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Sex differences in cocaine/heroin users: Drug-use triggers and craving in daily life

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ABSTRACT

Background: Studies of sex differences have shown that men and women with drug-use disorders differ in course and outcome and in cue-induced activation of putative brain "control network" areas. We evaluated sex differences in daily functioning and subjective events related to drug use with ecological momentary assessment (EMA).
Methods: EMA data were collected from cocaine- and heroin-using outpatients (72 men; 42 women) in methadone maintenance in 2–5 randomly prompted (RP) entries per day and in participant-initiated entries for heroin or cocaine use or craving, for up to 25 weeks. Urine drug screens were conducted three times weekly. Data were analyzed via repeated-measures logistic regression, using sex as a predictor of responses.
Results: In RP reports, women and men reported significantly different patterns of drug-cue exposure, with women significantly more likely to report having seen cocaine or been tempted to use in the past hour. Women also had higher craving after past-hour exposure to drug cues. In reports of drug use, women, compared to men, were more likely to report that they had used more cocaine than they had meant to, tended to feel guilty more often after drug use, and to have used despite trying not to use.
Conclusions: These findings provide real-time behavioral evidence that women respond differently than men to exposure to drug cues and to drug use, consistent with laboratory and brain-imaging findings. This information may be useful for development of sex-specific treatment strategies.
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1. Introduction

Sex differences have been found in likelihood of drug-use initiation, progression to abuse and dependence, and responsiveness to treatment. Although prevalence of past-30-day use of illicit drugs is higher for males than females (11.2% vs. 6.8%; SAMHSA, 2011), women progress more quickly from initiation to addiction (Anglin et al., 1987b; Brady, 1999; Lynch et al., 2002) and enter treatment sooner than men (Anglin et al., 1987a; Hernandez-Avila et al., 2004).

Acutely, women and men respond differently to drug-associated cues. For example, in laboratory settings, cocaine-dependent women sometimes report more cue-induced craving than cocaine-dependent men (Elman et al., 2001; Robbins et al., 1999); the same is true in heroin dependence (Yu et al., 2007). These findings are complemented by sex differences in cue-induced brain activity (Kilts et al., 2004; Seo et al., 2011; Volkow et al., 2011). Sex differences in response to cocaine itself vary across laboratories and possibly across routes of administration (Collins et al., 2007; McCance-Katz et al., 2005; Mendelson et al., 1999; Sofuoglu et al., 1999); some studies have shown an effect of menstrual phase (Evans and Foltin, 2006; Sofuoglu et al., 2002).

Outside the laboratory, transient mental states are more difficult to measure. Probably the most sensitive method is ecological momentary assessment (EMA), which minimizes recall bias by having participants report experiences and behaviors in real time (Shiffman et al., 2008). In nonclinical samples, EMA studies have shown only modest sex differences in emotion: emotional responses to work strain were similar across sexes (Matthews et al., 2000), overall emotional intensity was only slightly greater in women, and only on some measures (Barrett et al., 1998), and, in healthy individuals with work or marital stress, self-reported coping strategies showed expected sex differences on trait-level questionnaires but not on EMA reports of actual "momentary" experience (Porter et al., 2000).

We know of only one EMA study of sex differences in addiction, an examination of cigarette smokers (173 women, 131 men). The only sex differences found were that (contrary to hypothesis) women's smoking was less driven by negative affect and more driven by craving than men's, and (as hypothesized) women were more responsive to posted smoking prohibitions (Shiffman and Rathbun, 2011).

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Table 1
Clinical and demographic characteristics of 114 heroin- and cocaine-dependent methadone-maintained outpatients, by sex.

	Women	Men	FDR-adjusted *p*
N	42	72	
Age	41.2 (SD 6.9)	40.7 (SD 8.7)	n.s.
Nonwhite race	74%	57%	.07
Employment status	unemployed: 55% full-time: 26% part-time: 19%	unemployed: 29% full-time: 39% part-time: 32%	.025
Marital status	never: 55% sep/divorced: 29% married: 16%	never: 68% sep/divorced: 28% married: 4%	.06
Education (years)	11.8 (SD 1.3)	11.8 (SD 1.5)	n.s.
Heroin use past 30 days	29.4 (SD1.8)	29.2 (SD 3.8)	n.s.
Heroin use (years)	14.7 (SD 9.2)	13.0 (SD 8.1)	n.s.
Heroin route of administration	intravenous: 55% intranasal: 45%	intravenous: 64% intranasal: 36%	n.s.
Cocaine use past 30 days	19.6 (SD 9.4)	20.2 (SD 9.0)	n.s.
Cocaine use (years)	12.3 (SD 8.7)	11.1 (SD 8.6)	n.s.
Cocaine route of administration	smoked: 62% intravenous: 31% intranasal: 7%	smoked: 42% intravenous: 48% intranasal: 10%	n.s.
# of drug abuse treatments	2.31 (SD 2.2)	2.18 (SD 2.5)	n.s.
Money spent on drugs	$1762 (SD $1220)	$1968 (SD $1236)	n.s.
Methadone dose (mg)	97.9 (SD 7.8)	97.2 (SD 7.4)	n.s.

We used EMA in a large sample of methadone-maintained cocaine and heroin abusers. Our previous analyses of our EMA data have focused on craving and use patterns (Epstein et al., 2009; Preston et al., 2009), periods of use and abstinence (Epstein and Preston, 2010), and stress (Preston and Epstein, 2011). In the analyses reported here, we examined sex differences in activities, moods, drug use, and responses to drug use.

2. Methods and materials

2.1. Participants and setting

Participants were cocaine- and heroin-using outpatients. Inclusion criteria were: (1) age 18–65, (2) physical dependence on opioids, (3) cocaine use. Exclusion criteria were: (1) current DSM-IV psychotic disorder, history of bipolar disorder, current major depressive disorder, (2) current dependence on alcohol or sedative-hypnotics, (3) cognitive impairment severe enough to preclude informed consent or valid self-report, and (4) medical illness that would compromise participation.

Methadone maintenance began at enrollment and continued for up to 28 weeks at a treatment research clinic in Baltimore, MD. Participants attended daily for oral methadone (target dose, 100 mg/day); individual counseling was provided weekly, and urine was tested thrice weekly. The IRB of the NIDA Intramural Research Program approved the study. Participants gave written informed consent.

2.2. Study design

The study was designed to assess craving and lapse. At the end of the third week, each participant received a personal digital assistant (PDA; i.e., Palm Zire or Palm Zire 21, Palm, Inc., Sunnyvale, CA) running our electronic-diary software (Vahabzadeh et al., 2004). EMA began at week 3 of the study to allow for stabilization of methadone and acclimatization to treatment. Participants were informed that none of their EMA responses would be seen by their counselors, though counselors could monitor their compliance.

Participants were instructed to make two types of entries: randomly prompted and event-contingent. Random prompts occurred 2–5 times per day for up to 25 weeks during each participant's typical waking hours. Participants were asked to initiate an event-contingent entry whenever they used cocaine, heroin, or both, or craved without using. For all entries, participants reported where they were, whom they were with, and what they were doing. Mood was assessed in random prompts with adjectives (happy, relaxed, tired, irritated, stressed, and bored) in six items worded "Right now, do you feel. . ." and rated on a four-point scale. Craving for cocaine, heroin, and tobacco was assessed on the same scale and worded: "Right now, do you crave . . .?".

At each random prompt, participants also answered a series of questions beginning with, "In the past hour. . .," which were designed to assess exposure to putative triggers of drug craving or drug use (Epstein et al., 2009). The questions were originally derived from post-relapse interviews (Heather et al., 1991; Marlatt and Donovan, 2005). We administered the same "trigger" items in drug-use and craving (event contingent) entries with the wording "I think it happened because. . ." to assess participants' attributions for those events in their immediate aftermath.

2.3. Data analysis

Demographics were compared across sexes with *t*-tests or chi-squares. Study retention across sexes was analyzed by survival analysis (SAS Proc Lifetest). Random-prompt compliance was compared across sexes by *t*-test.

EMA responses were compared across sexes using repeated-measures linear regression (SAS Proc Mixed) for continuous dependent variables, or repeated-measures logistic regression (SAS Proc Glimmix) for categorical dependent variables. Sex was the only between-subjects predictor in each model. An autoregressive error structure was used. In some additional Proc Mixed models, we tested for sex differences in cocaine craving and stress "right now" in random-prompt entries as a function of past-hour exposure to putative triggers, with past-hour exposure reported retrospectively in the same entries. In those models, the between-subject predictors were sex, past-hour trigger exposure, and (of greatest interest) their interaction.

Because men were significantly more likely than women to be employed, we reran our analyses of some of the EMA data, using current employment status (full-time, part-time, or unemployed) as a time-varying covariate. We restricted these supplementary analyses to EMA variables that would logically be expected to vary with employment status (location, activities, companions, and past-hour exposure to putative triggers). Current in employment status was inferred from reviews of counselors' weekly progress notes. It was sometimes difficult to assign such changes to precise time points. Nonetheless, these supplementary analyses provided some assurance that our observed sex differences were not artifacts of differences in employment status.

Urine-screen data for cocaine and heroin (up to 80 urine specimens per participant across 27 weeks) were analyzed similarly in Glimmix models, with sex as the only between-subjects predictor.

Alpha was set at .05, with trends noted at .10. To adjust for multiple tests of significance (142 in all for the EMA-response comparisons, not all shown here), we entered all obtained *p* values into the SAS procedure Multtest to obtain false-discovery rate (FDR) *p* values, which are the ones we report here. FDR correction reduced the number of *p* values $\leq$.05 from 65 to 57, and reduced the number of additional *p* values $\leq$.10 from 11 to 7. All tests were two-tailed.

3. Results

3.1. Demographics, drug use, and EMA compliance

A total of 130 participants (84 men, 46 women) enrolled; 114 (72 men, 42 women) provided sufficient data for the analyses reported here. All met DSM-IV criteria for cocaine dependence by structured interview (Robins et al., 1995) at study intake, though this was not an inclusion criterion.

There was no significant sex difference on any of the drug-related intake variables (Table 1). Women were more likely to