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Caffeine increases the motivation to obtain non-drug reinforcers in rats

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Abstract

BACKGROUND—Caffeine is widely considered to be a reinforcer in humans, but this effect is difficult to measure in non-human animals. We hypothesized that caffeine may have dual reinforcing effects comparable to nicotine - limited primary reinforcing effects, but potent reinforcement enhancing effects. The present studies tested this hypothesis by investigating the effect of caffeine on responding for non-drug rewards.

METHODS—In two experiments, rats were shaped to respond on a progressive ratio (PR) schedule for sucrose solution (20% w/v; Experiment 1) or a fixed ratio 2 (FR2) schedule for a moderately reinforcing visual stimulus (VS; Experiment 2). Pretreatment with various doses of caffeine (0–50 mg/kg, intraperitoneal injection) were administered prior to tests over successive week days (M-F). In Experiment 1, acute administration of low-moderate caffeine doses (6.25–25 mg/kg) increased responding for sucrose under the PR schedule. This effect of caffeine declined over the initial 15 test days. In Experiment 2, only acute pretreatment with 12.5 mg/kg caffeine increased responding for the visual stimulus and complete tolerance to this effect of caffeine was observed over the 15 days of testing. In follow up tests we found that abstinence periods of 4 and 8 days resulted in incomplete recovery of the enhancing effects of caffeine.

CONCLUSION—The findings suggest that caffeine enhances the reinforcing effects of non-drug stimuli, but that the pharmacological profile of these effects may differ from other psychomotor stimulants.

Keywords

caffeine; self-administration; reinforcement; motivation

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Contributors. A. Brianna Sheppard wrote the majority of the manuscript, conducted all of the statistical analyses and assisted in conducting the experiments. Sarah Pavelka and Skyler Gross oversaw and conducted the experimental procedures for Experiments 1 and 2, respectively and assisted with data processing and analyses. Melanie Hall conducted original pilot work for the experiments, without which dose-selection would have been misinformed. She also assisted with data collection, processing, and analyses for Experiment 1. Dr. Palmatier designed the experiments and supervised all other aspects of the research presented in the manuscript.

Conflict of Interest. All authors declare that they have no conflicts of interest.

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1. INTRODUCTION

Caffeine is found in several over-the-counter medications, foods, and beverages and has been described as the most commonly used psychoactive drug in the world (Glade, 2010). Many of the foods and medicines which contain caffeine have only moderate amounts which do not produce detectable psychoactive effects (Heckman et al., 2010). However, caffeine-containing beverages such as coffee, tea, and carbonated drinks have higher levels which can produce subjective stimulant effects (Heckman et al., 2010). Recent increases in the popularity of these beverages, as well as energy drinks and caffeinated alcoholic beverages, have stimulated interest in the psychoactive effects of caffeine.

The psychoactive effects of caffeine share many characteristics with nicotine. Both drugs produce subjective effects that are characteristic of psychomotor stimulants (Benwell and Balfour, 1992; Lau and Falk, 1995); however, these effects are moderate in comparison to the more prototypical stimulants such as amphetamine (Antoniou et al., 1998; Boye et al., 2001). Both drugs increase attention and vigilance (Brunye et al., 2010; Caballero et al., 2011; Vangkilde et al., 2011) and neither of the drugs is a strong intoxicant – intoxicating effects are limited to high dosages and are often described as aversive (Perkins et al., 2003; Sigmon and Griffiths, 2011). Both drugs are reinforcers in humans (Griffiths and Chausmer, 2000; Perkins et al., 2004), however, their abuse liability has been questioned, which may stem from another shared characteristic of nicotine and caffeine: the difficulty of measuring their reinforcing effects in non-human subjects (Atkinson and Enslen, 1976; Hoffmeister and Wuttke, 1973; Myers and Izbicki, 2006). While this difficulty has been the subject of much scrutiny for nicotine (Caggiula et al., 2009; Caggiula, 2001; Rose, 2006; Sorge and Clarke, 2009), it has not received as much attention in characterization of the psychoactive effects of caffeine (see Griffiths and Chausmer, 2000 for review).

Caffeine presents a paradox; the drug is widely used for its psychoactive effects and can produce a pattern of use which is characteristic of dependence (Griffiths and Chausmer, 2000). Caffeine serves as a primary reinforcer in humans (Griffiths and Chausmer, 2000; Schuh and Griffiths, 1997), and can also establish novel tastes as conditioned reinforcers (Yeomans et al., 2005; Yeomans et al., 2007), yet the evidence for primary reinforcement in non-human animals is limited (Atkinson and Enslen, 1976; Hoffmeister and Wuttke, 1973; Myers and Izbicki, 2006). Caffeine, like nicotine, is often taken in the context of other potent stimuli – especially taste stimuli. More importantly, despite limited success demonstrating primary reinforcement by caffeine (Atkinson and Enslen, 1976) there have been several studies demonstrating that caffeine increases the reinforcing effects of other drugs. Caffeine administration increases alcohol drinking (Kunin et al., 2000), cocaine self-administration (Schenk et al., 1994), and reinstates extinguished cocaine-seeking behavior (Green and Schenk, 2002; Worley et al., 1994). Prior exposure to caffeine also increases the psychomotor stimulant effects of amphetamine (Palmatier et al., 2003; Simola et al., 2006), nicotine (Celik et al., 2006; Palmatier et al., 2003) and cocaine (Schenk et al., 1994) as well as the primary reinforcing effects of cocaine (Horger et al., 1991) and nicotine (Jones and Griffiths, 2003; Shoaib et al., 1999).

The effects of caffeine on operant behavior suggest that the drug may be a more potent reinforcement enhancer than primary reinforcer. Therefore, the present studies investigated whether caffeine could enhance the motivation to obtain non-drug rewards. In Experiment 1, rats were shaped to respond for a sucrose reward (20% w/v) under a progressive ratio (PR) schedule. In Experiment 2, rats responded for a visual stimulus (30-s extinction of ambient lighting) under a fixed ratio 2 (FR2) reinforcement schedule. Tests were conducted on consecutive weekdays (Monday through Friday) with a break on Saturday and Sunday. This

procedure has been used in the past with nicotine and we have found that the reinforcement enhancing effects of nicotine tend to grow with repeated tests (Palmatier et al., 2007).

2. METHOD

2.1. General method

2.1.1. Subjects—Male Sprague-Dawley rats (Charles River, MI) weighing approximately 200–250 g upon arrival were housed individually in a temperature- and humidity-controlled vivarium maintained on a reversed 12:12 h light:dark cycle. Rats had free access to water, food was restricted to 20g/day for after a 1-week free feeding habituation period. All subjects were naïve except four rats assigned to the saline control condition of Experiment 1. These rats were part of the same shipment as the naïve rats, but had participated in a previous experiment which involved access to a nose-poke operant response. All procedures were approved by the Institutional Animal Care and Use Committee at Kansas State University.

2.1.2. Apparatus—All experimental sessions were conducted in standard operant conditioning chambers that were housed in sound attenuating cubicles (Med Associates, Georgia, Vermont). Chambers were equipped with two retractable levers, liquid dippers/receptacles containing 0.1 ml dipper cups, and a white house-light. Levers, dipper wells, and the ambient light source were located on the same wall of the chamber.

2.1.3. Drugs and Stimuli—Caffeine, anhydrous (Sigma-Aldrich, St. Louis, MO) was dissolved in 0.9% saline and was administered via intraperitoneal (ip) injection at a volume of 2 ml/kg 15 minutes prior to each session. Sucrose (20% w/v) delivered in 0.1 ml dipper cups for 4 s. For the visual stimulus (VS), ambient light in the experimental chamber was extinguished for 30 s when the operant schedule was met. We have previously used a comparable stimulus as a primary reinforcer in rat subjects (Chaudhri et al., 2006a; Palmatier et al., 2007).

2.1.4. Magazine Training and Shaping—All rats (Experiments 1 and 2) were initially shaped to associate the activation of the dipper with access to 20% sucrose. During subsequent shaping sessions, levers were inserted into the chamber and each lever press resulted in delivery of the 20% sucrose reinforcer. In Experiment 1 (sucrose reinforcer) rats were shaped to respond for sucrose on both levers to prevent a side bias. Because there were no systematic effects of caffeine on the ‘inactive’ lever in Experiment 1 (see Results), rats were only shaped on the ‘active’ lever in Experiment 2.

2.2. Specific Experiments

2.2.1. Experiment 1: Effect of caffeine on the motivation to obtain sucrose—The first five weeks of testing occurred in 1-h sessions conducted 5 days per week (M-F), with the sucrose reinforcer delivered under a progressive ratio (PR) reinforcement schedule and placebo injections given 15 minutes prior to placement in the operant chamber. Under this schedule, each reinforcer earned increased the response requirement for the next reinforcer. The ratio requirement was calculated according to the exponential function $5[\text{EXP}(R*0.12)]-5$, where R is equal to the number of reinforcers earned plus one (Richardson and Roberts, 1996). The sessions were terminated after rats met a 20 min breaking point (20 consecutive min without earning a sucrose reinforcer) or 60 total min, whichever came first. Although not all rats met the 20 min breaking point (21 out of 24 rats regularly met the breaking point criterion prior to caffeine administration), additional breaking points were calculated at 5, 10, and 15 min intervals and each of these breaking points was met during testing by all rats. After meeting a stability criterion of <30%

variance from a 3-day mean in responding on the active lever, subjects began testing with caffeine. Rats were randomly assigned to one of 5 groups (0, 6.25, 12.5, 25 or 50 mg/kg caffeine; n=6–8 per group) with the constraint that active lever responses and final ratio completed did not differ between groups during the final 3 days of testing under placebo conditions. In order to habituate rats to the handling/injection procedures, all rats received placebo injections 15 min prior to at least 3 testing sessions before moving on to the caffeine test phase. Tests with caffeine began on a Monday and continued for 3 weeks (15 total test sessions).

The 5-day per week caffeine dosing regimen resulted in tolerance to the reinforcement enhancing effects of caffeine (see Results). “Tolerance is defined as a decrease in pharmacologic response following repeated or prolonged drug administration” (Dumas and Pollack, 2008; p.538). Complete tolerance is operationally defined here as a complete loss of observable drug effect such that the effect of drug treatment does not differ from relevant controls. After a 3-day washout period (no behavioral tests or injections) all groups began testing under an intermittent dosing schedule for 8 consecutive test days. Rats were injected with their designated caffeine dose 15 minutes prior to behavioral testing on odd test days (1,3,5,7) with placebo injections administered prior to testing on intervening days (2,4,6,8). Note that for the 0 mg/kg caffeine group, saline was administered every day.

2.2.2. Experiment 2: Effect of caffeine on responding for a reinforcing visual stimulus—Handling and injection habituation procedures were identical to Experiment 1. Testing began under the 5-day week regime with sessions conducted M-F. VS presentations were earned on a fixed ratio 1 (FR1) schedule for making one response on the active lever. The 30-s VS also served as a time-out, responses were recorded but no additional VS presentations could be earned while the house-light was out. After rats met the stability criterion under the FR1 schedule ($\leq 30\%$ variability from a 3-day mean calculated from active lever presses for 3 consecutive sessions) the response requirement was increased to an FR2. All subsequent placebo and caffeine operant tests were carried out under this reinforcement schedule.

Rats were randomly assigned to one of four groups (0, 6.25, 12.5, or 25 mg/kg; n=6 per group) with the constraint that mean active lever responding did not differ between groups on the FR2 schedule under placebo conditions. The assigned caffeine injections were administered 15 minutes prior to test sessions and testing began similarly to Experiment 1 – with caffeine injection tests beginning on a Monday and conducted M-F for three weeks. One rat was eliminated from the 25 mg/kg group as caffeine administration increased responding on both the active and inactive levers – the magnitude of this increase resulted in responses that were at least 3 standard deviations above the average number of responses for all subjects.

Similar to Experiment 1, the 5-day per week dosing produced tolerance to the reinforcement enhancing effects of caffeine (see Results). Thus, a 4-day washout period (no injections or testing) was instituted and rats were subsequently re-tested after injection with their assigned caffeine dose. The reinforcement enhancing effect was observed in rats receiving 25.0 mg/kg caffeine at this time point (see Results). Therefore, the 5-day/week test schedule was resumed; however saline injections preceded subsequent tests. After an additional 8 days of without caffeine administration, rats were administered their originally assigned caffeine dose 15 min prior to testing to determine whether the effect was present after a longer washout period.

2.3. Data Analysis

For progressive ratio tests (Experiment 1) analysis of breaking points revealed that the number of reinforcers earned and the final ratio completed during the session did not differ from number of reinforcers earned and the final ratio completed prior to the 15-min breaking point ($p = 0.26$, see later). Therefore, the final ratio completed and total number of reinforcers earned during test sessions were calculated for each subject and included as a dependent variable in statistical analyses. For fixed ratio tests (Experiment 2) active lever responding, including responses made during the timeout period was the principal dependent measure of interest. Mixed factor analyses of variance (ANOVAs) were used to determine the statistical reliability of effects of drug treatment on operant responses and the number of rewards earned during testing. Significant interactions involving repeated tests (Session) and significant main effects involving two or more multiple level independent variables were examined using simple effects analyses (Keppel and Zedeck, 1987) in which one factor (e.g., Dose) was examined at different levels of the other factor (e.g., Session). Tukey's honestly significant differences (HSD) tests were used to detect differences between the caffeine doses in each experiment. All analyses were conducted using SPSS (Armonk, NY) and statistical significance was declared at $p = 0.05$ alpha.

3. RESULTS

3.1. Experiment 1: Effect of caffeine on the motivation to obtain sucrose

Acute administration of 6.25, 12.5, or 25 mg/kg prior to behavioral testing produced a significant increase in number of active lever presses made relative to subjects administered 0 or 50 mg/kg caffeine. However, this effect declined in two of the three groups, and a reinforcement enhancing effect of caffeine was only observed in the 12.5 mg/kg group at the end of the initial 15-day test period. This finding was confirmed by omnibus ANOVA on active lever responses (Figure 1A) with significant main effects of Dose and Session as well as a significant Dose $\times$ Session interaction ($F_s = 2.47$, $p = 0.05$). An identical pattern of main effects and interactions was observed in analyses of final ratio completed and reinforcers earned. Simple effects analyses were performed on active lever responses occurring after acute (Session 1) and chronic (Session 15) caffeine administration (Figure 1B). The analyses confirmed that rats receiving 6.25–25 mg/kg caffeine responded more on the active lever than rats injected with 0 or 50 mg/kg caffeine on the acute test ($p = 0.01$). However, on the chronic test, only rats in the 12.5 mg/kg caffeine group responded more than the 0 mg/kg controls ($p < 0.01$) – these rats also made more active-lever responses than all other groups ($p < 0.01$). This result suggests that a moderate dose of caffeine (e.g. 12.5 mg/kg) does not result in complete tolerance to the reinforcement enhancing effect of caffeine. The identical pattern of simple effects was observed for the other dependent measures (final ratio completed and reinforcers earned, data not shown). As illustrated in Figure 1B, significant decreases were observed across days for rats pretreated with 6.25 and 25 mg/kg caffeine ($p < 0.05$). However, no differences were observed for rats pretreated with 0, 12 or 50 mg/kg caffeine ($p = 0.12$). This pattern of effects was identical for reinforcers earned and final ratio completed.

Omnibus analyses of inactive lever responses (Figure 1A) showed significant main effects of Session, Dose, and a Dose $\times$ Session Interaction [$F_s = 2.91$, $p = 0.003$]. Simple effects analyses showed that rats receiving 6.25 mg/kg caffeine made significantly more inactive lever presses than rats in the 50.0 mg/kg group after acute administration ($p < 0.05$) but they were not significantly different from any other group, $p = 0.29$. There were no significant dose-dependent differences in the number of inactive lever responses made after chronic caffeine administration ($p = 0.26$, Figure 1C).

The reinforcement enhancing effects of 12.5 mg/kg caffeine did not change during the intermittent testing (Figure 2). This finding was confirmed by 3-way ANOVA with significant main effects of Dose, Test (caffeine vs. placebo) and a Dose $\times$ Test interaction [F_s 4.72, $ps < 0.01$] – there were no main effects or interactions involving Session [F_s 1.31, ps 0.28]. Analyses of reinforcers earned and breaking points yielded an identical pattern of main effects and interactions. Simple effects follow up analyses revealed that the 12.5 mg/kg group made more active lever responses on each caffeine test relative to saline control tests ($ps < 0.05$). However, in all of the other groups active lever responses did not differ across test type ($ps > 0.05$).

3.2. Experiment 2: Effect of caffeine on responding for a reinforcing visual stimulus

Administration of 12.5 mg/kg caffeine increased responding for the VS, but this was the only dose to result in a reinforcement enhancing effect of caffeine and this effect declined over the 5-day per week dosing period (Figure 3A and B). This finding was confirmed by the omnibus ANOVAs of active lever responding with significant main effects of Dose, Session and a significant Dose $\times$ Session interaction, [F_s 1.76, $ps < 0.01$]. A similar pattern was observed for reinforcers earned, however, the Dose $\times$ Session interaction did not reach statistical significance ($p = 0.09$). Simple effects analyses examining the effects of caffeine dose on acute (Session 1) and chronic (Session 15) caffeine administration were performed to probe the significant Dose $\times$ Session interaction on active lever presses. Only the 12.5 mg/kg group made significantly more active lever presses than the 0 mg/kg control group after acute caffeine administration ($p < 0.01$), however no group differed from the 0 mg/kg controls after chronic administration, ps 0.29 (Figure 3B). As illustrated in Figure 3B, there were significant decreases from Day 1 to Day 15 for the 6.25 and 12.5 mg/kg groups ($ps < 0.01$). There were no differences across these test days for the 0 or 25 mg/kg groups for any measure (ps 0.28). Analyses of reinforcers earned were comparable, however, the reduction in responding across days in the 6.25 mg/kg group did not reach statistical significance ($p = 0.057$) for this measure.

Despite the experimenter-imposed abstinence periods (no caffeine administration), no systematic recovery of the reinforcement enhancing effects of caffeine were observed (Figure 4). This finding was confirmed by mixed factors ANOVA contrasting active lever responses over Acute (1st caffeine exposure), Chronic (15th day of caffeine exposure during the 5-day/week tests), AB4 (exposure after 4 days of abstinence) and AB8 (exposure after 8 days of abstinence). There were significant main effects of Dose and Test [F_s 6.37, $ps < 0.01$], but no interaction ($p > 0.05$).

4. DISCUSSION

The present studies confirm that caffeine increases the reinforcing effects of non-drug stimuli and that this effect of caffeine is selective to dose. In both experiments, acute pretreatment with caffeine dose-dependently increased responding at the active lever. With repeated treatments over consecutive days, this effect of caffeine declined considerably. To further establish whether this profile of responding resulted from tolerance to the reinforcement enhancing effects of caffeine, we tested for reinforcement enhancing effects with varying intervals between injections. These follow-up tests suggest that tolerance to the reinforcement enhancing effect of caffeine is long-lasting; experimenter-imposed abstinence periods of 2, 4 and 8 days produced limited and inconsistent recovery of the tolerance observed in this study. The present findings suggest that the reinforcement enhancing effects of caffeine follow a pharmacological profile that is distinct from the reinforcement enhancing effect of nicotine (Palmatier et al., 2007).

The goal of the present studies was to confirm that caffeine could increase responding and motivation for non-drug stimuli, however, the pattern of reinforcement enhancing effects and the dosing schedule of caffeine emerged as an interesting feature of this phenomenon. Semi-chronic dosing under the 5-day/week schedule produced tolerance to the reinforcement enhancing effects of caffeine. The psychomotor stimulant effects of caffeine also depend critically on dosing schedule; consecutive daily injections of caffeine result in hyperactivity which becomes weaker over repeated treatments (Lau and Falk, 1995). In contrast, intermittent dosing (48 h between injections) increases the psychomotor stimulant effects of caffeine (Celik et al., 2006; Simola et al., 2006); this 'sensitization' is comparable to that seen with other psychomotor stimulants such as nicotine (Bevins and Palmatier, 2003), amphetamine (Bevins et al., 1997) and cocaine (Flagel et al., 2008). The reinforcement enhancing effects of caffeine are consistent with the psychomotor stimulant effects.

The putative psychomotor stimulant effects of caffeine also raise some questions in regard to the present findings. We found that during the Acute test, 6.25 mg/kg caffeine increased responding on the inactive lever relative to rats exposed to 50 mg/kg caffeine (Experiment 1). This effect is probably due to modest motor stimulant effects of the low dose and suppressant effects of the high dose. In addition, there was a trend for the 25 mg/kg dose to increase inactive lever responses in Experiment 2, although only in two of the six rats originally assigned to this dose. This effect was not statistically reliable. Notably, nicotine (Palmatier et al., 2008), caffeine (Schenk et al., 1994; present studies), amphetamine (Glow and Russell, 1973), and cocaine (Chaudhri et al., 2006b) all increase responding for drug and/or non-drug reinforcers. All of these drugs are classified as psychomotor stimulants. For caffeine and nicotine, the profile of sensitization or tolerance to these effects are consistent with the profile of reinforcement enhancing effects (Palmatier et al., 2007; present studies), and some investigators have argued that the 'reinforcement enhancing effects' are simply 'activational' or motor stimulant effects (Frenk and Dar, 2004).

The premise that increased activity is a more parsimonious account for the effects observed in the present study is based on a flawed assumption: that activational and motivational effects of psychomotor stimulants are separable constructs (c.f. Wise and Bozarth, 1987). We and others (Besheer et al., 2004; Olausson et al., 2003) have found repeatedly that 'activation' by nicotine tends to produce behavior directed toward motivationally salient stimuli and that these increases are systematically related to the motivational salience of the stimulus (Palmatier et al. 2011). Moreover, experimental demonstration of the activational effects of stimulant drugs typically use relatively novel open-field arenas – but exploration of novel environments and objects is commonly considered to be an appetitively motivated behavior in rat subjects (Bevins et al., 2002; Cain et al., 2006). Reactivity to a novel environment, in which subjects are confined to a novel open-field, is well established as a predictor of the activational (e.g., Mathews et al., 2010), rewarding (e.g., Orsini et al., 2004), and reinforcing (e.g., Cain et al., 2005; Piazza et al., 1990) effects of psychomotor stimulants. The activational effects of psychomotor stimulants are typically stronger in environments which have been paired with the effects of drug reinforcers in the past, relative to unpaired environments (e.g., Rademacher et al., 2007). Finally, pairing a novel arena with a food reward also produces psychomotor activation, relative to 'unpaired' controls (Matthews et al., 1996a; Matthews et al., 1996B) and this food-conditioned hyperactivity is potentiated by administration of a psychomotor stimulant such as amphetamine (Matthews et al., 1996a). Indeed, the 'activational' effects of psychomotor stimulants are not necessarily simple increases in behavior, but may involve complex effects of these drugs on both motor and incentive systems of the brain. However, in the present studies the motivational stimuli were well controlled, and the effects of caffeine were limited to responses that were oriented toward the motivational stimuli.

Another important aspect of the present findings is that, whereas the reinforcement enhancing effects of caffeine are readily observed (Green and Schenk, 2002; Horger et al., 1991; Schenk et al., 1994), the primary reinforcing effects of caffeine have not been well described in non-human subjects. Few studies have attempted to establish caffeine as a primary reinforcer and fewer still have met with success. In one of the first published demonstrations of intravenous caffeine self-administration, rats were permitted to self-administer caffeine after 98 h of continuous intravenous caffeine exposure (Atkinson and Enslen, 1976). Only a subset of subjects self-administered caffeine and these subjects stopped responding after 4 days of access to intravenous infusions. Others have dismissed caffeine self-administration as ‘unreliable’ but demonstrated that caffeine administration increases operant responding for cocaine (e.g., Kuzmin et al., 2000; Schenk et al., 1994) and opiates (Sudakov et al., 2002). Notably, Kuzmin and colleagues (Kuzmin et al., 2000) found that 10 days of forced exposure to caffeine in drinking water (approx 150 mg/kg/day) reduced the effect of caffeine on responding for cocaine. These prior findings (Atkinson and Enslen, 1976; Kuzmin et al., 2000) converge with the profile observed in the present studies as well as the previous literature in human subjects. The putative primary reinforcing effects of caffeine may be observed only at low to moderate dosages (Myers and Izbicki, 2006) and in paradigms that limit caffeine exposure to sub-chronic or intermittent access paradigm (Simola et al., 2006; present studies). Although this hypothesis needs to be tested directly, it is worthwhile to note that every previous investigation of primary reinforcement by caffeine has used daily consecutive exposures (Atkinson and Enslen, 1976; Hoffmeister and Wuttke, 1973; Kuzmin et al., 2000; Myers and Izbicki, 2006), often with extensive prior exposure to caffeine (Atkinson and Enslen, 1976; Kuzmin et al., 2000).

The present studies confirm that caffeine is a reinforcement enhancer and have extended these effects of caffeine to non-drug reinforcers and schedules of reinforcement that can measure reinforcer efficacy and motivation. These motivational effects of caffeine may have important implications for human caffeine consumption – especially the recent trend for increased caffeine consumption in alcoholic beverages. Consumption of energy drinks with alcoholic beverages can lead to increases in binge drinking and subjective intoxication (Ferreira et al., 2006; Thombs et al., 2010). Increased motivation to drink could lead to binge drinking and could have important implications for public health, as individuals who consume alcohol with caffeinated energy drinks tend to engage in more risky behaviors, relative to alcoholic beverages alone (Marczinski et al., 2011; O’Brien et al., 2008).

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References

- Antoniou K, Kafetzopoulos E, Papadopoulou-Daifoti Z, Hyphantis T, Marselos M. D-amphetamine, cocaine and caffeine: a comparative study of acute effects on locomotor activity and behavioural patterns in rats. *Neurosci Biobehav Rev.* 1998; 23:189–196. [PubMed: 9884112]
- Atkinson J, Enslen M. Self-administration of caffeine by the rat. *Arzneimittelforschung.* 1976; 26:2059–2061. [PubMed: 1037248]
- Benwell ME, Balfour DJ. The effects of acute and repeated nicotine treatment on nucleus accumbens dopamine and locomotor activity. *Br J Pharmacol.* 1992; 105:849–856. [PubMed: 1504716]

- Besheer J, Palmatier MI, Metschke DM, Bevins RA. Nicotine as a signal for the presence or absence of sucrose reward: a Pavlovian drug appetitive conditioning preparation in rats. *Psychopharmacology*. 2004; 172:108–117. [PubMed: 14530902]
- Bevins RA, Besheer J, Palmatier MI, Jensen HC, Pickett KS, Eures S. Novel-object place conditioning: behavioral and dopaminergic processes in expression of novelty reward. *Behav Brain Res*. 2002; 129:41–50. [PubMed: 11809493]
- Bevins RA, Klebaur JE, Bardo MT. Individual differences in response to novelty, amphetamine-induced activity and drug discrimination in rats. *Behav Pharmacol*. 1997; 8:113–123. [PubMed: 9833007]
- Bevins RA, Palmatier MI. Nicotine-conditioned locomotor sensitization in rats: assessment of the US-preexposure effect. *Behav Brain Res*. 2003; 143:65–74. [PubMed: 12842297]
- Boye SM, Grant RJ, Clarke PB. Disruption of dopaminergic neurotransmission in nucleus accumbens core inhibits the locomotor stimulant effects of nicotine and D-amphetamine in rats. *Neuropharmacology*. 2001; 40:792–805. [PubMed: 11369033]
- Brunye TT, Mahoney CR, Lieberman HR, Giles GE, Taylor HA. Acute caffeine consumption enhances the executive control of visual attention in habitual consumers. *Brain Cogn*. 2010; 74:186–192. [PubMed: 20832925]
- Caballero M, Nunez F, Ahern S, Cuffi ML, Carbonell L, Sanchez S, Fernandez-Duenas V, Ciruela F. Caffeine improves attention deficit in neonatal 6-OHDA lesioned rats, an animal model of attention deficit hyperactivity disorder (ADHD). *Neurosci Lett*. 2011; 494:44–48. [PubMed: 21362462]
- Caggiula AR, Donny EC, Palmatier MI, Liu X, Chaudhri N, Sved AF. The role of nicotine in smoking: a dual-reinforcement model. *Nebr Symp Motiv*. 2009; 55:91–109. [PubMed: 19013940]
- Caggiula AR, Donny EC, White AR, Chaudhri N, Gharib M, Booth S, Sved AF. Non-contingent nicotine enhances responding maintained by behaviorally contingent environmental cues. *Soc Neurosci Abstr*. 2001
- Cain ME, Green TA, Bardo MT. Environmental enrichment decreases responding for visual novelty. *Behav Processes*. 2006; 73:360–366. [PubMed: 16987609]
- Cain ME, Saucier DA, Bardo MT. Novelty seeking and drug use: contribution of an animal model. *Exp Clin Psychopharmacol*. 2005; 13:367–375. [PubMed: 16366767]
- Celik E, Uzbay IT, Karakas S. Caffeine and amphetamine produce cross-sensitization to nicotine-induced locomotor activity in mice. *Prog Neuropsychopharmacol Biol Psychiatry*. 2006; 30:50–55. [PubMed: 16084635]
- Chaudhri N, Caggiula AR, Donny EC, Booth S, Gharib M, Craven L, Palmatier MI, Liu X, Sved AF. Operant responding for conditioned and unconditioned reinforcers in rats is differentially enhanced by the primary reinforcing and reinforcement-enhancing effects of nicotine. *Psychopharmacology*. 2006a; 189:27–36. [PubMed: 17019569]
- Chaudhri N, Caggiula AR, Donny EC, Palmatier MI, Liu X, Sved AF. Complex interactions between nicotine and nonpharmacological stimuli reveal multiple roles for nicotine in reinforcement. *Psychopharmacology*. 2006b; 184:353–366. [PubMed: 16240165]
- Dumas E, Pollack G. Opioid tolerance development: a pharmacokinetic/pharmacodynamic perspective. *AAPS J*. 2008; 110:537–551. [PubMed: 18989788]
- Ferreira SE, de Mello MT, Pompeia S, de Souza-Formigoni ML. Effects of energy drink ingestion on alcohol intoxication. *Alcohol Clin Exp Res*. 2006; 30:598–605. [PubMed: 16573577]
- Flagel SB, Watson SJ, Akil H, Robinson TE. Individual differences in the attribution of incentive salience to a reward-related cue: influence on cocaine sensitization. *Behav Brain Res*. 2008; 186:48–56. [PubMed: 17719099]
- Frenk H, Dar R. Reward potentiation or behavioral activation? A comment on Donny et al. *Psychopharmacology*. 2004; 171:472–473. [PubMed: 14566447]
- Glade M. Caffeine-not just a stimulant. *Nutrition*. 2010; 26:932–938. [PubMed: 20888549]
- Glow PH, Russell A. Effects of dexamphetamine, amylobarbitone sodium and their mixture on sensory contingent bar pressing behaviour in the rat. *Psychopharmacologia*. 1973; 31:239–251. [PubMed: 4732727]

- Green TA, Schenk S. Dopaminergic mechanism for caffeine-produced cocaine seeking in rats. *Neuropsychopharmacology*. 2002; 26:422–430. [PubMed: 11927167]
- Griffiths RR, Chausmer AL. Caffeine as a model drug of dependence: recent developments in understanding caffeine withdrawal, the caffeine dependence syndrome, and caffeine negative reinforcement. *Nihon Shinkei Seishin Yakurigaku Zasshi*. 2000; 20:223–231. [PubMed: 11326548]
- Heckman M, Weil J, Gonzalez de Mejia E. Caffeine (1, 3, 7-trimethylxanthine) in foods: a comprehensive review on consumption, functionality, safety, and regulatory matters. *J Food Sci*. 2010; 75:R77–87. [PubMed: 20492310]
- Hoffmeister F, Wuttke W. Self-administration of acetylsalicylic acid and combinations with codeine and caffeine in rhesus monkeys. *J Pharmacol Exp Ther*. 1973; 186:266–275. [PubMed: 4198215]
- Horger BA, Wellman PJ, Morien A, Davies BT, Schenk S. Caffeine exposure sensitizes rats to the reinforcing effects of cocaine. *Neuroreport*. 1991; 2:53–56. [PubMed: 1768850]
- Jones HE, Griffiths RR. Oral caffeine maintenance potentiates the reinforcing and stimulant subjective effects of intravenous nicotine in cigarette smokers. *Psychopharmacology (Berl)*. 2003; 165:280–290. [PubMed: 12434259]
- Kunin D, Gaskin S, Rogan F, Smith BR, Amit Z. Caffeine promotes ethanol drinking in rats. Examination using a limited-access free choice paradigm. *Alcohol*. 2000; 21:271–277. [PubMed: 11091031]
- Kuzmin A, Johansson B, Semenova S, Fredholm BB. Differences in the effect of chronic and acute caffeine on self-administration of cocaine in mice. *Eur J Neurosci*. 2000; 12:3026–3032. [PubMed: 10971643]
- Lau CE, Falk JL. Dose-dependent surmountability of locomotor activity in caffeine tolerance. *Pharmacol Biochem Behav*. 1995; 52:139–143. [PubMed: 7501656]
- Marczynski C, Fillmore M, Bardgett M, Howard M. Effects of energy drinks mixed with alcohol on behavioral control: risks for college students consuming trendy cocktails. *Alcohol Clin Exp Res*. 2011; 35:1282–1292. [PubMed: 21676002]
- Mathews I, Morrissey M, McCormick C. Individual differences in activity predict locomotor activity and conditioned place preference to amphetamine in both adolescent and adult rats. *Pharmacol Biochem Behav*. 2010; 95:63–71. [PubMed: 20006968]
- Matthews K, Hall FS, Wilkinson LS, Robbins TW. Retarded acquisition and reduced expression of conditioned locomotor activity in adult rats following repeated early maternal separation: effects of prefeeding, d-amphetamine, dopamine antagonists and clonidine. *Psychopharmacology*. 1996a; 126:75–84. [PubMed: 8853220]
- Matthews K, Wilkinson LS, Robbins TW. Repeated maternal separation of preweanling rats attenuates behavioral responses to primary and conditioned incentives in adulthood. *Physiol Behav*. 1996b; 59:99–107. [PubMed: 8848498]
- Myers K, Izicki E. Reinforcing and aversive effects of caffeine measured by flavor preference conditioning in caffeine-naïve and caffeine-acclimated rats. *Physiol Behav*. 2006; 88:585–596. [PubMed: 16806323]
- O'Brien MC, McCoy TP, Rhodes SD, Wagoner A, Wolfson M. Caffeinated cocktails: energy drink consumption, high-risk drinking, and alcohol-related consequences among college students. *Acad Emerg Med*. 2008; 15:453–460. [PubMed: 18439201]
- Olausson P, Jentsch JD, Taylor JR. Repeated nicotine exposure enhances reward-related learning in the rat. *Neuropsychopharmacology*. 2003; 28:1264–1271. [PubMed: 12700688]
- Orsini C, Buchini F, Piazza PV, Puglisi-Allegra S, Cabib S. Susceptibility to amphetamine-induced place preference is predicted by locomotor response to novelty and amphetamine in the mouse. *Psychopharmacology*. 2004; 172:264–270. [PubMed: 14600800]
- Palmatier MI, Coddington SB, Liu X, Donny EC, Caggiula AR, Sved AF. The motivation to obtain nicotine-conditioned reinforcers depends on nicotine dose. *Neuropharmacology*. 2008; 55:1425–1430. [PubMed: 18809417]
- Palmatier MI, Fung EY, Bevins RA. Effects of chronic caffeine pre-exposure on conditioned and unconditioned psychomotor activity induced by nicotine and amphetamine in rats. *Behav Pharmacol*. 2003; 14:191–198. [PubMed: 12799520]

- Palmatier MI, Matteson GL, Black JJ, Liu X, Caggiula AR, Craven L, Donny EC, Sved AF. The reinforcement enhancing effects of nicotine depend on the incentive value of non-drug reinforcers and increase with repeated drug injections. *Drug Alcohol Depend.* 2007; 89:52–59. [PubMed: 17240084]
- Perkins KA, Jacobs L, Ciccocioppo M, Conklin C, Sayette M, Caggiula A. The influence of instructions and nicotine dose on the subjective and reinforcing effects of smoking. *Exp Clin Psychopharmacol.* 2004; 12:91–101. [PubMed: 15122953]
- Perkins KA, Jetton C, Keenan J. Common factors across acute subjective effects of nicotine. *Nicotine Tob Res.* 2003; 5:869–875. [PubMed: 14668070]
- Piazza PV, Deminiere JM, Maccari S, Mormede P, Le Moal M, Simon H. Individual reactivity to novelty predicts probability of amphetamine self-administration. *Behav Pharmacol.* 1990; 1:339–345. [PubMed: 11175418]
- Rademacher D, Napier TC, Meredith G. Context modulates the expression of conditioned motor sensitization, cellular activation and synaptophysin immunoreactivity. *Eur J Neurosci.* 2007; 26:2661–2668. [PubMed: 17970739]
- Rose JE. Nicotine and nonnicotine factors in cigarette addiction. *Psychopharmacology (Berl).* 2006; 184:274–285. [PubMed: 16362402]
- Schenk S, Valadez A, Horger BA, Snow S, Wellman PJ. Interactions between caffeine and cocaine in tests of self-administration. *Behav Pharmacol.* 1994; 5:153–158. [PubMed: 11224263]
- Schuh KJ, Griffiths RR. Caffeine reinforcement: the role of withdrawal. *Psychopharmacology (Berl).* 1997; 130:320–326. [PubMed: 9160847]
- Shoaib M, Swanner LS, Yasar S, Goldberg SR. Chronic caffeine exposure potentiates nicotine self-administration in rats. *Psychopharmacology (Berl).* 1999; 142:327–333. [PubMed: 10229056]
- Sigmon SC, Griffiths RR. Caffeine choice prospectively predicts positive subjective effects of caffeine and d-amphetamine. *Drug Alcohol Depend.* 2011; 118:341–348. [PubMed: 21600707]
- Simola N, Cauli O, Morelli M. Sensitization to caffeine and cross-sensitization to amphetamine: influence of individual response to caffeine. *Behav Brain Res.* 2006; 172:72–79. [PubMed: 16740323]
- Sorge RE, Clarke PB. Rats self-administer intravenous nicotine delivered in a novel smoking-relevant procedure: effects of dopamine antagonists. *J Pharmacol Exp Ther.* 2009; 330:633–640. [PubMed: 19448141]
- Sudakov SK, Papazov IP, Lyupina Y, Medvedeva OF, Figurina IV, Rusakova IV. Effects of acute and chronic caffeine intake on intravenous self-administration of morphine in two rat strains. *Bull Exp Biol Med.* 2002; 134:400–402. [PubMed: 12533771]
- Thombs DL, O'Mara RJ, Tsukamoto M, Rossheim ME, Weiler RM, Merves ML, Goldberger BA. Event-level analyses of energy drink consumption and alcohol intoxication in bar patrons. *Addict Behav.* 2010; 35:325–330. [PubMed: 19954894]
- Vangkilde S, Bundesen C, Coull JT. Prompt but inefficient: nicotine differentially modulates discrete components of attention. *Psychopharmacology (Berl).* 2011; 218:667–680. [PubMed: 21629997]
- Wise RA, Bozarth MA. A psychomotor stimulant theory of addiction. *Psychol Rev.* 1987; 94:469–492. [PubMed: 3317472]
- Worley CM, Valadez A, Schenk S. Reinstatement of extinguished cocaine-taking behavior by cocaine and caffeine. *Pharmacol Biochem Behav.* 1994; 48:217–221. [PubMed: 8029293]
- Yeomans MR, Durlach PJ, Tinley EM. Flavour liking and preference conditioned by caffeine in humans. *Q J Exp Psychol B.* 2005; 58:47–58. [PubMed: 15844377]
- Yeomans MR, Mobini S, Chambers L. Additive effects of flavour-caffeine and flavour-flavour pairings on liking for the smell and flavour of a novel drink. *Physiol Behav.* 2007; 92:831–839. [PubMed: 17675193]

Figure 1.

Panel A shows the average active (filled symbols) and inactive (open symbols) lever responses for rats exposed to each caffeine dose. There was a significant dose-dependent increase in responding for sucrose as a result of caffeine administration. Panel B shows the average active lever responses on the first (Acute) and 15th (Chronic) caffeine tests as a function of caffeine dose. Simple effects analyses of active lever responses confirmed that rats receiving 6.25–25 mg/kg caffeine made more active lever responses than those administered 0 or 50 mg/kg ($p < 0.001$; indicated by *) after acute caffeine administration (Session 1). Rats in the 6.25 and 25 mg/kg caffeine group also made more active lever responses on the acute (session 1) relative to the chronic (Session 15) caffeine tests ($p < 0.05$;

indicated by ^). Rats in the 12.5 mg/kg caffeine group responded more than all other groups after chronic (Session 15) administration ($p < 0.001$; indicated by #). Panel C shows inactive lever responses from the Acute and Chronic caffeine tests. Simple effects analyses of inactive lever responses showed that rats receiving 6.25 mg/kg caffeine made more inactive lever responses than those administered 50 mg/kg after acute (Session 1) caffeine administration ($p < 0.05$; indicated by \$). There were no significant differences in inactive lever responses after chronic caffeine administration, $p > 0.26$.

Figure 2.

Panels A–D illustrate average active lever responses for rats in the 6.25–50 mg/kg caffeine groups, respectively, during the alternating caffeine (filled symbols) and saline (open symbols) test phase. In each panel, average active lever responses for the 0 mg/kg caffeine group (filled squares) are included for comparison. Data from the 0 mg/kg group were taken from test days in which the 6.25–50 mg/kg groups were injected with caffeine before testing; these rats received placebo injections throughout this test phase. Subjects receiving 12.5 mg/kg caffeine on intermittent days made significantly more active lever responses than the 0 mg/kg controls ($p < 0.05$; indicated by *). No other groups differed from placebo condition during these tests ($p_s = 0.61$).

Figure 3.

This figure shows the average active (filled symbols) and inactive (open symbols) lever responses for rats in each caffeine dose. Active lever responses decreased at all doses after chronic administration. Panel B shows active lever responses as a function of caffeine dose on the first (Acute) and 15th (Chronic) caffeine exposures. Subjects receiving 6.25 and 12.5 mg/kg caffeine made significantly more active lever responses compared to 0 and 25 mg/kg groups after acute administration ($p < 0.001$; indicated by *), but not chronic administration ($p = 0.4$).

Figure 4.

This figure shows average active lever responses after the first (Acute) and 15th (Chronic) caffeine exposures as well as the caffeine exposure tests conducted after 4 (AB4) and 8 (AB8) days of abstinence (no caffeine administration). The reinforcement enhancing effect of caffeine was seen after 4 days without caffeine administration in the 25 mg/kg group-the number of active lever responses during the AB4 test was higher than the Chronic test, but only in the 25 mg/kg group ($p < 0.05$).