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THE INFLUENCE OF COCAINE-RELATED IMAGES ON INHIBITORY CONTROL IN COCAINE USERS

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THE INFLUENCE OF COCAINE-RELATED IMAGES ON INHIBITORY CONTROL IN COCAINE USERS

DISSERTATION

A dissertation submitted in partial fulfillment of the
requirements for the degree of Doctor of Philosophy in the
College of Arts and Sciences
at the University of Kentucky

By
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Lexington, Kentucky

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ABSTRACT OF DISSERTATION

THE INFLUENCE OF COCAINE-RELATED IMAGES ON INHIBITORY CONTROL IN COCAINE USERS

Cocaine users display impaired inhibitory control. The influence of cocaine-related stimuli on inhibitory control has not been assessed. The Attentional Bias-Behavioral Activation (ABBA) task uses cocaine and neutral images as cues to determine if drug-related images impair inhibitory control in cocaine users. This dissertation was designed to assess the influence of cocaine images on inhibitory control in cocaine users through the conduct of studies designed to address four aims. The first aim was to demonstrate that cocaine users display impaired inhibitory control following cocaine images compared to neutral images on the ABBA task. This was accomplished through the conduct of two experiments. The first experiment piloted the ABBA task and cocaine users completed the cocaine go (n = 15) or neutral go condition (n = 15) of the task. The second experiment consisted of two studies designed to develop a within-subjects methodology for using the ABBA task. In the first study, cocaine users completed either the cocaine go (n = 20) or neutral go (n = 20) condition of the ABBA task and all participants also completed the Cued Go/No-Go task, with geometric shapes as cues. In the second study, cocaine users (n = 18) completed the cocaine go condition of the ABBA task and a modified version of the ABBA task with all neutral images as cues to further refine a possible within-subjects methodology. The second aim was to demonstrate that inhibitory failures occur most often when cues are presented for short compared to longer durations of time. Data collected during other protocols (n = 91) were combined to investigate the influence of stimulus onset asynchrony (SOA; i.e., the amount of time a cue is presented before a target indicated a response should be executed or withheld) on inhibitory control following cocaine-related and neutral cues on the ABBA task. The third aim was to demonstrate impaired inhibitory control following cocaine images on the ABBA task is specific to cocaine users. Cocaine users (data collected in the second experiment of the first aim) and non-using control participants (n = 16) completed the cocaine go and all neutral conditions of the ABBA task and the Cued Go/No-Go task. The fourth aim was to demonstrate the feasibility and acceptability of inhibitory control training to cocaine-related stimuli with cocaine users. A small pilot clinical trial was conducted and cocaine users were randomly assigned to complete inhibitory control training to cocaine images or geometric shapes. Cocaine images impaired inhibitory control on the ABBA task, as demonstrated by an increased proportion of inhibitory failures in the cocaine go condition compared to the neutral go condition in Experiments 1, 2, and 4. The proportion of inhibitory failures following cocaine images in Experiment 4 was increased at short (i.e., 100, 200) compared to long SOAs. Cocaine images also impaired inhibitory control

compared to the Cued Go/No-Go Task in Experiment 2, however there were no differences in the proportion of inhibitory failures between the cocaine go and all neutral conditions of the ABBA task. There were no differences between cocaine users and controls in Experiment 3 for the proportion of inhibitory failures on the ABBA or Cued Go/No-Go tasks, but controls responded faster indicating a speed/accuracy trade off occurred in the control group. Inhibitory control training as an approach to improve treatment outcomes is feasible, as indicated by attendance and accuracy on the training task, and participants rated the overall procedure as satisfactory in Experiment 5. A better understanding of inhibitory control in the presence of cocaine related cues could be crucial to better understand how drug cues contribute to the risk for relapse and the continued use of drugs because both occur in the presence of drug cues.

KEYWORDS: Cocaine, Inhibitory Control, Reaction Time, Cue, Attentional Bias-Behavioral Activation task

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THE INFLUENCE OF COCAINE-RELATED IMAGES ON INHIBITORY CONTROL IN COCAINE USERS

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6/13/17
Date

DEDICATION

I am dedicating my dissertation to my mom, Cynthia Anthony. She would have liked to see how this all turned out.

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Chapter 1

INTRODUCTION

Cocaine dependence is a significant problem. In 2015, over 38 million individuals aged 12 or older reported lifetime use of cocaine. Additionally, 1.8 million individuals aged 12 and older reported using cocaine within the past month, which indicates how many individuals are current users, and this number increased significantly from 1.5 million in 2014. Of these cocaine users, almost 900,000 met Diagnostic and Statistical Manual of Mental Disorders, 4th Edition, (DSM-IV) criteria for cocaine abuse or dependence in 2015. Among individuals aged 12 years and older who received substance use treatment in the last year, over 600,000 reported that cocaine was the substance they were seeking treatment for during the current or most recent time they received treatment, which represents 16.7% of the total population seeking treatment (Center for Behavioral Health Statistics and Quality, 2016).

While there are a number of individuals using cocaine and seeking treatment for their cocaine use, relapse rates remain high (Vocci and Montoya, 2009). Impulsivity may contribute to high rates of relapse. In an early study, a group of individuals seeking treatment for cocaine dependence were asked the primary reason they relapsed (Miller and Gold, 1994). Over 40% of the sample reported an impulsive action was the reason they relapsed. By comparison, the next most common reasons provided were feeling anxious or tense at 22% combined. Impulsive action was cited as the primary reason for relapse almost four times more often than any other single reason (Miller and Gold, 1994). Impulsivity clearly contributes to cocaine relapse and warrants further research. The overarching goal of this dissertation is to systematically characterize impulsivity in cocaine using individuals. A review of the literature pertaining to impulsivity and cocaine dependence is provided below.

Impulsivity

Impulsivity is a multifaceted trait that encompasses a range of behaviors including a tendency to act without forethought or the consideration of future consequences, the choice of smaller rewards available immediately over larger rewards available after a delay, and general poor decision-making. Behavioral impulsivity is a construct that can be thought of as two domains: poor inhibitory control and poor decision-making, both of which have been used to assess impulsivity in cocaine users (Grant and Chamberlain, 2014; Hamilton et al., 2015a, 2015b). In clinical settings, self-report measures assess impulsivity as a stable trait characteristic.

Inhibitory control

Poor inhibitory control, which has been referred to as rapid response impulsivity, is defined as "a tendency toward immediate action that is out of context with the present demands of the environment and that occurs with diminished forethought" (Hamilton et al., 2015a). Poor inhibitory control also involves the inability to inhibit prepotent responses (Moeller et al., 2001). Poor inhibitory control can be further broken down into two types of inhibitory failures (e.g., failure to stop the initiation of an action and failure to stop an ongoing or prepotent action), which have distinct neurobiological underpinnings (Hamilton et al., 2015a). Failure to stop an ongoing or prepotent action can be assessed using tasks such as the Stop Signal task, which activates the thalamus and left insula (Swick et al., 2011; reviewed in Hamilton et al., 2015a). Failure to stop the initiation of an action can be assessed using tasks such as the Go/No-Go task and activate right-lateralized clusters in the middle and superior frontal gyri, the inferior parietal lobule, and the precuneus (Swick et al., 2011; reviewed in Hamilton et al., 2015a). Both Stop Signal and Go/No-Go tasks activate the bilateral insular regions and the supplementary/pre-supplementary motor areas, which are involved in a "salience network" and executing response inhibition (Swick et al., 2011; reviewed in Hamilton et al., 2015a).

Stop Signal task. The Stop Signal task is designed based on the stop-signal model of behavior (Logan, 1994; Logan et al., 1984; Verbruggen and Logan, 2008). Participants complete the task on a computer and are required to execute responses to go-signals and withhold responses following stop signals. Go-signals are typically a letter (i.e., X or O) presented one at a time and participants use keys on the keyboard to identify which letter was presented. Stop signals are a brief auditory tone, which occur at variable stimulus onset asynchronies (e.g., 50-300 ms) following the presentation of a letter. When stop signals occur participants are required to withhold their response. Stop signals only occur on a portion of trials, creating a situation where participants are prepared to respond following the presentation of a letter and must suppress the response when the stop signal occurs. Response inhibition is measured as both the probability of successfully inhibiting a response following stop signals and the latency to inhibit responses (i.e., the stop signal reaction time [SSRT]; reviewed in Fillmore, 2003).

Go/No-Go tasks. Go/No-Go tasks require participants to respond to certain stimuli (e.g., the letter X) and to withhold their response to other stimuli (e.g., the letter O; Fillmore and Weafer, 2013; Hamilton et al., 2015a). A prepotency to respond is created by instructing participants to respond as quickly as possible and presenting go stimuli more often than no-go stimuli (Hamilton et al., 2015a). The Cued Go/No-Go task is a variation of a Go/No-Go task, which uses geometric shapes as cues to indicate when a response will be required to be executed or withheld. In one version of the task, empty vertical rectangles are used as the go cue, which is presented on the screen for one of five stimulus onset asynchronies (SOA; i.e., 100, 200, 300, 400, or 500 ms). After the SOA, the vertical rectangles fill in green (i.e., go target) indicating that the participant should execute a response on 80% of trials and fill in blue (i.e., no-go target) indicating participants should withhold a response on 20% of trials. In this version of the task, empty horizontal rectangles are presented for one of five SOAs (i.e., 100, 200, 300, 400, or 500

ms). Following the SOA, the horizontal rectangles (i.e., no-go targets) fill in blue (i.e., no-go target) on 80% of trials, indicating that the response should be withheld, and fill in green, indicating the response should be executed, on 20% of trials (Miller et al., 1991).

Impulsive decision-making

Poor decision-making, which has been conceptualized as choice impulsivity, involves the selection of smaller rewards that are delivered immediately over larger rewards available after a delay (reviewed in Hamilton et al., 2015b; Jentsch et al., 2014; and Lamb and Ginsburg, 2017). Lack of planning and lack of regard for future consequences, two aspects of impulsivity, are involved in poor decision-making (Hamilton et al., 2015b). Poor decision-making may be associated with the choice to use a substance for the immediate rewarding effects over the longer-term rewards associated with abstinence such as employment or health benefits (de Wit and Richards, 2004). Selection of risky choices is another form of poor decision-making. Choices involving procuring a reward inherently include some risk of loss or negative consequences. Impulsive decision-making may relate to why some individuals make poor choices even after having experienced the negative consequences of the choice (Jentsch et al., 2014). Activation of the ventral striatum and medial prefrontal cortex are associated with the choice of small, immediate outcomes and activation of cortical areas, including the dorsolateral and ventrolateral prefrontal cortex, are associated with the selection of larger, delayed outcomes (McClure et al., 2004; reviewed in Hamilton et al., 2015b). The hippocampus is also involved in delay discounting and may support the construction of events, while the medial rostral prefrontal cortex is involved in understanding reward magnitude (Benoit et al., 2011; Peters and Büchel, 2011; reviewed in Hamilton et al., 2015b).

Hypothetical discounting tasks. Delay discounting is a measure of impulsive decision-making that can be assessed in humans using a variety of models including monetary choice questionnaires, which require participants to choose between an amount of money

available after a delay and another amount of money available immediately. The rewards may be actual or hypothetical and the task has also been modified for choices between amounts of drugs (reviewed in Hamilton et al., 2015b and Jentsch et al., 2014). Hyperbolic discounting functions are the best way to represent delay discounting curves (reviewed in Hamilton et al., 2015b and Jentsch et al., 2014). The equation for hyperbolic discounting functions is $V = A/(1+kD)$. V is the present value for the reward or indifference point. A is the amount of the reinforcer. kD represents the delay to reward, where k is the steepness of the discount function and D is the delay. Higher k values are indicative of increased impulsive choice (Hamilton et al., 2015b).

Comparison of inhibitory control and decision-making

Poor inhibitory control and poor decision-making are both factors of impulsivity, but are different constructs and processes. Each has unique neurobiological underpinnings and is assessed using different types of behavioral tasks (reviewed in Hamilton et al., 2015a, 2015b). In a study of impulsivity in nicotine sensitivity, different measures of impulsivity are grouped based on a factor analysis (Perkins et al., 2008). Factors included "Response Disinhibition," which included stop signal (referred to as "stop/go") performance and scores on the Barratt Impulsiveness Scale, and "Probability/Delay Discounting," which included performance on both probability and delay discounting tasks. The intercorrelation between these two factors was only 0.06, indicating there was not a relationship between these factors (Perkins et al., 2008). Other studies have also shown no relationship between performance on inhibitory control tasks (e.g., Stop Signal task) and delay discounting tasks (Crean et al., 2000; Reynolds et al., 2006, 2008).

Clinical measures

The Barratt Impulsiveness Scale-11 (BIS-11; Patton et al., 1995) is a self-reported measure of trait impulsivity that is used in clinical settings. The BIS-11 consists of 30 questions and participants rate their answers on a scale of 1 (Rarely/Never) to 4 (Almost

Always/Always). The BIS-11 can be either measured as a total score or broken down into separate factors: attentional impulsiveness, motor impulsiveness, and non-planning impulsiveness (Patton et al., 1995).

Impulsivity and Cocaine Abuse

Impulsivity in cocaine users has been assessed using a variety of inhibitory control, decision-making, and clinical impulsivity tasks. Across different measures of inhibitory control, impulsive decision-making, and clinical measures cocaine users display more impulsive behavior compared to non-using controls (Coffey et al., 2003; Colzato et al., 2007; Ersche et al., 2011, 2012; Fernández-Serrano et al., 2012; Fillmore and Rush, 2002; Heil et al., 2006; Johnson et al., 2015; Kirby and Petry, 2004; Lane et al., 2007; Liu et al., 2011; LoBue et al., 2014; Patkar et al., 2004; Verdejo-García et al., 2007; Verdejo-García and Pérez-García, 2007; Vonmoos et al., 2013).

Inhibitory control

Five studies have compared cocaine users and controls on the Stop Signal task. In a seminal study assessing inhibitory control in cocaine users, 22 cocaine users and 22 non-cocaine-using controls completed the Stop Signal task, a measure of inhibitory control, along with detailed drug use and health history questionnaires (Fillmore and Rush, 2002). Cocaine users displayed a reduced probability to inhibit responses following stop signals. Cocaine users also displayed longer stop signal reaction times (SSRT) than controls. When individuals were required to execute a response, there were no differences in reaction time between cocaine users and controls. There were also no differences in the rate of errors between cocaine users and controls. Cocaine users displayed an impaired ability to inhibit responses and required more time to successfully inhibit responses, but otherwise performed similarly to the controls (Fillmore and Rush, 2002). Other studies have systematically replicated the finding that cocaine users display poorer performance on the Stop Signal task compared to non-using controls (Colzato et al., 2007; Ersche et

al., 2011, 2012). Abstinent cocaine users also displayed a longer SSRT than controls, however they also displayed an increase in post-signal slowing, which may indicate diminished performance monitoring (Li et al., 2006). When analyses were conducted to control for post-signal slowing the difference in SSRT between abstinent cocaine users and controls was no longer significant (Li et al., 2006).

Another study demonstrated no difference between recreational or dependent cocaine users and controls on Stop Signal performance (Vonmoos et al., 2013). Cocaine users display impaired performance on Go/No-Go tasks, another measure of inhibitory control (Lane et al., 2007; Verdejo-García et al., 2007; Verdejo-García and Pérez-García, 2007; Fernández-Serrano et al., 2012).

Impulsive decision-making

Cocaine users also display impulsive or poor decision-making on delay discounting tasks (Coffey et al., 2003; Heil et al., 2006; Johnson et al., 2015; Kirby and Petry, 2004). In one study, cocaine dependent individuals discounted hypothetical money more than non-users on a monetary delay-discounting task as indicated by calculated *k* values (Coffey et al., 2003). Cocaine dependent individuals also discounted the value of hypothetical cocaine faster than the value of hypothetical money as indicated by calculated *k* values (Coffey et al., 2013). Other studies have replicated these findings of higher discounting rates in cocaine users compared to non-drug using controls (Heil et al., 2006; Johnson et al., 2015; Kirby and Petry, 2004).

Clinical measures

Several studies have demonstrated that cocaine users report higher levels of impulsivity on the BIS-11, a clinical measure of impulsivity, than non-cocaine using controls (Ersche et al., 2011; Liu et al., 2011; Patkar et al., 2004; Vonmoos et al., 2013). While studies have shown that cocaine users report higher levels of impulsivity compared to controls, the question remains whether or not these differences are clinically meaningful

and able to discriminate between cocaine users and non-users. To address this limitation, a study was conducted to not only compare BIS-11 scores between cocaine users and controls, but also assess if the differences were clinically meaningful. Recently abstinent cocaine users reported scores greater than 1.5 standard deviations above those reported by controls, which indicates a difference that is likely to be clinically meaningful and potentially able to detect individuals at risk for poor outcomes (LoBue et al., 2014).

Summary of impulsivity and cocaine abuse

While many studies have shown that cocaine users display impaired inhibitory control and higher levels of impulsivity compared to controls, these cross-sectional studies are unable to determine if increased impulsivity is a risk factor to developing cocaine dependence or a consequence of a history of cocaine use. A recent review summarizes some of the evidence for the role of impulsivity across a range of substances both prospectively and retrospectively (Weafer et al., 2014). Future longitudinal studies are needed to better understand the role of impulsivity in the initiation of substance use, continuation of use, and risk of relapse.

Impulsivity as a Predictor of Treatment Outcome

Cocaine users display higher levels of impulsivity compared to controls and several studies have assessed the relationship between impulsivity and treatment outcomes. One study assessed the relationship between delay discounting, a measure of impulsive decision-making and treatment retention in a sample of patients enrolled in an intensive inpatient program (Stevens et al., 2015). Individuals who displayed higher rates of discounting stayed in treatment for less time than those who displayed lower rates of discounting. Further analysis showed that treatment readiness was an important factor in this relationship. Those who displayed higher discounting reported lower treatment readiness, which was associated with less time spent in treatment (Stevens et al., 2015). In another study, individuals with poor response inhibition on the Stop Signal task at

baseline reporting using cocaine on more days in the last 30 days in treatment than those with better response inhibition (Nuijten et al., 2016).

The majority of studies investigating the relationship between impulsivity and cocaine treatment outcomes have used the BIS-11, a clinical measure of impulsivity (Brewer et al., 2008; Carpenter et al., 2006; Moeller et al., 2001; Nuijten et al., 2016; Patkar et al., 2004; Streeter et al., 2008; Winhusen et al., 2013). In a multi-site clinical trial, for example, the Barratt Impulsiveness Scale-11 (BIS-11) was used to assess the relationship between impulsivity and stimulant use treatment (Winhusen et al., 2013). Cocaine-dependent individuals completed the BIS-11 at baseline prior to the initiation of treatment. Individuals who did not complete treatment had significantly higher scores on the motor impulsiveness scale of the BIS-11 and there was a trend toward overall score on the BIS-11 also being associated with treatment non-completion (Winhusen et al., 2013). In another clinical trial testing buspirone for the treatment of cocaine dependence, individuals were split into high and low impulsivity groups based on baseline BIS-11 score (Moeller et al., 2001). Those who reported high levels of impulsivity on the BIS-11 dropped out of treatment earlier than those in the low impulsivity group (Moeller et al., 2001). Several theoreticians have called for the consideration of cognitive enhancement or remediation of cognitive deficits (e.g., impaired inhibitory control) as targets to improve treatment outcomes (Copersino, 2017; Sofuoglu, 2010; Sofuoglu et al., 2013, 2016; Vocci, 2008).

Summary

Inhibitory control can be assessed using a variety of tasks that measure behavioral and self-reported impulsivity. Cocaine users display impaired inhibitory control on both behavioral and self-reported measures (Coffey et al., 2003; Colzato et al., 2007; Ersche et al., 2011, 2012; Fernández-Serrano et al., 2012; Fillmore and Rush, 2002; Heil et al., 2006; Johnson et al., 2015; Kirby and Petry, 2004; Lane et al., 2007; Liu et al., 2011; LoBue et al., 2014; Patkar et al., 2004; Verdejo-García et al., 2007; Verdejo-García and

Pérez-García, 2007; Vonmoos et al., 2013). Impaired inhibitory control has also been associated with poor treatment outcomes, such as early dropout (Brewer et al., 2008; Carpenter et al., 2006; Moeller et al., 2001; Patkar et al., 2004; Streeter et al., 2008; Winhusen et al., 2013).

Contribution of Attentional Bias to Inhibitory Control

Research on the relationship between drug cues and substance use suggests that drug cues are associated with motivational states to obtain or use drugs (Field and Cox, 2008; Ryan, 2002). Following this association, drug cues in the environment capture and receive preferential attention (Robinson and Berridge, 1993, 2003, 2008; reviewed in Field and Cox 2008; Leeman et al, 2014). According to incentive sensitization theory, through repeated exposure to drugs and cues associated with their use neuroadaptations attribute incentive salience to those drugs and their related cues (Robinson and Berridge, 2008). This incentive salience can be expressed in either implicit behaviors (i.e., wanting) or explicit behaviors (i.e., craving). Incentive salience also produces preferential attentional processing directed toward cues that have been associated with drugs of abuse (Robinson and Berridge, 2008). Attentional bias toward cues and craving interact to motivate drug-seeking behavior (Field and Cox 2008). In cocaine use disorder, craving is promoted by higher levels of attentional bias toward substance-related cues (reviewed in Leeman et al., 2014). While attentional bias and craving can promote substance use, executive functioning inhibits or controls automatic behaviors, such as habitual substance use (Wiers et al., 2013; reviewed in Leeman et al., 2014). Salience of stimuli in the environment (e.g., drug cues) and inhibitory control (i.e., one component of executive functioning) are theorized to interact contribute to substance abuse (Goldstein and Volkow, 2002; Robinson and Berridge, 2008).

Previous work from our laboratory has shown that cocaine users display an attentional bias toward cocaine-related images compared to neutral images (Marks et al., 2014a,

2014b, 2015a, 2015b). These studies used eye-tracking technology with the Visual Probe task to measure attentional bias as the difference in the time spent fixating on cocaine images relative to non-drug-related images. Increased time spent fixating on cocaine images is specific to cocaine users and is not observed in non-using controls (Marks et al., 2014b). Attentional bias, as measured by fixation time on the Visual Probe task, is also specific to the drug of abuse, as shown by an increased attentional bias toward cocaine images, but not alcohol images in individuals with cocaine dependence only relative to those with comorbid cocaine and alcohol dependence (Marks et al., 2015b). Cigarette smokers who did not use cocaine similarly did not show an attentional bias toward cigarette or cocaine cues in a later study, but cocaine users showed a significant attentional bias measured by fixation time to cocaine cues (Marks et al., 2016). Attentional bias as measured with eye-tracking technology is also stable over time, as indicated by test-retest reliability, and is not influenced by the interval between measurements, which ranged from 7 to 336 days (Marks et al., 2014a).

To begin to elucidate the relationship between inhibitory control and attentional bias, recent studies have used to Attentional Bias-Behavioral Activation (ABBA) task with drinkers to show that alcohol-related images impair inhibitory control. The ABBA task is a modified Cued Go/No-Go task, which uses alcohol-related and non-alcohol-related cues to predict when a response will be required to be executed or withheld (Weafer and Fillmore, 2012, 2015). Fifty adult beer drinkers completed the pilot study testing the ABBA task with half prepared to respond following alcohol images and half prepared to respond following neutral images. Individuals prepared to respond following alcohol images displayed a higher proportion of inhibitory failures to no-go targets following go cues compared to those prepared to respond following neutral images. There were no group differences for reaction time to go targets following go or no-go cues or the proportion of inhibitory failures to no-go targets following no-go cues (Weafer and Fillmore, 2012).

Participants also completed the Scene Inspection Paradigm, where eye-tracking technology was used to measure fixation time on alcohol content imbedded within complex images. Attentional bias on the Scene Inspection Paradigm was correlated with increased response activation (i.e., faster reaction times) following alcohol images on the ABBA task (Weafer and Fillmore, 2012). This study provides evidence for the contribution of attentional bias toward drug-related images to impaired inhibitory control in alcohol drinkers. Drinkers displayed an increase in inhibitory failures following alcohol-related images compared to neutral images and those who showed an attentional bias toward alcohol stimuli also tended to respond faster following alcohol images (Weafer and Fillmore, 2012).

While previous studies from our laboratory have demonstrated that cocaine users display an attentional bias toward drug-related images (Marks et al., 2014a, 2014b, 2015a, 2015b), it is not known whether cocaine images might further impair inhibitory control. Cocaine users previously displayed an attentional bias on the Cocaine Stroop task, as demonstrated by slowed reaction times to indicate the color of cocaine-related words relative to non-drug-related words. Cocaine users in this study also reported increased BIS-11 scores (Liu et al., 2011). Reaction times on the Stroop task may not be a reliable measure of attentional bias however (Marks et al., 2014b). Whether drug-related images would impair inhibitory control in cocaine users similarly to the results observed in drinkers is not yet known.

Purpose of Dissertation

Impaired inhibitory control could contribute to the continuation of substance use or relapse. A further understanding of inhibitory control in the presence of substance related cues could be crucial to preventing relapse or the continued use of drugs because both occur in the presence of drug cues. Impaired inhibitory control in the presence of drug cues suggests that individuals would have an increasingly difficult time avoiding or

discontinuing drug use in the presence of drugs or paraphernalia, thus contributing to continued drug use. Specifically, the presence of drug paraphernalia may signal the presence of a drug, thus making it more difficult for individuals to inhibit initiation of drug use. An individual's ability to inhibit responding in the presence of drug cues could also relate to their ability or inability to stop taking drugs once use has already been initiated, as the discontinuation of use would also occur in the presence of drug cues.

The influence of drug-related images on inhibitory control in cocaine users is not yet known. Investigating the influence of drug-related stimuli on all components of impulsivity (i.e., inhibitory control, impulsive decision-making, and clinical measures) in cocaine users in this dissertation would not be feasible. Due to the theorized influence of impulsivity and drug-related stimuli in substance abuse the overarching goal of this dissertation is to fill a gap in the literature and demonstrate the influence of cocaine-related images on inhibitory control in cocaine users.

Previous studies have demonstrated that cocaine users display impaired inhibitory control (Colzato et al., 2007; Ersche et al., 2011, 2012; Fillmore and Rush, 2002; Li et al., 2006; Lane et al., 2007; Verdejo-García et al., 2007; Verdejo-García and Pérez-García, 2007; Fernández-Serrano et al., 2012). These studies did not assess the influence of cocaine-related stimuli on inhibitory control. The ABBA task was used with drinkers to demonstrate that alcohol images impair inhibitory control (Weafer and Fillmore, 2012, 2015). The ABBA task was modified to include cocaine-related and neutral images to determine if drug-related images impair inhibitory control in cocaine users similar to the results observed with drinkers.

The goal of this dissertation was accomplished through the conduct of experiments designed to address four aims. **The first aim was to demonstrate that cocaine users display impaired inhibitory control following cocaine images compared to neutral images on the Attentional Bias-Behavioral Activation (ABBA) task.** This aim was

accomplished through the conduct of three experiments. The first experiment was designed to pilot the use of the ABBA task with cocaine users (*n* = 30). Participants completed the cocaine go or neutral go condition of the ABBA task during a screening appointment. The second experiment developed a within-subjects methodology for using the ABBA task to assess the influence of drug-related stimuli on inhibitory control. The experiment consisted of two studies. The first was designed to demonstrate that the proportion of inhibitory failures on the neutral go condition of the ABBA task and the Cued Go/No-Go task are similar. Cocaine users completed either the cocaine go (*n* = 20) or neutral go (*n* = 20) condition of the ABBA task and all participants also completed the Cued Go/No-Go task. Participants responded faster on the Cued Go/No-Go task than on the ABBA task, which is a limitation of using this task in place of the neutral go condition of the ABBA task. In the second study, cocaine users (*n* = 18) completed a modified version of the ABBA task, which used all neutral images as cues, and the cocaine go condition of the ABBA task.

The second aim was to demonstrate that inhibitory failures occur most often when cocaine-related images are presented for short compared to longer durations of time. This aim was based on Event Related Potential (ERP) studies showing that frontal lobe engagement to inhibit behavior occurs approximately 150 ms following stimulus onset (Fabre-Thorpe et al., 2001; Thorpe et al., 1996). This experiment combined data from the ABBA task collected during several protocols to investigate the influence of stimulus onset asynchrony (SOA) on inhibitory control following cocaine-related (*n* = 46) and neutral (*n* = 45) cues. SOA is the amount of time cues are presented before they turn into go or no-go targets. Investigating the influence of SOA on inhibitory control could provide a better understanding of the impact of substance-related images on inhibitory control.

The third aim was to demonstrate that impaired inhibitory control following cocaine images on the ABBA task is specific to cocaine users. Cocaine users (data

collected in the second experiment of the first aim) and non-using control participants (*n* = 16) completed the cocaine go condition of the ABBA task, the Cued Go/No-Go task, and the all neutral condition of the ABBA task.

The fourth aim was to demonstrate the feasibility and acceptability of inhibitory control training to cocaine-related stimuli as a novel treatment approach for cocaine use disorder. This aim was accomplished through the conduct of a small pilot clinical trial. Cocaine users were randomly assigned to complete inhibitory control training to cocaine-related images or non-image geometric shapes. Outcome measures included session attendance, performance on the inhibitory control training task, and ratings on the Treatment Acceptability Questionnaire.

Chapter 2

THE INFLUENCE OF DRUG-RELATED IMAGES ON INHIBITORY CONTROL IN COCAINE USERS

(EXPERIMENT 1; Pike et al., 2013)

Introduction

Studies have shown impaired inhibitory control and increased attention bias in cocaine users using independent tasks, however the influence of cocaine-related stimuli on inhibitory control has not yet been investigated within the same task (Fillmore and Rush, 2002; Lane et al., 2007; Liu et al., 2011; Verdejo-García et al., 2007; Verdejo-García and Pérez-García, 2007). The Attentional Bias-Behavioral Activation (ABBA) task is a modified Cued Go/No-Go task, which was originally developed for use with alcohol drinkers (Weafer and Fillmore, 2012). In the ABBA task, empty rectangles are replaced with alcohol-related (e.g., beer bottles) and neutral (e.g., paper towel rolls) images. The ABBA task is designed similarly to the Cued Go/No-Go task, with go and no-go cues followed by go and no-go targets, respectively, on 80% of trials (Weafer and Fillmore, 2012). Drinkers completing the ABBA task in the alcohol go condition displayed a higher proportion of inhibitory failures to no-go targets following go cues compared to the neutral go condition (Weafer and Fillmore, 2012, 2015). These studies build on traditional inhibitory control tasks to show that drinkers display decreased inhibitory control when they are prepared to respond following alcohol-related images. Whether the finding of increased inhibitory failures following alcohol cues in drinkers translates to other substances, such as cocaine, is unknown.

The purpose of the present study was to investigate the influence of cocaine-related cues on inhibitory control in cocaine users using a modified version of the Attentional Bias-Behavioral Activation task (Weafer and Fillmore, 2012). Response inhibition was measured by proportion of inhibitory failures to no-go targets and activation was measured

by reaction times to respond to go targets. I hypothesized that the proportion of inhibitory failures to no-go targets following cocaine images as a go cue would be significantly greater than to no-go targets following neutral images as the go cue. Reaction time following go cues should not be influenced by image type. The proportion of inhibitory failures to no-go targets should be low following no-go cues and reaction time to go targets following no-go cues should be slowed regardless of image type.

Methods

Participants

Thirty adult participants were primarily recruited through word of mouth and postings on community bulletin boards to complete this study. All participants were required to be at least 18 years of age and report using cocaine within the last month. Potential participants were excluded if they reported a history of or current serious physical disease (e.g., COPD, diabetes), psychiatric disease requiring medication, or a prescription for centrally acting medication. Potential participants were also excluded if they reported dependence on any drug that could produce significant withdrawal symptoms during testing (e.g., opiates or benzodiazepines), as participants were asked to abstain from drug use for 12 hours prior to testing. Participants were paid for their participation. The University of Kentucky Institutional Review Board approved all procedures and recruitment methods.

Procedure

Potential participants were initially screened using a phone interview to assess health history and an overview of their drug use history. Potential participants who qualified based on the phone screen were invited to the University of Kentucky Laboratory of Human Behavioral Pharmacology (LHBP) to complete a detailed health and drug use history screening packet. Participants were instructed to abstain from drug and alcohol use for 12 hours prior to their appointment (i.e., arrive sober) and abstain from caffeine for

four hours prior to their appointment. Participants were also instructed to bring a form of photo identification that includes their birthdate to verify they were at least 18 years of age. Upon arrival to the laboratory all participants provided an expired air sample that was tested for the presence of alcohol using a handheld Alco-Sensor Breathalyzer (Intoximeters, St. Louis, MO) and performed a standard field sobriety test (e.g., count backward by fives, walk heel to toe forward and back). Following sobriety testing, participants read and signed an informed consent document prior to completing the screening packet. Participants also completed a short mental status exam to assess orientation to place and time, basic recall, and cognitive functions (e.g., repetition of a series of numbers, stating the current date and day of the week) following the informed consent and prior to completing the screening packet.

The screening packet included measures of basic demographics, physiological health, detailed physical and mental health histories, and a detailed drug use history. Physiological measures included blood pressure and heart rate, height and weight, and carbon monoxide level assessed using a Bedfont Scientific Smokerlyzer piCO+ handheld carbon monoxide meter (CoVita, Haddonfield, NJ). Participants provided a urine sample that was tested for the presence of amphetamines, barbiturates, benzodiazepines, cocaine, methadone, methamphetamine, opiates, and oxycodone (Clia Waived, San Diego, CA). A urine pregnancy test was also completed for female participants (NDC Inc., La Vergne, TN). The health history included questions on any current physical health symptoms, past illnesses and surgeries, and any medications the participant takes either prescribed or over the counter. Mental health questionnaires included the Adult ADHD Self-Report Scale (Kessler et al., 2005), the Beck Depression Inventory (Beck et al., 1961, 1988), and a general questionnaire of past or current psychiatric treatment. Drug use history included screening questionnaires for alcohol, drug, and nicotine abuse and dependence. Alcohol abuse questionnaires included the Michigan Alcohol Screening Test

(MAST; Selzer 1971) and the Alcohol Use Disorders Identification Test (AUDIT; Saunders et al., 1993). Drug abuse was assessed using the Drug Abuse Screening Test (DAST; Skinner 1992). Nicotine dependence was assessed using the Fagerstrom Test for Nicotine Dependence (FTND; Heatherton et al., 1991). Past and current use of alcohol, amphetamines, cocaine, barbiturates, benzodiazepines, hallucinogens, inhalants, marijuana, and opiates was assessed including questions on first use, frequency of use, and routes of administration. The Zuckerman-Kuhlman Personality Questionnaire (ZKPQ), which assesses impulsivity and sensation-seeking traits (Zuckerman et al., 1993), was also included in the screening packet.

After completing the screening packet, eligible participants completed the Attentional Bias-Behavioral Activation (ABBA) task during the same appointment. A between-subjects design was used, such that half of the participants were assigned to the cocaine go condition and half to the neutral go condition described below. The two groups were matched on demographic and drug use factors (e.g., age and years of cocaine use). A between-subjects design was used because participants learn to anticipate which cue signals a go or no-go target and having participants switch conditions (i.e., cocaine and neutral go cues) may disrupt the learning that takes place during the task.

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 (Weafer and Fillmore, 2012). The task took approximately 15 minutes to complete and consisted of five blocks of 50 trials. A trial involved a sequence of events during which a fixation point (+) was presented for 800 ms, followed by a blank white screen for 500 ms, a cue image (cocaine or neutral) was presented for one of five stimulus onset asynchronies (SOA; i.e., 100, 200, 300, 400, 500 ms), and finally a go or no-go target, which was displayed until a response occurred or 1,000 ms elapsed. A sample trial of the

cocaine go condition is shown in Figure 2.1. There was a 700 ms interval between all trials. The presentation of cocaine and neutral images was divided evenly between trials. Participants were prepared to respond (i.e., go cue), but needed to inhibit their response (i.e., no-go target) on 25 of the 250 trials.

The cues consisted of cocaine-related images (e.g., powder with a razor blade, crack cocaine) or neutral images (e.g., stapler, paper towel roll). All images (15 cm x 11.5 cm) were presented in the center of the computer monitor against a white background. After a SOA, the cue image turned either solid green (go target) or solid blue (no-go target). Participants were instructed to press the forward slash (/) key on the keyboard, which was marked with a green sticker, as soon as a green (go) target appeared. Participants were instructed to withhold responses when a blue (no-go) target appeared.

The task consisted of two conditions: a cocaine go condition and a neutral go condition. In the cocaine go condition 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 condition 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 condition 80% of go targets were preceded by a neutral cue and 20% were preceded by a cocaine cue. In the neutral go condition 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 participants, cocaine images served as the go condition and for the other half, neutral images served as the go condition.

Criterion measures and data analysis. An alpha level of $p \leq 0.05$ was used to determine significance for statistical outcomes of *a priori* hypotheses (Keppel, 1991a). Independent-samples *t*-tests were used to compare demographics for each group (i.e., the cocaine go and neutral go conditions) for continuous variables and chi-square analyses were conducted to compare sex and race distributions between groups. Performance on the cocaine go and neutral go conditions were compared to assess the

degree to which cocaine images decreased response inhibition and increased response activation. Proportion of inhibitory failures and reaction time were analyzed to assess differences in response inhibition and activation, respectively (Weafer and Fillmore, 2012). Unpaired *t*-tests were used for between-groups comparisons of the proportion of inhibitory failures when no-go targets were presented following go cues and reaction time to go targets following go cues.

Sample size justification. The sample size was based on a power calculation using the average effect size from those observed when the ABBA task was completed by drinkers and the difference between cocaine users and controls on the Stop Signal task (Weafer and Fillmore, 2012; Fillmore and Rush, 2002, respectively). The previous study using the ABBA task with drinkers found an effect size (*d*) of 0.63 for the difference in the proportion of inhibitory failures to no-go targets following go cues between the alcohol and neutral go groups (Weafer and Fillmore, 2012). On the Stop Signal task, the effect size (*d*) for the difference in the proportion of inhibitions between cocaine users and non-using controls was 2.87 (Fillmore and Rush, 2002). Using an effect size of 1.75 and an error probability of 0.05, 15 participants per group provided ≥ 90% power to detect a significant difference between the groups.

Results

Demographics

The groups did not differ significantly on any of the demographic characteristics or drug-use variables (Table 2.1).

ABBA Task Performance

Response Inhibition and Activation Following Go Cues. The *t*-test revealed a significant increase in the proportion of inhibitory failures to no-go targets following cocaine images as the go cue compared to neutral images as a go cue ($t_{28} = 2.30$, $p < 0.05$; Figure

2.2 top panel). There were no significant differences in reaction time to go cues following cocaine or neutral images (Figure 2.2 bottom panel).

Response Inhibition and Activation Following No-Go Cues. There were no significant differences between groups for the proportion of inhibitory failures following no-go cues or for reaction time to go targets following no-go cues.

Discussion

Participants exposed to a cocaine-related image as a go cue had a greater proportion of inhibitory failures to a no-go target than their counterparts exposed to a neutral cue. This finding is consistent with findings from research with alcohol users (Weafer and Fillmore, 2012). Importantly, the groups did not differ in reaction time to go targets following go or no-go cues, which suggests that the effect observed (i.e., increased proportion of inhibitory failures to no-go targets following cocaine cues) was not caused by a decrease in reaction time in the cocaine cue group. Moreover, demographics were similar between the two samples of cocaine abusers, suggesting that the observed effect was not likely due to group differences. Differences between the cocaine and neutral image groups for inhibitory failures to no-go targets or reaction time to go cues following no-go cues were not observed, which indicated that impairment of inhibitory control was specific to when participants were prepared to respond, but must inhibit a response, as no-go cues most often preceded a no-go target. Thus, cocaine images alone did not increase the proportion of inhibitory failures; rather it was the interaction of the cocaine image usually predicting that a response would be required followed by the need to inhibit responding.

Cued Go/No-Go tasks are designed to provide additional information beyond a Stop Signal or Go/No-Go task, as they model environmental cues that predict when a response will be required to be activated or inhibited (Fillmore, 2003). The ABBA task builds on traditional Cued Go/No-Go tasks by using ecologically relevant cues (i.e., cocaine

images), which may provide additional information about the behavioral processes that promote continued drug use despite negative consequences. Specifically, the presence of drug paraphernalia may signal the presence of a drug, thus making it more difficult for individuals to inhibit initiation of drug use. An individual's ability to inhibit responding in the presence of drug cues could also relate to their ability or inability to stop taking drugs once use has already been initiated, as the discontinuation of use would occur in the presence of drug cues. Research on the relationship between drug cues and substance use suggests that drug cues are associated with motivational states to obtain or use drugs (Ryan, 2002). Thus, individuals with impaired inhibitory control and increased attentional bias to drug cues may have an increasingly difficult time resisting or discontinuing drug use in the presence of drug cues. To my knowledge, this is the first study that has assessed the influence of cocaine-related cues on inhibitory control in cocaine users within the same task. Previous research has shown a negative correlation between inhibitory control and attentional bias to cocaine stimuli in cocaine users, but separate tasks were used to assess inhibitory control and attentional bias (Liu et al., 2011). However, the present study did not assess attention bias directly through a method such as collecting eye-tracking data or calculating a difference between reaction times to cocaine-related and neutral stimuli. Although calculating the difference between reaction times to cocaine-related and neutral stimuli is possible with these data, the outcome would be confounded by the fact that there should be a slower reaction time to targets following no-go cues. Thus, whether participants who had poorer inhibitory control also attended more to cocaine images is unknown. Future studies should investigate the relationship between attentional bias to cocaine cues and inhibitory control on the ABBA task, which could provide insight into the underlying mechanism driving the decrease in inhibitory control when cocaine-related images are used as cues. Also, the relationship between performance on the ABBA task, attentional bias, and drug use should be further

investigated to determine if impaired inhibitory control and/or high attentional bias are related to drug use outside of the laboratory.

The current study had a few additional limitations, which could provide directions for future research. Participants only had to report cocaine use in the last month to qualify for the study and verification with a cocaine-positive urine screen was not required. However, the majority of participants provided a cocaine-positive urine sample and the number of positive samples was not significantly different between groups. The between-subjects design may be a limitation, as groups may have differed on some unmeasured, but relevant, variable. Future research should be done to further modify the ABBA task so that it would be amenable to within-subject use to circumvent the current need to use a between-subjects design with this task.

Overall, the present study used an innovative task to show that cocaine-related stimuli decreased inhibitory control in cocaine users, which may relate to an individual's inability to avoid or cease drug use in the presence of drug cues. Future research is needed to determine how cue-related disinhibition and potential changes in this behavior impact drug use in the natural ecology. Only through the conduct of this type of research can the clinical relevance of human laboratory studies be ascertained.

Table 2.1

Demographics of the Cocaine Group, Neutral group (Mean [SEM]), and *t*-values from comparisons between group means (no significant differences were observed between groups)

Measure	Cocaine Group	Neutral Group	*t*-value
Age	42.5 (2.1)	38.2 (2.4)	1.4
Sex (# male)	10	7	0.1
Race [a]			2.2
African American	10	11	
Caucasian	5	3	
Hispanic	0	1	
Years of Education	12.1 (0.5)	11.5 (0.5)	0.8
Alcohol			
Drinks per Day	0.7 (0.7)	2.5 (2.4)	0.8
Drinks per Week	10.3 (4.7)	15.5 (9.5)	0.5
Drinks per Month	47.2 (20.2)	75.4 (47.0)	0.6
Cigarettes per Day	7.6 (1. 8)	12.9 (2.3)	1.8
Marijuana			
Days per Month	10.7 (3.4)	13.9 (2.9)	0.7
Years Used	25.3 (2.1)	25.2 (2.6)	0.0
Cocaine			
Days per Week	3.5 (0.7)	4.0 (0.5)	0.7
Days per Month	14.6 (3.0)	16.5 (2.3)	0.5
Years Used	18.6 (2.6)	16.5 (2.2)	0.6
Positive Urine Screen	0.7 (0.1)	0.8 (0.1)	0.8

[a] Chi square analysis for race used the expected values of 9 African American and 6 Caucasian participants per group, as that is consistent with the racial representation observed in our previous studies

Figure 2.1

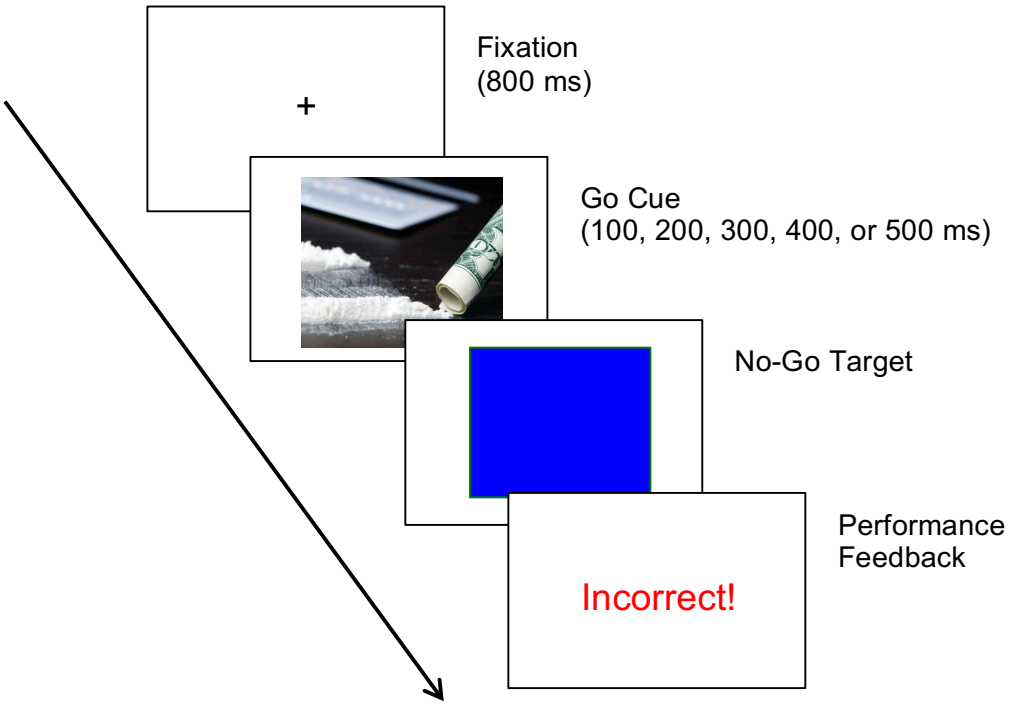

Figure 2.1. Sample trial from the cocaine go condition of the ABBA task.

Figure 2.2

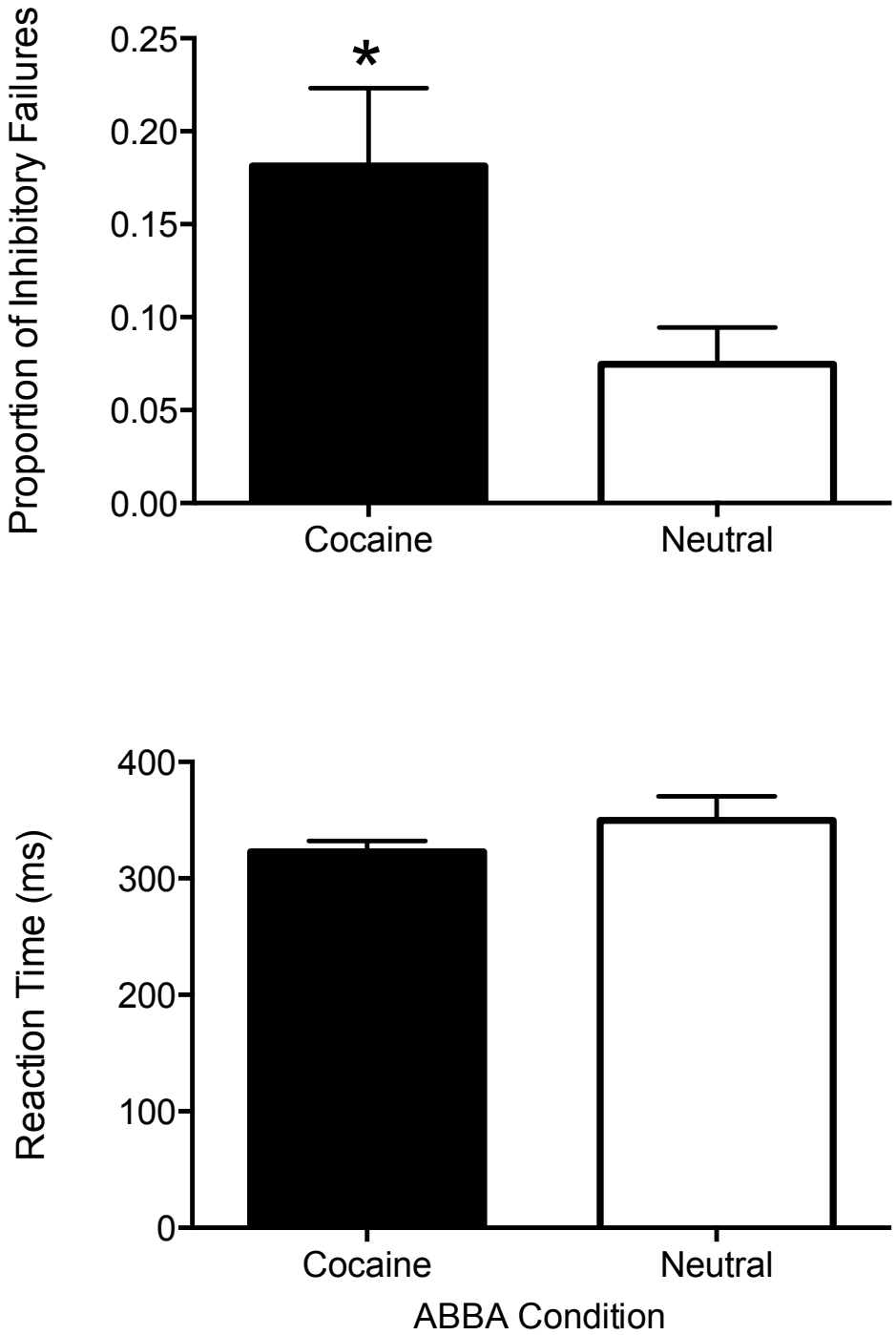

Figure 2.2. Proportion of inhibitory failures to no-go targets following go cues (top panel) and reaction time to respond to go targets following go cues (bottom panel). An asterisk (*) indicates a significant difference between groups.

Chapter 3

DEVELOPING A WITHIN-SUBJECTS METHODOLOGY FOR ASSESSING THE INFLUENCE OF DRUG-RELATED IMAGES ON IHIBITORY CONTROL IN COCAINE USERS

(EXPERIMENT 2)

Introduction

Recent studies from our laboratory investigated the influence of cocaine-related images on inhibitory control in cocaine users using the Attentional Bias-Behavioral Activation (ABBA) task (Pike et al., 2013, 2015). In the ABBA task there are two conditions, a cocaine go condition, in which cocaine-related images are followed by a target requiring a response on 80% of trials, and a neutral go condition, in which non-cocaine-related neutral images are followed by a target requiring a response on 80% of trials (Pike et al., 2013, 2015). Cocaine users assigned to the cocaine go condition of the ABBA task display a significant increase in the proportion of inhibitory failures when required to withhold a response compared to their counterparts in the neutral go condition. Reaction time to go targets does not differ between the groups suggesting that the increase in the proportion of inhibitory failures is not due to participants trading accuracy for speed.

Participants learn which image type usually predicts whether a response will be required in the ABBA task. Due to this learning process, participants cannot complete both versions of the task (i.e., cocaine and neutral go cue). As such, a between-subjects design has always been used in previous ABBA research (Pike et al., 2013, 2015; Weafer and Fillmore, 2012). Between-subjects designs require more participants to complete the study than a within-subjects design, since a different group of participants is enrolled to test each condition (Keppel, 1991b). Within-subjects designs enroll the same group of participants to complete each condition, thus are more efficient and require fewer participants. Between groups differences are also less of a concern with within-subjects designs, since

participants complete all conditions and their performance is compared to themselves. A within-subjects design would allow for testing how different manipulations influence inhibitory control following cocaine-related cues without requiring enrollment of two independent samples of cocaine users.

The purpose of the present study was to develop a methodology, which would allow for within-subjects assessments using the ABBA task. This aim was accomplished through the conduct of two studies. The first study paired ABBA task administration with the Cued Go/No-Go task to determine whether the non-picture cues of the Cued Go/No-Go task could eventually be substituted for the neutral go condition. Two groups of participants completed either the cocaine go condition or the neutral go condition of the ABBA task and all participants completed the Cued Go/No-Go task. Response inhibition was measured as the proportion of inhibitory failures to no-go targets and response activation was measured by reaction time to respond to go targets. I hypothesized that there would be an interaction for the proportion of inhibitory failures, such that they would be increased in the cocaine go condition of the ABBA task compared to the neutral go condition of the ABBA task and the Cued Go/No-Go task, but that there would be no difference between the neutral go condition of the ABBA task and the Cued Go/No-Go task. Reaction time to go targets following go cues would not be influenced by image type.

The second study was designed, because reaction times on the Cued Go/No-Go task were significantly faster than on the ABBA task when the first study was initially analyzed using an ANCOVA with days used cocaine in the last week included as a covariate, due to between groups differences (reaction times following go cues $F_{1, 37} = 4.55$, $p = 0.04$). The proportion of inhibitory failures are negatively correlated with reaction times ($r = -0.43$, $p = 0.00$, $n = 91$, data from Experiment 4). The second study paired the cocaine go condition of the ABBA task with a modified version of the ABBA task that used all neutral images as cues, because one potential explanation for the faster reaction times on the

Cued Go/No-Go task could be that it takes less time to determine the orientation of a rectangle than the content of an image. Data from the first study were compared to the second study. I hypothesized that there would be an interaction for the proportion of inhibitory failures on the ABBA task, such that there would be an increase in the cocaine go condition compared to the neutral go condition and the all neutral condition, but there would be no difference between the neutral go condition and the all neutral condition. Reaction time to go targets following go cues should not be influenced by image type.

Methods

Participants

Forty adult participants were primarily recruited through word of mouth and postings on community bulletin boards to complete the first study. Eighteen adult participants were recruited to complete the second study. All participants were required to be at least 18 years of age and report using cocaine within the last month. Potential participants were excluded if they reported a history of or current serious physical disease (e.g., COPD, diabetes), psychiatric disease requiring medication, or a prescription for centrally acting medication. Potential participants were also excluded if they reported dependence on any drug that could produce significant withdrawal symptoms during testing (e.g., opiates or benzodiazepines), as participants were asked to abstain from drug use for 12 hours prior to testing. Participants were paid $40 plus an allotment for travel (e.g., $5 for participants living in Fayette County, Kentucky) for their participation in the first study. In the second study, participants were paid $20 plus an allotment for travel (e.g., $5 for participants living in Fayette County, Kentucky). The difference in payment was based on the appointment during which participants completed the assigned tasks. The University of Kentucky Institutional Review Board approved all procedures and recruitment methods.

Procedure

After completing the initial screening, which is described above in Experiment 1, eligible participants in the first study completed the Attentional Bias-Behavioral Activation (ABBA) and Cued Go/No-Go tasks during the same appointment. The order in which participants completed the ABBA and Cued Go/No-Go tasks was counterbalanced across participants. A between-subjects design was used, such that half of the participants were assigned to the cocaine go condition and half to the neutral go condition of the ABBA task. The two groups were matched on demographic and drug use factors (e.g., age and years of cocaine use). A between-subjects design was used because participants learn to anticipate which cue signals a go or no-go target and there were concerns that having participants switch conditions (i.e., cocaine and neutral go cues) would disrupt the learning that takes place during the task.

In the second study, eligible participants completed the assigned tasks on a follow-up appointment scheduled after they completed the initial screening, which is described above in Experiment 1. Participants all completed the cocaine go condition and the all neutral condition of the ABBA task. The order in which participants completed the tasks was counterbalanced across participants.

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 (Weafer and Fillmore, 2012). The task took approximately 15 minutes to complete and consisted of five blocks of 50 trials. A trial involved a sequence of events during which a fixation point (+) was presented for 800 ms, followed by a blank white screen for 500 ms, a cue image (cocaine or neutral) was presented for one of five stimulus onset asynchronies (SOA; i.e., 100, 200, 300, 400, 500 ms), and finally a go or no-go target, which was displayed until a response occurred or 1,000 ms elapsed. A sample trial of the

cocaine go condition is shown in Figure 2.1. There was a 700 ms interval between all trials. The presentation of cocaine and neutral images was divided evenly between trials. Participants were prepared to respond (i.e., go cue), but needed to inhibit their response (i.e., no-go target) on 25 of the 250 trials.

The cues consisted of cocaine-related images (e.g., powder with a razor blade, crack cocaine) or neutral images (e.g., stapler, paper towel roll). All images (15 cm x 11.5 cm) were presented in the center of the computer monitor against a white background. After a SOA, the cue image turned either solid green (go target) or solid blue (no-go target). Participants were instructed to press the forward slash (/) key on the keyboard, which was marked with a green sticker, as soon as a green (go) target appeared. Participants were instructed to withhold responses when a blue (no-go) target appeared.

In the first study the task consisted of two conditions: a cocaine go condition and a neutral go condition. In the cocaine go condition 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 condition 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 condition 80% of go targets were preceded by a neutral cue and 20% were preceded by a cocaine cue. In the neutral go condition 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 participants the cocaine image served as the go condition and for the other half, the neutral image served as the go condition.

In the second study, the task consisted of the cocaine go condition described above and an all neutral condition. In the all neutral condition images of plants served as the go cue and were followed by go targets on 80% of trials and no-go targets on 20% of trials. Animal images served as no-go cues and were followed by no-go targets on 80% of trials

and go targets on 20% of trials. In the second study, all participants completed the cocaine go and all neutral conditions of the ABBA task.

Cued Go/No-Go task. The Cued Go/No-Go task is a reaction time task, which was administered using E-prime experiment generation software (Psychology Software Tools, Pittsburgh, PA) on a PC computer (Miller et al., 1991). The task took approximately 15 minutes to complete and consisted of five blocks of 50 trials. A trial involved a sequence of events during which a fixation point (+) was presented for 800 ms, followed by a blank white screen for 500 ms, a cue (horizontal or vertical empty rectangle) was presented for one of five stimulus onset asynchronies (SOA; i.e., 100, 200, 300, 400, 500 ms), and finally a go or no-go target, which was displayed until a response occurred or 1,000 ms elapsed. There was a 700 ms interval between all trials. The presentation of horizontal and vertical empty rectangles was divided evenly between trials. Participants were prepared to respond (i.e., go cue), but needed to inhibit their response (i.e., no-go target) on 25 of the 250 trials.

The cues consisted of vertical empty rectangles (i.e., go cues) or horizontal empty rectangles (i.e., no-go cues). After a SOA, the cue rectangle filled in either solid green (go target) or solid blue (no-go target). Participants were instructed to press the forward slash (/) key on the keyboard, which was marked with a green sticker, as soon as a green (go) target appears. Participants were instructed to withhold responses when a blue (no-go) target appeared.

Criterion measures and data analysis. An alpha level of $p \leq 0.05$ was used to determine significance for statistical outcomes of *a priori* hypotheses. Independent-samples *t*-tests were used to compare demographics for each group (i.e., the cocaine go and neutral go conditions of the ABBA task in study one and the group from study two) for continuous variables and chi-square analyses were conducted to compare sex and race distributions between groups.

Proportion of inhibitory failures and reaction times on the ABBA and Cued Go/No-Go tasks for Study 1 were analyzed using a mixed-model analysis of variance (ANOVA; IBM SPSS Statistics Version 22, Armonk, NY, USA). The between-subjects factor was go cue condition of the ABBA task (i.e., cocaine go or neutral go), the within-subjects factor was inhibitory control task (i.e., ABBA and Cued Go/No-Go). Fisher's Least Significant Difference test was used to assess differences between proportion of inhibitory failures or reaction times based on significant ANOVA outcomes ($p < 0.05$).

Proportion of inhibitory failures and reaction times on the ABBA and Cued Go/No-Go tasks for comparisons between Study 1 and 2 were analyzed using a mixed-model analysis of variance (ANOVA; IBM SPSS Statistics Version 22, Armonk, NY, USA). The between-subjects factor was Group (i.e., Study 1 Cocaine Go Condition, Study 1 Neutral Go Condition, and Study 2) and the within-subjects factor was inhibitory control task (i.e., ABBA cocaine or neutral go and Cued Go/No-Go or all neutral ABBA). Fisher's Least Significant Difference test was used to assess differences between proportion of inhibitory failures or reaction times based on significant ANOVA outcomes ($p < 0.05$). Since the sample sizes between groups differed slightly between Study 1 and Study 2, the sample size from Study 2 ($n = 18$) was used for Fisher's *post* hoc tests, as this was more conservative than using the sample size from Study 1 ($n = 20$). Proportion of inhibitory failures and reaction time were analyzed to assess differences in response inhibition and activation, respectively (Weafer and Fillmore 2012), with performance on the cocaine go and neutral go conditions of the ABBA task compared across groups to assess the degree to which cocaine images increased inhibitory failures. Performance on the ABBA task was compared to the Cued Go/No-Go or all neutral condition of the ABBA task within groups to assess the influence of images compared to geometric shape (i.e., rectangles) or all neutral image cues on response inhibition. Performance on the Cued Go/No-Go and all neutral ABBA tasks were compared across groups to evaluate group differences.

Sample size justification. The proposed sample size was based on a power calculation using an effect size of 1.75, which was described in Experiment 1, two between-subjects factors (go cue condition), two within-subject factors (inhibitory control task), and 0.05 for error probability. Based on these calculations, 20 participants per group will provide ≥ 80% power to detect a significant interaction.

Results

Demographics

Comparisons between participants assigned to complete the ABBA task with cocaine and neutral images as the go cue in Study 1 revealed a significant difference between groups for the number of days participants reported using cocaine in the last week (p = 0.02). Participants assigned to complete the cocaine go condition of the ABBA task reported using cocaine on more days in the last week compared to participants in the neutral go condition. No other significant differences were observed between the groups (Table 3.1). Equal variances were not assumed for comparisons of cocaine positive urine samples. For cigarettes per day and measures of marijuana use only a portion of the full sample was included, due to participants reporting never using the substance, these sample size differences are noted in Table 3.1.

Comparisons between participants in Study 1 and Study 2 revealed significant differences between the groups for age, days used cocaine in the last week, days used cocaine in the last month, years since first use of cocaine, whether or not participants provided a cocaine positive urine sample, and years since first marijuana use (p's < 0.05; Table 3.1). Participants in Study 2 were older, reported using cocaine on more days in the last week and month, reported a greater number of years from the first time they used cocaine, more participants provided a cocaine positive urine sample, and reported a greater number of years from the first time they used marijuana compared to participants in Study 1. For some measures only a portion of the full sample was included, due to

participants reporting never using the substance, these sample size differences are noted in Table 3.1. For comparisons between both groups in Study 1 and Study 2 equal variances were not assumed for years of education and cocaine positive urine samples. Equal variances were not assumed for comparisons between the cocaine go condition of Study 1 and Study 2 for years since first marijuana use.

Study 1 Task Performance

ANOVA revealed a significant Group by Task interaction for proportion of inhibitory failures to no-go targets following go cues ($F_{1, 38}$ = 8.08, p = 0.01). Participants in the cocaine go condition had a significantly higher proportion of inhibitory failures on the ABBA task than those in the neutral go condition. In the cocaine go condition, participants displayed a higher proportion of inhibitory failures on the ABBA task than on the Cued Go/No-Go task. In the neutral go condition, the proportion of inhibitory failures on the ABBA and Cued Go/No-Go tasks did not differ. There was no difference between the groups for the proportion of inhibitory failures on the Cued Go/No-Go task. ANOVA revealed a significant interaction for ABBA task condition and inhibitory control task on the proportion of inhibitory failures following no-go cues ($F_{1,38}$ = 5.48, p = 0.03). Participants in the neutral go condition displayed a significantly lower proportion of inhibitory failures on the Cued Go/No-Go compared to their performance on the ABBA task and compared to the cocaine go condition on the Cued Go/No-Go task.

ANCOVA revealed a significant main effect of Task for reaction times to go targets following no-go cues ($F_{1, 38}$ = 16.06, p = 0.00). Reaction times to go targets following no-go cues were faster on the Cued Go/No-Go task than the ABBA task regardless of ABBA task condition, ANOVA revealed no significant effects for reaction times to go targets following go cues (p > 0.05).

Comparison of Study 1 and Study 2 Task Performance

ANOVA revealed a significant Group by Task interaction for proportion of inhibitory failures to no-go targets following go cues ($F_{2, 55}$ = 4.88, p = 0.01; Figure 3.1 top panel). Fisher's LSD *post hoc* tests showed that within the group assigned to complete the cocaine go condition of the ABBA task in Study 1, participants displayed a higher proportion of inhibitory failures on the ABBA task compared to the Cued Go/No-Go task. Participants also displayed an increased proportion of inhibitory failures on the cocaine go condition compared to the neutral go condition of the ABBA task in Study 1 based on Fisher's LSD *post hoc* test. Participants in Study 2 displayed a significantly higher proportion of inhibitory failures on the cocaine go condition of the ABBA task compared to the neutral go condition of the ABBA task from Study 1. Participants in Study 2 displayed a significantly higher proportion of inhibitory failures on the all neutral ABBA task compared to the Cued Go/No-Go task only for the group assigned to complete the neutral go condition of the ABBA task in Study 1. Comparisons between the all neutral ABBA task and Cued Go/No-Go task performance of those assigned to the cocaine go condition of the ABBA task approached significance. No other significant differences were observed between task performance within groups or between groups for each respective task (i.e., ABBA cocaine go or neutral go and Cued Go/No-Go task or all neutral ABBA).

ANOVA revealed a significant Group by Task interaction for proportion of inhibitory failures to no-go targets following no-go cues ($F_{2, 55}$ = 4.16, p = 0.02). Participants in the neutral go condition in Study 1 displayed a lower proportion of inhibitory failures on the Cued Go/No-Go task compared to when they completed the ABBA task and compared to the other groups on the Cued Go/No-Go and all neutral ABBA tasks. No other significant differences were observed between task performance within groups or between groups for each respective task (i.e., ABBA cocaine go or neutral go and Cued Go/No-Go task or all neutral ABBA).

ANOVA revealed a significant main effect of Task for reaction time to go targets following and no-go cues ($F_{1, 55}$ = 12.79, p = 0.001). Reaction times to go targets following no-go cues were faster on the Cued Go/No-Go task than the ABBA task regardless of ABBA task condition, ANOVA revealed no significant main effects of interactions for reaction time to go targets following go cues (p > 0.05).

Discussion

The ABBA task has traditionally required a between-subjects design because participants learn which image types serve as go and no-go cues. These studies were designed to develop a within-subjects methodology to assess the influence of cocaine-related images on inhibitory control. Within-subjects designs have several advantages over between-subjects designs (Keppel 1991b). Within-subjects designs have more power than between-subjects designs, thus allowing for smaller sample sizes. Within-subjects designs compare the performance of an individual to themselves, which reduces concerns regarding group differences on measured and unmeasured variables.

The data from Study 1 suggest that the non-picture cues of the Cued Go/No-Go task can be substituted for the neutral go condition of the ABBA task. There were consistent proportions of inhibitory failures on the ABBA and Cued Go/No-Go tasks within the neutral go group, as well as between groups on the Cued Go/No-Go task. Participants displayed an increased proportion of inhibitory failures following cocaine-related images compared to neutral images or geometric shapes. The increased proportion of inhibitory failures following cocaine-related compared to neutral images replicates previous findings (Pike et al., 2013, 2015). Impaired inhibitory control is specific to when cocaine users are prepared to respond to a drug-related cue, but must withhold the response at the last moment, as increased inhibitory failures occurred when drug-related images served as the go cue.

Study 2 was designed to address the limitation of significantly faster reaction times on the Cued Go/No-Go compared to the ABBA task when the data were initially analyzed using days of cocaine use in the last week as a covariate by using the all neutral condition of the ABBA task with animal and plant images as cues instead of the Cued Go/No-Go task. Performance on the cocaine-go condition of the ABBA task in Study 2 replicated previous studies, where the proportion of inhibitory failures was significantly increased compared to the neutral go condition of the ABBA task and was not different from performance in the cocaine go condition of the ABBA task in Study 1 (Pike et al., 2013, 2015). The proportion of inhibitory failures on the all neutral ABBA task was not different from the cocaine go condition of the ABBA task on within group comparisons. Proportion of inhibitory failures on the all neutral condition of the ABBA were significantly increased compared to when the neutral go condition in Study 1 completed the Cued Go/No-Go task and approached significance for comparisons to the cocaine go condition based on Fisher's *post hoc* test. These results suggest that the all neutral condition of the ABBA task as tested in this study would not be a viable control condition for assessing how cocaine-related images impact inhibitory control. Future research should be done to further refine either a version of the ABBA or the Cued Go/No-Go task to allow for within-subjects assessments of the influence of cocaine-related images on inhibitory control.

The studies in this experiment had a few limitations that are worth noting. First, participants did not have to provide a cocaine-positive urine screen; rather they only had to report cocaine use in the last month to qualify for the studies used in these analyses. However, the majority of participants overall provided a cocaine-positive urine sample. Second, significant differences were observed between the group demographics. These differences could influence performance on the ABBA and control tasks, however the analyses controlled for the differences observed between the groups. Other significant, but unmeasured differences between the groups may have also influenced performance

on the tasks. This limitation is one of the main reasons why it is important to develop a within-subjects methodology for use with the ABBA task.

Overall, the programmatic pair of studies in this experiment used an innovative approach to support the use of a within-subjects design in future studies with the ABBA task. The ability to adopt a within-subjects design to assess the influence of cocaine-related images on inhibitory control is advantageous for both future research studies and treatment. Future research should be conducted to further refine a control task for assessing the influence of cocaine-related images on inhibitory control. A within-subjects design could be used to investigate the role of inhibitory control following cocaine-related cues in predicting treatment outcomes, such as time to relapse. A within-subjects design would also be useful to assess the efficacy of interventions designed to improve inhibitory control in treatment seeking cocaine users or changes in inhibitory control over time throughout treatment.

Table 3.1

Demographics of the Cocaine Group (*n* = 20) and Neutral Group (*n* = 20) from Study 1 and group from Study 2 (*n* =18). Bold values indicate a significant difference between groups in Study 1, italicized values indicate a difference between Study 1 Cocaine Group and Study 2, and underlined values indicate a significant difference between Study 1 Neutral Group and Study 2 ($p < 0.05$)

Measure	Study 1 Cocaine Group	Study 1 Neutral Group	Study 2
Age [a]	41.4 (2.1)	38.8 (1.8)	44.7 (1.4)
Sex (# male) [b]	13	17	14
Race [b]			
African American	14	13	14
Caucasian	5	5	2
Other	1	2	2
Years of Education [a]	11.4 (0.5)	11.8 (0.4)	11.9 (0.3)
Alcohol [a]			
Drinks per Week	24.9 (7.5)	32.0 (14.6)	19.1 (6.2)
Drinks per Month	116.4 (36.0)	134.4 (62.0)	87.9 (27.6)
Cigarettes per Day [a]	14.2 (1.9)	15.5 (3.2)	12.1 (2.4)
Marijuana [a]			
Days per Month	12.8 (3.0)	10.4 (2.7)	8.0 (2.9)
Years Used	24.9 (2.3)	23.8 (2.2)	29.9 (1.6)
Cocaine [a]			
Days per Week	**3.6 (0.5)**	2.2 (0.4)	4.8 (0.4)
Days per Month	14.1 (2.2)	11.4 (1.6)	*21.6 (2.0)*
Years Used	17.2 (2.4)	14.8 (1.8)	23.4 (2.5)
Positive Urine Screen	0.8 (0.1)	0.5 (0.1)	0.9 (0.1)

[a] Mean (SEM) and *t*-values reported

[b] Sample size and chi square values reported

The sample size was reduced for the following measures: Cocaine Group days used marijuana in the last month and years since first marijuana use *n* = 19; Neutral Group cigarettes per day *n* = 18; Study 2 cigarettes per day, days used marijuana in the last month, and years since first marijuana use *n* = 16

Figure 3.1

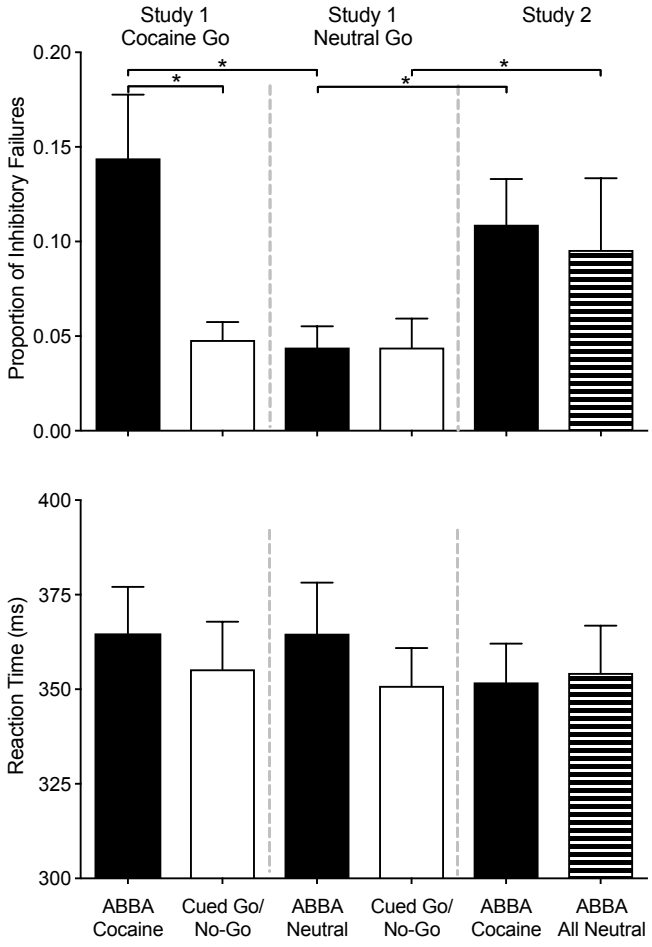

Figure 3.1. Proportion of inhibitory failures to no-go targets following go cues (top panel) and reaction times to go targets following go cues (bottom panel) for Study 1 and Study 2 of Experiment 2. In both panels, solid black bars represent the ABBA task as it was originally designed, solid white bars represent the Cued Go/No-Go task, and black and white striped bars represent the all neutral condition of the ABBA task. The left two bars are performance from participants assigned to complete the cocaine go condition of the ABBA task in Study 1. The middle two bars are performance from participants assigned to complete the neutral go condition of the ABBA task in Study 1 (*n* = 20 per group). The right two bars are performance from participants in Study 2 (*n* = 18). Asterisk (*) indicates a significant difference based on Fisher's LSD *post hoc* test.

Chapter 4

ASSESSING THE SPECIFICITY OF THE ATTENTIONAL BIAS-BEHAVIORAL ACTIVATION TASK: A COMPARISON BETWEEN COCAINE USERS AND CONTROLS (EXPERIMENT 3)

Introduction

The ABBA task assesses inhibitory control following cocaine-related cues to determine the influence of drug-related stimuli on the ability to inhibit prepotent responses. Cocaine users fail to inhibit responses when they are prepared to respond following cocaine-related images more often than following non-cocaine-related images (Pike et al., 2013, 2015). However, previous studies have not compared performance of cocaine users and non-cocaine using controls to determine if the increase in inhibitory failures following cocaine images is specific to cocaine users. Cocaine users display impaired inhibitory control compared to non-drug users on other inhibitory control tasks including the Stop Signal (Colzato et al., 2007; Ersche et al., 2011, 2012; Fillmore and Rush 2002) and Go/No-Go (Lane et al., 2007; Verdejo-García et al., 2007; Verdejo-García and Pérez-García, 2007; Fernández-Serrano et al., 2012).

The purpose of the present study was to demonstrate that the increase in inhibitory failures in the cocaine go condition of the ABBA task is specific to cocaine users. Two groups of participants, cocaine users and non-using controls, completed the cocaine go condition of the ABBA task and the Cued Go/No-Go task. Response inhibition was measured as the proportion of inhibitory failures to no-go targets and response activation was measured by reaction time to respond to go targets. I hypothesized that cocaine users would display an increased proportion of inhibitory failures on the cocaine go condition of the ABBA task compared to controls. I hypothesized that cocaine users would also display an increased proportion of inhibitory failures on the Cued Go/No-Go and all neutral ABBA tasks, but that the magnitude of the difference would be lower than on the cocaine go

condition of the ABBA task. Reaction time to go targets following go cues should not be influenced by image type or group.

Methods

Participants

Sixteen adult non-cocaine using participants were primarily recruited through word of mouth and postings on community bulletin boards to complete this study. Cocaine using participants who completed the cocaine go condition of the ABBA task (*n* = 38), the Cued Go/No-Go task (*n* = 40), and all neutral condition of the ABBA task (*n* = 18) in Experiment 2 served as the comparison groups for this study. Eligible non-cocaine using participants reported no cocaine use within the last year and having used cocaine on five or fewer occasions in their lifetime. Potential participants were excluded if they reported a current prescription for a psychiatric or centrally acting medication or dependence on any drug that could produce significant withdrawal symptoms during testing (e.g., opiates or benzodiazepines). Participants were asked to abstain from drug use for 12 hours and caffeine for 4 hours prior to testing. Participants completed screening questionnaires on current and past physical and mental health, measures of current psychological functioning, and a detailed drug use history, which is described above in Experiment 1. Control participants must not meet criteria for cocaine abuse or dependence on the computerized version of the Structured Clinical Interview for DSM-IV (SCID). The criteria for cocaine abuse or dependence from the DSM-IV was used rather than cocaine use disorder from the DSM-V because these studies were designed and conducted prior to the release of the DSM-V. A sample of controls who reported no current cocaine use, minimal other substance use, and no diagnosis of a psychiatric disorder categorized by disinhibition (e.g., Attention Deficit Hyperactivity Disorder) were selected to allow for the greatest chance to detect a group difference between performance on the inhibitory control tasks. Participants were paid $20 plus an allotment for travel (e.g., $5 for

participants living in Fayette County, Kentucky) for their participation. The University of Kentucky Institutional Review Board approved all procedures and recruitment methods.

Procedure

After completing the initial screening appointment, eligible participants were invited back to the laboratory to complete the SCID, the cocaine go and all neutral conditions of the ABBA, and Cued Go/No-Go tasks during the same appointment. The order in which participants completed the tasks was randomized across participants. All participants completed the cocaine go and all neutral conditions of the ABBA task and the Cued Go/No-Go task. Data from control participants was compared to cocaine using participants who completed the cocaine go and all neutral conditions of the ABBA task and the Cued Go/No-Go task in Experiment 2.

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 (Weafer and Fillmore, 2012). The task took approximately 15 minutes to complete and consisted of five blocks of 50 trials. A trial involved a sequence of events during which a fixation point (+) was presented for 800 ms, followed by a blank white screen for 500 ms, a cue image (cocaine or neutral) was presented for one of five stimulus onset asynchronies (SOA; i.e., 100, 200, 300, 400, 500 ms), and finally a go or no-go target, which was displayed until a response occurred or 1,000 ms elapsed. A sample trial of the cocaine go condition is shown in Figure 2.1. There was a 700 ms interval between all trials. The presentation of cocaine and neutral images was divided evenly between trials. Participants were prepared to respond (i.e., go cue), but needed to inhibit their response (i.e., no-go target) on 25 of the 250 trials.

The cues consisted of cocaine-related images (e.g., powder with a razor blade, crack cocaine) or neutral images (e.g., stapler, paper towel roll). All images (15 cm x 11.5 cm)

were presented in the center of the computer monitor against a white background. After a SOA, the cue image turned either solid green (go target) or solid blue (no-go target). Participants were instructed to press the forward slash (/) key on the keyboard, which was marked with a green sticker, as soon as a green (go) target appears. Participants were instructed to withhold responses when a blue (no-go) target appears. Go targets followed cocaine cues 80% of the time and 20% of go targets were preceded by a neutral cue. No-go targets followed neutral cues 80% of the time and 20% of no-go targets were preceded by a cocaine cue.

In the all neutral condition images of plants served as the go cue and were followed by go targets on 80% of trials and no-go targets on 20% of trials. Animal images served as no-go cues and were followed by no-go targets on 80% of trials and go targets on 20% of trials.

Cued Go/No-Go task. The Cued Go/No-Go task is a reaction time task, which was administered using E-prime experiment generation software (Psychology Software Tools, Pittsburgh, PA) on a PC computer (Miller et al., 1991). The task took approximately 15 minutes to complete and consisted of five blocks of 50 trials. A trial involved a sequence of events during which a fixation point (+) was presented for 800 ms, followed by a blank white screen for 500 ms, a cue (horizontal or vertical empty rectangle) was presented for one of five stimulus onset asynchronies (SOA; i.e., 100, 200, 300, 400, 500 ms), and finally a go or no-go target, which was displayed until a response occurred or 1,000 ms elapsed. There was a 700 ms interval between all trials. The presentation of horizontal and vertical empty rectangles was divided evenly between trials. Participants were prepared to respond (i.e., go cue), but needed to inhibit their response (i.e., no-go target) on 25 of the 250 trials.

The cues consisted of vertical empty rectangles (i.e., go cues) or horizontal empty rectangles (i.e., no-go cues). After a SOA, the cue rectangle filled in either solid green (go

target) or solid blue (no-go target). Participants were instructed to press the forward slash (/) key on the keyboard, which was marked with a green sticker, as soon as a green (go) target appeared. Participants were instructed to withhold responses when a blue (no-go) target appeared.

Criterion measures and data analysis. An alpha level of $p \leq 0.05$ was used to determine significance for statistical outcomes of *a priori* hypotheses. Independent-samples *t*-tests were used to compare demographics for each group (i.e., the cocaine using and control groups) for continuous variables and chi-square analyses were conducted to compare sex and race distributions between groups.

Proportion of inhibitory failures and reaction times following go and no-go cues on the cocaine go condition of the ABBA, all neutral ABBA, and Cued Go/No-Go tasks were compared between groups using independent samples *t*-tests. Proportion of inhibitory failures and reaction time were analyzed to assess differences in response inhibition and activation, respectively (Weafer and Fillmore 2012), with performance compared across groups to assess the ability of the ABBA task to discriminate between cocaine users and non-using controls.

Sample size justification. The proposed sample size was based on a power calculation using an effect size of 1.75, which was described in Experiment 1, two between-subjects factors (cocaine using or control group), three within-subject factors (inhibitory control task), and 0.05 for error probability. Based on these calculations, 16 participants per group will provide ≥ 80% power to detect a significant interaction.

Results

Demographics

Comparisons between cocaine using and control participants revealed significant differences between the groups for years of education, race distribution, and BIS scores (Table 4.1). Equal variances were not assumed for some outcomes noted on Table 4.1.

Controls reported completing more years of education and lower BIS scores compared to cocaine users. More cocaine users were African American compared to controls. The groups also differed on substance use history including cocaine use, alcohol use, and marijuana use, as expected. For some measures only a portion of the full sample was included, due to participants reporting never using the substance or missing data (i.e., one cocaine user excluded from analysis for BIS) and sample sizes for each variable are noted in Table 4.1.

Proportion of Inhibitory Failures to No-Go Targets Following Go and No-Go Cues

No differences were observed between cocaine users and controls for the proportion of inhibitory failures to no-go targets following go cues (Figure 4.1 top panel) on the cocaine go condition of the ABBA task (t_{52} = 1.12, p = 0.27), Cued Go/No-Go task (t_{54} = 0.85, p = 0.40), or all neutral condition of the ABBA task (t_{32} = 0.41, p = 0.68). No differences were observed between cocaine users and controls for the proportion of inhibitory failures to no-go targets following no-go cues on the cocaine go condition of the ABBA task (t_{52} = 0.69, p = 0.49), Cued Go/No-Go task (t_{54} = 1.22, p = 0.23), or all neutral condition of the ABBA task (t_{32} = 0.20, p = 0.85).

Reaction Times to Go Targets Following Go and No-Go Cues

Controls displayed significantly faster reaction times to go targets following go cues (Figure 4.1 bottom panel) on the cocaine go condition of the ABBA task (t_{52} = 2.52, p = 0.02), Cued Go/No-Go task (t_{54} = 2.07, p = 0.04), and all neutral condition of the ABBA task (t_{32} = 2.24, p = 0.03). Controls also displayed significantly faster reaction times to go targets following no-go cues on the cocaine go condition of the ABBA task (t_{52} = 2.10, p = 0.04), Cued Go/No-Go task (t_{54} = 2.04, p = 0.05), and all neutral condition of the ABBA task (t_{32} = 2.83, p = 0.01).

Discussion

This experiment was designed to demonstrate that the increase in inhibitory failures following cocaine images on the ABBA task is specific to cocaine users by comparing performance between cocaine users and non-using controls. In this study both cocaine users and controls completed the cocaine go condition of the ABBA task, the Cued Go/No-Go task, and the all neutral condition of the ABBA task. No differences were observed between cocaine users and controls for the proportion of inhibitory failures to no-go targets following go cues on any of the tasks. The results of the present study are discordant with the majority of previous research comparing cocaine users and controls on inhibitory control performance. Cocaine users display impaired inhibitory control compared to non-drug users on the Stop Signal (Colzato et al., 2007; Ersche et al., 2011, 2012; Fillmore and Rush 2002) and Go/No-Go tasks (Fernández-Serrano et al., 2012; Lane et al., 2007; Verdejo-García et al., 2007; Verdejo-García and Pérez-García, 2007). One study, however, showed no differences between cocaine users and controls on Stop Signal task performance (Vonmoos et al., 2013).

Significant differences were observed between cocaine users and controls for reaction times to go targets following go and no-go cues. Controls responded significantly faster to go targets compared to cocaine users on all three inhibitory control tasks. The significantly faster reaction times could indicate that the proportion of inhibitory failures are increased in the control group due to a speed/accuracy trade-off. Controls displayed faster reaction times in some previous studies, but did not show a corresponding increase in inhibitory failures (Ersche et al., 2011; Lane et al., 2007). In the instructions, participants are informed that they are completing a reaction time task and as such they should respond as quickly as possible to go targets when they appear. The instructions go on to say that the task will display their reaction time to go targets in milliseconds after they make a response and that lower numbers are better. While the instructions also state that

responses should be withheld to no-go targets and the task will provide feedback about incorrect responses to no-go targets, participants in the control group may have placed more emphasis on responding as quickly as possible rather than balancing speed and accuracy. The instructions create a prepotent response following go cues, where participants learn that on the majority of trials they will need to execute a quick response following go cues. Another possibility is controls relied on cues to predict when responses would be required and they may have initiated responses before the target appeared in order to reduce their reaction times.

The present study has a few limitations worth noting that provide directions for future research. First, the sample size of control participants is small. While it appears that within controls a speed accuracy trade-off occurred due to significantly faster times, it is possible that the controls enrolled in the present study generally display poor inhibitory control on behavioral tasks. In a larger sample, poor inhibitory performance by one or two individuals would have less of a significant effect on the overall sample mean. Also, selecting a control sample is not as simple as selecting individuals who have limited substance use histories, since environmental and developmental factors can contribute to the risk of developing a substance use disorder. Collecting data using a method like Amazon's mTurk would allow for a larger sample to be collected with less reliance on local availability of individuals who are willing and able to complete behavioral studies in the laboratory. Second, the cocaine using and control samples differed on years of education, race distribution, and total BIS scores. Similar to the point above, recruiting a larger sample, particularly using an online resource would allow for better matching of cocaine using and control samples. Third, performance was only measured on one session and it is possible that the cocaine images in the cocaine go condition of the ABBA task were novel and shocking or interesting to the control participants. The proportion of inhibitory failures on the cocaine go condition of the ABBA task was higher than for the other tasks. If this increase were due to novelty of the

stimuli either presenting a series of substance-related images prior to testing or assessing test-retest reliability may have shown performance on the cocaine go condition of the ABBA task was more similar to the other two tasks when the stimuli was less novel and evocative.

Overall, no differences were observed in the proportion of inhibitory failures between cocaine users and controls on any of the inhibitory control tasks. Controls responded significantly faster on all of the tasks, compared to cocaine users, which may suggest that they placed more emphasis on fast responses over accurate responding representing a speed-accuracy trade-off. The failure to detect a difference between cocaine users and controls on the Cued Go/No-Go task is discordant with previous research showing that cocaine users display impaired inhibitory control compared to non-users (e.g., Fillmore and Rush 2002; Verdejo-García et al., 2007). Understanding whether or not the increase in inhibitory failures following cocaine-related images is specific to cocaine users would provide more information on the mechanism underlying the increase following drug-related cues. Research suggests that drug cues are associated with motivational states to obtain or use drugs and this association leads to drug cues capturing attention (Field and Cox, 2008; Ryan, 2002). Salience of stimuli in the environment (e.g., drug cues) and inhibitory control interact and contribute to substance abuse (Goldstein and Volkow, 2002). If preferential attention and a prepotent response to execute a behavior in the presence of drug cues are contributing to the increase in inhibitory failures observed in cocaine users on the cocaine go condition of the ABBA task non-drug using controls should not display differences in performance between the cocaine go condition of the ABBA task and the neutral go condition of the ABBA task, all neutral ABBA task, or Cued Go/No-Go task. Future research should continue to investigate the mechanism behind the increase in the proportion of inhibitory failures on the cocaine go condition of the ABBA task compared to the neutral go condition and the Cued Go/No-Go task.

Table 4.1

Demographics of cocaine users from Experiment 2, controls from Experiment 3, sample sizes, and statistical values from comparisons between group means. Bold values indicate a significant difference between groups ($p < 0.05$)

Measure	Cocaine Users	n	Controls	n	Statistical Value
Age [a]	41.5 (1.1)	58	39.7 (2.8)	16	0.61[c]
Sex (# male) [b]	44	58	9	16	2.37
Race [b]		58		16	**21.77**
African American	41		1		
Caucasian	12		12		
Other	5		3		
Years of Education [a]	11.7 (0.2)	58	14.2 (0.7)	16	**3.29**[c]
BIS-11 [a]	62.9 (1.2)	57	48.7 (1.6)	16	**6.00**
Alcohol [a]					
Drinks per Week	25.6 (5.9)	58	4.8 (2.0)	14	**3.33**[c]
Drinks per Month	113.8 (25.8)	58	22.4 (7.7)	14	**3.39**[c]
Cigarettes per Day [a]	14.0 (1.4)	54	13.3 (4.8)	3	0.11
Marijuana [a]					
Days per Month	10.5 (1.6)	55	1.9 (1.2)	9	**4.31**[c]
Years Used	25.9 (1.2)	55	21.4 (3.1)	9	1.36
Cocaine [a]					
Days per Week	3.4 (0.3)	58	0.0 (0.0)	2	**12.24**[c]
Days per Month	15.5 (1.2)	58	0.0 (0.0)	2	**12.42**[c]
Years Used	18.3 (1.4)	58	7.0 (3.0)	2	1.53
Positive Urine Screen	0.7 (0.1)	58	0.0 (0.0)	16	**11.73**[c]

[a] Mean (SEM) and *t*-values reported
[b] Sample size and chi square values reported
[c] Equal variances not assumed for *t*-tests

Figure 4.1

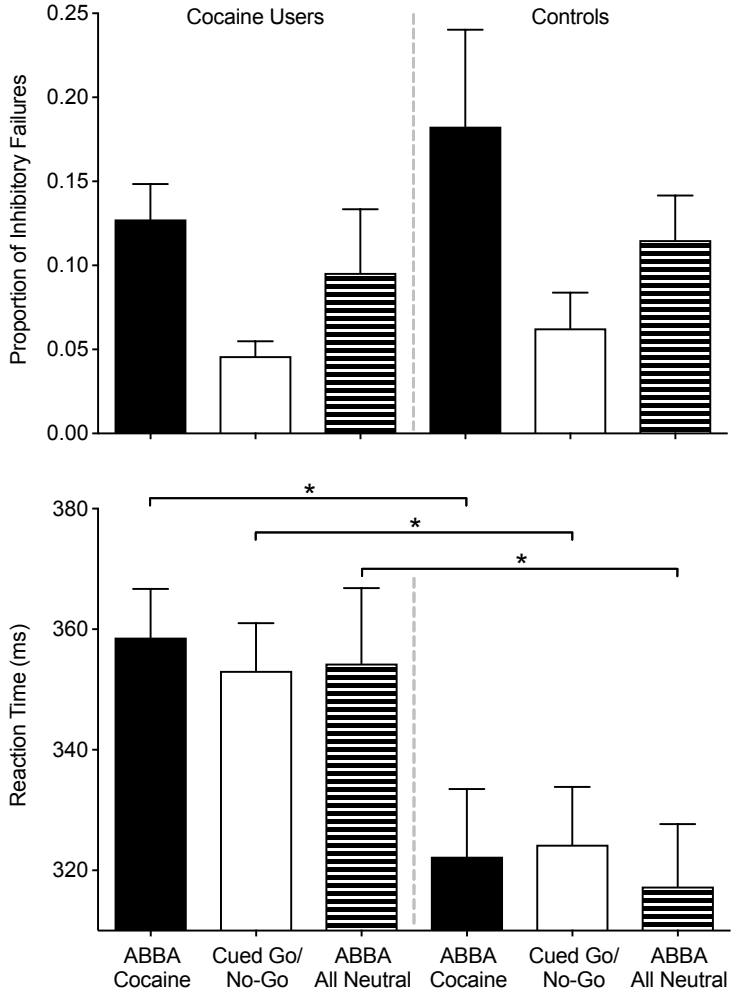

Figure 4.1. Proportion of inhibitory failures to no-go targets following go cues (top panel) and reaction times to go targets following go cues (bottom panel) for cocaine users and controls. Solid black bars represent performance on the cocaine go condition of the ABBA task. Solid white bars represent data from the Cued Go/No-Go task. White and black striped bars represent data from the all neutral condition of the ABBA task. The left three bars are data from cocaine users in Studies 1 and 2 of Experiment 2 (ABBA cocaine go n = 38, Cued Go/No-Go n = 40, all neutral ABBA n = 18). The right three bars are data from controls (n = 16). Asterisk (*) indicates a significant difference between groups based on t-tests ($p < 0.05$).

CHAPTER 5

THE INFLUENCE OF STIMULUS ONSET ASYNCHRONY ON INHIBITORY CONTROL FOLLOWING DRUG-RELATED IMAGES IN COCAINE USERS

(EXPERIMENT 4; Pike et al., 2015)

Introduction

Cocaine users who display impaired inhibitory control also have poorer treatment outcomes (Brewer et al., 2008; Carpenter et al., 2006; Streeter et al., 2008). However, these clinical trials did not assess inhibitory control following the presentation of substance-related cues. Inhibitory control in the presence of substance related cues could be crucial to preventing relapse or the continued use of drugs because both occur in the presence of drug cues. Theories on the role of substance-related cues in substance abuse posit that over repeated pairings cues become associated with motivational states to obtain or use drugs (Field and Cox, 2008; Ryan, 2002). Following this association, drug cues in the environment capture attention and receive preferential attention (Field and Cox, 2008). This preferential attention may impair inhibitory control.

Cued Go/No-Go tasks assess inhibitory control in the presence of environmental cues that predict when a response will be required (Fillmore, 2003). The Attentional Bias-Behavioral Activation (ABBA) task is a modified Cued Go/No-Go task that uses substance-related and neutral images rather than horizontal and vertical rectangles (Pike et al., 2013; Weafer and Fillmore, 2012, 2015). Drinkers displayed impaired inhibitory control following alcohol-related compared to neutral cues on the ABBA task (Weafer and Fillmore, 2012, 2015). In Experiment 1, cocaine users displayed significant increases in the proportion of inhibitory failures to no-go targets following cocaine images as the go cue compared to their counterparts who saw neutral images as the go cue (Pike et al., 2013). Cues in the ABBA task are presented for one of five stimulus onset asynchronies (SOA), which is the amount of time that the cue is displayed before the presentation of the target: 100, 200,

300, 400, or 500 milliseconds (ms). The influence of SOA on inhibitory control could provide a more fine-grained understanding of the impact of drug-related stimuli on discontinuing or inhibiting the initiation of drug use, because both behaviors occur in the presence of drug-related stimuli. Increased inhibitory failures at short SOAs would suggest that the failures are related to the initial orientation of attention or rapid shifting of attention whereas increased inhibitory failures at long SOAs would suggest that participants are unable to disengage attention from the cue and employ cognitive mechanisms to inhibit behavior following the cue (Field and Cox, 2008). Understanding the influence of SOA on inhibitory control following the presentation of drug-related stimuli could also direct future interventions to improve inhibitory control in the presence of drug cues and lead to improved treatment for cocaine users with poor treatment prognosis due to inhibitory control deficits.

The purpose of the present study was to demonstrate that SOA impacts the proportion of inhibitory failures to no-go targets following cocaine-related and neutral images as the go cue. I hypothesized that the proportion of inhibitory failures to no-go targets following cocaine images as a go cue would be significantly greater than to no-go targets following neutral images as the go cue. Second, I hypothesized that the proportion of inhibitory failures to no-go targets following cocaine images as the go cue compared to neutral images as the go cue would be increased following short SOAs compared to long SOAs, based on Event Related Potential (ERP) studies showing that frontal lobe engagement to inhibit behavior occurs approximately 150 ms following stimulus onset (Fabre-Thorpe et al., 2001; Thorpe et al., 1996). Reaction time to go targets following go cues should not be influenced by image type.

Methods

Participants

Data were combined from studies where adult participants completed the ABBA task either during a screening appointment (i.e., Experiment 1 and Experiment 2 Study 1) or a practice session of a study where no medications were administered (Pike et al., under review). Ninety-one participants (33 women and 58 men) were included in the analyses and demographics shown in Table 5.1. Participants were primarily recruited through word of mouth and postings on community bulletin boards. All participants were required to be at least 18 years or age and report using cocaine within the last month. Potential participants were excluded if they reported a history of or current serious physical disease (e.g., COPD, diabetes), psychiatric disease requiring medication, or a prescription for centrally acting medication. Potential participants were also excluded if they reported dependence on any drug that could produce significant withdrawal symptoms during testing (e.g., opiates or benzodiazepines), as participants were asked to abstain from drug use for 12 hours prior to testing. Participants completed screening questionnaires on current and past physical and mental health, measures of current psychological functioning, and a detailed drug use history, which is described above in Experiment 1. Participants were paid between $25 and $45 for their participation, based on the research activities they were scheduled to do on the day they completed the ABBA task. The University of Kentucky Institutional Review Board approved all procedures and recruitment methods.

Procedure

Participants completed the ABBA task either during screening or practice sessions for other laboratory protocols. A between-subjects design was used, such that half of the participants were assigned to the cocaine go condition and half to the neutral go condition. Within the respective studies, the two groups were matched on demographic and drug

use variables (e.g., age, days used cocaine in the last month). A between-subjects design was used because participants learn to anticipate which cues signal go or no-go targets. Having participants switch conditions (i.e., cocaine and neutral go cues) would disrupt the learning that takes place during the task.

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 (Weafer and Fillmore, 2012). The task took approximately 15 minutes to complete and consisted of five blocks of 50 trials. A trial involved a sequence of events during which a fixation point (+) was presented for 800 ms, followed by a blank white screen for 500 ms, a cue image (cocaine or neutral) was presented for one of five stimulus onset asynchronies (SOA; i.e., 100, 200, 300, 400, 500 ms), and finally a go or no-go target, which was displayed until a response occurred or 1,000 ms elapsed. A sample trial of the cocaine go condition is shown in Figure 2.1. There was a 700 ms interval between all trials. The presentation of cocaine and neutral images was divided evenly between trials. Participants were prepared to respond (i.e., go cue), but needed to inhibit their response (i.e., no-go target) on 25 of the 250 trials.

The cues consisted of cocaine-related images (e.g., powder with a razor blade, crack cocaine) or neutral images (e.g., stapler, paper towel roll). All images (15 cm x 11.5 cm) were presented in the center of the computer monitor against a white background. After a SOA, the cue image turned either solid green (go target) or solid blue (no-go target). Participants were instructed to press the forward slash (/) key on the keyboard, which was marked with a green sticker, as soon as a green (go) target appeared. Participants were instructed to withhold responses when a blue (no-go) target appeared.

The task consisted of two conditions: a cocaine go condition and a neutral go condition. In the cocaine go condition 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 condition 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 condition 80% of go targets were preceded by a neutral cue and 20% were preceded by a cocaine cue. In the neutral go condition 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 participants the cocaine image served as the go condition (n = 46) and for the other half, the neutral image served as the go condition (n = 45).

Criterion measures and data analysis. An alpha level of $p \leq 0.05$ was used to determine significance for statistical outcomes of *a priori* hypotheses (Keppel, 1991a). Data on proportion of inhibitory failures and reaction times from the ABBA were analyzed using a mixed-model analysis of variance (ANOVA). The between-subject factor was Go Cue Condition (i.e., cocaine go or neutral go) and the within-subject factor was SOA (i.e., 100, 200, 300, 400, or 500 ms). Fisher's Least Significant Difference test was used to assess differences between proportion of inhibitory failures and reaction times at each SOA and between SOAs within each condition based on significant F-values from the ANOVAs. Cohen's d was used to calculate effect sizes for all significant between-groups differences as determined by Fisher's Least Significant Difference test. Data on proportion of inhibitory failures from the ABBA were also analyzed using a second mixed-model analysis of variance (ANOVA) to assess performance over the course of the task. The between-subject factor was Go Cue Condition (i.e., cocaine go or neutral go) and the within-subject factor was Block (i.e., Block 1, Block 2, Block 3, Block 4, and Block 5). Pearson correlations were used to assess associations between primary outcomes from the task and demographic and drug use variables. A Bonferroni correction for multiple correlations was used for these *post hoc* analyses, which adjusted the significant p-value to $\leq$ 0.0031.

Sample size justification. The proposed sample size was based on a power calculation using an effect size of 1.75, which was described in Experiment 1, two between-subjects factors (go cue condition), and five within-subject factors (SOA) and 0.05 for error probability. Based on these calculations, 45 participants per group will provide ≥ 80% power to detect a significant interaction.

Results

ABBA Task Performance

Response Inhibition Following Go Cues. The ANOVA revealed a significant interaction between Go Cue Condition and SOA for inhibitory failures to no-go targets following go cues ($F_{4,356} = 2.50$, $p = 0.04$). Comparisons using Fisher's Least Significant Difference test revealed significant increases in the proportion of inhibitory failures in the cocaine go condition compared to the neutral go condition following the all of the SOAs (Cohen's d = 0.71, 0.84, 0.44, 0.52, and 0.32, respectively). Within the cocaine go condition, participants had significantly increased inhibitory failures following the 100 and 200 ms SOAs relative to the 300, 400, and 500 ms SOAs. Within the neutral go condition, there were no differences in inhibitory failures following any of the SOAs (Figure 5.1 top panel).

The ANOVA assessing the proportion of inhibitory failures to no-go targets following go cues by block revealed a significant main effect of Go Cue Condition ($F_{1,356} = 15.74$, p = 0.000). Proportion of inhibitory failures was higher in the cocaine go condition compared to the neutral go condition during all blocks.

Response Activation Following Go Cues. The ANOVA revealed a significant main effect of SOA for response time to go targets following go cues ($F_{4,356} = 5.56$, $p = 0.0002$). Regardless of condition, participants had significantly decreased reaction times following the 200, 300, 400, and 500 SOAs relative to the 100 ms SOA (Figure 5.1 bottom panel).

Response Inhibition Following No-Go Cues. The ANOVA revealed a significant main effect of SOA for proportion of inhibitory failures to no-go targets following no-go cues

($F_{4,356}$ = 5.40, p = 0.0003). Within the cocaine and neutral go conditions, participants had significantly increased inhibitory failures at shorter SOAs (i.e., 100 and 200 ms) compared to longer SOAs (data not shown).

The ANOVA assessing the proportion of inhibitory failures to no-go targets following no-go cues by block revealed a significant main effect of Block ($F_{4,356}$ = 11.99, p = 0.000). Both groups displayed generally improved performance throughout the course of the task.

Response Activation Following No-Go Cues. The ANOVA revealed a significant interaction between Go Cue Condition and SOA for response time to go targets following no-go cues ($F_{4,356}$ = 2.89, p = 0.02). Comparisons using Fisher's Least Significant Difference test revealed significant decreases in reaction time to go targets following no-go cues in the cocaine go condition compared to the neutral go condition following the 300, 400, and 500 ms SOAs (Cohen's d = 0.51, 0.22, and 0.45, respectively), but not following the 100 and 200 ms SOAs. Within the cocaine go condition, there were non-systematic differences in reaction time across SOAs (e.g., reaction times were significantly faster following the 300 ms SOA than the 100 and 400 ms SOAs). Within the neutral go condition, participants displayed a general increase in reaction time as SOA increased (data not shown).

Post Hoc Correlations. There was a significant positive correlation between reaction time following go cues and age (r = 0.31, p = 0.0031). There were no other significant correlations between inhibitory failures or reaction times following go and no-go cues and demographic variables.

Discussion

Participants who saw a cocaine-related image as a go cue displayed a greater proportion of inhibitory failures than their counterparts exposed to a neutral cue, which replicates the results of a previous study from our laboratory (Pike et al., 2013). Importantly, reaction time following go cues did not differ between cocaine and neutral go

conditions as demonstrated by a non-significant main effect of go cue condition on reaction time following go cues. This suggests that the increased proportion of inhibitory failures following cocaine go cues was not caused by decreased reaction time. Overall, cocaine and neutral conditions had similar proportions of inhibitory failures following no-go cues, although non-systematic differences were observed between the go conditions when analyzed by SOA. The presentation of a cocaine image alone did not increase the proportion of inhibitory failures; rather it was the interaction of the cocaine image usually predicting that a response would be required followed by the need to inhibit responding.

The present study expanded upon previous findings to show that SOA influenced the proportion of inhibitory failures following cocaine images as the go cue. Cocaine users had an increased proportion of inhibitory failures following cocaine-related go cues compared to neutral go cues. The increases in inhibitory failures following cocaine-related images were significantly higher at shorter (i.e., 100 and 200 ms) compared to longer (i.e., 300, 400, and 500 ms) SOAs.

The mechanism underlying the increase in inhibitory failures at short, but not long, SOAs is not known, but previous studies with ERP and behavioral tasks may provide some insight. ERPs have been used to examine neuronal activity while participants completed a Go/No-Go task that required them to identify whether or not an image presented for only 20 ms contained an animal (Fabre-Thorpe et al., 2001; Thorpe et al., 1996). The average brain ERPs generated by go and no-go trials diverged at 150 ms following stimulus onset with no-go trials producing a potential that was more negative than go trials. The time course and increased negative response of this ERP activity was consistent with the effect of frontal lobes in inhibiting behavior on no-go trials (Fabre-Thorpe et al., 2001; Thorpe et al., 1996).

The divergence observed previously between go and no-go trials at 150 ms is also consistent with our finding that inhibitory failures are significantly greater following 100 and

200 ms SOAs for cocaine images. Thus, the increase in inhibitory failures following cocaine images at the shorter SOAs may relate to the initial orientation of attention to the cocaine image (Field and Cox, 2008) and the expectation that a cocaine image is most often followed by a go target requiring a response. Participants may then be unable to engage the frontal lobe to inhibit responding following the cue at short SOAs given that ERP studies show frontal lobe activation involved in inhibiting behavior occurs at approximately 150 ms (Fabre-Thorpe et al., 2001; Thorpe et al., 1996).

Other evidence suggests that only salient cues can be processed at very short SOAs. In a series of experiments, the salience of cues to aid in the execution of a behavioral response was assessed (Donk and Soesman, 2010). Cues were presented for one of three SOAs (i.e., 42, 158, or 483 ms). Following the SOA, a target was presented and participants were required to indicate the location of the target. When cues were presented for the shortest SOA (i.e., 42 ms), salience of the cue aided in detection of the target as indicated by a reduced reaction time. At the longest SOA, cue salience did not influence reaction time (Donk and Soesman, 2010). The increase in inhibitory failures following cocaine images at short SOAs is concordant with these outcomes because cocaine-related cues are likely more salient than neutral cues to cocaine users. At the longer SOAs, the salience of the cocaine-related cues relative to neutral cues is less influential.

Post hoc analyses showed that there were significantly fewer inhibitory failures within the cocaine go condition following longer SOAs (i.e., 300, 400, and 500 ms). Longer SOAs provide sufficient time for multiple shifts of attention from the cocaine-related cue (Field and Cox, 2008). This time allows participants to disengage attention from the cocaine-related cue and employ cognitive mechanisms to inhibit responding to a no-go target. Similarly, there was an increase in inhibitory failures following no-go cues at short SOAs compared to long SOAs, but differences between the go cue conditions were not

systematic especially when compared to the outcomes observed when participants are prepared to execute a response (i.e., seeing a cocaine go cue followed by a no-go target).

The proportion of inhibitory failures to no-go targets following go and no-go cues were assessed by block to determine how the inhibitory failures were distributed across the task. This was of interest was to determine if participants exhibited more failures toward the end of the task, indicating a lack of persistence in maintaining accurate responses. Participants in the cocaine go condition displayed a higher proportion of inhibitory failures to no-go targets following go cues across all blocks, which is consistent with previous research and with the SOA findings that inhibitory failures are increased following cocaine-related images (Pike et al., 2013). Inhibitory failures to no-go targets following no-go cues generally improved across the blocks, indicating participants were learning that no-go cues generally predict that responses will need to be withheld.

Drug cues are associated with motivational states to obtain or use substances (Ryan, 2002). Inhibitory control in the presence of drug cues may relate to the ability to abstain from or discontinue drug use. Specifically, the presence of drug cues (e.g., paraphernalia) may signal the presence of a drug, thus making it more difficult for individuals to inhibit initiation of drug use. Based on our findings, inhibition following the initial orientation to a drug-related cue would be particularly difficult, as the processes involved in inhibitory control are not yet engaged. Additionally, the continuation of use would occur in the presence of drug cues. When cocaine users complete the ABBA task, inhibitory failures in the presence of drug-related cues occur when individuals anticipate a response will be required following a drug cue and then have to inhibit the response (Pike et al., 2013). This increase in inhibitory failures models how impaired inhibitory control could contribute to initiation or the continuation of drug use, as the individual would need to inhibit the anticipated response following the presence of drug cues. Although previous studies have shown that impaired inhibitory control on the Stroop task was associated with poor

treatment outcomes (Brewer et al., 2008; Carpenter et al., Streeter et al., 2008), the influence of inhibitory control following drug cues on treatment outcomes is not known and should be investigated in future research. Future research should also further investigate the influence of SOA on inhibitory control to better understand the mechanisms involved.

The current study had a few limitations, which could provide additional directions for future research. Participants did not have to provide a cocaine-positive urine screen; rather they only had to report cocaine use in the last month to qualify for the studies used in these analyses. However, the majority of participants provided a cocaine-positive urine sample and the number of positive samples was not significantly different between conditions. The between-subjects design may be a limitation. Even though the cocaine go and neutral go conditions were similar on the measured demographic or drug use variables, participants in the go cue conditions may have differed on some unmeasured, but relevant, variable. Future research should be done to further modify the ABBA task so that it would be amenable to within-subject use to circumvent the current need to use a between-subjects design with this task.

Overall, the present study replicated previous findings showing that cocaine-related stimuli decreased inhibitory control in cocaine users (Pike et al., 2013), which could be related to the inability to avoid or cease drug use in the presence of drug cues. This study extended the previous findings to show that the disruption in inhibitory control by cocaine images occurs at short (i.e., 100 and 200 ms) SOAs, but not at longer (i.e., 300, 400, and 500 ms) SOAs. The influence of SOA on inhibitory control could significantly impact attempts to improve or modify inhibitory control in the presence of drug cues. Further research is needed to better understand the nature of cue-related disinhibition and its impact on drug use in the natural ecology.

Table 5.1

Demographics of the Cocaine Group, Neutral Group (Mean [SEM])

Measure	Cocaine Group	Neutral Group
Age	40.70 (1.22)	39.16 (1.24)
Sex (# male) [a]	29	29
Race [a]		
African American	33	28
Caucasian	11	14
Multiple Races	2	3
Years of Education	11.83 (0.28)	11.51 (0.29)
Alcohol		
Drinks per Day	1.04 (0.41)	3.61 (1.98)
Drinks per Week	17.29 (3.76)	33.80 (12.91)
Drinks per Month	81.33 (17.78)	149.34 (55.66)
Cigarettes per Day	11.21 (1.23)	13.08 (1.61)
Marijuana		
Days per Month	11.37 (1.87)	12.04 (1.75)
Years Used	23.78 (1.35)	24.84 (1.39)
Cocaine		
Days per Week	3.13 (0.34)	2.82 (0.30)
Days per Month	12.96 (1.45)	13.22 (1.20)
Years Used	16.33 (1.42)	14.96 (1.20)
Positive Urine Screen	0.70 (0.07)	0.62 (0.07)

[a] Sample size reported for sex and race.

Figure 5.1

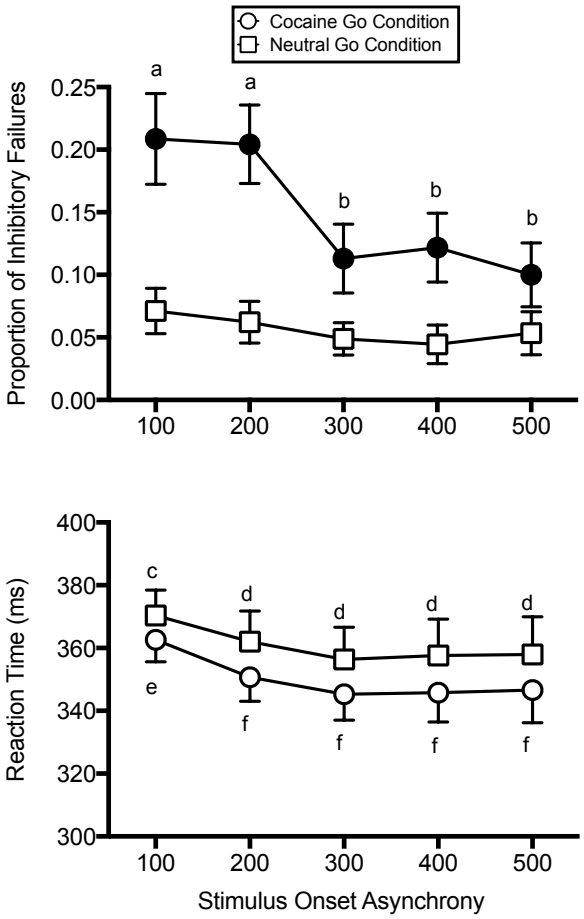

Figure 5.1. Top panel: Proportion of inhibitory failures to no-go targets following go cues by SOA from Experiment 4. Filled symbols indicate a significant difference between go cue conditions. Symbols marked with an “a” are significantly different from symbols marked with a “b,” but are not different from other symbols marked with an “a” as determined by Fisher’s Least Significant Difference test. Symbols marked with a “b” are not different from each other. Bottom panel: Reaction time to go targets following go cues by SOA from Experiment 4. Symbols marked with a “c” are significantly different from symbols marked with a “d” as determined by Fisher’s Least Significant Difference test. Symbols marked with a “d” are not different from each other. Symbols marked with an “e” are significantly different from symbols marked with an “f” as determined by Fisher’s Least Significant Difference test. Symbols marked with an “f” are not different from each other.

Chapter 6

A SMALL PILOT CLINICAL TRIAL TO ASSESS THE FEASIBILITY AND ACCEPTABILITY OF INHIBITORY CONTROL TRAINING AS A TREATMENT FOR COCAINE DEPENDENCE

(EXPERIMENT 5)

Introduction

Inhibitory control is impaired in cocaine users as measured by a variety of tasks (e.g., the Cued Go/No-Go and Stop Signal tasks; Fillmore and Rush, 2002; Lane et al., 2007; Verdejo-García et al., 2007), perhaps contributing to continued drug abuse and relapse. The cost to society of continued cocaine use in the US has been estimated at over $45 billion/year (Cartwright 2000).

Cocaine users display impaired inhibitory control on the Stop Signal task compared to controls (Fillmore and Rush, 2002). These findings were extended by showing that cocaine users fail to inhibit prepotent responses following cocaine images significantly more often than following neutral images using the Attentional Bias-Behavioral Activation task (ABBA; Pike et al., 2013, 2015). In the ABBA task, cocaine images serve as a go cue in that they generally predict when a response will be required (i.e., on 80% of trials). The trials of interest are the 20% when a participant sees a cocaine image, is prepared to respond, but must inhibit the response at the last moment. Impaired inhibitory control in the presence of drug cues suggests that individuals would have an increasingly difficult time avoiding or discontinuing drug use in the presence of drugs or paraphernalia, thus contributing to continued drug use. Specifically, the presence of drug paraphernalia may signal the presence of a drug making it more difficult for individuals to inhibit initiation of drug use. An individual's ability to inhibit responding in the presence of drug cues could also relate to their ability or inability to stop taking drugs once use has already been

initiated, as the discontinuation of use would occur in the presence of drug cues. Research on the relationship between drug cues and substance use suggests that drug cues are associated with motivational states to obtain or use drugs (Ryan, 2002). Individuals with impaired inhibitory control and increased attentional bias to drug cues may have an increasingly difficult time resisting or discontinuing drug use in the presence of drug cues.

Training heavy alcohol drinkers to inhibit prepotent responses to alcohol images results in reduced alcohol use (Houben et al., 2010, 2011). Recent meta-analyses have further supported inhibitory control training modeled after Go/No-Go tasks to reduce appetitive behaviors (i.e., food and alcohol consumption; Allom et al., 2016; Jones et al., 2016). A recent study in our laboratory showed that one day of acute inhibitory control training to cocaine-related images and rectangles resulted in improved performance on the Stop Signal task (Alcorn et al., 2017). Cocaine users in that study completed an inhibitory control training task to either cocaine-related images or rectangles (i.e., the control task) five times across one day. Change in cocaine use following training was not assessed, but that study did show that acute training on an inhibitory control task resulted in improved inhibitory control on a different task. The efficacy and feasibility of applying similar training methods to improve inhibitory control to cocaine-related stimuli in cocaine abusers over a longer period of time, and the effect on drug taking, has yet to be determined. The purpose of the present study was to demonstrate that inhibitory control training in cocaine users is feasible and the procedures used are acceptable when conducted over a longer period of time. I hypothesized that conducting inhibitory control training with cocaine users would be feasible, as shown by retention in the study and performance on the inhibitory control training task. I hypothesized that participants would rate the procedures used in the study to be acceptable on the Treatment Acceptability Questionnaire. I hypothesized that all participants, regardless of inhibitory control training task, would display improved inhibitory control on the Stop Signal task as demonstrated

following acute training (Alcorn et al., 2017). No significant differences should be observed between groups on self-reported cocaine use, proportion of cocaine positive urine samples, or the amount of benzoylecgonine (i.e., a cocaine metabolite) present in the urine samples, since the participants in the study were not explicitly seeking cocaine treatment.

Methods

Participants

Twenty-five cocaine users completed this pilot study to test the feasibility and acceptability of an innovative inhibitory control training procedure used to reduce cocaine use and improve inhibitory control. Potential participants were required to be 18 years of age or older, self-report cocaine use in the week prior to screening, provide a cocaine-positive urine sample at screening, meet criteria for cocaine abuse or dependence based on the SCID, and be able and willing to commit to completion of the protocol. Potential participants were excluded if they reported current or past medical or psychiatric illness that would interfere with study participation (e.g., physical dependence on any drug requiring medically managed detoxification). Participants were paid for their participation, which is described in detail below. The University of Kentucky Institutional Review Board approved all procedures and recruitment methods.

Procedure

On the first screening day after providing informed consent, participants completed a packet of questionnaires including a detailed health and drug use history and assessments for ADHD and depression, which is described above in Experiment 1. Participants also completed the SCID to assess potential psychiatric diagnoses and substance dependence. The experiment consisted of a total of nine sessions: one screening, one Baseline, two Training, four Follow-Ups, and one Final Session, which is outlined in Table 6.1. The study took approximately 2.5 weeks to complete. Urine was screened for drugs

of abuse using qualitative testing at all visits to ensure accurate monitoring of cocaine use (i.e., cocaine can be detected in urine up to 72 hours after use). Once weekly starting on the first Training Session quantitative testing was conducted to estimate the amount of cocaine metabolites present in the sample to assess changes in cocaine use over the course of the study.

On the Baseline Session, participants completed the Stop Signal task, which was the primary measure of inhibitory control for this study. This task required participants to inhibit responses only when a tone is presented, rather than using cues to predict what targets would be presented. Participants also completed a battery of cognitive tasks, including the Barratt Impulsiveness Scale, a measure of hypothetical discounting for cocaine, and the Visual Probe task with eye-tracking technology to assess attentional bias.

The Stop Signal task was used to measure change in inhibitory control because the inhibitory control training tasks were variations of the ABBA and Cued Go/No-Go tasks. Retesting inhibitory control using either the ABBA or Cued Go/No-Go tasks could confuse participants by altering the probability that go and no-go targets follow go and no-go cues. Also, retesting inhibitory control using either the ABBA or Cued Go/No-Go tasks could potentially undo the cocaine inhibitory control training, as no-go cues predict no-go targets only 80% of the time in the standard, non-training, tasks.

After completing screening and Baseline testing, but prior to the first Training Session (i.e., Day 3), participants were assigned using urn randomization to a condition in which they were trained to inhibit responding to cocaine images or neutral images (rectangles), as are presented in the traditional Cued Go/No-Go task. The urn randomization procedure matched subjects on basic drug use and demographic variables (i.e., past month cocaine use, sex, education). Participants completed the Training Sessions as detailed in Table 6.2. The cocaine images training task, which is described in detail in the Inhibitory Control Training task section below, was a variation of the ABBA task during which cocaine images

preceded no-go targets 100% of the time. The control training task, which is described in detail below, was a variation of the traditional Cued Go/No-Go task during which a horizontal rectangle predicted no-go targets 100% of the time. Thus, image type predicted whether or not a response was required 100% of the time and participants were instructed that the images were there to help them prepare to respond, but they were not explicitly told the condition to which they were assigned. By the end of the first Training Session, participants were required to respond with no more than 5% errors on the training task in order to continue with the study. One participant was excluded for failing to meet accuracy criteria on the training task. To engage participants in the training, they were able to earn a $5.00 bonus per Training Session (i.e., approximately $1.65 per task), but were informed that they would lose $0.05 of their bonus for each mistake on the training task (i.e., failing to respond when required to or responding when required to inhibit). Previous studies demonstrated that drinkers trained to inhibit responding to alcohol images on similar inhibitory control training tasks have reduced alcohol use following training compared to those trained to inhibit to neutral images (Houben et al., 2010, 2011). As it was not possible to blind the research assistant who was conducting the training with participants as to which training task participants are completing, one research assistant conducted training sessions and a different research assistant conducted questionnaires to assess self-reported drug use and completed the Timeline Follow-Back (TLFB) to assess drug use since the last session.

Participants were paid for their participation and earned approximately $215 (i.e., approximately $10 per hour spent in the laboratory, plus bonus payments for performance on the inhibitory control training tasks). Participants earned $40 for Days 1, 3, 10; $20 for Days 2 and 17; and $10 for Days 5, 7, 12, 14. To maximize session attendance and completion of the entire study, starting on day 3 half of the participant's payment was held until the end of the study and given to them when they completed the protocol on Day 17.

Inhibitory Control Training task. The Inhibitory Control Training task is a modified version of the ABBA and Cued Go/No-Go tasks (Weafer and Fillmore, 2012; Miller et al., 1991, respectively). The training task was administered using E-prime experiment generation software (Psychology Software Tools, Pittsburgh, PA) on a PC computer. The task took approximately 15 minutes to complete and consisted of five blocks of 50 trials. A trial involved a sequence of events during which a fixation point (+) was presented for 800 ms, followed by a blank white screen for 500 ms, a cue image (cocaine or neutral) was presented for one of five stimulus onset asynchronies (SOA; i.e., 100, 200, 300, 400, 500 ms), and finally a go or no-go target, which was displayed until a response occurred or 1,000 ms elapsed. There was a 700 ms interval between all trials.

The task consisted of two conditions: cocaine inhibitory control training and control inhibitory control training, which is referred to as the rectangles condition from here on. In the cocaine inhibitory control training condition, cocaine images served as no-go cues and neutral images served as go cues. In the rectangles inhibitory control condition, horizontal rectangles served as no-go cues and vertical rectangles served as go cues. Rectangles were used in the control condition rather than switching which image type was the go and no-go cues, because training drinkers to respond following alcohol images resulted in increased drinking and I was concerned about the potential risk of increasing cocaine use (Houben et al., 2010, 2011). In both conditions, cues predicted which target was presented 100% of the time. Half of the participants were assigned to complete each condition.

In the cocaine inhibitory control training task, the cues consisted of cocaine-related images (e.g., powder with a razor blade, crack cocaine) or neutral images (e.g., stapler, paper towel roll). In the rectangles inhibitory control training task, the cues consisted of empty vertical and horizontal rectangles. The presentation of cocaine and neutral images were divided evenly between trials in the cocaine Inhibitory Control Training task. The presentation of horizontal and vertical rectangles was divided evenly between trials in the

rectangles Inhibitory Control Training task. All cues were presented in the center of the computer monitor against a white background. After a SOA, the cue turned either solid green (go target) or solid blue (no-go target). Participants were instructed to press the forward slash (/) key on the keyboard, which was marked with a green sticker, as soon as a green (go) target appeared. Participants were instructed to withhold responses when a blue (no-go) target appeared.

Treatment Acceptability Questionnaire. The Treatment Acceptability Questionnaire was administered on a Macintosh computer and participants rated their response to five statements on a 100-mm visual analog scale. The scale ranged from “Not at All” on the left side (i.e., score of 0) to “Extremely” on the right side (i.e., score of 100). Participants rated their overall satisfaction with the study, the acceptability of sessions occurring three times per week, the acceptability of providing an observed urine sample, the acceptability of completing the training task three times on Training Sessions, and the acceptability of completing the training task during Follow-Up Sessions.

Timeline Follow-Back (TLFB) calendar. The Timeline Follow-Back (TLFB) calendar is a self-report paper and pencil assessment. Participants indicated when they used cocaine and how much they used over the last three months (Sobell and Sobell, 1992). At baseline participants completed the full three-month calendar and at each following appointment they completed only back to the previous appointment. Outcomes of interest included days used cocaine in the week, month, and three months prior to baseline and days used cocaine following the initiation of training.

Stop Signal task. The Stop Signal task was administered using E-prime experiment generation software (Psychology Software Tools, Pittsburgh, PA) on a PC computer. Letters (i.e., X or O) were presented on the screen one at a time and participants were instructed to respond on the computer keyboard to identify the letter that was presented. On approximately 30% of trials a tone occurred and participants were instructed to

withhold their response. Tones occurred 10, 70, 150, 230, or 300 ms after the presentation of the letter and the presentation of tones was divided evenly between letters. Participants were instructed to respond as quickly as possible to letters and not to wait to see if tones occurred. Outcomes included the reaction time for responses that occurred following stop signals (SSRT) and proportion of trials participants failed to withhold their response.

Barratt Impulsiveness Scale-11 (BIS-11). The Barratt Impulsiveness Scale-11 (BIS-11; Patton et al., 1995) is a self-reported measure of trait impulsivity. The BIS-11 consists of 30 questions and participants rate their answers on a scale of 1 (Rarely/Never) to 4 (Almost Always/Always). The total score was the primary outcome on the BIS-11.

Hypothetical Discounting for Cocaine. The Hypothetical Discounting for Cocaine task was administered on a computer and was developed based on a cocaine discounting task described previously (Coffey et al., 2003). Participants made hypothetical choices between an amount of cocaine available now and an amount of cocaine available after a delay. The amount of cocaine available immediately ranged from 0.2 grams and 5.0 grams and adjusted by 0.2 grams. The delay for 5.0 grams of cocaine ranged from 5 minutes to one year. For each delay, an indifference point was measured. The *k* parameters were determined using Excel 2011 for Mac using a procedure described previously (Reed et al., 2012). *K* parameters estimate the degree of discounting by measuring the steepness of the decrease in indifference points as the delay increases. Higher *k* values indicate greater impulsivity (Reed et al., 2012)

Visual Probe task. The Visual Probe task was used to assess attentional bias (Marks et al., 2014a, 2014b; Roberts et al., 2012). The Visual Probe task was administered using E-prime experiment generation software (Psychology Software Tools, Pittsburgh, PA) on a PC computer and eye movements were recorded using a Tobii X2-60 eye tracker (Tobii Technology, Sweden). For each critical trial, two images (a cocaine-related image and a matched neutral image) were presented side-by-side on a computer screen for 1000 ms.

The amount of time the participant spent looking at the cocaine and neutral images was measured. Following the image pair, a visual probe (X) appeared either on the left or the right side of the screen. The amount of time to respond to the probe was measured. Participants were instructed to look at both images and to respond as quickly as possible to the probe by pressing one of two response keys indicating on which side of the screen the probe appeared. The outcome of interest was the attentional bias score to cocaine related images, which was determined by subtracting the average fixation time on neutral images from the average fixation time on cocaine-related images.

Outcomes

The outcomes used to assess feasibility were attendance to the study sessions. This was measured as total number of session attended, total number of sessions missed, number of Training Sessions attended, number of Follow-Ups attended, number of Follow-Ups missed, and whether or not the Final Session was attended. Performance on the training task, including number correct responses to go targets and number of no-go targets to which responses were withheld, was also used to assess feasibility. Acceptability was assessed using responses on the Treatment Acceptability Questionnaire.

Secondary outcomes included results from urine tests, self-reported substance use, and performance on measures of cognitive functioning. Urine samples were tested for quantitative levels of the cocaine metabolite benzoylecgonine using ELISA analysis at the University of Kentucky Biochemical Analysis Laboratory. Urine samples were tested using qualitative analysis for drugs of abuse at the LHBP and two research assistants verified all urine results. Urine samples obtained on each session starting on Training 1 were observed following standard procedures (e.g., Kampman et al., 2013; Winhusen et al., 2012), and were tested for temperature and adulterants. The other cocaine use outcome variable originated from the TLFB. Change in self-reported drug use, amount of

benzoylecgonine present in the urine samples, and number of cocaine-positive urine screens were compared between groups to determine if training resulted in decreased substance use. Inhibitory control was assessed following training using the Stop Signal task as opposed to the ABBA or Cued Go/No-Go task, as described previously. Change in SSRT and proportion of inhibitory failures on the Stop Signal task were compared between Baseline and on the Final Session to determine if training improved general inhibitory control. Responses on the BIS-11, performance on the Hypothetical Discounting task and attentional bias scores on the Visual Probe task were compared between Baseline and the Final Session between groups to determine if inhibitory control training had any effect on these measures of cognitive performance.

Criterion measures and data analysis. Demographic data from participants in each of the training conditions, cocaine images or rectangles, were compared using independent samples *t*-tests and chi square analyses. Demographic data from participants who were randomized (n = 21) and those who only completed baseline testing (n = 4) were compared using independent samples *t*-tests and chi square analyses.

Attendance was compared between participants assigned to each training condition using independent samples *t*-tests. Comparisons were made for the total number of sessions attended, total number of missed sessions, number of Training Sessions attended, number of Follow-Up Sessions attended, number of Follow-Up Sessions missed, and whether or not the Final Session was attended.

Performance on the training task was assessed using mixed-model ANOVAs. The first assessed number of responses participants correctly executed and withheld following go and no-go targets, respectively, during Training Sessions with the within-subjects factors of Session (i.e., Training Day 1 and Training Day 2) and Task Number (i.e., First, Second, and Third time the task was completed on each training day). The between-subjects factor

was Training Condition (i.e., Cocaine Images or Rectangles). The second assessed the number of responses participants correctly executed and withheld following go and no-go targets, respectively, during Follow-Up Sessions. The within-subjects factor was Session (i.e., Follow-Up 1, 2, 3, and 4) and the between-subjects factor was Training Condition (i.e., Cocaine Images or Rectangles).

Ratings on the Treatment Acceptability Questionnaire were compared between participants assigned to each training condition using independent samples *t*-tests. Comparisons were made for ratings of overall satisfaction, acceptability of attending appointments three times per week, acceptability of providing observed urine samples, acceptability of the training task on Training Sessions, and acceptability of the training task on Follow-Up Sessions.

Quantitative urine results were compared using a mixed-model ANOVA. The within-subjects factor was Session (i.e., Training 1, Training 2, Final) and the between-subjects factor was Training Condition (i.e., Cocaine Images or Rectangles). Qualitative urine results were compared using a mixed-model ANOVA. The within-subjects factor was Session (i.e., Baseline, Training 1, Follow-Up 1, Follow-Up 2, Training 2, Follow-Up 3, Follow-Up 4, Final) and the between-subjects factor was Training Condition (i.e., Cocaine Images or Rectangles).

Number of days used cocaine in the last week, month, and three months reported on the Timeline Follow-Back Calendar were compared using mixed-model ANOVAs. The within-subjects factor was Session (i.e., Baseline, Training 1, Follow-Up 1, Follow-Up 2, Training 2, Follow-Up 3, Follow-Up 4, Final) and the between-subjects factor was Training Condition (i.e., Cocaine Images or Rectangles).

Mean stop signal reaction time and mean inhibitory failures on the Stop Signal Task were compared using mixed-model ANOVAs. The within-subjects factors were Session

(i.e., Baseline and Final) and Task Number (i.e., 1 and 2). The between-subjects factor was Training Condition (i.e., Cocaine Images or Rectangles).

Independent samples *t*-tests were used to compared performance at Baseline and at the Final Session between participants in each training condition for Barratt Impulsiveness Scale total score, attentional bias (i.e., gaze time), and hypothetical discounting for cocaine (i.e., AUC and *k*).

Independent samples *t*-tests were used to compared performance at Baseline between participants who were randomized and those who completed Baseline only for qualitative urine result, days used cocaine in the last week, month, and three months on the TLFB, Barratt Impulsiveness Scale total score, attentional bias (i.e., gaze time), and hypothetical discounting for cocaine (i.e., AUC and *k*).A mixed-model ANOVA was used to compare stop signal reaction times and proportion of inhibitory failures on the Stop Signal task with the within-subjects factor of Task Number (i.e., 1 and 2) and the between-subjects factor of Randomized (i.e., Randomized or Baseline Only).

For any of the ANOVA where the assumption of sphericity was violated, as determined by a significant result on Mauchly's Test of Sphericity, the Greenhouse-Geisser correction was used for determining significance of ANOVA outcomes. For *t*-tests where Levene's Test for Equality of Variances was significant, *p*-values for equal variances not assumed were used. Analyses that used either correction are noted in the results.

Sample size justification. Consistent with the strong recommendations of Leon et al. (2011), this pilot study is designed to assess the feasibility and acceptability of the study procedures and the potential effects of cocaine-based inhibitory control training versus rectangles inhibitory control training on the outcomes of interest. Pilot studies are not, however, efficacy trials; thus, it is inappropriate to power them based on sample size requirements to detect statistically significant effects. I selected a sample size (n = 25) that

would allow me to realistically examine each aspect of the study design and future clinical trials will be designed to assess the efficacy of inhibitory control training. Because I have designed a parallel-arms, repeated-measures study with 9 assessments for each of 25 participants, I would be able to identify a "signal" between the training conditions (i.e., cocaine images or rectangles) in the trajectories of cocaine use (as measured by quantitative levels of benzoylecgonine) between the groups.

Results

Demographics

Within participants who were randomized, the groups did not differ significantly on any of the demographic characteristics or drug-use variables (cocaine images group n = 11, rectangles group n = 10; p's > 0.05; Table 6.3). Data from one participant in the cocaine images group was not included for days used marijuana in the last week and years since first marijuana use, because they reported never using marijuana. No significant differences were observed between participants who were randomized (n = 21) and those who dropped out after baseline testing (n = 4) for any demographics (p's > 0.05; Table 6.4). Equal variances were not assumed for days used cocaine in the last week and in the last month.

Attendance

There were no significant differences between the groups for total number of sessions attended, total number of sessions missed, number of Training Sessions attended, number of Follow-Up Sessions attended, number of Follow-Up Sessions missed, or whether or not the Final Session was attended (p's > 0.05; Figure 6.1).

Inhibitory Control Training task

ANOVA revealed a significant interaction of Session and Task Number for number of responses correctly withheld in response to no-go targets on the inhibitory control training task on Training Sessions (cocaine images group n = 10, rectangles group n = 9; $F_{2, 34}$ =

3.70, $p = 0.04$). In both groups the number of no-go targets where participants correctly withheld responses increased across Training Session 1 to reach a maximum of approximately 124 no-go responses withheld. Over Training Session 2 the number of correct no-go responses started at almost 125, but decreased slightly to 124. ANOVA revealed no significant main effects or interactions for number of correctly withheld responses to no-go targets on the inhibitory control training task during Follow-Up Sessions ($n = 8$ per group; $p > 0.05$).

ANOVA, using the Greenhouse-Geisser correction, revealed no significant main effects or interactions for the number of responses correctly executed in response to go targets on the inhibitory control training task on Training Sessions (cocaine images group $n = 10$, rectangles group $n = 9$; $p > 0.05$) or Follow-Up Sessions ($n = 8$ per group; $p > 0.05$).

Treatment Acceptability Questionnaire

There were no differences between the groups for ratings on any items on the Treatment Acceptability Questionnaire ($n = 9$ per group; $p > 0.05$; Figure 6.2). Equal variances were not assumed for overall satisfaction with the study, the acceptability of completing the training task three times on Training Sessions, and the acceptability of completing the training task during Follow-Up Sessions. Average ratings of overall satisfaction were approximately 82 for the cocaine images group and 85 for the rectangles group (all measures shown in Figure 6.2).

Urine Samples

ANOVA revealed no significant main effects or interactions for quantitative urine results ($n = 9$ per group; $p > 0.05$; Figure 6.3 top panel) or qualitative urine results ($n = 8$ per group; $p > 0.05$; Figure 6.3 bottom panel).

Timeline Follow-Back Calendar

ANOVA, using the Greenhouse-Geisser correction, revealed a significant main effect of Session for self-reported days used cocaine in the last month (n = 8 per group; $F_{7, 98}$ = 4.81, p = 0.03; Figure 6.4 middle panel). For both groups, participants generally reported using more days in the last month throughout the course of their participation. ANOVA, using the Greenhouse-Geisser correction, revealed no significant differences between the groups for self-reported days used cocaine in the last week or three months (n = 8 per group; p > 0.05; Figure 6.4 top and bottom panels, respectively).

Stop Signal task

ANOVA revealed a significant main effect of Task Number for stop signal reaction times (n = 9 per group; $F_{1, 16}$ = 6.83, p = 0.02; Figure 6.5 top panel). Stop signal reaction times decreased between the first and second time participants completed the Stop Signal task on Baseline and the Final Session, respectively. ANOVA also revealed a significant main effect of Task Number for inhibitory failures (n = 9 per group; $F_{1, 16}$ = 11.16, p = 0.004; Figure 6.5 bottom panel). The proportion of inhibitory failures decreased between the first and second time participants in the cocaine images group completed the Stop Signal task on Baseline and the Final Session, respectively. The proportion of inhibitory failures decreased between the first and second time participants in the rectangles group completed the Stop Signal task on Baseline only.

Barratt Impulsiveness Scale-11

ANOVA revealed no significant main effects or interactions for scores on the Barratt Impulsiveness Scale-11 (n = 9 per group; p > 0.05).

Hypothetical Discounting for Cocaine

ANOVA revealed no significant main effects or interactions for AUC or k parameters on the hypothetical discounting task (n = 9 per group; p > 0.05).

Visual Probe task

ANOVA revealed a significant main effect of Time on attentional bias scores on the Visual Probe task (n = 9 per group; $F_{1,16}$ = 8.55; Figure 6.6). Both groups displayed a decreased attentional bias toward cocaine images during the Final Session compared to Baseline.

Baseline Performance Between Participants Randomized and Participants Dropped Out

Participants who only completed baseline reported using cocaine on more days in the last month on the TLFB calendar compared to those who were randomized (t_{23} = 2.47, p = 0.02). No other differences were observed between participants who were randomized (n = 21) and those who only completed baseline (n = 4) for performance on the baseline tasks (p's > 0.05). On the Stop Signal Task, the ANOVA revealed a significant main effect of Task Number for both stop signal reaction time ($F_{1, 23}$ = 9.71, p = 0.01) and proportion of inhibitory failures ($F_{1, 23}$ = 17.87, p = 0.000), but the interaction or between-subjects factor of Group was not significant (p > 0.05). Both groups displayed decreased stop signal reaction times and proportion of inhibitory failures between the first and second times they completed the Stop Signal task. For the Visual Probe task, one person was excluded in the analysis from the baseline only group due to a medical condition making it impossible to track his eye movements with the eye tracker.

Discussion

This study was designed to evaluate the initial feasibility and acceptability of using more than one session of inhibitory control training with cocaine users as a potential adjunct for treating cocaine use disorder. Previous research has shown that one day of inhibitory control training to alcohol-related cues reduced alcohol consumption following training (Houben et al., 2010, 2011). In cocaine users, one day of acute inhibitory control training resulted in improved performance on the Stop Signal task (Alcorn et al., 2017).

Inhibitory control training is feasible to conduct with cocaine users. On average, participants attended seven of eight possible sessions. Four participants dropped out of the study after completing only the Baseline Session. Sixteen of the 21 participants randomized completed all sessions. Only three participants who were randomized did not attend the Final Session. Overall participants who were enrolled in the study attended the majority of, if not all, sessions from Baseline through the Final Session.

The other measure used to assess feasibility was performance on the Inhibitory Control Training task. Participants displayed a high level of accuracy in responses to go targets and no significant effects of session or training condition were observed. Participants also displayed accurate withholding of responses to no-go targets. An interaction of Session and Task Number was observed for inhibitory control training task performance on Training Sessions. Participants generally displayed improved performance across the first Training Session and performance slightly decreased across the second Training Session, but on average participants were still withholding responses to 124 no-go targets at the end of Training Session 2. No differences were observed between the training conditions. These data show that participants were engaged in performing the task accurately. Participants were paid a bonus based on their task performance, which would be expected to motivate participants to engage in the task and exhibit accurate performance. The maximum possible bonus for task performance was $1.65, however, and each mistake only subtracted $0.05 from the bonus. On Training Sessions, participants could earn up to $5.00 based on their task performance, which would be enough to purchase a fast food meal or most of a pack of cigarettes, but is not a substantial amount of money.

The procedures used in this study to assess inhibitory control training were generally acceptable to the participants who completed the study. Overall acceptability was rated as 82/100 for the cocaine images condition and 85/100 for the rectangles condition.

Participants in the cocaine images training condition rated the acceptability of the training task on both Training and Follow-Up Sessions as 78/100. Participants in the rectangles condition reported the acceptability of the Training task on Training and Follow-Up Sessions as 80/100 and 90/100, respectively. The lowest ratings were given for the acceptability of providing an observed urine sample (i.e., 55/100 and 75/100 for the cocaine images and rectangles groups, respectively), but no participants refused to provide an observed urine sample or decided not to participate when informed during consent that urine samples would be observed during the course of the study.

This study was also designed to provide preliminary data on the effect of inhibitory control training on cocaine use during the course of training. There were no significant changes in the amount of benzoylecgonine detected in the urine samples through quantitative analyses. In the cocaine images training group benzoylecgonine levels decreased between Sessions 1 and 2, but were increased at the Final Session. In the rectangles group benzoylecgonine levels initially increased then decreased. One limitation of the ELISA analysis used to detect benzoylecgonine levels is the analysis only provides an estimate of the amount of benzoylecgonine after approximately 500 ng/ml. Despite this limitation, these analyses provide a preliminary measure to indicate if the amount of cocaine metabolites present in the urine samples decreased, even if the qualitative measures still indicated cocaine was present in the urine samples. Analyses of qualitative urine results also showed no significant changes in the number of cocaine-positive urine samples provided by participants. Self-reported cocaine use was measured using TLFB calendars. Participants did report using cocaine on more days in the last month throughout the course of the study, however no significant increases were observed for days used in the last week or in the last three months. Between both groups, participants reported using cocaine on approximately 13 days in the last month at Baseline and this increased to approximately 15 days by the Final Session. While these data are discordant with a meta-

analysis showing inhibitory control training produced behavior change for alcohol and food consumption (Allom et al., 2016; Jones et al., 2016), it is important to note that the participants in the present study were not explicitly treatment seeking. The participants in the present study did not express a desire to stop or decrease their cocaine use and it is not expected that any treatment approach could produce a decrease in substance use if the individual is not interested in changing their behavior. One concern with showing individuals cocaine-related images in the inhibitory control training task is that cocaine images may increase craving and contribute to cocaine use. In a previous study, no differences were observed on a cocaine craving questionnaire administered prior to and following the completion of the ABBA task (t_{49} = 0.18, p = 0.86) with mean total craving scores of 2.7 out of 12 at both time points. Inhibitory control training may also be best used as an adjunct to other treatment approaches, such as pharmacotherapy or Cognitive Behavioral Therapy, rather than as a stand-alone treatment approach since the effect size of inhibitory control training to reduce health-risk behaviors was small (Allom et al., 2016).

On the Visual Probe task, attentional bias toward cocaine-related images decreased between Baseline and the Final Session for participants in both groups. Previous research from our laboratory demonstrated attentional bias toward cocaine-related images in cocaine users is stable over time (Marks et al., 2014a). In that study, the average period of time between assessments of attentional bias was 91.6 days, but the range was from 7 to 336 days. In the present study, the Final Session was approximately 2 weeks after Baseline, which would fall within the range assessed previously. One possible explanation for the reduction in attentional bias is inhibitory control training may be effective by devaluing the appetitive stimuli (reviewed in Allom et al., 2016), however this was not supported in another meta-analysis (Jones et al., 2016). If the change in attentional bias was simply due to a devaluation of cocaine-related stimuli, however, reductions in attentional bias should have only been observed in the cocaine images training condition

rather than both training conditions. Also of interest is the change in attention allocation was different between the groups (Figure 6.7). In the cocaine images training condition, participants spent a similar amount of time fixating on cocaine-related images between Baseline and the Final Session. On the Final Session, participants in the cocaine images condition displayed an increased fixation time to neutral images compared to on Baseline. In the rectangles training condition, fixation time to both cocaine-related and neutral images decreased from Baseline to the Final Session, but the decrease was greater for cocaine-related images. When attentional bias was compared between cocaine users and controls, fixation time to cocaine images was not different between the groups, but cocaine users spent less time fixating on neutral images compared to controls. While controls fixated on both cocaine-related and neutral images for an equal amount of time, cocaine users spent a disproportionate amount of time fixating on cocaine images. This difference may be due to non-drug-images may be less salient to cocaine users (Marks et al., 2014b). Increased time fixating on neutral images is more similar to performance observed previously in non-drug-users (Marks et al., 2014b) and future research should investigate how this change in attentional allocation may relate to a change in drug taking behavior.

Inhibitory control training did not produce a change in self-reported impulsivity or inhibitory control between Baseline and the Final Session. No changes were observed for the total score on the BIS, however this is a measure of trait impulsivity (Patton et al., 1995) and as such these scores would be expected to remain relatively stable over time. For the Stop Signal task stop signal reaction time, which is an estimate of the amount of time to inhibit a response (Logan, 1994), decreased in both groups between the first and second time participants completed the task during Baseline and Final Sessions, respectively. Both groups displayed improvements in the proportion of inhibitory failures between the first and second time participants completed the task during the Baseline session, but only the cocaine images condition displayed improvements during the Final

Session. These improvements are likely due to a practice effect, since participants complete the task twice, one immediately after the other, on each session. These results are discordant with a recent study from our laboratory showing that one day of acute inhibitory control training improved both stop signal reaction time and proportion of inhibitory failures on the Stop Signal task, regardless of training condition (Alcorn et al., 2017). In a meta-analysis of behavior change following inhibitory control training, however, it was suggested that inhibitory control training using tasks modeled after Go/No-Go tasks may produce changes in automatic response inhibition, which translated to improvements in health behaviors. Inhibitory control training tasks similar to the Stop Signal task, on the other hand, may be better at producing changes in controlled response inhibition (e.g., Stroop performance), but training with these tasks was not associated with changes in behavior (Allom et al., 2016). The results from this meta-analysis suggest that change in behavioral outcomes does not require changes to be observed on other measures of inhibitory control, which would mean that the absence of improvement across sessions on the Stop Signal task should not be viewed as a signal that inhibitory control training in cocaine users would not be effective in reducing cocaine use in treatment seekers.

This study has a few limitations worth noting that should be used to direct the development and design of future studies. First, the participants enrolled in the present study did not report seeking treatment to reduce or stop their use of cocaine. This limits the ability of the procedures used to produce a change in cocaine use, but the primary aim of the study was to determine initial feasibility and acceptability of inhibitory control training. Future pilot clinical trials should be conducted with participants seeking treatment to stop or reduce their cocaine use to determine the initial efficacy of inhibitory control training as a treatment approach or adjunct to other treatment approaches. Second, inhibitory control was not assessed during the Baseline Session using the ABBA or Cued Go/No-Go task, so it is not known if the participants enrolled in the present study displayed

poor inhibitory control. If the participants did not display impaired inhibitory control at Baseline, then there would be no room to improve inhibitory performance using the Inhibitory Control Training task. Future studies should assess inhibitory control performance at Baseline and only enroll participants who display impaired inhibitory control, thus have room to improve their performance. Third, this study did not assess cocaine use beyond the training, so the long-term effect of training on cocaine use cannot be determined. Fourth, the sample size was small and some analyses only included a sub-sample of the participants due to missed sessions. A larger sample would have been more adequately powered to detect statistically significant differences, however it is apparent that participants attended sessions, performed the training task accurately, and rated the overall study as acceptable.

Overall this study demonstrates that inhibitory control training is feasible for use with cocaine users and the procedures used were acceptable to the participants. Following inhibitory control training participants displayed decreased attentional bias toward cocaine-related images on the Visual Probe task, but the nature of the change in attentional allocation was different between the training conditions. In the cocaine images training condition, participants displayed an increase in fixation time on neutral images similar to the pattern of attention displayed by non-drug-using controls in a previous study (Marks et al., 2014b). These findings suggest future research is warranted assessing inhibitory control training in a sample of treatment seeking cocaine users to determine if inhibitory control training could improve treatment outcomes when used in combination with other treatment approaches (e.g., cognitive behavioral therapy or pharmacotherapy). Future studies should also continue to assess changes in other measures of cognitive functioning (e.g., attentional bias) to better understand how inhibitory control training influences other cognitive domains.

Table 6.1

Experimental Procedures for Experiment 5

Day	Activities Completed
1	Screening packet, SCID, Urine Screened for Drugs of Abuse
2	Stop Signal Task, TLFB, Hypothetical Discounting for Cocaine, BIS-11, Visual Probe with Eye Tracking, Urine Screened for Drugs of Abuse
3	Training Day 1, TLFB, Urine Screened for Drugs of Abuse
5	Follow-Up 1, TLFB, Urine Screened for Drugs of Abuse
7	Follow-Up 2, TLFB, Urine Screened for Drugs of Abuse
10	Training Day 2, TLFB, Urine Screened for Drugs of Abuse
12	Follow-Up 3, TLFB, Urine Screened for Drugs of Abuse
14	Follow-Up 4, TLFB, Urine Screened for Drugs of Abuse
17	Stop Signal Task, TLFB, Hypothetical Discounting for Cocaine, BIS-11, Visual Probe with Eye Tracking, Urine Screened for Drugs of Abuse, Final Payment

Table 6.2

Daily Activities for Inhibitory Control Training Sessions

Time	Activities Completed
0800	Participant arrives to the LHBP, field sobriety test
0830	Training task
0900	Break, light meal served, follow-up, TLFB, Urine Screened for Drugs of Abuse
1000	Training task
1015	Break
1115	Training task
1130	Payment, release

Table 6.3

Demographics of the Cocaine Images (*n* = 11) and Rectangles (*n* = 10) training conditions (Mean [SEM])

Measure	Cocaine Images	Rectangles	Statistical Value
Age [a]	42.0 (2.8)	42.2 (1.7)	0.06
Sex (# male) [b]	7	8	0.69
Race [b]			1.49
African American	10	7	
Caucasian	1	3	
Years of Education [a]	11.8 (0.4)	12.8 (0.6)	1.37
Alcohol [a]			
Drinks per Week	20.2 (9.4)	22.4 (5.2)	0.20
Drinks per Month	83.3 (37.3)	94.1 (21.6)	0.24
Cocaine [a]			
Days per Week	3.0 (0.6)	3.7 (0.6)	0.81
Days per Month	14.0 (2.9)	14.0 (2.3)	0.00
Years Used	19.0 (2.7)	18.9 (2.3)	0.04
Cigarettes per Day [a]	7.9 (2.1)	9.3 (2.2)	0.44
Marijuana [a]			
Days per Month (*n* = 20)	6.8 (3.3)	10.7 (3.4)	0.83
Years Used (*n* = 20)	23.7 (3.2)	27.7 (3.0)	0.91

[a] Mean (SEM) and *t*-values reported

[b] Sample size and chi square values reported

Table 6.4

Demographics of the Participants Randomized (*n* = 21) and Participants Who Only Completed Baseline (*n* = 4; Mean [SEM])

Measure	Randomized	Baseline Only	Statistical Value
Age [a]	42.1 (1.6)	39.5 (2.8)	0.65
Sex (# male) [b]	15	2	0.71
Race [b]			0.07
African American	17	3	
Caucasian	4	1	
Years of Education [a]	12.3 (0.4)	12.8 (0.5)	0.53
Alcohol [a]			
Drinks per Week	21.3 (5.4)	25.7 (10.5)	0.33
Drinks per Month	88.4 (21.6)	109.3 (44.9)	0.39
Cocaine [a]			
Days per Week	3.3 (0.4)	3.0 (0.4)	0.56
Days per Month	14.0 (1.8)	12.0 (1.6)	0.82
Years Used	18.9 (1.7)	19.0 (3.8)	0.02
Cigarettes per Day [a]	8.5 (1.5)	15.6 (3.6)	1.89
Marijuana [a]			
Days per Month (*n* = 24)	8.8 (2.3)	15.5 (6.1)	1.16
Years Used (*n* = 24)	25.7 (2.2)	26.0 (3.7)	0.06

[a] Mean (SEM) and *t*-values reported

[b] Sample size and chi square values reported

Figure 6.1

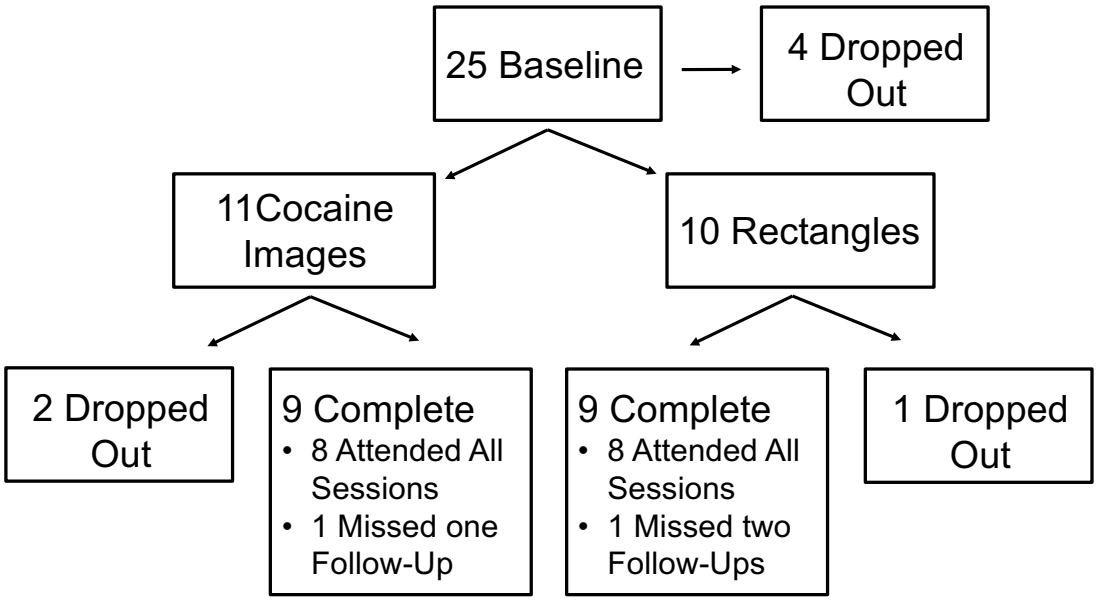

Figure 6.1. Attendance for each group throughout the study.

Figure 6.2

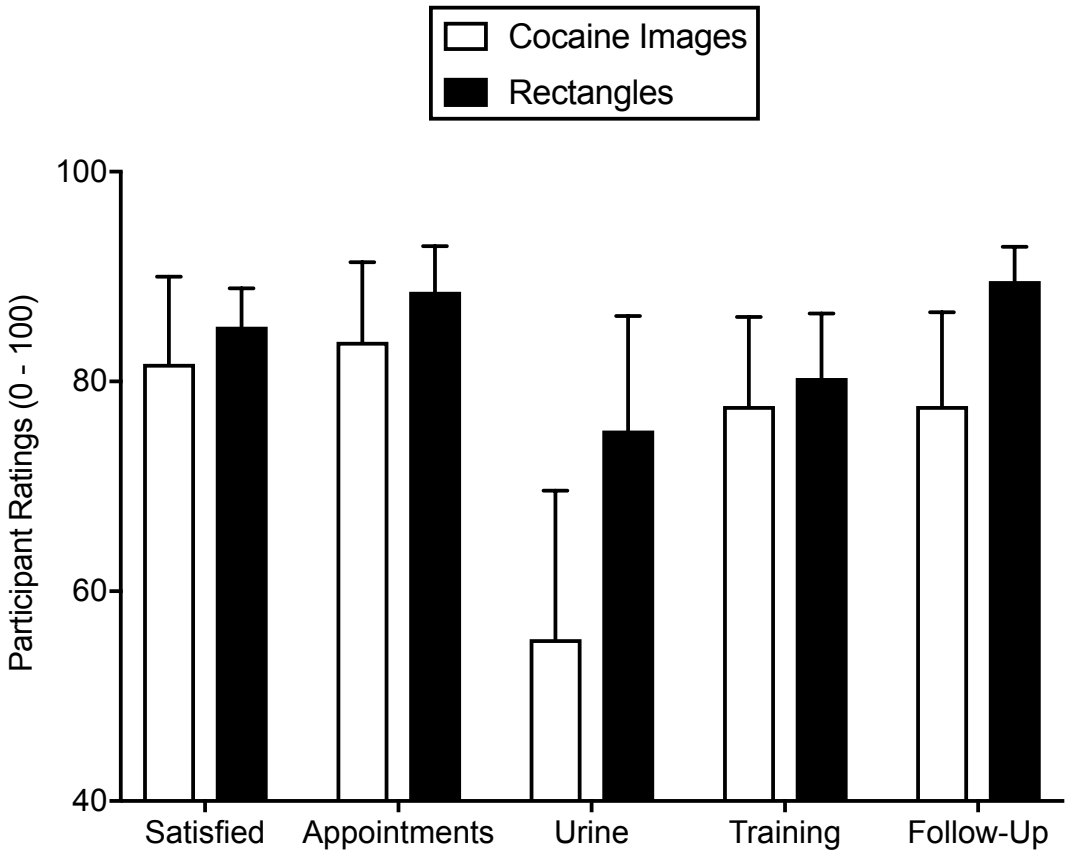

Figure 6.2. Responses on the Treatment Acceptability Questionnaire completed on the Final Session (*n* = 9 per group). Solid white bars represent data from the cocaine images training condition and solid black bars represent data from the rectangles training condition.

Figure 6.3

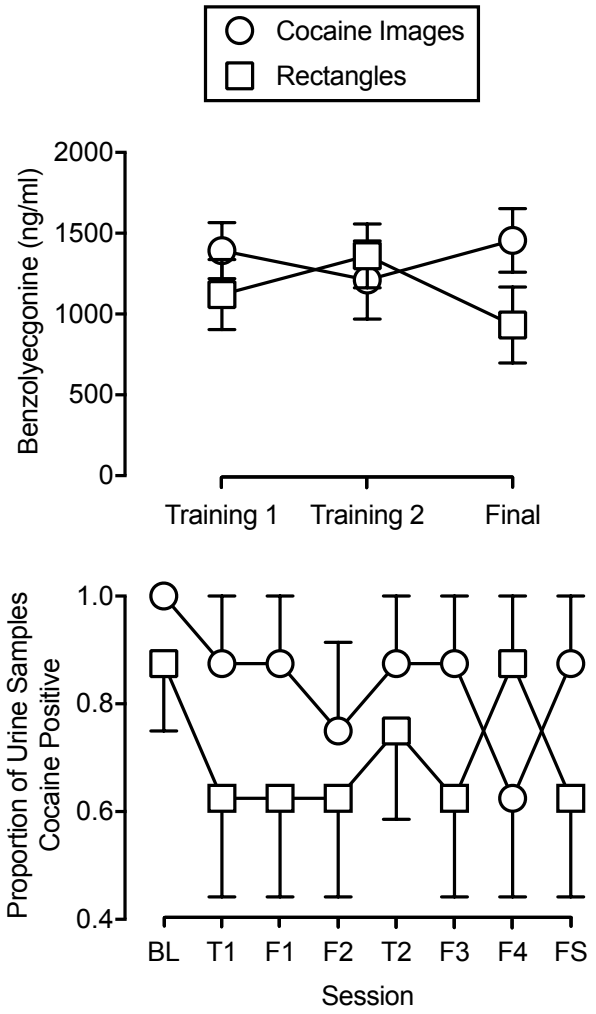

Figure 6.3. Quantitative (top panel) and qualitative (bottom panel) urine results from Experiment 5. In both panels, circles represent data from participants assigned to the cocaine images training condition and squares represent data from participants in the rectangles training condition. Quantitative results for the amount of benzoylecgonine present in the urine samples on Training 1, Training 2, and Final session are shown in the top panel (n = 9 per group). Proportion of samples positive for cocaine based on qualitative analyses on each session is shown in the bottom panel (n = 8 per group). Sessions included Baseline (BL), Training 1 (T1), Follow-Up 1 (F1), Follow-Up 2 (F2), Training 2 (T2), Follow-Up 3 (F3), Follow-Up 4 (F4), and Final Session (FS).

Figure 6.4

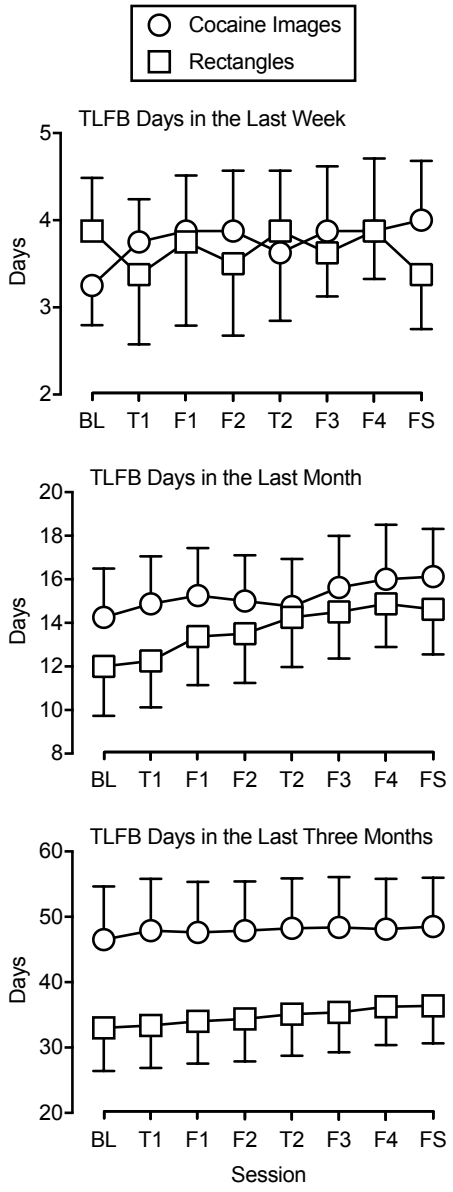

Figure 6.4. Self-reported days used cocaine in the last week (top panel), month (middle panel), and three-months (bottom panel) on the Timeline Follow-Back calendar across sessions. Sessions included Baseline (BL), Training 1 (T1), Follow-Up 1 (F1), Follow-Up 2 (F2), Training 2 (T2), Follow-Up 3 (F3), Follow-Up 4 (F4), and Final Session (FS). Circles represent data from the cocaine images training condition (*n* = 8) and squares represent data from the rectangles training condition (*n* = 8).

Figure 6.5

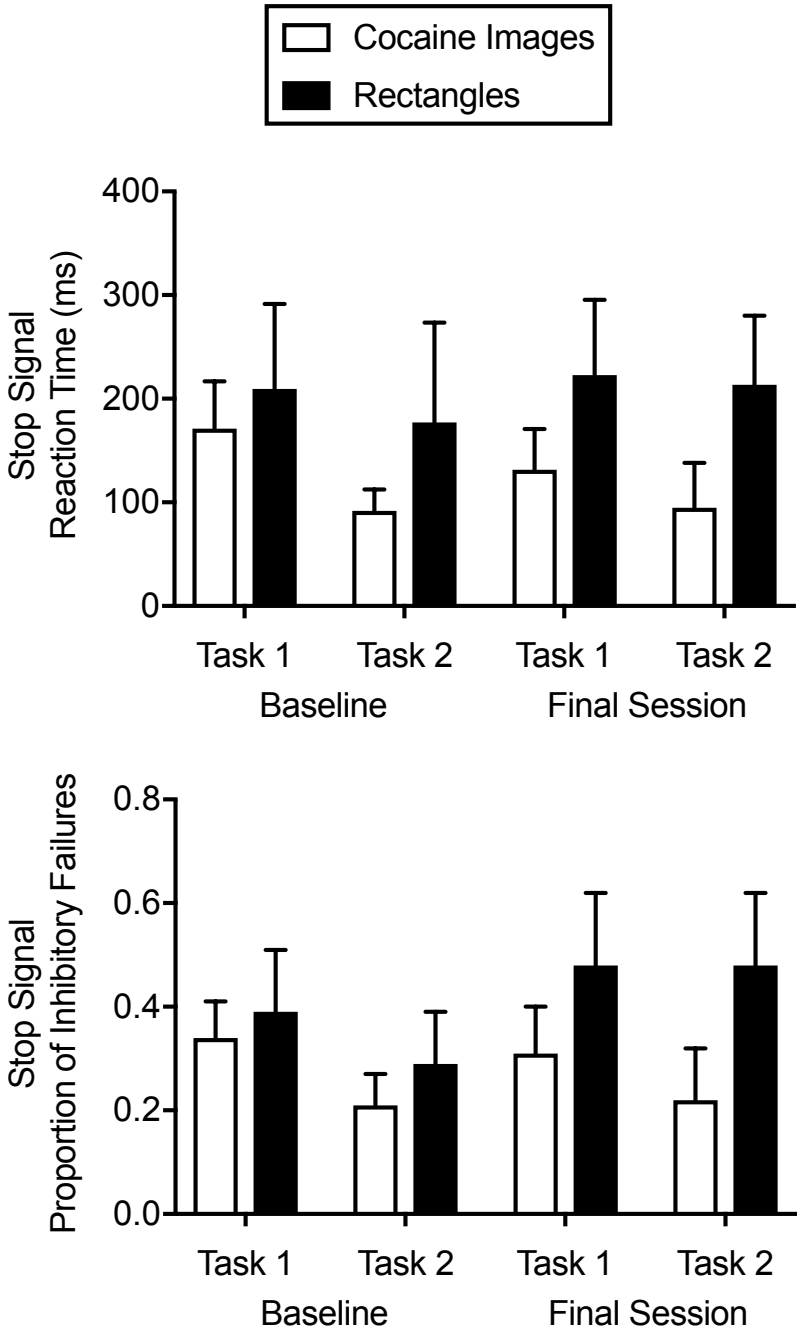

Figure 6.5. Stop signal reaction times (ms; top panel) and proportion of inhibitory failures during stop signal trials (bottom panel) from the Stop Signal task. Solid white bars represent data from the cocaine images training condition (*n* = 9) and solid black bars represent data from the rectangles training condition (*n* = 9).

Figure 6.6

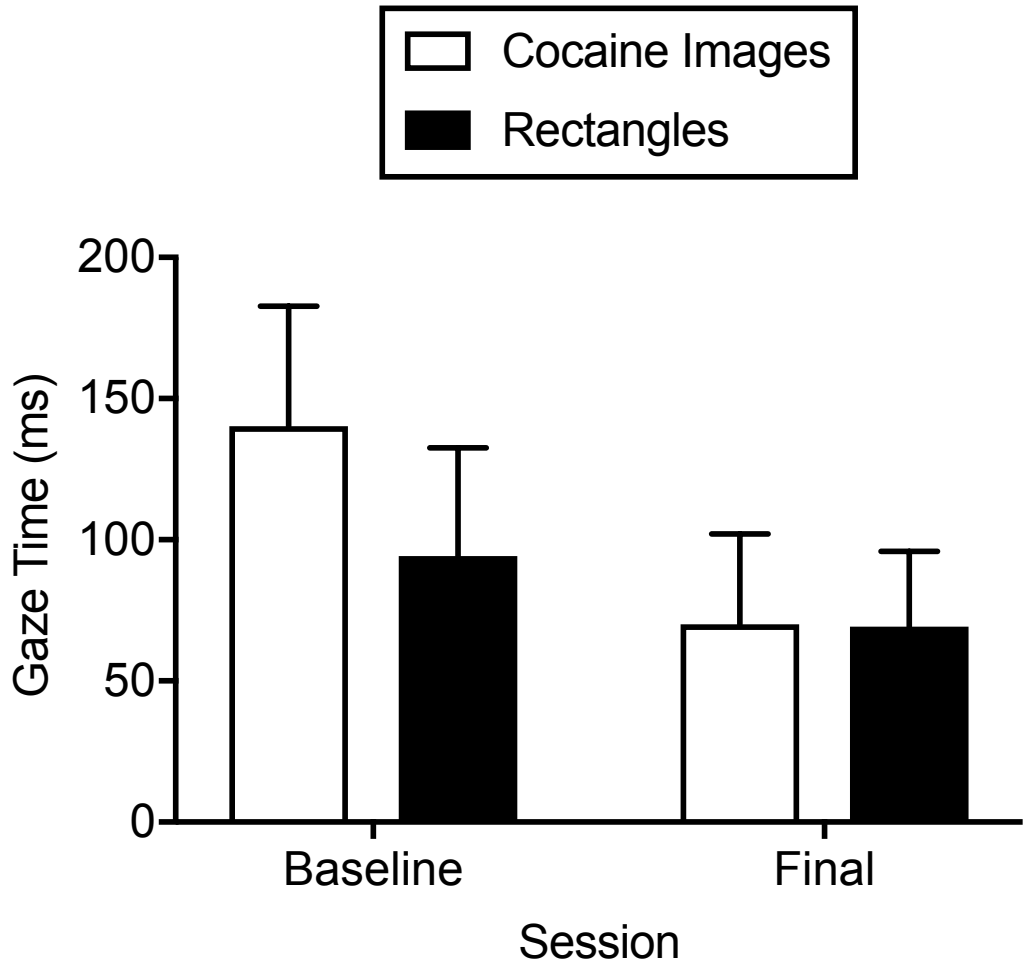

Figure 6.6. Attentional bias scores (i.e., fixation time in milliseconds on cocaine-related images minus fixation time in milliseconds on neutral images) from the Visual Probe task with eye-tracking technology measured at Baseline and on the Final Session. Solid white bars represent data from the cocaine images training condition (*n* = 9) and solid black bars represent data from the rectangles training condition (*n* = 9).

Figure 6.7

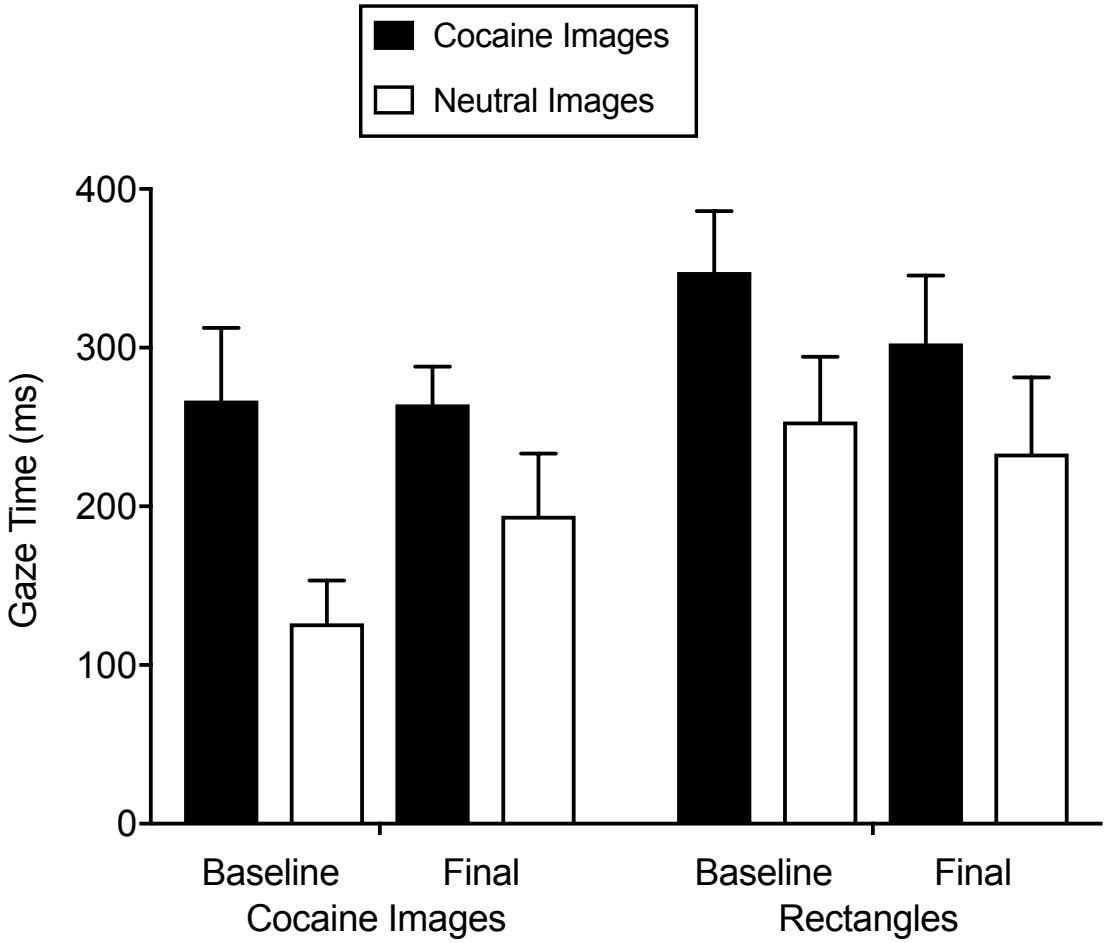

Figure 6.6. Fixation time in milliseconds to cocaine-related (i.e., solid black bars) and neutral images (i.e., solid white bars) on the Visual Probe task with eye-tracking technology. The left four bars are data from participants in the cocaine images training condition (n = 9) and the right four bars are data from participants in the rectangles training condition (n = 9). Within each condition, the left two bars are measurements from the Baseline Session and the right two bars are measurements from the Final Session.

Chapter 7

GENERAL DISCUSSION

Summary of Findings

This dissertation reports a programmatic series of experiments designed to assess the influence of cocaine-related images on inhibitory control in cocaine users. The first aim was to demonstrate that cocaine users display impaired inhibitory control following cocaine images compared to neutral images on the Attentional Bias-Behavioral Activation (ABBA) task. Experiment 1 was the first to demonstrate that cocaine users display impaired inhibitory control when they are prepared to respond following cocaine-related cues compared to neutral cues on the ABBA task. Studies 1 and 2 of Experiment 2 and Experiment 4 systematically replicated these findings by also showing an increase in the proportion of inhibitory failures following cocaine-related cues compared to neutral cues on the ABBA task. Experiment 4 extended these findings to address the second aim and demonstrate that the impairment of inhibitory control is most significant when cocaine cues are displayed for a short period of time (i.e., 100 and 200 ms) compared to a longer cue presentation (i.e., 300, 400, and 500 ms). These experiments also consistently demonstrated that there are no differences in the reaction times to respond to go targets following cocaine-related and neutral cues, which indicates that the increased proportion of inhibitory failures observed in the cocaine go condition of the ABBA task is not due to a speed accuracy trade-off.

The third aim was to demonstrate that impaired inhibitory control following cocaine images on the ABBA task is specific to cocaine users. In Experiment 3 cocaine users and controls who reported no use of cocaine in the last year and an overall limited history of cocaine use completed the cocaine go condition of the ABBA task, the Cued Go/No-Go task, and the all neutral condition of the ABBA task. No differences were observed between cocaine users and controls for any of the inhibitory control tasks, which failed to

support my hypothesis and is discordant with previous research showing cocaine users display impaired inhibitory control on behavioral tasks compared to controls (Colzato et al., 2007; Ersche et al., 2011, 2012; Fillmore and Rush, 2002; Lane et al., 2007; Verdejo-García et al., 2007; Verdejo-García and Pérez-García, 2007; Fernández-Serrano et al., 2012). Controls displayed significantly faster reaction times on all three tasks compared to cocaine users, which suggests that the increased proportion of inhibitory failures observed may be due to an overemphasis on fast responses, rather than balancing responding as quickly as possible while still responding accurately.

The fourth aim was to demonstrate the feasibility and acceptability of inhibitory control training to cocaine-related stimuli as a novel treatment approach for cocaine use disorder. In Experiment 5, cocaine users completed two weeks of inhibitory control training to either cocaine images or rectangles. Inhibitory control training appeared to be feasible to use with cocaine users, as demonstrated by participants attending nearly all sessions for those who completed through the Final Session and very few participants dropped out of the study. Participants also performed the Inhibitory Control Training task as it was designed with accurate responses to go targets and responses withheld to no-go targets. Participants in both the cocaine images and rectangles training conditions reported that the procedures used in the study were overall acceptable.

This dissertation presents series of experiments to first show and further replicate the finding that cocaine-related images impair inhibitory control in cocaine users on the ABBA task. Consistently these studies show an increased proportion of inhibitory failures following cocaine-related compared to neutral cues, but no differences in reaction times following either cue type (Pike et al., 2013, 2015). Increased levels of impulsivity and impaired inhibitory control are associated with poor treatment outcomes, including shorter periods of retention in treatment (Brewer et al., 2008; Carpenter et al., 2006; Moeller et al., 2001; Patkar et al., 2004; Stevens et al., 2015; Streeter et al., 2008; Winhusen et al.,

2013). The findings from ABBA performance taken with the results of studies of inhibitory control training with drinkers (Houben et al., 2010, 2011) lead to the development of a novel treatment approach of using inhibitory control training to improve treatment outcomes in cocaine users. Acute inhibitory control training with cocaine users improved Stop Signal task performance (Alcorn et al., 2017). In Experiment 5, however, inhibitory control training conducted over multiple sessions did not produce changes in Stop Signal task performance between Baseline and the Final Session, which is discordant with the result observed following acute inhibitory control training (Alcorn et al., 2017). Inhibitory control training conducted over multiple sessions did produce a decrease in attentional bias toward cocaine related cues and future research should continue to investigate how inhibitory control training and attentional bias are related and if changes in attentional bias would also result in improved treatment outcomes. Further research is needed to fully understand the convergent validity between inhibitory control following cocaine cues and treatment outcomes and how that association can lead to improved treatment outcomes.

Directions for Future Research

Future research using the ABBA task to assess the influence of cocaine-related images on inhibitory control in cocaine users can be taken in a number of directions to address gaps in the literature. Below I will address three directions for future research.

Parametric Studies on the ABBA task

Further parametric studies are needed to better understand how cocaine-related images impair inhibitory control on the ABBA task. Future studies should continue to work toward developing a within-subjects methodology for administering the ABBA task. Studies 1 and 2 in Experiment 2 attempted to design a within-subjects methodology, but both procedures had limitations. The all neutral condition of the ABBA task failed substitute for the neutral go condition of the ABBA task, since it would be expected that a control inhibitory control task should be produce significantly fewer inhibitory failures compared

to the cocaine go condition of the ABBA task. The control inhibitory control task should also produce a similar proportion of inhibitory failures as the neutral go condition of the ABBA task. In Study 1, participants displayed a significantly lower proportion of inhibitory failures on the Cued Go/No-Go task compared to the cocaine go condition of the ABBA task and there were no differences compared to the neutral go condition of the ABBA task. The limitation of this study was that participants responded faster on the Cued Go/No-Go task compared to both conditions of the ABBA task and when analyses were conducted with days of cocaine use in the last week as a covariate these differences were statistically significant. I am not convinced that this limitation is significant enough to invalidate the Cued Go/No-Go task as a control task for assessing the influence of cocaine-related cues on inhibitory control. In the ABBA task reaction time is primarily used to determine if a speed accuracy trade-off contributed to an increase in inhibitory failures in the cocaine go condition. For a speed accuracy trade-off to be possible participants should display significantly faster reaction times in the condition where they also display an increase in inhibitory failures. This is the opposite situation to what is observed between the ABBA and Cued Go/No-Go tasks. While significantly faster reaction times limit the ability to determine if a speed accuracy trade-off occurred, a number of studies have replicated the finding that cocaine-related images impair inhibitory control in cocaine users (Pike et al., 2013, 2015) and comparisons could be made by assessing change from baseline. Future studies should be conducted with a larger sample to determine if the Cued Go/No-Go task continued to produce a proportion of inhibitory failures that is lower than the cocaine go condition and similar to the neutral go condition without reaction time differences.

Throughout the conduct of the experiments discussed in this dissertation and other studies that have used the ABBA task with cocaine users over 100 unique individuals have completed the ABBA task. Many of these individuals have completed the task more than once, however the test-retest reliability of the ABBA task has yet to be determined either

with cocaine users or in other groups (e.g., alcohol drinkers). Understanding whether or not the results observed on the ABBA task are reliable over time would direct how the ABBA task could be used in the future either for assessing or predicting treatment outcomes or testing the utility of pharmacologic manipulations to improve inhibitory control in the presence of drug-related images.

Implications Related to Treatment Outcomes

First, future research should continue to investigate inhibitory control training as a method to improve treatment outcomes for individuals with cocaine use disorders. Inhibitory control training appears to be feasible and acceptable for use with cocaine users, as shown in Experiment 5, and pilot clinical trials should be conducted to determine the feasibility and initial efficacy of inhibitory control training with treatment seekers. The cocaine images Inhibitory Control Training task that was tested in Experiment 5 is a modified version of the ABBA task and recent meta-analyses of inhibitory control training for reducing appetitive behaviors both support the use of modified Go/No-Go tasks for reducing health-risk behaviors (Allom et al., 2016; Jones et al., 2016). One of these meta-analyses also demonstrated that accuracy in inhibitions toward appetitive cues predict the effect size of the inhibitory control training (Jones et al., 2016) and the data from Experiment 5 show that the participants displayed highly accurate responding on the cocaine images Inhibitory Control Training task. Pilot clinical trials should be designed to administer inhibitory control training as an adjunct to another treatment approach (e.g., pharmacotherapy or Cognitive Behavioral Therapy), since in some studies the overall effect size of inhibitory control training alone on behavior change is modest (Allom et al., 2016). These future clinical trials should also include pre- and post-training assessments of cognitive performance to better understand how inhibitory control training changes behavior, including other measures of inhibitory control, over time.

Second, research should be conducted to determine if inhibitory control performance following cocaine-related images predicts treatment outcomes (e.g., treatment retention). Performance on other measures of inhibitory control and self-reported levels of impulsivity are related to negative treatment outcomes (e.g., higher levels of impulsivity related to poor treatment retention; Brewer et al., 2008; Carpenter et al., 2006; Moeller et al., 2001; Patkar et al., 2004; Stevens et al., 2015; Streeter et al., 2008; Winhusen et al., 2013). If performance on the ABBA task is also related to poor treatment outcomes, that would allow clinicians identify individuals who would benefit from additional services to improve treatment outcomes. The ABBA task is easy to administer on a PC laptop and could be adapted for use with a smart phone, tablet, or online, making it an accessible tool for treatment programs. Interpretation of the results does not require any specialized equipment or training, as the program provides results in a Microsoft Excel file that are straightforward to understand.

Influence of Pharmacologic Manipulations on ABBA Performance

The influence of cocaine administration on inhibitory control performance following cocaine-related cues is yet to be determined. In drinkers, alcohol administration further increased the proportion of inhibitory failures following alcohol related images on the ABBA task compared to baseline performance (Weafer and Fillmore, 2015). Cocaine administration reduced the proportion of inhibitory failures on the Cued Go/No-Go task in cocaine users (Fillmore et al., 2005; 2006). In the first of these studies, cocaine also reduced cue dependency, which is the difference in the proportion of inhibitory failures following invalid (i.e., go) cues minus the proportion of inhibitory failures following valid (i.e., no-go cues; Fillmore et al., 2005). Lower cue dependency scores would indicate that participants are less reliant on cues to signal whether or not a response should be executed or withheld. Cocaine administration also reduced stop signal reaction times on the Stop Signal task (Fillmore et al., 2006). At lower doses, however, cocaine decreased

the probability of inhibiting responses following stop signals in cocaine users and had no effect on stop signal reaction time (Fillmore et al., 2002). When the dose effects of cocaine on performance was assessed by task, cocaine produced linear dose effects on performance on the Cued Go/No-Go task. Cocaine produced quadratic dose effects on the Stop Signal task, such that 100 and 200 mg cocaine reduced stop signal reaction times, but stop signal reaction times following 300 mg were not different from placebo (Fillmore et al., 2006). These findings suggest that cocaine administration should produce dose dependent decreases in inhibitory failures on the ABBA task, since the ABBA is similar to the Cued Go/No-Go task, and failure rates following cocaine related images should be similar to those following neutral images due to reduced cue dependency. Understanding the effect of cocaine on inhibitory control following cocaine-related images could provide a better understanding of the role of inhibitory control in relapse and the continued use of substances. If cocaine improves inhibitory control on the ABBA task, it may be that inhibitory control is involved in the initial lapse to use rather than continuing to use following the initial lapse.

Overall Conclusion

Despite decades of research directed toward identifying a universally effective treatment for cocaine use disorder, one has yet to be identified. The experiments presented in this dissertation take a programmatic approach to first demonstrate that inhibitory control in cocaine users is impaired following cocaine-related images and second use those findings to develop an innovative Inhibitory Control Training task as a novel treatment approach for cocaine use disorder. Attempting to improve cognitive control in substance users is a growing treatment approach and several researchers have identified cognitive performance as a potential target to improve treatment outcomes (Copersino, 2017; Sofuoglu, 2010; Sofuoglu et al., 2013, 2016; Vocci, 2008). The results of the experiments reviewed in this dissertation are consistent with current interests in

cognitive performance in substance use disorders. These findings support continued research on the influence of cocaine-related images on inhibitory control in cocaine users, how this performance relates to treatment outcomes, and the use of inhibitory control training to improve outcomes in treatment for cocaine use disorder.

REFERENCES

Alcorn III J. L., Pike E., Stoops W. W., Lile J. A., Rush C. R. A pilot investigation of acute inhibitory control training in cocaine users. *Drug Alcohol Depend* 2017; **174**: 145-149.

Allom V, Mullan B., Hagger M. Does inhibitory control training improve health behaviour? A meta-analysis. *Health Psychology Review* 2016; **10**: 168-186.

Beck A. T., Ward C. H., Mendelson M., Mock J., Erbaugh J. An inventory for measuring depression. *Archives of General Psychiatry* 1961; **4**: 561-571.

Beck A. T., Steer R.A., Garbin M.G. Psychometric properties of the Beck Depression Inventory: Twenty-five years of evaluation. *Clinical Psychology Review* 1988; **8**: 77-100.

Benoit R. G., Gilbert S. J., Burgess P. W. A neural mechanism mediating the imact of episodic prospection on farsighted decisions. *The Journal of Neuroscience* 2011; **31**: 6771-6779.

Brewer J. A., Worhunsky P. D., Carroll K. M., Rounsaville B. J., Potenza M. N. Pretreatment brain activation during Stroop task is associated with outcomes in cocaine-dependent patients. *Biological Psychiatry* 2008; **64**: 998-1004.

Carpenter K. M., Schreiber E., Church S., McDowell D. Drug Stroop performance: Relationships with primary substance of use and treatment outcome in a drug-dependent outpatient sample. *Addictive Behaviors* 2006; **31**: 174-181.

Cartwright W.S. Cocaine medications, cocaine consumption and societal costs. *Pharmacoeconomics* 2000; **18**: 405-413.

Center for Behavioral Health Statistics and Quality. 2015 National Survey on Drug Use and Health: Detailed Tables. Substance Abuse and Mental Health Services Administration, Rockville, MD; 2016.

Coffey S. F., Gudleski G. D., Saladin M. E., Brady K. N. Impulsivity and rapid discounting of delayed hypothetical rewards in cocaine-dependent individuals. *Experimental and Clinical Psychopharmacology* 2003; **11**: 18-25.

Colzato L. S., van den Wildenberg W. P. M., Hommel B. Impaired inhibitory control in recreational cocaine users. *PLoS One* 2007; **11**: 1-5.

Copersino M. L. Cognitive mechanisms and therapeutic targets of addiction. *Current Opinion in Behavioral Sciences* 2017; **13**: 91-98.

Crean J. P., de Wit H., Richards J. B. Reward discounting as a measure of impulsive behavior in a psychiatric outpatient program. *Experimental and Clinical Psychopharmacology* 2000; **8**: 155-162.

de Wit H., Richards J. B. Dual determinants of drug use in humans: Reward and impulsivity. In: *Motivational Factors in the Etiology of Drug Abuse. Volume 50 of the Nebraska Symposium on Motivation*. Lincoln, NE: University of Nebraska Press; 2004, p. 19-55.

Donk M., Soesman L. Salience is only briefly represented: Evidence from probe-detection performance. *J Exp Psychol Hum Percept Perform* 2010; **36**: 286-302.

Ersche K. D., Barnes A., Jones P. S., Morein-Zamir S., Robbins T. W., Bullmore E. T. Abnormal structure of frontostriatal brain systems is associated with aspects of impulsivity and compulsivity in cocaine dependence. *Brain* 2011; **134**: 2013-2024.

Ersche K. D., Jones P. S., Williams G. B., Turton A. J., Robbins T. W., Bullmore E. T. Abnormal brain structure implicated in stimulant drug addiction. *Science* 2012; **335**: 601-604.

Fabre-Thorpe M., Delorme A., Marlot C., Thorpe S. A limit to the speed of processing in ultra-rapid visual categorization of novel natural scenes. *Journal of Cognitive Neuroscience* 2001; **13**: 171-180.

Fernández-Serrano M. J., Perales J. C., Moreno-López L., Pérez-García M., Verdejo-García A. Neuropsychological profiling of impulsivity and compulsivity in cocaine dependent individuals. *Psychopharmacology* 2012; **219**: 673-683.

Field M., Cox W. M. Attentional bias in addictive behaviors: A review of its development, causes, and consequences. *Drug and Alcohol Dependence* 2008; **97**: 1-20.

Fillmore M. T. Drug abuse as a problem of impaired control: Current approaches and findings. *Behavioral and Cognitive Neuroscience Reviews* 2003; **2**: 1-19.

Fillmore M. T., Rush C. R. Impaired inhibitory control of behavior in chronic cocaine users. *Drug and Alcohol Dependence* 2002; **66**: 265-273.

Fillmore M. T., Rush C. R., Hays L. Acute effects of oral cocaine on inhibitory control of behavior in humans. *Drug and Alcohol Dependence* 2002; **67**: 157-167.

Fillmore M. T., Rush C. R., Hays L. Cocaine improves inhibitory control in a human model of response conflict. *Experimental and Clinical Psychopharmacology* 2005; **13**: 327-335.

Fillmore M. T., Rush C. R., Hays L. Acute effects of cocaine in two models of inhibitory control: Implications of non-linear dose effects. *Addiction* 2006; **101**: 1323-1332.

Fillmore M. T., Weafer J. Behavioral inhibition and addiction. In: *The Wiley-Blackwell Handbook of Addiction Psychopharmacology, First Edition*. Hoboken, NJ: Johen Wiley & Sons, Ltd; 2013, p. 135-164.

Goldstein R. Z., Volkow N. D. Drug addiction and its underlying neurobiological basis: Neuroimaging evidence for the involvement of the frontal cortex. *The American Journal of Psychiatry* 2002; **159**: 1642-1652.

Grant J. E., Chamberlain S. R. Impulsive action and impulsive choice across substance and behavioral addictions: Cause or consequence? *Addictive Behaviors* 2014; **39**: 1632-1639.

Hamilton K. R., Littlefield A. K., Anastasio N. C., Cunningham K. A., Fink L. H., Wing V. C., Mathias C. W., Lane S. D., Schütz C. D., Swann A. C., Lejuez C. W., Clark L., Moeller F. G., Potenza M. N. Rapid-response impulsivity: Definitions, measurement issues, and clinical implications. *Personality Disorders: Theory, Research, and Treatment* 2015a; **6**: 168-181.

Hamilton K. R., Mitchell M. R., Wing V. C., Balodia I. M., Fillmore M., Lane S. D., Lejuez C. W., Littlefield A. K., Luijten M., Mathias C. W., Mitchell S. H., Napier T. C., Reynolds B., Schütz C. G., Setlow B., Sher K. J., Swann A. C., Tedford S. E., White M. J., Winstanley C. A., Yi R., Potenza M. N., Moeller F. G. Choice impulsivity: Definitions, measurement issues, and clinical implications. *Personality Disorders: Theory, Research, and Treatment* 2015b; **6**: 182-198.

Heatherton T. F., Kozlowski L. T., Frecker R. C., Fagerstrom K. The Fagerstrom test for nicotine dependence: A revision of the Fagerstrom Tolerance Questionnaire. *British Journal of Addiction* 1991; **86**: 1119-1127.

Heil S. H., Johnson M. W., Higgins S. T., Bickel W. K. Delay discounting in currently using and currently abstaining cocaine-dependent outpatients and non-drug-using matched controls. *Addictive Behaviors* 2006; **31**: 1290-1294.

Houben K., Havermans R.C., Wiers R.W. Learning to dislike alcohol: Conditioning negative implicit attitudes toward alcohol and its effect on drinking behavior. *Psychopharmacology* 2010; **211**: 79-86.

Houben K., Nederkoorn C., Wiers R.W., Jansen A. Resisting temptation: Decreasing alcohol-related affect and drinking behavior by training response inhibition. *Drug Alcohol and Dependence* 2011; **116**: 132-136.

Jentsch J. D., Ashenhurst J. R., Cervantes M. C., Groman S. M., James A. S., Pennington Z. T. Dissecting impulsivity and its relationships to drug addictions. *Annals of the New York Academy of Sciences* 2014; **1327**: 1-26.

Johnson M. W., Bruner N. R., Johnson P. S. Cocaine dependent individuals discount future rewards more than future losses for both cocaine and monetary outcomes. *Addictive Behaviors* 2015; **40**: 132-136.

Jones A., Di Lemma L. C. G., Robinson E., Christiansen P., Nolan S., Tudur-Smith C., Field M. Inhibitory control training for appetitive behaviour change: A meta-analytic investigation of mechanisms of action and moderators of effectiveness. *Appetite* 2016; **97**: 16-28.

Kampman K. M., Pettinati H. M., Lynch K. G., Spratt K., Wierzbicki M. R., O'Brien C. P. A double-blind, placebo-controlled trial of topiramate for the treatment of comorbid cocaine and alcohol dependence. *Drug and Alcohol Dependence* 2013; **133**: 94-99.

Keppel G. Planned comparisons. In: *Design and Analysis: A Researcher's Handbook, Third Edition*. Upper Saddle River, NJ: Prentice Hall; 1991a, p. 165-166.

Keppel G. Within-Subjects Design. In: *Design and Analysis: A Researcher's Handbook, Third Edition*. Upper Saddle River, NJ: Prentice Hall; 1991b, p. 19.

Kessler R.C., Adler L., Ames M., Demler O., Faraone S., Hiripi E., Howes M.J., Jin R., Secnik K., Spencer T., Ustun T.B., Walters E.E. The World Health Organization Adult ADHD Self-Report Scale (ASRS). *Psychological Medicine* 2005; **35**: 245-256.

Kirby K. N., Petry N. M. Heroin and cocaine abusers have higher discount rates for delayed rewards than alcoholics or non-drug-using controls. *Addiction* 2004; **99**: 461-471.

Lamb R. J., Ginsburg B. C. Addiction as a BAD, Behavioral Allocation Disorder. *Pharmacology, Biochemistry and Behavior* 2017 In Press.

Lane S. D., Moeller F. G., Steinberg J. L., Buzby M., Kosten T. R. Performance of cocaine dependent individuals and controls on a response inhibition task with varying levels of difficulty. *American Journal of Drug and Alcohol Abuse* 2007; **33**: 717-726.

Leeman R. F., Robinson C. D., Waters A. J., Sofuoglu M. A critical review of the literature on attentional bias in cocaine use disorder and suggestions for future research. *Experimental and Clinical Psychopathology* 2014; **22**: 469-483.

Leon A. C., David L. L., Kraemer H. C. The role and interpretation of pilot studies in clinical research. *Journal of Psychiatric Research* 2011; **45**: 626-629.

Li C. R., Milivojevic V., Kemp K., Hong K., Sinha R. Performance monitoring and stop signal inhibition in abstinent patients with cocaine dependence. *Drug and Alcohol Dependence* 2006; **85**: 205-212.

Liu S., Lane S. D., Schmitz J. M., Waters A. J., Cunningham K A., Moeller F. G. Relationship between attentional bias to cocaine-related stimuli and impulsivity in cocaine-dependent subjects. *American Journal of Drug and Alcohol Abuse* 2011; **37**: 117-122.

LoBue C., Cullum M., Braud J., Walker R., Winhusen T., Suderajan P., Adinoff B. Optimal neurocognitive, personality and behavioral measures for assessing impulsivity in cocaine dependence. *The American Journal of Drug and Alcohol Abuse* 2014; **40**: 455-462.

Logan G. D. On the ability to inhibit thought and action: A user's guide to the stop signal paradigm. In: *Inhibitory Processes in Attention, Memory, and Language*. San Diego, CA: Academic Press; 1994, p. 189-239.

Logan G. D., Cowan W. B., Davis K. A. On the ability to inhibit simple and choice reaction time responses: A model and a method. *Journal of Experimental Psychology: Human Perception and Performance* 1984; **10**: 276-291.

Marks K. R., Alcorn III J. L., Stoops W. W., Rush C. R. Cigarette cue attentional bias in cocaine-smoking and non-cocaine-using cigarette smokers. *Nicotine & Tobacco Research* 2016; **18**: 1915-1919.

Marks K. R., Pike E., Stoops W. W., Rush C. R. Alcohol administration increases cocaine craving but not cocaine cue attentional bias. *Alcoholism: Clinical and Experimental Research* 2015a; **39**: 1823-1831.

Marks K. R., Pike E., Stoops W. W., Rush C. R. Test-retest reliability of eye tracking during the visual probe task in cocaine-using adults. *Drug and Alcohol Dependence* 2014a; **145**: 235-237.

Marks K. R., Pike E., Stoops W. W., Rush C. R. The magnitude of drug attentional bias is specific to substance use disorder. *Psychology of Addictive Behaviors* 2015b; **29**: 690-695.

Marks K. R., Walters W., Stoops W. W., Pike E., Fillmore M. T., Rush C. R. Fixation time is a sensitive measure of cocaine cue attentional bias. *Addiction* 2014b; **109**: 1501-1508.

McClure S. M., Laibson D. I., Loewenstein G., Cohen J. D. Separate neural systems value immediate and delayed monetary rewards. *Science* 2004; **306**: 503-507.

Miller N. S., Gold M. S. Dissociation of "conscious desire" (craving) from and relapse in alcohol and cocaine dependence. *Annals of Clinical Psychiatry* 1994; **6**: 99-106.

Miller J., Schäffer R., Hackley S. A. Effects of preliminary information in a Go versus No-go task. *Acta Psychologica* 1991; **76**: 241-292.

Moeller F. G., Dougherty D. M., Barratt E. S., Schmitz J. M., Swann A. C., Grabowski J. The impact of impulsivity on cocaine use and retention in treatment. *Journal of Substance Abuse Treatment* 2001; **21**: 193-198.

Nuijten M., Blanken P., Van der Brink W., Goudriaan A. E., Hendriks V. M. Impulsivity and attentional bias as predictors of modafinil treatment outcome for retention and drug use in crack-cocaine dependent patients: Results of a randomised controlled trial. *Journal of Psychopharmacology* 2016; **30**: 616-626.

Patkar A. A., Murray H. W., Mannelli P., Gottheil E., Weinstain S. P., Vergare M. J. Pre-treatment measures of impulsivity, aggression and sensation seeking are associated with treatment outcome for African-American cocaine-dependent patients. *Journal of Addictive Diseases* 2004; **23**: 109-122.

Patton J. H., Stanford M. S., Barratt E. S. Factor structure of the Barratt Impulsiveness Scale. *Journal of Clinical Psychology* 1995; **51**: 768-774.

Perkins K. A., Lerman C., Coddington S. B., Jetton C., Karelitz J. L., Scott J. A., Wilson A. S. Initial nicotine sensitivity in humans as a function of impulsivity. *Psychopharmacology* 2008; **200**: 529-544.

Peters J., Büchel C. The neural mechanisms of inter-temporal decision-making: Understanding variability. *Trends in Cognitive Sciences* 2011; **15**: 227-239.

Pike E., Stoops W. W., Fillmore M. T., Rush C. R. Drug-related stimuli impair inhibitory control in cocaine abusers. *Drug and Alcohol Dependence* 2013; **133**: 768-771.

Pike E., Marks K. R., Stoops W. W., Rush C. R. Cocaine-related stimuli impair inhibitory control in cocaine users following short stimulus onset asynchronies. *Addiction* 2015; **110**: 1281-1286.

Pike E, Marks KR, Stoops WW, Rush CR (under review). Influence of alcohol administration and cocaine-related images on inhibitory control in cocaine users.

Reed D. D., Kaplan, B. A., Brewer, A. T. A tutorial on the use of Excel 2010 and Excel for Mac 2011 for conducting delay-discounting analyses. *Journal of Applied Behavior Analysis* 2012; **45**: 375-386.

Reynolds B., Ortengren A., Richards J. B., de Wit H. Dimensions of impulsive behavior: Personality and behavioral measures. *Personality and Individual Differences* 2006; **40**: 305-315.

Reynolds B., Penfold R. B., Patak M. Dimensions of impulsive behavior in adolescents: Laboratory behavioral assessments. *Experimental and Clinical Psychopharmacology* 2008; **16**: 124-131.
Roberts W., Fillmore M. T., Milich R. Drinking to distraction: Does alcohol increase attentional bias in adults with ADHD? *Experimental and Clinical Psychopharmacology* 2012; **20**: 107-117.
Robinson T. E., Berridge K. C. Addiction. *Annual Reviews of Psychology* 2003; **54**: 25-53.
Robinson T. E., Berridge K. C. The incentive sensitization theory of addiction: Some current issues. *Philosophical Transactions of the Royal Society B* 2008; **363**: 3137-3146.
Robinson T. E., Berridge K. C. The neural basis of drug craving: An incentive-sensitization theory of addicton. *Brain Research Reviews* 1993; **18**: 247-291.
Ryan F. Detected, selected, and sometimes neglected: Cognitive processing of cues in addiction. *Experimental and Clinical Psychopharmacology* 2002; **10**: 67-76.
Saunders J. B., Aasland O. G., Babor T. F., Delafuente J. R., Grant M. Development of the alcohol-use disorders identification test (AUDIT): WHO collaborative project on early detection of persons with harmful alcohol-consumption. *Addiction* 1993; **88**: 791-804.
Selzer M.L. The Michigan Alcoholism Screening Test (MAST): The Quest for a New Diagnostic Instrument. *American Journal of Psychiatry* 1971; **3**:176-181.
Skinner H. A. The drug abuse screening test. *Addictive Behaviors* 1992; **7**: 363-371.
Sobell L. C., Sobell M. B. Timeline follow-back: A technique for assessing self reported alcohol consumption. In: *Measuring alcohol consumption: Psychosocial and biochemical methods*. Totowa, NJ: Humana Press; 1992, p. 41-72.
Sofuoglu M. Cognitive enhancement as a pharmacotherapy target for stimulant addiction. *Addiction* 2010; **105**: 38-48.
Sofuoglu M., DeVito E. E., Waters A. J., Carroll K. M. Cognitive enhancement as a treatment for drug addictions. *Neuropharmacology* 2013; **64**: 452-463.
Sofuoglu M., DeVito E. E., Waters A. J., Carroll K. M. Cognitive function as a transdiagnostic treatment target in stimulant use disorders. *Journal of Dual Diagnosis* 2016; **12**: 90-106.
Stevens L., Verdejo-García A., Roeyers H., Goudriaan A. E., Vanderplasschen W. Delay discounting, treatment motivation and treatment retention among substance-dependent individuals attending an in inpatient detoxification program. *Journal of Substance Abuse Treatment* 2015; **49**: 58-64.
Streeter C. C., Terhune D. B., Whitfield T.H., Gruber S., Sarid-Segal O., Silveri M. M., Tzilos G., Afshar M., Rouse E. D., Tian H., Renshaw P. F., Ciraulo D. A., et al. Performance on the Stroop predicts treatment compliance in cocaine-dependent individuals. *Neuropsychopharmacology* 2008; **33**: 827-836.
Swick D., Ashley V., Turken A. U. Are the neural correlates of stopping and not going identical? Quantitative meta-analysis of two response inhibition tasks. *Neuroimage* 2011; **56**: 1655-1665.
Thorpe S., Fize D., Marlot C. Speed of processing in the human visual system. *Nature* 1996; **381**: 520-522.
Verbruggen F., Logan G. D. Response inhibition in the stop-signal paradigm. *Trends in Cognitive Sciences* 2008; **12**: 418-424.
Verdejo-García A. J., Perales J. C., Pérez-García M. Cognitive impulsivity and heroin polysubstance abusers. *Addictive Behaviors* 2007; **32**: 950-966.
Verdejo-García A. J., Pérez-García M. Profile of executive deficits in cocaine and heroin polysubstance users: Common and differential effects on separate executive components. *Psychopharmacology* 2007; **190**: 517-530.

Vocci F. J. Cognitive remediation in the treatment of stimulant abuse disorders: A research agenda. *Experimental and Clinical Psychopharmacology* 2008; **16**: 484-497.
Vocci F. J., Montoya I. D. Psychological treatments for stimulant misuse, comparing and contrasting those for amphetamine dependence and those for cocaine dependence. *Current Opinion in Psychiatry* 2009; **22**: 263-268.
Vonmoos M., Hulka L. M., Preller K. H., Jenni D., Schultz C., Baumgartner M. R., Quednow B. B. Differences in self-reported and behavioral measures of impulsivity in recreational and dependent cocaine users. *Drug and Alcohol Dependence* 2013; **133**: 61-70.
Weafer J., Fillmore M. T. Alcohol-related stimuli reduce inhibitory control of behavior in drinkers. *Psychopharmacology* 2012; **222**: 489-498.
Weafer J., Fillmore M. T. Alcohol-related cues potentiate alcohol impairment of behavioral control in drinkers. *Psychology of Addictive Behaviors* 2015; **29**: 290-299.
Weafer J., Mitchell S. H., de Wit H. Recent translational findings on impulsivity in relation to drug abuse. *Current Addiction Reports* 2014; **1**: 289-300.
Wiers R. W., Gladwin T. E., Hofmann W., Salemink E., Ridderinkhof K. R. Cognitive bias modification and cognitive control training in addiction and related psychopathology: Mechanisms, clinical perspectives, and ways forward. *Clinical Psychological Science* 2013; **1**: 192-212.
Winhusen T., Brady K. T., Stitzer M., Woody G., Lindbald R., Kropp F., Brigham G., Liu D., Sparenborg S., Sharma G., VanVeldhuisen P., Adinoff B., Somoza E. Evaulation of buspirone for relapse-prevention in adults with cocaine dependence: An efficacy trial conducted in the real world. *Contemporary Clinical Trials* 2012; **33**: 993-1002.
Winhusen T., Lewis D., Adinoff B., Brigham G., Kropp F., Donovan D. M., Seamans C. L., Hodgkins C. C., DiCenzo J. C., Botero C. L., Jones D. R., Somoza E. Impulsivity is associated with treatment non-completion in cocaine- and methamphetamine-dependent patients but differs in nature as a function of stimulant-dependence diagnosis. *Journal of Substance Abuse Treatment* 2013; **44**: 541-547.
Zuckerman M., Kuhlman D. M., Joireman T. J., Kraft, M. A comparison of three structural models of personality: The big three, the big five, and the alternative five. *Journal of Personality and Social Psychology* 1993; **65**: 757-768.

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EDUCATION:

University of Kentucky

M.S.

- Graduation date: May 2013
- Program in Experimental Psychology (Behavioral Neuroscience and Psychopharmacology)

University of Michigan – Flint

B.S.

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- Program in Clinical/Community Psychology
- Graduated with Honors from the Honors Program in Psychology

PUBLICATIONS:

1. Alcorn III JL, **Pike E**, Lile JA, Stoops WW, Rush CR (2017). A pilot investigation of acute inhibitory control training in cocaine users. Drug and Alcohol Dependence, 174, 145-149.

2. **Pike E**, Stoops WW, Rush CR (2016). Acute buspirone dosing enhances abuse-related subjective effects of oral methamphetamine. Pharmacology, Biochemistry, and Behavior, 150-151, 87-93.

3. Marks KR, **Pike E**, Stoops WW, Rush CR (2015). The magnitude of drug attentional bias is specific to substance use disorder. Psychology of Addictive Behaviors, 29, 690-695.

4. Marks KR, **Pike E**, Stoops WW, Rush CR (2015). Alcohol administration increases cocaine craving but not cocaine cue attentional bias. Alcoholism, Clinical and Experimental Research, 39, 1823-1831.

5. **Pike E**, Marks KR, Stoops WW, Rush CR (2015). Cocaine-related stimuli impair inhibitory control in cocaine users following short stimulus onset asynchronies. Addiction, 110, 1281-1286.

6. Stoops WW, **Pike E**, Hays LR, Glaser PE, Rush CR (2015). Naltrexone and bupropion, alone or combined, do not alter the reinforcing effects of intranasal methamphetamine. Pharmacology, Biochemistry, and Behavior, 129, 45-50.

7. **Pike E**, Stoops WW, Hays LR, Glaser PE, Rush CR (2014). Methamphetamine self-administration in humans during d-amphetamine maintenance. Journal of Clinical Psychopharmacology, 34, 675-681

8. Marks KR, Stoops WW, **Pike E**, Roberts W, Fillmore MT, Rush CR (2014). Fixation time is a sensitive measure of cocaine cue attentional bias. Addiction, 109, 1501-1508.

9. Marks KR, **Pike E**, Stoops WW, Rush CR (2014). Test-retest reliability of eye tracking during the visual probe task in cocaine-using adults. Drug and Alcohol Dependence, 145, 235-237.

10. **Pike E**, Stoops WW, Fillmore MT, Rush CR (2013). Drug-related stimuli impair inhibitory control in cocaine abusers. Drug and Alcohol Dependence, 133, 768-771.

11. **Pike E**, Marks KR, Stoops WW, Rush CR (under review). Influence of alcohol administration and cocaine-related images on inhibitory control in cocaine users.

RESEARCH PROJECTS AND PRESENTATIONS:

1. **Pike E**, Studts CR, Stoops WW, Rush CR (June 2017). *A pilot feasibility and acceptability trial of inhibitory control training with cocaine users*. Poster presented at the Annual Meeting of the College on Problems of Drug Dependence, Montreal, Canada.

2. Alcorn III JL, **Pike E**, Stoops WW, Lile JA, Rush CR (June 2016). *Acute inhibitory control training in cocaine users: A pilot study*. Poster presented at the Annual Meeting of the College on Problems of Drug Dependence, Palm Springs, CA.

3. Rush CR, Alcorn III JL, **Pike E**, Stoops WW, Lile JA (March 2016). *Acute inhibitory control training in cocaine users: A pilot study*. Poster presented at the Collaborative Perspectives on Addiction, San Diego, CA.

4. **Pike E**, Marks KR, Lile JA, Stoops WW, Glaser PEA, Hays LR, Rush CR (September 2015). *Separate and combined effects of naltrexone and extended-release alprazolam on the reinforcing, subject-rated, and physiological effects of methamphetamine*. Poster presented at the Joint Meeting of the European Behavioural Pharmacology Society and European Brain Behaviour Society, Verona, Italy.

5. Marks KR, **Pike E**, Stoops WW, Rush CR (September 2015). *Alcohol administration increases cocaine craving but not cocaine cue attentional bias*. Poster presented at the Joint Meeting of the European Behavioural Pharmacology Society and European Brain Behaviour Society, Verona, Italy.

6. **Pike E**, Marks KR, Stoops WW, Rush CR (August 2015). *Cocaine images impair inhibitory control in cocaine users*. Poster presented at the 123rd annual meeting of the American Psychological Association, Toronto, Canada.

7. Marks KR, **Pike E**, Stoops WW, Rush CR (August 2015). *Eye tracking is sensitive to clinically relevant differences in substance abuse*. Posted presented at the 123rd annual meeting of the American Psychological Association, Toronto, Canada.

8. **Pike E**, Marks KR, Stoops WW, Rush CR (June 2015). *Cocaine images and alcohol administration impair inhibitory control*. Poster presented at the Annual Meeting of the College on Problems of Drug Dependence, Phoenix, AZ.

9. Marks KR, **Pike E**, Stoops WW, Rush CR (April 2015) *Measuring attentional bias to substance-related stimuli using eye-tracking technology*. Poster presented at the Association for Clinical and Translational Science 2015 Annual Meeting, Washington DC.

10. Marks KR, **Pike E**, Stoops WW, Rush CR (March 2015) *Measuring attentional bias to substance-related stimuli using eye-tracking technology*. Poster presented at the 10th annual University of Kentucky Center for Clinical and Translational Science Spring Conference, Lexington, KY.

11. **Pike E**, Marks KR, Stoops WW, Rush CR (July 2014). *Drug-related stimuli impair inhibitory control in cocaine abusers*. Poster presented at the Annual Meeting of the International Society for Research on Impulsivity, Cambridge, UK.

12. Marks KR, **Pike E**, Stoops WW, Rush CR (2014). Attentional bias and impulsivity. Poster presented at the Annual Meeting of the International Society for Research on Impulsivity, Cambridge, UK.

13. **Pike E**, Stoops WW, Rush CR (June 2014). *Cocaine images impact inhibitory control: A within- and between-subjects comparison*. Poster presented at the Annual Meeting of the College on Problems of Drug Dependence, San Juan, PR.

14. Rush CR, **Pike E**, Stoops WW (June 2014). *Influence of buspirone on the cardiovascular and subject-rated effects of methamphetamine*. Poster presented at the Annual Meeting of the College on Problems of Drug Dependence, San Juan, PR.

15. Stoops WW, **Pike E**, Hays LR, Glaser PEA and Rush CR (June 2014). *Influence of Bupropion, Naltrexone and Bupropion+Naltrexone on Methamphetamine Self-Administration in Humans*. Talk presented at the College on Problems of Drug Dependence: San Juan, PR.

16. **Pike E**, Stoops WW, Rush CR (March 2014). *Drug-related stimuli impair inhibitory control in cocaine abusers*. Poster presented at the Kentucky Psychological Foundation Spring Academic Conference, Wilmore, KY.

17. **Pike E**, Stoops WW, Rush CR (March 2014). *Within-subjects comparison of the influence of cocaine images on inhibitory control in cocaine users*. Poster presented at the 9th Annual CCTS Spring Conference, Lexington, KY.

18. Glaser P, **Pike E**, Hays L, Stoops WW, Rush CR (December 2013). *Intranasal methamphetamine self-administration in humans during d-amphetamine maintenance.* Poster presented at the 52nd annual meeting of the American College of Neuropsychopharmacology, Hollywood, FL.

19. **Pike E**, Stoops WW, Glaser PEA, Hays LR, Rush CR (June 2013). *Methamphetamine self-administration in humans during d-amphetamine maintenance*. Poster presented at the 75th annual meeting of the College on Problems of Drug Dependence, San Diego, CA.

20. Marks KR, Stoops WW, **Pike E**, Roberts W, Fillmore MT, Rush CR (June 2013). *Gaze time as a sensitive measure of cocaine-related attentional bias.* Poster presented at the 75th annual meeting of the College on Problems of Drug Dependence, San Diego, CA.

21. Marks KR, Stoops WW, **Pike E**, Roberts W, Fillmore MT, Rush CR (April 2013). Measuring attentional bias to cocaine using eye-tracking technology. Poster presented at the 2nd annual Tobii Eye Tracking Conference on Behavioral Research, Boston, MA.

22. Marks KR, **Pike E**, Stoops WW, Rush CR (August 2012). *Agonist replacement therapy for cocaine dependence: A translational review*. Poster presented at the 120th Annual American Psychological Association Convention, Orlando, FL.

23. **Pike E**, Marks KR, Stoops WW, Rush CR (June 2012). *Years of stimulant use as a biobehavioral marker for methamphetamine dependence*. Poster presented at the 74th Annual Meeting of the College on Problems of Drug Dependence, Palm Springs, CA.

24. **Pike E** (May 2009). *Investigating the relationship between perceived control of attention deficit hyperactivity disorder symptoms and substance use in college students*. Poster presented at the annual Meeting of Minds Undergraduate Conference, University of Michigan-Dearborn, Dearborn, Michigan.

25. Shaughnessy S, **Pike E**, Wojtkowicz M, Berkuchel S, Abu-Aita A (May 2007). *What would Mickey do? A behavioral analysis of mice response to cat hair*. Poster presented at the annual Meeting of Minds Undergraduate Conference, University of Michigan-Flint, Flint, Michigan.

26. **Pike E** (April 2007). *The problem of prescription stimulant misuse among high school and college students*. Paper presented at the Honors Colloquium- Papers on independent study topics, University of Michigan-Flint.

FELLOWSHIPS AND AWARDS:

National Institute on Drug Abuse T32 Pre-Doctoral Traineeship 2016 - Present
University of Kentucky; National Institute on Drug Abuse

BNP Student Achievement Award 2017

Graduate School Year Academic Fellowship 2012 - 2014
University of Kentucky

American Psychological Foundation Ungerleider/Zimbardo Travel Scholarship 2015

European Behavioural Pharmacology Society Travel Award 2015

EXPERIENCE:

AIDS Volunteers of Lexington, Lexington, KY 2016 - Present
Volunteer Certified in HIV Testing

University of Kentucky, Department of Psychology, Lexington, KY 2014 - 2015
Graduate Student Representative on the Graduate Student Executive Committee

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University of Kentucky, Department of Psychology, Lexington, KY 2011 - 2012
Teaching Assistant

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Taylor Psychological Clinic, Flint, MI 2009
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Hurley Medical Center, Research Center, Flint, MI 2008 - 2009
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University of Kentucky, Psychiatry Research, Lexington, KY 2008
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