

## Review

# The incentive sensitization theory of addiction: some current issues

Terry E. Robinson\* and Kent C. Berridge

Department of Psychology (Biopsychology Program), The University of Michigan, East Hall,  
530 Church Street, Ann Arbor, MI 48109, USA

We present a brief overview of the incentive sensitization theory of addiction. This posits that addiction is caused primarily by drug-induced sensitization in the brain mesocorticolimbic systems that attribute incentive salience to reward-associated stimuli. If rendered hypersensitive, these systems cause pathological incentive motivation ('wanting') for drugs. We address some current questions including: what is the role of learning in incentive sensitization and addiction? Does incentive sensitization occur in human addicts? Is the development of addiction-like behaviour in animals associated with sensitization? What is the best way to model addiction symptoms using animal models? And, finally, what are the roles of affective pleasure or withdrawal in addiction?

**Keywords:** sensitization; dopamine; habits; cocaine; amphetamine; motivation

## 1. INTRODUCTION

At some time in their life, most people try a potentially addictive drug (e.g. alcohol). However, few become addicts. Addiction implies a pathological and compulsive pattern of drug-seeking and drug-taking behaviours, which occupies an inordinate amount of an individual's time and thoughts, and persists despite adverse consequences (Hasin *et al.* 2006). Addicts also find it difficult to reduce or terminate drug use, even when they desire to do so. Finally, addicts are highly vulnerable to relapse even after long abstinence and well after symptoms of withdrawal have disappeared. Thus, a key question in addiction research is: what is responsible for the transition to addiction in those few susceptible individuals?

Over the last 20 years or so there has been increasing recognition that drugs change the brain of addicts in complex and persistent ways, so persistent that they far outlast other changes associated with tolerance and withdrawal. It is important to identify the brain changes that cause the transition to addiction from casual or recreational drug use, and the features that make particular individuals especially susceptible to the transition (Robinson & Berridge 1993; Nestler 2001; Hyman *et al.* 2006; Kalivas & O'Brien 2008). Persistent drug-induced changes in the brain alter a number of psychological processes, resulting in various symptoms of addiction. We suggested in the incentive sensitization theory of addiction, originally published in 1993, that the most important of these psychological

changes is a 'sensitization' or *hypersensitivity to the incentive motivational effects of drugs and drug-associated stimuli* (Robinson & Berridge 1993). *Incentive sensitization* produces a bias of attentional processing towards drug-associated stimuli and pathological motivation for drugs (compulsive 'wanting'). When combined with impaired executive control over behaviour, incentive sensitization culminates in the core symptoms of addiction (Robinson & Berridge 1993, 2000, 2003). Incentive sensitization has drawn considerable interest in the past 15 years and, therefore, we thought it worthwhile to update our perspective. We present here a brief and idiosyncratic overview of this view of addiction and raise some current issues.

## 2. WHAT IS INCENTIVE SENSITIZATION THEORY AND WHAT IS THE ROLE OF LEARNING?

The central thesis of the incentive sensitization theory of addiction (Robinson & Berridge 1993) is that repeated exposure to potentially addictive drugs can, in susceptible individuals and under particular circumstances, persistently change brain cells and circuits that normally regulate the attribution of incentive salience to stimuli, a psychological process involved in motivated behaviour. The nature of these 'neuroadaptations' is to render these brain circuits hypersensitive ('sensitized') in a way that results in pathological levels of incentive salience being attributed to drugs and drug-associated cues. Persistence of incentive sensitization makes pathological incentive motivation (wanting) for drugs last for years, even after the discontinuation of drug use. Sensitized incentive salience can be manifest in behaviour via either implicit (as unconscious wanting) or explicit (as conscious craving) processes, depending on circumstances. Finally, the *focus* on drugs in particular in addicts is produced by an interaction between incentive salience

\* Author and address for correspondence: Biopsychology Program, Department of Psychology, University of Michigan, East Hall, 525 East University Avenue, Ann Arbor, MI 48109-1109, USA (ter@umich.edu).

One contribution of 17 to a Discussion Meeting Issue 'The neurobiology of addiction: new vistas'.

mechanisms with associative learning mechanisms that normally direct motivation to specific and appropriate targets. Learning specifies the object of desire, but it is important to note that learning *per se* is not enough for pathological motivation to take drugs. Thus, we argue that pathological motivation arises from sensitization of brain circuits that mediate Pavlovian conditioned incentive motivational processes (i.e. incentive sensitization). However, it is important to emphasize that associative learning processes can *modulate* the expression of neural sensitization in behaviour at particular places or times (and not others), as well as guide the direction of incentive attributions. This is why behavioural sensitization is often expressed only in contexts in which the drugs have previously been experienced (Stewart & Vezina 1991; Anagnostaras & Robinson 1996; Robinson *et al.* 1998), and may reflect the operation of an ‘occasion-setting’ type of mechanism (Anagnostaras *et al.* 2002). Learning might be viewed as layered onto basic sensitization processes in a top-down fashion, similar to how learning regulates the expression of such non-associative motivation processes as stress and pain. The contextual control over the expression of sensitization provides an additional mechanism that accounts for why addicts ‘want’ drugs most particularly when they are in drug-associated contexts.

Finally, by spreading beyond the associative focus of wanting on drug targets, incentive sensitization can also sometimes spill over in animals or humans to other targets, such as food, sex, gambling, etc. (Mitchell & Stewart 1990; Fiorino & Phillips 1999a,b; Taylor & Horger 1999; Nocjar & Panksepp 2002). For example, treatment with dopaminergic medications in some patient populations can lead to a ‘dopamine dysregulation syndrome’ (DDS) that is manifest not only by compulsive drug use but also sometimes by ‘pathological gambling, hypersexuality, food bingeing ... and punding, a form of complex behavioral stereotypy’ (Evans *et al.* 2006, p. 852).

#### (a) *Incentive sensitization: more than just learning*

It has become popular to refer to addiction as a ‘learning disorder’ (Hyman 2005), but we think that this phrase may be too narrow to fit reality. Learning is only one part of the process and probably not the one that contributes most to the pathological pursuit of drugs.

The most influential type of ‘learning hypothesis’ suggests that drugs promote the learning of strong ‘automatized’ stimulus–response (S–R) *habits*, and it is then supposed that by their nature S–R habits confer compulsivity to behaviour (Tiffany 1990; Berke & Hyman 2000; Everitt *et al.* 2001; Hyman *et al.* 2006). However, it is difficult to imagine how any influence of drugs on *learning* processes alone could confer compulsivity on behaviour, unless an additional motivational component was also involved, and S–R habits by definition are not modulated by motivational factors (Robinson & Berridge 2003). Do automatic S–R habits really become compulsive merely by virtue of being extremely well learned? We have doubts. Strong S–R habits do not necessarily lead to compulsive behaviour: activities such as tying shoes, brushing

teeth, etc. are not performed compulsively by most people, even after being performed more than 10 000 times. Additional motivational processes seem needed to explain why an addict waking up in the morning with no drug spends the day engaging in a complex and sometimes new series of behaviours, such as scamming, stealing and negotiating, all seemingly motivated to procure drug. Addicts do what they have to do and go where they have to go to get drugs, even if actions and routes that have never been performed before are required. Such focused yet flexible behaviour in addiction shows pathological motivation for drugs that cannot be explained by evoking S–R habits. Indeed, a strict S–R habit theory would require the addict, upon waking up in the morning with no drug available, to engage ‘automatically’ in exactly the same old sequence of habitual actions they used previously to get drugs, whether the actions were currently effective or not. Yet addicts in the real world are not S–R automatons; they are, if nothing else, quite resourceful.

On the other hand, everyone must agree that S–R habits probably contribute to the automatized behaviours and rituals involved in *consuming* drugs once obtained (Tiffany 1990), and it has been shown that treatment with drugs facilitates the development of S–R habits in animals (Miles *et al.* 2003; Nelson & Killcross 2006), perhaps via recruitment of the dorsal striatum (Everitt *et al.* 2001; Porrino *et al.* 2007). We also note that habits may be especially prominent in standard animal self-administration experiments, where only a single response is available to be performed (e.g. press a lever) thousands of times in a very impoverished environment to earn injections of drugs. Thus, we think studies on how drugs promote the learning of S–R habits will provide important information about the regulation of *drug consumption behaviour* in addicts, but this is not the core problem in addiction.

#### (b) *Relation of incentive sensitization to cognitive dysfunction*

The incentive sensitization theory focuses on sensitization-induced changes in incentive motivational processes and related changes in the brain, but we have acknowledged that other brain changes contribute importantly to addiction too, including damage or dysfunction in cortical mechanisms that underlie cognitive choice and decision making (Robinson & Berridge 2000, 2003). Many studies have documented that changes in ‘executive functions’, involving how alternative outcomes are evaluated and decisions and choices made, occur in addicts and animals given drugs (Jentsch & Taylor 1999; Rogers & Robbins 2001; Bechara *et al.* 2002; Schoenbaum & Shaham 2008). We agree that the impairment of executive control plays an important role in making bad choices about drugs, especially when combined with the pathological incentive motivation for drugs induced by incentive sensitization.

### 3. WHAT IS SENSITIZATION?

It is easy to get the impression from the literature that behavioural sensitization might be equivalent to ‘sensitization of locomotor activity’, but locomotion is

only one of many different psychomotor effects of drugs that undergo sensitization, most of which are dissociable (Robinson & Becker 1986). It is important to remember that in this context the word sensitization simply refers to an increase in a drug effect caused by repeated drug administration. What is critical for the incentive sensitization theory is not 'locomotor sensitization', or even 'psychomotor sensitization', but incentive sensitization. Insofar as psychomotor activation is thought to reflect the engagement of brain incentive systems, including mesotelencephalic dopamine systems (Wise & Bozarth 1987), psychomotor sensitization may often be used as evidence (albeit indirect evidence) for hypersensitivity in relevant motivation circuitry. But it is the hypersensitivity in this motivation circuitry, not the locomotion circuitry, which contributes most to addictive wanting for drugs.

#### (a) Direct evidence for incentive sensitization

What evidence is there for this main postulate of incentive sensitization theory that repeated drug use sensitizes neural substrates responsible for the attribution of incentive salience to reward-related stimuli? First, prior exposure to a number of drugs of abuse enhances the incentive effects of drugs measured using a variety of behavioural paradigms. Thus sensitization facilitates the later acquisition of drug self-administration behaviour, conditioned preferences for locations paired with drug and the motivation to work for drug as indicated by 'break point' on a progressive ratio schedule (Lett 1989; Vezina 2004; Ward *et al.* 2006).

More specific evidence for incentive sensitization comes from studies designed to more directly assess drug-induced changes in the incentive salience attributed to reward-related stimuli, and to exclude alternative explanations for increases in reward-directed behaviour based on habit learning, etc. Stimuli acquire incentive properties by being associatively paired with a reward, and 'conditioned stimuli' (CS) that have been imbued with incentive salience have three fundamental characteristics (Berridge 2001; Cardinal *et al.* 2002). (i) They can elicit approach towards them (become 'wanted'), acting as 'motivational magnets' (measurable by Pavlovian conditioned approach behaviour or 'sign tracking'). (ii) They can energize ongoing actions by eliciting cue-triggered wanting for their associated unconditioned rewards (measurable by Pavlovian instrumental transfer). (iii) They can act as reinforcers in their own right, reinforcing the acquisition of a new instrumental response (measurable by conditioned reinforcement). Thus, the most direct evidence for incentive sensitization comes from studies showing that past drug treatment, which produces psychomotor sensitization, facilitates all three features of incentive stimuli: Pavlovian conditioned approach behaviour (Harmer & Phillips 1998); Pavlovian instrumental transfer (Wyvell & Berridge 2001); and conditioned reinforcement (Taylor & Horger 1999; Di Ciano 2007).

It should be acknowledged, however, that in most studies on incentive sensitization pairing with natural rewards (usually food or water), not a drug reward, was used to confer CS with incentive motivational properties. It is difficult to address the question of whether

prior sensitization directly facilitates the incentive properties of *drug*-associated stimuli in animal experiments because the pairing of a stimulus with drug administration may itself produce sensitization. In fact, it has only been reported very recently that a cue paired with drug administration in a Pavlovian manner (i.e. independent of any action) can come to elicit approach towards itself (Uslaner *et al.* 2006). It is important, therefore, that in a recent study Di Ciano (2007) found that cocaine sensitization did facilitate the conditioned reinforcing effects of a cocaine-associated stimulus, consistent with incentive sensitization. Of course, the fact that patients with DDS pathologically want drugs is also consistent with the concept of incentive sensitization (Evans *et al.* 2006). Nevertheless, this is an area that deserves much more investigation.

Another way of approaching whether incentive sensitization occurs is to ask the question from the brain's point of view. That is, does sensitization increase neural activations in brain systems that code the incentive value of a reward stimulus? Several studies indicate that it does (Tindell *et al.* 2005; Boileau *et al.* 2006; Evans *et al.* 2006). For example, amphetamine sensitization in rats increases specific firing patterns of neurons in mesolimbic structures that code the incentive salience of a reward CS (Tindell *et al.* 2005). In humans, repeated amphetamine treatment is reported to sensitize amphetamine-stimulated dopamine 'release' in the ventral striatum, even a year after the last drug treatment (Boileau *et al.* 2006), and a sensitization of dopamine release has also been reported in patients with DDS (Evans *et al.* 2006). In conclusion, even if we are unsure at this point about exactly which of the many changes in the brain produced by drugs underlie the psychological change of incentive sensitization, we suggest that the evidence provided above indicating that repeated drug exposure alters the relevant behaviours, psychological processes and brain structures themselves in the predicted directions is *prima facie* evidence for the thesis.

#### 4. DOES SENSITIZATION OCCUR IN HUMANS?

One criticism we heard frequently about incentive sensitization theory in its first decade was that there was no evidence that humans showed behavioural or neural sensitization. However, in the last few years, several studies have now demonstrated both behavioural and neural sensitization in people (we refer readers to a thoughtful review of the subject by Leyton 2007). Of course, even earlier it was recognized that humans showed sensitization to the paranoia-related psychotomimetic and stereotypy-inducing ('punding') effects of psychostimulant drugs, though the relevance of this to incentive salience was not widely recognized. It is interesting, therefore, that a sensitized incentive salience-type mechanism has been proposed to contribute to the symptoms of schizophrenia and stimulant psychoses (Kapur *et al.* 2005).

Briefly, regarding evidence in humans for incentive sensitization, the repeated intermittent administration of amphetamine in humans can produce persistent behavioural sensitization (e.g. eye-blink responses, vigour and energy ratings), especially at high doses

(Strakowski *et al.* 1996; Strakowski & Sax 1998; Boileau *et al.* 2006). Also, in drug addicts, attention is biased to visual drug-associated cues at an immediate and implicit level, as measured by eye-tracking, as though drug cues were more attractive and attention grabbing in a way consistent with incentive sensitization (Wiers & Stacy 2006). Neural evidence of sensitization has also been described recently in humans, as mentioned above. Repeated intermittent administration of amphetamine causes sensitization of dopamine release in humans, even when a drug challenge is given a year later (Boileau *et al.* 2006), and drug cues also elicit a vigorous dopamine response in the same reward-related brain structures (Boileau *et al.* 2007; see also Childress *et al.* 2008). Intriguingly, a similar sensitized dopamine response to L-DOPA occurs in Parkinson's patients with the so-called DDS (Evans *et al.* 2006). In these patients, L-DOPA induces unusually high levels of dopamine release in the ventral striatum as though sensitized. Behaviourally, patients with DDS compulsively take dopaminergic drugs at excessive levels, and show other compulsive activities, including gambling and punting (a complex form of behavioural stereotypy). Perhaps most interestingly, increased dopamine release is associated with increased ratings of drug wanting but not drug 'liking' in patients who take excessive amounts of their drug (Evans *et al.* 2006). All of these effects are consistent with incentive sensitization, and indeed are difficult to explain by other views of addiction.

However, it must be acknowledged that the current literature contains conflicting results about brain dopamine changes in addicts. For example, it has been reported that detoxified cocaine addicts actually show a decrease in evoked dopamine release rather than the sensitized increase described above (Volkow *et al.* 1997; Martinez *et al.* 2007). However, these reports need to be interpreted with caution, because many variables interact in complex ways to determine whether sensitization is expressed at any particular place or time. In particular, as discussed by Leyton (2007), the role of context is crucial in gating the expression of sensitization in general, and thus of sensitized increases in dopamine release. Animal studies have shown that the expression of sensitization is powerfully modulated by the context in which drugs are administered (Robinson *et al.* 1998), and humans are likely to be even more sensitive to psychological contexts (Leyton 2007). For example, sensitization and enhanced dopamine release typically are not manifest if animals are tested in a context where drugs have never before been experienced (Fontana *et al.* 1993; Anagnostaras & Robinson 1996; Duvauchelle *et al.* 2000). Therefore, based on the animal literature, human drug addicts should not be expected to display behavioural sensitization or sensitized dopamine release if the environment in which they are given a drug 'challenge' (e.g. a scanner) is dramatically different from contexts where drugs were taken before. It is noteworthy that in the best demonstration so far of sensitized dopamine release in humans, investigators took care to keep contexts similar by giving sensitizing drug treatments in the same context later used for testing (the scanner; Boileau *et al.* 2006). Thus, in

future studies, context needs to be considered before assuming that what is seen in the laboratory setting reflects what happens when addicts take drugs in their usual setting. Finally, it is also important not to test for sensitization too soon after the discontinuation of drug use but rather to wait until tolerance has subsided, both because tolerance can mask the expression of sensitization, and because sensitization is expressed best after a period of 'incubation' (Robinson & Becker 1986; Dalia *et al.* 1998).

Another finding in humans that seems inconsistent with sensitization is that cocaine addicts are reported to have low levels of striatal dopamine D<sub>2</sub> receptors even after long abstinence (Volkow *et al.* 1990; Martinez *et al.* 2004). This suggests a hypodopaminergic state rather than a sensitized state (Volkow *et al.* 2004). However, again, there are grounds for caution. First, psychostimulant treatments in rats, including cocaine self-administration, cause behavioural supersensitivity to direct-acting D<sub>2</sub> agonists, as though D<sub>2</sub> receptors were increased or more sensitive (Ujike *et al.* 1990; De Vries *et al.* 2002; Edwards *et al.* 2007). The reason for this discrepancy is not clear, but one potential resolution is raised by considering that dopamine D<sub>2</sub> receptors can exist in one of the two interconvertible affinity states: a high-affinity state (D<sub>2</sub><sup>high</sup>) and a low-affinity state (D<sub>2</sub><sup>low</sup>), and dopamine exerts its functional effects by action on only D<sub>2</sub><sup>high</sup> receptors (Seeman *et al.* 2005). Many treatments that produce D<sub>2</sub> supersensitivity also cause increases in striatal D<sub>2</sub><sup>high</sup> receptors in rats, but do not change or even decrease total D<sub>2</sub> binding (Seeman *et al.* 2005). Most important for the discussion here, cocaine self-administration experience (Briand *et al.* 2008) and sensitization to amphetamine (Seeman *et al.* 2002, 2007) have also been reported to produce a persistent increase in the number of striatal D<sub>2</sub><sup>high</sup> receptors, with no change in total D<sub>2</sub> binding (and therefore presumably a proportionate decrease in D<sub>2</sub><sup>low</sup> receptors). Ligands used thus far for *in vivo* studies of dopamine D<sub>2</sub> receptors in humans do not discriminate between the low- and high-affinity states of the D<sub>2</sub> receptor, and therefore could miss changes that are specific to D<sub>2</sub><sup>high</sup> receptors, and give a misleading impression about dopamine function (Seeman *et al.* 2005). Thus, it will be important to conduct studies with ligands that can specifically quantify D<sub>2</sub><sup>high</sup> receptors in humans before concluding that addicts have increased or reduced D<sub>2</sub> receptor signalling.

## 5. DO PROCEDURES THAT PRODUCE 'ADDICTION-LIKE' BEHAVIOUR IN ANIMALS ALSO PRODUCE SENSITIZATION?

Most animal studies of addictive drugs have used procedures and methods that do not necessarily mimic human addiction. For example, evidence now indicates that limited access to self-administered drugs is not as effective in producing symptoms of addiction in animals as giving more extended access, either by extending the number of days animals are allowed to self-administer drugs (Wolffgramm & Heyne 1995; Heyne & Wolffgramm 1998; Deroche-Gamonet *et al.* 2004), or by extending to several hours the amount of

time drugs are available each day (Ahmed & Koob 1998). In one study, it took several months of intravenous (IV) cocaine self-administration before some rats began to develop addiction-like symptoms (Deroche-Gamonet *et al.* 2004), including continued drug seeking in the face of punishment or when drugs were known to be unavailable, increased motivation to obtain drugs, and a greater propensity to 'relapse' after enforced abstinence. Similarly, Ahmed & Koob (1998) reported that rats allowed to self-administer IV cocaine for 6 h d<sup>-1</sup> (extended access), but not 1 h d<sup>-1</sup> (limited access), developed addiction-like behaviours. These included an escalation of intake (Ahmed & Koob 1998; Mantsch *et al.* 2004; Ferrario *et al.* 2005), increased motivation to take drug (Paterson & Markou 2003), continued drug seeking in the face of adverse consequences (Vanderschuren & Everitt 2004; Pelloux *et al.* 2007) and a greater propensity for reinstatement (Ahmed & Koob 1998; Ferrario *et al.* 2005; Knackstedt & Kalivas 2007). Some of these effects have also been described after extended access to heroin (Ahmed *et al.* 2000).

#### (a) Cognitive deficits after extended access

Extended access to cocaine also produces symptoms of prefrontal cortex dysfunction in animals, apparently similar to those reported in human addicts (Jentsch & Taylor 1999; Rogers *et al.* 1999). For example, Briand *et al.* (2008) recently found a persistent decrease in dopamine D<sub>2</sub> (not D<sub>1</sub>) receptor mRNA and protein in the medial prefrontal cortex in rats given extended, but not limited, access to cocaine (0.4 mg kg<sup>-1</sup> per injection), accompanied by persistent deficits on a sustained-attention task that were indicative of decreased cognitive flexibility. George *et al.* (2007) have reported that extended, but not limited, access to cocaine (0.5 mg kg<sup>-1</sup> per injection) produced deficits on a working memory task that requires the frontal cortex, which was associated with cellular alterations in that brain region. Finally, using higher doses (0.75 mg kg<sup>-1</sup> per injection), Calu *et al.* (2007) found that rats allowed to self-administer cocaine for 3 h d<sup>-1</sup> showed persistent deficits in reversal learning.

In summary, there is now considerable evidence that extending access to drugs facilitates the development of addiction-like symptoms and cognitive deficits in animals. This is presumably because extended access facilitates greater drug intake than limited access, and produces greater corresponding changes in the brain responsible for addiction-like behaviour (Mantsch *et al.* 2004; Ahmed *et al.* 2005; Ferrario *et al.* 2005; Briand *et al.* 2008).

#### (b) Does extended access to self-administered cocaine produce sensitization?

The incentive sensitization theory posits that sensitization-related changes in the brain are important for the transition from casual to compulsive drug use. Therefore, given that extended access procedures provide the best models for this transition, we would predict that extended access should also produce robust behavioural sensitization and related changes in the brain. We have some evidence to suggest that this is indeed the case. Ferrario *et al.* (2005) allowed rats extended access to cocaine (6 h d<sup>-1</sup> for approx. three

weeks) and then were tested for sensitization later, one month after the last exposure to drug. Rats that had extended access to cocaine showed more robust psychomotor sensitization than rats given limited access (1 h d<sup>-1</sup>), and greater sensitization-related changes in their brains: a much larger increase in the density of dendritic spines on medium spiny neurons in the core of the nucleus accumbens. Such increases in spine density specifically in the accumbens core have previously been associated with the development of psychomotor sensitization (Li *et al.* 2004).

Conversely, if sensitization-related changes in the brain help cause addiction, it might be predicted that prior sensitizing treatments with drug would facilitate the subsequent development of addiction-like behaviours when rats were given extended access to drugs. This seems to be the case. We have found that an amphetamine treatment regimen that produced psychomotor sensitization accelerated the subsequent escalation of cocaine intake, when animals were later allowed to self-administer cocaine (Ferrario & Robinson 2007). Of course, as mentioned above, repeated treatment with a number of drugs increases subsequent motivation for drug (Vezina 2004; Nordquist *et al.* 2007), and even facilitates the development of S-R habits, which are a symptom of addiction (Nelson & Killcross 2006; Nordquist *et al.* 2007). These studies suggest that the neural changes underlying sensitization may be sufficient to promote subsequent addiction-like behaviours.

However, it is worth noting that there is some confusion in the literature about whether extended access to self-administered cocaine produces psychomotor sensitization. A few reports claim that extended access to cocaine produces psychomotor sensitization, but no greater sensitization than limited access (Ahmed & Cador 2006; Knackstedt & Kalivas 2007), and there is even one report that extended access results in a 'loss' of sensitization (Ben-Shahar *et al.* 2004). But these latter studies may have measured the wrong behaviours: behavioural sensitization was over-narrowly defined as increases in locomotor activity alone. The studies failed to measure other behaviours that reflect even more intense psychomotor sensitization (e.g. the emergence of qualitative changes in behaviour, including motor stereotypies, which at high levels compete with locomotion). Consistent with these studies, we also found no differential effect of limited versus extended access when locomotor activity was the only measure used (Ferrario *et al.* 2005). But, at the same time, we found that extended access to cocaine actually produced much more robust psychomotor sensitization than limited access when drug-induced stereotyped head movements were also measured. As pointed out long ago by Segal (1975, p. 248), one of the pioneers in research on behavioural sensitization, 'characterization of the various components of the behavioural response is required because drug effects on behaviour may be competitively related'. Locomotor measures alone are often not sensitive to the transition from behaviour dominated by forward locomotion to that involving motor stereotypy, as occurs with robust sensitization (Segal 1975; Post & Rose 1976), and thus the sole use of locomotor

behaviour as an index of psychomotor sensitization can lead to erroneous conclusions.

Over-interpretation of negative results in cases like this can plague the field because negative results are next to impossible to interpret without additional information. Only in the case of a positive result can a single measure such as locomotion alone be decisive. [Flagel & Robinson \(2007\)](#) reiterated this point recently, showing that, at a given dose, there might be no group difference in cocaine-induced locomotor activity (e.g. distance travelled or crossovers), but large group differences in both the pattern of locomotion (velocity of each bout of locomotion) and in other behaviours (e.g. the frequency and the number of head movements; see [Crombag et al. \(1999\)](#) and [Flagel & Robinson \(2007\)](#) for an extensive discussion of this issue). Future studies of sensitization after extended access would benefit from keeping in mind that sensitization can manifest in several different ways and measure more than one.

## 6. DOES EXPERIMENTER-ADMINISTERED DRUG PRODUCE CHANGES IN THE BRAIN RELEVANT TO ADDICTION?

Another controversy concerns whether it is possible to produce changes in the brain and behaviour in animals relevant to human addiction when drugs are given by an experimenter, rather than self-administered by the animal. In thinking about this, it may be more important to consider the similarity of *symptom outcomes* to human addiction than the *mode of administration*. Of course, the most appropriate models or procedures are those that produce behavioural, psychological or neurobiological outcomes most similar to those in human addiction. And, therefore, the question is, which procedures can do this in animals?

We suggest that both experimenter- and self-administered drugs can produce relevant outcomes, *as long as they produce neural sensitization*. Indeed, one can make a case for an even more radical proposition: that experimenter-administered drug administration procedures that produce robust sensitization may in some ways more effectively model addiction than self-administration procedures that fail to produce robust sensitization (such as limited access procedures). For example, limited access self-administration may fail to produce either robust sensitization or symptoms of addiction, as discussed above. Conversely, sensitizing treatments with experimenter-administered drugs are sufficient to produce increased motivation for drug reward ([Vezina 2004](#)), incentive sensitization of cue wanting ([Robinson & Berridge 2000](#); [Di Ciano 2007](#)), cognitive impairment ([Schoenbaum & Shaham 2008](#)) and stronger S–R habits ([Miles et al. 2003](#); [Nelson & Killcross 2006](#)), all of which may contribute to the transition to addiction. In addition, experimenter-administered drug that induces sensitization also changes the brain in ways related to the propensity to relapse, such as enhancing glutamate release in the core of the accumbens ([Pierce et al. 1996](#)). Sensitization induced by experimenter-administered drugs even shows a kind of ‘incubation effect’ (growing over a period of drug-free abstinence; [Paulson & Robinson 1995](#))

that seems to facilitate the propensity to relapse ([Grimm et al. 2001](#)), and can accelerate the escalation of drug intake ([Ferrario & Robinson 2007](#)). It is possible, therefore, that, under conditions that result in robust sensitization, experimenter-administered drugs may not only be effective in producing behavioural, psychological or neurobiological outcomes relevant to addiction, but also be even more effective than self-administration procedures that fail to produce robust sensitization.

There may be many reasons for this, but one could be that some self-administration procedures are not especially effective in producing robust sensitization-related changes in the brain. Many interacting factors influence whether exposure to a drug produces sensitization-related changes in the brain, including dose, the number of exposures, pattern of exposure (intermittency), rate of drug administration, the context in which the drug is experienced, individual predisposition, etc. Take just intermittency—injections given close together in time are relatively ineffective in producing sensitization ([Post 1980](#); [Robinson & Becker 1986](#)). This may be the reason for limited access self-administration procedures producing only relatively modest sensitization: this would produce a sustained increase in plasma levels of cocaine throughout a test session, which is not optimal for producing sensitization. Of course, 6 hours of extended access each day would also result in sustained plasma levels of drug, but in this situation the escalation of intake, and the large amount of drug eventually consumed, may overwhelm other factors that would otherwise limit sensitization. Experimenter administration may circumvent those limiting factors by combining relatively high doses with intermittent treatment ([Robinson & Becker 1986](#)). In fact, this may better capture the situation early in the development of addiction when drug use may be erratic and intermittent.

## 7. WHAT IS THE ROLE OF AFFECTIVE PROCESSES IN ADDICTION: WANTING VERSUS LIKING?

Many potentially addictive drugs initially produce feelings of pleasure (euphoria), encouraging users to take drugs again. However, with the transition to addiction, there appears to be a decrease in the role of drug pleasure. How can it be that drugs come to be wanted more even if they become ‘liked’ less? According to incentive sensitization theory, the reason for this paradox is because repeated drug use sensitizes only the neural systems that mediate the motivational process of incentive salience (wanting), but not neural systems that mediate the pleasurable effects of drugs (liking). Thus, the degree to which drugs are wanted increases disproportionately to the degree to which they are liked and this dissociation between wanting and liking progressively increases with the development of addiction. The dissociation between wanting and liking solves the puzzle that otherwise has led some neuroscientists to conclude that ‘one prominent prediction of an incentive sensitization view would be that, with repeated use, addicts would take less drug’ ([Koob & Le Moal 2006](#), p. 445). Of course, that is the opposite of what we predict: if sensitization makes

addicts want more drugs, then they should take more drugs, not less.

In a related but opposite way, the separation of wanting from liking also frees the control of addiction from being driven solely by the negative affective dysphoria that often follows cessation of drug use, at least for a few days or weeks. Withdrawal states may well contribute to drug taking while they last (Koob & Le Moal 2006). But addiction typically persists long after withdrawal states dissipate. Sensitization-related changes in the brain, which can persist long after withdrawal ends, provide a mechanism to explain why addicts continue to want drugs and are liable to relapse even after long periods of abstinence, and even in the absence of a negative affective state.

## 8. CONCLUSION

In conclusion, addiction involves drug-induced changes in many different brain circuits, leading to complex changes in behaviour and psychological function. We have argued that the core changes leading to addiction occur when incentive sensitization combines with defects in cognitive decision making and the resulting 'loss of inhibitory control over behaviour and poor judgement, combined with sensitization of addicts' motivational impulses to obtain and take drugs, makes for a potentially disastrous combination' (Robinson & Berridge 2003, pp. 44–46). Thus, bolstered by the evidence that has accumulated over recent years, we remain confident in concluding '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*. 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' (Robinson & Berridge 2003).

The research by the authors was supported by grants from the National Institute on Drug Abuse (USA).

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