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Laboratory-Induced Stress and Craving among Individuals with Prescription Opioid Dependence

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Abstract

Background—Stress and conditioned drug cues have been implicated in the initiation, maintenance and relapse to substances of abuse. Although stress and drug cues are often encountered together, little research exists on whether stress potentiates the response to drug cues.

Method—Participants ($N = 75$) were 39 community recruited individuals with current prescription opioid (PO) dependence and 36 healthy controls. Participants stayed overnight in the hospital for one night and then completed laboratory testing the following morning. During laboratory testing, participants were randomly assigned to a stress task (Trier Social Stress Task; TSST) or a no-stress condition. Following the stress manipulation, all participants completed a PO cue paradigm. Immediately before and after the stress and cue tasks, the following were assessed: subjective (stress, craving, anger, sadness, happiness), physiological (heart rate, blood pressure, galvanic skin response), and neuroendocrine responses (cortisol and dehydroepiandrosterone).

Results—Internal validity of the stress task was demonstrated, as evidenced by significantly higher subjective stress, as well as cortisol, heart rate and blood pressure in the TSST compared to the no-stress group. Individuals with PO dependence evidenced significantly greater reactivity to

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Contributors:

Sudie E. Back was principal investigator of the project and lead author of the manuscript as a whole. Daniel F. Gros wrote the introduction section and provided significant editing of the entire manuscript through the revision process. Matthew Price completed the analyses and authored the results section and related tables. Steve LaRowe and Julianne Flanagan authored the discussion section. Kathleen T. Brady supervised the development and completion of the project and related manuscript. Charles Davis aided in the coding and interpretation of the medication and biological findings. Maryanne Jaconis created the figures and assisted with editing the manuscript. Jenna L. McCauley contributed to the introduction and discussion sections.

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Conflict of Interest:

There are no conflicts of interest to disclose.

the stress task than controls. Craving increased significantly in response to the drug cue task among PO participants. No stress $\times$ cue interaction was observed.

Conclusions—In this study, heightened stress reactivity was observed among individuals with PO dependence. Exposure to acute stress, however, did not potentiate craving in response to conditioned drug cues.

Keywords

stress; Trier; cues; prescription opioids; opiates

1. INTRODUCTION

Stress and conditioned drug cues are key factors associated with the etiology and maintenance of substance use disorders (SUD; Brady and Sinha, 2005; Enoch, 2011; Hyman and Sinha 2009; Bruchas et al., 2010; Koob, 2009; Sinha, 2001; 2007; Stewart, 2003). Several models of addiction have attempted to explain the connection between stress and motivation to use alcohol or drugs (Breese et al., 2011; Sinha, 2001). These models relate that, for many individuals with SUD, substances are employed as a means of reducing negative affect; a pattern that is negatively reinforcing and may contribute to the subsequent development of SUD (Khantzian, 1985; Shiffman, 1982; Wills and Shiffman, 1985). However, not all substance use or relapses are precipitated by stress or negative affect. For example, Shiffman (1982) found that approximately one-third of relapses to nicotine were precipitated by smoking-specific stimuli (i.e., conditioned cues), in particular seeing someone else smoking.

The concept of craving also has a central role in theories concerning the development and maintenance of SUD (Breese et al., 2005; Childress et al., 1988; Drummond et al., 1990; Franken et al., 2000; Tiffany, 1990). One particularly salient feature that occurs during abstinence from drug use is the ability of drug-associated environmental cues to elicit craving, and consequently reinstate drug-seeking and drug-taking behaviors. The systematic investigation of craving has occurred largely through studies employing cue reactivity (Carter and Tiffany, 1999), which have given rise to a variety of theoretical models (Kosten et al., 2006; O'Brien et al., 1998; See, 2002; Siegel, 1999; Siegel and Ramos, 2002). Findings suggest that, through a process of associative learning, previously neutral stimuli (e.g., pill bottle, pharmacy) acquire incentive-motivational properties following repeated pairing with drug consumption. Conditioned stimuli thus play a critical role in ongoing drug-seeking behavior and relapse after periods of abstinence (Buffalari et al., 2014; Childress et al., 1988; O'Brien et al., 1998).

Stress and cues are frequently encountered together by patients, and the presence of stress may influence or change the rewarding value of a subsequently encountered conditioned stimuli (Bruchas et al., 2010). For example, if a person has an altercation with a coworker (stress) and then sees a billboard advertising their preferred alcoholic beverage (cue) on the commute home that day, does the stress experienced prior to seeing the cue modify the impact that the cue has on the person's craving or drug seeking behaviors? If the person had not experienced a stressful situation that day, would he/she have noticed the billboard, and if

so would the effect of the billboard have been as strong? The primary question of interest in the current study is whether exposure to a stressor potentiates reactivity (e.g., craving, physiological arousal) to a conditioned drug cue.

Given the notable contribution of stress and conditioned cues on addictive behaviors, an increasingly robust literature has investigated their ability to prompt drug-seeking behavior in preclinical and human laboratory studies. A number of different types of clinical laboratory-based stress induction tasks have been employed to study the influence of stress and cues on addictive responses. Sinha and colleagues were the first to demonstrate in a controlled human laboratory setting that acute stress increased craving in cocaine-dependent individuals (Sinha et al., 1999). Our group and others have also demonstrated that physical stressors (e.g., cold pressor task), psychological stressors (e.g., Trier Social Stress Task [TSST]; Kirschbaum et al., 1993) and pharmacological stressors (e.g., corticotropin releasing hormone) increase stress and craving among individuals with nicotine, cocaine, alcohol, or marijuana dependence (Back et al., 2005, 2010; Buchmann et al., 2010; Brady et al., 2006; Childs and de Wit, 2010).

Several clinical and preclinical studies have investigated the interactive effects of stress and cues, and the data are equivocal. Thomas and colleagues (2011) demonstrated that, among individuals with alcohol dependence, the TSST resulted in significantly increased subjective stress, as well as cortisol, ACTH, and blood pressure as compared to controls, and the alcohol cue paradigm resulted in significant craving. However, no interaction between the TSST and alcohol cues was revealed. McRae-Clark and colleagues (2011) demonstrated similar findings in that prior exposure to a laboratory-based stress task did not enhance craving response to drug cues in individuals with marijuana dependence. In contrast to these clinical studies, Liu and Weiss (2002) found that footshock stress and ethanol conditioned drug cues interacted to augment the resumption of ethanol seeking behavior following extinction in rats. Rats exposed to both footshock stress and ethanol cues, as compared to stress or cues alone, demonstrated twice as many lever presses and the response rate was sustained for a longer period of time. In addition, Buffalari and colleagues (2009) showed that while footshock stress and conditioned drug cues reinstate drug-seeking when presented in isolation, their interaction resulted in potentiated reinstatement.

The current study is focused on prescription opioid (PO) use disorders, which have been steadily increasing over the past decade and represent a significant public health concern (Back et al., 2010; Calcaterra et al., 2013; Garland et al., 2013; Hall et al., 2008; Kuehn, 2007; McHugh et al., 2015). To date, there have been no studies of the interaction of stress and cues in PO dependent individuals. In contrast to other types of SUD, individuals with PO use disorders may have different initiation histories (e.g., prescribed the drug by their physician, initially consumed by some for legitimate physical health reasons) and may present with different comorbidities, such as chronic pain, that could exert influences on stress reactivity. Using a human laboratory stress induction task (Back et al., 2014), the current study examined stress reactivity among individuals with and without PO dependence, as well as the interaction of stress and conditioned PO drug cues. Human laboratory paradigms offer a high degree of methodological precision and control, and are a reliable method of investigating the complexities of stress (Foley and Kirschbaum, 2010)

and conditioned drug cues. We hypothesized that the PO group would demonstrate increased reactivity to the stress task, and that exposure to stress would potentiate craving in response to the drug cue task.

2. METHODS

2.1 Participants

Participants ($N = 75$) were individuals with current (past 6 months) PO dependence ($n = 39$; 57.9% female) or healthy controls ($n = 36$; 50.0% female). PO dependence was defined as meeting the DSM-IV (American Psychiatric Association, 2002) criteria for substance dependence on opioid analgesics (e.g., oxycodone, hydrocodone). Newspaper and other media advertisements were the primary source of recruitment. Potential participants were initially screened by telephone using a brief form that was created for the purposes of this study and screened for current PO use and symptoms of SUD. 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 that could affect the HPA axis (e.g., bipolar disorder, post-traumatic stress disorder); use of methadone 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. 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); history of abuse was allowed. Participants were compensated \$150 for completing the study.

2.2. Measures

2.2.1 Substance Use—The Structured Clinical Interview for DSM-IV (SCID; First et al., 2002) and the Mini International Neuropsychiatric Interview (MINI; Sheehan et al., 1998) were used to assess substance use disorders and other Axis I psychiatric disorders. Urine drug screens tests were performed using the On Track Test Cup®. Breathalyzer tests were administered to test for the presence of alcohol. Opioid withdrawal symptoms were assessed at the time of hospital admission using the Short Opioid Withdrawal Scale (Gossop, 1990). The Timeline Follow Back (TLFB; Sobell Sobell and Sobell, 1992) is a calendar-based assessment that was used to measure PO use during the one month prior to the laboratory test.

2.2.2 Subjective Reactivity—A visual analog scale derived from the Within Session Rating Scale (Childress et al., 1986) and anchored with adjective modifiers (from 0 = “not at all” to 10 = “extremely”) was used to assess subjective responses: craving, stress, anger, happiness, sadness, how hard it would be to resist using their opioid of choice, and the amount of money participants would be willing to spend on opioids (i.e., the “market value”). Participants responded to questions immediately before and after the TSST and at several time points after the drug cue paradigm (i.e., immediately, 15-, 30-, and 60-minutes post). The State-Trait Anxiety Inventory (STAI, Form Y1; Spielberger, 1983) was

completed immediately before and after the TSST, and then immediately, 15-, 30- and 60-minutes after the drug cue paradigm.

2.2.3 Neuroendocrine Assay—Unstimulated salivary samples were collected at baseline, immediately after the TSST, immediately after the drug cue paradigm, and at 15-, 30-, and 60-minutes post. Dehydroepiandrosterone (DHEA) was assayed in duplicate using a salivary DHEA enzyme immunoassay system that has an intra-assay precision of 5.6% with a sensitivity of 5pg/mL. For cortisol, samples were assayed in duplicate using a high sensitivity salivary cortisol enzyme immunoassay system that has an intra-assay precision of 3.35% - 3.65% with a sensitivity of <0.003 ug/dL. Both DHEA and cortisol were analyzed using a PowerWave HT Microplate Spectrophotometer in conjunction with a Precision Series Automated Liquid Handling System.

2.2.4 Physiological Reactivity—Heart rate (HR) was collected via electrodes along the bottom of the participant's ribcage and collarbone. 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 $[(2 \times \text{DBP}) + \text{SBP}] / 3$. Two measurements of HR, SBP and DBP were taken 15 minutes apart at baseline before testing began; the average of these two measurements was used as the baseline value. Physiological measures were then taken immediately after the TSST, immediately after the drug cue paradigm, and at 15-, 30-, and 60-minutes post drug cue paradigm.

2.3. Laboratory Procedures

All procedures were approved by the local institutional review board. Participants were informed about all study procedures, including the laboratory stress provocation. Written informed consent was obtained before any study procedures occurred. Eligible participants (both PO and controls) were scheduled for a one-night hospital stay and testing was completed. Three days of abstinence from alcohol and other substances (except caffeine and nicotine), as evidenced by self-report, breathalyzer and urine drug screen, as well as the absence of significant withdrawal symptoms were required prior to hospital admission for the overnight stay. Participants were admitted to the hospital at 2000h on the evening prior to testing to allow for the control of extraneous variables (e.g., sleep, caffeine intake) that could potentially affect stress sensitivity. Cigarette smokers were provided 24-hour nicotine replacement therapy throughout the hospital stay (20 cigarettes/day = 21 mg patch; 10–19 cigarettes/day = 14 mg patch; 5–9 cigarettes/day = 7 mg patch).

A detailed description of the test day procedures is included in Table 1. Participants were provided a standard breakfast at 0730h and then escorted for laboratory testing. Sedentary activities were allowed during a 60- minute acclimation period from 0830–0930h. Pre-assessments were conducted at 0930h and 0945h, and testing began at 0950h. Participants were randomly assigned, using urn randomization (Wei and Lachin, 1988), to either the TSST or a no-stress condition. In the no-stress condition, participants sat quietly and relaxed. The TSST is a standardized, 15-minute stress provocation (Kirschbaum et al., 1993) which consists of three components: (a) participants are given 5 minutes to think about and prepare to give a speech, (b) participants deliver a 5-minute speech to 3 confederates, and

then (c) participants verbally complete serial subtractions for 5 minutes before the same audience. Following the TSST or no-stress condition, all participants completed a 15-minute PO drug cue paradigm (Back et al., 2014). The drug cue paradigm consists of three components: (a) a 5-minute audio induction script, which guides participants to relax and then think about the last time they used POs in detail; (b) 5 minutes viewing and handling drug paraphernalia; and (c) 5-minute watching a video depicting people using POs in a variety of ways. Following the drug cue paradigm, participants were assessed for 60-minutes post task and then debriefed, compensated, and discharged.

2.4. Statistical Analyses

Reactivity to the stress condition (TSST or no-stress) was measured as the change from baseline rating of a domain to the maximum response (i.e., peak) during post-task assessment. This previously established method results in a change score in which higher scores indicate greater reactivity (Back et al., 2008; Carpenter et al., 2007; Daughters et al., 2009; McRae-Clark et al., 2011). Distributions of change scores were checked to ensure that they conformed to the assumptions of a normal distribution. Distributions that violated normality were transformed according to the recommended guidelines (Tabachnick and Fidell, 2010). Drug cue reactivity was measured as the peak rating after exposure to the drug cue task. Differences in stress reactivity were assessed with a series of 2 (stress condition: TSST or no-stress) $\times$ 2 (drug status group: PO or healthy controls) ANCOVAs. Time since last use was included as a covariate in this analysis based on prior literature indicating pre-study substance use is highly correlated with post-study substance use (Paliwal et al., 2008). Post-hoc comparisons were used to identify differences in the event of a significant interaction.

3. RESULTS

Table 2 includes the sample characteristics. As can be seen, the average age was 34 years old. Approximately half of participants were male and 81% were Caucasian. Significantly more individuals in the PO group, as compared to the control group, endorsed nicotine use, as well as a history of treatment for addiction and chronic pain. Among the PO group, the most commonly used opioids included: OxyContin/ oxycodone (33.4%), Percocet (25.6%) and Lortab (15.4%). The average age of first PO use was 22.3 years old and the average age of onset of PO dependence was 27.6 years old. In the past 30 days prior to study entry, individuals in the PO group reported using POs approximately 18 out of 30 days. The most common routes of administration were oral (66.7%) and nasal (i.e., crush and snort, 28.2%).

3.1 Stress Task

Table 3 presents the pre and post stress task ratings, as well as the post cue task ratings. The interaction between the stress condition (TSST or no stress) and drug status group (PO or healthy controls) was significant for subjective ratings of stress ($F(1, 58) = 0.003, p = 0.046$, partial $\eta^2 = 0.07$), craving ($F(1, 58) = 9.03, p = 0.004$, partial $\eta^2 = 0.14$), and anger ($F(1, 58) = 6.56, p = 0.013$, partial $\eta^2 = 0.10$; see Table 3). Post-hoc comparisons showed that subjective stress significantly increased for both PO participants ($F(1, 28) = 28.07, p < 0.001$, partial $\eta^2 = 0.50$) and control participants ($F(1, 30) = 25.08, p < 0.001$,

partial $\eta^2 = 0.46$) following the TSST. However, the magnitude of the change was greater for PO participants as compared to controls (mean change 4.2 vs. 2.4; see Figure 1A). Post-hoc comparisons showed that craving significantly increased for PO participants ($F(1, 28) = 8.45, p = 0.007$, partial $\eta^2 = 0.23$) and, as expected, there was no change for control participants ($F(1, 30) = 0.00, p = 0.99$, partial $\eta^2 = 0.00$). For anger, post-hoc comparisons indicated that anger significantly increased for both PO participants ($F(1, 28) = 17.75, p < 0.001$, partial $\eta^2 = 0.39$) and control participants ($F(1, 30) = 4.69, p = 0.038$, partial $\eta^2 = 0.14$), but the magnitude of change was greater for the PO group as compared to controls (mean change 3.4 vs. 1.2; see Figure 1B). Post-hoc comparisons revealed that the amount of money participants were willing to spend on opioids significantly increased for PO participants ($F(1, 28) = 5.68, p = 0.024$, partial $\eta^2 = 0.17$) and, as expected, there was no change among control participants ($F(1, 30) = 0.00, p = 0.99$, partial $\eta^2 = 0.00$). There were no significant main effects or interactions for subjective ratings of resistance, sadness, or happiness.

There was a significant main effect of stress condition for HR ($F(1, 58) = 6.50, p = 0.014$, partial $\eta^2 = 0.14$), cortisol ($F(1, 58) = 9.60, p = 0.003$, partial $\eta^2 = 0.14$; see Figure 1C) and blood pressure ($F(1, 58) = 9.39, p = 0.003$, partial $\eta^2 = 0.14$). Across these effects, levels in the TSST condition were significantly higher than the no-stress condition. There were no significant main effects for drug group and there were no stress $\times$ drug cue interactions for HR, blood pressure, cortisol or DHEA.

3.2 Drug Cue Task

As previously reported (Back et al., 2014), exposure to the drug cue task alone resulted in significant increases from pre to post in subjective (craving, stress, anger, difficulty resisting opioids), physiological (heart rate), and cortisol levels among PO participants, but not controls. Physiological and neuroendocrine responses to the stress task were predictive of these same responses to the drug cue paradigm. Specifically, GSR ($\beta = 0.66, p = 0.038$) and cortisol ($\beta = 0.49, p = 0.007$) sensitivity to the stress condition predicted GSR and cortisol response to the drug cue paradigm. Similarly, HR response to the stress condition predicted HR response to the drug cue paradigm ($\beta = 0.88, p = 0.014$). When probed at different conditions of the stress condition, HR response to the TSST was positively associated with HR response to the drug cue paradigm ($b = 1.04, p < 0.001$); this was not true for response in the no-stress condition ($b = 0.07, p = 0.80$). No other significant main effects or interactions were observed (Table 5).

4. DISCUSSION

The present study examined stress reactivity as well as potential stress $\times$ drug cue interactions on subjective ratings, physiological symptoms, and neuroendocrine levels in participants with and without PO dependence. All participants reacted to the stress condition in terms of subjective and physiological indices compared to the no stress condition, thus supporting the internal validity of the stress task. However, participants with PO dependence demonstrated a greater increase in subjective ratings of stress, anger and the amount of money they were willing to spend on opioids compared to control participants. PO

dependent individuals also demonstrated increased craving in response to the stress task. This is the first study to our knowledge to show increased craving in response to a laboratory stressor among individuals with PO dependence. Examination of a potential stress $\times$ cue interaction revealed that the stress task and drug cue task alone both increased subjective and physiological reactivity, but did not interact (i.e., the stress task did not elevate response to the cue). These findings are consistent with previous clinical studies in individuals with alcohol and marijuana use disorders (McRae-Clark et al., 2011; Thomas et al., 2011). Together, these studies demonstrate a consistent pattern of responses across different types of stress induction procedures, study teams, and substances in human trials.

The present study is the first to investigate the interaction of stress and PO drug cues, a unique type of SUD with regard to initiation history (e.g., typically prescribed by a physician) and comorbidities (e.g., chronic pain; Back et al., 2010). Contrary to hypothesis, the stressor task did not potentiate reactivity to the drug cue. One potential reason for the unexpected finding may be the stressor and cue paradigms employed. A robust stress response was observed in reaction to the TSST, and a robust craving response was seen as a reaction to the drug cue task; thus, a ceiling effect may have limited the ability to detect differences. Two prior investigations examining stress $\times$ cue interactions among humans also failed to observe an interaction utilizing the TSST. In the future, it may be useful to examine other types of stressors (e.g., the cold pressor test; McRae et al., 2006) or drug cues (e.g., Sinha et al., 2009), which may produce a greater range of physiological and subjective responses. Additionally, other types of stress tasks may be more relevant to individuals with PO disorders, such as tasks employing physical stress (e.g., quantitative sensory testing), and it may be helpful to explore more naturalistic methods of examining stress. Several prior studies, however, have investigated the effects of negative mood on cue reactivity in patients with alcohol use disorders, and no interaction between negative mood and subsequent cue reactivity were observed (Cooney et al. 1997; Litt et al., 1990; Mason et al. 2008). This suggests that the negative results of the current and previous studies regarding stress $\times$ cue interactions are likely not solely due to the stress task employed.

Although further research is clearly needed, the extant literature suggests that while stress may lead to increase craving and drug-seeking behaviors it does not appear to do so by enhancing the incentive value of drug cues. A study by Ray and colleagues (2013) examined the effects of varenicline on nicotine craving and found differential effects. Subjects (N=40) were first exposed to guided imagery (stress or neutral) and then all subjects were exposed to in vivo cigarette cues. Results indicated that varenicline resulted in significantly reduced craving to the cues among subjects in the neutral imagery condition, but not the stress condition. The authors speculate that the absence of stress-specific reductions in craving following varenicline may be interpreted in light of the dissociation between neural mechanisms of stress- and cue-induced craving (Schank et al., 2011). Furthermore, Snelleman and colleagues (2014) conducted a review of studies (N=12) to examine the evidence supporting the relationship between stress and cue sensitivity. The findings were mixed and although an association between stress and cues exists, the exact nature of that association is unclear. Snelleman and colleagues noted that the few studies that did observe increased cue sensitivity following exposure to a stressor (vs. neutral task) were focused on patients with PTSD and/or individuals who were heavy drinkers with a primary motive of

‘drinking to cope.’ Finally, it was noted that, in general, stress states induced by acute laboratory tasks, such as the TSST, have no link or association with past substance use and therefore do not enhance reactivity to cues (Snelleman et al., 2014).

From a clinical perspective, the current findings suggest that PO dependent individuals may present for treatment with heightened stress reactivity, which may confer increased risk for relapse, although not necessarily in a direct fashion, and should be addressed in treatment. Among individuals with heroin dependence, recent studies demonstrate that a single maintenance dose of heroin reduces subjective anxiety and craving, and normalizes hypothalamic-pituitary-adrenal (HPA) axis activity; this highlights the emotion regulation effects of heroin among heroin-dependent individuals which is likely a contributing factor to maintaining drug-seeking behaviors (Walter et al., 2013). More recently, Schmidt and colleagues (2015) used a cross-over, double-blind design to examine neural responses to fearful faces among heroin dependent individuals and healthy controls, after heroin and placebo administration. The findings showed hyperactive amygdala-related connectivity during fearful faces among the heroin dependent individuals as compared to controls, which was normalized after heroin administration. These studies point to neurobiological mechanisms that may underline the stress regulation effect of heroin in dependent patients. In addition, empirical evidence demonstrates dysfunctional connectivity of the prefrontal cortex and anterior cingulate cortex at rest among heroin users as compared to controls, and shows that the level of dysfunction at rest is associated with greater craving in response to heroin cues (Liu et al., 2011). Future research examining these mechanisms and associations among patients with PO dependence would be useful and may inform the development of treatment interventions.

Physicians prescribing PO medications should consider assessing stress level and coping resources, in addition to standard pain assessments, to determine the appropriateness of prescribing POs as compared to alternate medications with lower misuse potential. One potential alternative may be duloxetine, which is a dual selective serotonin and norepinephrine inhibitor that has been shown to address pain, as well as stress and depressed mood (Lunn et al., 2009; Thor et al., 2007). Other alternatives include tricyclic antidepressants (e.g., amitriptyline), anticonvulsants (e.g., gabapentin), topical or transdermal agents (e.g., lidocaine patch), and alternative medicines (Lee and Raja, 2011; Rowbotham, 2015). In addition to pharmacologic treatments, psychosocial interventions targeting improved stress management may be helpful for PO dependent patients endorsing high stress and/or poor stressing coping skills. For example, behavioral activation psychotherapy has been shown to be quick and effective for reducing stress and improving mood, is easily administered, and can be adapted to primary care settings (Gros and Haren, 2011). Psychoeducation regarding adaptive ways to cope with both stress- and cue-induced cravings, including stimulus control and mindfulness techniques, may be helpful (Garland et al., 2010). The systematic exposure to drug cues (e.g., exposure and response prevention) coupled with pharmacologic agents used to augment extinction learning may also play a role in the future treatment of patients with PO dependence (Kamboj et al., 2012; Marissen et al., 2007; Rohsenow et al., 1995). The findings from this study indicate that additional research is needed to more clearly identify the influence of stress and cues in PO disorders.

Several limitations of the present study warrant consideration. The salience of the TSST and the drug cue paradigm may have limited our ability to differentiate highly sensitive participants from those with lower levels of sensitivity. Furthermore, the use of an acute stressor may have limited the findings – more chronic forms of stress may have yielded a different result. The order of tasks was not counterbalanced, as our aim was to examine the effects of stress on subsequent exposure to drug cues. This limited our ability to examine the effects of exposure to drug cues on subsequent stress. In addition, the study did not include a neutral-cue condition. This would have allowed us to investigate the effects of stress alone, the cue alone, and the interaction of stress and cues. Finally, the assessments of substance use relied heavily on participant self-report and blood levels of opioids were not obtained. Despite these limitations, the study utilized a well-controlled human laboratory paradigm, had participants stay overnight in the hospital prior to testing, and included subjective, physiological, and neuroendocrine measures.

In summary, the findings demonstrate that the psychosocial stress task employed elicited salient subjective, physiological and neuroendocrine responses from PO dependent participants, in particular. Exposure to the stressor was also associated with an increase in craving among PO dependent participants. However, exposure to the stressor did not potential response to the drug cue. Further preclinical and clinical investigations are needed to expand the current findings and increase understanding of the link between stress and cues in hopes of better addressing the growing epidemic of PO dependence.

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Highlights

- Stress and cues implicated in the initiation and maintenance of drug abuse
- Participants completed stress or no-stress conditions and then drug cue paradigm
- Heightened stress reactivity and craving observed in PO group compared to controls
- Exposure to stress did not potentiate craving in response to drug cues
- Stress response is not by enhancing the incentive salience of drug cues.

Figure 1.
Subjective and neuroendocrine reactivity among individuals with or without prescription opioid (PO) dependence

Table 1

Laboratory test day procedures

Time	Procedure
7:30–8:30 am	Standard breakfast and then escorted to laboratory
8:30 am	Electrodes attached
8:30–9:30 am	Acclimation period (sedentary activities)
9:30–9:49 am	Baseline Assessments: <ul style="list-style-type: none"> • Baseline measurement # 1 and salivary sample • Rest • Baseline measurement # 2
9:50–10:05 am	Trier Social Stress Task (TSST) or no-stress
10:06–10:07 am	Salivary sample + assessments #3
10:07–10:22 am	Prescription opioid drug cue paradigm
10:23–10:24 am	Salivary sample + assessment #4 (immediate)
10:39–10:40 am	Salivary sample + assessments #5 (15 min)
10:55–10:56 am	Salivary sample + assessments #6 (30 min)
11:11–11:12 am	Salivary sample + assessments #7 (60 min)
11:15 am	Debriefing, compensation, discharge

Table 2

Sample characteristics (N=75)

Variable	Control Group (n = 36)	PO Group (n = 39)
Age, <i>M (SD)</i>	33.58 (12.41)	34.59 (12.55)
Gender, % Male	50.0	51.3
Education, % Some College	97.2	69.2
Employment		
% Employed Full Time	83.3	23.1
% Unemployed	8.3	59.0
Race		
% Caucasian	80.6	82.1
% African-American	11.1	5.1
% Other	8.3	12.8
Relationship Status		
% Married	41.7	10.3
% Single, Never Married	44.4	59.0
% Divorced, Separated	13.9	20.5
Smoker (nicotine), % Yes	11.1	82.1 *
History of chronic pain treatment	0.0	33.3 *
History of addiction treatment	0.0	41.0 *
Opioid use in the past month		
Total # days using	0.2 ^t	18.1 *
Average # pills per day	0.007 ^t	2.79 *
Average # pills per using day	0.07 ^t	4.16 *
Comorbid psychiatric conditions [#]		
Alcohol use disorder	0.0	10.3
Sedative use disorder	0.0	5.1
Marijuana use disorder	0.0	7.7
Cocaine use disorder	0.0	0.0
Major depression	0.0	5.1
Panic disorder	0.0	15.4 *
PTSD	0.0	0.0
Bipolar disorder	0.0	0.0
Pain disorder	0.0	7.7

Note. PO = prescription opioid. *M(SD)* = Mean(Standard Deviation).

* p<.05 between-group differences.

[#] Current conditions.

^t Two control patients reported medical use of opioids during the month prior to study entry. Both subjects used the medication as prescribed for acute medical procedures, had not used the medication in the past 5 days prior to laboratory testing and had negative urine drug screen tests.

Table 3

Descriptive information for pre and post stress task and drug cue task

	PO Group						Control group					
	Stress			No Stress			Stress			No Stress		
	<i>M</i>	<i>SD</i>	<i>M</i>	<i>SD</i>	<i>M</i>	<i>SD</i>	<i>M</i>	<i>SD</i>	<i>M</i>	<i>SD</i>	<i>M</i>	<i>SD</i>
<i>Pre Stress Task</i>	Stress	3.76	1.99	3.37	2.63	0.37	0.76	0.71	1.36	0.00	0.00	0.00
	Crave	4.82	2.79	4.95	2.68	0.16	0.69	0.00	0.00	0.00	0.00	0.00
	Resist using	7.65	3.16	7.11	3.26	0.16	0.69	0.00	0.00	0.00	0.00	0.00
	Anger	0.94	1.48	1.42	2.04	0.00	0.00	0.41	1.23	0.00	0.00	0.00
	Sad	1.88	1.80	1.95	2.59	0.05	0.23	0.41	1.06	0.00	0.00	0.00
	Happy	3.53	2.18	4.21	2.20	5.63	1.64	5.88	2.83	0.00	0.00	0.00
	Market Value	27.53	18.86	29.89	31.93	0.00	0.00	0.00	0.00	0.00	0.00	0.00
	HR	69.92	10.51	71.26	9.64	68.77	11.34	62.99	10.03	0.00	0.00	0.00
	GSR	3.99	3.12	5.66	5.60	2.76	2.55	3.35	3.16	0.00	0.00	0.00
	Cortisol	0.26	0.12	0.26	0.14	0.21	0.10	0.23	0.15	0.00	0.00	0.00
	DHEA	151.60	110.49	187.17	116.07	134.96	199.94	146.24	112.48	0.00	0.00	0.00
	Blood Pressure	86.39	10.10	83.48	9.74	81.39	8.51	77.89	9.88	0.00	0.00	0.00
<i>Post Stress Task</i>	Stress	8.00	1.97	2.84	2.67	2.79	2.49	0.35	0.79	0.00	0.00	0.00
	Crave	6.94	3.23	4.89	2.89	0.00	0.00	0.00	0.00	0.00	0.00	0.00
	Resist using	8.06	3.01	7.37	3.20	0.00	0.00	0.00	0.00	0.00	0.00	0.00
	Anger	4.35	3.39	1.05	1.81	1.16	2.63	0.06	0.24	0.00	0.00	0.00
	Sad	2.94	3.07	1.26	1.91	0.00	0.00	0.35	0.86	0.00	0.00	0.00
	Happy	1.88	2.21	4.26	2.81	5.68	1.92	6.12	2.76	0.00	0.00	0.00
	Market Value	45.31	33.24	30.53	34.19	0.00	0.00	0.00	0.00	0.00	0.00	0.00
	HR	85.88	17.30	80.98	9.27	81.89	12.91	68.08	18.92	0.00	0.00	0.00
	GSR	6.19	3.97	6.30	6.81	7.24	5.14	10.82	25.87	0.00	0.00	0.00
	Cortisol	0.39	0.32	0.24	0.15	0.26	0.15	0.19	0.13	0.00	0.00	0.00
	DHEA	242.59	163.07	218.26	113.47	140.88	205.61	147.17	170.01	0.00	0.00	0.00
	BP	92.16	12.28	84.53	9.16	87.89	11.65	77.27	11.30	0.00	0.00	0.00

<i>Pre Stress Task</i>	PO Group						Control group					
	Stress			No Stress			Stress			No Stress		
	<i>M</i>	<i>SD</i>	<i>M</i>	<i>SD</i>	<i>M</i>	<i>SD</i>	<i>M</i>	<i>SD</i>	<i>M</i>	<i>SD</i>	<i>M</i>	<i>SD</i>
<i>Post Cue Task</i>												
Stress	6.00	3.25	5.89	3.27	0.84	1.80	0.24	0.44				
Crave	8.19	1.97	7.83	2.77	0.00	0.00	0.00	0.00				
Resist	9.13	1.20	8.00	2.57	0.00	0.00	0.00	0.00				
Anger	2.69	2.50	3.39	2.85	0.37	1.21	0.12	0.49				
Sad	2.94	3.21	2.44	3.05	0.05	0.23	0.47	1.07				
Happy	3.88	2.53	4.94	3.17	6.74	1.76	7.00	2.42				
Market Value	66.81	78.94	57.44	91.58	0.00	0.00	0.00	0.00				
HR	87.92	15.87	87.10	8.22	85.14	11.82	75.62	12.12				
GSR	8.95	6.83	9.84	6.71	7.14	4.94	7.77	5.49				
Cortisol	0.32	0.17	0.34	0.19	0.26	0.14	0.19	0.13				
DHEA	255.43	183.14	277.43	149.37	197.64	148.17	203.07	196.13				
BP	96.37	13.56	91.61	8.27	84.97	9.21	82.88	12.38				

Note. HR = heart rate. GSR = galvanic skin response. DHEA = dehydroepiandrosterone. BP = blood pressure.

ANCOVA examining stress-drug cue interaction

	PO Group			Control Group							
	Stress		No Stress		Stress		No Stress		P for Stress Main Effect	P for interaction	
	Adjusted Mean Difference	SEM	Adjusted Mean Difference	SEM	Adjusted Mean Difference	SEM	Adjusted Mean Difference	SEM			
Stress	4.17 ^a	0.56	0.86 ^b	0.55	2.41 ^c	0.55	0.04 ^b	0.55	0.266	<0.001	0.046
Crave	2.26 ^a	0.43	-0.25 ^b	0.43	0.00 ^b	0.04	0.00 ^b	0.04	0.022	0.004	0.004
Resist	0.28 ^a	0.28	0.0 ^a	0.27	0.06 ^a	0.27	0.06 ^a	0.27	0.93	0.35	0.35
Anger	3.31 ^a	0.52	-0.39 ^b	0.51	0.71 ^c	0.5	-0.41 ^b	0.5	0.017	<0.001	0.013
Sad	1.08 ^a	0.44	-0.48 ^a	0.58	-0.03 ^a	0.43	-0.03 ^a	0.43	0.467	0.073	0.073
Happy	-1.44 ^a	0.59	0.13 ^a	0.58	0.19 ^a	0.56	0.25 ^a	0.58	0.161	0.16	0.194
Market Value	20.22 ^a	4.35	-0.28 ^a	4.12	-1.56 ^a	4.06	-1.56 ^a	4.06	0.108	0.100	0.100
HR	37.3 ^a	3.43	24.41 ^b	3.21	38.34 ^a	3.14	20.1 ^b	3.14	0.914	<0.001	0.833
GSR	1.66 ^a	3.96	0.63 ^a	3.6	4.87 ^a	3.67	8.06 ^a	3.56	0.18	0.769	0.564
Cortisol	0.14 ^a	0.04	-0.02 ^b	0.04	0.05 ^a	0.04	-0.05 ^b	0.04	0.151	0.003	0.431
DHEA	106.06 ^a	35.5	18.03 ^a	31.01	21.9 ^a	33.91	4.06 ^b	30.7	0.165	0.108	0.283
BP	5.8 ^a	1.69	1.67 ^b	1.67	5.44 ^a	1.7	-0.54 ^b	1.64	0.47	0.003	0.576

Note. Means are adjusted for days since last use. Superscripts denote significant differences.

SEM = standard error of the mean. HR = heart rate. GSR = galvanic skin response. DHEA = dehydroepiandrosterone. BP = blood pressure.