Published in final edited form as:

Psychiatry Res. 2016 February 28; 248: 110–118. doi:10.1016/j.psychresns.2016.01.001.

Converging effects of cocaine addiction and sex on neural responses to monetary rewards

Anna B. Konova^a, Scott J. Moeller^b, Muhammad A. Parvaz^b, Monja I. Froböse^c, Nelly Alia-Klein^b, and Rita Z. Goldstein^{b,*}

^aCenter for Neural Science, New York University, New York, NY 10003 ^bDepartments of Psychiatry & Neuroscience, Icahn School of Medicine at Mount Sinai, New York, NY 10029

^cCentre for Cognitive Neuroimaging, Donders Institute for Brain, Cognition and Behaviour, Nijmegen, Netherlands

Abstract

There is some evidence that cocaine addiction manifests as more severe in women than men. Here, we examined whether these sex-specific differences in the clinical setting parallel differential neurobehavioral sensitivity to rewards in the laboratory setting. Twenty-eight (14 females/14 males) cocaine-dependent and 25 (11 females/14 males) healthy individuals completed a monetary reward task during fMRI. Results showed that the effects of cocaine dependence and sex overlapped in regions traditionally considered part of the mesocorticolimbic brain circuits including the hippocampus and posterior cingulate cortex (PCC), as well as those outside of this circuit (e.g., the middle temporal gyrus). The nature of this ‘overlap’ was such that both illness and female sex were associated with lower activations in these regions in response to money. Diagnosis-by-sex interactions instead emerged in the frontal cortex, such that cocaine-dependent females exhibited lower precentral gyrus and greater inferior frontal gyrus (IFG) activations relative to cocaine-dependent males and healthy females. Within these regions modulated both by diagnosis and sex, lower activation in the hippocampus and PCC, and higher IFG activations, correlated with increased subjective craving during the task. Results suggest sex-specific differences in addiction extend to monetary rewards and may contribute to core symptoms linked to relapse.

*Corresponding Author: Rita Z. Goldstein, Department of Psychiatry, Icahn School of Medicine at Mount Sinai, The Leon and Norma Hess Center for Science and Medicine, 1470 Madison Ave., New York, NY 10029; tel. (212) 824-9312; fax (212) 996-8931; rita.goldstein@mssm.edu.

Publisher's Disclaimer: This is a PDF file of an unedited manuscript that has been accepted for publication. As a service to our customers we are providing this early version of the manuscript. The manuscript will undergo copyediting, typesetting, and review of the resulting proof before it is published in its final citable form. Please note that during the production process errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

Author Contributions

A.B.K., N.A.-K., and R.Z.G. designed the research. A.B.K., S.J.M., and M.A.P. collected the data. A.B.K., S.J.M., M.A.P., analyzed the data. A.B.K. and R.Z.G. wrote the manuscript. S.J.M., M.A.P., M.I.F., and N.A.-K. provided critical revisions of the manuscript for important intellectual content. All authors approved the final version.

Disclosure/Conflict of Interest

The authors declare no conflict of interest.

Keywords

addiction; cocaine; craving; monetary reward; functional MRI; sex differences

1. Introduction

Despite overall lower rates of substance use, women tend to report an earlier age of onset of drug use, progress more rapidly from initial use to dependence, and are at greater risk for relapse following abstinence than men (Becker and Hu, 2008; Becker et al., 2012). Such sex differences in addiction have been studied in laboratory settings primarily in the context of reactivity to drug-related and stress cues. For example, drug-related cues increased cerebral blood flow to a greater extent in cocaine-dependent men than women in the amygdala and portions of the ventromedial prefrontal cortex while the reverse (women>men) was true for other parts of the frontal and sensorimotor cortices (Kilts et al., 2004). Using FDG-PET, which captures neural activity over 30 min, we also previously found that in female but not male cocaine users drug-related cues decreased glucose metabolism in the inferior frontal gyrus (IFG) and the anterior and posterior cingulate cortices (Volkow et al., 2011b). When exposed to both drug-related and stress cues, cocaine-dependent as compared with healthy women showed greater activations in the amygdala, striatum, and insula in response to stress-related cues; cocaine-dependent as compared with healthy men showed greater activations in similar regions but in response to drug-related cues rather than stress cues (Potenza et al., 2012). Sex-specific differences in the anterior and posterior cingulate cortices were further associated with stress-induced craving in women (Lejuez et al., 2005) and drug cue-induced craving in men (Potenza et al., 2012). Together, these studies provide evidence for sex influences on drug and negative emotional cue reactivity in reward-related and limbic regions and those involved in the regulation of mood states, which may underlie core symptoms of addiction (craving).

It is not known, however, if these sex differences in cocaine addiction extend to other salient reinforcers including rewarding stimuli. It is possible that there is a more global impact of sex on value processing in addiction, which could have implications for treatments seeking to stabilize the value of alternative reinforcers. Sex differences in reward processing are expected given that dopamine, which is modulated by sex hormones (Becker, 1999), has a prominent role in both reward signaling (Schultz, 2001) and addiction (Sulzer, 2011). This interaction between sex hormones and dopamine during repeated drug intake—that is, the purported mechanism through which sex interacts with drug addiction to modulate reward responses—can result in a number of downstream effects that influence more than just the subjective experience of the drug [see (Bobzean et al., 2014) for review]; indeed, sex-specific organizational changes in the reward and extended limbic circuitry have been documented including changes in brain structure (Franklin et al., 2014; Rando et al., 2013).

In healthy individuals, sexual dimorphisms emerge in brain circuits involved in social cognition and reward processing (Caldu and Dreher, 2007). For example, while social rewards (e.g., humor, smiling faces) activated reward and limbic circuits in both women and men (Kohn et al., 2011; Spreckelmeyer et al., 2009), these motivationally significant stimuli

activated executive control networks only in men (Kohn et al., 2011). Of particular relevance to the study of drug addiction, differences between healthy men and women were also found during the anticipation and receipt of money in a distributed network of brain regions that included the putamen (men>women) and the hippocampus, ventromedial prefrontal cortex, and lateral prefrontal cortex (women>men) (Dreher et al., 2007). Although differences in neurobehavioral sensitivity to money have been observed in cocaine addicted individuals across the sexes in much of the same regions (Bustamante et al., 2013; Jia et al., 2011; Konova et al., 2012; Rose et al., 2014) and in individuals with family history of alcoholism as a function of sex [e.g., (Petry et al., 2002; Villafuerte et al., 2012)], to our knowledge, no study has specifically examined sex differences in monetary reward processing in addiction, although elucidating the interaction between sex and addiction in this context has implications for understanding and potentially treating this disease.

Therefore, in the present study, we sought to examine the influence of sex on monetary reward processing in cocaine dependence. Participants completed a monetary reward task that has been used in our previous studies of cocaine addiction (Goldstein et al., 2009; Goldstein et al., 2007; Konova et al., 2012). Our primary goal here was to explore differences on this task between female and male cocaine users who were well-matched on basic clinical and demographic characteristics. To determine specificity to cocaine dependence, we also included a comparison group of healthy men and women. More specifically, in our analyses, we sought to identify brain regions where the effects of diagnosis and sex overlap (i.e., where the effects of sex overlap with the effects of illness, suggesting additive influence of these two factors) and where they interact (i.e., where sex has stronger or opposite effects in addicted compared with healthy individuals). Following the literature reviewed above, and based on meta-analytic data which has identified the most consistent brain responses to a range of rewards (e.g., monetary, food, and social) (Bartra et al., 2013; Liu et al., 2011; Sescousse et al., 2013), we anticipated that such overlapping or interactive effects could emerge in the striatum, ventromedial prefrontal cortex (medial orbitofrontal and anterior cingulate cortex), posterior cingulate, hippocampus/amygdala, and the lateral prefrontal cortex. As in previous studies, we also examined whether sex-specific differences in response to money are differentially associated with craving in women and men.

2. Materials & Methods

2.1. Participants

Fifty-three adults provided written informed consent to participate in this study which was approved by the local Institutional Review Board. Participants were in good health and not taking any medications. Their psychiatric history was ascertained by a comprehensive clinical interview, consisting of the Structured Clinical Interview for DSM-IV Axis I Disorders [research version (First et al., 1996; Ventura et al., 1998)] and Addiction Severity Index (McLellan et al., 1992). Exclusion criteria were: (1) head trauma, loss of consciousness for >30 min, or neurological disease; (2) abnormal vital signs and presence of major medical conditions; (3) history of psychosis and neurodevelopmental disorders; (4) except for cocaine, positive urine screen for psychoactive drugs or their metabolites; (5)

pregnancy; and (6) contraindications to the MRI environment (non-removable metal in the body, claustrophobia). Additional exclusionary criteria for healthy controls were past or present diagnosis of any Axis I disorder other than past alcohol abuse restricted to college or military service.

Participants were 28 cocaine users (14 females/14 males) and 25 healthy controls (11 females/14 males). Data from 5 cocaine users (4 females/1 male) and 11 controls (3 females/8 males) were partially reported in (Konova et al., 2012), where we focused on diagnosis effects in brain structure and function but did not assess potential contributions of sex. The groups were matched on all demographic and neuropsychological measures except for age, where controls were on average younger than cocaine users (Table 1). Cocaine users also reported more depressive symptoms as assessed with the Beck Depression Inventory (BDI) (Beck et al., 1996) than controls (though note that scores were in the mild range). Therefore, age and BDI scores were included as covariates in all analyses involving cocaine users and controls.

All cocaine users identified cocaine as their primary drug of choice and met DSM-IV criteria for cocaine dependence, including cocaine dependence in full ($n=6$) or partial ($n=3$) early remission and the rest meeting current dependence criteria (5 females/4 males). Table 2 shows drug use characteristics of the sample. Ten (5 females/5 males) were seeking treatment and participated in inpatient or outpatient treatment programs at the time of the study. Despite the heterogeneity in abstinence duration, excluding long-term abstinent participants (i.e., >1.5 years; $n=1$ female and $n=2$ males) did not significantly change our results (Supporting Information). Current comorbid disorders were marijuana abuse ($n=1$) and posttraumatic stress disorder ($n=1$). Past comorbid disorders included alcohol ($n=11$), marijuana ($n=11$), amphetamine ($n=1$), and phencyclidine ($n=1$) use disorders, posttraumatic stress disorder ($n=3$), and major depressive disorder ($n=3$). Females were significantly more likely than males to have a lifetime history of comorbid mood disorder ($\chi^2_1=6.09$, $P=0.01$). There were no significant differences in lifetime history of comorbid substance use disorder ($\chi^2_1=2.49$, $P=0.12$). There were also no significant differences in rates of nicotine, alcohol, or cocaine use or in the level of self-reported abstinence, craving, or withdrawal from cocaine (Table 2). Healthy controls did not report regular use of any substance other than nicotine. Further, only 5 controls were current or past smokers as compared with most ($n=23$) cocaine users, and this represented a significant difference that could not be accounted for reliably in our analyses (Miller and Chapman, 2001). We note however that within current smokers, the number of cigarettes smoked per day and years of nicotine use were comparable between the groups ($P>0.24$), and these variables (in smokers) as well as regular alcohol use (in cocaine users) did not appear to significantly contribute to any of our results (see Supporting Information).

2.2. Craving Measures

Craving was assessed via self-report ratings of “cocaine wanting” [“how much do you want cocaine right now?” rated on a scale from 0 (not at all) to 10 (very much)] that were collected at 4 time points during the experiment (twice before, once in the middle, and once immediately after the fMRI task). To capture task-related changes in craving, for each

participant, we computed a change score subtracting the average of the second two time points from the average of the first two (baseline). As expected, cocaine users reported greater changes in craving than healthy controls but there were no significant differences by sex (Table 1).

2.3. fMRI Task

Participants performed a blocked monetary reward paradigm that has been described in detail elsewhere (Goldstein et al., 2009; Goldstein et al., 2007; Konova et al., 2012; Moeller et al., 2012). This task required successful button pressing for the color of drug and neutral words to earn money. There were 4 money conditions (0¢, 1¢, 25¢, or 50¢), each comprised of four blocks of 20 trials (for a total of 80 trials per money condition). Each block began with a 3000 ms window informing participants of the amount of money they could earn for every correct trial in that block. The trial structure consisted of fixation (500 ms), presentation of the word cue (2000 ms), response (500 ms), and feedback indicating the amount gained for a correct response (500 ms); in the case of an error, an “X” rather than money was displayed. During the response window, participants pressed 1 of 4 buttons (blue, yellow, green, or red) matching the color of the word they had just read. The amount of money earned on the task was entirely contingent on performance (mean $\pm$ SEM: \$63.25 $\pm$ 1.25, with no differences between the groups in this amount, $P>0.45$). Because we did not observe any main or interaction effects with word type (drug, neutral) on behavior in the present study ($P>0.15$) or on behavior or brain activity in our previous studies (Goldstein et al., 2009; Goldstein et al., 2007; Konova et al., 2012), we collapsed the data across word type. Furthermore, because we previously found that behavioral and neural sensitivity to money was maximal for the differential of the highest reward (50¢) compared with the non-reward (0¢) condition (Konova et al., 2012) [which was also the case in the current study, where across participants, fewer errors were committed for the 50¢ condition than the 0¢ condition ($P=0.001$)], we also limited the present analyses to this 50¢>0¢ contrast (described below). See Fig. S2 in the Supporting Information for analyses with the linear contrast 50¢>25¢>1¢>0¢ in a reduced sample which showed similar results to 50¢>0¢.

2.4. Image Acquisition

Scanning was performed on a 4T whole-body Varian/Siemens MRI scanner. Blood-oxygen-level-dependent (BOLD) responses were measured as a function of time using a T2*-weighted single-shot gradient-echo EPI sequence (TE/TR=20/1600 ms, 3.125 $\times$ 3.125 mm² in-plane resolution, 4 mm slice thickness, 1 mm gap, 33 coronal slices, 20 cm FOV, 64 $\times$ 64 matrix size, 90°-flip angle, 200 kHz bandwidth with ramp sampling, 128 time points, and 4 dummy scans, discarded to avoid non-equilibrium effects in the BOLD signal). A modified T2-weighted Hyperecho image (TE/TR=42/10000 ms, echo train length=16, 256 $\times$ 256 matrix size, 30 coronal slices, 0.86 $\times$ 0.86 mm in-plane resolution, 5 mm slice thickness, no gap, 2 min scan time) was also acquired and reviewed by a neurologist to rule out gross structural brain abnormalities.

2.5. Image Processing and Analysis

Subsequent analyses were performed in SPM8 (Wellcome Department of Cognitive Neurology, London UK). A six-parameter rigid body transformation (3 rotations, 3 translations) was used for image realignment and to correct for head motion; less than 2 mm displacement and 2° rotation in any of the axes were used as criteria for acceptable motion. Spatial normalization to a standard EPI template [Montreal Neurological Institute (MNI)] was performed using a 12-parameter affine transformation, resulting in a final voxel size of 3×3×3 mm. An 8 mm³ full-width at half maximum Gaussian kernel was used to smooth the data.

A general linear model and a box-car design (initiated at the onset of the 3000 ms money reminder cue and spanning the length of the 20 trial block) convolved with a canonical hemodynamic response function and high-pass filter (1/520 s) were used to calculate individual beta maps. Contrast maps reflecting % signal change for the 50¢ versus 0¢ money conditions (50¢>0¢) were calculated for each participant and used in second-level analyses.

2.6. Statistical Analyses

The effects of diagnosis and sex on neural responses to money (50¢>0¢) were examined with a whole-brain 2 (diagnosis: cocaine-dependent, control) × 2 (sex: female, male) analysis of covariance (ANCOVA) in SPM8, with age, BDI scores, and reaction times (which significantly differed by sex; see Table 1 and Results) as covariates of no interest. A voxel-wise threshold of $P<0.005$ was applied, combined with a minimum cluster-extent of 26 contiguous voxels (702 mm³), to yield a corrected cluster-level false positive rate of $P<0.05$ as determined by Monte Carlo simulations (<http://www2.bc.edu/~slotnics/scripts.htm>).

The average percent signal change (50¢>0¢) in significant clusters was extracted with the EasyROI toolbox (http://www.sbirc.ed.ac.uk/cyril/cp_download.html) for follow-up analyses in SPSS 20.0 (SPSS Inc., Chicago, IL) that examined associations with craving and cocaine use (age of onset, years of regular use, and frequency of current use) within the cocaine group. (Note that while both cocaine users and controls completed the craving ratings for experimental consistency, to avoid issues with circularity, the correlation analysis with craving was performed in the cocaine group only.) To minimize the potential for Type I error in these follow-up analyses, significance was set to Bonferroni-corrected $P<0.007$ ($P=0.05/7$ analyses) for craving and $P<0.002$ ($P=0.05/21$ analyses) for the cocaine use variables.

3. Results

3.1. Effects of Diagnosis and Sex on Task Behavior

Differential accuracy (50¢>0¢) on the task was not influenced by diagnosis or sex. While there were no significant differences between cocaine users and controls in differential reaction times for correct responses, men were faster than women (Table 1).

3.2. Effects of Diagnosis and Sex on fMRI Response to Money

Money main effects ($50\text{¢} > 0\text{¢}$ or $50\text{¢} < 0\text{¢}$) across participants are reported in Table S1 and Fig. S1. Because these overall task effects of the monetary reward paradigm have been described in detail previously (Goldstein et al., 2009; Goldstein et al., 2007; Konova et al., 2012), here we focused instead on novel findings related to sex. Irrespective of sex, cocaine users showed greater activations to money ($50\text{¢} > 0\text{¢}$) compared with controls in the right putamen, left inferior parietal lobe, bilateral dorsal cingulate, left calcarine sulcus, and left fusiform gyrus extending to the hippocampus. Controls showed greater activations compared with cocaine users in the right lingual gyrus and left middle/posterior cingulate. Irrespective of diagnosis, females showed greater activations compared with males in the left postcentral gyrus. Males showed greater activations compared with females in the bilateral middle/posterior cingulate and right parahippocampal gyrus/hippocampus (all $P < 0.05$ corrected; Table 3).

Because we were specifically interested in regions that were modulated both by diagnosis and sex, we performed a conjunction analysis where we searched for overlap in the main effects of these two factors. This analysis revealed overlap in the right hippocampus (MNI peak coordinates: 27, -13, -17), left and right middle/posterior cingulate (BA 23; 6, -37, 34; -12, -25, 46; and -6, -34, 37), and left middle temporal gyrus (BA 21; -57, -49, 13) (threshold for conjunction: $P < 0.005$ uncorrected; Fig. 1A–C). The pattern of response was such that both cocaine dependence and female sex were associated with reduced activation in these regions.

We also found diagnosis-by-sex interactions in the right precentral gyrus and left IFG (Table 3). The interaction in the precentral gyrus was explained by reduced precentral gyrus activity in the female cocaine users, which was significantly lower than that observed in male cocaine users and female controls (Fig. 1D). In contrast, the interaction in the IFG was explained by increased IFG activity in the female cocaine users, which was significantly greater than that observed in male cocaine users and female controls; female controls instead activated this region to a lesser extent than male controls (Fig. 1E). No other main or interaction effects were observed at the corrected threshold.

3.3. Association with Task-Related Craving in the Cocaine Group

Correlation analyses between the regional activations modulated by diagnosis and sex [the hippocampal, three middle/posterior cingulate, and middle temporal gyrus clusters identified in the conjunction analysis and the right precentral gyrus and left IFG identified in the diagnosis $\times$ sex interaction (7 in total)] and task-induced change in cocaine wanting (from before the task, i.e., baseline) revealed that, across all cocaine users, lower hippocampal and posterior cingulate activation and greater left IFG activation to money ($50\text{¢} > 0\text{¢}$) were all associated with greater increases in craving [after removing one male outlier, where Cook's $d > 1$, from these analyses: $R > |0.52|$, $P < 0.005$] (Fig. 2A–C). No additional correlations reached significance at $P < 0.007$. While follow-up analyses conducted separately in each sex indicated that these correlations were somewhat stronger in females ($R > |0.52|$, $P < 0.054$) than in males ($R < |0.47|$, $P > 0.10$), a direct comparison of the correlation coefficients

indicated that this difference between the sexes was not significant (Fisher's $Z < |0.93|$, $P > 0.35$).

We also inspected for associations between brain activation and cocaine use behaviors but results of these analyses did not survive correction for multiple comparisons ($R < |0.37|$, $P > 0.05$).

4. Discussion

We examined the additive and interactive effects of cocaine dependence diagnosis and sex on monetary reward processing, as well as the relationship between brain regions modulated by these two factors and task-related changes in cocaine craving. Consistent with our hypotheses, these data corroborate the presence of sex differences in cocaine dependence that extend beyond drug and emotional cue reactivity (Kilts et al., 2004; Lejuez et al., 2005; Potenza et al., 2012; Volkow et al., 2011b) to include neural processing of monetary rewards, suggesting that these sex-specific differences may stem from a more global influence of sex on value systems. Specifically, we found that while the effects of diagnosis and sex overlapped in some regions, they interacted in others, and in some cases these differential patterns of response correlated with task-related changes in craving.

During the task, cocaine users (as compared with healthy controls) and women (as compared with men) showed reduced activations to monetary rewards, such that these effects of cocaine dependence diagnosis and female sex were independent and additive in the hippocampus, middle/posterior cingulate, and middle temporal gyrus. The hippocampus is purported to play a role in reward-motivated memory formation (Adcock et al., 2006), possibly via its interactions with the striatum and prefrontal cortex (Murty and Adcock, 2014; Shigemune et al., 2014). The posterior cingulate has been linked to the representation and updating of value signals for primary and secondary rewards including money (Bartra et al., 2013; Liu et al., 2011; Sescousse et al., 2013) and, along with the middle temporal gyrus, personality traits affecting reward-related dispositions [e.g., positive emotionality (Volkow et al., 2011a)]. Indeed in the current study, as in our prior study that specifically inspected the nature of a graded money effect on this task (Konova et al., 2012), activity in the posterior cingulate (together with other regions including the ventromedial prefrontal cortex and IFG) scaled with the amount of money at stake.

Interestingly, the hippocampus, posterior cingulate, and middle temporal gyrus are also core nodes within the default mode network, a set of brain regions preferentially engaged during mentalizing processes (Buckner et al., 2008). Studies examining interactions among regions of the default mode network during rest have found higher functional connectivity density (Tomasi and Volkow, 2012a, b; Zuo et al., 2010) and cerebral blood flow (Baxter et al., 1987; Gur et al., 1995) in healthy women than in men and higher network connectivity in heroin users than in healthy controls (Ma et al., 2011). The finding that female cocaine users exhibited the lowest activations in these regions is also notable in light of the role of the default mode in rumination (Berman et al., 2011; Cooney et al., 2010) and depression (Sheline et al., 2009), factors that may have a more profound effects in cocaine-dependent women than men [e.g., women are hypothesized to initiate drug use primarily to cope with

these problems (Becker et al., 2012)]. Indeed, comorbidity of drug addiction with mood and anxiety disorders is high, and in some instances it is reported to be higher in women than in men (Conway et al., 2006), including the present study. However, abnormal responses in cocaine-dependent women were observed even when we controlled for the level of self-reported depression, suggesting that these abnormalities are due to (or at least exacerbated by) chronic cocaine use above and beyond history of comorbid mood disorders, as further supported by the relationship to craving (discussed further below).

We also found evidence for diagnosis-by-sex interactions in the frontal cortex, such that female cocaine users exhibited the lowest precentral gyrus and greatest IFG activations to money relative to the other groups. A previous study found that cocaine-dependent had less gray matter volume in the IFG than healthy women (Rando et al., 2013). Interestingly, in keeping with our functional results, this prior study also found sex differences in the posterior cingulate (women < men, across healthy and cocaine-dependent individuals), which together may be related to the functional differences observed in these regions in our study. While unexpected, and subject to replication, findings in the precentral gyrus, which houses the primary motor cortex, could be related to abnormalities in the interaction between motivation and action in female cocaine users (as possibly supported by the slower reaction times observed in women than men) (Padmala and Pessoa, 2010).

The distinct patterns of response in the posterior cingulate, hippocampus, and IFG are further qualified by their differential association with task-related cocaine craving, where reduced activation in the posterior cingulate and hippocampus and increased activation in the IFG to money was associated with greater task-induced increases in craving. The strength and/or direction of this relationship in female cocaine users did not significantly differ from that observed in males, suggesting that unlike craving induced by drug and stress cues, sex-specific differences in response to money are not differentially associated with changes in craving in females and males. Nevertheless, in the absence of a behavioral advantage, this finding suggests that female cocaine users may have needed to increase differential response in the IFG (and decrease response in the other regions) to a greater extent than their male counterparts and healthy females to regulate their craving and meet task demands. This suggestion is in keeping with the known role of the IFG in response inhibition (Aron et al., 2004; Swick et al., 2008), the selective focusing of attention (Gazzaley et al., 2004; Hampshire et al., 2007; van Schouwenburg et al., 2013), and the regulation of craving (Kober et al., 2010). This suggestion is also consistent with studies in smokers that show that an inverse coupling between executive control regions (including the IFG) with the posterior cingulate and hippocampus underlies improvements in cognitive withdrawal symptoms (Cole et al., 2010).

Irrespective of the underlying mechanism, our data suggest that cocaine-dependent women exhibit vulnerabilities in reward processing that are in some instances more severe (e.g., in the hippocampus, posterior cingulate, and middle temporal gyrus) or distinct (e.g., in the IFG and precentral gyrus) from those observed in cocaine-dependent men. Measures of brain function as elucidated by degree of reward modulation may be clinically relevant, and they raise the possibility that these neural alterations could be an important target for treatment in women. Indeed, there is evidence that these regions, and the functional

networks of which they are part, are responsive to the pharmacological effects of stimulant medications (Goldstein et al., 2010; Schmaal et al., 2013), and to self-relevant cognitive-based interventions targeting motivations (Chua et al., 2011; Chua et al., 2009) and self-control (Kober et al., 2010; Volkow et al., 2010) in addiction. It is possible that these interventions may benefit women specifically.

A limitation of our study is that we did not measure gonadal hormone levels and therefore cannot account for the effects of circulating sex hormones. Previous research in healthy women (Dreher et al., 2007) suggests that menstrual cycle phase influences reward system reactivity, potentially due to the effects of sex hormones (estrogen, progesterone) on dopamine (Andersen et al., 2012), such that reward system response is diminished during the luteal phase when progesterone levels are highest. However, in this same study differences between men and women were also found across menstrual cycle phases, consistent with the idea that circulating sex hormones likely explain only a small portion of observed sex differences (Cahill, 2006). In our study women were studied across the menstrual cycle, and this variability would work against rather than for revealing sex effects. Second, although comparable to sample sizes reported in the neuroimaging literature of sex differences in addiction, the modest sample size in each group and particularly of healthy women, may have reduced our power to detect additional effects (e.g., in the ventromedial prefrontal cortex and striatum). As women are generally understudied in addiction research, future studies may need to take advantage of multi-site, collaborative efforts to overcome this limitation. Third, because we used a blocked design, we were unable to separate potential differences in the effects of sex on anticipatory vs. outcome related brain activity. However, meta-analytic data suggest vastly overlapping neuroanatomical correlates of anticipation of reward and reward outcome (Liu et al., 2011), and thus this distinction may not be critical. This is particularly relevant in the case of money where reward delivery is always delayed and therefore somewhat anticipatory even in event-related studies [e.g., note “real” vs. hypothetical money has similar neural and behavioral correlates (Bickel et al., 2010)]. Fourth, because participants were exposed to both drug words and money during the task, we cannot conclude that our craving measure captures craving elicited by either stimulus alone. The main effect of money, but not of word type, on task performance however would suggest that the money cues may have been perceived as more salient. Lastly, because only a few (20%) healthy controls and most (82%) cocaine users were cigarette smokers, we were unable to control for differences in smoking between the groups (Miller and Chapman, 2001). As nicotine use rates in our sample of cocaine users are comparable to those reported in previous studies (Grant et al., 2004; Jia et al., 2011; Kalman et al., 2005; Weinberger and Sofuoglu, 2009), this may be an inherent feature of this population and future studies would need to recruit more cigarette smoking controls to better address this potential confound.

In summary, while preliminary, our data support the presence of at least two pathways to altered value processing in women: via the influence of sexual dimorphisms and chronic cocaine use. These factors may interact or combine to produce neural vulnerabilities, which in the case of the hippocampus, posterior cingulate, and IFG, may contribute to the greater sensitivity to cue-induced craving (Kennedy et al., 2013) and higher rates of relapse (Becker and Hu, 2008; Becker et al., 2012) observed in women. Our findings bridge previous

research into sex-specific differences in reward processing in healthy individuals [e.g., (Dreher et al., 2007; Kohn et al., 2011; Spreckelmeyer et al., 2009)] and drug cue and emotional reactivity in cocaine addicted individuals [e.g. (Kilts et al., 2004; Lejuez et al., 2005; Potenza et al., 2012; Volkow et al., 2011b)], further highlighting the importance of considering sex in the examination of other cognitive and emotional functions impacted by cocaine addiction. If further studies uncover a similar relationship between these neural abnormalities and craving reported in naturalistic settings, treatment providers could consider an individual's sex in determining which therapeutic interventions might best target craving and relapse (e.g., ones focused on rewards/motivations for women).

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

This work was supported by grants from the National Institute on Drug Abuse (grant number 1R01DA023579 to R.Z.G.; 1F32DA030017-01 to S.J.M; and 1F32DA033088 to M.A.P.) and the National Institute of Mental Health (T32MH019524 training award in Systems and Integrative Neuroscience to A.B.K.).

References

- Adcock RA, Thangavel A, Whitfield-Gabrieli S, Knutson B, Gabrieli JD. Reward-motivated learning: mesolimbic activation precedes memory formation. *Neuron*. 2006; 50:507–517. [PubMed: 16675403]
- Andersen ML, Sawyer EK, Howell LL. Contributions of neuroimaging to understanding sex differences in cocaine abuse. *Experimental and clinical psychopharmacology*. 2012; 20:2–15. [PubMed: 21875225]
- Aron AR, Robbins TW, Poldrack RA. Inhibition and the right inferior frontal cortex. *Trends in cognitive sciences*. 2004; 8:170–177. [PubMed: 15050513]
- Bartra O, McGuire JT, Kable JW. The valuation system: a coordinate-based meta-analysis of BOLD fMRI experiments examining neural correlates of subjective value. *NeuroImage*. 2013; 76:412–427. [PubMed: 23507394]
- Baxter LR Jr, Mazziotta JC, Phelps ME, Selin CE, Guze BH, Fairbanks L. Cerebral glucose metabolic rates in normal human females versus normal males. *Psychiatry research*. 1987; 21:237–245. [PubMed: 3498176]
- Beck, AT.; Steer, RA.; Brown, GK. Beck Depression Inventory Manual. 2nd. San Antonio: The Psychological Corporation; 1996.
- Becker JB. Gender differences in dopaminergic function in striatum and nucleus accumbens. *Pharmacology, biochemistry, and behavior*. 1999; 64:803–812.
- Becker JB, Hu M. Sex differences in drug abuse. *Frontiers in neuroendocrinology*. 2008; 29:36–47. [PubMed: 17904621]
- Becker JB, Perry AN, Westenbroek C. Sex differences in the neural mechanisms mediating addiction: a new synthesis and hypothesis. *Biology of sex differences*. 2012; 3:14. [PubMed: 22676718]
- Berman MG, Peltier S, Nee DE, Kross E, Deldin PJ, Jonides J. Depression, rumination and the default network. *Social cognitive and affective neuroscience*. 2011; 6:548–555. [PubMed: 20855296]
- Bickel WK, Jones BA, Landes RD, Christensen DR, Jackson L, Mancino M. Hypothetical intertemporal choice and real economic behavior: delay discounting predicts voucher redemptions during contingency-management procedures. *Experimental and clinical psychopharmacology*. 2010; 18:546–552. [PubMed: 21186929]
- Bobzean SA, DeNobrega AK, Perrotti LI. Sex differences in the neurobiology of drug addiction. *Experimental neurology*. 2014; 259:64–74. [PubMed: 24508560]

- Buckner RL, Andrews-Hanna JR, Schacter DL. The brain's default network: anatomy, function, and relevance to disease. *Annals of the New York Academy of Sciences*. 2008; 1124:1–38. [PubMed: 18400922]
- Bustamante JC, Barros-Loscertales A, Costumero V, Fuentes-Claramonte P, Rosell-Negre P, Ventura-Campos N, Llopis JJ, Avila C. Abstinence duration modulates striatal functioning during monetary reward processing in cocaine patients. *Addiction biology*. 2013
- Cahill L. Why sex matters for neuroscience. *Nature reviews. Neuroscience*. 2006; 7:477–484. [PubMed: 16688123]
- Caldu X, Dreher JC. Hormonal and genetic influences on processing reward and social information. *Annals of the New York Academy of Sciences*. 2007; 1118:43–73. [PubMed: 17804523]
- Chua HF, Ho SS, Jasinska AJ, Polk TA, Welsh RC, Liberzon I, Strecher VJ. Self-related neural response to tailored smoking-cessation messages predicts quitting. *Nature neuroscience*. 2011; 14:426–427. [PubMed: 21358641]
- Chua HF, Liberzon I, Welsh RC, Strecher VJ. Neural correlates of message tailoring and self-relatedness in smoking cessation programming. *Biological psychiatry*. 2009; 65:165–168. [PubMed: 18926523]
- Cole DM, Beckmann CF, Long CJ, Matthews PM, Durcan MJ, Beaver JD. Nicotine replacement in abstinent smokers improves cognitive withdrawal symptoms with modulation of resting brain network dynamics. *NeuroImage*. 2010; 52:590–599. [PubMed: 20441798]
- Conway KP, Compton W, Stinson FS, Grant BF. Lifetime comorbidity of DSM-IV mood and anxiety disorders and specific drug use disorders: results from the National Epidemiologic Survey on Alcohol and Related Conditions. *The Journal of clinical psychiatry*. 2006; 67:247–257. [PubMed: 16566620]
- Cooney RE, Joormann J, Eugene F, Dennis EL, Gotlib IH. Neural correlates of rumination in depression. *Cogn Affect Behav Neurosci*. 2010; 10:470–478. [PubMed: 21098808]
- Dreher JC, Schmidt PJ, Kohn P, Furman D, Rubinow D, Berman KF. Menstrual cycle phase modulates reward-related neural function in women. *Proceedings of the National Academy of Sciences of the United States of America*. 2007; 104:2465–2470. [PubMed: 17267613]
- First, MB.; Spitzer, RL.; Gibbon, M.; Williams, J. Structured Clinical Interview for DSM-IV Axis I disorders - Patient Edition (SCID-I/P, Version 2.0). In: Williams, J., editor. Biometrics Research Department. New York: New York State Psychiatric Institute; 1996.
- Franklin TR, Wetherill RR, Jagannathan K, Johnson B, Mumma J, Hager N, Rao H, Childress AR. The effects of chronic cigarette smoking on gray matter volume: influence of sex. *Plos One*. 2014; 9:e104102. [PubMed: 25090480]
- Gazzaley A, Rissman J, D'Esposito M. Functional connectivity during working memory maintenance. *Cogn Affect Behav Neurosci*. 2004; 4:580–599. [PubMed: 15849899]
- Goldstein RZ, Alia-Klein N, Tomasi D, Carrillo JH, Maloney T, Woicik PA, Wang R, Telang F, Volkow ND. Anterior cingulate cortex hypoactivations to an emotionally salient task in cocaine addiction. *Proceedings of the National Academy of Sciences of the United States of America*. 2009; 106:9453–9458. [PubMed: 19478067]
- Goldstein RZ, Tomasi D, Rajaram S, Cottone LA, Zhang L, Maloney T, Telang F, Alia-Klein N, Volkow ND. Role of the anterior cingulate and medial orbitofrontal cortex in processing drug cues in cocaine addiction. *Neuroscience*. 2007; 144:1153–1159. [PubMed: 17197102]
- Goldstein RZ, Woicik PA, Maloney T, Tomasi D, Alia-Klein N, Shan J, Honorio J, Samaras D, Wang R, Telang F, Wang GJ, Volkow ND. Oral methylphenidate normalizes cingulate activity in cocaine addiction during a salient cognitive task. *Proceedings of the National Academy of Sciences of the United States of America*. 2010; 107:16667–16672. [PubMed: 20823246]
- Grant BF, Hasin DS, Chou SP, Stinson FS, Dawson DA. Nicotine dependence and psychiatric disorders in the United States: results from the national epidemiologic survey on alcohol and related conditions. *Arch Gen Psychiatry*. 2004; 61:1107–1115. [PubMed: 15520358]
- Gur RC, Mozley LH, Mozley PD, Resnick SM, Karp JS, Alavi A, Arnold SE, Gur RE. Sex differences in regional cerebral glucose metabolism during a resting state. *Science*. 1995; 267:528–531. [PubMed: 7824953]

- Hampshire A, Duncan J, Owen AM. Selective tuning of the blood oxygenation level-dependent response during simple target detection dissociates human frontoparietal subregions. *J Neurosci*. 2007; 27:6219–6223. [PubMed: 17553994]
- Jia Z, Worhunsky PD, Carroll KM, Rounsaville BJ, Stevens MC, Pearlson GD, Potenza MN. An initial study of neural responses to monetary incentives as related to treatment outcome in cocaine dependence. *Biological psychiatry*. 2011; 70:553–560. [PubMed: 21704307]
- Kalman D, Morissette SB, George TP. Co-morbidity of smoking in patients with psychiatric and substance use disorders. *Am J Addict*. 2005; 14:106–123. [PubMed: 16019961]
- Kennedy AP, Epstein DH, Phillips KA, Preston KL. Sex differences in cocaine/heroin users: drug-use triggers and craving in daily life. *Drug and alcohol dependence*. 2013; 132:29–37. [PubMed: 23357742]
- Kilts CD, Gross RE, Ely TD, Drexler KP. The neural correlates of cue-induced craving in cocaine-dependent women. *The American journal of psychiatry*. 2004; 161:233–241. [PubMed: 14754771]
- Kober H, Mende-Siedlecki P, Kross EF, Weber J, Mischel W, Hart CL, Ochsner KN. Prefrontal-striatal pathway underlies cognitive regulation of craving. *Proc Natl Acad Sci U S A*. 2010; 107:14811–14816. [PubMed: 20679212]
- Kohn N, Kellermann T, Gur RC, Schneider F, Habel U. Gender differences in the neural correlates of humor processing: implications for different processing modes. *Neuropsychologia*. 2011; 49:888–897. [PubMed: 21320516]
- Konova AB, Moeller SJ, Tomasi D, Parvaz MA, Alia-Klein N, Volkow ND, Goldstein RZ. Structural and behavioral correlates of abnormal encoding of money value in the sensorimotor striatum in cocaine addiction. *The European journal of neuroscience*. 2012; 36:2979–2988. [PubMed: 22775285]
- Lejuez CW, Aklin W, Bornovalova M, Moolchan ET. Differences in risk-taking propensity across inner-city adolescent ever- and never-smokers. *Nicotine & tobacco research : official journal of the Society for Research on Nicotine and Tobacco*. 2005; 7:71–79. [PubMed: 15804679]
- Liu X, Hairston J, Schrier M, Fan J. Common and distinct networks underlying reward valence and processing stages: a meta-analysis of functional neuroimaging studies. *Neuroscience and biobehavioral reviews*. 2011; 35:1219–1236. [PubMed: 21185861]
- Ma N, Liu Y, Fu XM, Li N, Wang CX, Zhang H, Qian RB, Xu HS, Hu X, Zhang DR. Abnormal brain default-mode network functional connectivity in drug addicts. *PloS one*. 2011; 6:e16560. [PubMed: 21298074]
- McLellan AT, Kushner H, Metzger D, Peters R, Smith I, Grissom G, Pettinati H, Argeriou M. The Fifth Edition of the Addiction Severity Index. *J Subst Abuse Treat*. 1992; 9:199–213. [PubMed: 1334156]
- Miller GA, Chapman JP. Misunderstanding analysis of covariance. *Journal of abnormal psychology*. 2001; 110:40–48. [PubMed: 11261398]
- Moeller SJ, Tomasi D, Woicik PA, Maloney T, Alia-Klein N, Honorio J, Telang F, Wang GJ, Wang R, Sinha R, Carise D, Astone-Twerell J, Bolger J, Volkow ND, Goldstein RZ. Enhanced midbrain response at 6-month follow-up in cocaine addiction, association with reduced drug-related choice. *Addict Biol*. 2012; 17:1013–1025. [PubMed: 22458423]
- Murty VP, Adcock RA. Enriched encoding: reward motivation organizes cortical networks for hippocampal detection of unexpected events. *Cerebral cortex*. 2014; 24:2160–2168. [PubMed: 23529005]
- Padmala S, Pessoa L. Interactions between cognition and motivation during response inhibition. *Neuropsychologia*. 2010; 48:558–565. [PubMed: 19879281]
- Petry NM, Kirby KN, Kranzler HR. Effects of gender and family history of alcohol dependence on a behavioral task of impulsivity in healthy subjects. *Journal of studies on alcohol*. 2002; 63:83–90. [PubMed: 11925063]
- Potenza MN, Hong KI, Lacadie CM, Fulbright RK, Tuit KL, Sinha R. Neural correlates of stress-induced and cue-induced drug craving: influences of sex and cocaine dependence. *The American journal of psychiatry*. 2012; 169:406–414. [PubMed: 22294257]

- Rando K, Tuit K, Hannestad J, Guarnaccia J, Sinha R. Sex differences in decreased limbic and cortical grey matter volume in cocaine dependence: a voxel-based morphometric study. *Addict Biol.* 2013; 18:147–160. [PubMed: 23167305]
- Rose EJ, Salmeron BJ, Ross TJ, Waltz J, Schweitzer JB, McClure SM, Stein EA. Temporal difference error prediction signal dysregulation in cocaine dependence. *Neuropsychopharmacology* : official publication of the American College of Neuropsychopharmacology. 2014; 39:1732–1742. [PubMed: 24569319]
- Schmaal L, Goudriaan AE, Joos L, Kruse AM, Dom G, van den Brink W, Veltman DJ. Modafinil modulates resting-state functional network connectivity and cognitive control in alcohol-dependent patients. *Biological psychiatry.* 2013; 73:789–795. [PubMed: 23399373]
- Schultz W. Reward signaling by dopamine neurons. *The Neuroscientist : a review journal bringing neurobiology, neurology and psychiatry.* 2001; 7:293–302.
- Sescousse G, Caldu X, Segura B, Dreher JC. Processing of primary and secondary rewards: a quantitative meta-analysis and review of human functional neuroimaging studies. *Neuroscience and biobehavioral reviews.* 2013; 37:681–696. [PubMed: 23415703]
- Sheline YI, Barch DM, Price JL, Rundle MM, Vaishnavi SN, Snyder AZ, Mintun MA, Wang S, Coalson RS, Raichle ME. The default mode network and self-referential processes in depression. *Proceedings of the National Academy of Sciences of the United States of America.* 2009; 106:1942–1947. [PubMed: 19171889]
- Shigemune Y, Tsukiura T, Kambara T, Kawashima R. Remembering with gains and losses: effects of monetary reward and punishment on successful encoding activation of source memories. *Cerebral cortex.* 2014; 24:1319–1331. [PubMed: 23314939]
- Spreckelmeyer KN, Krach S, Kohls G, Rademacher L, Irmak A, Konrad K, Kircher T, Grunder G. Anticipation of monetary and social reward differently activates mesolimbic brain structures in men and women. *Social cognitive and affective neuroscience.* 2009; 4:158–165. [PubMed: 19174537]
- Sulzer D. How addictive drugs disrupt presynaptic dopamine neurotransmission. *Neuron.* 2011; 69:628–649. [PubMed: 21338876]
- Swick D, Ashley V, Turken AU. Left inferior frontal gyrus is critical for response inhibition. *BMC neuroscience.* 2008; 9:102. [PubMed: 18939997]
- Tomasi D, Volkow ND. Aging and functional brain networks. *Molecular psychiatry.* 2012a; 17:471. 549–458. [PubMed: 21727896]
- Tomasi D, Volkow ND. Gender differences in brain functional connectivity density. *Human brain mapping.* 2012b; 33:849–860. [PubMed: 21425398]
- van Schouwenburg MR, Zwiers MP, van der Schaaf ME, Geurts DE, Schellekens AF, Buitelaar JK, Verkes RJ, Cools R. Anatomical connection strength predicts dopaminergic drug effects on fronto-striatal function. *Psychopharmacology.* 2013; 227:521–531. [PubMed: 23404064]
- Ventura J, Liberman RP, Green MF, Shaner A, Mintz J. Training and quality assurance with the Structured Clinical Interview for DSM-IV (SCID-I/P). *Psychiatry Res.* 1998; 79:163–173. [PubMed: 9705054]
- Villafuerte S, Heitzeg MM, Foley S, Yau WY, Majczenko K, Zubieta JK, Zucker RA, Burmeister M. Impulsiveness and insula activation during reward anticipation are associated with genetic variants in GABRA2 in a family sample enriched for alcoholism. *Molecular psychiatry.* 2012; 17:511–519. [PubMed: 21483437]
- Volkow ND, Fowler JS, Wang GJ, Telang F, Logan J, Jayne M, Ma Y, Pradhan K, Wong C, Swanson JM. Cognitive control of drug craving inhibits brain reward regions in cocaine abusers. *NeuroImage.* 2010; 49:2536–2543. [PubMed: 19913102]
- Volkow ND, Tomasi D, Wang GJ, Fowler JS, Telang F, Goldstein RZ, Alia-Klein N, Woicik P, Wong C, Logan J, Millard J, Alexoff D. Positive emotionality is associated with baseline metabolism in orbitofrontal cortex and in regions of the default network. *Molecular psychiatry.* 2011a; 16:818–825. [PubMed: 21483434]
- Volkow ND, Tomasi D, Wang GJ, Fowler JS, Telang F, Goldstein RZ, Alia-Klein N, Wong C. Reduced metabolism in brain “control networks” following cocaine-cues exposure in female cocaine abusers. *Plos One.* 2011b; 6:e16573. [PubMed: 21373180]

- Weinberger AH, Sofuoglu M. The impact of cigarette smoking on stimulant addiction. *Am J Drug Alcohol Abuse*. 2009; 35:12–17. [PubMed: 19152200]
- Zuo XN, Kelly C, Di Martino A, Mennes M, Margulies DS, Bangaru S, Grzadzinski R, Evans AC, Zang YF, Castellanos FX, Milham MP. Growing together and growing apart: regional and sex differences in the lifespan developmental trajectories of functional homotopy. *J Neurosci*. 2010; 30:15034–15043. [PubMed: 21068309]

- Female and male substance users differ in their course of illness
- We observed additive effects of cocaine addiction and sex on PCC and hippocampus response to monetary rewards
- Interaction effects of these factors were also observed in the IFG
- The pattern of response in these three regions was related to subjective craving
- Treatments that target these neural disturbances could specifically benefit females

Figure 1.

Effects of diagnosis and sex on neural processing of monetary reward. Additive, and overlapping, effects of diagnosis (red) and sex (blue) were observed in the (A) right hippocampus, (B) bilateral middle/posterior cingulate cortex, and (C) right middle temporal gyrus (voxels of overlap between the main effects of diagnosis and sex are shown in violet), while diagnosis-by-sex interactions (yellow) were observed in the (D) right precentral gyrus and (E) left inferior frontal gyrus. Activation maps are thresholded at $T>1.5$ for display purposes only. Asterisks indicate significant pairwise group differences: * $P < 0.05$, ** $P < 0.01$, *** $P < 0.001$.

Figure 2.

Relationship between sex-specific differences in neural response to money and task-related change in craving. Across all cocaine-dependent individuals, reduced (A) right hippocampus and (B) left middle/posterior cingulate cortex activation (regions of overlap from Fig. 1A & B) and greater (C) left inferior frontal gyrus activation (region of interaction from Fig. 1E) to money were all associated with greater increases in cocaine craving. Note that one male cocaine user was identified as an outlier (Cook's $d > 1$) and removed from these analyses. Significance at $P < 0.007$ Bonferroni-corrected.

Table 1

Demographic characteristics and task behavior of the study sample

	Cocaine Females (n=14)	Cocaine Males (n=14)	Control Females (n=11)	Control Males (n=14)	Effect	P
Age, y	44±2	44±1	40±3	40±1	Diagnosis Sex Diagnosis × Sex	0.04 0.97 0.94
Race, No. African-American/Caucasian/Hispanic	12/2/0	12/2/0	9/1/1	10/1/3	Diagnosis Sex Diagnosis × Sex	0.08 0.65 --
Education, y	13±0	13±0	14±1	14±0	Diagnosis Sex Diagnosis × Sex	0.08 0.39 0.69
Socioeconomic Status: Hollingshead Index	33±2	33±3	38±6	36±3	Diagnosis Sex Diagnosis × Sex	0.21 0.84 0.80
Verbal IQ: Wide Range Achievement Test III – Reading Scale	96±5	94±3	97±3	95±3	Diagnosis Sex Diagnosis × Sex	0.82 0.53 0.87
Nonverbal IQ: Wechsler Abbreviated Scale of Intelligence – Matrix Reasoning Scale	9±1	9±1	11±1	10±1	Diagnosis Sex Diagnosis × Sex	0.09 0.47 0.65
Depressive Symptoms: Beck Depression Inventory II	5±1	5±1	2±1	3±1	Diagnosis Sex Diagnosis × Sex	0.005 0.60 0.47
Task Behavior: Average Correct <i>a</i>	50% 0%	17±1 16±1	15±1 14±1	16±1 14±1	Diagnosis Sex	0.65 0.19

	Cocaine Females (<i>n</i> =14)	Cocaine Males (<i>n</i> =14)	Control Females (<i>n</i> =11)	Control Males (<i>n</i> =14)	Effect	<i>P</i>
	1±1	1±1	1±1	2±1	Diagnosis × Sex	0.19
<hr/>						
Task Behavior: RT Correct (ms) ^a						
50¢>0¢:	256±4	258±4	275±5	263±5	Diagnosis	0.92
0¢:	254±5	260±4	266±6	272±6	Sex	0.01
50¢>0¢:	2±4	-2±3	10±5	-9±5	Diagnosis × Sex	0.09
<hr/>						
Craving: Cocaine Wanting (Task>Baseline) ^{a,b}						
Task:	1.4±0.6	1.6±0.7	0.0±0.0	0.0±0.0	Diagnosis	0.009
Baseline:	0.7±0.4	1.5±0.7	0.2±0.2	0.2±0.2	Sex	0.26
Task>Baseline:	0.7±0.5	-0.1±0.1	-0.2±0.2	-0.2±0.2	Diagnosis × Sex	0.07

Values are frequencies or means + standard error of the mean (SEM) unless otherwise specified;

^a Analysis of covariance on the differentials (50¢>0¢ or Task>Baseline), controlling for age and BDI scores;

^b One outlier (cocaine dependent male) was removed from this analysis (Cook's *d*>1).

Table 2

Drug use characteristics of the cocaine dependent sample

	Females (n=14)	Males (n=14)	P
Cigarette Smokers, No. Current or Past / Nonsmokers ^a	13/1	10/3	0.63
Cigarettes/d, Current Smokers Only	9±2	7±2	0.43
Duration of Alcohol Use to Intoxication, y	7±2	7±3	0.84 ^b
Days of Alcohol Use to Intoxication, No. in Past 30 d	1±1	1±1	0.39 ^b
Cocaine Urine Status, No. Positive / Negative	4/10	6/8	0.43
Current Cocaine Abstinence, d Since Last Use	0 – 548 (median=27)	0 – 2555 (median=8)	0.89 ^b
Age of Onset of Cocaine Use, y	23±2	27±2	0.14
Duration of Cocaine Use, y	16±2	15±2	0.73
Preferred Route of Admin., No. Smoked / Intranasal	13/1	12/2	0.54
Money Spent per Use, \$ ^c	59±31	68±35	0.42 ^b
Days of Cocaine Use, No./Week in Past 30 d	2±1	3±1	0.10
Days of Cocaine Use, No./Week in Past 12 mo	3±1	3±1	0.79
Withdrawal Symptoms: 18-item CSSA (0–126)	13±3	15±3	0.65
Severity of Dependence Scale (0–15)	8±1	8±1	0.78
Cocaine Craving: 5-item Questionnaire (0–45)	10±2	15±3	0.17
Lifetime History of Substance Use Disorder, ^d yes / no	11/3	7/7	0.12
Lifetime History of Mood Disorder, yes / no	5/9	0/14	0.01

Values are frequencies or means + standard error of the mean (SEM) unless otherwise specified;

^aMissing data for one male participant;

^bThe nonparametric Mann-Whitney U was used due to the skewed distribution of the variable;

^cMissing data for 2 female and 6 male participants;

^dIncludes current or past diagnosis of substance use disorder other than for cocaine or nicotine.

Table 3

Results from the whole-brain diagnosis $\times$ sex analysis of covariance on response to monetary reward (50¢) versus no reward (0¢)^a

MNI Coordinates							
	BA	Side	Cluster Size	Peak <i>T</i>	X	Y	Z
<i>Cocaine Users > Controls</i>							
Putamen		R	163	4.3	30	8	7
					27	14	22
Inferior parietal/supramarginal gyrus	2	L	42	3.7	-45	-28	28
					-45	-28	37
Anterior/middle cingulate gyrus	24,32	R,L	73	3.7	6	17	34
					-9	11	31
Calcarine sulcus	18	L	30	3.6	-3	-70	19
Fusiform gyrus/hippocampus	20	L	41	3.5	-33	-7	-23
<i>Controls > Cocaine Users</i>							
Lingual gyrus	19	R	32	3.6	24	-85	-8
Middle/posterior cingulate	23	L	45	3.2	-24	-40	40
					-9	-37	34
<i>Males > Females</i>							
Middle/posterior cingulate	23,26	R,L	130	3.7	-9	-25	46
					0	-37	22
					-9	-31	37
Parahippocampal gyrus/hippocampus	37	R	26	3.2	24	-37	-8
					30	-34	7
<i>Females > Males</i>							
Postcentral gyrus	3,4	L	48	3.6	-51	-13	40
<i>Diagnosis × Sex Interaction</i>							

MNI Coordinates						
	BA	Side	Cluster Size	Peak <i>T</i>	X	Y Z
Precentral gyrus	6	R	26	3.5	33	-16 46
Inferior frontal gyrus	44	L	29	3.5	-39	8 25

^a Analysis of covariance, controlling for age, BDI scores, and reaction times;

Results are reported at $P<0.05$ cluster-corrected for multiple comparisons (equal to a height threshold of voxel-level $P<0.005$ uncorrected and a minimum of 26 contiguous voxels);

Abbreviations: BA, Brodmann area; MNI, Montreal Neurological Institute.