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Laboratory-Induced Cue Reactivity among Individuals with Prescription Opioid Dependence

Sudie E. Back, Ph.D.[1,2], **Daniel F. Gros, Ph.D.**[1,2], **Jenna McCauley, Ph.D.**[1], **Julianne Flanagan, PhD**[1], **Elizabeth Cox, M.D.**[1], **Kelly Barth, M.D.**[1], and **Kathleen T. Brady, M.D., Ph.D.**[1,2]

[1]Medical University of South Carolina, Department of Psychiatry and Behavioral Sciences, Clinical Neuroscience Division, Charleston, SC 29425

[2]Ralph H. Johnson Veterans Affairs Medical Center, Charleston, SC 29401

Abstract

Prescription opioid (PO) dependence is a critical health problem. Although examination of drug cue reactivity paradigms has advanced the understanding of risk factors for relapse for a variety of substances (e.g., cocaine, alcohol, nicotine), no PO specific drug cue paradigm has been developed. The current study addressed this gap in the literature and evaluated the ability of a newly developed PO drug cue paradigm to elicit subjective, physiological, and neuroendocrine changes among PO-dependent participants (n = 20) as compared to controls (n = 17). The drug cue paradigm included an induction script, viewing and handling paraphernalia (e.g., bottle of oxycontin pills, pill crusher) and watching a video depicting people using POs as well as places related to POs (e.g., pharmacies). Consistent with hypotheses, the PO group demonstrated significant pre- to post-cue increases on subjective ratings of craving, difficulty resisting POs, stress, and anger. The control group did not demonstrate significant changes on any of the subjective measures. Both the PO group and the control group evidenced significant pre- to post-cue increases in physiological responses (e.g., blood pressure, skin conductance), as expected given the arousing nature of the drug cue stimuli. The PO group, but not the control group, evidenced a significant pre- to post-cue increase in heart rate and salivary cortisol levels. The

Corresponding Author: Sudie E. Back Ph.D., Department of Psychiatry and Behavioral Sciences, Clinical Neuroscience Division, Medical University of South Carolina, 67 President Street, MSC861, Charleston, SC 29425. Telephone (843) 792-5215, Fax (843) 792-0528. backs@musc.edu.

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development and validation of a drug cue paradigm for POs may help inform future research and treatment development efforts for patients with PO dependence.

Keywords

Prescription opioids; opiates; prescription drugs; drug cue reactivity; drug cue paradigm

Introduction

Prescription opioid (PO) dependence represents a critical health concern in the U.S. and internationally (Dhalla, Persaud, & Juurlink, 2011; Fischer, Nakamura, Rush, Rehm, & Urbanoski, 2010). PO dependence has increased significantly over the past two decades (Bagot, Heishman, & Moolchan, 2007) and recent surveys suggest that PO use is more commonly initiated than any other drug except marijuana (SAMHSA, 2012). Approximately 14% of individuals in the U.S. general population endorse lifetime non-medical use of POs (Back et al., 2010), a figure totaling nearly two million individuals (SAMHSA, 2011). The rapid rise of PO dependence in recent years is also of great concern due to its associations with serious negative outcomes, particularly unintentional overdose fatalities (Haug, Sorensen, Gruber, & Song, 2005; Veilleux, Colvin, Anderson, York, & Heinz, 2010). In fact, PO dependence is implicated in more overdose fatalities than heroin and cocaine combined (Warner, Chen, Makuc, Anderson & Minino, 2007).

Advances in Treatment and Challenges Associated with PO Dependence

Recovery from PO dependence is a significant challenge for clinicians across health care fields. Nearly 10% of individuals seeking treatment for a substance use disorder report current PO abuse or dependence, amounting to a tenfold increase during the past decade (SAMHSA, 2010). The societal costs of PO use disorders in the U.S. are estimated at over $55 billion. Opioid dependence generally, and PO dependence specifically, are particularly challenging to treat due to a variety of factors, including: withdrawal from opioid use may be long-lasting and characterized by substantial discomfort; increased prescribing of POs for legitimate use has increased the availability of POs for diversion in the community; and dependence on POs may develop following legitimate use under a prescriber's care (Joranson et al., 2000; Katz et al., 2007; Zacny, Bigelow, Compton, Foley, Iguchi, & Sannerud, 2003). Because many individuals who struggle with PO dependence initiated PO use to manage chronic pain conditions under a physician's care, the cessation of PO use may exacerbate one's discomfort and decrease motivation to maintain abstinence (Back et al., 2011; Barth et al., 2013; Joranson, 2002;). While many individuals are able to complete detoxification and abstain from PO use for short periods of time, relapse remains highly prevalent (Tkacz, Severt, Cacciola, & Ruetsch, 2012). For example, in a recent study by Weiss and colleagues (2011), 30% of the treatment-seeking sample of individuals with PO dependence had received treatment prior to the current intervention. At week 16, 74% of participants had relapsed and by week 24, 91% had relapsed. Indeed, the essential feature of successful treatment for opioid dependence lies with relapse prevention rather than facilitating the initial cessation of use (O'Brien, Childress, Ehrman et al., 1998; Stewart,

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2003; Tkacz, Severt, Cacciola, & Ruetsch, 2012). In summary, PO dependence is a chronic and relapsing disease characterized by complex barriers to treatment.

One critical advancement in the treatment of opioid dependence over the past several decades is the use of pharmacological interventions. Clinical trials investigating the efficacy of several medications (e.g., Buprenorphine, Suboxone) alone and in combination with psychotherapy have yielded promising results (Carroll et al., 2001; Tkacz et al., 2012; Weiss et al., 2011). However, the generalizability of these findings to PO-dependent individuals may be limited because they have focused primarily on heroin-dependent individuals. Considering that PO dependence is currently 20 times more prevalent than heroin use, and approximately twice as many individuals seek treatment for PO dependence than heroin dependence (Office of Applied Studies, 2009), there is a great need for investigations to identify factors that exacerbate drug craving and predict drug consumption among PO dependent individuals.

Cue Reactivity and Relapse

Cue reactivity is a laboratory methodology in which an individual's subjective, behavioral, biological, and/or physiological responses to drug-related cues are measured. Previous laboratory studies have shown that exposure to drug-related cues, as compared to neutral cues, increases craving and induces changes in mood states and physiological measures (Carter & Tiffany, 1999; Shi et al., 2009; Yu et al., 2007). Importantly, cue reactivity in the laboratory has been found to predict relapse to drug use outside of the laboratory among cocaine and nicotine-dependent individuals (Back et al., 2010; Sinha et al., 2009).

Studies of cue reactivity have given rise to a variety of theoretical models, most of which use classical conditioning principles to explain drug cue-elicited craving and reactivity (O'Brien et al., 1998; See, 2002; Siegel, 1999; Siegel & Ramos, 2002). These findings suggest that, through a process of associative learning, previously neutral stimuli acquire incentive-motivational properties following repeated pairing with drug consumption. Cue reactivity, therefore, is a conditioned response that occurs as a result of learned association between the cue and drug intake (Drummond, 2000). Thus, conditioned stimuli play a critical role in sustaining ongoing drug-seeking behavior and relapse after periods of abstinence (Childress et al., 1988; O'Brien et al., 1998; Sinha et al., 2000; Stewart, 2003).

Most studies have assessed cue reactivity among alcohol, cocaine or nicotine dependent individuals (Drobes, 2002; Niaura et al., 1988; Reynolds & Monti, 2012) and several studies have examined heroin dependent individuals (Childress et al., 1986a, 1986b; Daglish et al., 2001; Sell et al., 2000; Franken et al. 1999; Powell et al., 1990). To our knowledge, there have not been any studies examining cue reactivity among individuals with PO dependence. This critical gap in the literature is likely due to the fact that no drug cue paradigm for POs has been developed.

The development of a drug cue paradigm specific to PO dependent individuals is essential in order to facilitate research aimed at identifying factors that predict relapse and testing novel relapse prevention interventions. Therefore, the goal of this study was to assess the ability of a newly developed PO drug cue paradigm to elicit: (1) subjective responses (e.g., craving,

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stress, negative emotion); (2) physiological reactions (heart rate, blood pressure, skin conductance); and (3) neuroendocrine changes (cortisol) in PO-dependent participants as compared to healthy control participants. We hypothesized that PO-dependent participants would demonstrate greater cue-induced increases in subjective, physiological and neuroendocrine responses compared to control participants.

Methods

Participants

Participants were non-treatment seeking, PO dependent individuals (n = 20) and healthy control participants who did not have PO or any other substance use disorders (n = 17). PO dependence was defined as meeting current (i.e., past 6 months) Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV; American Psychiatric Association, 2000) criteria for substance dependence on opioid analgesics (e.g., oxycodone, hydrocodone). Newspaper and other media advertisements were the primary source of recruitment. Participants were recruited as part of a larger study on the relationship between stress, drug cues, and the hypothalamic-pituitary-adrenal (HPA) axis.

Potential participants were initially screened by telephone and individuals meeting preliminary eligibility criteria came into the office for a clinical assessment and a history and physical examination. Exclusion criteria included: pregnancy or nursing; BMI ≥ 39; major medical problems (e.g., diabetes, HIV, Addison's or Cushing's disease) or comorbid psychiatric conditions (e.g., current major depressive disorder or post-traumatic stress disorder, current or history of bipolar affective disorder or psychotic disorder) that could effect the HPA axis; use of methadone or other opioid replacement therapies in the past three months; use of antihypertensive medications, beta-blockers, synthetic glucocorticoid therapy, or treatment with other agents that may interfere with stress response in the past month; or DSM-IV criteria for substance dependence (except caffeine or nicotine) within the past 60 days. Individuals who met criteria for abuse of other substances had to identify POs as their primary drug of choice. Controls were excluded if they met DSM-IV criteria for current or history of substance dependence (except caffeine or nicotine). Participants were informed about all study procedures. IRB-approved written informed consent was obtained before any study procedures occurred. Eligible participants (both PO and healthy controls) were scheduled for a one-night hospital stay at a large southeastern university medical center and testing was completed the next morning.

Assessments

Substance Use—The Structured Clinical Interview for DSM-IV (SCID; First, Spitzer, Gibbon, and Williams, 2002) and the Mini International Neuropsychiatric Interview (MINI; Sheehan et al., 1998) were used to assess substance use disorders (SCID) and other Axis I psychiatric disorders (MINI). Urine drug screen tests were performed using the On Track Test Cup® (Roche Diagnostics). Breathalyzer tests (AlcoSensor III, Intoximeters Inc., St. Louis) were administered to test for the presence of alcohol. The Addiction Severity Index – Lite (ASI) was administered to assess seven functional domains related to addictions, including drug use, alcohol use, medical status, psychiatric status, family and social status,

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employment status, and legal status (McLellan, Cacciola, Alterman, Rikoon, & Carise, 2006).

Subjective Reactivity—To assess craving, stress, anger, happiness, and sadness a visual analog scale that was derived from the Within Session Rating Scale was used (Childress, McLellan, and O'Brien, 1986b). It was anchored with adjective modifiers from 0 = "not at all" to 10 = "extremely". The State-Trait Anxiety Inventory (STAI; Form Y1; Spielberger et al., 1983), a 20-item self-report form, measured stress and anxiety on a 4-point Likert scale (1 = "not at all" to 4 = "very much so") immediately before the drug cue paradigm and then at 15, 30 and 60 minutes post.

Physiological Reactivity—Heart rate (HR) was collected via electrodes along the bottom of the participant's ribcage and collar bone. Systolic (SBP) and diastolic blood pressure (DBP) were measured using a GE Pro 400 Dinamap automated monitor. Mean arterial pressure (MAP) was calculated using the formula [(2 x DBP)+SBP/3]. Normal range of MAP is 70 – 110 mmHg. Two measurements (taken 15 minutes apart) of HR, SBP and DBP were taken at baseline before testing began, and the average of these two measurements was used as the baseline value. Physiological measures were then taken immediately after the drug cue paradigm and at 15, 30 and 60 minutes post.

Neuroendocrine Assay—Unstimulated salivary samples were collected by passive drool in polypropylene vials and immediately iced. Samples were aliquoted into 1.8 nunc tubes and saliva was then frozen at −70°C until assayed. Samples were assayed in duplicate using a high sensitivity salivary cortisol enzyme immunoassay system that has an intra-assay precision (coefficient of variation, CV) of 3.35% – 3.65% with a sensitivity of <0.003 ug/dL (Salimetrics LLC). Samples were analyzed using a PowerWave HT Microplate Spectrophotometer in conjunction with a Precision Series Automated Liquid Handling System (BioTek Instruments, Inc.). Salivary samples were collected immediately before the drug cue paradigm and then at 15, 30 and 60 minutes post.

Laboratory Procedures

Three days of abstinence from alcohol and other substances (except caffeine and nicotine), as evidence by self-report, breathalyzer and urine drug screen, were required prior to admission for the overnight stay. Participants were admitted to the hospital at 2000h the evening prior to testing to allow for the control of extraneous variables (e.g., sleep, caffeine intake) that could potentially affect reactivity. Cigarette smokers were provided with a nicotine patch upon admission. Twenty-four hour nicotine replacement therapy was maintained throughout the hospital stay (≥ 20 cigarettes/day = 21 mg; 10–19 cigarettes/day = 14 mg patch; 5–9 cigarettes/day = 7 mg patch).

Participants were provided a standard breakfast at 0730h and then escorted by research staff to the laboratory for testing. Sedentary activities, such as reading, were allowed during a 60-minute acclimation period from 0830–0930h. Pre-testing assessments were conducted at 0930h and 0945h, and testing began at 0950h.

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During testing, all participants (PO dependent and controls) underwent a 15-minute drug cue paradigm. A variety of cue presentation modalities have been developed for other drugs of abuse and include imaginal, *in vivo*, audio, video, pictorial and virtual reality techniques (Conklin, 2006). The complex nature of drug-related cues suggests that traditional cue reactivity techniques (e.g., pictures) may be insufficient to present the complexity of addictive behaviors. Thus, we conducted focus groups (N=24) with individuals with PO dependence to inquire about what types of stimuli or places trigger cravings to use POs and incorporated that information into the development of a multi-modal PO drug cue paradigm (Back et al., 2011). The paradigm consists of three five-minute components: (1) a five-minute audio induction script, in which the participant listens to a recorded script that guides them to relax and then think, in as much detail as possible, about the last time they used POs. They were encouraged to think as specifically as possible about the PO use episode (e.g., experiencing the feeling of chalkiness on their tongue from the pill); (2) five minutes of viewing and handling drug paraphernalia (e.g., a sealed bottle of real oxycontin pills, spoon, glass of water, pill crusher, straw, small square piece of aluminum foil, money, a handout of various POs); and (3) a five-minute video depicting people using POs in a variety of ways (e.g., crushing and snorting, orally, injecting) and of places related to POs (e.g., pharmacies).

Results

Demographics

Table 1 presents the demographic characteristics. As expected, two-variable χ^2 tests revealed group differences in education and employment status (χ^2s > 4.9; *p*s < .05). No other demographic differences were observed. One-way analyses of variance (ANOVA) revealed significantly higher ASI subscale scores for drug use, legal status, and psychiatric symptoms among the PO group, as compared to controls (*F*s > 6.2; *p*s < .05).

Effects of Drug Cue on Subjective Ratings

Table 2 presents the within- and between-group findings for the subjective ratings in the PO and control groups. One-way ANOVAs were used to investigate between group differences in baseline subjective ratings. These findings demonstrated significantly higher subjective ratings for stress (Figure 1), craving (Figure 2), difficulty resisting use, anger, amount willing to pay to use, and state anxiety (STAI) as well as significant lower happiness in the PO group compared to the control group (*F*s > 3.9; *p*s < .055). Paired *t*-tests were used to investigate pre- to post-cue changes in each of the subjective ratings. The peak post-cue response was selected from the four time points (immediate, 15 minutes, 30 minutes, and 60 minutes) and used in all analyses. As can be seen in Table 2, the control group did not demonstrate significant pre- to post-cue changes in any of the subjective ratings. In contrast, the PO group evidenced significant pre- to post-cue changes on subjective ratings of craving (Figure 1), stress (Figure 2), difficulty resisting use, and anger (*t*s > 2.8; *p*s < .05). Finally, analysis of covariance (ANCOVA) was used to investigate the effect of the drug cue paradigm across the two groups (PO vs. control) with the pre-cue scores entered as covariates. Separate ANCOVAs were run for each of the subjective indices. The findings revealed a significant group effect for the post-cue ratings of craving, stress, difficulty

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resisting use, and anger after controlling for pre-cue ratings (Fs > 13.5; ps < .01; η_p > .283), suggesting that participants in the PO group evidenced greater craving and negative affect in response to the drug cue paradigm than the participants in the control group (see Table 2).

Effects of Drug Cue on Physiological Reactivity

Table 3 presents the within- and between-group findings for the physiological indices in the PO and control groups. Similar to the analyses of subjective ratings, one-way ANOVAs were used to investigate between-group differences in baseline physiological reactivity. The findings demonstrated significantly higher MAP and HR in the PO group compared to the control group (Fs > 3.9; ps ≤ .05). Paired t-tests were used to investigate pre- to post-cue changes in each measure of physiological reactivity, with the peak post-cue response being used in all analyses. Both the PO and control groups demonstrated increased MAP and GSR in response to the drug cue (ts > 4.9; ps < .01). However, the PO group (t = 3.3, p < .01), but not the control group (t = 1.9; p > .05), demonstrated increased HR in response to the drug cue. This HR finding was further supported by a significant group effect on post-cue HR in the ANCOVA (F = 4.4; p < .05).

Effects of Drug Cue on Neuroendocrine Response

Although the baseline cortisol level was higher among the PO as compared to the control group (Figure 3), this difference was not significant. In response to the drug cue paradigm the PO group, but not the control group, demonstrated a significant pre- to post-cue increase in cortisol (t = 2.3; p < .05). An ANCOVA was run for cortisol levels across the two groups (PO vs. control) with the pre-cue scores entered as covariates. A significant group effect on post-cue cortisol was revealed (F = 5.6; p < .05; Figure 3). The cortisol response was reversed across the two groups with a significant increase in cortisol in the PO group and a non-significant reduction in cortisol in the control group.

Discussion

Results indicate that the newly developed PO drug cue paradigm effectively elicits differential subjective and biological responses among PO dependent individuals as compared to healthy controls. To our knowledge, this is the first study to develop and validate a drug cue paradigm specific to prescription opioids; that is, containing triggers that are directly address POs (e.g., a bottle of opioid pills, images of pharmacies, handling a pill crusher). Cue reactivity paradigms have contributed significantly to advancements in addictions research for a variety of substances, including alcohol, cocaine, heroin, and nicotine (Carter & Tiffany, 1999a,b). The current study represents a critical step toward extending this literature in PO dependent individuals.

Consistent with cue reactivity paradigms for other substances of abuse (Carter & Tiffany, 1999a), the 15-minute PO paradigm combines three modalities of cue exposure: audio-guided imagery, in-vivo (e.g., handling pill bottles, pill crusher), and video. At baseline, PO dependent individuals presented with significantly more negative affect (e.g., stress, anger) and craving. As expected, the PO group evidenced significantly greater increases in pre- to post-cue craving, stress, anger, and inability to resist using in response to the drug cue

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paradigm compared to the control group. Stress, anger, and sadness either improved or stayed the same following cue administration among controls. The moderate to large effect sizes for these subjective responses are consistent with prior cue reactivity research and suggest that subjective ratings are especially sensitive to the specificity of the cues administered (Carter & Tiffany, 1999). Subjective results also show that the newly developed paradigm elicited negative affect in addition to craving among PO dependent individuals. These responses are often identified as interrelated (Schlauch, Gwynn-Shapiro, Stasiewicz, Molnar, & Lang, 2013) and are consistent predictors of relapse among other substance dependent populations (Hendershoot, Witkiewitz, George, & Marlatt, 2011; Li et al., 2012).

With regard to physiological indices of reactivity, responses were largely consistent with the incentive or appetitive-motivational model which predicts that cue reactivity will be congruent with the drug effect (Stewart, deWit, & Eikelboom, 1984). Responses were also consistent with prior cue reactivity research among heroin dependent individuals (Behera, Goswami, Khastiger, & Kumar, 2003). Consistent with expectations, HR and GSR indices were higher at baseline among the PO than control group. Participants in both the PO and control group demonstrated significant pre- to post-cue increases in MAP and GSR. Contrary to our hypothesis, only the HR response among the PO group was significantly greater than the amount of response observed among the control group. The increase in physiological response among control participants may be attributed to the arousing nature of some elements of the drug cue paradigm. For example, subjects were exposed to drug paraphernalia (e.g., syringe), as well as graphic video-images of individuals using POs in various manners (e.g., injecting, crushing and snorting). In fact, normative data on the International Affective Picture System (Lang, Ohman, & Vaitl, 1988), involving a wide range of affective pictures with valence and arousal ratings, suggest that pictures of drug related behaviors and cocaine paraphernalia receive moderate arousal ratings, and are therefore likely to cause physiological arousal in most participants, including non-using healthy controls (Cuthbert, Bradley, & Lang, 1996). Future research would benefit from dismantling procedures or studies designed to isolate those stimuli that generate physiological arousal only in PO dependent individuals and not in control participants.

As hypothesized, only the PO dependent group evidenced a significant pre- to post-cue salivary cortisol increase. Among the control group, cortisol levels decreased slightly from pre- to post-cue administration. In prior drug cue paradigm research, post-cue elevations in cortisol have been found to be indicative of a stress response that is correlated with drug craving, and predictive of future relapse (Back et al., 2010; Fatseas et al., 2011). These findings emphasize the utility of examining neuroendocrine correlates of drug cue reactivity. Further, these findings suggest that measures of HPA function were consistent with participants' subjective and physiological responses, lending further support to the validity of the drug cue paradigm developed here.

The development and validation of a PO-specific cue paradigm has potential utility in extending advances in drug abuse research to the study of PO use disorders. As an example of potential future applications for the current paradigm, cue reactivity paradigms have been successfully used to elucidate neural substrates and networks implicated in the craving

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response for an array of substances including nicotine, cocaine, and alcohol (Cunningham & Anastasio, 2013; Engelmann et al., 2012; Lou et al., 2012; Mainz et al., 2012; Schacht, Anton, & Myrick, 2013), as well as to examine potential gender differences in cue-elicited craving (Saladin et al., 2012). Further, these paradigms have demonstrated utility in predicting substance use behaviors – including self-initiated abstinence, latency to use, and relapse – among a variety of substance dependent populations (Conklin, Parzynski, Salkeld, Perkins, & Fonte, 2012; Fatseas et al., 2011; Garland, Carter, Ropes, & Howard, 2012; Shiffman et al., 2013). Similarly, as with cue reactivity paradigms for other substances of abuse (e.g., Modesto-Lowe & Kranzler, 1999), the current paradigm may be applied to investigate the effects of pharmacological interventions (e.g., buprenorphine, suboxone, oxytocin), on cue-induced and stress-induced craving.

Limitations

Several limitations of the current study should be noted. First, this was the initial validation of the PO cue reactivity paradigm and the findings are in need of replication with a larger sample of PO dependent individuals. In addition, the PO group was comprised of non-treatment seeking individuals. As such, the findings may not be generalizable to treatment-seeking individuals. All participants had abstained from PO use for at least three days prior to their participation in the study. Acute abstinence has been noted as limitation of cue paradigms for other substances (e.g., Adams & Munafo, 2013); experience of mild PO withdrawal symptoms may have influenced reactivity.

Conclusions

In light of the continuing epidemic rise in misuse, abuse, and dependence on POs, the development of cue reactivity paradigms that are specific to POs is needed to help enhance assessment, treatment and relapse prevention. The cue reactivity paradigm developed and validated by the current study is one such tool with the potential for empirical and clinical utility to address the problem of PO dependence.

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Highlights

- Prescription opioid (PO) dependence is a critical health problem
- Drug cue reactivity paradigms have the advanced understanding of substances
- Present study assessed PO drug cue in PO dependent and healthy participants
- PO group demonstrated pre to post cue increases in subjective/physiological indices
- Findings support utility of a PO specific drug cue paradigm for understanding PO

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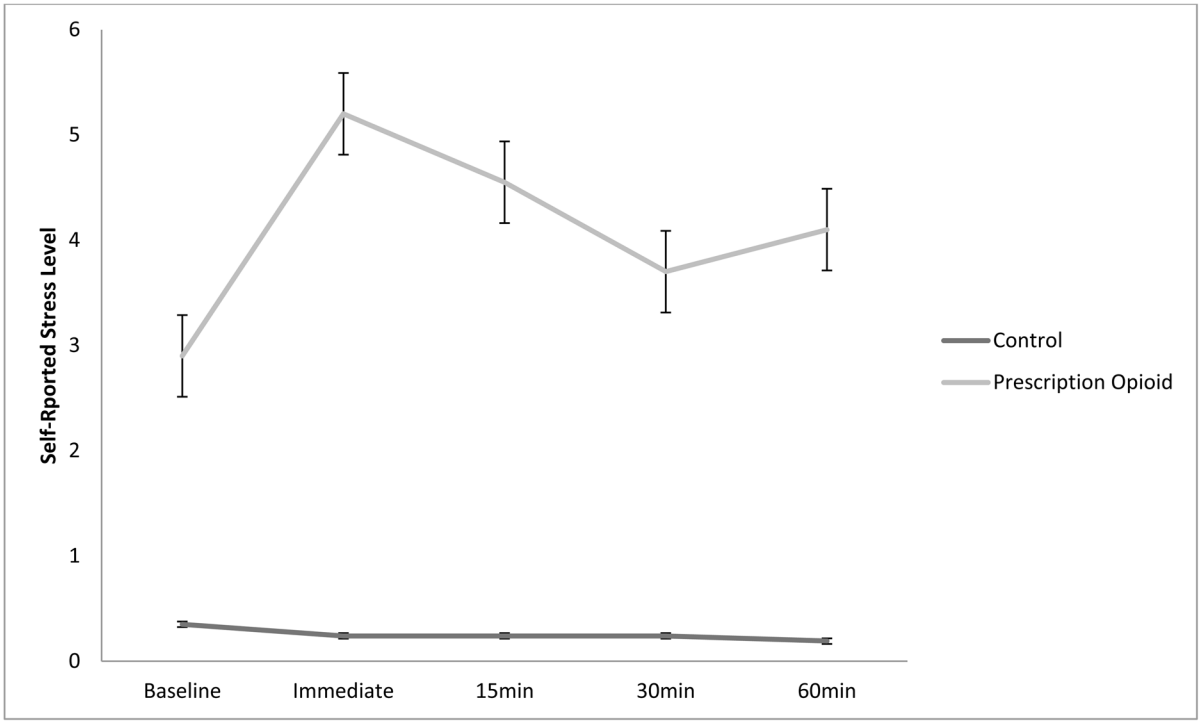

Figure 1.

Subjective stress response to the drug cue paradigm among individuals with prescription opioid dependence vs. controls.

Note. Baseline = immediately pre drug cue paradigm. Immediate = immediately post drug cue paradigm.15 min, 30 min and 60 min = post drug cue paradigm.

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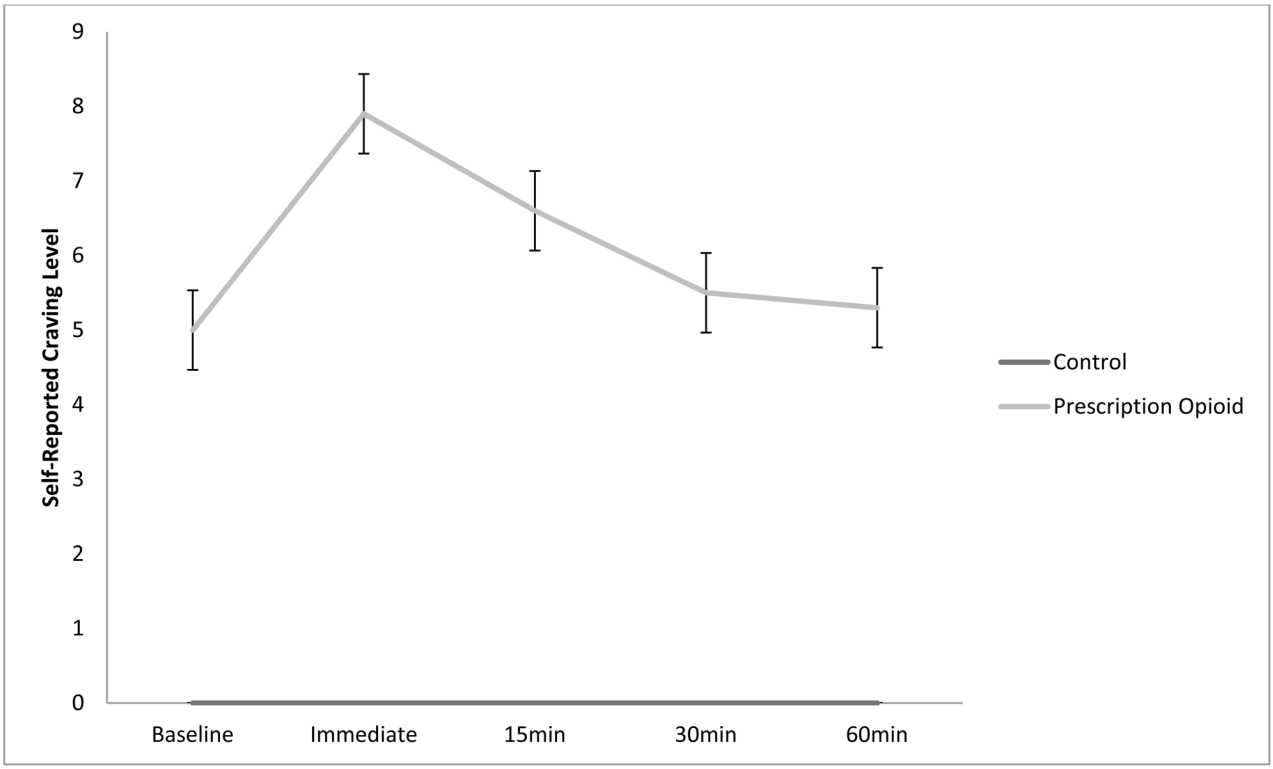

Figure 2.

Subjective craving response to the drug cue paradigm among individuals with prescription opioid dependence.

Note. Baseline = immediately pre drug cue paradigm. Immediate = immediately post drug cue paradigm.15 min, 30 min and 60 min = post drug cue paradigm.

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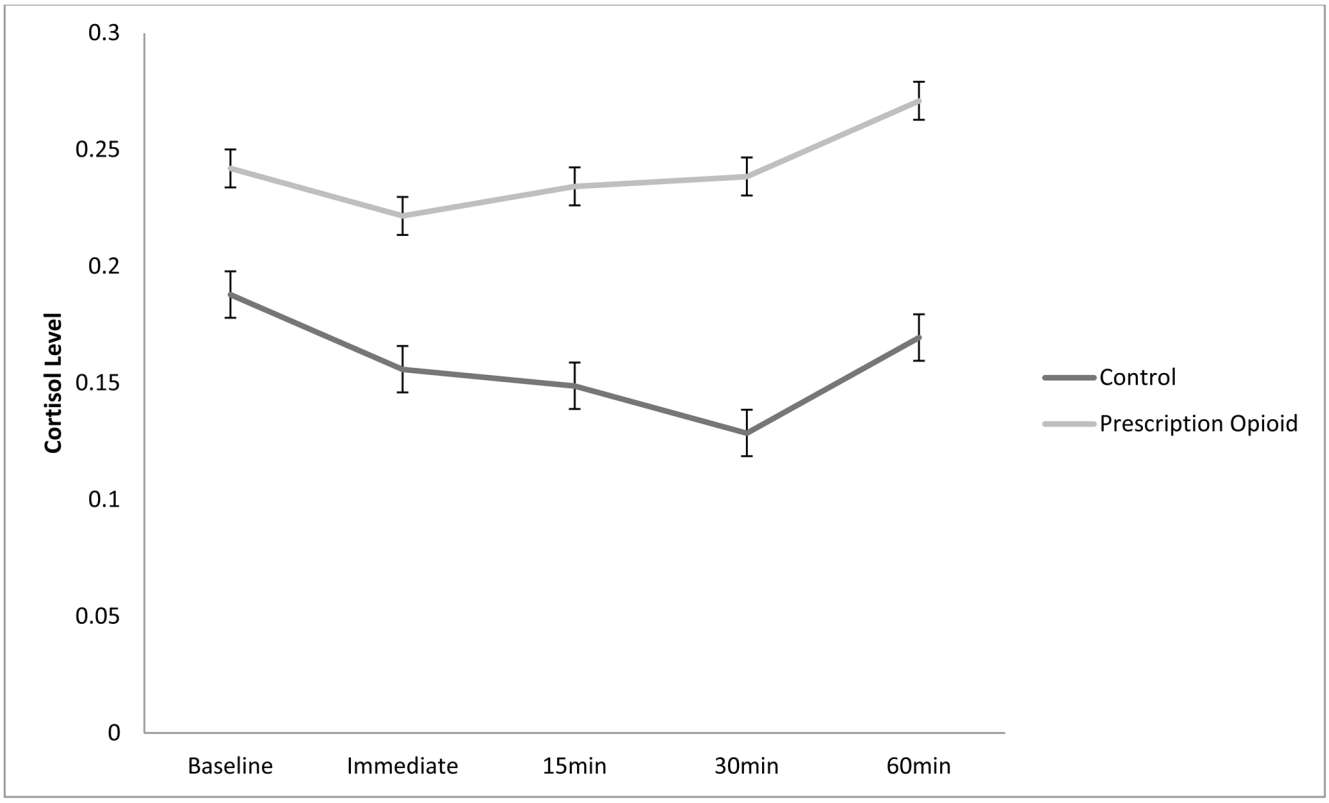

Figure 3.

Cortisol response to the drug cue paradigm among individuals with prescription opioid dependence vs. controls.

Note. Baseline = immediately pre drug cue paradigm. Immediate = immediately post drug cue paradigm.15 min, 30 min and 60 min = post drug cue paradigm.

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Table 1

Demographic Characteristics

Scale (groups)	Control (*n* = 17)	Prescription Opioid (*n* = 20)	χ^2/F
Age, Mean (SD)	33.5 (13.0)	33.4 (12.7)	0.0
Gender (2)	47% Male/53% Female	50% Male/50% Female	0.0
Race (5)	76.5% Caucasian/23.5% Non-Caucasian	80.0% Caucasian/20.0% Non-Caucasian	3.1
Education (2)	0.0% High School/100.0% College	20.0% High School/80.0% College	4.9*
Relationship (5)	41.2% Single/41.2% Married	50.0% Single/10.0% Married	6.6
Employment (3)	76.5% Employed/17.5% Unemployed	10.0% Employed/65.0% Unemployed	16.9**

Note. SD = standard deviations. Non-Caucasian = African American, Hispanic/Latino, Asian American, or Native American. College = some college or more (e.g., associate's degree, bachelor's degree, or graduate degrees).

* $p < .05$;

** $p < .01$.

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Table 2

Effect of Drug Cue on Subjective Ratings

	Control (n = 17) Within Group Effect				Prescription Opioid (n = 20) Within Group Effect				Between Groups	
Scale (Range)	**Pre-Cue**	**Post-Cue Peak**	***t***	***d***	**Pre-Cue**	**Post-Cue Peak**	***t***	***d***	***F***	η_p^2
Crave (0–10)	0.0 (0.0)	0.0 (0.0)	-	-	5.0 (2.9)	8.1 (2.7)	6.5**	1.11	40.1**	.541
Resist (0–10)	0.0 (0.0)	0.0 (0.0)	-	-	7.4 (3.1)	8.2 (2.5)	2.8*	0.28	34.0**	.500
Stress (0–10)	0.4 (0.8)	0.2 (0.4)	1.0	0.32	2.9 (2.6)	5.7 (3.4)	5.8**	0.97	21.3**	.385
Anger (0–10)	0.1 (0.2)	0.1 (0.5)	1.0	0.00	1.2 (1.9)	3.4 (2.9)	4.8**	0.90	13.5**	.284
Sad (0–10)	0.4 (0.9)	0.5 (1.1)	1.0	0.10	1.4 (1.9)	2.4 (3.0)	1.6	0.40	2.6	.072
Happy (0–10)	6.1 (2.8)	7.0 (2.4)	1.6	0.35	4.2 (2.8)	5.0 (3.0)	1.7	0.28	0.9	.027
Willing to Pay ($)	0.0 (0.0)	0.0 (0.0)	-	-	30.5 (33.3)	54.2 (87.2)	1.2	0.36	0.8	.022
STAI (20–80)	23.1 (4.2)	23.1 (3.4)	0.0	0.00	34.3 (10.0)	35.6 (10.4)	−0.8	0.13	2.8	.077

Note. Pre-Cue and Post-Cue Peak columns are presented as means (standard deviations). STAI = State Trait Anxiety Inventory.

** $p < .01$;

* $p < .05$

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Table 3

Effect of Drug Cue on Physiological and Neuroendocrine Reactivity

	Control (n = 17) Within Group Effect				Prescription Opioid (n = 20) Within Group Effect				Between Groups	
Measurement	**Pre-Cue**	**Post-Cue Peak**	***t***	***d***	**Pre-Cue**	**Post-Cue Peak**	***t***	***d***	***F***	η_p^2
Heart Rate	68.1 (18.9)	75.6 (12.1)	1.9	0.47	81.0 (9.0)	87.1 (8.0)	3.3**	0.72	4.4*	.118
MAP	77.3 (11.3)	83.2 (11.3)	5.0**	0.52	85.0 (8.8)	91.4 (7.8)	5.2**	0.77	1.0	.030
GSR	4.7 (4.9)	7.7 (5.7)	6.4**	0.56	6.1 (6.7)	9.6 (6.6)	6.2**	0.53	0.4	.011
Cortisol	0.19 (.134)	0.18 (.131)	0.5	0.04	0.24 (.146)	0.33 (.189)	2.3*	0.51	5.6*	.145

Note. Pre-Cue and Post-Cue Peak columns are presented as means (standard deviations). MAP = Mean Arterial Pressure; GSR = Galvanic Skin Response.

** $p < .01$;

* $p < .05$.