Animal models of drug addiction: Where do we go from here?

Mary C. Olmstead

Queen's University, Kingston, Ontario, Canada

Compulsion and impulsivity are both primary features of drug addiction. Based on decades of animal research, we have a detailed understanding of the factors (both environmental and physiological) that influence compulsive drug use, but still know relatively little about the impulsive aspects of drug addiction. This review outlines our current knowledge of the relationship between impulsivity and drug addiction, focusing on cognitive and motor impulsivity, which are particularly relevant to this disorder. Topics to be discussed include the influence of chronic drug administration on impulsivity, the mechanisms that may explain drug-induced impulsivity, and the role of individual differences in the development of impulsive drug use. In addition, the manner in which contemporary theories of drug addiction conceptualize the relationship between impulsivity and compulsion is examined. Most importantly, this review emphasizes a critical role for animal research in understanding the role of impulsivity in the development and maintenance of drug addiction.

Drug addiction is a lay term that refers to maladaptive drug use and an obsession with securing and consuming the drug. The more specific medical terms substance abuse and substance dependence (American Psychiatric Association, 1994) include diagnostic criteria such as repeated, unsuccessful attempts to stop using the drug, disruption of personal activities due to drug use, consuming drugs in larger amounts or over longer periods than was intended, and continued drug use despite knowledge of adverse consequences. Although drug tolerance and withdrawal often occur with these symptoms, they are not necessary features of either substance dependence

or substance abuse. Both lay and medical definitions, therefore, emphasize two distinct and defining behavioural traits of addiction: compulsion to take the drug and loss of control in limiting drug intake (Koob & Le Moal, 2001).

Behavioural traits of drug addiction

Compulsion

Compulsive drug use in humans is associated with craving, which reflects the desire to reexperience the psychoactive effects of a drug (Markou et al., 1993). Despite the difficulty of assessing affective processes in nonhumans, most researchers agree

Correspondence should be addressed to Mary C. Olmstead, Department of Psychology, Queen's University, 62 Arch Street, Kingston, ON, K7L 3N6, Canada. Email: olmstead@post.queensu.ca

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that drug seeking provides a quantifiable measure of craving in laboratory animals. Second-order or progressive ratio schedules of reinforcement provide ideal opportunities to measure drug seeking in that both institute high response requirements for a single presentation of the reinforcer. Although employed less frequently, choice responding under concurrent schedules of reinforcement may provide valuable insight into drug seeking because the impact of alternative (i.e., competing) reinforcers, and the work required to obtain each, can be measured simultaneously. Some researchers describe the preference for an environment previously associated with a drug injection (i.e., a conditioned place preference) as drug seeking, but this measure lacks construct validity to the human condition of craving. That is, time in the drug-paired compartment provides no indication of how hard animals will work to obtain the drug. More importantly, none of these measures dissociate drug seeking (i.e., craving) from drug taking (i.e., self-administration), despite evidence that the two processes are mediated by distinct mechanisms (Robinson & Berridge, 1993).

In order to address this issue, we developed a novel paradigm in which animals respond for drug under a heterogeneous chain schedule: drug-seeking responses give access to a drug-taking lever (Olmstead, Parkinson, Miles, Everitt, & Dickinson, 2000). The fact that drug seeking and drug taking are differentially affected by dose, time-out period (Olmstead et al., 2000), and duration of opiate abstinence (Hellemans, Shaham, & Olmstead, 2002) confirms that the two measures are independent. This paradigm provided the means to examine psychological mechanisms that mediate drug seeking in rats (Hutcheson, Everitt, Robbins, & Dickinson, 2001; Olmstead, Lafond, Everitt, & Dickinson, 2001; Vanderschuren & Everitt, 2004). One of the most interesting findings is that extended experience with cocaine self-administration decreases the ability of an aversive cue to suppress cocaine seeking (Vanderschuren & Everitt, 2004). The implication of this work is that compulsive drug use reflects an insensitivity to adverse

outcomes associated with drug intake. Importantly, the study ruled out altered reward sensitivity as an explanation for changes in drug seeking. Compulsive drug seeking, therefore, may reflect the development of habitual responding (Tiffany, 1990), particularly as cocaine seeking in this paradigm is goal directed (i.e., mediated by a response–outcome association) when access to the drug is limited (Olmstead et al., 2001).

At the same time, chronic drug administration clearly alters brain reward systems, which may contribute to enhanced drug seeking in other paradigms or situations (Babe & Serafin, 1996; Everitt, Dickinson, & Robbins, 2001; Robinson & Berridge, 1993; Wise, 1988). In addition, environmental factors such as conditioned cues (Everitt & Robbins, 2000) and stress (Marinelli & Piazza, 2002; Shaham, Erb, & Stewart, 2000) have a profound impact on drug seeking, and these effects interact with drug experience. Thus, thorough and intensive animal research over the last 20 years suggests that compulsive drug use is due to some combination of habitual responding, altered reward sensitivity, disruptions in learning, and altered responses to stress.

If this is true, compulsion in drug addiction must be mediated through multiple brain sites. Most researchers agree that altered reward sensitivity is associated with changes in the mesolimbic dopamine (DA) system (Everitt et al., 2001; Robinson & Berridge, 1993; Wise, 1988), manifested at the molecular level (Nestler, 2001). In contrast, the development of habitual responding probably reflects a contribution of the dorsolateral striatum (Yin, Knowlton, & Balleine, 2004). Given that abused drugs share the common feature of enhancing DA release in striatal regions (Wise & Bozarth, 1987), repeated drug administration could increase both the incentive value of drugs and the development of stimulus-bound behaviour (N. M. White, 1996). The control of behaviour by conditioned drug cues occurs through interactions with the basolateral amygdala and mesolimbic DA system (Everitt et al., 1999), whereas stress-induced alterations in drug seeking are mediated through

corticotrophin releasing factor in the bed nucleus of the stria terminalis (Shaham et al., 2000).

Impulsivity

In contrast to this extensive and thorough knowledge of the behavioural and neurobiological factors that contribute to compulsive drug use, relatively little is known about the loss of inhibitory control in drug addiction. Five years ago, Leshner (2000) pointed out that "determining whether there are biological explanations for behavioural disinhibition requires further investigation". Despite this, in a subsequent series of reviews on drug addiction (*Journal of Neuroscience*, 2002, Vol. 22) none of the seven papers discussed behavioural disinhibition, and most did not mention it.

Disinhibition is one aspect of impulsivity, which itself is a multifactorial construct encompassing several different processes (Evenden, 1999). These include the inability to delay gratification, the inability to withhold a response, acting before all of the relevant information is provided, and decision making that is inappropriate, risky, or generally ill conceived. Drug addicts consistently choose the immediate rewards of intoxication over the long-term rewards of abstinence and are unable to refrain from further drug taking, particularly when they are in a drug-induced state. The two aspects of impulsivity that are most relevant for the study of addiction, therefore, are delay of gratification and an inability to withhold a response; these are often referred to as cognitive and motor impulsivity, respectively (Brunner & Hen, 1997).

Experimental evidence confirms that drug addicts show a greater tendency to choose small, immediate rewards (drugs or money) over larger, delayed rewards (Kirby, Petry, & Bickel, 1999; Moeller et al., 2002; Petry, 2001; Vuchinich & Simpson, 1998), and discount their drug of choice faster than they do monetary rewards of equal value (Madden, Petry, Badger, & Bickel, 1997). Moreover, some drug addicts show deficits in a gambling task that models the uncertainty of real-life decision making (Bechara & Damasio, 2002). Fewer studies have examined motor impulsivity in drug addicts, but existing evidence points

to increases in perseveration (Bechara et al., 2001; Beatty, Katzung, Moreland, & Nixon, 1995; Ornstein et al., 2000) and disinhibition (Fillmore & Rush, 2002). Drug addicts also self-report higher levels of impulsivity on many different personality scales (Moeller et al., 2002; Morgan, 1998; O'Boyle & Barratt, 1993; von Knorring, von Knorring, Smigan, Lindberg, & Edholm, 1987), and there is a high rate of substance abuse in clinical populations with impulse control disorders (Lesch & Merschedorf, 2000). Thus, both trait and state impulsivity are increased in addicts, although the relationship between personality and behavioural measures of impulsivity probably depends on the specific questionnaire (Mitchell, 1999; Richards, Zhang, Mitchell, & de Wit, 1999b).

In terms of neural mechanisms, both cognitive and motor impulsivity are associated with dysfunction in serotonin (5-HT) and/or prefrontal cortex (PFC) systems. First, reductions in 5-HT activity increase the choice of a small immediate reward over a large delayed reward (Bizot, Le Bihan, Puech, Hamon, & Thiebot, 1996; Evenden & Ryan, 1999); 5-HT agonists have the opposite effect (Poulos, Parker, & Le, 1996). Second, 5-HT depletions increase behavioural disinhibition (Franklin et al., 2002; Roberts, Loh, Baker, & Vickers, 1994) and premature responding in a reaction time task (Harrison, Everitt, & Robbins, 1997). The effects of 5-HT agents on cognitive and motor impulsivity appear to be mediated through subtypes of the 5-HT receptor (Evenden, 1998) and specific serotonergic pathways (Fletcher, 1993). Third, disinhibition is particularly notable in frontal lobe patients (Miller, 1992) and in rats following lesions (Weissenborn, Robbins, & Everitt, 1997; Wilcott, 1982) or DA depletion (Sokolowski & Salamone, 1994) of the PFC. Finally, cognitive impulsivity may be mediated by subregions of the PFC because destruction of one region (ventromedial PFC) produces an inability to delay gratification (Bechara, Tranel, & Damasio, 2000), and choosing between small likely and large unlikely rewards activates another (orbitofrontal PFC; Rogers et al., 1999; for alternate

view, see Cardinal, Pennicott, Sugathapaia, Robbins, & Everitt, 2001).

Given the co-occurrence of impulsivity and drug addiction, it is not surprising that addicts show abnormalities in 5-HT and PFC systems. These are most common in cocaine addicts and include upregulation of 5-HT transporters in the dorsal raphe (Jacobsen, Staley, Malison, Zoghbi, Seibyl, Kosten, & Innis, 2000), and increases in 5-HT levels post mortem (Little, Patel, Clark, & Butts, 1996). As well, increases in monoamine transporters in the orbitofrontal cortex (Little et al., 1998), reductions in grey matter density in orbitofrontal and cingulate cortices (Franklin et al., 2002), and reduced functional activity in the ventromedial PFC (Hommer et al., 1997; London, Ernst, Grant, Bonson, & Weinstein, 2000; Stapleton et al., 1995; Volkow & Fowler, 2000) are evident following long-term cocaine use. Structural changes in the PFC of addicts correlate with functional deficits, and both are apparent up to 6 weeks into abstinence (Fein, Di Sclafani, & Meyerhoff, 2002). Importantly, at least some drug addicts exhibit deficits in a decision-making task known to be sensitive to PFC damage (Bechara & Damasio, 2002).

The prevalence of both impulse control disorders and neural changes in drug addicts has led to the hypothesis that chronic drug use produces alterations in neural systems that mediate impulsivity, thereby leading to further drug use (Jentsch & Taylor, 1999; Koob & Le Moal, 2001). Although a causal relationship is difficult to establish in humans, reductions in 5-HT transporter levels are correlated with lifetime alcohol intake (Heinz, Mann, Weinberger, & Goldman, 2001), the extent of decision-making deficit in stimulant abusers is correlated with years of abuse (Bechara et al., 2001; Grant, Contoreggi, & London, 2000; Rogers et al., 1999), and PFC lesions may render subjects more vulnerable to drug abuse (Bechara et al., 2001). Alternatively, increased levels of impulsivity may predate drug use and thereby predispose individuals to develop an addiction (Cloninger, Svarkic, & Przybeck, 1993; Scourfield, Stevens, & Merikangas, 1996). There is currently no

resolution to this issue, either in human or animal studies.

Compulsion–impulsivity interactions in addiction

Despite the distinction between the two behavioural traits of addiction, some researchers suggest that sensitization of the mesolimbic DA neurons produces both compulsion and impulsivity (Goldstein & Volkow, 2002; Kelley & Berridge, 2002; Koob & Le Moal, 2001). It is not that these theories equate the two processes, rather that they employ a very broad definition of compulsion that includes altered decision making and disinhibited responding. This is contrary to clinical definitions of compulsion, which include the following characteristics: (a) recurrent and persistent thoughts, impulses, or images that cause marked anxiety or distress; (b) engaging in an activity that is designed to reduce this anxiety; (c) ritual-like motor movements when engaging in the activity; (d) elicitation of the ritualized behaviour by environmental stimuli; and (e) a recognition that engaging in the activity is excessive or unreasonable (American Psychiatric Association, 1994; Szechtman et al., 2001). The compulsive aspect of drug addiction is manifested as preoccupation with securing and consuming the drug (i.e., craving in humans and drug seeking in animals), but none of these characteristics describes either cognitive or motor impulsivity. Indeed compulsion and impulsivity do not co-occur in most psychiatric conditions, and brain dysfunctions associated with the two disorders are distinct. For example, compulsive disorders (obsessive compulsive disorder, Tourette's syndrome, Huntington's chorea, etc.) are linked to basal ganglia deficits (Pitman, 1989; Rapoport, 1990; Szechtman & Woody, 2003) whereas impulse control disorders typically involve disruptions in frontal cortical systems (Chow, 2000). Thus, there is no *a priori* reason to consider that impulsivity and compulsion should overlap in addiction.

In recognition of this distinction, some researchers are beginning to emphasize that impulsivity and compulsion may be two separate

processes that interact to influence drug use. In one of the first thorough conceptualizations of this relationship, Jentsch and Taylor (1999) describe addiction as the synergism of two distinct phenomenon: enhancement of the rewarding value of drugs and drug-paired stimuli (i.e., compulsion) combined with an inability to withhold responding to these cues (i.e., disinhibition). Importantly, these two processes are mediated by separate neural systems (limbic-amygdala connections and PFC), which are simultaneously altered by chronic drug administration. Goldstein and Volkow (2002) also suggest that alterations in the PFC (specifically orbitofrontal cortex and anterior cingulate gyrus) underlie the response inhibition problems in drug addicts. Most recently, Robinson and Berridge (2003) include poor judgement and inappropriate decision making (i.e., cognitive impulsivity) as a consequence of altered PFC function in addicts. These theories are built on the premise that addiction is a progressive disorder (as described previously; Robinson & Berridge, 1993), in which increasing changes in brain systems alter behaviour in a feedforward manner (Carlezon & Nestler, 2002; Koob & Le Moal, 2001). Although the specific details of each theory may vary, they all emphasize that this transition through behavioural stages results in compulsive drug use and loss of control over drug taking, both of which exacerbate the drug-taking cycle.

Even if compulsion and impulsivity interact in drug addiction, investigating these as two separate phenomena will help to isolate the behavioural (and ultimately neural) traits of addiction. For example, addicts may display compulsion and impulsivity simultaneously in that craving is often accompanied by a focus on immediate rewards (cognitive impulsivity) and inappropriate responding (motor impulsivity). In other circumstances, the two processes may compete to control behaviour: Obtaining and securing drugs (drug seeking) often takes considerable planning and execution; rash, spontaneous behaviour (motor impulsivity) as well as an inability to consider future consequences (cognitive impulsivity) would interfere with those activities. In sum, although there is still considerable insight to be

gained from studying compulsion in drug addiction, there is now a pressing need to understand how impulsivity contributes to addiction (and vice versa).

A role for animal research

A major limitation of research examining the relationship between impulsivity and addiction in humans is that these studies are both correlational and retrospective. Thus, it is almost impossible to determine whether any behavioural differences between addicts and controls (i.e., in impulsivity measures) are a cause, or a consequence, of chronic drug use. One recent study (Block, Erwin, & Ghoneim, 2002) assessed premorbid intellectual function in addicts using historical records of achievement test scores. In this limited sample, addicts exhibited a preexisting deficit in cognitive function, which may have predicted subsequent drug use. In most cases, however, it is difficult or even impossible to objectively measure any pre-addiction function, particularly with behavioural traits such as impulsivity. Therefore, an important next step in this research programme is to experimentally manipulate and control drug experience using animal paradigms. As with many scientific questions, animal research provides the ideal opportunity to establish true causal relationships (in this case between drug administration, impulsivity, and neural changes) because factors such as prior drug experience can be varied systematically.

Animal research provides indirect evidence that drug use contributes to impulsivity in that chronic stimulant administration produces structural (Robinson, Gorny, Mitton, & Kolb, 2001; Robinson & Kolb, 1999) and neuropathological (Melega et al., 1996; Ryan, Linder, Martone, & Groves, 1990) changes in the PFC. In addition, although chronic cocaine does not alter basal levels of cortical 5-HT (Baumann, Raley, Partilla, & Rothman, 1993; Johnson, Fiorella, & Rabin, 1993), it does cause regionally specific alterations in 5-HT uptake binding (Belej, Maji, Sioutis, Barros, & Nobrega, 1996; Burchett & Bannon, 1997; Cunningham, Paris, & Goeders, 1992) and

decreased 5-HT turnover rates in the frontal cortex (Dworkin, Co, & Smith, 1995). Most importantly, these changes are dose dependent and many persist long after the cessation of drug use. An alternative view is provided by a limited number of animal experiments suggesting that impulsivity predates drug use: In rats, cognitive impulsivity correlates with voluntary ethanol intake (Poulos, Parker, & Le, 1998), and displays of impulsivity in monkeys predict patterns of ethanol drinking (Higley & Linnoila, 1997). This work obviously needs to be expanded to include other drugs of abuse and other measures of impulsivity. In that regard, the work of Piazza and colleagues (Piazza & Le Moal, 1996) on drug-induced sensitization and locomotor responses (presumed to reflect sensation seeking in humans; Nadal, Armario, & Janak, 2002) provides an excellent model to evaluate the relationship between preexisting differences in impulsivity and vulnerability to self-administer drugs.

If animal research is to provide insight into the relationship between chronic drug use and impulsivity, it should attempt to model, as closely as possible, the conditions under which humans abuse different drugs. These include drug doses, route of administration, and pattern of intake (e.g., binges). In addition, the effects of active versus passive drug administration should be considered as these can have differential effects on brain function (Di Ciano, Blaha, & Phillips, 1996; Wilson et al., 1994). This difference probably reflects an effect of the drug on neural systems that mediate learned associations (Everitt et al., 2001; Wise, 2000). The inclusion of a yoked control group provides a relatively simple but powerful control for the effects of active versus passive drug administration. Signalling the infusion in the yoked control group would isolate further the contribution of conditioned cues to behavioural (and neural) changes. Even less appreciated is the fact that learning an operant contingency itself produces brain changes, which undoubtedly interact with drug-induced effects. This highlights a problem in self-administration studies when animals are trained initially to respond for a different reinforcer (e.g., food or another drug). Under these

conditions, the effects of various manipulations (including brain lesions or pharmacological challenges) are difficult to assess because altered responses to the previously learned association cannot be distinguished from drug effects. For an excellent discussion of the issues surrounding active versus passive drug administration, including changes in molecular and cellular mechanisms associated with each, see Jacobs, Smit, De Vries, and Schoffelmeier (2003).

In the last few years, animal researchers have undertaken an important investigation of how age of drug exposure alters the propensity to develop an addiction (Andersen, 2003; Laviola, Macri, Morley-Fletcher, & Adriani, 2003; R. F. Smith, 2003). Virtually all of this work has related age-dependent behavioural (Laviola, Wood, Kuhn, Francis, & Spear, 1995; Spear & Brake, 1983) and neural (Adriani et al., 2004; Andersen, 2002) changes to functioning of the mesocortico-limbic DA system. Drug administration during adolescence, however, may have a greater impact on neural circuits associated with impulsivity because these undergo the greatest developmental change from adolescence to adulthood (Paus, 2005). For example, frontal cortical regions mature through adolescence due to increases in myelination and axon diameter (Paus et al., 1999). Metabolic activity declines with development, and the PFC is the last brain region to go through this process (Chugani, Phelps, & Mazziotta, 1987). During adolescence, the size of the PFC relative to the rest of the brain increases while the density of white matter decreases, a likely reflection of synaptic pruning (Sowell, Thompson, Tessner, & Toga, 2001). These developmental changes probably explain why inhibitory control improves through adolescence (Williams, Ponesse, Schachar, Logan, & Tannock, 1999) and why adolescents have a particularly high rate of gambling and impulse control problems (Chambers & Potenza, 2003). Notably, adolescent rodents also exhibit increased risk taking and sensation seeking (Laviola et al., 2003).

Given these profound developmental changes, brain regions mediating impulsivity may be

particularly susceptible to drug-induced alterations during adolescence. In support of this idea, adolescent, but not adult, guinea pigs treated chronically with cocaine show increased aggression (which is often associated with impulsivity), due to the drug's effect on serotonergic mechanisms (Deleon, Grimes, Connor, & Melloni, 2002). Moreover, chronic ethanol intake in adolescent, but not adult, rats disrupts behavioural functions that are mediated by the PFC, both when rats are intoxicated (A. M. White, Ghia, Levin, & Swartzwelder, 2000) and when they are not (Garcia-Moreno et al., 2002). In humans, adolescents show increased sensitivity to various abused substances (Harrison, Fulkerson, & Beebe, 2003), which may explain the higher rate of cocaine dependence with lower rates of drug use in this age group (Chen & Kandel, 2002).

On the other hand, developmental changes that occur prior to adulthood may provide the opportunity to redirect potentially harmful consequences of brain insult (including drug exposure; Andersen, Arvanitogiannis, Pliakas, LeBlanc, & Carlezon, 2005). Our own work suggests that cocaine exposure during adolescence has fewer detrimental effects in a PFC-mediated task (Paine, McElvie, Dringenberg, & Olmstead, 2004). In that study, adult cocaine-treated animals displayed deficits in the simple discrimination stage of a set-shifting task (Birrell & Brown, 2000) that were absent in animals treated during adolescence. Although ceiling effects in adolescent animals may have confounded the findings (i.e., errors to criterion across the task were higher in this group), electrophysiological measures paralleled the behavioural results. That is, the induction of long term potentiation (LTP) in the PFC was reduced in adult, but not adolescent, cocaine-treated animals. If synaptic plasticity in the PFC is altered by cocaine treatment only in adulthood, it could indicate that adolescence is a period during which PFC mechanisms are protected, at least partially, against insult. This protection may enhance exploration of novel environments, risk taking, and sensation seeking in adolescents because the impact of long-term consequences and adverse outcomes would be minimized.

From an evolutionary perspective, it would function to promote the development of adult behaviours, including mating outside of the family and community.

The relevance of age-dependent differences in drug responses to the development of addiction is unlikely to be resolved in the near future. For one thing, even in controlled animal experiments, the effect of age on behavioural responses to abused drugs varies with the dependent measure. Compared to adults, adolescent rodents are less sensitive to nicotine's effects in the conditioned taste aversion paradigm (Wilmouth & Spear, 2004) and more sensitive to the drug's effects in the elevated plus maze (Adriani et al., 2004). Similarly, the effect of stimulants on locomotor sensitization (Collins & Izenwasser, 2002) and place preference conditioning (Adriani & Laviola, 2003) are both reduced in adolescence, whereas cross-sensitization to stimulant-induced locomotion is greater in adolescent than in adult rats (Collins & Izenwasser, 2004). It appears, therefore, that the effect of drugs on various behavioural processes differs with age; the important question is how these interact to alter the susceptibility to drug addiction. Human research into this issue is difficult to interpret because early experimentation with drugs is often associated with other factors that may contribute to addiction, such as conduct disorder, socio-economic status, familial environment, and so on. In contrast, animal research can isolate the contribution of drug exposure and age from these extraneous factors. A resolution to this issue (if there is one) may help to explain why drug use during adolescence is one of the strongest predictors of drug abuse in adulthood (Kandel, Yamaguchi, & Chen, 1992) and has important ramifications for the "gateway" hypothesis of drug addiction, which is extremely controversial (Morrall, McCaffrey, & Paddock, 2002).

In sum, the causal relationship between drug use and impulsivity can be examined most effectively in animal experiments. Animal studies have already provided detailed knowledge of how neural systems that mediate compulsive drug use are altered with chronic drug administration

(Carlezon & Nestler, 2002; Kalivas, Sorg, & Hooks, 1993; Stewart & Badiani, 1993), and the relevance of these changes to the rewarding effects of drugs, self-administration, and relapse is becoming apparent (Everitt & Wolf, 2002; Hyman & Malenka, 2001). The same model of investigation should be extended to study the impulsive aspects of drug addiction. This research could address how different drugs of abuse alter impulsive behaviours, the parameters (e.g., age of drug administration, pattern of intake, etc.) that are critical for behavioural changes, and the neural mechanisms that mediate these changes. In the end, these investigations may provide information on broader questions beyond the field of addiction, such as how different neural mechanisms control the various components of impulsivity.

Drug-induced impulsivity

Cognitive impulsivity

Within the last few years, we initiated a research programme to investigate the relationship between impulsivity and drug addiction. One of the first questions that we addressed was whether drugs induce impulsive responding in rats or humans. Although disinhibited behaviours and risky decision making are often associated with drugged states, controlled laboratory studies have not always confirmed this assumption. For example, neither amphetamine (de Wit, Enggasser, & Richards, 2002) nor alcohol (Ortner, MacDonald, & Olmstead, 2003; Richards et al., 1999b) affect cognitive impulsivity in humans, measured as the choice of an immediate small reward over a delayed large reward. Even in rats, the effects of these drugs are not straightforward: Amphetamine increases impulsivity in the Delayed Reinforcement task (Everden & Ryan, 1996), whereas both amphetamine and methamphetamine decrease impulsivity in the Adjusting Amounts procedure (Richards, Sabol, & de Wit, 1999a; Wade, de Wit, & Richards, 2000). Both tasks measure the ability to delay gratification, but the Adjusting Amounts procedure systematically varies the amount of the immediate

small reward to determine the quantity of this alternative, which equates to the large delayed reward at each interval. In contrast, the Delayed Reinforcement paradigm assesses the preference for set amounts of small and large rewards when the delay to the latter is varied. Thus, one paradigm provides a measure of how much the immediate reward is valued, and the other which of two alternatives is preferred. This methodological difference could account for the conflicting effects of amphetamine in the two paradigms, but it is more likely that the presence (Adjusting Amounts) versus the absence (Delayed Reinforcement) of a cue signalling the delay to the large reward explains the discrepancy: Amphetamine decreases choice of a large delayed reward when no cue is present and increases the choice when a cue is present (Cardinal, Robbins, & Everitt, 2000).

Despite the pharmacological similarities between amphetamine and cocaine, we have never observed an effect of cocaine on cognitive impulsivity in rats (Paine & Olmstead, unpublished observation), even though we used three different Delayed Reinforcement paradigms and tested animals with and without a cued delay. Thus, there may be a dissociation between the effects of psychostimulants on this measure. In addition, alcohol increases the choice of a small immediate reward over a large delayed reward in both free-operant (Hellems, Nobrega, & Olmstead, 2005) and discrete-trials (Poulos et al., 1998) versions of the Delayed Reinforcement task, although the effect is not observed in human studies. The differential effect of these three drugs on the ability to delay gratification in rats (amphetamine increases or decreases depending on the cue, alcohol increases, and cocaine does not change) is further evidence that cognitive impulsivity is mediated by specific pharmacological mechanisms.

The apparent contradiction between laboratory results and real-life situations, and between human and rat studies of cognitive impulsivity, raises the possibility that drug-induced changes in behaviour are due to an effect on other processes. One suggestion is that drugs, such as alcohol, alter

decision making because intoxicated individuals focus almost exclusively on the most salient cues in their environment (Steele & Josephs, 1990). According to this "alcohol myopia" theory, alcohol produces impulsive behaviour in real-life situations (e.g., drunk driving, aggression, unprotected sex) because the cues that signal immediate short-term rewards (e.g., sexual gratification) are generally more salient than the possible negative, long-term consequences (e.g., contracting AIDS). If this is true, behaviour under the influence of alcohol should be controlled by salient cues, regardless of whether they impel or inhibit responding. In support of this idea, intoxicated individuals report less intention to engage in risky behaviour if the strength of the cues inhibiting their behaviour is increased (MacDonald, Fong, Zanna, & Martineau, 2000; MacDonald, Zanna, & Fong, 1996). Based on these findings, we suggested that cognitive impulsivity is reduced in intoxicated individuals tested in the laboratory (Ortner et al., 2003) because the laboratory setting (e.g., presence of the experimenter, knowledge that the experimenter would later view the data, etc.) may have provided salient inhibiting cues. This would fit with the evidence that ethanol produces positive subjective effects when consumed in a social situation and aversive effects when consumed in isolation (Doty & de Wit, 1995).

In order to further examine the phenomenon of alcohol myopia, we developed a rat model of myopia using a modified version of the delayed reinforcement t-maze task (Olmstead, Hellems, & Paine, *in press*). In this paradigm, a light in one arm predicts either a small immediate (2 sucrose pellets) or a large delayed (12 sucrose pellets after 10 s) reward, but the arm paired with the light varies across trials. Alcohol dose-dependently increased the choice of the lit arm, regardless of whether it signalled the small or the large reward. This indicates that rats, like humans, are influenced by cue salience when intoxicated. The fact that alcohol did not alter impulsivity (i.e., it did not increase the choice of the immediate reward) in this paradigm suggests that myopia, not impulsivity, was controlling

behaviour under the influence of the drug. We are now testing whether other drugs induce myopic responding in order to determine whether altered decision making under the influence of psychoactive substances may be explained in terms of a general theoretical framework. If so, it may explain why amphetamine decreases cognitive impulsivity in humans who are tested in a laboratory (de Wit et al., 2002).

The suggestion that intoxicated individuals are myopic is consistent with evidence that alcohol induces cognitive impairments (Brooks, Henneberry, McAlpin, Norman, & Little, 2002; Hoaken, Assaad, & Phil, 1998; Rossetti et al., 2002). That is, alcohol myopia theory states that alcohol restricts cognitive processes such that intoxicated individuals are unable to simultaneously process multiple pieces of information (i.e., they display cognitive short-sightedness). At the same time, it is unlikely that alcohol caused severe amnesia or general confusion in our myopia paradigm because the choice of the lit arm under the influence of alcohol was greater than 50% (i.e., random responding). Whether reports of cognitive deficits in other paradigms can be explained by alcohol myopia remains an open question.

The concept of alcohol (or drug-induced) myopia also fits with descriptions of behavioural stereotypy that occurs following administration of stimulants (Creese & Iversen, 1974; Randrup & Scheel-Kruger, 1966) or alcohol (Devenport & Merriman, 1983). Drug-induced stereotypy and locomotion are mediated through distinct pharmacological mechanisms (Sahakian, Robbins, Morgan, & Iversen, 1975), and the two behaviours may compete with one another. That is, with increasing drug doses, forward locomotion decreases as behaviour directed toward specific stimuli increases (Blanchard et al., 1998). Thus, both myopia and stereotypy describe the drugged state as a narrowing of behavioural repertoire produced by a focus on salient environmental cues. This fits with the suggestion that tasks whose mastery entails repetition, few topographies, and a rigid structure will improve with alcohol administration, whereas those requiring

change and the sampling of new strategies will be impaired (Devenport & Merriman, 1983). One fascinating observation is that rats displaying stereotypy during cocaine binge sessions can disengage from the stereotypic response to lever press for the drug (Paine, Krendler, & Olmstead, unpublished observation). Stereotypy, therefore, is not simply a "locking in" of a behavioural response but may reflect the concept of probability dependency in which the effect of the drug depends, in part, upon the baseline probability of a response (Hobbs, Rall, & Verdoorn, 1996; Schwartz & Marchok, 1974).

The idea that drugs increase the control of behaviour by salient environmental cues is reminiscent of the gain theory of mesolimbic DA (Cohen & Servan-Schreiber, 1992). Like alcohol myopia theory, this position explains drug-induced behavioural changes as altered responses to salient cues, although neither theory specifies whether a cue becomes more salient or whether the behaviour evoked by a cue is magnified in a drugged state. The fact that increases in DA are associated with compulsion in drug addiction raises an important issue of how to distinguish the effects of drugs on impulsivity and compulsion. That is, if cognitive impulsivity reflects myopia, myopia is equated with DA gain, and DA gain is responsible for compulsion, are the two behavioural traits of addiction separable? Again, the obvious way to approach this issue is through controlled animal experiments. For example, if alcohol-induced impulsivity is really myopia, the two should be mediated by similar neuropharmacological mechanisms. Surprisingly, there is little understanding of the mechanisms underlying alcohol-induced impulsivity, despite the link between 5-HT and impulsivity and the evidence that alcohol affects serotonergic transmission (Hobbs et al., 1996; Lovinger, 1999). Our work suggests that the increased choice of a small immediate reward (i.e., cognitive impulsivity) following ethanol administration is reduced by the 5-HT agonist, p-chloroamphetamine (Olmstead et al., in press). The same manipulation had minimal effects in the myopia paradigm suggesting that alcohol-induced myopia and

impulsivity may be distinct processes. If these results are confirmed, we may conclude that myopia and impulsivity are each manifested under specific environmental conditions, in this case the task requirements of the two paradigms. We also examined the relationship between myopia and DA by testing whether manipulations of the mesolimbic DA system alter responding in the myopia paradigm. These studies should shed light on what myopia reflects, how it is related to cognitive impulsivity, and whether the two processes are distinct, overlapping or mediated by some third, unknown, factor.

Motor impulsivity

Like cognitive impulsivity, the effect of drugs on motor impulsivity is controversial, at least when it is measured in the laboratory. For example, in both rats and humans, alcohol increases (de Wit, Crean, & Richards, 2000; Feola, de Wit, & Richards, 2000) or does not affect (Hellemans et al., 2005; Ortner et al., 2003) motor impulsivity, and psychostimulants are associated with increases (Cole & Robbins, 1987; Fillmore & Van Selst, 2002; Ridley, Baker, & Weight, 1980) and decreases (de Wit et al., 2000; de Wit et al., 2002; Feola et al., 2000) in this measure. Individual differences may explain some of these discrepancies in that the effect of drugs on motor impulsivity depends on preexisting traits such as reaction time (de Wit et al., 2000), baseline inhibitory control (Feola et al., 2000), and working memory capacity (Finn, Justus, Mazas, & Steinmetz, 1999). More importantly, because drugs act on multiple neural systems, behavioural measures of disinhibition may be confounded by disruptions in other motor or cognitive abilities.

In our own study, therefore, we examined the effect of cocaine on motor impulsivity in rats and tested whether any observed deficit was due to changes in other processes (Paine & Olmstead, 2003). We used an asymmetrically reinforced go/no-go task in which disinhibition is reflected as a selective increase in responding during no-go intervals (Fletcher, 1993). Because accurate performance in this task depends on the ability to use conditional rules (i.e., lever press in one

stimulus condition but not the other) and to detect and respond to visual stimuli, we also tested the effect of cocaine in conditional discrimination and vigilance tasks. In the conditional discrimination task, rats learn the rule "in the presence of one stimulus press the right lever, in the presence of another stimulus press the left lever" (Chudasama, Bussey, & Muir, 2001). In order to obtain an independent measure of disinhibition, we measured responding during a 1-s delay prior to the stimulus onset. Cocaine disrupted conditional discrimination and increased premature responding, consistent with evidence that psychomotor stimulants increase premature responding in the 5-choice serial reaction time task (Cole & Robbins, 1987), and decrease interresponse times on differential-reinforcement-of-low-rates schedules (McClure & McMillan, 1997; Sabol, Richards, Layton, & Seiden, 1995; Wenger & Wright, 1990; Woolverton, Kandel, & Schuster, 1978). The deficit in conditional discrimination was not eliminated by increasing the stimulus duration, suggesting that cocaine does not alter attentional processes. This was confirmed in a vigilance task (Chudasama & Muir, 2001) which assesses the ability to detect and respond to a brief stimulus presented randomly throughout a session. In sum, we concluded that cocaine increases behavioural disinhibition and that this increase may be independent of an impairment in conditional discrimination.

Our finding that cocaine produces behavioural disinhibition is consistent with some reports (Cole & Robbins, 1987; Fillmore et al., 2002; Ridley et al., 1980), but contradicts others (de Wit et al., 2000; de Wit et al., 2002; Feola et al., 2000). Task differences may explain some of these inconsistencies in that, in the stop task (Feola et al., 2000), animals must stop a response in progress in order to make an alternative response whereas, in the go/no-go task (our study), animals must refrain from making responses during no-go intervals. Given that amphetamine improves stop-task performance (Feola et al., 2000), and cocaine impairs go/no-go performance (Paine & Olmstead, 2003), psychostimulants may improve the ability to

switch responses, but impair the ability to withhold responding. Alternatively, these discrepancies may be explained by the consequences of inappropriate responding: In the stop task, reward is withheld when stop failures occur, whereas responding during no-go intervals has no programmed consequences. This may produce motivational differences associated with inhibited responding in the two tasks, which could interact with drug effects. That said, cocaine increased premature responses in the conditional discrimination task, thereby terminating the trial without the ability to attain reward. Thus, the motivation for inhibited responding should be similar in our experiment and in the stop task. It is more likely, therefore, that differences in response requirements explain the disparate effects of psychostimulants on behavioural disinhibition. Finally, we cannot rule out the possibility that cocaine and amphetamine have different effects on motor impulsivity, or that either drug would produce different effects in a symmetrically reinforced go/no-go task (i.e., animals are reinforced for not responding during no-go intervals).

All of the studies noted above (including our own) examined the effects of drugs on motor impulsivity when animals were responding for natural rewards (food or water). Although this design allows the experimenter to control drug doses and exposure, inhibitory mechanisms may be mediated by different processes when subjects are responding for drug. The fact that blood alcohol levels correlate with the self-reported desire to consume more alcohol (Ortner et al., 2003) suggests that the ability to limit drug intake may be reduced in intoxicated states. Certainly, unlimited access to stimulants produces periods of disinhibited and uncontrolled drug intake in both humans (Gawin & Ellinwood, 1988) and rats (Bozarth & Wise, 1985). During these binge sessions, regular patterns of responding break down, and activities not directed towards the drug (e.g., grooming, sleeping, eating and drinking) are reduced. As the binge progresses, interinfusion intervals become increasingly erratic, although rats still maintain a constant hourly intake of cocaine when the dose is varied

(Tornatzky & Miczek, 1999). This suggests that short- but not long-term regulatory mechanisms break down during the binge. Changes in response rates, therefore, cannot be explained by a change in reinforcing efficacy, but may reflect changes in inhibitory processes. If so, behavioural changes across binge sessions should correlate with changes in neural systems associated with impulsivity. Moreover, if these neural changes are long lasting, rats that have undergone binge sessions should exhibit increased impulsivity, even in the absence of the drug. Although we do not have answers to these specific question, related issues are currently being addressed (see recent work of K. A. Miczek, A. G. Phillips, D. C. S. Roberts and their colleagues), which should yield some important information.

One of the biggest obstacles to understanding the mechanisms underlying bingeing is that there is no consensus on what constitutes a drug binge. This is particularly true in the human literature, which generally employs a loose criterion of a minimum amount of drug consumed per occasion (often with no time specified for the occasion). Because there is no consideration of individual differences in regulated intake (i.e., during non-binge periods) or of changes in rate of intake across the occasion, there is no way to determine whether these binges represent periods of disinhibited drug intake. Even in rat studies, we have no operational definition of the breakdown in regulatory control that is assumed to occur during drug binges. Tornatzky and Miczek (2000) have provided the best characterization of behavioural changes during binges by calculating changes in interinfusion intervals across time. This analysis of root mean square of successive differences provides a statistically reliable measure of variability over a specified time period. Nonetheless, in order to determine the point of transition from regular to irregular drug intake, we require an algorithm that characterizes the regular intake pattern for individual rats during limited access sessions and in the initial phase of unlimited access sessions. These data (including means, variability, and successive differences of interinfusion intervals) would then be

used as a template during the binge sessions to determine deviations from regularity (i.e., breakdown in behavioural control). For example, irregular intake could be defined as a period during which the standard deviation of the root mean squared of successive differences lies outside the standard deviation range of the regular intake patterns, but the standard deviation of the interinfusion interval is not significantly altered. That is, the variability in intake patterns is significantly increased, without changing the overall level of intake. This formula would distinguish irregular intake from abstinence periods, which also occur throughout the binge sessions. Obviously, a critical issue is time resolution and the need to validate any algorithm by applying it to a large sample of binge sessions.

Once the criteria for regular and irregular intake are established, the behavioural patterns associated with each period need to be mapped to neurochemical changes. We have some knowledge of the changes that occur during "binge" sessions in which the drug is administered by the experimenter (Kuczenski & Segal, 1997; Lindholm, Rosin, Dahlin, Georgieva, & Frank, 2001; Maisonneuve & Kreek, 1994; Segal & Kuczenski, 1999; Zhang, Schlussman, Ho, & Kreek, 2001), but all of these studies focus on dopaminergic mechanisms in the striatum. If irregular or binge patterns of intake represent a breakdown in impulse control, they are more likely to be reflected by changes in 5-HT mechanisms in the PFC, although there is also evidence for cortical DA dysfunction in these conditions (Dalley, Theobald, Eagle, Passetti, & Robbins, 2002a). Experiments combining self-administration and microdialysis techniques are obviously laborious, but certainly not without precedent. And they could address critical questions concerning drug-induced impulsivity such as what are the neurochemical correlates of bingeing, do these change with repeated binge sessions, how do they interact with brain reward systems, and why do some drugs of abuse not instil binge patterns of intake. Understanding the effect of drugs on motor impulsivity is an important issue because the loss of inhibitory control under the influence of drugs

could lead to further drug taking and ultimately contribute to the cycle of addiction.

Chronic drug exposure

In addition to our investigations of drug-induced effects, we are investigating the impact of chronic drug exposure on impulsivity. First, we tested whether chronic cocaine administration alters cognitive or motor impulsivity in rats, using the delayed reinforcement and go/no-go tasks, respectively. Although our treatment regime (20 mg/kg, three times per day for 14 days) increased behavioural sensitization scores (Kilbey & Ellinwood, 1977), it only produced a transient increase in cognitive impulsivity that recovered across testing (Paine, Dringenberg, & Olmstead, 2003). These data contradict previous evidence that chronic methamphetamine reduces indifference points in an Adjusting Amounts procedure (Richards et al., 1999a), although impulsivity scores across days are not presented in the Richards et al. paper making direct comparisons between the two experiments difficult. Nonetheless, dosing regimes and time of testing were similar, so the discrepancy may be related to differences in behavioural procedures in the two studies. More specifically, the Adjusting Amounts procedure systematically varies the magnitude of the immediate reward; indifference points are calculated as the reward quantity that equates the immediate and delayed rewards. In contrast, indifference points in the Delayed Reinforcement paradigm reflect the delay to the large reward that equates the two alternatives. Furthermore, the delay to the large reward is signalled by a cue (light) in the Adjusting Amounts procedure, which can influence the choice of the small or large reward (Cardinal et al., 2000). Whether these procedural differences explain the contradictory effects of chronic stimulant administration on cognitive impulsivity remains an open question.

We also found that chronic cocaine had no effect on motor impulsivity (Paine et al., 2003), despite evidence that chronic methamphetamine increases perseverative errors in a reversal-learning

paradigm in monkeys (Jentsch, Olsson, De La Garza, & Taylor, 2002). To the extent that impaired inhibition of a previously learned response and the inability to withhold responding in the presence of a discriminative stimulus reflect similar processes, the two studies produced contradictory results. Indeed we were surprised at the minimal behavioural effects that we observed, particularly as similar dosing regimes can produce pronounced neural and behavioural changes (Burchett & Bannon, 1997; Unterwald, Ho, Rubenfield, & Kreek, 1994;). Moreover, cortical serotonergic mechanisms were partially compromised in our study in that the 5-HT receptor antagonist, methiothepin, was more effective in blocking electrocorticogram (ECoG) activity in cocaine- than in saline-treated animals.

A possible explanation for the discrepancy between our study and both the Richards et al. (1999a) and Jentsch and Taylor (2003) studies is the chronically administered drug: cocaine versus methamphetamine. Both stimulants produce their rewarding effects by blocking DA transporter mechanisms in the nucleus accumbens (Wise, 1996) and induce similar behavioural profiles when administered in binge patterns (Segal & Kuczenski, 1997a, 1997b). Nonetheless, repeated administration of methamphetamine and cocaine have different effects on striatal DA and 5-HT transporter function in vivo (Fleckstein et al., 1999), and prolonged exposure to cocaine does not produce the same level of neurotoxic effects on striatal DA or 5-HT systems as that observed with chronic methamphetamine administration (Kleven, Woolverton, & Seiden, 1988).

This raises an important question of how long-term administration of different drugs may influence behavioural processes. If impulsivity is a consequence and not a cause of addiction, drugs that produce the most dramatic effect on PFC or 5-HT systems should be associated with higher levels of impulsivity. In that respect, the street drug 3,4-methylenedioxymethamphetamine (MDMA or Ecstasy) is an obvious candidate: it preferentially targets the 5-HT transporter system, increasing synaptic levels of 5-HT following acute administration (Rudnick & Wall, 1992).

In contrast, chronic MDMA administration induces selective 5-HT loss in both rats and non-human primates, particularly in forebrain and cortical regions (Morgan, 2000). MDMA use in humans is associated with reduced CSF levels of 5-HT and its metabolites (McCann, Ridenour, Shaham, & Ricaurte, 1997), upregulation of 5-HT receptors (Reneman, Booij, Schmand, Van den Brink, & Gunning, 2000), and reduced neuronal activity in the PFC (Reneman, Majoie, Schmand, Van den Brink, & den Heeten, 2001). Given these changes, it is not surprising that MDMA users display high-risk behaviours (Klitzman, Pope, & Hudson, 2000) and increased impulsivity (Morgan, 1998). At the same time, Kish (2002) argues that the evidence for 5-HT dysfunction in MDMA users is equivocal, partly because self-reports of prior drug use are unreliable. Again, this is an obvious place for animal research to address a controversial question. At least one study suggests that chronic MDMA administration increases motor impulsivity in rats, reflected as an inability to withhold inappropriate responses in an appetitive conditioning paradigm (Taylor & Jentsch, 2001). Importantly, neither cocaine nor amphetamine treatment produced similar effects. These data support the hypothesis that the behavioural effects of long-term drug use are determined by alterations in specific neural systems and that these vary with drug class. In line with this idea, the nature of cognitive deficit in drug addicts depends, at least in part, on the addicts' drug of choice (Ornstein et al., 2000; Rogers et al., 1999). This hypothesis may also explain the distinct patterns of drug use associated with different drug classes. That is, only some drugs (e.g., cocaine, amphetamine, and alcohol) produce binge-like patterns of drug intake, and MDMA and hallucinogens do not produce compulsive drug seeking that is characteristic of cocaine, alcohol, nicotine, and, to some extent, opiates.

The study of individual differences

Even if chronic drug administration produces neural changes that increase the propensity to

abuse drugs, preexisting individual differences undoubtedly contribute to differential rates of addiction. In support of this idea, drug addiction is associated with specific personality traits (Cloninger et al., 1993; Scourfield et al., 1996), and, in rats, the propensity to self-administer drugs can be predicted by locomotor responses to novelty and glucocorticoid responses to stress (Piazza & Le Moal, 1996). The latter effect is due to enhanced activity of the mesolimbic DA system, which increases the reinforcing efficacy of abused drugs. This mechanism, therefore, could underlie compulsive drug seeking, but it is unlikely that it mediates either cognitive or motor impulsivity associated with addiction. Thus, although it seems intuitive, there is little or no empirical evidence that trait differences in impulsivity predict patterns of drug intake. Nor do we understand how these preexisting differences may interact with drug experience. Again, these questions could be examined most effectively in animal paradigms because factors such as prior drug experience can be varied systematically. Indeed, the work of Piazza and colleagues on drug-induced sensitization and locomotor responses (presumed to reflect sensation seeking in humans; Nadal et al., 2002) provides an excellent model to evaluate the relationship between individual differences in impulsivity and vulnerability to self-administer drugs. To date, there is limited evidence on this question: In rats, cognitive impulsivity correlates with voluntary ethanol intake (Poulos et al., 1998), and displays of impulsivity in monkeys predict patterns of ethanol drinking (Higley & Linnoila, 1997). This work obviously needs to be expanded to include other drugs of abuse and other measures of impulsivity.

Individual differences in impulsivity are determined partially by genetics (Brunner & Hen, 1997), although nongenetic factors also play a major role in most complex behavioural traits (Crabbe, Phillips, Buck, Cunningham, & Belknap, 1999). One important factor may be early life experience in that childhood abuse increases the incidence of both addiction (Harrison, Fulkerson, & Beebe, 1997) and impulsivity (Brodsky et al., 2001). Moreover, early

parental neglect in monkeys is associated with decreased 5-HT levels, increased impulsivity, and excessive alcohol intake (Higley & Linnoila, 1997). Neurobiological data provide indirect evidence for a link between adverse early experience and impulsivity: Rearing rats in social isolation reduces 5-HT neurotransmission, metabolite levels, and turnover in the PFC (Hall, 1998); isolation rearing in gerbils reduces DA input to the orbitofrontal cortex (Neddens, Lesting, Dawirs, & Teuchert-Noodt, 2002); and PFC lesions and isolation rearing induce the same selective attentional deficit in rats (Schrijver & Wurbel, 2001). The effect of isolation rearing interacts with genetic factors in that monkeys with adverse early experiences are differentiated by genotype in cerebrospinal fluid concentrations of the 5-HT metabolite 5-hydroxyindoleacetic acid, whereas monkeys reared normally are not (Bennett et al., 2002).

Given the behavioural and neural profiles of animals reared in social isolation, we predicted that this adverse early experience would alter impulsivity in adult rats. On the contrary, our data show that isolation rearing does not affect on motor impulsivity and only affects cognitive impulsivity when rats are intoxicated (Hellemans et al., 2005). Although contrary to our hypothesis, these data are consistent with evidence that isolation rearing enhances behavioural responses to ethanol (Hall, Huang, Fong, Pert, & Linnoila, 1998a) and does not effect impulsivity in an attentional task, except under the influence of amphetamine (Dalley, Theobald, Pereira, Li, & Robbins, 2002b). These findings led us to conclude that the relationship between adverse early experience and impulsivity is mediated by an intervening variable such as stress, which may be induced by drug administration.

If isolation rearing alters some behavioural process (such as impulsivity), which then interacts with drug experience, it may explain why research examining the effect of isolation rearing on drug self-administration is so controversial. Isolation rearing has been reported to increase (Alexander, Coombs, & Hadaway, 1978; Boyle, Gill, Smith, & Amit, 1991; Deatherage, 1972;

Schenk, Lacelle, Forman, & Amit, 1987; Schenk, Gorman, & Amit, 1990; Schenk, Robinson, & Amit, 1988), decrease (Hill & Powell, 1976; Phillips, Howes, Whitelaw, Robbins, & Everitt, 1994a; Phillips et al., 1994b), or not change (Bozarth, Murray, & Wise, 1989; Kazmaier, Butcher, Senter, & Stutz, 1973; Rockman, Hall, Markert, & Glavin, 1988) drug intake. Some of these discrepancies may be explained by shifts in the dose-response curve with isolation rearing (Howes, Dalley, Morrison, Robbins, & Everitt, 2000) or by strain differences, which interact with the effects of isolation rearing on responses to drugs (Hall, Huang, Fong, Pert, & Linnoila, 1998b). At the same time, given the multitude of neurochemical and behavioural changes in isolation-reared rats (Robbins, Jones, & Wilkinson, 1996), it is likely that adverse early experience alters the propensity to abuse drugs through a variety of mechanisms. These may include changes in the likelihood that an individual will experiment with drugs, experience anxiolytic effects with early drug use, continue drug use despite adverse consequences, develop compulsive behaviours, exhibit disinhibited drug intake, self-medicate withdrawal symptoms, and so on. These processes may be dissociable in that high levels of depression, anxiety, and stress all predict drug self-administration (Homberg et al., 2002; Markou, 1998), but the three conditions are associated with distinct neurochemical profiles.

Recently, an emphasis has been placed on prenatal drug exposure as a predictor of adult differences in addiction rates (Baer, Sampson, Barr, Connor, & Streissguth, 2003; Buka, Shenessa, & Niaura, 2003; Hellstrom-Lindahl & Noberg, 2002; Mattson, Schoenfeld, & Riley, 2001). In utero exposure to cocaine, heroin, TCH, nicotine, or alcohol produces cognitive and motor deficits in both humans and animals (Baglenova, Birru, Pandiella, & Breese, 2004; Gendle et al., 2003; Harvey, 2004; Iqbal, Dringenberg, Brien, & Reynolds, 2004; Mattson et al., 2001; Singer et al., 2004; A. M. Smith, Fried, Hogan, & Cameron, 2004) that are associated with alterations in brain reward systems

(Chen, Maier, & West, 1997; Choong & Shen, 2004; Glatt, Trksak, Cohen, Simeone, & Jackson, 2004; Kane, Fu, Matta, & Sharp, 2004; Salvatore et al., 2004; Shen, Hannigan, & Kapatos, 1999). Despite these findings, the effects of prenatal drug exposure on subsequent drug self-administration in animals is inconclusive (Keller, LeFevre, Raucci, & Carlson, 1996; Ramsey, Niesink, & Van Ree, 1993; Rocha, Mead, & Kosofsky, 2002). As in the social isolation model, in utero drug exposure probably induces numerous behavioural effects that may alter the propensity to self-administer drugs. The evidence for increased impulsivity in humans following prenatal drug exposure is compelling, both for alcohol (Kodituwakku, May, Clericuzio, & Weers, 2001; Mattson & Riley, 1998; Nanson & Hiscock, 1990; Streissguth, Martin, Barr, & MacGregor-Sandman, 1984) and for tetrahydrocannabinol (THC) (A. M. Smith et al., 2004), although isolating one behavioural effect in humans with multiple problems (e.g., foetal alcohol syndrome) is difficult, if not impossible.

Our own work investigated the relationship between in utero alcohol exposure and behavioural effects, using a guinea pig model of chronic prenatal ethanol exposure (CPEE; Abdollah, Caitlin, & Brien, 1993). The guinea pig is the most parsimonious model to examine prenatal ethanol exposure because its extensive prenatal brain development parallels that of humans. In particular, the brain growth spurt is a perinatal event in humans and guinea pigs, but a postnatal event in the rat and mouse (Dobbings & Sands, 1979). In addition, the guinea pig has a placenta that is most similar to human placenta among small animal species, and it has a trimester-equivalent gestation that is similar to that of the human (Martensson, 1984). In our study, CPEE induced a pronounced behavioural deficit in a lever-pressing task, manifested as a high magnitude of responding during extinction trials (Hayward et al., 2004). This result is remarkably consistent across multiple paradigms that measure response inhibition in animals (Abel, 1982; Driscoll, Streissguth, & Riley, 1990; Riley, Lochry, & Shapiro, 1979; Riley, Shapiro, Lochry, & Broida, 1980). In subsequent

work, we confirmed that CPEE guinea pigs exhibit higher levels of motor impulsivity in a go/no-go task, with no perseverative deficit in a reversal learning task (Martin & Olmstead, unpublished observation). CPEE-treated animals also exhibit alterations in gamma-aminobutyric acid (GABA) and glutamatergic mechanisms in the hippocampus (Richardson, Byrnes, Brien, Reynolds, & Dringenberg, 2002), although the behavioural changes in response inhibition are more likely due to deficits in PFC mechanisms.

Thus, there are many factors that may mediate the relationship between individual differences and drug addiction. To date, animal research has focused on describing the relationship between sensation seeking (i.e., sensitized locomotor responses) and drug self-administration, but future studies should focus on understanding the contribution of other factors, including impulsivity. In that respect, the role of both genetic and environmental factors should be examined, as well as how these variables interact with chronic drug use. Finally, although the studies are more problematic, animal research could also investigate whether individual differences (produced by both genetic and environmental variables) predict differential responses to various classes of abused drugs.

CONCLUSIONS

Understanding the relationship between impulsivity and addiction is related to the more general question of how drug administration (both acute and chronic) affects cognitive processes. First, cognitive impulsivity is measured as an increased choice of small immediate over large delayed rewards, but this effect may be produced by deficits in attention, an inability to discriminate reward magnitude, disruptions in time perception, a misunderstanding of response contingencies, an inability to consider future events, a distortion in the value of long-term consequences, and so on. Similarly, apparent deficits in motor impulsivity may be produced by disruptions in sensory, motor, or timing abilities, even if the ability to withhold a prepotent response is intact.

To further complicate the issue, some cognitive deficits may be explained by changes in impulsivity because tests of cognitive function (i.e., discrimination) can be disguised as impulsivity tasks (e.g., go/no-go). Again, an advantage of animal research is that it provides dissociable measures of individual processes and can rule out alternative hypotheses with the proper control conditions. As an example, gonadal hormones have distinct effects on impulse control and divided attention in rats (Jentsch & Taylor, 2003), and separate neurochemical systems mediate attention and response control in the 5-choice serial reaction time task (Ruotsalainen, Miettinen, MacDonald, Koivisto, & Sirvio, 2000).

Even if the components of cognition and impulsivity can be dissociated in the laboratory, it is likely that the two processes interact. For example, working memory and conditioned associative learning can modulate disinhibition (Finn et al., 1999), and cognitive deficits are associated with increased impulsivity (Lau, Pihl, & Peterson, 1995). This interaction may be an important factor in addiction as drug-induced impulsivity could reflect a lowered threshold for the cognitive modulation of impulsivity (Finn et al., 1999; Lau et al., 1995). Even so, of the few theories that emphasize cognitive factors in addiction (Everitt et al., 1999; Tiffany, 1990; N. M. White, 1996; Wise, 1999), none explicitly discuss impulsivity.

In some cases, the relationship between the two is implicit. For example, according to Tiffany (1990), drug action schema (i.e., drug-taking behaviours) are automatic processes elicited by environmental stimuli. These may be blocked by voluntary cognitive processes that promote abstinence. The two cognitive processes (automatic and nonautomatic) compete with one another and with other cognitive processes, such as those activated by negative affect (e.g., withdrawal). Ultimately, this increase in effortful cognitive processing leads to relapse by breaking down the inhibition of prepotent or automatic drug-taking responses.

In contrast, Wise (1999) explains drug self-administration in rodents as the product of immediate and historical antecedents, rather than

knowledge about the consequences of the action. In other words, drug taking is controlled by learned expectancies of local stimulus-reward associations and not the consideration of long-term events. This essentially describes cognitive impulsivity (i.e., the choice of immediate over delayed rewards), although Wise would disagree that the contingencies associated with each choice are "understood". He does point out that cognitive factors may have a greater impact on addiction-related impulsivity in humans than in rats. In particular, drug taking is inhibited in rats during withdrawal, whereas culturally transmitted beliefs, insights into physiological states, and so on may disinhibit this behaviour in humans.

Finally, several theories emphasize that drugs of abuse interact with forebrain systems that mediate different cognitive processes (Everitt et al., 1999; Wise, 1999). Because these systems influence working memory, decision making, and control of behaviour by conditioned cues, they may ultimately impact, either directly or indirectly, on impulsivity. One goal of animal research should be to identify if and when altered decision making, under the influence of drugs, can be explained by impulsivity, as well as whether drugs can influence cognitive processes without affecting impulsivity. Understanding the role of cognitive factors in addiction (and how these interact with other factors such as impulsivity) is important because addicts display cognitive deficits (Bolla, Funderburk, & Cadet, 2000) that may seriously impair treatment options (Bates, Bowden, & Barry, 2002; Bowden, Crews, Bates, Fals-Stewart, & Ambrose, 2001).

While still focusing on compulsion, therefore, future research should place increasing emphasis on the role of impulsivity in the establishment and maintenance of drug addiction. This review focuses on motor and cognitive impulsivity as being particularly important to addiction and emphasizes that the two processes are dissociable. The suggestion that the primary features of cognitive and motor impulsivity can be identified and measured independently is consistent with the idea that impulsivity is not a unitary construct (Barratt & Patton, 1983). Moreover, the fact that

behavioural measures of the two processes do not always correlate supports evidence that subcomponents of impulsivity are mediated by distinct (although possibly overlapping) neuropharmacological substrates (Evenden, 1999). Some theories conceptualize the different subcomponents of impulsivity within a single framework (Gerbing, Ahadi, & Patton, 1987), but this position does not presume that the subcomponents can not act independently. In addition, analyses of drug-taking behaviour using economics models (Bickel & Marsch, 2001) may provide insight into the factors that influence impulsivity in drug addicts.

A critical issue in addiction research is how compulsion and impulsivity interact: Do the two traits develop independently or simultaneously, or does the development of one maladaptive behaviour (e.g., compulsion) lead to the other (e.g., impulsivity)? These questions are particularly difficult to address because drugs of abuse interact with numerous neural substrates, and no brain system can be considered in isolation. Any post hoc or correlational analysis of brain-behaviour relationships, therefore, will provide an incomplete account of addiction. The most effective way to understand maladaptive drug use is to combine these studies with carefully controlled animal experiments that allow the dissociation of neural systems and the isolation of behavioural processes. In the end, determining the relative contribution of compulsion and impulsivity to addiction will provide an important piece in the puzzle of this disorder.

In conclusion, the most comprehensive description of drug addiction will incorporate mechanisms of both impulsivity and compulsion. Currently, our understanding of compulsion (both neural and behavioural processes) far outweighs that of impulsivity, even though impulsivity is a significant predictor of level of abuse and of treatment retention (Moeller et al., 2002). Nonetheless, as emphasized many times in the past, the development of drug addiction is affected by social, cultural, and developmental factors, which ultimately impact on biological and psychological processes. Even though impulsivity is only one component, understanding how it impinges

on drug addiction will improve our ability to treat this debilitating disorder. There is no doubt that animal research can contribute to this knowledge.

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