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Effects of yohimbine and drug cues on impulsivity and attention in cocaine-dependent men and women and sex-matched controls

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ABSTRACT

Background: Deficits in executive function have been associated with risk for relapse. Data from previous studies suggest that relapse may be triggered by stress and drug-paired cues and that there are significant sex differences in the magnitude of these responses. The aim of this study was to examine the impact of the pharmacological stressor and alpha-2 adrenergic receptor antagonist yohimbine and cocaine cues on executive function in cocaine-dependent men and women.

Methods: In a double-blind placebo controlled cross-over study, cocaine-dependent men ($n = 12$), cocaine-dependent women ($n = 27$), control men ($n = 31$) and control women ($n = 25$) received either yohimbine or placebo prior to two cocaine cue exposure sessions. Participants performed the Connors' Continuous Performance Test II prior to medication/placebo administration and immediately after each cue exposure session

Results: Healthy controls had a significant increase in commission errors under the yohimbine condition [RR (95% CI) = 1.1 (1.0–1.3), $\chi^2_1 = 2.0$, $p = 0.050$]. Cocaine-dependent individuals exhibited a significant decrease in omission errors under the yohimbine condition [RR (95% CI) = 0.6 (0.4–0.8), $\chi^2_1 = 8.6$, $p = 0.003$]. Cocaine-dependent women had more omission errors as compared to cocaine-dependent men regardless of treatment [RR (95% CI) = 7.2 (3.6–14.7), $\chi^2_1 = 30.1$, $p < 0.001$]. Cocaine-dependent women exhibited a slower hit reaction time as compared to cocaine-dependent men [Female 354 ± 13 vs. Male 415 ± 14; $t_{89} = 2.6$, $p = 0.012$].

Conclusions: These data add to a growing literature demonstrating significant sex differences in behaviors associated with relapse in cocaine-dependent individuals.

1. Introduction

Substance use disorders are characterized by compulsive drug-seeking behavior despite the deleterious consequences of repeated drug use. Relapse rates are particularly high among cocaine-dependent (CD) populations (McKay et al., 1995; McMahon, 2001; Sinha et al., 1999). Recent studies suggest that prior stress enhances the ability of drug-paired cues to elicit craving and relapse (Feltenstein et al., 2011; Feltenstein and See, 2006; Moran-Santa Maria et al., 2014). In addition, deficits in executive function appear to play a critical role in the maintenance of substance use disorders. For example, among cocaine-dependent individuals engaged in cognitive behavioral therapy, baseline performance on tests of impulsivity and attention predicted treatment retention, engagement and relapse (Carroll et al., 2011). Moreover, data from neuroimaging studies of cocaine-dependent individuals demonstrate hyperactivity in the anterior cingulate and orbitofrontal cortices during exposure to drug cues and hypoactivity during performance on tests of executive function, suggesting that chronic drug use alters executive control of impulsive behavior and underscores attentional bias to drug-paired cues (Goldstein and Volkow, 2002; Copersino et al., 2004; DiGirolamo et al., 2015; Hester and Garavan, 2004; Kaufman et al., 2003). Despite these data surprisingly little is known about the impact of stress and drug-paired cues on executive function in cocaine dependent men and women.

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Impulsive action is an aspect of executive function that involves the inability to inhibit inappropriate behavior. Impulsive action can be measured in the laboratory using continuous performance tests that require the participants to inhibit the initiation of a response to a non-target. Failure to inhibit responding to a non-target is considered a commission error. In general, human laboratory tests suggest that cocaine-dependent individuals exhibit greater commission errors than healthy controls (Fillmore and Rush, 2002; Gooding et al., 2008; Kaufman et al., 2003). Impairments in impulsive action such as using more drug than intended, failure to reduce drug use, failure to inhibit drug taking despite the consequences are characteristic of substance use disorders (APA 2013 DSM-V). However, the extent to which exposure to triggers of relapse affects impulsive action has not been assessed in cocaine-dependent individuals.

Sustained attention is also a critical component of executive function and involves the ability to establish and maintain focus during a goal directed task. In the laboratory continuous performance tests assess sustained attention by the average number of times the participant fails to respond to a target (omission errors). Cocaine-dependent individuals demonstrate significantly more omission errors than healthy controls (Gooding et al., 2008; Moeller et al., 2005; Soar et al., 2012). With regard to substance use disorders deficits in sustained attention predict poorer responses to behavioral treatments that require active participation in therapy and learning of coping skills (Aharonovich et al., 2008; Verdejo-Garcia et al., 2012). In addition, a breakdown in attention control mechanisms has been hypothesized to contribute to impulsive action and relapse (Kenemans et al., 2005; Sutherland et al., 2012). Understanding the impact of stress and cues on sustained attention could provide significant insight into the relapse process.

A growing literature suggests that risk for cue-induced relapse may be potentiated by prior exposure to a stressor (Feltenstein et al., 2011; Moran-Santa Maria et al., 2014). For example, the alpha-2 adrenergic receptor antagonist yohimbine potentiates cue-induced reinstatement of both cocaine and heroin seeking behavior in rodents and in humans (Banna et al., 2010; Feltenstein et al., 2011; Moran-Santa Maria et al., 2014). In addition, footshock potentiates cue-induced reinstatement of cocaine and ethanol-seeking behavior in rodents (Buffalari and See, 2011; Liu and Weiss, 2002). In addition, there are significant sex differences in responses to stress and drug cues (Feltenstein et al., 2011; Moran-Santa Maria et al., 2014). Despite these findings, little is known about the relationship between relapse triggers and executive function in cocaine-dependent men and women.

Of note, studies of executive function in cocaine-dependent subjects have mostly been conducted in men. This is particularly noteworthy as studies of heavy drinkers have found that women appear to exhibit greater deficits in inhibitory control as compared to men (Nederkoorn et al., 2009; Townshend and Duka, 2005). In addition, women may be more vulnerable than men to stress and cue-related drug craving and relapse. For example, cocaine-dependent women reported greater anxiety and drug craving in response to yohimbine and drug-paired cues than cocaine-dependent men (Moran-Santa Maria et al., 2014). Compared with male rodents, female rodents exhibit greater stress potentiation of cue-induced cocaine-seeking behavior (Feltenstein et al., 2011). Moreover, cocaine-dependent women demonstrate significantly greater cue-related deactivation in brain regions involved in executive control as compared to cocaine-dependent men (Volkow et al., 2011). Studies examining the effects of stress and drug cues on executive function in cocaine-dependent men and women may contribute to our understanding of the relapse process.

This study was conducted as part of a larger study examining sex differences in stress and cue reactivity in cocaine-dependent men and women (Moran-Santa Maria et al., 2014). Specifically, the overarching goal of the larger project was to identify the potentiative effects of yohimbine on conditioned response to drug-paired cues in cocaine-dependent men and women and sex matched controls. As part of this study we examined the impact of the yohimbine and drug-paired cues on different aspects of executive function using a continuous performance test in cocaine-dependent men and women and sex-matched control groups. Given our previous findings, we hypothesized that together yohimbine and drug cues would increase impulsivity and inattention in comparison to drug cues alone (Moran-Santa Maria et al., 2014).

2. Materials and methods

2.1. Subjects

Male and female cocaine-dependent individuals and sex-matched healthy controls were recruited for the larger parent study. Study participants were recruited primarily via media advertisements over a 48-month period. Written informed consent was obtained from each participant before the study assessments were administered. Inclusion criterion for the cocaine-dependent groups included meeting Diagnostic and Statistical Manual of Mental Disorders-IV (DSM-IV) criteria for cocaine-dependence in the 90-days prior to the study. Exclusion criterion for the cocaine-dependent groups included (1) DSM-IV criteria for substance dependence except alcohol or marijuana within the past 60 days. Exclusion criteria for the control groups included (1) DSM-IV criteria for current or lifetime dependence on alcohol or any drugs of abuse and (2) DSM-IV criteria for current abuse of alcohol or any illicit drugs. General exclusion criteria included (1) pregnancy, nursing, or ineffective means of birth control; (2) premenstrual dysphoric disorder; (3) history of or current significant hematological, endocrine, cardiovascular, pulmonary, renal, gastrointestinal, or neurological diseases; (4) history of or current psychotic, panic, eating, or bipolar affective disorders; (5) current major depressive and PTSD; (6) history of or current medical conditions that might affect HPA axis activity; (7) synthetic glucocorticoid or exogenous steroid therapy within one month of testing; (8) psychotropic medications with the exception of selective serotonin reuptake inhibitors, opiates or opiate antagonists, benzodiazepines, antipsychotics, b-blockers and other medications that might interfere with HPA axis activity or physiologic measurements; (9) acute illness or fever; (10) body mass index >35 and (11) unwillingness or inability to maintain abstinence from alcohol and other drugs of abuse (except nicotine) for three days prior to the cue-reactivity sessions.

2.2. Assessment

Participants meeting pre-screening criteria were evaluated for study eligibility using the Mini-International Neuropsychiatric Interview (Sheehan et al., 1998). The substance use module of the Structured Clinical Interview for DSM-IV was used to assess current and lifetime substance use disorders (First et al., 1994). A medical history and physical examination were completed to assess for medical exclusions. Participants meeting inclusion criteria and no exclusion criteria were scheduled to complete the study procedures. A total of 232 individuals were consented but did not meet study criteria. Fifty eight individuals were consented, met study criteria were enrolled and did not complete study procedures.

2.3. Study procedures

Participants completed two cue reactivity sessions conducted on consecutive days. On the first day of testing, participants arrived at the Medical University of South Carolina's (MUSC's)