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ORIGINAL INVESTIGATION

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Mild opioid deprivation increases the degree that opioid-dependent outpatients discount delayed heroin and money

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Abstract *Rationale:* A growing literature suggests that excessive temporal discounting of delayed rewards may be a contributing factor in the etiology of substance abuse problems. Little is known, however, about how drug deprivation may affect temporal discounting of delayed rewards by drug-dependent individuals. *Objective:* To examine the extent to which opioid deprivation affects how opioid-dependent individuals discount small, medium and large quantities of delayed heroin and money. *Methods:* Thirteen opioid-dependent individuals maintained on buprenorphine completed a hypothetical choice task in which they choose between a constant delayed reward amount and an immediate reward amount that was adjusted until they expressed indifference between both outcomes. The task was completed for three values of heroin and money rewards during eight sessions under conditions of opioid deprivation (four sessions) and satiation (four sessions). *Results:* Across conditions, hyperbolic functions provided a good fit for the discounting data. Degree of discounting was significantly higher when subjects were opioid deprived. Consistent with previous findings, degree of discounting was higher for heroin than money and inversely related to the magnitude of the reward. *Conclusion:* Opioid deprivation increased the degree to which dependent individuals discounted delayed heroin and money. Understanding the conditions that affect how drug-dependent individuals discount delayed rewards might help us understand the myopic choices made by such individuals and help improve treatment outcomes.

Keywords Delay discounting · Heroin addicts · Opioid withdrawal · Opioid satiation

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Introduction

Perhaps one of most pervasive paradoxes in the substance abuse field is that many individuals who *voluntarily* participate in outpatient treatment programs continue abusing drugs while in treatment (e.g. Magura et al. 1998; Best et al. 1999; Preston et al. 2000; Sees et al. 2000). Although such participants have declared a preference for not using by *voluntarily* entering treatment, they choose to continue using rather than remain abstinent. One factor that may contribute to this preference reversal is temporal discounting of delayed consequences (Rachlin and Green 1972). Drug-dependent individuals might make "self-controlled" choices during a counseling session by stating that they prefer to remain abstinent, when both the opportunity to use drugs and the positive consequences of abstinence are delayed. That same individual, however, might subsequently act "impulsively" by choosing to use drugs later that same day because the drugs are immediately available and the benefits of abstinence remain delayed and diffuse.

Indeed, a rapidly growing literature indicates that individuals with substance dependencies might be generally more susceptible to behavioral problems that may stem from diminished sensitivity to delayed outcomes (Bickel and Marsh 2001). For example, individuals dependent on cigarettes or opioids and problem drinkers discount delayed rewards to a greater degree than matched non-drug-using controls (Madden et al. 1997,

1999; Vuchinich and Simpson 1998; Bickel et al. 1999b; Kirby et al. 1999). Second, the degree of discounting differs depending on the type of reward, or commodity presented. Drug-dependent individuals discount the drugs they are dependent on more rapidly than non-drug rewards such as money (Vuchinich and Simpson 1998; Bickel et al. 1999b; Kirby et al. 1999; Madden et al. 1999). Finally, degree of risk-proneness may co-vary with degree of discounting of delayed consequences. Drug-dependent individuals with gambling problems, or who reported they would share needles, discount delayed rewards to a greater degree than do drug-dependent individuals without such co-morbid problems (Petry and Casarella 1999; Odum et al. 2000). Together, these studies indicate that drug-dependent individuals are controlled to a greater extent by smaller more immediate consequences at the expense of larger more delayed consequences.

The shape of delay discounting curves has been empirically demonstrated to be hyperbolic. That is, devaluation of delayed rewards is roughly proportional to their delay (Mazur 1987; Ainslie 1992). For each incremental increase in delay to delivery, the reward's present value decreases by an increasingly smaller proportion (Kirby 1997). The following quantitative model of delay discounting was introduced by Mazur (1987):

$$\underline{V} = \underline{A}/(1 + \underline{kD}) \quad (1)$$

In Eqn 1, V is the present discounted value of a delayed reward (i.e. point of indifference between the immediate and delayed reward), A is the amount of the delayed reward, k is an empirically estimated constant that is proportional to the degree of discounting, and D is the duration of delay. Equation 1 has been found to provide an accurate representation of discounting of food and water by non-humans (e.g. Mazur 1987; Rodriguez and Logue 1988; Richards et al. 1997), of real and hypothetical money amounts by human subjects (e.g. Rachlin et al. 1991; Green et al. 1994a; Myerson and Green 1995; Kirby 1997), of hypothetical drug amounts in human subjects (Madden et al. 1997; Bickel et al. 1999b; Kirby et al. 1999) and or real monetary amounts in current and never smokers (Baker et al. 2002).

The empirically derived parameter k in Eqn 1 provides a useful index of sensitivity to delayed consequences; k varies proportionally with degree of discounting. That is, the larger the value of k, the lower the discounted value (V), for any given reward (A) at any given delay (D). Thus, derived k values provide a basis for comparison of degree of discounting across conditions or subjects.

Another factor that may contribute to an increase in the likelihood of relapse to drug use among abstinent drug users is drug deprivation. The positive reinforcing effects of drugs play a critical role in initiating drug self-administration behavior; however, once an individual becomes drug-dependent, negative reinforcement plays a role in the maintenance of drug use by attenuating the aversive withdrawal symptoms associated with abstinence (Koob 2000). An extensive animal literature indicates that relative to drug satiation, drug deprivation increases responding for drug (Heyser et al. 1997; Stafford et al. 1998), consumption of drug (Heyne and Wolffgramm 1998; Spangel and Hotler 1999) and preference for drug (Holter et al. 1998; Cowen et al. 1999). Similar findings have been observed in human subjects (e.g. Epstein et al. 1991; Willner et al. 1995; Madden and Bickel 1999). Together, these studies suggest that drug deprivation increased the value (i.e. responding for and consumption of) the drug of dependence in animal and human subjects. The effect of drug deprivation on the discounting of delayed rewards, however, has not been studied in any population of drug-dependent individuals. The current study was designed to fill this gap in the scientific literature by examining how opioid deprivation influences the degree that opioid-dependent individuals discount delayed rewards. There is good reason to think that drug deprivation may increase the degree of delay discounting. In general, people who are hungry, thirsty, or otherwise deprived tend to exhibit impulsivity, indeed, sometimes extreme levels, toward the type of reward they are deprived of (Loewenstein 1996). For example, when an organism is water deprived, providing access to gallons of water after a 5-year delay is unlikely to control as much behavior as providing access to 8 ounces of water immediately. Under such conditions the efficacy of delayed water to act as a reinforcer would pale compared to that of immediately available water. Previous research suggests that drug-related deprivation exerts a potent impact on impulsivity (Loewenstein 1999).

In the current study, opioid deprivation was manipulated with a less than daily buprenorphine (i.e. a partial μ opioid agonist used to treat opioid dependence) dosing schedule in which subjects completed the set of six discounting measures 5 days after they received five buprenorphine maintenance doses simultaneously (e.g. a quintuple dose). Research at our clinic has demonstrated that opioid-dependent outpatients can be comfortably maintained on a less than daily dosing schedule by administering multiple maintenance doses of buprenorphine simultaneously. For example, administering two maintenance doses (a double dose) of buprenorphine at once prevents opioid withdrawal symptoms for 48 h. Administering up to four maintenance doses (a quadruple dose) of buprenorphine at once prevents withdrawal for up to 96 h (Petry et al. 2000). However, administering five maintenance doses (a quintuple dose) of buprenorphine at once does not prevent withdrawal symptoms beyond 4 days. That is, by day 5 after receiving a quintuple dose, subjects experience mild opioid withdrawal symptoms (Bickel et al. 1999a; Gross et al. 2001; Petry et al. 2000). A quintuple dosing procedure was used to establish mild opioid deprivation in the current study. For example, subjects received five maintenance doses of buprenorphine, then 5 days later, when subjects were mildly opioid deprived, they completed a set of six delay discounting measures. Note, subjects were required to remain abstinent from opioids throughout this study. In

opioid satiated conditions, subjects completed the set of six delay discounting measures 2 h after receiving buprenorphine. Buprenorphine peak effects (i.e. opioid satiation) occur within 60–120 min after dosing (Bickel and Amass 1995).

The present study assessed how opioid deprivation (e.g. deprived and satiated) affect discounting of small ($1000), medium ($3000) and large ($10,000) magnitudes of delayed money and individually yoked amounts of heroin in opioid-dependent outpatients maintained on buprenorphine. By assessing the delay discounting of multiple reward magnitudes, this study is designed to replicate the previous studies that showed magnitude affects discounting in drug-dependent individuals. Previous research suggests that larger magnitude delayed rewards are discounted to a lesser degree than smaller magnitude rewards among drug-dependent individuals (Kirby et al. 1999), consistent with numerous studies documenting a similar "magnitude effect" (Loewenstein and Prelec 1992; Green et al. 1997) with money and other rewards (see Frederick et al. 2002, for a review of magnitude effects and a wide range of other anomalous discounting phenomena in humans).

This study might provide valuable information on how the choices of opioid-dependent individuals are controlled more by immediate consequences and how deprivation increases the control exerted by immediate consequences. Specifically, this study sought to answer two empirical questions: (1) does opioid deprivation increase opioid-dependent individuals' discounting of delayed heroin and money rewards relative to opioid satiation? (2) Are small magnitude rewards discounted more rapidly than medium and large magnitude rewards? We also sought to replicate the previous finding that drug rewards are discounted to a higher degree than money rewards.

Materials and methods

Subjects

Thirteen subjects (eight male and five female), mean age =37.5 years (SD=7.6 years) who met DSM-IV criteria for opioid dependence and FDA criteria for methadone maintenance, completed the study. Subjects reported an average of 11.9 years of opioid dependence (SD=8.7 years), used an average of five bags of heroin intravenously per day (SD=3.4 bags). At intake, all subjects reported having shared needles at some point in the past. The procedures were reviewed and approved by the University of Vermont's Institutional Review Board and all subjects provided written informed consent prior to participation in the research study after receiving a full explanation of the procedures. Another 13 subjects (seven male and six female) either dropped out after intake, or were discontinued from participation in this study for failing to comply with opioid abstinence requirements (see below). The incomplete delay discounting data from these subjects were excluded from analyses to maintain the integrity of the deprivation manipulation. However, separate independent *t*-tests revealed dropouts' age (mean=34.61 years; SD=7.63; P=0.36, ns), duration of self-reported heroin dependence (mean=12.15 years; SD=8.05; P=0.93, ns), and amount of heroin used daily (mean=7.14 bags; SD=6.78 bags; P=0.15, ns) were not significantly different from the subjects whose data are presented below. All discontinued subjects reported that they used heroin intravenously, and have shared needles. Since these subjects either dropped out before the first session, or were opioid positive for the first two sessions, we were unable to collect, or analyze their delay discounting data. However, since the baseline characteristics of discontinued subjects were not significantly different from subjects who completed this study, it is unlikely their discounting data would have been different from study completers.

Procedures

General

Following dose induction and stabilization, subjects completed a set of six delay discounting measures in eight separate sessions, over 8 weeks (e.g. two sessions during each 2-week cycle). Each set comprised six discounting measures for small, medium, and large magnitudes of heroin and money. Four sets of six discounting measures were collected when the subject was opioid deprived (i.e. he or she made choices after and prior to receiving buprenorphine) 5 days after receiving a quintuple buprenorphine dose. The remaining four sets of six discounting measures were collected when the subject was opioid satiated (i.e. he or she made choices 2 h after receiving buprenorphine). Subjects were required to abstain from illicit opioid use throughout their participation. To ensure compliance, subjects provided urine samples under observation, which were screened for the presence of opioids on days when they were scheduled to receive buprenorphine.

Attendance/urinalysis screening

Participation in this study was contingent on subjects submitting opioid negative urine samples and attending all scheduled clinic visits. If a subject submitted an opioid positive urine sample, their participation in this study was temporary discontinued. Any data collected on that day were omitted from analyses. Subjects resumed participation in the study the next time they submitted an opioid-negative urine sample. If an individual missed a scheduled clinic visit, they risked having their participation in the study discontinued. Subjects who tested positive for opioids on any two occasions had their participation in the study discontinued and they were offered a buprenorphine detoxification.

During the dose induction and stabilization period, urinalyses were conducted three times per week (Mondays, Wednesdays, and Fridays). Subsequently, urinalyses were conducted at every clinic visit (2–3 times per week). Urine samples were collected and analyzed immediately onsite for the presence of opioids (opiates, methadone, and propoxyphene) using the Enzyme Multiplied Immunoassay Technique (Sylva Corp., San Jose, Calif., USA). Samples were also analyzed for the presence of benzodiazepines, and cocaine on one randomly selected scheduled urinalysis day each week.

Buprenorphine administration

Only subjects who were eligible to receive a daily maintenance dose of 4 mg/70 kg (n=2) or 8 mg/70 kg (n=11) participated. Buprenorphine doses were determined according to procedures successfully used and previously described in the literature (Johnson et al. 1989; Bickel and Amass 1995). Each subject's maintenance dose was determined during the first week of participation. Subjects were initially placed on a 2 mg/70 kg dose on day 1 and 4 mg/70 kg on day 2. If observable withdrawal symptoms were evident on days 3 through 7, the dose was increased to 8 mg/70 kg.

Buprenorphine hydrochloride was prepared as a stock concentration of 20 mg/ml in 35% ethanol (vol/vol) for sublingual administration. Stock solutions containing 2, 4, 8, 12, and 16 mg/ml in 35% ethanol (vol/vol) were prepared from serial dilutions of the

Table 1 Overview of dosing schedule and delay discounting assessments during the 8-week period of delay discounting assessment cycles. The set of six delay discounting (*DD*) measures assessed on each of eight occasions: four when opioid deprived, four when opioid satiated. Sessions were held 5 days after a quintuple buprenorphine dose. In sessions, subjects completed DD measures when opioid satiated (e.g. 2 h after receiving buprenorphine on the session day), when opioid deprived (e.g. prior to receiving buprenorphine on the session day). The order of presenting deprived and satiated conditions was randomly assigned within subject. Small, medium and large numbers of heroin bags were individually yoked to money amounts by asking each subject how many bags he or she could purchase for $1000, $3000 or $10,000

Cycle day	Dose	Timing of dose	
		Opioid satiated	Opioid deprived
Day 0	Quintuple	NA	NA
Day 5	Quintuple	2 h before first set DD assessments	After first set DD assessments
Day 10	Maintenance	2 h before second set DD assessments	After second set DD assessments
Day 11	Double	NA	NA
Day 13	Double	NA	NA
Day 15/0	Repeat cycle	NA	NA

20 mg/ml stock concentration. Individual doses were prepared as daily maintenance doses in a constant volume for each subject. Medications were administered with Ped-Pod Oral Suspensors (SoloPak Laboratories, Frankling Park, Ill., USA). Each dose was held under the tongue for a period of 5 min without speaking. Under less-than-daily dosing conditions, subjects were administered multiple doses (i.e. one daily maintenance dose for each day of the inter-dosing interval). For example, under quintuple dosing, five daily maintenance doses were administered sequentially over a period of 25 min.

Laboratory dose run-up session

Prior to participation in the study, all subjects were administered the highest dose of buprenorphine in the clinic, under medical observation to ensure safely of the quintuple dose. Thus, only those subjects who safely tolerated quintuple their daily maintenance dose of buprenorphine were allowed to participate in this study.

Buprenorphine dosing schedule

Participation commenced on the first Monday after subjects completed the laboratory run-up session. During the first week, subjects were administered one maintenance dose daily. Subsequently, subjects were dosed according to the 14-day dosing cycle, described below, during the 8-week period when delay discounting measures were collected (see Table 1). During each 14-day cycle, subjects participated in two sessions in which they completed a set of six delay discounting measures. On day 0, subjects received a quintuple dose of buprenorphine. On day 5, subjects completed the first set of six discounting measures and received another quintuple dose. On day 10, subjects completed the second set of six discounting measures and received a maintenance dose. Thus, quintuple dosing and a 5-day period proceeded every occasion when subjects completed a set of discounting measures. On days 11 and 13, subjects received double doses before repeating the 14-day cycle. The additional alternate-day dosing on days 11 and 13 was necessary to synchronize the cycle of completing discounting measures with a 5-day workweek. Subjects completed four, 2-week buprenorphine dosing cycles over an 8-week period.

During the 8-week period, subjects participated in eight sessions where delay discounting measures were collected. A set of six delay discounting measures was collected in each session. Therefore, each subject completed eight sets of six discounting measures (i.e. each set comprised of small, medium, and large magnitudes of heroin and money commodities). Four sets of discounting measures were completed when the subject was opioid deprived and four were completed when the subject was opioid satiated. In sessions when discounting measures were collected under opioid deprived conditions, subjects arrived, waited 2 h, completed the discounting assessments, received their buprenorphine dose and then they were released. Under opioid satiated conditions, subjects arrived, received their buprenorphine dose, completed the discounting assessments and then they were released (see Table 1). The sequence of opioid deprived and opioid satiated conditions was randomized for each subject.

Dependent measures and data analysis

Delay discounting

Subjects chose between immediate and delayed rewards to assess the effects of delay on the discounting of three hypothetical heroin and three hypothetical monetary rewards on eight occasions. Table 1 shows the buprenorphine dosing schedule and the set of six discounting measures that were assessed on eight occasions. To assess delay discounting, subjects were presented with a standard stimulus and an adjusting stimulus. The magnitude of the adjusting stimulus was varied until the subject rated the two stimuli as subjectively equivalent. For example, subjects were asked to choose between a standard delayed reward (e.g. $1000 delivered in 1 year) and an immediate reward. We adjusted the magnitude of the immediate reward until the subject rated the two rewards as subjectively equivalent. The point where the subject rated the delayed and immediate rewards as equivalent was defined as the indifference point for that particular delay interval. Identifying indifference points for several delays permits an indifference curve to be plotted that shows how reward value varies as a function of delay.

Subjects were presented with a series of 27 choices between an immediate reward that was adjusted and a delayed reward that was fixed. The value of the immediate reward decreased across choices and ranged from 100% to 0.1% of the delayed reward (actual values=100%, 99%, 96%, 92%, 85%, 80%, 75%, 70%, 65%, 60%, 55%, 50%, 45%, 40%, 35%, 30%, 25%, 20%, 15%, 10%, 8%, 6%, 4%, 2%, 1%, 0.5%, and 0.1%). Indifference points for each of the six hypothetical rewards were determined at seven delays (1 week, 2 weeks, 1 month, 6 months, 1 year, 5 years, and 25 years).

Each set of six discounting measures including three magnitudes of each reward type was completed in each of the eight sessions that discounting measures were collected. Small ($1000), medium ($3000), and large ($10,000) dollar amounts were the same for each subject. Heroin amounts were yoked to the monetary amounts based on the number of heroin bags each subject estimated he or she could purchase for $1000. For example, some subjects indicated that they could purchase 100 bags of heroin for $1000, while others indicated they could purchase 30 bags of heroin for $1000. The numbers of bags corresponding to the $3000 and $10,000 amounts was calculated by multiplying the number of bags the subject indicated that he or she could buy for $1000 by three and 10, respectively. For example, if a subject indicated he could

purchase 30 bags of heroin for $1000, we calculated that he could purchase 90 bags for $3000 and 300 bags for $10,000. The subjective value of each of the six rewards was individually assessed at each of the seven delays. For each combination of reward type, magnitude, and delay, subjects made 27 discrete choices between descending immediate amounts of the reward and a fixed delayed amount of the reward. The 27 choices were printed on an 8.5×11 inch sheet of paper. For each choice, the subjects were instructed to state whether they preferred the immediate amount or the delayed amount of each item. Subjects were asked to make their choices as they would either before coming into treatment, or when they were actively using opioids.

Within each subject and treatment condition, non-linear regression (SAS, PROC NLIN) was used to fit the hyperbolic discounting function (Eqn 1) to data corresponding to the seven indifference points obtained at the seven delays. This resulted in estimates of each subject's discounting parameter (k) for each treatment condition. Because the distribution of estimated k parameters tends to be non-normal and subject to outliers, a nonparametric repeated measures analysis of variance based on ranks was used to test for differences in estimated k parameters across treatment conditions. This non-parametric analysis is a generalized version of Friedman's Rank test applied to data with a 2×2×3 factorial structure, i.e. deprivation level (satiated and deprived), commodity (heroin and money) and magnitudes (small, medium, and large). Median k-parameters for each condition are presented as a representative measure of central tendency.

Observer and subject ratings of opioid agonist and withdrawal effects

In addition to examining delay discounting, pupil radius assessments (i.e. an objective, physiologic index of opioid agonist/withdrawal effects) and subjective reports of opioid agonist and withdrawal symptoms were completed at the beginning, middle, and end of each clinic visit. The opioid agonist assessment consisted of a five item (e.g. high, drug effect, good effect, bad effect, and like) visual analogue scale that subjects responded to along a 100 mm line from none (0) to severe (100). The opioid withdrawal symptoms assessment consisted of 15 items (muscle cramps, painful joints, yawning, hot/cold flashes, upset stomach, irritable, runny nose, sweating, restless, watery eyes, abdominal cramps, chills/gooseflesh, backache, bothered by noises, skin clammy and damp, nausea), which subjects responded to on a 10-point Likert scale from none (0) to severe (9). Mean scores were calculated for each measure (e.g. pupil radius, opioid agonist, opioid withdrawal) across subjects, within condition (e.g. deprived and satiated). A repeated measure ANOVA was used to determine whether these mean scores on each measure differed between satiated and deprived conditions.

Results

The hyperbolic discounting function provided appropriate fit to subjects discounting of both commodities (median R^2=0.89 and 0.91 for money and heroin, respectively). The first empirical question of interest is whether opioid deprivation increased delay discounting. Figure 1 shows that subjects discounted both heroin (squares) and money (circles) significantly more rapidly when they were opioid deprived (open symbols) compared to when opioid satiated (filled symbols) at each magnitude [$F(1,132)=26.16$, $P<0.001$]. There was no evidence that the difference in discounting between deprived and satiated conditions was dependent on commodity or magnitude ($P>0.70$ for all interactions).

The second empirical question of interest is whether discounting was inversely related to reward magnitude. Figure 2 reveals that median discounting parameters were

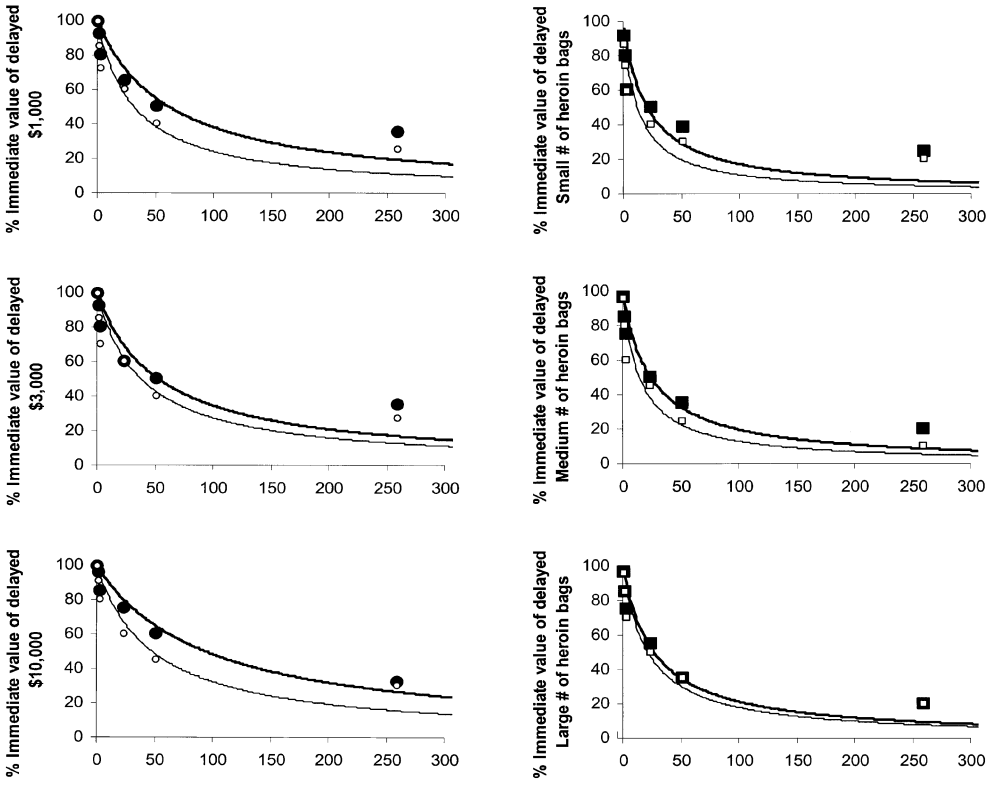

Fig. 1 Indifference curves averaged across subjects under opioid deprived (*open symbols*) and opioid satiated (*filled symbols*) conditions, for small (*top*), medium (*middle*), large (*bottom*) magnitudes of money (*circles: left three plots*) and heroin (*squares: right three plots*). Note, the *x*-axis represents 1, 2, 4, 26, 52, 260-week delays. Since the hyperbolic curves were well defined through the 260-week delay, the hyperbolic function systematically overestimated the degree of discounting at the 1300-week delay (e.g. 25 years), we have omitted the 25-year delay from each subplot to better display the observed differences between conditions at the shorter delays, which play a major role in defining the derived hyperbolic function

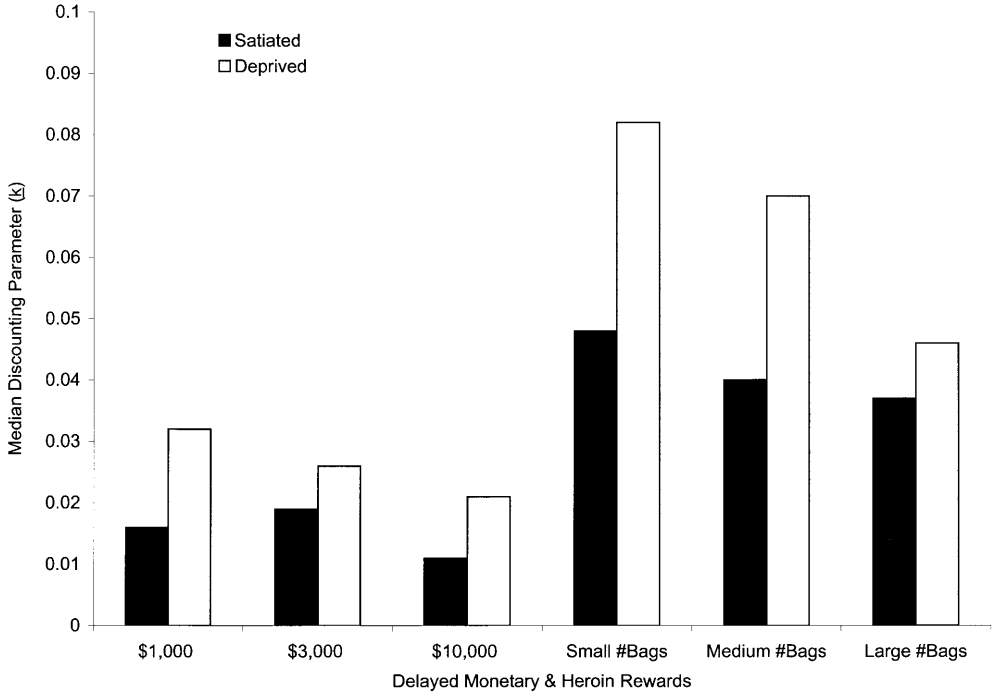

Fig. 2 Median delay discounting rate (k parameters) under opioid satiated (*filled bars*) and opioid deprived (*open bars*) conditions, for $1000, $3000 and $10,000 (*left*), small (MDN=100 bags), medium (MDN=300), large (MDN=1000 bags) quantities of heroin (*right*), which were individually yoked to monetary amounts

significantly different among low, medium and high magnitudes rewards [$F(2,132)=7.67$, $P<0.001$). Pairwise comparisons based on Fisher's Least Significance Difference (LSD) revealed that median discounting parameters for low and medium magnitudes were each significantly higher than large magnitudes ($P<0.05$); however, median discounting parameters at low and medium magnitudes were not significantly different from each other. Though the magnitude effect was somewhat more evident under the deprived state, there was no evidence of an interaction between magnitude and state ($P=0.83$) or between magnitude and commodity ($P=0.72$).

We also sought to replicate the previous finding that delayed heroin is discounted to a higher degree than money. Figures 1 and 2 reveal that delayed heroin was discounted significantly more rapidly than money under both the satiated and deprived conditions [$F(1,132)=104.22$, $P<0.0001$).

Analyses of within-session opioid agonist ratings, opioid withdrawal ratings and pupil radius revealed differences that were consistent with opioid deprived and satiated conditions. Opioid withdrawal ratings at the time of discounting assessments were significantly increased [$F(1,12)=7.02$, $P=0.02$] when subjects were opioid deprived (mean=3.6, SD=1.8) versus satiated (mean=2.4, SD=0.9). Pupil radius were significantly increased [$F(1,12)=76.5$, $P<0.001$] when subjects were opioid deprived (mean=5.8, SD=0.7) versus satiated (mean=5.0, SD=0.7). Opioid agonist ratings were significantly increased [$F(1,12)=10.6$, $P=0.007$] when subjects were opioid satiated (mean=1.4, SD=1.3) versus deprived (mean=0.9, SD=1.1).

Discussion

Opioid deprivation increased the degree that opioid-dependent subjects discount three magnitudes of delayed heroin and of money in a within-subjects experimental design. The results showed, first, that opioid-dependent adults discounted delayed rewards to a greater degree when opioid deprived compared to when they were opioid satiated. Second, degree of discounting was highest for small and medium magnitudes of delayed rewards, relative to large magnitudes. Finally, we replicated previous findings and showed that delayed heroin was discounted to a greater degree than delayed money. The findings and related issues that might influence their interpretation will be discussed.

When opioid-dependent adults were opioid deprived, they discounted delayed heroin and monetary rewards to a greater degree compared to when they were opioid satiated. To our knowledge this is the first study to show that drug deprivation increases discounting of delayed rewards in any drug-using population. These results extend previous research that showed opioid-dependent outpatients discounted monetary rewards more rapidly than matched non-drug using controls when using hypothetical rewards (Madden et al. 1997), and real rewards (Kirby et al. 1999). Although drug dependence status influenced delay discounting in these earlier studies, those studies could not determine why drug-dependence increased discounting. Our results indicate that drug-deprivation may be one factor that contributes to increased delay discounting among opioid-dependent adults. These results are consistent with, and extend previous research that showed increased self-control for food in humans who were food satiated (Kirk et al. 1997).

In that study, 14 adult, female college students were food deprived for 4 h. When food satiated, subjects showed significantly more self-control for food (chose a larger magnitude, delayed access to apple juice over a smaller magnitude, more immediate access) than when they were food deprived prior to self-control testing. The current results extend previous research by comparing discounting of three magnitudes of drug and non-drug rewards within subject, when opioid-dependent adults were opioid deprived and satiated.

Subjects discounted small and medium magnitudes significantly more rapidly than large magnitude delayed rewards. This finding is consistent with other reports that showed reward magnitude was inversely related to discounting rates (Thaler 1981; Benzion et al. 1989; Raneri and Rachlin 1993; Green and Myerson 1994; Green et al. 1994a, 1994b; Kirby and Marakovic 1995, 1996; Kirby et al. 1999; Petry and Casarella 1999; Johnson and Bickel 2002). The finding in the current study that small and medium magnitudes were not discounted significantly different from one another might stem from choosing a medium magnitude that was too close to the small magnitude (e.g. $1000 and $3000). Nevertheless, the present study extends previous findings of a magnitude effect between small and large amounts across two commodities and two levels of deprivation within-subjects.

Subjects discounted delayed heroin significantly more rapidly than delayed money. This finding supports previous research showing that among drug-dependent individuals, the drug of dependence is discounted more rapidly than non-drug rewards delayed in time (Bickel et al. 1999b; Madden et al. 1997, 1999; Odum et al. 2000). For example, Madden and colleagues (1999) found that opioid-dependent subjects discounted $1000 by 50% at the 52-week delay, whereas a matched amount of heroin was discounted by 50% at the 1-week delay. The present study showed similar findings. In the opioid satiated condition, opioid-dependent subjects discounted $1000 by 50% at the 62-week delay, whereas a matched amount of heroin was discounted by 50% at the 21-week delay. In the opioid deprived condition, $1000 was discounted by 50% at the 33-week delay, whereas a matched amount of heroin was discounted by 50% at the 12-week delay. Similarly, heroin was discounted more rapidly than money at medium ($3000) and large ($10,000) magnitudes. Although, relative to opioid satiation, opioid deprivation increased the degree that subjects discounted delayed drug and non-drug commodities, there was no evidence of an interaction between commodity or deprivation level. These findings are consistent with the observation of operant behavior theory that an immediate reinforcer is more effective than a reinforcer delivered after a delay. For example, the results of the present study suggest that opioid deprivation may have served as an establishing operation that functionally decreased the reinforcing value of delayed rewards and thereby increased the reinforcing effectiveness of *immediate* reinforcers. Delay discounting holds that the subjective value of delayed rewards is decreased as a function of delay interval. That is, as the delay to reward delivery increases, the subjective value of the delayed reward decreases along with its capacity to motivate behavior. With sufficient discounting of the subjective value of delayed rewards, preference shifts in favor of smaller, more immediate rewards (Kagel et al. 1986).

One compelling finding of the present study was that opioid deprivation increased the discounting of delayed money. One interpretation of these results is that drug deprivation makes drug-dependent individuals generally less sensitive to delayed outcomes. Another possible interpretation of this finding is that money served as a proxy or economic substitute for heroin. For example, subjects might have calculated the quantity of heroin they could purchase while completing the discounting task for money. However, the commodity effect observed in the current and previous studies does not support a proxy interpretation. That is, degree of discounting for heroin and money should be equal if subjects used money as a proxy for heroin; however, heroin was discounted two to three times more rapidly than money. The proxy interpretation could be retained, only if money were an imperfect, or partial, substitute for heroin. Support for this hypothesis, however, is contingent upon additional research investigating temporal discounting of qualitatively different reinforcers under varied motivational conditions.

Animal research on the acute effects of alcohol administration on delay discounting demonstrated that rats became less impulsive after (1) acute non-disruptive doses of pre-session methamphetamine (METH), whereas they became more impulsive after (2) repeated acute behaviorally disruptive doses of METH administered post-session (Richards et al. 1999a). Previous human research with healthy adult volunteers found that a moderate acute dose of ethanol that was administered pre-session had no effect on discounting (Richards et al. 1999a). However, the Richards et al. study did not concurrently assess the effects of acute alcohol administration in alcohol-dependent and non-dependent adults. The results of the current study provide novel information on the effects of opioid satiation (e.g. acute drug administration) and deprivation in an opioid-dependent population. We might postulate that drug dependence may be an establishing operation for acute drug administration to influence delay discounting. However, additional research is needed to disentangle the separate and combined effects of dependence status and acute drug administration on delay discounting.

Although we demonstrated differences in delay discounting between deprived and satiated conditions, small and large magnitude rewards, and between heroin and monetary rewards, a potential criticism of the current findings is that all choices were made between hypothetical rewards. However, recent research suggests that choices, which involved hypothetical and real rewards, produced similar delay discounting functions (Baker, Johnson, and Bickel, unpublished data; Johnson and Bickel 2002). Importantly, these studies show no differ-

ences in delay discounting were observed between real and hypothetical monetary commodities. Therefore, the delay discounting data obtained in the current study using hypothetical rewards would likely not differ if we used real rewards. Moreover, using hypothetical rewards is an ethical means of assessing delay discounting for illicit drug commodities among opioid-dependent individuals.

The findings of the current study have important clinical implications. Namely, interventions for opioid dependence should provide alternative reinforcers that are both immediate and sufficiently large enough to compete effectively with the reinforcement clients derive from drugs when they are drug-deprived. The myopic temporal horizon of opioid-dependent individuals radically reduces the value of delayed rewards, making the immediate reward the most highly valued reward with the greatest influence on behavior. For example, interventions such as contingency management might improve treatment outcomes by providing immediate, tangible consequences for abstinence (Bickel et al. 1997; Gross et al. 2002). Similarly, 12-step approaches, and other addiction counseling strategies, typically provide immediate social reinforcement for abstinence, and withhold praise during periods of relapse.

In this study, we found that opioid deprivation increased the degree that opioid-dependent adults discounted delayed rewards. This novel finding might help explain why opioid-dependent individuals are more likely to engage in risky behaviors when they experience opioid withdrawal symptoms. For example, the results might explain why drug-dependent individuals make impulsive choices when experiencing withdrawal, such as buying heroin with the rent money, engaging in risky sex in exchange for money, or sharing needles with others. Determining the environmental factors that cause drug-dependent individuals to make "short-sighted" choices is an important step in developing more effective interventions for this difficult-to-treat population. Research shows that interventions for opioid-dependence that provide incentives for abstinence, such as contingency management, yield promising outcomes.

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