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The impacts of caffeine administration, expectancies, and related stimuli on coffee craving, withdrawal, and self-administration

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Abstract

Background: Caffeine is the most commonly consumed psychoactive substance, yet its potential reinforcing properties have been understudied.
Aims: This study examined the impact of caffeine administration and expectancy on coffee-related craving, withdrawal, and cue reactivity via a balanced-placebo design.
Methods: Following 18-h caffeine abstinence, 65 daily coffee consumers (54% male) received either caffeine-containing (100 mg) or placebo gum, along with either accurate or inaccurate information regarding the gum's caffeine content. Participants were exposed to neutral and coffee-related stimuli using different sensory modalities (visual and combined auditory/olfactory). Craving, withdrawal, and heart rate were assessed at baseline and after each cue presentation. Following the cue-reactivity assessments, participants were provided with an opportunity to self-administer units of coffee.
Results: Caffeine expectancy was associated with reduced subjective withdrawal 30 min following the gum administration but was not significantly impacted by actual caffeine administration. The presentation of coffee-related cues was found to increase self-reported craving and heart rate, regardless of the expectation that caffeine had been administered. Visual, but not auditory/olfactory, cue reactivity appeared blunted when participants received a prior dose of caffeine. Prior caffeine ingestion also reduced the probability of subsequent coffee self-administration.
Conclusion: To our knowledge, this is the first examination of the impact of caffeine administration and expectancy on cue-elicited coffee craving and coffee consumption. Although there was some evidence that caffeine expectancy and administration were found to impact subjective withdrawal and self-administration respectively, neither was found to exert strong consistent effects on cue reactivity.

Keywords
Caffeine, coffee, cue reactivity, craving, expectancy, withdrawal

Introduction

Caffeine is the most commonly used psychoactive substance in North America, with most adults (80%–90%) consuming it regularly (Centre for Addictions and Mental Health, 2011; Johnson, 2012), with coffee consumption being the most predominant source (Reyes and Cornelis, 2018; Verster and Koenig, 2018). Many individuals who consume caffeine on a regular basis exhibit dependence-like behaviors and have difficulty in quitting or reducing caffeine intake (Hughes et al., 1998; Juliano and Griffiths, 2004; Meredith et al., 2013). Despite this, there has been some debate regarding the extent to which caffeine has reinforcing properties that are akin to those associated with other commonly used psychoactive substances, such as alcohol or tobacco (Meredith et al., 2013).

One method commonly used to assess the incentive motivational properties of substances used by humans is the cue-reactivity paradigm (Drummond, 2001; Siegel, 1975; Stewart et al., 1984; Tiffany, 1990). Exposure to drug salient stimuli has been shown to reliably provoke both significant self-reported craving and physiological responses in users of a variety of psychoactive self-administered substances including tobacco, alcohol, heroin, and cocaine (Carter and Tiffany, 1999; Johnson et al., 1998; Schlagintweit and Barrett, 2016; Schlagintweit et al., 2014; Witteman et al., 2015; Wray et al., 2011; Zhao et al., 2012). In tobacco users, photographic cues have been shown to elicit robust cue-reactivity effects, particularly self-reported craving (Wray et al., 2011); when exposed to lit cigarettes, smokers showed an increase in both self-reported craving and skin conductance (Carter and Tiffany, 1999). A Dutch study on alcohol cue reactivity found significant craving and physiological responses to alcohol-related video clips (Witteman et al., 2015). In former heroin users, exposure to heroin-related video cues resulted in increased heroin craving, skin conductance, heart rate, and blood pressure, relative to a control group of never-users and to exposure to neutral cues (Zhao et al., 2012). A study investigating cue reactivity in cocaine users found significant effects for craving and physiological responses (heart rate, skin conductance, and skin temperature) and found that these effects differed

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depending on the cue-sensory modality used to elicit the response (Johnson et al., 1998). To our knowledge, no study to date has investigated the extent to which coffee-associated cues provoke coffee-related cravings.

Although the extent to which coffee-associated stimuli provoke cravings among coffee consumers is currently unknown, other studies have investigated conditioned responses to coffee-related stimuli. One study by Flaten and Blumenthal (1999) showed that stimuli associated with coffee elicited an increase in both physiological and subjective measures of arousal. The authors found that the taste and smell of coffee (via decaffeinated coffee) increased arousal relative to a caffeine-free juice. More recently, a study examined the impact of a coffee-like scent on participants' expectations and performance on an analytical reasoning task (Madzharov et al., 2018). The authors showed that the coffee-like scent alone, resulted in heightened performance expectations and, in turn, in increased performance. There is some evidence that caffeine cravings can be impacted by non-pharmacological manipulations. For example, in a recent study, 24-h deprived caffeine users reported significant decreases in caffeine withdrawal and cravings following the administration of decaffeinated coffee only when they were led to believe the coffee-contained caffeine (Mills et al., 2016). Another study, which directly compared the relative impacts of actual and perceived caffeine administration (Juliano et al., 2019) on responses to decaffeinated and caffeine-containing coffee, showed that caffeine expectancy was sufficient to reduce abstinence-related caffeine cravings, but only the administration of caffeinated coffee was associated with improved cognitive performance as well as reduced withdrawal symptoms.

The purpose of present study was to investigate the impact of acute caffeine administration and expectancy on responses to coffee-related stimuli and coffee ingestion in daily coffee consumers. Cue reactivity was investigated via visual and a combination of auditory and olfactory stimuli. This study used a balanced-placebo design to allow for the simultaneous manipulation of caffeine pharmacology and caffeine expectancies (via the administration of caffeinated and noncaffeinated gum along either accurate or inaccurate information regarding their actual contents). It was hypothesized that (1) participants who received caffeine would have less coffee craving, withdrawal, and subsequent self-administration than those who did not receive caffeine; (2) participants who expected to receive caffeine would have less coffee craving, withdrawal, and subsequent self-administration than those who did not expect to receive caffeine; (3) coffee-related stimuli would increase physiological arousal and craving, across different sensory modalities, regardless of caffeine administration and expectancy. Interactions between caffeine administration and caffeine expectancy were included as exploratory analyses.

Method

Participants

Following a power analysis based on a study with similar methodology (Schlagintweit et al., 2014), 65 participants (35 male) were recruited from the Halifax Regional Municipality, Nova Scotia; recruitment was conducted via online and community bulletin boards. An initial telephone screening was conducted with all potential participants to confirm that they met eligibility requirements. Specifically, participants were required to be daily coffee consumers (averaging at least 300 mg of caffeine per day) for the past year and to be free of any serious medical condition, current psychiatric diagnosis according to the diagnostic and statistical manual of mental disorders (DSM-5; American Psychiatric Association, 2013) diagnosis or neurological disease, or current use of psychotropic medications, confirmed via self-report. Potential participants were also excluded if they were daily cigarette smokers, or if they reported any previous use of caffeine-containing pills or gum.

Participants were required to abstain from caffeine use for 18 h prior to their study session. This abstinence period was selected to correspond to approximately three caffeine half-lives (White et al., 2016). Participants were randomly assigned to receive either a caffeine-containing or a caffeine-free gum, as well as congruent or incongruent instructions regarding its content. This resulted in participants being divided into four different conditions: (a) told caffeine, received caffeine ($n = 16$); (b) told caffeine, received placebo ($n = 16$); (c) told placebo, received caffeine ($n = 17$); and (d) told placebo, received placebo ($n = 16$). The average age of participants was 34 ($SD = 12.7$) years. All participants reported daily coffee use over the previous month, with reported values for past-week caffeine consumption averaged 421.9 ($SD = 167.48$) mg of caffeine per day. On average, participants had first tried coffee at 15.2 ($SD = 5.06$) years of age and had been a daily coffee drinker for an average of 14.6 ($SD = 11.99$) years. No significant differences were observed between conditions on any of these variables (p-values > 0.05). All participants provided informed, written consent to participate in the study; they were compensated $12 (Canadian) per hour for their time and an additional $10 for abstaining from caffeine for 18 h prior to the study session. The study received ethical approval from the Nova Scotia Health Authority Research Ethics Board.

Materials and measures

Gum. The caffeinated gum contained 100 mg of caffeine per piece, similar to an 8 oz cup of drip coffee (Military Energy Gum, MarketRight, Inc., Plano, IL, USA). Caffeine-containing gum has been shown to be safe, with no adverse effects in healthy adults (Kamimori et al., 2002). The placebo (caffeine-free) gum was obtained from the same company as the caffeinated gum; it was matched in appearance and flavor to the caffeinated gum.

Heart rate. Heart rate was measured using a Polar H10 Heart Rate Sensor (Polar Electro Canada, Inc., Lachine, QC, Canada). This device was worn on a chest strap underneath participants' clothing, which allowed heart electrical pulses to be measured directly. Heart rate measurement was taken over 1-min intervals at different points in the session, as the equipment did not allow for a continuous recording.

Caffeine withdrawal. The Caffeine Withdrawal Symptom Questionnaire (CWSQ; Juliano et al., 2012) is a 23-item questionnaire used to assess caffeine withdrawal. The CWSQ has been shown to have high internal consistency ($\alpha = 0.90$) and to be sensitive to caffeine abstinence in daily caffeine users (Juliano

et al., 2019) and has been tested in samples comparable to ours (Juliano et al., 2012).

Craving and gum liking. Visual analog scales (VAS) were used to measure coffee craving ("crave coffee"), caffeine craving ("crave caffeine"; reported in Supplemental Material), as well as gum liking. Each item was rated on a scale from 1 to 10, with the endpoints labeled "not at all" and "extremely." VAS have been demonstrated to be valid, reliable, and sensitive to subjective individual experiences across a multitude of age ranges and with many different substances (Bond and Lader, 1974).

Demographics and caffeine use. A Demographic and Caffeine Use Questionnaire was used to collect demographic (age and sex) and caffeine use information (age of first use, caffeine use frequency, typical coffee consumed, and whether participants drank coffee for its taste or its stimulating properties).

Timeline Followback Calendar. This weeklong calendar was used to help participants recall their caffeine use over the past week. The type and amount of caffeine-containing product was recorded; caffeine content was calculated using online databases.

Concluding questions. These questions were used as a manipulation check to verify whether participants believed the information provided regarding the caffeine content of the gum, by having them select whether they received caffeinated gum, caffeine-free gum, or were unsure which gum they received.

Procedure

Study procedures are outlined in Figure 1. During the telephone screening interview, participants were informed of typical sources for caffeine and that an 18-h caffeine abstinence period was required to participate in the study. An 18-h abstinence period was chosen to allow sufficient elimination of caffeine from the system (three half-lives of caffeine) and to enable for the emergence of early withdrawal symptoms (Juliano and Griffiths, 2004). Additionally, participants were told that a saliva sample may be taken to ensure compliance. Given that there is no established salivary caffeine concentration cutoff for 18 h of abstinence, this instruction served as a bogus pipeline (Roese and Jamieson, 1993) intended to enhance abstinence compliance. Instead, abstinence was verified by self-report. Participants were also informed that they would be asked to chew a piece of gum that may or may not contain caffeine.

All sessions were conducted in the morning, between 8 am and 12 pm. Following verbal verification of abstinence (yes/no), participants completed the Timeline Followback Calendar, making note of all caffeine use over the past week; the Timeline Followback Calendar served as a secondary abstinence check as well as gathering information on participants' daily caffeine use. Next, participants completed the CWSQ and the craving assessments and had their heart rate measured for 1 min (baseline). Participants were randomly assigned to one of the four drug/instruction conditions and were given a piece of gum. Participants were either told that the gum contained caffeine (as much caffeine as a small cup of coffee), or that it contained no caffeine (a regular piece of gum); in two of the groups, the information given was incongruent with the true caffeine content of the gum. Both the researcher and the participant were blind to the actual caffeine content of the gum; the packaging of the gum matched the information provided by the researcher. The participants then chewed the gum in a standardized manner over a 10-min period (i.e., the gum was chewed in time with an audio recording), such that 99% of the caffeine in the caffeine-containing gum would be released (Newman et al., 2013). Following the gum administration, participants completed a single-item VAS assessing gum liking, followed by a 30-min waiting period to allow for blood caffeine to reach peak levels (Syed et al., 2005).

Following the 30-min waiting period, craving and withdrawal were reassessed using the CWSQ and VAS, and heart rate was measured again. Next, participants were presented with neutral and coffee cues. Neutral cues were presented to all participants prior to coffee cues in order to avoid carryover effects on ratings of craving (Sayette et al., 2010). Both the neutral and coffee visual cue presentations lasted for 2 min, each comprising 40 high-resolution images. The coffee cues consisted of coffee-related images (e.g., cups of coffee and coffee being poured into a cup), whereas the neutral cues consisted of water-related images (e.g., water bottles and water being poured into glasses). The coffee and neutral cues were visually matched with one another and were free of imagery associated with other psychoactive self-administered substances (McGrath et al., 2015). During the first minute of both the neutral and coffee visual cue presentations, participants' heart rate was measured; immediately following each set of visual cues, participants completed the CWSQ and VAS. After a 10-min washout period, participants were exposed to neutral and coffee-related auditory and olfactory stimuli for 4 min each. Auditory and olfactory cues were presented simultaneously. For the neutral cues, sounds of running water were played and participants were instructed to attend to the ambient scent of the room. For the coffee-related cues, a pot of coffee was brewed out of view of the participant, producing both auditory and olfactory stimuli. As with the visual cues, heart rate was measured during the first minute of each cue presentation, whereas the CWSQ and VAS were completed following the exposure to each set of cues.

Upon completion of the questionnaires, participants were given the opportunity to drink coffee. Participants were provided with a 4-oz coffee mug (1 unit of coffee), the coffee brewed during the olfactory cue presentation, and their preferred condiments. They were told that they could consume anywhere between 0 units and 3 units of coffee; for each unit of coffee they did not drink, participants received an extra $1. Participants were required to remain in the lab for 30 min following the olfactory cue presentation, regardless of whether they consumed coffee; they could choose to consume their units of coffee at any time during this period. This coffee administration task was adapted from a smoking lapse task developed by McKee (2009) to examine tobacco-related reinforcement.

At the end of the session, participants completed the concluding questions, which included a manipulation check, where participants were asked about the caffeine content of the gum they had received at the beginning of the session.

Statistical analyses

To determine whether there were any expectancy or drug effects of gum administration, we conducted a series of two-way

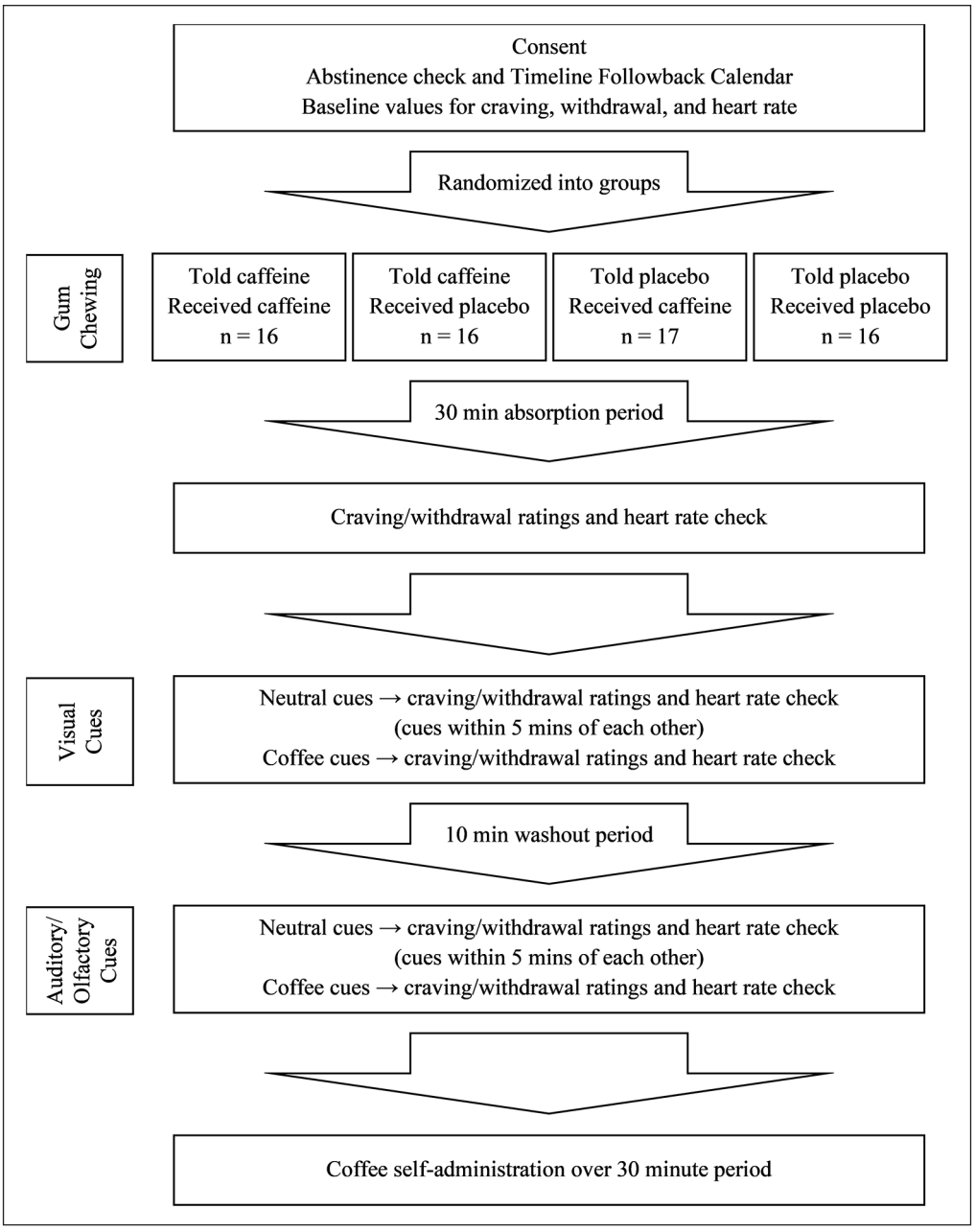

Figure 1. Study flowchart depicting the procedure.

ANCOVAs with expectancy (told caffeine vs. told placebo) and dose (given caffeine vs. given placebo) as between-subjects factors, controlling for baseline values. To determine whether there were any cue-induced effects, we conducted a series of three-way ANOVAs with expectancy (told caffeine vs. told placebo) and dose (given caffeine vs. given placebo) as between-subjects factors and cues (coffee vs. placebo) being a within-subjects factor. These ANOVAs were conducted once for visual cues and once for the combined auditory/olfactory cues, to investigate each of the cue modalities separately. The dependent measures of interest in these ANCOVAs and ANOVAs were self-reported ratings of coffee and caffeine craving, caffeine withdrawal symptoms, and physiological responses (maximum and average heart rate).

Additional analyses were conducted to compare gum liking rating and units of coffee consumed between the experimental conditions; these were completed using two-way ANOVAs, with expectancy (told caffeine vs. told placebo) and dose (given caffeine vs. given placebo) being between-subjects factors. Further, chi-square tests of independence were conducted to determine whether the probability of self-administering any coffee at the penultimate stage of the study was associated with the dose or expectancy conditions.

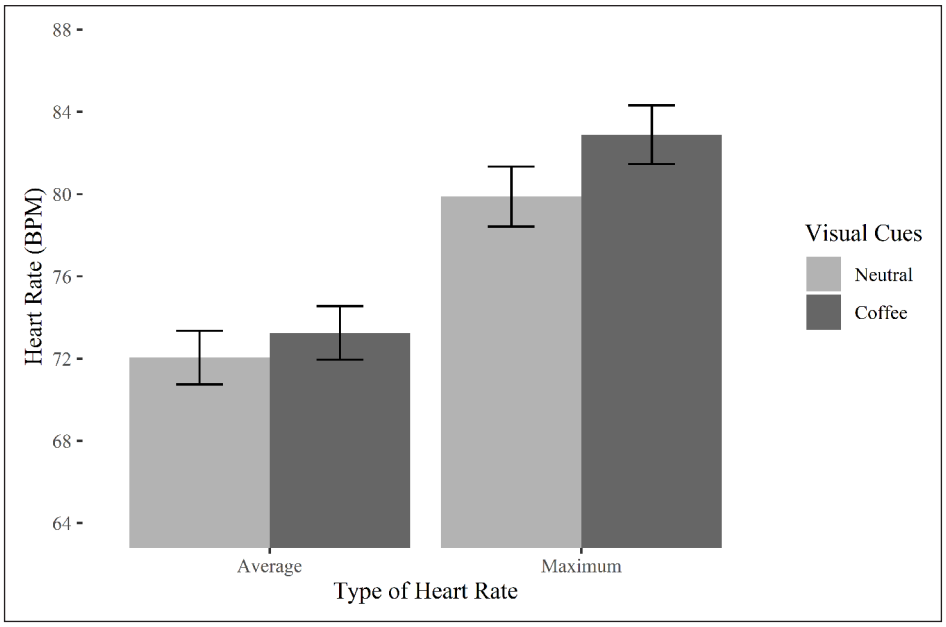

Figure 2. Estimated marginal means (±standard error (SE)) for average and maximum heart rates in beats per minute (BPM). Participants had elevated average and maximum heart rates during the coffee visual cue presentation relative to the neutral visual cue presentation, $p=0.002$.

All tests were conducted in SPSS version 25 (SPSS Inc., Chicago, IL, USA). Alpha was set at $p<0.05$, and all tests were two-tailed. To control for familywise type 1 error, the Benjamini–Hochberg procedure was conducted with the false detection rate (FDR) set at 0.05; when $p<0.05$ but FDR >0.05, findings were considered to be false positives.

Results

Results for all participants

Estimated marginal means (standard error, SE) and test statistics for main effects of expectancy, main effects of dose, and dose by expectancy interactions for 30 min post-gum administration analyses, as well as main effects of cues, expectancy by cues interactions, and dose by cues interactions for all cues-based analyses are presented in Supplemental Material.

Gum liking. There was a main effect of dose, $F(1,61)=31.75$, $p<0.001$, $\eta^2_p=0.342$, indicating that gum-liking ratings for the placebo gum ($M=6.50$, $SE=0.39$) were significantly higher than gum-liking ratings for the caffeine-containing gum ($M=3.39$, $SE=0.39$). The effect of expectancy was not significant, $F(1,61)=3.62$, $p=0.062$, $\eta^2_p=0.056$, nor was there a significant interaction, $F(1,61)=0.60$, $p=0.443$, $\eta^2_p=0.010$.

Expectancy and drug effects post-gum administration. There were no significant main effects of expectancy or dose nor interactions for coffee craving 30 min post-gum administration (all p-values >0.10). There was, however, a main effect of expectancy for caffeine withdrawal, $F(1,60)=6.62$, $p=0.013$, $\eta^2_p=0.099$, indicating that caffeine withdrawal symptoms in the told placebo condition ($M=30.23$, $SE=1.13$) were significantly higher than in the told caffeine condition ($M=26.10$, $SE=1.14$). The effect for dose was not significant, $F(1,60)=0.05$, $p=0.829$, $\eta^2_p=0.001$ nor was there a significant interaction, $F(1,60)=1.56$, $p=0.217$, $\eta^2_p=0.025$. Maximum and average heart rates at 30 min post-gum administration were analyzed in a similar fashion. There were no significant main effects or interactions (all p-values >0.20).

Visual cues. For coffee craving, there was a main effect of cues, $F(1,61)=18.02$, $p<0.001$, $\eta^2_p=0.228$. Participants reported higher coffee craving after viewing the coffee cues ($M=7.60$, $SE=0.31$) relative to the neutral cues ($M=7.04$, $SE=0.31$). There was also a dose by cues interaction for coffee craving, $F(1,61)=4.68$, $p=0.034$, $\eta^2_p=0.034$. For participants who received caffeinated gum, there was no significant change in coffee craving between the neutral visual cues ($M=7.28$, $SE=0.44$) and coffee visual cues ($M=7.55$, $SE=0.43$), $p=0.143$; alternatively, those who received placebo gum had an increase in coffee cravings from the neutral visual cues ($M=6.81$, $SE=0.44$) to the coffee visual cues ($M=7.66$, $SE=0.43$), $p<0.001$. Although, the FDR for the overall interaction exceeded 5% (adjusted $p=0.068$), a near identical dose by cues interaction for "caffeine craving" was also evident (adjusted $p=0.032$) (see Supplemental Material).

For maximum heart rate, there was a main effect of cues, $F(1,61)=10.99$, $p=0.002$, $\eta^2_p=0.153$ (see Figure 2); with higher maximum heart rates being observed in the presence of the visual coffee cues ($M=82.89$, $SE=1.43$) relative to the neutral cues ($M=79.88$, $SE=1.46$). For average heart rate, there was a significant main effect of cues, $F(1,61)=10.70$, $p=0.002$, $\eta^2_p=0.149$. Average heart rate was significantly increased in the presence of the coffee visual cues relative to the neutral visual cue. Additionally, there was a dose by expectancy by cues interaction for average heart rate, $F(1,61)=4.76$, $p=0.033$, $\eta^2_p=0.072$. Participants in matched told/received conditions (i.e., told

placebo/received placebo and told caffeine/received caffeine) had significant increases in average heart rate from neutral visual cues to coffee visual cues, $p=0.009$; however, those in unmatched conditions had no differences in average heart rate across cues, p-values >0.400. Ultimately, this interaction did not pass the FDR of 5%.

Auditory/olfactory cues. There was a significant main effect of cues on coffee craving, $F(1,60)=8.42$, $p=0.005$, $\eta^2_p=0.123$; participants reported higher levels of coffee craving following the coffee auditory/olfactory cues ($M=7.93$, $SE=0.31$) relative to the neutral auditory/olfactory cues ($M=7.59$, $SE=0.32$).

For maximum heart rate, there was again a main effect of cues, $F(1,60)=25.72$, $p<0.001$, $\eta^2_p=0.300$; this indicates that participants' maximum heart rate was significantly higher during the coffee auditory/olfactory cues ($M=82.68$, $SE=1.43$) than during the neutral auditory/olfactory cues ($M=77.43$, $SE=1.53$). For average heart rate, there was a significant main effect of cues, $F(1,60)=10.07$, $p=0.002$, $\eta^2_p=0.144$. There was an increase in average heart rate from the neutral auditory/olfactory cue presentation ($M=70.87$, $SE=1.37$) to the coffee auditory/olfactory cue presentation ($M=72.68$, $SE=1.29$). Additionally, there was a dose by expectancy by cues interaction for average heart rate, $F(1,60)=5.35$, $p=0.024$, $\eta^2_p=0.082$. Participants who were told placebo but received caffeine had a significant increase from the neutral olfactory/auditory cues ($M=68.35$, $SE=2.65$) to the coffee olfactory/auditory cues ($M=73.29$, $SE=2.49$), $p<0.001$; all other groups had nonsignificant changes from neutral to coffee olfactory/auditory cues. However, this interaction did not ultimately pass the FDR of 5%.

Coffee self-administration. Coffee self-administration was compared between groups via a two-way ANOVA with two levels of expectancy (told placebo and told caffeine) and two levels of dose (received placebo and received caffeine). There were no significant main effects or interaction when analyzing the number of coffee units consumed. As this analysis had a limited range of possible values, it may have lacked sensitivity. Post hoc analyses were conducted to determine whether there was a relationship between dose or expectancy condition and participants' choice to consume any versus no units of coffee. There was a significant difference in proportion of participants drinking any coffee between those who received caffeine and those who received placebo, $X^2(1, N=64)=8.45$, $p=0.004$. About 15 of 33 (45.5%) participants in the received caffeine condition chose to consume at least 1 unit of coffee compared with 25 of 31 (80.6%) of participants in the received placebo condition (see Figure 3). There was no significant difference in the proportion of participants who chose to drink coffee between those who were told they received placebo and those who were told they received caffeine, $X^2(1, N=64)=1.07$, $p=0.439$.

Results for believers

At the conclusion of the study sessions, 11 of 65 participants (16.9%) were found to not believe or to be unsure about the accuracy of the caffeine content information provided to them at the time of gum administration (see Table 1). To determine the impact of removing "nonbelievers" from the analyses, data were re-analyzed including the believers only. All previously reported main effects and interactions remained statistically significant and no new effects were evident.

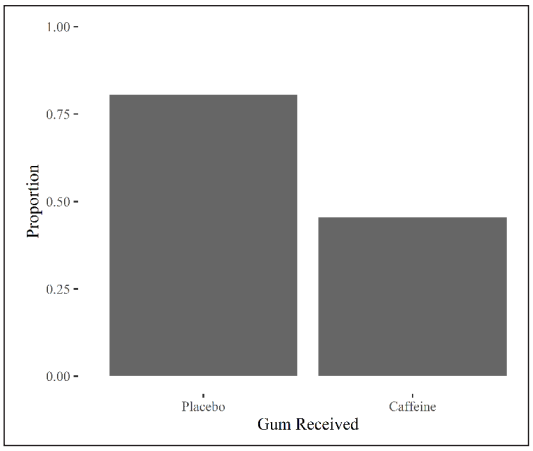

Figure 3. Proportion of participants who consumed any coffee in the received placebo (80.6%) and received caffeine (45.5%) conditions in the penultimate stage of the study. The difference between groups was significant, $p=0.004$.

Table 1. Number of participants who believed the information they received pertaining to the caffeine content of their gum.

Condition	Original *n*	Believer *n*	Believer %
Told caffeine/received caffeine	16	15	93.8
Told caffeine/received placebo	16	11	68.8
Told placebo/received caffeine	17	14	82.4
Told placebo/received placebo	16	14	87.5

Discussion

The present study aimed to investigate the impact of coffee-related stimuli and caffeine expectancy on coffee craving, withdrawal, and subsequent self-administration. While the presentation of coffee specific cues was found to increase both subjective craving and heart rate, cue reactivity was not significantly impacted by the belief that caffeine had been administered. In contrast, visual cue reactivity appeared to be blunted among participants who had actually received a prior dose of caffeine, and caffeine administration was also associated with a reduced probability of subsequent coffee self-administration.

Previous studies have shown the ability of caffeine-related stimuli to elicit subjective and physiological responses. Flaten and Blumenthal (1999) demonstrated that the smell and taste of decaffeinated coffee was enough to elicit an arousal response in daily coffee drinkers. Yeomans et al. (2005) demonstrated an attentional bias to caffeine-related words in high caffeine consumers. The scent of coffee has been shown to produce higher performance on an analytical task (Madzharov et al., 2018). However, to our knowledge, no study has demonstrated craving as a response to coffee-related stimuli. As such, the present findings represent the first demonstration that coffee-specific cues

can elicit subjective and physiological craving responses in coffee users.

Although previous research has demonstrated that drug salient stimuli associated with variety of other substances can reliably provoke both subjective and physiological craving and withdrawal in users, in contrast to these other substances, caffeine appears to devoid of dopaminergic effects that are characteristic of drug reinforcement. Rodent models suggest that doses of caffeine comparable to those typically consumed by humans do not significantly increase dopamine in the mesolimbic circuit (Acquas et al., 2002; De Luca et al., 2007), whereas in human studies caffeine does not appear to increase dopamine transmission in brain regions that are known to be involved in reinforcement and reward (Nehlig et al., 2010; Volkow et al. 2015). Although caffeine appears to be devoid of prototypical dopaminergic reinforcing effects, it is possible that it possesses significant reinforcement enhancing effects. For example, one recent study that examined caffeine self-administration in rats found that oral caffeine at moderate doses (0.5–1.0 mg/kg) increased the rats' motivation to consume saccharin (Bradley and Palmatier, 2019), and there is also evidence that caffeine may enhance the psychomotor stimulant properties of prototypical psychostimulants, such as cocaine via striatal adenosine A_{2A}-dopamine D_2 receptor heteromers (Ferré, 2016). Furthermore, Volkow et al. (2015) found that although caffeine did not increase dopamine transmission in the striatum, caffeine increased D_2/D_3 receptor availability in the putamen and ventral striatum. As such, it is possible that caffeine acts to enhance the reinforcing effects of the vehicle of consumption as opposed to possessing significant primary reinforcing effects (Bradley and Palmatier, 2019). Insofar as caffeine serves as a reinforcement enhancer, one might expect heightened reactivity to caffeine-associated stimuli.

The expectation that caffeine had been consumed was found to be associated with reductions in self-reported withdrawal symptoms 30 min post-gum administration. However, this effect appeared to diminish over time and was no longer evident following the presentation of the cues. Moreover, neither craving nor subsequent coffee self-administration was found to be impacted by caffeine expectancy. These results contrast with findings of a recent study that manipulated caffeine content expectations of caffeine-containing or decaffeinated coffee, where the expectation caffeine had been administered was associated with significant decreases in craving but not withdrawal symptoms (Juliano et al., 2019). However, an earlier study with a longer abstinence period (24 h) found that the expectancy that caffeine had been administered decreased both caffeine withdrawal symptoms and caffeine craving (Mills et al., 2016). It is possible that a longer abstinence period would have produced the same effects in all three studies. Additionally, caffeine was administered via caffeinated gum in the present study, which was not the typical route of administration for any participant; all participants administered their daily caffeine via coffee. Expectancy is based on a combination of factors: information regarding active drug content and dose, anticipated effects of the substance, but also past experience. Thus, the lack of participant experience with caffeinated gum may have muted the expectancy effect.

Similarly, in this study, few pharmacological effects of caffeine on subjective and physiological measures were observed. Caffeine administration was associated with relatively blunted subjective craving in response to coffee-salient visual cues as well as a reduced probability of voluntary administering coffee, but not with reliable changes in subjective withdrawal or heart rate at any time point. It is possible that the null subjective and physiological findings may be related to the dose of caffeine administered. On average, participants reported typically consuming over 400 mg of caffeine per day; frequently, participants consumed their daily caffeine before noon, via successive cups of coffee. The amount of caffeine in each piece of gum (100 mg) was approximately one-quarter of a participant's typical intake. Future examinations of caffeine's pharmacological actions should ensure that dosages used are directly comparable to those typically administered by participants.

The present results should be interpreted in the light of the following methodological considerations. First, it is possible that the 18-h abstinence period was too short to provoke significant withdrawal. Because caffeine's half-life is estimated to be approximately 6 h (White et al., 2016), 18 h should be sufficient for the elimination of most caffeine. However, caffeine withdrawal symptoms typically do not peak until after 20–51 h of abstinence (Juliano and Griffiths, 2004), and it is possible that a longer abstinence period would have increased our sensitivity to detect withdrawal related effects. It is possible that we missed the critical period with at least some of our participants. Second, participants in this study were recruited on the basis of having above-average levels of daily caffeine use, and the generalizability of the present findings to less frequent caffeine users is unknown. Third, caffeine abstinence was confirmed by self-report only. Although we informed participants during the telephone interview that we may or may not take a saliva sample to confirm abstinence (to increase the chance of compliance), we did not directly verify compliance. Fourth, craving was assessed via a single-item question. Research has shown that craving is better captured by multi-item questionnaires that examine multiple aspects of craving (Tiffany and Wray, 2014); however, at this point in time, no valid and reliable questionnaire exists for coffee. Fifth, the caffeinated gum was less liked overall relative to the caffeine-free gum. Because the gum was aversive, it potentially tempered some of the expectancy affects, particularly those related to the positive effects of caffeine. Finally, the cues in the study were presented in the same order to each participant, which opens the possibility that the cue reactivity may be attributable to a time-dependent reaction. However, the neutral and coffee-related cues for each modality were presented within 5 min of each other, leaving little room for time-dependent increases in craving. Additionally, there were no differences in craving from post-gum administration to the neutral visual cue presentation, or from the coffee-related visual cues to the neutral auditory/olfactory cues; thus, it is unlikely that these effects were simply due to the passage of time.

Conclusion

In conclusion, although we did not find strong support for all of our predicted hypotheses, this study is the first to demonstrate cue-elicited coffee craving. Additionally, there was some evidence that expectancy effects can impact subjective caffeine withdrawal, and that actual caffeine administration can impact subsequent craving and use. However, strong links

between caffeine expectancy, administration, and cue reactivity were not apparent.

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Supplemental material

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References

Acquas E, Tanda G and Di Chiara G (2002) Differential effects of caffeine on dopamine and acetylcholine transmission in brain areas of drug-naive and caffeine-pretreated rats. *Neuropsychopharmacology* 27: 182–193. DOI: 10.1016/S0893-133X(02)00290-7.

American Psychiatric Association (2013) *Diagnostic and Statistical Manual of Mental Disorders*. 5th ed. Arlington, VA: American Psychiatric Publishing.

Bond A and Lader M (1974) The use of analogue scales in rating subjective feelings. *Psychol Psychother Theory Res Pract* 47: 211–218. DOI: 10.1111/j.2044-8341.1974.tb02285.x.

Bradley CA and Palmatier MI (2019) Intravenous and oral caffeine self-administration in rats. *Drug Alcohol Depend* 203: 72–82. DOI: 10.1016/j.drugalcdep.2019.05.033.

Carter BL and Tiffany ST (1999) Meta-analysis of cue-reactivity in addiction research. *Addiction* 94: 327–340. DOI: 10.1046/j.1360-0443.1999.9433273.x.

Centre for Addictions and Mental Health (2011) *Caffeine*. Available at: https://www.camh.ca/en/health-info/mental-illness-and-addiction-index/substance-use/caffeine (accessed 8 November 2020).

De Luca MA, Bassareo V, Bauer A, et al. (2007) Caffeine and accumbens shell dopamine. *J Neurochem* 103: 157–163. DOI: 10.1111/j.1471-4159.2007.04754.x.

Drummond DC (2001) Theories of drug craving, ancient and modern. *Addiction* 96: 33–46. DOI: 10.1046/j.1360-0443.2001.961333.x.

Ferré S (2016) Mechanisms of the psychostimulant effects of caffeine: Implications for substance use disorders. *Psychopharmacology* 233: 1963–1978. DOI: 10.1007/s00213-016-4212-2.

Flaten MA and Blumenthal TD (1999) Caffeine-associated stimuli elicit conditioned responses: An experimental model of the placebo effect. *Psychopharmacology* 145: 105–112. DOI: 10.1007/s002130051038.

Hughes JR, Oliveto AH, Liguori A, et al. (1998) Endorsement of DSM-IV dependence criteria among caffeine users. *Drug Alcohol Depend* 52: 99–107. DOI: 10.1016/S0376-8716(98)00083-0.

Johnson BA (2012) *Addiction Medicine: Science and Practice*. New York, NY: Springer.

Johnson BA, Chen YR, Schmitz J, et al. (1998) Cue reactivity in cocaine-dependent subjects: Effects of cue type and cue modality. *Addicit Behav* 23: 7–15. DOI: 10.1016/S0306-4603(97)00014-2.

Juliano LM and Griffiths RR (2004) A critical review of caffeine withdrawal: Empirical validation of symptoms and signs, incidence, severity, and associated features. *Psychopharmacology* 176: 1–29. DOI: 10.1007/s00213-004-2000-x.

Juliano LM, Huntley ED, Harrell PT, et al. (2012) Development of the caffeine withdrawal symptom questionnaire: Caffeine withdrawal symptoms cluster into 7 factors. *Drug Alcohol Depend* 124: 229–234. DOI: 10.1016/j.drugalcdep.2012.01.009.

Juliano LM, Kardel PG, Harrell PT, et al. (2019) Investigating the role of expectancy in caffeine withdrawal using the balanced placebo design. *Hum Psychopharmacol* 34: e2692. DOI: 10.1002/hup.2692.

Kamimori GH, Karyekar CS, Otterstetter R, et al. (2002) The rate of absorption and relative bioavailability of caffeine administered in chewing gum versus capsules to normal healthy volunteers. *Int J Pharm* 234: 159–167. DOI: 10.1016/S0378-5173(01)00958-9.

Madzharov A, Ye N, Morrin M, et al. (2018) The impact of coffee-like scent on expectation and performance. *J Environ Psychol* 57: 83–86. DOI: 10.1016/j.jenvp.2018.04.001.

McGrath DS, Peloquin MP, Ferdinand JC, et al. (2015) Acute effects of nicotine on alcohol cue-reactivity in nondependent and dependent smokers. *Exp Clin Psychopharmacol* 23: 29–36. DOI: 10.1037/a0038606.

McKee SA (2009) Developing human laboratory models of smoking lapse behavior for medication screening. *Addict Biol* 14: 99–107. DOI: 10.1111/j.1369-1600.2008.00135.x.

Meredith SE, Juliano LM, Hughes JR, et al. (2013) Caffeine use disorder: A comprehensive review and research agenda. *J Caffeine Res* 3: 114–130.

Mills L, Boakes RA and Colagiuri B (2016) Placebo caffeine reduces withdrawal in abstinent coffee drinkers. *J Psychopharmacol* 30: 388–394. DOI: 10.1177/026988116632374.

Nehlig A, Armspach J-P and Namer IJ (2010) SPECT assessment of brain activation induced by caffeine: No effect on areas involved in dependence. *Dialogues Clin Neurosci* 12: 255–263.

Newman RA, Kamimori GH, Wesensten NJ, et al. (2013) Caffeine gum minimizes sleep inertia. *Percep Mot Skills* 116: 280–293. DOI: 10.2466/29.22.25.PMS.116.1.280-293.

Reyes CM and Cornelis MC (2018) Caffeine in the diet: Country-level consumption and guidelines. *Nutrients* 10: 1772. DOI: 10.3390/nu10111772.

Roese NJ and Jamieson DW (1993) Twenty years of bogus pipeline research: A critical review and meta-analysis. *Pschol Bull* 114: 363–375. DOI: 10.1037/0033-2909.114.2.363.

Sayette MA, Griffin KM and Sayers WM (2010) Counterbalancing in smoking cue research: A critical analysis. *Nicotine Tob Res* 12: 1068–1079. DOI: 10.1093/ntr/ntq159.

Schlagintweit HE and Barrett SP (2016) Does acute tobacco smoking prevent cue-induced craving? *J Psychopharmacol* 30: 468–473. DOI: 10.1177/0269881116639288.

Schlagintweit HE, Good KP and Barrett SP (2014) The impact of anticipated and unanticipated smoking opportunities on cigarette smoking and nicotine lozenge responses. *J Psychopharmacol* 28: 773–779. DOI: 10.1177/0269881113519508.

Siegel S (1975) Evidence from rats that morphine tolerance is a learned response. *J Comp Physiol Psychol* 89: 498–506. DOI: 10.1037/h0077058.

Stewart J, De Wit H and Eikelboom R (1984) Role of unconditioned and conditioned drug effects in the self-administration of opiates and stimulants. *Psychol Rev* 91: 251–268. DOI: 10.1037/0033-295X.91.2.251.

Syed SA, Kamimori GH, Kelly W, et al. (2005) Multiple dose pharmacokinetics of caffeine administered in chewing gum to normal healthy volunteers. *Biopharm Drug Dispos* 26: 403-409. DOI: 10.1002/bdd.469.

Tiffany ST (1990) A cognitive model of drug urges and drug-use behavior: Role of automatic and nonautomatic processes. *Psychol Rev* 97: 147–168. DOI: 10.1037/0033-295X.97.2.147.

Tiffany ST and Wray JM (2014) The clinical significance of drug craving. *Ann N Y Acad Sci* 1248: 1–17. DOI: 10.1111/j.1749-6632.2011.06298.x.

Verster JC and Koenig J (2018) Caffeine intake and its sources: A review of national representative studies. *Crit Rev Food Sci Nutr* 58: 1250–1259. DOI: 10.1080/10408398.2016.1247252.

Volkow ND, Wang G-J, Logan J, et al. (2015) Caffeine increases striatal dopamine D_2/D_3 receptor availability in the human brain. *Transl Psychiatry* 5: e549. DOI: 10.1038/tp.2015.46.

White JR, Padowski JM, Zhong Y, et al. (2016) Pharmacokinetic analysis and comparison of caffeine administered rapidly or slowly in coffee chilled or hot versus chilled energy drink in healthy young adults. *Clin Toxicol (Phila)* 54: 308–312. DOI: 10.3109/15563650.2016.1146740.

Witteman J, Post H, Tarvainen M, et al. (2015) Cue reactivity and its relation to craving and relapse in alcohol dependence: A combined laboratory and field study. *Psychopharmacology* 232: 3685–3696. DOI: 10.1007/s00213-015-4027-6.

Wray JM, Godleski SA and Tiffany ST (2011) Cue-reactivity in the natural environment of cigarette smokers: The impact of photographic and in vivo smoking. *Psychol Addict Behav* 25: 733–737. DOI: 10.1037/a0023687.

Yeomans MR, Javaherian SJ, Tovey HM, et al. (2005) Attentional bias for caffeine-related stimuli in high but not moderate or non-caffeine consumers. *Psychopharmacology* 181: 477–485. DOI: 10.1007/s00213-005-0004-9.

Zhao M, Fan C, Du J, et al. (2012) Cue-induced craving and physiological reactions in recently and long-abstinent heroin-dependent patients. *Addict Behav* 37: 393–398. DOI: 10.1016/j.addbeh.2011.11.030.