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Recent Translational Findings on Impulsivity in Relation to Drug Abuse

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Abstract

Impulsive behavior is strongly implicated in drug abuse, as both a cause and a consequence of drug use. To understand how impulsive behaviors lead to and result from drug use, translational evidence from both human and non-human animal studies is needed. Here, we review recent (2009 or later) studies that have investigated two major components of impulsive behavior, inhibitory control and impulsive choice, across preclinical and clinical studies. We concentrate on the stop-signal task as the measure of inhibitory control and delay discounting as the measure of impulsive choice. Consistent with previous reports, recent studies show greater impulsive behavior in drug users compared with non-users. Additionally, new evidence supports the prospective role of impulsive behavior in drug abuse, and has begun to identify the neurobiological mechanisms underlying impulsive behavior. We focus on the commonalities and differences in findings between preclinical and clinical studies, and suggest future directions for translational research.

Keywords

Impulsive behavior; Inhibitory control; Stop-signal task; Impulsive choice; Delay discounting; Drug abuse

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Compliance with Ethics Guidelines

Conflict of Interest Jessica Weafer, Suzanne H. Mitchell and Harriet de Wit declare no conflict of interest.

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Introduction

Impulsive behavior is strongly implicated in drug abuse, as both a cause and a consequence of drug use. The role of impulsive behavior in drug abuse has been investigated extensively, as described in several recent reviews [1–4]. These reviews confirm that impulsive behavior is multifaceted, and that specific components of impulsivity relate to distinct stages of drug abuse. There is now convincing evidence that impulsive behavior is both a determinant and consequence of drug abuse, but there is still a need to identify which factors predispose individuals to use, and which result from drug use, either after acute administration or after extended periods of use. There is also a need to investigate the underlying neurobiological mechanisms involved in impulsivity to develop effective prevention and treatment strategies.

To understand how impulsive behaviors lead to, and result from, drug use, translational evidence from both human and non-human animal studies is needed, and translational research requires valid and sensitive behavioral models of impulsivity. Here, we critically examine recent studies that have investigated two major components of impulsive behavior, inhibitory control and impulsive choice, across preclinical (i.e., studies involving nonhumans) and clinical studies (i.e., studies involving humans). To reduce overlap with previous reviews, we focus on studies published in 2009 or later, and concentrate our review on the stop-signal task as the measure of inhibitory control and delay discounting as the measure of impulsive choice. We will first review the task methodologies. We will then review recent studies comparing task performance in drug users and non-users, as well as recent preclinical and clinical studies that prospectively predict drug use from these impulsive behaviors. We will also present results of studies investigating the acute effects of drugs on these tasks, because drug consumption can produce state-level disruption of impulsive behavior, and may provide some indirect information regarding chronic drug effects. Finally, we review findings on the neurobiological mechanisms of impulsive behavior in both non-human animals and humans. Our focus is on the commonalities and differences in findings between preclinical and clinical studies, and an assessment of the strengths and limitations of current approaches.

Task Descriptions

Stop-Signal Task

The stop-signal task is one of the most commonly used measures of inhibitory control. This task measures the ability to inhibit an instigated or ‘prepotent’ response [5]. In human versions of this task, subjects are instructed to respond as quickly as possible to Go signals by making a key press, but occasionally to inhibit their response when a Stop signal occurs (typically an auditory tone). The Stop signal is presented shortly after the Go signal and the experimenter measures the time an individual needs between the Go and Stop signal to successfully inhibit a response. In one commonly used version of the task, the onset of the Stop signal is adjusted to target a 50 % successful inhibition rate. A stop signal reaction time (SSRT) may be calculated (i.e., the difference between mean Go reaction time and mean stop signal delay), providing a quantitative index of inhibitory control. Greater SSRT values indicate poorer response inhibition. In animal studies, the stop-signal task can be arranged in

a similar manner by adjusting the onset of the stop signal based on performance [6]. However, more commonly, the stop signal onset is varied in a pre-planned sequence across blocks and the percent of trials on which stopping occurs is measured. SSRT is obtained by interpolating the time at which 50 % stopping would occur [7].

Delay Discounting Task

Delay discounting tasks are the gold standard to measure impulsive choice. These tasks measure the degree to which the value of a reward decreases as a function of the delay in time to its delivery [8–11]. In human versions of the task, subjects make choices between small rewards (usually money) delivered immediately or larger rewards delivered after a delay. A curve is plotted based on the subject's points of indifference between immediate and delayed rewards, and steeper discounting curves indicate greater delay discounting. These tasks can be administered as both paper and pencil or computerized versions. In preclinical studies, several variants are commonly used. Similar to tasks used with human subjects, some identify indifference points by titrating the length of the delay to the large reward [12] or the size of the immediate reward [13], until an indifference point is reached. Other procedures assess choices of the larger, later reward over a series of fixed delays presented during the course of a session [14] and use percent choice at the various delays as their measure of discounting.

Studies Comparing Drug Users and Non-Users

Studies comparing drug users and non-users provide important information about behavioral tendencies that make it difficult for users to resist drugs during attempts to abstain. However, the origin of these differences is difficult to discern because users and nonusers differ on many other dimensions (e.g., trait differences or differences in experience), and because it is not possible to determine whether differences predate, or result from, the drug use. Nevertheless, evidence that drug users are more impulsive on certain measures may guide development of treatment strategies, and guide preclinical prospective studies examining behavioral risk factors.

Stop-signal Task

Drug users have poorer inhibitory control as measured by the stop-signal task compared with non-users [1, 4]. Recent findings generally support this conclusion, although there are some interesting exceptions, and the findings vary across drug types. Alcohol-dependent individuals (inpatient and outpatient) exhibited poorer performance on the stop-signal task than healthy controls [15, 16], but among nondependent drinkers the findings are less clear. Smith and Mattick [17] found that longer SSRTs predicted binge drinking and alcohol problems in women, but two other studies observed no differences between binge and non-binge drinkers [18, 19], and a third study reported that stop-signal task performance did not predict consumption in nontreatment-seeking problem drinkers [20]. Additional studies have reported longer SSRTs in cannabis users [18] and cocaine-dependent individuals [21], although two other studies failed to observe these group differences [22, 23]. The inconsistent results across studies remain to be explained, but these studies provide some

evidence that drug users have poor inhibitory control. The association appears to be most pronounced for dependent alcohol users, and less consistent for cannabis and cocaine users.

Delay Discounting

Substance users also exhibit greater delay discounting than non-users [1,4, 24, 25], and this conclusion is supported by findings in the last 5 years. In most studies examining delay discounting in relation to habitual alcohol consumption, heavier drinkers discounted more [20, 15, 26•, 18, 27]; although see [28]. One study found an association in African Americans but not European Americans [29], and another study found that discounting predicted drinking in females but not males [30]. In studies of cigarette smokers, discounting was also related to severity of nicotine dependence [31–35], but see [36], and individuals who were both drinkers and smokers discounted more than drinkers or smokers only [37]. Similarly, both cocaine- and opiate-dependent individuals discounted more than healthy controls [21, 38–40], although see [41], and delay discounting was greater for early or intermediate onset opiate dependence compared with late-onset [42]. In regard to cannabis, discounting predicted use in recreational users [18], but not dependent individuals [33]. Finally, among users of multiple substances, discounting was greater in users of cocaine, nicotine, or both, compared with controls [43], although no difference was observed in polysubstance-using rave attenders compared with controls [44]. Taken together, these studies add to a large body of evidence that steeper discounting is greater in substance users, including alcohol, nicotine, cannabis, cocaine, and opiate users, compared with non-users.

Summary

In sum, studies reviewed in this section provide further evidence that drug users exhibit both poor inhibitory control and steep delay discounting. The associations are observed across drug classes, including alcohol, stimulants, and opiates, and they tend to be more pronounced in individuals meeting criteria for substance dependence. The following sections provide updated preclinical and clinical evidence regarding the causality of this relationship and whether drug users are likely to be more impulsive even before drug use, or whether the behaviors change as a consequence of drug use, or whether other factors (e.g., smoking) contribute to the relationship between impulsivity and drug use.

Impulsive Behavior as a Determinant of Drug Use

Inhibitory Control: Preclinical Studies

Our literature search produced no relevant preclinical studies examining stop-signal task performance as a determinant of drug use. However, a number of studies have been conducted using the 5-choice serial reaction time task (5-CSRTT [45]), which examines responses occurring prematurely to a Go signal. Several studies have shown that ‘high’ impulsivity, based on the number of premature responses, is a predictor of drug self-administration in laboratory animals (e.g., [46–48]).

Inhibitory Control: Clinical Studies

We found only one recent prospective study that examined stop-signal task performance as a predictor of drug use in humans. This study, done by Fernie et al. [49•], assessed inhibitory

control and delay discounting as predictors of alcohol consumption every 6 months over a period of 2 years, in adolescents aged 12–13 years. Prospective analyses showed that stop-signal task performance consistently predicted alcohol consumption 6 months later across the 2-year period, consistent with the idea that poor inhibition may precede and perhaps play a causal role in increased alcohol use. This is consistent with two earlier reports showing that stop-signal task performance predicted future drug and alcohol use in adolescents and young adults [50, 51]. However, as in any prospective study of this type, it is difficult to rule out other individual difference factors that might covary with stop-signal task performance and mediate the observed relationship [4].

Delay Discounting: Preclinical Studies

Consistent with earlier studies [1, 4], recent experiments suggest a relationship between steeper discounting and drug self-administration in laboratory animals. Anker et al. [52] reported that rats selected for high levels of choice impulsivity acquired cocaine self-administration more quickly than animals that discounted less. Compatible with these results, Koffarnus and Woods [53] demonstrated that rats with steeper discounting functions were less sensitive to increasing response costs to earn cocaine infusions (low elasticity of demand), but they were not less sensitive to increasing cost of nondrug, sucrose reinforcers. Diergaarde et al. [54•] observed the same relationship using a different stimulant, nicotine, but not for ethanol as the reinforcer. In a somewhat different paradigm, Yates et al. [55] reported that rats selected for high levels of impulsive choice developed a conditioned place preference for amphetamine (several doses), whereas low impulsive animals did not develop a conditioned place preference for amphetamine at any dose; suggesting that steeper discounting was predictive of amphetamine reward, as measured by the place preference procedure. In sum, recent preclinical studies suggest that steeper discounting is a predictor of indices of drug use, but this association is only robust for stimulants.

Delay Discounting: Clinical Studies

Fernie et al. [49•], mentioned earlier, found that steeper discounting prospectively predicted greater alcohol consumption among adolescents over the following 2-year period. This result differs from the Diergaarde et al. [54•] finding that discounting in rats did not predict alcohol consumption, but many differences between the clinical and preclinical studies could account for this dissimilar outcome. In another study, Brody et al. [56] examined delay discounting as a predictor of drug use 1 year later in 19–20-year-old African Americans. Although delay discounting did not predict drug use at follow-up in the sample as a whole, steeper discounting did predict drug use among men with high catecholamine levels (i.e., epinephrine and norepinephrine). To our knowledge, these are the first studies to prospectively assess delay discounting as a predictor of drug use in humans, and together they provide some preliminary evidence suggesting delay discounting may have a prospective role in drug abuse.

Summary of Preclinical and Clinical Studies

In sum, recent preclinical and clinical studies add to a growing literature supporting the prospective role of delay discounting in drug abuse. The stop-signal task has not been thoroughly tested as a predictor of drug reward in laboratory animals, although there is some

evidence that another measure of inhibitory control, the 5-CSRTT, does predict drug self-administration. A relatively small number of prospective studies with humans suggest that both poor inhibitory control and delay discounting predict drug use in children and adolescents. However, there are substantial methodological and conceptual challenges in identifying common predictors of drug reward in humans and laboratory animals, and for now we can only speculate about the causal determinants in humans.

Impulsivity as a Consequence of Drug Use

It has been proposed that drug users become more impulsive as a result of chronic exposure to drugs [57]. Although the effects of chronic drug use can readily be studied in animal models, it is extremely difficult to demonstrate that cognitive dysfunction is a result of chronic drug use in humans. However, some indirect evidence may be gleaned from studies with acute drug administration in humans. Single doses of drugs have marked effects on impulsive behaviors, which provide important information about safety, and may contribute to risk for continued use within a drug-using occasion. The acute effects may also shed light on the effects of chronic exposure to the drugs.

Inhibitory Control (Acute Drug Effects): Preclinical Studies

In their previous review, Perry and Carroll [4] concluded that stimulant drugs improve stop-signal task performance in laboratory animals, especially in animals with poor baseline inhibition, and that alcohol and other sedatives impair performance. Only two recent preclinical studies have examined the acute effects of drugs on the stop-signal task, both with rats (see Table 1). Pattij et al. [58] reported that neither morphine nor naloxone altered stop-signal task performance but, consistent with earlier reports, Eagle et al. [59] reported that d-amphetamine dose-relatedly decreased SSRT. Thus, similar to earlier reports, these preclinical studies provide further evidence that stimulants improve inhibitory control, and provide new evidence suggesting that opioid drugs do not affect inhibition.

Inhibitory Control (Acute Drug Effects): Clinical Studies

Consistent with preclinical studies, previous reviews concluded that stimulant drugs tend to improve stop-signal task performance, especially in individuals with poor baseline inhibition, whereas sedative drugs, including alcohol and THC, impair stop-signal task performance [1, 4]. Recent reports have examined the effects of alcohol, marijuana smoking, and oxycodone on inhibitory control in humans (Table 1). Caswell et al. [60] found that alcohol dose-dependently increased SSRT in young adult social drinkers. Metrik et al. [61] found that smoked marijuana significantly impaired performance on the stop-signal task in young adult marijuana users. By contrast, oxycodone did not alter stop-signal task performance among healthy young adults [62]. In sum, consistent with prior reports of acute drug effects on stop-signal task performance [4], alcohol and THC appear to impair inhibitory control while oxycodone does not.

Delay Discounting (Acute Drug Effects): Preclinical Studies

Although results have been mixed, prior preclinical studies indicate that acute doses of stimulant drugs decrease delay discounting whereas alcohol increases it [4]. Numerous

studies have since examined the effects of drugs of abuse on delay discounting performance (see Table 2 for details). The results are complex and it appears that the effects of drugs depend on genetic factors; for example, Wooters and Bardo [63] observed that methylphenidate decreased delay discounting in Wistar-Kyoto rats but not Sprague-Dawley or Spontaneously Hypertensive rats. Further, for some drugs, the behavioral effects are closely linked to dose; for example, Huskinson and Anderson [64] reported that in Fischer 344 rats low doses of diazepam reduced delay discounting but high doses increased discounting, while in Lewis rats diazepam did not affect discounting at any dose. Pre-drug levels of discounting may also be important, as was seen in the "Impulsive behavior as a determinant of drug use" section, but this variable is as yet unexamined.

Delay Discounting (Acute Drug Effects): Clinical Studies

As reported in earlier studies, there are relatively few reports that acute administration of drugs change delay discounting in humans [1, 4]. This pattern is continued in recent studies with alcohol, marijuana, d-amphetamine and oxycodone (Table 2). In one exception, Reed et al. [65] found that alcohol increased delay discounting in both heavy and light drinking women tested in the follicular phase of the menstrual cycle. Bidwell et al. [66] found no effect of alcohol on delay discounting in social drinkers, although this study did not include a placebo condition. Other studies found no effects of smoked marijuana [61], d-amphetamine [67], or oxycodone [62] on delay discounting in healthy subjects. It has been proposed that the delay discounting task typically used with humans is not sensitive to the effects of drugs [68], perhaps because of differences in time frame of the delay (i.e., seconds in rats and weeks or months in humans) or because of differences in the rewards (i.e., food vs money).

Summary of Preclinical and Clinical Studies

There are discordant findings on the acute effects of drugs on discounting in humans and laboratory animals. Few drugs affect discounting in humans, whereas in laboratory animals drugs have more consistent effects, although the findings depend on strain and dose. As discussed previously, it is likely that methodological differences in human and nonhuman discounting tasks (e.g., time of reward delivery and type of reward) influence the differences in findings across species.

Neurobiological Mechanisms of Impulsive Behavior and Drug Abuse

Recent advances in neurobiological research techniques have improved our understanding of neural mechanisms of impulsive behavior in relation to drug abuse. Preclinical studies have focused on identifying neuroanatomical correlates of task performance, and could provide important information regarding neurobiological mechanisms related to impulsive behavior that might serve as a predictor of drug use. By contrast, clinical studies have examined differences between drug users and non-users in brain activation during task performance, and thus provide initial information regarding correlations between drug use and brain function.

Inhibitory Control: Preclinical Studies

Several strategies have been used to examine the neurobiological regions implicated in stop-signal task performance in laboratory animals: inactivating or lesioning areas of interest, or recording activity in areas of interest. The neurochemical basis of inhibition has also been studied in laboratory animals, but because there is no comparable research method in humans, we do not review these studies. To validate a mouse model of the stop-signal task, one recent study performed excitotoxic lesions of mouse medial prefrontal cortex and reported impaired stopping, as has been reported in earlier research with rats [69]. Two others recorded activation patterns using multiunit cellular recordings to provide localization information. Chen et al. [70] reported activation using intracranial local field potentials in the supplementary motor area (SMA), and Schmidt et al. [71] used multiunit recordings from rats to describe a circuit in which neurons of the subthalamic nucleus respond to stop cues, regardless of whether stopping subsequently occurs. Only activity of cells downstream of the subthalamic nucleus, in the substantia nigra pars reticulate, was reliably coupled to successful stopping.

Inhibitory Control: Clinical Studies

In humans, imaging techniques have investigated brain activation during stop-signal task performance in substance users and non-users. These studies take into account differences in behavioral task performance, because poorer performance on the tasks may explain differences in brain activation. Fortunately, from the point of view of interpreting the results, only two of the studies reviewed below found group differences in task performance [72•, 73]. In general, substance abusers appear to exhibit less prefrontal activation during response inhibition than control subjects, even in the absence of performance differences.

Brain activation during stop-signal task performance is typically studied using fMRI. Li et al. [74] showed that alcohol-dependent individuals had less activation in the dorsolateral prefrontal cortex (DLPFC) during response inhibition on the stop-signal task compared with controls. Similarly, among nontreatment-seeking problem drinkers, alcohol-use severity was associated with less functional connectivity in fronto-striatal networks during the stop-signal task [75]. Among smokers, heaviness of smoking was negatively correlated with PFC activation during response inhibition in adolescents [76], and heavy-smoking adults displayed decreased dorsomedial PFC activation relative to controls [77]. Stimulant-dependent individuals displayed decreased activation in the ventrolateral PFC (VLPFC) during successful inhibitions relative to controls [73], as well as reduced white matter integrity in this region, which was inversely related to SSRT [72•]. Finally, Elton et al. [78] observed reduced activation during response inhibition in cocaine-dependent individuals relative to controls in a frontal-parietal network (including DLPFC, VLPFC and insula) and in a dorsomedial PFC network, as well as negative correlations between activation of these networks and SSRT. Thus, the findings are consistent that drug users, including problem drinkers, smokers, and stimulant users, exhibit less activation in dorsomedial, dorsolateral, and ventrolateral regions of the PFC during response inhibition on the stop-signal task.

Delay Discounting: Preclinical Studies

Several studies have examined performance on a delay discounting task in laboratory animals after lesions or inactivation of specific brain areas. These studies of the neuroanatomical correlates of delay discounting have tended to focus on the orbitofrontal cortex (OFC) because of its role in executive function and possible correspondence to ventromedial PFC (vmPFC) in humans. However, several studies have not found any effect of neurotoxic lesions to or inactivation of the OFC on impulsive choice [79, 80]. This failure may be due to the different roles played by the medial and lateral portions of this region. Mar et al. [81] reported that neurotoxic lesions to OFC cortex increased discounting if lesions were confined to the medial area, but lateral area lesions were associated with the opposite effect (but see also [82] using inactivation techniques). A second region of interest is the nucleus accumbens due to its role in reinforcement and reward processes. However, here too the data are inconsistent between lesion and inactivation studies. Lesions of the nucleus accumbens core increase delay discounting [83, 84]; but also see [82] who temporarily inactivated this region. Finally, a single lesion study of the subthalamic nucleus did not identify a role for this structure [85], while Abela and Chudasama [79] did report that rats with ventral hippocampal lesions showed increased impulsive choice.

Delay Discounting: Clinical Studies

In humans, several recent studies have examined brain activation during delay discounting tasks in drug users compared with nonusers. These studies typically compare patterns of brain activation when subjects opt for the delayed reward versus decisions for the immediate reward. Consistent with the behavioral studies reviewed above, all but one [86] of the fMRI studies reviewed here found that users discounted more steeply than non-users. As noted above, these group differences on task performance must be taken into account when interpreting the findings. Among problem drinkers, individuals with more severe alcohol use disorders discounted more steeply and showed greater activation of several brain regions, including the anterior insula, inferior frontal gyrus, SMA/rostral anterior cingulate cortex (ACC), DLPFC, and precuneus when selecting delayed options relative to immediate options, suggesting functional anomalies and insufficient neural processing underlying impulsive choice in problem drinkers [87, 88]. In smokers, greater activation was observed in the medial PFC and anterior insular cortex when choosing the delayed option relative to the immediate option for money and cigarettes [89]. Meade et al. [86] found that among cocaine-using HIV patients, the increase in activity in fronto-parietal regions (including precentral gyrus, ACC, and right DLPFC, VLPFC, and OFC) was less than that in non-users when making hard decisions compared with easy decisions (although they did not differ in discounting rates). Finally, Camchong et al. [90•] found that cocaine-dependent individuals discounted more steeply and had higher resting functional connectivity within a network comprising the perigenual ACC and frontal and temporal regions (i.e., DLPFC, middle temporal gyrus, and superior frontal gyrus) compared with controls. In sum, these studies confirm earlier reports of greater discounting in substance abusers, and suggest that steeper discounting is associated with increased prefrontal activation when making decisions for delayed rewards.

Summary of Preclinical and Clinical Studies

Taken together, some commonalities in neurobiological findings exist across preclinical and clinical studies. In both preclinical and clinical studies, stop-signal task performance is associated with activity in the prefrontal cortex and SMA. Studies of delay discounting have been less consistent, but there appears to be a role for medial regions of the prefrontal cortex in both humans and laboratory animals. It will be important for future preclinical studies to compare neurobiological correlates of task performance in drug-naïve and non-drug-naïve animals to more directly compare findings across species.

Conclusions and Future Directions

In sum, findings over the last 5 years provide further support for the role of impulsive behavior in drug abuse, both as a determinant and a consequence of use. However, the degree to which impulsivity functions as a predisposing factor to drug abuse and the degree to which it is a result of drug abuse is still not well understood. Regarding the latter, preclinical evidence suggests that delay discounting in drug-naïve animals predicts later drug administration, but longitudinal studies testing this relation in humans are limited. Similarly, there is a growing body of evidence from preclinical studies showing that poor inhibitory control, as measured by the 5-CSRTT, is associated with multiple indices of drug-taking. However, analogs of this task are just now being developed for use in human studies [19, 91, 92], which will enable researchers to assess parallels between preclinical and clinical studies using this task. Regarding impulsive behavior as a result of drug use, there is some evidence that impulsive choice increases after chronic drug administration in animal models [93–97], but as mentioned earlier this is very difficult to study in humans. Evidence showing acute effects of drugs on impulsive behavior likely provides some indirect evidence regarding chronic effects, but it is not known whether acute effects on either impulsive action or impulsive choice bear any relation to changes in behavior after chronic administration of the drug (as in drug abusers). It seems intuitively logical that if acute behavioral impairments are continued over a long period of time they may lead to chronic changes in behavior, but again, longitudinal studies are needed to directly test this hypothesis. Finally, we are just beginning to understand the neurobiological mechanisms underlying impulsivity and drug abuse. Future translational assessments of the neural mechanisms underlying impulsive behavior and drug abuse will likely provide exciting new information and further our understanding of impulsive behavior as both a cause and consequence of drug abuse.

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Table 1

Acute drug effects on stop-signal task performance

Subjects (M:F)	Drug (dose)	Dose	Effect on SSRT	Reference
Preclinical studies				
Lister-hooded rats (n=24)	D-amphetamine	0, 0.3, 1 mg/kg	↓	[59]
Wistar rats (n=16/group)	Morphine	0, 0.3, 1, 3 mg/kg	–	[58]
	Naloxone	0, 0.3, 1, 3 mg/kg	–	
Human studies				
Healthy adults (24:24)	Alcohol	0, 0.4, 0.8 g/kg	↑ (0.8 g/kg)	[60]
Healthy marijuana smokers (88:48)	Marijuana cigarettes	0, 2.8 % THC	↑	[61]
Healthy adults (n=7)	Oxycodone	0, 5, 10, 20 mg	–	[62]

Note. All preclinical studies used males only. *SSRT* Stop signal reaction time, ↑ SSRT increased, ↓ SSRT decreased, – no drug effect.

Table 2

Acute drug effects on delay discounting task performance

Subjects (M:F)	Drug	Dose	Effects on delay discounting	Reference
Preclinical studies				
Wistar rats (n=30)	Amphetamine	0, 0.5 mg/kg	↓	[98•]
Lewis rats (n=8)	Amphetamine	0, 0.1, 0.3, 1.0, 1.7 mg/kg	↓ (dose-related)	[96]
Fischer 344 rats (n=8)	Amphetamine	0, 0.1, 0.3, 1.0, 1.7 mg/kg	↑ (1, 1.7 mg/kg)	[96]
Sprague-Dawley rats (n=24)	Amphetamine	0, 0.032, 0.1, 0.32, 1.0 mg/kg	No systematic effect	[99]
Sprague-Dawley rats (n=8)	Amphetamine	0, 0.1, 0.3, 1.0, 1.8 mg/kg	↓	[100]
Sprague-Dawley rats (n=8)	Amphetamine	0, 0.32, 1.0, 1.78 mg/kg	↑ (1, 1.78 mg/kg; only descending delay order)	[101]
High alcohol preferring 1 mice (15:15)	Amphetamine	0, 0.4, 0.8, 1.2 mg/kg	↓ (dose-related; dependent on length of delay)	[102]
Sprague-Dawley rats (n=16)	Amphetamine	0, 0.1, 0.3, 1.0, 1.7, 3.0 mg/kg	↑ (1, 1.7 mg/kg)	[103]
Sprague-Dawley rats (n=12)	Amphetamine	0, 0.1, 0.32, 0.56, 1.0, 1.78 mg/kg	Dose-related; ↑ (for increasing delays) ↓ (for decreasing delays)	[104]
Spontaneously hypertensive rats (n=8)	Amphetamine	0, 0.1, 0.3, 0.56, 1.0 mg/kg	–	[63]
Wistar Kyoto rats (n=8)	Amphetamine	0, 0.1, 0.3, 0.56, 1.0 mg/kg	–	[63]
Sprague-Dawley rats (n=8)	Amphetamine	0, 0.1, 0.3, 0.56, 1.0 mg/kg	–	[63]
Spontaneously hypertensive rats (n=8)	Methylphenidate	0, 1, 3, 5.6, 10 mg/kg	↓ (0.3 mg/kg)	[105]
Sprague-Dawley rats (n=5)	Methylphenidate	0, 1, 3, 10 mg/kg (d-, l-, dl-isomers)	↓ (dose-related; especially for d- and dl-isomers)	[106]
Sprague-Dawley rats (n=12)	Methylphenidate	0, 1, 3.2, 10, 17.8 mg/kg	Dose-related; ↑ (for increasing delays) ↓ (for decreasing delays)	[104]
Spontaneously hypertensive rats (n=8)	Methylphenidate	0, 1, 3, 5.6, 10 mg/kg	–	[63]
Wistar Kyoto rats (n=8)	Methylphenidate	0, 1, 3, 5.6, 10 mg/kg	↓ (5.6, 10 mg/kg)	[63]
Sprague-Dawley rats (n=8)	Methylphenidate	0, 1, 3, 5.6, 10 mg/kg	–	[63]
Lewis rats (n=8)	Nicotine	0, 0.1, 0.3, 1.0 mg/kg	↓ (0.3 mg/kg)	[107]
Fischer 344 rats (n=8)	Nicotine	0, 0.1, 0.3, 1.0 mg/kg	↓ (1.0 mg/kg)	[107]
Long Evans rats (n=5)	Nicotine	0, 0.8 mg/kg	–	[108]
Long Evans rats (n=5)	Nicotine	0, 1.2 mg/kg	↑	[108]
Fischer 344 rats (n=8)	Diazepam	0, 0.3, 0.56, 1.0, 3.0, 10 mg/kg	↑ (10 mg/kg)	[64]
Rhesus macaque monkeys (n=2; female)	Diazepam	0, 0.1, 0.32, 1.0 mg/kg	–	[109]
Sardinian alcohol-preferring rats (n=8)	Ethanol	0, 0.25, 0.5 g/kg	–	[110]
Sardinian non-alcohol-preferring rats (n=8)	Ethanol	0, 0.25, 0.5 g/kg	–	[110]
Alko alcohol-preferring rats (n=8)	Ethanol	0, 0.25, 0.5 g/kg	–	[110]
Alko non-alcohol-preferring rats (n=8)	Ethanol	0, 0.25, 0.5 g/kg	–	[110]

Subjects (M:F)	Drug	Dose	Effects on delay discounting	Reference
Rhesus macaque monkeys (n=2; female)	Ketamine	0, 0.1, 0.32 mg/kg	↑ (similarly for both doses)	[109]
Sprague-Dawley rats (n=5)	Pentobarbital	0, 1, 3, 10 mg/kg	–	
Sprague-Dawley rats (n=10)	THC	0, 0.32, 1.0, 3.2, 5.6 mg/kg	↑ (dose-related)	[104]
Rhesus-macaque monkeys (n=2, female)	Morphine	0, 0.1, 0.32 mg/kg	↑ (0.32 mg/kg dose)	[109]
Wistar rats (n=16)	Morphine	0, 0.3, 1, 3, 6 mg/kg	↑ (dose-related; especially at 6 mg/kg; negated by 1.0 mg/kg naloxone)	[58]
Sprague-Dawley rats (n=5)	Morphine	0, 0.3, 1, 3, 10 mg/kg	No systematic effect	[106]
Sprague-Dawley rats (n=10)	Morphine	0, 1, 3.2, 5.6, 10 mg/kg	↑ (dose-related)	[104]
High Alcohol Preferring 2 mice (20:20)	Naltrexone	0, 3, 10 mg/kg	–	[102]
Human studies				
Healthy adults (5:1)	Amphetamine (intranasal and oral)	0, 16, 24, 32 mg	–	[67]
Healthy women (n=46)	Alcohol	0, 0.5, 0.75 g/kg	↑	[65]
Healthy adults (13:14)	Alcohol	40 mg/dl, 80 mg/dl	–	[66]
Healthy marijuana smokers (88:48)	Marijuana cigarettes	0, 2.8 %	–	[61]
Healthy adults (6:6)	Oxycodone	0, 5, 10, 20 mg	–	[62]

Note. Preclinical studies used males only unless otherwise noted. ↑ delay discounting increased, ↓ delay discounting decreased, – no drug effect.