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Cue-Induced Craving in Patients with Cocaine Use Disorder predicts Cognitive Control Deficits toward Cocaine Cues

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Abstract

Introduction—Cue-induced craving is a clinically important aspect of cocaine addiction influencing ongoing use and sobriety. However, little is known about the relationship between cue- induced craving and cognitive control toward cocaine cues. While studies suggest that cocaine users have an attentional bias toward cocaine cues, the present study extends this research by testing if cocaine use disorder patients (CDPs) can *control* their eye movements toward cocaine cues and whether their response varied by cue- induced craving intensity.

Methods—30 CDPs underwent a cue-exposure procedure to dichotomize them into high and low craving groups followed by a modified antisaccade task in which subjects were asked to *control* their eye movements toward either a cocaine or neutral drug cue by looking away from the suddenly presented cue. The relationship between breakdowns in cognitive control (as measured by eye errors) and cue- induced craving (changes in self-reported craving following cocaine cue exposure) was investigated.

Results—CDPs overall made significantly more errors toward cocaine cues compared to neutral cues, with higher cravers making significantly more errors than lower cravers even though they did not differ significantly in addiction severity, impulsivity, anxiety, or depression levels. Cue-induced craving was the only specific and significant predictor of subsequent errors toward cocaine cues.

Conclusion—Cue- induced craving directly and specifically relates to breakdowns of cognitive control toward cocaine cues in CDPs, with higher cravers being more susceptible. Hence, it may

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GJD designed the experiment, GJD and DS created the protocol, NG created the stimuli and tested all the participants, GJD and NG prepared the materials and analyzed the data; GJD wrote the first draft, DS and NG made significant contributions to the manuscript. All authors approve the final manuscript.

Conflicts of Interest:

All authors declare that they have no conflicts of interest.

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be useful identifying high cravers and target treatment toward curbing craving to decrease the likelihood of a subsequent breakdown in control.

Keywords

Cocaine; Craving; Antisaccades; Cognitive Control; Addiction

1. Introduction

Cocaine dependence is a significant public health problem with a severe illness course, moderately successful psychosocial interventions [1] and no FDA approved medications [2]. Craving is a prominent feature in cocaine addiction, recently added to DSM-V, and often serves as a target in pharmacotherapy [3]. Craving exists despite the negative outcomes associated with abuse [4, 5]. Unfortunately, the field still struggles to understand the mechanisms that directly or indirectly precipitate cue- induced craving (CIC) and drive subsequent behavior [6, 7]. Understanding the relationship between CIC and breakdowns in cognitive control is further complicated by inter-subject variability [8–10]. In some cocaine use disorder patients (CDPs), exposure to evocative cocaine cues results in increased craving [11–14]. Craving can also arise through stress, emotions, perceived availability, and drug priming [15–17]. Cue type also affects the variability of the craving intensity, with more personal cues engendering higher craving [18, 19]. What remains unknown, however, is whether higher craving translates into greater loss of cognitive control toward cocaine cues.

Lack of cognitive control has frequently been measured as the amount of attention given to drug stimuli [for a review, see, 20], amount of time looking at drug cues [21], or delays in responding [22, 23]. CDPs demonstrate an attentional bias for cocaine-related stimuli, with greater bias predicting poorer outcomes during drug-treatment programs [24]. While these types of studies have investigated CDPs' preferences or attentional biases toward cocaine pictures or words, they have not asked CDPs to control their behavior toward cocaine cues. A hallmark of drug use cessation and relapse prevention [25] is the ability to control behavior toward cocaine cues [26–28]. Therefore, the current study investigated the ability of CDPs to control their eye movements toward generic neutral and cocaine cues, and familiarized neutral and cocaine cues and examined directly the relationship between high versus low CIC and cognitive control. In short, does cocaine CIC explain subsequent cue-elicited breakdowns in cognitive control toward cocaine cues?

2. Materials and Methods

2.1 Participants & Assessments

30 CDPs, identified by clinicians as cocaine dependent and not actively psychotic, were recruited from in-patient addiction treatment centers. CDPs provided informed consent and completed assessments included demographics; quantity and frequency of cocaine use; Voris Cocaine Craving Scale [VCCS, 29]; the Beck Depression Inventory [BDI, 30]; Beck Anxiety Inventory [BAI, 31]; Severity of Dependence Scale [SDS, 32]; and Barratt Impulsiveness Scale [BIS, 33]. One patient did not complete the VCCS and his data was not used when craving was included as a factor in the analyses. As Table 1 shows, the majority

of the participants were crack cocaine users, with only 5 of the 30 CDPs using solely powder cocaine.

2.2 Cue-Induced Craving Procedure

Following assessments, CDPs completed a relaxing computer task and the VCCS. CDPs handled either the five cocaine-related (e.g., crack pipe, lighter, vial) or the five neutral (e.g., shell, pine cone, twig) cues in a block design (counterbalanced for order effects). Each object in the group (drug or neutral) was handled for 30 seconds and after handling all five objects in that group (for a total of 150 seconds of handling cocaine cues, or 150 seconds of handling neutral cues), participants rated their craving. For cocaine cues, CDPs recalled the last time they had used such an object while taking cocaine. For neutral cues, they recalled the last time they had encountered such an object. CDPs completed the VCCS before and after handling each group of cues. Pictures of CDPs' hands holding the neutral and cocaine cues were digitized and then used in the antisaccade task. Because these cues were shown and handled by the patients (and now included their own hands in the images), we call these cues Familiarized Drug or Familiarized Neutral. The cue exposure procedure ended with a relaxation exercise [see also, 34].

2.3 Antisaccade Task

The antisaccade task included pictures of generic neutral and cocaine cues as well as the familiarized neutral and cocaine cues taken previously for each participant. Eye movements were recorded (SR Research Eyelink 1000) while CDPs faced a computer screen with their heads in a chin rest. Each trial began with two white boxes (8.19° of visual angle, VA) presented to the left and right (7.7° VA) of a central fixation. The fixation (and boxes) remained until CDPs had fixated for 200 ms. The fixation then disappeared, and the cue (8.10° VA) appeared 400 or 700 ms later (balanced and randomized across cue type) to prevent predictability in cue onset. CDPs were instructed to make an eye movement to the opposite location (an antisaccade). The picture remained on the screen for 800 ms and was followed by a 500 ms blank screen. An eye movement was classified as a saccade when its velocity reached 30 deg/sec, or its acceleration had reached 8000 deg/sec². Trials in which the eye movements were executed under 80 ms after the onset of the go signal were considered anticipations and discarded [35], as were trials where an eye blink occurred. The speed of the eye movement (saccadic reaction time; sRT) was calculated from the onset of the cue until the initiation of the eye movement. For every trial, the first saccade following the cue onset was labeled either an error if the eye moved toward the cue, or a correct response if the eye moved toward the box opposite the cue.

The antisaccade task used a block design. Blocks consisted of 20 generic and 5 familiarized cues from one category (e.g., cocaine), and 5 generic cues from the other category (e.g., neutral), with these 30 cues randomly intermixed and repeated twice. Hence, each block consisted of 60 trials, with 50 trials of one cue type and 10 trials of the other cue type. The task consisted of 8 (4 neutral and 4 cocaine) blocks, with the block order randomized and counterbalanced across CDPs. A 30s fixation period was included after every other block.

2.4 High vs. Low Cravers

Because our specific aim was to examining the role of high and low cue- induced craving in breakdowns in cognitive control toward cocaine cues, we analyzed the data in two ways. First, we dichotomize the 30 CDPs into two groups (high and low cravers) based on a median split of changes in self- reported cocaine cue- induced craving (Voris Cocaine Craving Scale; Q1) from baseline to after handling the cocaine cues. Second, we performed regression analyses on error rates treating increased cue- induced craving as a continuous variable. Note, we intentionally have not included a control group in this study. Our main analyses were to directly examine the relationship between CIC craving and breakdowns in cognitive control toward cocaine cues. Any non-cocaine using group would show no CIC to cocaine cues, and would not be included in either of our two main analyses. Moreover, the CDPs would likely significantly differ from any control group on the other main assessments in Table 1; hence, we would be unable to differentiate cocaine craving from psychological differences in depression, anxiety, or impulsivity if any differences were found between the CDPs and a nominal control group. By comparing our CDPs to each other, we can, however, examine these factors and analyze directly any differences based on our factor of interest: cocaine CIC.

3. Results and Discussion

As Table 1 summarizes, these 30 CDPs were severely dependent on cocaine as assessed by the SDS [36], highly impulsive as assessed by the BIS [37], moderately anxious as assessed by the BAI [38], moderately depressed as assessed by the BDI [30], and had, overall, significantly increased craving after cocaine cue exposure ($t(28)=6.37, p<.00001$).

Dichotomized high cravers ($N=15$) had a significantly greater increase in cue-induced craving ($M=25.06, SE=2.27$) after handling the cocaine cues than lower cravers ($N=14$) with $M=5.14, SE=2.12, (t(27)=6.40, p<.0001)$. Importantly, higher vs. lower cravers did not significantly differ on SDS, BDI, BAI, or BIS scores ($t<1$, in all cases). These two groups only significantly differed on their CIC (see Table 2). CDPs with higher CIC made significantly more errors toward cocaine cues than CDPs with lower CIC on generic ($t(27)=2.32, p<.03$) and familiarized ($t(27)=2.66, p<.02$) cocaine cues. These data suggest that higher cravers have more impaired function in cognitive control toward cocaine cues because of their increased craving.

Next we analyzed the data using CIC as a continuous variable across all participants to examine the relationship between these errors to cocaine cues and measures of CIC, addiction severity and psychological traits using a regression analyses. A significant portion of errors toward generic cocaine cues was explained by a combination of CIC, BDI, BAI, SDS, and BIS, $R^2=0.42, F(5, 22)=3.20, p<.03$. Only the CIC ($t(22)=2.56, p<.02$) significantly predicted the number of errors that CDPs made toward generic cocaine cues; neither the severity of the addiction, impulsivity, anxiety or depression predicted cognitive control errors ($p>.13$). Likewise, a significant portion of the variance in errors toward familiarized cocaine cues was explained by a combination of CIC for cocaine, BDI scores, BAI, SDS, and BIS, $R^2=0.49, F(5, 22)=4.24, p<.008$. Again, only the CIC ($t(22)=3.44, p<.003$) significantly predicted the number of errors that CDPs made toward familiarized

cocaine cues; neither the severity of the addiction, impulsivity, anxiety or depression predicted cognitive control errors ($p = .15$). When these factors were put into a model to explain neutral cue errors (generic or familiarized), neither of the models was significant ($p = .16$ in both cases).

To further explore this result, we also performed two additional analyses. First, because of the potential for multicollinearity between our factors (i.e., the factors may be correlated with each other), we also tested each factor individually in a separate regression against the participants' familiarized cocaine cue errors and their generic cocaine cue errors. As before, CIC craving was a significant predictor for both familiarized cocaine cue errors ($t(27) = 3.45$, $p < 0.003$) and generic cocaine cue errors ($t(27) = 2.52$, $p < 0.03$). Additionally, impulsivity as measured by the BIS, significantly predicted both familiarized cocaine cue errors ($t(27) = 2.45$, $p < 0.03$) and generic cocaine cue errors ($t(27) = 2.57$, $p < 0.02$). These data suggest that impulsivity may also be contributing to errors. To test the contribution of CIC and impulsivity specific to breakdowns toward cocaine cues, we calculated a difference score between overall error rates to cocaine cues minus overall error rates to neutral cues. This measure indexes the specific increase in breakdowns of control toward drug cues while controlling for factors that may influence error rate regardless of cue type. We then performed a regression analysis on this measure testing both CIC and BIS in separate models. CIC significantly predicted this index of drug specific breakdowns in control, with $t(27) = 2.31$, $p < 0.03$. The BIS was not a significant predictor even when tested as the sole factor, with $t(27) = 1.24$, $p = 0.22$. CIC explains the breakdowns in cognitive control seen in these CDP patients and is not a generic predictor of breakdowns in control (i.e., errors on the task), but is specific to increased breakdowns in cognitive control toward cocaine cues. Impulsivity, on the other hand, may be a general predictor of breakdowns in cognitive control, but it is not specific to drug cue- induced breakdowns in cognitive control. In short, higher impulsivity suggests less control regardless of the domain, while higher cocaine CIC means less control specific to increased cocaine cue-elicited breakdowns in control.

Finally, overall, CDPs made significantly more errors toward cocaine cues than they did toward neutral cues ($F(1, 29) = 11.64$, $p < .003$). They also made more errors toward familiarized cues than generic cues ($F(1, 29) = 8.39$, $p < .008$). There was no hint of an interaction ($F < 1$) with CDPs making significantly more errors toward generic cocaine cues than generic neutral cues, and significantly more errors toward familiarized cocaine cues than toward familiarized neutral cues. The speed at which errors or successful antisaccades were made between the cue types (Cocaine vs. Neutral) did not differ in any comparison, with $t < 1$, in both cases (see Table 2).

The overall error rates for CDPs in this antisaccade task are higher than one would expect from the literature for this age range. Adults typically make 10%–15% errors on an antisaccade task, [39–41] until individuals become elderly [42]. This increased error rate may also have been augmented because the stimuli for the antisaccade task were pictures and not simple dots. This task is a new drug antisaccade task and is the first, to our knowledge, to combine the antisaccade task with drug cues creating a new paradigm for testing cognitive control in addiction. Even with this increased overall error rate in this new

paradigm, CDPs were significantly more impaired to cocaine cues than neutral cues, and this cocaine cue-elicited breakdown in control was greater for higher cravers than lower cravers.

Craving has previously been tied to attentional preference in cocaine dependent individuals [23, 43]. The present study demonstrates a direct relationship between cocaine CIC and cue-elicited breakdowns in cognitive control specific to cocaine cues. These data are consistent with previous studies [44, 45] and theories postulating a deficit in cognitive control in drug addiction [44, 46]. Cognitive control deficits likely contribute to ongoing use [26–28, 47] and, hinder a client's ability to maintain sobriety [25], particularly when confronted with cocaine paraphernalia. Kaufman [48] demonstrated hypoactive cognitive control brain networks in current cocaine users, and Connolly et al [49] showed that the neural circuitry of cognitive control rebounds in cocaine abstinent patients; hence, successful rehabilitation of cocaine addiction may require good cognitive control and its neural substrates. Based on the current findings, one important factor that may drive the ability of CDPs to exercise cognitive control is whether the patient has high or low cue- induced cocaine craving. Hence, cognitive control deficits may be prevalent in cocaine addiction and an important aspect of treatment, which is hindered by craving differences. Craving is clinically relevant as increased craving is associated with subsequent treatment failure [50, 51] and craving predicts subsequent cocaine use outside of treatment [52]. Higher cravers are more likely to relapse relative to lower cravers [53], in agreement with the current data of higher cravers having more breakdowns in cognitive control toward cocaine cues. In a recent functional imaging study [26], CDPs who actively tried to exert cognitive control over their craving changed neural activity in reward areas, suggesting that control over craving is possible. This study, however, did not dichotomize their participants into high and low cravers and it is unclear if high cravers would be able to control their neural activity to cocaine cues. Nevertheless, it may be possible for CDPs to learn how to specifically exert control over their own CIC and decrease the likelihood of relapse, though these mechanisms might differ for high and low cravers.

The small sample size, the few number of familiarized cues, and the single method of testing cognitive control limit the present study. Nevertheless, our data have demonstrated a breakdown in cognitive control toward cocaine cues in CDPs, and the specificity of cocaine cue-induced craving leading to cocaine cue-elicited breakdowns in control in CDPs.

Conclusions

CDPs who are higher cravers have less control over their ability to control their behavior toward cocaine cues and craving is a specific predictor of this loss of control toward cocaine cues. In short, CIC directly relates to the breakdown of cognitive control toward cocaine cues in CDPs. Hence, it may be useful for targeting individuals in treatment by identifying high cravers and applying anti-craving interventions to decrease the likelihood of a subsequent breakdown in control toward cocaine. Future studies using functional neuroimaging might elucidate the direct relationship between CIC and cognitive control.

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Highlights

- CDPs make more antisaccade errors to cocaine cues than neutral
- High cravers make more errors than low cravers to cocaine cues
- Impulsivity is a predictor of general errors
- Cue-induced craving is a specific predictor of errors toward cocaine cues
- Cognitive control is disrupted in CDPs

Table 1

Demographics, Drug History, Psychological Assessments and Cocaine Craving Scores in Cocaine Use Disorder Patients.

Assessment	N	M	SE
Gender (Male)	23 of 30		
Race (Caucasian)	23 of 30		
Crack as Primary Drug	25 of 30		
Age	30	37.87	1.59
Days of Use (Last 30)	30	14.00	3.44
Years of Use	30	16.27	1.92
Previous Drug Treatments	30	17.00	3.08
Severity of Dependence Scale (SDS)	30	11.43	0.40
Barratt Impulsivity Scale (BIS)	30	82.23	2.82
Beck Depression Index (BDI)	30	23.67	2.19
Beck Anxiety Index (BAI)	30	18.20	2.12
Cue-induced Craving Increase After Cocaine Cue Exposure	29	15.45	2.42

Table 2

Psychological and Eye Movement assessments in High and Low Craving Cocaine Use Disorder Patients (Means and SEM). Eye movement measures include the number of errors in each condition, the speed (saccadic reaction time; sRT) of the eye movement error, and the sRT of a correct antisaccade.

Assessments	High Cravers (N=15)	Low Cravers (N=14)
Cue-induced Craving Increase After Cocaine Cue Exposure	25.07 (2.26)	5.14 (2.12)
Severity of Dependence Scale (SDS)	11.53 (0.41)	11.29 (0.74)
Barratt Impulsivity Scale (BIS)	82.60 (3.89)	80.50 (4.30)
Beck Depression Index (BDI)	23.87 (3.00)	23.57 (3.55)
Beck Anxiety Index (BAI)	20.07 (3.20)	15.79 (2.97)
Generic Drug Errors (%)	46 (7.23)	26 (5.19)
Generic Drug Errors sRT (ms)	197 (5.70)	192 (11.54)
Generic Drug Successful sRT (ms)	372 (32.0)	337 (21.1)
Familiarized Drug Errors (%)	51 (6.35)	29 (5.36)
Familiarized Drug Errors sRT (ms)	198 (6.49)	223 (15.53)
Familiarized Drug Successful sRT (ms)	360 (33.0)	338 (24.01)
Generic Neutral Errors (%)	38 (5.25)	23 (4.64)
Generic Neutral Errors sRT (ms)	191 (6.09)	201 (10.42)
Generic Neutral Successful sRT (ms)	357 (20.99)	339 (21.17)
Familiarized Neutral Errors (%)	42 (6.92)	26 (5.47)
Familiarized Neutral Errors sRT (ms)	211 (9.56)	202 (9.66)
Familiarized Neutral Successful sRT (ms)	340 (18.95)	338 (21.27)