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EXAMINING THE BEHAVIORAL MECHANISM OF COCAINE CUE ATTENTIONAL BIAS

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EXAMINING THE BEHAVIORAL MECHANISM OF COCAINE CUE ATTENTIONAL BIAS

DISSERTATION

A dissertation submitted in partial fulfillment of the
requirements for the degree of Doctor of Philosophy in the
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By
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ABSTRACT OF DISSERTATION

EXAMINING THE BEHAVIORAL MECHANISM OF
COCAINE CUE ATTENTIONAL BIAS

Heightened attentional bias towards cocaine-related stimuli relative to neutral stimuli is a characteristic observed in cocaine-use disorders. Response time is an indirect measure of attention and research has failed to consistently demonstrate evidence of clinical relevance. Eye tracking presents a novel tool for directly measuring attentional allocation. The aim of this dissertation was to assess the sensitivity, reliability, and specificity of attentional bias through fixation and response time during the visual probe task.

In the visual probe task, substance-related and matched neutral images were presented side-by-side on a computer screen. Eye-tracking technology measured time spent fixating on each image. A probe then replaced one image and time to respond was measured. Attentional bias was defined as the difference between neutral and substance-related images for fixation time and response time. A programmatic series of experiments was conducted using the visual probe task to demonstrate the sensitivity, reliability, and specificity of attentional bias as measured by fixation time during the visual probe task.

Cocaine users displayed a robust and reliable cocaine cue attentional bias as measured by fixation time. Non-cocaine-using controls did not display a cocaine cue attentional bias. Fixation time was specific to substance use history. Individuals dependent on both cocaine and alcohol displayed an attentional bias to both substances, whereas individuals dependent on cocaine only displayed an attentional bias towards cocaine, but not alcohol. Fixation time also correlated with craving and deprivation. Cigarette cue attentional bias correlated positively with self-reported cigarette craving. Response time was a less sensitive measure of attentional bias, displayed low reliability, and did not correlate with substance use severity.

Unlike response time, eye tracking applied to the visual probe task is a sensitive, reliable, and specific measure of attentional bias in cocaine users. Importantly, fixation time during the visual probe task is sensitive to clinically relevant differences in substance abuse. This outcome is consistent with incentive motivational hypotheses, proposing that reward-paired cues obtain incentive salience. These findings provide future directions for attentional bias research, such as applying eye tracking to treatment-related outcomes.

KEYWORDS: Cocaine, Cue, Attentional Bias, Visual Probe, Eye Tracking

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Chapter 1

INTRODUCTION

Cocaine use is a significant public health concern. Data from the National Survey on Drug Use and Health indicate that in 2013 approximately 1.5 million Americans over 12 years of age reported current (i.e., past month) cocaine use (SAMHSA, 2014a). Nearly 70% of those users meet criteria for abuse or dependence. Despite treatment efforts such as contingency management, cognitive behavioral therapy, and pharmacotherapy, prevalence use and rates of relapse to cocaine remain discouragingly high (SAMHSA, 2014a). Thus, new treatment targets need to be identified.

Drug cues play an important role in drug-taking behavior and reactivity to drug cues may be one such treatment target (Childress et al., 1999; Kosten et al., 2006; Sinha and Li, 2007; Volkow et al., 2008). The goal of this dissertation is to examine the behavioral mechanisms underlying cocaine cue attentional bias in individuals who use cocaine. Below, I review the extant attentional bias literature. First, I will present a general overview of substance cue attentional bias and discuss the methods used to study attentional bias. Next, I will compare and contrast the hypothesized theoretical mechanisms responsible for attentional bias. I will then review the cocaine cue attentional bias literature as well as discuss the factors that might influence cocaine cue attentional bias. I conclude the introduction by presenting an overview of the aims of this dissertation as well as the five experiments.

Substance Cue Attentional Bias

Stimuli (i.e., pictorial and word cues) relevant to the substance use disorder of the individual capture attention (Field and Cox, 2008). This allocation of a disproportionate amount of time attending to substance-related stimuli is referred to as attentional bias (Gross et al., 1993). Attentional bias has been demonstrated across a variety of addictive behaviors including alcohol (Townshend and Duka, 2001), tobacco

(Field et al., 2004b), marijuana (Field et al., 2004a), heroin (Marissen et al., 2006), caffeine (Yeomans et al., 2005), food (Castellanos et al., 2009), and gambling (McCusker and Gettings, 1997). For example, cannabis users attend to the cannabis-related cues (e.g., a joint) significantly longer than to neutral cues (e.g., a pen). In contrast, non-cannabis-using controls do not display a cannabis cue attentional bias (Field et al., 2006). Likewise, heavy social drinkers attend to alcohol-related cues significantly longer than to neutral cues, whereas occasional social drinkers do not display this attentional bias (Townshend and Duka, 2001).

Attentional bias has also been demonstrated in other addictive disorders such as compulsive overeating. For example, obese and normal-weight individuals completed an attentional bias task under food-deprived and food-sated conditions (Castellanos et al., 2009). Under the deprived condition, both groups displayed an attentional bias towards food-related images. Under the sated condition, attentional bias decreased in the normal-weight group whereas it remained elevated in the obese group. The results of this experiment and the abovementioned studies are representative of the attentional bias literature, which supports the notion that attentional bias is a unique characteristic of addictive disorders.

A number of attentional bias studies have also examined the relationship between attentional bias and substance use history (Field et al., 2004a; Ryan, 2002; Townshend and Duka, 2001; Weafer and Fillmore, 2012; Yeomans et al., 2005). The results of several of those studies provide evidence that substance use history correlates positively with attentional bias. In one study, Field and colleagues (2004a) demonstrated that the attentional bias of recreational cannabis users correlated positively with self-reported number of joints smoked in the past month. Previous research has found similar results with alcohol users (Miller and Fillmore, 2010; Weafer and Fillmore, 2012). Individuals with greater alcohol cue attentional bias reported drinking more, being drunk

more, and having more binge days in the month prior than individuals with low alcohol cue attentional bias (Weafer and Fillmore, 2012). These data indicate that attentional bias is proportionate to the severity of substance use.

Measures of Attentional Bias

In this section, the three primary measures of attentional bias will be discussed. These indices include both indirect (i.e., response time) and direct (i.e., fixation time) measures of attention. Each measure has strengths and limitations.

Modified Stroop Task. Attentional bias has been most commonly studied using the modified Stroop task (Cox et al., 2006). The primary strengths of the modified Stroop task are its ease of administration and widespread availability. In this task, a substance-related or a neutral word is presented on a computer screen or an index card. Participants are instructed to identify as quickly as possible the color of the text while ignoring the semantic content of the word. The expected result is that response time to substance-related words is slower than to neutral words. This interference, or preoccupation with substance-related words, has been labeled as attentional bias.

Cognitive interference produced by substance-related words has been observed in a variety of substance use disorders including alcohol (Field et al., 2013; Stormark et al., 2000), heroin, (Marissen et al., 2006), marijuana (Cousijn et al., 2013), and tobacco (Munafò et al., 2003). For example, Marissen and colleagues (2006) measured cognitive interference in 110 abstinent, heroin-dependent individuals using the modified Stroop task. Participants were slower to identify the color of the heroin-related words relative to neutral words, suggesting attentional bias towards the heroin-related words.

The primary limitation of the modified Stroop task is that it is not a direct measure of attention. First, the bias captured during the modified Stroop is more complex than attentional allocation and includes other cognitive and emotional processes including perceived threat (Greenaway et al., 2012; De Ruiter and Brosschot, 1994) and impaired

inhibitory control (Crunelle et al., 2012; for reviews see Cox et al., 2006; Williams et al., 1996). From a cognitive perspective, Stroop words activate the current goals, memories, or concerns of the individual (e.g., Klinger and Cox, 2004; Mathews and Klug, 1993; McKenna and Sharma, 1995). From an emotion-based perspective, the emotional valence of the Stroop words produces automatic, preconscious emotions that delay color naming (e.g., Gilboa-Schechtman et al., 2000). Other processes such as avoidance of substance-related words, craving, and increased semantic processing might also contribute to the delay in color naming (see Field and Cox, 2008). Although the precise mechanism has not been identified, it is clear that the modified Stroop task manipulates a variety of processes in addition to attention in order to produce response time interference. Labeling this task as a measure of attentional bias fails to represent the complexity of the behavioral response.

Second, the dependent variable in the modified Stroop task, response time, is an indirect measure of cognitive processing (Field and Cox, 2008). The task relies upon a motoric response to approximate the abovementioned processes that are hypothesized to contribute to Stroop interference. Interpretation of the data is contingent upon the assumption that slowed response time is a result of the increased cognitive load produced by substance-related words. Response time, therefore, is a nonspecific measure of attention. Given the indirect nature of the modified Stroop task, it is not surprising that the Stroop effect has been observed in non-substance using control groups (Bauer and Cox, 1998; Ryan, 2002; Stetter et al., 1994). For example, Ryan (2002) measured alcohol cue attentional bias in 34 treatment-seeking, alcohol dependent individuals and 33 normal controls and found that both groups displayed Stroop interference.

In addition to being indirect, the reliability of the modified Stroop task is low (Ataya et al., 2012; Spiegelhalder et al., 2011). Ataya and colleagues (2012) assessed

the internal reliability of the modified Stroop in a retrospective analysis of four alcohol and three tobacco attentional bias studies conducted in their laboratory. Chronbach's alpha was calculated to determine the internal reliability of response time to substance and neutral image pairs across all studies. Alpha coefficients ranged from 0.5 – 1.0, with only two studies achieving the minimum threshold for acceptable reliability (0.7; Kline et al., 1999). Ataya and colleagues (2012) concluded that the modified Stroop procedure utilized in their laboratory was generally unreliable. In another study, Spiegelhalder and colleagues (2011) assessed the test-retest reliability of the modified Stroop task by measuring cigarette cue attentional bias in nicotine-dependent participants at two time points separated by an average of 108 days. A Pearson correlation of -0.2 indicated that attentional bias between the two assessments did not significantly correlate, suggesting low test-retest reliability across extended assessments.

Visual Probe Task (Figure 1.1). In the visual probe task, a substance-related cue and a neutral cue are briefly presented side-by-side on a computer screen (Allport, 1989; LaBerge, 1995). A probe (i.e., an X) then replaces one of these images and the participant must make a choice response to indicate the location of the probe. The time to respond to the location of the probe is measured. A response time attentional bias score is determined as the mean difference in response time between substance-related and neutral images across trials. Participants might respond more quickly to probes replacing the substance-related cue, presumably because they were already attending to the substance-related cue, due to its incentive salience, when the probe appeared (Posner et al., 1980).

Attentional bias as measured by the visual probe task has been observed in a variety of substance use disorders including alcohol (Townshend and Duka, 2001), caffeine (Yeomans et al., 2005), marijuana (Field et al., 2004a), prescription opioids (Garland et al., 2013), and tobacco (Ehrman et al., 2002). For example, Ehrman and

colleagues (2002) measured tobacco cue attentional bias in 67 tobacco smokers and 25 non-smoking-controls. Tobacco smokers were faster to respond to probes replacing tobacco images than neutral images compared to controls, indicating attentional bias towards tobacco-related images. Heavy social drinkers were also faster to respond to probes that replaced alcohol-related images than occasional, social drinkers (Townshend and Duka, 2001).

Like the modified Stroop task, the visual probe task is widely accessible and easy to administer. An additional strength of the visual probe task is increased ecological and face validity as compared to the modified Stroop task. Drug-related images better approximate the stimuli encountered in the environment than drug-related words. This design is also a more direct index of attention because response time to the probe location depends upon the allocation of visual attention immediately prior to the presentation of the probe (Field et al., 2004a). However, since response time only approximates the final gaze direction prior to the presentation of the probe, attention during the presentation of the image set is not assessed.

The primary limitation of the visual probe task is that the dependent variable is response time, which as described above is an indirect measure of attention. Response time, particularly in the visual probe task, may not be an optimal measure of attentional bias as internal reliability (Ataya et al., 2012) and test-retest reliability (Spiegelhalder et al., 2011) are low resulting in inconsistent findings across investigative groups and drug classes (Field et al., 2004a, 2006, 2013; Miller and Fillmore, 2011; Mogg et al., 2003; Schoenmakers et al., 2008). Spiegelhalder and colleagues (2011) assessed the test-retest reliability of the visual probe task by measuring cigarette cue attentional bias in nicotine-dependent individuals at two time points. A Pearson correlation of 0.3 indicated that the attentional bias between the two assessments did not significantly correlate, indicating low test-retest reliability.

Visual Probe Task and Eye Tracking Technology. Recognizing the limitations of response time, investigators have argued for using more direct measures of attention to quantify attentional bias (Field and Cox, 2008; Miller and Fillmore, 2011). Eye-tracking technology directly measures visual attention by recording how participants direct their gaze (Godijn and Theeuwes, 2003). Infrared light creates a reflection pattern on the cornea and pupil of the eye. These reflections are recorded as coordinates and algorithms analyze the calculated vectors to determine fixation direction every 16.6 milliseconds (ms) (Tobii, 2013). When eye tracking is applied to the visual probe task, the amount of time spent fixating on each image is measured. An attentional bias score is determined for each participant as the mean difference in fixation time between substance-related and neutral images. Attentional bias is defined as longer fixation time toward substance-related images compared to neutral images.

Fixation time is an effective means of detecting attentional bias towards alcohol (Miller and Fillmore, 2010, 2011), cannabis (Field et al., 2006), and tobacco-related images (Baschnagel, 2013; Mogg et al., 2003). Cannabis users, for example, fixate on cannabis-related images approximately 160 ms longer than neutral images during a visual probe task (Field et al., 2006). Tobacco smokers also fixate on smoking-related cues longer than non-smokers (Mogg et al., 2003). Baschnagel (2013) simulated an environment within the laboratory that contained smoking-related cues (i.e., a cigarette pack and a poster depicting an individual smoking) and neutral cues. Fixation time to the cigarette cues was measured using a mobile eye-tracker. Smokers made more fixations on smoking-related images than on neutral images.

Evidence suggests that fixation time is sensitive to attentional bias that goes undetected by response time (Fernie et al., 2012; Field et al., 2006; Miller and Fillmore, 2011). Miller and Fillmore (2011) measured fixation time and response time during the visual probe task and observed that social drinkers fixated on alcohol-related images

longer than neutral images but response time to probes replacing both alcohol and neutral images did not significantly differ. As described above, fixation time measures attention across the duration of the image set presentation (typically 2,000 ms), whereas response time is likely only assessing the final gaze direction prior to the presentation of the probe.

Fixation time also has greater internal reliability than response time. Field and Christiansen (2012) assessed the internal reliability of the visual probe task in a retrospective analysis of two cannabis-related attentional bias studies conducted in their laboratory. The Chronbach's alpha coefficients were 0.7 and 0.5 for fixation time and response time, respectively. A coefficient of 0.7 is considered the minimum threshold for acceptable reliability (Kline et al., 1999). Field and Christiansen (2012) concluded that fixation time is a more internally reliable measure of attentional bias than response time. The test-retest reliability of fixation time, however, has not been published. Taken together, the superior sensitivity and internal reliability of fixation time relative to response time indicates that fixation time should be the preferred method of measuring attentional bias. Unfortunately, the relative expense of eye tracking technology has limited its application in attentional bias studies.

Theories of Attentional Bias

Substance-related cues are known to be important in maintaining drug-taking behavior (Childress et al., 1999; Kosten et al., 2006; Sinha and Li, 2007; Volkow et al., 2008). The mechanism responsible for the salience of substance-related cues, however, has not been empirically determined. Identifying the mechanism responsible for attentional bias will provide clinically relevant information about drug-seeking, craving, and relapse. In this section, learning and cognitive theories of attentional bias will be reviewed. Although the theories are presented independently, attentional bias likely results from the interaction of the theories presented below.

Learning Theories. The selective processing of substance-related cues was originally conceptualized as a Pavlovian conditioned response. During classical conditioning, the substance functions as an unconditioned stimulus (US), which elicits an unconditioned response (UR). This UR includes physiological arousal and craving, both of which could result in attentional bias. Through repeated associative pairings with the US, neutral stimuli acquire effects similar to the US, becoming conditioned stimuli (CS+) and eliciting a conditioned response (CR). Substance-related cues, therefore, acquire incentive salience in active substance users and elicit attentional bias (e.g., Ehrman et al., 1992; Foltin and Haney, 2000; Mayo and de Wit, 2015; Robbins et al., 1999). In an elegant human laboratory experiment, Foltin and Haney (2000) demonstrated this conditioning process. Neutral cues were repeatedly paired with either placebo or smoked cocaine. When the CS+ associated with cocaine was subsequently presented alone, the stimulus elicited a CR (i.e., increased ratings of craving, heart rate, and systolic blood pressure). In contrast, the CS- associated with placebo did not elicit changes in subject ratings or physiological response. Importantly, classical conditioning also increases attentional bias. For example, oral methamphetamine paired with novel stimuli produced increased attentional bias to the CS+ during a visual probe task (Mayo and de Wit, 2015).

Incentive theories of drug addiction, such as incentive sensitization, build upon the classical conditioning model by further acknowledging that chronic substance use sensitizes dopamine pathways in brain regions associated with attribution of incentive salience and reward (Robinson and Berridge, 1993). Incentive salience refers to a 'wanting' or motivation for the substance (Robinson and Berridge, 1993). Over repeated associative pairings with the substance and substance-related cue, incentive salience for the substance transfers to the substance-related cue causing the cue to become a conditioned incentive stimulus and to elicit a conditioned motivational state in active

substance users (Goldstein and Volkow, 2002; Robinson and Berridge, 1993; Robinson et al., 2014). This increased motivation and salience causes attention to be biased in favor of cocaine-related cues in the environment and, in a process referred to as Pavlovian-to-Instrumental transfer, promotes drug taking (Franken, 2003; Klinger and Cox, 2004; Lyvers, 2000; Robinson and Berridge, 2001).

Operant theories of conditioning additionally acknowledge that reinforcement strengthens behavior. Substances of abuse serve as reinforcers and, by definition, increase the likelihood of future drug taking behavior. Through repeated associative pairings with the reinforcing substance, substance-related cues acquire the properties of a discriminative stimulus. Discriminative stimuli signal the opportunity to obtain the reinforcer. By inference then, attention should to be directed toward stimuli that predict the opportunity to obtain a reinforcer. As an example, marijuana can be smoked when a pipe is present. Thus, the presence of a pipe sets the occasion for administering the reinforcer, marijuana. The presentation of a pipe alone is likely to elicit attention and promote drug-taking behavior.

Cognitive Theories. Cognitive theories of attentional bias emphasize the role of cognitive processing of substance-related stimuli and the construct of craving. Franken (2003) proposed that in addition to the processes of incentive sensitization, cognitive processes mediate the relationship between attentional bias and the operant behaviors of drug seeking and taking. Specifically, he describes attentional bias as a "hyperattentive state" which produces subjective craving. Franken argues that craving is responsible for drug use and relapse. In a related model, Ryan (2002) proposed that chronic substance use produces cognitive biases that preattentively prioritize the salience of substance-related cues. This selective attention increases craving and in turn, heightens selective attention. This cyclical relationship, he argues, perpetuates substance use.

A meta-analysis of cue reactivity following exposure to substance-related stimuli supports the notion that craving is involved in the behavioral response to substance-related cues. Carter and Tiffany (1999) analyzed 41 studies in which substance user's self-reported craving and physiological response was measured following the presentation of substance-related stimuli. The average effect size (η^2) produced by craving was 0.17 whereas the effect size produced by physiological indices (e.g., heart rate) ranged from -0.01 to 0.04. Effect sizes of 0.01 are considered to be small, 0.06 are medium, and 0.14 are considered to be large (Cohen, 1988). More recently, Field and colleagues (2009) conducted a meta-analysis of the relationship between craving and attentional bias. They found a small but significant positive correlation (r = 0.19) between craving and attentional bias. Importantly, the strength of this relationship was larger when attention was measured by fixation time rather than response time.

Cocaine Cue Attentional Bias

Licit substance use has been the primary focus of attentional bias research. A PubMed primary literature review using the key terms "attentional bias" in combination with "alcohol" returned 151 citations and "smoking" returned 102. In contrast, "cocaine" returned 35 citations and "marijuana" returned 15. The emphasis on licit substances is likely due to convenience sampling. Illicit substance use, however, is a significant public health concern. With approximately 1.5 million Americans over the age of 12 reporting current cocaine use, cocaine cue attentional bias requires more direct scrutiny (SAMHSA, 2014a). Although it is hypothesized that similar behavioral processes underlie licit and illicit cue attentional bias, this has not been empirically demonstrated. In the following section, the results of studies measuring cocaine cue attentional bias either indirectly or directly will be described.

Attention to cocaine-related cues has primarily been studied using the modified Stroop task. The modified Stroop task is informative in understanding the relationship

between cocaine-related stimuli and the behavioral response of cocaine-using individuals. As described above, the popularity of this task is largely a result of its ease of use and widespread availability. The primary limitation of this task, however, is that it is an indirect measure of attention. As such, the specific role of attentional bias in the modified Stroop task remains unclear and results of cocaine cue attentional bias studies utilizing this task should be interpreted with this understanding.

Studies using the modified Stroop task to measure cocaine cue attentional bias have produced mixed results with outcomes being dependent upon sample selection and experimental design. The Stroop effect is mostly commonly observed in cocaine-dependent individuals or individuals providing urine samples positive for cocaine. In a seminal modified Stroop study, 23 cocaine-using individuals with urine samples positive for cocaine and 22 non-cocaine-using controls completed the word and picture versions of the modified Stroop task (Hester et al., 2006). In the picture version, cocaine and neutral images were presented with a colored border. Individuals were instructed to identify as quickly as possible the border color. In the modified Stroop tasks, cocaine users, but not controls, were slower to indicate the color (i.e., word color and border color) of the cocaine-related stimuli relative to the matched neutral stimuli. This finding has been systematically replicated by an independent group of investigators (Liu et al., 2011). Response time to cocaine-related words and matched-neutral words was measured in 37 cocaine dependent individuals and 32 controls. Individuals in the cocaine-using group were significantly slower than the controls to respond following the presentation of cocaine-related words compared to neutral words.

Modified Stroop interference is predictive of treatment-related outcomes (Carpenter et al., 2006, 2012; Marhe et al., 2013; Streeter et al., 2008; Waters et al., 2012). Waters and colleagues (2012) provide evidence that modified Stroop performance correlates positively with subsequent cocaine use in treatment-seeking,

cocaine dependent individuals. Using Ecological Momentary Assessment, modified Stroop interference increased during self-reported temptations to relapse to cocaine. Individuals who relapsed during the study displayed greater modified Stroop interference than individuals who did not relapse (Marhe et al., 2013). Carpenter and colleagues (2006) also observed a relationship between modified Stroop performance and treatment outcomes. Response time to cocaine-related and neutral words was measured in treatment-seeking individuals who met criteria for cocaine dependence. Individuals who displayed greater modified Stroop interference were more likely to provide cocaine positive urine samples throughout treatment as well as to drop out of treatment earlier. In a later study conducted by the same research team, 25 abstinent, treatment-seeking, cocaine dependent individuals completed the modified Stroop prior to enrolling in a 24-week outpatient treatment program (Carpenter et al., 2012). A modest, positive correlation was detected between interference scores and treatment outcomes when a voucher system was in place to reinforce abstinence.

Studies that did not detect Stroop interference either failed to experimentally control for confounding variables (Copersino et al., 2004; Vadhan et al., 2007) or enrolled light cocaine users (Montgomery et al., 2010). In one study, 20 treatment-seeking and 17 non-treatment-seeking, cocaine-dependent individuals completed the modified Stroop task (Vadhan et al., 2007). Treatment-seeking individuals responded slower to cocaine-related words than neutral words. In contrast, non-treatment-seeking individuals did not display modified Stroop interference. Interpretation of the results was confounded by group differences such as amount of cocaine used per week, preferred route of administration, employment status, race, and co-morbid mood disorders. In addition, treatment-seeking individuals were actively receiving treatment. In a second study confounded by group variables, the modified Stroop task was administered to 23 cocaine dependent individuals with co-morbid schizophrenia, 20 cocaine-dependent

individuals without a co-morbid diagnosis, and 19 individuals with schizophrenia only (Copersino et al., 2004). Stroop interference was present in the cocaine-dependent-only group, but not in the two groups diagnosed with schizophrenia. The results of this experiment were confounded by psychiatric medication. Nearly half the individuals diagnosed with schizophrenia were receiving a neuroleptic or atypical antipsychotic, which likely affected the primary dependent variable, psychomotor performance. As a result, both studies described above failed to identify the specific variables that influence performance on the modified Stroop. A third study enrolled lighter cocaine users and failed to detect modified Stroop interference (Montgomery et al., 2010). In that study, Stroop interference was measured in 32 non-dependent, non-treatment-seeking current cocaine users and 40 non-cocaine-using controls following alcohol administration. In a between-subjects design, response time to cocaine-related and neutral words was measured following placebo (0.0 g/kg) and alcohol administration (0.4 g/kg). Stroop interference was not detected following placebo or alcohol administration in either group. By enrolling light cocaine users that did not display Stroop interference under the placebo condition, the effect of alcohol administration could not be determined. As Stroop interference had not previously been demonstrated in light cocaine users, the influence of alcohol remains unclear.

To summarize, cocaine-dependent individuals are slower to indicate the color of cocaine-related stimuli than neutral stimuli during the modified Stroop task and interference scores correlate positively with treatment-related outcomes. Stroop interference is not observed in matched, non-cocaine-using controls in studies that fail to experimentally control for confounding variables or enroll light cocaine users. The specific role of attentional bias to cocaine-related cues during the modified Stroop task, however, remains unclear. A notable gap in the cocaine-cue literature has been

demonstrating attentional bias to cocaine-related cues using a more direct measure of attentional bias (i.e., visual probe task).

The first task developed to measure cocaine cue attentional bias was a hybrid between the modified Stroop and visual probe task (Franken et al., 2000). Cocaine-related or neutral words were presented on the left or right side of the screen and response time was measured to a probe that either replaced the word or appeared on the opposite side of the screen. Response time did not differ between cocaine and neutral words, indicating no attentional bias. Attentional bias scores (difference between response time to cocaine and neutral words), however, correlated positively with self-reported craving for cocaine as well as obsessive thoughts regarding cocaine.

Three studies have measured cocaine cue attentional bias using the visual probe task. The first study measured cocaine cue attentional bias following alcohol administration (Montgomery et al., 2010). Participants were 32 non-treatment-seeking current cocaine users and 40 non-cocaine-using controls. Response time to probes replacing cocaine-related and neutral images was measured following alcohol administration (0 and 0.4 g/kg) in a between-subjects design. Following placebo, cocaine-using individuals did not display a cocaine cue attentional bias (-11.2 ms). Following alcohol administration, cocaine-using individuals responded faster to cocaine-related images than neutral images, indicating an increased attentional bias (13.2 ms). Controls did not display an attentional bias under either condition.

The second study measured cocaine cue attentional bias in a sample of cocaine dependent individuals with or without borderline personality disorder (BPD; Bardeen et al., 2014). In a within-subjects design, the visual probe task was conducted immediately following a personalized emotionally evocative script and a neutral script. Following the neutral script, attentional bias scores did not differ significantly from zero indicating that participants did not display an attentional bias. Following the emotional script, men with

BPD displayed a significantly larger cocaine cue attentional bias than men without BPD, and women.

Both visual probe studies described above failed to demonstrate attentional bias in their control conditions (i.e., following placebo or neutral script). A third study measuring cocaine cue attentional bias during the visual probe task did not report response time to cocaine-related and neutral stimuli or statistically analyze the difference between these values (Tull et al., 2011). As such, attentional bias cannot be determined. The absence of attentional bias in cocaine-using individuals is not consistent with the larger attentional bias literature, which has more reliably demonstrated that the visual probe task is a sensitive measure of attentional bias (Field and Cox, 2008). The complexity of the experimental designs might contribute to this effect (i.e., administering alcohol or manipulating emotional state). These studies demonstrate the value of organized, programmatic research in which basic experimental designs are validated prior to testing more advanced hypotheses. Specifically, an experiment in which cocaine dependent individuals and non-cocaine-using controls complete the visual probe task is a critical first step that has been overlooked. From this, the clinical relevance of cocaine cue attentional bias can then be determined.

The most direct method of studying cocaine cue attentional bias is to use eye-tracking technology during the visual probe task. This has not yet been conducted in cocaine-using individuals. One previous study approximated attentional allocation by measuring the visual scanning patterns of 19 treatment-seeking, cocaine dependent individuals (Rosse et al., 1993; 1997). In this task, participants were presented with a cocaine image (i.e., crack pipe) and then a neutral image (i.e., flower on stem). Each image was independently viewed for 90 s. Eye-scanning paths were then analyzed qualitatively (Rosse et al., 1993) and quantitatively (Rosse et al., 1997) to determine how closely scanning paths mapped onto the images. In the qualitative analysis, visual

scanning patterns more closely traced the cocaine-related images than the neutral images, suggesting more attention being directed towards the cocaine-related image. In addition, individuals who scanned the cocaine-related images more closely also reported increased cocaine cravings and urge to use (Rosse et al., 1993). In the quantitative analysis, cocaine craving correlated positively with the number of attentive fixations and correlated negatively with the number of preattentive saccades and fixations (Rosse et al., 1997). These results suggest that sophisticated eye-tracking technology is the most sensitive measure of cocaine cue attentional bias.

Summary and Proposal

Cue saliency plays a critical role in drug use and relapse. Through incentive sensitization, substance-related cues acquire incentive motivational properties. As a result, substance-related cues are uniquely salient to substance users. Attentional bias during the visual probe task with eye-tracking technology is a direct measure of the cue's salience and attentional bias has been observed to a variety of substances (e.g., alcohol, marijuana, tobacco). A notable gap in the literature has been demonstrating attentional bias to cocaine cues using this direct measure of attention. In addition, the behavioral mechanism and clinical relevance of cocaine cue attentional bias is poorly understood. The overarching goal of this dissertation is to demonstrate cocaine cue attentional bias using the visual probe task with eye-tracking technology and to explore the mechanism of cocaine cue attentional bias. This dissertation endeavors to achieve this by addressing three aims.

The first aim of this dissertation is to demonstrate that fixation time is a sensitive and reliable measure of cocaine cue attentional bias. This aim will be accomplished through the conduct of Experiments 1 and 2. Previous attentional bias research has used indirect measures of attention that are not sensitive to cocaine cue attentional bias and unreliable across repeated assessments. A sensitive and reliable

measure of cocaine cue attentional bias will provide the foundation for the conduct of subsequent studies examining the mechanism of attentional bias.

Experiment 1 will demonstrate that fixation time is a sensitive and stable measure of cocaine cue attentional bias. Fifteen cocaine-using participants and fifteen non-cocaine-using controls will complete the visual probe task with eye tracking and the modified Stroop at two time points. The hypotheses are: 1) cocaine users will fixate on cocaine-related images longer than neutral images, 2) non-cocaine-using controls will not display an attentional bias, 3) cocaine cue attentional bias will be stable across repeated measures in cocaine users, 4) cocaine cue attentional bias will correlate with indices of drug use severity.

Experiment 2 will demonstrate that the visual probe task using eye-tracking technology is a reliable measure of cocaine cue attentional bias. Replication is a main tenet of experimental research and enrolling a larger sample of cocaine-using individuals will provide sufficient power to conduct regression analysis to determine the test-retest reliability of the visual probe task across two repeated measures. Data from 36 participants will be aggregated from two studies measuring cocaine cue attentional bias using the visual probe task. It is hypothesized that cocaine cue attentional bias, as measured by visual probe fixation, is reliable across repeated measures.

The second aim of this dissertation is to determine whether the magnitude of attentional bias, as measured by fixation time, is specific to clinically relevant differences in substance use. Specificity is necessary to determine the validity of the visual probe task as well as to describe the mechanism of attentional bias. Experiment 3 will demonstrate that attentional bias is specific to the substance use disorder of the individual. Twenty participants who meet criteria for cocaine dependence and twenty participants who meet criteria for cocaine and alcohol dependence will complete a visual probe task with eye-tracking technology. During this task, cocaine cue attentional bias

and alcohol cue attentional bias will be assessed. It is hypothesized that if attentional bias is specific to substance use disorder, then 1) the magnitude of cocaine cue attentional bias will be larger than alcohol cue attentional bias in individuals who meet criteria for cocaine dependence only, and 2) the magnitude of cocaine and alcohol cue attentional bias will not differ in individuals who meet criteria for both cocaine and alcohol dependence.

Experiment 4 will determine how the magnitude of cigarette cue attentional bias differs in individuals who abuse cocaine and smoke cigarettes relative to individuals who only smoke cigarettes. The results of epidemiological studies indicate that individuals meeting dependence criteria for both cocaine and nicotine use cocaine at an earlier age, use more grams per occasion, and use cocaine at a more frequent rate (Budney et al., 1993; Roll et al., 1996). However, the magnitude of cigarette cue attentional bias has not previously been measured in cocaine-abusing individuals. Twenty cocaine-using smokers and twenty non-cocaine-using smoking controls will complete a visual probe task with eye-tracking technology. During this task, the magnitude and specificity of cocaine and cigarette cue attentional bias will be assessed. The hypotheses are: 1) cocaine-using smokers will fixate on cocaine-related images longer than neutral images, 2) non-cocaine-using smoking controls will not display a cocaine cue attentional bias, 3) both groups will display a cigarette cue attentional bias, and 4) the magnitude of cigarette cue attentional bias will be larger in the cocaine-using individuals given the additional behavioral and pharmacological conditioning history between cocaine and cigarette smoking.

The third aim of this dissertation is to identify factors related to substance use history that correlate with cocaine cue attentional bias. Identifying specific behavioral and demographic factors will help inform the mechanism responsible for cocaine cue attentional bias. In Experiment 5, the relationship between cocaine cue

attentional bias and substance use history will be assessed in a large sample aggregated from five studies measuring cocaine cue attentional bias using the visual probe task. The hypotheses are: 1) participants will display an attentional bias for cocaine-related cues and 2) cocaine cue attentional bias will correlate with substance use history (e.g., DSM-IV diagnostic criteria, cocaine-positive urine).

Figure 1.1

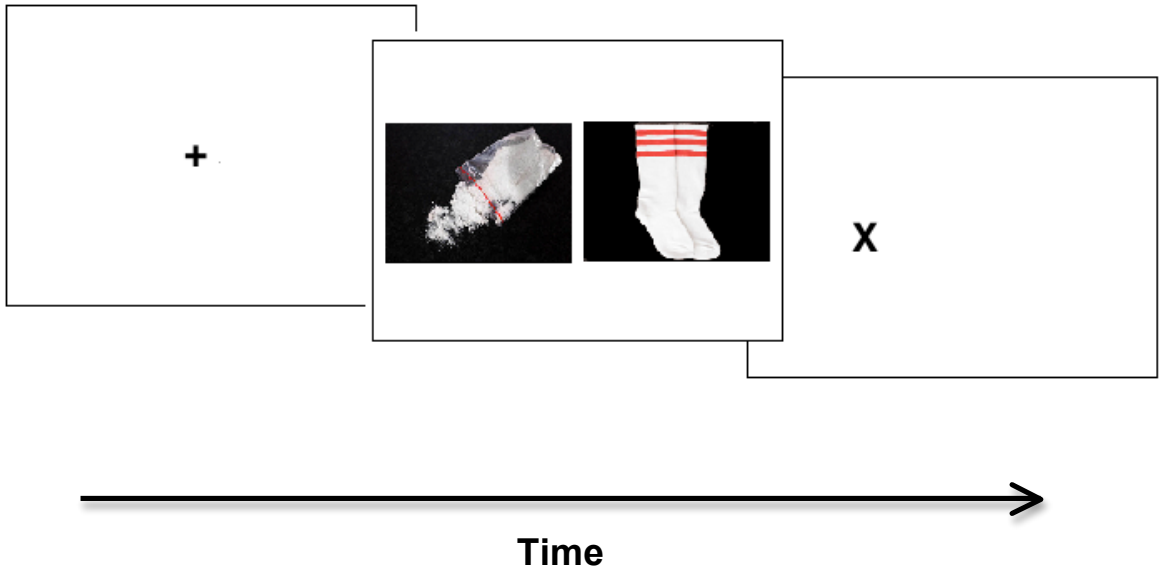

Figure 1.1. Schematic overview of visual probe task. A fixation point appears at the center of the screen followed a substance-related and a neutral image presented side-by-side. A probe (i.e., an X) then replaces one of these images and the participant must make a choice response to indicate the location of the probe.

Chapter 2

FIXATION TIME IS A SENSITIVE MEASURE OF COCAINE CUE ATTENTIONAL BIAS (STUDY 1; Marks et al., 2014b)

Introduction

Incentive theories of drug addiction acknowledge that chronic substance use sensitizes dopamine pathways in brain regions associated with attribution of incentive salience and reward (Robinson and Berridge, 1993). This dopaminergic hypersensitivity produces an increased 'wanting' or motivation for the substance. Over repeated associative pairings with the substance, incentive salience for the substance transfers to the substance-related cue causing the cue to elicit a conditioned motivational state in active substance users (Goldstein and Volkow, 2002). This motivational state results in attention biased in favor of substance-related cues (Lyvers, 2000; Robinson and Berridge, 1993). Consequently, substance users will selectively attend to substance-related cues in the environment (Franken, 2003; Klinger and Cox, 2004; Robinson and Berridge, 1993). This allocation of a disproportionate amount of time attending to substance-related stimuli is referred to as attentional bias. The central role of attentional bias in drug-seeking behavior makes it a promising treatment target in the human laboratory and clinic.

Substance-related attentional bias has been most commonly studied using the modified Stroop. In this task, a substance-related or a neutral word is presented on a computer screen. Participants are instructed to identify the color of the text as quickly as possible while ignoring the semantic content of the word. The expected result is that response time to substance-related words is slower than to neutral words. This interference with substance-related words has been labeled as attentional bias. The bias captured in the modified Stroop, however, is more complex than attentional allocation and includes other cognitive and emotional processes (Cox et al., 2006; Williams et al.,

1996). In addition, response time is an indirect measure of Stroop interference as it relies upon a motoric response to approximate speed of processing and attentional allocation (Field and Cox, 2008). Therefore, other more direct measures of visuo-spatial attention have been developed (Field et al., 2004a).

A more recent measure of attentional bias is the visual probe task (Allport; 1989; LaBerge, 1995). In the visual probe task, a substance-related image and a neutral image are briefly presented side-by-side. A probe (i.e., an X) then replaces one of these images and the participant must make a choice response based on the location of the probe. Participants respond more quickly to probes replacing the substance-related image, presumably because they were already fixating on the substance-related image when the probe appeared due to its incentive salience (Posner et al., 1980). This task is a more direct index of attention than the modified Stroop because response time is dependent upon allocation of visual attention immediately prior to the presentation of the probe. Like the modified Stroop, however, this strategy relies on response time and thus remains an indirect measure of attentional bias. In addition, response time only approximates the final gaze direction and not attention during the presentation of the images (Field and Cox, 2008). Response time, particularly in the visual probe task, has low internal reliability (Ataya et al., 2012) and test-retest reliability (Spiegelhalder et al., 2011) resulting in inconsistent findings across investigative groups and drug classes (Field et al., 2004b, 2006; Miller and Fillmore, 2011; Mogg et al., 2003; Schoenmakers et al., 2008).

Recognizing the limitations of response time, some investigators have argued for using more direct measures to quantify attentional bias (Miller and Fillmore, 2011). Eye-tracking technology directly measures visual attention by recording how participants direct their gaze (Godijn and Theeuwes, 2003). When applying eye tracking to the visual probe task, the amount of time spent fixating on each image type is measured. Unlike

response time to the probe, visual attention is an objective measure of attentional allocation to two concurrently presented stimuli that matches the relative reinforcing value and availability of the stimuli presented (Schroeder and Holland, 1969; Theeuwes and Belopolsky, 2012). Attentional bias is defined as longer fixation time toward substance-related images compared to neutral, control images. Fixation time is an effective method of measuring attentional bias to cannabis (Field et al., 2004a), alcohol (Miller and Fillmore, 2010, 2011), and nicotine (Mogg et al., 2003). Fixation time is also a more sensitive measure of alcohol and cannabis cue attentional bias than response time (Field et al., 2006; Miller and Fillmore, 2011) and has greater internal reliability (Ataya et al., 2012; Field and Christiansen, 2012). The stability of attentional bias as measured by fixation time across repeated measurements, however, is unknown.

A notable gap in the literature has been demonstrating attentional bias to cocaine cues using fixation time as the dependent measure in a visual probe task. Studies that have utilized the visual probe have only measured response time and have found little evidence of cocaine cue attentional bias in cocaine-using individuals in their control conditions (Bardeen et al., 2014; Montgomery et al., 2010; Tull et al., 2011). One study has approximated attentional allocation by measuring visual scanning patterns and found that attentive fixations to a cocaine image, but not a neutral image, were positively correlated with cocaine craving (Rosse et al., 1993). The aims of this study were to demonstrate that fixation time as measured by the visual probe task is a sensitive and stable measure of cocaine cue attentional bias.

Methods

Participants

Thirty-nine individuals were recruited to participate in this research study. Seven were screen fails and two were lost to follow up between the first and second sessions. Participants were 15 adults who reported using cocaine within the past month and 15

adults who did not report cocaine use in the past year and reported no more than five lifetime uses. Participants were matched on age to control for age-related differences in response time (Fozard et al., 1994). Participants were also matched on years of education to further equate the groups. Participants were primarily recruited through word of mouth and postings on community bulletin boards. Potential participants were excluded if they reported a current prescription for a psychiatric medication or dependence on any drug that could produce significant withdrawal symptoms during testing (e.g., opioids or benzodiazepines). The Institutional Review Board of the University of Kentucky Medical Center approved this experiment and participants gave their written informed consent before participating. Participants were compensated for their time.

Procedures

Participants completed two sessions separated by 7 to 14 days (mean = 8.1 days; SEM = 0.3). Participants were told that the purpose of the experiment was to study the behavioral effects of cocaine use. Prior to each session, participants were instructed not to consume stimulants (excluding nicotine) within four hours of their scheduled session to decrease the likelihood of participants being acutely intoxicated during testing. Participants who smoked tobacco were permitted to smoke prior to, but not during, sessions. All participants underwent a field sobriety test and provided a breath sample negative for alcohol prior to each session to ensure that they were not currently intoxicated.

During Session 1, participants completed the visual probe task followed by the modified Stroop operated using E-prime experiment generation software (Schneider et al., 2002) and performed on a PC. Participants also completed screening questionnaires on current and past physical and mental health, measures of current psychological functioning, and detailed substance use history (Sevak et al., 2011). Included in the

questionnaires were the Drug Abuse Screening Test (DAST; Skinner, 1982), the Michigan Alcohol Screening Test (MAST; Selzer, 1971), and the Fagerstrom Test for Nicotine Dependence (FTND; Heatherton et al., 1991). The Timeline Followback (TLFB) procedure was used to assist participants in reporting the frequency and amount of cocaine used in the past month (Sobell and Sobell, 1992). During Session 2, participants completed the visual probe task followed by the modified Stroop as well as the TLFB to assess interim cocaine use. The TLFB included a screener question. If a participant denied cocaine use in the time period specified by the TLFB, the participant was instructed to move on to the next questionnaire.

Behavioral Tasks

Visual Probe Task. Attentional bias was measured using the visual probe procedure based on Roberts and colleagues (Roberts et al., 2012). For each trial, two 13 cm x 18 cm images (a cocaine-related image and a matched neutral image) were presented side-by-side, 3 cm apart, on a computer screen for 1000 ms. The amount of time (ms) fixating on the cocaine and neutral image was measured. Upon offset of the image pair, a visual probe (X) appeared either on the left or the right side of the screen, in the same location as one of the previously presented images. The amount of time (ms) to respond to the probe was measured. Participants were instructed to look at both images and then to respond as quickly as possible to the probe by pressing one of two response keys indicating on which side the probe appeared. Participants completed ten practice trials to ensure that they understood the task requirements.

Critical task stimuli were ten cocaine images matched with ten neutral images (i.e., non-cocaine-related). Cocaine images contained crack or powder cocaine as well as related paraphernalia. Neutral images were matched by the investigators on the number of objects in the image, the size of those objects, and the color scheme. Images were presented four times each once for each of the four image/probe combinations (i.e.,

left and right image locations and visual probe locations). In addition, 40 filler trials consisting of ten pairs of additional neutral images were intermixed with the test trials. Stimuli in filler trials were a separate set of neutral images (e.g., shoes, telephone) unrelated in content to the cocaine images or their matched, neutral images.

Fixation data were collected using Tobii T120 and X2-60 eye trackers (Tobii Technology, Sweden). Eye movement was sampled at 60 Hz. Onsets of fixations were defined as periods of at least 100 ms during which the line of gaze had a standard deviation of less than 0.5° of visual angle. Offsets of fixation were determined by periods of at least 50 ms in which the gaze position was at least 1° of visual angle away from the initial fixation position. A fixation on a cue was defined as looking within the borders of the image. Mean fixation time for cocaine and neutral images was calculated by summing the total fixation time for critical trials and then dividing by the total number of critical trials (40). An attentional bias score was determined for each participant as the mean fixation time difference between cocaine and neutral images. A response time score was determined for each participant as the mean response time difference between cocaine and neutral images across the critical trials.

Modified Stroop Task. The modified Stroop is an alternative measure of attentional bias previously described by Liu and colleagues (2011). Modeled after the emotional Stroop, participants were presented with ten cocaine-related words (e.g., crack, high) and ten length-matched neutral words (e.g., couch, lamp) on a computer screen. The text was colored red, blue, or green and participants were instructed to respond as quickly as possible on a keyboard to indicate the color in which the word was written. Each word was presented on the screen until the participant made a response or 1800 ms had passed. Words were separated by 500 ms intertrial interval. Cocaine-related words were presented in four blocks of 30 trials, as were neutral words. Cocaine blocks alternated equally with neutral blocks.

Data Analysis

Independent samples *t*-tests were conducted to compare demographics for continuous variables and a chi-square analysis was conducted to compare sex and race distribution between groups (i.e., cocaine-using individuals and controls). The outcome measures described above were analyzed using a mixed-model analysis of variance (ANOVA) for the visual probe task and modified Stroop (StatView, Cary, NC, USA). The within-groups factors were cue type (cocaine and neutral) and session (session 1 and session 2) and the between-groups factor was group (cocaine and control). The mean-square error term was used to conduct Tukey's Honestly Significant Difference (HSD) *post hoc* tests to determine potential differences between conditions. *Post hoc* tests were considered significant at $p < 0.05$, with Cohen's *d* effect sizes reported for all *post hoc* comparisons. Pearson product-moment correlations were conducted between attentional bias scores in the cocaine-using group during session 1 and key indices of cocaine use. Pearson correlations were considered significant with a Bonferroni corrected value of $p < 0.01$.

Results

Demographics

Table 2.1 presents the mean, standard deviation (SD), *t*-value and chi-square value for comparisons between group means. The individuals in the cocaine-using group reported significantly greater cocaine use (preferentially via the smoked route) as well as higher DAST and MAST scores than the control group. The groups did not differ significantly on any other demographic characteristics.

Visual Probe Fixation Time

On average, fixations were recorded for 92% of trials. Missing fixations occurred because participants fixated outside of areas of interest, made saccades faster than 100 ms, and failure of the eye tracking equipment to capture gaze direction. Table 2.2 shows

the ANOVA results for fixation time during the visual probe task. A main effect of cue type was subsumed under a significant interaction between cue type and group for visual probe fixation time. All other effects were non-significant. Cocaine users fixated on cocaine-related images longer than neutral images during session 1 and session 2, indicating a significant attentional bias during both sessions (Table 2.3). In contrast, the control group did not differ in fixation time for cocaine and neutral images during either session 1 or 2. *Post hoc* comparisons between groups indicated that the cocaine-using group did not fixate on cocaine-related images significantly longer than the control group. The control group, however, fixated on neutral images longer than the cocaine-using group during session 1 and session 2.

Pearson product-moment correlations were conducted between attentional bias scores during session 1 and indices of cocaine use in the cocaine-using group. Cocaine cue attentional bias as measured by fixation time during the visual probe task correlated positively with self-reported lifetime cocaine use (Table 2.4). Other indices of cocaine use did not significantly correlate with fixation time.

Visual Probe Response Time

Response time data only included critical trials in which a correct response was made longer than 100 ms after the probe appeared (98% of trials). The ANOVA results revealed no significant interactions or main effects of group, cue type, or session, indicating no attentional bias as measured by visual probe response time (Table 2.2). Response time during the visual probe task did not correlate significantly with any indices of cocaine use (Table 2.4).

Modified Stroop Response Time

Response time data only included correct responses (93% of trials). The ANOVA results revealed a significant main effect of session (Table 2.2). Response time for both groups was faster on session 2 than session 1 (Table 2.3). All other effects were non-

significant. Response time during the modified Stroop task did not correlate significantly with any indices of cocaine use (Table 2.4).

Discussion

This experiment demonstrated that cocaine users attend more to cocaine-related images than neutral images, whereas, controls allocate attention equally to both cocaine and neutral images. This bias is most evident when visual attention is directly measured (i.e., fixation time), such that cocaine users display a longer mean fixation time towards cocaine images compared to neutral images. The salience of cocaine-related cues is consistent with a large cue reactivity literature demonstrating that substance users display attentional bias to substance-related cues (Field and Cox, 2008; Robbins and Ehrman, 2004). The present study extends this literature by demonstrating that this robust attentional bias as measured by fixation time does not change significantly over repeated measurements, indicating stability of the mean.

Importantly, fixation time correlated positively with self-reported lifetime cocaine use. Lifetime use uniquely approximates overall frequency of use, and is likely a proxy of an individual's conditioning history with a substance. Recent conditioning history variables, such as past month use, however, did not significantly correlate with the attentional bias. Taken together, these findings indicate that attentional bias, as measured by fixation time, may be a product of long-term conditioning history with cocaine. This relationship provides further validation for fixation time as a sensitive measure of cocaine cue attentional bias. Research measuring alcohol cue attentional bias with fixation time has similarly found a positive correlation between attentional bias and substance use history, however only recent use (i.e., past 12 weeks) was assessed (Weafer and Fillmore, 2012). The present finding provides additional support for incentive models of attentional bias, which predict that attentional allocation shifts as a function of increased substance use. Likewise, operant models of attention predict that

attentional allocation will match the relative reinforcing value of the stimuli presented (Schroeder and Holland, 1969; Theeuwes and Belopolsky, 2012).

The control group did not display a cocaine cue attentional bias as measured through fixation time or response time across repeated measurements. This result is also consistent with the extant attentional bias literature, which finds that non-users do not display a substance-related attentional bias when measured by fixation time (Field et al., 2004a; Mogg et al., 2003). Worth noting is that the cocaine-using group did not fixate longer on the cocaine-related images than the control group. Instead, the cocaine-using group engaged less attention towards non-cocaine-related stimuli than individuals in the control group. This pattern of attentional bias indicates that substance-using individuals are not necessarily more attentive to substance-related stimuli than controls, but less attentive to alternative, non-substance-related stimuli. Visual inspection of data from two previous studies measuring fixation time to substance-related images similarly suggests that the substance users and controls differed in their fixation time to neutral images, but not to the substance-related images (Field et al., 2004a; Mogg et al., 2003). These results may provide new insight into the mechanism of attentional bias as measured by fixation time. Both incentive motivational and operant models of attentional bias hypothesize that substance-related stimuli acquire unique salience in the environment as a result of the conditioning history with the substance of abuse. The present results alternatively suggest that substance-related stimuli are not more salient or reinforcing to substance users. Instead, non-substance-related stimuli may be less salient or reinforcing to substance users. A future study testing the alternative hypothesis that chronic substance use devalues non-substance-related stimuli (i.e., neutral images) might provide further insight into how incentive value is assigned to cues.

The visual probe task did not detect a cocaine cue attentional bias through response time to probe locations. Previous studies measuring response time using the

visual probe task have similarly failed to find strong evidence for cocaine cue attentional bias in the absence of moderators such as alcohol administration or post-traumatic stress disorder (Montgomery et al., 2010; Tull et al., 2011). The results of this study suggest that the direct measurement of attentional allocation through fixation time is a more sensitive assessment of cocaine cue attentional bias than psychomotor response time. The dissociation between fixation time and response time may be attributed to the differing components of attention that each outcome is designed to assess. As described above, fixation time directly measures sustained attentional allocation across the presentation of the images whereas response time only approximates the direction of the final gaze (Field and Cox, 2008).

The modified Stroop similarly failed to detect a significant difference in response time between cocaine-related words and neutral words. Participants responded faster to both word types in the second session, which is likely attributed to a practice effect. Previous studies have produced discrepant results with some studies detecting an attentional bias (Copersino et al., 2004; Ersche et al., 2010; Liu et al., 2011; Vadhan et al., 2007) and others not finding the bias (Carpenter et al., 2012; Vadhan et al., 2007). Self-reported cocaine use in the present study resembled the rate of use reported by both Vadhan and colleagues (2007) and Liu and colleagues (2011). The discrepant results between the present study, which did not detect modified Stroop interference, and previous studies that have detected modified Stroop interference may be attributed to the treatment-seeking status of the participants recruited. Vadhan and colleagues (2007) observed modified Stroop interference in treatment-seeking individuals but not non-treatment-seekers. Liu and colleagues (2011) also observed greater modified Stroop interference in treatment-seekers relative to non-treatment-seekers. Thus, the absence of modified Stroop interference observed in the present study may be a result of the population recruited, which included only non-treatment-seeking individuals. The

abovementioned studies also recruited a larger sample size. However, the small effect size detected in the present study suggests that null effect was not due to the study being underpowered. As a limitation, the modified Stroop was administered following the visual probe. It may be that exposure to the cocaine-related images during the visual probe task influenced performance on the modified Stroop.

In summary, fixation time during the visual probe task was the only behavioral measure sensitive to cocaine cue attentional bias in a sample of heavy cocaine users. Fixation time is a more direct measure of attentional bias than response time and less prone to non-specific changes in performance over time as was observed in the modified Stroop. This finding is in line with previous studies, which found visual probe fixation time to be a more sensitive and direct measure of substance cue attentional bias than response time (Field et al., 2006; Miler and Fillmore, 2011). In addition, mean attentional bias remained stable across sessions and correlated with self-reported lifetime cocaine use. The neurocognitive mechanisms leading to the formation of attentional bias (e.g., incentive salience, incentive motivation) and the functional importance of attentional bias, however, remain unclear. Nonetheless, the identification of a sensitive measure of cocaine cue attentional bias could guide a wide array of future studies. Specifically, cocaine cue attentional bias may function as a novel measure with which to assess the efficacy of an intervention, predict the likelihood of relapse, or it may itself serve as the target of an intervention (Schoenmakers et al., 2010).

Table 2.1

Mean, standard deviation (SD), t-value, and chi-square value for comparisons between group means.

Measure	Cocaine-Using Group (n = 15)		Control Group (n = 15)		Test of Significance	
Age	38.2	(11.1)	38.9	(9.3)	$t_{(28)} = 0.2$	
Females	9		8		$\chi^2_{(1)} = 0.3$	
Race					$\chi^2_{(2)} = 4.6$	
African American	13		9			
Caucasian	2		5			
Other	0		1			
Years of education	12.4	(2.0)	13.6	(2.3)	$t_{(28)} = 1.5$	
FTND	2.7	(3.1)	1.6	(2.6)	$t_{(28)} = 1.0$	
DAST	12.5	(6.4)	2.7	(3.3)	$t_{(28)} = 5.3$	*
MAST	13.4	(14.9)	5.2	(5.7)	$t_{(28)} = 2.0$	*
Days used per month						
Amphetamines	0.2	(0.8)	0.3	(1.3)	$t_{(28)} = 0.3$	
Benzodiazepines	0.7	(1.4)	0.2	(0.6)	$t_{(28)} = 1.2$	
Marijuana	9.5	(11.7)	6.5	(12.5)	$t_{(28)} = 0.7$	
Opioids	0.6	(1.1)	0.1	(0.3)	$t_{(28)} = 1.9$	
Cocaine						
Days used per month	16.6	(9.4)	0.0	(0.0)	$t_{(28)} = 7.0$	*
Days used per week	4.1	(2.1)	0.0	(0.0)	$t_{(28)} = 7.6$	*
Lifetime uses	2321.5	(2480.0)	0.2	(0.4)	$t_{(28)} = 3.6$	*
Years used	13.8	(9.3)	0.2	(0.4)	$t_{(28)} = 5.8$	*

* Asterisk indicates a significant difference between groups, $p < 0.05$.

Table 2.2

ANOVA effects (f) for visual probe and modified Stroop task.

	Visual Probe		Modified Stroop
	Fixation Time	Response Time	Response Time
		f	
Group	2.0	3.1	3.1
Cue Type	36.8 *	0.5	1.4
Cue Type x Group	13.5 *	1.1	0.1
Session	3.4	1.7	16.0 *
Session x Group	0.1	0.5	0.0
Session x Cue	2.0	2.4	0.1
Session x Cue Type x Group	0.2	0.0	0.0

* Asterisk indicates a significant effect, $p < 0.05$.
df (1, 28) for all effects.

Table 2.3

Mean, standard error mean (SEM), and effect size (Cohen's d) for visual probe and modified Stroop scores (milliseconds).

	Cocaine-Using Group						Control Group					
	Session 1			Session 2			Session 1			Session 2		
	Cocaine	Neutral	*d*	Cocaine	Neutral	*d*	Cocaine	Neutral	*d*	Cocaine	Neutral	*d*
Visual Probe												
Gaze Time	359.8 (37.9) [a]	209.3 (23.9)	1.2	372.0 (20.0) [a]	239.4 (14.3)	1.9	342.4 (22.2)	289.4 (18.8)[b]	0.7	355.5 (27.4)	339.2 (22.1)[b]	0.2
Response Time	518.7 (30.6)	535.3 (27.5)	0.1	518.9 (27.7)	520.8 (25.3)	0.0	474.6 (22.7)	481.3 (18.2)	0.1	460.4 (24.8)	450.6 (19.1)	0.1
Modified Stroop												
Response Time	843.6 (24.2)	833.0 (26.5)	0.1	805.6 (30.0)	796.6 (25.3)	0.1	776.3 (25.3)	768.5 (25.4)	0.1	739.2 (29.6)	736.7 (28.6)	0.0

Effect size reported between cocaine and neutral stimuli.

[a] Tukey *post hoc* analysis determined significant difference between cocaine and neutral fixation time in same session, $p < 0.05$.

[b] Tukey *post hoc* analysis determined significant difference between cocaine and control group neutral fixation time, $p < 0.05$.

Table 2.4

Pearson correlations between visual probe and modified Stroop scores of the cocaine-using group and indices of cocaine use.

	Visual Probe		Stroop
	Fixation Time	Response Time	Response Time
		r	
Lifetime uses	0.64 *	0.25	0.30
Years used	0.02	0.09	0.05
Days used past month	0.38	0.02	0.35
Days used past week	0.26	0.30	0.42
DAST	0.26	0.22	0.32

* Asterisk indicates a significant correlation, $p \leq 0.01$

Figure 2.1

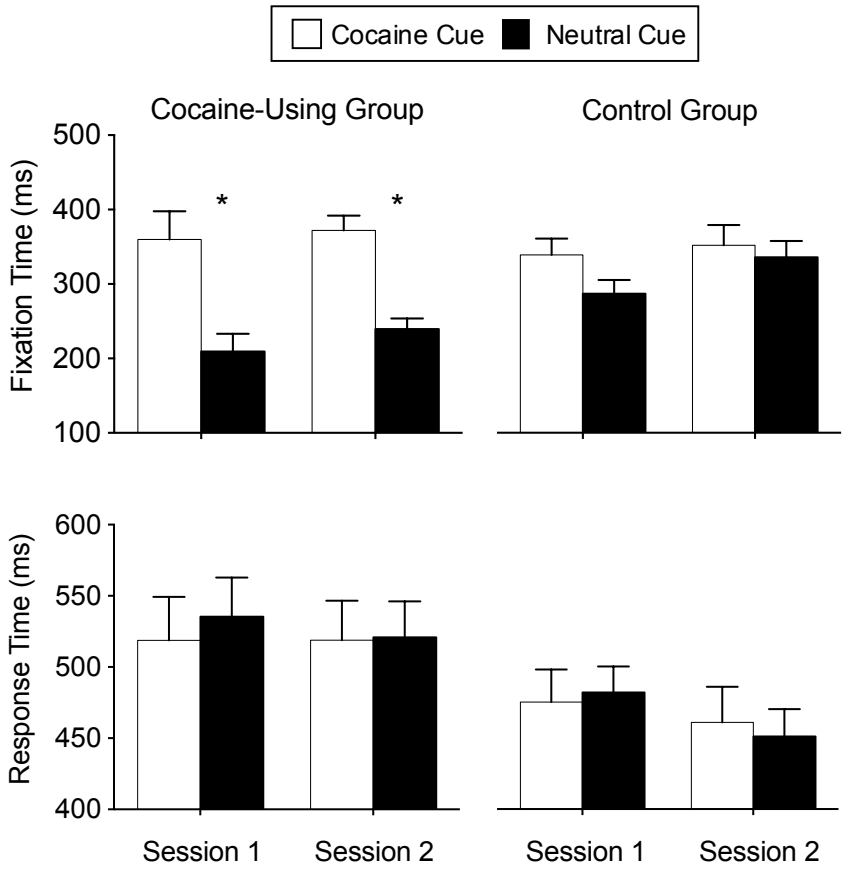

Figure 2.1. Mean fixation time and response time (milliseconds) to cocaine and neutral images for the cocaine-using group (n=15) and control group (n=15) during Session 1 and 2 of the visual probe task. Capped vertical lines indicate standard error of the mean.

Chapter 3

TEST-RETEST RELIABILITY OF EYE TRACKING DURING THE VISUAL PROBE TASK IN COCAINE-USING ADULTS

(STUDY 2; Marks et al., 2014a)

Introduction

Stimuli associated with substance use capture attention (Field and Cox, 2008). Allocating a disproportionate amount of time attending to substance-related stimuli, relative to control stimuli, is referred to as attentional bias. The central role of attentional bias in drug-seeking behavior makes it a promising treatment target in the human laboratory and clinic, but the utility of measuring attentional bias is contingent upon the reliability of the measure. Attentional bias can be directly and objectively measured with eye-tracking technology because fixation direction and duration indicate fine grain patterns in attentional allocation (Rayner, 1998).

The visual probe task adapted with eye-tracking technology is a sensitive measure of attentional bias in individuals who abuse cocaine (Marks et al., 2014b). Our laboratory previously adapted eye-tracking technology to the visual probe task to measure cocaine cue attentional bias (visual probe task described in detail in Marks et al., 2014b). Cocaine-using individuals (n=15) fixated on cocaine-related images significantly longer than neutral images, whereas controls (n=15) did not display an attentional bias, indicating discriminant validity. Importantly, this bias remained stable across two sessions, separated by an intersession interval of 7 to 14 days. Test-retest reliability, however, was not directly assessed previously due to the small sample size. No other studies have been conducted to examine the test-retest reliability of fixation time during the visual probe task.

The utility of studying attention to cocaine-related cues depends upon the identification of a reliable measure of attentional bias. Studies that have assessed the

reliability of the visual probe task have only measured response time, consistently finding poor test-retest reliability (Schmukle, 2005; Spiegelhalder et al., 2011) and internal reliability (Ataya et al., 2012). This study sought to demonstrate the test-retest reliability of cocaine cue attentional bias as measured by fixation time during the visual probe task.

Methods

Participants

Data from 36 adult participants who reported current cocaine use (i.e., past 30 days) and completed the visual probe task on two separate occasions were included in this analysis. No participants were excluded from any analyses. The sample size was determined by a power analysis indicating that with a significance level of 0.05, the power to detect a Pearson's *r* correlation of 0.50 would be at least 80 percent. All participants provided written informed consent and completed screening questionnaires on current and past physical and mental health, measures of current psychological functioning, and detailed substance use history (Sevak et al., 2011). Individuals with a current prescription for a psychiatric medication or dependence on any drug that could produce significant withdrawal symptoms during testing (e.g., opioids or benzodiazepines) were excluded. The Institutional Review Board of the University of Kentucky approved all protocols and informed consent documents.

Procedure

Data were gathered during routine screening and laboratory protocols, employing identical experimental procedures during collection of the visual probe data. Participants completed the visual probe task, after sobriety was verified, at two separate time points (mean interval = 91.6 days, SD = 100.3, range = 7 - 336). Before each measurement, participants were instructed not to consume stimulants (excluding nicotine) within four hours of their scheduled session to decrease the likelihood of participants being acutely

intoxicated during testing. Participants who smoked tobacco were permitted to smoke prior to each session. All participants passed a field sobriety test and provided a breath sample negative for alcohol prior to each session. Drug urine screens were conducted at the outset of each session as described previously (Marks et al., 2014b).

Visual Probe Task

Participants completed the visual probe task operated using E-prime experiment generation software (Psychology Software Tools, Pittsburgh, PA) on a PC. Fixation time data were collected using Tobii T120, T60-XL, and X2-60 eye trackers (Tobii Technology, Sweden). Three models were utilized due to shared resources with another laboratory and upgrades to technology over time. The Time 2 assessment was completed on the same eye tracker for 26 participants and on different eye trackers for 10 participants. Attentional bias was measured using the visual probe procedure described previously (Marks et al., 2014b). The primary outcome variables were fixation time to cocaine and neutral images and response time to probe location (ms).

Data Analysis

Statistical significance was set at the $p < 0.05$ level for all analyses. Descriptive and graphical methods were used to determine that data were normally distributed. Attentional bias scores were analyzed across the three eye trackers at Time 1 and 2 using unpaired *t*-tests. Attentional bias scores did not differ significantly as a function of eye tracker at either Time 1 (*t* values = -1.1 – 0.5, $p > 0.05$) or Time 2 (*t* values = -1.4 – 1.5, $p > 0.05$). Eye tracker model was not included as a covariate in subsequent analyses.

Fixation and response time data were analyzed using a two-way, repeated-measures analysis of variance (ANOVA; StatView, Cary, NC, USA). The factors were cue type (cocaine and neutral) and time (time 1 and time 2). The mean-square error term was used to conduct Tukey's honestly significant difference (HSD) *post hoc* tests.

Cohen's *d* effect sizes were reported for all *post hoc* comparisons. Bivariate Pearson correlations (*r*) assessed test-retest reliability and the correlation between fixation and response time. Partial correlational analyses (*pr*) controlled for the influence of time between measurements.

Results

Demographics

Thirty-six participants (19 female, 17 male) completed the study. Thirty were African American, five were Caucasian, and one was of mixed race. Participants were 39 ± 9 (mean ± SD) years old with 12 ± 2 years of education. All participants reported current cocaine use, using 11 ± 8 days in the month prior to screening, and 14 ± 8 years in total. Thirty-one participants reported consuming alcohol (15 ± 14 standard drinks per week). Twenty-nine participants were daily cigarette smokers (11 ± 8 cigarettes per day). In the past 30 days, twenty-seven participants reported marijuana use (13 ± 11 days), eleven reported opiate use (4 ± 4 days), seven reported benzodiazepine use (3 ± 2 days), and two reported amphetamine use (2 ± 1 days).

Visual Probe Fixation Time

On average, fixations were made on 87 ± 3% of trials. The ANOVA results revealed a significant main effect of cue type, $F_{(1,35)} = 56.5$, $p < 0.0001$. Participants fixated on cocaine-related images significantly longer than neutral images during time 1 and 2 (Table 3.1). The main effect of time, $F_{(1, 35)} = 0.3$, $p = 0.6$, and the interaction between cue type and time, $F_{(1,35)} = 1.4$, $p = 0.2$, were non-significant indicating stability of the group means across the two measurements. A positive bivariate Pearson correlation between attentional bias scores at time 1 and 2 indicates significant test-retest reliability (Fig. 3.1). The partial correlation is consistent with the bivariate correlation, indicating that the time interval between measurements did not influence the test-retest reliability of cocaine cue attentional bias (Table 3.1).

Visual Probe Response Time

Response time data only included critical trials in which a correct response was made longer than 100 ms after the probe appeared (97 ± 3 % of trials). The ANOVA results revealed a significant main effect of time, $F_{(1,35)} = 7.3$, $p = 0.01$. Mean response time to probes replacing both cocaine and neutral images was significantly faster on time 2 than 1 (Table 3.1). The non-significant bivariate Pearson correlation between attentional bias scores at time 1 and 2 indicates low test-retest reliability. The partial Pearson correlation indicates that the time interval between measurements did not influence the reliability estimate (Table 3.1). Response time did not correlate significantly with fixation time at time 1 ($r = 0.26$, $p = 0.12$) or time 2 ($r = 0.19$, $p = 0.27$).

Discussion

This study replicates previous research, finding that cocaine-using individuals fixate on cocaine-related images significantly longer than matched, neutral images and extends those results by demonstrating that the magnitude of this attentional bias is reliable across two repeated measurements (Marks et al., 2014b). To our knowledge, the present study is the first to report the test-retest reliability of fixation time during the visual probe task. The test-retest reliability of attentional bias (i.e., the difference in fixation time between cocaine-related images and neutral images) therefore indicates that attentional allocation to both cocaine-related images and neutral images remains stable over time. This reliability of fixation time, as an index of attentional bias, indicates that it is well suited for longitudinal research both in the human laboratory as well as the clinic.

In contrast to fixation time, response time to probes replacing cocaine and neutral images did not differ. Previous studies measuring response time using the visual probe task have similarly failed to find strong evidence for cocaine cue attentional bias in the absence of moderators such as alcohol administration (Marks et al., 2014b;

Montgomery et al., 2010). In addition, the present study found that response time for both cocaine and neutral stimuli decreased at time 2, which may be due to practice effects. The low test-retest reliability of response time during the visual probe task is consistent with previous reports (Marks et al., 2014b; Schmukle, 2005; Spiegelhalder et al., 2011).

Several limitations of the present study should be noted. First, the test-retest reliability of attentional bias at time intervals shorter than one week has not been assessed. Repeated cue exposure at shorter intervals might decrease cue salience and thus, attentional bias. Second, with an average time interval of three months between measurements, test-retest reliability might be inflated due to a potential "washout period". However, partial Pearson correlations indicate that the time interval did not influence test-retest reliability, suggesting that fixation time attentional bias is a robust effect. The variable time interval may therefore be interpreted as a strength of the experimental design. Third, test-retest reliability is contingent upon the quality of the eye-tracking technology. However, three different eye-tracking models were employed in the present study and attentional bias did not differ as a function of model. This finding is promising for future studies utilizing different eye trackers models. Fourth, a non-cocaine-using control group would further inform whether this attentional bias is specific to cocaine users. A previous study, however, demonstrated that non-cocaine users do not display a cocaine cue attentional bias (Marks et al., 2014b).

Converging evidence indicates that fixation time is a sensitive and reliable method of measuring attentional allocation to cocaine-related cues. In contrast, response time during the visual probe task has not demonstrated reliability. Future studies, which seek to test hypotheses necessitating repeated assessments of cocaine cue attentional bias, should examine attentional allocation by measuring fixation time during the visual probe task.

Table 3.1

Mean attentional bias difference score [± 95% confidence interval] and Cohen's d effect size between cocaine and neutral images (milliseconds). Correlations and partial correlations reported between Time 1 and 2 attentional bias scores.

	Time 1		Time 2		Correlation	
Measure	Attentional Bias Score	*d*	Attentional Bias Score	*d*	r_{xx}	*pr*
Fixation Time	136.1 * [98.9 - 173.2]	1.3	113.8 * [76.7 - 151.0]	1.2	0.51 *	0.5 *
Response Time	12.0 [-25.1 - 49.2]	0.1	5.3 [-31.9 - 42.4]	0.1	0.24	0.24

[a] Asterisk indicates a significant effect, $p < 0.05$.

[b] *d* indicates Cohen's *d*

[c] r_{xx} indicates Pearson correlation

[d] *pr* indicates partial correlation

Figure 3.1

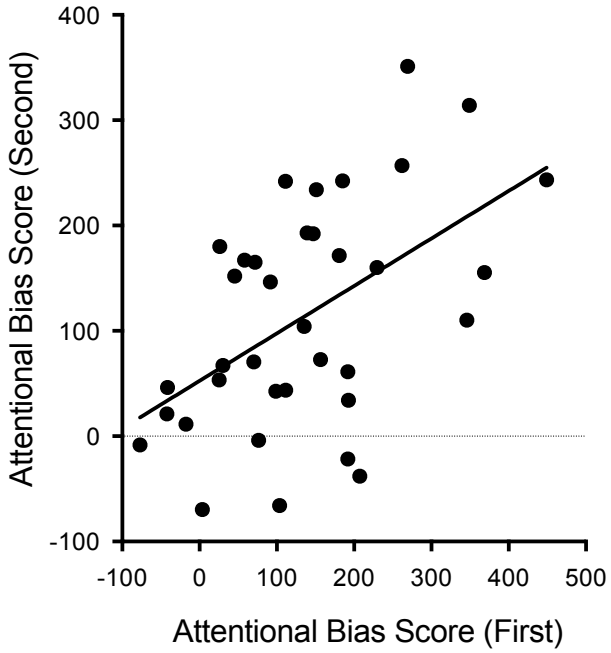

Figure 3.1. Regression line showing the significant positive correlation (r = 0.51) between cocaine cue attentional bias as measured by fixation time during the visual probe task at Time 1 and 2.

Chapter 4

THE MAGNITUDE OF DRUG ATTENTIONAL BIAS IS SPECIFIC TO SUBSTANCE USE DISORDER

(STUDY 3; Marks et al., In Press)

Introduction

Substance-related stimuli acquire incentive motivation and consequently, increased salience in the environment following chronic substance use (Robinson and Berridge, 1993). As such, individuals who abuse a substance display an attentional bias towards those substance-related images relative to neutral images (see Field and Cox, 2008). Attentional bias is defined as the allocation of a disproportionate amount of time attending to substance-related stimuli relative to neutral stimuli. Cocaine cue attentional bias can be directly and reliably measured using eye tracking during the visual probe task (Marks et al., 2014a, 2014b). Eye-tracking technology directly measures visual attention by recording where participants direct their gaze (Godijn and Theeuwes, 2003). Robust attentional bias has been demonstrated towards cocaine-related cues in cocaine-using individuals, but not non-cocaine-using controls (Marks et al., 2014b). The visual probe task, however, has only been designed to measure attentional allocation to one substance of abuse at a time.

Given that the majority of individuals who abuse cocaine also abuse other substances, the ecological validity of the single substance visual probe task is limited. Fifty-three percent of individuals who meet diagnostic criteria for cocaine dependence also endorse alcohol abuse or dependence (SAMHSA, 2012). Furthermore, 62% of those who report relapsing to cocaine within six months of treatment report consuming alcohol the same day (McKay et al., 1999). Despite high rates of comorbidity, alcohol-related cues have been studied independent of cocaine cues. Alcohol cue attentional bias has been observed in heavy drinkers, with a larger magnitude of bias in heavy

drinkers than in moderate or social drinkers (Townshend and Duka, 2001; Weafer and Fillmore, 2012). To improve ecological validity, attentional bias to cocaine and alcohol-related cues should be examined in individuals who abuse both cocaine and alcohol.

One study that attempted to examine attentional bias to multiple substance-related cues presented cocaine, heroin, marijuana, mixed, and neutral words in a modified Stroop task to treatment-seeking individuals who met criteria for a primary substance dependence of cocaine, heroin, or marijuana (Carpenter et al., 2006). Contrary to their hypothesis, response time to words specific to primary substance dependence did not produce greater Stroop interference. The negative result might be attributed the methodological constraints such as the number of substance-related stimuli presented and participants' treatment-seeking status. In addition, response time as measured by both the modified Stroop and visual probe task, is an indirect measure of attention as it relies upon a motoric response to approximate speed of processing and attentional allocation (Field and Cox, 2008).

In contrast to response time outcomes, the visual probe task with eye tracking is a direct and sensitive measure of attentional bias (Marks et al., 2014a, 2014b; Miller and Fillmore, 2011). Alcohol cue attentional bias, however, has not previously been measured in individuals who abuse cocaine. To this end, the visual probe task was modified to measure both cocaine and alcohol cue attentional bias using eye-tracking technology. This task was then administered to individuals who met diagnostic criteria for cocaine dependence or both cocaine and alcohol dependence. In addition to improving the ecological validity of the visual probe task, the present study was designed to determine whether attentional bias is specific to substance use disorder. Incentive motivational hypotheses predict that cue salience is the result of conditioning history associated with substance use. Over repeated associative pairings, incentive salience for the substance transfers to the substance-related cue causing the cue to become a

conditioned incentive stimulus and elicit a conditioned motivational state in active substance users (Robinson and Berridge, 1993). The relative salience of the substance-related cues should therefore be a function of substance use history. To achieve these aims, the magnitude of cocaine and alcohol cue attentional bias was directly compared. It was hypothesized that if attentional bias is specific to substance use disorder, then the magnitude of cocaine cue attentional bias, as measured by fixation time, should be larger than alcohol cue attentional bias in individuals who meet criteria for cocaine dependence only. In contrast, the magnitude of cocaine and alcohol cue attentional bias should not differ in individuals who meet criteria for both cocaine and alcohol dependence.

Methods

Participants

Forty-six individuals were recruited to participate in this research study. Four did not meet inclusion criteria and eye-tracking data were insufficient for two additional participants (i.e., greater than 2 standard deviations below the mean for number of fixations recorded). Participants were forty adults reporting current cocaine use (i.e., past 30 days) and fulfilling diagnostic criteria for cocaine dependence as determined by a computerized version of the Structured Clinical Interview for the Diagnostic and Statistical Manual-IV (SCID). Twenty of the 40 participants also fulfilled diagnostic criteria for alcohol dependence as determined by the SCID. Participants were primarily recruited through word of mouth and postings on community bulletin boards. Individuals with a current prescription for a psychiatric medication or dependence on any drug that could produce significant withdrawal symptoms during testing (e.g., opioids or benzodiazepines) were excluded. Individuals meeting criteria for alcohol dependence who reported current physiological withdrawal symptoms from alcohol were also excluded for safety. All participants provided written informed consent and completed

screening questionnaires on current and past physical and mental health, measures of current psychological functioning (i.e., 30-item mental status exam), and detailed substance use history (Sevak et al., 2011). The Institutional Review Board of the University of Kentucky approved all protocols and informed consent documents. Participants were compensated for their time.

Procedure

Data were gathered during routine screening for ongoing laboratory protocols. Participants completed a visual probe task during one outpatient session. Participants were instructed to abstain from drug use (excluding nicotine) for 12 h and caffeine use for 4 h prior to testing to decrease the likelihood of being under the acute effects of a substance. Participants who smoked tobacco were permitted to smoke prior to, but not during, session. All participants passed a field sobriety test and provided a breath sample negative for alcohol. Drug urine screens were conducted at the outset of the session as described previously (Marks et al., 2014b).

Visual Probe Task

Fixation data were collected using Tobii T60-XL and X2-60 eye trackers as described previously (Marks et al., 2014b; Tobii Technology, Sweden). Two different 60-hertz eye tracker models were utilized due to upgrades to technology over time, but eye-tracker model does not significantly influence fixation time data (Marks et al., 2014a). Attentional bias was measured using a modified visual probe procedure. For each trial, two 13 cm x 18 cm images (a substance-related and a matched neutral image) were presented side-by-side, 3 cm apart, on a computer screen for 1000 ms. The amount of time (ms) fixating on the substance and neutral image was measured. Upon offset of the image pair, a visual probe (X) appeared either on the left or the right side of the screen, in the same location as one of the previously presented images. The amount of time (ms) to respond, by pressing one of two response keys indicating on which side of the

screen the probe appeared, was measured. Response time data only included critical trials in which a correct response was made longer than 100 ms after the probe appeared. Participants completed ten practice trials containing only neutral images to ensure that they understood the task requirements.

Critical task stimuli consisted of five cocaine images matched with five neutral images (i.e., non-cocaine-related) and five alcohol images matched with five neutral images (i.e., non-alcohol-related). Cocaine images depicted crack or powder cocaine as well as related paraphernalia. Alcohol images contained a solitary image of an alcoholic beverage. Neutral images were matched on the number of objects in the image, size, and color scheme (e.g., a crack pipe matched with a pencil or a beer can matched with a soda can). Previous research has demonstrated robust attentional bias to these cocaine and alcohol images (Marks et al., 2014b; Miller and Fillmore, 2011). Important to note is that cocaine images were never presented side-by-side with alcohol images. Instead, cocaine images and their matched, neutral images were presented in separate trials as alcohol-images and their matched, neutral images. Images were presented four times, once for each of the four possible image/probe combinations for a total of 40 test trials, in random order. Forty filler trials consisting of ten pairs of additional neutral images were intermixed with the test trials as described previously (Marks et al., 2014b).

Data Analysis

Statistical significance was set at $p < 0.05$ for all analyses. Independent samples *t*-tests were conducted to compare demographics for continuous variables and chi-square analyses was conducted to compare categorical variables between groups. To assess potential baseline differences in performance between groups, response time (ms) to the 40 filler, neutral trials was analyzed using an unpaired *t*-test.

Mean fixation time (ms) was calculated by summing the total fixation time for each image type (cocaine, neutral-cocaine, alcohol, neutral-alcohol) and dividing by the

total number of trials (20). Attentional bias (fixation time and response time) was first assessed using a mixed-model analysis of variance (ANOVA**;** StatView, Cary, NC, USA) with substance (cocaine and alcohol) and cue type (substance and neutral) as the within-groups factors and group (cocaine and cocaine-alcohol dependent) as the between-groups factor. The mean-square error term was used to conduct Fisher's Protected LSD tests to determine potential differences between conditions. An analysis of covariance (ANCOVA) was conducted for the response time outcome. Substance (cocaine and alcohol) and cue type (substance and neutral) were the within-groups factors, group (cocaine and cocaine-alcohol dependent) was the between-groups factor, and response time to filler trials was included as a covariate to control for pre-existing skill or deficits.

Next, the total number of fixations on each image type (cocaine, non-cocaine-related neutral, alcohol, and non-alcohol-related neutral) was compared between groups (cocaine and cocaine-alcohol dependent) using independent samples *t*-tests to assess for group differences in fixation rates. Fixations were defined as gazes of at least 100 ms in duration with standard deviations of less than 0.5 degrees of visual angle.

Finally, an attentional bias score was calculated as the difference in fixation or response time between cocaine or alcohol images and their neutral images. Fixation and response time attentional bias scores were analyzed using an ANOVA with substance (cocaine and alcohol) as the within-groups factor and group (cocaine and cocaine-alcohol dependent) as between-groups factor. Fisher's Protected LSD tests were conducted as described above. An effect size (*d*) was calculated for all significant effects (Cohen, 1988). Bivariate Pearson correlations (*r*) were conducted between fixation and response time, and key indices of cocaine and alcohol use.

Results

Demographics

Table 4.1 presents the mean, standard deviation, *t*-value and chi-square value for comparisons between groups. The cocaine-alcohol dependent group reported more standard drinks per drinking episode and more total standard drinks in the past 30 days. The cocaine-alcohol dependent group also endorsed higher scores on the Michigan Alcohol Screening Test (MAST; Selzer, 1971), Alcohol Use Disorders Identification Test (AUDIT; Saunders et al., 1993), and Drug Abuse Screening Test (DAST; Skinner, 1982).

Visual Probe Fixation Time

The ANOVA results revealed a significant interaction between substance, cue type, and group, $F_{(1,38)} = 4.4$, $p < 0.05$ (Figure 3.1). Table 4.2 presents the mean and standard error of the mean for fixation time to substance-related and neutral images. The cocaine-dependent group displayed a significant attentional bias towards cocaine, but not alcohol. Fixation time for cocaine-related images was significantly longer than matched neutral images, $t_{(1,19)} = 5.3$, $p < 0.05$, whereas fixation time for alcohol-related images did not differ from matched neutral images, $t_{(1,19)} = 2.0$, $p > 0.05$. Cocaine cue attentional bias was significantly larger in magnitude than alcohol cue attentional bias ($d = 0.75$) in the cocaine-dependent group.

In contrast, the cocaine-alcohol dependent group displayed a significant attentional bias towards both cocaine and alcohol (Figure 4.1). Fixation time for both the cocaine, $t_{(1,19)} = 2.3$, $p < 0.05$, and alcohol-related images, $t_{(1,19)} = 3.2$, $p < 0.05$, was significantly longer than their respective, matched neutral images. The magnitude of cocaine and alcohol attentional bias did not differ significantly ($d = 0.22$). The magnitude of cocaine cue attentional bias, however, was significantly smaller in the cocaine-alcohol dependent group compared to the cocaine-dependent group ($d = 0.68$). Neither cocaine

nor alcohol cue attentional bias correlated with substance use history (e.g., AUDIT, DAST, MAST, urine drug testing, self-reported use).

Groups did not differ on the total number of fixations made to cocaine ($t_{(38)}$ = 1.6, p > 0.05), non-cocaine-related neutral ($t_{(38)}$ = 0.1, p > 0.05), alcohol ($t_{(38)}$ = 0.9, p > 0.05), or non-alcohol-related neutral ($t_{(38)}$ = 1.0, p > 0.05) images (Table 4.3).

Visual Probe Response Time

Response time to filler images did not differ significantly between the cocaine-dependent group (mean = 485.8, SD = 75.8) and the cocaine-alcohol group (mean = 498.2, SD = 105.8). The ANCOVA results revealed no significant main effects or interactions of response time during the visual probe task (*p's* > 0.05). Response time did not differ as a function of substance, cue type, or group. Table 4.2 presents the mean and standard error of the mean for response time to substance and neutral images. Response time attentional bias scores did not correlate significantly with fixation time attentional bias scores for cocaine (r = 0.02, p > 0.05), alcohol (r = 0.11, p > 0.05), or with substance use history. Response time to filler images did not differ significantly between the cocaine-only group (mean = 485.8, SD = 75.8) and the cocaine-alcohol group (mean = 498.2, SD = 105.8).

Discussion

The present experiment demonstrated that attentional bias, as measured by fixation time during the visual probe task, is specific to the substance use diagnosis of the individual. Cocaine-dependent participants displayed an attentional bias towards cocaine, but not alcohol. In contrast, cocaine-alcohol dependent participants displayed an attentional bias to both cocaine and alcohol and the magnitude of these biases did not differ. Despite reporting regular drinking, participants who did not meet criteria for alcohol dependence displayed a significantly smaller magnitude of alcohol cue attentional bias relative to cocaine cue attentional bias. This specificity in attention

suggests that the salience of substance-related cues is not merely a function of substance use, but severity of substance use (i.e., meeting dependence criteria). Previous studies using the visual probe task have detected a relationship between the magnitude of attentional bias and substance use history (e.g., Marks et al., 2014b; Townshend and Duka, 2001; Weafer and Fillmore, 2012). However, the present study is the first to report a relationship between attentional bias and diagnostic category as determined by DSM-IV criteria for cocaine and alcohol dependence using eye-tracking technology. Meeting the criteria for cocaine or alcohol dependence captures a more complex and relevant array of behavior that better predicts the salience of substance-related cues relative to individual substance use measures (e.g., days used past month).

The large cocaine cue attentional bias observed in the cocaine-dependent group replicates previous studies conducted in our laboratory, which have similarly observed a robust cocaine cue attentional bias as measured by fixation time during the visual probe task (Marks et al., 2014a, 2014b). Likewise, the more modest alcohol cue attentional bias is consistent with previous studies of heavy and moderate drinkers (Miller and Fillmore, 2011; Weafer and Fillmore, 2012). The consistency in cocaine and alcohol cue attentional bias scores across studies suggests that the visual probe task was successfully modified to measure attentional bias to two separate substance-related cues. However, given the small sample size of the groups and preliminary nature of this research design, future studies should attempt to replicate these results in a larger sample. In addition, the inclusion of an alcohol-dependent-only group, would further informed the specificity of cocaine and alcohol cue attentional bias.

Unexpectedly, the magnitude of cocaine cue attentional bias was significantly smaller in the cocaine-alcohol dependent group than the cocaine-dependent group. The reason for this group divergence remains unclear. Groups did not differ in the total number of fixations made on each image type (cocaine, cocaine-neutral, alcohol,

alcohol-neutral). The smaller magnitude cocaine cue attentional bias observed in the cocaine-alcohol dependent group therefore cannot be attributed to differences in engagement of attention to cocaine images (each group made the same number of initial fixations), but rather to the maintenance and/or disengagement of attention. In other words, the duration of fixations accounts for the differences in attentional bias between groups. The shorter duration of fixations towards cocaine-related images, but not cocaine-matched neutral images, suggests that the salience of cocaine cues might be attenuated in individuals dependent on both cocaine and alcohol. As such, attentional bias might play a less influential role in individuals with multiple substance dependencies. The smaller magnitude of cocaine cue attentional bias cannot be attributed to the allocation of attention towards alcohol images, as cocaine and alcohol images were never presented side-by-side. Presenting both cocaine and alcohol cues within the same image might increase their salience for cocaine and alcohol dependent individuals, as the substances are often used in combination, which represents a future direction for research.

Important to note is that fixations were recorded only if a gaze occurred for at least 100 ms. The present analysis does not address whether the groups might have differed in their rapid saccadic eye movement (i.e., fixations shorter than 100 ms). Shifts in attention within the same spatial location only require approximately 50 ms (Duncan et al., 1994). It is possible that rapid saccadic eye movement in the cocaine-alcohol dependent group might also account for the decreased cocaine cue attentional bias. Applied to the incentive salience model, if a cocaine and alcohol dependent individual is presented in rapid succession with a variety of salient images (i.e., cocaine and alcohol images), attentional bias to a single stimulus might be attenuated in order to facilitate rapid scanning of all the potentially salient stimuli.

As would be expected based upon inclusion criteria, groups differed on indices related to alcohol use, further validating the alcohol dependence diagnoses. The cocaine-alcohol dependent group endorsed higher DAST scores, likely as a function of the negative consequences associated with multiple substance dependencies. The DAST scores, however, did not correlate with attentional bias. Groups did not differ on any other measured substance use variables. Although participants did not differ significantly on number of cigarettes smoked per day, time of last cigarette prior to completing the visual probe task was not recorded.

The absence of attentional bias to cocaine and alcohol-related cues as measured by response time is consistent with previous visual probe research that did not detect a bias in the absence of manipulation such as alcohol administration (Adams et al., 2012; Marks et al., 2014b; Miller and Fillmore, 2011; Montgomery et al., 2010). Poor sensitivity and reliability is attributed to the indirect nature of response time for measuring attention (Schmukle, 2005; Spiegelhalder et al., 2011). It is unlikely that groups differed in their ability to perform the task due to differences in substance use history, as response time to probes following filler, neutral trials did not differ between groups. As a limitation, individuals reporting current physiological withdrawal symptoms were excluded from participation for safety. Whether physical dependence on alcohol impacts cocaine or alcohol cue attentional bias remains unknown.

The present results replicate previous research demonstrating that the visual probe task with eye tracking, but not response time, is a sensitive measure of cocaine and alcohol cue attentional bias (Marks et al., 2014b; Miller and Fillmore, 2011). Importantly, this study extends these findings by demonstrating that fixation time during the visual probe task is sensitive to clinically relevant differences in substance use disorder. This outcome is consistent with incentive motivational hypotheses, whereby cue salience is reflected by fixation time during the visual probe task (Robinson and

Berridge, 1993). The present results suggest that cocaine cue attentional bias is not a homogenous trait in cocaine dependent individuals. The incentive value of cocaine cues may differ for individuals who are also dependent on alcohol. Treatment approaches, particularly as they address the role of substance-related cues in use and relapse, should be tailored for multiple substance dependencies. Continued effort should be invested in understanding and addressing the interaction of cocaine and alcohol cues in individuals who meet criteria for both cocaine and alcohol dependence.

As a future direction, the relationship between attentional bias and each criterion for a substance dependence diagnosis should be examined. For example, cue salience might correlate with spending a great deal of time on activities necessary to obtain, use, and recover from the effects of the substance (American Psychiatric Association, 2000). The effort exerted obtaining and using the substance might be closely related to the incentive value of the substance, which is what attentional bias measures. Additionally, the incentive value of the substance might be reflected by criteria such as endorsing withdrawal symptoms and taking the substance in larger amounts than intended (i.e., loss of control). Unlike measuring the rate of use, diagnostic criteria such as these quantify the value of the substance and its associated cues.

Table 4.1

Mean, standard deviation (SD), t-value, and chi-square value for comparisons between group means.

Measure	Cocaine Dependent		Cocaine-Alcohol Dependent		Test of Significance	
Age	43.4	(8.1)	43.4	(6.9)	$t_{(38)} = 0.0$	
Females	6		6		$\chi^2_{(1)} = 0.0$	
Race					$\chi^2_{(2)} = 0.6$	
African American	11		13			
Caucasian	7		6			
Other	2		1			
Mental status exam score	28.9	(1.7)	28.4	(1.5)	$t_{(38)} = 1.0$	
Years of education	11.8	(1.7)	12.5	(1.5)	$t_{(38)} = 1.6$	
Cigarettes per day	9.1	(6.9)	13.2	(7.6)	$t_{(38)} = 1.8$	
DAST	8.8	(4.1)	13.4	(5.7)	$t_{(38)} = 3.0$	*
MAST	7.4	(6.1)	21.3	(13.5)	$t_{(38)} = 4.2$	*
AUDIT	6.9	(5.2)	12.5	(5.7)	$t_{(38)} = 3.3$	*
Cocaine						
Positive urine screen	16		14		$\chi^2_{(1)} = 0.5$	
Days used past week	3.4	(1.7)	2.6	(2.0)	$t_{(38)} = 1.4$	
Days used past month	13.7	(6.1)	9.8	(7.3)	$t_{(38)} = 1.8$	
Years used	16.2	(7.7)	16.2	(7.0)	$t_{(38)} = 0.0$	
Alcohol (past month)						
Drinks per episode	4.7	(3.2)	8.1	(5.5)	$t_{(38)} = 2.4$	*
Drinking episodes	12.3	(8.3)	16.0	(9.7)	$t_{(38)} = 1.3$	
Total drinks	66.7	(62.2)	113.7	(80.8)	$t_{(38)} = 2.1$	*
Other: days used past month						
Amphetamines	0.1	(0.4)	0	(0.0)	$t_{(38)} = 1.0$	
Benzodiazepines	0.1	(0.3)	0.4	(1.2)	$t_{(38)} = 1.1$	
Marijuana	8.5	(10.9)	6	(9.6)	$t_{(38)} = 0.8$	
Opioids	1.3	(1.8)	1	(2.2)	$t_{(38)} = 0.5$	

* Asterisk indicates a significant difference between groups, $p \leq 0.05$.

Table 4.2

Mean and standard error of the mean (SEM) for visual probe attentional bias scores (milliseconds).

Measure	Group							
	Cocaine Dependent (n = 20)				Cocaine-Alcohol Dependent (n = 20)			
	Cocaine	Neutral	Alcohol	Neutral	Cocaine	Neutral	Alcohol	Neutral
Fixation Time	384.0 (22.4)	248.7 (22.1)	333.4 (23.7)	282.3 (23.9)	305.3 (22.7)	245.1 (24.0)	324.9 (28.2)	241.8 (18.8)
Response Time	495.2 (20.6)	494.2 (17.1)	507.0 (21.8)	498.3 (17.2)	498.7 (25.3)	498.1 (21.9)	510.1 (24.5)	518.3 (27.0)

Table 4.3

Mean of the total number of fixations toward each image type for participants in the cocaine and cocaine-alcohol dependent groups.

Group	Image Type			
	Cocaine	Neutral	Alcohol	Neutral
Cocaine Dependent	40.9	27.6	33.2	33.8
Cocaine-Alcohol Dependent	30.4	28.9	28.9	25.7

Figure 4.1

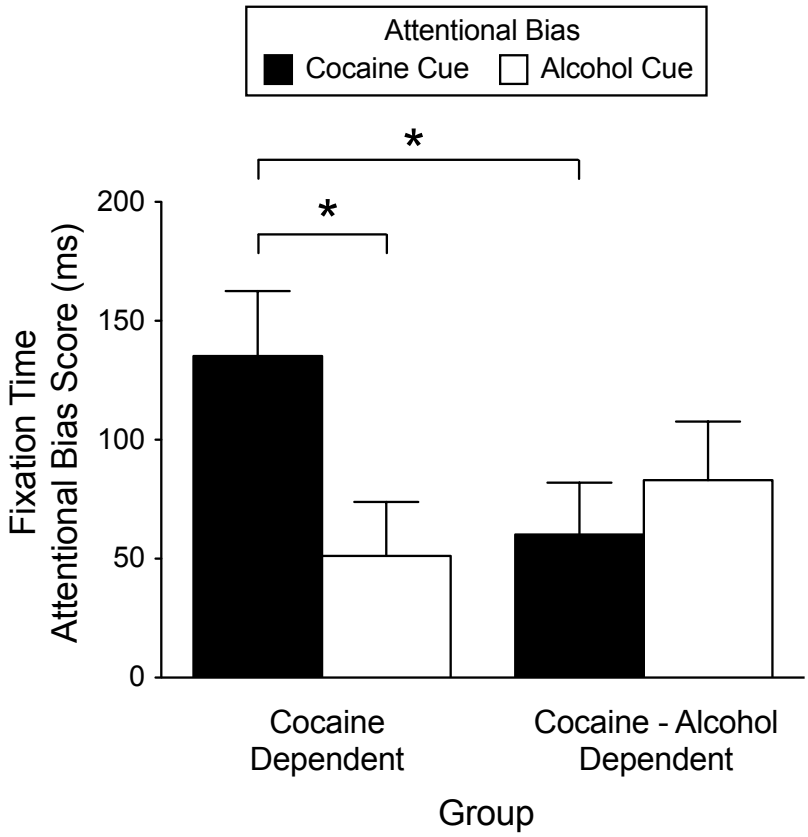

Figure 4.1. Cocaine and alcohol cue attentional bias scores as measured by mean fixation time (milliseconds) for participants in the cocaine-dependent (n = 20) and cocaine-alcohol dependent (n = 20) groups. An asterisk indicates a significant difference between attentional bias scores ($p < 0.05$). Capped vertical lines indicate standard error of the mean.

Chapter 5

COCAINE AND CIGARETTE CUE ATTENTIONAL BIAS

(STUDY 4; Marks et al., In Preparation)

Introduction

Seventy-six percent of Americans reporting current cocaine use also report current cigarette smoking, which is nearly four times higher than the national prevalence (SAMHSA, 2014b). The results of epidemiological studies further indicate that individuals meeting dependence criteria for both cocaine and tobacco use cocaine at an earlier age, use more grams per occasion, and use cocaine at a more frequent rate (Budney et al., 1993; Roll et al., 1996). Importantly, cigarette smoking predicts poorer treatment outcomes for cocaine-dependent individuals (Harrell et al., 2011, but see Roll et al., 1996). In a retrospective analysis of 200 co-morbid cocaine and heroin-dependent individuals, the number of cigarettes smoked per day correlated positively with the percent of cocaine-positive urine samples during outpatient treatment (Harrell et al., 2011). Cocaine-using individuals who smoke cigarettes are also at higher risk for negative consequences of tobacco use than non-smokers (Roll et al., 1996). Conversely, smoking cessation increases the likelihood of cocaine abstinence (Shoptaw et al., 1996, 2002; Winhusen et al., 2014). In a 12-week smoking cessation study, smoking abstinence reinforced by contingency management correlated positively with cocaine-free urines (Shoptaw et al., 2002). Winhusen and colleagues (2014) similarly found that cocaine-dependent individuals who stopped smoking remained abstinent from cocaine longer than those who did not stop smoking.

The pharmacological mechanism by which cocaine and nicotine interact has been well studied (see Weinberger and Sofuoglu, 2009). Nicotinic acetylcholine receptors are located on dopaminergic neurons in the neural pathways associated with cocaine-maintained behaviors (i.e., the ventral tegmental area and nucleus accumbens;

Clarke and Pert, 1985). Several preclinical and human behavioral pharmacology studies have demonstrated that nicotine pretreatment enhances the discriminative stimulus and reinforcing effects of cocaine, as well as cue-induced craving for cocaine (Bechtholt and Mark, 2002; Brewer et al., 2013; Freeman and Woolverton, 2009; Horger et al., 1992; Mello and Newman, 2011; Reid et al., 1998). For example, a human laboratory study demonstrated that cue-induced cocaine craving increased following acute nicotine administration (Reid et al., 1998). Furthermore, an ecological momentary assessment study found that ratings of cigarette smoking and craving were higher during periods of cocaine use compared to periods of cocaine abstinence (Epstein et al., 2010).

The salience of cigarette cues alone, in the absence of nicotine administration, has not been well studied in cocaine-using individuals. Chronic substance use sensitizes dopamine pathways in brain regions associated with the attribution of incentive salience and reward. Incentive salience for the substance transfers the substance-related cues causing the cues to become conditioned incentive stimuli and elicit a conditioned motivational state (Goldstein and Volkow, 2002; Robinson and Berridge, 1993). This conditioned motivational state results in attentional bias. Attentional bias is defined as the allocation of a disproportionate amount of time attending to substance-related stimuli (Gross et al., 1993). Cocaine-using individuals, but not non-cocaine-using controls, display a robust attentional bias towards cocaine-related stimuli (Marks et al., 2014b). Likewise, cigarette smokers display an attentional bias towards cigarette-related stimuli (e.g., Baschnagel, 2013; Field et al., 2004b; Mogg et al., 2003). Importantly, a meta-analysis of clinical neuroscience studies found that cue-induced neural activation to both cocaine and nicotine cues occur in the same brain regions (i.e., ventral striatum, anterior cingulate cortex, amygdala; Kühn and Gallinat, 2011). Despite the overlapping pharmacological and behavioral mechanisms of cocaine and tobacco smoking, the

magnitude of cigarette cue attentional bias has not previously been measured in cocaine-using individuals.

The aim of this experiment was to determine how the magnitude of cigarette cue attentional bias differs in individuals who abuse cocaine and smoke cigarettes relative to individuals who only smoke cigarettes. Daily cigarettes smokers who use cocaine and daily cigarette smokers who do not use cocaine completed a visual probe task with eye-tracking technology to measure cocaine cue and cigarette cue attentional bias. It was hypothesized that cocaine-using smokers would display an attentional bias to cocaine-related and cigarette cues. In contrast, non-cocaine-using smoking controls would display an attentional bias toward cigarette cues, but not cocaine cues. The magnitude of cigarette cue attentional bias was hypothesized to be larger in the cocaine-using individuals given the behavioral and pharmacological conditioning history between cocaine use and cigarette smoking.

Methods

Participants

Fifty individuals were recruited through word of mouth and postings on community bulletin boards. Eight did not meet inclusion criteria and eye-tracking data were insufficient for two additional participants (i.e., greater than 2 standard deviations below the mean for number of fixations recorded). Participants were 20 non-treatment-seeking adults who reported using cocaine within the past month and fulfilled diagnostic criteria for cocaine abuse or dependence as determined by a computerized version of the Structured Clinical Interview for the Diagnostic and Statistical Manual-IV (SCID) and 20 adults who did not report cocaine use in the past year and reported no more than five lifetime uses. All participants reported smoking 10 – 20 cigarettes per day in the past 30 days. Individuals trying to reduce their tobacco use or who had made a recent quit attempt (i.e., past 30 days) were excluded from participation. Individuals with a current

prescription for a psychiatric medication or dependence on any drug that could produce significant withdrawal symptoms during testing (e.g., opioids or benzodiazepines) were excluded. All participants provided written informed consent and completed screening questionnaires on current and past physical and mental health, measures of current psychological functioning, and detailed substance use history. The Institutional Review Board of the University of Kentucky approved all protocols and informed consent documents. Participants were compensated for their time.

Procedure

Data were gathered during routine screening for ongoing laboratory protocols and participants completed this study during one outpatient session. Participants were instructed to abstain from drug use for 12 h and caffeine use for 4 h prior to testing to decrease the likelihood of being under the acute effects of a substance. Participants were also instructed to smoke their last cigarette no closer than 1 h prior to their scheduled session. Upon arrival, all participants passed a field sobriety test and provided a breath sample negative for alcohol. Drug urine screens were conducted at the outset of the session as described previously (Marks et al., 2014b). Participants provided an expired breath carbon monoxide (CO) sample on a Smokerlyser (Bedfont Scientific, Bedford, UK) and reported the time they smoked their last cigarette. Next, participants smoked one cigarette under staff supervision. Participants completed the visual probe task 1.5 h following completion of the cigarette in order to reduce the possibility of psychomotor stimulant effects on task performance and to control for acute nicotine withdrawal, which increases tobacco craving (Schuh and Stitzer, 1995) but attenuates cigarette cue attentional bias (Field et al., 2004b).

Immediately following the visual probe task, participants completed questionnaires regarding smoking craving. The Minnesota Nicotine Withdrawal Scale – Revised consists of 15 items (Hughes and Hatsukami, 1986). Participants were asked to

rate themselves on different aspects of withdrawal for the period of the last 24 hours using a five-point rating scale (*None, Slight, Mild, Moderate, Severe)*. The Questionnaire of Smoking Urges – Brief consists of ten items (Cox et al., 2001). Participants were instructed to indicate numerically how strongly they agreed or disagreed with each statement regarding cigarette craving along a 100-unit scale anchored with *Strongly Disagree* on the left and *Strongly Agree* on the right.

Visual Probe Task

Fixation data were collected using a Tobii X2-60 eye tracker as described previously (Marks et al., 2014b; Tobii Technology, Sweden). Attentional bias was measured using a visual probe procedure. For each trial, two 13 cm x 18 cm images (a substance-related and a matched neutral image) were presented side-by-side, 3 cm apart, on a computer screen for 1000 ms. The amount of time (ms) fixating on the substance and neutral image was measured. Upon offset of the image pair, a visual probe (X) appeared either on the left or the right side of the screen, in the same location as one of the previously presented images. The amount of time (ms) to respond, by pressing one of two response keys indicating on which side of the screen the probe appeared, was measured. Response time data only included critical trials in which a correct response was made longer than 100 ms after the probe appeared. Participants completed ten practice trials containing only neutral images to ensure that they understood the task requirements.

Critical task stimuli consisted of five cocaine images matched with five neutral images (i.e., non-cocaine-related) and five cigarette images matched with five neutral images (i.e., non-cigarette-related). Cocaine images depicted crack or powder cocaine as well as related paraphernalia. Cigarette images depicted lit and unlit cigarettes. Neutral images were matched on the number of objects in the image, size, and color scheme (e.g., a crack pipe matched with a pencil or a cigarette matched with a stick).

Important to note is that cocaine images were never presented side-by-side with cigarette images. Instead, cocaine images and their matched, neutral images were presented in separate trials as cigarette images and their matched, neutral images. Images were presented four times, once for each of the four possible image/probe combinations for a total of 40 test trials, in random order. Forty filler trials consisting of ten pairs of additional neutral images were intermixed with the test trials as described previously (Marks et al., 2014b).

Data Analysis

Independent samples *t*-tests were conducted to compare demographics for continuous variables and chi-square analyses were conducted to compare categorical variables between groups (i.e., cocaine-users and non-cocaine-using). Mean fixation time (ms) was calculated by summing the total fixation time for each image type (cocaine, neutral-cocaine, cigarette, neutral-cigarette) and then dividing by the total number of trials (20). Attentional bias (fixation time and response time) was first assessed using a mixed-model analysis of variance (ANOVA; StatView, Cary, NC, USA) with substance (cocaine and cigarette) and cue type (substance and neutral) as the within-groups factors and group (cocaine-using and non-cocaine-using) as the between-groups factor. The mean-square error term was used to conduct Fisher's Protected LSD tests to determine potential differences between conditions.

Next, a cocaine cue attentional bias score was determined for each participant as the difference in fixation or response time between the cocaine or cigarette images and their matched, neutral images. Fixation and response time attentional bias scores were analyzed using a mixed-model ANOVA with substance (cocaine and cigarette) as the within-groups factor and group (cocaine and control) between-groups factor. Fisher's Protected LSD tests were conducted as described above. An effect size (*d*) was calculated for all significant effects (Cohen, 1988). Statistical significance was set at $p <$

0.05. Bivariate Pearson correlations (*r*) assessed the correlation between fixation and response time, and key indices of cocaine and cigarette use. Correlates of cocaine-cue attentional bias were analyzed in the cocaine-using group only (n = 20) whereas correlates of cigarette cue attentional bias were analyzed using both the cocaine-using and non-cocaine-using smoking groups (n = 40). A bonferroni corrected *p*-value was used for all bivariate correlations ($p \leq 0.005$).

Results

Demographics

Table 5.1 presents the mean, standard deviation, *t*-value and chi-square value for comparisons between groups. Individuals in the cocaine-using group endorsed higher DAST and MAST scores than the control group. Groups also differed in race distribution and self-reported opiate use in the past month. The groups did not differ significantly on any other demographic characteristics. As a note, the mean and *t*-test for past month opiate use were calculated with 19 participants in the control group due to missing data from one participant.

Fixation Time Attentional Bias

Figure 5.1 (top panel) displays the cocaine and cigarette cue attentional bias scores for the cocaine-using and non-cocaine-using groups. The ANOVA revealed a significant interaction of cue type, image type, and group, $F_{(1,38)} = 4.3$, $p < 0.05$. Individuals in the cocaine-using group fixated on cocaine-related images longer than neutral images, indicating a significant cocaine cue attentional bias ($d = 1.2$). In contrast, fixation time to cocaine and neutral images did not differ in the non-cocaine-using group ($p > 0.05$). Fixation times to smoking and neutral images did not significantly differ in either the cocaine-using or the non-cocaine-using groups ($p > 0.05$) and the magnitude of the cigarette cue attentional bias scores did not differ between groups ($p > 0.05$).

Cigarette cue attentional bias scores correlated positively with the item "I have a desire for a cigarette right now" on the Questionnaire of Smoking Urges – Brief, $r = 0.43$, $p = 0.005$. With the bonferroni correction, a trend towards significance was also observed for the items "I have an urge for a cigarette", $r = 0.37$, $p = 0.02$, and "a cigarette would taste good now", $r = 0.34$ $p = 0.03$. Cigarette cue attentional bias did not correlate with other indices of smoking including the time since last smoked, Fagerstrom Test for Nicotine Dependence (FTND; Heatherton et al., 1991), Minnesota Nicotine Withdrawal Scale – Revised (Hughes and Hatsukami, 1986), or breath carbon monoxide levels (p's > 0.005).

Cocaine cue attentional bias scores correlated positively with self-reported number of days since last using cocaine, $r = 0.71$, $p < 0.005$, (Figure 5.2, top panel). One participant reported last using cocaine 19 days prior to testing, which is more than 4 standard deviations from the group mean. Although this data point was an outlier due to restriction in sample range and not sampling error, it was removed to test its influence on the model. After removing this variable, the correlation between self-reported number of days since last used cocaine and cocaine cue attentional bias remained significant, $r = 0.50$, $p = 0.03$, (Figure 5.2, bottom panel). Cocaine cue attentional bias scores did not correlate significantly with other indices of cocaine use including days used past week, month, years used, or lifetime cocaine use (p's > 0.05) in the cocaine-using group.

Visual Probe Response Time

Figure 5.1 (bottom panel) displays the cocaine cue and cigarette cue attentional bias scores for response time to probes in the cocaine-using and non-cocaine-using groups. Neither the main effects of group, cue, or image, nor an interaction between these factors were significant for response time during the visual probe task, $F_{(1,38)} = 0.2$, $p > 0.05$.

Discussion

The present experiment sought to compare the magnitude of cocaine and cigarette cue attentional bias. Daily cigarette smokers who met criteria for cocaine abuse or dependence and daily cigarette smokers with no significant history of cocaine use completed a visual probe task with eye-tracking technology. Cocaine-using smokers displayed a cocaine cue attentional bias. In line with previous research, a cocaine cue attentional bias was not present in non-cocaine-using controls (Marks et al., 2014b). However, neither the cocaine-using group, nor the non-cocaine-using group, displayed a cigarette cue attentional bias.

It was hypothesized that individuals in the cocaine-using group would display a larger magnitude cigarette cue attentional bias due to the pharmacological and behavioral overlap between using cocaine and smoking cigarettes. However, the present results indicate that cigarette cue attentional bias in cocaine users did not differ from non-cocaine-users. Furthermore, cigarette-related cues did not influence the salience of cocaine-related cues as the magnitude of cocaine cue attentional bias was comparable to previous studies in which only cocaine cue attentional bias was assessed in active cocaine users (e.g., Marks et al., 2014b).

Factors independently related to cocaine and cigarette use correlated with the magnitude of cocaine and cigarette cue attentional bias. The number of days since last using cocaine correlated with cocaine cue attentional bias. Likewise, self-reported desire for a cigarette correlated positively with cigarette cue attentional bias. Important to note is that the positive correlation between cigarette cue attentional bias and craving was observed in both the cocaine-using and non-cocaine-using control groups. This provides additional evidence that cocaine-users do not differ from non-cocaine-users in their attentional bias towards cigarette cues.

These findings are consistent with incentive-sensitization theory. The incentive

sensitization model predicts that chronic substance use results in substance-related cues acquiring strong motivational effects, which results in attentional bias. Deprivation and craving are hypothesized to reflect the same underlying process of incentive motivation (Field et al., 2009). Therefore, increases in craving or deprivation should correlate with increased attentional bias. Cognitive models extend this by hypothesizing a reciprocal relationship between craving and attentional bias (Franken, 2003; Ryan, 2002). Attentional bias promotes craving, craving enhances attentional bias, and both contribute to drug taking. By inference, the magnitude of craving and deprivation should correlate with attentional bias.

Previous studies have observed a positive, albeit modest correlation between attentional bias and craving (Field et al., 2009; Gass et al., 2104). In a formative eye tracking study, Rosse and colleagues (1997) measured fixation allocation to a cocaine-related and neutral image in cocaine-dependent individuals. Peak craving correlated positively with the number of attentive fixations to the cocaine-related, but not neutral image. Cocaine craving was not measured in the present study. Ostensibly, cocaine users were in a state of deprivation (i.e., craving) as participants reported last using cocaine, on average, two to three days prior to testing. In another study, Mogg and colleagues (2003) measured cigarette cue fixation time during visual probe task. Smokers, but not non-smokers, displayed a significant cigarette cue attentional bias, which correlated positively with self-reported urge to smoke a cigarette.

Contrary to the hypothesis, neither cocaine-using smokers nor non-cocaine-using smokers displayed a cigarette cue attentional bias. Previous studies measuring attentional bias to cigarette and neutral images during the visual probe task have produced discrepant results with some detecting cigarette cue attentional bias through fixation time (Field et al., 2004b; Mogg et al., 2003) and response time (Field et al., 2009; Kerst and Waters, 2014; Mogg et al., 2002, 2003; Waters et al., 2003a), and

others not (Baschnagel, 2013; Begh et al., 2015; Kwak et al., 2007). Differences in experimental designs across studies might provide insight the experimental parameters necessary to observe cigarette cue attentional bias.

First, nicotine deprivation increases cigarette cue attentional bias (Field et al., 2004b, but see Baschnagel, 2013). For example, in a previous study smokers complete two conditions in which they abstained from cigarettes for 10 hours or smoked normally (Field et al., 2004b). Relative to the satiation condition, following deprivation smokers fixated on smoking-related images significantly longer. In the deprived condition, participants also reported greater levels of craving and rated the smoking images as more pleasant than the neutral images. In the present study, attentional bias was measured 1.5 hours after smoking a cigarette, which most closely approximates the satiation condition in the prior study. Like the prior study, very little cigarette cue attentional bias was detected. Taken together with the finding that cocaine deprivation (i.e., time since last cocaine use) correlates with cocaine cue attentional bias, the duration of deprivation plays an important role in incentive salience. Future studies should examine the salience of cigarette-related cues in cocaine-users following prolonged nicotine deprivation.

Second, the duration of image presentation during the visual probe task influences attentional bias (Field and Cox, 2008). In the prior studies, cigarette cue attention bias was detected when fixation time was measured for 2000 ms (Field et al., 2004b; Mogg et al., 2003), but not 500 ms duration (Begh et al., 2015). In the present study, images were presented for 1000 ms. Longer stimulus presentations engage both initiation, maintenance, and disengagement of attention whereas shorter stimulus presentations primarily only capture the initiation of attention. The 1000 ms duration was selected because cocaine cue attentional bias can be reliably measured within this timeframe (e.g., Marks et al., 2014b). However, a longer duration of stimulus

presentation might be necessary to capture cigarette cue attentional bias.

Third, the present study was the first to measure cocaine and cigarette cue attentional bias during the same task. Although cocaine and cigarette images were not presented side-by-side, carryover effects from the cocaine-related image sets might influence cigarette cue attentional bias. However, a previous study conducted in this laboratory provides evidence that illicit (cocaine) and licit (alcohol) attentional bias can be assessed with the same task without carryover effects (Marks et al., In Press).

The primary aim of this study was to determine how the magnitude of cigarette cue attentional bias differs in individuals who abuse cocaine relative to individuals who only smoke cigarettes. These results suggest that the salience of cigarette-related cues does not differ as a function of cocaine-use history but rather as a function of cigarette craving. Likewise the salience of cocaine-related cues is primarily influenced by level of cocaine deprivation. Future studies should closely examine how deprivation, craving and, alternatively, satiation, moderate attentional bias and subsequent substance use. A secondary aim of this study was to examine the specificity of cocaine cue attentional bias in cocaine-users and non-cocaine-using controls. Cocaine users displayed a robust cocaine cue attentional bias as has been previously demonstrated (Marks et al., 2014a, 2014b; Marks et al., In Press). This study is the first to replicate an earlier experiment demonstrating that non-cocaine-using smoking controls do not display a cocaine cue attentional bias (Marks et al., 2014b). The absence of cocaine cue attentional bias in the control group demonstrates the sensitivity and specificity of attentional allocation, as measured by fixation time during the visual probe task.

Table 5.1

Mean, standard deviation (SD), t-value, and chi-square value for comparisons between group means.

Measure	Cocaine-Using		Control		Test of Significance	
Age	41.2	(7.0)	38.3	(12.4)	$t_{(38)} = 0.9$	
Females	8		12		$\chi^2_{(1)} = 3.3$	
Race	15		8		$\chi^2_{(2)} = 10.2$	*
African American	4		10			
Caucasian	1		2			
Other						
Years of education	12.2	(1.3)	12.5	(1.1)	$t_{(38)} = 0.9$	
Smoking						
Cigarettes per day	15.7	(4.7)	16.1	(4.3)	$t_{(38)} = 0.3$	
FTND	5.3	(2.1)	4.5	(1.6)	$t_{(38)} = 1.4$	
Carbon Monoxide Level	18.5	(10.9)	17.1	(8.6)	$t_{(38)} = 0.5$	
Hours since last cigarette	3.2	(4.1)	2.9	(3.8)	$t_{(38)} = 0.3$	
QSU (mean)	60.6	(31.6)	46.7	(20.2)	$t_{(38)} = 1.7$	
MNWS (sum)	5.4	(5.3)	8.7	(7.7)	$t_{(38)} = 1.6$	
Cocaine						
Days since last use	2.7	(4.0)				
Days used past week	3.6	(1.7)				
Days used past month	12.8	(6.1)				
Days used past 3 months	38.9	(21.3)				
Years used	16.0	(7.1)				
Other: days used past month						
Amphetamines	0.1	(0.3)	1.3	(5.6)	$t_{(38)} = 0.9$	
Benzodiazepines	1.0	(2.1)	0.1	(0.2)	$t_{(38)} = 1.9$	
Marijuana	10.3	(11.7)	4.6	(10.2)	$t_{(38)} = 1.6$	
Opioids	1.4	(2.5)	0.2	(0.5)	$t_{(37)} = 2.1$	*
DAST	12.9	(5.6)	3.0	(2.1)	$t_{(38)} = 7.4$	*
MAST	10.2	(10.3)	3.6	(4.2)	$t_{(38)} = 2.7$	*

* Asterisk indicates a significant difference between groups, $p \leq 0.05$.

Figure 5.1

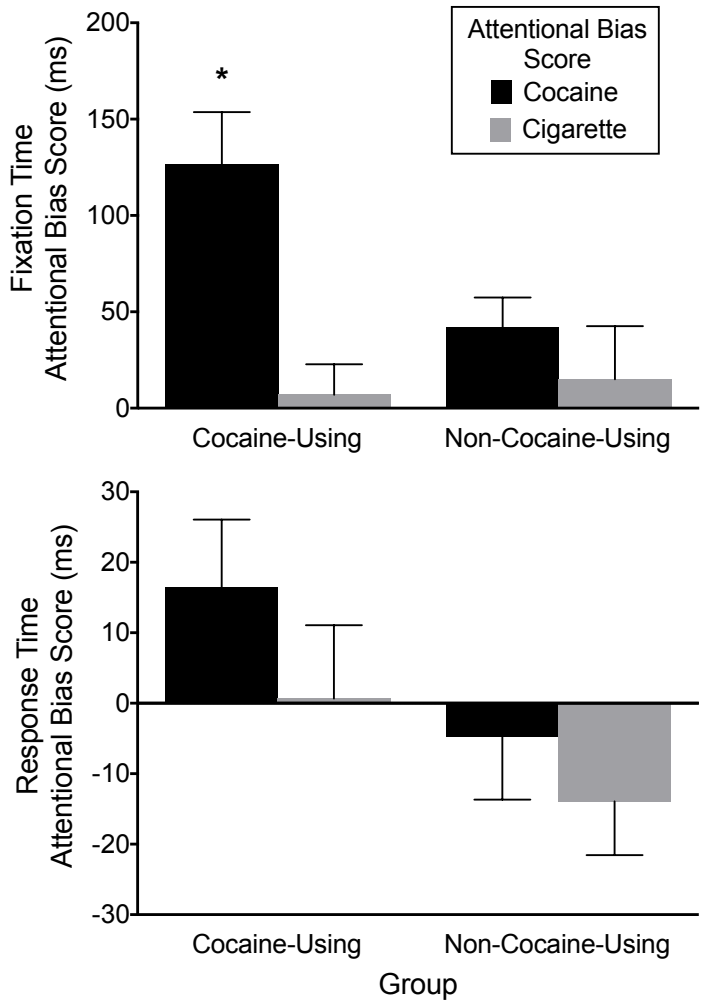

Figure 5.1. Top Panel: Cocaine and cigarette cue attentional bias score as measured by fixation time (milliseconds). Bottom Panel: Cocaine and cigarette cue attentional bias score as measured by response time (milliseconds). Asterisk indicates a significant difference in magnitude from all other conditions.

Figure 5.2

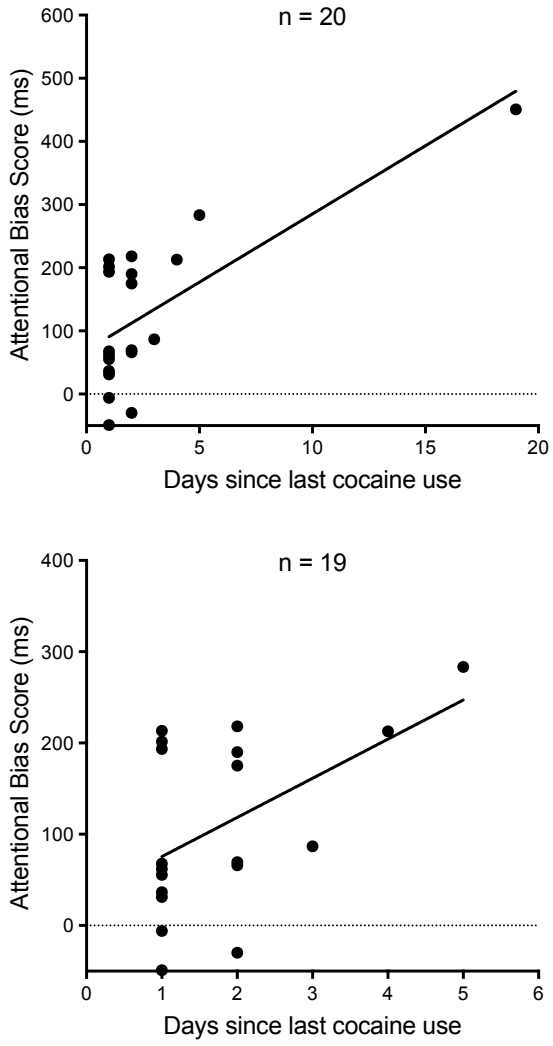

Figure 5.2. Top Panel: Regression line showing the significant positive correlation (*r* = 0.70) between number of days since last cocaine use and cocaine cue attentional bias as measured by fixation time (n = 20). Bottom Panel: Regression line showing the significant positive correlation (*r* = 0.50) between number of days since last cocaine use and cocaine cue attentional bias as measured by fixation time after removing one outlying data point (n = 19).

Chapter 6

CORRELATES OF COCAINE CUE ATTENTIONAL BIAS

(STUDY 5; Marks et al., in preparation)

Introduction

Individuals who use cocaine display a robust cocaine cue attentional bias as measured by fixation time during the visual probe task (Marks et al., 2014b). Attentional bias indicates that cocaine-related cues acquire heightened salience in the environment relative to non-cocaine-related cues. The mechanism by which cocaine-related cues acquire salience, however, has not been demonstrated. Incentive motivational theories hypothesize that attentional bias is a product of dopaminergic neuroadaptations and conditioning history. More specifically, chronic substance use sensitizes dopamine pathways in brain regions associated with attribution of incentive salience and reward (Robinson and Berridge, 1993). Through associative pairings between the cocaine and the cocaine-related cues, incentive salience transfers to the cocaine-related cues.

Several behavioral and biological factors are hypothesized to moderate the attribution of incentive salience, and thus attentional bias. Severity of use (i.e., meeting DSM-IV criteria for cocaine dependence) is hypothesized to influence the magnitude of attentional bias. The severity of use as measured by criteria such as tolerance, withdrawal, and persistent use despite negative consequences are hypothesized to quantify the degree of incentive motivation associated with cocaine use. For example, a previous study conducted in this laboratory demonstrated that individuals meeting criteria for alcohol dependence display an attentional bias towards alcohol whereas individuals not meeting alcohol dependence criteria did not display this attentional bias (Marks et al., In Press).

The recency of cocaine use (e.g., days since last cocaine use, cocaine-positive urine) is also hypothesized to moderate the incentive motivation associated with cocaine

cues. Individuals who have not used cocaine recently and who are in a state of deprivation or abstinence are hypothesized to display a greater attentional bias than individuals who have used recently (Field et al., 2004b; Gross et al., 1993; Waters and Feyerabend, 2000). In support of this hypothesis, Study 4 of this dissertation demonstrated that the number of days since last using cocaine correlated positively with cocaine cue attentional bias.

Converging preclinical (see Dalla and Shors, 2009) and human laboratory evidence suggests that sex moderates the attribution of incentive salience to drug-related cues. Females display greater cue reactivity as measured by self-reported craving (Elman et al., 2001; Field and Duka, 2004; Robbins et al., 1999) and brain glucose metabolism (Volkow et al., 2011) than males. Volkow and colleagues (2011) hypothesized that greater reactivity in brain regions associated with top down cognitive control (i.e., prefrontal cortex, cingulate gyrus, thalamus) following cocaine-cue exposure in female cocaine users might impair executive functioning (e.g., attention) relative to male cocaine users. Relatedly, impulsivity is hypothesized to influence attentional bias through conditioning as well as the central role of dopamine in both attention and impulse control disorders. A meta-analysis of studies examining the correlation between attentional bias and impulsivity found that behavioral, but not self-report measures of impulsivity, correlate positively (r = 0.22), albeit modestly, with attentional bias (Coskunpinar and Cyders, 2013).

Attentional bias studies, thus far, have enrolled relatively small sample sizes (i.e., 15 – 25 participants) that were underpowered to conduct sophisticated regression analyses to test the above hypotheses. Despite small sample sizes, several studies provide evidence that attentional bias correlates with substance use history. The purpose of the present experiment was to explore the relationship between substance use history, relevant demographic variables, and cocaine cue attentional bias. To this

end, data were aggregated from five previous studies conducted in this laboratory to provide sufficient power to test the hypothesis that cocaine cue attentional bias, as measured fixation time, correlates with conditioning history.

Methods

Five studies conducted in the University of Kentucky Laboratory of Human Behavioral Pharmacology were included in this retrospective analysis (Marks et al., 2014b; Marks et al., In Press; Marks et al., in preparation; Pike et al, unpublished data a, unpublished data b). Each study measured cocaine cue attentional bias in current, cocaine-using individuals. If participants completed the visual probe task more than once, only data from the first session was included in this analysis. All studies employed identical experimental procedures during collection of the visual probe data. Independent samples *t*-tests confirmed that mean cocaine cue attentional bias scores did not differ significantly between studies ($p > 0.05$).

Participants

Data from 98 adult participants who reported current cocaine use (i.e., past 30 days) and completed the visual probe task were included in this analysis. One participant was excluded for insufficient eye-tracking data (i.e., greater than 2 standard deviations below the mean for number of fixations recorded). Participants were 97 adults who reported using cocaine within the past 30 days. All participants were between the ages of 18 – 60 and none reported a current prescription for a psychiatric medication or dependence on any drug that could produce significant withdrawal symptoms during testing (e.g., opioids or benzodiazepines). The Institutional Review Board of the University of Kentucky Medical Center approved these experiments and participants gave their written informed consent before participating. Participants were compensated for their time.

Procedures

Data were gathered during routine screening for ongoing laboratory protocols and during outpatient experimental sessions. Participants were instructed to abstain from drug use (excluding nicotine) for 12 h and caffeine use for 4 h prior to testing to decrease the likelihood of participants being under the acute effects of a psychoactive substance. Participants who smoked tobacco were permitted to smoke prior to, but not during, session. All participants passed a field sobriety test and provided a breath sample negative for alcohol prior to session to ensure that they were not currently intoxicated. Drug urine screens were conducted at the outset of the session as described previously (Marks et al., 2014b).

Participants completed the visual probe task operated using E-prime experiment generation software (Schneider et al., 2002) on a PC. Participants also completed screening questionnaires on current and past physical and mental health, measures of current psychological functioning, and a detailed substance use history (Sevak et al., 2011). The Timeline Followback (TLFB) procedure was used to assist participants in reporting frequency of cocaine used over the past 90 days (Sobell and Sobell, 1992).

Visual Probe Task

Attentional bias was measured using the visual probe procedure described previously (Marks et al., 2014b). Fixation time data were collected using Tobii T120, T60-XL, and X2-60 eye trackers (Tobii Technology, Sweden). Three models were utilized due to upgrades to technology over time, but eye-tracker model does not significantly influence fixation time data (Marks et al., 2014a). Attentional bias was measured using the visual probe procedure described previously (Marks et al., 2014b). The primary outcome variables were fixation time to cocaine and neutral images and response time to probe location (ms).

Data Analysis

Data analysis proceeded in the following steps. First, descriptive statistics were obtained to describe the sample. Second, attentional bias as measured by fixation and response time was analyzed using a one-way analysis of variance (ANOVA) with cue type (cocaine and neutral) as the factor. Third, associations between attention to cocaine and neutral cues and categorical demographic variables were assessed. An ANOVA was conducted with cue type (cocaine and neutral) as the within-subject variable and DSM-IV diagnosis (cocaine dependent, non-cocaine dependent) as the between-subject variable. The non-cocaine dependent group included individuals meeting (n = 6) and not meeting (n = 17) criteria for cocaine abuse. Next, an ANOVA was conducted with cue type (cocaine and neutral) as the within-subject variable and recent cocaine use (benzoylecgonine positive and negative) as the between-subjects variable. Recent cocaine use was verified with drug urine tests for the cocaine metabolite, benzoylecgonine, which can be detected 24 to 60 hours following cocaine use (CLIAwaived Inc., San Diego, CA). Finally, an analysis of covariance (ANCOVA) was conducted with cue type (cocaine and neutral) as the within-subject variable and sex (male and female) as the between-subject variable. Age, days used cocaine past month, and DAST score were included as model covariates to control for potential differences in cocaine use between males and females. Statistical significance was set at $p < 0.05$. Fourth, bivariate *Pearson* correlations were conducted to assess associations between cocaine cue attentional bias scores and the following key demographic and drug use variables: days used cocaine in the past week, past month, number of years used cocaine, lifetime cocaine uses, Zuckerman-Kuhlman Personality Questionnaire on Impulsivity and Sensation Seeking (ZKPQ; Zuckerman et al., 1993), Adult ADHD Self-Report Scale (ASRS; Kessler et al., 2005), or Drug Abuse Severity Test (DAST: Skinner, 1982). Bonferroni corrected effects for all bivariate analyses were considered significant

for $p \leq .006$.

Results

Demographics

Ninety-seven participants (64 male, 33 female) completed the study. Seventy-one were African American, 22 were Caucasian, and four were of mixed race. Participants were 41 ± 8 (mean ± SD) years old with 12 ± 2 years of education. All participants reported cocaine use in the past 30 days, using 11 ± 8 days in the month prior to screening, and 15 ± 8 years in total. Seventy-three participants provided a cocaine-positive urine on the session day. Eighty-six participants reported consuming alcohol (15 ± 17 standard drinks per week). Eighty-eight participants were cigarette smokers (12 ± 7 cigarettes per day), scoring a 3 (± 3) on the Fagerstrom Test for Nicotine Dependence (Heatherton et al., 1991). In the 30 days prior to testing, 76 participants reported marijuana use (13 ± 11 days), 38 reported opiate use (4 ± 4 days), 23 reported benzodiazepine use (3 ± 3 days), and seven reported amphetamine use (3 ± 5 days).

Attentional Bias

Table 6.1 presents the mean, standard deviation, and Cohen's *d* effect size for fixation time and response time during the visual probe task. For fixation time, the ANOVA revealed a significant main effect of cue, $F_{(1,96)} = 103.0$, $p < 0.0001$. Cocaine-users fixated on cocaine-related images significantly longer than neutral images. For response time, the main effect of cue was not significant, $F_{(1,96)} = 2.7$, $p > 0.05$.

A mixed-model ANCOVA with cue type (cocaine and neutral) as the within-subject factor and sex (male and female) as the between subject factor was conducted for fixation time. The ANCOVA revealed a significant main effect of cue type, $F_{(1,92)} = 4.9$, $p < 0.05$. Both females and males fixated on cocaine images longer than neutral images demonstrating a cocaine cue attentional bias. The ANCOVA also reveal a significant

main effect of sex, $F_{(1,92)} = 4.3$, $p < 0.05$, indicating that females fixated on cocaine and neutral images significantly longer than males. Attentional bias did not differ as a function of other categorical variables including DSM-IV diagnosis for cocaine dependence and cocaine-positive urines ($p > 0.05$).

Bivariate Pearson analyses were conducted to identify significant correlations between the cocaine cue attentional bias scores and key demographic and drug use variables. Cocaine cue attentional bias, as measured by fixation time and response time, did not correlate significantly with recent or long-term cocaine use, impulsivity, or drug use severity. Pearson *r* correlation range; 0.00 – 0.14, *p's* > 0.02.

Discussion

Cocaine-using individuals display a robust cocaine cue attentional bias as measured by fixation, but not response time. This result contributes to a consistent and steadily growing literature that eye tracking during the visual probe task is a sensitive measure of cocaine cue attentional bias (Marks et al., 2014b, Marks et al., In Press). Incentive motivational theories propose that attentional bias is the result of the attribution of incentive salience to reward-paired cues. Self-reported substance use history and relevant demographic variables were hypothesized to approximate these associative pairings and incentive value. The results of the present analysis suggest that neither recent, long-term, nor severity of cocaine use correlates with cocaine cue attentional bias. This finding does not provide evidence that cocaine cue attentional bias is not a result of incentive sensitization. Rather, these findings indicate that substance use history as measured by recent, long-term, and severity of cocaine use is not proportionate to the incentive value of cocaine in heavy, long-term cocaine users. Self-reported substance use history might approximate the incentive salience of cocaine-related cues in a sample of lighter, less experienced cocaine users. Participants included in the present analyses were approximately 40 years old and reported using cocaine for

15 years, on average. With such an extensive cocaine conditioning history, it might be difficult to detect the relationship between substance use history and attentional bias. Future studies should assess these variables in lighter, less experienced cocaine users.

One previous study conducted in our laboratory detected a significant correlation between cocaine cue attentional bias and self-reported lifetime number of cocaine uses (Marks et al., 2014b). Procedural differences in data collection might account for the difference in findings across studies. In the earlier study, self-reported cocaine use was assessed through a structured interview in which individuals were provided verbal instructions on how to estimate their lifetime cocaine use (multiply the average number of times used per month by the total number of months used cocaine) whereas in subsequent studies, cocaine use was collected via paper and pencil self-report and participants were not provided instructions on how to estimate their use. Future studies should be mindful of how data collection might influence participant reporting, particularly as it relates to substance-use history.

This analysis is the first to report sex differences in attention as measured by fixation time, but not response time, during the visual probe task. Cocaine-using females fixated on both cocaine-related and neutral images longer than males and these effects remained significant after controlling for potential differences in demographic variables (age, recent cocaine use, DAST scores) between females and males. These results suggest that females better attend to stimuli in the environment than males. The content of the stimuli, whether drug related or not, however, does not influence attention. These results are in partial support of previous preclinical and human laboratory finding that attentional processes differ in females and males. However, the present study did not find that females are more sensitive to cocaine-paired cues than males, as has been previously demonstrated (Dalla and Shors, 2009; Elman et al., 2001; Field and Duka, 2004; Robbins et al., 1999; Volkow et al., 2011).

The present analysis provides insight in to the mechanism underlying attentional bias as well as identifies important gaps in understanding. First, attentional bias assesses a novel aspect of behavior that operates independently from existing measures substance-related behavior. Informative behavioral assays should correspond to the constructs that they are hypothesized to measure while still providing additional, unique information. Further research is therefore needed to identify how attentional bias relates to other indices of substance use. Previous studies (i.e., Study 4) suggest that indices such as craving and deprivation might inform this relationship. Second, the magnitude of cocaine cue attentional bias is not influenced by chronic cocaine use (e.g., number of years used, DSM-IV diagnosis). Supporting this notion, a previous study conducted in this laboratory demonstrated that fixation time is stable across repeated measurements ranging from 7 to 336 days (Marks et al., 2014a). The stability of fixation time, therefore, might make cocaine cue attentional bias a difficult behavior to modify. Future studies should identify the parameters under which fixation time to cocaine-related cues might be attenuated. Third, self-reported impulsivity and attentional control does not correlate with cocaine cue attentional bias. A meta-analysis of studies examining the correlation between attentional bias and impulsivity found that behavioral, but not self-report measures of impulsivity, correlate positively (r = 0.22) with attentional bias (Coskunpinar and Cyders, 2013). Future studies should therefore examine the relationship between cocaine cue attentional bias, as measured by fixation during the visual probe task, and behavioral measures of impulsivity.

An important limitation of this analysis is that the range of data might be restricted in number of ways. First, the sample was comprised primarily of heavy cocaine users. All participants reported cocaine use in the past 30 days with most using approximately half the days in the past month and for fifteen years. A sample including lighter, recreational cocaine users whom only use once a month or less might reveal

relationships between cocaine cue attentional bias and substance-use history. Relatedly, the sample was primarily comprised of individuals meeting DSM-IV diagnostic criteria for cocaine dependence. In fact, only six of the 97 participants met criteria for cocaine abuse. Including more participants who meet criteria for cocaine abuse but not dependence might reveal a relationship between attentional bias scores and DSM-IV diagnosis. In support of this notion, a previous study conducted in this laboratory demonstrated that individuals meeting criteria for alcohol dependence display a significant alcohol cue attentional bias whereas individuals who used alcohol but did not endorse dependence criteria did not display this attentional bias (Marks et al., In Press). Second, there was a restriction of range in demographic variables, particularly ethnicity. The ethnicity of present sample was primarily African American, thereby limiting the generalizability of the findings as well as the ability to conduct secondary analyses. Future studies should oversample underrepresented cocaine-using groups and examine social and culturally relevant predictors of attentional bias.

Taken together, this large sample replicates the results of previous studies finding that fixation time, but not response time, is a sensitive measure of cocaine cue attentional bias (Marks et al 2014a, Marks et al, In Press). Cocaine cue attentional bias did not correlate with the indices of substance use collected in the present study. Future studies should explore the relationship between biologically or behaviorally-based factors and attentional bias, rather than self-report measures. Additionally, although attentional bias may not serve as a behavioral marker of retrospective cocaine use, this to not preclude the possibility that attentional bias plays an active role in substance use. Prospective, longitudinal studies therefore should be conducted to better understand the temporal relationship between attentional bias and cocaine use.

Table 6.1

Mean, standard deviation (SD), and Cohen's d effect size for attentional bias scores (milliseconds).

	Cue Type		
Measure	Cocaine	Neutral	*d*
Fixation Time	339.1 (117.8)	219.0 (99.3) *	1.1
Response Time	518.4 (96.3)	525.2 (91.5)	0.1

* Asterisk indicates a significant difference between cocaine and neutral conditions.

Cohen's *d* effect size reported between cocaine and neutral images.

Figure 6.1

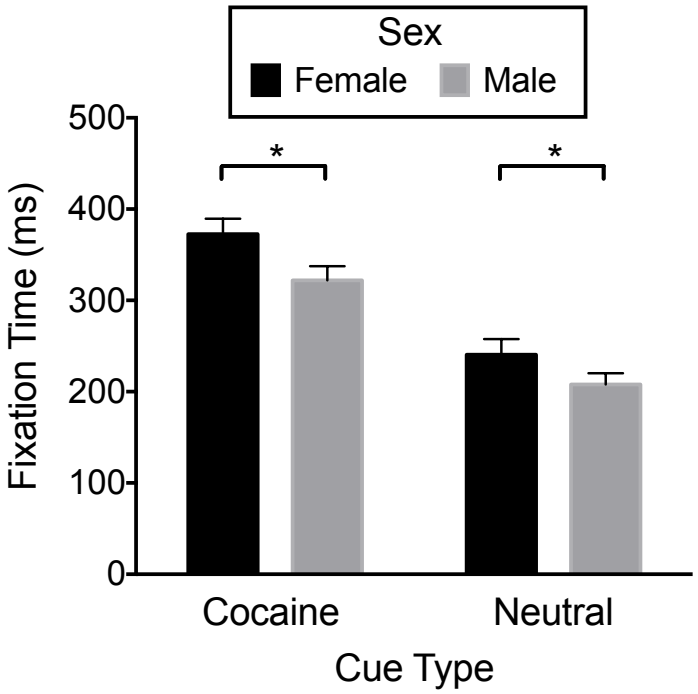

Figure 6.1. Mean fixation time (milliseconds) for cocaine and neutral images in females (n = 33) and males (n = 64). The asterisk indicates a significant difference between conditions.

Chapter 7

GENERAL DISCUSSION

Summary of Findings

This dissertation encompasses a programmatic series of experiments designed to elucidate the behavioral mechanisms underlying cocaine cue attentional bias during the visual probe task. The first aim of this dissertation was to demonstrate that fixation time is a sensitive and reliable measure of cocaine cue attentional bias. Experiment 1 demonstrated that cocaine users, but not non-cocaine-using controls, display an attentional bias to cocaine as measured by fixation time. Experiment 2 demonstrated the test-retest reliability of attentional bias as measured by fixation time. The second aim of this dissertation was to determine whether the magnitude of attentional bias, as measured by fixation time, is specific to clinically relevant differences in substance use. Experiment 3 demonstrated that the magnitude of cocaine and alcohol cue attentional bias differs as a function of cocaine and alcohol use severity. Experiment 4 assessed the magnitude of cocaine and tobacco cue attentional bias. Cocaine users displayed a large magnitude cocaine cue attentional bias, which was absent in non-cocaine-using controls, thus replicating the outcome of Experiment 1. Smokers did not display an attentional bias towards cigarettes cues, however cigarette cue attentional bias correlated positively with cigarette craving. Likewise, cocaine cue attentional bias correlated positively with the number of days since last using cocaine. The third aim of this dissertation was to identify factors related to demographic and substance use history that correlate with cocaine cue attentional bias. Craving and deprivation correlated with attentional bias whereas factors such as cocaine use history, impulsivity, and drug use severity did not.

Taken together, this dissertation presents compelling evidence that current cocaine users display a robust cocaine cue attentional bias. Interestingly, the magnitude of cocaine cue attentional bias is larger than attentional bias to licit substances (i.e.,

alcohol and tobacco). Leeman and colleagues (2014) reviewed the cocaine cue attentional bias literature and drew similar conclusions (i.e., cocaine-related cues are more salient than licit, substance-related cues). The salience of cocaine cues therefore makes cocaine cue attentional bias a better target for clinical intervention than other substances (Leeman et al., 2014). However, it should be noted that the robust magnitude might also be a limitation as it may be more difficult to attenuate attentional bias that is highly stable. This dissertation also demonstrates that fixation time, but not response time, during the visual probe task is a sensitive, reliable, and specific measure of cocaine cue attentional bias. Analyzing the psychometric properties of fixation time represents a significant contribution to the field of attentional bias research and provides convincing evidence for the application of eye-tracking technology in future research. This organized, programmatic series of experiments enables the conduct of future studies seeking to test more advanced hypotheses relating to attentional bias.

Directions for Future Research

Below, I describe three directions for attentional bias research that should be pursued in the future. Each are rooted in exploring the clinical utility of attentional bias research.

Assessing Impairment: This dissertation demonstrated that current cocaine users display an attentional bias to cocaine-related cues. However, the extent to which attentional bias impairs goal-directed behavior is not known. For example, if an individual in recovery attempts to avoid cocaine-related stimuli in the environment, does the salience of cocaine-related images impair attentional control? A task in which individuals are explicitly instructed to avoid or ignore cocaine-related cues (i.e., inhibit attentional bias) might better assess the extent to which individuals are impaired by their attentional bias (see Wilcockson and Pothos, 2015). For example, in a gaze contingency paradigm, individuals are instructed to direct their gaze away from alcohol-related or neutral images

and to maintain focus on a fixation point. Failure to inhibit attentional bias is then measured with eye tracking. In one study, failures to inhibit saccades towards alcohol-related images (i.e., alcohol cue attentional bias) correlated positively with alcohol consumption outside the laboratory (Wilcockson and Pothos, 2015). These results suggest that individuals who consume more alcohol are more impaired by attentional bias. This promising procedure has not yet been tested in a cocaine-using population.

Operant Contingencies: Attentional bias, as measured by the visual probe task, assesses attentional processing under extinction (i.e., no primary reinforcer is obtained). However, the likelihood of obtaining a reinforcer following the visual probe task influences the magnitude of attentional bias (Field et al., 2011; Hogarth et al., 2006; Jones et al., 2012). Hogarth and colleagues (2006) conducted a creative experiment in which shapes (i.e., neutral stimuli) were paired with obtaining a cigarette (i.e., a reinforcer) or not obtaining a cigarette across a series of trials. Fixation time attentional bias to the drug-paired discriminative stimulus was measured under extinction. The drug-paired discriminative stimulus produced an attentional bias, but only for the group able to identify the contingency between the discriminative stimulus and the cigarettes. The authors concluded that attentional bias is the result of operant conditioning processes, but that drug expectancy is necessary for stimulus control of attention.

Jones and colleagues (2012) built upon this expectancy theory by manipulating the probability of reinforcement and measuring subsequent attentional bias. In that study, participants were informed of the probability (0%, 50%, or 100%) of acquiring a reinforcer (alcohol or chocolate). An alcohol-related and matched neutral image or a chocolate-related and matched neutral image was then presented and attentional bias was measured using eye tracking. Attentional bias was observed for both alcohol and chocolate. However, attentional bias was greater if the probably of receiving the alcohol or chocolate was 100% compared to 0%. The authors concluded that expectancy for a

reinforcer increases attentional bias. These results suggest that large magnitude cocaine cue attentional bias might be even more robust if participants anticipate acquiring cocaine following the task. Future research implementing a hypothetical or non-hypothetical contingency of reinforcement with cocaine-related cues represents a more ecologically valid and clinically relevant direction for future research.

Pharmacological Manipulations: Taken one step further, the influence of cocaine administration on cocaine cue attentional bias should be determined. A priming dose of cocaine has been shown to precede relapse under controlled laboratory conditions that imposed abstinence and increase choice for cocaine over alternative reinforcers (Donny et al., 2004; McKay et al., 1999). Additionally, acute pretreatment with oral cocaine enhances the subject-rated drug effects of intravenous cocaine (Johanson et al., 2007) and is associated with increased self-reported craving for cocaine (Mahoney et al., 2007). Cocaine administration also increases dopaminergic activity in brain regions such as the anterior cingulate cortex, amygdala, and nucleus accumbens, which are all involved in attentional processing (see Franken, 2003). These findings suggest that cocaine administration should modify also cocaine cue attentional bias (Luijten et al., 2014). This hypothesis, however, has not yet been tested with direct measures of attentional bias. Previous research measuring alcohol cue attentional bias following alcohol administration has observed both increased and decreased attentional bias that varied as a function of dose, severity of substance use, and time of measurement along the blood alcohol curve (Fernie et al., 2012; Roberts and Fillmore, 2014; Schoenmakers et al., 2008; Weafer and Fillmore, 2012). Understanding how attentional bias increases or decreases, in the presence of cocaine and following the acquisition of cocaine will further indicate the clinical relevance of attentional bias.

Clinical Relevance

The potential relevance of attentional bias in clinical settings is multifaceted. First, a number of studies have explored the link between prospective substance use and attentional bias. The results of several of those studies demonstrate that attentional bias informs prospective substance use (e.g., Carpenter et al., 2012; Cox et al., 2002 Marissen et al., 2006; Waters et al., 2003b, 2012), however, several studies have failed to replicate these findings (see Christiansen et al., 2014 for review). Promising new research suggests that Ecological Momentary Assessment is a direct way to test the predictive validity of attentional bias. Ecological Momentary Assessment facilitates the collection of behavioral and cognitive data outside the human laboratory. Using this technique, Waters and colleagues (2012) demonstrated that modified Stroop interference increased during self-reported temptations to relapse to cocaine. Furthermore, individuals who relapsed displayed greater modified Stroop interference than individuals who did not relapse (Marhe et al., 2013). As eye-tracking technology becomes integrated into portable devices, direct measurements of attentional bias can be incorporated into such studies and the clinical utility of measuring attentional bias will continue to expand.

Second, attentional bias is hypothesized to serve as a treatment target aimed at reducing cocaine use. The premise of attentional bias modification is that initial and sustained attention can be trained away from substance-related cues, leading to improved substance use outcomes. In a prototypical retraining procedure, the visual probe task is modified such that the probe always appears behind neutral images. In theory, participants learn to attend almost exclusively to neutral images in order to better predict and respond to the location of a subsequent probe. By improving attentional control and devaluating the salience of substance-paired cues, decreased attentional bias should lead to decreased substance use (Fadardi and Cox, 2009).

In the past 12 months, 36 attentional bias retraining manuscripts targeting substance and mood disorders have been published on PubMed. Despite their popularity, discrepant and in many cases negative findings have predominated the literature. Several prominent research groups have written reviews criticizing the clinical value of attentional bias retraining (e.g., Christiansen et al., 2014; Cox et al., 2014; Field et al., 2014). Negative findings, however, are likely a result of underpowered experimental designs and an insufficient number of retraining sessions. Despite varying levels of optimism, the authors are in agreement that attentional bias modification has not been tested in a sufficiently rigorous manner.

Another limitation of many attentional bias modification studies is that the primary dependent variable is an indirect measure of attention (i.e., response time). As a consequence, many studies do not reliably detect an attentional bias prior to retraining, at baseline. If attentional bias is absent at baseline, it cannot be determined whether the intervention was unsuccessful or whether the task was not a sensitive measure of attentional retraining. Furthermore, there is no clear theoretical justification for attempting to train an absent attentional bias to be “more absent” (i.e., attend more to neutral images than substance-related images).

This dissertation has presented convincing evidence that a direct measure of attention (i.e., eye tracking) is necessary to reliably measure attention to cocaine-related stimuli. Currently, the only intervention utilizing eye-tracking technology to modify attention is the anti-saccade task (Hallett, 1978). The purpose of this task is to train oculomotor inhibitory control. One investigative group attempted to modify laboratory alcohol consumption through an oculomotor inhibitory retraining task (Jones and Field, 2013). Social drinkers were trained to primarily emit anti-saccades (i.e., look away) from alcohol-related images and pro-saccades (i.e., look towards) towards neutral images. The retraining resulted in slower saccades towards alcohol-related images, however this

did not improve oculomotor inhibitory control or decrease laboratory alcohol consumption. Despite the negative findings, this procedure is highly innovative and should continue to be explored in a cocaine-using population.

Other retraining programs such as in-home (McGeary et al., 2014), portable device (Kerst and Waters, 2014), and "gamified" (Cox et al., 2014) interventions are gaining momentum. The advantages of non-laboratory-based interventions include training in the environment in which the individuals uses substances, training during episodes of craving or stress, and training that is better spaced over time (Cox et al., 2014). An additional benefit of measuring attentional bias across continuous time points outside the laboratory is that transient, "state" changes in attention produced by environmental or physiological events can be better understood (de Wit, 2009). Taken together, given the wide range of potential utility, the clinical relevance of attentional bias should not be readily dismissed.

Final Impressions and Remarks

Despite concerted efforts to identify interventions to manage cocaine use disorders, no widely effective treatment has been demonstrated. The consensus of the scientific community, however, is that no single intervention will be widely effective. Instead, progress will be defined by the incremental advances in understanding the mechanism underlying cocaine use disorders and by addressing them with a variety of tools. Evidence suggests that attentional bias is one such tool. Despite recently published critical review articles that have suggested that this line of research be abandoned due to flaws in experimental designs and statistical analyses, I do not share in their pessimism (Christiansen et al., 2014; Cox et al., 2014; Field et al., 2014). This dissertation has demonstrated that attentional bias, as measured by fixation time during the visual probe task, is a unique and specific behavioral assay with promising future

applications. As such, attentional bias research should continue to be pursued in a rigorous and meticulous scientific manner.

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Waters, A. J., Shiffman, S., Bradley, B. P., & Mogg, K. (2003a). Attentional shifts to smoking cues in smokers. *Addiction, 98*(10), 1409-1417.
Waters, A. J., Shiffman, S., Sayette, M. A., Paty, J. A., Gwaltney, C. J., & Balabanis, M. H. (2003b). Attentional bias predicts outcome in smoking cessation. *Health Psychology, 22*(4), 378-387.
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Weinberger, A. H., & Sofuoglu, M. (2009). The impact of cigarette smoking on stimulant addiction. *American Journal of Drug and Alcohol Abuse, 35*(1), 12-17.
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Zuckerman, M., Kuhlman, D. M., Joireman, T. J., & Kraft, M. (1993). A comparison of three structural models of personality: The big three, the big five, and the alternative five. *Journal of Personality and Social Psychology, 65*, 757-768.

VITA

KATHERINE ROSE MARKS

EDUCATION

Murray State University — 2004 - 2007
B.A., Magna Cum Laude, Psychology — Murray, KY

American University — 2008 - 2010
M.A., Biological and Experimental Psychology — Washington, DC

University of Kentucky — 2014 - Present
Graduate Certificate in Clinical and Translational Science — Lexington, KY

TRAINING & PROFESSIONAL EXPERIENCE

Pathways Center for Eating Disorder Recovery — 2004
Mental Health Technician — Louisville, KY

Youth Villages — 2006
Counselor Intern — Linden, TN

American University — 2008 - 2010
Graduate Research Assistant — Washington, DC

Edelson & Associates Neuropsychological Services — 2009
Staff Intern — Louisville, KY

Stress, Health, and Addiction Research Program — 2010 – 2011
Faculty Research Assistant — College Park, MD

National Institute on Drug Abuse — 2010 – 2011
Guest Researcher — Baltimore, MD

University of Kentucky — 2011 – 2012
Graduate Teaching Assistant — Lexington, KY

Laboratory of Human Behavioral Pharmacology — 2011 – Present
Graduate Research Assistant — Lexington, KY

HONORS, AWARDS, AND FELLOWSHIPS

Featured in American University's "Catalyst" Science Magazine — 2010
Article entitled, "Rat Neuroscience: Burrowing into the Depths of Addiction"

Student Travel Funding — 2012 – 2014
University of Kentucky

Travel Award for Early Career 2012
Poster Session at the American Psychological Association Conference
National Institute on Drug Abuse
National Institute on Drug Abuse T32 Pre-Doctoral Traineeship 2012 – 2014
University of Kentucky Department of Behavioral Science
Clinical and Translational Science TL1 Predoctoral Scholar 2014
University of Kentucky Center for Clinical and Translational Science
Best Conference Poster 2014
Eye Track Behavior: Tobii Eye Tracking Conference

PUBLICATIONS

Book Chapters:

1. Leukefeld, C.G., **Marks, K.R.**, Stoops, W.W., Reynolds, B., Lester, C., Sanchez, L., & Martin, C.A. (2015). Treatment and Prevention of Substance Misuse and Abuse in Adolescence. In T.P. Gulotta and G.R. Adams (Eds.). Handbook of Adolescent Behavior Problems, 2nd Edition.
2. Leukefeld, C.G., **Marks, K.R.**, Young, A., Stevens-Watkins, D., & Leach, R. (In Press). Behavioral Health and Substance Abuse. In D. Scutchfield and B. Keck (Eds.). Principles of Public Health Practice, 4th Edition.

Peer-Reviewed Manuscripts:

Marks, K.R., Kearns, D.N., Christensen, C.J., Silberberg, A., & Weiss, S.J. (2010). Learning that a cocaine reward is smaller than expected: A critical test of Redish's computational model of addiction. Behavioural Brain Research, 212, 204-207.

Kearns, D.N., Tunstall, B., **Marks, K.R.**, & Weiss, S.J. (2011). Extinction of goal-tracking also eliminates the conditioned reinforcing effects of an appetitive conditioned stimulus. Psychonomic Bulletin and Review, 19, 135-138.

Marks, K.R., Lile, J.A., Stoops, W.W., & Rush, C.R. (2014). Separate and combined impact of acute naltrexone and alprazolam on subjective and physiological effects of oral *d*-amphetamine in stimulant users. Psychopharmacology, 231, 2741-2750.

Marks, K.R., Roberts, W., Stoops, W.W., Pike, E., Fillmore, M.T., & Rush, C.R. (2014). Fixation time is a sensitive measure of cocaine cue attentional bias. Addiction, 109, 1501-1508.

Marks, K.R., Pike, E., Stoops, W.W., & Rush, C.R. (2014). Test-rest reliability of fixation time during the visual probe task in cocaine using adults. Drug and Alcohol Dependence, 145, 235-237.

Marks, K.R., Pike, E., Stoops, W.W., & Rush, C.R. (In Press). The magnitude of drug attentional bias is specific to substance use disorder. Psychology of Addictive Behaviors.

Pike, E., **Marks, K.R.**, Stoops, W.W., & Rush, C.R. (In Press). Cocaine-related stimuli impair inhibitory control in cocaine users following short stimulus onset aysnchronies. Addiction

Posters and Presentations:

Marks, K.R., Gorka, S.M., & Daughters, S.B. (2010). Distress tolerance in adolescence: A gender specific biological stress response. University of Maryland School of Public Health Research Interaction Day, College Park, MD.

Daughters, S.B., Gorka, S.M., **Marks, K.R.**, & Richards, J.M. (2011). Gender specific relationship between distress tolerance and HPA axis response to stress among adolescents. Poster presented at the 73rd annual meeting of the College on Problems of Drug Dependence, Hollywood, FL.

Marks, K.R., Pike E., Stoops, W.W., & Rush, C.R. (2012). Agonist replacement therapy for cocaine dependence: A translational review. Poster presented at the 120th annual meeting of the American Psychological Association, Orlando, FL.

Pike E., **Marks, K.R.**, Stoops, W.W., & Rush, C.R. (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.

Marks, K.R. (2013). Gaze time as a sensitive measure of cocaine cue attentional bias. Talk presented at the 2013 NIDA Training Grant Symposium, Lexington, KY.

Marks, K.R., Stoops, W.W., Pike, E., Roberts, W., Fillmore, M.T., & Rush, C.R. (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.

Marks, K.R., Stoops, W.W., Pike, E., Roberts, W., Fillmore, M.T., & Rush, C.R. (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.

Marks, K.R. (2014). Cocaine Cue Attentional Bias: Validating a Measure. Talk presented at the 2014 NIDA Training Grant Symposium, Lexington, KY.

Marks, K.R., Stoops, W.W., & Rush, C.R. (2014). Cocaine dependent subjects display attentional bias toward cocaine-related but not alcohol-related stimuli. Talk presented at the 76th annual meeting of the College on Problems of Drug Dependence, San Juan, Puerto Rico.

Marks, K.R., Pike E., Stoops, W.W., & Rush, C.R. (2014). Attentional bias and impulsivity. Poster presented at the International Society for Research on Impulsivity, Cambridge, England.

Marks, K.R., Pike E., Stoops, W.W., & Rush, C.R. (2014). Measuring attentional bias to substance-related stimuli using eye-tracking technology. Poster presented at Eye Track Behavior: Tobii Eye Tracking Conference, Washington, DC.

Marks, K.R., Pike E., Stoops, W.W., & Rush, C.R. (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.

Marks, K.R., Pike E., Stoops, W.W., & Rush, C.R. (2015). Eye tracking is sensitive to clinically relevant differences in substance abuse. Abstract accepted at the 123rd annual meeting of the American Psychological Association, Toronto, Canada.

Marks, K.R., Lemons, A., Stoops, W.W., Lile, J.A., & Rush, C.R. (2015). Laboratory drug administration does not increase use in the natural ecology immediately following study discharge. Abstract accepted at the 76[7h] annual meeting of the College on Problems of Drug Dependence, Phoenix, AZ.

Marks, K.R., Pike E., Stoops, W.W., & Rush, C.R. (2015). Measuring attentional bias to substance-related stimuli using eye-tracking technology. Abstract accepted at the Association for Clinical and Translational Science Annual Meeting, Washington DC.

Pike, E., **Marks, K.R.**, Stoops, W.W., & Rush, C.R. (2015). Cocaine images impair inhibitory control: Influence of alcohol administration. Abstract accepted at the

123rd annual meeting of the American Psychological Association, Toronto, Canada.

Pike, E., **Marks, K.R.**, Stoops, W.W., & Rush, C.R. (2015). Cocaine images impair inhibitory control: Influence of alcohol administration. Abstract accepted at the 76^{7h} annual meeting of the College on Problems of Drug Dependence, Phoenix, AZ.

Bolin, B.L., Lile, J.A., Marks, K.R., Sites, J.P., Crush, C.R., & Stoops, W.W. (2015). Influence of buspirone maintenance on the pharmacodynamics effects of cocaine and sexual risk taking in cocaine users. Abstract accepted to the 76th annual College on Problems of Drug Dependence, Phoenix, AZ.

PROFESSIONAL ACTIVITY AND SERVICE

Scientific Membership:

American Psychological Association — 2012 – Present
Student Member

The College on Problems of Drug Dependence — 2013 - Present
Member-in-Training

Association for Psychological Science — 2014
Graduate Student Member

Journal Peer Reviewing Activities:

Ad Hoc: Neuropsychopharmacology — 2012

Drug and Alcohol Dependence — 2015

Service:

Science Blog Co-Author — 2011
Association for Psychological Science Convention

Co-coordinator of weekly Behavioral Neuroscience and Psychopharmacology Brown Bag Meeting; University of Kentucky — 2012 - 2013

Advocacy Coordinating Team — 2012 – 2013
University of Kentucky Campus Representative
American Psychological Association Graduate Student Program

Roots & Heritage Festival Volunteer — 2013
University of Kentucky Center for Clinical and Translational Science

National Clinical Research Education Day Volunteer — 2013
University of Kentucky Center for Clinical and Translational Science

Manuscript Reviewer for the National Conference of Undergraduate Research — 2014
University of Kentucky

Grant Reviewer for The Student Grant Competition — 2014
Association for Psychological Science