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Relationship between Attentional Bias to Cocaine-Related Stimuli and Impulsivity in Cocaine-Dependent Subjects

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INTRODUCTION

The emotional Stroop task is widely used to measure attentional bias to words associated with concerns relevant to a subject's clinical condition (1, 2). It requires participants to indicate the color of the words while inhibiting their response to the distracting salient feature of the same word (1, 2). Studies using the cocaine emotional Stroop task showed that cocaine-dependent subjects had slower reaction time (RT) to name the color of cocaine-related words compared with neutral words (3, 4), while controls did not show this RT difference (3), suggesting that cocaine-related stimuli acquired incentive properties in cocaine-dependent subjects. An addiction treatment study (5) suggests that attentional bias in cocaine-dependent subjects was associated with worse treatment outcome but this study reported a large number of small correlations and more convincing data are needed to confirm this association. Attentional bias was also associated with higher cocaine craving ratings (6, 7). Taken together, these studies support the experimental utility of investigating attentional bias in cocaine-dependent subjects using the cocaine Stroop task.

In addition to attentional bias to cocaine-related stimuli, cocaine-dependent subjects also show increased trait impulsivity and impaired inhibitory control. On the Barratt Impulsiveness Scale version 11 (BIS-11), cocaine-dependent subjects scored significantly higher than controls (8, 9). Several behavioral tasks such as the Continuous Performance Test (CPT), Go/Nogo task and Stop Signal task have been used to measure response inhibition, one component of impulsivity. Our laboratory has found that cocaine-dependent subjects had a higher commission error rate on the Immediate Memory Task (IMT), a variant of the CPT, than controls, indicating a deficit in inhibitory control in cocaine-dependent subjects (8, 9). Other studies using the Stop Signal task found that cocaine-dependent subjects showed a deficit in inhibitory control expressed as increased stop signal RT (10, 11). However, how impulsivity and inhibitory control affect attentional bias is not well-studied. Since the cocaine Stroop task requires subjects to inhibit their response to the distracting feature of cocaine-related words (2, 12), cocaine-dependent subjects with higher

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impulsivity and poorer inhibitory control may have a more pronounced attentional bias to cocaine-related stimuli. Thus, we hypothesized that attentional bias to cocaine-related words would correlate with impulsivity, as measured by BIS-11 and inhibitory control, as measured by the IMT commission error rate.

METHODS

Subjects

The sample consisted of 32 controls and 37 active cocaine-dependent subjects recruited from an ongoing neuroimaging study. All subjects were recruited through newspaper advertisements and screened for psychiatric disorders using the Structured Clinical Interview for DSM-IV (SCID-I) (13) and a medical history and physical examination. All subjects were tested for urine cocaine (benzoylecgonine), THC, opiates, amphetamine, and benzodiazepines using integrated E-Z split key cup II (Innovacon Company, San Diego, CA) on each visit. Cocaine-dependent subjects met current DSM-IV criteria for cocaine dependence, had at least one cocaine-positive urine during screening, did not meet DSM-IV current dependence criteria for abused drugs other than cocaine, marijuana or alcohol, did not have current or past medical disorders affecting the central nervous system (CNS), and did not have axis I disorders other than substance abuse or dependence. Cocaine-dependent subjects included non-treatment-seekers and treatment-seekers. The treatment-seekers were tested during the baseline period of a treatment study, prior to the start of medication or cognitive-behavioral therapy. Controls consisted of participants who did not have a positive drug screen and did not have any current or past DSM-IV axis I disorder (including substance dependence) or medical disorder affecting the CNS. All subjects were free of alcohol at the time of testing as determined by a breathalyzer (Intoximeters, Inc., St. Louis, MO). Because of the potential risk of the neuroimaging study, female subjects were excluded if they had a positive urine pregnancy test. The study was performed in the Center for Neurobehavioral Research in Addictions of University of Texas Health Science Center at Houston, before the neuroimaging phase began. Subjects were fully informed of the nature of the research and provided written consent for their involvement in accordance with the Declaration of Helsinki. The study was approved by the Committee for the Protection of Human Subjects of University of Texas Health Science Center at Houston.

Barratt Impulsiveness Scale version 11 (BIS-11)

The BIS-11 is a 30-item questionnaire which has been extensively used in research on impulsivity and impulse control disorders. Each item is rated from 1 (never) to 4 (always) (25). The BIS-11 has three subscales determined by factor analysis (25): (1) motor impulsiveness or acting without thinking; (2) attentional impulsiveness or inability to focus attention or concentrate; (3) nonplanning impulsiveness or lack of future planning or forethought. The total score and the scores for each subscale were calculated.

Cocaine Stroop Task

This task was used to measure attentional bias to cocaine-related stimuli (3, 4). Each session included 60 practice trials and 240 test trials. The stimuli in the practice trials were colored repeated single letters matched to cocaine-related words in length (e.g., XXX, MMMMM). The stimuli in the test trials included 10 cocaine-related words: "COCAINE", "CRACK", "ROCKS", "HIGH", "DEALER", "HIT", "SMOKE", "PUFF", "PIPE", "FREEBASE" and 10 length-matched neutral words: "CABINET", "COUCH", "SOFA", "OVEN", "FLOOR", "WINDOW", "RUG", "ARMCHAIR", "LAMP", "ROOM". In each trial, the word was presented against a black background in one of three colors: red, blue, or green. The subjects were asked to press mouse buttons covered by colored stickers to indicate the color of the words as quickly and as accurately as possible while ignoring the meaning of the words. A

short beep sounded if the subject made an incorrect response. The stimulus stayed on the screen until the subject made a button press or until 1800 msec had elapsed. The inter-trial interval was 500 msec. The test trials included four blocks of trials with cocaine-related words and four blocks of trials with neutral words. Each block included 30 trials, in which each word was randomly presented three times in three different colors. The two types of blocks were distributed alternatively, and counterbalanced across subjects. The trials with correct responses and RTs larger than 200 msec were used to calculate mean RTs. The difference in mean RTs between trials with cocaine-related words and those with neutral words was used as a measure of attentional bias to cocaine-related words. The difference of accuracies between trials with cocaine-related words and those with neutral words was also calculated.

Immediate Memory Task (IMT)

The IMT is a Continuous Performance Test in which subjects were presented a series of 5-digit numbers via a computer monitor (14). Subjects were told to press the mouse button if the number was identical and to withhold their response if the number was not identical to the preceding number. The trials were presented as follows: identical to (33% of the total trials), differed by 1 digit (33% of the total trials) or differed by all 5 digits (34% of total trials) from the previous number. The three trial types were randomly presented. Additional details can be found in previous work (14). The commission error rate was defined as the rate of the incorrect responses when the number differed by 1 digit from the previous number. It is conceptually related to impulsivity in that the inability to withhold an inappropriate behavioral response is a key aspect of some definitions of impulsivity (15-16). The correct detection rate was measured as the rate of the correct responses when the number was identical to the previous number.

Statistical Analyses

Differences in demographic variables between groups were compared using the Student's *t* test for continuous variables and the Chi-square test for categorical variables. Differences between controls and cocaine-dependent subjects were analyzed using Analysis of Covariance (ANCOVA), with age and gender as covariates. Differences in attentional bias between the two groups were also assessed using two way repeated ANOVA and post hoc paired *t*-test. Relationships between attentional bias and other measures were analyzed using Pearson Correlation analysis.

RESULTS

Demographics and Cocaine Use History

The two groups did not differ significantly in ethnicity ($\chi^2=3.86$, $p=0.28$; 22 African Americans, 5 Caucasians, and 5 others in control vs. 27 African Americans, 8 Caucasians, and 2 others in cocaine-dependent group) or educational level ($t=1.67$, $p=0.10$; 13.74 $\pm$ 1.93 years (19 – 50 years-old) in control vs. 12.95 $\pm$ 1.97 years (24 – 54 years-old) in cocaine-dependent group). Cocaine-dependent subjects reported using cocaine for 13.64 $\pm$ 7.36 years. They used cocaine in 13.43 $\pm$ 9.0 days of the last 30 days and started to use cocaine at 26.12 $\pm$ 6.99 years-old. Twenty-four and 27 percent of cocaine-dependent subjects were also diagnosed as having past cannabis and alcohol dependence, respectively. The cocaine-dependent subjects were older ($t=4.14$, $p < 0.0001$) than controls (32.91 $\pm$ 7.71 vs. 40.54 $\pm$ 7.56 years old) and differed in gender distribution compared with controls ($\chi^2=11.18$, $p=0.0008$; 17 male, 15 female in control vs. 33 male, 4 female in cocaine-dependent group).

Cocaine Stroop Task Performance

Attentional bias to cocaine-related words was calculated as mean RT for cocaine-related words minus mean RT for neutral words (17). ANCOVA results indicated higher attentional bias in cocaine-dependent subjects than in controls ($F_{(1,67)}=7.06$, $p=0.01$, Figure 1A) while cocaine-related words did not change accuracy ($F_{(1,67)}=1.72$, $p=0.19$, Figure 1B). Two way repeated ANOVA results showed a main effect of group ($F(1, 67) = 16.60$, $p < 0.0001$) and a significant group $\times$ word type interaction ($F(1, 67) = 7.64$, $p = 0.0074$) but did not show a main effect of word type ($F(1, 67) = 3.12$, 0.0821). Post hoc paired t-test showed that in the cocaine group, reaction time for cocaine-related words (709 ± 157 msec) was significantly slower than that for neutral words (689 ± 150 msec; $t = 2.67$, $p = 0.01$) while in the control group, reaction times for cocaine-related (570 ± 94 msec) and neutral words (576 ± 93 msec) were not significantly different ($t = -1.14$, $p = 0.26$). Among the cocaine-dependent subjects, treatment-seekers showed a significantly higher attentional bias than non-treatment-seekers (38 ± 56 msec vs. 7 ± 32 msec; $t = 2.16$, $p = 0.037$)

Impulsivity Measures

The IMT commission error rate was significantly higher ($F_{(1,67)}=4.94$, $p=0.03$) in cocaine-dependent subjects than in controls but there was not a significant difference in correct detection rate between the two groups ($F_{(1,67)}=1.31$, $p=0.25$, Table 1). Cocaine-dependent subjects also showed significantly higher BIS-11 total score ($F_{(1,67)}=10.60$, $p=0.002$), attention score ($F_{(1,67)}=7.04$, $p=0.01$), motor score ($F_{(1,67)}=4.51$, $p=0.04$) and nonplanning score ($F_{(1,67)}=10.79$, $p=0.002$) than controls (Table 1).

Relationship between Attentional Bias and Impulsivity

Since cocaine-dependent but not control subjects showed attentional bias to cocaine-related words, relationships between attentional bias and impulsivity were assessed only in cocaine-dependent subjects. The results showed that attentional bias was significantly correlated with the IMT commission error rate in cocaine-dependent subjects ($r=0.33$, $p=0.04$, figure 2). This correlation between attentional bias and IMT commission error rate was significant ($r=0.56$, $p=0.007$) in non-treatment seeker while not reaching significance in treatment seeker ($r=0.32$, $p=0.246$). Attentional bias was not significantly correlated with BIS11 total or subscale scores, IMT correct detection rate, and drug use history (days to use cocaine in past 30 days, years to use cocaine, age to start using cocaine) in the cocaine-dependent subjects.

DISCUSSION

We found that cocaine-dependent subjects showed an attentional bias to cocaine-related words expressed as a significantly larger RT difference (cocaine-related words – neutral words), confirming the increased salience of cocaine-related stimuli in this population (3, 4). We also found an increased IMT commission error rate and BIS-11 scores in cocaine-dependent subjects compared with controls, suggesting impaired inhibitory control and increased impulsivity in cocaine-dependent subjects, which is consistent with previous studies (8, 9, 19). The most important finding of the study, however, was the observed association between attentional bias and inhibitory control, as measured by IMT commission error rate, in cocaine-dependent subjects. At a theoretical level, it is possible that individuals with poor inhibitory control are less able to engage strategic processes to override the attentional bias. This finding is consistent with a recent study (20) showing a positive correlation between the alcohol-related attentional bias and impulsive decision-making in a delay discounting task in heavy drinking adolescents. The significant association between attentional bias and inhibitory control supports the hypothesis that “substance abusers with severely compromised inhibitory control are particularly susceptible to the attention-

grabbing properties of substance-related stimuli” (18, p 12), although further research is needed to delineate the nature of the relationship between attentional bias and inhibitory control.

Cognitive deficits in cocaine-dependent subjects have been examined using neuroimaging techniques (10, 11, 19, 21). When cocaine-dependent subjects performed the cocaine Stroop task, task performance produced hypoactivation in the rostro-ventral anterior cingulate cortex (ACC)/medial orbitofrontal cortex compared with baseline activity (21, 22). This change in brain activity was larger in cocaine-dependent subjects than controls (22) and was larger when the cocaine-dependent subjects were exposed to cocaine-related words than when they were exposed to neutral words (21). Similar results were obtained in ACC using the Stop Signal and Go/NoGo tasks (23, 24). It follows that ACC activity may underlie the significant correlation between attentional bias to cocaine-related words and the IMT commission error rate in cocaine-dependent subjects found in the present study.

No significant correlation between attentional bias and drug use behaviors (total years, days in past 30 days and age to start cocaine use) was observed in cocaine-dependent subjects. Similarly, Hester et al. (3) did not find a relationship between attentional bias and drug use history in cocaine-dependent subjects. However, among users of alcohol or cannabis, attentional bias to drug-related cues was higher in heavy users than in light users (18). In our study, all cocaine users were cocaine-dependent subjects. Perhaps no further increments in attentional bias occur once cocaine users have reached the state of dependence. Consistent with this, in heavy cannabis users there was no significant relationship between the user’s quantity or frequency of cannabis use and the degree of their attentional bias (18).

Consistent with Vadhan et al. (4), we also found that treatment-seeking cocaine-dependent subjects had a higher attentional bias to cocaine-related words than non-treatment-seeking cocaine-dependent subjects. This difference in attentional bias may be related to other factors that differ between treatment-seeking and non-treatment-seeking cocaine-dependent subjects, such as variance in the adverse consequences of cocaine use (26). Further research is needed to investigate this relationship.

One major limitation of the current study is that there were significant differences in age and gender distribution between control and cocaine-dependent subjects. However, for the controls, we did not find a significant correlation between age and attentional bias ($r = -0.05$, $p = 0.77$) nor between age and impulsivity (for age and BIS-11 total score, $r = 0.08$, $p = 0.64$; for age and IMT commission error rate, $r = 0.04$, $p = 0.81$). Furthermore, we did not find a significant difference in attentional bias or impulsivity between female and male subjects. Covariance analysis with age and gender as covariates also did not change the significance of the outcomes. Future studies of attentional bias may benefit from greater control over the sociodemographic variables, as well as more detailed quantitative information regarding recency and amount of cocaine use and use of other drugs. Another limitation is that we did not exclude cocaine-dependent subjects with marijuana or alcohol dependence because of the high percentage of marijuana and alcohol dependence in this population. We did exclude subjects whose urine THC screening or breath alcohol test was positive before behavioral tests to exclude potential acute effects of marijuana or alcohol on performance during behavioral tests. Discrepancies in the proportion of current cigarette use between cocaine-dependent (80%) and control subjects (14%) is also a potential confounding factor in the difference on behavioral test performance between the two groups. Future studies will need to attend carefully to nicotine use across all subject groups.

In summary, the present study showed that cocaine-dependent subjects had an attentional bias to cocaine-related words, poorer inhibitory control measured by the IMT, and higher

impulsivity measured by BIS11. Attentional bias was positively correlated with the commission error rate in the IMT. This positive correlation between attentional bias and inhibitory control suggests that a potential behavioral mechanism of impaired inhibition may underlie poor clinical outcomes in impulsive cocaine users, although further research is warranted to elucidate this mechanism. Behavioral techniques and medications aimed at improving impulse control and remediating attentional bias may prove to be helpful tools in the treatment of cocaine dependence.

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Figure 1.

An attentional bias to cocaine-related words in cocaine-dependent subjects. A. Attentional bias was expressed as the difference of reaction times (cocaine-related words – neutral words, mean±SEM); * $p < 0.05$, vs. control subjects, Analysis of Covariance with age and gender as covariates. B. Difference of Accuracy Change by cocaine-related words (cocaine-related words – neutral words, mean±SEM) between two groups was not significant; $p > 0.05$, Analysis of Covariance with age and gender as covariates.

Figure 2. Significant correlation between attentional bias to cocaine-related words and IMT commission error rate in cocaine-dependent subjects but not in control subjects. In cocaine-dependent subjects, $r = 0.33$, $p = 0.04$ for Pearson's Correlation analysis.

Table 1

Comparison of IMT performance and BIS-11 scores between control and cocaine-dependent subjects. The data show Mean $\pm$ SD for each group.

	Control Subjects	Cocaine-dependent Subjects
Immediate Memory Task		
Commission Error Rate(%)	21.95 $\pm$ 13.06	31.07 $\pm$ 15.88 *
Correct Detection Rate(%)	82.08 $\pm$ 12.86	83.33 $\pm$ 12.32
BIS -11		
Total score	55.37 $\pm$ 7.99	68.14 $\pm$ 14.08 **
Attention score	13.27 $\pm$ 2.90	16.00 $\pm$ 4.17 *
Motor score	21.03 $\pm$ 3.94	24.71 $\pm$ 6.00 *
Nonplanning score	21.07 $\pm$ 4.27	27.43 $\pm$ 6.02 **

*
p < .05,

**
p < .01:

Analysis of Covariance with age and gender as covariates.