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Natashia Swalve  
*University of Nebraska-Lincoln*

Scott T. Barrett  
*University of Nebraska-Lincoln, [scott.barrett@unl.edu](mailto:scott.barrett@unl.edu)*

Rick A. Bevins  
*University of Nebraska-Lincoln, [rbevins1@unl.edu](mailto:rbevins1@unl.edu)*

Ming Li  
*University of Nebraska-Lincoln, [mli2@unl.edu](mailto:mli2@unl.edu)*

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## Examining the Reinforcement-Enhancement Effects of Phencyclidine and Its Interactions with Nicotine on Lever-Pressing for a Visual Stimulus

Natashia Swalve, Ph.D.\* , Scott T. Barrett, Ph.D., Rick A. Bevins, Ph.D., and Ming Li, Ph.D.  
Department of Psychology, University of Nebraska-Lincoln, Lincoln, NE, 68588, USA

### Abstract

Nicotine is a widely-abused drug, yet its primary reinforcing effect does not seem potent as other stimulants such as cocaine. Recent research on the contributing factors toward chronic use of nicotine-containing products has implicated the role of reinforcement-enhancing effects of nicotine. The present study investigates whether phencyclidine (PCP) may also possess a reinforcement-enhancement effect and how this may interact with the reinforcement-enhancement effect of nicotine. PCP was tested for two reasons: 1) it produces discrepant results on overall reward, similar to that seen with nicotine and 2) it may elucidate how other compounds may interact with the reinforcement-enhancement of nicotine. Adult male Sprague-Dawley rats were trained to lever press for brief visual stimulus presentations under fixed-ratio (FR) schedules of reinforcement and then were tested with nicotine (0.2 or 0.4 mg/kg) and/or PCP (2.0 mg/kg) over six increasing FR values. A selective increase in active lever-pressing for the visual stimulus with drug treatment was considered evidence of a reinforcement-enhancement effect. PCP and nicotine separately increased active lever pressing for a visual stimulus in a dose-dependent manner and across the different FR schedules. The addition of PCP to nicotine did not increase lever-pressing for the visual stimulus, possibly due to a ceiling effect. The effect of PCP may be driven largely by its locomotor stimulant effects, whereas the effect of nicotine was independent of locomotor stimulation. This dissociation emphasizes that distinct pharmacological properties contribute to the reinforcement-enhancement effects of substances.

### Keywords

nicotine; phencyclidine; reinforcement; rats; operant behavior

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\*Corresponding author: University of Minnesota, 680A Diehl Hall, 550 Essex Street SE, Minneapolis, MN 55455, 612-624-8432, nlswalve9220@gmail.com.

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**Conflicts of interest:** None

## 1. Introduction

Tobacco use is a costly and deadly health problem in the United States and globally. Every year, more Americans die from tobacco related disease than the total number of US casualties across the entirety of World War II (United States Department of Health and Human Services, 2014). Scientists generally agree that nicotine is the main constituent of tobacco to which users develop dependence (LaViolette & van der Kooy, 2004; United States Department of Health and Human Services, 1988; Karan et al., 2003; Rose, 2006). This agreement is notable in light of the growing literature suggesting that nicotine may have limited primary reinforcing effects (Donny et al., 2003; Chaudhri et al., 2006; Caggiula et al., 2009; Palmatier et al., 2006; Henningfield & Goldberg, 1983; Dougherty et al., 1981).

One possible mechanism that may bridge the gap between limited reinforcing effects and the prevalence of chronic tobacco use is the reward or reinforcement-enhancement effect of nicotine. For the smoker, this means that other reinforcers ongoing while smoking (i.e., self-administering nicotine) may be more potent than when not smoking (see Caggiula et al., 2009 for a review). In laboratory studies, this effect is shown by increased operant responding in rodents for a variety of rewards such as food (Barrett and Bevins, 2013; Palmatier et al., 2013) and visual stimuli (Donny et al., 2003; Barrett and Bevins, 2012) after nicotine exposure. In addition, this effect is not specific to non-human animals, as increased levels of responding for music has been shown in humans after nicotine exposure (Perkins and Karelitz, 2013). Importantly, this enhancement effect on operant responding by nicotine appears to be indicative of a change in the value of maintaining reinforcement, rather than the result of the locomotor stimulating properties of nicotine (cf. Donny et al., 2004; Barrett and Bevins, 2012; 2013).

This reinforcement-enhancement effect has been seen with a number of drugs other than nicotine; these include caffeine, amphetamine, cocaine, and pipradrol (Shepard et al., 2012; Hill, 1970; Phillips and Fibiger, 1990; Robbins and Koob, 1978; Beninger et al., 1980; 1981). Notably, this effect has not been tested in phencyclidine (PCP). The importance of examining reinforcement-enhancement in PCP is twofold: 1) studies on the primary reinforcer value of phencyclidine have yielded discrepant results in rodents (Hillhouse et al., 2014; Amitai et al., 2009; Kornetsky & Esposito, 1979; Carlezon & Wise, 1993, 1996; Collins et al., 1984; Lydall et al., 2010; Crider, 1986; Barr et al., 1985; Iwamoto, 1986) and 2) PCP exposure is a commonly used preclinical model of positive, negative and cognitive symptoms of schizophrenia in rodents and schizophrenia has a particularly high incidence of comorbidity with nicotine dependence (Neill et al., 2010; Jones et al., 2011; Jentsch & Roth, 1999; Kumari & Postma, 2005; Hughes et al., 1986; O'Farrell et al., 1983).

Nicotine and PCP share similarities with respect to abuse liability. Both are abused by humans although their primary reinforcing properties could be considered to be relatively weak. Though humans, primates and rodents will self-administer PCP, the rate of self-administration is relatively low in comparison to other drugs of abuse such as opiates and stimulants (Newman et al., 2006, 2008; Crider, 1986; Balster & Woolverton, 1980; Carroll et al., 1981). Further, self-administration of PCP in rodents has also been particularly difficult to find (Collins et al., 1984). In other experimental situations, conclusions regarding

the overall rewarding effect of PCP have been mixed. Intracranial self-stimulation tasks have shown an increase and decrease in stimulation thresholds depending on the time point studied and measurement procedure, suggesting a decrease and increase in reward-related behavior, respectively (Amitai et al., 2009; Kornetsky & Esposito, 1979; Carlezon & Wise, 1993, 1996). In addition, acute and chronic exposure to PCP in a sucrose-licking task found no effect on the total amount of sucrose consumed separate from motor confounds (Lydall et al., 2010). Given the abuse liability of PCP, the divergent findings with PCP on reward-related behaviors suggest an additional mechanism might be important.

It is also unclear whether there is an interaction between the reinforcement-enhancement effect in nicotine and other drugs. Nicotine (in tobacco form) is widely used in conjunction with other drugs such as alcohol and cocaine (Grant et al., 2004; Epstein et al., 2010). Notably, rates of smoking are 2 to 4 times higher in patients with another substance-use disorder (Gulliver et al., 2005, 2000; Budney et al., 1993; Kalman et al., 2005). There has been little attention to how the reinforcement enhancement effects of nicotine interact with the effects of other drugs of abuse. To this end, the present study examined whether PCP shows a reinforcement-enhancement effect similar to that of nicotine and whether the combination interacts in a unique manner to alter reinforcer enhancement effects in rats. Lever-pressing for a visual stimulus was trained in drug-naïve rats and then tested after treatment with nicotine, PCP, or nicotine plus PCP. Previous studies in our lab using a similar procedure found robust differences between nicotine- and saline-treated rats (Barrett & Bevins, 2012; 2013). If PCP has a reinforcement-enhancement effect, we should observe selective increases in active-lever pressing maintained by visual stimuli, similar to that found with nicotine. If PCP alters the reinforcement-enhancement effect of nicotine, the rats that received the combination should differ from the nicotine alone and PCP alone groups. An increase would suggest a synergism (e.g., summative effect), whereas a decrease would suggest interference (e.g., antagonism).

## 2. Materials and methods

### 2.1 Subjects

Forty-eight adult male Sprague Dawley rats (226-250 g upon arrival, Charles River, Portage, MI) were used. One rat was unable to complete the study and was not included in the analysis. Rats were individually-housed in clear rectangular polycarbonate tubs (48.3 cm × 26.7 cm × 20.3 cm) under 12-h light/dark conditions (light on between 6:30 am and 6:30 pm). Room temperature was maintained at 22±1° C with a relative humidity of 45-60%. Water was continuously available in the home cage. Access to food was restricted to maintain rats at 90% of their free-feeding weight. After four weeks, the target weight was increased by 2 g. Animals were allowed 5 days of habituation to the animal facility before being used in experiments. During the final two days of this habituation period, each experimenter handled each rat for approximately 2.5 min per day. All experiments were performed during the light cycle and all procedures were approved by the Institutional Animal Care and Use Committee at the University of Nebraska-Lincoln.

## 2.2 Drugs

Phencyclidine hydrochloride (PCP, received from the NIDA Chemical Synthesis and Drug Supply Program) was dissolved in 0.9% saline (w/v). (-)Nicotine tartrate salt (Sigma, St. Louis, MO) was dissolved in 0.9% saline and adjusted to a pH of  $7.0 \pm 0.2$  with a dilute NaOH solution. Saline, nicotine, and PCP were all administered subcutaneously. Nicotine dose was based on previous research showing that 0.4 mg/kg nicotine produced a robust reinforcement-enhancement effect (Barrett & Bevins, 2012; 2013). The dose of PCP was 2.0 mg/kg and was chosen based on pilot data suggesting that this dose would not significantly differ from other doses on locomotor activity or operant behavior measures and has been frequently used to produce psychoactive effects of PCP (Smith et al., 2011; Idris et al., 2005; Schreiber et al., 2000; Corbett et al., 1995; Jarbe et al., 1975; White & Holtzman, 1983). All drugs were administered at a volume of 1 ml/kg.

## 2.3 Apparatus

Sessions were conducted in eight conditioning chambers (ENV-008CT; Med Associates, Inc., St. Albans, VT;  $30.5 \times 24.1 \times 21.0$  cm,  $l \times w \times h$ ) enclosed in light- and sound-attenuating cubicles fitted with a fan used to mask noise and provide airflow. The sidewalls of the chambers were aluminum while the ceiling and front and back walls were clear polycarbonate. One sidewall featured a dipper receptacle, occupying a  $5.2 \times 5.2 \times 3.8$  cm ( $l \times w \times h$ ) recessed space, into which a dipper arm when raised provided 0.1 ml of 26% sucrose solution (w/v) into the receptacle. Retractable levers were featured on either side of the dipper receptacle, approximately 5 cm from the chamber floor. White 28V DC lamps (100 mA) were located 3 cm above each lever, which will be referred to as cue lights. Two external 28V 100-mA DC lamps were also located above the chamber but within the sound attenuating cubicle, which will be referred to as the house light. An infrared emitter/detector unit positioned 4 cm above the rod floor bisected the chamber 14.5 cm from the sidewall featuring the dipper receptacle monitored general locomotor activity during experimental sessions. A computer running Med Associates interface and software (MedPC for Windows, IV) controlled stimulus presentations and recorded data.

## 2.4 Procedure

Lever-press training. All rats were first trained to lever-press maintained by sucrose in four consecutive sessions, approximately an hour in length. During these sessions, non-contingent sucrose was available on a variable time (VT) schedule, starting with a VT 30 s on day one and fading to VT 180 s on the final day. Sucrose was also contingently available during these sessions on a fixed-ratio 1 (FR1) schedule by a lever-press on either the right or left lever. Both levers were presented initially and each lever-press resulted in a 4-sec presentation of sucrose followed by retraction of that lever and presentation of the opposite lever. This procedure ensured that rats received equal experience with reinforcement on both levers. The house light was illuminated throughout all lever-press training sessions and no cue lights were presented. To ensure all rats were lever-pressing at relatively high levels, there were 4 additional days of lever press training. During these additional days, the house light remained on and a randomly selected lever was inserted into the chamber. A lever-press or a lapse of 15 sec resulted in a sucrose delivery, retraction of the lever, and a 20-

second timeout. Following the timeout, a randomly selected lever was inserted into the chamber with the condition that the same lever was not presented more than twice in a row. The session ended after 60 sucrose deliveries (range = 65-80 min). One rat did not reach criterion (at least 80% of sucrose deliveries from lever-pressing) by the final day of training and was excluded from the study.

Lever-pressing for a visual reinforcer. For the first five days of this phase, rats were trained to lever-press for a visual stimulus on a variable ratio 2 schedule (VR2). The active lever was pseudo-randomly assigned for each rat. Completion of the VR2 resulted in 60 sec termination of the houselights with a concurrent illumination of the cue lights for the initial 5 sec. Responses on the inactive lever produced no programmed consequence but were recorded. Lever-pressing during this training procedure was relatively low (mean  $\pm$  SEM) and lever discrimination was not consistently at high levels of active to inactive pressing so all rats were switched to a FR1 schedule for the next ten days of training to ensure a stable baseline.

Drug testing. After 10 days of training, rats were pseudo-randomly assigned into one of six groups with the condition that lever-pressing did not differ between groups. The six groups (n= 7-8 per group) were based on the drugs administered before each testing session: SAL-SAL, SAL-0.2N, SAL-0.4N, PCP-SAL, PCP-0.2N, or PCP-0.4N. On testing days, rats were injected with saline or PCP (2 mg/kg) 10 min before placement into the chamber. Rats were then injected with saline or nicotine (0.2 or 0.4 mg/kg) 5 min before placement in the chamber. Rats were allowed to lever press for visual stimuli arranged on a fixed ratio schedule over 60-min sessions, as described earlier. The FR schedule of visual-stimulus reinforcement increased over blocks of five sessions according to the following sequence: FR1, FR2, FR4, FR8, FR16, and FR32.

After thirty days of testing, all rats were left undisturbed in their home cages for seven days before undergoing four challenge days. During the challenge days, rats were tested on an FR2 schedule as reliable differences between groups were seen on this reinforcement schedule during the previous testing phase. For the first three days, all rats, regardless of group, were challenged with saline, 0.2 mg/kg nicotine, or 0.4 mg/kg nicotine in a counterbalanced fashion. After each challenge day, rats had one full day in their home cage to minimize potential carryover effects. Finally, two weeks later the fourth and final challenge of PCP (2 mg/kg) was given to all rats.

## 2.5 Dependent Measures and Statistical Analyses

The primary dependent measures throughout the experiment were number of lever presses on the active or inactive lever and the number of breaks of chamber infrared beam (i.e., activity). Data across the nicotine and PCP administration sessions of the escalating FR schedule were analyzed using targeted mixed-factor analyses of variance (ANOVA) with Group and FR Schedule as between- and within-subjects factors, respectively. For the nicotine and PCP challenge tests, one-way ANOVAs across groups were conducted. To reduce the risk of Type I and Type II errors, we conducted separate ANOVAs to evaluate the effects of nicotine in the absence of PCP (SAL-SAL vs SAL-0.2N vs SAL-0.4N), the effects of PCP in the absence of nicotine (SAL-SAL vs PCP-SAL), and the effects of PCP

on each dose of nicotine (SAL-0.2N vs PCP-0.2N and SAL-0.4N vs PCP-0.4N). Mauchly's test of sphericity (1940) was included as part of the ANOVAs; when sphericity was violated, Greenhouse-Geisser corrections was employed to determine significant main effects and interactions. Post-hoc pairwise comparisons were made using Fisher's Least Significant Difference (LSD) test and are reported as LSD minimum mean differences. A conventional alpha value of less than 0.05 was used to determine statistical significance.

### 3 Results

#### 3.1 Nicotine on Active Lever- Pressing

Figure 1A portrays the effects of administration of 0.2 or 0.4 mg/kg nicotine on active lever pressing as a function of FR schedule (groups SAL-SAL, SAL-0.2N and SAL-0.4N). Nicotine dose-dependently increased active lever pressing and this effect appeared enhanced with increases in FR schedule. Three factor, mixed factors ANOVA revealed significant main effects of Group [ $F(2,20)=5.34$ ;  $p=0.014$ ] and Schedule [ $F(5,100)=6.89$ ;  $p=0.005$ ], as well as a significant Group  $\times$  Schedule interaction [ $F(10,100)=3.64$ ;  $p=0.020$ ]. Post-hoc comparisons revealed that active lever pressing in the SAL-0.2N was significantly higher than SAL-SAL on schedules FR4 through FR32 [LSD =25.0]. Active lever pressing in the SAL-0.4N group was significantly higher than the SAL-SAL group across all FR schedules [LSD =25.0]. Active lever pressing was significantly higher in the SAL-0.4N group compared to the SAL-0.2N group on schedules FR8 through FR32. Changes in FR schedule produced no significant effects on active lever pressing in the SAL-SAL group. In the SAL-0.2N group, active lever pressing was higher on schedules FR8 and FR16 compared to FR1, and FR8 responding also differed from FR2. In the SAL-0.4N group, active lever pressing on schedules FR8 through FR32 was higher than on FR1 through FR4; responding on FR4 was also higher than responding on FR1.

#### 3.2 Nicotine on Inactive Lever-Pressing

Figure 1B depicts the effects on nicotine administration on inactive lever pressing across FR schedules. Both doses on nicotine increased inactive lever pressing, but this effect did not vary systematically with FR schedule. Analysis revealed a significant main effect of Group [ $F(2,20)=3.83$ ;  $p=0.039$ ], but not of Schedule [ $F(5,100)=2.25$ ;  $p=0.102$ ]. A significant Group  $\times$  Schedule interaction was also detected [ $F(10,100)=3.26$ ;  $p=0.012$ ]. Post-hoc comparisons revealed significantly higher inactive lever pressing in the SAL-0.2N and SAL-0.4N groups compared to SAL-SAL across all FR schedules [LSD =4.63]. Additionally, inactive lever pressing was significantly higher in the SAL-0.4N group compared to SAL-0.2N on FR16 and FR32.

#### 3.3 Nicotine on Activity

The effects of nicotine administration on locomotor activity are shown in Figure 1C. Nicotine at either dose increased locomotor activity above saline, though this effect did not vary with FR schedule. Analysis of the data revealed a significant main effect of Group [ $F(2,20)=15.9$ ;  $p<0.001$ ], but not of Schedule and no Group  $\times$  Schedule interaction [Fs 2.60;  $ps$  0.091]. Post-hoc comparisons on the effect of Group revealed that groups

SAL-0.2N and SAL-0.4N exhibited higher activity compare to SAL-SAL, but did not differ significantly from each other [LSD =242].

### 3.4 PCP on Lever-Pressing

The panels of Figure 2 depict the effects of PCP administered alone on lever pressing and locomotor activity as a function of FR schedule. PCP increased active lever pressing above saline levels. There was a tendency for this effect to increase with FR schedule (Figure 2A). The omnibus ANOVA revealed a significant main effect of Group [F(1,14)=6.53;  $p=0.023$ ]. The main effect of Schedule [F(5,70)=1.74;  $p=0.206$ ] and the Group  $\times$  Schedule interaction [F(5,70)=2.20;  $p=0.153$ ] were not significant. PCP also increased inactive lever pressing above saline levels, but this effect did not vary systematically with FR schedule (Figure 2B). The ANOVA revealed a significant effect of Group [F(1,14)=6.05;  $p=0.027$ ], but no main effect of Schedule [F(5,70)=1.05;  $p=0.353$ ] or Group  $\times$  Schedule interaction [F(5,70)=1.82;  $p=0.189$ ]. Finally, PCP increased locomotor activity relative to saline and this effect was also insensitive to changes in FR schedule (Figure 2C). Analysis revealed a significant effect of Group [F(1,14)=28.8;  $p<0.001$ ], but no main effect Schedule or Group  $\times$  Schedule interaction [Fs 1.01;  $ps$  0.343].

### 3.5 Interaction of 0.2 mg/kg Nicotine and PCP

The interaction of PCP administration with the behavioral effects of 0.2 mg/kg nicotine is shown in the panels of Figure 3. Active lever pressing in the PCP-0.2N group was elevated above that of the SAL-0.2N group across FR schedules (Figure 3A). Statistical analysis revealed significant main effects of Group [F(1,13)=5.26;  $p=0.039$ ] and of Schedule [F(5,65)=4.36;  $p=0.019$ ]; the Group  $\times$  Schedule interaction was not significant [F<1]. Post-hoc comparisons on the main effect of Schedule found significantly higher responding on schedules FR4 through FR32 compared to FR1 [LSD =20.2]. Inactive lever pressing was also higher in the PCP-0.2N group than the SAL-0.2N group across FR schedules (Figure 3B). The ANOVA revealed a significant main effect of Group [F(1,13)=8.57;  $p=0.012$ ]. There was no main effect of Schedule or Group  $\times$  Schedule interaction [Fs 1.24;  $ps$  0.30]. Finally, although rats in the PCP-0.2N group exhibited a tendency for greater locomotor stimulation that those of the SAL-0.2N group, this effect was not significant (Figure 3C; [Fs<1.09;  $ps>0.315$ ]).

### 3.6 Interaction of 0.4 mg/kg Nicotine and PCP

The effects of 0.4 mg/kg nicotine administered after saline or PCP are portrayed in the panels of Figure 4. In the PCP-0.4N and SAL-0.4N groups, active lever pressing increased as a function of FR schedule, with a tendency for higher responding in the PCP-0.4N group (Figure 4A). However, statistical analysis revealed only a main effect on Schedule [F(5,70)=8.78;  $p=0.005$ ]; there was no main effect of Group or an interaction [Fs 2.89;  $ps$  0.111]. Follow-up pairwise comparisons on the effect of Schedule found significantly higher responding on FR16 and FR32 compared to schedules FR1 through FR4, and significantly higher responding on FR8 compared to FR1 [LSD =41.7]. Inactive lever pressing had a tendency to be higher in the PCP-0.4N group (Figure 4B), but the main effects and interaction were not statistically significant [Fs 2.81;  $ps$  0.116]. Likewise,



analysis of the locomotor data (Figure 4C) found no effects of Group or Schedule, and no interaction [Fs 2.67;  $ps$  0.124].

### 3.7 Effects of PCP on Nicotine Dose Effect

An analysis of the effects of Group and Schedule between the PCP-SAL, PCP-0.2N and PCP-0.4N groups reveals no significant Group main effect or Group  $\times$  Schedule interaction [Fs 2.36;  $ps$  0.119]. There was a significant main effect of Schedule [F(5,105)=7.12;  $p=0.006$ ].

### 3.8 Demand Analysis

To determine whether an alternative measure of reinforcement value would corroborate our findings with lever-pressing rates, we fit the reinforcer demand model (Hursh and Silberberg, 2008) to the data in the present experiment, and conducted two-factor ANOVAs on the model estimate of “essential value” ( $\alpha$ ) with Nicotine and PCP conditions as between-subject factors. Analyses revealed that nicotine significantly enhanced “essential value” of VS presentation as a reinforcer [F(2,39)=3.78;  $p=0.032$ ] while PCP had no effect and there was no interaction between Nicotine and PCP conditions [Fs 2.39;  $ps$  0.130].

### 3.9 Challenge Days

Analyses of the challenge test data found no significant effects of Group on active lever-pressing, inactive lever-pressing, or activity following challenge with 0.2 mg/kg nicotine, 0.4 mg/kg nicotine, or 2 mg/kg PCP [Fs 3.62;  $ps$  0.078]. That is, none of the groups differed from each other in responsiveness to PCP or either dose of nicotine despite their differential histories with nicotine and PCP.

## 4. Discussion

The current study was designed to determine whether PCP had a reinforcement-enhancement effect on responding for a visual stimulus similar to that reported for nicotine. We also assessed the potential interaction between PCP and nicotine on operant responding for a visual stimulus. PCP and nicotine increased active lever presses for a visual stimulus in comparison to saline controls and this effect was sustained as the FR schedule increased to an FR32. Interestingly, PCP further enhanced responding when given with a low dose of nicotine (0.2 mg/kg). This effect was dose-dependent, as the combination of PCP and the high dose of nicotine did not change responding.

One notable finding from this study is that PCP increased active lever-pressing for a visual stimulus. We also found that nicotine, at both doses, and PCP increased rates of general locomotor activity but only when compared to rats that only received saline (i.e., SAL-SAL). That is, both drugs produced locomotor activation, but the combination of nicotine and PCP administration had no detectable additive effects on general activity. While the effects of nicotine and PCP are parallel for general activity, PCP also increased rates of inactive lever pressing as a function of FR Schedule, while nicotine did not. Put simply, PCP enhanced levels of general activity and lever pressing *irrespective of lever*, whereas nicotine enhanced general activity and lever pressing *specific to the active lever*. In a similar vein,

PCP did not show an increase of active lever pressing across FR values, which would be expected given that an increasing number of lever presses are required for each presentation of the visual stimulus. Combined, the present findings suggest that while both nicotine and PCP increase levels of operant responding for sensory stimuli, the effect of nicotine reflect an enhancement of the reward value of the visual stimulus, whereas the effect of PCP appears to be driven more by motor stimulation. There are many ways that changes in reinforcement value can be assessed; of which response rates on ratio-based schedules of reinforcement is one approach. Previous work from our laboratory (Barrett and Bevins, 2012) and that of Dallery and colleagues (Cassidy and Dallery, 2012) have demonstrated how the application of behavioral economic modeling provides a power method for the quantitative assessment of the value-altering effects of nicotine. Briefly, by fitting the reinforcer demand model proposed by Hursh and Silberberg (2008) to the data of individuals, one can quantifiably estimate the “essential value” of a reinforcer under different conditions as a reflection of sensitivity of individuals toward defending levels of reinforcer consumption (i.e., number of VS presentations earned) in the face of increasing response cost (i.e. FR schedule). Such an analysis here revealed that nicotine increased the essential value measure, whereas there was no effect of PCP. This demand analysis supports the earlier conclusion that nicotine enhanced the value of the VS reinforcer in the present study, yet PCP under the conditions of this study had no effect on reinforcement value.

The effects of PCP alone on this measure are somewhat surprising given previous work on the effects of PCP on reward. Pre-treatment with PCP produces a threshold increase in intracranial self-stimulation. However, this effect was attenuated and ultimately reversed after repeated PCP treatment, suggesting that initial PCP exposure produced an anhedonic-like effect which eventually dissipates and even leads to increased reward functioning (Amitai et al., 2009). This conversion from deficit to reward has been seen in the place conditioning procedures as well, with the initial conditioned place aversion switching to a conditioned place preference after repeated treatment (Kitaichi et al., 1996). In addition, PCP at the dose used in this work (2.0 mg/kg) in the 5-CSRTT paradigm produced initial non-specific response-depressant effects (Amitai et al., 2007). However, in the present task, PCP produced an increase in lever-pressing on all FR schedules, beginning on the 1<sup>st</sup> day. The lack of the similar effects in these behavioral tasks is somewhat puzzling but could reflect the inherent differences between operant responding for a visual stimulus and the more cognitively-focused 5-CSRTT task. Either way, further examination of the influences of PCP on measures of reinforcement value could be illuminating, especially by utilizing a procedure less susceptible to being influenced by alterations in activity.

Co-administration of PCP and nicotine increased lever-pressing relative to the nicotine-alone groups, suggesting that there may be an interaction between these two drugs. The increase in responding for the PCP-0.2N group may be due to an additive influence of PCP-induced hyperlocomotion combined with the reinforcement-enhancement effect of nicotine. This interpretation is supported by the lack of interactions between group and schedule as well as the lack of change in responding over FR values. In addition, a combined analysis showed that active lever-pressing in the PCP-SAL group did not vary significantly with changes in FR schedule, but the addition of 0.2 or 0.4 mg/kg nicotine in the PCP-0.2N and PCP-0.4N groups resulted in significant effects of FR schedule in both of these groups.

A potential limitation of this study is the use of a single dose of PCP. It may be possible that the lack of a reinforcement-enhancement effect seen in this study is specific only to the dose used. However, this is relatively unlikely. Preliminary data showed no main effect between this dose of PCP and two other doses (PCP 1.0 mg/kg and PCP 3.0 mg/kg) over 5 days of lever-pressing on an FR1 for a visual stimulus. In addition, higher doses of PCP (2.5 mg/kg and higher) have shown to significantly decrease operant behavior over a number of schedules (Gilmour et al., 2009).

PCP increased lever-pressing for a visual stimulus similar to that seen with nicotine and co-administration of PCP and low dose nicotine led to an increase in lever-pressing over nicotine alone. However, in comparison to the reinforcement-enhancement effect of nicotine, the reinforcement-enhancement effect of PCP seems to be primarily controlled by the locomotor potentiation effect of PCP. In addition, the interaction effect seems to be driven by the effects of PCP, which again could be due to its locomotor effects. Further exploration of the reinforcement-enhancement effect of PCP is warranted, specifically in a model of reinforcement-enhancement that may not be as influenced by differences in activity. The interaction of PCP as well as other drugs and the reinforcement-enhancement effect could provide valuable information on the comorbidity of nicotine use and other substances.

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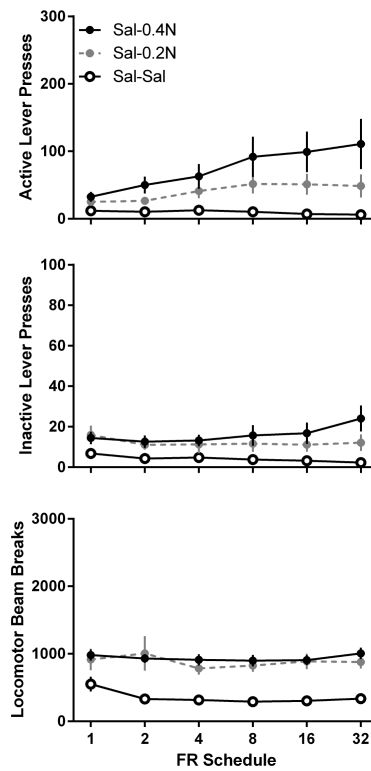
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### Highlights

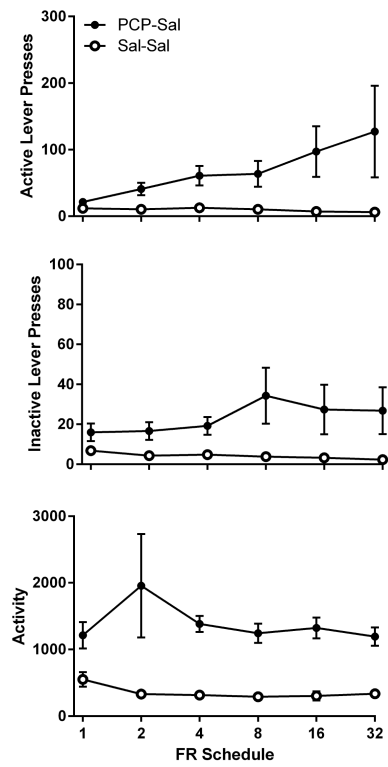
- ▶ PCP increased lever-pressing for a visual stimulus.
- ▶ Two doses of nicotine increased lever-pressing for a visual stimulus.
- ▶ The combination of PCP and nicotine did not increase lever-pressing.
- ▶ The effect of PCP on lever-pressing may be due to motor activation.



**Figure 1.**

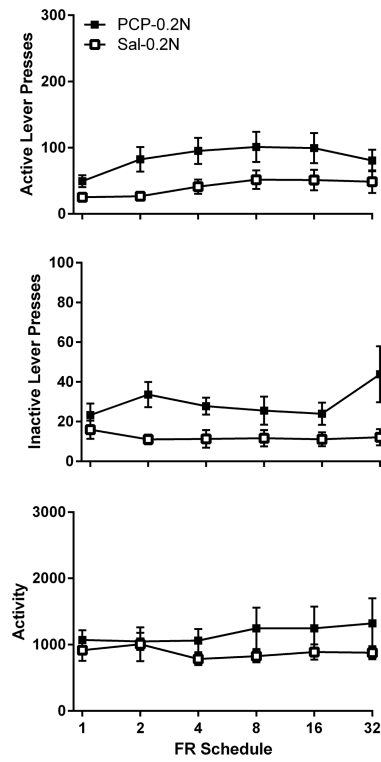
Panel A displays active lever pressing for visual stimulation as a function of FR schedule in animals treated with saline alone or either dose of nicotine. Panel B shows inactive lever-pressing and Panel C shows overall activity as measured by locomotor beam breaks for the same groups. Data is expressed as the mean ( $\pm$  SEM) over the terminal three sessions of each 5 session FR schedule block.





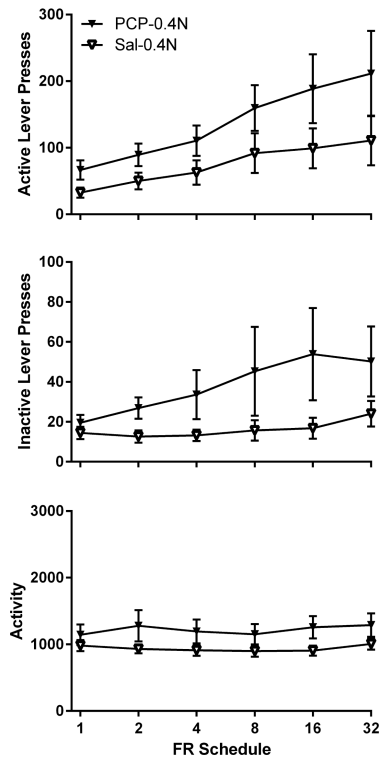
**Figure 2.**

Panel A displays active lever pressing for visual stimulation as a function of FR schedule comparing animals treated with PCP to animals treated with saline. Panel B shows inactive lever-pressing and Panel C shows overall activity as measured by locomotor beam breaks for the same groups.



**Figure 3.**

Panel A displays active lever pressing for visual stimulation as a function of FR schedule comparing animals treated with PCP and NIC 0.2 mg/kg to animals treated with NIC 0.2 mg/kg. Panel B shows inactive lever-pressing and Panel C shows overall activity as measured by locomotor beam breaks for the same groups.



**Figure 4.**

Panel A displays active lever pressing for visual stimulation as a function of FR schedule comparing animals treated with PCP and NIC 0.4 mg/kg to animals treated with NIC 0.4 mg/kg. Panel B shows inactive lever-pressing and Panel C shows overall activity as measured by locomotor beam breaks for the same groups.