Research Square

Preprints are preliminary reports that have not undergone peer review.
They should not be considered conclusive, used to inform clinical practice,
or referenced by the media as validated information.

Yohimbine Stress Moderates the Relationship Between Opioid Craving and Seeking Behavior

Nicole A. Kouri
Wayne State University
Mark K. Greenwald
mgreen@med.wayne.edu
Wayne State University

Research Article

Keywords: Stress, Yohimbine, Noradrenaline, Opioid, Craving, Seeking, Moderation

Posted Date: November 19th, 2026

DOI: https://doi.org/10.21203/rs.3.rs-11235755/v1

License: This work is licensed under a Creative Commons Attribution 4.0 International License.
Read Full License

Additional Declarations: No competing interests reported.

Abstract

The linkage between drug craving and seeking behavior is theoretically and clinically important but poorly understood. This secondary data analysis examined the association between opioid craving and seeking in regular heroin users exposed to the pharmacological stressor yohimbine. We hypothesized that acute noradrenergic activation would strengthen the opioid craving/seeking linkage, such that opioid craving would be positively associated with seeking during yohimbine but not placebo. Participants (N = 21) were out-of-treatment, chronic regular heroin users stabilized on buprenorphine 8 mg/day, which suppressed baseline withdrawal symptoms. Across two similar studies, participants were pretreated with oral yohimbine (32.4 mg; NCT00684840: Study 1, n = 10] or 27 mg; NCT01536925: Study 2, n = 11]) or placebo on different session days under randomized, double-blinded conditions, and could work (progressive ratio schedule; 12 trials/session) to earn units of IM hydromorphone (1.5 mg/trial) or money ($2/trial). Opioid craving and vital signs were repeatedly measured each session. A two-level moderation model examined the relationship between opioid craving and seeking and whether the relationship differed as a function of placebo vs. yohimbine challenge. As hypothesized, exposure to yohimbine significantly moderated the relationship between opioid craving and opioid-seeking behavior. Increased systolic blood pressure relative to each participant's mean level similarly acted as a moderator, indicating the role of physiological stress as a link between craving and seeking. These findings support the idea that acute noradrenergic activation, a key driver of the physiological stress response, facilitates increased risk of opioid use, independent of withdrawal symptoms.

Introduction

Opioid craving has sometimes been observed to be associated with opioid use (Biernacki et al. 2022; Boyett et al. 2021; McHugh et al. 2014; Tsui et al. 2014), yet the exteroceptive and interoceptive conditions in which self-reported craving leads to drug-seeking or use behavior remain unclear. An individual's reactivity to stressors (stimuli that disrupt homeostasis) is a potential moderator of the relationship between drug craving and use. Physiological and perceived stress have both been positively associated with drug craving (Hyman et al. 2008; MacLean et al. 2019; Panlilio et al. 2021; Preston et al. 2017), and their relationship to opioid use is partially supported (MacLean et al. 2019; Preston et al. 2018). More specific to the present analysis, yohimbine, a noradrenergic activator and interoceptive stressor, has been shown to facilitate craving (Stine et al. 2002) and drug seeking (Greenwald et al. 2013; Greenwald et al. 2024b) in persons with opioid use disorder (OUD). Given yohimbine's independent exacerbating effects on both craving and opioid seeking, this study examined whether yohimbine exposure also moderates the association between opioid craving and seeking in regular opioid users.

Yohimbine activates the sympathetic nervous system by blocking central nervous system (CNS) presynaptic α_2-autoreceptors, facilitating release of noradrenaline (Doxey et al. 1984; Goldberg and Robertson 1983). Yohimbine is useful for examining the relationship between craving and drug seeking, as it occasions noradrenaline-mediated increases in blood pressure, opioid withdrawal symptoms, and anxiety, while reducing positive mood, even during buprenorphine stabilization (Greenwald et al. 2013;

Greenwald et al. 2024b). Findings from animal studies have implicated noradrenaline in opioid self-administration (Davis et al. 1975; Shaham et al. 2000; Ventura et al. 2005; Wang et al. 2001; Weinshenker and Schroeder 2007) and the somatic and motivational symptoms of opioid withdrawal (Maldonado 1997; Monroe and Radke 2023; Nestler et al. 1999; Van Bockstaele et al. 2001). Specifically, noradrenaline is activated in the locus coeruleus (LC) and areas A1 and A2 of the caudal medulla during opioid withdrawal (Aston-Jones and Kalivas 2008; Solecki et al. 2019). Indeed, the α_2-adrenergic receptor agonists clonidine and lofexidine are often used clinically to treat opioid withdrawal (Urits et al. 2020).

More broadly, LC noradrenaline activity facilitates behavioral execution and operant learning and is necessary for sustaining attention on a task (Breton-Provencher et al. 2021). Also, LC noradrenaline spreads to multiple brain regions, including the amygdala. Noradrenaline innervation and activation of the amygdala is essential for encoding and retaining emotional memories (Tully and Bolshakov 2010). NE's involvement in operant learning and memory consolidation is highly relevant to opioid craving and seeking: Strong negative affect concurrent with opioid withdrawal is state-dependently bound to increased opioid craving, motivating individuals to seek relief from this aversive state (i.e., negative reinforcement). Research strongly supports the notion that emotional experiences result in long-lasting memories of those experiences (Tully and Bolshakov 2010).

We hypothesize that, in chronic opioid users, opioid craving becomes inextricably linked with drug seeking due to repeated lifetime episodes of stress-induced release of noradrenaline during opioid withdrawal (e.g., disruption of typical use pattern during drug non-availability). As stress-induced noradrenaline release is not specific to opioid withdrawal, drug seeking may be a conditioned response to opioid craving when the context of stress—i.e., noradrenaline activation—is induced, even in the absence of withdrawal symptoms or external reminders of drug use.

This study aimed to elucidate the relationship between opioid craving and seeking in regular heroin users undergoing an experimentally induced physiological stress response (interoceptive stimulus) in the absence of drug-paired cues (exteroceptive stimuli) and in the absence of baseline withdrawal symptoms (due to stabilization on buprenorphine). We hypothesized that acute noradrenergic activation would strengthen the relationship between opioid craving and seeking, such that opioid craving would be positively associated with seeking after receiving yohimbine vs. a placebo dose. We further hypothesized that changes to diastolic and systolic blood pressure (a robust index of yohimbine response) would similarly moderate opioid craving's association with opioid seeking.

Materials and Methods

Participants and selection criteria

The Wayne State University IRB approved all procedures for the two source studies, which were registered on ClinicalTrials.gov (NCT00684840 [registration date: 03/01/2008], NCT01536925

[registration date: 12/01/2011]). Participants provided separate written informed consent for screening and their study.

Male and female volunteers from 18–55 years old, self-identifying as regular heroin users and not presently seeking treatment for their problematic opioid use, were recruited using advertisements and word-of-mouth referral. Candidates were screened using medical history, routine blood and urine chemistry, electrocardiogram, tuberculin test, physical exam, and psychiatric interview (SCID-IV; First et al. 1996). Volunteers were excluded who met DSM-IV criteria for current Axis I disorders (except Opioid and Nicotine Dependence), serious psychiatric conditions (psychosis, bipolar, major depression not substance-induced), reported chronic health problems or taking prescribed medications, had verbal IQ < 80 based on the Shipley Institute of Living Scale (Zachary 1991), or scored > 15 on the 10-item Injection and Blood Withdrawal Phobia subscale of the Medical Fear Survey (Kleinknecht et al. 1999). Women who were pregnant (urine HCG), lactating or heterosexually active and not using medically-approved birth control (self-report) were excluded; to improve feasibility of recruiting female participants, hormonal birth control was allowed.

During screening, volunteers had to provide a urine sample positive for opioids (> 300 ng/ml) and negative for methadone (due to buprenorphine maintenance), benzodiazepines (< 300 ng/ml) and barbiturates (< 200 ng/ml). Urine samples positive for cocaine (> 300 ng/ml) or THC (> 50 ng/ml) were allowed. Volunteers had to provide an alcohol-free breath sample (< .02%). The two studies were conducted prior to widespread adulteration of the heroin supply with synthetic opioids (e.g., fentanyl) and other illicit substances including noradrenergic drugs (e.g., xylazine, medetomidine). Thus, exclusions for urine drug screen results were likely based on intentional use and not a contaminated supply.

Study design

Design and procedures for Studies 1 and 2 are described in detail elsewhere (Greenwald et al. 2013 and Greenwald et al. 2024b, respectively). Briefly, participants first passed a screening test to determine whether intramuscular hydromorphone would function as a reinforcer. All participants were stabilized on buprenorphine 8-mg/day for ≥ 10 outpatient days before inpatient admission. Residential living, staff observation, and daily urinalyses ensured abstinence from unsanctioned drug use during study procedures. Testing was conducted on consecutive weekdays. During non-experimental periods (evenings and weekends), volunteers could engage in recreational activities on the unit. Cigarette smoking or use of nicotine replacement products (provided by research staff) were allowed *ad libitum* on the residential unit and, on session days, permitted before and after the protocol was completed.

Yohimbine or placebo was administered in the morning. The choice task lasted 3 hours. Vital signs were measured at session baseline and every 30 minutes following yohimbine or placebo administration. Opioid craving was evaluated at session baseline and 0.3 hours (before choice task), 2 hours (early during choice task), and approximately 4 hours (immediately after choice task) following yohimbine or

placebo administration. Study 1 involved completing six test conditions in a 3 x 2 design reflecting three yohimbine pretreatment doses (0, 16.2 and 32.4 mg oral) combined with being able to work for two hydromorphone unit doses (1-mg or 2-mg, relative to $2.00 per trial) in different sessions. For this secondary analysis, we include data only from the yohimbine placebo and 32.4 mg conditions, and we averaged opioid-seeking responses across the two hydromorphone unit doses (1 mg and 2 mg), thereby simulating an average 1.5-mg unit dose in this study.

Study 2 had nine test conditions in a 3 x 3 design reflecting the combination of three yohimbine pretreatment doses (0, 27 and 54 mg oral) and three hydrocortisone doses (0, 20 and 40 mg) and the participant could work for a single hydromorphone unit dose (1.5-mg relative to $2.00 per trial) in different sessions. For this secondary analysis, we include data only from the yohimbine placebo and 27 mg conditions during placebo hydrocortisone.

Drug administration

Buprenorphine. Participants consumed buprenorphine 8-mg sublingual tablets during initial outpatient and inpatient periods (Subutex™; supplied by Research Triangle Institute, Research Triangle Park, NC). During the experimental (inpatient) study, buprenorphine was administered at 8:00pm. The 8-mg/day buprenorphine dose was selected to minimize opioid withdrawal symptoms, but insufficient to block reinforcing effects of high-dose hydromorphone (Greenwald et al. 2014; Greenwald et al. 2024a). Following completion of each study, participants were provided with a standardized three-week outpatient buprenorphine dose taper (not relevant to this analysis).

Hydromorphone. Doses of hydromorphone (Dilaudid-HP™ in 50 mg/5 ml ampoules) were injected (constant volume = 2.4 ml) into the deltoid muscle. Maximum earned doses were 12 mg or 24 mg in Study 1 (collapsed average = 18 mg), or 18 mg in Study 2.

Yohimbine. In Study 1, the 32.4 mg yohimbine dose was prepared by crushing 6 commercial tablets (5.4 mg each; Glenwood Pharmaceuticals, Englewood, NJ) and encapsulating the powder with lactose filler (placebo) in opaque capsules. In Study 2, the 27 mg yohimbine dose was prepared by weighing yohimbine hydrochloride USP powder (Spectrum Chemical Manufacturing, Gardena, CA) on a Mettler balance, and encapsulating with lactose filler (placebo) in opaque capsules.

Measures

Physiological measures. We measured blood pressure, heart rate, oxygen saturation, and breathing rate. For this secondary analysis, we focus on systolic and diastolic blood pressure, which are most sensitive to yohimbine.

Opioid craving. In Study 1, heroin craving was measured with a 10-item total score (S.T. Tiffany, personal communication, 11/23/99); which derives from the 34-item Heroin Craving Questionnaire (HCQ; Schuster

et al. 1995). In Study 2, the 34-item HCQ was used. Given these two different versions of the HCQ, we applied *z*-score standardization to obtain scaled scores. Additional subjective effects were measured in each study (e.g., opioid agonist and withdrawal symptoms, visual analog ratings of drug effect, mood state), but these measures are unrelated to this secondary analysis.

Opioid reinforcement. The primary measure of opioid reinforcing efficacy was hydromorphone breakpoint, i.e., the greatest number of responses (i.e., mouse clicks) on the progressive ratio schedule (for details, see Greenwald et al. 2013; Greenwald et al. 2024b).

Data analysis

All participants ($N = 21$) had complete data and there were no multivariate outliers. We conducted independent samples *t*-tests comparing mean years of heroin use, opioid craving and seeking across the two studies to ensure there were no study-level differences in participants and variables of interest. We also compared two unconditional models: in the first one, data were nested by participant and study and in the second one, data were nested by participant only. The log-likelihood test was insignificant, but the Akaike and Bayesian Information Criterion (AIC and BIC) values for the second model were smaller, therefore, we only nested the data within participants. Additionally, the intraclass correlation coefficient (ICC) for study equaled 0, suggesting that drug breakpoint was not likely to differ between studies. We therefore combined data from the two studies for all subsequent analyses.

A two-level moderation model (model 1), with a random intercept and fixed slope, was built to examine the relationship between opioid craving (measured at the 3.7 hr post-yohimbine time point) and seeking (drug breakpoint) and whether the relationship differed as a function of experimental stress condition (i.e., placebo or yohimbine) nested within participants.

The level-1 equation for the final model can be expressed as

$$Y_{ij} = \beta_{0j} + \beta_{1j}x_{1ij} + \beta_{2j}x_{2ij} + \beta_{3j}x_{1ij}\,x_{2ij} + r_{ij}$$

where Y_{ij} is the drug breakpoint value for observation *i* for participant *j*; x_{1ij}, and x_{2ij} are the two level-1 covariates, opioid craving and experimental condition (i.e., placebo or yohimbine), respectively for observation *i* for participant *j*, and $x_{1ij}x_{2ij}$ is the interaction between the two level-1 covariates.

Further, β_{0j} is the intercept of the regression equation for participant *j*, β_{1j} and β_{2j} are the main effects of opioid craving and experimental condition respectively, β_{3j} is the within-level interaction between x_{1ij} and x_{2ij}, and r_{ij} is the observation- and group-specific residual. The random effects of the intercept are expressed in the level-2 equation:

$$\beta_{0j} = \gamma_{00} + u_{0j}$$

$$\beta_{1j} = \gamma_{10}$$

$\beta_{2j} = \gamma_{20}$

$\beta_{3j} = \gamma_{30}$

where γ's represent the fixed regression coefficients and u_{0j} represents participant-specific deviations from the intercept. The reduced form of the two equations is

$Y_{ij} = (\gamma_{00} + \gamma_{10}x_{1ij} + \gamma_{20}x_{2ij} + \gamma_{30}x_{1ij}\, x_{2ij}) + (u_{0j} + r_{ij})$

Both predictors were person-mean centered to separate the within-level (i.e., within person) and between-level (i.e., between people) variance, such that the regression coefficients capture the main effects of opioid craving (γ_{10}) and experimental condition (γ_{20}), and their interaction (γ_{30}) within person (Enders and Tofighi 2007; Yaremych et al. 2021). More specifically, the intercept (γ_{00}) represents the mean drug breakpoint for a person experiencing their mean opioid craving across experimental conditions, γ_{10} represents the main effect of opioid craving on drug breakpoint given a person's mean opioid craving across experimental conditions, γ_{20} represents the mean difference on drug breakpoint between the yohimbine and placebo conditions within person, on average, and γ_{30} represents the interaction effect of opioid craving and experimental condition on drug breakpoint within person.

The model was fit using restricted maximum likelihood (lme4 package; Bates et al. 2015). We conducted inferential tests for fixed effects using *t*-tests with Satterthwaite degrees of freedom approximations (CR2 package; Huang and Zhang 2022). Robust standard errors with the bias-reduced linearization adjustment for small samples were calculated to compensate for heteroscedastic residuals (Bell and McCaffrey 2002; Pustejovsky and Tipton 2018). The effect of yohimbine on the relationship between opioid craving and seeking was then examined using simple slopes analysis (Preacher et al. 2006).

The experimental condition (i.e., placebo vs. yohimbine) is a crude representation of the latent continuous construct of interest—a person's physiological response to the stressor. In a second set of two-level moderation models, we therefore examined how changes in diastolic (model 2) and systolic (model 3) blood pressure during the placebo and yohimbine conditions impacted the relationship between opioid craving and seeking within-cluster. As in the first model, we person-centered the predictors, such that the regression coefficients captured the effect of opioid craving and diastolic and systolic blood pressure given their mean levels of all three across experimental conditions. We also adjusted for small sample size and violations in heteroscedasticity of the residuals described above. Lastly, when moderations were significant, we examined how changes to diastolic and/or systolic blood pressure affected the relationship between opioid craving and seeking using simple slopes and Johnson-Neyman regions of significance analyses (Preacher et al. 2006).

Results

T-tests revealed no differences in the mean number of years participants reported using heroin, percent change in opioid craving from baseline to 3.7 hr, diastolic and systolic blood pressure measured at baseline and 3.7 hours, and drug breakpoint scores across studies (see **Table 1** for results).

Table 2 includes results for the three multilevel moderation models. The first two-level moderation (model 1) tested the relationship between opioid craving and drug breakpoint and whether the relationship differed as a function of yohimbine nested within participants. The ICC (.74) indicated considerable between-person variance. The main effects of opioid craving (*B*=887.61, *95% CI* [-1606.24, 3381.45], *p*=.377) and yohimbine (*B*=776.38, *95% CI* [-176.23, 1728.99], *p*=.104) within person were insignificant. **Figure 1** illustrates that the moderation was significant: Greater increase in heroin craving from a person's mean level was associated with higher opioid breakpoint during the yohimbine but not placebo condition (*B*=4693.11, *95% CI*[251.72, 9134.50], *p*=.041). The fixed effects explained 12.0% of variance in drug breakpoint.

A simple slopes analysis revealed that the slope of the relationship between opioid craving and seeking was not significant during yohimbine (*B*=3234.16 (1632.09), *t*=1.98, *p*=.063), placebo (*B*=-1458.95 (906.34), *t*=-1.61, *p*=.128) or across conditions (*B*=887.61 (892.61), *t*=0.99, *p*=.341).

In model 2, we substituted experimental condition for person-centered diastolic blood pressure as the moderator. Like in model 1, the ICC indicated large between-person variance (.73). Results revealed that opioid craving (*B*=929.91, *95% CI*[-1210.04, 3069.85], *p*=.291), diastolic blood pressure (*B*=13.73, *95% CI* [-98.34, 125.80], *p*=.792), nor their interaction (*B*=63.72, *95% CI* [-297.94, 425.39], *p*=.688) were significantly related to opioid seeking.

Lastly, in model 3, we examined the moderating effect of person-centered systolic blood pressure on the relationship between opioid craving and seeking. Similar to models 1 and 2, there was a high degree of between-person variance (ICC=.72) in model 3. Neither craving nor systolic blood pressure were significantly associated with drug breakpoint (*B*=586.78, *95% CI* [-1052.16, 2225.71], *p*=.383; *B*=17.22, *95% CI* [-29.01, 63.44], *p*=.428 respectively). Consistent with model 1, systolic blood pressure significantly moderated the relationship between opioid craving and seeking, such that an increase in systolic blood pressure from a person's mean level strengthened the relationship between opioid craving and seeking for that person (*B*=141.13, *95% CI* [1.17, 281.09], *p*=.049). The fixed effects explained 10.5% of variance in drug breakpoint.

As depicted in **Figure 2**, simple slopes analysis revealed that opioid craving positively related to seeking when the change in systolic blood pressure was one standard deviation above the mean (*B*=2610.58 (998.49), *t*=2.61, *p*=.016). The slope was not significant when change to systolic blood pressure was one standard deviation below the mean (*B*=-1242.27 (978.51), *t*=-1.27, *p*=.222) nor at the mean (*B*=684.15 (602.60), *t*=1.14, *p*=.273). More precisely, simple slopes were significant when systolic blood pressure increased 5.88 mmHg above the individual's mean. The lower boundary of the Johnson-Neyman region, -38.29, fell outside the observed range of values and is therefore not interpretable. Values below 5.88 and within the observed range (-21.2 and 5.88) were insignificant (**Figure 3**).

Discussion

People affected by OUD report disruptive opioid craving and repeated return to opioid use despite negative mental and physical health and social consequences (MacLean et al. 2019). Although it is often assumed that craving precipitates drug use, research has not established when craving leads to seeking/use. Stress-reactivity has been proposed as a key mechanism in the cycle of addiction (Cleck and Blendy 2008; Greenwald 2018) and has been linked with stronger opioid craving (MacLean et al. 2019; Marlatt and Donovan 2005; Preston et al. 2017). Further, preclinical research has demonstrated a relationship between stress-exposure and opioid seeking/self-administration behaviors (Kamens et al. 2023). However, the relationship between self-reported stress and drug use is only partially supported in humans (MacLean et al. 2019).

This study tested whether experimental physiological stress induced by yohimbine, a CNS-penetrant noradrenergic activator, moderates the association between opioid craving and seeking behavior in people who use heroin regularly. As hypothesized, yohimbine significantly moderated the relationship between craving and seeking. Furthermore, when systolic blood pressure increased relative to the person's mean, opioid craving was significantly related to drug-seeking behavior, providing support for physiological stress as a link between drug craving and seeking. In contrast, increased diastolic blood pressure did not moderate the relationship between opioid craving and seeking. The specific moderating role of systolic, but not diastolic, pressure is noteworthy. First, various psychological and physiological stressors differ in their engagement of sympathetic and parasympathetic mechanisms (Koriakina et al. 2026; Moses et al. 2023). In each source study contributing to this analysis, yohimbine produced a reliable, sustained increase in blood pressure whereas heart rate did not increase (Greenwald et al. 2013; Greenwald et al. 2024b). Thus, heart rate change was not explored here as a moderator of the craving/seeking relationship. Second, extensive experimental research has linked task-based increases in systolic (but not diastolic) blood pressure and/or cardiac stroke volume to behavioral mobilization proportional to performance demand and/or outcome importance, i.e. motivational intensity (Richter et al. 2016). In this paradigm, blood pressure elevation induced by yohimbine may support increased drug-motivational intensity (greater progressive ratio responding); thus, yohimbine's effect on systolic pressure may create a sort of "physiological glue" that binds opioid craving (anticipation) and effortful seeking behavior (mobilization) to earn drug reinforcement. Notably, yohimbine has been found to produce a relative increase in cerebral blood flow in brain regions underlying addictive motivation including the medial frontal cortex, insula and thalamus, and in motor control regions including the cerebellum (Cameron et al. 2000). Also, recent evidence indicates that acute stress exposure can fragment brain-modular communication (i.e. reduce connectivity between the default mode, salience, and central executive networks) (Braun et al. 2026). One possibility for future testing is that, under normal conditions (e.g. placebo in this study), craving and seeking behavior could remain independent due to 'checks and balances' in network communication (e.g., executive > salience network); whereas stress-induced disaggregation of network connectivity could disinhibit this process, leading to a more automated pathway that connects drug craving and seeking.

In this study, yohimbine was used as a proxy for stress-induced noradrenergic activity. Noradrenaline is released during opioid withdrawal and is a stressful event that results in somatic and motivational symptoms, including an increase in opioid craving (Solecki et al. 2019). This is why, in each study, participants were stabilized on moderate-dose buprenorphine, and we found that this approach mitigated opioid withdrawal as a tonic source of noradrenergic activation, so that the direct phasic effect of yohimbine could be isolated (Greenwald et al. 2013; Greenwald et al. 2024b). Given noradrenaline's broader role in learning and memory, the release of LC noradrenaline during withdrawal (which chronic heroin users repeatedly experience) or during stress-exposure may facilitate instrumental learning, such that cumulative experiences of withdrawal and stress link opioid craving and seeking.

Another consideration is that, in the CNS, yohimbine mimics noradrenaline activation so it may have reactivated an emotionally laden sense memory in which craving and seeking are strongly associated with each other. Yohimbine-induced noradrenergic signaling is the interoceptive context cue binding the stimulus and behavioral response. This supports the idea that noradrenaline activity, part of the physiological stress response, facilitates return to use, regardless of withdrawal symptoms. Indeed, Greenwald et al. (2024b) observed a dose-dependent relationship between noradrenergic/glucocorticoid stimulation (i.e., stress-exposure) and opioid seeking in participants with elevated basal HPA-axis function. Moreover, Biernacki et al. (2020) found that opioid craving mediated the relationship between perceived stress and opioid use over eight outpatient weeks in people with OUD. In that study, participants with greater LC noradrenergic function and integrity determined from high-resolution neuromelanin-sensitive MRI, reported stronger craving during exposure to naturalistic stressors, which suggests that LC noradrenaline sensitization may play a role in the relationship between stress, craving and use (Biernacki et al. 2020).

Our methodology also allowed us to isolate the relationship between craving and seeking within person. The results suggest that increases in craving may be associated with greater drug seeking, given a person's average craving level, when exposed to an interoceptive stressor. This is important because research suggests that people who use drugs frequently report stronger cravings than those who use more sporadically despite reporting equivalent levels of stress (Panlilio et al. 2021). Panlilio et al. (2021) also found that craving temporally preceded seeking in participants who used regularly or rarely, but not sporadically. It may be that the unclear relationship between drug craving and seeking is explained by individual and contextual differences in stress reactivity (Preston and Epstein 2011; Preston et al. 2009; Preston et al. 2018).

This study focused on physiological stress, rather than perceived or psychological stress. Associations between physiological and psychological stress are inconsistent (e.g., Cohen et al. 2000; Hjortskov et al. 2004; Lackschewitz et al. 2008; Schlotz et al. 2008). Therefore, a limitation of this study is that we did not examine whether subjective ratings of stress similarly moderate the relationship between craving and use. Future studies could examine how perception of physiological stress contributes to this relationship. Using ecological momentary assessment, Preston et al. (2018) found that craving preceded drug use, but it was less clear whether perceived stress increased prior to reported drug use. It may be

that involvement of LC noradrenaline is key to the association between craving and seeking and that noradrenergic activation does not always accompany perceived stress. The importance of noradrenaline may be due to its role in opioid withdrawal and consolidating memories of withdrawal-induced cravings and subsequent use. Additionally, the experience of an increase in blood pressure and/or heart rate may serve as additional reminders of opioid withdrawal. Future research should incorporate ratings of stress, negative emotion and interoceptive awareness to examine the extent to which appraisal of physiological stress plays a role in the relationship between opioid craving and seeking.

Another limitation of the study is that it did not establish a directional relationship between stress, opioid craving and seeking. The positive association between opioid craving and drug seeking was stronger in the presence of physiological stress, but it cannot be unequivocally established that stress precipitated craving which then *led* to seeking. This secondary data analysis did not examine the role of opioid dose. Instead, it averaged across hydromorphone doses to make cross-study analysis possible. Future studies should examine whether opioid unit dose interacts with yohimbine to moderate the relationship between craving and seeking. Given the small sample size and large standard errors, all results should be interpreted with caution.

Results of this study indicate a significant stress-moderated relationship between opioid craving and drug seeking that is relevant to the treatment of OUD. Stress, craving and use are all associated with early dropout from treatment (MacLean et al. 2019). Pharmacological interventions, like clonidine, that attenuate the physiological stress response have been shown to lengthen abstinence duration and partially decouple stress from craving (Kowalczyk et al. 2015). Providers can also work with patients to bring awareness to the relationship between stress, craving and use, and how that relationship shows up in patients' daily lives. With that recognition, counselors can assist patients with reducing stress-exposure where possible and learning and implementing emotion regulation skills to disrupt stress-induced and craving-fueled drug seeking.

Declarations

Funding

NIH R01 DA015462 (MKG) from the National Institute on Drug Abuse, the Gertrude Levin Endowed Chair in Addiction and Pain Biology (MKG), and the Michigan Department of Health and Human Services (Helene Lycaki/Joe Young, Sr. funds), supported this research. Funding sources had no role in the design or conduct of this study, nor in the preparation of this manuscript.

Conflicts of interest

Dr. Greenwald previously received compensation as a consultant and speaker for Indivior Inc., unrelated to this study. Indivior indirectly provided active and placebo buprenorphine tablets for the source studies through a materials transfer agreement with Research Triangle Institute, but played no role in the design, conduct, analysis, or publication of the study.

Ethics approval

The Wayne State University IRB approved all procedures for the two source studies, which were registered on ClinicalTrials.gov (NCT00684840, NCT01536925).

Consent

Informed consent was obtained from all individual participants included in the study. All participants consented to have their anonymized data published.

Data availability

Data will be made available upon reasonable request.

CRediT authorship contribution statement

Nicole Kouri: Conceptualization, Formal analysis, Visualization, Writing – original draft and editing. **Mark Greenwald**: Funding acquisition, Project administration, Conceptualization, Methodology, Supervision, Data curation, Validation, Visualization, Formal analysis, Writing – original draft & editing.

References

1. Aston-Jones G, Kalivas PW (2008) Brain norepinephrine rediscovered in addiction research. Biol Psychiatry 63(11):1005–1006. https://doi.org/10.1016/j.biopsych.2008.03.016
2. Bates D, Mächler M, Bolker B, Walker S (2015) Fitting linear mixed-effects models using lme4. J Stat Softw 67(1):1–48. https://doi.org/10.18637/jss.v067.i01
3. Bell RM, McCaffrey DF (2002) Bias reduction in standard errors for linear regression with multi-stage samples. Surv Methodol 28(2):169–182 Statistics Canada, Catalogue 12-001-XPB
4. Biernacki K, Bonagura D, Wengler K, Cassidy C, Horga G, Konova A (2020) How do stress and craving lead to relapse in opioid use disorder? Determining sensitization effects in the locus coeruleus norepinephrine system in humans. Biol Psychiatry 87(9):S182–S183. https://doi.org/10.1016/j.biopsych.2020.02.479
5. Biernacki K, Lopez-Guzman S, Messinger JC, Banavar NV, Rotrosen J, Glimcher PW, Konova AB (2022) A neuroeconomic signature of opioid craving: how fluctuations in craving bias drug-related and nondrug-related value. Neuropsychopharmacology 47(8):1440–1448. https://doi.org/10.1038/s41386-021-01248-3
6. Boyett B, Wiest K, McLeod LD, Nelson LM, Bickel WK, Learned SM, Heidbreder C, Fudala PJ, Le Moigne A, Zhang Y (2021) Assessment of craving in opioid use disorder: psychometric evaluation and predictive validity of the opioid craving VAS. Drug Alcohol Depend 229:109057. https://doi.org/10.1016/j.drugalcdep.2021.109057
7. Braun J, Patel M, Woods W, Keatch C, Lambert E, Kameneva T (2026) Acute stress induces coordinated reorganization across interacting brain networks. J Appl Physiol 140:1311–1319.

https://doi.org/10.1152/japplphysiol.00584.2025

8. Breton-Provencher V, Drummond GT, Sur M (2021) Locus coeruleus norepinephrine in learned behavior: anatomical modularity and spatiotemporal integration in targets. Front Neural Circuits 15:638007. https://doi.org/10.3389/fncir.2021.638007
9. Cameron OG, Zubieta JK, Grunhaus L, Minoshima S (2000) Effects of yohimbine on cerebral blood flow, symptoms, and physiological function in humans. Psychosom Med 62(4):549–559. https://doi.org/10.1097/00006842-200007000-00014
10. Cleck JN, Blendy JA (2008) Making a bad thing worse: adverse effects of stress on drug addiction. J Clin Investigat 118(2):454–461. https://doi.org/10.1172/JCI33946
11. Cohen S, Hamrick N, Rodriguez MS, Feldman PJ, Rabin BS, Manuck SB (2000) The stability of and intercorrelations among cardiovascular, immune, endocrine, and psychological reactivity. Ann Behav Med 22(3):171–179. https://doi.org/10.1007/BF02895111
12. Davis WM, Smith SG, Khalsa JH (1975) Noradrenergic role in the self-administration of morphine or amphetamine. Pharmacol Biochem Behav 3:477–484. https://doi.org/10.1016/0091-3057(75)90059-3
13. Doxey JC, Lane AC, Roach AG, Virdee NK (1984) Comparison of the alpha- adrenoceptor antagonist profiles of idazoxan (RX 781094), yohimbine, rauwolscine and coynanthine. Naunyn-Schmeidebergs Arch Pharmacol 325:136–144. https://doi.org/10.1007/BF00506193
14. Enders CK, Tofighi D (2007) Centering predictor variables in cross-sectional multilevel models: a new look at an old issue. Psychol Methods 12(2):121–138. https://doi.org/10.1037/1082-989X.12.2.121
15. First MB, Spitzer RL, Gibbon M, Williams JBW (1996) Structured Clinical Interview for DSM–IV Axis Disorders—Patient Edition (SCID-I/P, Version 2.0). New York State Psychiatric Institute, Biometrics Research, Department, New York
16. Goldberg MR, Robertson D (1983) Yohimbine: a pharmacological probe for study of the α_2-adrenoceptor. Pharmacol Rev 35:143–180
17. Greenwald MK (2018) Anti-stress neuropharmacological mechanisms and targets for addiction treatment: a translational framework. Neurobiol Stress 9:84–104. https://doi.org/10.1016/j.ynstr.2018.08.003
18. Greenwald MK, Comer SD, Fiellin DA (2014) Buprenorphine maintenance and *mu*-opioid receptor availability in the treatment of opioid use disorder: implications for clinical use and policy. Drug Alcohol Depend 144:1–11. https://doi.org/10.1016/j.drugalcdep.2014.07.035
19. Greenwald MK, Lundahl LH, Steinmiller CL (2013) Yohimbine increases opioid-seeking behavior in heroin-dependent, buprenorphine-maintained individuals. Psychopharmacology 225:811–824. https://doi.org/10.1007/s00213-012-2868-9
20. Greenwald MK, Sogbesan T, Moses TEH (2024a) Relationship between opioid cross-tolerance during buprenorphine stabilization and return to use during buprenorphine dose tapering. Psychopharmacology 241:1151–1160. https://doi.org/10.1007/s00213-024-06549-1

21. Greenwald MK, Woodcock EA, Moses TEH, Lundahl LH (2024b) Baseline cortisol level modulates stress-induced opioid-seeking behavior. Neurobiol Stress 33:100684. https://doi.org/10.1016/j.ynstr.2024.100684
22. Hjortskov N, Rissén D, Blangsted AK, Fallentin N, Lundberg U, Søgaard K (2004) The effect of mental stress on heart rate variability and blood pressure during computer work. Eur J Appl Physiol 92(1):84–89. https://doi.org/10.1007/s00421-004-1055-z
23. Huang F, Zhang B (2022) CR2: Compute cluster robust standard errors with degrees of freedom adjustments. R package version 0.1.1. https://CRAN.R-project.org/package=CR2
24. Hyman SM, Fox H, Hong KIA, Doebrick C, Sinha R (2007) Stress and drug-cue-induced craving in opioid-dependent individuals in naltrexone treatment. Exp Clin Psychopharmacol 15(2):134–143. https://doi.org/10.1037/1064-1297.15.2.134
25. Kamens HM, Flarend G, Wickenheisser A, Horton WJ, Cavigelli S (2023) The effect of stress on opioid addiction-related behaviors: a review of the preclinical literature. Exp Clin Psychopharmacol 31(2):523–540. https://doi.org/10.1037/pha0000588
26. Kleinknecht RA, Kleinknecht EE, Sawchuk CN, Lee T, Lohr JM (1999) Medical Fear Survey: psychometric properties. Behav Ther 22:109–119
27. Koriakina M, Lukov M, Nikishkina U, Kirsanov A, Dmitrieva E, Blagovechtchenski E (2026) Social and physiological stress elicit divergent psycho-physiological dynamics and motor cortex activation. Front Psychol 17:1760772. https://doi.org/10.3389/fpsyg.2026.1760772
28. Kowalczyk WJ, Phillips KA, Jobes ML, Kennedy AP, Ghitza UE, Agage DA, Schmittner JP, Epstein DH, Preston KL (2015) Clonidine maintenance prolongs opioid abstinence and decouples stress from craving in daily life: a randomized controlled trial with ecological momentary assessments. Am J Psychiatry 172(8):760–767. https://doi.org/10.1176/appi.ajp.2014.14081014
29. Lackschewitz H, Hüther G, Kröner-Herwig B (2008) Physiological and psychological stress responses in adults with attention-deficit/hyperactivity disorder (ADHD). Psychoneuroendocrinology 33(5):612–624. https://doi.org/10.1016/j.psyneuen.2008.01.016
30. MacLean RR, Armstrong JL, Sofuoglu M (2019) Stress and opioid use disorder: a systematic review. Addict Behav 98:106010. https://doi.org/10.1016/j.addbeh.2019.05.034
31. Maldonado R (1997) Participation of noradrenergic pathways in the expression of opiate withdrawal: biochemical and pharmacological evidence. Neurosci Biobehav Rev 21(1):91–104. https://doi.org/10.1016/0149-7634(95)00061-5
32. Marlatt GA, Donovan DM (eds) (2005) Relapse prevention: Maintenance strategies in the treatment of addictive behaviors. Guilford Press, New York
33. McHugh RK, Fitzmaurice GM, Carroll KM, Griffin ML, Hill KP, Wasan AD, Weiss RD (2014) Assessing craving and its relationship to subsequent prescription opioid use among treatment-seeking prescription opioid dependent patients. Drug Alcohol Depend 145:121–126. https://doi.org/10.1016/j.drugalcdep.2014.10.002

34. Monroe SC, Radke AK (2023) Opioid withdrawal: role in addiction and neural mechanisms. Psychopharmacology 240(7):1417–1433. https://doi.org/10.1007/s00213-023-06370-2
35. Moses TEH, Gray E, Mischel N, Greenwald MK (2023) Effects of neuromodulation on cognitive and emotional responses to psychosocial stressors in healthy humans. Neurobiol Stress 22:100515. https://doi.org/10.1016/j.ynstr.2023.100515
36. Nestler EJ, Alreja J, Aghajanian GK (1999) Molecular control of locus coeruleus neurotransmission. Biol Psychiatry 46(9):1131–1139. https://doi.org/10.1016/s0006-3223(99)00158-4
37. Panlilio LV, Stull SW, Bertz JW, Burgess-Hull AJ, Lanza ST, Burtis BL, Phillips KA, Epstein DH, Preston KL (2021) Beyond abstinence and relapse II: momentary relationships between stress, craving, and lapse within clusters of patients with similar patterns of drug use. Psychopharmacology 238(6):1513–1529. https://doi.org/10.1007/s00213-021-05782-2
38. Preacher KJ, Curran PJ, Bauer DJ (2006) Computational tools for probing interactions in multiple linear regression, multilevel modeling, and latent curve analysis. J Educ Behav Stat 31(4):437–448. https://doi.org/10.3102/10769986031004437
39. Preston KL, Epstein DH (2011) Stress in the daily lives of cocaine and heroin users: relationship to mood, craving, relapse triggers, and cocaine use. Psychopharmacology 218(1):29–37. https://doi.org/10.1007/s00213-011-2183-x
40. Preston KL, Kowalczyk WJ, Phillips KA, Jobes ML, Vahabzadeh M, Lin J-L, Mezghanni M, Epstein DH (2017) Context and craving during stressful events in the daily lives of drug-dependent patients. Psychopharmacology 234:2631–2642. https://doi.org/10.1007/s00213-017-4663-0
41. Preston KL, Kowalczyk WJ, Phillips KA, Jobes ML, Vahabzadeh M, Lin J-L, Mezghanni M, Epstein DH (2018) Before and after: craving, mood, and background stress in the hours surrounding drug use and stressful events in patients with opioid-use disorder. Psychopharmacology 235:2713–2723. https://doi.org/10.1007/s00213-018-4966-9
42. Preston KL, Vahabzadeh M, Schmittner J, Lin J-L, Gorelick DA, Epstein DH (2009) Cocaine craving and use during daily life. Psychopharmacology 207(2):291–301. https://doi.org/10.1007/s00213-009-1655-8
43. Pustejovsky JE, Tipton E (2018) Small-sample methods for cluster-robust variance estimation and hypothesis testing in fixed effects models. J Bus Econ Stat 36(4):672–683. https://doi.org/10.1080/07350015.2016.1247004
44. Richter M, Gendolla GHE, Wright RA (2016) Three decades of research on motivational intensity theory: what we have learned about effort and what we still don't know. In: Elliot AJ (ed) Advances in Motivation Science, vol 3. Elsevier Academic, pp 149–186. https://doi.org/10.1016/bs.adms.2016.02.001
45. Schlotz W, Kumsta R, Layes I, Entringer S, Jones A, Wüst S (2008) Covariance between psychological and endocrine responses to pharmacological challenge and psychosocial stress: a question of timing. Psychosom Med 70(7):787–796. https://doi.org/10.1097/PSY.0b013e3181810658

46. Schuster CR, Greenwald MK, Johanson C-E, Heishman SJ (1995) Measurement of drug craving during naloxone-precipitated withdrawal in methadone maintained volunteers. Exp Clin Psychopharmacol 3:424–431. https://doi.org/10.1037/1064-1297.3.4.424
47. Shaham Y, Highfield D, Delfs J, Leung S, Stewart J (2000) Clonidine blocks stress-induced reinstatement of heroin seeking in rats: an effect independent of locus coeruleus noradrenergic neurons. Eur J Neurosci 12:292–302. https://doi.org/10.1046/j.1460-9568.2000.00899.x
48. Solecki WB, Kus N, Gralec K, Klasa A, Pradel K, Przewlocki R (2019) Noradrenergic and corticosteroid receptors regulate somatic and motivational symptoms of morphine withdrawal. Behav Brain Res 360:146–157. https://doi.org/10.1016/j.bbr.2018.11.041
49. Stine SM, Southwick SM, Petrakis IL, Kosten TR, Charney DS, Krystal JH (2002) Yohimbine-induced withdrawal and anxiety symptoms in opioid-dependent patients. Biol Psychiatry 51(8):642–651. https://doi.org/10.1016/s0006-3223(01)01292-6
50. Tsui JI, Anderson BJ, Strong DR, Stein MD (2014) Craving predicts opioid use in opioid-dependent patients initiating buprenorphine treatment: a longitudinal study. Am J Drug Alcohol Abuse 40(2):163–169. https://doi.org/10.3109/00952990.2013.848875
51. Tully K, Bolshakov VY (2010) Emotional enhancement of memory: how norepinephrine enables synaptic plasticity. Mol Brain 3:15. https://doi.org/10.1186/1756-6606-3-15
52. Urits I, Patel A, Zusman R, Virgen CG, Mousa M, Berger AA et al (2020) A comprehensive update of lofexidine for the management of opioid withdrawal symptoms. Psychopharmacol Bull 50(3):76–96. https://doi.org/10.64719/pb.4615
53. Van Bockstaele EJ, Bajic D, Proudfit H, Valentino RJ (2001) Topographic architecture of stress-related pathways targeting the noradrenergic locus coeruleus. Physiol Behav 73(3):273–283. https://doi.org/10.1016/s0031-9384(01)00448-6
54. Ventura R, Alcaro A, Puglisi-Allegra S (2005) Prefrontal cortical norepinephrine release is critical for morphine-induced reward, reinstatement and dopamine release in the nucleus accumbens. Cereb Cortex 15:1877–1886. https://doi.org/10.1093/cercor/bhi066
55. Wang X, Cen X, Lu L (2001) Noradrenaline in the bed nucleus of the stria terminalis is critical for stress-induced reactivation of morphine-conditioned place preference in rats. Eur J Pharmacol 432(2–3):153–161. https://doi.org/10.1016/s0014-2999(01)01487-x
56. Weinshenker D, Schroeder JP (2007) There and back again: a tale of norepinephrine and drug addiction. Neuropsychopharmacology 32:1433–1451. https://doi.org/10.1038/sj.npp.1301263
57. Yaremych HE, Preacher KJ, Hedeker D (2021) Centering categorical predictors in multilevel models: best practices and interpretation. Psychol Methods 28(3):613–630. https://doi.org/10.1037/met0000434
58. Zachary RA (1991) Shipley Institute of Living Scale: Revised Manual. Western Psychological Services, Los Angeles, CA

Tables

Tables 1 and 2 are available in the supplementary files section

Figures

Figure 1

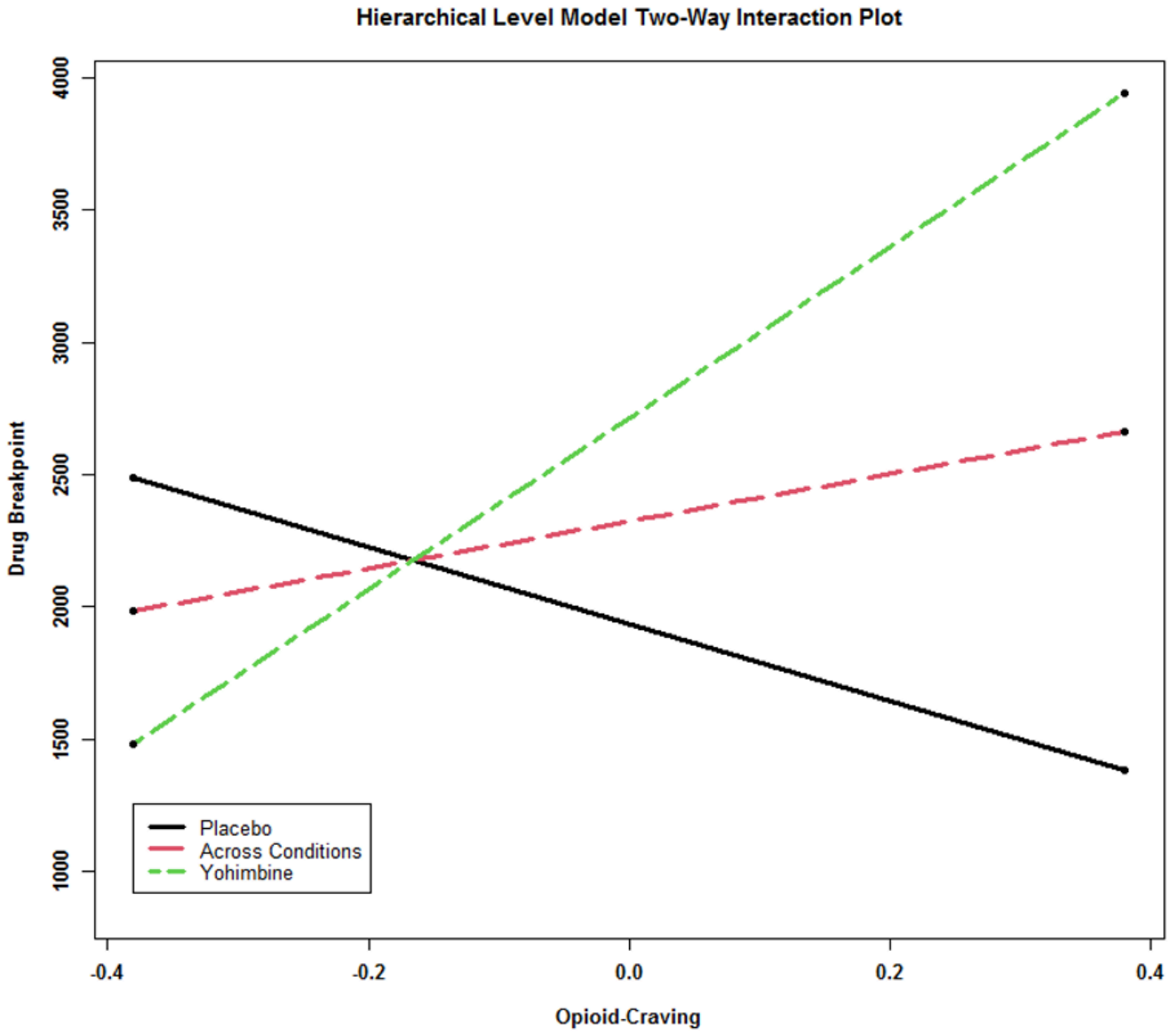


Figure 1

Hierarchical level model two-way interaction plot showing the moderating effect of yohimbine on the relationship between opioid craving and seeking. *Notes:* Mean plot illustrating the interaction of opioid craving and experimental conditions. The relationship between opioid craving and seeking significant

differed between conditions but were not significantly different from zero within the yohimbine condition (green), the placebo condition (black), or across experimental conditions (red).

Figure 2

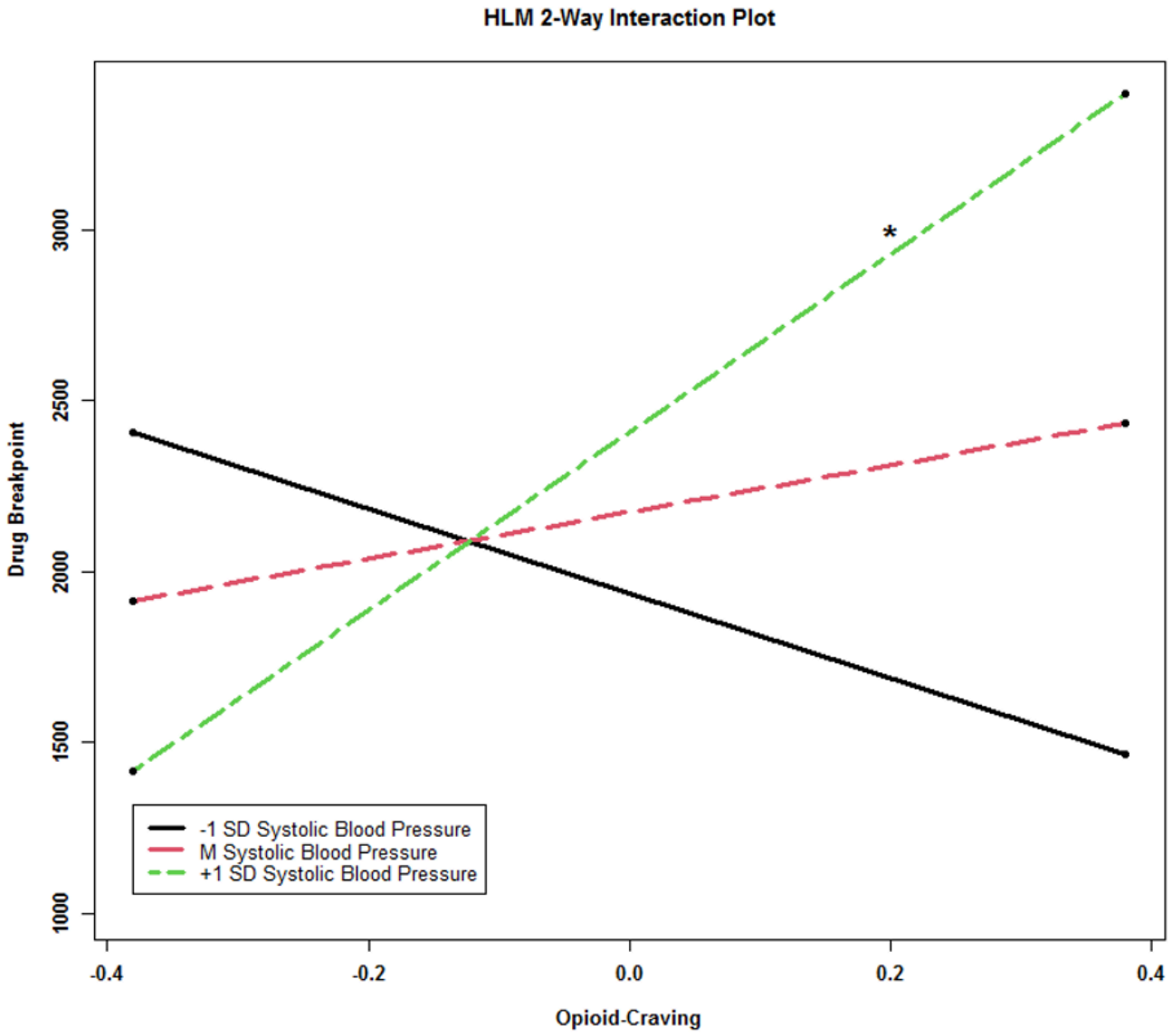


Figure 2

A hierarchical level model two-way interaction plot showing the moderating effect of systolic blood pressure on the relationship between opioid craving and seeking. *Notes.* Mean plot illustrating the interaction of opioid craving and systolic blood pressure. Opioid craving and seeking were positively associated as systolic blood pressure increased (green; asterisk denotes significant slope).

Figure 3

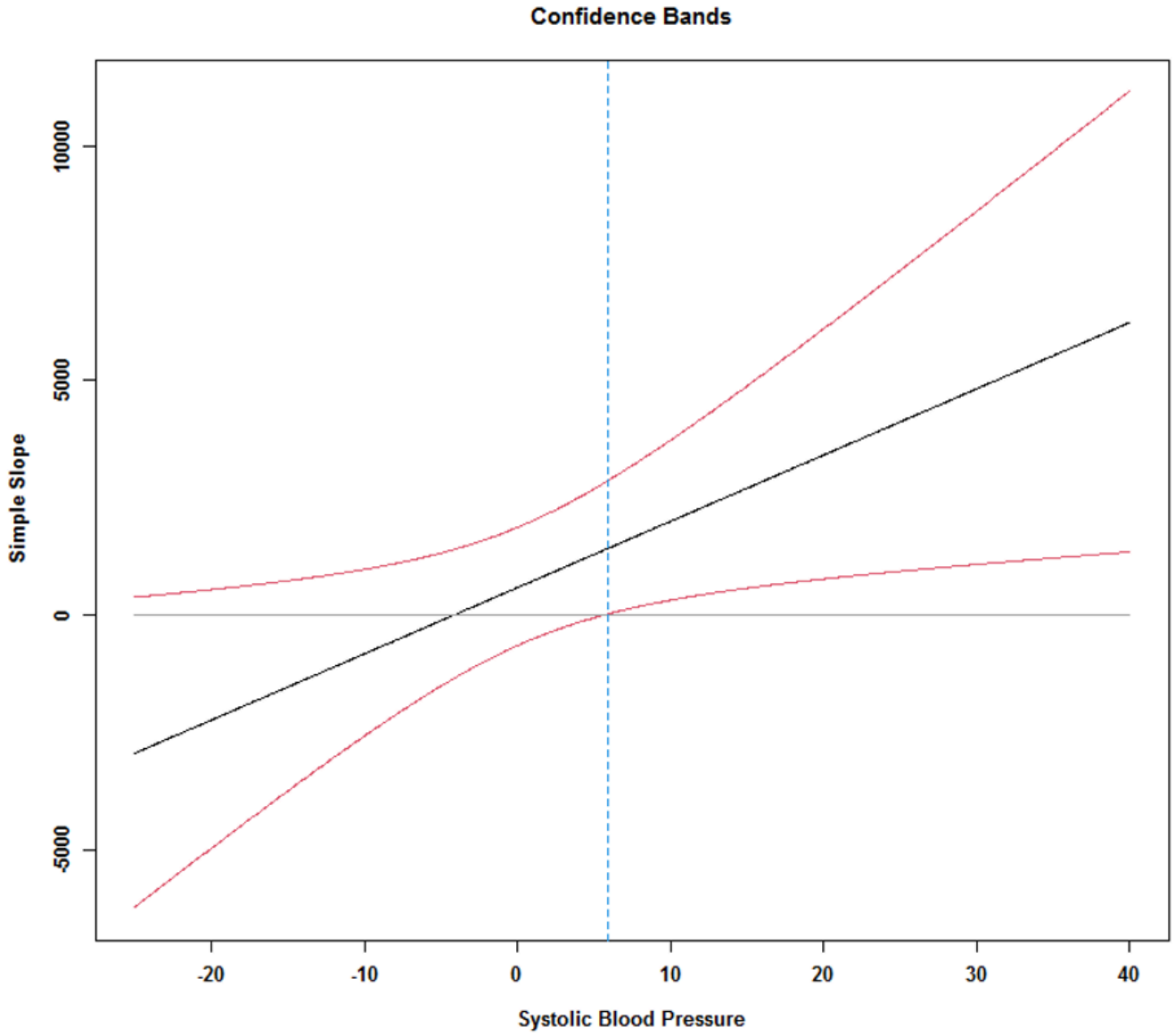


Figure 3

The region of significance and 95% confidence bands for observed sample values of systolic blood pressure. *Notes.* The *x*-axis represents change to systolic blood pressure relative to the person-centered mean and the *y*-axis represents conditional values of opioid breakpoint regressed onto opioid craving. The simple slope of opioid breakpoint regressed onto opioid craving is significantly different from zero for change values to the right of the dotted line, because the confidence bands do not include simple slopes of zero.

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- Tables.docx