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Fixation Time is a Sensitive Measure of Cocaine Cue Attentional Bias

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Abstract

Background and Aims—Attentional bias has been demonstrated to a variety of substances. Evidence suggests that fixation time is a more direct measure of attentional bias than response time. The aims of this experiment were to demonstrate that fixation time during the visual probe task is a sensitive and stable measure of cocaine cue attentional bias in cocaine using adults compared to controls.

Design—A between-subject, repeated-measures experiment.

Setting—An outpatient research unit.

Participants—Fifteen cocaine using and fifteen non-cocaine-using adults recruited from the community.

Measurements—Participants completed a visual probe task with eye tracking and a modified Stroop during two experimental sessions.

Findings—A significant interaction between cue type and group (F = 13.5; P = 0.001) indicated that cocaine users, but not controls, displayed an attentional bias to cocaine-related images as measured by fixation time. There were no changes in the magnitude of attentional bias across sessions (F = 3.4; P = 0.08) and attentional bias correlated with self-reported lifetime cocaine use (r = 0.64, P = 0.01). Response time on the visual probe (F = 1.1; P = 0.3) as well as on the modified Stroop (F = 0.1; P = 0.72) failed to detect an attentional bias.

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Conclusions—Fixation time on cocaine-related stimuli (propensity to remain focused on the stimulus) is a sensitive and stable measure of cocaine cue attentional bias in cocaine-using adults.

Keywords

cocaine; attentional bias; cue reactivity

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 [1]. 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 [2]. This motivational state results in attention biased in favor of substance-related cues [1, 3]. Consequently, substance users will selectively attend to substance-related cues in the environment [1, 4, 5]. 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 [6, 7]. In addition, response time is an indirect measure of Stroop interference [8] as it relies upon a motoric response to approximate speed of processing and attentional allocation. Therefore, other more direct measures of visuo-spatial attention have been developed [9].

A more recent measure of attentional bias is the visual probe task [10, 11]. 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 [12] due to its incentive salience. 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 [8]. Response time, particularly in the visual probe task, has low internal reliability [13] and

test-retest reliability [14] resulting in inconsistent findings across investigative groups and drug classes [15–19].

Recognizing the limitations of response time, some investigators have argued for using more direct measures to quantify attentional bias [17]. Eye-tracking technology directly measures visual attention by recording how participants direct their gaze [20]. 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 [21, 22]. 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 [15], alcohol [17, 23], and nicotine [18]. Fixation time is also a more sensitive measure of alcohol and cannabis cue attentional bias than response time [15, 17] and has greater internal reliability [13, 24]. 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 [25–27]. 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 [28]. 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 one lifetime use. Participants were matched on age to control for age-related differences in reaction time [29]. 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 [30] 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 [31]. Included in the questionnaires were the Drug Abuse Screening Test (DAST) [32], the Michigan Alcohol Screening Test (MAST) [33], and the Fagerstrom Test for Nicotine Dependence (FTND) [34]. The Timeline Followback (TLFB) procedure was used to assist participants in reporting the frequency and amount of cocaine used in the past month [35]. 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—Attentional bias was measured using the visual probe procedure based on Roberts and colleagues [36]. 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).

Modified Stroop—The modified Stroop is an alternative measure of attentional bias previously described by Liu and colleagues [37]. 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 $P \leq 0.05$, 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 $P \leq 0.01$.

RESULTS

Demographics

Table 1 presents the mean, standard error of the mean, and *t*-values for comparisons between groups. The individuals in the cocaine-using group reported significantly greater cocaine use (preferentially via the smoked route) as well as higher DAST 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 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 3). In contrast, the control group did not differ in fixation time for cocaine and neutral images during either Session 1 or Session 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 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). Response time during the visual probe task did not correlate significantly with any indices of cocaine use (Table 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). Response time for both groups was faster on Session 2 than Session 1 (Table 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 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 [8, 38]. 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. The stability of the attentional bias suggests that cocaine-related images remain salient across time and exposure and are not transient.

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 [39]. 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 [21, 22].

The control group did not display a cocaine cue attentional bias as measured through fixation time or response time. The absence of attentional bias remained stable 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 [15, 18]. 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 [15, 18]. 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.

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 [26, 27]. 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 [8].

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 [37, 40–42] and others not finding the bias [42, 43]. Self-reported cocaine use in the present study resembled the rate of use reported by both the Vadhan and colleagues [42] and Liu and colleagues [37]. 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, 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 [15, 17]. In addition, this 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 and stable 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 [44].

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Table 1

Mean, standard error mean (SEM), and *t*-values for comparisons between group means.

Measure	Cocaine Users	Controls	*t*-Value
Age	38.2 (2.9)	38.9 (2.4)	0.20
Females #	9	8	0.3
Race #			4.6
African American	13	9	
Caucasian	2	5	
Other	0	1	
Years of education	12.4 (0.5)	13.6 (0.6)	0.1
Cigarettes per day	8.6 (2.7)	4.2 (1.8)	0.2
FTND	2.7 (0.8)	1.6 (1.3)	1.0
DAST	12.5 (1.7)	2.7 (0.8)	5.3 *
MAST	13.4 (3.8)	5.2 (1.5)	2.0
Days used past month			
Amphetamines	0.2 (0.2)	0.3 (0.3)	0.3
Benzodiazepines	0.7 (0.4)	0.2 (0.1)	1.2
Marijuana	9.5 (3.0)	6.5 (3.2)	0.7
Opioids	0.6 (0.3)	0.1 (0.1)	1.9
Cocaine			
Days used past month	16.6 (2.4)	0.0 (0.0)	7.0 *
Days used past week	4.1 (0.5)	0.0 (0.0)	7.6 *
Lifetime uses	2321.5 (640.3)	0.2 (0.1)	3.6 *
Years used	13.8 (2.4)	0.2 (0.1)	5.8 *

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

Sample size and chi square values reported for sex and race.

Table 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 3

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

	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) *	209.3 (23.9)	1.2	372.0 (20.0) *	239.4 (14.3)	1.9	342.4 (22.2)	289.4 (18.8)[a]	0.7	355.5 (27.4)	339.2 (22.1)[a]	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.

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

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

Table 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, $P \leq 0.01$