can depress neural processing in frontal regions and distort functions of the prefrontal cortex. For example, persistent changes in frontocortical blood flow and glucose utilization have been described in amphetamine and cocaine addicts (Volkow et al. 1991, 1992; Biggins et al. 1997; Bolla et al. 1998), and in polysubstance abusers there is even a decrease in the volume of the prefrontal cortex (Liu et al. 1998). In rats structural anomalies in the dendrites of pyramidal neurons in the prefrontal cortex have been found after extended cocaine self-administration (Robinson et al. 2001). This neurobiological evidence is augmented by reports that some addicts show a variety of neuropsychological deficits shared with patients who have frontal dysfunction (Bolla et al. 1998, Jentsch & Taylor 1999, Robbins & Everitt 1999b, Rogers et al. 1999, Bechara & Damasio 2002, Bechara et al. 2002). For example, Rogers et al. (1999) studied psychological function in chronic amphetamine or opiate users and found deficits in decision making "indicative of difficulties in resolving competing choices" similar to those of patients with lesions of the orbital frontal cortex (p. 325). Jentsch & Taylor (1999) have argued that dysfunction in frontostriatal systems involved in cognitive inhibitory control over behavior leads to behavior unduly dominated by "pre-potent tendencies," resulting "in a condition associated with profound impulsivity that may contribute to compulsive drug-seeking and drug-taking behavior" (p. 374).

Thus, drug-induced impairments in frontocortical function may contribute in important ways to the suboptimal choices and decisions addicts make concerning drug use. In addition, decreased activity in the prefrontal cortex may increase activity in subcortical dopamine systems (Carlsson et al. 2001, Jackson et al. 2001, Meyer-Lindenberg et al. 2002). This raises the interesting possibility that

frontocortical dysfunction may not only lead to poor decision-making and judgment, but it could further exacerbate incentive-sensitization. A loss of inhibitory control over behavior and poor judgment, combined with sensitization of addicts' motivational impulses to obtain and take drugs, makes for a potentially disastrous combination.

OTHER ADDICTIONS?

Are any of the factors we have discussed involved in other so-called addictions, such as addictions to food, sex, gambling, etc.? It is difficult to see how factors such as opponent withdrawal states or drug-induced cortical dysfunction would be involved in these other addictions. The activation of NAcc-related circuitry and incentive-salience systems might more plausibly play a role in food binging, sexual compulsions, etc., but it is simply unknown whether such compulsive motivations involve any brain features at all similar to those associated with drug sensitization. Alternatively, these kinds of compulsions might only involve the activation of NAcc-related circuitry within normal limits, with other psychological factors playing more primary causal roles. Although the question clearly is of interest, in the absence of data anything we might say further would be too wildly speculative.

SUMMARY

In contrast to hedonic/withdrawal views of addiction, we suggest that drug pleasure becomes less and less important during the transition to addiction. Even relief from withdrawal symptoms does not account for the compulsive character of drug-seeking and drug-taking behavior in addicts or for their vulnerability to relapse after detoxification (especially upon encountering drug cues and contexts). In contrast to aberrant learning theories, we suggest that no abnormality of associative learning explains the compulsive yet flexible behaviors addicts employ in their pursuit of drugs (even if abnormal associations contribute to rigid drug-taking rituals). The transition to addiction instead is due, we suggest, to the incentive-motivational consequences of drug-induced alterations in NAcc-related circuitry that mediates incentive salience. This circuitry is activated by implicit S-S associations, but the S-S associations themselves may remain quite normal, even in addicts. It is the response of the neural system that generates incentive salience that is abnormal: It results in pathological wanting. This is directed especially to drug-associated cues because excessive incentive salience is attributed chiefly to these cues, making drug-related cues into effective triggers of relapse (Figure 3).

This excessive implicit "wanting" may be compounded further in some addicts by drug-induced dysfunction in prefrontal cortical systems normally involved in decision-making, judgment, emotional regulation and inhibitory control over behavior. Cognitive deficits in the ability to inhibit or properly assess the future consequences of one's actions due to prefrontal dysfunction, combined with

excessive incentive salience due to sensitization of NAcc-related circuitry, leads to the compulsive pursuit of drugs out of proportion to the pleasure drugs provide and in the face of negative consequences for all those concerned.

DEDICATION

This paper is dedicated to the memory of Dr. Cindy L. Wyvell, who died in December 2001 shortly after completing the dissertation studies described here and after years of struggle against cancer. Throughout, Cindy evinced a degree of courage and dedication that we can only describe as heroic. Her premature death was a loss to psychology as well as to those who knew her.

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