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Letter to the Editor

Cortisol reactivity and situational drug use in cocaine-dependent females

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ABSTRACT

In this double-blind study, cocaine-dependent women were administered a pharmacological stressor or placebo prior to two cue-reactivity procedures. The Inventory of Drug Taking Situations is a self-report questionnaire measuring antecedents to relapse and is comprised of three subscales: negative, positive, and temptation situational drug use. It was hypothesized that women with higher IDTS scores would have a greater cortisol response to the cue-reactivity task while receiving yohimbine versus placebo. All three subscales showed significance during the same times after yohimbine administration and immediately post-cue exposure. Our results may suggest an association between situational and physiological risk factors in this population.

Dear editors, Cocaine use disorder (CUD) has a complex etiology involving biological, psychological, and social factors. Despite a growing understanding of these mechanisms, relapse rates remain high. Stress has been identified as one key factor in maintaining the cycle of relapse. Stress is associated with decreased prefrontal brain functioning, which contributes to problems in behavior, cognition, and impulse control (Sinha, 2007).

When stress is perceived, a chain of physiological reactivity begins resulting in the release cortisol from the hypothalamic-pituitary-adrenal (HPA) axis. The HPA axis is naturally motivated by life-sustaining processes (Sinha, 2007) and repeated use of drugs or alcohol can compromise these relationships in favor of drug-seeking (Lovallo, 2006). This physiological susceptibility may be especially salient to female substance-dependent populations, as evidenced by their increased relapse rates and severity of detoxification symptoms (Tuchman, 2010). The stress-vulnerability model of addiction suggests that there is a feedback loop between risk factors (i.e., emotionality, poor executive function, and stress) and alterations in corticostriatal-limbic pathways associated with repeat drug use (Anderson et al., 2006). The way stress interacts with external and emotional cues in cocaine dependence is complex; a better understanding of the mechanisms that reinforce these risk factors could confirm the need for future research. This study examined the effect of situational drug use and a pharmacological stressor on cortisol response during a cue-reactivity paradigm in cocaine-dependent women.

In this double-blind, within-subjects, placebo-controlled study, cocaine-dependent non-treatment seeking women (N = =23) were administered a pharmacological stressor (yohimbine hydrochloride; YOH) (21.6 mg) or placebo (PBO), in counterbalanced order, prior to two drug cue-reactivity procedures. This included visual and auditory cocaine cues and handling of paraphernalia. Cortisol measurements began at 11:00 am, and continued for 5, 15, and 30-min increments at multiple points before and after medication (12:00pm) and cue-reactivity (2:00 pm). The Inventory of Drug Taking Situations (IDTS), administered at baseline, is a self-report questionnaire measuring antecedents to relapse and is comprised of three subscales: negative, positive, and temptation situational drug use (Turner et al., 1997). It was hypothesized that cocaine-dependent women with higher IDTS scores would have a greater cortisol response to the cue-reactivity task while receiving YOH versus PBO. A general linear model for repeated measures was initially conducted adjusting for baseline cortisol levels. There was no main effect of treatment or time on cortisol response. The three-way interactions between treatment, time, and each of the three IDTS subscales were significant [Negative ($F(5, 40) = 9.83$, $p < .001$), positive ($F(5, 40) = 8.83$, $p < .001$), and temptation ($F(5, 40) = 5.88$, $p < .001$)]. Post-hoc pairwise comparisons were conducted using IDTS median splits where participants fell into “high” or “low” group for each of the subscales. Participants in the “high” IDTS group for each of the three subscales had significantly higher cortisol levels at certain time points following YOH administration, but not PBO. For temptation, the significance occurred at 15-min pre-cue ($p = .017$), 5-min pre-cue ($p = .013$), and 5 min post-cue ($p = .017$). For the negative subscale, significance occurred at 15-min pre-cue ($p = .028$), 5-min pre-cue ($p = .016$) and 5 min post-cue ($p = .019$). In addition, those who scored highly on the negative IDTS scale showed marginally higher cortisol levels 15-min post-cue ($p = .075$). The positive subscale had significant time points for the YOH “high” IDTS group at each of the 15-min pre-cue ($p = .028$), 5-min pre-cue ($p = .016$), and 5-min post-cue ($p = .019$) time-points.

To test whether the IDTS groups differed on cocaine use characteristics, independent samples t-tests were conducted. Across each of the IDTS subscales there were no significant differences at baseline between “high” and “low” groups in using days per month, age of first use, dollar amount spent during heaviest use period, and using days per month during heaviest use period (all p-values $>.05$). Additional independent sample t-tests were conducted to compare craving scores between high and low groups on each study day. High and low positive and temptation groups did not have significantly different mean craving scores on YOH or PBO administration days. However, the high negative IDTS group did have significantly higher mean craving on both days as

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compared to low negative IDTS group.

As predicted, the participants who scored highest on the IDTS subscales also had higher cortisol reactivity on the yohimbine administration day. All three subscales showed significance during the same times after yohimbine administration and immediately post-cue exposure. This homogeneous outcome aligns with IDTS author research that reports "undifferentiated" profiles between the three subscales and "high" scoring to be indicative of frequent use across all situations (Turner et al., 1997). However, though preliminary, our data suggest that negative situational use may pose a greater risk. The negative subscale was marginally significant up to the 15 min post-cue time point. In addition, post-hoc analysis revealed that, compared to the low group, the high negative IDTS group reported significantly greater craving on both study days. Therefore, negative antecedents may heighten relapse risk for longer periods of time, especially when exposed to drug cues while experiencing a physiological stressor.

Although these results are intriguing, there were several limitations to consider. First, our sample size was small. Our statistical power determined that we would need 30 women for a 95% confidence interval. As such, we may have limited power for this investigation. The analyses also lacked a comparison group, which was left out of this preliminary analysis due to sample size discrepancy. Future research including men would enrich our understanding of sex differences in this context. Data on withdrawal severity prior to the task was not compared between IDTS groups. However, groups were not significantly different on a number of cocaine use characteristics at baseline. Lastly, interpretation of findings would be improved with follow-up data on cocaine use. Despite these limitations, the current study offers novel data on the interaction of situational and physiological factors associated with cocaine use in women.

In this analysis, elevated situational use factors (negative, positive, and temptation as defined by the IDTS) were associated with higher cortisol reactivity. Given the timing of cortisol elevation during the paradigm (i.e. 5 min. post-cue), our results suggest an association between situational and physiological risk factors among cocaine-dependent women.

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Declaration of Competing Interest

None.

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