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COCAINE-RELATED STIMULI IMPAIR INHIBITORY CONTROL IN COCAINE USERS FOLLOWING SHORT STIMULUS ONSET ASYNCHRONIES

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Abstract

Background and Aims—Cocaine users display a significant increase in inhibitory failures following cocaine-related images compared with neutral images in a modified cued go/no-go task, the Attentional Bias-Behavioral Activation (ABBA) task. The aim of this study was to demonstrate that stimulus onset asynchrony (SOA) impacts inhibitory failures on the ABBA task.

Design—A between-subjects experiment.

Setting—An outpatient research unit in the USA.

Participants—Ninety-one cocaine users recruited from the community.

Measurements—Participants were assigned to groups in which they saw either cocaine ($n = 46$) or neutral ($n = 45$) images as the go condition. Cues were presented for one of five SOAs (i.e., 100, 200, 300, 400, or 500 ms) before a go or no-go target was displayed.

Findings—Participants in the cocaine go condition had a significantly higher proportion of inhibitory failures to no-go targets ($F_{4,356} = 2.50$, $p = 0.04$) with significantly more inhibitory failures following all SOAs ($p < 0.05$), than those in the neutral go condition. Within the cocaine go condition, significantly more inhibitory failures were observed following the 100 and 200 ms SOAs than after the 300, 400, or 500 ms SOAs ($p < 0.05$).

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Conclusions—Cocaine-related stimuli appear to decrease inhibitory control in cocaine users at short (100 and 200 ms) stimulus onset asynchronies (SOAs: the amount of time between the start of one stimulus and the start of another stimulus), but not at longer (300, 400, and 500 ms) SOAs.

Keywords

cocaine; response inhibition; inhibitory control; response activation; stimulus onset asynchrony

INTRODUCTION

Inhibitory control is impaired in cocaine users, as measured by stop-signal [1], go/no-go [2–5], and Stroop tasks [5]. The results of previous studies have shown that when individuals are prepared to respond but must withhold their response at the last moment, cocaine-using individuals fail to inhibit responding more frequently than matched controls [1–5].

Cocaine users who display impaired inhibitory control also have poorer treatment outcomes [6–8]. However, these clinical trials did not assess inhibitory control following the presentation of substance-related cues. Inhibitory control in the presence of substance related cues could be crucial to preventing relapse or the continued use of drugs because both occur in the presence of drug cues. Theories on the role of substance-related cues in substance abuse posit that over repeated pairings cues become associated with motivational states to obtain or use drugs [9]. Following this association, drug cues in the environment capture attention and receive preferential attention [9]. This preferential attention may impair inhibitory control, as described below.

Cued go/no-go tasks assess inhibitory control in the presence of environmental cues that predict when a response will be required [10]. The Attentional Bias-Behavioral Activation (ABBA) task is a modified cued go/no-go task that uses substance-related and neutral images rather than horizontal and vertical rectangles [11, 12]. Drinkers displayed impaired inhibitory control following alcohol-related compared to neutral cues on the ABBA task [12]. In a pilot study in our laboratory, cocaine users displayed significant increases in the proportion of inhibitory failures to no-go targets following cocaine images as the go cue compared to their counterparts who saw neutral images as the go cue [11]. Cues in the ABBA task are presented for one of five stimulus onset asynchronies (SOA), which is the amount of time that the cue is displayed before the presentation of the target: 100, 200, 300, 400, or 500 milliseconds (ms). The small sample size in the previous study prohibited analyses of the influence of SOA on proportion of inhibitory failures. The influence of SOA on inhibitory control could provide a more fine-grained understanding of the impact of drug-related stimuli on discontinuing or inhibiting the initiation of drug use, because both behaviors occur in the presence of drug-related stimuli. Increased inhibitory failures at short SOAs would suggest that the failures are related to the initial orientation of attention or rapid shifting of attention whereas increased inhibitory failures at long SOAs would suggest that participants are unable to disengage attention from the cue and employ cognitive mechanisms to inhibit behavior following the cue [9]. Understanding the influence of SOA on inhibitory control following the presentation of drug-related stimuli could also direct future interventions to improve inhibitory control in the presence of drug cues and lead to

improved treatment for cocaine users with poor treatment prognosis due to inhibitory control deficits.

The purpose of the present study was to demonstrate that SOA impacts the proportion of inhibitory failures to no-go targets following cocaine-related and neutral images as the go cue. We hypothesized that we would replicate our previous findings, such that the proportion of inhibitory failures to no-go targets following cocaine images as a go cue would be significantly greater than to no-go targets that followed neutral images as the go cue [11]. Second, we hypothesized that the proportion of inhibitory failures to no-go targets following cocaine images as the go cue compared to neutral images as the go cue would be increased following short SOAs compared to long SOAs, based on Event Related Potential (ERP) studies showing that frontal lobe engagement to inhibit behavior occurs approximately 150 ms following stimulus onset [13, 14]. Finally, based on previous studies we hypothesized that there would be no differences between go cue conditions in reaction time to go targets following go cues [11].

METHODS

Participants

Ninety-one adult participants (33 women and 58 men), primarily recruited through word of mouth and postings on community bulletin boards, completed this study. All participants reported using cocaine within the last month. 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., opiates or benzodiazepines), as participants were asked to abstain from drug use for 12 hours prior to testing. Participants completed screening questionnaires on current and past physical and mental health, measures of current psychological functioning, and a detailed drug use history [15]. Participants were paid between \$25 and \$45 for their participation, based on the research activities they were scheduled to do on the day they completed the ABBA task. The University of Kentucky Institutional Review Board approved all procedures and recruitment methods.

Procedure

Participants completed the ABBA task either during screening or practice sessions for other laboratory protocols. A between-subjects design was used, such that half of the participants were assigned to the cocaine go condition ($n = 46$) and half to the neutral go condition ($n = 45$; see below). The two groups were matched on demographic and drug use variables (e.g., age, years of education, and days used cocaine in the last month). Group demographics are shown in Table 1. A between-subjects design was used because participants learn to anticipate which cues signal a go or no-go target. Having participants switch conditions (i.e., cocaine and neutral go cues) would disrupt the learning that takes place during the task.

Attentional Bias-Behavioral Activation (ABBA)

The ABBA task is a modified cued go/no-go reaction time task, which was administered using E-prime experiment generation software (Psychology Software Tools, Pittsburgh, PA)

on a PC computer [11, 12]. The task took approximately 15 minutes to complete and consisted of five blocks of 50 trials. A trial involved a sequence of events during which a fixation point (+) was presented for 800 ms, followed by a blank white screen for 500 ms, a cue image (cocaine or neutral) was presented for one of five SOAs (i.e., 100, 200, 300, 400, 500 ms), and finally a go or no-go target, which was displayed until a response occurred or 1,000 ms elapsed. There was a 700 ms interval between all trials. The presentation of cocaine and neutral images was divided evenly between trials and image SOA was randomized throughout trials. The total number of trials during which participants were prepared to respond (i.e., go cue), but needed to inhibit responding (i.e., no-go target) occurred on 25 of the 250 trials.

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

The task consisted of two conditions: *cocaine go* condition and *neutral go* condition. In the cocaine go condition, 80% of go targets were preceded by a cocaine cue and 20% of go targets were preceded by a neutral cue. For no-go targets, 80% were preceded by a neutral cue and 20% were preceded by a cocaine cue. In the neutral go condition, 80% of go targets were preceded by a neutral cue and 20% were preceded by a cocaine cue. For no-go targets, 80% were preceded by a cocaine cue and 20% were preceded by a neutral cue. For half of the participants the cocaine image served as the go cue and for the other half, the neutral image served as the go cue.

Criterion Measures and Data Analysis

An alpha level of $p = 0.05$ was used to determine significance for statistical outcomes of *a priori* hypotheses [16]. Data on proportion of inhibitory failures and reaction times from the ABBA were analyzed using a mixed-model analysis of variance (ANOVA). The between-subject factor was go cue condition (i.e., cocaine go or neutral go) and the within-subject factor was SOA (i.e., 100, 200, 300, 400, or 500 ms). Fisher's Least Significant Difference test was used to assess differences between proportion of inhibitory failures and reaction times at each SOA and between SOAs within each condition based on significant ANOVA outcomes. Cohen's d was used to calculate effect sizes for all significant between-groups differences as determined by Fisher's Least Significant Difference test. Pearson correlations were used to assess associations between primary outcomes from the task and demographic and drug use variables. A Bonferroni correction for multiple correlations was used for these *post hoc* analyses, which adjusted the significant p -value to 0.0031 .

RESULTS

ABBA Task Performance

Response Inhibition Following Go Cues—The ANOVA revealed a significant interaction between go cue condition and SOA for inhibitory failures to no-go targets following go cues ($F_{4,356} = 2.50, p = 0.04$). Comparisons using Fisher's Least Significant Difference test revealed significant increases in the proportion of inhibitory failures in the cocaine go condition compared to the neutral go condition following the all of the SOAs (Cohen's $d = 0.71, 0.84, 0.44, 0.52$, and 0.32 , respectively). Within the cocaine go condition, participants had significantly increased inhibitory failures following the 100 and 200 ms SOAs relative to the 300, 400, and 500 ms SOAs. Within the neutral go condition, there were no differences in inhibitory failures following any of the SOAs (Figure 1, top panel).

Response Activation Following Go Cues—The ANOVA revealed a significant main effect of SOA for response time to go targets following go cues ($F_{4,356} = 5.56, p = 0.0002$). Regardless of condition, participants had significantly decreased reaction times following the 200, 300, 400, and 500 SOAs relative to the 100 ms SOA (Figure 1, bottom panel).

Response Inhibition Following No-Go Cues—The ANOVA revealed a significant main effect of SOA for proportion of inhibitory failures to no-go targets following no-go cues ($F_{4,356} = 5.40, p = 0.0003$). Within the cocaine and neutral go conditions, participants had significantly increased inhibitory failures at shorter SOAs (i.e., 100 and 200 ms) compared to longer SOAs (data not shown).

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

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

DISCUSSION

Participants who saw a cocaine-related image as a go cue displayed a greater proportion of inhibitory failures than their counterparts exposed to a neutral cue, which replicates the results of a previous study from our laboratory [11]. Importantly, reaction time following go cues did not differ between cocaine and neutral cue go conditions as demonstrated by a non-

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

We expanded upon previous findings to show that SOA influenced the proportion of inhibitory failures following cocaine images as the go cue. Cocaine users had an increased proportion of inhibitory failures following cocaine-related go cues compared to neutral go cues.

The increases in inhibitory failures following cocaine-related images were significantly higher at shorter (i.e., 100 and 200 ms) compared to longer (i.e., 300, 400, and 500 ms) SOAs. The mechanism underlying the increase in inhibitory failures at short, but not long, SOAs is not known, but previous studies with ERP and behavioral tasks may provide some insight. ERPs have been used to examine neuronal activity while participants completed a go/no-go task that required them to identify whether or not an image presented for only 20 ms contained an animal [13, 14]. The average brain ERPs generated by go and no-go trials diverged at 150 ms following stimulus onset with no-go trials producing a potential that was more negative than go trials. The time course and increased negative response of this ERP activity was consistent with the effect of frontal lobes in inhibiting behavior on no-go trials [13, 14].

The divergence observed previously between go and no-go trials at 150 ms is also consistent with our finding that inhibitory failures are significantly greater following 100 and 200 ms SOAs for cocaine images. Thus, the increase in inhibitory failures following cocaine images at the shorter SOAs may relate to the initial orientation of attention to the cocaine image [9] and the expectation that a cocaine image is most often followed by a go target requiring a response. Participants may then be unable to engage the frontal lobe to inhibit responding following the cue at short SOAs given that ERP studies show frontal lobe activation involved in inhibiting behavior occurs at approximately 150 ms [13, 14].

Other evidence suggests that only salient cues can be processed at very short SOAs. In a series of experiments, the salience of cues to aid in the execution of a behavioral response was assessed [17]. Cues were presented for one of three SOAs (i.e., 42, 158, or 483 ms). Following the SOA, a target was presented and participants were required to indicate the location of the target. When cues were presented for the shortest SOA (i.e., 42 ms), salience of the cue aided in detection of the target as indicated by a reduced reaction time. At the longest SOA, cue salience did not influence reaction time [17]. The increase in inhibitory failures following cocaine images at short SOAs is concordant with these outcomes because cocaine-related cues are likely more salient than neutral cues to cocaine users. However at the longer SOAs, the salience of the cocaine-related cues relative to neutral cues is less influential.

Post hoc analyses showed that there were significantly fewer inhibitory failures within the cocaine go condition following longer SOAs (i.e., 300, 400, and 500 ms). Longer SOAs provide sufficient time for multiple shifts of attention from the cocaine-related cue [9]. This time allows participants to disengage attention from the cocaine-related cue and employ cognitive mechanisms to inhibit responding to a no-go target. Similarly, there was an increase in inhibitory failures following no-go cues at short SOAs compared to long SOAs, but differences between the go cue conditions were not systematic especially when compared to the outcomes observed when participants are prepared to execute a response (i.e., seeing a cocaine go cue followed by a no-go target).

Drug cues are associated with motivational states to obtain or use substances [18]. Inhibitory control in the presence of drug cues may relate to the ability to abstain from or discontinue drug use. Specifically, the presence of drug cues (e.g., paraphernalia) may signal the presence of a drug, thus making it more difficult for individuals to inhibit initiation of drug use. Based on our findings, inhibition following the initial orientation to a drug-related cue would be particularly difficult, as the processes involved in inhibitory control are not yet engaged. Additionally, the continuation of use would occur in the presence of drug cues. When cocaine users complete the ABBA task, inhibitory failures in the presence of drug-related cues occur when individuals anticipate a response will be required following a drug cue and then have to inhibit the response [11]. This increase in inhibitory failures models how impaired inhibitory control could contribute to initiation or the continuation of drug use, as the individual would need to inhibit the anticipated response following the presence of drug cues. Although previous studies have shown that impaired inhibitory control on the Stroop task was associated with poor treatment outcomes [6–8], the influence of inhibitory control following drug cues on treatment outcomes is not known and should be investigated in future research. Future research should also further investigate the influence of SOA on inhibitory control to better understand the mechanisms involved.

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

Overall, the present study replicated our previous findings showing that cocaine-related stimuli decreased inhibitory control in cocaine users, which could be related to the inability to avoid or cease drug use in the presence of drug cues. We extended the previous findings to show that the disruption in inhibitory control by cocaine images occurs at short (i.e., 100 and 200 ms) SOAs, but not at longer (i.e., 300, 400, and 500 ms) SOAs. The influence of SOA on inhibitory control could significantly impact attempts to improve or modify

inhibitory control in the presence of drug cues. Further research is needed to better understand the nature of cue-related disinhibition and its impact on drug use in the natural ecology.

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Figure 1.

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

Table 1

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

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

^a Sample size reported for sex and race.