HHS Public Access

Author manuscript

Am J Drug Alcohol Abuse. Author manuscript; available in PMC 2018 September 27.

Published in final edited form as:

Am J Drug Alcohol Abuse. 2018 ; 44(5): 512–523. doi:10.1080/00952990.2018.1454934.

Sex Differences in Daily Life Stress and Craving in Opioid-dependent Patients

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Abstract

Background: Responses to stress and drug craving differ between men and women. Differences in the momentary experience of stress in relation to craving are less well-understood.

Objectives: Using ecological momentary assessment (EMA), we examined sex differences in real-time in two areas: 1) causes and contexts associated with stress, and 2) the extent to which stress and drug cues are associated with craving.

Methods: Outpatients on opioid-agonist treatment (135 males, 47 females) reported stress, craving, and behavior on smartphones for 16 weeks. They initiated an entry each time they felt more stressed than usual (stress event) and made randomly prompted entries 3 times/day. In stress-event entries, they identified the causes and context (location, activity, companions), and rated stress and craving severity.

Results: The causes reported for stress events did not differ significantly by sex. Women reported arguing and being in a store more often during stress events, and men reported working more often during stress events, compared to base rates (assessed via random prompts). Women showed a greater increase in opioid craving as a function of stress ($p<0.0001$), and had higher stress ratings in the presence of both stress and drug cues relative to men ($p<0.01$). Similar effects were found for cocaine craving in men ($p<0.0001$).

Conclusion: EMA methods provide evidence based on real-time activities and moods that opioid-dependent men and women experience similar contexts and causes for stress but differ in stress- and cue-induced craving. Assessment of both sex and person-level differences may help to develop better tailored treatments.

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Keywords

Ecological momentary assessment; sex differences; opioid dependence; stress; craving; cue-induced craving

Introduction

Differences in the trajectory of substance use disorders (SUDs) in women versus men are well documented. Although more men than women use addictive drugs (1, 2), it has been suggested that women may progress to SUDs more quickly (3, 4), and tend to enter drug rehabilitation sooner (5). Women also experience shorter periods of drug abstinence (3), and more frequently report psychiatric, medical and employment problems related to drug use, while men report more legal and alcohol-related problems (5). Better understanding of the biological and cultural bases for these differing trajectories could lead to improved treatment and prevention in both women and men.

One area of potential differences is response to drug cues; drug cues, along with stress, are believed to play a major role in relapse (6, 7), and may affect men and women in different ways. Some studies have reported sex differences in self-reports of craving in response to various drug cues (8–11), but similar cue reactivity in men and women have also been observed (11–13). Studies on cue-induced brain activity have also shown mixed results for sex differences. Greater activation has been demonstrated in women after exposure to alcohol cues (9) and cocaine cues (13), but men have also shown more activity relative to women in response to cues related to alcohol (8) and cigarettes (14) as well as stress-related cues (9). Variations in experimental design, including types of cues, how they are presented, and the level of current substance use among participants may contribute to some conflicting findings.

Work in our laboratory suggests that men and women differ in their momentary experiences of drug cues. Using ecological momentary assessment (EMA), we have found that women report more cocaine craving in the presence of drug cues compared to when cues were absent; craving reported by men did not change as a function of cues (15). Participants were also asked to indicate the reason for their craving from a checklist developed from Marlatt and Gordon's relapse classification scheme (16). Multiple reasons for craving were endorsed more frequently by men than women, but none were endorsed more by women than men. One possible reason was that research used to develop the classification scheme was derived primarily from interviews with male drug users (16). A substantial gap remains, necessitating both more qualitative and quantitative research on women's experiences with drug craving and use.

In the present study, we extended our work to investigate possible sex differences in the influence of stress on drug use and craving. Stress is known to be a common precipitant of addiction and relapse; several theories of addiction suggest that substance use is a coping strategy for managing negative emotional states and enhancing mood (17–19). Some evidence of sex differences in stress responses related to drug craving and use has been reported. For example, abstinent cocaine-dependent women show greater brain activation in

corticostriatal-limbic regions in response to stress-related imagery relative to men (20). In female cigarette smokers, cortisol levels have been shown to be blunted in response to laboratory stressors, while blood pressure and subjective responses to the stressors were stronger compared to that of male smokers (21). Greater sensitivity to stressors or dysregulated modulation of stress may increase the likelihood of relapse.

We have previously reported on associations between stressful events and craving (22) as well as sex differences in triggers for drug craving and use (15), but as noted earlier, information on triggers more specific to women is lacking. Here we sought to test the hypotheses that 1) there are sex differences in the contexts and reasons for stress, as a potential trigger for craving, and 2) there are sex differences in the influence of daily stress and drug cue exposure on craving.

Methods

Participants:

The participants (N=226) were methadone- or buprenorphine-treated opioid-dependent polydrug users at a treatment-research clinic in Baltimore, MD. All were participating in a 46-week natural-history study of stress, geographical location, and drug use. Study candidates were evaluated with the Addiction Severity Index (ASI; 23) and the Diagnostic Interview Schedule (DIS IV; 24), and were given physical examinations and psychological testing. The main inclusion criteria were: age 18 to 75 years, physical dependence on opioids, and (due to the behavioral-geography focus of the parent study) residence in Baltimore City or one of the surrounding counties. The main exclusion criteria were: history of any DSM-IV psychotic disorder, bipolar disorder, or current Major Depressive Disorder; current dependence on alcohol or sedative-hypnotics; cognitive impairment precluding informed consent or valid self-report; conditions that preclude urine collection; or medical illness or medications that would compromise research participation. The Institutional Review Board of the National Institute on Drug Abuse Intramural Research Program approved the study, and all participants gave written informed consent.

Procedure:

Participants attended clinic five to seven days a week; methadone or buprenorphine was administered daily, and individual counseling was given weekly. Participants provided urine and breath samples under observation thrice weekly to test for the presence of opiates (codeine/morphine), buprenorphine, oxycodone, methadone, cocaine metabolite, amphetamines, benzodiazepines, barbiturates, cannabinoids, phencyclidine, and alcohol.

Participants' self-reported craving and mood were assessed by ecological momentary assessment (EMA). After two weeks of treatment, each participant was issued a device (e.g., smartphone) and trained in its use as an electronic diary (ED). For up to 16 weeks, the ED randomly prompted participants three times a day to answer a series of questions. Participants answered stress, craving, and mood questions, and reported whether drug cues were encountered in the hour before the prompt. Participants also initiated entries whenever they experienced a stressful event.

For the stress event entries, we asked participants to initiate an entry any time they felt "more stressed, overwhelmed, or anxious than usual". To quantify the event, participants rated "how bad was that feeling" on a 0–10 scale (0 = not bad at all; 10 = the worst you have ever felt). They also indicated what had caused the feeling by selecting from a list of: conflict with someone; had too much to do; problems with money; surroundings were unsafe or threatening; was inconvenienced; injury or health problem; legal problem; just started thinking about stressful things; or "other." For other entries, participants were asked to type in a description of the event. Participants also rated how much they craved opioids and cocaine on a 1 to 5 scale (1 = not at all; 5 = extremely), and reported whom they were with, what they were doing, and where they were from drop-down lists.

In randomly prompted entries, participants rated their stress level on a 1–5 scale (1 = not at all; 5 = extremely), and how much they craved opioids and cocaine and indicated whom they were with, what they were doing, and their location from drop-down lists. Participants were also asked to indicate if they had recently seen, been offered, or seen others using drugs, alcohol, or tobacco. The participants were paid $10 each week for completing at least 82% of random prompts (23 out of 28 possible), or were given a warning if they did not meet the criterion. If the participant did not meet the 82% completion criterion for 2 weeks after being warned, they were removed from the study and assisted with transfer into community-based addiction treatment.

Data Analysis:

Demographics and drug use history were compared between sexes with independent samples t-tests or chi-squares. We tested associations among variables using either general or generalized linear mixed models. In the first stage of our analyses, we used generalized linear mixed models (SAS Proc Glimmix) to test whether different reasons and contexts (companions, locations, and activities) for stress were more likely to be reported by men compared to women in stress events. Proc Glimmix was also used to test for differences in base rates of context reported in random prompts. Then we included both types of entry (stress event vs. random prompt) and sex as predictors of context. Contexts and reasons for stress were analyzed as dichotomous measures (being with friends vs. not being with friends).

In the second stage of our analyses, we used general linear mixed models (SAS Proc Mixed) to assess the relationship between stress severity (predictor variable) and craving (dependent variable), as well as to test the effects of sex, drug cues, and stress on craving. In the latter analyses, presence of drug cues and presence of stress (rating > 1) were dichotomized. We also examined how many participants conformed to the overall patterns of group-level sex differences to assess person-level heterogeneity in the data (25). Analyses on cocaine craving included only participants who reported past 30-day use or a history of regular use at intake, or who had any cocaine-positive urine specimens during the study.

In all of the mixed models, we used a first-order autoregressive error structure and a random intercept. Alpha was set at .05, two-tailed, for all analyses.

Results

Participants and EMA reporting and compliance

Data were collected between July 14, 2009 and June 4, 2015. Of 226 individuals who signed consent, 182 provided EMA data for at least two weeks (135 men, 47 women), 12 provided EMA data for less than two weeks, and 32 left the study before providing any EMA data. There were 33,885 total random prompts completed by men and 10,839 completed by women. Of the 182 participants who provided EMA data, there were 158 participants (87%; 114 men, 44 women) who reported at least one stress event entry for a total of 1,787 stress event entries (1,520 from men; 279 from women). The demographic and drug-use histories of all 182 participants who provided EMA data and the 158 who made stress event entries were similar; these results were previously published (22). Demographic characteristics did not differ between men and women; differences in drug use history as reported in the ASI were found, however (Table 1). Men reported a significantly greater number of years of heroin use, and cocaine route of administration also differed; more women reported smoking, and more men reported intravenous use. Years of heroin use was included in mixed models to assess relationships between stress and opioid and cocaine craving, and cocaine route of administration was included in mixed models on stress and cocaine craving.

Stress events

Across all stress event entries, the participants' mean (SEM) rating of "how bad" the stress event felt was 5.04 (0.07) on a 0–10 scale. There was no significant difference in stress event ratings between men and women [men, 5.07 (0.08); women, 4.8 (0.19)]. The reported reasons for stress are shown in Table 2. The most frequently endorsed reason for stress was interpersonal conflict, followed by just thinking about stressful things, money problems, having too much to do, being inconvenienced, "other", injury or health problems, legal problems, and unsafe surroundings. There were no differences between men and women in how often they reported each cause of stress, but men tended to report "having too much to do" more than women ($p=0.09$).

Context of stress events and background (random prompt) entries in men vs. women

The context, i.e., whom the participants were with, where they were, and what they were doing, at the time of the entry of the stressful events is shown in Table 3. Categories for location (abandominium/vacant home, church, shelter) and activities (hustling, copping, illegal activities) reported 10 or fewer times within the 1,747 total stress event entries are not included. The results of statistical comparison of the frequency of reports for individual items in stress events versus random prompt entries have been previously reported (22).

To assess base rates of reported contexts, we first looked at differences in random prompt entries. As shown in Table 3, several significant differences were found between men and women in their reported companions, locations, and activities. For companions, men reported being with no one, other family, friends, coworkers, acquaintances, and strangers more often than women did; women reported being with their spouse/partner, children, a person who uses, or a person with whom they used before more often than men did. For locations, men were more likely to report being at work, in a vehicle, at a store, or waiting

for a ride, bus or other transportation; women were more likely to report being at home. For activities, men were more likely to report arguing, thinking/planning, working, walking or riding somewhere, taking care of children or elders, shopping or running errands, being on the phone, listening to music, and waiting; women reported watching TV more often than men.

In stress event entries, men and women were generally similar in their reported companions, locations, and activities, with a few differences (Table 3). As in random prompts, men reported thinking/planning and waiting for a ride, bus or other transportation more often than women, and women reported being with someone with whom they used drugs before and with someone who uses drugs more often than men. Women were more likely to report being at a store during stress events, which was the reverse pattern seen in random prompts.

When sex and type of entry (stress event vs. random prompt) were both included in the model, there were significant sex x type of entry interactions for arguing [$F(1,155)=4.6$, $p<0.05$], being at work [$F(1,156)=4.1$, $p<0.05$], and being at a store [$F(1,156)=6.5$, $p<0.05$]. Men reported being at work and women reported arguing and being at a store more often during stress events compared to random prompts.

Stress and Craving

Opioid and cocaine craving ratings increased linearly across stress-severity ratings in relationship to background stress as assessed in random prompt entries [opioids: $F(1,554) = 1021.6$, $p<0.001$; cocaine, $F(1,491) = 346.6$, $p<0.001$]. This relationship was observed for both men and women [men: opioids, $F(1, 407)=781.8$, $p<0.0001$; cocaine, $F(1, 360)=235.0$, $p<0.0001$; women: opioids, $F(1, 143) = 305.6$, $p<0.0001$; cocaine, $F(1, 127) = 116.9$, $p<0.0001$]. There was also a sex x stress severity interaction on opioid craving, $F(4,550)=6.7$, $p<0.0001$, and on cocaine craving, $F(4, 403)=20.4$, $p<0.0001$. The increase in opioid craving as a function of stress was greater for women than men; whereas men showed a greater increase in cocaine craving as a function of stress (Figure 1).

In stress events, opioid and cocaine craving ratings also increased linearly across stress-severity ratings, as shown in Figure 2 [opioids: $F(1,130)=53.1$, $p<0.0001$; cocaine: $F(1, 117)=6.4$, $p<0.05$]. There was no main effect of sex on craving, but there was a sex x stress severity interaction for opioid craving, $F(9,120)=2.1$, $p<0.05$, and for cocaine craving, $F(7,75)=3.1$, $p<0.01$. When assessing men and women separately, men showed a linear increase in opioid craving, $F(1,110)=54.3$, $p<0.0001$, and cocaine craving, $F(1,100)=4.17$, $p<0.05$, with stress severity, but there was not enough data to determine a relationship between craving and stress in women (i.e., there were 10 or fewer stress events reported at each level of stress, on the 0–10 scale).

In random prompts, in which participants were asked about current exposure to drug cues, there was a significant sex x stress x cue interaction on opioid craving, $F(1, 140) = 7.6$, $p<0.01$ (Figure 3, top panel). Both men and women reported greater opioid craving when both stress and cues were also reported, but women showed a greater increase in craving in the presence of both stress and cues compared to either alone (see Figure 3). The main effects of cue, $F(1,170)=193.4$, $p<0.0001$, and stress, $F(1,176)=458.6$, $p<0.0001$, were also

significant, as well as all two-way interactions [stress x cue: $F(1,140)=80.2$, $p<0.0001$; sex x cue: $F(1,170)=7.2$, $p<0.01$; sex x stress: $F(1,176)=3.9$, $p<0.05$]; the main effect of sex was not significant.

For cocaine craving in random prompts, the main effects of cue, $F(1,125)=168.6$, $p<0.0001$, and stress, $F(1,127)=341.8$, $p<0.0001$, were significant, as well as the sex x stress interaction, $F(1,127)=61.0$, $p<0.0001$, and stress x cue interaction, $F(1,100)=5.8$, $p<0.05$. Men showed a greater increase in craving when both stress and cues were present, relative to women. There was neither a main effect of sex, nor a sex x stress x cue interaction.

A descriptive assessment of person-level differences in the random prompt reports of stress and craving was generally consistent with the above findings. A large proportion of participants had an absolute increase in mean opioid craving when they reported stress or drug cues, relative to craving when stress and cues were absent (stress: 49% of men, 57% of women; cue: 47% of men; 48% of women). Similar patterns were observed for cocaine craving (stress: 41% of men; 57% of women; cue: 41% of men; 35% of women). When both stress and cue were present, a plurality of participants showed an absolute increase in craving relative to craving in the presence of either stress or cues alone (opioids: 42% of men; 40% of women; cocaine: 47% of men; 45% of women).

These differences were not tested for statistical significance; their purpose was to show concretely the extent to which our model-based inferences apply to individual participants.

Discussion

Men and women did not differ on reported causes of stress, and showed few differences in reported context for stress. Differences were most apparent in the relationship between stress and craving in random prompts: women reported greater opioid craving with increases in stress compared to men, and also reported greater opioid craving when both stress and drug cues were present, whereas men reported higher cocaine craving in response to stress and cues.

Our participants were primarily opioid-dependent; not all participants were currently using cocaine (~25% were negative for cocaine throughout the experiment), but most reported a history of regular cocaine use. Consistent with this use history, ratings of cocaine craving were lower than those for opioid craving, but the relationship between cocaine craving and stress was significant. The more prominent effect of stress on cocaine craving in men was surprising, given the number of studies that have shown heightened craving in response to stress in women (26, 27). The differences seen between men and women here may be more representative of those who occasionally use cocaine or have previously used regularly. These relationships should be further studied in people with regular cocaine use or cocaine dependence to see if the pattern observed here may be more pronounced.

Stress event reports also showed differences in craving between men and women across stress severity, but the smaller number of stress reports by women across all possible ratings of stress (at least partly attributable to fewer female participants) did not allow for a complete analysis of sex differences. Men showed linear increases in opioid and cocaine

craving with increases in stress severity. Craving in women seems to peak at more moderate stress levels, but again, the averages for women shown in figure 2 are derived from a small number of participants (10 or fewer) and have large variability. In general, however, both men and women reported increases in opioid and cocaine craving with stress.

Although men and women in this study generally reported the same contexts and causes of stress, women were more likely to be with a person with whom they had used drugs, or who is still using drugs, regardless of whether it was during a stress event or a random prompt entry. A previous study found that women who inject heroin report that they are more influenced by social pressure and by their sexual partners who also inject heroin (28); they are also more likely to have been introduced to injection by their sexual partners (29). For the present study, we did not examine whether the participants used drugs while with a person they previously used with or who still uses. However, if these types of companions are present during times of greater stress, which is also highly related to craving, it is possible that women may be more likely to use as a result.

In addition to larger epidemiological reports, several studies have described sex differences in the characteristics of substance use disorders. In a sample of treatment-seeking opioid-dependent individuals, men more frequently reported legal and alcohol-related problems on the Addiction Severity Index at the initial intake visit, and women reported more problems related to drug use, employment, family, and mental and physical health (30). Women also reported significantly higher craving, although withdrawal symptoms did not differ between men and women (30). Reasons for drug use also tend to differ between men and women. Men report using substances primarily for positive rewarding effects, while women often use substances, including opioids, to cope with negative emotions and interpersonal stress (31). In the present study, women were more likely to report arguing during stress events relative to random prompts, which may be an interpersonal stressor that could potentially increase craving or use (which we did not assess here). These differences in experiences related to substance use disorders can be used to modify treatment approaches appropriately.

Across various substances, men and women also exhibit differences in response to substance-related cues and stress or negative mood. For example, women who are social drinkers tend to report a lower incentive value of alcohol following negative mood and stress compared to men (8, 32), whereas the reverse sex difference is reported in people diagnosed with alcohol use disorder (33). Cocaine-dependent women report greater feelings of anxiety and sadness in response to stress, but the same or lower HPA-axis reactivity as male cocaine or nicotine users (34, 35). These different responses to stress and cue-related craving may be partly attributable to hormonal changes over the menstrual cycle. Positive subjective effects of cocaine tend to increase with higher levels of estradiol during the follicular phase, and are reduced during the luteal phase when progesterone levels are higher (36). Similar effects have not been reported in women who use opioids, but opioid-dependent women often have disrupted menstrual cycles (37), making it difficult to determine the influence, if any, of gonadal hormones on craving or use. Nonetheless, the differences in opioid craving observed in this study could potentially be partly due to changes over the menstrual cycle, which should be explored in further studies.

The main limitation of this study is the relatively low number of female participants, which mostly constrained our analysis of the self-initiated stress event entries. A greater percentage of the female participants completed at least one stress event entry compared to the male participants (94% vs. 84%), but the lower overall number of entries was not adequate to assess the relationship between stress severity and craving in women during stress events. The small number of differences reported in the context of stress events between men and women may also be due to the sample size. Several sex differences were seen in context for random prompts, which occurred three times each day, providing a greater number of entries for both men and women. Stress events were only entered as often as participants experienced and chose to report events, which, for most participants, was typically not daily. Another limitation of this study is that we did not assess the effects of comorbid affective disorders, which are more common in substance-using women relative to men (38, 39). Potential participants with current mood disorders were excluded from this study, but the influence of mental health factors on stress and craving is an important area for further research and would allow for greater generalizability to the population of individuals with comorbid affective and substance use disorders.

Further research on sex differences in addiction is needed, with targeted recruitment of female participants, who tend not to enroll in substance use studies as frequently as men (40). The results of this study suggest that men and women experience similar causes and contexts for stress, but that they may differ in the consequences of stress, such as craving for opioids and cocaine. Other, more long-term outcomes of stress in conjunction with drug use also tend to be more pronounced in women, such as psychiatric, medical and employment-related problems (5). Interventions to address specific vulnerabilities to relapse may be developed through the availability of more qualitative data on craving and mood in both men and women. Interventions should consider sex differences as well as individual variability; as shown in this study, not all participants conformed to the overall group differences. Gender-specific interventions have been shown to be effective in specific populations; for example, Greenfield et al. (41) found that women with higher baseline psychiatric severity and lower self-efficacy had better treatment outcomes when assigned to a women's recovery group compared to a mixed-gender group.

The participants in this study also carried a GPS device along with the phone to track location. Further analyses will incorporate the GPS data to determine the effects of environment on craving and use. Sex differences have been reported in the impact of perceptions of the environment and overall neighborhood quality on walking (42) and in the relationship between health and neighborhood environment (43). Information on geographical location in real time should provide a more precise examination of how the environment may influence men and women differently.

In summary, EMA methods provide evidence based on real-time activities and moods that opioid-dependent men and women experience similar contexts and causes of stress, but may differ in stress- and cue-induced craving. Better understanding of sex and personal-level differences in responses to stressors, as well as contexts related to stressors and drug cues, can help to modify treatments that can lessen the risk of relapse.

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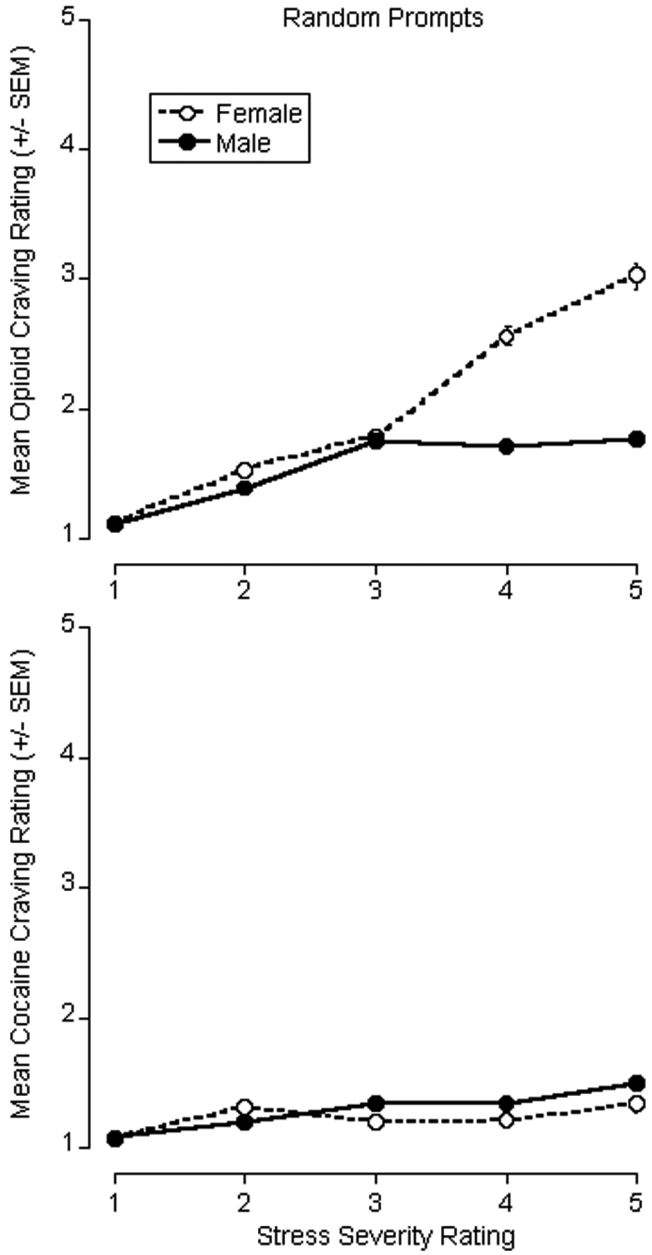

Figure 1.

Mean (±SEM) ecological momentary assessment (EMA) ratings of craving on a 1 to 5 scale (1 indicating no craving) for opioids (top panel) and cocaine (bottom panel) across ratings of stress in random prompt entries. The increase in opioid craving as a function of stress was greater for women than men [sex x stress severity, $F(4,550)=6.7$, $p<0.0001$]; whereas men showed a greater increase in cocaine craving as a function of stress [sex x stress severity, $F(4, 403)=20.4$, $p<0.0001$].

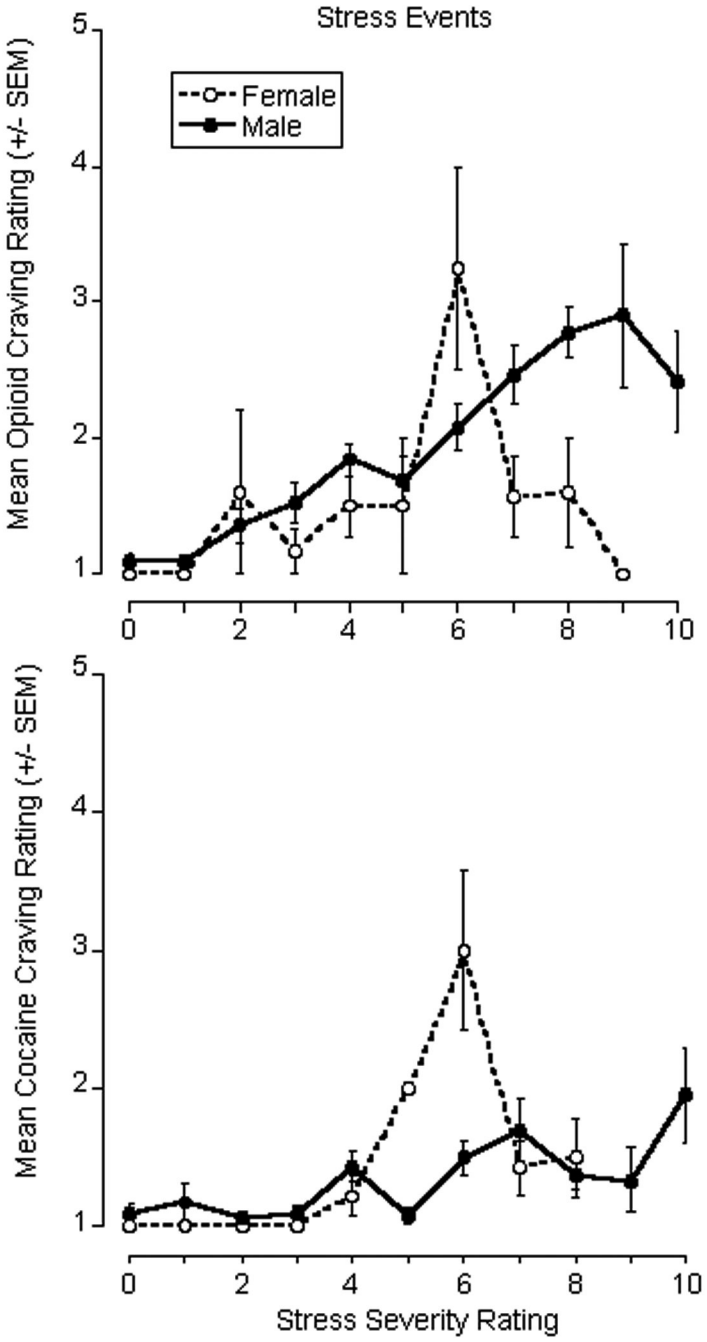

Figure 2.

Mean (±SEM) ecological momentary assessment (EMA) ratings of craving on a 1 to 5 scale (1 indicating no craving) for opioids (top panel) and cocaine (bottom panel) across ratings of stress in stress event entries. Opioid and cocaine craving ratings increased linearly across stress-severity ratings, [opioids: $F(1,130)=53.1$, $p<0.0001$; cocaine: $F(1, 117)=6.4$, $p<0.05$]. Men showed a linear increase in opioid craving, $F(1,110)=54.3$, $p<0.0001$, and cocaine craving, $F(1,100)=4.17$, $p<0.05$, with stress severity, but there was not enough data to determine a relationship between craving and stress in women (i.e., there were 10 or fewer stress events reported at each level of stress, on the 0–10 scale).

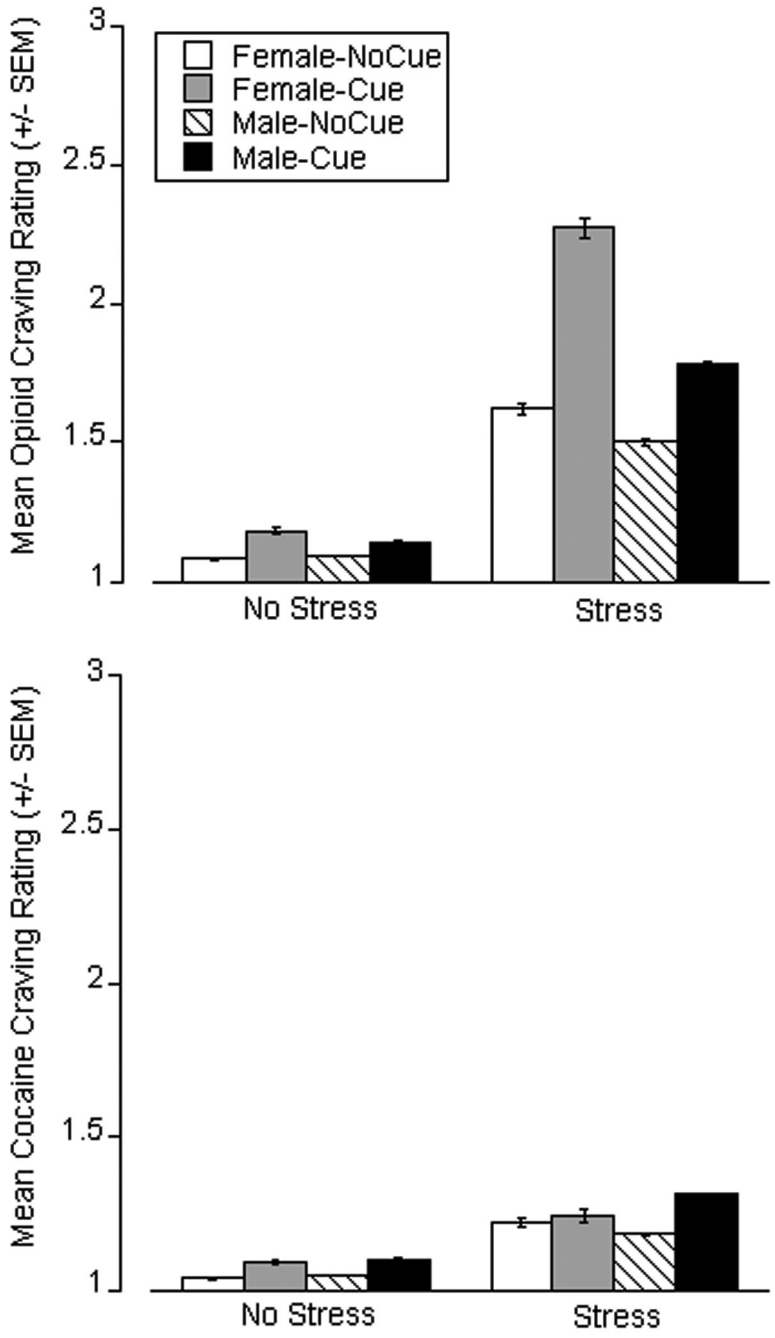

Figure 3.

Mean (±SEM) ecological momentary assessment (EMA) ratings of craving on a 1 to 5 scale (1 indicating no craving) for opioids (top panel) and cocaine (bottom panel) in random prompt entries in which participants either reported no stress or any stress (on a 1 to 5 scale; 1 indicating no stress), and reported the absence or presence of any drug cues. Women showed a greater increase in opioid craving relative to men in the presence of both stress and cues compared to either alone [sex x stress x cue, $F(1, 140) = 7.6$, $p<0.01$]. Men showed a greater increase in cocaine craving relative to women when stress was present [sex x stress, $F(1,127)=61.0$, $p<0.0001$]. The effect of cues on cocaine craving was greater when stress

was also present [stress x cue, $F(1,100)=5.8$, $p<0.05$]; this relationship is more apparent in men.

Table 1.

Clinical and demographic characteristics

	Men (n = 135)		Women (n = 47)		Comparison
	Mean/ %	SD	Mean/%	SD	
Opioid agonist treatment					χ^2 (1, n = 182) = 0.05, p = 0.83
Methadone	59.3		57.4		
Buprenorphine/naloxone	40.7		42.6		
Age (years)	42.0	9.6	41.6	9.3	t(180) = −0.2, p=0.82
Race					χ^2 (1, n = 178) = 0.82, p = 0.36
African American	63.9		70.2		
European American	35.3		27.6		
Years of education	12.0	1.5	12.2	1.6	t(180) = 0.8, p=0.42
Marital status					χ^2 (2, n = 182) = 1.45, p = 0.48
Married	14.9		8.5		
Never married	24.6		29.8		
Separated/divorced/widowed	60.4		61.7		
Employment status					χ^2 (3, n = 182) = 4.46, p = 0.22
Full time	50.0		36.2		
Part time	23.1		21.3		
Unemployed	21.6		36.2		
Retired/disability/controlled	5.2		6.4		
Drug use history					
Days used in last 30					
Heroin	19.6	11.6	18.2	12.8	t(180) = −0.7, p=0.50
Other opioids	8.0	6.2	8.5	10.4	t(180) = 0.32, p = 0.75
Cocaine	4.4	8.8	4.7	7.6	t(180) = 0.18, p = 0.85
Years using					
Heroin	15.6	10.0	11.5	10.4	t(180) = −2.4, p<0.05
Other opioids	1.2	2.4	2.1	3.3	t(180) = 1.6, p = 0.13
Cocaine	6.0	8.2	6.1	7.7	t(180) = 0.11, p = 0.91
Route of administration					
Heroin					χ^2 (2, n = 170) = 1.88, p = 0.39
Intranasal	57.8		69.0		
Intravenous	41.4		31.0		
Other opioids					
Intranasal	7.9		5.7		χ^2 (2, n = 136) = 0.79, p = 0.67
Oral	91.1		91.4		
Smoking	1.0		2.9		

	Men (n = 135)		Women (n = 47)		Comparison
Cocaine					χ^2 (2, n = 133) = 6.69, p<0.05
Intranasal	26		18.2		
Smoking	48		72.7		
Intravenous	26		2.3		
Urine drug screen results					
Opioids mean % negative	64.1	35.7	55.3	37.3	t(180) = 1.45, p=0.15
Cocaine mean % negative	67.6	38.6	61.9	42.4	t(180) = 0.86, p=0.39

Table 2.

Reasons for stress during self-initiated reports of stress events in women vs. men

	Odds Ratio (95% CL)[a] ***df=156***	***p***
Was the feeling mostly because…		
you had an injury or health problem?	0.69 (0.30 - 1.60)	0.38
your surroundings were unsafe or threatening?	0.84 (0.30 - 2.36)	0.74
you just started thinking about stressful things?	0.84 (0.57 - 1.25)	0.39
you had a conflict with someone?	0.87 (0.60 - 1.28)	0.48
you had problems with money?	0.91 (0.60 - 1.39)	0.66
you had a legal problem?	1.01 (0.37 - 2.74)	0.99
you were inconvenienced?	1.34 (0.79 - 2.27)	0.28
you had too much to do?	1.57 (0.93 - 2.66)	0.09

[a]Reference group - Women.

Table 3.

Companions, location, and activities reported during randomly prompted entries and self-initiated reports of stress events in women vs. men

	Random Prompts		Stress Events	
	Odds Ratio (95%CL)[a]		Odds Ratio (95%CL)[a]	
	df = 180	*p*	*df = 156*	*p*
Companion				
Child(ren)	0.59 (0.53 – 0.66)	<.0001	0.66 (0.35 - 1.28)	0.22
Spouse/Partner	0.63 (0.58 – 0.68)	<.0001	0.82 (0.52 - 1.30)	0.39
Out the gate partner	2.26 (1.47 – 3.46)	<.0001	0.82 (0.20 - 3.34)	0.78
No one	1.23 (1.15 – 1.32)	<.0001	0.94 (0.65 - 1.36)	0.75
Acquaintances	1.21 (1.02 – 1.42)	<.05	0.94 (0.53 - 1.68)	0.84
Clinic staff/Patients	0.85 (0.75 – 0.96)	<.01	0.96 (0.45 - 2.07)	0.92
Friends	1.58 (1.40 – 1.78)	<.0001	1.26 (0.70 - 2.26)	0.43
Coworkers	1.22 (1.03 – 1.44)	<.05	1.28 (0.53 - 3.12)	0.58
Other family	1.56 (1.41 – 1.72)	<.0001	1.36 (0.76 - 2.42)	0.30
Strangers	1.57 (1.36 – 1.82)	<.0001	1.64 (0.75 - 3.63)	0.22
Were you with at least one person who you have ever used with?	0.59 (0.53 – 0.66)	<.0001	0.47 (0.23 - 0.94)	<0.05
Were you with at least one person who still uses?	0.67 (0.59 – 0.76)	<.0001	0.42 (0.21 - 0.86)	<0.05
Location				
Store	1.42 (1.19 – 1.68)	<.0001	0.47 (0.25 - 0.89)	<0.05
Restaurant	1.24 (0.97 – 1.58)	0.09	0.61 (0.17 - 2.23)	0.45
Walking from one place to another	0.95 (0.83 – 1.08)	0.43	0.78 (0.42 - 1.42)	0.41
Home	0.65 (0.62 – 0.69)	<.0001	0.81 (0.57 - 1.14)	0.22
Clinic / doctor	0.92 (0.83 – 1.02)	0.11	0.88 (0.49 - 1.58)	0.67
Another'homes home	1.30 (1.18 – 1.46)	<.0001	1.06 (0.48 - 2.38)	0.9
Outside hanging out	1.50 (1.25 – 1.80)	<.0001	1.17 (0.48 - 2.84)	0.73
Vehicle (car, bus, train)	1.10 (1.02 – 1.19)	<.01	1.19 (0.74 - 1.90)	0.47
Work	1.86 (1.61 – 2.16)	<.0001	1.67 (0.74 - 3.79)	0.22
Waiting for ride, bus, etc.	1.22 (1.10 – 1.35)	<.0005	2.07 (1.10 - 3.90)	
Bar / club	2.84 (1.34 – 6.01)	<.01	2.41 (0.31 - 18.72)	0.40
Activity				
On Internet	1.02 (0.86 – 1.22)	0.83	0.57 (0.22 - 1.49)	0.25
Arguing	1.33 (1.01 – 1.75)	<.05	0.78 (0.43 - 1.44)	0.43
Talking on phone	1.48 (1.25 – 1.75)	<.0001	0.82 (0.47 - 1.43)	0.48
Walking/riding/travelling	1.12 (1.05 – 1.18)	<.0005	0.86 (0.60 - 1.22)	0.40
Shopping/Errands	1.27 (1.07 – 1.51)	<.01	0.86 (0.35 - 2.08)	0.73
Household chores or personal hygiene	0.77 (0.69 – 0.86)	<.0001	0.90 (0.47 - 1.71)	0.74
Eating or preparing food	0.88 (0.81 – 0.97)	<.01	0.95 (0.50 - 1.80)	0.86
Talking/Socializing	1.11 (1.02 – 1.21)	<.05	1.04 (0.70 - 1.56)	0.84
Sports/Games/Other recreation	1.47 (1.14 – 1.89)	<.005	1.04 (0.23 - 4.69)	0.96
Resting/Sleeping	1.00 (0.93 – 1.07)	0.97	1.12 (0.70 - 1.78)	0.63

	Random Prompts		Stress Events	
	Odds Ratio (95%CL)[a]		Odds Ratio (95%CL)[a]	
	df = 180	*p*	*df = 156*	*p*
Working	1.87 (1.63 – 2.13)	<.0001	1.12 (0.57 - 2.19)	0.74
Listening to music	1.93 (1.63 – 2.29)	<.0001	1.22 (0.52 - 2.90)	0.65
Waiting	1.20 (1.06 – 1.35)	<.005	1.22 (0.66 - 2.26)	0.52
Watching TV/videos/DVD	0.83 (0.78 – 0.88)	<.0001	1.51 (0.90 - 2.55)	0.12
Thinking/planning	1.87 (1.65 – 2.11)	<.0001	1.76 (1.04 - 2.96)	<0.05
Reading	1.04 (0.88 – 1.23)	0.66	2.06 (0.58 - 7.38)	0.26
Child care / Elder care	3.03 (2.21 – 4.16)	<.0001	4.09 (0.27 - 61.87)	0.31

[a]Reference group - Women.