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Increased Depression and Anxiety Symptoms are Associated with More Breakdowns in Cognitive Control to Cocaine Cues in Veterans with Cocaine Use Disorder

Gregory J. DiGirolamo, Ph.D.[1,2,3], **Gerardo Gonzalez, M.D.**[3], **David Smelson, Psy.D.**[3], **Nathan Guevremont, B.A.**[1,3], **Michael I. Andre, B.A.**[1], **Pooja O. Patnaik, B.A.**[1], and **Zachary R. Zaniewski, B.A.**[1,2]

[1]Department of Psychology, College of The Holy Cross, University of Massachusetts-Medical School

[2]Department of Radiology, University of Massachusetts-Medical School

[3]Department of Psychiatry, University of Massachusetts-Medical School

Abstract

Objective: Cue-elicited craving is a clinically important aspect of cocaine addiction directly linked to cognitive control breakdowns and relapse to cocaine taking behavior. However, whether craving drives breakdowns in cognitive control toward cocaine cues in veterans, who suffer from significantly more co-occurring mood disorders, is unknown. The present study tests whether veterans have breakdowns in cognitive control because of cue-elicited craving or current anxiety or depression symptoms.

Methods: Twenty-four veterans with cocaine use disorder were cue-exposed, then tested on an antisaccade task in which subjects were asked to *control* their eye movements toward cocaine or neutral cues by looking away from the cue. The relationship between cognitive control breakdowns (as measured by eye errors), cue-induced craving (changes in self-reported craving following cocaine cue exposure) and mood measures (depression and anxiety) was investigated.

Results: Veterans made significantly more errors toward cocaine cues than neutral cues. Depression and anxiety scores, but not cue-elicited craving, were significantly associated with increased subsequent errors toward cocaine cues for veterans.

Conclusion: Increased depression and anxiety are specifically related to more cognitive control breakdowns toward cocaine cues in veterans. Depression and anxiety must be considered further in the etiology and treatment of cocaine use disorder in veterans. Furthermore, treating depression and anxiety as well, rather than solely alleviating craving levels, may prove a more effective combined treatment option in veterans with cocaine use disorder.

Corresponding Author: Dr. Gregory J. DiGirolamo, Department of Psychology, College of the, Holy Cross, Worcester, MA 01610, gdigirol@holycross.edu.

6. Disclosure

Ms. Patnaik, Mr. Andre, Mr. Guevremont, Mr. Zaniewski, and Drs. DiGirolamo, Gonzalez, and Smelson report no financial relationships with commercial interests nor any conflict of interests with this work.

Keywords

Cocaine; Veterans; Mood Disorders; Antisaccades; Cognitive Control; Addiction

1. Introduction

Cocaine use disorder remains a significant public health problem among civilian populations with more than 900,000 people reaching criterion for this disorder (Quality, 2015). While drug use is lower than the general population in active military, monthly prevalence rates for cocaine use are one percent in active military (Institute, 2009) and cocaine is one of the most frequent positive drug urine tests (Institute, 2009). Cocaine use disorder is even further elevated in veterans, with a 2002–2013 survey of Veteran's Affairs (VA) data (Center, 2016) demonstrating that 19.18% of all substance use diagnoses were for this diagnosis. Even more disconcerting than the high prevalence rate in veterans is a lack of a Food and Drug Administration-approved pharmacological treatment for cocaine use disorder (Negus & Henningfield, 2015), though several medications have been tried (Gonzalez et al., 2007). Thus, treatment relies less on medication and more on understanding and treating the factors that contribute to use and relapse. Two factors of particular importance in understanding cocaine use and relapse are breakdowns in cognitive control to cocaine cues (DiGirolamo, Guevremont, & Smelson, 2015; Marks et al., 2014; Volkow, Wang, Tomasi, & Baler, 2013) and cue-elicited craving (Childress, McLellan, & O'Brien, 1993; Smelson, Roy, Roy, & Santana, 1998).

The ability to exert cognitive control over behavior toward cocaine cues is commonly regarded as a hallmark of drug use cessation and relapse prevention (Goldstein & Volkow, 2002a, 2002b; Marhe, Luijten, van de Weterin, Smits, & Franken, 2013; Marhe, van de Wetering, & Franken, 2013; Volkow et al., 2013). Cognitive control is the neural processes that allow information processing and behavior to vary adaptively from moment to moment depending on goals, rather than inflexible responding to powerful stimuli in the environment or based on habitual response (Aron, 2007; Posner & DiGirolamo, 1998). And, cognitive control deficits are common in patients with substance use disorder, including cocaine use disorder (DiGirolamo et al., 2015; DiGirolamo et al., 2016; Lyvers, 2000; van der Plas, Crone, van den Wildenberg, Tranel, & Bechara, 2008). Patients demonstrate deficits in cognitive control abilities across a range of tasks even those not using cocaine cues (Hester & Garavan, 2004; Hester, Simoes-Franklin, & Garavan, 2007; Volkow et al., 2010; Volkow et al., 2013). These deficits including inhibiting their response (Fillmore & Rush, 2002) and filtering irrelevant information (Streeter et al., 2008). Patients who will eventually drop out of treatment exhibit poorer filtering of irrelevant information than patients who will complete treatment (Streeter et al., 2008). Moreover, awareness of errors is also impaired and this marker is associated with treatment outcome even when controlling for other mitigating factors affecting relapse (Marhe, van de Wetering, et al., 2013). Hence, cognitive control deficits are prevalent in patients with cocaine use disorder and are critical for use and relapse. However, cognitive control breakdowns to cocaine cues are themselves influenced by other factors including craving severity (DiGirolamo et al., 2015).

Despite the importance of craving as a diagnostic symptom in DSM-5 (American Psychiatric Association, 2013), and over 450 craving studies reported in the literature, few studies have focused on individual differences in cue-elicited cocaine craving (changes in craving following exposure to a drug cue), and the impact of craving on cognitive control (c.f.,DiGirolamo et al., 2015). Higher craving patients use more cocaine and are at higher risk for relapse in comparison to lower cravers (Paliwal, Hyman, & Sinha, 2008) and intensity of cue-elicited craving is related to levels of dependence (Childress et al., 1993; Smelson et al., 1998).

While the intensity of cue-elicited craving varies across patients (Kilts, 2004; Smelson et al., 2013; Smelson, Kilker, et al., 2002), the ability to control behavior is impaired generally across all patients with cocaine use disorder (Hester & Garavan, 2004; Hester et al., 2007; Volkow et al., 2010; Volkow et al., 1992; Volkow et al., 2013). Both cue-elicited craving and cognitive control are factors that are separately associated with drug use and relapse (Marhe, van de Wetering, et al., 2013; Paliwal et al., 2008; Streeter et al., 2008). Furthermore, a recent study (DiGirolamo et al., 2015) demonstrated that cue-elicited craving and cognitive control are significantly related to each other. DiGirolamo et al. (2015) tested a group of civilian patients with cocaine use disorder on a modified drug antisaccade task (see also, DiGirolamo et al., 2016) in which patients were instructed to look away from a cocaine cue. Overall, patients with cocaine use disorder made more errors (looked toward the cue) toward cocaine cues than neutral cues demonstrating a breakdown of cognitive control. Higher cravers had more breakdowns in cognitive control than lower cravers and increased craving was a significantly associated with cognitive control deficits across all patients. Craving, therefore, is directly related to the ability to assert cognitive control in response to cocaine-cues and higher craving corresponds to more cognitive control deficits. Higher and lower cravers had similar levels of depression and anxiety, suggesting that craving alone is associated with cognitive control deficits in civilian patients with cocaine use disorder.

However, it is unclear whether craving is associated with cognitive control deficits across all populations of patients with cocaine use disorder. The veteran population, for example, has a higher prevalence of cocaine use disorder compared to the civilian population (Center, 2016) and higher rates of co-occurring mental health issues with 36.9 to 50.2 percent of veterans suffering from depression or anxiety, making veterans two to five times more likely to suffer mood disorders than the civilian population (Substance Abuse and Mental Health Services Administration, 2012). While depression and anxiety are strongly associated with substance use, the direction and causality of that relationship is complex (Grant et al., 2004), with some studies showing no relationship between increased depression and pretreatment drug use, (Brown et al., 1997) and decreases in depression or anxiety are not associated with subsequent abstinence (though abstinence is associated with decreases in depression; Milby et al., 2015). Given the notable depression and anxiety rates in veterans, and some studies showing clear associations between mood and substance use (e.g., Grant et al., 2004), these factors might have an effect on cognitive control abilities to cocaine cues in the veteran population. Moreover, anxiety (Bishop, Duncan, Brett, & Lawrence, 2004) and depression (Rogers et al., 2004) have been related to decreased cognitive control and dysfunction in the neurocircuitry of the cognitive control circuit. Hence, cognitive control deficits in veterans might be particularly tied to their anxiety and depression symptoms. The current pilot study looks at the cognitive control to cocaine cues in a veteran population, and association between craving, anxiety and depression and cognitive control breakdowns to cocaine cues in the modified drug antisaccade task (DiGirolamo et al., 2015; DiGirolamo et al., 2016) among a veteran population.

2. Methods

2.1 Participants & Assessments

Twenty-four veterans were recruited at the Department of Veteran Affairs. Veterans were included if they were: 1) over 18, 2) English speaking, 3) completed the eighth grade 4) identified cocaine as their primary drug of choice, 5) seeking treatment for cocaine use disorder and 6) used cocaine within the last year. Subjects were excluded if they: 1) were unable to provide informed consent, 2) had a history of traumatic brain injury or 3) were actively psychotic. This study was approved by the VA Institutional Review Board (IRB) and veterans provided informed consent before completing any assessments.

2. Assessments and Procedures

Procedures for the study followed exactly our previous study (DiGirolamo et al., 2015). Baseline demographic data, as well as quantity and frequency of cocaine use was collected using the drug history questions from the Addiction Severity Index (McLellan, Luborsky, Woody, & O’Brien, 1980) and clinical interview. Additional mental health assessments included the Beck Depression Inventory (BDI, Beck, Steer, & Carbin, 1988); Beck Anxiety Inventory (BAI, Beck, Epstein, Brown, & Steer, 1988); Severity of Dependence Scale (SDS, Gossop et al., 1995); and Barratt Impulsiveness Scale (BIS, Patton, Stanford, & Barratt, 1995).

To index craving severity, veterans completed a Voris Cocaine Craving Scale (Voris, Elder, & Sebastian, 1991) before and after handled either five cocaine-related cues or five neutral cues in a block design.

The antisaccade task utilized cocaine and neutral visual cues. Veterans were asked to look away from peripherally presented cues. Participants completed 440 trials with equal numbers of cocaine and neutral cues. An eye movement was classified as a saccade when its velocity reached 30 degrees/second, or its acceleration had reached 8000 degrees/second^2. As is standard in the antisaccade task, trials in which the eye movements were executed under 80 milliseconds (ms) after the onset of the go signal were considered anticipations and discarded, as were trials where an eye blink occurred (Wenban-Smith & Findlay, 1991). 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. Average error rates were calculated for each participant in each category (drug or neutral) by dividing the number of prosaccadic errors (looks toward the cue) by the total number of valid trials. Likewise, the speed of the eye movement, from the onset of the cue until the initiation of the eye movement (saccadic reaction time), was averaged for each participant in each category (drug or neutral).

2.3 Analytic Strategy

Cocaine craving and cognitive control breakdowns were treated in two ways. First, veterans were dichotomized into higher and lower craving groups using a median split on their cue-induced craving score (pre-cocaine cue craving – post cocaine cue craving). Errors and saccadic reactions times were compared across category with repeated measures analysis of variance with standard checks for normality, or mixed effects analyses of variance when comparing assessments across groups (high and low cravers).

Next, cocaine craving was treated as a continuous variable, along with mental health and baseline characteristics to evaluate the association with breakdowns in cognitive control in the antisaccade task. It was anticipated that mental health characteristics would be highly co-linear. Because of the extreme multi-collinearity between depression, anxiety and impulsivity (see, DiGirolamo et al., 2015), individual regression analyses were performed with each factor included in a separate model, after testing the collinearity of the factors.

3. Results

As shown in Table 1, veterans were primarily white and identified crack cocaine as their drug of choice. Assessments (SDS, BIS, BDI, and BAI) indicated participants were severely dependent on cocaine (Kaye & Darke, 2002), highly impulsive (Stanford et al., 2009), mildly depressed (Beck, Steer, et al., 1988), and mildly anxious (Fydrich, Dowdall, & Chambless, 1992). Participants craving increased significantly after cocaine cue exposure, with $F(1, 23) = 34.68$, $p < 0.0001$.

Overall, veterans made significantly more errors to cocaine cues than neutral cues, $F(1, 23) = 9.72$, $p < 0.006$. There was no difference in the speed of the errors toward cocaine cues versus neutral cues, with $F(1, 23) = 2.07$, $p = 0.16$, nor did the speed of the correct response differ between the cocaine cues and neutral cues, with $F(1, 23) = 0.36$, $p = 0.55$.

Next, we divided the veterans into higher and lower cravers (see, DiGirolamo et al., 2015) based on being above or below the median craving change. To confirm our grouping allocation, we tested the change in craving and our higher craving veterans had significantly more cue-induced craving than our lower craving veterans, with $F(1, 22) = 51.35$, $p < 0.001$. Higher craving veterans had also significantly more previous treatment failures than lower craving veterans, with $F(1, 22) = 4.85$, $p < 0.04$. In addition, there was a trend for higher craving veterans to have higher severity scores than lower craving veterans, with $F(1, 22) = 3.97$, $p = 0.059$. The higher and lower craving veterans did not differ in age ($F(1, 22) = 0.01$, $p = 0.91$), years of use ($F(1, 22) = 0.62$, $p = 0.44$), or last time used ($F(1, 22) = 0.24$, $p = 0.88$). Nor did they differ on measures of impulsivity ($F(1, 22) = 0.83$, $p = 0.37$), anxiety ($F(1, 22) = 0.01$, $p = 0.92$), or depression ($F(1, 22) = 0.001$, $p = 0.98$). Most telling, the higher and lower craving veterans did not differ in the number of increased errors they made to cocaine cue ($F(1, 22) = 0.003$, $p = 0.96$), the speed of those errors ($F(1, 22) = 0.04$, $p = 0.84$) or the speed of their successful antisaccades ($F(1, 22) = 0.02$, $p = 0.88$). In short, higher and lower craving veterans did not differ on any measure of cognitive control (c.f., DiGirolamo et al., 2015).

Then, we analyzed the craving data as a continuous variable in a regression model to test the association with cognitive control breakdowns. Increased cue-elicited craving was not associated with increased errors to cocaine cues, with no hint of an effect with $F(1, 22) = 0.18$, $p = 0.68$. In short, in veterans with cocaine use disorder, cue-elicited craving is not associated with cognitive control breakdowns to cocaine cues (c.f., DiGirolamo et al., 2015).

We next analyzed the other factors individually because of the clear collinearity (Gorman, 1996). Indeed, within our own data (see Table 2), as expected, depression and anxiety were highly related ($r = 0.66$, $p < 0.001$); hence, we analyzed each factor's individual association with cognitive control breakdowns. Neither severity of dependence ($F(1, 22) = 0.26$, $p = 0.62$) nor impulsivity ($F(1, 22) = 1.56$, $p = 0.23$) were associated with cognitive control breakdowns. However, both depression ($F(1,22) = 8.85$, $p < 0.008$) and anxiety ($F(1,22) = 4.64$, $p < 0.05$) were significantly positively associated with breakdowns in cognitive control to cocaine cues with increases in either depression or anxiety resulting in more errors toward cocaine cues.

4. Discussion

These results demonstrate that in veterans with cocaine use disorder, anxiety and depression are associated with cognitive control breakdowns to cocaine cues. The veterans in this study had only mild depression and anxiety and yet, these minor disturbances in mood were associated with higher errors toward cocaine cues. Levels of depression and anxiety are not associated with cognitive control breakdowns in non-veterans (DiGirolamo et al., 2015) in this task. In the current data, veterans with mild increases in depression and anxiety are showing increased breakdowns in cognitive control to cocaine cues and the amount of breakdown in cognitive control is directly associated with slightly elevated levels of depression and anxiety and not their cue-elicited craving.

Depression or anxiety driving breakdowns in cognitive control in veterans may not be altogether unexpected. Veterans with depression have a 4.68 times increase of having a substance use disorder (SUD) than non-depressed veterans (Seal et al., 2011). Moreover, mildly depressed veterans, with similar depression scores as the current sample, show more drug use three months after completing service in comparison to non-depressed veterans (Nace, Meyers, O'Brien, Ream, & Mintz, 1997). Additionally, veterans, whose depression scores ranged from mild to moderate were 2.9 times more likely to relapse than non-depressed veterans, and those with severe depression were 4.9 times more likely to relapse three months post-treatment (Curran, Flynn, Kirchner, & Booth, 2000). While there is a relationship between severity of depression and risk of relapse in the veteran population, risk of relapse is still significantly increased even in mildly depressed veterans in comparison to non-depressed veterans.

Veterans in this study are demonstrating a different underlying mechanism (depression and anxiety) accounting for cognitive control breakdowns to cocaine cues in our modified drug antisaccade task from our previous data in civilian populations (DiGirolamo et al., 2015). We note that in our previous study (DiGirolamo et al., 2015), the non-veterans had numerically higher depression and anxiety scores than the current veteran sample, but these factors were not associated with breakdowns in control to cocaine cues in the non-veteran sample. It is possible that other factors (e.g., length of abstinence) could also differentiate the results of our previous study of non-veterans from this group of veterans. However, a larger study would be required to tease apart other factors besides depression and anxiety that might influence deficits in cognitive control to cocaine cues in veterans and non-veterans. In the current study, increases in depression or anxiety are crucial for breakdowns in control for these veterans with cocaine use disorder and this deficit occurs even with the mildest increases in depression or anxiety.

The current conclusions must be tempered by several factors: the small size and makeup of our sample in this pilot study, the short-term abstinence of our sample at time of testing, and the lack of a Post-Traumatic Stress Disorder (PTSD) assessment. Our sample was small and composed of mostly white participants, so further replication in a larger and more diverse population is needed. In addition, this population of veterans had not used cocaine for approximately 3 months. Replicating these results across a range of abstinence length would be useful to see if the factors that influence cognitive control breakdowns to cocaine cues in veterans (or civilians) changes over time. Finally, while we found a significant relationship between depression and anxiety and breakdowns in cognitive control, it is possible that PTSD may also play a role. We note that the levels of depression and anxiety at the time of testing in our sample were very mild, suggesting that any PTSD would be equally mild given the overlapping symptoms of depression and PTSD.

Nevertheless, our results suggest that, for veterans, mood factors are more relevant for breakdowns in cognitive control than cue-elicited craving. While craving remains a treatment target (Childress & O'Brien, 2000; Smelson, Losonczy, et al., 2002; Smelson et al., 2004) and a core diagnostic criterion (American Psychiatric Association, 2013) in substance use disorders, craving may not be the fundamental driver of breakdowns in cognitive control to cocaine cues in veterans. This data encompasses a small sample; hence, more research is needed. However, it is suggestive that the role of depression and anxiety must be considered further in the etiology and treatment of SUDs in the veteran population. Furthermore, treating depression and anxiety as well, rather than solely alleviating craving levels, may prove a more effective combined treatment option in helping veterans manage their substance use and abuse.

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Table 1

Demographics, Drug History, Psychological Assessments, Cocaine Craving Scores, and antisaccade performance in Veterans with Cocaine use disorder.

Assessment	N	M	SEM (Range)
Gender (Male)	24 of 24		
Race	16 of 24 (White) 8 0f 24 (African-American)		
Crack as Primary Drug	16 of 24		
Age	24	42.54	1.88 (26–55)
Days Since Last Use	24	121.54	15.51 (21–285)
Years of Use	24	16.54	1.84 (2–34)
Previous Drug Treatments	24	14.96	5.62 (0–100)
Severity of Dependence Scale (SDS)	24	11.17	0.67 (3–15)
Barratt Impulsivity Scale (BIS)	24	76.00	3.00 (48–107)
Beck Depression Index (BDI)	24	18.04	2.46 (1–48)
Beck Anxiety Index (BAI)	24	14.04	1.95 (0–34)
Cue-induced Craving Increase	24	19.68	3.34 (−17.5–44.5)
Cocaine Cue Errors (%)	24	34.17	0.05 (2–81)
Speed of Cocaine Cue Errors (msecs)	24	212.79	07.36 (152–316)
Speed of Successful Cocaine Antisaccades (msecs)	24	318.65	11.88 (221–450)
Neutral Cue Errors (%)	24	28.00	0.04 (1–82)
Speed of Neutral Cue Errors (msecs)	24	203.57	7.63 (154–329)
Speed of Successful Neutral Antisaccades (msecs)	24	315.62	10.76 (209–414)

Note. Msec = Milliseconds; SEM = standard error of the mean.

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Table 2

Correlations of factors that were tested with cognitive control errors toward cocaine cues in veterans with cocaine use disorder.

***N* = 24**	**Beck Depression Index Scores**	**Beck Anxiety Index Scores**	**Barratt Impulsivity Scale Scores**	**Cue-induced Craving Scores**	**Severity of Dependence Scale Scores**
Beck Depression Index Scores	1				
Beck Anxiety Index Scores	0.66 **	1			
Barratt Impulsivity Scale Scores	0.66 **	0.63 **	1		
Cue-induced Craving Scores	0.13	0.11	0.23	1	
Severity of Dependence Scale Scores	−0.12	−0.14	0.09	0.32	1

Note. Due to the clear collinearity, regressions were run on each individual factor.

** are significant correlations with $p < 0.01$