MECHANISMS OF ACTION OF ADDICTIVE STIMULI

Incentive-sensitization and addiction

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Abstract

The question of addiction concerns the process by which drug-taking behavior, in certain individuals, evolves into compulsive patterns of drug-seeking and drug-taking behavior that take place at the expense of most other activities, and the inability to cease drug-taking, that is, the problem of relapse. In this paper we summarize one view of this process, the "incentive-sensitization" view, which we first proposed in 1993. Four major tenets of the incentive-sensitization view are discussed. These are: (1) potentially addictive drugs share the ability to alter brain organization; (2) the brain systems that are altered include those normally involved in the process of incentive motivation and reward; (3) the critical neuroadaptations for addiction render these brain reward systems hypersensitive ("sensitized") to drugs and drug-associated stimuli; and (4) the brain systems that are sensitized do not mediate the pleasurable or euphoric effects of drugs (drug "liking"), but instead they mediate a subcomponent of reward we have termed incentive salience (drug "wanting").

Introduction

Most contemporary explanations of addiction posit that addicts are motivated to take drugs primarily for one of two reasons, by "the desire to experience the positive hedonic effects of the drug … and the desire to avoid aversive withdrawal symptoms …" (Markou *et al.*, 1993, p. 176). In other words, it is generally thought that addicts are motivated to take drugs either for the pleasure drugs produce (basically to achieve remembered pleasure), or to avoid the unpleasant consequences of withdrawal. We have argued, however, that the compulsive drug-seeking and drug-taking behavior that char-acterizes addiction often are not motivated by either the desire to obtain pleasure or by the desire to relieve withdrawal (see Robinson & Berridge, 1993 and 2000, for a critique of withdrawal avoidance and pleasure-seeking views of addiction). If this is true, then why do addicts compulsively seek drugs? We have attempted to address this question by proposing the concept of "incentive-sensitization" (Robinson & Berridge, 1993, 2000; Berridge & Robinson, 1995), which can be summarized in four points.

(1) Potentially addictive drugs share the ability

to produce long-lasting changes in brain organization.

(2) The brain systems that are changed include those normally involved in the process of incentive motivation and reward.

(3) The critical neuroadaptations for addiction render these brain reward systems hypersensitive ("sensitized") to drugs and drug-associated stimuli.

(4) The brain systems that are sensitized do not mediate the pleasurable or euphoric effects of drugs (drug "liking"), but instead they mediate a subcomponent of reward we have termed incentive salience or "wanting" (Berridge, Venier & Robinson, 1989; Berridge & Valenstein, 1991; Robinson & Berridge, 1993; Berridge & Robinson, 1995, 1998; Berridge, 1996). We posit the psychological process of incentive salience to be specifically responsible for instrumental drug-seeking and drug-taking behavior (drug "wanting").

We have hypothesized that when sensitized, this incentive salience process produces compulsive patterns of drug-seeking behavior (Robinson & Berridge, 1993; Berridge & Robinson, 1995). Through associative learning the enhanced incentive value becomes focused specifically on drug-related stimuli, leading to increasingly compulsive patterns of drug-seeking and drug-taking behavior. Furthermore, the persistence of neural sensitization is hypothesized to leave addicts susceptible to relapse even long after the discontinuation of drug use. In the following we will review briefly some of the evidence for incentive-sensitization, and elaborate some of the major features of this view of addiction.

Psychomotor sensitization

Most studies showing that the repeated administration of drugs of abuse can produce sensitization (i.e. an increase in drug effect) involve measures of the psychomotor activating effects of drugs, such as their ability to enhance locomotor activity, rotational behavior or stereotyped motor patterns (Segal, Geyer & Schuckit, 1981; Robinson & Becker, 1986; Robinson & Berridge, 1993; Stewart & Badiani, 1993). Studies on the psychomotor activating effects of drugs are thought to be relevant to addiction because of the assumption that the neural substrate that mediates these effects is either the same as, or at least overlaps with, the neural substrate responsible for the rewarding effects of drugs (Wise & Bozarth, 1987). This neural substrate is, of course, the mesotelencephalic dopamine system, and especially dopamine projections to the nucleus accumbens and accumbens-related circuitry (often called the mesolimbic or mesocorticolimbic dopamine system).

There is now a wealth of evidence showing that the repeated intermittent administration of a variety of drugs of abuse results in a progressive increase in their psychomotor activating effects, and although most studies of psychomotor sensitization involve the administration of psychomotor stimulants, such as amphetamine or cocaine, psychomotor sensitization has been reported with methylphenidate, fencamfamine, morphine, phencyclidine, MDMA, nicotine and ethanol (Robinson, 1993; Robinson & Berridge, 2000; for references). Psychomotor sensitization is a very complex and rich phenomenon. For example, it is dose-dependent (Kalivas *et al.*, 1988; Browman, Badiani & Robinson, 1998a, 1998b), it is usually seen only when drugs are administered intermittently (Post, 1980, Robinson & Becker, 1986), it is often more evident long after the discontinuation of repeated drug treatment than shortly after the discontinuation of drug treatment (Antelman, 1988), and perhaps the most remarkable feature of sensitization is its persistence. Once sensitized, animals may remain hypersensitive to the psychomotor activating effects of drugs for months or years (Robinson & Becker 1986; Paulson, Camp & Robinson, 1991). Finally, sensitization is seen not only following experimenter-administered drug, but drug self-administration experience can also induce psychomotor sensitization (Hooks *et al.*, 1994; Phillips & Di Ciano, 1996; Marinelli, Le Moal & Piazza,1998).

Two other important features of sensitization deserve mention. One is that there is enormous individual variation in susceptibility to sensitization (Robinson, 1988). Some individuals show rapid and robust sensitization with a given dose of a drug, whereas others sensitize very little, if at all. There are many factors that contribute to individual variation in the susceptibility to sensitization, including genetic, hormonal and experiential factors (Shuster, Yu & Bates, 1977; Antelman *et al.*, 1980; Robinson, 1988), although how they do so is largely unknown.

Nevertheless, the incentive-sensitization theory posits that factors which render people susceptible to sensitization will also contribute to individual variation in susceptibility to addiction.

Another important feature of psychomotor sensitization is that it is not an inevitable consequence of repeated exposure to drugs. Instead, the ability of drugs to induce or express sensitization is powerfully modulated by learning and the circumstances surrounding drug administration (Robinson *et al.*, 1998). There are at least two ways that the circumstances surrounding drug administration modulate sensitization. The first is modulation of the expression of neural sensitization that has already been induced. Perhaps the best example of environmental modulation of expression is the phenomenon of context-specific sensitization. This refers to the observation that if animals are tested (i.e. receive a drug challenge) in an environment different from the one in which they received prior drug treatments, sensitization is often not expressed in behavior (Post *et al.*, 1981; Pert, Post & Weiss, 1990; Anagnostaras & Robinson, 1996; Terelli & Terry, 1999). Despite this powerful conditioned stimulus control over the expression of *behavioral* sensitization there are at least two reasons to believe that in this situation *neural* sensitization has developed, even though animals do not express it in behavior. The first is that animals receiving drug treatments in an environment other than the test environment develop normal behavioral sensitization in their drug treatment environment; they simply do not express it in a different environment that has never been paired with drug administration (Anagnostaras & Robinson, 1996). Secondly, neural sensitization has been described under conditions that preclude the influence of contextual stimuli on the neurobiological expression of the drug response, for example, in striatal tissue slices *in vitro* or in anesthetized animals (Robinson & Becker, 1982; Castañeda, Becker & Robinson, 1988; Henry & White, 1991; Nestby, Vanderschuren & De Vries, 1997; Kantor, Hewlett & Gnegy, 1999; Vanderschuren *et al.*, 1999a).

It appears, therefore, that repeated exposure to amphetamine may *induce* neural sensitization non-associatively, but whether the consequences of neural sensitization are *expressed* at a particular place or time is determined to a large extent by conditional stimuli (especially contextual stimuli) that have been associatively paired with drug administration (Anagnostaras & Robinson, 1996). Indeed, it needs to be remembered that the ability of sensitized neural systems to gain control over behavior is constantly modulated or gated by environmental (and probably interoceptive) stimuli that have been associated with drug administration. It may be that this interaction of neural sensitization with associative learning is responsible for the focus on drug-associated stimuli in addicts, whereby the acts and objects associated with drug-taking become especially powerful incentives themselves. Contextual modulation of the expression of sensitization may contribute to the critical role that context plays in precipitating relapse. That is, an implication for addiction is that the expression of sensitization to the incentive properties of drug-related stimuli may be strongest in contexts that have been also distinctly related to drug-taking in the past. The ability of context to act as an occasion-setter and to modulate sensitization would interact with the ability of specific drug-associated conditioned stimuli to trigger craving as a classically conditioned response, combining to provide very strong contextual control over both craving and relapse (Robinson & Berridge, 1993; Anagnostaras & Robinson, 1996; Robinson & Berridge, 2000).

The second way in which the circumstances surrounding drug administration may modulate sensitization is to influence whether neural sensitization is induced in the first place (or at least the rate and extent of sensitization produced by a given dose of a drug). For example, there are now a number of reports that when low to moderate doses of amphetamine or cocaine are administered in the environment where an animal lives (i.e. at "home") they are less effective in inducing psychomotor sensitization than if the same doses are given in a relatively distinct test environment (one that is novel to the animal until its first pairing with the drug; Badiani, Anagnostaras & Robinson, 1995; Badiani, Browman & Robinson, 1995; Crombag, Badiani & Robinson, 1996; Badiani, Camp & Robinson, 1997; Browman, Badiani & Robinson, 1998a; Robinson *et al.*, 1998; Fraioli *et al.*, 1999). Further studies have established that the effect of environmental context is not to completely preclude sensitization, but to shift the dose-effect curve for the induction of sensitization. When high enough doses of either cocaine or amphetamine are given sensitization is induced re-

gardless of environmental condition (Browman *et al.*, 1998a, 1998b).

The ability of environmental context to modulate the induction of sensitization may be related to its ability to modulate the neural circuitry engaged by drugs. Badiani and colleagues (1998) reported, for example, that the ability of amphetamine to induce c-*fos* mRNA in the striatum is modulated powerfully by the environmental context in which amphetamine is administered. Indeed, it appears that that environmental context can modulate which cell populations in the striatum are engaged by amphetamine. When given at home amphetamine induced c-*fos* only in striatal neurons also positive for dopamine D1 receptor mRNA (not in cells positive for D2 receptor mRNA). However, when given in association with environmental novelty amphetamine induced c-*fos* in both D1 and D2 mRNA-positive neurons (Badiani *et al.*, 1999).

In summary, sensitization is not an inevitable consequence of exposure to potentially addictive drugs. That is, it is not a simple pharmacological phenomenon. Both the expression and the induction of sensitization can be powerfully modulated by non-pharmacological factors, including environmental factors associated with drug administration. The influence of environmental factors on sensitization has important implications not only for understanding the phenomenon, but for thinking about therapeutic approaches in treating addiction.

Sensitization and drug reward

The studies reviewed above on sensitization to the psychomotor activating effects of drugs indicate that addictive drugs induce neural sensitization; but by themselves they provide only indirect evidence that sensitization occurs to the incentive motivational or rewarding effects of drugs (Wise & Bozarth, 1987). More direct evidence that the neural substrate that is sensitized is involved in mediating drug reward comes from two other sources. The first are studies showing that not only do the psychomotor stimulant effects of drugs sensitize, but so do their rewarding effects (Schenk & Partridge, 1997). There are a number of reports that prior exposure to a variety of potentially addictive drugs enhances the later acquisition of both a drug self-administration habit (Woolverton, Goldberg & Ginos, 1984; Piazza *et al.*, 1989, 1990; Horger, Shelton

& Schenk, 1990; Horger, Giles & Schenk, 1992; Valadez & Schenk, 1994; Pierre & Vezina, 1997; Pierre & Vezina, 1998) or a conditioned place preference (Lett, 1989; Gaiardi *et al.*, 1991; Shippenberg & Heidbreder, 1995; Shippenberg, Heidbreder & Lefevour, 1996; Shippenberg, Lefevour & Heidbreder, 1996). Previous sensitization to amphetamine also increases the "breakpoint" for amphetamine self-administration when rats are tested using a progressive ratio schedule (Mendrek, Blaha & Phillips, 1998; Lorrain, Arnold & Vezina, 2000), and the enhanced responding for a conditioned reward produced by intra-accumbens amphetamine is potentiated by cocaine sensitization (Taylor & Horger, 1999). Furthermore, sensitization to amphetamine facilitates behavior guided by Pavlovian learning (Harmer *et al.*, 1997; Harmer & Phillips, 1998, 1999a, 1999b). Finally, in recent studies Deroche, Le Moal & Piazza (1999) have found that experience with self-administered cocaine later enhances the motivation to seek cocaine in, for example, a runway apparatus, and De Vries and colleagues in the Netherlands have reported that the ability of different drugs to reinstate (prime) drug-seeking behavior is related positively to whether they also show cross-psychomotor sensitization (De Vries *et al.*, 1997, 1998, 1999; Vanderschuren *et al.*, 1999b).

The second line of evidence that the neural substrate sensitized by drugs of abuse is involved in mediating drug reward, comes from studies on the neurobiology of sensitization. There is not space here to review this large literature, but suffice to say there is now considerable evidence that behavioral sensitization is associated with neuroadaptations in dopamine and accumbens-related circuitry (Robinson & Becker, 1986; Kalivas & Stewart, 1991; Robinson & Berridge, 1993; Stewart & Badiani, 1993; Pierce & Kalivas, 1997; White & Kalivas, 1998; Wolf, 1998). This is important because it is well established that these neural systems play an important role in mediating the rewarding effects of drugs and other incentives (Wise & Bozarth, 1987; Koob & Bloom, 1988; Smith, 1995). Thus, if sensitization-related neuroadaptations are found in this mesocorticolimbic circuitry this is strong evidence that at least one neural system known to be critical for mediating drug reward undergoes "neural sensitization".

Both pre- and post-synaptic neuroplastic adaptations have been described in the

dopamine/accumbens system of sensitized animals. An example of a presynaptic adaptation is a persistent increase in the ability of a variety of drugs to increase the overflow of dopamine in the nucleus accumbens and striatum of sensitized animals, *in vitro* and *in vivo* (Robinson & Becker, 1982, 1986; Kalivas & Stewart, 1991; Robinson & Berridge, 1993; Nestby *et al.*, 1997; Pierce & Kalivas, 1997; Kantor *et al.*, 1999; Vanderschuren *et al.*, 1999a). Examples of postsynaptic adaptations include an increase in the sensitivity of dopamine D1 receptors (Henry & White, 1991; White & Kalivas, 1998) and a decrease in the sensitivity of glutamate receptors (White *et al.*, 1995) in the nucleus accumbens of sensitized animals (see Clark & Overton, 1998; Wolf, 1998 for a review of the role of excitatory amino acids in sensitization). More recently it has been reported that both amphetamine and cocaine sensitization are also accompanied by persistent structural modifications in the morphology of output neurons in both the nucleus accumbens and prefrontal cortex (Robinson & Kolb, 1997, 1999). Repeated treatment with amphetamine or cocaine increases the length of dendrites on medium spiny neurons in the nucleus accumbens and on pyramidal neurons in the prefrontal cortex. This is accompanied by an increase in spine density on the distal dendrites of these cells. On medium spiny neurons there is an especially large increase in the number of branched spines; that is, spines with multiple heads. Furthermore, cocaine self-administration experience has similar effects (Robinson *et al.*, 1999). These data suggest that sensitization may involve changes in patterns of synaptic connectivity in brain reward systems, changes that may be similar to those seen in other neural systems in association with other forms of experience-dependent plasticity (Robinson & Kolb, 1997, 1999).

To reiterate the basic thesis of the incentive-sensitization view of addiction, it was originally proposed (Robinson & Berridge, 1993) that addictive drugs share the ability to produce persistent neuroadaptations in brain regions involved in the process of incentive motivation and reward, adaptations that render these regions hypersensitive ("sensitized"). It should be clear from the above that there is now a wealth of evidence to support this claim. The incentive-sensitization view also posits that it is largely because of sensitization of a neural substrate that mediates

drug reward that with repeated drug use drugs gradually become more and more attractive (i.e. they acquire greater and greater incentive value), and become increasingly able to control behavior. Studies on sensitization of drug reward and the neurobiology of sensitization support this claim. Furthermore, we have suggested that sensitization enhances the probability of relapse, even long after the discontinuation of drug use, and animal studies on the relationship between psychomotor sensitization and reinstatement support this claim. Of course, the hypothesis that incentive-sensitization mediates addiction in humans is more speculative, and is predicated on the assumption that repeated exposure to drugs of abuse can induce neural sensitization in humans. It is one thing to demonstrate incentive-sensitization in animals models, but—as critics of our theory occasionally point out—quite another to demonstrate its occurrence in addicts.

Sensitization in humans

As might be expected from the difficulty in studying this issue in humans, there has been very little research on the topic of whether sensitization actually occurs in the brains of human addicts. Until recently, the only direct evidence that repeated exposure to psychostimulant drugs can produce sensitization in humans came from studies on the phenomenology of amphetamine and cocaine psychosis (Post & Contel, 1983; Segal & Schuckit, 1983; Sato *et al.*, 1983; Sato, 1986; Angrist, 1994). There is a considerable clinical literature which suggests that repeated exposure to amphetamine or cocaine results in a progressive increase in their psychotomimetic effects (Angrist, 1994), and that this enhanced sensitivity may persist long after the discontinuation of drug use (Utena, 1966; Sato *et al.*, 1983; Sato, 1986). Related effects have been described in non-human primates (Castner & Goldman-Rakic, 1999).

More direct evidence for sensitization to the psychomotor effects of amphetamine in humans has been lacking until only very recently, but there are now two reports of psychomotor sensitization in humans. Strakowski *et al.* (1996) first reported the results of a double-blind, placebo-controlled study in drug-naive volunteers given two treatments (48 hours apart) with 0.25 mg/kg d-amphetamine. They found that the second treatment with amphetamine elicited a

significantly greater increase than the first in four behavioral measures: activity/energy, mood, rate and amount of speech and eye-blink rate. In a second study Strakowski & Sax (1998) replicated and extended these findings to see if three treatments with amphetamine would produce a progressive increase in drug effect, as is usually seen in animal experiments. Two measures increased progressively with repeated amphetamine treatment: activity/energy and eye-blink rate. Indeed, for eye-blink rate there was no effect of the first treatment with amphetamine, relative to placebo, but an increase in eye-blink rate emerged with subsequent drug treatments even though the dose was the same. Finally, evidence supporting the concept of incentive-sensitization in humans, relevant specifically to drug taking, comes from the interesting tentative observation of Bartlett *et al.* (1997) that cocaine users who developed sensitization to the psychotomimetic effects of the drug have an elevated incidence of relapse, as indicated by more frequent rehospitalizations.

In summary, although there is little research in humans and it is fraught with technical limitations, the available evidence suggests that repeated exposure to psychostimulant drugs can sensitize some drug effects in humans. Further studies on behavioral sensitization in humans will be critical in testing the notion of incentive-sensitization, but it is worth injecting a note of caution in interpreting negative behavioral studies. It is not obvious *a priori* which behavioral measures in humans will provide the most sensitive indicators of a sensitization process. This is a difficult issue even in animal studies. For example, it is often difficult to quantify behavioral sensitization using measures of locomotor activity, unless exactly the right dose and treatment conditions are used (Crombag *et al.*, 1999). Also, even in rats, some behaviors show robust sensitization, such as rotational behavior, repetitive sniffing and repetitive head movements, whereas other seemingly related stereotyped behaviors do not, such as oral movements (Robinson & Becker, 1986; Crombag *et al.*, 1999).

Finally, one needs to keep in mind that for the most part indices of *behavioral* sensitization are important only as secondary measures because they provide indicators of underlying neuroadaptive processes (*neural* sensitization), and it is *neural* sensitization that we posit to be crucial to addiction. The incentive-sensitization hypothesis makes strong predictions regarding neural sensitization and drug-seeking in human addicts, but not necessarily about what which specific observable other behaviors might best reflect neural sensitization. The critical prediction made by the incentive-sensitization view of addiction is this: the brains of human addicts who compulsively crave drugs will contain a neural substrate that has been rendered *sensitized* by drugs. A role of that neural substrate will be to mediate the incentive salience of drug rewards. Further, individuals will differ in their susceptibility for sensitization of that neural substrate, and those who sensitize most readily will be most at risk for addiction. These predictions are testable, and so the incentive sensitization theory of addiction can be confirmed or disproved on the basis of empirical evidence.

A better understanding of the nature of neural sensitization, based on animal studies, will be crucial to developing proper tests of the theory in human addicts. Once we understand the neural basis of sensitization in non-human animals we should be able to determine if the same neuroadaptions exist in the brains of addicts. If they do not, the incentive-sensitization theory is proved wrong. Of course, this proof first requires that we understand which neurobiological adaptations produced by repeated treatment with drugs are causally related to the sensitization of which behaviors. Secondly, it will require that adequate technological tools be developed to quantify the relevant neuroadaptations, in the relevant brain regions in humans, which given the rapid advances in this field, should appear in the future. Thus, future research on neuroadaptations engendered by drug use in humans, derived from an understanding of the development of neural sensitization in animal models, will eventually provide a final test of the notion of incentive-sensitization.

"Wanting" versus "Liking"

The final issue we would like to address concerns the nature of the psychological process that is mediated by the neural substrate that undergoes sensitization. To the extent this is the dopamine/accumbens system it concerns the nature of the incentive and reward function mediated by this circuitry. This leads us to the topic that we have termed "wanting" versus "liking" (Berridge & Valenstein, 1991; Robinson & Berridge, 1993;

Berridge & Robinson, 1995, 1998; Berridge, 1996, 1999). The incentive-sensitization theory posits explicitly that hedonic affect, either as subjective pleasure or its underlying core process ("liking"), is not the component of drug reward that is sensitized in addiction, and is not the psychological process that is mediated by do-pamine systems (Robinson & Berridge, 1993; Berridge, 1996; Berridge & Robinson, 1998). Instead, we have hypothesized that a different component of incentive motivation is sensitized in addiction, a component we have termed "wanting" (Robinson & Berridge, 1993; Berridge, 1996; Berridge & Robinson, 1998).

The idea that the process of incentive motiv-ation can be subdivided into at least two compo-nents is an extension of traditional psychological models of incentive motivation developed by the-orists such as Bindra (1978) and Toates (1986), and neurobiologically it is an extension of views proposed by Phillips, Fibiger and colleagues (Fibiger & Phillips, 1986; Blackburn *et al.*, 1989), Wise (1985, 1989; Wise & Bozarth, 1987) and Panksepp (1986a, 1986b). In tra-ditional models of incentive motivation it was hypothesized that a single process mediates both incentive value (how much an incentive is "wanted"), and hedonic value (how much it is "liked"). Incentives were hypothesized to have incentive value *because* of their ability to produce pleasure. Therefore, what we have called "wanting" and "liking" were necessarily connec-ted and treated as explanations for positive re-inforcement. There is evidence, however, that the psychological process and neural substrate responsible for motivating behavior, for deter-mining incentive value ("wanting"), is separable from the psychological process and neural sub-strate that mediates hedonics ("liking") (Berridge & Valenstein, 1991; Robinson & Berridge, 1993; Berridge, 1996; Berridge & Robinson, 1998). For example, drugs of abuse can promote drug-taking behavior in the absence of any subjective hedonic effects (Fischman, 1989; Lamb *et al.*, 1991; Fischman & Foltin, 1992), which is not consistent with the notion that the positive reinforcing effects of drugs can be equated with their hedonic impact. Further-more, there is considerable evidence that manip-ulations of dopamine neurotransmission exert powerful effects on motivated behavior ("wanting") without changing basic hedonic re-actions ("liking") to unconditioned rewards,

both in non-human animals (Berridge *et al.*, 1989; Berridge, 1996; Berridge & Robinson, 1998) and in humans (Brauer & DeWit, 1996, 1997; Ohuoha *et al.*, 1997) (see Berridge, 1996; Berridge & Robinson, 1998) for extensive review and discussion of this point). It is because of these kinds of experimentally established dissoci-ations between the apparent incentive value of drugs (and natural rewards, such as food), and their ability to engender pleasure, that we sug-gested a distinction be made between "wanting" and liking" (Berridge & Valenstein, 1991; Robinson & Berridge, 1993; Berridge, 1996).

More specifically, we have hypothesized that the neural and psychological processes underly-ing "wanting" involve the attribution of attract-ive salience to stimuli and their representations, a process we call *incentive salience* attribution. We have suggested it is the process of incentive salience attribution that transforms the sensory features of ordinary stimuli or, more accurately, the neural and psychological representations of stimuli, so that they become especially salient stimuli, stimuli that "grab the attention", that become especially attractive and wanted, thus eliciting approach and guiding behavior to the goal (Robinson & Berridge, 1993; Berridge, 1996; Berridge & Robinson, 1998). It is incen-tive salience that determines the value of incen-tives, and that controls seeking and instrumental behavior regarding them (Berridge & Robinson, 1998). Thus, when the neural systems that me-diate incentive salience become sensitized, and if the incentive salience attributed to drug-taking and to associated stimuli becomes pathologically amplified, then compulsive drug-seeking and drug-taking behavior may ensue.

Finally, we have argued that the neural system responsible for incentive salience attribution can sometimes produce goal-directed behavior ("wanting") not only in the absence of subjective pleasure (e.g. Lamb *et al.*, 1991), but in the ab-sence of conscious awareness of "wanting" itself (for a full discussion of this point see Robinson & Berridge, 1993, 2000; Berridge & Robinson, 1995; Berridge, 1996, 1999). That is, activation of this system may constitute an implicit rather than explicit psychological process, similar to implicit memory or to implicit perceptual pro-cesses (Tiffany, 1990; Weiskrantz, 1997), and can act sometimes as an unconscious motiva-tional process (Robinson & Berridge, 1993; Berridge & Robinson, 1995; Berridge, 1999).

We become aware of its activation only by engaging interpretive cognitive processes needed to translate implicit activation into explicit subjective feelings (Nisbett & Wilson, 1977; Hilgard, 1986; LeDoux, 1996; Berridge & Robinson, 1998). Indeed, it may be because these psychological processes sometimes operate outside of conscious awareness that addicts have so little insight into why they want drugs so much. Addicts may report that they are miserable, their life is in ruins, and that even the drug is not that great anymore, and they are themselves bewildered by the intensity of their compulsive behavior.

In summary, the major feature of our view of incentive motivation that distinguishes it from earlier models is that it posits there are at least two distinct psychological processes involved in reward: (1) subjective pleasure ("liking"), and (2) incentive salience attribution ("wanting"). These two psychological processes are mediated by different neural systems. Furthermore, it is suggested that the neural systems that are *sensitized* by addictive drugs are those involved specifically in incentive salience attribution (Robinson & Berridge, 1993). The neural systems that mediate the subjective pleasurable (hedonic) effects of drugs do not appear to sensitize. This may be why addiction is characterized by an increasing dissociation between the incentive value of drugs (how much they are wanted) and their subjective pleasurable effects (how much they are liked). With the development of an addiction drugs become pathologically wanted ("craved") and this can occur even if drugs are liked less and less. This hypothesis has important implications in thinking about the development of therapies for addiction (Robinson & Berridge, 2000, for discussion).

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