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ORIGINAL INVESTIGATION

Impulsivity as a behavioral measure of withdrawal of orally delivered PCP and nondrug rewards in male and female monkeys

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Abstract
Background Withdrawal of phencyclidine (PCP), ethanol (ETOH), and other drugs reduces operant responding maintained by food.
Objectives Experiment 1 examined the effects of withdrawing daily short access (2 h) to drug on impulsivity for saccharin (SACC) using a delay discounting task and comparing male and female rhesus monkeys. Experiment 2 examined the effects of withdrawing a nondrug substance (e.g., food or SACC) on impulsivity for PCP.
Materials and methods In experiment 1, either PCP or ETOH was available daily with water for 2 h under a fixed ratio 16 (FR 16) or FR 8 schedule, respectively. In a second component, SACC was available for 45 min under a delay discounting schedule. Next, water was substituted, and drug access was then restored. In experiment 2, PCP was available under a delay discounting schedule during food satiation or restriction or during concurrent SACC vs water access.
Results In experiment 1, withdrawal of 0.5 mg/ml PCP increased impulsivity for SACC, but not SACC intake, in males and females. During 16% ETOH access, impulsivity for SACC was elevated compared to baseline water access, and it returned to baseline levels during ETOH withdrawal. In experiment 2, food restriction resulted in increased PCP intake in males and females and increases in impulsivity for PCP that were greater in males than in females. SACC withdrawal had no effect on impulsivity for PCP or PCP intake.
Conclusions Withdrawal of PCP and reduced food access increased impulsivity for SACC or PCP, respectively. Impulsivity is a sensitive indicator of drug dependence.

Keywords Delay discounting · Food restriction · Food satiation · Ethanol · Impulsivity · Phencyclidine (PCP) · Rhesus monkeys · Saccharin · Sex · Withdrawal

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Introduction

Physical dependence on a drug is inferred by withdrawal signs and symptoms in substance-using individuals, and this is an important component of the addiction process, as relapse may be driven by withdrawal-associated effects. Physical dependence on self-administered drugs has been modeled in preclinical research by establishing self-administration and then removing drug access and measuring disruptions in operant responding reinforced by food or other nondrug rewards in rats (e.g., Barr and Phillips 1999; Corrigall et al. 1989; LeSage et al. 2006) and monkeys (Carroll 1987; Carroll and Carmona 1991; Perry et al. 2006). Disruption in behavior maintained by nondrug substances occurred during withdrawal from several drugs (e.g., amphetamine, nicotine, phencyclidine (PCP)) and after short access to the drug when no other physical signs of drug withdrawal were apparent (e.g., Carroll 1987; Carroll and Carmona 1991; Perry et al. 2006). The term withdrawal is used here to refer to the procedure of removing drug access and the mild behavioral disruptions that may represent a subtle form of physical dependence. This contrasts with

more traditional discussions of dependence in which chronic access to the drug is terminated and physiological signs and symptoms are subsequently measured (see review by Lyvers 1998). The main objective of the present research was to determine whether impulsive behavior for a nondrug substance would be increased after withdrawal from short-access (2 h) daily drug self-administration.

The goal of experiment 1 was to examine the effect of PCP or ethanol (ETOH) withdrawal on impulsive behavior under a delay discounting task maintained by a palatable saccharin (SACC) solution. This task involved a choice between a small immediate vs a large delayed SACC reward. A resulting impulsive choice has been compared to motor impulsivity (impaired inhibition) measured by the STOP, go/no-go, or five-choice serial reaction time (5-CSRT) tasks (Diergaarde et al. 2008; Evenden 1999; Robbins 2002; Robinson et al. 2009). Increased impulsive choice was reported in rats after termination of chronic treatment with cocaine (Simon et al. 2007) and nicotine (Dallery and Locey 2005; Counotte et al. 2009), and an increase in motor impulsivity on a 5-CSRT task for food was found during acute (1 or 4 days) but not chronic (13 days) withdrawal from cocaine self-administration (Winstanley et al. 2009). In humans, impulsive choice increased when opiate users (Giordano et al. 2002) and cigarette smokers (Field et al. 2006; Mitchell 2004) were acutely drug-deprived; however, after long-term drug abstinence, opiate users (Kirby and Petry 2004) but not cigarette smokers (Field et al. 2006) or cocaine abusers (Heil et al. 2006) decreased their impulsivity levels to those of nonusing controls. In experiment 2, reduction or withdrawal of a nondrug substance (e.g., food or SACC, respectively) was examined for its effects on delay discounting for PCP to determine whether changes in impulsivity found during drug withdrawal were specific to a drug or whether they occurred after withdrawal of a nondrug substance. PCP was used for the delay discounting component because an appetitive reward may have substituted for the food or SACC that was withdrawn.

Recent work measuring changes in food-maintained responding during PCP withdrawal indicated that male monkeys showed a more severe and longer duration of behavioral withdrawal effects than females when PCP access was terminated (Perry et al. 2006). These results were consistent with studies in rats injected with pentobarbital, ETOH (Devaud and Chadda 2001), morphine (Cicero et al. 2002; e.g., Suzuki et al. 1985), and methaqualone (Suzuki et al. 1988). There is also initial evidence in humans that men have had more severe physiological signs and symptoms of withdrawal than women (Woodstock-Striley et al. 2004).

That males show greater withdrawal effects than females is of particular interest because it is counter to the sex differences found in a large body of literature indicating that females exceed males in several phases of drug addiction (Becker and Hu 2008; Carroll et al. 2004; Lynch et al. 2002; Roth et al. 2004). These results provide initial evidence that females are more sensitive than males to the rewarding effects of drugs, while males are more sensitive to the aversive effects. Since there has been little research on sex differences in the withdrawal of drug or nondrug substances, an additional goal of this study was to examine sex differences in subtle effects (impulsivity) resulting from withdrawal of drug or nondrug substances.

Materials and methods

Animals

Twenty-nine (20 males, nine females) adult rhesus monkeys (*Macaca mulatta*) were used in separate groups for the PCP, ETOH, and SACC studies. However, the same monkeys were compared across the two PCP and two ETOH concentrations. Some of the female monkeys in the PCP studies were also used in the food restriction (RES) study, as there was a limited number of females. All monkeys had been previously trained to self-administer orally delivered PCP under FR and delay discounting schedules, and they were maintained at 85% of their free-feeding body weights (males=8–12.7 kg, females=4.7–9.1 kg), except briefly during experiment 2 when they were given unlimited access to food. Monkeys had unlimited access to water except during the delay discounting sessions in experiment 1 and during time out periods 2 h prior to and 1.5 h after each session.

Experiments were conducted in the individual home cages that were equipped with operant conditioning work panels for administering behavioral contingencies and dispensing drugs and water. The rooms, each containing 12 monkeys, were temperature- (23°C) and humidity-controlled, and lights were on from 0600 to 1800 hours. Enrichment objects were available in the chambers at all times including a hanging wooden log and a loose toy. Small healthy snacks and movies were provided during the intersession period. The experimental procedures were carried out in accordance with the Principles of Laboratory Animal Care (National Research Council 2003) and approved by the University of Minnesota Institutional Care and Use Committee under Protocol Number 0710A15141. Laboratory facilities were accredited by the American Association for the Assessment and Accreditation of Laboratory Animal Care.

Apparatus

Monkeys were housed and tested in stainless steel cages (83 cm in width×76 cm in height×100 cm in depth; Lab

Products, Maywood, NJ, USA) consisting of solid back and side walls, a barred front door, grid floors, and primate perch. A side wall of each cage was modified to accommodate an operant conditioning panel that contained two brass spouts (1.2 cm in diameter) extending 2.7 cm into the cage through circular apertures in the wall located 45 cm above the cage floor and equidistant from the center and sides of the cage. Two green-colored stimulus lights were located above the spouts, and one red stimulus light was located in the center of the panel. Each spout was mounted on clear Plexiglas with two green and two white lights embedded within it. The small green and white lamps were illuminated upon lip contact for PCP (ETOH or SACC) or water, respectively. When the scheduled number of lip-contact responses had been made, a solenoid valve opened allowing 0.6 ml of liquid to flow from reservoirs that were suspended above and outside the cage. Scheduling and recording experimental events were accomplished using Med-PC software (Med-PC® for Windows) and interfaces (Med Associates, St. Albans, VT, USA) located in an adjacent room.

Procedure

Experiment 1: the effect of oral drug self-administration and withdrawal of PCP or ETOH on delay discounting for an orally delivered SACC solution

The design and procedure were similar to those reported by Newman et al. (2008) and consisted of two components (FR and delay discounting) that occurred 7 days per week (see Tables 1 and 2). During the first component of the session, either PCP (0.25 or 0.5 mg/ml) or ETOH (8% or 16% wt/vol) was available with concurrent water from two spouts under independent but concurrent FR 8 (ETOH) or 16 (PCP) schedules. Sides for drug and water were reversed daily. During the second component, a SACC solution (0.3% *w*/*v*) was available from both spouts under a delay discounting procedure for 45 min or until 45 choice trials were completed.

During delay discounting, lip-contact responses on the spouts were reinforced under the FR schedule by a 0.6 ml liquid delivery through a 3-mm diameter aperture at the end of the spout. On the immediate side, one liquid delivery was contingent upon the completion of the FR requirement for lip contacts, and an additional lip contact (FR 1) was required to obtain the delivery. On the delayed side, after completion of the required FR, six deliveries were available, each contingent on completion of the FR 1. Drug (or SACC) vs water was signaled by flashing (10 Hz) or solid-on green lights, respectively, mounted above the spouts to control for side preferences sides were reversed for drug and water. Testing first at high or low PCP and ETOH concentrations was counterbalanced across animals. Behavioral stability was defined as no increasing or decreasing trend in the dependent measures, such as liquid deliveries, to capture stable and representative behavior in the within-subjects design. Both males and females were tested using PCP, but, due to the limited number of females, only males were used with ETOH in experiment 1 and SACC in experiment 2.

In the second component, after a 30-min timeout, a 45-min delay discounting task occurred, and SACC (0.3% *w*/*v*) was available from both spouts (signaled by the red light) with an FR 8 requirement to activate the immediate or delayed choice. Responses on the "immediate" spout were signaled by the green light above the spout, and they counted toward completion of the FR 8 and subsequent delivery of one SACC (0.6 ml), contingent on an FR 1 lip-contact response. Completion of an FR 8 on the delayed spout resulted in the flashing green light above the spout and a bundle of six 0.6 ml SACC deliveries, each contingent upon an FR 1 lip-contact response. Following the final delivery, the light above the spout was extinguished, and the center red light was illuminated to signal the next choice trial. The first two trials were forced trials to ensure sampling on both the right and left spout. The next 45 trials were free-choice trials. On the first day, the first delivery on the delayed spout started at 10 s. The delay for subsequent deliveries increased by 1 s after each delivery on the delay spout and decreased by 1 s after each delivery on the immediate spout. The average delay over the choice trials was referred to as the mean adjusted delay (MAD), and this dependent measure was calculated each day. After the first day, the starting delay was the final delay from the previous day. Sides were reversed for delayed and immediate conditions to control for side preferences.

The effects of removing drug access on delay discounting for SACC were studied by maintaining stable drug self-administration behavior for at least 10 days with drug available, then replacing the drug with water for 14 days and subsequently returning to concurrent drug and water access until at least 10 days of stable behavior were obtained. As a control condition, data were included from an earlier period when the monkeys self-administered only water from the two spouts during the FR components for several weeks to represent the rate of delay discounting for SACC when no drug was recently available. These data are referred to as baseline water (BL-W) and are used for comparison with the PCP and ETOH access and water substitution conditions.

Experiment 2: the effect of reduction (food) or withdrawal (SACC) of access to nondrug rewards on delay discounting for PCP

The purpose of this condition was to compare the changes in delay discounting that result from withdrawal of a nondrug

Table 1 Experimental design

Baseline 10 days		Withdrawal 14 days		Reinstatement 10 days	
Spout 1	Spout 2	Spout 1	Spout 2	Spout 1	Spout 2
Experiment 1					
Component 1 (9:45–11:45) self-administration					
PCP (M F) 0.25, 0.5 mg/ml FR 16	H_2O FR 16	H_2O FR 16	H_2O FR 16	PCP FR 16 0.25, 0.5 mg/ml	H_2O FR 16
ETOH (M) 8%, 16% *w/v* FR 8	H_2O FR 8	H_2O FR 8	H_2O FR 8	ETOH FR 8 8%,16% *w/v*	H_2O FR 8
Component 2 (12:15–13:00) DD					
SACC FR 8	SACC FR 8	SACC FR 8	SACC FR 8	SACC FR 8	SACC FR 8
1 immed	6 delayed	1 immed	6 delayed	1 immed	6 delayed
Experiment 2 (10:00–13:00) DD					
SAT (M F)		RES		SAT	
SACC bottle (M)		Water bottle		SACC bottle	
PCP DD	PCP DD	PCP DD	PCP 1 DD	PCP DD	PCP DD
1 immed	12 delayed	1 immed	12 delayed	1 immed	12 delayed
FR 32	FR 32	FR 32	FR 32	FR 32	FR 32

DD delay discounting, *SAT* food-satiated, *RES* food restriction

rewarding substance to the effect of PCP withdrawal (experiment 1). Two conditions were used; in the first, the monkeys responded under a delay discounting procedure for orally delivered PCP (0.25 mg/ml) under conditions of unlimited food access or food RES. In the second part of experiment 2, performance on a delay discounting task for PCP (0.25 mg/ml) was assessed during access or no access to a SACC solution from a drinking bottle.

All monkeys were initially trained to self-administer PCP (0.25 mg/ml) according to an FR 32 schedule of reinforcement on a delay discounting procedure during daily 3-h (1000–1300 hours) sessions. Completion of the FR requirement resulted in either one immediate delivery of PCP or 12 delayed deliveries of PCP over as many trials as possible within the 3-h session. The same response/cue contingencies were in place during delay discounting testing in the present experiment as in experiment 1 (see Tables 1 and 2).

Table 2 Summary of procedures

Experiment 1 PCP and ETOH withdrawal
8:00–9:45 time out, no food or liquid
9:45–11:45 component 1 drug and water concurrent FRs
11:45–12:15 time out, no food or liquid
12:15–13:00 component 2 SACC DD
13:00–14:30 time out, no food or liquid
14:30–8:30 intersession, only water available FR 1
Experiment 2 restricted food and SACC withdrawal
8:30–10:00 time out, no food or liquid
10:00–13:00 PCP DD, SACC, water, SACC bottle (for part of Experiment 2)
1:00–14:30 time out, no food or liquid
14:30–8:30 intersession, only water available FR 1, food (SAT, RES, SAT)

DD delay discounting, *SAT* food-satiated, *RES* food restriction

Food satiation and restriction

After reaching stability on the delay discounting procedure, under conditions whereby monkeys were maintained at 85% of their free-feeding weights, they were fed twice their 85% free-feeding food allotment during the intersession period (1300 to 0800 hours the next day) until they left at least 100 g of food uneaten. Monkeys remained on the satiation (SAT) condition for approximately 2 weeks and were then returned to the amount that maintained them at 85% of their free-feeding weight. Subsequently, they were retested under the SAT condition a final time in order to assess the effects of food reduction and restoration (see Table 1).

SACC access and removal

In the second study, the monkeys had access to a palatable SACC solution during daily sessions; then, SACC was replaced with water to examine the effect of withdrawal of a palatable substance. Details of the delay discounting procedure for PCP during access to SACC or water were similar to those described above for the food study; however, monkeys were maintained at 85% of their free-feeding body weight. The SACC was delivered in a nalgene bottle filled with a 0.3% solution or tap water at room

temperature during their daily experimental sessions (1000–1300 hours). The bottles were removed, following daily sessions, and the amount consumed was recorded. None of the monkeys consumed their entire daily allotment (1,900 ml) of either liquid during a single session. This condition was held constant for at least 14 days. After behavior stabilized for 6 days, water was substituted for SACC for at least 14 days, and the first 6 days of this condition were used to evaluate SACC withdrawal. Subsequently, SACC was restored for at least 14 days, and the last 6 days were used in the analysis.

Drugs

PCP HCI was obtained from the National Institute of Drug Abuse (Research Triangle Institute, Research Triangle Park, NC, USA). The PCP concentration (0.25 or 0.5 mg/ml) refers to the weight of HCI salt mixed with tap water. SACC sodium salt was obtained from Sigma (St. Louis, MO, USA), and SACC was mixed with tap water to produce a 0.3% (wt/vol) solution. The ETOH concentrations (8 or 16% wt/vol) refer to percent weight mixed in a volume of tap water. ETOH (95%) was obtained from the University of Minnesota Storehouse. Solutions were mixed with tap water before daily use, and they were stored at room temperature.

Data analysis

Dependent measures were drug, water, and SACC deliveries, and milligram per kilogram of PCP or gram per kilogram of ETOH intake under the FR components and SACC deliveries and MADs during the delay discounting components. Data for each monkey represented a 6-day mean from the last 6 days of stable behavior under each condition, except under the 10 days when drug access was removed; the first 6 days were used to capture the initial effects of removing drug or nondrug substances. Previous work indicated that the withdrawal effect persisted at that level for weeks until drug access was restored (Carroll 1987). Mean data obtained from six to eight monkeys per group were analyzed with repeated-measures analyses of variance (ANOVAs; GB-Stat, Dynamic Microsystems, Inc., Silver Spring, MD, USA). For experiment 1, the dependent measures were examined under the repeated liquid condition (BL-W), drug, water, drug, in males and females, and across PCP concentration in a three-factor repeated-measures ANOVA. In the ETOH study, a two-factor repeated-measures ANOVA was used to compare concentrations over repeated liquid conditions; BL-W, ETOH, water, and ETOH, in males only. For experiment 2, the dependent measures (PCP deliveries, milligram per kilogram intake, MAD, SACC, and water intake in milliliter from the bottle) were compared under the sequential feeding conditions of food SAT or RES (SAT, RES, SAT) in the first study or in the second study SACC, water, SACC access. For the SAT, RES, SAT condition, a two-factor repeated-measures ANOVA was used to compare sex and repeated feeding conditions. Additional two-group comparisons were made on MAD values between groups in different experiments using Bonferroni-corrected *t* tests. For all ANOVA, an overall significance level of $p<0.05$ was observed.

Results

Experiment 1: the effect of oral PCP or ETOH self-administration and withdrawal on delay discounting for a SACC solution

PCP

The data for 0.25 and 0.5 mg/ml PCP were analyzed together to directly compare PCP concentration, liquid condition, and sex. Figure 1 summarizes the results of substituting water for 0.25 PCP on delay discounting for SACC and illustrates in males (a) and females (b) the number of BL-W deliveries, PCP (0.25 mg/mg) deliveries during PCP self-administration, and water deliveries during PCP withdrawal. SACC deliveries (0.6 ml) under the delay discounting schedule in males (c) and females (d), and the impulsivity measure or MAD for SACC under the delay discounting schedule in males (e) and females (f) are also compared in Fig. 1. Water deliveries that were earned under the concurrent FR 16 schedule when PCP was available were negligible and did not vary pre- vs post-PCP withdrawal or by sex or concentration; thus, concurrent water data are not presented. The four sets of bars in each frame represent the last 6 days of BL-W, the last 6 days of PCP self-administration (PCP), the first 6 stable days of substitution of water for PCP (out of 10), and the last 6 days of PCP withdrawal, respectively.

As shown in Fig. 1a, b for liquid deliveries, there was a significant main effect of liquid (BL-W, PCP, water, PCP; $F_{3,\ 111}=55.05$, $p<0.0001$), but no significant sex or concentration main effect. There was also a sex×liquid condition interaction ($F_{3,\ 111}=4.48$, $p<0.05$) and a PCP concentration×liquid condition interaction ($F_{3,\ 111}=2.83$, $p<0.05$). Post hoc analyses revealed significant ($p<0.05$) sex differences in PCP deliveries (male > female) during the first PCP access period. PCP deliveries were significantly higher than water deliveries during BL-W and during PCP withdrawal ($p<0.01$). Water deliveries during PCP withdrawal were significantly lower than during PCP access ($p<0.01$), but they did not differ from BL-W or

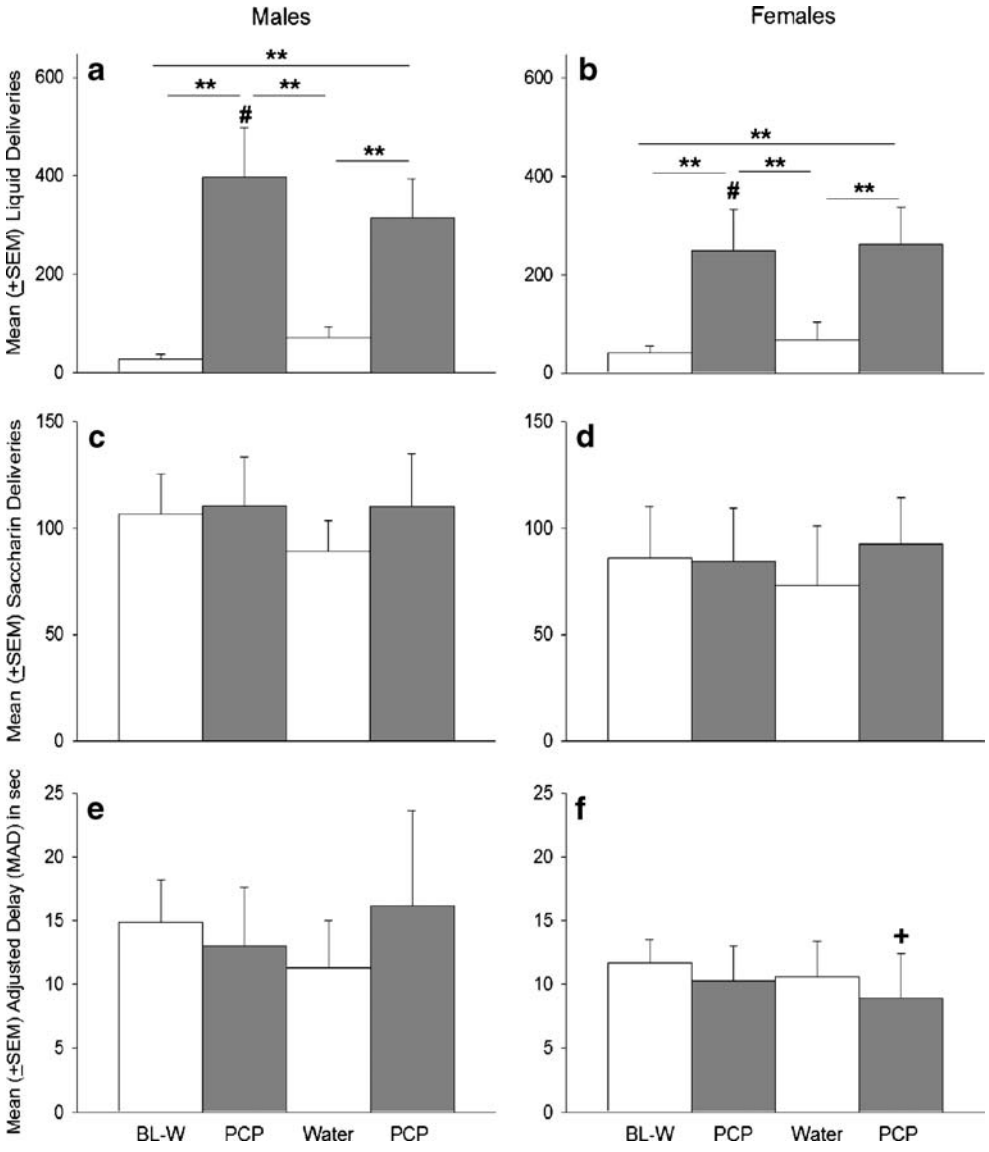

Fig. 1 Mean (±SEM) values are presented for eight males (*left frames*) and six females (*right frames*) for: **a** and **b** BL-W, PCP (0.25 mg/ml), water deliveries during PCP withdrawal and PCP reinstatement; **c** and **d** SACC deliveries during the DD component; and **d** and **e** MADs for SACC for males and females, respectively, under the four separate liquid conditions. *Gray bars* represent mean data from the last 6 days of PCP access when behavior had reached stability criteria. The *first white bar* represents the last 6 days of the BL-W condition, and the *second white bar* is the mean of the first 6 days of PCP withdrawal * = significant differences ($p<0.01$), *($p<0.05$) in PCP vs water deliveries, # = sex differences ($p<0.05$), + =concentration difference ($p<0.05$)

vary by sex or PCP concentration. In Table 3, PCP deliveries were converted to milligram per kilogram to account for the differences in body weight between males and females, but there were no sex or concentration differences. Thus, males consumed more PCP deliveries than females, but there were no sex differences in milligram per kilogram intake.

SACC deliveries during BL-W, PCP access, withdrawal, and PCP reinstatement are shown in Fig. 1c, d, and there was no main effect of sex, PCP concentration, or liquid access condition and no significant interaction. An analysis of the SACC MADs when 0.25 mg/ml PCP was available is shown in Fig. 1e, f, and there was a significant main effect for the liquid access condition ($F_{3,\ 111}=5.54$, $p<0.005$). There was also a significant PCP concentration × liquid access condition interaction ($F_{3,\ 111}=4.66$, $p<0.005$), but post hoc tests revealed that the only significant effect was a concentration difference (0.25 vs 0.5 mg/ml) in the MAD for the second PCP access period. Impulsivity was lower at 0.5 than 0.25 mg/ml PCP (Figs. 1f vs 2f). There were no behavioral signs of physiological dependence or stress.

Figure 2a, b show a main effect of liquid condition in the liquid deliveries at 0.5 mg/ml PCP for males and females, respectively. Results were similar to that shown in Fig. 1a for 0.25 mg/ml PCP, as well as the sex × liquid condition and concentration × liquid condition interactions. Post hoc analyses revealed significant ($p<0.05$) sex differences in PCP deliveries (male > female) during the second PCP access period. PCP deliveries were significantly higher than BL-W and water during PCP withdrawal ($p<0.01$). Water deliveries during PCP withdrawal were significantly lower than during PCP access ($p<0.01$ for males, $p<0.05$ for females), but they did not

Table 3 Mean (±SEM) drug intake adjusted for body weight during baseline, substance withdrawal, and reinstatement of drug (PCP mg/kg or ETOH g/kg) and nondrug rewards (food, SACC)

		Baseline	Withdrawal	Recovery
Drug/substance	Sex	Drug	Water	Drug
Experiment 1		Drug intake for PCP (mg/kg) or ETOH (g/kg)		
0.25 mg/ml PCP	M	5.8 (1.2)		4.6 (0.9)
	F	4.7 (1.5)		5.2 (1.2)
0.5 mg/ml PCP	M	7.3 (1.4)		8.4 (1.3)
	F	9.2 (1.4)		7.5 (0.9)
8% ETOH	M	1.1 (0.2)		1.2 (0.2)
16% ETOH	M	1.1 (0.2)		1.2 (0.2)
Experiment 2		Drug intake for PCP (mg/kg)		
Food	Sex	SAT	RES	SAT
	M	3.4 (0.4)[a]	5.2 (1.1)[a]	2.4 (0.5)[a]
	F	2.6 (0.9)	5.2 (2.0)	2.7 (0.9)
SACC		SACC	Water	SACC
	M	4.9 (1.2)	4.5 (1.4)	3.8 (1.2)

[a] Indicates conditions are significantly different

differ from BL-W in females or vary by sex or PCP concentration.

Figure 2 shows for males (c) and females (d) that there were no differences in SACC deliveries under the delay discounting schedule. Post hoc tests showed that MAD values were significantly higher during PCP access than PCP withdrawal in males and females and higher than BL-W in males. In males (e) and females (f), MAD values at 0.5 mg/ml also showed a PCP concentration effect, whereby MADs were significantly higher during the second PCP access period at 0.5 (vs 0.25) mg/ml PCP in females, suggesting that PCP may have reduced impulsivity in females but not in males. The MAD values across all conditions are summarized in Table 4.

Overall, PCP withdrawal (water substitution) resulted in a decrease in liquid deliveries, indicating that PCP was functioning as a reinforcer. There were also sex differences in PCP deliveries, with males consuming more than females; however, since females weigh less than males, this was not reflected in a difference in milligram per kilogram intake (Table 3). During withdrawal of 0.25 mg/ml PCP, SACC deliveries during delay discounting did not change, indicating that this was not a sensitive measure of PCP withdrawal. The MAD values for SACC during PCP withdrawal at the 0.5-mg/ml PCP concentration were significantly lower than during PCP conditions preceding and following the PCP withdrawal in both males and females indicating increased impulsivity for SACC, while SACC intake did not change. Comparisons with the BL-W data showed that the MADs in males decreased to below the water baseline data during PCP withdrawal or increased impulsivity. The lack of a MAD difference between the BL-W and PCP access conditions indicated that PCP had no direct increasing or decreasing effects on impulsivity for SACC.

ETOH

The effects of ETOH withdrawal are presented in Fig. 3 for the 8% (left) and 16% (right) concentrations in males only. Liquid deliveries (Fig. 3a, b) were significantly lower during BL-W and during ETOH withdrawal than when ETOH was available ($F_{3,\ 75}=52.37$, $p<0.0001$). There was also a main effect of concentration ($F_{1,\ 75}=12.96$, $p<0.005$), and a concentration×liquid condition interaction ($F_{3,\ 75}=8.51$, $p<0.001$). Post hoc analyses revealed that 8% and 16% ETOH deliveries were significantly higher than BL-W and water deliveries during ETOH withdrawal ($p<0.01$). Post hoc analyses also showed that ETOH deliveries were lower at the 16% (wt/vol) concentration (b) compared with 8% (a).

As indicated in Fig. 3c, d, neither ETOH withdrawal nor ETOH concentration had an effect on SACC deliveries. However, Fig. 3e, f show that there was a main effect of liquid for the MAD values but no significant interaction between liquid condition and ETOH concentration. The MADs for SACC were significantly lower when ETOH was available compared with BL-W and during ETOH withdrawal ($F_{3,\ 71}=3.75$, $p<0.05$), indicating an impulsivity-increasing effect of ETOH. Supporting these findings, Table 4 shows that the MADs for SACC when ETOH was available were significantly lower (greater impulsivity) than when PCP was available. In contrast, the MADs for BL-W and when water was substituted for ETOH were not significantly different from those obtained when PCP was available at both concentrations (see Fig. 1 and 2e, f, Table 4). Thus, ETOH withdrawal returned MADs to levels that were the same as when PCP was available, and it did not increase impulsivity as in the case of PCP withdrawal (Fig. 2e, f). The lower MAD values for ETOH show that ETOH withdrawal restored MADs to BL-W levels, and no observable behavioral signs of removing ETOH access were noted. Overall, ETOH withdrawal at the concentrations and 2-h access that was used did not alter impulsivity for SACC as did PCP withdrawal.

Experiment 2: the effect of changes in access to nondrug rewards, reduction (food) or withdrawal (SACC), on delay discounting for PCP

Food

Figure 4 shows the effects of reducing access to food on PCP intake (a, b) and impulsivity (d, e) for PCP in males

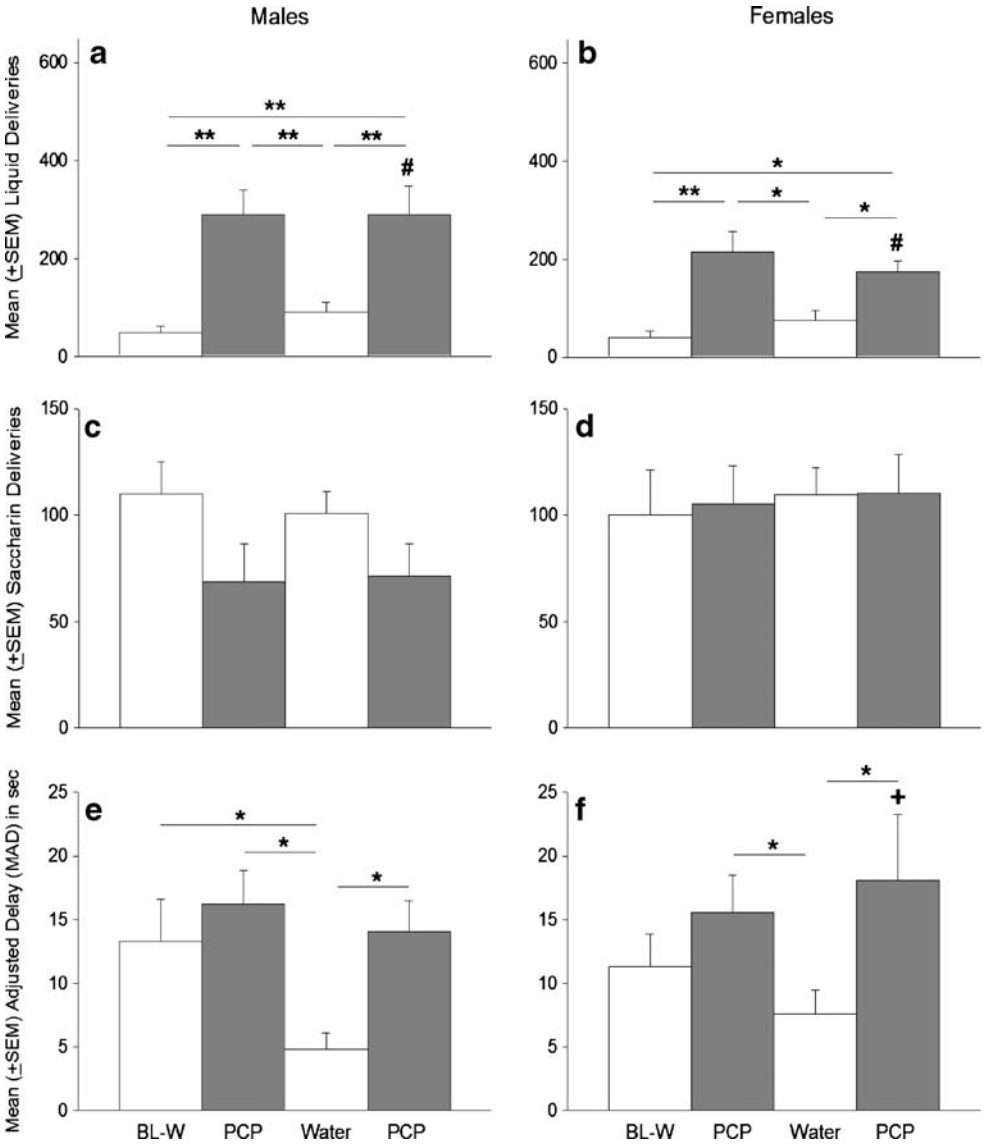

Fig. 2 Mean (±SEM) values are presented for eight males (*left frames*) and six females (*right frames*) for: **a** and **b** BL-W, PCP (0.5 mg/ml), and water deliveries during PCP withdrawal and PCP reinstatement during the FR self-administration component; **c** and **d** SACC deliveries during the delay discounting component; and **e** and **f** MAD for SACC under the four separate conditions for males and females, respectively. *Gray bars* represent mean data from the last 6 days of PCP access when behavior had reached stability criteria. The *first white bar* represents the last 6 days of the BL-W condition, and the *second white bar* is the mean of the first 6 days of PCP withdrawal. ** = significant differences ($p<0.01$) in PCP vs water deliveries and MADs, * = $p<0.05$, # = significant sex differences ($p<0.05$), + = concentration difference ($p<0.05$)

Table 4 Comparison of MAD values for SACC or PCP during baseline, withdrawal, and reinstatement for drug and nondrug rewards during SAT and RES

Experiment 1, component 2			Baseline	Withdrawal	Recovery
			Impulsivity (MAD) for SACC		
Drug/substance	Sex	BL water	Drug	Water	Drug
0.25 mg/ml PCP	M	14.9 (3.3)	13.0 (4.6)	11.3 (3.7)	16.2 (7.4)
	F	11.7 (1.8)	10.3 (3.5)	10.6 (3.6)	8.9 (3.5)[c]
0.5 mg/ml PCP	M	13.3 (2.7)[a]	16.2 (2.7)[a, e]	4.8 (1.3)[a]	14.1 (2.4)[a, d, e]
	F	11.3 (2.6)	15.6 (3.0)[a]	7.6 (2.0)[a]	18.1 (5.2)[c]
8% ETOH	M	13.1 (2.4)[a]	9.2 (3.4)[a]	13.5 (6.5) [a]	7.8 (2.2)[a, d, e]
16% ETOH	M	13.6 (2.5)[a]	7.5 (2.7)[a, e]	11.6 (4.2)[a]	6.0 (1.9)[a]
Experiment 2		Impulsivity (MAD) for PCP			
Food	Sex	SAT	RES	SAT	
	M	15.3 (4.2)[a, b]	7.0 (3.2)[a, b]	20.4 (6.4)[a, b]	
	F	37.2 (9.6)[a, b]	14.7 (3.3)[a, b]	44.93 (7.8)[a, b]	
SACC		SACC	Water	SACC	
	M	9.7 (3.6)	12.6 (4.5)	12.4 (5.1)	

[a] Indicates conditions are significantly different across rows

[b] Indicates significant sex differences

[c] Indicates 0.25 vs 0.5 mg/ml PCP difference

[d] Indicates differences between 0.5 mg/ml PCP and 8% ETOH

[e] Indicates differences between 0.5 mg/ml PCP and 16% ETOH

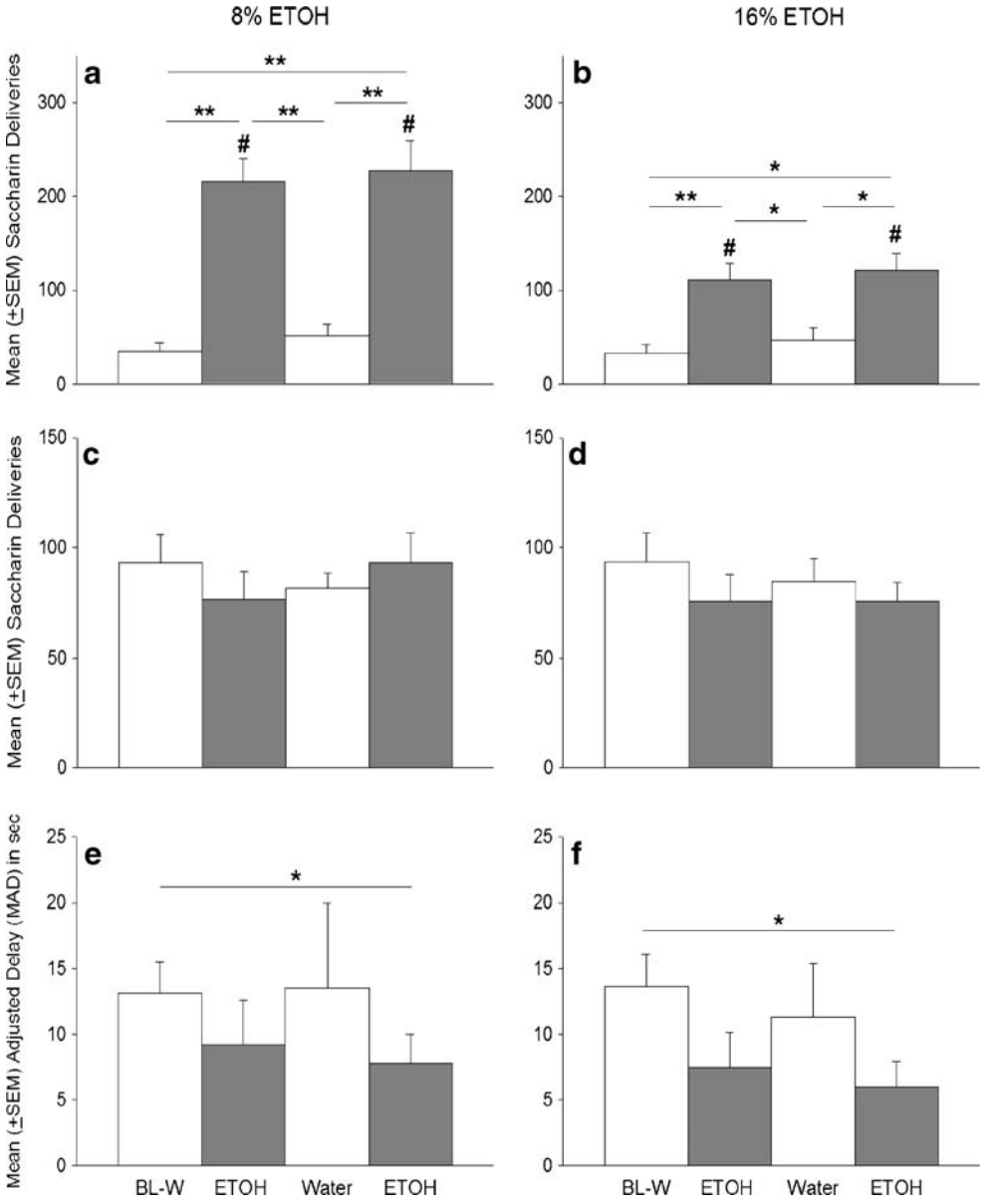

Fig. 3 Mean (±SEM) values are presented for eight males with access to 8% ETOH (*left frames*) and 16% ETOH (*right frames*) for: **a** and **b** BL-W, ETOH, and water deliveries during ETOH withdrawal and ETOH reinstatement; **c** and **d** SACC deliveries during the delay discounting component; and **e** and **f** MAD for SACC under four separate liquid access conditions: ETOH and water available (ETOH), only water available (water), and ETOH for the 8% and 16% concentrations, respectively. *Gray bars* represent mean data from the last 6 days of ETOH access when behavior had reached stability criteria. The *first white bar* represents the last 6 days of the BL-W condition, and the *second white bar* is the mean of the first 6 days of ETOH withdrawal. * = significant differences ($p<0.05$), ** ($p<0.01$) in ETOH vs water deliveries and MADs at both concentrations, # = significant sex differences ($p<0.05$)

(a, c) and females (d, e). Figure 4a, b shows that PCP deliveries were significantly increased in both males and females ($F_{2,\ 38}=10.4641$, $p<0.001$) when food access was restricted compared with the previous and subsequent satiation phases. However, there were no sex differences in PCP deliveries (a, b) nor a sex × feeding condition interaction. Figure 4c, d shows a significant main effect of MAD values in both males and females ($F_{2,\ 38}=13.8615$, $p<0.0001$), indicating increased impulsivity for PCP during food RES. There were also sex differences in the MADs ($F_{1,\ 38}=11.4013$, $p<0.01$), with males (c) showing significantly lower MADs (greater impulsivity) than that in females (d) during all three feeding conditions; however, there was not a significant feeding condition × sex interaction. No observable behavioral signs were noted during food RES. These results show that withdrawal of a nondrug reinforcer increases intake and impulsivity for a drug reward; whereas, in experiment 1, PCP withdrawal did not change SACC intake, but it increased impulsivity for SACC.

SACC

During SACC withdrawal and replacement with water, SACC consumption was significantly above that of water ($F_{2,\ 23}=9.5333$, $p<0.005$), revealing its reinforcing effects. However, even with high intakes of SACC (e.g., ~800 ml) and very low intake of water (e.g., 150 ml) during SACC withdrawal, PCP intake and impulsivity for PCP were not altered by SACC withdrawal despite different behavioral schedules. PCP deliveries were also comparable to those

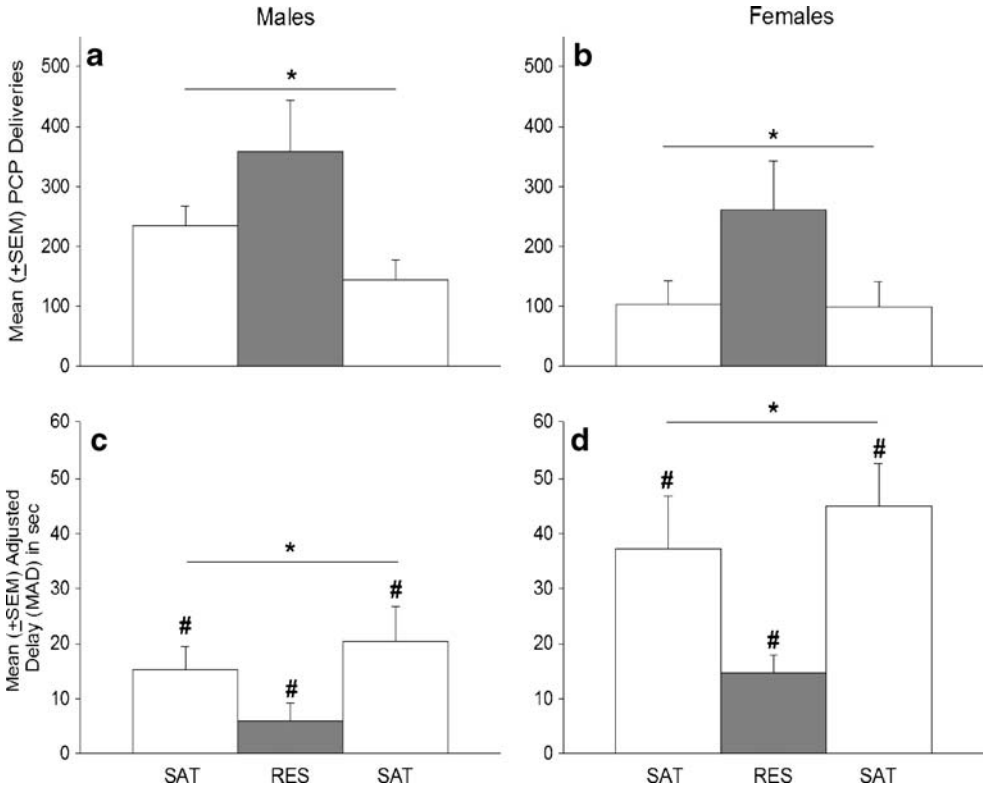

Fig. 4 Mean (±SEM) values are presented for eight males (*left frames*) and five females (*right frames*) under the delay discounting schedule for: **a** and **b** PCP (0.25 mg/ml) deliveries and **c** and **d** MAD for PCP under three separate conditions, food SAT, RES, and SAT, for males and females, respectively. *Gray bars* represent mean data from the last 6 days of each condition when behavior had reached stability criteria. *White bars* indicate the mean of the first 6 days of RES * = significant differences ($p<0.05$) in PCP deliveries and MADs for PCP over SAT and RES conditions, #=sex differences ($p<0.05$)

obtained in experiment 1. Table 4 shows that the MAD values for PCP were comparable to those for PCP during food RES and for SACC before and after PCP withdrawal.

Discussion

The results demonstrated that impulsivity under a delay discounting for SACC and PCP was a sensitive indicator of PCP withdrawal or reduction in food access, respectively. Experiment 1 showed that impulsivity for SACC increased significantly in males and females during withdrawal of 0.5-mg/ml PCP access, while SACC intake did not change. These results were consistent with those of Perry et al. (2006) who found that PCP withdrawal disrupted food-maintained performance (FR 64) to a greater extent in males than females. In the present study, the MAD values for SACC during PCP FR access were not different than during BL-W; thus, PCP intake did not alter impulsivity for SACC, while PCP withdrawal clearly increased it. There were no sex differences in the increased impulsivity (lower MADs) for SACC during PCP withdrawal as there were for food-maintained FR responding during PCP withdrawal in the study by Perry et al. (2006). In that study, males showed greater suppression of food-maintained behavior during PCP withdrawal. The present results were consistent with previous studies showing no sex differences in impulsivity measures in rats (Perry et al. 2008).

In the present study, the length of the disturbance produced by PCP withdrawal on delay discounting performance was protracted (14 days), as it was for decrements in food-maintained responding during PCP withdrawal in previous studies (Carroll 1987; Perry et al. 2006). Thus, the delay discounting task offered a reliable and sensitive behavioral measure of PCP withdrawal and added another behavioral dimension. Both impulsive behavior and the previously reported decrements in responding on high FRs (see Carroll 1987; Perry et al. 2006) showed enduring behavioral aberrations that outlasted accounts of physiological signs of PCP withdrawal reflecting a mild form of dependence (see Carroll 1987). In the present study, while no somatic withdrawal signs were noted, PCP withdrawal produced subtle but stable changes that were the same magnitude on the first and successive days until drug access was restored.

Effects of ETOH withdrawal in the present study were opposite to those of PCP. Since ETOH access increased impulsivity (lower MADs) for SACC during baseline, ETOH withdrawal resulted in higher MADs, similar to those found during BL-W and PCP access. Therefore, 16% ETOH increased impulsivity for SACC, while withdrawal of 16% returned MADs to baseline. Others have reported similar effects of ETOH on impulsive choice (delay discounting) in rats (Evenden and Ryan 1999; Olmstead 2006; Poulos et al. 1998) and in humans using the Stop Signal Reaction Time Task (de Wit et al. 2000; Fillmore et

al. 2003; Marczinski et al. 2005; Marczinski and Fillmore 2003; Reynolds et al. 2006) and several other measures of impulsivity (impaired inhibition) in both rats and humans (see review by Perry and Carroll 2008). The present results with PCP and ETOH withdrawal indicate that the effects on delay discounting for a nondrug substitute are specific to the drug class.

Another explanation for the different effect of ETOH vs PCP withdrawal is that the amount of PCP consumed could have produced a mildly aversive physiological condition during withdrawal, while ETOH intake may not have produced this effect. Previous studies indicated that PCP withdrawal effects were reliably produced when the length of access and concentration of PCP were higher (Carroll 1987), suggesting a threshold for a physiological or other disturbance that was reached at the 0.5-mg/ml but not the 0.25-mg/ml PCP concentration.

The current findings of increased impulsivity during PCP withdrawal are consistent with other preclinical investigations, and clinical reports that have documented a close relationship between drug abstinence, impulsive behavior, and interaction of drug and nondrug rewards. In rats, chronic administration of cocaine increased impulsive choice for food pellets that lasted 3 months after cocaine treatment ended (Simon et al. 2007). Repeated nicotine injections increased impulsive choice during exposure, and impulsivity remained elevated above baseline when nicotine injections ended (Dallery and Locey 2005). Using a 5-CSRT task, Dalley et al. (2007) found increased impulsivity during termination of iv MDMA self-administration in rats, and following nicotine exposure with the 5-CSRT task but not delay discounting (Counotte et al. 2009). The relationship between impulsive behavior and drug withdrawal has also been illustrated by preselecting rats for high (vs low) impulsivity and shows greater reinstatement of cocaine-seeking behavior after cocaine-primed (Perry et al. 2008) or cue-induced reinstatement of nicotine-seeking behavior (Diergaarde et al. 2008) in the high vs low impulsive group.

We are not aware of other studies in monkeys that examined the effects of drug withdrawal on intake of palatable substances such as SACC; however, this method has been used frequently in rats injected with drugs to measure withdrawal effects on intake of a sweetened liquid, contingent on performance on a progressive ratio (PR) schedule. In contrast to the present findings with monkeys, results from the rat studies demonstrated a decrease in breakpoint (lower motivation) for sweetened solutions when amphetamine (Barr and Phillips 1999; Orsini et al. 2001; Schwabe and Koch 2007), methamphetamine (Hoefer et al. 2006), morphine (Zhang et al. 2007), and nicotine (LeSage et al. 2006) treatments were stopped. These results are consistent with previous reports of decreased FR performance for food when access to self-administration of PCP was terminated (Carroll 1987, 1989; Carroll and Carmona 1991; Carroll et al. 1994).

In contrast, the elevated impulsivity for SACC during PCP withdrawal in the present study was consistent with a finding in rats that access to sucrose decreased somatic signs of withdrawal in opiate-dependent rats (Jain et al. 2004). Furthermore, in human laboratory studies, glucose tablets decreased tobacco craving that occurred after smoking cessation (West et al. 1990) and tobacco craving after overnight abstinence (West et al. 1999). Other effects of drug withdrawal have been noted in rats such as increased stress responses during nicotine withdrawal (Jonkman et al. 2008), increased anxiogenic effects during ETOH withdrawal (Gatch and Lal 2001; Varlinskaya and Spear 2004) or cocaine withdrawal in zebrafish (Lopez-Patino et al. 2008a) which was later shown to be greater in males than in females (Lopez-Patino et al. 2008b). Thus, behaviors that characterize the abstinence or withdrawal phase (impulsivity, motivation, stress, anxiety, reward seeking, and craving) are complex and interrelated.

In experiment 2, reduction of access to a nondrug reward (food) increased impulsivity for PCP similar to that reported in experiment 1 in which impulsivity for SACC increased during PCP withdrawal. Others have shown that, when access to a nondrug reinforcer was discontinued, there was a resurgence of alcohol-seeking behavior in rats that had previously self-administered alcohol, even though alcohol was no longer available (Podlesnik et al. 2006).

The results with food RES in experiment 2 suggest that increased impulsivity for an alternative substance may occur during withdrawal of a nondrug substance or event. This mechanism is particularly relevant to the high comorbidity between drug abuse and eating disorders or drug abuse and other addictive behavior (e.g., gambling, sex), whereby cessation of one form of excessive behavior leads to impulsive behavior directed toward another substance or behavior (Carroll et al. 2009). Thus, a deprivation state may not only increase the probability of relapse to the same drug or substance, but it may prompt other potentially addictive behaviors.

In contrast, withdrawal of a palatable SACC solution did not change delay discounting for PCP. Thus, the elevated impulsivity found with food RES and PCP withdrawal may have been due to the ability of these conditions to produce putatively aversive physiological states leading to increased impulsivity for another rewarding substance (SACC or PCP). Unlike food, SACC is noncaloric and not needed for physiological homeostasis, and, although SACC was highly reinforcing, SACC withdrawal may not have produced a physiological imbalance needed to reveal increases in impulsivity for an alternative reinforcer (PCP).

The effect of reducing food access was greater in males than in females, which is consistent with previous findings of a PCP withdrawal effect on food-maintained behavior in

monkeys (Perry et al. 2006). Increased impulsivity during food RES in male vs female rats is in agreement with other studies in which male rats were more sensitive than females to acoustic startle and reduced intake of an ETOH-paired flavored solution ETOH during ETOH withdrawal (Dess et al. 2005) as well as earlier studies that involved experimenter-administered drug and withdrawal (Cicero et al. 2002; Devaud and Chadda 2001; Suzuki et al. 1985, 1988). The present results support the hypothesis that males are more sensitive to the aversive effects of drugs than females.

The present data may also be viewed as a case of adding an alternative reinforcer (e.g., unlimited food) to the environment and decreasing the intake and impulsivity associated with an existing reinforcer (PCP). In the present study, food satiation dramatically decreased PCP intake and impulsivity for PCP in both males and females, although the magnitude of the decrease in impulsivity was proportionally greater in females than in males (Fig. 4c, d). This apparent "treatment" effect of reducing drug intake and impulsivity for the drug was greater in females than males (Fig. 4c, d, Table 4) and was consistent with the sex differences (females > males) found in several other studies using behavioral approaches, such as adding nondrug rewards like SACC in monkeys (Cosgrove and Carroll 2003), access to a running wheel in rats (Cosgrove et al. 2002), or pharmacological treatments (Campbell et al. 2002; Carroll et al. 2001b; Cosgrove and Carroll 2004). These results suggest that females are more sensitive to rewarding effects of drugs and to treatments than males, and they may be more reward sensitive and/or less responsive to aversive events than males. Mechanisms underlying the increases in impulsivity for an alternate reward when drug or nondrug substances are removed need further examination.

In conclusion, PCP withdrawal or reduction of a nondrug (food) substance increased impulsivity for a nondrug or drug reinforcer, respectively, supporting the notion of interchangeability between drug and nondrug rewards (Carroll et al. 2001a, 2008). Withdrawal of a drug or nondrug reinforcer may not result in observable physiological signs of distress; however, a subtle change in homeostatic mechanisms may increase impulsivity for an alternative reward. These findings may apply to human substance abusers who, while attempting to limit use of one substance, may become more impulsive toward and vulnerable to another. If drug abstinence results in increased impulsive choice, this condition along with other sequelae of drug withdrawal (e.g., stress, anxiety) predicts a lower probability of successful abstinence and treatment effects. Relapse to drug use, in turn, would elevate impulsive behavior, further increasing drug abuse. Activation of impulsive behavior, either through drug taking or withdrawal, may underlie the chronic relapsing characteristic of drug abuse. Thus, development of behavioral and pharmacological methods to reduce impulsivity would be an important adjunct to drug abuse treatment.

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