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INFLUENCE OF COCAINE-RELATED IMAGES AND ALCOHOL ADMINISTRATION ON INHIBITORY CONTROL IN COCAINE USERS

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Abstract

Background—Alcohol use and impulsivity, including decreased inhibitory control, predict poor treatment outcomes for individuals with cocaine use disorders. This study sought to determine the effects of alcohol administration on inhibitory control following cocaine-related and neutral cues on the Attentional Bias-Behavioral Activation (ABBA) task in cocaine users. We hypothesized that the proportion of inhibitory failures would increase following cocaine cues compared to neutral cues. We further hypothesized that there would be an interaction between alcohol administration and task version, such that alcohol would impair inhibitory control following cocaine, but not neutral cues.

Methods—Fifty current cocaine users completed this mixed-model, double-blind, placebo-controlled, cross-over study over two experimental sessions. The ABBA task was completed following alcohol administration (0.0 and 0.65 g/kg). Subject-rated drug-effect and physiological measures were collected prior to and after alcohol administration.

Results—Proportion of inhibitory failures was increased following cocaine-related cues compared to neutral cues independent of alcohol dose. Alcohol administration also produced prototypical subject-rated drug-effects.

Conclusions—A better understanding of the relationship between alcohol consumption and inhibitory control in cocaine users could direct the development of interventions to decrease the risk of relapse in individuals who drink and display impaired inhibitory control.

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Keywords

cocaine; inhibitory control; alcohol; response inhibition; cocaine cues

Introduction

Comorbid cocaine and alcohol use is a significant problem, which contributes to increased use and relapse. In 2014, nearly half of individuals who met criteria for cocaine dependence also met criteria for comorbid alcohol dependence (United States Department of Health and Human Services, 2016). Individuals who use cocaine in combination with alcohol report using increased amounts of both substances when used together compared to when using only one substance (Gossop et al., 2006). This finding was also observed in the human laboratory, wherein alcohol pretreatment increased choice for cocaine over money alternatives (Higgins et al., 1996). In the clinic, alcohol use precedes cocaine relapse following treatment. Among individuals who relapsed within 6 months following cocaine treatment, 62% reported using alcohol on the day they relapsed (McKay et al., 1999).

Higher levels of impulsivity also predict poorer cocaine treatment outcomes (e.g., Brewer et al., 2008; Carpenter et al., 2006; Patkar et al., 2004; Streeter et al., 2008; Winhusen et al., 2013). One multi-site clinical trial used the Barratt Impulsiveness Scale-11 (BIS-11) to assess the relationship between baseline self-reported impulsivity and stimulant use treatment retention (Winhusen et al., 2013). Individuals who did not complete treatment were more likely to have higher scores on the motor impulsiveness scale of the BIS-11 (Winhusen et al., 2013). In another clinical trial, increased interference scores on the Stroop task, which represents impaired inhibitory control, since subjects have to inhibit reading the word to identify the color of the text, were associated with cocaine treatment non-completion (Streeter et al., 2008).

Despite high rates of comorbid cocaine and alcohol use disorders (United States Department of Health and Human Services, 2016) and alcohol consumption preceding relapse following treatment (McKay et al., 1999), it is not known how alcohol contributes to relapse or the continued use of cocaine. One potential explanation could be the inhibitory control impairing effects of alcohol as has been shown in the human laboratory (e.g., Dougherty et al., 1999; Marczinski and Fillmore, 2003, 2005; Weafer and Fillmore, 2015). In one study, 12 adult drinkers completed the Cued Go/No-Go task following a range of alcohol doses (i.e., 0.00, 0.45, and 0.65 g/kg). Alcohol dose dependently increased the proportion of inhibitory failures in the presence of alcohol cues (Marczinski and Fillmore, 2003). Cocaine users also display impaired inhibitory control (e.g., Fillmore and Rush, 2002; Lane et al., 2007; Verdejo-García et al., 2007). Impaired inhibitory control has been shown to predict poor cocaine treatment outcomes (e.g., Brewer et al., 2008; Carpenter et al., 2006; Patkar et al., 2004; Streeter et al., 2008; Winhusen et al., 2013). A better understanding of the interaction between alcohol administration and inhibitory control following cocaine cues could inform treatment approaches to improve outcomes.

The Attentional Bias-Behavioral Activation (ABBA) task is a behavioral measure of inhibitory control. Cocaine-related and non-cocaine-related (i.e., neutral) images serve as

cues to signal the likelihood of whether a response should be executed or withheld (Pike et al., 2013, 2015; Weafer and Fillmore, 2012, 2015). In the ABBA task, subjects are assigned to complete a version of the task with either cocaine-related or neutral images as go cues that are followed by a target requiring subjects to execute a response (i.e., go targets) on 80% of trials. Cocaine users display impaired inhibitory control on the ABBA task when they are prepared to respond following cocaine cues compared to neutral cues (Pike et al., 2013, 2015).

Similar results have been observed when alcohol drinkers complete the ABBA task with alcohol-related and non-alcohol-related (i.e., neutral) images as cues (Weafer and Fillmore, 2012, 2015). Furthermore, alcohol administration significantly increases the proportion of inhibitory failures following alcohol, but not neutral, cues among alcohol drinkers (Weafer and Fillmore, 2015). In that study, 40 adults who reported moderate to heavy drinking completed the ABBA task with either alcohol or neutral images as the go cue following 0.00 and 0.65 g/kg alcohol administration. Alcohol administration increased the proportion of inhibitory failures in the alcohol go version, but not in the neutral go version. Reaction times to go targets were slowed following alcohol administration compared to placebo for both the alcohol and neutral go versions (Weafer and Fillmore, 2015).

The purpose of this experiment was to determine the effects of alcohol administration on inhibitory control following cocaine-related and neutral cues in cocaine users. We hypothesized that the proportion of inhibitory failures would increase following cocaine-related cues compared to neutral cues following both alcohol and placebo administration. We further hypothesized that there would be an interaction between alcohol administration and task version, such that alcohol would impair inhibitory control following cocaine, but not neutral cues, similar to the outcomes observed for alcohol cues following alcohol administration (Weafer and Fillmore, 2015). Finally, we hypothesized that reaction times would be slowed following alcohol administration regardless of task version.

Materials and Methods

Study Population, Inclusion/Exclusion Criteria, and Screening

Fifty non-treatment seeking adult subjects with recent histories of cocaine use, primarily recruited through word of mouth and postings on community bulletin boards, completed this mixed-model, double-blind, placebo-controlled, cross-over study. Two subjects enrolled in the study (i.e., signed the consent document), but did not complete the practice session. Three subjects enrolled and completed the practice session, but did not complete the first experimental session. Three subjects also completed the study using a different procedure, but following their participation the study was redesigned due to subject fatigue during cognitive testing. The data from these 8 subjects were not included in the analyses. The Institutional Review Board of the University of Kentucky Medical Center approved this study and subjects gave their written informed consent prior to participating. Subjects were informed that during the study they would be given a drink that could contain placebo (i.e., water) or alcohol. Subjects were informed that the purpose of the study was to see how alcohol affects mood and performance on a computerized task. Subjects were blind to the

specific drink they received in individual sessions and were not informed of expected outcomes or task performance. Subjects were paid for their participation.

Prior to enrollment in the experimental protocol, all subjects underwent a comprehensive physical and mental health screening, including measures of current and past physiological disease, self-report checklists for psychological disorders (e.g., ADHD and depression), and a detailed substance use history. Subject demographics are shown in Table 1. Subjects also completed the computerized Structured Clinical Interview for DSM-IV (SCID). The SCID uses DSM-IV criteria and subjects could endorse items related to substance abuse or dependence and these categories for substance were collapsed into criteria for a substance use disorder (e.g., cocaine abuse and/or dependence collapsed to cocaine use disorder). Subjects had to meet the following inclusion criteria: self-reported cocaine and alcohol use in the last month on a Timeline Follow-Back (TLFB; Sobell and Sobell, 1992) Calendar and be at least 21 years of age. Potential subjects with histories of serious physical disease or current physical disease (e.g., impaired cardiovascular functioning, chronic obstructive pulmonary disease), seizure, head trauma or central nervous system tumors, or current or past histories of serious psychiatric disorder (i.e., Axis I of *DSM-IV*) other than substance abuse or dependence, were excluded from participation. All subjects were physically and psychologically healthy with no contraindications to alcohol.

Study Procedures

The experiment consisted of 3 total outpatient sessions (1 practice and 2 experimental). For all sessions, subjects arrived at the University of Kentucky Laboratory of Human Behavioral Pharmacology at approximately 9:30 AM. Subjects completed a field sobriety test and provided an expired breath sample that was tested for the presence of alcohol using a handheld Alco-Sensor Breathalyzer (Intoximeters, St. Louis, MO) prior to the beginning of each session. Subjects also provided a urine sample that was tested for drugs of abuse, as well as pregnancy for female subjects. Subjects tested positive for cocaine on the practice session ($n = 35$), on the session where placebo was administered ($n = 36$), and on the session where alcohol was administered ($n = 34$). Subjects also occasionally tested positive for THC. Subjects had to pass a standard field sobriety test and were asked at the beginning of each session when they last used any substances to verify that they were not acutely intoxicated. Alcohol administration occurred 2.5 hours after subjects arrived to the laboratory, which is over two times the half-life of cocaine (Javaid et al., 1983; Jeffcoat et al., 1989). All female subjects tested negative for pregnancy throughout their participation and reported using a medically verified birth control method (e.g., condoms) or abstinence. Subjects were instructed to abstain from drugs and alcohol for 12 hours prior to their session. Subjects were also instructed to abstain from food and caffeine for 4 hours prior to each session and were given a low-fat meal at the beginning of each session (i.e., 9:30 AM). Sessions were rescheduled if subjects provided a breath sample positive for alcohol, a urine sample that was positive for any substances other than cocaine and/or THC, or reported consuming food or caffeine within 4 hours of the session.

Practice Session

A practice session was conducted to familiarize subjects with the Attentional-Bias Behavioral Activation (ABBA) task, subject-rated drug-effects questionnaires, and timeline of experimental sessions, as described below. No drink was administered during the practice session.

Experimental Sessions

Experimental sessions started at 9:30 AM and lasted approximately 7.5 hours. All subjects who reported smoking were allowed to smoke one cigarette in the morning between 9:30 AM and 10:15 AM and one cigarette at lunch around 2:00 PM during sessions. Subjects were asked to keep their smoking behavior consistent throughout the experiment in order to keep nicotine exposure consistent within subjects.

At 12:00 PM, subjects received the drink (i.e., alcohol or placebo mixed with lemon-lime soda; described in detail in the section Alcohol Administration below) for the session. Subjects were instructed to consume the drink through a straw within 10 minutes and two research assistants verified that the entire drink was consumed. Subjects completed subject-rated drug-effects questionnaires and DSST approximately 30 minutes before drink administration and 15, 30, 120, 180, 240, and 300 minutes following drink completion. Blood pressure and heart rate were recorded approximately 30 minutes before drink administration and 15, 30, 60, 120, 180, 240, and 300 minutes following drink completion. Breath alcohol concentration (BrAC) was recorded 15, 30, 60, 120, 180, 240, and 300 minutes following drink completion. Subjects completed the ABBA task 60 minutes following drink completion. Subjects were released once their BrAC fell below 20 mg/100 ml and no physical or behavioral alcohol effects were detected at least 5 hours following drink administration.

Attentional Bias-Behavioral Activation (ABBA) Task

The ABBA task is a modified Cued Go/No-Go reaction time task, which was administered using E-prime experiment generation software (Psychology Software Tools, Pittsburgh, PA) on a PC computer (described in detail Pike et al., 2013, 2015; Weafer and Fillmore, 2012). The task consists of 250 trials divided into 5 blocks of 50 trials (sample trials are shown in Figure 1). All trials consist of a fixation point, followed by the presentation of a cue image, which fills in either solid blue or green as a target, and subjects are given feedback (i.e., correct with reaction time or incorrect) depending on their response to the target. The cues consist of cocaine-related images (e.g., powder with a razor blade, crack cocaine) and neutral images (e.g., stapler, paper towel roll). After a variable period of time or stimulus onset asynchrony (i.e., 100, 200, 300, 400, or 500 milliseconds [ms]), the cue image turns either solid green (go target) or solid blue (no-go target). Subjects are instructed to press the forward slash (/) key on the keyboard, which is marked with a green sticker, as soon as a green (go) target appears. Subjects are instructed to withhold responses when a blue (no-go) target appears. The total number of trials during which subjects are prepared to respond (i.e., go cue), but need to inhibit responses (i.e., no-go target) occur on 25 of the 250 trials.

Two versions of the ABBA task were administered: a *cocaine go* version and a *neutral go* version. In the cocaine go version, 80% of go targets were preceded by a cocaine cue and 20% of go targets were preceded by a neutral cue. In the cocaine go version, 80% of the no-go targets were preceded by a neutral cue and 20% of no-go targets were preceded by a cocaine cue. In the neutral go version, 80% of go targets were preceded by a neutral cue and 20% were preceded by a cocaine cue. In the neutral go version, 80% of the no-go targets were preceded by a cocaine cue and 20% of the no-go targets were preceded by a neutral cue. For half of the subjects cocaine images served as the go cue ($n = 25$) and for the other half neutral images served as the go cue ($n = 25$). Any subjects who completed the ABBA task in a previous study were assigned to the version they completed previously ($n = 11$ in the cocaine go version and $n = 10$ in the neutral go version). During the ABBA task, subjects learn which cues precede go and no-go targets and previous studies have not investigated how long this learning persists. For this reason, subjects were assigned to the same version they completed previously. Subjects who had never completed the ABBA task ($n = 29$) were randomly assigned to complete either the cocaine go ($n = 14$) or neutral go ($n = 15$) version. Independent samples t -tests showed no differences in performance (i.e., proportion of inhibitory failures or reaction times following go or no-go cues) during the practice session between participants who had previously completed the ABBA and those who had not for either version of the task ($t[23] < 1.7, p > 0.10$).

Data collected from the ABBA task included the proportion of inhibitory failures to no-go targets (i.e., responses executed that should have been withheld) following go and no-go cues. Reaction time to go targets (i.e., speed to execute correct responses) following go and no-go cues was also collected. Proportion of inhibitory failures and reaction times were collected as mean values following each cue type from throughout the task and were also broken down by stimulus onset asynchrony (i.e., 100, 200, 300, 400, and 500 ms) and block (i.e., Block 1, Block 2, Block 3, Block 4, and Block 5). The total number of correct responses executed to go targets following go and no go cues were also measured.

Subject-Rated Drug-Effect Questionnaires and Performance Measure

Two subject-rated drug-effect questionnaires were administered using an Apple computer with a mouse attached in a fixed order throughout the session. On the Cocaine Craving Questionnaire (Dudish-Poulsen and Hatsukami, 1997; Marks et al., 2015), subjects rated how much they Want Cocaine, Need Cocaine, and Crave Cocaine from Not at All (i.e., score of 0) to Extremely (i.e., score of 4). On the Drug Effect Questionnaire (Rush et al., 2011) subjects rated how the drink made them feel on a 100-mm visual analog scale. Items included Stimulated, Sedated, Anxious, Light-Headed, Sleepy, Sick, High, Drunk, and Drink More. Subjects also completed the Digit-Symbol-Substitution Task (DSST; McLeod et al., 1982), during which subjects recreated patterns presented on the computer screen within 90 seconds with an attached nine-digit keypad. The primary outcomes of interest were the number of patterns attempted and number of patterns that were completed correctly.

Physiological Measures

Heart rate, blood pressure, and BrAC were measured at regular intervals throughout the session. The alcohol doses would be held if systolic pressure was 150 mmHg or higher,

diastolic pressure was 100 mmHg or higher, or heart rate was 100 bpm or higher. No doses were held for exceeding these parameters. Participation would be discontinued if systolic blood pressure, diastolic blood pressure, or heart rate exceeded 180, 110, or 130, respectively, but no subjects were excluded for exceeding these parameters.

Alcohol Administration

Alcohol (0.00 and 0.65 g/kg) was administered in a double-blind fashion using a cross-over design. Each dose was administered during experimental sessions separated by at least 24 hours. The doses of alcohol should produce peak BrACs of approximately 0 and 80 mg/100 ml, respectively (Fillmore et al., 2005; Marczinski and Fillmore, 2005). The alcohol drink was mixed in a ratio of 3 parts lemon-lime soda to 1 part alcohol (0.65 g/kg). The placebo drink was mixed in a ratio of 3 parts lemon-lime soda to 1 part water to match the volume of the active dose. To better mask the dose conditions, 3 mL of alcohol was floated on the surface of the drink. The drink was administered in an insulated, opaque tumbler with a lid and subjects were instructed to consume the drink through a straw. Subjects had 10 minutes to consume the entire drink. The order of alcohol dose administration was determined with a random number generator.

Statistical Methods

For all statistical analyses, effects with $p < 0.05$ were considered significant.

Independent-samples *t*-tests were used to compare demographics for continuous variables and chi-square analyses were conducted to compare categorical variables between groups (i.e., the cocaine go and neutral go versions of the ABBA task).

Data from the ABBA task were analyzed using a two-factor mixed-model analysis of variance (ANOVA; Statview, Cary, NC and IBM SPSS Statistics Version 22, Armonk, NY, USA). The between-subjects factor was Task Version (i.e., Cocaine Go or Neutral Go) and the within-subjects factor was Alcohol Dose (i.e., 0.00 and 0.65 g/kg). Four analyses were completed with the outcomes of inhibitory failures to no-go targets following go and no-go cues and reaction time to go targets following go and no-go cues. Outcomes were selected based on previous research (Weafer and Fillmore, 2011, 2015) and power to detect group differences. The proportion of inhibitory failures to no-go targets was the primary outcome of interest related to inhibitory control. Reaction time was used to detect changes in behavioral activation. An increased proportion of inhibitory failures in either group with a corresponding decrease in reaction time was likely related to a speed accuracy trade-off (e.g., responses executed faster with less concern for accurate responses leading to an increase in incorrectly executed responses to no-go targets). Analyses of Covariance were conducted on ABBA task outcomes controlling for the differences between the groups in days used alcohol in the last month and three months on the TLFB (see Demographics, below), however the outcomes did not change from the repeated-measures ANOVAs so results of the analysis without covariates are reported. Tukey's Honest Significant Difference (HSD) *post hoc* test was used to assess differences between the alcohol and placebo doses within each group and between groups within each dose condition based on significant main effects or interactions observed in the ANOVA outcomes.

Data from the Cocaine Craving Questionnaire, Visual Analog Scale, and DSST were analyzed using a mixed-model ANOVA. The between-subjects factor was Task Version (i.e., Cocaine Go or Neutral Go) and the within-subjects factors were Alcohol Dose (i.e., 0.00 and 0.65 g/kg) and Time (i.e., Pre, 15, 30, 120, 180, 240, and 300 minutes post-alcohol administration). For all measures where the ANOVA did not reveal a significant interaction with or a main effect of Task Version, data were collapsed across task versions and repeated-measures ANOVAs were conducted with the within-subjects factors of Alcohol Dose and Time. Physiological data were analyzed in the same method as the subject-rated effects, however for systolic blood pressure, diastolic blood pressure, and heart rate the within-subjects factor of Time included Pre, 15, 30, 60, 120, 180, 240, and 300 minutes post-alcohol administration. For BrAC the within-subjects factor of Time included 15, 30, 60, 120, 180, 240, and 300 minutes post-alcohol administration. Tukey's Honest Significant Difference (HSD) *post hoc* test was used to assess differences between the alcohol and placebo doses at each time point when a significant main effect or interaction was observed in the ANOVA outcomes.

Results

Demographics

Subjects randomly assigned to the neutral go version reported drinking more days in the last month ($t[48] = 2.90, p = 0.01$) and three months ($t[48] = 2.77, p = 0.01$) compared to those in the cocaine go version on the TLFB. No other significant differences between subjects assigned to the cocaine go and neutral go version were observed ($p > 0.05$; Table 1). Race distribution between groups approached significance ($X^2 = 5.86, p = 0.054$) and was likely due to more Caucasian subjects randomly assigned to the neutral go version. Data were missing from one subject in the cocaine go version for number of alcohol drinks per occasion and from two subjects in the neutral go version for years of marijuana use.

ABBA Performance

ANOVA revealed a significant main effect of Task Version on the proportion of inhibitory failures to no-go targets following go cues ($F[1, 48] = 4.72, p = 0.03$). The proportion of inhibitory failures to no-go targets following go cues was significantly greater in the cocaine go version compared to the neutral go version following both placebo and alcohol administration according to Tukey's HSD *post hoc* test (Figure 2 top panel). The main effect of Alcohol Dose ($F[1, 48] = 1.53, p = 0.22$) and the interaction ($F[1, 48] = 0.55, p = 0.46$) were not significant.

ANOVA also revealed significant main effects of Alcohol Dose on reaction times to go targets following go and no-go cues ($F[1, 48] = 21.26, p < 0.01$ and $F[1, 48] = 30.87, p < 0.01$, respectively). Tukey's HSD *post hoc* test showed reaction times following go cues were significantly increased in both groups following alcohol administration compared to placebo (Figure 2 bottom panel). Reaction times following no-go cues were also significantly increased following alcohol administration compared to placebo according to Tukey's HSD *post hoc* test (data not shown). In the cocaine go version, reaction times increased from 384.49 ms following placebo to 417.40 ms following alcohol administration.

In the neutral go version, reaction times increased from 365.70 ms following placebo to 392.48 ms following alcohol administration.

No significant main effects or interactions were observed on the proportion of inhibitory failures to no-go targets following no-go cues (data not shown).

Subject-Rated Drug-Effects

Cocaine Craving Questionnaire—ANOVA revealed an interaction of Alcohol Dose and Time for the total score on the Cocaine Craving Questionnaire ($F[6, 294] = 4.06, p < 0.01$; Figure 3 top panel). Scores were significantly increased at 15 and 30 minutes following alcohol administration compared to placebo according to Tukey's HSD *post hoc* test.

Visual Analog Scale—ANOVA revealed an interaction of Alcohol Dose and Time for ratings of Anxious ($F[6, 294] = 6.21, p < 0.01$), Drunk ($F[6, 294] = 17.55, p < 0.01$; Figure 3 middle panel), High ($F[6, 294] = 25.03, p < 0.01$; Figure 3 bottom panel), Light Headed ($F[6, 294] = 10.37, p < 0.01$), Sedated ($F[6, 294] = 5.80, p < 0.01$), and Stimulated ($F[6, 294] = 23.72, p < 0.01$). Ratings were significantly increased following alcohol administration compared to placebo according to Tukey's HSD *post hoc* test and decreased as a function of time.

ANOVA revealed a three-way interaction of Alcohol Dose, Task Version, and Time for ratings of Drink More ($F[6, 288] = 4.86, p < 0.01$). Ratings were significantly increased in the neutral go version for 15, 30, and 120 minutes following alcohol administration compared to placebo according to Tukey's HSD *post hoc* test. Alcohol administration only increased ratings at 120 minutes in the cocaine go version compared to placebo according to Tukey's HSD *post hoc* test.

ANOVA revealed an interaction of Alcohol Dose and Time ($F[6, 288] = 8.43, p < 0.01$) and an interaction of Task Version and Time ($F[6, 288] = 2.13, p = 0.05$) for ratings of Sleepy. Both groups displayed significant increases in ratings following alcohol administration that decreased over time based on Tukey's HSD *post hoc* test. Subjects in the cocaine go version reported higher ratings than those in the neutral group 120, 180, and 240 minutes after alcohol administration, but both groups reported similar ratings throughout the rest of the sessions.

ANOVA revealed main effects of Alcohol Dose ($F[1, 294] = 8.80, p < 0.01$) and Time ($F[6, 294] = 2.16, p = 0.05$), but not an interaction of these factors, for ratings of Sick. Ratings were increased slightly following alcohol administration, but these differences were not significant based on Tukey's HSD *post hoc* test.

Overall, alcohol administration generally increased prototypical subject-rated drug-effects ratings, which decreased over time. Some measures showed group differences (e.g., ratings for Drink More and Sleepy) and these differences were related to the magnitude of the increase produced by alcohol administration being higher at individual time points in one group compared to the other.

Digit-Symbol-Substitution Task—ANOVA revealed an interaction of Alcohol Dose and Time ($F[6, 288] = 2.71, p = 0.01$) and a main effect of Task Version ($F[1, 288] = 5.67, p = 0.02$) for total number of patterns completed correctly on the DSST (data not shown). According to Tukey's HSD *post hoc* test, no significant differences were observed between number of patterns completed correctly following placebo and alcohol administration for either group. Following both doses, individuals in the cocaine go version completed fewer patterns correctly compared to those in the neutral go version.

ANOVA revealed a significant interaction of Alcohol Dose and Time ($F[6, 294] = 4.62, p < 0.01$) for total number of patterns attempted on the DSST (data not shown). Alcohol administration produced transient decreases in the number of patterns attempted according to Tukey's HSD *post hoc* test.

Physiological Effects

ANOVA revealed an interaction of Alcohol Dose and Time for systolic blood pressure ($F[7, 343] = 3.58, p < 0.01$), diastolic blood pressures ($F[7, 343] = 12.40, p < 0.01$), heart rate ($F[7, 343] = 7.82, p < 0.01$), and BrAC ($F[6, 294] = 365.60, p < 0.01$). Tukey's HSD *post hoc* tests revealed no significant differences between the alcohol doses for systolic blood pressure (data not shown). For diastolic blood pressure, alcohol administration produced an initial increase, followed by a decrease over time (Figure 4 middle panel). Alcohol administration produced increases in heart rate compared to placebo administration (Figure 4 bottom panel). Alcohol administration produced prototypical increases and decreases in BrAC over time (Figure 4 top panel).

Discussion

The purpose of this experiment was to determine the effects of alcohol administration on inhibitory control following cocaine-related and neutral cues in cocaine users. Alcohol administration may impact inhibitory control following cocaine cues, because these substances are commonly used in combination. The majority of subjects in the sample reported using cocaine and alcohol in combination. This outcome is consistent with epidemiological findings in that nearly half of individuals who met criteria for cocaine dependence also met criteria for comorbid alcohol dependence in the US (United States Department of Health and Human Services, 2016). Cocaine users displayed impaired inhibitory control following cocaine cues (Pike et al., 2013, 2015). Alcohol impairs inhibitory control in drinkers (e.g., Dougherty et al., 1999; Marcinski and Fillmore, 2003, 2005; Weafer and Fillmore, 2015). Alcohol consumption and impulsivity have both been shown to contribute independently to relapse following cocaine treatment (e.g., McKay et al., 1999; Winhusen et al., 2013).

Subjects in the cocaine go version displayed a higher proportion of inhibitory failures to no-go targets following go cues compared to the neutral go version following both placebo and alcohol administration. This finding supports our hypothesis and replicates previous studies showing cocaine users display a higher proportion of inhibitory failures when prepared to respond following cocaine compared to neutral images (Pike et al., 2013, 2015). No differences in reaction times to respond to targets following go cues were observed between

the groups within each respective alcohol dose. This suggests that the increase in inhibitory control failures among subjects in the cocaine go version was not caused by trading accuracy for faster reaction times. Previous studies have shown no differences between the cocaine go and neutral go versions for reaction times on the ABBA task (Pike et al., 2013, 2015).

Given the relationship observed in the human laboratory and clinic between cocaine and alcohol use, we hypothesized that alcohol administration would impair inhibitory control following cocaine, but not neutral cues. Alcohol administration did not significantly increase the proportion of inhibitory failures, but non-significant increases were observed in the cocaine go version. This increase is consistent with the finding that alcohol administration (0.65 g/kg) increased the proportion of inhibitory failures following alcohol images on the ABBA task in drinkers (Weafer and Fillmore, 2015). With drinkers, however, the magnitude of the increase in the proportion of inhibitory failures was larger and an interaction between alcohol dose and task version was observed (Weafer and Fillmore, 2015).

The reason alcohol administration did not significantly increase the proportion of inhibitory failures in the present study is not known. Subjects reported drinking approximately six standard drinks per occasion, which is double the dose administered. The alcohol dose tested may have been too low to produce significant impairments in inhibitory control. Although subjects may be tolerant to the effects of a lower dose of alcohol, they reported increases on the subject-reported drug-effects questionnaire following alcohol administration. Subjects also displayed motor impairment, as demonstrated by slowed reaction times on the ABBA task and a decrease in the number of patterns attempted and completed correctly on the DSST following alcohol administration, indicating that a behaviorally active dose was tested. Subjects in the cocaine go version failed to inhibit responses following go cues 16% of the time following placebo administration, which may have made it difficult to detect a significant increase following alcohol administration. A significant main effect of alcohol dose was observed on reaction times to go targets following go and no-go cues, which supports our last hypothesis. Both groups displayed slowed reaction times following alcohol administration compared to placebo. This is consistent with findings from drinkers on the ABBA task following alcohol administration (Weafer and Fillmore, 2015) demonstrating that 0.65 g/kg alcohol is a behaviorally active dose.

The discordance between the present study and the previous study assessing ABBA performance following alcohol administration in non-cocaine using alcohol drinkers (Weafer and Fillmore, 2015) is most parsimoniously explained by methodological differences. The ABBA task was administered 60 minutes following alcohol administration in this study, which was on the descending limb of the blood alcohol concentration curve. In the study by Weafer and Fillmore, the ABBA task was administered 30 minutes following alcohol administration and significant impairments in inhibitory control performance were observed (Weafer and Fillmore, 2015). Peak BrAC across both groups (i.e., 82 mg/100 ml) was recorded at 30 and 60 minutes after drink administration in the present study. The timing of ABBA task administration likely contributed to the lack of an effect of alcohol administration on the proportion of inhibitory failures. Future studies should administer the ABBA task on the ascending limb of the blood alcohol concentration curve to more closely

replicate the previous studies (e.g., Weafer and Fillmore, 2015) and evaluate whether the discordance is related to the timing of ABBA task administration.

The sample in the present study was also different from samples most commonly used in alcohol research. Subjects in the present study all reported recent use of cocaine and most endorsed either cocaine or alcohol use disorder criteria, if not both. In two previous studies assessing ABBA performance in drinkers, individuals who reported a substance use disorder were excluded from participation (Weafer and Fillmore, 2012, 2015). Subjects in the present study were also older (i.e., mean age of approximately 39–40) compared to the samples of drinkers (i.e., mean age 21–29; Weafer and Fillmore, 2012, 2015). Differences across other variables such as years of education, cigarette smoking, or socioeconomic status may also have contributed to the discordance in results.

The limited range of behavior observed on the ABBA task, indicating a possible ceiling effect, may also make it difficult to detect changes in inhibitory control following alcohol dosing. Subjects are instructed to inhibit responses to no-go targets following go cues on only 25 trials in the ABBA task. Subjects are given feedback when they execute an incorrect response, which likely decreases the number of errors executed. Following alcohol administration, subjects in the cocaine go version responded incorrectly to approximately 5 targets out of 25. In the study where drinkers performed the ABBA task, subjects in the alcohol go version failed to inhibit responses to between 7 and 8 of the possible 25 trials, which is an increase of only 2 to 3 errors compared to the performance of subjects in the present study. This suggests that even when inhibitory control is impaired by alcohol, the magnitude of increase is small.

Alcohol administration produced prototypical subject-rated (e.g., drink more, drunk, sedated) and physiological (e.g., blood pressure, heart rate, BrAC) drug-effects consistent with the findings of other studies with cocaine users (Higgins et al., 1993, 1996; Marks et al., 2015). Replicating a novel finding observed previously in our laboratory, cocaine craving was increased following alcohol administration (Marks et al., 2015). The previous study was the first to show an increase in cocaine craving in cocaine users following 0.325 and 0.65 g/kg alcohol administration (Marks et al., 2015). This critical replication of induced cocaine craving in a larger sample may help to explain the mechanism by which alcohol consumption contributes to cocaine relapse. However, findings from the present study do not suggest that increases in cocaine craving following alcohol administration are directly associated with changes in inhibitory control.

The present study has a few limitations worth noting, which should be used to direct future research. First, the alcohol dose tested (i.e., 0.65 g/kg) was low compared to the average amount of alcohol subjects consumed per occasion, as noted above. Although a higher alcohol dose would have better represented the subjects' naturalistic drinking patterns, 0.65 g/kg alcohol was a behaviorally active dose and in previous research significantly increased the proportion of inhibitory failures on the ABBA task following alcohol cues (Weafer and Fillmore, 2015). Administration of 0.65 g/kg alcohol reliably increases ratings of subject-rated drug-effects (Fillmore et al., 2005; Marcziński and Fillmore, 2005; Marks et al., 2015; Weafer and Fillmore, 2015). This dose is also socially relevant as it produces peak

BrACs of approximately 80 mg/100ml, which is the legal limit for intoxication for driving in the United States. Second, the majority of the sample reported using cocaine and alcohol in combination, however combined alcohol and cocaine use topography compared to use of either drug alone was not assessed. Future studies should more fully characterize the topography of use of cocaine and alcohol when taken in combination and independently. Third, the groups differed on days reported consuming alcohol in the last month and three months on the TLFB questionnaire and self-reported liking of snorted or intranasal cocaine. Controlling for the differences in self-reported alcohol use on the TLFB did not change the ABBA outcomes and the groups did not differ on self-reported number of alcohol drinks per week, per month, or per occasion. This study utilized a between-subjects design, however, and it is possible that some unmeasured demographic differences contributed to the observed differences in the ABBA task. Fourth, this study used a double-blind procedure to minimize knowledge of the dose being tested for both the research assistant and subject. Research assistants were given a cup with the subject number and session number for each dose, which had been measured by a separate experimenter, and no indication was given whether the dose was alcohol or placebo. The drink was mixed in a kitchen away from the subject, but on the majority of sessions the same research assistant mixed and administered the drink. Subjects were likely aware of the dose (i.e., active or placebo) for the session once they began consuming the drink.

Alcohol administration produced slight, but not significant, increases in inhibitory failures when cocaine users were prepared to respond following cocaine images. Clinically, failure to stop responses to drug cues could contribute to relapse or the continued use of cocaine. Alcohol consumption could further impair the ability to resist using in the presence of cocaine cues, by increasing cocaine craving consistent with the observation that alcohol use is frequently associated with relapse following treatment (McKay et al., 1999). Future studies should continue to investigate the relationship between impaired inhibitory control, particularly following cocaine cues, and alcohol consumption. Future studies should also address the relationship between cocaine administration and inhibitory control following cocaine cues. Cocaine may impair inhibitory control following cocaine cues similarly to how alcohol impaired inhibitory control in drinkers (Weafer and Fillmore, 2015). A better understanding of this relationship could direct the development of interventions to decrease the risk of relapse in individuals who drink and display impaired inhibitory control to improve treatment outcomes.

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Figure 1. Sample trials shown of the cocaine go version (top row) and neutral go version (bottom row) of the ABBA task. For both versions, a sample trial following a go cue is shown on the left and a sample trial following a no-go cue is shown on the right.

Figure 2.

Data of proportion of inhibitory failures to no-go targets following go cues (top panel) and reaction time to go targets in milliseconds (ms) following go cues (bottom panel) on the ABBA task. Alcohol dose is presented on the x-axis. Data from the cocaine go version are presented in the left two columns and the neutral go version in the right two columns. Data following placebo (0.00 g/kg) administration are presented in the white columns and alcohol (0.65 g/kg) administration are presented in the black columns. ANOVA revealed a main effect of Task Version for the proportion of inhibitory failures to no-go targets following go

cues ($F[1, 48] = 4.72$) and a main effect of Alcohol Dose for reaction time to go targets following go cues ($F[1, 48] = 21.26$). Significant differences between doses or task versions based on Tukey's HSD *post hoc* test are indicated with an asterisk (*).

Figure 3.

Subject-rated drug-effect data ($N = 50$) are shown across time (in minutes) after drink administration (x-axes). Data are shown collapsed across ABBA task version. Circles indicate ratings following placebo (0.00 g/kg) administration and squares indicated ratings following alcohol (0.65 g/kg) administration. Cocaine Craving Questionnaire total scores are shown in the top panel. Drug Effects Questionnaire ratings for Drunk and High are shown in the middle and bottom panels, respectively. Filled symbols indicate a significant difference

between ratings following alcohol and placebo administration according to Tukey's HSD *post hoc* test at that time point.

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Figure 4.

Physiological measures measured across time (in minutes) following drink administration collapsed across ABBA task version. BrAC is shown in the top panel. Diastolic blood pressure (mmHg) is shown in the middle panel. Heart rate (beats per minute) is shown in the bottom panel. For all panels circles indicate readings following placebo (0.00 g/kg) administration and squares are following alcohol (0.65 g/kg) administration. Filled symbols

indicate a significant difference between readings following alcohol and placebo administration according to Tukey's HSD *post hoc* test at that time point.

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Table 1

Demographics of the Cocaine Group, Neutral Group, and statistical values from comparisons between group means.

Measure	Cocaine Go Version	Neutral Go Version	Statistical Value
Age ^a	40.2 (1.4)	39.0 (1.6)	0.53
Sex (# male) ^b	16	14	0.33
Race ^b			5.86
African American	21	14	
Caucasian	2	9	
Multiple Races	2	2	
Years of Education ^a	12.3 (0.3)	12.1 (0.2)	0.44
Alcohol ^a			
TLFB Days Last Month	7.0 (0.8)	12.0 (1.5)	2.90*
TLFB Range Days Last Month	1 – 16	1 – 30	
TLFB Days Last Three Months	20.0 (2.5)	34.5 (4.6)	2.77*
TLFB Range Days Last Three Months	1 – 45	2 – 88	
Drinks per Week	15.5 (2.3)	22.5 (4.6)	1.35
Drinks per Month	76.8 (16.0)	86.7 (14.0)	0.47
Drinks per Occasion (<i>n</i> = 49)	6.0 (1.0)	5.6 (0.7)	0.36
Cocaine ^a			
TLFB Days Last Month	6.8 (1.1)	7.2 (0.9)	0.25
TLFB Range Days Last Month	1 – 21	1 – 21	
TLFB Days Last Three Months	19.4 (3.4)	21.9 (2.9)	0.55
TLFB Range Days Last Three Months	1 – 67	3 – 70	
Years Used	15.2 (1.6)	14.4 (1.9)	0.36
Liking Ratings ^a			
Smoked Cocaine (<i>n</i> = 45)	3.3 (0.2)	3.1 (0.2)	0.49
Snorted Cocaine (<i>n</i> = 47)	3.2 (0.2)	2.1 (0.3)	3.03*
Alcohol	2.8 (0.2)	2.7 (0.2)	0.54
SCID Use Disorder Criteria Endorsed ^b			1.01
Cocaine and Alcohol	11	8	
Cocaine without Alcohol	7	7	
Alcohol without Cocaine	2	3	
Neither Cocaine nor Alcohol	5	7	
Combined Use of Cocaine and Alcohol ^b	20	15	2.38
Cigarettes per Day ^a	9.5 (1.5)	13.0 (1.6)	1.60
Marijuana ^a			
Days per Month	10.7 (2.5)	9.4 (2.2)	0.39
Years Used (<i>n</i> = 48)	22.2 (1.8)	23.6 (1.9)	0.53

^aMean (SEM) and *t*-values reported.

^b Sample size and chi square values reported.

Note. Asterisks (*) indicate a significant difference between groups ($p \leq 0.05$); sample size is noted for items that did not include the full sample; Timeline Follow Back (TLFB); Liking ratings ranged from 0 (Not at All) to 4 (Very Much So).

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