Pharmacology, Biochemistry and Behavior 100 (2012) 370–376

Contents lists available at ScienceDirect

Pharmacology, Biochemistry and Behavior

journal homepage: www.elsevier.com/locate/pharmbiochembeh

# High impulsivity in rats predicts amphetamine conditioned place preference ☆

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ARTICLE INFO

*Article history:*
Received 23 May 2011
Received in revised form 8 July 2011
Accepted 17 July 2011
Available online 23 July 2011

*Keywords:*
Impulsivity
Individual differences
Conditioned place preference
Locomotor activity
Amphetamine
Delay discounting
Rat

ABSTRACT

Stimulants such as d-amphetamine (AMPH) are used commonly to treat attention-deficit hyperactivity disorder (ADHD), but concerns have been raised regarding the use of AMPH due to its reinforcing and potentially addictive properties. The current study examined if individual differences in impulsive choice predict AMPH-induced hyperactivity and conditioned place preference (CPP). Rats were first tested in delay discounting using an adjusting delay procedure to measure impulsive choice and then were subsequently tested for AMPH CPP. High impulsive (HiI) and low impulsive (LoI) rats were conditioned across four sessions with 0.1, 0.5, or 1.5 mg/kg of AMPH. AMPH increased locomotor activity for HiI and LoI rats following 0.5 mg/kg but failed to increase activity following 0.1 and 1.5 mg/kg. CPP was established for HiI rats with both 0.5 and 1.5 mg/kg of AMPH, whereas LoI rats did not develop CPP following any dose of AMPH; HiI and LoI groups differed significantly following 0.5 mg/kg of AMPH. These results indicate that HiI rats are more sensitive to the rewarding effects of AMPH compared to LoI rats, which is consistent with research showing that high impulsive individuals may be more vulnerable to stimulant abuse.



## 1. Introduction

Impulsivity is a multifaceted construct that includes lack of inhibitory control, lack of forethought, and inability to delay gratification (Evenden, 1999; Olmstead, 2006; Whiteside and Lynam, 2001). Impulsivity has also become a common diagnostic criterion for several psychiatric disorders, including borderline personality disorder, antisocial personality disorder, mania, dementia, bulimia nervosa, and substance use disorders (Whiteside and Lynam, 2001). Individuals diagnosed with attention deficit hyperactivity disorder (ADHD) display hyperactivity, inattentiveness, and impulsiveness (American Psychiatric Association, 1994). ADHD is a common disorder in children, adolescents, and young adults, affecting approximately 2 to 14% of this population (Robbins, 2002). Current treatments for ADHD include the stimulants d-amphetamine (AMPH; Adderall, Dexedrine) and methylphenidate (Concerta, Ritalin) and the norepinephrine reuptake inhibitor atomoxetine (Strattera). Some controversy has surrounded the use of AMPH and methylphenidate for the treatment of ADHD due to their potential for abuse (Biederman and Faraone, 2005). Both of these stimulants have been shown to be self-administered in animal models (Balster and Schuster, 1973; Collins et al., 1984; Marusich et al., 2010; Nielsen et al., 1984; Pickens, 1968) and can serve as reinforcers in humans (Rush et al., 2001; Stoops, 2008; Stoops et al., 2004, 2005).

Impulsivity has been fractioned into two broad categories: impulsive action and impulsive choice (Winstanley et al., 2010). Impulsive action is conceptualized as motor impulsivity; human and non-human animals that fail to inhibit prepotent responses are considered to have higher levels of motor impulsivity. The primary behavioral tasks to measure impulsive action are the stop signal reaction time (SSRT) task, the go/no go task, and the five-choice serial reaction time (5CSRT) task (see Winstanley et al., 2010 for a full review). Impulsive choice is conceptualized as the inability to delay gratification. The primary task used to study impulsive choice is the delay discounting (DD) task. In DD, subjects choose between a small reward delivered immediately and a larger reward delivered after a delay. Subjects are considered more impulsive if they choose the small, immediate reward over the larger, delayed reward (Ainslie, 1975).

In both human and non-human animals, research has demonstrated a link between impulsivity and drug use. According to de Wit (2009), this relationship is not necessarily one directional, as impulsivity can serve as a determinant or consequence of drug use. Clinical cross-sectional studies have indicated that drug users are more impulsive compared to nonusers (Moeller et al., 2001; Sher and Trull, 1994). In humans, individuals who are drug-dependent show more impulsive choice in DD compared to non-dependent individuals (Baker et al., 2003; Bickel et al., 1999; Coffey

☆ The authors report no conflict of interest.

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0091-3057/$ – see front matter © 2011 Published by Elsevier Inc.
doi:10.1016/j.pbb.2011.07.012

et al., 2003; Kirby et al., 1999; Madden et al., 1997; Mitchell, 1999; Petry, 2001; Vuchinich and Simpson, 1998). High impulsive (HiI) rats consume more ethanol (Poulos et al., 1995) and acquire cocaine self-administration at a faster rate than low impulsive (LoI) rats (Perry et al., 2005, 2008a). Furthermore, increased impulsivity predicts escalation of cocaine self-administration (Anker et al., 2009; Dalley et al., 2007), compulsive cocaine self-administration (Belin et al., 2008), and reinstatement of nicotine and cocaine self-administration (Diergaarde et al., 2008; Economidou et al., 2009). HiI rats also self-administer more methylphenidate at a low unit dose and self-administer more nicotine compared to LoI rats (Diergaarde et al., 2008; Marusich and Bardo, 2009).

Drug exposure also affects impulsivity. For example, cocaine self-administration has been shown to increase impulsive choice (Mendez et al., 2010), and withdrawal from cocaine increases impulsivity in a 5CSRT task (Winstanley et al., 2009). Methamphetamine (Richards et al., 1999) and methylphenidate (Bizot et al., 2007; Pitts and McKinney, 2005) reduce impulsive choice, but methylphenidate increases impulsivity in the 5CSRT task (Milstein et al., 2010). Research with AMPH has yielded mixed results. AMPH has been shown to increase (Evenden and Ryan, 1996; Gipson and Bardo, 2009; Hand et al., 2009; Perry et al., 2008b) and decrease (Evenden and Ko, 2005; van Gaalen et al., 2006; Wade et al., 2000; Winstanley et al., 2003, 2005b) impulsivity.

One potential interpretational problem with previous preclinical experiments is that HiI rats may not respond more for drug because of its reinforcing properties; instead, they may be more sensitive to reward-associated stimuli (Diergaarde et al., 2009). For example, Diergaarde et al. (2009) allowed HiI and LoI rats to nose poke for sucrose in an operant task in the presence of a discrete cue, and then the response was extinguished. Compared to LiI rats, HiI rats showed more vigorous nose-poking during training and greater reinstatement of cue-induced sucrose seeking after extinction. Furthermore, HiI rats exhibit more sign-tracking conditioned responses compared to LoI rats (see Tomie et al., 2008 for a review). "Sign-trackers" spend more time interacting with conditioned stimuli (i.e., cue light, lever, nose-poke aperture), whereas "goal-trackers" spend more time exploring the area where the reinforcer is expected to be delivered. Evidence suggests that sign-trackers are more impulsive in DD (Tomie et al., 1998, but see Lovic et al., 2011) and a 2CSRT (simplified version of the 5CSRT) and a differential reinforcement of low rates of responding task (Lovic et al., 2011). In addition, lesions to the subthalamic nucleus decrease both impulsive choice and sign-tracking behavior (Winstanley et al., 2005a). Therefore, HiI rats may choose small immediate reward and earn more drug infusions because they attribute more incentive salience to stimuli associated with immediate reinforcement (non-drug or drug) relative to LoI rats.

The purpose of the current study was to determine if HiI animals are more sensitive to drug reward using a non-operant task such as conditioned place preference (CPP; Bardo and Bevins, 2000). In CPP, animals learn to associate diffuse contextual cues with the drug. The properties of the drug serve as the unconditioned stimulus, and contextual cues serve as the conditioned stimuli. During conditioning, the previously neutral contextual cues act as conditioned stimuli that can elicit approach to the environment previously paired with the drug (Tzschentke, 2007). Thus, the current study determined if HiI rats show greater AMPH CPP than LoI rats. Rats were trained initially on an adjusting delay task in which they were required to choose between a small, immediate reward (one sucrose pellet) and a larger, delayed reward (three sucrose pellets). Following 21 days of the adjusting delay procedure, rats were tested for CPP using 0.1, 0.5, or 1.5 mg/kg of AMPH (each dose tested in a separate experiment). Locomotor activity was also assessed during conditioning sessions to determine if any differences in AMPH CPP generalized to AMPH-induced hyperactivity.

## 2. Material and methods

### 2.1. Subjects

Fifty-four male Sprague Dawley rats (250–275 g; n = 18 for each experiment) were obtained from Harlan Industries (Indianapolis, IN). They were acclimated to a colony room and handled for 5 days prior to the experiment. Rats were housed individually in a colony room held at constant temperature. Light and dark phases were on a 12:12 h cycle, and all experiments occurred in the light phase at approximately 07:00 h. Rats were food restricted (85% of free feed body weight) during the DD procedure and had unlimited access to food during the CPP paradigm. Rats had unlimited access to water in their home cage. All procedures were in accordance with the "Guide for the Care and Use of Laboratory Animals" (National Research Council, 1996) and were approved by the Institutional Animal Care and Use Committee at the University of Kentucky.

### 2.2. Apparatus

Operant chambers (28 × 21 × 21 cm; ENV-008; MED Associates, St. Albans, VT) located inside sound-attenuating chambers (ENV-018 M; MED Associates) were used for the DD task. The front and back walls of the experimental chambers were made of aluminum, while the side walls were made of Plexiglas. There was a recessed food tray (5 × 4.2 cm) located 2 cm above the floor in the bottom-center of the front wall. A 28-V white cue light was located 6 cm above each response lever. A white houselight was mounted in the center of the back wall of the chamber. All responses and scheduled consequences were recorded and controlled by a computer interface. A computer controlled the experimental session using Med-IV software.

A 3-compartment chamber (68 × 21 × 21 cm; ENV-013; MED Associates) located inside a sound-attenuating chamber (ENV-020 M; MED Associates) was used to measure locomotor activity and CPP. The three compartments were separated by sliding guillotine doors. The middle compartment (12 × 21 × 21 cm) had gray walls with a smooth gray PVC floor. The end compartments (28 × 21 × 21 cm) provided different contexts, with one compartment having black walls with a stainless steel grid rod floor and the other end compartment having white walls with a stainless steel mesh floor. Recessed trays were located 2 cm below each compartment. A computer controlled the experimental session using Med-IV software. A series of infrared photobeams (6 beams in the black and white compartments and 3 beams in the gray compartment) were used to detect the rats' presence in a particular compartment and record the amount of time spent in that compartment, as well as to record locomotor activity during conditioning sessions.

### 2.3. Procedure

#### 2.3.1. Delay discounting

In all 3 experiments, rats were first tested for 21 days on an adjusting delay task using procedures similar to those described previously (Gipson and Bardo, 2009; Marusich and Bardo, 2009; Perry et al., 2008a). Daily sessions began at 07:30 and ended following the completion of 60 trials or 2 h, whichever occurred first. Each session included 15 blocks of four trials in which two trials were forced trials, and two trials were free choice trials. Each session began with illumination of the houselight. Trial blocks began with one forced-left and one forced-right trial; the order of these two trials alternated randomly within- and between-sessions. Forced trials began with extension of the active lever and illumination of a white stimulus light above the lever. Following a lever press response, the lever was retracted immediately, followed by either one or three sucrose-based 45 mg pellets (F0021 dustless precision pellet, Bio-Serve, Frenchtown, NJ) delivered immediately or after a delay, respectively. The third and

fourth trials in each block were free choice trials, which were signaled by illumination of both stimulus lights above each lever. Following each four-trial block, both levers were retracted. A response to one lever resulted in delivery of one sucrose pellet immediately, and a response to the other lever resulted in delivery of three pellets following an adjusting delay. To control for any lever bias, the side of the lever associated with the immediate or delayed reinforcer alternated daily.

Following each trial, an adjusting inter-trial interval occurred such that each trial lasted 60 s. After 60 s elapsed, the next trial began. During the inter-trial interval, all lights were turned off, and responses on the levers had no programmed consequence. The initial delay for the larger reinforcer was 0 s. Subsequent responses for the larger reinforcer resulted in a 1-s increase in the delay, and a response for the small immediate reinforcer resulted in a 1-s decrease in the delay to the larger delayed reinforcer (although a minimum delay of 0 s and a maximum delay of 45 s to the larger reinforcer were imposed). The delay to the larger reinforcer was adjusted according to responses on only the third and fourth trials in each block (i.e., the free choice trials). During the delay, the stimulus lights turned off, although the houselight remained illuminated until the delivery of three pellets. The delay on the final free choice trial on each session was used as the initial delay on the next session. The main outcome measure, a mean adjusted delay (MAD), was calculated at the end of each session by averaging all adjusting delays on free choice trials. After the last session, the MAD scores for the last 10 days were averaged. Rats with MAD scores in the upper third were considered to be less impulsive while rats with MAD scores in the lower third were considered to be more impulsive. Rats that had a MAD score in the middle third were excluded from data analysis. Thirty-six rats were used in the final analyses.

#### 2.3.2. Conditioned place preference

Two days after completing the DD phase, rats in each experiment were tested for 10 consecutive days in a CPP paradigm. During the first session (pretest), the guillotine doors were opened, and rats were placed in the gray compartment and were allowed to explore all three compartments for 15 min. The duration spent in each compartment was recorded. Following the pretest, rats went through 8 days of conditioning, in which rats were confined by the guillotine door to either the black or white compartment for 30 min. HiI and LoI rats were given a subcutaneous injection of AMPH (0.1, 0.5 or 1.5 mg/kg; Experiments 1, 2 and 3, respectively) and were placed immediately in the least preferred compartment every other day. On alternate days, each rat received saline (SAL) and was placed immediately in the preferred compartment. The order in which rats received drug was counterbalanced within each treatment group. During the posttest, the guillotine doors were opened, and rats were allowed to explore all three compartments for 15 min. The time spent in each compartment was recorded. Locomotor activity was also recorded during each conditioning session by measuring the total number of photobeam breaks.

### 2.4. Drug

d-Amphetamine sulfate (Sigma, St. Louis, MO) was prepared in sterile 0.9% NaCl (SAL).

### 2.5. Statistical analyses

To determine if MAD scores differed across each experiment, MAD scores for HiI and LoI rats were averaged and compared by an analysis of variance (ANOVA) with Dose and Group (HiI vs. LoI) as between-subjects factors. Since no main effect of Group or a Dose × Group interaction were observed, MAD scores for each experiment were collapsed and compared by a mixed factor analysis of variance with Session as a within-subjects factor and Group as a between-subjects factor. Independent-samples *t* tests (with Bonferroni correction) were performed comparing HiI and LoI rats for sessions 12–21. These comparisons were made since the last 10 days were used to determine HiI and LoI groups.

Locomotor activity was compared with a mixed-factor ANOVA with Treatment (SAL vs. AMPH) and Session as within-subjects factors and Group (HiI vs. LoI) and Dose as between-subjects factors. Because significant differences were observed between the 3 experiments, three separate mixed-factor ANOVAs with Treatment and Session as within-subjects factors and Group as a between-subjects factor were conducted. Main effects were probed with Fisher's LSD post hoc tests. Significant interactions were probed by conducting separate ANOVAs and paired-samples *t* tests (with Bonferroni correction) when appropriate.

For CPP, a difference score was calculated by taking the amount of time spent in the chamber paired with AMPH and subtracting it by amount of time spent in the chamber paired with SAL during the posttest. A difference score of 0 indicated no preference for either chamber, with scores above 0 designating a preference and scores below 0 designating an aversion. ANOVA with Group (HiI vs. LoI) and Dose as between-subjects factors was conducted. Independent-samples *t* tests were performed for each experiment to determine if difference scores differed between HiI and LoI rats. One-sample *t* tests were performed to determine if each difference score was significantly different from 0. All tests were considered significant at $p<.05$.

## 3. Results

### 3.1. Mean adjusted delay (MAD) scores

Using the top and bottom third of MAD scores from all rats tested, an initial ANOVA only revealed a main effect of Group ($F(1, 30) = 90.92$, $p<.01$). However, no main effect of Dose or a Dose × Group interaction were revealed (data not shown). MAD scores from the three experiments were collapsed and analyzed in a single ANOVA. ANOVA revealed main effects of Session ($F(20, 680) = 18.65$, $p<.01$) and Group ($F(1, 34) = 79.24$, $p<.01$) and a significant Session × Group interaction ($F(20, 680) = 11.98$, $p<.01$). Independent-samples *t* tests revealed significant differences between HiI and LoI rats for sessions 12–21 (all *p*'s<.005; Fig. 1).

### 3.2. Locomotor activity

When the data were collapsed across all 3 experiments, an overall ANOVA revealed main effects of Treatment ($F(1, 30) = 13.13$, $p<.01$) and Dose ($F(2, 30) = 17.81$, $p<.01$), as well as significant Treatment × Dose ($F(2, 30) = 14.67$, $p<.01$), Treatment × Session ($F(3, 90) = 3.92$,

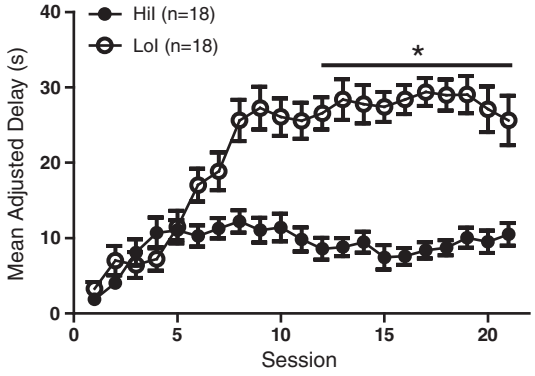


**Fig. 1.** MAD scores (mean ± SEM) for high impulsive (HiI; n = 18) and low impulsive (LoI; n = 18) rats, defined as the top and bottom thirds across all rats tested in Experiments 1–3. *$p<.005$, compared to HiI following Bonferroni correction.

$p<.05$), and Treatment × Dose × Session ($F(6, 90)=2.68$, $p<.05$) interactions. To explore the Treatment × Dose x Session interaction, separate ANOVAs with Session as a within-subjects factor and Dose as a between-subjects factor were conducted for each Treatment. Following AMPH, ANOVA revealed main effects of Session ($F(3, 99)=5.55$, $p<.01$) and Dose ($F(2, 33)=p<.01$), as well as a significant Session × Dose interaction ($F(6, 99)=3.41$, $p<.01$). Fisher's LSD post hoc tests showed that 0.5 mg/kg of AMPH increased activity relative to 0.1 and 1.5 mg/kg of AMPH ($p$'s<.01). Following SAL, only a main effect of Dose ($F(2, 33)=6.45$, $p<.01$) was observed. Fisher's LSD post hoc tests revealed that rats in the 1.5 mg/kg AMPH experiment had decreased activity following SAL relative to rats in the 0.1 and 0.5 mg/kg AMPH experiments ($p<.01$ and $p<.05$, respectively).

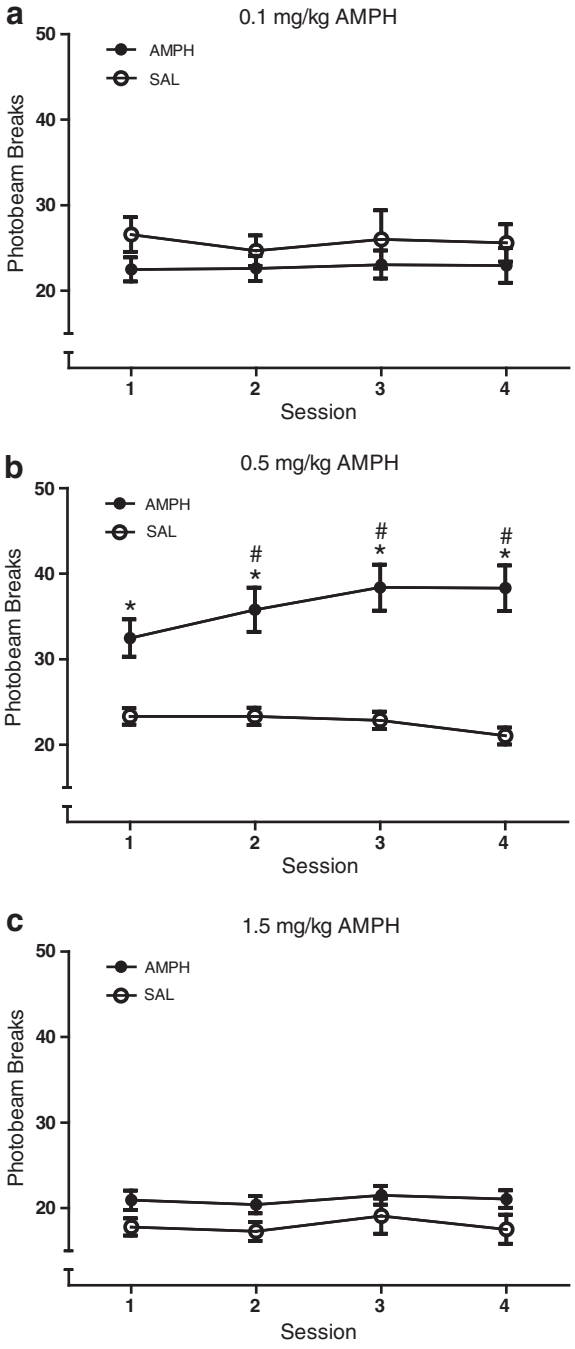


**Fig. 2.** a) Total number of photobeam breaks (mean ± SEM) for rats (n = 12) on sessions following 0.1 mg/kg of AMPH or SAL in Experiment 1. b) Total number of photobeam breaks (mean ± SEM) for rats (n = 12) on sessions following 0.5 mg/kg of AMPH or SAL in Experiment 2. c) Total number of photobeam breaks (mean ± SEM) for rats (n = 12) on sessions following 1.5 mg/kg of AMPH or SAL in Experiment 3. *$p<.01$, compared to SAL following Bonferroni correction. #$p<.05$, compared to Session 1.

### 3.2.1. Experiment 1: 0.1 mg/kg AMPH

ANOVA revealed no main effects or interactions (Fig. 2a).

### 3.2.2. Experiment 2: 0.5 mg/kg AMPH

ANOVA for activity following 0.5 mg/kg of AMPH revealed a main effect of Treatment ($F(1, 10)=46.42$, $p<.01$), as well as a significant Treatment × Session interaction ($F(3, 30)=7.24$, $p<.01$). However, since no differences were observed between HiI and LoI rats, the data for these groups were collapsed (Fig. 2b). To explore further the Treatment × Session interaction, two separate ANOVAs with Session as the within-subjects factor were conducted for each Treatment. There was an effect of session following AMPH ($F(3, 33)=13.26$, $p<.01$), but not following SAL. Fisher's LSD post hoc tests showed that AMPH-treated rats had increased activity on sessions 2, 3, and 4 compared to Session 1 (Session 2: $p<.01$; Session 3: $p<.01$; Session 4: $p<.05$), an effect indicative of sensitization. To compare locomotor activity following AMPH and SAL, paired-samples $t$ tests were conducted (with Bonferroni correction). AMPH increased activity compared to saline for all 4 sessions (all $t$'s>4.74; all $p$'s<.01).

### 3.2.3. Experiment 3: 1.5 mg/kg AMPH

ANOVA for activity following 1.5 mg/kg of AMPH revealed no significant main effects or interactions (Fig. 2c).

## 3.3. Conditioned place preference

When the data were collapsed across all 3 experiments, an overall ANOVA revealed main effects of Group ($F(1, 30)=5.17$, $p<.05$) and Dose ($F(2, 30)=10.21$, $p<.01$). Fisher's LSD post hoc tests revealed that rats treated with 0.5 and 1.5 mg/kg of AMPH had significantly higher difference scores relative to rats treated with 0.1 mg/kg of AMPH ($p$'s<.01).

### 3.3.1. Experiment 1: 0.1 mg/kg AMPH

Neither HiI nor LoI rats had difference scores significantly different from 0 (Fig. 3, left bars); no significant difference was observed between HiI and LoI rats.

### 3.3.2. Experiment 2: 0.5 mg/kg AMPH

HiI rats had a preference for the chamber previously paired with AMPH ($t(5)=6.97$, $p<.01$); however, LoI rats showed no significant preference for either chamber (Fig. 3, center bars). HiI rats had a

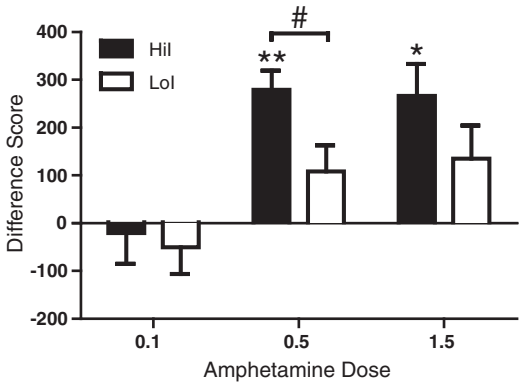


**Fig. 3.** Difference score for HiI (n = 6 per dose) and LoI (n = 6 per dose) rats; each dose was tested in a separate experiment. A difference score of 0 indicates no preference for either chamber, a difference score above 0 indicates a preference for the chamber previously paired with AMPH, and a difference score below 0 indicates a preference for the chamber previously paired with SAL. *$p<.05$, compared to a difference score of 0; **$p<.01$, compared to a difference score of 0; #$p<.05$, compared to LoI.

significantly higher difference score relative to LoI rats ($t(10) = 2.52$, $p < .05$).

*3.3.3. Experiment 3: 1.5 mg/kg AMPH*

HiI rats had a preference for the chamber previously paired with AMPH ($t(5) = 3.97$, $p < .05$); however, LoI rats showed no significant preference for either chamber (Fig. 3, right bars). No significant difference was observed between HiI and LoI rats.

## 4. Discussion

This study demonstrates that HiI rats assessed in DD are more sensitive than LoI rats to the rewarding effects of AMPH measured by CPP. HiI rats developed CPP for the compartment previously paired with 0.5 and 1.5 mg/kg of AMPH, while LoI rats failed to develop CPP to any dose. Direct comparisons between groups revealed that HiI rats had significantly higher CPP following 0.5 mg/kg AMPH compared to LoI rats. It is surprising LoI rats failed to develop CPP to any dose tested, although the nonsignificant trend observed in Fig. 3 suggests that higher doses and/or more conditioning trials could potentially induce CPP in LoI rats. In any case, these results are consistent with previous research showing that rats high in impulsive choice consume more ethanol (Poulos et al., 1995) and self-administer more of a low unit dose of MPH compared to rats low in impulsive choice (Marusich and Bardo, 2009). Moreover, these results are consistent with evidence that HiI rats acquire cocaine self-administration at a faster rate than LoI rats (Perry et al., 2005, 2008a) and transition to escalated (Dalley et al., 2007) and compulsive (Belin et al., 2008) cocaine self-administration. These findings extend the literature by demonstrating that the ability of DD to predict drug reward generalizes to a non-operant Pavlovian procedure (CPP), thus ruling out possible interpretations based on individual differences in incentive salience of the manipulandum and discrete reward-associated stimuli (i.e., sign-tracking; Tomie et al., 1998, 2008).

Traditionally, drug self-administration has been considered to measure the direct reinforcing effects of a drug, whereas CPP has been viewed as assessing the conditioned rewarding effects of a drug (Bardo and Bevins, 2000). Generally, drugs that are self-administered produce CPP, although some discrepancies exist. Pentobarbital and phencyclidine are self-administered by rats but do not support CPP; conversely, lysergic acid diethylamide (LSD), buspirone, and pentylenetetrazole produce CPP but are not self-administered (Bardo and Bevins, 2000). In addition, Bardo et al. (1999) found no correlation between AMPH CPP and self-administration in rats. Further, rats housed in environmental enrichment display greater AMPH CPP (Bardo et al., 1995; Bowling and Bardo, 1994) but self-administer less AMPH (Bardo et al., 2001; Green et al., 2002) compared to isolated and socially housed rats. Similarly, environmentally enriched rats show enhanced cocaine CPP but self-administer less cocaine (Green et al., 2010). These discrepancies indicate clearly that drug self-administration and CPP are not isomorphic, but instead measure different aspects of drug reward. Self-administration requires operant conditioning and models drug-taking behavior, whereas CPP relies on Pavlovian conditioning and models how drug-associated cues maintain addictive behavior (Aguilar et al., 2009). According to Bardo and Bevins (2000), contextual and environmental cues contribute to addiction because these cues set the occasion for drug-taking behavior. Furthermore, context contributes to drug relapse following abstinence (see Bouton, 2002 for a review). Although these paradigms are not isomorphic, they both contribute to an understanding of the abuse potential of drugs, and thus together suggest that impulsive choice is a useful predictor of drug abuse liability.

One potential limitation to this experiment is that, similar to self-administration, CPP may result from sign-tracking (Newlin, 1992). That is, HiI rats may spend more time in the compartment previously paired with AMPH because they attribute incentive salience to the diffuse contextual cues that have been paired with drug exposure. However, Flagel et al. (2009) have suggested that behavior during CPP testing does not likely result from sign-tracking. For example, while discrete visual cues can be used to produce CPP, they are ineffective when presented in different spatial locations within the contextual compartment (Cunningham et al., 2006), a finding that would not be predicted if animals were sign-tracking to the discrete visual stimulus. Clearly, more work needs to be conducted to elucidate the relationship between incentive salience and CPP.

Another potential confound with CPP is the influence of novelty-seeking behavior during the posttest. According to Bardo and Bevins (2000), pairing the drug in one context can block familiarization to that context. Subsequently, this context will be more novel relative to the context paired with saline during the posttest. In the current experiment, a three compartment CPP apparatus was used, such that on the test day one compartment was drug-paired, one was saline-paired, and one was non-paired (novel). Previous research has demonstrated that animals prefer a context previously paired with drug relative to a novel context (Mucha and Iverson, 1984; Parker, 1992). Therefore, the influence of novelty-seeking does not likely account for the differential sensitivity of AMPH reward between HiI and LoI rats in the current study.

Although the current results do not address directly the neural mechanisms involved in the association between DD and AMPH CPP, it is well known that AMPH exerts its rewarding effects, at least in part, by increasing dopamine (DA) levels in the nucleus accumbens (Berman et al., 2009; Ranaldi et al., 1999). The neural basis for impulsivity is complex and involves several brain structures, with both DA and 5-HT influencing this behavior (Bechara, 2001). Impulsive choice has been linked to DA activity in orbitofrontal cortex (OFC) since damage to this region with excitotoxic or DA-depleting agents increases impulsivity measured by DD (Kheramin et al., 2004; Mobini et al., 2002; Rudebeck et al., 2006, but see Winstanley et al., 2004). The nucleus accumbens has also been implicated in impulsive choice since damage to this region increases preference for small, immediate rewards in a DD task (Cardinal et al., 2001; Pothuizen et al., 2005). Thus, it is possible that the relation between DD and AMPH CPP reported here relates to individual differences in overlapping DA systems.

No differences were observed between HiI and LoI rats to the locomotor stimulant effects of AMPH in the current study. Administration of 0.1 mg/kg of AMPH failed to increase locomotor activity, which is congruent with a previous finding (Bardo et al., 1999). In contrast, locomotor activity increased in HiI and LoI rats following acute administration of 0.5 mg/kg of AMPH, and sensitization was observed across repeated injections. When 1.5 mg/kg of AMPH was administered, no changes in locomotor activity were observed, which was unexpected because at least one study reported increased activity in rats following s.c. administration of this dose (Olmstead and Franklin, 1994). One possible explanation for the current outcome is that 1.5 mg/kg of AMPH produced stereotypic behavior that competed with horizontal locomotion. Fritts et al. (1997) observed that rats given 2 mg/kg of AMPH (s.c.) displayed stereotypic behavior. However, since the current study did not measure stereotypy, it is not possible to ascertain if stereotypy influenced locomotion at the highest AMPH dose tested.

In conclusion, this study demonstrates that rats classified as HiI or LoI are differentially sensitive to the rewarding effect of AMPH, a common pharmacotherapy for ADHD patients. These results are concordant with previous preclinical results demonstrating that increased levels of impulsivity predict ethanol consumption (Poulos et al., 1995), cocaine self-administration (Belin et al., 2008; Dalley et al., 2007; Perry et al., 2005, 2008a), and methylphenidate self-administration (Marusich and Bardo, 2009). Thus, these results strengthen the evidence indicating that impulsive behavior is a risk factor for stimulant abuse.

## Acknowledgements

This research was supported by NIH grant P50 DA05312.

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