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Conditioned cues and the expression of stimulant sensitization in animals and humans

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Abstract

Repeated intermittent exposure to psychostimulants can lead to long-lasting sensitization of the drugs' behavioral and biochemical effects. Such findings have figured importantly in recent theories of drug addiction proposing that sensitized nucleus accumbens (NAcc) dopamine (DA) overflow in particular acts in concert with other alterations in the neurochemistry of this nucleus to promote drug seeking and self-administration. Yet, experiments in rodents, nonhuman primates and humans have not always detected behavioral or biochemical sensitization following drug exposure, bringing into doubt the utility of this model. In an effort to reconcile apparent discrepancies in the literature, this review assesses conditions that might affect the expression of sensitization during testing. Specifically, the role played by conditioned cues is reviewed. A number of reports strongly support a potent and critical role for conditioned stimuli in the expression of sensitization. Findings suggest that stimuli associated either with the presence or absence of drug can respectively facilitate or inhibit sensitized responding. It is concluded that the presence or absence of such stimuli during testing for sensitization in animal and human studies could significantly affect the results obtained. It is necessary to consider this possibility especially when interpreting the results of studies that fail to observe sensitized responding.

Keywords

conditioned inhibition; conditioning; dopamine; drug addiction; drug self-administration; excitatory Pavlovian conditioning; facilitation; occasion setters; sensitization

1. Sensitization in animals and humans

There is general agreement that rats repeatedly exposed to psychostimulants like amphetamine will exhibit enhanced - sensitized - locomotor responding when subsequently challenged with the drug some time later. In these animals, the reactivity of mesoaccumbens dopamine (DA) neurons to the drug challenge is also enhanced (for critical reviews of the preclinical literature, see Kalivas and Stewart, 1991; Vanderschuren and Kalivas, 2000; Vezina, 2004). These are long-lasting effects in the rat. Sensitized locomotor responding has been reported up to one year (Paulson et al., 1991) and enhanced nucleus accumbens (NAcc) DA overflow up to three

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months following drug exposure (Hamamura et al., 1991). Notably, the magnitude of amphetamine-induced DA overflow in the NAcc increases with time following exposure to the drug (Vezina, 2007).

Given the importance of the mesocorticolimbic DA pathways in the generation of appetitive behaviors including the seeking and consumption of abused drugs, it follows that long-lasting enhancements in the reactivity of these pathways could lead to long-lasting enhancements in appetitive behavioral output. This possibility has figured importantly in the formulation of an influential theoretical view of addiction proposing that sensitized NAcc DA overflow acts in concert with other alterations in the neurochemistry of this nucleus to enhance the appetitive effects of drugs and promote their pursuit and self-administration (Robinson and Berridge, 1993). Consequently, a large number of systems, cellular and molecular biological level investigations have focused on the mechanisms that might underlie altered reactivity in midbrain DA neurons and those systems they interact with (Hyman et al., 2006).

It remains, however, that most of the experimental support for enhanced DA overflow stems from experiments conducted in rodents, while findings obtained in nonhuman primates and humans have been equivocal. For example, functional neuroimaging studies suggest a profile in limbic regions of reduced rather than augmented drug-induced DA responses in cocaine addicted patients compared to controls (e.g., Volkow et al., 1997). This has led to arguments that sensitization of NAcc DA responsivity as a mechanism for drug abuse and other forms of pathology is of limited value as it does not extend to the human condition. Recent evidence has emerged, however, demonstrating that amphetamine-induced DA release from ventral striatum can in fact be sensitized in human subjects (Boileau et al., 2006).

Below we first review the evidence for behavioral and dopaminergic sensitization in animals and humans as it relates to drug seeking and drug taking. Evidence that the expression of sensitization can be regulated by conditioned cues is then reviewed. The review of the animal literature is restricted to reports of experiments conducted in rats as these have provided the majority of the preclinical evidence in these areas. In an effort to reconcile apparent discrepancies in the literature, we specifically explore the possibility that the expression of sensitization can be facilitated in some cases and inhibited in others. It is argued that such effects must be considered when interpreting the results of studies that fail to observe sensitized responding.

1.1. Sensitization in animals

Amphetamine increases extracellular levels of DA in the terminal and cell body regions of mesoaccumbens DA neurons by reversing DA transport and preventing its uptake via the DA transporter (Seiden et al., 1993). In the NAcc, this effect has been associated with its ability to produce locomotor activity and support self-administration (Hoebel et al., 1983; Vezina and Stewart, 1990). Both effects are blocked by DA receptor antagonists or 6-OHDA lesions of DA nerve terminals in the NAcc (Joyce and Koob, 1981; Lyness et al., 1979; Phillips et al., 1994; Vezina, 1996).

In rats previously exposed to repeated intermittent psychostimulant injections, these effects are enhanced (see Box 1). Long-lasting sensitized locomotor and NAcc DA responding have been reported (Kalivas and Stewart, 1991; Vanderschuren and Kalivas, 2000; Vezina, 2004). In the latter case, the enhanced ability of drugs like amphetamine to increase extracellular levels of DA in the NAcc represents the neuroadaptation most consistently associated with the expression of behavioral sensitization. It increases with time, and has been observed in vitro and in vivo weeks to months following drug exposure (Hamamura et al., 1991; Kolta et al., 1989; Paulson and Robinson, 1995; Robinson, 1988, 1991; Segal and Kuczenski, 1992; Wolf et al., 1994; Vezina, 2007; cf, Kuczenski et al., 1997). The induction of sensitization by

psychostimulants, on the other hand, has been found to occur in the ventral tegmental area (VTA), site of the cell bodies of mesoaccumbens DA neurons. Both locomotor and NAcc DA sensitization are produced by amphetamine in the VTA in a D1 DA receptor dependent manner (Bjijou et al., 1996; Cador et al., 1995; Dougherty and Ellinwood, 1981; Hooks et al., 1992; Kalivas and Weber, 1988; Perugini and Vezina, 1994; Vezina, 1993, 1996; Vezina and Stewart, 1990). It is likely that both types of sensitization are produced by a cascade of neuronal events initiated by increases in extracellular levels of DA in the VTA (Kalivas and Duffy, 1991). These certainly involve glutamate-DA interactions as activation of all three glutamate receptor subtypes (NMDA, AMPA and metabotropic) is required for the induction of locomotor sensitization by amphetamine (Vanderschuren and Kalivas, 2000; Vezina and Suto, 2003; Wolf, 1998).

There is also convincing evidence that repeated exposure to psychostimulants leads to their enhanced self-administration. As a limbic-motor interface (Mogenson, 1987) receiving rich sensory encoding projections from the VTA and forebrain regions like the prefrontal cortex, hippocampus and basolateral amygdala, the NAcc is well positioned to play a central role in the generation of adaptive motor responses to behaviorally relevant stimuli. Because activity in mesoaccumbens DA neurons is linked not only to the locomotion produced but also to the self-administration supported by drugs like amphetamine, it is reasonable to expect that sensitized reactivity in these neurons will affect drug seeking and drug self-administration. It has been argued that activity in mesoaccumbens DA neurons encodes the incentive valence of a drug effect (Robinson and Berridge, 1993; Stewart et al., 1984; Vezina et al., 1999). If this were the case, sensitization in these neurons should similarly enhance the incentive to pursue the drug and those stimuli associated with it. Many reports supporting this view have now established that previous exposure to a number of drugs leads to enhanced conditioned place preference (Gaiardi et al., 1991; Lett, 1989; Shippenberg and Heidbreder, 1995) as well as facilitated acquisition of drug self-administration (Horger et al., 1990, 1992; Piazza et al., 1989, 1991; Pierre and Vezina, 1997; Valadez and Schenk, 1994) and, once the behavior is acquired, enhanced motivation to obtain the drug (Lorrain et al., 2000; Mendrek et al., 1998; Vezina et al., 2002). As observed with sensitized locomotion and NAcc DA overflow, the development of these effects on drug self-administration also requires the activation of D1 DA and glutamatergic receptors in the VTA (Pierre and Vezina, 1998; Suto et al., 2002, 2003).

1.2. Sensitization in humans

In the last 10-15 years, functional neuroimaging techniques have been developed such as positron emission tomography (PET) that use radioactively labeled benzamide ligands for D2/3 DA receptors and can be coupled to magnetic resonance imaging (MRI). These have permitted studies of the effects of abused drugs on DA reactivity in human forebrain that recently have achieved sufficient spatial resolution to allow assessment of different striatal subregions. As established in rodents, these studies indicate that extracellular levels of DA are also increased in human striatum (especially ventral subregions) following the acute administration of various abused drugs including amphetamine (Volkow et al., 1994, 1997, 1999, 2001; Laruelle et al., 1995; Breier et al., 1997; Drevets et al., 2001; Leyton et al., 2002; Martinez et al., 2003, 2007; Abi-Dargham et al., 2003; Oswald et al., 2005; Riccardi et al., 2006a; Boileau et al., 2006, 2007; Munro et al., 2006; Casey et al., 2007) and cocaine (Schlaepfer et al., 1997; Cox et al., 2006). These drug-induced increases in extracellular DA were found to correlate with positive mood states and craving as well as novelty and sensation seeking.

While human studies are understandably more complex than those conducted in rodents, evidence that sensitization can occur to the behavioral effects of drugs has been reported, although not without some apparent inconsistencies (for a critical review of the human literature, see Leyton, 2007). When sufficiently high amphetamine concentrations were

administered to non-drug dependent subjects (see Box 2), sensitization to a number of drug effects was observed, including potentiated indices of vigor and energy levels as well as potentiated eye-blink and mood-elevating responses (Strakowski et al., 1996, 2001; Strakowski and Sax, 1998; Boileau et al., 2006). In one study (Sax and Strakowski, 1998), sensitized drug-induced elevation in mood correlated positively with the personality trait of novelty seeking. In the longest study, augmented amphetamine-induced increases in vigor were observed a full year later (Boileau et al., 2006). Sensitization to how much the subjects liked the amphetamine was not typically observed in these studies, a finding consistent with evidence suggesting that NAcc DA is linked more to the motivational salience of drugs and the cues they are associated with than to the pleasure derived from their consumption (Stewart et al., 1984; Stewart, 1992; Blackburn et al., 1992; Robinson and Berridge, 1993; Berridge and Robinson, 1998; Ikemoto and Panksepp, 1999; Leyton, 2008). Interestingly, tolerance to the euphoric effects of psychostimulant drugs has been reported in cocaine dependent abusers despite enhanced drug seeking (Volkow et al., 1997; Mendelson et al., 1998). These individuals have also been reported to fail to show sensitized subjective or physiological responses following 2-4 daily cocaine administrations (Nagoshi et al., 1992; Rothman et al., 1994; Gorelick and Rothman, 1997).

Studies assessing sensitization of the striatal DA effects of psychostimulants are considerably smaller in number but their findings are somewhat consistent with the behavioral results reviewed above. When conducted in non-drug abusing subjects, significantly greater amphetamine-induced ventral striatal DA release was observed two weeks and again one year following the administration of three drug doses over a one week period (Boileau et al., 2006). The extent of DA sensitization correlated positively with sensitization of energy level and eye-blink rate as well as the personality trait of novelty seeking. However, when conducted in detoxified patients with a history of cocaine dependence, less rather than more striatal DA release was observed in response to a psychostimulant challenge (Volkow et al., 1997; Martinez et al., 2007). Importantly, this reduced DA response could not be explained as a failure of the DA system to respond as these individuals are capable of exhibiting drug cue-induced increases in DA release (reported selectively in the dorsal striatum; Volkow et al., 2006; Wong et al., 2006).

A number of significant differences exist between studies conducted in healthy subjects and drug abusing patients that might account for the different results reported. In the latter case, subjects have been exposed to substantial amounts of drug and it is possible that even in detoxified patients the intensity of this exposure may interfere with the subsequent expression of sensitization. In the rat, enhanced drug-induced NAcc DA overflow is not observed in the days following exposure but rather weeks to months later (Hamamura et al., 1991; Hurd et al., 1989; Segal and Kuczenski, 1992; Paulson and Robinson, 1995). The withdrawal period necessary to observe sensitization may be longer in humans and longer still following prolonged intense drug exposure (see Dalia et al., 1998; Vezina et al., 2007). Another critical difference between studies conducted in healthy and drug abusing subjects may involve the various environmental stimuli surrounding drug taking and those constituting the testing conditions. Drug-paired and drug-unpaired cues may differentially influence drug-induced DA responsivity in these two groups. The constellation of stimuli afforded by the PET testing environment, for example, would be expected to exert different effects in individuals that have received drug only in their presence, compared to others that have associated these cues with the absence of drug. The evidence supporting this possibility is outlined below.

2. Conditioned cues and the expression of sensitization

It has been known for some time that the expression of behavioral sensitization can come under strong conditioned environmental stimulus control. The primary evidence for this comes from

experiments showing that rats previously exposed to the drug in one environment (Paired) show a greater locomotor response to the drug on a test for sensitization conducted in this environment compared to rats previously exposed to the drug elsewhere (Unpaired) or Control rats previously exposed to saline in both environments. Indeed, under these conditions, Unpaired rats fail to show any evidence for locomotor sensitization when tested with the drug, even though they have previously received the same pharmacological exposure to the drug as Paired rats. Such environment-specific expression of locomotor sensitization has been reported with different drugs including morphine, amphetamine and cocaine (Vezina and Stewart, 1984; Stewart and Vezina, 1987; Vezina et al., 1989; Pert et al., 1990; Stewart and Vezina, 1991; Anagnostaras and Robinson, 1996; Anagnostaras et al., 2002; Wang and Hsiao, 2003; Mattson et al., 2008; for reviews, see Stewart and Vezina, 1988; Stewart, 1992). Recently, this approach was used to demonstrate environment-specific sensitization of amphetamine-induced NAcc DA overflow as well (Guillory et al., 2006).

In these experiments, a discrimination procedure is often used to simultaneously expose animals to a drug and allow for associations to form between the drug unconditioned stimulus (UCS) and the environment conditioned stimulus (CS) complex (Figure 1). In locomotor activity experiments, rats in a Paired group receive drug in activity monitoring chambers on one day and saline in another environment (often the home cage) the next day. Rats in an Unpaired group receive the same number of drug injections but in the other environment and saline in the activity chambers; these rats are thus exposed to drug but unpaired with the activity chambers. Finally, a third group of Control animals is exposed equally to both environments but never to drug. This procedure allows for the subsequent testing of conditioned responding when rats in all groups are administered saline before the test and sensitized responding when all rats are administered a challenge drug injection before testing (Figure 1). Inevitably, enhanced responding is observed in Paired animals on both of these tests: conditioned locomotion on the test for conditioning and environment-specific sensitization on the test for sensitization (Figure 2).

2.1. Excitatory Pavlovian conditioning and the expression of sensitization

Not surprisingly, early attempts to account for environmental stimulus control of the expression of sensitization proposed that it was due simply to the summation of the drug UCS and the growing conditioned response to the drug-paired CS (Hinson and Poulos, 1981; Pert et al., 1990). In the rat, a number of CS-elicited conditioned responses have been demonstrated following drug-CS pairings including locomotor activity, stereotypy and rotational behavior (Beninger and Hahn, 1983; Vezina and Stewart, 1984; Carey, 1986; Drew and Glick, 1987; Hiroi and White, 1989; Pert et al., 1990; Stewart and Vezina, 1991; Anagnostaras and Robinson, 1996) as well as NAcc DA overflow (Fontana et al., 1993; Gratton and Wise, 1994; Di Ciano et al., 1998; Ito et al., 2000). Similarly, a number of CS-elicited conditioned responses have been reported in humans, including craving as well as increased euphoria, energy, drug liking, drug wanting, heart rate and systolic blood pressure (Foltin and Haney, 2000; Panlilio et al., 2005; Berger et al., 1996; Leyton et al., 2005; Boileau et al., 2007). Cue-elicited conditioned striatal DA release has also been reported in humans (Volkow et al., 2006; Wong et al., 2006; Boileau et al., 2007). However, while conditioned drug effects have been proposed to play potentially important roles in motivating drug seeking in animals and humans (Stewart et al., 1984; Childress et al., 1988; Stewart, 2004), their contribution to environment-specific sensitization is less clear. For example, the simple combination of a conditioned response and the drug UCS does not always summate to the perceived sensitized response (Anagnostaras and Robinson, 1996). In addition, some exposure regimens, such as infusing amphetamine into the VTA, do produce locomotor and NAcc DA sensitization but do not elicit an unconditioned response or lead to the development of a conditioned response, so that the expression of sensitization is context independent (Vezina and Stewart, 1990; Perugini

and Vezina, 1994; Vezina, 1996; Scott-Railton et al., 2006). Similarly, in vitro striatal slice experiments showing sensitized DA release necessarily do so in the absence of contextual stimuli (Castaneda et al., 1988; Robinson and Becker, 1982), making it necessary to consider alternative explanations for how drug associated environmental cues regulate the expression of sensitization. These findings clearly show that sensitization is a non-associative phenomenon that can nonetheless come under environmental stimulus control.

2.2. Facilitation and conditioned inhibition can regulate the expression of sensitization

Anagnostaras and Robinson (1996) reported compelling findings supporting the idea that stimuli acting as facilitators (also referred to as occasion setters) can account for environment-specific sensitization. Facilitating properties are bestowed on stimuli subjected to contingencies that allow them to reliably predict the occurrence of another stimulus. Once established, these stimuli can then function as occasion setters by modulating the excitatory strength of other stimuli. Unlike conditioned excitators, facilitators do not necessarily elicit conditioned responses but rather control the ability of other stimuli to do so (Rescorla, 1985; Holland, 1992). In the case of sensitization, Anagnostaras and Robinson (1996) show that an environmental stimulus complex that comes to predict the presence of a drug can also acquire the ability to set the occasion for the sensitized response on the test day without the need to elicit an excitatory conditioned response of its own. Thus, sensitized responding was observed only in animals tested in the presence of the facilitating stimulus complex (Paired animals in Figure 1). It should be noted that the results of Anagnostaras and Robinson (1996) indicate that facilitators not only set the occasion for CSs but can also do so for drug UCSs as well (see Box 1).

Somewhat overlooked has been the additional possibility that cues specifically unpaired with the drug can come to act as conditioned inhibitors (Rescorla, 1969; LoLordo and Fairless, 1985) to prevent the expression of the sensitized response. Different lines of evidence support this possibility, proposed by Stewart and Vezina (1988, 1991; Stewart, 1992). First, the discriminative conditioning procedure outlined in Figure 1 and used in drug conditioning and sensitization studies is known to establish stimuli explicitly unpaired with the UCS as conditioned inhibitors (Mackintosh, 1974). Second, when used in a summation procedure, conditioned inhibitors reduce responding not only to conditioned excitators but to unconditioned stimuli as well (Rescorla, 1969; Thomas, 1972). Thus, as proposed by Anagnostaras and Robinson (1996) for facilitators, conditioned inhibitors could in the same way modulate responding to the unconditioned effects of a drug (Stewart, 1992). Third, procedures known to extinguish conditioned inhibition (Lysle and Fowler, 1985; Kasproff et al., 1987; Hallam et al., 1990; Fowler et al., 1991) can selectively disinhibit the expression of locomotor and NAcc DA sensitization by amphetamine to reveal sensitized responding in Unpaired animals (Guillory et al., 2006; see also Stewart and Vezina, 1991). Finally, Anagnostaras et al. (2002) showed that using electroconvulsive shock to induce retrograde amnesia disinhibited responding selectively in Unpaired rats on a test for sensitization, suggesting that these animals were normally indeed sensitized but inhibited from expressing enhanced responding. In addition to conditioned inhibition of the expression of sensitization, evidence for the conditioned inhibition of the development of tolerance to the analgesic (Siegel et al., 1981), sedative (Fanselow and German, 1982) and hypothermic (Hinson and Siegel, 1986) effects of other drugs has been reported as well.

Together, the above findings demonstrate that the expression of sensitization can come under strong environmental stimulus control. Thus, the expression of sensitized responding can be promoted by stimuli that have come to predict the presence of drug and inhibited by stimuli that have come to signal its absence. Moreover, there is no reason to suspect that such processes are mutually exclusive. Although certainly considerably more complex, such facilitating and

inhibitory stimuli would also be expected to exercise strong control over the expression of sensitization in humans.

2.3. Implications for the expression of sensitization in humans

It is interesting to review some of the findings reported in human drug sensitization studies in light of the above findings. Although not the only distinction, one of the most salient differences between experiments conducted in healthy and drug abusing subjects regards the stimuli surrounding drug administration during exposure and those constituting conditions during testing. To the extent that the stimuli associated by drug abusing individuals with drug procurement and consumption most probably differ considerably from those present at the time of testing, the opportunity for either inhibition or lack of facilitation of sensitized behavioral and striatal DA responding could interfere with the expression of sensitization at test (e.g., Nagoshi et al., 1992; Rothman et al., 1994; Gorelick and Rothman, 1997; Volkow et al., 1997; Mendelson et al., 1998). Conversely, when drug naïve individuals are administered drug exclusively in the presence of testing cues, the conditions for facilitation of sensitized behavioral and DA responding could promote the expression of sensitization at test (e.g., Strakowski et al., 1996, 2001; Strakowski and Sax, 1998; Boileau et al., 2006). Consistent with this interpretation, when stimuli relevant to drug abusing subjects were made available during testing (mirror, razor blade, straw, and cocaine powder) and subjects were allowed to prepare the powder into one or two lines and to ingest it intra-nasally in their usual fashion, past psychostimulant drug use correlated positively with striatal DA response (Cox et al., 2006). Similar experiments in which these cues were not present (the drug challenge was administered non-contingently via a nondescript capsule described as a medication; no drug paraphernalia or drug-paired cues were present), past psychostimulant drug use predicted a smaller striatal DA response (Casey et al., 2007). Interestingly, a recent study reported that drug-related stimuli that - unlike those in Cox et al. (2006) - did not lead to drug taking, failed to elicit enhanced striatal DA release in drug abusing subjects (Volkow et al., 2008). These findings again confirm the importance of environmental stimuli in drug responding in that withholding of an expected reinforcer is known to diminish DA responding (Schultz et al., 1997).

3. Conclusions

An accumulating animal literature indicates that the expression of sensitization is susceptible to a wider range of factors than is usually considered. Particularly relevant are features of the drug exposure regimen prior to testing (e.g., intensity of drug exposure and duration of withdrawal) as well as the presence or absence of drug-related cues during testing (for reviews, see Leyton, 2007; Vezina et al., 2007). In this review, evidence is presented showing that the expression of sensitization to drugs of abuse can come under strong environmental stimulus control. Stimuli that predict the availability of the drug (facilitators, occasion setters) promote sensitized responding whereas stimuli that predict its absence (conditioned inhibitors) inhibit the expression of sensitization. While initially limited to locomotor responding in rodents, these results were recently extended to include the conditioned inhibition of sensitized neurochemical responses as well.

It is argued here that similar effects occur in humans. The results of a number of experiments in humans suggest that the presence of cues predicting drug availability is associated with sensitized responding while the absence of these cues or the presence of stimuli predicting the absence of drug is associated with the absence of sensitized responding. Such cues capable of affecting the expression of sensitization may thus influence vulnerability to addiction, the waxing and waning of relapse susceptibility, and the exaggerated salience attached to drug cues. Studies that do not control for these factors might not detect sensitization even when the

relevant neuroadaptations have occurred and their potential to significantly alter behavior is present.

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CONDITIONING/EXPOSURE

	CS+	CS-
Paired	drug	saline
Unpaired	saline	drug
Control	saline	saline

TEST FOR CONDITIONING

	CS+	}	Excitatory Pavlovian Conditioning → drug UCS – test environment CS+ association → conditioned response to CS+ in Paired animals
Paired	saline		
Unpaired	saline		
Control	saline		

TEST FOR SENSITIZATION

	CS+	}	Facilitation → drug UCS – test environment CS contingency → facilitation of sensitized response in Paired animals
Paired	drug		
Unpaired	drug		Inhibition → drug UCS – test environment CS contingency → inhibition of sensitized response in Unpaired animals
Control	drug		

Figure 1.

Outline of the discriminative conditioning procedures often used in drug conditioning and sensitization experiments. During the Conditioning/Exposure phase, animals can be subjected to several blocks of injections with each block consisting of two injections, the CS+ injection on one day and the CS- injection the following day. Stimulus configuration is relative to Paired animals: CS+, drug paired or predicting stimulus; CS-, stimulus explicitly unpaired with drug. Unpaired animals are subjected to the opposite configuration. Testing for conditioning (following saline injection) and sensitization (following drug challenge) is conducted days to weeks later. Testing for conditioning can reveal excitatory Pavlovian conditioning in Paired animals. Testing for sensitization can reveal facilitation of sensitized responding in Paired animals and inhibition of sensitized responding in Unpaired animals.

Figure 2.

Results obtained on tests for conditioning (**A**) and sensitization (**B**) in rats previously exposed to saline (Control) or amphetamine (1.0 mg/kg, IP) either Paired or Unpaired with the locomotor activity monitoring chambers. Data are shown as 2-hr total locomotor counts (+SEM) obtained following (**A**) a saline or (**B**) an amphetamine injection (0.5 mg/kg, IP). **, $P < 0.01$, significantly greater than two other groups. Adapted from Stewart and Vezina (1991).

Box 1

Terms and Definitions

Conditioned Inhibitor. Stimulus that inhibits the ability of another stimulus (CS or UCS) to elicit a response. Established by giving a conditioned inhibitor B the ability to signal the absence of the relation between a stimulus A and a UCS as in A+/AB-9,10. Has also been proposed to reduce responding to a UCS, including inhibition of sensitized responding to a drug UCS2,5,9,13,15,17. Closely related is the **negative occasion setter** which is established using serial stimulus components (A+/B-→-) and is also capable of inhibiting responding to a CS6

Conditioned Response (CR) Response elicited by a CS usually in the absence of the UCS. The CR is often but not always similar to the UCR4,8. See Figure 1

Conditioned Stimulus (CS) A previously neutral stimulus that with training achieves a relationship with the UCS. In the simplest cases, this relationship consists of a perfect positive or negative correlation. In the former, the CS reliably predicts the occurrence of the UCS and elicits a CR when the UCS is not presented. Also referred to as a **Pavlovian** or **conditioned excitator** or CS+8. In the latter case, the CS reliably predicts the absence of the UCS and is established as a **conditioned inhibitor** (CS-)8,9,10. See Figure 1

Facilitator Stimulus that promotes the ability of another stimulus (CS or UCS) to elicit a response. Unlike a **conditioned excitator**, a facilitator does not necessarily elicit a CR on its own. Traditionally established by giving a facilitator B the ability to signal the presence of the relation between a stimulus A and a UCS as in A-/AB+10. Has also been proposed to promote responding to a UCS as in sensitized responding to a drug UCS1. Also referred to as a **positive occasion setter** that promotes or “sets the occasion” for responding to a CS or enhanced responding to a UCS6

Incentive A stimulus (CS or UCS) that elicits approach. **Incentive motivation** refers to a central motivational state that enhances the salience and effectiveness of incentives3,13,16. The **incentive sensitization** view of Robinson and Berridge argues that sensitization of a neuronal system that mediates attribution of incentive salience underlies the enhanced motivation to seek and self-administer drugs11,12

Sensitization In drug sensitization experiments, refers to the progressive enhancement of a drug UCR produced by repeated administration of the drug. A descriptor preceding this term refers to the effect sensitized, as with a behavioral (e.g., **behavioral** or **locomotor sensitization**) or neurochemical UCR (e.g., **neurochemical** or **DA sensitization**). Sensitization of psychological processes has also been proposed as in **incentive sensitization** to refer to the enhancement of neuronal drug effects mediating the incentive valence of drug cues11,12,13,16. See **Incentive**

Summation Procedure A test used to measure **conditioned inhibition** in which presentation of a **conditioned inhibitor** B is predicted to reduce responding to a **conditioned excitator** A previously paired with a UCS10. This procedure has also been proposed to reduce responding to a UCS, including inhibition of sensitized responding to a drug UCS2,5,9,13,15,17. In a related class of procedures (**retardation** or **resistance to reinforcement**), **conditioned inhibition** is measured as resistance to the development of excitatory conditioning to an already established **conditioned inhibitor**7,9

Test for Conditioning A test that assesses the ability of a CS to elicit a CR in the absence of the UCS. In drug conditioning experiments, this usually entails injecting animals with saline and placing them in a test environment previously Paired with the drug (CS+). Controls include animals previously exposed to the drug but not in association with the CS+ (Unpaired) and Control animals previously not exposed to the drug UCS14,15. See text and Figure 1

Test for Sensitization A test that assesses the ability of a UCS to elicit a UCR that is greater than that observed when the UCS was first administered. In drug sensitization experiments, this entails administering animals the drug on a test conducted some time after animals were repeatedly administered the drug. Comparisons can be made **within-subject** (compare responding to the first and last drug injections in the same animals) or **between-subject** (compare responding to the test drug injection in animals previously exposed to drug or saline). As illustrated in Figure 1, testing for sensitization in test environments previously paired or unpaired with the drug UCS provides the opportunity to assess the relation between **sensitization** and **conditioning**14,15. See **Test for Conditioning**

Unconditioned Stimulus (UCS) A stimulus that unconditionally elicits an **unconditioned response (UCR)**8. Thus, a UCS elicits a UCR without the need for training

1. Anagnostaras and Robinson, 1996. 2. Anagnostaras et al., 2002. 3. Bindra, 1978. 4. Eikelboom and Stewart, 1982. 5. Guillory et al., 2006. 6. Holland, 1992. 7. LoLordo and Fairless, 1985. 8. Mackintosh, 1974. 9. Rescorla, 1969. 10. Rescorla, 1985. 11. Robinson and Berridge, 1993. 12. Robinson and Berridge, 2003. 13. Stewart, 1992. 14. Stewart and Vezina, 1988. 15. Stewart and Vezina, 1991. 16. Stewart et al., 1984. 17. Thomas, 1972.

Box 2Dose-dependent development of sensitization to repeated *d*-amphetamine in healthy subjects

Amphetamine Dose	Number of Doses	Sensitization	Reference
5.0 mg, p.o.	5	No - mood, drug tablets chosen	Johanson and Uhlenhuth, 1981
10.0 mg, p.o.	6	No - speech rate, smoking, stimulant effects, liking	Kelly et al., 1991
20.0 mg, p.o.	2	No - subjective and psychomotor effects	Wachtel and de Wit, 1999
~20.0 mg, p.o. (0.25 mg/kg)	2	Yes - energy, eye-blink, mood, speech rate	Strakowski et al., 1996
~20.0 mg, p.o. (0.25 mg/kg)	3	Yes - energy, eye-blink	Strakowski and Sax, 1998
~20.0 mg, p.o. (0.25 mg/kg)	3	Yes - energy, euphoria	Strakowski et al., 2001
~20.0 mg, p.o. (0.30 mg/kg)	4	Yes - energy, eye-blink	Boileau et al., 2006