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REVIEW

The role of impulsive behavior in drug abuse

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Abstract
Background Impulsivity is a multifaceted construct that has recently been recognized as a factor contributing to enhanced vulnerability to drug abuse.
Objectives In the present review, we focus on two facets of impulsivity (and tasks that measure them): (1) impulsive choice (delay discounting task) and (2) inhibitory failure (go/no-go, stop signal reaction time, and five-choice serial reaction time tasks). We also describe how performance on each of these tasks is associated with drug-related behavior during phases of drug abuse that capture the essential features of addiction (acquisition, escalation, and reinstatement of drug-seeking after drug access has terminated). Three hypotheses (H) regarding the relationship between impulsivity and drug abuse are discussed: (1) increased levels of impulsivity lead to drug abuse (H1), (2) drugs of abuse increase impulsivity (H2), and (3) impulsivity and drug abuse are associated through a common third factor (H3).
Conclusion Impulsivity expressed as impulsive choice or inhibitory failure plays a role in several key transition phases of drug abuse. There is evidence to support all three nonexclusive hypotheses. Increased levels of impulsivity lead to acquisition of drug abuse (H1) and subsequent escalation or dysregulation of drug intake. Drugs of abuse may increase impulsivity (H2), which is an additional contributor to escalation/dysregulation. Abstinence, relapse, and treatment may be influenced by both H1 and H2. In addition, there is a relationship between impulsivity and other drug abuse vulnerability factors, such as sex, hormonal status, reactivity to nondrug rewards, and early environmental experiences that may impact drug intake during all phases of addiction (H3). Relating drug abuse and impulsivity in phases of addiction via these three hypotheses provides a heuristic model from which future experimental questions can be addressed.

Keywords Abstinence · Acquisition · Animal models · Delay discounting · Drug abuse · Dysregulation · Escalation · Five-choice serial reaction time task · Go/no-go task · Impulsive choice · Impulsivity · Inhibition · Relapse · Stop signal reaction time task · Treatment

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Introduction

A growing number of studies using behavioral, neurobiological, and imaging techniques have confirmed a strong association between impulsivity and addictive behaviors such as drug abuse, binge eating, and gambling. The purpose of this review is to analyze the relation between impulsive behavior and drug abuse, an addictive behavior that has been studied most extensively. The main goals of this review are (1) to highlight the main measures of impulsive behavior that have been used in studies that have increased our knowledge of the connection between impulsivity and drug abuse, (2) to show how impulsivity may drive drug-seeking behavior during critical phases of drug abuse that are hallmarks of addiction, and (3) to examine fundamental questions about impulsivity and drug abuse in terms of three hypotheses (H): H1, *impulsivity causes drug abuse*; H2, *drug abuse causes impulsivity*; and H3, *impulsivity is related to a third factor that controls*

drug abuse. To date, research findings concerning the relationship between impulsivity and drug abuse have been related to these three main hypotheses. It is essential to evaluate the results to date, select strong and consistent findings, and establish principles that will allow us to advance in designing future studies to further probe the key issues/hypotheses that are identified in this review.

A variety of definitions and measures of impulsivity have been used, and an analysis of the causes and consequences of impulsivity in drug abuse must take the operational definitions of impulsivity into account. Accordingly, impulsivity has been defined as the inability to stop a behavior that has negative consequences, preference for immediate over delayed gratification, tendency to engage in risky behaviors, heightened novelty-seeking, behaving without forethought or consideration of outcomes, being impatient when asked to wait, having a short attention span, and difficulty persisting at a particular activity (e.g., for reviews, see Evenden 1999; Mitchell 2004; Olmstead 2006). A variety of tools, such as questionnaires and operant conditioning tasks (i.e., tasks that require a subject to make a response, such as a lever press or key strike, to receive a contingent reinforcer), have been used to provide operational definitions of impulsivity, and there is not always reliability among these measures (e.g., Barratt and Patton 1983; Crean et al. 2000). This suggests that impulsivity is multidimensional and consists of several different and possibly independent features (e.g., Barratt and Patton 1983; Evenden 1999). There are no comprehensive animal or human laboratory models that take all features of impulsivity into account, but individual laboratory measures of many of the elements of impulsivity have been successfully used to examine the connection between impulsivity and drug abuse. Two facets of impulsivity seem to predominate in the drug abuse literature (Olmstead 2006), *impulsive choice* (choice of a small, immediate reinforcer over a large, delayed reinforcer) and *impaired inhibition* (inability to stop a prepotent behavior), and these will be the focus of our review.

Operational measures of impulsivity

This section describes the attempts to operationally define impulsive choice and impaired inhibition, and it demonstrates how various measures agree and translate from animals to humans. Operational tasks may measure a more circumscribed definition of impulsivity than questionnaires (Mitchell 1999), and this may be the reason that there is not always a consistent relationship between self-report and operational measures (e.g., de Wit et al. 2000; Reynolds et al. 2006a; Swann et al. 2002). However, it is also possible that limitations in individuals' abilities to report the cognitive processes underlying their behavior (Nisbett and Wilson 1977) play a role in the inconsistency between self-report and operational measures of impulsivity. There are three main features of operational measures of impulsivity that allow for valid translation from human to animal subjects. First, the underlying processes needed for these tasks, such as attention and working memory, are present in both humans and animals. Second, the tasks should be relatively easy to administer to either species, and in many cases, they should require only a modest amount of training. Third, these tasks should measure the subject's current state and not rely on introspective measures or recall of past events. The ability of these tasks to assess the subject's current state is important because it allows for monitoring changes in impulsivity during various states of drug use.

Performance on laboratory measures of impulsive choice and inhibition are not necessarily related in humans (Dalen et al. 2004; Solanto et al. 2001; Sonuga-Barke 2003; Sonuga-Barke et al. 2003) or rats (Van den Bergh et al. 2006). There are most likely individual differences in the extent to which these two manifestations of impulsivity are present. An important focus of ongoing research is to identify how these operational measures relate to each other (if at all) and to determine what specific mechanisms underlie performance on each task. Thus, when studying impulsivity, it is important to use several models to obtain converging evidence regarding the underlying aspects of impulsivity that are associated with the behavior of interest. In this review, the delay discounting (DD) task will be discussed as an operational measure of impulsive choice, and the go/no-go, stop signal reaction time (SSRT), and five-choice serial reaction time (5CSRT) tasks will be discussed as operational measures of inhibitory control.

Impulsive choice

Drug abuse has been conceptualized as choosing a smaller, immediate reinforcer (e.g., immediate euphoric effects) over a larger reward that occurs in the future, such as good health, good relationships, or occupational success (de Wit and Richards 2004; Madden et al. 1997). In other words, drug abuse may occur because the value of the delayed consequences of drug abstinence is discounted or decreased in favor of the immediate drug effects. This aspect of impulsivity has been studied in animals and humans using DD procedures and with that task comparable results have been obtained across species (see review by de Wit and Richards 2004).

Delay discounting

In the DD paradigm, a subject is typically asked to choose between a small reinforcer delivered immediately

and a larger reinforcer delivered after a delay. Human subjects are shown two options on a computer screen and asked to respond on the computer key that is associated with the reinforcer that they would prefer. The reinforcers are typically monetary, although hypothetical health outcomes (e.g., the onset of a serious drug-related illness) and drug use (e.g., Madden et al. 1997; Petry 2001) have also been used. For a discussion of the differences between discounting of hypothetical or actual rewards, see Bickel and Marsch (2001) and Kirby (1997). If actual reinforcers are used, one trial is chosen at random at the end of the session and the participant receives the reinforcer they chose on that particular trial. Immediate reinforcers are given at the end of the session, and delayed reinforcers are given after both the session and the specified delay has elapsed. In preclinical research, animals are trained to make an operant response, such as a lever press, to obtain a food, water, or drug reinforcer. A response on one device yields a small magnitude of the reinforcer immediately, whereas a response on the other device yields a larger magnitude of the reinforcer after a delay. In contrast to human research, reinforcers are given after each trial.

In both human and animal research, the delay at which the small, immediate reinforcer and the large, delayed reinforcer are chosen equally can be calculated, and it is referred to as the indifference point. To find an indifference point, the amount of the large reinforcer and the delay to its delivery are held constant and the amount of the small, immediate reinforcer is varied until subjects choose each alternative approximately equally (e.g., Madden et al. 1997; Richards et al. 1999b). The delay to the larger reinforcer is then changed and another indifference point is obtained. Graphing a typical plot of four to six indifference points on an *x*–*y* coordinate where the measure of the relative value of the reward (*y*-axis) is plotted as a function of the delay to the larger reinforcer (*x*-axis) yields a hyperbolic curve (see Fig. 1). This function is described by the equation $V=A/(1+kD)$ where V is the value of the reinforcer, A is the amount of the delayed reinforcer, D is the delay to the reinforcer, and k is used to describe the steepness of the curve (Mazur 1987). As the gradient of the curve becomes steeper, impulsivity increases (preference for the smaller immediate reinforcer increases). The discounting rate arises from a combination of the type of commodity offered (e.g., monetary, drug of choice, heath outcomes), whether the outcome is a loss or a gain, and the magnitude of the outcome (Baker et al. 2003; Bickel and Marsch 2001). The shape of the discount functions obtained in rats and humans are remarkably similar (i.e., both are hyperbolic), despite different reinforcer types, magnitudes, and delays (de Wit and Richards 2004); however, the discounting rate varies across species.

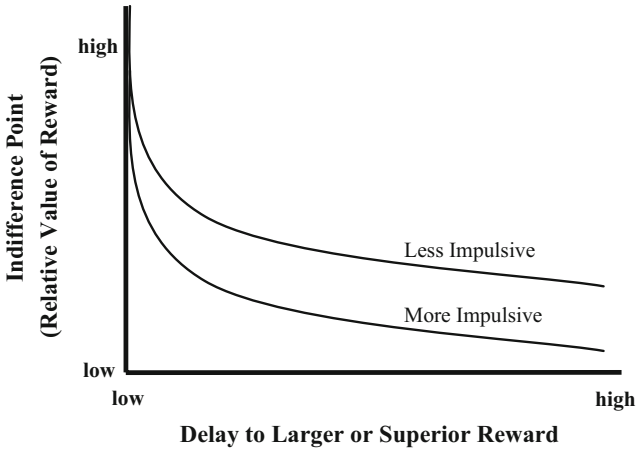

Fig. 1 An example of the type of hyperbolic curve created in DD experiments. The curve is created by the equation $V=A/(1+kD)$ where V is value, A is the amount of the delayed reward, D is the delay to the reward, and k is used to describe the steepness of the curve. The *y*-axis represents the indifference point or the value of the smaller (or inferior) reinforcer at which both reinforcers were chosen equally

Performance on DD in pigeons and rodents is typically impulsive (Mazur and Logue 1978), whereas choice in human adults is typically more self-controlled (Logue 1988; Logue et al. 1986). Initial work with nonhuman primates (rhesus monkeys) self-administering i.v. cocaine suggests a low discounting rate with significant self-control that is comparable to humans (Woolverton et al. 2007). It is also apparent that animals and humans have differential sensitivities to changes in reinforcer magnitude. In humans, increasing reinforcer magnitude has consistently decreased impulsive choice (e.g., Baker et al. 2003; Johnson and Bickel 2002). However, results from animal studies are inconsistent. Increasing the amount of the delayed reinforcer decreased impulsive choice (Wade et al. 2000), had no effect (Green et al. 2004; Perry et al. 2007; Richards et al. 1997), or increased impulsive choice (Farrar et al. 2003; Woolverton et al. 2007).

Impaired inhibition

The go/no-go (Newman et al. 1985), SSRT (Logan et al. 1984), and 5CSRT (Carli et al. 1983; Robbins 2002) tasks have been used to measure inhibitory control. The go/no-go and SSRT tasks are similar in that they both measure inhibition of a prepotent response; however, the difference between them is that the go/no-go task requires subjects to either execute **(**go**)** or inhibit **(**no-go**)** a response and the SSRT task requires subjects to inhibit a response they have already initiated **(**stop**)**. In the 5CSRT task, subjects are required to suppress responses until a stimulus signals that it is appropriate to respond. In studies not involving drugs, performance on the go/no-go and SSRT tasks is positively correlated in humans (r=0.278, Reynolds et al. 2006a),

suggesting that the tasks measure common underlying features. An advantage of the go/no-go and SSRT tasks is that they have been widely used in both human and nonhuman subjects, and the results have been concordant across species (e.g., de Wit and Richards 2004). A variant of the 5CSRT task has been used in humans (e.g., Sahakian et al. 1993); however, performance on this task has not yet been compared to other tasks or across species. It would be useful to conduct these experiments in an effort to understand whether these tasks measure similar aspects of inhibitory control. All three inhibitory tasks were sensitive to the effects of drugs of abuse (e.g., de Wit and Richards 2004; Fillmore 2003; Robbins 2002).

Go/no-go task

In the go/no-go task (Fig. 2), responding in the presence of a specific discriminative stimulus is reinforced. For example, human participants are shown repeated presentations of eight different numbers, four of which are designated "correct" numbers and the other four are designated "incorrect" numbers. They are required to respond to correct stimuli (go) and withhold responses to incorrect stimuli (no-go). Correct responses are reinforced with points, money, or social reinforcers and incorrect responses are either unreinforced or penalized. Similarly, in rats, a light or tone is typically the discriminative stimulus and a lever press is the appropriate behavior after the presentation of the discriminative stimulus to obtain a food reward. Food-restricted animals are reinforced with a food pellet after an appropriate response to a go stimulus and not reinforced during the no-go stimulus condition. Typically, human studies employ discrete-trial go/no-go tasks and animal studies use either continuous- or discrete-trial go/no-go tasks. In both continuous- and discrete-trial go/no-go tasks, errors of omission (withholding a response when a correct stimulus is presented) and errors of commission or "false alarms" (responding when an incorrect stimulus is presented) are the dependent measures. Impulsivity in this task is defined by the number of false alarms. Reaction time (RT) or the time it takes to make a response (response latency) can also be measured in this task, and that is another measure used to determine whether there are nonspecific effects of a particular manipulation on the time needed to activate a response.

Stop signal reaction time task

The SSRT task (see Fig. 3) measures the speed (or RT) at which subjects are able to inhibit a response that was

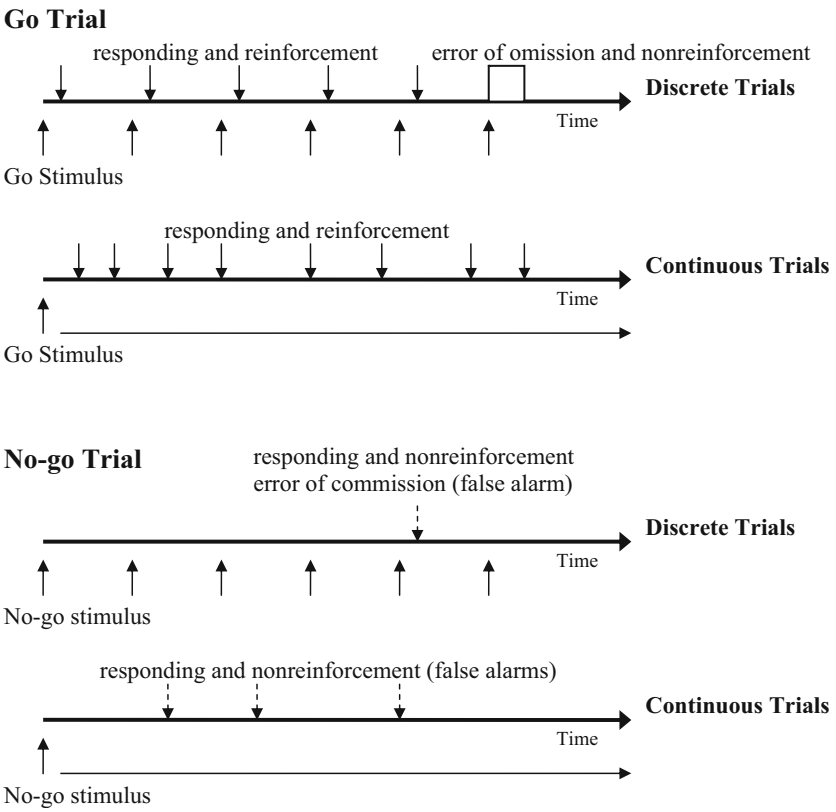

Fig. 2 Diagram of the go/no-go task. When a *go stimulus* is presented, subjects are asked to respond. When a *no-go stimulus* is presented, subjects are asked to withhold their responding

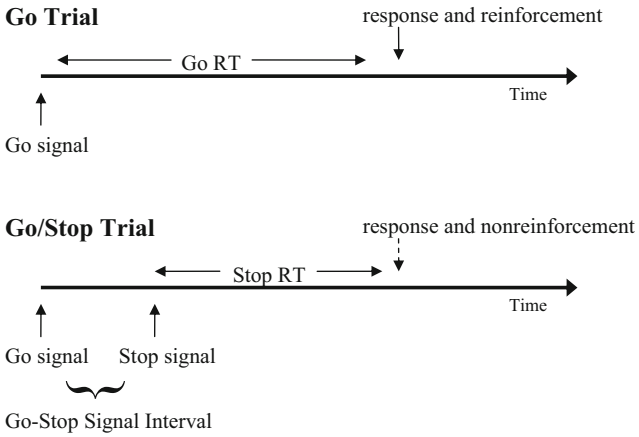

Fig. 3 Diagram of the SSRT task. Subjects are asked to respond as quickly as possible after a *go signal*. The *go RT* is the time between the go signal presentation and the subject's response. On *go/stop trials*, subjects must inhibit their response or perform a different response after presentation of the *stop signal*. The *go–stop signal interval* is adjusted until the subject inhibits its responses on 50% of the trials, and the *stop RT* is calculated by subtracting the *go–stop signal interval* from the Go RT

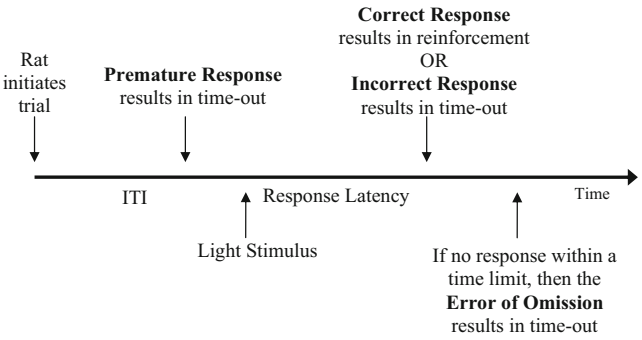

Fig. 4 Diagram of the 5CSRT task (adapted from Robbins 2002). Trials are initiated by a head insertion into a food magazine. After an intertrial interval, a stimulus light appears and a response is required within a specified time limit. Impulsivity is defined as the number of prepotent responses emitted

previously maintained by a reinforcer (the stop RT). The stop RT is compared to the speed at which subjects perform a response (the go RT). This task is based on a "race" theory of impaired inhibition in which there is a 'go' process (the initial reaction time to execute a response) and a 'stop' process (the time needed to inhibit the response) and the ability to inhibit a behavior is a competition or race between these two processes (Logan et al. 1984). In human research, subjects are typically asked to respond on a keyboard as quickly as possible when a go signal (e.g., a specific letter of the alphabet) is presented on a computer screen. When a stop signal (e.g., a tone) is presented shortly after presentation of the go signal, subjects must inhibit the response they have begun or perform a different response (e.g., press a different key on the keyboard) to acknowledge the stop signal. In animal research, subjects perform one response (e.g., a lever press, nose poke) when a go signal (e.g., a light) is presented and a different response (e.g., press a different lever, nose poke) when a stop stimulus (e.g., a tone) is presented.

In both human and animal research, the stop signal is randomly presented after the go signal on a proportion of trials. Reliably presenting the go signal on every trial produces a prepotency to respond, and subjects must overcome this tendency to suppress responses when the stop signal is presented. Impulsivity in this task is quantified as the stop RT.

Five-choice serial reaction time task

In the 5CSRT task (see Fig. 4), animals are required to withhold responding until a stimulus is presented that indicates that it is appropriate to respond (i.e responses will be reinforced). Each trial is initiated by a head-insertion response into a food magazine. After an intertrial interval (ITI), a brief stimulus light appears at the rear of one of five holes (Fig. 4 shows only activity at the active hole and its consequences). A nose-poke response in the hole in which the stimulus light appeared results in the presentation of food pellets in the food magazine. Errors of omission (failure to respond after the presentation of the light stimulus), errors of commission (responding in a hole that did not have a stimulus light on), and premature responses (responding during the ITI) are punished by a brief time out. After the time out, a subsequent trial can be initiated by a head insertion into the food magazine. Premature responses are used as the measure of impulsivity because they are considered to be inhibitory failures of prepotent responses.

The effects of impulsivity during key phases of addiction

Tasks measuring both impulsive choice and impaired inhibition have been used to address the hypotheses (which are not mutually exclusive) regarding the relationship between impulsivity and drug abuse; for example, H1—*that increased levels of impulsivity could lead to drug abuse* and H2—*that drugs of abuse may increase impulsivity* during several key transition phases of the addiction process such as acquisition, escalation/dysregulation, abstinence, relapse, and treatment (see Fig. 5). The measures of impulsivity described above are especially sensitive to these critical transition phases of drug abuse. It is important to consider the relationship between impulsivity and drug-related behavior in each phase separately because addiction is a multistep, evolving process for which we have excellent laboratory models that are providing consistent findings across laboratories and experimental conditions. It should be noted that H1 and H2 are not mutually exclusive,

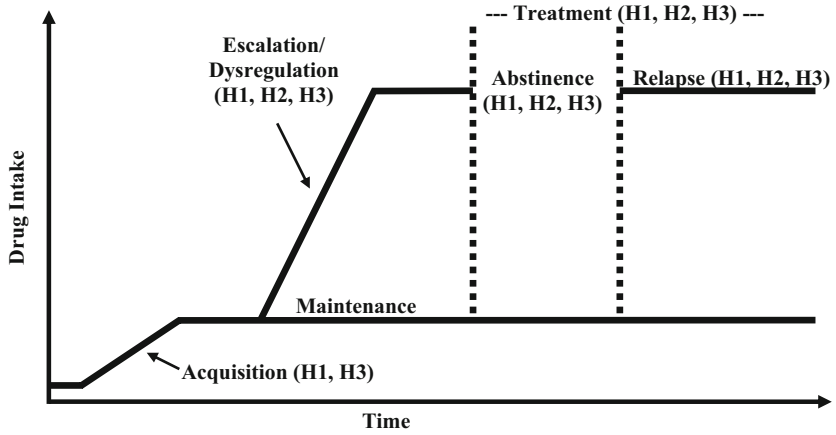

Fig. 5 Phases of drug abuse (adapted from Carroll et al. 2004). Impulsivity expressed as impulsive choice or inhibitory failure may play a role in each of these phases. In the acquisition phase, it is likely that increased levels of impulsivity lead to drug abuse (*H1*). Drugs of abuse may increase impulsivity (*H2*), resulting in escalation/dysregulation of drug intake, and the increases in impulsivity caused by drugs of abuse may continue despite drug cessation, resulting in shorter abstinence, reduced likelihood of treatment success, and greater likelihood of relapse. Individual differences in impulsivity may also influence abstinence, treatment, and relapse (*H1*). Alternatively, impulsivity and drug abuse may be associated through a third factor that influences drug intake during all phases of addiction (*H3*)

and they can cooccur to various degrees in each of the phases.

One phase we will not discuss in this review is the maintenance phase, because maintenance is typically studied under very limited access conditions, and impulsivity does not appear to be related to the patterns of steady, regular drug intake that occur under these conditions. For example, DD in rodents was not associated with differential drug intake under a fixed-ratio (FR) 1 schedule (Perry et al. 2008a) or a progressive-ratio (PR) schedule (Anker et al., in preparation). In this review, the critical transition phases that most reliably predict drug abuse are highlighted. In the first example, initiation of drug-taking behavior, we provide evidence that H1 is most applicable to explain how impulsive behavior predicts drug abuse. In the next phase, escalation, H1 and H2 are both relevant to escalation of drug intake, and finally, both H1 and H2 play a role in abstinence, relapse, and treatment. In addition, H3—*impulsivity and drug abuse are associated through a third factor* will be discussed in a subsequent section providing initial evidence on how other factors predisposing drug-seeking and drug-taking are related to impulsivity during key phases of addiction.

Acquisition

Acquisition of drug self-administration is defined as the transition from a single, initial drug use to continued, regular daily or weekly abuse (e.g., Campbell and Carroll 2000). This phase can be uniquely modeled in drug-naïve animals, and the hypothesis that *impulsivity predates drug use* (H1) may be the most applicable in this phase. For example, animals can be behaviorally screened as high or low on measures of impulsivity, and subsequent initiation of drug-taking can be studied. This would model human behavior in which individuals may make the impulsive choice to initiate drug use because they value the immediate euphoric effects of a drug over larger future benefits, such as personal, educational, social, and economic success or well-being (de Wit and Richards 2004; Madden et al. 1997). Alternatively, individuals with impaired inhibitory control may be unable to resist environmental cues (e.g., peer pressure) that lead them to abuse drugs (de Wit and Richards 2004).

Impulsive choice

Humans Consistent with theories that individuals may begin to abuse drugs because of greater devaluation of delayed rewards (H1), in a longitudinal study, impulsive choice at age 3 was correlated with adolescent social and personal problems that are associated with substance abuse, although it is important to note that other factors may have played a role (H3; Mischel et al. 1988; Wills et al. 1995). In humans, it is impossible to determine which came first, impulsive behavior or drug abuse (H1 vs H2); but there are correlational findings to suggest that impulsive behavior and drug abuse are related. Individuals who discounted delayed reinforcers began abusing alcohol, marijuana, and cigarettes at a younger age, and they abused a greater number of illicit drugs compared to individuals who discounted delayed reinforcers less (Kollins 2002). Adolescence is a period of enhanced impulsivity, risk-taking, and novelty-seeking behavior, and it is also a time when individuals are highly vulnerable to addiction (for reviews, see Chambers et al. 2003; Kelley et al. 2004). Higher levels

of discounting were found in adolescent smokers compared to nonsmokers (Audrain-McGovern et al. 2004; Reynolds et al. 2007, but see Reynolds et al. 2003) and in heavy adolescent alcohol drinkers compared to light adolescent drinkers (Field et al. 2007). Adolescents who discounted more had lower grades and self-esteem and greater involvement with cigarettes, alcohol, and marijuana (Wulfert et al. 2002).

Several researchers have reported that, similar to adolescents, adult drug abusers discounted delayed reinforcers more than nonusers. For instance, opioid-dependent individuals discounted delayed monetary reinforcers more than nonusers (Kirby and Petry 2004; Kirby et al. 1999; Madden et al. 1997), and opioid-dependent individuals who shared needles discounted delayed reinforcers to an even greater extent than their opioid-dependent counterparts who did not share needles (Odum et al. 2000). Similarly, heavy social drinkers (Vuchinich and Simpson 1998) and alcoholics (Petry 2001, but see Kirby and Petry 2004) discounted monetary reinforcers more than light social drinkers and nonalcoholics, respectively. Cocaine abusers (Coffey et al. 2003; Heil et al. 2006; Kirby and Petry 2004), methamphetamine abusers (Hoffman et al. 2006; Monterosso et al. 2007), and cigarette smokers (Baker et al. 2003; Bickel et al. 1999; Heyman and Gibb 2006; Mitchell 1999; Reynolds et al. 2004b, but see Johnson et al. 2007; Ohmura et al. 2005) also discounted future monetary rewards to a greater extent than nonusers. To address H2 in humans, that drug ingestion elevated impulsive behavior, it would be necessary to show that elevated impulsivity during use returned to and remained at lower levels (equivalent to nonusers) in ex-users (e.g., Bickel et al. 1999). In contrast, a finding of continued elevation of impulsivity in ex-users may support H1 or H2, as an innate impulsivity trait and/or the previous drug use may be responsible. Even when longitudinal studies suggest H1, the possibility that a *third factor covaries with impulsivity and drug abuse* (H3) would also need to be carefully examined.

Animals Preclinical models offer the longitudinal measures that are useful for distinguishing between H1 and H2 by studying the relationship between initial DD and subsequent initiation of drug intake. In carefully controlled laboratory studies using rodents, DD can be measured and compared to subsequent rates of drug self-administration. In one study, rats were allowed to choose between two food pellets delivered immediately and 12 pellets delivered after a 15-s delay (Poulos et al. 1995). Rats that selected the small, immediate reward on at least 75% of the trials (high impulsive) subsequently consumed more of a 12% ethanol solution than rats that chose the small, immediate reinforcer on 45–60% (medium impulsive) or 5–30% (low impulsive) of the trials (Poulos et al. 1995). In a second study, impulsive choice determined by a DD procedure predicted the subsequent rate of acquisition of cocaine self-administration. Rats selected for high impulsivity (HiI) acquired cocaine self-administration in greater numbers and at a faster rate than those selected for low levels (LoI) of impulsivity (Perry et al. 2005, 2008a). Together, these data support the hypothesis that impulsive choice predicts vulnerability to acquisition of drug intake (H1). To address H2, that *drug self-administration increases impulsivity*, a longitudinal study could be proposed in which groups with equal responding on a DD task for food would then be exposed to drug or vehicle self-administration, and they would later be retested on the DD food procedure when drug access had terminated. An increase in impulsivity in the drug-exposed group (vs vehicle-exposed) would indicate a change in impulsivity due to drug experience.

Impaired inhibition

Animals Impaired inhibition is also related to the propensity to initiate drug use. That is, current drug abusers have impaired inhibition compared to nonusers. For example, cocaine (Fillmore and Rush 2002; Li et al. 2006) and methamphetamine (Monterosso et al. 2005) abusers displayed inhibitory deficits on the SSRT task compared to nonusers. Cocaine users (Hester and Garavan 2004; Kaufman et al. 2003; Verdejo-Garcia et al. 2007) and alcoholics (Noel et al. 2007) also showed inhibitory deficits on a go/no-go task compared to controls; however, there were no differences between 3,4-methylendioxymethamphetamine (MDMA) or cannabis users and nonusers (Quednow et al. 2006). Cigarette smokers also showed decreased inhibitory control compared to nonsmokers, and the number of packs smoked per day was positively related to the number of inhibitory failures (Spinella 2002). In another study, no differences were found between smokers and nonsmokers (Dinn et al. 2004), but the lack of effect may have been due to low levels of participant smoking. Again, these correlational findings do not explain the causality of the results (H1 vs H2), and they emphasize the need for within-subject comparisons of users/ex-users vs nonusers that could be applied to H2 or a longitudinal examination of impulsivity before the onset of drug abuse that could be applied to H1. The results of the studies described above could also have been explained by a third factor (H3) such as cognitive deficits in working memory (Hester and Garavan 2004) and decision-making (Bechara et al. 2001) that may contribute to impaired inhibition in drug abusers.

Animals Preclinical studies may be useful in determining the relationship between inhibitory control and other cognitive processes in the acquisition phase. In a recent preclinical study, rats selected for HiI based on 5CSRT task

performance subsequently made significantly more responses in the nicotine-paired hole during acquisition of nicotine self-administration compared with LoI rats (Diergaarde et al. 2008). In another study, HiI rats (selected on the 5CSRT task) subsequently self-administered larger amounts of cocaine than LoI rats (Dalley et al. 2007a). Converging evidence also indicated that HiI rats also had fewer D2 dopamine receptors (vs LoI rats) in the ventral striatum, a part of the neurocircuitry thought to be involved in reward, movement, and response to novelty. However, caution may be warranted, as studies showing that impulsivity predicts cocaine self-administration (Dalley et al. 2007a; Perry et al. 2005) may be subject to alternative interpretations. For example, HiI rats may have greater reactivity to novelty or food-associated discriminative or conditioned/reinforcing stimuli (Uhl 2007)—other factors that are associated with cocaine self-administration (H3). Nevertheless, in both studies, neither impulsivity nor cocaine self-administration were correlated with locomotor activity (Dalley et al. 2007a; Perry et al. 2005). Together, the above sections provide preclinical evidence for the hypothesis that increased levels of impulsivity (expressed as both impulsive choice and inhibitory failure) predict vulnerability to drug abuse in the acquisition phase (H1), and methods for testing H1 and H2 in humans are suggested.

Escalation/dysregulation

Escalation or dysregulation of drug use is another critical phase and a hallmark of addictive behavior. It is thought to represent the switch from 'control' to 'loss of control' in addiction (e.g., Koob and Kreek 2007; Koob and Le Moal 2001). This phase is defined as a transition from low levels of controlled, regulated drug use to uncontrolled, dysregulated large levels of intake (Ahmed and Koob 1998, 1999) and binge drug use (Shaffer and Eber 2002), and it may also be driven by H1 or result in H2. In preclinical studies, this phase is typically modeled in animals by allowing extended access to drug self-administration (e.g., 5–12 h/day) because the pattern of drug self-administration that emerges approximates the features of bingeing or "out of control" drug-taking mentioned above (Ahmed and Koob 1998, 1999). An escalating or dysregulated pattern of drug abuse could reflect increased impulsivity attributable to the *acute* or *chronic* effects of the drug (H2), and *chronic* drug effects may be different in individuals with high and low baseline levels of impulsivity (H1).

Escalation/dysregulation may occur because of a change in the ability to control responses, so that increased drug use is accompanied by decreased inhibitory control. Escalated/dysregulated patterns may also reflect a relative increase in the value of the immediate rewards of drug use compared to the delayed rewards associated with drug abstinence. In fact, when motivation for drugs was assessed by a PR schedule, dose–response functions (the willingness to work for a given dose) were elevated after escalation (Carroll et al. 2004; Roth and Carroll 2004; Wee et al. 2007), indicating increased reward value or decreased inhibitory control. It is important to consider whether *impulsive individuals are more prone than those who are less impulsive to escalation of drug use* (H1) and whether *drug use increases impulsivity* (H2) that leads to escalation because this phase is one of the most devastating in the development of drug abuse and it is where irreversible changes in patterns of drug-taking occur. We are unaware of studies of the effects of escalation of drug self-administration on impulsivity that would address H2 specifically. The possibility that *acute* or *chronic* administration of drugs may result in increased impulsivity has been examined in both humans and animal models and is discussed in subsequent sections. In addition, *acute* or *chronic* administration of therapeutic drugs that reduce impulsivity could be a means of preventing the escalation of drug self-administration and ultimately limiting the progression of this addictive behavior. Currently, there are only a few examples of attempts to limit the escalation process. For example, a corticotropin-releasing factor 1 (CRF1) receptor antagonist (Specio et al. 2008) and progesterone (Larson et al. 2007) reduced the escalation of i.v. cocaine self-administration in rats. Nondrug substitutes for drug also reduce escalation. Lenoir and Ahmed (2008) reported that access to sweetened water reduced escalated heroin consumption. The application for further studies of drug abuse is that prevention efforts could involve screening for impulsivity with standard, computerized tests for impulsive choice or inhibitory failure, and targeted prevention/intervention efforts could then be implemented.

Impulsive choice

We are unaware of any studies that have been conducted in humans to examine the relationship between impulsive choice and escalation/dysregulation of drug intake. Recent preclinical research with rats selected as HiI or LoI using a DD task with food reinforcers showed that HiI rats significantly escalated cocaine intake over repeated daily 6-h sessions compared with LoI rats that did not show significant escalation (see review by Carroll et al. 2008a). In addition, the HiI rats (but not LoI rats) also showed a significant pre–post increase in cocaine infusions during short-access (2 h) periods that occurred before and after the long access. These results were consistent with the acquisition data that showed greater acceleration of cocaine intake in HiI (vs LoI) rats (Perry et al. 2005), and together, the results

support H1, suggesting that highly impulsive individuals are more prone to this accelerating phase of drug abuse.

Impaired inhibition

To date, the relationship between impaired inhibition and escalation of drug intake has not been examined in humans; however, rats screened for HiI using a 5CSRT task showed higher levels of cocaine intake compared to their LoI counterparts (Dalley et al. 2007a, b). The rats acquired self-administration of a maximum of 50 cocaine infusions in 5 h, and they were subsequently allowed to self-administer up to 150 infusions in 8 h. Rats screened as HiI showed greater escalation of cocaine intake than LoI, supporting H1. In addition, a recent report indicated that HiI rats were more likely to progress from initiation of drug taking to compulsive drug-seeking behavior, measured by animal models of three DSM-IV criteria (Belin et al. 2008). Addiction scores were higher in HiI vs LoI rats based on a go/no-go task, a PR schedule, and punished (shock) responding for cocains infusions. In summary, the responsiveness of escalation to impulsivity suggests that developing strategies to reduce impulsivity and/or escalation would successfully interrupt the addiction process.

Abstinence, relapse, and treatment

Individual levels of impulsivity are related to failures in the ability to maintain abstinence and overall treatment success (H1). In addition, if drugs of abuse cause long-term increases in impulsivity (H2) that persist beyond cessation of drug use, users will have a more difficult time maintaining abstinence, resulting in lower likelihood of treatment success. For example, individuals that scored high on questionnaire measures of impulsivity were more likely to drop out of treatment for cocaine abuse, and they remained in treatment for a shorter time than those with lower impulsivity scores (Moeller et al. 2001). Impulsive individuals also experience increased drug craving during withdrawal and greater likelihood of relapse. For instance, impulsive (as measured by a questionnaire) smokers exhibited increased craving in response to cigarette cues (Doran et al. 2007), and they relapsed more quickly (Doran et al. 2004) than less impulsive smokers.

In rodents, abstinence (extinction) and relapse (reinstatement) can be modeled using a procedure such as that developed by de Vries et al. (1998). This procedure is modeled after the human condition in which drug use ceases, resulting in an abstinence period. Subsequent exposure to cues or contexts previously associated with drug-taking typically elicits drug-seeking and relapse. Similarly, in animal models, subjects self-administer moderate doses of a drug under short-access (e.g., 2 h/day) conditions, and after about 2 weeks, the drug is replaced with saline, and responding on the previously drug-paired lever continues to be measured for approximately 2–3 weeks (extinction). Subsequently, an injection of saline or the previously self-administered drug is given (drug-primed reinstatement) and/or the animal is exposed to cues that were previously paired with the drug (cue-induced reinstatement), and responding on the lever previously paired with the drug is measured. Conditions that are reported to contribute to relapse in humans (e.g., stress, drug-associated cues, drug exposure) reinstate responding in this model (Shalev et al. 2002; Epstein et al. 2006). However, some aspects of this procedure deviate from the human condition, and its substitutability as a model for relapse in humans has been extensively discussed elsewhere (e.g., Epstein et al. 2006; Katz and Higgins 2003; Shaham and Miczek 2003; Shaham et al. 2003). For the purposes of this review, the reinstatement procedure is discussed as a useful and well-accepted model to study aspects of relapse that are difficult to study in humans. The topic of interest is whether impulsivity directly predicts reinstatement/relapse.

Impulsive choice

Humans In support of the hypothesis that impulsive individuals have higher rates of relapse or are more resistant to treatment than less impulsive smokers (H1), impulsive adolescents were less likely to achieve abstinence from smoking in a 4-week treatment program compared to adolescents that were less impulsive (Krishnan-Sarin et al. 2007). In a 1-year treatment study of pregnant and recently postpartum women using abstinence-contingent voucher-based incentives, greater DD at baseline was associated with greater likelihood of smoking relapse at 24 weeks postpartum (Yoon et al. 2007). In addition, smokers with higher rates of discounting were more likely to smoke in a laboratory model of abstinence reinforcement (Dallery and Raiff 2007).

It may be difficult to persuade drug abusers to abstain, even with voucher-based incentives, because they respond more impulsively to their drug of abuse than money. For example, opioid-dependent individuals (Giordano et al. 2002; Madden et al. 1997, 1999; Odum et al. 2000), crack-cocaine abusers (Coffey et al. 2003), and cigarette smokers (Bickel et al. 1999) discounted the value of hypothetical future receipt of their primary drug of abuse to a greater extent than money. Drug-dependent individuals also discounted the value of future changes in their health status (e.g., the onset of a serious drug-related illness) more than nonusers (e.g., Odum et al. 2000).

Drugs of abuse may cause long-term increases in impulsivity, but short-term drug deprivation in abusers can

also increase impulsivity. For example, opiate users (Giordano et al. 2002) and cigarette smokers (Field et al. 2006) were more impulsive when drug-deprived than when drug-satiated. However, after a long-term period of abstinence from *chronic* smoking, ex-smokers discounted delayed money to the same extent as those who had never smoked, and both discounted less than current smokers (Bickel et al. 1999). Drug abstinence was also associated with lower levels of impulsivity in heroin abusers (Kirby and Petry 2004), but not in smokers (Field et al. 2006), cocaine abusers (Heil et al. 2006; Kirby and Petry 2004), or alcohol abusers (Kirby and Petry 2004). These results suggest that *chronic* abuse of some drugs increased impulsive choice (H2), and after drug abuse was terminated, impulsive behavior returned to a level similar to that of nonusers, while with other drugs, impulsivity was not reversed after an abstinence period. Contingency management studies indicate that vouchers can effectively compete with drug use, but drug-positive status at treatment entry predicts less success with voucher-based incentives (Stitzer et al. 2007a, b). In fact, drug-positive status at treatment entry predicts poorer response to treatment in general, not just with contingency management (e.g., Alterman et al. 1996, 1997; Ehrman et al. 2001; Kampman et al. 2001; Petry et al. 2004; Sofuoglu et al. 2003). Thus, if drug use increases impulsivity, impulsivity may underlie the relationship between drug-positive status at treatment entry and treatment success, and this has been shown in several studies (Krishnan-Sarin et al. 2007; Yoon et al. 2007).

Conditioned drug-augmented impulsivity may have also influenced relapse such that the drug abuser continues to exhibit impulsive behavior in the presence of drug- and impulsivity-related stimuli that previously signaled drug-induced impulsivity. Conditioned impulsivity may lead an individual to relapse because they are not able to inhibit drug-taking behavior after exposure to drug-related cues. The conditioned incentive value of drugs of abuse could play a role in this process, as the impulsive user may value the immediate rewarding effects of the drug over the positive long-term benefits of drug abstinence. With some forms of drug abuse, treating impulsivity in drug abusers could result in longer periods of abstinence and decreased likelihood of relapse.

Animals To date, few animal studies have focused on the relationship between withdrawal from *chronic* drug administration and impulsive choice. In rats, *chronic* administration of cocaine increased impulsive choice that persisted 3 months after cocaine treatment ended (Simon et al. 2007). Repeated injections of nicotine also dose-dependently increased impulsivity (Dallery and Locey 2005), and rats continued to respond impulsively after discontinuation of nicotine injections, but impulsive choice gradually returned to baseline over an abstinence period. These results are similar to findings in humans (Bickel et al. 1999), suggesting that nicotine exposure can produce long-lasting, but reversible, increases in impulsive choice, but cocaine exposure produces long-term (>30 days) increases in impulsive choice (Heil et al. 2006; Kirby and Petry 2004).

Using the reinstatement paradigm, HiI female rats showed greater cocaine-primed reinstatement of cocaine-seeking behavior than LoI female rats (Perry et al. 2008a). In a separate study, HiI rats showed greater cue-induced reinstatement of nicotine-seeking behavior than LoI rats (Diergaarde et al. 2008). Withdrawal from chronic exposure to orally self-administered phenycyclidine resulted in increased impulsive choice for a palatable saccharin solution in male and female rhesus monkeys (see review by Carroll et al. 2008a). Together, these studies provide evidence that impulsivity can predict shorter duration of abstinence, reduced treatment efficacy, and increased likelihood of relapse (H1; Dallery and Raiff 2007; Diergaarde et al. 2008; Krishnan-Sarin et al. 2007; Perry et al. 2007b; Yoon et al. 2007). In addition, *chronic* exposure to drugs of abuse increases impulsivity (H2), and with some drugs, impulsivity remains elevated even after drug abuse ceases (e.g., Heil et al. 2006; Kirby and Petry 2004; Simon et al. 2007), which in turn could influence abstinence, treatment, and relapse.

Impaired inhibition

We are unaware of any human studies that have examined the role of inhibitory failure in abstinence, treatment, and relapse. However, conditioned drug-augmented impulsivity may influence relapse in that the drug abuser becomes conditioned not to inhibit their behavior in the presence of drug- and impulsivity-related stimuli. Accordingly, alcoholics showed greater impulsivity on the go/no-go task in response to alcohol-related stimuli compared to neutral stimuli (Noel et al. 2007).

Relapse in impulsive individuals may be due to individual differences in inhibition (difficulty preventing responses that previously led to drug abuse). For example, rats that showed high levels of responding during cocaine-primed reinstatement of cocaine-seeking behavior showed greater deficits in inhibitory control on the go/no-go task compared with rats that had lower levels of reinstatement responding (Deroche-Gamonet et al. 2004). Rats screened for HiI on the 5CSRT task showed greater resistance to extinction after nicotine self-administration compared to LoI rats; however, there were no differences between impulsivity groups in cue-induced reinstatement of nicotine-seeking behavior (Diergaarde et al. 2008). Le Dzung et al. (2008) found a neurobiological link between reinstatement and inhibitory failure. Inactivation of the median

raphe nucleus via local muscimol injections resulted in increases in impulsive responding on the 5CSRT and reinstatement of alcohol-seeking behavior, suggesting that inhibitory failure and reinstatement are indeed related.

Withdrawal from *chronic* exposure to drugs of abuse may also contribute to impaired inhibition. On the 5CSRT task, withdrawal from methamphetamine and MDMA resulted in increased inhibitory failure (Dalley et al. 2007b); however, there were no increases in inhibitory failure after withdrawal from D-amphetamine, cocaine, heroin, or nicotine (Dalley et al. 2005a, b; Shoaib and Bizarro 2005). Based on these data, it is possible that individual differences in inhibitory failure predict abstinence, treatment, and relapse outcomes (H1), and that increased inhibitory failure during drug withdrawal may contribute to shorter abstinence periods, reduced likelihood of treatment success, and greater relapse. Future studies in both humans and animal models should focus on treating the underlying inhibitory failure as a strategy to reduce the probability of relapse.

The effects of drugs on impulsivity

Most of the discussion thus far has been concerned with how impulsivity affects drug abuse. There is a large body of literature showing the reciprocal phenomenon, that drugs affect impulsivity. Given the role of impulsivity on the key phases of drug abuse as described above, it is essential to understand how drugs influence the impulsive behavior that is in turn determining drug-seeking and drug-taking behavior that leads to addiction. Not only can drugs increase impulsivity, and impulsivity may, in turn, accelerate drug-seeking, leading to out of control behavior with associated morbidity and mortality, but drugs can reduce impulsivity, and they may be useful to medication development efforts to prevent escalation to out of control use or relapse after abstinence has occurred. The following section will summarize the effects of drugs on impulsive choice (see Table 1) and inhibitory failure (see Table 2), comparing human and rat studies and different classes of drugs that have abuse and therapeutic potential. If *administration of drugs of abuse results in increased levels of impulsivity* (H2), then there may be a greater likelihood of drug-seeking and drug-taking behavior at the various phases.

Impulsive choice

Humans A number of studies with drugs from different classes support the hypothesis that drugs of abuse increase impulsive choice (a summary is presented in Table 1), and higher levels of drug intake have been related to greater DD. For example, higher levels of nicotine exposure in chonic smokers were correlated with greater discounting of delayed monetary reinforcers (Ohmura et al. 2005; Reynolds et al. 2004b). Heyman and Gibb (2006) showed that regular smokers discounted more than chippers (occasional smokers); however, Johnson et al. (2007) found that light smokers discounted monetary rewards similarly to heavy smokers. These data may support the hypothesis that *drug abuse influences subsequent impulsivity measures* (H2); however, it is also possible that *individuals self-select nicotine intake based on their baseline levels of impulsivity* (H1).

The *acute* effects of several drugs of abuse on DD have also been determined. *Acute* administration of the stimulants methylphenidate (Pietras et al. 2003) and D-amphetamine (de Wit et al. 2002) decreased impulsive choice in humans; however, administration of alcohol (Ortner et al. 2003; Richards et al. 1999b), diazepam (Reynolds et al. 2004a), and Δ^9-tetrahydrocannabinol (THC; McDonald et al. 2003) did not change DD. A possible explanation for the negative findings is that the laboratory setting provides intoxicated participants with cues that inhibit impulsive choice (Olmstead 2006; Ortner et al. 2003). Because intoxicated individuals may focus on the most salient environmental cues (Steele and Josephs 1990), they could be responding to cues in the laboratory environment that cause them to inhibit the impulsive behavior that may normally be displayed outside the laboratory. It is also possible that the DD procedure lacks the sensitivity to measure the *acute* state changes expected after alcohol, diazepam, or THC administration (McDonald et al. 2003; Reynolds et al. 2006b; Reynolds and Schiffbauer 2004). Therefore, preclinical models may be useful to determine the *acute* effects of drugs of abuse on impulsivity.

Animals Administration of psychostimulants had mixed effects on DD in rats (see Table 1). In agreement with data from human laboratory studies, methylphenidate (Pitts and McKinney 2005; van Gaalen et al. 2006b), atomoxetine (Robinson et al. 2007), and methamphetamine (Richards et al. 1999a) decreased impulsive choice, but amphetamine produced mixed effects on impulsive choice (Charrier and Thiebot 1996; Evenden and Ryan 1996; Isles et al. 2003; van Gaalen et al. 2006a, b; Wade et al. 2000; Winstanley et al. 2003) in rodents. There are several factors that could account for the discrepancies in stimulant-induced changes in impulsive choice: type of reinforcer offered; cues associated with the larger, delayed reinforcer; dosing regimens; species; and basal levels of impulsivity. For example, Wade et al. (2000) and Richards et al. (1999a) found stimulant-induced decreases in impulsivity using water reinforcers in water-deprived rats; whereas, Evenden and Ryan (1996) and Charrier and Thiebot (1996) found stimulant-induced increases in impulsivity using food

Table 1 The acute effects of drugs on impulsive choice (measured by DD)

Drug	Subjects	Cue?[a]	Dose (mg/kg)	Impulsivity	Reference
Psychostimulants					
Amphetamine	Humans	N/A	10.0 mg[b]	–	de Wit et al. 2002
		N/A	20.0 mg[b]	↓	de Wit et al. 2002
	Rats	No	0.3	–	Cardinal et al. 2000; Evenden and Ryan 1996; Winstanley et al. 2003
		No	1.0, 1.5, 1.6, 2.3	↑	Cardinal et al. 2000; Evenden and Ryan 1996; Winstanley et al. 2003
		Yes	0.3	↓	Cardinal et al. 2000
		Yes	0.5	–	Wade et al. 2000
		Yes	1.0	↓; –	Cardinal et al. 2000; Wade et al. 2000
		Yes	1.6	–	Cardinal et al. 2000
		SRO	0.2	↓	van Gaalen et al. 2006b
		SRO	0.5	↓	Charrier and Thiebot 1996; van Gaalen et al. 2006b
		SRO	1.0	↓; –	Charrier and Thiebot 1996; van Gaalen et al. 2006b
	Mice	No	0.4, 0.6	↓	Isles et al. 2003
		No	0.8, 1.0	↑	Isles et al. 2003
Atomoxetine	Rats	No	0.3	–	Robinson et al. 2007
		No	1.0	↓	Robinson et al. 2007
		No	3.0	–	Robinson et al. 2007
Methamphetamine	Rats	Yes	0.5	–	Richards et al. 1999b
		Yes	1.0, 2.0	↓	Richards et al. 1999b
Methylphenidate	Humans	N/A	0.15	–	Pietras et al. 2003
		N/A	0.3	↓	Pietras et al. 2003
		N/A	0.6	–	Pietras et al. 2003
	Rats	Yes	1.0	–	Pitts and McKinney 2005[c]
		Yes	3.0, 5.6	↓	Pitts and McKinney 2005[c]
		Yes	10.0	–	Pitts and McKinney 2005[c]
		SRO	0.3	–	van Gaalen et al. 2006b
		SRO	1.0, 3.0	↓	van Gaalen et al. 2006b
Nicotine	Rats	Yes	0.03	–	Dallery and Locey 2005
		Yes	0.1, 0.3, 1.0	↑	Dallery and Locey 2005
Sedative/hypnotics					
Alcohol	Humans	N/A	500, 700, 800	–	Ortner et al. 2003; Richards et al. 1999a
	Rats	No	300	–	Evenden and Ryan 1999
		No	1,000	↑	Evenden and Ryan 1999
		N/A	600	↑; –	Olmstead 2006; Poulos et al. 1998
		N/A	900, 1,200, 1,800	↑	Olmstead 2006; Poulos et al. 1998
Chlordiazepoxide	Rats	No	1.0, 3.2, 5.6	–	Cardinal et al. 2000
		No	10.0	↑	Cardinal et al. 2000
		Yes	1.0, 3.2	–	Cardinal et al. 2000
		Yes	5.6, 10.0	↑	Cardinal et al. 2000
Diazepam	Humans	N/A	5.0, 10.0 mg[b]	–	Reynolds et al. 2004a, b
	Rats	No	0.3, 1.0	↓	Evenden and Ryan 1996
		SRO	2.0, 4.0	–	Charrier and Thiebot 1996
Morphine	Rats	Yes	0.3, 1.0	–	Kieres et al. 2004; Pitts and McKinney 2005[c]
		Yes	1.8	↑	Kieres et al. 2004
		Yes	3.0, 5.6, 10.0	↑	Pitts and McKinney 2005[c]
THC	Humans	N/A	7.5, 15.0 mg[b]	–	McDonald et al. 2003

[a] The cue column indicates whether a cue was present during the delay to the larger reinforcer.
[b] Total dose given (body weight was not accounted for).
[c] No statistics were employed in this study, but modest and variable effects were reported.
Yes: delay-specific stimuli presented during the delay, *No*: all cues turned off during delay, *SRO*: stimuli signaling availability of delayed reinforcer remained on until delivery of that reinforcer, *N/A*: not applicable, ↑: increases in impulsivity, –: no change in impulsivity, ↓: decreases in impulsivity

Table 2 The acute effects of drugs on impulsivity (measured by the go/no-go, SSRT, and 5CSRT tasks)

Drug	Subjects	Task	Dose (mg/kg)	Impulsivity	Reference
Psychostimulants					
Amphetamine	Humans	Go/no-go	5.0 mg[a]	↑	Fillmore et al. 2003
		Go/no-go	10.0 mg[a]	– (LoI), ↓ (HiI); –	de Wit et al. 2002; Fillmore et al. 2003
		Go/no-go	20.0 mg[a]	– (LoI), ↓ (HiI); ↑	de Wit et al. 2002; Fillmore et al. 2003
		SSRT	7.5, 15.0 mg/70 kg	–	Fillmore et al. 2005a
		SSRT	10.0, 20.0 mg[a]	– (LoI), ↓ (HiI)	de Wit et al. 2000, 2002
	Rats	SSRT	0.125, 0.25	–	Feola et al. 2000
		SSRT	0.3	↓ (HiI)	Eagle and Robbins 2003
		SSRT	0.5	–	Feola et al. 2000
		SSRT	1.0	– (LoI), ↓ (HiI)	Feola et al. 2000
		5CSRT	0.03, 0.1, 0.2	–	Bizarro and Stolerman 2003; Bizarro et al. 2004; van Gaalen et al. 2006a
		5CSRT	0.3	↓	Bizarro and Stolerman 2003
		5CSRT	0.4	↓	Bizarro et al. 2004
		5CSRT	0.5	↑	van Gaalen et al. 2006a
		5CSRT	0.8	↓	Bizarro et al. 2004
		5CSRT	0.9	↓	Bizarro and Stolerman 2003
		5CSRT	1.0	↑	van Gaalen et al. 2006a
Atomoxetine	Humans	SSRT	60 mg[a]	↓ (ADHD)	Chamberlain et al. 2007
	Rats	SSRT	0.6	–	Robinson et al. 2007
		SSRT	1.0, 1.8	– (LoI); ↓ (HiI)	Robinson et al. 2007
		5CSRT	0.1	–	Navarra et al. 2008
		5CSRT	0.5	↓	Navarra et al. 2008
		5CSRT	0.6	–	Robinson et al. 2007
		5CSRT	1.0	↑; ↓	Navarra et al. 2008; Robinson et al. 2007
		5CSRT	1.8	–	Robinson et al. 2007
Caffeine	Humans	Go/no-go	2.0, 4.0	–	Marczinski and Fillmore 2003
Cocaine	Humans	Go/no-go	100 mg[a]	–	Fillmore et al. 2005b, 2006
		Go/no-go	200, 300 mg[a]	↓	Fillmore et al. 2005b, 2006
		SSRT	50 mg[a]	–	Fillmore et al. 2002
		SSRT	100 mg[a]	↑; ↓	Fillmore et al. 2002, 2006
		SSRT	150 mg[a]	↑	Fillmore et al. 2002
		SSRT	200 mg[a]	↓	Fillmore et al. 2006
		SSRT	300 mg[a]	–	Fillmore et al. 2006
	Rats	Go/no-go	5.0, 10.0	–	Paine and Olmstead 2004
		Go/no-go	15.0	↑	Paine and Olmstead 2004
		5CSRT	5.0, 10.0, 20.0	↑	van Gaalen et al. 2006a
MDMA	Humans	Go/no-go	75, 100 mg[a]	–	Ramaekers and Kuypers 2006
		SSRT	75, 100 mg[a]	↓	Ramaekers and Kuypers 2006
Methylphenidate	Humans	SSRT	0.3	↓ (ADHD); – (ADHD)	Tannock et al. 1989, 1995
		SSRT	0.6, 0.9, 1.0	↓ (ADHD)	Tannock et al. 1989, 1995; Potter and Newhouse 2004[b]
	Rats	SSRT	0.3	↑ (LoI); ↓ (HiI)	Eagle et al. 2007
		SSRT	1.0	↑ (LoI); – (HiI)	Eagle et al. 2007
		5CSRT	0.063–2.0	–	Paine et al. 2007
		5CSRT	2.5, 5.0	↑; ↓	Bizarro et al. 2004; Navarra et al. 2008
		5CSRT	10.0	↓	Bizarro et al. 2004
Modafinil	Rats	SSRT	3.0	–	Eagle et al. 2007
		SSRT	10.0	– (LoI); ↓ (HiI)	Eagle et al. 2007
		SSRT	30.0	–	Eagle et al. 2007
Nicotine	Humans	SSRT	7 mg[a]	↓ (ADHD)	Potter and Newhouse 2004
	Rats	5CSRT	0.025	↑; –	Bizarro et al. 2004; Bizarro and Stolerman 2003
		5CSRT	0.05	↑; ↑; –	Bizarro et al. 2004; Bizarro and Stolerman 2003; Mirza and Stolerman 1998
		5CSRT	0.1	↑; ↑; –; ↓	Bizarro et al. 2004; Bizarro and Stolerman 2003; Hahn et al. 2002; van Gaalen et al. 2006a
		5CSRT	0.15	↑	Mirza and Stolerman 1998

Table 2 (continued)

Drug	Subjects	Task	Dose (mg/kg)	Impulsivity	Reference
		5CSRT	0.2	↑; ↓	Bizarro et al. 2004; Bizarro and Stolerman 2003
		5CSRT	0.3	↑	Blondel et al. 1999, 2000; van Gaalen et al. 2006a
		5CSRT	0.4	↑	Mirza and Stolerman 1998
		5CSRT	1.0	↑	van Gaalen et al. 2006a
Sedative/hypnotics					
Alcohol	Humans	Go/no-go	450, 560, 650	↑	Marczinski and Fillmore 2003, 2005a, b; Marczinski et al. 2005; Easdon et al. 2005
		Go/no-go	700	–	Ortner et al. 2003
		Go/no-go	800	↑	Easdon et al. 2005
		SSRT	200	–	de Wit et al. 2000
		SSRT	400	↑	de Wit et al. 2000; Reynolds et al. 2006b
		SSRT	540	↑	Mulvihill et al. 1997
		SSRT	620	↑	Easdon and Vogel-Sprott 2000; Mulvihill et al. 1997; Fillmore and Vogel-Sprott 1999
		SSRT	650	↑	Fillmore and Blackburn 2002
		SSRT	800	↑	de Wit et al. 2000; Reynolds et al. 2006b
	Rats	SSRT	250	–	Feola et al. 2000
		SSRT	500, 750	↑	Feola et al. 2000
		5CSRT	400, 800	–	Bizarro et al. 2003
		5CSRT	1200, 1600	↓	Bizarro et al. 2003
Diazepam	Humans	Go/no-go	5, 10 mg[a]	–	Reynolds et al. 2004a
		SSRT	5, 10 mg[a]	–	Reynolds et al. 2004a
THC	Humans	Go/no-go	7.5, 15.0 mg[a]	–	McDonald et al. 2003
		SSRT	7.5 mg[a]	–	McDonald et al. 2003
		SSRT	15 mg[a]	↑	McDonald et al. 2003
Triazolam	Humans	SSRT	0.125, 0.25 mg[a]	↑	Fillmore et al. 2001

[a] Total dose given (body weight was not accounted for).
[b] Participants were administered the dose of methylphenidate that they were currently prescribed.
↑: increases in impulsivity, –: no change in impulsivity, ↓: decreases in impulsivity

reinforcers in food-restricted rats. The cues present during the delay between the response and the delivery of the larger, delayed reinforcer are also important factors because when the delays to the larger reinforcer were not signaled, stimulants increased impulsivity (Charrier and Thiebot 1996; Evenden and Ryan 1996); whereas, when the delays were cued, stimulants decreased impulsivity (Richards et al. 1999a; Wade et al. 2000). The larger, delayed reinforcer cue may become a conditioned reinforcer, thus enhancing responding after stimulant administration (e.g., Beninger et al. 1981; Hill 1970; Robbins 1978; Robbins et al. 1983). The differences noted in the above studies may be more attributable to stimulus control of behavior than impulsivity, and further studies designed to dissect these variables would be informative. Other variables such as dosing regimens (e.g., high vs low; Isles et al. 2003) and species (e.g., rat vs mouse) also influence the effects of stimulants on DD. The effects of stimulants on DD may also be dependent upon baseline performance. For example, *acute* administration of D-amphetamine increased impulsive choice in LoI rats, and it decreased impulsive choice in HiI rats (Perry et al. 2008b). In addition, methylphenidate *acutely* decreased impulsive choice in HiI rats, but it had no effect on LoI rats (Perry et al. 2008b).

Alcohol administration in rats produced a dose-dependent increase in impulsive choice (Evenden and Ryan 1999; Poulos et al. 1998), contrasting with the lack of alcohol-induced effects on DD in humans. Benzodiazepine administration produced mixed effects on DD in rats. Similar to humans, diazepam decreased impulsivity in one study (Evenden and Ryan 1996); however, it produced no change in another (Charrier and Thiebot 1996), and chlordiazepoxide increased impulsivity (Cardinal et al. 2000). Morphine also increased impulsive choice (Kieres et al. 2004; Pitts and McKinney 2005). Species differences may be accounted for by drug dosing or other procedural differences, such as reinforcer magnitude, the time until reinforcer is delivered (after experimental sessions in humans vs during experimental sessions in animals), or the range of reinforcers/delays experienced.

In addition to delineating the *acute* effects of drugs of abuse, preclinical models may also be better suited than

human studies to explore the effects of *chronic* drug administration on impulsive choice. In rats, repeated administration of methamphetamine (Richards et al. 1999a) or cocaine (Logue et al. 1992; Paine et al. 2003) resulted in increased impulsive choice. Repeated injections of nicotine also dose-dependently increased impulsivity (Dallery and Locey 2005). Like *acute* effects, *chronic* drug effects may differ as a result of baseline levels of impulsivity. For example, HiI rats that received 10 daily injections of D-amphetamine became less impulsive; whereas, LoI rats receiving the same treatment became more impulsive (Perry and Bardo, unpublished data). In addition, HiI mice and rats exhibited greater locomotor sensitization after repeated exposure to ethanol (Mitchell et al. 2006) and D-amphetamine (Perry and Bardo, unpublished data) than LoI mice and rats, respectively, indicating that there are baseline-dependent changes in the drug-induced behavior of HiI and LoI rats.

Summary and future directions In support of the hypothesis that *drug use increases impulsivity* (H2), alcohol and morphine *acutely* increased impulsive choice in rats. In addition, chronic administration of psychostimulants increased impulsivity in rats (supporting H2), and there is evidence that *psychostimulant-induced changes in impulsivity may be baseline-dependent* (H1). Thus, it is possible that escalation of drug intake results from a combination of H1 and H2. Longitudinal studies in humans would be helpful to assess the extent to which impulsive choice increases as drug use escalates and to determine whether interventions that reduce impulsive choice could also result in lower levels of drug use.

Impaired inhibition

Humans Psychostimulants generally improve inhibitory control (decrease impulsivity) in humans with low baseline levels of inhibitory control. For example, in individuals with attention deficit hyperactivity disorder (ADHD), methylphenidate (Potter and Newhouse 2004; Tannock et al. 1989, 1995), atomoxetine (Chamberlain et al. 2007), and nicotine (Potter and Newhouse 2004) increased inhibitory control on the SSRT task. Amphetamine improved inhibitory control on the go/no-go task in individuals who initially showed poor levels of response inhibition (de Wit et al. 2000, 2002) and in chronic cocaine abusers (Fillmore et al. 2003), but it did not influence response inhibition on the SSRT task in healthy volunteers (Fillmore et al. 2005a). Cocaine (Fillmore et al. 2006, but see Fillmore et al. 2002) and MDMA (Ramaekers and Kuypers 2006) improved inhibitory control on the SSRT task in cocaine and MDMA users, respectively. Long-term stimulant abusers displayed neurological impairments, including deficits in inhibitory control (Fillmore and Rush 2002). Therefore, the stimulant-facilitated improvements in inhibitory control in cocaine and MDMA abusers is comparable to improvements in individuals with ADHD or those who had initially poor levels of inhibition. Thus, the results may represent rate-dependent effects or varying effects upon performance depending on whether the subject's baseline response rate was low or high, such that there was an inverse relationship between the baseline response rate and the effects of the drug (e.g., Dews 1958; Dews and Wenger 1977; Kelleher and Morse 1968; Robbins and Sahakian 1979). This suggests that psychostimulants may decrease inhibitory control in individuals with high baseline levels of inhibitory control. There have been no systematic evaluations of this hypothesis, but it would be an important area for future study.

In contrast to psychostimulants, alcohol dose-dependently impaired inhibition (de Wit et al. 2000; Easdon et al. 2005; Fillmore and Blackburn 2002; Fillmore and Vogel-Sprott 1999; Marczinski et al. 2005; Marczinski and Fillmore 2003, 2005a, b; Mulvihill et al. 1997; Ramaekers and Kuypers 2006, but see Ortner et al. 2003). In addition, the expectation of alcohol-induced decreases in performance (Fillmore and Blackburn 2002), behavioral treatment (Fillmore and Vogel-Sprott 1999), and caffeine (Fillmore and Vogel-Sprott 1999) all reversed alcohol-induced impairments in inhibition, suggesting that behavioral or pharmacological interventions may also augment alcohol's impulsivity-increasing effects. Similar to alcohol, benzodiazepines produced dose-dependent decreases in inhibitory control. While low doses of diazepam produced no changes in inhibition (Reynolds et al. 2004a), higher doses of diazepam (Acheson et al. 2006) and triazolam (Fillmore et al. 2001) impaired inhibition (see Table 2).

Unlike psychostimulants and sedative/hypnotics, the *acute* effects of THC on response inhibition appear to be task-dependent. A high dose of THC increased impulsive responding on the SSRT task; however, it did not affect responding on the go/no-go task (McDonald et al. 2003). It is possible that the inconsistencies between the SSRT task and the go/no-go task indicate that they are measuring different underlying processes or the tasks could differ in sensitivity or parametric features (Reynolds et al. 2006b). Given that performance on these two tasks is positively correlated in the absence of drugs (Reynolds et al. 2006a), the latter possibility may be more likely.

Animals In animal studies, inhibitory responses to *acute* administration of drugs have been comparable to those obtained in humans (see Table 2). Consistent with the rate-dependency hypothesis (e.g., Dews 1958; Kelleher and Morse 1968; Robbins and Sahakian 1979), amphetamine (Eagle and Robbins 2003; Feola et al. 2000), methylphenidate (Eagle et al. 2007), and modafinil (Eagle et al. 2007)

improved inhibition on the SSRT task in rats with poor baseline inhibitory control. Conversely, methylphenidate impaired inhibition on the SSRT task in rats with high baseline inhibitory control (Eagle et al. 2007). Regardless of baseline response rate, atomoxetine improved inhibition on the SSRT task (Robinson et al. 2007); whereas, alcohol impaired inhibition on the SSRT task (Feola et al. 2000), and cocaine impaired inhibition on the go/no-go (Paine and Olmstead 2004) and 5CSRT (van Gaalen et al. 2006a) tasks.

Unlike results from studies in which the go/no-go and SSRT tasks were employed, results from studies using the 5CSRT were largely mixed with some studies showing drug-induced increases in inhibitory failure and others showing drug-induced decreases. This was true of atomoxetine (Navarra et al. 2008; Robinson et al. 2007), methylphenidate (Bizarro et al. 2004; Navarra et al. 2008; Paine et al. 2007), amphetamine (Bizarro et al. 2004; Bizarro and Stolerman 2003; van Gaalen et al. 2006a), and nicotine (e.g., Bizarro et al. 2004; Blondel et al. 2000; Mirza and Stolerman 1998; van Gaalen et al. 2006a). Between-study differences in intertrial intervals, duration of stimulus presentation, and other procedural differences likely contributed to the discrepancies in these studies (Stolerman et al. 2000). It will be important for future research to determine experimental conditions that allow for comparison between the 5CSRT, go/no-go, and SSRT tasks. Together, the results from studies measuring inhibition in animal models typically provide comparable results to human research, implying construct validity for these tasks.

Summary and future directions In summary, alcohol, diazepam, and triazolam in humans (and cocaine in rodents) *acutely* decreased inhibitory control, supporting the hypothesis that drug use increases impulsivity (H2). However, in both humans and rats, stimulants increased inhibitory control (decreased impulsivity) in impulsive individuals. In addition, *acute* administration of amphetamine, methylphenidate, atomoxetine, and nicotine in rodents produced mixed results on the 5CSRT task. Thus, it is unclear whether *acute* administration of drugs of abuse can increase impulsivity and enhance escalation/dysregulation of drug intake. Systematic studies of the effects of *chronic* administration of drugs of abuse on inhibitory control may provide evidence that *drugs of abuse increase impulsivity* (H2); however, we are unaware of studies that have addressed this question. There is need for these studies, as discovery of drugs that decrease impulsive behavior may be useful for harm reduction in users, and identification of drugs that increase impulsivity related to drug use could explain accelerated use and resistance to abstinence/treatment. In these cases, behavioral management of impulsive behavior may be of value.

Individual differences related to impulsivity and/or drug abuse

The third hypothesis under consideration (H3) suggests that *impulsivity and drug abuse are associated through another factor* (e.g., sex, hormonal status, general reactivity to rewards, early experiences) that interacts with and affects both impulsivity and drug abuse. Thus, impulsivity may not be independently influencing drug abuse, but it may covary with other factors that have a strong influence. In fact, impulsivity and other factors may have an additive influence on vulnerability to various aspects of drug abuse. This section focuses on factors that have been related to impulsivity and enhanced vulnerability to drug abuse with an emphasis on preclinical research. The vulnerability factors may be related to genetic or environmental conditions, such as sex and hormonal status, reactivity to nondrug rewards, and early life experiences (e.g., abuse/impoverished rearing conditions, prenatal drug exposure). In addition, these factors may be differentially related to different facets of impulsivity: impulsive choice or impaired inhibition. For example, extinction learning and aggression were both related to impulsive choice; however, neither was related to impaired inhibition (Van den Bergh et al. 2006).

Sex and hormonal factors

Sex appears to be a major factor in human and animal drug consumption with females exhibiting greater drug-seeking behavior than males under a wide range of conditions (for reviews, see Carroll et al. 2004; Lynch et al. 2002; Lynch 2006; Roth et al. 2004). However, currently, more men report problems with drug abuse than women, but the gender gap appears to be closing (Substance Abuse and Mental Health Services Administration 2006). For example, men are more likely than women to have an initial opportunity to use drugs due to cultural factors, but once the opportunity to use occurs, women may be more likely than men to make a transition to continued abuse (Anglin et al. 1987; Brecht et al. 2004; Hernandez-Avila et al. 2004).

In preclinical models, females acquired drug self-administration faster than males (e.g., Carroll et al. 2000; Lynch and Carroll 1999), escalated their drug intake (Carroll et al. 2005; Roth and Carroll 2004), and regulated their drug intake less precisely (Lynch et al. 2000) showing more binge-like patterns (Morgan et al. 2002) than males. Females also maintained higher rates of responding during extinction and after drug-primed (but not cue-primed, Fuchs et al. 2005) reinstatement than males, suggesting that they are less likely to cease drug use and more likely to relapse than males (Lynch and Carroll 2000). Hormonal status (e.g., presence of estrogen/progesterone) plays a major role in sex differences in drug abuse. For example, in

rats, estrogen facilitated acquisition of cocaine (Hu and Becker 2003; Jackson et al. 2006; Lynch et al. 2001) and heroin (Roth et al. 2002) self-administration, escalation of cocaine self-administration (Larson et al. 2007), and reinstatement of drug-seeking behavior (Larson et al. 2005), and progesterone attenuated estrogen's effects on cocaine escalation (Larson et al. 2007) and reinstatement (Anker et al. 2007).

Several of these drug-related behaviors may be attributed to impulsivity (e.g., acquisition, escalation, extinction, reinstatement); however, clinical studies of sex differences in impulsivity produced mixed results. For example, women have lower (Kirby and Marakovic 1996), higher (Wallace 1979; Reynolds et al. 2006a), or the same (Fillmore and Weafer 2004; Reynolds et al. 2006b; Skinner et al. 2004) levels of impulsivity compared to males. Experimental conditions also play an important role in the determination of sex differences in impulsivity. In one study, women discounted delayed hypothetical reinforcers at a higher rate than men, but when real reinforcers were offered, men discounted at a higher rate than women (Heyman and Gibb 2006).

Age may be interrelated as well. In adolescents (but not adults), the relationship between impulsivity and drug abuse was stronger in males than females (Labouvie and McGee 1986). The interaction between impulsivity and sex may be drug-specific. Impulsivity was associated with higher levels of nicotine use in females, but in males, impulsivity was associated with heightened caffeine use (Waldeck and Miller 1997). Others have found no sex differences in the relationship between impulsivity and alcohol use (Nagoshi et al. 1991; Waldeck and Miller 1997). There is also evidence for sex differences in drug-induced changes in impulsivity. Men displayed more alcohol-induced inhibitory impairments than women in one study (Fillmore and Weafer 2004), but in other studies, there were no sex differences (Mulvihill et al. 1997; Reynolds et al. 2006a, b). Procedural differences may account for the discrepancies in these results; however, the lack of consistent sex differences in any of the above studies illustrates that further research with standard procedures is needed to characterize the relationship between sex, impulsivity, and drug abuse.

To date, few preclinical studies have examined sex differences in impulsivity. Using a go/no-go task, Jentsch and Taylor (2003) found that males had higher levels of responding during the no-go period than females, indicating higher levels of impulsivity. However, this interpretation may have been confounded by feeding conditions, as males and females were fed the same amount of food, despite the sex difference in body weights. Thus, the males had relatively more severe food restriction than the females and presumably greater motivation to respond for presentation of food. In a study conducted in our laboratory, there were no sex differences on a DD task for food or cocaine reinforcement; however, the results could be attributed to a floor effect because approximately 70% of the rats were impulsive on the task (Perry et al. 2008a). However, when we compared other studies of rats selectively bred for low saccharin intake (LoS) on the same task, there was less impulsivity and greater room for variation in impulsivity scores, and females were more impulsive than males (Perry et al. 2007). In another study using the high and low saccharin (HiS, LoS) rats and the go/no-go procedure for cocaine self-administration, a similar finding emerged. Female rats exceeded males on both go (self-administration) and no-go (inhibitory failure) responding in both the HiS and LoS lines (Anker and Carroll 2008). Van Haaren et al. (1988) also found that female rats discounted food reinforcers more than males. Thus, the data currently available suggest that females are more impulsive than males with respect to food and drug rewards.

Sex differences in impulsivity and drug abuse may be mediated by circulating gonadal hormones. For example, sham-operated males had the highest levels of impulsivity, while sham-operated females had the lowest, and gonadectomized males and females had intermediate levels of impulsive responding (Jentsch and Taylor 2003). These results suggest that gonadal hormones influence impulsivity; however, as mentioned above, feeding conditions were a confounding variable in this study. Svensson et al. (2000) also found that gonadectomy decreased impulsivity, and this effect was reversed in rats that received testosterone substitution after gonadectomy. Thus, two studies are in agreement that testosterone in males is related to higher levels of impulsivity; however, in a third study, there was no relationship between plasma testosterone and impulsivity in male rats (Van den Bergh et al. 2006). Results from another study suggested that testosterone's effects may be baseline-dependent (Takahashi et al. 2006); that is, testosterone enhanced impulsive choice in nonimpulsive men, and it decreased impulsive choice in impulsive men (Takahashi et al. 2006). The role of female gonadal hormones in impulsivity remains to be determined. Future studies are needed to adequately understand the relationship between sex, gonadal hormones, impulsivity, and how the combination of these factors interacts with drug abuse.

Reactivity to rewards

Another determinant of the vulnerability to drug abuse (and possibly impulsivity) is reactivity to natural rewards, such as dietary (e.g., sweets, fats) substances (Carr 2002; Carroll 1999; Grigson 2002) or exercise, such as wheel running (Larson and Carroll 2005). For example, rats selectively bred for HiS consumed more ethanol than their LoS

counterparts (Dess et al. 1998). HiS rats also acquired i.v. cocaine self-administration faster and in greater numbers than LoS rats (Carroll et al. 2002). HiS rats escalated their drug intake to higher levels and showed greater reinstatement of cocaine-seeking behavior than LoS rats (Perry et al. 2006). In addition, HiS females showed greater dysregulation of cocaine intake than LoS females (Carroll et al. 2007b) and higher rates of cocaine-induced locomotor activity (Carroll et al. 2007a). HiS males and females were also more impulsive on a DD task rewarded with food (Perry et al. 2007) and a go/no-go task rewarded by i.v. cocaine self-administration (Anker and Carroll 2008) compared to LoS males and females. These findings appear to be unidirectional, as HiI and LoI rats do not show differences in saccharin intake in a two-bottle choice test (Carroll et al. 2008b). In another study of reactivity to natural rewards and impulsivity, adolescent humans and rats were more impulsive than their adult counterparts, and they also showed a preference for sweeter sucrose solutions compared to adults, although there were no correlations between impulsivity measures and sucrose preferences (Vaidya et al. 2004). Excessive intake of palatable substances, such as sucrose or saccharin may be considered a form of impulsivity; however, further studies are necessary to explore the relationship between these addiction-prone behavioral phenotypes. The relationship between impulsivity and other phenotypes with high levels of reactivity to natural rewards may be revealed in future studies (e.g., high and low wheel runners), and this would indicate that impulsivity is related to a more fundamental construct.

Early environmental experiences

Traumatic experiences in early childhood, such as maltreatment or abuse have been associated with enhanced risk of subsequent alcohol and substance abuse (e.g., for review, see De Bellis 2002). (e.g., for reviews see Olmstead 2006; Spear and Molina 2005). Humans who have experienced detrimental early life experiences, such as abuse or prenatal exposure to drugs, also show high levels of impulsivity (for review, see Olmstead 2006). Similarly, in animal models, rats reared in an impoverished environment self-administered more amphetamine infusions under FR (Bardo et al. 2001) and PR (Green et al. 2002) schedules of reinforcement compared to rats reared in an enriched environment (but see Bardo and Dwoskin 2004; Olmstead 2006 for limitations on these findings). Rats reared in isolation also showed increased impulsive choice compared with rats reared in an enriched environment (Perry et al. 2008b). Others have reported no differences in impulsive choice (Adriani et al. 2006; Hellemans et al. 2005) or inhibition (Dalley et al. 2002; Hellemans et al. 2005) between rats that were socially or individually housed as adolescents. However, individually housed rats that experienced perinatal asphyxia were more impulsive as adults compared with socially housed rats that experienced perinatal asphyxia (Adriani et al. 2006). Earlier studies showed that animals (rats and monkeys) living in an environment with restricted food access (vs unlimited access) showed elevated drug self-administration and reinstatement of drug-seeking behavior (relapse, Carroll 1998; Campbell and Carroll 2000). Recent research with monkeys indicated that the restricted feeding condition resulted in increased impulsivity for orally delivered phencyclidine (PCP) compared to the unlimited food condition (Carroll et al. 2008a, b).

Another early life experience that predicts subsequent vulnerability to drug abuse is early (i.e., prenatal, fetal, or infantile) exposure to drugs of abuse (e.g., for reviews see Olmstead 2006; Spear and Molina 2005). In addition, *chronic* prenatal ethanol exposure in guinea pigs resulted in impaired inhibition (Olmstead 2006). Overall, these results suggest that impulsivity is influenced by adverse and early life experiences; however, stress may be a confounding factor. Stress is also associated with higher rates of acquisition of drug self-administration (Tidey and Miczek 1997) and impulsivity (Piazza and Le Moal 1998). Further research is needed to determine the relationship between stress, adversity, and impulsivity, and whether stress mediates the relationship between traumatic early experiences, impulsivity, and ultimately drug abuse.

In summary, impulsivity may be related to other factors (e.g., sex, reactivity to rewards, or early environmental experiences) that predict vulnerability to drug abuse (H3). A relationship between sex and impulsivity (F>M) is emerging. Now it will be important to examine the role of female gonadal hormones in impulsivity to determine its influence in other aspects of drug abuse. Reactivity to rewards (e.g., preference for a saccharin solution) and early environmental experiences (e.g., environmental enrichment) were related to impulsive choice and behavioral inhibition, and they were both related to vulnerability to drug abuse (H3). However, given that HiI and LoI rats do not differ in saccharin preference (Carroll et al. 2008b), it appears that impulsivity and reactivity to rewards are separate, but related constructs.

General discussion

A review of the literature suggests that impulsivity is a construct with multiple facets (e.g., Evenden 1999), and it is important to use several different measures of impulsivity to obtain converging evidence when assessing the effect of an experimental manipulation on impulsivity. The first goal of this review was to highlight the main measures of impulsive behavior that have increased our knowledge regarding the connection between impulsivity and drug

abuse. To that end, we have described two aspects of impulsivity that have been associated with drug abuse: impulsive choice (measured by DD) and impaired inhibition (measured by the go/no-go, SSRT, and 5CSRT tasks). Although these definitions reflect different aspects of impulsivity, drug abusers show deficits in both impulsive choice and inhibition. Performance on tasks measuring impulsive choice and impaired inhibition is related to vulnerability during several phases of addiction (i.e., acquisition, escalation/dysregulation, abstinence, treatment, and relapse), and these tasks all appear to be sensitive to *acute* or *chronic* administration of drugs of abuse. It is important to note that the majority of the results from rodent models of impulsive choice and inhibition concur with findings in humans, indicating the face validity of the animal models. However, more research is needed to examine the variables controlling responding on these tasks (e.g., whether delays are cued in the DD task, ITI in the 5CSRT task). In addition, it remains unclear whether tasks proposed to study inhibitory control are related or whether they measure different aspects of inhibition. Clarifying the specific mechanisms that underlie performance on these tasks would greatly add to our understanding of current models of impulsivity and allow us to develop new models that more accurately capture the essence of several aspects of impulsivity.

A second goal of this review was to show how impulsivity may drive drug-seeking behavior during several phases of drug abuse, and to accomplish this, we have examined the relationship between impulsivity and drug abuse using three hypotheses (the third goal of this review). H1 states that *increased levels of impulsivity expressed as impulsive choice or inhibitory failure leads to drug abuse*, and H1 plays a role in acquisition, escalation/dysregulation, abstinence, treatment, and relapse. Drug abusers show deficits in impulsive choice and inhibition, although it is impossible to know whether differences in impulsivity caused or were caused by drug abuse. Preclinical models show that impulsive choice predicted elevated alcohol intake (Poulos et al. 1995), faster acquisition of cocaine self-administration (Perry et al. 2005), greater escalation of cocaine intake (Anker et al., in preparation), and greater drug- (Perry et al. 2008a) and cue-induced (Diergaarde et al. 2008) reinstatement of drug-seeking behavior. Impaired inhibition also predicted elevated cocaine self-administration (Dalley et al. 2007a), higher levels of responding during acquisition of nicotine self-administration (Diergaarde et al. 2008), and reinstatement of cocaine-seeking behavior (Deroche-Gamonet et al. 2004). Impulsive choice in humans predicted greater likelihood of relapse (Krishnan-Sarin et al. 2007; Yoon et al. 2007). With respect to H1, it will be important for future research to extend these initial findings in preclinical and human laboratory models by answering the following questions: (1) Does impulsive choice or impaired inhibition influence acquisition of drug-taking in humans? (2) How do baseline levels of impulsivity influence an individual's response to drugs of abuse? (3) If impulsive choice and/or impaired inhibition predict greater likelihood of acquisition/escalation/relapse, will treating underlying impulsivity also reduce the likelihood of acquisition/escalation/relapse?

H2, that *acute* or *chronic* exposure to *drugs of abuse increase impulsivity*, is particularly relevant to escalation/dysregulation of drug intake and to abstinence, treatment, and relapse. To date, it is unclear whether a single drug exposure is sufficient to increase impulsivity, yet determining the influence of subtle procedural variations, such as dosing, behavioral history, and stimulus control on drug-induced impulsivity will undoubtedly clarify the existing results. Unlike *acute* dosing regiments, *chronic* dosing of nicotine (Dallery and Locey 2005), cocaine (Logue et al. 1992; Paine et al. 2003), and methamphetamine (Richards et al. 1999a) produced increases in impulsive choice that may contribute to escalation of intake (although there have not been any studies that have specifically examined this). We are unaware of any studies that have determined the effects of *chronic* administration of drugs on inhibitory control; however, these studies will be important for determining the role of *chronic* drug administration on inhibitory control and escalation/dysregulation. Additional work using self-administration in animal models or within-subject longitudinal comparisons in humans should examine impulsivity as drug intake progresses from low to high levels to further assess the role of H2 in escalation/dysregulation of drug intake.

The increases in impulsivity caused by *chronic* administration of drugs of abuse (H2) may continue despite drug cessation, resulting in shorter abstinence, faster relapse, and reduced likelihood of treatment success. For example, in both humans and rodents, nicotine (Bickel et al. 1999; Dallery and Locey 2005) and cocaine (Heil et al. 2006; Kirby and Petry 2004; Simon et al. 2007) exposure produced reversible increases in impulsive choice that persisted even after drug use was discontinued. Less is known about the relationship between inhibitory failure and withdrawal, but withdrawal from some drugs of abuse (i.e., methamphetamine, MDMA) increased impulsivity on the 5CSRT task (Dalley et al. 2007b), which may increase likelihood of subsequent relapse. A goal of future research in this area should be to determine how drug- or withdrawal-induced increases in impulsivity influence abstinence and treatment success, and whether reducing impulsivity would increase the length of abstinence and overall treatment success.

We have also presented evidence in support of H3, which suggests that *impulsivity is associated with drug*

abuse through a third factor (e.g., sex, hormonal status, reactivity to rewards, early environmental experiences) that interacts with and affects both impulsivity and drug abuse during all phases of abuse. This hypothesis has been studied less frequently than H1 or H2; however, it appears that there is a relationship between impulsivity and sex (F>M). Reactivity to rewards and early environmental experiences also appears to be related to impulsivity, and predicts of vulnerability to drug abuse. Future studies with sensitive behavioral measures should examine the relationship between impulsivity, and phenotypes with high levels of reactivity to natural rewards. The relationship between stress, adversity, and impulsivity should also be studied to determine whether stress mediates the relationship between early experiences, impulsivity, and drug abuse.

It will be important for future research to continue to characterize the relationship between drug abuse and impulsivity using both human and animal models, several different drugs of abuse, and several different measures of impulsivity (i.e., DD, go/no-go, SSRT, and 5CSRT tasks). Factors that contribute to individual differences in impulsivity, such as behavioral history, motivation, neurobiology, and genetics should be studied to better understand the behavioral manifestations and neurobiology underlying impulsive behavior and drug abuse. For example, variants of the dopamine transporter, the dopamine D4 receptor, and the serotonin transporter have been linked to both impulsivity and alcoholism (Kreek et al. 2005), and understanding how each of these impacts impulsivity and alcoholism may yield new pharmacotherapies that decrease both impulsivity and drug abuse.

It may also be important to determine whether compulsive behavior is related to impulsivity and drug abuse. Compulsive behavior differs from impulsive behavior in that compulsive actions reduce anxiety (negative reinforcement); whereas, impulsive behaviors are thought to produce pleasure or gratification (positive reinforcement; American Psychiatric Association 2000). Certainly, both processes play a role in drug abuse (e.g., Le Moal and Koob 2007; Olmstead 2006). It has been suggested that impulsivity and compulsivity are on opposite ends of a continuum, and the initial phases of drug abuse are driven by impulsivity, while subsequent phases (e.g., escalation, relapse, reacquisition) are driven by compulsivity (e.g., Belin et al. 2008; Le Moal and Koob 2007). However, the relationship between impulsivity and compulsivity is complicated and both occur at different times or cooccur in the same individual (Grant and Potenza 2006). Therefore, it will be important to examine the relationships between compulsivity, impulsivity, and drug abuse.

Studying factors that contribute to individual differences in impulsivity may result in a greater understanding of how these forms of behavior contribute to critical phases of the addiction process. Future research should also focus on the relationship between impulsivity and other major vulnerability factors (e.g., sex, hormonal status, reactivity to rewards, early environmental experiences) and how the combination of these factors may influence drug abuse. Such research would result in the ability to recognize vulnerable phenotypes and focus prevention strategies on those with heightened vulnerability to drug abuse. It will also be important for researchers to determine whether present behavioral or pharmacological treatments decrease impulsivity and whether tasks that measure impulsivity would be useful in screening new treatments for drug abuse. The intent would be to find pharmacological and behavioral treatments that will decrease impulsivity and drug abuse simultaneously and to examine how effective behavioral and pharmacological treatments are in individuals differing in impulsivity.

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